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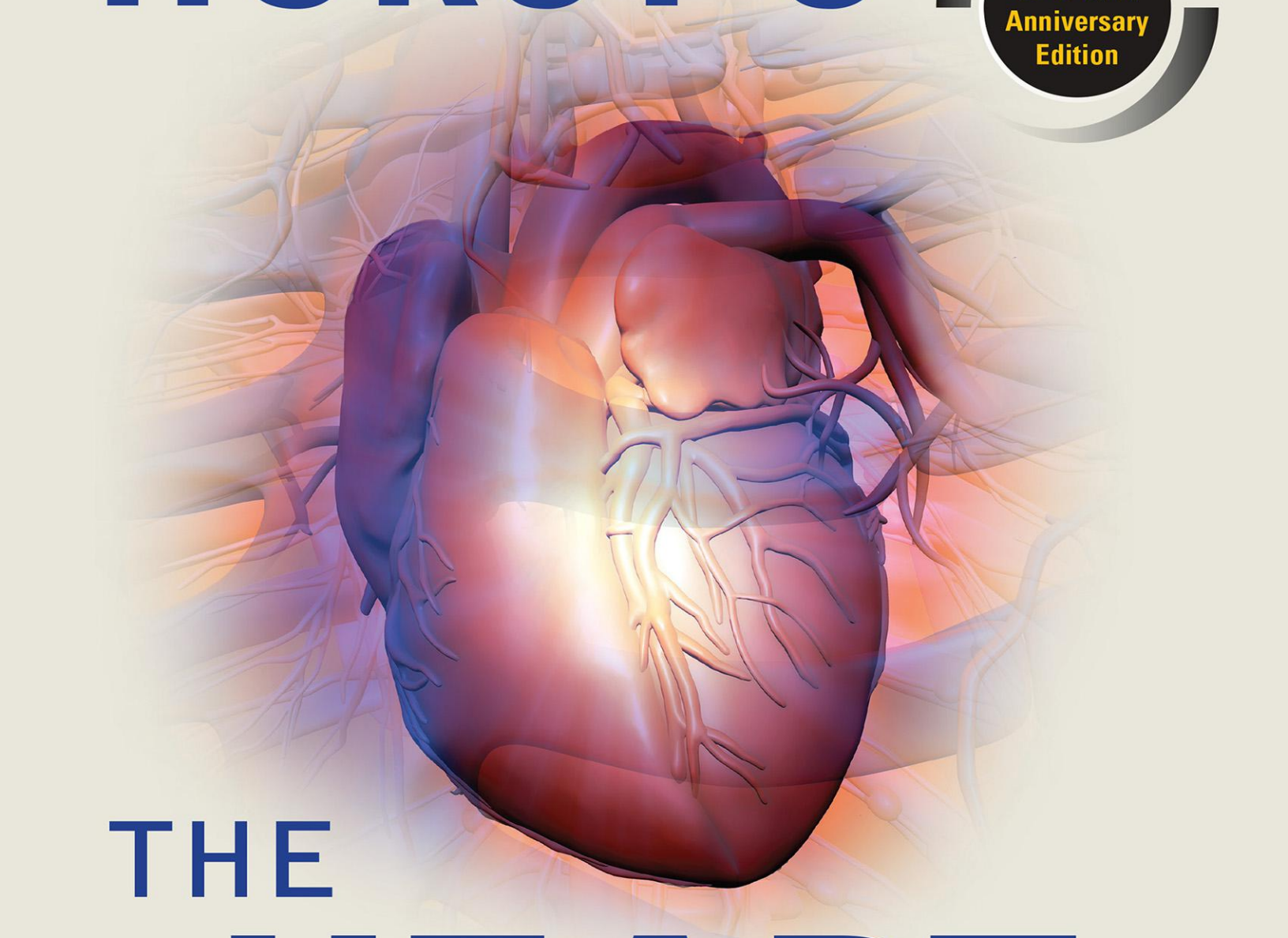

THE HEART

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PREFACE

Although we are excited to bring you the fourteenth edition of *Hurst's The Heart* as the book completes its 50 years since the publication of its first edition (1966), we also mourn the sad passing of the first legendary editor of this book, J. Willis Hurst. We will sorely miss his consistent support and encouragement. Through 13 earlier editions of this first multidisciplinary and comprehensive textbook on cardiovascular disease, *The Heart* has always represented a cornerstone of current scholarship in the discipline. Cardiologists, internists, and trainees from around the world have relied on its authority, breadth of coverage, and clinical relevance to keep up to date on advances in the field and to help optimize patient care. The fourteenth edition of *The Heart* continues the standard-setting tradition with numerous new features, chapters, and authors.

The new edition features an enhanced and reader-friendly design and covers need-to-know clinical advances as well as issues that are becoming increasingly vital to physicians practicing cardiology worldwide. The book is now interactive: it is available online and is committed to providing you with timely updates. The interactive models have been developed by numerous young faculty members from the Mount Sinai, Duke University, and Stanford University Schools of Medicine, who look forward to receiving your feedback. The pathology, pathogenesis, and genetics of all diseases have been provided in a concise fashion in colored boxes for your ready reference and provide an entirely new translational experience to busy clinical practioners. Eloisa Arbustini and Jennifer Hall have edited these boxed enclosures. Smaller color-boxed entries also offer the national and international demographics, prevalence, and incidence statistics of all cardiovascular disorders; these entries have been painstakingly prepared by Gregory Roth, Andrew Moran, and Donald Lloyd-Jones. Through the 16 thematic sections of text, the reader will find the most complete overview of cardiovascular topics available, plus a timely new focus on evidence-based medicine, health outcomes, and health care quality. We also welcome Bryony Mearns, the previous Editor-in-Chief of *Nature Reviews (Cardiovascular Medicine),* who has helped to completely transform the illustrations. The two volumes of the book have been extensively rearranged.

For this fourteenth edition of *The Heart,* we welcome Jagat Narula and Zubin J. Eapen as new editors. Dr. Richard A. Walsh has retired as one of the editors of *The Heart* after having made enormous contributions to the past editions, and we will miss him. We will also miss the associate editors, Sharon Hunt, Spencer King III, Ira Nash, Eric Prystowsky, Robert Roberts, and Eric Rose. We warmly thank the authors for their extraordinary dedication and commitment to a rigorous time schedule that allowed publication of this edition. We greatly appreciate the steady support and understanding of Maria Fuster, Rhonda Larsen Harrington, Navneet Narula, and Rose John Eapen for the successful completion of the book. The secretarial support of Robinson Santana and Alfred Kemp is greatly appreciated. Finally, we extend our appreciation to James Shanahan and his associates at McGraw-Hill Education, especially Karen Edmonson, for their energetic support and for helping to make the fourteenth edition available promptly all over the world.

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ABBREVIATIONS

βARK1	βAR kinase 1
1D	one-dimensional
2D	two-dimensional
3D	three-dimensional
4D	four-dimensional
5-HT	5-hydroxytryptamine
^{99m}Tc	technetium-99m
AAA	abdominal aortic aneurysm
AAC	American College of Cardiology
AACE	American Association of Clinical Endocrinologists
AAD	antiarrhythmic drug
AAR	area at risk
AAV	antineutrophil cytoplasmic antibody-associated vasculitides
AAV1	adeno-associated virus 1
ABI	ankle-brachial index
ABL	ablation catheter
ABR	arterial-bronchial diameter ratio
ACA	anterior cerebral artery
ACAT	acyl-coenzyme A: cholesterolacyltransferase
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACE	angiotensin-converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ACHA	Adult Congenital Heart Association
ACHD	adult congenital heart disease
ACM	arrhythmogenic cardiomyopathy
A-CMP	alcoholic cardiomyopathy
ACS	acute coronary syndrome
ACTH	adrenocorticotropic hormone
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
AD	autosomal dominant
ADA	American Diabetes Association
ADCM	atrial dilated cardiomyopathy
ADH	antidiuretic hormone
ADHERE	Acute Decompensated Heart Failure National Registry
ADM	adrenomedullin
ADP	adenosine diphosphate
AEC	absolute eosinophilic count
AED	automated external defibrillator
AF	atrial fibrillation
AFD	Anderson Fabry disease
Afib	atrial fibrillation
AFL	atrial flutter
AHA	American Heart Association
A-HeFT	African American Heart Failure Trial
AHF	acute heart failure
AHI	apnea-hypopnea index
AI	aortic insufficiency
A-IAB	advanced interatrial block
AIDS	acquired immunodeficiency syndrome
AIVR	accelerated idioventricular rhythm
AKI	acute renal injury
AL	allostatic load; light chain (amyloidosis)
ALL	acute lymphoblastic leukemia
AMA	American Medical Association
AMC	aorto-mitral continuity
AME	apparent mineralocorticoid excess
AMI	acute myocardial infarction
AMP	adenosine monophosphate
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibody
Ang II	angiotensin II
ANP	atrial natriuretic peptide
AO	aorta
AoP	aortic pressure
AoV	aortic valve
AP	anteroposterior
APAH	associated pulmonary arterial hypertension
APC	angiogenic progenitor cell
APD	action potential duration
APHRS	Asia-Pacific Heart Rhythm Association
apo	apolipoprotein
apo(a)	apolipoprotein(a)
apoE	apolipoprotein E
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
APVR	anomalous pulmonary venous return
AR	adrenergic receptor; aortic regurgitation; autosomal recessive
ARB	angiotensin receptor blocker
ARC	arrhythmogenic right, left, and biventricular cardiomyopathy
ARF	acute rheumatic fever
ARH	autosomal recessive hypercholesterolemia
ARIC	Atherosclerosis Risk in Communities
ARNI	angiotensin receptor-neprilysin inhibition
ARVC	arrhythmogenic right ventricular cardiomyopathy
AS	aortic stenosis
ASA	alcohol septal ablation; aspirin
ASCVD	atherosclerotic cardiovascular disease
ASD	atrial septal defect
ASE	American Society of Echocardiography
ASNC	American Society of Nuclear Cardiology
ASO	arteriosclerosis obliterans
ASV	adaptive servo-ventilation
AT III	antithrombin 3
AT	antithrombin; atrial tachycardia

ATP	adenosine triphosphate; antitachycardia pacing
ATPase	adenosine triphosphatase
ATS	arterial tortuosity syndrome
ATTR	transthyretin (amyloidosis)
AU	arbitrary units
AUC	appropriate use criteria
AV	aortic valve; arteriovenous ; atrioventricular
AVA	aortic valve area
AVB	atrioventricular block
AVID	Antiarrhythmics Versus Implantable Defibrillators (registry)
AVM	arteriovenous malformation
AVNRT	atrioventricular nodal reentrant tachycardia
A-VO_2	arteriovenous oxygen difference
AVP	arginine vasopressin
AVR	aortic valve replacement
AVRT	atrioventricular reentrant tachycardia
B19V	human parvovirus B19
BARC	Bleeding Academic Research Consortium
BAT	baroreflex activation therapy
BAV	bicuspid aortic valve
BB	β-blocker
BBR	bundle-branch reentry
BH4	tetrahydroxybiopterin
BiPAP	bilevel positive airway pressure
BM	bone marrow
BMI	body mass index
BMMNC	bone marrow-derived mononuclear cell
BMP	bone morphogenetic protein
BMS	bare metal stent
BMV	balloon mitral valvotomy
BNP	B-type natriuretic peptide; brain natriuretic peptide
BOLD	Burden of Obstructive Lung Disease study
BP	blood pressure
BPD	biliopancreatic diversion with or without duodenal switch
BREATHE-5	Bosentan Randomized Trial of Endothelin Antagonist Therapy-5
BRS	baroreflex sensitivity; bioresorbable scaffolds
BrS	Brugada syndrome
BSA	body surface area
BTT	bridge to transplantation
BV	biventricular
BVS	bioresorbable vascular scaffold
Ca	calcium
CA	cancer antigen
CABG	coronary artery bypass graft
CAC	coronary artery calcium/calcification
CACS	coronary artery calcium score
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
Cai	intracellular calcium
CAID	chronic atrial and intestinal dysrhythmia
CaMKII	calcium-calmodulin kinase II
cAMP	cyclic adenosine monophosphate
CAR	coxsackievirus-adenovirus receptor
Carl	cardiac apoptosis-related lncRNA
CAS	coronary artery stenting
cath lab	catheterization laboratory
CAV	cardiac allograft vasculopathy
CCA	common carotid artery
CCB	calcium channel blocker
CCS	Canadian Cardiovascular Society; computed tomography-derived coronary artery calcium/calcification score
CCTA	cardiac/coronary computed tomography angiography
CD	Chagas disease
CDC	cardiosphere-derived cell
CDLS	Cornelia de Lange syndrome
CDRIE	cardiac device–related infective endocarditis
CDT	catheter-directed thrombolysis
CEA	carcinoembryonic antigen
CEA	carotid endarterectomy
CE-CMR	contrast-enhanced cardiovascular magnetic resonance
CE-MRA	contrast-enhanced magnetic resonance angiography
CETP	cholesteryl ester transfer protein
CFD	color-flow Doppler; computational fluid dynamics
CFR	coronary flow reserve
CGM	continuous glucose monitoring
cGMP	cyclic 3′,5′-guanosine monophosphate
CHA_2DS_2-VASc	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category
$CHADS_2$	congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
Chast	cardiac hypertrophy-associated transcript
CHD	congenital heart disease; coronary heart disease
CHP	capillary hydrostatic pressure

CI	chronotropic incompetence; confidence interval
CICR	calcium-induced calcium release
CIED	cardiac/cardiovascular implantable electronic device
CIN	contrast-induced nephropathy
CIPO	chronic intestinal pseudo-obstruction
CK	creatine kinase
CKD	chronic kidney disease
CK-MB	creatine kinase myocardial band
CLI	critical limb ischemia
CLS	closed loop stimulation
CM	cardiomyopathy
CMAP	compound motor action potential
CMD	coronary microvascular disease/dysfunction
CMDS	cardiometabolic disease staging system
CML	chronic myeloid leukemia
CMP	cardiomyopathy
CMR	cardiac/cardiovascular magnetic resonance
cMRI	cardiac magnetic resonance imaging
CMS	Centers for Medicare and Medicaid Services
cMs	centimorgans
CMV	closed mitral valvotomy
CNI	calcineurin inhibitor
CNP	C-type natriuretic peptide
CNS	central nervous system
CO	carbon monoxide; cardiac output
CO_2	carbon dioxide
CONCOR	CONgenital CORvitia
CoNS	coagulase-negative staphylococci
COPD	chronic obstructive pulmonary disease
COPE	Colchicine for Acute Pericarditis
COX	cyclooxygenase
CP	constrictive pericarditis
CPAP	continuous positive airway pressure
CPB	cardiopulmonary bypass
CPET	cardiopulmonary exercise testing
CPR	cardiopulmonary resuscitation
CPTP	cyclopentyltriazolopyrimidine
CPVT	catecholaminergic polymorphic ventricular tachycardia
CR	cardiac rehabilitation
Cr	creatinine
CRCD	chemotherapy-related cardiac dysfunction
CREDO	Clopidogrel for the Reduction of Events during Observation; Coalition to Reduce Racial and Ethnic Disparities in Cardiovascular Disease Outcomes
CRIS	Cardiac Risk Index Score
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CS	carcinoid syndrome; coronary sinus
CS_2	carbon disulfide
CSA	central sleep apnea; cross-sectional area
CsA	cyclosporine A
CSNRT	corrected sinus node recovery time
CSR	Cheyne-Stokes respiration
CSS	Churg-Strauss syndrome
CT FFR	computed tomography fractional flow reserve
CT	computed tomography
CTA	computed tomography angiography
CTCAE	Common Terminology Criteria for Adverse Events
CTEPH	chronic thromboembolic pulmonary hypertension
CTLA4	cytotoxic T-lymphocyte–associated antigen 4
cTn	cardiac troponin
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CTP	computed tomography perfusion
CTPA	computed tomography pulmonary angiography
CTRCD	chemotherapy-related cardiac dysfunction
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events
CURRENT	Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes
CV	cardiovascular
CV-B3	coxsackievirus B3
CVD	cardiovascular disease
CVR	coronary vasodilatory reserve
CW	continuous-wave
Cx	circumflex
CYFRA 21-1	cytokeratin 19 fragment
CYP	cytochrome P450
CZT	cadmium-zinc-telluride (detector)
D2B	Door-to-Balloon Initiative
DAD	delayed afterpolarization
DAG	diacylglycerol
DALY	disability-adjusted life-year
DAPT	dual antiplatelet therapy
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DBT	door-to-balloon time
DC	direct current
DCA	directional coronary atherectomy

DCD donation after circulatory death
DCM dilated cardiomyopathy
DCM-DYS dilated cardiodystrophinopathy
DCM-EMD dilated cardioemerinopathy
DCM-LMNA dilated cardiolaminopathy
DENSE displacement encoded echoes
DES drug-eluting stent
DHHS Department of Health and Human Services
DHP CCB dihydropyridine calcium channel blocker
DIL drug-induced systemic lupus erythematosus
DM dermatomyositis; myotonic dystrophy
DM-CMP diabetes mellitus-related cardiomyopathy
DMD Duchenne muscular dystrophy
DNA deoxyribonucleic acid
DOAC direct-acting oral anticoagulant
DOCA deoxycorticosterone acetate
DORV double-outlet right ventricle
DPP-IV dipeptidyl peptidase IV
DR Dahl salt-resistant
DS Dahl salt-sensitive; diameter stenosis
DSA digital subtraction angiography
DSCR Down syndrome critical region
DSE dobutamine stress echocardiography
DT destination therapy
DTI direct thrombin inhibitor
DTS Duke treadmill score
DVT deep vein thrombosis
DWORF dwarf open reading frame
EA effective arterial elastance
EAD early after depolarization
EARLY ACS Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome
EBCT electron beam computed tomography
EBV Ebstein-Barr virus
EC excitation-contraction
ECG electrocardiogram; electrocardiography
ECGI electrocardiographic imaging
ECM extracellular matrix
ECMO extracorporeal membrane oxygenation
ECV effective circulatory volume; extracellular volume
ED emergency department; endothelial dysfunction
EDC endocrine-disrupting compound
EDCF endothelium-derived constricting factor
EDHF endothelium-derived hyperpolarizing factor
EDP end-diastolic pressure
EDPVR end-diastolic pressure-volume relationship
EDRF endothelium-derived relaxing factor
EDS IV Ehlers-Danlos syndrome
EDV end-diastolic volume
EEM external elastic membrane
Ees end-systolic elastance
EET epoxyeicosatrienoic (acid)
EF ejection fraction
EFFECT Enhanced Feedback for Effective Cardiac Treatment
EFNB2 ephrin-B2
EGE early gadolinium enhancement
eGFR estimated glomerular filtration rate
EGPA eosinophilic granulomatosis with polyangiitis
EHRA European Heart Rhythm Association
ELI energy loss index
ELISA enzyme-linked immunosorbent assay
EMB endomyocardial biopsy
EMF endomyocardial fibrosis
EMI electromagnetic interference
EMS emergency medical services
EMT epithelial-to-mesenchymal transition
ENaC epithelial sodium channel
EndMT endothelial-to-mesenchymal transition
eNOS endothelial nitric oxide synthase type III
EOA effective orifice area
EP electrophysiology
EPC endothelial progenitor cell
EPD embolic protection device
EPDC epicardial-derived cells
EPS electrophysiologic study
ER endoplasmic reticulum
ERA endothelin receptor agonist
ERK extracellular signal-regulated kinase
EROA effective regurgitant orifice area
ERP effective refractory period
ERS early repolarization syndrome
ESC embryonic stem cell; European Society of Cardiology
ESCAPE Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization and Effectiveness
ESPVR end-systolic pressure-volume relationship
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
ESS endothelial shear stress

ESSENCE Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events
ESV end-systolic volume
ET endothelin
ET-1 endothelin-1
ET_A endothelin receptor type A
ET_B endothelin receptor type B
ETT exercise treadmill test
EVEREST Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
FA femoral artery; fibroatheroma
FAC fractional area change
FAP familial amyloid polyneuropathy
FCTC Framework Convention on Tobacco Control
FD fractal dimension
FDA US Food and Drug Administration
FDCM familial dilated cardiomyopathy
FDG fluorodeoxyglucose
FFR fractional flow reserve
FFRCT fractional flow reserve computed tomography
FGF fibroblast growth factor
FH familial hypercholesterolemia
FHF first heart field
FH-I familial hyperaldosteronism type I
FH-II familial hyperaldosteronism type II
FMD fibromuscular dysplasia
FMF familial Mediterranean fever
FRDA Friedrich ataxia
FRS Framingham Risk Score
FSE fast spin echo
FTAAD familial thoracic aortic aneurysm and dissection
FXa factor Xa
GAS group A *Streptococcus*
GBCA gadolinium-based contrast agent
GBD Global Burden of Disease
GCA giant-cell arteritis
GCM giant cell myocarditis
GCV great cardiac vein
GDF-15 growth differentiation factor-15
GDP gross domestic product
GEP gene expression profile
GFR glomerular filtration rate
GH growth hormone
GI gastrointestinal
GLP-1 glucagon-like peptide-1
GLS global longitudinal strain
GP glycoprotein
GPI glycoprotein IIb/IIIa inhibitor
GRACE Global Registry of Acute Coronary Events
GRK G protein-coupled receptor kinase
GSK-3 glycogen synthase kinase-3
GSV great saphenous vein
GUSTO Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
GWAS genome-wide association studies
GWTG Get with the Guidelines
GWTG-HF Get with the Guidelines-Heart Failure
HAART highly active antiretroviral therapy
HACEK *Haemophilus* species, *Actinobacillus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species
HAID heritable autoinflammatory disorder
HANA HIV-associated non-AIDS illnesses
HBP His bundle pacing
HCII heparin cofactor II
HCM hypertrophic cardiomyopathy
HCMV human cytomegalovirus
HCN hyperpolarization-activated cyclic nucleotide-gated channel
HD hemodialysis
HDAC histone deacetylase
HDE high-dose epinephrine
HDL high-density lipoprotein
HDL-C high-density lipoprotein cholesterol
HES hypereosinophilic syndromes
HETE hydroxyeicosatetraenoic acid
HF heart failure
HFpEF heart failure with preserved ejection fraction
HFQRS high-frequency mid-QRS
HFrEF heart failure with reduced ejection fraction
HH hereditary hemochromatosis
HHV human herpesviruses
HIF hypoxia-inducible factor
H-ISDN hydralazine plus isosorbide dinitrate
HIT heparin-induced thrombocytopenia
HITS high-intensity transient signals
HIV human immunodeficiency virus
HLA human leukocyte antigen
HMG-CoA hydroxymethylglutaryl-coenzyme A
hNET1 human norepinephrine transporter 1
HOCM hypertrophic obstructive cardiomyopathy
HPAH heritable pulmonary arterial hypertension
HR hazard ratio; heart rate
HR_{max} maximum heart rate
HRS Heart Rhythm Society
HS hemorrhagic stroke
hs-CRP high-sensitivity C-reactive protein
hsTn highly sensitive troponin
I-1 (protein phosphatase) inhibitor-1
IAB intra-aortic balloon
IABP intra-aortic balloon pump
IC intracoronary

I_{Ca}	calcium current
ICA	internal carotid artery; invasive coronary angiography
$I_{Ca,L}$	L-type calcium current
ICAM	intercellular adhesion molecule
ICD	implantable cardioverter-defibrillator; International Classification of Diseases
ICE	International Collaboration on Endocarditis; intracardiac echocardiography
ICM	ischemic cardiomyopathy
IDF	International Diabetes Foundation
IDTCFA	intravascular ultrasound–derived thin cap fibroatheroma
IDU	injection drug user
IE	infective endocarditis
IEM	internal elastic membrane
I_f	hyperpolarization-activated pacemaker current
IFN	interferon
IFN-β	interferon-β
iFR	instantaneous wave-free ratio
Ig	immunoglobulin
IGF-1	insulin-like growth factor-1
IHA	idiopathic hyperaldosteronism
IHCA	in-hospital cardiac arrest
IHD	ischemic heart disease
IHR	intrinsic heart rate
I_K	potassium channel
I_{KAS}	apamin-sensitive SK current
I_{Kr}	rapid outward potassium current
I_{Ks}	slow outward potassium current
IL	interleukin
ILD	interstitial lung disease
IMR	index of microcirculatory resistance; ischemic mitral regurgitation
I_{Na}	sodium channel current
I_{NaL}	late sodium current
I_{NCX}	sodium-calcium exchange current
iNOS	inducible nitric oxide synthase type II
INR	international normalized ratio
$InsP_3$	inositol 1,4,5-triphosphate
INTERMACS	Interagency Registry of Mechanically Assisted Circulatory Support
IOM	Institute of Medicine
IP_3	inositol triphosphate
IPAC	Investigations of Pregnancy-Associated Cardiomyopathy
IPAH	idiopathic pulmonary arterial hypertension
IPC	ischemic preconditioning
IPF	idiopathic pulmonary fibrosis
IPH	inferoposterior hemiblock
IPost	ischemic postconditioning
iPSC	induced pluripotent stem cell
iPSC-CM	induced pluripotent stem cell-derived cardiomyocyte
IQR	interquartile range
IRI	ischemia/reperfusion injury
IRIS	immune reconstitution inflammatory syndrome
IS	ischemic stroke
ISAR-REACT	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
ISFC	International Society and Federation of Cardiology
ISHLT	International Society of Heart and Lung Transplantation
IST	inappropriate sinus tachycardia
I_{to}	transient outward current
IUGR	intrauterine growth restriction
IV	intravenous
IVC	inferior vena cava
IVDC	intraventricular conduction defect
IVIG	intravenous immunoglobulin
IVPA	intravascular photoacoustic (imaging)
IVUS	intravascular ultrasound
IVUS-VH	intravascular ultrasound virtual histology
JMH	Japanese Ministry of Health
JNC	Joint National Committee
JNK	c-Jun N-terminal kinase
K_m	Michaelis constant
KO	knockout
KS	Kaposi sarcoma
LA	left atrial/atrium
LAA	left artery/atrial appendage
LAD	left anterior descending (coronary artery)
LAE	left atrial enlargement
LAO	left anterior oblique
LAP	low attenuation plaque
LBBB	left bundle-branch block
LCAT	lecithin-cholesterol acyl transferase
LCC	left coronary cusp
LCP	lipid core plaque
LCSD	left cardiac sympathetic denervation
LCX	left circumflex artery
LDF	laser Doppler fluximetry
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LDS	Loeys-Dietz syndrome
LGB	laparoscopic gastric banding

LGE late gadolinium-enhanced (imaging)
LIMA left internal mammary artery
LM left main
LMICs low- and middle-income countries
LMWH low-molecular-weight heparin
lncRNA long ncRNA
LOE level of evidence
LOX lysyl-oxidase
Lp(a) lipoprotein(a)
LPL lipoprotein lipase
LQTS long QT syndrome
LRI lower-rate interval
LSS laminar shear stress
LUCAS Lund University Cardiac Arrest System
LV left ventricle/ventricular
LVAD left ventricular assist device
LVE left ventricular enlargement
LVEDP left ventricular end-diastolic pressure
LVEF left ventricular ejection fraction
LVH left ventricular hypertrophy
LVNC left ventricular noncompaction cardiomyopathy
LVOT left ventricular outflow tract
LVOTO left ventricular outflow tract obstruction
MA mitral annulus; mycotic aneurysm
MAC mitral annual/annulus calcification
MACCE major adverse cardiovascular and cerebrovascular events
MACE major adverse cardiac event
MAF minor allele frequency
MAGE Mean Amplitude Glucose Excursions
MAGGIC Meta-Analysis Global Group in Chronic Heart Failure
MAP mean arterial pressure
MAPK mitogen-activated protein kinase
Mbp million base pairs
MC4R melanocortin 4 receptors
MCA middle cerebral artery
MCP-1 monocyte chemotactic protein-1
MCS mechanical circulatory support
MDCT multidetector computed tomography
MEN multiple endocrine neoplasia
MESA Multi-Ethnic Study of Atherosclerosis
MET metabolic equivalent
MetS metabolic syndrome
MFS Marfan syndrome
MHC myosin heavy chain
MI myocardial infarction
MIM Mendelian Inheritance in Man
MIRACL Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
miRNA microRNA
MLA minimum luminal (cross-sectional) area
MLC myosin light chain
MLC2 myosin light chain 2
mLCK myosin light-chain kinase
MLD minimal lumen diameter
MMP metalloproteinase
MMP-9 matrix metallopeptidase 9
MOGE(S) morphofunctional phenotype, organ(s) involvement, genetic inheritance pattern, etiologic annotation including genetic defect or underlying disease/substrate, and functional status of the disease
MONICA Monitoring of Trends and Determinants in Cardiovascular Disease
MP microparticle
MPA microscopic polyangiitis
mPAP mean pulmonary artery pressure
MPHR maximum predicted heart rate
MPI myocardial perfusion imaging
MPO myeloperoxidase
MPR myocardial perfusion reserve
MPTP mitochondrial permeability transition pore
MR mineralocorticoid receptor; mitral regurgitation
MRA magnetic resonance angiography; mineralocorticoid receptor antagonist
MRI magnetic resonance imaging
MRMPI magnetic resonance myocardial perfusion imaging
mRNA messenger ribonucleic acid
MRproADM midregional pro-adrenomedullin
MRSA methicillin-resistant *Staphylococcus aureus*
MRV magnetic resonance venography
MS mitral stenosis
MSA multiple system atrophy
MSC mesenchymal stem cell
MSH melanocyte stimulating hormone
mtDNA mitochondrial DNA
mTOR mammalian target of rapamycin
MTP microsomal triglyceride transfer protein
MTRI maximal tracking rate interval
MUGA multi-gated acquisition
MV mitral valve
MVA mitral valve area
MVB mixed venous blood

MVC maximal voluntary contraction
MVO microvascular obstruction
MVO_2 maximal venous oxygen
MVO_2 myocardial oxygen demand
MVP mitral valve prolapse
MVR mitral valve replacement
MyBP-C myosin-binding protein C
Na^+-K^+ ATPase sodium-potassium adenosine triphosphatase
NADPH nicotinamide adenine dinucleotide phosphate
NBT nitroblue tetrazolium
NBTE nonbacterial thrombotic endocarditis
NC noncompacted
NC/C noncompacted-to-compacted ratio
NCD noncommunicable disease
NCDR National Cardiovascular Data Registries
NCEP National Cholesterol Education Program
ncRNA non-protein-coding RNA
ncWnt noncanonical Wnt
NCX Na^+-Ca^{2+} exchanger
NE norepinephrine
NEFA nonesterified fatty acid
NET neuroendocrine tumor
NF normal flow
NFAT nuclear factor of activated T cells
NGF nerve growth factor
NGS next-generation sequencing
NHANES National Health and Nutrition Examination Survey/Study
NHIS National Health Interview Survey
NHLBI National Heart, Lung, and Blood Institute
NICM nonischemic cardiomyopathy
NIMHD National Institute on Minority Health and Health Disparities
NIPT noninvasive prenatal testing
NIRF near-infrared fluorescence
NIRS near-infrared spectroscopy
NIS Nationwide Inpatient Sample
$NLRP_3$ Nod-like receptor P_3
nNOS neuronal nitric oxide synthase type I
NNRTI non-nucleoside reverse transcriptase inhibitor
NO nitric oxide
NOAC new orally active anticoagulant; non-vitamin K antagonist oral anticoagulant; novel oral anticoagulant
NOS nitric oxide synthase; nitrous oxide synthase
NOS1 nitrous oxide synthase type I
NOS3 nitrous oxide synthase type III
nPA lanoteplase
NPH neutral protamine Hagedorn (insulin)
NPPA natriuretic peptide precursor A
NPV negative predictive value
NPY neuropeptide Y
NRMI National Registry of Myocardial Infarction
NRT nicotine replacement therapy
NRTI nucleoside reverse transcriptase inhibitor
NSAID nonsteroidal anti-inflammatory drug
NSF nephrogenic systemic fibrosis
NSTE-ACS non–ST-segment elevation acute coronary syndrome
NSTEMI non-ST-segment elevation myocardial infarction
NSVT nonsustained ventricular tachycardia
NTG nitroglycerin
NT-proBNP N-terminal pro–B-type natriuretic peptide
NURD nonuniform rotation distortion
NVE native valve endocarditis
NYHA New York Heart Association
OASIS Organization for the Assessment of Strategies for Ischemic Syndromes
OCT optical coherence tomography
OFDI optical frequency domain imaging
OFT outflow tract
OHCA out-of-hospital cardiac arrest
OM obtuse marginal
OMIM Online Mendelian Inheritance in Man
OMT optimal medical therapy
OMV open mitral valvotomy
OPCAB off-pump coronary artery bypass
OPO organ procurement organization
OPTIMIZE-HF Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
OR odds ratio
OSA obstructive sleep apnea
PA pulmonary artery
PAC premature atrial contraction; pulmonary arterial catheter
$PaCO_2$ partial pressure of arterial carbon dioxide
PAD peripheral arterial/artery disease; public-access defibrillation
PAF pure autonomic failure

PAH	pulmonary artery hypertension
PAHO	Pan-American Health Organization
PAI-1	plasminogen-activator inhibitor type 1
PAIN	priority risk, advanced risk, intermediate risk, and negative/low risk
PAN	polyarteritis nodosa
PaO_2	arterial oxygen partial pressure
PAP	positive airway pressure
PAPS	pyrin-associated periodic fevers/ syndrome
PAR	protease-activated receptor
PASP	pulmonary artery systolic pressure
PAV	percent atheroma volume
PBDE	polybrominated diphenyl ether
PBF	pulmonary blood flow
PBMC	peripheral blood mononuclear cell
PC	phase contrast
PCA	posterior cerebral artery
PCB	polychlorinated biphenyl
PCCD	progressive cardiac conduction disease
PCD	phlegmasia cerulea dolens; primary ciliary dyskinesia
PCI	percutaneous coronary intervention
PCNA	Preventive Cardiovascular Nurses Association
PCO_2	partial pressure of carbon dioxide
PCORI	Patient-Centered Outcomes Research Institute
PCr	phosphocreatine
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin/ kinexin 9
PCTA	percutaneous transluminal coronary angioplasty
PCW	pulmonary capillary wedge (pressure)
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDE	phosphodiesterase
PDE-5	phosphodiesterase-5
PDGF	platelet-derived growth factor
PDK1	protein kinase-1
PE	pulmonary embolism
PECAM	platelet endothelial cell adhesion molecule
PES	programmed electrical stimulation
PESI	Pulmonary Embolism Severity Index
PESP	postextrasystolic potentiation
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFAA	perfluoroalkyl acid
PFO	patent foramen ovale
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanyl sulfonate
PGC-1β	proliferator-activated receptor coactivator 1β
PGH_2	prostaglandin H_2
PGI_2	prostaglandin I_2
PH	pulmonary hypertension
PHV	prosthetic heart valve
PHVT	prosthetic heart valve thrombosis
P-IAB	partial interatrial block
PIIINP	N-terminal type III collagen peptide
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
PISA	proximal isovelocity surface area
PKA	protein kinase A
PKB	protein kinase B
PKC	protein kinase C
PKC-α	protein kinase C-α
PLATO	Study of Platelet Inhibition and Patient Outcomes
PlGF	placenta growth factor
PM	particulate matter; positive remodeling
PMT	pacemaker-mediated tachycardia
PMVT	polymorphic ventricular tachycardia
PO_2	partial pressure of oxygen
POMC	proopiomelanocortin
POTS	postural orthostatic tachycardia syndrome
PP	protein phosphatase; pulse pressure
PPACA	Patient Protection and Affordable Care Act
PPAR	peroxisome proliferator-activated receptor
pPCI	primary percutaneous coronary intervention
PPCM	peripartum cardiomyopathy
PPH	primary pulmonary hypertension
PPI	postpacing interval
PPMI	postprocedural myocardial infarction
PPV	positive predictive value
PR	pulmonic regurgitation
PRF	pulse repetition frequency
PROSPECT	Providing Regional Observations to Study Predictors of Events in the Coronary Tree
PROVE IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PRP	pressure rate product
PS	primitive streak; pulmonic stenosis
PSC	pluripotent stem cell
PSG	polysomnography

PSI	proliferation signal inhibitor
PSVT	paroxysmal supraventricular tachycardia
PTLD	post-transplant lymphoproliferative disorder
PTP	permeability transition pore
PTS	postthrombotic syndrome
PTSD	posttraumatic stress disorder
PURE	Prospective Urban Rural Epidemiology (study)
P-V	pressure-volume
PV	pulmonic valve
PVA	pressure-volume area
PVAD	paracorporeal ventricular assist device
PVARP	postventricular atrial refractory period
PVC	premature ventricular complex; premature ventricular contraction
PVI	pulmonary vein isolation
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
PWD	pulsed-wave Doppler
PXE	pseudoxanthoma elasticum
Q	(cardiac) output
QA	quality assessment
QALY	quality-adjusted life-year
QCA	quantitative coronary angiography
QI	quality improvement
R	(cardiac) resistance
RA	rheumatoid arthritis; right atrial/atrium
RAAS	renin-angiotensin-aldosterone system
RAE	right atrial enlargement
RAO	right anterior oblique
RBBB	right bundle-branch block
RBC	red blood cell
RCA	right coronary artery
RCC	right coronary cusp
RCM	restrictive cardiomyopathy
RCT	randomized controlled trial
RDN	renal denervation
REPLACE	Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events
RF	radiofrequency; rheumatic fever; rheumatoid factor
RHD	rheumatic heart disease
RIC	remote ischemic conditioning
RIFLE	risk, injury, and heart failure, loss, and end-stage renal disease
RIHP	renal interstitial hydrostatic pressure
RISK	reperfusion injury salvage kinase
RNA	radionuclide angiography; ribonucleic acid
rNAPc2	recombinant nematode anticoagulant protein c2
ROI	region of interest
ROS	reactive oxygen species
ROSC	return of spontaneous circulation
rPA	reteplase
RPF	renal plasma flow
RR	relative risk; risk ratio
RT3D	real-time three-dimensional
rtPA	recombinant tissue plasminogen activator
RV	right ventricle/ventricular
RVE	right ventricular enlargement
RVEDV	right ventricular end-diastolic volume
RVNC	right ventricular noncompaction
RVOT	right ventricular outflow tract
RyGB	Roux-en-Y gastric bypass
RYR2	ryanodine type 2 receptor
SA	sideroblastic anemias; sinoatrial
SACT	sinoatrial conduction time
SAECG	signal-averaged electrocardiogram
SAFE	survivor activator factor enhancement
SAH	subarachnoid hemorrhage; superoanterior hemiblock
SAM	systolic anterior motion
SAN	sinoatrial node
SAP	serum amyloid P component; stable angina pectoris
SAS	subaortic stenosis
SAVR	surgical aortic valve replacement
SBP	systolic blood pressure
SC	spotty calcifications; subcutaneous
Sca-1	stem cell antigen-1
SCAD	small capillary and arteriolar dilatation; spontaneous dissection of the coronary artery
SCD	sudden cardiac death
SD	standard deviation
SDB	sleep-disordered breathing
SDE	single-dose epinephrine
SDS	summed differences score
SERCA	sarcoplasmic-endoplasmic reticulum calcium ATPase
SERCA2	sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase
SES	sirolimus-eluting stent; socioeconomic status
SFA	subcutaneous fat aspiration
SG	sleeve gastrectomy
SGNA	stellate ganglion nerve activity
SHF	second heart field
S-ICD	subcutaneous ICD
SIDS	sudden infant death syndrome
SIHD	stable ischemic heart disease
SK	small conductance calcium-activated potassium current; streptokinase

SLE	systemic lupus erythematosus
SND	sinus node dysfunction
SNP	single nucleotide polymorphism
SNRT	sinus node recovery time
SNS	sympathetic nervous system
SNV	single nucleotide variant
SOICR	store overload-induced calcium release
SP	secondary prevention
SPECT	single-photon emission tomography
sPESI	Simplified Pulmonary Embolism Severity Index
SPRINT	Systolic Blood Pressure Intervention Trial
SQTS	short QT syndrome
SR	sarcoplasmic reticulum
SRS	summed rest score
SS	SYNTAX Score
SSFP	steady-state free precession
SSS	sick sinus syndrome; summed stress score
sST2	soluble ST2
SSV	small saphenous vein
START	Screening Tool to Alert Doctors to the Right Treatment
STE-ACS	ST-segment elevation acute coronary syndrome
STEMI	ST-segment elevation myocardial infarction
STIR	short tau inversion recovery
STOPP	Screening Tool of Older People's Potentially Inappropriate Prescriptions
STP	superficial thrombophlebitis
STS	Society of Thoracic Surgeons
SUDS	sudden unexpected death syndrome
SUMO-1	small ubiquitin-like modifier 1
SUR	sulfonylurea receptor
SUV	standard uptake value
SV	stroke volume
SVAS	supravalvar aortic stenosis
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors
SYNTAX	Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery
T2D	type 2 diabetes
TA	Takayasu arteritis; tricuspid valve
TAA	thoracic aortic aneurysm
TAAD	thoracic aortic aneurysm and dissection
TAH	total artificial heart
TAP	transmembrane action potential
TAPSE	tricuspid annular plane systolic excursion
TARP	total atrial refractory period
TAV	total atheroma volume
TAVR	transcatheter aortic valve replacement
TBR	target-to-background ratio
TCAR	transcarotid artery revascularization
TCCD	2,3,7,8-tetraclo-ro-*p*-dibenzodioxin
Tcf/Lef	T-cell factor/lymphoid enhancer factor
TCFA	thin cap fibroatheroma
$TCPO_2$	transcutaneous oxygen pressure measurement
TCPV	transcatheter pulmonary valve
TD	time-domain
TDI	tissue Doppler imaging
TD-OCT	time-domain optical coherence tomography
TDP	torsades de pointes
TEE	transesophageal echocardiography
TENS	transcutaneous electric nerve stimulation
TF	tissue factor; transcription factor
TGA	transposition of the great arteries
TGF	transforming growth factor
TGF-β	transforming growth factor beta
TGRL	triglyceride-rich lipoprotein
TH	therapeutic hypothermia
TIA	transient ischemic attack
TID	transient ischemic dilation
TIMACS	Timing of Intervention in Acute Coronary Syndrome
TIMI	thrombolysis in myocardial infarction
TIMP	tissue inhibitor of metalloproteinase
TIMP-1	tissue inhibitor of metalloproteinases 1
TIPS	transjugular intrahepatic portosystemic shunt
TKI	tyrosine-kinase inhibitor
TLE	transvenous lead extraction
TLR	toll-like receptor
TMCR	transcatheter mitral valve replacement
TnC	troponin C
TNF	tumor necrosis factor
TNF-I	tumor necrosis factor inhibitor
TnI	troponin I
TNK	tenecteplase
TNM	tumor-node-metastasis
TnT	troponin T
ToF	tetralogy of Fallot
TOF	time of flight
TOK	triangle of Koch

TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist	TUNEL	terminal deoxynucleotidyl transferase dUTP nick-end labeling	VCAM	vascular cell adhesion molecule	VTC	virtual ring to coronary ostial distance
		TV	tricuspid valve; transplant	VCD	vascular closure device	VTE	venous thromboembolism
TOS	The Obesity Society		vasculopathy	VCG	vectorcardiography	VV	ventrovenous
TP	thromboxane	TVR	transcatheter heart valve	V_{co2}	carbon dioxide elimination	vWF	von Willebrand factor
tPA	tissue plasminogen activator	TWA	T-wave alternans	VE	vascular endothelial; volume of expired gas	WBC	white blood cell
		TWI	T-wave inversion			WC	waist circumference
TPD	total perfusion deficit	TXA_2	thromboxane A_2	VEGF	vascular endothelial growth factor	WCD	wearable cardioverter-defibrillator
		TZD	thiazolidinedione				
TPR	total peripheral (vascular) resistance	UA	unstable angina	VF	ventricular fibrillation	WG	Wegener granulomatosis
		UF	ultrafiltration				
		UFH	unfractionated heparin	VHA	Veterans Health Administration	WHF	World Heart Federation
TR	tricuspid regurgitation	UI	uncertainty interval	VHD	valvular heart disease	WHO	World Health Organization
TRFS	time-resolved spectroscopy	UK	United Kingdom	VH-IVUS	virtual histology intravascular ultrasound	WOEST	What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting
TRITON	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel	UNOS	United Network for Organ Sharing				
		UPR	unfolded protein response	VinV	valve-in-valve (therapy)		
		URI	upper rate interval	VKA	vitamin K antagonist		
		URL	upper reference limit	VLDL	very low-density lipoprotein		
		USPIO	ultra-small superparamagnetic particles of iron oxide	V_m	membrane potential		
TRO	triple rule-out						
TS	tricuspid stenosis			VO_2	oxygen uptake	WPW	Wolff-Parkinson-White (syndrome)
TTC	triphenyl tetrazolium chloride	UTR	untranslated region	VO_{2max}	maximal oxygen consumption		
TTE	transthoracic echocardiography	V/Q	ventilation-perfusion	VRP	ventricular refractory period	WRF	worsening renal function
TTM	Therapeutic Temperature Management	VA	venoarterial; ventriculoatrial; vertebral artery	VSD	ventricular septal defect	XL	x-linked
						XLR	x-linked recessive inheritance
				VSMC	vascular smooth muscle cell		
TTR	transthyretin	VAD	ventricular assist device			YLDs	years lived with disability
TTS	Takotsubo syndrome			VT	ventricular tachycardia		
		VC	vena contracta			YLLs	years of life lost

Hurst's
The Heart

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SECTION 1

Cardiovascular Disease: Past, Present, and Future

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CHAPTER 1

A HISTORY OF THE CARDIAC DISEASES, AND THE DEVELOPMENT OF CARDIOVASCULAR MEDICINE AS A SPECIALTY

Robert A. Harrington, Mark E. Silverman*, and Charles F. Wooley*

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The heart … is the beginning of life; the sun of the microcosm … for it is the heart by whose virtue and pulse the blood is moved, perfected, made apt to nourish, and is preserved from corruption and coagulation; it is the household divinity which, discharging its function, nourishes, cherishes, quickens the whole body, and is indeed the foundation of life, the source of all action. —William Harvey, 1628[1]

*Deceased

The history and our still emerging understanding of the heart are a remarkable story, with origins in antiquity, centered initially on clinical observations. Thought at one time to be the center of the soul and impervious to disease, the heart was long a source of mystery and wonder, studied in science and fascinated about in literature and the arts. Most historians agree that William Harvey's discovery of the circulation of blood in the early 17th century is a good place to start the modern history of cardiovascular medicine. Following Harvey, cardiology pursued a pathway of descriptive anatomy and pathology in the 17th and 18th centuries, auscultation and its correlations in the 19th century, an understanding of cardiac disease and its pathophysiology in the second half of the 19th and first half of the 20th centuries, and major advances in the diagnosis and treatment of heart disease from there into the 21st century.[2-5] What has emerged in the 21st century is a medical specialty with incredible tools of diagnosis, including blood biomarkers and multiple imaging modalities; numerous medical treatment options that include drugs, biologics, and devices; and surgical options involving complex operations that both repair and replace dysfunctional anatomy.

What has also emerged in the 21st century is a far less positive story: the growing global epidemic of atherosclerotic heart disease and its ischemic complications; an epidemic created by the exportation of tobacco products around the world; a change in dietary patterns with decreasing amounts of fresh fruits and vegetables; and an increase in more sedentary lifestyles, in some ways facilitated by technology.[6-9] The United Nations and the World Health Organization have identified the noncommunicable diseases as major global public health problems that threaten or limit the overall financial and social stability of the global community in both developed and developing nations.[10] The increasing burden of obesity has led to major increases in diabetes, which is expected to increase the incidence of cardiac diseases.[11] The aging of the population has also been associated with a marked increase in the incidence of atrial fibrillation and the attendant risk of embolic stroke.[12]

The introduction of the first instruments of precision—blood pressure measurement, the chest x-ray, and the electrocardiogram—in the 1890s and early 20th century, led to the creation of the specialty of cardiology. Since the 1950s, following the advent of cardiac catheterization and surgery, cardiology has evolved into multiple, highly specialized disciplines focusing on coronary artery disease, heart failure, arrhythmias, imaging, and preventive care. Early diagnosis of cardiac risk and aggressive medical treatment of cardiac diseases coupled with increasing attention to prevention have led to a gradual decrease in mortality for cardiac disease.[13] A hallmark of cardiovascular medicine in the early 21st century has been its emergence at the forefront of the evidence-based medicine movement with an intense commitment to quality care[14-16] through continuous investigation and incorporation of new knowledge into clinical practice guidelines by the major professional societies and public health organizations.[17,18] Moving toward 2020, we see the adoption of digital and mobile technologies in medical care for prevention, diagnosis, and treatment. At the forefront of these movements is a focus on cardiac health and fitness and the potential for more tools for patients to directly monitor and manage their cardiac disorders, including heart failure, arrhythmias, and hypertension.[19] There is also the issue of how to use "big data" in both research and the clinical management of cardiovascular disease. This will include routinely incorporating genomics and other "omics" in the assessment of cardiovascular risk and disease.

Many of the initial key discoveries are now recalled as eponyms attached to diseases or physical signs. As the number of investigators has grown exponentially and internationally, it is increasingly difficult to assign singular credit to contributions for which many are ultimately responsible. Taking all of these considerations into account, we have chosen to provide a condensed narrative by subject, selectively

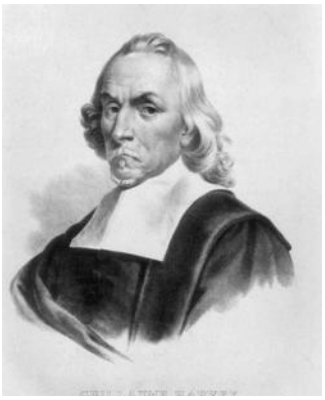

FIGURE 1–1. William Harvey. Used with permission from the National Library of Medicine.

highlighting important events and key figures in the grand story of cardiovascular medicine written by our illustrious predecessors.[1-5,20-26]

WILLIAM HARVEY AND THE CIRCULATION OF THE BLOOD

Early civilizations considered the heart to be a source of heat and believed that the blood vessels carried *pneuma*, the life-sustaining spirit of the vital organs. This concept was most fully elaborated by Claudius Galen (AD 130-200), whose erroneous teachings were entrenched for 1300 years, until Andreas Vesalius corrected his anatomy (1543), and William Harvey proposed that blood circulates because of the force of the heart (1616).[2,3]

Harvey's discovery of the circulation of blood (Fig. 1–1) is considered to mark the beginning of modern cardiology as well as the introduction of experimental observation. Starting in 1603, Harvey dissected the anatomy and observed the motion of the cardiac chambers and flow of blood in more than 80 species of animals. His experimental questions "to seek unbiased truth" can be summarized in the following questions. What is the relationship of the motion of the auricle to the ventricle? Which is the systolic and which is the diastolic motion of the heart? Do the arteries distend because of the propulsive force of the heart? What purpose is served by the orientation of the cardiac and venous valves? How does blood travel from the right ventricle to the left side of the heart? Which direction does the blood flow in the veins and the arteries? How much blood is present and how long does its passage take?

After many experiments and without knowledge of the capillary circulation of the lungs, which was not known until 1661, Harvey stated: "It must of necessity be concluded that the blood is driven into a round by a circular motion and that it moves perpetually; and hence does arise the action or function of the heart, which by pulsation it performs." This was published in 1628 as *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*.[1] This revolutionary concept eventually became accepted in Harvey's lifetime and remains the foundation of our understanding of the purpose of the heart.

THE CARDIAC EXAMINATION

THE ARTERIAL PULSE

Until the 17th century, the clinical examination consisted of palpating the pulse and inspecting the urine to reveal disease and predict prognosis. In Chinese acupuncture, the pulse was timed according to the physician's respiration whereas digital pressure was applied to elicit information. Galen wrote 18 books on the arterial pulse in the 2nd century, providing elaborate descriptions that influenced clinical practice well into the 18th century.[2,3] The 1-minute pulse watch, invented by Floyer in 1707, offered the first opportunity to measure the heart rate accurately; however, this did not become a routine part of medical practice until the mid-19th century.[3] Since the 19th-century observations of Dominic Corrigan, the carotid arterial pulse has been linked to aortic valve disease and is essential for timing systole at the bedside. In 1847, Carl Ludwig in Leipzig invented the kymograph, a pulse writer that would elevate physiology to a new level and be used to inscribe arterial and venous pulses. Pulsus alternans was described by Ludwig Traube in 1872, and Adolf Kussmaul called attention to the paradoxical pulse in 1873, noting that the arterial pulse could transiently disappear on inspiration even though the heart sounds were still audible. Before electrocardiography, arterial pulse recordings were applied to diagnose arrhythmias, as shown by James Mackenzie in *The Study of the Pulse* (1902).[27]

PERCUSSION

In 1761, Leopold Auenbrugger, a Viennese physician, published a book proposing "percussion of the human thorax, whereby, according to the character of the particular sounds thence elicited, an opinion is formed of the internal state of that cavity."[2] He had observed his father, an innkeeper, use this technique to check the wine levels in his casks. Percussion was reintroduced by Jean-Nicolas Corvisart in early 19th-century France and became an essential addition to the chest examination until it was mostly supplanted by the chest x-ray.

THE JUGULAR VENOUS PULSE

Jugular venous wave recording was initiated in France, in the mid-19th century, by Pierre-Carl Potain. In the 1870s, Mackenzie sought to interpret arrhythmias by understanding arterial and venous pulse waves. Using a kymograph, then an ink-writing polygraph, Mackenzie applied his intuitive skills to the interpretation of jugular waves, which he labeled "a, c, and v."[28] Thomas Lewis, a disciple of Mackenzie, described the technique of bedside assessment of jugular venous pressure relative to the sternal angle in 1930.

AUSCULTATION

Auscultation of the chest was first practiced by Hippocrates (460-370 BC), who applied his ear directly to the chest. The invention of the wooden monaural stethoscope (Greek: *stethos,* chest; *skopein,* to view or to see) by René Laennec in Paris (1816) introduced a powerful, although initially difficult, technique to listen to cardiovascular sound.[29,30] This method spread to Europe and Great Britain—where it was promoted by Skoda, Stokes, Hope, Williams, and others—and to America, where Austin Flint became its champion. By the mid-19th century, the stethoscope was established as an indispensable tool for the examination of the heart and lungs. Diagnoses based on percussion and auscultation were subjected to the critical analysis of the autopsy by Corvisart, Laennec, Rokitansky, and Skoda, and murmurs were assigned according to their underlying pathology. Symptoms not supported by auscultatory or autopsy findings were often thought to be functional or unreliable. The stethoscope evolved from a monaural to a binaural device in 1855, and separate heads were developed by Bowles (1894) and Sprague (1926). Grading of systolic murmurs was introduced by Samuel Levine in 1933. The acoustic principles of cardiovascular sound became better understood through the work of Rappaport and Sprague (1940s), and correlations were made with phonocardiography and cardiac catheterization by Paul Wood, Aubrey

Leatham, Samuel Levine, and others between 1950 and 1975. In 1961, physiologist Robert Rushmer proposed the acceleration-deceleration theory that remains the concept of the generation of normal and abnormal heart sounds. Auscultation continues to be valuable although less relied on today as imaging tools such as the cardiac echocardiogram make visualization of cardiac structures straightforward, reproducible, and reliable.

TECHNOLOGY AND THE HEART

THE ELECTROCARDIOGRAM

In 1856, von Kölliker and Müller demonstrated that the heart also produced electricity. Augustus Waller, with a capillary electrometer device (1887), detected cardiac electricity from the limbs, a crude recording that he called an "electrogram." Willem Einthoven, a physiologist in Utrecht, devised a more sensitive string galvanometer (1902), for which he received the Nobel Prize, and the modern electrocardiogram was born. Initially weighing 600 lb and requiring five people to operate, the 3-lead electrocardiograph would eventually become portable, 12 leads, routine, and capable of providing both static and continuous recordings of cardiac rhythm (Table 1–1).[31]

Nineteenth-century researchers debated whether the heartbeat was stimulated by the heart muscle or was caused by external nervous or local ganglionic control—the myogenic versus the neurogenic theory. The answer was finally provided by the anatomic discovery and descriptions of the electrical system of the heart: the Purkinje fibers (1839), bundle of His (1893), bundle branches (1904), atrioventricular node (1906), and sinus node (1907).[32] With the electrocardiogram, the activation and sequence of stimulation of the human heart could now be measured, and the anatomic basis for the conduction system confirmed. Thomas Lewis in London was the first to realize its great potential, beginning in 1909, and his books on disorders of the heartbeat became essential for aspiring electrocardiographers.[2,24] Disorders of the heartbeat and abnormalities in the activation of the human heart, heretofore unknown or inferred from pulse tracings or experimental observations, became new clinical currency; palpitations became premature atrial or ventricular beats, and tachycardias and atrioventricular block could be understood. When electrocardiography was added to the chest x-ray and cardiac fluoroscopy in the early 20th century, clinical cardiology became a field of its own, inextricably linked to technology, a trend that continues in the 21st century. Those who interpreted the complicated tracings, known as cardiologists, became practitioners of this new specialty.[25] By the 1930s, the electrocardiogram had become 12 leads and a necessary confirmation for myocardial ischemia or infarction. When electrocardiography was combined with the Master "two-step" exercise test (1940s), bicycle and treadmill stress testing (1960s), and nuclear and echocardiography imaging (1970s), a superior diagnostic approach to patients with chest pain became available. Continuous bedside monitoring (Paul Zoll, 1956) and the ambulatory detection of arrhythmias (Holter, 1961) became commonplace in the 1960s; and implanted loop recording appeared in 1999. Today, continuous ambulatory electrocardiographic monitoring can be performed for several weeks at a time[33] with a novel adhesive patch. And, using smartphone applications, single-lead electrocardiograms can be readily obtained and easily transmitted as needed to the health care system.[34]

Pacing the heart in cardiac standstill was first carried out by John MacWilliam in Aberdeen in 1887. Experiments with external pacemakers in the 1920s to 1930s by Mark Lidwill in Australia and Albert Hyman in the United States showed their feasibility. A temporary pacemaker was inserted in 1952 by Zoll, and an internal pacemaker was inserted in a human by William Chardack in 1960.[35] Although initially plagued by faulty operation, lead breakage, infection, and early battery failure, pacemakers eventually became a marvel of reliability, complexity, and durability. Progressive advances include transvenous leads (1965), lithium iodine batteries (1972), multiprogrammability (1972), dual-chamber pacing (1980), rate adaptive modes, and antitachycardia programs. Biventricular pacing (1998) for patients with left ventricular dysfunction coupled with defibrillation capability has improved the quality of life and reduced mortality among some groups of patients with systolic heart failure.[36]

Electrophysiologic testing in humans began as an offshoot of basic catheterization laboratory investigations in the early pacemaker era. Intracardiac potentials were first measured in 1945. Catheter techniques were used to localize the His bundle (Scherlag and Damato, 1967) and to identify accessory pathways (Jackman, 1983). Programmed electrical stimulation of the heart was introduced to localize, provoke, and terminate arrhythmias (Durrer, Wellens, and Coumel, 1967). Mapping techniques, applied to the surface of the heart for the localization and resection of accessory pathways (1968) and the surgical ablation of ventricular arrhythmias (1974) and atrial fibrillation (1991), became an essential method of investigation. As catheter methods of ablation improved, first coupled with intracardiac high-energy shock of the atrioventricular node (1982) and then with radiofrequency current (1987), ablation moved from the surgery suite into the laboratory setting, populated by a new subspecialty group—the electrophysiologists. Catheter ablation of atrioventricular nodal reentry was the next great success story. Atrial flutter and fibrillation and ventricular tachycardia are the newest targets for catheter ablation as the understanding of arrhythmias evolves through the use of more sophisticated intracardiac electrocardiograms coupled with a more detailed correlation with anatomy using magnetic resonance imaging (MRI) and computed tomography (CT) imaging to help guide procedures.[37,38] Through an understanding of the mechanisms of arrhythmias and the identification of genes encoding cardiac ion channels—especially the long-QT and Brugada syndromes—electrocardiography has reemerged as a critical diagnostic and investigative tool.[39-41]

THE CARDIAC CATHETER

If the ability to measure cardiac rhythm using the electrocardiograph was a touchstone for the identification of the cardiologist at the dawn of the 20th century, it was the ability to invasively measure cardiac pressures and oxygen saturation as well as the imaging of cardiac structures using the cardiac catheter that marked the transition to the modern definition of the cardiovascular specialist. Many of the fundamentals of modern cardiovascular instrumentation and physiology originated in France in the mid-19th century. Claude Bernard in 1844 was the first to insert a catheter into the heart of animals to measure temperature and pressure.[2] In the 1860s, Etienne Jules Marey combined the kymographic instrumentation created by Ludwig in Leipzig in 1847 with an air-filled manometer for the graphic registration of biological phenomena.[20] Marey's pulse writer—the sphygmograph—was used for recording the external pulsation of the heart and arteries and was a prototype for noninvasive devices in cardiology. In the early 1860s, Auguste Chauveau, a veterinary physiologist, and Marey collaborated to develop a system of devices called *sounds*, forerunners of the modern cardiac catheter, which they used to catheterize the right heart and left ventricle of the horse.[20] They recorded values of intracardiac pressure with superb tracings and correlated the intracardiac events with precision to show the relation of atrial and ventricular systole to the apex impulse. In 1870, Adolph Fick provided his oximetric formula to measure cardiac output.

TABLE 1–1. Selected Advances in Cardiac Diagnosis and Technology

ANCIENT TIMES

General inspection

Palpation of the pulse (Egypt, China, India)

18TH CENTURY

Physician's 1-min pulse watch (1707)

Percussion of the chest (1761)

19TH CENTURY

Stethoscopic auscultation of the heart (1816)

Pleximeter (1826)

Kymographic recording of pulses (1847)

Sphygmograph for blood pressure measurement (1855, 1863)

Polygraphic recording of pulses (1883)

Chest x-ray (1895)

Fluoroscopy (1896)

20TH CENTURY

1900-1929

Electrocardiogram (1902)

Auscultation of blood pressure (1905)

Phonocardiogram (1907)

Leukocytosis in myocardial infarction (1916)

Electrocardiography for myocardial infarction (1920)

Vectorcardiography (1920)

Portable electrocardiogram (1928)

First cardiac catheterization (1929)

1930-1959

Bedside measurement of venous pressure (1930)

Cardiac output measurement (1870, 1930)

Circulation time (1931)

Precordial electrocardiography (1932)

Unipolar electrocardiography leads (1932)

Angiography (1931, 1937)

Sedimentation rate for myocardial infarction (1933)

Development of cardiac catheterization (1941)

Augmented unipolar leads (1942)

Master "two-step" exercise test (1942)

Scintillation scanner (1949, 1952)

Left heart catheterization (1950)

Image intensification (1953)

M-mode echocardiography (1954)

Serum glutamic oxaloacetic transaminase (1954)

Treadmill exercise testing (1956)

Cardiac monitoring (1956)

Selective coronary arteriography (1958)

1960-1979

Computed electrocardiography (1961)

Ambulatory monitoring (1961)

Creatine phosphokinase (1965)

His bundle recording (1967)

Transfemoral catheterization (1967)

Contrast echocardiography (1968)

Swan-Ganz flotation catheter (1970)

Digoxin level (1971)

Computed tomographic scanning (1971)

Electrophysiologic testing (1972)

Nuclear stress cardiology (1973)

Two-dimensional echocardiography (1974)

Doppler echocardiography (1975)

Positron emission tomography (1979)

Stress echocardiography (1979)

Ultrafast computed tomography (1979, 1990)

1980-1999

Signal-averaged electrocardiography (1981)

Doppler color-flow echocardiography (1982)

Magnetic resonance imaging of the heart (1984)

ST-segment monitoring (1984)

Transesophageal echocardiography (1985)

Dobutamine stress echocardiography (1986)

Troponin T (1991)

Heart rate variability (1973, 1987)

Electron beam tomography for coronary calcium (1990)

Troponin I (1992)

B-type natriuretic peptide (1994)

Single-photon emission computed tomography (1990s)

Intracoronary ultrasound (1996)

Implanted loop recorder (1999)

21ST CENTURY

Three-dimensional echocardiography (2003)

64-slice computed tomography scanning (2005)

Complex intracardiac electrophysiological mapping (2005)

Optical coherence tomography imaging (2006)

Fractional flow reserve invasive measurements (2007)

Adhesive wireless rhythm monitoring (2012)

Smartphone health applications (2012)

High-sensitivity troponin (2012)

Fractional flow reserve noninvasive measurements (2014)

Leadless pacemakers (2016)

Cardiac catheterization in humans was thought an inconceivable risk until Werner Forssmann, a 29-year-old surgical resident in Germany, performed a self-catheterization in 1929.[42,43] Interested in discovering a method of injecting adrenaline to treat cardiac arrest, Forssmann passed a ureteral catheter into his antecubital vein and confirmed its right atrial position using x-ray. The next year he attempted to image his heart using an iodide injection. However, he was reprimanded by superiors and did not experiment further. Catheterization began in earnest in the early 1940s in New York and London. André Cournand and Dickinson Richards at Bellevue, interested in respiratory physiology, developed and demonstrated the safety of complete right heart catheterization, for which they shared the Nobel Prize with Forssmann in 1956.[20,23]

The cardiac catheter was viewed initially as an instrument to measure pressure and cardiac output, sample blood contents, or deliver contrast agents for cardiovascular angiography. Brannon and Warren in Atlanta were the first to apply the catheter to diagnose heart disease—an atrial septal defect—in 1945. It was the impetus of cardiac surgery requiring an accurate diagnosis, initially for congenital heart and rheumatic mitral disease, that brought cardiac catheterization out of the physiology laboratory and to the forefront of clinical cardiology in the 1950s. Improved catheters and pressure manometers, automatic film changers, and the introduction of retrograde left heart catheterization by Henry Zimmerman (1950) and a percutaneous approach by Sven Seldinger (1953) advanced the technique, accompanying heart surgery into the era of valve replacement in the 1960s. Mason Sones's accidental injection of contrast directly into a right coronary artery (1958) was a serendipitous leap forward, demonstrating that the epicardial coronary arteries could be safely visualized using percutaneous techniques. The Judkin transfemoral approach (1967) simplified selective coronary catheterization. Visualization of the coronary circulation ultimately led to the introduction of coronary bypass surgery by René Favoloro (1967) and percutaneous transluminal coronary angioplasty (PTCA) by Andreas Grüntzig (1977).[43,44] Since then, the versatile cardiac catheter has continued to evolve, carrying delivery systems or instruments ranging from ultrasound, balloons, and stents to defibrillators (Table 1–2; see also Table 1–1). Recent advances in catheter delivery technologies now allow percutaneous replacement of the aortic valve and repair of a regurgitant mitral valve.[45] The modern descendant of Forssmann and others is now an endovascular specialist, capable of both diagnosing and treating diseases of cardiac structure and function as well as diseases of the peripheral arterial and venous circulations.[46]

IMAGING OF THE HEART

Radiography

Modern imaging technology began with Konrad Roentgen's discovery of x-rays in 1895, for which he was awarded the Nobel Prize in Physics in 1901.[47,48] Within a year, fluorescent screens were available to view cardiac pulsations. Contrast agents incorporating sodium iodide were necessary to visualize the organ cavities. Moniz in Lisbon (1931) and Castellanos in Cuba (1937) were the first to image the interior of the heart with intravenous angiograms.[2] In the mid-20th century, electronic x-ray technology with the image intensifier allowed enhanced viewing of dynamic events in real time (see Table 1–1). Angiography became the focal point of cardiovascular imaging for several decades after the mid-20th century, vital to the diagnosis and management of coronary disease during the 1960s, and it continues to play a central role as the dominant imaging technique for the diagnosis and treatment of coronary and vascular obstructions.

Nuclear Cardiology

Nuclear cardiology began with Herrman Blumgart, who injected radon to measure the circulation time in 1927; followed by G. Liljestrand, who determined normal blood volume in 1939; and Myron Prinzmetal, who monitored the transit of radiolabeled albumin through the heart in 1948.[20,49] Following World War II, radioactive isotopes and scintillation cameras became available for imaging purposes. Hal Anger's gamma camera, a key development introduced in 1952, provided a high-resolution scanning capability that could visualize the cardiac chambers and assess function and shunting without moving the patient. Electrocardiographic gating, starting in the early 1970s, greatly improved the analysis of wall motion and ejection fraction, as did single-photon emission computed tomography (SPECT) in the 1990s. Nuclear stress testing for ischemia was introduced by Zaret and Strauss in 1973 using potassium 43 as the tracer. Redistribution studies, taking advantage of the properties of thallium 201 and technetium 99m, have improved the performance of the test, and pharmacologic stress testing has expanded their use.[20,49] Advances combining positron emission tomography (PET) or SPECT scanning with CT allow the integration of knowledge of anatomy with cardiac function. Imaging of "vulnerable" atherosclerotic plaque that would allow detection of patients at risk for acute ischemic events remains a laudable but elusive diagnostic goal.[50]

Echocardiography

Ultrasound imaging dates back to the production of sound waves from piezoelectric crystals in 1880 and the military use of sonar for the detection of reflected sound waves during World War II.[20] Cardiac ultrasound was introduced in Sweden by Inge Edler and Helmuth Hertz, who detected the anterior mitral leaflet with postmortem correlation—an ice pick through the chest into the mitral leaflet (1954). Starting in the mid-1960s with the detection of pericardial effusion and left ventricular size, M-mode echocardiography became a powerful clinical technique developed by Harvey Feigenbaum, who taught the first generation of echocardiographers. Contrast echocardiography (1969), two-dimensional echocardiography (1974), pulsed Doppler hemodynamics (1975), stress echocardiography (1979), Doppler color-flow (1982), and transesophageal imaging (1985) have added to its enormous success. Intraoperative transesophageal monitoring and the intrauterine diagnosis of congenital heart disease have become possible. Additions include the assessment of diastolic function along with tissue strain rate and three-dimensional capabilities. Digital recording has significantly transformed the acquisition, storage, and interpretation of studies. Echocardiography has safely and brilliantly illuminated the heart and its function, becoming the main imaging tool of choice given its ready availability, its ease of use, and extensive investigations supporting its use as a diagnostic tool.[47,48,51,52] Adding to the attractiveness of echocardiography as a mainstay among the cardiologist's tools are smaller, pocket-sized devices that bring the technology to the bedside and the ability of smartphone technology to allow immediate sharing of high-quality images, thus speeding diagnosis and clinical decision making.[53]

Computed Tomography and Magnetic Resonance Imaging

The three decades following the introduction of the gamma camera and ultrasound brought transformative expansion to the medical imaging field, including CT (1963-1971), SPECT (1963-1981), PET (1975-1987), and MRI (1972-1981), each delivering its own exciting ability to look at the structure and/or function of the heart in a different way (see Table 1–1). Each of these imaging techniques has spawned new clinical disciplines in cardiology and radiology that continue to the present. Electron-beam CT, introduced in 1990, has been used to detect early

TABLE 1–2. Selected Advances in Medical Therapy: 1900 to the Present

Available in 1900 (alphabetically)

Alcohol
Amyl nitrite (1867)
Atropine (1833, 1867)
Caffeine (1879)
Chloroform (1831)
Diet
Digitalis (1785)
Ether (1842)
Exercise
Leeches
Morphine (1821)
Nitroglycerine (1879)
Quinine (1745)
Salicylic acid (1876)
Southey trocars
Spa therapy
Squill (17th century)
Theobromine (1879)
Venesection
Veratrum viride (1859)

1900-1949

Adrenaline (1900)
Oxygen (1908)
Quinidine (1914)
Mercurial diuretics (1920)
Heparin (1935)
Magnesium (1935)
Penicillin (1940)
Dicoumarol (1941)
Rice diet (Kempner, 1944)
Cation exchange resins (1946)
Open chest defibrillation (1947)
Reserpine (1949)

1950-1959

Hexamethonium (1950)
Hydralazine (1951)
Procainamide (1951)
Ambulation post–myocardial infarction(1952)
Carbonic anhydrase inhibitors (1952)
External cardiac pacing (1952)
Warfarin (1954)
Alpha methyl dopa (1955)
Closed chest defibrillation (1956)
Chlorothiazide (1957)
Streptokinase for myocardial infarction (1958)
Guanethidine (1959)

1960-1969

Closed chest cardiac massage (1960)
Cardioversion of ventricular tachycardia (1960)
Amiodarone (1961)
Coronary care units (1961)
Beta-blockers (1962)
Synchronized cardioversion (1962)
Disopyramide (1963)
Lidocaine (1963)
Furosemide (1964)
Balloon atrial septostomy (Rashkind procedure, 1966)
Programmed electrophysiologic stimulation (1967)
Mobile intensive care unit (1967)
Bretylium tosylate (1968)
Outpatient cardiac rehabilitation (1968)

1970-1979

Calcium channel blocking agents (1970)
Vasodilator therapy (1971)
Stenting of patent ductus arteriosus (1971)
Dopamine (1972)
Intravenous verapamil (1972)
Nitroprusside (1974)
Beta-blockers for heart failure (1975)
Dobutamine (1975)
Catheter closure of atrial septal defect (1976)
Coronary angioplasty (1977)
Intracoronary thrombolysis (streptokinase) (1979)
Intravenous nitroglycerine

1980-1989

Phosphodiesterase inhibitors (1980)
Propafenone (1980)
Angiotensin-converting enzyme inhibitors (1981)
Flecainide (1982)
Atrioventricular nodal ablation (1982)
Catheter ablation of Wolff-Parkinson-White (1984)
Low-molecular-weight heparin (1986)
HMG-CoA reductase inhibitor (1986)
Intravenous thrombolysis (1987)
Aspirin for acute coronary disease (1988)
Aspirin for primary prevention (1989)
Ticlopidine (1989)

1990-1999

Hirudin (lepirudin) (1991)

(*continued*)

TABLE 1–2. Selected Advances in Medical Therapy: 1900 to the Present (*Continued*)

Endovascular graft for aneurysm and dissection (1991)	Dabigatran (2010)
Angiotensin II receptor blocking agents (1992)	Ticagrelor (2011)
Glycoprotein IIb-IIIa inhibitor (1993)	Rivaroxaban (2011)
Carvedilol (1995)	Apixaban (2012)
Nesiritide (1996)	Vorapaxar (2014)
Clopidogrel (1998)	Cangrelor (2015)
Dofetilide (1999)	Edoxaban (2015)
2000-2009	Sacubitril/Valsartan (2015)
Bivalirudin (2000)	Ivabradine (2015)
Brachytherapy (2000)	Alirocumab (2015)
Prasugrel (2009)	Evolocumab (2015)

coronary atherosclerosis. The multislice CT angiogram (2005) provides detailed coronary anatomy along with ventricular wall motion.[54] With the possibility of perfusion scanning being added to CT capabilities, CT is competing with coronary angiography and nuclear imaging as the initial imaging study for patients with suspected coronary artery disease, although there are concerns about the cumulative effects of radiation exposure that accompanies cardiac imaging.[55]

Cardiac MRI has emerged as a powerful tool to visualize cardiac structures with clarity and precision.[56] For example, MRI can be useful in the very accurate quantification of myocardial infarct size that correlates well with pathologic examination.[57] Because MRI does not involve ionizing radiation, it has emerged as a very helpful imaging modality in the sequential care of children and adults with complex congenital heart disease, including to follow up and plan for percutaneous and surgical repairs. MRI techniques can be used for perfusion scanning using vasodilating stress agents.[58,59] Finally, magnetic resonance angiography, or MRA, allows contrast-enhanced imaging of vascular structures that often can provide the endovascular specialist with a "roadmap" for therapeutic interventions. As with other imaging modalities, collaborations among academics, clinicians, and industry, leveraging the advantage of the information processing capabilities of the computer, have provided the basis for each technological advance.

CORONARY ARTERY DISEASE

DIAGNOSIS OF CORONARY ARTERY DISEASE AND ITS ETIOLOGY

On July 21, 1768, William Heberden presented "Some Account of a Disorder of the Breast" to the Royal College of Physicians, London: "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris."[2,60] Heberden appropriated the term *angina* from the Latin word for strangling. His classic account marks the beginning of our appreciation of coronary artery disease and myocardial ischemia. Edward Jenner and Caleb Parry were the first to suspect a coronary etiology, which Parry published in 1799. Allan Burns, in Scotland, likened the pain of angina pectoris to the discomfort brought about by walking with a tight ligature placed on a limb (1809), a prescient concept that remains relevant today. Nevertheless, a coronary cause of angina pectoris was not readily accepted until the late 19th century.[43] The term *arteriosclerosis* was coined by Johann Lobstein (1833). Key pathologic observations were made by Rudolf Virchow, who established the importance of thrombosis of arteries as a cause of disease (1846); Richard Quain, who associated the fatty degeneration of cardiac muscle with coronary obstruction (1850); Karl Weigert, who described the pathology of myocardial infarction and remarked on the importance of collateral vessels (1880); and Karl Huber, who suggested that atheroma could cut off the blood supply and lead to myocardial fibrosis (1882).[60] Adam Hammer was the first to report the premortem diagnosis of myocardial infarction (1878).

By the late 19th century, angina pectoris was linked with coronary artery disease, although there was confusion about the association between angina pectoris and myocardial infarction. Coronary disease was thought to be uncommon at that time. Julius Cohnheim taught that coronary arteries were end arteries, noting that experimental ligation of a coronary artery resulted in ventricular fibrillation (1881). In 1901, Osler called the anterior branch the "artery of sudden death," later stating that "the tragedies of life are largely arterial." The concept that coronary thrombosis was always fatal was finally dispelled by James Herrick (1912).[61,62] He concluded "there is no inherent reason why the stoppage of a large branch of a coronary artery, or even of a main trunk, must of necessity cause sudden death." Herrick was the first to grasp the variable course of myocardial infarction. The three-lead electrocardiogram was used by Herrick and Smith to diagnose experimental infarction (1918) and in humans by Pardee (1920).[31] Precordial leads, introduced by Frank Wilson in the 1930s, furthered the diagnosis. Between 1928 and 1950, large series of patients—analyzed by John Parkinson and Evan Bedford in London, Samuel Levine and Paul Dudley White in Boston, Charles Friedberg in New York, and others—provided a broad understanding of the clinical, electrocardiographic, and laboratory findings of myocardial infarction as well as its prognosis and autopsy correlations.[24] By the 1930s, myocardial infarction was a familiar diagnosis believed to be increasing in frequency. This change in epidemiology tracked the urbanization of American society, the reduction in deaths from infectious diseases (resulting from both public health improvements as well as the discovery of antibiotics) and, probably most contributory, increasing tobacco use among adults.

The clinical-pathologic correlations of atherosclerosis and thrombosis with infarction were greatly strengthened by the 1940 postmortem

coronary injection studies of Blumgart, Schlesinger, and Davis. Autoradiographic postmortem studies by Fulton in Glasgow (1976) and DeWood's seminal coronary arteriographic studies in patients with acute myocardial infarction (1980) finally proved that a thrombus was the causative event leading to acute coronary obstruction. The "vulnerable plaque" hypothesis has gained widespread support as the cause of acute coronary disease and sudden death. Inflammation, ignited by risk factors such as smoking, hypertension, hyperlipidemia, and diabetes, underlies "atherothrombosis," and plaque disruption (rupture, fissure, erosion followed by repair) is now realized to be a complex interplay of events but one largely driven by inflammatory cells such as monocytes and macrophages and the response to vascular injury of the hemostatic system.[63-66]

TREATMENT OF ANGINA PECTORIS

Treatment of angina pectoris began with amyl nitrite used by Lauder Brunton (1867) and nitroglycerine by William Murrell (1879). Before 1970, xanthine derivatives, sedatives, opiates, diet, prolonged rest, alcohol, long-acting nitrites, paravertebral alcohol injections, dorsal sympathectomy, induction of myxedema, instillation of talc or bone dust into the pericardium, denervation of the heart, radiation to the anterior chest, and carotid sinus pacing enjoyed temporary support. β-Adrenergic blockade, beginning in the early 1970s, greatly improved the management of angina; clinical trials in the 1980s showed that the risk of myocardial infarction among certain groups of patients (such as those with a first myocardial infarction) could be reduced by the use of β-blockade. Calcium channel blockers and nitroglycerine administered by paste and intravenously were introduced in the late 1970s (Table 1–3). PTCA using balloon inflations for alleviating angina was the concept of Grüntzig, working in Zürich (1977). He was influenced by Charles Dotter's 1964 demonstration that peripheral atherosclerosis was malleable. Balloon angioplasty was improved by bare metal stenting of coronary arteries (1986), primary angioplasty for acute infarction (1988), brachytherapy (2000), and eventually drug-eluting stents (2001).[44,67] Restenosis with subsequent need for repeat revascularization, the Achilles heel of balloon angioplasty, has fallen from a range of 30% to 40% to approximately 5% with the latest generation of drug-eluting stents. Technology advances with both devices and adjunctive pharmacology has allowed percutaneous coronary intervention (PCI) to be applied to more complicated patients (eg, older patients with more comorbidities) and more complex coronary anatomy (eg, left main and multivessel coronary artery disease). Challenges remain with stent thrombosis, bifurcation disease, saphenous vein graft disease, and chronic total coronary occlusions. Patients with advanced coronary artery disease not thought to be amenable to current revascularization techniques represent an important and growing group for whom investigation with novel approaches such as cellular therapies holds promise.[68]

TREATMENT OF ACUTE CORONARY SYNDROMES

Strict bedrest for 6 to 8 weeks was rigidly advised for heart attacks until 1952, when Levine and Lown suggested an "armchair" approach was better. Anticoagulation, strongly recommended by Wood and others for myocardial infarction in the 1950s, became controversial in the 1960s. Before the defibrillator and coronary care units, the in-hospital mortality associated with acute myocardial infarction was approximately 30%. With the development of the defibrillator by William Kouwenhoven, Claude Beck and Paul Zoll were able to prove that rescue of cardiac arrest victims was possible. Beck's concept that "the heart is too good to die" instilled optimism into the care of coronary patients and aggressiveness into their providers. Myocardial infarction was no longer a disease to be watched but rather one that might benefit from aggressive therapeutic interventions. Zoll reported closed chest defibrillation in 1956 and cardioversion of ventricular tachycardia in 1960. The monitoring of patients in close proximity to skilled nursing personnel who could perform cardiopulmonary resuscitation was a logical next step suggested by Desmond Julian in 1961. Since then, coronary care has gone through a series of recognizable phases: first, cardiac resuscitation and the essential role of the nurse; second, prevention and treatment of life-threatening arrhythmias; third, hemodynamic catheter monitoring (the pulmonary artery or Swan-Ganz catheter)[69] and treatment of pump failure; fourth, reduction of infarct size—first with adjunctive medical therapies such as β-blockers and then with reperfusion therapies, including fibrinolytic therapy (1987) and primary angioplasty; and, finally, the current phase devoted to developing and implementing coordinated systems with multidisciplinary teams to efficiently deliver complex cardiac care, including acute coronary care with invasive management techniques and advanced heart failure with mechanical ventricular support devices.

Fibrinolytic therapy for acute myocardial infarction, using small doses of intravenous streptokinase, was first tried in 1958 by Fletcher and Sherry and given as an intracoronary infusion by Boucek and Murphy in 1960 and Chazov in 1976.[70] The rationale for thrombolysis derives from a 1977 report by Reimer and colleagues describing the "wavefront" phenomenon of myocardial infarction and stating that necrosis from infarction progresses over a period of 3 to 6 hours, suggesting that early restoration of epicardial coronary blood flow can salvage threatened myocardium and limit infarct size. Its current use, emphasizing that "time is muscle," began with intracoronary infusion of streptokinase in 1979 by Rentrop and was followed by intravenous streptokinase (1983) and intravenous tissue plasminogen activator in 1987. Small clinical trials first suggested that primary angioplasty was superior to medical reperfusion with fibrinolysis, and aggregated analyses of these trials solidified the role of primary PCI in the initial care of the myocardial infarction patient.[71]

There is no question that the rapid delivery of reperfusion therapy improves coronary blood flow, reduces infarct size, and improves mortality. The challenges now center around improving early detection of symptoms and entry into the emergency medical system, rapid diagnosis and triage, transfer to facilities offering the most appropriate level of acute cardiac care, and rapid administration of reperfusion therapy by experienced providers.[72,73] Additionally, the advanced elderly (> 75 years) present unique challenges in myocardial infarction management that require further investigation. Cardiogenic shock remains a major challenge for the modern cardiac care unit, with this cohort of myocardial infarction patients accounting for the majority of short-term mortality. New insights into shock that consider it as an inflammatory disorder open up avenues of needed research to further decrease acute myocardial infarction mortality.[74] Important adjuncts to reperfusion therapy include β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and antithrombotic therapy, including antiplatelet and anticoagulant therapies.[75,76] Insights gained from hypothermia survivor observations have led to the concept of therapeutic hypothermia to improve cardiac survival among those who have sudden death as a complication of myocardial infarction. Earlier detection of patients at risk for sudden cardiac death is one of the next frontiers in acute myocardial infarction research.[77]

PREVENTION OF CORONARY ARTERY DISEASE

Cardiovascular epidemiologic studies, advocated by Paul Dudley White, began in earnest with the National Institutes of Health (NIH)-sponsored

TABLE 1–3. Selected Advances in Cardiovascular Surgery and Intervention

19TH CENTURY

Drainage of pericardial effusion (1810)
Introduction of ether anesthesia (1842)
Removal of foreign body from heart (1873)
Surgical closure of stab wound of heart (1896)

20TH CENTURY

1900-1925

End-to-end arterial anastomosis (1902)
Animal heart transplantation (1905)
Arterial patch graft (1910)
Coronary artery bypass in animal (1910)
Insufflation endotracheal anesthesia (1910)
Attempted external dilatation of aortic stenosis (1912)
Pericardial resection for constriction (1913)
Sympathectomy (1917)
Mitral stenosis valvulotomy (1923)
Pulmonary embolectomy (1924)
Lumbar sympathectomy (1925)
Mitral stenosis dilatation by finger (1925)

1926-1950

Cardio-omentopexy (1930s)
Thyroidectomy for angina pectoris (1933)
Ligation of patent ductus arteriosus (1938)
Coarctation repair (1944)
Subclavian artery to pulmonary artery anastomosis for tetralogy of Fallot (Blalock-Taussig shunt, 1944)
Cardiac missile removal (World War II)
Side-to-side anastomosis of aorta to pulmonary artery for tetralogy of Fallot (Potts procedure, 1946)
Valvotomy for pulmonic stenosis (Brock procedure, 1947)
Closed mitral commissurotomy (1948)
Resection of infundibulum of right ventricle (1948)
Atrial septostomy (Blalock-Hanlon procedure, 1950)
Internal mammary tunnel implant into myocardium (Vineberg, 1950)
Hypothermia (1950)

1951-1975

Closure atrial septal defects (1950s)
First prosthetic ball valve—into aorta for aortic regurgitation (1952)
Resection abdominal aortic aneurysm (1952)
Extracorporeal circulation (1953)
Pulmonary artery banding (1953)
Aortic dissection repair (1954)
Carotid endarterectomy (1954)
Closure ventricular septal defect (1954)
Cross-circulation of oxygenated blood (1954)
Tetralogy of Fallot repair (1954)
Potassium cardioplegia (1955)
Aortic valvotomy (1956, 1958)
Transection of ventricular septum for idiopathic hypertrophic subaortic stenosis (1957)
Resection ventricular aneurysm (1958)
Superior vena cava to pulmonary artery shunt (Glenn procedure, 1959)
Transposition of great vessels repair (Senning procedure, 1959)
Aortic ball and cage valve (1960)
Implantable pacemaker (1960)
Mitral ball and cage valve replacement (1960)
Excision of ventricular aneurysm (1961)
Atrioventricular synchronous pacemaker (1962)
Homograft valve (1962)
Intra-aortic balloon pump (1962)
Aortopulmonary window (Waterston procedure, 1963)
Catheter embolectomy (Fogarty procedure, 1963)
Left ventricular assist (1963)
Transposition of aorta with intra-atrial baffle (Mustard procedure, 1963)
Double-outlet right ventricle repair (1964)
Internal mammary artery to coronary artery bypass (1964)
Pulmonary autograft for aortic valve disease (Ross procedure, 1966)
Cardiac transplantation (1967)
Saphenous vein to coronary artery bypass (1968)
Truncus arteriosus repair (1968)
Wolff-Parkinson-White surgery (1968)
Extracardiac conduit (Rastelli procedure, 1969)
Heart and lung transplant (1969)
Tilting disk valve (1969)
Bioprosthetic valve (1970)
Connection of right atrial appendage to pulmonary artery for tricuspid atresia (Fontan procedure, 1970)
Annuloplasty ring (1971)
Bovine pericardial valve (1971)
Mitral valve repair (1971)
Stenting of patent ductus arteriosus (1971)
Lithium battery pacemaker (1972)
Porcine valve (1975)

1976-1999

Arterial switch procedure for transposition of great vessels (1976)
Tilting disk valve (1977)
Bileaflet hinged valve (1977)
Pericardial valve (1980)
Dual-chamber pacing (1980)
Automatic implanted defibrillator (1980)

(*continued*)

TABLE 1–3. Selected Advances in Medical Therapy: 1900 to the Present (*Continued*)

Transmyocardial laser (1981)	Minimally invasive bypass surgery (1997)
Artificial heart (1982)	Robotic surgery (1998)
Antitachycardia pacemaker (1982)	**21ST CENTURY**
Heart transplants in infants with hypoplastic left heart (1984)	**2000-Present**
Catheter ablation of Wolff-Parkinson-White (1984)	Drug-eluting stent (2001)
Cardiomyoplasty (1985)	Ventricular assist device (2002)
Coronary artery stents (1986)	Automated external defibrillator (2002)
Modified Fontan procedure for single ventricle (late 1980s)	Transcatheter aortic valve replacement (2011)
Directional atherectomy (1993)	Noninvasive mitral repair (2013)
Biphasic cardioversion-defibrillation (1996)	Bioabsorbable coronary stent (2016)
Carotid artery stent (1997)	

Framingham study (1948) and the work of Ancel Keys in Minnesota. These landmark studies emphasized prevention of coronary disease through recognition and treatment of risk factors. The metabolic syndrome, first described in 1983 and now an epidemic driven by visceral obesity, has risen to become a public health problem of global significance.[78,79] The vascular protective and relaxing role of the endothelium, through its generation of nitric oxide, and the dangers of endothelial dysfunction were key basic science discoveries (1970s) for which the Nobel Prize was awarded in 1998.[80] The hydroxyl methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (known widely as "statins"), isolated by Akira Endo in Japan (1976) and commercially available since 1986, have dramatically decreased mortality, heart attacks, and strokes among a broad spectrum of patients with or at risk of cardiovascular disease. With a continuing target of further decreasing low-density lipoprotein (LDL) levels, the proprotein convertase subtilisin kexin 9 inhibitors offer the ability to lower LDL to near birth levels. Whether this profound reduction in LDL translates into clinical benefit awaits the results of large ongoing clinical trials.[81] More recently, attention has turned to elevating high-density lipoprotein (HDL) levels to stabilize or reverse atheroma. However, no HDL-raising therapy to date has resulted in an improvement in clinical outcomes in large randomized trials. Diabetes has become a global problem with resultant increases in cardiac diseases, including among the young and in countries with emerging economies. Linked to obesity and sedentary lifestyles, its prevention and treatment threaten to consume huge portions of global health care spending. Managing this will be one of the key medical and scientific priorities of the next few decades.[82,83]

VALVULAR HEART DISEASE

Valvular pathology was described in the 17th and 18th centuries; however, Laennec was the first to describe audible heart murmurs, calling them "blowing, sawing, filing, and rasping."[29] Originally, he attributed the noise to actual valvular disease, but he later decided that they were caused by spasm or contraction of a cardiac chamber. James Hope in England was the first to classify valvular murmurs in *A Treatise on the Diseases of the Heart and Great Vessels* (1832).[84] He interpreted physical findings in early physiologic terms and provided detailed pathologic correlations.[85] Constriction of the mitral valve was recorded by John Mayow (1668) and Raymond Vieussens (1715); the latter also recognized that it could cause pulmonary congestion.[86] The presystolic murmur of mitral stenosis was described by Bertin (1824), timed as both early diastolic and presystolic by Williams (1835), and placed on firmer grounds by Fauvel (1843) and Gairdner (1861). Aortic stenosis was first described pathologically by Rivière (1663), and Laennec pointed out that the aortic valve was subject to ossification (1819).[87] Corvisart showed an astute grasp of the natural history of aortic stenosis (1809) commenting:

> *When it is considered how narrow the opening is, which these constrictions leave, it is difficult to conceive how such an organic derangement can continue for years. It is evident, if such an obstacle to the circulation were suddenly introduced into a healthy subject, death would immediately follow; but as these obstacles are slowly formed, the circulation is gradually impeded, and nature seems in some measure to be habituated to such a perversion of her laws.*

Early descriptions of aortic regurgitation were by William Cowper (1706) and Raymond Vieussens (1715),[88] whereas Giovanni Morgagni recognized the hemodynamic consequences of aortic regurgitation (1761). In 1832, Corrigan provided his classic description of the arterial pulse and murmur of aortic regurgitation. Flint added that the presystolic murmur was sometimes heard with severe aortic regurgitation (1862).[30] The etiology of valvular disease in the 19th and first half of the 20th century revolved about the role of rheumatic fever. David Pitcairn was the first to suggest rheumatism of the heart (1788), and William Charles Wells described acute rheumatic fever with cardiac involvement in 1812.[24,89] Jean-Baptiste Bouillaud established that acute articular rheumatism was associated with inflammation leading to valvular deformities (1836).[22] Acceptance of the association between *rheumatism*—rheumatic fever—and subsequent valvular heart disease was gradually accepted. By the late 1800s, treatment of rheumatic episodes with salicylic acid had been introduced. Over time, the link between the throat, heart, and rheumatic fever was clarified; the role of the *Streptococcus* was identified; and attention was paid to environmental factors—poverty, overcrowding, and malnutrition. Diagnostic criteria for acute rheumatic fever were established by T. Duckett Jones in 1944 with revisions through 1992. Antibiotic therapy has contributed to the great decrease in rheumatic fever in the Western world, but it should be noted that rheumatic heart disease remains a major global public health problem.[90]

Beginning with cardiac catheterization in the 1950s and supplemented by echocardiographic imaging in the 1970s and now with MRI and CT scanning, the severity of valvular disease is readily analyzed and its progression followed. Our understanding of the etiology of valvular heart disease changed dramatically with the recognition of many nonrheumatic causes of valvular disease, especially the "floppy mitral valve" with prolapse by Reid and Barlow in the early 1960s.[91] Since 1997, inflammation of the aortic valve, attributed to atherosclerotic risk factors, has been shown to play a central role in the development of adult aortic stenosis, although treatment with anti-inflammatory drugs such as the statins or other lipid-lowering therapies have not yet been shown to alter the course of the valvular disease.

Today, there is no "typical" patient with valvular heart disease; treatment involves medical, surgical, and interventional care, all guided by sophisticated imaging. The care of these patients is the purview of experts in the broader category of structural heart disease that includes valve disease as well as structural abnormalities such as septal defects and septal hypertrophy. The development of transcatheter aortic valve replacement, or TAVR, and its subsequent introduction into routine clinical practice has altered the approach to patients with aortic stenosis and opened avenues into considering other percutaneous approaches to valvular and structural heart disease.[92]

CARDIOMYOPATHY

At mid-20th century, Henry A. Christian published *Non-Valvular Heart Disease*. He considered this to be the most frequent form of heart disease among individuals past middle age. At that time, acute or chronic myocarditis was thought to be the major cause; however, he considered the role of hypertension, ventricular hypertrophy and dilatation, heart failure without enlargement, and familial occurrence. Subsequent writers gradually shifted the emphasis from myocarditis to primary (idiopathic) myocardial disease.

The term *cardiomyopathy,* referring to the noncoronary cardiomyopathies, was introduced by Wallace Brigden in 1957. During this period, a dynamic form of subaortic stenosis was discovered and its hemodynamics investigated, and John Goodwin in London presented a new classification based on hypertrophy, dilatation, or restriction (1961).[93] Myocardial biopsy, new imaging modalities, and biochemical and genetic studies have reshaped the understanding of cardiomyopathy along with more precise definition of the etiology of myocarditis. There is also a growing understanding of the contributory role of genetics in the development of the congenital/idiopathic cardiomyopathies.[94]

CONGENITAL HEART DISEASE

Early textbooks in cardiology by Jean-Baptiste Senac (1749) and Allan Burns (1809) included comments on cardiac malformations. Cyanotic heart disease is mentioned; however, its mechanism was debated because some patients with septal defects had cyanosis although others did not. An early, comprehensive book devoted to cyanotic and acyanotic congenital heart disease, *On Malformations of the Human Heart,* was published in 1858 and 1866 by Thomas Bevill Peacock, a physician in London with a special interest in pathology.[2] In his book, Peacock reviews the previous literature and provides detailed case studies, engravings of the pathology, personal insights, and an anatomic classification of more than 100 patients.

Following Peacock's book, advances in congenital heart disease were limited primarily to pathologic descriptions and summaries until the seminal work of the pathologist Maude Abbott. Beginning in 1908, Abbott catalogued the pathology collection at the Montreal General Hospital, compiling 1000 cases that were fully analyzed in her 1936 classic, *Atlas of Congenital Heart Disease*.[20,95] Her meticulous work provided a new classification correlating the history, examination, and postmortem findings with illustrations and became the foundation for the study of congenital heart disease. Maternal rubella studies (1940) brought attention to viral influences on cardiac development.

The pivotal breakthrough in thinking about congenital abnormalities came from Helen Taussig and Alfred Blalock at Johns Hopkins Hospital with their "blue baby operation." Taussig had observed that patients with cyanotic heart disease worsened when their ductus arteriosus closed. She suggested creating an artificial ductus to improve oxygenation.[96] Blalock, assisted by Vivian Thomas, successfully created a shunt from the subclavian to the pulmonary artery in November 1944. This innovative operation, in which a blue baby was dramatically changed to a pink one—the Blalock-Taussig shunt—was highly publicized, and other shunt operations soon followed (see Table 1–2). Taussig's *Congenital Malformations of the Heart,* a 1947 compendium with schematics explaining the pathophysiology of the defect, became the ultimate authority on congenital heart disease. Studies in the 1950s correlated the clinical with the cardiac catheterization findings and led to a firmer physiologic basis for selecting patients who might benefit from the upcoming advances in congenital heart surgery. Natural history studies helped to clarify their prognosis.

In 1966, Rashkind introduced the balloon septostomy, a novel catheter therapeutic technique that bought time for severely cyanotic infants with transposition of the great arteries.[20] In the 1980s, catheters were adapted to dilate stenotic aortic and pulmonic valves as well as aortic coarctation. Today, transcatheter closure of patent ductus arteriosus (1971), atrial septal defects (1976), and ventricular septal defects (1987) has become routine. Indomethacin therapy to enable closure of a patent ductus in the premature infant (1976) and prostaglandin infusion to maintain ductal patency (1981) profoundly changed the medical management of fragile newborns. Stents now help keep the ductus open as well as alleviate right ventricular obstruction in tetralogy of Fallot.

Until the 1970s, confirmation of a complex clinical diagnosis, mandatory for critical surgical decisions, required cardiac catheterization and angiography. In the late 1970s and 1980s, two-dimensional and color-flow Doppler echocardiography and later MRI became available to provide a quick diagnosis. With aggressive medical and catheter management, the approach to neonates, including intrauterine intervention, has radically changed. Improvements in operative techniques allowed innovative surgeons to operate earlier on smaller and sicker hearts while offering palliation or complete repair for congenital defects. With continued improvement in surgical techniques coupled with advances in postoperative intensive care, repair of previously lethal congenital abnormalities has now become possible. Adult congenital heart clinics have been an offshoot of the increased survival of children with congenital heart disease; there are now more adults than children with congenital heart disease.[97]

AORTIC DISEASE

Aristotle (384-322 BC) named the great arterial vessel the *aorta.* Vesalius (1514-1564) is credited with the first description of an aneurysm of the abdominal and thoracic aorta (1555). Aneurysm (from the Greek word *dilatation*) of the aorta caught the attention of many early anatomists, especially Giovanni Maria Lancisi (1654-1720), whose 1728 book, *De Moto Cordis et Aneurysmatibus,* provided a definition and

classification, separated true from false aneurysms, discussed possible etiologies, and included case studies. Trauma and syphilis were particularly singled out as causes of aneurysms by Lancisi and his followers. Coarctation of the aorta (from the Latin *coarctatus,* meaning pressed together, contracted) was best described by M. Paris (1791).

Aortic dissection was not distinguished as a separate entity until *The Seats and Causes of Diseases,* published by Morgagni in 1761. He reported a 50-year-old woman who cried, "Oh!" and then died instantly. At autopsy, he "observed the blood had, by degrees, made itself a way through one of the intervals of this kind, and had come out under the external coat of the artery … as a large kind of ecchymosis … had burst through this external coat in one place, and had poured itself out within the pericardium." Laennec provided the term *l'anévrysme disséquant* (dissecting aneurysm) in 1826. Over the next century, the separation of a true aneurysm from a dissecting aneurysm, the pathogenesis from an initial transverse tear to a distal entry, the association of coarctation with a bicuspid aortic valve and hypertension, the significance of cystic medial necrosis, and the natural history of a large series of patients with dissection were recognized. More recently, there has been a greater recognition of heritable disorders of connective tissue and the vulnerability of the vascular system to risk factors and inherited disorders. Cardiovascular imaging has clarified the overlap of intramural hematoma, aortic dissection, and penetrating atherosclerotic ulcers. More advanced vascular imaging with MRI and CT that allow three-dimensional reconstruction of the aorta and great vessels has permitted increasingly complex surgical repair and reconstruction of disorders of the thoracic aorta and has paved the way for percutaneous endovascular approaches.[98]

BLOOD PRESSURE MEASUREMENT AND HYPERTENSION

Stephen Hales, an English country parson, reported in his *Statical Essays* (1733) that the arterial blood pressure of the cannulated artery of a recumbent horse rose more than 8 feet above the heart—the first true measurement of arterial pressure and the beginning of sphygmometry.[2,3,99] His pioneering efforts stood alone until 1828 when Jean Poiseuille introduced a mercury manometer device to measure blood pressure.[100,101] Over the next 60 years, various sphygmomanometric methods were developed—notably by Ludwig (1847), Vierordt (1855), and Marey (1863)—to refine the measurement of the arterial pressure. An inflatable arm cuff coupled to the sphygmograph, a device small enough to allow measurement outside the laboratory, was invented by Riva-Rocci (1896), who also noted the "white-coat effect" on blood pressure.[102] Nicolai Korotkoff, a Russian military surgeon, first auscultated brachial arterial sounds (1905), a discovery that marked the advent of modern blood pressure recording. This auscultatory approach eventually ensured its widespread use by the 1920s. In 1939, blood pressure recordings were standardized by committees of the American Heart Association (AHA) and the Cardiac Society of Great Britain and Ireland.

Richard Bright was the first to note the association among kidney disease, hypertrophy of the heart, dropsy (congestive failure), and hardening of the arteries (1827).[101] In the 1870s, the studies of Frederick Mahomed in London established that elevated blood pressure could occur in the absence of nephritis and produce secondary kidney and arteriolar disease.[102] Secondary causes of hypertension were discovered. Robert Tigerstedt in Stockholm discovered a pressor substance in the renal cortex, which he named renin in 1898; however, Goldblatt's experiments, showing that renal artery stenosis induced ischemia and hypertension (1934), eventually led to the understanding of the renin, angiotensin, and aldosterone interaction by Pickering, Page, Braun-Menendez, Laragh, and others.[103] Beginning in the late 19th century, vasomotor, neurohormonal, and baroreceptor reflexes as well as genetic determinants of blood pressure became known. The crucial role of sodium was further delineated by Guyton in the 1960s. Pickering and Platt debated whether or not there was a precise demarcation between normal and abnormal blood pressure in the late 1950s. In 1972, Pickering stated: "There is no dividing line. The relationship between arterial pressure and mortality is quantitative: the higher the pressure, the worse the prognosis."[89] Subsequent studies have been supportive and the level where treatment should begin has been lowered, although optimal blood pressure across age groups has yet to be defined by appropriate clinical studies.

In 1913, Janeway showed that patients, once diagnosed with hypertensive heart disease and symptoms, lived an average of 4 to 5 years. However, the asymptomatic state of most patients with hypertension, the lack of effective treatment, and a prevalent view that lowering the blood pressure would be deleterious to the kidney and brain lulled most physicians into accepting the condition as being normally associated with aging. In the 1970s, reports from the Framingham Heart Study showed hypertension to be a major contributing cause to stroke, heart attack, and heart and kidney failure. Hypertension was labeled "the silent killer." Other studies followed indicating that treatment of even mild hypertension could reduce stroke and heart failure, although not necessarily heart attacks. National High Blood Pressure Education Programs, beginning in 1972, urged physicians to treat blood pressure elevation, and outposts to measure blood pressure became common. The initial emphasis was on the treatment of diastolic hypertension. More recently, systolic hypertension and wide pulse pressure in seniors has been found to be serious, warranting aggressive treatment.

TREATMENT OF HYPERTENSION

President Franklin Roosevelt's death in 1945 from severe hypertension and stroke called international attention to the consequences of hypertension and its inadequate treatment—he had been managed with diet, digitalis, and phenobarbital. Effective oral treatment became possible in 1949, first with reserpine and then with hydrochlorothiazide.[104] Lumbar sympathectomy and adrenalectomy (1925), the last resort, was abandoned. Subsequently, β-adrenergic blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blocking agents, and direct renin inhibitors have brought antihypertensive relief to many (see Table 1–3). Severe salt restriction, as practiced earlier with the Kempner rice diet, has taken a lesser role, whereas the Dietary Approaches to Stop Hypertension (DASH) diet, exercise, and alcohol restriction are encouraged. Since 1973, recommendations published by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) have been very helpful. Nevertheless, the majority of patients are imperfectly controlled, and many remain undetected. Programs by the AHA focus public attention on the need for better blood pressure detection and control. As technologies continue to evolve, more direct patient engagement with ambulatory devices, including ones that can store and transmit blood pressure data via a smartphone and the Cloud, offer the possibility of much better treatment adherence and blood pressure control. From a guidelines perspective, the JNC recommendations remain the standard of care in hypertension management.[105]

HEART FAILURE

Medieval physicians commented on suffocative catarrh, dyspnea, asthma, orthopnea, and dropsy but failed to recognize a connection with the

heart.[106] This was primarily because of the entrenched teachings of Galen that the purpose of the heart was to generate heat and distribute vital spirit. Marcello Malpighi believed that dyspnea could be caused by retarded circulation in the pulmonary vessels (1660s). Vieussens (1706) and Lancisi (1707) were the first to fault the heart as the direct cause of failure, a concept more fully elaborated by Albertini (1726).[20,106]

Initially, clinical observation was based on case reports describing signs and symptoms. In this setting, clinicians understood that valve obstruction, the most commonly recognized cardiac problem at that time, caused dyspnea and fluid accumulation. The autopsy findings of hypertrophy and dilatation of the heart were a particular puzzle for 18th-century physicians. Morgagni was the first to comprehend that overload from valvular disease could elicit a compensatory hypertrophic response and dilatation, leading to congestive failure (1761). At the beginning of the 19th century, Corvisart's distinction between the causes of hypertrophy and dilatation led to an appreciation of the beneficial effects of hypertrophy and the harmful effects of dilatation. The primary role of the myocardium versus valvular disease in the production of symptoms and a basis for prognosis followed, was lost, and was then rediscovered. Richard Bright's 1836 discovery of the relationship of cardiac hypertrophy and dropsy to shrunken kidneys introduced the kidneys as a cause of heart failure long before hypertension was known.[99] Toward the end of the 19th century, the beneficial role of hypertrophy was questioned by Schroetter (1876), Osler (1892), and others, who saw that it was harmful in its later stages. Mackenzie, in his influential 1908 textbook, *Diseases of the Heart,* stressed the functional role of the heart muscle and its reserve force, downplaying valvular disease as "an embarrassment to the heart muscle." He believed that it was exhaustion of the heart muscle that led to symptoms and signs of heart failure.[24] His insistence that "a heart is what a heart can do" was the beginning of a functional classification that redirected thinking toward physiology and away from just the presence of murmurs and arrhythmias.

The definition of normal circulatory physiology was the precursor for an understanding of abnormal circulatory phenomena. In the late 19th and early 20th centuries, the hemodynamic physiologists Otto Frank, Ernest Starling, and Carl Wiggers established the basic principles of cardiac function, pressure, and flow abnormalities in the failing heart.[20] In the mid-20th century, studies by Sarnoff, Braunwald, and others heightened our understanding of the performance of normal and abnormal heart muscle. The widespread application of cardiac catheterization, selective angiography, and imaging studies has resulted in more precise diagnostic criteria and hemodynamic information for differentiating ischemic heart disease, hypertensive heart disease, as well as nonischemic, dilated, and hypertrophic forms of cardiomyopathies. *Congestive heart failure* was a term first used in the 1920s, although a definition for heart failure based on its pathogenesis has been controversial.[24] The debate initially centered on whether the elevated venous pressure was a primary or secondary event. Two opposing camps evolved: the first held that *backward failure,* or an upstream obstruction (eg, aortic stenosis), was the central factor, and the second championed *forward failure*, that is, when myocardial dysfunction with low cardiac output was the problem. Over time, the rigid concepts embodied in *backward* and *forward failure, right-sided* and *left-sided failure,* have given way to definitions based on the cardiac output as the discriminator: *low-output* and *high-output failure.* More recently, heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) have emerged as the preferred clinical lexicon. The discovery of B-type natriuretic peptide has revealed that the heart is also an endocrine organ. Cell biochemistry and biophysics continue to add to our understanding of the abnormalities in cardiac contraction, relaxation, and energetics, whereas molecular and cell biology are helping to define the pathways responsible for alterations in growth, offering up potential novel mechanisms for treatment.

TREATMENT OF HEART FAILURE

In the late 19th and early 20th centuries, heart failure was treated with venesection, digitalis, saline purges, a low-salt diet, mercurial cathartics, incision and drainage of edema (Southey tubes) or ascites, bromides, theophylline or urea for diuresis, and carbonic acid baths at a spa. By the 1930s, cathartics had been replaced by intramuscular mercurial injections to remove fluid. Thyroidectomy was advised in advanced cases. The introduction of potent oral diuretics, beginning with chlorothiazide (1957) and then furosemide (1964), brought miraculous relief to volume-overloaded cardiac patients, ending the common practice of twice-weekly *merc shots.* Cohn's concept of afterload reduction with vasodilators (1971) soon led to nitroprusside (1974), ACE inhibitors (1981), and angiotensin receptor blockers (1992), which have greatly improved the quality of life and prognosis for heart failure patients (see Table 1–3). β-Adrenergic blockers, initially thought to be absolutely contraindicated, were suggested to be otherwise in 1975 by Wagstein and, after large-scale randomized trials demonstrated their association with marked improvements in mortality, are now a first-line treatment. Recently, use of angiotensin receptor neprilysin inhibitors has shown further reductions in mortality in HFrEF patients. How these therapies will be incorporated into the multidrug regimens of these patients still needs to be determined in practice guidelines. Unfortunately, there has been far less progress in finding effective therapies for patients with HFpEF.

The 21st century has seen an increased emphasis on aggressive device and surgical treatment for patients with advanced heart failure, especially systolic heart failure. Advanced training in heart failure and cardiac transplant is now recognized as an important subspecialty within cardiovascular medicine.[107] Biventricular pacing, introduced in 2000, has been proven beneficial in selected patients. Cardiac transplantation, once considered a last resort for selected patients after its inception in the late 1960s, has become increasingly common although limited by an insufficient organ supply. More recently, mechanical support for the failing ventricle with left (and right) ventricular assist devices (LVAD) is being used both as a bridge to cardiac transplant and as destination therapy.[108] Cell transplant therapy for cardiac repair remains a promising although still unproven approach to regenerate myocardium.[109] In addition to this increased emphasis on very aggressive treatment of the patient with advanced heart failure, important societal questions have arisen about costs of therapy, effects on quality of life, and end-of-life decision making.[110]

CARDIAC SURGERY

The Nobel Prize in Physiology or Medicine in 1912 was awarded to Alexis Carrel, a French experimental surgeon working at the Rockefeller Institute, "in recognition of his work on vascular suture and the transplantation of blood vessels and organs." His many contributions to the basic science of surgery provided the essential foundation and encouragement for the clinical surgeons who would eventually follow his bold path[20] (see Table 1–2). A few attempts were made to suture cardiac wounds in the late 19th century and to remove pericardial adhesions and effusion or improve valvular disease in the first quarter of the 20th century; however, the surgeon was thwarted by the interrelated problems of establishing the correct diagnosis, cerebral oxygenation, pneumothorax, anesthesia, bleeding, infection, arrhythmias, blood pressure control, metabolic management, and others.[111] Comroe pointed out that 25 separate bodies of knowledge had to evolve to

permit successful open-heart surgery.[112] Extracardiac surgery—ligation of a patent ductus by Gross (1938), repair of coarctation of the aorta by Crafoord (1944), the Blalock-Taussig shunt (1944), and removal of intracardiac missile fragments by Harken during World War II—led the way in establishing cardiac surgery as a distinct therapeutic discipline.[111]

Simple and quick intracardiac surgery, such as repair of an atrial septal defect, was successfully accomplished using hypothermia in the 1950s by John Lewis and others, although the risk of ventricular fibrillation and air embolism presented a hazard. John Gibbons's development of extracorporeal circulation became the essential platform for safe intracardiac surgery.[113] In 1953, his pump-oxygenator provided 45 minutes to repair an atrial septal defect, and the surgeon finally had time to operate safely and explore new horizons.[98] In the early 1950s, mitral stenosis was a major clinical problem, and mitral valvotomy was performed by Bailey, Harken, and Lillehei with increasing success.[20,89] Surgery for congenital heart defects was next, including tetralogy of Fallot (Lillehei, 1954). More complicated surgery, including mechanical prosthetic valve replacement (Starr and Harken, 1960), homograft valve (Donald Ross, 1962), cardiac transplantation (Christiaan Barnard and Norman Shumway, 1967), bioprosthetic valve replacement (1970), mitral valve repair (Alain Carpentier, 1971), and repair of complex congenital heart disease followed as diagnostic and surgical techniques, artificial valves, and intensive postoperative care improved.[111,112]

In 1910, Alexis Carrel attempted the first experimental coronary bypass, fashioning an anastomosis between the descending aorta and the left coronary artery. Efforts to improve the coronary circulation using pericardial irritants (Beck, 1934), omental or pectoral grafts (O'Shaunessy, Beck, 1930s), internal mammary implants tunneled directly into the heart muscle (Vineberg, 1950), and coronary endarterectomy (Bailey, Long-mire, 1956) were touted but provided inconsistent clinical benefit. Vaselii Kolesov, in Russia, pioneered internal mammary to coronary artery bypass grafts beginning in 1964 and, in 1962, David Sabiston performed a coronary bypass using a patient's leg vein but the patient died following the operation. René Favaloro, an Argentine cardiac surgeon working at the Cleveland Clinic, is usually credited for successfully ushering in the era of coronary bypass surgery (1968).[114,115] Coronary artery bypass graft surgery remains one of the mainstays in the treatment of advanced coronary artery disease and one of the most frequently performed surgical operations. Widespread use of arterial conduits as bypass grafts has improved both the long-term patency of grafts as well as the survival benefit of the operation.[116]

Aortic surgery, initially dealing with late-stage complications, advanced from the ligation of aortic aneurysms to wrapping the aorta with various materials and finally to resection. Attempted surgical repair of aortic dissection dates from 1935, but operative success was not achieved until 1954 when DeBakey, Cooley, and Creech reestablished aortic continuity. Vascular reconstruction and endarterectomy, insertion of prosthetic grafts, percutaneous insertion of endovascular grafts for aneurysms and dissection (1991), and stenting of carotid artery stenosis (1997) have transformed the management of vascular disease.

Mortality rates from all cardiac surgery have progressively fallen while surgeons have offered increasingly complex surgeries to an older population with increasing numbers of cardiac and noncardiac comorbidities. Cardiac transplantation has become common and the use of LVADs as destination therapy is increasing, but attempts to manufacture an artificial heart have been disappointing. Off-pump and robotic-assisted surgery are routine in many centers although some uncertainties remain in establishing their incremental benefit over other standard techniques. Increasingly, surgeons and interventional specialists are collaborating in offering hybrid procedures and advanced endovascular care that require the skills and expertise of both groups of providers.

CARDIOVASCULAR CARE IN THE 21ST CENTURY

Although clinical outcomes among patients with a variety of cardiac diseases have improved over recent decades, the incidence of diseases such as heart failure and ischemic heart disease continues to increase as the population ages. Additionally, as the globe grows increasingly smaller and previously rural populations are exposed to modern Western diets and habits such as tobacco use, there has been an explosion of atherosclerotic disease around the world, including in countries with emerging economies.[117,118] The global epidemics of obesity, diabetes, and cardiovascular disease require global collaborations addressing prevention, detection, and treatment of cardiac disease (http://www.world-heart-federation.org).

The practice of cardiovascular medicine has evolved as well from one centered on observation and treatment based on empiricism to one reliant on science, guidelines, and the delivery of measurable quality care.[119] The challenge of the next decade will be to establish which therapies truly work best for which patients,[120] to move toward the goal of precision health/medicine,[121] and to advocate for the successful delivery of those therapies to patients with cardiovascular disease.

Imaging technologies will continue to improve in their technical sophistication, but societal cost demands will place the burden for establishing their incremental benefit back on the cardiovascular community, which must be poised to both understand and participate in the required research that demonstrates the added/incremental value. Endovascular and surgical techniques will evolve and encourage greater collaboration among sub-subspecialists to offer state-of-the-art vascular care to an increasingly older population afflicted with multiple cardiac and noncardiac comorbid conditions. Concepts related to multidisciplinary care teams will become increasingly important as care becomes increasingly complex, requiring the expertise and talents of diverse groups of professionals. Notions of patient-centric care and engagement of patients in collaborative decision making with clinical providers around their care will be central to cardiovascular practice and research. Measuring and reporting patient outcomes will be critical in advancing cardiovascular care, and demonstrating quality and value will be critical in a health care system increasingly pressured to reduce costs while raising quality.[122]

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CHAPTER 2

THE GLOBAL BURDEN OF CARDIOVASCULAR DISEASES

Catherine P. Benziger, Andrew E. Moran, and Gregory A. Roth

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CARDIOVASCULAR DISEASES IN THE CONTEXT OF GLOBAL HEALTH

Cardiovascular diseases (CVDs) are the most common cause of premature death in the world. Although there has been a steady decrease in mortality rates for CVDs beginning in the last third of the 20th century for high-income countries, many low- and middle-income countries (LMICs) have not benefited from this favorable trend. As a result, in 2013 more than 17 million people died from CVDs, and as a result of the large populations in many LMICs, nearly 70% of CVD deaths occurred in LMICs and 50% were in women. CVDs account for 50% of all noncommunicable disease (NCD) deaths in the world each year and represent a significant threat to human welfare and sustainable development. CVDs are the leading cause of death in every region of the world, with the exceptions of sub-Saharan Africa—where infectious diseases are still the leading cause of death—and South Korea and Japan, where cancers cause more deaths.

Despite this profound health burden, CVD has until recently been left out of the global health agenda by governments, development aid agencies, and foundations. Development aid for health for all NCDs taken together was no more than 2% of all aid funds delivered in 2014.[1] Recently, there has been an increased global focus on NCD prevention and control. An international effort to address the burden of CVD was proposed at the 66th World Health Assembly and was endorsed by the World Health Organization (WHO). The WHO Global Action Plan for the Prevention and Control of NCDs (2013-2020) (resolution WHA66.10) stands as the first coordinated global effort toward the reduction of NCDs, including CVDs, cancer, chronic lung disease, and diabetes mellitus. The Global Action Plan is a paradigm shift for global health efforts, bringing broad attention to NCDs while simultaneously providing policy options for WHO member states. Member states have now agreed to meet nine NCD health and policy targets by 2025. These targets include a reduction in premature mortality from each NCD by 25% by 2025 as well as implementation of a monitoring framework with 25 indicators to track mortality and morbidity, assess progress in addressing risk factors, and evaluate the implementation of nation strategies and plans.[2]

This chapter is an introduction to the global burden of CVDs, aimed at health care providers and students, public health researchers, epidemiologists, and policymakers seeking to better understand this field. This overview emphasizes cause-specific and region-specific trends and associated risk factors as estimated for the Global Burden of Disease (GBD) study.[3] GBD is an ongoing effort to compile, catalog, and integrate all available information for over a thousand disease states. GBD is a consortium of more than 1500 researchers in 120 countries working to produce annual estimates and collaborating with governments to implement evidence-based policies to improve health.

We provide an overview of trends in CVD starting with its two largest components, ischemic heart disease (IHD) and cerebrovascular disease. Next, geographic patterns in CVD are considered. Although not the primary focus of this chapter, risk factors for CVD are also considered at a broad level, including not only traditional cardiometabolic risks but also emerging related risks, including mental illnesses, air pollution, and human immunodeficiency virus (HIV). From this same broad perspective, we briefly review general principles of prevention and health care delivery in the context of global efforts to coordinate the care of CVD. In this light, we also consider efforts to forecast the global burden of CVDs into the future. A summary of GBD methods, including data sources and case definitions relevant to CVD, are provided at the chapter's end.

AN OVERVIEW OF GLOBAL HEALTH IN 2013

Human health has improved significantly over the past two decades, with a steady decline in age-standardized rates of disability-adjusted life-years (DALYs) globally.[4] The DALY is a core summary measure of health that represents the gap between a population's actual health and an ideal standard (GBD methods are summarized at the end of this chapter). Between 1990 and 2013, the number of global DALYs decreased from 2.54 billion [95% uncertainty interval (UI), 2.40-2.70 billion] to 2.45 billion (2.23-2.68 billion) (Fig. 2–1). There were large increases in disease burden for HIV and malaria, with smaller increases for road injuries and a wide range of NCDs, including low back and neck pain, IHD, diabetes, chronic obstructive pulmonary disease (COPD),

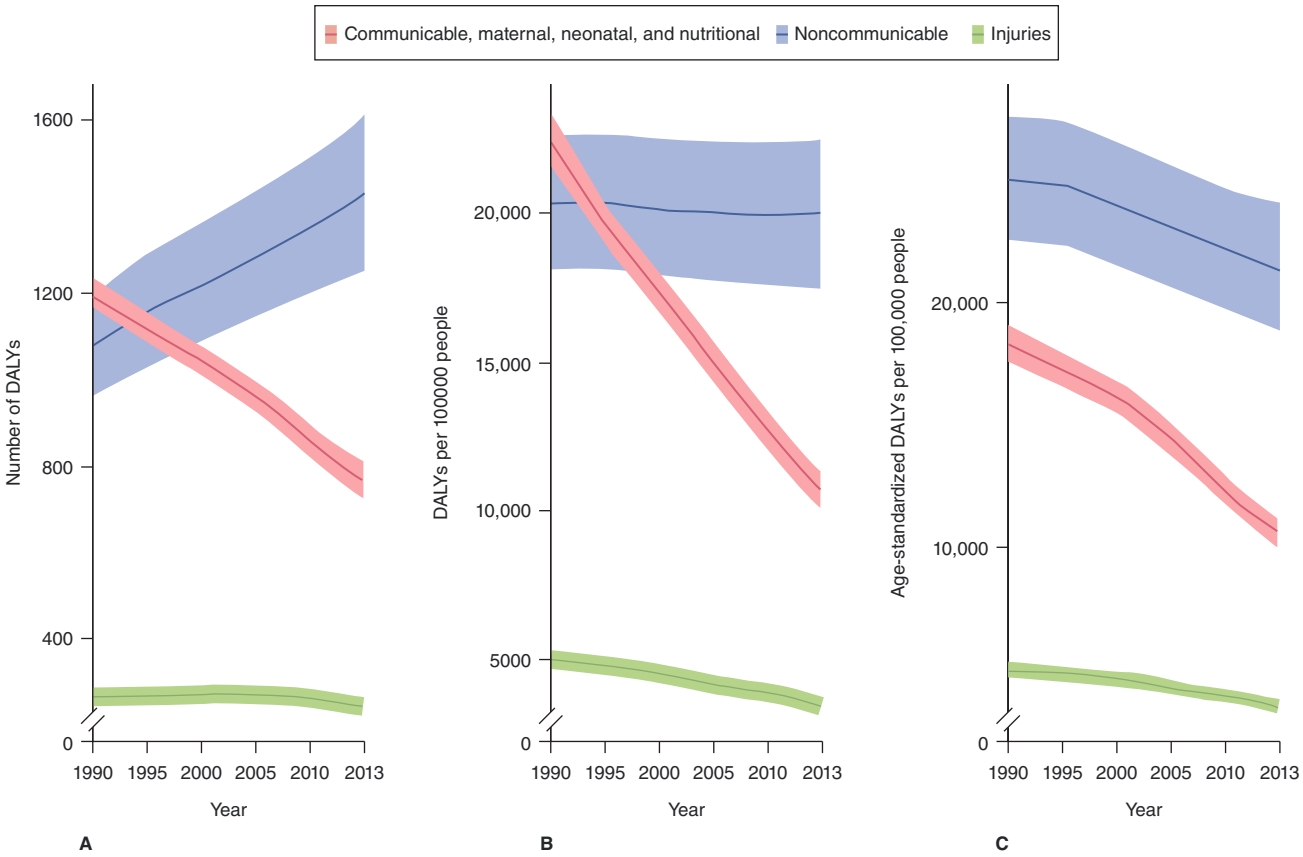

FIGURE 2–1. Total disability-adjusted life-years (DALYs), crude DALY rates, and age-standardized DALY rates from 1990 to 2013. Changes in global DALYs caused by communicable, maternal, neonatal, and nutritional disorders, noncommunicable diseases, and injuries shown in terms of numbers of DALYs (**A**), DALY rates per 100,000 people (**B**), and age-standardized DALY rates per 100,000 people (**C**). The difference in trends between **A** and **B** is caused by population growth and the difference between **B** and **C** because of changes in the percentage distribution of the population by age. Shaded areas show 95% uncertainty intervals. Reproduced with permission from GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al: Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition, *Lancet*. 2015 Nov 28;386(10009):2145-2191.[71]

depression, stroke, and sense organ disorders (Fig. 2–2). Most DALY increases from 1990-2013 were caused by aging of the population and population growth.[3]

The 20-year trends in age-standardized DALY rates for leading categories of disease are shown in Fig. 2–3. There were significant reductions in certain infectious diseases, such as measles, meningitis, and tuberculosis; however, the disease burden from HIV and malaria substantially increased. Overall, the age-standardized DALY rates for IHD, lower respiratory infections, and cerebrovascular disease declined, although not sufficiently for these conditions to be replaced as the leading causes of disease burden worldwide. The ranks of low back and neck pain, road injuries, and COPD have all increased. However, the overall age-standardized rates decreased significantly for 16 of the 25 leading causes of DALYs in 2013.[3]

GLOBAL PATTERNS IN CARDIOVASCULAR DISEASE MORTALITY

CVD was the primary cause of 17 million deaths in 2013, with an estimated US $863 billion in direct health care costs and productivity losses worldwide.[5]

Table 2–1 shows the total estimated CVD-related deaths for each cause in 2013. The leading cause of CVD-related death was IHD, accounting for more than eight million deaths (95% UI, 7,322,942-8,758,490), followed by ischemic and hemorrhagic strokes, with more than three million deaths each (95% UI, 2,812,654-3,592,562 for ischemic stroke and 95% UI, 2,885,717-3,719,684 for hemorrhagic stroke). Rheumatic heart disease (RHD), although not the leading cause of death, was a significant contributor to the global burden and a leading cause of highly preventable death with approximately 275,000 deaths in 2013 (95% UI, 222,622-353,938) (see Table 2–1). The age-standardized death rates are shown by country on the map in Fig. 2–4. Globally, the death rate as a result of CVD was 376 per 100,000 (95% UI, 361-389) in 1990 and fell to 293 per 100,000 (95% UI, 280-306) by 2013, a 22% reduction.[6] However, there are regional variations with the highest CVD mortality rates in Central Asia and Eastern Europe and the lowest rates in the high-income countries. In addition, males have higher age-standardized death rates than females (Fig. 2–5). Despite the steady decrease in death rate for both sexes over the past 20 years, the total number of deaths is increasing as a result of population growth and aging, which disproportionately affects LMICs (Fig. 2–6). Globally, the total number of CVD deaths increased from 12.3 million (95% UI, 11.8-12.8) to 17.3 million (95% UI, 16.5-18.1), a 41% increase between 1990 and 2013.[6]

Figure 2–7 shows the percentage of deaths as a result of CVD in 1990 and 2013 by sex. The high-income countries saw a significant (43%) decline in the age-standardized death rate for males and females. However, the number of CVD-related deaths did not change significantly (3.14 million; 95% UI, 2.97-3.23 in 1990 to 3.12 million; 95% UI, 3.00-3.44 in 2013).[6] There is an increased proportion of deaths caused by CVD in LMICs (see Fig. 2–7). Therefore, the burden of CVD deaths has shifted and is disproportionately affecting those in LMICs where

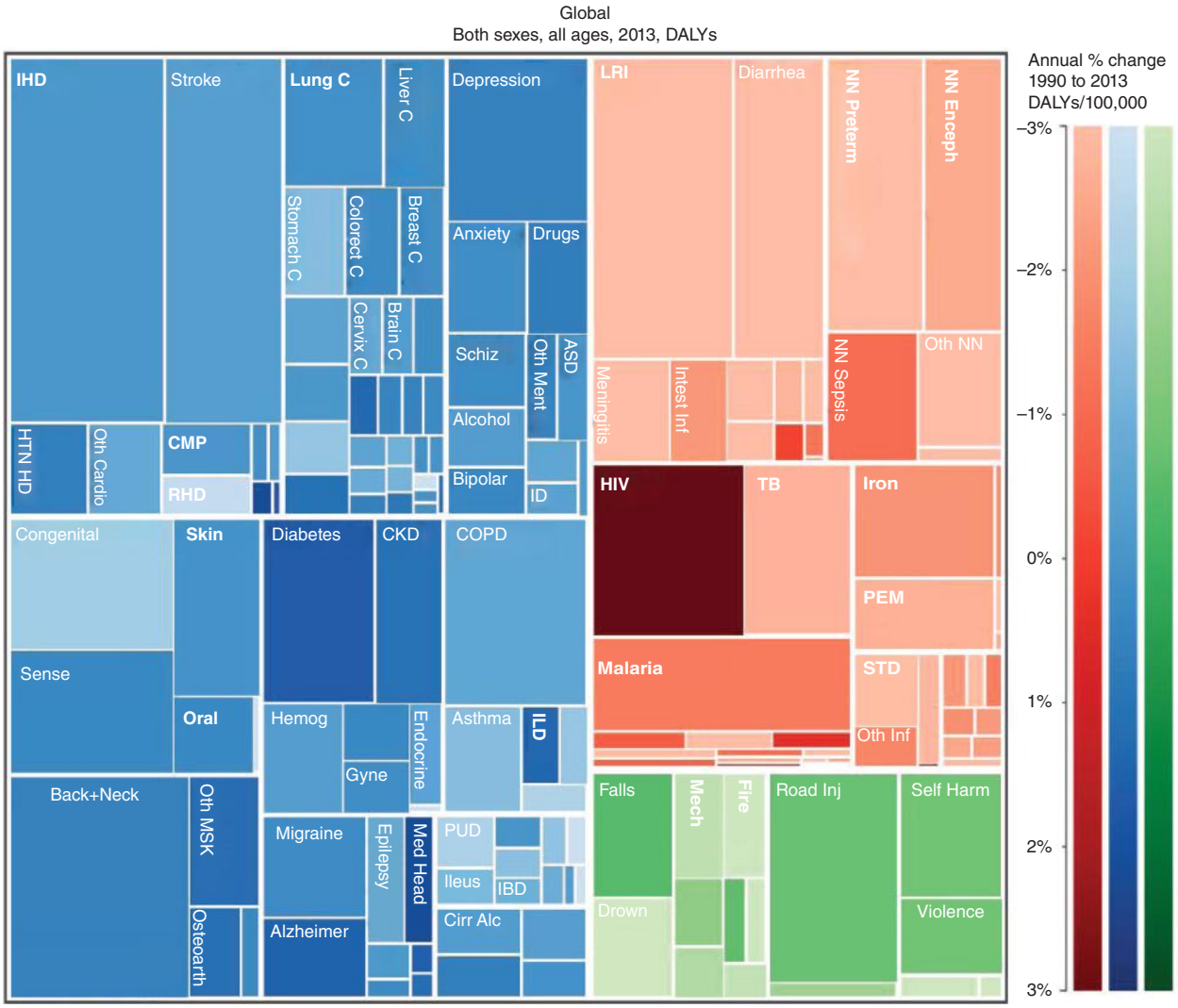

FIGURE 2–2. Global disability-adjusted life-years (DALYs) for Global Burden of Disease level three causes from 2013. Within this tree map, the size of the rectangle for each cause is proportional to the magnitude of the DALYs for each cause. Dark shading shows statistically significant changes and light shading shows changes that are not significant. Alcohol, alcohol use disorders; Alzheimer, Alzheimer disease and other dementias; Anxiety, anxiety disorders; Back and neck, low back and neck pain; Breast C, breast cancer; Bipolar, bipolar disorder; Cirr Alc, cirrhosis caused by alcohol use; Cirr Hep C, cirrhosis caused by hepatitis C; CKD, chronic kidney disease; CMP, cardiomyopathy and myocarditis; Colorect C, colon and rectum cancer; Congenital, congenital anomalies; COPD, chronic obstructive pulmonary disease; Depression, depressive disorders; Diabetes, diabetes mellitus;. Diarrhea, diarrheal diseases; Disaster, exposure to forces of nature; Drugs, drug use disorders; Fire, fire, heat, and hot substances; Hemog, hemoglobinopathies and hemolytic anemias; HTN HD, hypertensive heart disease; IHD, ischemic heart disease; ILD, interstitial lung disease and pulmonary sarcoidosis; Iron, iron-deficiency anemia; Liver C, liver cancer; LRI, lower respiratory infections; Lung C, tracheal, bronchus, and lung cancer; Mech, exposure to mechanical forces; Nematode, intestinal nematode infections; NN Enceph, neonatal encephalopathy caused by birth asphyxia and trauma; NN hemol, hemolytic disease and other neonatal jaundice; NN preterm, preterm birth complications; NN sepsis, neonatal sepsis and other neonatal infections; Oral, oral disorders; Oth MSK, other musculoskeletal disorders; Oth NN, other neonatal disorders; PEM, protein-energy malnutrition; RHD, rheumatic heart disease; Road Inj, road injuries; Sense, sense organ diseases; Skin, skin and subcutaneous diseases; STD, sexually transmitted diseases excluding HIV; Stroke, cerebrovascular disease; TB, tuberculosis; Violence, interpersonal violence; War, collective violence and legal intervention; Whooping, whooping cough; ASD, atrial septal defect; Oth Ment, other mental health disorders; Schiz, schizophrenia; C, cancer; Oth Cardio, other cardiovascular; ID, idiopathic developmental intellectual disability; Gyne, gynecological diseases; PUD, peptic ulcer disease; IBD, inflammatory bowel disease; Intest Inf, intestinal infections; HIV, human immunodeficiency virus; Drown, drownings. Reproduced with permission from GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al: Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition, *Lancet*. 2015 Nov 28;386(10009):2145-2191.[71]

there are complex interactions between environmental exposures, demographic changes, cardiometabolic risk factors, and access to quality health care.[7] In high-income countries, population-level changes in risk factor prevalence and improvements in health care were large contributors to the decreased CVD death rates; whereas, in LMICs there has been significant population growth, as well as aging populations.[6]

Although most countries have seen an increased national income per capita over this time, the decrease in the number of CVD deaths cannot be entirely explained by economic growth. Figure 2–8 shows the complex relationship between national income and CVD mortality in different countries. Every country is represented by a blue diamond, which indicates the country's percentage change in the number of CVD deaths as a result of change in the age-, sex-, and cause-specific CVD death rate alone, separate from the effect of population growth and aging, and the change in gross domestic product (GDP) per capita (in international dollars) between 1990 and 2013. The countries are shown separately by the four World Bank groups (high-income, upper-middle income, lower-middle income, and low-income); the decline in age-specific CVD mortality does not correlate well with increases in country income (GDP), except weakly in upper-middle income countries. Therefore, it appears unlikely that economic growth alone will improve a country's burden of CVD.

TABLE 2–1. Total Estimated Cardiovascular Disease–Related Deaths for Each Cause in 2013

Cause	Deaths in 2013	95% Uncertainty Interval
Ischemic heart disease	8,139,852	(7,322,942-8,758,490)
Ischemic stroke	3,272,924	(2,812,654-3,592,562)
Hemorrhagic and other nonischemic stroke	3,173,951	(2 885 717-3,719,684)
Hypertensive heart disease	1,068,585	(849,758-1,242,160)
Other cardiovascular and circulatory diseases	554,588	(499,143-654,152)
Cardiomyopathy and myocarditis	443,297	(370,111-511,997)
Rheumatic heart disease	275,054	(222,622-353,938)
Aortic aneurysm	151,493	(124,201-179,954)
Atrial fibrillation and flutter	112,209	(97,716-126,677)
Endocarditis	65,036	(48,593-79,435)
Peripheral vascular disease	40,492	(35,487-44,883)

Reproduced with permission from Roth GA, Huffman MD2, Moran AE, et al: Global and regional patterns in cardiovascular mortality from 1990 to 2013, *Circulation*. 2015 Oct 27;132(17):1667-1678.[6]

THE IMPACT OF POPULATION GROWTH AND AGING ON CARDIOVASCULAR DISEASE

Despite an overall decrease in the global age-specific CVD death rate, a continued increase in the number of CVD deaths is expected as a result of demographic changes. The United Nations estimated that the global population in 2015 was 7.3 billion and will increase to a total of 8.5 billion by 2025 and 9.7 billion by 2050. When population growth slows down as a result of a reduction in fertility, the population ages and the proportion of older persons aged 60 or older increases over time. In 2015, about 10% of the population was aged 60 or older, and the number of adults in this age group is projected to more than double by 2050 and more than triple by 2100, with more than two-thirds of these older adults residing in LMICs.

There are regional variations in the contribution of population growth and population aging to trends in the burden of CVD. Demographic changes over the past two decades can be classified into one of six general categories, shown in Table 2–2. Categories 1, 2, and 3 represent regions in which population aging and population growth served to drive relative increases in the number of CVD-related deaths. Categories 4, 5, and 6 represent regions in which gains in cardiovascular health, represented by declines in the age-specific CVD-related death rate, appear to have partially or completely negated the increase

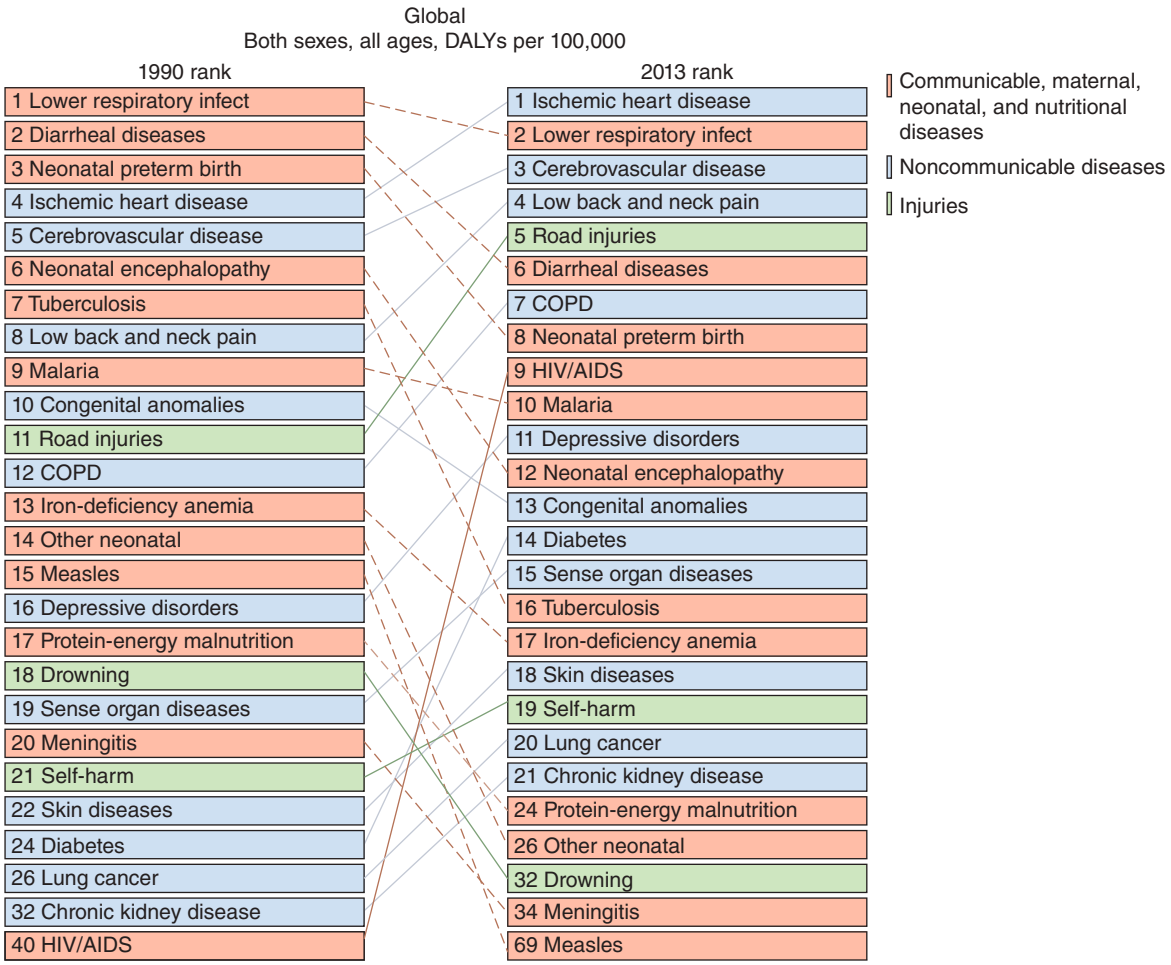

FIGURE 2–3. Twenty-three most common Global Burden of Disease (GBD) level three causes of global disability-adjusted life-years (DALYs) for both sexes combined, 1990 and 2013. Ranks are based on the number of DALYs. Communicable, maternal, neonatal, and nutritional disorders causes are shown in red, noncommunicable causes in blue, and injuries in green. COPD, chronic obstructive pulmonary disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome. Adapted with permission from GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al: Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition, *Lancet*. 2015 Nov 28;386(10009):2145-2191.[71]

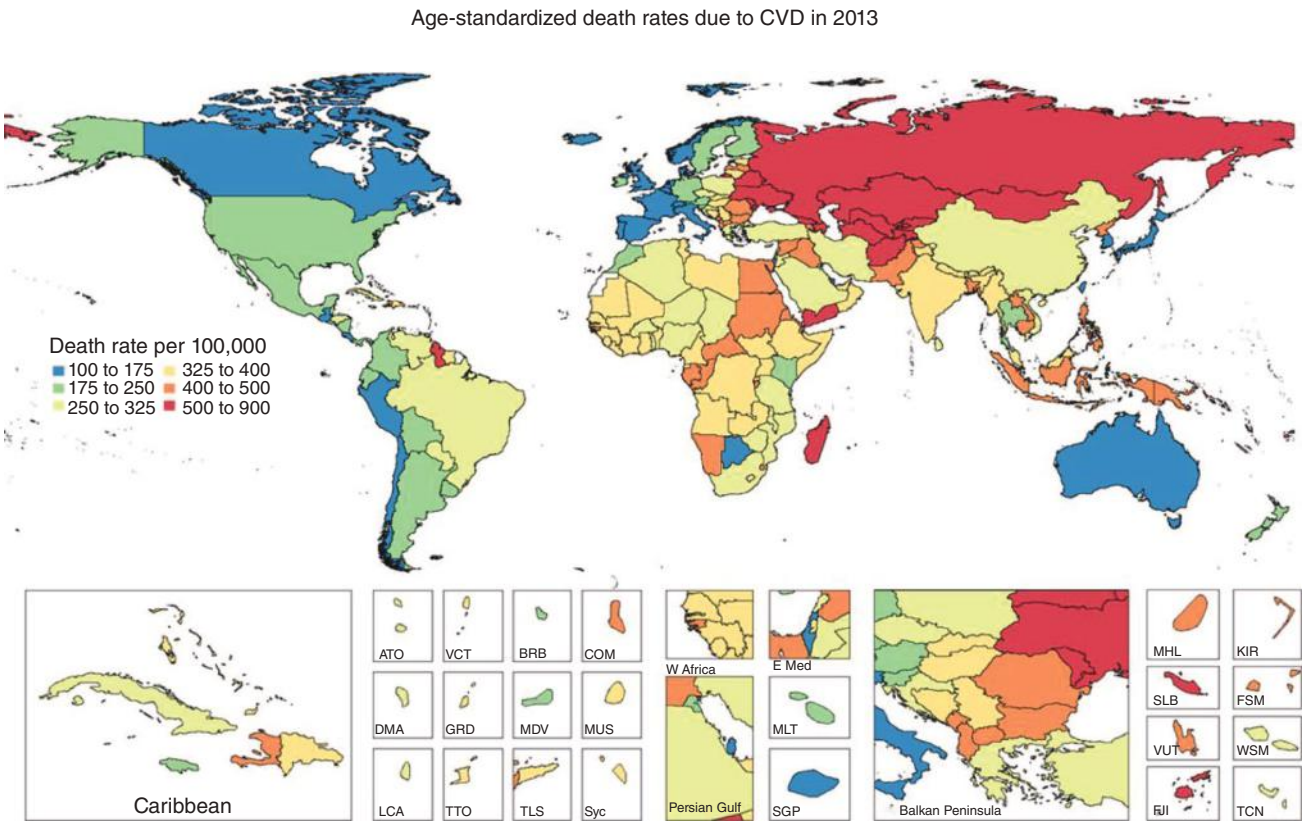

FIGURE 2–4. Map of age-standardized death rates attributable to cardiovascular disease (CVD), 2013. Countries in blue and green have the lowest death rates, whereas those in orange and red have the highest. Reproduced with permission from Roth GA, Huffman MD2, Moran AE, et al: Global and regional patterns in cardiovascular mortality from 1990 to 2013, *Circulation*. 2015 Oct 27;132(17):1667-1678.[6]

in CVD-related deaths caused by population growth and aging. The joint effects of population growth, population aging, and age-specific CVD death rate and CVD mortality are also illustrated in Fig. 2–9. There is substantial variation in each geographical region, with only Central and Western Europe showing substantial decreases in CVD deaths caused by improvements in cardiovascular health (see Fig. 2–9).[8] Some regions, such as southern Latin America, Australasia, and high-income North America had no detectable change in the number of deaths because demographic changes balanced out declines in age-specific death rates. Only one region, western sub-Saharan Africa, had an increase in cardiovascular deaths due largely to epidemiologic changes. The high-income Asia-Pacific region has had a rapidly aging population, but the increase in cardiovascular mortality was offset by a significant decline in age-specific cardiovascular death rates since 1990. South Asia showed a worrisome pattern, with a dramatic rise in CVD deaths without a significant decline in deaths caused by epidemiologic

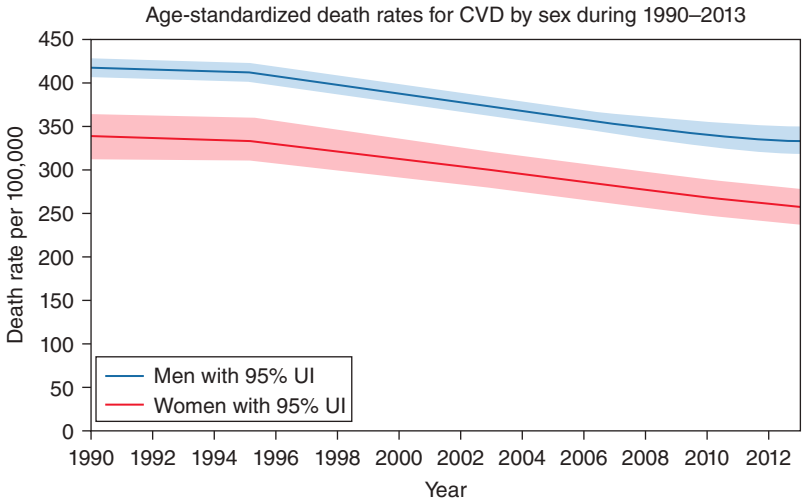

FIGURE 2–5. Age-standardized death rates for cardiovascular disease (CVD) stratified by sex, 1990 to 2013. UI, uncertainty interval. Reproduced with permission from Roth GA, Huffman MD2, Moran AE, et al: Global and regional patterns in cardiovascular mortality from 1990 to 2013, *Circulation*. 2015 Oct 27;132(17):1667-1678.[6]

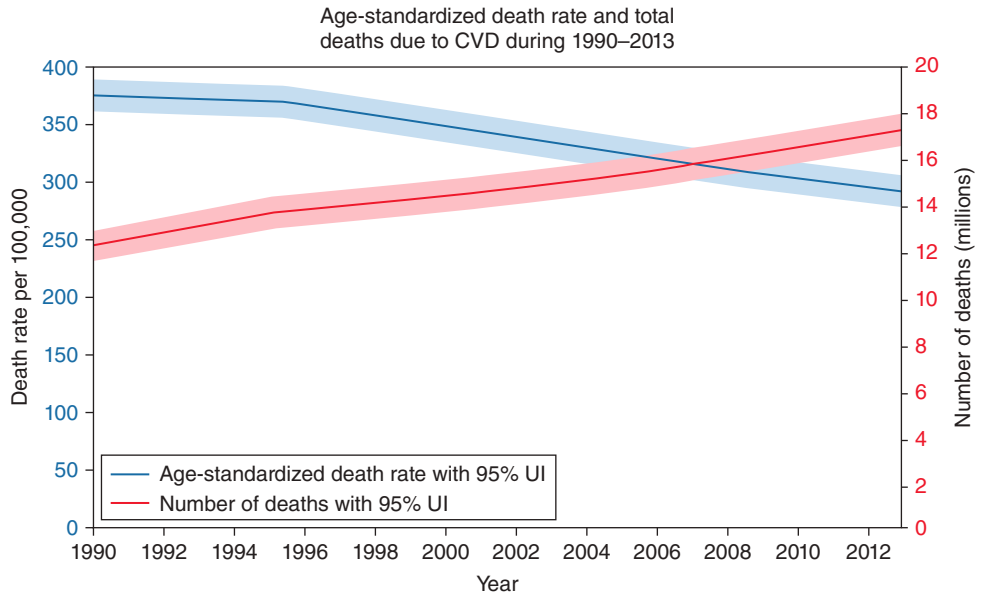

FIGURE 2–6. Change in age-standardized cardiovascular disease (CVD) death rate and total number of CVD deaths, 1990 to 2013. UI indicates uncertainty interval. Reproduced with permission from Roth GA, Huffman MD2, Moran AE, et al: Global and regional patterns in cardiovascular mortality from 1990 to 2013, *Circulation*. 2015 Oct 27;132(17):1667-1678.[6]

changes. North Africa and the Middle East offset a similar trend in population growth and aging with a significant reduction in age-specific death rates.[8]

ISCHEMIC HEART DISEASE

IHD is the leading cause of death worldwide. IHD encompasses myocardial infarction and all other acute coronary syndromes as well as long-term sequelae of coronary heart disease, including angina pectoris and ischemic cardiomyopathy, as well as surgical or percutaneous revascularization and the need for chronic medical therapy when available. Measuring the global burden of IHD is difficult given the challenge of collecting information not only on acute events but also chronic disease that may often go undiagnosed.

Efforts to track international patterns of IHD epidemiology began with the Seven Countries Study starting in the late 1950s and the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) studies starting in the 1980s.[9,10] It is difficult to accurately measure IHD prevalence.[11] Efforts to apply standard provocative diagnostic testing, such as exercise treadmill tests, in population-based surveys have been uncommon and have rarely been repeated since the heyday of cardiovascular epidemiology in the late 1970s. Furthermore, nonfatal IHD incidence and prevalence do not always correlate with IHD mortality. For example, one population may have improved acute and chronic IHD treatments, which may lead to

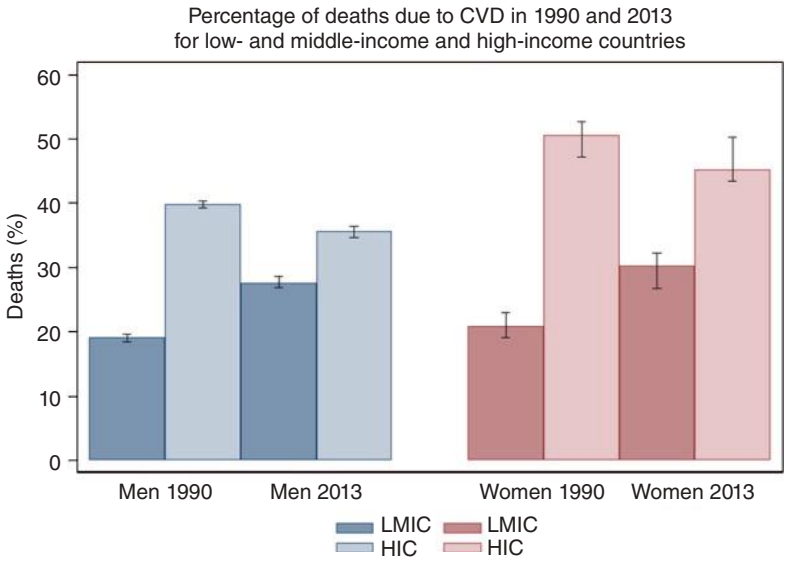

FIGURE 2–7. Proportion of total deaths attributable to cardiovascular disease (CVD) in high-income countries versus low- and middle-income countries (LMICs) stratified by sex, 1990 to 2013. Reproduced with permission from Roth GA, Huffman MD2, Moran AE, et al: Global and regional patterns in cardiovascular mortality from 1990 to 2013, *Circulation*. 2015 Oct 27;132(17):1667-1678.[6]

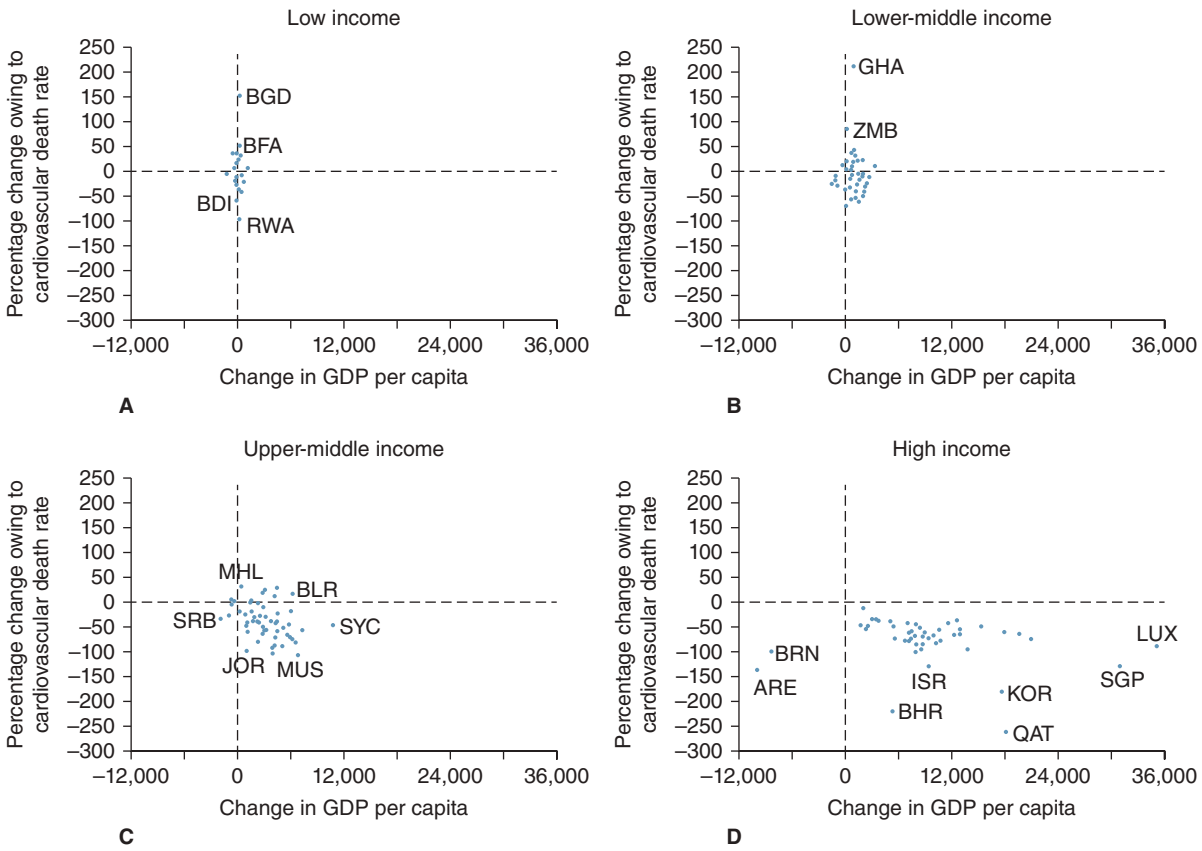

FIGURE 2–8. Percentage change in the cardiovascular death rate owing to changes in age-, sex-, and cause-specific death rates, according to change in country income level per capita, 1990-2013. Pearson's correlation coefficients for the four levels of income were as follows: low income, r = 0.20, *P* = .24; lower-middle income, r = –0.08, *P* = .60; upper-middle income, r = –0.33, *P* = .02; and high income, r = –0.19, *P* = .18. Spearman's rho coefficients were as follows: low income, r = 0.16, *P* = .37; lower-middle income, r = –0.14, *P* = .35; upper-middle income, r = –0.37, *P* = .006; and high-income, r = –0.27, *P* = .05). Every country included in the study is represented by a blue diamond, which indicates the country's percentage change in the number of cardiovascular deaths as a result of change in the age-, sex-, and cause-specific cardiovascular death rate alone, separate from the effect of population growth and aging, and the change in gross domestic product (GDP) per capita (in international dollars) between 1990 and 2013. Outlier countries identified by their International Organization for Standards (ISO) country code. ARE, United Arab Emirates; BDI, Burundi; BFA, Burkina Faso; BGD, Bangladesh; BHR, Bahrain; BLR, Belarus; BRN, Brunei; GHA, Ghana; ISR, Israel; JOR, Jordan; KOR, South Korea; LUX, Luxembourg; MHL, Marshall Island;, MUS, Mauritius; QAT, Qatar; RWA, Rwanda; SGP, Singapore; SRB, Serbia; SY,C Seychelle;, and ZMB, Zambia. Reproduced with permission from Roth GA, Forouzanfar MH, Moran AE, et al: Demographic and epidemiologic drivers of global cardiovascular mortality, *N Engl J Med*. 2015 Apr 2;372(14):1333-1341.[8]

decreased IHD mortality with a growing population of chronic IHD survivors, whereas another population may have a high IHD incidence with a high case fatality rate that may lead to a relatively low prevalence. Furthermore, stable angina prevalence is based on self-reported symptoms and does not necessarily correlate directly with acute coronary syndrome event incidence: in fact, in many surveys stable angina prevalence is higher in women, despite the higher acute IHD event risk in men.[12] The global burden IHD (in DALYs) is dominated by life-years lost caused by its fatal component, whereas disability from nonfatal IHD, including acute nonfatal acute coronary syndromes, makes a smaller contribution.[13]

Globally, the age-standardized acute myocardial infarction incidence decreased in all ages from 1990 to 2010, from 222.7 to 195.3 in males and from 136.3 to 115.0 in females.[13] However, an IHD epidemic has emerged in certain regions. For example, in Eastern Europe, there was an increased IHD incidence (62 per 100,000 population in males and 17 in females), as well as increased IHD mortality between 1990 and the mid-2000s. This trend was correlated with changing sociopolitical circumstances after the breakup of the Soviet Union in the early 1990s.[13] The reason for this increased incidence is controversial but may be due in part to unhealthy patterns of alcohol consumption as peak death rates coincided with economic downturns and the largest fluctuations occurred in non–myocardial infarction portion of IHD deaths.[13-15] Eastern Europe and Central Asia experienced a combined 21 million years of life lost (YLLs) in 2010 because of IHD, second only to South Asia, despite having less than a fifth of South Asia's population (Table 2–3).

Since the 1990s, the high-income regions, specifically Australasia, Western Europe, and North America, have seen dramatic declines in the age-standardized IHD mortality[13] (Fig. 2–10). There has been a steady and continuous decline in the deaths attributable to IHD in both males and females (11% decline in males and 14% decline in females).[6] However, IHD mortality has increased in other regions, including Central Asia, South Asia, and East Asia, leading to an increased burden of disease in these areas. The large population in these regions and relatively young age at IHD death leads to more life-years lost per fatal case and a higher DALY burden. Current estimates suggest nearly two-thirds of global IHD DALYs occurred in middle-income countries.[16] There is significant variation in age-standardized DALYs within regions, with the most variation in middle-income countries and lowest variation in high-income countries (Fig. 2–11). Although IHD burden falls largely on those aged older than 70 years in high-income regions, the age of IHD deaths is much younger in other regions, with a mean age of onset of IHD events

TABLE 2–2. Patterns of Demographic and Epidemiologic Change in Cardiovascular Mortality

Category	Change in Cardiovascular Deaths, 1990–2013	Effect of Population Growth	Effect of Population Aging	Effect of Age-Specific Cardiovascular Death Rate	Regions
Category 1—Population growth and aging: Regions with large and continuous increases in the number of cardiovascular deaths due to population growth or aging but little change in age-specific rates of death	Increase	Large (≥ 20%)	Large (> 30%)	Small (decline < 30%)	Oceania, South Asia, Southeast Asis, Caribbean
Category 2—Population growth: Regions with increases in deaths due mostly to population growth	Increase	Large (> 80%)	Small (< 10%)	Small (decline < 30%)	Central sub-Saharan Africa, Western sub-Saharan Africa, Eastern sub-Saharan Africa
Category 3—Population aging: Regions in which cardiovascular deaths rose and then fell during the preceding 20 years, resulting in a net increase in deaths due to population aging and only a small decrease in age-specific rates of cardiovascular death	Increase then decrease	Very small (< 20%)	Moderate (> 20%)	Very small (decline < 15%)	Eastern Europe, Central Asia
Category 4—Improved health moderating effect of population aging: Regions in which large increases in the number of cardiovascular deaths due to population aging were moderated by a fall in age-specific rates of death	Increase	Small (< 30%)	Very large (> 70%)	Large (decline > 30%)	High-income Asia-Pacific, East Asia
Category 5—Improved health moderating effect of population growth and aging: Regions with large relative increases in the number of cardiovasular deaths due to both population growth and aging that were moderated by a fall in age-specific rates of death	Increase	Large (> 30%)	Large(> 30%)	Large (decline > 30%)	Central Latin America, Tropical Latin America, Andean Latin America, Southern sub-Saharan Africa, North Africa and Middle East
Category 6—Improved health exceeding effect of population growth and aging: Regions in which large declines in age-specific cardiovascular death rates have led to only small increases or even a decline in the number of cardiovascular deaths despite the large effects of an aging population	Small increase or decrease	Small (< 40%)	Large (> 30%)	Large (decline > 30%)	Southern Latin America, Australasia, high-income North America, Central Europe, Western Europe

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before age 50 years in more than 29% of males and 24% of females in North Africa/Middle East and South Asia.[13,16] Also. although the age-standardized IHD DALYs have decreased in most countries, the DALYs for South Asia have increased.

As more patients with IHD survive their initial event, the IHD death rate and case fatality will no longer be the sole public health benchmark for success; improved symptom control and overall quality of life and access to adequate treatment will be important secondary outcomes.[13] The mainstays of treatment include standard, low-cost medications that are insufficiently used in LMICs. The Prospective Urban Rural Epidemiological (PURE) study found that only 11% of patients from high-income countries were not taking standard secondary prevention medications, whereas, 80% of low income region patients were taking none of the recommended medications.[17,18]

CEREBROVASCULAR DISEASE

Global stroke burden continues to rise with LMICs contributing 80% of incident cases, 75% of deaths, and 81% of stroke-related DALYs[19-21] (Fig. 2–12). Since 1990, there have been a significant increase in: (1) the absolute number of DALYs caused by ischemic stroke (IS), (2) deaths from IS and hemorrhagic stroke (HS), and therefore (3) survivors and incident events for both IS and HS.[22]

Overall, the age-standardized rates of stroke mortality have decreased worldwide in the past two decades. However, similar to IHD, the absolute number of people living with stroke is increasing. In 2013, there were an estimated 25.7 million stroke survivors (71% with IS), 6.5 million deaths from stroke (51% died from IS), 113 million DALYs caused by stroke (58% as a result of IS), and 10.3 million new strokes (67% IS).[19]

Figure 2–13 represents the incidence rates of HS and IS broken down into 5-year age bands for male and females in 1990 and 2013. Overall, incidence rate remained similar over the 20-year period for HS, whereas the global age-adjusted incidence of IS showed a downward trend in both males and females, but no significant change was detected as the UIs overlapped between 1990 and 2013. Stroke prevalence rates were significantly higher for males compared with females in both 1990 and 2013. The increase in number of prevalent cases of stroke between 1990 and 2013 despite significant declines in incident stroke are consistent with change caused by population growth, population aging and, for some regions, decreases in stroke-related mortality.[19] Therefore, there were no detectable change in age-standardized prevalence rates for IS from 1990 to 2013. In contrast

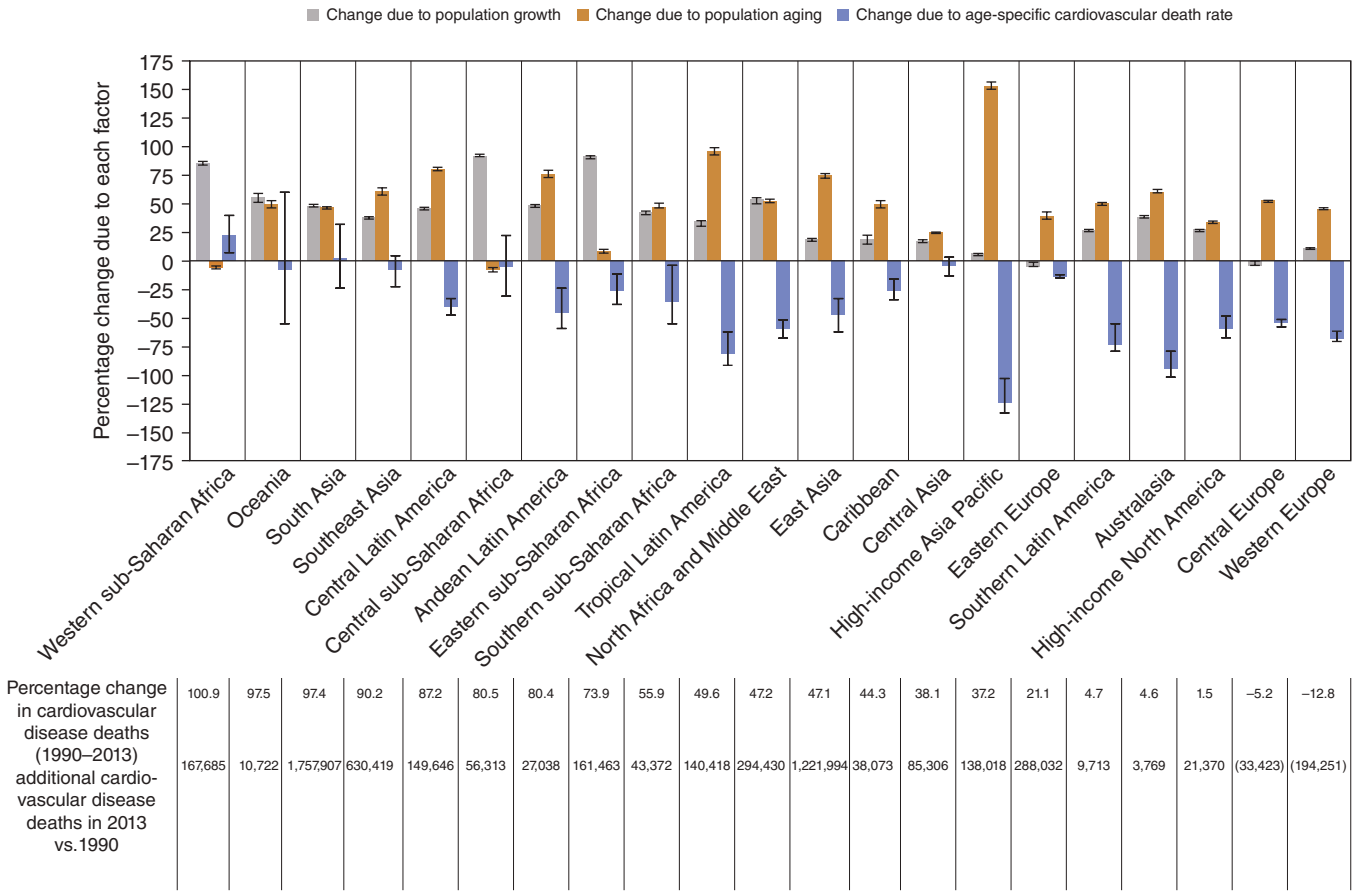


FIGURE 2–9. Contribution of changes in population growth, population aging, and rates of age-specific cardiovascular death to changes in cardiovascular mortality, 1990–2013. Reproduced with permission from Roth GA, Forouzanfar MH, Moran AE, et al: Demographic and epidemiologic drivers of global cardiovascular mortality, *N Engl J Med*. 2015 Apr 2;372(14):1333-1341.[8]

to IS rates, HS age-standardized prevalence rates increased over time for both sexes.[19]

As with IHD, there was significant regional variation in the age-adjusted incidence, prevalence, and mortality rates of IS and HS. The highest prevalence rate of IS (1,015-1,184 per 100,000) was found in developed countries (particularly in the United States), with the lowest (up to 339 per 100,000) in developing countries (Fig. 2–14). The highest IS mortality rates (124 to 174 per 100,000 person-years) were observed in Russia and Kazakhstan, with the lowest (at or below 25 per 100,000 person-years) were seen in Western Europe, North and Central America, Turkmenistan, and Papua New Guinea. Prevalence rates of HS were highest (232 to 270 per 100,000) in the United States, and lowest (up to 78 per 100,000) in Latin America, Africa, Middle East, France, Eastern Europe, the northern part of Asia, and Russia. HS mortality rates were highest (159 to 222 per 100,000 person-years) in Mongolia and Madagascar, and lowest (up to 32 per 100,000) in North America, most parts of Western Europe, Russia, Iran, Saudi Arabia, Morocco, Japan, Australia, and New Zealand.[19]

IS incidence and prevalence rates in developed countries were greater and demonstrated a steeper increase with age than that in developing countries at younger ages, whereas, IS mortality rates after the age of 49 years were greater in developing countries[19] (see Fig. 2–13). The age-related patterns of increase in IS mortality rates were similar in developed and developing countries. The prevalence rate of HS, age-specific incidence and mortality rates of HS were statistically significantly greater in developing countries in younger individuals, but there was no statistically significant difference in the age-specific prevalence rates between developed and developing countries after 54 years of age.[19]

Stroke was the second largest contributor to DALYs globally and in developing countries, whereas it was the third largest contributor to DALYs in developed countries (after IHD and lower back and neck pain), with significant regional variation in disease burden across both developed and low- to middle-income countries.[19] There is a diverging trend between developed and developing countries, with a significant increase in stroke DALYs and deaths in developing countries, and no measurable change in the proportional contribution of DALYs and deaths from stroke in developed countries.[23] Globally, the proportional contribution of stroke-related DALYs as a proportion of all diseases increased from 3.5% in 1990 (95% UI, 3.11-4.00) to 4.6% in 2013 (95% UI, 4.01-5.30). The deaths caused by stroke also increase from 9.7% (95% UI, 8.47-10.70) in 1990 to 11.8% (95% UI, 10.45-13.31) in 2013.

In order to reduce the rising burden of stroke worldwide, urgent prevention and management strategies are needed. Prevention of risk factors remains key to reversing the stroke pandemic, and universal access to organized stroke services needs remain a priority, especially in LMICs.[24]

ABDOMINAL AORTIC ANEURYSM

Abdominal aortic aneurysm (AAA) is a focal dilation of the abdominal aorta of at least 1.5 times the normal diameter or an absolute value of 3.0 cm or greater. Risk factors include male sex, smoking, hypertension, atherosclerosis, and history of AAA in a first-degree relative.

TABLE 2–3. Years of Life Lost Owing to Ischemic Heart Disease, Males and Females, by Region, 1990 and 2013 and the Global Burden of Disease 2013 Study

	1990			2013		
	Number of YLLs	Lower 95% UI	Upper 95% UI	Number of YLLs	Lower 95% UI	Upper 95% UI
East Asia	16,166,144	14,248,275	18,904,933	23,629,387	18,298,245	26,934,516
Southeast Asia	5,805,238	5,274,543	6,526,045	10,827,933	9,596,391	12,406,186
Oceania	185,287	136,184	250,987	348,936	242,094	491,527
Central Asia	2,495,327	2,368,524	2,679,165	3,495,234	3,213,832	3,835,862
Central Europe	5,845,148	5,247,710	6,152,958	4,074,461	3,841,321	4,606,280
Eastern Europe	13,065,024	12,300,526	14,074,284	15,178,798	13,891,655	16,138,753
High-income Asia Pacific	1,935,087	1,652,010	2,109,672	1,780,013	1,548,003	2,043,040
Australasia	600,920	541,126	625,033	410,254	375,590	490,311
Western Europe	13,331,625	12,218,994	13,963,439	8,221,819	7,698,246	9,440,252
Southern Latin America	1,268,638	1,095,141	1,333,533	973,942	881,170	1,222,578
High-income North America	9,729,367	9,010,538	10,127,612	8,037,462	7,358,600	9,130,906
Caribbean	774,870	696,534	835,048	985,975	896,085	1,121,045
Andean Latin America	340,283	312,790	392,878	581,499	510,293	672,751
Central Latin America	1,896,541	1,741,099	2,054,797	3,214,217	2,948,253	3,476,786
Tropical Latin America	2,910,943	2,458,855	3,088,411	3,408,651	3,076,118	4,008,804
North Africa and Middle East	7,052,299	6,224,946	7,601,207	9,447,151	8,689,317	10,319,117
South Asia	23,127,206	20,162,298	26,185,245	44,248,102	37,019,030	51,981,028
Central sub-Saharan Africa	401,360	330,621	478,251	766,522	633,592	917,756
Eastern sub-Saharan Africa	1,134,463	954,288	1,306,883	1,931,640	1,615,269	2,202,575
Southern sub-Saharan Africa	641,861	400,306	763,636	642,384	549,660	814,819
Western sub-Saharan Africa	1,080,427	950,254	1,321,934	2,230,063	1,940,036	2,764,299

Abbreviations: GBD, Global Burden of Disease; IHD, ischemic heart disease; UI, uncertainty interval; YLLs, years of life lost.

Reproduced with permission from Moran AE, Forouzanfar MH, Roth GA, et al: Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study, *Circulation*. 2014 Apr 8; 129(14):1483-1492.[89]

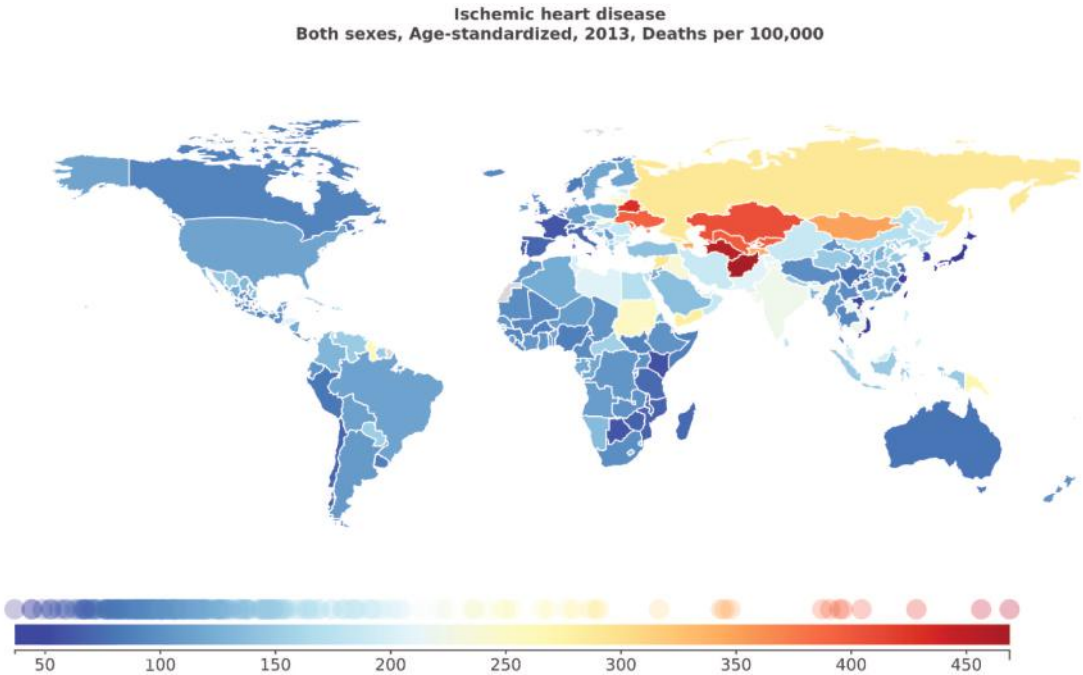


FIGURE 2–10. Map of age-standardized ischemic heart disease mortality rate per 100,000 persons in 21 world regions, 2013: the Global Burden of Disease 2013 Study. Reproduced with permission from Moran AE, Forouzanfar MH, Roth GA, et al: Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study, *Circulation*. 2014 Apr 8;129(14):1483-1492.[89]

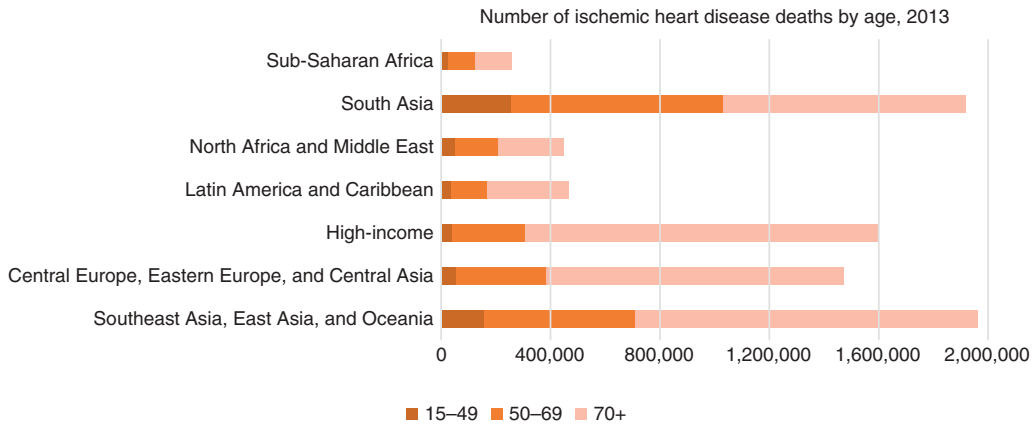


FIGURE 2–11. Age composition of absolute numbers of ischemic heart disease (IHD) disability-adjusted life-years (DALYs) in 2013, by super-region, the Global Burden of Diseases, Injuries, and Risk Factors 2013 study. From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington, 2015. Available from http://vizhub.healthdata.org/gbd-compare (Accessed February 2, 2016).

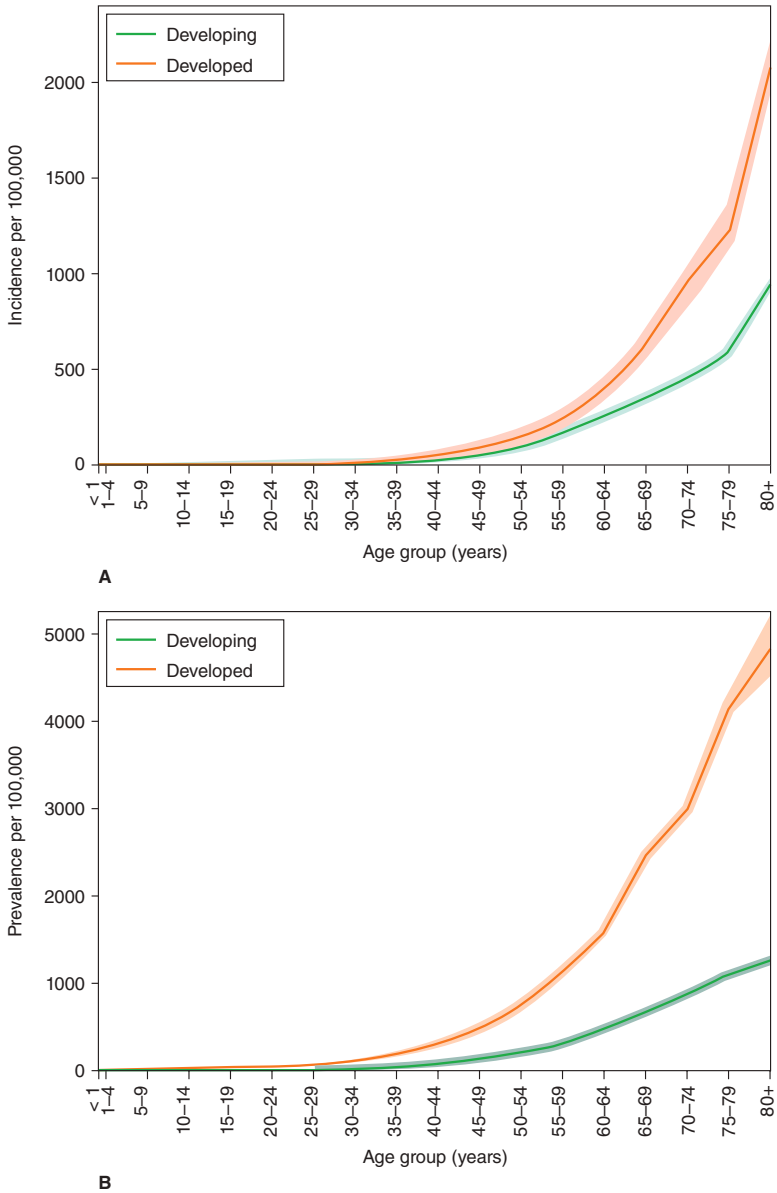


FIGURE 2–12. Age-specific incidence, prevalence and mortality rates of ischemic stroke (IS) per 100,000 people per year by country development status in 2013 (shadowed area around solid lines represents 95% uncertainty intervals [UIs]). IS incidence by age and development status. Reproduced with permission from Feigin VL, Krishnamurthi RV, Parmar P, et al: Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study, *Neuroepidemiology*. 2015;45(3):161-176.[93]

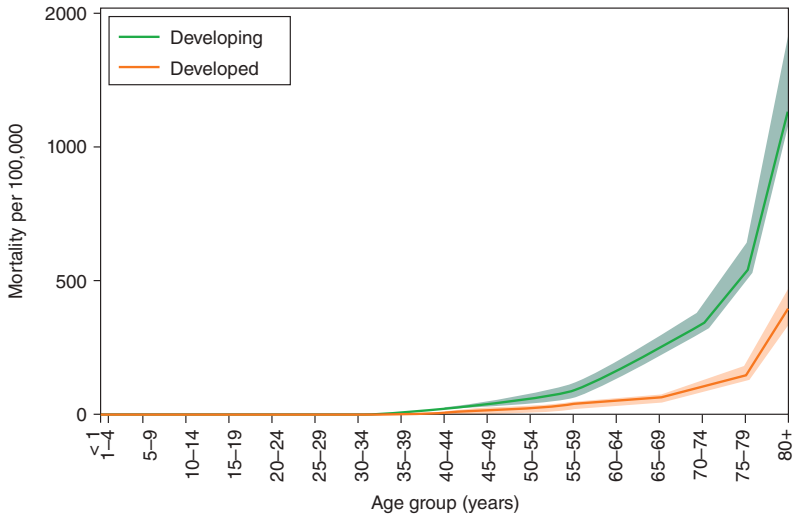


FIGURE 2–12. (*Continued*)

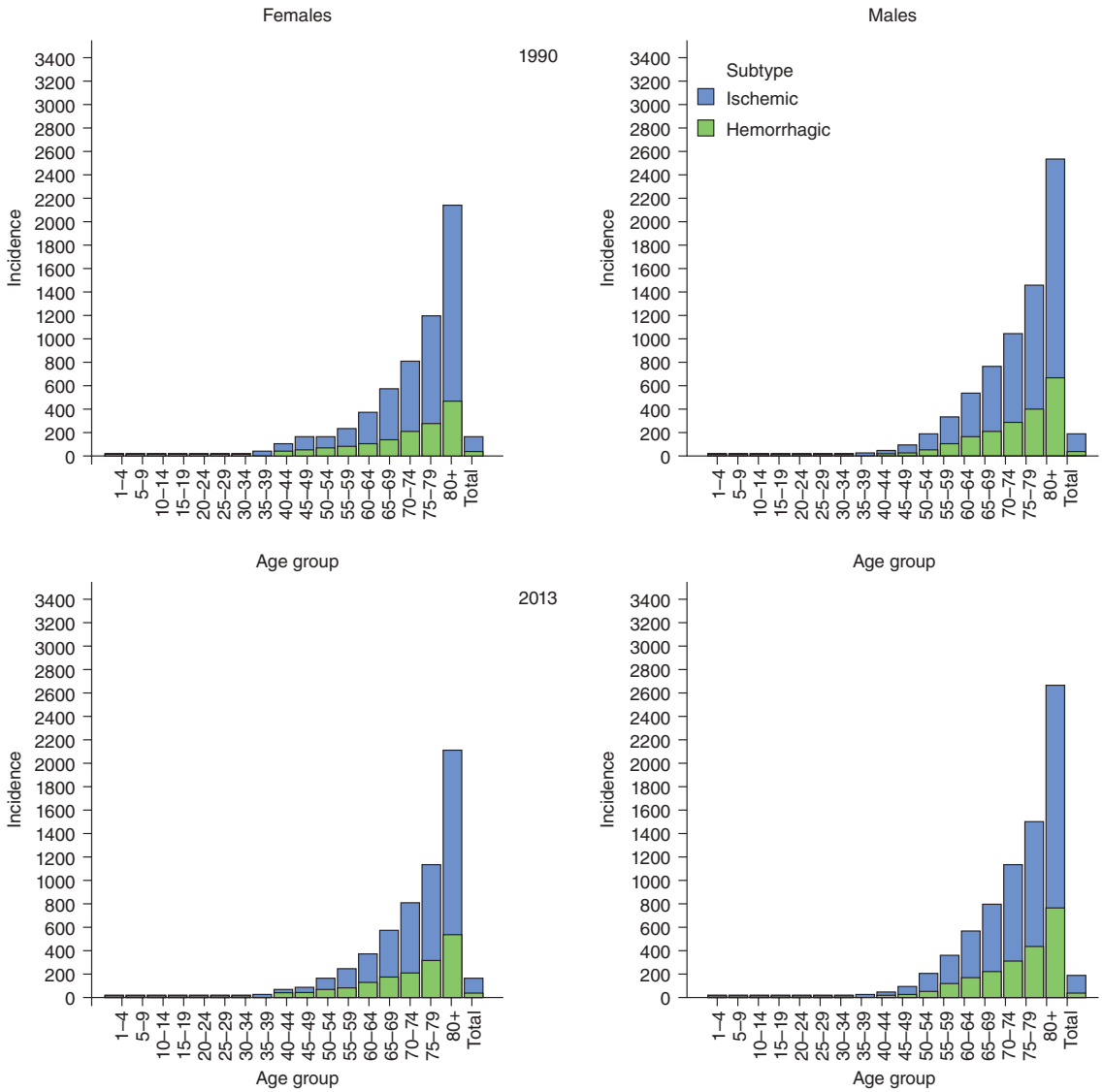


FIGURE 2–13. Incidence per 100,000 of ischemic stoke (IS) and hemorrhagic stroke (HS) in females and males by 5-year age bands in 1990-2013. Reproduced with permission from Barker-Collo S, Bennett DA, Krishnamurthi RV, et al: Sex Differences in Stroke Incidence, Prevalence, Mortality and Disability-Adjusted Life Years: Results from the Global Burden of Disease Study 2013, *Neuroepidemiology*. 2015;45(3):203-214.[19]

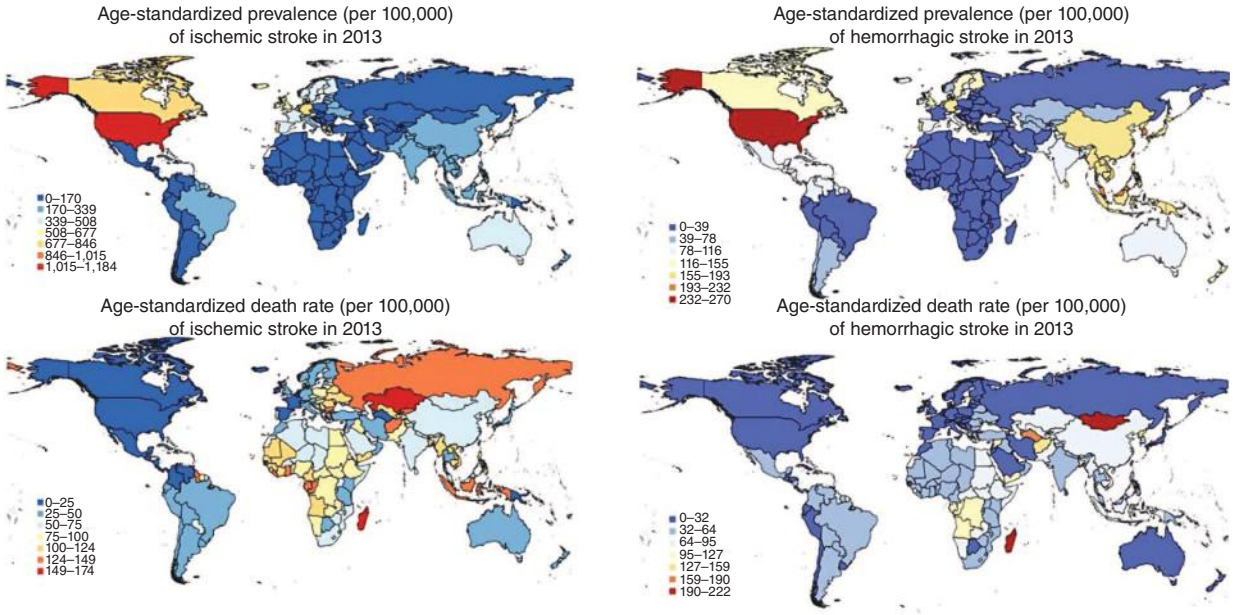


FIGURE 2–14. Age-standardized prevalence and mortality of ischemic stoke (IS) and hemorrhagic stroke (HS) per 100,000 person-years in various regions in 2013. Reproduced with permission from Feigin VL, Krishnamurthi RV, Parmar P, et al: Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study, *Neuroepidemiology*. 2015;45(3):161-176.[93]

Mortality is high for those previously undiagnosed, and up to 90% die if rupture occurs outside the hospital. The global age-specific prevalence and incidence rates increase with age, are higher in males than females, are higher in developed countries than developing countries, and were higher in 1990 than they are today.

In 2010, the age-specific prevalence rate per 100,000 ranged from 7.9 (95% confidence interval [CI], 6.54-9.59) to 2274 (95% CI, 2,149.77-2,410.17). Prevalence was higher in developed versus developing nations. The age-specific annual incidence rate per 100,000 also ranged between 0.83 (95% CI, 0.61-1.11) to 164.6 (95% CI, 152.20-178.78). The highest prevalence was in Australasia at 310.27 (95% CI, 289.01-332.94).[25] The global mortality rates associated have decreased consistently over the past 20 years, but significant regional variations are seen. The Asia-Pacific high-income countries had an increase in mortality, which was largely driven by rising rates in females.[25] Reducing the burden of AAA will require significant risk factor reduction, especially smoking, as well as improvements in the diagnosis, treatment, and overall disease surveillance.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is a circulatory problem in which narrowed arteries reduce blood flow to the limbs and causes symptoms of leg pain with walking (claudication). PAD is defined as ankle brachial index (ABI) lower than or equal to 0.90. Globally, the burden of PAD is increasing. In 2010, there were more than 200 million people living with PAD, 69.7% of them in LMICs, including 54.8 million in Southeast Asia and 45.9 million in the western Pacific Region[26] (Fig. 2–15). The burden of PAD has steadily increased over time, but the rate of change is higher in LMICs (the number of individuals with PAD between 2000 and 2010 increased by 28.7% in LMICs and 13.1% in high-income countries).

The age distribution varies by region. In developed countries, among adults aged 45 to 49 years, the prevalence is similar for males and females and is around 5%. The prevalence increase to around 18% for males and females in those aged 85 to 89 years.[26] In developing countries, the same age groups, the prevalence is around 6% for females and 3% for males and increases to 15% in females and 14% in males.[26] In high-income regions, notably Europe and North America, the largest age group with PAD was more than 55 years of age, compared to western Pacific and Southeast Asia regions where the majority of cases were in people younger than 55 years.[26]

Smoking is an important risk factor with and odds ratio for current smoking of 2.72 [95% CI, 2.39-3.09 (CI, confidence interval)] in high-income countries and 1.42 (95% CI, 1.25-1.62) in LMICs, followed by diabetes, hypertension, and hypercholesterolemia.[26]

Disability and mortality associated with PAD has increased over the past 20 years, and this increase in burden has been greater among women than among men. The largest relative change in median death rate was in the Asia-Pacific–high income region and was largely driven by higher death rates in women: +17.36 (95% CI, 1.79-32.01) versus +1.25 (95% CI, 0.13-2.39) in men. The median DALYs for PAD was larger in developing nations than in developed nations (1.15; 95% CI, 0.80-1.66 in developing vs 0.77; 95% CI, 0.55-1.08 in developed).[27]

The burden of PAD is no longer confined to the elderly population but now involves young adults. Similar to IHD, there is an increasing burden of PAD in developing regions and exceeds the increases in developed areas.[27] Multifaceted approaches that address the risk factors, such as avoiding smoking initiation and promoting smoking cessation, promoting exercise and healthful diet, as well as improvements in the diagnosis, treatment, and prevention of this disease are all urgently needed in order to reduce the burden of PAD globally.[26]

ATRIAL FIBRILLATION

Atrial fibrillation (AF) and atrial flutter are irregular heart rhythms that often cause a rapid heart rate and can increase the risk of stroke, heart failure, and other heart-related complications. During AF, the atria beat chaotically and out of "sync" with the ventricles. Symptoms include heart palpitations, shortness of breath, and weakness. Overall, there is a lower estimated AF prevalence rate and death rate in lower-income countries[28,29] (Fig. 2–16). It is unclear whether the significantly

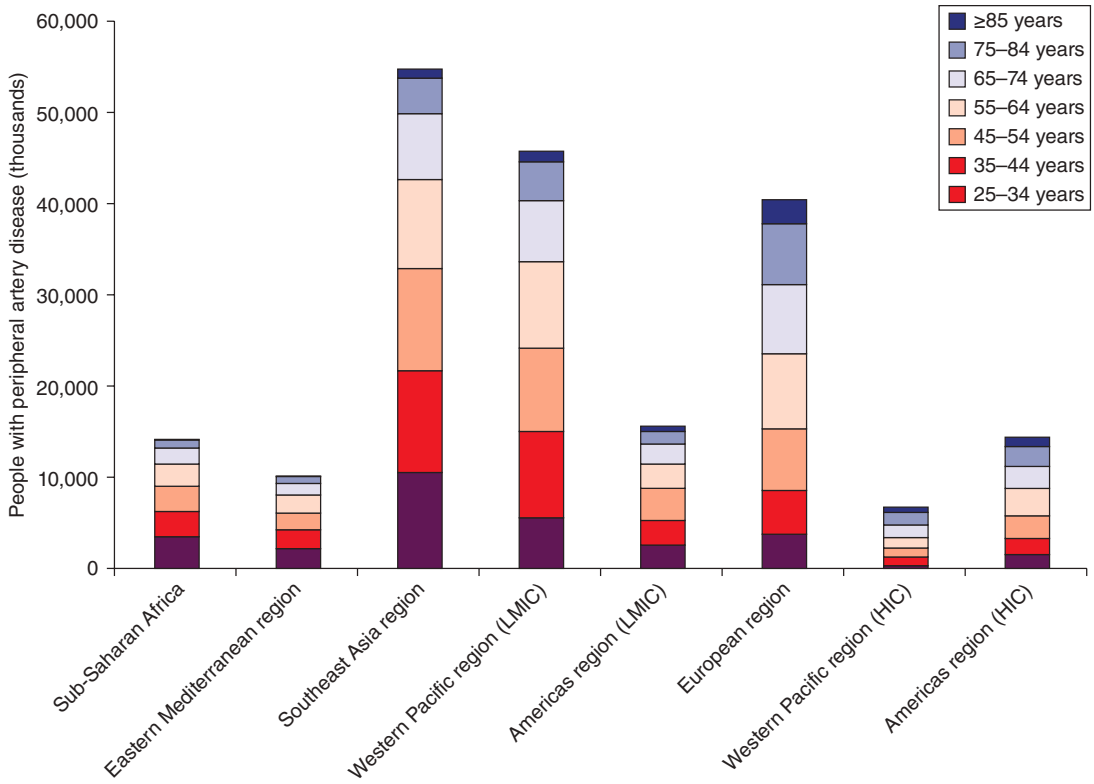


FIGURE 2–15. Estimate of the number of cases, and contributing age groups, in eight WHO regions in the year 2010 LMIC, low-income and middle-income countries; HIC, indicates high-income countries. Reproduced with permission from Fowkes FG1, Rudan D, Rudan I, et al: Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis, *Lancet*. 2013 Oct 19;382(9901):1329-1340.[26]

lower estimated burden of AF in developing countries represents less AF or lower rates of detection caused by less awareness of the condition or decreased access to diagnostic technology such as electrocardiograms. AF in developing countries is more likely to be valvular in nature, caused by RHD, compared with the nonvalvular AF most commonly seen in high-income countries. As a result, AF may be less recognized as a separate condition and less reported as an underlying cause of death in developing countries.

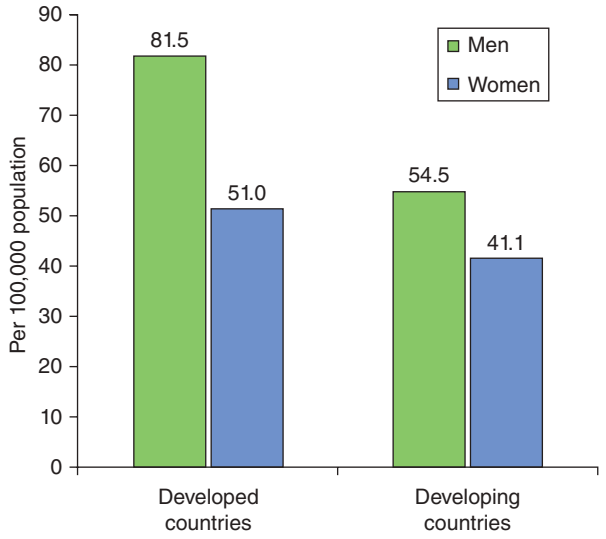


FIGURE 2–16. Age-adjusted disability-adjusted life year rates of atrial fibrillation for men and women in developed versus developing countries (2010). Reproduced with permission from Chugh SS, Roth GA2, Gillum RF, etal: Global burden of atrial fibrillation in developed and developing nations, *Glob Heart*. 2014 Mar;9(1):113-119.[29]

Changes in awareness and detection may also explain the 2-fold increase in age-adjusted mortality rate for AF among males (95% UI, 2.0-2.2) and 1.9-fold increase among females (95% UI, 1.8-2.0) between 1990 and 2010. In 2010, the estimated age-standardized DALYs resulting from AF was 65 per 100,000 population (95% UI, 47-84) in males and 46 (95% UI, 36-59) in females, which was an increase of 18.8% (95% UI, 16-19) and 19% (95% UI, 16-24) for males and females since 1990, respectively[29] (see Fig. 2–16). The rapid rise in AF has been observed in death records in the United States since the year 2010 despite little evidence for significant changes in AF incidence or survival in that country.[30,31] One possible explanation for increasing AF DALY rates, beyond increased awareness and detection of the condition, is that improved treatment of IHD has allowed individuals to reach older ages at which embolic stroke as a result of AF is more common. Higher burden in men compared with women may reflect actual disease rates or poorer access to medical care among women in resource-poor settings.

INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is an infection caused by bacteria, or other infectious pathogens, that enter the bloodstream and cause inflammation in the heart tissues, often on a valve. Because of the lack of direct blood supply, the heart valves are particularly susceptible to bacterial colonization and are neither protected by the typical immune response nor easily reached by antibiotics. IE is a serious illness with up to 22% in-hospital and 40% 5-year mortality rates.[32] It is also associated with heart failure, usually caused by severe valvular insufficiency and embolic

stroke. Valve surgery, either by replacement or repair, may be lifesaving and reduce embolic events. The crude incidence is low and ranges between 1.5 and 11.6 cases per 100,000 population; however, data are available for only 10 countries.[33] A global collaboration was formed to assess the current characteristics of patients with IE via a large, prospective multicenter registry, called the International Collaboration on Endocarditis (ICE). ICE found that contemporary infective endocarditis is most often an acute disease with high rate of infection with *Staphylococcus aureus* and involving the mitral (41.1%) and aortic (37.6%) valves. Common complications included stroke (16.9%), embolization other than stroke (22.6%), heart failure (32.3%), and intracardiac abscess (14.4%); these often required surgical intervention (48.2%). In-hospital mortality was high (17.7%).[34] Unfortunately, there were few sites in Asia and Africa included in the registry, which limits the ability to assess geographic differences in patient and microbiologic characteristics in these areas. IE is estimated to have resulted in 65,000 deaths (95% UI, 48,593-79,435) and 1.9 million DALY (95% UI, 1.4-2.3 million) in 2013.

More complete knowledge and improved surveillance is needed in all world regions.[35]

DIFFERENCES IN CARDIOVASCULAR DISEASE IN HIGH- AND LOW-INCOME COUNTRIES

There is significant variation in the patterns of CVD around the world, a fact often obscured by discussions of global trends in CVD. The variation occurs both between large regions but is also striking among even adjacent countries. This profound heterogeneity extends even within countries, and has been shown among states and provinces, counties, cities, and even neighborhoods.[36,37]

Some regions, led by Central Asia, face high rates of premature death from IHD, whereas sub-Saharan Africa and Asia suffer disproportionately from deaths caused by stroke (Fig. 2–17). This figure illustrates the YLLs because of the top causes of CVD in each region. Cardiomyopathy (in orange) is more common in sub-Saharan Africa and Eastern Europe than elsewhere. Stroke (in green) dominates over IHD (in light blue) as the leading cause of death in East and Southeast Asia. Understanding these global trends and regional variation is important in order to help create policies and health interventions that can be tailored and scaled for a broad range of local conditions with the ultimate goal of improving cardiovascular health.

There are large differences in the mortality rate for CVD in high-income countries, with Japan having the lowest rates (110 per 100,000; 95% UI, 101-125) and Taiwan (125 per 100,000; 95% UI, 118-137).[6] In Western Europe, France, Spain, Switzerland, Italy, Iceland, the Netherlands, Norway, and the United Kingdom have similarly low rates, as well as Israel, Australia, and Canada. Germany has the highest death rate in Western Europe (192 per 100,000; 95% UI, 183-210),[6] likely per the higher risk factor burden in this country.[38,39] CVD mortality rates in the United States, Austria, Finland, and Sweden are even higher than Germany, possibly because of their specific dietary patterns and other risk factors, as well as quality of health care services.[6]

The lowest income countries have many challenges to overcome in reducing CVD burden. This challenges include their persistent "double

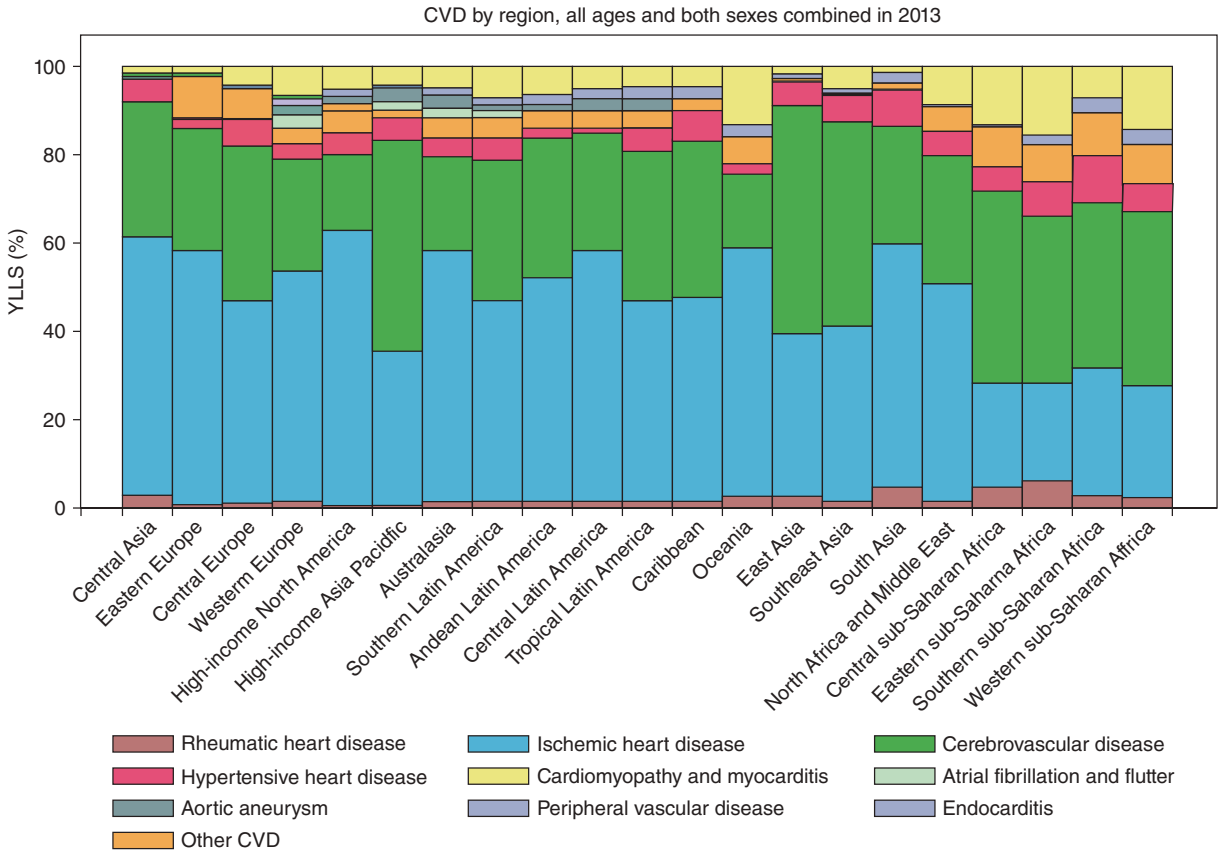


FIGURE 2–17. Proportion of years of life lost (YLLs) because of cardiovascular disease (CVD) stratified by global region, 2013. YLL is a measure of premature mortality calculated by using a normative goal for survival computed from the lowest observed death rate across countries. Reproduced with permission from Roth GA, Huffman MD2, Moran AE, et al: Global and regional patterns in cardiovascular mortality from 1990 to 2013, *Circulation*. 2015 Oct 27;132(17):1667-1678.[6]

burden" related to infectious disease, including HIV, tuberculosis, and malaria; limited availability of data on CVD and risk factors; inadequate primary health care infrastructure and access to medical care and medications; financial constraints on the individual and country level; inadequate training and retention of health professionals; and limited awareness of CVD and risk factors. The sub-Saharan Africa region has experienced the lowest levels of CVD burden over the past 20 years (only 5.5% of the global CVD deaths), but the number of CVD deaths is rising as adult population grows rapidly.[16,40] In 2013, CVD caused nearly one million deaths in sub-Saharan Africa, constituting 38.3% of NCD deaths and 11.3% of deaths from all causes in that region.[40] These estimates are limited as a result of scarce data available from this region and reflect, among other sources, verbal autopsy surveys showing 9% to 13% of deaths attributable to CVD, especially stroke.

Contrary to trends in high-income regions, the age-adjusted mortality rate for CVD in sub-Saharan Africa has not declined. The age-standardized CVD mortality rate in 1990 was 327.6 per 100,000 (95% CI, 306.2-351.7) and 330.2 per 100,000 (95% CI: 312.9-360.0) in 2013, representing only a nonsignificant 1% increase in more than two decades.

Hypertensive heart disease and cardiomyopathy represent a much larger proportion of total death in sub-Saharan Africa than in other regions and are suspected to represent untreated hypertension and rheumatic disease (see Fig. 2–17). Endomyocardial fibrosis, an uncommon idiopathic disease of heart muscle tissue, has become rare in communities where it used to be common and its etiology continues to be elusive.[40] The average age of death caused by IHD for sub-Saharan Africa was the youngest in the world, at 64.9 years (95% UI, 64.4-65.4 years) compared with 67.6 to 81.2 years for the rest of the world, reflecting the higher all-cause mortality and shorter lifespan in this region.[41]

Although CVDs are not the leading causes of death in sub-Saharan Africa, they represent a significant number of deaths caused by population growth, aging, and the epidemiological transition from infectious diseases to NCDs, with increasing prevalence of risk factors for CVD. This transition is faced not only in sub-Saharan Africa but also across many rapidly developing LMICs, for example India, Brazil, Indonesia, and China. Promotion of cardiovascular health and CVD prevention, treatment, and control is needed, as well as investments in human resources, infrastructure, technical capacity, and funding.[40] Efforts are needed to improve data collection via household surveillance studies, death certification, and burden of disease estimates, as well as increased data on health care capacity and quality, adherence to medications, and microeconomic costs experienced by patients and their families. Such costs include catastrophic spending on health, distress financing, and other measures of financial risk associated with disease.[6]

ENDEMIC CARDIOVASCULAR DISEASES

In this section, we review two common endemic CVD conditions, Chagas disease and RHD. Both conditions are the result of initial infection. We use the term *endemic* to suggest their specific geographic distribution as compared with atherosclerotic diseases found broadly throughout almost all human populations. Both conditions are significant causes of death and disability, but only in the regions where transmission vectors and resulting inflammatory response occur.

Chagas Disease

Chagas disease is a disease of poverty and is localized to Latin America because it is primarily transmitted through bites from the nocturnal "kissing bug," *Triatoma infestans*, which is endemic to this region. The infection can be asymptomatic but can eventually lead to premature morbidity and mortality, especially in young women of childbearing age. There are rapid diagnostic tests that can detect the causative parasite, *Trypanosoma cruzi,* in serum and diagnose chronic infections. Pesticides have been developed for vector control programs, but much is still unknown about this disease. In any case, prevention and elimination of the vector remains the keys to Chagas control.

The disease has three phases: acute, indeterminate, and chronic. The acute phase immediately follows infection and is often asymptomatic but produces fever and malaise in up to 5% of people. The indeterminate phase is asymptomatic, with more than 50% of those infected remaining in this phase for life without any long-term sequelae. After a decade or more, approximately 30% of people will experience chronic cardiovascular Chagas disease, with symptoms including heart failure, arrhythmias, and thromboembolism.[42] Deaths are rare in the acute phase, and most deaths attributable to Chagas disease result from downstream cardiovascular sequelae. In addition, approximately 15% to 20% of people will experience chronic gastrointestinal disease sequelae, including megaesophagus and megacolon.

Between 5 and 18 million people are currently infected, and the infection is estimated to cause more than 10,000 deaths annually.[43] The burden of Chagas disease is challenging to determine because it requires estimating the prevalence of the infection, the prevalence of each of its sequelae among those with the infection, and the number of deaths attributable to the infection.[43] Prevalence had been limited to Central and South America, but increased immigration has expanded the prevalence to Latin American immigrant populations in North America, Europe, Australia, and Japan.[44] The Pan-American Health Organization's (PAHO) country-level seroprevalence estimates for 2005 range from less than 1 per 10,000 (0.01%) in Panama to nearly 7% in Bolivia. In 2010, Chagas disease was responsible for 550,000 (95% UI, 274,000-1,069,000) DALYs[3] (Fig. 2–18). Approximately 4.2% of Chagas-related DALYs and 21.7% Chagas-related health care costs occur outside of Latin America.[45]

Treatment has been controversial and even if it proves effective, primary prevention will have by far the most powerful effect on burden of Chagas disease at the population level. Chagas eradication has been effectively achieved in many areas in Latin America, such as much of Chile, Uruguay, and Brazil, but requires strong public health infrastructure and policies to implement vector control programs in the remaining parts of South and Central America. In certain underserved and rural areas of Argentina, Paraguay, Mexico, and Bolivia, inadequate housing and lack of vector control remain a big problem, and the disease continues to disproportionately affect people living in extreme poverty and who lack access to health care and treatment. Insufficient prevention propagates the vicious cycle of ill-health and subsequent poverty in these areas.

Rheumatic Heart Disease

RHD is an endemic disease that is common in settings of poverty. It is caused by group A streptococcus infection and leads to mitral stenosis and premature mortality, particularly in young, predominantly female, poorer individuals living in Oceania, South Asia, Central Asia, Africa, and the Middle East. Approximately 60% of all acute rheumatic fever cases will develop RHD, based on data from Aboriginal Australian populations, and 1.5% of patients with RHD will die each year.[46] Globally in 2010, RHD affected more than 34 million people, causing more than 345,000 deaths and 10 million DALYs lost per year, almost all in LMICs[3] (Fig. 2–19). The age-standardized death rates range from 5 to 15 per 100,000, but as a result of misclassification, vital registration systems in certain regions are likely underrepresenting the true disease burden.[6] Figure 2–19 shows the 2015 estimates of number of RHD deaths and prevalent cases by age. Population-based screening programs of children ages 5 to 14 years suggest a prevalence of 0.3 to

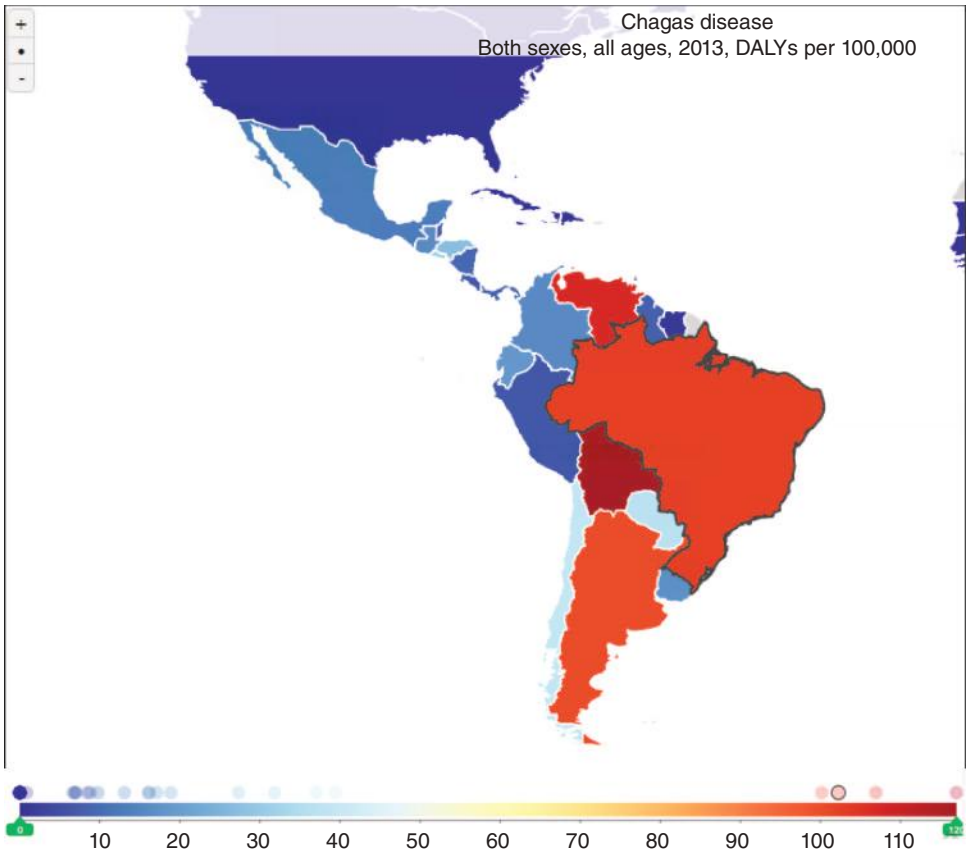


FIGURE 2–18. Disability-adjusted life years (DALYs) attributable to Chagas disease, per 100,000 people, for 2013 by country. From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington, 2015. Available from http://vizhub.healthdata.org/gbd-compare (Accessed February 2, 2016).

5.7 cases per 1000 individuals, with the highest values from studies that included echocardiographic screening.[46]

The disease can progress to cause moderate to severe multivalvular disease, leading to congestive heart failure, pulmonary hypertension, or AF. RHD also contributes (3%–7.5%) to an estimated 144,000 to 360,000 incident strokes each year. There is a high prevalence of major cardiovascular complications in these patients, and untimely death is a huge problem. Many patients in LMICs are first diagnosed with advanced disease, at a stage when the chance of a good outcome is unlikely in the absence of surgical intervention. Unfortunately, surgery is not a luxury available to the poor. RHD is at least as severe in low-income countries as it is in LMICs, yet only 11% of surgical interventions occurred in low-income countries compared with 61% in high-income countries.[48]

Treatment with oral anticoagulants, secondary antibiotic prophylaxis, and contraception is often indicated in RHD patients, but these are often underprescribed. Even when these treatments are prescribed, they are often inadequately dosed. The Global Rheumatic Heart Disease Registry, or REMEDY study, found that oral anticoagulants are only prescribed in 69.5% (n = 946) of patients with mechanical valves (n = 501), AF (n = 397), and high-risk mitral stenosis in sinus rhythm (n = 48).[47] Furthermore, only 28.3% (n = 269) of patients taking anticoagulants had a therapeutic international normalized ratio. Among women of childbearing age (12–51 years), only 3.6% (n = 65) were on contraception. Overall, there is suboptimal utilization of secondary antibiotic prophylaxis, oral anticoagulation, and contraception, and in the use of percutaneous and surgical interventions, particularly in low-income countries.[47]

GLOBAL BURDEN OF CARDIOVASCULAR DISEASE RISK FACTORS

Exposure to known risk factors for CVD remain alarmingly common and presents one of the largest barriers to improved global health. Most CVD premature deaths are linked to these common risk factors, including high blood pressure, high body mass index, tobacco use, and unhealthy diet with low fruit intake and high sodium[48] (Fig. 2–20). Estimates for the individual and joint CVD effect of the metabolic, environmental, and behavioral risk factors are shown in Fig. 2–21. Among the most important observations we can make from this assessment of risk factors is that the vast majority of CVD is a result of the combination of preventable behavioral and metabolic risk factors. Globally, CVD prevention emphasizes healthy lifestyle behaviors (not smoking, ideal body weight, adequate physical activity, and healthy diet) and optimal biologic factors (control of blood pressure, cholesterol, and glucose). However, certain regions may need to expand their priority list to include nontraditional risk factors that are specific to their region, such as air pollution in South and East Asia and infectious risks in sub-Saharan Africa.

MODIFIABLE CARDIOVASCULAR RISK FACTORS

Hypertension

Elevated blood pressure is estimated to be the single largest contributor to the global burden of disease and global mortality. It is a normally distributed biological variable with the threshold for the diagnosis of

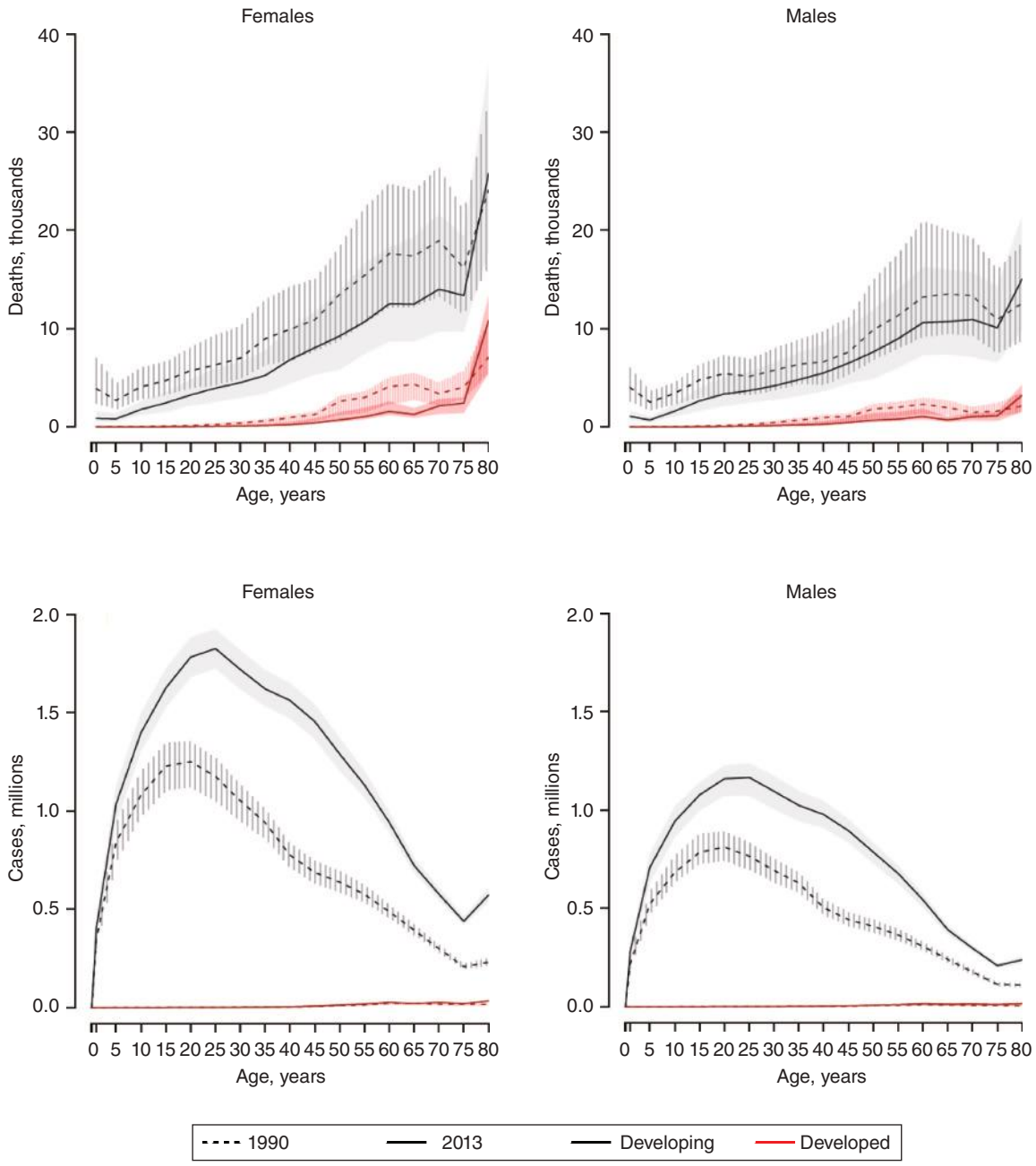


FIGURE 2–19. Numbers of rheumatic heart disease (RHD) deaths and prevalent cases by age, sex by development status. Used with permission from G. Roth, personal communication of manuscript in preparation.

hypertension traditionally set as a systolic blood pressure (SBP) measured in a clinic or office of at least 140 mm Hg, a diastolic blood pressure (DBP) of at least 90 mm Hg, or both.[49,50] Screening is key to diagnosis as it is largely an asymptomatic condition. The development of hypertension is associated with dietary exposures, such as excess intake of salt, saturated fats, and alcohol; reduced exercise; and inadequate intake of fresh fruit and vegetables. High blood pressure is also positively associated with overweight and lack of physical activity. There are gaps in the awareness, treatment, and control of hypertension globally. High blood pressure in populations appears to occur in tandem with economic development but notably in the highest income countries individuals with lower socioeconomic status are the group most likely to be untreated.[50,51] Primary, or essential, hypertension mostly arises in middle or older age as a result of the interaction between lifestyle and genetic factors.[52] Secondary causes of hypertension are less common and generally have an earlier age of onset, no family history, and a clear cause such as renal or endocrine disorder, or an iatrogenic trigger such as oral contraceptives.

Many people with hypertension are unaware of their diagnosis and are often left untreated and uncontrolled for years. In Africa, hypertension is thought to be the leading cause of heart failure, whereas at global levels, hypertension is linked to the development of atherosclerotic vascular disease. In high-income countries, it is estimated to be responsible for 25% of deaths from stroke, 20% of deaths from IHD, and for more than 17% of all global deaths.[53]

In 2008, the age-standardized mean SBP worldwide was 128.1 mm Hg (95% UI, 126.7-129.4) in males and 124.4 mm Hg (95% UI, 123.0-125.9)

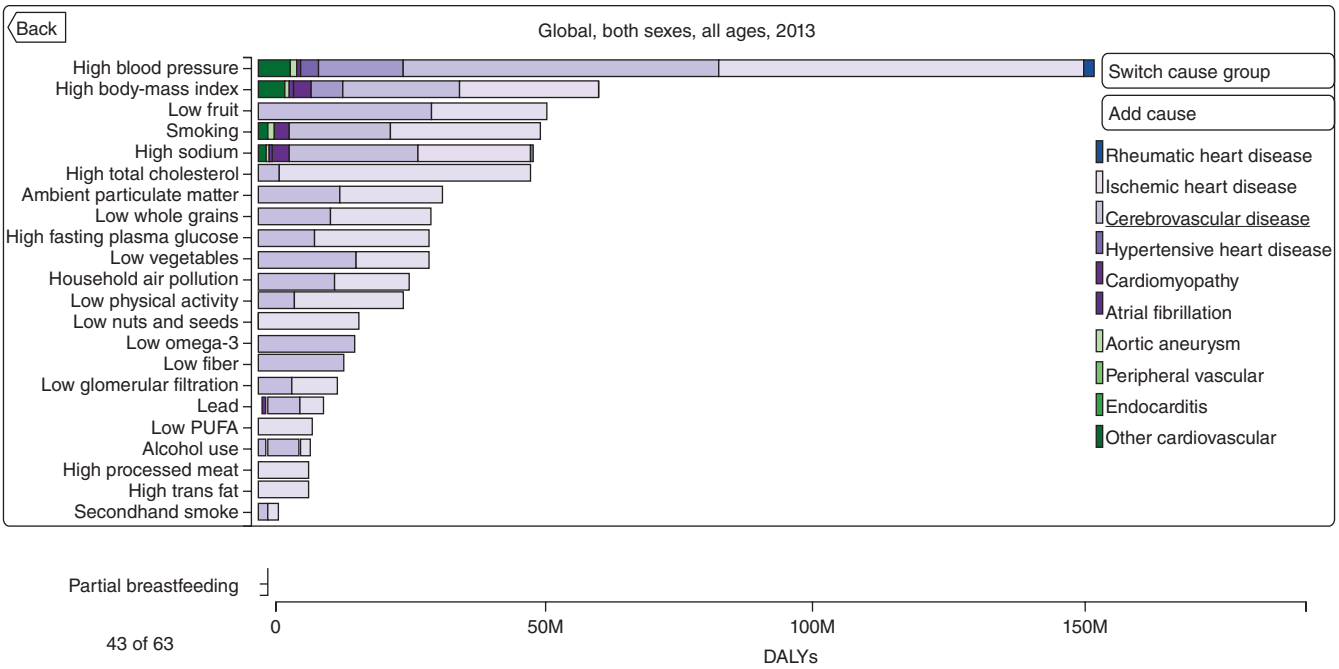


FIGURE 2–20. Number of cardiovascular disease disability-adjusted life years (DALYs) attributable to avoidable risk factors in 2013, by cardiovascular disease subtype. From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington, 2015. Available from http://vizhub.healthdata.org/gbd-compare (Accessed February 2, 2016).

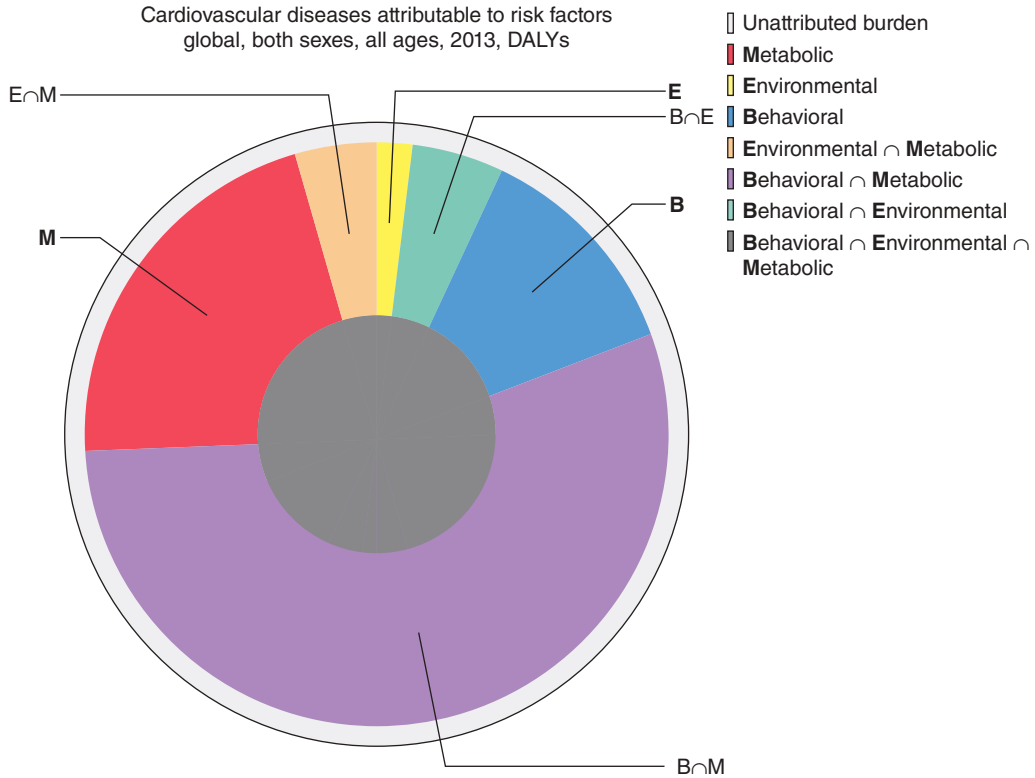


FIGURE 2–21. Joint effects of metabolic, environmental, and behavioral risk factors as proportions attributable to cardiovascular diseases. From Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington, 2015. Available from http://vizhub.healthdata.org/gbd-compare (Accessed February 2, 2016).

in females (Fig. 2–22). The age-standardized prevalence of uncontrolled hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) was 29% (95% UI, 27-31) in 2008 in males and 25% (95% UI, 23-27) in females. The number of people with uncontrolled hypertension was 978 million (921-1040 million) in 2008, a substantial increase from 605 million (537-680 million) in 1980, largely as a result of population growth and aging.[54]

Overall, there has been a decreasing trend in population mean SBP over the past 30 years, with highest reductions in high-income North America for males, and Western Europe and Australasia for both males and females. However, mean SBP rose in certain regions, including Oceania, East Africa, and South and Southeast Asia for both sexes and in West Africa for women. The highest mean SBP for females was greater than 135 mm Hg in some east and west African countries, whereas for males it was highest in Baltic and east and west African countries, with mean SBP of greater than 138 mm Hg.[54] The PURE study found a difference in the prevalence between high- and low-income countries, with prevalence of 36.4% in urban regions of high-income countries and 46.9% in rural upper-middle-income countries.[55]

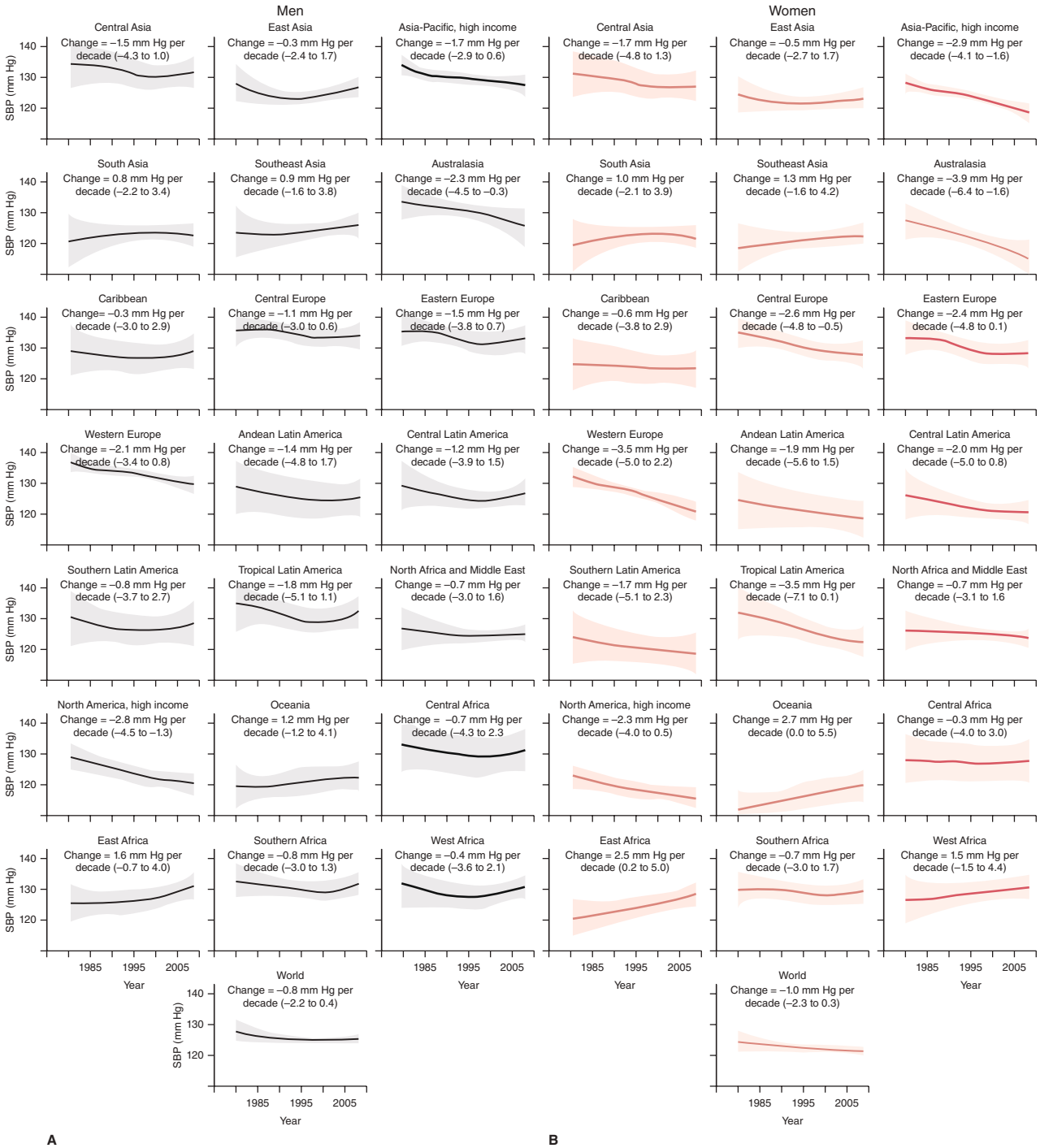


FIGURE 2–22. Trends in age-standardized mean systolic blood pressure (SBP) by subregion between 1980 and 2008 for men (A) and women (B). The solid line represents the posterior mean and the shaded area the 95% uncertainty interval. Reproduced with permission from Danaei G, Finucane MM, Lin JK, et al: National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants, *Lancet*. 2011 Feb 12;377(9765):568-577.[54]

Obesity

There has been a global rise in obesity among adults, as well as adolescents and children, with little success over the past 30 years to modify the upward trend. Overweight is defined as a body mass index (BMI) greater than or equal to 25 kg/m^2 and obesity is defined as a BMI greater than or equal to 30 kg/m^2. The prevalence of obesity is higher in developed countries than developing countries, and there are age and sex differences by region (Fig. 2–23). Overall, the number of people who are overweight and obese is increasing. The prevalence rate of overweight and obesity is higher in males than females in developed countries, whereas, in developing countries, females have higher rates of overweight and obesity than males (Fig. 2–24).

Research has shown that the peak age of obesity was slightly older in females than males in developed countries, with nearly 25% of men and 31.3% of women areas obese. In developing countries, the prevalence was much lower, with the highest level of obesity was around age 55 years for women with a rate of 14.4% (13.5-15.5) and 45 years for men with a rate of 8.1% (7.5-8.8).[56] In developed countries, overweight and obesity peaked in men at about 55 years of age, with two of three men overweight and one in four obese; for women, the peak age was closer to 60 years with 31.3% (95% UI, 28.9–33.8) obese and 64.5% (95% UI, 62.5–66.5) overweight or obese.[56]

Diet

Ideal diet, as defined by the American Heart Association (AHA), involves eating a balanced diet that includes at least a variety of fruits and vegetables daily; whole grains; fat-free and low-fat dairy products; fish, legumes, poultry, and lean meats; and limited intake of

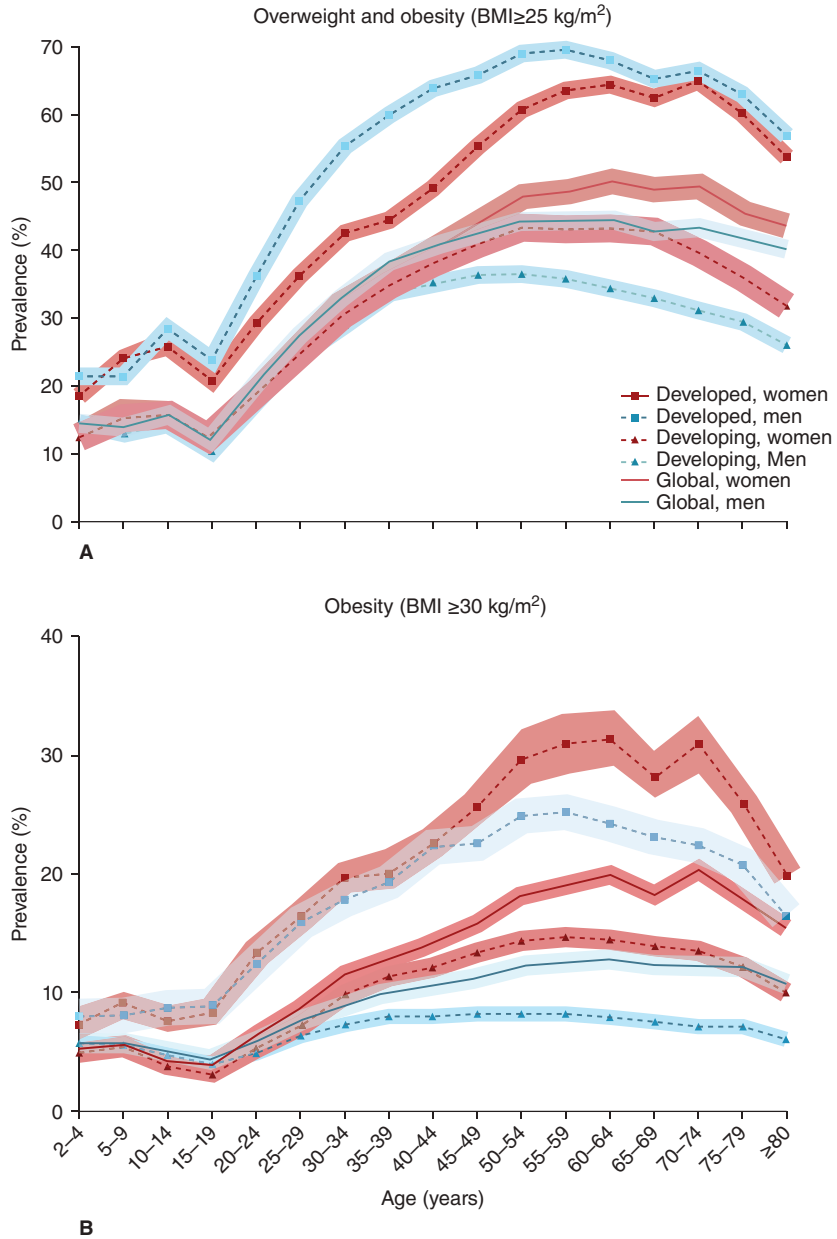


FIGURE 2–23. Prevalence of overweight and obesity and obesity alone, by age and sex, 2013. BMI indicates body-mass index. Reproduced with permission from Ng M, Fleming T, Robinson M, et al: Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013, *Lancet*. 2014 Aug 30;384(9945):766-781.[56]

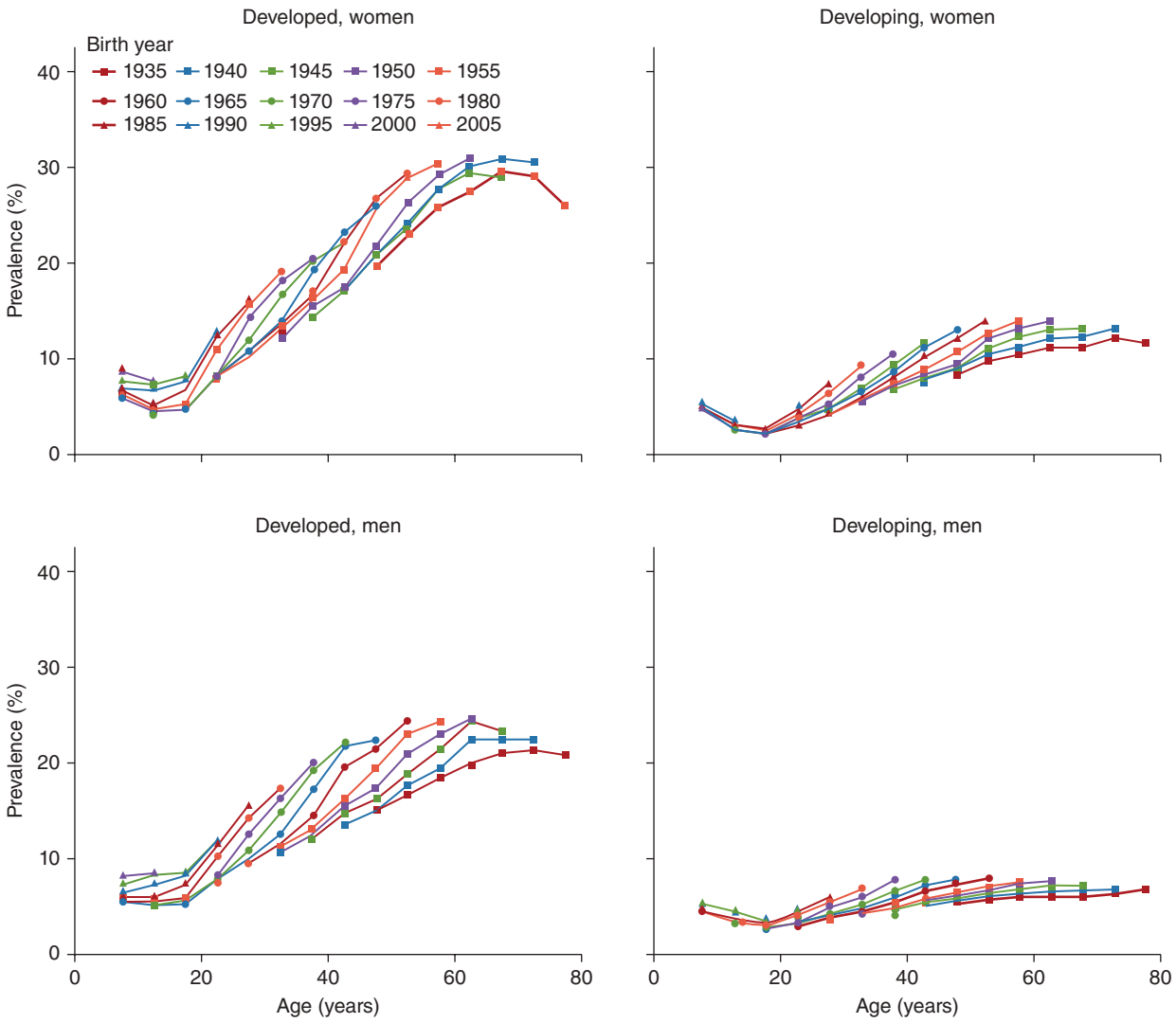


FIGURE 2–24. Prevalence of obesity by age across birth cohorts for men and women in developed and developing countries. Reproduced with permission from Ng M, Fleming T, Robinson M, et al: Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013, *Lancet*. 2014 Aug 30;384(9945):766-781.[56]

salt (sodium chloride < 5 g/d), alcohol (no more than one drink per day for women and two drinks per day for men), and saturated fats and cholesterol.[57] The goal of the AHA dietary guidelines is to assist individuals in achieving and maintaining cardiovascular and overall health, and they are designed for the general population. Increasingly, dietary guidelines are being developed for specific regions that are tailored to local diet and culture.[58] Low fruit and high salt are significant contributors to overall CVD deaths, accounting for 2.7% and 2.6% of total global DALY in 2013, respectively.[53,59] The burden of high dietary sodium, estimated as above approximately 5 g/d, is highest in Central Asia. Men are more affected then women. Other dietary risk factors for CVD include low consumption of whole grains, vegetables, nuts and seeds, omega-3 and polyunsaturated fats, and fiber and high consumption of processed meats and trans fats.[53]

Dyslipidemia

The excessive levels of serum cholesterol contribute to 2.6% of total global DALYs in 2013. The burden of disease related to high cholesterol is estimated to be highest in Eastern Europe and Central Asia, with almost 9% of total DALYs related to this risk in Belarus and more than 7% in Russia.[53,60] The awareness, treatment, and control of levels for hypercholesterolemia mirror the suboptimal patterns for poor diet as well as access to treatment with effective therapy such as statin medications.

Smoking

Tobacco continued to cause 5.7 million deaths, 6.9% of YLLs, and 5.5% of DALYs in 2010.[61] Although daily cigarette use has declined from 41.2% (95% UI, 40.0-42.6%) in 1980 to 31.1% (95% UI, 30.2-32.0) in 2012 for males and from 10.6% (95% UI, 10.2-11.1) to 6.2% (95% UI, 6.0-6.4) for females, the number of daily smokers increased from 721 million (95% UI, 700 million–742 million) in 1980 to 967 million (95% UI, 944 million–989 million) in 2012[61] (Fig. 2–25).

The prevalence rates vary greatly by age, sex, and region, with rates below 10% for males in some African countries to more than 55% for males in Timor-Leste and Indonesia (Fig. 2–26). For females, estimated prevalence rates ranged from more than 30% in three countries (Greece, Bulgaria, and Kiribati), to 1% or lower in a number of countries, including Azerbaijan, Algeria, Cameroon, Eritrea, Ethiopia, Gambia, Lesotho, Libya, Morocco, Oman, Sri Lanka, and Sudan.[61] There are also large variations within regions, with Chile and Uruguay having much higher estimated prevalence rates than other countries in Latin America. Estimated age-standardized prevalence of daily

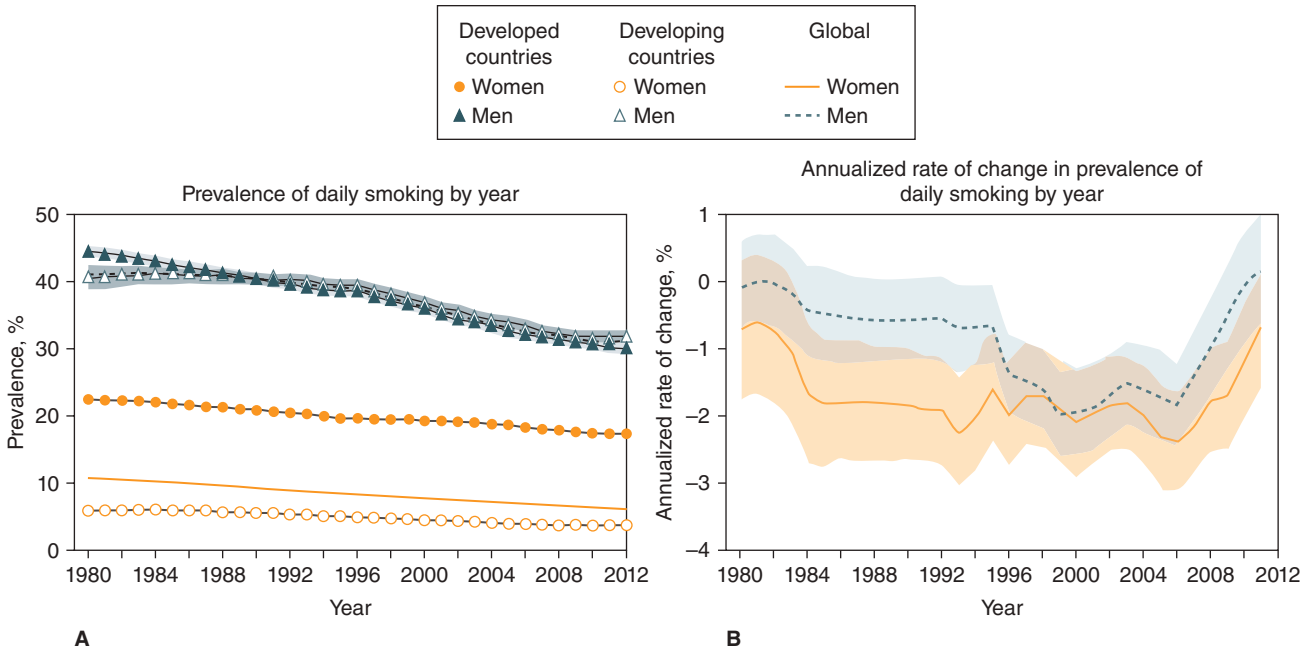


FIGURE 2–25. Estimated age-standardized prevalence of daily smoking and annualized rate of change, 1980-2012. **A.** Global (187 countries) age-standardized prevalence estimates by sex and separately for developed countries (50 countries) and developing countries (137 countries) from 1980 to 2012. **B.** Annualized rate of change in age-standardized prevalence by sex from 1980 to 2012. Annualized rates of change are plotted at the beginning of the time interval they correspond to (eg, the rate of change shown for 2011 is the rate of change between 2011 and 2012). Shaded areas designate 95% uncertainty intervals.

smoking in males is only weakly correlated with that in females in 2012 (r = 0.38), with prevalence in males exceeding that in females in all countries except Sweden.[61] Interestingly, the number of cigarettes per smoker per day varies widely across countries and is not correlated with prevalence.

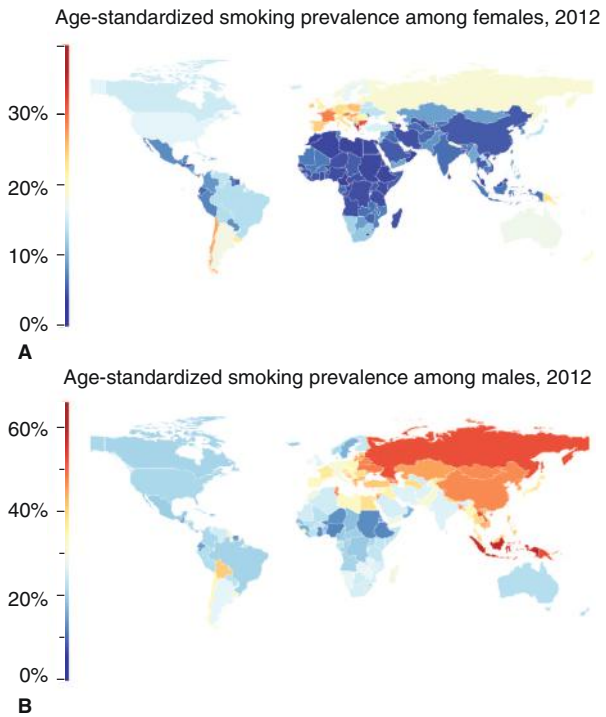


FIGURE 2–26. Estimated age-standardized prevalence of daily smoking in women (**A**) and men (**B**) in 2012. Available from http://vizhub.healthdata.org/tobacco. (Accessed October 19, 2016).

Diabetes

Hyperglycemia and diabetes mellitus are significant contributors to CVD worldwide. Unlike blood pressure, age-standardized mean fasting plasma glucose has continued to rise for males and females over the past 30 years (Fig. 2–27), with no country having a meaningful decrease in fasting plasma glucose. In 2008, the age-standardized prevalence rate of diabetes was 9.8% (95% UI, 8.6-11.2%) for males and 9.2% (8.0-10.5%) in females, which corresponds to nearly double the number of people living with diabetes today than in 1980. Nearly half of these individuals reside in China and India (approximately 138 million), with another 10% (approximately 36 million) in the United States and Russia.[62] The change in the past 30 years is largely attributable to population growth and aging but approximately 30% is attributable to a rise in age-specific prevalence. The trends over time ranged from a slight decrease of 2% in the East and Southeast Asia region and to a substantial increase of 60% in Oceania. Although East and Southeast Asia have no increase in prevalence, their aging and population growth has caused the number of diabetics to continue to rise. In Oceania, North Africa, and the Middle East, there is a significant increase in mean fasting plasma glucose, likely partly attributable to the rise in body mass index in this region.[60,62]

Air Pollution and Cardiovascular Disease

Multiple mechanisms have been considered as the cause for the association between air pollution and CVD, including inflammation, autonomic nervous system imbalance, changes in vascular responsiveness and compliance, and altered cardiac structure and promotion of atherosclerosis (Fig. 2–28). Air pollution has now been shown to increase preclinical risk factors such as atherosclerosis, endothelial dysfunction, and hypertension. Particulate matter (PM) is generally used to describe types of air pollution and is classified by size into PM_{10} (< 10 μm mean aerodynamic diameter), coarse (< 10 μm and > 2.5 μm diameter), fine ($PM_{2.5}$; < 2.5 μm diameter), and ultrafine (< 0.1 μm diameter) fractions (Fig. 2–29). High levels of $PM_{2.5}$ can occur with domestic combustion of

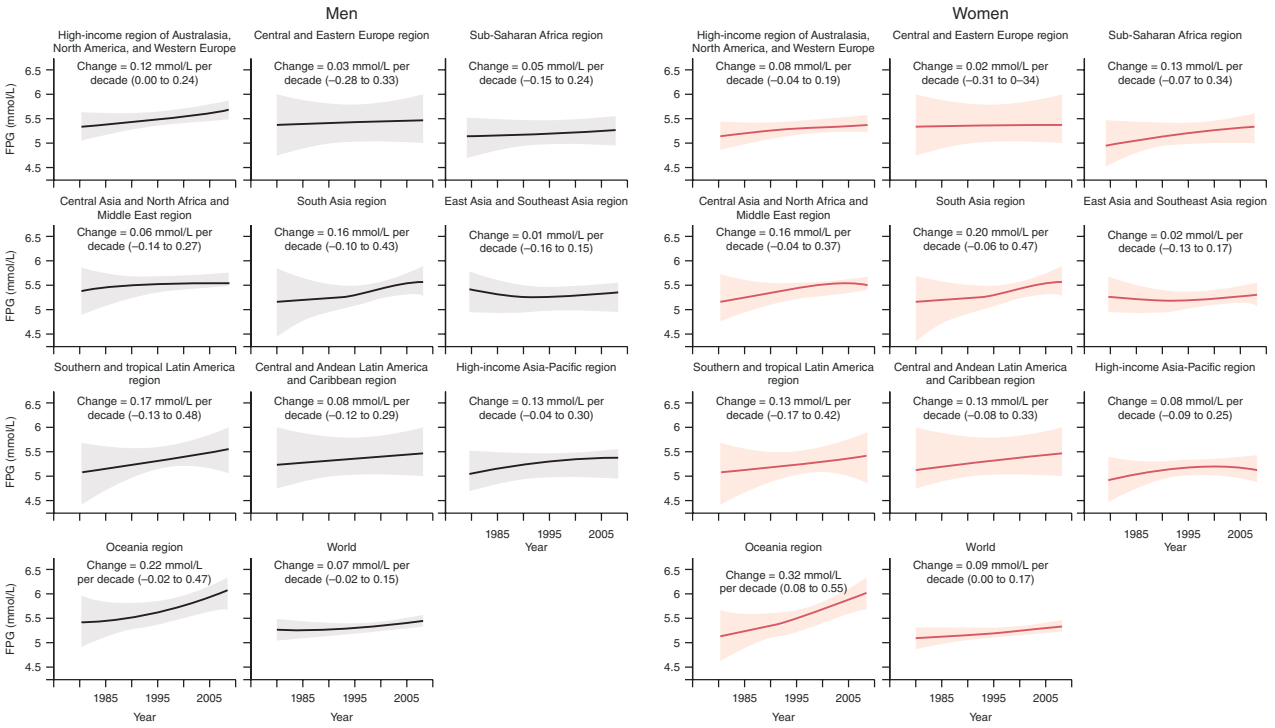


FIGURE 2–27. Trends in the age-standardized mean fasting plasma glucose between 1980 and 2008 for men (A) and women (B). Reproduced with permission from Danaei G, Finucane MM, Lu Y, et al: National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants, *Lancet*. 2011 Jul 2;378(9785):31-40.[62]

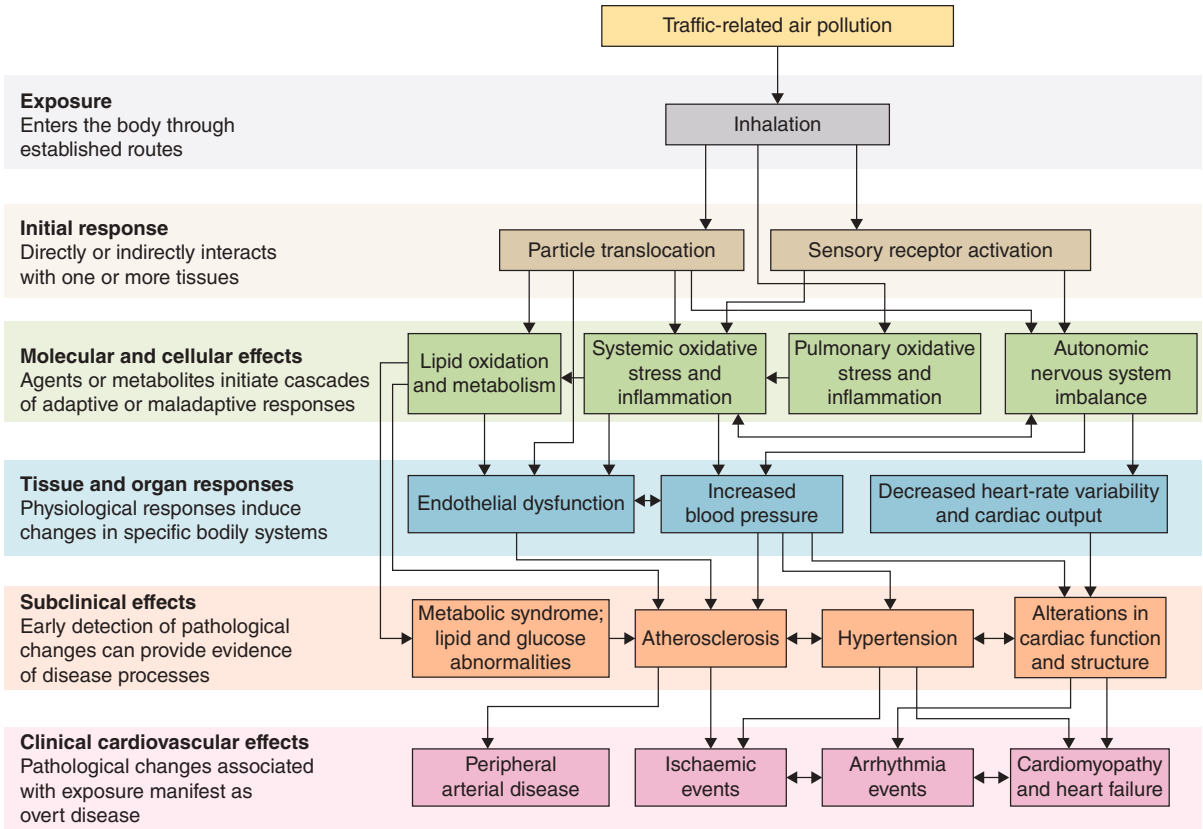


FIGURE 2–28. Cardiovascular effects and proposed mechanisms of chronic exposure to traffic-related air pollution. Inhaled pollutants can activate receptors in the lung, or potentially cross at the alveolar level to enter the systemic circulation. Molecular and cellular effects lead to responses in various tissues and organs, to subclinical effects, and eventually to clinical cardiovascular effects. Reproduced with permission form Cosselman KE, Navas-Acien A2, Kaufman JD: Environmental factors in cardiovascular disease, *Nat Rev Cardiol*. 2015 Nov;12(11):627-642.[63]

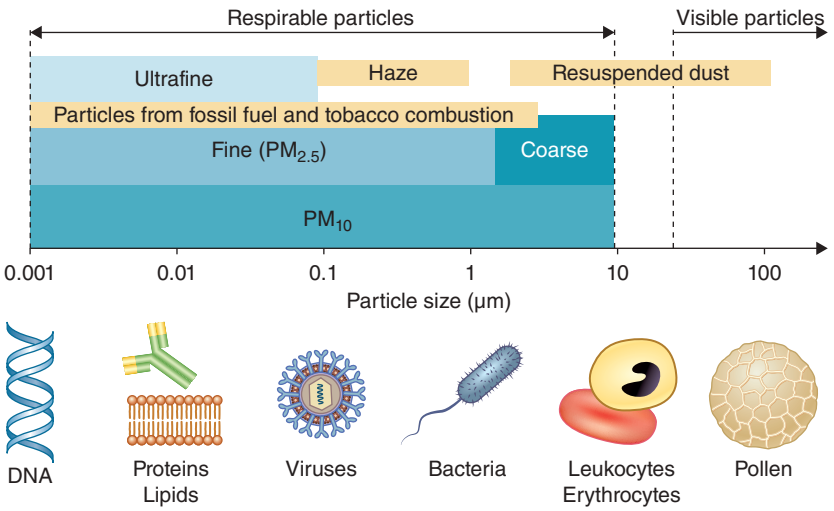


FIGURE 2–29. Size categorization of airborne pollutants. The particulate matter that contributes to airborne pollution is categorized according to the mean aerodynamic diameter of the particles. The broadest category (PM_{10}) includes all particles less than 10 μm diameter. This category is subdivided into coarse, fine, and ultrafine particles. Fine particles less than 2.5 μm diameter are also known as $PM_{2.5}$. Biological entities representative of this range of sizes are also shown. Reproduced with permission form Cosselman KE, Navas-Acien A2, Kaufman JD: Environmental factors in cardiovascular disease, *Nat Rev Cardiol*. 2015 Nov;12(11):627-642.[63]

biomass, coal, or kerosene for cooking and heating and is predominantly seen in low-income countries.[63] Upon inhalation, particles less than 10 μm diameter can deposit in the airways and lungs, with smaller particles effectively reaching the alveolar periphery. The deposited particles can activate sensory receptors, induce inflammatory and stress responses, or cross the permeable epithelial barrier into the systemic circulation.

Billions of people are exposed to indoor and outdoor air pollution, and such pollution ranks as the largest single environmental health risk factor, with more than 2.9 million deaths attributed to outdoor air pollution and a similar number attributed to indoor air pollution.[64] The estimated excess risk of cardiovascular mortality rises 11% per 10 $\mu g/m^3$ rise in levels of PM, with no threshold level below which long-term exposure to urban air pollution had no ill-effect on cardiovascular health.[63] The strongest associations between air pollution are with IHD, heart failure, and stroke, as well as contributions to obesity and type 2 diabetes. There are data that suggests that both short-term exposure to elevated levels of air pollutants, as well as long-term exposure, triggers CVD in susceptible populations.[65]

Physical Inactivity

Physical inactivity has become a leading risk factor for CVD globally. There is an increased risk of death associated with physical inactivity, contributing to 1.8% of total DALYs in 2013, much of which appears to be via its contribution to increased body weight and abdominal fat deposition.[53] This risk is estimated to begin as early as 25 years of age. The WHO adopted a Global Strategy on Diet, Physical Activity and Health, which specifically aims to promote physical activity and reduce sedentary behavior; ensure locations for physical activity in attractive; allow for a safely built environments; promote accessible public spaces and infrastructure; and provide equal opportunities for physical activity, regardless of gender, age, income, education, ethnicity, or disability.[66] However, physical inactivity remains common.[67] Low physical activity levels are common in most high-income countries, as well as Eastern Europe, Central Asia, North Africa and the Middle East, tropical Latin America, and the Pacific Islands.[53]

Mental Illness and its Impact on Cardiovascular Disease

The relationship of mental health disorders with CVD is complex but receiving increasing attention as an important comorbid condition. Those with CVD are at higher risk for developing depression while, simultaneously, those with mental disorders are at greater risk for developing risk factors, as well as CVDs.[68] There is evidence for a causal association between depression and CVD even after adjustment for traditional CVD risk factors.[69]

The estimated global prevalence in the prior 12 months of any mood, anxiety, or substance use disorder is extremely high, estimated at 29.2%.[70] Globally, mental health disorders account for approximately 21% of the global burden of disability, with a 45% increase in the years lived with disability (YLDs) between 1990 to 2013.[71] The prevalence of mental disorders has regional variation and is higher in English-speaking countries and lowest in North and Southeast Asia; however, it is unclear if this is a true difference in prevalence or whether it can be attributed to limited validity in diagnostic criteria or lack of measurement equivalence.[70,72] In studies that assumed the association between depression and CVD to be causal, an estimated 4 million, or 3% of IHD, DALYs were attributable to major depression. However, no randomized trials have demonstrated that treating depression reduces IHD risk. There is significant heterogeneity in the epidemiologic studies in this area, as well as a lack of data from many LMICs.[73]

Cardiovascular Disease in the HIV-infected Population

CVD has become more common among individuals with HIV, as survival improves as a result of highly active antiretroviral treatment. One study found that HIV-infected individuals have at least a 50% increase (relative risk 1.61; 95% CI, 1.43-1.81) in the development of myocardial infarction than uninfected individuals, even when controlling for the effects of traditional risk factors, such as hypertension and smoking.[74,75] HIV also appears to increase the risk of heart failure and hypertension.[76,77] A study using coronary computed tomography angiography and nuclear imaging suggests that there is an increased prevalence of plaque and increased arterial inflammation among HIV-infected men compared to age-matched uninfected control groups.[78] The underlying mechanism is thought to be immune activation and inflammation leading to more vulnerable atherosclerotic plaque and a higher rate of acute myocardial infarction.[78] Antiretroviral drugs may induce dyslipidemias, reduce insulin sensitivity, and promote body fat redistribution that contributes to CVD risk. Sustained HIV suppression reduced systemic inflammatory markers and is associated with a moderate reduction in CVD events.[75]

PREVENTION OF CARDIOVASCULAR DISEASE

The traditional clinical approach to CVD prevention considered interventions on risk proximate risk factors before (primary prevention) and after a patient's initial health event (secondary prevention). Primary prevention includes tobacco cessation and control of high blood sugar, blood pressure, and cholesterol. Improved detection and aggressive management of the cardiometabolic risks associated with diabetes are primary prevention measures essential for slowing progression to microvascular and macrovascular complications.[62]

More recently, primordial CVD prevention has been considered as an approach that examines even more upstream causes of CVD than found in routine clinical practice. Primordial risks are the determinants of adverse risk factor exposures (ie, "causes of causes") that include those found in early social and environmental conditions, maternal factors, fetal development, as well as exposures during infancy and early childhood. Primordial risk factors are an increasingly important target for policy interventions, given that they are often beyond the traditional reach of health care systems. Primordial prevention includes healthful diet, sufficient physical activity, and clean air.

Secondary prevention is defined as any strategy aimed at reducing the probability of a recurrent cardiovascular event in patients with known atherosclerotic CVD, including IHD, cerebrovascular artery disease, PAD, and atherosclerotic aortic disease. Recent studies have shown effective therapy can be delivered with a low-dose fixed combination "polypill" that improves medication adherence, lowers blood pressure, and lowers cholesterol.[79] Randomized trials looking at outcomes for secondary prevention are ongoing.[80]

Strategies that include these type of low-cost generic medications are likely to play a major role in expanding access to secondary prevention therapies globally. But significant barriers exist to the successful implementation of CVD prevention strategies. For example, barriers to prevention of hypertension include inadequate access to health care, insufficient and inadequately trained health care personnel, uneven distribution of health care providers, lack of medication availability and access, and lack of diagnostic tools. Interventions that target environmental determinants and effective implementation of trial-based therapies (eg, with multidrug combinations) are urgently needed to reduce the burden of CVD globally.[81]

FIGURE 2–30. The World Health Assembly Noncommunicable Disease Voluntary Global Targets for 2013-2020. Used with permission from World Health Organization.

GLOBAL TARGETS FOR CARDIOVASCULAR DISEASE PREVENTION

The WHO and all member states (194 countries) agreed in 2013 to a Global NCD Action Plan, which aims to reduce the number of premature deaths from NCDs by 25% by 2025 through nine voluntary global targets (Fig. 2–30). Two of the global targets directly focus on preventing and controlling CVD. The sixth target calls for a global reduction in the prevalence of high blood pressure by 25%. The seventh target calls to halt the rise in diabetes and obesity. The eighth target in the plan states that at least 50% of eligible people should receive drug therapy and counseling (including glycemic control) to prevent heart attacks and strokes. In 2015, countries set national targets and agreed to measure progress based on 2010 baseline data. The World Heart Federation (WHF) proposed three road map plans aimed at reducing premature CVD mortality. The first two road maps—on secondary prevention and on hypertension—are primarily focused on health system issues and identify roadblocks on the care pathway for patients with prevalent CVD or raised blood pressure.[81,82] The third road map, on tobacco, summarizes key elements of the Framework Convention on Tobacco Control (FCTC) and its guidelines, describes the main roadblocks for their implementation and proposes strategies for overcoming them. The WHF has worked with tobacco control experts from around the world to simplify and synthesize the guidance from the FCTC guidelines.[83]

In 2010, an Institute of Medicine (IOM) report concerning promotion of cardiovascular health described four essential functions that need to be achieved to better promote CVD globally, including (1) building priorities, advocacy, and funding at global and national levels; (2) developing policy and program implementation; (3) improving systems for data management and conducting locally relevant research; and (4) global coordination and reporting. The IOM made 12 specific recommendations and guidance for achieving them (Fig. 2–31).[84] Subsequently, concrete examples of successful programs and road maps for improved global cardiovascular health have been described.[82,85,86]

THE FUTURE OF GLOBAL CARDIOVASCULAR DISEASE

Modeling studies have shown that significant reductions in premature CVD are possible by 2025 if multiple risk factor targets are achieved. If current trends continue, the probability of dying prematurely from CVD is projected to remain unchanged in some of the world's most

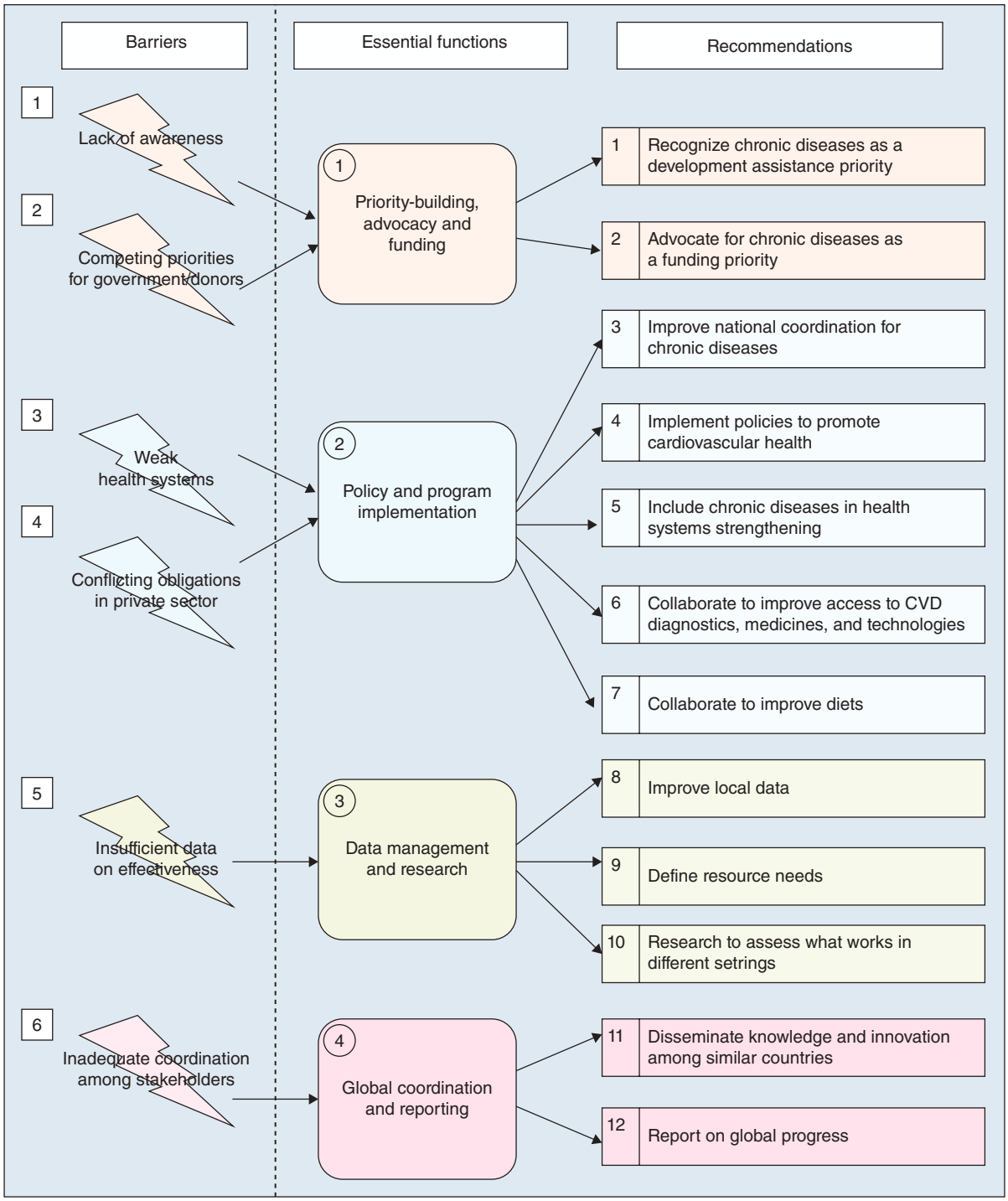
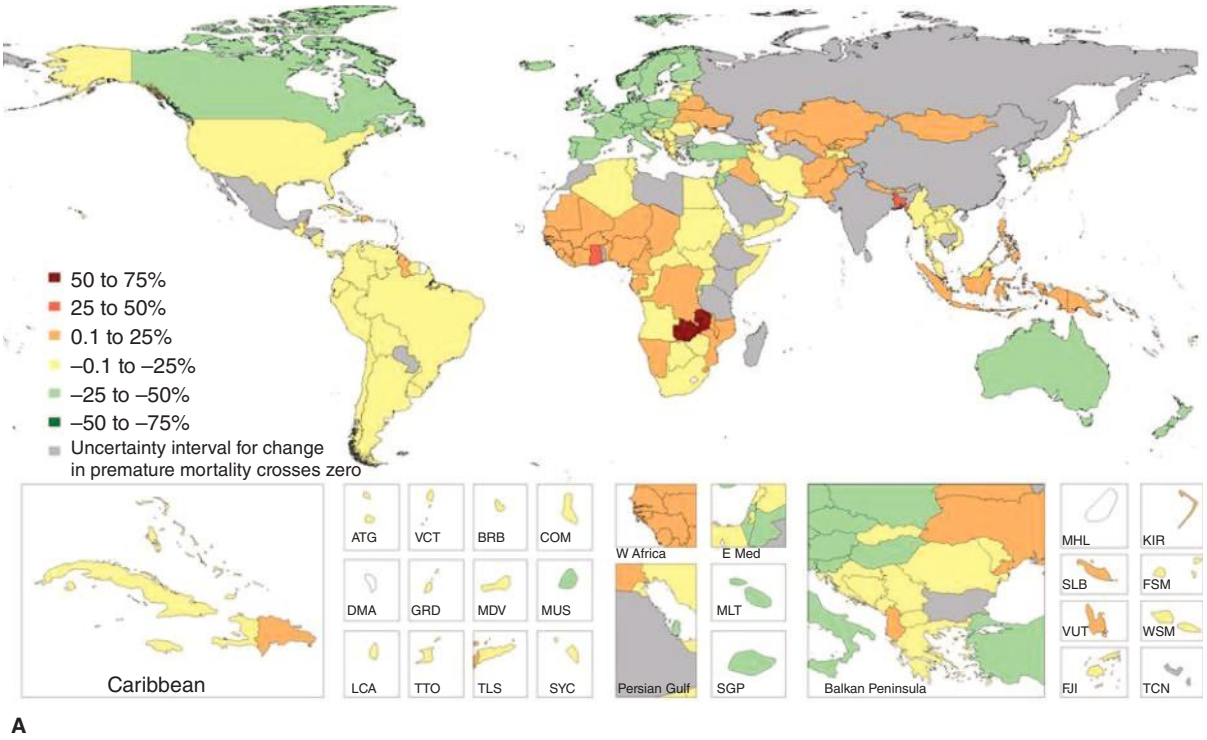


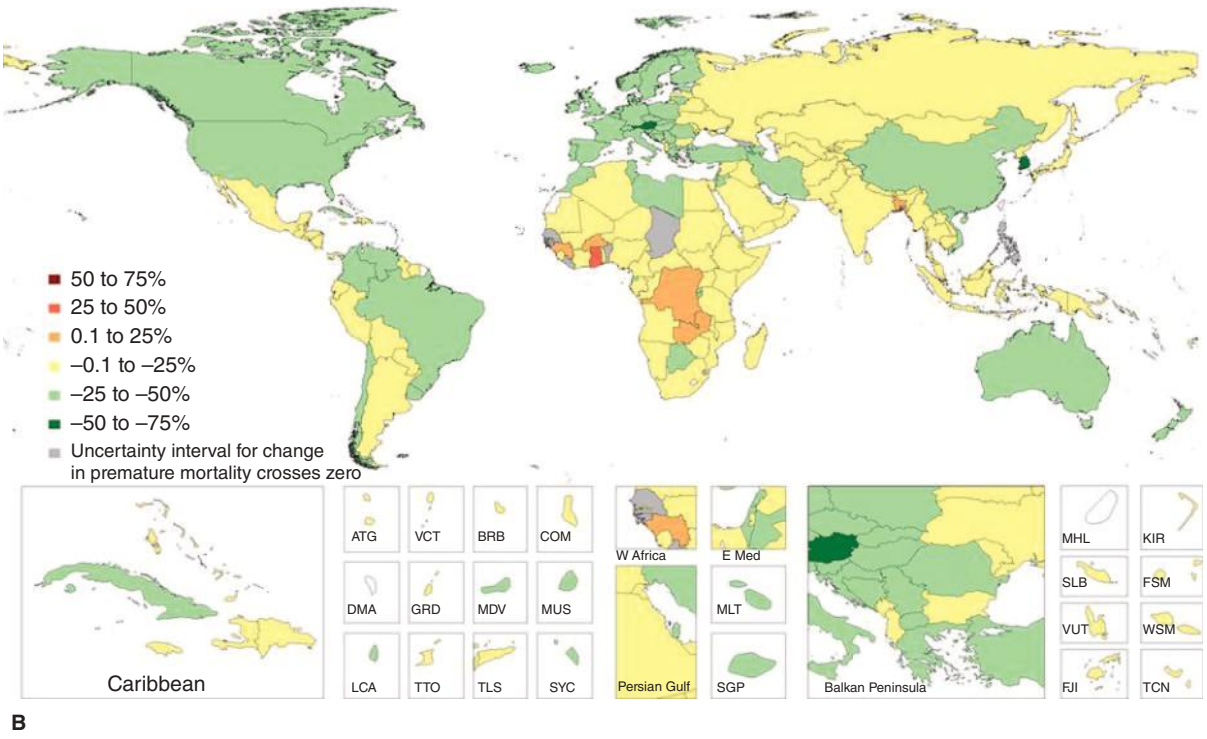
FIGURE 2–31. Barriers to control global cardiovascular disease and essential functions and recommendations to overcome those barriers. Reproduced with permission from Fuster V, Kelly BB, Vedanthan R: Promoting global cardiovascular health: moving forward, *Circulation*. 2011 Apr 19;123(15):1671-1678.[85]

populous regions. Trends in tobacco use, diabetes mellitus, obesity, and blood pressure are projected to lead to a rise in premature CVD deaths from 5.9 million in 2013 to an estimated 7.8 million in 2025 with no significant change in the global probability of premature CVD deaths. Achieving these four risk factor targets would result in only 5.7 million deaths, with a 26% reduction for males and a 23% reduction for females in the global risk of premature CVD death (Fig. 2–32).[87]

Certain regions account for a larger burden of premature CVD death, including South Asia, East Asia, and Southeast Asia (together accounting for 60% of these deaths). The risk of a premature CVD death in 2025 would be highest for males in Central Asia and Eastern Europe (both 0.28; 95% UI, 0.26-0.30 and 0.27-0.29, respectively) and for females in Oceania (0.19; 95% UI, 0.13-0.26). Western Europe, high-income Asia-Pacific regions, and Australasia would have the lowest risk (0.03 for males and 0.01 for females) (Figs. 2–33 and 2–34). Globally, the risk factor change that would lead to the largest reduction in premature mortality would be the decreased prevalence of hypertension, followed by tobacco smoking prevalence for men and obesity for



A



B

FIGURE 2–32. **A.** Global map of percentage change in premature cardiovascular mortality from 2013 to 2025 if risk factors continue the current trend. **B.** Global map of percentage change in premature cardiovascular mortality from 2013 to 2025 if all risk factor targets are achieved in 2025. Reproduced with permission from Roth GA, Nguyen G, Forouzanfar MH, et al: Estimates of global and regional premature cardiovascular mortality in 2025, *Circulation*. 2015 Sep 29;132(13):1270-1282.[87]

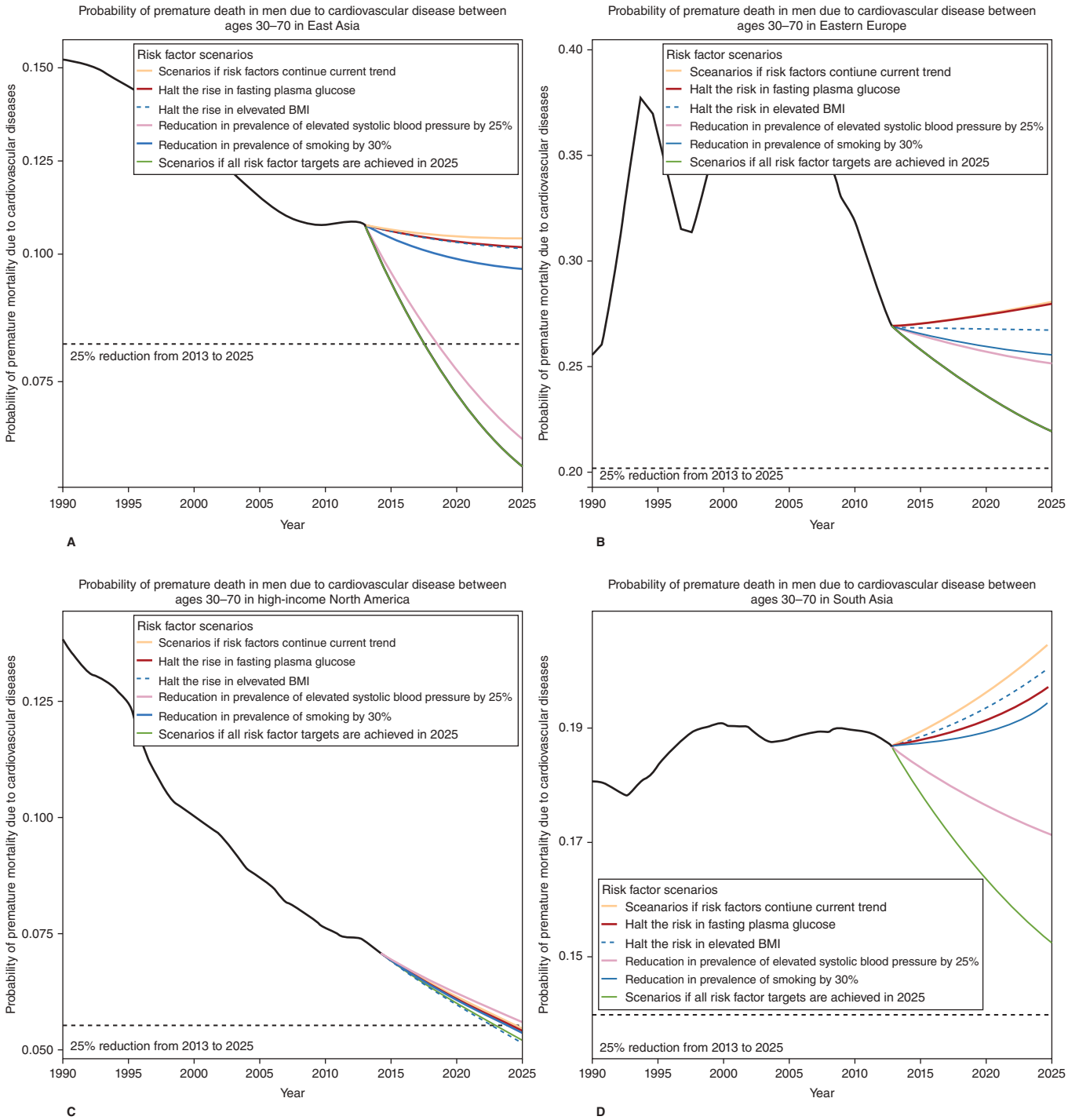


FIGURE 2–33. Observed and projected cardiovascular mortality for men in selected regions, 1990 to 2025: (**A**) East Asia, (**B**) Eastern Europe, (**C**) high-income North America, and (**D**) South Asia. The scenario for halting the rise in body mass index (BMI) uses the association with death adjusted to be independent of its effect on blood pressure and fasting plasma glucose and therefore underestimates the effect of BMI on mortality. The inflection point seen in 2013 to 2014 represents the change from observed mortality to results based on the projection method. Reproduced with permission from Roth GA, Nguyen G, Forouzanfar MH, et al: Estimates of global and regional premature cardiovascular mortality in 2025, *Circulation*. 2015 Sep 29;132(13):1270-1282.[87]

women. Results vary by region because of differences in risk factor and disease trends. Tobacco smoking would contribute the most reductions for men in North Africa and Middle East, Central Asia, and Central sub-Saharan Africa and for women in high-income Asia Pacific and Western Europe.[87]

Regions that have already experienced rapid declines in CVD mortality will see a relatively small benefit from proportional reductions in risk factor levels. However, for many low- and middle-income regions, a 25% reduction in premature CVD mortality would occur only in a scenario in which multiple risk factor targets are achieved.[87]

CONCLUSION

CVD continues to account for the largest loss of health globally, with the majority of premature deaths occurring in LMICs. Declining age-standardized rates of CVD in many high-income regions is a result

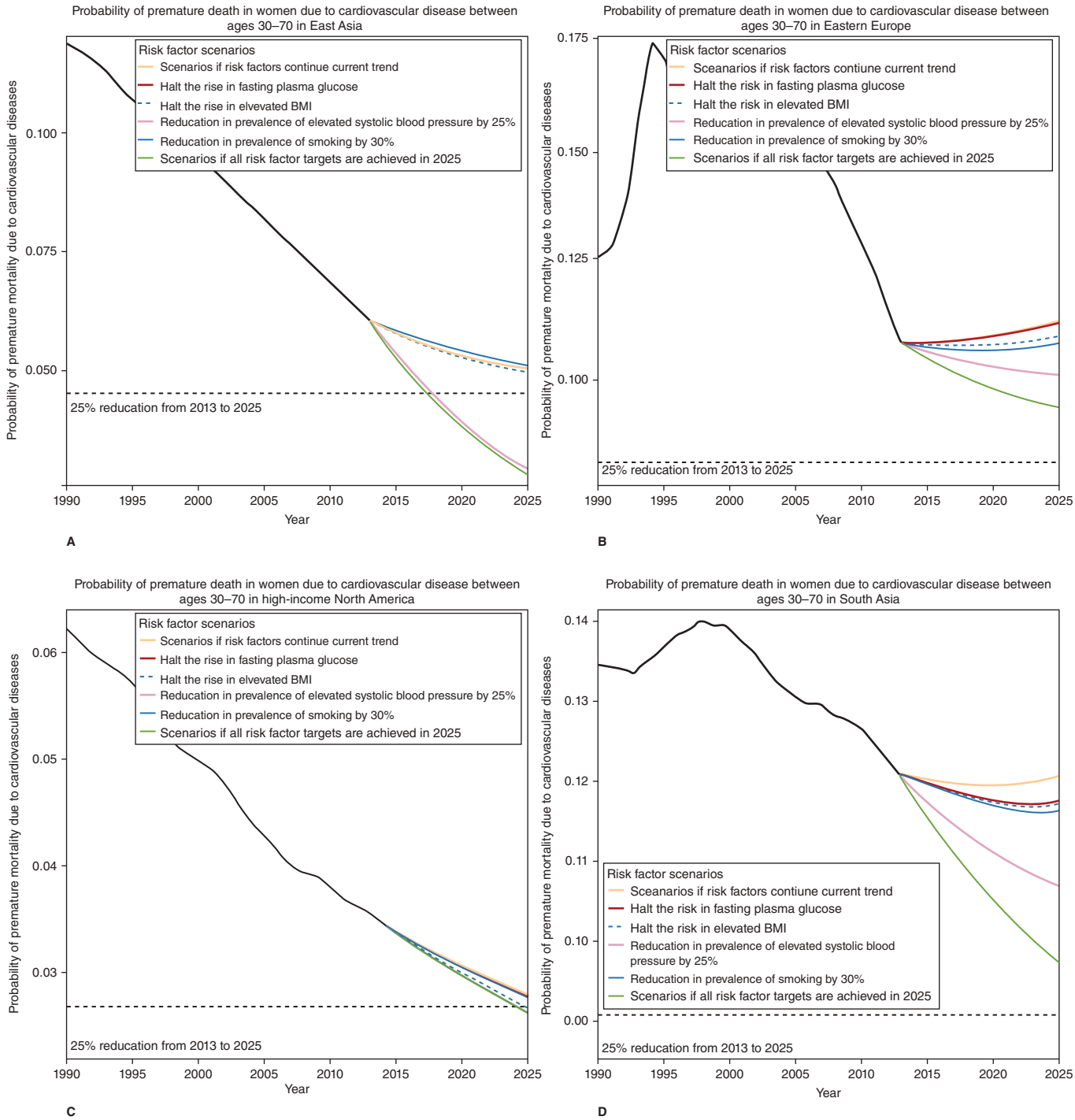


FIGURE 2–34. Observed and projected cardiovascular mortality for women in selected regions, 1990 to 2025: (A) East Asia, (B) Eastern Europe, (C) high-income North America, and (D) South Asia. The scenario for halting the rise in body mass index (BMI) uses the association with death adjusted to be independent of its effect on blood pressure and fasting plasma glucose and therefore underestimates the effect of BMI on mortality. The inflection point seen in 2013 to 2014 represents the change from observed mortality to results based on the projection method. Reproduced with permission from Roth GA, Nguyen G, Forouzanfar MH, et al: Estimates of global and regional premature cardiovascular mortality in 2025, *Circulation*. 2015 Sep 29;132(13):1270-1282.[87]

of improved prevention and treatment of CVD, as well as improved health care systems. However, the number of people in the world with CVD is increasing steadily as a result of population growth and aging, a trend that is increasingly burdening LMICs and their developing health care systems. IHD remains a significant cause of death globally, and the patterns of CVD are complex and reflect regional differences in both risk factors and disease incidence. Both stroke and endemic CVDs, such as Chagas disease and RHD, have a varied geographic and demographic distributions. Understanding the regional variations in traditional risk factors, such as high blood pressure and cholesterol, tobacco, unhealthy diet, and inadequate physical activity, as well as nontraditional risk factors, such as air pollution, mental health disorders, and HIV, are important for determining priorities for prevention of atherosclerotic vascular diseases.

Achieving the four primary risk factor targets outlined by the WHO would likely result in more than a 20% reduction in the global

risk of premature CVD death by 2025. However, to achieve a large-scale reduction in the global burden of CVDs, evidence-based clinical and population-level interventions that address traditional and non-traditional risks factors will need to be broadly adopted, especially in LMICs. Efforts to improve health education, access to primary health care, and access to healthy foods are likely to form the foundation of such efforts. To be sustained and successful, these efforts will require a much broader recognition of the massive impact of CVD on global health.

METRICS AND METHODS

SUMMARY MEASURES OF HEALTH

The DALY is a core summary measure of health that represents the gap between a population's actual health and an ideal standard. DALYs combine information regarding premature death (YLLs) and disability caused by the condition (YLDs). YLLs are calculated by multiplying observed deaths for a specific age in the year of interest by the age-specific reference life expectancy estimated by the use of life table methods (eg, 86.0 years at birth as the longest observed life expectancy in Japan).[88] YLDs are calculated by multiplying disease prevalence (in number of cases for a year) by a health state–specific disability weight representing a degree of lost functional capacity. One DALY corresponds to 1 lost year of health, either caused by death or disability, and is the sum of a number of YLLs plus a number of YLDs.[89] YLLs and YLDs can be reported for specific diseases and, as cause-specific DALYs, serve as a useful tool for comparing health loss among disparate conditions. Just as with mortality rates, both crude and age-standardized DALY rates can be calculated by dividing the annual number of DALY by the population at risk in a given year.

DEFINING DISEASE CATEGORIES

Any consistent evaluation of CVD requires the adoption of case definitions. In the GBD study, CVD is estimated separately for the nine most common causes of CVD-related death as well as an "other" category for less common causes (see Table 2–1). These causes are IHD, IS, hemorrhagic and other stroke, AF, peripheral vascular disease, aortic aneurysm, hypertensive heart disease, endocarditis, RHD, and a category for other CVD conditions.[3,90,91] Death is defined following international standards governing the reporting of death certificates. For example, IHD is defined as an underlying cause of death across International Classification of Diseases (ICD) revisions (most recently ICD-10 I20-I25, ICD-9 410-414).[13] A proportion of deaths are erroneously assigned on death certificates to either nonfatal ICD conditions (eg, "senility") or conditions not defined as an underlying cause of death (eg, heart failure or hypertension). The GBD study developed methods for systematically reallocating these undefined or erroneously assigned deaths to CVD causes based on the total distribution of actual causes of death by country, sex, age, and year.[90,91]

Prevalent cases of IHD represent estimates of four distinct disease states: acute myocardial infarction, chronic stable angina, chronic IHD, and heart failure caused by IHD (eg, ischemic cardiomyopathy). The definition for myocardial infarction follows the WHO definition, based on the case-finding approach from the MONICA studies, which includes out-of-hospital sudden cardiac death and did not require a troponin level.[24,92] Cerebrovascular disease case definitions also follow the WHO[93,94] and represents both acute strokes and chronic disability following a stroke. Peripheral vascular disease is considered as an ABI less than 0.9, with disability attributed only to those reporting claudication. Prevalent AF is defined electrocardiographically, assumes either a paroxysmal or permanent state, and included atrial flutter as well as AF. Hypertensive heart disease is considered to be symptomatic heart failure as a result of hypertension (eg, New York Heart Association class 2 or greater). Endocarditis and RHD are considered to be diagnosed clinically, which includes cases identified either by auscultation or standard echocardiographic criteria for definite disease. For example, valve disease on a screening echocardiogram consistent with only "possible" rheumatic disease is not included; however, definite valvular disease confirmed by a clinician is included.

DATA SOURCES AND ANALYTIC METHODS

In brief, the most recent GBD studies from 2010 and 2013 used all available data, including country-level surveillance, verbal autopsy, vital registration, published and unpublished disease registries, and published scientific literature. These data sources are available online via the Global Health Data Exchange (http://ghdx.healthdata.org/). Regional income, metabolic and nutritional risk factors, and other covariates were estimated from surveys and published systematic reviews. Statistical approaches were used to produce estimates for all countries, including the small number without available data. Analysis of mortality adopted an ensemble model approach that includes covariates such as the levels of CVD risk factor exposures and national income while borrowing strength across space, time, and age groups.[95] Analysis of disease prevalence used custom disease modeling software, DisMod-MR, which accounts for study-level differences in measurement method and standard assumptions about the interrelationships among disease-specific incidence, prevalence, case fatality, and mortality.[3,96-98]

REGIONS OF THE WORLD

GBD 2013 reported results for 21 world regions as well as 188 countries. In some sections, we collapse these regions into seven "super-regions": high-income, East Asia/Pacific, North Africa/Middle East, sub-Saharan Africa, Latin American and Caribbean, Eastern Europe/Central Asia, and South Asia. GBD 2013 high-income regions were North America, Western Europe, Australasia (Australia and New Zealand), and Asia-Pacific (Japan, South Korea, Brunei, and Singapore); the remainder of countries were grouped into regions by geographic proximity and broadly similar epidemiological patterns.

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CHAPTER 3

ASSESSING AND IMPROVING THE QUALITY OF CARE IN CARDIOVASCULAR MEDICINE

Yashashwi Pokharel and John A. Spertus

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The Trustees of Hospitals should see to it that an effort is made to follow up each patient they treat, long enough to determine whether treatment given has permanently relieved the condition or symptom complained of . . . A layman could not enter authoritatively into the details . . . but he could insist that the End Results System should be used.—Ernest A. Codman

Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives.—Willa A. Foster

For more than a century, there has been growing recognition of both the importance of, and rigor required to improve, the quality of health care. In the United States, health care expenditure accounted for nearly 17.5% of the gross domestic product in 2014 and is expected to reach 19.6% by 2024.[1] In a recent report, the US health system ranked lowest among 11 countries with respect to access, equity, quality, efficiency, and healthy lives,[2] despite spending the most on health care.[3] Although there has been some improvement in the quality of health care in the United States over the past decade, it is nowhere near the level desired or expected, thus creating a critical challenge to the profession to provide higher value care to Americans.[4-6] Despite many technologic and therapeutic advances, particularly in the cardiovascular field, the timely, systematic translation of new knowledge into clinical practice remains a challenge,[7] as an ideal health care system should be able to rapidly deploy new knowledge to improve the value of health care.

It is often thought that high-quality health care is dependent on the increased discovery and delivery of novel diagnostic and therapeutic interventions. However, prior studies suggested that more use of expensive medical care was actually associated with worse quality and outcomes.[8,9] Woolf and Johnson[10] have extended this concept to mathematically quantify the trade-off between the development of new interventions and the more consistent delivery of known therapies. They argue that despite tremendous scientific and technologic advancements, the failure to consistently deliver proven therapies dilutes and reduces the overall quality of a health care system. Thus, money spent on improving this actual delivery of care may be equally or even more critical than money spent on improving technology to result in improved quality of both routine and specialized health care. By using a mathematical nomogram, it has been shown that it is easier to save lives by improving the delivery of care to all patients than by improving the efficacy of care through further technologic advances.[10] For example, a new drug must yield dramatic, often unrealistic, increases in efficacy to do more good than could be accomplished by improving the delivery of care to all patients in need—the break-even point.[10] In addition, such new therapeutic choices are usually more expensive than existing therapies, making Woolf and Johnson's argument even more compelling.

Health care value, a key aspiration for the profession, is defined as patients' outcomes and experiences, divided by cost. Moreover, high-value health care ought to be provided consistently and reproducibly across providers and institutions. These goals were highlighted in the Affordable Care Act, which was signed into law in March, 2010. A myriad of mechanisms to advance this goal, such as accountable care organizations, bundled payments, and value-based purchasing, that tie provider reimbursement to quality metrics and public reporting, are emerging to accelerate the focus of health care on value. Key strategies led by the profession and payers to advance evidence-based practice and to reduce variability include the development of clinical guidelines, performance measures, and appropriate use criteria. This chapter provides an overview of these tools in the context of accepted frameworks to maximize quality and safety and highlights emerging strategies to further improve care.

CARDIOVASCULAR CARE IN THE UNITED STATES

The United States invested an estimated $3.0 trillion dollars in health care in 2014, with a projected *annual* growth rate of 5.8% over the next 10 years (Fig. 3–1).[1] For a country that spends more money than any other nation in the world, however, the United States ranks poorly on most standardized health indices[11] and quality metrics.[2,6] In the United States, cardiovascular disease (CVD) remains the leading cause of death and disability,[6] with an estimated annual total cost of $656 billion in 2015.[12] Such a magnitude of disease burden and cost demands careful scrutiny of the quality of care being delivered to elevate the value earned from the money invested.

PROGRESS IN CARDIOVASCULAR CARE

Cardiovascular medicine in the United States has benefitted enormously from the investment in scientific discovery and clinical research, leading to many advances in the knowledge and treatment of the disease process. Importantly, the past several decades have witnessed substantial improvements in age-adjusted mortality rates caused by CVD, coronary artery disease, and stroke,[6] a likely reflection of the successful adoption of primary and secondary prevention, coupled with improved treatments for acute cardiac conditions. The new

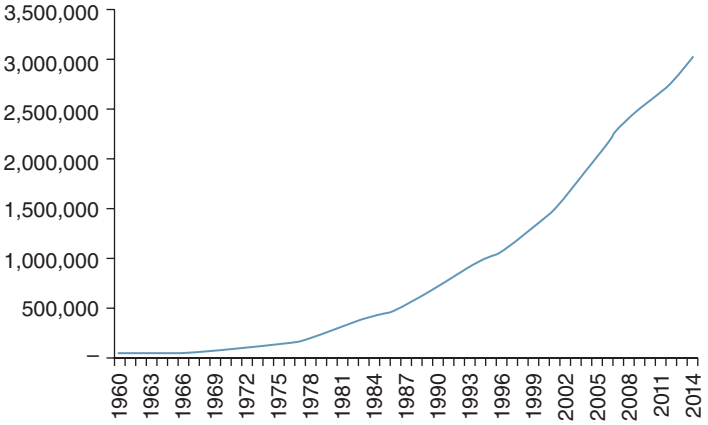

FIGURE 3–1. Trend in health care spending in the United States. Originally published in Centers for Medicare & Medicaid Services. Reproduced with permission from Centers for Medicare & Medicaid Services. National Health Expenditure Data. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html. Accessed December 8, 2015.[1]

cardiovascular diagnostic and therapeutic advances will serve best if the right choice of treatment and preventive therapies can be delivered to the right patient at the right time with minimal variation in care, while also allowing patients to choose among equally effective alternative choices, according to their preferences and values.

Cardiovascular professionals have led highly visible national initiatives to promote the use of evidence-based medicine in clinical practice.[13,14] Acute myocardial infarction (AMI), in particular, has been at the forefront of quality initiatives, resulting in reduced AMI hospitalizations, mortality, and gender-based disparities.[13,15-20] Similarly, there have been reductions in hospitalizations for unstable angina,[19] heart failure,[19,21] and ischemic stroke[19] as well as reductions in associated mortality and readmissions.[19] Despite this progress, differences still exist across racial and socioeconomic strata, indicating a need for further improvement.[16,17,22,23] These developments are critical and underscore the systematic efforts of the profession in achieving meaningful improvements in outcomes throughout the United States. However, it must be noted that despite these successes, multiple studies have elaborately documented marked inconsistencies in cardiovascular care across geographic regions[24-29] and in patient risk status.[28,30,31] Collectively, these variations, some examples of which are reviewed in the subsequent section, underscore the thesis of the Institute of Medicine (IOM) that "there is not a gap between what the healthcare is now and what could be, but rather a chasm."[7]

VARIABILITY AND APPROPRIATENESS OF HEALTH CARE DELIVERY

A critical goal of efforts to disseminate high-quality care is to ensure rational and efficient use of effective treatment to those who derive the most benefit.[7] Yet, surveys evaluating processes of care have shown that, on an average, only one in two US adults receives recommended care when receiving health care services.[31] An ideal health care system aims to minimize the variation in care provided so that patients who could derive the benefit receive the care, regardless of other factors such as gender, ethnicity, race, geographic location, and socioeconomic status. Studies have shown a number of sources of such variation.

Variation by Clinical Status: The Risk-Treatment Paradox

Beyond concerns about overall disparities in care, there is emerging evidence that among the patients eligible for treatments, those with the least potential to benefit are preferentially treated, whereas those with the most to gain are systematically undertreated. Referred to as the *risk-treatment paradox*, numerous investigators have shown that high-risk patients—who would be expected to benefit more than lower risk patients—are preferentially treated less aggressively, whereas lower risk patients are treated more aggressively.[32-37] For example, although the use of bleeding avoidance strategies in percutaneous coronary intervention (PCI) (eg, radial access, bivalirudin, or closure devices) are most beneficial in patients at the highest risk of bleeding, the variations across physicians in treating the most high-risk patients shows marked variability and little evidence of tailoring treatment to risk[32] (Fig. 3–2).

Variation by Sociodemographic Factors

Several studies have suggested marked variations in the use of evidence-based treatments of CVD as a function of gender, age, race, education, income, and insurance status.[31,38-40] A study examining explanations for differences in treatment of myocardial infarction showed that although blacks lived closer to hospitals considered high-quality and having revascularization capability than whites, blacks were less likely than whites to be admitted to revascularization-capable and high-quality hospitals.[41] Although recent data have suggested that some of these differences are narrowing, significant variations that can be avoided still persist.[38,42] These differences in the processes of care run counter to established ethical principles of equity and underscore the need for tools to systematically elevate the quality of care for all.[7]

Variation by Providers, Facilities, and Geographic Regions

Further emphasizing the need to monitor the quality of care has been the observation of marked variations in the processes of care by geographic region. Pioneering work from the Dartmouth Atlas series,

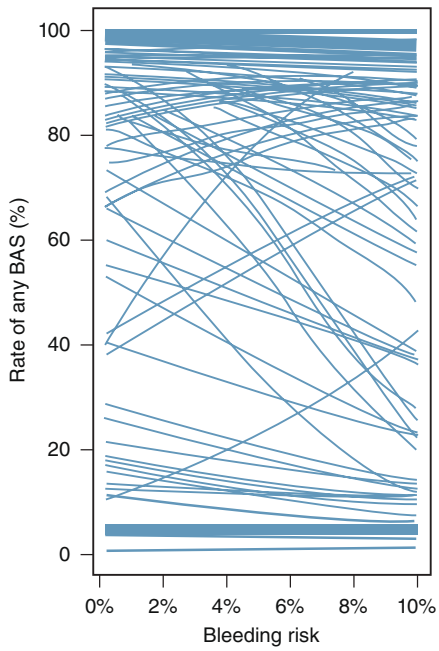

FIGURE 3–2. Variability in the use of bleeding avoidance strategy. Some physicians never used bleeding avoidance strategy (BAS), even among patients at highest risk for bleeding, whereas others used BAS in all of their patients, even among those with lowest bleeding risk. Each line represents a physician in the study. Originally published in Spertus JA, Decker C, Gialde E, et al. Precision medicine to improve use of bleeding avoidance strategies and reduce bleeding in patients undergoing percutaneous coronary intervention: prospective cohort study before and after implementation of personalized bleeding risks. Reproduced with permission from Spertus JA, Decker C, Gialde E, et al: Precision medicine to improve use of bleeding avoidance strategies and reduce bleeding in patients undergoing percutaneous coronary intervention: prospective cohort study before and after implementation of personalized bleeding risks, *BMJ*. 2015 Mar 24;350:h1302.[32]

a comprehensive evaluation of health care services provided to Medicare beneficiaries, has documented broad variation in the use of both diagnostic and treatment modalities in CVD as a function of the site of care.[43] For example, in the first Dartmouth Atlas of Cardiovascular Health Care, Wennberg and colleagues found wide variations in the use of echocardiograms, ranging from 56 per 1000 beneficiaries in Portland, Oregon, to 339 per 1000 beneficiaries in Miami.[43] Considerable differences were also observed in the use of angioplasty, with rates ranging from less than 3 to greater than 20 per 1000 patients, after adjustment for age, gender, and race.[43] These patterns of unexplained variation extend into other processes of care and range from acute events, such as resuscitating patients experiencing a cardiac arrest[27] to heart failure.[24,25] The challenge, of course, with documenting variations is knowing which rate is "right."[7] This had encouraged additional efforts to better assess variability, as described below (see Appropriate Use Criteria).

FRAMEWORKS FOR ASSESSING THE QUALITY OF CARE

It is estimated that, on average, it takes about 17 years for guidelines to be incorporated into clinical practice,[7] even with an intervention as simple as aspirin use at the time of myocardial infarction (Fig. 3–3). There can be several levels of barriers in effective implementation of clinical evidence and guidelines in routine practice. These exist at policy, societal, system/organizational, provider, and patient levels. In the following paragraphs, we describe the framework for quality metrics in the care of CVD and tools to improve the quality of care.

DEFINING QUALITY

Lohr and Schroeder broadly define quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[44] The US Agency for Healthcare Research and Quality has proposed a similar definition: "Quality healthcare means doing the right thing at the right time in the right way for the right person and having the best results possible."[45] The Institute for Healthcare Improvement recommends that to improve the United States' health care system requires simultaneous pursuit of three aims, called the "Triple Aim"—improving the patient experience of care (including satisfaction), improving outcomes (of individuals and populations), and reducing the per capita cost of health care.[46] Achieving the best quality of care as marked by highest quality patient outcome and experience with the lowest possible cost is what a health care system usually strives to achieve (see Fig. 3–1). Although the concept of quality health care is intuitive and relatively straightforward to understand, to actually measure, monitor, and improve quality necessitates the use of a clear conceptual framework that encompasses important relevant aspects of health care.

FRAMEWORKS FOR QUANTIFYING QUALITY

Conceptualizing quality is critically dependent on the perspective of the observer. This, in turn, influences the approach to quality assessment (QA), namely, determining *who* is being assessed, *what processes* are being monitored, and *what expected outcomes* are being evaluated. Health care is a complex multidimensional phenomenon with a myriad of factors influencing both the delivery and quality of care provided. Multiple organizations have undertaken initiatives to quantify delivery and quality and, in so doing, have pursued different goals, perspectives, and tools. The following sections highlight the two most common approaches for performing QA/quality improvement (QI) initiatives.

The Donabedian Framework

One of the earliest approaches to conceptualizing the components of QA was proposed by Donabedian.[47] This framework considers quality as being comprised of three main domains: structure, process, and

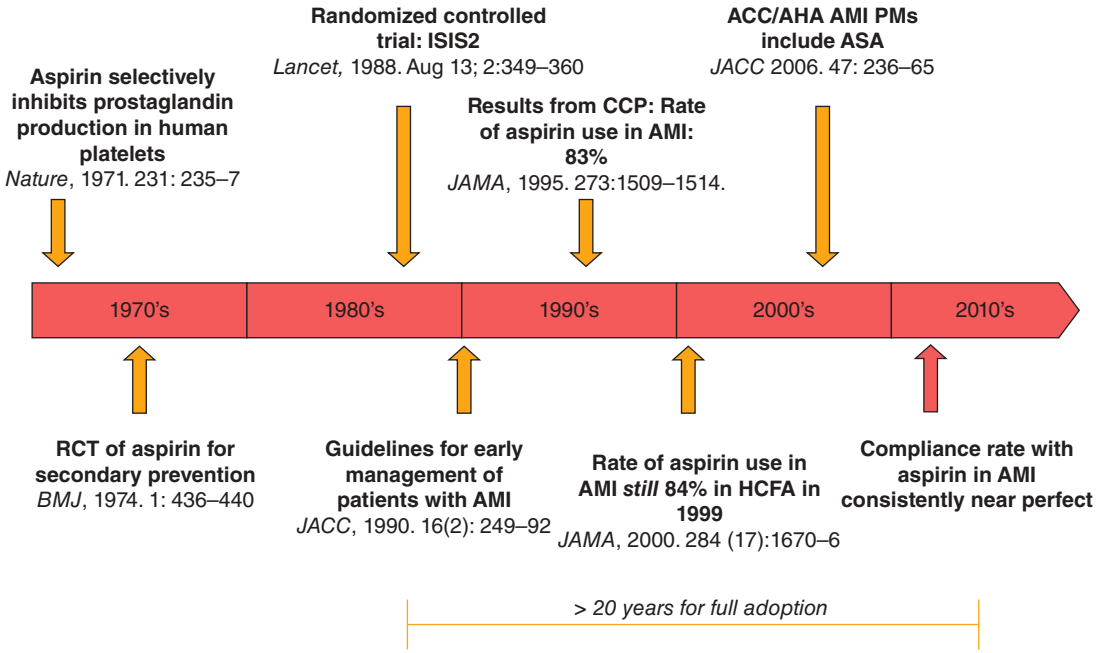

FIGURE 3–3. Slowness in adoption of aspirin therapy in acute myocardial infarction. ACC/AHA, American College of Cardiology/American Heart Association; AMI, acute myocardial infarction; ASA, acetylsalicylic acid; CCP, ISIS-2: Second International Study of Infarct Survival; ACC/AHA: American College of Cardiology/American Heart Association; PM: Performance Measure; ASA: Aspirin; AMI: acute myocardial infarction; CCP: Cooperative Cardiovascular Project; HCFA: Health Care Financing Administration.

outcome. *Structure* refers to the attributes of settings where care is delivered and includes aspects that exist independently of the patient. Examples of structural attributes include provider training and experience, availability of specialized treatments, nurse-to-patient ratios, and treatment and discharge plans. *Process* refers to whether or not good medical practices are followed and incorporates concepts such as the medications given and timing of their administration, the use of diagnostic and therapeutic procedures, and patient counseling. *Outcome* refers to tangible measures that capture the consequences of care and range from manifestations of disease progression (eg, mortality and hospitalizations) to patient-centered outcomes of health status and treatment satisfaction. As noted by Donabedian, these three components of quality are interdependent and built on a framework that primarily focuses on the delivery of care that aids in linking delivery to outcomes.

The Quality Hexagon

The current driving force and roadmap for QI initiatives in American health care is the IOM's landmark report, "Crossing the Quality Chasm: A New Health System for the 21st Century."[7] In this report, the IOM recognized substantial deficiencies in the current status of American medicine while concurrently recognizing that individual practitioners were deeply committed to providing high-quality care. They thus focused on the need for a major overhaul of the health care system with a view to placing the patient at the center of QI initiatives.

The IOM recognized the following principal thematic dimensions needed to guide QI in health care:

- Safety—avoiding injuries to patients from the care that is intended to help them
- Effectiveness—providing services based on scientific knowledge to those who could benefit while refraining from providing services to those not likely to benefit
- Patient-centeredness—providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions
- Timeliness—reducing waits and sometimes harmful delays in care
- Efficiency—avoiding waste, including waste of equipment, supplies, ideas, and energy
- Equity—providing care that does not vary in quality because of personal characteristics such as sex, ethnicity, geographic location, and socioeconomic status

Both the Donabedian components and the IOM principles are landmark frameworks that have helped steer the health care system in the United States to improve quality and safety. To better understand the use of QA tools, we describe a prototypical framework that combines the IOM principles and the Donabedian components in the context of the delivery of health care (Fig. 3–4). Consider a patient who enters the health care system for management of an AMI. Delivery of care extends from the initiation of prehospital care by emergency medical services to treatment and posthospitalization follow-up. The structural component of QA/QI includes the systems responsible for the provision of care, the material resources on which those systems depend, and the organizational structures that guide their interactions. *Patient care systems* include the prehospital services, the emergency department, inpatient resources, and the outpatient system to which the patients are referred for postdischarge care (eg, availability of cardiac rehabilitation). *Material resources* refer to the personnel (their number, training, and competence) and equipment available for patient treatment, and *organizational systems* encompass an institution's policies and procedures, reminder systems, disease management programs, and quality measurement/improvement activities. Process of care largely centers on what providers "do" for patients, the treatments and educational actions that they take in managing the patient. It encompasses the judicious use of proven diagnostic

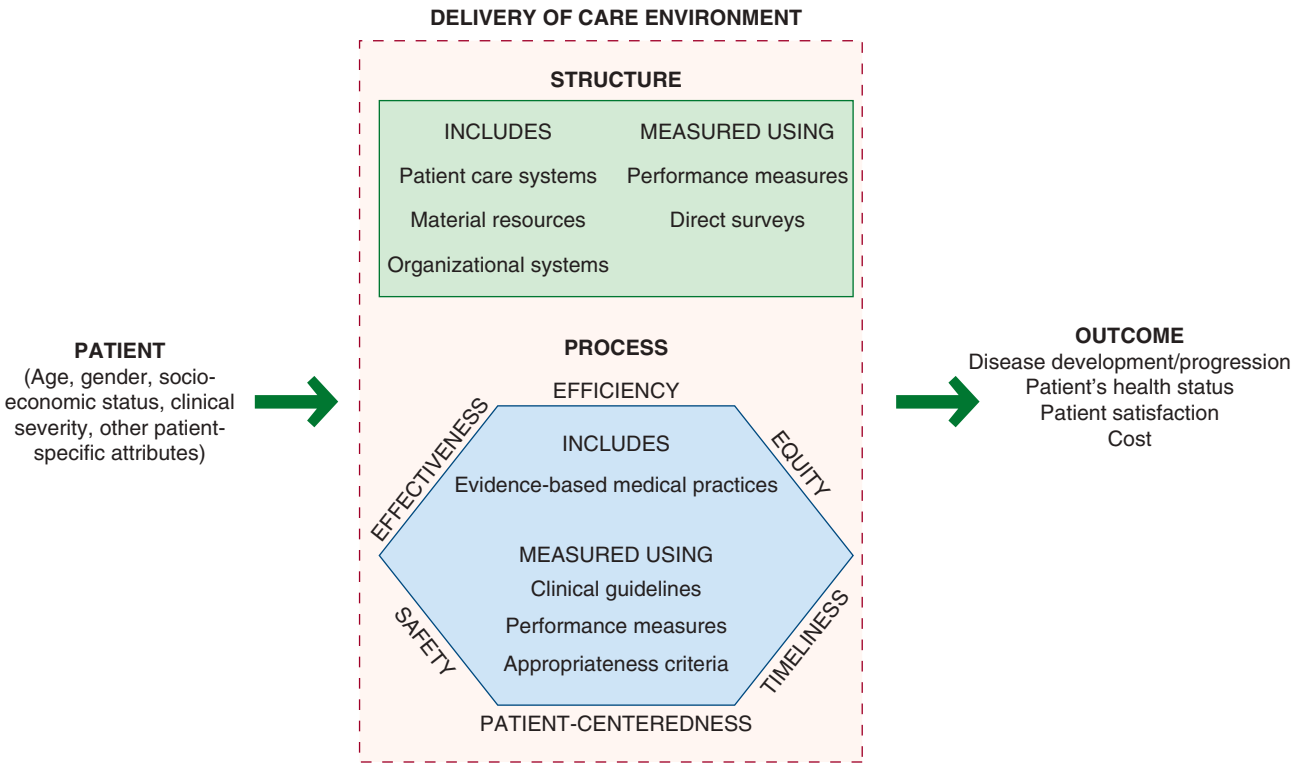

FIGURE 3–4. An integrated model for quality assessment and improvement in the delivery of health care.

and therapeutic modalities and the application of evidence-based interventions to optimize care and outcomes, such as those endorsed by clinical guidelines. In the setting of AMI, this includes, but is not limited to, timely reperfusion and administration of recommended medications (eg, aspirin, β-blockers). This delivery of optimal processes of care is articulated by the IOM concepts of high-quality care to include safety, efficacy, timeliness, equity, efficiency, and patient-centeredness. The outcomes of care include clinical events (eg, death, recurrent myocardial infarction, heart failure), patients' health status (their subsequent symptoms, function, and quality of life), satisfaction with care, and the costs of care.

Thus, depending on the perspective and goals of the entities involved, measurement of quality can be achieved across the spectrum of health care delivery using various relevant tools. In the following sections, we provide an overview of three such tools—clinical guidelines, performance measures, and appropriate use criteria—developed and promoted for QA/QI initiatives.

TOOLS TO IMPROVE THE QUALITY OF CARDIOVASCULAR CARE

To better understand and improve the quality of cardiovascular care, the profession, led by the American College of Cardiology (ACC) and American Heart Association (AHA), has created an infrastructure to advance QA/QI. These efforts include the development of data standards, evidence-based clinical guidelines, performance measures, and appropriate use criteria (AUC). Each of these tools serves a distinct yet complementary role in improving care (Fig. 3–5) and is described in detail in the following sections.

CLINICAL DATA STANDARDS

To measure and improve care, one first needs to know both how and what to measure. It is critical to have standardized data definitions that enable the reproducible collection of data across different hospitals and settings. To create the foundation for clear, explicit data capture, the ACC/AHA Clinical Data Standards were developed to serve as a foundation for implementing and evaluating the other ACC/AHA quality tools.[48] These data standards are a set of standardized definitions of particular conditions and treatments that can and should be applied in both QA/QI activities and, importantly, clinical trials. Inclusion in clinical trials is particularly important to support both comparability across studies and their incorporation into guidelines, performance measures and clinical care. In particular, standardized definitions support the consistent definition of symptoms, comorbidities, and outcomes in many areas of CVD (eg, acute coronary syndromes, congestive heart failure, PCI).[48] The more these data standards are used in clinical trials, observational registries, and QA/QI efforts, the greater the ability will be to translate the emerging knowledge from clinical research to clinical care.

CLINICAL PRACTICE GUIDELINES

To distill the rapidly expanding body of cardiovascular literature, professional agencies, such as the AHA and ACC, have commissioned expert committees to synthesize the available evidence into clinical practice guidelines.[49-51] These guidelines are an evidence-based application of published studies, ideally large-scale clinical trials, within a particular area of CVD. When substantial randomized clinical trial data are lacking, smaller clinical trials or expert panel consensus are used to recommend clinical care in specific circumstances.[50] Clinical practice guidelines are written in the spirit of suggesting diagnostic or therapeutic interventions that appear to be effective (or not) for patients in most circumstances. They are the primary activity through which the rapidly evolving literature is synthesized for practicing clinicians and form the foundation for other quality tools, such as performance measures and AUC.[49-51]

The first clinical practice guideline was developed in 1984,[52] when overutilization of pacemaker implantation led governmental regulators to ask the ACC and AHA to evaluate the available evidence and develop recommendations for practice. Since then, there has been an exponential growth in the work performed by the ACC/AHA Task Force on Practice Guidelines,[49-51] which now currently monitors almost all areas of cardiovascular care.[53] To remain current, the guidelines undergo periodic revisions and updates, as needed by emerging science. Importantly, the development of guidelines has shifted from procedure-related guidelines to disease-based guidelines, where the population of patients is more reflective of clinical care rather than being restricted to the subset of patients referred for a particular procedure. Although these guidelines are intended to assist providers in clinical decision making, they do so by describing broad principles and generally acceptable approaches for a particular disease condition.[49-51]

The creation of guidelines requires writing committees to systematically review the medical literature and to assess the strength of evidence for particular treatment strategies. This necessitates ranking the types of research from which knowledge is generated. Randomized controlled trials are given the highest weight. When these are not available, other study designs, including preintervention and postintervention studies, observational registries, and clinical experience are used. To transparently communicate the strength of a recommendation and the evidence on which it is generated, a class recommendation (Class I = strongly indicated, Class IIA = probably indicated, Class IIB = possibly indicated, or Class III = not indicated) and strength of the evidence (Level A evidence [data derived from multiple randomized trials] through Level C [data derived from expert opinion, case studies, or standard of care]) are provided.[51]

Despite being evidenced-based, there are important limitations in the development of clinical guidelines. Although summarizing all of the available evidence is a requirement, it results in lengthy and difficult-to-read documents, sometimes longer than 400 pages. To address this, the ACC/AHA also publishes pocket guidelines, executive summaries, and web-based applications that are distillations of the key recommendations without the justification for those recommendations. Another

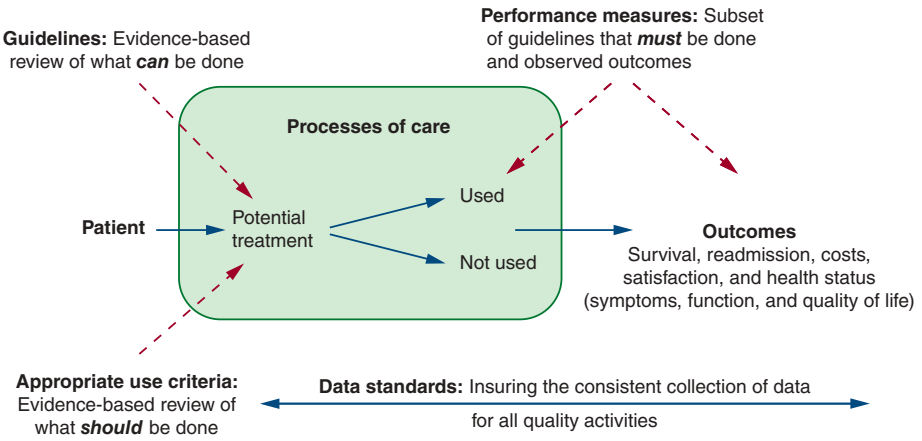

FIGURE 3–5. Overview of data standards, guidelines, performance measures, and appropriate use criteria.

limitation of guidelines is that they tend to become outdated as a result of an inherent time lag in the process of developing these documents. The ACC/AHA now releases timely focused updates to minimize the delay between the generation of new evidence and its incorporation into practice. Another important criticism is that the current method used to rank the strength of the evidence is focused on clinical trials that show some benefit, regardless of whether or not the amount of benefit is clinically important (or the benefit may be seen in a surrogate outcome, rather than a clinically meaningful outcome).[54] Importantly, the summary of clinical trials, which report the average benefit across the entire population, fail to emphasize the heterogeneity of treatment benefit, whereby some patients may benefit greatly and others do not. Ongoing efforts, using Bayesian analyses and other modalities that can exploit the heterogeneity of treatment benefit, are being explored to improve the quality of the guidelines development process.[54] Notwithstanding these limitations, clinical guidelines are an important resource that serve as the foundation for all other QI efforts in professional cardiology.

PERFORMANCE MEASURES

At times, the evidence supporting (or for avoiding) a particular diagnostic or therapeutic action is so strong that failure to perform such actions jeopardizes patients' outcomes. Performance measures represent that subset of the guidelines for which the strongest evidence exists and for which their routine use (or avoidance) is felt to be an important advance to elevating quality.[55-57] Creating performance measures entails a distinct methodology from that of guidelines creation[55,57] and, as such, is undertaken by a separate ACC/AHA Task Force writing committee.

Performance measures are often constructed as a set of measures that quantify a range of health care processes and outcomes (Fig. 3–6) and are designed to identify multiple points in the continuum of care for which clinical inertia—the failure to implement or titrate recommended therapies—can occur.[58,59] Once the relevant domains are identified, then those guideline recommendations with the strongest evidence and highest correlation with clinically meaningful outcomes are selected for performance measure creation. Constructing process-of-care performance measures requires the explicit articulation of the denominator of eligible patients, what constitutes compliance with the measure, over what period of care such compliance is needed, what source of data will be used to define these characteristics, and how the measure will be analyzed and reported.[57] Once prototypical measures are proposed, their feasibility, interpretability, and actionability need to be established. In contrast to performance measures for processes of care, outcomes of care can also serve as performance measures if they fulfill established criteria and have the capacity to be risk-adjusted for patient characteristics present prior to the initial delivery of care.[60]

Various organizations are involved in the development of performance measures. Scientific bodies such as the ACC and the AHA are involved in the science behind these performance measures. However, organizations such as the Centers for Medicare & Medicaid Services, the Joint Commission, the National Quality Forum, the National Committee for Quality Assurance, and the Ambulatory Quality Care Alliance play key roles in either developing performance measures or adjudicating their value for national QI efforts. Established performance measures are now assuming an important role in public accountability and pay-for-performance initiatives.[61,62] These are rapidly evolving initiatives and warrant the attention of clinicians in their recommendation, interpretation, and application. In addition to the more traditional clinician-focused conceptualization of performance measures, patient participation as part of performance measures is encouraged to improve patients' outcomes, including health status.[63] Similarly, challenging the historical exclusions of resource utilization and costs considerations in guideline developments and performance measures (although often implicitly considered), newer documents have started to consider cost in measure selection.[64]

APPROPRIATE USE CRITERIA

Over the past several decades, the United States has witnessed a substantial increase in the use of diagnostic testing and therapeutic procedures in cardiovascular care. For example, the National Heart, Lung, and Blood Institute estimated that more than 1.3 million coronary angiography procedures were performed in 2008, an increase of almost 350% since 1979.[65] However, this increase was not uniform and had marked regional variations, such as that documented by the Dartmouth Atlas.[66]

Given the nation's increasing concerns about the escalating costs of health care, there was a pressing need to understand such regional variability. This has led to the conceptualization of appropriateness, which includes underuse (the failure to provide services from which the patient would benefit), misuse (performing procedures in the correct patients but doing so in a manner that results in harm; see Performance Measures), and overuse (where tests and procedures may not be needed or even be harmful to the patient). Inappropriate use of tests and therapies clearly accelerate costs to both patients and society and exposes patients to potential harms.

To address the demand for clearer insights into the appropriateness of care, the ACC, along with the AHA and other professional organizations, created a framework to begin evaluating the selection of patients for specific diagnostic tests and therapeutic interventions. In 2005, the ACC published their methodology for creating appropriate use criteria in cardiovascular imaging.[67] They defined a procedure as appropriate if "the expected incremental information, combined with clinical judgment, exceeds the expected negative consequences by a sufficiently wide margin for a specific indication that the procedure is generally considered acceptable care and a reasonable approach for the indication."[67]

The AUC differ from clinical guidelines and performance measures in several important ways. First, they estimate the relative benefits and harms of a procedure or a test for a specific indication. This is done by first creating prototypical patient scenarios commonly encountered in clinical practice. Using guidelines, clinical evidence, and contemporary practices as a guide, an expert committee then evaluates the strength of the indication for that procedure or test. After an adaptation of the

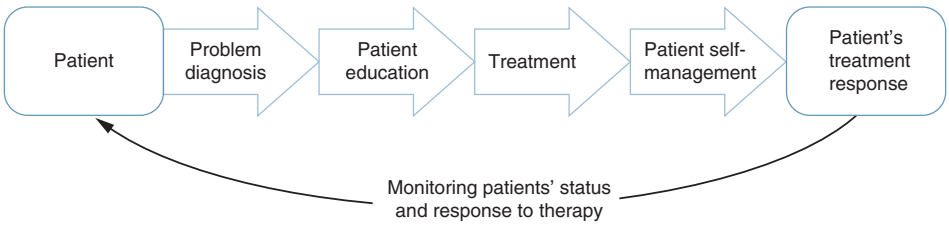

FIGURE 3–6. Example of care dimensions for ambulatory care: the care continuum. Reprinted from Spertus JA, Eagle KA, Krumholz HM, Mitchell KR, Normand SL. American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying the quality of cardiovascular care. Reproduced with permission from Spertus JA, Eagle KA, Krumholz HM, et al: American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying the quality of cardiovascular care, *J Am Coll Cardiol*. 2005 Apr 5;45(7):1147-1156.[57]

RAND Delphi approach,[68] a multistep process is pursued that engages the multidisciplinary expert panel to individually and collectively rate the appropriateness of a test. Ratings range from inappropriate (1–3), to uncertain (4–6), to appropriate (7–9).[67] The mean value of the collective responses and the degree of agreement with these ratings are then reported and form the initial AUC for that procedure or test. This methodology is continually updated as experience accrues,[69] which changes the nomenclature and expands the AUC framework for all cardiovascular technologies and procedures.

The AUC thus help identify what specific tests and procedures to perform and when and how often and, as such, have the potential to more transparently document the clinical rationale for performing tests and procedures. They overcome the limitation of the Dartmouth Atlas by providing a framework against which to judge observed variations. Since 2005, published AUC documents have assessed many areas of cardiovascular medicine, such as echocardiography (both transthoracic and transesophageal, as well as pediatric cardiology),[70,71] stress echocardiography,[72] cardiac computed tomography[73] and cardiac magnetic resonance imaging,[74] single-photon emission computed tomography myocardial perfusion imaging,[75] joint criteria for utilization of cardiovascular imaging,[76] utilization of imaging in heart failure,[77] multimodality detection and risk assessment of stable ischemic heart disease,[78] diagnostic catheterization,[79] coronary revascularization,[80] and peripheral vascular ultrasound and physiological testing.[81] Future directions for these efforts are to explicitly contrast the relative appropriateness of alternative diagnostic modalities for specific clinical indications.

Adoption of AUC in routine practice has resulted in marked improvement in certain areas of cardiovascular care, such as coronary revascularization. A study examining the appropriateness of PCI showed that between July 2009 and September 2010, 98.6% of PCIs were classified as appropriate, 0.3% uncertain, and 1.1% inappropriate for acute indications (AMI and high-risk unstable angina).[82] However, for nonacute indications, 50.4% were classified as appropriate, 38.0% uncertain, and 11.6% inappropriate. Similarly, although there was minimal variation in the proportion of inappropriate PCI across hospitals for acute indications, there was substantial variation for nonacute indications (median hospital rate, 10.8%; interquartile range, 6.0%–16.7%).[82] In a separate study, inappropriate PCIs for nonacute indications were more common in men, whites, and patients who had private insurance, suggesting overuse in traditionally privileged groups.[83] Recently, the trends in appropriateness over time have been reported. This showed that since the publication of the original AUC for coronary revascularization in 2009 there were significant reductions in the volume of nonacute PCI, particularly among those classified as inappropriate nonacute PCIs (26.2%–13.3%).[28] Despite this, hospital-level variation of inappropriate PCIs persisted (median, 12.6%; interquartile range, 5.9%–22.9%) in 2014.[28]

Although AUCs are a promising method for the profession to guide the more cost-effective use of expensive technology, there are potential challenges with the AUC. First, developing AUC is limited by rigorous scientific evidence for a number of common clinical scenarios. Thus, validation of these criteria—establishing that those with more appropriate indications obtain more benefit from the procedure than those with less appropriate indications—is important. Although this has been shown for the coronary revascularization AUCs,[84,85] it has not yet been assessed for the other AUC ratings. Second, AUC are a general guide to clinical care and cannot possibly address the many extenuating factors that might lead to very rational decisions in real-world practice. This has an important implication on the interpretation of AUC results in clinical practice. In the use of performance measures, inclusion and exclusion criteria for the denominator often mean that the expected goal of compliance with performance measures is 100%. This will not be the case with AUC. There will be patients who are rated as uncertain or inappropriate, using the coarse definitions with which the AUC were created, who would clearly benefit from a procedure. However, it is unlikely that such patients will differ markedly by practice. Thus, those practices that are outliers, as compared with others, warrant careful evaluation of their treatment practices. For example, finding that a practice in which less than 50% of patients are deemed appropriate will raise concerns of overuse, whereas a practice in which 100% of patients are considered appropriate may suggest underuse of the procedure in patients who might benefit. More experience with the use of AUC will improve their use and interpretation as the country struggles to maximize the value of cardiovascular care.

LEVERAGING THE TOOLS TO IMPROVE QUALITY: ONGOING QUALITY INITIATIVES

Although clinicians work hard to provide the highest quality of care to their patients and usually believe that they are accomplishing this goal, without explicitly measuring one's performance it is impossible to know how well one is doing. The infrastructure of tools, including data standards, guidelines, performance measures, and AUC, especially when supplemented with outcomes measures, can create a powerful infrastructure to assess and improve the quality of cardiovascular care. Outcomes that are proving to be increasingly actionable assessments of care include long-term mortality, readmission rates, and patient-centered outcomes, as assessed by such measures as the Seattle Angina Questionnaire[86] and the Kansas City Cardiomyopathy Questionnaire.[87] Often, these are most efficiently executed when integrated into prospective data collection systems. Over the past decade, several national registries have been developed to support the prospective collection of data for assessing performance and guidelines compliance within hospitals. These include, for example, procedural registries, such as the ACC National Cardiovascular Data Registries (NCDR) for cardiac catheterization/PCI, implantable cardioverter defibrillator implantation, and carotid stenting, as well as disease-based clinical registries, such as the AHA Get with the Guidelines registries for heart failure and stroke and the Acute Coronary Treatment and Intervention Outcomes Network, or ACTION, acute coronary syndrome registry. To supplement these inpatient registries, as a prelude for examining the transitions of care to the outpatient settings, new initiatives of the AHA and ACC seek to quantify the quality of outpatient care. The ACC's Practice Innovation and Clinical Excellence, or PINNACLE, and the AHA's Get with the Guidelines—outpatient registries are examples of these new efforts. All of these registries require a substantial commitment from hospitals and practices to abstract the necessary data for these registries, but in return, they receive benchmarked assessments of their performance, with which they can develop local QI programs to improve care. It is expected that registries will be even more important given that they are closely intertwined with performance measure development. Registries will be crucial in assessment of different types of measures, such as process measures, risk-adjusted outcome measures and resource use measures, all of which are important to patients, clinicians, purchasers, and other stakeholders.[88]

Some of the most exciting opportunities to improve care come from the combination of these registries and national coalitions to target significant gaps in care. A dramatic example of this is the Door-to-Balloon (D2B) initiative. The ACC, in partnership with 38 partner organizations, worked to increase the proportion of patients with ST-segment elevation myocardial infarction receiving primary PCI within 90 minutes of hospital presentation.[89] Launched in 2006, this initiative sought to increase the proportion of ST-segment elevation myocardial infarction

patients receiving prompt reperfusion from approximately 50% to more than 75%. This program supplemented data collected through the NCDR CathPCI registry with explicit recommendations about how to improve performance (Fig. 3–7),[90] including (1) activation of the catheterization laboratory (cath lab) by emergency department physicians, (2) single-call activation of the cath lab, (3) expectations of having the cath lab team assembled within 30 minutes, (4) prompt data feedback to the emergency department and cath lab staff, and (5) activation of the cath lab based on prehospital ECGs and targeted times to first ECG acquisition for chest pain patients within 10 minutes. Between January 2005, and September 2010, this effort led to a decline in median D2B time of 96 minutes in December 2005, to a median of 64 minutes in September 2010.[91] There were corresponding increases in the proportion of patients undergoing primary PCI within 90 minutes (from 44.2% to 91.4%), and within 75 minutes (from 27.3% to 70.4%). The declines in median times were greatest among groups that had the highest median times during the first period.[91] The success of this initiative is an extraordinary example of the cardiovascular profession critically evaluating its performance, setting goals for improvement, and implementing those changes to improve the care of patients. Its success lays the foundation for future efforts and serves as an example for all areas of medicine.

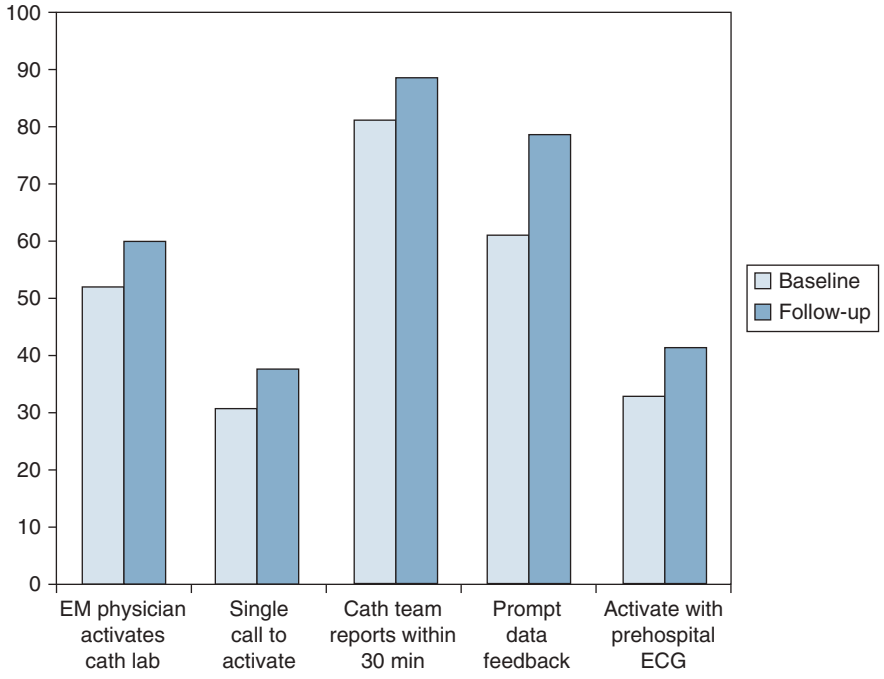

FIGURE 3–7. Percentage of door-to-balloon alliance hospitals reporting use of recommended strategies at baseline and follow-up surveys. Analyses were conducted for hospitals that responded to the selected item in both the baseline and the follow-up surveys; therefore, numbers vary by strategy because of missing data on selected survey items: n = 683 for the first two strategies listed, n = 664 for the third strategy listed, n = 598 for the fourth strategy listed, and n = 608 for the last strategy listed. Proportions at follow-up were significantly greater than proportions at baseline for each strategy (McNemar test for difference in proportions, $P < .001$). cath lab, catheterization laboratory; D2B, door-to-balloon; ECG, electrocardiogram; EM, emergency medicine. Reproduced with permission from Bradley EH, Nallamothu BK, Herrin J, et al: National efforts to improve door-to-balloon time results from the Door-to-Balloon Alliance, *J Am Coll Cardiol*. 2009 Dec 15;54(25):2423-2429.[90]

FUTURE DIRECTIONS AND CONCLUSION

FUTURE DIRECTIONS: PATIENT-CENTERED QUALITY OF CARE

This chapter outlines the challenges and opportunities to improve the quality of care. Although data continue to emerge regarding the variability in care and the poor association between the intensity and costs of care with outcomes, there are emerging opportunities to systematically study and improve care. Through the use of guidelines, performance measures, AUC, and expanded outcomes assessments, the health care delivery system has an ever-increasing opportunity to assess and improve its care. When combined with national commitments to improve care, dramatic improvements in both the processes (eg, D2B times) and outcomes (eg, the reduction in AMI mortality) can occur. Although past accomplishments are exciting, they also create a compelling case to expand these efforts in other areas, such as heart failure and arrhythmias. They also challenge the profession to consider new directions to assess and improve care.

Understanding outcomes from patients' perspectives and incorporating their preferences into QI efforts are particularly exciting directions for the field. During the past decade, a focus on patient perceptions of care and patient satisfaction has emerged as an important concern in health care systems.[92] Studies that have examined the association between patients' perceptions of quality and other objective measures of performance have consistently demonstrated that patients' perceptions of quality differ from technical aspects of care (such as processes of care).[92,93] One emerging strategy to link patients' perceptions with QA/QI has been the development of patient-centered tools that explicitly quantify patients' perceptions of their health status (their symptoms, function, and quality of life).[94] These range from disease-specific health status measures as a means to assess the control of patients' symptoms to patient satisfaction surveys, such as the Consumer Assessment of Healthcare Providers and Systems.[95] Over the next few years, these tools are expected to be used more frequently because they have been endorsed by various performance measures.[55,57,96] The Centers for Medicare & Medicaid Services is also examining hospital-level patient reported experience of care and risk-adjusted Medicare spending for hospitalizations and 30 day post–hospital care using data from Hospital Consumer Assessment of Healthcare Providers and Systems.[97] The use of patient-centered indicators will increase the focus of quality measurement on aspects of health care that matter most to patients.

SHARED DECISION MAKING

An important objective of the Affordable Care Act is to provide patient-centered care. The IOM defines patient-centered care as "care that is respectful of and responsive to individual patient preferences, needs, and values . . . that patient values guide all clinical decisions."[7] From patients' perspective several characteristics were identified as indicators of quality and safety such as respect for patient's values, preferences, and expressed needs; clear, high-quality information and education for patients and families; physical comfort; emotional support; involvement of families and friends, as appropriate; coordinated care; continuity of care; and access to care.[98] Delivering patient-centered care will be an important indicator of future quality metrics.

For some acute conditions, there is clearly one dominant treatment strategy (eg, surgery for acute appendicitis, and antibiotics for acute bacterial meningitis). However, for many chronic conditions there can be more than one equally effective alternative, with different side-effects profiles and other attributes related to the quality of life.

The value of a treatment from a clinician's perspective can be different from a patient's, and it can also vary between any two patients. Therefore, the benefits and potential harms of any therapy can have different meaning and implications for any two given patients. Shared decision making involves discussion of treatment options between a clinician and patient, including benefits and harms, understanding patient's values and preferences, and letting the patient decide what can be the best treatment choice for him or her.[99] This can be facilitated with the use of decision aids, which are evidence-based tools delivered online, or as materials in a print or video format informing patients of the risks and benefits, relative effectiveness, and costs of a treatment. A Cochrane review of 115 clinical trials showed that use of decision aids was associated with improvement in patients' knowledge, accurate risk perceptions, values concordant medical decisions, reduced level of internal decisional conflict, and fewer patients remaining passive or undecided.[100] In addition to patients receiving the proper treatment for themselves,[100] using decision aids was also associated with lower health care costs.[101,102] Efforts to certify decision aid standards are in progress.[103] It has been suggested that the use of decision aids should be developed as a quality metric and tied with reimbursement; how to quantify the quality of decision making is still being developed.[103]

One important consequence of explicitly measuring and integrating patient-centered outcomes will be the ability to explicitly define patients' preferences in medical decision making. This will alter the current framework for interpreting adherence to guidelines and performance measures. Guidelines and performance measures seek to reduce the variation in cardiovascular care (Fig. 3–8A). Using this paradigm, improvement in outcomes occurs as variations in practice decrease,

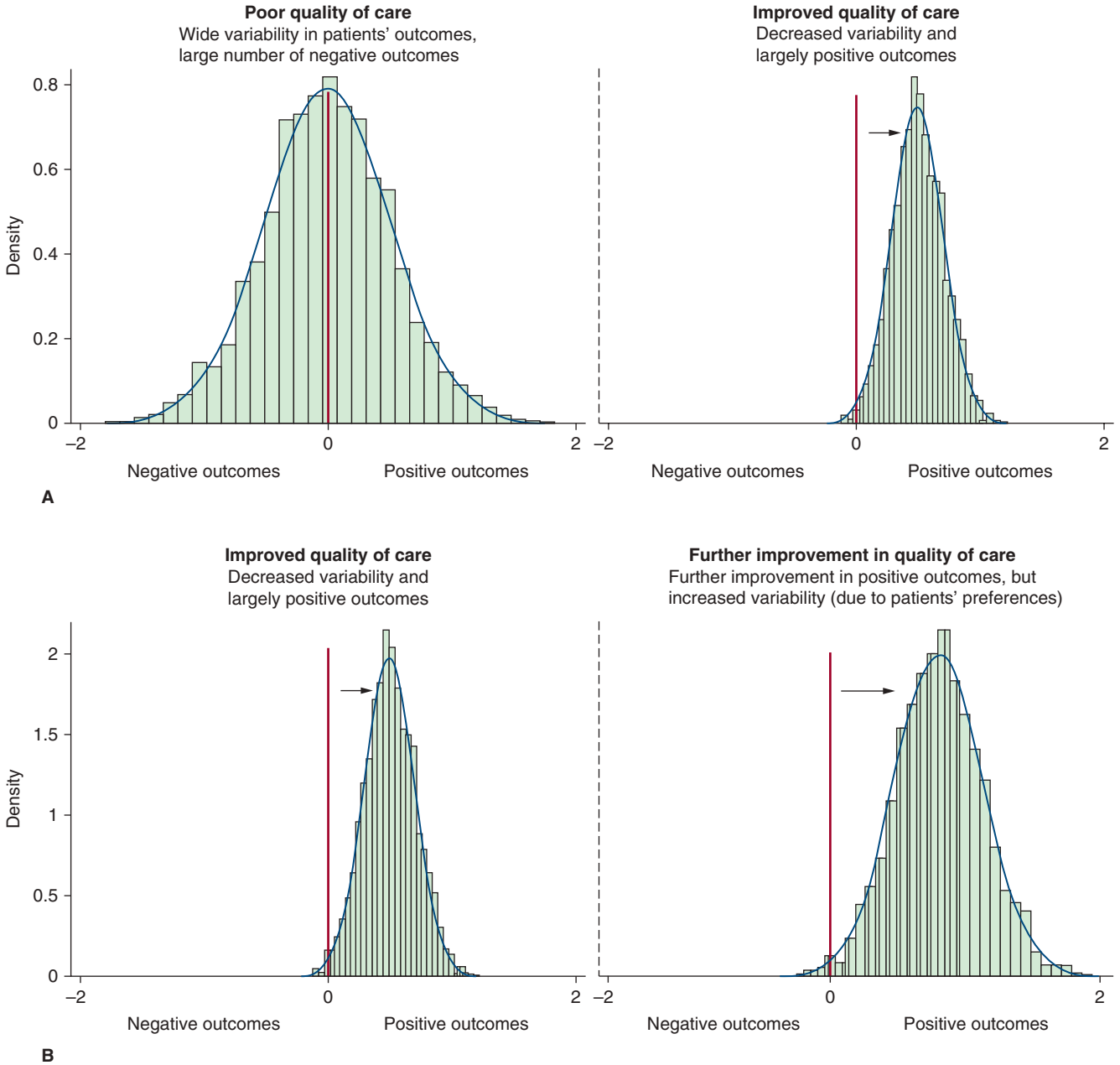

FIGURE 3–8. A new concept of improving quality by monitoring the degree of variation in clinical practice. **A.** Graphs demonstrating improvements in quality when physician variability is decreased and outcomes are improved. **B.** Graphs demonstrating improvements in quality when patient preferences drive variations in care.

resulting in both a favorable shift in performance and a narrowing of the distribution of performance. Although variation in clinical practice caused by differences in physician and hospital treatment is a poor indicator of quality, variations in practice caused by patient preference may reflect better care—care that is tailored to the individual goals and preferences of patients. This progressive idea stems from the philosophy that inclusion of patient preferences in medical decision making reflects higher quality of care (Fig. 3–8B). However, the current guidelines, performance measures, and most quality improvement programs are aimed at reducing variation, and consequently, variation in practice caused by patient preference may be misrepresented as poor quality. More research is needed to better define when variation is caused by patient preference, as opposed to clinicians' failure to apply evidence into practice.

CONCLUSION

The measurement and creation of interventions to improve the delivery of health care is an immensely exciting field and one that is growing in importance. It is fundamental to the goals of medicine—improving patients' outcomes. It is becoming increasingly important for the medical profession to accelerate its focus on health care quality and developing clinically and scientifically valid methods for quantifying and improving care. In the current era of increasing costs and growing scrutiny of the rational use of care, our profession has an ever-greater responsibility to reproducibly provide care that maximizes the benefits, decreases the risks and costs of care, and is most resonant with patients' individual goals and values. Professional organizations, including the ACC and AHA, are developing the tools to measure and improve care, and outcomes researchers are developing novel approaches for the analysis and interpretation of these data. Collectively, we all have the opportunity to elevate care so that the IOM's guiding principles of quality can be realized and care can be routinely delivered that is safe, effective, timely, efficient, equitable, and patient centered.

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CHAPTER 4

FUNCTIONAL ANATOMY OF THE HEART

Joseph F. Malouf, Joseph J. Maleszewski, A. Jamil Tajik, and James B. Seward

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BACKGROUND

The study of the heart and great vessels has expanded since the days of Andreas Vesalius, the great 16th-century anatomist who recognized the impact of anatomy on the practice of medicine. During the European Renaissance, the tomographic approach to the study of cardiac anatomy became popular because of its artistically based correlations. This is vividly depicted in the drawings of Leonardo da Vinci[1] (Fig. 4–1), the first comparative anatomist since Aristotle (see Chap. 1). During the ensuing nearly 400 years, however, interest in cardiac anatomy was very sporadic and limited to a few zealous and pioneering physicians, anatomists, and artists. The 19th century ushered in the era of anatomic dissection for the study of physiologic and pathophysiologic processes, and correlations. Virchow in 1885 described the inflow-outflow method of cardiac dissection, which followed the direction of blood flow.[2] It was quick and simple and became the dissection method of choice. The works of Virchow and Osler paved the way to understanding the pathophysiologic basis of such diseases as pulmonary embolism, endocarditis, and heart failure.[2] Renewed interest in the study of cardiac anatomy and pathology was facilitated by the rise in autopsy rates in Europe and North America during the first half of the 20th century.[3] Herrick described the clinical features of coronary thrombosis.[3] Later, Blumgart, Schlesinger, and Zoll advanced our understanding of coronary artery disease through elegant clinicopathologic correlations.[3]

These achievements notwithstanding, however, were limited to postmortem examinations. The advent of cardiac surgery in the 1950s, followed by coronary angiography, was a major impetus for promoting the study of in vivo clinicopathologic anatomic correlations. Although cardiac surgeons were quick to appreciate the importance of having a detailed understanding of cardiac anatomy, clinical cardiologists were more interested in pathophysiology. However, with the introduction of noninvasive imaging techniques (echocardiography, computed tomography [CT], magnetic resonance imaging [MRI], and single photon-emission computed tomography [SPECT]) over the past three decades, the perception of cardiac anatomy and pathophysiology radically changed for all of medicine in general and cardiology in particular.

With increasing use of tomographic techniques in the diagnosis and management of cardiovascular diseases, there has been a corresponding decrease in the use of autopsy for anatomic correlations. The reasons for this decrease are complex and controversial and include an increased confidence in antemortem laboratory and imaging technologies, and rescinding the mandate for autopsies for hospital accreditation.[2] Nonetheless, autopsy still uncovers unexpected processes in upward of 40% of cases and remains an invaluable tool for quality assurance and educational programs.

Today, there is a growing resurgence in the clinicopathologic correlative approach to cardiovascular morphology. In particular, the tomographic presentation of cardiac structure, which had remained dormant for more than a century, has become relevant because the diagnostic techniques used today are tomographic in nature.[4] The specialties associated with cardiovascular diseases have been quick to embrace these newer anatomic presentations. Echocardiography was brought into the operating room and cardiac catheterization laboratory, and with the advent of transesophageal echocardiography, the cardiologist became an indispensable member of the surgical team and structural heart disease interventional cardiology team (see Chap. 15).[5,6]

The interest in cardiac anatomy among cardiologists is by no means limited to those instances involved in imaging the heart. Over the past few years, there has been an explosion of interest in anatomically guided electrophysiologic mapping and ablation techniques, which are increasingly guided by intracardiac ultrasound (see Chap. 15).[7,8] It has thus become feasible to accurately pinpoint the anatomic location of the source of many arrhythmias[7,8] (Figs. 4–2 and 4–3). By providing the electrophysiologist with a real-time visual road map, the search-and-destroy mission during an ablation procedure will be made much easier, and results, as well as complications, will be recognized immediately.[7,8] By providing a new window to the heart, real-time anatomic-electrophysiologic correlations can also help to enhance our understanding of the mechanisms of propagation of various arrhythmias. There has also been a recent surge in anatomically guided percutaneous catheter-based procedures to repair or replace a diseased native or bioprosthetic cardiac valve, and to close atrial and ventricular septal defects.[9] The successful implementation of these

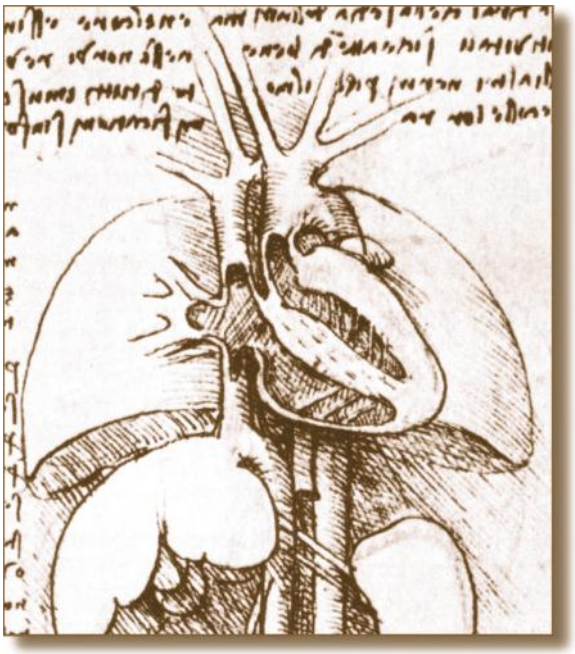


FIGURE 4–1. Four-chamber tomographic section of the heart as illustrated by Leonardo da Vinci. Note the thin-walled right ventricle and thick-walled left ventricle and detailed anatomic connections. Reproduced with permission from O'Malley CD, Saunders JB. Leonardo da Vinci on the Human Body. New York: Greenwich House; 1982.[1]

increasingly more sophisticated surgical and percutaneous catheter-based techniques requires closer interaction among the cardiac surgeon, interventional cardiologist, and the noninvasive cardiologist, as well as precise diagnostic tools with greater spatial and temporal resolution to guide the planning of these procedures.[5,6,9,10] This is being met by rapid technological advances that currently include the ability to reconstruct and display cardiac anatomy/pathology in a readily familiar three-dimensional (3D) format, be it imaging alone or translation to a physical model with the increased utilization of 3D printing.[9-12]

Because of all these developments, a new appreciation of cardiac anatomy has emerged as the cornerstone for clinical cardiology. The purpose of this chapter is to describe the anatomy of the heart by principally using the tomographic format prevalent in current CT,

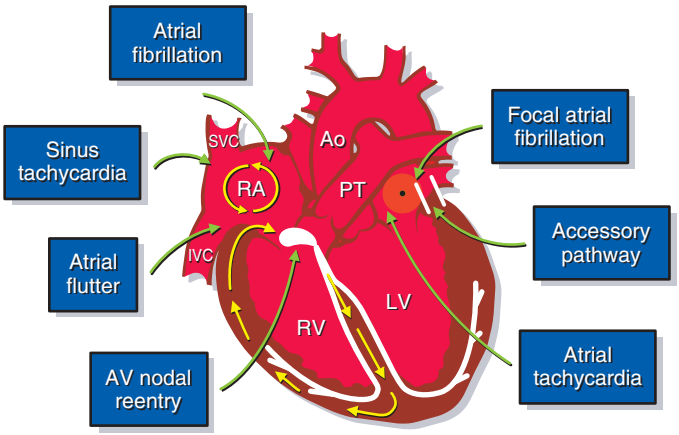


FIGURE 4–2. Anatomic considerations in the treatment of supraventricular arrhythmias. AV indicates? atrioventricular; Ao, ascending aorta; IVC, inferior vena cava; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; SVC, superior vena cava. Used with permission from Dr. Douglas L Packer, Mayo Clinic, Rochester, MN.

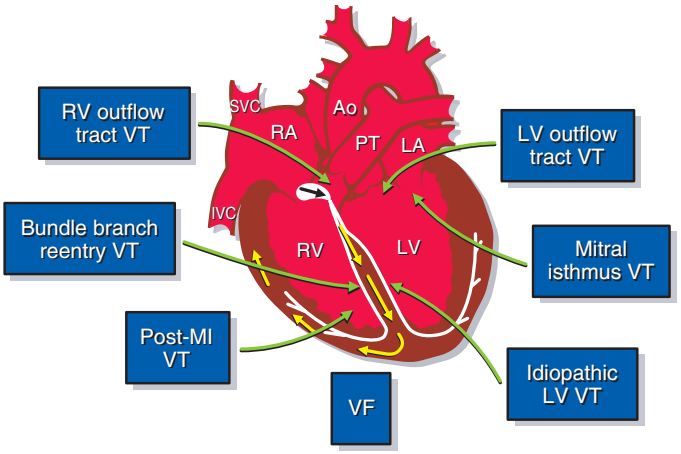


FIGURE 4–3. Anatomic considerations in the treatment of ventricular arrhythmias. LA, left atrium; LV, left ventricle; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia; other abbreviations as in Fig. 4–2. Used with permission from Dr. Douglas L Packer, Mayo Clinic, Rochester, MN.

MRI, and echocardiography, with special emphasis and focus on clinically relevant anatomic details. We will make only passing note of the next generation of imaging techniques (ie, molecular, parametric, quantum). The intent is to emphasize the important anatomic features of various cardiovascular disease processes relative to diagnosis and management.

ORIENTATION OF THE HEART WITHIN THE THORAX

The body can be viewed in three standard orthogonal anatomic planes: (1) frontal (coronal), (2) horizontal (transverse), and (3) sagittal.[4,5] However, the three primary planes of the heart (short axis [transverse], four-chamber [frontal], and long-axis [sagittal]) do not correspond to the standard anatomic planes of the body[4,5] (Fig. 4–4). *Incorrect photographic or artistic orientation of surgical or autopsy specimens of the heart, presented out of context, can result in the display of two-dimensional (2D) images in nonanatomic positions and actually contribute to misconceptions regarding the position of the heart within the thorax*[4] (Fig. 4–5). As we enter into the 3D era, anatomic realism will become absolutely essential.

Thus, first, in describing the orientation of a specific organ such as the heart, one must take into account both the position of the heart

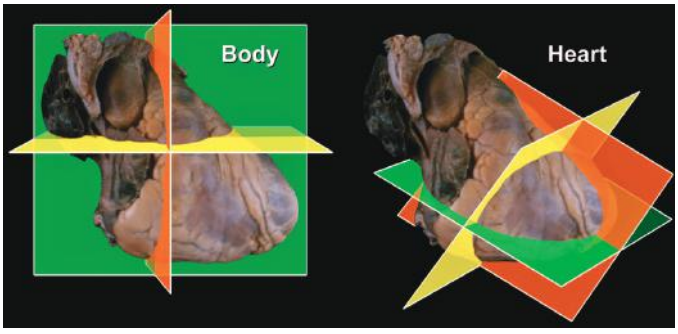


FIGURE 4–4. The three primary planes of the body (*left*) and heart (*right*). Note that the planes of the body are aligned with vertical midline structures, such as the esophagus. In contrast, the major axis of the heart is oriented obliquely. Thus the heart's long and short axes do not lie in the same plane as the body's long and short axes. The body planes cut the heart obliquely and not in its primary planes. Conversely, the heart's primary planes cut the body obliquely.

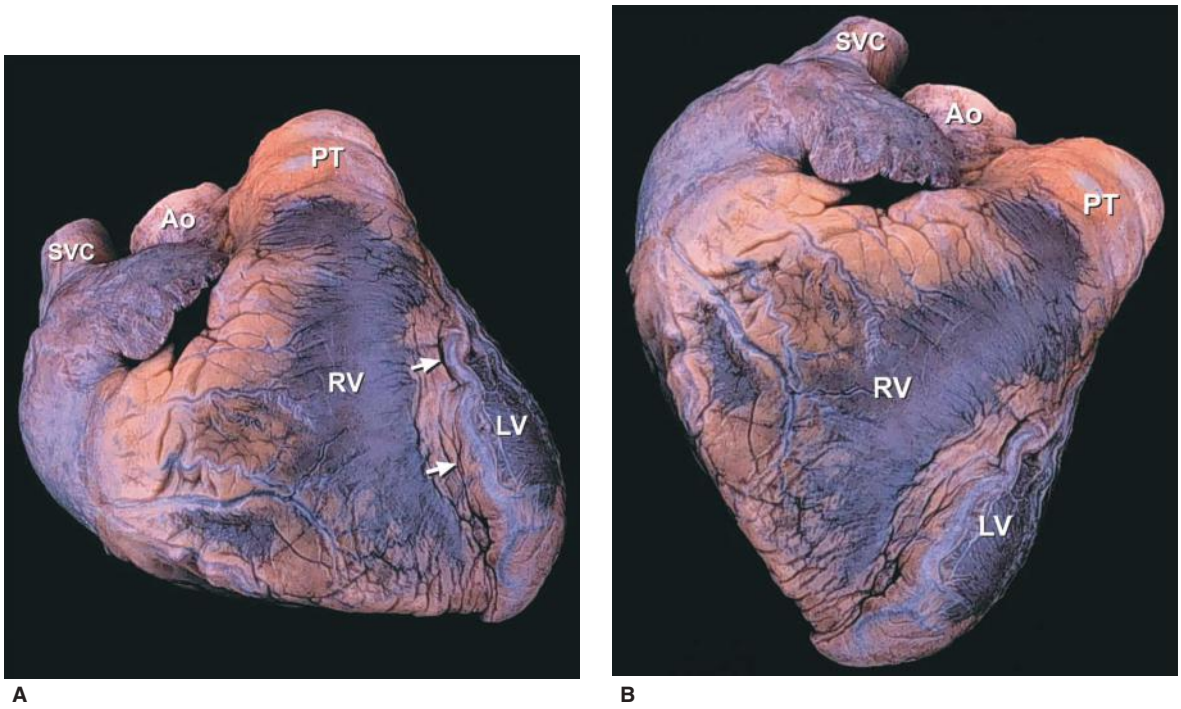


FIGURE 4–5. **A.** Anterior view of the heart in its usual anatomic position with its apex directed from right to left. Arrows point to the anterior interventricular groove. **B.** Nonanatomic positioning of the normal heart with its apex directed downward, thereby resembling a "valentine." The position of the cardiac apex is normally leftward (levocardia) but can anomalously be rightward (dextrocardia) or midline and inferiorly (mesocardia). Ao, ascending aorta; LV, left ventricle; PT, pulmonary trunk; RV, right ventricle; SVC, superior vena cava.

and the position of adjacent structures such as the thoracic aorta and esophagus. In interpreting 2D or 3D images, clinicians must avoid making correlations that yield impossible anatomy[4] (Fig. 4–6). Accurate anatomic diagnoses require close interdisciplinary interactions among cardiovascular pathologists, cardiologists, radiologists, anesthesiologists, and surgeons and emphasize a critical need for teamwork and a "common language" in describing cardiac anatomy and pathology. This is of paramount importance when guiding catheter-based interventions (see Sec. 8 and Chap. 88).

METHODS USED TO STUDY CARDIAC ANATOMY

The two conventional approaches to the study of cardiac anatomy that have stood the test of time are (1) the inflow-outflow method (Fig. 4–7) and (2) the tomographic ventricular slice method[4] (Fig. 4–8). Although the inflow-outflow method readily demonstrates disease processes in a given cardiac chamber or valve, it does not allow simultaneous visualization of the effects of that process on contiguous structures.[4] Furthermore, the inflow-outflow method does not correspond

FIGURE 4–6. Apex-down four-chamber view of the heart (*left*) and mirror-image photograph (*right*). Mirror-image depiction (commonly used in publications) to depict normal four-chamber, apex-up echocardiographic anatomic images does not correspond to normal anatomic reality. Obviously, 3D anatomic correctness is essential for accurate clinicopathologic correlations. LA, left atrium.

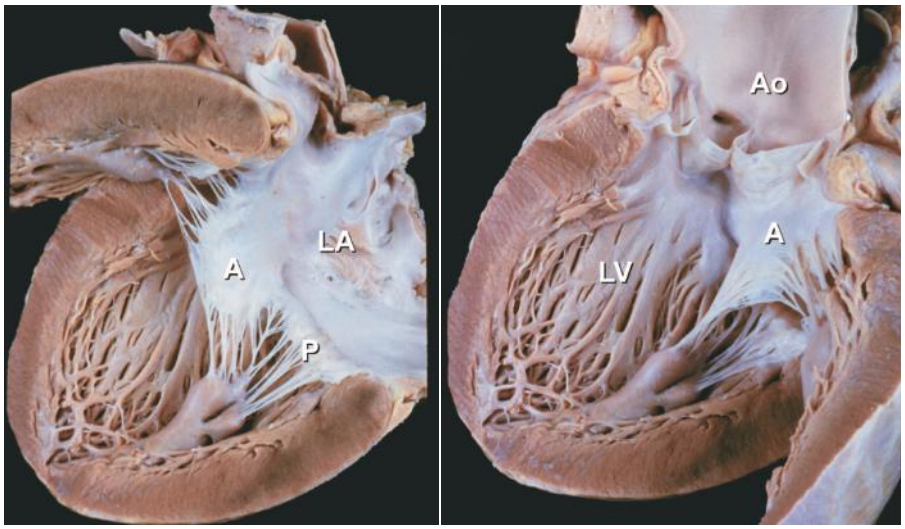


FIGURE 4–7. Inflow-outflow method of cardiac dissection. **A.** Left ventricular inflow view. **B.** Left ventricular outflow view. A, anterior mitral leaflet; Ao, ascending aorta; LA, left atrium; LV, left ventricle; P, posterior mitral leaflet.

well to clinical tomographic imaging modalities except possibly cavitary angiography.[4] With the ventricular slice technique (see Fig. 4–8), the ventricles are "bread sliced" perpendicular to the plane of the ventricular septum. This technique is ideal for the evaluation of ischemic heart disease but may have to be carried basally, well beyond the papillary muscle tips.[4]

TOMOGRAPHIC METHOD

Renaissance anatomists such as da Vinci used the tomographic approach principally because of its artistic correlations.[1] Modern anatomists and pathologists have resorted to this method because it correlates with conventional tomographic imaging techniques. With this method, cardiac dissection involves bisecting the heart into two pieces using a single plane of section.[4] Anatomy contained within the depth of each section fosters a perception of 3D anatomy. Commonly used planes bisect the heart perpendicular to the base-apex axis (short-axis transverse views) (Fig. 4–9) or parallel to it (long-axis and four-chamber frontal views)[4] (Fig. 4–10). Planes that bisect the heart parallel to the conventional body planes (frontal coronal, transverse short-axis, and sagittal long-axis views) (Fig. 4–11) replicate body tomography.[4,13]

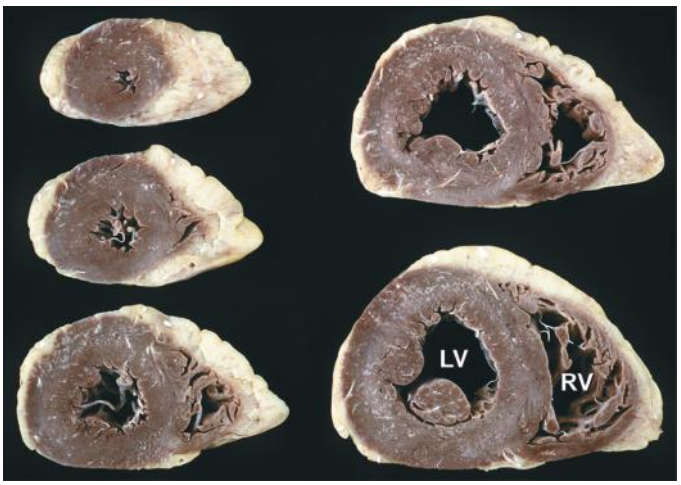


FIGURE 4–8. Ventricular slice method of cardiac dissection. Display of five slices (LV, left ventricle; RV, right ventricle) viewed as though looking from the base of the heart toward the apex.

The short-axis tomographic planes[4,5] of the heart (Fig. 4–12) are similar to the ventricular slice method but differ in two important respects. The "bread slicing" of the heart is continued to the base of the heart and great vessels, and the slices are oriented as though the heart were being viewed from the apex toward the base rather than in the opposite direction, as has been the case with the ventricular slice technique. Photographs should correspond with diagnostic tomographic scans.

The long-axis and four-chamber planes are orthogonal to the short-axis planes. The four-chamber planes of cardiac dissection (Fig. 4–13) involve sectioning the heart along both lateral walls, from apex to base, such that both ventricles and both atria are included in the plane of section.[4,5] The long-axis two-chamber method (Fig. 4–14) involves bisecting the heart from the left ventricular apex through the mitral orifice and into the left atrium.[4,5] The long-axis plane can cut through both the left ventricular inflow tract (including the left atrium and mitral valve) and the left ventricular outflow tract (including the ventricular septum, anterior mitral leaflet, and ascending aorta) (Fig. 4–15A). This plane also cuts obliquely through the right ventricular outflow tract.[4,5]

These three anatomic tomographic planes of the heart have been particularly useful in echocardiography and more recently CT and MRI (Fig. 4–15B). Serial sections within each plane produce a collage of anatomic slices (Fig. 4–16) that can be used for 3D and higher-dimensional reconstructions, which is beyond the scope of this chapter. The tomographic planes of section can be tailored to the different imaging modalities. Thus echocardiography and SPECT generally use the primary planes of the heart. In contrast, CT and MRI use the primary planes of the body. The parasagittal or oblique planes of the body serve radionuclide angiography and left ventriculography.[4] When the tomographic examination is not configured to the primary planes of the heart but rather to the planes of the body, the terms *short*, *long*, and *frontal* can be misleading (Figs. 4–17 and 4–18).

Pathologic lesions in both congenital and acquired heart diseases often involve contiguous chambers, valves, or vessels. The tomographic

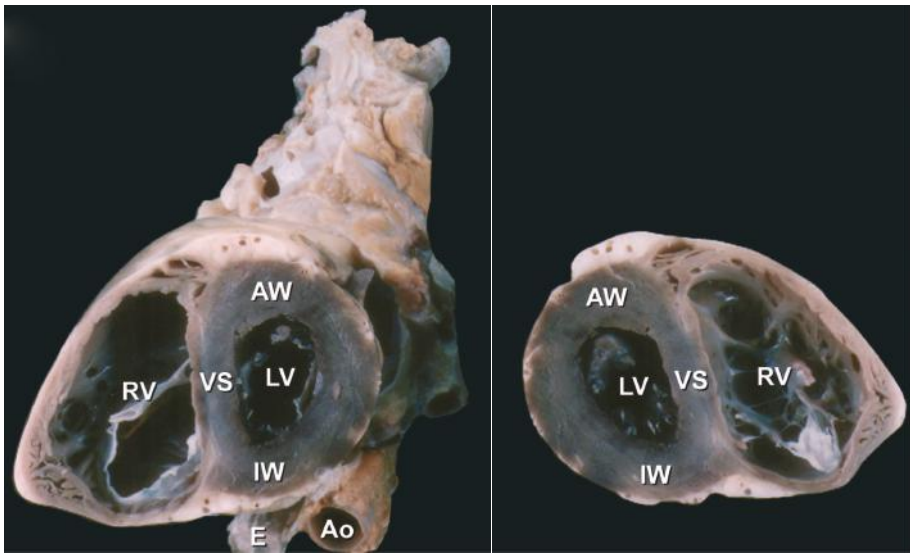


FIGURE 4–9. Bisected cardiac specimen, viewed in the short axis. **A.** The specimen is viewed from the apex toward the base. The esophagus (E) is posterior and adjacent to both the thoracic aorta (Ao) and the inferior wall of the left ventricle (LV). The right ventricular (RV) cavity is to the left. **B.** The other half of the bisected specimen is viewed as though looking from the base toward the apex (compare with Fig. 4–8). AW, anterior wall; IW, inferior wall; VS, ventricular septum.

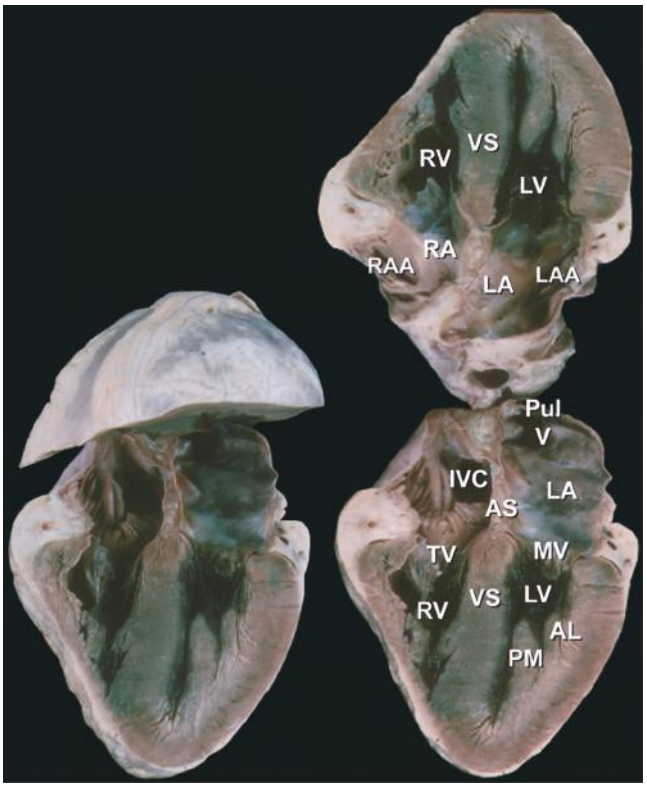


FIGURE 4–10. Bisected cardiac specimen in the four-chamber view parallel to the base-apex axis of the heart. The bisected specimen (*left*) has been partially opened to show the relative relationship of the bisected halves. The two components of the bisected specimen (*right*) are opened completely. Note the positions of the pulmonary veins posteriorly and the positions of the atrial appendages at the atrioventricular groove. AL, anterolateral papillary muscle; AS, atrial septum; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PM, posteromedial papillary muscle; PulV, pulmonary vein; RA, right atrium; RAA, right atrial appendage; RV, right ventricle; TV, tricuspid valve; VS, ventricular septum.

method is the optimal technique for demonstrating intracardiac relationships and is ideal for any disease that involves several cardiac chambers. The proliferation of noninvasive tomographic imaging techniques makes this method particularly ideal for clinicopathologic correlations. Limitations of tomographic dissection can be overcome by photography, computer imagery, and interestingly, the use of glue. After each tomographic section has been produced and photographed, the bisected specimens can be glued back together using any cyanoacrylate glue, such as Krazy Glue or Superglue, and resectioned along a different tomographic plane.[6] Step-by-step photographic documentation is necessary, because once the specimen has been glued and recut, the preceding tomographic plane of section will be available only in the photograph and not in the actual specimen.

CORRELATIVE ANATOMY

This section provides an illustrated review of applied cardiac anatomy. The clinical significance of the anatomy described is highlighted in italics.

PERICARDIUM

The pericardium is a vaguely conical structure that adheres to and envelops the heart as the serous (visceral) and fibrous (parietal) pericardia, respectively. The fibrous pericardium is a resilient sac that surrounds the heart and attaches onto the great vessels.[14] The main pulmonary artery, portions of both venae cavae, distal pulmonary veins, and nearly the entire ascending aorta are intrapericardial (Fig. 4–19). *These are important anatomic features to remember in evaluating diseases of the pericardium. Given the intrapericardial location of the ascending aorta, diseases such as localized aortic wall hematoma, aortic dissection, or aortic rupture can produce a rapidly fatal hemopericardium. Because the sac is collagenous, with little elastic tissue, it cannot stretch acutely. However, the pericardium is capable of remodeling such that chronically it can accommodate relatively large volumes in excess of one liter without causing tamponade.*[15] *In patients with total anomalous pulmonary venous connection, the confluence of pulmonary veins is intrapericardial. In*

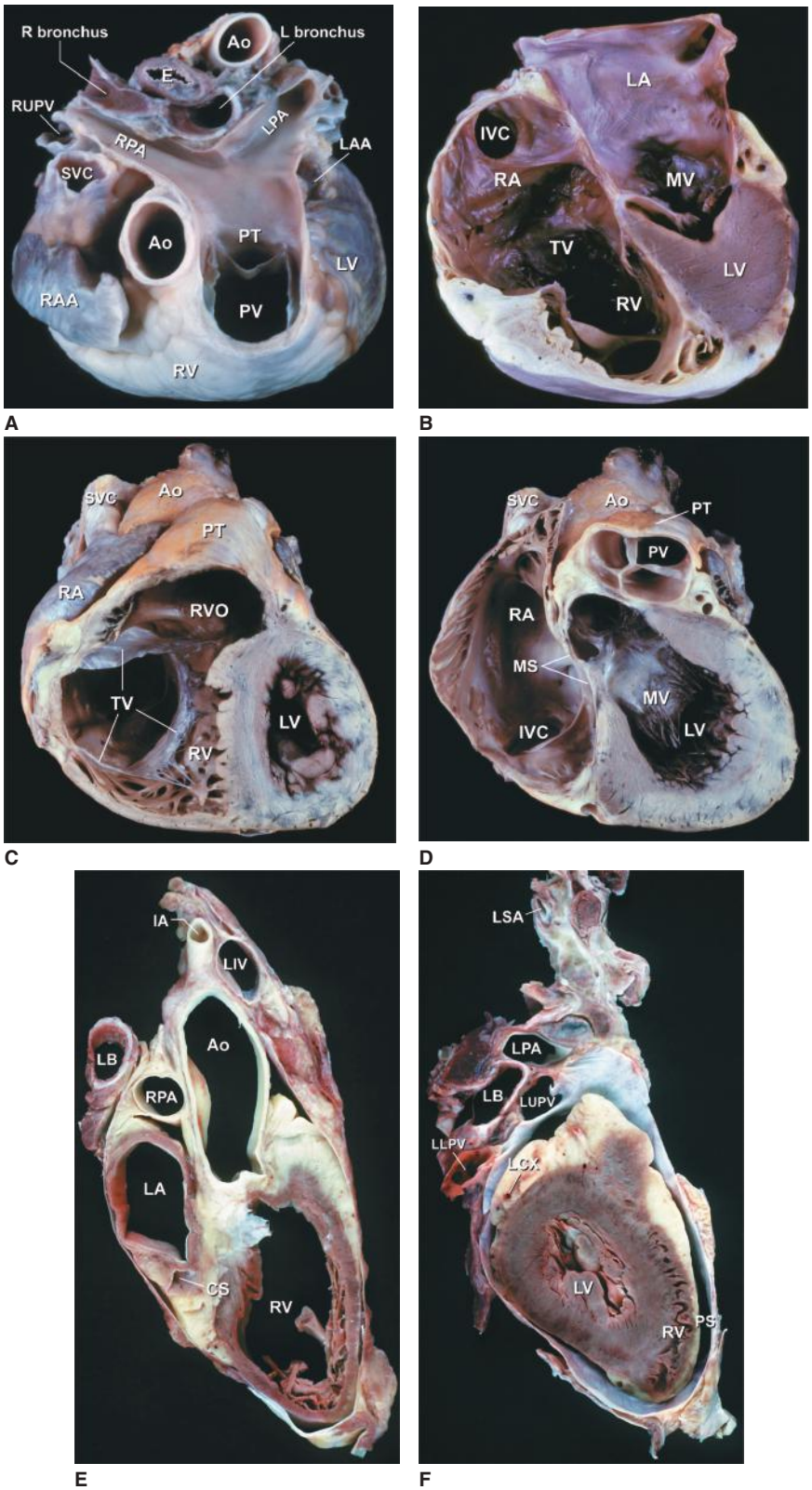


FIGURE 4–11. Tomographic cardiac dissection along the body primary planes. **A, B.** Transverse sections (looking from head toward feet) at the level of the great vessels (**A**) or the cardiac chambers (**B**).The aortic arch travels over the left bronchus and the right pulmonary artery. **C, D.** Frontal sections (looking from anterior to posterior) through both ventricles (**C**) or left ventricle and right atrium (**D**). **E, F.** Parasagittal sections looking from right (**E**) to left (**F**).Ao, ascending aorta; CS, coronary sinus; E, esophagus; IA, innominate artery; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LB, left bronchus; LCX, left circumflex coronary artery; LIV, left innominate vein; LLPV, left lower pulmonary vein; LPA, left pulmonary artery; LUPV, left upper pulmonary vein; LSA, left subclavian artery; LV, left ventricle; MS, membranous ventricular septum; MV, mitral valve; PS, pericardial sac; PT, pulmonary trunk; PV, pulmonary valve; RA, right atrium; RAA, right atrial appendage; RPA, right pulmonary artery; RUPV, right upper pulmonary vein; RV, right ventricle; RVO, right ventricular outflow; SVC, superior vena cava; TV, tricuspid valve.

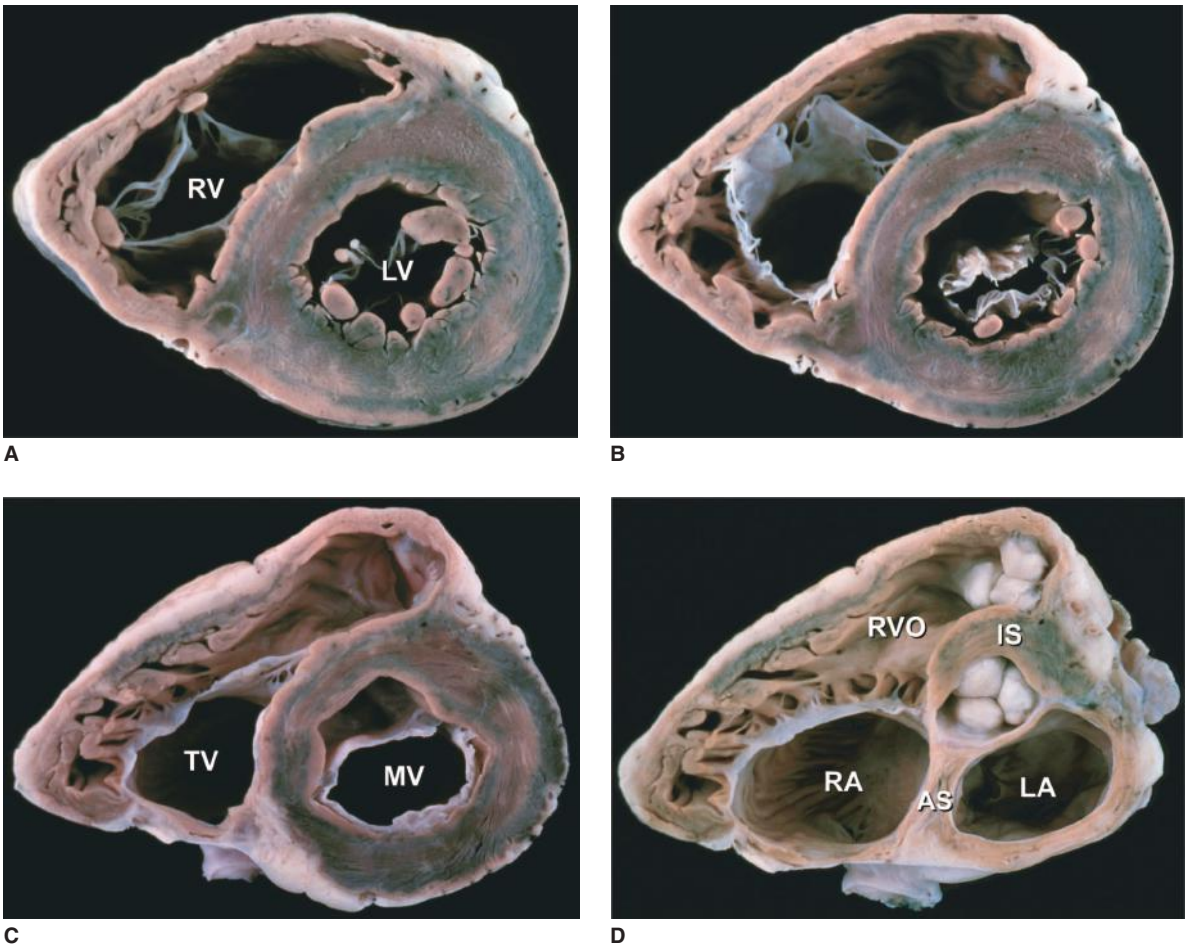


FIGURE 4–12. A–D. Tomographic cardiac dissections along the heart's primary short-axis plane. This method of tomographic dissection shows the crescentic right ventricle (RV) and circular left ventricle (LV). The atrioventricular valves are sectioned at the level of their papillary muscles (*in* **A**), chordae tendineae (*in* **B**), atrioventricular valve leaflets (*in* **C**), and their annuli and the semilunar valves (*in* **D**). The infundibulum septum (IS) separates the pulmonary and aortic valves. The atrial septum (AS) separates the tricuspid and mitral valves and abuts the posterior (noncoronary) cusp of the aortic valve. LA, left atrium; MV, mitral valve; RA, right atrium; RVO, right ventricular outflow; TV, tricuspid valve.

contrast, the right and left pulmonary arteries and ductal artery (ductus arteriosus) are extrapericardial structures.[16]

The serous pericardium forms the delicate inner lining of the fibrous pericardium and continues onto the surface of the heart and great vessels at the pericardial reflection. Over the heart, it is referred to as the epicardium, and it contains the epicardial coronary arteries and veins, autonomic nerves, lymphatics, and a variable amount of adipose tissue. The junctions between the visceral and parietal pericardium lie along the great vessels and form the pericardial reflections. The reflections along the pulmonary veins and venae cavae are continuous and form a posterior midline cul-de-sac known as the oblique sinus (Fig. 4–20). Behind the great arteries, the transverse sinus forms a tunnel-like passageway that separates the great arteries anteriorly from the great veins posteriorly (see Fig. 4–20). *After open-heart surgery, localized accumulation of blood within the oblique sinus can produce isolated left atrial tamponade.*[16] *Similarly, a hematoma adjacent to the low-pressure right atrium can cause isolated right atrial compression tamponade.* With increasing age and with obesity, fat can accumulate within the parietal pericardium and epicardium (see Fig. 4–33).[16] *In imaging the heart, it is important not to misinterpret epicardial fat as an abnormal structure or a tumor.*

CARDIAC SKELETON

The four major cardiac valves are anchored to their annuli, or valve rings. These fibrous rings, at the base of the heart, join to form the fibrous skeleton of the heart[16] (Fig. 4–21). The centrally located aortic valve forms the cornerstone of the cardiac skeleton, and its fibrous extensions abut each of the other three valves. The cardiac skeleton contains not only the four major valve annuli but also the membranous septum and the aortic intervalvular, right, and left fibrous trigones. The fibrous trigones form the anatomic substrate for mitral-aortic continuity[16] (Fig. 4–22; see also Fig. 4–21). The intervalvular fibrosa also forms part of the floor of the transverse sinus (see Fig. 4–22). *In patients with infective endocarditis of the mitral or aortic valves, infection can burrow through the intervalvular fibrosa and produce characteristic fistulas between the left ventricle and the adjacent left atrium, ascending aorta, or transverse sinus* (see Chap. 67).[17] The right fibrous trigone (see Fig. 4–21), also known as the *central fibrous body*, welds together the aortic, mitral, and tricuspid valves and forms the largest and strongest component of the cardiac skeleton. It is through the right fibrous trigone that the atrioventricular (AV) (His) bundle passes. Otherwise, the fibrous cardiac skeleton serves to electrically isolate the atria from the ventricles. *Diseases or surgical alterations of one valve can affect*

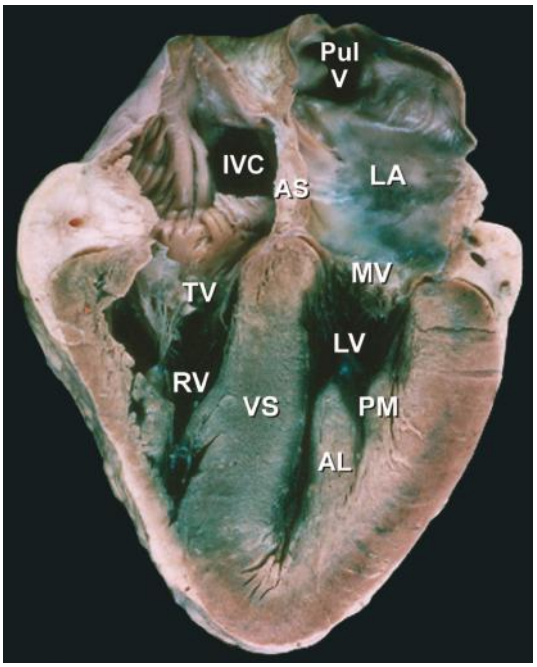
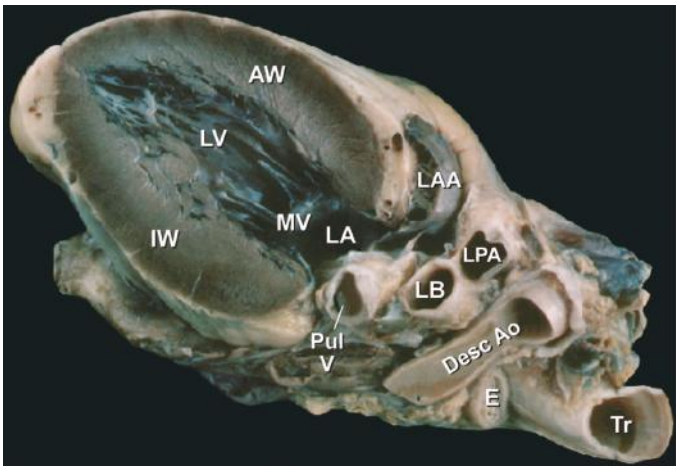
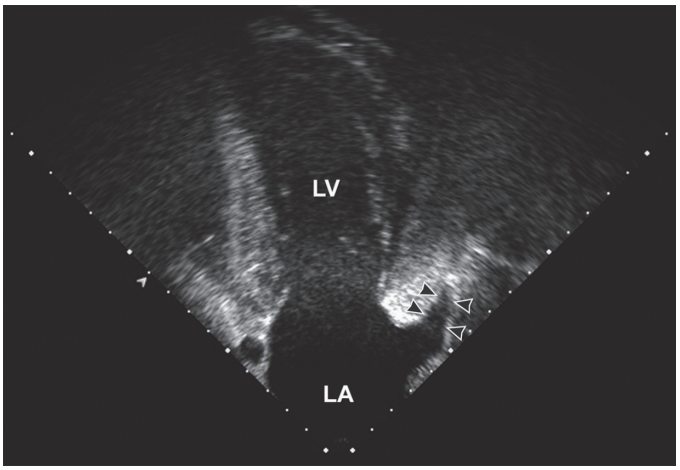


FIGURE 4–13. Tomographic cardiac dissection along the heart's primary four-chamber plane. The heart is viewed as though one were looking from the anterosuperior surface toward the posteroinferior surface. In the floor of the right atrium is the orifice of the inferior vena cava (IVC). The pulmonary veins (PulV) enter the posterior aspect of the left atrium. AL, anterolateral mitral papillary muscle; AS, atrial septum; LA, left atrium; LV, left ventricle; MV, mitral valve; PM, posteromedial mitral papillary muscle; RV, right ventricle; TV, tricuspid valve; VS, ventricular septum.



A



B

FIGURE 4–14. Tomographic cardiac dissection along the heart's primary long-axis plane. **A.** Tomographic section showing the left ventricle and left atrium. The mitral valve is also well demonstrated. The left atrial appendage is located anteriorly. The specimen is viewed as though one were looking from the tip of the left scapula toward the right nipple. **B.** Two-chamber transesophageal echocardiography (TEE) analogous to the two-chamber transthoracic echocardiography (TTE). *Arrowheads* point to the left atrial appendage. AW, anterior wall; DAo, descending thoracic aorta; E, esophagus; IW, inferior wall; LA, left atrium; LAA, left atrial appendage; LB, left bronchus; LPA, left pulmonary artery; LV, left ventricle; MV, mitral valve; PulV, pulmonary vein; Tr, trachea.

the shape or angulation of adjacent valves (eg, aortic valve replacement causing severe mitral regurgitation) and can affect the nearby coronary arteries or conduction tissue.[17]

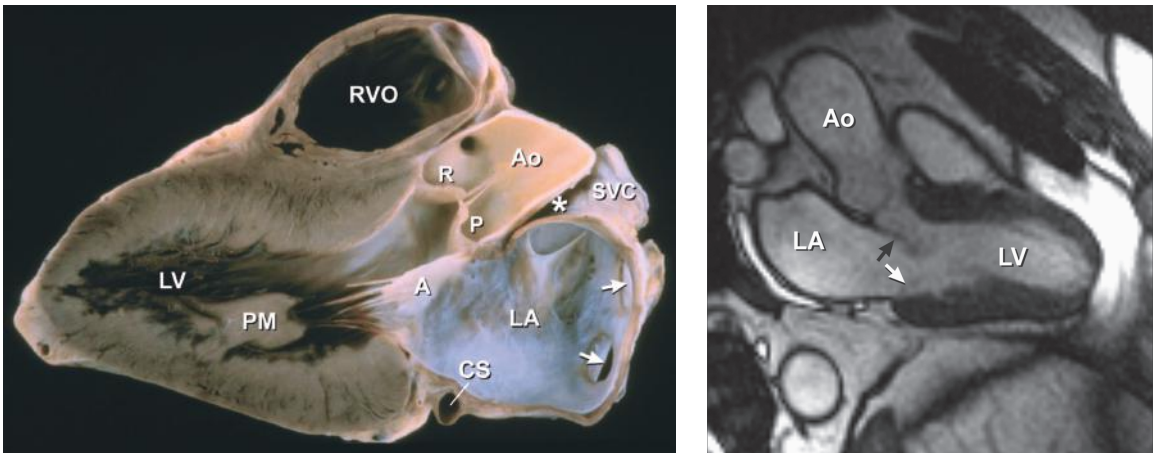
TRICUSPID VALVE

The tricuspid valve is comprised of five components (ie, annulus, leaflets, commissures, chordae tendineae, and papillary muscles). The anterior tricuspid leaflet is the largest and most mobile and forms an intracavitary curtain that partially separates the inflow and outflow tracts of the right ventricle (Fig. 4–23). The posterior leaflet is usually the smallest. The septal leaflet is the least mobile because of its many direct chordal attachments to the ventricular septum. A relatively distensible annulus is unique to the tricuspid valve owing to discontinuity of collagenous tissue on the right AV free wall.[17] Consequently, dilatation of the right ventricle commonly produces circumferential tricuspid annular dilatation resulting in variable degrees of tricuspid valve regurgitation (see Chap. 51).[16]

MITRAL VALVE

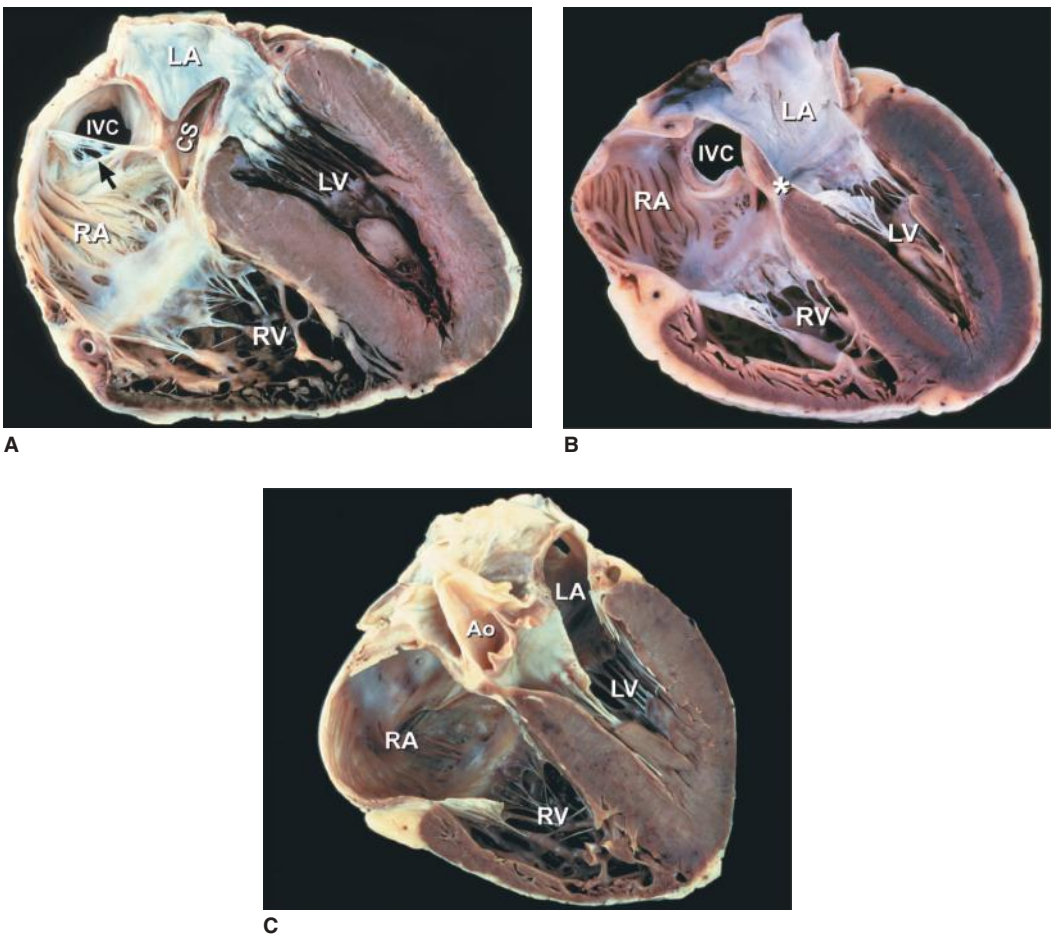
The mitral apparatus is composed of the same five components as the tricuspid valve. Competent mitral valve function is a complex process that requires the proper interaction of all components, as well as adequate left atrial and left ventricular function. *Abnormalities of the mitral valve apparatus can involve any of these components or combinations thereof. The pattern of pathologic involvement often determines the feasibility of mitral valve repair* (surgical or percutaneous) (see Chaps. 48, 49, and 50).[18] The mitral valve annulus forms a complete fibrous ring that is firmly anchored along the circumference of the anterior leaflet by the tough fibrous skeleton of the heart[17] (see Fig. 4–21). Therefore, dilatation of the mitral valve annulus primarily affects the posterior leaflet. *All current operative mitral valve repair techniques are based on this principle of asymmetric annular dilatation. Mitral valve annuloplasty reduces the mitral valve inlet area by reducing the contribution of the posterior leaflet.*[17] *This is the rationale for using a partial posterior annuloplasty ring.* The mitral and tricuspid annuli are not planar but rather saddle-shaped with dynamic motion throughout the cardiac cycle. The nonplanar conformation is maintained throughout systole and diastole but is slightly more pronounced during systole.[19]

The mitral valve has only two leaflets. The anterior leaflet is large and semicircular, and it partially separates the ventricular inflow and outflow tracts (see Fig. 4–23). However, unlike its right-sided counterpart, it also forms part of the outflow tract. *In patients with hypertrophic obstructive cardiomyopathy, the anterior mitral leaflet can be pulled anteriorly toward the basal ventricular septum, resulting in midsystolic outflow obstruction and mitral regurgitation.*[16] The posterior mitral



A B

FIGURE 4–15. **A.** Left ventricular long-axis method of tomographic cardiac dissection (looking from left flank toward the midsternum). Continuity between mitral and aortic valves is clearly seen. The transverse sinus (*) abuts the wall of the left atrium; *arrows* point to the right upper and lower pulmonary veins. **B.** Comparable MRI long-axis view. *Black arrow* points to the anterior mitral leaflet and *white arrow* points to posterior mitral leaflet. A, anterior mitral leaflet; Ao, ascending aorta; CS, coronary sinus; LA, left atrium; LV, left ventricle; P, posterior aortic cusp; PM, posteromedial mitral papillary muscle; R, right aortic cusp; RVO, right ventricular outflow; SVC, superior vena cava.



A B C

FIGURE 4–16. Collage of four-chamber tomographic sections cutting from inferior wall to anterosuperior wall showing **A.** coronary sinus, **B.** internal cardiac crux (*), and **C.** aortic valve. Ao, ascending aorta; CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; *arrow* in *A* points to a fenestrated eustachian valve.

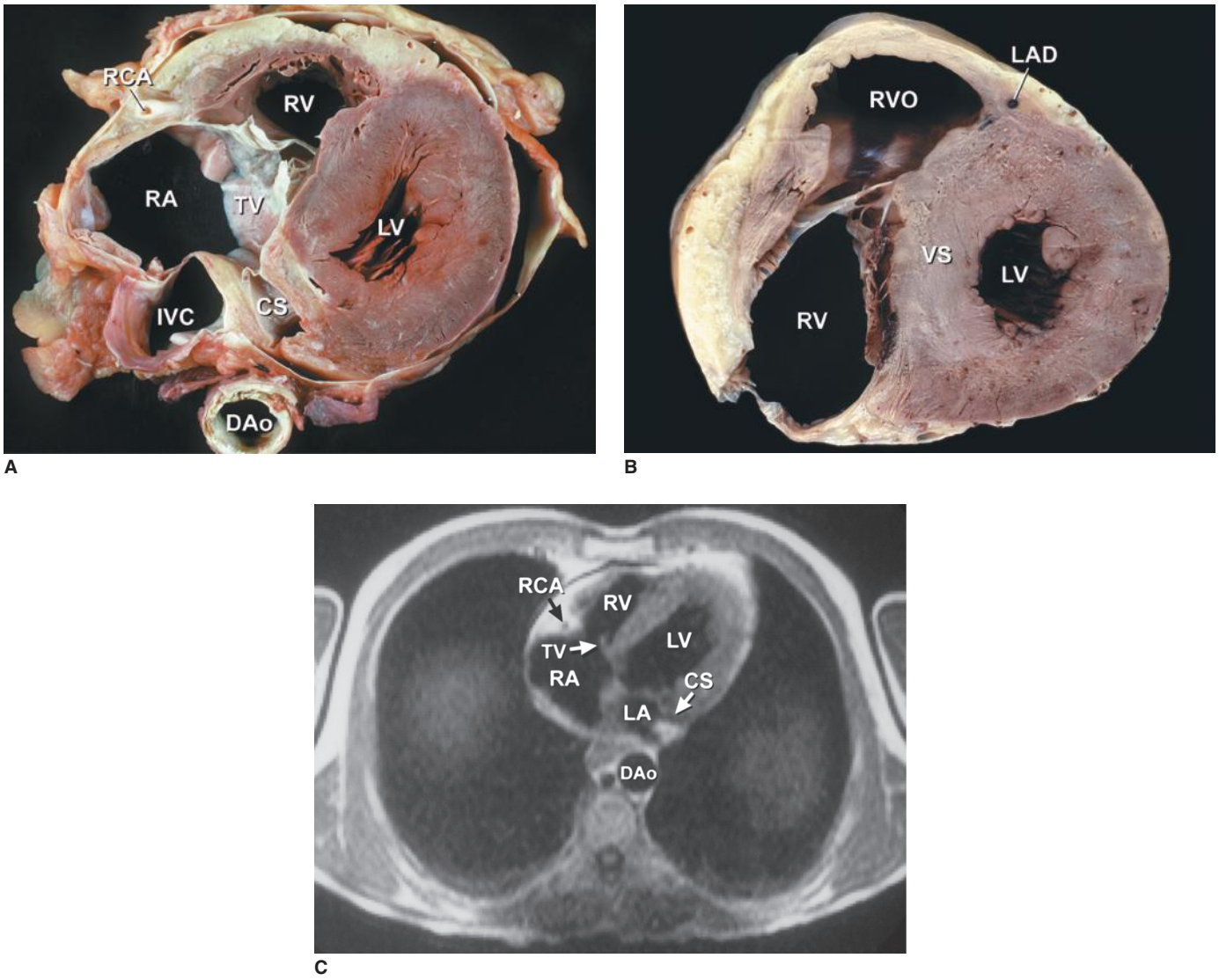


FIGURE 4–17. Tomographic sections of the heart in the transverse (**A**) and frontal (**B**) planes of the body. A tomographic section in the transverse plane of the body (**A**) results in an on-off axis four-chamber view of the heart. A tomographic section along the frontal plane of the body (**B**) results in an oblique short-axis view of the heart. **C.** MRI image corresponding to (**A**). CS, coronary sinus; DAo, descending thoracic aorta; IVC, inferior vena cava; LA, left atrium; LAD, left anterior descending coronary artery; LV, left ventricle; RA, right atrium; RCA, right coronary artery; RV, right ventricle; RVO, right ventricular outflow; TV, tricuspid valve; VS, ventricular septum.

leaflet is more shallow and is usually divided into three scallops (ie, P1, P2, and P3). The middle scallop (P2) is the largest of the three in more than 90% of normal hearts. Occasionally, however, either the anterolateral (P1) or the posteromedial scallop (P3) is larger, and rarely there are accessory scallops[16,17] (Fig. 4–24). *Posterior mitral leaflet prolapse usually involves the middle scallop and can be associated with chordal rupture.* Both mitral leaflets are normally similar in area. The anterior leaflet is twice the height of the posterior leaflet but has half its annular length.[17] With advanced age, the mitral leaflets thicken somewhat, particularly along their closing edges.[17]

The commissures are incomplete splits in the leaflet tissue that represent the sites of separation of the leaflets (Figs. 4–25 and 4–26A). Beneath the two mitral commissures lie the anterolateral and posteromedial papillary muscles, which arise from the left ventricular free wall (see Figs. 4–18B and 4–25). Commissural chords arise from each papillary muscle and extend in a fan-like array to insert into the free edge of both leaflets adjacent to the commissures (major commissures)[17] (see Figs. 4–24 and 4–26A) or into two adjacent scallops of the posterior leaflet (minor commissures) (see Figs. 4–24 and 4–25). Normal posterior leaflet interscallop indentations formed by minor commissures are superficial and do not affect mitral valve closure. *Commissures, both major and minor, are to be distinguished from gaps and clefts. Clefts divide one leaflet into two and may or may not reach the level of the annulus. They are most commonly seen in the setting of AV canal defects. Unlike commissures, clefts have no papillary muscles beneath them and no chordal insertions along their edge. Some authors have also used the term cleft to describe deep divisions between scallops that are occasionally observed in myxomatous mitral valve disease, which may impact valve function and/or repair (Figs. 4-27A–C). Gaps are abnormal spaces between two leaflets, often at the usual site of a commissure. They are most frequently encountered in the setting of AV canal defects and tetralogy of Fallot, where the anterior and septal tricuspid leaflets may exhibit separation. Because the commissural chords are seldom elongated, they serve as accurate reference points for determining the proper*

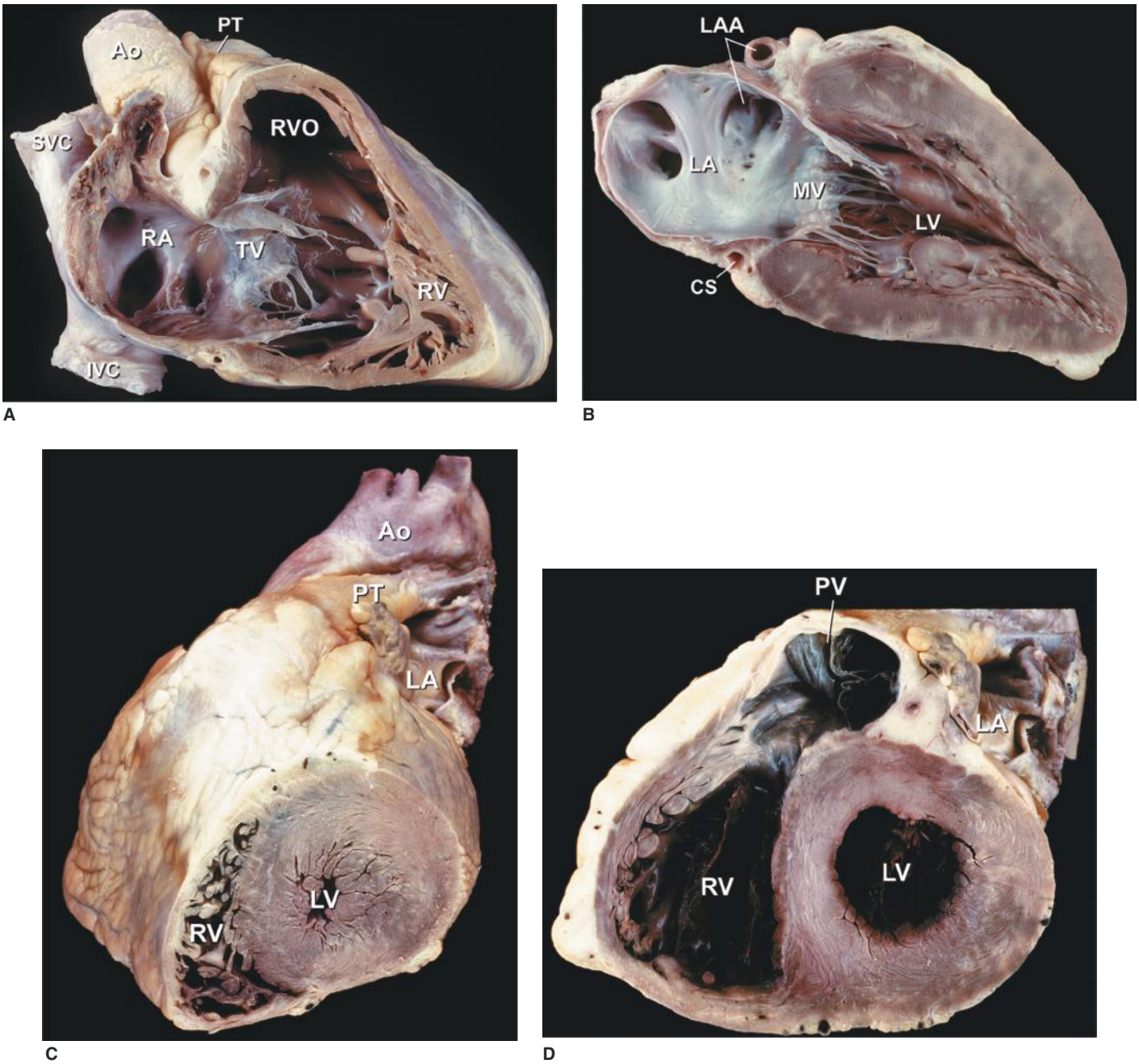


FIGURE 4–18. Oblique methods of tomographic cardiac dissection. **A, B.** Right anterior oblique sections, viewed from the right, are taken parallel to the ventricular and atrial septa, can include the right side of the heart (**A**) or the left side of the heart (**B**), and are similar to the two-chamber tomographic sections. **C, D.** Left anterior oblique sections, viewed from the apex toward the base, can be taken at various levels and are similar to the short-axis tomographic sections. Ao, ascending aorta; CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PT, pulmonary trunk; PV, pulmonary valve; RA, right atrium; RV, right ventricle; RVO, right ventricular outflow; SVC, superior vena cava; TV, tricuspid valve.

closing plane for the leaflets during surgical repair. Percutaneous edge-to-edge mitral valve repair involves grasping the free edges of the anterior and posterior leaflets at the site of mitral regurgitation (see Chap. 48).

The anterolateral papillary muscle is commonly single and usually has a dual blood supply from the left coronary circulation.[16] In contrast, the posteromedial papillary muscle usually has multiple heads and is most commonly supplied only by the dominant coronary artery.[16] Small left atrial branches supply the most basal aspects of the mitral leaflets.[17]

Papillary muscle contraction pulls the two leaflets toward one another and thereby promotes valve closure. The line of closure for either mitral leaflet is not its free edge but an ill-defined junction between a thin, clear zone and a thicker, rough zone[17] (see Fig. 4–26). Chordae tendineae progressively arborize from their anchoring point on the papillary muscle to their ultimate insertion on the free edge (so-called primary chords) and the rough zone (so-called secondary chords). The primary chords serve to prevent leaflet prolapse during ventricular systole, whereas the secondary chords help to maintain left ventricular geometry throughout the cardiac cycle. Two particularly prominent secondary chords, referred to as strut chords, insert along each half of the ventricular surface of the anterior mitral leaflet and provide additional leaflet support.[17] They can contain cardiac

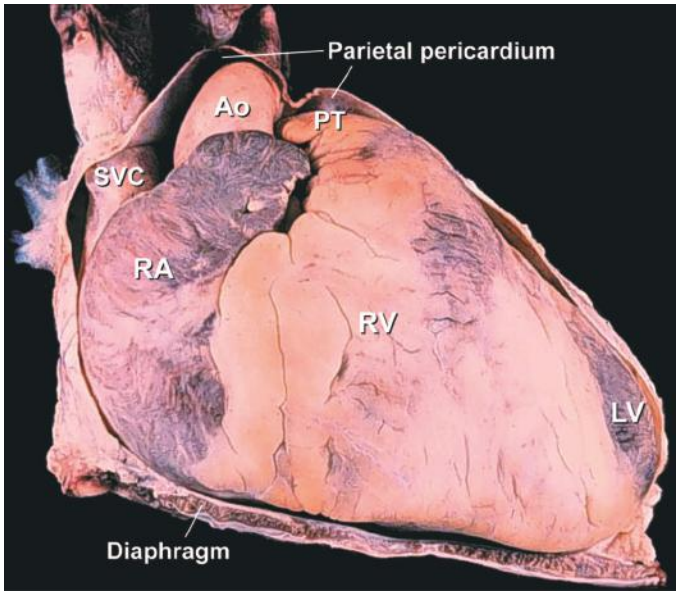


FIGURE 4–19. Anterior view of the heart. The anterior portion of the parietal pericardium has been removed, exposing the intrapericardial portions of the superior vena cava (SVC), ascending aorta (Ao), and pulmonary trunk (PT). LV, left ventricle; RA, right atrium; RV, right ventricle.

muscle and tend to calcify with age. Unlike the tricuspid valve, the normal mitral leaflets have no chordal insertions into the ventricular septum.[16] *The functional orifice of the mitral valve is defined by its narrowest diastolic cross-sectional area. This can be at the annulus when there is extensive annular calcification or close to the papillary muscle tips in patients with rheumatic mitral stenosis.*

Mitral valve prolapse is characterized by thickened and redundant leaflets, annular dilatation (with or without calcium), and thickened and elongated chordae tendineae (with or without rupture). Prolapse of the posterior leaflet occurs more frequently than that of the anterior leaflet.

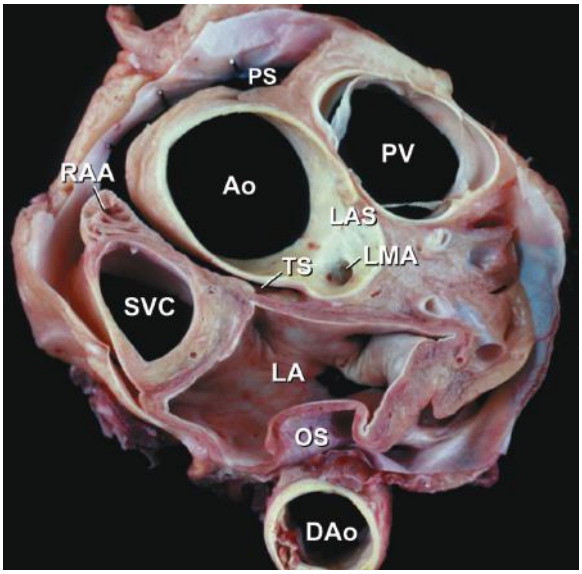
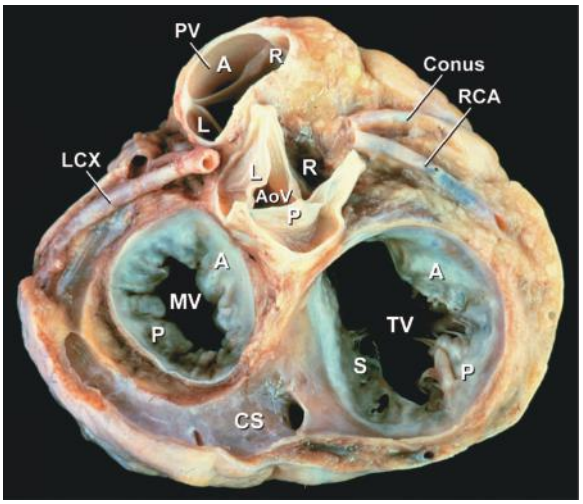
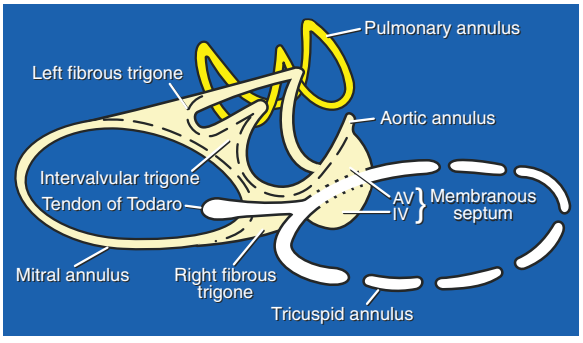


FIGURE 4–20. Tomographic section in the short-axis plane of the body, looking from apex toward the base, showing the oblique (OS) and transverse (TS) pericardial sinus. Ao, ascending aorta; DAo, descending thoracic aorta; LA, left atrium; LAS, left aortic sinus; LMA, left main coronary artery; PS, pericardial sac; PV, pulmonary valve; RAA, right atrial appendage; SVC, superior vena cava.



A



B

FIGURE 4–21. Base of heart. **A.** Section through the base of the heart, looking from base toward apex, with the atria and great arteries removed, shows all four cardiac valves. **B.** A comparable schematic diagram of the fibrous cardiac skeleton. The centrally located aortic valve forms the cornerstone of the cardiac skeleton. Its fibrous extensions anchor and support the other three valves. A, anterior; AoV, aortic valve; AV, atrioventricular; CS, coronary sinus; IV, interventricular; L, left; LCX, left circumflex coronary artery; MV, mitral valve; P, posterior; PV, pulmonary valve; R, right; RCA, right coronary artery; S, septal; TV, tricuspid valve.

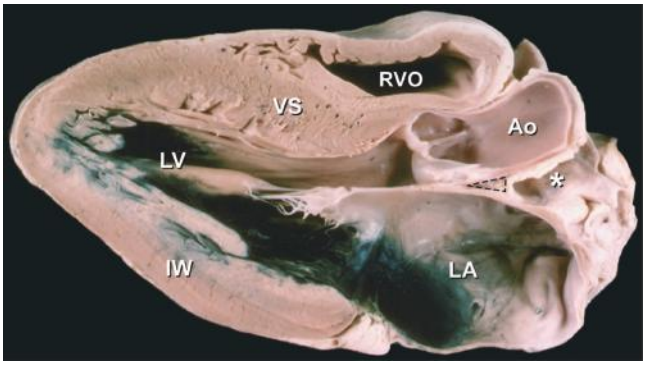


FIGURE 4–22. Long-axis section of the left ventricle. The intervalvular fibrosa (*dashed triangle*) lies between the anterior mitral leaflet and the posterior cusp of the aortic valve and abuts the floor of the transverse pericardial sinus (*). Ao, ascending aorta; IW, inferior wall; LA, left atrium; LV, left ventricle; RVO, right ventricular outflow; VS, ventricular septum.

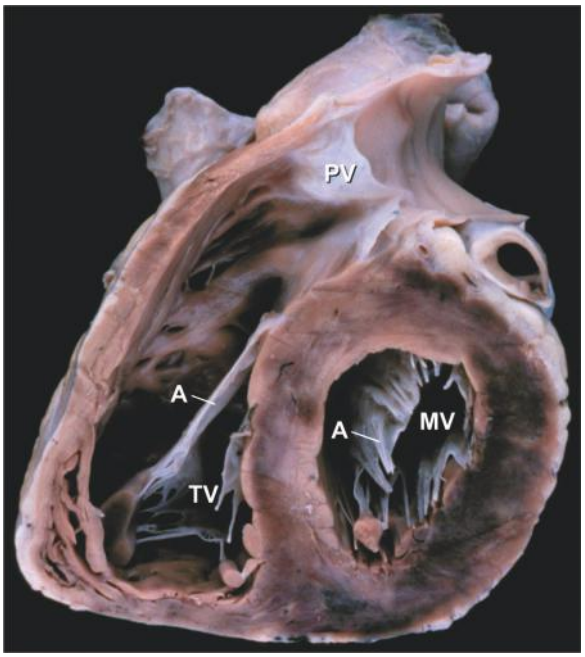


FIGURE 4–23. This oblique short-axis view of the heart shows the triangular-shaped tricuspid orifice (TV) and the elliptical mitral orifice (MV) at midleaflet level. The anterior tricuspid and anterior mitral leaflets (A) separate the inflow and outflow tracts of the right and left ventricles, respectively, and are parallel to one another. PV, pulmonary valve.

Rheumatic involvement of the mitral valve causes chordal shortening and thickening without annular dilatation. Rheumatic mitral stenosis is produced by chordal and commissural fusion, often with calcification, whereas rheumatic mitral insufficiency results from scar retraction of leaflets and chords.[14] *Chronic postinfarction mitral regurgitation is associated with left ventricular dilatation and scarring of a papillary muscle and its subjacent ventricular free wall. Leaflet tethering and annular dilatation cause malcoaptation of the contact surfaces of the mitral leaflets. Acute postinfarction mitral regurgitation can be associated with partial or complete rupture of a papillary muscle, usually the posteromedial one. Three-dimensional imaging of the atrial (surgical view) and ventricular (interventional cardiologist fluoroscopic view) surfaces of the mitral valve is now possible with echocardiography (see Chap. 15).*

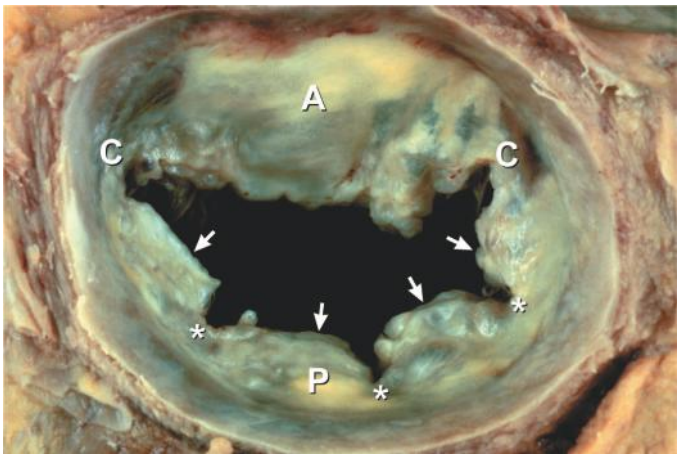


FIGURE 4–24. Mitral valve, viewed from left atrial aspect. Minor commissures (*) divide the posterior leaflet into four scallops (*arrows*). A, anterior; C, major commissures; P, posterior.

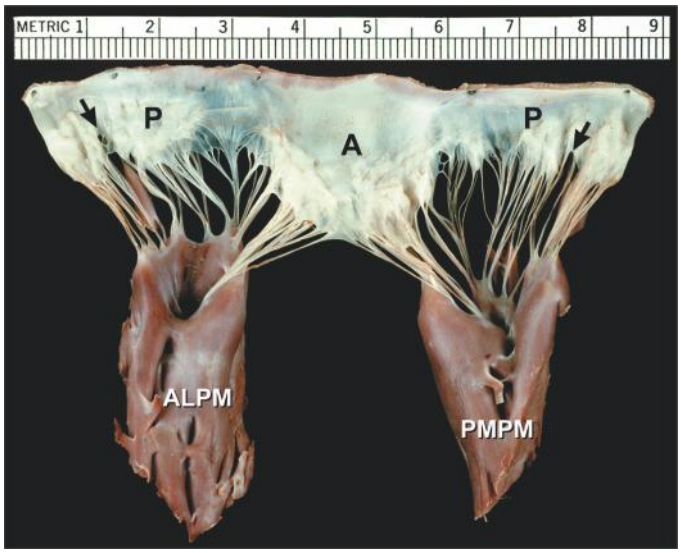


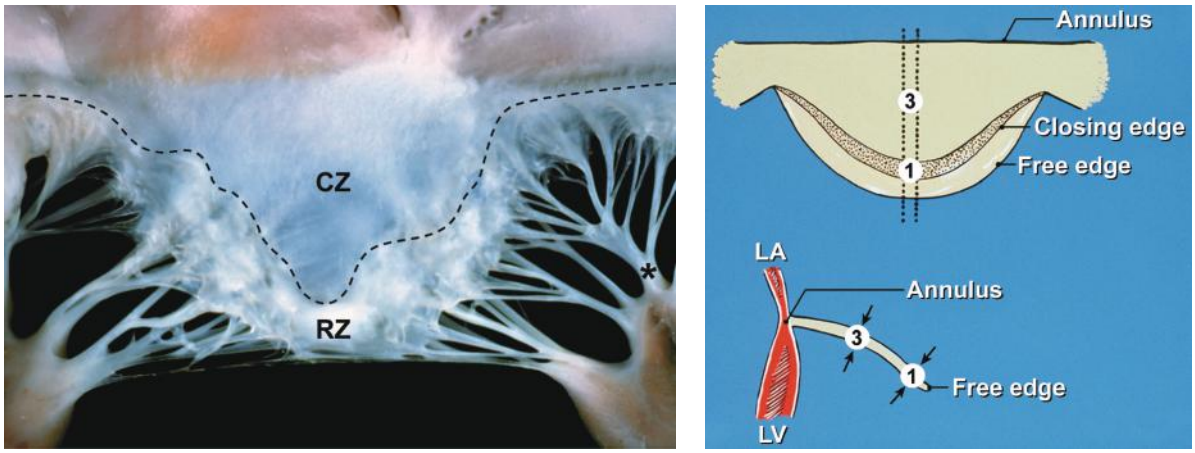
FIGURE 4–25. Gross anatomy of the mitral valve and papillary muscles–chordal apparatus, as demonstrated in an excised and unfolded valve. Each commissure overlies a papillary muscle. *Arrows* point to minor commissures. A, anterior leaflet; ALPM, anterolateral papillary muscle; P, posterior leaflet; PMPM, posteromedial papillary muscle.

Anatomically important structures during percutaneous or surgical mitral valve repair or replacement include the left circumflex coronary artery, which courses within the left AV groove near the anterolateral commissure, and the coronary sinus, which courses within the left atrioventricular groove adjacent to the annulus of the posterior mitral leaflet[17] (see Fig. 4–21A).

AORTIC VALVE

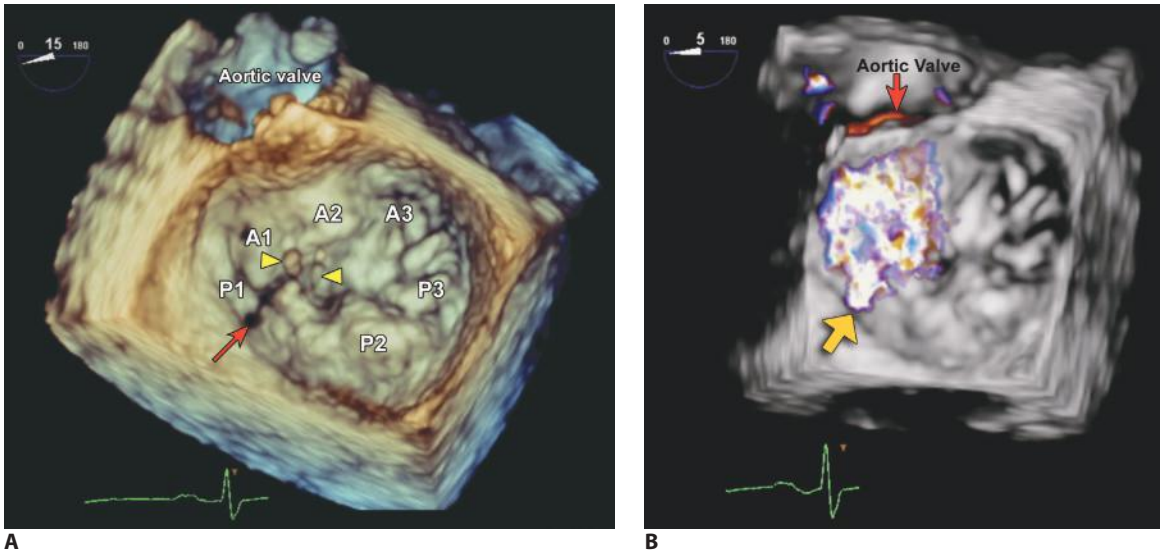
The aortic valve, like the pulmonary valve, is composed of three components (ie, annulus, cusps, and commissures). In contrast to the mitral and tricuspid valves, the two semilunar valves have no tensor apparatus (ie, chordae tendineae or papillary muscles). The commissures form tall, peaked spaces between the attachments of adjacent cusps (Figs. 4–28 and 4–29) and attain the level of the aortic sinotubular junction, the ridge that separates the sinus and tubular portions of the ascending aorta (originally described by da Vinci as the "supraortic ridge")[14] (see Fig. 4–29). The functional aortic valve orifice can be at the sinotubular junction or proximal to it.[17]

The three half moon–shaped (semilunar) aortic cusps form pocket-like tissue flaps that are avascular. In only approximately 10% of hearts are they truly equal in size. In 67% of hearts, either the right or posterior cusp is larger than the other two.[17] Just below the free edge of each cusp is a biscalloped ridge-like closing edge (see Fig. 4–29). At the center of each cusp, the closing edge meets the free edge and forms a small fibrous mound, the nodule of Arantius[14] (see Fig. 4–29). Between the free and closing edges, to each side of the nodule are two crescent-shaped areas known as the closing surface or *lunulae,* which represent the sites of cusp apposition during valve closure.[14] Lunular fenestrations, near the commissures, are common and increase in size and incidence with age[14] (Fig. 4–30). However, owing to their position distal to the closing edge, they rarely produce valvular incompetence.[17] When viewed from above, the linear distance along the closing edge of a cusp is much greater than the straight-line distance between its two commissures[14] (see Fig. 4–28). This extra length of cusp tissue is necessary for nonstenotic opening and nonregurgitant closure of the valve.[14] A virtual line connecting the bases of each cusp forms the basal



A B

FIGURE 4–26. Components of the mitral valve. **A.** Each leaflet has a large clear zone (CZ) and a smaller rough zone (RZ) between its free edge and closing edge (*dotted line*). A fan-like commissural chordae tendinea (*) connects the tip of the papillary muscle to the commissure. **B.** Schematic diagram of an open anterior mitral leaflet comparable to **A.** Section obtained along the *dotted lines* shows the relationship of the mitral annulus and free edge to the closing edge.



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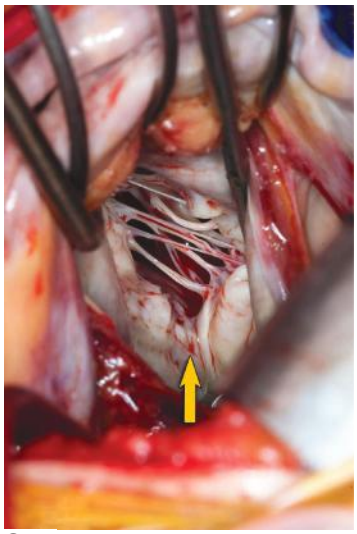


C

FIGURE 4–27. Flail P2 segment. Enface three-dimensional TEE LA view of mitral valve showing mitral cleft (*red arrow*) between the P1 and P2 scallops. *Arrowheads* point to ruptured chordae (**A**). Mitral regurgitation (*yellow arrow*) through the P1-P2 cleft (**B**). Intraoperative view of the mitral cleft (*arrow*) (**C**). A1-A2-A3, lateral to medial anterior leaflet scallops; *LA, left atrium*; P1-P2-P3, lateral to medial posterior mitral leaflet scallops; *TEE, transesophageal echocardiogram*. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

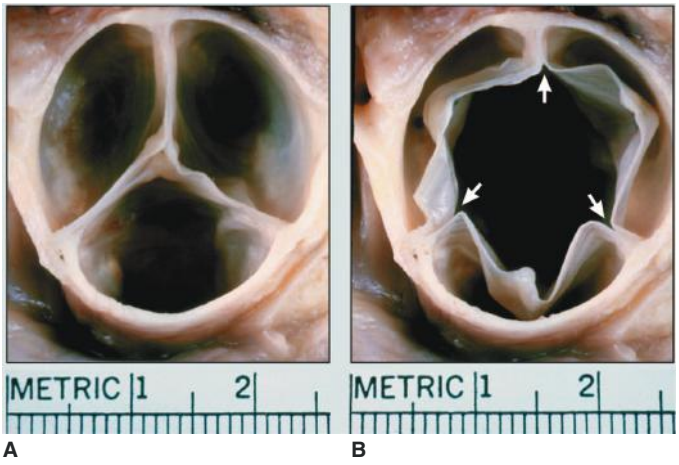


FIGURE 4–28. Each cusp of a semilunar valve is pocket-shaped. The aortic valve is viewed from above in simulated closed (**A**) and open (**B**) positions, showing the three commissures (*arrows*). Note that the length of the closing edge exceeds the straight-line distance between the commissures.

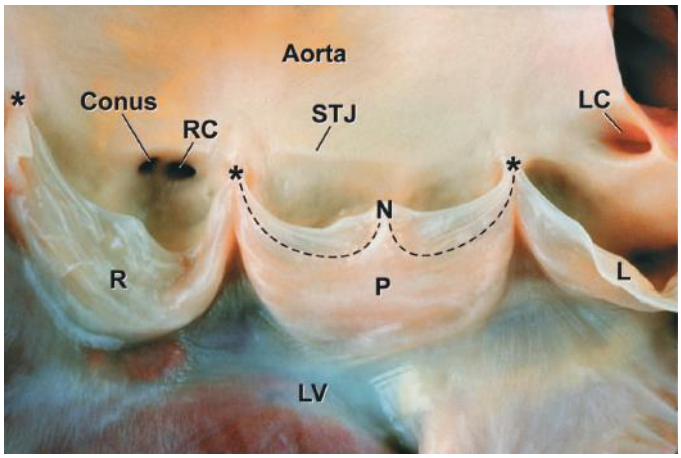


FIGURE 4–29. An opened aortic valve shows the right (R), left (L), and posterior (P) cusps. The *dashed line* marks the closing edge. Between the free and closing edges of each cusp are two lunular areas, representing the surfaces of apposition between adjacent cusps during valve closure. The commissures (*) attain the level of the aortic sinotubular junction (STJ). Conus, conus coronary ostium; LC, left coronary ostium; LV, left ventricle; N, nodule of Arantius; RC, right coronary ostium.

ring, although the true ventriculoarterial junction is just distal to it. The diameters of the basal ring and sinotubular junction are usually similar and represent the narrowest portions of the aortic root.[6] *Accurate measurements of these regions are critical to success of transcatheter or surgical aortic valve replacement.*

Lunular fenestrations (see Fig. 4–30), depending on their severity, may preclude the ability to perform valve-sparing aortic root replacement in patients with aortic root aneurysms. In hearts from adults with bicuspid valves and other congenital aortic valve disease, the annular diameter is usually enlarged. In contrast, patients with normal aortic cusps and central aortic regurgitation show enlargement at the level of the sinotubular junction.[6] A prebypass intraoperative transesophageal long-axis view of the left ventricular outflow tract is used to measure the aortic valve annular diameter prior to replacement by a homograft. In doing so, precious bypass time is saved while the homograft is being prepared.[6] Disease processes that produce commissural fusion such as rheumatic valvulitis or decrease cusp mobility such as fibrosis or calcification can lead to aortic stenosis.[14] In contrast, those disorders that decrease cusp size, such as rheumatic valvulitis, or that cause aortic root dilatation can lead to aortic regurgitation.[14] Combinations of these processes can produce combined stenosis and regurgitation.

The commissure between the right and posterior aortic cusps overlies the membranous septum (Fig. 4–31) and contacts the commissure between the anterior and septal leaflets of the tricuspid valve (see Fig. 4–42). The commissure between the right and left aortic cusps contacts its corresponding pulmonary commissure and overlies the infundibular septum (see Fig. 4–12D). The intervalvular fibrosa, at the commissure between the left and posterior aortic cusps, fuses the aortic valve to the anterior mitral leaflet.[14,17]

The central location of the aortic valve (see Fig. 4–21) provides the electrophysiologist with a unique vantage point from which arrhythmias in the right or left ventricular outflow tract, right or left atrium, can be ablated.[8] During surgical or transcatheter aortic valve replacement, the anterior mitral leaflet, left bundle branch, or coronary ostia can be injured inadvertently.[17] Annular abscesses caused by infective endocarditis involving the aortic valve can burrow into adjacent structures and thereby produce endocarditis of the other valves; conduction disturbances with septal involvement: aortoatrial, aortopulmonary artery, or aortoventricular fistulas; pericarditis; or fatal hemopericardium.[14]

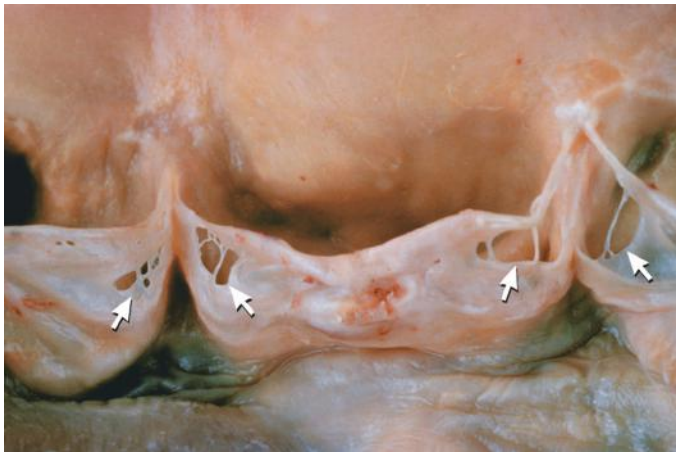


FIGURE 4–30. Aortic cusp fenestrations (*arrows*) occurring in the lunular regions near the commissures. This is a common age-related degenerative finding and normally accounts for little or no aortic valve regurgitation.

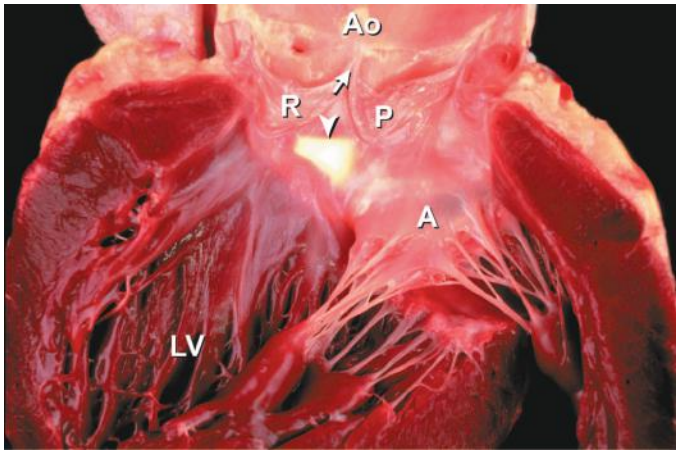


FIGURE 4–31. The commissure between the right and posterior aortic cusps (*arrow*) overlies the transilluminated membranous septum (*arrowhead*). A, anterior mitral leaflet; Ao, ascending aorta; LV, left ventricle; P, posterior aortic cusp; R, right aortic cusp.

PULMONARY VALVE

The pulmonary valve is virtually identical in design to the aortic valve.[17] The pulmonary artery sinuses are partially embedded within the muscle bundles of the right ventricular infundibulum, particularly adjacent to the right and left sinuses.[16,20] *In pulmonary valve atresia with an intact ventricular septum, hypertrophy of the muscle bundles and the narrow right ventricular outflow tract accentuate this relationship.*[20] Also, unlike the aortic valve, which is continuous with the mitral valve, the pulmonary and tricuspid valves are separated by infundibular muscle.[17] *Ventricular arrhythmias can originate from the pulmonary valve or supravalvular portion of the pulmonary arteries.*[8] The pulmonic valve is typically cephalad to the aortic valve (see Fig. 4–35) such that the supravalvular portion of the aortic valve lies in immediate proximity to portions of the pulmonary valve. *This relationship is important for the electrophysiologist.*[8]

AGE-RELATED VALVE CHANGES

Several age-related changes in the cardiac valves can have clinical significance.[21] In normal hearts, the thickness of the aortic and mitral leaflets increases progressively with each decade, particularly along their closure margins.[21] Probably the most common clinical manifestation of these changes is aortic valve sclerosis, characterized by valve thickening without hemodynamic dysfunction.[21] However, age-related degenerative calcification of an otherwise anatomically normal-appearing aortic valve can result in progressive aortic stenosis.[21]

Age-related thickening along the nodule of Arantius and closing edges can be associated with the formation of whisker-like projections called Lambl excrescences. These fine fibrous-like strands also can develop on the mitral valve.[17] *Lambl excrescences can be detected by echocardiography and have been associated with cardioembolic stroke.*[22] *Larger lesions with complex branching, having the appearance of a sea anemone, are considered to be either neoplastic or reactive and are known as papillary fibroelastomas.*[23]

The circumferences of all four major cardiac valves increase with age in normal hearts. This is particularly evident in the semilunar valves.[21] Age-related annular dilatation of the aortic valve can result in aortic regurgitation.[21] Mitral annular calcification (MAC) is rare in women younger than 70 years of age but is present in 40% of women older than 90 years.[21] *MAC almost invariably involves only the posterior leaflet and forms a C-shaped ring of annular and subannular calcium.*[17] *It can impede subannular ventricular contraction, thereby resulting in mitral regurgitation, and marked MAC can result in severe mitral inflow stenosis that may be amenable to valve–in–native valve implantation (see Chap. 50). Three-dimensional reconstruction of intracardiac structures such as heart valves from CT or MRI images using 3D printing is now available*[11,12] *and allows for testing of feasibility of transcatheter interventions. Because of the proximity of the posteromedial commissure to the AV (His) bundle, MAC can be associated with AV block.*[21] *Because of the increasing size of the aging population, degenerative calcific aortic disease is increasing in frequency.*[21]

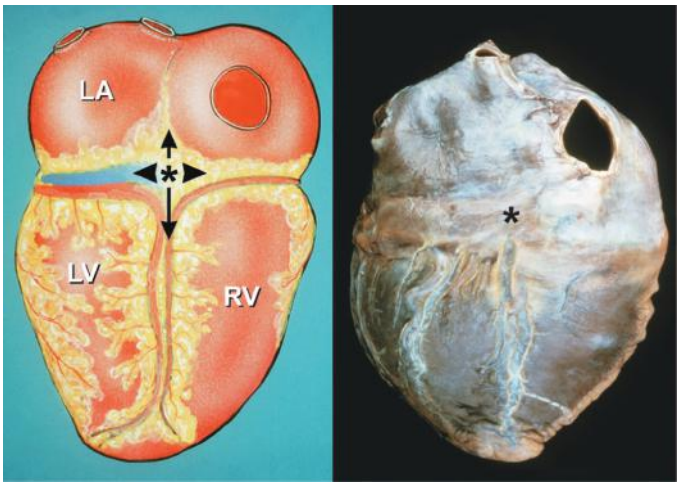


FIGURE 4–32. External cardiac crux. View of the diaphragmatic aspect of the heart shows the intersection of the atrioventricular (*arrowheads*), posterior interventricular (*long arrow*), and interatrial (*small arrow*) grooves at the external cardiac crux (*). **A.** Diagram. **B.** Cardiac specimen. LA, left atrium; LV, left ventricle; RV, right ventricle.

CARDIAC GROOVES, CRUX, AND MARGINS

The AV groove (or sulcus) encircles the heart and defines its base. It separates the atria from the ventricles (Fig. 4–32). The two ventricles are separated by the anterior and posterior (inferior) interventricular grooves (or sulci), which define the plane of the ventricular septum (see Figs. 4–5A and 4–32).

With age, fat tends to accumulate in increasing amounts in the epicardium, particularly in the AV grooves.[21,24] *Increased epicardial fat deposits can be associated with increased risk of cardiac rupture after acute transmural myocardial infarction.*[24] Excess fat in the atrial septum is called lipomatous hypertrophy of the atrial septum (see Fig. 4–48) and can result in a thickness exceeding that of the ventricular septum. *Fat in the right ventricular free wall can be detected on CT (Fig. 4–33); its excess*

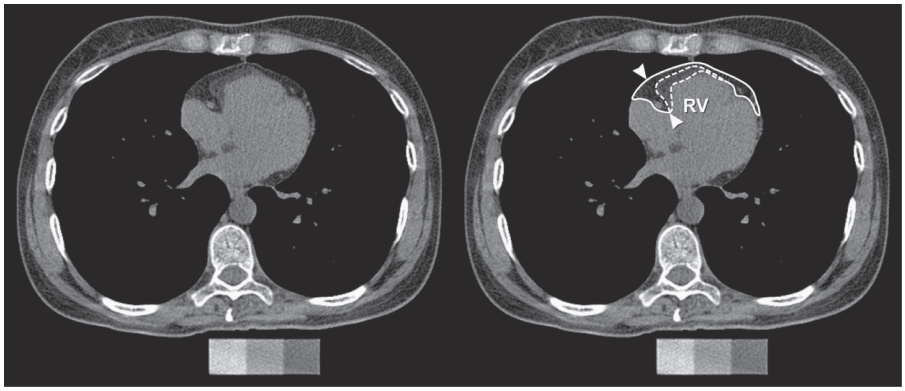


FIGURE 4–33. Noncontrast CT four-chamber view of the heart. Fat is seen within the epicardium (*solid lines*), and right ventricular free wall (*dashed lines*). *Arrowheads* point to fat in the atrioventricular groove. RV, right ventricle.

accumulation can be associated with increasing age, obesity, myocardial injury or arrhythmogenic cardiomyopathy.[25]

Along the surface of the heart, the right and circumflex coronary arteries travel in the right and left AV grooves, respectively, and the left anterior and posterior descending coronary arteries course along the anterior and posterior (or inferior) interventricular grooves, respectively (see Figs. 4–5A and 4–32). The external cardiac crux is the cross-shaped intersection between the atrioventricular, posterior interventricular, and interatrial grooves (see Fig. 4–32). Its internal counterpart (internal crux) is the posterior intersection between the mitral and tricuspid annuli and the atrial and ventricular septa (see Figs. 4–16B and 4–36).

The junction between the anterior and inferior free walls of the right ventricle forms a sharp angle known as the acute margin. The rounded lateral wall of the left ventricle forms the obtuse margin.[14]

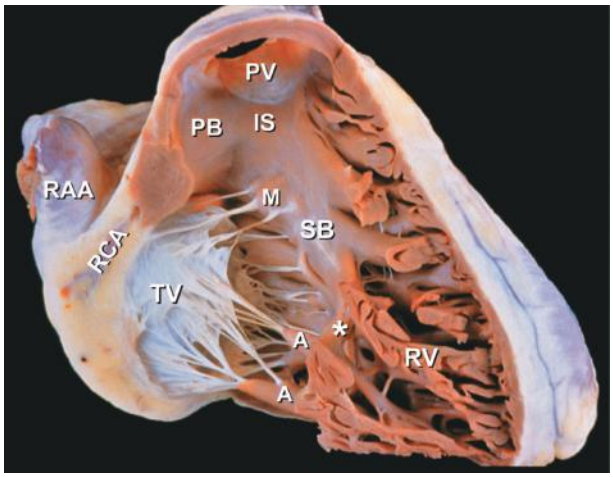
RIGHT VENTRICLE

The right ventricle is a right-anterior structure. It is comprised of an inlet and trabecular and outflow segments[14] (Fig. 4–34). The inlet component extends from the tricuspid annulus to the insertions of the papillary muscles. An apical trabecular zone extends inferiorly beyond the attachments of the papillary muscles toward the ventricular apex and about halfway along the anterior wall.[14] *This muscular meshwork is the usual site of insertion of transvenous ventricular pacemaker electrodes and the preferred site for positioning of the tip of an implantable cardioverter defibrillator lead. During right ventricular endomyocardial biopsy, tissue generally is obtained from the septum, usually under echocardiographic or fluoroscopic guidance. Disruption of a portion of the tricuspid valve tensor apparatus is a potential complication of right-sided heart instrumentation (eg, right ventricular endomyocardial biopsy).*[17] The outflow portion, also known as the conus (meaning cone) or infundibulum (meaning funnel), is a smooth-walled muscular subpulmonary channel[14,17] (see Fig. 4–34).

A prominent arch-shaped muscular ridge known as the crista supraventricularis separates the tricuspid and pulmonary valves. It is made up of three components (ie, parietal band, infundibular septum, and septal band) that can appear as distinct structures or can merge together[14,17] (see Fig. 4–34). The parietal band is a free-wall structure, whereas the adjacent infundibular septum is intracardiac and separates the two ventricular outflow tracts beneath the right and left cusps of both semilunar valves[14,17] (Fig. 4–35; see also Fig. 4–12D). The septal band forms a Y-shaped muscle, the two upper limbs of which cradle the infundibular septum. From this branching point of the septal band emanates the medial tricuspid papillary muscle[14,17] (see Fig. 4–34). The moderator band forms an intracavitary muscle that connects the septal band with the anterior tricuspid papillary muscle (see Fig. 4–34A).

LEFT VENTRICLE

The left ventricle, like the right ventricle, is made of an inlet portion comprised of the mitral valve apparatus, a subaortic outflow portion, and a finely trabeculated apical zone.[17] The left ventricular free wall is normally thickest toward the base and thinnest toward the apex, where it averages only 1 to 2 mm in thickness, even in hypertrophied hearts.[17] Structurally, the left and right ventricles differ considerably.[14,17] Normally, the left ventricular free-wall and septal thicknesses are three times the thickness of the right ventricular free wall. The mitral and aortic valves share fibrous continuity, whereas the parietal band separates the tricuspid and pulmonary valves. Whereas the mitral valve has an elliptical orifice and no septal attachments, the tricuspid valve has a triangular orifice and numerous direct septal attachments (see Fig. 4–23). The right ventricular apex is much more coarsely trabeculated than



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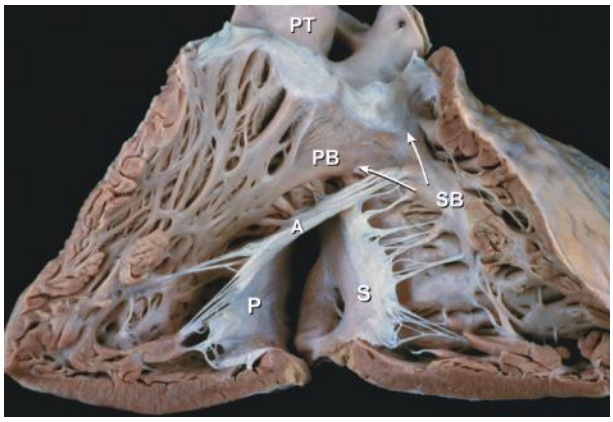


B

FIGURE 4–34. Right ventricle. **A.** The right ventricular free wall has been removed to show the arch-like crista supraventricularis (CSV), which consists of the parietal band (PB), infundibular septum (IS), and septal band (SB). The moderator band (*) joins the septal band to the anterior tricuspid papillary muscle (A). The anteroapical portion of the chamber is heavily trabeculated. M, medial tricuspid papillary muscle; PV, pulmonary valve; RAA, right atrial appendage; RCA, right coronary artery; TV, tricuspid valve. **B.** The right ventricle has been opened by the inflow-outflow method to show the parietal band (PB) separating the tricuspid and pulmonary valves, as well as the two upper limbs (*arrows*) of the septal band (SB). A, anterior leaflet of the tricuspid valve; P, posterior leaflet of the tricuspid valve; PT, pulmonary trunk; S, septal leaflet of the tricuspid valve; other abbreviations as in **A**.

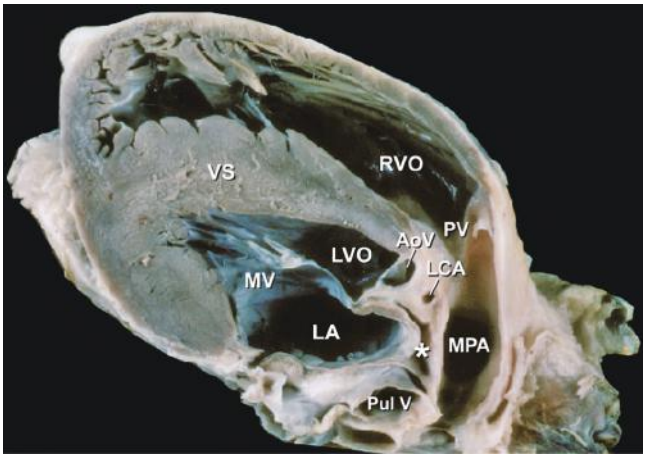


FIGURE 4–35. Long-axis view of the right ventricular outflow (RVO) tract showing the pulmonary valve (PV) and main pulmonary artery (MPA). AoV, aortic valve; LA, left atrium; LCA, left coronary artery; LVO, left ventricular outflow; MV, mitral valve; PulV, pulmonary vein; VS, ventricular septum; *, transverse pericardial sinus.

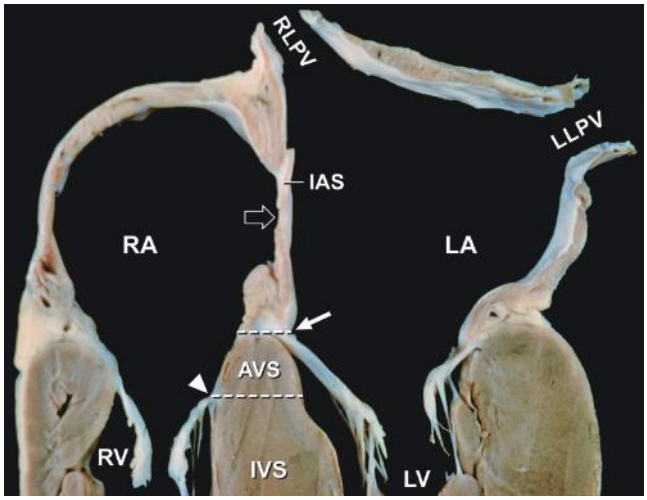


FIGURE 4–36. Internal cardiac crux. Four-chamber slice of the heart shows the characteristic normal apical displacement of the tricuspid valve septal leaflet insertion (*arrowhead*) when compared with septal insertion of the mitral valve (*solid arrow*). This tomographic section also shows the interatrial septum (IAS), atrioventricular septum (AVS), and interventricular septum (IVS). Open arrow points to fossa ovalis. LA, left atrium; LLPV, left lower pulmonary vein; LV, left ventricle; RA, right atrium; RLPV, right lower pulmonary vein; RV, right ventricle.

its counterpart on the left (see Figs. 4–9B and 4–18C). *The distinctive differences in apical trabeculations persist even in markedly hypertrophied or dilated hearts.*[17]

The annular attachment of the septal leaflet of the tricuspid valve inserts more apically than that of the anterior mitral leaflet, allowing distinction between the right and left ventricles by four-chamber imaging (Fig. 4–36). *Exceptions include partial AV septal defects and double-inlet ventricles in which the two valve annuli are at the same level. Ebstein anomaly is characterized by exaggeration of apical displacement of the septal and posterior tricuspid leaflets resulting in an atrialized portion of the right ventricular chamber.*[16,17] *Morphologic differentiation of the right and left ventricles is particularly important in congenital heart disease.* The morphologic tricuspid valve virtually always connects to a morphologic right ventricle, whereas the morphologic mitral valve connects to a morphologic left ventricle.[14,16] Because of the rightward bulging of the ventricular septum, the left ventricular chamber appears circular in cross-section, whereas the right ventricular chamber has a crescentic appearance (see Fig. 4–23). Tomographic segmental left ventricular anatomy is reviewed in the following section on the coronary arteries.

Left ventricular false tendons, also referred to as pseudotendons or bands,[26] are discrete, thin, cord-like fibromuscular structures that connect two walls, the two papillary muscles, or a papillary muscle to a wall, usually the ventricular septum (Fig. 4–37). However, false tendons, as the name implies, are not attached to the mitral leaflets. *Chordal attachments between the mitral leaflets and the ventricular septum are abnormal and are usually associated with AV septal defects or straddling AV valves.*[16] False tendons are common anatomic variants of the normal left ventricle, occurring in 50% of hearts, and can become calcified with age (Fig. 4–38). They are more frequently observed in men, but their incidence does not appear to be age related.[26] *It has been suggested that they can be the cause of innocent systolic musical murmurs and rarely form part of an arrhythmogenic conduction circuit.*[26] *Although they are readily detectable by echocardiography, they can be misinterpreted by the inexperienced sonographer as pathologic structures such as ruptured chords, mural thrombi, or vegetations.*[17,26]

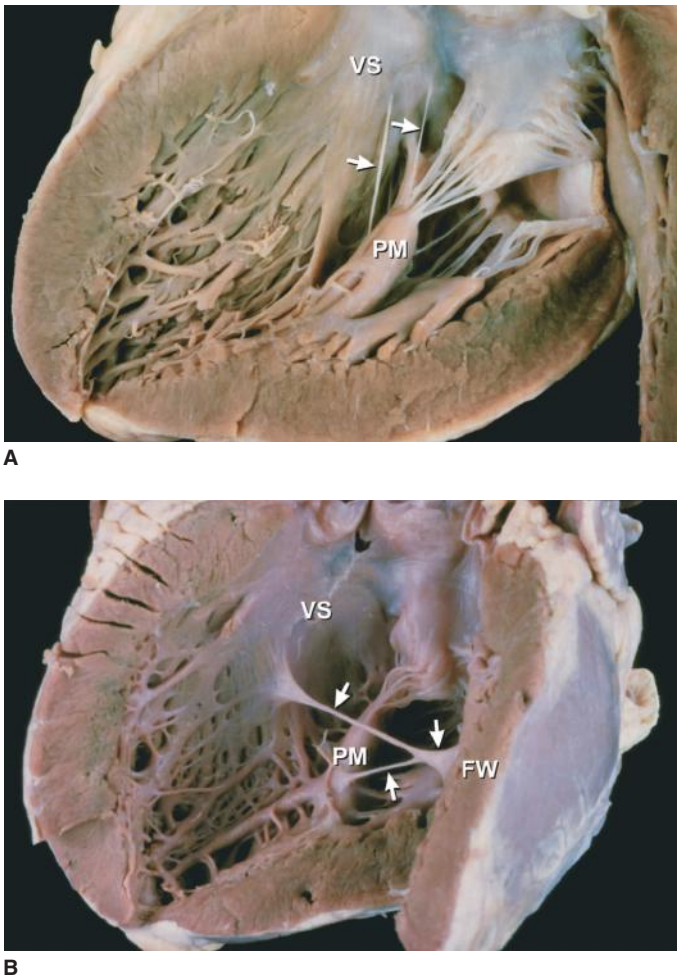


FIGURE 4–37. Various locations of left ventricular false tendons. **A.** Two false tendons (*arrows*) from posteromedial mitral papillary muscle (PM) to ventricular septum (VS), representing the most common location. **B.** Complex branching false tendon (*arrows*) with origin from the left ventricular free wall (FW) and insertions into the ventricular septum (VS) and base of posteromedial mitral papillary muscle (PM).

Prominent left ventricular trabeculations[27] are another common anatomic normal variant that can be an even greater source of misinterpretation by 2D echocardiography in patients with suspected mural thrombus. They are defined as discrete, thick muscle bundles that generally connect the free wall to the septum (Fig. 4–39). Less common

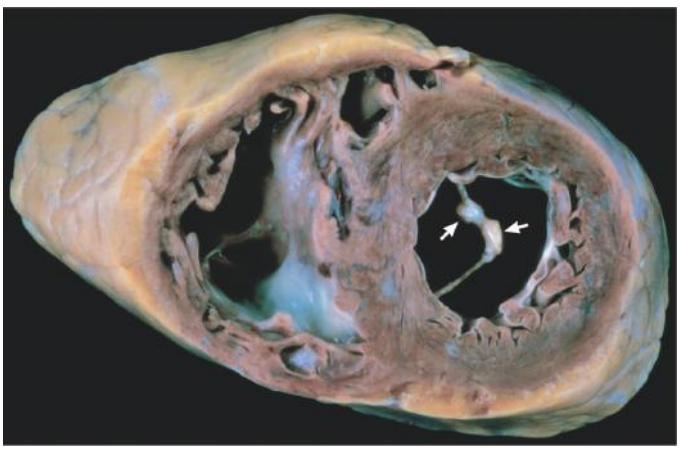


FIGURE 4–38. Calcified left ventricular false tendon (*arrows*) seen in short-axis view.

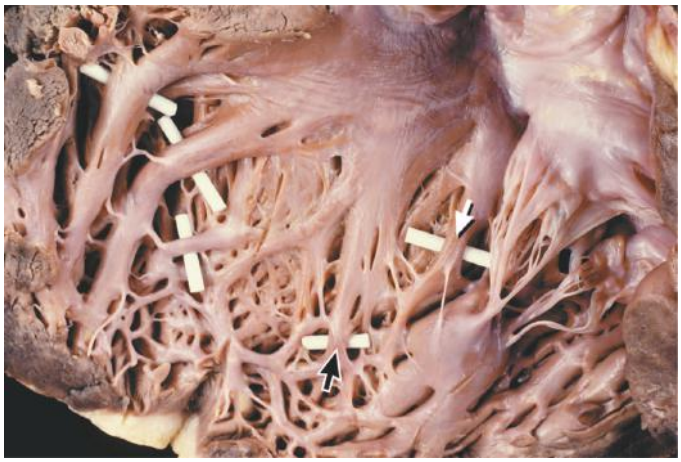


FIGURE 4–39. Prominent left ventricular trabeculations. Multiple large muscle bundles extend from the anterior free wall to the septum (*probes*). A single muscle bundle extends from the posteromedial mitral papillary muscle to the posterior septum (*probe with white arrow*), and one bundle extends from one portion of the posterior septum to another (*probe with black arrow*). Such trabeculations are more prominent in noncompaction cardiomyopathy.

attachments include papillary muscle to the septum, septum to septum, or free wall to free wall. *In noncompaction of the left ventricular myocardium,*[28,29] *also known as spongy myocardium, there is persistence of prominent ventricular trabeculations and deep intertrabecular recesses caused by arrest in the normal in utero process of myocardial compaction. The associated clinical manifestations and age at onset of symptoms (ie, typically a dilated cardiomyopathy) are highly variable.*

VENTRICULAR SEPTUM

The ventricular septum is a complex intracardiac partition and is comprised of four parts: (1) inlet, (2) trabecular, (3) membranous, and (4) infundibular. The plane of the infundibular portion (see Figs. 4–12D and 4–35) is different from that of the three other portions. *This anatomic relationship is important in many forms of congenital heart disease in which the infundibular septum is dissociated from the remainder of the ventricular septum (eg, malalignment forms of ventricular septal defects in tetralogy of Fallot and in double-outlet right ventricle).*[14,16,17]

The ventricular septum also can be divided into muscular and membranous portions[14,16,17] (Figs. 4–40 and 4–41). The membranous septum lies beneath the right and posterior (noncoronary) aortic cusps (see Fig. 4–31) and contacts the mitral and tricuspid annuli (Fig. 4–42). The membranous septum in conjunction with the right fibrous trigone with which it is continuous fuses the commissure between the right and posterior aortic cusps to the commissure between the anterior and septal tricuspid leaflets (see Fig. 4–21B). *The majority of clinically significant ventricular septal defects involve the membranous septum.*[17] Because of normal angulation between the infundibular septum and remaining ventricular septum, the septal surface follows the course of an inverted "S" (moving from apex to aortic valve). The basal half of the ventricular septum is smooth walled, whereas the apical half is characterized by numerous small and irregularly arranged trabeculations.[14,16,17]

Clinically relevant age-related anatomic changes include a disproportionate increase in ventricular septal thickness regardless of sex and in the absence of a history of hypertension.[21] This is associated with an appreciable increase in the ratio of ventricular septal to left ventricular free-wall thickness, often exceeding 1.3 in patients older than 60 years[21] (Fig. 4–43). This can be caused in part by the accentuation

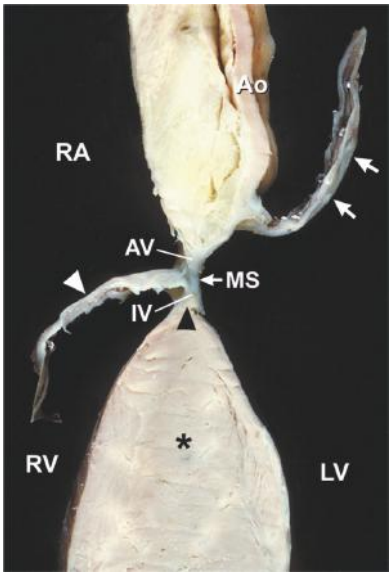


FIGURE 4–40. Four-chamber tomographic slice through the aortic root (Ao) and aortic valve right coronary cusp (*two arrows*) showing the small membranous (MS) and large muscular (*) portion of the ventricular septum. The membranous septum is divided into atrioventricular (AV) and interventricular (IV) components by the septal tricuspid leaflet (*white arrowhead*). *Black arrowhead* points to the expected location of the AV (His) bundle. LV, left ventricle; RA, right atrium; RV, right ventricle.

of the sigmoid shape of the basal septum[14,21] (Fig. 4–44). *Age-related ventricular septal angulation can have clinical importance because it can morphologically mimic hypertrophic cardiomyopathy,*[14,21] particularly if complicated by the indiscriminate use of volume-depleting diuretics or afterload-reducing agents.

ATRIAL SEPTUM

When viewed from its right aspect, the atrial septum is composed of interatrial and AV regions[16,17] (see Fig. 4–36). The interatrial portion is characterized by the fossa ovalis, which is the anatomic hallmark of a morphologic right atrium (Fig. 4–45A). Its outer muscular rim is a horseshoe-shaped limbus, and its central depression is the valve of the fossa ovalis[16,17] (see Fig. 4–45A). The potential interatrial passageway

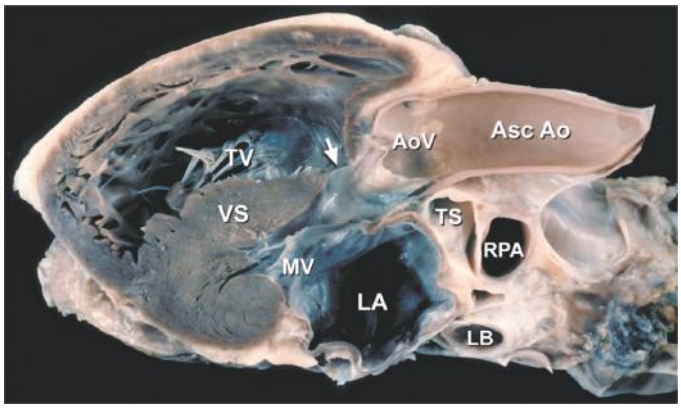


FIGURE 4–41. Tomographic section of the heart along a long-axis plane of the body. The aortic root lies in this plane. The left ventricle and aortic valve are cut obliquely. The membranous ventricular septum (*arrow*) lies beneath the right and posterior aortic cusps. AoV, aortic valve; Asc Ao, ascending aorta; LA, left atrium; LB, left bronchus; MV, mitral valve; RPA, right pulmonary artery; TS, transverse sinus; TV, tricuspid valve; VS, muscular ventricular septum.

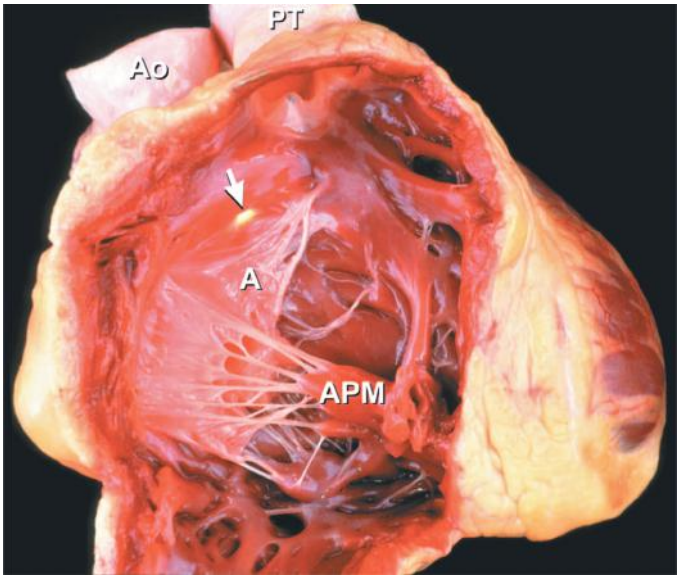


FIGURE 4–42. A view of the right ventricle. Transilluminated membranous ventricular septum (*arrow*) in contact with the commissure between the anterior and septal leaflets of the tricuspid valve. A, anterior tricuspid leaflet; Ao, ascending aorta; APM, anterior tricuspid papillary muscle; PT, pulmonary trunk.

between the limbus and the valve (which is patent throughout fetal life) is the foramen ovale (Figs. 4–45B and 4–46). When viewed from the left atrium, the atrial septum is entirely interatrial because the AV component lies below the mitral annulus between the left ventricle and right atrium. Likewise, the limbus of the fossa ovalis is completely covered by its opaque valve and is not directly visible from the left atrium.[14] *The fossa ovalis and surrounding anatomy can be readily imaged by 3D transesophageal echocardiography (Fig. 4–47A and B).*

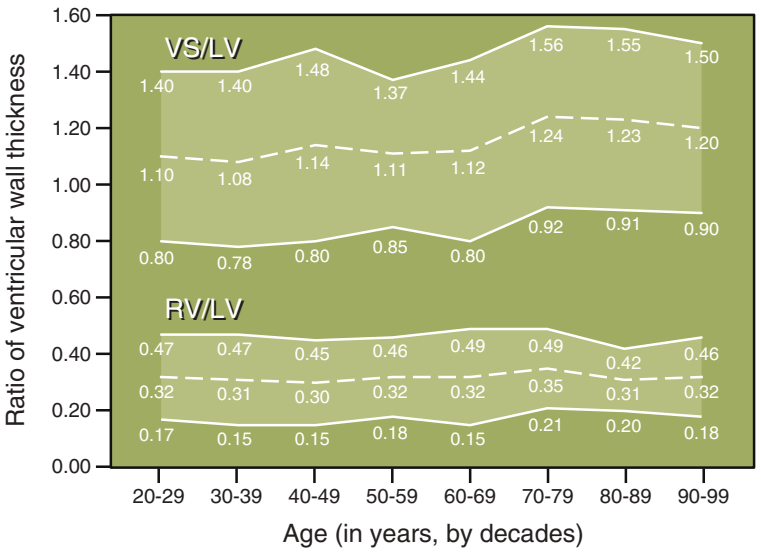


FIGURE 4–43. Ratios of ventricular wall thicknesses (means ±2 standard deviations) versus age. RV/LV, ratio of right-to-left ventricular wall thickness; VS/LV, ratio of ventricular septal to left ventricular free wall thickness. Reproduced from Kitzman DW, Scholz DG, Hagen PT, Ilstrup DM, Edwards WDI. Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. Reproduced with permission from Kitzman DW, Scholz DG, Hagen PT, et al: Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old, *Mayo Clin Proc*. 1988 Feb;63(2):137-146.

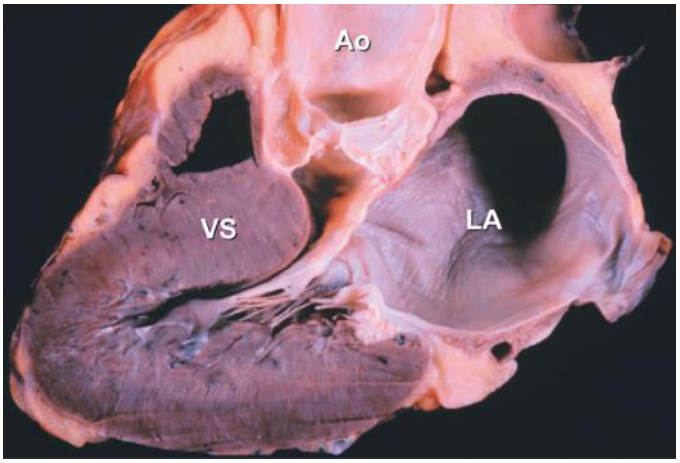


FIGURE 4–44. Age-related changes in the left-sided cardiac structures. Normal heart from an 84-year-old man demonstrates shortening of the base-to-apex (long-axis) dimension, decreased internal left ventricular dimension, aortic root dilatation, left atrial enlargement, and sigmoid-shaped septum. (Compare with Fig. 4–15A from an 18-year-old man.) Ao, ascending aorta; LA, left atrium; VS, ventricular septum.

The foramen ovale is anatomically closed in approximately two-thirds of adults, but in the remaining one-third it remains patent and, therefore, a potential source for shunts and paradoxical embolism. Stretching of the atrial septum, when the atria are markedly dilated, can transform a patent foramen ovale into an acquired atrial septal defect. The posterior aortic sinus abuts against the interatrial septum anterior and superior to the limbus (see Fig. 4–12D). During transseptal procedures, care must be taken to stay within the confines of the valve of the fossa ovalis to avoid perforation of an aortic sinus.[16] *Besides fluoroscopy, transesophageal echocardiography may be used to guide the transseptal puncture during catheter-based left heart interventions. Congenital atrial septal defects most often occur in the region of the valve of the fossa ovalis (so-called secundum-type defects). Redundant valve tissue can form an aneurysm of the valve of the fossa ovalis.*

The AV portion of the atrial septum is made of major muscular and minor membranous components and separates the right atrium from the left ventricle[16,17] (see Figs. 4–36 and 4–40). *This explains why there is a potential for left ventricular–to-right atrial shunts.*[16,17] *The AV septum corresponds roughly to the triangle of Koch (see Fig. 4–77), an important anatomic surgical landmark because it contains the AV node and proximal portion of the AV (His) bundle. Thus, during tricuspid annuloplasty procedures and patch closures of membranous ventricular septal defects, care must be taken to avoid injury to the conduction system.*[16,17] The muscular component of the AV septum is interposed between the membranous septum anteriorly and the internal cardiac crux posteriorly.

When defects occur in the muscular AV septum, the mitral annulus usually drops to the same level as the tricuspid annulus, so the defect becomes primarily interatrial (primum-type atrial septal defect), and the AV conduction tissues are displaced inferiorly. Lipomatous hypertrophy of the atrial septum is characterized by excessive accumulation of adipose tissue within the limbus of the fossa ovalis but always sparing the valve of the fossa[5,14,17] (Fig. 4–48). Lipomatous hypertrophy of the atrial septum occurs commonly, but not exclusively, in older and obese persons.[14,16,17] *Although readily detected by echocardiography, it can be misinterpreted as a thrombus or neoplasm.*[5]

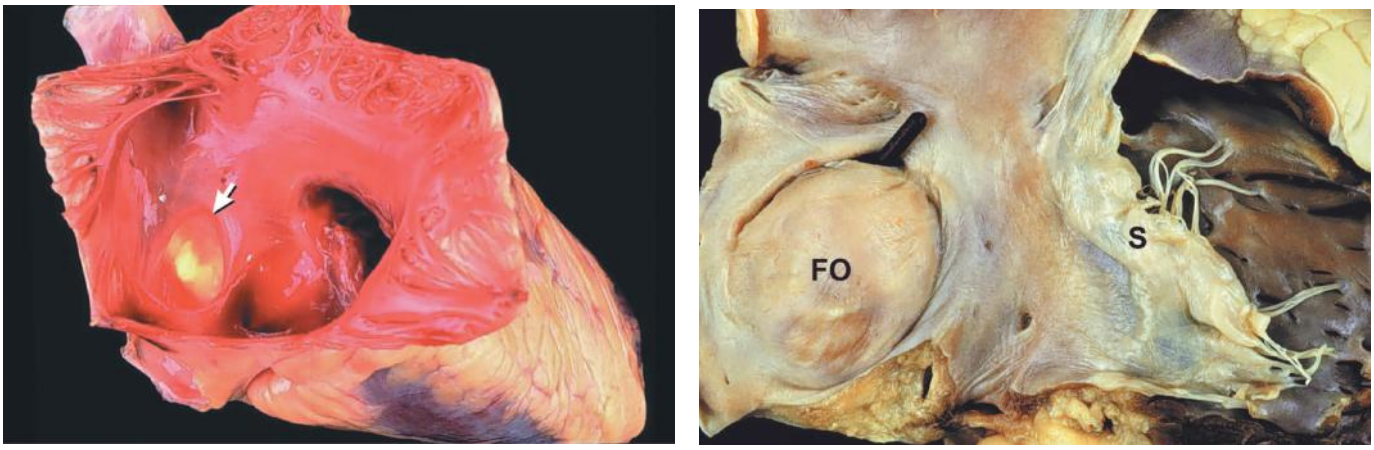


FIGURE 4–45. **A.** Fossa ovalis. Opened right atrium shows the thick muscular limbus of the atrial septum (*arrow*), in contrast to the thin valve of the fossa ovalis (*transilluminated*). **B.** Patent foramen ovale (*black probe*) as seen from the right atrium. There is also an aneurysm of the valve of the fossa ovalis (FO). S, septal leaflet of the tricuspid valve.

RIGHT ATRIUM

A prominent muscular ridge inside the right atrium, the crista terminalis (Fig. 4–49), separates the right atrial free wall into a smooth-walled posterior region (sinus venarum) that receives the venae cavae and coronary sinus and a muscular anterior region that is lined by parallel pectinate muscles.[14,16,17] Pectinatus is Latin for *comb*, and the pectinate muscles and crista terminalis resemble the teeth and backbone of a comb, respectively (Fig. 4–50).[17] The right atrial appendage abuts the right aortic sinus and overlies the proximal right coronary artery (see Fig. 4–58). *The right atrial free wall is paper-thin between pectinate muscles and therefore can be perforated easily by stiff catheters (see Fig. 4–50).*[14-17] *The atrial lead of a dual-chamber pacemaker is normally positioned within the trabeculations of the right atrial appendage. The cavotricuspid isthmus, a frequent target of atrial flutter ablation, is a well-defined region of atrial tissue that is bordered by (1) the eustachian ridge and valve posteriorly and (2) the tricuspid valve annulus anteriorly* (Fig. 4–51). Inferior vena caval blood flow is directed by the eustachian valve toward the foramen ovale, and superior vena caval blood is directed toward the tricuspid valve[21] (Fig. 4–52). *Thus transseptal cardiac catheterization is more easily accomplished via the inferior vena cava, whereas instrumentation of the right ventricular apex (eg, endomyocardial biopsy or placement of a lead) is more easily accomplished via the superior vena cava.*[14]

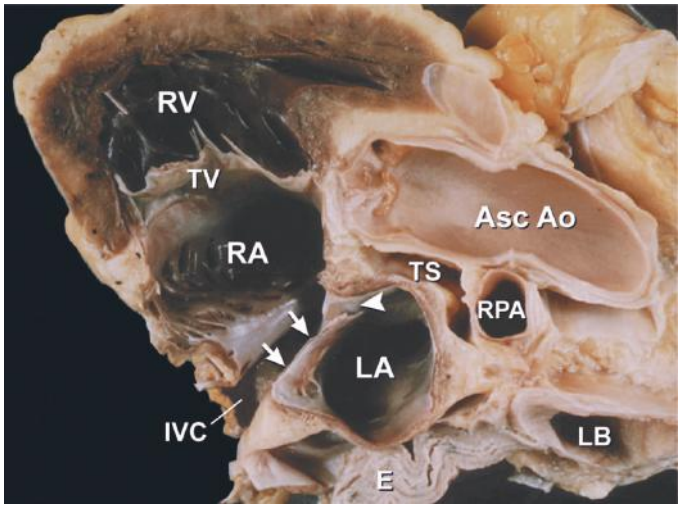
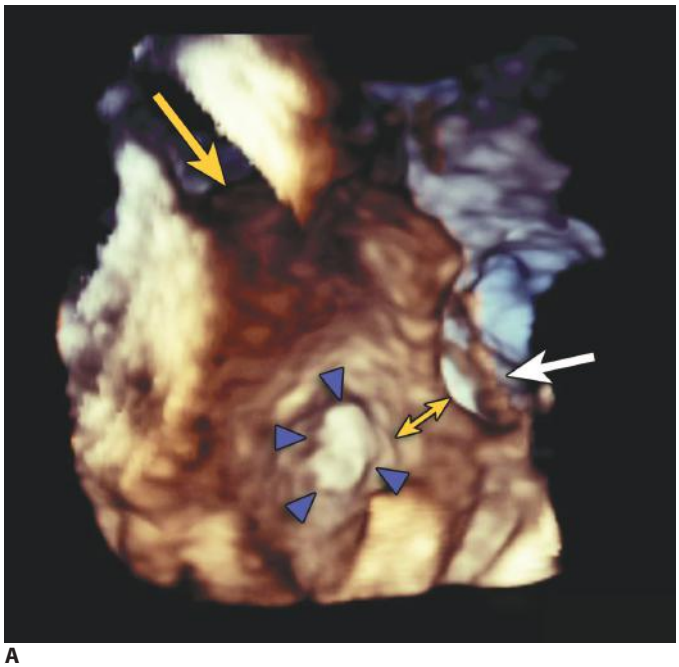


FIGURE 4–46. Tomographic section of the heart along a long axis of the body. The valve of the fossa ovalis (*arrows*) and a patent foramen ovale (*arrowhead*) are seen in this view. Asc Ao, ascending aorta; E, esophagus; IVC, inferior vena cava; LA, left atrium; LB, left bronchus; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; TS, transverse sinus; TV, tricuspid valve.

LEFT ATRIUM

The pulmonary vein orifices lie on the posterolateral (left pulmonary veins) and posteromedial (right pulmonary veins) aspects of the left atrial cavity. The left and right upper pulmonary veins are directed anterosuperiorly, whereas the lower veins enter the left atrium nearly perpendicular to the posterior atrial wall[14-17] (Fig. 4–53; see also Fig. 4–15A). *Left atrial muscle extends some distance within the pulmonary veins. The resultant cuff of muscle acts as a sphincter during atrial systole and can be the source of focal atrial fibrillation that is amenable to catheter ablation*[9,10] (see Fig. 4–2).

The atrial appendage arises anterolaterally and lies in the left AV groove atop the proximal portion of the left circumflex coronary artery and, in some individuals, the left main coronary artery[16] (see Figs. 4–21A and 4–53). The left atrial appendage (LAA) is usually multilobed (Fig. 4–54) and narrower than its right atrial counterpart, and it exhibits more variability in shape.[14-17,30] Four basic morphologic patterns of LAA have been described: windsock, cactus, cauliflower, and chicken wing[31] (Fig. 4–55). Importantly, there is some relationship between stroke and LAA morphology, with the chicken wing variety showing less likelihood of embolic events.[31] There are also age- and sex-related differences in the dimensions of the appendage.[21] *With increasing use of transesophageal echocardiography to search for a cardiac source of embolism and to guide cardioversion and percutaneous balloon valvuloplasty procedures, a thorough appreciation of the variations in normal left atrial appendage morphology has become important, because a thrombus can be missed if all lobes in the appendage are not visualized. Appreciation of LAA morphology and accurate measurements of LAA dimensions are crucial to successful device closure of the LAA in patients with atrial fibrillation. In contrast to the right atrial free wall, the left has no crista terminalis and no pectinate muscles outside its appendage.*[14-17] *Either atrial appendage may serve as a vantage point to access and ablate arrhythmias in the adjacent segment of the right ventricular outflow tract (see Figs. 4–34A and 4–53).*[8]



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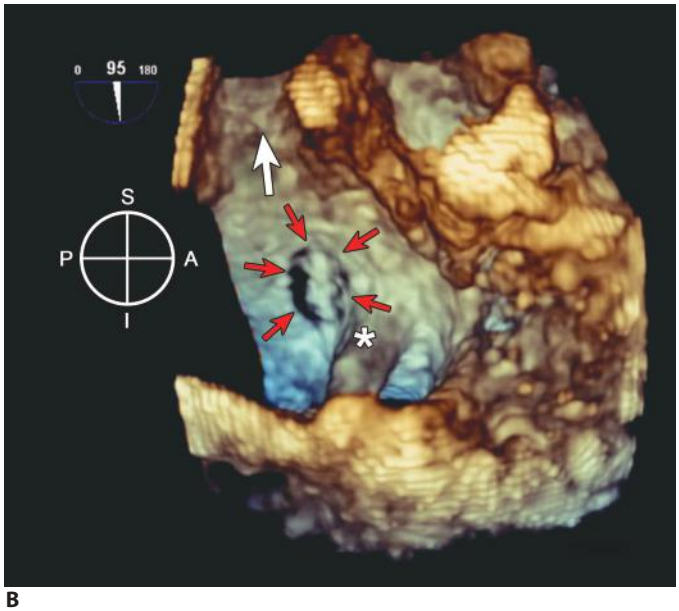


B

FIGURE 4–47. Three-dimensional TEE RA view of the fossa ovalis and surrounding anatomy. The fossa ovalis is seen as an oval shaped crater (*arrowheads*). The atrial wall anterior to the fossa (*double-headed arrow*) abuts the posterior aortic sinus. *White arrow* points to aortic root. *Yellow arrow* points to the SVC (A). Spatial relationships of fossa ovalis (*red arrows*). *White arrow* points to SVC superiorly; an asterisk marks the eustachian ridge inferiorly (B). A, anterior; I, inferior; P, posterior; RA, right atrium; S, superior; SVC, superior vena cava; TEE, transesophageal echocardiogram. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

The coronary sinus travels along the posterior wall of the left atrium within the left AV groove (see Fig. 4–21A). *In patients with persistent left superior vena cava, which most commonly drains into a dilated coronary sinus, the left-sided cava courses between the left atrial appendage and the left upper pulmonary vein.*[17] *The venous structure can be misinterpreted as the descending thoracic aorta, a mass, or a pathologic cavity.*

The esophagus and descending thoracic aorta are in contact with the posterior left atrial wall (see Figs. 4–20 and 4–53). *Accordingly, esophageal carcinomas can compress, infiltrate, or perforate the left atrium, and descending thoracic aortic aneurysms can compress this chamber.*[14] *A large hiatal hernia also can abut against the left atrium and present as a mass.*

FIGURE 4–48. Four-chamber slice through the heart showing lipomatous hypertrophy of the atrial septum (*arrows*).

The marked increase in the incidence of atrial fibrillation from the fourth to the ninth decades of life can be caused by dilatation of the left atrium consequent to left ventricular diastolic dysfunction or mitral valve disease.[32]

CORONARY ARTERIES AND VEINS

A detailed description of the spectrum of coronary artery anatomy including the many variations in the number and size of branches and course of the different arteries is beyond the scope of this chapter. The interested reader is referred to the elegant anatomic work by Wallace McAlpine published in 1975.[33] The focus of the following discussion, therefore, is to introduce the reader to the clinically relevant anatomy of the coronary circulation, with special emphasis on tomographic analysis of regional blood flow.

From the right and left aortic sinuses arise the right and left coronary arteries, respectively, and their ostia, which normally originate about two-thirds the distance from the aortic annulus to the sinotubular junction and about midway between the aortic valve commissures[14,16,17] (Fig. 4–56; see also Fig. 4–29). Whereas the right coronary artery arises nearly perpendicularly from the aorta, the left arises at an acute angle[21] (Fig. 4–57). Rarely, the anterior descending and circumflex arteries arise separately from a double-barrel left coronary ostium.[14,16,17] *Ostial stenosis most commonly results from atherosclerosis and degenerative calcification of the aortic sinotubular junction, which often overlies the right aortic sinus.*[17] *Less often it is caused by aortic dissection or by aortitis associated with syphilis or ankylosing spondylitis. Stenosis of the right coronary ostium is much more frequent than that of the left. Iatrogenic ostial injury can complicate coronary angiography, intraoperative coronary perfusion, or aortic valve replacement.*[14,16,17] *Atherosclerosis or thrombosis of the most proximal portion of either coronary artery can mimic true ostial stenosis.*

The right coronary artery is embedded in adipose tissue throughout its course within the right AV groove. *Tricuspid annuloplasty or replacement can be complicated by injury to the right coronary artery.*[17] In 50%

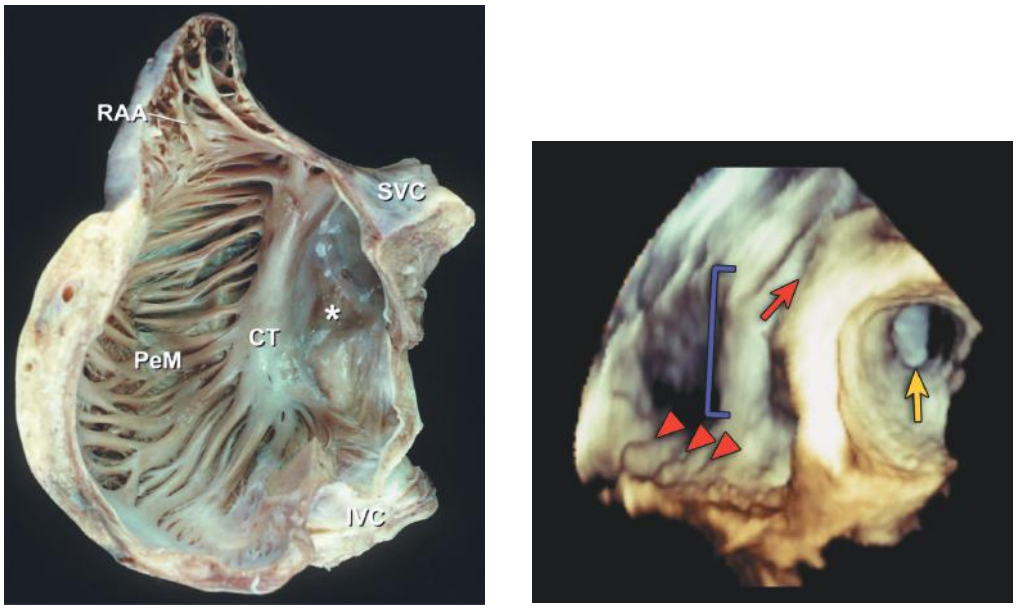


FIGURE 4–49. (**A**) Right atrial free wall showing separation of the posterior smooth-walled (*) portion from the anterior muscular portion with its pectinate muscles (PeM) and right atrial appendage (RAA) by the crista terminalis (CT). (**B**) Three-dimensional TEE view of the atria showing the crista terminalis (blue range), pectinate muscles (*arrowheads*), RSPV (*yellow arrow*). and SVC (*red arrow*). IVC, inferior vena cava; RSPV, right superior pulmonary vein; SVC, superior vena cava. Part **B** used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

to 60% of persons, its first branch is the conus artery (Fig. 4–58), which supplies the right ventricular outflow tract and forms an important collateral anastomosis (circle of Vieussens), just below the pulmonary valve, with an analogous branch from the left anterior descending (LAD) coronary artery.[14,16,17] In approximately one-third of patients, the conus artery arises independently from the aorta.[17] The infundibular septum is supplied by the descending septal artery, which usually originates from the proximal right or conus coronary artery.[14,16,17] Among the numerous marginal branches of the right coronary artery that supply the remainder of the right ventricular free wall, the largest branch travels along the acute margin from base to apex[14,16,17] (see Fig. 4–56). In at least 70% of human hearts, the posterior descending artery arises from the distal right coronary artery (see Fig. 4–56). The posterior descending and distal posterolateral branches of a dominant right coronary artery supply the basal and middle inferior wall, basal (inlet) inferior septum, right bundle branch, AV node, AV (His) bundle, posterior portion of the left bundle branch, and posteromedial mitral papillary muscle.[17]

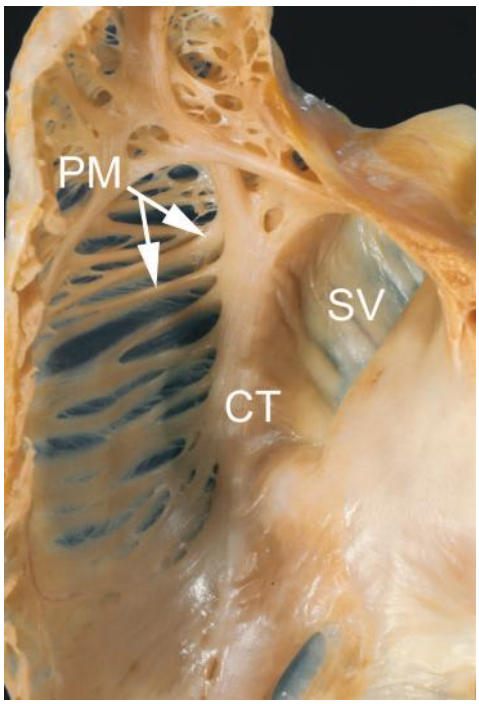


FIGURE 4–50. Crista terminalis and pectinate muscles. Note the paper-thin right atrial free wall between pectinate muscles. CT, crista terminalis; PM, pectinate muscles; SV, sinus venarum. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

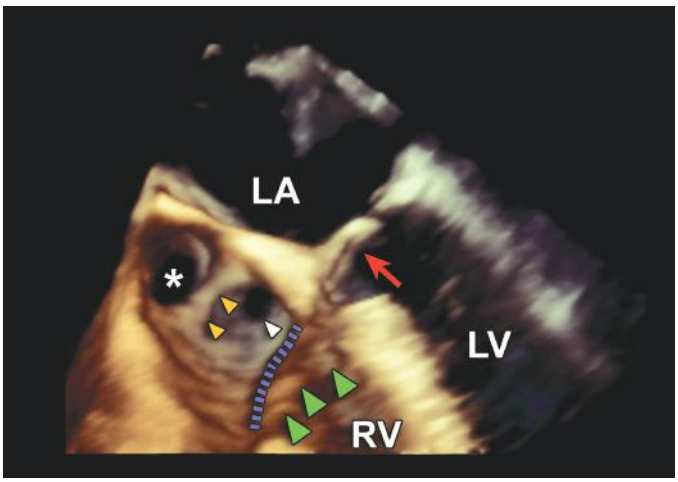


FIGURE 4–51. Three-dimensional view of the four cardiac chambers. The cavotricuspid isthmus is a well-defined region of right atrial tissue that is bordered by the eustachian ridge (*yellow arrowheads*) and valve posteriorly, and the tricuspid valve annulus (*interrupted blue line*) anteriorly. *White arrowhead* points to ostium of the coronary sinus and *green arrowheads* point to the tricuspid valve. *Red arrow* points to the mitral valve. Asterisk marks the inferior vena cava. LA, left atrium; LV, left ventricle; RV, right ventricle. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

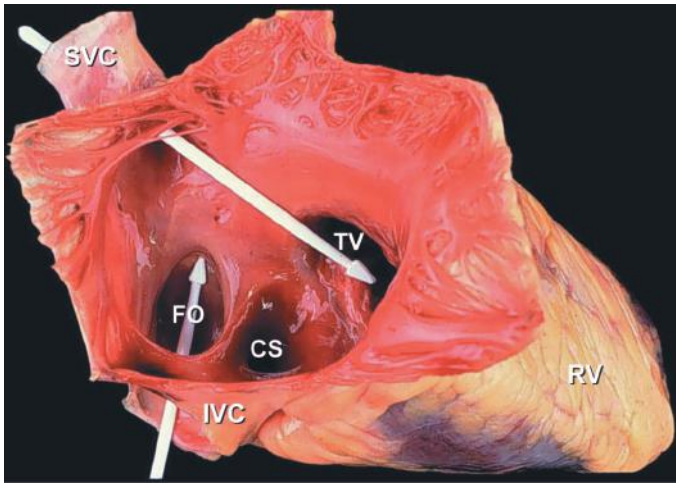


FIGURE 4–52. Opened right atrium. Two arrow-shaped probes show that superior vena caval flow is directed toward the tricuspid orifice and inferior vena caval flow is directed toward the fossa ovalis (FO). CS, coronary sinus; IVC, inferior vena cava; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve.

The left main coronary artery travels for a very short distance along the epicardium between the pulmonary trunk and left atrium (see Figs. 4–56 and 4–58). It then divides into anterior descending and circumflex arteries (see Figs. 4–56 and 4–58). An intermediate artery (ramus intermedius) also may arise at this division, thus forming a trifurcation rather than a bifurcation, and follow the course of a circumflex marginal branch[14,16,17] (see Fig. 4–58).

The LAD courses within the epicardial fat of the anterior interventricular groove, wraps around the cardiac apex, and travels a variable distance along the inferior interventricular groove toward the cardiac base. Its septal perforating branches supply the anterior septum and apical septum. The first septal perforating branch supplies the AV (His) bundle and proximal left bundle branch[17] (Fig. 4–59). *In patients with symptomatic hypertrophic obstructive cardiomyopathy, nonsurgical septal reduction by percutaneous transluminal occlusion of septal branches of the LAD is a therapeutic approach aimed at reducing the outflow gradient.*[34] The epicardial diagonal branches of the LAD supply the anterior left ventricular free wall, part of the anterolateral mitral papillary muscle, and the medial one-third of the anterior right ventricular free wall.[14,16,17] Although short segments of the LAD can travel within the myocardium (covered by a so-called myocardial bridge) (Fig. 4–60), the resulting systolic luminal narrowing is probably benign in the vast majority of people.[17] *However, whereas the prevalence of angiographically recognized myocardial bridging is only 0.5% to 1.6% in the general population, it is reported to be 28% in children and 30% to 50% in adults with hypertrophic cardiomyopathy.*[35] *More important, myocardial bridging appears to be associated with a poor prognosis (higher incidence of myocardial ischemia and sudden death) in patients with hypertrophic cardiomyopathy regardless of age.*[35]

The left circumflex coronary artery courses within the adipose tissue of the left atrioventricular groove (see Fig. 4–21A) and commonly terminates just beyond its large obtuse marginal branch (see Fig. 4–56). It supplies the lateral left ventricular free wall and a portion of the anterolateral mitral papillary muscle.[14,16,17]

Along the inferior surface of the heart, the length of the right coronary artery varies inversely with that of the circumflex artery.

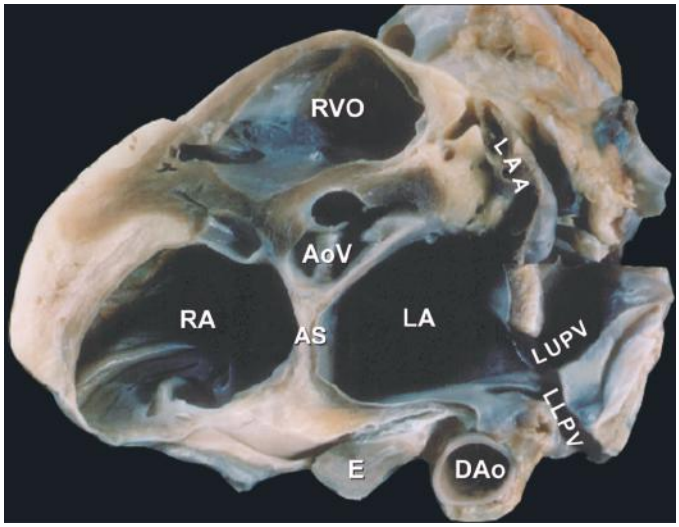
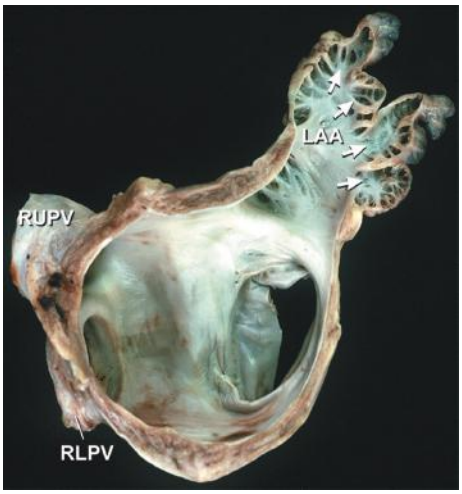


FIGURE 4–53. Oblique, short-axis cut at the base of the heart. The esophagus (E) is posterior and adjacent to the left atrium (LA) and adjacent to the descending thoracic aorta (DAo). The left upper pulmonary (LUPV) and left lower pulmonary vein (LLPV) are clearly seen. The right ventricular outflow tract (RVO) is anterior. AS, atrial septum; AoV, aortic valve; LA, left atrium; LAA, left atrial appendage; RA, right atrium.



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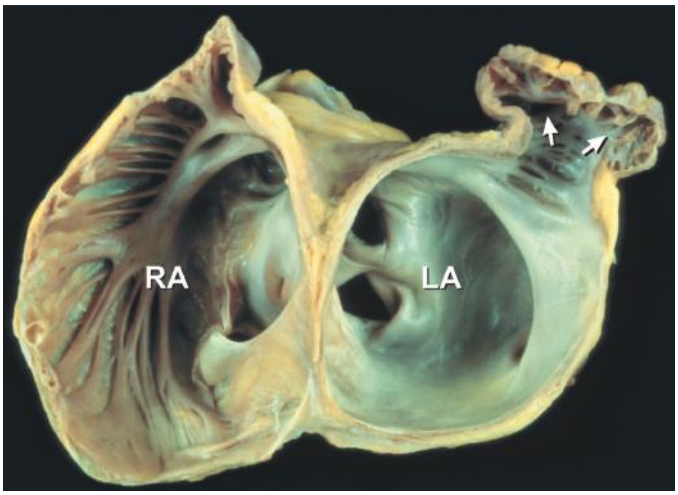

B

FIGURE 4–54. Left atrial appendages (LAA). **A.** Left atrial free wall showing appendage with four lobes (*arrows*). **B.** Biatrial specimen demonstrating left atrial appendage with two lobes (*arrows*). LA, left atrium; RA, right atrium; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein.

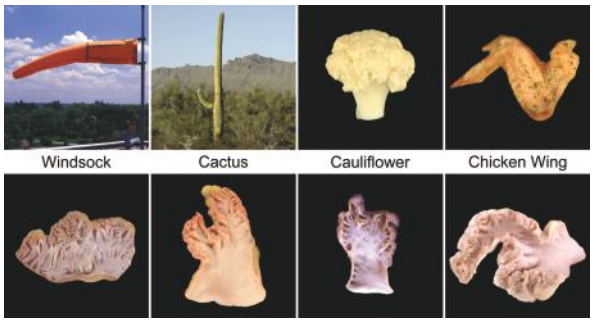

FIGURE 4–55. Four basic morphologic patterns of left atrial appendage. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

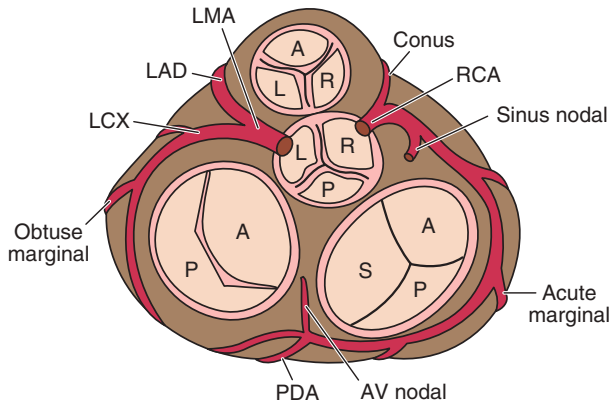

FIGURE 4–56. Schematic diagram of coronary artery distribution viewed at the base of the heart. In this right-dominant system, the right coronary artery (RCA) gives rise to the posterior descending artery (PDA), and the left main coronary artery (LMA) gives rise to the left anterior descending (LAD) and left circumflex (LCX) branches. A, anterior; AV, atrioventricular; L, left; P, posterior; R, right; S, septal.

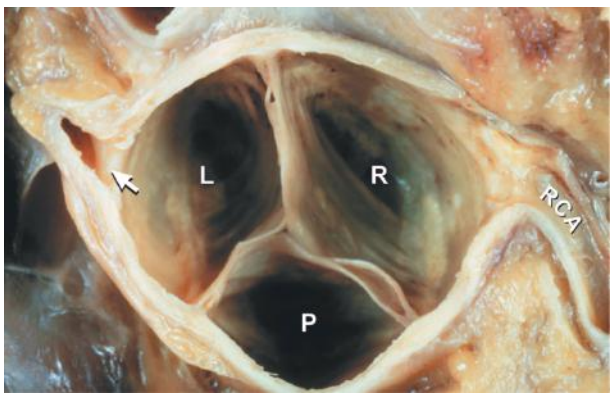

FIGURE 4–57. Differences in angulation at the origins of the right (RCA) and left main (*arrow*) coronary arteries. L, left aortic cusp; P, posterior aortic cusp; R, right aortic cusp.

The artery that crosses the cardiac crux and gives rise to the posterior descending branch represents the dominant coronary artery. Dominance is right in 70% of human hearts, left in 10%, and shared in 20%.[14,16,17] *In patients with a congenitally bicuspid aortic valve, the incidence of left coronary dominance is 25% to 30%.*[17] *Recent advances in CT technology allow for 3D reconstruction of the epicardial coronary arteries and veins* (Fig. 4–61).

The coronary venous circulation is comprised of coronary sinus, cardiac veins, and thebesian venous systems[14,16,17] (Fig. 4–62).

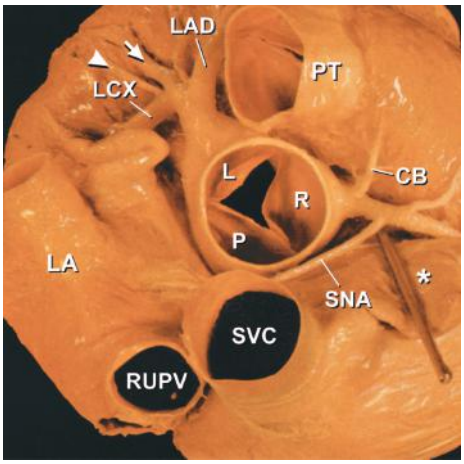

FIGURE 4–58. The right coronary artery gives rise to the conus branch (CB). A rod retracts the right atrial appendage (∗) to disclose the sinus node artery (SNA). *Arrow* points to an intermediate left coronary artery; *arrowhead* points to a circumflex marginal branch. L, left aortic cusp; LA, left atrium; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; P, posterior aortic cusp; PT, pulmonary trunk; R, right aortic cusp; RUPV, right upper pulmonary vein; SVC, superior vena cava. Reproduced with permission from McAlpine W. *Heart and Coronary Arteries: An Anatomic Atlas for Radiologic Diagnosis and Surgical Treatment*. New York, NY: Springer-Verlag; 1975.

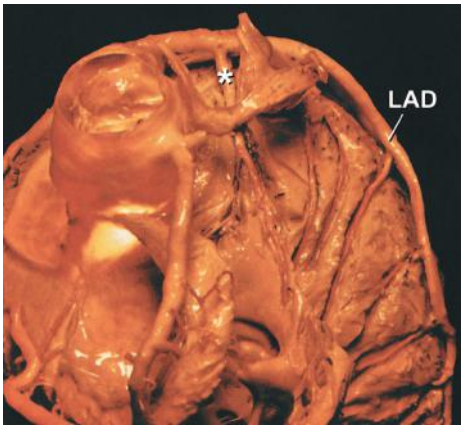

FIGURE 4–59. Septal branches of the left anterior descending coronary artery (LAD); ∗ points to the first septal perforator. Reproduced with permission from McAlpine W: *Heart and Coronary Arteries: An Anatomic Atlas for Radiologic Diagnosis and Surgical Treatment*. New York: Springer-Verlag; 1975.

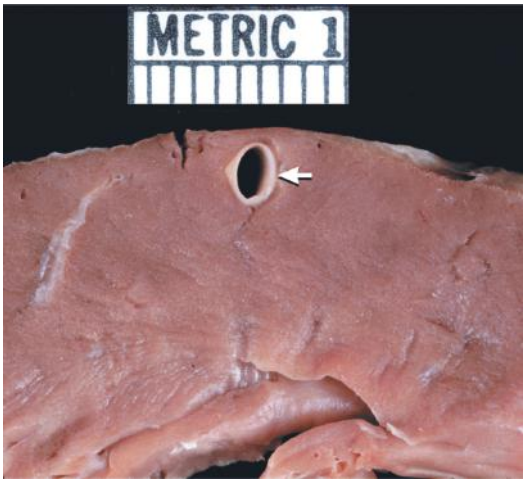

FIGURE 4–60. Intramyocardial course of the left anterior descending coronary artery (*arrow*).

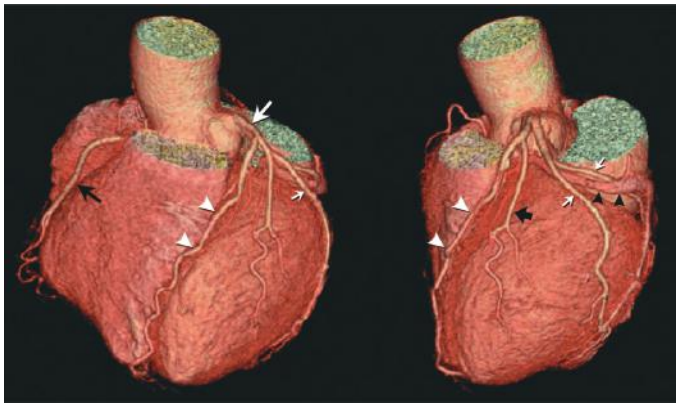

FIGURE 4–61. Three-dimensional reformatted images of CT coronary angiograms showing the right coronary artery (*long black arrow*), left main (*large white arrow*), left anterior descending coronary artery (*white arrowheads*) and a diagonal branch (*short black arrow*), and left circumflex coronary artery (*small white arrows*). A segment of the coronary venous circulation is also seen (*black arrowheads*).

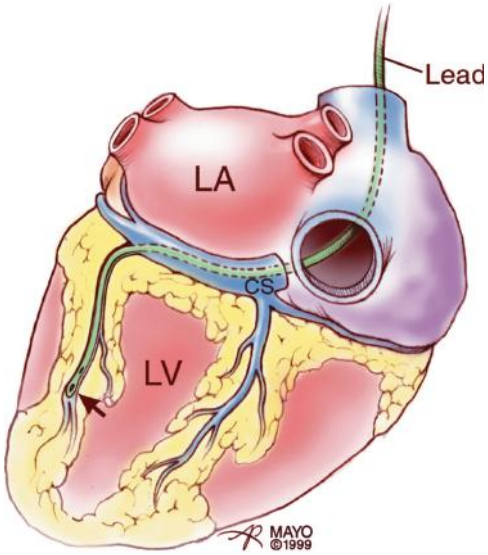

FIGURE 4–63. Schematic diagram shows placement of the tip of a pacing/mapping catheter within a coronary vein (*arrow*) via the coronary sinus (CS). LA, left atrium; LV, left ventricle.

The great cardiac vein travels in the anterior interventricular groove beside the left anterior descending coronary artery and in the left AV groove beside the left circumflex artery.[14,16,17] The great cardiac vein and other cardiac veins, such as the left posterior and middle cardiac veins, drain into the coronary sinus, which courses along the posteroinferior aspect of the left AV groove and empties into the right atrium[14,16,17] (see Fig. 4–21A). The ostium of the coronary sinus is guarded by a crescent-shaped valvular remnant, the thebesian valve. Rarely, the coronary sinus drains directly into the left atrium.[17]

During cardiac operations, cardioplegic solution can be administered retrograde into the coronary sinus. In patients with the Wolff-Parkinson-White preexcitation syndrome and left-sided bypass tracts, the ablation catheter during electrophysiologic studies can be positioned within the coronary sinus and great cardiac vein adjacent to the mitral valve ring to localize the aberrant conduction pathway.[17] Coronary venous anatomy is extremely variable, however. This can have important practice implications. The coronary veins, via the coronary sinus, provide access to percutaneous epicardial mapping and pacing of the ventricles and ablation of subepicardial arrhythmogenic foci[36] (Fig. 4–63). For biventricular pacing, optimal left ventricular pacing lead position is within the posterolateral branch of the coronary sinus, followed by the lateral branch.

Coronary artery disease is associated with regional abnormalities in ventricular structure and function. Because analysis of segmental myocardial perfusion or contractility is the cornerstone of tomographic imaging techniques (stress echocardiography, SPECT imaging, positron emission tomography [PET], and MRI), for clinicopathologic correlations (Fig. 4–64), a combined tomographic and segmental approach to coronary artery anatomy is recommended.[17,37,38] Ventricular mass is made of the left and right ventricular free walls and the partitioning ventricular septum. Three levels (ie, basal, midventricular, and apical) are used to divide the base-apex length of the left ventricle into thirds (Fig. 4–65). The basal third includes that portion between the mitral annulus and the tips of the papillary muscles. The midventricular third is from the papillary muscle to the most apical insertion point of these muscles into the left ventricular free wall. The apical third includes the remainder of the ventricle, from the insertion of the papillary muscles to the left ventricular apex. A similar approach can be applied to the right ventricle.[14,16,17,37] The ventricular septum can be divided into anteroseptal and inferoseptal segments, and the left ventricular free wall is divided into anterior, lateral, and inferior segments at the basal and midventricular levels (see Fig. 4–65). The left ventricular apical level consists of four segments (ie, septum, inferior, lateral, and anterior) (see Fig. 4–65).

This regional approach is not arbitrary and has been verified by studies of normal, dilated, and hypertrophied hearts. According to this system, there are 16 left ventricular segments that can be evaluated for regional abnormalities. This regional approach can also be used to assess transmural infarct size, because the percentage of left ventricular

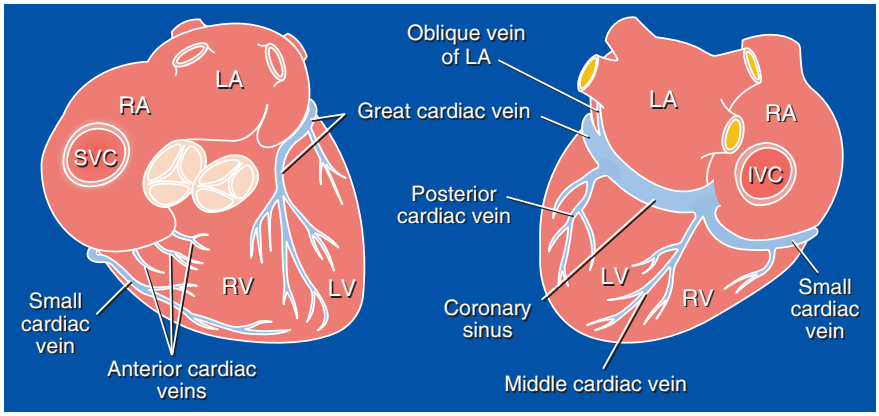

FIGURE 4–62. Schematic diagram of the coronary venous circulation. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

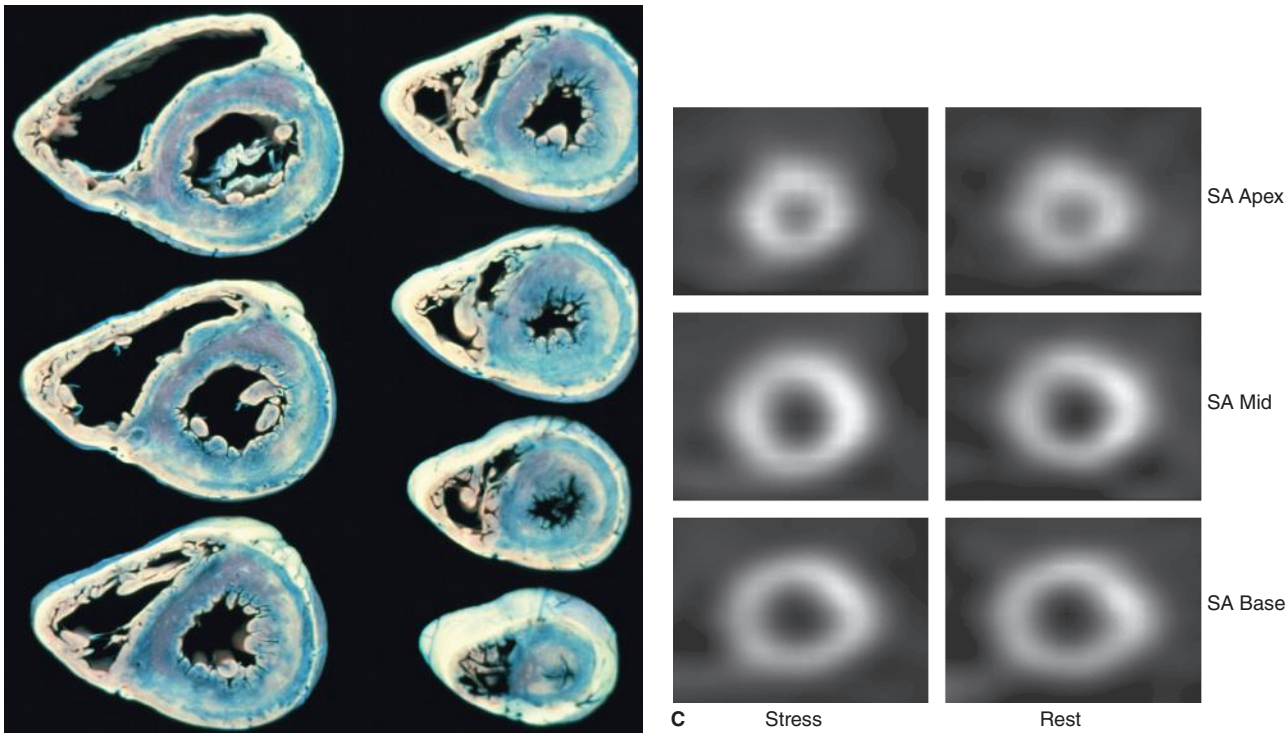

FIGURE 4–64. Short-axis views. **A.** Collage of anatomic sections obtained by "bread slicing" the heart in its short-axis plane viewed from the apex toward the base of the heart. **B.** Comparable MRI images. **C.** Comparable sestamibi SPECT images of the left ventricle showing normal myocardial perfusion at rest and with exercise. SA, short axis.

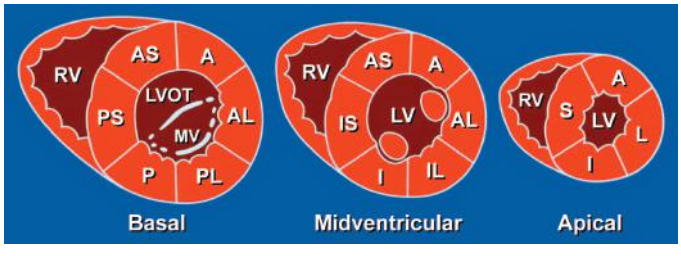

FIGURE 4–65. Schematic diagram of the three levels of short-axis tomographic views used in echocardiography for 16-segment wall motion analysis. A, anterior; AL, anterolateral; AS, anterior ventricular septum; I, inferior; IL, inferolateral; IS, inferior ventricular septum; L, lateral; LV, left ventricle; LVOT, left ventricular outflow tract; P, posterior; PL, posterolateral; PS, posterior ventricular septum; RV, right ventricle; S, septum. The most basal segment of the inferior wall is the anatomically true posterior segment. At this level, the adjacent ventricular septum is commonly referred to as either the *basal posterior septum* or the *basal inferior septum* and the adjacent lateral wall as either the *basal posterolateral wall* or the *basal inferolateral wall*.

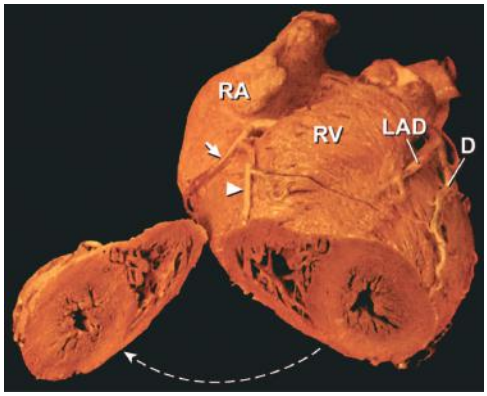

FIGURE 4–66. Regional coronary flow, with a short-axis slice of the heart. A large diagonal branch (D) of the left anterior descending coronary artery (LAD) supplies the lateral wall, and an acute marginal branch (*arrowhead*) of the right coronary artery (*arrow*) supplies the anterior right ventricular free wall. The distal segment of the LAD is intramural. RA, right atrium; RV, right ventricle. Reproduced with permission from McAlpine W. *Heart and Coronary Arteries: An Anatomic Atlas for Radiologic Diagnosis and Surgical Treatment*. New York, NY: Springer-Verlag; 1975.

mass contributed by any particular region is not altered in any significant manner by symmetric hypertrophy or dilatation.[17]

REGIONAL CORONARY ARTERY SUPPLY

The ventricular regions described tend to correlate well with common patterns of coronary artery distribution[14,16,17] (Figs. 4–66 and 4–67). Any specific epicardial coronary artery generally will supply a certain cluster of regions. For example, in a typical right-dominant system, the LAD would supply the midventricular and basal segments of the anterior and anterolateral walls and anterior septum and all apical segments. The left circumflex artery would supply the midventricular and basal inferolateral segments, and the right coronary artery would supply the midventricular and basal inferior wall and inferior septum (see Fig. 4–67). However, because the patterns of coronary distribution are so highly variable, these correlations between coronary blood flow and regional anatomy are not precise. For example, a hyperdominant right coronary artery can supply the apex, and a large, obtuse marginal branch of the circumflex artery can supply the anterolateral or inferior wall. Also, any given myocardial region can, in some people, receive its blood supply from the branches of two independent major epicardial arteries.[14,16,17] In old age, the coronary arteries become dilated and tortuous (Fig. 4–68). *Ultrafast electron beam CT is very useful for the detection of calcified plaques within the coronary arteries.*

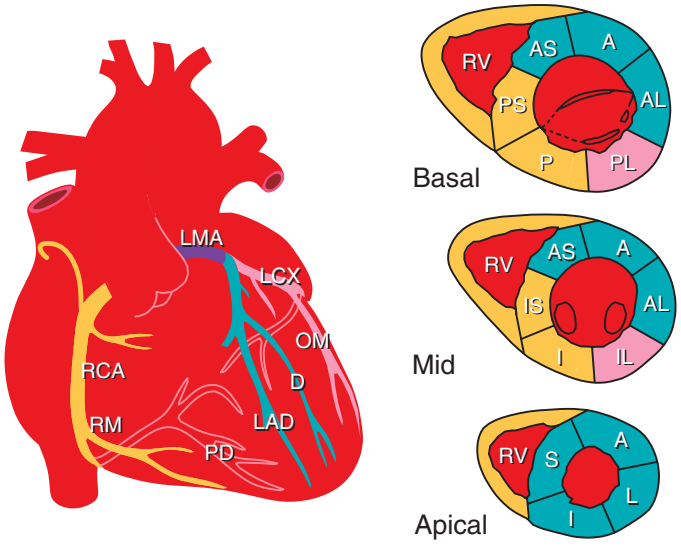

FIGURE 4–67. Coronary distribution using a 16-segment model. D, diagonal branch of the left anterior descending coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMA, left main coronary artery; OM, obtuse marginal branch of the circumflex coronary artery; PD, posterior descending coronary artery; RCA, right coronary artery; RM, right marginal branch; other abbreviations as in Fig. 4–59.

CORONARY COLLATERALS AND MICROCIRCULATION

Collateral channels provide communication between the major coronary arteries and their branches.[17] If stenosis of an epicardial coronary artery produces a pressure gradient across such a vessel, the collateral channel can dilate with time and provide a bypass avenue for blood flow beyond the obstruction. Such functional collaterals can develop between the terminal extensions of two coronary arteries, between the side branches of two arteries, between branches of the same artery, or within the same branch (via the vasa vasorum). These are most common in the ventricular septum (between septal perforators of the anterior and posterior descending arteries), in the ventricular apex (between anterior descending septal perforators), in the anterior right ventricular free wall (between anterior descending and right or conus arteries), in the anterolateral left ventricular free wall (between anterior descending diagonals and circumflex marginals), at the cardiac crux, and along the atrial surfaces (between the right and left circumflex arteries).[17]

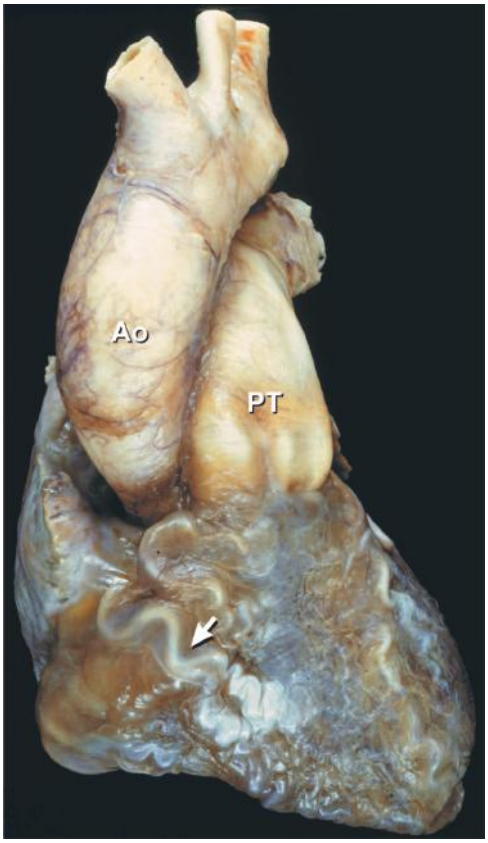

FIGURE 4–68. Tortuous coronary arteries (*arrow*) typically seen in the elderly with nondilated hearts. Ao, ascending aorta; PT, pulmonary trunk.

The intramural coronary vessels form the microcirculation. There are age-related variations in the pattern of distribution of the coronary microcirculation.[39] Angina-like chest pain in some patients with angiographically normal epicardial coronary arteries (ie, syndrome X, or microvascular angina) can be secondary to abnormal vasodilator reserve or vasoconstriction of the coronary microcirculation.[40] Abnormal flow reserve of the coronary microcirculation is seen in both dilated and hypertrophied hearts. In the latter, structural changes in the coronary arterioles can be found on histologic examination of the myocardium.[41-44] *In patients with symptomatic hypertrophic cardiomyopathy without angiographic evidence of epicardial coronary artery disease, myocardial tissue obtained during surgical myectomy can show smaller than normal coronary arteriolar lumina.*[43] *Postmortem analysis of hearts with hypertrophic cardiomyopathy also has revealed coronary arterioles with abnormally thick walls.*[43] *With contrast echocardiography, it can be possible to noninvasively visualize intramyocardial arterioles and study coronary flow reserve.*[5] *Demonstration of an intact microvascular circulation in akinetic myocardium following acute myocardial infarction, using PET or SPECT imaging or contrast echocardiography, is evidence of viability of the affected segment.*[5] *The creation of intramyocardial channels with CO_2 laser transmyocardial revascularization has been associated with augmentation of collateral flow to ischemic myocardium through angiogenesis.*[44]

CARDIAC LYMPHATICS

The myocardial lymphatics drain toward the epicardial surface, where they merge to form the right and left lymphatic channels, which travel in retrograde fashion with their respective coronary arteries. These two lymphatic channels travel along the ascending aorta and merge before draining into a pretracheal lymph node beneath the aortic arch. This single lymphatic channel then travels through a cardiac lymph node, between the superior vena cava and innominate artery, and finally empties into the right lymphatic duct. Obstruction of epicardial lymphatics by a metastatic process can produce a pericardial effusion.[14-17]

GREAT VESSELS

The subclavian and internal jugular veins merge bilaterally to form the right and left innominate veins (Fig. 4–69). Valves in the subclavian and internal jugular veins, near their junctions with the innominate veins, are important anatomic structures that help maintain unidirectional antegrade blood flow not only in the normal state but also in the setting of elevated right-sided heart filling pressures.[45] Subclavian and internal jugular venous valves are absent in 2% and 6% of individuals, respectively, and venous valves can be damaged by catheter-induced trauma or age.[45] *Absent or malfunctioning valves can interfere with the success of closed-chest cardiopulmonary resuscitation and contribute to the development of brain edema during such a procedure.*[45]

The left innominate vein is two to three times the length of its right-sided counterpart. It travels anteriorly to the aortic arch along the right anterolateral border of the ascending aorta, where it joins the shorter right innominate vein to form the superior vena cava[14,16,17] (see Fig. 4–69). *Transesophageal echocardiographic imaging of the upper ascending aorta can show a double lumen (ie, aorta and adjacent innominate vein) that can be misinterpreted as aortic dissection by an inexperienced echocardiographer.*[5]

The superior vena cava lies anterior to the right pulmonary artery (Fig. 4–70) and receives the azygos vein posteriorly before draining into the superior aspect of the right atrium, just posterior to the atrial

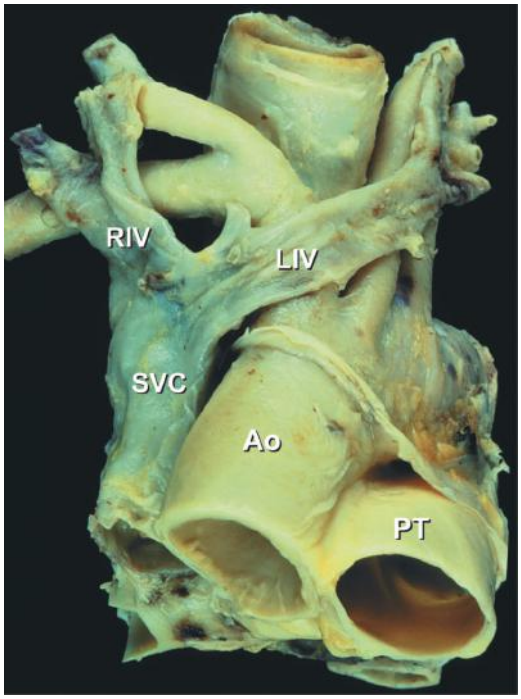

FIGURE 4–69. The longer left (LIV) and shorter right (RIV) innominate veins normally join to form the right superior vena cava (SVC). Ao, ascending aorta; PT, pulmonary trunk.

appendage[14,16,17] (see Figs. 4–49, 4–52, and 4–70). *The superior vena cava has important spatial relations with the right upper pulmonary vein (see Fig. 4–58) and the aortocaval ganglion, each an important target site when ablating atrial fibrillation.*[46,47] *The vein of Marshall forms the terminal connection between a persistent left superior vena cava and the coronary sinus. Its vestigial remnant in normal adults is the ligament of Marshall (Fig. 4–71). Both vein and ligament are a potential source of arrhythmias.* The ostium of the inferior vena cava is guarded by a crescent-shaped, often fenestrated flap of tissue, the eustachian valve[14,16,17] (see Fig. 4–16A), which is readily seen by echocardiography. Although generally small, the eustachian valve can become so large that it can produce a double-chambered right atrium.[16] Also, when either the

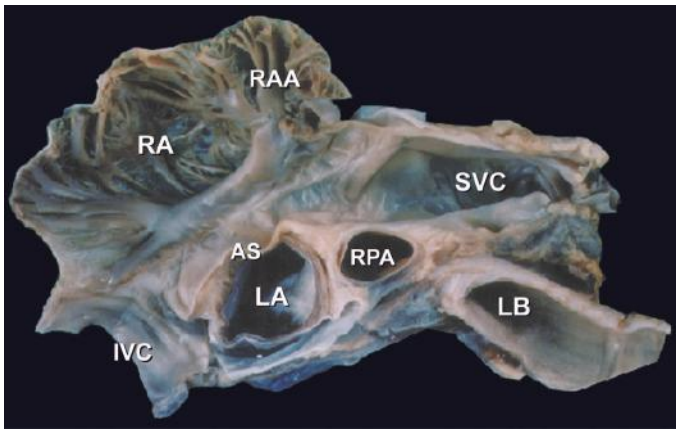

FIGURE 4–70. Long-axis view of the superior vena cava (SVC) and inferior vena cava (IVC). The specimen is viewed from the left looking toward the free wall of the right atrium. The right atrium (RA) and its appendage (RAA) are anterior. This is a commonly used tomographic plane in transesophageal echocardiography (TEE). AS, atrial septum; LA, left atrium; LB, left bronchus; RPA, right pulmonary artery.

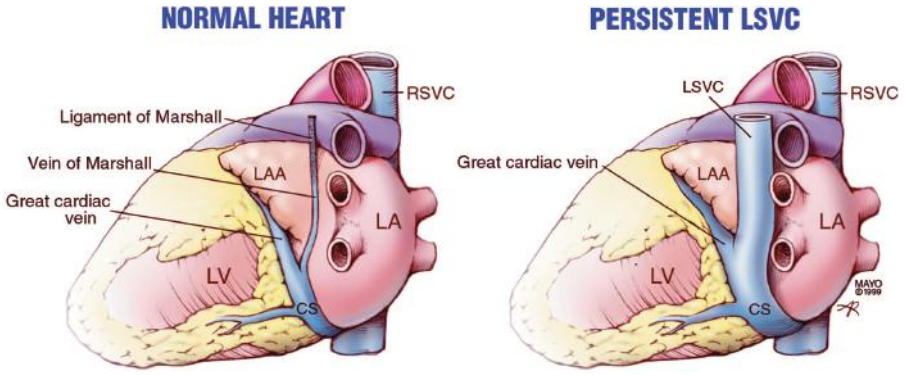

FIGURE 4–71. Schematic diagrams showing the ligament/vein of Marshall in normal hearts (*left*) and persistent left superior vena cava (LSVC) (*right*). CS, coronary sinus; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; RA, right atrium; RSVC, right superior vena cava.

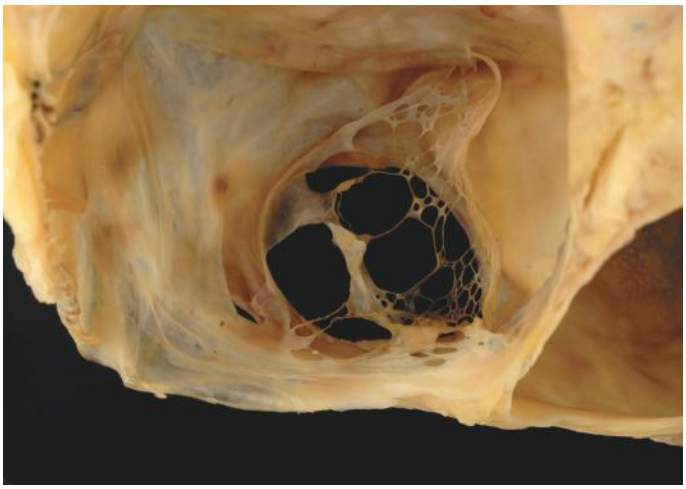

FIGURE 4–72. Fenestrated Chiari net. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

eustachian or the adjacent thebesian valve of the coronary sinus is large and fenestrated, it is referred to as a Chiari net (Fig. 4–72).[14,16,17] *By echocardiography, a Chiari net can be misinterpreted as a mass lesion.* The thoracic aorta arises at the level of the aortic valve and is divided into three segments: ascending aorta, aortic arch, and descending thoracic aorta (Fig. 4–73). The ascending aorta consists of sinus and tubular portions, which are demarcated by the sinotubular junction (Fig. 4–74; see also Fig. 4–29). *This is the site at which supravalvular aortic stenosis is often most severe.*[14,16,17] *The entire thoracic aorta can be readily imaged by CT and MRI* (Fig. 4–75).

Behind the aortic valve cusps are three outpouchings, or sinuses (of Valsalva). The right aortic sinus abuts against the ventricular septum and right ventricular parietal band and is covered in part by the right atrial appendage (see Figs. 4–31 and 4–58). In contrast, the left aortic sinus rests against the anterior left ventricular free wall and a portion of the anterior mitral leaflet, abuts the left atrial free wall, and is covered in part by the pulmonary trunk and left atrial appendage (see Figs. 4–20 and 4–21A). The posterior (noncoronary) aortic sinus overlies the ventricular septum and a part of the anterior mitral leaflet, forms part of the transverse sinus, abuts the atrial septum, and indents both atrial free walls[14,16,17] (see Figs. 4–12D and 4–22). *Rupture of the right and posterior aortic sinuses of Valsalva can result in a communication with the right ventricular outflow tract or right atrium, whereas rupture of the left aortic sinus of Valsalva leads to a communication with the left atrium or left ventricular outflow tract. Annuloaortic ectasia is associated with hypertension, aortic medial degeneration, and advanced age and can produce aortic regurgitation, ascending aortic aneurysm, or aortic dissection.*[14,16,17] Sleeves of left ventricular myocardium can extend above the aortic valve and to variable lengths into the aorta. A variety of arrhythmias can be ablated in the aorta and aortic valve cusps.[8] The superior vena cava and proximal ascending aorta are closely related (see Fig. 4–20). *As a result of this proximity, supra-aortic valvular arrhythmias may be mapped or ablated from the superior vena cava.*[47]

The aortic arch gives rise to the innominate, left common carotid, and left subclavian arteries in that order (see Fig. 4–73). In approximately 10% of individuals, the innominate and left common carotid arteries share a common ostium, and in 5% of individuals, the left vertebral artery arises directly from the aortic arch, between the left common carotid and left subclavian arteries.[17] The ligamentum arteriosum represents the vestigial remnant of the fetal ductal artery, which, when patent, connects the proximal left pulmonary artery to the under-surface of the aortic arch.[17] *Most coarctations occur just distal to the left subclavian artery. When thoracic aortic dissection does not involve the ascending aorta (DeBakey type III and Stanford type B), the intimal tear is commonly near the ligamentum arteriosum or*

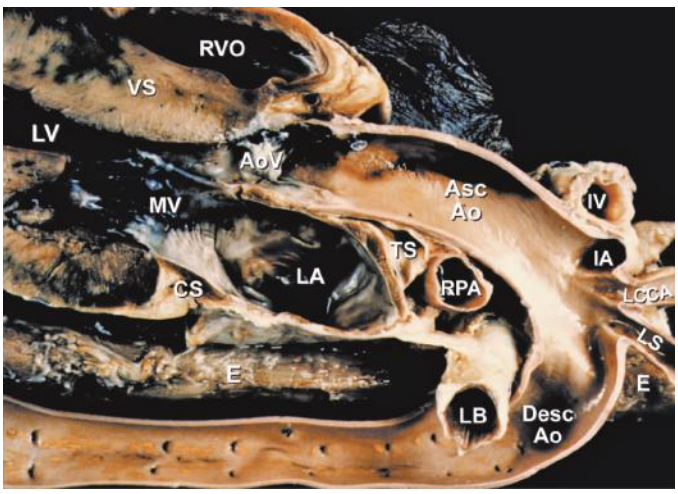

FIGURE 4–73. Thoracic aorta. The entire thoracic aorta has been cut in a tomographic manner. The aortic arch travels over the left bronchus and the right pulmonary artery. Asc Ao, ascending aorta; AoV, aortic valve; CS, coronary sinus; DAo, descending thoracic aorta; E, esophagus; IA, innominate artery; IV, innominate vein; LA, left atrium; LB, left bronchus; LCCA, left common carotid artery; LS, left subclavian artery; LV, left ventricle; MV, mitral valve; RPA, right pulmonary artery; RVO, right ventricular outflow; TS, transverse sinus; VS, ventricular septum.

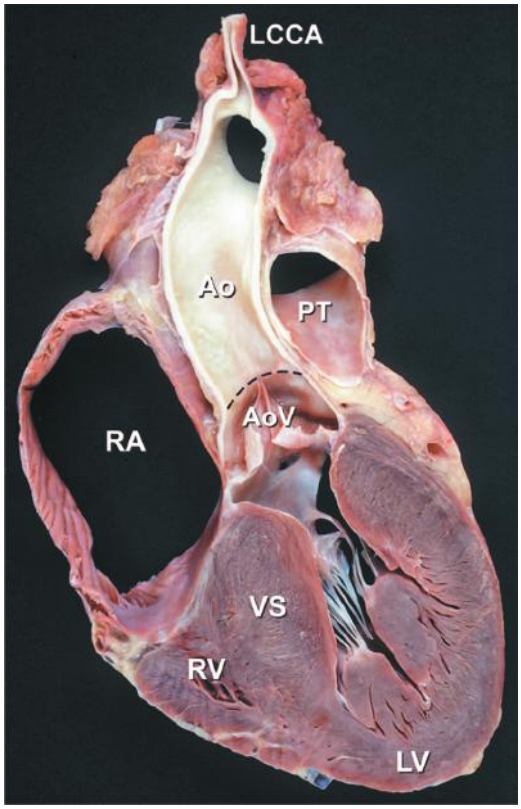

FIGURE 4–74. Tomographic section of the heart in the frontal plane of the body showing the aortic sinotubular junction (*dashed line*). Ao, ascending aorta; AoV, aortic valve; LCCA, left common carotid artery; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; LV, left ventricle; VS, ventricular septum.

the ostium of the left subclavian artery.[17] *Nonpenetrating deceleration-related chest trauma, as can occur in motor vehicle accidents, commonly involves the aorta in the region between the aortic arch and descending thoracic aorta and can be associated with aortic transection or pseudoaneurysm formation.*[17]

The descending thoracic aorta lies adjacent to the left atrium, esophagus, and vertebral column. The pulmonary trunk (or main pulmonary artery) emanates from the right ventricle and travels to the left of the ascending aorta. As it bifurcates, the left pulmonary artery courses over the left bronchus, whereas the right pulmonary artery travels beneath the aortic arch and behind the superior vena cava (see Figs. 4–11A and 4–70). Thus the left bronchus and the right pulmonary artery normally travel beneath a left-sided aortic arch. In cases of right-sided aortic arch, commonly seen with conotruncal malformations (eg, tetralogy of Fallot), the arch will travel over the right bronchus and the right pulmonary artery. Thus, the laterality of the aortic arch is determined by the bronchus over which it travels.

FIGURE 4–75. Real-time three-dimensional reconstructions of a normal thoracic aorta by (**A**) CT and (**B**) MRI.

CARDIAC CONDUCTION SYSTEM

The cardiac conduction system consists of the sinus node, internodal tracts, AV node, AV (His) bundle, and right and left bundle branches[14,16,17] (Fig. 4–76). The sinus node is located subepicardially in the terminal groove, close to the junction between the superior vena cava and right atrium. The sinus node artery arises from the right coronary artery in 55% of persons. Its course can place it in contact with the base of the right atrial appendage and the superior vena cava–right

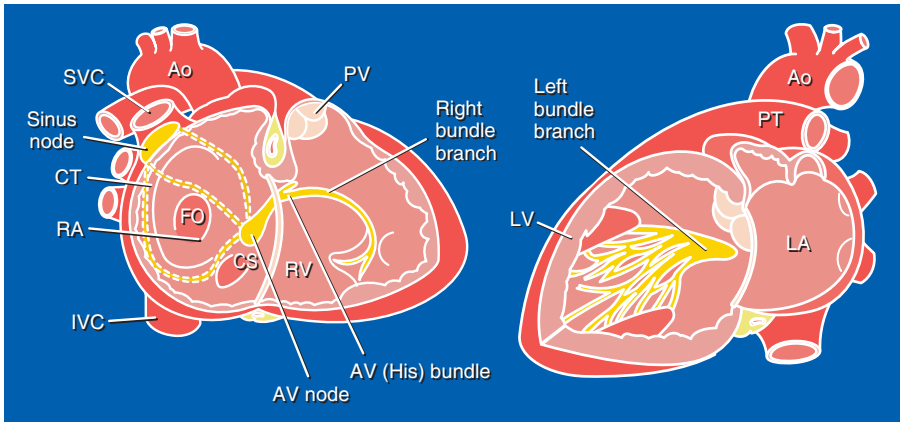

FIGURE 4–76. Schematic diagram of the cardiac conduction system. The right side of the heart (*left*) showing the sinus node, atrioventricular (AV) node, AV (His) bundle, and right bundle branch. The left side of the heart (*right*) showing incomplete anatomic separation of the left bundle into anterior and posterior fascicles. Ao indicates ascending aorta; AV, atrioventricular; CS, coronary sinus; CT, crista terminalis; FO, fossa ovalis; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary valve; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

atrial junction (see Fig. 4–58). When the sinus node artery arises from the left circumflex artery (45%), it can course close to the left atrial appendage. *During such surgical operations as the Mustard and Fontan procedures, the sinus node and its artery are susceptible to injury.*[16,17] By light microscopy, there are no morphologically distinct conduction pathways between the sinus and AV nodes.[17] However, electrophysiologic studies support the concept of functional preferential pathways that travel along the crista terminalis and atrial septum including the limbus but not the valve of the fossa ovalis.[17] *Internodal conduction disturbances therefore are not expected as a result of transseptal procedures. With the Mustard operation for complete transposition of the great arteries, there can be severe disturbance of internodal conduction because the entire septum is resected, and the surgical atriotomy can disrupt the crista terminalis.*[17] *Lipomatous hypertrophy of the atrial septum can interfere with internodal conduction and induce a variety of atrial arrhythmias. Ventricular preexcitation is most commonly associated with aberrant bypass tracts that span the annulus of the tricuspid or mitral valve (see Fig. 4–2).*

The AV node, in contrast to the sinus node, is a subendocardial structure that is located within the triangle of Koch[14,16,17] (Fig. 4–77). The triangle of Koch is bordered by the coronary sinus ostium posteroinferiorly and the septal tricuspid annulus anteriorly. Because of its right atrial location near the tricuspid annulus, the AV node is susceptible to injury during tricuspid annuloplasty and during plication procedures for Ebstein anomaly.[14,16,17]

The AV (His) bundle arises from the distal portion of the AV node and travels along the ventricular septum adjacent to the membranous septum[14,16,17] (see Fig. 4–77). *The AV conduction tissue is generally remote from the defect in the outlet, inlet, and muscular forms of ventricular septal defect but travels along the inferior margin of a membranous ventricular septal defect. The AV bundle travels through the central fibrous body (right fibrous trigone) and therefore is closely related to the annuli of the aortic, mitral, and tricuspid valves. Thus, during operative procedures involving these valves or a membranous ventricular septal defect, care must be taken to avoid injury to the His bundle. Whereas in normal hearts, the AV bundle courses along the posteroinferior rim of the membranous septum, it courses along the anterosuperior rim of the membranous septum in hearts with AV discordance.* The AV bundle receives a dual blood supply from the AV nodal artery and the first septal perforator of the left anterior descending coronary artery.[17]

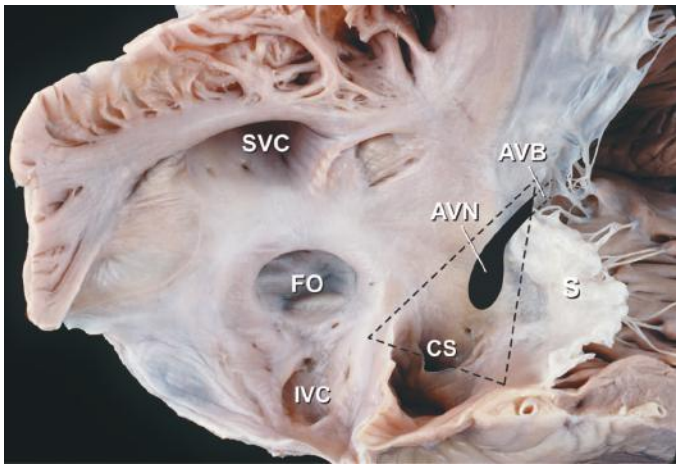

FIGURE 4–77. The atrioventricular node (AVN) lies within the triangle of Koch (*dashed triangle*), and the AV (His) bundle (AVB) travels through the tricuspid annulus to rest along the summit of the ventricular septum. CS indicates coronary sinus; FO, fossa ovalis; IVC, inferior vena cava; S, septal leaflet of the tricuspid valve; SVC, superior vena cava.

The right bundle branch emanates from the distal portion of the AV bundle and forms a cord-like structure that travels along the septal and moderator bands toward the anterior tricuspid papillary muscle (see Fig. 4–76). In contrast, the left bundle branch represents a broad fenestrated sheet of subendocardial conduction fibers that spread along the septal surface of the left ventricle[14,16,17] (see Fig. 4–76). The right and left bundle branches receive dual blood supply from the septal perforators of the LAD and posterior descending coronary artery.[17] Left ventricular pseudotendons can contain conduction tissue from the left bundle branch.[17] *The left bundle branch can be disrupted following surgical myectomy, whereas the right bundle branch can be damaged during percutaneous alcohol septal ablation.*[48] *Following right ventriculotomy for reconstruction of the right ventricular outflow tract, the electrocardiogram shows a pattern of right bundle-branch block even though the right bundle is not disrupted.*[16]

NEW DEVELOPMENTS AND FUTURE CHALLENGES

The future holds promise for an integrated multidimensional approach to the study of cardiac anatomy that incorporates static 3D data, the elements of time (the fourth dimension) and motion, and physiologic (pressure and perfusion) and metabolic parameters.[49,50] Until recently, the geometric fusion of anatomy and function was not possible without physically invading the body. With the currently available imaging techniques, multidimensional anatomy and physiology are mentally reassembled from the sequential tomographic images using echocardiography, MRI or CT, or multiple scintigraphy, as well as SPECT imaging.[49] With the advances in medical technology propelled by the rapid developments in computer technology, digital imaging, and data-storage techniques, it has become possible to electronically perform virtual dissection and reconstruction of the heart and cardiovascular system.[49,50] Furthermore, multidimensional imaging allows continued study of any human organ of interest because of the ability to permanently store anatomic images and the contained physiologic features for retrieval, comparison for change, and ultimately, replication in a more familiar 3D and four-dimensional (4D) presentation.[49,50]

The potential realization of virtual anatomy notwithstanding, standardization of the various tomographic approaches to image acquisition in a manner that conforms to familiar anatomic presentation remains a major challenge that has to be overcome if multidimensional cardiac imaging is to become a clinical reality. There is current progress in this direction. Real-time 3D reconstruction of the heart using identical CT and 2D tomographic sectioning of the heart is now possible. Virtual human vivisection might soon become reality. The goal is virtual surgery (dry runs prior to the actual operation) and dissection of the heart into its various components, be it anatomic, functional, or metabolic, either separately or in various combinations. Moreover, 3D printing[11,12] allows for imaging data to be translated to the physical realm whereby specimens can be studied in detail to assist in planning for intervention or education. Because of advances in multimedia technology, the centuries-old great divide between physiologists and anatomists is about to become relegated to the history books.

ANATOMY NOT ADDRESSED AND QUANTUM COMPUTING

Fine-detailed anatomy such as that of the conduction system and microvasculature is not readily available to the usual anatomic dissection by computer-based imaging. Additionally, tissue histology or molecular biological assessment is not obtained routinely by imaging. At the other end of the spectrum, 3D gross anatomic dissection of contiguous structures is also normally not available (eg, how does metastatic cancer throughout the system relate to a primary tumor in the gut?).

These and other macroscopic and microscopic dissections await the future of increasingly sophisticated computer technology and information management. Both pathologic and living tissues someday will be dissected and analyzed not by destructive cutting but by higher dimensional imagery. Today's computers have introduced the information era. Information has become a commodity expanding our ability to access useful data. It is possible that we will soon evolve into the "Quantum Era," where all that has been discussed in this chapter plus gross and microscopic anatomy will be possible within an electronic environment. Reality will be expressed as base parts or characteristics (eg, quanta, molecules, pixels) and reformatted in 3D or 4D geometry relative to the desired information. Gross anatomy, physiology, tissue characteristics, and even histopathology will be dissected and presented as a quantifiable geometric image. The concept of a *living autopsy* may become a reality.

ACKNOWLEDGMENTS

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CHAPTER 5

NORMAL PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

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The principal function of the cardiovascular system is to deliver oxygen and nutrients to metabolizing tissues and remove carbon dioxide and wastes from these tissues. This is accomplished by means of two specialized circulations in series: a low-resistance pulmonary and a high-resistance systemic circulation driven by specialized muscle pumps, the right and left heart (each in turn composed of a thin-walled atrium and thicker-walled ventricle), respectively. Although cardiovascular physiology can be understood at a number of hierarchical levels, the complex interplay among the intrinsic properties of the cardiomyocytes and isolated muscle, chamber mechanics, and their modulation by variable cardiac-loading conditions and neurohormonal and renal compensatory mechanisms determines the integrated performance of the cardiovascular system. Accordingly, cardiovascular physiology will be examined at cellular, isolated muscle, and organ (isolated heart and integrated systems) levels.

CELLULAR BASIS OF CONTRACTION

EXCITATION: THE ACTION POTENTIAL

The rhythmic beating of the heart distinguishes it from all other organs. The normal heartbeat is initiated by a complex flow of electrical signals called *action potentials*. The action potential results from highly coordinated, sequential changes in ion conductances through gated sarcolemmal membrane channels (Fig. 5–1).

Increases in transmembrane potential from a resting value of –80 to –90 mV to approximately +30 mV (depolarization) represents phase 0 (the rapid upstroke) of the action potential and results primarily from a sudden increase in sodium (Na^+) permeability; this permits a large inward current of Na^+ ions to flow down an electrochemical gradient by means of voltage-and time-dependent fast Na^+ channels. The upstroke is caused by a regenerative process: that is, depolarization leads to Na^+ influx, which leads to further depolarization. The rapid opening of the activation gates for the fast Na^+ channel is immediately followed by a slower closing of inactivation gates, which interrupts the influx of Na^+ into the cell. The membrane must be fully repolarized for inactivation gates to reopen and conduct another action potential, a process called *recovery*.

Phase I (the *notch*) is the initial rapid repolarization phase of the action potential, which is carried by potassium (K^+) and to a lesser extent, chloride (Cl^-) ion conductance. Phase II of the action potential is unique to cardiac muscle; this *plateau phase* results from a balance of inward calcium (Ca^{2+}) and outward K^+ currents. The slow inward (L-type) Ca^{2+} channel is activated at threshold potentials above –50 mV, is maximal at approximately 0 to 10 mV, peaks rapidly, and inactivates slowly. Some Na^+ channels remain active and carry a late Na^+ current throughout the action potential plateau; increased activity of this channel contributes to the abnormal repolarization and increased intracellular calcium in heart failure and ischemic heart disease. Phase III is the final *rapid repolarization* that restores resting potential and is caused by inactivation of the Ca^{2+} current and an increase in the outward K^+ current. Several ionic K^+ pumps contribute to the plateau and repolarization: (1) the inwardly rectifying K^+ current (I_{K1}), a K^+ conductance that generates the resting potential, turns off during phase 0 and is inactive until repolarization begins—it also generates a small outward current late in repolarization; (2) the transient outward K^+ current (I_{TO}), responsible for the initial phase I repolarization; and (3) the delayed outward K^+ current (I_K), the primary current responsible for initiating final repolarization turns on slowly at the final phase of the action potential. After repolarization, the Na^+K^+ adenosine triphosphatase (ATPase) pump extrudes accumulated intracellular Na^+ and pumps extracellular K^+ into the cell. Ionic balance across the sarcolemmal membrane is also maintained by the action of a sodium–calcium exchanger.[1,2]

All myocardial cells are excitable: that is, when adequately stimulated, they can generate an action potential. However, only specialized cells are capable of reaching threshold potential and firing without such an outside stimulus (automaticity). Phase IV of the action potential represents the slow, spontaneous diastolic depolarization responsible for the property of automaticity. Normally, action potentials reach threshold potential and depolarize spontaneously and rhythmically only in the primary pacemaker of the heart, the sinoatrial (SA) node. However, cells in other areas (atrial cells near the ostium of the coronary sinus,

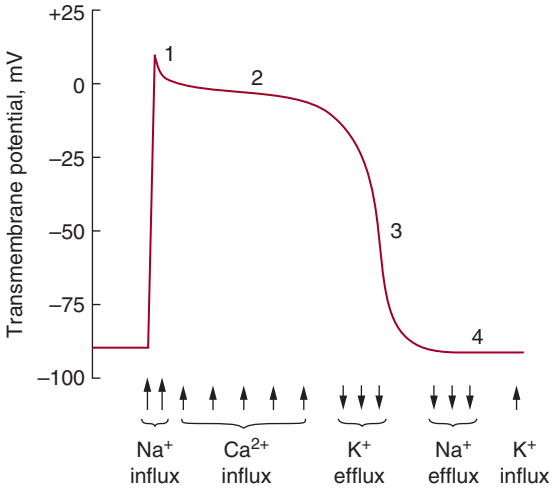

FIGURE 5–1. Phases of the action potential and major associated currents in ventricular myocytes. The initial phase 0 spike is not labeled. See discussion of excitation in text. In specialized conduction system tissue, there is spontaneous depolarization during phase IV. Ca^{2+}, calcium; K^{+}, potassium; Na^{+}, sodium. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: Hurst's The Heart, 11th ed. New York: McGraw-Hill, 2004.

the distal atrioventricular [AV] node, and the His-Purkinje fibers) are capable of automaticity when not suppressed by the faster firing of the SA node. The slope and maximal diastolic potential of the pacemaker potential and the threshold potential determine the rate of impulse formation; the former is modulated by the autonomic nervous system (sympathetic stimulation increasing the slope of the pacemaker potential and accelerating the rate of firing, and parasympathetic stimulation producing the opposite effects). Several ionic currents, specific for the site of impulse genesis, can be involved in the pacemaker current. In the SA node, an inward Ca^{2+} current and an outward delayed K^{+} current that is activated during the plateau and deactivated during phase IV contribute to depolarization. The "funny" current (pacemaker current; I_F), which slowly activates on hyperpolarization, is a critical determinant of the slope of diastolic depolarization and is therefore a key regulator of pacemaker activity.[3] The T-type Ca^{2+} channel is present in the developing heart and adult atrium (and ventricular myocytes from hypertrophied and failing hearts), plays a role in the cardiac pacemaker current, and is involved in release of Ca^{2+} from internal stores.

Effective cell-to-cell communication is essential for rapid, uniform conduction of action potentials and a resultant effective, synchronized myocardial contraction. The organized distribution of local currents that comprise the depolarization wave flow from cell to cell by means of gap junctions. These clusters of transmembrane channels connect the plasma membranes of adjacent myocytes and form low-resistance pathways.[4-6] These channels are composed of two connexons; each connexon is a hexamer of connexins, members of a multigene family of conserved proteins.

EXCITATION–CONTRACTION COUPLING

The cascade of biological processes that begins with the cardiac action potential and ends with myocyte contraction and relaxation defines cardiac excitation–contraction (E–C) coupling (Fig. 5–2). The E–C coupling is intimately related to calcium homeostasis, myofilament calcium sensitivity, and functions of cytoskeletal and sarcomeric proteins

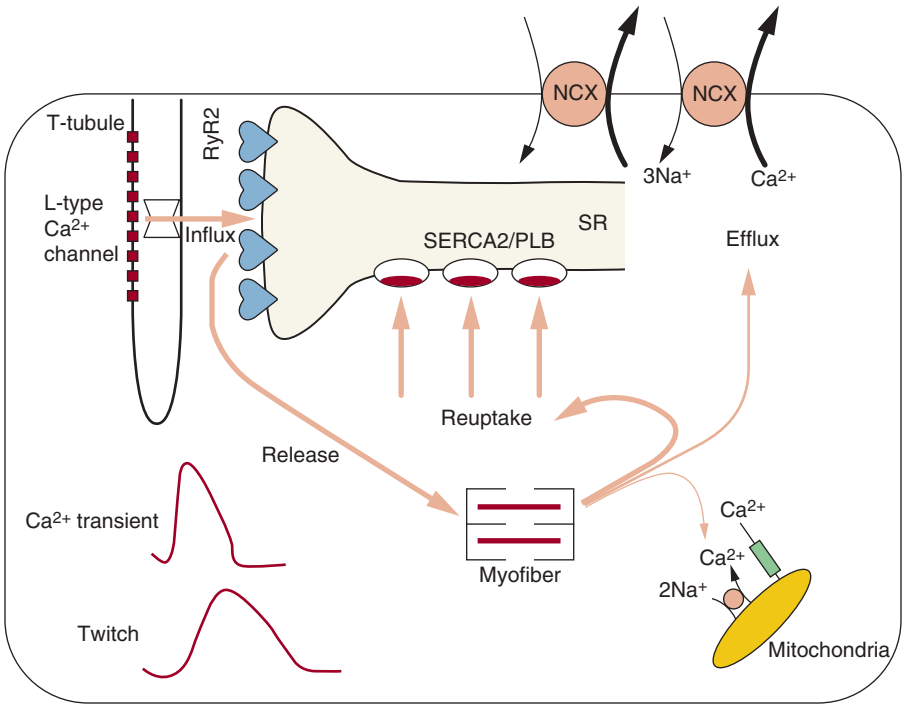

FIGURE 5–2. Major components of excitation–contraction coupling (E–C coupling). Influx of calcium is predominantly through the L-type calcium channel. The *arrow* through the channel denotes the amount of activator calcium and is an index of the E–C coupling gain. The relative magnitudes of calcium release, reuptake, and efflux are denoted by the *arrow* widths. The resultant calcium transient and muscle twitch are shown in the *lower left* of the cell. Ca^{+}, calcium; Na^{+}, sodium; RyR2, ryanodine receptor; SERCA2, sarcoplasmic-endoplasmic reticulum calcium ATPase; SR, sarcoplasmic reticulum. Adapted with permission from Scoote M, Poole-Wilson PA, Williams, AJ, et al: The therapeutic potential of new insights into myocardial excitation-contraction coupling, *Heart*. 2003 Apr;89(4):371-376.

and forms the biophysical underpinnings of the inotropic state of the heart.[7,8] Because E–C coupling is a direct manifestation of myocyte calcium handling, an understanding of the calcium transient and calcium homeostasis is essential.

The calcium transient is initiated in response to sarcolemmal depolarization by extracellular calcium (Ca^{2+}) influx through voltage-dependent L-type Ca^{2+} channels, which instigate the release of stored Ca^{2+} from the cardiomyocyte endoplasmic reticulum, sarcoplasmic reticulum (SR), via spatially proximate Ca^{2+} release channels (ryanodine receptor 2 [RyR2]).

This latter step, fittingly termed *calcium-induced calcium release* (CICR), amplifies the amount of calcium available for myofilament binding and force generating actin–myosin cross-bridges. Relaxation results from closure of the release channels, resequestration of Ca^{2+} by the sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase (SERCA2), and cross-bridge dissolution. To maintain steady-state calcium homeostasis, the amount of Ca^{2+} entering the cell with each contraction must be removed before the subsequent contraction. To this end, the Na^+-Ca^{2+} exchanger (NCX) acting in the *forward* mode competes with SERCA2 for Ca^{2+} and pumps $[Ca^{2+}]_i$ into the extracellular space.

The magnitude of the $[Ca^{2+}]_i$ transient modulates the force developed by myofilaments, and factors that modify calcium cycling and/or Ca^{2+} sensitivity of myofilaments can alter significantly the force and extent of myocyte contraction. The determinants of the cardiac myocyte $[Ca^{2+}]_i$ transient are as follows. Factors responsible for the $[Ca^{2+}]_i$ transient amplitude include (1) the calcium current (I_{Ca}), primarily caused by Ca^{2+} influx through the L-type Ca^{2+} channel, but in small part caused by *reverse mode* NCX; (2) SR $[Ca^{2+}]_i$ content, which determines the amount of releasable calcium; (3) the efficiency of E–C coupling, or the *gain* (ie, the amount of calcium released by the SR for the calcium current, $\Delta[Ca^{2+}]_i/I_{Ca}$); and (4) intracellular Ca^{2+} buffers. The decline of the $[Ca^{2+}]_i$ transient is caused by (1) Ca^{2+} reuptake into SR by SERCA2 (a process modulated by a phosphorylatable regulatory protein termed *phospholamban*); (2) Ca^{2+} extrusion from the cell by the NCX; (3) Ca^{2+} extrusion from the cell by the sarcolemmal Ca^{2+}-ATPase; (4) Ca^{2+} accumulation by mitochondria; and (5) Ca^{2+} binding to intracellular buffers (including fluorescent indicators that are used in experimental systems to measure the transient).[9]

Calcium sparks (localized $[Ca^{2+}]_i$ transients) are the elementary SR Ca^{2+} release events that trigger E–C coupling in heart muscle.[10] The basis for the generally accepted *local control* theory of E–C coupling is that Ca^{2+} sparks are triggered by a local $[Ca^{2+}]_i$ established in the region of the RyR2s by the opening of a single L-type Ca^{2+} channel. The amplitude of Ca^{2+} sparks is determined by SR Ca^{2+} load and gating properties of the RyR2. Although the exact nature and origin of Ca^{2+} sparks are not completely understood, the prevailing view is that the global $[Ca^{2+}]_i$ transient is produced by the temporal and spatial summation of a large number of Ca^{2+} sparks.[10] The mechanisms responsible for terminating sparks are not clear, but proteins accessory to the RyR2 (eg, sorcin [FKB12]) have been suggested as playing a key role.[11,12]

Components of Excitation–Contraction Coupling

Sarcolemma The sarcolemma is the site where calcium enters and leaves the cell through a distribution of ion channels, transporters, and pumps. The T-tubules are invaginations of the sarcolemma and glycocalyx and are both longitudinal and oblique in their orientation; this system forms a permeability barrier between the cytosol and the extracellular space.[13] The membranous surface areas are tissue (atrial cells have poorly developed T-tubules) and species specific. T-tubules play a complex regulatory role in the calcium transient; for example, the I_{Ca} is more sensitive to βAR stimulation and intracellular Ca^{2+} at the T-tubules than at the surface membrane.[13] The structural specialization of the sarcolemma include (1) SR coupling in the form of dyads by means of the T-tubule; (2) caveolae, which are invaginations of the sarcolemma that increase surface area and form a scaffold for signaling molecules such as nitric oxide (NO) synthase and protein kinase C (PKC); and (3) the intercalated disk, which takes the form of a gap junction, intermediate junction, or desmosome. Ankyrins are sarcolemmal adaptor proteins that are implicated in the proper expression and membrane localization of ion channels, transporters, dystrophin, and other proteins.

Sarcoplasmic Reticulum The SR is an intracellular membrane-bounded compartment comprised of terminal, longitudinal, and corbular components (Fig. 5–3). The free walls of the terminal cisternae are apposed to the walls of the T-tubules and form the dyadic cleft; the RyR2 receptors are located in the walls of the terminal cisternae (*feet*) and face the dyadic cleft. Longitudinal SR is fairly homogenous and contains primarily the SR Ca^{2+}-ATPase proteins, SERCA2, and the associated phosphoprotein phospholamban. In its dephosphorylated state, phospholamban is an endogenous inhibitor of SERCA2. Phosphorylation by PKA (at amino acid serine 16) and calcium-calmodulin kinase II (CaMKII) (at threonine 17) lowers the Michaelis constant (K_m) of sarcoplasmic endoplasmic reticulum calcium ATPase (SERCA) and results in enhanced calcium uptake. SR calcium is transported from the tubular lumen of the SR to the terminal cisternae, where it is stored mostly bound to calsequestrin, a low-affinity, high-capacity, calcium-binding protein. Calsequestrin forms a complex with the proteins junctin, triadin, and RyR2. Junctional SR does not come into contact with the sarcolemma; corbular SR is a form of junctional SR that contains calsequestrin and RyR2s but is not coupled to the well-recognized calcium-cycling events.[14,15]

Myofilaments Myofilaments comprise the contractile machinery of the cell and occupy 45% to 60% of the ventricular myocyte volume (Fig. 5–4). The fundamental unit of the myofilament is the sarcomere,

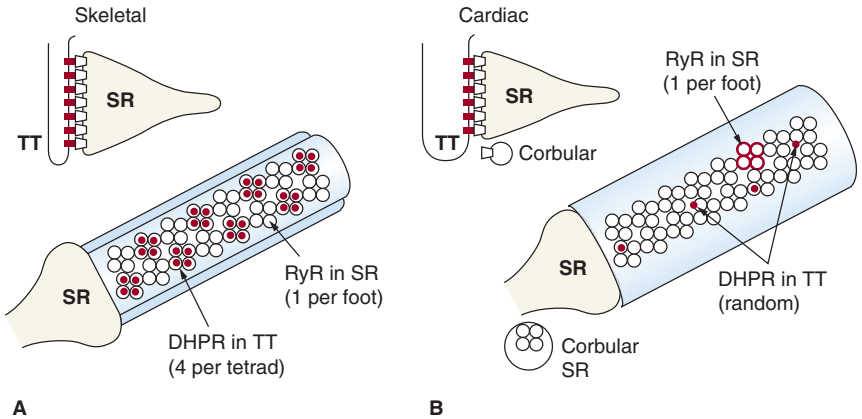

FIGURE 5–3. Organizational differences between skeletal and cardiac T-tubule junction. The *upper panels* are side views of the junction (*trapezoids* are ryanodine receptors [RyRs], and *filled ovals* are the dihydropyridine receptors [DHPRs]). The *lower panels* are views from inside the T-tubule at the junction. Note that DHPRs are sparse and less aligned in the heart. RyR, ryanodine receptor; SR, sarcoplasmic reticulum; TT, T-tubules. Reproduced with permission from Bers DM. *Excitation-Contraction Coupling and Cardiac Contractile Force*, 2nd ed. Norwell, MA; Kluwer Academic Publishers; 2001.

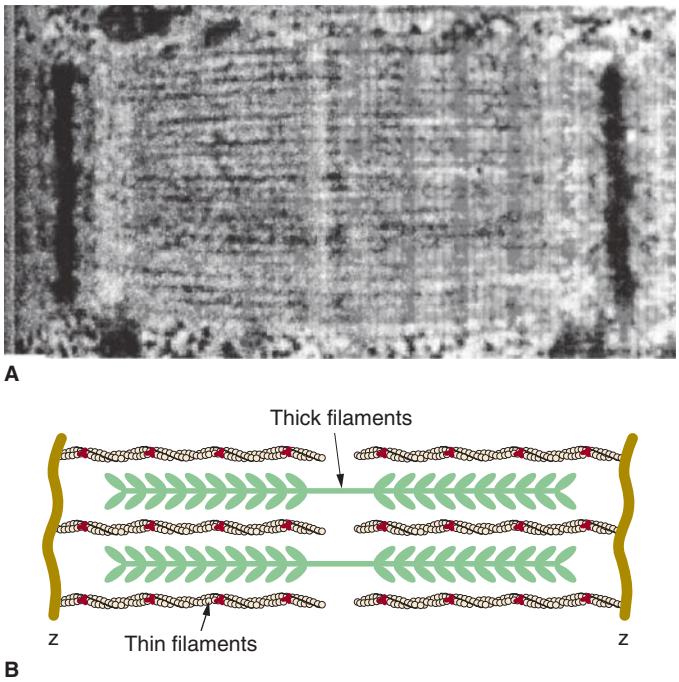

FIGURE 5–4. Electron micrograph (**A**) and schematic diagram (**B**) of a sarcomere. The darkly staining regions that flank the sarcomere are the Z lines. Myosin-containing thick filaments are in the center of the sarcomere and interact with actin-containing thin filaments by way of myosin heads that protrude from the thick filaments. Thin-filament regulatory proteins, the troponin and tropomyosin, provide calcium regulation of the actin–myosin interface. Thin filaments are anchored to the Z line, which is enriched in proteins such as α-actinin and Cap Z. (*Right*) Membrane complexes that concentrate over Z lines. The dystrophin–glycoprotein complex. Reproduced with permission from Walsh RA: *Molecular Mechanisms of Cardiac Hypertrophy and Failure*. London: Taylor and Francis; 2005.

bounded by Z lines on each end, from which the thin actin filaments extend toward the center. At the center of the thick myosin filament is the M line, where the thick filaments are interconnected by M protein and myosin. Titin runs from the M line to the Z line in association with myosin and myosin-binding protein C (MyBP-C); this large structural sarcomeric protein acts as a scaffold for myosin deposition, stabilizes the thick filament, functions as a molecular spring, and plays a critical role in determining the passive stiffness of the heart.[16] Changes in titin stiffness occur during cardiac development and disease states through shifts in the relative expression of the compliant N2BA and stiff N2B titin isoforms.[16] Acute changes in titin stiffness (and as a result, diastolic ventricular function) is produced by PKC and PKG-mediated phosphorylation of an I band–specific domain of titin.[17] The functions of MyBP-C are not entirely clear; it may play a role in regulation of contraction by limiting the reach of myosin heads toward the thin filament. It may also play a prominent role in myofilament calcium sensitivity, cross-bridge cycling rate, and length-dependent activation. Mutations in the *MyBP-C* gene are responsible for a significant proportion of familial hypertrophic cardiomyopathy.[18,19] The Z lines are the sites of anchor for cytoskeletal intermediate filaments and actin filaments at the intercalated disks and at focal adhesions. The two major structural complexes involved in the connections between sarcomeric proteins and the extracellular matrix (ECM) are the membrane-spanning integrin complex and the dystrophin complex, which links actin to laminin and collagen.

Myosin The myosin molecule consists of two heavy chains with a globular head, a long α-helical tail, and four myosin light chains (Fig. 5–5). The myosin head forms cross-bridges with the thin actin filament through an actin-binding domain. Transduction of chemical to mechanical energy and work is the function of myosin ATPase, located in the myosin heads. Myosin heavy chain exists as two isoforms, α (fast ATPase and cross-bridge formation) and β (slow ATPase and cross-bridge formation). In higher mammals, including humans, the β-myosin isoform predominates, but in small mammals, such as mice and rats, the α form is dominant. The most accepted model of energy transduction is the sliding filament theory based on the formation and dissociation of cross-bridges between the myosin head and the thin filament that transition through different energetic states. Two myosin light chains (the alkali or essential light chain [MLC1] and the phosphorylatable or regulatory light chain [MLC2]), are associated with each myosin head and confer stability to the thick filament. Phosphorylation of the myofilament regulatory protein troponin modulates the activity of myosin ATPase. Although phosphorylation of MLC2 by myosin light-chain kinase (MLCK) is critical for smooth muscle cell contraction (see the following section), its physiological significance in cardiac muscle (increased calcium sensitivity and rate of force development) is controversial.

Thin Filaments The backbone of thin filament is helical double-stranded actin. Tropomyosin is a long, flexible, double-stranded (largely α-helix) protein that lies in the groove between the actin strands and inhibits the interaction between actin and myosin (see Fig. 5–5). The troponin complex is composed of a calcium-binding subunit, troponin C (TnC); an inhibitory subunit that binds to actin, troponin I (TnI); and a

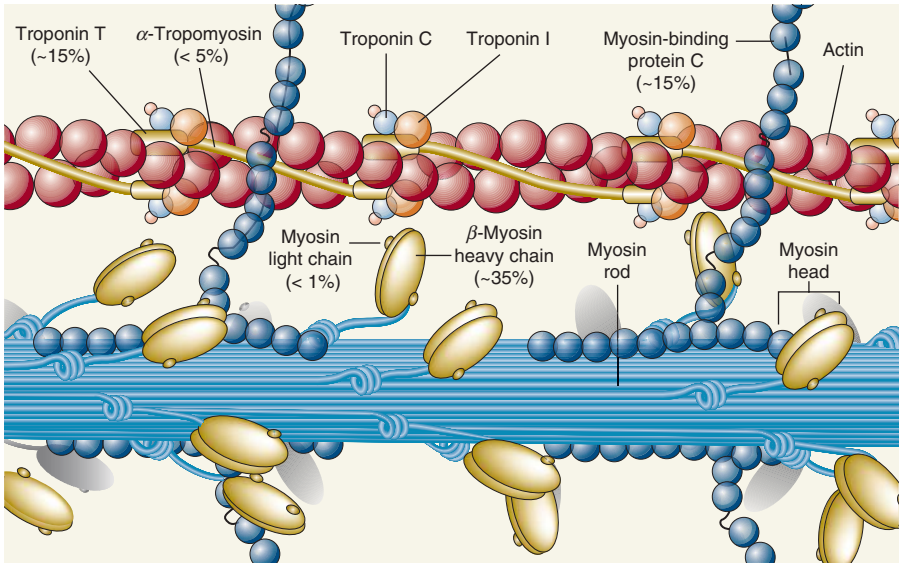

FIGURE 5–5. The sarcomeric proteins. Titin, which runs from the M line to the Z line in association with myosin and myosin-binding protein C, is not shown. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: *Hurst's The Heart*. 11th ed. New York: McGraw-Hill; 2004.

tropomyosin-binding subunit, troponin T (TnT), which is attached to tropomyosin. In the resting state, when $[Ca^{2+}]_i$ is low, calcium-binding sites of TnC are unoccupied, and TnI preferentially binds to actin; this favors a configuration in which the troponin–tropomyosin complex sterically hinders myosin–actin interaction. In this configuration, cross-bridges are in both detached and weakly attached non–force-producing states. When $[Ca^{2+}]_i$ rises, calcium binds to the calcium-specific sites on TnC and strengthens the interaction of TnC and TnI; TnI then dissociates from actin, and a conformational change removes the steric hindrance to myosin–actin interaction. Strong binding of actin to myosin begins when the actin–myosin inhibition is relieved. Binding Ca^{2+} to troponin causes the process of cross-bridge formation to spread down the actin filament, and by means of ATP hydrolysis, transitions are made from detached or weakly bound states to force-producing states. Release of conformational energy leads to rotation of the myosin head that propels the thin filament along the thick filament. Usually the systolic $[Ca^{2+}]_i$ only submaximally activates muscle; the steep relation between $[Ca^{2+}]$ and tension is thought to result from both nearest neighbor interaction and strong actin–myosin binding, which allows for contractile reserve with modest changes in $[Ca^{2+}]_i$. Although this is the most accepted model, other potential explanations exist; all models incorporate the concept that myofilaments are dynamically involved in their state of activation and not simply subject to passive changes in $[Ca^{2+}]_i$. A simplified mechanical model of cross-bridge formation is presented in Fig. 5–6.

Mitochondria Mitochondria comprise approximately 35% of ventricular myocyte volume and according to their cellular location are designated as either subsarcolemmal or interfibrillar. Mitochondria are the sites of oxidative phosphorylation and ATP generation. Although they have the capacity to buffer large amounts of Ca^{2+} and are a potential source of activator calcium, classical teaching is that their contribution to E–C coupling is minimal in view of the short time constants involved; variation in mitochondrial Ca^{2+} during a twitch is imperceptible and thus plays a very minor role in beat-to-beat changes in calcium homeostasis. However, the kinetics of mitochondrial Ca^{2+} uptake during E–C coupling have recently become controversial.[20,21] Nevertheless, slower increases in mitochondrial Ca^{2+} content are important with respect to mitochondrial function and energetics; for example, the matrix enzymes pyruvate dehydrogenase, nicotinamide adenine dinucleotide–dependent isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase are activated by low $[Ca^{2+}]$. In addition, the ability to accumulate large amounts of Ca^{2+} under pathological conditions (eg, ischemia) can help protect against myocyte Ca^{2+} overload; however, Ca^{2+} accumulation by mitochondria ultimately slows ATP production.

ROLE OF NITRIC OXIDE

NO is produced by the myocardium and regulates cardiac function through both vascular-dependent and -independent effects.[22] In terms of vascular-dependent effects, NO acts as a peripheral vasodilator and reduces afterload, thereby changing pressure–volume (P–V) and force–tension relationships, and ultimately increasing stroke volume. Although these issues are discussed later in the chapter, this section focuses on the vascular-independent effects of NO. NO has a modest positive inotropic effect on basal contractility in isolated myocytes and the isolated perfused heart but a negative inotropic effect in vivo,[23] possibly because of nitrosylation of ion channels responsible for E–C coupling (eg, L-type channel, RyR2). The negative inotropic effects on β-adrenergic stimulated contractility are greater and less controversial and can comprise a critical component of negative feedback over contractile reserve. NO's positive effects on relaxation or lusitropy (and in part, for negative inotropic effects) are likely to be caused by cyclic 3′, 5′-guanosine monophosphate (cGMP)-mediated reduction in myofilament Ca^{2+} sensitivity.[23,24] Finally, mitochondrial NO reduces maximal venous oxygen (MVO_2) consumption and increases mechanical efficiency (stroke work/MVO_2), suggesting that NO regulates energy production as well influencing consumption.

The effects of NO on E–C coupling are confusing and controversial because of the presence of three nitric oxide synthase (NOS) isoforms that are spatially localized to highly controlled microdomains and linked to disparate signaling pathways and effectors. For example, NOS type III (NOS3) is compartmentalized to the sarcolemmal and T-tubule caveolae, associated with the L-type channel, inactivated by the scaffolding protein caveolin-3, and activated by Ca^{2+}/calmodulin and Akt phosphorylation. NOS3 produces its negative inotropic and positive lusitropic effects by means of cGMP activation.

In contrast, NOS type I (NOS1), which is also activated by Ca^{2+}/calmodulin and can be inactivated by caveolin-3, is localized to cardiac SR and is involved with calcium homeostasis. NOS1 increases the open probability of the cardiac RyR2

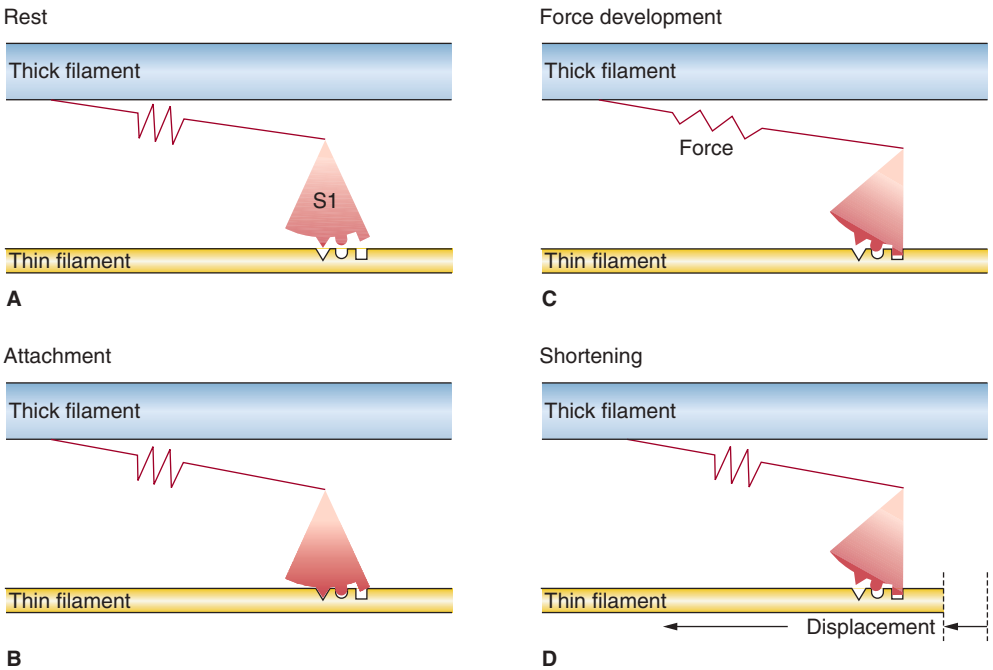

FIGURE 5–6. A mechanical model of the cross-bridge cycle. **A.** Detached cross-bridge. **B.** Cross-bridge before developing force. **C.** Attached cross-bridge developing force stored in the elastic component. **D.** Cross-bridge rotated and translated so the filaments slide relative to one another. Each step in the cycle can be related to energetically different chemical states. Reproduced with permission from Bers DM. *Excitation-Contraction Coupling and Cardiac Contractile Force*, 2nd ed. Norwell, MA; Kluwer Academic Publishers; 2001.

and modulates β-adrenergic mechanics, calcium transients, and the force–frequency relationship, although the mechanisms are still under investigation.[24] Nevertheless, accumulating data suggest that NO plays an important role in E–C coupling vis-à-vis modulation of Ca^{2+} channel activity, myofilament Ca^{2+} sensitivity, and mitochondrial respiration.[23]

NON–STEADY-STATE EXCITATION–CONTRACTION COUPLING

Heart rate dependence of cardiac contractility reflects basic cycling kinetics of calcium and is critically dependent on SR function. Processes related to force–interval behavior (eg, mechanical restitution, force–frequency, postextrasystolic potentiation [PESP]) are important insofar as they represent fundamental physiological control mechanisms, they are used as indices of myocardial function, and they play a role in the response to exercise and the development and maintenance of heart failure. Non–steady-state aspects of E–C coupling provide the basis for these phenomena.

Mechanical restitution is the relative refractory period that immediately follows a contraction and is usually explained by the recovery of the RyR2 receptors (because I_{Ca} and SR Ca^{2+} content recover rapidly).[25] Mechanical restitution is the basis for PESP, the strong contraction following a weaker extrasystole, because lower $[Ca^{2+}]$ on the extrasystole results in increased I_{Ca} (less Ca^{2+}-induced inactivation of the L-channel), less Ca^{2+} efflux from NCX, and increased SR Ca^{2+} loading on the postextrasystolic beat. The result is a greater amount of released Ca^{2+} and therefore a stronger contraction. In the intact heart, the effect of changing preload (and the impact on Frank-Starling and calcium sensitivity) is an important additional mechanism. PESP contributes to the beat-to-beat variability of the pulse in atrial fibrillation. Mechanical alternans, the alternating contraction amplitude at a constant heart rate that is seen in heart failure, is explained by a similar interplay of RyR2 refractoriness (which is increased in heart failure), I_{Ca} in-activation, NCX competition, and SR Ca^{2+} load.[15,26]

The relationship between pacing rate and force (force–frequency relationship) can be understood similarly by these non–steady-state phenomena. Increased pacing rate overcomes the encroachment on mechanical restitution and produces an increase in force because of rate-dependent increases in I_{Ca}, I_{Na} (which results in less Ca^{2+} efflux by the NCX), diastolic $[Ca^{2+}]_i$ (less time for efflux and greater influx/second), releasable SR Ca^{2+} content, and fractional SR Ca^{2+} release.[27,28] A phenomenon similar to the force–frequency relationship is observed when the effects of heart rate on the time constant of isovolumic relaxation are examined. Thus, similar to the effect on contraction, relaxation is augmented at higher rates of stimulation.

EXCITATION–TRANSCRIPTION COUPLING

An emerging concept is that the molecular machinery of E–C coupling is involved in the long-term regulation of gene expression by a process known as *excitation–transcription* (E–T) coupling. Despite periodic oscillations of $[Ca^{2+}]$ from 100 nM to 1 μM during E–C coupling, transcription regulatory proteins (eg, NFκB, janus N-terminal kinase [JNK], nuclear factor of activated T cells [NFAT]) are calcium activated. The amplitude and duration of the calcium signal; the presence of microdomains and anchoring proteins; and linkages through calmodulin, kinases, and phosphatases are important mechanisms for discriminating important regulatory cues and resolving this apparent paradox.[29] For example, in adult ventricular myocytes, inositol 1,4,5 triphosphate ($InsP_3$) receptors localized to the nuclear envelope are involved in the local control of Ca^{2+} (so-called *reactive signaling*) for a CaMKII-mediated activation and regulation of a histone deacetylase.[30]

CaMKII regulates proteins involved in calcium transport; ion channels; and cell contraction, metabolism, and proliferation by phosphorylation. Phosphorylation substrates for CaMKII that are involved in modulating contraction–relaxation include phospholamban (PLB), SERCA2a, L-type Ca^{2+} channels, and the RyR2.[31,32] CaMKII phosphorylates the transcription factor cyclic adenosine monophosphate (cAMP) response element binding, which promotes transcription of c-Fos.[31] In addition, CaMKII has autoregulatory properties that are dependent on the frequency of Ca^{2+} spikes, a process thought to have a role in neuronal memory. Little is known about in vivo CaMKII activation, but biochemical data suggest that CaMK might be *primed* to respond to Ca^{2+} spikes. Thus, calcium-dependent regulation by calmodulin and CaMKII has both acute responses affecting E–C coupling and chronic responses that influence the expression levels of proteins involved in E–C coupling.[33] In vascular smooth muscle cells, the L-type channel (via the RhoA/ROK pathway) and the calcineurin/NFAT pathway are involved in the regulation of cell differentiation.[34]

VASCULAR EXCITATION–CONTRACTION COUPLING

Arterial smooth muscle cells exist in the partially constricted state. The principal determinant of vascular tone is membrane potential, which is achieved through activation of voltage-gated calcium channels. There is a steep relation between $[Ca^{2+}]$ and vascular tone, and therefore membrane potential must be highly regulated to maintain appropriate vascular resistance. The resting potential of smooth muscle cells ranges from –40 to –70 mV, lower than cardiac muscle because of greater Na^+ permeability. Thus, the rising phase of the action potential is produced by inward calcium current through the slow L-type Ca^{2+} channels. Contraction results directly from depolarization-induced Ca^{2+} influx and indirectly by means of CICR-activation of the contractile apparatus. Relaxation results from lowering cellular Ca^{2+} via Ca^{2+} ATPase pumps and hyperpolarization of the cell by activation of K^+ channels.

A distinctive feature in smooth muscle is that Ca^{2+} acts as a second messenger to activate MLCK, which phosphorylates the myosin light chains and produces force. Ca^{2+} binds to calmodulin, and this complex activates MLCK. Phosphorylation of the 20-kD light chain stimulates actin-activated myosin ATP hydrolysis and contraction. Relaxation occurs when there is dissociation of Ca^{2+} from calmodulin, inactivation of MLCK, and dephosphorylation of myosin by myosin light-chain phosphatase (Fig. 5–7).

Unlike myocardial cells, both cAMP and cGMP inhibit the activity of the slow Ca^{2+} channels. Thus, both NO (which increases cGMP) and β-adrenergic agonists (which increase cAMP) are vasodilators. Stimulation of delayed rectifier channels and sarcolemmal Ca^{2+} pumps produce vasodilation. Angiotensin II and α-agonists cause vasoconstriction by phospholipase C–mediated production of inositol trisphosphate (IP_3; which releases Ca^{2+}) and diacylglycerol (DAG), which stimulates PKC phosphorylation of the Ca^{2+} channel and inhibition of the delayed rectifier channel.

PROPERTIES OF MYOCARDIAL CONTRACTION

FUNDAMENTALS OF MYOCARDIAL CONTRACTILITY

Fundamental to cardiac muscle function are the relationships between force and muscle length, velocity of shortening, calcium, and heart rate. The maximal force developed at any sarcomere length is determined by the degree of overlap of thick and thin filaments and therefore the number of available cross-bridges.[35] Force increases linearly until a sarcomere length with maximal overlap (~2.2 μm) is achieved

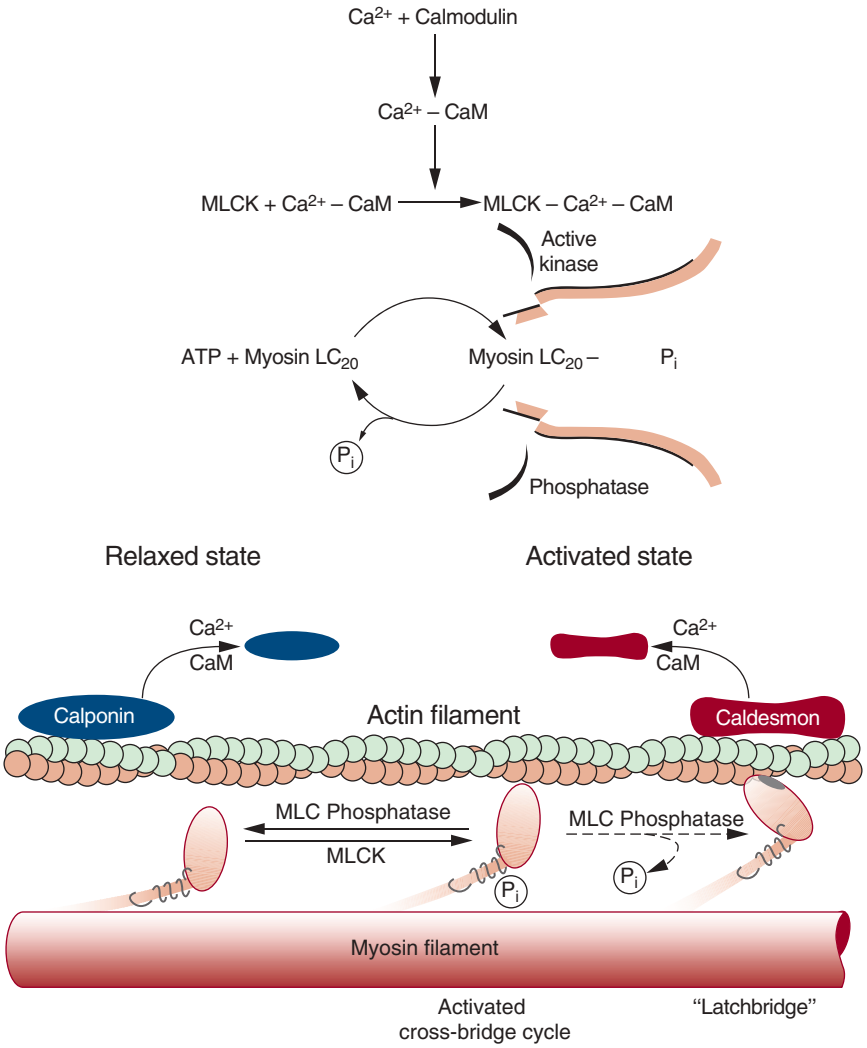

FIGURE 5–7. The molecular basis of regulation of smooth muscle contraction. Stimulation of muscarinic receptors increases the $[Ca]_i$ because of entry of external calcium (Ca^{2+}) and release of Ca^{2+} from internal stores. Ca^{2+} binds to calmodulin (CaM) and the Ca^{2+}–CaM complex subsequently binds to and activates myosin light-chain kinase (MLCK). Phosphorylation of myosin by MLCK stimulates actin-activated myosin-ATP hydrolysis, which produces contraction. Relaxation begins with the cessation of agonist stimulation, resulting in decreased $[Ca]_i$, dissociation of Ca^{2+} from CaM, inactivation of MLCK because of dissociation of CaM, dephosphorylation of myosin by phosphoprotein phosphatases, and relaxation. Reproduced with permission from Sperelakis N, Banks RO: *Essentials of Basic Science: Physiology*. 2nd ed. Boston: Little, Brown and Company; 1996.

(Fig. 5–8), beyond which force and overlap gradually declines to zero (ie, the *descending limb*). The descending limb of the length–tension relationship is prevented by the strong parallel elastic component in cardiac muscle. The ascending limb of the length–tension relationship (equivalent to the Frank-Starling relationship that relates preload to cardiac performance) is also caused by a length-dependent increase in myofilament calcium sensitivity (Fig. 5–9A). This has been explained by enhanced calcium binding to TnC, narrower interfilament gaps at long sarcomere length, and increased SR calcium release and uptake at longer sarcomere lengths.[35]

The relationship between force and velocity of contraction is hyperbolic (Fig. 5–9B); at maximum force (isometric force), shortening cannot occur, and at zero force (ie, *unloaded* muscle), velocity is at a maximum (V_{max}), reflecting the maximum turnover rate of myosin ATPase. Therefore, alterations in the myosin isoform (ie, α, fast; β, slow) such as those seen in response to pressure overload, have an effect on V_{max}.

Another fundamental property of cardiac muscle is the force pCa^{2+} relation. Shorter sarcomere lengths decrease Ca^{2+} sensitivity, and caffeine and various inotropic drugs (eg, levosimendan) are potent calcium sensitizers. β-Adrenergic stimulation results in a cAMP-dependent phosphorylation of cardiac TnI and a resultant decrease in myofilament calcium sensitivity; thus, for a positive β-adrenergic receptor (βAR)–inotropic effect, the amplitude of the calcium transient must more than compensate for reduced βAR-mediated myofilament sensitivity.[15,36]

The final property relates heart rate to contraction and relaxation. Increasing the heart rate increases contractility; this is related to the Ca^{2+} capacity and load of the SR. A related phenomenon, frequency-dependent acceleration of relaxation, results from CaMKII phosphorylation of phospholamban (or by some other mechanism that increases SR Ca^{2+} transport).[33,37] CaMKII might be activated by the increased $[Ca^{2+}]_i$ that occurs with increased stimulation rates; however, the precise mechanisms are unresolved. The physiologic implications for faster relaxation at increased heart rates, when the diastolic filling periods are shortened, are discussed in the following section.

ISOLATED MUSCLE: MECHANICS OF CONSTITUENT MUSCLE FIBERS

When a strip of heart muscle is attached at both ends so that the length is fixed and then electrically stimulated, the muscle develops force without shortening (Fig. 5–10A). A fundamental property of striated muscle is that the strength of this isometric twitch is dependent on the initial resting muscle length, or preload (Fig. 5–10B). As cardiac muscle is stretched passively, the resting tension rapidly rises and prevents overstretching of the sarcomeres. If additional load is applied before contraction (ie, the preload), stimulation causes contraction with an increased peak tension and rate of tension development (dT/dt). Thus, total tension includes both active and passive tension. The length–tension relationship, which forms the basis for the Frank-Starling relationship, is depicted in Fig. 5–10C. The inotropic state is defined operationally as a change in the rate or extent of force development that occurs independently of the loading conditions. The biophysical basis of the inotropic state includes the subcellular processes that regulate myocyte cytosolic calcium and actin–myosin cross-bridge cycling. In isolated cardiac muscle, changes in the inotropic state are measured by changes in the peak isometric tension and dT/dt at a fixed preload.

If isolated cardiac muscle is allowed to shorten, the contraction is termed *isotonic* (Fig. 5–10D). Initial muscle length is determined by applying a preload; an additional load known as the *afterload*, affects muscle behavior after stimulation. Muscle shortening occurs when tension development equals the total load (preload plus afterload). During shortening, tension remains constant. With dissipation of the active state, the muscle returns to its initial preloaded length, and tension finally declines. If preload is altered while the afterload is kept

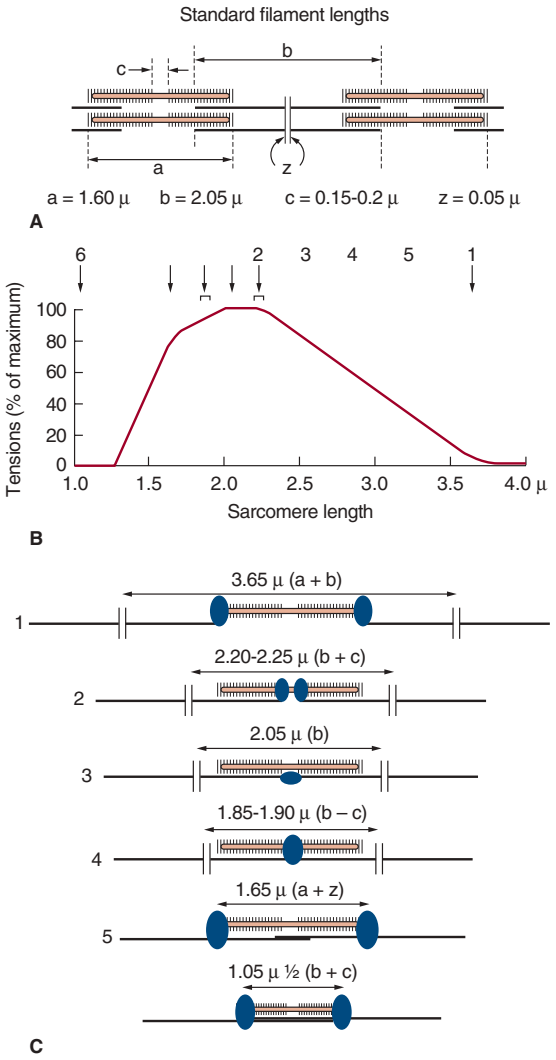

FIGURE 5–8. Structural basis for the active isometric force–length relationship. **A.** Sarcomere Z line to Z line minimal sarcomere length. **B.** Optimal sarcomere length with maximal cross bridge overlap. **C.** H line with no possible cross bridge attachment. Reproduced with permission from Gordon AM, Huxley AF, Julian FJ. The variation in isometric tension with sarcomere length in vertebrate muscle fibres, *J Physiol*. 1966 May;184(1):170-192.

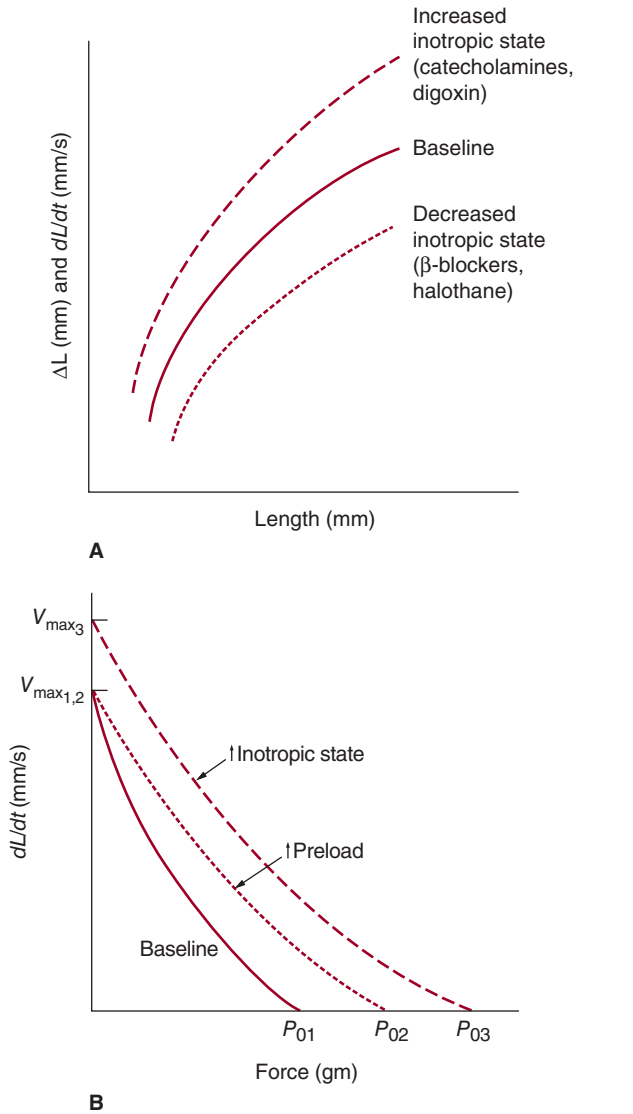

FIGURE 5–9. **A.** Length–shortening and length–velocity relationships from isotonic contractions at a constant afterload. As muscle length (preload) increases, shortening (ΔL) and velocity of shortening (dL/dt) increase. An increased inotropic state shifts the curve upward and to the left; conversely, a decreased inotropic state shifts the curve downward and to the right. **B.** Force–velocity relationship from variably afterloaded contractions. Increased preload causes an increase in the maximum isometric tension (P_{01} to P_{02}) without a change in the extrapolated velocity of an unloaded contraction (V_{max}). An increase in the inotropic state increases P_0 and V_{max} (dL/dt = velocity of contraction). Reproduced with permission from Sperelakis N, Banks RO: *Essentials of Physiology*. 2nd ed. Boston: Little, Brown and Company; 1996.

constant, length–shortening and length–velocity curves (analogous to the length–tension curve seen in isometric muscle) are derived.

The force–velocity curve describes an inverse hyperbolic curve relating afterload and the initial velocity of shortening and can be obtained from a series of variably afterloaded contractions (see Fig. 5–9B). When the afterload is so great that the muscle cannot shorten, the contraction becomes isometric (P_0). The velocity of an unloaded contraction (V_{max}) is determined by the physicochemical properties unique to cardiac muscle and is therefore considered a measure of the inotropic state. However, because load always exists, V_{max} must be extrapolated from the force–velocity curve. Although changes in preload shift P_0 without changing V_{max}, a positive inotropic agent increases V_{max} and P_0 by means of a parallel upward shift of the force–velocity curve; a negative inotropic agent causes the opposite effect. Similar operational definitions of the inotropic state can be applied to the preloaded isotonic contraction, in that a positive inotropic agent produces an upward shift of the length–shortening and length–velocity curves.

An important property of cardiac muscle is that the isometric passive length–tension curve establishes the limits of tension for an isotonic contraction. In other words, the tension at the end of an isotonic contraction is the same as the tension developed from an isometric contraction at the same resting muscle length.

Besides load and the contractile state, cardiac muscle performance is influenced by the frequency of stimulation. An increase in stimulation frequency causes an increase in tension in isolated cardiac muscle, known as the *Bowditch phenomenon*.[38] This is the force–frequency relationship previously described.

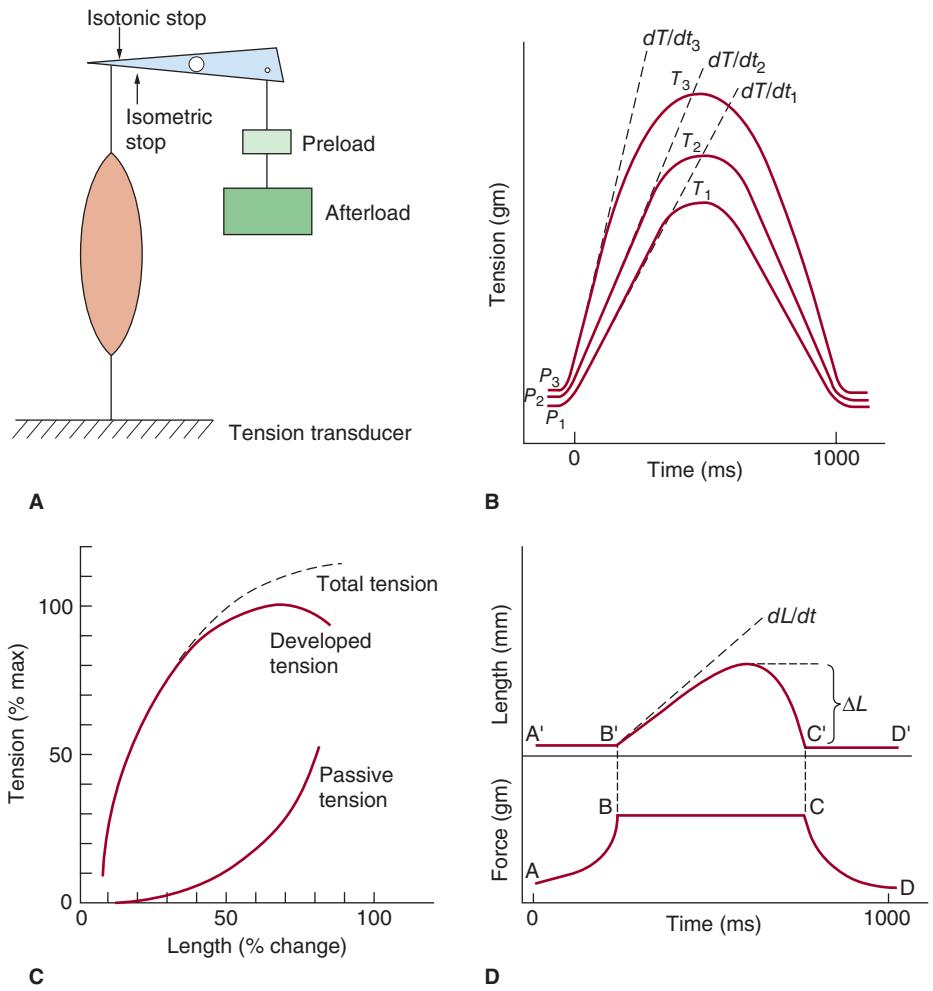

FIGURE 5–10. Contractions in isolated muscle. **A.** Isolated muscle preparation. Muscle is attached to a level arm at one end and fixed to a tension transducer at the other. The muscle is stretched by applying a weight (preload) at one end of the lever arm. A stop prevents muscle shortening. **B.** Tension–time curves of isometric twitches at three levels of preload. With increased preload, peak tension (*T*) and the maximum rate of tension development (*dT/dt*) are increased. The time to peak tension is unchanged. **C.** Length–total tension relationship and its components, passive and active tension. As muscle is stretched, the absolute passive and total tension increase. **D.** Superimposed tension–time and length–time recordings from afterloaded isotonic contractions. After preload is applied, a stop is placed to prevent further stretching. Afterload is added, and the muscle is stimulated. Muscle shortens when generated tension equals total load (preload and afterload). Measures of shortening in the isotonic contraction include total shortening (Δ*L*) and the initial velocity of contraction (*dL/dt*). Reproduced with permission from Ross J: *Best & Taylor's Physiological Basis of Medical Practice*, 12th ed. Baltimore: Williams & Wilkins; 1990.

CARDIOVASCULAR PHYSIOLOGY AT THE ORGAN LEVEL

For all the advantages of studying isolated myocytes and muscle fibers, an integrated and more realistic analysis of cardiovascular function regards the left ventricle (LV) as a muscle pump coupled to the systemic and venous circulations. In contrast to isolated cardiac muscle, contraction of the intact LV is auxotonic, in that force increases and decreases during ejection of viscous blood into a viscoelastic arterial system. Moreover, attempts to extrapolate results from isolated muscle to the intact LV are hampered by the complexity of chamber geometry and myocardial fiber orientation, which make it difficult to estimate initial fiber length (preload) and the force opposing LV ejection (afterload). Finally, unlike isolated cardiac muscle, ventricular performance is modulated by neurohumoral influences, right and LV interaction, restraining effects of the pericardium, and atrial function. At the organ level, the preceding events are initiated by the electrical activation of the heart and structured by the sequence of events in a heartbeat, the cardiac cycle.

THE ELECTROCARDIOGRAM

The electrocardiogram (ECG) (Fig. 5–11) records the pattern of electrical activation of the heart on the body surface. Electrical currents generated by differences in potential between depolarized and polarized regions of the heart are conducted through the body, detected by electrodes, and amplified and recorded on calibrated moving paper. The ECG provides important clinical information regarding the electrical orientation of the heart in three-dimensional space, the relative size of the cardiac chambers, and the presence of conduction system defects and provides evidence for a variety of underlying pathologic conditions, such as ischemia, infarction, cardiomyopathy, and hypertrophy.

The SA node is the primary pacemaker of the heart and is located at the junction of the superior vena cava and the right atrium. The action of the SA node is electrically silent, although a measurable conduction time between sinus node discharge and atrial depolarization (denoted by a P wave) can be measured on intracardiac electrograms. Action potentials travel rapidly (1.0-1.5 ms) through the atrial myocardium and generate an atrial contraction. Preferential conduction in specialized bundles of muscle fibers (*the internodal tracts of Bachmann*, *Wenckebach*, and *Thorel*) nearly simultaneously activate the atrial musculature and ensure that the action potential reaches the AV node in a timely fashion. Excitation of the ventricles spreads by means of the AV node and the His-Purkinje system (bundle of His and bundle branches). The impulse travels slowly (0.02–0.05 ms) through the AV node. In contrast, conduction velocity through the Purkinje system is very fast (2.0–4.0 ms). The PR interval includes atrial depolarization, AV nodal conduction, and His-Purkinje activity. Activation of ventricular myocardium (conduction velocity 1.0–2.0 ms) occurs after most of the conduction system is depolarized and is represented by the QRS complex. Ventricular repolarization occurs during the T wave.

The ECG is essentially a voltmeter that measures and records potential differences between pairs of electrodes or leads. Three bipolar leads (I, II, II), three unipolar limb leads (aVR, aVL, aVF), and six precordial leads (V1-V6) record the distribution of the potentials on the frontal and horizontal planes of the heart (see Fig. 5–11). Depolarization and repolarization of the heart results in differences in electrical potential, and the ECG measures these changes in potential over time. The external surface of a depolarized membrane becomes electrically negative relative to quiescent, polarized areas. The direction of the propagated impulse travels from the depolarized to polarized areas. By convention, the direction of the propagation wave toward the positive pole

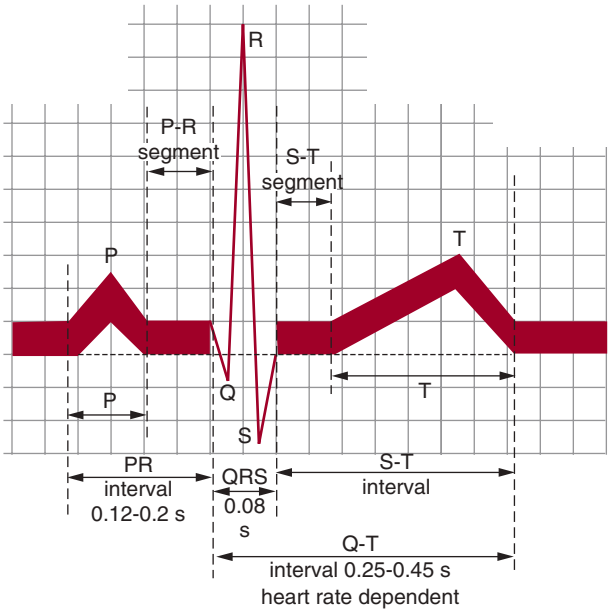

FIGURE 5–11. Nomenclature of the deflections, intervals, and segments of the normal electrocardiogram. Reproduced with permission from Sperelakis N, Banks RO: *Essentials of Physiology*. 2nd ed. Boston: Little, Brown and Company; 1996.

of a bipolar lead system or exploring electrode produces an upright defection and conversely, if the propagation wave is toward the negative pole or away from an exploring electrode, a negative deflection is produced. Depolarization progresses from cell to cell in an orderly fashion from endocardium to epicardium from the apex to base of the heart. In contrast, repolarization does not occur as a propagated wave; nevertheless, it is represented by a single vector that integrates multiple areas of potential difference. Local circuit currents precede the depolarization wavefront, depolarize the adjacent membrane, and bring the membrane to threshold potential; with depolarization, the local circuit currents flow through low-resistance gap junctions (the major component of which is connexin) and depolarize a neighboring cell. Thus, the myocardium functions as a functional syncytium. The ECG is discussed in detail in Chap. 12.

THE CARDIAC CYCLE

The cardiac cycle describes pressure, volume, and flow phenomena in the ventricles as a function of time. This cycle is similar for both the LV and right ventricle (RV), although there are differences in timing stemming from differences in the depolarization sequence and the levels of pressure in the pulmonary and systemic circulations. For simplicity the cardiac cycle for the left heart during one beat will be described (Fig. 5–12).

The QRS complex on the surface ECG represents ventricular depolarization. Contraction (*systole*) begins after an approximately 50-ms delay and results in closure of the mitral valve. The LV contracts isovolumetrically until the ventricular pressure exceeds the systemic pressure; at this time, the aortic valve opens and ventricular ejection occurs. Bulging of the mitral valve into the left atrium during isovolumic contraction causes a slight increase in left atrial pressure (*c* wave). Shortly after ejection begins, the active state declines, and ventricular pressure begins to decrease. Left atrial pressure rises during ventricular systole (*v* wave) as blood returns to the left atrium by means of the pulmonary

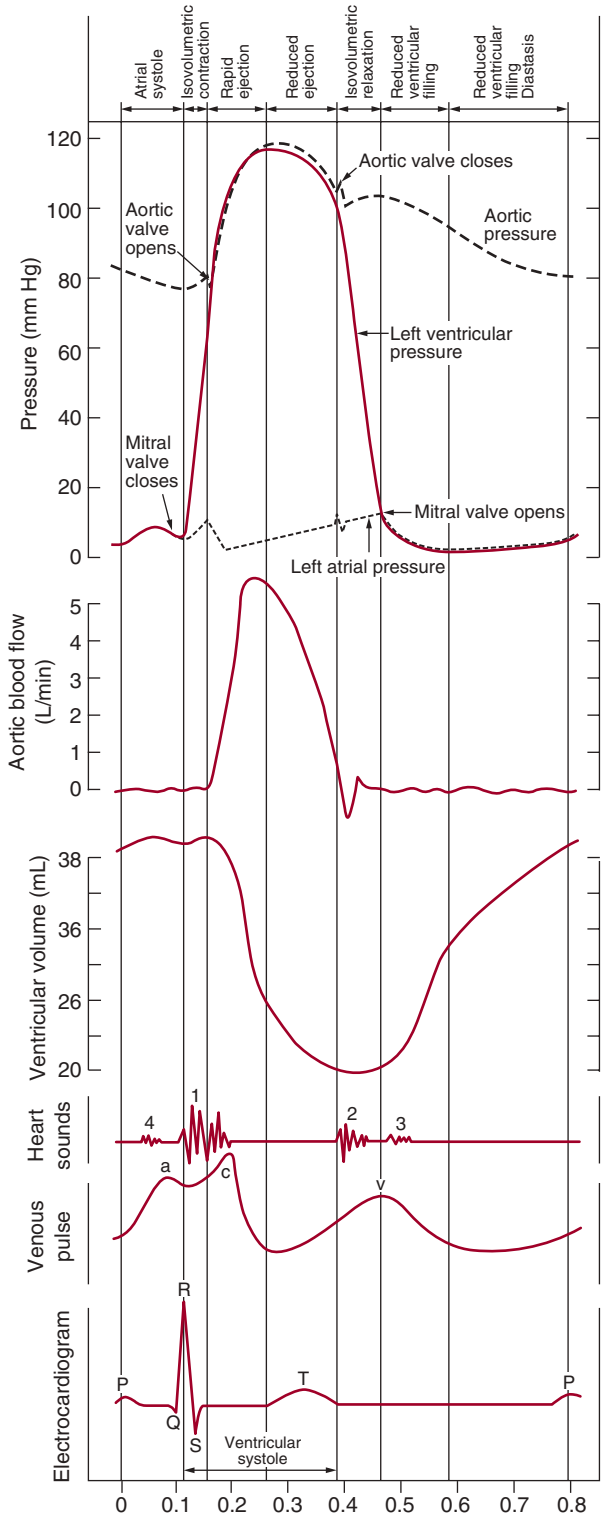

FIGURE 5–12. Pressure, flow, volume, electrocardiographic and phonocardiographic events constituting the cardiac cycle. Reproduced with permission from Berne RM, Levy MN: *Physiology*, 2nd ed. St. Louis: Mosby; 1988.

veins. The aortic valve closes when LV pressure falls below aortic pressure; momentum briefly maintains forward flow despite greater aortic than LV pressure. Ventricular pressure then declines exponentially during isovolumic relaxation when both the aortic and mitral valves are closed. This begins ventricular diastole. When ventricular pressure

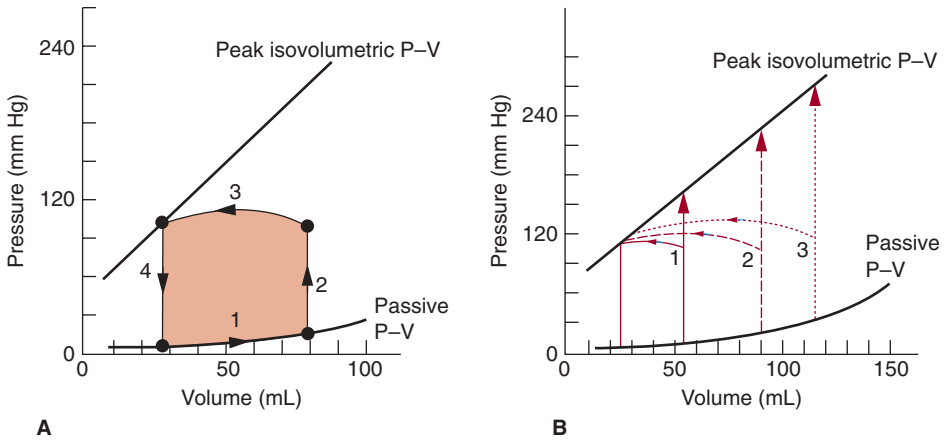

FIGURE 5–13. A. Left ventricular pressure–volume (P–V) loop, the segments of which correspond to events of the cardiac cycle: diastolic ventricular filling along the passive P–V curve (phase I), isovolumetric contraction (phase II), ventricular ejection (phase III), and isovolumetric relaxation (phase IV). **B.** The ventricle ejects to an end-systolic volume determined by the peak isovolumetric P–V line; an isovolumetric contraction (*large arrowheads*) from varying end-diastolic volumes (preload). Reproduced with permission from Sperelakis N, Banks RO: *Essentials of Physiology*. 2nd ed. Boston: Little, Brown and Company; 1996.

declines below left atrial pressure, the mitral valve opens, and ventricular filling begins. Initially, ventricular filling is very rapid because of the relatively large pressure gradient between the atrium and ventricle. Ventricular pressure continues to decrease after mitral valve opening because of continued ventricular relaxation; its subsequent increase (and the decrease in atrial pressure) slows ventricular filling. Especially at low end-systolic volumes, ventricular early rapid filling can be facilitated by ventricular suction produced by elastic recoil. Ventricular filling slows during diastasis when atrial and ventricular pressures and volumes increase very gradually. Atrial depolarization is followed by atrial contraction; increased atrial pressure (*a* wave); and a second, late rapid-filling phase. A subsequent ventricular depolarization completes the cycle.

Valve closure and rapid-filling phases are audible with a stethoscope placed on the chest and can be recorded phonocardiographically after electronic amplification. The first heart sound, resulting from cardiohemic vibrations with closure of the AV (mitral, tricuspid) valves, heralds ventricular systole. The second heart sound, which is shorter and composed of higher frequencies than the first, is associated with closure of the semilunar valves (aortic and pulmonic) at the end of ventricular ejection. Third and fourth heart sounds are low-frequency vibrations caused by early, rapid filling and late diastolic atrial contractile filling, respectively. These sounds can be heard in normal children, but in adults usually indicate disease.

An alternative time-independent representation of the cardiac cycle is obtained by plotting instantaneous ventricular pressure and volume (Fig. 5–13). During ventricular filling, pressure and volume increase nonlinearly (phase I). The instantaneous slope of the P–V curve during filling (dP/dV) is diastolic stiffness, and its inverse (dV/dP) is compliance. Thus, as chamber volume increases, the ventricle becomes stiffer. In a normal ventricle, *operative* compliance is high because the ventricle operates on the flat portion of its diastolic P–V curve. During isovolumic contraction (phase II), pressure increases and volume remains constant. During ejection (phase III), pressure rises and falls until the minimum ventricular size is attained. The maximum ratio of pressure to volume (maximal active chamber stiffness or elastance) usually occurs at the end of ejection. Isovolumic relaxation follows (phase IV), and when LV pressure falls below left atrial pressure, ventricular filling begins. Thus, end-diastole is at the lower right hand corner of the loop, and end-systole is at the upper left corner of the loop. LV P–V diagrams illustrate the effects of changing preload, afterload, and inotropic state in the intact ventricle (see the following).

A P–V loop can also be described for atrial events. During ventricular ejection, descent of the ventricular base lowers atrial pressure and thus assists in atrial filling. Filling of the atria from the veins results in a *v* wave on the atrial and venous pressure tracing. When the mitral and tricuspid valves open, blood stored in the atria empties into the ventricles. Atrial contraction, denoted by an *a* wave on the atrial pressure tracing, actively assists ventricular filling. The resultant atrial P–V diagram has a figure-of-eight configuration with a clockwise V loop, representing passive filling and emptying of the atria, and a counterclockwise A loop, representing active atrial contraction. Thus, the atria function as a reservoir, a conduit for venous flow (during ventricular systole and diastole, respectively), and a booster pump for ventricular filling late in diastole.[39]

PRESSURE–VOLUME RELATIONSHIPS IN THE ISOLATED HEART

Isolated, perfused, isovolumically contracting hearts are useful preparations to study preload dependency of ventricular performance (the Frank-Starling relation) and fully relaxed, end-diastolic P–V relationships without the confounding, uncontrolled changes in either neurohumoral activation or coronary perfusion. These preparations are especially well-suited for quantifying end-systolic elastance (stiffness), a relatively load-independent index of ventricular function. The time-varying elastance model of ventricular contraction is based on the experimental observations in which ventricular volume and loading are altered under conditions of unvarying contractility (Fig. 5–14). At any time, *t*, following the onset of contraction, the relation between pressure (P) and volume (V) is linear according to the relation: $P(t) = E(t) - [V(t) - V_0]$, where

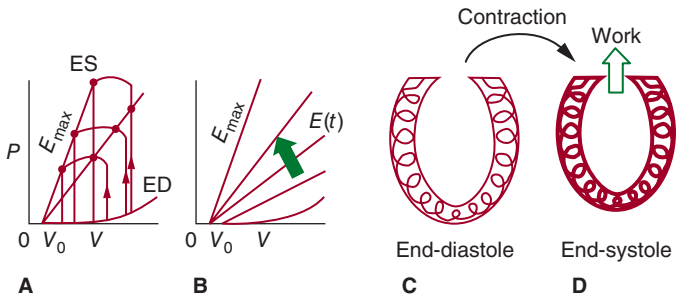

FIGURE 5–14. The time-varying elastance concept. **A.** A series of variably loaded pressure–volume areas (PVAs). The relationship between pressure and volume at any time, *t*, during variably loaded contractions under constant contractility conditions is linear and reaches a maximum value at end-systole. *Filled circles* connected by *straight lines* occur at the same time, *t*, during contraction. E_{max} is the line connecting the points at end-systole (ES). **B.** Elastance, $E(t)$ increases at each time, *t*, during contraction until it reaches maximal values at ES. Increasing contractility increases the slope at any time, *t*, including ES (E_{max}). **C,D.** The concept that the ventricle behaves as an elastic *spring* with a stiffness (elastance) that increases during systole and decreases during diastole (EES or E_{max}). D, diastole; P, pressure; S, systole; V, volume; V_0, dead volume. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: *Hurst's The Heart*. 11th ed. New York: McGraw-Hill; 2004.

E is the time-varying elastance and V_0 is the volume at zero pressure or dead volume; this relation becomes progressively steeper until it reaches a maximum at end-systole. Thus, the ventricle behaves like a spring with a stiffness (elastance) that increases during contraction and decreases during relaxation. The slope of the end-systolic P–V relationship, end-systolic elastance (Ees) changes directly as a function of acute changes in contractility without a change in dead volume (V_0). Appropriate changes in Ees are also observed with increases in beating frequency (eg, force–frequency relationships).

The elastance concept has been extended to the study of ventricular mechanoenergetics by proposing that the P–V area (PVA) bounded by the LV P–V loop is a measure of the total mechanical energy of LV contraction.[40,41] The PVA concept is shown schematically in Fig. 5–15. The total mechanical energy of contraction can be considered to consist of two components: (1) external work, the area enclosed within the P–V loop; and (2) potential energy stored in the ventricular *spring* at ES: that is, the area between the end-systolic pressure relation on the left and the end-diastolic P–V relation on the right.

The myocardial oxygen consumption (MVO_2)–PVA relationship is obtained by measuring P–V area loops and LV MVO_2 at several steady-states. There is a highly linear correlation ($r > .98$) between LV VO_2/beat and PVA/beat over a wide range of experimental conditions

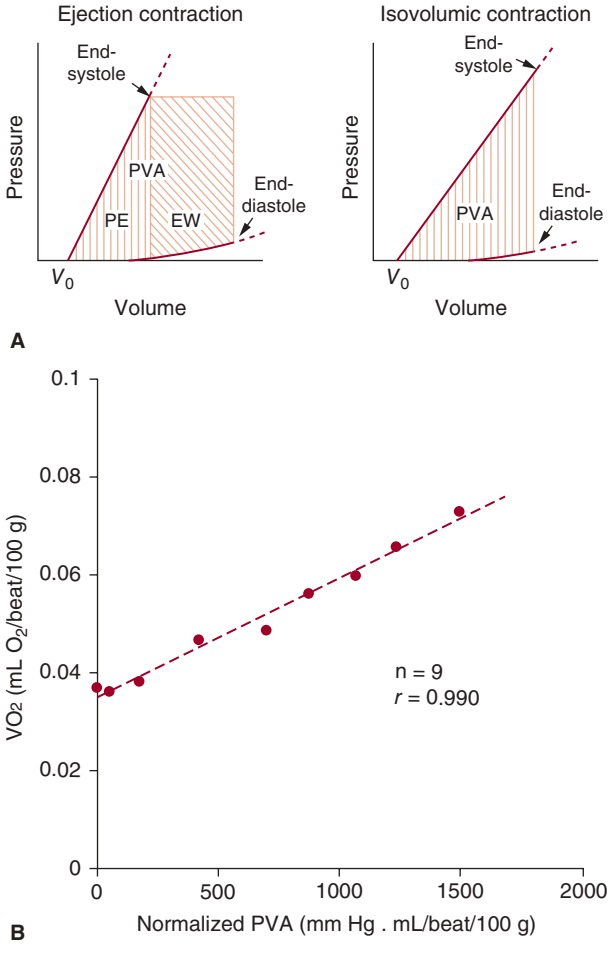

FIGURE 5–15. **A.** Schematic of the VO_2–PVA (pressure–volume area) concept. In ejecting contractions, PVA = EW + PE; in isovolumic contraction, PVA = PE only. **B.** Correlation of PVA with VO_2. P–V, pressure– volume; VO_2, oxygen consumption. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: *Hurst's The Heart*. 11th ed. New York: McGraw-Hill; 2004.

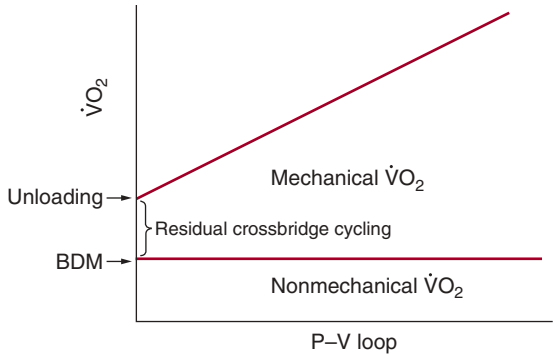

FIGURE 5–16. Schematic of the relationship between VO_2/beat and the pressure–volume area (PVA). The diagonal VO_2–PVA line is obtained by mechanical unloading of the ventricle; the *y* intercept is the unloaded VO_2. Mechanically unloaded VO_2 is subdivided into VO_2 for residual cross-bridge cycling and that for nonmechanical VO_2 (BDM, which inhibits cross-bridge cycling). The latter consists of VO_2 for excitation–contraction (E–C) coupling and basal metabolism. P–V, pressure–volume; VO_2, oxygen consumption. Reproduced with permission from LeWinter MM, Suga H, Watkins MW: *Cardiac Energetics: From Emax to Pressure-Volume Area*. Norwell: Kluwer Academic Publishers; 1995.

(see Fig. 5–15, bottom), indicating the accuracy of the PVA as a measure of total mechanical energy. The VO_2 intercept of the VO_2–PVA relationship is the unloaded VO_2 (PVA–independent VO_2), which in an isovolumically contracting heart, corresponds to a point at which LV peak pressure is 0 mm Hg (Fig. 5–16). At this point, except for a low level of cross-bridge cycling caused by shape changes, there is neither mechanical energy produced nor energy expended for cross-bridge cycling.[41] The VO_2 under unloaded conditions reflects energy used for E–C coupling and basal metabolism; the latter can be eliminated experimentally by arresting the heart. In this manner, changes in E–C coupling energy consumption have been detected as shifts in the unloaded VO_2. Oxygen consumption used by the contractile apparatus for cross-bridge cycling is PVA-dependent VO_2, which increases linearly and directly with PVA. Because PVA-dependent VO_2 is the energy input and the PVA is the total energy output of the contractile machinery, the inverse slope of the VO_2–PVA relationship is a dimensionless measure of the thermodynamic efficiency of the contractile machinery. Unlike efficiency expressed as the external work/total VO_2, efficiency expressed by the VO_2–PVA relationship is relatively insensitive to load. The VO_2–PVA relationship is sensitive to metabolic changes and impacts the efficiency of ATP production.

DETERMINANTS OF LEFT VENTRICULAR FUNCTION

Measures of Ventricular Performance

Measures of overall ventricular performance typically include cardiac output (the quantity of blood delivered to the circulation, calculated as the stroke volume and heart rate), stroke volume (quantity of blood ejected/beat, which equals the ventricular end-diastolic volume minus the end-systolic volume), and stroke work (the product of pressure and stroke volume, which equals the area bounded by the ventricular PVA and which can be approximated in the clinical setting as ([Mean LV systolic – Diastolic pressure] × Stroke volume × 0.0136). Cardiac output responds to changes in the oxygen requirements of tissues, for example, as occurs with exercise. The extraction of nutrients by tissue can be expressed as the arteriovenous difference across the tissue. According to the Fick principle, the consumption of a particular nutrient (eg, oxygen) by a tissue equals the rate of delivery of that nutrient: that is, the cardiac

output times the arteriovenous difference of that nutrient. Changes in cardiac output necessary to meet the metabolic needs of the tissues can be produced by changes in the stroke volume, heart rate, or both. Changes in stroke volume are mediated by altered loading conditions, inotropic state, and heart rate. Thus, factors that influence the strength of contraction in isolated muscle are the same factors that determine cardiac output. The stroke volume expressed as a function of the end-diastolic volume is the ejection fraction (EF). Thus, EF = (End-diastolic volume – End-systolic volume)/End-diastolic volume.

Preload The influence of preload on measures of ventricular performance defines the LV function curve, known as the *Frank-Starling curve.*[42,43] Increasing LV end-diastolic volume increases stroke volume in ejecting beats and increases peak LV pressure in isovolumic beats. The modulation of ventricular performance by changes in preload, termed *heterometric regulation,* operates on a beat-by-beat basis and is responsible for matching outputs of the right and LVs, as with changes in posture and breathing. The Frank-Starling curve also represents an important compensatory mechanism that maintains LV stroke volume (vis-à-vis increasing LV end-diastolic volume) when LV shortening is impaired, owing either to myocardial contractile dysfunction or to excessive afterload. The atria also exhibit a Frank-Starling curve that becomes clinically important during exercise and when there is resistance to early diastolic LV filling.

Because a representative fiber length (ie, preload) is difficult to determine in the LV, changes in the myocardial fiber length are estimated from changes in either the LV end-diastolic volume or LV end-diastolic pressure. In the clinical setting, end-diastolic pressure and pulmonary capillary wedge pressure are used frequently as measures of preload. However, the passive P–V relationship, analogous to the passive length–tension curve in isolated muscle, is not linear but exponential. Thus, the ratio of change in LV pressure to volume is greater at higher than at lower LV volumes. Not surprisingly, under certain circumstances, ventricular pressure can inaccurately reflect the ventricular volume. Moreover, changes in ventricular volume can erroneously be inferred from changes in cardiac pressures, which can result only from alterations in ventricular compliance. For example, whereas chronic volume overload can shift the ventricular diastolic pressure relationship rightward so that volume is increased at a normal end-diastolic pressure, chronic pressure overload can shift the diastolic P–V relationship leftward and for the same end-diastolic pressure result in a smaller ventricular volume. Compliance of the LV is affected by pericardial pressure, RV pressure and volume, and coronary artery perfusion (*turgor*) in addition to changes in the intrinsic elastic properties of the LV.

Afterload Afterload in the intact heart can be considered as the tension in the LV wall that resists ventricular ejection (wall stress during systole) or as the arterial input impedance (the ratio of instantaneous change in pressure to instantaneous change in flow). Although forces within the ventricular wall are difficult to measure, initial estimates of systolic wall stress can be derived from application of the Laplace relationship in which wall tension = $(P \cdot r)/2\,h$, where P refers to pressure, r to ventricular radius, and h to wall thickness. More complex derivations based on various geometric assumptions are used to calculate end-systolic wall stress. Input impedance is a complex function of arterial pressures, elasticity, vessel dimension, and blood viscosity, which requires measurement of instantaneous aortic pressure and flow and is therefore impractical to measure in the clinical setting. Because of its simplicity, aortic pressure is often used as a surrogate for afterload. An increase in afterload causes a decrease in stroke volume and the velocity of LV shortening. The resulting stress–shortening and stress–velocity curves are analogous to those obtained from variably afterloaded isotonic contractions in isolated muscle.

Inotropic State The ideal method of measuring the inotropic state in the intact LV should incorporate the variables of force, length, velocity, and time; be independent of external loading conditions; and relate to physicochemical processes at the sarcomeric level. Because of these constraints, changes in inotropic state are usually defined operationally by shifts of the various ventricular function curves, which, by definition, are independent of loading conditions. For example, a drug with positive inotropic activity (eg, dobutamine) shifts the Frank-Starling curve (analogous to the length–shortening curve in papillary muscle preparations) upward and to the left, and changes in the stress–shortening relationship (analogous to the force–velocity curve) upward and to the right.

The rate of pressure development in the LV during isovolumic systole (dP/dt) is used frequently as an index of the inotropic state. Although LV + dP/dt_{max} provides a measure of the rate of tension development and of myocardial contractility, this index is preload dependent, caused in part by length-dependent changes in myofilament Ca^{2+} sensitivity. However, LV + dP/dt_{max} is largely independent of afterload, provided that the maximum rate of increase occurs before aortic valve opening. Although changes in the maximal rate of increase of ventricular pressure are highly sensitive to acute changes in contractility and are useful to assess directional changes in inotropic state, absolute dP/dt_{max} is not as useful for assessment of basal contractility as are the ejection phase indices, such as LVEF (stroke volume/end-diastolic volume ×100). Furthermore, dP/dt_{max} cannot be corrected for changes in muscle mass produced by LV hypertrophy, in which case it is best to compare peak stress, which incorporates pressure, volume, mass, and geometry. Because of the direct influence of preload on dP/dt—dP/dt at a common developed pressure (LV systolic minus diastolic pressure) and the slope of the dP/dt end-diastolic volume curve (preload recruitable stroke work; see the following) have been proposed as preload independent indices of the inotropic state.[40]

End-systolic P–V points from ejecting beats obtained from variably preloaded or afterloaded contraction fall reasonably close to the isovolumetric P–V line for a given inotropic state (vide supra). Thus, changes in the inotropic state, independent of the loading conditions can be identified by changes in the slope of the end-systolic P–V relationship (Ees). By acutely altering loading conditions (eg, transient vena caval occlusions or phenylephrine boluses), a family of PVAs is obtained (single-beat methods designed for clinical use have been proposed). End-systole can be defined as end ejection or as the time of maximal elastance (the maximal P–V ratio) during systole. In the normal heart, these two points are closely related in time. In practice, the end-systolic P–V relationship (ESPVR) is constructed by connecting the end-systolic points of each loop; the relationship is relatively linear and defines the properties of the chamber when maximally activated.[40]

However, Ees does have a modest degree of load dependence, likely caused by the load dependence of activation. Moreover, the *linear* ESPVR is really curvilinear, particularly at the extremes of the contractile state. The effects of nonlinearity are particularly important when the P–V relationship is acquired over a narrow range of pressures and volume. A single slope in the latter instance will not uniquely characterize the ESPVR and therefore the contractile state. In addition, the extrapolated V_0 is unlikely to represent dead volume. Finally, V_0 is not entirely independent of inotropic state. Thus, more than Ees is needed to compare two contractile states; interpretation must take into account V_0, and analysis of covariance, or a multiple linear regression analysis with dummy variables is desirable.[40]

Other considerations for the use of P–V relations to characterize contractility are (1) specialized and invasive instruments are necessary for its measurement; (2) methods used to alter load should be free of

inotropic effects; (3) because changes in autonomic tone and heart rate can complicate analysis, loading changes should be as rapid as possible; (4) arrhythmias may occur and complicate the analysis; (5) changes in coronary perfusion pressure that can alter the P–V relationship occur with changes in load; and (6) changes in mass and geometry of the ventricle make changes in the ESPVR ambiguous. In addition to Ees, preload recruitable stroke work (slope of the end-diastolic volume–stroke work relationship) and the slope of the end-diastolic volume–dP/dt_{max} relationship are derived as indices of contractility from P–V analysis. Each of these approaches is linear and afterload independent. Preload recruitable stroke work is independent of heart size, and the slope of the end-diastolic volume–dP/dt_{max} is more sensitive to inotropic state than is Ees.[40]

Heart Rate Heart rate is normally determined by the interplay between the intrinsic automaticity of the SA node and the activity of the autonomic nervous system. Increasing heart rate causes a small but measurable increase in the inotropic state through the force–frequency relationship. In addition, heart rate is a major determinant of cardiac output. However in a normal heart, pacing between heart rates of 60 and 160 beats/min has little effect on cardiac output because the diminished diastolic filling time offsets the modest increase in inotropic state.

DIASTOLE AND DIASTOLIC FUNCTION

Diastole is the summation of processes by which the heart keeps latent its ability to generate force and shorten, and returns to its precontractile state. Diastolic properties of the ventricle are complex and multifactorially determined and are related to the speed and synchrony of myocardial relaxation and inactivation, loading conditions, viscoelasticity, heart rate, atrial function, and ventricular interaction. Diastole occurs in a series of energy-consuming steps beginning with release of calcium from TnC, detachment of actin–myosin cross-bridges, SERCA2a-induced calcium sequestration into the SR, NCX-induced extrusion of calcium from the cytoplasm, and return of the sarcomere to its resting length. Adequate ATP must be present for these processes to occur at a sufficient rate and extent.

The P–V relationship during early diastole reflects the lusitropic (relaxation) state of the heart, analogous to the inotropic (contraction) state measured during systole. The rate of LV relaxation can be estimated from the maximal rate of pressure decay ($-dP/dt_{max}$) and indices (eg, relaxation half-time [$RT_{1/2}$]) that are related to the time necessary for ventricular relaxation, but these measurements are highly dependent on the prevailing load of the intact circulation. In contrast, τ, the time constant of LV relaxation during isovolumic relaxation, provides a more accurate, less load-dependent measure of relaxation; τ is shortened by β-adrenergic stimulation (cyclase-dependent phosphorylation of phospholamban and TnI) and prolonged with β-adrenergic antagonists.[44] Although several mathematical models of the exponential decay of LV pressure exist, a simple monoexponential model that declines to zero is frequently used: $P(t) = P_o e - t/\tau$ where $P(t)$ is the LV pressure at any time, t; τ is the relaxation constant; P_o is the LV pressure at the onset of relaxation; and e is the base of the natural logarithm. The natural logarithmic transformation of both sides of the equation yields $lnP = -1/T + ln\ P_o$. Thus, τ is derived by obtaining the negative of the reciprocal of the slope of $lnP\ (t)$ versus time, t, from aortic valve closure to mitral valve opening (isovolumic relaxation). High-fidelity catheter tip micromanometers are necessary for accurate measurement of $-dP/dt_{max}$ and τ.

In addition to relaxation, the passive viscoelasticity of the ventricle, dependent both on intracellular and extracellular structures, is a major determinant of diastolic function. During contraction, cytoskeletal proteins such as titin and microtubules are deformed by actin–myosin cross-bridge cycling and sarcomere contraction, which act like viscoelastic springs during diastole.[45] This reclaimed potential energy constitutes a recoiling force that helps restore the myocardium to its resting configuration. In addition, ECM proteins such as collagen contribute to the establishment of resting force and length.

Chamber stiffness is quantified from the relationship between diastolic LV pressure and volume. LV diastolic pressure can be changed either by a volume-dependent change in operating stiffness (equal to the slope of a tangent drawn to the P–V curve at any point) or by a volume-independent change in the overall chamber stiffness because of a change in properties either intrinsic (eg, hypertrophy) or extrinsic (eg, pericardial) to the ventricle (Fig. 5–17, Table 5–1). Operating stiffness

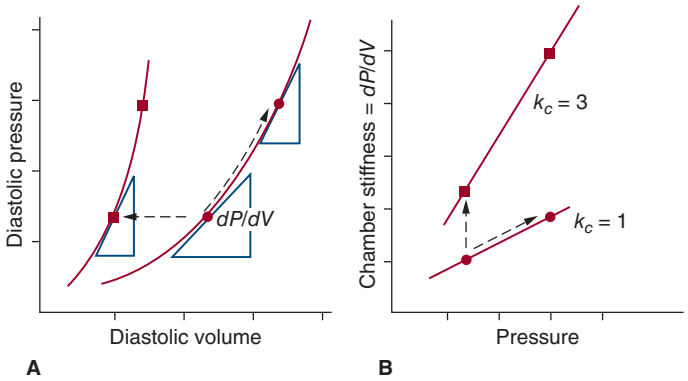

FIGURE 5–17. A. End-diastolic pressure–volume relationship (EDPVR) in two ventricles with differing passive diastolic properties. Chamber stiffness is dP/dV at any point on the EDPVR. The stiffer chamber on the left has a steeper overall slope. **B.** The same data plotted as pressure versus chamber stiffness. Because of the exponential nature of EDPVR, the relation between chamber stiffness and pressure is a straight line whose slope is the chamber stiffness constant (k_c) that characterizes the overall slope of the EDPVR. A similar relationship holds for stress and strain. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: *Hurst's The Heart*. 11th ed. New York: McGraw-Hill; 2004.

TABLE 5–1. Factors Influencing Left Ventricular Chamber Stiffness

Physical properties of the LV
LV chamber volume and mass
Composition of the LV wall
Viscosity, stress relaxation, and creep
Intrinsic factors
Myocardial relaxation
Coronary turgor
Extrinsic factors
Pericardial restraint
RV interaction
Atrial contraction
Pleural and mediastinal pressure

LV, left ventricle/ular; RV, right ventricle/ular.

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changes throughout filling, such that stiffness (*dP/dV*) is less at smaller volumes and greater at larger volumes. Because the diastolic P–V relationship is generally exponential, the relationship between *dP/dV* and pressure is linear. The slope of this relationship is called the *modulus of chamber stiffness* (k_c) and has been used to quantitate chamber stiffness. Thus, when chamber stiffness is increased, the P–V curve shifts to the left, the slope of the *dP/dt* versus pressure relationship becomes steeper, and k_c is increased.

Diastolic chamber stiffness, similar to the systolic chamber stiffness index, Ees, is dependent on both material (myocardial) stiffness and ventricular chamber characteristics (eg, volume, mass). Myocardial stiffness is quantified from the relationship between diastolic LV wall stress (ε) and strain (σ). Strain is the deformation of the muscle produced by an applied force and is expressed as the percent change in length from the unstressed length. At any given strain throughout diastole, myocardial stiffness is equal to the slope ($d\sigma/d\varepsilon$) of a tangent drawn to the stress–strain curve at that strain. Because the stress–strain relationship is generally exponential, the relationship between ($d\sigma/d\varepsilon$) and stress is linear. The slope of this relationship is the modulus of myocardial stiffness (K_m) and has been used to quantitate myocardial stiffness. Thus, when myocardial stiffness is increased, the stress–strain relationship shifts to the left, the slope of the ($d\sigma/d\varepsilon$) versus stress relationship becomes steeper, and K_m increases.

The end-diastolic P–V relationship (EDPVR) is constructed by connecting the end-diastolic points (lower right hand) of a series of PVAs; the relationship is nonlinear and defines the passive properties of the chamber when it is fully relaxed. The nonlinearity of the EDPVR results from the different types of structural proteins being stretched over the range of pressures and volumes. Thus, at the low end of the relationship, where operative stiffness is low, stiffness is caused by compliant elastin and sarcomeric titin. As volume increases and operative stiffness increases, the slack length of collagen and titin are exceeded, and stretch is resisted. At the other extreme (subphysiologic volumes), negative pressures are required to reduce volume (diastolic suction); however, negative pressures are rarely recorded in vivo, and less stringent criteria to establish the presence of diastolic suction are required. It is important to recall that changes in intrathoracic pressure, pericardial constraint, and ventricular interaction all influence the EDPVR. Analytic limitations similar to the ESPVR are present for the EDPVR; that is, comparisons of EDPVR should account for covariance of the parameters.[40]

A variety of curve fits for EDPVR using nonlinear regression analysis have been proposed, but single value indices of stiffness, such as the stiffness constant, have met with limited success. Chamber stiffness (k_c) and myocardial stiffness (K_m) provide load and chamber size-independent parameters of passive chamber and myocardial properties, respectively; however, when comparing hearts of different sizes, a simple approach is to measure the volume at a specified pressure.[40]

VENTRICULOARTERIAL COUPLING

In isolated muscle, loading conditions represent the force applied to muscle before and after (preload and afterload, respectively) the onset of contraction. In the intact ventricle, preload and afterload are also determined by the volume status of the individual and the characteristics of the arterial and venous circulations (pulmonary and systemic circulations for the RV and LV, respectively). Thus, loading conditions are not only important direct determinants of ventricular performance, but they also function indirectly by coupling the ventricle to the vascular system.

Ventricular contraction transfers blood from the venous to the arterial side of the circulation, and arterial and venous capacitances (the change in volume per change in pressure, *dV/dP*) determine the respective pressures that result from the shift in blood volume. These pressures determine the driving force across the peripheral resistance (where resistance equals pressure gradient for flow divided by the cardiac output) and are primarily responsible for venous return to the heart.

The venous return curve describes the inverse relationship between venous pressure and cardiac output (Fig. 5–18A, B). In contrast to convention, the venous return curve plots the independent variable (cardiac output) on the vertical axis and the dependent variable (venous pressure) on the horizontal axis. The *x*-intercept is the mean circulatory pressure (ie, that pressure in the vascular system in the absence of cardiac pumping). The mean circulatory pressure is a function of the capacitance of the vascular system and the total blood volume. The plateau of the venous return curve and the *y*-intercept represents the maximal obtainable cardiac output as venous pressure is reduced. In the normal heart, cardiac output is limited by venous return, and the operating venous pressure is near the plateau of the venous return curve.

Coupling of the venous system of the heart is graphically represented in Fig. 5–18C. In this analysis, the intersection of the ventricular function (Frank-Starling) curve and the venous return curve represents the steady-state operating values of cardiac output and venous pressure. At this equilibrium point, the ability of the venous system to provide venous return at a given pressure is matched with the ability of the ventricle to pump that venous return when distended to the same pressure.

Increased blood volume and venoconstriction shift the venous function curve upward and to the right, increasing the mean circulatory pressure and the maximal cardiac output (Fig. 5–18D). The venous system contains the major fraction of blood in the vascular system because of the greater capacitance of veins than of arteries. As a result, venoconstriction shifts significant quantities of blood from the peripheral to central circulation. Because arteries contain only a small percentage of the total blood volume, their contractile state does not affect the mean circulatory pressure. Moreover, because venous pressure varies inversely with systemic vascular resistance, arteriolar constriction (increased afterload) shifts the curve downward and to the left without changing the mean circulatory pressure. Conversely, arteriolar dilation shifts the curve upward and to the right. An increased inotropic state shifts the ventricular function curve to the left without significantly altering the venous return curve. Conversely, in chronic heart failure, there is a rightward shift of the ventricular function curve and because of renal salt and water retention, a parallel rightward shift of the vascular function curve. In this way, cardiac output is initially maintained at the expense of increased venous pressure and congestion. If the compensatory mechanisms fail, venous pressure increases further, and cardiac output falls.

Ventriculoarterial coupling can also be expressed in the P–V framework (Fig. 5–19). Arterial properties are represented by effective arterial elastance (*EA*), which incorporates the mean resistance and pulsatile features of the arterial load. *EA* is estimated by *PES/SV*, where *PES* is the end-systolic pressure and *SV* is the stroke volume. The *EA/Ees* ratio has been used as an index of ventriculoarterial coupling and has been shown to be a critical determinant of pump performance and efficiency. With increases in *EA*, stroke work initially increases, reaches a plateau, and then decreases. Maximum stroke work occurs when arterial and ventricular properties are equal (ie, when *EA* = *Ees*). Similar changes with increases in *EA* occurs with ventricular efficiency, defined as external stroke work/MVO_2/beat, and are maximum when

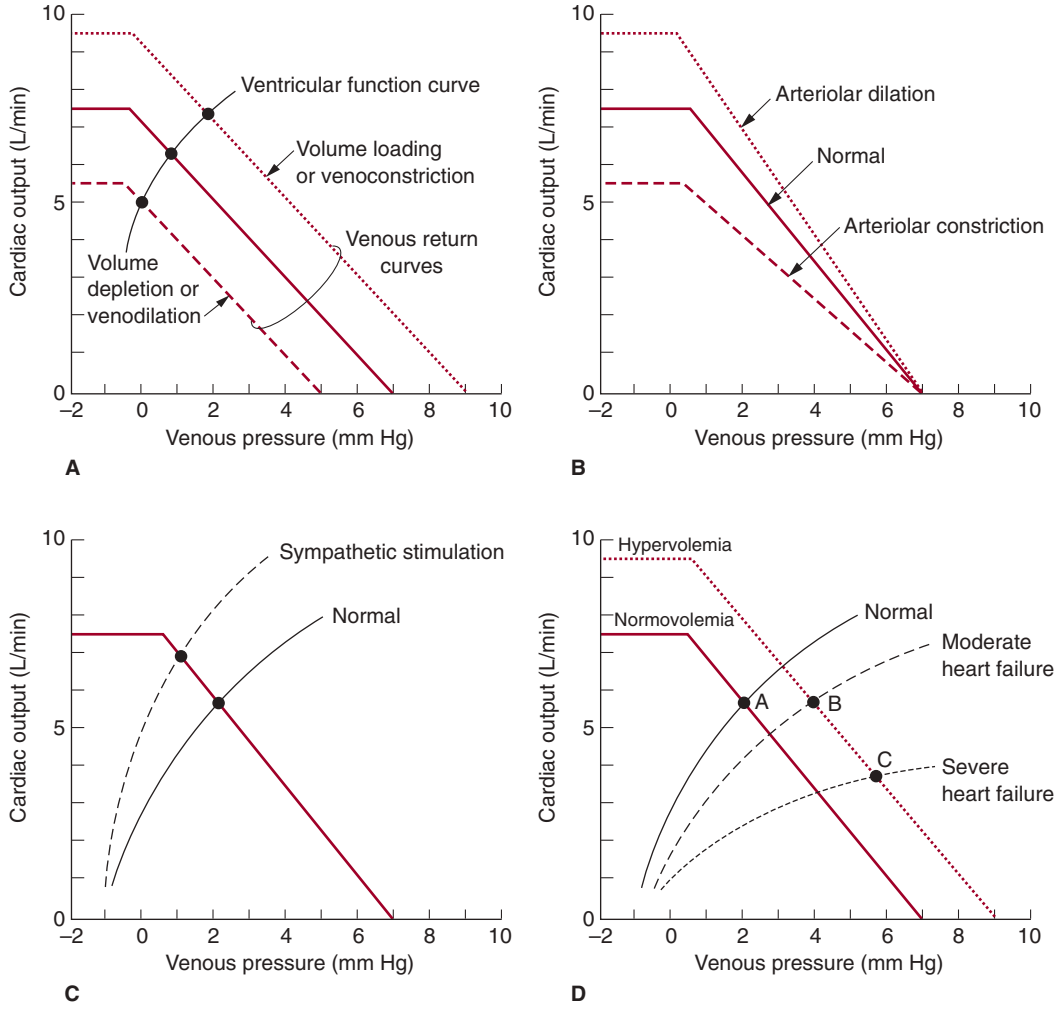


FIGURE 5–18. Venous pressure–cardiac output curves. The equilibrium point is defined by the intersection of the ventricular function curve with the venous return curve. **A.** Volume loading and venoconstriction shift the venous return curves to the right, resulting in an equilibrium point with a higher cardiac output and higher mean circulatory pressure. Volume depletion and venodilation shift the curve to the left, resulting in an equilibrium point with a lower cardiac output and a smaller mean circulatory pressure. **B.** The effects of arteriolar constriction and dilation on the venous return curves are more complex. At **B** (moderate heart failure), cardiac output is preserved at the expense of venous pressure. **C.** Sympathetic nerve stimulation causes a leftward shift of the ventricular function curve, resulting in an equilibrium point with a lower venous pressure and higher cardiac output. At **C** (severe heart failure), cardiac output is decreased and venous pressure further increased. **D.** Chronic heart failure causes rightward shifts of both the ventricular function and venous return curves. Reproduced with permission from Berne RM, Levy MN: *Physiology*, 2nd ed. St. Louis: Mosby; 1988.

$EA = Ees/2$. Therefore, in this conceptual framework, energetically optimal ventriculoarterial coupling exists when the EA/Ees ratio ranges from 0.5 to 1.0.

HEMODYNAMICS

CARDIAC OUTPUT AND BLOOD FLOW

Cardiac output is determined by a relationship analogous to Ohm's law governing current, voltage, and resistance—that is, cardiac output (Q) increases with an increase in the pressure gradient ($P_1 - P_2$) generated by the heart or a decrease in the resistance (R) according to the relationship $Q = (P_1 - P_2)/R$. The normal cardiac output at rest is approximately 5 to 6 L/min and can increase approximately five-fold during strenuous exercise (see Fig. 5–19A). The relative distribution of the cardiac output changes dramatically with exercise, such that blood flow to the skin and skeletal muscle increases to constitute as much as 85% of the cardiac output; blood flow to the heart increases three- to five-fold; and the brain receives the same amount as it does at rest, and the renal and splanchnic circulations receive about half of their basal flow. Physical factors, metabolic products, and peptides that operate through autocrine (regulation of cell function by the producing cell), paracrine (regulation of neighboring cells by the producing cell), or endocrine (regulation of distant cells by the producing cell) mechanisms and neural regulation control the relative distribution of regional blood flow.

Blood flow refers to the bulk flow of fluid in the circulation. Blood flow velocity refers to the speed with which blood moves along the circulation in any particular segment and is related directly to blood flow and inversely to cross-sectional area. Thus, blood flow velocity is greatest in the aorta and least in the capillary beds (Fig. 5–20). In the normal circulation, blood flows predominantly in a streamline or laminar pattern. Friction between the blood vessel wall and adjacent blood flow causes blood flow velocity to approach zero next to the wall; centerline velocities are the highest. Shear stresses between adjacent concentric layers of blood cause blood to flow in a laminar pattern resembling a parabola in much of the circulation. The laminar

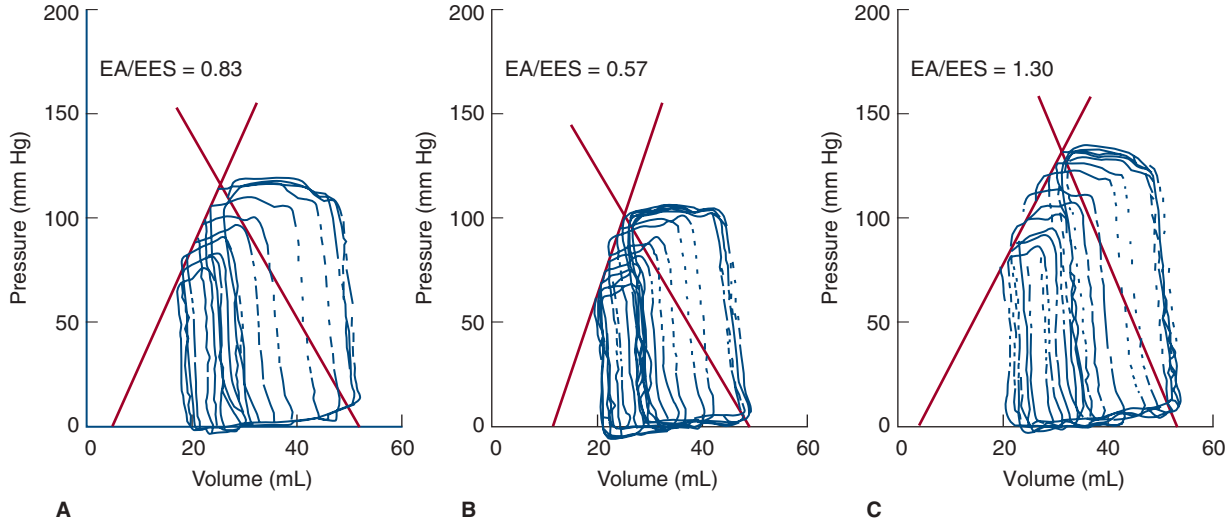


FIGURE 5–19. Ventriculoarterial coupling using the arterial elastance-LV end-systolic relation (EA/EES). **A.** Baseline. **B.** Nitroprusside increases EES with little change in EA, resulting in a decrease in EA/EES. **C.** Angiotensin II increases EA without a change in EES, resulting in an increase in EA/EES. LV, left ventricular. Reproduced with permission from LeWinter MM, Suga H, Watkins MW: *Cardiac Energetics: From Emax to Pressure-Volume Area*. Norwell: Kluwer Academic Publishers; 1995.

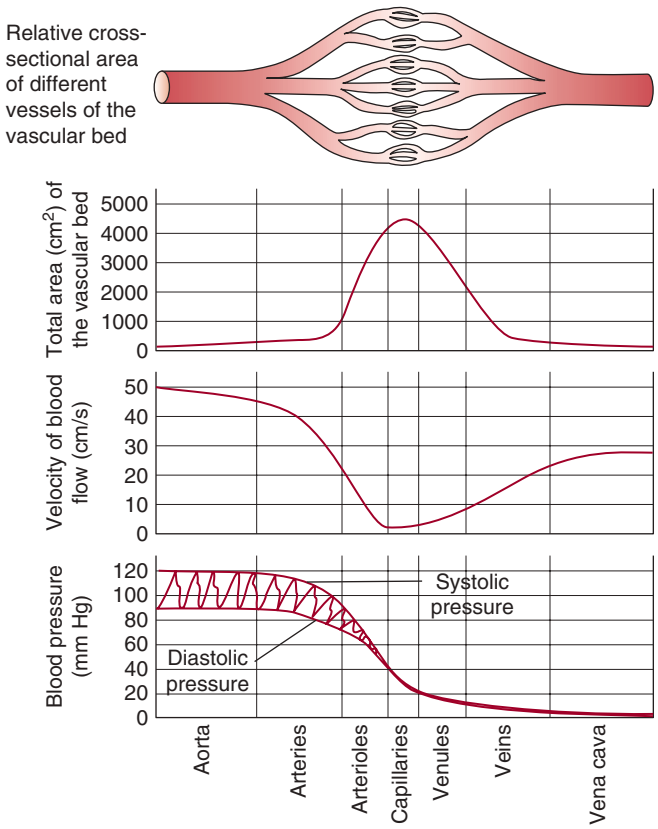


FIGURE 5–20. Relationships between total cross-sectional area of the vascular bed, velocity of blood flow, and blood pressure in various vessels in the systemic circulation. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: *Hurst's The Heart*. 11th ed. New York: McGraw-Hill; 2004.

pattern of blood flow is interrupted and converted to a turbulent flow pattern in the ventricles, at bifurcations in the circulation, and when there is an abrupt change in vessel diameter (eg, from atherosclerosis), which causes blood flow to increase above a critical, dimensionless value (related to cross-sectional area, mean velocity of flow, and kinematic viscosity of the fluid) called the *Reynolds number*.

PRESSURE

As blood courses through the large arteries, systolic pressure increases slightly, and diastolic pressure decreases. Because the decrease in diastolic pressure is greater than the increase in systolic pressure, the pulse pressure (systolic-diastolic) increases gradually, and mean arterial blood pressure (⅓ systolic pressure + ⅔ diastolic pressure) decreases in the systemic arteries as the distance from the heart increases. The arterioles provide the greatest resistance to blood flow in the circulation. Consequently, absolute blood pressure decreases by the greatest amount in the arterioles; in addition, the oscillations of blood pressure are abolished in the arteriolar portion of the systemic circulation. Blood enters the capillaries of the systemic circulation with pressures of approximately 35 mm Hg. As blood flows though the capillaries, the blood pressure decreases to approximately 20 mm Hg, and in the venules, it decreases to approximately 5 mm Hg. Blood pressure decreases further in the large veins and vena cava, so blood returns to the right atrium with an absolute pressure nearly equal to the atmospheric pressure. The RV generates lower pressures than the left (0-30 mm Hg vs 3-120 mm Hg). Similar to the systemic circulation, the arterioles exert the greatest resistance to blood flow; however, pulmonary arterioles do not completely dampen the pressure pulses.

Transformation of the ventricular pressure pulse, with its intermittent flow and large pressure changes, into the peripheral pulse, with its continuous flow and smaller pressure changes is caused by the initial transfer of kinetic to potential energy in the aorta in systole and subsequent reclamation of this stored energy in diastole. The arterial pulse is altered by several factors, including heart rate (increased diastolic pressure with increased heart rate), stroke volume (systolic and pulse pressure increase with increased stroke volume), aortic valve function (increased pulse pressure and decreased diastolic pressure with aortic insufficiency, decreased pulse pressure and a slow rate of increase of pressure with aortic stenosis), arterial compliance (increased pulse pressure and peaked waveform with decreased compliance), and transmission of the pressure wave through the arterial circulation. The latter results from waves reflected at branch points, changes in arterial

compliance, and differential transmission between the high-frequency and low-frequency components of the arterial pressure waveform.

RESISTANCE

Total peripheral vascular resistance is the sum of all regional resistances in the systemic circulation that must be overcome by the ejecting LV. This is calculated as Mean aortic—Mean right atrial pressure/Cardiac output for the systemic circulation and as Pulmonary arterial pressure—Pulmonary venous pressure)/Cardiac output for the pulmonary circulation. However, the circulation is composed of a number of circuits (eg, coronary, skeletal, and splanchnic) arranged in series as well as in parallel. Each circuit provides resistance to blood flow, and the type of circuit determines its contribution to total peripheral resistance. For a circuit that has resistances arranged in series, the total resistance is equal to the sum of component resistances. For resistances connected in parallel, the reciprocal of the total resistance is equal to the sum of the reciprocals of the component resistances. Resistances connected in parallel are more efficient than resistances connected in series because the heart does not have to generate a large driving pressure to perfuse multiple beds. In addition, because arterial pressure is maintained within narrow limits, a marked change in the resistance of one circuit changes only slightly blood flow to other circuits. Thus, when one circuit is eliminated, total resistance and arterial blood pressure increase immediately; the increase is sensed by baroreceptors that mediate changes that cause pressure to return to its original value, maintaining blood flow to other areas of the circulation relatively constant (Fig. 5–21). Although less efficient, series resistance units are sometimes necessary (eg, the portal venous connection between the gastrointestinal tract and liver).

Several factors influence resistance (R) to blood flow. The most important factor is the vessel radius (r), such that R $1/r^4$; thus, when the radius is halved, resistance increases by a factor of 16. Another factor is viscosity; the energy required to overcome frictional forces necessary for fluid movement is directly related to viscosity. For a homogeneous fluid such as water or plasma at a given temperature, viscosity is constant (ie, it is a Newtonian fluid). At 98.6°F (37°C), the viscosity of plasma is approximately 1.7 times that of water. However, for a suspension solution such as blood, viscosity is not constant, that is, it is non-Newtonian. In large blood vessels, laminar blood flow and the alignment of red blood cells parallel to the axis of motion greatly reduce viscosity. However, as the shear rate increases, the cells fall out of alignment and stack like coins called *rouleaux*, which increases apparent viscosity. The following factors also affect blood viscosity: temperature; hematocrit; plasma viscosity; red blood cell deformability and aggregation; and protein concentration, mainly through increasing red blood cell aggregation at low shear rates, with a minor effect on plasma viscosity. The relationship between viscosity, length, and vessel radius is quantified by Poiseuille's law: $R = 8nL\pi r^4$ by substituting $R = (P_1 - P_2)/Q$ and rearranging $Q = (P_1 - P_2\pi r^4/8nL)$. Although this relationship was originally developed to describe the flow of a homogeneous fluid through a rigid tube, it approximates the steady-state flow of the circulation.

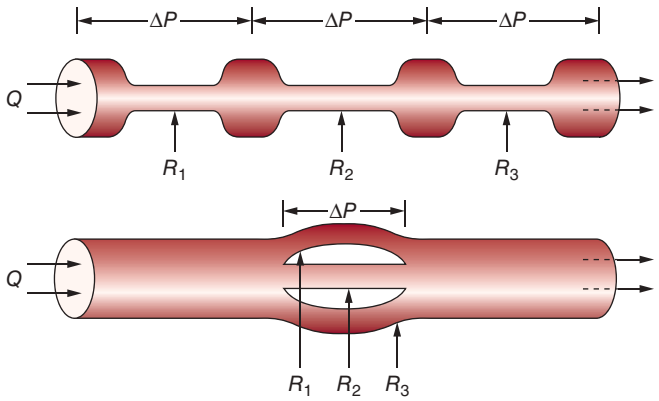


FIGURE 5–21. Illustration of the principle of resistance elements arranged in series versus parallel. (*Top*) If the driving pressure (ΔP) across each series resistance is 3 mm Hg and flow (Q) is 1 mL/min, each resistance (R) would be 3 mm Hg/mL ($\Delta P/Q$), and total resistance (R_t) would be 9 mm Hg/mL. (*Bottom*) In parallel resistances, if driving pressure is 3 mm Hg and flow is 1 mL/min, total resistance is $1/R_1+1/R_2+1/R_3$, or 1 mL/min. When three resistances are in parallel, total resistance is only one-ninth that with resistances in series. Thus, it would take a ΔP of only 1 mm Hg to produce a 1-mL/min flow. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: *Hurst's The Heart*. 11th ed. New York: McGraw-Hill; 2004.

THE MICROCIRCULATION

The microcirculation is composed of arterioles, capillaries, and venules. Arterioles range from 10 to 150 μm in diameter and regulate the distribution of blood flow to capillaries (0.5–1.0 μm); small arterioles (metarterioles) can bypass the capillary beds, shunting flow directly into the small venules (10–40 μm). The independent vasoactivity of different-sized arterioles produces blood flow patterns that vary in speed and direction. Although flow in the arterioles is usually rapid, continuous, and unidirectional, capillary flow is highly variable. Capillaries have a single layer of endothelial cells through which oxygen and nutrients diffuse to adjacent tissues. Venules have an endothelial cell layer surrounded by an adventitia and contractile pericytes and are involved in transvascular exchange of fluid and macromolecules across the vascular wall. The larger venules and veins collect and store blood for return to the heart. The cellular and molecular mechanisms that control blood flow in the microcirculation are only beginning to be understood.[46,47]

Important determinants of capillary exchange through the endothelial cell membrane (*diffusion*) include (1) the capillary density, which is directly related to the metabolic activity of tissue; (2) lipid solubility of the material to be exchanged; (3) the free diffusion coefficient (small molecules and molecules with very little net electric charge have very high free diffusion coefficients); and (4) the relative concentrations of the material in the blood and the tissue interstitium. Thus, the rate of diffusion for a substance Q moving from the vessel to the interstitial space, dQ/dt is proportional to the capillary wall area ($2\pi rl$), the difference in concentration of the substance (ΔC), which represents the driving force for the movement across the vessel wall, and the permeability (P) which is a function of lipid solubility and the free diffusion coefficient: $dQ/dt = (2\pi rl)(P)(\Delta C)$. Permeability for substances varies by capillary bed (eg, whereas capillaries in the brain restrict the diffusion of almost all solutes, liver capillaries have a very high permeability to large solutes such as albumin). Endothelial transport across restrictive beds is accomplished by other processes such as pinocytosis and vesicular transport. Pores occupy less than 1% of the total capillary surface area; there are more present on the venular than arteriolar end of the capillary system, and therefore lipid-insoluble materials (eg, glucose, small ions) exchange slowly. Thus, whereas lipid-soluble materials are considered *flow limited*, lipid-insoluble materials (except water) are considered to be relatively *limited by diffusion.*

The transvascular exchange of water occurs primarily through the bulk flow of water through the pores in the capillary walls (Q_{H_2O}); the amount of bulk flow is a function of the difference in hydrostatic

pressure in the vessel (*CHP*, variable, depending on tissue bed) and interstitium (*THP*, small but variable), the capillary filtration coefficient (*CFC*), the plasma colloid osmotic pressure (*COP*, caused by protein in blood plasma, ~20 mm Hg), and the tissue colloid osmotic pressure (*TOP*, caused by proteins in the interstitial space, ~4.5 mm Hg). Thus, the net force out of the vessel (*filtration*) is a hydrostatic force, and the net force into the vessel (*reabsorption*) is a colloid osmotic force. The effect of these forces on transvascular water flow is described in the Starling equation: Q_{H_2O} = CFC[(CHP – THP) –σ(COP – TOP)], where σ is the reflection coefficient for the movement of proteins across the capillary wall (the inverse of the permeability of the vessel wall to protein). The capillary filtration coefficient is the product of capillary surface area and permeability and is related to number and size of the pores through which water can pass through the vessel. Because the balance of forces is different across the length of a capillary bed, filtration occurs near the arterial end and reabsorption near the venule end of the capillary.

Of these forces, capillary hydrostatic pressure (CHP) is the principal mechanism responsible for transcapillary exchange of water. CHP increases whenever arterial pressure increases, venous pressure increases, venule resistance to flow increases, or arteriole resistance to flow decreases. Mathematically, CHP = $(R_V/R_A)P_A + P_V$, where R_V/R_A is the ratio of venule-to-arteriolar resistance, P_A is approximately mean arterial pressure, and P_V is approximately central venous pressure. Capillary pressure is far more sensitive to changes in venous pressure than changes in arterial pressure. The ratio of venule-to-arteriole resistance (R_V/R_A) is approximately 0.1; thus, arterial pressure must increase 10 mm Hg to cause a 1-mm Hg increase in capillary hydrostatic pressure, but a 1-mm Hg increase in venous pressure will cause a similar increase in capillary hydrostatic pressure. Greater filtration than reabsorption produces tissue lymph flow; the total volume of lymph fluid (important in returning plasma proteins that leaked from the microcirculation and transport of chylomicrons) is approximately 3 to 4 L/d.

SPECIAL CIRCULATIONS

The relative proportions of cardiac output that perfuses various circulations at rest and with strenuous exercise are summarized in Fig. 5–22. These circulations are discussed below.

CORONARY CIRCULATION

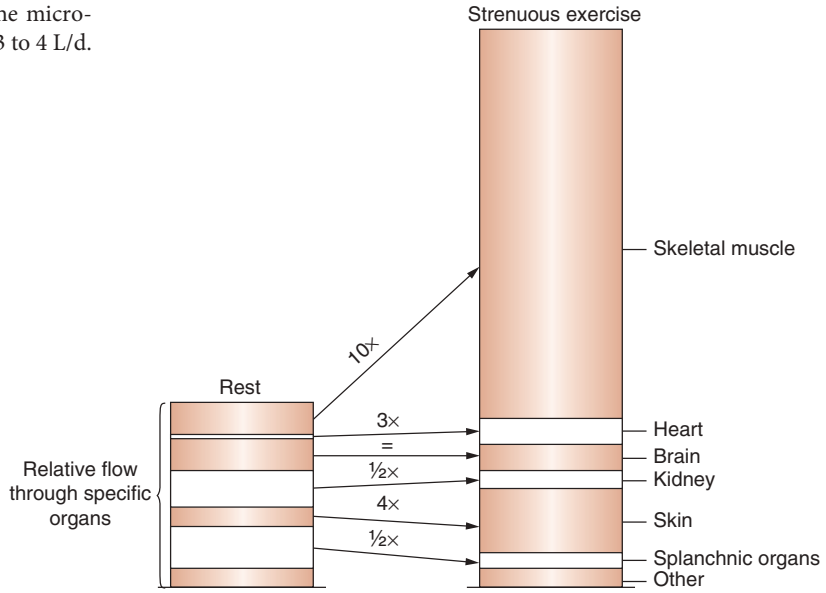
Two major coronary arteries arise from the aortic sinuses; subdivide on the epicardial surface of the heart; and give off small, penetrating branches and an extensive network of intramural arteries, arterioles, and capillaries. Commensurate with the high oxygen requirements of the myocardium, capillary density is very high (accounting for ~15% of the total cardiac mass), which facilitate the diffusion of nutrients and wastes to and from the cardiomyocytes. Myocardial capillaries feed into a network of intramural venules that drain into large epicardial collecting veins. The majority of the LV venous blood drains into the coronary sinus, which runs along the AV groove and empties into the right atrium. Other drainage is by means of thebesian veins, which drain directly into the right heart, and anterior cardiac veins that empty into the right atrium. Small intramural collateral vessels connect the coronaries and can enlarge after coronary obstruction, providing near-normal flow at rest to the distal segment of the diseased artery. However, the capacity to augment myocardial blood flow during exercise or stress (ie, the coronary reserve) is usually limited in collateral vessels.

Myocardial Metabolism

Cardiac muscle metabolism requires sustained oxidative phosphorylation to synthesize the ATP that powers the continuous cycles of E–C coupling and relaxation. A smaller amount of energy (~15%–20%) is needed for electrical excitation and basal housekeeping activities of the cardiomyocyte. Accordingly, myocardial oxygen requirements are high (~8 mL/min/100 g myocardium). During stress or exercise, oxygen requirements increase abruptly. However, unlike skeletal muscle, extraction of oxygen in cardiac muscle is near maximal at rest; therefore, to augment oxygen supply, coronary blood flow must increase.

Compared with other tissues, the myocardium contains a low concentration of high-energy phosphates, given the constant requirement for energy. ATP levels are buffered in the heart by the much larger concentration of phosphocreatine (PCr), which regenerates ATP, by the creatine (Cr) kinase-catalyzed reaction ADP + PCr = ATP + Cr. Regeneration of ATP from PCr can protect the heart from ATP depletion during a mild or brief increase in energy demand, but the heart is fundamentally dependent on continuous resynthesis of mitochondrial ATP.

A variety of substrates are used for myocardial ATP synthesis. Under normal resting conditions, the heart generates 60% to 70% of its ATP from β oxidation of free fatty acids and 30% from metabolism of carbohydrates. Amino acids and ketones are also used as substrates but to much lesser extent. During exercise, the large amount of lactate



Cardiac output	6 L/min	18 L/min
Heart rate	70 beats/min	160 beats/min
Ejection fraction	60%	80%
Arterial pressure	120/80 mm Hg	150/80 mm Hg
Central venous pressure	2 mm Hg	2 mm Hg

FIGURE 5–22. Relative flow through various vascular beds during rest and strenuous exercise. Reproduced with permission from Mohrman DE, Heller LJ: *Cardiovascular Physiology*, 6th ed. New York: McGraw-Hill; 2006.

produced by skeletal muscle becomes a major substrate, entering the Krebs cycle after conversion to pyruvate. Oxidation of free fatty acids is inhibited, and carbohydrates become the predominant substrate for energy metabolism; which it is also the case in the failing heart.[48,49]

Control of Coronary Blood Flow

Resting coronary blood flow is normally between 60 and 90 mL/min/100 g of myocardium and can rapidly increase four- to five-fold during exercise or other conditions requiring augmented flow. The coronary flow rate is determined by the coronary artery perfusion pressure and by the resistance to flow exerted by forces generated within and outside the coronary vascular bed; the complexity of these forces is highlighted by the unexpected finding that the coronary diastolic pressure at the time of zero flow (eg, after a long diastole) is greater than coronary sinus pressure. Control of coronary blood flow is metabolic, mechanical, autonomic, and endothelial.[47] However, the exact local feedback control mechanisms that match coronary blood flow to myocardial oxygen consumption are poorly understood.

Metabolic Control: Autoregulation

A sudden change in aortic pressure is met by a rapid adjustment of coronary vascular resistance so that blood flow remains constant. This autoregulatory phenomenon protects the myocardium from inadequate blood flow owing to a decline in coronary perfusion pressure. Autoregulation at high aortic pressures may attenuate endothelial wall stress and protect the vasculature from damage resulting from elevated coronary distending pressures. The normal coronary vascular bed usually autoregulates over a range of systemic arterial pressures ranging from 60 to 140 mm Hg. Above or below these limits, autoregulation fails, and coronary flow increases or decreases in a linear fashion, with corresponding increases or decreases in aortic pressure, respectively. Autoregulation also occurs in localized areas of the coronary vasculature when a partial obstruction of an artery causes a decrease in the coronary perfusion pressure. The vessel distal to the obstruction dilates, thus normalizing flow by decreasing coronary vascular resistance.

Autoregulatory reserve refers to the maximum degree of vasodilation in the coronary vascular bed and determines the range of decreased perfusion pressures over which myocardial flow can be maintained. Autoregulatory reserve depends on the level of chronic vasodilation in the coronary vasculature as a whole or in any specific region of the heart. If a region of the vascular bed is already vasodilated in an effort to compensate for a localized decrease in coronary perfusion pressure, the capacity to autoregulate during additional reductions in aortic diastolic pressure will be impaired. Thus, the affected area of myocardium becomes vulnerable to transient decreases in aortic pressure. This impairment in autoregulation is the basis for perfusion scans used to diagnose myocardial ischemia.

Autoregulation is mediated by both myogenic (a change in tone in response to changes in pressure and flow) and metabolic (related to washout of vasoactive metabolites) means. The most compelling evidence suggests that adenosine, a breakdown product of ATP, is a major mediator of autoregulation. Adenosine is a potent vasodilator that is generated continually in myocardial cells from adenosine monophosphate by the action of 5′ nucleotidase located at the inner surface of the cell membrane. Adenosine diffuses freely across the cell membrane, and any decrease in perfusion pressure, by causing an initial decrease in coronary artery flow, leads to a diminished rate of adenosine washout and an increase in local tissue concentration. This in turn results in increased vasodilation and a subsequent increase in the coronary flow rate. Tissue pO_2 and the level of other metabolic products in tissue (eg, carbon dioxide), by changing slightly as perfusion pressure increases and decreases, can also directly affect coronary artery tone. In addition, local release of potassium (K^+) and adenosine-induced activation of ATP-sensitive K^+ channels can also mediate autoregulation in the coronary circulation.

Mechanical Control

The pattern of blood flow to the LV, which receives the greatest proportion of coronary flow, is unique in that arterial flow is markedly decreased during systole because of the intramyocardial pressure generated by contracting myocardial fibers. Thus, most of the coronary flow to the LV occurs during diastole, and coronary perfusion pressure is largely determined by aortic diastolic pressure. Blood flow to the RV myocardium is also phasic, but because the systolic pressure transmitted to the RV myocardium is much lower, the difference between systolic and diastolic flow is less marked.

Several factors affecting blood flow are markedly different in the inner, subendocardial, and outer, subepicardial, layers of myocardium. Systolic compression is greater in the subendocardial layers (mechanical interference with flow in late diastole because of chamber distension may also occur). In the subepicardium, flow is slightly higher in systole than diastole. In the midwall, flow is approximately equal in systole and diastole. Vascular density is increased in the subendocardium so that net flow is augmented despite the almost complete absence of blood flow in the subendocardium during systole. In addition, the intrinsic coronary vascular resistance in subendocardial arteries is lower, so that the ratio of subendocardial to subepicardial flow is approximately 1.1:1. Although this suits the increased oxygen requirements because of increased wall stress and shortening, the lower resting coronary resistance limits the coronary reserve of the subendocardial vessels and makes it more vulnerable to injury if coronary perfusion pressure drops or coronary flow is impeded. Thus, subendocardial injury is common when myocardial oxygen requirements increase, such as with severe hypertension.

Autonomic Control

The autonomic nervous system influences the smooth muscle tone of the coronary arteries, and this modulates coronary flow to some extent, although under normal conditions, its role is overshadowed by metabolic and mechanical influences. The larger epicardial coronary arteries have both α-adrenergic receptors, which mediate vasoconstriction, and β-adrenergic receptors, which mediate vasodilation. Parasympathetic muscarinic coronary vasodilation has also been demonstrated, but its role in regulation of coronary flow is unclear.

Release of norepinephrine during sympathetic stimulation can cause coronary artery vasoconstriction, but this response is normally overridden by metabolic factors because sympathetic stimulation also increases heart rate and contractility, thereby augmenting myocardial oxygen consumption, ATP turnover, and vasodilation by metabolic mechanisms. Although there is a small degree of resting coronary vasoconstrictor tone, the significance of sympathetic innervation of the normal coronary arteries is unclear. Abnormal increases in vasoconstrictor tone have been suggested as a mechanism underlying ischemic heart disease.

Stimulation of β_2-adrenergic receptors in the smaller coronary arteries by endogenous circulating catecholamines or by pharmacologic β-agonists results in coronary vasodilation. The extent to which coronary β-receptors contribute to coronary blood flow regulation is difficult to assess because β stimulation of the myocardium increases oxygen consumption, leading to metabolically mediated vasodilation. However, during exercise, sympathetic β-adrenergic–mediated feed-forward arteriolar vasodilation contributes approximately 25% of the increase in coronary blood flow, and α-adrenergic–mediated

vasoconstriction in medium and large coronary arteries helps maintain blood flow to the vulnerable subendocardium.[50]

Endothelial Control

Endothelium-derived relaxing factor (EDRF) is a potent vasodilator that is elaborated by vascular endothelial cells in response to a number of stress signals, such as hypoxia, and ADP accumulation. EDRF release is also stimulated by distending forces in the vascular wall, which can amplify the coronary flow in response to conditions such as exercise when it can be appropriate for both coronary perfusion pressure and flow to increase. This is in contrast to autoregulation, which keeps flow constant during inappropriate changes in coronary perfusion pressure.

Nitric oxide (NO) is the principal EDRF. Reactive hyperemia, myogenic vasodilation, and the vasodilator effects of acetylcholine and bradykinin are mediated by NO. NO-independent vasodilation increases shear stress, which stimulates endothelial NO synthase, generates NO, and prolongs vasodilation.[47]

CEREBRAL CIRCULATION

The brain cannot survive on anaerobic metabolism; therefore, powerful mechanisms exist to maintain constant cerebral blood flow. Cerebral blood flow is also controlled by autoregulation of blood flow in the face of perfusion pressures ranging from approximately 60 to 150 mm Hg. When arterial blood pressure decreases below 60 mm Hg and cerebral blood flow decreases, brain tissue begins to become ischemic; this elicits a powerful stimulation of the peripheral sympathetic nervous system, resulting in generalized vasoconstriction and an increase in arterial blood pressure. This response is effective down to blood pressures of 15 to 20 mm Hg and is so powerful that blood flow to other areas can decrease to zero in an effort to preserve cerebral blood flow. Myocardial blood flow increases because the intense sympathetic stimulation increases myocardial work (heart rate and contractility).

There is also a positive curvilinear relationship between cerebral blood flow and arterial CO_2 tension, mediated partly through changes in extracellular pH; small increases in arterial blood CO_2 tension above normal values produce large increases in cerebral blood flow. Decreases in CO_2 decrease blood flow. There is also an inverse relationship between arterial O_2 content and cerebral blood flow that helps maintain cerebral O_2 delivery constant.

Although cerebral blood vessels are innervated, neural mechanisms modify cerebral blood flow only weakly and are overpowered by other factors that regulate cerebral blood flow.

SKELETAL MUSCLE CIRCULATION

Blood flow to resting skeletal muscle is relatively low, normally only 3 to 4 mL/min/100 g of muscle. Whereas only 10% of the capillary beds are perfused, this is sufficient to meet the basal metabolic needs of resting muscle. Blood vessels in skeletal muscle are innervated and constrict in response to α-adrenergic stimulation and dilate in response to β-adrenergic or cholinergic stimulation. Adrenergic and cholinergic vasodilation is largely mediated by endothelial NO.[51] When skeletal muscle is inactive and blood flow is needed in other vascular beds, neural mechanisms constrict muscle vessels to divert blood to the needed areas. When skeletal muscle is active, however, neural influences on blood flow are overridden by powerful local metabolic and vascular control mechanisms. The primary regulators of skeletal muscle blood flow during exercise are metabolic factors. A decrease in oxygen tension and increases in concentration of carbon dioxide, lactic acid, hydrogen ions, and potassium ions directly increase muscle blood flow. As the increase in blood flow washes out these substances, tissue concentrations return to normal. Strenuous exercise can increase blood flow to muscle by as much as 25-fold, to a maximum of approximately 80 mL/min/100 g, and opens previously unperfused capillary beds. With aerobic exercise, blood flow is maintained at a steady level, albeit one higher than normal, commensurate with the increase in metabolic rate. Skeletal muscle can depend on anaerobic metabolism for short periods of time by generating an oxygen debt; at the end of exercise, muscle blood flow remains elevated until the concentration of all effector substances return to normal.

INTEGRATED PHYSIOLOGY

Integrated control of the circulation results from both intrinsic (eg, myogenic tone, endothelial function) and extrinsic (eg, autonomic nervous system) mechanisms to the vascular wall.

The cardiac output is delivered to the peripheral tissues by the aorta and large conductance arteries. These vessels have relatively little smooth muscle in their walls and are not significantly affected by the preceding vascular control mechanisms. Importantly, however, they contain mechanoreceptors (the aortic arch and carotid sinus baroreceptors) that initiate circulatory reflexes important in controlling systemic arterial pressure. The elastic tissue of the aorta and its branches converts pulsatile cardiac flow into a continuous, steady-state flow optimal for perfusion of the smaller arteries and arterioles. These smaller vessels are surrounded by layers of smooth muscle cells in direct contact with endothelium on the luminal side and are richly innervated on the adventitial side. Regulatory input from both the endothelium and neural connections together determines the tension in the vascular smooth muscle and the cross-sectional area of the vessel. The effective cross-sectional area in the muscular arteries, arterioles, and venules is the principal determinant of steady-state peripheral resistance.

In contrast to arteries, veins are highly distensible and together with the venules and venous sinuses contain approximately 60% of the blood volume. By regulating the functional cross-sectional area of the venous compartment, blood can be translocated from the venous to the arterial side of the circulation. Thus, an increase in the venomotor tone decreases venous capacitance and redistributes blood volume thereby increasing cardiac output; a decrease in venomotor tone has the opposite effect. Local external pressures (intra-abdominal, intrathoracic) influence the large veins as they return blood to the right heart. Because venous pressures are relatively low and capacitance is large, these external forces can facilitate or inhibit venous return.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system affects vasomotor tone and cardiac function through its sympathetic and parasympathetic divisions. It also influences systemic volume and peripheral resistance by modulating the release of certain peptide hormones (eg, angiotensin II). Neural control involves assimilation of inputs from the cerebral cortex and specialized sensors (ie, the mechanoreceptors, chemoreceptors, osmoreceptors, and thermoreceptors), integration into several specialized regions of the brain (hypothalamus, pons, medulla), and transmission of efferent nerve activity to the periphery over the sympathetic and parasympathetic pathways. The dynamic balance between these two systems determines the net, integrated response.

The overall organization of the vasomotor area is complex, but there appear to be three functionally overlapping anatomic zones that interact extensively. These are (1) a vasoconstrictor area in the upper anterolateral medulla, (2) a vasodilator area in the lower anterolateral medulla, and (3) a sensory area that integrates the vasoconstrictor and

vasodilator areas located bilaterally in the nucleus tractus solitarii of the posterolateral medulla and lower pons. Regions modifying heart rate are located in the thalamus, posterior, and posterolateral regions of the hypothalamus and the dorsal region of the medulla.

Stimulation and withdrawal of sympathetic nervous activity are the most powerful factors controlling the peripheral circulation. In addition to cardiovascular reflex regulation, mechanisms involving central interactions between angiotensin II and NO contribute to sympathetic excitation.[52] Fibers travel either in specific sympathetic nerves, which innervate the viscera and heart or join the paravertebral sympathetic chain and synapse in secondary ganglia that give rise to the spinal nerves that innervate peripheral vessels. The vascular nerves terminate on small arteries, arterioles, venules, and veins and modulate resistance and vascular volume. Cardiac nerves, many of which descend from the stellate ganglia, innervate the atria and ventricles.

Reflex sympathetic stimulation causes vasoconstriction by releasing norepinephrine from sympathetic nerve endings. Sympathetic nerve stimulation to a limb increases local vascular resistance and decreases blood flow and capillary pressure; as a result, local interstitial fluid is absorbed, and blood volume is displaced from the limb. In a metabolically active organ, local influences are likely to override the autonomic ones. Although most reflex sympathetic stimulation produces vascular constriction, a subset of fibers originating in the cerebral motor cortex releases acetylcholine rather than norepinephrine. These neurons innervate the vasculature of skeletal muscle and bring about an anticipatory increase in local blood flow before exercise. Sympathetic stimulation of these fibers also releases epinephrine from the adrenal medullae. Unlike norepinephrine, epinephrine stimulates both α and β receptors. The effect of epinephrine is biphasic; at low concentrations, epinephrine produces vasodilation and cardiac stimulation; at higher concentrations, vasoconstriction predominates.

Reflex sympathetic stimulation is important because it increases cardiac output necessary during exercise or other forms of stress. These cardiac-stimulating effects of the sympathetic nervous system increase the metabolic requirements of heart muscle. Sympathetically mediated actions are largely responsible for maintaining systemic arterial pressure and vital organ perfusion during hypovolemic states and cardiac dysfunction. The inhibition of sympathetic outflow allows vessels to dilate and respond to local humoral and myogenic stimuli.

The parasympathetic nervous system consists of a cranial division, which supplies the blood vessels of the head and viscera, and a sacral division, which innervates the vessels of the genitalia, bladder, and large intestine. Because these fibers supply only a small percentage of the resistance vessels, the parasympathetic division of the autonomic nervous system plays a minor role in arterial pressure regulation. It does, however, play an important role in modulating the heart rate. Fibers traveling in the vagus nerve innervate the SA and AV nodes and atrial myocardium. Changes in heart rate arise from slower intrinsic rates of depolarization and changes in membrane depolarization secondary to acetylcholine stimulation. When the vagus nerve is stimulated, the heart rate and the force of atrial contraction both decline. These effects, coupled with the development of AV block, can lower cardiac output by as much as 40% to 50%. Effects of vagal stimulation are evident after external massage of the carotid sinus, which stimulates the glossopharyngeal afferent limb of the baroreceptors reflex and modifies efferent parasympathetic outflow.

BARORECEPTOR CONTROL

The baroreceptor system consists of the carotid sinus and aortic arch mechanoreceptors, central vasomotor integrating areas, and autonomic efferents. The baroreflex system operates as an open loop with negative feedback and cushions changes in arterial pressure, such as those produced by changes in posture. Under resting conditions, the system is static; however, it can be modified by periodic or transient perturbations, such as respiration or exercise, and therefore is also dynamic. The neural outflow from the vasomotor centers modulates the smooth muscle tone of resistance vessels, the force of myocardial contraction, and the heart rate and thereby buffers changes in systemic arterial pressure. Activation of the baroreceptors by an arterial blood pressure-induced stretch produces an increase in afferent impulses traveling through the vagus and glossopharyngeal nerves. In the central vasomotor centers of the pons and medulla, sympathetic efferent nerve activity to the heart, resistance vessels, and veins is inhibited; parasympathetic outflow to the heart increases. The result is cardiac slowing and a decrease in blood pressure.

The carotid sinus baroreceptor is located at the bifurcation of the common carotid artery. The receptors are located in the adventitia of the sinus wall and are innervated by a branch of the glossopharyngeal nerve, which carries afferent activity to the nucleus tractus solitarii in the medulla. Strain energy density (ie, the force required to bring about an incremental stretch) in the wall of the sinus is linearly related to pressure over a wide range of values from 50 to 250 mm Hg. Over this range, the relationship between deformations produced by an increase in pressure and afferent nerve activity is directly linear. The rate of afferent nerve discharge is largely influenced by the mean arterial pressure and to a lesser extent by pulse pressure. Thus, for a given mean pressure, a narrower pulse pressure decreases afferent activity. Factors that modify the distensibility of the carotid sinus (eg, hypertension, atherosclerosis) also change the relationship between intraluminal pressure and stretch. The ability of baroreceptors to cushion chronic increases in mean arterial pressure is limited by *resetting*, a rightward shift in the relationship between baroreceptor firing and mean arterial pressure.[53] Baroreflex resetting (in this case closer to threshold) also occurs during exercise, which increases the ability of the reflex to buffer hypertensive stimuli.[54] Carotid baroreceptor denervation causes an increase in blood pressure variability but not sustained hypertension.[55]

The aortic arch baroreflex system is similar to that of the carotid sinus. Nerve endings concentrated at the junction between the adventitia and media of the aortic arch serve as stretch receptors with their afferent impulses traveling in the vagus nerve. The threshold of pressure stimulation for aortic receptors is approximately 90 mm Hg compared with 60 mm Hg for the carotid receptors. Therefore, the carotid sinus is important in modulating blood pressure and heart rate at lower pressures, a feature that may be important for maintaining cerebral perfusion in an upright posture.

CHEMORECEPTOR CONTROL

Arterial chemoreceptors are located in the carotid arteries and aortic arch in the same regions as baroreceptors. These receptors are composed of excitable cells that release neurotransmitters and activate afferent nerves (type I receptors) and inexcitable cells that function as a sensor for hypoxia and acidosis (type II receptors). The carotid bodies are innervated by a branch of the glossopharyngeal nerve, and the aortic bodies are supplied by a branch of the vagus. Nerve activity is stimulated by decreases in pH or pO_2 or by an increase in the CO_2 tension and temperature. For any given arterial pO_2, the number of discharges increases at higher pCO_2; conversely, for any given pCO_2, the number of impulses increases with lower pO_2. The carotid and aortic body chemoreflexes are responsible for reflex systemic arterial hypertension, which is mediated by sympathetic outflow from the vasomotor areas. Increases in heart rate, contractility, and cardiac output are most likely caused by the combined effects of central nervous system hypoxia

and increased ventilation because chemoreceptor denervation does not abolish the cardiac responses, but lung denervation largely prevents or reverses them. Moreover, carotid chemoreceptor denervation eliminates the ventilatory responses to hypoxia and hypercapnia.

MECHANORECEPTOR CONTROL

Mechanoreceptors in the heart possess both vagal and sympathetic afferents. Sensors on the atria and ventricles receive vagal afferents, and sensors on the pulmonary veins and coronary vessels receive sympathetic afferents. However, the cardiac mechanoreceptors are much less involved than are the baroreceptors in the short-term regulation of arterial pressure.

Atrial A and B receptors are located at the venoatrial junctions and have distinct functions. Type A receptors react primarily to heart rate but adapt to long-term changes in atrial volume. Type B receptors increase their discharge during atrial distension. C fibers arise from receptors scattered through the atria; these discharge with a low frequency and respond with increased discharge to increase in atrial pressure. The A and B receptors are thought to mediate the increase in heart rate associated with atrial distension (such as can occur with intravenous infusions) known as the *Bainbridge reflex*. In contrast, activation of atrial C fibers generally produces a vasodepressor effect (bradycardia and peripheral vasodilation).

Ventricular mechanoreceptor afferent discharge decreases periodically with inspiration. Ventricular C fibers are located primarily in the epicardium and discharge more rapidly in response to increase in both systolic and diastolic pressure. They exhibit a sharp threshold, discharging only at high systolic pressures, but progressively increase as diastolic pressures increase from 5 to 20 mm Hg. Ventricular distension can produce a powerful depressor reflex called the *Bezold-Jarisch reflex*; vagal afferents of this cardiopulmonary reflex are also activated by chemical stimulation (eg, prostanoids, cytokines, serotonin, and classically, *Veratrum* alkaloids).[56] The central connections for this reflex are in the nucleus tractus solitarii, which has both sympathetic and parasympathetic synapses. Cardiac C-fiber activation also induces gastric relaxation by means of vagal noncholinergic fibers, which is part of a more generalized activation of the vomiting reflex.

The sympathetic afferents are less well understood than the vagal afferents. Atria and ventricular receptors can affect the release of vasopressin and the renal release of renin by modifying efferent sympathetic outflow. Atrial fibers increase activity with increases in atrial pressure and volume and respond to phasic changes in atrial volume. Ventricular fibers increase their discharge rate when ventricular end-diastolic pressure (via unmyelinated fibers) or systolic pressure (via myelinated fibers) is elevated. Afferents on the coronary vessels discharge more rapidly as blood flow or intracoronary pressures decrease and may be important during myocardial ischemia.

LOCAL INFLUENCES AND CIRCULATORY CONTROL

Vascular tone is greatest in the small muscular arteries. The level of tone represents the integration of excitatory and inhibitory pathways of metabolic, endothelial, and neurotransmitter origin. However, vascular smooth muscle constricts in response to pressure or stretch in the absence of the endothelium. The mediator of this myogenic response is uncertain but may be integrins, stretch-activated cation channels, and cytoskeletal proteins. Signaling pathways involved in the myogenic response include phospholipase C/PKC and calmodulin-mediated myosin light-chain phosphorylation. In addition, calcium sensitivity of the contractile proteins is produced by inhibition of myosin light-chain phosphatase, which dephosphorylates and inactivates myosin.

Flexible and precise circulatory control is possible because vascular smooth muscle can change its tension in response to both centrally transmitted signals and local factors. Vasodilators include atrial natriuretic peptide (ANP), kinins, NO, and prostacyclins; vasoconstrictors include thromboxane A_2, prostaglandin H_2, superoxide anion, endothelins, arginine vasopressin (AVP), and angiotensin II. The endothelium is an important modulator of tone because it releases many of these vasoactive substances.[57] Vasoactive molecules are released in response to both physical and chemical stimulation. For example, flow-induced shear produces vasodilation and normalization of elevated shear stress.

An important endothelium-derived relaxing factor is the simple gas NO, which is synthesized from L-arginine by NOS. There are three isoforms of NOS that vary in their calcium dependence and type of regulation: neuronal NOS, inducible NOS, and endothelial NOS. As mentioned earlier, these isoforms are spatially localized to highly controlled microdomains and are linked to disparate signaling pathways and effectors. In the vasculature, NO exerts paracrine control by means of vasodilation by the action of cGMP. The endothelium is also the source of substances that initiate smooth muscle contraction.

Angiotensin II is a powerful vasoconstrictor peptide that has endocrine functions crucial to salt and water homeostasis but is also locally produced and plays critical autocrine and paracrine roles in organ perfusion and growth.

The endothelins are a group of peptides cleaved from larger inactive precursors that constrict arterial and venous smooth muscle. Endothelins (and the other G protein–coupled receptor ligands, angiotensin II and α_1-adrenergic agonists) function by activating phospholipase, which produces IP_3 and DAG; $InsP_3$ releases Ca^{2+} into the cytoplasm from endoplasmic reticulum stores, and DAG activates PKC. Arterial constriction increases peripheral resistance, and venoconstriction decreases capacitance and increases cardiac preload; the former usually predominates.

ANP is a direct-acting vasodilator that is released in response to atrial stretch, β-adrenergic stimulation, and increased heart rate. ANP stimulates the second messenger, membrane-bound cGMP, to produce arterial and venous dilation. The resultant hemodynamic effects include a dose-dependent decrease in arterial pressure and cardiac output. ANP also blocks the effects of angiotensin II on aldosterone release and lowers angiotensin II level. Although ANP is elevated in heart failure, its effects are offset by the action of potent vasoconstrictors and sodium retention.

Kinins are polypeptide vasodilators that are synthesized and circulate as large, inactive molecules and are locally bioconverted to active moieties. Bradykinin is formed from kallikrein and performs vital roles in inflammation and local circulatory control.

AVP is synthesized in neurons of the hypothalamic nuclei and is released from nerve endings of the neurohypophysis. AVP is also a neurotransmitter found in central regions involved in circulatory control. AVP is important in maintaining arterial pressure in the presence of reduced blood volume and regulates osmolality. AVP modulates volume by inhibiting systemic ANP when arterial and atrial receptors are activated.

Substance P is a neurotransmitter peptide that is widely distributed in the brain and peripheral nervous system. Its cardiovascular regulatory potential is suggested by its relatively high concentration in the vasomotor area, where it may interact with the opioid peptide system. In addition, it is present in the nerves that supply virtually every vascular bed, where its release triggers vasodilation through a specific receptor.

Opioids such as the enkephalins and endorphins are also widely distributed in the brain and spinal cord. Although infusion of these

neurotransmitters produces transient vasodilation, they are thought to cooperate with and modulate the response of other neurotransmitters operating in the same synaptic cleft. They appear to be most involved in the behavioral responses to pain and exercise.

Vasoactive intestinal polypeptide is found in the brain, gut, salivary glands, uterus, and skeletal muscle. It is a potent vasodilator and increases heart rate above that obtained with sympathetic stimulation alone.

Endocannabinoids are synthesized from membrane phospholipids in cardiovascular tissues and activate specific G protein–coupled cannabinoid CB1 and CB2 receptors, the former resulting in arterial vasodilation and decreased ventricular contractility. Tonic activation of CB1 has been implicated in the genesis of acquired cardiovascular risk factors, and CB2 stimulation is immunomodulatory.[58]

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CHAPTER 6

MOLECULAR AND CELLULAR BIOLOGY OF THE HEART

Roger J. Hajjar, Kiyotake Ishikawa, and Thomas Thum

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INTRODUCTION

Biology of the heart is meticulously orchestrated by various mechanisms, including receptor-mediated signal transduction, post-translational modification, protein degradation, and transcriptional regulation. To maintain the hemodynamic homeostasis, the heart uses these processes in a chronologically regulated manner. Because the time between heart beats is usually less than one second, instant changes in the body blood demand must be rapidly adapted. This is achieved by modifying β-adrenergic signaling and subsequent phosphorylation/dephosphorylation of proteins related to excitation–contraction coupling. In contrast, chronically altered hemodynamic status, such as hypertension, is adapted via network of signal transductions leading to reprogramming of the gene expression. Emerging evidence indicates that microRNAs, long noncoding RNAs, or circular RNAs are also critically involved in these transcriptional regulations. Sustained activation of certain pathways initially induces adaptive responses, however, eventually become maladaptive, causing pathological hypertrophy, contractile dysfunction, cell loss, and extracellular remodeling. These changes are clinically represented as heart failure and predispose patients to increased morbidity and mortality. With the rapid advances in the development of small molecule inhibitors and gene therapy approaches that can possibly target key pathological pathways in vivo, we are approaching the point of being able to readily manipulate these pathways in patients. Noncoding RNAs not only play crucial roles in orchestrating the genome and cellular pathways but also can be used as novel therapeutic targets and diagnostic markers. Therefore, understanding the molecular mechanisms governing cardiac pathophysiology is essential to understanding the signaling networks that regulate heart failure development. In this chapter, we will highlight the role of important regulators and biological molecular principles in cardiac homeostasis and disease.

β-ADRENERGIC RECEPTORS

Activation of cardiac β-adrenergic receptors (ARs) represents a powerful system to increase cardiac contractility and heart rate. ARs are a family of G protein–coupled receptors, and agonist binding to β-ARs induces dissociation of heterotrimeric G protein αβγ into active Gα and free heterodimer Gβγ. These subunits activate their respective downstream signal transductions.[1] Switching off the activated β-adrenergic signaling is mediated by phosphorylation of β-ARs through G protein–coupled receptor kinases (GRKs)[1] (Fig. 6–1).

Among the nine members of AR—three α_1, three α_2, and three β (β_1, β_2, and β_3)—the mammalian heart expresses all three β-AR subtypes.[2] In the healthy heart, the majority (ie, 60%–80%) of receptors is of the β_1-subtype in most species, whereas the β_2-subtype accounts for a minor fraction of total β-ARs. A third β-AR subtype, the β_3-AR, was initially thought to be limited to adipose tissue, but was later detected also in the heart. This subtype has recently attracted attention for its potential cardioprotective effects in heart failure setting[3] and its role and the mechanism of action are actively investigated in experimental and clinical studies.[4]

β_1- and β_2-ARs are potent stimulators of cardiac contraction and relaxation in the human heart.[2,5] As direct effectors of the sympathetic nervous system, they serve to rapidly adapt cardiac performance to an increased hemodynamic demand. Both β_1 and β_2 receptor subtypes couple to the stimulatory G protein (G_s), thereby activating adenylyl cyclase and leading to conversion of ATP to cAMP. The formation of the second messenger cAMP then leads to activation of protein kinase A (PKA), which phosphorylates several key regulators of the cardiac excitation–contraction machinery. This includes phospholamban, the L-type Ca-channel, the ryanodine receptor, troponin T and I, myosin-binding protein C, and the small protein phosphatase inhibitor-1.[5] These events lead to rapid (within seconds) changes of the cardiomyocyte calcium transient and enhanced myofilament sensitivity for calcium, resulting in potent inotropic effects.

Historically, β-adrenergic agonism was long taken as a surrogate parameter for beneficial effects in heart failure in the light of short-term experimental studies improving cardiac contractility. Emergence

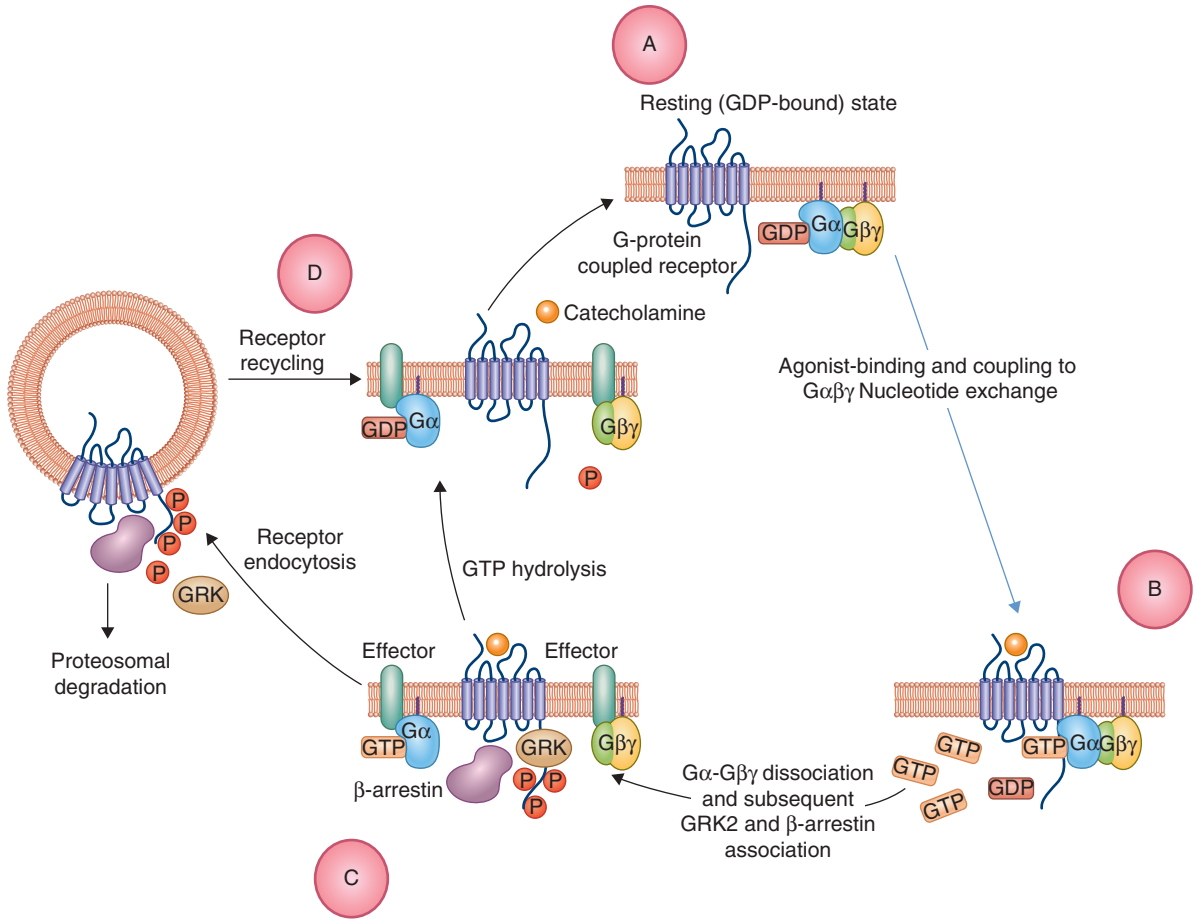

FIGURE 6–1. G protein–coupled receptor activation and GRK-mediated desensitization. **A.** At rest, G protein–coupled receptors and Gαβγ are not associated. **B.** Agonist (catecholamine) binding leads to receptor-Gαβγ association, followed by GDP release and subsequent binding of GTP on Gα. **C.** Gα and Gβγ become dissociated and mediate respective downstream signaling. Active receptors are soon phosphorylated by GRKs, which induce conformational changes and subsequent recruitment of β-arrestins. Arrestin binding to the receptor inhibits G-protein coupling and terminates signaling, a process termed desensitization. **D.** β-arrestin bound receptors are then endocytosed and processed for degradation or recycling. GTP on the Gα is hydrolyzed and Gα become available for next coupling event. GRK, G protein–coupled receptor kinase. Reproduced with permission from Sato PY, Chuprun JK, Schwartz M, et al: The evolving impact of g protein-coupled receptor kinases in cardiac health and disease, *Physiol Rev*. 2015 Apr;95(2):377-404.[1]

of transgenic mice models of β-adrenergic system contributed enormously to reveal the detrimental effects of chronic β-AR stimulation and the beneficial effects of receptor blockade during activated sympathetic nervous system. β_1-AR transgenic mice display cardiomyocyte hypertrophy, followed by fibrosis and finally heart failure.[6] Enhanced apoptosis, impaired calcium transients in cardiomyocytes, together with altered expression pattern of sarcoplasmic reticulum (SR)-proteins were found in these animals.[7] These data indicate that the β_1-AR system, which is ideally suited to provide short-term increases in cardiac contraction, causes marked structural and functional damage to the heart after extended periods of either receptor stimulation or overexpression.

Transgenic mice with ventricular overexpression of the human β_2-AR have led to a multitude of new insights about β_2-adrenergic signaling in the heart. In the initial report by Milano et al, a mouse model with more than a 1000-fold overexpression led to marked enhancement of basal cardiac contractility, which could not be further augmented by β-agonist treatment.[8] This dramatic level of receptor density remarkably did not result in overt cardiac pathology[9]; thus β_2-AR gene therapy was proposed to enhance myocardial function of failing hearts. However, overexpression of the human β_2-AR in disease models complicated the interpretation. High-density overexpression of the β_2-AR worsened cardiac function after aortic banding, whereas it rescued some of the consequences of myocardial infarction.[10] A study comparing different levels of β_2-AR overexpression on cardiac structure and function in transgenic mice showed that moderate (ie, 50-fold) overexpression was well tolerated, whereas very high densities of transgenic β_2-AR receptors (350-fold) induced cardiac pathology.[11] Thus, for the purpose of enhancing cardiac function by β_2-ARs, there seems to exist an optimum level of β_2-AR overexpression, with higher levels being detrimental.

Cardiac overexpression of the β_1- and the β_2-AR exhibits remarkable differences between the two β-receptor subtypes. In contrast to predominant coupling of β_1-AR to G_s, the dual sequential coupling of the β_2-AR to G_s and G_i (inhibitory) proteins has been reported (first G_s and then G_i).[12] In addition to coupling to G_i proteins, several "alternative" signaling pathways have been described to be activated directly by the β_2-AR, including mitogen-activated protein kinase (MAPK)-pathway and phosphatidylinositol-3-kinase (PI3-K).[12,13] Additionally, distinct temporal and spatial compartmentation of the classical cAMP pathway may play a role in AR subtype functional differences.[14]

One of the key mechanisms that drives heart failure development on chronic stimulation of cardiomyocyte β-ARs is apoptosis.[2,5] Induction of cardiomyocyte apoptosis was found after stimulation of isolated rat cardiomyocytes with high doses of isoproterenol.[15] In this follow-up study, it was demonstrated that β_1- and the β_2-AR subtypes

present opposing effects on cardiomyocyte apoptosis, with the β_1-subtype being proapoptotic and the β_2-subtype mediating antiapoptotic effects.[16] These results have been confirmed by several groups, including the studies of Xiao et al,[17] who isolated adult cardiomyocytes from β_1-/β_2-receptor double knockout mice and reintroduced the individual receptor subtypes by adenoviral gene transfer, resulting in "pure" β_1- and β_2-receptor expressing myocytes. Several responsible intracellular signaling pathways for antiapoptotic effects mediated by β_2-receptor have been proposed, including Akt-kinase via G_i, reactive oxygen species, and PKA-independent activation of Ca^{2+}/calmodulin-dependent protein kinase (CaMK). Interestingly, recent study suggests that there exists cardioprotective pathway in β_1-adrenergic signaling, and selective inhibition of proapoptotic pathway may represent an alternative therapeutic approach.[18]

CHANGES OF β-ADRENERGIC SIGNAL TRANSDUCTION IN HEART FAILURE

Desensitization of β-adrenergic signal transduction in heart failure was first discovered by Bristow et al.[19] Central findings to explain this phenomenon of reduced responsiveness to β-adrenergic stimulation were a reduction of β1-ARs density in failing human myocardium,[19] a decrease of norepinephrine reuptake, subsequently a decrease in cardiac norepinephrine stores, and finally an increased G_i protein expression and GRK2-activity.[1] Although initially considered detrimental, the observed desensitization of β-ARs is now realized as an adaptation process to the highly increased levels of catecholamines in heart failure. Thus, the β-adrenergic signal transduction cascade is operative but with its sensitivity adjusted to high catecholamine levels, to minimize the detrimental effects of chronic stimulation of the myocardium.[2]

The desensitization pattern of the two main cardiac β-AR-subtypes, β_1 and β_2, is also different. Although the β_1-subtype shows prominent downregulation (by about 50%), the β_2-subtype is nearly unaffected in its density.[20] The selective loss of the β_1-AR-subtype in human heart failure leads to a β_1:β_2 ratio of approximately 1:1, thus enhancing the relative contribution of the β_2-AR-subtype. It is to be taken into account, however, that the relevant ligand in vivo, norepinephrine, which is released by sympathetic nerve endings and the adrenal gland, is significantly β_1-selective (about 10- to 20-fold) and norepinephrine levels are enhanced in many heart failure patients.[5] Thus, the overall signal will still be dominated by the β_1-subtype. Recently, altered spatial distribution pattern of β_2-AR has been reported, and abnormal cAMP compartmentation was suggested as a potential contributor to the heart failure phenotype.[21]

After the first description of elevated GRK activity and GRK2 (synonymous for βAR kinase1 [βARK1]) expression in heart failure, numerous studies have confirmed elevated GRK2 activities in heart failure.[1] Elevated GRK activity is often regarded as a major factor contributing to the progression of heart failure through desensitization of the β-adrenergic signal transduction pathway. Evidence for this argument comes mainly from studies using a C-terminal peptide of GRK2 (termed βARKct) that not only has been demonstrated to effectively block desensitization of the β-AR in vitro[22] but that also proved to be an effective therapeutic agent.[23] The βγ-scavenging properties of the βARKct-peptide result in reduced translocation of GRK2 to the membrane, thereby reducing receptor-phosphorylation.[22] This inhibition of β-AR desensitization is regarded as the protective mechanism through increasing inotropy and preventing the internalization and coupling to "alternative" signaling mechanisms such as the activation of src-dependent pathways.[24] Despite the deregulated GRK2 expression in heart failure, it is interesting to find that GRK2-transgenic mice do not show obvious signs of overt cardiac pathology or heart failure.[25] This suggests that, although it is evident that GRK2 is critically involved in heart failure pathogenesis, GRK2 may not be the primary promoter of heart failure but rather collaborates with other signals that can be modified by interfering Gβγ-related pathways.

β-BLOCKERS AS THERAPEUTICS IN HEART FAILURE

β-AR blockade is now regarded as the single most effective therapeutic in heart failure treatment.[2,26] Despite the discovery of antagonists for the β-AR more than half a century ago, it took a long time for the β-blockers to be introduced into the clinical treatment of heart failure. After several large clinical trials, a marked benefit of this therapeutic approach in heart failure therapy was realized.[27,28] Because angiotensin-converting enzyme (ACE) inhibitors had been already introduced into heart failure therapy, the effect of β-blocker treatment in heart failure had to be tested not versus placebo but versus the patients already treated with established treatment regime, including ACE inhibitors. Nevertheless, β-blockade led to impressive reductions of mortality (ranging from 35% to 60%[27-29]), with larger effects than ACE inhibitors tested versus placebo. In contrast to ACE inhibitors, β-blockers not only reverse remodeling, but also increase systolic function after several months of treatment.[5]

Several large clinical trials with carvedilol, metoprolol, and bisoprolol have demonstrated a significant benefit in large placebo-controlled trials.[27-29] On the contrary, two β-blockers (xamoterol and bucindolol) with intrinsic sympathomimetic activity as a result of partial β-AR agonism have failed to reduce mortality or even increased mortality.[30,31] These drugs can increase the peripheral vascular resistance and may offset the beneficial effects; thus they are currently not recommended for use in patients with heart failure.

Carvedilol as an unselective β-blocker with multiple other pharmacological effects has been compared to the β_1-selective metoprolol in a landmark clinical trial, COMET.[32] Carvedilol showed a 6% higher reduction in overall mortality (17% higher relative to metoprolol).[28] In addition, carvedilol led to a significantly greater reduction of heart rate (short-term) and blood pressure (long-term) than did metoprolol—likely caused by the α1-AR blockade.[26]

MUTATIONS IN ADRENERGIC RECEPTOR GENES LEADING TO ALTERED SIGNALING PROPERTIES

In addition to the general principles of receptor regulation and dysregulation in health and disease as discussed above, there is increasing evidence that genetic polymorphisms of key proteins of the β-adrenergic signaling cascade can significantly influence the signaling properties in individual patients. Both the α_2-ARs as the principal presynaptic regulators of norepinephrine-release and the β-ARs as the principal effectors have been extensively studied, and numerous polymorphisms with potential significant clinical impact have been identified (Table 6–1).[33,34] Although the β_1-AR variants were significantly associated with worse clinical outcomes, that of β_2-AR variants seems less apparent. Among the presynaptic α_2-receptors, a deletion mutant of the α_{2C}-subtype has been shown to be significantly associated both with enhanced norepinephrine release and the risk of developing heart failure.[34] Thus, the clinical data from these variants of the β-AR signal transduction system are consistent with the experimental evidence that chronic β_1-adrenergic signaling is detrimental and β_2-AR signaling is protective. With the emerging gene sequencing technologies, it is reasonable to expect that our picture of genetic variations in receptors and other key proteins of the β-adrenergic signaling cascade will soon be refined, with more variants to be discovered and more reliable clinical data to be obtained.

TABLE 6–1. Major Adrenergic Receptor Polymorphisms Associated with the Heart

Receptor	AA position	Common	Rare	Frequency of Rare Allele (%)*	Minor phenotype (vs Major)
β1-AR	389	Arg	Gly	24–26	Lower AC activity on agonist binding and less receptor desensitization
β1-AR	49	Ser	Gly	12–28	Receptor desensitization and downregulation
β2-AR	16	Gly	Arg	38–59	No apparent difference in ligand binding and AC activation
β2-AR	27	Gln	Glu	7–46	No apparent difference in ligand binding and AC activation
β2-AR	164	Thr	Ile	0–4	Lower ligand biding affinity with reduced AC activity
α2-AR	322–325 deletion			4–62	Enhanced NE release caused by reduced receptor function

*Frequency of rare allele is variable among the race. Detailed race differences are reviewed in Brodde.[34]

Abbreviations: AA, amino acid; AC, adenylyl cyclase; AR; adrenergic receptor; NE, norepinephrine.

EXCITATION–CONTRACTION COUPLING

In the mammalian heart, depolarization of the cell membrane leads to the opening of voltage-gated L-type Ca^{2+} channels, located in the T-tubular regions of the myocytes, allowing the trans-sarcolemmal influx of Ca^{2+} into the cell[35] (Fig. 6–2). T-tubules invaginate the plasma membrane, rendering L-type Ca^{2+} channels in close proximity to the Ca^{2+} release channels, known as ryanodine receptors (RyRs). RyRs are located on the SR, the major Ca^{2+} storing organelles in the cardiomyocyte. Ca^{2+} entering the cells through a single L-type Ca^{2+} channel triggers the opening of one or a cluster of RyRs, inducing the local release of Ca^{2+} from the SR.[35,36] During membrane depolarization, a large number of L-type Ca^{2+} channels are opened, triggering a large release of Ca^{2+} from the SR, raising cytosolic Ca^{2+} from 0.1 to 0.2 μM to 2 to 10 μM, namely the Ca^{2+} spark.[35] The distance of the cleft between the cell plasma membrane, where L-type Ca^{2+} channel exists, and the SR membrane, which is roughly 12 nm in normal cardiomyocytes, is very critical for such a kind of coupling and signal transduction. Extension of the distance between them by pulling the plasma membrane impairs the signaling reliability.[37] The activity of individual RyRs and the number of the RyRs recruited during a spark play an important role in the spark morphology. The more active RyRs are, the more Ca^{2+} would be released and as a consequence, the increased Ca^{2+} spark size would be observed. SR Ca^{2+} content also regulates Ca^{2+} sparks, because stored Ca^{2+} plays a critical role in regulating RyR by increasing the activity of the RyRs and by sensitizing the threshold of RyR for activation to the stimulus.

The release of Ca^{2+} into the myofibrillar space in turn results in cross-bridge formation and contraction[35,38] (Fig. 6–3). The force–frequency relationship also contributes to the regulation of contractile strength in

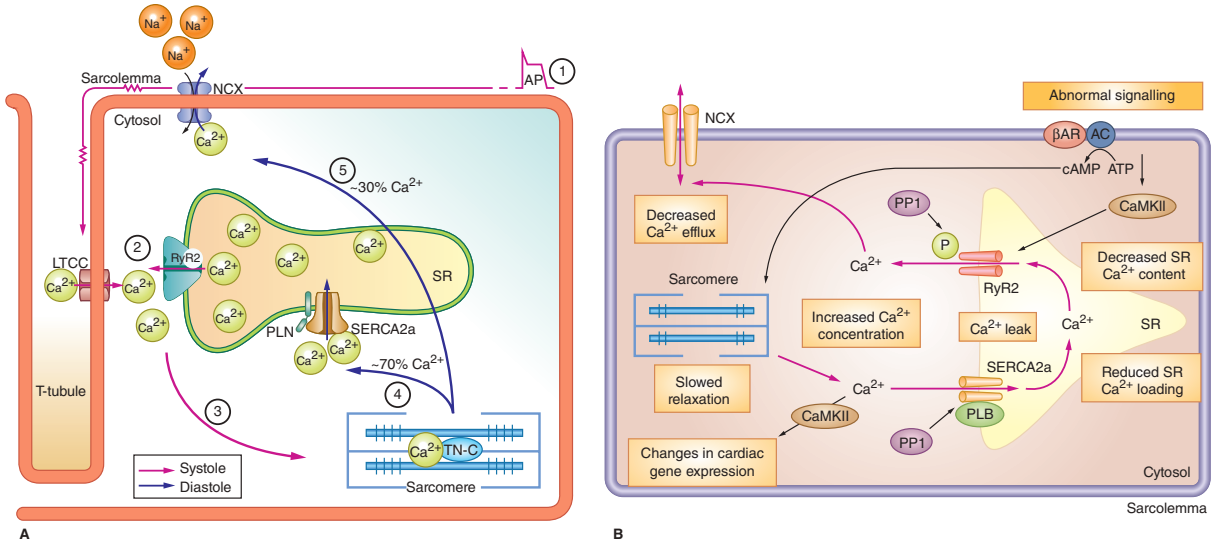

FIGURE 6–2. Excitation-contraction coupling and its dysregulation in heart failure. **A.** Excitation–contraction coupling. 1. During systole, the action potential depolarizes the sarcolemma and the extracellular Ca^{2+} enters cytosol via LTCC. 2. Ca^{2+} entry induce calcium-induced calcium release from RYR causing Ca^{2+} spark. 3. The intracellular Ca^{2+} concentration increases and binding of Ca^{2+} to TN-C activates myofilaments, resulting in muscle contraction. 4. Removal of cytosolic Ca^{2+} during diastole is primarily mediated by SERCA2a, which sequesters Ca^{2+} to the SR. 5. Some Ca^{2+} also exits the cell through NCX. The decrease in intracellular Ca^{2+} leads to dissociation of Ca^{2+} from TN-C and muscle relaxation. Reproduced with permission from Gorski PA, Ceholski DK1, Hajjar RJ: Altered myocardial calcium cycling and energetics in heart failure—a rational approach for disease treatment, *Cell Metab*. 2015 Feb 3;21(2):183-194.[38] **B.** Abnormal intracellular Ca^{2+} handling in failing cardiomyocytes results in reduced contractile force and prolonged relaxation. Decreased SERCA2a activity, SERCA2a downregulation, decreased PLB/SERCA2a ratio, and PLB hypophosphorylation lead to increased cytoplasmic Ca^{2+} concentration during diastole, resulting in prolonged intracellular Ca^{2+} transients, reduced SR Ca^{2+} loading, and slowed cardiomyocyte relaxation. SR Ca^{2+} leak resulting from impaired RyR function and increased PP1 activity can also reduce SR Ca^{2+} content and increase cytosolic Ca^{2+} concentration during diastole. An increase in NCX levels might be a compensatory response to prevent Ca^{2+} overloading. Although increased NCX activity would be initially adaptive, excessive or sustained NCX activation can contribute to decreased SR Ca^{2+} content by removing cytosolic Ca^{2+} and reducing systolic Ca^{2+} transients and contractile function. β-AR stimulation increases cAMP, which activates PKA. Hyperactive PKA decreases the Ca^{2+} sensitivity of the myofilaments and prolongs relaxation. Intracellular Ca^{2+} overload stimulates CaMKII, which contributes to SR diastolic Ca^{2+} leak by hyperphosphorylating RyR and induces the transduction of pathological Ca^{2+} signaling. AC, adenylate cyclase; AP, action potential; β-AR, β-adrenergic receptor; CaMKII, Ca-CaM-dependent protein kinase II; GPCR, G protein–coupled receptor; LTCC, L-type Ca^{2+} channel; NCX, Na^+/Ca^{2+} exchanger; P, phosphorylation; PLB, phospholamban; PP1, protein phosphatase 1; RyR2, ryanodine receptor 2; SERCA2a, sarcoplasmic/endoplasmic reticulum calcium ATPase 2a; SR, sarcoplasmic reticulum; TN-C, troponin C. Reproduced with permission from Kho C, Lee A, Hajjar RJ: Altered sarcoplasmic reticulum calcium cycling—targets for heart failure therapy, *Nat Rev Cardiol*. 2012 Dec;9(12):717-733.[48]

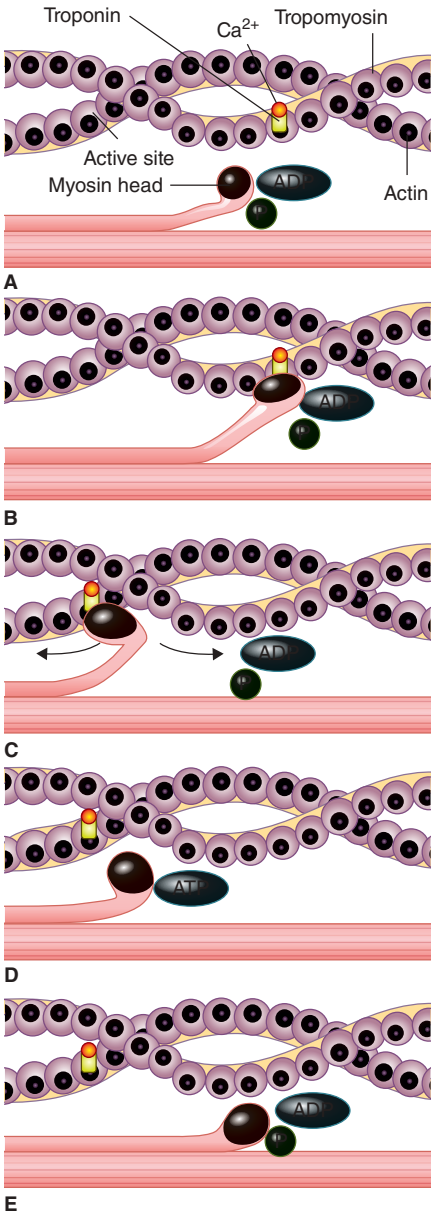

FIGURE 6–3. Cross-bridge cycling. When the cytosolic Ca^{2+} is low, the tropomyosin-troponin complex is positioned in such a way that the myosin heads cannot interact with actin. This is caused by the bond linking troponin I to actin. When cytosolic Ca^{2+} increases, it binds to troponin C strengthening the bond between troponin C and troponin I and weakening the bond linking troponin I to actin. **A.** This leads to a conformational change of the tropomyosin-troponin C complex, which allows the myosin head to interact with actin. **B.** When Ca^{2+} binds to troponin C, the active site of the thin filament is exposed, permitting the myosin head to interact with the actin filaments. **C.** Inorganic phosphate is released and a power stroke occurs, which moves the actin molecule 5 to 10 nm, locking the myosin head into a rigor state. Then the myosin head releases ADP and is ready to accept ATP. **D.** ATP binding to the myosin head dissociates the actin filaments and the myosin detaches from actin. **E.** ATP is hydrolyzed to ADP and inoraganic phosphate, moving back the myosin head to start the next cycle. Modified with permission from Ketchum H and Bright E: OU Human Physiology: Muscle Fiber Contraction and Relaxation Derived from Muscle Fiber Contraction and Relaxation. http://cnx.org/contents/8iuXPvsN@1/OU-Human-Physiology-Muscle-Fib. Access 12-8-16

the heart. In a normal heart, increasing heart rate results in enhanced trans-sarcolemmal Ca^{2+} influx secondary to high frequency–induced recruitment of Ca^{2+} currents, resulting in more Ca^{2+} release from the SR and stronger contraction. In addition, length-dependent activation of the myofilaments, known as Frank-Starling mechanism, serves as a largely Ca^{2+}-independent mechanism for the short-term regulation of the strength of contraction.

Relaxation occurs when calcium detaches from troponin C and is sequestered back into the SR by the cardiac isoform of the Ca^{2+} ATPase pump (sarcoplasmic reticulum Ca^{2+}-ATPase [SERCA2a]) or extruded extracellularly by the sarcolemmal Na^{+}/Ca^{2+} exchanger (NCX) (see Fig. 6–2). The contribution of each of these mechanisms for lowering cytosolic Ca^{2+} varies among species. The relative contribution of SERCA2a to diastolic calcium removal seems to be significantly lower in larger mammals compared to rodents. In humans, approximately 75% of the Ca^{2+} is removed by SERCA2a, and approximately 25% by the NCX and the role of the exchanger becomes more important in failing hearts.[35] SERCA2a transports Ca^{2+} back to the luminal space of the SR against a Ca^{2+} gradient by an energy-dependent mechanism (one molecule of ATP is hydrolyzed for the transport of two molecules of Ca^{2+}), where it binds to calcium-buffering proteins.

The Ca^{2+} pumping activity of SERCA2a is negatively regulated by phospholamban.[38,39] In its unphosphorylated state, phospholamban inhibits the SERCA2a, whereas phosphorylation of phospholamban by cAMP-dependent PKA and by calcium-calmodulin kinase II (CaMKII) reverses this inhibition. Consistently, gene therapy approaches applying inhibition of phospholamban have remarkably ameliorated the failure phenotype in vitro and in animal models of heart failure.[40,41] Mutation in phospholamban that inhibits the phosphorylation of wild type allele has been found in humans.[42] Interestingly, a heterozygous mutation (thus more inhibition of SERCA2a by phospholamban) has been demonstrated to cause heart failure in a family with hereditary cardiomyopathy.[42] In contrast, a human phospholamban mutation coding for a premature stop-codon also caused heart failure both in the heterozygous and the homozygous state.[43] At present, it is unclear how these findings can be integrated with the data obtained in animals except the notion that any form of altered phospholamban function might be detrimental in human.

Recent evidence supports an active role of phosphatases in cardiomyocytes excitation–contraction coupling.[39] Heart failure is accompanied by an increase in global protein phosphatase (PP) activity. Increased dephosphorylation is expected to aggravate the imbalance between phosphorylation and dephosphorylation, resulting in a net decrease in steady-state phosphorylation of target proteins. Protein phosphatase inhibitor-1 (I-1) is an endogenous negative regulator of PP1, which is activated by PKA and attenuates PP1 activity.[39] I-1 exerts an amplifier role in β-adrenergic signaling in cardiomyocytes.[44] Both transgenic mice overexpressing PP1 as well as I-1 knockout mice were associated with depressed basal cardiac function with blunted response to β-AR stimulation.[45] Additional evidence for the critical role of PP1 and I-1 in cardiac contractility comes from a study in protein kinase C-alpha (PKC-α), a negative regulator of I-1.[46] Overexpression of PKC-α reduced the I-1 interaction with PP-1, resulting in increased PP-1 activity and reduced cardiac contractility.

CHANGES IN HEART FAILURE

In cardiomyocytes isolated from patients with heart failure, contraction and relaxation exhibit a similar set of abnormalities regardless of the etiology. These can be attributed to alterations in cellular processes within the myocytes, including the sarcolemmal ionic channels, receptors, the intracellular pumps, the myofilaments, and the metabolic pathways that generate ATP. Abnormal calcium dynamics is a key causal component in the failing cardiomyocyte.[36,47] Cardiac cells isolated from failing human hearts exhibit three important characteristics: (1) a decrease in systolic Ca^{2+}, (2) an increase in diastolic Ca^{2+}, and (3) a prolonged relaxation phase.[35] In addition, a critical characteristic

of a failing cardiomyocyte is the negative frequency response: that is, a decrease in contraction and calcium release with increasing frequency.

Because calcium handling is regulated by the previously described pivotal proteins, including voltage-dependent L-type Ca^{2+} channel, RyR, the SERCA2a–phospholamban complex, and the NCX, studies have focused on the relative changes in these proteins between heart failure and normal hearts. The coupling between the L-type Ca^{2+} channels and the RyRs from patients with dilated cardiomyopathy has been shown to be defective, such that in failing myocardial cells L-type Ca^{2+} channels have a reduced ability to activate the adjacent RyRs. In addition, hyperphosphorylation of RyRs has been implicated in the pathogenesis of heart failure.[48] PKA phosphorylation modulates RyR function by changing the sensitivity of RyR to Ca^{2+}, resulting also in "leaky" channels that may cause diastolic Ca^{2+} release and generate delayed after depolarizations.[35,49]

In both failing human hearts and in experimental models of heart failure, there is a reduction in the expression and enzymatic activity of SERCA2a.[39,48] Reduced SERCA2a protein level and activity result in impaired intracellular Ca^{2+} uptake into the SR (see Fig. 6–2). Enhanced expression of the NCX has been also reported as a compensatory mechanism for the reduction of SERCA2a because the exchanger can operate to extrude Ca^{2+} out from the cell.[38] The elevated intracellular diastolic Ca^{2+} is central to the heart failure pathophysiology; therefore, therapies to enhance SERCA2a activity have emerged as a rational approach. Gene transfer of SERCA2a in human failing cardiomyocytes rescued the depressed contractility and improved myocardial energetic.[50] The beneficial effects of restoring SERCA2a levels were also confirmed in vivo using experimental animal models of heart failure.[38,48,51] The evidence for key regulatory role of SERCA2a in calcium handling has been recently fortified by two gene transfer studies. Post-translational modification of SERCA2a by small ubiquitin-like modifier 1 (SUMO-1) called SUMOylation has been shown to be critical for maintaining SERCA2a stability and activity.[52] In heart failure, SERCA2a SUMOylation was significantly decreased, and gene transfer of SUMO-1 or small molecule activators of SUMO-1 restored the SERCA2a level, which led to improved cardiac function.[53] S100A1 is a calcium-binding protein abundantly expressed in the normal heart, and it promotes cardiac contraction and relaxation via SERCA2a and RyR activation. The S100A1 level is decreased in heart failure, whereas overexpression of S100A1 restored contractility by increasing SERCA2a activity and modulating RyR.[54]

In contrast to decreased SERCA2a expression and activity in heart failure, phospholamban appears to maintain its protein levels, resulting in relative increase in SERCA2a inhibition.[38] In addition, phospholamban phosphorylation is reduced, further augmenting the inhibitory effect. PP1-protein expression is unchanged whereas global PP1 activity is increased in failing hearts.[39] This discrepancy can be explained by reduction in I-1 mRNA, protein, and phosphorylation levels, which have been found to be reduced by 50%, 60%, and 80%, respectively, in failing human hearts.[44] Expression of a constitutively active I-1 rescued function of isolated cardiomyocytes as well as failing hearts.[45,55,56]

A functional imbalance between signaling elements that increase diastolic calcium (Ca channel, RyR, partly also NCX) and those that reduce it (SERCA, possibly also NCX) would elevate cytosolic free Ca^{2+} as described above. It appears possible that this is a final pathway of many alterations that lead to heart failure. What might be the downstream mechanisms exerting the detrimental action of cytosolic calcium? A multitude of experimental studies has refined our picture how enhanced Ca^{2+} levels might chronically harm cardiomyocytes. Specifically, activation of calcineurin[57] and the calmodulin/CaMK[47] pathway appear to be critically involved in Ca^{2+}-mediated cardiomyocyte hypertrophy as described later in this chapter.

CONTRACTILE PROTEINS

A number of abnormalities also occur at the level of the contractile proteins in failing myocardium. There is a decrease in the fast isoform of the myosin heavy chain (α-MHC) and an increase in the slower isoform β-MHC.[58] This isoform switch correlates with systolic dysfunction, and its reversal by β-blockers was associated with functional restoration.[59] An increase in β-MHC results in a decrease in cross-bridge cycling rate and an increase in energy conservation because fewer ATP molecules are split. It also leads to a slower contraction and relaxation phases which are characteristic of failing myocardium. Omecamtiv mecarbil, an activator of cardiac myosin, increases the transition rate of myosin into the actin-bound state and prolongs systolic ejection time without increasing calcium transient.[60] Intravenous administration of omecamtiv was recently shown to increase stroke volume in a phase II clinical trial in patients with stable heart failure.[61]

SIGNALING PATHWAYS IN HYPERTROPHY AND HEART FAILURE

Hypertrophy is the predominant method for the heart to increase its size and mass, because cardiomyocytes are terminally differentiated and have very limited capacity for hyperplastic growth. It is usually categorized to physiologic hypertrophy and pathologic hypertrophy.[62,63] Physiologic hypertrophy occurs in response to growth, exercise, and pregnancy without apparent abnormalities in both systolic and diastolic function. In contrast, pathologic hypertrophy takes place in chronically increased cardiac load represented by hypertension and valvular diseases. Pathologic hypertrophy is described as concentric (characterized by addition of sarcomeres in parallel, leading to increased thickness of the myocyte) and eccentric (characterized by the addition of sarcomeres in series, leading to increased length).[62] If the load placed on the heart is not normalized, the heart may continue to hypertrophy, eventually leading to elevated filling pressures caused by increased ventricular stiffness. The hypertrophied heart may also begin to decompensate in the long-term, leading to progressive dilatation and systolic dysfunction. Not surprisingly, cardiac hypertrophy is a significant risk factor for the development of heart failure and, in addition, for sudden death.[64]

Irrespective of the type of hypertrophy, the processes of hypertrophy require a dramatic reprogramming of gene expression to upregulate gene products necessary for growth of the cardiomyocytes. These include genes encoding contractile elements and proteins of the basic transcriptional and translational machinery that allow new protein production and the genes encoding proteins that remodel the extracellular matrix, allowing growth to proceed. This process of reprogramming occurs in response to respective growth signals that are generated from a multitude of sources. In order to reprogram gene expression, these signals must be sensed at the cardiomyocyte membrane and transmitted into the interior of the cell, eventually into the nucleus, by a process called signal transduction. A large number of growth factors as well as signaling molecules have been reported to induce growth. Here, we will focus on the major arms for which strong evidence exist implicating components of the pathway in the hypertrophic response.

THE SIGNAL AT THE CELL MEMBRANE

Two types of stimuli are believed to trigger the hypertrophic response: mechanical deformation of the membrane (cell stretch) and growth-promoting ligands binding to their cognate receptors in the myocyte cell membrane. Stretch of cardiomyocytes in culture leads to gene transcription and protein synthesis in a pattern that closely resembles the

load-induced hypertrophic response in vivo.[65] Stretch triggers responses both via the direct activation of signaling molecules and by inducing the release of humoral factors. Direct activation involves recruitment of integrin signaling and stretch-activated ion channels.[66] For example, melusin, an integrin bound protein, is activated by mechanical stretch and promote adaptive hypertrophy via PI3-kinase/Akt and GRK3.[67]

The release of growth factors acts in an autocrine or paracrine fashion to amplify hypertrophic responses. Angiotensin II activates a number of prohypertrophic signaling pathways.[68] The interleukin-6 family of cytokines, including cardiotrophin-1, is another group of factors released by mechanical stretch, which act via receptors specific to the cytokine and via the common receptor, gp130.[69] A wealth of data implicates that the insulin-like growth factor-1 (IGF-1) signaling is also activated by a variety of stimuli that induce hypertrophy. Many of the prohypertrophic peptides bind to receptors that are linked to heterotrimeric G proteins of the Gq family. These G proteins convert receptor activation into mobilization of intracellular signaling pathways, and are the initial trigger for downstream events.[70] Cardiac-specific overexpression of the α subunit of Gq led to cardiac hypertrophy.[71] Later, it was reported that expressing a peptide that inhibits Gq-dependent signaling significantly limits the hypertrophic response to pressure overload in vivo.[72] These studies, taken together, confirm a critical role of Gq in hypertrophic signaling and in the hypertrophic response to pressure overload. Activation of these proximal mediators of the stretch response results in increased cytosolic calcium, which plays a role in activating several signaling pathways, including calcineurin.

SIGNALING WITHIN THE CELL

There are two essential features of hypertrophic growth: reprogramming of gene expression and protein synthesis. Each is regulated by a series of intracellular pathways that are activated by events occurring at the membrane as described above. Signal transmission from the cell membrane to the nucleus is essential for gene reprogramming.[46] This is generally accomplished by linear cascades of proteins, most commonly protein kinases and also by the protein phosphatase calcineurin, activating one another in sequence, culminating in the phosphorylation and activation of one or more transcription factors. The transcription factors then bind to promoter elements, promoting the gene transcription. Each transcription factor will usually target several genes, and the net result of the activation of the entire set of genes is the hypertrophic response. Characteristic of the response is a reestablishment of a gene program often described as "embryonic" or "fetal," because some of the gene expression pattern resembles that of normally expressed in utero. The genes induced by the hypertrophic response are often divided into three groups based on their time of expression: immediate early, intermediate, and late. Immediate early genes include the neurohormonal mediator, brain natriuretic peptide, and several stress-induced genes or genes involved in growth control. These include c-Fos, c-Jun, c-Myc, Egr-1, and heat shock protein 70 (HSP70). Intermediate response genes include atrial natriuretic peptide and angiotensinogen as well as several sarcomeric components, β-MHC (and corresponding downregulation of α-MHC), myosin light chain-2, and skeletal α-actin (replacing cardiac α-actin). Late response genes include ACE and the NCX.

IN-DEPTH EVALUATION OF CALCIUM-DEPENDENT HYPERTROPHIC SIGNALING

The calcineurin pathway is the most consistently reported pathway that has been shown to regulate hypertrophic growth in a number of different models. Calcineurin, also known as protein phosphatase 2B (PP2B), is a calcium-calmodulin–activated protein phosphatase, and it is uniquely activated by sustained elevations in intracellular calcium[35] (Fig. 6–4). Transgenic mice overexpressing an activated

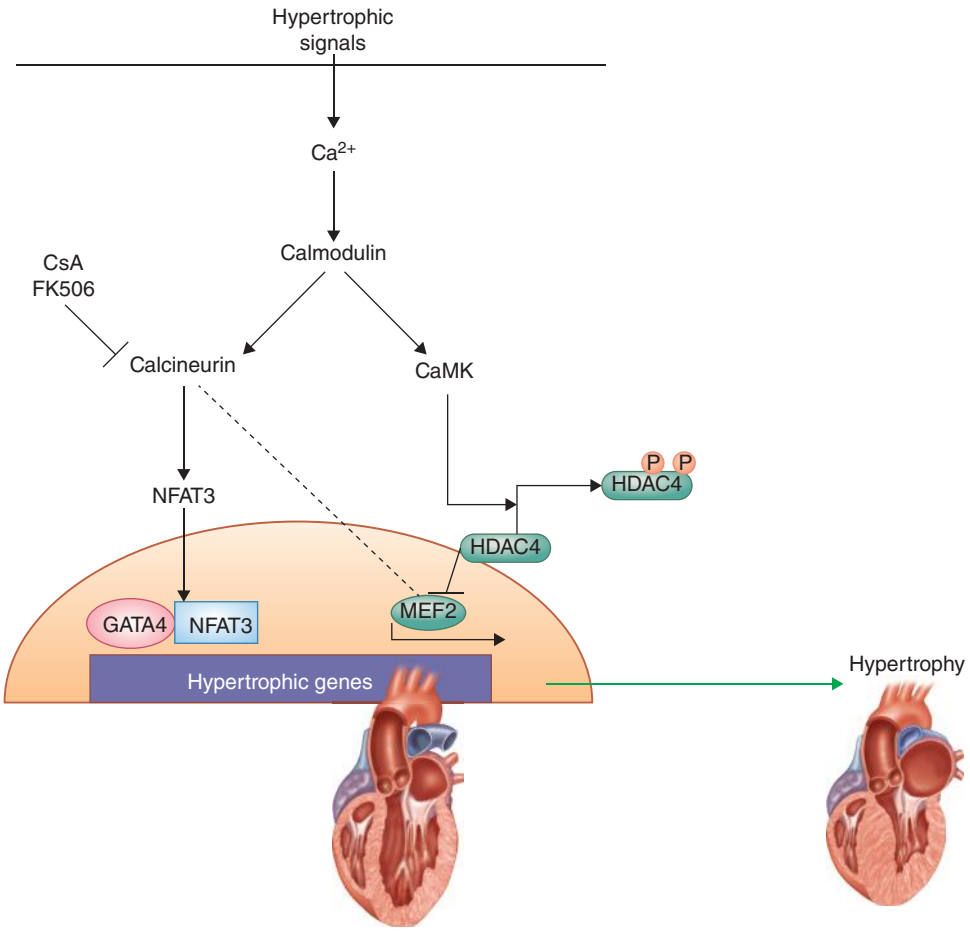

FIGURE 6–4. Calcineurin pathway in hypertrophy. Stimuli that induce hypertrophic signaling increases cytosolic calcium levels. When the intracellular calcium level rises to 10^{-5} M, four Ca^{2+} ions bind to calmodulin, and this Ca^{2+}-calmodulin complex activates many calmodulin (CaM)-dependent enzymes, including the phosphatase calcineurin and the CaM-dependent kinases, CaMKII. Once activated, calcineurin directly dephosphorylates members of the NFAT transcription factor family in the cytoplasm, promoting their translocation into the nucleus. In the nucleus, NFAT family members participate in the transcriptional induction of various immune response genes. CaMKII phosphorylates the HDACs to induce their nuclear export and relieve the inhibition on the transcription factor MEF-2. These signals reprogram gene expression resulting in cardiac hypertrophy. CsA and FK506 are calcineurin inhibitors. CaM, calmodulin; CaMKII, Ca–CaM-dependent protein kinase II; CsA, cyclosporin A; HDAC, histone deacetylases; MEF2, myocyte enhancer factor-2; NFAT, nuclear factor of activated T-cells. Modified with permission from Passier R, Zeng H, Frey N, et al: CaM kinase signaling induces cardiac hypertrophy and activates the MEF2 transcription factor in vivo, *J Clin Invest*. 2000 May;105(10):1395-1406.

form of calcineurin in the hearts induced a profound hypertrophic response (two- to three-fold increase in heart size) that rapidly progressed to dilated heart failure within 2 to 3 months.[57] Such data implicate calcineurin as a sufficient inducer of the hypertrophic response and as a potential causative factor associated with the transition to decompensation and heart failure. Calcineurin catalytic activity can be inhibited by the immunosuppressive drugs cyclosporine A (CsA) and FK506. Inhibition of calcineurin with either CsA or FK506 can antagonize cardiac hypertrophy and/or disease progression in pleiotropic rodent models.[73] However, their potential usefulness in humans remains uncertain because both CsA and FK506 have a number of side effects in humans, including nephrogenic and neurogenic toxicity and immunosuppression.

CaMKII is another target of calcium–calmodulin activation. CaMKII is involved in intracellular Ca^{2+} handling regulation, affecting contractility and relaxation of the cardiomyocytes.[47] This molecule also modulates gene transcription by phosphorylating several transcription factors including class II histone deacetylases, thereby enhancing the myocyte enhancer factor 2 activity. Increased CaMKII activity was found in hypertrophied and failing myocardium.[47] CaMKII overexpression induced cardiac hypertrophy,[74] whereas loss of CaMKII was associated with attenuated cardiac hypertrophy on hypertrophic stimulation.[75]

In summary, these pathways illustrate the paradigm of how a signal, increased cytosolic Ca^{2+}, generated in response to either deformation of the membrane or to hypertrophic agonist binding to its receptor, activates key signaling factors (calcineurin/CaMKII), which then activates transcription factors that, in turn, reprogramming gene expression.

REGULATION OF PROTEIN SYNTHESIS

The second critical component of hypertrophic growth is the ability to dramatically upregulate protein synthetic capabilities. This is regulated by two very complex, interacting pathways. One is the PI3-kinase pathway that, in addition to its role in regulating protein synthesis, also plays a major role in reprogramming gene expression. The other is the mammalian target of rapamycin (mTOR) pathway. These pathways are essential in determination of cell, organ, and body size (ie, normal growth) in species as diverse as Drosophila and human, but they are also recruited in, and regulate the response to, pathologic stress-induced hypertrophic growth. Both the PI3-K and mTOR pathways regulate protein synthesis by modulating the activity of various translation factors.

The Phosphoinositide 3-Kinase Pathway

This highly conserved pathway (Fig. 6–5) is remarkable in the fact that virtually every component of the pathway has been shown in animal models to regulate cell and organ growth, including growth of the heart. The pathway is activated by most (if not all) of the agonists implicated in inducing cardiac hypertrophy including pressure overload.[63] When activated, the PI3-K phosphorylates the integral membrane phospholipid, phosphatidylinositol, leading to the recruitment of the protein kinase, Akt (also known as protein kinase B, PKB) to the cell membrane. This brings PKB/Akt into proximity to its activator, the 3-phosphoinositide-dependent protein kinase-1 (PDK1), and results in activation of PKB/Akt.[76] PKB/Akt then plays a role in activating mTOR and consequently, p70S6K and the protein translation machinery.[77] Consistent with this, all PI3-K, PDK1, and PKB/Akt have been shown to regulate cell and organ size, including size of the heart. Recently, inhibition of PI3-K p110γ has been shown to normalize β-AR density and improve cardiac contractility in mouse heart failure,[78] and its efficacy in humans is explored in clinical trials.[4]

Evaluation of mTOR

The importance of the protein kinase mTOR is illustrated by its conservation throughout evolution, from yeast to human. The critical importance of mTOR in regulating hypertrophic growth in vivo was demonstrated when its inhibitor, rapamycin, was found to attenuate the hypertrophic response to pressure overload in mice.[79] Distinct functions of mTOR are reflected in its assembly as structurally distinct multiprotein complexes, mTORC1 and mTORC2 (see Fig. 6–5). Growth factors, including those leading to cardiac growth such as insulin and IGF-1 activate mTORC1. Activation of mTORC1 leads to disinhibition of translation initiation factor, eukaryotic initiation factor 4E, resulting in enhanced protein synthesis.[77] Because mTORC pathway is also required for physiological hypertrophic response, complete inhibition of this pathway results in rapid ventricular dilatation and dysfunction upon pressure overload.[80] In contrast, partial inhibition of mTORC1 seems to be able to reduce only pathological hypertrophy.[77]

OTHER PATHWAYS INVOLVED IN GROWTH REGULATION

Involvement of MAPKs in a repertoire of biological processes has been reported including proliferation, differentiation, metabolism, motility, survival, and apoptosis.[13] Stress-activated MAPKs, the c-Jun N-terminal kinases (JNKs), and the p38 have been exhaustively studied (see Fig. 6–5); however, their exact role in hypertrophy remains obscure.[13] Given the central role of these kinases in very basic responses of all cells to a wide range of cellular stressors (eg, oxidant stress, ionizing radiation, cytokine stimulation, osmolar stress, heat shock), compensatory adaptations are likely to be profound in various circumstances. Assessment of the present data suggest that the JNKs and p38 may be more involved in the progression of heart failure, including remodeling of the matrix, and may play much less of a role in hypertrophic growth.[81] The extracellular signal-regulated kinases ERK family of MAPKs is also potently activated by hypertrophic stimuli. Interestingly, cardiac-specific overexpression of MEK1 (one of the immediate upstream activators of the ERKs) produced concentric cardiac hypertrophy, but unlike most other models, the MEK1 transgenic animals did not progress to contractile failure.[82] These data raised the concept of "beneficial" hypertrophy versus "detrimental" hypertrophy by clearly demonstrating that hypertrophy per se need not inexorably progress to heart failure. This may have to do with the fact that the ERKs (in contrast to many other prohypertrophic signaling molecules, including calcineurin, the JNKs, and the p38) are in many circumstances, cytoprotective.[13]

Glycogen synthase kinase-3 (GSK-3) is another target of PKB/Akt involved in hypertrophic signaling. GSK-3β is a negative regulator of cardiac growth. Transgenic animals expressing GSK-3β have dramatic reductions in normal cardiac growth and also have a markedly reduced hypertrophic response to pressure overload.[83] Furthermore, inhibition of GSK-3β is necessary for the hypertrophic response to a number of agonists, likely mediated via several mechanisms. The GSK-3β targets include the nuclear factor of activated T cells (NFATs), and thus GSK-3β acts in opposition to the calcineurin pathway.[84] Other known growth regulators negatively regulated by GSK-3β include c-Myc, GATA-4, β-catenin, and c-Jun.[85]

ALTERATIONS IN SIGNALING IN THE DISEASED HUMAN HEART

Despite the continuous efforts to characterize molecular pathways in hypertrophy using transgenic and pressure overload animal models, analysis in human heart tissues exhibits somewhat inconsistent results. For example, in one study, various signaling factors (calcineurin, ERK1/2, JNK, p38, PKB/Akt, and GSK-3) were examined in

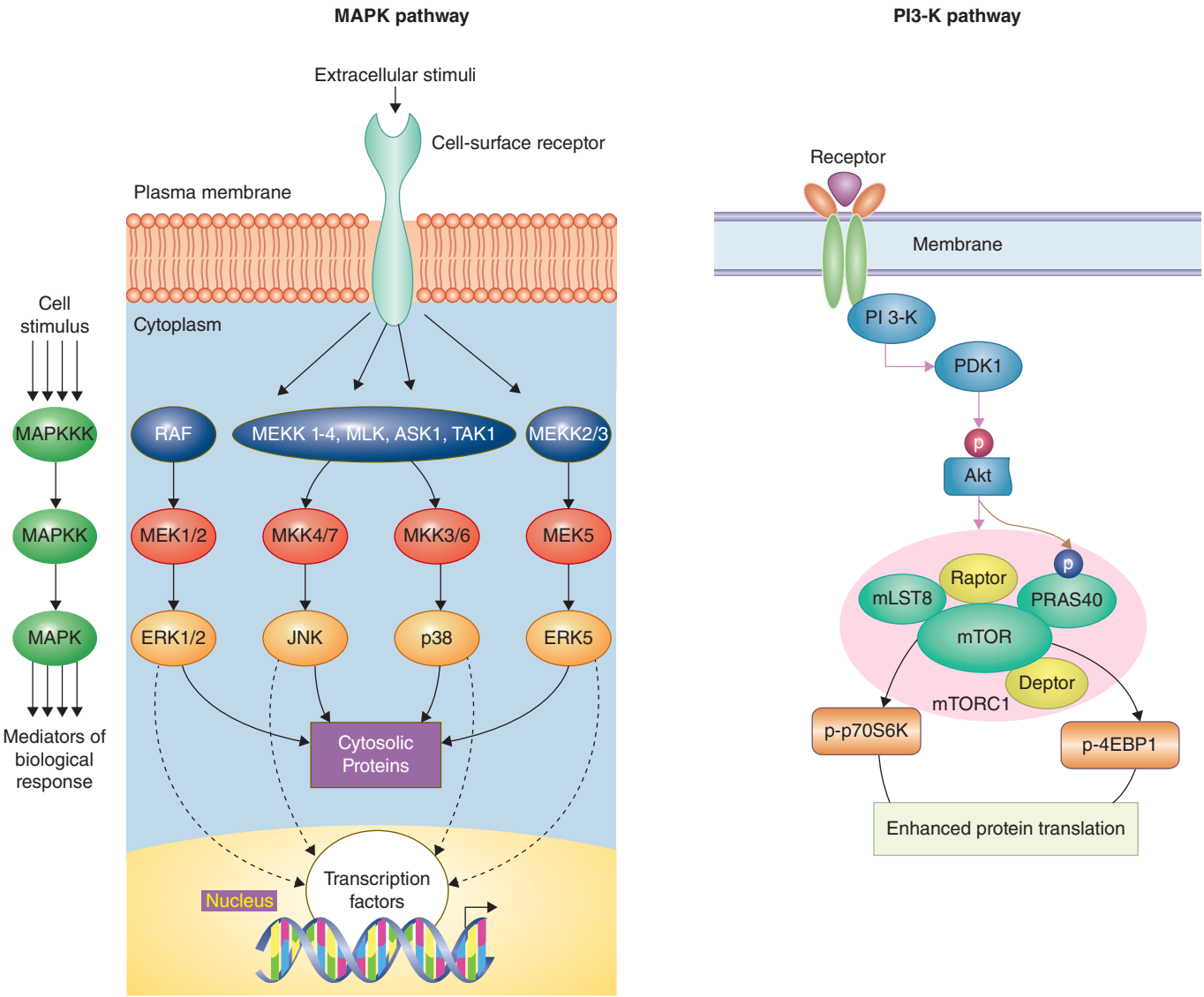

FIGURE 6–5. MAPK and PI3K pathways in hypertrophy. *Left:* MAPK pathway. MAPK signaling pathway transmits signals through a stream of several serial kinase reactions. Extracellular stimuli activate the MAPK pathways. Once MAPKKKs, such as RAF, MEKK and TAK, are activated, they phosphorylate MAPKKs. The relayed signals eventually trigger activation of three major distal MAPKs including ERKs, p38, and JNKs. These activated MAPKs can translocate to the nucleus and phosphorylate numbers of transcription factors thereby altering gene expression. Reproduced with permission from Rose BA, Force T, Wang Y: Mitogen-activated protein kinase signaling in the heart: angels versus demons in a heart-breaking tale, *Physiol Rev*. 2010 Oct;90(4):1507-1546. *Right:* PI3-K pathway. PI3-K activation recruits Akt to the plasma membrane through activation by PDK1. Akt promote complex assembly of mTORC1 through a series of signaling pathways. On activation, mTORC1 phosphorylates its two major downstream targets p70S6K and eukaryotic initiation factor 4EBP1 and mediates cell growth, proliferation, and cell survival. mTORC1 consists of the regulatory-associated protein of mTOR (Raptor), the proline-rich Akt substrate 40 kDa (PRAS40), the mammalian lethal with Sec13 protein 8 (mLST8), and the DEP domain-containing mTOR interacting protein (Deptor). Reproduced with permission from Chong ZZ, Maiese K: Mammalian target of rapamycin signaling in diabetic cardiovascular disease, *Cardiovasc Diabetol*. 2012 Jul 16;11:45. 4EBP1, 4E-binding protein 1; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; MEKK = MAPK/ERK kinase kinase; MAPK, mitogen-activated protein kinase; MAPKK, MAPK kinase; MAPKKK, MAPK kinase kinase, mTORC1, mammalian target of rapamycin complex 1; PDK1, phosphoinositide dependent kinase 1; p70S6K, p70 ribosome S6 kinase; PI3-K, phosphatidylinositol 3-kinase; TAK , TGFβ-activated kinase.

the hypertrophic heart without heart failure, and calcineurin was the only factor that was consistently found to be activated.[86] In contrast to the paucity of data on hypertrophied hearts, several studies have examined the signaling profile of hearts explanted from patients with advanced heart failure undergoing either transplant or left ventricular assist device placement. Where examined, calcineurin expression and activity were increased significantly.[87,88] Activation of p38 was generally reported, although there seems to be a substantial variability.[81] Meanwhile, no consistent results have been reported for JNKs and ERKs. PKB/Akt was found to be activated, irrespective of the etiology of the heart failure, and accordingly, its downstream target, GSK-3β, was inhibited.[89] Variabilities among the studies could be accounted for by a number of factors, including different medical therapies, device therapies, status of the patient, and methods of preserving the tissue.

To summarize, current data are insufficient to conclude whether any signaling alterations are causal or simply a consequence of the hypertrophy and heart failure. The complexity of the heart failure signaling abnormalities and the changing activities of various pathways at various times in the progression of disease creates a "moving target" and leads to significant challenges to determine the key pathways. The patients with compensated hypertrophy versus advanced heart failure are obviously at different ends of the pathophysiologic spectrum of heart failure, and in between these points, including the transition to

and early progression of heart failure, we have very little data on what pathways might be reasonable targets.

MECHANISMS OF CELL DEATH

Myocardial cell loss by any mechanism is an important component in the genesis of heart failure. Although necrosis has been regarded as the predominant mode of myocardial cell death, there is increasing evidence that cells die through a variety of programmed and nonprogrammed mechanisms. In addition to necrosis, cardiac cells may be lost through apoptosis as well as by misfolded protein accumulation associated with protein degradation mechanisms. The proportion of cells dying through each mechanism may differ at various stages in the natural history of heart failure, and therapeutic interventions may radically alter the fate of cells dying of each mechanism. Apart from mechanistic insights, understanding of such mechanisms of cell survival and death may offer clue for novel therapeutic approaches.

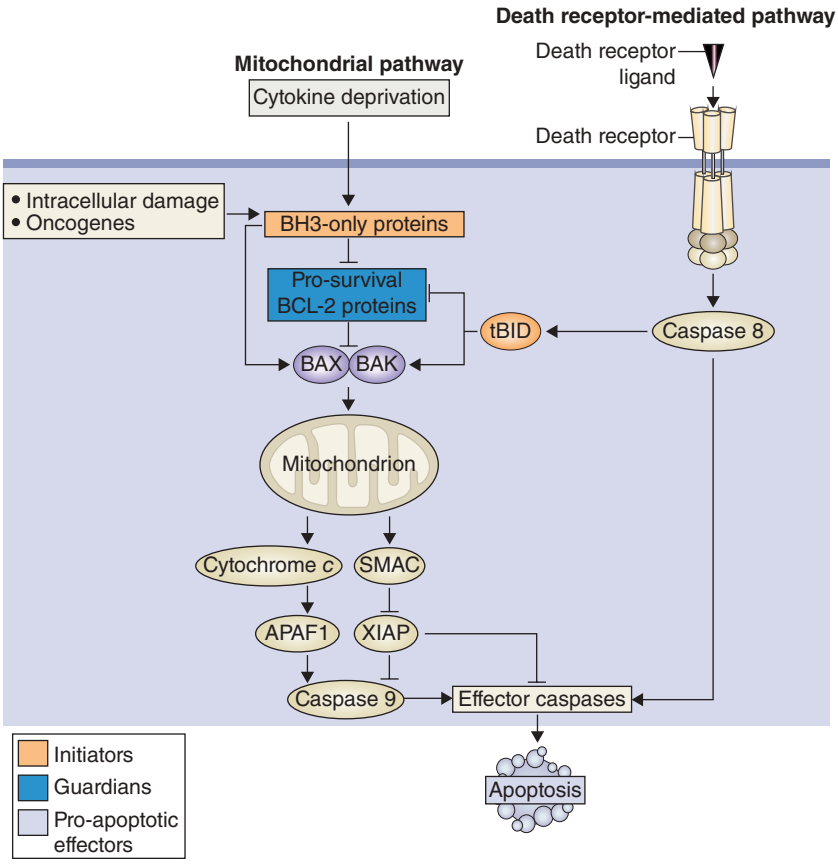

FIGURE 6–6. Apoptosis pathway. Two distinct, but not mutually exclusive, pathways of apoptotic cell death have been well desribed: extrinsic and intrinsic pathways. In the *extrinsic* pathway, soluble or cell surface death ligands, such as TNF-α and Fas ligand, bind to the corresponding death receptors inducing activation of upstream caspases, such as caspase-8, followed by activation of downstream effector caspases. In the *intrinsic* pathway, cytochrome c is released from mitochondria into the cytoplasm, often initiated by stress stimuli such as ischemia, oxidative stress, genotoxic stress, and calcium excess. These stimuli activate BH3-only family members and inhibit the prosurvival BCL-2-like proteins. Cytoplasmic cytochrome c in presence of dATP/ATP binds Apaf-1 to activate caspase-9 and subsequently downstream effector caspases. Once activated, the effector caspases fragment intracellular proteins resulting in the orderly destruction of the cell. The effector caspases also activate DNAses and lead to fragmentation of nuclear DNA.[226] The death receptor and mitochondrial pathways are linked by Bid, which stimulates cytochrome c release through interactions with the proapoptotic Bcl-family members, Bax and/or Bak.[227] The antiapoptotic Bcl-family members, Bcl-2 and Bcl-xL inhibit cell death by competing with Bax and Bak.[228] When apoptosis is induced, in addition to cytochrome c, SMAC is also released from the mitochondria that binds to XIAP precluding its inhibition of caspases. APAF1, apoptotic protease-activating factor 1; SMAC, second mitochondria-derived activator of caspases; tBID, truncated form of BID; TNF, tumor necrosis factor; XIAP, X-linked inhibitor of apoptosis protein. Reproduced with permission from Czabotar PE, Lessene G, Strasser A, et al: Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy, *Nat Rev Mol Cell Biol*. 2014 Jan;15(1):49-63.

CELL DEATH BY NECROSIS IN HEART FAILURE

The causes of necrotic cell death in heart failure are multiple.[90,91] Ongoing ischemia and the injury following reperfusion are the most common causes and infringe on aerobic oxidative respiration. Infective agents, postinfective immune processes, hypersensitivity phenomenon, and autoimmune diseases result in predominant inflammatory injury. In addition, chemical insults including alcohol and doxorubicin toxicity are infrequent causes of myocardial damage. Regardless of the inciting agent, several common biochemical pathways mediate cell necrosis, the most important of which is ATP depletion, which occurs commonly during hypoxia and ischemia. Partially reduced reactive oxygen species, produced during oxidative phosphorylation, are exaggerated during reperfusion injury and lead to cellular damage.[92] In addition to ATP depletion and oxidative stress, an increase in intracellular calcium activates potentially deleterious enzymes, such as phospholipases, proteases, ATPase, and endonucleases. These biochemical events contribute to mitochondrial and cell membrane damage. Formation of a permeability transition pore in the mitochondrial membrane leads to loss of mitochondrial membrane potential, which is critical for oxidative phosphorylation. On the other hand, the loss of integrity of the cell membrane, which is the hallmark of necrotic cell death, leads to cell swelling, extrusion of intracellular content and induction of inflammation.[93] Morphologically, there is severe disruption of cell membrane in necrosis that is associated with loss of cell contents.[94] Most necrotic cells and their debris are removed by a combined process of digestion and fragmentation, with phagocytosis of particulate debris. If not destroyed and removed, they attract calcium salts and other minerals and develop dystrophic calcification. Recently, a programed necrosis, namely necroptosis, was focused as another form of necrosis,[95] and its role in the progression to heart failure is actively explored.[96]

CELL DEATH BY APOPTOSIS IN THE FAILING MYOCARDIUM

Apoptosis is a genetically programmed and energy-requiring series of events that permits the cell to die without inducing an inflammatory response. The classical changes of apoptosis include cell shrinkage and formation of apoptotic bodies.[97] The activation of DNAses results in cleavage of chromatin into multimers of oligonucleosomal-length DNA fragments, evident on agarose gel electrophoresis. Sarcolemmal integrity is preserved but progressive convolution of membrane breaks up the cell into clusters of membrane-bound subcellular organelles referred to as apoptotic bodies. Unlike necrosis, because cell swelling and sarcolemmal disintegration do not occur, cytoplasmic contents are not released and inflammation not provoked. Apoptotic bodies are phagocytosed and removed.

External and internal stimuli can trigger death receptor-mediated (also known as extrinsic) or mitochondrial-mediated (intrinsic) apoptosis[94] (Fig. 6–6). Both involve activation of highly specific proteolytic enzymes referred to as caspases.[98] Apoptosis in human heart failure was

initially demonstrated by Narula et al[99] based on the histochemical demonstration of DNA fragmentation; apoptosis occurred both in ischemic and dilated cardiomyopathy. It was proposed that slow ongoing apoptotic loss of myocytes (rate of 0.12%–0.70%)[94] may contribute to inexorable progression of chronic heart failure. The ultrastructural studies in explanted hearts demonstrated cytochrome c release from mitochondria to cytoplasm in failing hearts.[100] Downstream to cytochrome c release, caspase 3 was also found to be activated in the cardiomyopathic hearts. Although the majority of myocytes demonstrate ultrastructural evidence of cytochrome c release and there is variable loss of cytoplasmic proteins, the nuclei in all these cells remain essentially normal.[101] Intactness of nuclei suggests the viability of cardiomyocytes. Lack of clear damage to nucleus despite the induction of apoptotic process in cardiomyocytes appears to be different from that seen in the classic apoptosis. A myocyte that maintains its nuclear integrity, but has compromised its respiratory chain and oxidative phosphorylation and allows variable destruction of its contractile proteins should contribute to systolic dysfunction of the cell.[101] Such cells with intact nucleus may be amenable to recovery and can be a therapeutic target.

ROLE OF UBIQUITIN–PROTEASOME PATHWAY AND AUTOPHAGY IN MYOCYTE DEATH IN HEART FAILURE

There are multiple mechanisms that the body uses to remove inappropriately folded or damaged proteins. In the failing heart, these defective proteins increase as a result of the endoplasmic reticulum (ER) stress and play important roles in heart failure pathophysiology.[102] Failing to remove abnormal proteins in cardiomyocytes can form toxic aggregates, which leads to development of cardiomyopathies. Two major protein degradation systems are the ubiquitin–proteasome system and autophagy. The evolutionarily highly conserved ubiquitin system labels substrate proteins with a ubiquitin molecule on lysine residues en route to degradation. The ubiquitination-protease system is responsible for 80% to 90% of protein degradation in vivo with a high specificity.[103] Numbers of experimental animal and human heart tissue studies suggest impaired function of the ubiquitin-proteasome system,[104] rendering it as an attractive therapeutic target. Autophagy is another protein quality control system that is involved in a bulk degradation of long-lived proteins and aggregated proteins. Damaged proteins are isolated in double-membrane vesicles, known as autophagosomes, and degraded by lysosome. Autophagy is activated in heart failure; however, this is likely a secondary activation, and whether inhibiting autophagy is beneficial currently remains controversial.[105]

Unfolded protein response (UPR) is a mechanism in which the cells try to protect themselves from increased ER stress stimuli such as ischemia, altered redox status, or impaired calcium homeostasis.[106] UPR serves to relieve the ER stress by downregulating the protein translation, generating chaperone proteins, and degrading proteins through ER-associated degradation as well as autophagy.[105,107] Such mechanisms help the cells survive by reducing the entry of new proteins into the ER, and increasing protein translocation out of it. Activation of UPR is found in heart failure; however, prolonged ER stress can lead to accumulation of protein aggregates, which eventually triggers cell death signals.

CROSS-TALK IN DEATH PATHWAYS

It is becoming clearer that various forms of death may be a part of the same spectrum, and multiple morphologies of cell death may coexist in a very close proximity.[108] It has been demonstrated that inhibiting one pathway of death may simply switch it to die by another pathway.[109,110] One could speculate that cross-talk in death pathways might be dependent on a number of associated factors such as the energy state of cell and intensity of damage. Preserved energy states and lower intensity stimuli can drive a cell toward "energy hungry" death pathways such as apoptosis. On the other hand, exhaustion of energy during these (energy-requiring processes) and exaggeration of severity of inducing stimuli may upset calcium homeostasis and mediate necrosis. For instance, a low-intensity stress, such as a short period of ischemia or interruption of ischemia by reperfusion, may lead to apoptotic death, whereas a longer period of ischemia may bring on necrotic death. Repletion of the cytosolic ATP pool before irreversible damage may redirect the death program toward energy-dependent death pathways.

CARDIAC FIBROSIS

A number of pathways and regulators discussed above play crucial roles in cardiac biology, mainly in contractile cardiomyocytes. Another cell type involved is the fibroblast and indeed a hallmark of cardiac remodeling processes usually in response to stress is cardiac fibrosis. Myocardial fibrosis refers to a variety of both quantitative and qualitative changes in the interstitial myocardial collagen network that ususally is the consequence of cardiac insults or other forms of cardiac stress such as pressure overload of the left ventricle. Cardiac fibrosis describes a multidimensional process of exaggerated activity of cardiac fibroblasts, as well as inflammatory reactions leading often to excessive extracellular matrix production within the myocardium with detrimental consequences. Thus, cardiac fibrosis leads to significant changes in the myocardial architecture facilitating the development of cardiac dysfunction caused by cardiac stiffness, but also the occurrence of cardiac arrhythmias and ischemia at the cellular level. Next to a focus on the cardiomyocyte, it is thus clear that alterations of the cardiac extracellular matrix leading to myocardial fibrosis play also a major role in the development and evolution of cardiac disease.[62] Fibrosis is generally part of a maladaptive cardiac remodeling process. *Remodeling* is a term that is used to describe a cardiac pathological condition in response to ischemia or pressure and/or volume overload of the heart.[62,111] There are also various genetic forms of cardiac diseases showing enhanced fibrosis such as hypertrophic cardiomyopathies.[112]

BIOLOGY OF CARDIAC FIBROBLASTS AND COLLAGEN TURNOVER

Myocardial fibrosis occurs when the net effects of collagen turnover become unbalanced (ie, increased synthesis predominates over unchanged or decreased degradation).[113,114] Excess collagen may accumulate in the interstitial and perivascular space.[115] At the cellular level, cardiac cells are reactive in response to pathological stress, such as myocytes, endothelial cells, and interstitial cells such as cardiac fibroblasts. Although cardiomyocytes represent the majority of the cardiac mass, in terms of numbers they only present about 30% to 50% of the cell types that build up the heart. A considerable number of cells are "cardiac fibroblasts," which is a heterogeneous population of important and as yet not well characterized cells contributing to myocardial homeostasis. The origin of cardiac fibroblasts is debated and may be multifarious: that is, there are resident cardiac fibroblasts but also those that may transdifferentiate from other cell types such as inflammatory cells, mesenchymal, epicardial or endothelial cells.[116,117.] However, a recent finding suggests that the majority of fibroblasts responsible for the cardiac fibrosis response originate from endogenous cardiac tissue–derived fibroblasts.[118]

Like the fibroblasts residing in other organs, the main function of cardiac-derived fibroblasts is the production and homeostatic

maintenance of the extracellular matrix. This extracellular matrix surrounds the cardiomyocytes and provides a solid, flexible scaffold to a tissue that is constantly subject to great mechanical workloads. Thus, alterations of the composition of the extracellular matrix may have strong impact on the cardiac function.[114] In the normal heart, the extracellular matrix is composed of a network of macromolecules, including collagens, elastin, glycoproteins and proteoglycans, with type I collagen being the main component.[119] In healthy conditions, the net deposition of collagen in the cardiac interstitium is rather low, with a good balance between production and degradation. This homeostasis is severely impaired during diseased states of the heart; high collagen deposition is a consequence of either reparative or reactive fibrosis.[120] Here, cardiac fibroblasts may differentiate into more specialized myofibroblasts, which are characterized by increased expression of contractile proteins such as alpha smooth muscle actin. Myofibroblasts are critically involved in the normal scar formation and contraction processes occurring after tissue injuries such as myocardial infarction.[121] Importantly, the extracellular matrix is capable of electrically isolating regions of the myocardium.[122] This has both a physiological relevance in the sinoatrial node, where thicker and thinner sheets of connective tissue determine the expansion of excitation signals in a correct direction, as well as a pathological relevance. Excessive deposition of extracellular matrix can favor the development of detrimental arrhythmias in the remodeling myocardium.[123,124]

FIBROBLAST CHARACTERIZATION

So far, cardiac fibroblasts are defined based on some markers and phenotypical characteristics such as a flat, spindle-shaped morphology, with multiple processes originating from the cell body and lack of a basement membrane.[125] Characterization of fibroblasts of several tissue origins is difficult because of the lack of specific molecular markers, a feature that represents a limiting factor for in vivo investigations on fibroblast biology. However, several substitute markers have been used over time, especially in vitro, for the evaluation of purity in primary cardiac fibroblast cultures, but also in vivo, in order to map the origin of proliferating and collagen-producing fibroblasts during cardiac injury. Examples of such markers are vimentin, FSP1, DDR2, periostin, TCF21 and prolyl-4-hydroxylase. However, it remains to be shown which of those can serve as rather specific markers for identifying cardiac fibroblasts. Furthermore, common in vitro cell culture models do not reliably reproduce the in vivo properties of cardiac fibroblasts because of a spontaneous differentiation of cells toward a myofibroblast phenotype[126] and because of the lack of a three-dimensional structural organization and interrelation with myocytes. For these reasons, characterization of cardiac fibroblasts from a molecular point of view is still ill defined. Treating cardiac fibrosis may prevent the onset of arrhythmias and improve the functional performance of the heart in several disease conditions. It thus will be critical to identify new profibrotic mechanisms not targeted by currently available therapies and to translate these mechanisms into individualized diagnostic tools and specific therapeutic targets. There is a tremendous need for a systematic and collaborative interaction between clinical investigators and basic scientists, as well as with the industry—to introduce more advanced approaches and methodologies into the field of myocardial fibrosis.

MicroRNAs IN CARDIAC HYPERTROPHY AND FAILURE

From a historical perspective, proteins such as transcription factors were thought to be the main players in gene expression regulation, but with the development of new, high-resolution technologies for the analysis of the transcriptome such as next-generation RNA deep sequencing, this paradigm has fallen. In fact, it has now been determined that although about three-fourths of the mammalian genome is transcribed, less than 2% is ultimately translated into proteins[127] (Fig. 6–7). These non–protein-coding transcripts form a relatively unexplored non–protein-coding RNA (ncRNA) dimension that we have only recently started to study. The fundamental importance of this new ncRNA world becomes more clear by noticing that the degree of complexity of a species correlates better with the amount of DNA that is transcribed into ncRNA than with the number of protein-coding genes.[128] As of today, various ncRNAs with a gene regulatory function have been identified and were shown to act at various steps along the protein biosynthetic process, including transcription, RNA maturation,

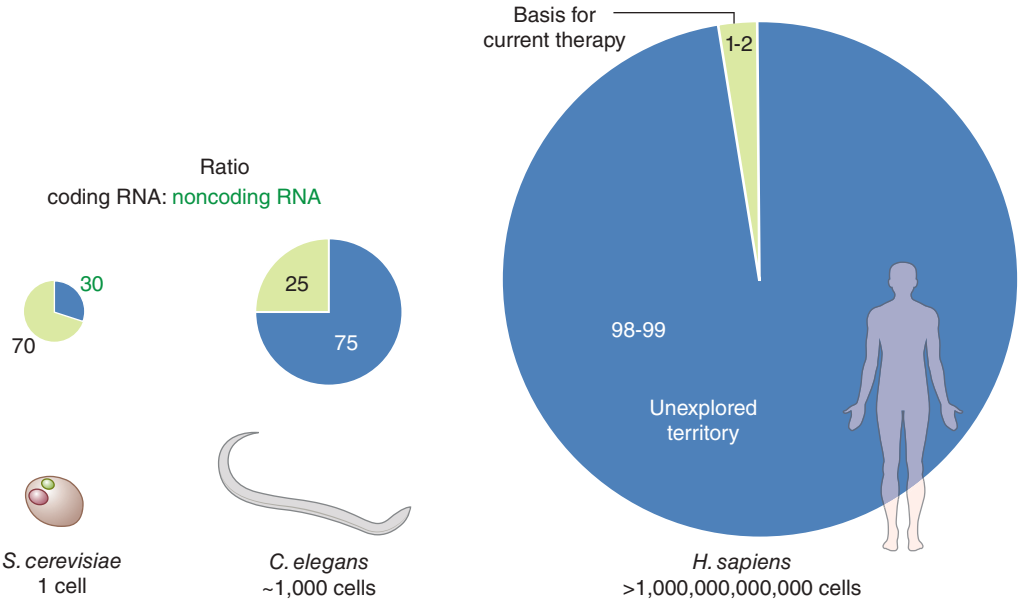

FIGURE 6–7. The ratio of coding RNAs to noncoding RNAs dramatically differs in species. Whereas lower organisms have more coding RNAs than noncoding RNAs, this completely turns around in human beings. Indeed, in humans only 1% to 2% of the RNA encode for proteins, whereas the rest is still a relatively "unexplored" territory.

translation, and protein degradation. These discoveries add to a new level of understanding also in cardiovascular pathophysiology.

Based on their size, ncRNAs can be subdivided into two major groups: (1) small ncRNAs (< 200 nucleotides long) include microRNAs (miRNAs), PIWI-interacting RNAs, and endogenous short interfering RNAs, and (2) long ncRNAs (lncRNAs), which have a length between 0.2 and 2 Kb.[129-132] Indeed, ncRNAs emerged as crucial players in animal and human pathology, including that of the cardiovascular system.[133-135] Around 1500 to 2000 human miRNAs have been catalogued and are believed to regulate about half of all messenger RNAs (mRNAs)—maybe more. Many of the miRNAs show developmental stage– and cell type/tissue–specific patterns of expression. MiRNAs regulate gene expression at the level of mRNA translation, via binding to mRNAs leading to repression and/or degradation.[135] In the following, a number of examples are given where miRNAs have been shown to be directly involved in cardiac pathological processes.

MicroRNAs INVOLVED IN CARDIAC HYPERTROPHY

One of the first studies that mechanistically investigated the importance of a miRNA in cardiac hypertrophy showed a miRNA termed miR-208 to be crucially involved in hypertrophic signaling.[136] Another early report demonstrated that left ventricular pressure–overloaded mice showed low cardiac miR-133 levels and that inhibition of miR-133 with an anti–miR-133 oligonucleotide-generated cardiac hypertrophy in vivo.[137] A first pioneering study showed then a therapeutic effect of miRNA modulation in a murine cardiovascular disease model.[138]

Some miRNAs become strongly activated during pathological stress, making them then functionally important during disease. An example is the miR-212/132 family, which becomes activated during heart failure in humans[139] and animal models.[140] This miRNA family regulates cardiac hypertrophy and autophagy, a crucial process to maintain cardiac homeostasis,[141] in cardiomyocytes by targeting the antihypertrophic and proautophagic transcription factor forkhead box O3, leading to hyperactivation of the prohypertrophic calcineurin/NFAT signaling pathway. Both genetic and pharmacologic inhibition of one of these miRNAs, miR-132, rescued cardiac hypertrophy and heart failure development in mice, offering a possible therapeutic approach for cardiac remodeling.[140] In addition, certain miRNAs regulate the intracellular calcium homeostasis, directly contributing to cardiac contractility. For instance, impaired myocardial SERCA2a activity is a hallmark of failing hearts. In studies with rats, it was shown that SERCA2 therapy after myocardial infarction restored miR-1 levels, leading to normalized expression levels of the NCX1.[142] MiR-214 also has a cardioprotective role during ischemic/reperfusion injury by repression of NCX1, a key regulator of Ca^{2+} influx.[143] Several miRNAs, such as miR-25 or miR-132, directly regulate SERCA2; thus their inhibition might be beneficial for general calcium handling in the cardiomyocyte.[144]

MicroRNAs IN CARDIAC FIBROSIS

As described on p. 11 under "Cardiac Fibrosis," cardiac fibrosis is the exaggerated activation of (mostly) resident cardiac fibroblasts, leading to increased secretion of extracellular matrix proteins, growth factors, cytokines, as well as genetic material. There are several miRNAs enriched in cardiac fibroblasts that have been shown to serve as powerful regulators of various fibrotic processes, including fibroblast proliferation and growth factor secretion. For instance, miR-133 and miR-30, which control expression of connective tissue growth factor—a protein tightly linked to fibrosis development—are also usually downregulated under cardiac stress.[145] MiR-21 was shown to silence the ERK–MAP kinase inhibitor sprouty-1, which is mechanistically involved in fibrosis development.[138] Because miRNAs usually have dozens of targets, it is interesting that miR-21 has also been found to promote cardiac fibrosis by regulating other targets, such as transforming growth factor beta 1 receptor III[146] and matrix metalloprotease-2.[147] Surprisingly, miR-21 knockout (KO) mice still developed cardiac fibrosis under cardiac stress,[148] whereas pharmacologic inhibition of miR-21 inhibited fibrosis in the heart[138,149,150] and other organs, such as lung[151] and kidney.[152] In contrast to miR-21, which is activated during cardiac stress, miR-29 is downregulated and leads to a derepression of many fibrosis-related genes, such as collagens, elastin, and fibrillin.[153] Both miR-21 and miR-29 have been shown to serve as potential therapeutic targets for cardiac fibrosis. Interestingly, circulating levels of miR-29 were found to positively correlate with hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy.[154] Thus, other functions of this miRNA (eg, in cardiomyocyte hypertrophy) might be expected, and monitoring the level of this or other miRNAs could be a useful for prognostic /therapeutic purposes in this clinical setting.

MicroRNAs REGULATING CARDIAC VESSEL DENSITY

Each cardiomyocyte in the heart is usually surrounded by several capillaries to provide sufficient energy and oxygen transport. This balance is derailed under cardiac stress, such as with myocardial infarction, cardiac fibrosis, or heart failure. There is a growing interest in strategies to improve vessel density leading to smaller scar formation after myocardial infarction.[155] Endothelial knockout of Dicer—a key protein involved in miRNA maturation—led to endothelial dysfunction, demonstrating the key role of miRNAs in endothelial biology.[156] The endothelial cell-enriched miRNA, miR-126, was found to mediate developmental angiogenesis in vivo.[157] Indeed, deletion of miR-126 led to loss of vascular integrity and defects in endothelial cell proliferation, migration, and angiogenesis. Thus, approaches to deliver miR-126 are likely to be beneficial to endothelial cells and the improvement of vascular integrity and repair.[158] Also, an miRNA involved in cardiac angiogenesis is miR-92a.[159,160] This miRNA is expressed in human endothelial cells, but also elsewhere in many other cells, and it controls the growth of cancer cells,[161] blood vessel growth, and many other cellular functions throughout the body. By using mouse models of limb ischemia and myocardial infarction, it was shown that systemic blockade of miR-92a led to enhanced blood vessel growth and functional recovery of damaged tissue.[159]

Another miRNA involved in the regulation of cardiac vascularization is miR-24. This miRNA is one of the most highly expressed in cardiac endothelial cells and is further upregulated after ischemia in various organs.[162,163] High levels of miR-24–induced endothelial cell apoptosis and abolished endothelial capillary network formation, partly through targeting the endothelial transcription factor GATA2 and the p21-activated kinase PAK4. Importantly, blockade of endothelial miR-24 limited myocardial infarction size in mice, via enhancement of vascularity, eventually leading to preserved cardiac function and survival. In addition, miR-24 regulates smooth muscle cell functions, and miR-24 overexpression inhibited development of the vasculature in a model of engineered heart tissue.[164]

MicroRNAs REGULATING CARDIAC METABOLISM

Another important function of miRNAs in the heart is the control of energy homeostasis and metabolism. The idea that a failing heart is comparable with an engine out of fuel is relatively old.[165] A cardiac system to create energy is the creatine kinase system, which is controlled by several nuclear-receptor transcription factors, such as nuclear receptors of the peroxisome proliferator–activated receptor (PPAR) family, which also are responsible for substrate utilization from fatty acids to glucose.[166] Interestingly, the miR-199a/214 cluster shares PPARδ as a common target. Silencing of both miR-199a and miR-214 in mice undergoing pressure overload improved cardiac function and restored

mitochondrial fatty acid oxidation.[167] Thus, miRNA manipulation has been shown to modulate the metabolic shift from initial reliance on fatty acid utilization in the healthy myocardium toward increased reliance on glucose metabolism at the onset of heart failure. This may open up new miRNA-based therapeutic concepts to improve energy utility in the failing heart. A further regulator of energy homeostasis is the peroxisome proliferator-activated receptor γ coactivator 1β (PGC-1β), which is a transcriptional coactivator regulating metabolism and mitochondrial biogenesis through stimulation of nuclear hormone receptors. The PGC-1β gene harbors the genes for both miR-378 and its counterpart miR-378*, which counterbalance the metabolic actions of PGC-1β: indeed, mice genetically lacking miR-378 and miR-378* were resistant to high-fat diet-induced obesity.[168] Other targets of miR-378 and miR-378* include the carnitine O-acetyltransferase, which is a mitochondrial enzyme involved in fatty acid metabolism, as well as MED13, a component of the mediator complex. A heart-specific miRNA, miR-208a, directly regulates MED13, and pharmacologic inhibition of miR-208a in mice led to resistance to high-fat diet-induced obesity, demonstrating that a cardiac-specific miRNA may be of importance in regulating whole body energy hemostasis.[169]

MicroRNAs AS POTENTIAL BIOMARKERS AND PARACRINE MEDIATORS

MiRNAs can be released into the extracellular space and circulation either within small vesicles called exosomes or by binding to specific proteins.[170,171] The secretion of miRNAs can also occur via other vesicular bodies arising from the plasma membrane, by simple extrusion through membrane shedding, or by their presence within apoptotic bodies.[170] A number of reviews have covered the role of these circulating miRNAs as biomarkers of cardiovascular diseases.[135,172] Indeed, different kinds of vesicles are produced by cardiovascular cells, including apoptotic bodies, microvesicles, and exosomes. They all contain specific cargoes of protein, miRNA, and mRNA.[173] It was recently shown for exosomes that they are particularly enriched in small RNAs, such as miRNAs.[174] Exosomes with a mean diameter of 30 to 100 nm are membrane vesicles and are formed by fusion of multivesicular bodies with the plasma membrane, leading to a release of exosomes into the extracellular space. The RNA content of exosomes does not simply reflect the composition in the cytoplasm, suggesting a specific transport and shuttling system that very specifically brings only selected RNAs to the exosomes.

Of potential interest for the clinician, secreted exosomes can be isolated from biological fluids and their miRNA or other RNA profiles assessed, enabling them to serve as potential biomarkers for certain diseases.[170] This has recently been also suggested for extracellular long noncoding RNAs, which can be detected in the plasma of patients with myocardial infarction.[175,176] Of considerable biological importance are recent findings that demonstrate that secreted ncRNAs have a paracrine potential (eg, through uptake by recipient cells and subsequent binding to and regulation of the recipient cells' mRNAs[177]).

In addition, apoptotic bodies enriched in miR-126 have been reported to limit atherosclerosis development.[178] Further evidence for the crucial role of miR-126 as an important protector of the endothelial system was recently obtained with miR-126 KO mice, which have impaired endothelial proliferation.[179] A further example of atheroprotective actions based on miRNA trafficking was shown for shear stress–stimulated human endothelial cells that produced vesicles enriched in miR-143/145 that led to reduced atherosclerotic lesion formation in aortas of ApoE KO mice.[180] Other cell types with evidence of an ability to secrete miRNAs are cardiac fibroblasts and inflammatory cells, both involved in the cardiac fibrosis process.[181]

Thus, there is cumulative evidence that cardiovascular cells communicate with each other via the transfer of ncRNAs. Their use as diagnostic markers is intriguing and may open a new avenue for cardiovascular biomarker research. Finally, circulating vesicles containing ncRNAs may serve as new treatment targets, through manipulation of derailed intercellular communication systems.

LONG NONCODING RNAs AS NOVEL REGULATORS OF CARDIAC BIOLOGY

The lncRNAs are transcripts more than 200 nucleotides long that have no known protein-coding function.[182] However, this definition may be preliminary; in fact, many lncRNAs have been recently reported to encode short peptides in human tissues.[183] The lncRNAs can be classified as (1) sense lncRNAs, when they overlap one or more exons of another transcript on the same strand; (2) antisense lncRNAs, when they overlap one or more exons of another transcript on the opposite strand; (3) bidirectional lncRNAs, when their expression and that of a neighboring coding transcript on the opposite strand are initiated in close genomic proximity, (4) intronic lncRNAs, when they are derived from an intron of a second transcript; and/or (5) intergenic lncRNAs, when found as an independent unit within the genomic interval between two genes[134] (Fig. 6–8).

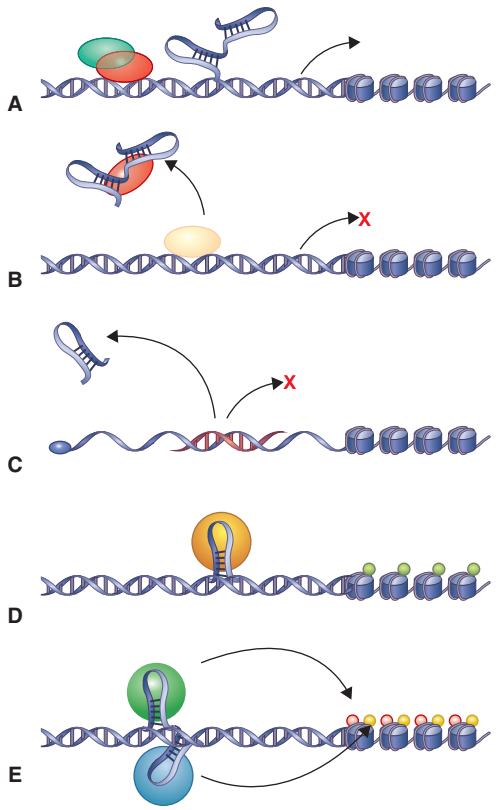

FIGURE 6–8. Scheme of the four types of long noncoding RNA (lncRNA) function. **A.** Signal lncRNA expression is the result of the combinatorial actions of transcription factors (*colored ovals*) or signaling pathways, regulating gene expression in space and time. **B.** Decoy lncRNAs can titrate transcription factors and other proteins away from chromatin or titrate the protein factors into nuclear subdomains; **C.** LncRNAs can also titrate microRNAs out from their target. **D.** Guide lncRNAs can recruit chromatin-modifying enzymes to target genes, either in cis (near the site of lncRNA production) or in trans to distant target genes. **E.** Scaffold lncRNAs facilitate the assembling of multiple proteins to form ribonucleoprotein complexes. The lncRNARNP (ribonucleoprotein) may act on chromatin, affecting histone modifications. In other instances, the lncRNA scaffold is structural and stabilizes nuclear structures or signaling complexes.

The detailed mechanisms of the various functions of lncRNAs are currently intensely investigated; lncRNAs can interact with many macromolecules within the cell, including other RNA species, proteins, and DNA. Complementary sites on the lncRNA allow them to recognize and bind to mRNAs, miRNAs, or even other lncRNAs and act as highly specific sensors for their regulation. On the other hand, protein-binding sites allow them to interact with proteins, generating specific ribonucleoprotein particles with different functions. Their ability for conformational switching is remarkable, whereby the activity of the lncRNA is activated or suppressed by an external signal, thus making them exquisite regulatory devices.[184] LncRNAs have a high folding energy, which distinguishes them from other mRNAs.[185]

In general, lncRNAs can be divided into nuclear lncRNAs and cytoplasmic lncRNAs, although many lncRNAs also may be present in both compartments or even shuttle between those compartments. Thousands of eukaryotic lncRNAs have been identified, with many found to be species specific, but less conserved than protein-coding genes.[186] However, the expression profile of lncRNAs is more cell-type specific than that of protein-coding genes, and the profile changes with differentiation and the developmental stage of an organism.[187] The lncRNAs are being implicated in many biological processes, including cardiovascular ones.[134,188,189]

Indeed, the role of lncRNAs in the heart has just begun to be uncovered. In the vascular system, *MALAT1,* LINC00323 or MIR503HG are enriched in endothelial cells and regulates the angiogenic features of vascular cells.[190,191]

An lncRNA *Braveheart* was shown to be crucial for cardiac development in mice but is not present in humans limiting translational relevance.[192] Another lncRNA, *Fendrr*, was able to control chromatin modifications and, thus developmental signalling also in the rodent heart.[193] In mice, the lncRNA *Chrf* was found to act as a ceRNA sequestering miR-489, a miRNA targeting the mRNA of myeloid differentiation primary response gene 88 (*Myd88*), the upregulation of which is known to induce hypertrophy.[194] Another lncRNA that has been very recently linked to cardiac pathology is cardiac apoptosis–related lncRNA (*Carl*).[195] In mouse cardiomyocytes, *Carl* bound to and sequestered miR-539, a miRNA found to target the mRNA of the PHB2 subunit of prohibitin, a protein localized to the inner mitochondrial membrane, where it has a role in mitochondrial homeostasis. *Carl* acted as the endogenous sponge for this miRNA, regulating mitochondrial morphology and cell death under normal conditions. One recent study identified the lncRNA *Mhrt*, which originates from MYH7 locus, is cardioprotective, and restoration of *Mhrt* levels protects the heart from hypertrophy and failure.[196] The mode of action of Mhrt is described in Fig. 6–9. A lncRNA that is conserved between rodents and humans is the cardiac hypertrophy–associated transcript (*Chast*) lncRNA. Chast has been identified in a wide screen of lncRNA profilling during pressure overload–induced cardiac remodelling in mice.[197] The human *CHAST* homolog is significantly upregulated in hypertrophic heart tissue from aortic stenosis patients and in human embryonic stem cell–derived cardiomyocytes on hypertrophic stimuli. Viral-based overexpression of *Chast* was sufficient to induce cardiomyocyte hypertrophy, whereas pharmacological silencing of *Chast* both prevented and attenuated TAC-induced pathological cardiac remodeling with no early signs on toxicological side effects. These results indicate that *Chast* can be a potential target to prevent cardiac remodeling and highlight a general role of lncRNAs in heart diseases.

In conclusion, the biology of lncRNAs is remarkable, and many new aspects in cardiovascular physiology and pathology are emerging. For instance, lncRNAs also may form circular structures, so-called circular

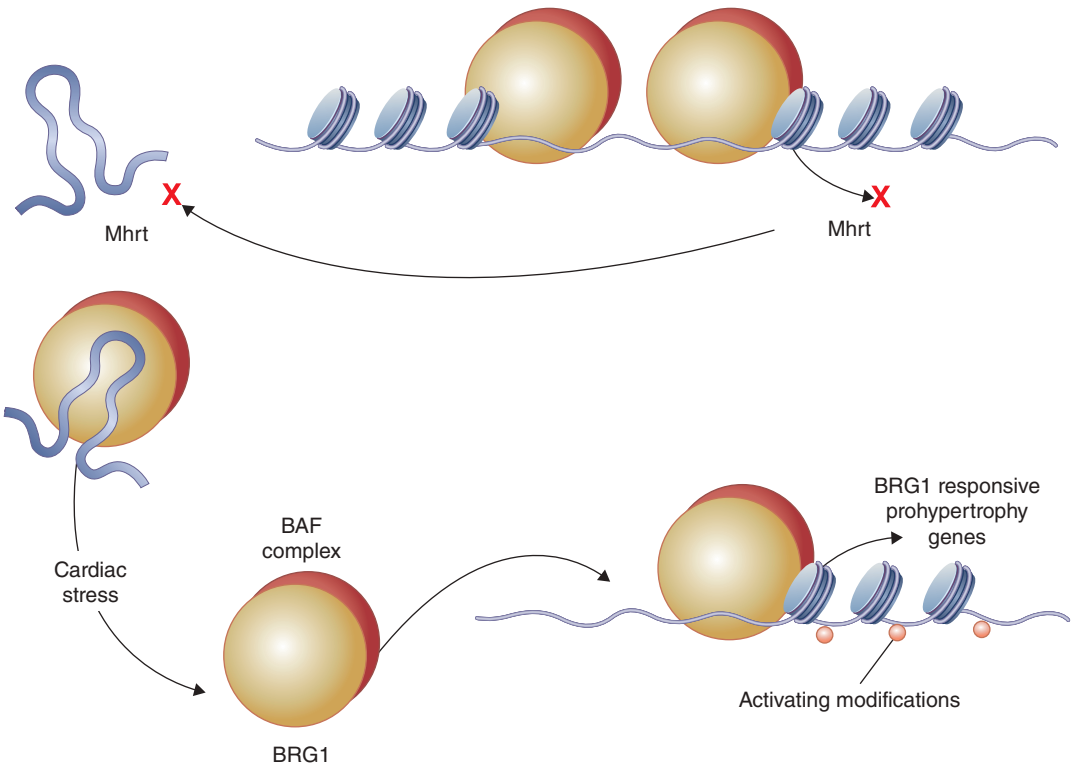

FIGURE 6–9. Schematic of the mechanism of Mhrt as an example of a long noncoding RNA involved in heart pathology. Under physiological conditions, Mhrt is expressed along with its host gene, Myh7. Mhrt then binds to BRG1 complexes, effectively sponging them up so as to blockade attachment to BRG1-responsive genes. Downregulation of Mhrt as a consequence of cardiac stress releases Mhrt-mediated BRG1 complex inhibition, allowing the opening up of chromatin and the transcription of hypertrophyrelated genes.

RNAs, for which also first examples for biological functions in the cardiovascular systems exist.[198,199] Also, lncRNAs may sometimes code for micropeptides with biological function; a putative muscle-specific lncRNA that encodes a peptide of 34 amino acids was named dwarf open reading frame (DWORF). DWORF is the only endogenous peptide known to activate the SERCA pump by physical interaction and provides a means for enhancing muscle contractility.[200]

CONCLUSION

We have reviewed representative classical pathways and newer mechanisms involved in cardiac pathophysiology. There remain numbers of important pathways/mechanisms that are not covered here and the readers are referred to recent reviews.[201-206] Successful clincial application of β-blockers and ACE-inhibitors was supported by not only the clinical trials but also by intense research in the molecular and cellular biology related to these drug pathways. Significant advances in our understanding of cell death, fibrosis, and microRNA have been achieved in the past deacade. Many new exciting discoveries about other noncoding RNAs such as lncRNAs and circular RNAs involved in the control of cardiovascular biology, including chances for new therapeutic concepts and diagnostic strategies, can be expected.

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CHAPTER 7

BIOLOGY OF THE VESSEL WALL

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INTRODUCTION

The pathogenesis of common cardiovascular diseases, including atherosclerosis and hypertension, involves diverse and complex pathways. Significant advances in our understanding of the underlying pathobiologies at a molecular and cellular level are increasingly leading to the development of new therapeutic strategies targeted at primary etiologies rather than secondary manifestations of vascular disease. Thus, it is essential for both inquisitive scientists and clinicians who are taking care of patients with cardiovascular disease to understand the normal physiology, signaling pathways, and function of the different cell types that constitute the layers of the vascular wall, in addition to the complex interactions between the vasculature, the heart and the entire human organism (Fig. 7–1). This chapter will provide relevant basic knowledge about the underlying physiology and function of each component of the vasculature and how disease conditions alter this carefully regulated system.

VASCULAR DEVELOPMENT

EARLY VESSEL FORMATION—VASCULOGENESIS

Vasculogenesis is the earliest form of vessel generation to occur; in fact, it is one of the earliest biologic programs in the developing embryo. Vasculogenesis has been recognized and studied for at least a century.[1] It is initiated soon after gastrulation (when the single-layered blastula is reorganized to form the ectoderm, mesoderm, and endoderm) by the aggregation of mesodermal progenitor cells into clusters referred to as *blood islands*, which are the earliest vascular structures. These clusters then undergo partial lineage commitment, with the outer cells becoming endothelial precursor cells (referred to as *angioblasts*) and the central cells becoming hematopoietic progenitor cells. Blood islands soon coalesce and fuse, and a central lumen emerges. These primitive vessels undergo progressive remodeling and maturation, and eventually a primitive vasculature emerges (Fig. 7–2).

Vascular endothelial growth factor (VEGF) and its receptor VEGF receptor-2 (VEGFR-2) are critical players during vasculogenesis, with *VEGFR-2* knockout leading to embryonic death caused by a severe defect in vasculogenesis in mouse models.[2] With respect to the key cells participating in vasculogenesis, it was once believed that a bipotent hemangioblast cell capable of differentiation into endothelial and hematopoietic cells was responsible for blood island formation and vasculogenesis. This dogma has now been challenged. Contemporary cell reprogramming studies have shown that during commitment to a hematopoietic fate, primitive cells may express endothelial markers in a transitory manner, but that they do not exist in a truly bipotent state.[3] Indeed, mounting evidence has now quite convincingly shown that *hemogenic endothelial cells* are responsible for definitive hematopoietic cells in the embryo[4-7] and that their hemogenic ability is reliant on a specific microenvironmental vascular niche.[7] Although this may appear to be a semantic point, the presumptive existence of a hemangioblast was the central rationale for the many cell therapy studies conducted in the past two decades seeking to use bone marrow (BM)-derived cells to generate new vessels in the adult.[8-10] The fact that these clinical studies failed to demonstrate efficacy for new vessel formation using BM-derived cell therapy[8] may be attributable to this likely incorrect assumption regarding the existence of a bipotent hemangioblast.

An additional important point with respect to vasculogenesis is the fact that it implies de novo vessel formation in the setting of blood islands and the concurrent deployment of hematopoietic progenitor cells. Although the potential for de novo new vessel formation in the adult continues to be debated, what is almost certain is that the classic developmental vasculogenesis program, including blood islands and hemogenic cells, does not arise in the adult.[9]

ANGIOGENESIS

It is an ongoing source of confusion in vascular biology that "angioblasts" are cells that are operative during vasculogenesis, whereas the process of angiogenesis does not involve angioblasts but rather new vessel formation from preexisting vessels. Specifically, angiogenesis is a well-described biologic program in development and the adult. It can be defined as the formation of new capillaries from preexisting vessels by the sprouting or splitting of these preexisting vessels by transcapillary

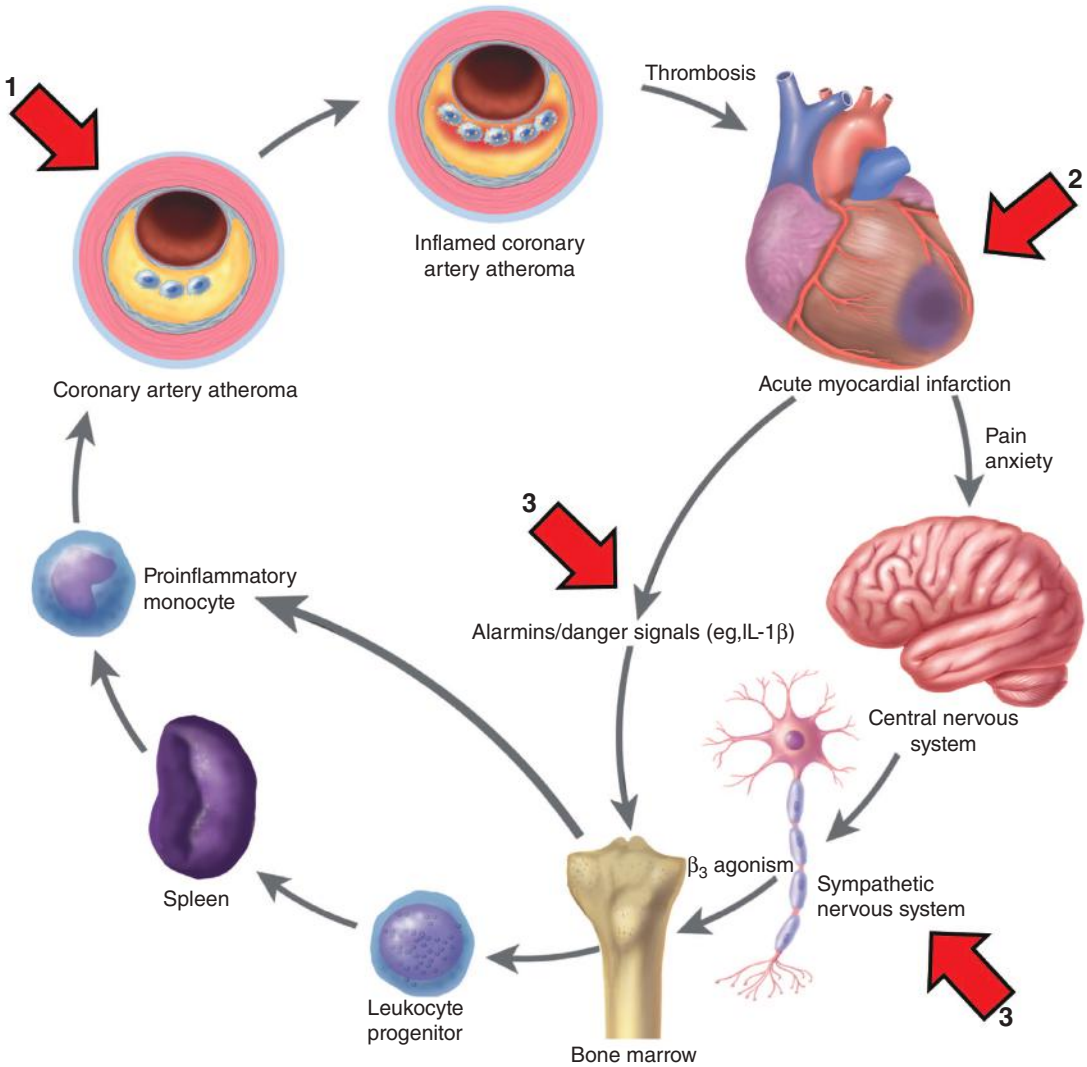


FIGURE 7–1. The integrative pathophysiology of atherosclerosis, ischemic heart disease, and the systemic inflammatory response. Atherosclerosis develops over many years (1) and can lead to myocardial infarction (2), while the stress of acute myocardial infarction (2) also produces an "echo" in atherosclerotic plaques (1). Acute myocardial infarction causes pain and anxiety that triggers sympathetic outflow from the central nervous system (3). β3 adrenergic stimulation mobilizes leukocyte progenitors from their bone marrow niche. These progenitor cells can migrate to the spleen, where they can multiply in response to hematopoietic growth factors. The proinflammatory monocytes then leave the spleen and enter the atherosclerotic plaque (1), where they promote inflammation that can render a plaque more likely to provoke thrombosis and hence acute myocardial infarction (2). IL, interleukin. Reproduced with permission from Libby P, Nahrendorf M, Swirski FK: Leukocytes Link Local and Systemic Inflammation in Ischemic Cardiovascular Disease: An Expanded "Cardiovascular Continuum," *J Am Coll Cardiol*. 2016 Mar 8;67(9):1091-1103.[192]

pillars or posts of extracellular matrix and/or cells (see Fig. 7–2).[10] To facilitate this capillary sprouting, endothelial cells possess a well-developed capacity for migration, which is under the control of VEGF and other cytokines.[11] Although angiogenesis occurs in the adult, it remains unclear if progenitor cell deployment is a requirement during angiogenesis. A contribution from BM-derived or circulating cells now appears less likely, but it remains possible that endothelial or other progenitor populations resident in the local vessel wall may participate in this process.[12,13]

ARTERIOGENESIS

Arteriogenesis is yet another mechanism of vessel formation, although in the strictest sense it is not truly a mechanism of de novo vessel formation but merely vessel remodeling. Arteriogenesis is defined as the formation of larger diameter arteries from preexisting capillaries or arterioarteriolar anastomoses, typically initiated by altered blood flow and shear stress, and involving vessel dilation and remodeling (see Fig. 7–2).[10] Recent exacting studies using mouse models permitting fate tracking of endothelial cells have demonstrated that arteriogenesis is the main mechanism of collateral vessel formation in the heart after myocardial infarction, which involves the remodeling and growth of preexisting arteries.[14]

The precise scenarios in the adult where vasculogenesis, angiogenesis, and arteriogenesis are the dominant vascular processes for new vessel formation remain to be clearly defined. As stated, we and others remain guarded about the existence of vasculogenesis in the adult.[9] With respect to angiogenesis, there are certain situations where this is clearly the dominant process, such as new vessel ingrowth into tumor tissue,[15] or capillary ingrowth into an advanced atherosclerotic plaque.[16] Conversely, where a preexisting vascular network exists and likely when the distances involved are greater, arteriogenesis is likely to be the most important process, such as following the occlusion of a major epicardial coronary artery.[14]

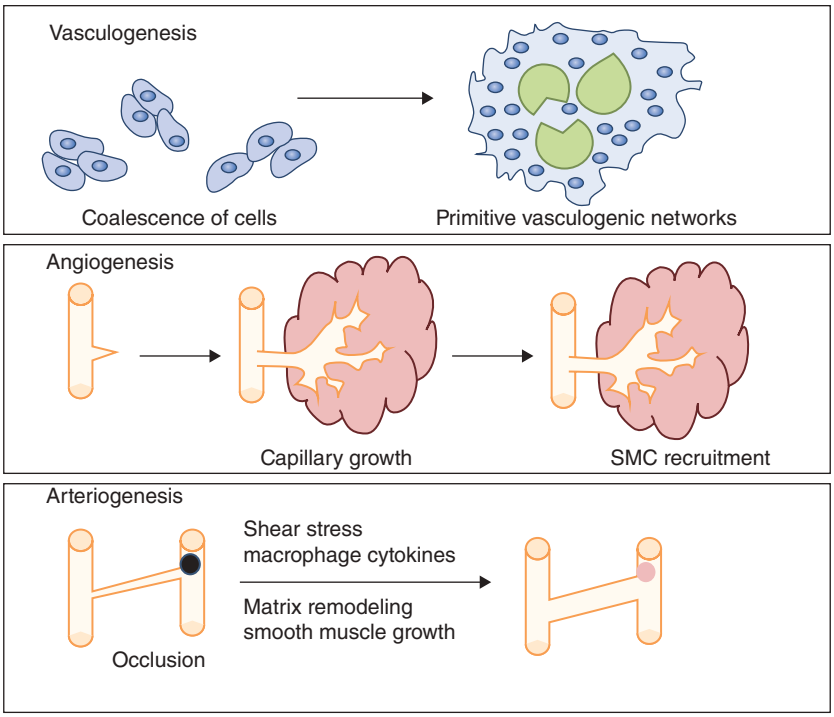


FIGURE 7–2. Mechanisms of vessel formation. Vasculogenesis (*top*) has been extensively described during development and involves the coalescence of primitive cells to form vasculogenic networks. Angiogenesis (*middle*) is the most common form of de novo new vessel formation in the adult, which is the formation of new capillaries from preexisting vessels that can occur by the sprouting or splitting of these preexisting vessels by transcapillary pillars or posts of extracellular matrix and/or cells. Arteriogenesis (*bottom*) is also important in adult vascular biology and is the formation of larger diameter arteries from preexisting capillaries or arterioarteriolar anastomoses, typically initiated by altered blood flow and shear stress, and involving vessel dilation and remodeling.

INTIMA AND ENDOTHELIUM

ENDOTHELIAL CELLS

The endothelium is strategically positioned as a critical interface between the blood and tissues (Fig. 7–3). Not surprisingly, endothelial cells are pivotal to maintaining vascular homeostasis, and multiple vascular diseases arise from endothelial dysfunction, including atherosclerosis and hypertension. The metabolic state of the endothelial cell is closely regulated by surrounding vascular and nonvascular parenchymal cells, all of which are supported by underlying capillary networks. The metabolic and functional state of the endothelium is influenced by multiple factors, including the degree of oxygenation,[17] physiological forces such as shear stress, metabolic changes, inflammatory responses, and the local cytokine milieu.[11]

Among its many functions, the endothelium is of particular importance for maintaining and protecting the integrity and function of the vascular wall, with specific roles. These include (1) functioning as a metabolic tissue that actively secretes vasoactive factors governing vascular tone; (2) acting as an anticoagulant and antithrombotic surface; (3) serving as a barrier to most circulating blood constituents; (4) regulating the transendothelial passage of specific molecules, proteins, and cells across this barrier, and (5) participating in the inflammatory response via active leukocyte recruitment and facilitation of leukocyte margination from the lumen into the vessel wall and adjacent tissues.

PERMEABILITY

The endothelium regulates vascular permeability at a macrovascular and microvascular level, with transendothelial fluid and macromolecule transport being differentially regulated depending on vessel size. In the microcirculation, endothelial permeability is a key factor that facilitates the delivery of nutrients to tissues as well as the exchange of by-products from various metabolic pathways. Larger caliber vessels typically function as vascular conduits, and in these vessels the endothelium generally acts more as a barrier. The endothelium also serves as a barrier to the underlying vascular smooth muscle; dynamic regulation allows for selective exposure of the underlying vascular wall and smooth muscle cells to mitogenic, thrombotic, and vasoactive agents that have specific downstream effects. As we discuss below, the principal mechanisms whereby molecules or substances can pass across the endothelium are transendothelial vesicular transport in caveolae and modulation of intercellular contacts.

Endothelial cell contact is maintained through adherens and tight junctions. Vascular endothelial (VE) cadherin is a cell junctional protein within adherens junctions and is important for interendothelial cell contacts. VE-cadherin interacts with the actin cytoskeleton,

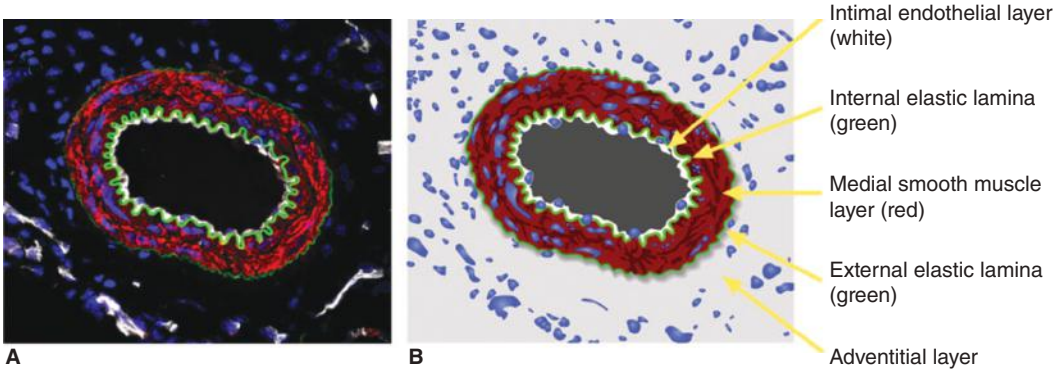


FIGURE 7–3. Anatomy of a medium-large sized artery in the adult. **A.** Four-color confocal microscope image of a mouse femoral artery. Staining was with 4′,6-diamidino-2-phenylindole (DAPI) shown in blue to mark nuclei, anti-SM22α to mark smooth muscle cells in red, and CD31 to mark endothelial cells in white. The internal and external elastic laminae (shown in green) were not stained, but were imaged using autofluoresence emitted when excited with a 488-nm laser line. **B.** Schematic representation of adjacent confocal image identifying vascular anatomic structures/layers. Reproduced with permission from Kovacic JC and Boehm M. Resident vascular progenitor cells: an emerging role for non-terminally differentiated vessel-resident cells in vascular biology, *Stem Cell Res*. 2009 Jan;2(1):2-15.[13]

plakoglobin, and catenins to promote cell adhesion.[18] Various tight junctions are formed between endothelial cells that include interaction between occludins, claudins, and junctional adhesion molecule-1. These interendothelial cell interactions are carefully regulated and important for mediating permeability changes to allow passage of macromolecules and extravasation of immune cells, and they are also of importance for other vascular functions such as control of angiogenesis. Vessel size and vascular bed location are related to the integrity of these interendothelial contacts. An important example of this is tight junctions in different vascular beds, with those forming the blood–brain barrier being among the most developed in the entire vascular system. Vasoactive agents, including VEGF, histamine, and prostaglandins, are active in capillaries and postcapillary venules and act to regulate permeability.[19] Tight junctions within arteries are less permeable to solute flux but are regulated by similar vasoactive agonists.

As an alternate means of transendothelial passage, vesicular transport is important for the transfer of water-soluble macromolecules from the luminal to abluminal surface of the endothelium. Caveolae, which are vesicles that contain the structural protein caveolin that are formed from the plasma membrane, are important for this process.[20] Caveolae are located at sites where other kinases, G proteins, docking proteins, and related receptors are present, which are important for signal transduction in the endothelium.[21]

Endothelial cell contraction is another aspect of endothelial barrier function. Contraction occurs in response to a variety of stimuli, including thrombin, histamine, and ionomycin, which leads to changes in cell shape that open intercellular gap junctions. This signaling cascade and the subsequent contractile response are thought to be the underlying mechanisms for tissue edema that occurs in response to histamine and bradykinin. The main intracellular pathways involved include activation of protein kinase C; myosin light-chain phosphorylation; tyrosine kinase activation; and stimulation of Rho, a small G protein.[22]

As well as functioning as a physical permeability barrier, it should be noted that the endothelium also modulates various signaling pathways and secretes factors that control permeability and are discussed in this section. Therefore, the endothelium has both a direct and an indirect role in the control of vascular permeability.

HEMOSTASIS

At rest under normal hemodynamic conditions, the endothelium presents an anti-thrombotic surface that inhibits the adhesion of platelets and activation of the coagulation cascade (Fig. 7–4). However, the endothelium can serve as a functional antithrombotic, thrombolytic or intermediate interface. Anticoagulants regulated by the endothelium include those that inhibit platelet aggregation such as prostacyclin and nitric oxide[23]; antithrombin III[24]; heparin-like molecules; and thrombomodulin, which activates endothelial protein C.[25] On the other hand, conditions of inflammation or cellular stress such as those produced by air pollution can induce an activated endothelial state, which is characterized by the production of procoagulants such as tissue factor,[26] factor VIII, factor Va, and plasminogen activator inhibitor 1. In particular, tissue factor production and release is regulated by multiple proinflammatory and proatherogenic pathways, with tissue factor being closely linked to complex atherosclerotic lesions.[27] Recently, an alternatively spliced tissue factor isoform was described, which is produced by

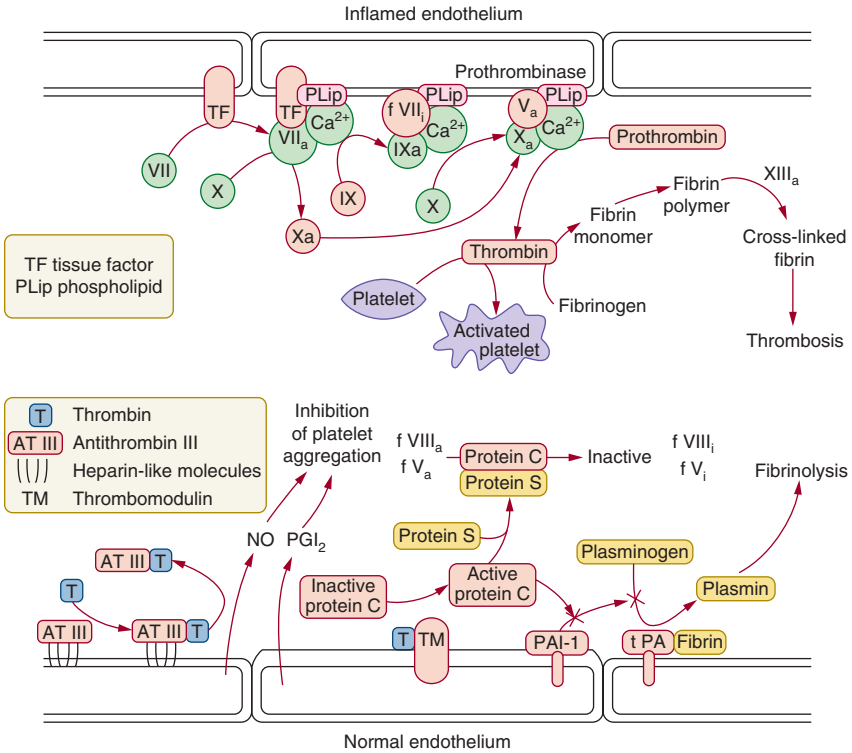


FIGURE 7–4. Pathways of thrombosis and thrombolysis. Under normal conditions, the endothelium is antithrombotic. Antithrombin III (AT III) binds thrombin and serves to clear thrombin from the circulation. Prostacyclin (prostaglandin I2 [PGI2]) inhibits platelet aggregation, and thrombomodulin (TM) activates protein C, which inhibits plasminogen activator inhibitor 1 (PAI-1) and interacts with protein S to inactivate activated factors V and VIII, thus limiting thrombosis. Because PAI-1 inhibits the tissue plasminogen activator (PA)–catalyzed conversion of plasminogen to plasmin, PAI-1 inhibition leads to accumulation of plasmin and fibrinolysis. With stimulation with inflammatory cytokines, there is increased expression of tissue factor on the endothelial cell surface. Tissue factor participates in the activation of factor X which, in turn, promotes assembly of the prothrombinase complex, producing thrombin. Under these conditions, endothelial cells thus amplify the thrombotic response. Used with permission from Bernard Lassègue, PhD.

activated endothelial cells and macrophages, and associated with angiogenesis, neointimal formation, and advanced atherosclerosis.[28] Interestingly, although it was long believed that factor VIII was produced by hepatocytes, it is now understood that endothelial cells are the major and potentially even the exclusive source of plasma factor VIII.[29] The underlying factors and regulatory mechanisms that govern endothelial cell hemostasis continue to be active areas of scientific research.

INFLAMMATION

Endothelial cells also modulate and contribute to inflammatory processes. Endothelial secretion of chemotactic molecules and upregulated expression of adhesion molecules function to recruit leukocytes to sites of inflammation. Infiltrating macrophages and T lymphocytes, in addition to cytokines and arachidonic acid metabolites, also stimulate secretion of these molecules from the endothelium. The vascular inflammatory response is predominantly mediated by chemokines, classified as CXC and CC ligands dependent on positioning of the first two cysteines in the amino acid sequence. These chemokines interact with G protein receptors classified as CXCR and CCR.[30,31]

Induction of the differential expression of the different adhesion molecules mediates the accumulation of various leukocyte classes at sites of inflammation. Many proinflammatory mediators are thought to contribute to the endothelial–leukocyte interaction, with the complete endothelial inflammatory response program being orchestrated by a multitude of molecular players. Among these, L- and P-selectins along with vascular cell adhesion molecule (VCAM)-1 are important for the initial capture of local leukocytes from blood flow to the site of active inflammation. Leukocyte rolling is then initiated by E- and P-selectins.[32] Interactions with beta2-integrins platelet endothelial cell adhesion molecule (PECAM) and CAM-1 with leukocytes leads to adhesion. At the sites of atherosclerotic plaques the surface expression of VCAM-1 and interactions between monocyte chemotactic protein-1 (MCP-1) and the monocyte receptor CCR2 facilitates leukocyte recruitment. This response is also mediated by interleukin (IL)-8 and its receptor CXCR2, as well as fractalkine and its receptor CX3CL1. As well as inflammation, these sequential steps of capture, adhesion, and migration are also relevant in tumor biology, when malignant cells undergo contact-initiated interactions with endothelial cells to facilitate transendothelial migration and cancer cell extravasation.[33]

VASCULAR TONE

Endothelial cells secrete an array of vasoactive metabolites that are important regulators of various vascular and systemic physiologic functions, including vascular tone. In turn, these factors play a key role in controlling both systemic blood pressure and regional blood flow to specific organs or tissue beds. These major vasoactive factors, summarized in Table 7–1, include potent relaxing factors such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factors, as well as constricting factors such as endothelin. This section will describe the most prominent regulatory molecules.

Nitric Oxide

Furchgott and Zawadzki[34] first described an endothelium-derived relaxing factor (EDRF) in the context of a dilatory response in aortic rings in response to acetylcholine; EDRF was subsequently determined to be nitric oxide (NO).[35] Central to NO biology, nitric oxide synthase (NOS) oxidizes guanidine nitrogens of L-arginine leading to the formation of citrulline and NO. NOS has three known isoforms in mammals that were first identified in various tissues: brain (nNOS, neuronal NOS type I), macrophages (iNOS, inducible NOS type II), and endothelial cells (eNOS, endothelial NOS type III). These three isoforms have binding sites for nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide, and flavin mononucleotide, in addition to a calcium-calmodulin binding site. Tetrahydrobiopterin is an important cofactor for NO synthases participating in electron transfer from the heme group of the enzyme to the L-arginine and is required for NO production by all three NO synthase isoforms.[36] Under normal conditions, these enzymes couple oxidation of the amino acid substrate L-arginine with the reduction of molecular oxygen to form NO and L-citrulline. Under conditions of oxidative stress, the electron transfer is shifted to oxygen, which results in the formation of a superoxide anion, termed *uncoupling* of NOS; this is thought to be important in various cardiovascular disease states.[36]

TABLE 7–1. Major Vasoactive Factors Produced by the Endothelium

Main Vasoactive Factors	Action
Prostacyclin, nitric oxide, endothelial derived hyperpolarizing factor	Vasodilation
Endothelin, prostanoids	Vasoconstriction
Factor VIII antigen, von Willebrand factor, tissue factor, thrombomodulin, and tissue plasminogen activator	Key regulators of the coagulation/fibrinolytic system
Collagen, elastin, glycosaminoglycans, fibronectin	Maintaining the structural components of the extracellular matrix
Matrix metalloproteinases, tissue inhibitors of metalloproteinases	Regulation of extracellular matrix, degradation and remodeling
Heparans and growth factors	Smooth muscle cell proliferation
Lipoprotein lipase, low-density lipoprotein (LDL) receptor, scavenger LDL receptor	Lipid metabolism

The release of NO from NOS is regulated by many factors, including acetylcholine, norepinephrine, bradykinin, thrombin, ATP, vasopressin, platelet-derived factors such as serotonin and histamine, fatty acids, ionophores, and hemodynamic factors such as shear stress. NO crosses the smooth muscle cell membrane and binds the heme moiety of soluble guanylate cyclase, which leads to formation of cyclic guanosine monophosphate (cGMP); cGMP reduces intracellular calcium concentrations, with subsequent dephosphorylation of myosin light chain and smooth muscle relaxation.[37,38] Nitroglycerin is a drug that exerts its vasodilatory effects through its conversion to NO.

Increased intracellular calcium levels act to activate eNOS by binding of calcium and calmodulin, with eNOS activity also regulated through enzyme phosphorylation. Different patterns of shear stress enhance eNOS expression, including high levels of shear and vasoprotective unidirectional laminar shear stress. Conversely, low shear stress and oscillatory shear stress are associated with reduced eNOS and are considered atherogenic.[39] Recently, it was established that laminar shear stress (LSS) activates a NOX2/p47phox complex to activate eNOS phosphorylation and NO production, while conversely, oscillatory shear stress activates a NOX1/NOXO1 complex to uncouple eNOS.[39]

Increased shear stress leads to an acute release of NO from the endothelium, with this response only dependent on calcium in the first few seconds and the continued activation of eNOS in response to shear stress being maintained by serine phosphorylation.[40] Physical activity also increases eNOS expression in endothelial cells, thought to be reflective of the increased shear stress secondary to high cardiac output during sustained exercise.[41] Reduced eNOS expression has

been shown in the presence of oxidized low-density lipoprotein (LDL) cholesterol, glycated LDL, hypoxia, and inflammation (tumor necrosis factor [TNF]-alpha).[42-44] Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") have been shown to stabilize eNOS messenger RNA, which leads to elevated eNOS levels. This is thought to be one of the underlying mechanisms that contribute to the pleiotropic beneficial clinical effects of these agents. As a unexpected paradigm shift, it was recently also shown that eNOS is expressed by circulating erythrocytes, with cross-bone marrow transplant studies demonstrating an important role for erythrocyte eNOS in blood pressure regulation.[45]

Endothelium-derived Hyperpolarizing Factors

Initial studies following the discovery of NO demonstrated that vascular smooth muscle cells could become hyperpolarized and that this was dependent on the presence of endothelium-derived factors following challenge with vasodilators. This was determined to be mediated by hyperpolarizing factors separate from NO.[46] Two further endothelium-derived hyperpolarizing factors (EDHFs) were then identified: 14,15-epoxyeicosatrienoic acid (14,15-EET) and hydrogen peroxide. The molecule 14,15-EET is a cytochrome P450 metabolite of arachidonic acid.[47] This epoxide and its metabolite 14,15-dihydroxyeicosatrienoic acid are both released from the endothelium, reach the adjacent vascular smooth muscle membrane, and open calcium-activated potassium channels. The subsequent efflux of potassium leads to hyperpolarization and closing of voltage-dependent calcium channels, smooth muscle cell relaxation, and vasodilatation.[48] 14,15-EET also has direct beneficial effects on the endothelium, and it has been shown to inhibit endothelial senescence via the mTORC2/Akt signaling pathway.[49] Hydrogen peroxide is also released by endothelial cells and mediates similar vasodilatory effects.[50-52] It has been noted that with decreasing caliber of vessels from large conduits to small arterioles, the role of NO is less dominant and EDHF-dependent vasodilatation is more prominent.[53] Interestingly, there is a regulatory relationship between NO and EDHF. EETs can induce NO production in various tissues, whereas some of the effects of EETs are regulated by the activation of NOS and increased NO production[54] As another example of the interplay among these pathways, excessive superoxide production leads to oxidative degradation of NO with subsequent loss of NO mediated vasodilation. Hydrogen peroxide is a by-product of superoxide production and can alternatively serve as an EDHF, which can maintain small-vessel vasodilatation.

Prostacyclin

Prostacyclin, or prostaglandin I2 (PGI2), is a prostanoid produced from cyclooxygenase (COX)-1 and COX-2 enzymatic activity on arachidonic acid. PGI2 is released from endothelial cells and exerts powerful vasodilatory effects by relaxation of vascular smooth muscle cells, which is mediated by an increase in intracellular cyclic adenosine monophosphate (cAMP) levels. Recent data suggest that hydrogen peroxide generation affects endothelial PGI2 production, with COX-1, and not COX-2, the main source of endothelial PGI2 under conditions of mild oxidative stress.[52] Prostacyclin also has an antithrombotic role and suppresses platelet activation and aggregation, as well as reducing growth factor release from macrophages and endothelial cells.[55] These various effects are thought to contribute to the adverse side-effect profile of COX-2 inhibitors, although these factors alone cannot fully account for the observed adverse effects of the COX-2 inhibitors.[52,56] Prostacyclin synthesis is stimulated predominantly by bradykinin (most potent), substance P, epidermal growth factor, platelet-derived growth factor (PDGF), and adenine nucleotides.[55] In eNOS knockout mice, prostacyclin was demonstrated to compensate for loss of NO.[57] Epoprostenol (a synthetic prostacyclin), iloprost (a chemically stable analog of prostacyclin), and treprostinil (a tricyclic benzidine analog of epoprostenol) have efficacy in the clinical treatment of pulmonary hypertension.[58]

Other Prostaglandins

In addition to prostacyclin, under pathologic conditions the endothelium can produce other prostaglandins with vasoconstrictive properties, including prostaglandin H2 (PGH2) and thromboxane. PGH2 is a product of COX-1 and COX-2 activity, and thromboxane is a product of the action of thromboxane synthase on PGH2.[59] Furthermore, hormones such as acetylcholine and endothelin-1 stimulate the release of endothelium-derived constricting factors (EDCFs) that act on the thromboxane or other receptors in models of hypertension. Depending on the model or clinical disease state, thromboxane A2, PGH2, prostaglandin F2α, prostaglandin E2, and paradoxically PGI2 can all act as EDCFs.[60]

Another cytochrome P450 metabolite of arachidonic acid with vasoconstrictive properties is 20-hydroxyeicosatetraenoic acid (20-HETE).[61] This metabolite depolarizes the vascular smooth muscle membrane through the inhibition of calcium activated potassium channels and subsequent promotion of vasoconstriction. Angiotensin II, endothelin, and catecholamines stimulate 20-HETE production whereas NO inhibits its production.[61] Production of 20-HETE is increased in many common diseases, including hypertension, diabetes, and kidney disease.

Angiotensin-Converting Enzyme

Endothelial cells, notably in the pulmonary vasculature, synthesize and express angiotensin-converting enzyme (ACE) on their cell surface. The main function of ACE is converting angiotensin I to the potent vasoconstrictor angiotensin II and degrading bradykinin. Interestingly, at the molecular level, it has been demonstrated that with ligand binding of ACE inhibitor, ACE can directly signal through its cytoplasmic tail, which leads to downstream changes in gene expression.[62] The relevance of this in different cardiovascular diseases is not yet well known. Vascular and cardiac cells contain most components of the renin/angiotensin system,[63] which supports the important contribution of locally produced angiotensin II to cardiovascular function. The local production of angiotensin II is also supportive evidence of the effectiveness of ACE inhibitors and angiotensin receptor antagonists when total circulating levels of renin or angiotensin II are not increased.

ACE-II is a carboxypeptidase enzyme that functions to cleave an amino acid from angiotensin I or angiotensin II. Its overall effect is a reduction in angiotensin II with subsequent increase in the metabolite angiotensin I to VII that has vasodilatory effects. The interplay between ACE-I and ACE-II regulates angiotensin II levels and vasomotor tone[64]

Endothelins

Endothelins (ETs) encompass a family of peptides that are synthesized and secreted by many cell types, including endothelial cells. Three ETs (ET-1, ET-2, and ET-3) are described, each being comprised of 18 amino acids. Initial synthesis starts with preproendothelin, which is processed and results in "big endothelin." Big endothelin is released and converted to its active form by ET-converting enzyme. Synthesis is stimulated by angiotensin II, hypoxia, oxidized LDL, inflammatory cytokines, and low shear stress.[65] ET mediates its effects on the vasculature through three described receptors: ET-A, ET-B, and ET-C. These receptors have specificity for different endothelins and lead to activation of different downstream cell signaling pathways. The ET-A receptor is expressed predominantly in vascular smooth muscle, and the ET-B receptor is found on endothelial cells. Activation of the ET-A receptor

stimulates potent vasoconstriction, whereas activation of ET-B stimulates the release of NO and vasodilatation.[66] ET-1 stimulates a slow, intense and sustained contraction thought to be mediated by activation of the phosphoinositide/protein kinase C pathway and opening of voltage-dependent L-type calcium channels.[67] Of note, low, subthreshold concentrations of ET-1 enhance vasoconstriction mediated by other metabolites, including serotonin, alpha-adrenergic agonists, and angiotensin II, also thought to be mediated via the protein kinase C pathway.

ET-1 is a growth factor for smooth muscle cells[68] as well as a chemoattractant for monocytes. In vitro, angiotensin II has been shown to stimulate the production of ET-1 in smooth muscle cells. In vivo it has been shown that the hypertensive effects of angiotensin II are mediated through ET. These data suggest that there is interplay between the endothelin and angiotensin pathways in the pathogenesis of diseases such as hypertension, diabetes, and heart failure. Several ET receptor antagonists are now approved for clinical use in pulmonary hypertension, including bosentan, ambrisentan, and macitentan. Bosentan is a mixed ET-A and ET-B receptor antagonist, whereas the newer agents ambrisentan and macitentan are selective for ET-A; therefore, they have theoretical benefits in terms of preserving NO activity and vasodilator functions mediated through ET-B receptors while antagonizing vasoconstriction and smooth muscle cell proliferation mediated by ET-A receptors.[58,69]

Hemodynamic Influences

Endothelial cells use mechanosensing to transduce the frictional force from blood flow (fluid shear stress) into biochemical and cellular signals, and in this fashion circulatory hemodynamics including stretch, strain, and shear stress, are able to modulate many endothelial functions.[70] Stretch of the vessel wall and shear stress have been shown to independently affect endothelial cell function and/or morphology. In vitro data have demonstrated that endothelial cell stretch leads to change in endothelial cell shape,[71] activation of intracellular signaling, increase in intracellular calcium and superoxide levels,[72] and cell proliferation.[73] Exposure of endothelial cells to shear stress leads to cytoskeletal changes with reorganization and alignment of the actin filaments and microtubules as well as cellular realignment in the direction of flow. Shear stress also alters the function of the endothelium, including activation of potassium currents; secretion of vasoactive and growth factors such as the production of various microRNAs, NO, endothelin, prostacyclin, and basic fibroblast growth factors; elevation of tissue factor expression; increased uptake of LDL; and enhanced tissue plasminogen activator secretion.[70,74]

Hemodynamics vary in different vascular beds. Low shear stress vascular areas such as branch points and curvatures demonstrate predilections for the formation of atherosclerotic lesions.[75] Oscillations of flow have been demonstrated in the proximal carotid arteries, carotid bulbs, and distal aorta.[76] Oscillatory shear stress leads to increased endothelial production of reactive oxygen species (ROS), increased expression of adhesion molecules and simulation of monocyte adhesion.[39,77]

The sensing and transduction of mechanical signals by endothelial cells is mediated by multiple factors, including extracellular glycosaminoglycans, selectin molecules, and PECAM-1. The coexpression of PECAM-1 and VE-cadherin has been shown to promote shear responsiveness to surrounding cells that are not normally affected by shear stress.[78] In addition, mechanosensors activate integrins that modify cytoskeletal properties and downstream signaling.[79,80] In turn, flow sensitive ion channels and selective G proteins act to modulate mechanotransduction.[81,82] Caveolae contain many signaling molecules including G proteins, which are significant in downstream signaling pathway activation in response to shear stress.[83]

ENDOTHELIAL-TO-MESENCHYMAL TRANSITION

Endothelial-to-mesenchymal transition (EndMT) is a pervasive biologic program whereby endothelial cells undergo a series of molecular and structural rearrangements and change their phenotype to that of a mesenchymal cell (Fig. 7–5).[84] EndMT is known to play a fundamental role in cardiac development[84] and has now been implicated in several cardiovascular disease states, including atherosclerosis,[85] vein graft remodeling,[86] cerebral cavernous malformations,[87] cardiac fibrosis,[88] vascular calcification,[89] and pulmonary hypertension.[90] Essentially, under the influence of TGF-β, fibroblast growth factor (FGF), and other signaling pathways, the pathological milieu that arises under these various pathologic states promotes this endothelial phenotypic switch, with some studies finding that EndMT gives rise to fibroblasts.[88] In contrast, in different disease models, we and others have identified that EndMT may give rise to vascular smooth muscle cells (VSMCs)[86] or even other mesenchymal cell types such as osteoprogenitor cells.[89] Importantly, EndMT is a specific subtype of the broader epithelial-to-mesenchymal transition (EMT) program.[84] EMT has been particularly well described in renal fibrosis, with current studies indicating that the cellular transition that occurs is only partial, such that EMT gives rise to

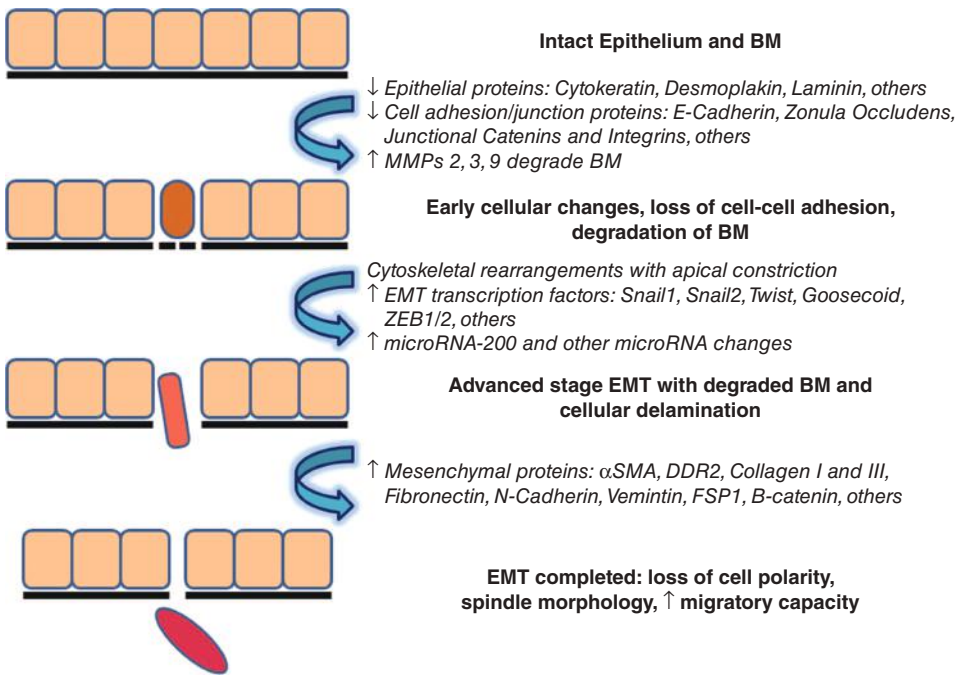


FIGURE 7–5. Key aspects of the molecular and cellular changes that occur with endothelial-to-mesenchymal transition. BM (*black line*), basement membrane; DDR2, discoidin domain receptor 2; EMT, epithelial-to-mesenchymal transition; FSP1, fibroblast specific protein 1; MMPs, matrix metalloproteinases; αSMA, alpha-smooth muscle actin. Reproduced with permission from Kovacic JC, Mercader N, Torres M, et al: Epithelial-to-mesenchymal and endothelial-to-mesenchymal transition: from cardiovascular development to disease, *Circulation*. 2012 Apr 10;125(14):1795-1808.[84]

fibroblast-like cells but not fully mature fibroblasts.[91,92] We identified a similar phenomenon with EndMT during vein graft remodeling, where EndMT gave rise to immature VSMCs that did not express the full array of mature smooth muscle cell contractile proteins.[86] As a common theme of these studies, EndMT has typically been associated with disease progression, and there appear to be multiple therapeutic opportunities for blocking this program in an effort to decrease disease severity.

MEDIA: FOCUS ON THE VASCULAR SMOOTH MUSCLE CELL

VASCULAR SMOOTH MUSCLE CELL CONTRACTION

Contraction and relaxation of the vascular wall is mediated by changes in medial VSMC tone, which as already mentioned can be affected by various signaling molecules, hormones, and other factors. As with the endothelium, similar biochemical pathways are activated through vasoactive agonists, with the ultimate smooth muscle cell contractile response determined also by the vascular microenvironment and macroenvironment.

Initial stimulation by vasoactive agonists leads to hydrolysis of phosphoinositides by phospholipase C, which results in generation of inositol triphosphate (IP3) and diacylglycerol (DAG).[93] IP3 conducts downstream signaling by binding an IP3 receptor on intracellular organelles with calcium stores that can be easily mobilized into the cytoplasm; release of calcium granules initiates downstream signaling that culminates in VSMC contraction.[94] IP3 activity is modulated by binding of IP3 to its receptor in addition to phosphorylation and binding of ATP and NADH.[95] Intracellular calcium stores are maintained by influx through L-type calcium voltage channels and transient receptor potential.[96] Calcium-mediated downstream signaling is disrupted with reuptake of calcium into the endoplasmic reticulum through sarcoplasmic reticulum calcium-ATPase and capture of calcium via calcium-ATPase on the plasma membrane.[97] Activation of phospholipase C also leads to generation of DAG, an activator of protein kinase C, an important calcium- and phospholipid-dependent enzyme that enhances contraction with elevated levels of intracellular calcium.[98] Metabolism of DAG produces glycerol, fatty acids, and ultimately leukotrienes and eicosanoids that also modulate VSMC tone.

Different vasoactive agonists induce differing magnitudes and lengths of contraction. There are two phases of smooth muscle contraction: an initial rapid component and a more sustained phase of contraction. The initial phase of contraction is dependent on the formation of actin-myosin cross-bridges in response to elevated levels of intracellular calcium; sustained contraction is present after the initial acute increase in intracellular calcium. Phasic contraction of smooth muscle is thought to be mediated by a sliding filament mechanism. Development of tension is regulated by myosin light-chain kinase (MLCK)-mediated phosphorylation of the myosin light chain (MLC) (Fig. 7–6). Hormonal stimulation leads to increased intracellular calcium, calmodulin binding, and association with MLCK and its transitioning to an active form. MLCK phosphorylates MLC, with subsequent actin activation of magnesium-ATPase and cross-bridge formation. With sequestration of calcium, there is a dissociation of calcium from calmodulin and subsequent deactivation of MLCK. Dephosphorylation of myosin via myosin phosphatase leads to cessation of cross-bridge action. Of note, during sustained contraction, there is a low calcium concentration and low-energy consumption state, which suggests there is a low cycling state. This state of slow, tonic contraction that achieves high levels of force with low energy expenditure is referred to as the *latch state* or *latch-bridge state*. This latch phenomenon is generally thought to be largely caused by the dephosphorylation of myosin during its attachment to actin. However, unphosphorylated myosin can bind to actin and although it may not be actively cycling, it likely contributes to force maintenance.[99] In turn, caldesmon enhances the binding force of unphosphorylated myosin to actin potentially contributing to the latch state, while extracellular signal-regulated kinase (ERK) phosphorylation of caldesmon decreases this binding force to very low levels.[100]

Contractility is also modulated by the small-molecular-weight guanosine triphosphatase (GTPase) Rho. The active Rho form (GTP bound) activates Rho kinase, which subsequently inhibits myosin phosphatase type 1.[101] This leads to a sustained MLC phosphorylation and sensitization of the contractile apparatus to calcium. Increased levels of Rho have been noted in hypertension, making it a therapeutic target.[102] Rho kinase inhibitors have been shown to lower vascular

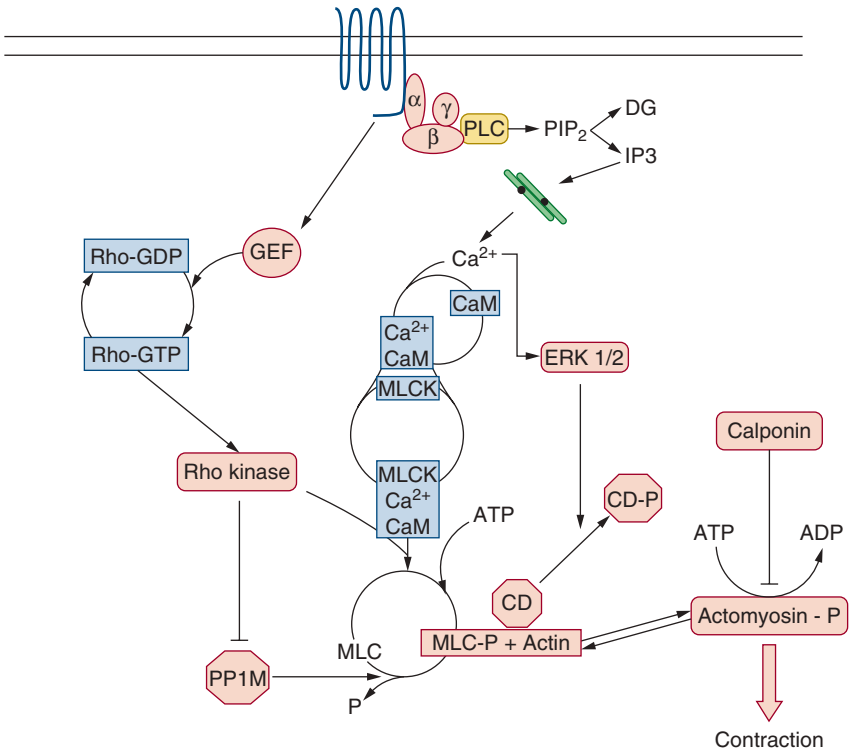


FIGURE 7–6. Contraction cascade. Activation of smooth muscle by a vasoconstrictor hormone leads to a cascade of biochemical signals, ultimately resulting in phosphorylation of actomyosin, cross-bridge formation, and force generation. The release of Ca^{2+} from intracellular stores is one of the major initiating events because Ca^{2+} combines with calmodulin (CaM) to activate myosin light-chain kinase (MLCK). This enzyme phosphorylates the myosin light chain (MLC), which is then able to interact with actin. In addition, activation of a guanine nucleotide exchange factor (GEF) for the small-molecular-weight G protein Rho leads to stimulation of Rho and Rho kinase, which inhibits myosin phosphatase (PP1M), thus enhancing MLC phosphorylation (MLCP). Caldesmon (CD), which normally inhibits actin–myosin interaction, becomes phosphorylated by extracellular signal–regulated kinase (ERK 1/2) and is released from this complex. Calponin acts by inhibiting myosin ATPase activity. αβγ, heterotrimeric G protein; Ca^{2+}, calcium; DAG, diacylglycerol; IP3, inositol triphosphate; P, phosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C. Used with permission from Bernard Lassègue, PhD.

resistance and blood pressure in animal models and may have efficacy as novel antihypertensive agents.[103,104]

VSMC contractile signaling is counteracted by relaxation stimuli, such as intracellular cyclic nucleotides, including cyclic AMP and GMP. NO binds to guanylate cyclase in VSMCs, leading to a reduction in intracellular calcium and reduction of MLC phosphorylation. Cyclic nucleotides are degraded by 3′,5′-cyclic nucleotide phosphodiesterases (PDEs).[105] These are the target of multiple therapeutic agents, including PDE type 5 inhibitors, such as sildenafil, that lead to increased cGMP levels. On the basis of their vasodilatory effects in the pulmonary circulation, PDE type 5 inhibitors are now widely used in the treatment of primary pulmonary hypertension.[58]

REGULATION OF VASCULAR SMOOTH MUSCLE CELL GROWTH AND HYPERTROPHY

In a nonpathological state, the VSMC is relatively refractory to growth stimuli and exists in a quiescent, differentiated, "contractile" state.[97] VSMC growth and proliferation is inhibited by a range of factors, including NO, prostacyclin, heparan sulfate, and transforming growth factor beta (TGF-β).[106-108] Although, depending on the context and strength of stimulus, TGF-β activity may also promote proliferation and phenotypic changes. VSMCs are maintained in a differentiated contractile state through signaling mediated by cyclic GMP-dependent protein kinase G. VSMCs are partially shielded from circulating factors through the protective endothelium. Disruption of the endothelial barrier leads to exposure of the VSMCs to promitogenic factors such as PDGF and thrombin, which leads to a mitogenic response and switch to the "synthetic" phenotype; repair of the endothelium inhibits further proliferation.

In pathological states, the vascular environment favors VSMC switching to the "synthetic" phenotype. Synthetic VSMCs are noted for their downregulation of contractile proteins/filaments, increased proliferation, and migratory capacity.[97] They are classically implicated in neointimal hyperplasia (see later section). Alternatively, degradation of the ECM also leads to a synthetic VSMC phenotype.[109] This is mediated through metalloproteinases released by activated cells within the vascular wall or infiltrated inflammatory cells. Agents that promote phenotypic switching from the quiescent contractile to the active synthetic state may be secreted by intrinsic vascular cells or invading immune cells. PDGF is a potent promitogenic agent involved in VSMC switching to the synthetic state; it is composed of two peptide chains (A and B) and can be secreted in multiple forms (heterodimer AB, or homodimer AA or BB). Various growth hormones regulate the release of PDGF from endothelial cells, including TGF-β, FGF, TNF, and thrombin.[110] PDGF promotes growth through suppression of the contractile phenotype[111] and activation of signaling pathways described above for vasoconstrictive agonists: hydrolysis of phosphoinositide, mobilization of calcium in addition to influx, and activation of protein kinase C. Insulin growth factor 1 (IGF-1) is another growth factor that facilitates movement of cells through the growth cycle and enhances PDGF-mediated mitogenic effects on VSMCs.[112] In turn, PDGF regulates IGF-1 production by endothelial cells.[113] Smooth muscle proliferation is also modulated by IL-1, FGF, and endothelin. The inflammatory cytokine IL-1 has many vascular effects, including effects on mitogenesis.[114] FGF is a potent agonist of the VSMC mitogenic response, which is particularly notable during neointimal hyperplasia.[115] FGF is found within the subendothelial matrix, and its release is triggered by heparin and proteinases.[116] Smooth muscle cell release of FGF is thought to be a key response to arterial injury. Endothelin-1 may also induce VSMC growth through binding at the ET-A receptor and downstream elevation in intracellular calcium, activation of protein kinase C, and increase in ROS production. Endothelin-1 production is modulated via hyperinsulinemia,[117] shear stress and pressure,[118] and angiotensin II.[119]

In terms of downstream intracellular signaling, VSMC stimulation by the previously mentioned factors leads to recruitment of different protein complexes that subsequently activate multiple cellular signaling cascades. Following activation, many growth factor receptors dimerize and self-phosphorylate tyrosine residues. Different protein complexes either bind directly to tyrosine kinase (phospholipase C-γ, the proto-oncogene c-Src, phosphatidylinositol 3-kinase) or through linker proteins Grb and Shc (pyk-2 paxillin). Grb and Shc link receptors to Ras (ubiquitous GTPase), which initiates a serine/threonine kinase signaling cascade involving mitogen-activated protein kinases (MAPKs), with the final response being VSMC growth (Fig. 7–7).

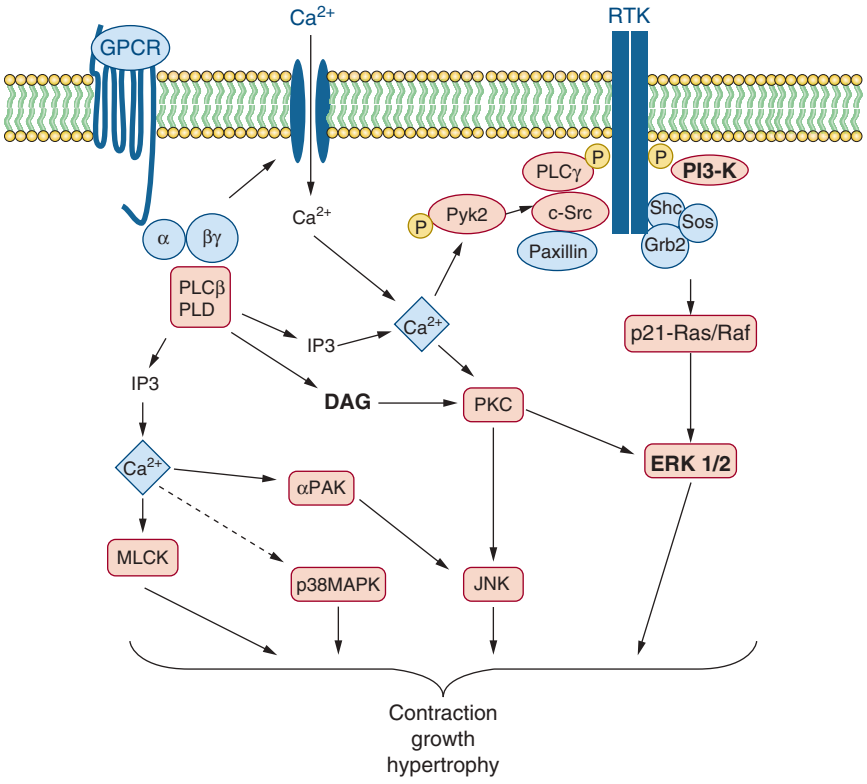


FIGURE 7–7. Signaling pathways in vascular smooth muscle. Vasoconstrictor agonists interact with specific G protein–coupled receptors (GPCRs) on vascular smooth muscle. These receptors are linked to a heterotrimeric G protein (αβγ), which then couples to one or more phospholipase Cs (PLCs) or phospholipase D (PLD). PLC cleaves the inositol phospholipids to yield diacylglycerol (DAG) and inositol phosphates, particularly inositol triphosphate (IP3). IP3 releases calcium from intracellular stores, and along with DAG, activates the Ca^{2+} and phospholipid-dependent enzyme protein kinase C (PKC). Ca^{2+} activates numerous other kinases, including p21-activated kinase (α-PAK), Pyk2, and myosin light-chain kinase (MLCK). PLD cleaves phosphatidylcholine to release phosphatidic acid, which is converted to DAG. PKC is involved in activation of the mitogen-activated protein kinase (MAPK) cascade, including extracellular signal-regulated kinases (ERK 1/2) and Jun kinase (JNK). Growth factors activate receptor tyrosine kinases (RTKs), Src, PLC-γ, and phosphatidylinositol 3-kinase (PI3-K). RTKs also phosphorylate and form a signaling complex with paxillin and adapter proteins such as Shc, which binds Grb-2 and Sos and ultimately mediates the conversion of Ras to its active form, Ras phosphorylates Raf1, which in turn leads to activation of the MAP kinase cascade. Used with permission from Bernard Lassègue, PhD.

Another kinase important to this response is c-Abl, an Src substrate that activates Rac, with subsequent effects on cytoskeletal rearrangement.[120] These protein complexes are also activated through G protein–coupled receptors.[121,122] This is thought to be the mechanism of action for the observed growth-promoting properties of vasoconstrictive agonists such as angiotensin II, thrombin, and ET-1. PDGF and other classic growth factors promote cell-cycle progression and proliferation through activation of cell-cycle proteins and inhibition of cell-cycle inhibitors. Hypertrophy-enhancing agents such as angiotensin have a more modest effect on cell-cycle proteins such as cyclins and enhance a cell cycle inhibitor.[123]

Another regulator of the growth pathway is ROS. Various growth-promoting agonists stimulate NADPH oxidases Nox1 and Nox5,[124,125] with production of hydrogen peroxide and superoxide, which can give rise to other ROS.[126,127] Hydrogen peroxide activates mitogen signaling molecules such as Src, Ras, p38MAPK, and Akt/protein kinase B, thus promoting entry into the cell cycle.[128-132] Hydrogen peroxide also inactivates protein tyrosine phosphatases, leading to prolonged phosphorylation of key signaling molecules.[133]

Notably, VSMC growth may occur through hyperplasia and/or hypertrophy. Classic growth factors stimulate hyperplasia, which is associated with the switch to an active synthetic phenotype. On the other hand, hypertrophy is a response to chronic stimulation with vasoconstrictor agonists. Hypertrophy is secondary to an increase in smooth muscle cell mass with increase in protein synthesis and no accompanying replication of DNA. For example, this can be seen in response to angiotensin II and thrombin[134,135] or as a pathologic response to hypertension in large vessels.

NONCODING RNA

Noncoding RNAs (ncRNAs) are a group of various types of RNA moieties that in general are not translated into proteins. As a relatively recent but very major paradigm shift, ncRNAs are being increasingly recognized as important regulators of gene and protein expression. The subtypes of ncRNAs and their mechanisms of action are comprehensively described in Chapter 6 and Figs. 6–7 to 6–9. In the vasculature, our knowledge of ncRNAs is in its infancy—but growing rapidly. Already, it is clear that ncRNAs are major players in the full spectrum of vascular biology, including all anatomical layers considered in this chapter (eg, endothelium, smooth muscle cells, intima, media, adventitia). Furthermore, various ncRNAs have been identified that are stable outside the cellular milieu in the blood. Specifically, circulating microRNAs (miRNA, a very short ncRNA moiety of ~22 nucleotides) exist in a stable extracellular form, and strong associations have been identified between the levels of specific miRNAs and various cardiovascular diseases such as acute myocardial infarction, coronary artery disease, heart failure, stroke, and hypertension.[136] Mechanistically, it is also being fast appreciated that ncRNAs play a major role in the biology of the vessel wall. However, at the present time our knowledge of these ncRNA pathways is obviously quite incomplete and appears more as an isolated potpourri of effects, rather than an integrated understanding. Nevertheless, the fact that certain ncRNA moieties can exist in the extracellular compartment has significant implications, because it means they can act as messengers between cells or even between organs within the body, akin to circulating hormones or cytokines.[137] Many hundreds or even thousands of ncRNAs are likely implicated in the biology of the vessel wall. The study of ncRNAs represents one of the areas of most intense current research in vascular biology. A summary of several recent studies describing a complete pathway of action of specific vascular miRNAs is presented in Fig. 7–8.

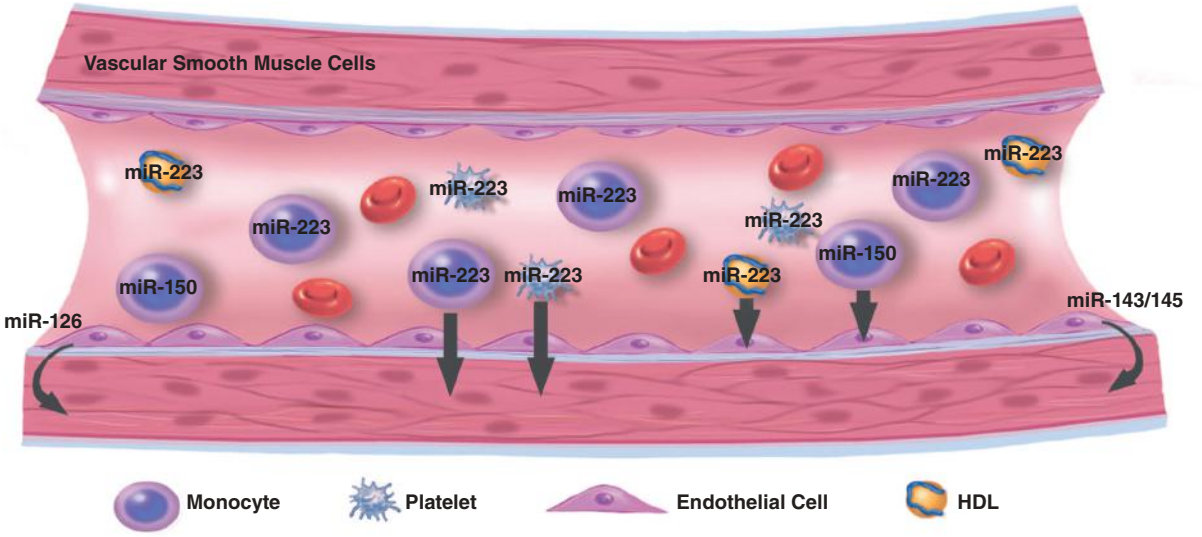
EXTRACELLULAR MATRIX

Extracellular matrix (ECM) is a major component of the vascular wall. It functions as a medium for transport of nutrients; a receptacle for secreted substances from surrounding cellular structures; and a mediator of migration and proliferation of VSMCs, endothelial cells, and monocytes. The ECM has various components, each of which has distinct roles in maintaining the integrity and function of the vasculature, summarized in Table 7–2. The interactions between the different components of the ECM and vascular cells comprise a complex, large signaling network involving numerous signaling receptors. These signaling networks ultimately affect various components of vascular cell development and biology, including response to hemodynamics, organ development, hypertrophy, angiogenesis, and development of atherosclerotic plaques.

The degradation and reformation of the ECM is an important component of multiple processes that maintain vascular wall function. Vascular cell hypertrophy, proliferation, and migration are dependent on initial degradation of the ECM. One of the early events in angiogenesis includes the degradation of the ECM to allow for capillary formation. Enzymes that selectively digest individual components of the ECM are known as metalloproteinases (MMPs); these are secreted by inflammatory and vascular cells (including endothelial cells, VSMCs, fibroblasts, and resident macrophages). In addition, these same cell populations also produce counterregulatory tissue inhibitors of metalloproteinases (TIMPs), which promote ECM stability.

MMPs belong to one of two classes: secreted or membrane-spanning (with an active site outside the cell). Secreted MMPs are divided into several groups: type IV collagenases (also referred to as gelatinases), stromelysins, and interstitial collagenases. Secreted MMPs are produced as inactive zymogens that can be activated by plasmin. Cytokines also regulate MMP and TIMP activity at a transcriptional and post-transcriptional level. The membrane-spanning MMPs are made up of disintegrin and metalloproteinase domain proteins. These are multifunctional proteins that contribute to cell adhesion as well as degrading matrix components to release paracrine factors, such as monocyte colony stimulating factor, TNF-alpha, Fas ligand, and Notch.[138]

MMP secretion and expression are regulated at multiple levels, with inflammation being a major global pro-MMP stimulus. Cytokine stimulation has been shown to increase expression and secretion of MMPs by VSMCs (MMP-1, MMP-9, MMP-3, MMP-2 zymogen), which facilitates degradation of major matrix components.[139-141] In microvascular and venous endothelial cells, MMP-3 and MMP-9 expression is also induced by cytokines.[142] The overall net effect of cytokines in the vascular wall appears to be a shift in balance between MMPs and TIMPs, with an end result of ECM degradation and remodeling. ROS have been shown to stimulate activation and expression of MMP-9.[143,144] This is thought to be significant in vascular pathologies that have increased levels of oxidative stress, such as atherosclerosis and hypertension. Importantly, TIMPs and MMPs play a pivotal role in the pathology of atherosclerotic plaques and aneurysms.[141,145] MMPs are highly expressed in the shoulder regions of atherosclerotic plaques[146] and predispose to plaque rupture. Although produced by several cell types as noted, in atherosclerosis, activated macrophages are especially notable for their production of MMPs and ROS.[143,146] Abdominal aneurysms also have an abundance of MMP activity.[141,147] Both vascular pathologies are mediated by oxidative stress, inflammation, and altered hemodynamics, which also likely contribute to the expression and activation of MMPs. Of note, expression of MMPs has also been shown in the aneurysms of patients with Marfan syndrome.[148]



	miR-223	miR-223	miR-150	miR-143/145	miR-126	miR-126
Source	Monocytes, platelets, MP	HDL	Monocytes, MP	ECs	Adoptotic bodies from ECs	ECs
Target Cell	VSMCs	ECs	ECs	VSMCs	Vascular cells	VSMCs
Signaling	Binds IGF-1R, inhibits PI3K-Akt in VSMCs	Binds and represses ICAM-1 in ECs	Binds and represses c-Myb in ECs	Produced in ECs under control of KLF2	Induces CXCL12 expression in recipient cells	Binds and represses FOXO3, BCL2 and IRS1 in VSMCs
Target Cell Effect	↑Apoptosis; ↓migration and proliferation	↓Neutrophil adhesion to ECs	↑Migration	Athero-Protective VSMC phenotype	Athero-Protective effects	↑Proliferation and neointimal formation

FIGURE 7–8. Recent in vivo studies elucidated the origin, target, signaling, and actions of micro ribonucleic acids (miRNAs; miR) in the vasculature.[193–198] BCL2, B-cell lymphoma 2; EC, endothelial cell; FOXO3, forkhead box O3; HDL, high-density lipoprotein; ICAM, intercellular adhesion molecule; IGF-1R, insulin-like growth factor 1 receptor; IRS1, insulin receptor substrate 1; KLF2, Krüppel-like factor 2; MP, microparticle; prolif, proliferation; PI3K, phosphatidylinositol 3-kinase; VSMC, vascular smooth muscle cell. Reproduced with permission from Kovacic JC: Unlocking the Many Secrets of Noncoding RNA, *J Am Coll Cardiol*. 2015 Jun 16;65(23):2538-2541.[137]

TABLE 7–2. Major Components of Extracellular Matrix (ECM)

ECM Component	Function
Collagens (types I, II)	Mechanical strength
Collagens (types IV, V, VI)	Component of basal lamina; attachment of vascular cells to the ECM; cross-linking of collagen to noncollagen structures
Elastin	Provides elasticity of the vascular wall
Fibronectin	Cell motility; cell–cell adhesion; cell–substrate adhesion; specific binding of collagen, heparin
Laminin	Endothelial cell attachment to collagen type IV
Proteoglycans	Regulation of cellular metabolism; permeability; ion exchange and filtration of the vascular wall; transport and deposition of elements from plasma; resistance to structural changes

SPECIFIC VASCULAR DISEASE STATES AND DISEASES

The pathobiology of most vascular diseases is notable for a complex interplay of all the previously mentioned cellular players and molecular pathways. Here we study several key disease states to further explore these relationships and their role in promoting disease.

ATHEROSCLEROSIS AND ENDOTHELIAL DYSFUNCTION

In many vascular diseases, there is notable endothelial dysfunction, which may manifest as loss of vasodilator response, prothrombotic events, initiation of leukocyte adhesion, and/or stimulation of VSMC migration and proliferation. However, this process is especially important in atherosclerosis, with endothelial dysfunction being clinically detectable before the macroscopic presence of formed atherosclerotic plaques. Among the many reports to demonstrate an association between endothelial dysfunction and vascular disease are several seminal clinical studies from the 1990s that demonstrated associations between endothelium-dependent arterial vasoreactivity and various cardiovascular risk states such as diabetes,[149] cigarette smoking,[150] and positive family history.[151] The fact that endothelium-dependent arterial vasoreactivity is an early event in atherosclerosis has been reinforced by a multitude of basic mechanistic studies. One of the hallmarks of impaired endothelium-dependent arterial vasoreactivity is impaired eNOS activation, with resulting decreased NO production.[152] Destabilization of eNOS mRNA under conditions of endothelial cell stress is an additional mechanism that leads to decreased NO production.[153] Inhibition of Rho GTPase through statins prevents this destabilization, which adds to the mechanisms through which HMG CoA reductase inhibitors mediate vasculoprotective effects.[154]

Recruitment of monocytes and macrophages into the vessel wall is another aspect of endothelial dysfunction.[155] LDL modification occurs

when the subintimal space becomes more oxidized. Modified LDL then activates various toll-like receptors (TLRs), including TLR-4, with subsequent induction of proinflammatory gene expression and infiltration of macrophages. TLR-4 antagonism reduces infiltration of monocytes/macrophages and expression of IL-6 and MMP-9 in atherosclerotic lesions of diabetic mice.[156] Adhesion molecule expression is amplified through secretion of inflammatory cytokines by activated macrophages and vascular cells. In humans, polymorphisms of the fractalkine receptor CX3CR1 have been demonstrated to alter adhesive and chemoattractant properties, influencing the likelihood of developing atherosclerosis and acute coronary syndromes.[157]

Intimal proliferation in atherosclerosis is secondary to migration and hyperplasia of VSMCs and myofibroblasts, in addition to ECM accumulation. Growth factors, including PDGF, FGF, and IGF-1, are thought to contribute to proliferation, which is also influenced by less well understood factors such as disruption of the integrity of the internal elastic lamellae.[158] These signaling pathways also become dysfunctional in the atherosclerotic endothelium, which can further enhance plaque progression.[85]

HYPERTENSION

Hypertension is characterized by dysfunction of the endothelium and VSMCs. In chronic disease, there is impairment in endothelium-dependent relaxation, as well as increased endothelium-dependent constrictor activity, which is influenced by endothelial Peroxisome proliferator-activated receptor gamma (PPARγ) and systemic angiotensin signaling.[159] Vessel wall mass is increased, with acute hypertension leading to thickening of the medial and adventitial layers and with significant adventitial hyperplasia.[160] VSMCs are an integral aspect of this response, with both smooth muscle hyperplasia and hypertrophy being more or less prominent depending on arterial size and muscularity.[161] Interestingly, nestin is an intermediate filament protein in smooth muscle cells that participates in the regulation of hypertension-mediated hyperplasia,[161] which is also governed by the cAMP-PKA-EGFR-CREB/ERK pathway.[162] However, the smooth muscle cell hypertrophic response to hypertension appears to be controlled by alternate signaling pathways.[161] Phenotypic VSMC modulation also occurs in response to hypertension, with altered smooth muscle contractile protein expression.[163]

NEOINTIMAL HYPERPLASIA

Neointimal hyperplasia is a hyperproliferative vascular smooth muscle cell response that arises in the weeks to months following acute arterial injury, although it also contributes to other pathologies such as pulmonary arterial remodeling in pulmonary hypertension and during vein graft remodeling on exposure of the donor segment of venous vessel to systemic arterial pressures. From the 1980s to the 2000s, intense efforts were devoted to understanding neointimal hyperplasia because it is the pathological process responsible for restenosis that arises following percutaneous coronary intervention (PCI; balloon angioplasty and stenting). In the setting of PCI, acute arterial injury arises from the physical trauma inflicted on the host vasculature by ballooning and stenting, which includes endothelial denudation, overstretch injury, and disruption of the elastic lamellae.

The cardinal feature of neointimal hyperplasia is VSMC proliferation. As stated, resting VSMCs exist in the "contractile state," expressing high levels of contractile proteins and reduced levels of inflammatory markers. On arterial injury, VSMCs undergo a phenotypic switch from the contractile to synthetic state, with reduced expression of contractile proteins and enhanced matrix and collagen expression. It is these synthetic VSMCs that largely comprise the neointima.[164] Neointimal formation occurs on the luminal side of the innermost aspect of the arterial elastic laminae, this being the intimal layer. Importantly, in healthy vessels, the intima is only one to two cells thick and comprised of endothelial cells and sometimes a subendothelial pericyte cell layer.[13] Exuberant VSMC proliferation with collagen and matrix production in this intimal layer, in this context called the *neointima*, may lead to significant neointimal formation with luminal narrowing.[165] In the context of clinical PCI, this may culminate in coronary stenosis or even complete coronary artery occlusion.

Interestingly, on acute arterial injury, a series of very early events arise that appear to dictate the subsequent hyperplastic response. One of the earliest events after acute arterial injury is rapid expression of MCP-1, RANTES, and other inflammatory cytokines by medial VSMCs.[166] This surge in expression of inflammatory and chemotactic cytokines triggers an early influx of inflammatory cells, including monocytes and T cells, which then orchestrate the injury repair and hyperplastic response.[166] However, many medial VSMCs succumb to the intense cellular and oxidative stresses and undergo cell apoptosis and death. Next, days to weeks after the initial injury, lineage tracking studies have shown that some of the surviving medial VSMCs are able to proliferate and give rise to new synthetic VSMCs that both repopulate the media and also give rise to the neointima.[165,167] The extent of neointimal hyperplasia is regulated by typical signaling proteins known to regulate VSMCs, such as PDGF ligand, TGF-β, FGF, stromal cell-derived factor 1 (SDF-1), and RANTES,[166,168] with higher order regulation from a range of factors, including $p21^{Cip1}$, p27, and p53.[168,169] Other factors that may dictate the extent of neointimal formation include the severity of the initial injury, whether or not the elastic laminae are fully disrupted and there is exposure of the underlying adventitia,[158] whether there is concurrent atherosclerosis, and how rapidly the endothelial layer is reestablished.[170]

Neointimal hyperplasia was a major clinical concern in the era of stand-alone balloon angioplasty and then the bare metal stent era, where clinically significant restenosis arose in 30% to 40% of lesions that had previously undergone intervention. However, in the contemporary era of drug-eluting stents (DES), clinically significant restenosis arises in only 5% to 10% of treated lesions.[171,172] Unlike bare metal stents, DES are loaded with specific drugs, often related to chemotherapeutic agents such as everolimus or sirolimus, with the primary effect of reducing VSMC hyperplasia. However, inhibition of reendothelialization was a detrimental off-target effect that was associated with stent thrombosis. Thankfully, with improved stent delivery platforms with thinner struts and better optimized drugs with improved release kinetics, the delayed endothelial healing seen with first-generation DES (Cypher and Taxus) has largely been overcome.[171,173] In turn, it is believed that this earlier reendothelialization that occurs with second-generation DES helps to further slow the intimal hyperplastic response.[170] Thus, it is pleasing that the clinical impact of neointimal hyperplasia has been dramatically reduced in recent years, attesting also to the vital importance of the well-conducted translational research that facilitated this progress.

During vein graft remodeling, when segments of vein must adapt to systemic arterial pressures such as in coronary artery bypass graft surgery or arteriovenous fistula formation, neointimal hyperplasia also arises. Interestingly, unlike acute injury where the endothelium is denuded, the pathobiology of intimal hyperplasia in vein graft remodeling appears to involve EndMT, with endothelial cells switching phenotype and giving rise to synthetic VSMCs under the governance of TGF-β pathway signaling.[86]

DIABETES

Diabetes has profound effects on the biology of the vessel wall, including the endothelium and VSMCs.[174,175] In the endothelium, diabetes

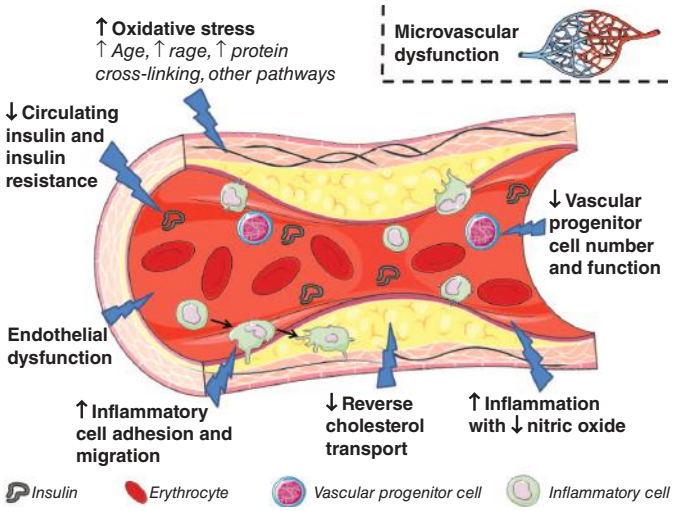


FIGURE 7–9. Key pathologic diabetic pathways affecting the vasculature. AGE, advanced glycation end product; RAGE, receptor for advanced glycation end products. Reproduced with permission from Kovacic JC, Castellano JM, Farkouh ME, et al: The relationships between cardiovascular disease and diabetes: focus on pathogenesis, *Endocrinol Metab Clin North Am*. 2014 Mar;43(1):41-57.[174]

increases the production of ROS and reduces available NO. This leads to impaired endothelium-dependent vasodilatation. However, additional mechanisms of diabetes-associated endothelial dysfunction are multifold. Vascular expression of proinflammatory genes is elevated in diabetes.[176] Diabetes and the metabolic syndrome also cause a range of detrimental changes in blood clotting, including increased clotting factor formation, low protein C levels, increased tendency for platelet aggregation, altered plasminogen activator inhibitor-1 levels, increased thrombin formation, hypofibrinolysis, and a prothrombotic fibrin clot phenotype.[177-179] The production of advanced glycated end products acting on endothelium, macrophages, and VSMCs is another final common pathway in diabetes that also increases the rate of progression of vascular disease. Histopathologically, in larger conduit vessels these events contribute to the formation of atherosclerotic lesions, but in resistance arteries there is arteriopathy, characterized by wall thickening, luminal narrowing, inflammation, and remodeling. This is seen in the associated vascular manifestations of diabetes, including retinopathy, nephropathy, and ischemia of peripheral tissues.[174] An overview of the key pathologic diabetic factors affecting the vasculature is shown in Fig. 7–9.

RESIDENT PROGENITOR CELLS

The vascular wall contains several populations of resident vascular progenitor cells that shall be briefly reviewed below. As an important note, the cardiovascular community has devoted intense efforts into defining the origins and role of endogenous stem cells in the heart, and despite these efforts numerous controversies and unanswered questions remain. The progenitor populations occupying the vascular wall are even less well understood, and we expect that significant advances will be made in this front in the near future.

ENDOTHELIAL PROGENITOR CELLS

Although there has been intense debate regarding the existence of circulating endothelial progenitor cells (EPCs),[10] presumed to have arisen from the bone marrow, an overlooked potential location for EPCs is the vessel wall itself. Indeed, in vitro, most vessel-derived endothelial populations may be passaged several times, attesting to their proliferative capacity. Whether all endothelial cells possess inherent capacity for a degree of expansion and proliferation, of whether there is a discrete EPC niche in the vessel wall remains to be rigorously defined. However, Ingram et al previously demonstrated that the vessel wall contains a complete hierarchy of EPCs, which can be defined based on both their clonogenic and proliferative potential.[180] Subsequently, Naito et al went on to define an EPC population that resides among other non-EPCs of the vessel wall. These resident progenitor endothelial cells comprise approximately 1% of all endothelial cells, are not derived from the bone marrow, and reside predominantly in veins and capillaries.[181]

PERICYTES AND MESENCHYMAL STEM CELLS

Increasingly, data are emerging to suggest that pericytes represent a type of mesenchymal stem (also called stromal) cell (MSC).[13,182] Although there is little question now that pericytes fulfill the formal criteria to be termed MSCs, including differentiation into adipocytes, chondrocytes, and osteocytes,[182] their role in vascular biology remains to be fully defined. Specifically, it is very well described that the investment of endothelial cells by pericytes is fundamental for the stabilization and maturation of new vessels.[183] Neither has the dependency of this vessel-stabilizing effect on MSC characteristics been defined, nor has the possibility that MSCs may contribute in other ways to vascular biology.

MEDIAL VASCULAR PROGENITOR CELLS

It has long been suspected that VSMC progenitor cells reside in the medial layer. Although the presence of any VSMC progenitor must be reconciled against the intrinsic capacity of VSMCs for proliferation and phenotypic switching. Recently, Tang et al[184] described the existence of a progenitor population residing in the outer aspect of the medial layer and that gave rise to VSMCs. However, these findings subsequently generated significant controversy[185] and remain to be replicated.

ADVENTITIAL PROGENITOR CELLS

Perhaps the most convincing data for the existence of resident vascular progenitor cells is from the adventitia. A series of studies from Majetsky et al showed that a murine stem cell antigen-1+ (Sca-1+) population resides in the adventitia and that it was potent in vitro for giving rise to smooth muscle cells and endothelial cells.[186] Using indirect methods, it was suggested that Sca-1+ progenitor cells can contribute to atherosclerotic plaque formation.[187] More recent data have emerged using Gli-1 as a marker of adventitial MSC-like cells.[188] Gli-1+ adventitial progenitor cells coexpress Sca-1 and can give rise to myofibroblasts that contribute substantially to organ fibrosis (Fig. 7–10). Accordingly, ablation of Gli-1+ cells substantially reduces organ fibrosis.[188] Interestingly, additional studies have also suggested that the adult adventitia may also harbor a resident macrophage progenitor cell population.[189] Whether or not resident adventitial progenitor cells can be harnessed for therapeutic applications requires further study.

CONCLUSION

Major clinical treatment advances that have impacted patient care have been made in the last decades, which owe their success to a core understanding of the biology of the vessel wall. Notable among these are major reductions in post-PCI restenosis by attenuating neointimal hyperplasia,[171] tailoring of antiplatelet therapies after PCI based on an understanding of reendothelialization and its kinetics after PCI,[190] anti-VEGF therapies that block angiogenesis and thereby exert antitumor

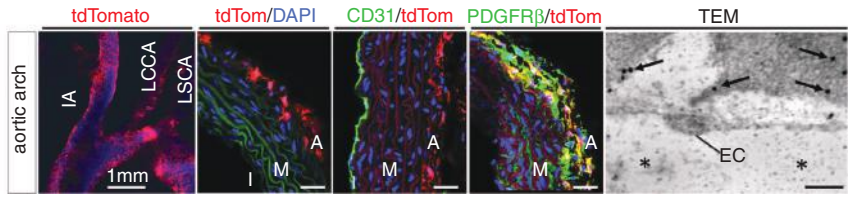


FIGURE 7–10. Gli1 expression defines a perivascular MSC-like cell population. **A.** Adult Gli1-CreERt2; tdTomato mice 48 hours after tamoxifen administration. In these mice, cells expressing Gli1 appear as red, with cell nuclei seen as blue (DAPI staining). Aortic root with innominate artery (IA), left common carotid artery (LCCA), and left subclavian artery (LSCA) are shown. Gli1+ cells reside in the adventitia (A) distant from CD31+ endothelial cells of the intima (I) and media (M) and are also PDGFRβ+. Scale bars, 20 mm or as indicated. **B.** Gli1+ cells also reside adjacent to CD31+ endothelial cells. Transmission electron microscopy (TEM) picture of immunogold-labeled (*arrows*) Gli1+ interstitial kidney cell adjacent to an endothelial cell (EC) is shown. Reproduced with permission from Kramann R, Schneider RK, DiRocco DP, et al: Perivascular Gli1+ progenitors are key contributors to injury-induced organ fibrosis, *Cell Stem Cell*. 2015 Jan 8;16(1):51-66.[188]

effects,[191] and the expanded arsenal of vasodilator therapies that are now available for use in patients with pulmonary hypertension.[58] Yet much remains still to be understood, including the details of EndMT and how it can be manipulated for therapeutic gain, resident vascular progenitor cells and their role in health and disease, and the complex interactions at the systemic level between the vasculature, the heart and the entire human organism (see Fig. 7–1). By understanding these and other aspects of vessel biology, untold therapeutic opportunities are likely to be disclosed. In sum, the importance of a thorough understanding of the vessel wall in health and disease cannot be gainsaid, and we foresee redoubled efforts in this field in the coming years.

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CHAPTER 8

MOLECULAR AND CELLULAR DEVELOPMENT OF THE HEART

Miguel Torres and Silvia Martín-Puig

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INTRODUCTION

Cardiac development is a fascinating journey that starts early in embryonic development and brings cells from a homogeneous pluripotent state to a highly specialized array of differentiated tissues organized in a complex functional architecture. Heart development has been addressed extensively in monographic texts,[1,2] and here we will focus in summarizing the aspects more relevant to understand its origin, morphogenesis, and physiology. The heart is the first functional organ in the mammalian embryo; however, its full development spans the whole intrauterine period and is finished only in the postnatal period. Therefore, most of the complex morphogenetic events and the cell proliferation, migration, and differentiation processes involved in heart formation take place in the context of a beating heart that provides the circulatory function essential for embryonic, fetal, and postnatal development. Cardiac malformations are the most frequent congenital malformations in humans (around 1%), which correlates with the complexity of generating a four-chambered heart from an initially linear cardiac tube. Although genetic determinants of cardiac malformation are increasingly being discovered, the precise understanding of how specific developmental defects lead to a malformed newborn heart is still a difficult task and will likely demand the development of systems biology approaches capable of modeling cardiac development in a predictive manner. Importantly, during development, cardiomyocytes proliferate extensively. However, this ability is limited in the adult heart and so is cardiac regenerative capacity. The molecular and cellular pathways involved in cardiac development therefore have become a paradigm for the design of cardiac regenerative strategies in the adult heart.[3,4] In this chapter, we will address the main aspects of cardiac embryonic development, including the origin of cardiac precursors, the formation of the cardiac crescent, the morphogenesis of the primary heart tube, and the recruitment of additional lineages from the epicardium and the neural crest. We will also discuss the progressive incorporation of second heart field precursors and the differentiation of the different cardiomyocyte subtypes. In addition, we will present current knowledge on the morphogenesis of cardiac chambers, septa, and valves. Finally, we will review the knowledge on cardiomyocyte proliferation, differentiation, and hypertrophy and how the surrounding signaling and cellular environment influences these processes. Our knowledge of cardiac development mainly derives from studies in animal models in which experimental embryology and genetic engineering is accessible. We will describe human cardiac development,[5] although the knowledge presented here on the mechanisms involved derives from experimental animal models, mainly mouse and chicken, which represent the genetic and embryological models closest to humans.

CARDIAC EMBRYOGENESIS

ALLOCATION AND SPECIFICATION OF CARDIAC PROGENITORS DURING GASTRULATION

Cardiac precursors are found shortly after gastrulation (the formation of the three embryonic layers: ectoderm, endoderm, mesoderm) within the mesodermal component of the splanchnopleural layer of the anteriormost lateral plate (Fig. 8–1).[2,6,7] This area is called the cardiogenic area and is formed by early gastrulating embryonic mesoderm. The cardiogenic area is single and crescent-shaped in the mouse and bilaterally paired in the human and avian embryos (see Fig. 8–1).[2] Before gastrulation, the embryonic part of the conceptus consists of a pseudostratified epithelium of pluripotent cells known as the epiblast, which is flat in avian and human embryos and cup-shaped in the mouse. The epiblast epithelium is covered at its basal side by a layer of primitive endoderm (outer in the mouse and underneath in the human and chick). At gastrulation, cells at the central-posterior position in the epiblast undergo epithelial-to-mesenchymal transition (EMT), forming the so-called primitive streak (PS).[8] Cells recruited to the EMT process at the PS migrate in between the epiblast and the endoderm to form the mesodermal layer and replace most of the primitive endoderm to form the definitive endoderm. PS formation starts posteriorly at the embryonic-extraembryonic interface and progresses in a posterior-to-anterior sequence. The pregastrulation epiblast already shows a large degree of regional specification and fate maps have been established identifying the prospective ectoderm and neuroectoderm, as well as various types of mesodermal compartments: cardiac, blood, vascular, axial paraxial, and lateral mesoderm.[9] Despite this regional specification and despite the fact that certain signals are already regionalized before gastrulation, epiblast cells remain pluripotent until they are recruited to the PS. Transplantation studies have shown, for example, that epiblast regions fated to produce brain transplanted to the cardiac-forming region will form the heart and vice versa.[9] These and other studies show that cells acquire their developmental fates depending on the specific position and timing of their transit through the PS.[8] Therefore, the regional specification of the epiblast does not result from autonomous properties being established in epiblast cells but from the fact that gastrulation is a highly ordered process and thus the position of a cell in the epiblast predicts the timing and position of its ingression through the PS.[8]

As mentioned above, instructive signals are already regionalized in the embryo before and during gastrulation, and accumulating data indicate that the history of external signals cells receive during their journey through gastrulation determines the differentiation pathway

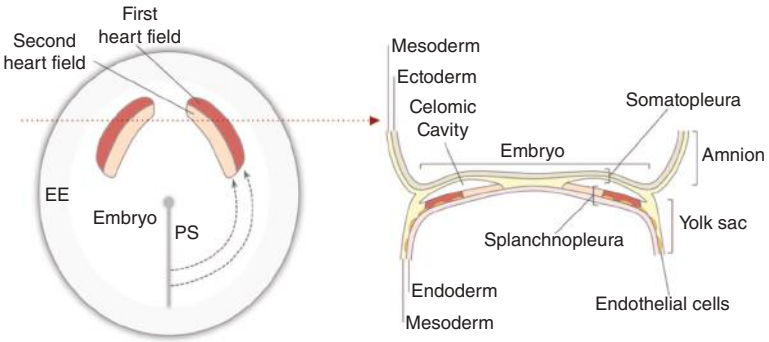

FIGURE 8–1. Early allocation of cardiac precursors. To the left, a schematic representation of a dorsal view of the 14-day human embryo (equivalent to approximately E7 mouse embryo). The arrows show the trajectories of the cardiac mesoderm during gastrulation from the primitive streak (PS) toward an anterolateral position. The dotted red arrow indicates the sectioning plane corresponding to the scheme on the right, showing the disposition of the embryonic and extraembryonic layers and the nascent celomic cavities, precursor of the pericardial cavity, are shown. The first heart field progenitors occupy the region closer to the extraembryonic membranes and those of the second heart field lie immediately medial to them. Interspersed endothelial precursors are present between the endoderm and the splanchnic mesoderm. EE, extraembryonic region. Modified with permission from Fuster V and Kalil Roberto: *Cardiovascular Medicine*, the Impact of Diseases. Atheneu; 2016.

they will adopt. The signal history includes not only the identity and intensity of the signals received but also the specific sequence in which these signals target the differentiating cells. The main factor determining an epiblast cell fate is therefore the position it occupies in the epiblast, because this will determine its gastrulation schedule and migration route and thereby, the signal sequence to which it will be exposed.

As cells move away from the PS, they make a 90-degree turn towards an anterior direction, so that the anterior-posterior order of cells in the PS is transformed in mediolateral positions. Cells from the anteriormost PS contribute to axial mesoderm, those at immediately posterior positions contribute to paraxial mesoderm, those that are more posterior contribute to lateral mesoderm, and the most posterior ones colonize the extraembryonic region (see Fig. 8–1). Because gastrulating cells move anteriorly as they exit the PS, the earlier the cells exit the PS, the more they colonize the anterior region. For example, the earliest paraxial mesoderm will contribute to the head region and then, in a temporal sequence, to cervical, lumbar, sacral, and caudal somites. At the lateral plate level, the first mesodermal cells produced will form the septum transversum and heart, then forelimbs, other viscera, hind limbs, and the genitalia. Except for the extraembryonic mesoderm, the cardiac and hepatic mesoderm is thus the first mesoderm being produced in the embryo. In the mouse, the cardiac mesoderm first colonizes the rim between the head folds and the extraembryonic region initially lying at the most anteriolateral embryonic region, forming horseshoe-shaped primordium. In the human and avian embryo, in contrast, two cardiac primordia are formed bilaterally without continuity across the anterior midline (see Fig. 8–1).

Experiments in zebrafish at the establishment of the cardiac fields[10] have shown that retinoic acid signaling forms a gradient from posterior to anterior. This gradient establishes the border between the cardiac and forelimb fields through the regulation of Hox transcription factors and promotes the atrial versus the ventricular fate.

Soon after gastrulation starts, Hensen's node is established at the anteriormost end of the PS. Oriented movements of Hensen's node cell cilia establish left-right patterning by localizing signaling molecules essential to start specific left-right asymmetry molecular program.[11] This left-right asymmetry program promotes the specific location and left-right orientation of internal organs, including the heart.

FORMATION OF THE PRIMARY HEART TUBE AND ESTABLISHMENT OF THE SECOND HEART FIELD

The outermost rim of the cardiac mesoderm closer to the extraembryonic region is the first region to show signs of cardiomyocyte differentiation and is known as first heart field (FHF) (see Fig. 8–1), which, at this stage, is arranged in the mouse in a crescent shape and thus named cardiac crescent.[7] As part of the general embryonic folding process that brings the endoderm to the inside of the embryo, the heart precursors are brought to their definitive position posterior and ventral to the head (Fig. 8–2). During these movements, the heart forming regions are always in close contact with the pharyngeal endoderm, being definitely placed ventrally to the foregut pocket (see Fig. 8–2). The rest of mesodermal cardiac precursors positioned posteromedially and immediately adjacent to the cardiac crescent in the splanchnopleura are known as the second heart field (SHF) (see Fig. 8–2).[12-15] The FHF gives rise to posterior heart structures, including the left ventricle and most of the atria. The contribution of FHF to the heart tube takes place "all-at-once" by simultaneous folding, fusion, and remodeling of the splanchnopleural mesoderm, but the SHF is maintained as a pool of undifferentiated proliferating cardiac precursors for about 2 days, during which it progressively contributes cardiac tissue for (1) the sequential generation of the right ventricle and outflow tract at the anterior pole and (2) part of the atria and inflow tract at the posterior pole (Fig. 8–3).[7,16,17] In the human and avian embryos, the initial cardiac fields occupy a paired bilateral position and do not span across the midline anterior to the head-forming region. Formation of the primary

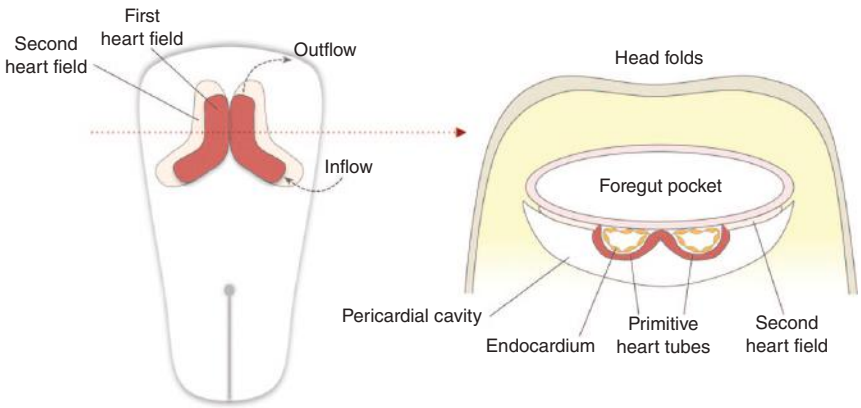

FIGURE 8–2. Formation of the paired primitive heart tubes. Schematic representation of the disposition of the primitive heart tubes in the 18-day human embryo (~E8 mouse embryo). The dotted red arrow indicates the sectioning plane corresponding to the scheme on the right. The first heart field precursors have differentiated into primary cardiomyocytes and folded toward the pericardial cavity to form two hemitubes. The endothelial precursors have formed a continuous endocardial tube along the primitive cardiac tubes. Although the myocardial wall has not closed dorsally, the continuous endocardial layer and the pharyngeal endoderm allow the enclosure of the cardiac lumen. Cardiomyocyte contraction has started in a peristaltic posterior-to-anterior fashion, which produces an incipient flow that starts to shape the peripheral vascular system (*dotted gray arrows in left schematic*). As a result of embryo folding, the cardiac fields have fused anteromedially and the first heart field–derived cardiac tubes now lie medial to the second heart field precursors, which remain attached to the pharyngeal endoderm. Modified with permission from Fuster V and Kalil Roberto: *Cardiovascular Medicine*, the Impact of Diseases. Atheneu; 2016.

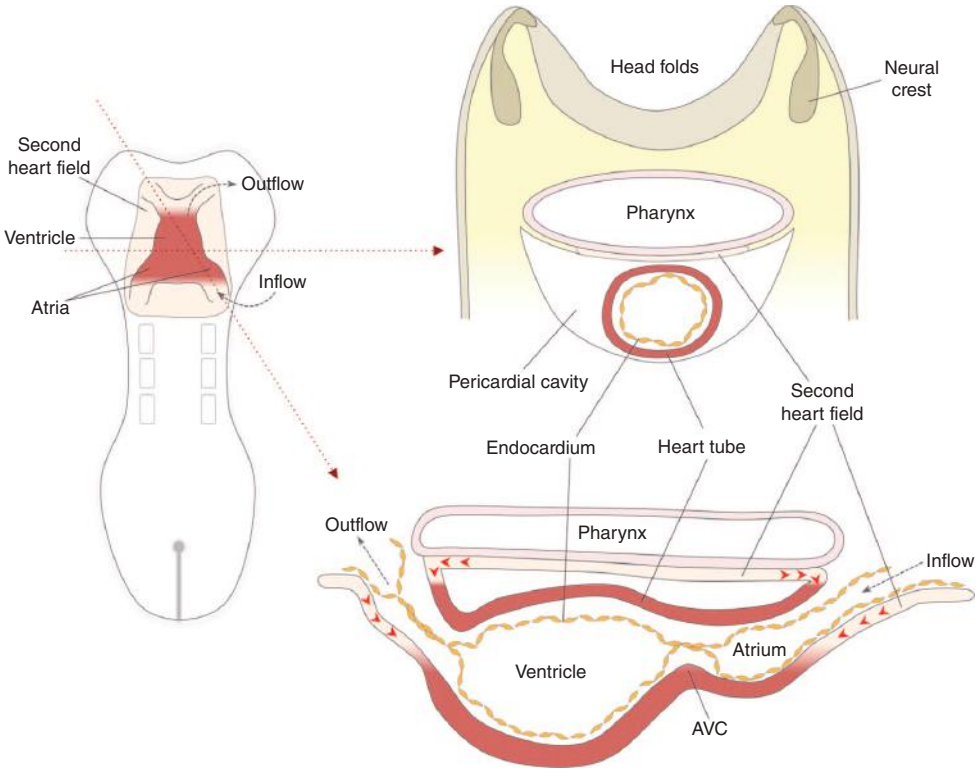

FIGURE 8–3. Formation of the primitive cardiac tube. The scheme on the left shows the shape and position of the cardiac tube in a 21-day human embryo (E8.5 in the mouse). Primordial ventricular and atrial chambers connecting with the arterial (outflow) and venous (inflow) poles of the linear heart tubes respectively are shown. The *red arrows* indicate the sectioning planes that are represented on the right. The two initial paired tubes have fused at the midline, forming a single tube that has become independent from the pharyngeal region, except at its inflow and outflow poles. The second heart field now forms a continuous sheet dorsal to the cardiac tube and in continuity with the outflow and inflow tracts. New cardiac precursors are continuously added to the forming heart tube from the second heart field though the arterial and venous poles (red arrowheads). As these precursors leave the pharyngeal region and incorporate to the heart tube, they progressively differentiate and start contracting. Chamber formation has started by increased local proliferation and working myocardium appears with higher contractile capacity and faster conductive ability than the primary myocardium. AVC, atrioventricular canal. Modified with permission from Fuster V and Kalil Roberto: *Cardiovascular Medicine, the Impact of Diseases. Atheneu*; 2016.

heart tube in these species thus involves the fusion of two primordial tubes initially formed bilaterally (see Fig. 8–2).[5,18] In the mouse, as mentioned above, the first cardiac cell differentiation takes place in a cardiac crescent already continuous across the midline and therefore does not require the same morphogenetic movements that take place in the human and avian embryos.[2] By the first signs of contractility, the cardiac tube is only a fold of the splanchnic mesodermal layer that is not closed dorsally (see Fig. 8–2). Endocardial cells beneath this fold, however, soon form a sealed tube enclosed between the endoderm and the primary cardiac tube and are therefore capable of circulating its contents as soon as contractions appear. With the closure of its dorsal aspect, the primary tube derived from the FHF is finished around 18 days in the human embryo (E8.0 in the mouse) (see Fig. 8–3).[5] At this stage, it is composed by the primordium of the left ventricle, attached by short outflow and inflow tracts to the SHF progenitors located in the pharyngeal mesoderm (see Fig. 8–3).

MOLECULAR PATHWAYS INVOLVED IN CARDIAC PROGENITOR CELL SPECIFICATION

Signals

As mentioned above, the acquisition of cardiac fate takes place during gastrulation and is governed by the sequential exposure of initially naive epiblast precursors to a number of signals.[6,19,20] This sequence of signals in turn starts the hierarchical activation of epigenetic modifications and a set of transcription factors whose activity leads to the activation of cardiac differentiation genes.[6,20,21] Interestingly, human and mouse embryonic stem cells can be driven to cardiac differentiation on sequential exposure to the same molecular pathways involved in cardiac specification during embryonic development.[22-24] The first signals that the prospective cardiac cells are exposed to are the transforming growth factor (TGF) family molecule Nodal and canonical Wnt (cWnt). Both Nodal and cWnt signals show a graded distribution across the epiblast and high Nodal/cWnt signal at the posteroproximal region of the epiblast results in the promotion of gastrulation and cardiac mesodermal fate.[8,21] In particular, several cWnt ligands are specifically expressed in the PS and drive its formation. Prospective cardiac mesoderm thus experiences transient cWnt signaling as it moves through the PS.

As cardiac mesoderm is produced, it migrates from the primitive streak toward the anterior pole of the embryo in close proximity to the extraembryonic tissues (see Fig. 8–1), which produce high levels of bone morphogenetic protein 4 (BMP-4), and in contact with endoderm, which produces BMP-2.[6] As the nascent mesoderm is subdivided in the somatic and splanchnic layers (see Fig. 8–1), BMP signaling stimulates the rapid differentiation of the splanchnopleural rim close to the extraembryonic region toward the cardiomyocyte lineage, forming the cardiac crescent in the mouse and the bilateral cardiac primordial in the human and chick. At the cardiac crescent stage, Sonic hedgehog (Shh) produced from the endoderm and notochord also contribute to promote the cardiac fate. cWnt signaling, initially required for early cardiac mesoderm specification, later needs to be repressed during cardiomyocyte differentiation.[8,21] Once the cardiac crescent is in place, cWnt ligands are produced by the neuroectoderm and the somatic mesoderm and restrict cardiac differentiation. After the primitive heart tube has formed (see Fig. 8–3), the SHF serves both as a reservoir of undifferentiated cardiac progenitors and as the source of new differentiating cardiomyocytes that will be added to both poles of the heart tube.[19] At this stage, equilibrium between cardiac progenitor proliferation and differentiation toward cardiomyocyte is essential for proper heart formation (Fig. 8–4). Excessive differentiation may lead to premature exhaustion of cardiac SHF progenitors, whereas insufficient cardiomyocyte production could lead to accumulation of precursors, both resulting in failure to extend the primary heart tube. In the SHF, cWnt signaling, Shh, and fibroblast growth factor (FGF) promote cardiac progenitor proliferation and restrict differentiation (see Fig. 8–4). In contrast, noncanonical Wnt signaling (ncWnt) signaling, involved in cytoskeletal reorganization, is activated and required for cardiomyocyte differentiation along with BMP. As cells are added to the cardiac tube, high BMP signaling and ncWnt signaling promote

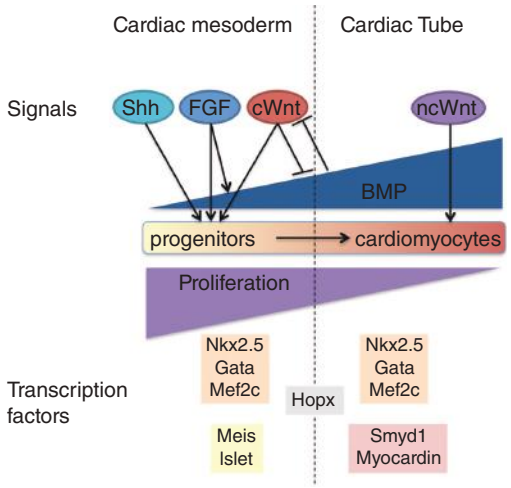

FIGURE 8–4. Molecular regulation of cardiomyocyte differentiation from cardiac mesoderm. A pool of cardiac mesodermal precursors is established after gastrulation (*left side of the diagram*). These progenitors are primed for differentiation to cardiomyocytes but maintained on hold and proliferating by sonic hedgehog (Shh), fibroblast growth factor (FGF), and canonical Wnt (cWnt) signals. Low bone morphogenetic protein (BMP) is also required to maintain and promote the cardiac fate of these precursors. Precursors are recruited to differentiate (right side of the diagram) in the cardiac crescent by high BMP signaling and noncanonical Wnt (ncWnt) signaling. Once the primary tube is established, precursors in the second heart field and cardiomyocytes in the heart tube coexist. Precursors continue proliferating and are progressively added to the forming cardiac tube. As they incorporate to the tube, they transit from high FGF/Shh and cWnt expression to high BMP and ncWnt exposure, which promotes their differentiation and proliferation stop. cWnt and BMP signals counteract each other in part through the activity of Hpx, a transcription factor critical for the transition from the precursor state to differentiation. The transcription factors generally required for cardiac mesoderm establishment and differentiation to the cardiomyocyte lineage are represented. Nkx2.5, Gata, and Mef2c are required in both the precursor and differentiating stages, whereas transcription factors such as Islet or Meis are specific of the precursor stage and Smyd1 and Myocardin of the differentiation phase.

cardiomyocyte differentiation and slower proliferation.[21,25] The graded regulation of BMP signaling is essential in this context, given that BMP activity is also required in the SHF and is promoted here by FGF. This fine regulation is achieved by cWnt signaling in the SHF, which represses BMP, so that only moderate levels of BMP unable to drive differentiation are allowed in the SHF. In addition, Notch signaling is essential to counteract cWnt function in the SHF, thereby limiting the expansion of progenitors in the SHF and promoting their differentiation[26] (see Fig. 8–4). Thus, the equilibrium between BMPs/ncWnt/Notch signals, which promote cardiomyocyte differentiation, and FGF/cWnt/Shh signals, which repress cardiomyocyte differentiation and promote cardiac progenitor proliferation, is essential for proper cardiac tube formation (see Fig. 8–4). As cardiogenesis proceeds, the specific tissues producing BMP and cWnt signaling and the specific ligands involved change accordingly with the new tissue disposition, but the effects on cardiomyocyte differentiation are maintained throughout cardiogenesis.

Transcription Factors

The transcription factors (TFs) activated during the transit between the pluripotent epiblast cell and the differentiated fetal cardiomyocyte are in charge of regulating multiple genes across the genome to achieve the correct transcriptional profile typical of each stage.[20,27] The first sign of cardiac progenitor specification is the activation of the TF eomesodermin in the posterior PS.[28] Eomesodermin in turn activates Mesp TFs, which are not cardiac-specific and are not expressed in the cardiac crescent but are essential for the activation of the cardiac specification program.[29] Shortly after gastrulation, as cells become allocated to the cardiac crescent, a set of TFs essential for cardiac specification appear (see Fig. 8–4). Some of these, such as Gata4, Nkx2.5, Mef2c, and Islet1, are expressed by most cardiac precursors in the FHF and SHF,[30-32] whereas others are restricted to regions contributing to specific structures of the heart. Tbx5 is restricted to the FHF or posterior tube, including the left ventricle and the atria[33]; Hand2, to all anterior SHF derivatives, including the right ventricle and outflow tract[34]; and Tbx1 to the part of the anterior SHF that contributes to the outflow tract. Tbx18 defines the posteriormost subpopulation of the SHF, contributing only to cava veins myocardium.[19,35,36] In addition, *Pitx2c* is expressed in the left side of the SHF, as part of its general role in left-right patterning of lateral plate derivatives in the embryo.[37]

The specific combination of TFs expressed by each region of the cardiac fields is important for the proper generation and differentiation of the different parts of the heart tube, although the exact cellular functions of these factors is not completely understood. Interestingly, some of the factors, such as Tbx1, Meis1, Meis2, and Islet1, are expressed at the precursor stage but are downregulated as they incorporate to the heart tube and differentiate, being therefore specifically associated with cardiac precursor properties. Others, such as Nkx2.5, Mef2c, and Gata4, are expressed in both the precursors and all the differentiated cardiac cardiomyocyte lineages. Nkx2.5 in cooperation with Mef2c provides functions important both for the maintenance of the undifferentiated precursor population and for their differentiation to cardiomyocytes.[38] *Nkx2.5* loss of function leads to cardiac tube truncation caused by the premature differentiation of the whole cardiac precursor pool toward the cardiomyocyte fate. However, proper cardiomyocyte differentiation is also blocked in the heart tube of *Nxk2.5* mutant mice.[39]

These results indicate that Nkx2.5 activity in the SHF needs to be selectively modulated to avoid the premature activation of its functions in cardiomyocyte differentiation. In part, this is achieved by the counteraction of Nkx2.5 by Islet1, which competes for binding to the same DNA regulatory sequences in key cardiac differentiation enhancers.[40] In cardiac precursors, in which both are expressed, the Nkx2.5 functions related to cardiomyocyte differentiation are repressed by Islet1, whereas Islet1 downregulation, as precursors incorporate to the heart tube, releases Nkx2.5 activity in promoting differentiation. In addition, Meis TFs have been identified as important hubs of the transcriptional control of cardiomyogenesis in embryonic stem cell differentiation models[23,24] During cardiac tube formation, *Meis* TFs is expressed in undifferentiated cardiac precursors at the SHF and in early differentiating cardiomyocytes of the outflow tract (OFT), where it competes with Nkx2.5 for DNA-binding sites in cardiac target genes.[41]

As mentioned above, the balance between activators and repressors of cardiomyocyte differentiation is controlled by the signals that control cardiac precursor maintenance versus those that promote cardiac differentiation (see Fig. 8–4). The TF Hopx is an essential regulator of the transition of cardiac precursors to differentiation as they are added to the heart tube[42] Hopx cooperates with BMP signaling to block cWnt signaling and promote cardiomyocyte differentiation. Expression of the TFs Smyd1[43] and Myocd[44] is then activated and required for the cardiomyocyte differentiation program (see Fig. 8–4).

Another important patterning system relevant in cardiac development is the Hox-TALE homeodomain transcription network. Hox TFs play essential and highly conserved roles in embryo patterning, being responsible for the specification of identities along the main embryonic axis. This role is conserved in metazoans and affects only the conserved bilaterians structures lying posterior to the midbrain-hindbrain junction. Cardiac mesoderm lies mostly anterior to this junction. However, areas of the SHF fated to the pulmonary branch of the outflow tract

and some areas of the atria have been shown to derive from precursors of the most anteriorly expressed Hox genes.[45] In addition, Hox genes regulate cardiac neural crest specification, which is required for proper arterial trunk septation. Furthermore, mutations affecting the TALE homeodomain TFs of the Pbx and Meis families, essential cofactors of Hox proteins, produce outflow tract defects in mouse and humans.[46-49]

Chromatin Regulation

Chromatin structure regulation is essential for filtering the accessibility of TFs to their regulated genes as well as to stably maintain the active or inactive states of the regulated genes. Chromatin structure is regulated at various levels by several large epigenetic regulatory complexes.[50] Key aspects of epigenetic regulation are histone modifications and nucleosome positioning, which determine the packaging degree of chromatin and the accessibility of regulatory elements in the DNA. Histone acetylation status represents a major level of chromatin regulation affecting transcriptional activation events. Whereas histone acetylation by the general transcriptional coactivators p300 and CBP promotes transcriptional activation, histone deacetylation by histone deacetylases (HDACs) leads to gene repression. During cardiac development p300/CBP association with cardiac TFs is essential to direct histone acetylation to cardiac genes, while various associations of HDACs with individual factors, such as Hopx and Smyd1, or within large chromatin remodeling complexes, such as NurD, result in the essential repression of noncardiac genes.[51,52] In addition, the SWI/SNF (or BAF) remodeling complex also interacts with the cardiac TFs to reposition nucleosomes at gene regulatory elements and promote their activation.[53,54] Overexpression of the chromatin remodeling factor Baf60c together with the TFs Gata4 and Tbx5 has been shown sufficient to drive cardiomyocyte specification and differentiation in the mouse embryo.[53] A further level of chromatin packaging regulation is that exerted by the polycomb complexes PRC1 and PRC2, which promote histone methylation repressive marks and heritable silent chromatin states. Elimination of the catalytic subunit of PRC2 -Ezh2- again results in defective cardiogenesis caused by the undesired expression of genes that should be repressed during cardiac differentiation.[55]

As it is the case for TFs, the basis for the specificity of large chromatin remodeling complexes activity during cardiogenesis remains largely unknown. An interesting observation in this context is the fact that the chromatin regulation complexes NurD, SWI/SNF, PRC1, and PRC2 incorporate tissue-specific variants for some of their components. Interestingly, the tissue-specific PRC1 factor Mel18 regulates a cardiac mesoderm differentiation program, showing that lineage-specific variants of chromatin complexes are essential in early specification of mesodermal precursors.[56] Additional specificity would be further gained through the interactions of the chromatin regulation complexes with the cardiac-specific TFs; however, the complexity of the interactions between TFs and chromatin regulation and how these are translated in the precise regulation of cardiac differentiation will require further investigation.

CARDIAC MORPHOGENESIS

Between 3.5 and 7 weeks of development (E8.5 to E11.5 in the mouse), the heart undergoes extensive growth and morphological modifications, leading to the formation of a partially septated four-chambered heart equipped with a set of primitive valves (Figs. 8–5 and 8–6). Subsequent outflow tract subdivision and complete interventricular and atrial septation lead, around the 12th week (~E16.5 in the mouse), to a heart bearing the gross morphological organization of a definitive adult heart (Fig. 8–7).[5]

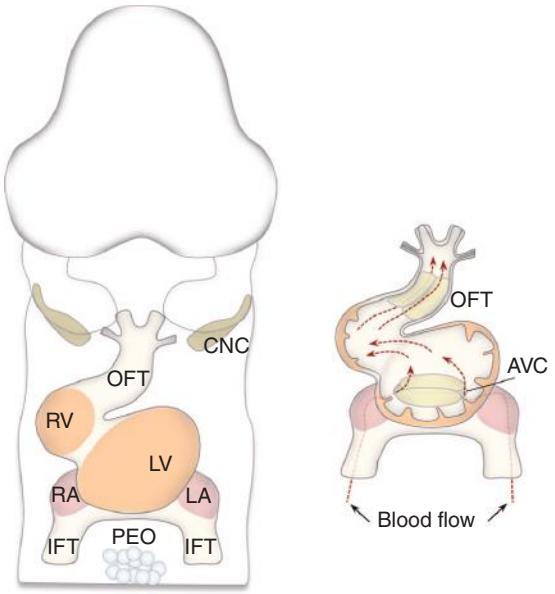

FIGURE 8–5. Heart looping, cushion formation, and trabeculation. The scheme on the left represents a frontal view of the cephalic region of a 24-day human embryo (~E9.5 in the mouse). The cardiac tube has increased in length mostly caused by the incorporation of new segments from the second heart field and has looped rightward, allowing the right and left ventricle aligning along the left–right axis. At the same time, the ventricles protrude, becoming positioned ventrally with respect to the atria. Internally (*right scheme*) the ventricular chambers have started to develop incipient trabeculae, and cushions have formed at the atrioventricular canal and the outflow tract, serving as functional valves at this stage. The aortic sac has established connections with the second branchial arch. *Red dotted arrows* indicate the trajectories of blood flow through the cardiac tube. AVC, atrioventricular canal; CNC, cardiac neural crest; IFT, inflow tract; LA, left atrium; LV, left ventricle; OFT, outflow tract; PEO, proepicardial organ; RA, right atrium; RV, right ventricle. Modified with permission from Fuster V and Kalil Roberto: *Cardiovascular Medicine*, the Impact of Diseases. Atheneu; 2016.

Chamber Formation

The first stage of this process is chamber formation. The initial heart tube is composed of a primary myocardium that shows poor contractility and low conduction velocity. Interiorly, the primitive cardiac tube is lined by the endocardium, which is separated from the myocardium by a mass of cardiac jelly (see Fig. 8–2). The cardiac jelly is a gelatinous acellular material secreted by cardiomyocytes and formed mainly by a network of collagen fibrils. Chamber formation is first detected by the ballooning of the primary heart tube. The first discernable chamber is the left ventricle, initially located in a central posterior position of the linear tube, between the outflow and inflow tracts (see Fig. 8–3). This stage is transitory as, immediately after, heart looping takes place. During heart looping, the cardiac tube undergoes a dextral bending that positions the right ventricle primordium in its definitive position with respect to left ventricle (see Fig. 8–5). Heart looping is concomitant with continuous chamber growth and progressive addition of the right ventricle primordium at the anterior pole and the atria primordia at the posterior pole. Genetic lineage tracing, expression analyses, and four-dimensional proliferation maps have shown that chamber formation takes place by the hyperproliferation of discrete regions leading to local ballooning of the linear tube walls.[15,57] The forming chamber myocardium progressively acquires fast conduction and high contractility and increasingly differentiated sarcomeric structures. In contrast, the nonchamber myocardium retains immature features and, after extensive repositioning of the chambers, contributes to form the base of the ventricles and the atrioventricular (AV) valves as well as the outflow and inflow tracts (see Fig. 8–5). In addition, cardiac jelly is excluded

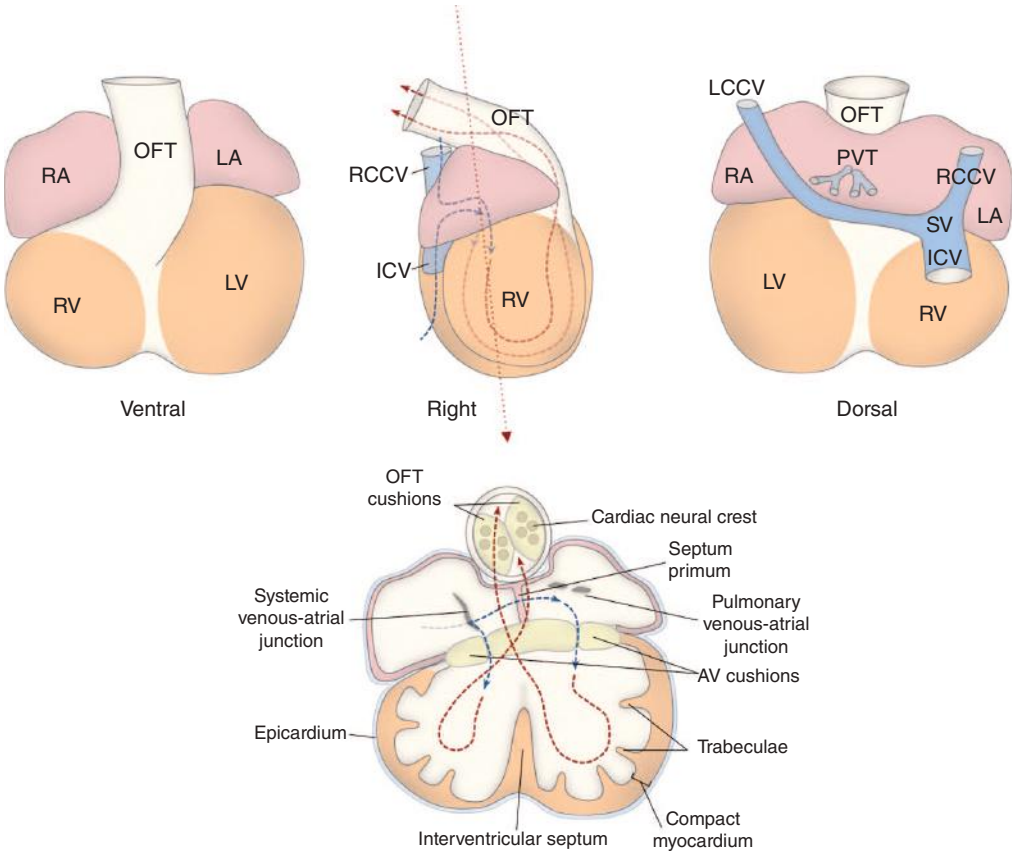

FIGURE 8–6. The four-chambered heart. Schemes above show ventral, lateral and dorsal views of the 6-week human heart (~E11.5 in the mouse). The scheme below shows a frontal section along the plane indicated in the lateral view above. At this stage, the four chambers have become aligned in their definitive position. The four chambers have enlarged considerably and ventricles have continued their rotation until being placed caudally to the atria, so that the four chambers are aligned in their definitive positions. Compact and trabecular myocardium are now well established. The atrioventricular canal has split in two, as the atria become separated by the septum primum, so that each ventricle receives blood from its corresponding atrium. The systemic blood now returns only to the right atrium and the left atrium shows the pulmonary vein connections (two at this stage). Despite this defined compartmentalization of the cardiac elements, the left and right heart sides are still communicated. The inflowing blood (*blue arrows*) enters the left atrium through the ostium primum, a communication between the atria, and then passes into ventricles, which remain in communication, and it is pumped as outflowing blood (*red arrows*) through the common outflow tract. The outflow tract is still a common arterial trunk and internally contains helicoid cushions that prefigure the future septation. The cardiac neural crest progenitors colonize the cushions and will be essential for outflow tract septation. Epicardium derived from the covers ventricular and atrial chambers. AV, atrioventricular; ICV, inferior cava vein; IFT, inflow tract; LA, left atrium; LCCV, left common cardinal vein; LV, left ventricle; OFT, outflow tract; PEO, proepicardial organ; PVT, pulmonary veins tree; RA, right atrium; RCCV, right common cardinal vein; RV, right ventricle. Modified with permission from Fuster V and Kalil Roberto: *Cardiovascular Medicine, the Impact of Diseases*. Atheneu; 2016.

from the forming chambers but remains at the outflow and AV canal areas, where it exerts a resistance to blood flow that prevents blood reflux until proper valves are formed (see Fig. 8–3).[5]

The delimitation of the chamber-forming regions within the cardiac tube is governed by a transcriptional network with a predominant role for the T-box family factors Tbx2, 3, and 20.[6,35] The first signs of chamber initiation are an increase in local proliferation and activation of the atrial natriuretic peptide–coding gene *Nppa*.[20] Tbx20 is expressed throughout the heart tube and is essential for chamber formation. In contrast, Tbx2 and Tbx3 are both expressed specifically in the nonchamber myocardium and are needed to maintain the primitive myocardial character and repress chamber formation in these regions. Tbx2/3 are transcriptional repressors themselves and may also recruit HDACs to promote repressed chromatin states in chamber-promoting genes. Sustained high levels of BMP signaling are responsible for the maintenance of Tbx2/3 expression in the nonchamber myocardium, whereas Tbx20 repression of BMP signaling excludes Tbx2/3 from the chamber-forming regions, which allows the development of the working myocardium in these areas.[6] A number of additional TFs such as those of the Iroquois family or Hand1 show chamber-specific expression and are likely involved in the establishment of chamber-specific differentiation and morphogenetic programs. The mechanisms by which the chamber-forming regions become specified in discrete regions of the initial cardiac tube, however, remain unknown.

Trabeculation

An essential process during chamber formation is trabeculation.[58] Trabeculae are internal protrusions arising from the myocardial wall of the chambers and are specially abundant and complex in ventricles. From E9.5 until E14.5 in the mouse, a subset of the compact layer cardiomyocytes migrates to form ridges that evolve into myocardial projections toward the chamber lumen, giving rise to the trabeculated myocardium. Trabeculae increase cardiac output and permit myocardium oxygenation prior to coronary vascularization without increasing heart size. Several signaling pathways, such as BMP, Notch, and Neuregulin are involved in trabecule development through reciprocal signaling between endocardium and myocardium.[21,59] Trabeculae are transient structures that get incorporated to the compact myocardium as fetal development progresses. Alterations in developmental signals

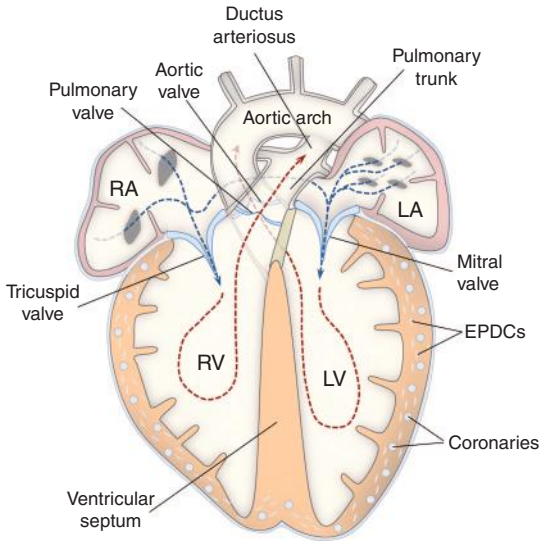

FIGURE 8–7. The mature fetal heart. The scheme shows represents the fetal human heart from 12 weeks onward, when the fetal heart shows an anatomy very similar to the adult heart (from ~E16 in the mouse). The right atrium is now fed by the superior and inferior cava veins and the left atrium is fed by the four definitive pulmonary veins. The cushions have differentiated into the main heart valves, which are aligned in a single plane and encased in the annulus fibrosus, a structure also derived from the cushions and with a strong contribution from epicardial-derived cells (EPDCs). The inflow and outflow connections have evolved to their definitive disposition, with complete septation of the outflow common arterial trunk in the aortic and pulmonary trunks. Arterial end venous blood, however, still mixes through the atrial septa communication and the ductus arteriosus, which connects the pulmonary and arterial trunks. These communications will only disappear after birth on breathing of the newborn. In the ventricles, the compact layer has increased notably, trabeculae start compacting, and differentiation of the coronary plexus and colonization by EPDCs and their derivatives is advanced. *Blue arrows* show inflow blood, and *red arrows* show outflow blood. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Modified with permission from Fuster V and Kalil Roberto: *Cardiovascular Medicine*, the Impact of Diseases. Atheneu; 2016.

such as those in the Notch pathway lead to congenital ventricular noncompaction, a condition that may evolve to malignant arrhythmias and heart failure.[60,61]

Septation

Establishment of the definitive cardiac anatomy requires division of the left and right aspects of the heart by septation.[62] Septation defects are the most common congenital heart malformations in humans.[63,64] Atrial and ventricular septation involves proliferation and ingrowth of the interchamber myocardium for the separation of left and right heart sides (see Fig. 8–6). Ventricular septation is a relatively early and simple process, which is completed around the 7th week (E14.5 in the mouse). Ventricular septation is produced by the ingrowth of the myocardial wall at the interface between the right and left ventricles and is finished by the adjoining of the myocardial septum with the mesenchymal areas continuous with the valve-forming areas, forming the so-called membranous part of the septum (see Fig. 8–7).

In contrast, atrial septation involves the sequential ingrowth of two septa that fuse with a mesenchymal protrusion from the dorsal mesocardium and with the AV valve region to separate left and right atrial sides (see Fig. 8–6).[65] During atrial septation, communications between the left and right atria maintain left-right circulation. Formation of the septum primum involves the ingrowth of the myocardium to fuse with a dorsal mesocardial protrusion that invades the atria promoted by a Tbx5-Shh pathway.[66] As the septum primum forms, it leaves a basal region incompletely septated, constituting the foramen primum. Once the foramen primum is closed, a foramen secundum appears above in the septum primum around the 6th week. A septum secundum develops around the 7th week from dorsal to ventral on the right side of the septum primum and containing a third foramen, the foramen ovale. The noncoincident position of the two foramen and the higher flexibility of the septum primum results in a valvular function that allows right to left atrial circulation but not the reverse. This communication closes only after birth with the fusion of the two atrial septa in a single septum.[65]

Venous Pole Development

Atrial septation is coordinated with the remodeling of the venous pole of the heart. Before cardiac septation, the paired embryonic veins (common cardinal, vitelline, and umbilical) drain to the sinus venosus, which opens independently into left and right atria. Before the septum primum develops (between the 4th and 5th week) the sinus venosus has partially incorporated to the atria and has undergone remodeling to drain exclusively into the right atrium, so that left and right common cardinal veins are connected to the right atrium (see Fig. 8–6). Later, the original left sinus is recruited to function as the coronary sinus and the former left cardinal vein constitutes the main coronary vein. In parallel, the left atrium develops the connections to the pulmonary veins. Initially, there is only one connection to a twice-bifurcated tree of pulmonary veins (see Fig. 8–6). The progressive incorporation of the roots of the pulmonary vein tree to the left atrium leads to the direct connection of four definitive independent veins (originally branches of the primary single vein) (see Fig. 8–7). In the definitive heart, all systemic return circulation drains through the superior and inferior cava veins in to the right atrium (see Fig. 8–7).

Valvulogenesis

Valves are essential to ensure unidirectional blood flow and form at the AV regions, connecting atria with ventricles, and at the base of the pulmonary and aortic trunks of the outflow tract (see Fig. 8–7). Valves derive from the original cardiac cushions, which are in turn derivatives of the original cardiac jelly, which gets shaped by morphogenetic processes and becomes populated by mesenchymal cells from various sources.[67] The OFT cushions are the primordium of the semilunar (aortic and pulmonary) valves, whereas the AV cushions are the primordium of the membranous part of the ventricular septum and the mitral and tricuspid valves with their associated connective tissues (see Fig. 8–6). Endocardial cushions are essential during early heart development, because they functionally divide aortic and pulmonary blood flows and chambers when valves and septa are not yet present.[6] In both, the AV canal and the outflow tract, cushions are populated by EMT of endocardial cells, in a process that is stimulated by BMP and TGFβ signaling from the myocardium and Notch signaling in the endocardium.[67] These signals are reinforced by a feedback loop with Tbx2, which also induces the expression of genes required for cardiac jelly deposition and endocardial cell migration.[68,69] The initial endothelial EMT (endocardial) phase requires Nuclear factor of activated T cells (Nfat)-mediated Vascular endothelial growth factor (Vegf) repression in the myocardium. During a second phase, strong myocardial-produced Vegf stops endoEMT. Finally, calcineurin/Nfatc activity in the endocardium blocks Vegf and promotes valve differentiation.[70]

The extent to which EMT contributes to AV and OFT cushions is different; while most of the AV cushion mesenchyme derives from endoEMT, most of the OFT cushion derives from pharyngeal mesoderm. Specific additional mesenchymal populations produced by EMT at later stages contribute to each of these two regions. In the region of the AV canal, a third mesenchymal population derives, again by EMT, from the epicardium (see below).

Before septation, additional intercalated cushions appear in the outflow tract and lateral cushions in the AV canal.[62] During septation, the cushions split between the left and right sides to contribute to the three leaflets of semilunar and tricuspid valves and two of the mitral valve. During maturation, valves elongate and are thinned by proliferation of mesenchymal cells at the growing edge and apoptosis at the base of the cushion (see Fig. 8–7).[62]

Arterial Pole and Aortic Arch Development

When the heart tube forms, the endocardial layer is already connected to a preexisting plexus of endothelial cells generated by vasculogenesis in the yolk sac and aortic regions. As soon as the heart tube starts to contract, flow across the nascent plexus drives angiogenic remodeling and maturation of the embryonic circulatory system. Aortic arch development involves the sequential development and then involution of five aortic arch artery pairs, corresponding to branchial arches I to IV and VI; the V pair is vestigial (Fig. 8–8). The arterial pole is initially connected to the dorsal aortas by the first pair of pharyngeal arteries. As development progresses, the aortic sac is connected to progressively more posterior arches by new arterial pairs and gets disconnected from the anterior ones, which degenerate.[19] Although the first two pharyngeal artery pairs and the right VI artery regress and do not produce any definitive contribution, after extensive remodeling, the left VI artery forms the pulmonary trunk and pulmonary arteries, the III pair forms the common carotid arteries, and the IV makes small contributions to the right subclavian artery and aortic arch (see Fig. 8–8). The pulmonary trunk remains attached to the aorta through the ductus arteriosus, which closes and involutes at birth, when the left and right side blood pressures change upon the onset of pulmonary function. Recent evidence supports a role for hemodynamic shear stress–responsive genes in the regulation of angiogenesis and aortic arch remodeling in the early embryo.

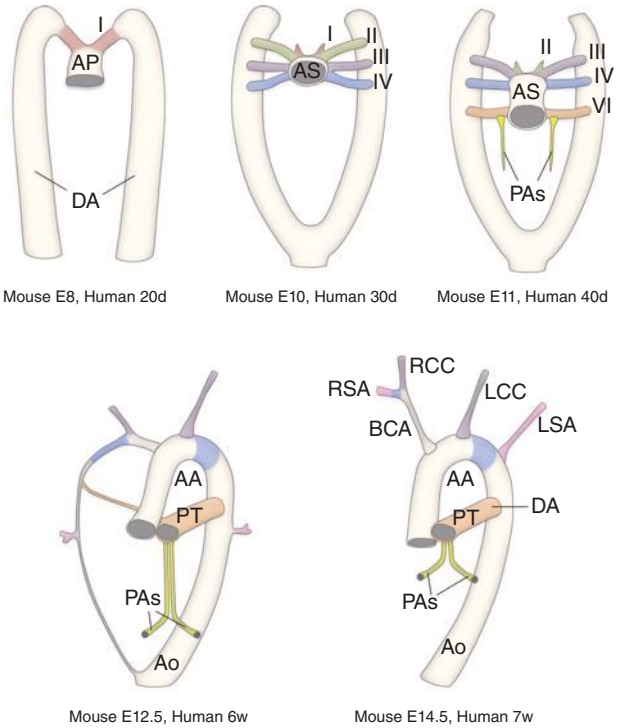

FIGURE 8–8. Aortic arch development. In the 20-day human embryo (E8 in the mouse), the first pair of pharyngeal arteries (I) have formed and connect the arterial pole of the heart with the paired dorsal aortas (DA). In the 30-day human embryo (~E10 in the mouse), the first arch artery has degenerated, and II, III, and IV are present and connected to the dorsal aortas and to the arterial pole of the heart (not shown) through the aortic sac (AS). The paired dorsal aortas have fused caudally to the heart. By 40 days (~E11 in the mouse), the arteries of the first two arches have regressed and those of arches III to VI are present. The pulmonary arteries (PAs) start sprouting out from the VI arch arteries, which are the precursors of the pulmonary trunk. In the 6-week embryo (E12.5 in the mouse), the right VI pharyngeal artery and the right dorsal aorta are in regression, and the left VI pharyngeal artery degenerate. The left VI pharyngeal arch artery splits from the aortic trunk to form the pulmonary trunk, which remains connected as the ductus arteriosus to the left dorsal aorta. By 7 weeks, the definitive aortic arch has formed with derivatives of the pharyngeal artery III forming the left and right common carotids (LCC and RCC) and those of the IV pharyngeal arteries making small contributions to the right subclavian artery and aortic arch. The left and right subclavian arteries (LSA and RSA) have remodeled their position to become connected, respectively, to the aortic arch and the brachycephalic artery (BCA; derived from the aortic sac). The right dorsal aorta has degenerated at this stage.

The arterial pole receives an essential third mesenchymal population deriving from the neural crest, which delaminates by EMT from the neural tube (see Fig. 8–4). This neural crest–derived population is essential for the septation of the initial outflow tract into the aortic and pulmonary trunks (see Fig. 8–5).[71] However, it represents a transient population that undergoes cell death and does not contribute significantly to the definitive valve structures. Outflow tract septation takes place in a distal-to-proximal progression and in a helicoid trajectory, resulting in the typical definitive arrangement of the pulmonary and aortic arteries (see Fig. 8–6).[72,73] Alterations in the SHF precursors of the arterial pole or in the neural crest migration will result in outflow tract abnormalities and/or affection of the proper morphogenesis of semilunar valves. Most aortic arch congenital anomalies are as a result of abnormal retention or absence of the mosaic vascular segments that contribute to its formation.

CARDIAC DIFFERENTIATION

THE CARDIAC LINEAGES, ORIGINS, AND DIVERSIFICATION

The adult heart is composed of cardiomyocytes and several other cell types, including vascular and perivascular cells, interstitial cells, and epicardial and endocardial cells (see Fig. 8–7). Most of these cellular components derive from the initial cardiac fields (see Fig. 8–1), which produce the cardiomyocyte and endocardial cells. However, later contributions from external sources such as the proepicardium and the cardiac neural crest (see Fig. 8–4) are produced after the generation of the primitive heart tube.[74] Although they are initially similar, cardiomyocytes soon specialize into different types of working myocardium (ventricular, atrial) or conduction system cardiomyocytes, each of which expresses a specific combination of TFs that drive their specific differentiation and functional program.[21] The molecular aspects of the differentiation programs are orchestrated by networks of specific microRNAs and long noncoding RNAs (lncRNAs) that confer robustness to the molecular pathway choices.[75] The extent to which these specializations are determined by lineage or by external cues remains largely undescribed,[74] although hierarchical cardiac cell lineages have been proposed. Interestingly, the SHF progenitors have been shown to behave as pluripotent cardiac progenitors, which are able to generate cardiomyocytes, endocardial cells, smooth muscle cells, and other cardiac mesenchymal cells.[74]

THE EPICARDIUM

The largest contribution to the non-cardiomyocyte populations of the heart derives from the epicardium.[76] The epicardium is the outermost layer of the heart. It derives from an extracardiac structure; the proepicardium, a mass of cells from the coelomic epithelium that forms soon after cardiac looping at the dorsal pericardial wall, caudal to

the venous pole of the heart, and protruding to the pericardial cavity (see Fig. 8–5).[77] The first epicardial cells adhere at the AV canal level and later on extend to cover all the myocardial surface (see Fig. 8–6) with a characteristic "cobblestone" appearance. The epicardium then undergoes a process of EMT and gives rise to epicardial-derived cells (EPDCs) that invade the myocardial layer and differentiate into several cell types within the developing heart (see Fig. 8–7). EPDCs contribute to interstitial mesenchyme, and endothelial[78] and smooth muscle cells of the coronary vasculature.[79,80] Contribution of the epicardium to the cardiomyocyte population has also been reported,[81-83] although this remains a controversial issue.[84,85]

Epicardial cells are heterogeneous and are composed of at least two proepicardial compartments containing progenitors with diverse differentiation potential. Although epicardial cells positive for the TFs Wt1 and Tbx18 give rise to mesenchymal and smooth muscle cells, those expressing the TF Scleraxis and the secreted factor Sema3a produce coronary endothelium and endocardium.[81-83,86] Whether these contributions derive from prespecified endothelial cells present in the proepicardium or from multipotent epicardial precursors is still debated. In addition to this heterogeneity established at the proepicardial organ, the epicardium receives a third population originated from hematopoietic precursors.[87] Starting at E12.5 in the mouse, cells expressing the hematopoietic marker CD45 and originated from the Vav1$^+$ lineage, which includes embryonic hematopoietic precursors, are observed in the subepicardium and epicardium. In the first days after birth, these cells form epicardial clusters enclosed in extracellular matrix.[87]

Following myocardial infarction in the adult mouse heart, both the Wt1 and the CD45+ epicardial cell populations undergo proliferative and invasive activation, giving rise to new vascular and perivascular cells in the myocardium.[87,88] Interestingly, stimulation with thymosin β4 activates epicardial cells to recapitulate an embryonic program and give rise to new vasculature and cardiomyocytes following a myocardial infarction.[89] These results support the notion that EPDCs in the adult heart can be a source of multipotent progenitor cells. However, treatment with thymosin β4 in a therapeutically relevant temporal window—after the myocardial infarction—does not reprogram epicardial cells into cardiomyocytes.[90]

CARDIOMYOCYTE PROLIFERATION AND TERMINAL DIFFERENTIATION

The final adult myocardium structure and functionality is acquired through a series of maturational steps. Quantitative three-dimensional reconstruction of cell proliferation patterns has allowed defining two strategies for the generation of cardiomyocytes.[5,57,91-93] Before primitive tube formation, the cardiogenic mesodermal area proliferates very actively. As the FHF cells are added to the tube, they undergo drastic reduction in cell proliferation, in coincidence with their differentiation to cardiomyocytes. For the next few days, the SHF cells, still residing in the pharyngeal area, continue proliferating at a high rate to provide new cardiac precursors that will be added sequentially to both the arterial and venous poles of the heart tube. As SHF cells are added to the heart tube and begin to differentiate into cardiomyocytes, they stop proliferating. The second strategy for cardiomyocyte proliferation starts around early looping stage and consists in the reactivation of cardiomyocyte cell cycle in the chamber-forming regions of the heart tube. As a result of the sequential incorporation of precursors to the heart, the reactivation of cell proliferation in the prospective chambers overlaps in time with the proliferation of cardiac progenitors still in the SHF (see Fig. 8–3).[15]

Trabeculae begin to appear soon after chamber formation starts, and they present specific features that distinguish them from the chamber compact myocardium (see Fig. 8–5).[21] In part, trabeculae maintain characteristics of the primary myocardium, showing poor sarcomeric maturation and low proliferation. However, they express high levels of connexins and are thought to function as the embryonic chamber conduction system and to generate the bundle branches and the peripheral ventricular conduction system of the adult myocardium. Although arising from a common precursor, trabeculated and compact myocardium show obvious structural and proliferative differences and gives rise to the ventricular conduction system and the working myocardium, respectively. During development, trabecular cardiomyocytes drastically reduce proliferation and display poorly developed sarcomeric structures, compared to working myocardium of the compact layer.[5] After septation of the chambers, the mammalian myocardium continues its maturational program, and even at birth, the sarcomeric structure is not fully organized and only within early postnatal life the ventricular muscle acquires its characteristic rod-like shape and mature contractile apparatus.[94] During the first days after birth, cardiomyocytes still proliferate and are mononucleated, but soon they stop cycling and switch from hyperplasia (growth by increasing the number of cells) to hypertrophy (growth by increase in size of existing cells), coinciding with polyploidization by binucleation (mouse) or endoreplication (human).[95] This process is accompanied by definitive maturation of the sarcomeric structure and complete silencing of the fetal cardiogenic program.

Therefore, during development, new cardiomyocytes are first generated by migration and differentiation of cardiac precursors and afterward by proliferation of cardiomyocytes. Hence, there is a correlation between morphogenesis and heart proliferation that is further supported by the observation of differential gene expression regulating chamber formation.[20] Notably, progenitor recruitment and differentiation is used only during a limited embryonic period and generates a limited number of cardiomyocytes, while the major part of the cardiomyocyte pool generation is achieved by symmetric division.[96]

An important component of the regulation of cardiomyocyte proliferation and differentiation is contributed by surrounding and supporting tissues. During heart growth, both epicardium and endocardium produce important signals for cardiomyocyte proliferation and maturation, including neuregulin from the endocardium and FGF from both endocardium and epicardium.[97] Moreover, signals from cardiac interstitial mesenchymal cells, mostly EPDCs, are essential to control the transit of cardiomyocytes from proliferation to cell cycle arrest and hypertrophy.[98]

Recent evidence points to some ability of the mammalian heart to generate new cardiomyocytes, which has fueled interest in exploring the extent to which new cardiomyocytes may arise from symmetric division or from differentiation of a reservoir of cardiac precursor cells. A modest but clear proliferation ability has been described in adult human cardiomyocytes using carbon dating.[99] According to this study, at the end of a human life, close to 50% of the cardiomyocytes derive from cardiomyocytes born postnatally, although most of these are born in the first years of life. The methodology used in this study does not allow determining whether the new cardiomyocytes arise from preexisting cardiomyocytes or from a pool of stem/precursor cells. DNA labeling and genetic fate map analyses in the mouse similarly suggest a modest but constant rate of cardiomyocyte proliferation in the adult heart—but no significant cardiomyocyte turnover in homeostatic conditions.[100,101] Interestingly, cardiomyocyte proliferation seems to increase after myocardial infarction around the borders of the infarcted area.[100,101] Recently, a specific population of proliferating cardiomyocytes has been identified in the adult mouse heart.[102] These proliferating cardiomyocytes are small and mononucleated and show activation of the hypoxia-inducible factor (Hif) pathway. Their frequency in the

adult heart matches the previously described rates of adult mouse and human cardiomyocyte proliferation.

In contrast to the limited cardiomyocyte renewal ability in adult mammals,[99,101] heart homeostasis is effective throughout life in zebrafish via cardiomyocyte hyperplasia and epicardial signals.[103] Furthermore, both fishes[104,105] and neonatal mammals[106] show a potent regenerative response against various types of cardiac injury. In both zebrafish[107,108] and neonatal mammals,[106] the regenerative response is mediated by symmetric cardiomyocyte proliferation, suggesting that stimulation of the limited endogenous cardiomyocyte proliferation ability might be an interesting strategy in cardiac regeneration.

THE CONDUCTION SYSTEM

Efficient blood pumping depends on the rhythmic sequential contraction of the heart. Specialized myocytes of the cardiac conduction system are essential to coordinate sequential contraction of cardiac atria and ventricles. In the adult heart, contraction propagates from the atria, where it is initiated, to the ventricles, which contract from the apex to the base. Importantly, contraction of the ventricles is delayed, in order to permit their complete filling with blood and the entry of the blood in the outflow vessels before a new atrial contraction occurs. A network of specialized cardiomyocytes, collectively referred to as conduction system, initiates and propagates contraction throughout the myocardium.[109] The sinoatrial node (SAN), at the insertion of the superior cava vein in the right atrium works, as the apical pacemaker, initiating each contraction. A second essential component of the conduction system is the AV node (AVN), which lies at the base of the ventricles, and is in charge of the AV delay and further transmission of the electric impulse through the His bundle, the bundle branches, and the Purkinje fibers (derivatives of the trabecular myocardium) for coordinated and synchronous ventricular contraction.

From the earliest stages of heart tube formation, pacemaker activity is localized to the inflow pole of the heart. Strong expression of the hyperpolarization-activated cation-selective nucleotide-gated channel 4 is associated with the pacemaker activity during all development, and somewhat lower expression is typical of the rest of the conduction system.[110] The SAN cardiomyocytes originate from Nkx2.5-negative and Tbx18-positive progenitor cells localized posterior to the primitive heart tube.[111,112] The TF Tbx3 is an essential component of SAN formation, because it activates the pacemaker gene program at the expense of the working myocardium gene program,[113] while both Tbx2 and 3 are cooperate in AVN specification.[114] The crucial role of Tbx3 is further confirmed by its ability to reprogram working cardiomyocytes into a pacemaker fate.[113,115]

Lineage tracing experiments have shown that the conduction system receives contribution from both the first and second heart fields, and, for example, the SAN is a hybrid derived from both fields,[116] indicating that the origin is less important than the adoption of a cardiac conduction differentiation pathway. In fact, "in situ" relatively late recruitment from ventricular myocytes has been found as a mechanism for the specification of the ventricular cardiac conduction system with the exception of AVN and His bundle.[116,117] Contrary to working cardiomyocytes, conduction system cardiomyocytes display poorly organized sarcomeres and few mitochondria. During development, cardiomyocytes of the conduction system show very early signs of divergence from working myocardium, displaying a specific gene expression program and lower contractility and proliferation than the working myocardium. Purkinje fibers derive from trabeculae that derive from cardiomyocytes of the compact myocardium, which, as they are recruited, stop proliferation and differentiate as conductive cardiomyocytes. Although the mechanisms by which cardiomyocytes are recruited to the conduction differentiation program are unknown, a network of TFs has been shown essential to confer specific properties to the ventricular conductive cardiomyocytes, including Irx3, Id2, Nkx2.5, and Tbx5.[1-18,119] Trabecule formation depends on differential Notch signaling in the inner ventricular wall, as discussed above.

THE CORONARY VASCULATURE

The early developing myocardium is a thin layer of a few cell diameter thickness and is relatively close to the endocardium, where oxygenated blood flows. During development, however, the ventricular walls develop a thick compact layer that sustain the heart contractile work load. Cardiomyocytes use fundamentally aerobic energy production, and therefore a strong demand of oxygen that cannot be supplied from the endocardium is needed as soon as compact myocardium increases its thickness. The coronary vasculature is in charge of supplying the required oxygen flow to the working myocardium and, accordingly, it starts to be functional around midgestation, when ventricular wall thickness increases.

The mature coronary plexus is fed from two main coronaries connected to the base of the aorta and feeds a network of fine and dense capillaries intimately intermingled with cardiomyocytes. The coronary venous system collects the blood from these capillaries and drains it to the right ventricle through the coronary sinus.[120] The earliest coronary endothelial precursors appear sometime after the heart has been covered by the epicardial epithelium. Initially, they are evident around the AV junctions and in 2 to 3 days, they extend to cover both ventricles and atria.[77,120] The coronary precursors initially form an immature plexus that is not connected to the circulation and has not invaded the myocardium, being placed at the subepicardial space, where the future coronary veins will form. In a second step, an endothelial plexus appears at deeper positions within the compact myocardium, where future arteries will form. Formation of this primary plexus requires an FGF-Shh signaling relay in cardiomyocytes.[121] Connection of the coronary plexus to the aorta takes place through the ingrowth of capillaries that develop independently at early stages in the OFT, before the chamber coronary precursors appear. These capillaries initially form multiple small connections than later coalesce into the two ostia that connect the base of the aorta with the stem of the coronary arteries. This process is regulated by the Hif-Vegf axis.[122] Once the blood flow is established, the coronary plexus remodels into a stereotyped arrangement of hierarchical vessels. Maturation of the vascular plexus involves also the recruitment of perivascular smooth muscle and mesenchymal cells, largely derived from the epicardium.[77] The origin of the coronary endothelium is very likely from multiple sources. In the avian model, proepicardium transplantation has shown epicardial contribution to coronary vascular endothelium.[78,123] In mammals, genetic lineage tracing revealed no endothelial potential of the epicardial Tbx18 lineage[82] and only a minor contribution from the Wt1 epicardial lineage.[81] However, the proepicardial Scleraxis and Sema3a lineages do contribute to coronary endothelium and other epicardial derivatives.[83] One important source of primary coronary endothelium is the sinus venosus endothelium. Angiogenesis from the sinus venosus promoted by angiopoietin-1 promotes the generation of the primary subepicardial plexus.[124] Clonal and lineage tracing analyses have shown that at least part of the coronary artery endothelium derives from the sinus venosus and that this contribution might take place by recruitment of the initial subepicardial endothelial plexus to deeper layers of the myocardium.[124,125] Additionally, the ventricular endocardium has been shown to contribute endothelium to coronary arteries by budding of the sac-like digitations of the endocardium between trabeculae.[126] More recently it has been described that the endocardium functions as

a source for de novo created coronary vessels in the inner half of the ventricular chamber during neonatal trabecular compaction.[127] Therefore, most likely, the coronary endothelium arises from various origins, although the extent to which each of these sources contributes and the exact sequence of the contributions remains incompletely understood.

The coronary vasculature also contains a lymphatic system that develops relative late from two different sources of lymphatic endothelial cells; those derived from venous sprouting and those derived from hemogenic endothelium.[128,129]

Finally, coronary development is also important for the innervation pattern of the heart. Sympathetic innervation of the heart originates in the stellate ganglia, which have a neural crest origin. Arterial vascular smooth muscle cells mediate proximal sympathetic axon extension by secretion of artemin,[130,131] neurotrophin 3,[132,133] and endothelins.[134] Once they arrive at the heart, the sympathetic fibers are directed by the coronary veins and arteries through the production of nerve growth factor by the vascular smooth muscle cells associated to them.[135]

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CHAPTER 9

GENETIC BASIS OF CARDIOVASCULAR DISEASE

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INTRODUCTION

Individual living organisms are unique because genes harbor a unique code of DNA. Human genetics explores variation, evolution, and deviation from "normal" genetic structure and function. Medical genetics studies genetic diseases caused by changes involving entire chromosomes to single nucleotides. Its application in medicine encompasses all disciplines as genetic diseases may affect multiple organs, often times in the same individual.

Genetic cardiovascular diseases include chromosomal disorders (ie, congenital heart defects, congenital heart disease), single-gene or monogenic diseases (ie, cardiomyopathies, heritable aortic diseases), and multigenic/multifactorial disorders (ie, ischemic heart disease, atherosclerosis, diabetes). They may occur in the context of syndromes or exclusively involve the heart (ie, cardiomyopathies) or vessels (ie, heritable aortopathies). The burden of monogenetic cardiovascular diseases is difficult to establish. Some cardiac genetic diseases are common (ie, hypertrophic cardiomyopathy, some congenital heart disease), whereas others are extremely rare (pure restrictive cardiomyopathy, arterial tortuosity syndrome); however, most of them demonstrate clinical and genetic heterogeneity. This chapter provides a short recall of the classification of genetic diseases[1] and the clinical and molecular genetic workup in cardiovascular diseases. It revises the clinical and molecular genetics of major and emerging groups of genetic cardiovascular diseases, highlighting disease-specific genetic needs.

CLASSIFICATION OF GENETIC DISEASES

CHROMOSOMAL DISORDERS

Chromosomal disorders occur when there is a gain or loss of chromosomes, or parts of them. Several chromosomal abnormalities are associated with cardiovascular diseases, both syndromes with cardiovascular involvement and heart defects as unique phenotypes. The three major categories of chromosomal disorders are:

1. Those that involve the number of autosomes,[2] typically trisomy 21 or Down syndrome that commonly shows atrioventricular septal defects
2. Those that are caused by structural abnormalities of autosomes, typically translocations of large segments of chromosomes, as well as smaller insertions, deletions, or rearrangements such as in 22q11 deletion syndromes that are associated with different congenital heart diseases (CHDs)[3]
3. Those that involve the sex chromosomes, typically Turner syndrome in females that in the classic form carries a unique X chromosome (45,X).[4] In addition to the typical traits of the syndrome (short stature, webbed neck, and incomplete or absent development of secondary sex characteristics, leading to infertility), this syndrome often manifests with bicuspid aortic valve, aortic coarctation and aortic aneurysm.

SINGLE-GENE DISEASES: MENDELIAN INHERITANCE

Single-gene diseases are caused by mutations affecting a specific gene. The vast majority of genetic CV diseases are inherited according to mendelian rules.[1] Based on inheritance pattern, they can be divided into autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL) diseases (Fig. 9–1).

AD diseases can be transmitted by either parent and clinically manifest in heterozygous patients, who receive a mutated allele from one parent and a normal allele from the other. The graphic view of families in pedigrees typically shows that the disease passes from one generation to the next (vertical transmission). The majority of genetic cardiovascular diseases are AD, such as:

- Familial cardiomyopathies (CMPs) (up to 90% of cases)[5]
- Marfan syndrome caused by mutations in the *FBN1* gene, and other heritable aortic aneurysmal diseases[6]
- AD familial hypercholesterolemia[7]
- Carney syndrome with atrial myxoma[8]
- Primary pulmonary hypertension caused by defects of the *BMPR2* gene[9]
- Atrial fibrillation caused by mutations in the *NPPA* gene[10]

In AR diseases, the effect of the mutated allele only manifests in homozygous (or compound heterozygous) mutation carriers. The pedigrees may show affected siblings with healthy parents (horizontal transmission). Known AR cardiovascular diseases are far less common than AD diseases, but they include rare CMPs such as atrial dilated cardiomyopathy (ADCM) caused by homozygous mutations in the

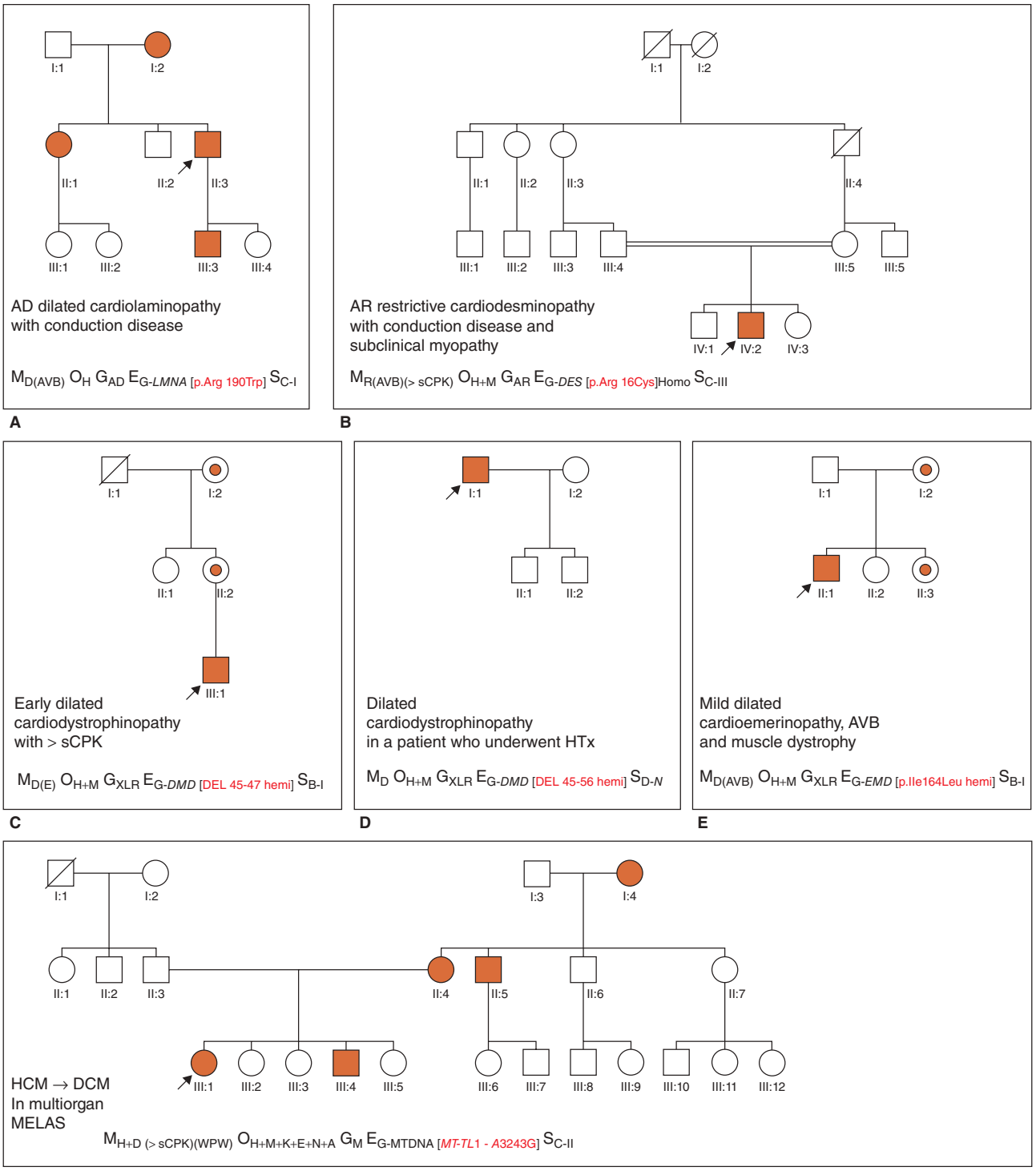


FIGURE 9–1. **A** to **E,** Mendelian inheritance, and **F,** maternal or matrilineal transmission. **A.** Autosomal dominant (AD) dilated cardiomyopathy (DCM) with conduction disease; in this family all mutation carriers are affected. The p.(Arg190Trp) is a fully penetrant mutation and one of the most common mutations in *LMNA* in patients with DCM. **B.** Autosomal recessive (AR) restrictive desminopathy with conduction disease and increased serum creatine phosphokinase (sCPK) and subclinical myopathy (IV:2) in one of the three children of consanguineous parents (III:4 and III:5), who are both healthy heterozygous carriers; the healthy brother and sister (IV:1 and IV:3) are carriers of the heterozygous mutation. **C.** X-linked recessive (XLR) early dilated cardiodystrophinopathy with mild increased levels of sCPK. The proband (III:1) inherited the DMD deletion from the mother, who is a healthy carrier as is the maternal grandmother. **D.** The proband (I:1) manifested severe DCM phenotype at the age of 35 years. The DMD deletion could be either de novo or inherited. The mother could not be tested. Both sons are obligate noncarriers. **E.** The proband (II:1) demonstrates early dilated cardioemerinopathy with conduction disease and clinically overt, mild, and slowly progressing muscle dystrophy. The mother (I:2) and sister (II:3) are healthy carriers of the mutation; occasional mild increased in sCPK has been recorded in the sister. **F.** The proband (III:1) is a young lady demonstrating short stature (151 cm), with a long history of muscle "weakness," renal failure, hypertrophic cardiomyopathy (HCM, which evolved through DCM), hearing loss, cryptogenic stroke, and optic neuritis. A similar phenotype is present in her brother (III:4). The mother (II:7) displays hearing loss, diabetes, and a mild hypertrophic and dilated heart. The maternal uncle (II:5) demonstrates diabetes, hearing loss, HCM complicated by CAD, and MI. The maternal grandmother (I:4) is alive with hearing loss, diabetes, and mild left ventricular hypertrophy. The heteroplasmic mutated mtDNA was present in higher percentage (> 70%) in both siblings (III:1 and III:4), and very low percentage, nearly absent in the three healthy siblings III:2, III:3, III:5. .

NPPA gene,[11] sick sinus syndrome caused by mutations in the *SCN5A* gene,[12,13] and aneurysmal diseases such as arterial tortuosity syndrome (ATS).[14] In addition, several lysosomal storage diseases involving heart and vessels are AR diseases.[15] Increased risk of AR diseases occurs in the setting of consanguinity or in the context of geographically isolate populations.

In XL diseases, the mutated gene is located on the X chromosome. Because most XL diseases demonstrate recessive inheritance (XLR), heterozygous females are phenotypically healthy. XLR diseases are characterized by absence of male-to-male transmission, obligate carrier status in daughters of affected males, and 50% probability that healthy heterozygous female carriers will pass the mutated gene to each child. In addition, male children who inherit the mutated gene will be hemizygotes and affected, and daughters who receive the mutated gene will be healthy carriers. Examples of XLR cardiovascular diseases include dilated cardiomyopathies (DCMs) caused by defects of dystrophin or emerin.[16,17] Female carriers may occasionally show mild and late-onset phenotypes as a result of nonrandom X inactivation [ie, mothers or sisters of patients with dystrophin defects may show increased serum creatine phosphokinase (CPK) levels or late-onset, slowly progressing DCM]. X-linked dominant diseases are extremely rare, and very few examples of cardiovascular genetic diseases may show this pattern (ie, rare aneurysmal diseases caused by mutations in *filamin A* [MIM# 300049[18]] and rare CMPs[19]).

NONMENDELIAN INHERITANCE: DISEASES CAUSED BY MITOCHONDRIAL DNA MUTATIONS

Human mitochondria contain several molecules of circular polycistronic mitochondrial DNA (mtDNA). Mitochondria are present in oocytes and nearly absent in spermatozoa; thus, only mothers can pass on diseases associated with defects in mitochondrial genes (maternal or matrilineal inheritance) (see Fig. 9–1F).[20] Therefore, affected mothers will pass on the mutation to all daughters and sons, and affected fathers cannot pass on the mtDNA mutation. The disease clinically manifests when the amount of mutated mtDNA is higher than threshold levels. Typical cardiovascular phenotypes include hypertrophic (symmetric), nonobstructive CMPs that evolve through end-stage dilation and dysfunction similar to DCM; a "family marker" of mtDNA-related diseases is the phenotype heterogeneity in family members who carry the mutation.[19,21,22] Depending on the amount of mutated DNA, some family members may have CMP; others may manifest with different combinations of encephalomyopathy, hearing loss, ocular defects, diabetes or renal failure (Fig. 9–2).

NONMENDELIAN INHERITANCE: ANTICIPATION AND TRIPLET EXPANSION

Triplet expansions within or near specific genes may show a distinct pattern of nonmendelian inheritance termed *anticipation*.[1] Specifically, the age of onset decreases and the severity increases with the increase of instability (number of triplet repeats). When a "full expansion" mutation is achieved, the inheritance follows mendelian rules. There are no known genetic "isolated" cardiovascular diseases demonstrating clinical anticipation through triplet expansion mechanisms.

Triplet expansion is well recognized in diseases such as Steinert muscle dystrophy[23] or Friedreich's ataxia that typically involve heart.[24] Steinert muscle dystrophy[23] is caused by mutant CTG expansion in the nontranslating region of the dystrophia myotonica protein kinase gene and typically shows conduction disease and possible DCM. In Friedreich's ataxia caused by GAA trinucleotide repeat expansion in intron 1 of the *Frataxin* gene, the heart shows early hypertrophic cardiomyopathy (HCM) that evolves through replacement fibrosis leading to recession of hypertrophy, reduction of global myocardial function,

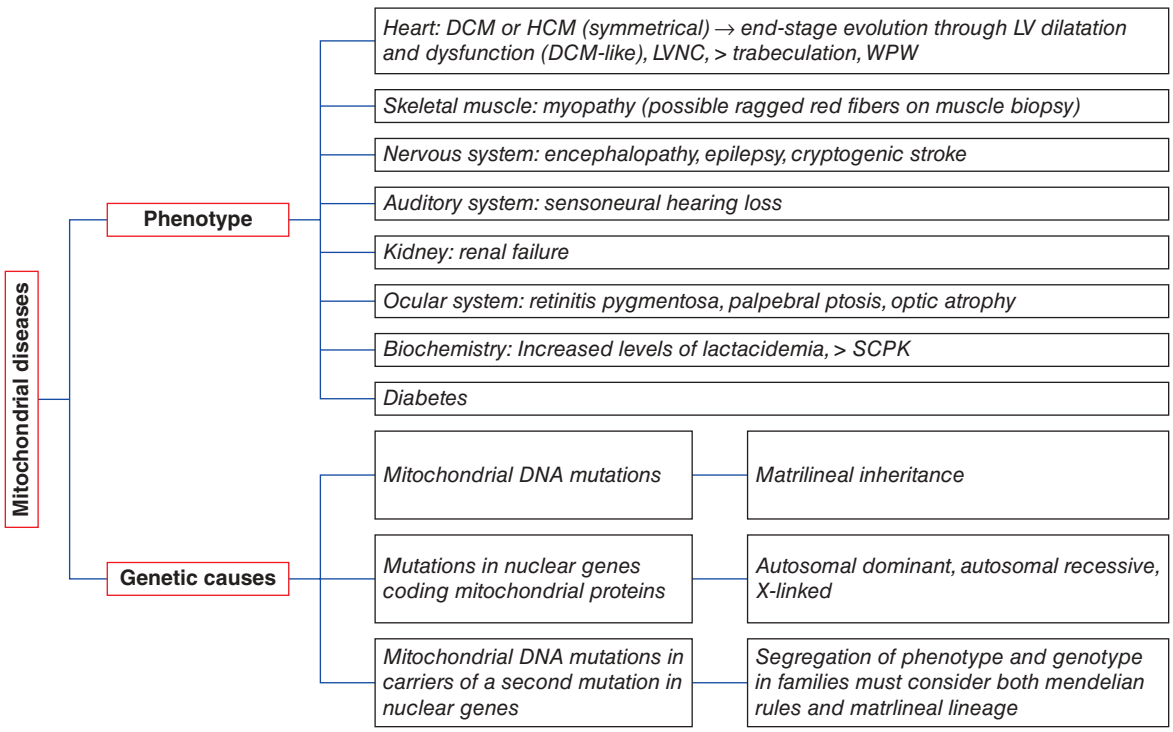


FIGURE 9–2. The figure shows the heterogeneous phenotypes associated with mutations in mitochondrial DNA. DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVNC, left ventricular noncompaction; SPCK, serum creatine phosphokinase; WPW, Wolff-Parkinson-White (syndrome).

and electrical instability.[24] Friedreich's hearts also show myocarditis and intramyocyte iron storage; the former finding should be differentiated from infectious myocarditis.[25] Both are examples of diseases in which cardiac involvement can be the major determinant of clinical outcome.

DISEASES ASSOCIATED WITH IMPRINTED GENE MUTATIONS

Imprinting involves a sex-specific modification of imprinted genes, resulting in nonequal expression and depending on the sex of the parent of origin.[1] Maternally imprinted genes are expressed when inherited from the father (Prader-Willi syndrome), and paternally imprinted genes are expressed when inherited from the mother (Angelman syndrome). Although there are no examples of imprinted genetic cardiovascular diseases, imprinted genes (ie, ZAC, zinc finger protein associated with apoptosis and cell cycle arrest, and HYMAI, imprinted in hydatidiform mole) have been identified as potential candidates in rare forms of diabetes (ie, transient neonatal diabetes). In addition, patients with Prader-Willi syndrome may show CHD,[26] develop DCM,[27] demonstrate increased cardiac mass when treated with growth hormone,[28] require heart rate monitoring during functional analysis evaluating self-injurious behaviors,[29] or deserve cardiac evaluation, including two-dimensional (2D) speckle tracking echocardiography to evaluate the frequent systolic dysfunction in children.[30]

MULTIFACTORIAL INHERITANCE

Multifactorial diseases are the most common human diseases: the contribution of small effects of multiple genes adds to the effects of exogenous, environmental factors, which result in disease manifestation.[1] Common multifactorial diseases include ischemic heart disease (IHD), hypertension, and diabetes.[31-33] Large genome-wide association studies (GWAS) have identified many gene loci, each of them potentially contributing to multiple disease states, including coronary atherosclerosis, IHD, classical risk factors, thrombosis, inflammation in coronary artery disease (CAD), and angioneogenesis (IHD; see Chap. 36). The risk of disease and recurrence is far from predictable, but in any case is much lower than in monogenic diseases and proportional to the number of affected relatives, closeness of familial relationship and, in the case of myocardial infarction (MI), when the affected relative is of the less commonly affected gender (female). Typically, sons of mothers who develop premature MI are at higher risk than sons of fathers who experience premature MI.

WORKUP IN GENETIC CARDIOVASCULAR DISEASES

CLINICAL GENETICS

Clinical genetic workup includes comprehensive phenotype evaluation/deep phenotyping in probands, genetic counseling, pedigree generation, and clinical family screening. When present, certain phenotypic traits, including learning disabilities, facilitate family studies and genetic evaluation. However, most genetic cardiovascular diseases only affect the heart or large vessels and, unless they cause symptoms, their presence can be undetected. Typical examples of such include CMPs,[34] familial aneurysmal diseases,[35] small myxomas in Carney complex,[36] early pulmonary hypertension, or asymptomatic CHD.

In probands, physical examination includes evaluation of anthropometric features, skin, eyes, hair, musculoskeletal traits, and central nervous system abnormalities, among others.[37] Cardiologic assessment also includes electrocardiography (ECG) and 2D echocardiography. A 24-hour Holter monitor may add information about nonperceived arrhythmias. Cardiac magnetic resonance or computed tomography (CT) can further contribute to phenotype characterization.[38] For syndromic genetic diseases involving the cardiovascular system, family screening is facilitated by common traits that may be seen in particular diseases, such as craniofacial, musculoskeletal, and ocular traits in patients with Marfan, Loeys-Dietz, or Ehlers-Danlos syndromes; myopathy or learning disabilities in Danon syndrome; muscle involvement in Duchenne, Becker, or Emery Dreifuss muscular dystrophy; and pigmented lesions of the skin or tumors in Carney complex[36] or LEOPARD syndrome.[39]

Clinical family screening is an extremely important tool for diagnosing familial disease. Current knowledge on heritable CMPs or nonsyndromic aortopathies strongly supports the strategy of investigating relatives regardless of genetic testing.[38] Baseline screening is noninvasive and includes physical examination, ECG and 2D echocardiography; further investigation can be performed if needed. Depending on the disease, relatives may have abnormalities in ECG and/or echocardiographic indices that predict the manifestation of the full phenotype. The collection of phenotype data in family members may contribute to the clinical diagnosis. Specifically, some traits of the disease can be present in early phases of the disease and lost in advanced phases; a representative example is the early short PR interval in the heart in Anderson Fabry disease (AFD) versus the late atrioventricular block in advanced Fabry CMPs.[40] Phenotype heterogeneity in affected family members can by itself be a marker of disease, with hearing loss, diabetes, renal failure, HCM, cryptogenic stroke, and ocular problems, differently manifested in the different family members with mtDNA-related diseases such as MELAS.[41]

GENETIC TESTING

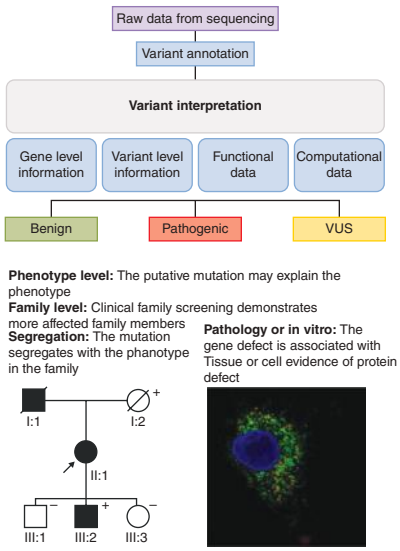
Depending on the disease, chromosomal analysis or sequencing-based genetic testing is performed in probands first and subsequently in relatives.

Chromosomal analysis is done in cells able to divide in culture: amniocytes, fibroblasts from skin biopsies, stimulated T cells, and bone marrow cells. A conventional prenatal test (amniocentesis or villocentesis) is going to be replaced in the near future by noninvasive prenatal testing (NIPT) using cell-free fetal DNA. Although NIPT currently has very high sensitivity and specificity for diseases such as Down syndrome and slightly lower sensitivity for Edwards and Patau syndromes, it is not 100% accurate and should not be used as a final diagnosis for positive cases.[42]

Gene analysis (test) is usually done using DNA isolated from blood samples. DNA can now be easily obtained from saliva, especially in children. In the past, each candidate gene was analyzed using Sanger-based automated sequencing, which was costly and time consuming. Today, genetic tests are routinely performed using next-generation sequencing (NGS) of multiple genes; Sanger sequencing is used for confirmation of the mutation identified by NGS and for cascade genetic testing in relatives.[43] Prenatal diagnosis can be performed on a regular basis, in particular for malignant diseases that are fully predicted by genetic testing. Noninvasive prenatal diagnosis for diseases such as dystrophinopathies seems to be accurate and reliable but requires further validation.[44]

Genetic testing identifies gene variants/mutations. Pathogenic mutations are single-base substitutions in coding, splicing-relevant and regulatory regions of disease genes, or microrearrangements such as microdeletions, microinsertions, combined microinsertions and microdeletions ("indels"), and macrodeletions. Single-base mutations can be characterized as missense (the majority) or nonsense, or they may affect canonic splice sites. In human genetic diseases, single-base substitutions are far more common than other types of gene defects. However, prevalence of the types of gene defects varies in different disease genes: that is, up to 80% of genetic defects causing

Evidence		Levels of information		Levels of interpretation of genetic tests
Criteria	**Description**	**Classification group**	**Tools**	**Molecular and computational**
Pathogenicity: evidence		*1) Gene-level information*		
Null variants	Nonsense, frameshift, canonical splice site, initiation codon, single or multi-exon deletions.	Implication in the disease	OMIM (http://www.omim.org)	
Previously established as pathogenic	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.	Inheritance pattern	OMIM (http://www.omim.org)	
De novo	Proven or suspected both maternity and paternity*.	*2) Variant level information*		
In vivo or in vitro confirmation	Functional studies should be validated and reproducible to guarantee a robust confirmation	Type of variant (missense, nonsense, frameshift, canonical splice site, initiation codon, single or multi-exon deletion)	Annotation tools: Annovar (http://www.annovar.org) VEP (http://www.ensembl.org/vep) SNPEff (http://www.snpeff.com)	
Located in a mutational hot-spot or critical functional domain	ie, active site of an enzyme	Frequency of variant in large population studies	Exome Variant Server (http://www.evs.org) 1000Genomes (http://www.1000genomes.org)	
Absent from controls	Or extremely rare in databases such as Exome variant Server, 1000Genomes	Segregation studies	Cascade family screening	
Cosegregation	With disease in multiple affected family members	Conservation in species	NCBI conserved domain database Blosum62 Phylogen	
Benign: evidence		*3) Functional data OR literature evidences*		
Allele frequency >5% or major than expected for disorder	In databases such as Exome variant Server, 1000Genomes	Variant description in databases	ClinVar dbSNP PUBMED	
In vitro studies confirmation	Functional studies show no damaging effect on protein function	*4) Computational data*		
Lack of segregation	In affected family members	Prediction of protein structure	Polyphen2 SIFT Muatation Taster CONDEL PAPI Mutation Assessor	
Suspect of modifier variation	ie, a missense variant in presence of a truncating variant known to cause the disease	Prediction of splicing	GeneSplicer Human Splicing Finder NNSplice MaxEntScan	
VUS: evidence				
- *The above criteria are not met* - *The criteria for benign and pathogenic are contradictory*				



*changeling

FIGURE 9–3. The figure shows the complex pipeline that should be implemented for novel variants and for variants that have been reported as pathogenic but not confirmed.

dystrophin-related diseases are large deletions. The interpretation of the pathogenicity of gene defects is a multistep process that starts with identification of the defects and progresses with possible functional or pathologic studies and family segregation studies. A pipeline for interpretation of genetic variants is summarized in Fig. 9–3.[45] In genes such as *MYBPC3* or *BMPR2,* mutations predicting premature truncation of the protein are common, whereas up to 90% of mutations in MYH7 associated with HCM are single nucleotide missense mutations. Caution should be advised in assigning a pathogenic role to frameshift mutations just because they predict a truncated protein. Frameshift variants such as p.Ala897LysfsX4 in *DSC2* (http://www.arvcdatabase.info/) clearly demonstrate that not all frameshift mutations are pathogenic. A recent systematic analysis of titin (TTN) truncating variants in publicly available reference populations, including the Exome Aggregation Consortium, found that 1 in 500 individuals carries a truncation in TTN A-band; this suggests that the penetrance of these potentially harmful variants is still poorly understood and that some of these variants do not necessarily manifest as AD DCM.[46]

Interpretation of the results of genetic testing is based on (1) family segregation studies (affected members are mutation carriers and nonaffected members do not carry the putative mutations),[47] (2) pathologic analysis in samples of affected tissues, (3) effects of the mutation on protein expression in vivo (ie, cardiolaminopathies, cardiodystrophynopathies, Danon disease, AFD) or in in vitro systems (Fig. 9–4).

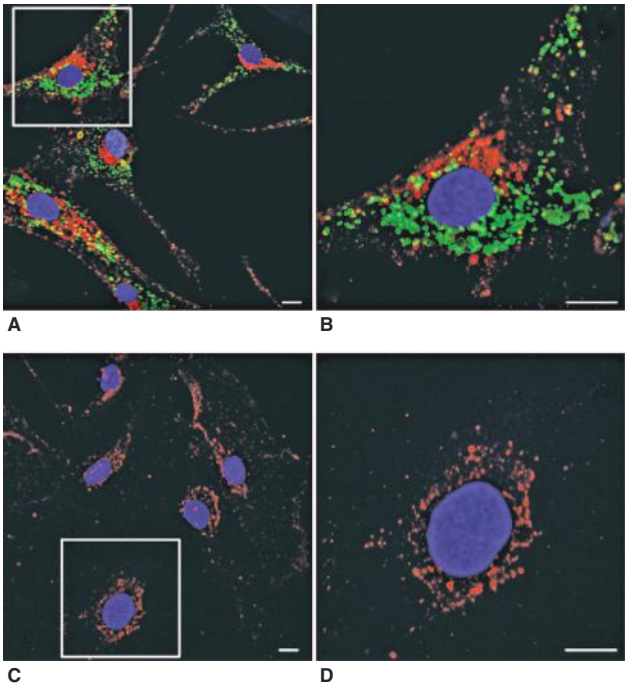


FIGURE 9–4. In vitro immunostaining with anti-Lamp2 (green) and lysosome marker (red) of cultured fibroblasts from a male patient diagnosed with Danon disease and carrier of a hemizygous mutation in *LAMP2* gene. **A** and **B**, control cells. **C** and **D**, cells from skin biopsy of the patient.

GENETIC CARDIOVASCULAR DISEASES

CARDIOMYOPATHIES: STILL PARADIGM OF IDIOPATHIC DISEASES?

Definition

CMPs are myocardial disorders characterized by structurally and functionally abnormal heart muscle and absence of other diseases sufficient to cause the observed myocardial abnormality.[48] The morphofunctional phenotypes DCM, HCM, restrictive cardiomyopathy (RCM), arrhythmogenic right, left and biventricular cardiomyopathy (ARC), and left ventricular noncompaction cardiomyopathy (LVNC) drive the currently used clinical classifications. In this context, LVNC is still a debated entity that is considered a genetic cardiomyopathy in the American Heart Association, or AHA, classification[49] and a nonclassified entity in the European Society of Cardiology (ESC) classification.[48]

More recently, the novel MOGE(S) nosology endorsed by WHF proposed a simple description of the trait in individuals with either normal left ventricular size and wall thickness and preserved systolic and diastolic function, or in combination with HCM, RCM or DCM or ARVC[19,34] (for classification of cardiomyopathies, see Chap. 57). Each subtype of cardiomyopathy is described in detail in Chaps. 58 to 60. Here, we aim to highlight concepts and workup shared by all CMPs.

CMPs have been considered for decades as being the paradigm of "*idiopathic myocardial diseases.*" This concept will be progressively abandoned as their causes are identified. Most of them in fact have a precise and detectable genetic cause. CMPs now represent one of the fields of development of precision cardiology, with progression from the past phenotype-based classification to an integrated morphofunctional, etiology-based classification.[19,34]

Epidemiology and Familial Cardiomyopathies

The burden of CMP is currently estimated on phenotype-based data: HCM in 1:500 young adults. A revised estimate of the combined prevalence of clinically expressed HCM and gene carriers (at risk for developing the disease phenotype), is placed at about 1 in 200.[50] The prevalence of nonamyloid primary RCM in adults is unknown; in children, the estimated annual incidence in the United States and Australia is 0.04 and 0.03 per 100,000 children, respectively,[51] and that of DCM and ARVC, 1:5000. These values are expected to increase as far as data on patients with early diagnoses in familial CMPs enter scientific literature. In fact, most CMPs have a genetic origin. Familial clustering and gene mutations segregating with the phenotype in families occur in more than 70% of HCM and nonamyloid RCM—and in 50% to 70% of DCM and ARVC.[38] The integration of clinical and genetic diagnoses will provide the basis for the molecular epidemiology of CMP. The overall burden of CMP will include patients with clinically overt, symptomatic CMP; asymptomatic patients diagnosed by family screening; and patients with "early" instrumental manifestation of CMP identified by family screening or incidentally in screening programs for sports, driving licensure, and professional suitability.[52] Several systematic family screening studies demonstrate familial aggregation.[53-66] For each subtype of CMP, several phenocopies exist, and they should be precisely recognized because each of them may be crucial for risk stratification or be associated with prevention strategies and/or disease-specific treatments.[37,38]

Cardiomyopathies as Clinically Heterogeneous, Chronic Diseases

CMPs are clinically heterogeneous diseases, and inheritance pattern (AD in up to 80% of cases; AR, XLR, and maternal in the remaining 20% of familial CMPs), age of onset, and disease progression and severity may differ even within affected members of the same family.[19,34,37,38] Beyond diagnostic criteria for each type of cardiomyopathy,[48] cardiac and extracardiac markers may recur in CMPs caused by defects of different genes. Imaging markers such as LVNC or increased trabeculation recur more commonly in rare CMPs affecting children such as Barth syndrome. Extracardiac traits can be associated with CMP. Such markers may be ocular (early cataract, retinopathy, palpebral ptosis), auditory (sensorineural hearing loss, dysmorphology of the ears), gastrointestinal (heritable autoinflammatory diseases), renal (spectrum from proteinuria to renal failure), central nervous system (transient ischemic attacks with white matter lesions to cryptogenic stroke), peripheral nervous system (acroparesthesias to overt peripheral neuropathies), skeletal muscle (mildly increased serum creatine phosphokinase to myopathies/dystrophies), hepatic (liver involvement in systemic storage diseases), musculoskeletal (syndactyly to severe skeletal deformations), or cutaneous/integumental (striae distensae to skin malignancies).[37] Cognitive impairment may also recur in patients with phenocopies of more typical cardiomyopathies, such as in Danon disease, lysosomal disorders, or mitochondrial diseases. When integrated in a *family cardiomyopathy "mindset,"* the pattern of inheritance and both cardiac and extracardiac traits may contribute to phenotype characterization, independently of the number of genes explored in NGS analysis, thus further contributing to the interpretation of genetic results. Each patient diagnosed with cardiomyopathy introduces a family case study.

Although the clinical onset may coincide with acute heart failure or cardiogenic shock, and past classification included syndromes such as left ventricular apical ballooning syndrome among CMPs,[48,49] typical CMPs are chronic disorders that require lifelong cardiovascular care. Once the diagnosis is consolidated, spontaneous restoration of normal left ventricular size and function in untreated patients does not occur. Current protocols with personalized optimal medical treatments may modify disease progression, extent of left ventricular remodeling, and risk and occurrence of arrhythmias, but cannot not cure affected hearts.

Genetic Heterogeneity

Heritable CMPs are a paradigmatic example of genetically heterogeneous diseases. More than 100 disease or candidate genes have been reported to date as associated with the different subtypes of CMP; several disease genes are not specifically associated with HCM or DCM or ARC but show genetic overlap.[67] Accordingly, mutations in genes coding sarcomeric proteins that typically cause HCM may also cause RCM or DCM; similarly, mutations causing DCM (ie, *LMNA*) may also cause ARC and vice versa. The complex heterogeneity of cardiomyopathies and related disease genes is shown in Fig. 9–5A and B.

The Future

Modern clinical workup in CMPs now includes deep phenotyping of the proband, clinical family screening, clinically oriented genetic testing when possible, or genetic screening of large panels of disease and candidate genes. The present challenge is accurate interpretation of the results of genetic testing, which includes both correct assignment of the causative role of the precise mutation to a disease and interpretation of mutations with possible modifier affects. Gene expression studies,[68] pathology studies of affected hearts testing the expression of a mutated protein,[69-71] computational tools, and bioinformatic pipelines contribute to the final interpretation of mutations as being pathologic and disease-causing; this means that, in the absence of the given mutations, the disease does not manifest.[45] However, no tool can substitute for segregation studies in families or pathologic demonstration of the effects of the mutation in the affected myocardium.[47] In vitro studies investigating gene expression, protein expression, and structural changes in mutated cells (induced pluripotent stem cell–derived cardiomyocytes) isolated from skin fibroblasts or peripheral mononuclear cells can provide a surrogate alternative to pathologic studies of affected myocardium. Future clustering of CMPs by phenotype, inheritance, and specific cause of disease can (1) generate data for precise clinical-genetic epidemiology and on the natural history of disease, and (2) highlight the need for development of therapies that can specifically target the cause.

HERITABLE ANEURYSMAL DISEASES

Heritable Thoracic Aortic Aneurysm and Dissection

Heritable thoracic aortic aneurysm and dissection (TAAD) includes more than 40 genetically different disorders (Table 9–1). Syndromic

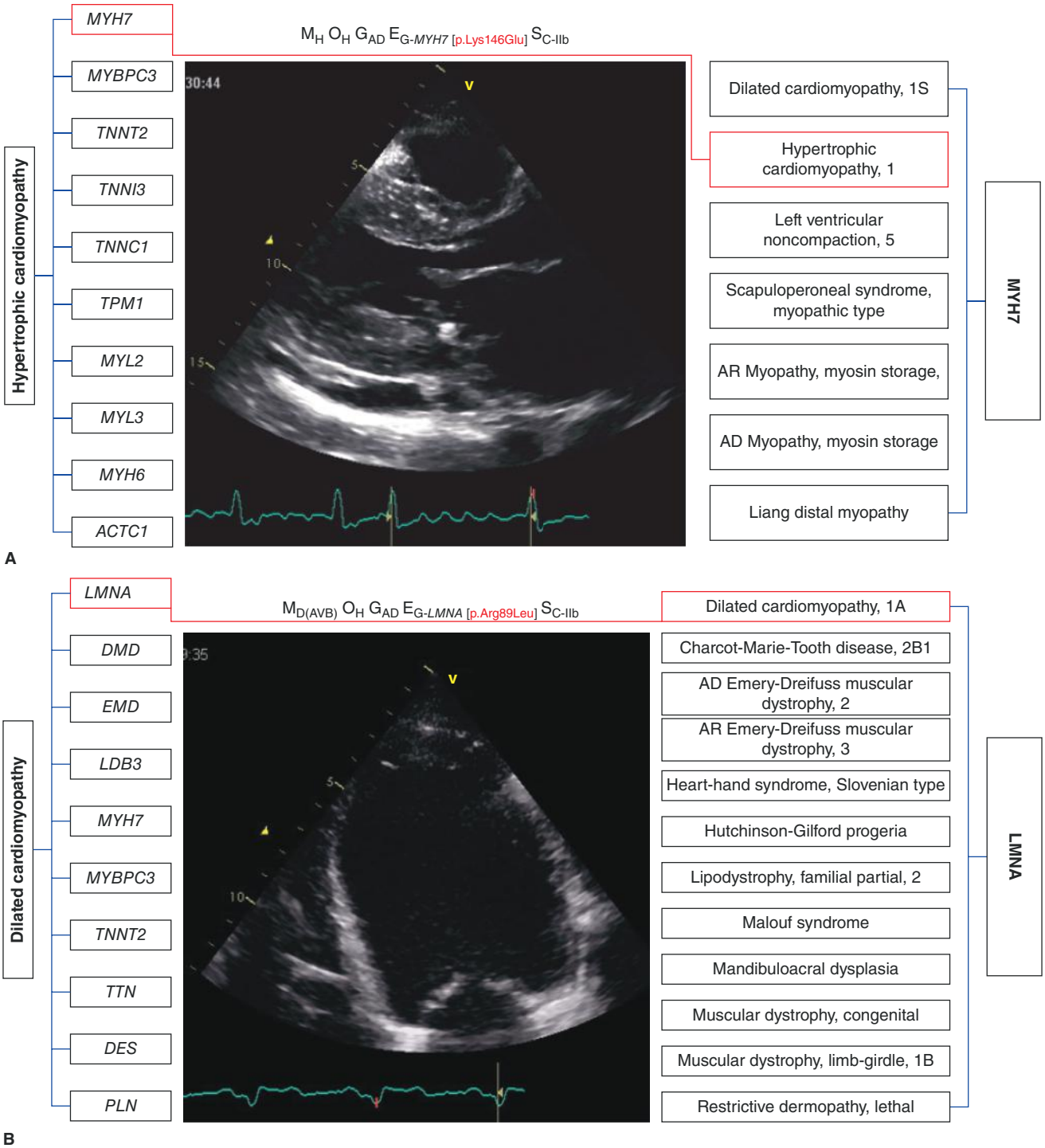


FIGURE 9–5. A. One gene ⟶ more diseases and vice versa: MYH7. The *left* side shows the most common disease genes for hypertrophic cardiomyopathy; *MYH7* is one of the most common disease genes in HCM (up to 30% of cases). The echocardiographic figure refers to a patient with hypertrophic cardiomyopathy (HCM), carrier of a mutation in MYH7. The right side of the figure shows the list of diseases formally included in the MIM catalog and associated with mutations in MYH7 gene. **B.** One gene ⟶ more diseases and vice versa: *LMNA*. The left side figure shows the most common disease genes for dilated cardiomyopathy; *LMNA* is one of the most common disease genes in dilated cardiomyopathy (DCM) (up to 7% of cases). The echocardiographic figure refers to a patient with DCM, carrier of a mutation in *LMNA*. The right side of the figure shows the list of diseases formally included in the MIM catalog and associated with mutations in the *LMNA* gene.

diseases such as Marfan syndrome (MFS), vascular Ehlers-Danlos syndrome (EDSIV), and Loeys-Dietz syndrome (LDS) are characterized by phenotypic traits that usually allow clinical diagnosis,[6] with genetic testing playing a confirmatory role. TAAD can further occur as isolated trait or in the context of less-known syndromes.

Genetic, familial TAAD (FTAAD) can be grouped according to the molecular pathway/structure in which disease genes are involved.[6,72] Genes encoding components of the *extracellular matrix* are associated with MFS (*FBN1 gene*) and other diseases allelic at the same locus (isolated FTAAD, MAAS, Weill-Marchesani syndrome, familial ectopia

TABLE 9–1. Disease Genes and Phenotypes in Which Aortic Aneurysm Recur[a]

MIM* Gene	Gene	Protein	Phenotypes/Diseases Allelic at the sSme Locus	Inheritance	Aortic Aneurysm	Extra-aortic Aneurysm	CHD/Valve Disease	Stroke, CAD	Tromboembolic Events	Arterial Tortuosity	Skeletal System	Facies	Ocular System	Nervous System	Integumantal System	Respiratory System	Craniosynostosis	Learning Disability	Hearing Loss
102620	*ACTA2*	*Actin, alpha-2, smooth muscle,*	Aortic aneurysm, familial thoracic 6	AD	x	x	x	x					X IF						
604539	*ADAMTS2*	*A disintegrin-like & metallo-proteinase with thrombo-spondin type 1 motif, 2*	Ehlers-Danlos syndrome, type VIIC	AR	x	x					x	x			x	x			
300011	*ATP7A*	*ATPase, Cu (2+)-transporting, a polypeptide*	Menkes syndrome	XLR	x	x					x	x		x	x			x	
613381	*CBS*	*Cystathionine beta-synthase*	Homocystinuria, B6-responsive and nonresponsive	AR	x	x			x	x	x		x EL	x	x			x	
608429	*CHST14*	*Carbohydrate sulfotransferase 14*	Ehlers-Danlos syndrome, musculocontractural, 1	AR		x	x			x	x	x	x	x	x	x	x	x	
120150	*COL1A1*	*Collagen, type 1, alpha-1*	Ehlers-Danlos syndrome, classic, VIIA	AD	x	x					x	x			x	x			
			Osteogenesis imperfecta I, II, III, IV		x		x				x		x BS		x	x			x
120160	*COL1A2*	*Collagen, type 1, alpha-2*	Ehlers-Danlos syndrome II, III, IV, VIIB, cardiac valvular form	AR	x	x	x				x		x BS	x	x				
120180	*COL3A1*	*Collagen, type 3, alpha-1*	Ehlers-Danlos syndrome, type IV	AD	x	x	x				x	x	x BS		x	x			
120130	*COL4A1*	*Collagen, type 4, alpha-1*	Tortuosity of retinal arteries, angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps, brain small vessel disease with or without ocular anomalies, porencephaly 1, susceptibility to hemorrhage, intracerebral.	AD						x	x	x	x	x	x			x	
120070	*COL4A3*	*Collagen, type 4, alpha-3*	Alport syndrome, autosomal dominant	AD	x					x	x		x						x
			Alport syndrome, autosomal recessive	AR	x								x						x
120131	*COL4A4*	*Collagen, type 4, alpha-4*	Alport syndrome, autosomal recessive	AR	x								x						x
303630	*COL4A5*	*Collagen, type 4, alpha-5*	Alport syndrome, X-linked	XLD	x								x		x				x
120215	*COL5A1*	*Collagen, type 5, alpha-1*	Ehlers-Danlos syndrome, classic type	AD	x		x				x		x	x	x				
120190	*COL5A2*	*Collagen, type 5, alpha-2*	Ehlers-Danlos syndrome, classic type	AD	x		x						x	x	x				
120110	*COL10A1*	*Collagen, type 10, alpha-1*	Metaphyseal chondrodysplasia, Schmid type	AD							x								
604633	*EFEMP2*	*EGF-containing fibulin-like extracellular matrix protein 2*	Cutis laxa, autosomal recessive, type IB	AR	x	x				x	x	x	x	x	x				
130160	*ELN*	*Elastin*	Cutis laxa; supravalvar aortic stenosis	AD	x	x	x				x			x	x	x			
134797	*FBN1*	*Fibrillin1*	Ectopia lentis, familial; Marfan syndrome; acromicric dysplasia; aortic aneurysm, ascending, and dissection; geleophysic dysplasia 2; Stiff skin syndrome; MASS syndrome; Weill-Marchesani syndrome 2, dominant	AD	x					x	x		x	x	x	x	x		
612570	*FBN2*	*Fibrillin 2*	Contractural arachnodactyly, congenital; macular degeneration, early onset	AD	x						x		x	x	x		x		
614505	*FKBP14*	*FK-506 binding protein 14*	Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy, and hearing loss	AR							x			x	x				x

(*continued*)

TABLE 9–1. Disease Genes and Phenotypes in Which Aortic Aneurysm Recur[a] (*Continued*)

MIM* Gene	Gene	Protein	Phenotypes/Diseases Allelic at the sSme Locus	Inheritance	Aortic Aneurysm	Extra-aortic Aneurysm	CHD/Valve Disease	Stroke, CAD	Tromboembolic Events	Arterial Tortuosity	Skeletal System	Facies	Ocular System	Nervous System	Integumantal System	Respiratory System	Craniosynostosis	Learning Disability	Hearing Loss
300017	*FLNA*	*Filamin A*	Cardiac valvular dysplasia, X-linked; heterotopia, periventricular; congenital short bowel syndrome; frontometaphyseal dysplasia; intestinal neuronal pseudoobstruction,	XLR/XLD	x	x		x			x		x	x	x			x	
609367	*KIAA1279*	*Kinesis-binding protein 1279*	Goldberg-Shprintzen megacolon syndrome	AR							x	x	x	x				x	
601468	*MAT2A*	*Methionine adenosyltransferase II, Alpha*		AD	x														
601103	*MFAP5*	*Microfibrillar-associated protein 5*	Aortic aneurysm, familial thoracic 9	AD	x						x								
160745	*MYH11*	*Myosin, heavy chain 11, smooth muscle*	Aortic aneurysm, familial thoracic 4	AD	x	x	x	x											
600922	*MYLK*	*Myosin light chain kinase*	Aortic aneurysm, familial thoracic 7	AD	x														
190198	*NOTCH1*	NOTCH, Drosophila, homolog of	Aortic valve disease; Adams-Oliver syndrome 5	AD	x		x						x		x				
153454	*PLOD1*	Procollagen-lysine, 2-oxoglutarate 5-dioxigenase	Ehlers-Danlos syndrome, type VI	AR							x		x	x	x	x			
176894	*PRKG1*	Protein kinase, cGMP-dependent, regulatory, type 1	Aortic aneurysm, familial thoracic 8	AD	x			x			x			x					
164780	*SKI*	V-ski avian sarcoma viral oncogene homolog	Shprintzen-Goldberg syndrome	AD	x		x			x	x	x	x	x	x		x	x	
606145	SLC2A10	Solute carrier family 2	Arterial tortuosity syndrome	AR	x	x		x	x	x	x	x	x	x	x		x	x	
608735	*SLC39A13*	Solute carrier family 39 (zinc transporter), member 13	Spondylocheirodysplasia, Ehlers-Danlos syndrome-like	AR							x		x BS					x	
603109	*SMAD3*	Mothers against Decapentaplegic, Drosophila, homolog Of, 3	Loeys-Dietz syndrome, 3	AD	x	x				x	x	x			x		x		
600993	*SMAD4*	Mothers against Decapentaplegic, Drosophila, homolog of, 4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; Myhre syndrome, polyposis, juvenile intestinal	AD	x						x				x				
190180	*TGFB1*	Transforming growth factor, beta-1	Camurati-Engelmann disease, cystic fibrosis lung disease	AD, AR	x						x				x				
190220	*TGFB2*	Transforming growth factor, beta-2	Loeys-Dietz syndrome, 4	AD	x	x				x	x	x	x	x	x				
190230	*TGFB3*	Transforming growth factor, beta-3	Loeys-Dietz syndrome 5, arrhythmogenic right ventricular dysplasia 1	AD	x	x				x	x	x	x	x	x				
190181	*TGFBR1*	Transforming growth factor-beta receptor, type I	Loeys-Dietz syndrome, 1; multiple self-healing squamous epithelioma	AD	x					x	x	x	x BS		x		x		
190182	*TGFBR2*	Transforming growth factor-beta receptor, type II	Colorectal cancer, hereditary nonpolyposis,6; esophageal cancer, Loeys-Dietz syndrome 2	AD	x	x				x	x	x	x BS	x	x				
600742	*TGFBR3*	Transforming growth factor-beta receptor, type III	Thoracic aortic aneurysm	AD		x													
600985	*TNXB*	Tenascin Xb	Ehlers-Danlos syndrome caused by tenascin X deficiency; vesicoureteral reflux 8	AR, AD			x				x				x				

[a]Describes major phenotypical traits reported in syndromic thoracic aortic aneurysm and dissection.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive BS, blue sclerae; CAD. coronary artery disease; CHD, congestive heart disease; EL, ectopia lentis; IF, iris flocculi; MASS, mitral valve prolapse, aortic enlargement, skin and skeletal findings; XLD, X-linked dominant; XLR, X-linked recessive.

lentis syndrome, and geleophysic and acromicric dysplasia)[1,72,73] as well as vascular EDSIV[74] caused by mutations in the *COL3A1* gene. Genes encoding components of the transforming growth factor-beta (TGF-beta) signaling pathway include *TGFBR1* and *TGBFR2* that cause LDS1 and LDS2 and FTAAD in patients who do not show common traits recurring in LDS1.[72,75] Mutations in the *SMAD3* gene (playing its role in the TGF-beta signaling pathway) cause the osteoarthritis-aneurysm syndrome.[76] Mutations in genes encoding structural components of vascular smooth muscle cells cause FTAAD either as an isolated trait or in association with recurrence of CHD such as patent ductus arteriosus, bicuspid aortic valve, premature stroke, CAD, and moyamoya disease.[77-79] Precise description of the phenotype (TAAD) and of the corresponding disease genes (eg, FTAAD-*SMAD3*, FTAAD-*TGFBR1*) incorporates the essential diagnostic information, providing a system to precisely communicate diagnoses.[6]

Bicuspid aortic valve (BAV) is common in the general population (1%). In 25% of cases, it is associated with dilation of the ascending aorta.[80] BAV-associated aortopathy constitutes a further independent subgroup of aortic diseases, which should be distinguished from that recurring in CHD (such as hypoplastic left heart syndrome, coarctation of aorta, septal defects) and in syndromes such as Andersen-Tawil, DiGeorge, Noonan, LEOPARD, and Turner syndromes.[80,81] Nonsyndromic familial BAV has been associated with mutations in *NOTCH1*[82] that encode a single-pass transmembrane receptor with signaling functions, and in *GATA5*,[83] which encodes a cardiac transcription factor. BAV associated with aortic dilatation has also been reported in isolated FTAAD-*TGFBR1*, FTAAD-*TGFBR2*, FTAAD-*SMAD3*, FTAAD-*TGFB2*, and FTAAD-*ACTA2*.[6]

In clinical practice, the phenotype-based approach to the diagnosis is distinctly useful for syndromes: most clinicians now recognize MFS patients by their typical skeletal traits, LDS1 patients by their typical craniofacial traits, or EDSIV patients from their skin and face morphology. This diagnostic impact is uniquely beneficial in emergency situations when aortic dissection coincides with the clinical onset of the disease. Additional clinically useful information for patients presenting with emergency aortic dissection is family history, exploring prior similar events or "unexplained" sudden death in relatives.

Genetic Workup

Genetic workup can be either thoracic aortic aneurysm (TAA)–oriented in patients presenting for genetic evaluation after an established diagnosis of arterial aneurysm (aorta or other arteries), or phenotype-based in patients referred for genetic evaluation of skeletal, craniofacial, or ocular traits or syndromes in which TAA may recur. The latter group of patients should undergo 2D echocardiography, wherein the morphology and dimensions of the aortic valve annulus, root, sinotubular junction, ascending aorta, arch, thoracic descending aorta, and abdominal aorta should be systematically annotated. Geneticists involved in TAAD multidisciplinary evaluation should be familiar with normal measures and calculation of corresponding z-scores.[84] Genetic workup starts with counseling and physical examination of probands; multidisciplinary evaluation can add value to the genetic visit via characterization of multiple phenotypic traits. The pedigree construction may (1) highlight a positive family history for the given syndrome or for isolated TAAD or (2) describe fatal events in relatives.

Diagnosis of Thoracic Aortic Aneurysm

Current guidelines provide detailed information on cardiovascular workup.[85,86] TAA is routinely diagnosed by cardiac/angioimaging, with 2D echocardiography playing a key role. Further imaging investigation includes magnetic resonance or angio-CT scan, either limited to the thorax or extended to the total arterial tree, exploring the entire aorta as well as nonaortic arteries. In syndromes such as EDSIV, aortic dilation is not the rule, whereas aneurysms of muscular arteries are common. Arterial tortuosity is a nonspecific marker but is far more common in LDS than in MFS,[87] with extreme manifestation in ATS.[88] Information on nonaortic arteries is essential both as marker of disease and as detection of potentially harmful extra-aortic aneurysms.

Thoracic Aortic Aneurysm in Children

Clinical genetic evaluation should carefully distinguish diseases in which the aortic aneurysm may affect children from those in which the aneurysm develop in young-adult age. Pediatric aortic aneurysms are uncommon in MFS but common in LDS. Other diseases such as Takayasu arteritis should be considered, especially when an aortic aneurysm is present as isolated, nonsyndromic trait.[89] Pediatric nonaortic arterial aneurysms may affect different vascular territories and may contribute to the diagnosis of malignant diseases such as vascular EDSIV.[90]

Inheritance

Most heritable isolated or syndromic TAADs are autosomal dominant diseases (Fig. 9–6). AR and X-linked TAAD are rare, and in small families, they may appear as sporadic diseases when a unique family member is affected. Typical examples of AR TAAD are ATS, homocystinuria, and cutis laxa type IB. Typical AR syndromes with aortic aneurysm include Alport syndrome and rare lysosomal diseases. Examples of X-linked TAADs include Menkes syndrome and diseases caused by defects of filamin A, which can be both XL recessive or dominant. Aortopathies can occur in patients with CHD, either as monogenic diseases or chromosomal disorders. TAA occurring in children or young and adult patients who do not carry known risk factors for aortic aneurysms should be suspected to have a genetic origin regardless of family history. De novo disease is common in syndromic TAAD, and possible in rare storage diseases such as AFD in which GB3 accumulates in vascular smooth muscle cells (Fig. 9–7). Two-dimensional echocardiography-based screening of relatives may demonstrate a familial TAAD. In fact, aortic dilation is asymptomatic, unless exerting some compressive effects on closer structures or manifesting with dissection.

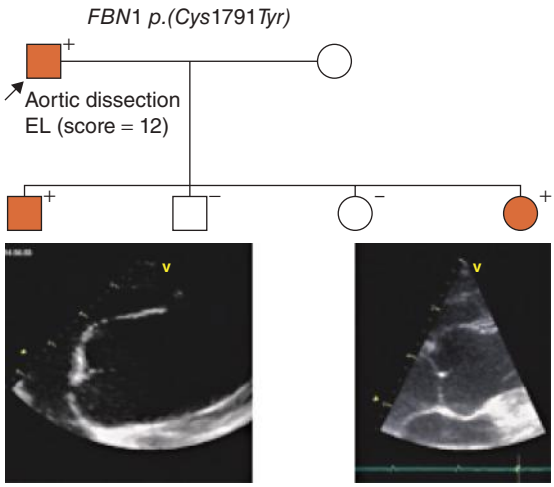


FIGURE 9–6. The figure shows the pedigree of a family with autosomal dominant Marfan syndrome; the proband is the father whose first diagnosis coincided with aortic dissection. Two of four are children affected. The affected son also has autosomal recessive epidemolysis bullosa and demonstrates a severe aortic aneurysm involving the root, with loss of sinotubular junction and dilation of the ascending aorta.

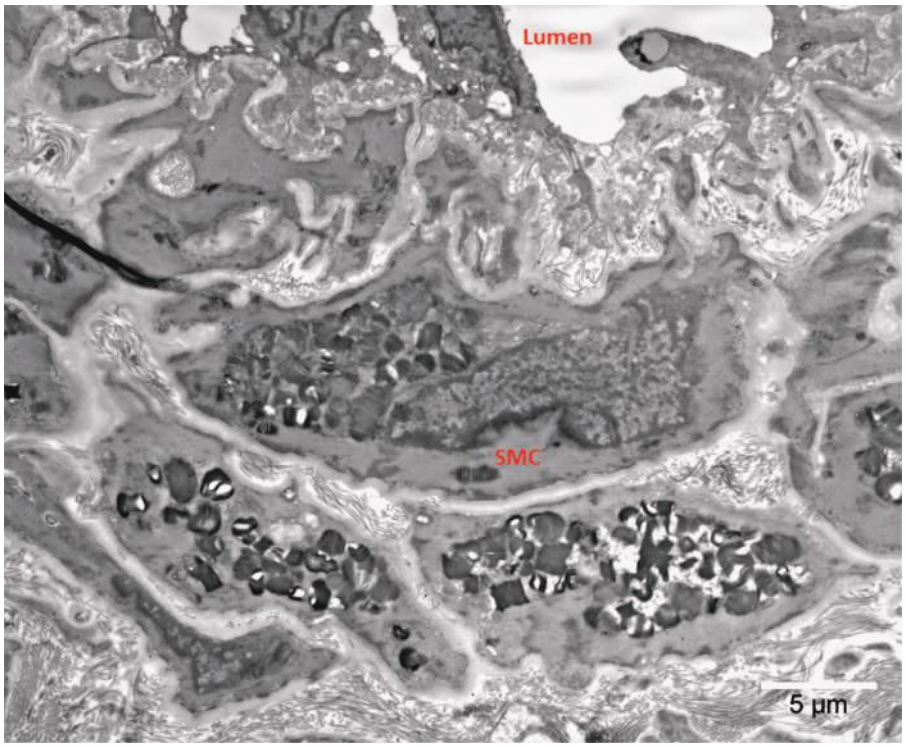


FIGURE 9–7. Electron micrograph of arteriolar smooth muscle cells (SMC) in a male patient diagnosed with Anderson Fabry disease. The cells show diffuse cytoplasmic accumulation of GB3.

Genetic Testing

The decision to proceed to genetic testing relies in part on the family pedigree. If there is no clear phenotype in other family members (all family members appear nonaffected), then the utility of genetic testing is reduced and less commonly pursued. However, isolated TAA can be present in asymptomatic family members who are not aware of their disease. Therefore, a negative family pedigree obtained on the narrative of the proband is not sufficient to exclude a familial TAA. The pedigree can be considered informative after clinical family screening including echocardiographic evaluation of first-degree relatives of the proband.

Genetic testing can be performed by sequencing a unique gene in the instance of a strong clinical diagnostic hypothesis. Alternatively, large panels of disease genes and exome sequencing are used to identify mutations in known disease genes or novel candidate/disease genes.[91-94] Depending on the disease gene, the interpretation of results may confirm the clinical diagnosis or play a diagnostic role in isolated, nonsyndromic TAAD. This highlights the need of deep phenotyping in isolated TAAD in order to identify traits specifically recurring in apparently nonsyndromic TAAD associated with mutations in different genes, so that physicians are able to ascertain markers of disease or traits predicting the occurrence of the aortic aneurysm. A representative example is iris flocculi that may recur in families with *ACTA2*-TAAD.[35,95] Prenatal diagnosis is now offered on a regular basis to couples in which one parent is affected by MFS.[96] Noninvasive prenatal and preimplantation diagnosis can be an alternative to a conventional prenatal diagnosis for couples that do not accept the risk of pregnancy loss.[97]

Genotype-phenotype correlation studies have been performed in several syndromic TAADs with the major aim of distinguishing highly malignant diseases from milder phenotypes. MFS is the most widely investigated disease; nosology has changed over time, from the pregenomic era, to the last 2010 revision,[98] in which genetic testing entered as a major diagnostic criterion. Genetic testing is recommended in newly suspected MFS, especially when two systems are involved, with at least one major system affected.[99] Patients who carry *FBN1* mutations and demonstrate only one major clinical criterion or only minor clinical criteria in one or more organ system represent 5% of the adult series.[100] The majority of clinical manifestations of MFS increase with age.[101] Infant carriers of mutations in the neonatal exons demonstrate severe phenotypes[102]; in children less than 1 year of age, a shorter survival was associated with presence of valve insufficiencies or diaphragmatic hernia in addition to a mutation in exons 25 or 26.[103] A higher risk of aortic dissection is reported in male patients.[104]

The Impact of Precise Genetic Diagnosis

In the past 10 years, it has been demonstrated that risk stratification for aortic dissection may vary based on the different subtypes of FTAAD and that preventive surgery should be planned considering both the individual patient and the disease-specific risk.[85] In addition, the proposed role of TGF-beta in aneurysmal diseases, and FBN1 mouse models treated with anti-TGF-beta antibodies or drugs acting on TGF-beta opened up the possibility of exploring the effects of angiotensin receptor blockers (ARBs) in patients with MFS. Many clinical trials have recently been concluded and others will conclude in the near future, comparing the role of ARBs with beta-blockers[105] (Table 9–2).[106-127] Based on results achieved to date, patients with Marfan syndrome and aortic root dilation should receive medical therapy, with either beta-blockers or ARBs or both. Medications seem to be more effective at reduction of aortic root z-score in younger subjects, which suggests that medical therapy should be prescribed even in the youngest children with early/mild aortic dilation. For patients without aortic dilation, indications for medical treatment are less clear. In patients with severe and/or progressive aortic dilation the combination of a beta-blocker and angiotensin receptor blocker should be considered, although current trial results are mixed with respect to the efficacy of combination therapy versus monotherapy.

Independent of the results, the message from these studies is the novel impact of precise diagnosis on the potential development of personalized, disease-oriented treatment of heritable aneurysmal diseases.

PULMONARY HYPERTENSION

Definition and Classification

Pulmonary arterial hypertension (PAH) is a rare, life-threatening disease, affecting between 1 to 2 per 100,000 and 1 per 1 million people[128] (see Chap. 74). In the 2016 ESC guidelines, pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure—at least 25 mm Hg at rest as assessed by right heart catheterization.[129] Current clinical classification is based on the principles of similarities in pathobiology, clinical features, and therapeutic options.[130] More than 40 different diseases are divided into 5 groups (updated classification, Nice, 2013):

1. Group 1: idiopathic, heritable, drug-induced pulmonary arterial hypertension, CHD with pulmonary hypertension, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis. This includes chromosomal deletion syndromes such as Williams-Beuren syndrome (deletion 7q11.23) and Alagille syndrome

TABLE 9–2. Clinical Trials in Patients with Marfan Syndrome[a]

Study	Nation	Single Center/ Multicenter	Medications	Study Type	Sample Size	Primary End Point*	Imaging*	Age	Result	Follow-up (years)
Nonrandomized Studies										
Shores et al.[106]	US	Single center	No treatment vs propranolol	Prospective, randomized, nonblinded	70 Control: 38 vs treated: 32	Aortic root dimensions	Echo	12-50 years; < 18 years at entry: control: 68% vs treated: 60%	BB was effective in slowing the rate of aortic dilatation and reducing the development of aortic complications	Control: 9.3 years vs treated: 10.7 years
Salim et al.[107]	US	Multicenter	Propranolol or atenolol vs no therapy	Prospective, nonrandomized, nonblinded	113	Aortic root growth rate	Echo CT MR	< 21 years at time of first visit	Treatment at a younger age blunted the aortic root growth rate to a greater extent	Control: 5.7 ± 1.8 years Group A: 5.5 ± 2.7 years; Group B: 4.2 ± 2.1 years
Rossi-Foulkes et al.[108]	US	Single center	Verapamil or β-blocker vs no therapy	Prospective, nonrandomized, nonblinded	44	Aortic root growth rate	Echo	Female: < 17 years Male: < 19 years	BB and CCB decreased aortic root growth rate	3.67 ± 2 years
Selamet Tierney et al.[109]	US	Multicenter	β-Blocker vs no β-blocker	Retrospective, nonrandomized, nonblinded	63 Control: 34 vs treated: 29	Rates of change in the aortic root measurements and their corresponding *z* scores over time	Echo	≤ 18 years	Rates of change of aortic root measurements and the corresponding *z* scores were not statistically different between the two groups	Control: 6.75 ± 4.49 years; treated: 6.36 ± 2.58 years
Ladouceur et al.[110]	France	Multicenter	No treatment vs β-blocker Atenolol: > 70% Nadolol: 17% Propranolol: 6%	Retrospective, nonrandomized, nonblinded	155	Aortic root growth rate	Echo	< 12 years	BB significantly decreased the rate of aortic-root dilatation by a mean of 0.16 mm/year compared to no treatment.	4.5 ± 3.7 years
Brooke et al.[111]	US	Single center	Losartan or irbesartan	Nonrandomized, retrospective, observational	18	Rate of change in aortic root diameter	Echo	1-16 years	ARB therapy significantly slowed the rate of progressive aortic root dilation	Median, 2.175 years; range, 1-3.92 years
Pees et al.[112]	Austria	Single center	Losartan monotherapy vs matched healthy cohort	Prospective, unselected cohort compared with matched healthy cohort	20	Aortic dimensions and elasticity indexes	Echo	1.7-21.6 years	Significant improvement with losartan only; therapy was proven in all affected proximal aortic segments with a better response to therapy when started at an earlier age and with a longer duration of therapy	2.75 ± 0.92 years

(continued)

TABLE 9–2. Clinical Trials in Patients with Marfan Syndrome (*Continued*)

Study	Nation	Single Center/ Multicenter	Medications	Study Type	Sample Size	Primary End Point*	Imaging*	Age	Result	Follow-Up (years)
Mueller et al.[113]	DE	Single center	Valsartan v. metoprolol	Nonrandomized, retrospective, observational	40	Aortic root growth rate	Echo	9.01 ± 5.7 years	Both ARBs and BBs led to a significant reduction in aortic root dilation	ARB: 1.4 ± 0.24 years vs BB: 5.51 ± 3.3 years
Yetman et al.[114]	US	Multicenter	Enalapril vs propranolol or atenolol	Prospective, nonrandomized, open label	58	Aortic elastic properties and aortic root growth rate	Echo	-	Treatment with enalapril improved aortic distensibility, reduced aortic stiffness index, decreased aortic root growth rate, and resulted in fewer clinical end points during follow-up compared with BBs	3 ± 0.2 years
Phomakay et al.[115]	US	Single center	Atenolol (46%), metoprolol (48%), and propranolol (6%). Lisinopril (13%), enalapril (85%), and captopril (2%)	Retrospective, nonrandomized	67	Aortic root growth rate	Echo	13±10 years	Angiotensin-converting enzyme inhibitor did not significantly decrease aortic root growth rate	7.6 ± 5.8 years
Randomized Clinical Trials										
Chiu et al.[116]	Taiwan	Single center	Atenolol or propranolol vs losartan with atenolol or propranolol	Randomized, open-label	28	Aortic root growth rate Efficacy and safety of losartan with BB treatment	Echo	6.8-19.4 years	Losartan combined with β-blocker therapy was safe and provided more effective protection to slow the progression of aortic root dilation than β-blocker alone	2.93 years
Ahimastos et al.[117]	Australia	Single center	BB with placebo vs BB with perindopril	Prospective, randomized, double-blind, placebo-controlled	17 Placebo: 7 Treated: 10	Arterial stiffness and aortic root diameter	Echo Carotid tonometry Doppler velocimetry Applanation tonometry	27-40 years	Perindopril reduced aortic stiffness and aortic root diameter in patients who received standard BB therapy	0.46 Year
Williams et al.[118]	UK	Multicenter	Atenolol vs perindopril vs verapamil	Prospective, randomized, double-blind, crossover trial	18	Large artery function: central aortic pressure, augmentation of central pressure, conduit arterial stiffness	Echo Applanation tonometry Pulse wave analysis	16-60 years	Perindopril, verapamil, and atenolol all reduced peripheral and central pressure	0.35 Year

Nonrandomized Studies										
Groenink et al.[119]	Netherlands	Multicenter	Losartan with baseline therapy vs no additional therapy (control)	Randomized, open-label, blinded assessments of end points	223	Aortic dilatation rate at 6 predefined aortic levels assessed with MRI or CT	MRI CT	≥ 18 years	Losartan reduced aortic root dilatation rate. After aortic root replacement, losartan reduced dilatation rate of the aortic arch	3.1 ± 0.4 years
Milleron et al.[120]	France	Multicenter	Losartan with baseline therapy vs placebo with baseline therapy (BB 86%)	Prospective, randomized, double-blind, placebo-controlled, parallel group, add-on trial	303	Aortic root growth rate, normalized to its theoretical value and expressed as mean change in *z*-score per year	Echo	≥ 10 years	Losartan did not reduce aortic dilatation during a 3-year period	3.5 years (median)
Lacro et al.[121]	US	Multicenter	Atenolol vs losartan	Prospective, randomized, participants and echo core laboratory blinded to treatment assignment	608	Rate of change in aortic root *z*-score (slope)	Echo	0.5-25 years	No significant difference in the rate of aortic root dilatation between the two treatment groups	3 years
Sandor et al.[122]	Canada	Multicenter	Atenolol (25-50 mg) vs losartan (25 mg)	Prospective, randomized, double-blind	17	Vascular function; pulse wave velocity	Echo Applanation tonometry	10.6-27.8 years	Atenolol and losartan might have different mechanisms of action on vascular function	1 Year
Bhatt et al.[123]	US	Multicenter	Losartan (100 mg) vs atenolol (50 mg)	Prospective, randomized, double-blind	34	Arterial stiffness values; carotid-femoral pulse wave velocity, central augmentation index; aortic diameter; left ventricular function	Echo Applanation tonometry	> 25 years	Atenolol improved pulse wave velocity; Losartan reduces central augmentation index	0.5 Year
Forteza et al.[124]	Spain	Multicenter	Atenolol vs losartan	Prospective, randomized, double-blind	150	Aortic growth and distensibility; prevention of adverse event	MRI	5-60 years	Aortic root diameter increased significantly in both groups: 1.1 mm (95% CI, 0.6-1.6) in the losartan and 1.4 mm (95% CI, 0.9-1.9) in the atenolol group, with aortic dilatation progression being similar in both groups: absolute difference between losartan and atenolol -0.3 mm (95% CI, -1.1 to 0.4, P = 0.382) and indexed by BSA -0.5 mm/m (2) (95% CI -1.2 to 0.1, *P* = .092). Similarly, no significant differences were found in indexed ascending aorta diameter changes between the losartan and atenolol groups: -0.3 mm/m (2) (95% CI -0.8 to 0.3, *P* = .326).	3 years

(continued)

TABLE 9–2. Clinical Trials in Patients with Marfan Syndrome (*Continued*)

Study	Nation	Single Center/ Multicenter	Medications	Study Type	Sample Size	Primary End Point*	Imaging*	Age	Result	Follow-Up (years)
Randomized Clinical Trials Still Open										
Gambarin et al.[125]	Italy	Single center	Nebivolol vs losartan vs nebivolol with losartan	Randomized, open label, phase III study	291	Aortic root growth rate	Echo	1-55 years	Pending	4 years
Moberg et al.[126]	Belgium	Single center	Losartan vs placebo with BB	Prospective, randomized, double-blind, placebo-controlled	174	Aortic root growth rate	Echo MRI	≥ 10 years	Pending	3 years
Mullen et al.[127]	UK	Multicenter	Irbesartan vs placebo	Prospective, randomized, double-blind, placebo-controlled	490	Absolute change in aortic root growth rate	Echo	6-40 years	Pending	4 years

(deletion 20p11-2) as well as monogenic diseases such as Keutal syndrome and cutis laxa, in which peripheral pulmonary artery stenosis may occur either as isolated defects or in association with other congenital heart defects.

2. Group 2: pulmonary venous hypertension or PAH caused by left heart disease
3. Group 3: PAH caused by lung diseases and/or hypoxia
4. Group 4: chronic thromboembolic PAH (CTEPH)
5. Group 5: miscellaneous disorders that can affect the pulmonary vasculature with unclear and/or multifactorial mechanisms.

The causes can be genetic in primary PAH, group 1, and group 5.

Genetic Workup and Assessment of Disease-specific Risk Factors

Genetic causes are well recognized in several forms of PAH. Accordingly, the diagnostic workup should systematically include counseling and, in case of monogenic diseases, clinical family screening, and cascade genetic testing. Genetic counseling explores personal and family medical history as well as exposure to known toxic agents and drugs, followed by genetic testing as recommended by scientific societies.[131] Disease-specific risk factors are classified as definite, likely, or possible on the basis of the strength of their association with PH and their probable causal role[130,132] (Table 9–3). A definite association is acknowledged in the case of appetite suppressants, or for drugs demonstrated as being associated with PAH in multicenter epidemiological studies. A likely association is considered when demonstrated in a single-center case-control study or multiple case series, or when clinical and hemodynamic recovery occurs after cessation of exposure (ie, dasatinib-induced PAH). The association is defined as possible for drugs with similar mechanisms of action as those in the two aforementioned categories, but have not yet been systematically studied, such as those used to treat attention deficit disorders. Genetic counseling should also explore autoimmune diseases, infections such as HIV, possible parasitic diseases, exposure to radiation, living environment (high altitude), chronic renal diseases, sarcoidosis, and prior splenectomy. In patients with CTEPH, the investigation should include history of venous thromboembolic events (when known) and thrombophilic disorders.[133,134] The pattern of inheritance is autosomal dominant in most patients with familial pulmonary hypertension; however, rare pulmonary veno-occlusive forms are inherited as recessive traits and may appear as sporadic, especially in small or noninformative families. Accordingly, genetic counseling, and eventually genetic testing, should be offered to all patients diagnosed with PAH (group 1) and pulmonary hypertension of unclear origin (group 5).

TABLE 9–3. Pulmonary Hypertension: Disease-Specific Risk Factors To Be Systematically Investigated in Genetic Counseling

Definite	Likely	Possible
Aminorex	Amphetamines	Cocaine
Fenfluramine	Dasatinib	Phenylpropanolamine
Dexfenfluramine	L-tryptophan	St John's wort
Toxic rapeseed oil	Methamphetamines	Amphetamine-like drugs
Benfluorex	Trichloroethylene (PVOD)	Interferon α and β
Selective serotonin reuptake inhibitors (> risk of persistent PH in newborns of treated mothers)		Chemotherapeutic (ie, alkylating agents such as mytomycin C, cyclophosphamide [in particular for pulmonary veno-occlusive disease])

Genetic Testing

More than one disease gene has been identified in primary pulmonary hypertension (PPH)[128,135] (Table 9–4). Genetic testing in probands can be clinically guided or performed through the screening of multigene panels by NGS. A clinically oriented approach is feasible for familial autosomal dominant PPH in which mutations of bone morphogenetic protein receptor 2 (*BMPR2*) recur in up to 80% of patients and families. *BMPR2* plays a role in the pathway of BMP and is members of the TGF-beta superfamily that regulates cell growth, differentiation, apoptosis, and development. Less common disease genes, such as *SMAD9*, play a role in the same BMP pathway as downstream modulators of the BMP signaling pathway and cause a phenotypically similar, autosomal dominant PPH. Other disease genes such as *ALK-1* and *endoglin (ENG)* play a role in the TGF pathway; these genes account for a minority of familial PPH, which is a major trait of Osler–Weber–Rendu disease. Defects in other rare disease genes such as *CAVEOLIN 3 (CAV3)* or genes coding ion channels such as *KCNH3*, result in a similar phenotype, but via different mechanisms. Novel candidate genes include *TOPBP1*[136] and *CYP1B1*.[137] Pulmonary veno-occlusive hypertension is allelic at the PPH1 locus (*BMPR2)*, whereas the recessive form is caused by mutations in *EIF2AK4*.[138] Finally, group 5 PAH includes a variety of acquired and heritable diseases such as the AD lymphangioleiomyomatos[139] and lysosomal storage diseases such as glycogen storage disease types 1 and 3[140,141] and Gaucher disease type 1.[142,143]

Interpretation of the Results of Genetic Tests

The type of mutation facilitates the interpretation of *BMPR2* testing results. Most mutations are truncation-predicting defects (frameshift, nonsense, splice site) ending in haploinsufficiency.[135] In carriers of missense mutations, family segregation studies, in silico analysis, and eventually pathologic studies when lung samples are available may contribute to clarify their role. Genetic tests should be expanded to all probands presenting with "idiopathic" PPH; up to 20% of patients with apparently sporadic PPH carry *BMPR2* mutations.

The segregation analysis of the genotype with phenotype can be complicated by incomplete penetrance because affected members of the same family may not show the phenotype at time of screening; regular clinical monitoring should be scheduled for clinically unaffected but genetically affected family members. Phenotype expression may be age-dependent or may be influenced by exposure to environmental factors. A double-hit hypothesis has been proposed to explain the variable clinical manifestations of the disease. The hypothesis of anticipation of the phenotype in younger members of the same family does not have corresponding molecular mechanisms. Current knowledge regarding the molecular basis of PPH1 does not include evidence of triplet expansion, and recent longitudinal studies do not seem to confirm this hypothesis.[144] Finally, incomplete penetrance can be a result of incomplete genotyping, being the spectrum of disease and modifier genes potentially involved in PPH are far from being fully elucidated.

Translational Impact

Clinical genetics with counseling and pedigree construction, search for known risk factors and annotation of novel potential risk factors, family investigation, and genetic testing are currently translated in the clinical setting. Clinical attention to PAH is encouraged by the availability of new medical treatments (endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase stimulators, and prostanoids) that continue to be tried in patients with idiopathic,

TABLE 9–4. Disease Genes, Gene loci (*), Phenotypes and Inheritance Pattern of Primary Pulmonary Hypertension, as well as Genes Associated with the Veno-Occlusive Form of Pulmonary Hypertension and with Hereditary Hemorrhagic Telangiectasia

WHO Group	Type	Gene	*Gene Locus	Protein	Inheritance
Primary Pulmonary Hypertension (PPH)					
1	PPH1	*BMPR2*[a]	*600799*	Bone morphogenetic protein receptor 2	AD
1	PPH2	*SMAD9*	*603295*	Mothers against decapentaplegic Drosophila, homolog of, 9	AD
1	PPH3	*CAV1*	*601047*[b]	Caveolin1	AD
1	PPH4	*KCNK3*	*603220*	Potassium channel, subfamily K, member 3	AD
1	Dexfenfluramine-associated PH	*CYP1B1*	*601771*	*Cytochrome P450; subfamily 1; polypeptide 1*	AD(?)
-	Phenotype not yet included in the OMIM catalog	*TOPBP1*	*607760*	Topoisomerase DNA binding II binding protein 1	AD
Pulmonary Venoocclusive Disease (PVOD)					
1	PVOD1	*BMPR2*	*600799*	Bone morphogenetic protein receptor 2	AD
1	PVOD2	*EIF2AK4*	*609280*	Eukaryotic translation initiation factor-2, alpha kinase 4	AR
Hereditary Hemorrhagic Telangiectasia (HHT)					
1	HHT1 (Rendu-Osler-Weber)	*ENG*	*131195*	*Endoglein (CD105)*	AD
1	HHT2	*ACVRL1*	*601284*	Activin A receptor, type II-like 1	AD
Lymphangioleiomyomatosis (LAM)					
5	Tuberous sclerosis-1; LAM	*TSC1*	*605284*	*Amartin*	AD
5	Tuberous sclerosis-2 and LAM somatic mutations	*TSC2*	*191092*	*Tuberin*	AD
Lysosomal Storage Diseases					
5	Glycogen storage disease type1	G6PC (1a)	*232200*	Glucose-6-phosphatase and glucose-6-phosphate translocase	AR
		SLC37A4(1b)	*232220*		
5	Glycogen storage disease types 3a and b	AGL	*610860*	Glycogen debrancher enzyme	AR
5	Gaucher disease type 1 (with or without splenectomy)	*GBA*	*606463*	Acid beta-glucosidase	AR

[a]Including fenfluramine-/dexfenfluramine associated PH.

[b]Disorders allelic at the same locus: "lipodystrophy, congenital, generalized type 3" and "partial lipodystrophy, congenital cataracts and neurodegeneration syndrome."

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

heritable, drug-induced, and connective tissue disease-associated PAH. Genetic workup significantly contributes to precise diagnosis.

INHERITED ATRIAL DISEASES

Genetic Atrial Diseases: Beyond Atrial Fibrillation

Heritable atrial diseases include rare atrial CMPs, AR or AD sick sinus syndrome, rare novel syndromes with extracardiac involvement, and a certain proportion of lone atrial fibrillation. The aim of this section is to highlight the genetic workup of rare heritable atrial diseases and familial lone AF (see AF in Chap. 83).

Atrial Dilated Cardiomyopathy

ADCM is a rare AR disease characterized by clinical onset in adulthood, biatrial dilatation up to giant size, early supraventricular arrhythmias with progressive loss of atrial electric activity to atrial standstill, thromboembolic complications, stable, normal left ventricular function and New York Heart Association functional class during the long-term course of the disease, and severely decreased levels of atrial natriuretic peptide. The disease is caused homozygous mutations in the natriuretic peptide precursor A (NPPA) gene; heterozygous carriers are healthy and demonstrate normal levels of atrial natriuretic peptides.[11] Phenotypically similar, adult-onset phenotypes have been reported in one Indian case,[145] two Australian patients,[146] and, more recently, children with isolated right atrial dilation.[147] Similar atrial disease and isolated atrial amyloidosis in three Japanese siblings[148] suggest a recessive inheritance, and the possible contribution of atrial amyloid deposits to the pathological substrates of atrial cardiomyopathies. In the past, these diseases were described as idiopathic atrial dilation or congenital atrial malformations.[149,150] A precise diagnosis influences decision on treatments such as ablation for arrhythmias and early anticoagulation that should be initiated in patients with atrial dilation regardless of the arrhythmias. When the disease is unrecognized, stroke can coincide with disease onset.

Sick Sinus Syndrome

Sick sinus syndrome (SSS) is clinically characterized by sinus bradycardia, sinus arrest, chronotropic incompetence and susceptibility to atrial arrhythmias.[151] SSS can be sporadic, such as the common SSS observed in older persons,[152] or familial, typically manifesting in young patients. Familial SSS are clinically and genetically heterogeneous diseases, either AD or AR. The onset of AR SSS (SSS1, MIM #608567) may occur in childhood and adolescence.[153-157] It is caused by mutations in *SCN5A* gene, which encodes the α-subunit of the cardiac Na+ channel. In small families, the disease may appear as sporadic; however, the young age of patients and the absence of other cardiac diseases that may explain the phenotype are by themselves sufficient to refer probands and families for genetic counseling. Clinical family screening demonstrates the absence of manifestations in parents. Parental consanguinity or origin of parents from geographic isolates may contribute to suspect

AR inheritance. Genetic testing demonstrating homozygous mutations or compound mutations in the *SCN5A* gene is uniquely useful to conclude the diagnostic workup.[158] The AD SSS (SSS2, MIM #163800) is caused by mutations in the *HCN4* gene that codes for hyperpolarization activated cyclic nucleotide-gated potassium channel.[159] Heterozygous mutations have been identified in patients with SSS complicated by life-threatening arrhythmias[160] and in familial asymptomatic sinus bradycardia.[161] The genetic diagnosis of SSS contributes to identify at-risk family members, to schedule monitoring for prevention of arrhythmias, and to support decisions for ablation of atrial arrhythmias or PM implantation.

Rare Novel and Known Syndromes: Cohesinopathies

Cohesinopathies are disorders caused by mutations in subunits or regulators of cohesin.[162] They may commonly affect the heart and manifest with arrhythmias and/or CHD. Atrial arrhythmias recur in chronic atrial and intestinal dysrhythmia (CAID) syndrome, a recently described AR disorder. CAID is clinically characterized by deregulation of the cardiac sinus node leading to SSS and of gastrointestinal motility resulting in chronic intestinal pseudo-obstruction (CIPO).[163] Both traits can represent distinct disorders associated with mutations in genes known to cause either SSS or CIPO. However, when SSS and CIPO coexist, the disease-causing gene is *Shugosin-like 1 (SGOL1*, MIM *609168), which has been recently identified in 16 French Canadians and 1 Swede; the gene encodes a component of the cohesin complex (made up of *SGO1* and *SGO2*) that protects centromeric integrity.[163] Atrial arrhythmias do not seem to be common in other cohesinopathies such as Cornelia de Lange syndrome (CDLS) in which CHD recur in up to 30% of cases[164]; left ventricular dilation and hypertrophy, right ventricular cardiomyopathy, and sudden death in CDLS have been reported in autopsy series[165] or in patients demonstrating HCM.[166] CDLS is a genetically heterogeneous disease entity, with five associated genes, all of which are active in the cohesin complex.[167]

The precise diagnosis of CAID has clinical implications for affected children and young adults, not only for atrial arrhythmias but also for treatments of CIPO, including both prokinetic agents used to relieve symptoms caused by gut dysmotility (ie, arrhythmogenic effect of cisapride)[168,169] and nonopioid drugs used to control abdominal pain.[170]

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia (1.5% of the general population), affecting health and quality of life. Lone AF accounts for about 5% to 10% of all AF. AF can be sporadic or familial[171,172]; about 30% of patients with AF have a positive family history,[173,174] and individuals with at least one parent with AF have a relative risk of AF of 85%.[173] Genetic studies are rapidly progressing, and numerous disease genes and chromosomal loci have been identified to date in familial AF[175] (Table 9–5).

The role of clinical genetics involves deep phenotyping patients presenting with lone AF to exclude presence of other traits or diseases that can explain the arrhythmia. In fact, some of the genes that have been linked to AF may also cause different cardiac and noncardiac diseases. In other words, AF can represent one of the early manifestations of genetic CMPs. Family studies should demonstrate that other affected members do not exhibit CMPs or other cardiac diseases; the distinction between lone familial AF versus AF complicating other genetic heart diseases prevents incorrect assignment of a causative role for AF to genes that cause CMPs in which AF may recur as part of the evolving phenotype.[176] A typical example is AF in patients with cardiolaminopathies. A systematic screening of *LMNA* in a cohort of 268 unrelated patients with idiopathic forms of familial and sporadic AF identified a unique, possible but nonconfirmed mutation, thus excluding this gene as a candidate for lone AF.[177] Disease genes identified by linkage analysis in well-phenotyped families have been confirmed both as cause of familial AF[178-180] and of different heritable atrial diseases *(NPPA*).[11] Genes such as *SCN5A* that cause long QTS, short QTS, or Brugada syndrome may also cause AF, and long-term follow-up of mutation carriers is necessary to exclude other arrhythmogenic phenotypes or explore why the same mutations may manifest different arrhythmogenic phenotypes.

Precision Diagnosis of Atrial Diseases

Genetic AF is an expanding area of precision cardiology but requires family screening and monitoring to confirm a disease gene for AF. Segregation studies are complicated by the need for long-term follow-up or recording systems to clinically identify family members at risk of developing AF. Paroxysms of AF can be clinically silent and unless implanting an ECG recording system, clinically silent episodes of AF can be missed. Clinical surveillance can reveal silent AF episodes, thus contributing to genotype-phenotype correlation studies, preventive treatments, and elucidation of the role of genetic mutations in AF. Electroanatomic mapping in patients with AF is now contributing to characterize structural fibrotic changes observed in patients with heritable atrial diseases.[180] Recently, the term *fibrotic atrial cardiomyopathy* has been introduced to describe the fibrotic substrate observed in patients with AF.[181] Unraveling whether fibrosis is the cause or effect in heritable AF may contribute to treatment decisions.

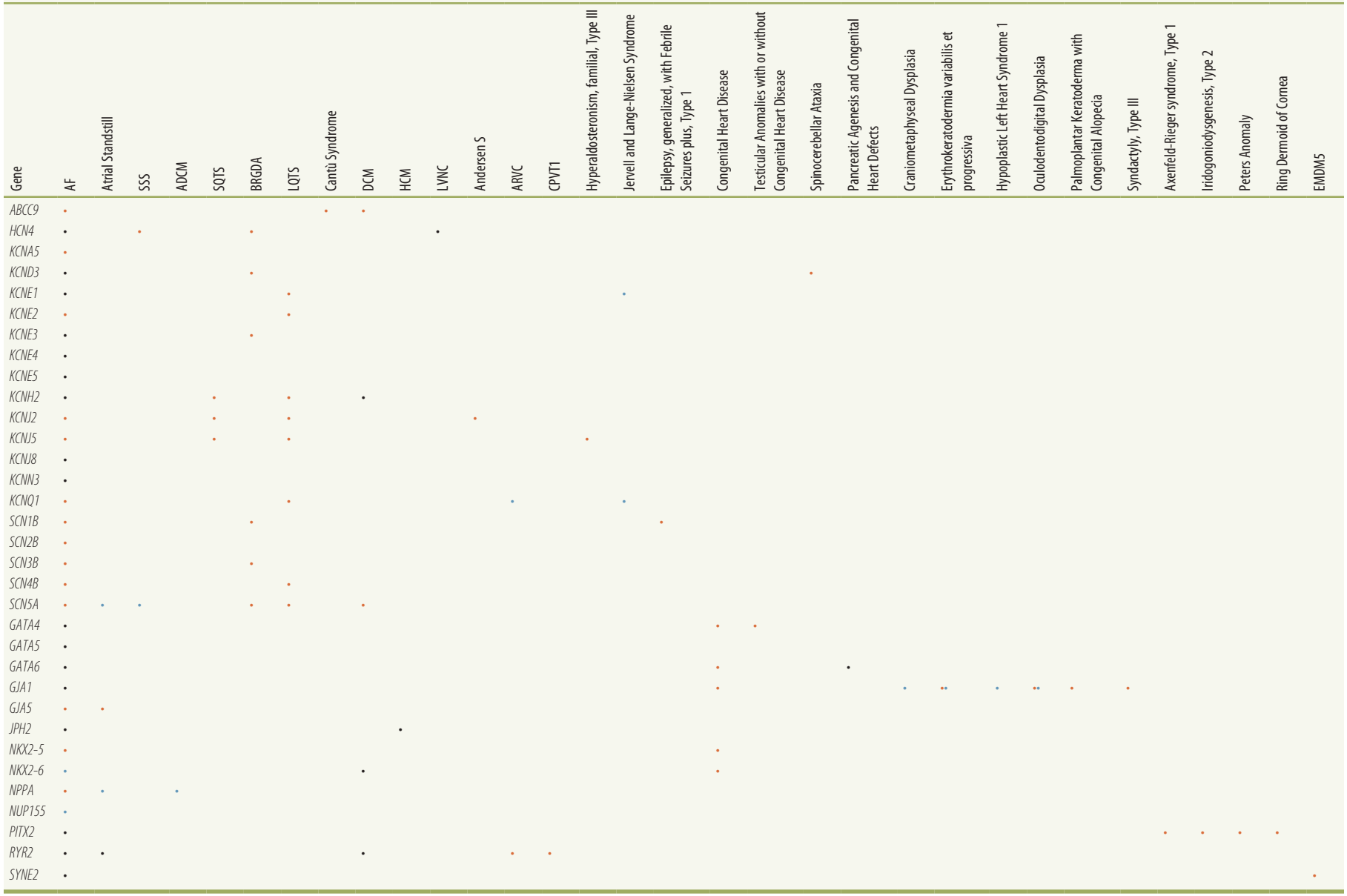
INHERITED CHANNELOPATHIES AND LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

Cardiochannelopathies encompass a large, genetically heterogeneous group of electrical abnormalities that can be associated with unexpected sudden death.[182,183] The majority of disease genes encode cardiac ion channels or proteins interacting with ion channels or involved in ion flux and metabolism (Table 9–6).[182,183] Genetic workup includes clinical evaluation, genetic testing, and post-test counseling. Genetic teams, including clinicians, geneticists, genetic counselors, basic scientists, and pharmacologists, should evaluate the phenotype, age, gender, family and drug history, comorbidities, patient preferences, and therapeutic alternatives before proceeding to genetic testing.[184,185] Patients and families are addressed to genetic counseling for (1) incidental observation of prolonged or short QT interval or Brugada pattern or early repolarization in ECG screening studies (eg, sport, professionals, army), (2) unexplained syncope, (3) resuscitated cardiac arrest (aborted sudden death), or (4) sudden death in a family member. The last condition represents the most complex diagnostic challenge when the DNA of the victim has not been preserved and medical records are not available. In this case, clinical family screening (ECG, 2D-echocardiography, 24-hour Holter monitoring) is the first step to establish whether relatives of the victim demonstrate ECG abnormalities or unperceived arrhythmias. The major groups of channelopathies associated with risk of sudden death include diseases that lengthen the QT interval—Brugada syndromes and catecholaminergic polymorphic ventricular tachycardia (CPVT). These disorders are extensively reviewed in Chapters 79, 80, and 91. In this session, we shortly recapitulate major arrhythmogenic cardiochannelopathies, inheritance, disease genes, and phenotypes to provide further information for genetic counseling and testing.

Long QT Syndrome

Long QT syndrome (LQTS) is an autosomal dominant arrhythmic disease characterized by a prolonged QT interval on resting 12-lead

TABLE 9–5. The Table Shows the List of Genes that have been Reported as Associated with Familial AF. The Red and Blue Dots Indicate Genes that have been Assigned to the Atrial Fibrillation (ATFB) Phenotype (#) in the MIM Catalogue; Red Dots (•) Indicate Autosomal Dominant And Blue Dot (•)Autosomal Recessive Inheritance. Dark Gray Dots (•) Indicate Genes in Which Mutations have been Reported in One or a Few Cases and are Not Yet Validated. The Table also Lists All Disorders that are Recognised to be Allelic at the Same Locus. Up To January 2016, AF Has Not Been Associated With Mutations In *ANK2* (LQT4), *CACNA1C* (LQT8, Thimoty Syndrome, Brugada Syndrome 3), *CAV3* (LQT9), *AKAP9* (LQT11), *SNTA1* (LQT12), *CALM1* (LQT14), *CALM2* (LQT15), *GPD1L* (Brugada Syndrome 3), *CACNB2* (Brugada Syndrome 4), and *HCN4* (Brugada Syndrome 8). This Latter Gene However is Involved in SSS Type 2, Autosomal Dominant.



Abbreviations: AF, atrial fibillation; ADCM, atrial dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; BRGDA, Brugada; DCM, dilated cardiomyopathy; EMDM5, Emery-Dreifuss muscular dystrophy; HCM, hypertropic cardiomyopathy; LQTS, long QT syndrome; LVNC, left ventricular non-compaction; SQTS, short QT syndrome SSS, sick sinus syndrome; CPVT1, catecholaminergic polymorphic ventricular tachycardia-1.

TABLE 9–6. Complex and Heterogeneous Spectrum of Genes That Have Been Reported in Association with Arrhythmogenic Syndromes[a]

Gene	MIM* Gene	Long QT Ayndrome	Short QT Syndrome	Brugada Syndrome	Catecholaminergic Polymorphic Ventricular Tachycardia
ABCC9	*601439			x	
ANK2	*106410	x			x
AKAP9	*604001	x			
CACNA1C	*114205	X[b]	x	x	
CACNA2D1	*114204		x		
CACNB2	*600003		x		
CALM1	*114180	x			x
CALM2	*114182	x			
CASQ2	*114251				x
CAV3	*601253	x			
GPD1L	*611788			x	
HCN4	*605206			x	
MOG1	*607954		x	x	
NOS1AP	*605551			x	
KCND3	*605411			x	
KCNE1	*176261	x[c]			
KCNE2	*603796	x			
KCNE3	*604433			x	
KCNE5	*300328	x		x	
KCNH2	*152427	x	x	x	
KCNQ1	*607542	x	x		
KCNQ2	*602235	x	x		
KCNJ2	*600681[d]	x	x	x	x
KCNJ5	*600734[e]	x			
KCNJ8	*600935			x	x
PKP2	*602861			x	
RYR2	*180902				x
SCN1B	*600235	x		x	
SCN2B	*601327			x	
SCN3B	*608214			x	
SCN4B	*608256	x			
SCN5A	*600163	x		x	
SCN10A	*604427			x	
SLMAP	*602701			x	
SNTA1	*601017	x		x	
TRDN	*603283				
TRPM4	*606936			x	x

[a]Also demonstrate that different phenotypes can be allelic at the same locus.

[b]Timothy syndrome.

[c]Jervell and Lange-Nielsen syndrome 2.

[d]Andersen-Tawil syndrome: periodic paralysis, ventricular arrhythmias, and distinctive dysmorphic facial or skeletal features.

[e]Familial type III hyperaldosteronism.

surface ECG in the absence of structural heart disease. Inheritance is AR in the rare Jervell and Lange-Nielsen syndrome. Patients with LQTS may remain asymptomatic during their entire life or manifest symptoms caused by ventricular arrhythmias; syncope, aborted cardiac arrest, or sudden cardiac death can be the first manifestation of the disease.[186] Although many genetically different types of LQTS are known, 90% of cases are associated with mutations in *KCNQ1* encoding Kv7.1 (LQT1), *KCNH2* encoding Kv11.1 (LQT2), and *SCN5A* encoding Nav 1.5 (LQT3).[187] In LQT1, T waves are broad-based and symptoms recur during exercise; in LQT2, T waves are low-amplitude, notched or biphasic and symptoms are induced by acoustic triggers; and in LQT3, narrow-based T waves are preceded by long isoelectric segment and symptoms occur during rest.[187,188] The remaining 10% of pathogenic mutations occur in genes encoding other ion channels or in genes encoding proteins interacting with ion channels (see Table 9–6).

The diagnosis of LQTS is based on consensus criteria.[189] A scoring system allows for the summation of points assigned to ECG findings at baseline and after exercise stress, evidence of torsade de pointes, history of syncope, congenital deafness, family history and members with LQTS, and unexplained sudden cardiac death (SCD) below age 30 among immediate family members.[190,191] A score equal to or greater than 3.5 points is the diagnostic cutoff, with a greater than 70% probability of identifying pathogenic mutations when the score is equal to or greater than 4. Genotype is not included in the score. The risk of life-threatening arrhythmias and events is high in (1) patients with QTc interval equal to or greater than 500 ms and a history of syncope, (2) LQT1 associated with missense mutations in residues of the cytoplasmic loop of the protein, and (3) females with LQTS2 and males with pore-loop missense mutations.[192-194]

Treatment includes beta-blockers (propranolol and nadolol) whose effectiveness may vary in the different subtypes of LQTS: highest for LQT1, less effective in LQT2 and LQT3.[195] Mexiletine and ranolazine can be used adjunct to beta-blockers in LQT3.[196,197] Implantable cardioverter defibrillator (ICD) therapy is indicated in patients who suffered syncope while treated with beta-blockers and in those with very long QTc (0.550-ms) intervals. Left cardiac sympathetic denervation is a possible added therapy for severely affected patients who are refractory to beta-blocker therapy.[189] For drugs to be avoided by patients with long QT syndrome, see https://crediblemeds.org/pdftemp/pdf/DrugsToAvoidList.pdf.

Short QT Syndrome

Short QT syndrome (SQTS) is an inherited arrhythmic disease associated with increased risk of AF, ventricular tachycardia/ventricular fibrillation (VT/VF), and SCD.[198] Current estimates indicate a prevalence of 0.02% to 0.1% in the adult population and 0.05% in children and adolescents.[199] The diagnosis is made when the QT interval is equal to or less than 330 ms in the absence of tachycardia or bradycardia. Gain-of-function mutations in three genes encoding potassium channels, *KCNQ1*, *KCNH2*, and *KCNJ2*, have been associated with SQTS. Given the high risk of SCD, prophylactic ICD therapy is appropriate; adjunctive pharmacological therapy such as quinidine that prolongs QT interval is beneficial in a subset of these patients.[189,200]

Brugada Syndrome

Brugada syndrome is an AD arrhythmogenic disease characterized by ST elevation with negative T wave in the right precordial leads in the absence of structural cardiac abnormalities.[201,202] Although clinical manifestations include syncope or cardiac arrest caused by ventricular fibrillation, the majority of patients remain asymptomatic lifelong. The disease burden is estimated to range from 5 to 20 individuals in 10,000,

with higher prevalence in Asian populations. Although the mean age of patients manifesting life-threatening arrhythmias is around 40 years, arrhythmic events can occur at any age; arrhythmias typically occur while sleeping or at rest, after heavy meals, or during episodes of fever.[202,203] To date, numerous genes have been associated with Brugada syndrome, but pathogenic mutations are identified in about 30% of patients, with *SCN5A* gene accounting for the majority of cases and other genes accounting for about 5% of genotyped cases.[204] Overlap phenotypes (long QT, short QT, and Brugada syndrome) are possible in affected members of the same families, given that the disease gene can be the same (eg, SCN5A).[205] A recent "oligogenetic inheritance" hypothesis postulates that mutations in more than one disease gene are needed to induce a clinical phenotype.[206] In patients with equivocal baseline ECG pattern as unique evidence of possible disease, ajmaline provocation tests can be performed.[189] Other diseases/factors potentially manifesting a Brugada-like ECG patterns (IHD, hyperkalemia, hypercalcemia, arrhythmogenic right ventricular dysplasia, myocarditis, mechanical compression of the right ventricular outflow tract, or pulmonary embolism) should be excluded. In symptomatic patients, risk stratification includes history of VT/VF, syncope and spontaneous coved-type ST-segment elevation. In asymptomatic patients risk stratification includes male gender and fragmented QRS, which is a marker of conduction abnormality and a predictor of prognosis.[207] The first-line therapy is ICD in patients with a history of VT/VF or syncope.[189] Administration of drugs that can trigger type 1 ECG changes and arrhythmias (www.brugadadrugs.org) should be avoided. For phenocopies, see www.brugadaphenocopy.com.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a rare disease (1:10,000) that typically presents with syncope or cardiac arrest triggered by exercise or emotion in children/adolescents.[27,208] Mortality is high in affected, unrecognized, and untreated patients. The baseline ECG is normal but exercise induces the polymorphic ventricular arrhythmias; a few patients may demonstrate bidirectional ventricular tachycardia.[208,209] The disease is genetically heterogeneous. CPVT1 (60%–70%) is AD and caused by mutations in the gene *RYR2* gene, and CPVT2 is AR and is associated with mutations in the cardiac calsequestrin gene (*CASQ2*).[210] Both *RYR2* and *CASQ2* are involved in myocyte calcium homeostasis.[209] Less common disease genes include *KCNJ2* (CPVT3), calmodulin *(CALM1*), and triadin *(TRDN).*[211,212] Risk factors for arrhythmic events include young age, male gender, history of cardiac arrest, occurrence of arrhythmias while taking beta-blockers, and mutation in the c-terminus of the *RYR2* gene.[213] All genotyped patients should be treated with beta-blockers at the highest tolerable dose, adding flecainide when beta-blockers do not control arrhythmias. In severely affected patients, ICD discharge can induce catecholamine release, causing ventricular storms.[214,215]

Overall, geneticists actively involved in counseling and testing patients with suspected cardiochannelopathies and potential risk of life-threatening ventricular arrhythmias should be part of multidisciplinary specialized teams and be cautious in the interpretation of the role of genetic variants identified by genetic testing. In fact, family segregation studies, which usually strongly contribute to support causality of mutations, may be limited by the difficult phenotype characterization of asymptomatic and "ECG-negative" relatives who may or may not manifest traits typically recurring in these diseases.

TUMORS OF THE HEART AND GENETICS

Rare and Genetic Tumors of the Heart

Tumors of heart are rare (see Chap. 101), with autopsy incidence ranging from 0.001% to 0.03%, including all primary benign and malignant neoplasms. In the revised World Health Organization 2015 classification, they are grouped as benign tumors, tumors of uncertain biologic behavior, germ cell tumors, and malignant tumors.[216] Among all, myxoma, rhabdomyoma, fibroma, and some tumor-like histiocytoid diseases of the heart may be present in the context of syndromes suspected based on their clinical presentation and confirmed by genetic testing.

Cardiac myxoma occurs in Carney complex and accounts for up to 10% of all cardiac myxomas,[217] but it may also occur as isolated neoplasm. Carney complex is clinically characterized by pigmented lesions of the skin and mucosa, recurrent cardiac, cutaneous and other myxomas, and multiple endocrine tumors.[218] Patients are usually younger than those with sporadic myxoma, and there is no female predominance. Carney complex type 1 is caused by mutations in the cyclic adenosine 5′-monophosphate-dependent protein kinase (*PRKAR1A* gene), whereas Carney complex type 2 has been mapped at 2p16 locus, but the gene is still unknown. A variant of Carney complex with distal arthrogryposis is associated with defects in the *MYH8* gene. The diagnosis is made in the presence of (1) two of the major criteria confirmed by histology, imaging, or biochemical testing or (2) one major criterion in addition to the presence of one supplemental criterion.[219,220] Pancreatic acinar cell carcinoma, adenocarcinoma, and intraductal pancreatic mucinous tumors have been reported in as many as 2.5% of patients.[221] Genetic counseling and testing are part of the diagnostic workup.

Rhabdomyoma typically occurs in patients with tuberous sclerosis, an AD disorder that is clinically characterized by the triad of neurofibromatous lesions, mental slowing, and cutaneous lesions.[222] Multiple rhabdomyomas are found in about half of children affected by tuberous sclerosis. The disease is caused by mutations in tumor suppressor genes [*TSC1* coding amartin (9q34) and *TSC2* coding tuberin (16p 13.3)] that also cause lymphangioleiomyomatosis and pulmonary hypertension. The inactivation of the tuberous sclerosis complex genes, *TSC1* and *TSC2*, and the activation of the mammalian target of the rapamycin (mTOR) pathway enhance cell proliferation and migration, lymphangiogenesis, metastatic spread, sex steroid sensitivity and deregulated autophagy.[223] The mTOR activation provides the basis for target therapy with mTOR inhibitors.[224]

Cardiac fibroma recurs in the AD basal nevus syndrome or Gorlin syndrome, causally linked with mutations in the tumor suppressor protein encoding patched Drosophila homolog *1 (PTCH1)* gene.[225,226] The *PTCH1* transmembrane protein represses transcription in specific cells of genes encoding members of the TGF-beta and Wnt families of signaling proteins. The penetrance of the *PTCH1* mutations is complete, but the clinical phenotype may vary, including skeletal abnormalities and increased risk of tumors—in particular, desmoplastic medulloblastoma. The diagnosis and management requires multidisciplinary collaboration because the disease is multisystemic. Genetic counseling for parents of affected children reveals the complex association of phenotypic traits, the relevance of early diagnosis, and the need for scheduled multidisciplinary monitoring of and decision making about the multiple lesions.[227]

Purkinje cell hamartoma, or cardiac hamartoma, also termed *histiocytoid cardiomyopathy* (or oncocytic cardiomyopathy), is an XL dominant disease. Endocardial or myocardial nodules that may involve the sinoatrial and atrioventricular nodes characterize the macroscopic view. Histologically, myocytes appear round and vacuolated and demonstrate conspicuous numbers of mitochondria. The disease has recently been associated with the de novo nonsense mutations in the NADH ubiquinone oxidoreductase subunit B11 gene (*NDUFB11*) in two unrelated female patients and with two de novo missense mutations in *NDUFAF2* and *NDUFB9* in a third female patient.[228] Although rare, diseases associated with mutations in *NDUFB11* are of special interest because they represent one of the very few examples of XL

dominant diseases (ie, linear skin defects with multiple congenital abnormalities 3, MIM #300952), and because of the possible synergy with additional mtDNA variants.

Somatic mutations in cardiovascular tumors are emerging as novel potential contributors to identify therapeutic targets. Target next-generation sequencing (tNGS) of oncogenes and tumor-suppressor genes in primary cardiac angiosarcomas have demonstrated that the p.R707Q mutation in phospholipase C gamma1 (*PLCG1*) constitutively activates the protein PLCγ1 and provides an alternative way of activation of kinase insert domain receptor (KDR)-PLCγ1 signaling in angiosarcomas. This evidence opens novel avenues for VEGF/KDR targeted therapies.[229] Intimal sarcomas of the heart have demonstrated mouse double minute 2 homolog (*MDM2)* gene amplification and overexpression of the MDM2 protein, again raising the possibility of targeted therapies.[229]

Identification of the Genetic Basis Facilitates Novel Treatment Strategies

Genetic tumors of the heart, both isolated or, more commonly, part of complex syndromes, can be clinically recognized by family screening and precisely diagnosed by testing corresponding disease genes. The precise diagnosis, including the pathology and the constitutive and somatic genetic defects, provide novel basis for targeted treatments. Clinical implications include scheduling of surgery for excising potentially recurring tumors (ie, atrial myxoma in Carney complex) especially in children, introducing mTOR inhibitors such as rapamycin for control of lymphangiogenesis, and tailored monitoring and interventions in syndromes with multiple tumors such as Gorlin syndrome. Somatic mutations in sarcoma cells can drive novel anticancer therapies in primary cardiac malignancies.

HERITABLE AUTOINFLAMMATORY DISEASES

Diseases That Should Be Included in the Differential Diagnosis of Inflammatory Heart Diseases

The heart can be involved in heritable autoinflammatory disorders (HAIDs). HAIDs are a group of monogenic diseases characterized by exaggerated inflammatory response through uncontrolled production of cytokines, which cause recurrent episodes of inflammation, followed by symptom-free periods of variable length.[174,230] HAIDs usually manifest with periodic fever syndromes. Cardiac involvement may occur as direct effect of the systemic inflammatory process. The onset may mimic infective pericarditis, myocarditis, or myocardial inflammation with fibrosis; in clinical practice, these conditions often remain labeled as idiopathic. Vascular involvement is rare.[231] Myocardial infection is usually the first diagnostic hypothesis in patients presenting with fever and either chest pain and normal coronary arteries, arrhythmias, or heart failure. Differential diagnosis now includes possible genetic origin of inflammatory heart disease.

Heritable Autoinflammatory Disorders: An Expanding Clinical Field

The number of clinically and genetically characterized autoinflammatory diseases is expanding. The feasibility of precise diagnoses and the increasing number of drugs specifically targeting key molecules that mediate tissue inflammation and damage are becoming vastly important in this field. HAIDs demonstrate the nonobligate relationship between cardiac inflammation and infections, and possible targeted treatment once patients have a precise diagnosis. Table 9–7 lists major diseases, genes, and organ involvement; for some of them, the type of cardiac involvement is known, whereas for others, cardiac involvement is not yet reported. Detailed description of all of these diseases goes beyond the scope of this section. We shortly discuss familial Mediterranean fever (FMF), which is the paradigmatic example of HAID demonstrating cardiac involvement (see also Chap. 61).

Familial Mediterranean Fever FMF is the most common familial autoinflammatory monogenic disease. It was first described as an autosomal recessive disease recurring in Eastern Mediterranean populations (Fig. 9–8).[232] The disease is caused by mutations in the *MEFV* gene that encodes pyrin, a component of the cellular inflammasome. After the identification of the *MEFV* gene, the genetic-driven name *pyrin-associated periodic fever syndrome* (PAPS) was proposed. Analogous to CMPs that have been recently reclassified integrating the phenotype-based, descriptive diagnosis with the specific cause of each subtype of CMP,[19] a precise nosology of HAIDs will be especially beneficial in the incoming era of precision cardiology, especially when target treatments are available and effective. PAPS is inherited as an AR disease[233,234] (see Fig. 9–1). Milder disease course, later onset, and less frequent and less severe inflammatory attacks may recur in patients who carry genetic variations that are not associated with the classical phenotype. Systematic sequencing of the whole *MEFV* exons showed that homozygous mutations recurred in 20% to 30% of patients with FMF.[235] Heterozygous carriers of MEFV mutations can develop a different inflammatory AD disease[236,237] or manifest the phenotype in the setting of exogenous triggers (ie, infections),[238] suggesting a double-hit hypothesis.[239-241]

Genetic Diagnosis and Recommendations Although the first recommendation for genetic diagnosis of FMF states that, "FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing" (level of evidence B), genetic testing and genotype-phenotype correlations are part of the modern diagnostic workup of PAPS. Of the eight recommendations provided by experts, level A evidence is for asymptomatic individuals homozygous for p.(Met694Val) mutations; these individuals should be evaluated and followed closely so that appropriate therapy is considered.[242]

MULTIFACTORIAL CARDIOVASCULAR DISEASES

Genetics in Multifactorial Diseases

Most cardiovascular diseases have a multifactorial origin. Common examples include atherosclerosis, CAD heart failure syndrome, hypertension, dyslipidemia, and diabetes. Each of them results from a complex interplay between environmental and genetic factors. The baseline risk in individuals with positive family history of MI, diabetes, hypertension, or dyslipidemia includes nonmodifiable factors (family history, gender, age).[243] Traditional risk factors and combinations thereof, age of onset and duration and treatments, are largely modifiable, even in heritable diseases such as AD familial hypercholesterolemia.[244] The risk of events (ie, acute MI) includes the global risk of the underlying disease (atherosclerosis) and the event-related risk that incorporates factors playing in local and systemic inflammation and arterial thrombosis.[243] The impact of positive family history varies in different multifactorial diseases. It is higher for CAD[245] and lower for "heart failure syndrome,"[246] in which risk stratification includes the primary cause of heart disease, the remodeling pathway, and the responsiveness to therapy.

Coronary Artery Disease as a Paradigm of Multifactorial Disease

Scientific and clinical achievements over the past 50 years (the post-Framingham era of cardiology) are tremendous. Identification of risk factors; prevention programs; drugs such as aspirin, statins, RAS

TABLE 9–7. Genes and Organs Involved in the Hereditary Autosomal Dominant or Autosomal Recessive Autoinflammatory Disorders

Gene	Protein	Phenotype (#MIM)	Inheritance	Pericarditis	Myocarditis	Cardiomyopathy	IHD	Eye	Arthritis	Hearing loss	Lipodystrophy	Skin	Nephropathy	Myopathy	Skeletal	Liver	Spleen	Brain
MEFV	Pyrin (marenostrin)	FMF (249100)	AR	•				•	•	•		•	•			•		
TNFRSF1A	TNF receptor type 1 (TNFRSF1A or CD120a)	TRAPS (142680)	AD	•	•		•	•	•						•			•
NLRP3	Cryopyrin (NLRP3)	FCAS (120100); MWS (191900); NOMID (607115).	AD	•			•	•	•	•		•	•		•			•
CARD14	CARD14	CAMPS (177900)	AD	•					•			•						
IL1RN	Interleukin-1 receptor antagonist	DIRA (612852)	AR		•	•		•	•			•					•	
IL36RN	Interleukin-36 receptor antagonist	DITRA (614204)	AR									•						
LPIN2	Lipin 2	MS (609628)	AR								•							
MVK	Mevalonate kinase	MKD (260920)	AR				•	•	•									•
NLRP12	Monarch 1	FCAS2 (609648)	AD				•			•		•		•				
NOD2	NOD2 (CARD15)	BS (186580)	AD			•			•			•						
PSTPIP1	CD2 antigen-binding protein 1	PAPAs (604416)	AD						•			•						
PSMB8	Inducible subunit β of the proteasome	CANDLEs (256040)	AR	•					•		•		•	•		•	•	
SLC29A3	Solute carrier family 29 (nucleoside transporter) Member 3	H syndrome (602782)	AR	Heart abnormalities		•	•		•	•								

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; BS, Blau syndrome; CAMPS, CARD14-mediated pustular psoriasis; CANDLEs, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome; DIRA, deficiency of interleukin-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; H syndrome, histiocytosis, lymphadenopathy + syndrome; IHD, ischemic heart disease; MKD, mevalonate kinase deficiency syndrome; MS, Majeed syndrome; MWS, Muckle-Wells syndrome; NLRP12-ad, NLRP12-autoinflammatory disorder; NNS: Nakajo- Nishimura syndrome; NOMID, neonatal onset multisystem inflammatory disease; PAPAs: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; TNF, tumor necrosis factor; TRAPS, tumor necrosis factor receptor-associated periodic syndrome.

inhibitors, and beta-blockers; and interventional procedures have modified the epidemiology and outcome of many multifactorial cardiovascular diseases.[247] Primary and secondary prevention programs as well as better diagnosis and treatments have resulted in increased survival, better quality of life, and increased life expectancy. In developed countries, the disease is decreasing,[248] whereas in developing countries, the disease is increasing.[249] Future contribution of genetics is expected to implement personalized precision medicine, which aims at tailoring risk, prevention, and treatments on individual clinical profiles and needs.[249]

The completion of the Human Genome Project,[250] the sustainable sequencing of large panels of genes or whole exome/genome sequencing, promises progressing individual genotyping and genetic characterization of individuals at risk (eg, association analysis in 63,746 CAD cases and 130,681 controls identifying 15 loci reaching genome-wide significance, taking the number of susceptibility loci for CAD to 46, and a further 104 independent variants ($r(2) < 0.2$) strongly associated with CAD at a 5% false discovery rate). Together, these variants explain approximately 10.6% of CAD heritability.[251] The study confirms that the four most significant pathways mapping to these networks are linked to lipid metabolism and inflammation, underscoring the causal role of these activities in the genetic etiology of CAD. A recent GWAS meta-analysis including about 185,000 CAD cases and controls and interrogating 6.7 million common (minor allele frequency [MAF] > 0.05) and 2.7 million low-frequency ($0.005 < MAF < 0.05$) variants, confirmed most known CAD-associated loci and further identified ten new loci (eight additive and two recessive) that contain candidate causal genes, newly implicating biological processes in vessel walls. The analysis shows that genetic susceptibility to this common disease is largely determined by common SNPs of small effect size.[252] Because loci identified by GWAS explain less than 10% of the genetic variance in CAD (90% of CAD heritability remains to be explained), systems genetics-building network models of relevant molecular processes can also capture environmental and modifiable influences on CAD. This combination is likely to be a lot more powerful for characterization of individuals with CAD than just DNA alone can deliver.[253]

Paradoxically, as far as new genetic information enters the scientific world, the translation calls for clinical skill, deep phenotyping, and family studies. New endovascular imaging and imaging markers (coronary artery calcium score, carotid intima-media thickness, and ankle-branchial index),[254] as well as new biomarkers (high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, secretory phospholipase A2)[255] will contribute to personalized diagnosis, risk stratification, and disease phenotyping.

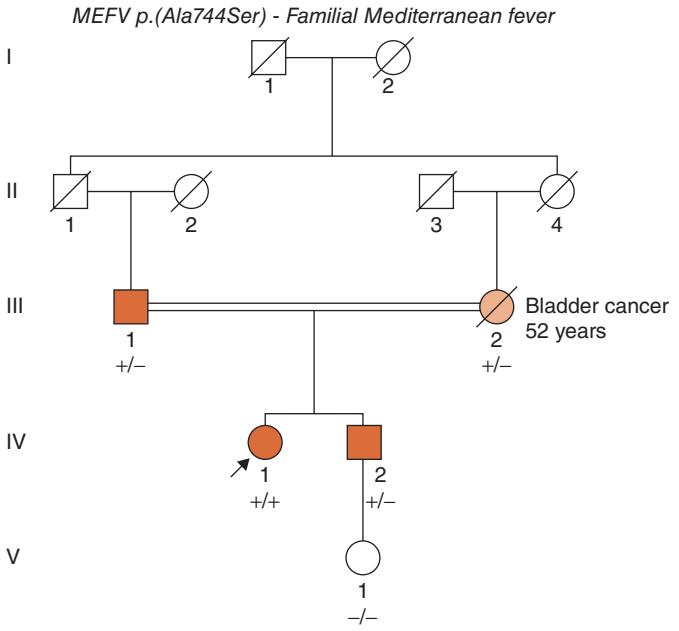


FIGURE 9–8. Pedigree of a family with autosomal recessive familial Mediterranean fever. Note parental consanguinity and minor involvement in heterozygous carriers of the *MEFV* mutation.

Monogenic Coronary Artery Disease

AD CAD (#608320, ADCAD1) associated with mutations in *MEF2A* gene (*600660; first reported AD MI[256] but later not confirmed[257]) and ADCAD2 (#610947) associated with mutations in the *LRP6* gene (*603507) are not confirmed. Susceptibility genes and loci to MI (*LRP8, GCLM, TNFSF4, LTA, GCLC, ESR1, OLR1, F7, PSMA6, ITGB3, MIAT, LGALS2*) should be considered provisional. The expansion of investigation for individual whole risk can beneficially start from comprehensive phenotype investigation, including evaluation of comorbidities, exposures to high risk environment, disease mapping clinical monitoring, and family studies exploring both events and risk factors.

Family History of Coronary Artery Disease

A positive family history, a nonmodifiable risk factor, is the sum of the low effect of multiple genetic variants and familial environmental risk factors. Gender-related imprinting contributes to family-related risk: the paternal history of MI may simply reflect the higher prevalence of MI in males, whereas the less common maternal history of MI carries a higher risk.[258] A gender-related parental effect also includes risk factors such as type 1 diabetes,[259] suggesting the involvement of imprinted genes. The relative risk of MI is higher in individuals with one or more affected first-degree relatives and further increases when relatives are affected at earlier ages[260] (Figs. 9–9 and 9–10). Studies in twins demonstrated a higher risk of coronary death after one twin died of premature CAD.[261] Twin studies also contributed to highlighting genetic factors[262,263] and dissecting genetic and environmental-related risk. Nonetheless, precise estimation of family-related risk remains difficult in clinical practice because its contribution is subject to classification errors and bias, as well as descriptive ability and recall of participants.

For risk factors such as cigarette smoking, metabolites associated with smoking behaviors could provide more precise data than those obtained by counting the number of cigarettes per day or packs per year,[264] facilitating accurate partition of components of positive family history, family-related environment, and entirely exogenous factors.

Familial environment can contribute to the risk. Dietary styles are influenced by familial lifestyles. The first quarter of an individual's life is spent within family; thereafter, each individual may either maintain the familial lifestyle or modify his or her habits. Well-balanced diets (plant- vs meat-based diets, intake of polyunsaturated fatty acids, low salt consumption) are protective; even factors such as salt taste, which is partially under genetic control,[265] can be regenerated[266] and therefore be modifiable. Regular, moderate exercise is protective against acute MI. Early childhood attitude to sport influences exercise levels throughout life: monozygotic twins demonstrated long-term familial aggregation of adherence to exercise.[267] Parental use of tobacco and reduced family cohesiveness are essential components of positive preteen attitudes toward smoking; family-based interventions can prevent children and adolescents from starting to smoke.[268] Common infections cluster in families and institutions, and the relationship between MI and chronic infections caused by *Helicobacter pylori*, cytomegalovirus, *Chlamydia pneumoniae*, hepatitis viruses, or oral pathogens is still a matter of debate.[269-271] Certain infections may influence systemic inflammation and therefore contribute to atherothrombosis.[272]

Factors that may influence the risk of, or protect from CAD, include (1) low-dose input of different genes playing roles in known pathways with biological plausibility with respect to current knowledge on risk and events and (2) pathways without immediate biological plausibility (ie, transcription factors and increased risk of MI).[272] The occurrence of MI in individuals without traditional risk factors highlights the existence of powerful, still unknown mediators that play their role independently of, or in addition to, the underlying coronary ATS. Genetic risk of CAD as a whole may not coincide with the genetic risk of MI. Studies distinguishing MI series from coronary atherosclerosis series demonstrated risk loci in patients with angiographic CAD (eg, the 15q25.1 ADAMTS7 locus) but not MI, as well as risk loci shared by both CAD and MI (9q34.2 ABO locus).[273,274] Replicated studies support the role of genes partaking in coagulation or inflammatory pathways, or of chromosomal loci in which still unknown candidate genes map. In a recent meta-analysis, patients with coronary atherosclerosis who carry the high-risk genotype of the 9p21-3 allele may be more likely to have multivessel CAD[275]; at present, SNP markers in the 9p21 chromosomal locus seem to be robust GWAS signals for CAD risk.[276] These data are not translated into current clinical practice.

GENE-ENVIRONMENT INTERACTIONS

Individuals who are genetically predisposed to MI (positive family history) but not exposed to acute or chronic environmental risk factors may not develop MI, and vice versa. Genetic predictors of minor risk in the overall population may predict a high risk in specific subsets of individuals as a result of gene-environment interactions, including cigarette smoking, infections, meals, and drugs. For example, the *CYP2B6* allele seems to increase the risk of tobacco dependence throughout adolescence.[277] The rs1051730 (C/T) SNP, which is a tag for multiple variants in the *CHRNA5-CHRNA3-CHRNB3* gene cluster, is associated with an increased risk of death in smokers[278] and variants in Rho-GTPase pathway genes seem to exert their effects in early-onset CAD.[279] Recent epigenome-wide methylation studies demonstrated that DNA hypomethylation in certain genes is associated with tobacco exposure.[219,280] Specific methylation markers may show gradual reversal

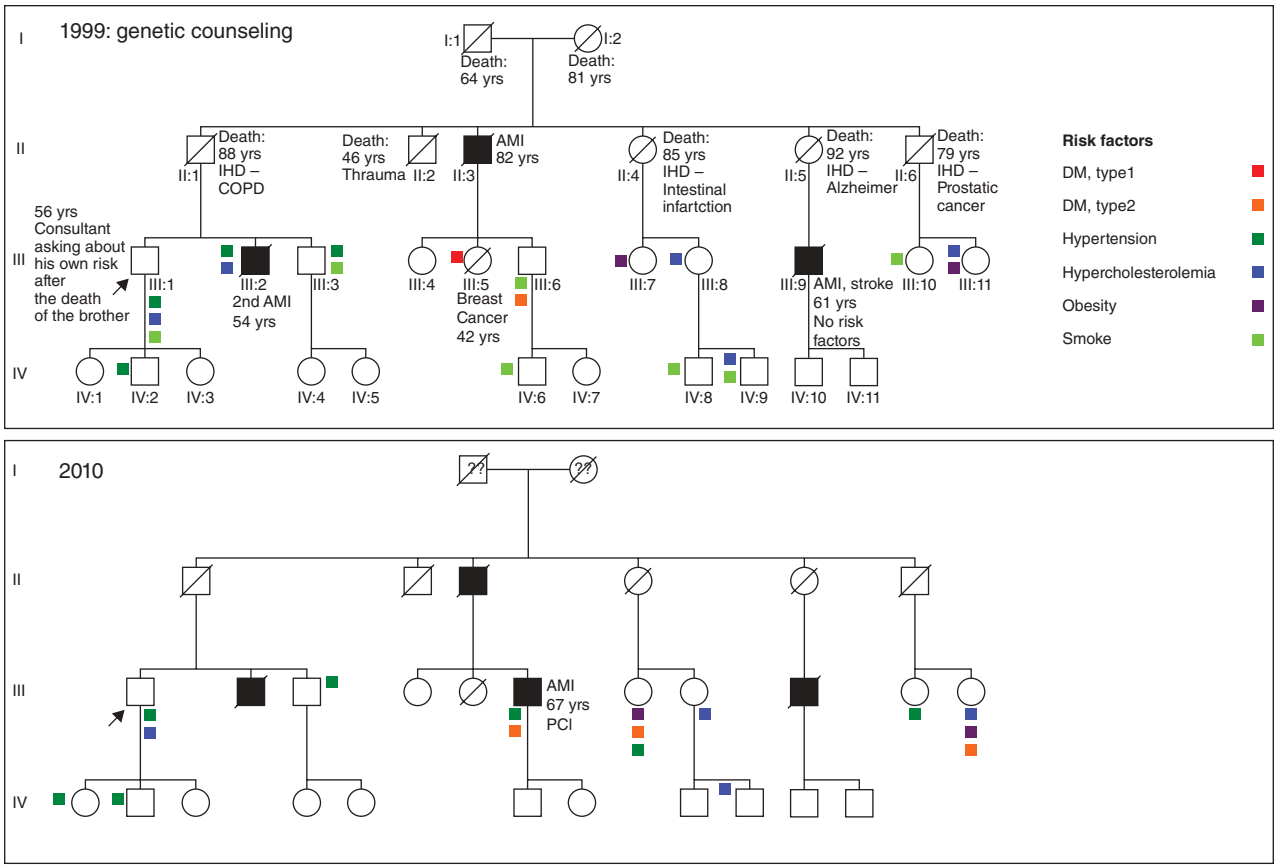


FIGURE 9–9. Routine genetic counseling and educational impact. 1999, the consultant (⟶ III:1), with hypertension, dyslipidemia, and tobacco use, asks about his risk of acute myocardial infarction (AMI) after the second and fatal AMI of his brother (III:2), who has hypertension and dyslipidemia but who was younger and a nonsmoker. His risk stratification included the three risk factors plus the nonmodifiable family history and gender. In 2010, he came again asking about his risk after the AMI of the cousin (III:6), who was regularly treated for both hypertension and type 2 diabetes mellitus (DM). He had stopped smoking after counseling and was treated for hypertension and hypercholesterolemia; the overall risk was lower but his age was greater (67 years). Of the six smoking members of the family, five stopped smoking. One with obesity and hypercolesterolemia (III:11) developed type 2 DM and one (IV:1) developed hypertension. COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease.

of methylation levels from those typical of current smokers to those have never smoked.[281] DNA methylation may also be associated with modulation of the risk related to diabetes mellitus, with *TXNIP* gene methylation being associated with sustained hyperglycemia levels (HbA1c ≥ 7%).[282]

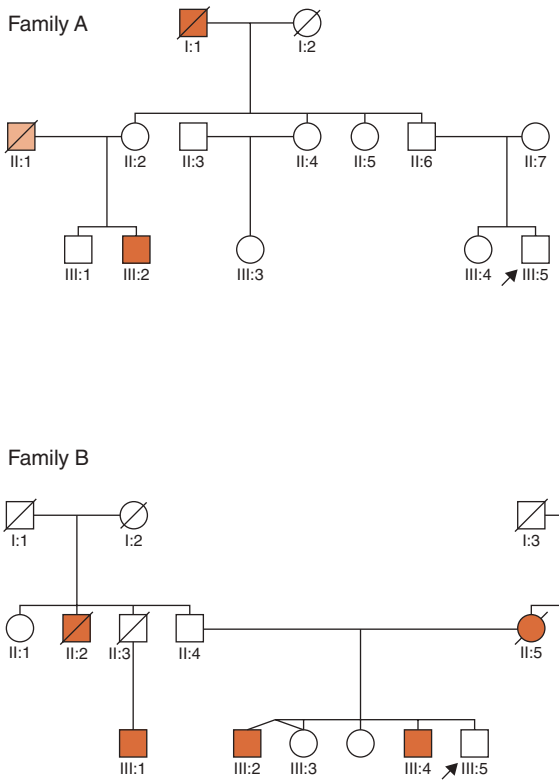
FUTURE DEVELOPMENTS

The awareness of clinical and molecular genetics in multifactorial diseases is modifying models of care and introducing novel outpatient models for genetic investigation,[283] including systematic genetic testing in phenotypically characterized high-risk patients (such as children with hypercholesterolemia),[284] and is expanding information on genetic risk of CAD and conventional risk estimates to patients.[285] Family history and deep phenotyping of patients and relatives may contribute to characterize correlations between genetic risk and overall risk, events, and outcome. New, targeted treatments are becoming available for subgroups of patients with well-characterized phenotype and genotype. These include gene-based agents, eg, mipomersen, approved in the United States for homozygous familial hypercholesterolemia; and Glybera, AAV1-LPLS447X gene therapy, conditionally approved in Europe for lipoprotein lipase deficiency[286] in carriers of null *LDLR* mutations who are at increased risk, even in the setting of early diagnosis and regular lipid-lowering treatments.

PERSPECTIVES

The burden of known and emerging heritable cardiovascular diseases is increasing, as a result of the translation of precise diagnosis of both deep phenotyping and genetic causes. The majority of these diseases were previously thought to have genetic bases, but many of them were simply included in the broad group of phenotypically similar disorders (such as CMPs, aortopathies, and lone AF, among others).

The tremendous progression of molecular genetics is now calling for a similar effort in deep phenotyping of different genetic cardiovascular diseases, with the major aim of characterizing specific disorders caused by mutations in different genes. This action includes systematic clinical family screening when patients are recognized as affected by a potential genetic disease. Genetic rules do not differ from those of other genetic diseases. However, phenotyping requires cardiologists to go back to clinics and pursue the physical examination of patients with an interdisciplinary "disease and genetically oriented" mindset. The fast rate of gene mutation and variant detection further makes it important to know the fundamentals for interpretation of genetic tests and to assess the segregation of genotype with phenotype in families. The enthusiasm supporting this effort comes from the increasing number of targeted treatments for specific diseases and from the realization that personalized care programs can be implemented for precisely diagnosed cardiovascular diseases.



Family A	Age (yrs)	Disease	Risk factors
I:1	68	AMI	Hypertension, treated
II:1	47	SD	None
III:2	33	N-STEMI	Hypercholesterolemia
Family B	**Age (yrs)**	**Disease**	**Risk factors**
II:2	48	AMI	None known
II:5	52 → 53	ACS → PCI;SD	Borderline hypertension
III:1	59	CABG	Smoking, hypertension, hypercholesterolemia
III:2	49	AMI	None; event: while playing tennis
III:4	45	N-STEMI	DM, type2

Consulting, Family A (III:5)	Consulting, Family B (III:5)
Low familial risk when affected relative:	High familial risk when affected relative/s:
• Is non-closely related: I:1, grandfather III:5, cousin • Experienced late onset AMI (I:1) • Is/are of the more commonly affected gender • Is the only affected in the family	• Is/are closely related: II:2, mother III:4, brother III:5, brother • Experienced premature AMI • Is of the less commonly affected gender • >1 close family members are affected (II:5, III:2, III:4)

FIGURE 9–10. The two pedigrees show two family members (family A, III:5 and family B III:5), both males but with different family risk—lower in the former and higher in the latter.

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CHAPTER 10

STEM CELLS AND THE CARDIOVASCULAR SYSTEM

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INTRODUCTION

Stem cell therapy has attracted considerable interest in the treatment of cardiovascular disorders. This is driven by the observation that the heart's regenerative capacity is insufficient to recover from ischemia or other cardiotoxic insults and the progressive nature of tissue ischemia in patients with coronary artery disease or peripheral arterial disease (PAD). Directed homing of bone marrow–derived stem cells after myocardial injury produced functional improvements in animal studies,[1,2] leading to the hypothesis that enhancing mobilization of bone marrow stem cells or their direct delivery can result in clinical improvement in acute or chronic cardiac injury. Similarly, evidence supporting the incorporation of circulating and bone marrow–derived progenitor cells into newly formed vasculature in limb ischemia models supported the premise that enhanced progenitor cell delivery can reverse tissue ischemia.[3,4]

Improvements in our understanding of stem cell biology, cardiac differentiation, and response to cardiovascular injury have advanced the field of cardiac cell therapy.[5,6] These findings have led to numerous studies investigating the efficacy of multiple bone marrow stem cell lineages and other stem cell sources on cardiovascular recovery. To date, no stem cell therapy is approved by the Food and Drug Administration for a cardiovascular indication, but the growing body of literature provides a promising signal to encourage multiple Phase III clinical trials. This chapter will examine the clinical experience and potential applications of stem cell therapy by reviewing each stem cell lineage (Table 10–1).

MECHANISMS UNDERLYING STEM CELL THERAPY

There are multiple mechanisms by which stem cells may exert a beneficial effect in the cardiovascular system (Fig. 10–1), but some common themes are important to highlight. First, the mechanism by which any stem cell lineage exerts a potential benefit in humans is not yet fully explained. Second, the inability to track stem cells or perform histopathological studies in human subjects impairs the ability to determine cell fate and mechanism of action. Third, most of the mechanisms hypothesized to play a role in the salutatory effect of stem cells are derived from animal models. Lastly, it is unknown (and unlikely) that all stem cell lineages exert their effect on the human cardiovascular system via the same mechanism.

Differentiation is the concept that stem cells form new cardiomyocytes to replace the ones that are lost in injury. This mechanism is now largely accepted to contribute minimally, if at all, to any improvement associated with cardiac functional recovery. Although pluripotent stem cells (PSCs), such as embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) have a robust potential to differentiate into cardiomyocytes, the differentiation capacity of other stem cell lines is more limited.[7] For example, bone marrow–derived stem cells demonstrate lineage commitment that predisposes them to divide into hematopoietic cells. But to divide into cardiomyocytes, they must *transdifferentiate*, which involves reversing their lineage commitment to a new somatic cell type. This process may occur in animals (and possibly in humans) endogenously throughout the course of lifetime,[7,8] but it is less likely to be a significant contributor to myocardial improvement as shown by the limited survival of these cells from studies involving direct intramyocardial injections of bone marrow–derived stem cells.[9-11]

Cell fusion is a phenomenon in which stem cells fuse with native cardiomyocytes and form a more functional cardiomyocyte that is capable of remodeling or regeneration. This infrequent phenomenon is hypothesized to contribute to a favorable remodeling response and has been validated in animal studies.[12,13] However, it remains unknown to what extent this occurs in the human studies performed.

Angiogenesis is the process of new blood vessel formation and is known to be defective in both ischemic and nonischemic cardiomyopathy patients as well as patients with PAD.[14] Thus, enhancing angiogenesis should improve blood flow in those conditions. However, whether stem cells can directly differentiate into new blood vessels or promote new blood vessel formation by secretory factors is currently controversial.[15,16]

Paracrine effects refer to changes to the myocardial or vascular environment driven by stem cells that may promote cardiovascular recovery or regeneration. These changes may be conveyed by changes in cytokines, growth factors or interstitium. This is currently the most accepted mechanism of benefit for all bone marrow–derived cell therapies due to the following reasons: (1) this hypothesis is in

TABLE 10–1. Summary of Stem Cell Types Used for Cardiac Applications

Category	Cell Type	Advantages	Disadvantages	Tested Clinically
Adult stem cells	Adipose-derived stem cells	Autologous cell population	Limited proliferation potential	Yes
		Involve relatively less invasive procedures	Inefficient or limited cardiac differentiation potential	
	Bone marrow mononuclear cells			Yes
	Mesenchymal stem cells			Yes
	Angiogenic progenitor cells			Yes
	Skeletal myoblasts			Yes
Cardiac progenitor cells	Cardiac stem cells	Improved cardiac differentiation potential	Procured by relatively invasive procedures	Yes
		Autologous cell population		
	Cardiosphere-derived cells			Yes
Pluripotent stem cells	Embryonic stem cells	Robust cardiac differentiation potential	Allogeneic transplant requires immunosuppression	Ongoing
			Raises ethical concerns	
			Cardiomyocytes have immature phenotype	
			Concern for uncontrolled differentiation leading to malignancy	
	Induced pluripotent stem cells	Robust cardiac differentiation potential	Cardiomyocytes have immature phenotype	No
		Autologous cell population	Concern over viral immune reaction or genetic integration into host genome, leading to genetic abnormalities or malignancy	

line with bone marrow cellular mobilization observed in ischemic and postinfarction patients; (2) cell tracking studies suggest that stem cells persist only for a brief period of time in the myocardium, with typically less than 1% survival at 4 weeks; and (3) animal studies show that cell extracts from stem cell cultures can exert a favorable effect on injured myocardium.[17]

Lastly, a novel concept in cardiac repair is modulation of dedifferentiation. Dedifferentiation is the process by which cardiomyocytes take on a gene and protein expression profile that is more similar to fetal cardiomyocytes or pluripotent stem cells.[18,19] This phenotype occurs more frequently in acute and chronic injury of the heart and seems to confer a potential survival advantage of these cardiomyocytes.

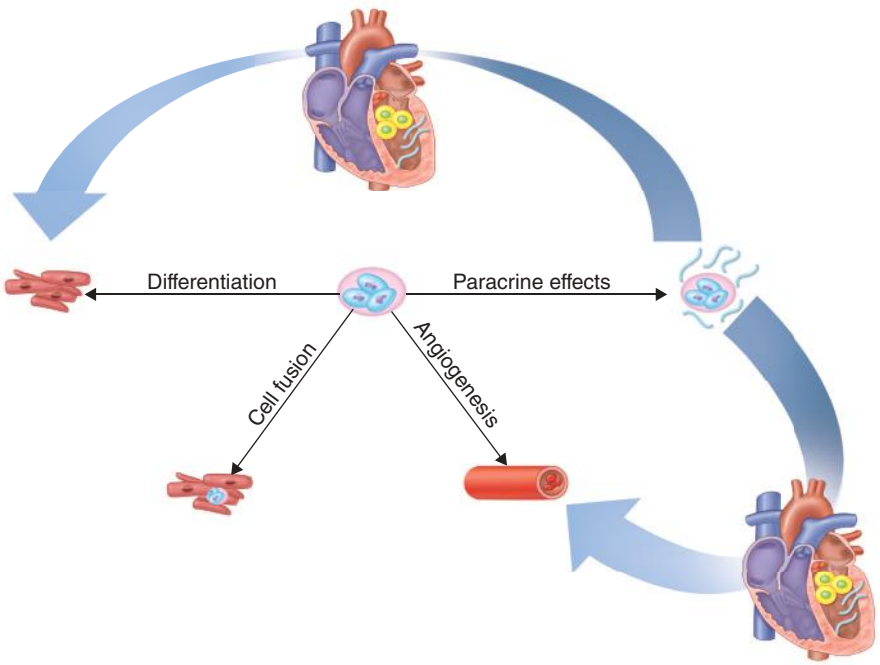

FIGURE 10–1. Possible mechanisms of stem cell–mediated cardiac recovery. Differentiation is the process of stem cell fate commitment to various cell lineages, including cardiomyocytes. Cell fusion occurs when the stem cells fuse with native cardiomyocytes to induce remodeling. Angiogenesis entails stem cells differentiating into new blood vessels. Paracrine effects are induced by stem cell–secreted factors and/or changes in the cardiac interstitium that may promote intrinsic progenitor cells to differentiate into new cardiomyocytes or make new blood vessels.

Furthermore, this early progenitor profile may increase the number of endogenous cardiomyocytes capable of dividing to replace lost cardiomyocytes. Prolonged activation of this phenomenon, however, may be deleterious and contribute to adverse cardiac remodeling. Cardiac dedifferentiation may serve as a future target for cardiac regeneration therapy.

METHODS OF CELL DELIVERY

Clinically tested methods of cell delivery include using blood as a carrier of stem cells to myocardium, by directly injecting the cells into the target tissue, and tissue engineering constructs. Blood-based approaches include intracoronary arterial infusion, intracoronary venous infusion, peripheral intravenous infusions, and peripheral arterial infusion. Intramyocardial delivery methods include surgical epicardial injection (transepicardial), catheter-based endocardial injection by accessing the left ventricular cavity (transendocardial), and injection by accessing the coronary venous circulation (transvenous myocardial). Direct injection in the case of PAD entails transcutaneous injection into ischemic tissue (most often lower limb). There are a host of tissue engineering constructs that deliver progenitor cells or cardiomyocytes to the cardiovascular system.[20] These methods constitute biological delivery systems of progenitor cells taking advantage of natural or synthetic chemicals to create a scaffold that can support the growth of progenitor cells (Table 10–2).

Intracoronary delivery is usually performed during cardiac catheterization after the coronary artery is engaged. Cells are infused into the artery with or without balloon inflations to interrupt flow and slow down stem cell washout from the myocardium. The advantages of intracoronary delivery are (1) it is technically easier, (2) it directly targets perfused areas of the myocardium where stem cells can survive, and (3) it does not require mapping or identification of viability. The disadvantages of this delivery method include the following: (1) it requires access to patent coronary arteries; (2) cells will be preferentially shunted to well-perfused areas, which means that ischemic or border zones will receive fewer cells; and (3) it has reduced retention compared to intramyocardial delivery.[21]

Transendocardial delivery aims to inject stem cell populations directly into the myocardium via a needle catheter by accessing the left ventricular (LV) cavity through the arterial system. This method is aided by electromechanical or magnetic resonance imaging guidance, which is necessary to identify target areas of injection. The cells are injected in healthy, ischemic or border zones—but not infarct zones. Infarct zones are nonperfused and therefore stem cells are unlikely to survive to exert a therapeutic benefit. Additionally, infarct zones are made up of thin scar tissue that is susceptible to perforation. Advantages of transendocardial delivery include the ability to target stem cells to ischemic or border zones and better cellular retention. Disadvantages of the delivery method include the technical complexity (especially if electromechanical mapping is done), cell leakage at injection site, and a higher risk of cardiac perforation or arrhythmia.[22]

Transepicardial delivery involves the surgical injection of stem cells by direct visualization into the myocardium, often in conjunction with other cardiac surgery procedures such as coronary artery

TABLE 10–2. Overview of Cardiac Delivery Methods for Stem Cell Therapies

Delivery	Description	Major Advantages	Major Disadvantages
Intravenous	Stem cells infused into peripheral or central venous circulation and home to injured myocardium	Minimally invasive	Poor myocardial retention of cells
Intracoronary arterial	Stem cells released into the blood after engagement of coronary artery with slow infusion or using serial balloon inflations to slow washout of injected cells	Can be done in conjunction with percutaneous coronary intervention Technically simpler and shorter procedure compared to transendocardial Stem cells reach perfusing areas thus enhancing survival	Requires patent coronary arteries Coronary flow to ischemic and border zones is reduced and thus cell delivery is limited to those areas Reduced retention compared to transendocardial delivery
Intracoronary venous	Stem cells released into the blood of the coronary venous system	Avoids stenotic or occluded coronary arteries	Coronary venous system more difficult to access and map
Transendocardial delivery	Stem cells injected into the myocardium via needle delivery through arterial catheter access of the left ventricle. Target areas are identified using imaging or electromechanical mapping.	Improved delivery to ischemic or border zones Improved myocardial cell retention compared to intracoronary	More complex and time-intensive procedure compared to intracoronary delivery Cell leakage at injection site Higher risk of myocardial perforation
Transepicardial delivery	Stem cells injected into the myocardium by epicardial needle injections during cardiac surgery	Ischemic and infarct zones can be visualized without mapping	Risk of cardiac surgery make this approach limited to those who have another indication for cardiac surgery
Transvenous myocardial delivery	Stem cells injected into the myocardium via needle delivery through a catheter that enters the cardiac venous system	Parallel injections may allow for higher cell retention Lower risk of cardiac perforation	Technically challenging Limited clinical experience
Tissue engineering	Stem cells grown on a biological scaffold are applied directly to the epicardium during cardiac surgery	Enhanced cell survival and delivery to injured myocardium	Potential reaction to biological scaffold material Requires cardiac surgery to be applied
In situ activation of resident stem cells	Chemical or genetic "activators" are delivered to enhance the activity of endogenous stem cells	No cell harvest, isolation, or expansion involved	Yet to be tested clinically

bypass graft (CABG) surgery. During the surgical injection, visual assessment of the myocardium is often used to determine the target sites for injection. However, the invasive nature of cardiac surgery limits the use of this method to patients undergoing concurrent cardiac surgery.[23]

A recent clinical trial compared intracoronary versus intramyocardial (transendocardial) delivery using radiolabeled $CD34^+$ cells in patients with non-ischemic cardiomyopathy.[24] The transendocardial group showed a higher rate of cardiac signal retention 18 hours postinjection. At the 6-month follow-up, the investigators observed a greater improvement in left ventricular ejection fraction (LVEF) for the transendocardial group. Additionally, the results suggested that *early* engraftment as detected by imaging can be used to predict *late* functional outcome, similar to results that were initially reported in animal models.[25] However, it is unknown whether these results can be extrapolated to all stem cell lineages or for other cardiac conditions such as acute myocardial infarction (AMI). Nevertheless, these studies highlight the potentially important role that molecular imaging may play in optimizing some of the delivery approaches for cardiac stem cell therapy.[26]

Another promising approach to cell therapy is endogenous activation of cardiac progenitor cells in host myocardium. This in situ approach entails delivery of viral or nonviral constructs that carry genetic or chemical signals that stand to activate resident stem cells in the cardiovascular system. This approach has shown positive results in animal models, but further studies are needed to validate and refine this approach for clinical testing.[27,28]

SKELETAL MYOBLASTS

Skeletal myoblasts are skeletal muscle precursor cells derived from skeletal muscle satellite cells. Interest in this population was supported by similarity to adult cardiomyocytes, the potential for autologous utilization, ease of expansion in vitro, and resistance to hypoxic environment. This lead to a series of early clinical studies that transplanted skeletal myoblasts into small cohorts of ischemic cardiomyopathy patients.[29-34] Subsequently multiple randomized double-blind placebo-controlled trials examined the broader safety and efficacy of skeletal myoblast in ischemic heart disease. The largest such study was the Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial, which randomized patients to high or low dose injection of skeletal myoblasts or placebo during CABG.[35] There was a small reduction in LV volumes in the high dose group at 6 months, but otherwise no difference in regional or global LV function. However, there was a higher incidence of ventricular arrhythmias in myoblast-treated patients. Three similar studies utilized a cardiac mapping system for transendocardial injections of skeletal myoblasts in ischemic cardiomyopathy patients.[36-38] These studies showed a small improvement or trend toward improvement in described functional status but no significant differences in systolic function, LV dimensions, or 6-minute walk tests.

The increased incidence of arrhythmia seen in the MAGIC trial and a large pilot study[39] raised significant concern about the long-term safety of skeletal myoblast therapy. This is further supported by histological analysis of skeletal myoblast–treated heart tissue showing islands of myotubes that are not electrically coupled to host myocardium.[40] Collectively, the clinical and histopathological findings along with animal studies showing increased arrhythmia[41] have tempered interest in this cell population for the treatment of myocardial disorders.

BONE MARROW MONONUCLEAR STEM CELLS

The bone marrow harbors a heterogeneous population of progenitor cells that give rise to mainly hematopoietic or endothelial cells. This is essentially a mixture of multiple stem cell lineages, and many of these populations were later isolated and investigated separately. Interest in bone marrow–derived mononuclear cells (BMMNCs) for cardiac repair was sparked by observations in animal studies that a subpopulation of bone marrow cells mobilize to the heart after myocardial infarction (MI), express early cardiac markers, and improve cardiac function.[1,2] Some animal studies indicated possible improvements after injecting BMMNCs in postinfarct animals.[1,2] These observations supported a hypothesis that bone marrow–derived cells might participate in myocardial recovery or regeneration. The unsorted population of BMMNCs was particularly attractive during the early cell therapy experience because of their relative accessibility via bone marrow biopsy, minimal sorting and processing, and experience utilizing the cells in bone marrow transplantation. With the realization that these progenitor cells mobilize in peripheral blood, some investigators attempted to harvest the progenitor cells from peripheral blood or unprocessed bone marrow extract, but most studies relied on bone marrow biopsy–derived mononuclear cells. The majority of clinical experience in cardiac stem cell trials to date remains with BMMNCs.

ACUTE MYOCARDIAL INFARCTION

Some of the earliest studies investigating the efficacy of BMMNCs in improving cardiovascular outcomes targeted patients with AMI. This was an attractive indication because of the acute and dramatic nature of cell loss and damage that occurs in the postinfarct period and the potential attenuation benefits of this response.[42] The trials largely targeted patients with ST elevation MI and treated them with intracoronary infusion of BMMNCs. The initial clinical experience was largely limited to single arm or nonrandomized trials.[43-48] These studies reported an improvement in LV systolic function and/or infarct size 3 to 6 months after cell therapy infusion and few safety issues.

These relatively positive early results led to a series of randomized controlled studies testing the safety and efficacy of BMMNCs (Table 10–3). Given the known risks associated with the coronary infusion process and bone marrow biopsy, these trials were not blinded, and they compared two arms of cell therapy or utilized a nonplacebo control. In other words, control patients underwent optimal standard of care without undergoing bone marrow biopsy or sham intracoronary infusion procedures. This nonuniform exposure to risk in the cell therapy group sometimes resulted in a higher number of periprocedural complications such as increases in cardiac biomarkers of injury or stent thrombosis. Nevertheless, these events did not translate into a significant difference in overall incidence of major serious adverse events. However, in terms of efficacy, the trials provided mixed results with respect to improvement in LVEF, LV volumes, and infarct or scar size. Even positive results were inconsistent as to the specific parameters that were improved among these studies.[49-63]

The third generation studies included randomized placebo-controlled studies that aimed to strengthen blinding and to add a placebo control arm as an alternative to the optimal medical therapy control arm that was utilized previously. These studies validated the safe nature of the bone marrow harvest and intracoronary infusion procedure but unfortunately have not provided a conclusive answer

TABLE 10–3. Summary of Major Randomized Controlled Trials of Bone Marrow–Derived Mononuclear Cells in Acute Myocardial Infarction

Study	Cell Type	Delivery Method	Study Design	Size	Follow-Up	Results of Cell Therapy Treatment	Serious Adverse Events
Wollert et al[55] (BOOST)	BMMNCs	Intracoronary	Randomized controlled study	60	6 months	Improved LVEF and regional contractility; no change in LV volumes	No[a]
Janssens et al[64]	BMMNCs	Intracoronary	Randomized double-blind placebo-controlled study	67	4 months	Reduction in infarct size, but no difference in LVEF	No[a]
Kang et al[205] (MAGIC-3 DES)	Circulating Progenitor Cells	Intracoronary	Randomized controlled study	96	6 months	Improved LVEF, reduced LVESV in acute MI group; no difference in old MI group	No[a]
Schachinger et al[65] (REPAIR-AMI)	BMMNCs	Intracoronary	Randomized double-blind placebo-controlled study	204	4 months	Improved LVEF and reduced composite end point of death, recurrence MI, and revascularization	No[a]
Lunde et al[52] (ASTAMI)	BMMNCs	Intracoronary	Randomized controlled study	97	6 months	No difference in LVEF, LV volumes, or infarct size	No[a]
Ge et al[56] (TCT-STAMI)	BMMNCs	Intracoronary	Randomized controlled study	20	6 months	Improved LVEF and perfusion	No[a]
Penicka et al[58]	BMMNCs	Intracoronary	Randomized controlled study	27	4 months	No difference in LVEF, infarct size, or LV volumes between groups.	Two patients suffered severe complications periharvest or infusion procedures and died
Meluzin et al[59]	BMMNCs	Intracoronary	Randomized controlled study	60	12 months	Improved LVEF in high-dose BMMNCs group, but no change in regional contractility.	Six patients experienced periprocedural complications Rate of restenosis no different between groups
Tendera et al[60]	BMMNCs or CD34+ CXCR4+ Cells	Intracoronary	Randomized controlled study	200	6 months	No significant difference in LVEF between groups	No[a]
Yao et al[63]	BMMNCs	Intracoronary single and repeat administration	Randomized placebo-controlled study	39	12 months	Improved LVEF and reduction in infarct size in repeat administration group	No[a]
Cao et al[66]	BMMNCs	Intracoronary	Randomized placebo-controlled study	86	4 years	Improved LVEF, LVESV and regional contractility; no difference in infarct size or LVEDV	No[a]
Nogueira et al[50]	BMMNCs	Intracoronary artery or vein	Randomized controlled study	30	6 months	No change in LVEF, regional contractility or LV volumes	Three cases of periprocedural cardiac enzyme elevation, one case of sudden death, and four cases of restenosis
Piepoli et al[62] (CARDIAC)	BMMNCs	Intracoronary	Randomized controlled study	38	12 months	Improved LVEF, peak VO2 and impedance measured cardiac output; no change in LV volumes	No[a]
Wohrle et al[67]	BMMNCs	Intracoronary	Randomized double-blind placebo-controlled study	42	7 months	No significant change in LVEF or LV volumes	No[a]
Grajek et al[61]	BMMNCs	Intracoronary	Randomized controlled study	45	12 months	Improved perfusion but no change in LVEF or LV volumes	Composite end point of death, acute MI, need for revascularization occurred more often in control group
Roncalli et al[51]	BMMNCs	Intracoronary	Randomized controlled study	101	3 months	No significant difference in myocardial viability, LVEF, or regional contractility.	No[a]
Hirsch et al[57] (HEBE)	BMMNCs or PBMCs	Intracoronary	Randomized controlled study	200	4 months	No change in LVEF, perfusion, or LV volumes	Three patients developed recurrent MI related to infusion, otherwise no significant difference in composite adverse events.

(*continued*)

TABLE 10–3. Summary of Major Randomized Controlled Trials of Bone Marrow–Derived Mononuclear Cells in Acute Myocardial Infarction (*Continued*)

Study	Cell Type	Delivery Method	Study Design	Size	Follow-Up	Results of Cell Therapy Treatment	Serious Adverse Events
Traverse et al[68] (LateTIME)	BMMNCs	Intracoronary	Randomized double-blind placebo-controlled study	87	6 months	No difference in LVEF, LV volumes, infarct volume, or regional contractility	Nov
Traverse et al[70]	BMMNCs	Intracoronary	Randomized double-blind placebo-controlled study	40	6 months	Reduced LVEDV but no change in LVEF	No[a]
Traverse et al[69] (TIME)	BMMNCs	Intracoronary	Randomized 2 × 2 factorial, double-blind, placebo-controlled study	120	6 months	No change in LVEF or regional contractility	Nov
Sürder et al[54]	BMMNCs	Intracoronary	Randomized controlled study	200	4 months	No change in LVEF	No[a]

[a]No significant difference in serious adverse events among groups or no major adverse events reported.

Abbreviations: BMMNC, bone marrow mononuclear cell; LV, left ventricle; LVED, left ventricular end-diastolic dimension; LVESV, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PBMC, peripheral blood mononuclear cell; VO2, maximal oxygen consumption.

to the efficacy question.[64-70] Several meta-analyses have attempted to combine data to determine efficacy but have likewise yielded mixed results.[41,71,72]

Several hypotheses have been generated to explain the conflicting results of the trials: the relatively small number of patients, variation in timing of cell infusion, differences in number of cells infused, and different modalities of measuring LV function and dimensions. Another important criticism of the studies is the appropriateness of the surrogate end point used to test for efficacy, namely LV size or function. For example, although angiotensin-converting enzyme (ACE) inhibitors provide superior survival benefit over hydralazine-nitrate in patients with heart failure and reduced LVEF, hydralazine-nitrates provide a greater improvement in LVEF, highlighting the limitation of using surrogate end points.[73] Thus, the more relevant question is whether BMMNC therapy provides a hard outcome improvement in AMI that would justify the associated risks and resources committed similar to other approved therapies such as percutaneous coronary intervention or use of thiopyridine antagonists. To answer this question conclusively, a 3000-patient multicenter randomized clinical trial, the Effect of Intracoronary Reinfusion of BMMNC on All Cause Mortality in Acute Myocardial Infarction (BAMI), is being conducted by European Union scientists, with an expected completion date in the spring of 2018 (retrieved from http://clinicaltrials.gov/ct2, identification NCT01569178).

CHRONIC HEART FAILURE

The use of BMMNCs for the treatment of chronic heart failure began with pilot studies that aimed to determine their safety, similar to studies for AMI indication.[74-84] The studies were mostly positive, showing a mix of symptomatic, contractile, and perfusion improvements regardless of the method of injection at follow-up intervals of 3 to 12 months. This led to multiple randomized trials to confirm efficacy, but the results thus far have been mixed (Table 10–4).[85-95]

In contrast to the AMI trials, in which cell delivery was largely intracoronary, the method of delivery in chronic heart failure trials included both intracoronary infusion and intramyocardial injections. A number of trials randomized ischemic cardiomyopathy patients undergoing CABG to receive injections of BMMNCs versus standard surgery. No single delivery method seemed to predict a consistent response or lack of response to delivered BMMNCs. The trials primarily targeted ischemic cardiomyopathy, and those that showed positive results found a small improvement in end points such as LVEF and New York Heart Association (NYHA) class. Interestingly, a randomized controlled study of nonischemic patients showed improvement in imaging parameters and functional status.[96] The safety profile of these studies collectively was once again reassuring. Meta-analysis of chronic heart failure studies did not yield a definitive answer to the question of efficacy.[97,98] Thus, the main conclusion that can be drawn from these studies is that treatment is largely safe and well tolerated, but larger studies will be needed to answer the question of efficacy of BMMNCs in cardiomyopathy patients.

PERIPHERAL ARTERIAL DISEASE

BMMNCs are the most tested cell therapy for the treatment of PAD (Table 10-5). The first pilot study to investigate the safety and efficacy of cell therapy in PAD examined the injection of BMMNCs versus peripheral blood mononuclear cells (PBMCs) into the gastrocnemius muscle of patients with chronic limb ischemia (CLI). The limbs injected with BMMNCs showed significant improvement in ankle brachial index (ABI), transcutaneous oxygen pressure ($TcPO_2$), rest pain, and pain-free walking time.[99] Subsequently, multiple randomized trials tested the safety and efficacy of BMMNCs in patients with PAD with conflicting results (Table 10–5).[100-109] Collectively, the data appear to point toward a small favorable response of measures such as ABI or $TcPO_2$, but end points such as amputation-free survival did not differ between groups. Two meta-analyses that used rigorous methodological standards concluded there is insufficient evidence for benefit of BMMNCs for the treatment of PAD.[110,111]

The majority of studies utilized intramuscular (IM) injection of cell therapy with a minority using intra-arterial (IA) injection. Klepanec et al randomized PAD patients to IM versus IA injection of BMMNCs and observed comparable improvements in quality-of life-questionnaire, $TcPO_2$ and pain scale in both groups.[107] Terra et al tested the effect of repeated IA infusion of BMMNCs against placebo in 161 patients with critical limb ischemia. After 6 months there was no difference in the primary end point of amputation-free survival or all-cause mortality.[109] There was no increased risk of adverse events associated with BMMNCs in randomized trials.

TABLE 10–4. Summary of Major Randomized Controlled Studies Utilizing Non–Bone Marrow Mononuclear Cells in Acute Myocardial Infarction

Study	Cell Type	Delivery Method	Study Design	Size	Follow Up	Results of Cell Therapy Treatment	Serious Adverse Events
Chen et al[118]	Bone marrow–derived mesenchymal stem cells	Intracoronary	Randomized placebo-controlled study	69	6 months	Improved LVEF, regional contractility, perfusion, and LV volumes	No[a]
Bartunek et al[134]	CD133+ cells	Intracoronary	Randomized controlled study	35	4 months	Improved LVEF and perfusion	Cell therapy group showed increased incidence of ventricular tachycardia and significant in-stent restenosis or new lesions in infusion artery
Hare et al[125] (prochymal)	Allogeneic mesenchymal stem cells	Intravenous infusion	Randomized double-blind placebo-controlled study	53	6 months	No difference in LVEF or 6-MWD	No[a]
Quyyumi et al[135]	CD34+ cells	Intracoronary	Randomized controlled study	31	6 months	Improved perfusion in high-dose cell group; no change in LVEF	More minor adverse events in cell therapy group but no difference in major adverse events
Houtgraaf et al[159] (APOLLO)	Adipose tissue derived regenerative cells	Intracoronary	Randomized double-blind placebo-controlled study	14	6 months	Reduction in infarct size in cell therapy group; no difference in LVEF	Significant bleeding with liposuction in two patients requiring change in anticoagulation/antiplatelet protocol; otherwise no significant difference
Makkar et al[171]	Cardiosphere-derived cells	Intracoronary	Randomized controlled study	25	6 months	Reduction in scar mass and improved regional contractility, but no change in LVEF	One patient in cell therapy group suffered NSTEMI, possibly related to infusion, but overall incidence of serious adverse events not different from control group
Gao et al[120]	Bone marrow–derived mesenchymal stem cells	Intracoronary	Randomized controlled study	43	2 years	No significant difference in LVEF or perfusion	One case of acute coronary artery occlusion during cell infusion procedure
Lee et al[119]	Bone marrow–derived mesenchymal stem cells	Intracoronary	Randomized controlled study	58	6 months	Improved LVEF	No[a]
Gao et al[129]	Wharton's jelly–derived mesenchymal stem cells	Intracoronary	Randomized, placebo-controlled study	116	18 months	Improved LVEF, LV volumes, and perfusion	No[a]

[a]No significant difference in serious adverse events among groups or no major adverse events reported.

Abbreviations: LV, left ventricle; LVEF, left ventricular ejection fraction; 6-MWD, 6-minute walk distance.

MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) are a population of stromal progenitor cells that are capable of differentiating into multiple cell types, including osteoblasts, adipocytes, and skeletal myocytes.[112-114] Initially thought to reside in the bone marrow, they have later been shown to exist in other organs.[115] Furthermore, animal studies have suggested that MSCs can differentiate into cardiac progenitors and improve cardiac function in infarct models,[10,116] sparking an interest in clinical application of MSCs for cardiac regeneration. MSCs are relatively accessible via bone marrow biopsy and can be autologous. MSCs have the added advantage of homing to injured myocardial tissue, which facilitates intravenous administration.[117] Lastly, MSCs are reported to be immune privileged, and this raises the possibility of using Allogeneic MSC populations. The clinical experience with MSCs is limited compared to BMMNCs, but the results to date are arguably more promising (see Table 10–3; Table 10–6).

ACUTE MYOCARDIAL INFARCTION

One of the earliest studies testing bone marrow–derived MSCs in a randomized fashion was by Chen et al, who randomized post-MI patients to receive MSCs or saline via intracoronary injection.[118] The MSC-treated group showed an improvement in LVEF and a reduction in infarct size. Lee et al saw a similar improvement in LVEF with intracoronary infusion of bone marrow–derived MSCs.[119] These results diverged from negative findings by Gao et al, who randomized AMI patients to receive intracoronary infusion of bone marrow–derived MSCs versus standard therapy.[120] Possible reasons for discordance among these studies may relate to differences in number of cells injected and timing of administration post-MI. Similar to the early studies of BMMNCs, one can conclude that MSC therapy has a reasonable safety profile, but larger trials are needed to test efficacy.

PERIPHERAL ARTERIAL DISEASE

The experience with MSCs in the treatment of PAD is limited to date but preliminary results appear to be positive (Table 10-5). Two randomized studies evaluated the safety and efficacy of bone marrow–derived MSCs in patients with CLI. At 12 weeks, both studies showed a signal toward improvement in the cell therapy group in terms of ulcer healing rate, and one study showed a decrease in amputation rate.[121,122] Subsequently, in a randomized double-blind placebo-controlled study, Gupta et al saw a similar improvement in ABI but not ulcer healing.[123] The comparative effectiveness of bone marrow–derived MSCs against BMMNCs was tested in a randomized study of 41 patients with CLI

TABLE 10–5. Summary of Major Randomized Control Trials Investigating Stem Cell Therapies in Peripheral Arterial Disease

Study[a]	Cell Type	Delivery Method	Study Design	Size	Follow-Up	ABI	TcPO2	Walking Time, Pain, or QOL	Wound Healing	Amputation
Tateishi-Yuyama et al[99]	BMMNCs	IM	Randomized controlled study	22	24 weeks	+	+	+		
Huang et al[100]	GCSF mobilized PBMCs	IM	Randomized controlled study	28	3 months	+			+	+
Arai et al[101]	Bone marrow aspirate vs GCSF vs control	IM	Randomized controlled study	39	1 month	Improvement in ABI, TcPO2, and wound healing in BM and GCSF groups				
Debin et al[122]	BMMSCs	IM	Randomized controlled study	50	12 weeks	+			+	+
Dash et al[121]	BMMSCs	IM	Randomized controlled study	24	12 weeks			+	+	
Procházka et al[102]	BMMNCs	IM	Randomized controlled study	96	120 days	-	-			+
Walter et al[103]	BMMNCs	IA	Randomized double-blind placebo controlled study	40	3 months	-		+	+	–
Lu et al[124]	BMMNCs vs BMMSCs vs control	IM	Randomized controlled study	41	6 months	BMMSC superior to BMMNC with respect to wound healing, painless walking, ABI, and $TcPO_2$				–
Benoit et al[104]	BMMNCs	IM	Randomized double-blind placebo-controlled study	48	6 months					-
Iafrati et al[105]	Bone marrow aspirate	IM	Randomized double-blind placebo-controlled study	48	12 weeks	–		–		–
Perin et al[150]	Aldehyde dehydogenase bright cells vs BMMNCs	IM	Randomized double-blind study	21	12 weeks	(Aldehyde dehydogenase bright cells showed an improvement in Rutherford category and ABI)				
Ozturk et al[106]	GCSF mobilized PBMCs	IM	Randomized controlled study	40	12 weeks	+	+	+	+	–
Powell et al[210]	Ixmyelocel-T	IM	Randomized double-blind placebo-controlled study	72	12 months	(Time to composite of death/amputation/gangrene or doubling of wound area) lower in Ixmyelocel-T				
Klepanec et al[107]	BMMNCs	IM vs IA	Randomized study	41	6 months	Improvement in IM and IA groups				
Losordo et al (ACT34-CLI)[211]	CD34+ Cells	IM	Randomized double-blind placebo-controlled study	28	12 months					–
Gupta et al[123]	BMMSCs	IM	Randomized double-blind placebo-controlled study	20	6 months	+		–		
Li et al.[108]	BMMNCs	IM	Randomized single-blind placebo-controlled study	58	6 months	+		+	+	
Szabo et al[151]	Circulating angiogenic progenitor cells	IA	Randomized controlled study	20	2 years	+ (at 3 and 24 months)	+ (at 3 and 24 months)			+ (at 3 months)
Raval et al[152]	CD133+ cells	IM	Randomized double-blind placebo-controlled study	10	12 months			-		–
Terra et al[109]	BMMNCs	Multiple IA	Randomized double-blind placebo-controlled study	160	6 months	–	–	–		-

+ indicates significant improvement in end point in cell therapy group.

– indicates no improvement or no difference in improvement in end point among groups.

Abbreviations: ABI, ankle brachial index; BMMNC, bone marrow mononuclear cell; BMMSC, bone marrow–derived mesenchymal stem cell; IA, intra-arterial injection; IM, intramuscular injection; PBMCs, peripheral blood mononuclear cells; QOL, quality of life (questionnaire); TcPO2, transcutaneous oxygen pressure.

and the results demonstrated improved outcomes in the bone marrow–derived MSCs group.[124] Multiple randomized trials are currently underway to further test the potential of this population in the treatment of PAD (retrieved from http://clinicaltrials.gov/ct2, identification NCT01456819, NCT01257776, NCT01351610, NCT02145897, NCT02336646, NCT02304588). Some of the trials target patients with intermittent claudication, which represents an earlier stage of ischemic disease and possibly better potential for tissue salvage.

ALLOGENEIC MESENCHYMAL STEM CELLS

Given the immune-privileged properties of MSCs, this opens the door to Allogeneic transplantation. Allogeneic transplantation has the advantage of having the cell therapy population ready in advance for clinical use so called "off the shelf" delivery. Several efforts have investigated the potential for Allogeneic bone marrow–derived MSCs. In a randomized double-blind placebo-controlled trial, Hare et al treated

TABLE 10–6. Summary of Major Randomized Control Trials Investigating Stem Cell Therapies in Cardiomyopathy

Study	Cell Type	Delivery Method	Study Design	Size	Population	Follow Up	Results of Cell Therapy Treatment	Serious Adverse Events
Lai et al[93]	BMMNCs	Intracoronary during CABG	Randomized controlled study	44	ICM undergoing CABG	48 hours	BMMNCs no different from cardioplegia in cardiac enzyme leak or cardiac function	No[a]
Pokushalov et al[87]	BMMNCs	Transendocardial	Randomized controlled study	109	ICM	6 months	Improved mortality, LVEF, perfusion, CCSC, and NYHA class	No[a]
Perin et al[90] (FOCUS-HF)	BMMNCs	Transendocardial	Randomized single-blind controlled study	30	ICM	6 months	Improved angina class and MLHFQ; no change in LVEF	No[a]
Hu et al[92]	BMMNCs	Intracoronary during CABG	Randomized double-blind placebo-controlled study	60	ICM	6 months	Improvement in LVEF, LVESV, regional contractility, 6-MWD and BNP	No[a]
Turan et al[206]	Bone marrow extract	Intracoronary	Randomized controlled study	56	ICM	12 months	Improvement in LVEF, infarct size, NYHA class and BNP level	No[a]
Bolli et al[170] (SCIPIO)	Cardiac stem cells	Intracoronary	Randomized controlled study	33	ICM	12 months	Improvement in LVEF, regional contractility and viability	No[a]
Perin et al[137]	Bone marrow–derived aldehyde dehydrogenase bright stem cells	Transendocardial	Randomized double-blind placebo-controlled study	20	ICM	6 months	Reduction in LVESV, no change in LVEF, MVO2, and perfusion	No[a]
Perin et al[89] FOCUS-CCTRN	BMMNCs	Transendocardial	Randomized double-blind placebo-controlled study	92	ICM	6 months	No difference in LVESV index, MVO2, and perfusion	In the cell therapy group, one patient experienced aortic dissection related to cell delivery procedure, two patients experienced death caused by pump failure and delayed myocardial infarction
Maureira et al[94]	BMMNCs	Intramyocardial during CABG	Randomized controlled study	14	ICM undergoing CABG	6 months	Increased perfusion mainly in patients with pre-operative viability.	No[a]
Honold et al[207]	Circulating progenitor cells or GCSF	Intracoronary	Randomized study	32	ICM	3 months	Improved regional contractility, no change in LVEF or NYHA class	No[a]
Hare et al[126] (POSEIDON)	Bone marrow–derived autologous versus allogeneic mesenchymal stem cells	Transendocardial	Randomized study	30	ICM	13 months	Autologous MSCs improved 6-minute walk test and MLHFQ. Allogeneic MSCs reduced LVEDV. Both reduced infarct size.	Two patients in allogeneic group showed sensitization at 6-month time point. No difference in serious adverse events between groups
Vrtovec et al[149]	Bone marrow–derived CD34+ cells	Intracoronary	Randomized controlled study	110	NICM	5 years	Improved LVEF, 6-MWD, and decreased NT-pro BNP	No[a]
Assmus et al[86] (CELLWAVE)	BMMNCs	Intracoronary	Randomized double-blind placebo-controlled study	103	ICM	4 months	Improved LVEF, regional contractility, and MACE in shock-wave and BMMNCs infusion group	In shock wave therapy group, one patient suffered NSTEMI, one required implantation of defibrillator, one suffered TIA, and one patient suffered a groin hematoma requiring surgical intervention

(*continued*)

TABLE 10–6. Summary of Major Randomized Control Trials Investigating Stem Cell Therapies in Cardiomyopathy (*Continued*)

Study	Cell Type	Delivery Method	Study Design	Size	Population	Follow Up	Results of Cell Therapy Treatment	Serious Adverse Events
Heldman et al[130] (TAC-HFT)	BMMNCs or mesenchymal stem cells	Transendocardial	Randomized double-blind placebo-controlled study	59	ICM	1 year	MSCs improved perceived functional capacity, 6-MWD, infarct size and regional contractility BMMNCs improved perceived functional capacity Neither improved LV volumes or EF	No[a]
Nasseri et al[145]	Bone marrow–derived CD133+ cells	Intramyocardial during CABG	Randomized double-blind placebo-controlled study	60	ICM undergoing CABG	6 months	Cell therapy group had lower LVEF despite better myocardial perfusion at rest, but no difference in scar mass, 6-MWD, angina or HF severity	No[a]
Ascheim et al[128]	Allogeneic mesenchymal precursor cells	Intramyocardial during LVAD implantation	Randomized double-blind placebo-controlled study	30	ICM or NICM undergoing LVAD implantation	12 months	No significant difference in development of donor HLA antibodies between groups; no difference in LVEF or ability to temporarily wean LVAD	No[a]
Perin et al[160] (PRECISE)	Adipose tissue–derived regenerative cells	Transendocardial	Randomized double-blind placebo-controlled study	27	ICM	18 months	Improved LV mass and regional contractility and more preserved MVO_2 over time	No[a]
Perin et al[127]	Allogeneic mesenchymal precursor cells	Transendocardial	Randomized single-blind placebo-controlled study	60	ICM or NICM	3 years	No difference in MACE-free survival between groups	No[a]

[a]No significant difference in serious adverse events between groups or no major adverse events reported.

Abbreviations: BMMNC, bone marrow mononuclear cell; BNP, brain natriuretic peptide; CAB, coronary artery bypass grafting; CCSC, Canadian Cardiovascular Society class; EF, ejection fraction; HF, heart failure; ICM, ischemic cardiomyopathy; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MACE, major adverse cardiac events; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MVO2, myocardial volume oxygen; 6-MWD, 6-minute walk distance; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association functional class; TIA, transient ischemic attack.

post-MI patients with intravenous injection of allogeneic bone marrow–derived MSCs 7 to 10 days after reperfusion.[125] The study showed a trend of LVEF improvement that did not meet statistical significance. However, there was no significant increase in antibodies in response to the allogeneic cells. In the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON) study, the investigators randomized ischemic cardiomyopathy patients to receive either intramyocardial injection of autologous or allogeneic MSCs.[126] Interestingly, the autologous MSCs group showed improved 6-minute walk distance and Minnesota Living with Heart Failure Questionnaire score, whereas the allogeneic MSCs group showed a reduction in LV end-diastolic dimension. Both groups showed a reduction in infarct size. Only a minor increase in antibody response was seen in the allogeneic group.

A similar safety profile was seen by Perin et al in a dose escalation study using allogeneic MSCs in patients with ischemic or nonischemic cardiomyopathy.[127] Lastly, a surgical study utilizing allogeneic mesenchymal precursor cells was performed in advanced heart failure patients undergoing left ventricular assist device (LVAD) implantation.[128] Although imaging surrogates for cardiac recovery failed to reach statistical significance, the study demonstrated no increase in incidence of human leukocyte antigen antibodies. A larger Phase II study investigating intramyocardial injection of MSCs during LVAD implantation is currently underway (retrieved from http://clinicaltrials.gov/ct2, identification NCT02362646). Thus, the aggregate results of these studies support the safety of allogeneic bone marrow-derived MSCs as a potential cell therapy population for clinical use.

NON-BONE MARROW–DERIVED MESENCHYMAL STEM CELLS

The safe use of allogeneic stem cells opens the door to utilizing MSCs from other sources that may have superior proliferation or engraftment ability. After seeing no effect with intracoronary infusion of bone marrow–derived MSCs in AMI patients,[120] Gao et al utilized Wharton's jelly-derived MSCs for intracoronary infusion in patients with AMI.[129] Wharton's jelly is a stromal cell population derived from umbilical cord, which the investigators obtained from healthy donors after full-term birth. At 18 months, the cell therapy population showed a significant improvement in LVEF, LV volumes, and perfusion compared to controls.

COMPARATIVE EFFECTIVENESS

To compare the relative efficacy of BMMNCs against bone marrow–derived MSCs, the Transendocardial Autologous Cells in Ischemic Heart Failure Trial (TAC-HFT) investigators randomized ischemic cardiomyopathy patients to receive intramyocardial injections with either cell therapy or placebo.[130] Treatment with MSCs improved infarct size, regional contractility, 6-minute walk distance, and Minnesota Living with Heart Failure score. BMMNC-treated patients saw an improvement in Minnesota Living with Heart Failure score but none of the other parameters.

FUTURE DIRECTIONS FOR MESENCHYMAL STEM CELL STUDIES

Overall, the bone marrow–derived MSC studies are early in the phase of testing compared to the BMMNC studies but appear promising. The early studies have validated the safety profile of cell delivery procedures by widespread inclusion of placebo control groups. Furthermore, there is a sufficient signal for potential efficacy to warrant further studies. Larger studies will be needed to answer the overall question of efficacy with a focus on the optimal source of MSCs, the optimal delivery method, and appropriate indications for use.

ANGIOGENIC PROGENITOR CELLS

This population of progenitor cells mainly give rise to endothelial cells.[4] Angiogenic progenitor cells (APCs) garnered considerable interest in regenerative capacity as a result of their proposed ability to promote angiogenesis. Improving the microcirculation in theory would provide considerable benefit to patients with cardiovascular disorders because they are known to have reduced number and impaired migratory ability of APCs.[131-133] A number of clinical trials investigated the therapeutic potential of APCs for multiple cardiovascular indications, finding a potential benefit for some cardiovascular indications.

ACUTE MYOCARDIAL INFARCTION

Two studies have tested APCs in MI in a randomized fashion. Bartunek et al randomized AMI patients to receive CD133$^+$ cells via intracoronary infusion versus optimal standard therapy and reported an increase in LVEF and perfusion.[134] The study showed an increased incidence of adverse events in the cell therapy group, although it is important to point out that the control group did not undergo placebo infusion procedure. Quyyumi et al randomized AMI patients to receive variable doses of CD34$^+$ cells and reported an improvement in perfusion in patients with high dose of the cell therapy but no change in LVEF.[135] The safety profile was adequate to allow further testing of this product in larger studies.

Aldehyde dehydrogenase bright stem cells are a population of stem cells that are thought to have a significant angiogenic and ischemia protective role.[136] These cells were tested in a small randomized placebo-controlled study by Perin et al, who found a statistically significant reduction in LV end systolic volume but not in peak oxygen consumption and perfusion.[137] The trial did achieve its primary end point, which is to demonstrate the safety of the cell therapy, thus opening the door for larger studies to investigate efficacy.

ANGINA

The angiogenic potential of CD34$^+$ cells was particularly attractive in the chronic angina population and was tested in multiple case pilot studies with an overall positive therapeutic response.[138-141] In the largest cell therapy study to treat angina to date, Losordo et al randomized 167 patients with refractory angina to receive intramyocardial injections of autologous CD34$^+$ cells versus placebo.[142] The cell therapy group However, the cell therapy group also experienced a higher incidence of small elevations in cardiac biomarkers of injury associated with cell mobilization and collection procedure. Similar results were seen by Wang et al using an intracoronary delivery method.[143] Arguably, the studies for angina have yielded some of the most positive results using stem cell therapy for any indication (Table 10–7), and phase III clinical trials to validate the efficacy of CD34$^+$ cells are being planned.

HEART FAILURE

In contrast to the largely positive results seen in acute MI and angina, the experience with APCs in ischemic cardiomyopathy is more mixed (see Table 10–4). Two surgical studies investigated the effects of APCs delivered via intramyocardial injection at the time of CABG using routine surgery as the control. One of the studies utilized CD34$^+$ cells and showed an increase in LVEF compared to CABG alone at the 6-month follow-up.[144] However, injection of CD133$^+$ cells led to improved

TABLE 10–7. Summary of Major Randomized Controlled Trials Investigating the Efficacy of Stem Cell Therapy for the Treatment of Angina

Study	Cell Type	Delivery Method	Study Design	Size	Population	Follow Up	Results of Cell Therapy Treatment	Serious Adverse Events
Tse et al (PROTECT-CAD)[208]	BMMNCs	Transendocardial	Randomized double-blind placebo-controlled study	28	CAD with angina	3 months	Improved exercise time, NYHA class, LVEF, LVESV, regional contractility, and perfusion; no difference in CCSC.	No[a]
van Ramshorst et al[209]	BMMNCs	Transendocardial	Randomized double-blind placebo-controlled study	50	CAD with angina	3 months	Improved perfusion, LVEF, angina severity, and exercise time; no change in LV volumes	One death and one revascularization in cell therapy group
Wang et al[143]	CD34+ cells	Intracoronary	Randomized double-blind placebo-controlled study	112	CAD with angina	6 months	Improved angina frequency and perfusion	No[a]
Losordo et al[142] (ACT34-CMI)	CD34+ cells	Transendocardial	Randomized double-blind placebo-controlled study	167	CAD with angina	12 months	Improved weekly angina severity and exercise tolerance	Cell mobilization and collection procedures were associated with elevation in biomarkers of cardiac injury

[a]No significant difference in serious adverse events between groups or no major adverse events reported.

Abbreviations: BMMNC, bone marrow mononuclear cell; CAD, coronary artery disease; CCSC, Canadian Cardiovascular Society class; LV, left ventricle, LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association functional class.

myocardial perfusion but resulted in a lower LVEF and no difference in functional capacity.[145] This study contradicted findings from prior nonrandomized studies that investigated CD133+ cells.[146]

Patients with heart failure, including nonischemic cardiomyopathy, have been shown to have an impairment in circulating APCs,[147] which led to the hypothesis that the restoration or mobilization of this cell population might improve heart failure symptoms. Vrtovec et al conducted one of the largest randomized trial with 110 nonischemic cardiomyopathy patients randomized to receive either CD34+ intracoronary infusion or standard therapy.[148,149] At 12 and 60 months, the CD34+ treatment group showed a significant improvement in LVEF and 6-minute walk distance. Additionally, patients with higher myocardial homing of injected cells showed the greatest improvement.

PERIPHERAL ARTERIAL DISEASE

Multiple studies have examined the role of APCs in the treatment of PAD with most showing an excellent safety profile with marginal to no benefit (see Table 10–5).[142,150-152] However, several factors prevent a conclusive determination of the role of APCs in the treatment of PAD. First, these studies were relatively small and primarily were designed to determine safety rather than efficacy. Second, the studies utilized different populations of APCs and thus grouping the results may not be appropriate. A larger study is currently underway to test the efficacy of aldehyde dehydrogenase bright cells on the treatment of PAD.[153]

ADIPOSE STEM CELLS

Adipose tissue harbors a heterogeneous population of progenitor cells that are primarily mesenchymal in nature and show analogous cardiac benefits to bone marrow–derived progenitor cells.[154-157] Adipose is more abundant in mesenchymal cell population than bone marrow and can be easily obtained by liposuction techniques.[158] Two pilot studies investigated the safety of this therapy. Houtgraaf et al randomized 14 patients with anterior AMI to receive intracoronary infusion of adipose-derived regenerative cells, finding the treatment to be safe, with a trend toward small reductions in infarct size.[159] In a pilot study, Perin et al randomized 27 ischemic cardiomyopathy patients to receive transendocardial injections of adipose stem cells or placebo.[160] There were no serious adverse events, and the researchers observed a signal toward slower decline of maximal oxygen consumption in the cell therapy group, increased LV mass, and improved regional contractility. Similarly, two published Phase I studies demonstrated the feasibility and safety of adipose-derived MSCs for the treatment of PAD.[161,162] Collectively, the studies support the safety of this cell population, although more testing is needed to investigate the potential efficacy of this treatment for cardiovascular indications and compare it to bone marrow cell populations.

CARDIAC PROGENITOR CELLS

Over a decade ago, researchers reported that a group of progenitor cells residing in the heart were capable of differentiating into cardiomyocytes, endothelial, and smooth muscle cells.[163-165] Furthermore, animal models suggested that these cells can promote cardiac regeneration in infarct models.[166] The identification of these cells added to the observations challenging the notion that the heart is a terminally differentiated organ.[167,168] Follow-up studies aimed to enrich this scant cell population in hopes of augmenting myocardial regeneration or recovery. Whether the beneficial effects of cardiac progenitor cells occur because of cardiomyocyte differentiation, angiogenesis, or paracrine effects is not fully understood, and these potential mechanisms are under investigation.[169] Nevertheless, two clinical trials have now tested the safety of subtypes of this cell population.

Cardiac stem cells were isolated and tested in randomized fashion in the Cardiac Stem Cell Infusion in Patients With Ischemic CardiOmyopathy (SCIPIO) trial.[170] Bolli et al isolated cardiac stem cells from harvested cardiac tissue during CABG and later injected them via an intracoronary route. The cardiac stem cell group experienced an improvement in LVEF, regional contractility, and NYHA class. In the CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dysfunction (CADUCEUS) trial, Makkar et al tested the safety and efficacy of cardiosphere-derived cells (CDCs), which are cardiac progenitor cells that are isolated from adherent clusters of progenitor cells known as cardiospheres.[171] The authors randomized 31 post-MI patients to receive intracoronary infusion of CDCs into the culprit artery. At 1 year, the CDC-treated patients had a reduction in infarct size and regional contractility compared to control patients but no overall improvement in LVEF or functional capacity. Both studies provided sufficient evidence for safety and potential efficacy to permit larger studies for further testing. A study investigating the combination of autologous bone marrow–derived MSCs and c-kit+ cardiac stem cells in ischemic cardiomyopathy patients is currently underway (retrieved from http://clinicaltrials.gov/ct2, identification NCT02501811).

EMBRYONIC STEM CELLS

First isolated in 1998, human ESCs are PSCs that exist in the inner cell mass of early stage dividing embryo (blastocyst).[172] The pluripotency of ESCs is defined by the ability of the cells to divide into all three germ layers and their cellular derivatives. The plasticity and differentiation potential of ESCs made them an attractive target for human cardiac regeneration. The ability to direct PSCs into cardiomyocytes has evolved over the past decade. Initial techniques relied on formation of embryoid bodies followed by isolation of beating clusters, but more recently monolayer differentiation methods have enabled the creation of cardiac populations with greater than 90% purity.[173,174]

However, there are several barriers to widespread adoption of ESCs. First, these cells are derived from human embryos, the use of which is still fraught with significant ethical concerns. Second, the robust differentiation potential of ESCs also carries a potential risk of uncontrolled differentiation that could result in neoplastic tumors.[175,176] Third, ESC derivatives are considered allogenic transplants, with a potential to provoke an immune response.[177,178] This means that the therapeutic use of ESCs may require use of immunosuppressive drugs, which are associated with significant risks of their own. Nonetheless, there have been some small endeavors in utilizing human ESC derivatives for noncardiac indications (mostly ESC-derived retinal pigment cells), all showing a good safety profile so far.[179,180]

The first study utilizing ESC-derived cardiac progenitor cells for patients with severe cardiomyopathy undergoing CABG is underway, with an estimated study completion date in June 2017 (retrieved from http://clinicaltrials.gov/ct2, identification NCT02057900).[181] This study employs the surgical implantation of a fibrin patch embedded with ESC-derived cardiac progenitor cells, which is one of many tissue engineering approaches under study to improve cell delivery and electromechanical coupling.[20,182,183]

INDUCED PLURIPOTENT STEM CELLS

In 2006, a pioneering paper by Shinya Yamanaka described induction of pluripotency from mouse somatic cells by transfecting them with a retrovirus carrying the pluripotency-associated transcription factors Oct3/4, Sox2, c-Myx, and Klf4.[184] This process was replicated with human fibroblasts a year later,[185] commencing the widespread

adoption of induced pluripotent stem cells (iPSCs). The mechanism underlying this process involves reprogramming somatic cells, such as skin fibroblasts or PBMCs, to express pluripotency transcription factors that allow them to acquire a pluripotent phenotype that closely resembles ESCs. The reprogramming can be driven by viruses, plasmids, microRNA, or proteins.[186] By inducing the adult cells to express major markers of pluripotency, iPSCs take on a phenotype very close to ESCs and are capable of differentiating into all three germ layers and subsequent stem cell types. As a potential source of cardiomyocytes for regenerative therapy, the cells bypass the ethical concerns associated with ESCs and can be used for autologous transplantation, hence lowering the risk of a significant immune response.[187] However, the most efficient reprogramming methods rely on viral vectors, which bring additional concerns of viral immune response (eg, Sendai virus) and integration into recipient genome (eg, lentivirus) that could result in malignant transformation. The first clinical trial utilizing iPSC-derived retinal pigment epithelial cells for treatment of macular degeneration commenced in Japan in 2014 (retrieved from http://www.who.int/ictrp/en/, WHO ICTRP JPRN-UMIN000011929). However, the study was temporarily halted (now restarted) as a result of single nucleotide variations and three copy-number variants identified in the second patient's iPSCs that were not detectable in the original fibroblasts.[179] To date, no human clinical trial utilizing iPSCs for cardiac regeneration is yet underway.

Independent of their regenerative potential, iPSCs have emerged as a powerful investigation tool in studying cardiovascular diseases driven by the fact that the cells are patient-specific, allowing them to express the underlying genome of the original somatic cell donor. This suggests that iPSC-derived cardiomyocytes (iPSC-CMs) can be surrogates for in vivo cardiomyocytes of the original somatic donor. This concept has led to multiple studies testing the ability of iPSC-CMs to recapitulate disease phenotype in a dish, and results thus far have shown a good correlation with clinical phenotype of long QT syndrome,[188-190] catecholaminergic polymorphic ventricular tachycardia,[191] arrhythmogenic right ventricular cardiomyopathy,[192] dilated cardiomyopathy,[193-195] dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular non-compaction,[197] and doxorubicin induced cardiotoxicity.[198] This technology provided the first reliable source of human-like cardiomyocytes that can be used for basic science studies, which have long relied on animal models for such investigations. In addition, iPSC-CMs are emerging as a superior platform for drug cardiac safety testing compared to heterologous expression models,[199,200] and they are being considered as part of the Comprehensive in Vitro Proarrhythmia Assay (CiPA) Initiative.[199] Furthermore, by providing a precision medicine platform for patients with hereditary cardiac disorders, this technology is expected to provide predictive power for improving screening, diagnosis, risk stratification or drug responses (Fig. 10–2).[202-204]

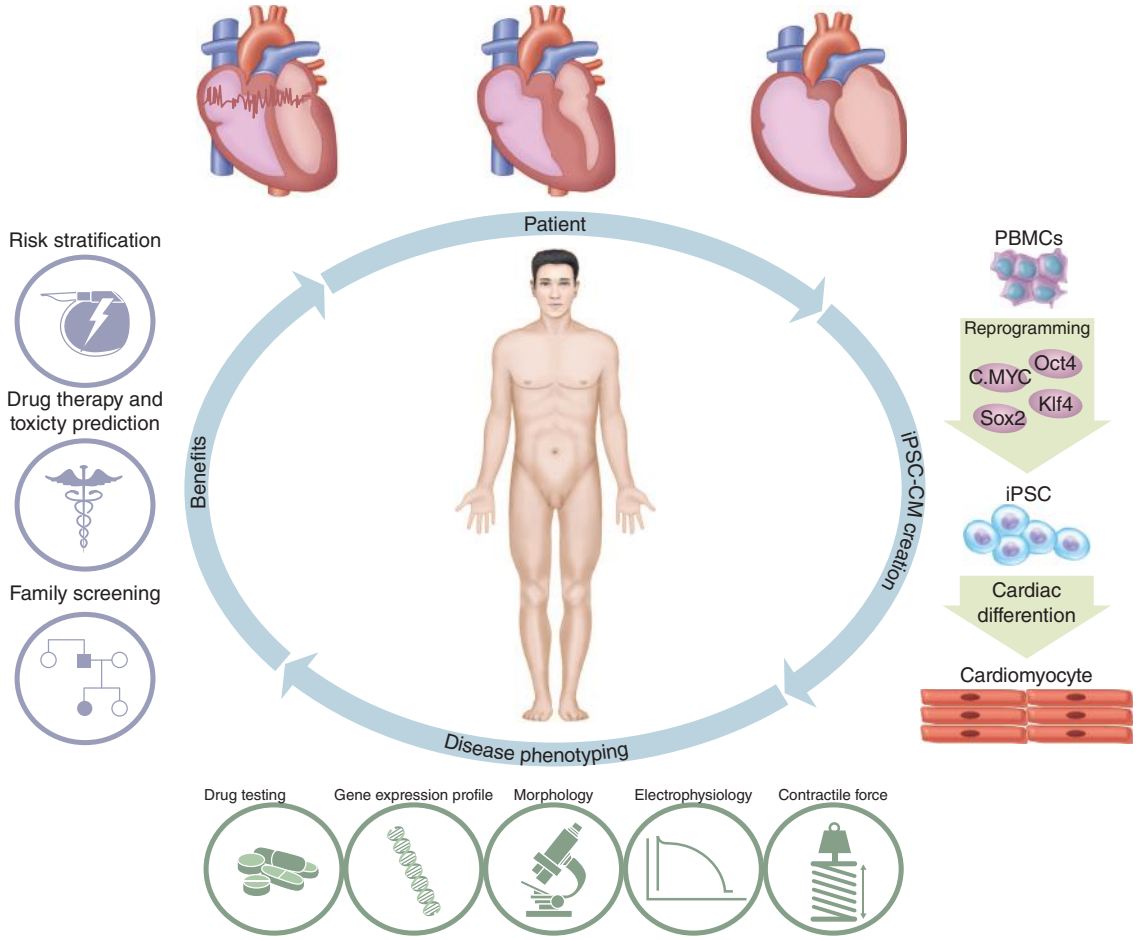

FIGURE 10–2. Future role that induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) can play in the clinical care of patients with hereditary cardiac disorders. The iPSC-CMs can be profiled using molecular, electrical, and mechanical measures as well as their responses to different pharmacological agents. These data can help provide input on the predicted severity of disease, associated risks, and response to therapy, which can be used to complement clinical decision making. In addition, functional characterization of the tissue might help elucidate causative candidate variants and assist in screening family members for the disease. PBMCs, peripheral blood mononuclear cells; iPSCs, induced pluripotent stem cells. Reproduced with permission from Sallam K, Kodo K, Wu JC: Modeling inherited cardiac disorders, *Circ J.* 2014;78(4):784-794.

CONCLUSIONS

The past decade witnessed a spurt in studies using stem cell therapy approaches for cardiovascular regeneration. More than 100 studies have been published using various subtypes of stem cells, delivery methods, and study populations. BMMNCs show mixed results in AMI, chronic heart failure, and PAD clinical trials, but they are currently under testing in a large Phase III study for AMI in Europe. $CD34^+$ cells appear to show an efficacy signal in treating chronic angina symptoms and will be tested in a Phase III study. MSCs and cardiac progenitor cells show encouraging preliminary results that promoted larger studies to test efficacy for cardiovascular indications. The first human ESC-derived cardiac progenitor cell trial is now underway. Fortunately, the most consistent finding of all these studies collectively is the relative safety of cell therapy and associated procedures. Moving forward, major efforts are needed to consolidate individual endeavors into larger, more rigorous clinical trials that aim to answer the question of efficacy through robust morbidity and mortality outcomes and not surrogate end points. Implementing mechanistic approaches to identify optimal stem cell type, delivery method, and indication will also be important in guiding the design of future clinical trials. The growing burden of cardiovascular disease for health care systems and societies worldwide speaks to the urgent need for new therapies to overcome the significant limitations of available medical and surgical therapies. The current science and clinical data support an optimistic view that stem cells will play a role in the treatment for cardiovascular disorders.

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CHAPTER 11

THE HISTORY, PHYSICAL EXAMINATION, AND CARDIAC AUSCULTATION

William R. Miranda and Rick A. Nishimura

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We are in danger of losing our clinical heritage and pinning too much faith in figures thrown up by machines. Medicine will suffer if this tendency is not checked.—Paul Wood (1950)[1]

INTRODUCTION

The history and physical examination have always been the cornerstone of the evaluation of the patient with known or suspected cardiovascular disease. In the past five decades, there has been an unprecedented development and implementation of cardiovascular diagnostic modalities, which provide high-resolution, real-time images of cardiac structure and measurements of cardiac function. The new generation of cardiovascular specialists is now relying more and more on the results of these tests to make clinical decisions, with decreasing emphasis on teaching and performing a proper history and physical examination. However, optimal patient care should use cardiovascular testing to confirm and supplement the clinical impression based on the history and examination—not replace it.

The initial interview with the patient is a necessity that has not changed over the decades. A properly taken history not only provides the richest source of clinical information regarding a patient's illness but is key to understanding the effect of the illness on the patient and family as well as individual needs and preferences. This knowledge, as well as the compassion and empathy that the physician can extend to the patient and family during this initial interaction, is of great importance not only in the clinical decision making but also in forming a trustful patient-physician relationship. It is important to always listen to patients. There are frequently subtle clues to the diagnosis that may be revealed by careful interrogation, but many times other clues are spontaneously brought forth by patients themselves. Finally, patients now present with multiple medical problems in addition to the cardiovascular problem, and a thorough history will provide insight into any contribution of noncardiac causes to the new onset or exacerbation of symptoms.

With the widespread availability of cardiac imaging, there has been an evolution in the detail and focus of the physical examination. It is no longer necessary to be able to obtain all the necessary information from the examination, because the imaging modalities will provide diagnostic and hemodynamic results with a greater degree of certainty and accuracy than even a master clinician can achieve. For instance, maneuvers performed on a patient with a diastolic rumble to differentiate mitral stenosis from an Austin-Flint murmur are no longer relevant; the question is easily answered from a comprehensive two-dimensional and Doppler echocardiogram. The severity of mitral stenosis is much more accurately obtained from a transmitral Doppler gradient as opposed to the subjective assessment of the A2-opening snap interval on the examination.

However, a well-performed physical examination is necessary to provide an initial clinical impression of the type and severity of cardiac disease as well as its effect on the patient. The subsequent diagnostic studies should then be used to confirm or refute this initial impression, and the final diagnosis can only be made if there is a concordance of the two. No test is 100% reliable, and many results are dependent on the performance of the test and interpretation of the data. The history and examination should be used to determine a "pretest probability" to which the results of the test can be applied.[2] For instance, a patient with symptoms and physical examination findings consistent with severe aortic stenosis but a low gradient on Doppler echocardiography represents discordant data. The clinician must be aware of the limitations of echocardiography, such as when a Doppler beam is not well aligned with the velocity jet, resulting in underestimation of the severity of stenosis. In this case, the results from the echocardiogram should be questioned, and further testing with either transesophageal echocardiography or cardiac catheterization will be required. Alternatively, a patient with a nonischemic cardiomyopathy may have the diagnosis of severe mitral regurgitation due to a large jet of mitral regurgitation on color flow imaging, but a barely audible apical murmur on physical examination will refute this diagnosis.

Several books dedicated to physical examination have been published, and our intent is not to replicate their work. We wish to present

an approach to the physical examination of correlating relevant findings on examination with key findings from our newer diagnostic modalities. It is essential to understand the underlying pathophysiology of the cardiac disease to guide optimal patient care. The findings on a well-performed physical examination provide not only diagnostic information but are also a window to normal and abnormal hemodynamics. The components of the examination when coupled with direct hemodynamic assessment by either Doppler echocardiography or cardiac catheterization provide the clinician with a tremendous overview of the hemodynamic effect of the disease on the cardiovascular system. When one hears a third heart sound at the bedside in a patient with heart failure, automatically a high E velocity on a transmitral Doppler velocity curve or a rapid filling wave on left ventricular invasive catheterization hemodynamic tracings should be expected. The paradoxical splitting of the second heart sound in a patient with hypertrophic cardiomyopathy should match the marked prolongation of ejection time produced by a pressure overload on the left ventricle from the dynamic obstruction. Only that way (ie, with a multimodality approach combined with clinical observations) can correlations between concordant/discordant clinical/imaging findings be made to provide the optimal patient care.[3] Our goal in this chapter is to provide a practical, contemporary approach to history taking and physical examination, correlating the findings to hemodynamic and imaging data from echocardiography and cardiac catheterization.

HISTORY

OVERVIEW

The clinical history is the cornerstone of the evaluation of patients with cardiovascular disease. However, like any other skill, taking a proper history requires practice and a methodology. Several things should be avoided. First, patients should always to be allowed to speak. Clinicians tend to interrupt their patients only minutes into the interview; this limits the amount of information a patient can provide and compromises the patient-provider relationship. Secondly, open-ended questions should be used initially ("how would you describe your chest pain?" versus "is the pain sharp?") and then directed questions used afterward to avoid influencing the patient's response. Thirdly, the examiner must confirm interpretation of the patient's description of symptoms. For example, angina pectoris due to myocardial ischemia can have multiple descriptions, such as pain, pressure, tightness, ache, burning, shortness of breath, or even an "uncomfortable feeling." The basic characteristics of each symptom should also be recorded: quality; location; severity; tempo (onset and progression); and aggravating or alleviating factors, including response to medications. Lastly, watch for gestures or body language to provide ancillary data; a classic example is the *Levine sign*—the clinched fist over the precordium suggesting angina as the cause of the chest pain.

We will briefly review the approach to the cardiac history. However, a comprehensive history should include past medical history, prior surgeries (extremely important in patients with valvular or congenital heart disease), social history (smoking, illicit drugs, and alcohol use) and family history (familial cardiomyopathies, sudden death, aortopathies, and aortic dissection). An important pertinent aspect of a patient's history should include the status of dental care, especially in patients being considered for intervention using prosthetic valves or material. Finally, it is of great importance to determine patients' emotional and physical reaction to their cardiac disease and how it is affecting their lives and their family's lives.

SPECIFIC SYMPTOMS

Chest Pain

Assessment of the etiology of chest pain is one of the most difficult tasks in the practice of cardiology. Given the adverse cardiovascular events associated with coronary artery disease, the main concern of a clinician is to rule in or rule out myocardial ischemia as the underlying cause. If details regarding the patient's pain (or discomfort) are not properly gathered, overtesting is frequently performed (biomarkers, exercise tests, or even coronary angiography) or other equally life-threatening entities might be missed (such as pulmonary embolus or aortic dissection). Not uncommonly, clinicians forego the description of patient symptoms, essentially jumping from the chief complaint ("chest pain") to the laboratory testing and imaging.

The duration of the symptoms is important in patients with chest pain. Angina typically lasts less than 5 minutes and will improve after exertion is discontinued or nitroglycerin taken; symptoms should not last more than 30 minutes unless coronary thrombosis with myocardial infarction has occurred. The chest pain in these patients with stable exertional angina occurs in response to an increase in myocardial oxygen demand; so it is precipitated by exertion, emotion, cold temperature and is worse after heavy meals. Rarely, patients will report that angina improves with continued exercise (ie, walk-through angina). Chest pain lasting hours and days without signs of myocardial injury/ischemia (troponin elevation or electrographic changes) significantly argues against angina. There is usually a progression in patients with coronary artery disease, with gradually increasing frequency of angina pectoris brought on by less and less exertion. However, plaque rupture will occur on top of hemodynamically insignificant lesions,[4] with the abrupt onset of rest discomfort in the absence of a recent progression of symptoms or even in the absence of a prior history of angina or cardiac disease.

Forrester and Diamond[5] categorized chest pain into *typical angina* (all three criteria were present), *atypical angina* (two criteria), and *noncardiac chest pain* (only one criterion). They based this classification on whether the pain (1) was substernal and pressure-like, (2) was precipitated by exertion or emotional stress and (3) was relieved by rest or nitroglycerin and lasted less than 30 minutes. In certain patient populations (eg, elderly men), this approach yielded such a high pretest probability of coronary artery disease that stress testing was unnecessary for the diagnosis of coronary atherosclerosis. This continues to be of value in clinical practice, particularly for male patients. It is commonly stated that women often present with atypical symptoms and the diagnosis of myocardial ischemia may be missed using these classic criteria. However, data suggest that anginal symptoms might be similar in men and women and that the concept of females frequently presenting with atypical symptoms might be misleading.[6] There are other etiologies of chest pain that require urgent diagnosis and intervention. These include but are not limited to aortic dissection, penetrating aortic ulcers, and pulmonary embolism. Table 11–1 provides specific characteristics of chest pain history according to the different etiologies; these are generalizations and may not apply to an individual patient, but application of these criteria is helpful in forming an initial impression of the etiology of the pain and can then direct the clinician to further targeted testing.

Dyspnea

The onset, progression, and triggers of dyspnea or breathlessness should be recorded. Shortness of breath that is cardiac in nature is usually exertional, and continuous dyspnea at rest is usually noncardiac unless there

TABLE 11–1. Characteristics of Chest Pain According to Different Etiologies

Etiology	Quality/Precipitating and Relieving Factors	Onset/Duration	Location/Radiation
Angina	Pressure, heaviness, tightness; precipitated by exertion or emotional stress; relieved by rest or nitroglycerin	Duration less than 10 minutes, typically 2 to 5 minutes; concern for myocardial infarction if it lasts more than 30 minutes	Substernal; typically radiates to arms and shoulders (left more commonly than right), jaw or neck
Pericarditis	Sharp, pleuritic, positional; relieved by sitting or leaning forward	Insidious onset; lasts hours or days	Substernal; might radiate to left shoulder
Aortic dissection	Tearing, ripping; typically severe at onset	Sudden onset	Anterior chest; radiates to the back or interscapular area
Pulmonary embolism	Sharp, pleuritic	Sudden onset	Typically ipsilateral to the involved lung
Costochondritis	Dull, occasionally sharp; may be reproduced by local pressure	Insidious onset; might last for days	Sternal/parasternal
Gastroesophageal reflux	Burning, worse in the supine position; relieved by antacids	Typically 10 to 60 minutes in duration, often postprandial	Substernal, epigastric
Esophageal spasm	Pressure, tightness; might improve with nitroglycerin	Sudden onset; duration less than 30 minutes	Substernal
Psychiatric	Vague, may simulate angina; often associated with anxiety	Variable duration and onset; might last hours or days	Variable; might be substernal

are signs on physical examination of severe fluid overload. Patients may describe a need to take deep breaths at rest; that symptom is rarely cardiac in origin. Pulmonary symptoms such as cough, wheezing, and sputum production suggest a noncardiac etiology. This is also suggested by very intermittent worsening or oscillating in symptoms ("good days and bad days"). However, fluid congestion from a cardiac etiology can result in features of bronchospasm as the initial manifestation.

Positional changes are important to document; orthopnea and paroxysmal nocturnal dyspnea suggest heart failure as the cause of the patient's dyspnea. True paroxysmal nocturnal dyspnea occurs several hours after a patient lays down, because there is redistribution of fluid from the venous capacitance vessels into the central circulation. Patients will feel agitated, need to sit up, and seek cold fresh air, with the dyspnea taking 10 to 15 minutes to subside. Patients who wake up at night feeling short of breath but are better within seconds after a few deep breaths do not have paroxysmal nocturnal dyspnea. Platypnea-orthodeoxia[7] (worsening dyspnea and hypoxia in the sitting position) can be seen in patients with intracardiac shunting (either through an atrial septal defect or patent foramen ovale[8]) or in hepatopulmonary syndrome.

Syncope

A thorough history is vital in the evaluation of patients with syncope and, perhaps, the best diagnostic tool for the evaluation of those patients. The circumstance of the syncopal spell (how the patient was feeling earlier that day or the day before) as well as warning and/or postictal symptoms should be noted. The combination of diaphoresis, nausea, prolonging standing, and exposure to warm places suggests a vasovagal etiology. Situational causes of syncope should be sought, such as micturition or bowel movements. Positional changes, in particular orthostatic changes, leading to syncope are important and suggest orthostatic hypotension as the underlying cause; this is particularly important in elderly. Exertional syncope is usually due to a structural abnormality with obstruction to outflow (aortic stenosis, hypertrophic cardiomyopathy), especially when the syncope occurs just after the cessation of exertion. Exertional syncope in pulmonary hypertension is rare, but it is a very ominous sign, typically seen in young females. Syncopal spells without any warning unrelated to exertion are particularly concerning for a cardiac arrhythmia and are of high concern in patients with diseases such as hypertrophic cardiomyopathy in which there is an underlying substrate for ventricular arrhythmias.

Palpitations

The duration, onset and offset, and associated symptoms (presyncope, chest discomfort) should be recorded. Concomitant neck pulsations are classic for atrioventricular reentrant tachycardia. Potential triggers such as caffeine, alcohol, or dehydration are important for diagnosis and management. It is helpful to ask patient to reproduce the cadence by tapping their fingers. A fast irregular pattern suggests atrial fibrillation, whereas single forceful taps suggest ectopic beats. It is important to remember that in patients with underlying structural heart disease, the onset of arrhythmias usually portends progressive hemodynamic deterioration.

Other Symptoms

Lower extremity edema is a common complaint in patients with heart disease. The distinction between edema from right heart failure and venous insufficiency can be difficult to establish by history and both may coexist, and edema occurring only at the end of the day suggests a primary venous etiology. Abdominal swelling due to ascites might be present in patients with severe heart failure, severe tricuspid regurgitation, or constrictive pericarditis but needs to be differentiated from primary liver disease, which may be a result of right heart failure. Ascites and edema are the most prominent symptoms of patients with constrictive pericarditis.

Fatigue and weakness are nonspecific symptoms and can be secondary to either cardiac or noncardiac issues; therefore, ascertaining that fatigue is a manifestation of a cardiac etiology is challenging. Fatigue as a cardiac symptom is common in patients with right ventricular failure or severe tricuspid regurgitation and constrictive pericarditis. Polypharmacy is common in cardiac and elderly patients, and fatigue might be a medication side effect (such as from beta-blockers) or a sign of medication-induced hypotension.

Systemic symptoms such as fever, chills, and malaise might be seen in the setting of infective endocarditis. Rarely, hoarseness and

TABLE 11–2. Canadian Cardiovascular Society Classification of Angina

Class I	Angina not induced by ordinary physical activity (walking or climbing stairs); develops only during strenuous, rapid, and/or prolonged exercise
Class II	Slight limitation of ordinary activities is present and is induced by the following: walking or climbing stairs rapidly, walking uphill, walking or climbing stairs postprandially, emotional stress, walking more than two blocks or climbing more than one flight of stairs at normal pace
Class III	Marked limitations of ordinary physical activity; angina develops on walking one or two blocks and climbing a single flight of stairs
Class IV	Inability to carry on any physical activity without developing angina; rest angina

dysphagia are caused by compression of contiguous structures in the setting of aortic aneurysm or severe left atrial enlargement (as in advanced mitral stenosis).

FUNCTIONAL CAPACITY

Assessment of functional capacity should be documented for management and follow-up purposes. The Canadian Cardiovascular Society[9] (Table 11–2) and the New York Heart Association[10] scales (Table 11–3) are widely used tools. In our experience, even a simple 1 (bedridden) to 10 (no physical limitations) Likert scale is helpful in the longitudinal assessment of patients and tends to correlate well with objective exercise capacity (exercise maximal oxygen consumption). In some diseases, there is such a gradual hemodynamic impairment that patients may not perceive a functional limitation; they will slowly decrease their activity level. Information obtained from a spouse or other close observer regarding activity level over years may be of value.

With the aging population, it is important to assess the presence and extent of frailty in patients being considered for interventions. The ability to perform activities of daily living is a necessary component of the frailty assessment. The degree of independence and interaction with family will be useful information for decision making regarding interventions in the elderly frail patient.

PHYSICAL EXAMINATION: INSPECTION, BLOOD PRESSURE, AND PALPATION

GENERAL EXAMINATION AND INSPECTION

A thorough general examination, including a funduscopic examination, should always be performed and signs of other comorbidities (such as cirrhosis, obstructive lung disease, or stroke) sought. Attention to patient's dentition is of major importance—in particular in patients with valve disease or for those undergoing preoperative evaluation. Visible pulsations should be noted, with respect to location and origin (arterial versus venous). Details regarding the noncardiovascular and eye examinations are, however, beyond the scope of this chapter.

Our patient population is aging, and frailty assessment should also be included as part of the physical examination. Gait speed (15-feet walk), handgrip strength, and muscle wasting should be recorded; multiple scores[11,12] have also been developed. This assessment should be a standard part of clinical evaluation and should be performed in patients undergoing catheter-based interventions or surgical treatment.

Several syndromes have been associated with cardiovascular disease, including aortopathies, congenital heart disease, or even cardiac tumors. Careful inspection of the facies, body habitus, and extremities are necessary in order to suspect the presence of a syndrome. Although these syndromes are rare, their identification can lead to the initial suspicion of the cardiac diagnosis, which may have life-saving implications for patients and their families. Some of those findings are illustrated in the Table 11–4.

TABLE 11–3. New York Heart Association Functional Classification

Class I	No limitation of physical activity; physical activity does not cause fatigue, palpitation, dyspnea, or angina
Class II	Slight limitation of ordinary activities; comfortable at rest; ordinary physical activity results in fatigue, palpitation, dyspnea, or angina
Class III	Marked limitations of physical activity; comfortable at rest; less than ordinary activities causes fatigue, dyspnea, or angina
Class IV	Inability to carry on any physical activity without symptoms; symptoms of heart failure of anginal might be present at rest If any activity is undertaken, discomfort is increased

TABLE 11–4. Genetic Syndromes and Associated Physical Examination Findings

Syndrome	Physical Examination Findings	Cardiovascular Features
Ehlers-Danlos	Joint hypermobility, scoliosis, lax thin skin; variable according to disease type	Arterial aneurysms, mitral valve prolapse
Fabry	Angiokeratomas	Infiltrative cardiomyopathy (may resemble hypertrophic cardiomyopathy), conduction abnormalities
Holt-Oram	Upper limb deformity due to aplasia or hypoplasia or radial and carpal bones	Congenital heart defects, most commonly atrial septal defects and ventricular septal defect
Loeys-Dietz	Hypertelorism, bifid uvula; dolichocephaly, enophthalmos, downslanting palpebral fissures, retrognathia, pectus carinatum, arachnodactyly, increased arm span	Aortopathy, vasculopathy, mitral valve prolapse
Marfan	Increased height, pectus excavatum, dolichocephaly, high-arched palate, flat feet, increased arm span, arachnodactyly, *thumb* and *wrist* signs	Aortopathy, mitral valve prolapse
Noonan	Short stature, strabismus, low-set ears, low hair line, shield shaped chest, hypertelorism	Pulmonary valve stenosis, atrial septal defect, hypertrophic cardiomyopathy
Turner	Short stature, webbed neck, cubitus valgus	Bicuspid aortic valve, aortopathy, aortic coarctation
Williams	"Elfin face," with broad forehead, short nose, wide mouth, flat nasal bridge	Supravalvular aortic stenosis, branch pulmonary artery stenosis

BLOOD PRESSURE MEASUREMENT

Blood Pressure: Technique

Although vital signs are frequently recorded by the ancillary staff prior to the encounter with the provider, we recommend that the measurements be repeated during physical examination by the clinician. This prevents abnormalities to be "missed" due to time constraints and also forces the examiner to certify that all the necessary steps for the measurement of blood pressure have been done (eg, that both arms are checked); this is particularly important during the patient's initial evaluation.

Blood pressure should be measured at rest (a common mistake is to measure it immediately after the patients have just walked into the room) and the appropriate cuff size used (the width of the inflatable bladder should correspond to 40% of the arm circumference). Smoking and caffeine should be avoided prior to measurement of the blood pressure. During initial assessment, blood pressure should be measured in both arms; differences in systolic blood pressure between arms are typically less than or equal to 20 mm Hg (usually higher in the right arm). This is a mandatory step prior to bypass surgery and in patients with internal mammary grafts who present with angina; a simple blood pressure check might be sufficient to diagnose subclavian stenosis.

Additional steps should be taken according to the clinical scenario. In patients complaining of syncope or presyncope, measurements in the supine, sitting, and standing positions must be performed. Systolic blood pressure should not fall more than 20 mm Hg on standing; diastolic blood pressure typically rises. Mild reflex tachycardia is common, but rates above 100 beats/min should not be expected. Newly hypertensive patients or patients with known bicuspid valve should have blood pressures measured in the lower extremity since coarctation of the aorta might be present. A large cuff should be applied to the patient's thigh and the popliteal artery auscultated. Alternatively, a smaller cuff can be applied to calf and the stethoscope applied to the dorsalis pedis artery. Normally, the lower extremity blood pressure tends to be 10 to 20 mm Hg higher than in the upper extremities.

Digital blood pressures cuffs have been shown to be reliable and accurate in most situations; however, major abnormalities might be missed if manual blood pressure measurement is not performed. Digital blood pressure cuffs may not be accurate in assessing pulse pressure in patients with aortic regurgitation or high output states; the digital cuffs will not be able to determine the presence of a pulsus paradox or pulsus alternans. Therefore, we recommend that manual blood pressure measurement should *always* be performed. With the stethoscope's diaphragm applied to the brachial artery, the ipsilateral radial pulse is palpated and the cuff inflated to 20 to 30 mm Hg above the level required to obliterate the pulse; the cuff should be then deflated slowly. Systolic blood pressure corresponds to the appearance of Korotkoff sounds (phase I) and diastolic blood pressure to the level where the Korotkoff sounds entirely disappear (phase V). In some patients, the Korotkoff sounds might disappear and became audible again at lower pressures (ie, the *auscultatory gap*). This is a common finding in elderly patients, and simultaneous palpation of the radial artery while the cuff is inflated prevents underestimation of the blood pressure. In hypotensive patients, Korotkoff sounds might not be audible; blood pressure should be determined by palpation of the radial artery.

Heart rate and the cardiac rhythm (regular, regularly irregular, or irregularly irregular) should also be recorded. Other vital signs (temperature and respiratory rate) and their abnormalities should be noted.

Blood Pressure Abnormalities

Pulse pressure (the difference between systolic and diastolic blood pressure levels) should be noted. A narrow pulse pressure is seen in shock and hypotension; the arterial pulse usually shows low amplitude. A wide pulse pressure is seen in hypertension (commonly in the elderly, due to noncompliant arteries), severe aortic regurgitation (secondary to lower diastolic blood pressure) or arteriovenous shunting (such as patent ductus arteriosus or dialysis fistula).

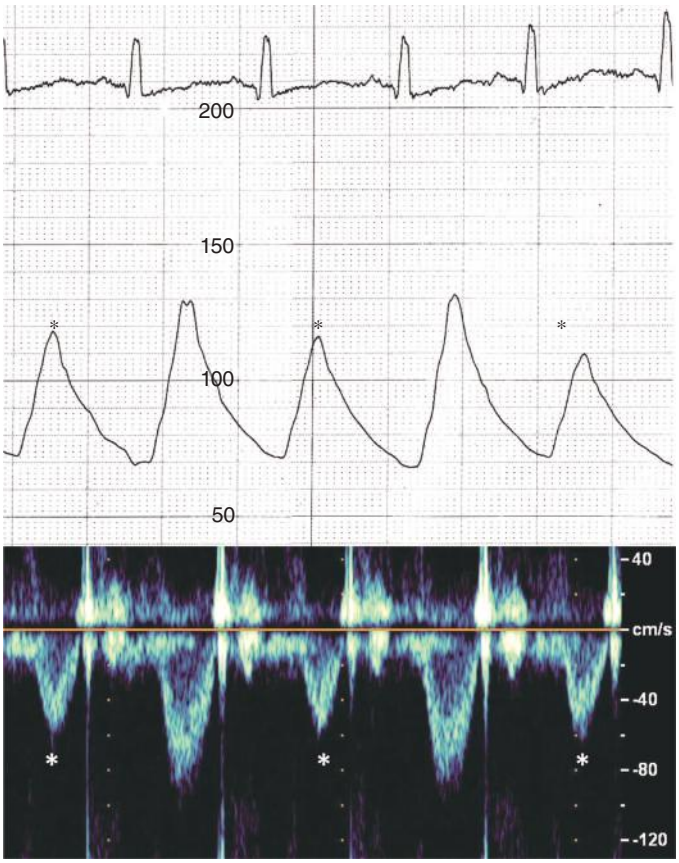

FIGURE 11–1. Pulsus alternans in a patient with severe left ventricular systolic dysfunction. Invasive aortic pressure tracing (*upper*) and left ventricular outflow tract pulsed-wave Doppler (*lower*) showing marked beat-to-beat reduction (*asterisk*) in left ventricular stroke volume.

Pulsus alternans (Fig. 11–1) corresponds to beat-to-beat changes in systolic blood pressure (or the intensity of Korotkoff sounds themselves); this can detected both by auscultation and by palpation, during which time the patient should be instructed to breathe calmly. Pulsus alternans is a sign of severe left ventricular systolic dysfunction.

Pulsus paradoxus (Fig. 11–2) corresponds to respirophasic changes in blood pressure. "Paradox" is a misnomer because minor drops in blood pressure with inspiration are normal. In pathologic situations, there is an exaggeration of this phenomenon. Normally, systolic blood pressure should not fall more than 10 mm Hg on inspiration. The presence of "pulsus" is a subtle finding and requires that proper technique is applied. The examiner should inflate the blood pressure cuff 15 to 20 mm Hg above the systolic blood pressure (determined by palpation and auscultation). The cuff should is then slowly deflated and the Korotkoff sounds auscultated while the patient breathes normally; the sounds will show respirophasic changes, decreasing or disappearing with inspiration. Eventually, those respirophasic changes will not be noticeable, and expiratory and inspiratory Korotkoff sounds will be have similar intensities. The "pulsus" will be the difference between the peak systolic blood pressure levels measured during expiration and inspiration, and more than 10 mm Hg is abnormal. Pulsus paradoxus is classically described as a sign of cardiac tamponade or constrictive

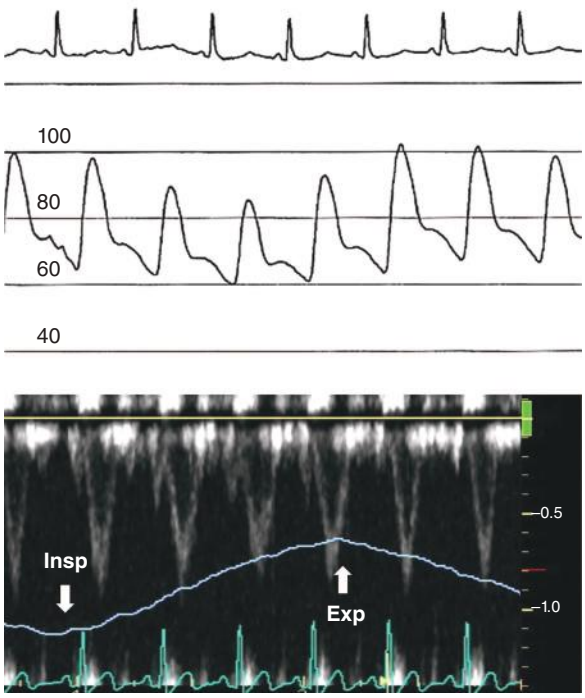

FIGURE 11–2. Pulsus paradoxus in a patient with cardiac tamponade. Invasive aortic pressure tracing (*upper*) and left ventricular outflow tract pulsed-wave Doppler (*lower*) with simultaneous respirometer tracing confirm marked decrease in left ventricular stroke volume with inspiration.

pericarditis due to the enhancement ventricular interdependence seen on those two entities (with inspiration right ventricular stroke volumes increases while left ventricular stroke volume falls; this is secondary to pericardial restraint). Pulsus paradoxus can also be seen in morbid obesity and in lung disease, as a result of major changes in intrathoracic pressures.

PERCUSSION

In the past, some authors recommended the use of percussion for the determination of cardiac position (levocardia vs dextrocardia) and its relation to abdominal viscera (situs solitus or inversus, based on gastric tympanic sounds). Today, this can be easily determined with chest radiography and echocardiography. Thus, cardiac percussion is not necessary in current practice.

PALPATION

Palpation is perhaps the most underemphasized part of the cardiovascular examination, both in medical education and bedside assessment. Proper technique includes palpation of the left and right ventricles as well as palpation of the cardiac base (great vessels). Via "simple" palpation, assessments of ventricular size, cardiac valve function, diastolic function (when third or fourth sounds are palpable), and pulmonary hypertension can be suspected. Masters of physical examination advocate that auscultation "merely" serves to confirm inspection and palpation findings.

Palpation of the great vessels is part of a comprehensive cardiovascular physical examination and should be performed over the second right intercostal space (aortic area) and left intercostal space (pulmonic area), best felt in the sitting position. A detectable pulsation represents palpable, and therefore, increased, aortic (A2) or pulmonic (P2) components of the second heart sound. A palpable A2 component is rare. A palpable P2, however, is a critical finding because it suggests severe pulmonary hypertension, which can either be due to etiologies associated with increased pulmonary vascular resistance or left-sided diseases.

Attention should be turned to the presence of *thrills*, palpable murmurs which have a marked increase in the degree of turbulence. Thrills can be present at the apex, left lower sternal border, cardiac base, suprasternal notch/neck, and the posterior chest. When present, the location, timing, and radiation of a thrill should be described. Diastolic thrills are very rare. In current practice, the most common source of a thrill is a ventricular septal defect, which manifests as a systolic thrill at the left lower sternal border. It should be emphasized that the presence of a thrill is not diagnostic of a specific cardiac lesion, and the diagnosis should be made based on the constellation of findings observed on examination.

Cardiac palpation should proceed with evaluation of the apical impulse. We recommend the term *apical impulse* instead *point of maximal impulse* because patients with significantly enlarged right ventricles might have parasternal lifts that are more prominent than the left ventricular apical impulse. The apical impulse might be visible, facilitating its localization; therefore, inspection should precede palpation. In addition, some of other palpable abnormities may also be visible (eg, a rapid filling wave that corresponds to a third heart sound). Palpation (and auscultation) must be performed directly over the skin. Thus, patients should *always* be offered an examination gown and a sheet used to preserve patient's privacy. Examination of the patient in his or her clothes compromises the quality of the examination and is discouraged.

With the patient in the supine position, if not visible, the examiner should look for the apical impulse using the entire right hand starting at the inframammary area. In patients with large breasts, the examiner's left hand should be used to mobilize the breast to locate the apex. Once a palpable pulsation is identified, the finger pads should be then used for analysis (Fig. 11–3). If the apical impulse cannot be palpated, the patient should be positioned in the left lateral decubitus position and asked to place his or her left hand underneath the pillow; slight elevation the head of the bed (30 degrees) might also be helpful. Both maneuvers facilitate expansion of the thorax, increasing the space between the ribs. Held expiration may also facilitate cardiac palpation. The apical impulse should be palpable in the majority of patients, even the ones with normal hearts.

FIGURE 11–3. Palpation of the apical impulse. Once the apical impulse has been located, the finger pads of the right hand are used for assessment of apical size, location, and contour.

Once the apical impulse is identified, the examiner should assess its location, size, and quality/contour. The apical impulse is usually located at the fifth intercostal space in the midclavicular line. With left ventricular enlargement, the apical impulse is deviated laterally and inferiorly while right ventricular enlargement displaces the apex laterally. Moving the patients from supine to a left lateral decubitus position only shifts the apical impulse laterally by 2 to 3 cm and should not be responsible for marked apical displacement.

When the left ventricular size is normal, the apical impulse occupies an area of 3 cm or less in diameter; the size of the apical impulse should be described in centimeters rather than fingerbreadths because it is more precise. Increase in the area occupied by the apical impulse suggests left ventricular dilatation, described as a *diffuse* apical impulse (as opposed to *localized*). Isolated left ventricular hypertrophy typically does not cause enlargement of the apical impulse; hypertrophy is associated with a sustained impulse. An enlarged apical impulse suggests an enlarged left ventricle due to a myopathic process or volume overload as seen in severe aortic or mitral regurgitation.

The contour of the apical impulse should be also be determined. Isovolumic contraction moves the apex closer to chest wall, allowing its palpation; as a consequence, the impulse is usually only palpable during the first two-thirds of ventricular systole (Fig. 11–4). Although simultaneous auscultation can help quantifying the duration of apical impulse, in practical terms the determination of a normal versus prolonged (described as *sustained*) apical impulse comes with experience. It is extremely important, therefore, for the clinician to perform cardiac palpation in every patient, including the ones with known normal hearts, so a sense of normality can be developed.

A *sustained* apical impulse can be found when ventricular mass is increased (ventricular hypertrophy or dilation) or when there is obstruction to left ventricular ejection (as observed in aortic stenosis or hypertrophy cardiomyopathy). Not only duration, but also the amplitude should be noted. In hypertrophy and obstruction to flow, the apical impulse is rather forceful, "pushing" the examiner's hands. Conversely, in patients with severe left ventricular dysfunction, the impulse can be quite feeble. In sinus tachycardia (eg, after exercise or related to infection), the apical impulse can be hyperdynamic. In patients with mitral stenosis and a pliable mitral valve, apical palpation results in a unique tactile (shock-like) sensation due to a prominent first heart sound—so-called *tapping* apical impulse—which is essentially pathognomic for rheumatic mitral stenosis. Patients with hypertrophic obstructive cardiomyopathy might also have a classic apical impulse—the so-called "*triple ripple*" (see Fig. 11–4). This corresponds to the presence of palpable systolic impulse in early and midsystole, separated by withdrawal of the apical impulse related to dynamic outflow obstruction; a palpable atrial contraction corresponds to the third impulse.

A palpable third or fourth heart sound may be suspected by inspection (sometimes placing the tip a pen over the apical impulse and watching the motion of the pen itself can be helpful). A palpable fourth heart sound follows atrial contraction and will be felt as a presystolic palpable impulse (preceding the rise of the apical impulse); the fourth heart sound tends to be more easily palpated than auscultated. A palpable third heart sound corresponds to the ventricular diastolic rapid filling phase and will occur in early diastolic; it can be felt as the apical impulse retracts. The third heart sound is usually more easily auscultated than palpated. Although systolic clicks and some diastolic sounds can be palpable, they are rarely felt.

Given its anterior position within the chest, an enlarged right ventricle can be palpated as a *parasternal lift* (or *heave*). It should be noted that in thin patients or patients with abnormalities of the sternum (such as *pectus excavatum*), a parasternal lift can be present in the setting of a normal right ventricular size. Palpation of the right ventricle can be accomplished several different ways (Fig. 11–5), being performed with patient in the supine position. The examiner should gently place his or her thenar/hypothenar surfaces on the patient's left lower sternal border. The right ventricle can also be palpated by placing the examiner's index, middle, and fourth fingers over the third, fourth, and fifth intercostal spaces, respectively, at the left parasternal line. A third form of palpation is to place the right hand in the subxiphoid area.

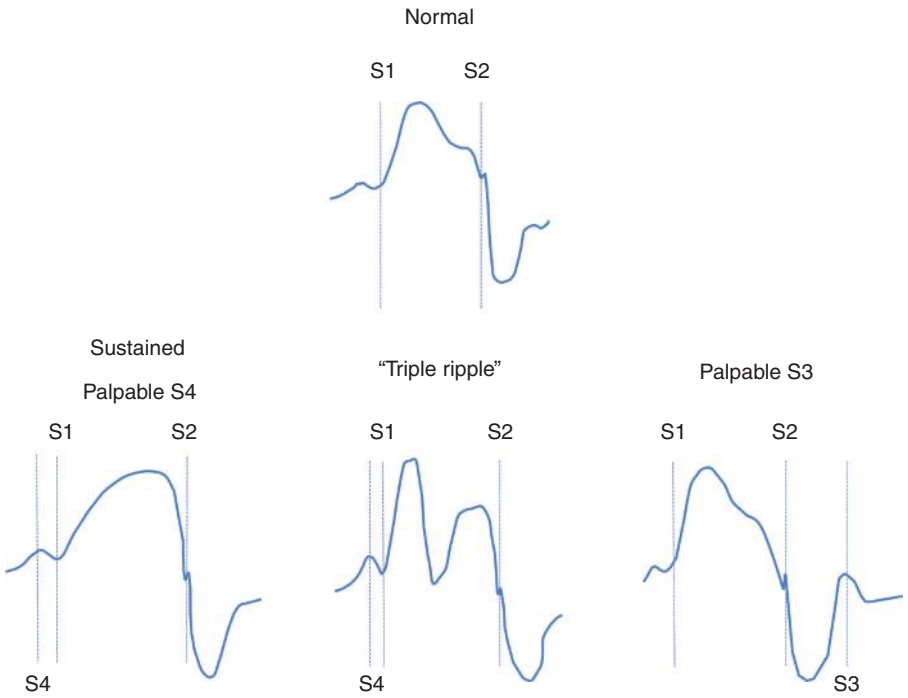

FIGURE 11–4. Apical impulse contour in a normal person and in various disease states.

FIGURE 11–5. Palpation of the right ventricle. Palpation of the right ventricle can be performed using the following approaches: the thenar/hypothenar surfaces of the examiner's right hand are placed on the patient's left lower sternal border (**A**); the examiner's right second, third, and fourth fingers are placed over the patients right third, fourth, and fifth intercostal spaces (**B**); or the examiner palpates the patient's right ventricle from the subxiphoid area (**C**). S1, first heart sound; S2, second heart sound; S3, third heart sound; S4, fourth heart sound.

This maneuver is particularly helpful in patients with obstructive lung disease. Abnormalities in the contour of the right ventricular impulse can be appreciated but are much less prominent than apical ones. Pulmonary stenosis can give rise to a sustained parasternal lift; presystolic and early diastolic waves can be also be appreciated on occasion.

PHYSICAL EXAMINATION: ARTERIAL AND VENOUS PULSE

ARTERIAL PULSE EXAMINATION

Technique

Analysis of the arterial pulse can be accomplished by palpation of the carotid and/or the brachial arteries. We encourage the examiner to be familiar with palpation of the brachial arteries, which can be particularly helpful in patients with increased neck circumference, previous cervical radiation, or in the presence of carotid disease. Palpation of the brachial arteries can be achieved by resting the patient's elbow on the examiner's right palm with palpation of the vessel being exerted with right thumb; the brachial pulse is usually deeper than others. The examiner's left hand should gently extend/flex the patient's arm in order to improve palpation of the vessel. Alternatively, palpation can also be performed directly by the examiner's left finger pads with the right fingers being used for extra pressure, if needed. Palpation of the carotid arteries should be performed with the right finger pads; the sternocleidomastoid muscle should be mobilized laterally to optimize palpation of the vessel. Once the artery has been properly identified, attention should to paid to the amplitude and contour of the arterial pulse (Fig. 11–6), as will be described below. Palpation of the other upper and lower extremity pulses is part of a comprehensive cardiovascular examination and should always be performed, particularly with simultaneous palpation of the radial and femoral pulse in patients with suspected coarctation of the aorta.

Abnormalities of Arterial Pulse

The classic arterial pulse contour described in *severe aortic stenosis* is tardus (slurred upstroke and delayed peak) and parvus (reduced in amplitude) (see Fig. 11–6). The degree of tardus (graded as 1+ to 4+) is a measure of the severity of the stenosis and reflected in the late peaking continuous wave velocity contour on Doppler echocardiography as well as the delayed upstroke on the central aortic pressure at cardiac catheterization (Fig. 11–7). Although frequently described in textbooks as one single pattern, one of the two components might prevail (more tardus than parvus), and they should be graded separately. Typically found in valvular aortic stenosis, it should be noted that the parvus and tardus pulse also accompany other forms of fixed left ventricular outflow obstruction (eg, supravalvular aortic stenosis). In this case, however, a normal aortic component of the second heart sound will indicate the aortic valve is spared. In dynamic left ventricular outflow obstruction (hypertrophic cardiomyopathy), the arterial pulse is usually of normal amplitude but has brisk upstroke, secondary to an unopposed forceful contraction in early systole (before obstruction develops) by the hypertrophied ventricle. Hypertrophic cardiomyopathy with obstruction is a cause of a *bifid* pulse, caused by the occurrence of obstruction starting in mid-systole. This is seen as a spike-and-dome pattern on aortic pressure (see Fig. 11–6) tracings, but the presence of this finding on examination is uncommon.

In *severe aortic regurgitation*, the associated volume overload and left ventricular dilatation cause an increase in stroke volume. The combination of increased stroke volume and the regurgitation itself gives rise to an arterial pulse that is increased in amplitude—"bounding"—which also collapses very quickly (see Fig. 11–6). This is so-called *water hammer pulse*, typical of severe isolated aortic regurgitation. This phenomenon is not only palpable but might also be manifested as visible arterial pulsations (carotids and brachial arteries, most commonly). When mixed aortic valve disease is present and the aortic regurgitation is the predominant lesion, an arterial contour with increased amplitude and two palpable systolic peaks can be present—the *bisferiens pulse*.

Other described abnormalities of the arterial contours include the *anacrotic pulse* of aortic stenosis, where a positive inscription can be palpated on the ascending limb of the aortic contour, or the *dicrotic pulse*, when there is an exaggeration of the dicrotic notch (palpated on descending limb of the aortic pulse), typically seen in shock and severe peripheral vasoconstriction. Hypotension and narrow pulse pressure are also usually present (see Fig. 11–6). In patients with severe left ventricular systolic dysfunction, *pulsus alternans* might be present, where the amplitude of the arterial pulse will vary with every heart beat; sometimes the amplitude might be so diminished that only every other beat can be palpated. As opposed to *pulsus paradoxus* (previously described in the vital signs section), those variations in amplitude are not respirophasic. The presence of *pulsus alternans* is an ominous sign suggesting very profound severe ventricular systolic dysfunction. These abnormalities can be easily noted invasively by arterial pulse recording or an ascending aortic pressure (see Figs. 11–1 and 11–2).

The examiner should also assess the amplitude of the arterial pulse as an indirect measurement of cardiac output; arterial pulse amplitude tends to be proportional to stroke volume. The presence of a low amplitude pulse in the absence of aortic stenosis should suggest reduced cardiac

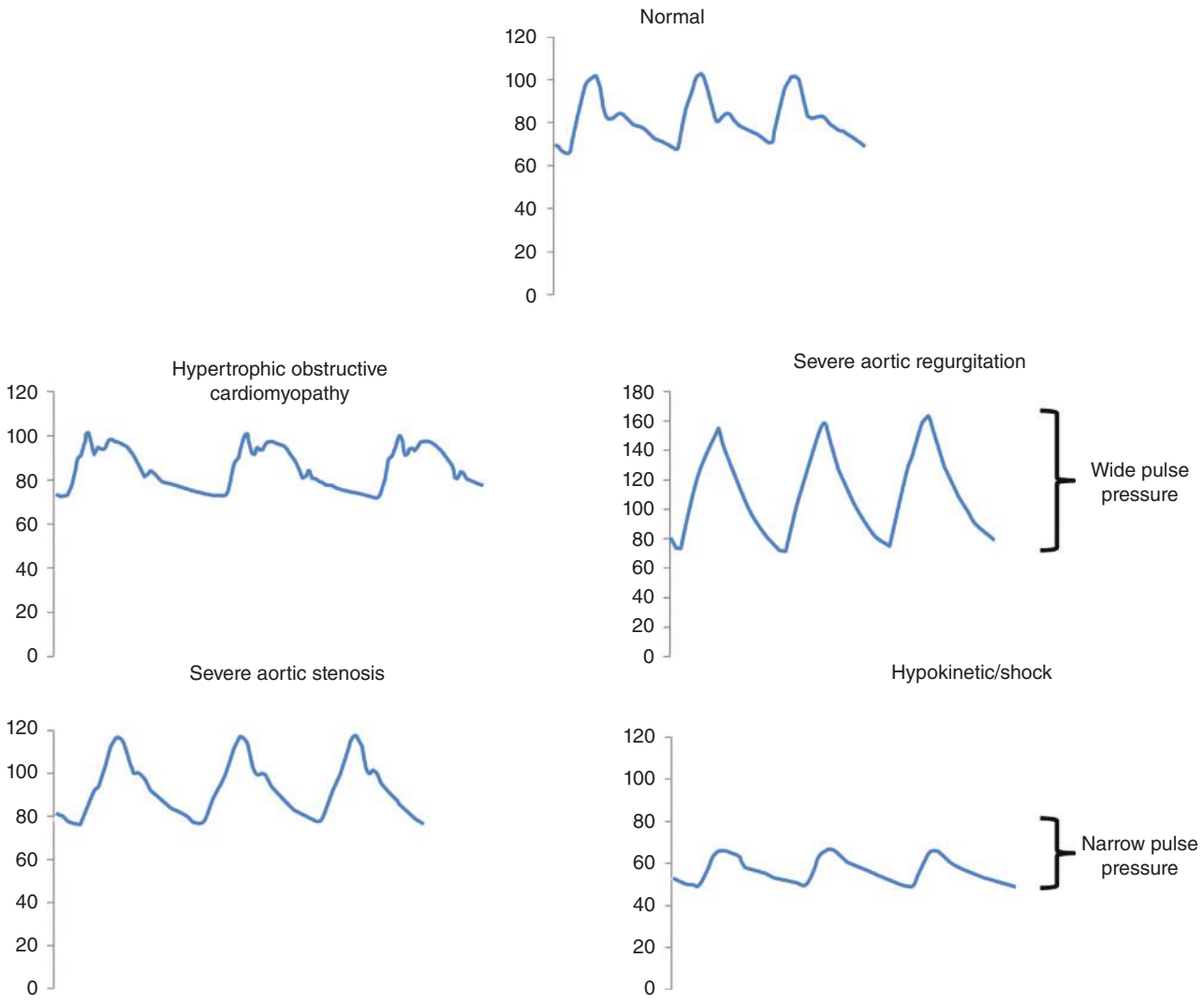

FIGURE 11–6. Normal arterial pulse waveform and abnormal arterial pulse waveform patterns seen in various disease states. These arterial pulse waveforms illustrate the expected findings on arterial pulse palpation.

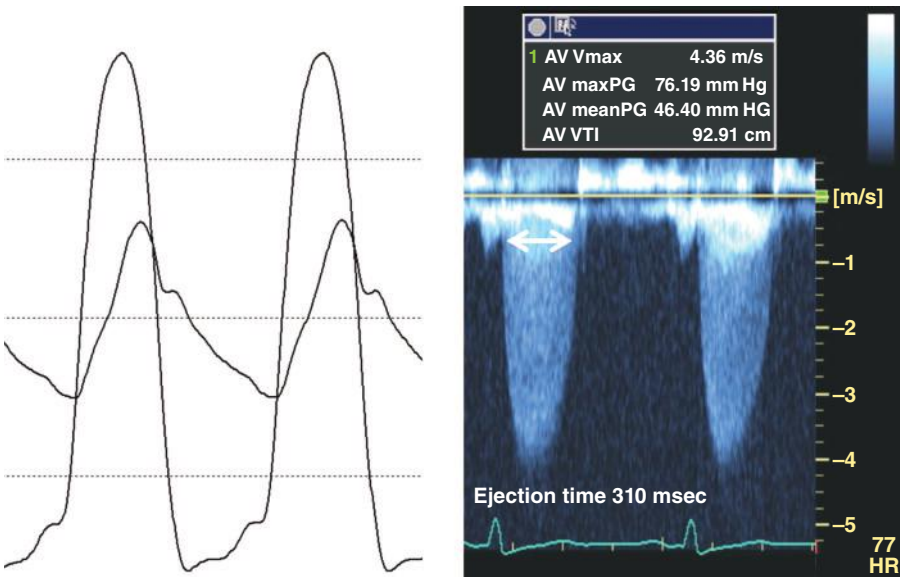

FIGURE 11–7. Arterial pulse waveform in severe aortic valve stenosis. Aortic and left ventricular pressure tracings (*left*) show the "parvus and tardus" pattern in a patient with severe aortic valve stenosis. The *right panel* illustrates the prolonged systolic ejection time and severely increased systolic mean gradient noted by aortic continuous-wave Doppler.

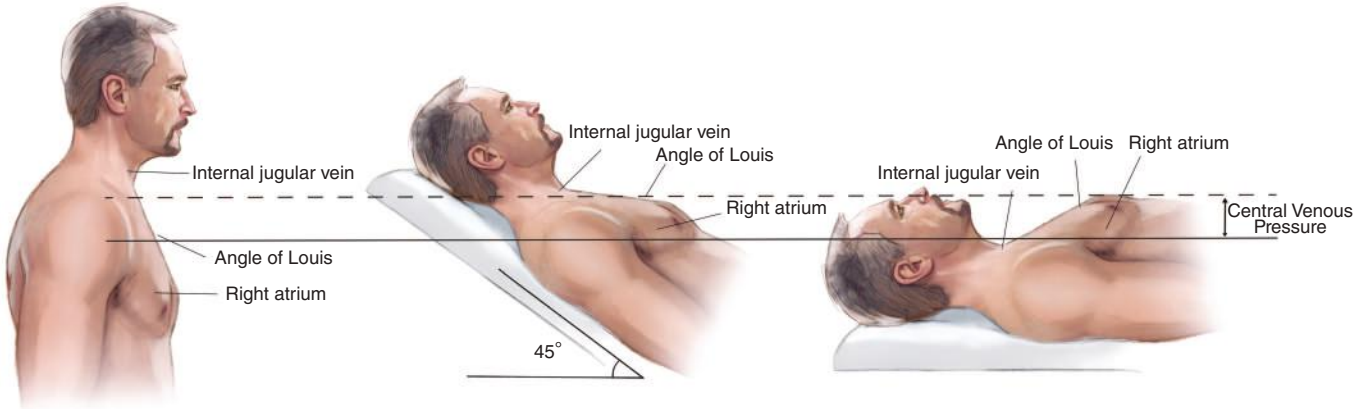

FIGURE 11–8. Estimation of central venous pressure. The central venous pressure corresponds to the vertical distance from the highest point of the visible jugular venous pulsation to the right atrium, irrespective of the angle at which the patient is examined. The examiner should adjust the head of the bed in order to optimize visualization of the jugular pulsations. In patients with low or normal right filling pressures, the venous pulsation might be hidden behind the sternum at higher angles. Conversely, in patients with very elevated central venous pressures, jugular pulsations might not be seen unless the patient is sitting upright or standing up.

output, such as with severe left ventricular systolic dysfunction, severe mitral stenosis, and constrictive pericarditis. Conversely, the combination of bounding pulses, left ventricular enlargement, and heart failure should suggest high-output failure, patent ductus arteriosus, or other arteriovenous fistulae. In shock, the arterial pulse is of decreased amplitude but also hyperdynamic as the result of accompanying tachycardia.

VENOUS PULSE EXAMINATION

Inspection

The first step in analyzing the venous pressure and the venous waveform contour is ascertaining that the visible pulsation is indeed venous. A carotid arterial pulsation seen below the angle of the jaw might be mistaken for severe elevation in venous pressure. Inspection of the internal instead of the external jugular vein has been traditionally preferred to determine the contour of the venous pulsations. Because it emanates from a low-pressure system, venous pulsations should disappear when light pressure is applied proximally (eg, above the clavicle), whereas arterial pulsation cannot be compressed and should "push" the examiner's fingers. In normal circumstances, the venous contour has two upstrokes and the arterial waveform has a single one. This feature, however, should not be used in isolation, because rhythm abnormalities (such as atrial fibrillation with loss of the *a* wave) or severe tricuspid regurgitation will lose the double venous upstroke. Lastly, venous waveforms show respirophasic changes with its waveforms becoming more prominent on inspiration, although the venous pressure itself might drop slightly or remain unchanged.

Estimation of Venous Pressure

The proper technique used in the estimation of central venous pressure is often confusing to the novice examiner. Estimation of central venous pressure is a crucial part of the physical examination; not only cardiologists, but all clinicians should to be very familiar with the method. Its importance in the diagnosis and management of patients is clearly stated in the American College of Cardiology/American Heart Association heart failure guidelines.[13] An elevated venous pressure is the equivalent of a dilated inferior vena cava on echocardiography, which does not collapse with inspiration and is the first clue to hemodynamic decompensation.

Estimated central venous pressure is measured in centimeters of water (H_2O) because it represents the height of a column of fluid. Thus, the venous pressure in cm of H_2O does not equal the right atrial measured in mm Hg at catheterization (1 cm of H_2O = 0.74 mm Hg). Central venous pressure is recognized on physical examination as the *vertical* distance from the highest point of the visible jugular venous pulsation to the right atrium. The internal jugular vein is typically the one analyzed. The sternal angle, or angle of Louis, which corresponds to the manubriosternal junction has been shown to lay 5 cm above the level of the mid–right atrium (Fig. 11–8). Therefore, estimated central venous pressure equals the vertical distance of the maximum visible jugular venous pulse to the angle of Louis plus 5 cm. The head of the bed should be adjusted in order to optimize analysis of the venous pulsations so that the *highest point* where venous pulsations can be identified is to be used as the reference point.

In patients with very elevated central venous pressures such as seen in constrictive pericarditis, the top of venous pulse might not be seen until the patient is standing. Conversely, in patients with low central venous pressures, the patient might be almost supine until venous pulsations can be appreciated. Thus, failure to perform inspection of the neck in different positions might lead to misinterpretation of central venous pressure.

There are two simple and practical ways that estimating central venous pressures can be done at the beginning of the physical examination while the patient is sitting at 45 degrees. The lack of a visible pulsation corresponds to a normal venous pressure of less than 8 cm of H_2O. A visible venous pulsation at the level of the clavicle corresponds to 10 cm of H_2O, midneck 15 cm of H_2O, and angle of jaw 20 cm of H_2O. Another method is to simply report out the height of the venous pulsation (in cm) above the angle of Louis at 45 degrees. In the normal patient without cardiac disease, the venous pressure is less than 3 cm above the angle of Louis. If pulsations cannot be visualized, the venous pressure is most likely normal, but it is necessary to lower the head of the bed until a pulsation is seen to ensure that the venous pressure is not so high that pulsations cannot be seen.

Although the terms *jugular venous distention* and *elevated central venous pressure* are frequently used interchangeably, the central venous pressure should always be quantitated objectively. Jugular venous distention might be seen in primary venous disorders (eg, in superior vena cava syndrome).

Normal Venous Pulse

After central venous pressure has been estimated, the examiner then should focus on the venous contour. Similar to the technique used for

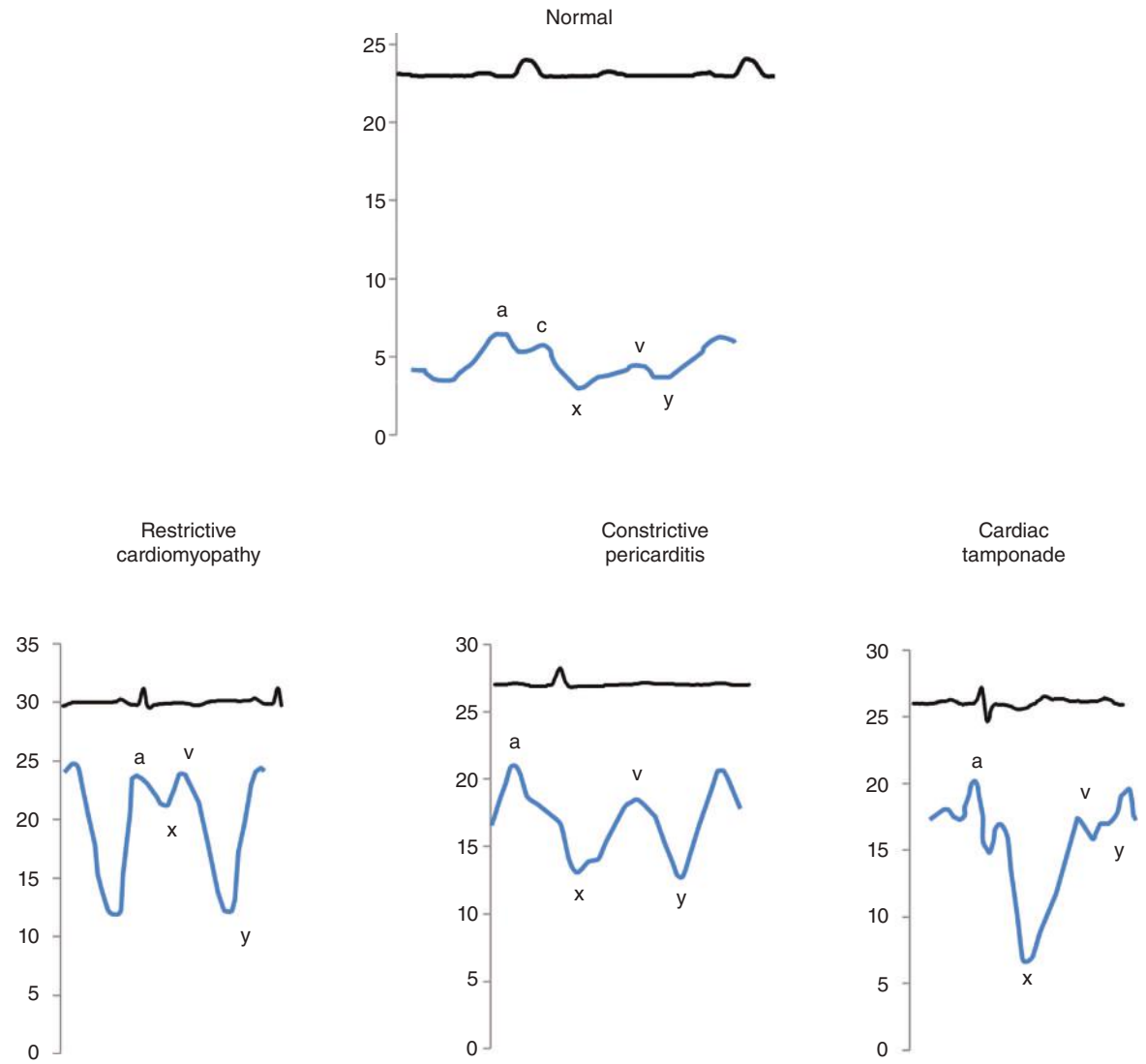

FIGURE 11–9. Normal right atrial pulse waveform and abnormal patterns seen in various disease states. The right atrial pulse waveform correlates with the expected findings on inspection of the jugular venous pulse.

the estimation of venous pressure, the head of bed should be adjusted to provide optimal visualization of the venous pulsations. The normal jugular venous contour has two upstrokes—*a* and *v* waves and two downstrokes—*x* and *y* descents (Fig. 11–9). A third positive wave—the *c* wave—is seen on right atrial pressure tracings but is not usually visualized on the neck veins.

Positive waves are typically more easily appreciated on inspection than the descents. The *a* wave corresponds to atrial systole and is followed by *x* descent, which is the result of two phenomena—atrial diastole and apical displacement of tricuspid annulus during ventricular systole. The origin of the *c* wave had been controversial, but it appears that the inflection seen on the jugular wave recordings results from the contiguous carotid pulsations rather than tricuspid valve closure. The *v* wave represents venous return, whereas the *y* descent occurs with opening of the tricuspid valve and early diastolic filling of the right ventricle. In normal subjects, right atrial *a* wave is larger than the *v* wave.

In order to analyze the waveforms themselves, it is necessary that each wave is accurately identified. Proper timing can be achieved by simultaneous palpation of the patient's left (or contralateral) carotid with the examiner's right hand or simultaneous auscultation of the precordium. The *a* wave precedes the carotid upstroke and the first heart sound; once the *a* wave has been identified, the second positive deflection should be *v* wave. When a single venous upstroke is present (as in atrial fibrillation), only a positive wave (*v* wave) following carotid upstroke will be noted. The radial pulse should not be used as the pulse reference because there is a small delay between the radial and carotid upstroke, which can lead to inaccurate conclusions, especially when tachycardia is present.

Jugular venous wave recording was readily available in the past but the technique has essentially disappeared with widespread use of echocardiography. In the current era, hepatic vein pulsed-wave Doppler provides an objective corresponding image of the jugular wave contour (S wave = *x* descent; D wave = *y* descent) (Fig. 11–10). Cardiac catheterization also provides the opportunity for the examiner to compare his or her noninvasive to invasive data with direct measurement of right atrial pressure. We would recommend that clinicians estimate right atrial pressure and waveforms prior to sending patients to the catheterization laboratory for hemodynamic assessment. This process will result in "calibration" of the examiner's physical examination skills and more accurate appreciation of the findings.

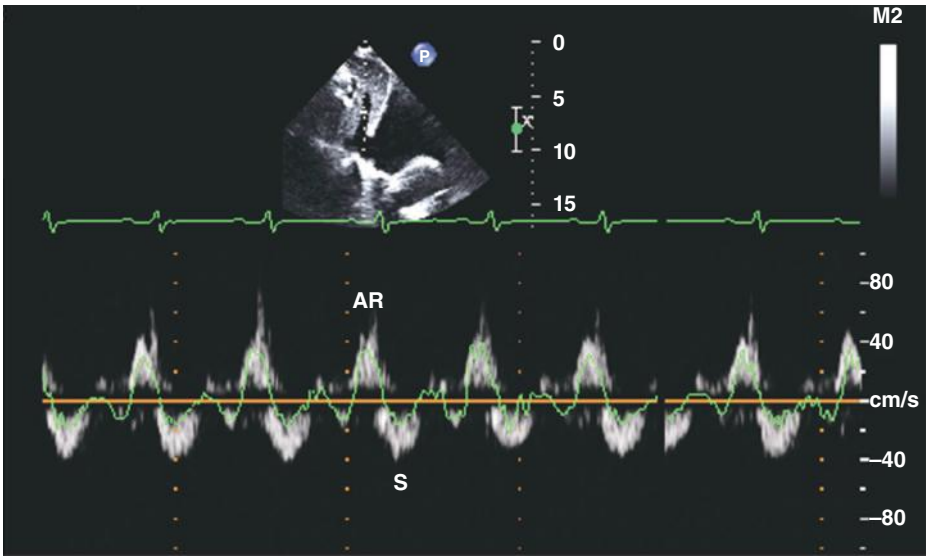

FIGURE 11–10. Simultaneous right atrial pressure tracings (*green*) and hepatic vein Doppler in a patient with pulmonary hypertension. The increased *a* wave is simultaneously reflected on the hepatic vein Doppler tracing as a prominent atrial reversal (AR). There are also prominent *x* descents with prominent systolic waves (S). Hepatic vein Doppler findings mirror right atrial pressure tracings and can be used for confirmation of jugular venous examination findings.

Abnormal Venous Pulse

Abnormalities of the a Wave Abnormalities of the *a* wave can result from primary right-sided valvular disease/hemodynamic abnormalities of the right ventricle or heart rhythm abnormalities. An increase in the amplitude of the *a* wave is seen in situations where there is increased contribution of atrial contraction to ventricular diastolic filling. An elevated atrial reversal velocity on the hepatic vein Doppler tracing corresponds to a large *a* wave. This can occur in the setting of right ventricular diastolic dysfunction and is typically seen in pulmonary hypertension, pulmonary stenosis, or less frequently in restrictive cardiomyopathies. Classically described in rheumatic tricuspid stenosis, very enlarged *a* waves—*giant a waves*—will be present secondary to atrial contraction against a stenotic tricuspid valve (Fig. 11–11). The occurrence of very large *a* waves (as opposed to large *v* wave) is primarily encountered in patients being evaluated for tricuspid prosthesis obstruction with an elevated diastolic gradient.

Atrial fibrillation is characterized by the absence of organized atrial contraction; thus in patients with atrial fibrillation, the *a* wave will be absent (Fig. 11–12). In atrial flutter, small, regular flutter waves can be seen instead of *a* waves. Initially described as a delay between *a* and *v* waves on the jugular venous pulse, the diagnosis of first-degree atrioventricular block or Wenckebach phenomenon features on neck veins is of historical interest. The presence of brisk, extremely prominent *a* waves, the so-called *cannon a waves*, are

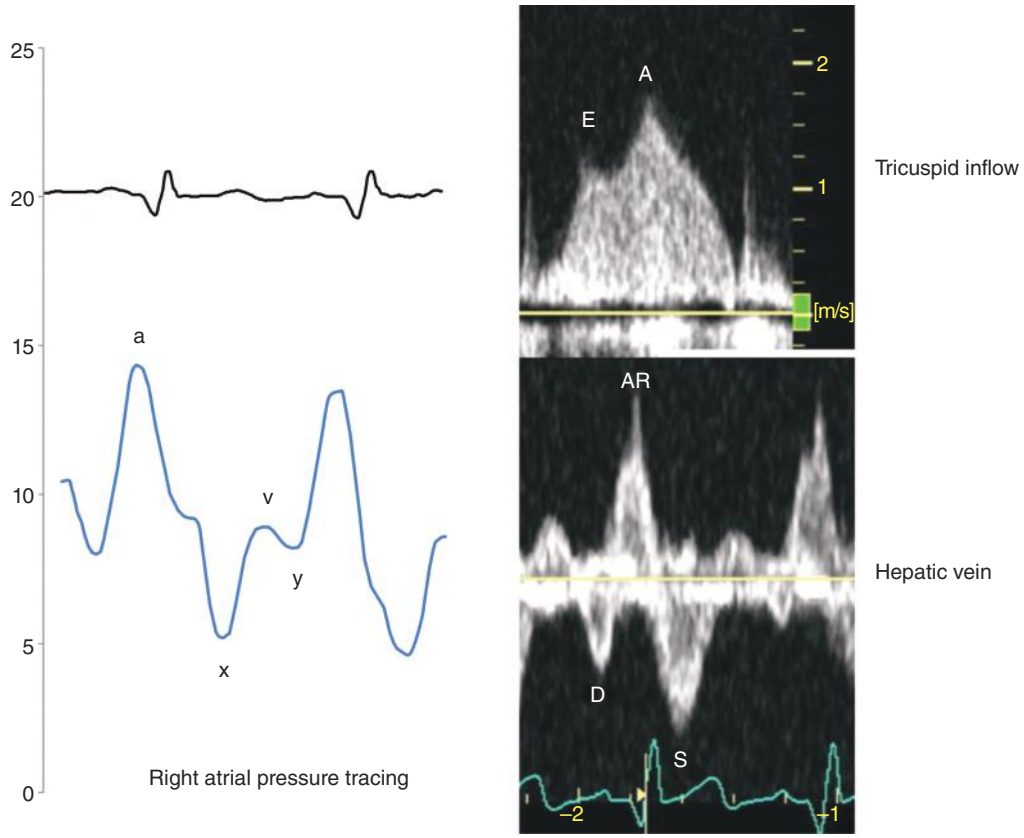

FIGURE 11–11. Giant *a* waves seen in tricuspid valve stenosis. Right atrial pressure tracings (*left*) showing very large a waves, which are also appreciated by hepatic vein pulsed-wave Doppler (large atrial reversals; *right lower*). Continuous-wave Doppler across the tricuspid valve confirmed the diagnosis of tricuspid stenosis (*right upper*). A, A wave; D, diastole; E, E wave; S, systole.

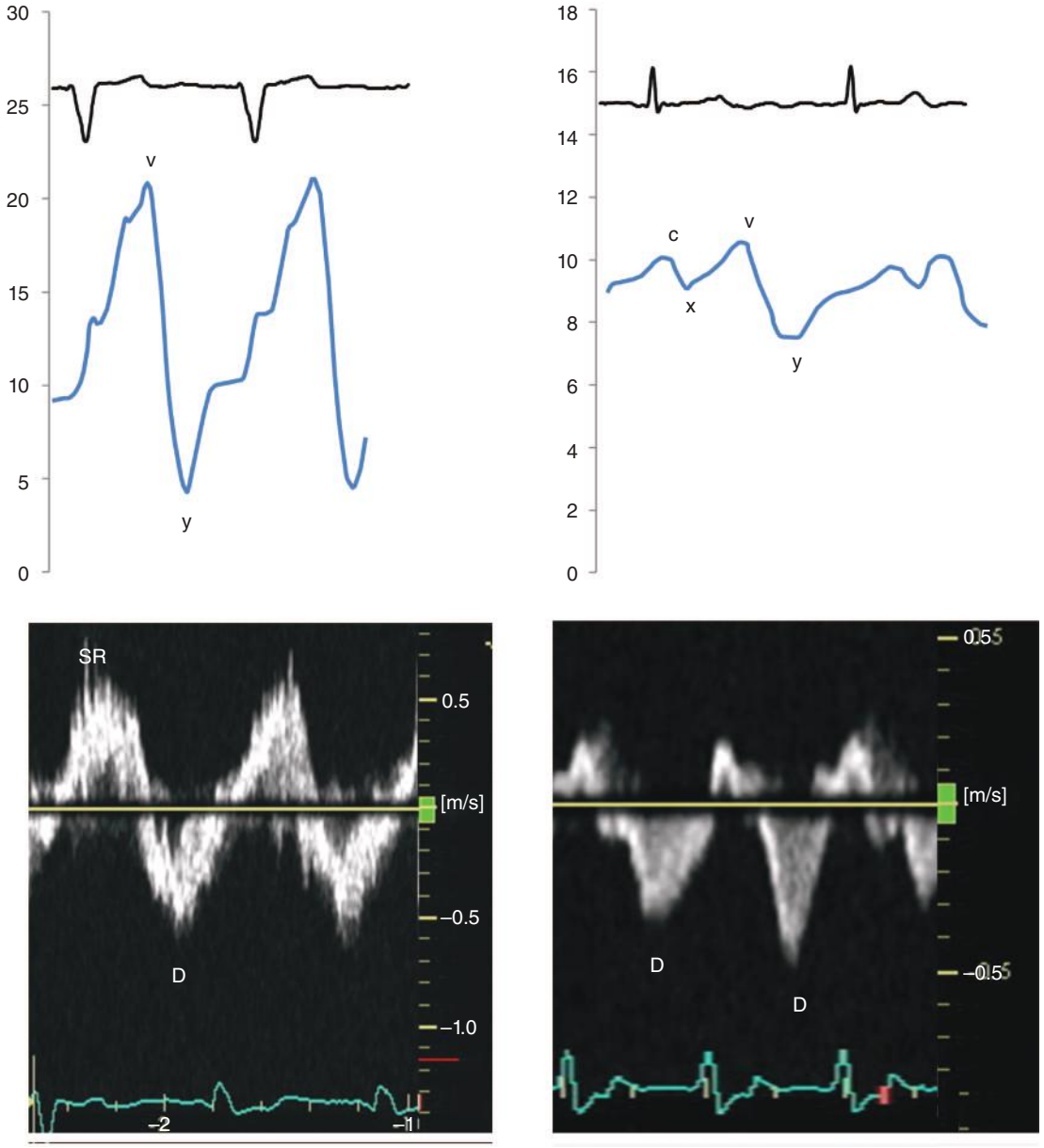

FIGURE 11–12. Right atrial pressure tracings in severe tricuspid regurgitation and atrial fibrillation. Right atrial pressure tracings show large *v* waves and prominent *y* descents in a patient with severe tricuspid regurgitation (*left upper*). Large systolic reversals (SR) and prominent diastolic (D) waves are also seen on hepatic vein pulsed-Doppler (*left lower*). In atrial fibrillation right atrial tracings (*right upper*) show loss of *a* waves with blunting of the *x* descent. This is also illustrated by hepatic vein Doppler (*right lower*), which shows absence of systolic waves (S) and prominent diastolic waves (D).

still valuable in clinical practice. These are the result of atrial contraction against a closed tricuspid valve. Variable cannon *a* waves suggest the diagnosis of complete heart block in patients with new-onset bradycardia, and its occurrence in wide complex tachycardia is diagnostic of ventricular tachycardia rather than aberrancy.

Abnormalities of the *x* Descent The most common abnormality observed in clinical practice is the blunting of *x* descent that is seen in atrial fibrillation. Atrial fibrillation results in a loss of atrial contraction, as well atrial relaxation, leading to this abnormality. The corresponding finding is a reduced or absent systolic forward flow (S wave) on the hepatic vein Doppler tracing (see Fig. 11–12). In patients with myopathic diseases, annular motion can be markedly reduced as evidenced by low tissue Doppler velocities, and, thus the *x* descent will be blunted (see Fig. 11–9). Lastly, in patients with tricuspid regurgitation, a positive *v* wave will take the place of the *x* descent. Increased amplitude of *x* descents—"*deep x* descents"—are classically seen in constrictive pericarditis (see Fig. 11–6), as the result of both enhanced annular descent and preserved atrial relaxation.

Abnormalities of the *v* Wave In severe tricuspid regurgitation, right atrial pressure rises as the tricuspid regurgitant volume enters the right atrium. This leads to two abnormalities of the *v* wave—an increase in its amplitude and a more premature inscription of its upstroke (see Fig. 11–12). The large *v* wave occurs throughout systole and, thus, should be timed with the carotid pulsation. The most extreme exemplification of this phenomenon is the occurrence of a single, large positive *v* wave, described as *ventricularization* of right atrial pressure tracings. This will manifest as a systolic reversal of flow on the hepatic vein Doppler tracing.

Abnormalities of the *y* Descent Increased amplitude of the *y* descent can be seen in any disease that leads to prominent rapid filling of the right ventricle in early diastole. This can be seen in tricuspid regurgitation with or without elevation in right heart filling pressures but also in abnormalities of right ventricular diastolic function, such as restrictive cardiomyopathy and constrictive pericarditis (see Fig. 11–9). The early rapid filling is seen as a prominent early diastolic forward flow on the hepatic vein Doppler velocity curve with a high initial E velocity and short deceleration time on the tricuspid inflow velocity curve.

Conversely, in cardiac tamponade there is blunting of the *y* descent given the impaired ventricular filling due to elevated intrapericardial pressures preventing early rapid filling (see Fig. 11–8). Reduction in amplitude and slope of the *y* descent is seen in tricuspid valve native or prosthetic stenosis.

Kussmaul Sign Kussmaul sign is characterized by an increase in jugular venous pressure associated with inspiration as opposed to usual drop that is seen in normal individuals (Fig. 11–13). Although described in constrictive pericarditis, the sign can be present in any disease associated with severe elevation in right-sided filling pressures.

Abdominojugular Reflux Also known as *hepatojugular reflux,* the term *abdominojugular reflux* better describes the maneuver, when the examiner applies gentle pressure to the center of the patient's abdomen (around the umbilicus). As abdominal pressure is applied, there is a transient, minor increase in jugular (central) venous pressure and an accentuation of jugular venous waveforms. The patient should be made aware of the maneuver in order avoid sudden abdominal muscle tensioning and an elevation of intrathoracic pressures (similar to the ones seen with Valsalva maneuver). Normally, these changes will only last a few beats (around 5 seconds) despite continued pressure and the venous pressure will return to baseline. A sustained response (lasting more than 10–15 seconds)[14] (Fig. 11–14) suggests elevated right-sided filling pressures.

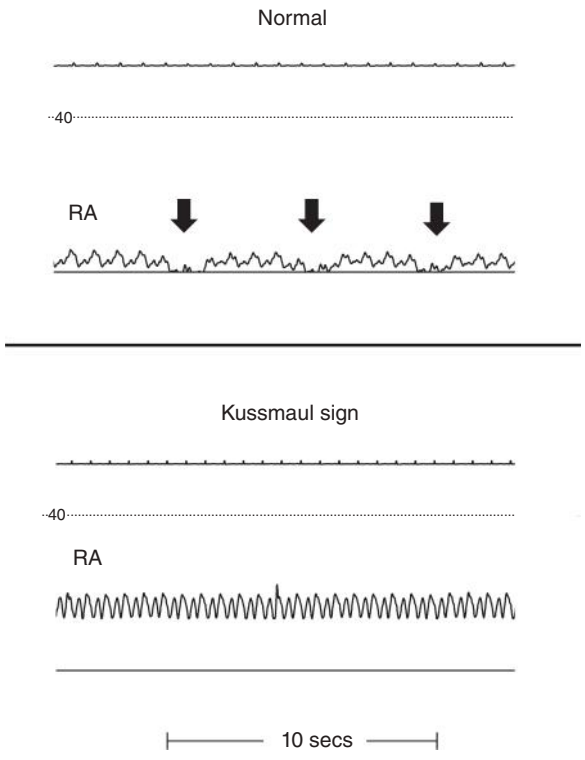

FIGURE 11–13. Kussmaul sign. Right atrial (RA) pressure tracings in a normal individual (*upper*) showing drops in mean right atrial pressure associated with inspiration (*arrows*). The Kussmaul sign (*lower*) corresponds to failure of mean right atrial pressure to drop on inspiration, as observed in this patient with constrictive pericarditis.

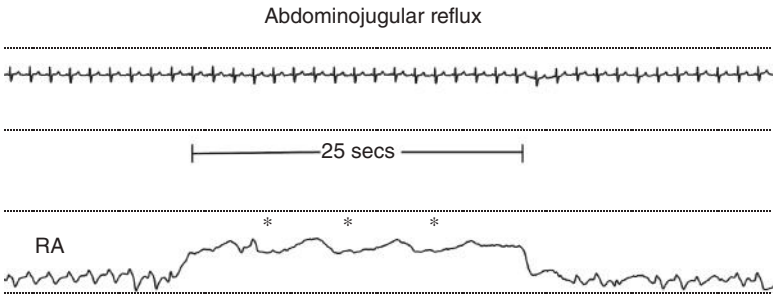

FIGURE 11–14. Abnormal abdominojugular reflux response in patient with heart failure. Right atrial (RA) pressure tracings illustrate the abnormal, sustained elevation in right filling pressures while pressure is applied to the patient's abdomen. The patient should to be instructed to breathe normally during the maneuver as illustrated here (inspiration marked by *asterisk*).

PHYSICAL EXAMINATION: AUSCULTATION HEART SOUNDS

TECHNIQUE

Proper technique must be reviewed prior to discussing auscultatory findings; this involves patient positioning, areas of auscultation, and the stethoscope itself. In order to avoid missing subtle findings, cardiac auscultation must be performed with the patient in three different positions: these positions include sitting, supine, and left lateral decubitus. The sitting position is important for auscultation of sounds emanating from the base of heart and great vessels as well as pericardial rubs and some tricuspid murmurs. Although most standard cardiac auscultation is performed with the patient supine, auscultation over the apex with the patient in the left lateral decubitus position brings out mitral murmurs and low-pitched cardiac sounds that might not be otherwise appreciated.

Five *areas* of auscultation have been classically described (Fig. 11–15)—*mitral* (over the apical impulse), *tricuspid* (fifth intercostal space at the left parasternal line), *pulmonic* (second intercostal space at the left parasternal line), *aortic* (second intercostal space at the right parasternal line) and *accessory aortic area* (third intercostal space at the left parasternal line); however, the stethoscope should not "jump" from one area to the other. Instead, the examiner should march the stethoscope from the apex toward the sternum, then up along the parasternal line, ending at the right parasternal area at the level of the second intercostal space. With the patient sitting, the opposite is then performed, using the right upper border at the starting point. This meticulous process ensures that abnormal auscultatory findings, heard over a very localized area, will not be missed as they might if only the five main areas are auscultated. When indicated, auscultation should also be extended to areas where murmurs typically radiate, such as the left axilla, neck, suprasternal notch, right infraclavicular area, and back. In each area, careful attention must be paid to each heart sound, systole, and diastole.

The examiner should always take full advantage of the two parts of the stethoscope—the bell and diaphragm. The bell is designed for auscultation of low-pitched sounds (third and fourth heart sounds, diastolic rumble, vascular bruits), whereas the diaphragm should be used for most heart sounds and murmurs. The bell should be gently

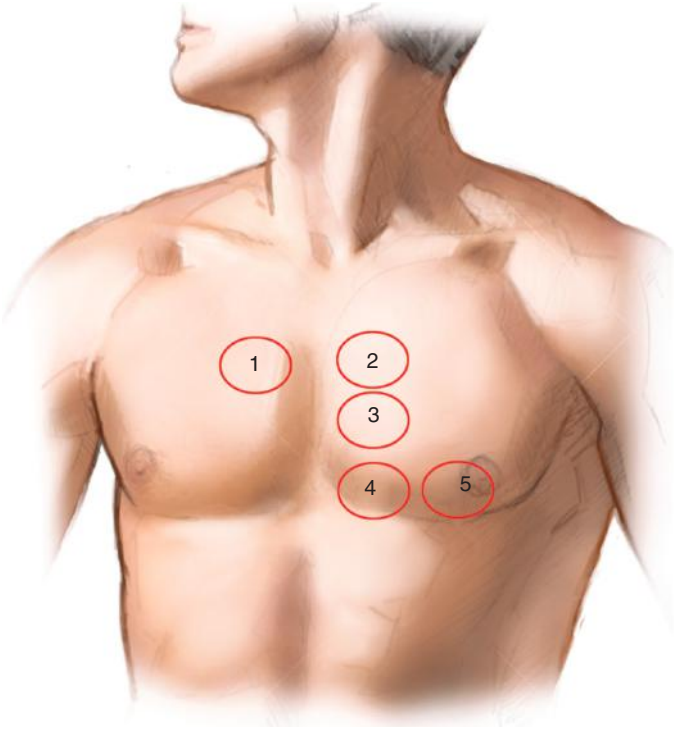

FIGURE 11–15. Areas of auscultation. The five classic areas of cardiac auscultation: 1 aortic (second intercostal space at the right parasternal line), 2 pulmonic (second intercostal space at the left parasternal line), 3 accessory aortic area (third intercostal space at the left parasternal line), 4 tricuspid (fifth intercostal space at the left parasternal), and 5 mitral (over the apical impulse).

applied to the bare chest; if excessive pressure is exerted the bell works as a diaphragm. The examiner, however, should also use this property in his or her favor—for example, in a patient with mitral stenosis variable stethoscope pressure should be used to focus on the rumble (bell) or the opening snap (diaphragm).

FIRST HEART SOUND

Normal First Heart Sound

The first heart sound (S1) corresponds to closure of the atrioventricular valves and, therefore, marks the end of diastole. It has two components—mitral (M1) and tricuspid (T1), with the latter following the former in normal circumstances. In most patients, M1 overshadows T1 and S1 is heard as a single sound. Sometimes, however, both components can be heard over the left lower sternal border, causing *splitting of S1*; this is a normal finding. Both components should have the same pitch and intensity and should be easily differentiated from a right-sided fourth heart sound (lower pitched) and an early systolic click (higher pitched and usually auscultated in a much wider area). Splitting of S1 might be slightly more prominent in patients with a right bundle branch block.

Abnormalities of the First Heart Sound

An increase in the intensity of the S1 can be encountered in situations where the PR interval is short, such as preexcitation or tachycardia. Sinus tachycardia associated with a hyperdynamic left ventricle is the most common cause of a loud S1 in clinical practice.

Mitral stenosis can lead to both increase and decrease in the intensity of S1, depending on degree of calcification and mobility of the valve leaflets. When mitral leaflets are pliable, the intensity of S1 is increased and this might be the only sign of rheumatic involvement of the mitral valve. The finding of a loud S1 also has therapeutic implications because it suggests that patient is likely a good candidate for percutaneous balloon valvuloplasty. In cases where the leaflets are calcific and immobile, the first heart sound becomes soft.

A decrease in the intensity of S1 is recognized in patients with prolonged PR interval or after long R-R intervals (diastolic periods) in patients with atrial fibrillation. Given the wide variability of R-R intervals in atrial fibrillation, S1 usually has variable intensity. Decreased S1 amplitude is also recognized in myopathic processes and in patients with severe reduction in systolic function due to a poorly contractile ventricle. Lastly, a soft S1 might also be observed in acute aortic regurgitation due to marked elevation in left ventricular diastolic pressures and early closure of the mitral valve.

Most clinical abnormalities alter intensity of the M1 component of the first heart sound. An exception is the patient with Ebstein anomaly when the large, sail-like anterior tricuspid leaflet gives rise to a loud T1 component.

SECOND HEART SOUND

Normal Second Heart Sound

The second heart sound (S2) corresponds to closure of the semilunar valves and has an aortic (A2) and a pulmonary (P2) component. The S2 sound is high pitched and best heard with the diaphragm. As opposed to S1, its two components are audible in the majority of patients. The S2 intensity and timing carry very valuable diagnostic information.

In order for the examiner to describe specific abnormalities of A2 and P2 (or to ensure that normality is indeed present), it is *mandatory* that both components are simultaneously auscultated and actively sought. P2 is typically audible in a limited area over the second left intercostal space and is sometimes only appreciated with the patient sitting. Therefore, one can only state that a *single S2* is present if appropriate auscultatory maneuvers are taken and a single component remains audible. In normal circumstances, both A2 and P2 should have similar intensities when auscultated simultaneously in the pulmonic position. A P2 should not be audible at other positions unless pulmonary hypertension is present.

Physiologic Splitting of S2

During normal inspiration, there is enhanced venous return to right-sided cardiac chambers, as well as increased capacitance in pulmonary vasculature. The combination of these two phenomena leads to an increase in right ventricular ejection time with inspiration and delay in closure of the pulmonary valve following inspiration. The normal lack of significant respirophasic change in left ventricular ejection time results in a single audible S2 during expiration (P2 occurring simultaneously with A2) and two distinct components on inspiration (with P2 following A2), so called physiologic splitting of S2 (Fig. 11–16).

Abnormal Splitting of S2

Nonphysiologic splitting of S2 can be categorized as paradoxical, persistent, or fixed (see Fig. 11–16). The abnormalities can be secondary to hemodynamic or conduction derangements. In *paradoxical splitting* of S2, there is a delay in aortic valve closure, with P2 preceding A2. S2 is split during expiration and becomes single during inspiration as P2 becomes closer to A2; hence the paradox (ie, the opposite of normal). This delay in A2 is secondary to a prolongation of left ventricular ejection time, which can be due to increase in afterload or nonuniform

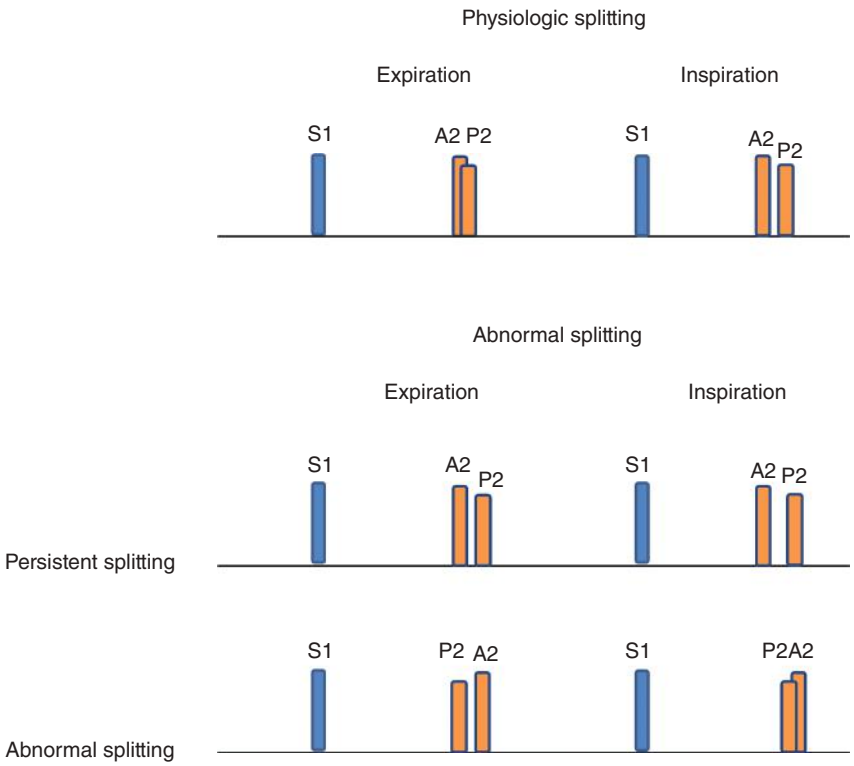

FIGURE 11–16. Respirophasic A2-P2 intervals in physiologic and abnormal splitting of second heart sound.

contraction of left ventricle (conduction abnormalities). The long ejection time can be measured from the duration of flow through the left ventricular outflow tract or across the aortic valve by Doppler echocardiography; it usually exceeds 300 milliseconds in these instances.

Although classically described in valvular aortic stenosis, paradoxical splitting of the S2 is more common in obstructive hypertrophic cardiomyopathy, suggesting severe dynamic left ventricular outflow obstruction. In severe aortic stenosis, the A2 component is either absent or diminished and splitting of S2 is rarely appreciated. In left bundle branch block, activation of left ventricular lateral wall is delayed, also prolonging ejection period. This is a sign of left ventricular dyssynchrony and, in our experience, patients with decreased left ventricular systolic function and paradoxical splitting of S2 appear to respond favorably to cardiac resynchronization therapy. Right ventricular pacing also promotes delayed activation of the left ventricle and paradoxical spitting of S2.

In *persistent splitting*, S2 is widely split at baseline (both A2 and P2 can be heard) but with inspiration the A2-P2 interval becomes longer. This is secondary to an underlying delay in the occurrence of P2. Wide splitting of S2, therefore, reflects abnormal right ventricular ejection hemodynamics. The most common cause in clinical practice is right bundle branch block, although severe increase afterload resulting from pulmonary hypertension can also lead to wide splitting of S2.

Fixed splitting of S2 is classically found in ostium secundum atrial septal defect, where wide splitting of S2 is present at baseline with minimal or no change in A2-P2 interval during inspiration. The wide S2 splitting on expiration is related to increased pulmonary vascular capacitance associated with increase pulmonary blood flow, delaying the P2 component. As a result of the interatrial communication, the decrease in venous return during expiration is compensated by an increase in left-to-right shunt without changes in right ventricular preload. The lack of significant respirophasic changes in both preload and afterload results in no change in right ventricular ejection period and, therefore, a fixed A2-P2 interval.

Abnormalities of S2 Components

A *loud P2* is a sign of pulmonary arterial hypertension; in severe cases of pulmonary hypertension, P2 is palpable. P2 is generally heard over a small area in the left upper chest; a P2 component that can be auscultated at other areas is a clue that P2 is increased. In general, a P2 heard at the left lower sternal border indicates moderate pulmonary hypertension and if audible at the apex indicates severe pulmonary hypertension.

A *diminished P2* is noted in patients with increased anteroposterior thoracic distance. The opposite is also true; patients with diminished anteroposterior thoracic dimension, such as patients with pectus excavatum, can have an abnormally loud P2. In patients with obstructive lung disease, increased lung volume contributes to decrease in P2, this being the most common cause for a single S2 in practice. A diminished or absent P2 is also noted in patients with severe valvular pulmonary stenosis. Lastly, a single S2 is a characteristic clinical finding in patients with congenitally corrected transposition, where the posterior location of the pulmonary valve prevents auscultation of P2 component.

A *loud A2* is expected in patients with severe systemic arterial hypertension. A very loud A2—*tambour like*—was also described in syphilitic aortitis, but the disease is almost rarely encountered nowadays.

A *diminished A2* is a classic finding of valvular calcific aortic stenosis and is also an important marker of disease severity, especially when the A2 component is absent. The presence of a normal A2 component in a patient with "severe aortic stenosis" and echo-Doppler findings of fixed obstruction should prompt investigation for subaortic or supravalvular obstruction.

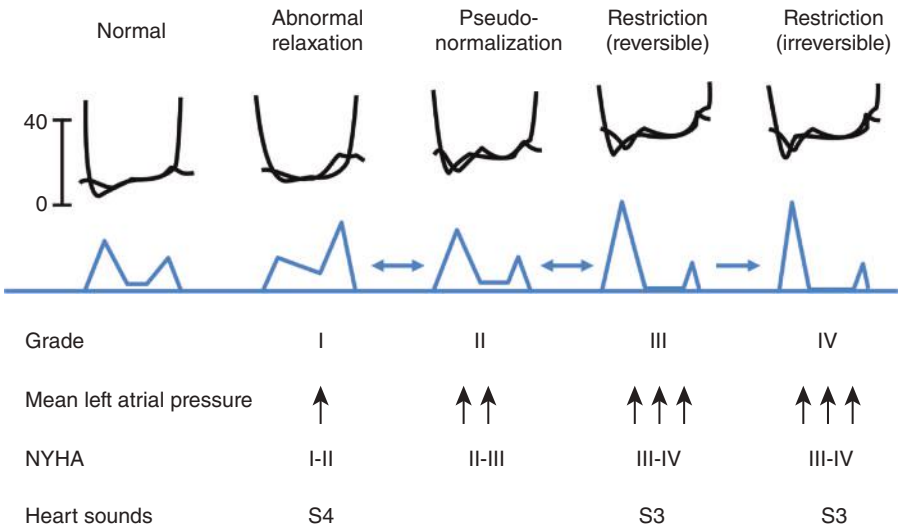

FIGURE 11–17. Auscultation findings in different stages of diastolic dysfunction. Left ventricular and left atrial pressure tracings (*black*) as well as mitral inflow Doppler pattern *(blue*) in different degrees of left atrial pressure elevation and diastolic dysfunction. Cardiac auscultation will reflect hemodynamic abnormalities and allows longitudinal assessment of filling pressures. NYHA, New York Heart Association.

FOURTH HEART SOUND

In the early phases of diastolic dysfunction, abnormal (prolonged) ventricular relaxation impairs early diastolic ventricular filling, decreasing the amount of filling in early diastole with a compensatory enhanced atrial contribution of diastolic filling.[15] An audible left heart fourth heart sound (S4) represents this prominent, forceful left atrial contraction into a noncompliant left ventricle. It occurs, therefore, in late diastole (presystole) and is never present in atrial fibrillation. A left-sided S4 is a low-pitched sound, typically only heard at the apex with the bell and easily missed if auscultation in the left lateral decubitus position is not performed.

Doppler echocardiographic findings that correlate to the presence of an audible S4 are that of an abnormal relaxation pattern (grade I pattern) (Fig. 11–17) on the transmitral flow velocity curve include a low E:A ratio and a prolonged deceleration time with a shortened duration of the *a* wave. There are also increased atrial reversal velocities on pulmonary vein echo-Doppler profiles. Left ventricular tracings will show a slow rate of fall of left ventricular pressure during isovolumic relaxation (reduced negative dP/dt), lack of rapid filling waves, and prominent *a* waves. Patients with impaired ventricular relaxation typically have normal mean left atrial pressures and thus are not in heart failure at rest but will develop shortness of breath with exertion as the diastolic filling period shortens. These patients rely on atrial contraction for diastolic filling, and thus loss of organized atrial contraction is generally poorly tolerated.

Abnormal ventricular relaxation occurs most frequently with left ventricular hypertrophy due to aortic stenosis, hypertrophic cardiomyopathy, and systemic hypertension. It also occurs with ongoing myocardial ischemia and is frequently observed as part of aging. Thus, an audible S4 is expected in all those entities, but should not be observed in young adults since myocardial relaxation is normal in that age group.

A right-sided S4 is usually associated with right ventricular pressure overload as seen in pulmonary hypertension, pulmonary stenosis, or early phases of restrictive cardiomyopathy. A right-sided S4 is usually heard at the left lower sternal border and increases with inspiration.

THIRD HEART SOUND

A third heart sound (S3) will occur when there is prominent early rapid ventricular filling during diastole. It is a low-pitched sound heard in early diastole, most likely due to tensing of the chordae as the left ventricle rapidly expands from the early filling. An S3 is best heard at the apex with the bell lightly placed and the patient in a left lateral decubitus position. It occurs 100 to 150 milliseconds after S2. This sound correlates with a high initial E velocity, an increased E:A ratio, and short deceleration time on the transmitral flow velocity curve.

There are a number of different etiologies for the generation of an S3. The most common is in a patient with an abnormal stiffness of the myocardium coupled with high filling pressures. The high left atrial pressure produces high driving pressure across the mitral valve to account for the early rapid filling, which is followed by a rapid increase in left ventricular diastolic pressure.[15] This is manifested as a steep rapid filling wave on left ventricular pressures tracing and large left atrial *v* waves (reflecting the pressure rise as pulmonary venous blood enters an overloaded left atrium). An S3 can be a dynamic finding and usually dependent on the volume status of the patient. If there is severe elevation of left atrial pressure, there will be an S3 on auscultation with a restrictive pattern on the transmitral flow velocity curve (high E:A ratio and short deceleration time) (see Fig. 11–17). However, with diuresis and lowering of the left atrial pressure, the transmitral flow pattern will change from a restrictive (grade III pattern) to pseudonormal (grade II pattern) and even delayed relaxation (grade I pattern) with disappearance of the S3 on examination. A persistent S3 despite treatment indicates the end stage of diastolic dysfunction (stage IV pattern) caused by severe irreversible fibrosis of the myocardium.

There are other etiologies for a S3 on examination, all of which reflect rapid early diastolic filling. Rapid early diastolic filling occurs in young healthy hearts due to vigorous ventricular relaxation, which "sucks" the blood in from left atrium to left ventricle in early diastole, allowing for a higher preload while maintaining low to normal pressures. The transmitral Doppler velocity curve will have the same appearance as a restrictive filling pattern (high E:A ratio and short deceleration time). However the mitral annular motion will be enhanced, seen as a high e′

velocity on the Doppler tissue velocity curve. Thus, S3s are often noted in young individuals, athletes, and pregnant patients. Conversely, they are rarely observed in patients older than 40 years; the presence of an S3 in patients older than age 40 suggests organic heart disease.

Constrictive pericarditis is also a form of severe diastolic heart failure, where the scarred, inelastic pericardium significantly impairs ventricular diastolic filling. Rapid filling waves on right and left ventricular hemodynamic tracings were some of the earliest hemodynamic signs of constrictive pericarditis described by cardiac catheterization. This prominent early diastolic filling is responsible for the *pericardial knock* heard in constrictive pericarditis. The knock tends to happen slightly earlier than the typical S3 and tends to have a higher pitch.

High E wave velocities and rapid filling waves on ventricular tracings can also be seen in severe mitral regurgitation. These are secondary to the large volume of blood rapidly returning from left atrium to left ventricle in early diastole. This increased rapid early diastolic filling can produce a low-pitched "filling sound" in mitral regurgitation and is a key marker of severe mitral regurgitation.

Although the findings described so far are related to left-sided etiologies (except for the pericardial knock, which is most likely originated from the right ventricle), the same rationale can be applied to right-sided lesions. A right-sided S3 can be heard in severe right ventricular diastolic dysfunction, such as severe right-sided heart failure and restrictive cardiomyopathy. Filling sounds can also be heard in severe tricuspid regurgitation and may be the only finding on auscultation; the systolic murmur may be barely audible due to equalization of the right atrial and right ventricular pressures during systole. Inspiration will enhance the intensity of a right-sided S3 and S4.

GALLOPS

When tachycardia is present in conjunction with a S3 or a S4, a *gallop rhythm* is said to be present. If both are present and diastolic periods are markedly diminished (due to faster heart rates), S3 and S4 will occur that same time—a *summation gallop*. This physical finding is analogous to the presence of fused E and A waves on mitral inflow echo-Doppler.

OPENING SNAP OF MITRAL STENOSIS

The opening snap of rheumatic mitral stenosis is an early diastolic, high-pitched sound originating from sudden tensing of abnormal leaflets and subvalvular apparatus during valve opening (equivalent of the "hockey stick deformity" on two-dimensional echocardiography). The finding of an opening snap has important clinical implications and deserves meticulous assessment. Because of its high pitch, the opening snap has a much wider area of radiation than the associated diastolic rumble of mitral stenosis; it can be heard at the left sternal border and even at the base of the heart in the aortic position. An opening snap has a much higher pitch than an S3, which is low pitched and heard only at the apex. It may be difficult to differentiate an opening snap from a loud P2, but a P2 should not be heard at the aortic position unless there are systemic levels of pulmonary hypertension.

The presence of a crisp opening snap suggests that the mitral leaflets are mobile and pliable and hence amenable to percutaneous balloon valvotomy. With more severe calcification and immobility of the leaflets, the opening snap becomes softer or disappears. The opening snap also allows the assessment of left atrial pressures and severity of the mitral stenosis. The mitral valve will open when left ventricular pressure drops below left atrial pressure. With mild degrees of stenosis, left atrial pressure is not severely elevated and mitral valve opening occurs late. The result is a long A2 (aortic valve closure) to opening snap (mitral valve opening) interval. With severe mitral stenosis, there is an elevated left atrial pressure with earlier opening of the mitral valve, generating a short A2-OS interval. Intervals of less than 70 milliseconds suggest severe mitral stenosis, whereas intervals greater than 100 milliseconds are compatible with mild obstruction.

SYSTOLIC CLICKS

Systolic clicks can arise from valvular and nonvalvular structures (eg, the great arteries). The two most common (and more relevant) clicks are the ones heard in bicuspid aortic valve and mitral valve prolapse. Although the former is typically described as an *ejection* click and the latter a *nonejection* click, a description based on timing is more appropriate.

The click of a bicuspid aortic valve (and sometimes of other congenitally abnormal aortic valves such as unicuspid valves) is secondary to the doming of the valve cusps in early systole as the aortic valve opens. The sound is high pitched (higher than S1) and sometimes quite loud; it should not be confused with a loud split S1 (two components of same pitch and intensity) or an S4 (low-pitched sound that vanishes if the bell is firmly pressed against the skin).

Doming of the cusps is also seen in valvular pulmonary stenosis, and an early systolic click is also typical. As in bicuspid aortic valve, the click of pulmonary stenosis introduces the systolic murmur. However, the click noted in pulmonary stenosis has a unique and important characteristic—it decreases in intensity with inspiration and moves closer to S1. This is the *only* right-sided auscultatory finding that diminishes with inspiration. As a result of increased venous return and increased right ventricular filling on inspiration, the pulmonary cusps acquire a more cephalad configuration. There is less cusp excursion during systole and a softer click.

Early systolic clicks can also arise from dilated great vessels (aorta or pulmonary artery). These are difficult to discern from the clicks associated with dysplastic or congenitally abnormal semilunar valves at the bedside. Another rare source of systolic clicks is an atrial septal aneurysm, arising from the motion of a very redundant valve of the fossa ovalis. These less common abnormalities should also be looked for when echocardiography studies are ordered for the evaluation of systolic clicks.

The systolic click(s) associated with mitral valve prolapse usually occurs in mid-to-late systole, when there is full excursion of the prolapsed mitral leaflet(s) into the left atrium. The click can be single or multiple (*salvo* of clicks). The timing of the click of mitral valve prolapse occurring later in systole helps to differentiate it from clicks arising from semilunar valves. With increased preload (squatting, supine) the click occurs later in systole, whereas decreased preload (Valsalva maneuver, standing) has the opposite effect.

MISCELLANEOUS

Pericardial rubs may have three components, one systolic and two diastolic. Systolic and presystolic sounds are most commonly present. The pericardial rubs are described as "scratchy," with a high pitch. Although the presence of pericardial rubs can be intermittent, the practitioner should optimize the patient's position in order to better detect the rub. Pericardial rubs are generally best heard with the patient sitting, leaning forward with held expiration.

There are extracardiac sounds that can be heard on auscultation of the heart. A mediastinal "crunch" is caused by inflammation or air in the mediastinum that is of high pitch and has a rhythm that corresponds to the cardiac contraction within this mediastinum; this sound is markedly enhanced during inspiration. Pleural rubs may be mistaken

for cardiac sounds, particularly in the patient who has tachypnea, and auscultation during held respiration is required to differentiate this sound from a cardiac etiology. Pacemaker wires can produce clicks and high-pitched "squeaks" resulting from excessive motion of the wires during the cardiac cycle.

PROSTHETIC HEART VALVES

Auscultation of prosthetic heart valves is an important component of the physical examination. All mechanical valves should produce a crisp, high-pitched sound during valve closure, irrespective of the type of valve. The older generation valves such as a ball–cage prosthesis and some of the tilting disk prostheses will produce a click during valve opening; however, the newer generation floating disk and bileaflet valves are usually silent with valve opening. There is always an intrinsic degree of obstruction with any prosthesis, which produces a short systolic ejection murmur in the aortic or pulmonic position, and may produce a diastolic rumble in the mitral or tricuspid valve position. However, murmurs of prosthetic valve regurgitation indicate pathology.

PHYSICAL EXAMINATION: AUSCULTATION MURMURS

Murmurs are the auscultatory equivalents of nonlaminar flow through an anatomic structure (eg, a cardiac valve or intracardiac shunt). When similar sounds originate from peripheral vessels, by convention, a *bruit* is described. In echocardiography, nonlaminar flow is manifest by turbulent high velocity flow and assessed by continuous-wave Doppler echocardiography. Although other factors play a role (eg, the size of an interventricular communication, the effective orifice area in a regurgitant atrioventricular valve or blood viscosity), murmurs tend to reflect the pressure difference between structures from which the murmur originates. The diastolic murmur from a stenotic atrioventricular valve (mitral or tricuspid) tends to be low-pitched and quiet, because atrial and ventricular diastolic pressures are typically low. The murmur of aortic regurgitation is a high-pitched "cooing" sound resulting from the high pressure difference between the aorta and left ventricular pressures during diastole.

When a murmur is identified, several characteristics need to analyzed and described; these include timing (systolic, diastolic, or continuous), pitch, intensity ("loudness"), contour (or shape, eg, crescendo vs decrescendo), and radiation. Dynamic changes, such as respirophasic or postextrasystolic changes and response to maneuvers should also be noted. The murmur intensity should be graded from I to VI (Table 11–5).

"Drawing" physical examination findings used to be part of clinical documentation, perhaps best exemplified in Paul Wood's legendary index cards. Although electronic clinical notes do not allow these features to be incorporated into patients' charts, we recommend trainees go through the exercise of drawing murmurs. These exercises force the examiner to critically review the auscultatory findings, which include the timing of onset and cessation of the murmur, the contour of the murmur, and its relationship to normal and abnormal heart sounds.

TABLE 11–5. Grading of Murmurs

Grade I	Faint murmur; heard only after few seconds of auscultation
Grade II	Moderately loud murmur heard immediately
Grade III	Loud murmur; not associated with a thrill
Grade IV	Loud murmur associated with a thrill
Grade V	Very loud; can be heard if only the edge of stethoscope is in contact with the skin
Grade VI	Loudest possible; can be heard with stethoscope just removed from the chest and not touching the skin

SYSTOLIC MURMURS

General Principles

The most commonly encountered systolic murmurs originate from regurgitant atrioventricular valves or from accelerated flow across semilunar valves. The shapes of those murmurs will reflect the differences in hemodynamics as well as dynamic changes in the valvular and subvalvular apparatus. These differences in timing of onset and cessation are reflected in the continuous-wave Doppler traces of the atrioventricular valve regurgitation and semilunar valve obstruction.

In typical atrioventricular regurgitation, the murmur starts at mitral valve closure and extends to the mitral valve opening (Fig. 11–18). As a result, the murmur will have its onset immediately after the first heart sound and will extend through the S2—*holosystolic*. Given the high pressure differences between ventricles and atria throughout systole, the murmur is high pitched and does not change in contour: hence the term *plateau*. An analogous process happens in ventricular septal defects, where the pressure gradient between left and right ventricles also extends from mitral valve closure (S1) to mitral valve opening.

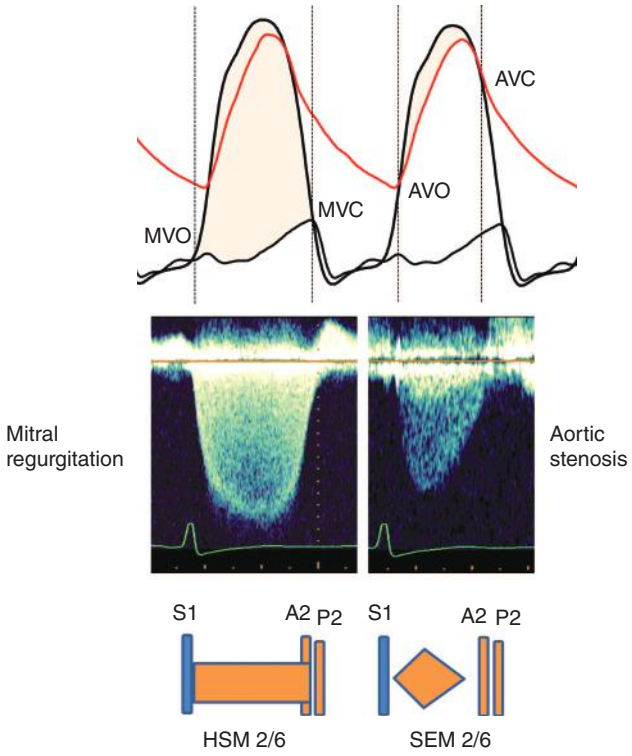

FIGURE 11–18. Auscultation findings in mitral regurgitation versus aortic stenosis. In mitral regurgitation (*left*), the murmur extends from mitral valve opening (MVO) to mitral valve closure (MVC) (*left upper*), which is appreciated by echo-Doppler (*left middle*). Note the murmur encompasses A2 (*left lower*). In aortic stenosis (*right*), the murmur will start at the end of isovolumic contraction (aortic valve opening [AVO], *right upper*) and terminates as isovolumic relaxation starts (aortic valve closure [AVC]). Echo-Doppler (*right middle*) also illustrates the shorter duration of aortic stenosis compared to mitral regurgitation. Note the murmur is ejection quality and does not encompasses A2 (*right lower*). HSM, holosystolic murmur; SEM, systolic ejection murmur.

Semilunar valves open when the ventricular pressure exceeds the pressure in the great vessels. Thus, these murmurs will start after S1 occurs (see Fig. 11–18). The shape of these murmurs will reflect the changes in ejection hemodynamics throughout systole giving rise to its diamond shape, where the murmur increases and then decreases in intensity (*crescendo-decrescendo)*. These systolic ejection murmurs have a harsher quality than the regurgitant murmurs.

Atrioventricular Valve Regurgitation: Holosystolic Murmurs

Mitral regurgitation murmurs are typically best heard over the cardiac apex, but radiation will vary depending on the underlying disease. When the mitral regurgitation jet is anteriorly directed (toward the aorta), as noted in patients with prolapse or a flail segment of the posterior mitral leaflet, the murmur radiates to the left sternal border. In posteriorly directed mitral regurgitation jets caused by prolapse or flail of the anterior mitral leaflet, the murmur radiates to the left axilla, back, and thoracic spine.

Although typically described as holosystolic and plateau in quality, *mitral regurgitation* murmurs will vary according to the underlying pathology. In regurgitation resulting from rheumatic mitral valve or flail mitral leaflet, the murmur will be holosystolic. In mitral valve prolapse with an intact chordal apparatus, the regurgitation starts after the leaflet has prolapsed into the left atrium; a gap between S1 and the murmur is then present, which frequently starts after a midsystolic click. The late occurrence of a murmur in mitral valve prolapse is of great diagnostic importance. First, it suggests that the tendinous cords are intact and no flail segment is present. Secondly, it suggests that the regurgitation is not severe; late (ie, nonholosystolic) murmurs are rarely severe. Doppler echocardiography will clearly demonstrate the difference between a holosystolic murmur and a late systolic regurgitation both on color flow imaging and continuous-wave Doppler velocity curves (Fig. 11–19).

In secondary mitral regurgitation (the mitral regurgitation results from a disease of the ventricle and not the valve), the murmur can be soft and underwhelming despite the presence of severe regurgitation; this is likely due to a combination of reduced ventricular contraction and a large regurgitant orifice. If the mechanism is annular dilation, the murmur tends to be holosystolic, whereas in ischemic mitral regurgitation the murmur may be late peaking. Ischemic mitral regurgitation can also be dynamic, with variation in the physical examination findings depending on the presence or absence of ischemia.

In *acute severe mitral regurgitation* secondary to papillary muscle rupture or mitral valve dehiscence, the left atrium is not accustomed to the severe volume overload. A very large *v* wave is generated because of lack of atrial compliance, and left ventricular and left atrial pressures essentially equalize in systole (Fig. 11–20). The auscultatory result is a very short, early systolic murmur or even absence of a murmur. Accordingly, color-flow and continuous-wave Doppler findings are also often very brief, making the diagnosis of acute mitral regurgitation challenging. Thus, a high clinical index of suspicion is needed. Patients with acute severe mitral regurgitation are in frank pulmonary edema and therefore sitting upright, whereas patient with ventricular septal defect can tolerate the supine position.

Tricuspid regurgitation is usually secondary to dilatation of the tricuspid valve annulus and manifested as a holosystolic murmur, best heard at the left lower sternal border. The murmur can be very subtle, rarely greater than a grade II in intensity. Although described as a classic sign in tricuspid regurgitation, an increase in the intensity of the holosystolic murmur (Carvallo sign) is not a sensitive sign. The clinical suspicion of severe tricuspid regurgitation is made more on the basis of a large V wave in the jugular venous contour rather than the presence of a murmur.

Ventricular septal defects, most often muscular, can also present as holosystolic murmurs. Small ventricular septal defects are usually associated with a loud murmur, frequent accompanied by a thrill,

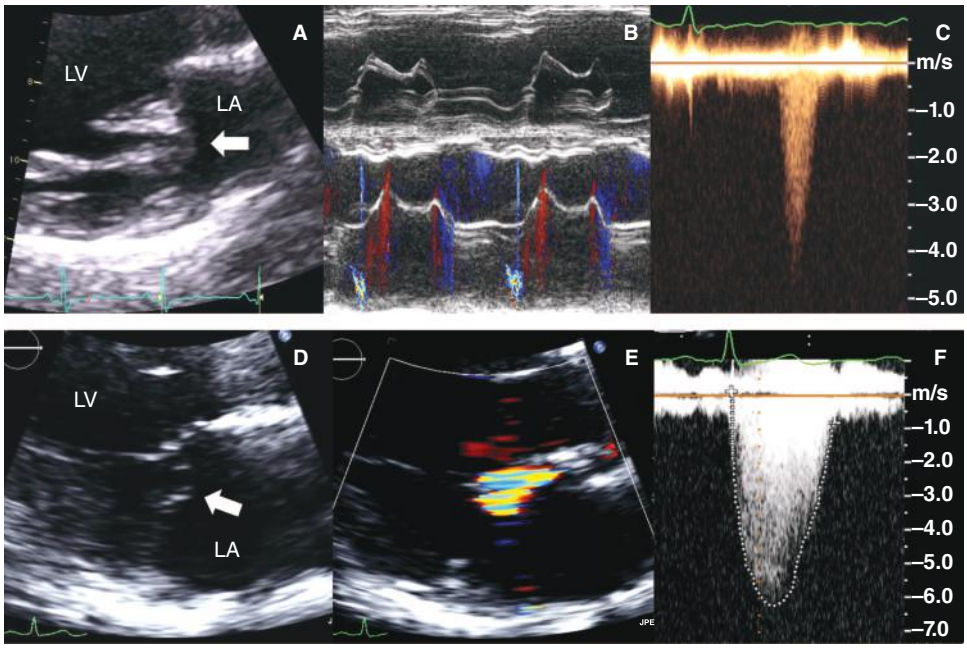

FIGURE 11–19. Echocardiographic findings in two patients with posterior mitral valve leaflet prolapse and left ventricular enlargement. *Upper* panels show two-dimensional (**A**), color M-mode (**B**) and continuous-wave Doppler (**C**) echocardiography findings in a patient with mild mitral regurgitation; auscultation revealed a late systolic murmur, consistent with mild mitral regurgitation. *Lower* panels show two-dimensional (**D**) and color Doppler (**E**) on a separate patient. Because of the eccentric jet, quantification of the severity of mitral regurgitation could not be performed by echocardiography. Physical examination, however, revealed a loud holosystolic murmur, suggestive of severe mitral regurgitation. The holosystolic nature of the murmur can also be appreciated by continuous-wave Doppler signal (**F**).

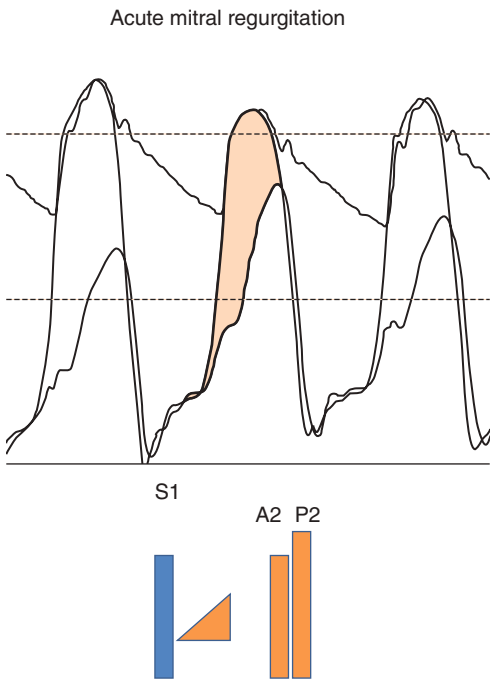

FIGURE 11–20. Acute mitral regurgitation. Aortic, left ventricular, and left atrial pressure tracings showing very large *v* waves in the setting of torrential, acute mitral regurgitation (*upper*). The murmur is short because of rapid equalization of pressures between the left ventricle and left atrium.

and best heard at the left lower sternal border. If there is a large septal defect, the murmur can be soft or even absent, particularly when an Eisenmenger's physiology is present.

Systolic Ejection Murmurs

In *aortic stenosis*, a diamond-shaped murmur can be auscultated at the third left intercostal space, second right intercostal space, or supraclavicular region, usually radiating to the carotids. In young patients with bicuspid valve–related aortic stenosis, the murmur is often quieter over the precordium and best heard toward the suprasternal notch. The murmur of aortic stenosis can radiate and, in fact, increase in intensity, toward to the apex—the *Gallavardin phenomenon*.[16] As the disease progresses; the peak of murmur occurs later in systole; it has an early systolic peak in mild and moderate aortic stenosis and late peak in severe aortic stenosis (Fig. 11–21). The duration of the murmur becomes longer as the severity increases, so that in severe aortic stenosis the murmur extends to the second heart sound. The pitch of the murmur also tends to change with more severe stages, when the murmur acquires a high-pitched, musical characteristic. The severity of aortic stenosis based on the quality of the murmur is reflected in the continuous-wave Doppler velocity curves, with early peaking velocities in mild stenosis and mid to late peak (longer acceleration time) in more severe aortic stenosis.[17] The more severe the stenosis, the longer the ejection time on the continuous-wave Doppler tracing.

Pulmonic stenosis is less common than aortic stenosis. There will be a systolic ejection murmur heard best in the pulmonic position at the left sternal border and radiate to the left clavicle. Early ejection clicks and abnormalities of S2 are frequently present as described previously.

In obstructive hypertrophic cardiomyopathy, two distinct systolic murmurs are audible. The harsh murmur related to subaortic obstruction is generally best heard at the left sternal border and will have crescendo-decrescendo contour with a midsystolic peak. A separate, murmur is heard best at the apex and starts in midsystole. It is caused by the secondary mitral regurgitation from distortion of the mitral valve apparatus related to systolic anterior motion of the mitral valve. This is of clinical importance because relief of the outflow obstruction will also reduce the mitral regurgitation. Both murmurs will increase in intensity during the strain phase of the Valsalva maneuver, on standing and post–premature ventricular beats. Both murmurs will also decrease with squatting. It is also important to note the dynamic changes in the apical murmur (in addition to the murmur associated with the left outflow tract obstruction) during maneuvers, particularly

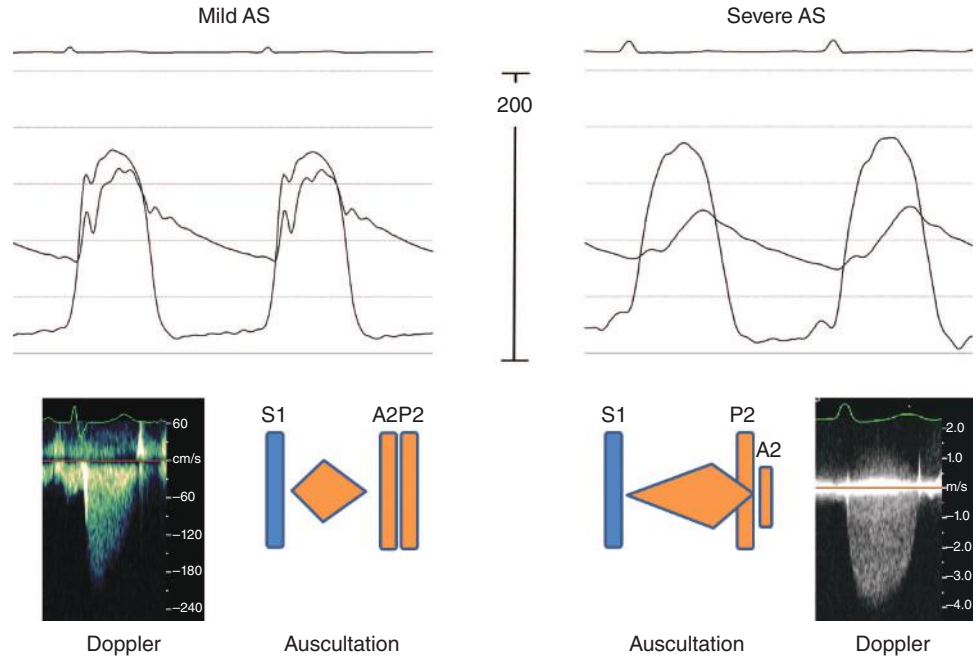

FIGURE 11–21. Invasive hemodynamic, echo-Doppler, and auscultatory findings in mild versus severe aortic valve stenosis. In mild aortic stenosis (AS), the peak aortic pulse occurs early in systole, as illustrated by cardiac catheterization (*left upper*) and echo-Doppler (*left lower*). At the bedside, this will be appreciated as an early peaking systolic ejection murmur (*left lower*). In severe aortic valve stenosis (*right*), the prolonged ejection time will result in late peaking of the aortic of aortic pressure tracing and continuous-wave Doppler signal (*right lower*).

with squatting. If the apical murmur does not change, a primary mitral valve problem should be suspected.

Pathologic murmurs should be differentiated from *innocent* or *benign* murmurs. Benign murmurs arise from increased flow through a semilunar valve and thus have a diamond-shape. However, they typically peak in early systole, and are usually grades II or less in intensity, and end before S2. Innocent murmurs change according to position, being more prominent in the supine compared to sitting position. In childhood, an innocent murmur is usually caused by increased flow across the pulmonic valve and is heard best in the pulmonic position at the upper left sternal border. In older age, aortic valve sclerosis occurs because of mild thickening of the aortic valve cusps, and a soft ejection murmur is heard at the aortic position in the upper right sternal border. In both of these cases, a normal carotid upstroke and normal components of S2 are used to help in differentiating these from pathological murmurs. *Functional* murmurs result from increased forward flow across a normally functioning semilunar valve. These murmurs can be observed in pregnancy, high-output state, or anemia. The high-output state associated with an arteriovenous fistula in patients with chronic renal failure is commonly associated with a loud functional murmur, which will decrease in intensity with temporary occlusion of the fistula.

DIASTOLIC MURMURS

General Principles

Diastolic murmurs can arise from atrioventricular valve stenosis and semilunar valve regurgitation. The timing and quality of the murmurs are based on the pressure differences across the abnormal valves, which are reflected in the continuous-wave Doppler velocity curves of these valve abnormalities. It is primarily the pitch and location of diastolic murmurs that defines the etiology.

Diastolic Rumbles

The *rumble of mitral stenosis* is a subtle, low-pitched murmur, best heard over the apex; occasionally the murmur is heard only with the patient in left lateral decubitus. The bell should be placed very lightly over the apex and the examiner should concentrate on listening during diastole. The duration of the murmur (early-mid to holodiastolic) tends to be directly proportional to the diastolic gradient and severity of stenosis. If sinus rhythm is present, the murmur increases during atrial contraction—*presystolic accentuation*. Because diastolic mean gradients are also directly related to heart rate, maneuvers that increase heart rate (sit-ups or phantom bike) facilitate detection of the murmur. Tricuspid stenosis is rare and usually occurs in conjunction with mitral stenosis. Faint diastolic rumbles are often noted in patients with prosthetic mitral or tricuspid tissue prostheses; however, the presence of a loud diastolic murmur in a patient with a mitral or tricuspid prosthesis should raise concern for dysfunction or thrombosis.

Functional diastolic rumbles can occur with increased forward flow across the atrioventricular valves (eg, in patients with atrial septal defect); a flow rumble is noted due to increased flow across the tricuspid valve related to the left-to-right shunt. A diastolic flow murmur is also heard in patients with severe mitral or tricuspid regurgitation caused by increased return flow across the valve. A middiastolic rumble—*the Austin-Flint murmur*—may be heard in aortic regurgitation when an eccentric jet hits the anterior leaflet of mitral valve, causing it to reverberate and generating the apical rumble.

Diastolic Decrescendo Murmurs

The murmur of *aortic regurgitation* is a diastolic decrescendo, high-pitched blowing murmur, usually heard best at the left intercostal border. It is best heard using the diaphragm placed firmly in the sitting position. To hear a soft murmur, the patient should lean forward with a breath held. The duration as well as the intensity of the murmur are generally related to the severity of the regurgitation. In mild regurgitation, the murmur is early diastolic, whereas a holodiastolic murmur suggests more severe regurgitation. However, it is the peripheral signs of a wide pulse pressure that are most indicative of severe aortic regurgitation. Aortic regurgitation murmurs heard over the second right intercostal space result from annular dilatation, whereas murmurs heard over the third left intercostal space result from a valvular process.

The murmur associated with pulmonary regurgitation is typically heard over the second left intercostal space, has a low pitch, and can be difficult to hear. The bell of the stethoscope is generally used. The murmur typically increases with inspiration, allowing its differentiation from aortic regurgitation. In very severe cases of pulmonary regurgitation, there is equalization of right ventricular and pulmonary artery diastolic pressures in early-to-mid diastole, rendering a rather short murmur. Functional pulmonary regurgitation can also be present when there is severe pulmonary hypertension—*the Graham-Steel murmur*. This murmur has a high pitch compared to primary pulmonary regurgitation and follows a loud pulmonary component of the second heart sound, suggesting the underlying association.

CONTINUOUS MURMURS

The continuous murmur is characterized by a "to-and-fro" sound with no interruption between systole and diastole. The pitch should be similar but the intensity can vary throughout the cardiac cycle. By definition, the continuous murmur envelops the heart sounds. This is distinctly different than a systolic and diastolic murmur, as noted in mixed aortic valve disease. In that case, one will hear a harsh, diamond-shaped systolic murmur, a second heart second (which might be single), and a diastolic murmur. These murmurs will have two distinctly different pitches.

The most common continuous murmur seen in current practice is secondary to iatrogenic arteriovenous fistulas (for hemodialysis), which is generally appreciated in the region of the clavicle on the respective side. Other causes of continuous murmurs are rare and include patent ductus arteriosus (best heard over the left infraclavicular area), ruptured sinus of Valsalva aneurysm, coronary fistula, intrathoracic arteriovenous fistulae, severe coarctation of the aorta, and a surgically created shunt (eg, Blalock-Taussig, Potts, Waterston).

The venous hum is a continuous murmur heard on auscultation of the neck. It results from a high flow in the internal jugular vein, which most likely causes a vibration of the venous wall. It is most commonly heard in young otherwise healthy individuals and is not associated with pathology. The venous hum will disappear with the supine position or with compression of the vein itself.

DYNAMIC AUSCULTATION

Dynamic auscultation should play an integral role in differentiating the etiology of systolic murmurs. It should also be performed during examination of young individuals engaged in competitive sports, in whom a latent obstruction from obstructive hypertrophic cardiomyopathy could be missed if maneuvers are not performed. Dynamic auscultation includes respirophasic changes and changes in murmur intensity on postectopic beats, as well as changes induced by specific maneuvers as well.

Inspiration increases venous return to the right cardiac chambers, augmenting right-sided murmurs and diastolic sounds. The exception to the rule is the systolic click of pulmonary stenosis, which diminishes with inspiration. Typically described as a classic sign of tricuspid

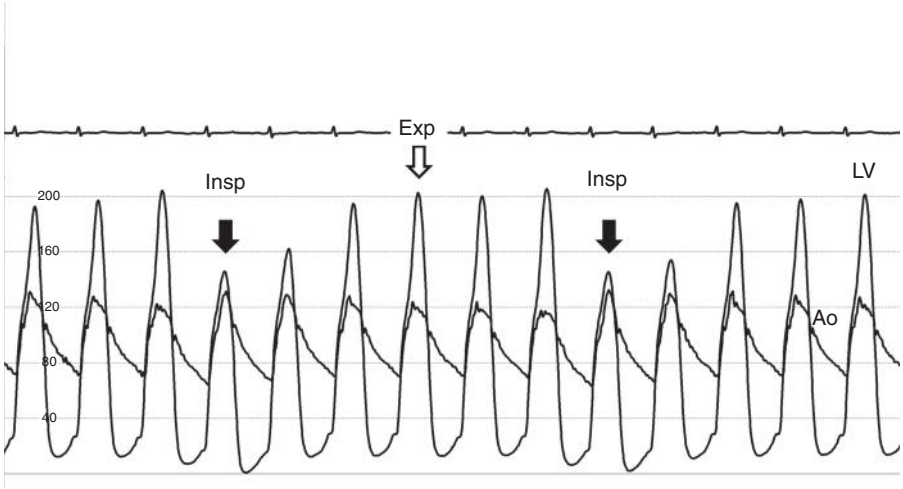

FIGURE 11–22. Respirophasic hemodynamic changes observed in hypertrophic obstructive cardiomyopathy. Inspiration leads to increased left ventricular afterload; as a result, the systolic gradient between the left ventricle and aorta decreases with inspiration. At the bedside, this is manifested by a decrease in the systolic ejection murmur noted with inspiration. The presence of this finding suggests dynamic instead of fixed outflow tract obstruction as the source of the murmur.

regurgitation (versus other systolic murmurs) is the Carvallo sign: an increase in the intensity of the murmur with inspiration. Negative intrathoracic pressures generated by inspiration lead to an increase in left ventricular afterload; therefore, the dynamic left ventricular outflow tract systolic murmur of hypertrophic cardiomyopathy will decrease on inspiration (Fig. 11–22).

In patients with systolic murmur, attention should be paid to the change in intensity of the murmur on the postectopic beats. There is an increase in ventricular contractility and a decrease in afterload on the postectopic beat; thus, there will be an increase in the intensity of the murmur with both fixed (aortic stenosis) and dynamic (hypertrophic cardiomyopathy) left ventricular outflow tract obstruction. This response is much more striking in the setting of obstructive hypertrophic cardiomyopathy because there will also be an increase in the degree of obstruction (Fig. 11–23). Alternatively, in patients with mitral regurgitation, there will be no change in the intensity of the murmur on the postectopic beat due to the decrease in afterload.

The *Valsalva maneuver* consists of expiration against a close glottis, generating in an increase in intrathoracic pressures of 30 to 40 mm Hg for a least 10 seconds. It is a method by which systolic murmurs may be differentiated. A simple way of performing the maneuver is by placing the examiner's hand over the patient's abdomen and asking the patient to push against it. The normal response to the maneuver consists of four phases[18]: phase I, a transient increase in systemic blood pressure during the strain phase secondary to the elevation in intrathoracic pressures; phase II, a decrease in pulse pressure and stroke volume to decreased venous return, which results in reflex tachycardia (the so-called *active phase*); phase III, further decrease in blood pressure due to the initial release of the straining phase; and phase IV, an overshot of blood pressure levels over the ones observed at baseline. Each of these phases is associated with changes in heart rate; the most important ones are the reflex tachycardia observed in phase II and reflex bradycardia in phase IV as blood pressures increases (Fig. 11–24).

Given the reduction in stroke volume occurring during phase II of the maneuver, most systolic murmurs will decrease during that phase; the exceptions are the murmurs of mitral valve prolapse and hypertrophic cardiomyopathy. In mitral valve prolapse, there is further atrial displacement of the leaflets during phase II, resulting in an earlier click

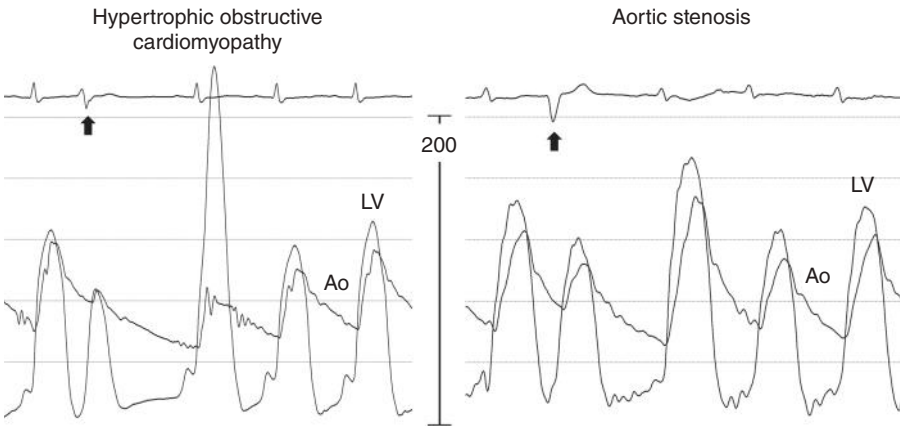

FIGURE 11–23. Postextrasystolic response in hypertrophic obstructive cardiomyopathy versus aortic valve stenosis. Aortic and left ventricular pressures tracings illustrate the postectopic beat (*arrow*) response in dynamic outflow tract obstruction (*left*) versus fixed aortic stenosis (*right*). Although systolic gradients increase in both diseases, the response is much more exuberant in hypertrophic cardiomyopathy. This phenomenon can also be appreciated at the bedside; the murmur of hypertrophic cardiomyopathy will become much louder compared to the murmur of aortic stenosis after a premature beat. Ao, aorta; LV, left ventricle.

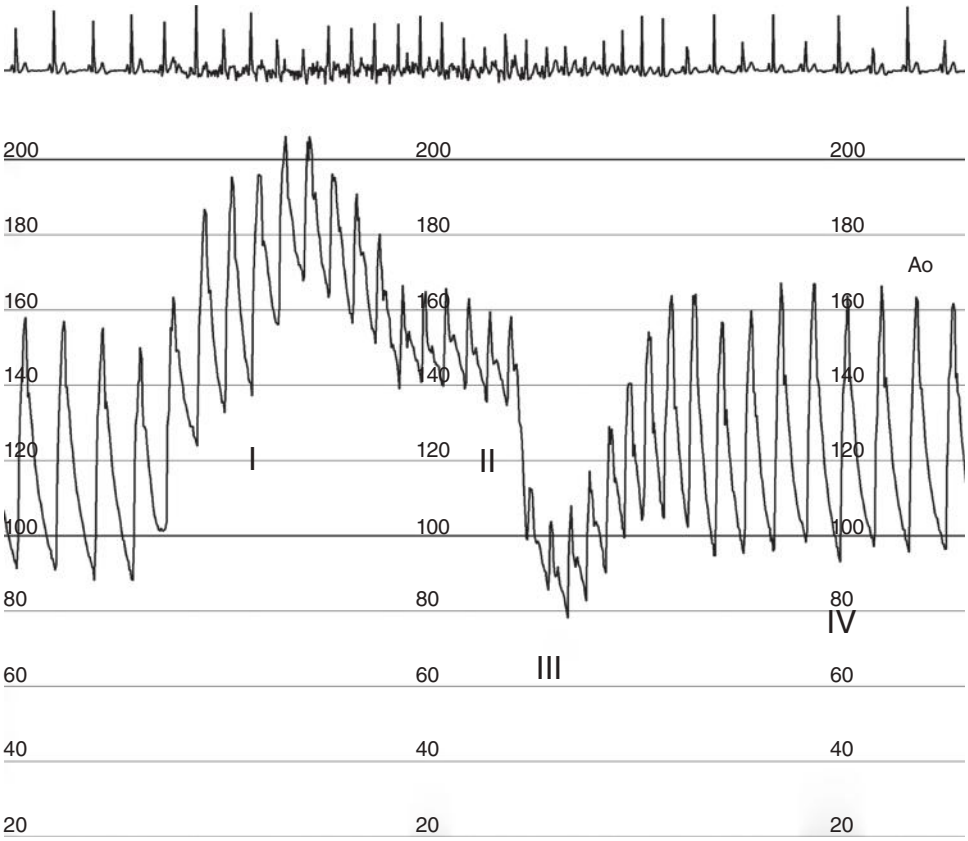

FIGURE 11–24. Valsalva maneuver. The normal hemodynamic changes during the four phases of the Valsalva maneuver are shown: phase I, transient increase in aortic pressure during the strain phase; phase II, decrease in pulse pressure with reflex tachycardia; phase III, further decrease in aortic pressure after the initial release of the strain phase; and phase IV, overshoot of the aortic pressure levels above baseline. Ao, aorta.

and longer and typically louder murmur. In hypertrophic cardiomyopathy, the smaller ventricular cavity will lead to more severe subaortic obstruction and a louder murmur. Of note, these changes tend to be more pronounced if the patient is sitting or upright. It is important to document the change in intensity of the murmur only after at least six to eight beats during the strain phase, because this is the time period during which the change in blood volume must circulate through the pulmonary circulation to reach the left side of the heart. The examiner should also note the changes in heart rate through the phase II of the maneuver. If there is not a tachycardia during phase II, there is autonomic dysfunction, autonomic blockade (eg, beta-blockers) or high filling pressures (Fig. 11–25). In these cases, the response of a murmur will not be useful. During phase 4, all murmurs usually increase, except with hypertrophic cardiomyopathy.

The stand-to-squat-to-stand maneuver is particularly helpful in patients with hypertrophic cardiomyopathy and mitral valve prolapse. Squatting increases both preload and afterload. As a result, squatting significantly diminishes (or even abolishes) the intensity of the murmur of obstructive cardiomyopathy. This is also true for mitral regurgitation that is secondary to systolic anterior motion of the mitral. In mitral valve prolapse, the systolic click occurs later in systole and the murmur becomes shorter (Fig. 11–26). All other murmurs will have either an increase in intensity or no change in intensity with squatting. On standing, there is an immediate decrease in afterload followed by a decrease in venous return after several beats. Thus, there will be an immediate and then progressive increase in the intensity of the dynamic outflow murmur of hypertrophic cardiomyopathy.

In instances where there are very soft murmurs out of proportion to the presenting symptoms, a reexamination after exercise may reveal a significant change in the intensity and characteristic of the murmur. This is important in patients with hypertrophic cardiomyopathy and a labile outflow tract obstruction or in patients with mitral stenosis. Exercise can be performed by either sit-ups on the examining table, step-ups on the bench, or even walking up and down hallways and stairwells. These exercise maneuvers are also useful to bring out an S3 if absent at rest. Handgrip isometric exercise to increase afterload and amyl nitrate to decrease afterload are maneuvers that have been used to differentiate the rumble of mitral stenosis from an Austin-Flint murmur, but they are no longer necessary with the advent of echocardiography.

PHYSICAL EXAMINATION: STEPWISE APPROACH TO THE PATIENT

Each clinician needs to develop his or her own stepwise approach to the cardiovascular examination. We wish to present our own approach (Table 11–6), which we apply in a general fashion to the majority of patients presenting with cardiovascular disease, understanding that the examination is always then focused on an individual patient's problem. We feel that the initial history should be taken with the patient fully dressed to allow a one-to-one relationship to be built. However, for a comprehensive physical examination, it is necessary for the patient to be undressed with an appropriate gown or cover-up. An examination should never be done placing the stethoscope under a shirt or blouse, and full inspection of the chest and extremities is always necessary.

The initial approach that we take is to approach the patient in the sitting position, looking at the overall appearance to determine if there

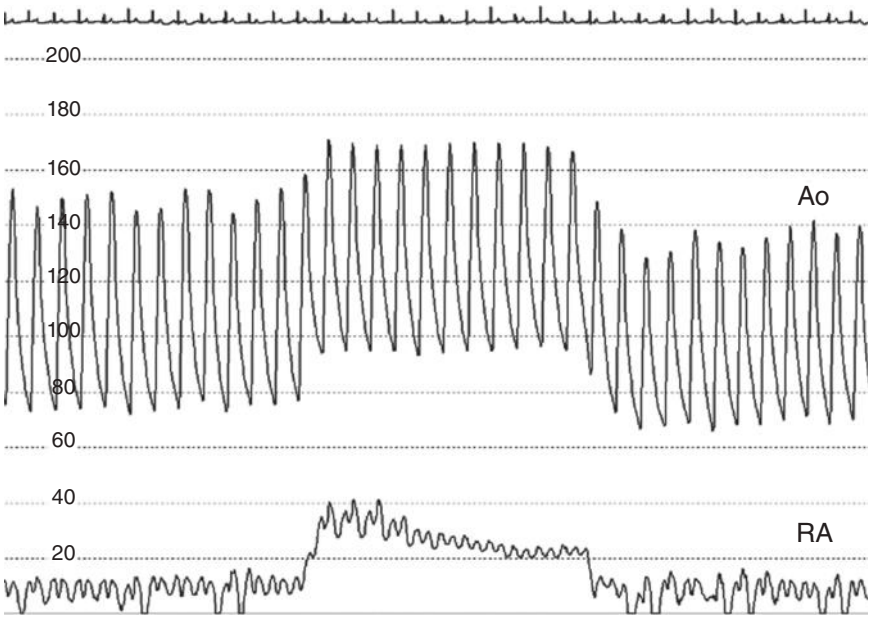

FIGURE 11–25. Valsalva maneuver in patient with increased left atrial pressure. Note the lack of tachycardia during the Valsalva maneuver. Although this response can be seen in elevated left-sided filling pressures, beta-blocker use or autonomic dysfunction might result in a similar response. Ao, aorta; RA, right atrium.

are unusual features that may suggest a syndrome. Shaking the hands will help in a frailty assessment as well as determining tissue perfusion. Palpating the radial pulse in both wrists will provide the heart rate and rhythm and any blood pressure differences in the two upper extremities. Looking at the nail beds is important for the presence of clubbing, cyanosis, or high pulse pressures. Then taking the blood pressure by cuff in both arms should be performed.

Inspection of the rest of the chest and extremities will identify skin lesions, skin infections, or prior surgical scars that may influence the diagnosis and decision making. Examining the venous pulsations in the sitting position will provide an initial clue as to whether there is elevation of venous pressure. Palpation of the carotid and brachial arteries is then

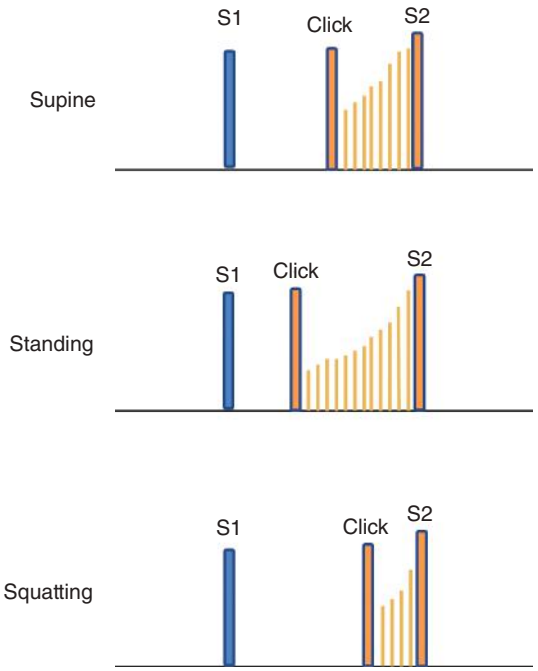

FIGURE 11–26. Positional changes in the systolic click and murmur of mitral valve prolapse. S1, first heart sound; S2, second heart sound.

TABLE 11–6. Basics Steps of the Cardiovascular Examination

Sitting position

1. General inspection, including dental examination
2. Shake hands and palpate radial pulse and inspect nail bed
3. Manual blood pressure measurement in both arms
4. Inspection of chest and lower extremities
5. Palpation and auscultation of the carotids
6. Palpation of the chest
7. Lung examination
8. Auscultation of the precordium with the diaphragm: start at the right upper sternal border, toward the right upper sternal, and finally down toward the apex

Sitting to supine position

9. Estimate of central venous pressures and venous contour (head of the bed might need to be lowered if venous pressure is normal)

Supine position

10. Inspection of the precordium
11. Palpation of the apical impulse and right ventricle
12. Auscultation of the precordium with the diaphragm from the apical area toward the sternal border, then up to left upper border, and finally at the right upper sternal border

Left lateral decubitus

13. Palpation of the apical impulse
14. Auscultation of the apex with the bell

Remaining parts of the general examination with particular attention to liver size, presence of ascites, leg edema, and vascular examination

performed, listening first for bruits. Palpation of the chest for thrills and palpable heart sounds is done next, followed by auscultation of the lungs.

Auscultation of heart sounds in the sitting position should be performed using the diaphragm starting at the base of the heart, inching across to the left sternal border, and then inferiorly to the lower left sternal border and then to the apex. In each position one should listen to S1, S2, systole and diastole. In particular, the splitting of S2 should be evaluated in the sitting position. Aortic and pulmonary outflow murmurs should be evaluated. Aortic and pulmonic regurgitant murmurs should be sought with the patient leaning over with breath held at end expiration. Pericardial rubs are best heard in this position.

Following the auscultation in the sitting position, an examination of the venous pressure and venous contour should be done, with a gradual change in the position of the patient from sitting at 90 degrees down to the supine position until the venous pulsations are visible in the internal jugular vein. Once the top of the pulsations is established the height of the venous pressure is estimated, usually at 45 degrees or less.

The patient is then placed in the supine position and palpation is then performed again, primarily to feel any parasternal lift and the position of the apical impulse. Auscultation is then performed starting from the apex to the left sternal border up to the base of the heart. Again, S1, S2, systole and diastole are listened to at each position.

The patient is then placed in the left lateral decubitus position. The apical impulse is palpated, this time to determine the contour of the impulse, whether localized or enlarged, sustained or hyperdynamic or feeble, and to feel for and palpable S4 or S3. Auscultation is then performed with the bell at the apex, specifically to listen for diastolic filling sounds and diastolic rumbles.

Finally, examination of the abdomen is performed, palpating for the liver and aorta, and listening for abdominal bruits. Examination of the lower extremities for edema, lesions, and palpation of all pulses should be done, always feeling the radial and femoral pulses simultaneously.

Additional focused parts of the examination should be performed depending on the clinical scenario. In patients with suspected constrictive pericarditis, a more detailed evaluation of the venous pressure and contour is required. In patients who present with exertional dyspnea and no significant findings on initial examination, repeating auscultation during exercise may elicit an S3 or diastolic rumble. Patients with hypertrophic cardiomyopathy should always undergo further dynamic auscultation with the Valsalva maneuver, stand-to-squat-to-stand, and even exercise to further evaluate a dynamic obstruction. Table 11–7 outlines the important physical findings for each individual cardiac lesion which add in diagnosis and determination of severity.

TABLE 11–7. Summary of Physical Examination Findings According to the Lesions[a]

	Jugular Venous Examination	Arterial Pulse	Palpation	Auscultation
Mitral regurgitation	Usually normal; increased *a* wave if pulmonary hypertension is present	Usually normal; sometimes brisk but low amplitude.	**Displaced and diffuse apical impulse**	Soft S1; **loud P2**; holosystolic or mid-late murmur (if so, hardly ever severe); **diastolic rumble** (flow murmur); **diastolic filling sound (S3)**
Mitral stenosis	Usually normal; increased *a* wave if pulmonary hypertension is present	Low amplitude	Normal or small apical impulse; tapping apical impulse; **parasternal lift**	Loud or soft S1; **loud P2**; opening snap **(A2-OS interval < 60–70 ms in severe cases)**; diastolic rumble with/without presystolic accentuation
Aortic stenosis	Usually normal	**Parvus and tardus**	**Localized sustained with a palpable S4**	**Single S2**; **paradoxical splitting of S2**; S4; crescendo-decrescendo systolic murmur **(late peaking and louder [≥ grade III] if severe)**
Aortic regurgitation	Usually normal	**Bounding; bisferiens; wide pulse pressure (diastolic blood pressure typically 60 mm Hg or less)**	**Displaced, diffuse, and sustained apical impulse**	Soft S1; S3, diastolic descrescendo murmur **(mid-to-late and late diastolic murmurs if severe)**; diastolic rumble, systolic flow murmur
Tricuspid regurgitation	**Elevated central venous pressure; large *v* wave**	**Low-amplitude pulses**	**Parasternal lift**	Holosystolic murmur (left lower sternal border); **right-sided filling sound; diastolic rumble** (flow murmur)
Obstructive hypertrophic cardiomyopathy	Usually normal; elevated venous pressure suggests an alternative diagnosis	Brisk pulses	Sustained apical impulse; palpable S4; "triple-ripple"	S4, **paradoxical splitting of S2**, crescendo-decrescendo systolic murmur (mid-peaking; **loud murmurs when severe)**
Constrictive pericarditis	Elevated central venous pressures; brisk *x* and *y* descents; Kussmaul sign	Low-amplitude pulse	Usually normal; pulsus paradoxus	Pericardial knock; friction rub if ongoing inflammation is present
Decompensated HFrEF	Elevated venous pressure, brisk *y* descents; hepatojugular reflux	Normal or low amplitude pulse; pulsus alternans in severe cases	Displaced and diffuse apical impulse; parasternal heave; left-sided	Soft S1; loud P2; holosystolic or mid-late murmur (if functional mitral regurgitation is present); S3
Compensated HFrEF	Normal venous pressure	Normal or low amplitude pulse	Displaced and diffuse apical impulse; parasternal heave; left-sided S4	Soft S1; normal P2; S4; holosystolic or mid-late murmur (if functional mitral regurgitation is present
HFpEF	Normal or mildly elevated; hepatojugular reflux	Normal	Sustained apical impulse; S4	Loud P2; S4

[a]For valvular lesions, signs of severity are marked in bold.

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

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CHAPTER 12

SURFACE ELECTROCARDIOGRAPHY

Antoni Bayés de Luna, Diego Goldwasser, Miquel Fiol, and Antoni Bayés-Genis

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VALUE AND LIMITATIONS OF ELECTROCARDIOGRAPHY

The surface electrocardiogram (ECG), introduced more than 100 years ago by Willem Einthoven, is the most common technique for the study of heart diseases. It is very useful for the evaluation of acute chest pain, palpitations, syncope, and acute dyspnea, and it is the gold standard for the diagnosis of cardiac arrhythmias, conduction disturbances, preexcitation syndromes, channelopathies, and some aspects of acute ischemic heart disease (IHD). Additionally, it is a fundamental tool to assess the evolution of heart diseases, in particular ischemic diseases, as well as in situations such as electrolyte disorders and drug therapy. It is also useful for epidemiologic studies and for screening and evaluation of athletes.

Despite its invaluable usefulness if used correctly, the interpretation of an ECG recording of normal appearance must be performed with caution. We should bear in mind that a relatively high percentage of patients with coronary heart disease, in the absence of chest pain, show a normal ECG recording. In approximately 5% to 10% of acute coronary syndromes (ACSs), the ECG is normal or borderline, especially in the early phases. Furthermore, the ECG may appear normal after a myocardial infarction (MI). Therefore, a normal ECG is not completely reassuring, because a patient may die from cardiac causes even on the same day a normal recording was taken. However, in the absence of any clinical symptoms or signs or family history of sudden death, the possibility of this occurring is very remote.

On the other hand, some subtle ECG abnormalities without evidence of heart disease may be observed occasionally. Notwithstanding, one must be cautious in such circumstances, and IHD, channelopathies, and preexcitation syndromes should be ruled out before relegating minor changes to nonspecific changes that are not meaningful. Therefore, it is necessary to read the ECG recordings while keeping in mind the clinical setting (eg, family history, chest pain, syncope) and, if necessary, taking sequential recordings.

In addition, normal variants may be observed in the ECG recording that are related to constitutional habits, chest malformations, age, or other factors. Even transient abnormalities may be detected due to a number of causes (eg, hyperventilation, hypothermia, glucose or alcohol intake, ionic abnormalities, or effect of certain drugs).

Today, the importance of the ECG goes beyond its established role of diagnosing abnormal patterns. It has become a tool to determine prognosis and perform risk stratification in many clinical situations, because it can provide insight into basic electrophysiology by ascertaining abnormalities at the molecular level, such as in channelopathies. Furthermore, it is sometimes the key technique to inform the need for such invasive devices as permanent pacemaker or cardiac resynchronization therapy. Therefore, as has been recently stated,[1] it could be said that we face a new renaissance of ECG.

These facts should be borne in mind before starting to learn a technique such as ECG, because the ECG assessment has to be done within the context of a given clinical condition. For example, the occurrence of minor ST-segment depression, if in conjunction with precordial pain, is more likely to be secondary to ischemia (ACS) than it is in the asymptomatic patient, when it is more likely explained by such noncardiac causes as ingestion of drugs or alcohol or hyperventilation.

In this chapter, the basis of the normal ECG and of the abnormal morphologic changes that may occur as a consequence of the enlargement of cavities, atrial and ventricular conduction disorders, preexcitation, and ischemia will be discussed. After that, the most relevant ECG abnormalities found in ischemic and other heart diseases, as well as in some special situations such as ionic imbalances, hypothermia, and athletes, will be summarized. ECG of arrhythmias and the other noninvasive (exercise ECG, Holter technology, body mapping) and invasive electrical technologies used for study of heart diseases are discussed elsewhere.

THE NORMAL ELECTROCARDIOGRAM

DIFFERENT METHODS FOR RECORDING THE ELECTRICAL ACTIVITY OF THE HEART

The ECG is a linear recording of the electrical activity of the heart that repeats over time, taken from outside the body by surface electrodes. For each cardiac cycle, different successive morphologies are recorded: atrial depolarization (*P wave*); ventricular depolarization, called the *QRS complex*; and ventricular repolarization (*T wave*). Occasionally, other waves, such as U waves, may be recorded. The smooth wave of atrial repolarization usually remains hidden in the QRS complex (Fig. 12–1A).

Between these waves, there are different intervals. Figure 12–1A shows these different waves and intervals that represent the successive activation (depolarization and repolarization) of atria and ventricles, which repeat one cycle after another. In this figure, the ECG morphology corresponds to the electrical activity measured from the surface of the left ventricle

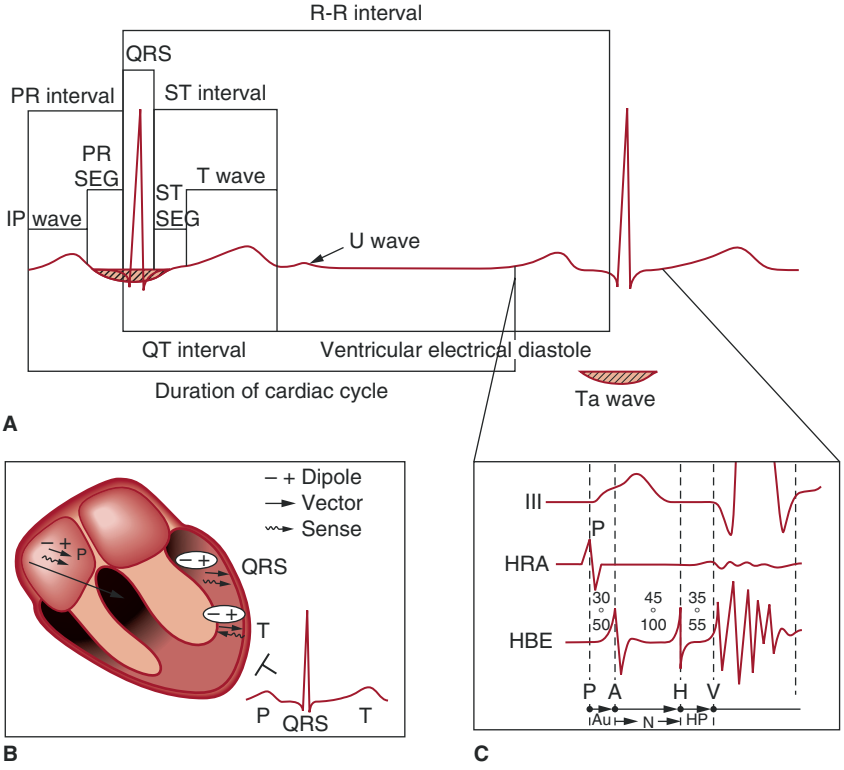


FIGURE 12–1. **A.** Temporal relationship between the different electrocardiography (ECG) waves and nomenclature of the various intervals and segments. Ta wave, T wave of atrial repolarization. **B.** Schematic representation of the vectors and sense of the phenomenon for each wave and its representation on surface ECG. **C.** Observe the different spaces of the PR interval. HRA, high right atrium; HBE, His bundle electrogram. PA interval extends from the upper right atrium—onset of the P wave in the surface ECG—to the first rapid lower right atrial deflection; this represents right intra-atrial conduction (Au); its normal value oscillates between 30 and 50 ms. AH interval extends from the first rapid deflection of the lower atrial electrocardiogram (A) until the bundle of His (H) deflection; this represents intranodal conduction (N), and its normal value oscillates between 45 and 100 ms. The value of the HV interval, which is the distance between the bundle of His and the ventricular muscle, ranges from 35 to 55 ms.

(Fig. 12–1B). The P, QRS, and T waves are positive because the electrode faces the head of the main depolarization vectorf (→) of the atria and left ventricle (see Fig. 12–1B) that moves toward the electrode and the head of the repolarization vector of the ventricles; yet during repolarization, the sense of the phenomenon (see Figs. 12–1B and 12–5) moves away from the electrode (from epicardium to endocardium). The vector of depolarization and repolarization of the ventricles is the vectorial expression on the exterior of the cell of a dipole caused by the propagation of depolarization and repolarization fronts (couple of electrical changes, – +, that initiate the process of depolarization and repolarization; see Fig. 12–1B). The small initial and terminal morphologies of QRS are negative because the initial and terminal forces of ventricular depolarization move away from the left ventricle electrode (see Fig. 12–1B).

Other forms of recording the electrical activity of the heart may be used, such as vectorcardiography (VCG), body mapping, and intracavitary recordings. VCG records the path that follows the electrical activity of the heart through closed loops that represent atrial depolarization (P loop), ventricular depolarization (QRS loop), and ventricular repolarization (T loop) (see Fig. 12–12). Each loop is formed by the sum of its multiple vectors and represents the pathway followed by the successive dipoles of depolarization of atria and ventricles and of repolarization of the ventricles. The head of these vectors is always located toward the positive part of the depolarization or repolarization dipoles (see Fig. 12–12).

A close correlation exists between VCG loops and the ECG curves. The ECG morphology may be deducted from the morphology of the VCG loops and vice versa. This reflects the *loop-hemifield correlation theory* (see The Dipole-Vector-Loop-Hemifield Correlation). According to this correlation (see Figs. 12–10 and 12–12), the morphology of different waves (P, QRS, and T) recorded from different sides (leads) varies. Because the heart is a three-dimensional organ, the projection of the loop's maximum vectors in the frontal and horizontal planes, in the positive and the negative hemifield of each lead (see Leads and Hemifields: Electrocardiography-Vectorcardiography Correlation]) is required to ascertain exactly the loop's location and deduct ECG morphology (Fig. 12–2; see also Fig. 12–10). However, the morphology of ECG not only depends on the maximum vector of a given loop but also on its rotation (see Figs. 12–2 and 12–10). This underscores the importance of considering the loop in its entirety, and not only its maximum vector, as most of the available texts do, to explain the ECG morphology.

Presently, the recording of the VCG has little practical application,[2-4] although it may be of interest for research purposes, and in the assessment of select conduction blocks and/or characterization of tissue necrosis. In addition, the correlation of the ECG with the VCG loop is extremely useful for educational purposes.

To summarize:

1. To have a clear understanding of ECG curves, it is essential to perform a deductive analysis of the electrical activation of the heart under normal and pathologic conditions with the use of VCG loop projection, knowing its clockwise or counterclockwise rotation, on the positive and negative hemifields of different leads (see The Dipole-Vector-Loop-Hemifield Correlation).

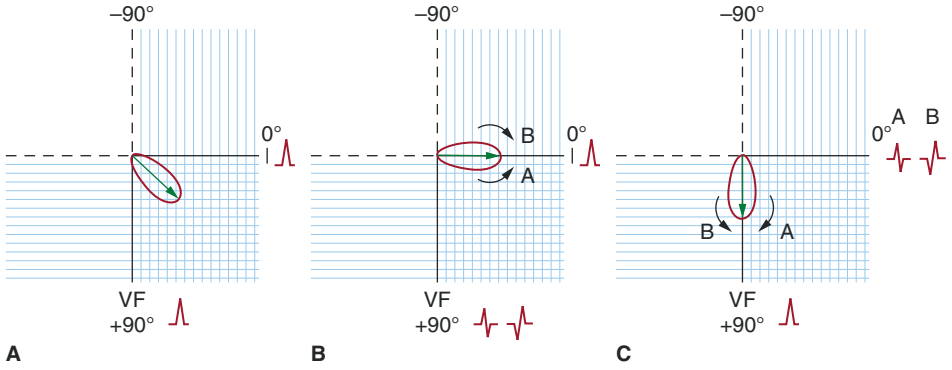


FIGURE 12–2. If the maximum vector of a loop falls in the limit of positive and negative hemifield of a certain lead, an isodiphasic deflection is recorded. However, according to the direction of loop rotation, the QRS complex may be positive-negative or negative-positive; see examples for leads VF and I in case of maximum vector directed to 0° (**B**) and +90° (**C**). In a loop with maximum vector at +45° (**A**), the loop always falls in the positive hemifield of I and VF independently of the sense of rotation.

2. The ECG-VCG correlation is a useful method to understand the ECG curves and is the method that we use for teaching purposes (see Figs. 12–2 and 12–10 and The Dipole-Vector-Loop-Hemifield Correlation).

THE ORIGIN OF ELECTROCARDIOGRAPHY MORPHOLOGY: FROM CELLULAR ELECTROGRAM TO HUMAN ELECTROCARDIOGRAM

When a microelectrode is placed outside and another inside a myocardial cell, a *transmembrane diastolic potential*, is recorded, which is stable in contractile cells (Fig. 12–3) and ascendant in pacemaker cells (see Fig. 12–11). Then, if is stimulated properly the contractile cell, the monophasic curve called the *transmembrane action potential* (TAP) is recorded, which corresponds to the depolarization and repolarization of the cell (Fig. 12–4).

The correlation between the TAP of the contractile cells and the human ECG is as follows (see Fig. 12–4): phase 0 corresponds with the QRS complex, phase 1 and the initial part of phase 2 correspond with the J point and start of the ST segment, the middle part of phase 2 corresponds with the isoelectric ST line, and the end of phase 2 and phase 3 correspond with the T wave.

The cellular electrogram and the human ECG represent the sum of the cellular or ventricular depolarization plus repolarization. Both cell and ventricle recordings are characterized by having a similar depolarization (QRS complex), but different repolarization (T wave). This is negative in the cellular electrogram and positive in the human ECG. In both cases, the T wave follows a period (ST segment) that in normal conditions is isoelectric.

Because of the work by Wilson et al,[5] it is accepted that this difference between the cellular electrogram and human ECG may be explained by the opposite direction of the human heart repolarization wave (T wave) with respect to the depolarization (QRS complex) (Fig. 12–5), whereas in the cellular electrogram, the repolarization wave follows the same direction.

It is well known[6] that the depolarization starts in the endocardium, specifically in three areas of the left ventricle (see Fig. 12–13), and that the epicardium depolarizes after the endocardium. Many experimental works performed in animals[7,8] and in human beings, through the separate recording of endocardium and epicardium TAPs during catheterization and cardiac surgery,[9] have shown that the areas with the shortest TAP, and thus the earliest repolarization, correspond to the epicardium. Therefore, it seems evident that a transmural repolarization gradient exists; although for some authors,[10] the middle section of the ventricular wall (M-cell zone) takes even longer to repolarize than the endocardium, whereas for other authors,[11,12] the repolarization gradient, more than transmural, is transregional (eg, between the apex and the base).

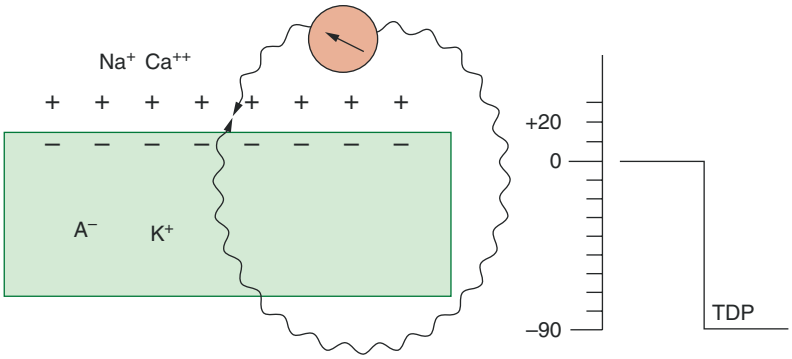


FIGURE 12–3. Two microelectrodes placed on the surface of a myocardial fiber during the resting phase record a horizontal reference line, indicating the absence of differences in potential on the cell surface. When one of the microelectrodes is inserted into the interior of the cell, there is a movement below the baseline corresponding to the difference in potential between the cell exterior (+) (Na, Ca) and interior (–) (predominance of nondiffusible anions [A]). This line, the diastolic transmembrane potential (DTP), is stable in contractile cells and more or less upsloping in automatic cells.

We explain the origin of the human ECG based on the fact that the epicardium repolarizes before the endocardium; this is because repolarization always starts in areas with more abundant perfusion, and physiologically (in normal conditions), the subendocardium is relatively underperfused (see Fig. 12–5). At a cellular level, the opposite happens because the zone distal to the electrode (equivalent to the endocardium) does not have this physiologic hypoperfusion, and therefore, the first zone to be depolarized (the zone distal to the electrode) is also the first to be repolarized.

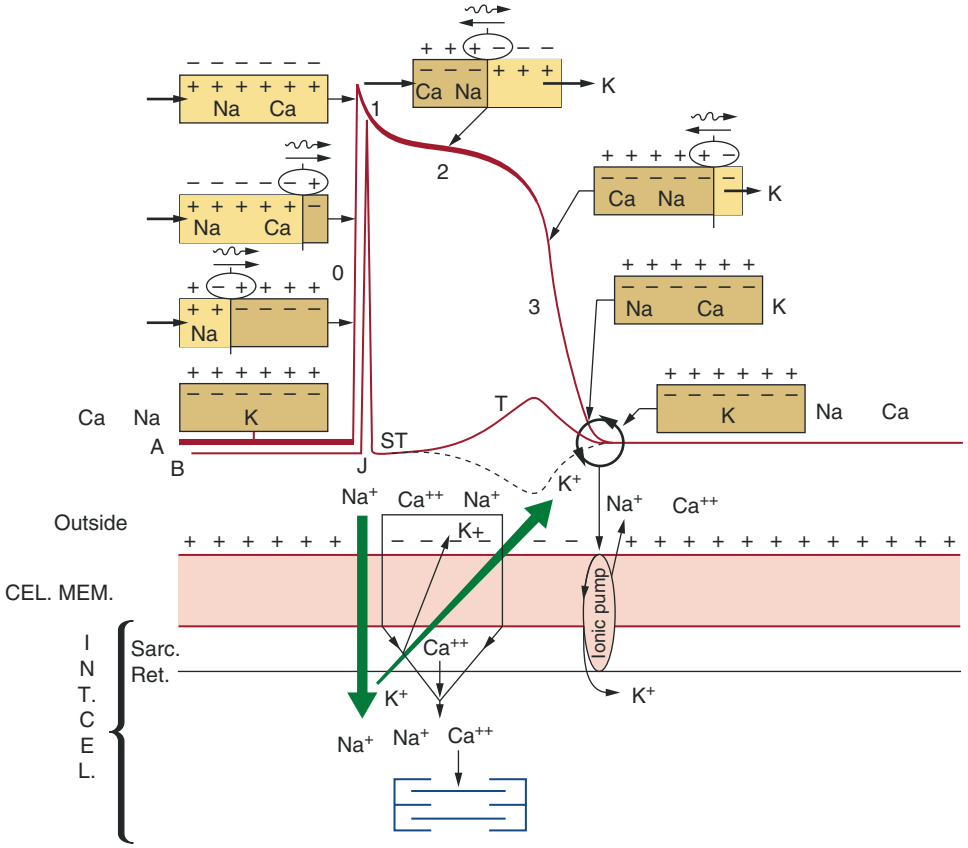


FIGURE 12–4. Diagram of the electronic correlation in a contractile cell (see text).

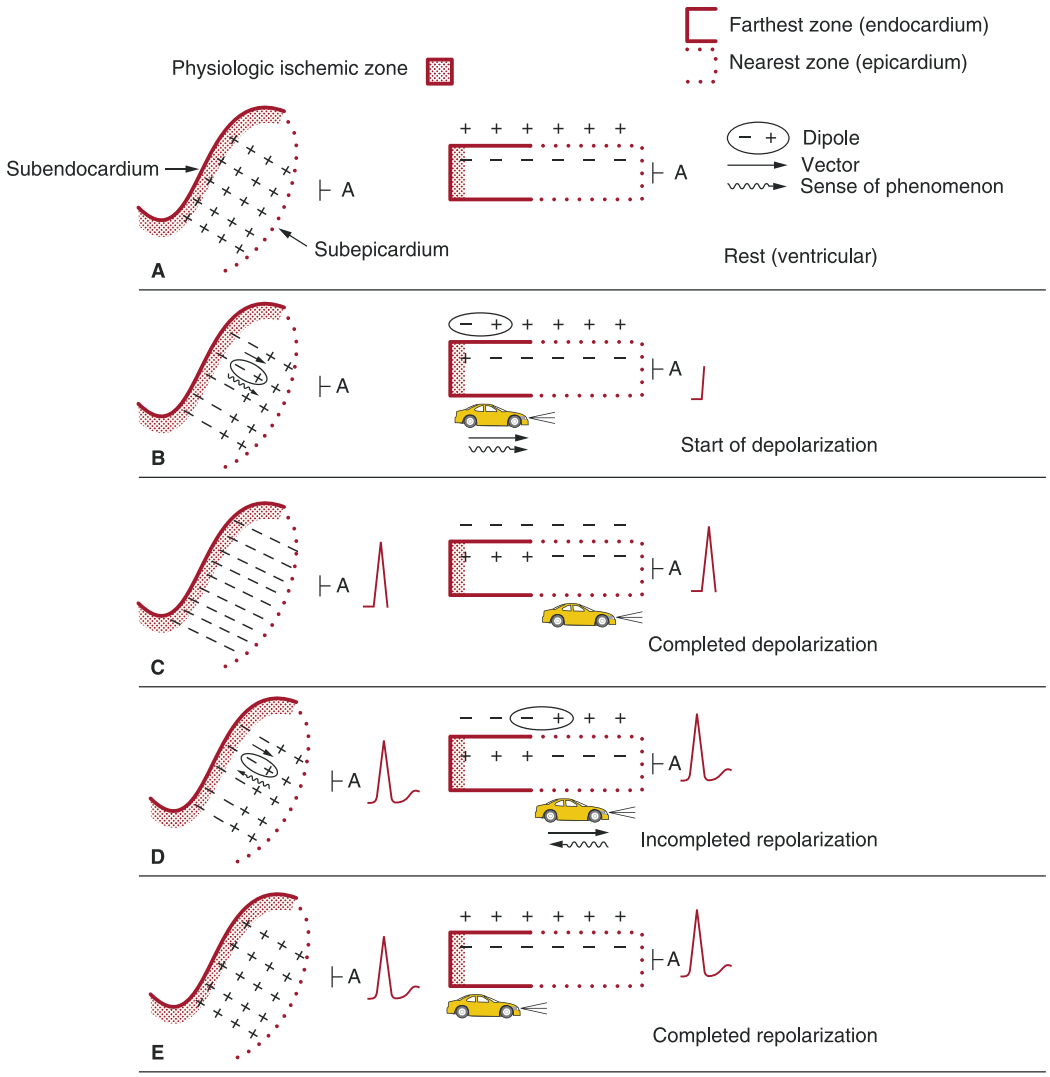


FIGURE 12–5. Diagram of depolarization (QRS) and repolarization (T) morphologies in the normal human heart. The figures to the left show a view of the free left ventricular wall from above, and only the distribution of the charges on the external surface of this enormous left ventricular cell is seen. In the right column is a diagram with a lateral view in which the intracellular changes in the electrical charges are observed. With electrode A in the epicardium, the QRS and T are positive because, in both cases (depolarization and repolarization), the electrode A faces the head of a vector. However, during depolarization, the direction of the phenomenon goes toward the electrode (**B** and **C**), and during repolarization, the direction moves away from the electrode (**D** and **E**). Nevertheless, in both cases, the lights of a car, used here as an example, are the head of the vector of depolarization and repolarization and are directed toward the electrode.

The approach to explain the human ECG arises from two different theories:

1. The first theory considers, in light of what has been discussed, that the curves of the human ECG are the sum of the successive dipoles (– +) of depolarization and repolarization recorded by an electrode located on the opposite side (epicardium) relative to the place (endocardium) where the stimulation initiates (depolarization) (see Fig. 12–5).
2. The second theory considers that the human ECG is the sum of the TAPs of the subendocardium, the farthest part to the recording electrode (which TAP starts before and ends later), and the subepicardium, the closest part to the electrode (which TAP starts later and ends before).

This is a simplification of how the ECG is produced because we have considered the left ventricle alone, and thus its depolarization can be represented by a single vector. Actually, this is not the case because there are more vectors in the human ECG. At least one vector is required, as the sum of all atrial vectors, to explain the pathway that is followed by the stimulus to depolarize the atrium. This is known as the *atrial depolarization loop* (*P wave*) (see Figs. 12–1A and 12–12A). Three vectors explain the pathway of the ventricular depolarization loop (QRS complex) (see Fig. 12–1B). The QRS complex is followed by the ventricular repolarization loop (T wave) (see Fig. 12–1C). Three vectors are required to explain the morphology of the ventricular depolarization loop (qRs or rSr′) and depend on the placement of the recording lead, although they actually represent many more vectors (see Figs. 12–1 and 12–11).

To summarize:

1. There is considerable evidence that in the human heart, the epicardium (the zone nearest to the exploring electrode) is the first part to repolarize; and therefore, the human ECG records a positive T wave (see Fig. 12–5), the opposite of what the cellular electrogram shows. The depolarization and repolarization dipole is expressed as a vector. The sum of the successive depolarization and repolarization dipoles and the vectors that express them, from an electrode located on the opposite side relative to the site were the stimulus originates, can explain the human ECG curve (see Fig. 12–5).

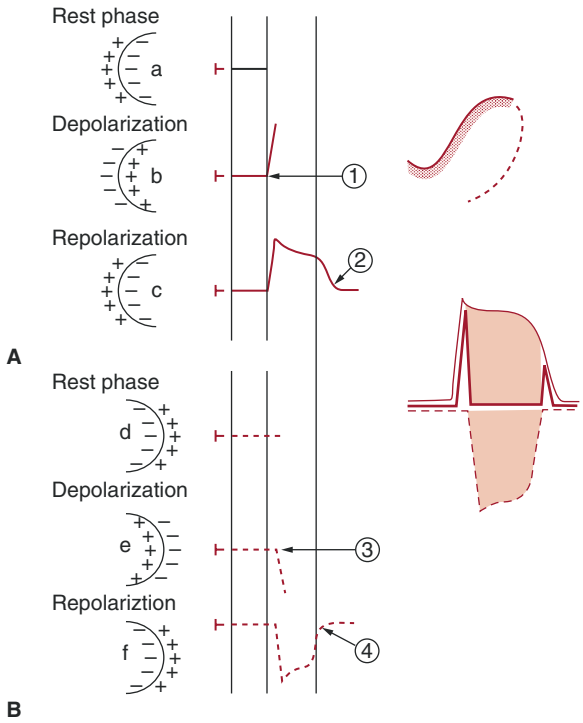


FIGURE 12–6. Correlation between transmembrane action potential (TAP) of the farthest (**A**) and the nearest (**B**) part of the left ventricle and electrocardiography curve. *1.* Beginning of the depolarization in the farthest zone. *2.* End of repolarization in the farthest zone. *3.* Beginning of depolarization in the nearest zone. *4.* End of repolarization in the nearest zone. At the end of depolarization (b), in the farthest zone (**A**), the electrode is confronted with this part depolarized (ie, negative on the outside and positive on the inside), and as an electrode faces the positive charges of inside an ascendant TAP, phase 0 is recorded. At the end of repolarization (c), the electrode faces internal negativity because repolarization has concluded and the curve returns to the isoelectric line. In the case of subepicardial TAP (**B**), the opposite occurs. When this TAP has started to be depolarized (e), which occurs later than in the subendocardial zone (compare 1 and 3), this zone presents external negativity. The electrode faces this negativity, and phase 0 is inscribed as negative. When this zone has finished the repolarization (f), because it takes place earlier than in the subendocardial zone, the electrode is confronted with positive external charges because repolarization has concluded, and the subepicardial TAP curve returns to the isoelectric line (point 4). The first and last parts of the sum of both TAPs produce the QRS complex and T wave. The rest of the two TAPS is canceled and seen as an isoelectric line (ST segment).

2. The human ECG can also be considered as the result of summation of the TAPs of the farthest (the subendocardium) and the nearest (the subepicardium) zones from the exploring electrode (Fig. 12–6).

LEADS AND HEMIFIELDS: ELECTROCARDIOGRAPHY-VECTORCARDIOGRAPHY CORRELATION

Leads and Hemifields

The ECG presents different morphologies as it is recorded from different sites, named *leads*. We currently use six frontal (I, II, III, VR, VL, and VF) and six horizontal (V_1 to V_6) leads (Figs. 12–7A, 12–7B, and 12–8C).

There are three bipolar leads (I, II, and III) in the frontal plane, which, according to the Einthoven law, should accomplish the equation II = I + III. These three leads form what we call the *Einthoven triangle* (see Fig. 12–7A). Figure 12–7C depicts how the projection of different vectors (or loops) explains the different morphologies found in leads I, II, and III. Bailey, by shifting the three leads toward the center, obtained a reference figure (*Bailey triaxial system*) (Fig. 12–8A). In the frontal plane, there are also three monopolar leads (VR, VL, and VF) (see Fig. 12–7B). By adding these three leads to the Bailey triaxial system, the *Bailey hexaxial system* is obtained (Fig. 12–8B).

All of the 12 leads located around the circumference in the frontal and horizontal planes have a positive line (Fig. 12–8D; see Fig. 12–8B) that goes from the place where the electrode is located up to the center of the heart. If lines perpendicular to the frontal and horizontal leads are drawn passing through the center of the heart, the positive and negative hemifields of these leads may be obtained (Fig. 12–9). The positive hemifield of lead I extends from +90° to –90° passing through 0°; that of lead II extends from –30° to +150° passing through +60°; that of lead III extends from +30° to –150° passing through +120°; that of VR extends from +120° to –60° passing through –150°; that of VL extends from –120° to +60° passing through –30°; that of VF extends from 0° to ±180° passing through +90°; that of V_2 extends from 0° to 180° passing through +90°; and that of V_6 extends from –90° to +90° passing through 0°. The rest of the hemifields corresponding to the horizontal plane leads can be obtained in the same manner, drawing lines that are perpendicular to the corresponding lead, passing through the center of the heart (see Fig. 12–9; Fig. 12–10). In all cases, the negative hemifields are opposed to the positive ones.

A loop of P, QRS, or T, or their maximum vectors, located in the positive or the negative hemifield or on the interface between both hemifields in any of the 12 leads, gives rise to, respectively, positive, negative, or isodiphasic deflections of P, QRS, or T waves in that given lead. An isodiphasic deflection has a maximum vector but may have a different morphology; it can be positive/negative or negative/positive, according to the direction of the loop rotation representing the pathway followed by the stimulus (see Fig. 12–2). The degree of positivity or negativity in each morphology depends on two factors: the magnitude and the direction of the loops or vectors. For a given magnitude, the vectorial result will have a greater positivity or negativity according the direction of the maximal vector of the loop; and for a given direction, the vector of the loop with a greater magnitude will cause a greater positivity or negativity (see Fig. 12–9).

THE DIPOLE-VECTOR-LOOP-HEMIFIELD CORRELATION

As previously mentioned, a pair of electric charges called a *dipole* (– +) is formed in both depolarization and repolarization processes of activation of the heart. The existence of these dipoles results from ionic changes and explains the formation of TAP (see Fig. 12–4 and legend). These dipoles

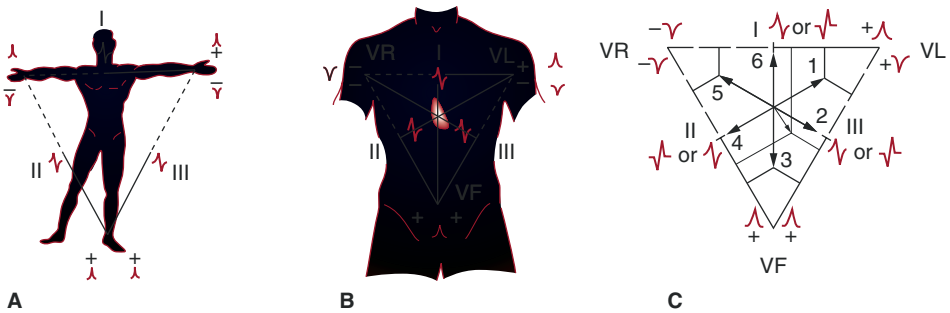


FIGURE 12–7. A. The Einthoven triangle. **B.** The Einthoven triangle superimposed on a human thorax. Observe the positive (*continuous line*) and negative (*dotted line*) part of each lead. **C.** Different vectors (from 1-6) produce different projections according to their location. For example, vector 1 has a positive projection in lead I, diphasic in II, and negative in III, whereas vector 3 is diphasic in I and positive in II and III.

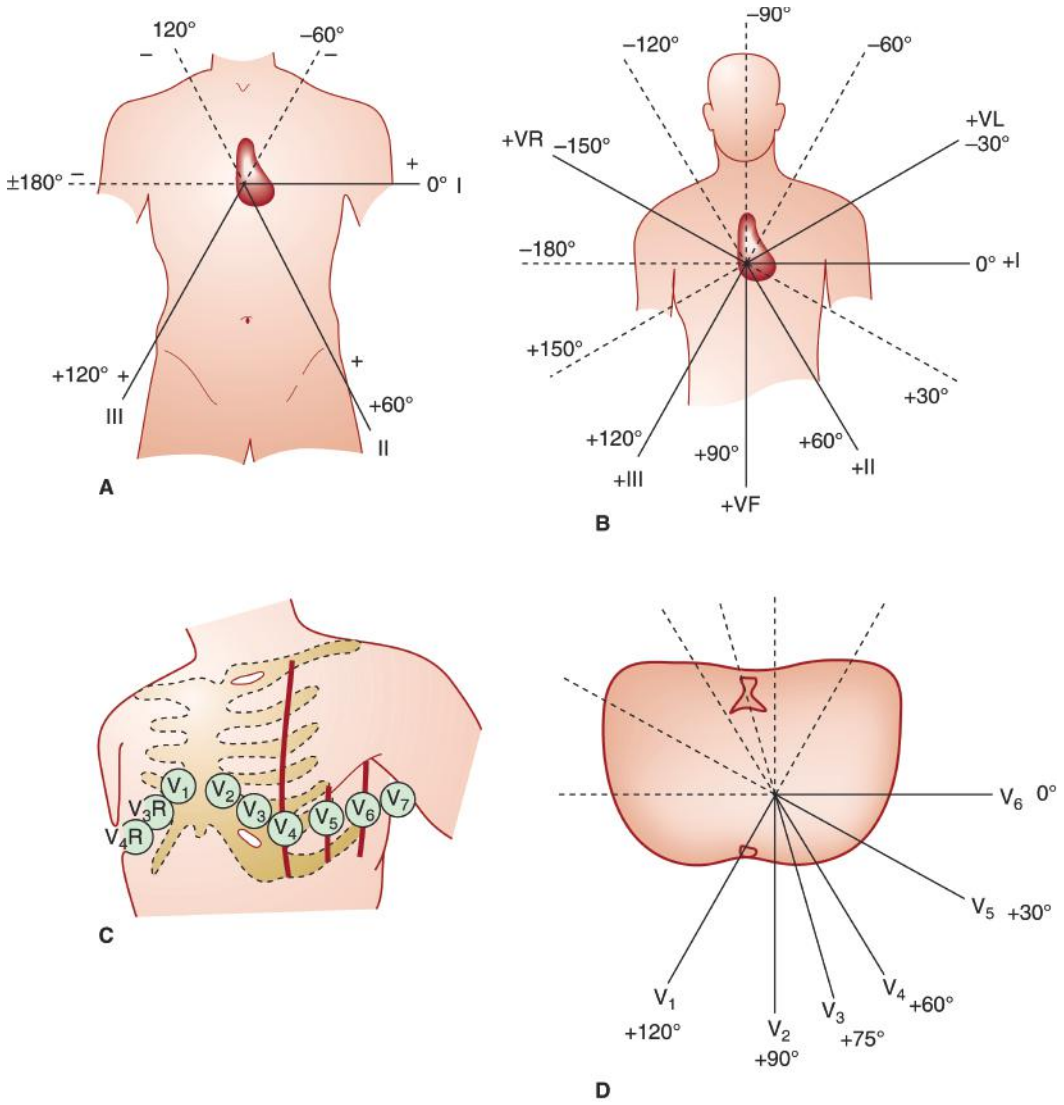


FIGURE 12–8. **A.** The Bailey triaxial system. **B.** The Bailey hexaxial system. **C.** Sites where the explorer electrodes are located in unipolar precordial leads. **D.** Sites where the positive poles of the six precordial leads are located.

have a vectorial expression, with the head of the vector located in the positive part of a dipole. An electrode that faces the head of the vector records positive deflection regardless of whether this dipole approaches the electrode or moves away. It has already been explained how the cellular and ventricular electrograms are formed and that, in human ECG, the repolarization wave (T wave) is positive because physiologically there is less perfusion in the subendocardial zone and the process of repolarization always starts in the more perfused zone. Therefore, in human ECG, this process begins in the subepicardium, the opposite of what occurs at the cellular level (see Fig. 12–5).

It is relevant to highlight that the P, QRS, and T loops are formed from the vectorial sum of depolarization and repolarization dipoles that express the pathway followed by electric stimulus during these processes (Fig. 12–11). As stated, only the simultaneous projection on two planes, frontal and horizontal, may provide exact information as to the direction of respective electric forces (frontal plane: upward-downward and rightward-leftward; horizontal plane: rightward-leftward and frontward-backward) (see Fig. 12–11). Each of these loops has a *maximum vector*, which is considered to be the result of all instantaneous vectors (see Fig. 12–11) and expresses the magnitude and the overall direction of a loop. Nevertheless, the morphology of a loop, especially the initial and terminal parts, and the loop rotation (clockwise or counterclockwise) have relevant added value (see Figs. 12–10 and 12–11; see also Fig. 12–2).

The tracing of atrial (P) and ventricular (QRS) wave activation explained by the VCG curve may be translated into ECG curves in different leads according to the VCG-ECG correlation. Figure 12–10 shows this correlation with VF and V_2 leads.

To summarize:

1. The following chain of events explains the ECG morphology: dipole → vector → loop → hemifield → ECG.
2. The P, QRS, and T loops overall have an orientation that may be expressed by a maximum vector. Although these vectors provide important information on ECG morphology in different leads, only the global contour of the loop, its sense of rotation, and the loop-hemifield correlation may explain the total ECG morphology (see Figs. 12–2, 12–10, and 12–11).
3. The rotation of the loop, clockwise or counterclockwise, explains why, for a given maximal vector, the morphology of the QRS may be either or (see Figs. 12–2 and 12–10).

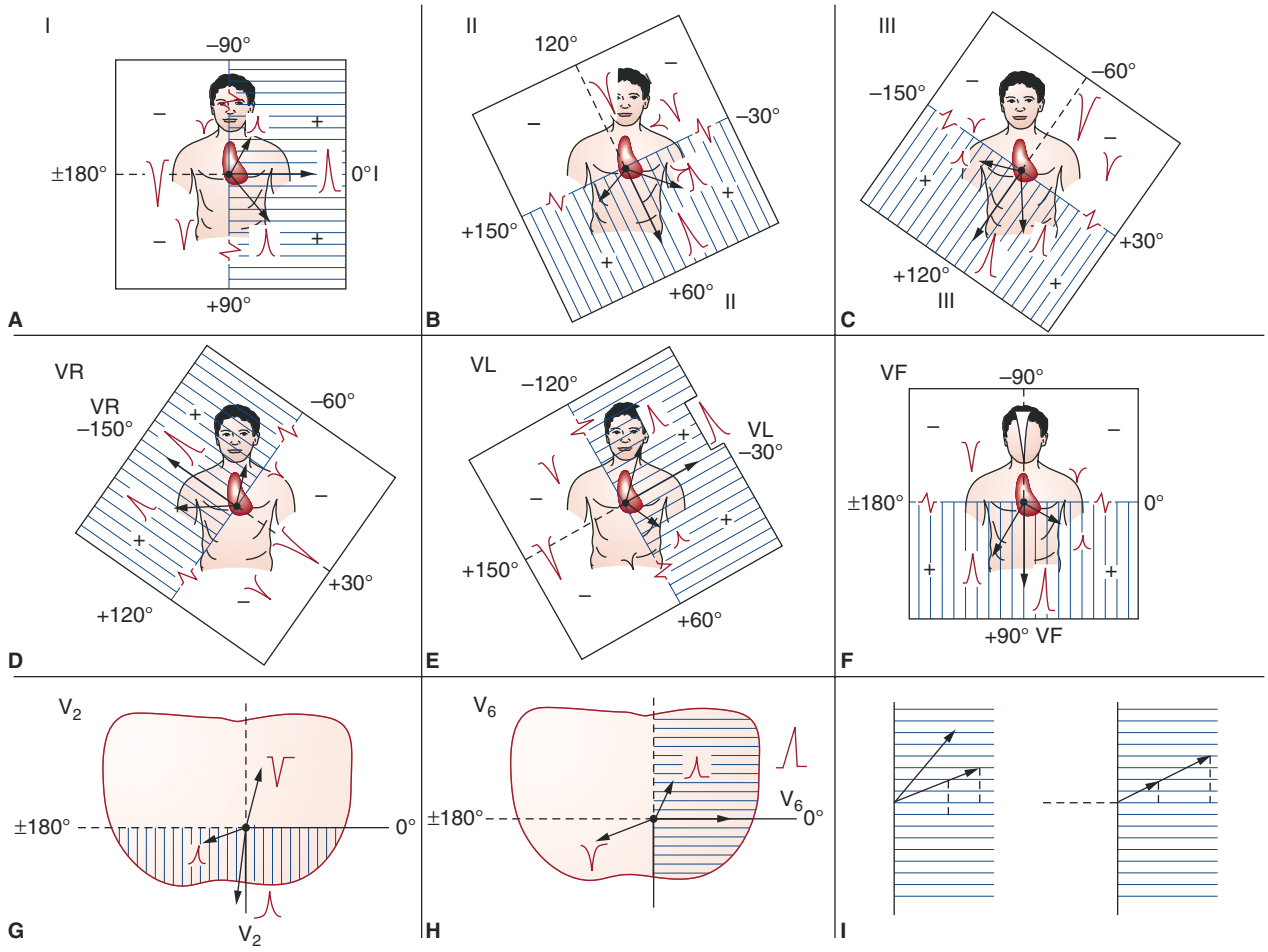


FIGURE 12–9. Positive and negative hemifields of the six frontal plane leads and the horizontal plane leads. Depending on the magnitude and direction of the different vectors (that represent the corresponding loops), positive and negative deflections with different voltages are originated (see text).

ACTIVATION OF THE HEART

The ECG tracing reflects the activation sequence (depolarization and repolarization) of the heart, starting with the stimulus arising in the sinus node (this is the structure with greater automaticity), up to the ventricular Purkinje network through the specific conduction system. Figures 12–1B and 12–11 show a summary of atrial depolarization and ventricular depolarization and repolarization that explains the ECG according to the dipole → vector → loop → hemifield theory, and Fig. 12–12 shows how the ECG may be also considered as the sum of different TAPs originating along the heart activation sequence from the sinus node to the ventricular muscle. The conduction speeds of different parts of the specialized conduction system are shown at the right in Fig. 12–12.

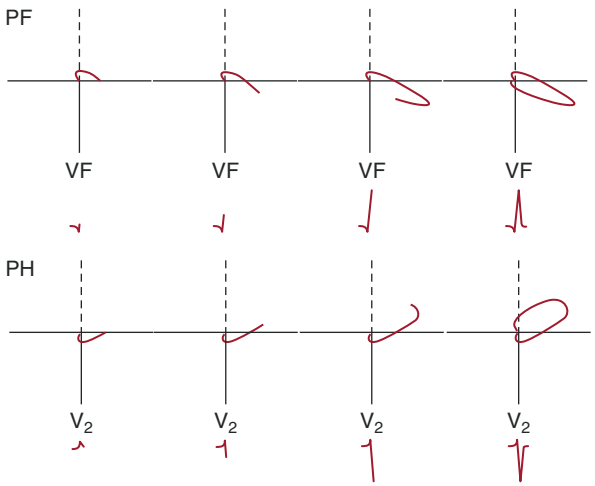


FIGURE 12–10. The correlation between the vectorcardiographic loop and the electrocardiographic image in VF and V_2.

The union of the heads of all atrial depolarization vectors represents the P loop, which is recorded on the ECG as the initial deflection, the P wave (see Fig. 12–11A). The loop-hemifield correlation explains the morphology of the P wave in the different leads. Generally, atrial repolarization (Ta wave) is seldom seen, being masked by the significant forces generated by ventricular depolarization that give rise to the QRS complex (see Fig. 12–1A).

Once atrial depolarization ends and prior to starting ventricular depolarization (PR segment in ECG), the electric stimulus depolarizes small structures, and therefore, no waves are recorded on the surface ECG (see Fig. 12–1). Nonetheless, depolarization of the bundle of His and its branches can be recorded with intracavitary recording techniques (His recording) (see Fig. 12–1C).

Ventricular depolarization occurs in three successive steps that give rise to the generation of three vectors (the expression of three dipoles) (see Fig. 12–11B and C). Each of the three vectors explains a deflection

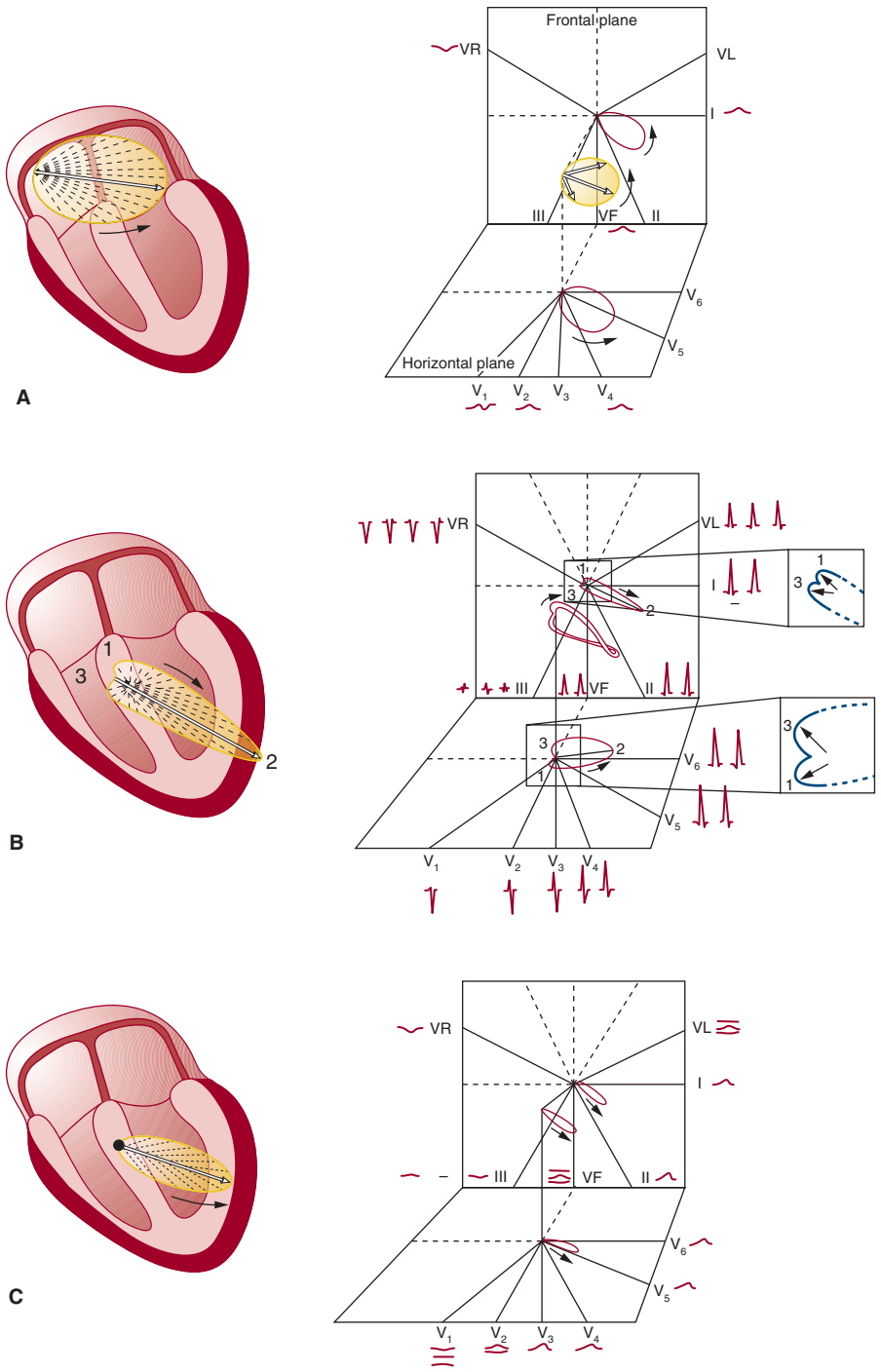


FIGURE 12–11. **A.** Right, left, and global atrial depolarization vector and P loop. The successive multiple instantaneous vectors are also pictured. The P loop and its projection on frontal and horizontal planes are shown. **B.** Observe the vectors and ventricular depolarization loop (left) and the projection of the cardiac vectors and loops on the frontal and horizontal planes (right) in a heart with no rotations. **C.** T loop and its representation in the space.

of the QRS.[13] Ventricular depolarization starts at three different sites in the left ventricle[6]: the areas of the anterior and posterior papillary muscles and a midseptal area (Fig. 12–13A and C). At almost the same time, the right ventricle begins its depolarization. These three initial depolarization sites in the left ventricle (black asterisks in Fig. 12–13A) dominate the small initial forces of the right ventricle and originate a joint depolarization dipole (vector), which is called the *first vector* (1) (Fig. 12–13B). This first vector is directed front-rightward and, generally, upward (see Fig. 12–11B), although in some patients, especially obese individuals, it may be also directed downward. Once this initial area in the left ventricle is depolarized, most of the right and left ventricular mass is depolarized at the same time, giving rise to a right depolarization vector (2r) and a left depolarization vector (2i). The sum of these vectors is directed toward the left, somewhat backward, and, generally, downward (see Fig. 12–11B) and is known as the *second vector*. In obese individuals, it is usually located around 0°. Finally, the

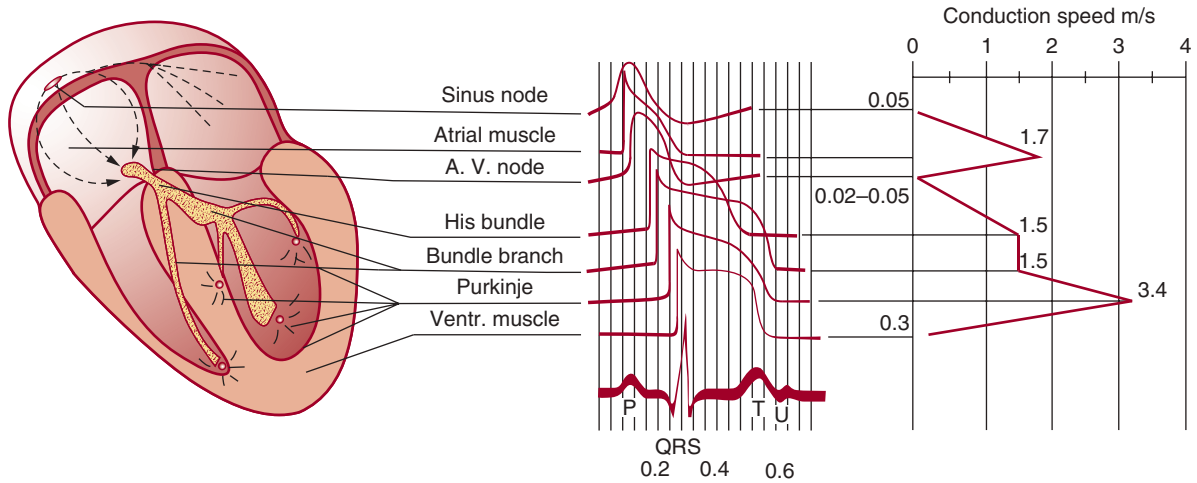


FIGURE 12–12. Diagram of the transmembrane action potential (TAP) morphologies of different structures of the specialized conduction system, the atrial and ventricular (Ventr.) muscle and the impulse conduction speed through these structures, and correlation with the curve of the electrocardiogram. AV, atrioventricular.

last areas to depolarize in both ventricles (the areas with fewer Purkinje fibers—that is, the basal septal areas) originate a *third vector* (3), which is directed upward, somewhat to the right, and backward (see Fig. 12–11B). As stated, the union of the heads of these three vectors, which is merely a simplification of the union of the heads of all the instantaneous vectors originated during ventricular depolarization, represents the pathway that the electrical stimulus follows when it depolarizes the ventricles and is called the *QRS loop*, which originates the QRS complex in the ECG (see Figs. 12–1B and 12–11). The loop-hemifield correlation explains the morphology of QRS in different leads (see Figs. 12–2 and 12–10).

Finally, ventricular repolarization takes place, which is mainly represented by the repolarization of the left ventricular free wall. From a physiologic viewpoint, the subendocardial area is relatively underperfused (physiologic hypoperfusion). As previously stated (see Fig. 12–1B), this explains the positivity in the last part of repolarization in the leads facing the left ventricle and the negativity in the opposite leads (VR). The initial pathway followed by repolarization does not produce any expression in the ECG and is recorded as an isoelectric ST segment. Later, when a repolarization dipole is formed, the union of the heads of all instantaneous vectors originates the T loop, which is recorded as a T wave in the ECG (see Fig. 12–12C).

After the T wave, which represents the end of ventricular systole, and prior to onset of the next atrial systole, an isoelectric line, corresponding to the resting phase of all cardiac cells, is recorded (see Fig. 12–12C). Sometimes, a small wave, called a *U wave*, which forms part of the repolarization process, is recorded after the T wave (see Fig. 12–1A).

ELECTROCARDIOGRAPHIC DEVICES AND RECORDING TECHNIQUES

The equipment for performing ECG is a conventional device that produces a paper recording of tracings. However, we are now immersed in the digital era, and in the field of ECG, this has given rise to the need for functional programs and devices that are portable, versatile, and interactive.

This means working in an integrated fashion with management and quality assurance in the different health institutional settings, independently of the types of technologies used. Currently, these systems allow us to work online and advance rapidly in the implementation of telemedical services, including diagnosis performed by an expert in real time through the Internet, which can be applied to multiple scenarios that otherwise would not have the same quality of assistance because of the geographic location or the associated economic costs.

The recording technique includes the following: (1) connection of the device and preparation of the patient, (2) placement of electrodes at their correct locations, (3) adjustment of baseline tracing, (4) checking of calibration, and (5) ensuring that the tracing is correctly obtained according to the Einthoven law (II = I + III). The misplacement of the electrodes and other clinical mistakes that will be discussed later (p. 14 [manuscript page 26]), may lead to several errors.

SYSTEMATIC INTERPRETATION OF THE ELECTROCARDIOGRAM

The names given to different waves and intervals are shown in Fig. 12–1, and the different morphologies of P, QRS, and T waves are shown in Fig. 12–14. In some pathologic situations, other waves may be recorded—a delta wave in Wolff-Parkinson-White pattern, an epsilon wave in arrhythmogenic right ventricular cardiomyopathy, and a J wave in hypothermia (Osborne wave) or other situations such as early repolarization.

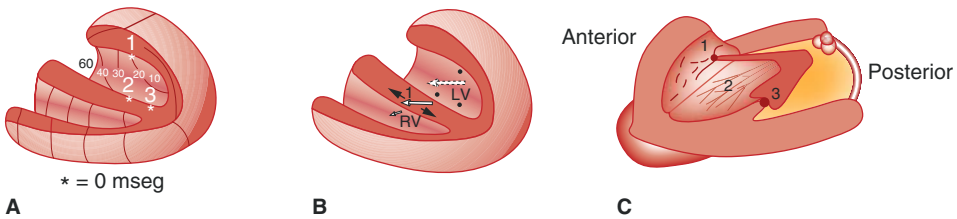


FIGURE 12–13. A. The three initial points (1, 2, and 3) of the ventricular depolarization are marked by an asterisk (*). The isochronic lines of the depolarization sequence can also be seen. (Adapted from Durrer et al.[6]) **B.** The first vector of the ventricular depolarization (*continuous line arrow*, 1) is the result of the sum of the initial depolarization vectors of the left and right ventricles (*dotted arrows*). The first initial vector of the left ventricle corresponds to the sum of depolarization of the three points indicated in panel A, and because it is more potent than the forces of the right ventricular vector, the global direction of vector 1 will be from left to right. **C.** Left lateral view showing the left papillary muscles and the divisions of the left bundle branch. 1, superoanterior; 2, mediosceptal (inconstant); 3, inferoposterior. There is an excellent correlation between superoanterior and inferoposterior divisions of the left bundle and the initial points 1 and 3 of ventricular depolarization. The correlation between middle fibers/septal fascicle and the point 2 of ventricular depolarization is not so well known.

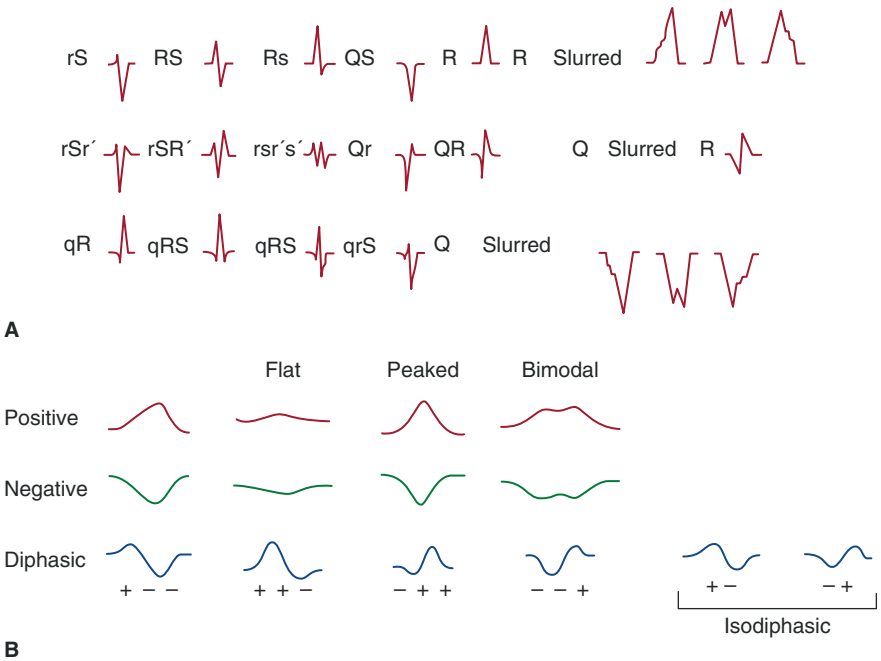


FIGURE 12–14. **A.** The most frequent QRS morphologies. **B.** P- and T-wave morphologies.

Different items should be routinely assessed when reading an ECG. The following sections will briefly discuss the most important aspects of the normal limits of these ECG parameters, as well as some relevant aspects of the abnormal values. For more detailed information, consult Bayés de Luna[2] and McFarlane et al.[14]

Lastly, to perform accurate measurements of different waves or intervals, it is sometimes necessary to use magnifying glasses and/or calipers.

Heart Rate

Sinus rhythm at rest normally ranges from 60 to 90 beats/min. Considering that the recording paper is divided into 5-mm rectangles (when the paper runs at 25 mm/s, it is equivalent to 0.20 second) each containing five smaller (1-mm) rectangles, the following methods may be used to measure the heart rate: (1) Observe the number of R-R intervals occurring every 6 seconds (every five 5-mm rectangles represent 1 second) and multiply this number by 10 (this is the best method when arrhythmia is present; or (2) use a proper ruler (Fig. 12–15).

Rhythm

Rhythm can be normal sinus rhythm or ectopic rhythm. Sinus rhythm produces positive P waves in leads I, II, aVF, and V_2 to V_6; positive or positive/negative waves in III and V_1; positive or negative/positive waves in aVL; and negative waves in aVR. Figure 12–16 explains, according to rotation of the loop (counterclockwise in sinus rhythm or clockwise in ectopic rhythm), the different bimodal morphologies in the P wave in both cases. For example, when the axis of the P loop is located around +30°, the morphology of a sinus P wave in III will be positive/negative (counterclockwise rotation of P wave; see Fig. 12–16) and negative/positive in case of ectopic rhythm (clockwise rotation). The same correlation is useful to explain the morphologies of P, QRS, or T waves seen in other leads.

The morphology of P wave in reentrant atrioventricular (AV) junctional arrhythmias and the morphology of atrial activation waves in other supraventricular arrhythmias will be discussed in Chap. 84.

PR Interval and Segment

PR interval is the distance from the beginning of the P wave to the beginning of the QRS complex (see Fig. 12–1A). The procedure for this measurement is shown in Fig. 12–15. Normal PR interval values in adult individuals range from 0.12 to 0.20 second (up to 0.22 second in the elderly and even < 0.12 second in the newborn). Longer PR intervals are seen in cases of AV block, and shorter PR intervals are seen in preexcitation syndromes.

The PR segment is the distance from the end of the P wave to the QRS onset and is usually isoelectric. However, with intracardiac recordings, the depolarization of the bundle of His may be seen. Figure 12–1C shows the different spaces of PR interval taken with this technique. Sympathetic overdrive may cause a descent in PR segment that forms part of an arch of circumference together with an ascendant ST segment (Fig. 12–17C). In pericarditis and other diseases affecting the atrial myocardium, as in atrial infarction, PR segment in lead II is depressed or, more frequently, an elevated PR segment in lead VR may be seen (see Fig. 12–25).

QT Interval

QT interval represents the sum of depolarization (QRS complex) and repolarization (ST segment and T wave). Often, particularly in the presence of a flat T wave or a U wave, it is difficult to measure the QT interval properly. It is commonly accepted that this measurement should be performed using a consistent method to ensure that equivalent measurements are taken when the QT interval is studied sequentially.[15] The most suitable method entails considering the end of repolarization in a point where the tangent line following the descendent slope of the T wave crosses the isoelectric line (see Fig. 12–15A and B). It is necessary to correct the QT interval by heart rate (QTc). In clinical practice, QTc may be measured with a ruler (see Fig. 12–15C), and it is considered that its duration should not exceed approximately 10% of the value corresponding to heart rate.

A long QT interval may be found in congenital long QT syndrome[16] (see Figs. 12–15B and 12–80) and also in diseases such as heart failure and IHD, in some electrolyte imbalances, and after the intake of different drugs. It is considered that a drug should not increase the QTc by more than 30 milliseconds and that a change of 60 milliseconds may result in torsade de pointes (TdP) and sudden cardiac death. Nevertheless, TdP rarely occurs unless the QTc exceeds 500 milliseconds.[17]

A short QT interval can be found in cases of early repolarization, digitalis effect, hypermagnesemia, acidosis, and other conditions and, rarely, in some genetic disorders associated with sudden death (short QT syndrome)[18] (see Figs. 12–15B and 12–81A). Usually, in the latter case, the QT is less than 300 milliseconds and the T wave is peaked and tall, especially in V_2 to V_3. In symptomatic short QT syndrome, the distance from the J point to the T peak is shorter (≅100 milliseconds) compared with asymptomatic short QT (see Fig. 12–15B).

P Wave

The P wave is the atrial depolarization wave (see Figs. 12–1 and 12–12A). In general, its height should not exceed 2.5 mm, and its width should be less than 120 milliseconds. It is rounded and positive, except

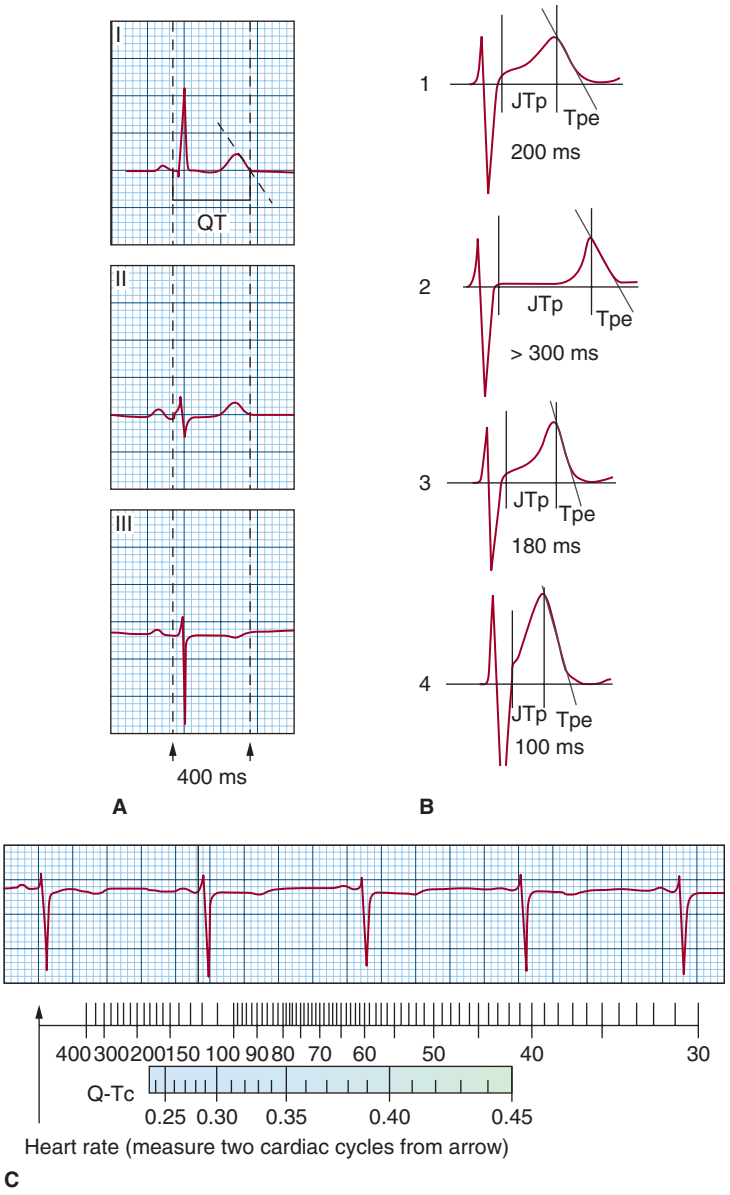


FIGURE 12–15. Measurement of P wave, PR and QT intervals, and the heart rate. **A.** Leads I, II, and III. The P wave and PR interval have to be measured at least with a three-channel device. The exact P wave duration is the distance from P wave start in any lead to the last end of the P wave also in any lead. The PR interval measurement is the distance from the earliest onset of the P wave in any lead (in this case, lead III) to the earliest onset of the QRS complex in any lead (in this case, also in lead III). Measurement of QT interval: The QT interval should be measured from the onset of the Q wave to the latest end of the T wave. The corrected QT (QTc; QT in relation to heart rate) is obtained with a ruler (**C**), which gives us the result when the end of two R-R cycles coincides with the QTc value obtained on a ruler; in this case, the QTc is 390 ms. the value of QT in this ECG, 400 ms, is equal to a QTc of 390 ms plus 10 ms. It is considered a normal value that does not exceed, as in this case, ± 10% to 15% of the QTc shown on the ruler. Measurement of the heart rate: The same ruler gives the heart rate, in this case approximately 60 beats/min. **B.** This panel shows (1) the normal QT interval; (2) an example of the long QT interval (LQT3; see Fig. 12–84B); (3) the short QT interval of asymptomatic people; and (4) the QT interval of symptomatic short QT syndrome (the distance between point J and T peak is short (7 < 100 ms; see Fig. 12–79A).

in VR, but may be positive/negative in V_1 and III and rarely in II and VF and negative/positive in VL according to the loop-hemifield correlation (see Figs. 12–1, 12–12A, and 12–16).

The P wave changes seen in atrial abnormalities are discussed later (see Atrial Abnormalities).

QRS Complex

The QRS complex corresponds to ventricular depolarization. Its morphology varies in the different leads according to the loop-hemifield correlation (see Figs. 12–10 and 12–12B). An example of this correlation in a heart without rotations is shown in Fig. 12–12B, and different morphologies of QRS are also presented in this figure. Figure 12–14 shows the different letters used to express these morphologies. The normal values of QRS and T in 12 leads according to age can be found elsewhere.[2,14]

The width of the Q wave should be less than 0.10 second, and the R wave height should not exceed 25 mm in leads V_5 and V_6 or 20 mm in leads I and VL, although in VL, heights of more than 15 mm are usually abnormal and suggest left ventricle hypertrophy (see Table 12–3).

Furthermore, the Q wave must be narrow (< 0.04 second) and of quick recording and should not exceed 25% of the following R wave, although some exceptions exist, mainly in leads III, VL, and VF. The presence of abnormal Q waves suggests myocardial necrosis but may be also observed in many other circumstances (see Table 12–14).

ST Segment and T Wave

The T wave, together with the preceding ST segment, is generated during ventricular repolarization (see Figs. 12–1B and 12–12C). According to the loop-hemifield correlation, in the adult, the T wave is positive in all leads, except VR (because the T loop is located in the negative hemifield of that lead) but being the slope up slower that the slope down. The T wave may be negative or flattened or, occasionally, slightly positive in V_1, and sometimes, it may also be flattened or slightly negative in V_2 and even in V_3 in women and black people. In III and VF, the T wave may be flattened or even slightly negative. In children, a negative T wave of characteristic morphology is seen in the right precordial leads (children's repolarization) (Fig. 12–17E).

Under normal conditions, the ST segment is isoelectric (see Fig. 12–1) or shows only a small downward slope (< 0.5 mm) with ascendant inclination. A small upward slope (1–2 mm) that is convex in relation to the isoelectric line is often seen in V_1 and V_2 as a normal variant (Fig. 12–17B).

Normal ST Variant Patterns Different examples of normal ST variants are shown in Fig. 12–17, and some of these are discussed here.

The rSr′ in V1 pattern (Fig. 12–17G) can be observed in healthy people, especially in those with pectus excavatum or when the V_1 and V_2 leads are located in a higher position (second intercostal space). In both cases, the P wave in V_1 is negative. This pattern should be differentiated from the type 2 Brugada pattern (see Fig. 12–81C). The best method to differentiate all cases that presents r' in V_1, is through morphologic features of r' the Baranchuk algorithm[19] (see Fig. 12–82).

The pattern of early repolarization (see Fig. 12–17D) entailing a 2- to 4-mm ST elevation with downward convexity, often preceded by the J wave, is particularly evident in midprecordial leads. In early repolarization, the ST-segment elevation normalizes with exercise. Recently, it has been described[20] that many patients with idiopathic ventricular fibrillation present with this pattern but with the malignant type (rectilinearly or slightly descendent ST in inferior leads especially). However, from an epidemiologic point of view, its presence only represents a slight increase in the risk of sudden death (11 in 100,000 vs 4 in 100,000 in a control group)[21] (see Fig. 12–81D).

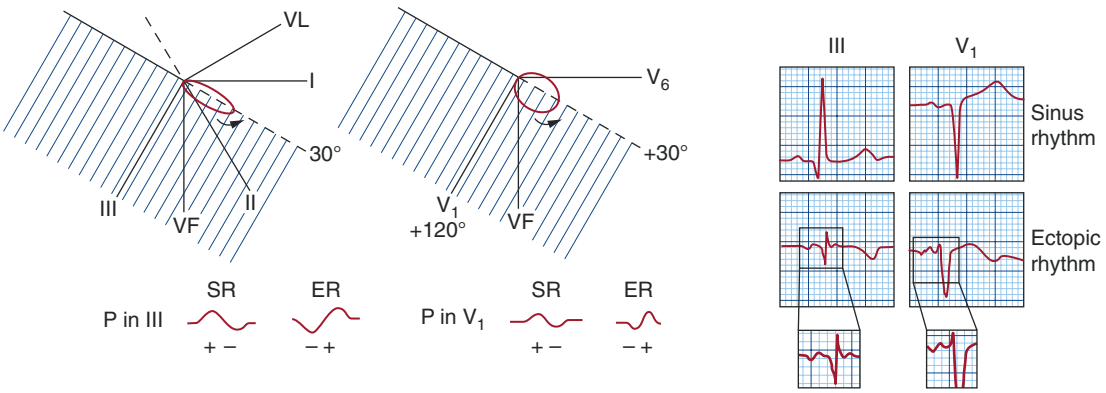


FIGURE 12–16. The sinus P wave (counterclockwise rotation in FP and HP and positive/negative morphology in III and V1 and negative/positive morphology in VL) and ectopic P wave (clockwise rotation and negative/positive morphology in III and V1 and positive/negative morphology in VL). ER, ectopic rhythm; SR, sinus rhythm.

Abnormalities of Repolarization The abnormalities of repolarization encompass T-wave disturbances and abnormal deviations of ST segment. We will only comment here that these abnormalities may be primary or secondary. Primary T-wave disturbances are changes in normal T wave (T wave higher than normal or flat/negative) resulting from delayed TAP in some regions of the heart or some layers of the left ventricle as a consequence of ischemia or other causes (see Changes in T Wave, p. 32). Primary ST deviations (abnormal elevations and depressions of ST) are caused by shape changes of TAP in some regions of the heart or some layers of the left ventricle as a consequence of ischemia or other causes (see Changes in ST Segment, p. 34). Finally, secondary abnormalities of repolarization (usually ST depression and asymmetric negative T waves) are caused changes in shape and duration of TAP at the ventricles secondary to conduction delays (bundle branch block) (see Fig. 12–32) and/or ventricular hypertrophy (strain pattern) (see Fig. 12–30). Sometimes a mixed pattern (primary and secondary) may be seen.

All changes in the normal morphology of the T wave and the abnormal deviations of the ST segment secondary to IHD or present in other heart diseases or situations will be discussed later in this chapter.

U Wave

Occasionally, especially in bradycardia, a small wave called the *U wave* is observed after the T wave, particularly in persons with vagal predominance and in the elderly.[2] Normally, it is smooth and has the same polarity as the T wave (see Fig. 12–1). If it is not, it is always pathologic. Characteristically, the presence of negative U waves in right precordial leads is suggestive of left anterior descending coronary artery occlusion.

Assessment of the QRS Electrical Axis in a Frontal Plane

When the QRS axis (ÂQRS) is at +60°, the morphology is positive in I, II, and III because the loop and its main vector fall in the positive hemifield of I, II, and III. However, it is more positive in II according to the rule that II = I + III (the same rule may be followed for the assessment of P and T wave axis) (Fig. 12–18A). When the axis shifts to the left from +60° to +30°, up to −120°, the QRS complexes become negative starting from lead III, changing from positive to isodiphasic and then from isodiphasic to negative for each shift of 30° to the left in the electrical axis (Fig. 12–18B). As the ÂQRS shifts to the right from +60° to +90°, up to −120°, the complexes again become negative, but starting from lead I, they change from positive to isodiphasic and then from isodiphasic to negative with every 30° shift to the right in the electrical axis (Fig. 12–18C). All of these changes may be explained by the correlation between loop location and the projection on different hemifields of I, II, and III in the frontal plane (see Fig. 12–18A, right) and the projection of the ÂQRS vector in leads I, II, and III in the Einthoven triangle (see Fig. 12–18A, left). Using this procedure, the ÂQRS may be calculated with a precision of 30°. To locate the ÂQRS more precisely, the morphology in the VR, VL, and VF leads has to be checked. For instance, a positive R wave in I, II, and III means that ÂQRS is approximately +60°. The QRS is exactly at +60° if QRS in VL is isodiphasic (). According to the loop-hemifield correlation, if the complex in VL is more positive than negative ( ), the major part of the loop is still located in the positive hemifield of VL, and the ÂQRS is between +30° and +60°; if the QRS complex is more negative than positive ( ), the greatest part of the loop is in the negative hemifield of VL,

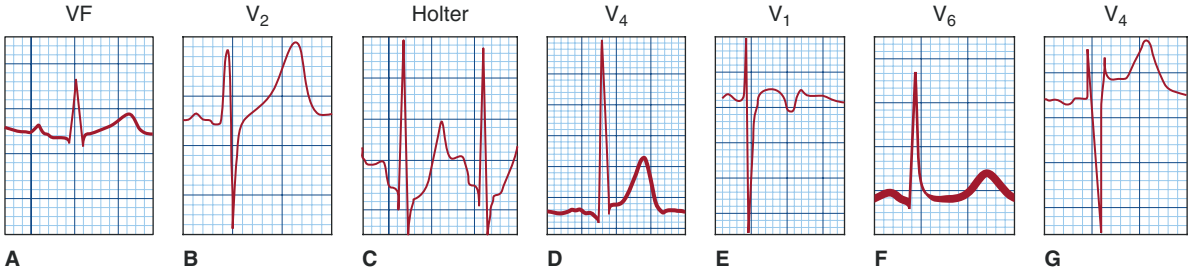


FIGURE 12–17. Different morphologies of normal variants of the ST segment and T wave in the absence of heart disease. **A** and **B.** Normal variants. **C.** Sympathetic overdrive: Electrocardiogram (ECG) of a 22-year-old male obtained with continuous Holter monitoring during a parachute jump. **D.** Early repolarization. **E.** Normal repolarization of a 3-year-old child. **F.** ECG of a 75-year-old man without heart disease but with rectified ST/T. **G.** ECG of a 20-year-old man with pectus excavatum. Normal variant of ST elevation (saddle morphology).

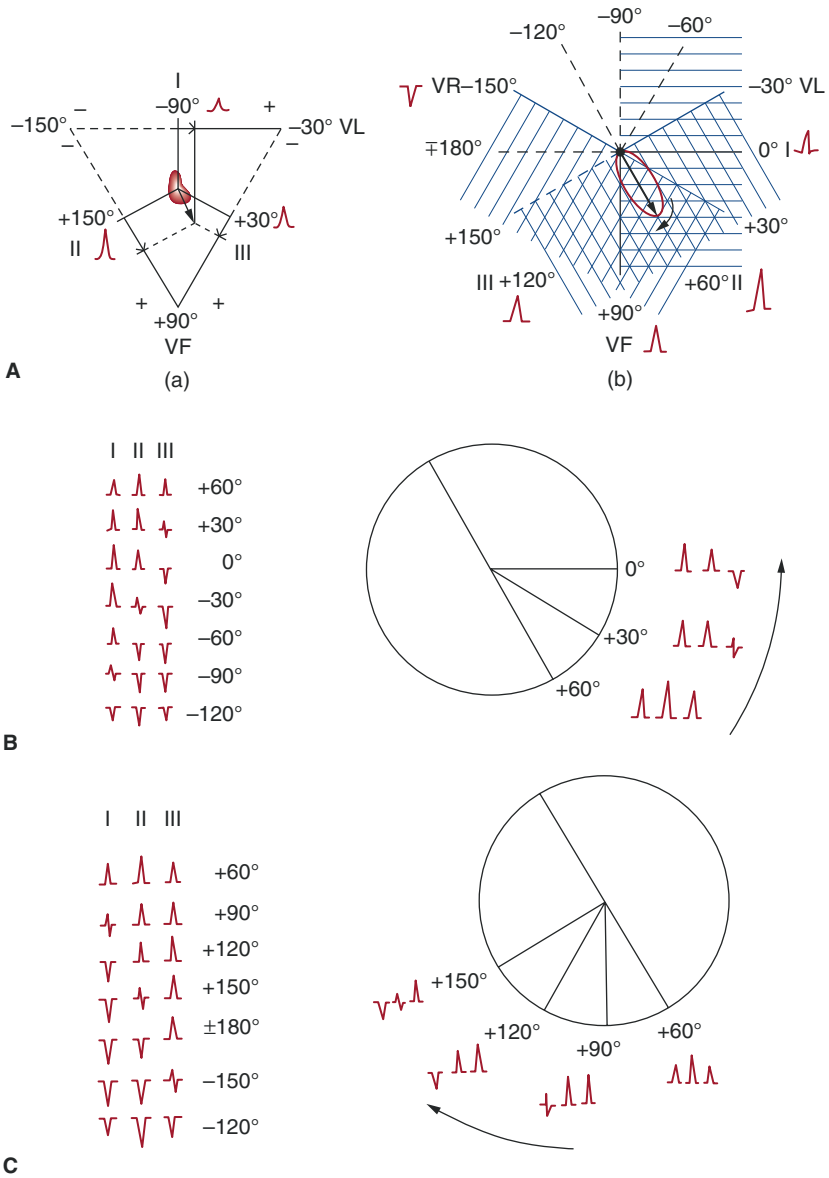


FIGURE 12–18. **A.** Calculation of the QRS axis (ÂQRS) at +60°. **B** and **C.** Changes in QRS morphology with 30° shifts of ÂQRS starting from +60° to the left and to the right.

and the ÂQRS is between +60° and +90°. The same can be done for VR and VF. With such an approach, at a glance, we can calculate the ÂQRS precisely (with an error < 10%).

The normal values of the P, QRS, and T electric axes are as follows. In more than 90% of normal cases, the P axis (ÂP) is located between +30° and +70°. The ÂQRS generally ranges from 0° to +80°, although it can be shifted somewhat more to the left in obese people and more to the right in very lean people. The T axis (ÂT) generally ranges from 0° to +70°. The ÂT is shifted more to the left when the ÂQRS is also shifted to the left. Nevertheless, on certain occasions, when ÂQRS is shifted to the right, the ÂT is between 0° and –30°.

Figure 12–19A shows a normal ECG with an ÂQRS of approximately +30° (the voltage of the QRS complex in lead III is isodiphasic and is positive in I and II).

Electrocardiographic Changes with Age

Infants, Children, and Adolescents The most important features of the ECG in healthy children (Fig. 12–19B) compared with normal adults can be summarized as follows:

1. There is a faster heart rate and a shorter PR interval.
2. Because of the physiologic right ventricular hypertrophy in infants, the heart is usually vertical, with an ÂQRS shifted to the right and negative or bimodal T waves in V_1 to V_3-V_4 and with a characteristic morphology (children's repolarization) that may be present until adolescence, particularly in females. The QRS loop goes to the left before going backward, which explains why the V_6 but not the V_1 morphology (there is higher R in V_1 compared with q in V_6) looks like the adult's morphology. Sometimes an rsr′ pattern is observed in V_1. In infants, especially if they are postterm, even R or qR patterns can be seen at birth with a somewhat positive T wave. The Rs pattern persists for a time, perhaps for years or even until adulthood (see Table 12–2). However, the T wave usually becomes flattened or negative in the days following birth.
3. In some adolescents, an R wave with high voltage in precordial leads ($SV_2 + RV_5 > 60$ mm) without the existence of left ventricular enlargement may be seen.
4. Sometimes, there is an evident increase in the heart rate with inspiration.

The Elderly The following phenomena can be considered age-related ECG variants of the elderly (Fig. 12–19C)[2,22]:

1. A slower heart rate and longer PR interval (normal up to 0.22 second).
2. Occasionally, an ÂP shifted more to the right is caused by pulmonary emphysema, with the S wave present in lead V_6 and an ÂQRS shifted to the left (from 0° to –30°).
3. A poor r progression from V_1 to V_3, probably resulting from septal fibrosis. This can produce differential diagnosis issues with septal necrosis.
4. Unspecific alterations of repolarization (slightly depressed ST segment and/or flattened T wave). A U wave is frequently present, particularly in the intermediate precordial leads.
5. An increase in the incidence of atrial and ventricular blocks as well as left ventricular hypertrophy.

Rotations of the Heart

In a heart without apparent rotation (intermediate position), the ÂQRS is situated around +30° (between +20° and +40°). The ECG of a heart featuring these characteristics is shown in Fig. 12–19A.

Nevertheless, the heart may present isolated or combined rotations, the most characteristic of which are rotations on the following axes: (1) the anteroposterior axis (vertical or horizontal heart; see VL and VF leads in Fig. 12–20A), and (2) the longitudinal axis (dextro- or levorotation; see precordial leads in Fig. 12–20B).

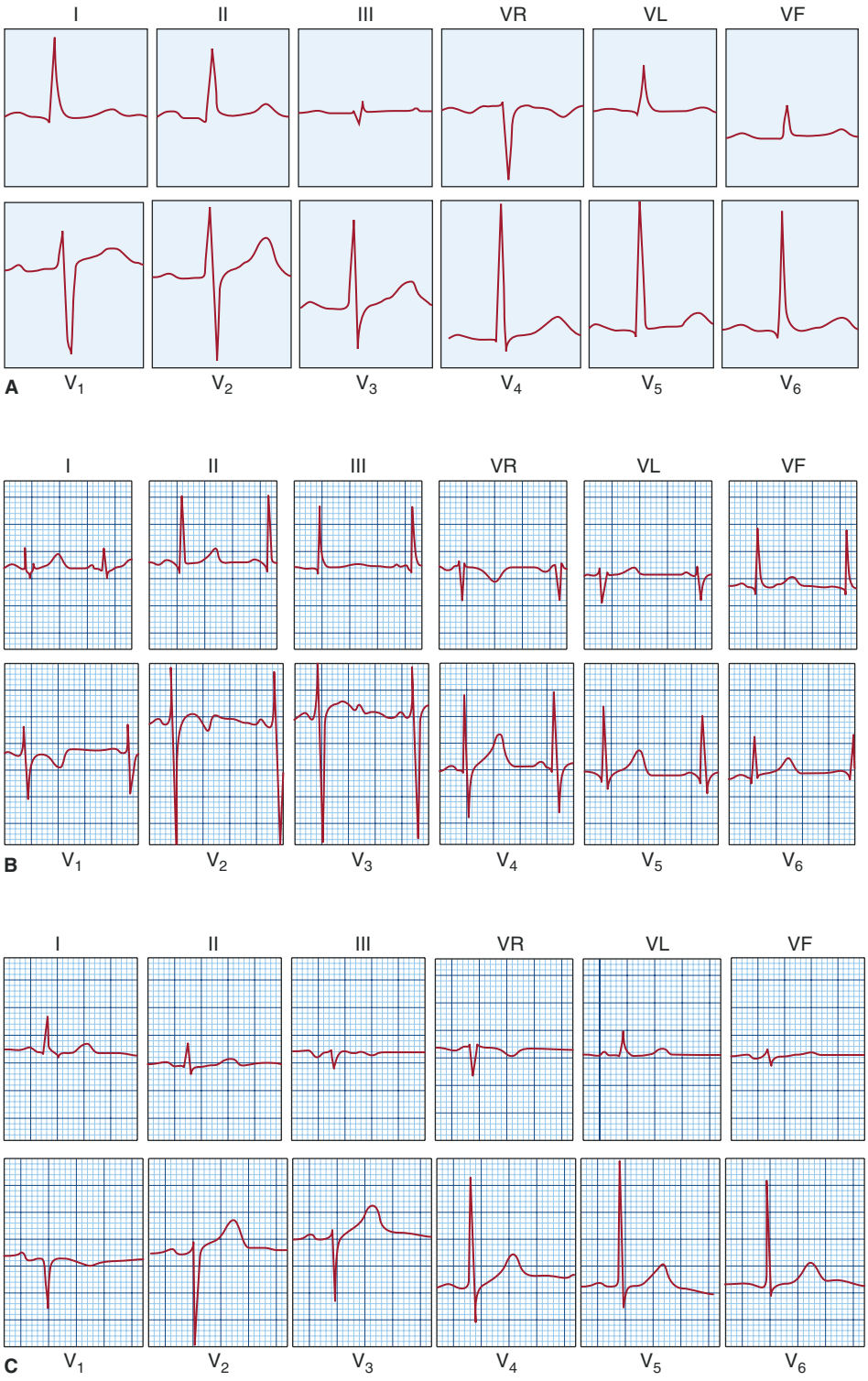


FIGURE 12–19. A. Normal electrocardiogram (ECG) from a healthy adult without rotation. **B.** ECG of a 3-year-old child. **C.** ECG of a normal 80-year-old man (see text).

Certain special types of rotation explain some variants of the normal pattern, such as S_I, S_{II}, and S_{III} (differential diagnosis with right ventricular enlargement [RVE])[23] and QR in III (differential diagnosis with previous inferior infarction). In the latter, the Q wave diminishes during inspiration. For more information, consult Bayés de Luna.[2]

Technical Mistakes during Electrocardiogram Recording

In addition to the knowledge of normal and pathologic patterns, the correct interpretation of ECG recordings requires the use of standard recording procedures.[22] The most frequent errors are a consequence of errors in limb and precordial electrodes placement, artifacts, and inadequate filter application.

1. Misplacement of electrodes may lead to a diagnosis of ectopic rhythm or dextrocardia (Fig. 12–21A) or to an incorrect diagnosis of Q wave MI.[24]
2. As a consequence of some artifacts, a false diagnosis of flutter or ventricular tachycardia may be made (Fig. 12–21B).
3. Finally, the inappropriate use of some filters may induce abnormal ST elevation in V_1 to V_2 or may suppress an otherwise visible J wave (Fig. 12–21C).

For more information, consult García-Niebla et al.[25]

Electrocardiography Criteria of Abnormality

For many conditions, such as blocks and arrhythmias, the ECG is the gold standard for the diagnosis. For other conditions, such as enlargement and some types of ischemia, the ECG diagnostic criteria have to be contrasted against some other gold standard (echocardiography, cardiovascular magnetic resonance [CMR], or coronary angiography). In these cases, it is important to know the diagnostic accuracy of the ECG criteria. For that purpose, we have to study the sensitivity, specificity, negative predictive value, and positive predictive value of each criterion. For further information, consult Bayés de Luna.[2]

ABNORMAL ELECTROCARDIOGRAPHY PATTERNS

ATRIAL ABNORMALITIES

The term *atrial abnormalities* encompasses atrial enlargement, atrial blocks, and abnormalities of atrial repolarization. The following general principles should be emphasized [2]:

1. Atria become dilated rather than hypertrophied.
2. P-wave voltage is influenced by extracardiac factors that increase it (eg, hypoxia, increased sympathetic tone) or decrease it (eg, emphysema, atrial fibrosis).
3. The atrial repolarization wave is usually hidden within the QRS complex (see Fig. 12–1).

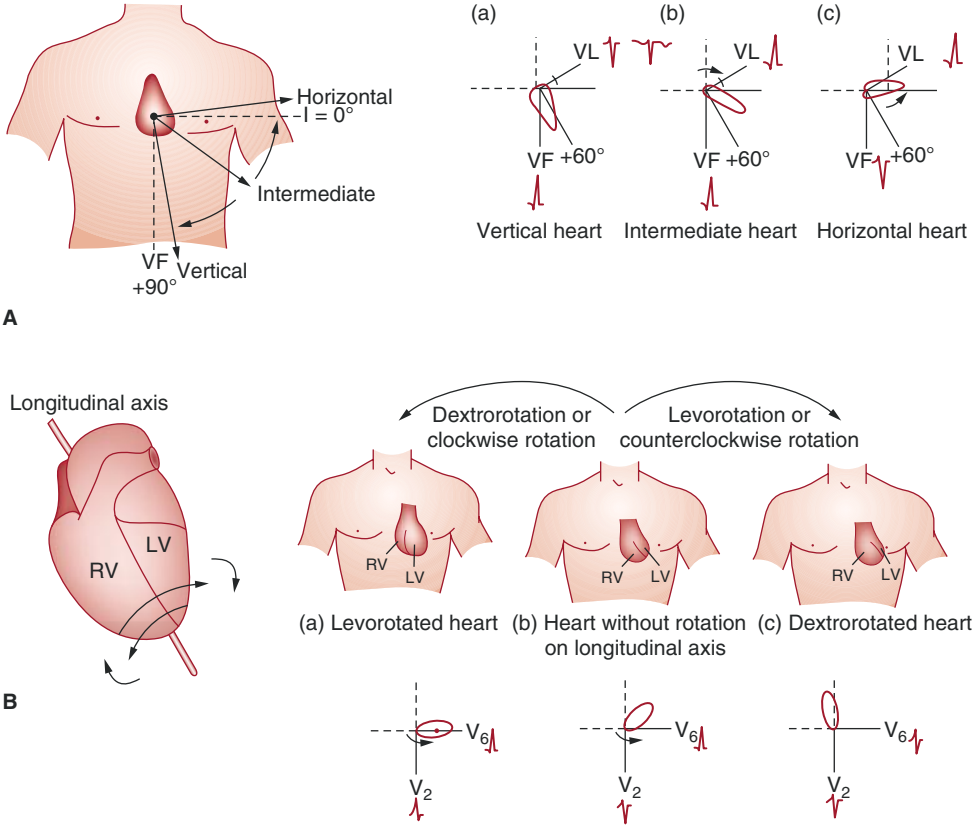


FIGURE 12–20. A. Rotation of the heart along the anteroposterior axis. Direction of the QRS axis (ÂQRS) in the vertical and horizontal heart. ÂQRS morphology in the vertical (a), intermediate (b), and horizontal heart (c). **B.** (a) Rotation of the heart along the longitudinal axis. (b) Scheme of dextrorotation and levorotation. (c) The respective loops and morphologies on the horizontal plane (V_2 and V_6) in levorotated heart, intermediate heart, and dextrorotated heart.

Right Atrial Enlargement (Figs. 12–22 and 12–23)

Right atrial enlargement (RAE) is mainly present in patients with congenital and valvular heart diseases affecting the right side of the heart and in patients with cor pulmonale (see Fig. 12–23B and C). Typically, the P wave is increased in voltage but not in length.

The diagnostic criteria of RAE are based on P-wave abnormalities (positive voltage of $P \geq 2.5$ mm in II and/or positive voltage > 1.5 mm in V_1). These criteria have low sensitivity and somewhat higher specificity.[2]

Left Atrial Enlargement

Left atrial enlargement (LAE) is seen in patients with mitral and aortic valvular disease, IHD, hypertension and some cardiomyopathies (see Figs. 12–22C and 12–23D). Typically, the P wave is bimodal in some leads and +/– in V_1 with evident final negative deflection.

The diagnostic criteria of LAE are as follows[2]: (1) P wave with a duration 0.12 second or longer, especially seen in leads I or II, generally bimodal, but with normal height, and (2) diphasic P wave in V_1 with evident final negative deflection of at least 0.04 second of duration because the second part of the loop is directed backward due to LAE (see Fig. 12–23D, horizontal plane). These two criteria have good specificity (close to 90%; few false-positive cases) but discrete sensitivity (< 60%; more false-negative cases). The +/– P-wave morphology in II, III, and VF with a *P* of at least 0.12 second is a very specific criterion and has a high positive predictive value (100% in valvular heart disease and cardiomyopathies). However, it has a low sensitivity and low negative predictive value for LAE.

Biatrial Enlargement

The most important diagnostic criteria are the following (see Fig. 12–23E)[2]: (1) P wave in lead II that is taller (≥ 2.5 mm) and wider (≥ 0.12 s) than normal, (2) first part of P wave that is positive and peaked in V_1-V_2 (positive mode > 1.5 mm) with a slow negative deflection (width ≥ 4 mm), (**3**) signs of LAE with right ÂP; the opposite case is not valid because the ÂP can be on the left side in isolated

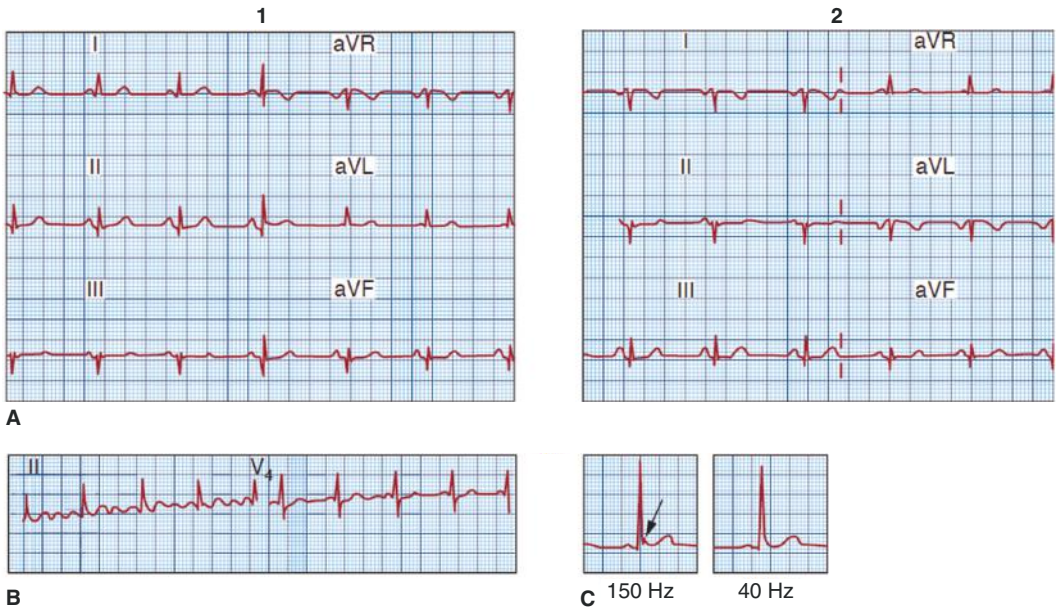


FIGURE 12–21. A. (**1**) Frontal plane leads in a healthy patient. (**2**) Interchanging left arm and right arm electrodes, the electrocardiogram (ECG) shows the classical pattern of P, QRS, and T as negative waves in lead DI and positive in aVR. **B.** Patient with Parkinson disease whose ECG simulates atrial flutter in DIII while V_4 clearly shows P waves. **C.** Lead V_5 in a healthy 23-year-old man with early repolarization. The J wave is visible on applying the low-pass filter at 150 HZ (*arrow*), but this disappears on reducing the frequency to 40 Hz.

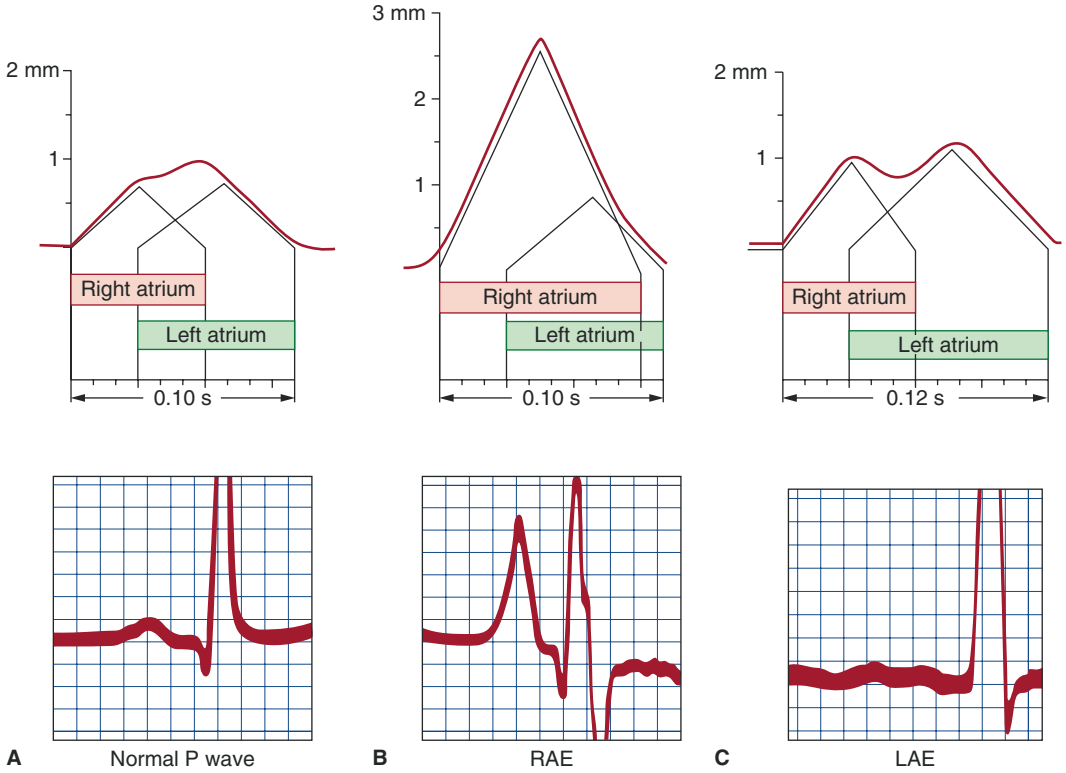


FIGURE 12–22. **Top:** Scheme of atrial depolarization in (**A**) normal P wave, (**B**) right atrial enlargement (RAE), and (**C**) left atrial enlargement (LAE). **Bottom:** three examples of these P waves.

RAE of patients with congenital heart diseases, and (4) presence of atrial fibrillation (AF) along with QRS changes suggestive of RAE. Frequently, more than one criterion is found (P ≥ 120 ms in FP + P± in V_1 with first part peaked and a slow negative mode).

Interatrial Blocks

The concept of a block means that in a certain part of the heart (sinoatrial junction, atria, AV junction, or ventricles), the electrical stimulus encounters overall significant difficulties for its conduction.

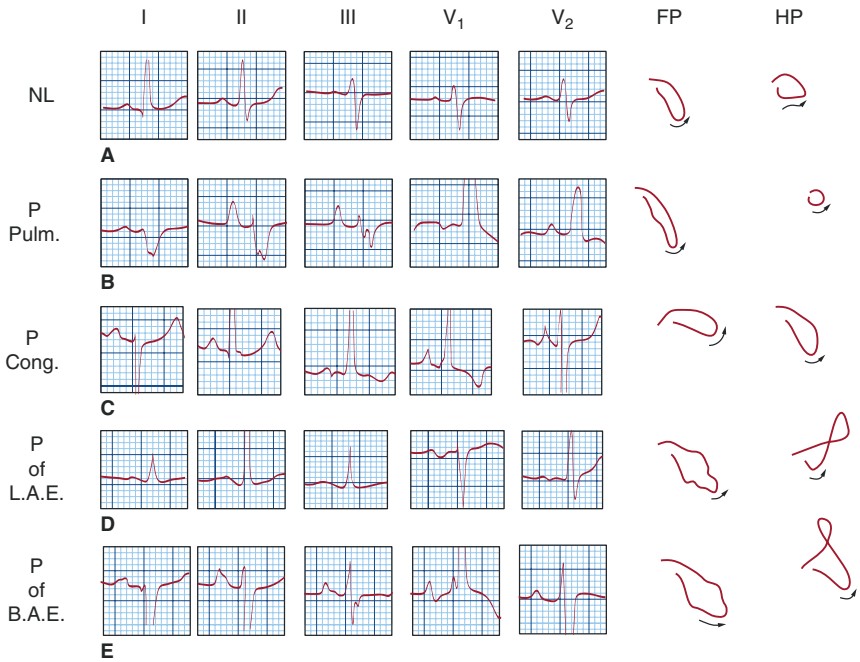


FIGURE 12–23. Morphology of P wave: (**A**) normal (NL); (**B**) right atrial enlargement—P pulmonale: P axis [∠P] to the right; (**C**) right atrial enlargement—P congenitale: ∠P slightly to the left); (**D**) left atrial enlargement (LAE; P mitrale); and (**E**) biatrial enlargement (BAE). FP, frontal plane; HP, horizontal plane.

A first-degree or partial block (P-IAB) occurs when conduction is slow but the stimulus passes through the area but with slow conduction. A third-degree or advanced block (A-IAB) is when the stimulus does not pass completely through the zone but perhaps could pass at a very slower heart rate; therefore, we call it advanced, not complete. A second-degree block is when the stimulus sometimes passes and sometimes does not[2].

The conduction delay in interatrial block occurs between the right and left atria (Fig. 12–24). Although usually associated with LAE, it may also exist as an isolated finding in cases of pericarditis, IHD, old age, and other conditions.[22]

In P-IAB, the stimulus reaches the left atrium via the normal pathway, but with certain delay. The diagnostic criterion of partial interatrial block is a P wave with a duration at least 0.12 second in the frontal plane.[26-28] The P-wave length and, consequently, the bimodal morphology of the P wave seen in lead II (which is the most typical lead to detect an isolated partial interatrial block) are similar to the P wave occurring in LAE. In fact, the delay in interatrial conduction, rather than the left atrium dilation, generally explains the morphology observed with an LAE. However, the morphology of the P wave in the horizontal plane, especially in V_1, is usually different. In case of isolated interatrial block (eg, pericarditis), the second part of the loop is not directed so much backward because there is no LAE, and consequently, the P-wave morphology in V_1 is positive or only presents a small negative part.

In A-IAB (see Fig. 12–24),[27,28] the stimulus does not reach the left atrium via the normal path but by retrograde left atrial activation.[28] The diagnostic criteria of advanced interatrial block are as follows[27]: (1) P wave with a duration of at least 0.12 second and +/– in II, III, and VF, and (2) often, P wave +/– in V_1 to V_3 or V_4. The prevalence of A-IAB increases with age, being very low before 50 years of age and

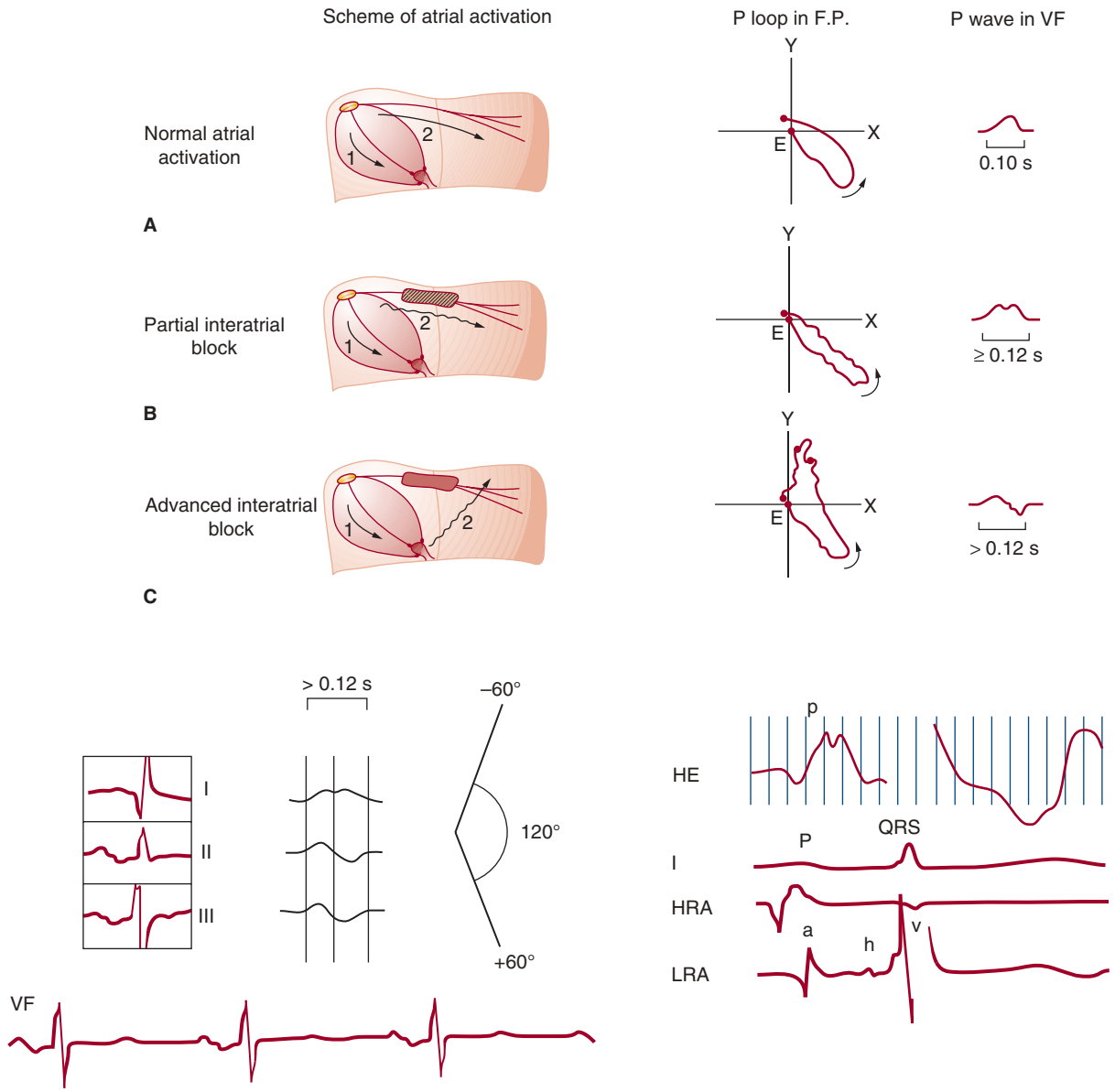


FIGURE 12–24. **Top:** Example of atrial activation and characteristics of the P loop in the frontal plane and the morphology of P wave in VF in normal conditions (**A**) and in a case of partial (**B**) and advanced (**C**) interatrial block with left atrial retrograde activation. **Bottom left:** Leads I, II, and III in advanced interatrial block with left atrial retrograde activation, with direction of the activation vectors of the first and second part of the P wave and three consecutive P waves with +/ morphology in VF. **Bottom right:** Esophageal and intracavitary recordings demonstrating the sequence of activation in this type of interatrial block (high right atrium [HRA], low right atrium [LRA], and high esophageal [HE] lead with –/+ morphology).

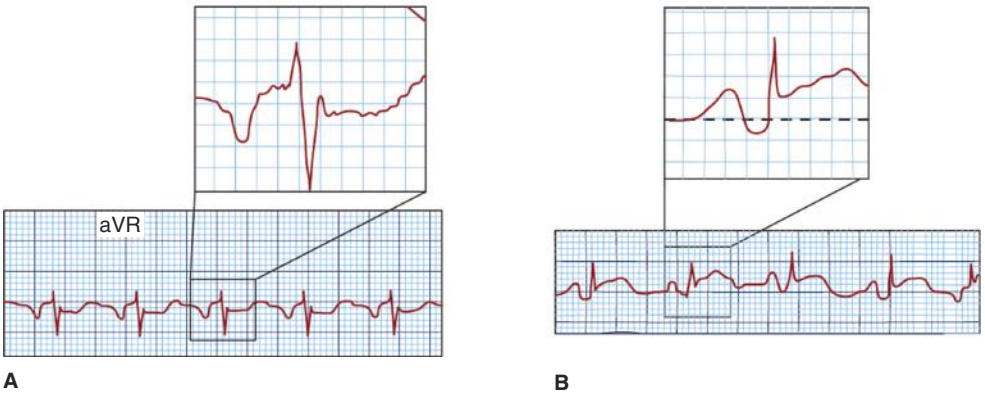


FIGURE 12–25. A. PR-segment elevation morphology in a case of pericarditis. **B.** PR depression in atrial extension of anterior myocardial infarction.

approaching 25% in centenarians in whom an increase of dementia and stroke associated with A-IAB has been detected.[22] This type of block is frequently accompanied, especially when it is present in patients with advanced heart disease, by supraventricular arrhythmias, particularly AF and/or atrial flutter (Bayes syndrome).[29-31]

Abnormalities of Atrial Repolarization

The atrial repolarization wave (ST-Ta) usually has a polarity opposed to the P wave and is not visible because it is hidden within the QRS complex. In cases of great sympathetic overdrive in normal individuals, an ST-Ta depression may be seen (see Fig. 12–17C). Moreover, in some cases of remarkable atrial enlargement, pericarditis, or atrial infarction, especially in the presence of a long PR interval, shifts of ST-Ta may be observed (Fig. 12–25).

VENTRICULAR ENLARGEMENT

Morphologies of ventricular enlargement are secondary to a hypertrophy rather than to dilatation, unlike what occurs in the atria. Slight or even moderate degrees of enlargement of either of the ventricles, mainly the right, or of both at the same time, may not produce abnormalities in the ECG.

The superiority of echocardiography over ECG for the diagnosis of ventricular enlargement, mainly of the left ventricle, is evident (the sensitivity is much higher, and the specificity is similar). However, when a ventricular enlargement is diagnosed with an ECG, the accuracy of the ECG is greater than that of the echocardiogram in predicting heart disease evolution and prognosis.

For details on the diagnosis of right and/or left ventricular enlargement combined with ventricular block (QRS complex duration > 120 milliseconds), the reader is referred to Bayés de Luna[2] and McFarlane and Lawrie.[14]

Right Ventricular Enlargement

RVE is found especially in congenital heart diseases, valvular heart diseases, and cor pulmonale. The changes produced by RVE move the loop rightward and either frontward or backward. This is more a result of a delay of activation of the right ventricle, rather than an increase of the right ventricle mass (which generally never overcomes the mass of the left ventricle). Figure 12–26 shows the changes that RVE may produce in ventricular activation expressed as ventricular loops and how these changes may explain the different ECG patterns. Basically, a large part of the QRS loop is going to the right (presence of S in V_6) but sometimes with an anterior loop (R or RS in V_1) and occasionally with a posterior loop (rS or QS in V_1).

The lower part of Fig. 12–26 shows three cases of RVE of different etiologies (see legend) in which the ECG pattern in V_1 (with more or less R wave) is related more to RVE degree than to RVE etiology.

The ECG criteria (low sensitivity, high specificity) most frequently used for the diagnosis of RVE are shown in Table 12–1.

- Morphology of V_1: (1) Morphologies with dominant or exclusive R wave in V_1 are very specific but not very sensitive (< 10%) for the diagnosis of RVE because the loop that gives rise to them (anterior and to the right; see

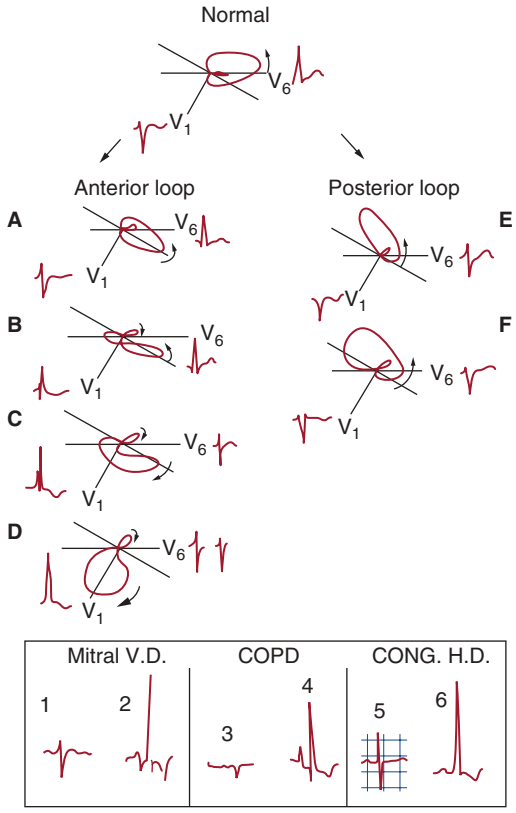


FIGURE 12–26. In right ventricular enlargement (RVE) with electrocardiographic repercussion, the horizontal loop of the QRS is always directed to the right, either forward or backward. When it is directed forward, different morphologies may be recorded (from **A** to **D** cases with more advanced degree of RVE). A patient may have a morphology changing from one to another during the course of the disease. However, in general, heart diseases with mild to moderate RVE present with type A or type B morphologies, and those with severe RVE present with type D. If the loop is directed posteriorly, then the morphologies are of types E or F. the QS morphology is seen in the V_1 lead in type **E**, whereas rS or rSr′ is seen in type **F**, in both cases accompanied by a significant S in V_6. The lower part of the figure shows that the morphology of QRS in V_1 depends more on the severity and grade of RVE than on the etiology of the disease. **Left:** Mild mitral stenosis (1) and advanced mitral stenosis with severe pulmonary hypertension (2). **Middle:** Long-standing chronic cor pulmonale without severe pulmonary hypertension (3) and subacute cor pulmonale with severe pulmonary hypertension (4). **Right:** Congenital moderate pulmonary stenosis (5) and severe valvular pulmonary stenosis (6). CONG. H.D, congenital heart disease; COPD, chronic obstructive pulmonary disease; Mitral V.D., mitral valve disease.

TABLE 12–1. Electrocardiographic Criteria of Right Ventricular Enlargement

	Criterion	Sensitivity (%)	Specificity (%)
V_1	R/S $V_1 \geq 1$	6	98
	R $V_1 \geq 7$ mm	2	99
	qR in V_1	5	99
	S in $V_1 < 2$ mm	6	98
	IDT in $V_1 \geq 0.35$ s	8	98
V_5–V_6	R/S V_5–$V_6 \leq 1$	16	93
	R V_5–$V_6 < 5$ mm	13	87
	S V_5-$V_6 \geq 7$ mm	26	90
$V_1 + V_6$	$HV_1 + SV_5$–$V_6 > 10.5$ mm ÂQRS $\geq 110°$	18	94
ÂQRS	S_I, S_{II}, S_{III}	15	96
		24	87

Abbreviations: ÂQRS, QRS axis; IDT, intrinsicoid deflection (time from QRS onset to R-wave peak).

Fig. 12–26B–D) is observed in a small number of cases with RVE (especially in some congenital heart diseases such as pulmonary stenosis). In these cases, the prominent R in V_1 is also seen in V_2 and V_3. Moreover, the repolarization presents an ST-segment depression and a negative and asymmetric T wave (strain pattern; Fig. 12–26, Fig. 12–27A), except in newborns because they may present with an exclusive R wave with a positive T wave. On the contrary, in cases of pulmonary stenosis from tetralogy of Fallot, the morphology in V_1 is similar to that in isolated pulmonary stenosis, but in V_2, there is an rS morphology. Other causes that may present a dominant R pattern in V_1 must be ruled out (Table 12–2). (2) The presence of rsR′ is especially typical of atrial septal defect and sometimes may also be seen in moderate pulmonary stenosis. (3) The rS or even the QS morphology in V_1, with RS in V_6, may often be observed in the early phases of RVE, or with rS in V_6 in advanced cases of chronic cor pulmonale (see Fig. 12–26B).

- Morphology of V_6. The presence of evident forces directed to the right, which are expressed as an evident S wave in V_5 to V_6, is one of the most important ECG diagnostic criteria (see Figs. 12–26 and 12–27; see Table 12–1).
- S_I, S_{II}, S_{III}. This morphology is frequently seen in chronic cor pulmonale with QS pattern in V_1 and RS pattern in V_6. Note that this pattern may be secondary to positional changes (p. 14 [manuscript page 26]) or it may simply be a normal variant.[2] Nonetheless, an abnormal P wave favors the diagnosis of RVE (see Fig. 12–27B).
- Electrical axis: ÂQRS of at least +110°. Inferoposterior hemiblock, vertical heart, and lateral infarction must be ruled out. This criterion is quite specific (> 95%) but relays low sensitivity.

The combination of more than one of these criteria increases the diagnostic possibilities. The differential diagnosis of exclusive or predominant R wave in V_1(R, Rs, or RSR′ pattern) is shown in Table 12–2.

The ECG signs indicative of right ventricle acute overload (decompensation of cor pulmonale or pulmonary embolism) are as follows[32]:

- Change in the ÂQRS (> 30° to the right of its usual position)
- Transient negative T waves, sometimes very evident in the right precordial leads
- S_I, Q_{III} with negative T_{III} pattern (McGinn-White pattern) in the frontal plane and an RS or rS pattern in V_6 (Fig. 12–28)
- Appearance of a complete right bundle branch block morphology, often with ST-segment elevation

The latter two criteria are highly specific but have low sensitivity for important pulmonary embolism (see Cor Pulmonale). Nevertheless, the clinical setting and comparison with previous ECGs are important to make a differential diagnosis of both processes.

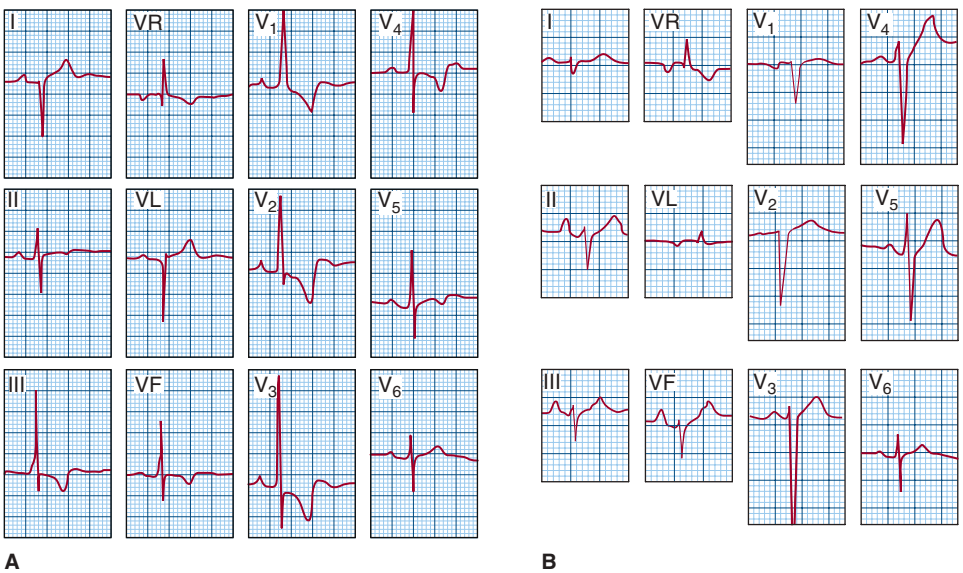


FIGURE 12–27. A. An 8-year-old patient with important pulmonary valve stenosis, with a gradient of more than 100 mm Hg. The patient presents a typical morphology of right ventricular enlargement (RVE) with R wave–type systolic overload (strain) from V_1 to V_3. **B.** Patient with RVE caused by advanced chronic obstructive pulmonary disease with posterior and right QRS loop types S_I, S_{II}, S_{III}.

Left Ventricular Enlargement

Left ventricular enlargement (LVE) is found in hypertension, IHD, valvular heart disease, cardiomyopathies, and some congenital heart diseases. In general, in patients with LVE, the maximum QRS vector of the loop increases its voltage and is directed more posteriorly than normal (Fig. 12–29). This explains why the QRS complex negativity predominates in the right precordial leads (see Fig. 12–29A–C). Occasionally, the maximum vector is not directed posteriorly (it is located close to 0°). This implies a tall R wave that is seen even in V_2, especially in cases of apical hypertrophic cardiomyopathy (see Fig. 12–29E).

The ECG pattern changes during disease evolution. The pattern of "strain" appears more in relation with the duration of the disease than with the presence of different types of hemodynamic overload. However, in aortic valve

TABLE 12–2. Morphologies with Dominant R or (r′) R′ in V_1: Clinical Setting, Typical Morphologies in V_1, QRS Width, and Morphology of P in V_1

Clinical Setting	Morphology in V_1 With Dominant R or R′	QRS Width	P-Wave Morphology in V_1
1. No heart disease			Negative in second ICS and + or
• Incorrect electrode placement		< 0.12 s	+/− in fourth ICS
• Abnormal variant (post-term infants, scant Purkinje fibers in anteroseptal zone)		< 0.12 s	Normal
• Chest anomalies		< 0.12 s	Normal
2. Typical right bundle branch block		From < 0.12 to ≥ 0.12 s	Normal
3. A typical right bundle branch block			Often tall and peaked and + or +/−
• Ebstein disease		Often ≥ 0.12 s Often ≥ 0.12 s	Often abnormal
• Arrhythmogenic right ventricular dysplasia		Sometimes ≥ 0.12 s	Normal
• Brugada syndrome		< 0.12 s	Often tall and peaked
4. R ight ventricular or biventricular enlargement		From < 0.12 to 0.2 s	Normal P, short PR
5. WPW syndrome		< 0.12 s	Normal P
6. Lateral myocardial infarction			

Abbreviations: ICS, intercostal space; WPW, Wolff-Parkinson-White

disease, a q wave in V_5 to V_6 is found more frequently in long-standing aortic regurgitation than in aortic stenosis (Fig. 12–30). The disappearance of the q wave in V_6 is probably more related to interstitial septal fibrosis, a substrate of partial left bundle branch block, than to hemodynamic overload[31] (see Figs. 12–29 and 12–30).

The presence of noticeable signs that are suggestive of LVE (high voltage of the QRS together with inverted ST-T wave—strain pattern) in an asymptomatic patient without heart murmur or hypertension suggests hypertrophic cardiomyopathy. The ECG does not correlate with the gene mutation,[33] but there are two at least ECG changes suggestive of hypertrophic cardiomyopathy: (1) the striking negative T waves (see Fig. 12–29E) and (2) the presence of a deep and narrow q waves (see Fig. 12–29D).

Sometimes the LVE pattern, at least partially, and especially the changes in ST-T may be resolved in a few months with pharmacologic treatment, as occurs in hypertension or after surgery (valvular heart disease).

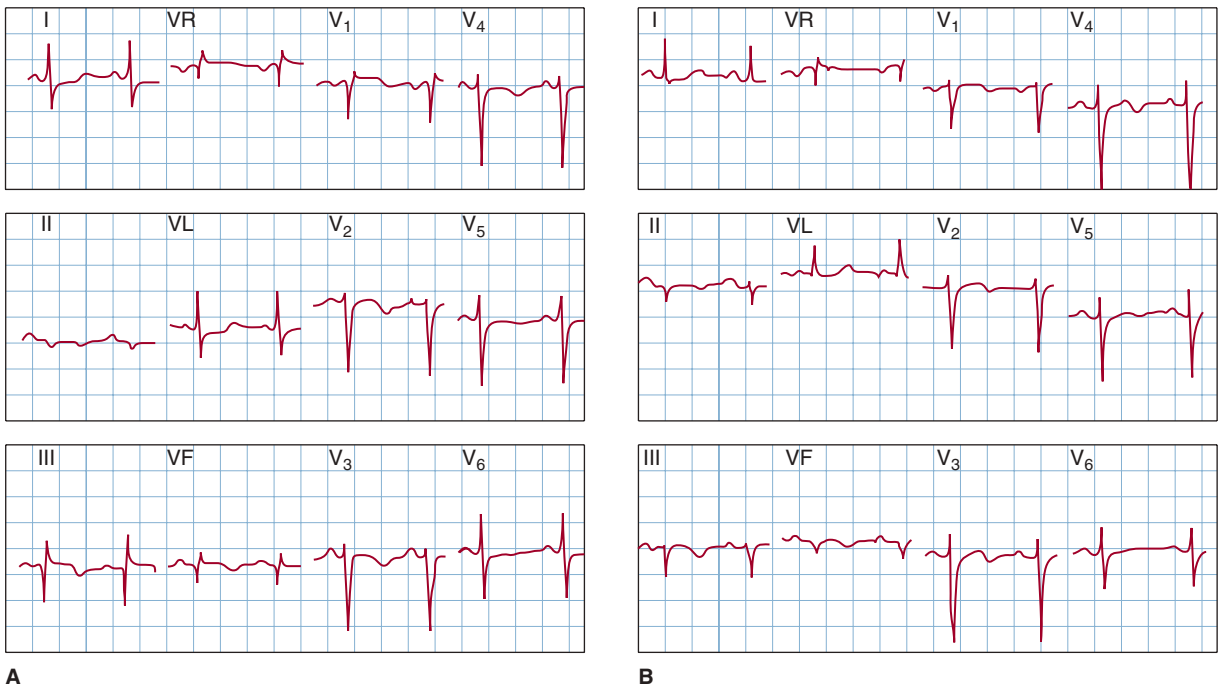


FIGURE 12–28. A. A 59-year-old patient presenting a typical McGinn-White pattern (SI, QIII with negative T wave in lead III and rSr′ in V_1) in the course of pulmonary embolism. **B.** The electrocardiogram findings after the recovery of the patient still show negative T waves in the precordial leads, but the McGinn-White pattern and the r′ in V_1 have disappeared.

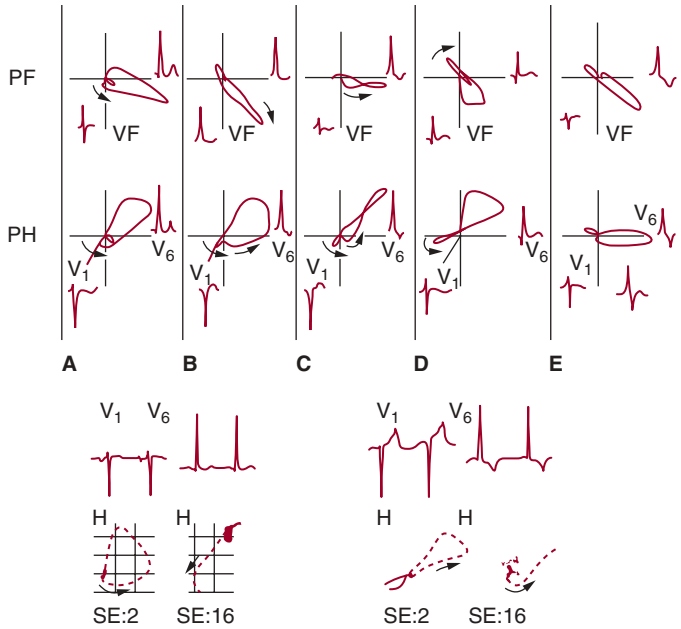


FIGURE 12–29. The most characteristic loops of left ventricular enlargement (LVE): (**A**) with the initial forces to the right and a positive T wave; (**B**) observed in cases of LVE that are not long-standing and with mild septal fibrosis; (**C**) QRS loops initially to the left and with counterclockwise rotation or figure-of-eight rotation on horizontal plane; corresponds to significant LVE seen in advanced heart diseases with significant septal fibrosis; (**D**) QRS loop with q wave of pseudonecrosis that occurs in cases of hypertrophic cardiomyopathy due to the presence of important septal vector; (**E**) QRS loop pointed approximately 0° on the horizontal plane with a very peaked T loop pointed upward, backward, and rightward characteristic for the apical type of hypertrophic cardiomyopathy. **Bottom:** Two examples of aortic valve disease, one (left) with mild septal fibrosis and normal ECG and VCG (presence of q wave in V6 as expression of first vector) and the other (right) with important septal fibrosis and abnormal electrocardiography (ST-T with strain pattern) and VCG (absence of q wave in V_6). See in the HP (H) with amplification of the loop (SE = 16) now in the left the qR in V_6 coincides with initial vector forces of the loop in the negative hemifield of V_6, and in the right with R in V_6 the initial forces go directly to the left.

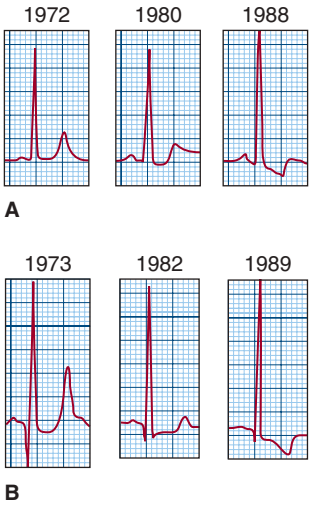


FIGURE 12–30. Examples of different electrocardiogram morphologies seen in the evolutionary course of aortic stenosis (note the appearance of strain pattern) (**A**) and aortic regurgitation (note the decrease of q wave and the appearance of strain pattern) (**B**).

TABLE 12–3. Electrocardiographic Criteria of Left Ventricular Enlargement

Voltage Criteria	Sensitivity (%)	Specificity (%)
1. $R_I + S_{II} > 25$ mm	10.6	100
2. RVL > 11 mm	11	100
3. RVL > 7.5 mm	22	96
4. $SV_1 + RV_5$-$V_6 \geq 35$ mm (Sokolow-Lyon)	22	100
5. RV_6-$V_6 > 26$ mm	25	98
6. RVL + $SV_3 > 28$ mm (men) or > 20 mm (women) (Cornell voltage criterion)	42	96
7. Cornell voltage duration measurement QRS duration × Cornell voltage > 2436 mm/seg	51	95
8. In V_1-V_6, the deepest S + the tallest R > 45 mm	45	93
9. Romhilt-Estes score > 4 points	55	85
10. Romhilt-Estes score > 5 points	35	95

Various diagnostic criteria exist for LVE,[34-37] with varying sensitivity and specificity, as shown in Table 12–3. It is usually possible to diagnose an LVE through an ECG in patients with severe hypertension, whereas this diagnosis is difficult in asymptomatic normotensive adults. However, the value of the ECG diagnostic criteria shown in Table 12–3 is lower in hypertensive patients. For these patients, the following criterion is useful: sum of the QRS voltage of 12 ECG leads greater than 120 mm.[37]

Biventricular Enlargement

The ECG diagnosis of biventricular enlargement is even more difficult than that of the enlargement of just one ventricle. This is true because the increased opposing forces of both ventricles often counterbalance each other or the notable predominance of the enlargement of one ventricle completely masks the enlargement of the other. Therefore, even those criteria that have fair specificity only have a moderate sensitivity.[38]

The following ECG patterns are used for the diagnosis of biventricular enlargement:

- Tall R wave with s in V_5 and V_6, rSR′ pattern in V_1, and P wave of biatrial enlargement
- Tall R wave in V_5 and V_6, with an ÂQRS shifted to the right (≥ 90°). The presence of an inferoposterior hemiblock associated with LVE and an asthenic body build must be ruled out.
- Small S wave in V_1, deep S wave in V_2, predominant R wave in V_5 and V_6, and an ÂQRS shifted to the right in the frontal plane or an S_I–, S_{II}–, S_{III}–type morphology
- The presence, especially in the elderly, of QRS complexes within normal limits but with significant repolarization abnormalities (negative T wave and depression of the ST segment), mainly when the patient presents with AF. This type of ECG can be found in the elderly with advanced heart diseases and biventricular enlargement.

VENTRICULAR BLOCKS

Blocks at the ventricular level can occur on the right side (Table 12–4) or on the left side (Table 12–5). They can affect the entire ventricle (*global block*) or only part of it (*zonal or divisional block*). The blockage of electrical impulses, in the ventricles or in the whole heart (see interatrial blocks) is called a *first-degree (partial) block* when the impulses pass through the area but with a delay; *second-degree block* when the stimulus sometimes passes and sometimes does not; and *third-degree (advanced) block* when the passage of stimulus is blocked.[2] The term *advanced* is preferred over *complete*, because one can not know whether the stimulus would pass at a very lower heart rate. Second-degree block is known as *aberrancy of conduction* and is explained in Section 6).

In global ventricular block, the conduction delay usually occurs in the proximal part of the right or left branches. For this reason, the global ventricular block is known as *bundle branch block*.

Advanced or third-degree bundle branch blocks, both right and left, have the following characteristics[2,13]:

1. Depolarization of the ventricle corresponding to the blocked branch that occurs transseptally, beginning at the contralateral ventricle. This phenomenon explains the QRS complex widening (≥ 0.12 second) caused by a small number of Purkinje fibers in the septum and the peculiar QRS complex morphology, both in right and left bundle branch blocks, caused by the loop-hemifield correlation (Figs. 12–31, 12–32, and 12–33).
2. Diagnosis is mainly based on data provided by the horizontal plane leads V_1 and V_6 and the frontal plane lead VR.
3. Slurring at the end of the small of the QRS is usually opposed to the T wave.
4. Septal repolarization dominates over that of the left ventricular free wall and is responsible for the ST-T changes.
5. In general, the anatomic changes are more diffuse than the ECG expression.

Partial or first-degree bundle branch block presents a QRS complex with a duration less than 120 milliseconds, which gives rise to morphologies that are sometimes indistinguishable from some patterns seen in homolateral ventricular enlargement (see Fig. 12–32).

TABLE 12–4. Right Ventricular Block

Global (right bundle branch block)

1. Third-degree (advanced): Morphologies corresponding to type III of the Mexican school[13]: slurred rSR′ in V_1 and qRS with slurred S in V_6 with QRS ≥ 0.12 s
2. First-degree (partial): Morphologies corresponding to type I: rSR′ in V_1 of the Mexican school with QRS < 0.12 s[13]
3. Second-degree: Intermittent block morphology; corresponds to a special type of ventricular aberrancy

Zonal or divisional

Experimentally, it originates ECG morphologies of the S_I, S_{II}, S_{III} or R_I, S_{II}, S_{III} type.[23] In clinical practice, these morphologies are difficult to differentiate from normal variants or right ventricular enlargement (the changes in P and T waves may help). The S_I, R_{II}, R_{III} morphology must also be explained by inferoposterior hemiblock.

TABLE 12–5. Left Ventricular Block

Global (left bundle branch block)

1. Third-degree (advanced): Corresponds to type III of the Mexican school[13]: slurred R in V_6 and QS of rS in V_1 with QRS ≥ 0.12 s
2. First-degree (partial): Corresponds to types I and II of the Mexican school[13]: isolated R in V_6 with more or less slurring but QRS < 0.12 s
3. Second-degree: Intermittent block morphology; corresponds to a special type of ventricular aberrancy

Zonal or divisional

- Hemiblocks[47,48]: The block is located in the superoanterior or inferoposterior divisions of the left bundle branch. Superoanterior hemiblock originates a qR pattern in leads I and VL and an rS pattern in leads II, III, and VF, whereas inferoposterior hemiblock originates an RS pattern in lead I and VL and a qR pattern in leads II, III, and VF.
- Block of the middle fibers probably produces RS morphologies in V_1, although the prominent R in V1 may also be explained by some degree of RBBB.

RBBB, right bundle branch block.

Zonal or divisional left blocks (hemiblocks) have been studied more in depth, both from the anatomic and electrophysiologic viewpoints, compared with right zonal blocks.

There are four intraventricular fascicles: right bundle branch, trunk of the left bundle branch, and the superoanterior and inferoposterior divisions of the left bundle. It may probably also be a block of the middle fibers (septal fascicle) of the left bundle (see later). Therefore, in addition to the block of one fascicle, blocks of two fascicles (bifascicular block) or three fascicles (trifascicular) may occur.

Advanced or Third-Degree Right Bundle Branch Block

In third-degree right bundle branch block (RBBB), the depolarization of the right ventricle occurs entirely through the septum from the left side, originating the formation of vectors 3 and 4 and causing the global change in QRS loop. The classic ECG morphologies, which result from the loop-hemifield correlation in the frontal and horizontal planes, are shown in Fig. 12–31. The repolarization is from right to left at septal level in case of proximal RBBB or at peripheral level in case of peripheral block. Because of that, the T wave is negative in V1 and positive in V6.

The blockade location, both in advanced and partial block, is usually proximal. Nevertheless, a block located in the distal part of the branch or in the right ventricle Purkinje network is often seen in some congenital heart diseases (eg, Ebstein anomaly, atrial septal defect, following surgery for tetralogy of Fallot) and in some cardiomyopathies (eg, arrhythmogenic right ventricular cardiomyopathy), giving rise to morphologies similar to those of classic complete or partial bundle branch block but with some specific patterns. See Table 12–2 concerning the differential diagnosis of tall R wave in V_1.

The presence of advanced RBBB does not usually represent a poor prognosis in the absence of overt heart disease. However, it predicts an adverse outcome if it appears after acute MI, concomitantly with acute dyspnea (resulting from probable pulmonary embolism) or during an ACS caused by occlusion of the left anterior descending (LAD) coronary artery proximal to the first septal branch, which is the branch perfusing the right bundle.[2]

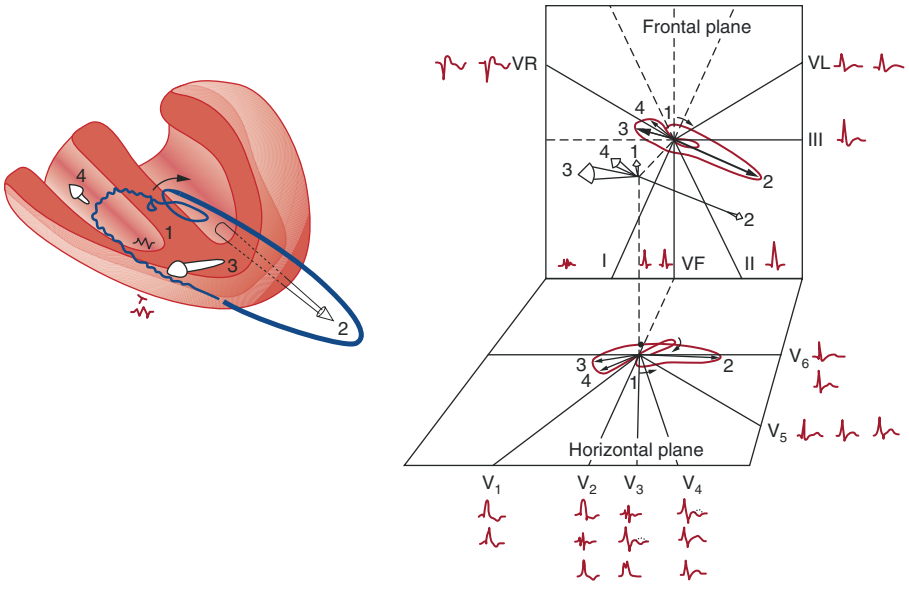


FIGURE 12–31. **A.** Example of how activation occurs in complete right bundle branch block and how the different lead morphologies are explained with the loop-hemifield correlation. **B.** A typical electrocardiogram of complete right bundle branch block (see text).

The ECG diagnostic criteria are as follows (see Fig. 12–31 and Table 12–4):

- QRS of at least 0.12 second with midfinal slurring
- V_1: rSR′ with slurred R wave and a negative T wave
- V_6: qRS with evident S wave slurring and positive T wave
- VR: QR with evident R wave slurring and negative T wave
- T wave with its polarity opposed to QRS slurring

Partial or First-Degree Right Bundle Branch Block

In first-degree RBBB, the delay of the activation in the entire ventricle is less important. This explains why the QRS is narrower and the morphology shows less prominent forces to the right (see Fig. 12–32).

The ECG diagnostic criteria are as follows:

- QRS complex duration less than 0.12 second
- Morphology with rsR′ or rsr′ pattern or even rs (RS) in V_1, final r in VR, and s wave in VL and V_6, but with fewer notches and slurring[2]

A similar pattern may be seen in some cases of RVE, as in atrial septal defect, because of a delay of activation of some parts of the right ventricle as a result of the enlargement (see Fig. 12–26C).

Right Zonal Blocks

Experimentally,[23,39] the injury of the fibers of the superoanterior zone of the right ventricle often causes ECG morphologies of the S_I, S_{II}, S_{III} types.[23] Less frequently, the injury of the inferoposterior zone, may originate S_I R_{II} R_{III} pattern. In clinical practice, these morphologies are difficult to differentiate from normal variants or RVE.[2] The changes in P and T waves may help in the differential diagnosis. The S_I, R_{II}, R_{III} morphology must also be found in the inferoposterior hemiblock.

Advanced or Third-Degree Left Bundle Branch Block

In third-degree left bundle branch block (LBBB), the left ventricle activation is through the septum from the right side and differs completely from normal activation. This transseptal activation causes the formation of four vectors, which are characteristic of this type of block and explain the global change in the QRS loop. The classic ECG morphologies, caused by the loop-hemifield correlation in the frontal and horizontal planes, are shown in Fig. 12–33. The repolarization in case of more advanced LBBB is directed from left to right with the T loop opposite in direction to QRS (discordant LBBB).[40] This explains the negativity of T wave in leads I, V5, and V6. The T wave is normally located opposite from slurring and dominant deflection of the QRS complex. In cases of less advanced LBBB, the T wave is often concordant with the QRS (T-wave positive in leads I, V5, and V6). Also, the concordant repolarization may be explained, in a few cases, by associated IHD.

The morphology of the distal blocks is similar to that of the classic proximal complete left ventricular block but with more significant final slurrings of the QRS complex. Wherever the global block is located (proximal or distal), when the delay is significant, an R-wave morphology in V_6 and a QS complex in V_1, with a QRS of at least 0.12 second, are generated.

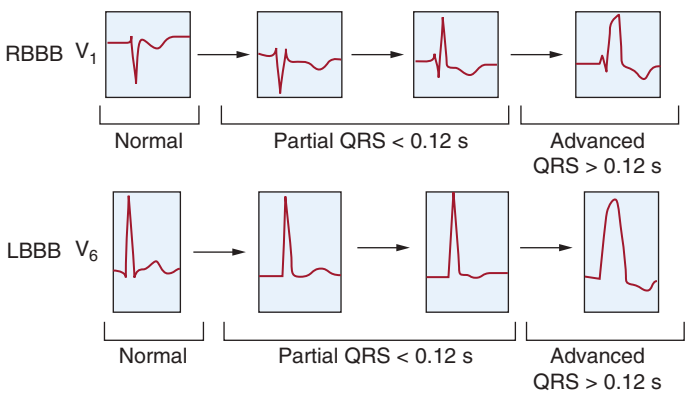
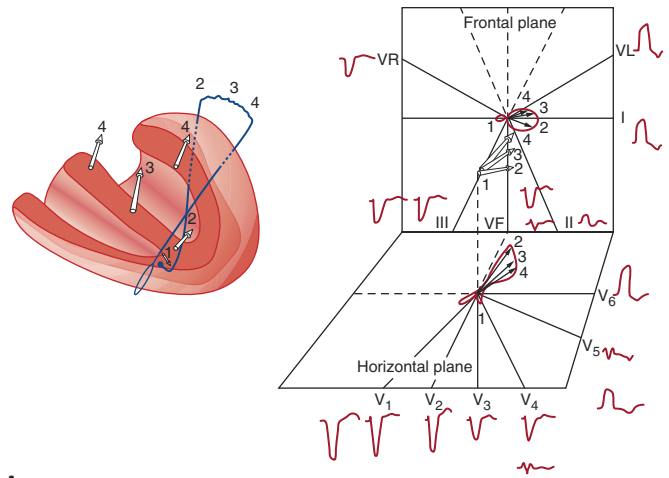
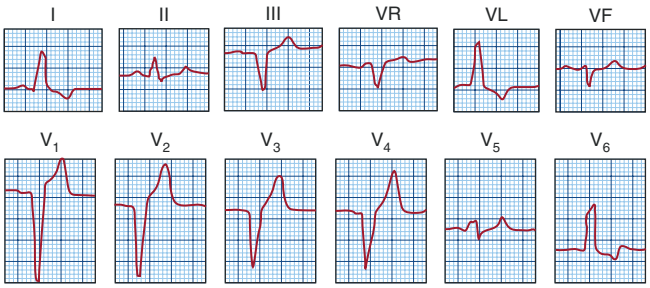


FIGURE 12–32. Different degrees of bundle branch block form normal ECG to partial and complete right bundle branch block (RBBB; **Top**) and left bundle branch block (LBBB; **Bottom**).



A



B

FIGURE 12–33. A. Example of how activation occurs in complete left bundle branch block and how different lead morphologies are explained by the loop-hemifield correlation. **B.** A typical electrocardiogram in complete left bundle branch block.

The presence of LBBB by itself necessitates the exclusion of heart disease and periodic surveillance. In the acute and chronic phase of IHD, as happens with RBBB,[2] LBBB is a marker of poor outcomes. The polarity of T wave concordant with QRS is associated with better prognosis and less comorbidity.[40] The presence of LBBB pattern after acute infarction[41] or that appears with exercise has worse prognosis.[42] Also associated with a worse prognosis is the LBBB that appear after transaortic valve implantation,[43] and in heart failure, especially, is associated to AF.[44,45] Finally, the morphology of QRS in V3 may help to diagnose the etiology of LBBB.[46]

The diagnostic criteria of third-degree LBBB are as follows (see Fig. 12–33 and Table 12–5):

- QRS of at least 0.12 second, sometimes greater than 0.16 second, especially with midportion slurring
- V_1: QS or rS with a tiny r wave and positive T wave
- I and V_6: single R with its peak after the initial 0.06 second
- VR: QS with positive T wave
- T-wave polarity is opposed to the QRS complex slurrings in more than two-thirds of cases (discordant LBBB)

Partial or First-Degree Left Bundle Branch Block

In first-degree LBBB, the activation delay in the entire ventricle is less significant (see Fig. 12–32) but is sufficient to conceal the first vector responsible for formation of r in V_1 and q in V_6. Because of this delay, this first vector is counteracted by the initial activation vector of RV and is not formed. The presence of septal fibrosis, demonstrated by biopsy in patients with aortic valve replacement also explains the lack of first vector (q wave) in LV leads (I, VL, V6).[2]

The ECG diagnostic criteria are as follows:

- QRS complex duration less than 0.12 second
- A QS complex or a tiny r wave in V_1 and a single R wave in I and V_6
- A similar morphology with disappearance of q in V_6, which may be seen because of the presence of septal fibrosis[31]
- Often present in LVE

Zonal (Divisional) Left Ventricular Block: Hemiblocks

These zonal blocks are much more known and well studied than the zonal blocks of the right ventricle, especially after the studies of Rosenbaum school.[47,48] In zonal (divisional) left ventricular block, the stimulus is blocked in either the superoanterior or inferoposterior division of the left branch (hemiblocks) (Figs. 12–34 and 12–35; see also Fig. 12–13C). Only the ECG criteria of well-established (advanced) superoanterior and inferoposterior division of the left branch (superoanterior or inferoposterior hemiblocks according to Rosenbaum) will be discussed.

A change in left intraventricular activation occurs in both hemiblocks. As a consequence, the blocked area is depolarized with certain delay, which explains the typical ECG changes that can be seen.

Superoanterior Hemiblock Figure 12–34A shows the activation of the left ventricle in superoanterior hemiblock (SAH) or superoanterior divisional block, and the loop-hemifield correlation in the frontal and horizontal planes. In Fig. 12–34B, a typical example of an SAH is depicted, as well as differences with the S_I, S_{II}, S_{III} pattern (see legend for Fig. 12–34). The diagnosis of SAH may be made only using the ECG criteria.

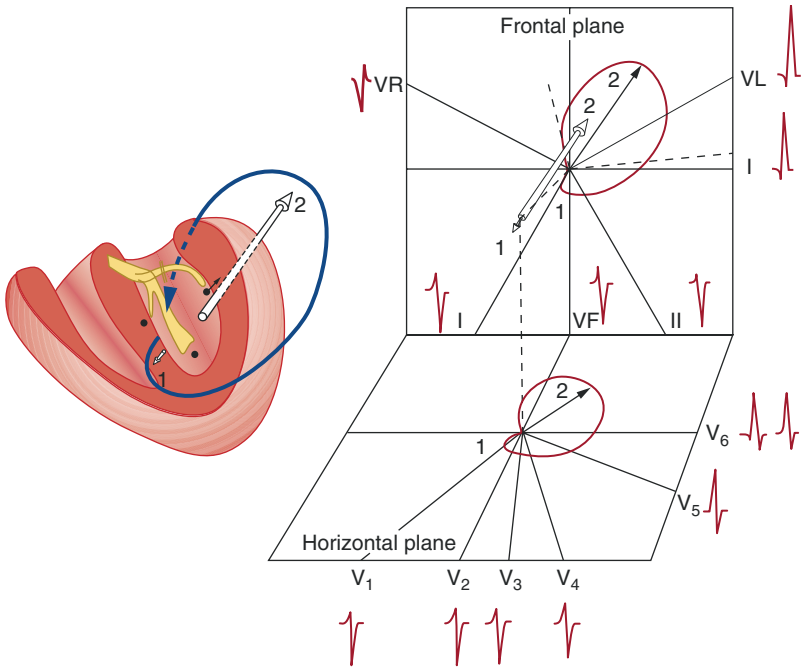
The diagnostic criteria are as follows:

- RS complex duration less than 0.12 second
- ÂQRS deviated to the left (mainly between −45° and −75°). For the differential diagnosis, it is necessary to rule out other diseases with leftward ÂQRS, such as inferior necrosis, type II Wolff-Parkinson-White (WPW) syndrome, pacemaker implant, and S_I, S_{II}, S_{III} pattern (see Fig. 12–34B)
- I and VL: qR; in advanced cases with slurring, especially in the descending part of the R wave
- II, III and VF: rS with $S_{III} > S_{II}$ and $R_{II} > R_{II}$.
- An S wave seen up to V_6, with intrinsic deflection in V_6 less than VL

Inferoposterior Hemiblock In inferoposterior hemiblock (IPH) or divisional block, typical ECG morphology and clinical conditions, mainly the absence of RVE and asthenic habit, have to be present. It is also usually considered that evidence of left ventricular abnormalities must exist. Figure 12–35A shows the location of the block and the activation of the left ventricle in the case of an IPH or inferoposterior divisional block. In this figure, the typical ECG morphology, in frontal and horizontal planes, explained by the loop-hemifield correlation, can also be observed. In this case, the diagnosis is assured if the ECG pattern appeared abruptly, in the absence of another possible explanation (see Fig. 12–35B and legend).

The diagnostic criteria are as follows:

- QRS complex duration less than 0.12 second
- ÂQRS shifted to the right (between +90° and 110° or more for some authors and +140° for others)



A

B

FIGURE 12–34. **A.** Location of the block and an example of how activation occurs in superoanterior hemiblock (SAH) and how different lead morphologies are explained by the loop-hemifield correlation. **B.** A typical example of SAH. Note the difference with the S_I, S_{II}, S_{III} pattern, in which case $S_{II} > S_{III}$ and S_I is present. This results from the fact that in SAH, the final vector of depolarization is directed upward and to the left, and in S_I, S_{II}, S_{III}, the morphology is upward and to the right.

- I and VL: RS or rS
- II, III, and VF: qR; in advanced cases with slurring, especially in the descending part of the R wave
- Precordial leads: S wave up to V_6, with an intrinsic deflection time in V_6 less than VF

Middle Fibers Block Block of the middle fibers, called *septal block* by the Brazilian school, probably produces RS morphology often with slurrings in S in V_2 and a prominent R wave in V_1. To confirm this diagnosis, the ECG pattern has to be transient. However, this intermittent RS pattern may be also recorded in the evolutive pattern of progressive RBBB.[2]

Bifascicular Blocks

In this section, the ECG criteria of the three most characteristic bifascicular blocks—complete (or advanced) RBBB plus SAH, complete RBBB plus IPH, and bilateral bundle branch block—are discussed.

The diagnostic criteria of advanced RBBB plus SAH are as follows (Fig. 12–36A and B):

- QRS complex duration greater than 0.12 second
- QRS complex morphology: The first portion is directed as in SAH, upward and toward the left, whereas the second portion is directed as in complete global RBBB, anteriorly and toward the right (see Fig. 12–45A). If there is a significant left delay, it can counteract the right forces, giving rise to anterior but left final forces. Therefore, a tall R wave can be seen in V_1, but without an S wave in I and, occasionally, also in V_6. In this case, a complete LBBB appears to exist in the frontal plane and a complete RBBB in the horizontal plane ("masked" block)[49] (see Fig. 12–36B). Sometimes this pattern may be transient.[50] A masked bifascicular block usually indicates a worse outcome, even if a pacemaker is implanted.[2]

The diagnostic criteria of advanced RBBB plus IPH (Fig. 12–36C) are as follows:

- QRS complex duration greater than 0.12 second
- QRS complex morphology: The first portion of the QRS complex is directed downward, as in IPH, whereas the second portion is directed anteriorly and toward the right, as in complete RBBB. This diagnosis requires the presence of some clinical conditions, as occurs in isolated IPH (see Inferoposterior Hemiblock section).

In bilateral bundle branch block, there is an alternation of complete RBBB and LBBB morphologies in the ECG. This diagnosis requires a pacemaker to be implanted.

Trifascicular Blocks

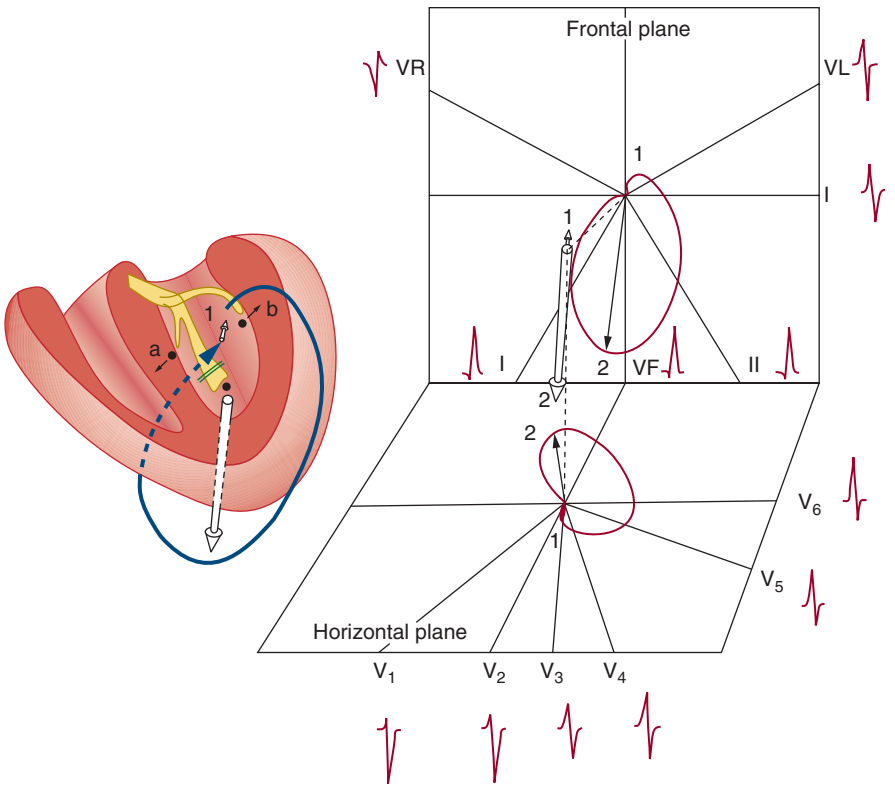
There are several types of trifascicular blocks, but their coverage is beyond the scope of this chapter (see Bayés de Luna[2]). The most frequent features are as follows:

- RBBB alternating with the block of one of two left bundle branch divisions (Rosenbaum-Elizari syndrome)[2,47] (Fig. 12–37)
- Once the block of three fascicles has been confirmed by an ECG (RBBB alternating with superoanterior and inferoposterior fascicle blocks) (see Fig. 12–37), a pacemaker should be implanted as soon as possible because the patient may suddenly develop a paroxysmal AV block.[2]
- Bifascicular blocks with a long PR segment. Note that a long PR segment may also be caused by a block at a proximal location (bundle of His); thus, electrophysiologic studies are required to confirm their occurrence.

VENTRICULAR PREEXCITATION

Ventricular preexcitation is considered to exist when the electric stimulus reaches the ventricles earlier (early excitation) than via the normal conduction system.[2] Early excitation can be explained by the presence of Kent bundles, which are accessory pathways with accelerated conduction that connect the atria with the ventricles (WPW-type preexcitation).[51] The conduction through the Kent bundles may be anterograde, retrograde, or in both directions. In rare cases, there are also other anomalous bundles (atypical preexcitation). In more than 80% of these cases, they consist of long slowly conducting atriofascicular or AV bypass tracts. Other rare anomalous bundles are the fasciculoventricular and nodofascicular tracts, which include the formerly named Mahaim fiber.[52] In addition, the presence of an accelerated AV conduction or the rare occurrence of an atrio-His bundle may cause a short PR-type preexcitation.[53]

The clinical importance of preexcitation lies in its association with supraventricular tachycardias; its potential to trigger malignant ventricular arrhythmia; and the risk of being confounded with other processes, especially in case of a WPW preexcitation (see the following section).



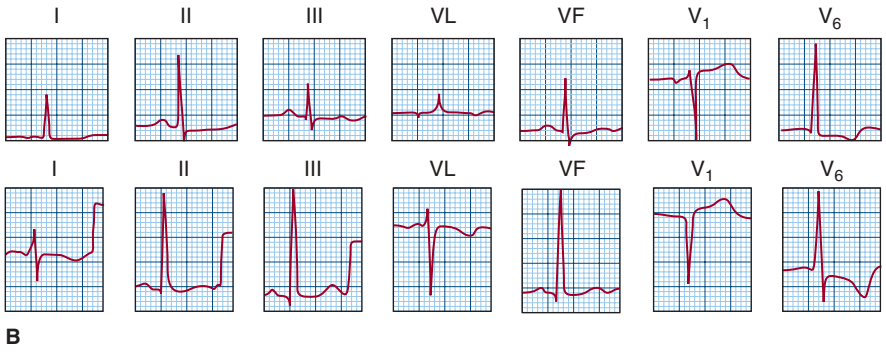


FIGURE 12–35. A. Location of the block and an example of how activation occurs in case of inferoposterior hemiblock (IPH) and how different lead morphologies are explained by the loop-hemifield correlation. **B.** Patient with QRS axis (ÂQRS) of approximately +50° (above) who presented suddenly during an acute coronary syndrome (ACS), an electrocardiogram showing ÂQRS of approximately +90° (below). This is a typical example of IPH (see text).

Wolff-Parkinson-White–Type Preexcitation

WPW-type preexcitation is diagnosed by an ECG that shows a short PR interval plus QRS-T abnormalities, primarily caused by a slurred upstroke at the beginning of the QRS complex known as the delta wave (Fig. 12–38).

- Short PR interval: The PR interval generally lasts between 0.08 and 0.11 second. However, a WPW-type preexcitation may also occur with a normal PR interval in the following instances: (1) conduction block in the anomalous pathway; (2) preexcitation far from the sinus node (left side), frequently with a long anomalous pathway; and (3) atypical preexcitation presenting normal PR intervals. The only way to corroborate that the PR interval is shorter, in order to confirm the diagnosis, is by making a comparison with the baseline ECG tracing without preexcitation.
- QRS-T abnormalities (Figs. 12–39 and 12–40): The QRS complexes show an abnormal morphology with a width greater than the baseline QRS complex (often > 0.11 second) and a characteristic initial slurring (delta wave). These features are secondary to the initial activation through the contractile myocardium where there are few Purkinje fibers. Different degrees of preexcitation (or delta wave) may be observed (see Fig. 12–38A–C).

The QRS complex morphology in the different surface ECG leads depends on the location of the epicardial zone of earlier excitation. The vector of the first 20 milliseconds on the ECG (first vector of the delta wave, which can be measured in the ECG) is located at different sites on the frontal plane according to where the earlier ventricular epicardial excitation occurred first (see Fig. 12–39). As a result, the WPW-type preexcitation may be divided into four types (see Fig. 12–39A–D).[2] Examples of these four types are displayed in Fig. 12–40.

Different algorithms have been proposed to predict the location of the anomalous pathway.[54] One of the most popular was published by Milstein et al.[55]

Repolarization is altered except in cases with minor preexcitation. Repolarization abnormalities are secondary to the alteration in depolarization, and the pathology is more severe when the T-wave polarity opposes that of the preexcited R wave, as when the preexcitation is greater (see Fig. 12–38A–C).

Changes in the degree of preexcitation are frequent, and they may be abrupt or progressive (Fig. 12–41). Preexcitation can increase if the conduction of the stimulus through the AV node is depressed (eg, vagal maneuvers, drugs), or in contrast, preexcitation can decrease if the AV node conduction is enhanced (eg, physical exercise).

Regarding the differential diagnosis of WPW-type preexcitation, type-A and type-B preexcitations (see Fig. 12–39) should be differentiated with LBBB (see Fig. 12–40A and B); type-C preexcitation (see Fig. 12–39) with inferolateral infarction, RBBB, or RVE (see Fig. 12–40C); and type-D preexcitation (see Fig. 12–39) with lateral infarction or RVE (see Fig. 12–40D). In all of these cases, the short PR interval and the presence of a delta wave are decisive data for the diagnosis of WPW-type preexcitation.

Paroxysmal arrhythmias in patients with WPW ECG pattern constitute the WPW syndrome. Patients with WPW preexcitation frequently present macro-reentrant paroxysmal tachycardia. They show a narrow QRS because the stimulus is activating the ventricles via normal AV conduction and a QRS-P′ less than P′-QRS (orthodromic tachycardia) (Fig. 12–42D). In case of paroxysmal reentrant tachycardia exclusively resulting from the intranodal (junctional) circuit, the P′ mimics the end of QRS or is hidden within it (see Chap. 84). Indeed, approximately 40% to 50% of paroxysmal tachycardias are attributed to a reentry, including an accessory pathway. In a few cases, the anterograde arm of the circuit is via the

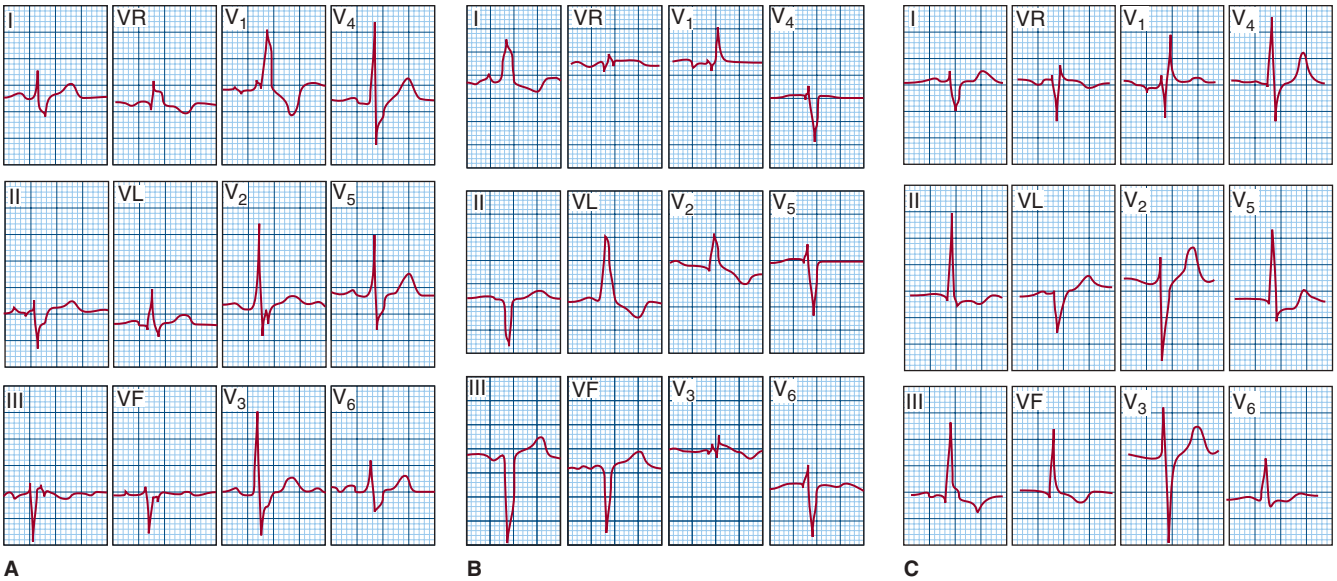


FIGURE 12–36. Types of bifascicular block. **A.** Advanced right bundle branch block and typical superoanterior hemiblock. **B.** "Masked" bifascicular block. **C.** Advanced right bundle branch block and inferoposterior hemiblock in a 56-year-old man with chronic ischemic heart disease but without asthenic body type and right ventricle enlargement (see text).

anomalous Kent bundle, and the QRS complex is wide during the tachycardia (antidromic tachycardia) (see Chap. 84).

AF and flutter episodes are also more frequent than in the general population. This is attributed to the rapid retrograde conduction, via the abnormal pathway, of a ventricular premature complex that may reach the atria during a vulnerable atrial period. Another possibility is that paroxysmal tachycardia triggers other arrhythmias, such as atrial fibrillation/flutter. The risk of these arrhythmias is two-fold. First, atrial fibrillation/flutter in patients with an ECG pattern of WPW can be mistaken for sustained ventricular tachycardia, with the associated consequences (Fig. 12–42A and B). Indeed, the differential diagnosis by surface ECG between atrial flutter in WPW syndrome and ventricular tachycardia is especially difficult (see Fig. 12–42B) The second potential risk, in the presence of atrial fibrillation/flutter, is that the accessory pathway may transmit to the ventricle more stimuli than normal, facilitating the possibility of reaching the ventricle in its vulnerable period. Consequently, this can result in ventricular fibrillation and sudden death (Fig. 12–42C).[56,57]

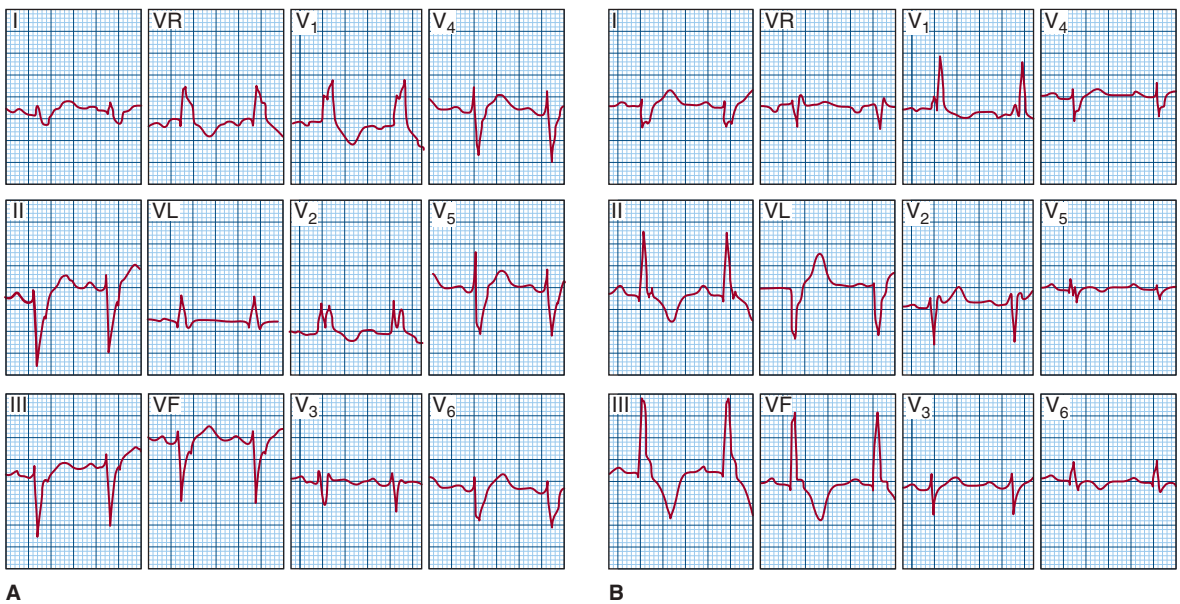


FIGURE 12–37. Alternating bifascicular block (Rosenbaum-Elizari syndrome). **A.** Advanced right bundle branch block plus superoanterior hemiblock (SAH) is shown. **B.** The following day, the frontal QRS axis (ÂQRS) changed from −60° to +130°, indicating the appearance of an inferoposterior hemiblock (IPH) instead of SAH.

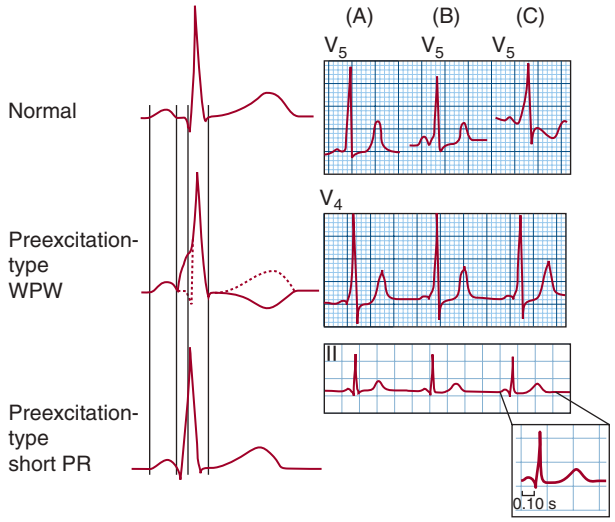


FIGURE 12–38. **Left:** Wolff-Parkinson-White (WPW)-type preexcitation and short PR-type preexcitation. **Right:** *Top*: Delta waves of different magnitude: (**A**) minor preexcitation and (**B, C**) significant preexcitation; *middle*: three consecutive QRS complexes with evident preexcitation; *below*: short PR-type preexcitation.

Atypical Preexcitation

In general, the atypical preexcitation that presents reentrant arrhythmias occurs through a long atriofascicular or AV pathway. The other bundles, which include the classic Mahaim fiber, are general bystanders and do not participate in the circuit in reentrant tachycardia.

The ECG in normal sinus rhythm is normal in the majority of cases or presents minimal preexcitation (absence of q wave in leads I and V_6 and rS morphology in lead III).[58]

The arrhythmias are less frequent and usually of reentrant junctional type. During preexcited tachycardia, the anterograde conduction is through an atypical bundle (antidromic tachycardia) with retrograde conduction by right bundle branch. Therefore, the morphology is usually of LBBB with left ÂQRS. Generally, there is a late R/S precordial transition zone (at V_4 to V_6), and in the cases of antidromic tachycardia through Kent bundle and LBBB pattern, the transition zone occurs earlier (R/S in V_2 to V_3) (see Chap. 84).

Short PR-Type Preexcitation

Short PR-type preexcitation, described by Lown et al,[53] is evidenced by a short PR interval without changes in QRS morphology (see Fig. 12–38).

By a surface ECG, it is impossible to differentiate between a hyperconductive AV node, the most frequent, and preexcitation occurring via an atrio-His bundle, which bypasses the AV node slow conduction area and, therefore, does not modify the QRS complex morphology. However, it is easy to differentiate them by intracavitary ECG because this will show a short AV interval in case of a hyperconductive AV node and a short HV interval or even an absent H deflection in the presence of an atrio-hisian tract.

The association with arrhythmias and sudden death is less frequent in short PR-type preexcitation than in the WPW-type preexcitation. Nevertheless, in case of AF, the ventricular response may be very fast because of the presence of a short PR-type preexcitation, and this can be a problematic situation.

ISCHEMIA

From the electrophysiologic point of view, according to the importance and duration of ischemia, the TAPs of myocardial cells present the following changes: (1) delay of the repolarization that corresponds to primary T-wave changes, (2) formation of "low-quality" TAP (change in shape) that corresponds to changes of ST, and (3) lack of formation of TAP that explains the presence of the Q wave.

From the surface ECG point of view, the most typical ECG changes resulting from ischemia are as follows[2,59-66]: (1) primary T-wave changes that include T waves that are wider, peaked, and/or taller and T-wave flat or negative; (2) primary ST deviations, including ST segments shifts (up and down) from baseline; and (3) changes of QRS (Q wave of necrosis and reciprocal patterns) and changes in the mid-late part of QRS (fractionated QRS).

However, ischemia may induce many other changes, including the following:

1. Prolongation of QT interval that may be considered a part of the changes in the T wave. It is present in the first moments of acute transmural ischemia when there is an increase in duration of TAP of the endocardium, making the T wave wider and taller and lengthening the QT interval.[67]
2. Changes in P wave, especially in atrial infarction[60]
3. Distortion of QRS complex, especially in very severe ischemia[59-61,68,69]
4. Appearance of different types of bradyarrhythmias (sinus bradycardia and AV block); tachyarrhythmias (especially AF and premature ventricular contractions, which may lead to ventricular tachycardia and unfortunately to ventricular fibrillation); and intraventricular block (eg, RBBB when the LAD occlusion is proximal to the first septal branch that perfuses the right bundle)[60]

First, we will explain how the different models of experimental occlusion of the coronary artery produce different ECG changes. Then, discussion will focus on the changes in T wave, ST segment, and QRS complex that are induced by experimental and clinical ischemia and their electrophysiologic mechanisms. Finally, the ECG changes that appear during the evolution of different clinical settings of IHD, their diagnostic criteria, and the most important clinical and prognostic implications of these ECG changes will be discussed.

Changes in Electrocardiography under Different Models of Experimental Ischemia Caused by Coronary Occlusion

After experimental coronary occlusion of the LAD coronary artery in dogs, performed with an open chest and with the electrodes located in the pericardial sac, Bailey and La Due[70] found (Fig. 12–43, 1) that the first ECG change induced by ischemia was negativity of the T wave, which was called *ECG pattern of ischemia*. This was followed by an ST elevation that he called *ECG pattern of injury*, and finally, a Q wave appeared, which was called *ECG pattern of necrosis* (see Fig. 12–43, 1). This terminology was accepted by several groups.[13] Thus, it was considered that in patients with IHD, the presence of a negative T wave represented a grade of acute ischemia that was less severe than an ST-segment elevation.

However, when the experiment to occlude the artery was performed in awake dogs with an unopened chest,[71] the changes in the ECG were similar to the ECG changes that occurred in coronary spasm or transmural MI in humans (Fig. 12–43, 2). The negative T wave only appeared as a late manifestation, when the acute ischemia was already vanishing or had already disappeared. Therefore, a flat or negative T wave represents postischemic changes rather than the first phase of acute ischemia. Thus, it is a frequent mistake to consider the presence of a negative T wave as an indicator of active ischemia.

Changes in T Wave

Morphology of T-Wave Changes and Electrophysiologic Experimental Mechanisms

It has been demonstrated by different experimental open chest

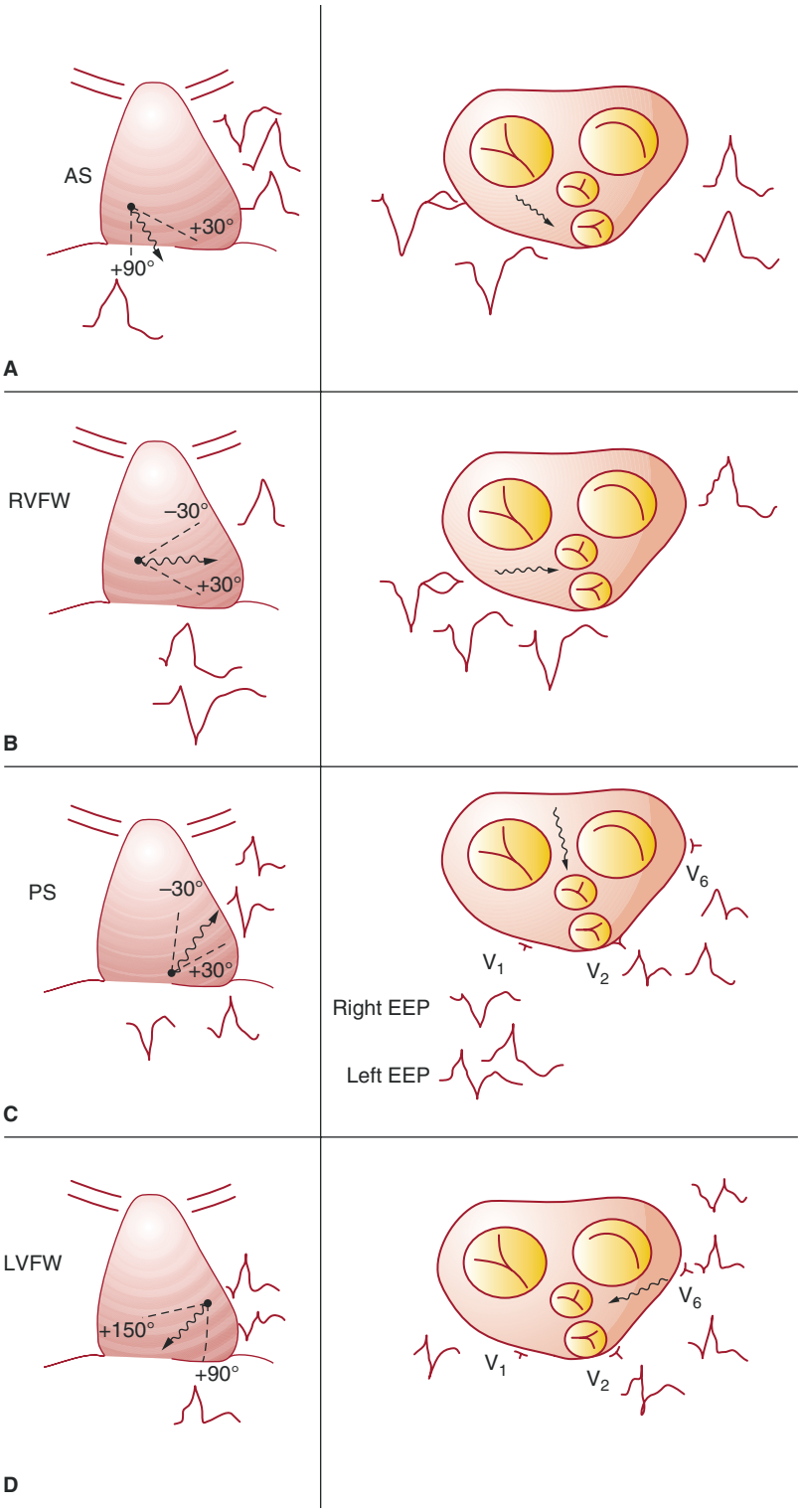


FIGURE 12–39. Morphologies in Wolff-Parkinson-White (WPW)-type preexcitation according to the ventricular location of the accessory atrioventricular pathway in the following zones: (**A**) right anteroseptal (AS); (**B**) right ventricular free wall (RVFW); (**C**) posteroseptal (PS); and (**D**) left ventricular free wall (LVFW). EP, early pre-exitation.

methods that when ischemia or similar effect is induced (eg, by cooling the tissue)[7,8,72] in the epicardium or in a part of tissue close to the recording electrode, the TAP of this zone presents a delay of repolarization without changing its shape, and a flat or negative T wave appears (Fig. 12–44B). When the same procedure is performed in the endocardium or in a part of tissue far from the electrode, a delay of repolarization is induced in this zone, and a peaked and usually taller T wave appears (Fig. 12–44A).

The electrophysiologic explanation of these changes in T wave (more positive T wave and flat or negative T wave) caused by experimental subendocardial and subepicardial ischemia, that are found in these areas that present delay of repolarization (prolonged TAP), may be explained (see Fig. 12–44) by two concepts: the summation of TAPs of subendocardium and subepicardium, (the longer is located in ischemic zone) and the concept of ischemic vector. According to these concepts, the area with delayed TAP (named *ischemic area*), either in the subendocardium or in the subepicardium, was not fully repolarized at the time when the other area was already repolarized. Therefore, it still presents negative charges. As repolarization starts in the zone that is more perfused, the sense of repolarization (see Fig. 12–44) will face the ischemic zone. However, as this zone presents more negative changes, a flow of current having a vectorial expression is generated going from more ischemic to less ischemic zones. Then, the vector of ischemia with the positive change in the head is directed away from the ischemic area and originates a more positive T wave in experimental subendocardial ischemia and a flat or negative T wave in experimental subepicardial ischemia. Note that the vector of necrosis is also directed away from the necrosis area (see Fig. 12–46), but on the contrary, the vector of the area with greater ischemia (injury area) is directed toward this area (see Figs. 12-49 and 12–50).

T-Wave Changes in Patients with Ischemic Heart Disease In clinical settings, the explanation of T-wave changes caused by ischemia is in some aspects different (see Electrocardiography in Ischemic Heart Disease; p. 39 [manuscript page 55]).[72,73]

- Peaked, symmetrical, wider, and/or taller T wave. This morphology, accompanied by a lengthening of the QT interval, appears in the beginning of acute transmural ischemia resulting from total coronary occlusion, sometimes accompanied by slight ST depression. As a consequence of the occlusion, there is first subendocardial involvement. Different factors explain the susceptibility of the subendocardium to the development of ischemia. These include the greater dependence of this region on diastole perfusion and the greater degree of energy expenditure of this area during systole.[60]

This initial subendocardial ischemia, also demonstrated by contrast-enhanced cardiovascular magnetic resonance (CE-CMR),[74] produces a delay of repolarization in this area and, as a result, a lengthening of the TAP of the subendocardium, explaining the increase of the QT interval and usually also the presence of wider, peaked, symmetric, and/or taller T waves (see Fig. 12–44A; Fig. 12–45).

As mentioned earlier, the results of animal experiments performed with unopened chest[71] coincide with the ECG changes that often appear in different clinical settings of transmural or near-transmural ischemia that are the consequence of total or near-total coronary occlusion, such as coronary spasm see (see Fig. 12–45),[75,76] hyperacute phase of ST-segment elevation ACS (STE-ACS; see Fig. 12–60A), and percutaneous coronary intervention (PCI).[63] In the majority of cases, after a short period of peaked T wave with QT prolongation, an evident ST-segment elevation

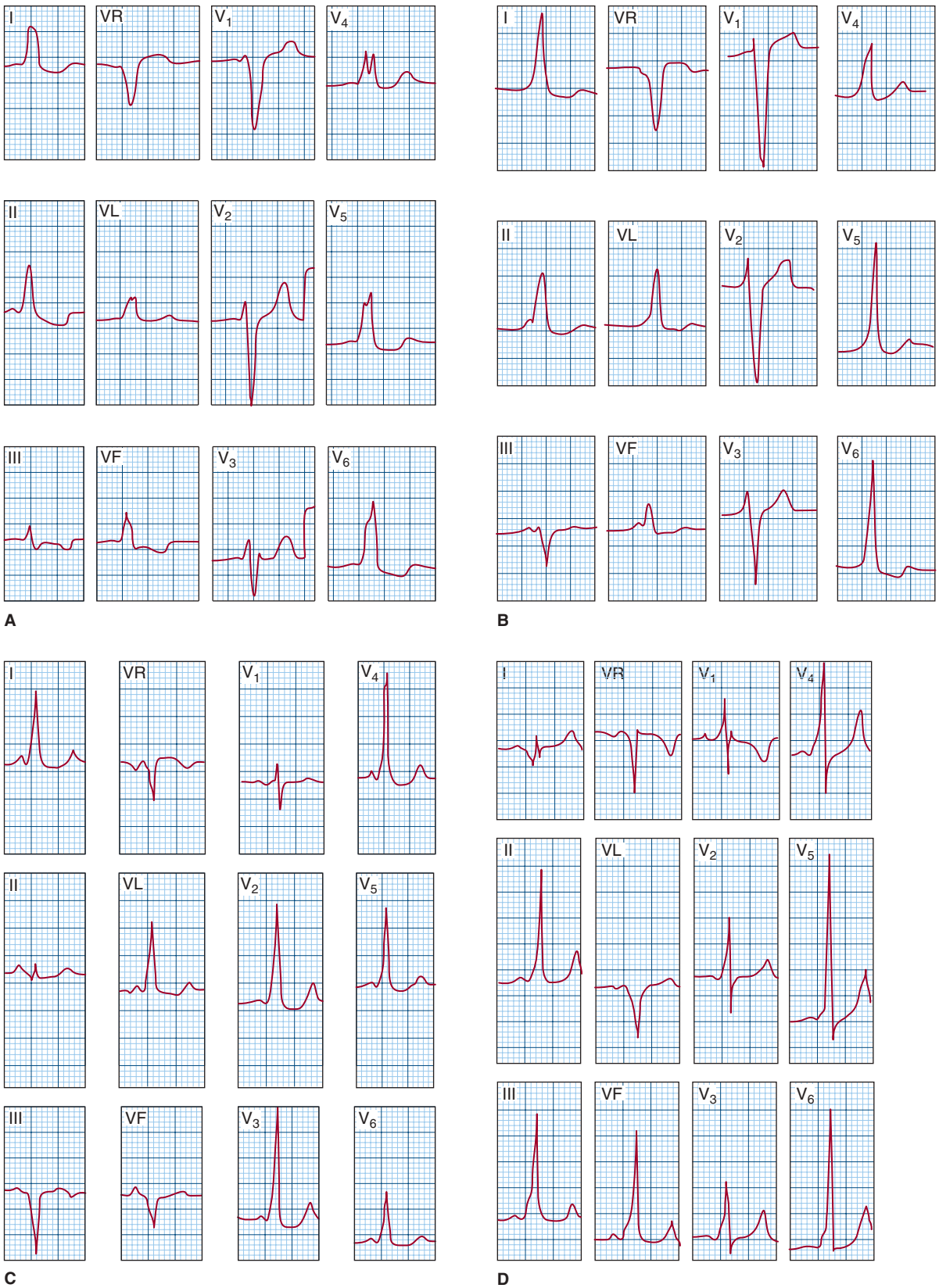


FIGURE 12–40. ECG examples in the Wolff-Parkinson-White (WPW)-type preexcitation with accessory atrioventricular pathway located in the right anteroseptal zone (**A**), right ventricular free wall (**B**), posteroseptal zone (**C**), and left ventricular free wall (**D**).

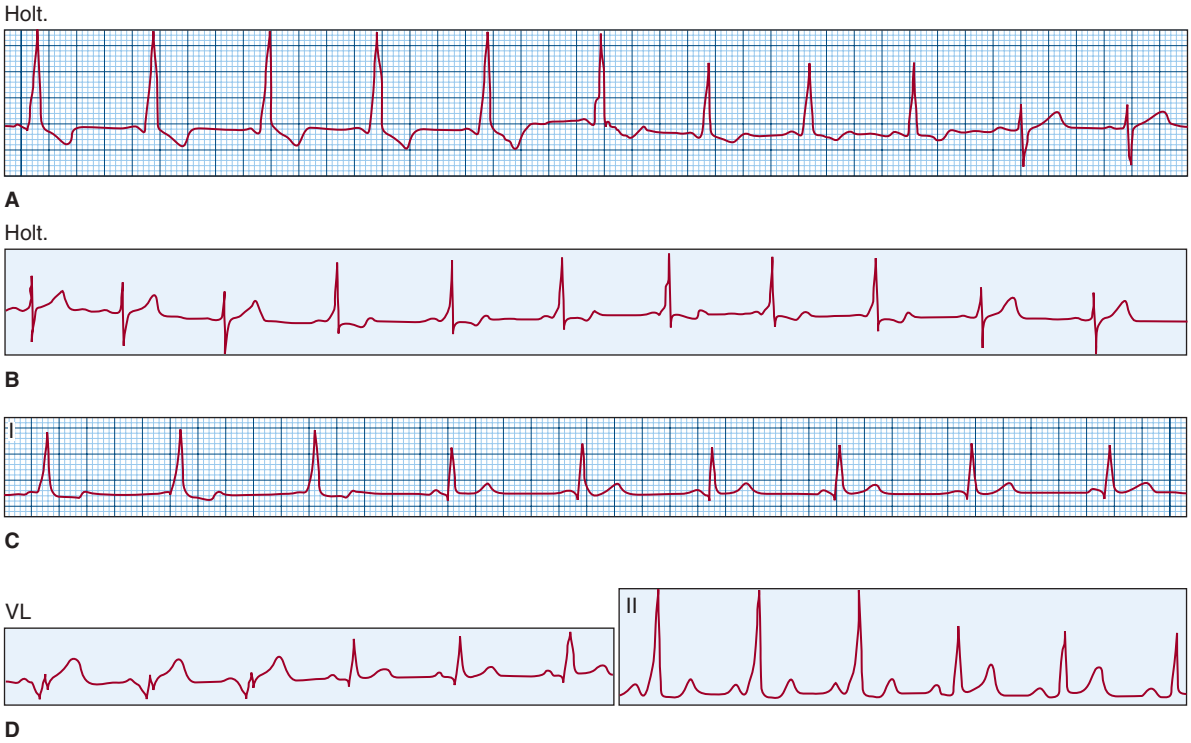


FIGURE 12–41. Different situations that manifest the variability of the Wolff-Parkinson-White (WPW)-type preexcitation. **A.** Accordion effect. The first five complexes are equal and present a short PR interval, whereas preexcitation decreases in the following four complexes, and the PR is somewhat less short (0.12 second). Finally, preexcitation disappears in the last three complexes, and the PR is 0.16 second. **B.** Conduction over the accessory pathway alternates with normal conduction. The PR interval, when the conduction is over the accessory pathway, is observed at the limit of normal (in this lead, 0.12 second), but it is shorter than with normal conduction (0.15 second). **C.** Intermittent preexcitation. In the first three complexes, there is a short PR interval (0.08 second) and a delta wave, whereas in the rest of the strip, the delta wave disappears, but the short PR persists (0.10 second). This allows us, from the surface ECG, to suggest the existence of two pathways, one that bypasses the atrioventricular (AV) node (short PR type) and the other with an abnormal AV bundle and a very short PR interval. **D.** Intermittent preexcitation that simulates lateral infarction.

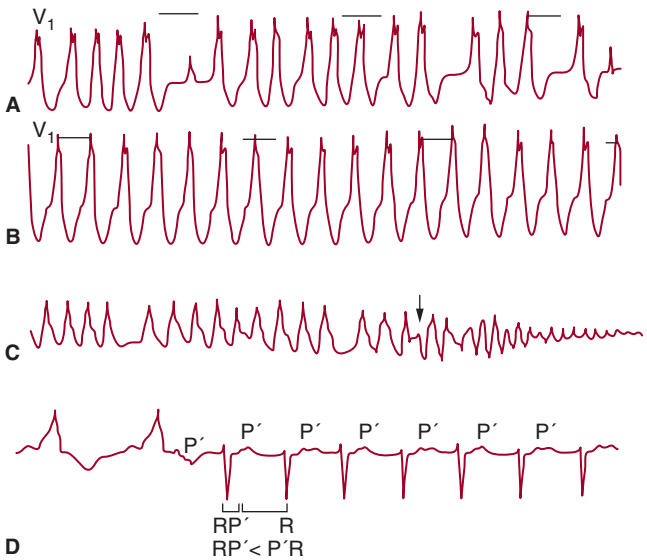


FIGURE 12–42. A 50-year-old patient with type IV Wolff-Parkinson-White (WPW) syndrome is shown, who presents with a crisis of atrial fibrillation (**A**) and atrial flutter (**B**) that mimics ventricular tachycardia. The diagnosis of atrial fibrillation is supported by the history (knowing that the patient has WPW syndrome) and the following characteristics of the ECG: (1) the wide complexes have a very irregular rhythm and are more or less wider (present more or less preexcitation); and (2) the narrow complexes (the sixth and the last one on the top) are sometimes close (the last complex) and sometimes far (sixth complex) to the previous QRS. In sustained ventricular tachycardia, the QRS complexes are regular, and in the presence of narrow complexes, the QRS complexes are always close to the previous one (capture beats). **B.** In WPW syndrome with flutter, the differential diagnosis with sustained ventricular tachycardia based only on ECG is more difficult because the RR are regular. **C.** Patient with crisis of atrial fibrillation with a very fast response of the ventricles (> 300 ×′) and, sometimes, very narrow R-R intervals (< 200 ms). After a very short R-R interval, a crisis of ventricular fibrillation was triggered (arrow), which had to be resolved by electric cardioversion. **D.** Patient with reciprocating tachycardia. The conduction in this circuit is retrograde over the accessory AV pathway and anterograde via the normal AV conduction. The RP′ ratio is smaller than P′R ratio, which is typical for reciprocating tachycardia that involves an accessory AV pathway.

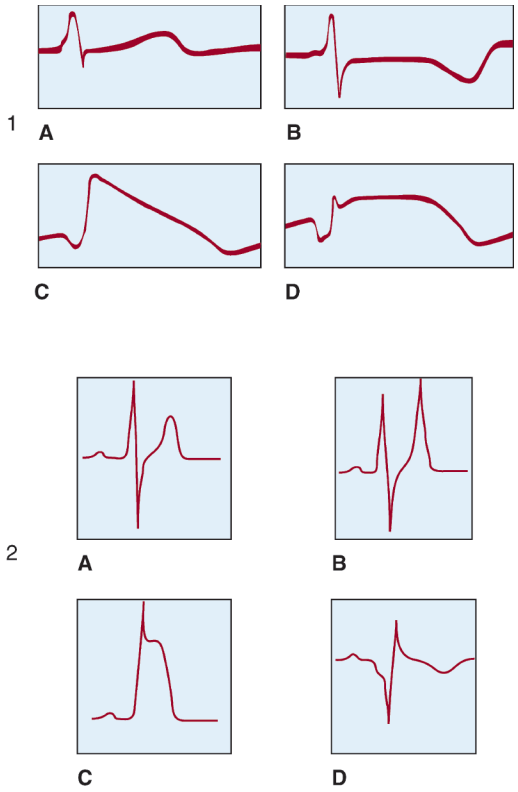


FIGURE 12–43. 1. Electrocardiographic patterns that are shown sequentially after the experimental acute occlusion of a coronary artery in a dog with open chest with the subsequent transmural infarction. The pattern that was seen was as follows: ischemia (negative T wave), injury (ST-segment elevation), and necrosis (pathologic q wave). **2.** Electrocardiographic recording after the occlusion of a coronary artery in an experimental animal with its thorax closed. It changes from a subendocardial ischemia pattern (tall and peaked T wave) (**B**) to a pattern of a subepicardial injury, transmural in clinical practice (ST-segment elevation) (**C**), when the acute clinical ischemia is more severe. Finally, the q wave of necrosis develops (**D**), accompanied as time passes by an increasingly evident pattern of subepicardial ischemia (it is transmural after the occlusion of a coronary artery, although it is expressed as experimental subepicardial in the ECG). In the chronic phase, the pattern of negative T wave is related more to changes that necrosis has induced in the repolarization than to a presence of clinical ischemia.

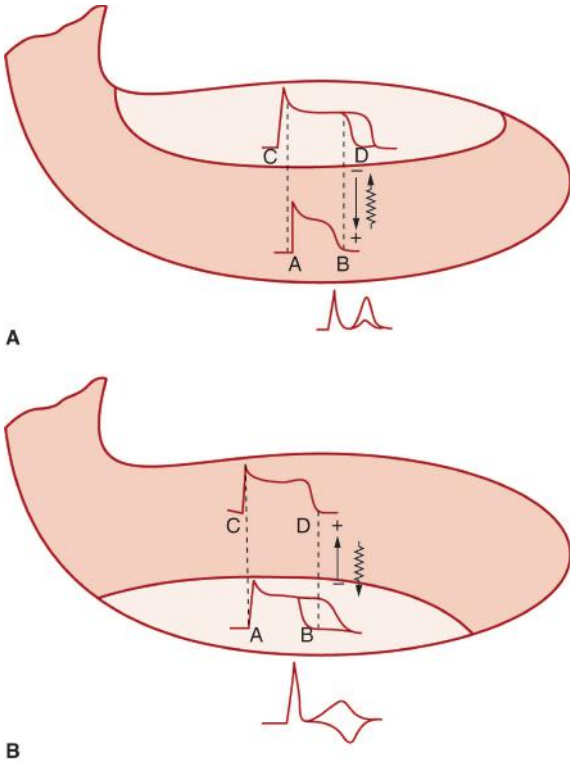


FIGURE 12–44. A. Experimental subendocardial ischemia. Subepicardial repolarization is complete, but the transmembrane action potential (TAP) in the subendocardium is longer than normal (TAP prolongation further beyond the normal at -D- point) because the subendocardium is not completely repolarized. Thus, the vector that is generated between the already polarized area in the subepicardium with positive charges and the subendocardial area still with incomplete repolarization with negative charges caused by the ischemia in that area, named *ischemic vector*, is directed from the subendocardium to the subepicardium, with the head facing the subepicardium, even though the direction of the repolarization phenomenon goes away from it because the direction of the phenomenon (⇢) goes from the less ischemic area (subepicardium) to the more ischemic area (subendocardium). Therefore, the subepicardium faces the ischemic vector head (positive charge of the dipole), which explains why the T wave is more positive than normal. In experimental subepicardial ischemia, a similar but inverse phenomenon (**B**) occurs, which explains the development of flattened or negative T waves.

appears (see Fig. 12–60A). Later on, if ischemia persists, the ECG pattern may evolve to Q-wave MI.

In addition, a tall, positive, and symmetrical T wave is frequently seen in a chronic phase of Q-wave MI. This is the expression of the mirror image of a negative T wave. The most frequent leads where this is seen are I, VL, and V_1 to V_3 as mirror images of inferolateral involvement (Fig. 12–46, 2).

- Flat or negative T wave. This morphology may be seen in different clinical situations of IHD, including the following:
  - A negative T wave, often deep, appears in the resolution process of Q-wave MI. Characteristically, this presents a mirror pattern in FP (ie, if negative in II, III, and VF, then positive in I and VL). This is important to perform differential diagnosis with the negative T wave of pericarditis that usually does not present mirror pattern (see Fig. 12–77C and D). The T wave in these cases may be very deep (see Fig. 12–52, 1) but usually decreases or even disappears with time (see Fig. 12–56). The appearance of a negative T wave in Q-wave MI is at least partially secondary to changes of depolarization (Q wave).
  - A negative T wave can be the manifestation of an open artery if it appears after fibrinolytic treatment or PCI. It may also be deep (see Fig. 12–52, 2).

CHANGES IN T WAVE

1. Peaked, wider, and/or taller T waves, accompanied by increased QT interval length:
   - These are usually the initial changes in case of total occlusion of a coronary artery.
   - The electrocardiographic (ECG) pattern is explained by the brusque presence of ischemia in the subendocardium that produces a delay of repolarization (transmembrane action potential [TAP]) in this area (long QT interval).
   - These may also be seen in chronic phase of ischemic heart disease as a mirror pattern.
2. Flat or negative T wave: The deepness of the negative T wave is variable, and the QT interval is usually prolonged.
   - Negative T waves do not usually represent acute active ischemia but rather are the expression of postischemic changes.
   - In Q-wave myocardial infarction, there is probably the consequence of the changes of depolarization resulting from necrosis.
   - In the other circumstances, the ECG pattern is explained, in the presence of transmural involvement, by the fact that the electrode is closer to epicardium than to endocardium and records the ECG changes that are present in the subepicardium (caused by delayed repolarization—delayed TAP), as occurs in experimental subepicardial involvement.

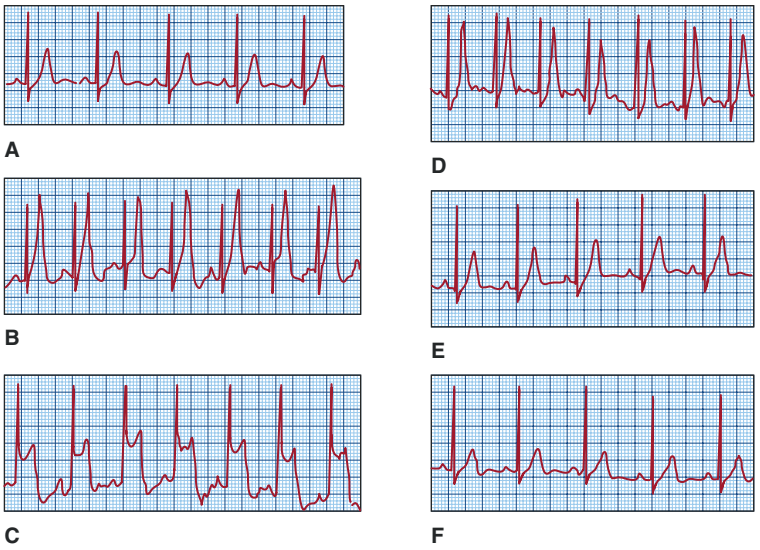


FIGURE 12–45. Crisis of coronary spasm (Prinzmetal angina) recorded by Holter ECG. **A.** Control. **B.** Initial pattern of a very tall T wave (subendocardial ischemia). **C.** Huge pattern of ST-segment elevation. **D** to **F.** Resolution toward normal values. Total duration of the crisis was 2 minutes.

- A negative T wave, frequently very deep, may appear in V_1 to V_4 in the evolutive phase of STE-ACS because of LAD subocclusion, which is usually tight. This situation is considered a marker of impending MI,[77] and if the patient has had angina in the previous few hours, it may evolve to complete occlusion (see Fig. 12–60B). However, currently with the new treatment of acute phase, this pattern often does not evolve and is the expression of an at least partially open artery, or if it is more closed, then there is very good collateral circulation. Therefore, it is necessary to perform PCI but not emergently.
- A negative flat T wave may also be seen in the evolutive phase of non–ST-segment elevation ACS (NSTE-ACS). The morphology of the T wave is usually symmetric and not deep. In fact, patients with NSTE-ACS and negative T waves have better a prognosis, probably because this indicates that the clinical acute phase of ischemia is over (see Fig. 12–62C). However, relatively often still coronary subocclusion even tight exists. Therefore, currently, we also recommend nonemergent PCI in these cases.
- Finally, a flat/negative T wave may be seen as a residual pattern in chronic IHD.

None of these clinical situations represents acute active ischemia. Rather, they indicate postischemic changes.

The involvement of the left ventricle wall is usually transmural in the presence of a flat/negative T wave. No clinical situation caused by ischemia presents exclusively with subepicardial involvement. Therefore, the theories that explain the presence of flat/negative T waves in experimental clinical ischemia (see Fig. 12–44B) are not useful in the clinical setting. Probably, the negative T wave seen in these clinical cases, associated with acute transmural ischemia (ST↑) that has subsided, may be explained by the mechanisms shown in Fig. 12–47.

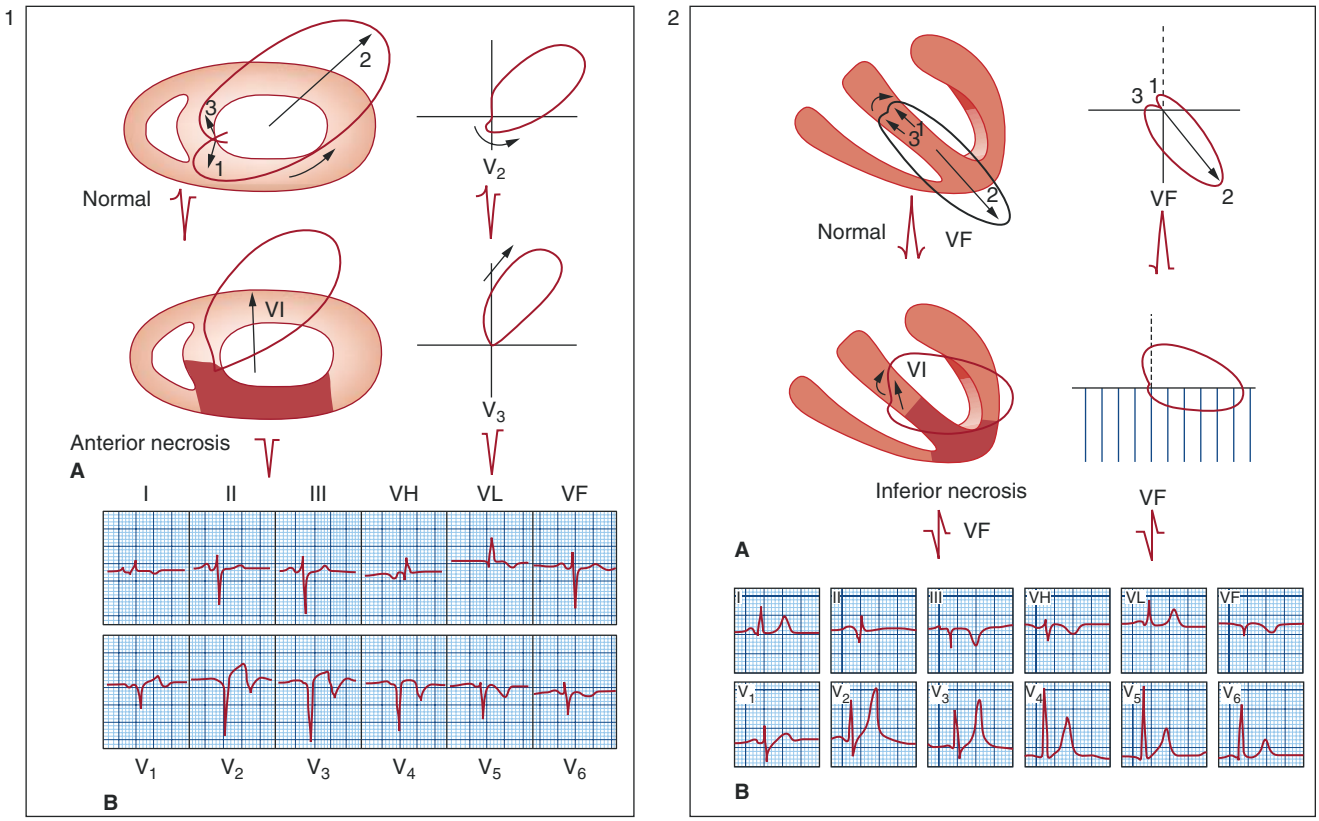


FIGURE 12–46. 1-A. Observe the comparison between the normal activation and the activation in an extensive anterior infarction. The vector of infarction (VI) is directed backward, and the loop-hemifield correlation explains the appearance of the Q wave in anterior leads. **1-B.** Example of myocardial infarction (MI) of anteroseptal zone. **2-A.** Note the comparison between normal activation and activation in inferior infarction with lateral extension (RS in V1). The vector of infarction is directed upward in the FP, and a loop-hemifield correlation explains the appearance of a Q wave in inferior leads. **2-B.** Example of MI of inferolateral zone.

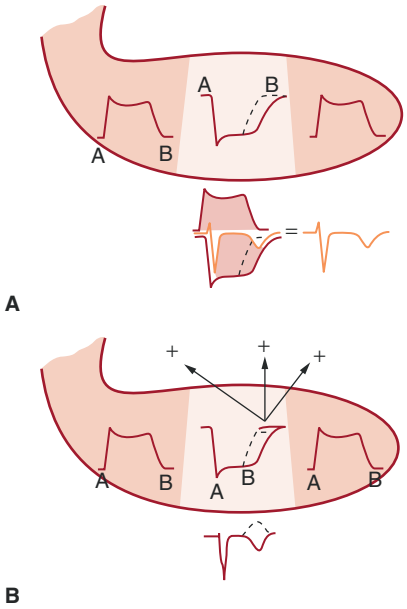


FIGURE 12–47. Origin of negative and deep T wave that appear after acute ST elevation in clinical setting. The ST elevation is hyperacute ischemia (the tsunami), and the negative T wave is the panoramic view that appear after the ischemia (the tsunami) is over. **A.** Because of the increased transmembrane action potential (TAP) duration of the transmural area affected, the sum of the TAP of this area with the shorter TAP of neighboring areas explains the negative T wave. **B.** The explanation based on ischemic vector theory .

Differential Diagnosis A long list of conditions, apart from IHD, may present with changes in the T wave (symmetric-wide and/or taller than normal, flat, or negative).[2,60] Tables 12–6 and 12–7 summarize the most important conditions, and Fig. 12–48 presents some of the most striking examples.

Concerning the cases of taller T waves of ischemic origin, it should be emphasized that they are very transient (see Figs. 12–45 and 12–60A). The persistent high-voltage T wave, seen in V_1 to V_2 in cases of chronic lateral infarction (see Fig. 12–46B), is an indirect (mirror) pattern, rather than a direct pattern, of tall T wave caused by ischemia.

Regarding the negative T wave, chronic pericarditis is the most important condition for a clinical differential diagnosis because this disease also presents with pain in the acute phase. The negative T wave of pericarditis (see Fig. 12–77) is usually more extensive, does not present mirror pattern in the frontal plane, and is less intensive (negative) than in cases of IHD, especially in post–Q wave MI (see Fig. 12–46).

TABLE 12–6. Causes of a More Positive Than Normal T Wave[a]

1. Normal variant: vagotonia, athletes, the elderly, and so on
2. Acute pericarditis
3. Alcoholism
4. Hyperkalemia
5. Moderate left ventricular hypertrophy in heart diseases with diastolic overload (eg, aortic regurgitation)
6. Stroke
7. Advanced atrioventricular block (tall and peaked T wave in the narrow QRS complex escape rhythm)
8. V_1-V_2 as a mirror image of inferolateral subepicardial ischemia or secondary to left ventricular hypertrophy

[a]Apart from ischemic heart disease (see Fig. 12–48, 2).

TABLE 12–7. Causes of Negative or Flattened T Waves[a]

1. Normal variants: children, black people, hyperventilation, and women (eg, right precordial leads); may sometimes be diffuse (global T-wave inversion of an unknown origin); frequently occurs in women
2. Pericarditis. In this condition, the image is usually extensive but generally not with significant negativity.
3. Cor pulmonale and pulmonary embolism
4. Myocarditis and cardiomyopathies
5. Mitral valve prolapse: not always. If it appears, it does so particularly in II, III, and VF and/or V_5 and V_6.
6. Alcoholism
7. Strokes; relatively infrequent
8. Myxedema: usually flat T wave or only slightly negative
9. Athlete, with or without ST-segment elevation. Hypertrophic cardiomyopathy, especially apical type, must be ruled out.
10. After the administration of certain drugs (eg, prenylamine, amiodarone) (flattened T wave)
11. In hypokalemia, the T wave can flatten.
12. Post-tachycardia
13. Abnormalities secondary to left ventricular hypertrophy or to left bundle branch block
14. Intermittent left bundle branch block and other situations of intermittent abnormal activation (eg, pacemakers, Wolff-Parkinson-White syndrome) "electrical memory"

[a]Apart from ischemic heart disease (see Fig. 12–48, 1).

Changes in ST Segment

Morphologies of ST Deviations and Electrophysiologic Experimental Mechanism The area of the myocardium with significant and persistent

ST CHANGES

1. ST depression is recorded in some patients with abrupt decreased blood flow without total occlusion, such as in non–ST-elevation acute coronary syndrome (non–STE-ACS), and in patients who present with ischemia due to increased demand, such as an angina of effort. The electrocardiographic (ECG) pattern is explained by important and predominant ischemia in the subendocardium that induces a more important change of the shape of the transmembrane action potential in this area (ST depression).
2. ST elevation is mainly recorded in patients with abrupt decreased blood flow that usually presents as a total coronary occlusion, such as in STE-ACS. The ECG pattern is explained in the presence of transmural clinical ischemia, because the electrode closer to the epicardium than the endocardium records the ECG changes that are present in the epicardium, as occurs in experimental subepicardial injury. The same pattern may be recorded in cases of transient acute ischemia with or without atherothrombosis (eg, coronary spasm).
3. The evaluation of direct and mirror images of ST deviations is important for diagnostic and prognostic purposes.

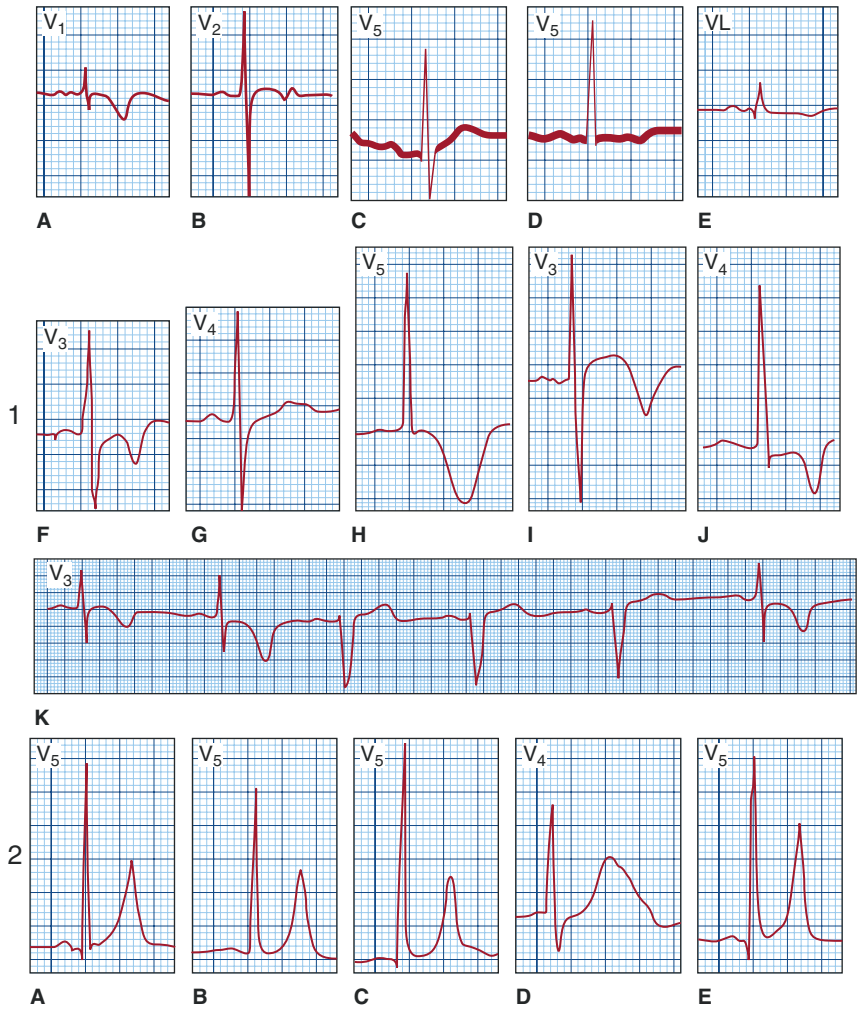


FIGURE 12–48. T wave morphologies in conditions other than ischemic heart disease. **1.** Some morphologies of flattened or negative T wave: (**A, B**) V_1 and V_2 of a healthy 1-year-old girl; (**C, D**) alcoholic cardiomyopathy; (**E**) myxedema; (**F**) negative T wave after paroxysmal tachycardia in a patient with initial phase of cardiomyopathy; (**G**) bimodal T with long QT frequently seen after long-term amiodarone administration; (**H**) negative T wave with very wide base, sometimes observed in stroke; (**I**) negative T wave preceded by ST elevation in an apparently healthy tennis player; (**J**) very negative T wave in a case of apical cardiomyopathy; and (**K**) negative T wave in a case of intermittent left bundle branch block in a patient with no apparent heart disease (cardiac memory according to Rosenbaum school). **2.** Tall peaked T wave in case of (**A**) variant of normality (vagotonia with early repolarization); (**B**) alcoholism; (**C**) left ventricular enlargement; (**D**) stroke; (**E**) hyperkalemia.

ischemia (called the *area of injury*) presents an evident diastolic depolarization. From an experimental point of view, two injury currents are generated as a consequence of an important ischemia—one occurring during systole and the other during diastole. However, the injury current generated during systole is the only one considered because the ECG equipment is adjusted by alternating current amplifiers to maintain a stable isoelectric baseline during diastole, despite the existence of diastolic depolarization that would change the QT interval. The area with systolic injury current presents a "low-quality" TAP (eg, slower upstroke, lower voltage, smaller area).

The ECG pattern of the ST segment during an important diastolic depolarization caused by an experimental injury induced in open chest animals varies depending on the location of the injury. Thus, an ST-segment depression is observed if the injury affects the subendocardium, whereas an ST-segment elevation is recorded if the experimental injury is transmural. These two situations may be explained considering the concepts of TAP summation and the vector of severe ischemia.[2,14,72,73]

1. Figure 12–49 shows how the sum of the TAPs of the subendocardium and the subepicardium with a TAP of subendocardium with slower upstroke and smaller size may explain the presence of ST-segment depression following a subendocardial injury (ECG pattern of subendocardial injury; see Fig. 12–49A) or of ST-segment elevation after transmural injury (ECG pattern of transmural ischemia that is known as ECG pattern of injury).
2. On the other hand, according to the concept of severe ischemia (injury vector) when the zone with low-quality TAP (injured zone) is on the subendocardium (Fig. 12–50A), at the end of depolarization (end of systole), this zone presents less negative charges. Consequently, a flow of current exists from the zone with more negative charges to the low-quality TAP zone with less negative charges. This originates an injury vector with less negative charges (relatively positive) in the head, which points to the zone with low-quality TAP, or the injured zone. If this zone is limited to subendocardium, therefore, the injury vector points toward the subendocardium (injured zone) and is expressed as an ST-segment depression in the surface leads (see Fig. 12–50A). Likewise, when the injured zone is more important and became transmural, this zone is relatively less negative (relatively positive), and the injury vector that starts in the subendocardium points toward this zone and is recorded in the surface lead as an ST-segment elevation (Fig. 12–50B).

ST-Segment Deviations in Patients with Ischemic Heart Disease See also Electrocardiography in Ischemic Heart Disease, p. 39 [manuscript page 55]. ST-segment depression appears in the following circumstances:

1. In patients usually with preexistent IHD who present with NSTE-ACS without total occlusion of the artery. In these cases, there is important involvement of subendocardial flow, as a consequence of sudden but not total cessation of blood flow. The ST-segment depression tends to normalize from the acute to the subacute phases (Fig. 12–51A; see legend).
2. In patients with IHD who, as a consequence of exercise or stress, have an increased demand for flow, but it cannot be supplied because there is a fixed stenosis and a decrease in subendocardial flow. In these cases, different types of ST-segment depression may appear (Fig. 12–51B). As the stenosis is fixed, there is no total occlusion and thus no transmural ischemia.

ST-segment depression in clinical practice usually appears because the subendocardium is more vulnerable to ischemic damage than the rest of the ventricular wall, and thus, it may be affected without transmural involvement if the occlusion is subtotal. When the subendocardial/subepicardial ratio is reduced to approximately 40%, the flow ratio decreases dramatically. This occurs during exercise and mental stress and also when there is an increased left ventricle end-diastolic pressure.[63] In these cases, the TAP of the subendocardium resulting from extensive and already existent ischemia shows a change in its shape but not a prolongation of the TAP duration, as happens in the first minutes of total occlusion in patients usually without previous ischemia.

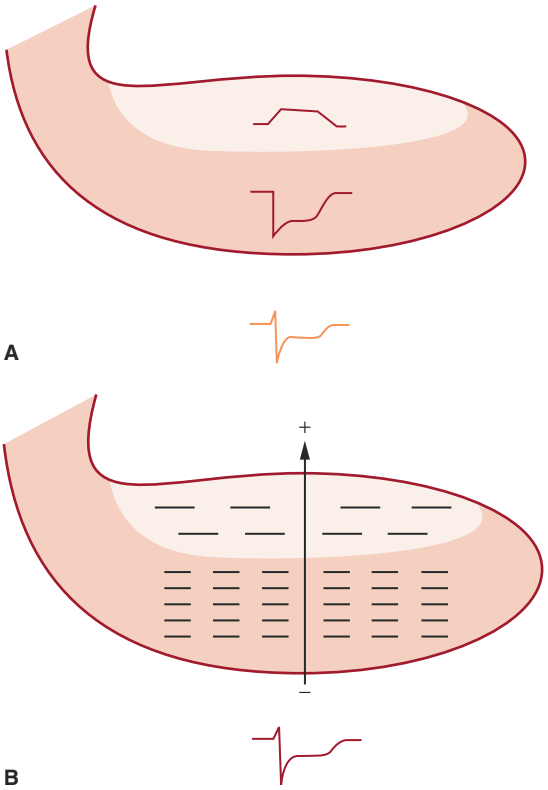


FIGURE 12–49. A. The sum of the transmembrane action potential (TAP) in the subendocardium (TAP with smaller area) and the TAP of the rest of V1 (normal) explains the ST depression. **B.** The area with severe subendocardial ischemia presents less negative charges than the rest of V1 and is thus relatively positive. For this reason the ischemic vector of this severe ischemic area (named injury vector) points to the subendocardium and is recorded as negative from the end of QRS in the surface electrocardiogram.

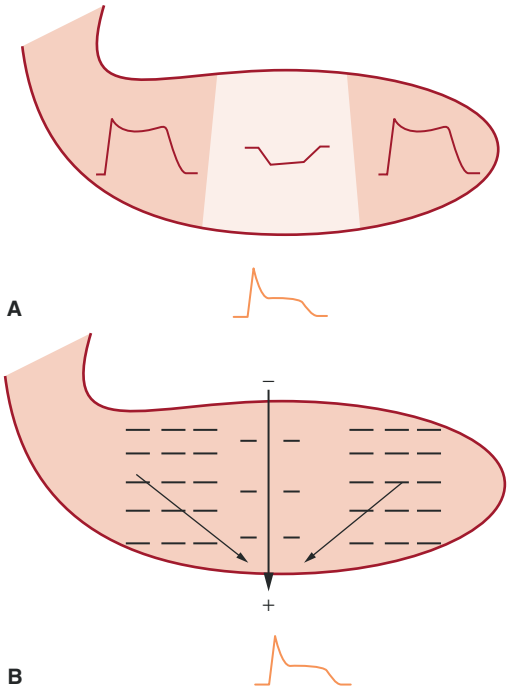


FIGURE 12–50. A. The transmembrane action potential (TAP) in the transmural zone affected by severe transmural ischemia presents an inverted polarity with a slower descent. The sum of this TAP with the normal TAPs of neighboring areas explains the electrocardiography morphology with ST elevation. **B.** The vector of severe transmural ischemia (historically called the subepicardial injury vector) is directed from the subendocardium to the subepicardium and is recorded as ST elevation. This is results from the lesser negative charges in the affected transmural zone compared to the rest of the myocardium and explain that this zone is relatively positive.

This explains why in one case, a taller T wave appears (see Fig. 12–44B), whereas in the other case, an ST-segment depression occurs (see Fig. 12–49B).

ST-segment elevation appears in transmural ischemia, often after a period of taller and wider T wave (STE-ACS). Usually, these patients do not present with a previous important ischemia. The ST-segment elevation tends to normalize from the acute to the chronic phases (Figs. 12–52 and 12–53) (see Acute Coronary Syndrome with Narrow QRS: Evolutionary Changes).

To explain the appearance of this pattern, we have to consider that even the injured zone is transmural and the surface electrodes located closer to the epicardium are recording the ECG pattern as in the case of the experimental subepicardial injury that presented a change of the TAP shape in the subepicardial layers and a less negative charge (relatively positive) (see Fig. 12–50B, *right*).

Because the injury patterns develop at the end of the depolarization, which corresponds to the end of generation of QRS at the beginning of repolarization, the ECG expression of injury starts during the first part of the ST segment. Therefore, in cases of relevant injury, there is an elevation of the S wave, which persists along the whole ST segment and usually encompasses a T wave that becomes negative

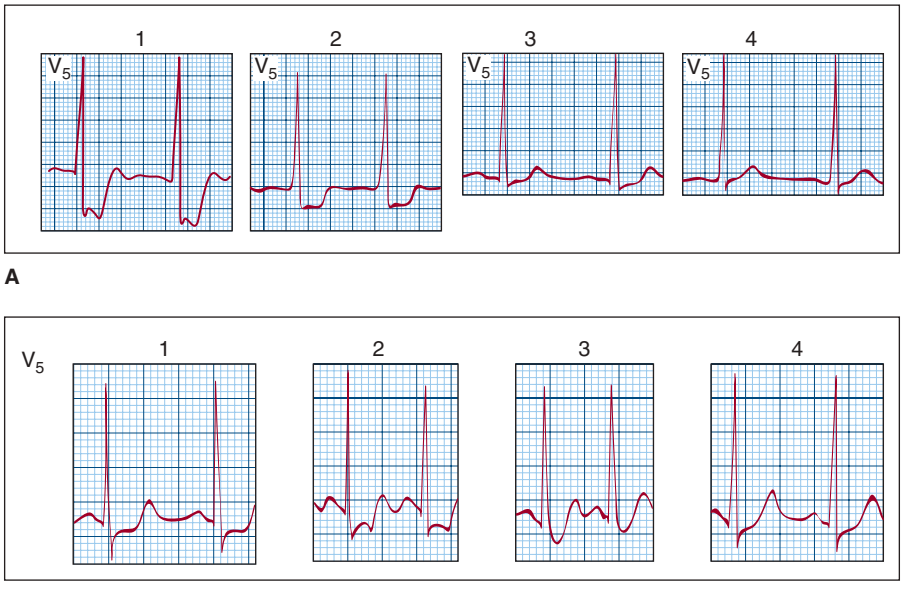


FIGURE 12–51. A. A 65-year-old patient with non–Q-wave infarction due to left main trunk subocclusion. Note the evolutionary patterns from 1 to 4 during the first week until the normalization of the ST segment. **B.** Different types of subendocardial injury patterns that appeared in the course of an exercise test: (1) horizontal displacement of the ST segment; (2) descendent displacement; (3) concave displacement; and (4) ST-segment depression from J point with ascendant morphology and with rapid up-sloping. This usually is seen in normal cases. The coronary angiography was abnormal in 1, 2, and 3, and normal in 4. These changes are especially visible in leads with dominant r wave, especially V_3, V_4, V_5, V_6, I, and VL, and/or inferior leads with dominant r wave.

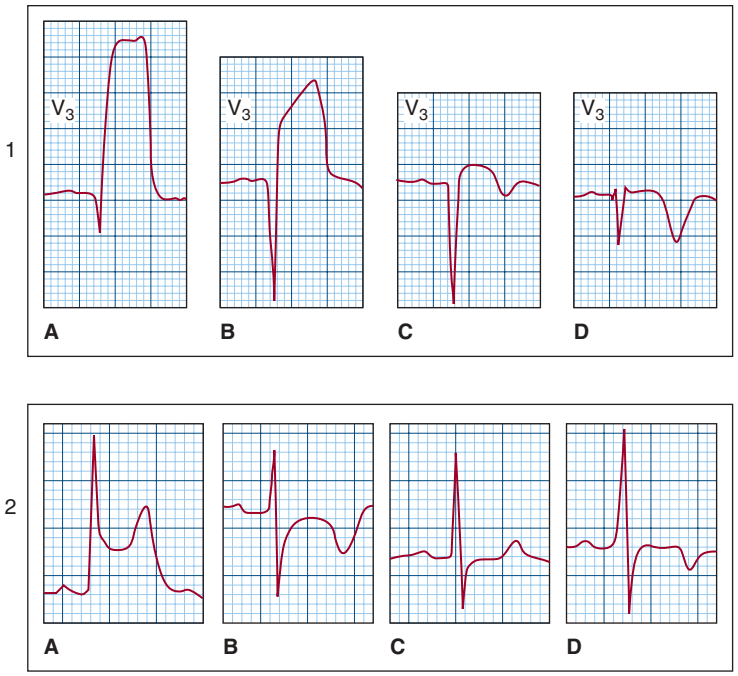


FIGURE 12–52. This figure shows the different evolution of ST-segment elevation acute coronary syndrome (STE-ACS) before reperfusion era in 1970 (especially primary percutaneous coronary intervention [PCI]) (*1*) and in 2010 (*2*) current treatment. **1.** In 1970 a 72-year-old patient with an extensive anterior infarction caused by left anterior descending proximal occlusion. Note the evolutionary patterns without current treatment (1970s): (**A**) 30 minutes after the onset of pain, (**B**) 3 hours later, (**C**) 3 days later, and (**D**) 3 weeks later. **2.** In 2010, (**A**) a 63-year-old man with significant STE-ACS; (**B**) after PCI, a negative T wave appears; (**C**) the patient presents with angina, the ST segment pseudonormalizes, and again, a new PCI was performed that demonstrated intrastent thrombosis; and (**D**) after the procedure, the electrocardiogram again shows a negative T wave.

(see Electrocardiogram in Acute Coronary Syndrome with ST-Segment Elevation).

An ST-segment elevation may also be recorded in other clinical settings that are not related to atherothrombosis, such as isolated coronary spasm[75,76] and Takotsubo syndrome (TTS)[60,78,79] (see Electrocardiographic Changes in Ischemia Not Related to Atherothrombosis) (p. 48 [manuscript page 65]).

The leads that face the head of the vector of injury in transmural acute ischemia record an ST-segment elevation, whereas the leads facing the tail of the injury vector record an ST-segment depression. The global study of direct and mirror images of the ST deviations in different leads is crucial to correctly diagnosis the location of the injury and to understand the corresponding prognostic implications (see Fig. 12–53 and Electrocardiogram in Acute Coronary Syndrome with ST-Segment Elevation).

QRS CHANGES

1. Q wave of necrosis may appear when there is, as a result of a myocardial infarction, a myocardial zone with important diastolic depolarization and lack of formation of transmembrane action potential. This zone usually surpasses the endocardium layer and encompasses part of the left ventricle that depolarizes within the first 40 to 50 ms.
2. The changes in the mid to late part of QRS (fractioned QRS) have the same cause but take place in the areas of late left ventricle activation.

Differential Diagnosis The list of conditions that, apart from IHD, may present an ST-segment elevation or depression is large.[2,60]

Tables 12–8 and 12–9 summarize the most important conditions of ST depression and elevation not caused by IHD. On the other hand, Fig. 12–54 shows the most typical variants that present with ST-segment elevation or depression. In the first phase of pericarditis, a disease that also presents with chest pain, the most striking change is an elevation of the ST segment. Many conditions can also present with ST-segment depression, although usually small. The most important factor to take into account is the correlation of the clinical symptoms with the deviations of the ST segment. The diagnostic criteria for considering the deviations (ups and downs) of ST suggestive of ACS and all their prognostic implications will be discussed later (see Acute Coronary Syndrome with Narrow QRS: Evolutionary Changes, p. 39 [manuscript page 56]).

Changes in QRS

Q Wave of Necrosis: Electrophysiologic Mechanisms The activation of the subendocardial area is very fast because the density of Purkinje fibers is so great that the electrodes located in this area do not record any positive deflection (1 and 2 in Fig. 12–55A). Later on, the subsequent activation of the other part of the left ventricle wall records progressively greater R waves until a unique R wave is recorded from the epicardium (5 in Fig. 12–55A).

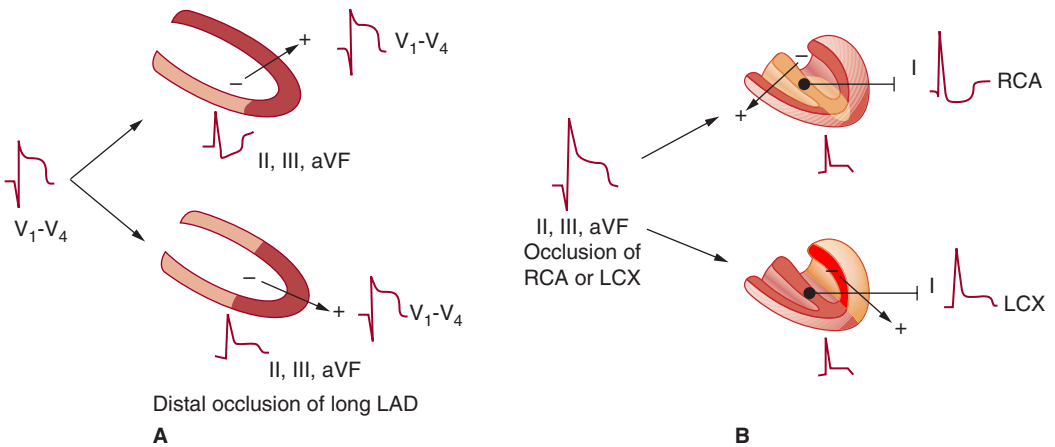


FIGURE 12–53. A. In ST-segment elevation in precordial leads, as a consequence of left anterior descending (LAD) occlusion, the ST segment changes in reciprocal leads (II, III, and aVF), allowing us to identify whether the occlusion is in the proximal (above) or distal LAD (below). **B.** In case of ST-segment elevation in inferior leads (II, III, and aVF), the ST changes in other leads, in this case lead I, providing information on whether the inferior infarction is caused by right coronary artery (RCA; above) or left circumflex artery (LCX; below) occlusion (see text).

TABLE 12–8. Most Frequent Causes of ST-Segment Elevation[a]

1. Normal variants: chest abnormalities, early repolarization, vagal overdrive. In vagal overdrive, ST-segment elevation is mild and generally accompanies the early repolarization image. T wave is tall and asymmetric.
2. Athletes. Sometimes an ST-segment elevation exists that even mimics an acute infarction with or without negative T wave, at times prominent. No coronary involvement has been found, but this image has been observed in athletes who die suddenly; thus, its presence implies the need to rule out hypertrophic cardiomyopathy.
3. Acute pericarditis in its early stage and myopericarditis
4. Pulmonary embolism
5. Hyperkalemia. The presence of a tall peaked T wave is more evident than the accompanying ST-segment elevation, but sometimes it may be evident
6. Hypothermia
7. Brugada syndrome
8. Arrhythmogenic right ventricular dysplasia
9. Dissecting aortic aneurysm
10. Left pneumothorax
11. Toxicity secondary to cocaine abuse, drug abuse, and so on

[a]Apart from ischemic heart disease (see Fig. 12–54A).

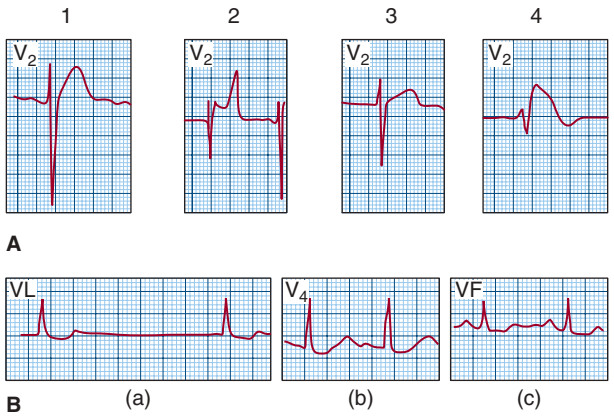


FIGURE 12–54. A. The most frequent cases of ST-segment elevation apart from ischemic heart disease: (1) pericarditis; (2) hyperkalemia; (3) athletes; and (4) typical Brugada pattern with coved ST-segment elevation. The saddle-type variant of Brugada syndrome has to be differentiated from normal variant. **B.** ST-segment depression resulting from causes other than ischemia: (1) digitalis effect (note the typical morphology with ST depression and short QT in patients with slow atrial fibrillation); (2) hypokalemia in a patient with congestive heart failure taking high doses of furosemide; and (3) mitral valve prolapse.

In presence of MI, the diastolic depolarization in the infarcted area is so important that it cannot be excited and does not originate a TAP. Therefore, a Q wave is generated when the infarcted area surpasses the subendocardium and affects part of the myocardium that is depolarized within the first 40 to 50 milliseconds[64] (Fig. 12–55B and C).

The Q wave of necrosis may be explained by two theories. The first theory is the theory of electrical window of Wilson. According to this theory, the transmural infarcted area acts as an electrical window and, consequently, the electrode that faces that area records the negativity of the intracavitary QRS (Q wave of necrosis) (see Fig. 12–55B).

The second theory is the theory of the infarction vector. This theory proposes that the infarcted area generates a vector (infarction vector) that has the same magnitude, but opposite direction to the one that would have been generated at the same zone in the absence of infarction. Therefore, the infarction vector moves away from the infarcted area (see Fig. 12–46). As we have stated, the ventricular depolarization changes that originate the Q wave occur when the infarction area is depolarized within the first 40 milliseconds of ventricular activation.

Fractioned QRS Anomalies in the mid to late part of QRS, such as slurring, rsr′, and low voltage in the left precordial leads (Fig. 12–55D), are

TABLE 12–9. Most Frequent Causes of ST-Segment Depression[a]

1. Normal variants (generally slight ST depression): sympathetic overdrive; neurocirculatory asthenia, hyperventilation, and so on
2. Drugs: diuretics, digitalis, and so on
3. Hypokalemia
4. Mitral valve prolapse
5. Post-tachycardia
6. Secondary to bundle branch block or ventricular hypertrophy. Mixed images are frequently generated.

[a]Apart from ischemic heart disease (see Fig. 12–54B).

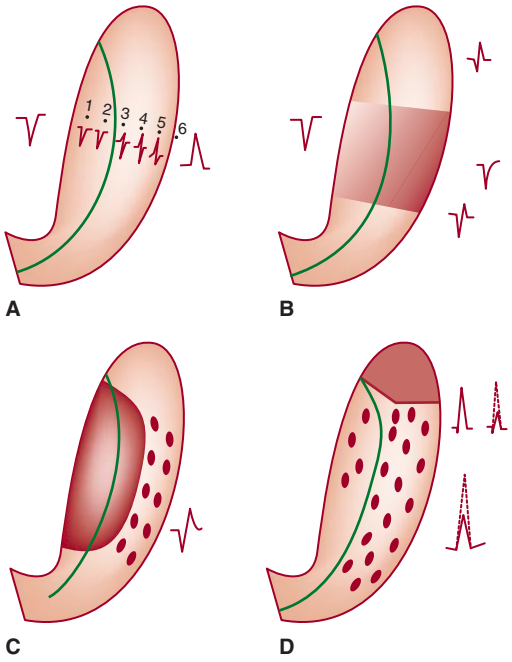


FIGURE 12–55. A. Normal ventricular depolarization, being very rapid in the subendocardium, does not generate detectable potentials because this zone is very rich in Purkinje fibers (QS in 1 and 2). Starting from the border zone with subepicardium (3), morphologies with an increasing R wave (rS, RS, and RS) are registered (3 to 5) up to exclusive R wave in the most external part of epicardium (6). As a consequence, in case of an experimental necrosis, the Q wave will be recorded only when it reaches subepicardium and then will originate Q waves of higher or lower voltage according to the extension of necrosis. A qR morphology will be recorded in 3 and QR in 4 and 5, up to QS if the necrosis is transmural. **B.** This figure shows, according to the theory of the electrical window of Wilson, how clinical transmural infarction originates QS morphology. **C.** An infarction affecting subendocardium and a part of subepicardium may give rise to QR morphology without necessarily being transmural. **D.** Finally, an infarction affecting basal areas or a part of myocardial wall, but in a form of patches, with necrosis-free zones, allows early formation of depolarization vectors that will be recorded as R waves but with slurrings or small voltage (fractioned QRS).

called *fractioned QRS*.[65,66] Fractioned QRS may occur as a consequence of alterations of ventricular activation after 40 to 50 milliseconds (basal segments according to standardized myocardial segmentation nomenclature by Cerqueira et al[80]). The fractioned QRS may appear either isolated or with a Q wave. It may be caused by a necrotic area that does not involve the whole wall (see Fig. 12–55D).

The MI with fractioned QRS forms part of the non–Q wave MI, which will be discussed later (see Myocardial Infarction Without Q Wave or Equivalent).

Changes in QRS in Patients with Ischemic Heart Disease (see Electrocardiography in Ischemic Heart Disease) The appearance of the Q wave of necrosis in the evolutionary changes of STE-ACS is demonstration that the patient has evolved to MI, involving an area that surpasses the subendocardium (see Fig. 12–55B). However, this is not an irreversible pattern. In fact, in a few cases, such as aborted MI and Prinzmetal angina, the presence of Q waves may be transient.

The criteria to diagnose a Q wave as abnormal and the location of MI, according to the presence of the Q wave in different leads, are discussed later in Q-Wave Myocardial Infarction (see Table 12–11).

As with changes in the T-wave and ST-segment deviations, the presence of a mirror image of the Q wave of necrosis is also very important for diagnostic purposes. It is especially evident that, in patients with IHD, the presence of a prominent R wave in V_1 may be the only manifestation of abnormality. It is currently known that this R wave result from a lateral, not a posterior, MI (see Q-Wave Myocardial Infarction).[81,82]

Recently, it has been reported that the presence of fractioned QRS provides a more accurate criterion for the diagnosis of necrosis than the existence of a Q wave.[65] However, it is necessary to match these morphologies with the clinical setting because they may also be seen in normal subjects.

The fractioned QRS also arises in other diseases or circumstances, such as ventricular aneurysm[83] and Brugada syndrome.[84]

Differential Diagnosis The specificity of the pathologic Q wave (Table 12–10) for diagnosing myocardial necrosis is relatively high. However, it must be noted that similar "Q" waves are seen in other processes. The diagnosis of acute MI is based not only on ECG findings, but also on the clinical setting, as well as on enzymatic changes. The presence of ST-T alterations accompanying a pathologic Q wave gives support to an IHD as the cause for this ECG pattern. However, as indicated later, in 5% to 25% of infarctions (higher incidence in inferior infarction), the Q wave disappears with time; thus, the sensitivity of the ECG for detecting old infarction is not very high (Fig. 12–56).

The principal causes of the pathologic Q wave, other than myocardial necrosis, are listed in Table 12–10.

Other Changes

As already stated, there are many other changes in the ECG parameters that are induced by ischemia. Some of them, such as lengthening of the QT interval, have already been discussed. For more information on other ECG changes, such as for instance those of the P wave in case of atrial infarction consult Bayés de Luna,[2] Surawicz,[12] and Bayés de Luna and Fiol-Sala.[60]

ELECTROCARDIOGRAPHIC CHANGES IN HEART DISEASE AND OTHER SITUATIONS

ELECTROCARDIOGRAPHY IN ISCHEMIC HEART DISEASE

Types of Myocardial Ischemia

Myocardial ischemia may occur by two different pathophysiologic mechanisms[85]: (1) when there is an abrupt decrease in the blood flow, usually in patients with coronary atherothrombosis, after the rupture or erosion of a vulnerable plaque; or (2) when there is an increased myocardial demand, such as in exercise or other form of stress, while the supply from the coronary tree is insufficient, usually because of a fixed atherothrombotic stenosis. In both cases, there are other causes besides atherothrombosis that may explain the presence of ischemia.

In the following sections, ECG changes in different clinical settings related to a decreased supply, usually caused by atherothrombosis, will be discussed, including ACS and its evolutionary changes up to the chronic phase (Q-wave and non–Q-wave MI). In addition, the ECG changes found in clinical situations with an increased demand, such as in classic exercise angina, and in exercise stress test will be described. Finally, ECG changes induced by ischemic damage that does not have an atherothrombotic etiology will be discussed.

Acute Coronary Syndrome with Narrow QRS: Evolutionary Changes

The majority of these ACS are caused by coronary atherothrombosis.[86-96] They may be classified into two types, either with ST-segment elevation (STE-ACS) or without ST-segment elevation (non–STE-ACS). Angiographically, STE-ACS frequently (> 90%) presents with a red clot that usually provokes a total occlusion of the vessel. In non–STE-ACS, however, the incidence of an angiographic white clot is lower (50%–70%) and does not produce a total occlusion. Even though this classification has clinical and therapeutic implications, not all cases of ACS that present STE-ACS show an ST-segment elevation as the most important ECG change, and other ECG pattern may be seen in the follow-up.[60,63] Furthermore, NSTE-ACS includes cases with ST-segment depression, negative T wave, and even normal ECG (Fig. 12–57).

Electrocardiography in Acute Coronary Syndrome with ST-Segment Elevation In many cases, STE-ACS will evolve to an MI, usually of Q-wave type (see Figs. 12–52, 12–53, 12–56, and 12–57). However, thanks to modern treatments, more MIs can now be aborted (unstable angina) (see Fig. 12–52).[60]

Electrocardiogram Patterns The typical ECG pattern is the ST-segment elevation. However, as already stated, others patterns may be seen.

1. Typical ECG pattern: The new occurrence of an ST-segment elevation greater than 2 mm at 60 milliseconds after the J point in V_2 to V_3 and greater than 1 mm in other leads, present in at least two consecutive leads, is considered abnormal and evidence of acute ischemia in the clinical setting of ACS (presence of precordial pain or equivalents). Whenever possible, it is important to compare this pattern with previous ECGs.

   The morphology of the ST-segment elevation is diverse, but the most characteristic morphology is a concave shape with respect to the isoelectric line, especially in QRS complexes with rS morphology. The height of the ST elevation may be very high, even more than 20 mm, and then it decreases along the acute-subacute phase. However, it may remain slightly elevated even in the chronic phase. Meanwhile, if the infarction is not aborted, the typical Q wave and negative T wave appear (see Fig. 12–52). In this case, the deepness of the T wave may be important (≥ 8 mm) and often disappears in the evolution (see Fig. 12–56).

   The ST elevation prevails in the leads facing the affected zone as a direct ECG pattern. In general, in some opposed leads, the ST-segment depression is seen as an indirect ECG pattern (see Fig. 12–53). These same features also occur in the chronic phase, with a Q wave as the direct pattern and an R wave as the indirect pattern (see Fig. 12–47).

   In STE-ACS, the global evaluation of direct and reciprocal changes (ups and downs of ST) is important for detecting which artery is the

TABLE 12–10. More Common Pitfalls in the Electrocardiogram Interpretation of Acute Coronary Syndrome[a]

ECG Patterns(•) and Pitfalls (*)	Type of ACS and Involved Artery	Zone and Characteristics of Involvement
A. • ST depression in V1-V4: (1) In the hyperacute phase, prominent ST depression in V1, horizontal/downsloping, without significant terminal positive T wave in V1-V2 (2) In more advanced stages, ST horizontal descent with + T wave * Consider it to be a non–STE-ACS and mirror image more evident than direct image	Probably, it is true STE-ACS (STE-ACS equivalent) mirror pattern due to LCX occlusion (rarely distal RCA) Patients have ongoing active symptoms	Transmural lateral involvement
B. • Leads V1-V4: Isoelectric ST segment with tall, wide, positive T wave; often a transient pattern * Consider that the ECG is normal because of few changes in the ECG; few mirror images	Hyperacute phase of STE-ACS; patient with angina Repeat ECG in few minutes Evolving to LAD total occlusion	Subendocardial involvement evolving to transmural involvement
C. • Leads V3-V5: ST ↓plus tall positive T wave, without tachycardia, that evolves to Q wave MI; change occurs in hours * Consider that the PCI is not emergent	Non–STE-ACS evolving to STE-ACS, usually in hours Usually LAD subocclusion evolving to total occlusion Patients have ongoing symptoms	Nontransmural involved wall evolving to transmural involvement
D. • Leads V1-V3: Non–SET-ACS with isoelectric ST segment with mild negative T wave in V1-V3 * Consider the problem is over	Resolution phase (spontaneous, drugs, PCI) of non–STE-ACS; LAD subocclusion that may be important Patients usually have resolution of symptoms	No transmural involvement
E. • Leads V1 to V4-V5: Isoelectric ST segment with deep symmetrical negative T wave; not angina at this moment * Consider to be NSTE-ACS	Resolution phase (spontaneous, drugs, PCI) of non–STE-ACS caused by LAD subocclusion (or occlusion with collaterals) Patients usually have resolution of symptoms	At least in some cases, transmural edema that disappears if pattern normalizes
F. • ST elevation in I and aVL without evident ST depression in V1-V2 * Consider LCX occlusion; often mirror image more evident than direct image	STE-ACS usually caused by first diagonal occlusion Patients usually have ongoing active symptoms	Transmural involvement mid/low anterolateral wall
G. • ST depression in ≥ 7 leads + ST elevation in aVR-V1 and without evident final positive T wave in V1-V2; in the absence of LVH, LBBB, IVCD * Do not consider it to be left main subocclusion	**Non–**SET-ACS of high risk Left main trunk or three-vessel disease subocclusion	No transmural involvement
H. • ST elevation in I, aVL, V2 to V3-6; no ST elevation in aVR and V1; frequent RBBB + superoanterior hemiblock; severe clinical/hemodynamic state * Do not recognize that it corresponds to a complete left main trunk occlusion	STE-ACS caused by left main trunk occlusion with severe hemodynamic state	Transmural involvement
I. • ST elevation < 1 mm in inferior leads or < 2 mm in precordial leads * Consider that it is a non–STE-ACS; often mirror image is more evident than direct image	Hyperacute phase of STEMI LAD, RCA, or LCX occlusion	Transmural ischemia
J. • LBBB pattern * Consider that alterations in repolarization are caused by the LBBB. Sgarbossa's criteria not identified	Hyperacute phase of STEMI LAD, RCA, or LCX occlusion	Transmural ischemia

[a]See ECG pattern, type of ACS and involved artery, and zone involved.[89]

Abbreviations: ACS, acute coronary syndrome; ECG, electrocardiogram; LAD; left anterior descending (coronary artery); LBBB; left bundle branch block; LCX, left circumflex artery; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; STE-ACS, ST-segment elevation–acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

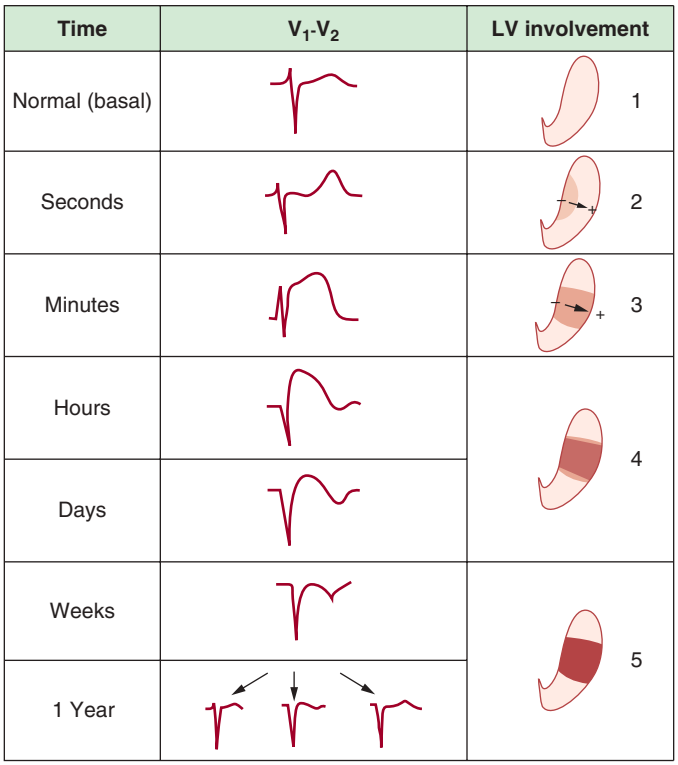


FIGURE 12–56. Spontaneous evolutionary pattern in V_1-V_2 seen in the case of myocardial infarction (MI) caused by occlusion of the left anterior descending coronary artery. Now, after current effective treatment, the changes may be very different (see Fig. 12–52). This is a typical case of ST-segment elevation MI that presents Q wave MI without residual ischemia. See on the right the scheme of the left ventricle wall: (1) normal, (2) with predominant subendocardial ischemia, (3) with transmural ischemia, (4) with necrosis and often surrounded by zone of ischemic tissue, (5) chronic necrosis without ischemic tissue.

culprit (the right coronary artery [RCA] or the left circumflex artery [LCX]) in case of ST elevation in II, III, and VF (Fig. 12–58; see also Fig. 12–53B), as well as to find the location of the LAD occlusion in the case of an ST elevation in the precordial leads (Fig. 12–59; see also Fig. 12–53A).[87,88] Table 12-10 presents the more common pitfalls in the ECG interpretation of ACS.[89,90]

2. Atypical ECG patterns (Fig. 12–60): The following patterns occur without ST elevation as the most striking ECG change.[90-92]
   - Presence of ST depression in V_1 to V_3 that is more evident than the ST elevation in II, III, VF, and/or V_5 to V_6 can occur. Nevertheless, the ST elevation is usually present at least in some leads. This is a clear pattern equivalent to the ST elevation that represents the mirror pattern of injury in the lateral zone. In this case, the occluded vessel is the LCX, and the ST elevation may be seen in the back leads (see Fig. 12–60C). These patients must be treated as for STE-ACS.
   - In many occasions, but usually only for a very brief period, the first recorded ECG change during hyperacute ischemia is a change in the T-wave morphology (wider and peaked and sometimes taller) accompanied by an increase in the Q interval. Often, a mild ST depression may be seen (see Fig. 12–60A). This pattern is not usually encountered in the emergency department because it is very transient and quickly followed by an ST-segment elevation (see Fig. 12–60A).

It has been described (see the following section) that STE-ACS with grade 1 ischemia may only present stable changes of the T wave (wider, peaked, and tall). In our experience, this rarely occurs.

   - Relatively often, during the evolution of an STE-ACS caused by an LAD proximal occlusion, when the artery has been spontaneously opened or after treatment and once the pain has vanished, a negative T wave, usually striking (> 4–5 mm), may appear[60] (see T-Wave Changes in Patients with Ischemic Heart Disease). This is a sign of an open artery or, at least, that a very good collateral circulation exists, but it is not a guarantee that the problem is resolved. Sometimes, the artery may reocclude (see Fig. 12–60B) with the appearance of pain; changes in the ECG; first pseudonormalization of the T wave; and often, but not always, reappearance of the ST elevation. Therefore, patients with deep negative T waves in the right precordial leads who have had anginal pain in the previous hours should be submitted to coronary angiography as soon as possible. Nonetheless, this situation is not considered an emergency, as in the case of a clear ST elevation.

Clinical and Prognostic Implications The characteristics of the ST elevation and mirror images have a great relevance for localizing the occlusion and area at risk, quantifying the ischemic burden, and detecting the grade of severity of ischemia.

- Location of occlusion and area at risk. Figure 12–59 shows in detail (see legend) the algorithm that allows one to predict the site of the LAD occlusion in the case of an ACS with STE in the precordial leads.[87] Figure 12–58 represents the algorithm to follow in case of ACS with STE in the inferior leads to distinguish between RCA or LCX occlusions.[88] In case of RCA occlusion, there are increased chances of a proximal occlusion and right ventricle involvement if an ST elevation in the right precordial leads (V_3R, V_4R) is present.[91] In our experience, we found that the presence of isoelectric or elevated ST in V_1 is also useful. Furthermore, in case of a dominant RCA occlusion, an ST elevation in V_5 to V_6 is usually seen.[92]
- Quantification of ischemic burden. Despite the fact that some limitations exist, as occurs in case of a proximal RCA occlusion that may mask the extension of ischemia because of present isodiphasic ST in V_1, the sum of the ST changes in all leads may estimate the myocardium at risk. More than 15 mm of ST deviation usually represents a great area at risk.[96]
- Grade of severity of ischemia. The morphology of QRS-ST may suggest the grade of ischemia. According to the Birnbaum-Sclarovsky ischemia grading system,[94,95] grade 1 ischemia presents a tall permanent T wave; grade 2 presents an ST elevation without distortion of the QRS complex; and grade 3 presents an ST elevation that sweeps the QRS complex upward, provoking a distortion of it (Fig. 12–61)[95,96]

Electrocardiography in Acute Coronary Syndrome with Non–ST-Segment Elevation Non–STE-ACS includes cases of ACS that present new ST depression (≥ 0.5 mm) and/or new flattened or negative T wave or negative U wave, in two or more consecutive leads, as the most prominent ECG changes. Obviously, all atypical cases of STE-ACS have to be excluded (see Fig. 12–60). Usually the deepness of the T wave in non–STE-ACS is not very important (< 3–4 mm). The deepness of the negative T wave in an atypical ECG pattern in case of LAD occlusion caused by ST-elevation MI (STEMI) is often more important (see Fig. 12–60B).

Electrocardiography Patterns and Clinical and Prognostic Implications Non–STE-ACS with ST depression may present two patterns:

1. ST depression in seven or more leads with more striking feature in V_3 to V_5, usually without positive T wave and with evident positive ST elevation in VR as a mirror pattern (Fig. 12–62A). This ECG pattern represents a left main coronary artery subocclusion or

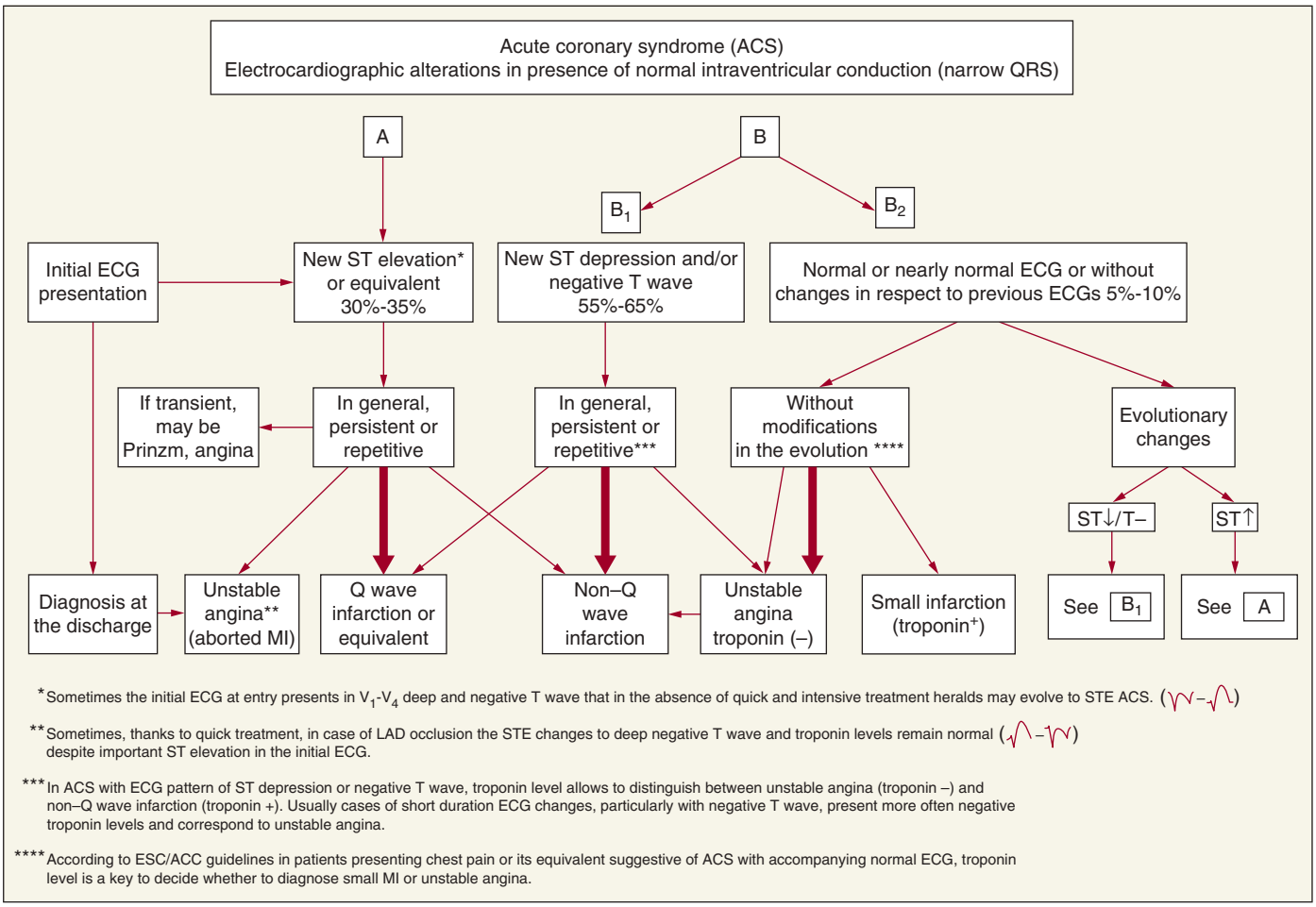


FIGURE 12–57. Electrocardiographic (ECG) alterations observed in patients with acute coronary syndromes presenting with narrow QRS and without confounding factors such as left ventricular hypertrophy (LVH). Observe the initial ECG presentation: (**A**) ST-segment elevation or equivalent; (**B**) non–ST-segment elevation; (**B1**) ST-segment depression/negative T wave; and (**B2**) normal or nearly normal ECG or without changes in respect to previous ECG with its approximate incidence and final discharge diagnosis according the evolution.

equivalent (2–3 proximal vessels disease). These cases correspond to a circumferential involvement and have a worse prognosis. Therefore, they need urgent catheterization and administration of the appropriate treatment.

2. ST depression in less than seven leads (regional involvement) usually with final positive T wave. These cases have a better prognosis. However, it is difficult to ascertain what artery is affected, although if the LAD is compromised, the ST depression is usually located between V_2 to V_3 and V_4 to V_5. However, three-vessel disease may be present, often with normal basal ECG and only small changes in exercise testing (Fig. 12–62B).[2,60,63]

The prognosis becomes worse in proportion with the number of leads involved and the importance of the ST depression.

In non–STE-ACS with only a flat/negative T wave, the negative T wave is usually not deep (usually < 3 mm) and not very diffuse (Fig. 12–62C). As previously mentioned, the prognosis is better than in cases with ST depression. However, a coronary subocclusion often exists and is generally significantly stenotic. Therefore, for these cases, we recommend nonemergent PCI.

Sometimes a normal ECG at entrance later evolves to a clear ACS (see Fig. 12–57). The ECG may remain normal in 5% to 10% of cases. The cases of non–STE-ACS that maintain a normal ECG usually have a good prognosis.

Acute Coronary Syndrome with Confounding Factors

In case of left ventricular hypertrophy (LVH) with strain pattern and/or wide QRS complex, the diagnosis of ACS is more difficult, especially if concurrent with non–STE-ACS. Performing a study of sequential pattern may be useful.

In the presence of bundle branch block, the diagnosis is possible if the block is an RBBB. However, in some cases of STE-ACS in the presence of LBBB or other situations with wide QRS (pacemaker or WPW), it is also possible to visualize the ST-segment elevation (Fig. 12–63). Sgarbossa et al[97] reported that, in cases clinically compatible with acute MI in the presence of LBBB, the diagnosis is supported by the following criteria: (1) ST elevation greater than 1 mm concordant with the QRS complex, (2) ST depression greater than 1 mm concordant with the QRS complex, and (3) ST elevation greater than 5 mm nonconcordant with the QRS complex. Similar criteria are also useful in the presence of a pacemaker.[98] On the contrary, the diagnosis of concurrent non–STE-ACS may be difficult using the surface ECG because there may be no visible changes or the changes may be confounded with the basal ones.

The scientific guidelines[99] consider new LBBB to be an ACS equivalent, in the right clinical context. However, when symptoms are atypical primary PCI protocol activation for LBBB should be considered after positive point-of-care troponin test 1 to 2 hours after symptom onset.

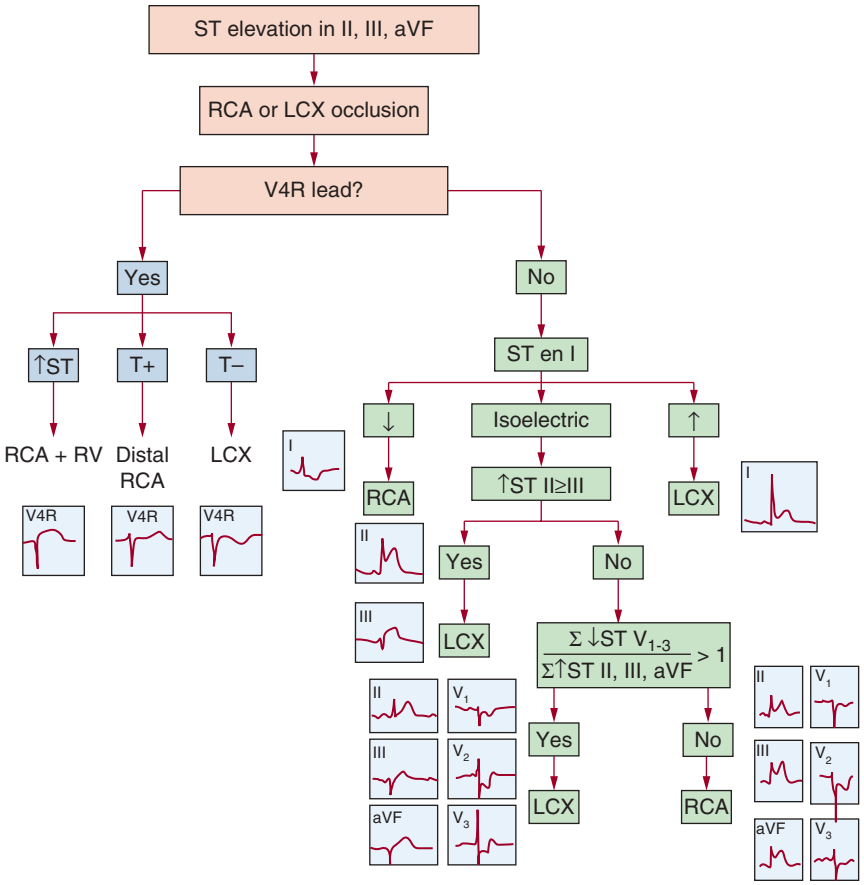


FIGURE 12–58. Algorithm to predict the culprit artery (right coronary artery [RCA] versus left circumflex artery [LCX]) in case of evolving myocardial infarction with ST elevation in inferior leads (see text for details).

Acute MI and the need for emergent revascularization are relatively uncommon among patients who present with LBBB, especially when symptoms are atypical.[99]

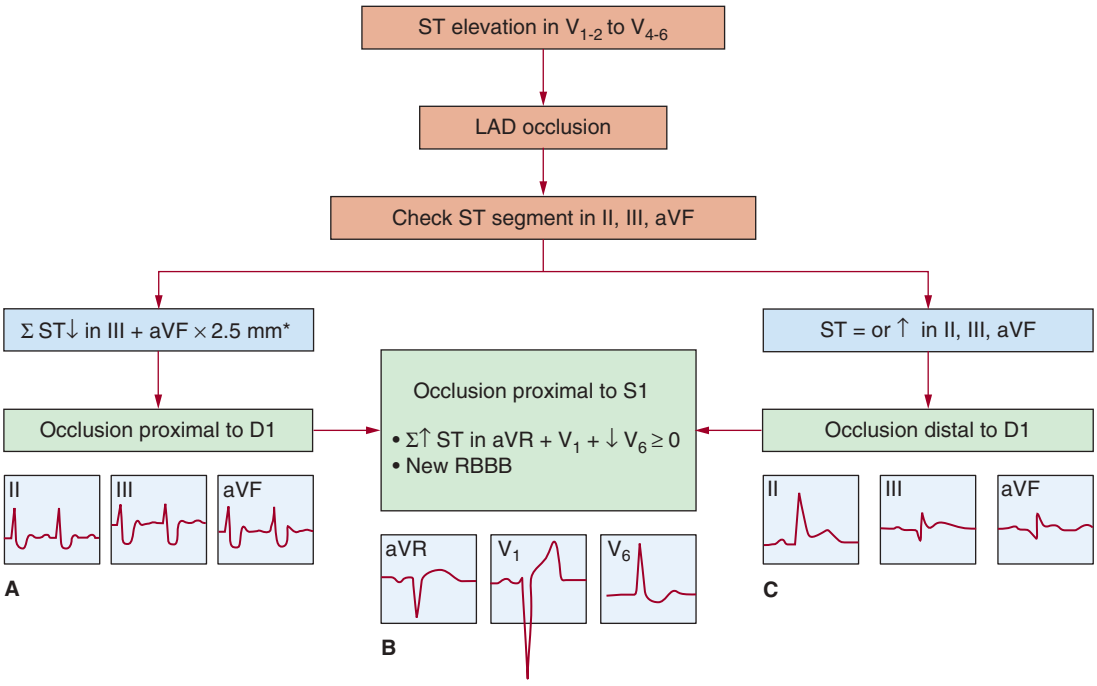
Electrocardiography in Chronic Myocardial Infarction with Narrow QRS

Before the era of reperfusion, it was relatively easy to predict the final Q-wave infarction pattern according to the acute phase of STE-ACS.[60] However, with current strategies of treatment, this is impossible because, if the treatment is started on time, the infarction may be aborted or faded.

Therefore, in patients with chronic Q-wave MI, it is presently impossible to know, from the correlation with the Q-wave pattern, the exact degree and location of the occlusion of the culprit artery. Nevertheless, the coronary lesion will be less than expected if reperfusion treatment had been applied. However, the location of the occlusion that produced the Q-wave MI could probably be predicted.

Furthermore in approximately more than 50% of cases with MI, the QRS complex does not show a Q wave of necrosis or equivalent (R in V_1-V_2). The MI without Q wave encompasses the classic non–Q-wave MI (ancient subendocardial MI) and many other types of MI, as shown in Table 12–13. Even in presence of an important ST depression in the evolutionary phase, the ST morphology may completely recovered.

Until relatively recently, it was thought that MIs of exclusive subendocardial location existed and were



* Cases with ST depression < 2.5 mm are difficult to classify in respect to D1, but if Σ↑ ST aVR + V_1 + ↓ ST V_6 < 0, are usually distal to S1.

FIGURE 12–59. Algorithm to precisely locate the left anterior descending (LAD) occlusion in the case of an evolving myocardial infarction with ST elevation in precordial leads (see the text for details).

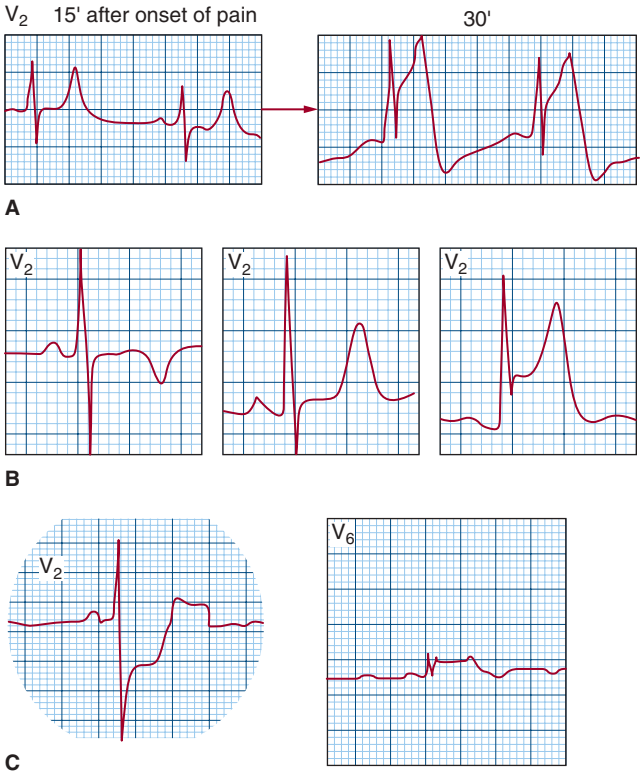


FIGURE 12–60. Atypical patterns of acute coronary syndrome (ACS) with ST elevation: (**A**) hyperacute transient pattern of T wave taller, wider, and symmetrical before ST elevation; (**B**) deep negative T wave in the evolutive process of reperfused occluded artery that may evolve to ST elevation in presence of new ischemic attack; and (**C**) ST depression in V_2 as a mirror pattern of ST elevation in back leads (see text).

electrically mute. However, the concepts that MI with Q wave is transmural and non–Q-wave MI only implies subendocardial compromise are false.[60,100] Now, it has been demonstrated that from a pathologic point of view, infarction of exclusive subendocardial location does not exist and that infarctions with predominant subendocardial involvement may or may not develop a Q wave.[100] However, some transmural MIs, such as those involving the basal areas of the left ventricle, do not exhibit a Q wave.[101]

CE-CMR is the ideal technique for infarct identification, transmural characterization, and infarct location and quantification.[102] CE-CMR has demonstrated that the Q-wave MIs are larger than non–Q-wave MIs, although not always have a deeper transmural extension.[60,103] Therefore, the terms *Q-wave MI* and *non–Q-wave MI* are useful in the chronic phase from a prognostic point of view.

Table 12–11 presents the new definition of MI according a committee appointed by the European Society of Cardiology and the American College of Cardiology.[104]

Q-Wave Myocardial Infarction A. The evolution of the ECG pattern. Since the beginning of the ECG, the pattern of established transmural infarction has been classically associated with the presence of pathologic Q wave or equivalents. Figures 12–52 and 12–56 show the evolutionary appearance of the Q wave and negative T wave in cases of Q-wave MI. Now, if quick current treatment is established, the evolution of the ECG may be very different (see Figs. 12–52B and 12–57).

B. Diagnostic criteria of Q-wave MI. Table 12–12 shows the accurate criteria for the diagnosis of Q wave of necrosis.[2]

C. Location of Q-wave MI. A statement from the International Society for Holter and Noninvasive Electrocardiology presented a new classification of Q-wave MI based on the correlation between the Q wave and the infarcted area as assessed by CE-CMR (Figs. 12–64, 12–65, and 12–66).[105-110] We have based our classification (see Fig. 12–66) on the following facts:

- The heart was divided into two regions (see Fig. 12–64): the anteroseptal, perfused by the LAD; and the inferolateral, perfused by the RCA or the LCX. Evidently, these two regions are not always equal, according to the anatomic variations of the arteries perfusing them (eg, length, dominance).
- The inferobasal segment of the left ventricle (former posterior wall) that corresponds to segment 4 of the statement by Cerqueira et al[80] (see Fig. 12–64), depolarizes after 40 to 50 milliseconds. Therefore, this cannot originate an R wave in V_1 that would be equivalent to the Q wave in the back of the heart.
- We have demonstrated that the inferobasal segment rarely bends upward, and therefore, a true posterior wall hardly ever exists. Thus, a vector that points to V_1 cannot usually be originated, even in the case that this vector may exist.

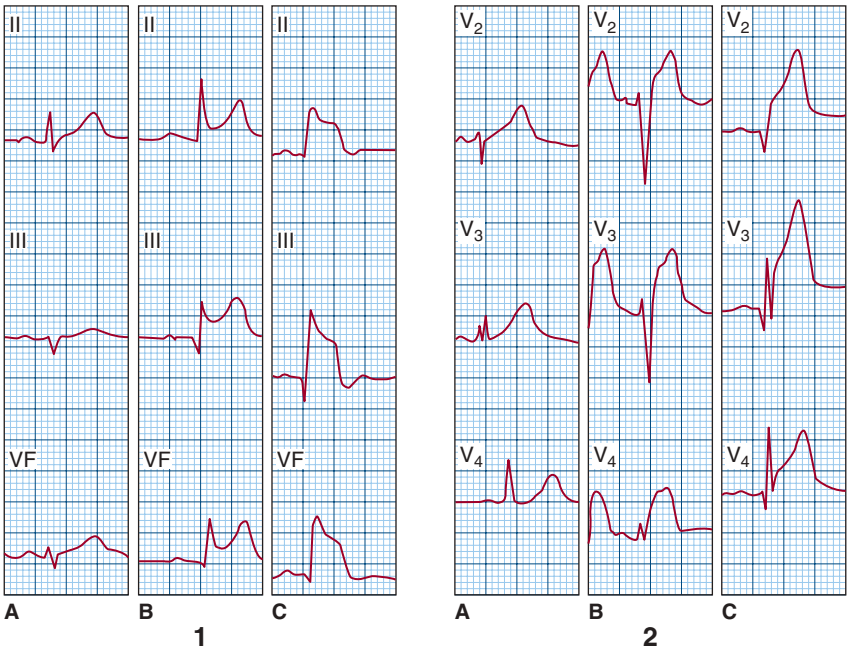
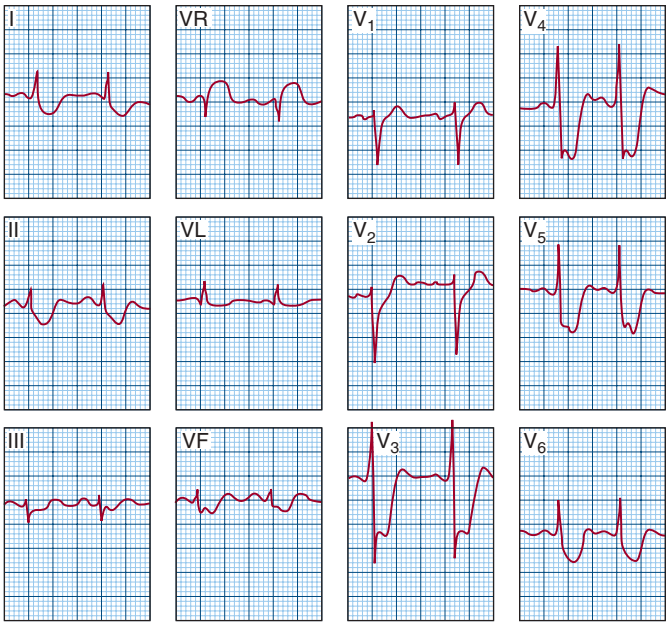
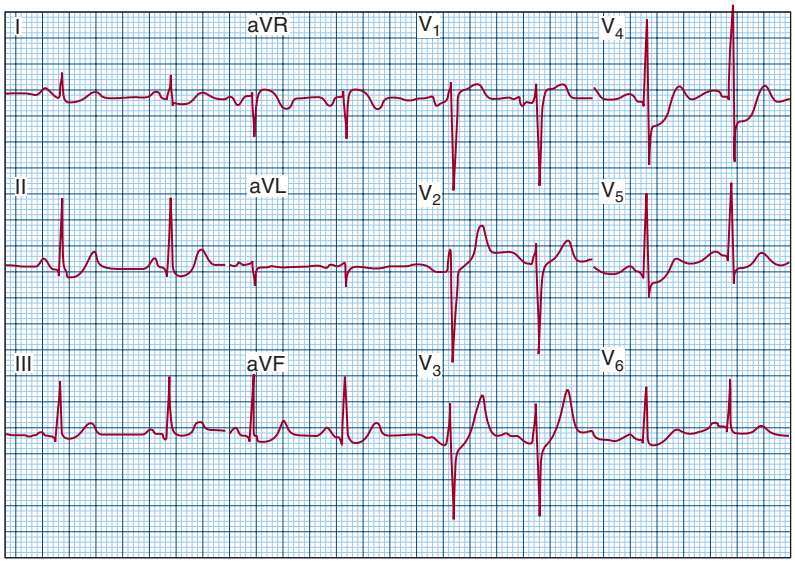


FIGURE 12–61. 1. The three types (Birnbaum-Sclarovsky grading) of repolarization abnormalities that may be seen in an acute phase of ST-elevation myocardial infarction involving the inferolateral zone: (**A**) tall and/or wide T waves in inferior leads; (**B**) abnormal ST-segment elevation, with no changes of the final part of QRS; and (**C**) important ST-segment elevation and distortion of the final part of QRS. **2.** The three types of repolarization abnormalities that may be seen in an acute phase of ST elevation myocardial infarction involving the anteroseptal zone wall: (**A**) tall and/or wide T waves especially seen in right precordial leads; (**B**) abnormal ST-segment elevation, with no changes of the final part of QRS; and (**C**) important ST-segment elevation and distortion of the final part of QRS.



A



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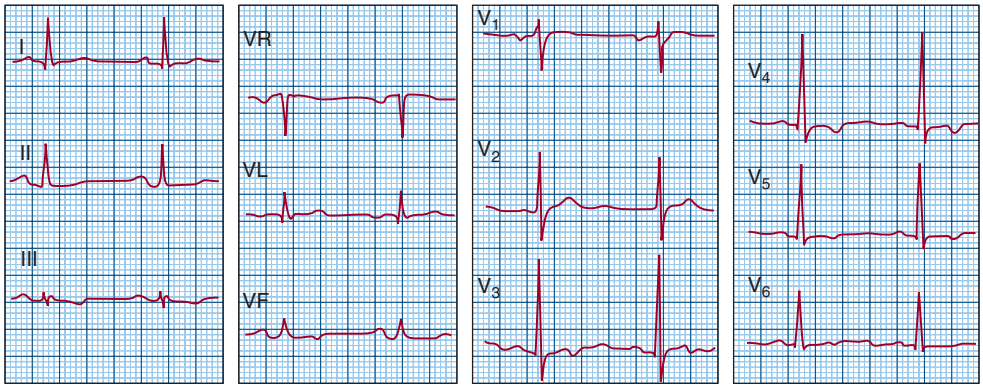


C

FIGURE 12–62. **A.** ST-segment depression in more than eight leads and ST-segment elevation in VR in case of acute coronary syndrome (ACS) caused by involvement of left main coronary artery. Note that the maximum depression occurs in V_3 to V_4, and an ST-segment elevation occurs in VR as a mirror image. **B.** Electrocardiography shows ST-segment depression, especially in precordial leads (V_3-V_6) with positive T wave evident in leads V_3 to V_5 (regional subendocardial ischemia). **C.** Patient with unstable angina (non–ST-segment elevation ACS) with new flattened or slightly negative T wave in various leads.

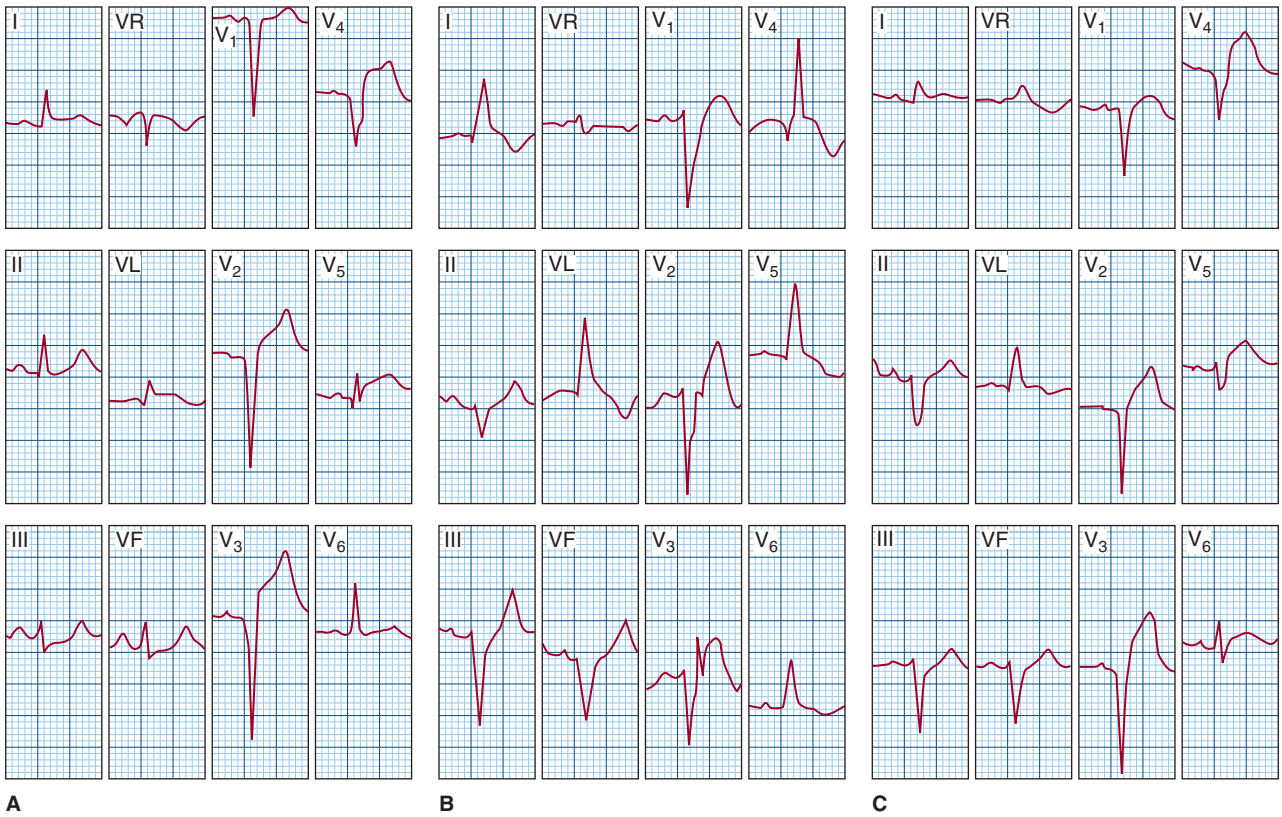


FIGURE 12–63. **A.** Acute myocardial infarction (MI) of anteroseptal zone due to left anterior descending (LAD) occlusion proximal to D_1 (ST-segment depression in III and VF) but distal to S_1 (non–ST-segment elevation in VR and V_1 and non–ST-segment depression in V_6). **B.** After a few hours, complete left bundle branch block (LBBB) appears (see q in I, VL, and V_4 and polyphasic morphology in V_3; see the Sgarbossa criteria; and see concordant ST-segment elevation in I, VL, and V_5-V_6). **C.** The complete LBBB disappears, but superoanterior hemiblock remains with the clear evidence of apical-anterior MI (QS from V_1-V_4 without q in VL and I).

- The oblique position of the heart into the thorax explains that the infarction vector of the inferobasal segment faces V_3 and that the infarction vector of the lateral wall faces V_1 (see Fig. 12–65).
- Therefore, it is clear that the posterior wall usually does not exist because the diaphragmatic wall usually does not bend upward and, even when it does, it cannot originate a prominent R wave in V_1 when necrotic, because activation arrives late. Furthermore, even if necrosis vector exists, it would be directed to V_3-V_4 and not V_1-V_2[82] (see Figs. 12–65 and 12–66; Fig. 12–67).

TABLE 12–11. QRS-Electrocardiogram Changes Associated with Prior Myocardial Infarction (Thygesen[104])

- Any Q-wave in leads V2-V3 ≥ 0.02 s or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 s and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)
- R-wave ≥ 0.04 s in V1-V2 and R/S ≥ 1 with a concordant positive T wave in the absence of a conduction defect

TABLE 12–12. Characteristics of the Necrosis Q Wave or Its Equivalent[a]

1. Duration: ≥ 30 ms in I, II, III,[b] VL,[c] and VF and in V_3-V_6; frequently presents slurrings. The presence of a Q wave is normal in VR. In V1[c] and V_2, all Q waves are pathologic. This is usually also true in V_3, except in case of extreme levorotation (qRS in V_3). However, the presence in two consecutive leads is necessary.
2. Q/R ratio: lead I and II > 25%, VL > 50%, and V_6 > 25%, even in presence of low R wave[c]
3. Depth: above the limit considered normal for each lead (ie, generally 25% of the r wave [frequent exceptions, especially in VL, III, and VF])
4. Even a small Q wave in leads where it does not normally occur (eg, qRS in V_1-V_3)
5. Q wave with decreasing voltage from V_3-V_4 to V_5-V_6
6. Equivalents of a Q wave: V_1: r wave duration ≥ 40 ms and/or r wave amplitude > 3 mm and/or r/S ratio > 0.5

[a]The changes of mid to late part of QRS (low r wave in lateral leads and fractioned QRS) are not included in this list, which mentions only the changes of the first part of QRS (Q wave or equivalent).

[b]The presence of isolated Q in lead III usually is nonpathologic. Check changes with inspiration. Usually in III and VF, Q/R ratios are not valuable when the voltage of r wave is low (< 5 mm).

[c]QS morphology may be seen in VL in a normal heart in special circumstances (eg, very lean individuals with vertical heart), and in V_1, sometimes an absent or tiny r wave may be seen in case of septal fibrosis (no q in V_6).

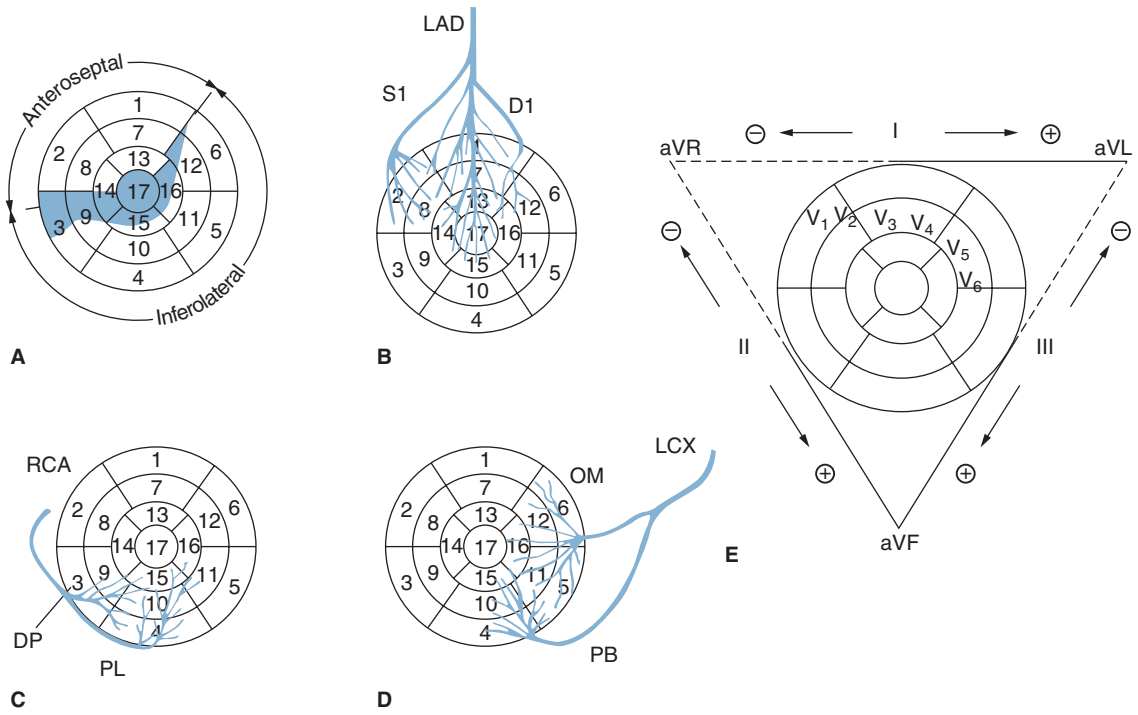


FIGURE 12–64. **A.** Segments of anteroseptal and inferolateral zones and areas of shared perfusion. **B** to **D.** Perfusion of these segments by the corresponding coronary arteries can be seen in a bull's eye perspective. **E.** The correlation with ECG leads. DP, descending posterior; LAD, left anterior descending; LCX, left circumflex artery; OM, marginal; PB, posterobasal; PL, posterolateral; RCA, right coronary artery.

- The ECG can distinguish well MIs of anteroseptal and inferolateral zones (see Fig. 12–66). The specificity of these criteria is very high, especially in MIs of the inferolateral zone, although the sensitivity is lower.

  The most important conclusions of these correlations are as follows:
- R/S of at least 1 in V_1 is never caused by MI of the inferobasal (old posterior) wall, but instead, is always caused by MI of the lateral wall (see Fig. 12–67A–C). Other new criteria for lateral MI (R/S > 0.5) in V_1 that are even more restrictive have been published.[81]
- MIs of exclusive inferior wall always present small r in V_1 (see Fig. 12–67D).
- Q wave in VL (and sometimes in I and small q in V_2-V_3) is not the result of high lateral MI but of midanterior MI caused by occlusion of the first diagonal (Fig. 12–68).
- In the presence of MI of anteroseptal zone with Q wave beyond V_2, the presence of Q in I and/or VL suggests that the infarction is more extensive than the apical zone (Fig. 12–69).
- It is difficult to differentiate the types of MI of anteroseptal zone especially when the location depends on the presence or not of Q wave in V_3 to V_5. This is because the location of electrodes in the appropriate place in these leads may change if the person who performs the ECG does not always follow the same methodology for location of electrodes. Because of this, the SE and SP of Q wave to differentiate distinct MI of anteroseptal zone may change if a non-strict methodology of location of electrodes is used.

D. Quantification of necrosis.[111-113] Selvester et al[111] described a 31-point scoring system based on 50 criteria (eg, presence of Q wave in different leads or R wave in V_1 to V_2 as mirror pattern). This scoring quantifies the amount of infarcted tissue (3% of the left ventricular mass for each point). At the individual level, the standard error of myocardial damage quantification using this score is large, such that its clinical usefulness is limited. The most important cause of errors with this scoring system comes from its inability to quantify basal infarcted areas, mainly the septal and lateral areas. Now, CE-CMR has demonstrated great accuracy in estimating the size of the infarcted mass, which makes this technique the "gold standard" for damage quantification. However, it is still necessary to develop standards that could be consistently applied for CE-CMR measurements.[113]

Myocardial Infarction without Q Wave or Equivalent MI without Q wave or equivalent includes all of the MIs listed in Table 12–13.

The presence of an R wave in V1 in post-MI patients may be equivalent to the Q wave as expression of a mirror image of the Q wave of a lateral MI.

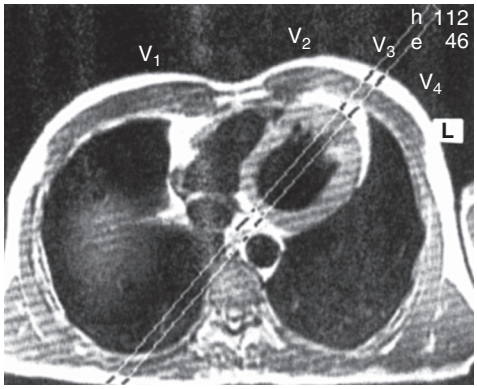
The most typical MIs of this type are the non–Q-wave MIs and the MIs with fractioned QRS complex (Fig. 12–70). In these cases, the diagnosis should be based on the presence of clinical symptoms of angina accompanied by enzymatic changes and repolarization alterations (ST and/or negative T wave).

According to the new classification of MI developed by the European Society of Cardiology and the American College of Cardiology,[106] the presence of increased enzymes allows one to differentiate a non–Q wave MI from unstable angina. The masked Q wave MI in case of wide QRS will be discussed in the following section.

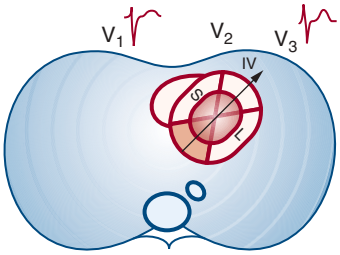
Other characteristics of non–Q wave MIs and other MIs without Q waves are listed in Table 12–14.

Myocardial Infarction in the Presence of Confounding Factors

We will briefly discuss the diagnosis of MI in chronic phase in the presence of ventricular blocks, pacemakers, and WPW preexcitation (see also Acute Coronary Syndrome with Confounding Factors, p. 47 [manuscript page 60]).



A



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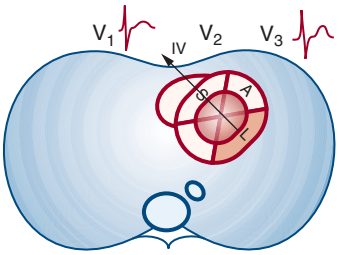


C

FIGURE 12–65. A. Magnetic resonance imaging. Thoracic horizontal axial plane. The four walls can be adequately observed: anterior, septal, lateral, and inferior. The latter is represented by the inferobasal portion of the wall (segment 4 of Cerqueira statement) that bends upward in this case. **B** and **C.** The real anatomic position of inferior wall (inferobasal) and lateral wall infarctions. The infarction vector of inferobasal and mid segment in lean individuals faces V_3 to V_4, and not V_1, and may contribute to the normal RS pattern seen in these leads. On the contrary, the vector of infarction of the lateral wall faces V_1 and may explain RS pattern in this lead. Therefore, prominent R in V_1 is an expression of an infarction of the lateral, not inferior, wall.

Right Bundle Branch Block In the chronic phase, because cardiac activation begins normally, the Q-wave MI may be generated as it is in cases with a normal QRS complex.

Left Bundle Branch Block Because of changes of ventricular activation even if important zones of the left ventricle are necrotic, the overall direction of the depolarization vector continues to point from the right to the left, and the Q wave of necrosis is usually not recorded. However, if the necrosis is extensive, an evident q wave in I, VL, V_5, or V_6 and/or an r in V_1 may be recorded (Fig. 12–71).

Hemiblocks Generally, in the presence of SAH, a Q wave of necrosis may be diagnosed without problems. The loop-hemifield correlation (Fig. 12–72) explains that in the presence of an SAH in lead II, there is no terminal r wave, whereas it is present in lead VR, which is the opposite pattern as occurs in isolated inferior MI. This is an example of how the ECG may provide the same information as the VCG loop. Some authors[114] have considered wrongly that the association of MI and SAH can only be diagnosed with the VCG.

In the presence of IPH, the change of activation may mask or decrease the Q wave in an inferior MI or may mask the Q wave in a small lateral MI.

Preexcitation and Pacemakers In both cases, it may be difficult to diagnose the presence of a Q-wave MI. In the case of pacemakers, the presence of a spike-qR pattern in V_5 to V_6 confers high specificity but low sensitivity as a sign of necrosis.

Electrocardiographic Changes in Ischemia Caused by Increased Demand

ECG changes resulting from ischemia caused by increased demand are explained by a coronary stenosis, resulting from a fixed-stable plaque, that produces at-rest impairment of subendocardium perfusion that is not usually so prominent as to change the basal ECG.[60] Because the vasodilatory capability of the subendocardium is low, it is more vulnerable to myocardial ischemia. Therefore, even though the ECG is frequently normal in the basal state, it presents ST-segment depression during exercise, which is the typical ECG change of subendocardial ischemia without total occlusion. These changes appear especially in leads with a predominant R wave.

Rarely, an ST elevation appears during exercise and is generally caused by coronary spasm.

The ECG changes during exercise angina may be detected by Holter monitoring (Fig. 12–73). They may also be reproduced during exercise testing (see Fig. 12–51B and Chap. 13).

Electrocardiographic Changes in Ischemia Not Related to Atherothrombosis

This section will discuss the ECG characteristics found in some of the clinical setting of myocardial ischemia not resulting from atherothrombosis. For more information, consult Bayés de Luna and Fiol-Sala[60] and Chap. 35.

In many cases, such as in coronary dissection,[115] congenital abnormalities of coronary arteries,[116] or hypercoagulation states,[117] the clinical and ECG changes reflect a clear STE-ACS evolving to a Q-wave MI.

TTS is included in the classification of transitory left ventricular ballooning (Fig. 12–74). This syndrome is difficult to differentiate from STEMI, caused by LAD middle occlusion, because it presents in typical cases the same ECG changes found in this STEMI (ST elevation in V_2-V_3 to V_4-V_5, but without ST elevation in VR).[78,79] However, ECG changes in TTS are often more widespread. The syndrome usually occurs in postmenopausal women, and presentation is typically precipitated by emotional or physical stress.[118-120] In TTS, the ST elevation evolves to very negative T waves (reperfusion pattern), which often is accompanied by a usually transient Q wave (see Fig. 12–74).

Coronary spasm presents the typical pattern of a very transient ST-segment elevation that is often (> 50% in our experience) preceded by a clear tall T wave that vanishes in a few minutes (see Fig. 12–46). Sometimes, the ECG only presents a small ST-segment depression or minimal changes in the T wave.[75,76]

Lastly, some conditions, such as the X syndrome,[121] present an ST depression as the most frequent abnormality, which is often only seen during exercise.

Electrocardiography in Other Heart Diseases

Heart Failure No clear ECG marker is suggestive of heart failure, but almost any ECG diagnostic entity may be found in its presence. Because heart failure with preserved ejection fraction is often found in elderly with hypertension, signs of LVH are the most common ECG changes observed in this type of heart failure. Now, we summarize the most interesting points of the ECG occurring in patients with heart failure with depressed ejection fraction.

In heart failure class III or IV of New York Heart Association, a normal ECG is very rare. Actually, a normal ECG would suggest that the heart failure is caused by high cardiac output states, such as beriberi.

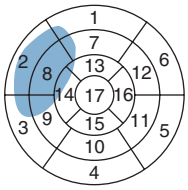
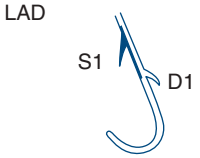
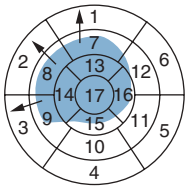
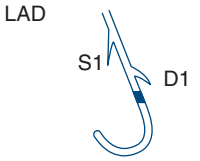
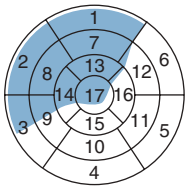
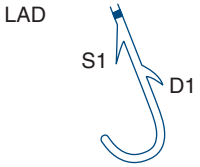
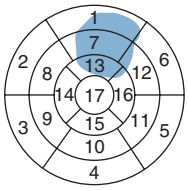
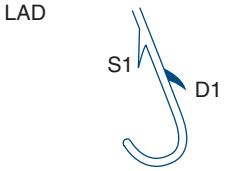
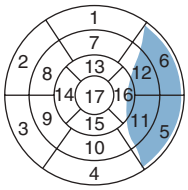
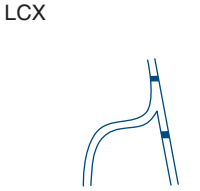
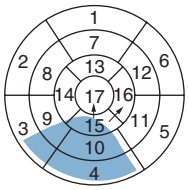
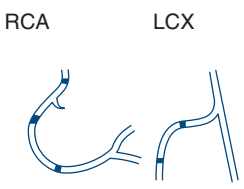
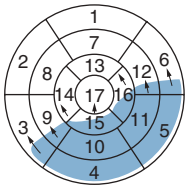
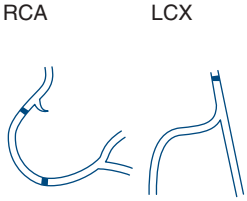
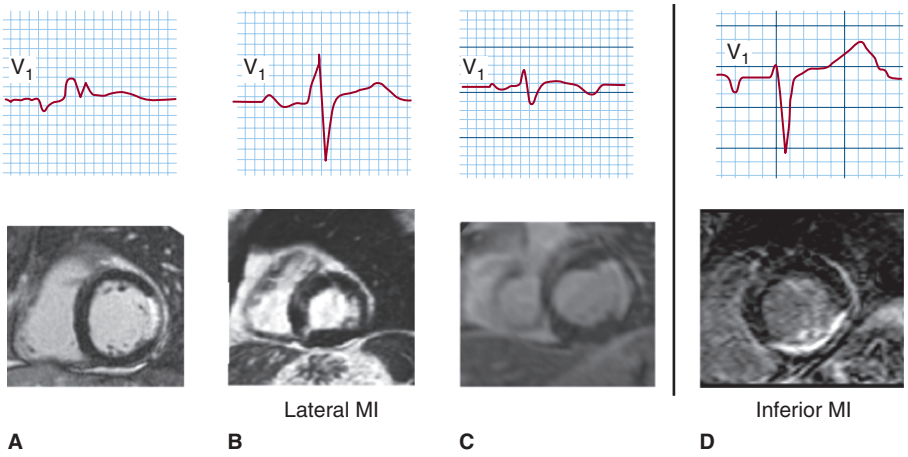
	Name	Type	ECG pattern	Infarction area (CE-CMR)	Most probable place of occlusion
Anteroseptal zone	Septal	A1	Q in V_1-V_2 SE: 100% SP: 97%		
	Apical anterior	A2	Q in V_1-V_2 to V_3-V_6 SE: 85% SP: 98%		
	Extensive anterior	A3	Q in V_1-V_2 to V_4-V_6, I and aVL SE: 83% SP: 100%		
	Mid-anterior	A4	Q (qs or qr) in aVL (I) and sometimes in V_2-V_3 SE: 67% SP: 100%		
Inferolateral zone	Lateral	B1	RS in V_1-V_2 and/or Q wave in leads I, aVL, V_6 and/or diminished R wave in V_6 SE: 67% SP: 99%		
	Inferior	B2	Q in II, III, aVF SE: 88% SP: 97%		
	Infero-lateral	B3	Q in II, III, Vf (B2) and Q in I, VL, V_5-V_6 and/or RS in V_1 (B1) SE: 73% SP: 98%		

FIGURE 12–66. Correlations between the different myocardial infarction (MI) types with the infarction area assessed by contrast-enhanced cardiovascular magnetic resonance (CE-CMR), electrocardiographic (ECG) pattern, name given to the infarction, and the most probable place of coronary artery occlusion. Because of frequent reperfusion treatment, usually the coronary angiography performed in the subacute phase does not correspond to the real location of the occlusion that produced the MI. The gray zones seen in the bull's eye view correspond to infarction areas, and the arrows correspond to their possible extension. D1, first diagonal; LAD, left anterior descending; LCX, left circumflex artery; RCA, right coronary artery; S1, first septal.



A: Unique R wave.
B: R/S ≈ 1 with large S wave and R wave > 3 mm.
C: R/S > 0.5 with small S wave and R wave < 3 mm.

FIGURE 12–67. A, B, and **C.** Different electrocardiogram morphologies of lead V_1 that can be found in lateral myocardial infarction (MI) (the necrosed areas are seen as gray-white with gadolinium enhancement). Note that the cardiovascular magnetic resonance imaging shows that the inferobasal segment (segment 4) is not affected. **D.** On the contrary, the inferobasal segment is completely affected in inferior MI, and the morphology in V_1 is normal rS pattern.

Patients with congestive heart failure are at high risk for malignant arrhythmias and death. We have developed a scoring method for the risk of death.[45] From the ECG point of view, the concomitant presence of LBBB and AF is a marker of a poor outcome.[44,45]

In cases of advanced heart failure, a heart transplantation may be the solution. The ECG of the transplanted heart presents the following characteristics:

1. The P wave of both the receptor and the donor (the latter linked to the QRS) can be seen on the surface ECG (Fig. 12–76). Occasionally, it is necessary to use a right atrial lead to make the P wave of the receptor visible.
2. Generally, the donor P wave is of a higher rate than the receptor P wave because there is no vagal control on the donor heart.
3. Other frequent ECG findings are repolarization alterations, RBBB morphology, interatrial blocks, atrial arrhythmias (flutter and fibrillation), and sinus bradycardia, sometimes severe, with evidence of sick sinus syndrome.[124]

The ECG is abnormal in patients with class IV heart failure, showing significant QRS and ST-T alterations, as an expression of chamber enlargement and/or intraventricular blocks or associated ischemic heart disease ECG changes. Furthermore, sinus tachycardia, interatrial blocks AF, and ventricular arrhythmias are frequent findings (Fig. 12–75).

Characteristically, patients with congestive heart failure often present with attenuated QRS voltage that may be related to pericardial, effusion, or to for peripheral edema.[122] However, attenuation of the amplitude of the P wave is only seen in patients with peripheral edema.[122,123] This observation is useful in the differential diagnosis of these two clinical conditions.

Valvular Heart Disease Usually, the presence of signs of LVE or RVE indicates that the disease is severe. This does not always correlate with the presence of important clinical symptoms.

Mitral stenosis produces a biphasic positive/negative P wave in V_1 and a wide and bimodal P wave in other leads, representing LAE (mitral P wave) (see Fig. 12–22). These patients usually develop AF during the natural history of their disease. Its occurrence is more probable when the P wave is more altered. The presence of a biphasic positive/negative P wave of at least 0.12 second in II, III, and VR is a specific marker of paroxysmal supraventricular arrhythmias at 1 year of follow-up (see Fig. 12–24). ECG signs of LVE are usually seen when there is associated a significant mitral regurgitation or aortic valvular disease.

Patients presenting with tricuspid regurgitation as a consequence of mitral valve disease usually have ECG findings of enlargement of the right chambers. Frequently, the presence of an evident R wave in V_1 but with rS pattern in V_6 is already suggestive of associated RVE (see Fig. 12–26).

Repolarization alterations in leads II, III, and VF and the left precordial leads and ventricular arrhythmias are common in patients with a mitral valve prolapse.

Isolated aortic valve disease, especially in the early evolutionary stages, is usually not accompanied by AF. Its presence should raise the suspicion of associated mitral valve disease.

In the initial stages of LVE caused by aortic valve disease, the QRS complex generally presents a qR with a positive T-wave pattern, which is more evident in aortic regurgitation than it is in aortic stenosis. Over the course of the disease, both aortic stenosis and aortic regurgitation can show a morphology with ST-segment depression called *strain pattern*. The qR morphology remains more frequently in aortic regurgitation, although

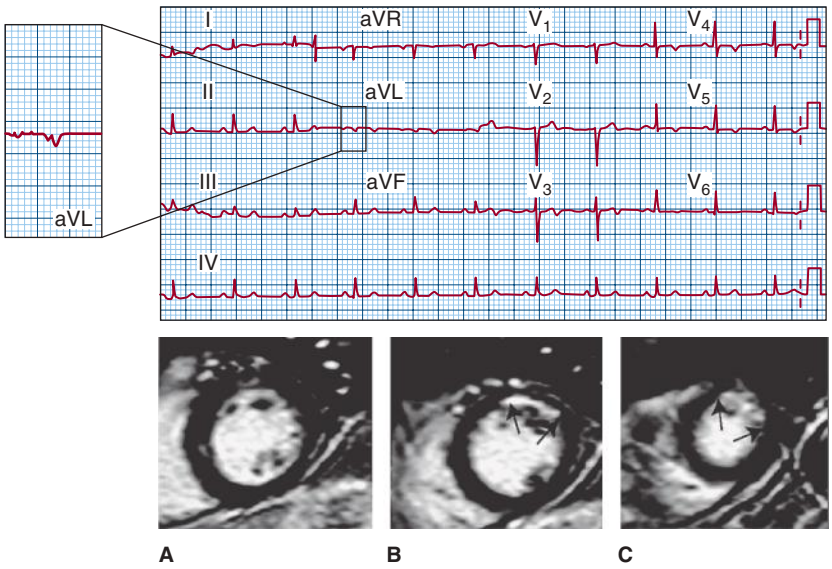


FIGURE 12–68. Correlation electrocardiogram–cardiovascular magnetic resonance in midanterior myocardial infarction (see text).

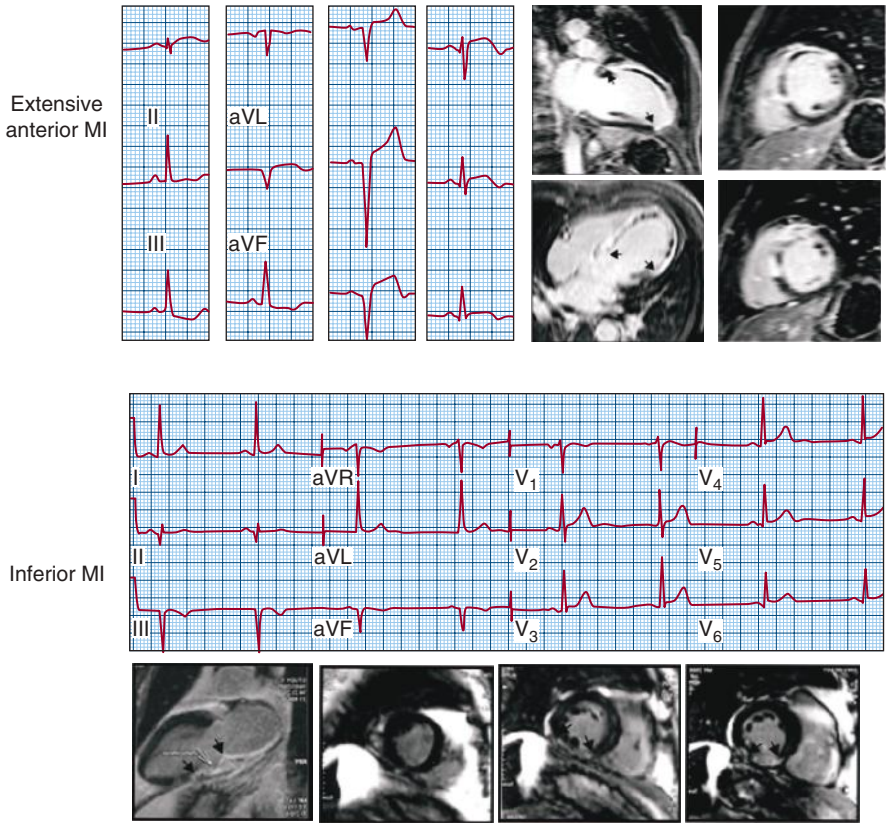


FIGURE 12–69. **Top:** Electrocardiogram (ECG)–cardiovascular magnetic resonance (CMR) correlation in a case of extensive anterior myocardial infarction (MI). **Bottom:** ECG-CMR correlation in case of inferior MI (see text and Fig. 12–67).

the presence of a q wave in V_5 to V_6 depends more on the degree of septal fibrosis (the greater the fibrosis, the smaller the q wave) than on the lesion type (stenosis or regurgitation) (see Figs. 12–29 and 12–30).

Cardiomyopathies In hypertrophic cardiomyopathy, the ECG may present different alterations. In only 5% of the cases, the ECG is normal. The most typical findings, which are characteristic but infrequent, are (1) a pseudonecrosis q wave; (2) the pattern of apical hypertrophic cardiomyopathy in which a giant negative T wave is usually seen (see Fig. 12–29D and E; this finding does not indicate a poor prognosis); and (3) often signs of a classical LVE type.

The presence of AF in hypertrophic cardiomyopathy is generally poorly tolerated and, together with the presence of ventricular arrhythmia in Holter recordings, septal hypertrophy greater than 20 mm, mild or no increase in blood pressure during the exercise test, and a family history of syncope or sudden death are signs of bad outcome.[125,126]

In dilated cardiomyopathy, the ECG usually reflects the signs of atrial and/or ventricular enlargement, but the most characteristic finding is the presence of a low-voltage, notched, wide QRS complex, particularly in the frontal plane (atypical morphologies of LBBB), sometimes with a q wave of pseudonecrosis (see Fig. 12–75).

In advanced cases of restrictive cardiomyopathy, striking patterns (eg, q wave of pseudonecrosis, P wave with large negative component in V_1, prominent R in V_1) may be seen.

In arrhythmogenic right ventricular cardiomyopathy, the most frequent ECG findings are as follows.[1] Atypical RBBB morphology presents in general, a single R of low voltage with notches and/or slurrings in the plateau, and a wide QRS complex (≥ 0.12 second) may be seen in 10% to 20% of cases.[2] Often, there are differences in the QRS complex duration (> 50 milliseconds) between V_1 and V_6, probably caused by an associated right ventricle parietal conduction block.[3] A symmetrical negative T wave is also frequently seen (with or without an RBBB pattern) from V_1 to V_3/V_4.[4] Notches resulting from delayed depolarization caused by parietal block may rarely be observed by the surface ECG at the end of the QRS complex (epsilon wave). These waves may be clearly seen on signal-averaged ECG recordings. Premature ventricular impulses generated in the right ventricle are often seen (Fig. 12–77).[6] The ECG is normal only in 20% of cases.

In myocarditis, the ECG is variable and nonspecific. Sometimes important repolarization alterations, especially deep negative T waves with slight ST-segment changes or even Q waves, may be seen, especially in precordial leads. It is necessary to make a differential diagnosis with IHD, including the Takotsubo syndrome.

Pericardial Disease Although it has been described that idiopathic pericarditis undergoes four typical phases in the evolutionary ECG,[127] often not all of them appear (Fig. 12–78). Remarkably, the ST elevation occurring in the acute phase of pericarditis with chest pain must be differentiated from an ACS. Frequently, the elevation or depression of the PR interval in lead VR, may help in the differential diagnosis (see Fig. 12–25).

Likewise, the repolarization abnormalities (flattened or negative T wave) of chronic pericarditis

TABLE 12–13. Myocardial Infarction without Q Wave or Equivalents

1. Non–Q-wave infarction
   - ST-segment depression and/or negative T wave: new ST ≥ 0.5 mm or new flat or negative T wave (see Fig. 12–51A)
   - Sometimes with the presence of changes (notches, slurrings) in mid to late QRS (fractioned QRS)
2. Infarctions located in areas that do not originate Q wave of necrosis
   - Atria (an isolated location never exists): infarction usually present in an extensive area (see Fig. 12–25B)
   - Basal segments: often secondary to the occlusion of a nonproximal left circumflex artery (LCX) or right coronary artery (RCA) (sometimes with fractioned QRS) (see Fig. 12–70).
   - Right ventricle (usually not isolated): usually accompanied by an inferior infarction. It is secondary to occlusion of a proximal RCA before the takeoff of the right ventricle marginal branches.
   - Microinfarction (enzymatic)
3. Aborted Q wave (see Fig. 12–52B)
   - Acute coronary syndrome with ST-segment elevation (evolving infarction) but with quite early and efficient reperfusion. Troponin levels will tell us whether it is an unstable angina or a non–Q-wave infarction.
4. Q wave of infarctions that disappear during the follow-up (see Fig. 12–56)
5. Masked Q wave: may sometimes show a pathologic Q wave (see Fig. 12–71)
   - Ventricular block
   - Wolff-Parkinson-White
   - Pacemakers

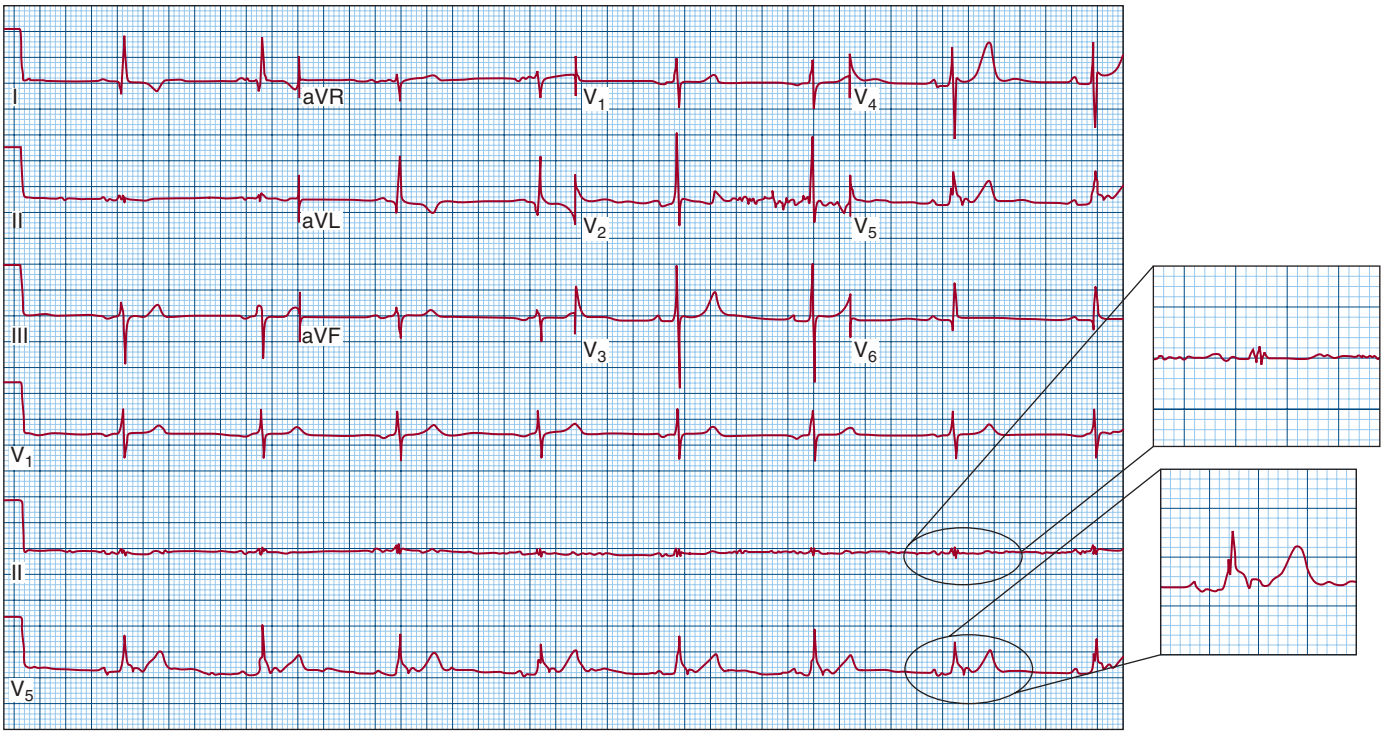


FIGURE 12–70. The electrocardiogram of a patient who has suffered two myocardial infarctions (MIs) of inferolateral zone and two bypass grafting surgeries. The patient presents important left ventricular aneurysm. Observe the presence of RS in V_1, q wave in lateral leads, and abnormal morphology of QRS (fractioned QRS) in several leads (see amplified leads II and V_5).

TABLE 12–14. Pathologic Q Wave Not Secondary to Myocardial Infarction

1. During the evolution of an acute disease involving the heart:
   - 1.1. Acute coronary syndrome with an aborted infarction
   - 1.2. Coronary spasm (Prinzmetal angina type)
   - 1.3. Presence of transient apical dyskinesia that also shows ST-segment elevation and a transient pathologic "Q" wave; probably corresponds to an aborted infarction
   - 1.4. Acute myocarditis
   - 1.5. Pulmonary embolism
   - 1.6. Miscellaneous: toxic agents, and so on
2. Chronic pattern:
   - 2.1. Recording artifacts
   - 2.2. Normal variants: VL in the vertical heart and III in the dextrorotated and horizontal heart
   - 2.3. QS in V_1 (hardly ever in V_2) in septal fibrosis, emphysema, the elderly, chest abnormalities, and so on
   - 2.4. Some types of right ventricular hypertrophy (chronic cor pulmonale) or left ventricular hypertrophy (QS in V_1–V_2, slow increase in R wave in precordial leads, or abnormal "Q" wave in hypertrophic cardiomyopathy) sometimes deep but narrow and usually with normal repolarization.
   - 2.5. Left bundle branch conduction abnormalities
   - 2.6. Infiltrative processes (eg, amyloidosis, sarcoidosis, tumors, chronic myocarditis, dilated cardiomyopathy)
   - 2.7. Wolff-Parkinson-White syndrome
   - 2.8. Congenital heart diseases (coronary artery abnormalities, dextrocardia)
   - 2.9. Pheochromocytoma

must be differentiated from similar T waves found in other processes (see Fig. 12–78C). Characteristically, the flat/inverted T-wave changes in pericarditis are usually seen in more leads, but the deepness is lower than in the negative T wave after Q-wave MI (see Figs. 12–46 and 12–78). However, the difference is not so visible with the negative T wave seen in non–STE-ACS (see Fig. 12–62C).

Characteristically, the more frequent ECG change found in constrictive pericarditis is the presence of an extensive flat or mildly negative T wave, without a mirror image in the frontal plane. However, the same morphology may also be seen after cardiac surgery or in other processes (eg, drugs, alcohol intake).

In some occasions, a striking QRS alternans may be seen in cases of cardiac tamponade (see Fig. 12–88A).

Cor Pulmonale The ECG can be normal in an acute cor pulmonale that is caused by pulmonary embolism, albeit this is not usually the case when the pulmonary embolism is significant. The most valuable diagnostic findings, which are poorly sensitive but highly specific, are as follows: (1) the McGinn-White pattern (S_I, Q_{III} with negative T_{III} pattern; see Fig. 12–28); (2) RBBB, which may be seen in cases of massive pulmonary embolism; (3) a right-directed shift of the ÂQRS; (4) repolarization alterations (negative T wave) in right precordial leads; and (5) sinus tachycardia, which is common in pulmonary embolism, except in elderly patients or in those with sinus node dysfunction.

Acute right heart decompensation, caused by respiratory infection or other processes, can lead to morphologies similar to a pulmonary embolism. Among other alterations, the characteristics are (1) a right-sided shift of the ÂQRS and (2) a transient negative T wave in the right precordial leads.

In chronic cor pulmonale, the ECG may or may not exhibit signs of RVE, although an RVE may exist without an evident ECG alteration. The ECG findings that suggest RVE are (1) ÂQRS in the frontal

FIGURE 12–71. Typical electrocardiogram pattern of necrosis in the presence of left bundle branch block. Observe the pathologic Q wave in I, VL, and V_6; r wave in V_1; and polyphasic morphology in V_4 to V_5.

plane with S_I, R_{II}, R_{III} or S_I, S_{II}, S_{III} patterns or (2) rS morphology in V_1 with an evident S in V_6 (see Fig. 12–26E and F).

In pulmonary emphysema, the ECG may show (1) ÂP between +60° and +90°; (2) a low-voltage P wave in leads I and V_1 and a relatively high-voltage P wave in leads II and III; (3) a QS in lead V_1 and sometimes in V_2 with S in V_6; (4) a low-voltage QRS in the frontal plane; and (5) ÂQRS somewhat to the right or with an S_I, S_{II}, S_{III} pattern.

Arterial Hypertension The ECG changes found in arterial hypertension are caused by LVE. In general, there is a strong correlation between the severity of arterial hypertension and the ECG findings. With treatment, these changes may decrease or revert to normal.

Occasionally, a primary factor (drugs or ischemia) modifies the repolarization that already presented a secondary repolarization abnormality (strain) due to LVH. Then, a mixed repolarization pattern is seen.

The criteria for the diagnosis of LVE in arterial hypertension that display a higher sensitivity (80%) include RV_5 to RV_6 greater than 26 mm and total QRS voltage in 12 leads greater than 120 mm.[36] Their specificity, however, especially for the first criterion (20%), is low. The sensitivity of the ECG criteria increases in proportion with the prevalence of LVH in the study population (Bayés theorem).[128] The utility of the ECG to diagnose LVE is high in severely hypertensive patients and low in the general population.

Note the following regarding the importance of ECG as a marker of prognosis in patients with hypertension. In patients with hypertension and ECG with LVH, ECG at entry has a worse prognosis if new ST abnormalities develop.[129] The presence of nonspecific left ventricle repolarization changes in hypertensive patients represents a risk factor for IHD.[130] The regression of LVH detected by Cornell criteria during antihypertensive treatment is associated with fewer hospitalizations for heart failure.[131] The presence of ventricular arrhythmias is a marker

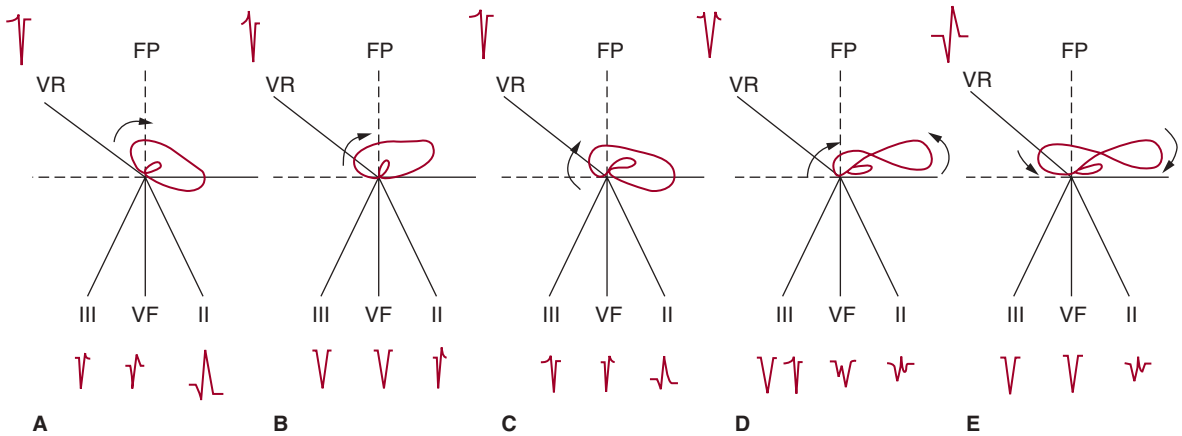


FIGURE 12–72. Vectorcardiography (VCG) loops in inferior myocardial infarction (MI) (**D** and **E**) associated with superoanterior hemiblock (SAH). In these latter cases, because of special rotation of the QRS loop, the final part of the loop falls always in the negative hemifield of II. Therefore, the morphology of QS (qrs) without terminal r in at least one of three inferior leads (II, III, and VF) (although a qrs morphology may be seen) and with the presence of terminal r in VR favors the presence of associated SAH. In the absence of SAH, even if the entire VCG loop falls above the x-axis (lead I) (**B**), there would be terminal r at least in II, but never terminal r in VR (**A** to **C**).

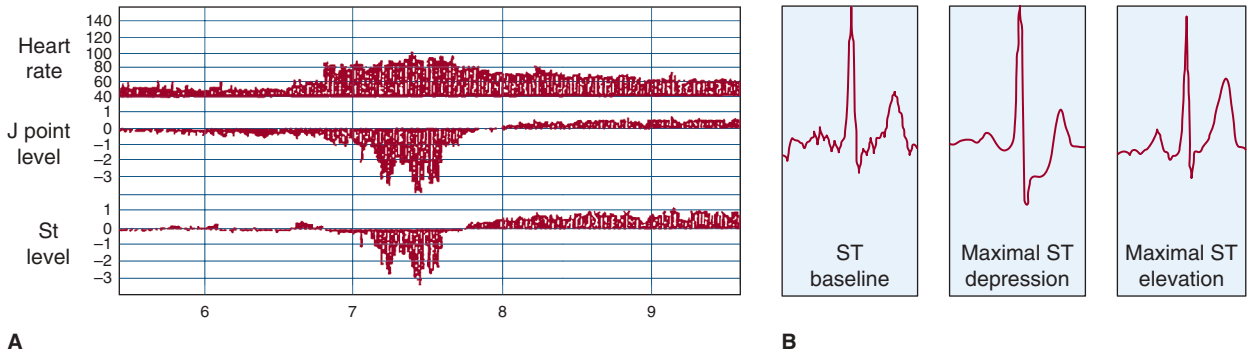


FIGURE 12–73. Changes of the ST segment in a patient with exercise angina. **A.** The trend of ST changes and heart rate. **B.** The different morphologies of ST.

of poor prognosis in hypertensive patients. It has been demonstrated[132] that both LVE and asymptomatic ST depression (silent ischemia) are independent predictors of ventricular arrhythmias in asymptomatic hypertensive patients.

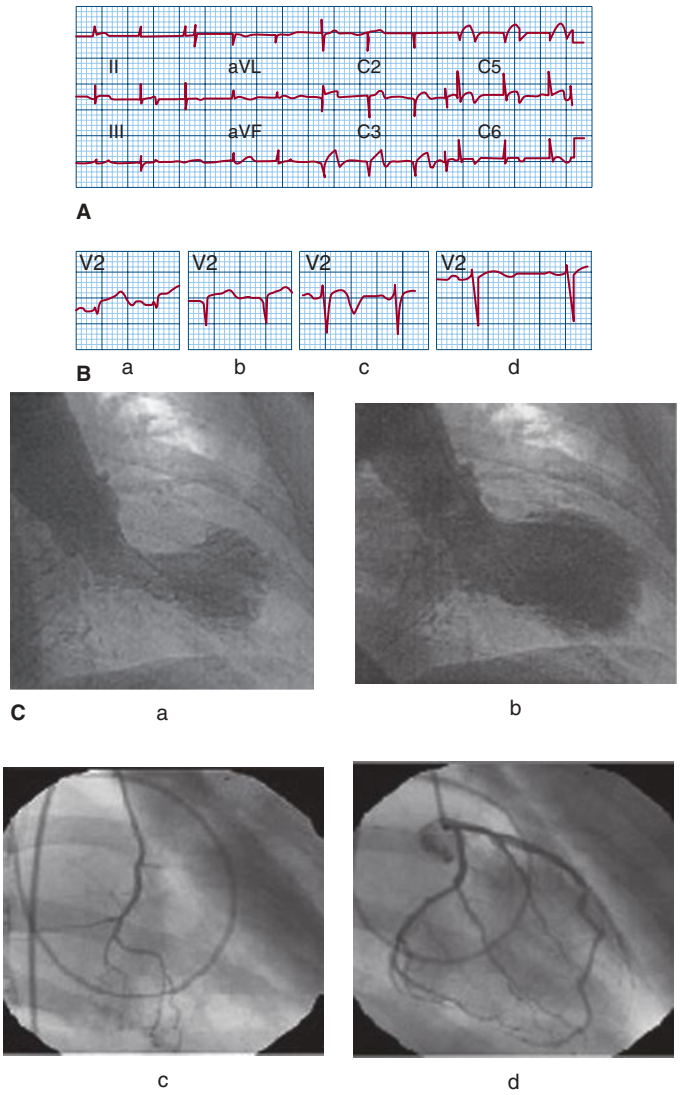


FIGURE 12-74. (**A**) Twelve-lead electrocardiogram (ECG) in subacute phase in a patient with typical transitory apical ballooning (Takotsubo syndrome). (**B**) ECG changes in V2 during the period of 3-4 days (a-d). Note the ECG pattern from ST elevation with Q wave to rS with deep negative T waves. (**C**) Typical angiographic image (a, b) and normal coronary tree (c, d).

Congenital Heart Disease A comprehensive review of ECG alterations in congenital heart disease is beyond the scope of this book. Furthermore, new imaging techniques are more useful for the diagnosis of congenital heart disease than ECG. However, there are some ECG signs that are highly suggestive of specific congenital heart diseases that are presented here.

Atrial Septal Defect (1) Presence of rsR′ pattern in lead V_1 with QSR < 0.12 second; (2) lack of sinus arrhythmia if the ASD is large; (3) in ostium primum–type ASD, ÂQRS is shifted sharply to the left; and (4) AF in adults.

Ventricular Septal Defect (1) Normal or almost normal ECG in small ventricular septal defects (VSDs); (2) signs of biventricular hypertrophy in large VSDs with hyperkinetic pulmonary hypertension, sometimes with high voltages in the intermediate precordial leads (Katz and Watchel morphology); and (3) tall R in lead V_1 when significant pulmonary hypertension is present (Eisenmenger syndrome).

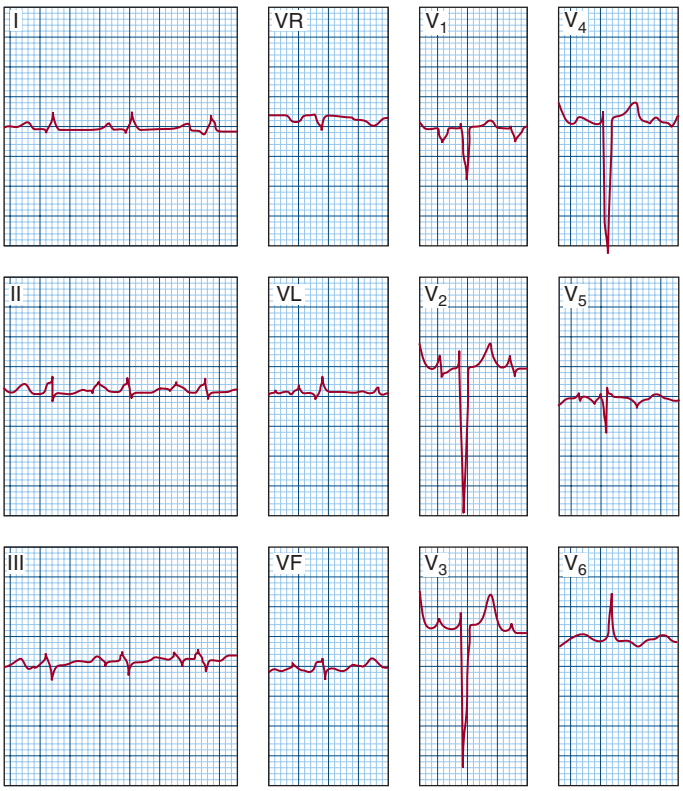


FIGURE 12–75. Patient who had dilated cardiomyopathy. The ECG shows the morphologic characteristics observed in this situation (sinus tachycardia, low voltage in FP, important alterations of P and QRS-T).

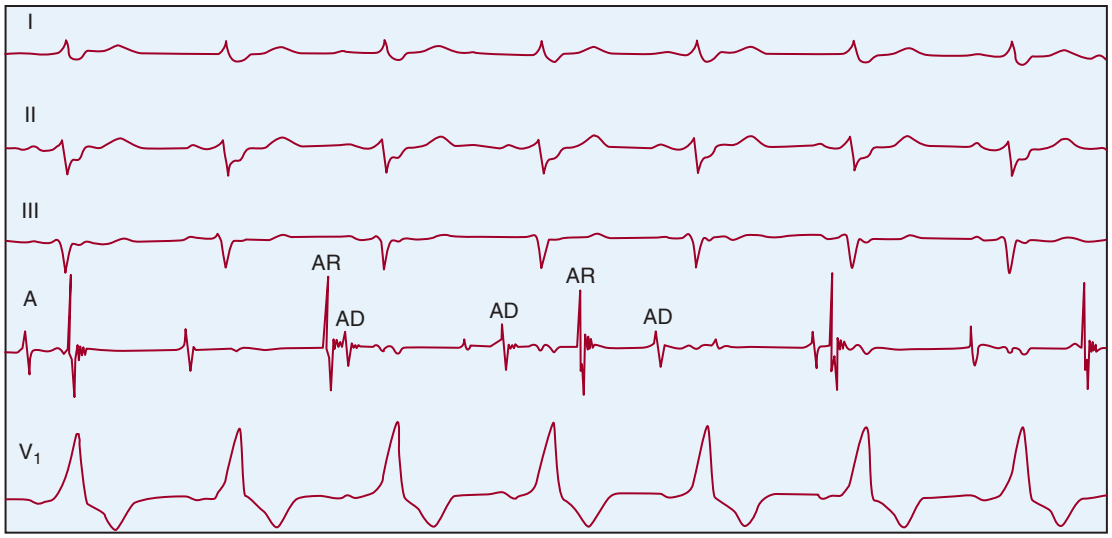


FIGURE 12–76. Leads I, II, III, and V1 and right atrial leads (A) of a patient who underwent a heart transplantation. Two atrial waves are observed, the wave of the patient (AR) and the wave of the donor (AD); the latter maintained cardiac rhythm.

Tricuspid Atresia (Fig. 12–79A) (1) ÂQRS sharply to the left; and (2) P wave of RAE.

Ebstein Disease (Fig. 12–79B) (1) High-voltage P wave, sometimes with large negative mode in V_1; (2) atypical right ventricular block morphology often with many deflections (rsr′s′) and sometimes with slight ST elevation in V_1 to V_2; (3) relatively often WPW-type preexcitation; (4) and occasionally, long PR interval.

Stenotic Lesions Stenotic lesions of the right heart (pulmonary stenosis and tetralogy of Fallot) and the left heart (aortic stenosis and coarctation of aorta) produce enlargement of the respective chambers when they are severe enough. Tight pulmonary stenosis presents R morphology in V_1 to V_2/V_3 (see Fig. 12–27A), and the tetralogy of Fallot pattern shows an R wave in V_1 and rS morphology in V_2. In newborns, RVE is observed in severe pulmonary stenosis and may

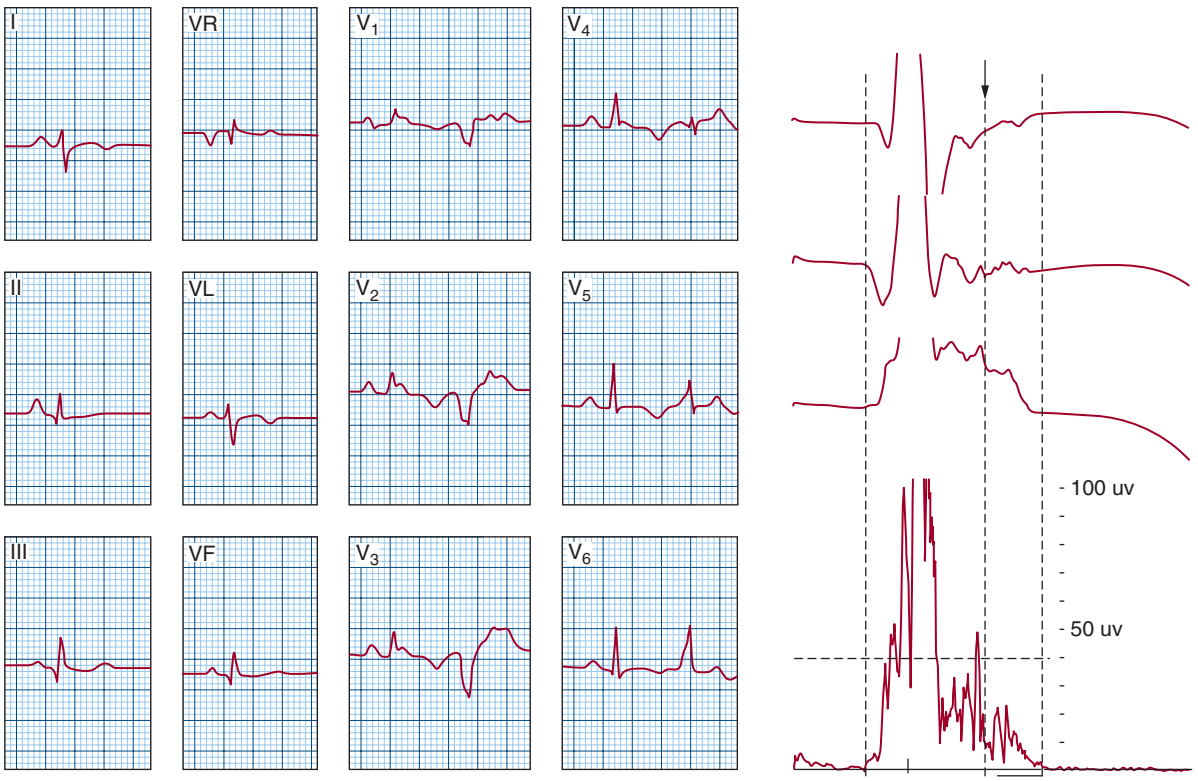


FIGURE 12–77. A 20-year-old patient with arrhythmogenic right ventricular dysplasia (ARVD). Note the pattern of atypical right bundle branch block, negative T wave in the V_1 to V_4 leads, and premature ventricular complexes of the right ventricle. QRS duration is much longer in V_1 to V_2 than in V_6. On the right, very positive late potentials are seen in the signal averaging electrocardiogram.

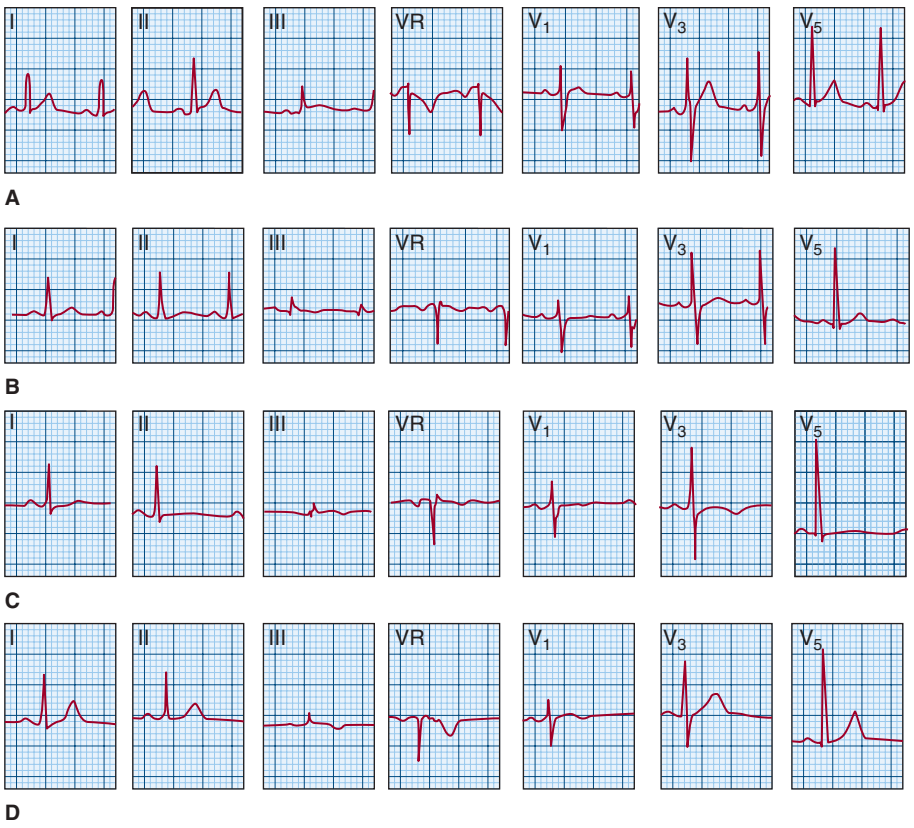


FIGURE 12–78. A 43-year-old man with pericarditis. Four examples of the evolutionary electrocardiogram are shown. Strips A, B, C, and D were recorded 1, 8, 10, and 90 days, respectively, after the onset of the event: (**A**) ST elevation is convex with respect to the isoelectric line, (**B**) flattening of the T wave, (**C**) inversion of the T wave, and (**D**) normalization. However, this sequence often is not seen.

- The presence of a delta wave requires Ebstein disease to be ruled out.
- A positive T wave in leads V_1 and V_2 from day 2 of life may suggest RVE.
- The presence of an R wave (not qR), possibly tall (> 15 mm), may be seen in newborns without congenital heart disease.

Channelopathies The concept of channelopathies includes heart diseases without apparent structural involvement. They are caused by mutations in certain genes that generate defects in the ionic transport through the channels. The first manifestation of the disease may be syncope or even sudden death resulting from ventricular tachycardia/ventricular fibrillation.

Characteristically, in the best-known channelopathies (long and short QT syndrome and Brugada syndrome), there is an important phenotype ECG expression. Figure 12–81 shows examples of the typical ECG pattern in case of long QT syndrome,[16] short QT syndrome,[18] and Brugada syndrome type 1 and 2[133-136]. In Fig. 12–81C, we may see how the descendent arm of r' allow to perform the differential diagnosis between Brugada pattern type 2 and many other cases with r' such as athletes. Figure 12–82 shows an algorithm (Baranchuk algorithm)[136] that allow to perform the differential diagnosis of all cases with r' in V1.

be accompanied by a positive T wave. After surgery for the tetralogy of Fallot and other congenital heart diseases, an advanced RBBB pattern frequently appears as a result of a distal lesion of the specialized conduction system caused by the surgery. In this case, the distance from the onset of ventricular depolarization to the right ventricular apex (V-apex) is not prolonged, in contrast to what occurs in cases of proximal block. Congenital aortic stenosis, even if it is severe, does not usually result in a typical LVE pattern within the first years of follow-up. However, over time, it may advance to the so-called *strain pattern* (see Fig. 12–30A).

Mirror-Image Dextrocardia The ECG is typical (Fig. 12–80). The same morphology may be recorded with the inverted limb leads and precordial leads located on the right side. This explains the negative P wave in lead I and the decreasing wave voltages of the precordial leads.

Electrocardiogram of the Newborn: Suspicion of Congenital Heart Disease The most interesting features of the newborn ECG with possible congenital cardiac malformation are as follows:

- Many neonates with congenital cardiac malformation exhibit a normal ECG on the first day of life. Thus, it is necessary to record the ECG sequentially.
- In a newborn with a left-sided QRS (beyond +30°), AV cushion defect, tricuspid atresia, and a single ventricle should be considered as probable causes.
- AV block may appear in VSD and corrected transposition. However, advanced congenital block may be an isolated finding without any associated heart disease.

ELECTROCARDIOGRAPHY IN SPECIFIC SITUATIONS

Other Diseases

In this section, the most striking ECG findings that may be found in the following diseases are briefly described.

Cerebral Disease Repolarization alterations appear with certain frequency, particularly in subarachnoid hemorrhage, and may include very negative T waves or wide-based positive T waves (Fig. 12–83) or ST-segment changes (depression or elevation).

Endocrine Disease ECG signs typical of myxedema are a low-voltage QRS complex, bradycardia, and flattening or inversion of the T wave. Some common features found in hyperthyroidism are sinus tachycardia and supraventricular arrhythmias, including AF.

Diabetes Diabetes frequently causes repolarization alterations. It has been demonstrated that these are more common in patients with coronary heart disease with type 2 diabetes than in patients with coronary heart disease without diabetes.

Miscellaneous There are many other pathologic processes in which ECG abnormalities range from minor repolarization alterations (eg, hepatic cirrhosis, anemia) to bundle branch block and/or necrosis patterns of some systemic diseases (eg, amyloidosis, hemochromatosis) and pheochromocytoma. Characteristically, the ECG pattern of restrictive cardiomyopathy is infiltrative, including amyloid, sarcoid, and Gaucher disease, or noninfiltrative, including hemochromatosis and Fabry disease. It presents in advanced phase, with some striking ECG patterns

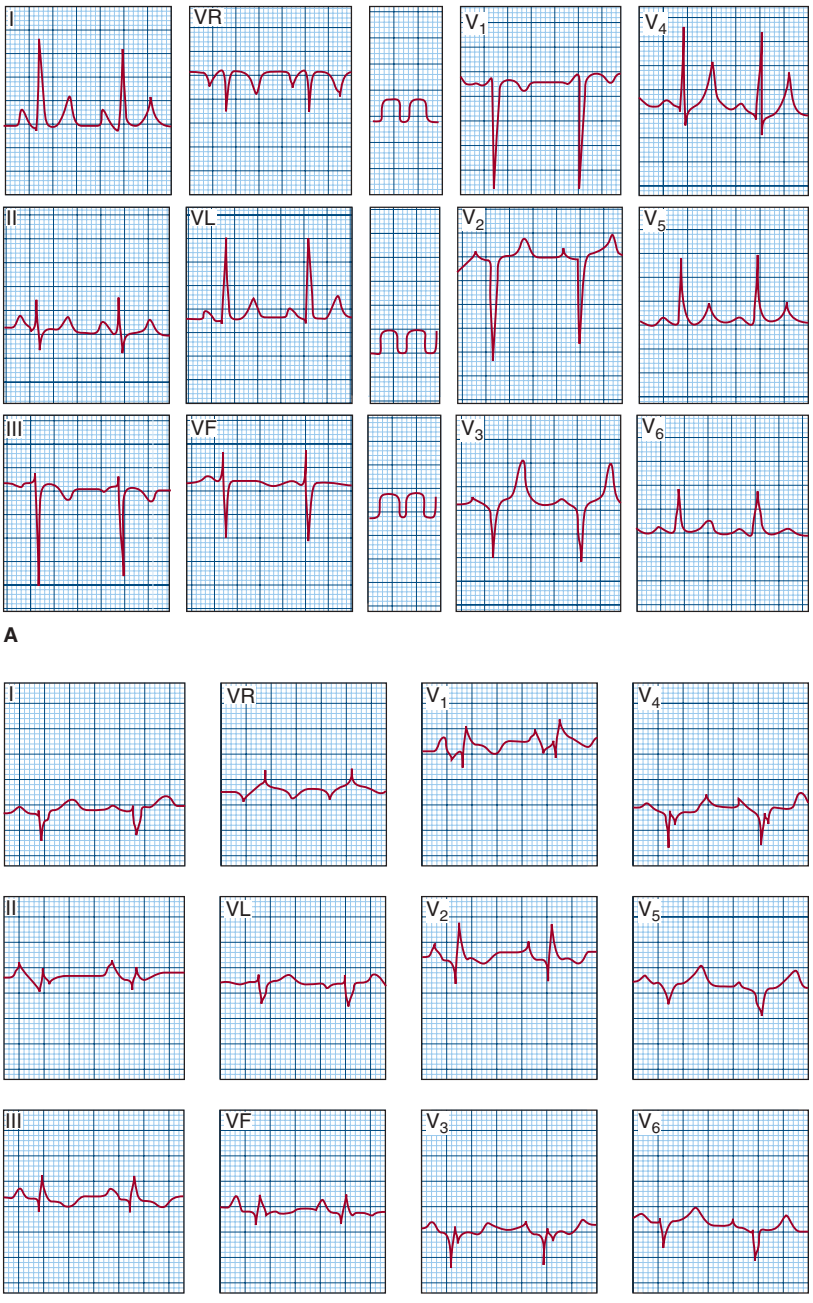


FIGURE 12–79. A. Typical electrocardiogram (ECG) of tricuspid atresia. Note the hyperdeviation of the QRS axis to the left and the signs of right atrial and left ventricular enlargement. **B.** A characteristic ECG of Ebstein disease. Note the atypical right ventricular block morphology and the important atrial pathology suggestive of right atrial enlargement.

that include (1) pseudonecrosis "q" wave; (2) low or normal QRS voltage in spite of Left ventricle hypertrophy (LVHf), (3) P wave with clear negative component in V1, of LAE, and (4) sometimes clear repolarization abnormalities.

In some neuromuscular diseases, such as Duchenne disease and Friedrich ataxia, patients may present ventricular enlargement an negative T wave.

Electrolyte Imbalance

The most remarkable ECG alterations in electrolyte imbalance are caused by changes in serum potassium levels. In Fig. 12–84, typical examples of hyperkalemia and hypokalemia are seen.[137]

In hypocalcemia, the QT may be prolonged at the expense of the ST segment, and in hypercalcemia, the QT may be short.

Hypothermia

Hypothermia produces typical ECG changes (Fig. 12–85),[138] the most frequent being baseline irregularities, slow heart rate, prolongation of the PR and QT intervals, and most typically, slurring of the final part of the QRS complex, called the J or Osborne wave.

Athletes

In trained athletes, the ECG is often altered, which suggests chamber enlargement (tall and/or bimodal P wave, rsr′ pattern in lead V_1, and high-voltage qR in leads V_5-V_6) (see Figs. 12-81C; Fig. 12–86).

Occasionally, there are prominent repolarization alterations that cannot be explained by myocardial ischemia. However, as already stated, athletes who experienced sudden death, in whom either hypertrophic cardiomyopathy (in younger athletes) or coronary heart disease were found on necropsy, often had these striking patterns. Echocardiography detects the presence of LVE and RVE, and in some cases, magnetic resonance imaging is useful.

Different types of arrhythmias are also common (eg, first- or second-degree AV block, bradycardia, ventricular premature impulses). The prognosis is usually good, but in the presence of heart disease or WPW syndrome, each case should be carefully evaluated. For preexcitation, accessory pathway ablation should be recommended.

In Table 12–15, various ECG findings are reported; these range from benign findings related to training (A) or those that may represent markers of disease (B) (see Fig. 12–86).

Alcoholism

Alcohol, even when ingested occasionally by healthy subjects, may produce transient repolarization alterations. Chronic alcoholics, particularly those with heart disease, may have persistent repolarization alterations, showing T waves taller than normal or, more characteristically, a low-voltage, bimodal, or slightly negative T wave (Fig. 12–87). Dilated cardiomyopathy may also be present.

However, it has been demonstrated that alcohol can trigger different arrhythmias (particularly premature atrial and ventricular impulses, which may disappear with abstinence). Small quantities of alcohol may be protective against IHD, but larger quantities are harmful.

Electrical Alternans

Electrical alternans is characterized by the alternans of the complex-to-complex morphology of the ECG. The electrical alternans of the QRS complex can be seen in sinus rhythm (for example, in cases of cardiac tamponade) (Fig. 12–88A) and during a crisis of paroxysmal tachycardia with narrow QRS complex. It usually occurs in an AV junctional reentrant tachycardia with participation of an anomalous pathway in the circuit (Fig. 12–88E).

The cases of electrical alternans at higher risk for malignant ventricular arrhythmias are those that appear during repolarization (ST-T waves). Although the detection of microscopic electrical alternans of the

FIGURE 12–80. A. A typical electrocardiogram (ECG) of a patient without heart disease but with mirror-image dextrocardia. **B.** The normalized ECG (see text).

T wave has been described as a risk marker for sudden death in postinfarction patients, we will now discuss those cases in which electrical alternans is visible in the surface ECG. In our experience, there are three well-defined clinical situations that show evident ST-T alternans in the surface ECG, and they are also accompanied by VT-TP/VF. These are as follows: (1) alternans of the T wave that often precedes a crisis of TdP in patients who have a long QT syndrome (Fig. 12–88D); (2) alternans of the T wave, often with acquired long QT, that can be seen in cases of shock and/or important ionic disturbances (Fig. 12–88C); and (3) alternans of ST-T as an expression of severe and hyperacute ischemia that can be seen in cases of ACS affecting a great ischemic area and also in cases of coronary spasm of a proximal artery (Fig. 12–88B).

Administration of Drug Therapy

Many drugs used in the treatment of heart failure such as diuretics and digitalis can induce changes in the ECG, some of them very typical (digitalis effect) (see Fig. 12–54B, a). Also recently has been described that arrhythmias, especially AF and ventricular tachycardia, may occur in relation to the administration of some chemotherapeutic drugs. In addition, the presence of QT prolongation and different bradyarrhythmias has been reported.[72]

Moreover, many antiarrhythmic agents may produce arrhythmias (proarrhythmic effect), which may lead to dangerous consequences. In fact, the Cardiac Arrhythmia Suppression Trial (CAST)[138] demonstrated that in postinfarction patients a control group without

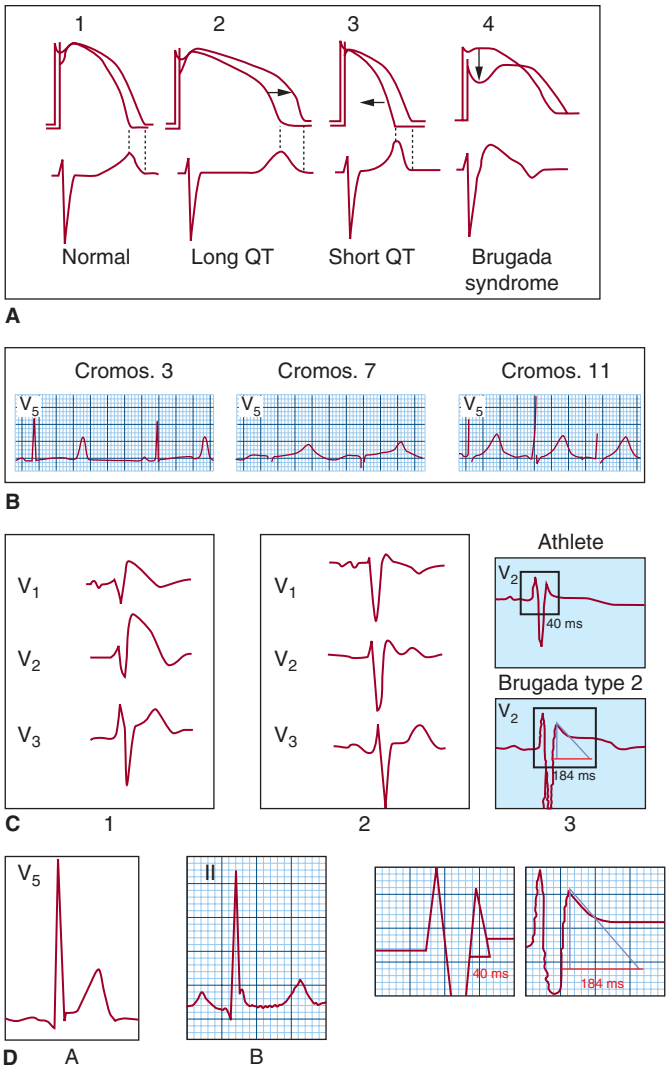


FIGURE 12–81. A. Schematic representation of normal action potentials from epicardial and subendocardial zone and the following QRS morphologies: (1) normal; (2) long QT syndrome; (3) short QT syndrome; and (4) Brugada syndrome. **B.** The genotype-phenotype electrocardiogram expression of long QT syndrome in the three more typical types of the syndrome. See the long QT and delayed peaked T wave in long QT-1 (cromosomos 3; cromos. 3), the broad T wave in long QT-2 (cromos. 7), and abnormal T wave in long QT-3 (cromos. 11). **C-1.** The typical morphology of Brugada pattern 1. **C-2.** The most frequent typical morphology of Brugada pattern 2. **C-3**. See the differences on the ST descending slope in athletes (3 above) and patients with Brugada type 2 pattern (3 below). **D.** See typical pattern of benign early repolarization (A) and potentially malignant pattern (recorded in inferior leads and with flat ST segment). The J wave is much less evident that in case of hypothermia (see Fig. 12–85).

antiarrhythmic agents (eg, quinidine, flecainide) presents less mortality after myocardial infarction. This means that physicians have to be cautious in the prescription of antiarrhythmic agents, especially of type I agents, in patients with ischemic heart disease or heart failure.

Anesthesia and Surgery

A preoperative ECG is recommended to rule out possible surgical complications, especially in adults. However, the ECG tracing should be examined together with other preoperative studies (eg, blood test, radiologic or clinical assessments), and the patient's status should be evaluated to correlate the information. A single normal ECG recording should not be considered sufficient to exclude heart disease.

In patients with IHD, it is necessary to carefully evaluate both the clinical and ECG abnormalities, because their risk to receive anesthesia and surgery varies from patient to patient. Thus, an MI within 2 to 3 months prior to surgery represents a clear risk, and it is a relative contraindication for any operation other than an emergency procedure. The risk is minor in patients with stable angina but clearly increases in those with recent unstable angina. Heart failure should be stabilized before surgery. When a pacemaker is indicated before a surgical intervention, it is usually advisable to implant a permanent pacemaker because the clinical situation would usually not disappear after surgery.

The ECG is a valuable tool during anesthesia and surgery, but it requires continuous monitoring to be useful. The ECG recorded in the operating room differs in two aspects from the conventional ECG. Artifacts are common, and there are rapid changes of morphology due to the effect of drugs, surgery, and anesthesia (eg, intubation, changes in position). In healthy individuals, there are ECG changes during surgery, albeit minimal, even in the absence of hypoxia or electrolyte imbalance. Furthermore, different arrhythmias are occasionally seen.

Continuous ECG monitoring is especially important for the detection of risk for a cardiac arrest, as well as to determine whether cardiac arrest results from ventricular fibrillation or asystole. The average incidence of cardiac arrest during anesthesia is less than 1 in 5000 patients, or more than 1 in 1000 patients if the patients are of advanced age or at high risk.

Generally, alarming signs appear prior to cardiac arrest, ranging from venous thromboembolism to sinus bradycardia. Hypoxia, hypotension, and hypercapnia may also be present. Anesthesia is considered to be a contributing factor in 20% of the cases of cardiac arrest during surgery.

The presence of arrhythmias during anesthesia usually indicates an abnormality that must be corrected. Antiarrhythmic agents should be given only after appropriate measures have been taken to correct hypoxia, hypercapnia, and hypotension and once the effects of reflex stimulants, such as mesenteric or pleural traction, have been excluded. Whenever required, antiarrhythmic treatment should be carefully administered. In critical situations, electrical cardioversion should be performed. The arrhythmias that were present before surgery, particularly premature ventricular impulses, may decrease in a properly anesthetized patient and are usually less common with general anesthesia than with epidural anesthesia.

The following ECG changes during anesthesia and surgery are signs of significant concern: (1) tachycardia with a rate greater than 160 beats/min, (2) bradycardia with a rate less than 45 beats/min, (3) bigeminal rhythm, (4) multifocal ventricular impulses, (5) marked repolarization alterations (ST-segment depression or elevation, T-wave inversion, or tall and peaked T waves with long QT interval), and (6) appearance of advanced bundle branch block or AV block.

Regarding postoperative ECG, patients with heart disease would be electrocardiographically supervised for the first week after surgery. The ECG should be repeated 24 hours after surgery in patients with coronary heart disease, arterial hypertension, peripheral vascular disease, or alterations in the baseline ECG. Approximately 2% to 4% of patients with IHD develop postoperative MI, often without chest pain. In high-risk cases, ECG monitoring should continue for a while after surgery.

During the postoperative period, an ECG would be urgently required in the following situations: (1) unexplained hypotension; (2) signs of heart failure (gallop rhythm and others); (3) appearance of arrhythmias, tachycardia, or bradycardia; (4) pain in the chest, arms, or back; and (5) dyspnea or syncope. Serial ECGs should be obtained to exclude the possibility of MI, even if the first recording was normal.

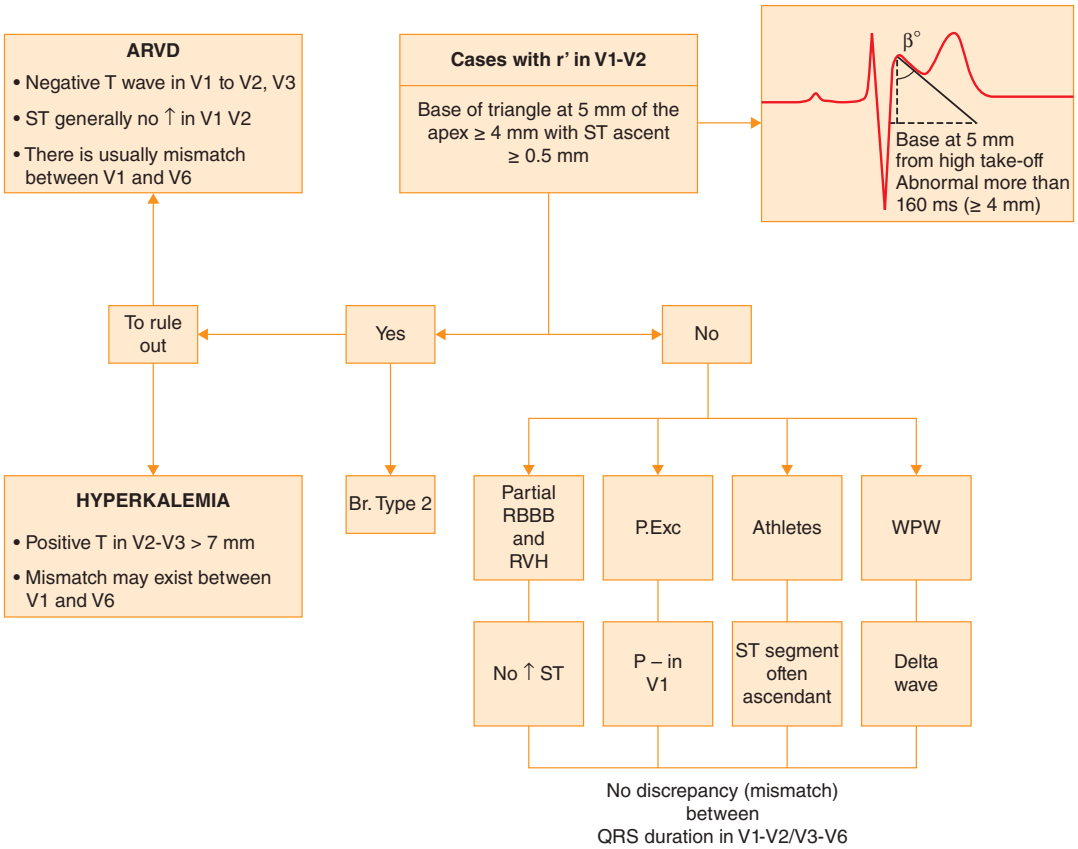


FIGURE 12–82. Proposed diagnostic algorithm (Baranchuk algorithm) for patients with r′ in leads V1-V2 with the most important differential diagnostic clues, including how to measure the characteristic of r′. ARVD, arrhythmogenic right ventricular dysplasia; P.Exc, Pectus Excavatum; RBBB, right bundle branch block; RVH, right ventricular hypertrophy WPW, Wolff-Parkinson-White (syndrome).

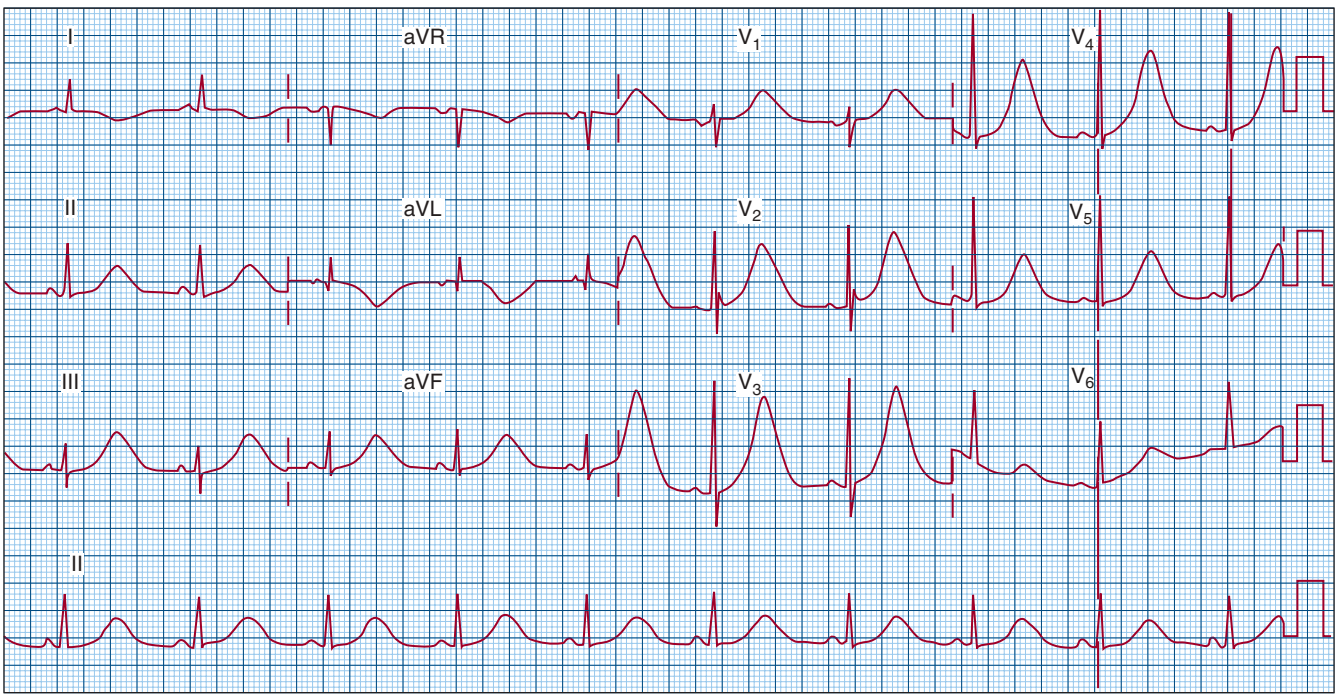


FIGURE 12–83. A 30-year-old patient with subarachnoid hemorrhage. The electrocardiogram shows an important repolarization alteration—a very long QT, mainly at the expense of a wide T wave, which is very positive in precordial leads but also negative in I and VL.

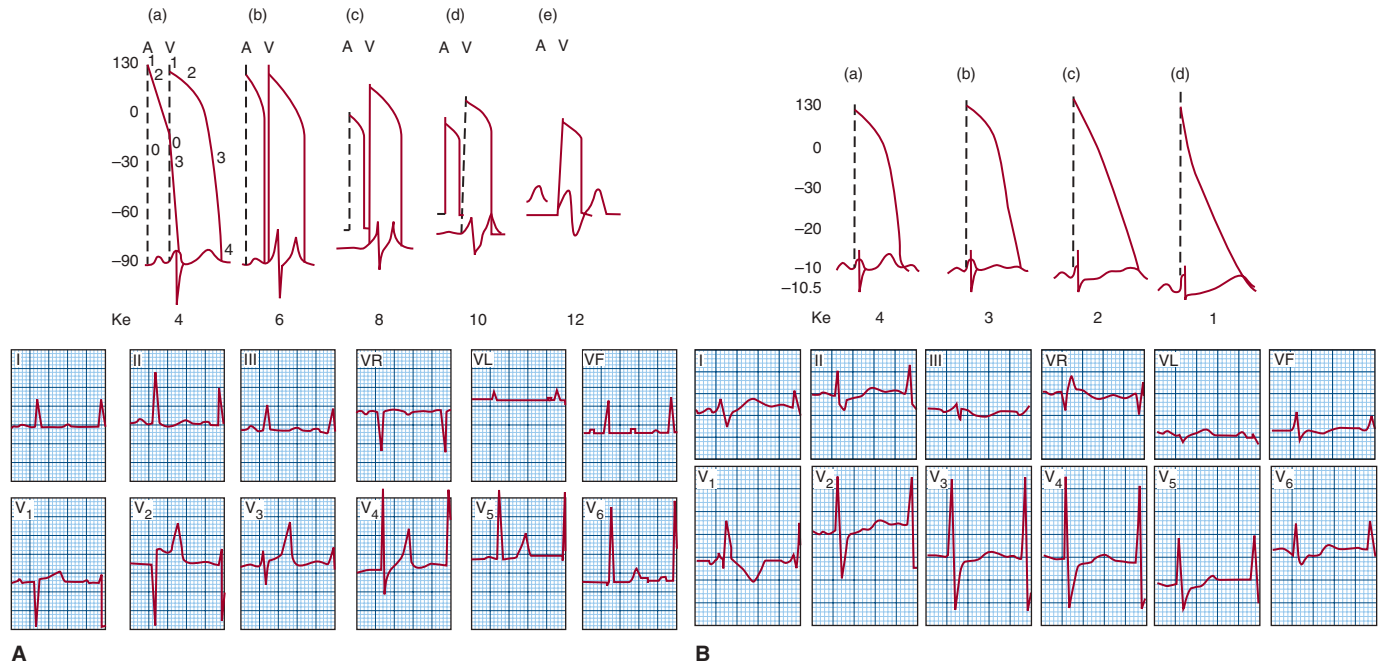


FIGURE 12–84. A. Above: Electrocardiographic (ECG) alterations observed in successive stages of hyperkalemia. The atrial and ventricular action potential has been superimposed. With the increase of potassium (Ke), the level of diastolic threshold potential (DTP), height of phase 0, and its rate of increase (the points on the dotted line are closer together) are all decreased. The surface ECG shows that the QRS duration is increased, and the P wave disappears. Below: A 20-year-old man with chronic renal failure who had periodic hemodialysis during the 2 years prior to the recording. There is severe hypertension (210/130 mm Hg) and an elevated potassium level (6.4 mEq/L). Note the tall and peaked T wave and elevation of the ST segment in V_2 and V_3. In leads I, II, and III, QT is relatively long at the expense of the ST segment caused by associated hypocalcemia. **B.** Above: ECG alterations observed in successive stages of hypokalemia. The ventricular action potential has been superimposed. On the left is the DTP value, and below is the Ke level. Note how the action potential duration progressively increases at the expense of a decrease in the velocity of phase 2. The ECG shows a progressively bigger U wave and lesser T wave, together with an evident descent of the ST segment. Below: A 45-year-old patient with advanced mitroaortic valve disease who was treated with excessive doses of digitalis and diuretics. The Ke value is 2.3 mEq/L. An ECG alteration representing phase C (above) is clearly seen, particularly in V_2 to V_4.

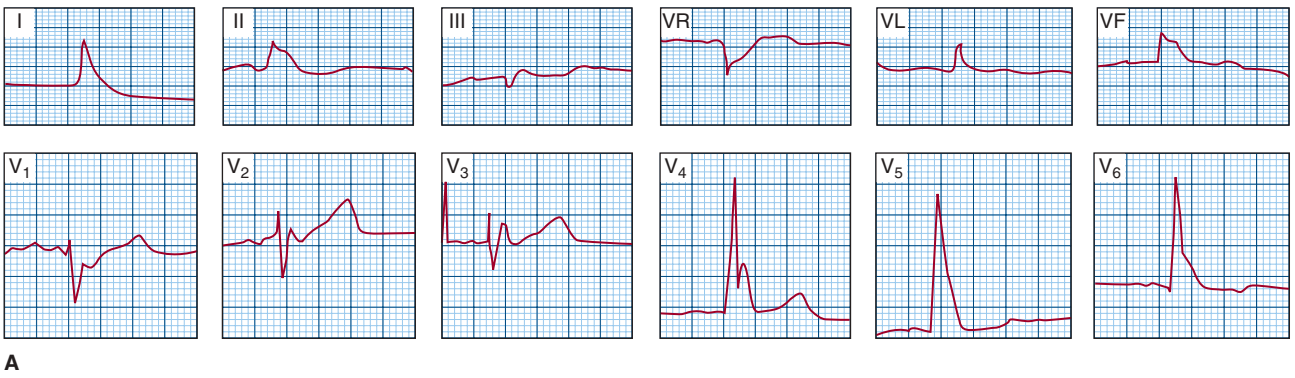


FIGURE 12–85. A. A 76-year-old patient with an acute disease and typical electrocardiogram of hypothermia, especially the J wave (Osborne) at the end of depolarization (see Fig. 12–80) (*continued*)

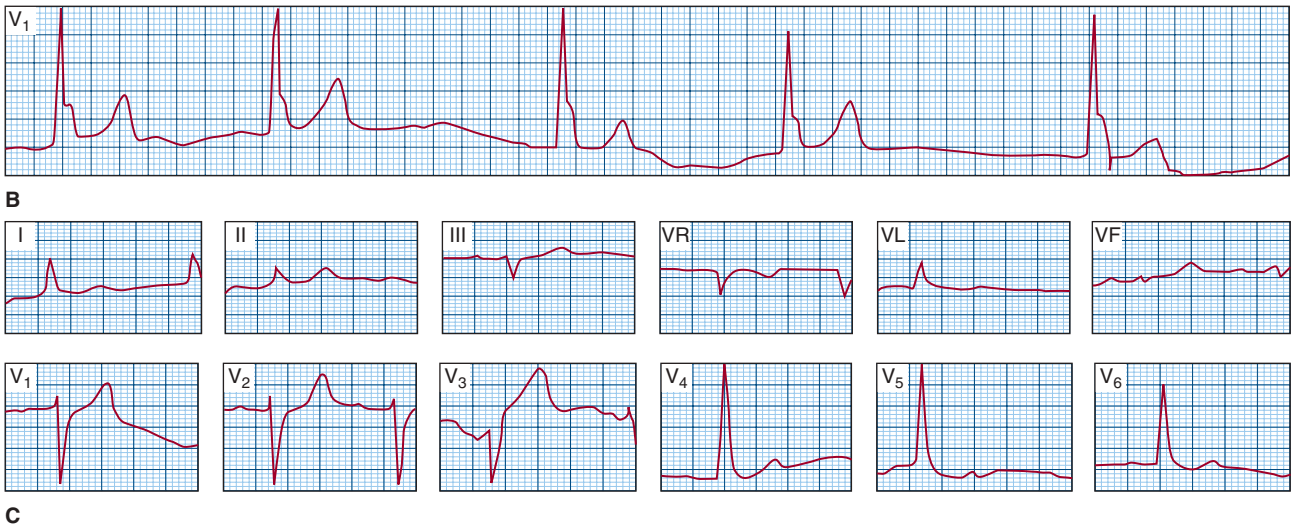


FIGURE 12–85. B. A continuous tracing in V_4 showing an irregular baseline and bradycardia. **C.** After therapy, the J wave disappears. (*continued*)

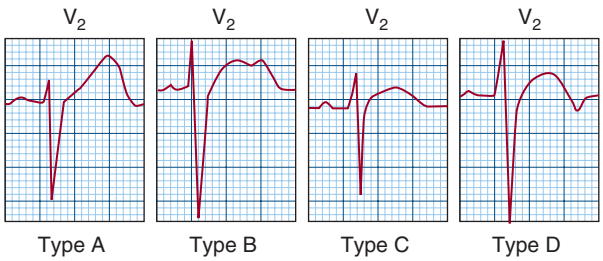


FIGURE 12–86. Examples of four types of repolarization alterations in V_2 that can be seen in athletes without heart disease. However, it is recommended to rule out associated heart disease.

TABLE 12–15. Surface Electrocardiography and Morphology Changes in Athletes

A. Training-related ECG findings. The morphology of ECG in athletes very frequently shows findings that may be training related and require no additional evaluation, such as:

- Sinus bradycardia
- First-degree AV block, or even Wenckebach-type second-degree AV block during rest (see below)
- Partial RBBB pattern
- High voltage of R wave in precordial leads in the absence of other criteria for left ventricular hypertrophy
- Isolated premature atrial or ventricular complexes
- Early repolarization (ER) pattern. In this case, we have to remember that this pattern has been recently associated with sudden death, although this is exceptional in the benign type of ER that is the pattern usually found in athletes (see Fig. 12–81D, part A).

B. Non–training-related ECG findings. In contrast, uncommon and non-training related ECG findings that may indicate further evaluation are:

- Negative T wave in at least two adjacent leads
- ST-segment depression or other evident abnormalities of repolarization (see Fig. 12–86)
- Pathologic Q waves
- Important atrial abnormalities
- Short or long QT interval
- Advanced bundle branch block or hemiblocks
- Evident criteria of right or left ventricular hypertrophy
- Abnormalities of QRS-ST in V1 suggestive of Brugada pattern
- The presence of some arrhythmias (runs or sustained atrial or ventricular tachycardia, vagal atrial fibrillation, advanced second-or third-degree AV block)

Abbreviations: AV, atrioventricular; ECG, electrocardiography.

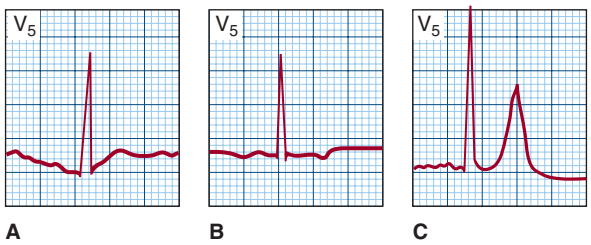


FIGURE 12–87. Example of T waves in alcoholism: (**A**) flattened and bimodal, (**B**) inverted, and (**C**) spinous.

FIGURE 12–88. Typical examples of electrical alternans: (**A**) alternans of QRS in a patient with pericardial tamponade, (**B**) ST-QT alternans in Prinzmetal angina, (**C**) repolarization alternans in significant electrolyte imbalance, (**D**) repolarization alternans in congenital long QT syndrome, and (**E**) in the case of junctional reentrant tachycardia with an accessory pathway.

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CHAPTER 13

ELECTROCARDIOGRAPHIC EXERCISE TESTING

Gregory S. Thomas and Myrvin H. Ellestad

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For 50 years, exercise testing has served as the backbone of the noninvasive evaluation of coronary artery disease (CAD) and as an essential component of a clinician's tool kit. Its rationale is compelling: it is simple, widely available, and inexpensive. Underused as stand-alone testing, a sophisticated and critical evaluation of the ECG and the patient during exercise and recovery and a true maximal exercise effort often provides the test sensitivity required for decision making without adjunctive nuclear or echocardiographic imaging. When adjunctive imaging is used, this same discriminatory power can enhance accuracy and confidence in the combined study.

CAUSES OF ISCHEMIA

When standardized exercise testing was developed by Master and colleagues in 1929,[1] the gold standard for exercise test accuracy was the development of angina and the occurrence of cardiac events.[2,3] The advent of coronary angiography in 1958[4] created a new gold standard, easily performed after exercise testing to study the correlation between exercise test results and coronary luminal anatomy. The following year, Prinzmetal and coworkers identified that ischemia could be caused by coronary vasospasm in the presence or absence of obstructive anatomic disease.[5] Coronary vasospasm was thought to be infrequent, however, and the accuracy of exercise testing continued to be measured by the presence of obstructive CAD on coronary angiography. A few decades later, the development of thallium- and technetium-based single photon emission computed tomography (SPECT) imaging allowed myocardial perfusion imaging (MPI) to be considered a gold standard.

Studies assessing the physiologic effect of coronary stenoses with fractional flow reserve (FFR) call the use of coronary angiography to predict ischemia, and thus serve as a gold standard, into question. Meanwhile, recent advances in quantitative positron emission tomography (PET) imaging create the opportunity to accurately measure global myocardial blood flow and cardiac magnetic resonance imaging (MRI) has been shown to accurately detect ischemia that is solely subendocardial. These two techniques may demonstrate ischemia associated with coronary lesions that are angiographically less than 50% stenotic. Thus, what is the proper gold standard against which exercise testing should be compared? As exercise testing detects ischemia that is predominately subendocardial, the assessment of global coronary flow by quantitative pharmacologic PET or ischemia by cardiac MRI should serve as the new gold standards. If ischemia in the distribution of a particular coronary artery needs to be evaluated, FFR can serve as the gold standard. Our previous understanding of the accuracy of exercise testing to detect ischemia must be tested against these new gold standards. The bulk of the extensive literature assessing the sensitivity and specificity of exercise stress testing used coronary angiography as the gold standard. As such, the basis of our understanding of exercise test sensitivity, specificity, and predictive values may be called into question. As new correlative studies have yet to be performed, we must rely on previous studies to best understand the accuracy of exercise testing, understanding that future research may challenge some of our assumptions.

TEST ACCURACY

Gibbons and fellow authors of the American College of Cardiology (ACC) and American Heart Association (AHA) 2002 guideline for exercise testing reviewed individual studies and meta-analyses evaluating the sensitivity and specificity of exercise testing.[6] They cited a meta-analysis by Detrano and colleagues of 147 exercise testing studies that found a mean sensitivity and specificity of 68% and 77%, respectively.[7] Sensitivity and specificity were altered by the selection of which cut point is used to discriminate between those with and without disease, particularly when measuring a continuous variable such as assessment

of CAD with an exercise test. The 147 studies discussed above used 1 mm (1 mV) of horizontal or downsloping ST depression as their cut point. The Bayes theorem of conditional probability states that the patient's pretest likelihood of disease affects the post-test likelihood of disease following a test. For example, if a patient with a low (eg, 5%) pretest likelihood of disease undergoes a test with a sensitivity of 70% and a specificity of 90% and the test is positive, the post-test likelihood of disease is only 27%. However, if the pretest likelihood is 50%, a positive test yields a post-test likelihood of disease of 80%.[8]

A change in a cut point to diagnose disease alters test sensitivity and specificity. If a more lenient cut point is used to diagnosis diabetes, such as a lower fasting blood sugar, sensitivity will increase but specificity will necessarily decrease and do so inversely with the increase in sensitivity. Sensitivity and specificity theoretically do not change with the prevalence of disease in a population, whereas positive and negative predictive values do change. Performing exercise testing in a population with low disease prevalence such as asymptomatic young men or women will result in a low positive predictive value, making testing unhelpful in such a cohort. However, exercise testing in an older population with symptoms suggestive of CAD would be doing so in a population with an intermediate likelihood of CAD yielding a higher and clinically acceptable positive predictive value.

Disease severity does influence sensitivity and specificity.[9,10] If those with the disease have a more severe form, the diagnostic test will be more accurate. This is relevant for exercise testing as patients now present with less advanced CAD, more often single vessel than multivessel. Ischemia is thus less likely to be demonstrated on exercise testing and its manifestations are often less obvious. In the case of exercise testing, less ST depression may be apparent. In this era of less CAD severity, it is appropriate to reconsider the traditional cut points used in the characterization of an exercise test as positive or negative.

Prior to delving further into exercise testing, a review of exercise physiology, adapted from Lipinski and Froelicher, is in order.[11]

BASIC PRINCIPLES

EXERCISE PHYSIOLOGY

Two basic principles of exercise physiology are central to exercise testing. The first is a physiologic principle: total body oxygen uptake and myocardial oxygen uptake are distinct in their determinants and in the way they are measured or estimated (Table 13–1). Total body or ventilatory oxygen uptake (volume oxygen consumption [VO_2]) is the amount of oxygen extracted from inspired air as the body performs work. The determinants of VO_2 are cardiac output and the peripheral arteriovenous oxygen difference. Maximal arteriovenous difference is physiologically limited to roughly 15 to 17 mL/dL. As maximal arteriovenous difference behaves more or less as a constant, maximal oxygen uptake serves as an indirect estimate of maximal cardiac output.

TABLE 13–1. Two Basic Principles of Exercise Physiology

Myocardial oxygen consumption	= Heart rate × systolic blood pressure (determinants include wall tension = left ventricular pressure × volume; contractility, and heart rate
Ventilatory oxygen consumption (VO_2)	= External work performed, or cardiac output[a] × A-VO_2 difference

[a]The arteriovenous O_2 difference is 15 vol% to 17 vol% at maximal exercise in most individuals; therefore VO_2max generally reflects the extent to which cardiac output increases.

A-VO_2, arteriovenous difference; VO_2, volume oxygen consumption; vol%, volume percent.

Myocardial oxygen uptake is the amount of oxygen consumed by the myocardium. The determinants of myocardial oxygen uptake include intramyocardial wall tension (left ventricular pressure and end-diastolic volume), contractility, and heart rate. Myocardial oxygen uptake can be estimated by the product of heart rate and systolic blood pressure (the double product or rate pressure product). This information is valuable clinically because exercise-induced angina often occurs at the same myocardial oxygen demand and thus double product. The higher the double product achieved, the better the myocardial perfusion and prognosis. Therefore, it is not surprising that the double product during exercise testing has long been known to be a significant independent predictor of myocardial ischemia[12] and prognosis.[13,14]

The second principle is one of pathophysiology: considerable interaction takes place between the exercise test manifestations of abnormal myocardial perfusion and function. The electrocardiographic response and development of angina are closely related to myocardial ischemia (and extent of CAD), whereas exercise capacity, systolic blood pressure, and heart rate response to exercise can be determined by the presence of myocardial ischemia, myocardial dysfunction, or peripheral responses. Exercise-induced ischemia can cause cardiac dysfunction, resulting in exercise impairment and a blunted systolic blood pressure response.

METABOLIC EQUIVALENTS

Because exercise testing fundamentally involves the measurement of work, there are several key concepts regarding work. The common biologic measure of total body work is oxygen uptake, which is usually expressed as a rate (making it a measure of power) in liters per minute. The metabolic equivalent of a task (MET) is a term used clinically to express the oxygen requirement of the work rate during an exercise test. One MET is equal to the resting metabolic rate (~3.5 mL of O_2/kg/min) and a MET value achieved from an exercise test is a multiple of the resting metabolic rate, either estimated from the maximal workload achieved or measured directly by oxygen uptake. It also represents a method of reporting work performed with different stress test protocols.

ACUTE CARDIOPULMONARY RESPONSES TO EXERCISE

Figure 13–1 summarizes the hemodynamic response to exercise. The cardiovascular system responds to acute exercise with a series of adjustments that ensure the following:

- Exercising muscles receive blood supply commensurate to their metabolic needs.
- Heat generated by the muscles is dissipated.
- Blood supply to the brain and heart is maintained.

This response requires a major redistribution of cardiac output, occurring in tandem with a number of local metabolic changes. The usual measure of the capacity of the body to deliver and use oxygen is the maximal oxygen consumption (VO_2max). Thus, the limits of the cardiopulmonary system are defined by VO_2max, which can be expressed by the Fick principle:

$$VO_2\text{max} = \text{maximal cardiac output} \times \text{maximal arteriovenous oxygen difference}$$

Cardiac output must closely match ventilation in the lung to deliver oxygen to the working muscle. VO_2max is determined by the maximal amount of ventilation (volume of expired gas [VE]) moving into and

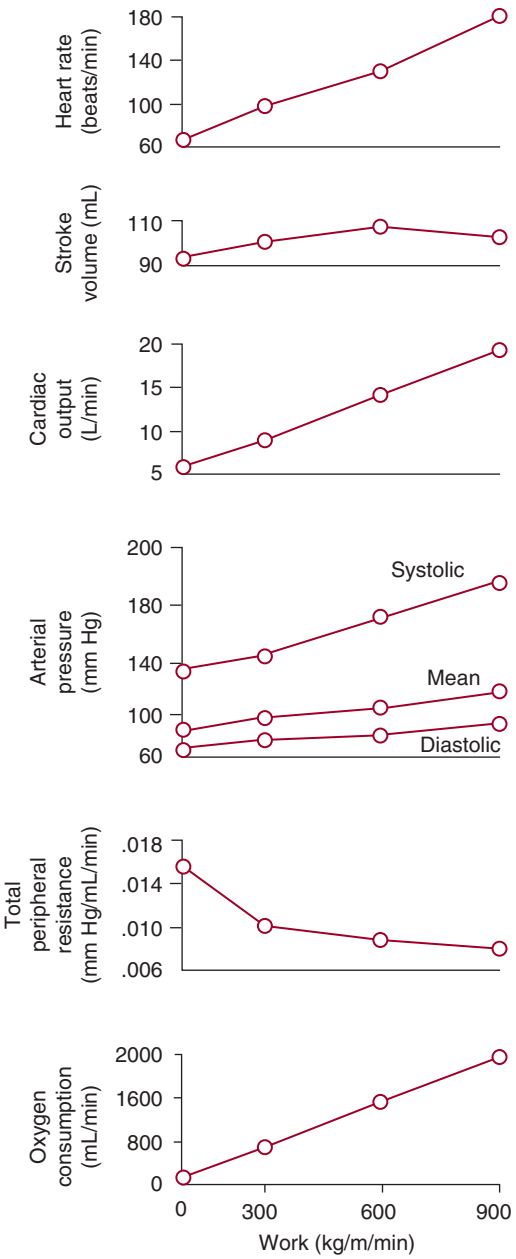


FIGURE 13–1. The hemodynamic response to exercise. Reproduced with permission from Aaronson PI, Ward JPT, Wiener CM: The *Cardiovascular System at a Glance*, 2nd edition. Massachusetts: Wiley-Blackwell Publishing; 2004.

out of the lung and by the fraction of this ventilation that is extracted by the tissues:

$$VO_2 = VE \times (FiO_2 - FeO_2)$$

where VE is minute ventilation, and FiO_2 and FeO_2 are the fractional concentration of oxygen in the inspired and expired air, respectively. To measure VO_2 accurately, CO_2 in the expired air (carbon dioxide elimination [VCO_2]) must also be measured; the main purpose of VCO_2 in this equation is to correct for the difference in ventilation between inspired and expired air. Because the rate of increase in VCO_2 relative to the work rate or ventilation parallels the severity of heart failure, VCO_2 is a valuable measurement clinically and a powerful prognostic marker for chronic heart failure patients.

Cardiopulmonary limits (VO_2max) are therefore defined by cardiac output, which describes the capacity of the heart to function as a pump, and the arteriovenous oxygen difference, which characterizes the capacity of the lung to oxygenate the blood delivered to it as well as the capacity of the working muscle to extract this oxygen from the blood.

CHIEF DETERMINANTS OF MAXIMAL OXYGEN CONSUMPTION

Heart Rate

Sympathetic and parasympathetic nervous system influences underlie the increase in heart rate, the cardiovascular system's first response to exercise. Vagal withdrawal is responsible for the initial 10 to 30 beats/min increase, whereas the remainder is thought to be largely caused by increased sympathetic outflow. Of the two major components of cardiac output, heart rate and stroke volume, heart rate is responsible for most of the increase in cardiac output during exercise, particularly at higher levels. Heart rate increases linearly with workload and oxygen uptake.

Stroke Volume

The product of stroke volume (the volume of blood ejected per heartbeat) and heart rate equals cardiac output. The stroke volume is equal to the difference between end-diastolic and end-systolic volumes. Thus, greater diastolic filling (preload) will increase stroke volume. Alternatively, factors that increase arterial blood pressure (afterload) will resist ventricular outflow and result in reduced stroke volume. During exercise, stroke volume increases up to about 50% to 60% of maximal exercise capacity, after which increases in cardiac output are a result of further increases in heart rate.

End-Systolic Volume

End-systolic volume depends on two factors: contractility and afterload. Contractility describes the forcefulness of the heart's contraction. Increasing contractility reduces end-systolic volume, which results in a greater stroke volume and thus greater cardiac output. Contractility is commonly quantified by the ejection fraction, the percentage of blood ejected from the ventricle during systole. Afterload is a measure of the force resisting the ejection of blood by the heart. Increased afterload (aortic pressure) results in a reduced ejection fraction and increased end-diastolic and end-systolic volumes. During dynamic exercise, the force resisting ejection in the periphery (total peripheral resistance) is reduced by vasodilation, secondary to the effect of local metabolites on the skeletal muscle vasculature. Thus, despite even a five-fold increase in cardiac output among normal subjects during exercise, mean arterial pressure increases only moderately.

Arteriovenous Oxygen Difference

Oxygen extraction by the tissues during exercise reflects the difference between the oxygen content of the arteries (~18–20 mL O_2/100 mL at rest) and the oxygen content in the veins (~13–15 mL O_2/100 mL at rest), yielding a typical arteriovenous oxygen difference (A-VO_2) at rest of 4 to 6 mL O_2/100 mL, approximately 23% extraction. During exercise, this difference widens as the working tissues extract greater amounts of oxygen; venous oxygen content reaches very low levels, and A-VO_2 can be as high as 16 to 18 mL O_2/100 mL with exhaustive exercise. Some oxygenated blood always returns to the heart, however, as smaller amounts of blood continue to flow through metabolically less active tissues that do not fully extract oxygen. The A-VO_2 is generally considered to widen by a relatively fixed amount during exercise, and differences in VO_2max are predominantly explained by differences

in cardiac output. Some patients with cardiovascular or pulmonary disease, however, exhibit reduced VO_2max values that can be attributed to a combination of central and peripheral factors. For example, in a patient with chronic obstructive pulmonary disease, impaired oxygen uptake will necessarily diminish VO_2max.

Determinants of Arterial Oxygen Content

Arterial oxygen content is related to the partial pressure of arterial oxygen, which is determined in the lungs by alveolar ventilation and pulmonary diffusion capacity and in the blood by hemoglobin content. In the absence of pulmonary disease, arterial oxygen content and saturation are generally normal throughout exercise. Patients with symptomatic pulmonary disease often neither ventilate the alveoli adequately nor diffuse oxygen from the lung into the bloodstream normally resulting in a decrease in arterial oxygen saturation during exercise.

Determinants of Venous Oxygen Content

Venous oxygen content reflects the capacity to extract oxygen from the blood as it flows through the muscle. It is determined by the amount of blood directed to the muscle and by capillary density. Muscle blood flow increases in proportion to the increase in work rate and thus oxygen requirements. The increase in blood flow is brought about not only by the increase in cardiac output, but also by a preferential redistribution of the cardiac output to the exercising muscle. Locally produced vasodilatory mechanisms along with possible neurogenic dilatation resulting from higher sympathetic activity reduce local vascular resistance and mediate the greater skeletal muscle blood flow. A marked increase in the number of open capillaries reduces diffusion distances; increases capillary blood volume; and increases mean transit time, facilitating oxygen delivery to the muscle.

THE EXERCISE TEST

As with any cardiac test, patient selection is critical and patient safety of foremost concern. In their seminal 1971 study of 170,000 exercise tests, Rochmis and Blackburn observed a mortality rate of approximately 1 in 10,000 exercise tests.[15] Eight subsequent studies summarized in 1993 found the mortality rate had decreased to 0 to 0.5 per 10,000 tests.[16] The clinician supervising the test, be it a physician, nurse, exercise physiologist, or another professional, should be very comfortable in his or her ability to interpret a rest and exercise electrocardiogram for ischemia and arrhythmia, recognize exercise induced symptoms of ischemia and cardiac failure, and handle an exercise-induced emergency. Given the significant potential for harm in patients with valvular heart disease, particularly severe aortic stenosis, the supervising clinician should also be skilled in cardiac auscultation, to be performed prior to exercise testing.

QUALIFICATIONS OF TESTING CLINICIANS

In the United States, exercise testing is increasingly supervised by nonphysicians. As reviewed by Myers and colleagues,[17] the AHA stated in 1979 that an experienced nonphysician could conduct exercise testing, although a physician must be immediately available during testing.[18] In 1990, a multispecialty task force of the ACC, AHA, and American College of Physicians recommended specific clinical competencies for physicians and nonphysicians in order to perform exercise testing.[19] Subsequent statements by these organizations, as well as the American College of Sports Medicine and American Association of Cardiovascular and Pulmonary Medicine, further defined the level of supervision during which patients can be safely tested by nonphysician providers and the detailed training required. Central to these recommendations are the risk stratification of patients prior to exercise testing and the immediate availability of a physician during patient testing. Personal supervision by a physician in the room is recommended for high-risk patients as listed in the bullets below adapted from Myers and colleagues.[17] These patients should be identified by careful *pretest* evaluation and good clinical judgment.

- Moderate to severe aortic or mitral valve stenosis with or without symptoms
- Hypertrophic cardiomyopathy: risk stratification and exercise gradient assessment
- History of malignant or exertional arrhythmias, sudden cardiac death
- History of exertional syncope or presyncope
- Intracardiac shunts
- Genetic channelopathies
- Within 7 days of myocardial infarction or acute coronary syndrome
- New York Heart Association class III heart failure
- Severe left ventricular dysfunction
- Severe pulmonary arterial hypertension
- In the broader context of potential instability resulting from noncardiovascular comorbidities, (eg, frailty, dehydration, orthopedic limitations, chronic obstructive lung disease)

All exercise laboratory staff assisting in exercise testing should be credentialed in basic life support. Supervising nonphysicians should be certified in Advanced Cardiac Life Support. If supervising physicians are not certified in Advanced Cardiac Life Support, they should be competent in identifying and handling such emergencies based on past and continued training and experience. Given a dearth of comprehensive continuing education pathways to achieve expertise in exercise testing, the training of nonphysicians, such as registered nurses, nurse practitioners, and physician assistants can be challenging. Previous cardiac experience can be leveraged with available continuing medical education courses, textbooks, and articles, as well as extensive on the job training and supervision to develop competence. Both nonphysicians and physicians should perform a minimum of 200 exercise tests during training to meet the level 1 Core Cardiology Training Symposium standard established by the ACC in 2008.[20] In general, a minimum of 50 tests should be performed annually to maintain and enhance competency. With substantial experience, nonphysicians may perform basic interpretation of the exercise test with the final responsibility for the report resting with the physician. Any physician supervising and ultimately responsible for the exercise test should meet ACC level 1 guidelines.[20] Physicians who are immediately available during testing by nonphysicians should either meet these guidelines or be skilled in emergency medicine.[17]

EXERCISE EQUIPMENT

Exercise testing can be performed with bicycle ergometry or treadmill testing. The latter is much preferred if space in the exercise laboratory allows, because higher workloads can be obtained with treadmill compared to bicycle exercise given the greater muscle mass involved.

Given the low but finite risk of prolonged myocardial ischemia, infarction, or arrhythmia, and of cardiac arrest, a "crash cart" should be immediately available, and supervising clinicians should have the knowledge to use the medications therein. A defibrillator should also be

immediately available, and staff should be trained in its use. Laboratory staff should be well versed in the laboratory's predefined plan to respond to an emergency. In an outpatient facility, this includes an understanding of who will directly attend to the patient, who will record unfolding events, and who will call for emergency medical transport personnel. When an event does occur, a postevent debriefing presents the opportunity to discuss opportunities for improvement.

PRETEST PREPARATION

Patient preparation is key and should begin on test scheduling. The patient should be provided with digital or printed information on what to expect. They should be advised to wear clothes and shoes fit for exercising. Because caffeine is a competitive antagonist of adenosine receptors and thus blocks the effect of dipyridamole, adenosine, and regadenoson, it should be withheld for at least 12 hours if there is a possibility of the patient undergoing vasodilator stress the same day. However, we are unaware of investigative data on the impact of caffeine on stand-alone exercise testing. Because the vast majority of persons consume caffeine regularly, testing caffeinated patients would be akin to testing them in their typical physiologic state. If there is little or no chance that a patient would undergo vasodilator stress the same day as an exercise test, prohibition against caffeine use prior to exercise testing is not required. We have also found that a light meal prior to the exercise test, if desired, does not present problems.

Tobacco has traditionally been prohibited for 3 hours prior to testing. Tobacco can potentiate vasospasm, which can result in a positive exercise test in the absence of obstructive CAD. However, if the patient smokes regularly, a test without a tobacco prohibition would reflect their day-to-day natural state. The prohibition can be implemented or relaxed depending on the clinical question to be answered.

Avoiding vigorous exercise on the day of exercise testing is appropriate to enhance the patient's ability to achieve maximum exercise on the test.

If the exercise test is being performed to determine if a patient has CAD and consequent ischemia, antianginal medications should be held to minimize their anti-ischemic impact. As best observed in studies of patients undergoing SPECT imaging, beta-blockers, nitrates, and calcium channel blockers can all turn a test from ischemic to nonischemic.[21,22] A practical approach to discontinuing medications for diagnostic testing is to hold beta-blockers for 24 hours and hold nitrates and calcium channel blockers the day of the study. Patients should be instructed to bring these medications to the test and to take them following the treadmill test. This is ideally accomplished while the patient is still in the exercise laboratory in order to facilitate compliance in restarting their medication.

Holding medications is particularly important when using exercise testing for patients being evaluated from the emergency department for chest pain. If a patient is already on antianginal therapy on arrival for exercise testing from the emergency department or elsewhere, sensitivity will be decreased. If the test is negative for ischemia, the reporting clinician may consider noting in the report either that test sensitivity may be decreased by the patient's medical regimen or that ischemia was not seen at the level of exertion or double product achieved. If the test is being performed for prognostic reasons—that is, if CAD is known to be present and the clinician wishes to determine if the patient is having ischemia on their current medical regimen—medications need not be withheld.

On arrival, staff should review the test protocol and obtain informed consent by informing the patient of the risks and benefits. Instructions should be provided on vocalizing if chest pain or other ischemic symptoms occur prior to, during, or after exercise.

EXERCISE PROTOCOLS AND TESTING

The most commonly used multistage treadmill protocols in the United States are those developed by Bruce and Ellestad, often regarded as the founders of exercise treadmill testing in the United States. Both protocols begin with what they regarded as a warm-up stage (stage 1), 1.7 miles/hour at 10% grade. For patients with limited ability to exercise, the Bruce protocol can be modified to include a stage 0 in which the patient exercises at 1.7 miles/hour at 0% grade for 3 minutes prior to moving into stage 1 of the standard Bruce protocol. Ideally, a protocol should be used such that patients exercise for 5 to 6 minutes or more.[23] A comparison of Bruce and Ellestad treadmill protocols is shown in Fig. 13–2.[24] Pollock and colleagues compared the physiologic parameters of these two protocols in a study of 51 men who underwent both tests.[24] Peak VO_2max, METs, heart rate, and systolic and diastolic blood pressures obtained were similar. As with other multistage treadmill protocols, VO_2max correlated directly with exercise duration (Fig. 13–3). Time to achieving peak exercise was about 1 minute sooner with the Ellestad protocol, likely secondary to its 2-minute stages following stage 1 compared to the 3-minute stages of the Bruce protocol.[25] Other protocols are available, including those by Naughton and Balke. Exercise duration correlates with VO_2max in each and achieves similar results.

A brief cardiac examination, including auscultation of the heart and lungs, should be performed prior to testing, and the patient should be questioned to determine the reason for the test and any symptoms that may have prompted the referral. Particularly important are any symptoms the patient may have been experiencing that could be cardiac in nature. If the symptoms being evaluated clinically appear consistent with ischemia and the patient develops these during exercise, test termination is generally indicated. Likewise, if the patient describes symptoms prior to exercise testing that are consistent with new onset unstable angina, which have not resolved, invasive coronary angiography or computed tomography (CT) coronary angiography will often be a safer choice than exercise testing. A careful history and clinical judgment are a prerequisite to the safe execution of exercise testing.

Electrocardiogram (ECG) lead placement should ensure proper contact in order to minimize artifacts, which can obfuscate the ability to interpret ischemia. The Mason-Likar "torso" ECG used for exercise testing distorts the axis rightward, which can result in a loss of inferior

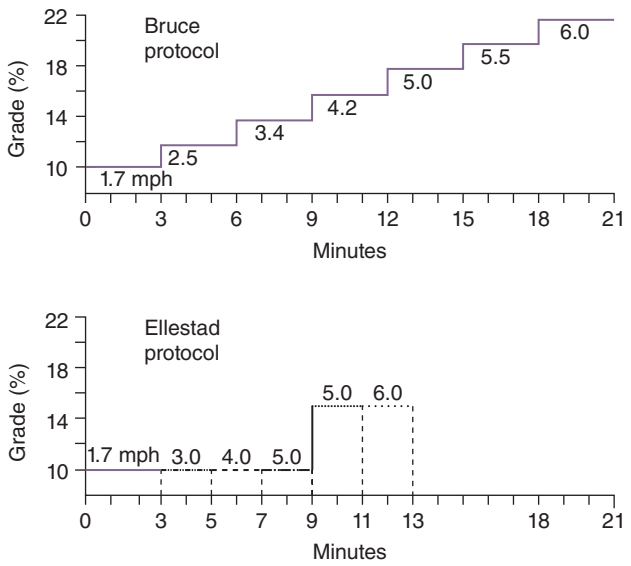


FIGURE 13–2. Exercise protocols. The number above or below the line indicates the mph of the stage. Adapted with permission from Ellestad MH: *Stress Testing: Principles and Practice*. New York: Oxford University Press; 2003.

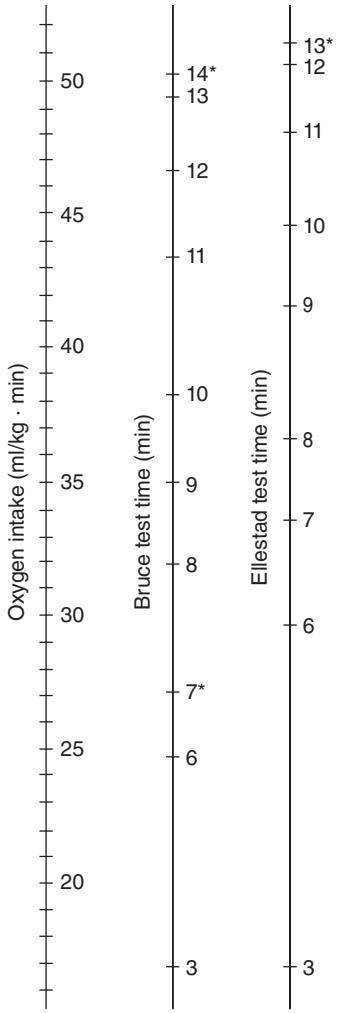


FIGURE 13–3. Oxygen requirements of the Bruce and Ellestad protocols. A horizontal line can be drawn from the minutes achieved on either protocol to the oxygen intake line to estimate VO_2max achieved. Peak METs obtained can be estimated by multiplying VO_2max by 3.5. Adapted with permission from Pollock ML, Bohannon RL, Cooper KH, et al: A comparative analysis of four protocols for maximal treadmill stress testing, *Am Heart J*. 1976 Jul;92(1):39-46.[24]

Q waves masking a previous inferior myocardial infarction (MI).[23] Nevertheless, this is the ECG that will be used as the comparator to the exercise ECG and should be reviewed prior to exercise testing. Ideally, a standard 12-lead ECG with electrodes placed on the limbs should be performed prior to exercise testing. Previous records, often accessed via an electronic medical record system, should be reviewed for pertinent symptoms and history, including past exercise testing and a recent resting ECG. Electrocardiographic tracings from the most recent exercise test allow a direct comparison of the timing of onset and extent of previous ECG changes. Comparing exercise duration between the previous and current test is particularly helpful. For example, if a patient undergoes a follow-up exercise test and the clinician performing and/or interpreting the test has expended the effort to review the patient's previous exercise duration and electrocardiographic response and finds them either unchanged or to have changed between the two tests, this information will be particularly helpful and appreciated by the referring clinician.

During this review, the patient and records should be carefully interrogated for clinical conditions in which the risk of exercise testing outweighs the benefits and is contraindicated (Table 13–2).[2,6] Relative contraindications are listed in Table 13–3.[2,26] Indications for the test should be assessed and directly matched to the most recent societal Appropriate Use Criteria.[27] If exercise testing does not appear to be indicated to address the patient's clinical condition, the ordering physician should be contacted to discuss their understanding of the clinical situation and potential alternatives to exercise testing.

The patient's usual level of activity should also be assessed to determine if the patient would be expected to achieve ≥ 85% of maximum predicted heart rate (MPHR) and if so, to determine whether to modify the planned protocol. Unfortunately, laboratories are increasingly using pharmacologic rather than exercise stress as the stressor for MPI. As American Society of Nuclear Cardiology guidelines recommend, pharmacologic stress is only appropriate if the patient is unable to achieve ≥ 85% MPHR and five METs.[28] Although pharmacologic MPI provides adequate perfusion images to assess ischemia, MPI performed with exercise provides key additional opportunities to assess ischemia, including exercise duration, assessment of symptoms, and electrocardiographic changes. With exercise, the expense and risks of the pharmacologic stress agent is also not incurred.

A review of the resting ECG should include an evaluation for ischemia, conduction defects, and arrhythmias, and it should be compared to prior tracings if they are available. Obtaining an ECG during

TABLE 13–2. Absolute Contraindications to Exercise Testing

Patients with an acute myocardial infarction
Patients suffering from acute myocarditis or pericarditis
Patients exhibiting signs of unstable progressive angina This includes patients who have long periods of angina of fairly recent onset while at rest
Patients with rapid ventricular or atrial arrhythmias at the time of the test
Patients with Mobitz type 2 second- or third-degree heart block
Patients with known severe left main disease
Acutely ill patients, such as those with infections, hyperthyroidism, or severe anemia.
Patients with locomotion problems
Severe aortic or other valvular stenosis
Acute pulmonary embolus
Uncontrolled symptomatic heart failure

Data from Ellestad MH: *Stress Testing: Principles and Practice*. New York, NY: Oxford University Press; 2003.

TABLE 13–3. Relative Contraindications to Exercise Testing[a]

Moderate aortic or other valvular stenosis
Left main stenosis or left main equivalent
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Severe (> 3 mm) ST segment depression at rest
Severe (> 200/110 mm) arterial hypertension
Recent tachyarrhythmias or bradyarrhythmias
Moderate to high-degree atrioventricular block

[a] Relative contraindications can be superseded if the benefits of exercise outweigh the risks.

Data from Ellestad, 2003 and Gibbons RJ, Balady GJ, Bricker JT, et al. *J Am Coll Cardiol*. 2002.

TABLE 13–4. Borg Scale of Perceived Exertion

6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

In many patients, particularly those younger and not on medication, a zero can be added to the Borg score to estimate the patient's exertional heart rate.

Reproduced with permission from Borg GA: Psychophysical bases of perceived exertion, *Med Sci Sports Exerc* 1982;14(5):377-381.[29]

hyperventilation should be avoided before testing. Subjects with and without CAD can exhibit ST-segment changes with hyperventilation; therefore, hyperventilation to identify false-positive responders is no longer considered helpful.

Once exercise is initiated, the technologist handling the treadmill and the supervising clinician should focus on the patient, the ECG tracings on the monitor, the intermittent 12-lead ECG obtained at the end of each stage, and the patient's symptoms and appearance. If changes suggestive of ischemia develop on the continuous monitor, a 12-lead ECG should be immediately performed. Electrocardiographic changes should also elicit a question to the patient about any associated symptoms.

For a stand-alone exercise test, if a patient develops convincing evidence of ischemia by ECG, symptoms, or both, the test can be terminated, because the question of the presence of ischemia has been answered.[3] If ischemia is not convincingly observed, the patient should continue until they can safely or comfortably go no further. A Borg-perceived exertion scale of 6 to 20 (Table 13–4) posted in the patient's view allows the patient to quantitate their level of exertion.[29] This is particularly useful during nuclear stress testing when judging how much more time the patient can exercise in order to gauge when to inject the radioisotope. A Borg scale of ≥ 15 suggests the anaerobic threshold has been met and > 18 generally indicates maximal exercise.[23] In many patients, particularly those younger and not on medication, a zero can be added to the Borg score to estimate the patient's exertional heart rate. This is by design.[29]

REASSURANCE

The clinician should talk intermittently to patients during the test, reassuring them as to their progress and asking how they feel. Toward the end of each stage, patients should be informed of the upcoming increase in treadmill speed and incline and asked if they can continue. Conversation during the test is reassuring, particularly for those undergoing testing for the first time.

MAXIMUM HEART RATE

Although age-adjusted predicted maximum heart rate has been assessed since the early years of treadmill testing, it has proved too variable among individuals to serve as a suitable end point to terminate an exercise test. If safe, patients should be encouraged to exercise as long as they are safely able. Exercise testing is meant to be symptom limited, not terminated by an arbitrary age-related heart rate of 85% or 100% of predicted maximum. Stopping exercise prematurely once 85% of an estimated maximal heart rate is achieved decreases exercise testing sensitivity and minimizes the opportunity to assess ischemia electrocardiographically and with adjunctive imaging.[30]

Obtaining a heart rate of at least 85% of maximum predicted heart rate is particularly relevant for exercise testing with nuclear or echocardiographic testing. Bairey and coworkers compared patients undergoing exercise MPI with a normal perfusion scan relative to whether they achieved 85% of MPHR. The annual event rate of death, nonfatal MI, or late revascularization was 1.9% for those who reached ≥ 85% MPHR compared to 8.6% for those who achieved < 85%.[31] In those who had not achieved 85% MPHR, the predictive value of MPI was minimized as a normal MPI study in the setting of a submaximal heart rate failed to adequately detect ischemia and thus failed to serve as an adequate risk stratifier. Iskandrian and colleagues found MPI sensitivity to be about 20% less among patients who achieved a heart rate < 85% of MPHR compared to those who achieved ≥ 85% MPHR or who stopped on reaching an ischemic end point. Given that ischemia as assessed by MPI is heart rate dependent, ischemia detection by ECG should be heart rate dependent as well.[32,33] Cumming demonstrated this concept in his comparison of submaximal to maximal bicycle exercise testing in 63 subjects who had an abnormal ECG response during maximal exercise or during recovery from maximal exercise.[34] Although all were ischemic by ECG at maximum exercise or in recovery, ischemic ECG changes were present at heart rates of 85% or less of MPHR in only 46% of subjects.

Noting that 40% of 100 consecutive laboratories applying for nuclear cardiology accreditation used 85% MPHR as their primary termination criteria for ending an exercise test, Jain and colleagues evaluated 232 patients in their own laboratory who had ischemic ECG changes at peak exercise and who exercised for more than 1 minute beyond the time at which they achieved ≥ 85% MPHR.[30] At 85% MPHR, the ECG was ischemic in only 144 (62%) patients. Mean ST-segment depression was 1.2 and 2.3 mm at 85% MPHR and peak exercise, respectively. They thus emphasized the admonition of Bruce and colleagues in the first description of Bruce's multistage treadmill protocol in 1963, that the patient should exercise until "exhausted by fatigue."[35] Achieving either maximum effort or an ischemic end point is key for exercise testing performed with or without imaging.

An anecdote of how the commonly used, easy-to-remember 220 – age formula was created to estimate MPHR is both interesting and highlights its limitations. On a plane to a medical convention in 1970, Haskell and Fox realized that in about 10 studies of young and middle-aged men undergoing exercise testing, maximum heart rate achieved could be roughly estimated by the formula 220 – age[36] The paper in which they define the formula describes its use not to estimate MPHR on an exercise test but to develop a patient's exercise prescription.[30,37] Formulas with a greater evidence base are recommended to estimate MPHR. Tanaka and colleagues, for example, found that 220 – age results in an underestimation of maximum heart rate, particularly in older patients.[38] In a meta-analysis of 351 studies involving 18,712 patients, the empirically derived formula of 208 – 0.7 × age best predicted the maximum heart rate. The formula was predictive in men and women and independent of habitual activity level. They then tested the formula

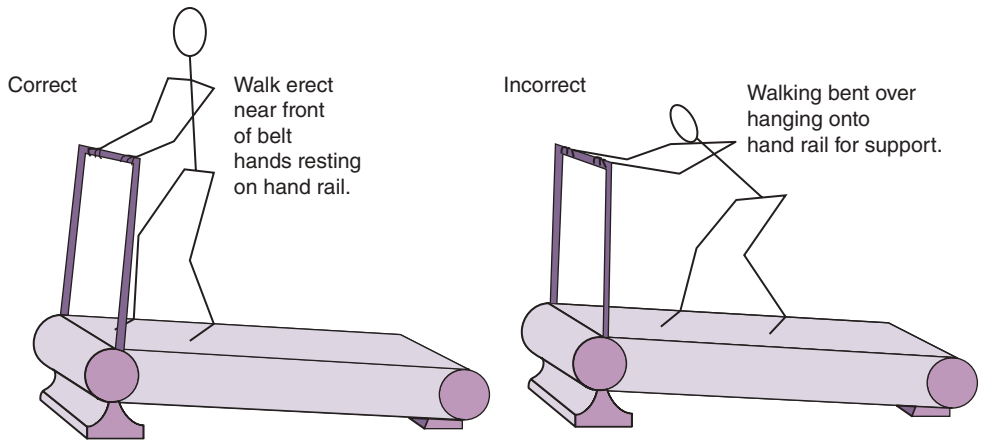


FIGURE 13–4. Proper posture on the treadmill. Correct and incorrect posture is represented for treadmill walking. Erect posture is all-important. Reproduced with permission from Ellestad MH: Stress Testing: *Principles and Practice*, 5th edition. New York: Oxford University Press; 2003.[2]

prospectively in 514 subjects finding excellent prediction of maximum heart rate. Evidence-based tables of age-related maximum heart rates can also be found in Sheffield[39] and Ellestad.[40] Of these examples, the formula of Tanaka and colleagues is preferred.

WALKING ON THE TREADMILL

Once exercise has started, patients should use the side rails of the treadmill for balance and safety but not to minimize exertional effort by a tight hold. Some patients will need to be briefly supported by the laboratory team as they start exercising to be certain they are comfortable walking on the belt of the treadmill. In patients unfamiliar with walking on a treadmill, the clinician will often need to ask that they stand erect, lengthen their stride, and move toward the front of the treadmill. This is illustrated in Fig. 13–4.

Symptoms should be carefully solicited and recorded. Chest pain that is intermittent and of only a few seconds' duration is far less suggestive of ischemia than chest pain that increases with exercise. If premature ventricular contractions or premature atrial contractions occur during exercise or recovery, patients should be asked if they feel them. In this case, patients can be informed of the cause of the feeling and likely reassured.

The clinician and assisting staff member should work to obtain artifact-free ECGs during exercise and recovery. This is particularly important for ECGs at peak exercise and in immediate recovery. Additionally, obtaining diagnostic and artifact-free ECGs during exercise may require obtaining ECGs more frequently than at the end of each stage. Blood pressure should be measured toward the end of each stage and when patients report or acknowledge symptoms. Although automated sphygmomanometers are available, manual blood pressure measurement is the most reliable method. It is often difficult to obtain an accurate blood pressure when patients are walking or jogging at speeds of greater than 4 mph on the treadmill. If this is the case, the general appearance of patients—their skin color and the apparent strength and vigor of their walk—will provide clues to the adequacy of their hemodynamic response.

RECOVERY PROTOCOLS

Two common protocol options exist for the recovery period: an immediate stop after peak exercise or a short cool-down period of 1 to 2 minutes of walking. An immediate stop provides the opportunity to obtain an artifact-free immediate postexercise ECG while the patient is still standing on the treadmill. The patient is then immediately laid supine or semirecumbent on a gurney or its equivalent. The cool-down option of slowing the patient down over 1 to 2 minutes can delay[41] or eliminate the appearance of ST-segment depression in recovery. The act of placing a patient supine immediately postexercise enhances ischemic electrocardiographic abnormalities in recovery, likely as a result of the supine position increasing venous return resulting higher left ventricular end-diastolic pressure and thus higher wall tension and oxygen consumption of the myocardium. A representative series of ECG tracings from a patient instructed to move from sitting to laying down at various times during recovery serves as an example of inducing worsening ST depression with the supine position (Fig. 13–5).[2] Given the advantages of an immediate stop and a swift move to the supine position, this recovery protocol is recommended for most patients undergoing stand-alone exercise testing.

A rapid stop may occasionally induce a vagal response. This occurs particularly in young persons exercising to exhaustion and may result in lightheadedness or presyncope. The alternative recovery protocol, a 1- to 2-minute slow cool-down walk, minimizes the vagal response and may be better tolerated. In patients undergoing stress echocardiography, the immediate stop protocol facilitates the patient quickly coming to the echocardiography machine. The immediate-recovery ECG can be performed immediately on the patient laying down for post–stress echocardiography. For patients undergoing MPI, the slow walking cool-down protocol is appropriate because some radioisotope will still be circulating and can be taken up by the myocardium during a slow walking recovery.

Recovery should last 6 or more minutes and include monitoring of the ECG and symptoms throughout with a 12-lead ECG and blood pressure obtained every minute. If any of these parameters remains abnormal, monitoring should continue until a return to normal and until any symptoms resolve. A markedly abnormal exercise test merits a prompt call to the referring physician and consideration of further care in an acute care setting.

INDICATIONS FOR TERMINATION OF EXERCISE

The patient should be continuously observed during exercise testing. The patient should stop exercising when they can go no further or are close to exhaustion, or if their ECG, symptoms, heart rhythm, or hemodynamics warrant stopping because of demonstration of ischemia or

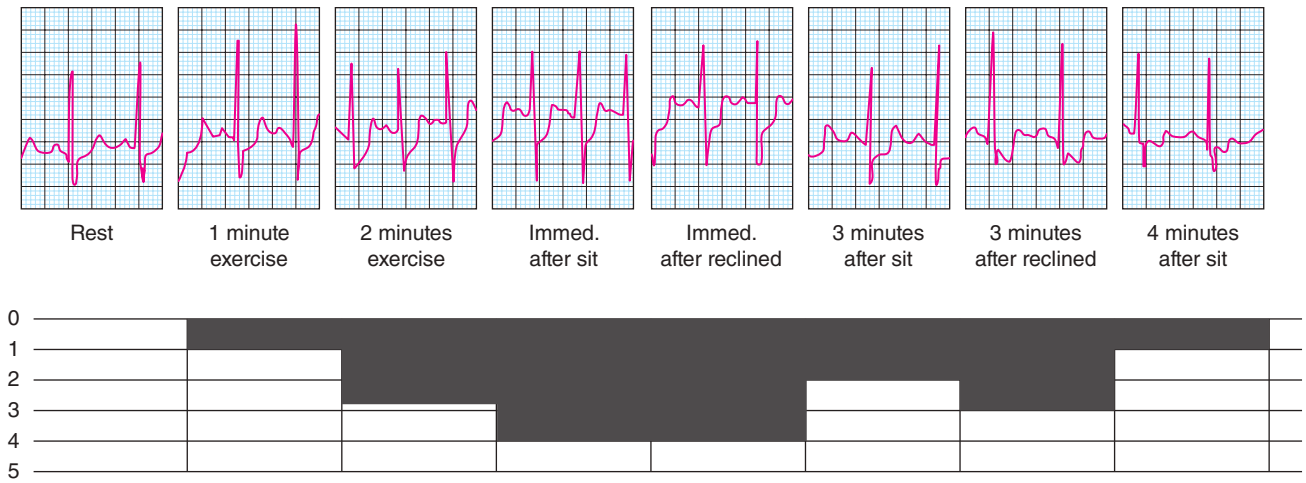


FIGURE 13–5. Worsening ST depression with reclining to the supine position from sitting. Each small box in the above 0 to 5 section represents 1 mm of ST depression. In this patient, upsloping ST depression is present in this patient with severe coronary artery disease during the first 1 to 2 minutes of exercise. It worsens in immediate recovery and worsens further when the patient moves from the sitting to the supine position. It improves on sitting again. Worsening of the electrocardiogram in the supine position is attributed to increased venous return and thus a higher left ventricular end-diastolic pressure. Adapted with permission from Ellestad MH: Stress Testing: *Principles and Practice*, 5th edition. New York: Oxford University Press; 2003.[2]

concern for safety. As adapted from those outlined in Ellestad[2] and by Gibbons and colleagues in the 2002 ACC/AHA guidelines,[6] exercise should be terminated when:

1. Anginal pain increases to moderate severity. This is a decision based on clinical judgment and consideration of the chronicity of symptoms and the clinical situation. In many patients, the development of mild angina can answer the question at hand and further exercise is not needed.
2. ST depression has become moderate, generally ≥ 2 mm.
3. ST depression is present at rest and there is a progressive increase in ST depression with modest exercise or ST depression increases by ≥ 2 mm.
4. ST elevation is ≥ 1 mm in precordial (anterior) or inferior leads that do not have a resting Q wave.
5. Atrial tachycardia, atrial fibrillation, or atrial flutter supervenes.
6. There is onset of Mobitz type 1 or 2 second-degree or third-degree heart block.
7. Premature ventricular contractions occur in pairs with increasing frequency as exercise increases, or when at least three-beat ventricular tachycardia occurs. Termination secondary to increasing ventricular arrhythmia should be influenced "by the company it keeps." If associated with ischemic electrocardiographic changes, termination would be prudent with increasing ventricular arrhythmia. If the test is being performed specifically to evaluate for induction of arrhythmia and is not associated with other markers of ischemia, more tolerance can be given.
8. Systolic blood pressure drops progressively in the face of continuing exercise, particularly if accompanied by another indication of ischemia.
9. The patient is unable to continue because of dyspnea, fatigue, or lightheadedness.
10. Musculoskeletal pain becomes moderate, such as that which might occur with arthritis or claudication.
11. The patient looks vasoconstricted—pale and clammy.
12. Systolic blood pressure becomes greater than 250 mm or diastolic blood pressure becomes greater than 115 mm.
13. The patient has reached or exceeded MPHR. As stated, if the patient is able and wishes to go further, he or she can do so in the absence of other indications for termination.
14. Equipment problems occur, such as loss of the ECG on the monitor.

ELECTROCARDIOGRAPHIC PATTERNS AND THEIR SIGNIFICANCE

ST-Segment Depression

The most common manifestation of ischemia during exercise testing is ST-segment depression. By convention, the magnitude of ST segment is measured 0.08 seconds (80 milliseconds; two boxes on a standard ECG tracing) after the J point of the QRS, which represents the end of the QRS complex and the beginning of the ST segment. The deviation of the ST segment is measured against the location on the ECG in millivolts (mV) at the beginning of the QRS complex (the PQ junction in mV). It is measured here because as the heart rate increases, the segment between the T wave and the P wave often shortens to the point where it is no longer interpretable.[42] One millivolt on the ECG corresponds to 1 mm and one box on the ECG. Two mm of ST depression was the initial criterion for an abnormal exercise test and was soon changed to 1.5 mm as the criteria for being abnormal.[2] However, studies using outcome or coronary angiography as the gold standard demonstrated that 1.0 to 1.5 mm of ST depression also predicted adverse outcomes or one or more stenoses of 50% or more on angiography.[43,44]

Studies as long ago as 1941, as well as more recently, observed either adverse clinical outcomes or angiographic coronary disease in individuals exhibiting ST depression of 0.5 to 1.0.[45,46] Although lowering the cut point (threshold) to characterize an exercise study with 0.5 to 1.0 of ST depression as abnormal increased sensitivity, specificity decreased to such a degree that a consensus developed to accept at least 1.0 mm of ST depression as the standard cut point for ischemia. However, if patients exhibit other signs of ischemia, those with 0.5 to 1.0 mm of ST depression are likely to have angiographically significant CAD.

The ST depression discussed immediately above refers to horizontal or downsloping ST depression. Figure 13–6 compares the normal ECG response to different categories of ST depression: J point, also called rapid upsloping, slow upsloping, horizontal, and downsloping.

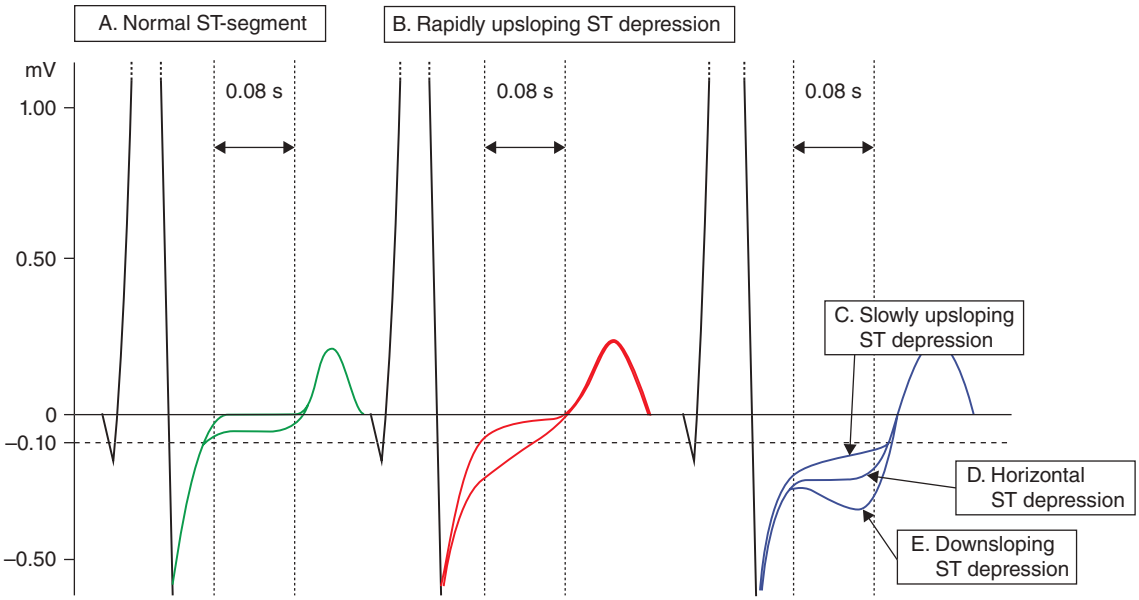


FIGURE 13–6. (**A**) Normal ST segment, (**B**) rapidly upsloping ST depression, (**C**) slowly upsloping ST depression with the ST depression measuring < 1 mm at 0.08 msec (also called J point ST depression), (**D**) horizontal ST depression, and (**E**) downsloping ST depression. Adapted from Hodnesdal C, Prestgaard E, Erikssen G, et al. Rapidly upsloping ST-segment on exercise ECG: a marker of reduced coronary heart disease mortality risk. Reproduced with permission from Hodnesdal C, Prestgaard E, Erikssen G, et al: Rapidly upsloping ST-segment on exercise ECG: a marker of reduced coronary heart disease mortality risk. *Eur J Prev Cardiol*. 2013 Aug;20(4):541-548.

Downsloping ST depression is most predictive of angiographic CAD whether it occurs during exercise or recovery, the latter termed "ischemic evolution" and is highly specific for CAD.[3] Horizontal ST depression is also predictive of angiographic CAD, although less so than if downsloping. More controversial is ST depression that is upsloping but remains 1 mm or more 0.08 seconds after the J point (slow upsloping ST depression). ST depression at the J point that slopes up rapidly such that the ST depression is < 1 mm at 0.08 seconds after the J point of the QRS is commonly observed and is not indicative of ischemia.[47]

Slow Upsloping ST Depression

In a 6-year outcome study by Stuart and Ellestad of 2700 patients undergoing exercise testing between 1964 and 1975, 438 had 2 mm or more of ST depression when evaluated in immediate recovery.[48] (When exercise treadmill testing was initially performed, ECGs were performed during recovery rather than during exercise and recovery.) Using a composite end point of cardiac death, nonfatal MI, and the onset or progression of angina, patients whose ST depression was downsloping had the worst prognosis, followed by those with ST depression that was either horizontal or slow upsloping (Fig. 13–7). Those with no or < 2 mm of ST depression experienced a favorable prognosis. In a separate group of patients in the same study who underwent coronary angiography and whose antecedent exercise test demonstrated at least 1 mm of ST depression, those whose ST depression was downsloping included numerically more subjects with two- or three-vessel CAD of *at least* 50% stenosis (62%) than those with horizontal (60%) or upsloping (57%) ST depression. This cohort of patients from several generations ago had substantially more CAD than patients currently undergoing exercise testing in the United States today,[49] resulting in increased test sensitivity.

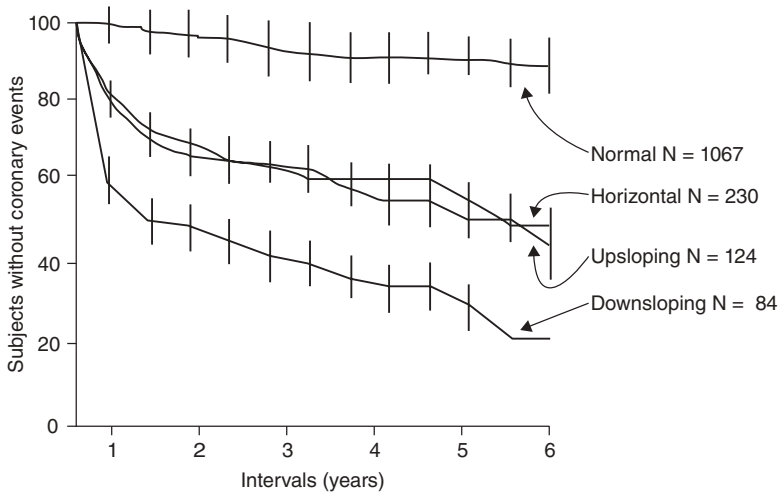


FIGURE 13–7. ST depression predicts coronary events. Using a composite end point of cardiac death, nonfatal myocardial infarction, and the onset or progression of angina, Stuart and Ellestad found that patients whose ST depression was downsloping had the worst prognosis, followed by those with ST depression that was either horizontal or slow upsloping. Adapted with permission from Stuart RJ, Ellestad MH: Upsloping S-T segments in exercise stress testing. Six year follow-up study of 438 patients and correlation with 248 angiograms, *Am J Cardiol*. 1976 Jan;37(1):19-22.[48]

Contemporary with the study of Stuart and Ellestad,[48] Brody,[50] Goldschlager,[3] and Kurita and colleagues[51] found 1.5 mm of upsloping ST depression to be highly predictive of angiographically significant CAD. Using 2 mm of upsloping ST depression as their threshold for a positive test, Rijneke and associates found improved sensitivity in men and women when adding upsloping ST depression to horizontal and downsloping ST depression.[32] Other investigators studying a more recent patient cohort found upsloping ST depression to predict CAD, but with specificity progressively decreasing if ≥ 2, ≥ 1.5, or ≥ 1 mm of upsloping ST depression was used as the threshold for positivity.[52]

RECOMMENDED CRITERIA FOR AN ABNORMAL ELECTROCARDIOGRAPHIC RESPONSE TO EXERCISE

The criteria for an abnormal ST-segment response of horizontal or downsloping ST depression of 1 mm or more was recommended by the AHA in a 2001 statement adding that slow upsloping ST depression of 2 mm or more was a borderline response.[23] In the ACC/AHA 2002 exercise testing guidelines, only at least 1 mm of horizontal or downsloping ST depression is characterized as abnormal.[6] Using only ST depression that is horizontal or downsloping diminishes the sensitivity of exercise testing. In their 2013 AHA scientific statement on exercise standards for testing and training, Fletcher and coauthors characterize ≥ 1 mm of slow upsloping as equivocal. If exercise testing is used to "screen" a population of normal individuals, disease prevalence is low enough to exclude slow upsloping ST depression as a criterion for positivity, as the positive predictive value would be too low. In patients referred for exercise testing, however, we recommend that slow upsloping ST depression of ≥ 1.5 mm be included as a criterion for a positive exercise test in addition to the conventional criterion of ≥ 1.0 mm of horizontal or downsloping ST depression.[40] The addition of ≥ 1.5 mm of slow upsloping ST depression facilitates opportune test sensitivity in an era of diminished CAD severity and allows a better use of exercise testing in patients actually referred for exercise testing.

In order to be reliable, the ST depression being measured should be present in multiple consecutive beats in at least one ECG lead. T-wave changes during exercise, such as the development of T-wave inversion with exercise or pseudonormalization, an inverted T wave at rest that becomes upright with exercise, are nonspecific findings.[2]

ONSET OF ST DEPRESSION

The earlier during exercise that ST depression occurs and the lower the rate pressure product of this depression, as well as the longer it lasts during recovery, the more severe the CAD as manifested by the incidence of multivessel and left main disease of coronary angiography.[3,12]

Although ST depression during exercise often persists into recovery, it may not manifest until exercise has been terminated. In a study of 214 subjects without known CAD who had asymptomatic ST depression during exercise testing, Rywik and colleagues observed ST depression only during recovery in 29% of patients. Over the ensuing 6 years, the development of angina, nonfatal MI or cardiac death was 2.5 times greater in those with ST depression regardless of whether it occurred during exercise or recovery (Fig. 13–8).[53]

In a study of 168 men with ST depression during exercise testing who underwent subsequent coronary angiography, Lachterman and coworkers found that 15% demonstrated ST depression only during recovery. Recovery-only ST depression had the same predictive power of angiographic CAD as ST depression occurring during exercise.[54] The work of Goldschlager and colleagues in a group of 330 patients undergoing exercise testing and coronary angiography emphasizes the importance of a careful review of the ECGs obtained during every minute of recovery. They found ST depression to occur more frequently and be more abnormal during the first 3 minutes of recovery than during exercise itself. For example, in the 90 patients who developed ≥ 2 mm of slow upsloping ST depression during exercise, 63% developed horizontal or downsloping ST depression of ≥ 1 mm during recovery, indicative of ischemic evolution.

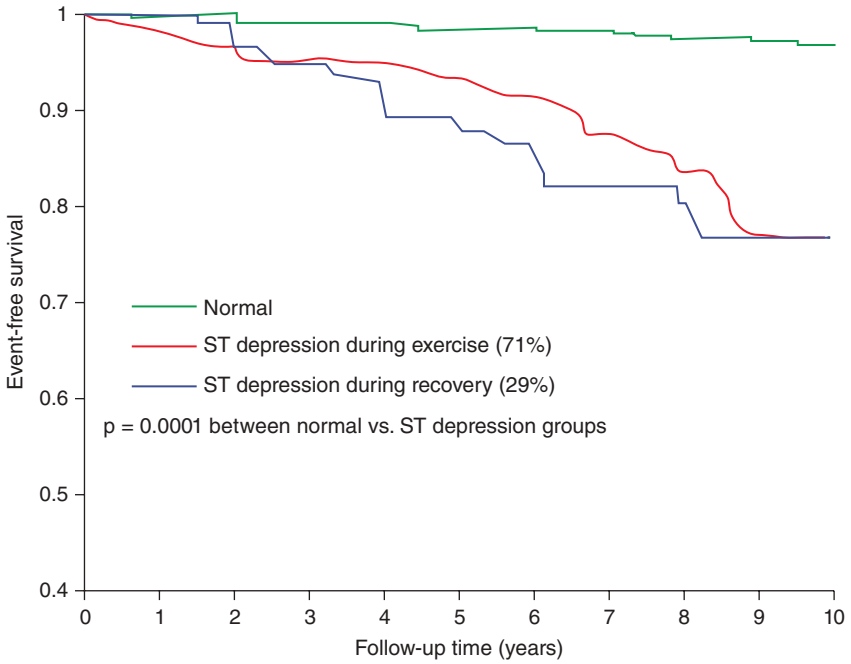


FIGURE 13–8. ST depression in recovery predicts 6-year outcomes. In a group of 1500 subjects without known coronary artery disease, 214 subjects developed horizontal or downsloping ST depression on exercise testing. Six-year freedom from the development of angina, nonfatal myocardial infarction, or cardiac death was not different between the 71% who developed ST depression during exercise or the 29% who developed ST depression only during recovery. Reproduced with permission from Rywik TM, Zink RC, Gittings NS, et al: Independent prognostic significance of ischemic ST-segment response limited to recovery from treadmill exercise in asymptomatic subjects, *Circulation*. 1998 Jun 2;97(21):2117-2122.[53]

LOCATION OF ST DEPRESSION

ST depression during exercise testing in the precordial leads is more predictive of CAD than in the inferior leads, potentially because of atrial depolarization affecting the ST segment in the inferior leads. Location of ST-segment depression does not predict the artery/region of myocardium involved.[43]

ST-SEGMENT ELEVATION

ST elevation occurring during exercise in contiguous leads without Q waves is a particularly ominous sign of ischemia and poor outcomes, often consistent with a high-grade proximal coronary lesion. It is also arrhythmogenic and is frequently accompanied by peaked T waves in the same leads, not unlike the ECG of a STEMI. Unlike ST depression during exercise testing, ST elevation during exercise in contiguous leads with an R wave localizes to the coronary artery involved.[55] Although ST depression is consistent with subendocardial ischemia, ST elevation is most consistent with transmural ischemia. Exercise is best terminated if ≥ 1 mm of ST elevation occurs during exercise testing; continuing exercise in the face of ST elevation in leads without Q waves creates substantial risk to the patient. If ST elevation in leads without Q waves is associated with angina or other high-risk features during exercise, coronary angiography should be considered, often urgently.[2] ST elevation present at rest in the setting of Q waves from a previous MI may result in an increase in ST elevation with exercise that is generally not indicative of ischemia.

LEAD AVR

Lead aVR is often unnecessarily neglected during exercise testing. On Einthoven's classic triangle, aVR represents current going toward –150 degrees, which is roughly opposite to the left ventricular apex. Thus, the ST segment responds in a reciprocal fashion, becoming elevated in the setting of subendocardial apical ischemia. Thus, ST depression in V2 to V6 or leads 2 and 3 is often reflected as ST elevation in aVR. At times, diffuse ischemia from three vessel or left main disease results in cancelling out ST deviation in other leads but ST elevation in AVR often remains.[2,56] Monitoring and evaluation of aVR with exercise is now endorsed within the 2013 AHA scientific statement on exercise standards for testing.[42]

OTHER TEST PARAMETERS

BLOOD PRESSURE RESPONSE

Systolic blood pressure should rise with increasing treadmill workload, whereas diastolic blood pressure usually remains approximately the same or decreases (see Fig. 13–1). Although exertional hypotension has been defined in many ways, it has been shown to predict severe angiographic CAD and is associated with a poor prognosis.[57] A drop in systolic blood pressure below preexercise values is the most ominous sign. A failure of systolic blood pressure to adequately increase is particularly worrisome in patients who have a past history of MI, although in some patients this may be secondary to aggressive blood pressure control with medical therapy.

EXERCISE DURATION

As emphasized by Bruce at the advent of treadmill testing, the longer the exercise duration, the better the prognosis. For a number of years, the chief parameter assessed during exercise testing was not a measure of ischemia per se, but exercise duration, measured in either METs or minutes of exercise on a treadmill protocol. A patient in whom exercise duration on a treadmill is prolonged, however, cannot always expect to have a good prognosis. In the Coronary Artery Surgery Study, Weiner and colleagues found prognosis to be good if the patient reached stage 4 on the standard Bruce protocol (10 METs). This held true as long as the patient had < 2 mm of ST depression. If the patient had > 2 mm of ST depression, prognosis was poor despite achieving stage 4 of the Bruce protocol (Fig. 13–9).[58]

INFLUENCE OF THE RESTING ELECTROCARDIOGRAM

The closer to normal the ECG is at rest, the more accurate the evaluation of the ECG during the heart rate increase of exercise. Among patients with ≥ 1 mm of ST depression at rest, an increase of > 2 mm in horizontal ST depression or > 1 mm of downsloping ST depression is considered an abnormal response. Left bundle branch block, ventricular preexcitation (ie, Wolff-Parkinson-White pattern), changes associated with digoxin use in the preceding 2 weeks, and ventricular paced rhythms preclude the ability to interpret ischemic changes electrocardiographically.[6] Left ventricular hypertrophy with repolarization abnormalities diminishes sensitivity, but specificity is maintained.[6]

CHRONOTROPIC RESPONSE

Ellestad and colleagues found that chronotropic response inversely predicted the development of the composite end point of cardiac death, nonfatal MI, and the onset or progression of angina.[43] From the same group, Chin and colleagues demonstrated that among patients not taking beta-blockers, a peak heart rate achieved on exercise testing that was two standard deviations less than MPHR predicted CAD.[2,59] Lauer and associates found that patients who were not taking beta-blockers and who did not reach 85% of MPHR (measured as 220 – age) experienced substantially increased all-cause mortality.[60]

HEART RATE RESPONSE IN RECOVERY

In their 1929 abstract first describing the standardized step test, Master and Oppenheimer described a rapid return of heart rate toward normal as indicative of "circulatory efficiency" or fitness.[1] The decrease in heart rate postexercise is considered to be a function of the reactivation of vagal tone.[61] Lauer further characterized this heart rate recovery response with quantitation and outcome evaluation. He found that that those who fail to decrease their heart rate by 12 beats/min 1 minute postexercise during a recovery walking 1.5 miles/hour at a grade of 2.5% experienced increased all-cause mortality.[62–64]

THE EFFECT OF MEDICATIONS

Antianginal medications diminish ischemia with exercise stress and thus the opportunity to observe ischemic ECG changes. The effect of beta-blockers is particularly important given their impact on the maximum heart rate achieved. Digoxin renders ST-segment evaluation difficult for up to 2 weeks following its last dose.

TREADMILL SCORES

The most widely used score to integrate parameters of exercise testing is the Duke Treadmill Score. This was developed in 1987 among a group of 2842 consecutive inpatients with angina undergoing treadmill testing within 6 weeks of coronary angiography performed between 1969 and 1980.[65] The derived score utilized the components of the

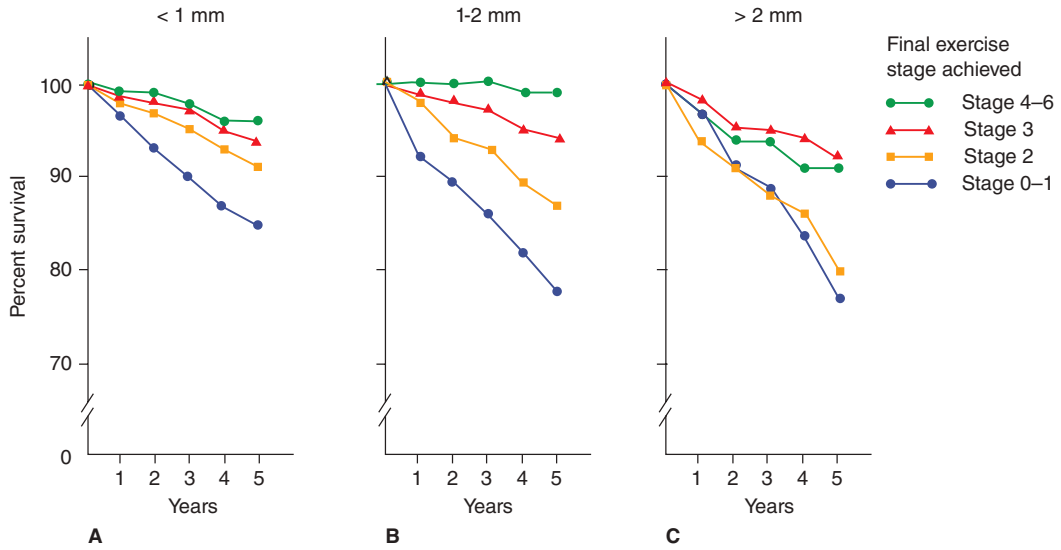


FIGURE 13–9. Overall survival (**A**) and myocardial infarction free survival (**B**) based on Duke Treadmill Score in 2842 consecutive inpatients with angina undergoing treadmill testing within 6 weeks of coronary angiography performed between 1969 and 1980. Reproduced with permission from Mark DB, Hlatky MA, Harrell FE Jr, et al: Exercise treadmill score for predicting prognosis in coronary artery disease, *Ann Intern Med*. 1987 Jun;106(6):793-800.[65]

exercise test that best predicted cardiovascular death or nonfatal MI over a mean 5 years of follow-up.

Duke Treadmill Score = Exercise time in minutes on the standard Bruce protocol − 5 × ST deviation (depression or elevation measured in mm in the lead with the greatest degree of ST deviation) − 4 × exercise angina index

In the exercise angina index,

0 = no angina on the treadmill

1 = angina occurred

2 = angina caused termination of exercise

Note that parameters that predict improved outcome are positive numbers (eg, duration of exercise), whereas negative predictors, such as ST deviation, are negative numbers. A score with an excellent prognosis would be +25. A poor prognostic score would be –25. The researchers arbitrarily grouped patients in the study into those at lowest risk (a score of +5 or greater), moderate risk (+4 to –10) and highest risk (–11 or lower). During follow-up, 24% of patients underwent coronary artery bypass grafting (CABG). They were censured at the time of surgery from further follow-up. To obtain the event-free survival outcomes shown in Fig. 13–10, 24% of patients crossed over from medical to surgical therapy.

Mark and colleagues further validated the score in a study of 613 consecutive outpatients undergoing Bruce protocol exercise testing and followed for a mean of 4 years using cardiovascular death as the end point.[66] As seen in Table 13–5, the score was a good predictor of outcome in both inpatients[65] and outpatients.[66] The crossover rate to CABG or percutaneous coronary angiography in the outpatient population was 8%. Because patients currently undergoing exercise testing have a lower burden of CAD compared to the study time period,[49,67] scores will be skewed to the lower risk category, resulting in less robust risk stratification. However, its use as a continuous variable and rather than a simple categorization into low, moderate, and high risk adds valuable predictive information to an exercise test report.

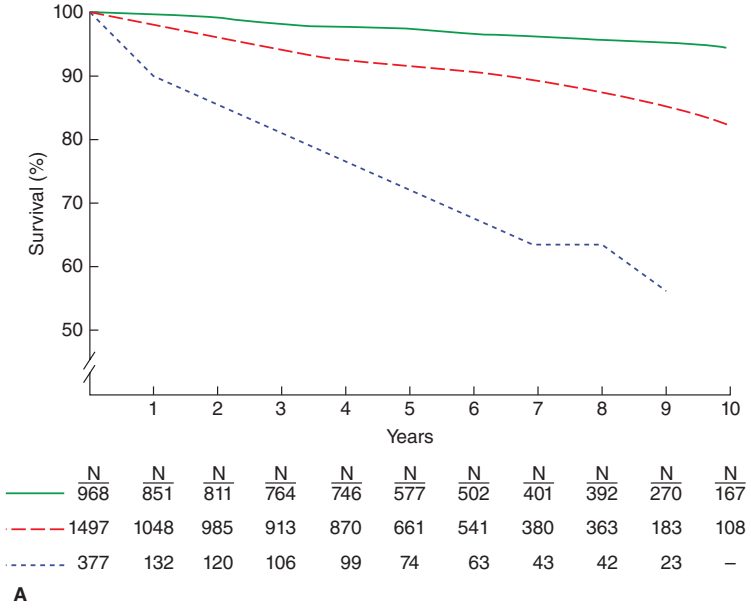
EXERCISE TESTING WITH A NEGATIVE EXERCISE MYOCARDIAL PERFUSION IMAGING STUDY

Because diagnostic test accuracy is greater for MPI than stand-alone exercise testing, there is a tendency to ignore the results of a positive exercise test if perfusion imaging is normal. In other words, accept the premise that imaging trumps the exercise ECG. However, applying Bayes theorem in this situation demonstrates that although a normal MPI study decreases the probability that the exercise ECG is falsely positive, it does not eliminate it. In 208 consecutive patients undergoing exercise thallium-201 MPI, Raiker and coworkers tracked cardiac death, nonfatal MI, and the development of unstable angina over 13 months. Of those with a normal or nondiagnostic exercise test and normal perfusion, the event rate was 2/175 (1%). A positive exercise test was defined as ≥ 2 mm of horizontal or downsloping ST depression. Among those with a positive ECG exercise test and normal perfusion, the event rate was 3 of 33 (9%). Thus, both perfusion and exercise response add information, and clinical judgment should be applied when they are discordant.

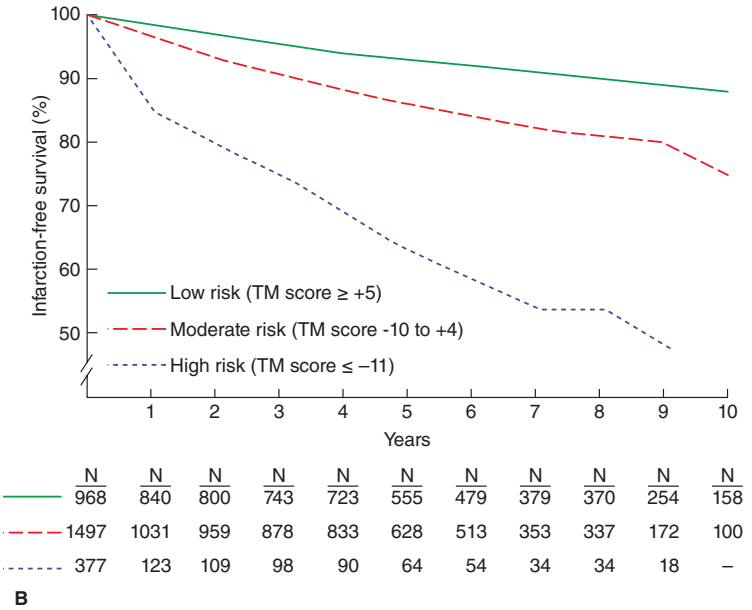
EXERCISE TESTING WITH A NEGATIVE EXERCISE STRESS ECHOCARDIOGRAM

McCully and colleagues followed 1325 patients for approximately 3 years following an exercise stress echocardiogram in which wall motion of all 17 segments that were normal at rest were either normal or hyperdynamic poststress—defined as a normal stress echocardiogram.[68] The cardiac event end point of cardiac death, nonfatal MI and coronary revascularization, averaged 0.9% per year over the time period. However, if the patient developed angina during exercise testing, despite the normal poststress wall motion, the relative risk of a subsequent cardiac event was 4.1 times greater than if they did not.

Rather than routinely accepting that imaging trumps the ECG and symptoms in patients undergoing exercise testing with adjunctive imaging, clinical judgment should be used in the evaluation entertaining the potential that imaging may be falsely negative. Depending on the pretest likelihood of CAD and degree of ECG changes or exercise induced symptoms, a calcium score with noncontrast cardiac computed tomography (CT) or CT coronary angiography can prove helpful in these situations.



A



B

FIGURE 13–10. ST depression and exercise time predicts prognosis. **A** and **B** demonstrate good prognosis for patients who achieved stage 4 or greater if ST depression was *less than* 2 mm. However, if ST depression was more than 2 mm, prognosis was poor regardless of exercise duration. Adapted with permission from Weiner DA, Ryan TJ, McCabe CH, et al: Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. *J Am Coll Cardiol*. 1984 Mar;3(3):772-779.[58]

TABLE 13–5. Four-year Survival from a Cardiovascular Cause of Death Based on Duke Treadmill Score[a]

Risk of Death	Inpatient n (%)	Inpatient Survival	Outpatient n (%)	Outpatient Survival
Low (≥ +5)	470 (34%)	98%	379 (62%)	99%
Moderate (+4 to –9)	795 (57%)	92%	211 (34%)	95%
High (< –10)	129 (9%)	71%	23 (4%)	79%

[a]A comparison of the frequency of Duke Treadmill Scores and survival with the avoidance of cardiovascular death for each score category among inpatients from the initial derivation study of 2842 inpatients (Mark DB. *Ann Intern Med*. 1987;106:793-800[65]) and 613 outpatients (Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med*. 1991;325:849-853[66]). The score had good predictive value in both inpatients and outpatients.

Adapted with permission from Mark DB, Shaw L, Harrell FE, et al: Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991 Sep 19;325(12):849-853.[66]

WHEN TO USE EXERCISE TESTING?

Like "plain old balloon angioplasty," stand-alone exercise testing may be less appealing to the clinician than exercise testing with adjunctive imaging. Exercise testing is, however, remarkably effective as an initial and often final test in patients able to exercise and with ECGs that do not preclude the interpretation of ischemia with exercise. The authors of the 2013 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease guidelines, written by representatives from leading US cardiology societies, recommend the stand-alone exercise stress test in appropriately selected patients.[27] The primary recommended use of adjunctive imaging is among patients who are either unable to achieve adequate exercise stress, have abnormal resting ECGs, or who require a test with greater sensitivity.[27]

The ACC/AHA 2002 guidelines for exercise testing include comprehensive indications for exercise testing.[26] One of the key class I recommendations is that exercise testing serve as the initial test for adult patients in the diagnosis of obstructive CAD with an intermediate pretest probability of CAD on the basis of age, sex, and symptoms.[6] Class III exclusions to this indication are patients in whom the ECG is uninterruptible, including those with ventricular preexcitation, paced ventricular rhythm, > 1 mm of resting ST depression, or left bundle branch block. Exercise testing is also a class I recommendation in the assessment of risk and prognosis in patients with symptoms or a prior history of CAD. This includes (1) patients with suspected or previously evaluated known CAD presenting with a change in clinical status, (2) low-risk unstable angina patients 8 to 12 hours after presentation who have been free of active ischemic or heart failure symptoms, and (3) intermediate-risk unstable angina patients 2 to 3 days after presentation who have been free of active ischemic or heart failure symptoms.

Submaximal exercise testing in which exercise is stopped at a predetermined end point, such as a peak heart rate of 120 beats/min, 70% of MPHR, or a peak MET level of 5, can be used as a class I indication 4 to 7 plus days post-MI for evaluation of medical therapy, prognostic assessment, and/or development of an activity prescription.

Exercise testing also has class I indications to demonstrate ischemia prior to revascularization and in the evaluation of patients with recurrent symptoms that suggest ischemia after revascularization.

EXERCISE TESTING IN WOMEN

Traditionally exercise testing has thought to be less accurate in women than men.[26] Levisman and colleagues point out, however, that many of the studies on which this premise is based excluded women older than 65 years, an age when CAD prevalence and severity are greater.[69] Levisman and colleagues thus age-stratified 111 women undergoing both exercise testing and coronary angiography. The positive predictive value (PPV) of exercise testing of the overall group was 51%. For women 35 to 50 years, PPV was 36%, compared to 68% for those older than 65 years. Among those with true positive tests, three-vessel disease was present in about 55% of those older than 65 years and about 25% of those 35 to 50 years. Thus, the expected lower sensitivity and specificity traditionally observed in women may be explained by differing CAD prevalence and severity. Testing in a population of women with CAD severity as great as in men, sensitivity is likely similar between the two sexes. Another challenge in evaluating test sensitivity in women is the use of obstructive CAD on coronary angiography as the gold standard. More than men, women experience ischemia and events, including MI, with coronary stenoses of < 50%.[68]

In the What is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial, Shaw and coworkers randomized 824 symptomatic women with interpretable ECGs who were expected to achieve five METs to stand alone exercise testing or to exercise MPI.[70] At the end of 2 years, there was no difference in the primary end point, survival free from a major cardiac adverse event (98.0% for exercise testing and 97.7% for MPI).

Kohli,[71] Borque and colleagues,[72] and Mieres and the coauthors of the AHA consensus statement on the role of noninvasive testing in women[73] emphasize the use of parameters other than only the use of ST-segment deviation in women. They comment on the powerful additional predictive information demonstrated in women as well as men of exercise duration, the Duke Treadmill Score, and heart rate recovery.

Consistent with the ACC/AHA 2002 guidelines for both sexes,[6] the 2014 AHA consensus statement on the role of noninvasive testing in women recommends exercise testing as the initial test for symptomatic women with interpretable ECGs who are able to exercise.[73]

NOVEL ELECTROCARDIOGRAM PARAMETERS

Building on previous work,[74] Sharir and colleagues evaluated the use of an advanced signal processing ECG lead system designed to measure low-amplitude, high-frequency electrical signals during the QRS complex.[75] These signals are termed high-frequency mid-QRS (HFQRS) waveforms. The amplitude of the standard waveforms measured on the standard ECG at rest and during exercise are measured in millivolts and at frequencies generally less than or equal to 100 Hz. HFQRS waveforms are about 100 times smaller in amplitude and are thus measured in microvolts rather than millivolts and are high frequency, 150 to 250 Hz. Abboud and colleagues previously demonstrated an approximately 33% decrease in HFQRS during ischemia induced by balloon inflation in a coronary artery.[74] As reviewed by Amit and colleagues, the normal extensive branching His-Purkinje system results in a vast array of myocardial activation sites and thus a depolarization wave front with numerous HFQRS signals.[76] Ischemia, however, slows myocyte-to-myocyte conduction, resulting in a decrease in the amplitude of high-frequency waveforms arising from this area of ischemia. This is useful for exercise testing, because the development of ischemia during exercise results in decreasing amplitude of HFQRS waveforms. In the 996-patient exercise testing study of Sharir, she found that when advanced signal processing to measure HFQRS was added to standard ST-segment analysis, this resulted in a significant increase in sensitivity and specificity using ischemia by MPI as the gold standard.[75]

Rosenbaum and colleagues evaluated the addition of HFQRS to ST-segment evaluation during exercise testing in 113 women. Using coronary angiography as the gold standard, the addition of HFQRS improved specificity. As well, the number of leads with decreased HFQRS amplitude correlated with the number of stenotic coronary arteries.[77] A large multicenter prospective trial evaluating the value and limitations of HFQRS analysis is strongly recommended to evaluate this promising technology.

COMBINING CALCIUM SCORING WITH EXERCISE TESTING

In a retrospective study of 153 symptomatic patients who underwent exercise testing, calcium scoring, and coronary angiography, Lamont and colleagues described how the combination of calcium scoring could theoretically enhance the accuracy of exercise testing.[78] Coronary calcification was present in 81% of the cohort and nearly 99% of those with angiographic CAD. Of the 27% of patients without CAD, 66% had no coronary calcium.

In 2013 Rozanski and colleagues coined the term the *calcium treadmill test*.[79] They suggested that this combination of exercise testing and a coronary artery calcium score (CAC) could evaluate not only ischemia and functional capacity with exercise testing but also

calcific coronary atherosclerosis with CAC. They posit the use of this combination test may be initially best used in stable, mildly symptomatic patients able to exercise.

Chang and coworkers evaluated the results of about 1000 patients who underwent exercise testing and CAC as part of previously published prospective trial.[80] Increasing CAC added substantial prognostic information over the 7-year follow-up period to the exercise test parameters of ST-segment depression, Duke Treadmill Score, and exercise capacity in the prediction of cardiac death, nonfatal myocardial infarction, and revascularization.

Thompson and coworkers previously evaluated how unprompted clinicians responded to a CAC score of more than 100 Agatston units performed in relation to an exercise or pharmacologic MPI that was normal. At a mean follow-up of 9 months, a CAC of more than 100 resulted in a significant increase in aspirin use and a near doubling in statin use.[81]

CAC results show great promise in appropriately influencing post-test management in patients with normal or abnormal exercise tests.[82] Prospective trials of the potential role of the calcium treadmill test are warranted.

CONCLUSION

Exercise testing is a powerful predictor of CAD diagnosis and prognosis. Its careful and thoughtful performance creates the opportunity for this inexpensive test to continue to serve as the backbone of the noninvasive evaluation of CAD.

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CHAPTER 14

CARDIAC RADIOGRAPHY

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With the advantages of echocardiography, magnetic resonance imaging (MRI), computed tomography (CT), and single-photon emission tomography as primary analytical and treatment planning tools for cardiovascular disease, the chest radiograph has less importance for primary cardiac assessment than it did in the past. Nevertheless, the ubiquity of chest radiography in medical care presents many opportunities for recognition of intrathoracic manifestations of cardiovascular pathology and pathophysiology that could then lead to definitive diagnosis with one of the aforementioned advanced imaging techniques. Moreover, within the acute care setting, chest radiography is a critical tool for assessing the position of supportive devices and for detecting life-threatening complications of such devices (eg, hemorrhage and pneumothorax).

Despite its loss of primacy for the assessment of many primary cardiac disorders,[1-4] a systematic search of the radiograph performed independent of the results of other imaging tests allows for recognition of such complications. Although some experts recommend performing the initial interpretation without clinical information to prevent erroneous information from misleading the radiographic interpretation, there are no published data to support this approach. Moreover, the development of the electronic health record and its associated widespread availability at the time of radiographic interpretation provides a basis for substantially greater value of an interpretation made within the context of prior information and leading to clinically actionable analyses. Nevertheless, bearing in mind the principle of blinded radiographic interpretation will prepare the interpreter to identify unexpected findings that might have been missed in a search directed by symptoms and medical history. Even when the interpreter prefers a blinded initial interpretation. the *final* radiographic diagnosis should be made only after correlating the radiographic findings with clinical information and other laboratory data.[5]

The radiographic examination for heart disease consists of four major steps. They are (1) radiographic examination for anatomy, (2) comparison to prior studies, (3) clinical correlation, and (4) conclusion and recommendations.

VISUAL SEARCH AND CHARACTERIZATION OF ABNORMALITIES

AN OVERVIEW

A detailed explanation of chest radiographic search and interpretation is beyond the scope of this chapter. As was mentioned, a search pattern that involves comprehensive evaluation of all thoracic structures is key to ensuring a thorough analysis. There is no one correct approach to the patterned search, but each search and assessment should include a dedicated assessment of all visible structures.

In the setting of cardiac disease, it is tempting to principally focus on the heart, but cardiac conditions can be manifest in noncardiac structures. For instance, a right-sided stomach with an absent inferior vena cava (IVC) margin suggests congenital interruption of the IVC with azygos continuation[6,7] (Fig. 14–1). A narrowed anteroposterior (AP) diameter of the thorax can be the cause of an innocent murmur[8] (Fig. 14–2).

ASSISTIVE DEVICES

In the setting of cardiac disease, devices that assist or support the monitoring of cardiac function are commonly encountered on the chest radiograph. In the outpatient setting, these devices include pacemakers (Fig. 14–3), implantable cardioverter-defibrillators (ICDs), and cardiac assist devices (Fig. 14–4). In addition to these devices, inpatients, particularly those in intensive care, may have central venous (Fig. 14–5A) and pulmonary arterial catheters (see Fig. 3–5B) or temporary venous pacemakers. A detailed assessment of the positioning and integrity of these devices is critical to the interpretation of cardiac radiography.

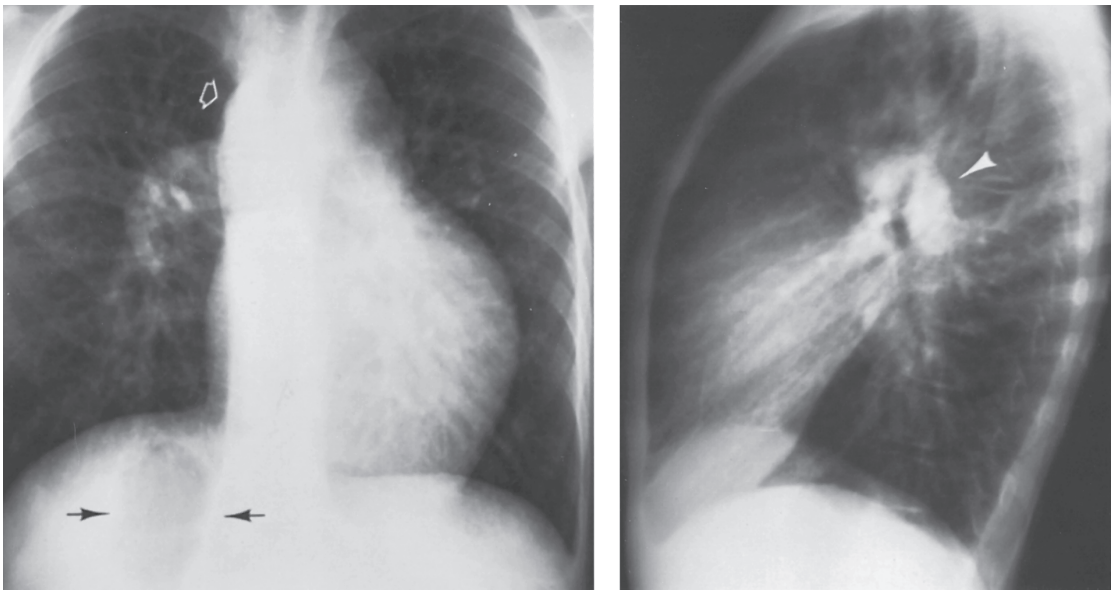
Pacemakers and ICDs are jointly classified as cardiac electronic implantable devices. The integrity of the leads that conduct and monitor current between a generator and regions of the myocardium is critical to their effective function. Radiography provides an excellent opportunity to evaluate lead integrity and requires both a well-penetrated radiograph and a disciplined search to maximize the likelihood that lead fractures will be recognized.[9]

Cardiac assist devices represent a diverse set of short- and long-term solutions to compensate for ventricular failure. Short-term devices include intra-aortic balloon pump (Fig. 14–6), extracorporeal membrane oxygenation, and a growing list of percutaneous or surgically inserted devices. Long-term devices, which traditionally served as a bridge to cardiac transplantation, are increasingly considered to be long-term solutions for patients with severe heart failure and for whom cardiac transplantation is not a viable option. Familiarity with the appearance and proper placement of these devices is critical to their correct radiographic assessment (see Fig. 14–4).[10]

With the pace of innovation and clinical introduction of increasingly sophisticated, smaller, and less invasive supportive cardiac devices, it is impossible to present a representative listing of these devices and their associated radiographic manifestations and complications within the context of this chapter. Greater details can be found in excellent reviews of these devices and their appearance.[9,10]

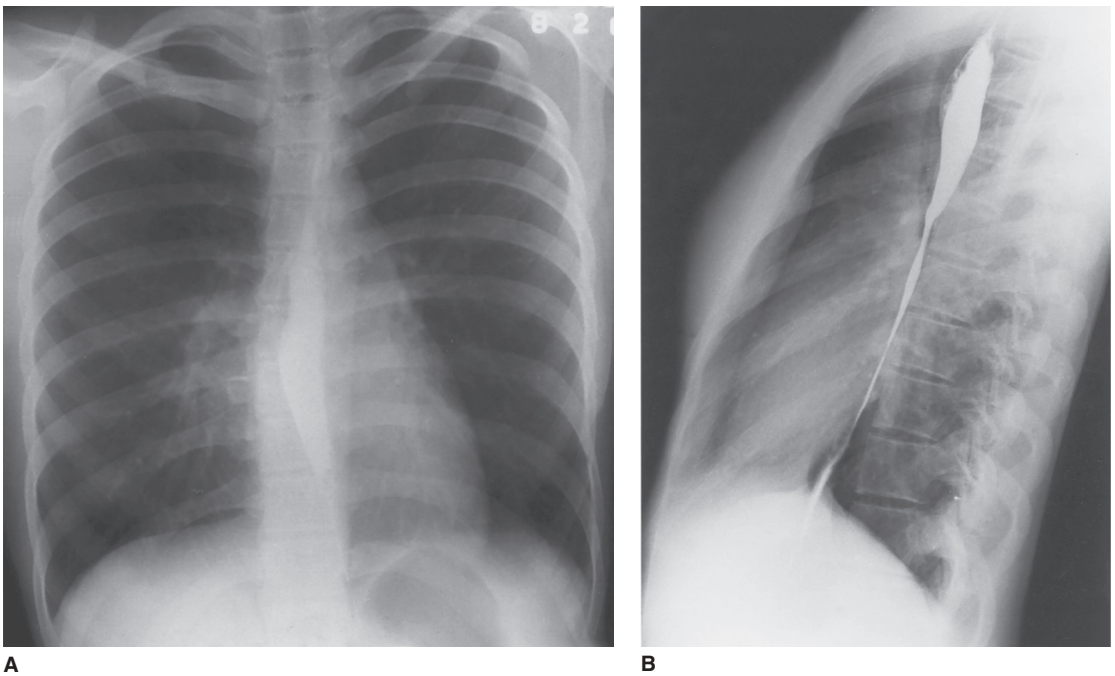
PULMONARY VASCULATURE

The lung can often reflect the underlying pathophysiology of the heart. For example, if uniform dilatation of all pulmonary vessels is present, the diagnosis of a left-to-right shunt (Fig. 14–7) is more likely than a left-sided obstructive lesion. The latter typically shows a cephalic pulmonary blood flow (PBF) pattern (see Fig. 14–4A).



A B

FIGURE 14–1. Patient with situs ambiguus, interruption of the inferior vena cava (IVC), ventricular septal defect, and polysplenia. **A.** Posteroanterior view shows that the aortic arch and the heart are left sided and the stomach (*lower arrows*) is right sided. The azygos vein (*upper arrow*) is markedly enlarged. The heart is mildly enlarged, and there is a moderate increase in pulmonary vascularity. **B.** The lateral view shows an absent image of the IVC. The azygos arch (*arrow*) is markedly dilated.



A B

FIGURE 14–2. A 16-year-old girl with straight-back syndrome. **A.** The posteroanterior radiograph shows normal pulmonary vascularity and normal heart size. Note the leftward displacement and rotation of the heart, making its left border unusually prominent. **B.** The lateral view shows that the anteroposterior diameter of the chest is extremely narrow. The heart is compressed, creating an innocent murmur. The esophagus is opacified following a barium swallow.

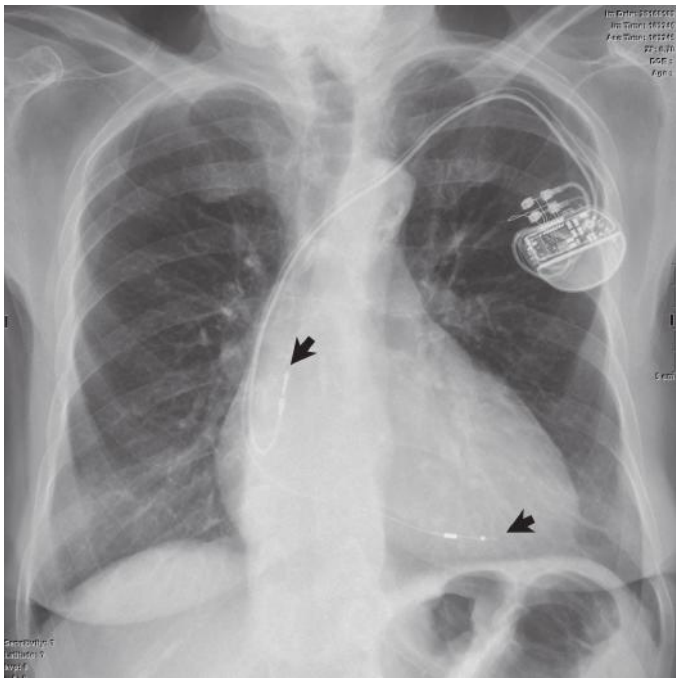


FIGURE 14–3. Fontal radiograph illustrating right atrial and right ventricular leads (*arrows*) from a left-sided subcutaneous pacemaker. Used with permission from Matthew Cham, MD, The Icahn School of Medicine at Mount Sinai.

A

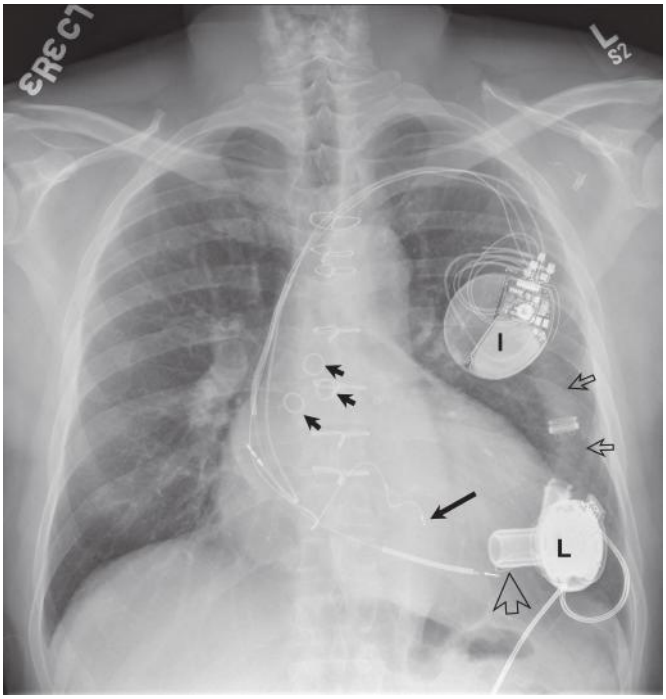
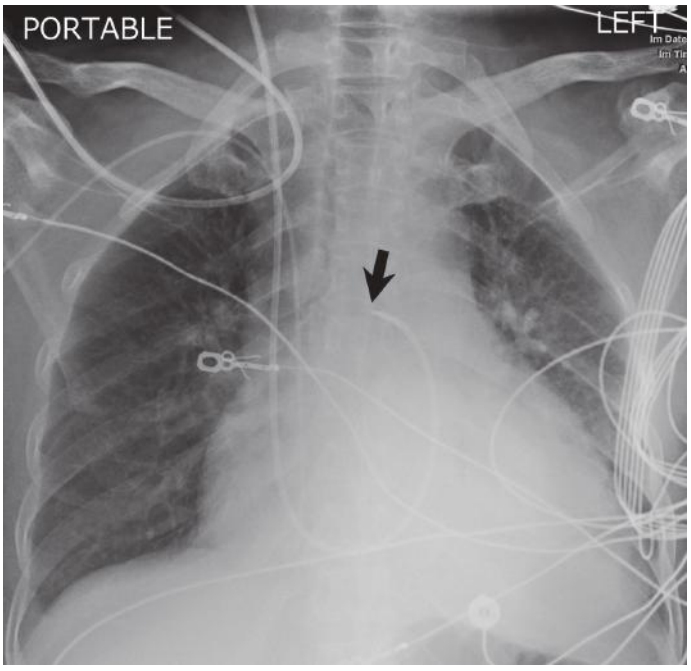


FIGURE 14–4. Frontal radiograph in a patient post–coronary artery bypass grafting with an implantable cardioverter-defibrillator (ICD) and left ventricular assist device (LVAD). The inflow cannula (*wide open arrow*) is engaged within the left ventricle, and the outflow cannula and barely visible conduit (*small open arrows*) carries the outflow to the aorta. Three coronary ostial ring markers (*short arrows*) are visible as well the LVAD (L) and ICD (I). In addition to the leads within the right atrium and right ventricle that contain the electrodes for defibrillation, a pacing lead is present within the coronary sinus (*long arrow*).



B

FIGURE 14–5. (**A**) Frontal portable radiograph demonstrates a right internal jugular venous catheter with tip near the cavoatrial junction (*arrow*). (**B**) Frontal portable radiograph obtained in a different patient with a right internal jugular Swan-Ganz catheter with tip in the proximal right pulmonary artery (*arrow*). A right subclavian venous catheter with tip in the right atrium is also present. Used with permission from Matthew Cham, MD, The Icahn School of Medicine at Mount Sinai.

FIGURE 14–6. Frontal portable radiograph demonstrated the tip of an intra-aortic balloon pump within the proximal descending thoracic aorta (*arrow*). The radiograph ensures that the pump is correctly positioned to function effectively and avoid interference with blood flow into the brachiocephalic branches of the aortic arch. Used with permission from Matthew Cham, MD, The Icahn School of Medicine at Mount Sinai.

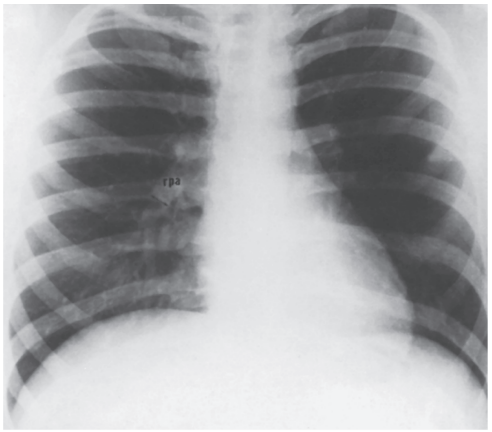
Normal Pulmonary Vascularity

The normal radiographic appearance of the pulmonary vasculature of an upright human being is typified by a caudal flow pattern because of gravity. The pressure differential between the apex and the base of the lung is approximately 22 mm Hg in adults in the upright position.[2,11] Therefore, more flow under higher distending pressure is expected in the lower lobe vessels than in the upper. Normally, whereas one sees very little vascularity above the hilum, more and larger vessels are found below the hilum. Because the pulmonary resistance is normal, all vessels taper gradually in a treelike manner from the hilum toward the periphery of the lung. The right descending pulmonary artery measures 10 to 15 mm in diameter in males and 9 to 14 mm in females[1,12] (see Fig. 14–7).

Abnormal Pulmonary Vascularity

Abnormal pulmonary vascularity can be classified into two categories, either in terms of volume or in terms of distribution[2,13,14] (Table 14–1).

Abnormalities in Volume In the evaluation of pulmonary vasculature, the caliber of the vessels is more important than the length or the number. As long as the PBF pattern remains normal, with a greater amount of flow to the bases than to the apices, the volume of the flow is proportional to the caliber of the pulmonary arteries (see Fig. 14–7). Besides measuring the right descending pulmonary artery, pulmonary blood volume can be assessed by comparing the size of the pulmonary artery



A

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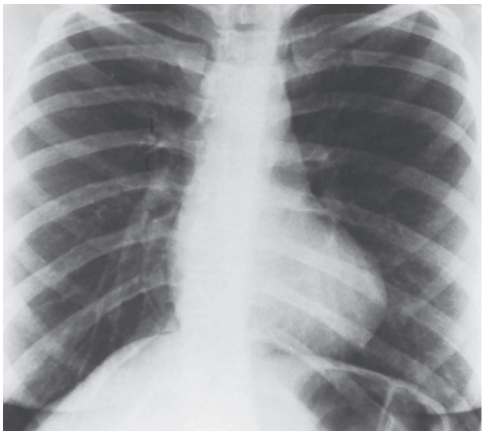


C

FIGURE 14–7. Radiographic assessment of the volume of pulmonary blood flow (PBF). **A.** Normal PBF. There is caudalization of the pulmonary vascularity because of gravity. The right descending pulmonary artery measures 13 mm in diameter in this young man. **B.** Increased PBF. Patient with a secundum atrial septal defect showing uniform increase in pulmonary vascularity bilaterally. The right descending pulmonary artery is markedly enlarged, measuring 27 mm. **C.** Decreased PBF. Patient with tetralogy of Fallot showing a boot-shaped heart and uniform decrease in pulmonary vascularity. The right descending pulmonary artery is much smaller than normal, measuring 6 mm in diameter.

TABLE 14–1. Pulmonary Vascularity

Normal
Caudal PBF pattern in upright position (PBF controlled by gravity)
Gradual branching, treelike
RDPA = 10–15 mm in men
RDPA = 9–14 mm in women
A/B ratio = 1
Abnormal
Volume with normal PBF pattern (distribution)
Increased, larger vessels (eg, ASD)
Decreased, smaller vessels (eg, ToF)
Distribution with abnormal PBF pattern
Cephalic (eg, MS)
Centralized (eg, Eisenmenger syndrome)
Lateralized (eg, Westermark sign)
Localized (eg, pulmonary AV fistulas)
Collateralized (eg, severe ToF)
Combined
Decreased volume and cephalization (eg, critical MS)
Lateralization and localization (eg, Scimitar syndrome)

Abbreviations: A/B, arterial/bronchial; ASD, atrial septal defect; AV, arteriovenous; MS, mitral stenosis; PBF, pulmonary blood flow; RDPA, right descending pulmonary artery; ToF, tetralogy of Fallot.

with that of the accompanying bronchus when these structures are viewed on end. This measurement is expressed as the arterial-bronchial diameter ratio (ABR). In the normal erect subject, upper lung arteries may be slightly larger than, equal in size to, or smaller than their accompanying bronchi, whereas the lower lung arteries are almost always larger than their accompanying bronchi (ABR: mean ± standard deviation, 1.34 ± 0.25). With progressive pulmonary venous hypertension, the ABR relationship between upper and lower lungs equalizes and then reverses such that upper lung ABR exceeds lower lung ABR in decompensated congestive heart failure.[15]

Increased Pulmonary Blood Flow In the case of mild to moderate left-to-right shunts, for example, the vessels dilate in proportion to the increased flow with no significant change in pressure, resistance, or flow pattern. This phenomenon is also called *shunt vascularity* or *equalization*. Equalization of the PBF between the upper and lower lung zones is only apparent rather than real; however, the lower lobes still receive a great deal more blood than the upper lobes, although the ratio of PBF between the two zones has changed—for example, from 5:1 to 4:1 or 3:1. A mild increase in pulmonary vascularity with slight cardiomegaly is commonly found in pregnant women and trained athletes with increased cardiac output (see Chap. 64).

Decreased Pulmonary Blood Flow Patients with pulmonic stenosis and associated ventricular septal defect (VSD) frequently show decreased pulmonary vascularity with smaller and shorter pulmonary arteries and veins and more radiolucent lungs (see Fig. 14–7C). Marked reduction in PBF is also encountered in patients with isolated right-sided heart failure without a right-to-left shunt (Fig. 14–8). This is attributed to the significant decrease in cardiac output from the right ventricle (RV).

Abnormalities in Distribution An abnormal distribution of PBF (or an abnormal PBF pattern) always reflects a changed pulmonary vascular resistance, either locally or diffusely (Fig. 14–9).

Cephalization In the presence of postcapillary pulmonary hypertension (PH), physiologic disturbances begin when the total intravascular pressure exceeds the oncotic pressure of the blood. As a result, fluid leaks out of the vessels and collects in the interstitium before filling the alveoli.

Pulmonary edema interferes with gas exchange, resulting in a state of hypoxemia. Alveolar hypoxia has a profound influence on the pulmonary vessels, causing them to constrict. Because there is greater alveolar hypoxia in the lung bases than in the apices, the basilar vessels constrict significantly, forcing the blood to flow upward. This phenomenon actually represents a reversal of the normal PBF pattern: redistribution or cephalization of the pulmonary vascularity.

Cephalization occurs in any of three conditions: (1) left-sided obstructive lesions—for example, mitral valvular[12] or aortic valvular stenosis; (2) left ventricular (LV) failure—for example, coronary heart disease or cardiomyopathies; and (3) severe mitral regurgitation (MR) even before pump failure of the LV occurs. It should be emphasized that unless there is obvious *constriction* of the lower-lobe vessels, the diagnosis of cephalization should not be made. Dilatation of the upper lobe vessels is of secondary importance and can be found without narrowing of the basilar vessels in a number of entities, most noticeably left-to-right shunts.

Centralization In the presence of precapillary PH, the pulmonary trunk and central pulmonary arteries dilate, and the distal pulmonary arteries constrict in a concentric fashion from the periphery of the lung toward the hilum. This phenomenon is called *centralization of the pulmonary vascularity*. It occurs in patients with primary PH, Eisenmenger syndrome, recurrent pulmonary thromboembolic disease, and severe obstructive emphysema (see Fig. 14–8A and B).

Lateralization Massive unilateral pulmonary embolism can cause a lateralized PBF pattern. Because one major pulmonary artery is obstructed, the blood is forced to flow through the healthy lung only. The paucity of pulmonary vascularity in the diseased lung with the obstructed pulmonary artery is termed the *Westermark sign* (see Fig. 14–9C). In the case of congenital valvular pulmonary stenosis, a jet effect from the stenotic valve can cause a lateralized PBF pattern in favor of the left side (Fig. 14–10).

Localization A localized abnormal flow pattern is exemplified by a pulmonary arteriovenous fistula (Fig. 14–11).

Collateralization Patients with markedly decreased PBF (eg, pulmonic stenosis) tend to show numerous small, tortuous bronchial arterial collaterals in the upper medial lung zones near their origin from the descending aorta. The native pulmonary arteries are extremely small, although smooth and gracefully branching.

Combined Abnormalities In reality, an abnormal pulmonary vascularity is often a mixed type. There is a great variety of possible combinations—for example, cephalization plus decreased flow in severe mitral stenosis (MS) or centralization with increased PBF in Eisenmenger atrial septal defect (ASD) (Fig. 14–12).

LUNG PARENCHYMA

With right heart failure, the lungs become unusually radiolucent because of decreased PBF. Conversely, significant left heart failure is characterized by the presence of pulmonary edema, a cephalic blood flow pattern, or both (Fig. 14–13). Long-standing, severe pulmonary venous hypertension can lead to hemosiderosis or ossification of the lung (or both).[14,16] When right heart failure results from severe left heart failure, the preexisting pulmonary congestion can improve because of the decreased PBF (see Fig. 14–13B).

CARDIOMEDIASTINAL SILHOUETTE

Contained within the mediastinum, the heart maybe indistinguishable from other structures of similar radiodensity within the mediastinum. The correct interpretation of the cardiac abnormalities is predicated by

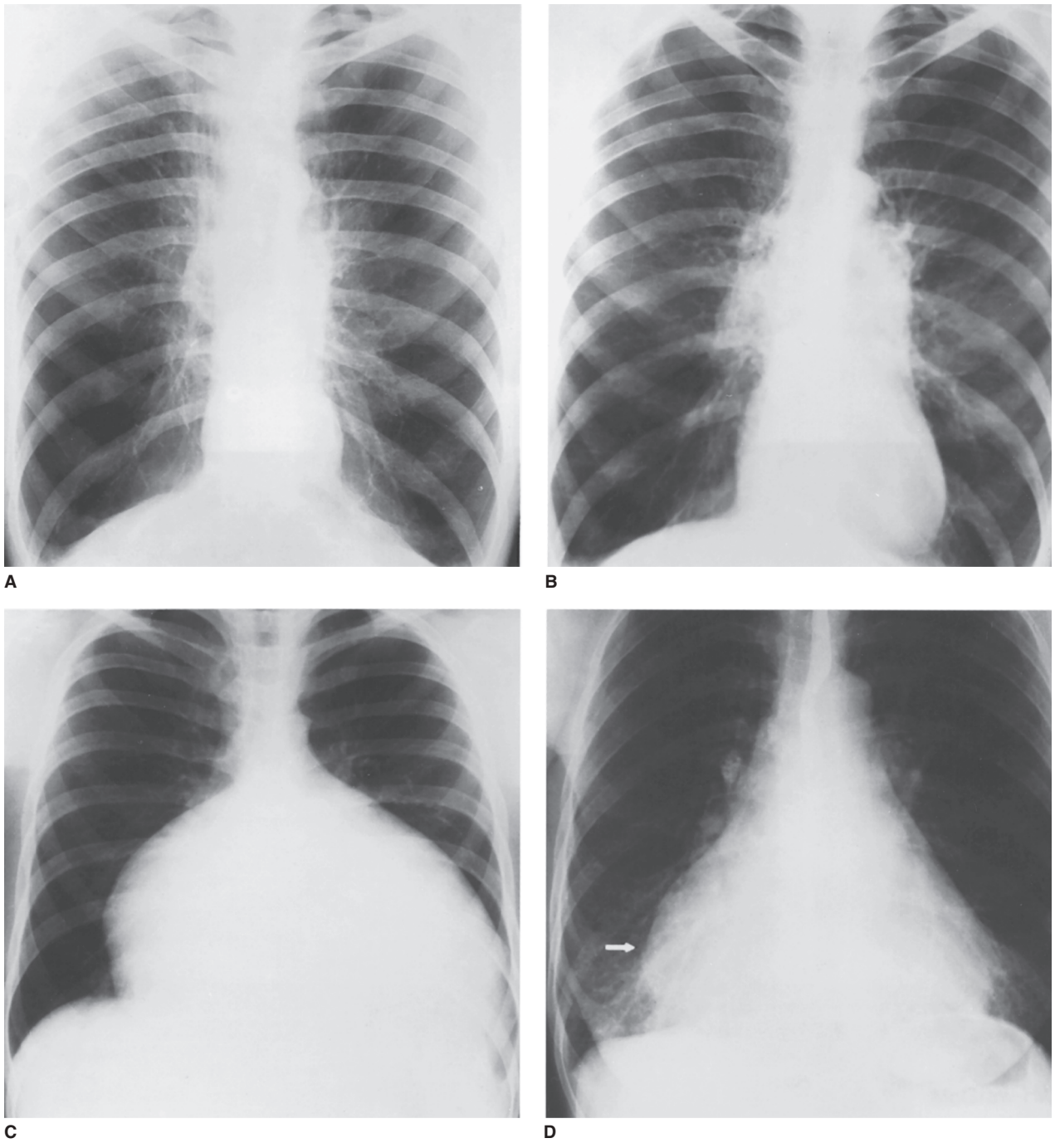


FIGURE 14–8. Radiographic appearance of right heart failure. **A.** A patient with severe obstructive emphysema showing overaeration of the lungs, centralized flow pattern, and a small heart size. **B.** Three years later, the patient was in frank right heart failure. Note that the heart enlarged as his emphysema worsened. The centralized flow pattern became more severe. **C.** Patient with Ebstein anomaly showing gross cardiomegaly with severe decrease in pulmonary vascularity. The right cardiac border represents the huge right atrium (RA), and the left cardiac border represents the giant right ventricle. **D.** Patient with mitral stenosis showing a giant RA (*arrow*) representing severe functional tricuspid regurgitation caused by unrelenting left-sided failure. The pulmonary venous congestion had improved after the onset of right-sided heart failure.

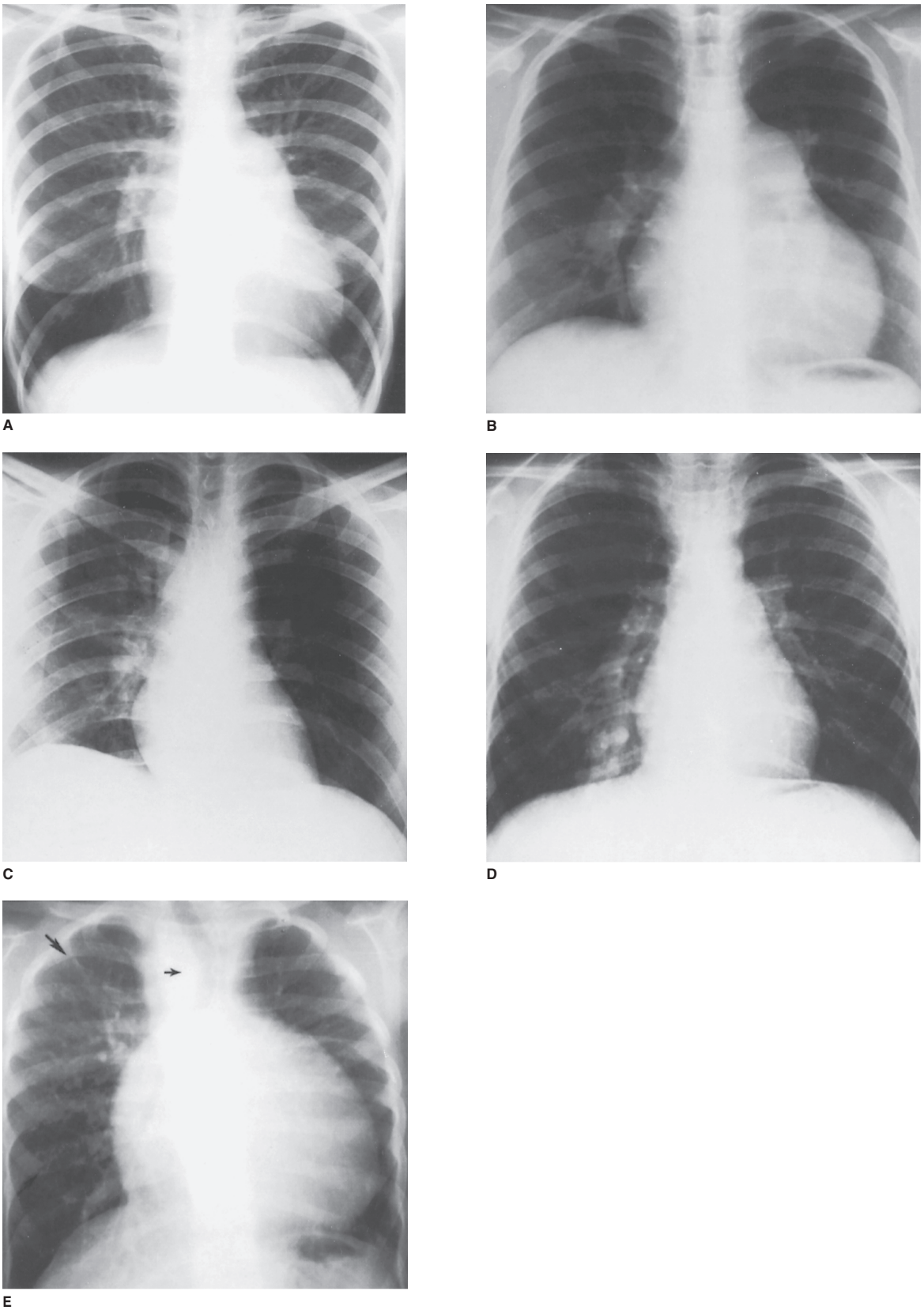


FIGURE 14–9. Abnormal pulmonary blood flow (PBF) patterns. **A.** Cephalization. Patient with severe mitral stenosis showing dilatation of the upper vessels with constriction of the lower vessels. **B.** Centralization. Patient with primary pulmonary hypertension showing marked dilatation of the pulmonary trunk and the central segments of both pulmonary arteries with pruning of the peripheral branches. **C.** Lateralization. Patient with massive pulmonary embolism obstructing the left main pulmonary artery. Note the uneven distribution of PBF between the two lungs in favor of the right. **D.** Localization. A cyanotic child showing localized vascular changes representing a large pulmonary arteriovenous fistula in the right lower lobe. **E.** Collateralization. A child with pseudotruncus arteriosus with cardiomegaly and a right aortic arch (*small arrow*). Note severe pulmonary oligemia with numerous small tortuous vessels (*large arrow*) in the upper medial lung zones, representing bronchial arterial collaterals.

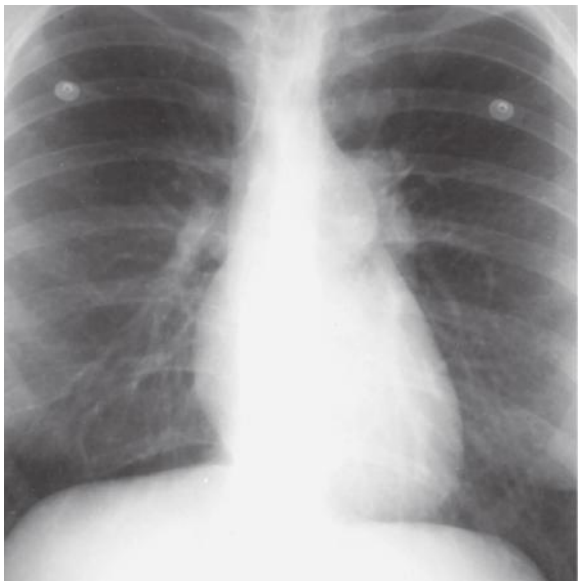
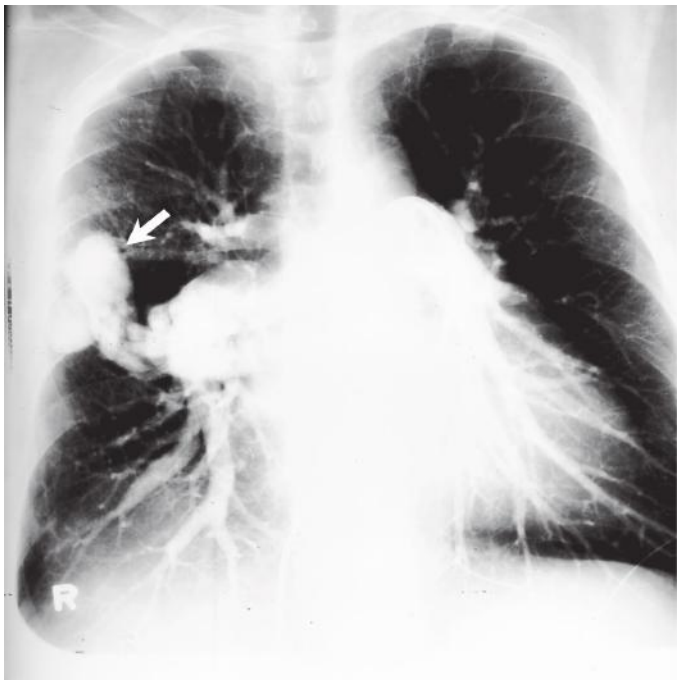


FIGURE 14–10. A 37-year-old woman with congenital valvular pulmonary stenosis. Note the enlarged pulmonary trunk and left pulmonary artery versus diminished right pulmonary artery. Also note the increased pulmonary blood flow on the left side and the decreased pulmonary blood flow on the right side.

FIGURE 14–12. Radiograph of a 42-year-old man with Eisenmenger physiology developing from unrepaired atrial septal defect. Note the increased pulmonary blood flow with a centralized pattern.

A



B

FIGURE 14–11. A. Frontal radiograph demonstrating enlarged right central and lower lobe pulmonary arterial and venous branches secondary to a large arteriovenous malformation (AVM; *arrow*). **B.** A pulmonary arteriogram clearly delineates the nidus of the AVM (*arrow*) and enlarged arterial branches.

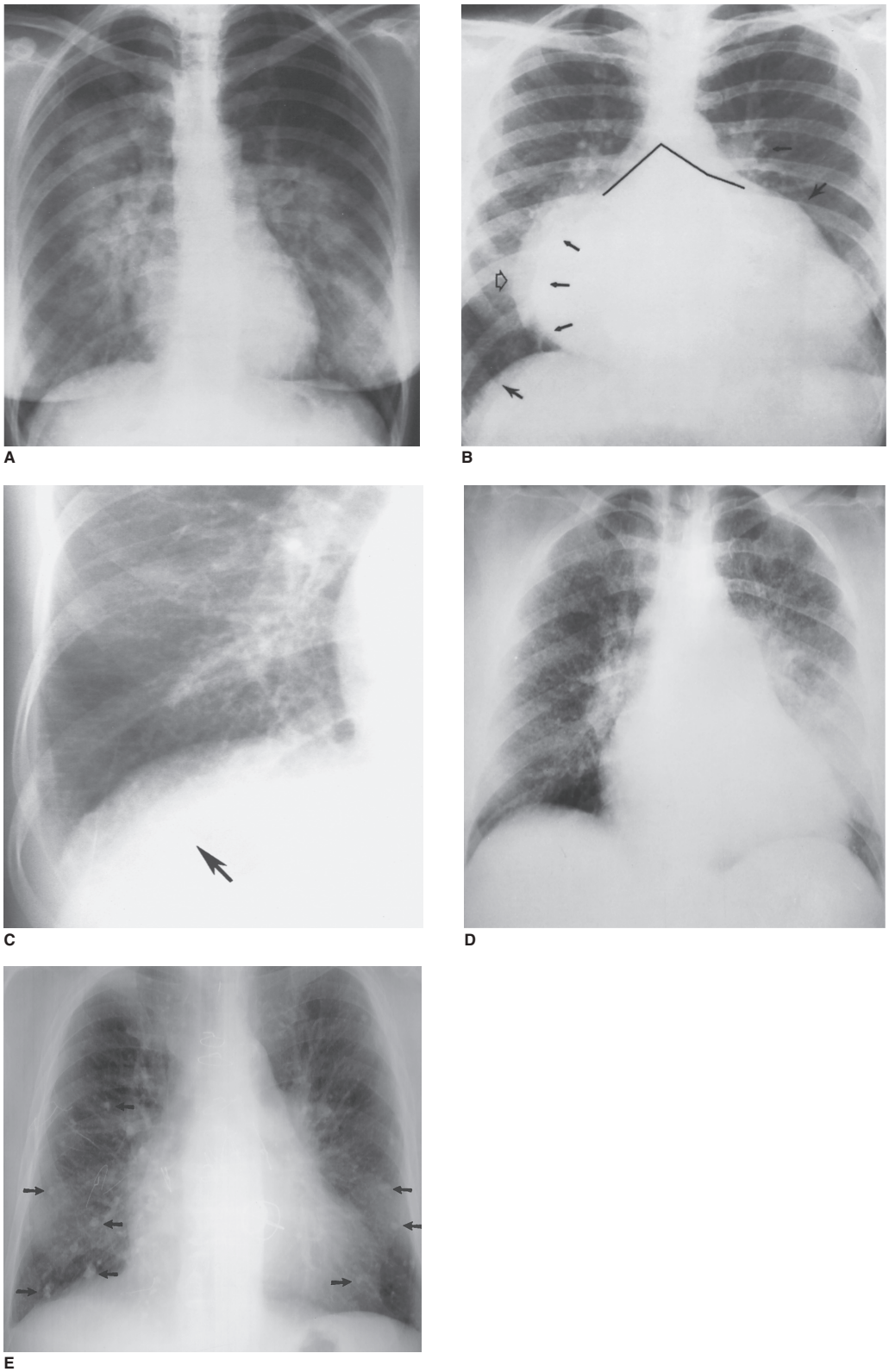


FIGURE 14–13. Radiographic appearance of left heart failure. **A.** Acute. Patient with acute mitral regurgitation because of rupture of chordae tendineae showing the "bat-wings" appearance of a severe alveolar type of pulmonary edema and a normal-sized heart. **B.** Chronic. Patient with severe mitral and tricuspid regurgitation and mild aortic regurgitation. This is a predominantly left-sided failure pattern. Note the gross cardiomegaly with striking cephalization and interstitial pulmonary edema. The giant left atrium forms the right cardiac border (*open arrow*), makes its appendage bulge outward on the left side (*upper large arrow*), and splays the mainstem bronchi wide apart (*solid lines*). The huge right atrium forms a double density within the right cardiac border (*three small arrows*). The *small upper arrow* marks the peribronchial cuffing of edema fluid. The *large lower arrow* points to multiple Kerley B lines. **C.** Magnified view of right costophrenic sulcus showing multiple Kerley B lines (*arrow*). **D.** A 44-year-old woman with severe mitral stenosis (MS). The radiograph shows a diffuse stippling with fine nodules representing hemosiderosis. Hemosiderin-laden macrophages were found in her sputa. **E.** Posteroanterior radiograph of a 63-year-old man with severe MS, status post–mitral valve replacement, shows multiple scattered bony nodules (*arrows*) 2 to 10 mm in diameter throughout the lower two-thirds of both lungs, compatible with pulmonary ossification.

an ability to discriminate noncardiac diseases from cardiac diseases, such as neoplasia from cardiac chamber enlargement. Conversely, severe cardiac disease may be present with an entirely normal cardiomediastinal silhouette. In general, radiographic evaluation of the heart focuses on assessment of cardiac size, cardiac contour, abnormal opacities or lucencies, and cardiac position.[17]

Cardiac Size

An enlarged heart is always abnormal; however, mild cardiomegaly may reflect a higher-than-average cardiac output from a normal heart, as seen in athletes with slow heart rates. The cardiothoracic ratio remains the simplest yardstick for assessment of cardiac size; the normal range on an upright posteroanterior radiograph is 0.5. However, a cardiothoracic ratio greater than 0.42 has been associated with worse in-hospital and long-term clinical outcome in patients with acute myocardial infarction.[18]

The nature of cardiomegaly can often be determined by the specific radiographic appearance. As a rule, when the PBF pattern remains normal, volume overload tends to produce a greater degree of cardiomegaly than do lesions with pressure overload alone. For example, patients with aortic stenosis (AS) typically show features of left ventricular hypertrophy without dilatation. Conversely, the LV both dilates and hypertrophies from aortic regurgitation (AR), producing a much larger heart even before the development of heart failure.

A smaller-than-average heart is encountered in patients with chronic obstructive pulmonary disease (see Fig. 14–8A), Addison disease, anorexia nervosa, and starvation. An abnormally small heart, however, is difficult to define except retrospectively after successful therapy.

Cardiac Contour

Any significant deviation from the normal cardiovascular contour can be a clue to the correct diagnosis.[19] For instance, *coeur en sabot*, a "boot-shaped heart" (see Fig. 14–7C), is characteristic of tetralogy of Fallot (ToF). A bulge along the left cardiac border with a retrosternal double density is virtually diagnostic of LV aneurysm (Fig. 14–14). A markedly widened right cardiac contour with a straightened left cardiac border is seen frequently in patients with severe MS leading to tricuspid regurgitation (TR) (see Fig. 14–8D). An elevated cardiac silhouette with lucency between the inferior cardiac border and the left hemidiaphragmatic silhouette is characteristic of congenital absence of the pericardium (Fig. 14–15).

Abnormal Opacities

Besides the familiar "double density" cast by an enlarged left atrium (LA), other increased opacities can be found within the cardiac shadow, indicating a variety of dilated vascular structures (eg, tortuous descending aorta, aortic aneurysm, coronary artery aneurysm, pulmonary varix).[2] Furthermore, large cardiac calcifications are readily seen in lateral and oblique views. If smaller calcific deposits are suspected, they should be verified promptly and can be further evaluated by CT (see Chap. 17). Any radiologically detectable calcification in the heart may be clinically important. In general, the heavier the calcification, the more significant it becomes (Fig. 14–16). Mitral annular calcification, a commonly encountered cause of cardiac calcification is rarely indicative of significant disease, but has been associated with increased risk of atherosclerotic cardiovascular disease.[20] The extent of valvular calcification tends to be proportionate to the severity of the valve stenosis regardless of the other radiographic signs of the disease.[1,2,21,22] Calcification of the coronary artery is almost always atherosclerotic in nature.

Abnormal Lucency

The abnormal lucent areas in and about the heart include (1) displaced subepicardial fat stripes caused by effusion or thickening of the pericardium (Fig. 14–17), (2) pneumopericardium (Fig. 14–18), and (3) pneumomediastinum. Pneumomediastinum is differentiated from pneumopericardium in that the former shows a superior extension of the air strip beyond the confines of the pericardium.

Cardiac Malpositions

Cardiac malpositions are diagnosed when either the heart or the stomach is out of the normal left-sided position. This definition is crucial in distinguishing an isolated right-sided aortic arch from a cardiac malposition.[6,7]

Dextrocardia with Situs Inversus

The term *dextrocardia* is used to indicate any congenital right-sided heart regardless of the position of abdominal viscera (Fig. 14–19). *Dextrocardia with situs inversus* indicates the mirror image of normal. In this situation, the incidence of congenital heart disease is only 5%, a nine-fold increase over the general population. The combination of dextrocardia, sinusitis, and bronchiectasis is known as the *Kartagener triad*.

Dextrocardia with Situs Solitus

This represents an anomaly with normal situs but a right-sided heart. Radiographically, normal situs (situs solitus) is a certainty when both the aortic knob and the gastric air bubble are on the left side. *Situs solitus* also means that both the abdominal viscera and the atria are in the normal positions. Under these circumstances, if the ventricles fail to swing from the primitive right-sided position to the normal left-sided position, abnormal relationships between the ventricles and the rest of the cardiovascular structures are bound to develop.

In patients with dextrocardia with situs solitus, the incidence of congenital heart disease has been estimated at 98%. More than 80% have congenitally corrected (or L loop) transposition of great arteries. The next most commonly associated lesions are a combination of VSD and pulmonary stenosis, a tetralogy-like pathophysiology (Fig. 14–20).

Levocardia with Situs Inversus This is a mirror image of dextrocardia with situs solitus, and it is associated with nearly a 100% incidence of cyanotic congenital cardiac lesions similar to those seen in dextrocardia with situs solitus.

Levocardia with Situs Solitus This is entirely normal.

Cardiac Malpositions with Situs Ambiguus In this group, the patient's heart can be on either the left or right side. The site is ambiguous because the aortic arch and the stomach are not on the same side. Under these circumstances, the patient has either asplenia or polysplenia syndrome. Patients with polysplenia syndrome tend to be acyanotic and frequently survive into adulthood. The associated lesions are bilateral left-sidedness, interruption of the IVC with azygos continuation (see Fig. 14–1), polysplenia, and a left-to-right shunt, most frequently an atrioventricular septal defect. Patients with asplenia tend to be cyanotic and critically ill and die in infancy.

HEART AND PULMONARY VASCULATURE IN HEART FAILURE

Heart failure is a common condition where chest radiography remains an important tool for assessing the patient's condition. In addition to specific chamber enlargement, the pulmonary vasculature uniquely portrays the underlying pathophysiology of heart failure. In the chronic

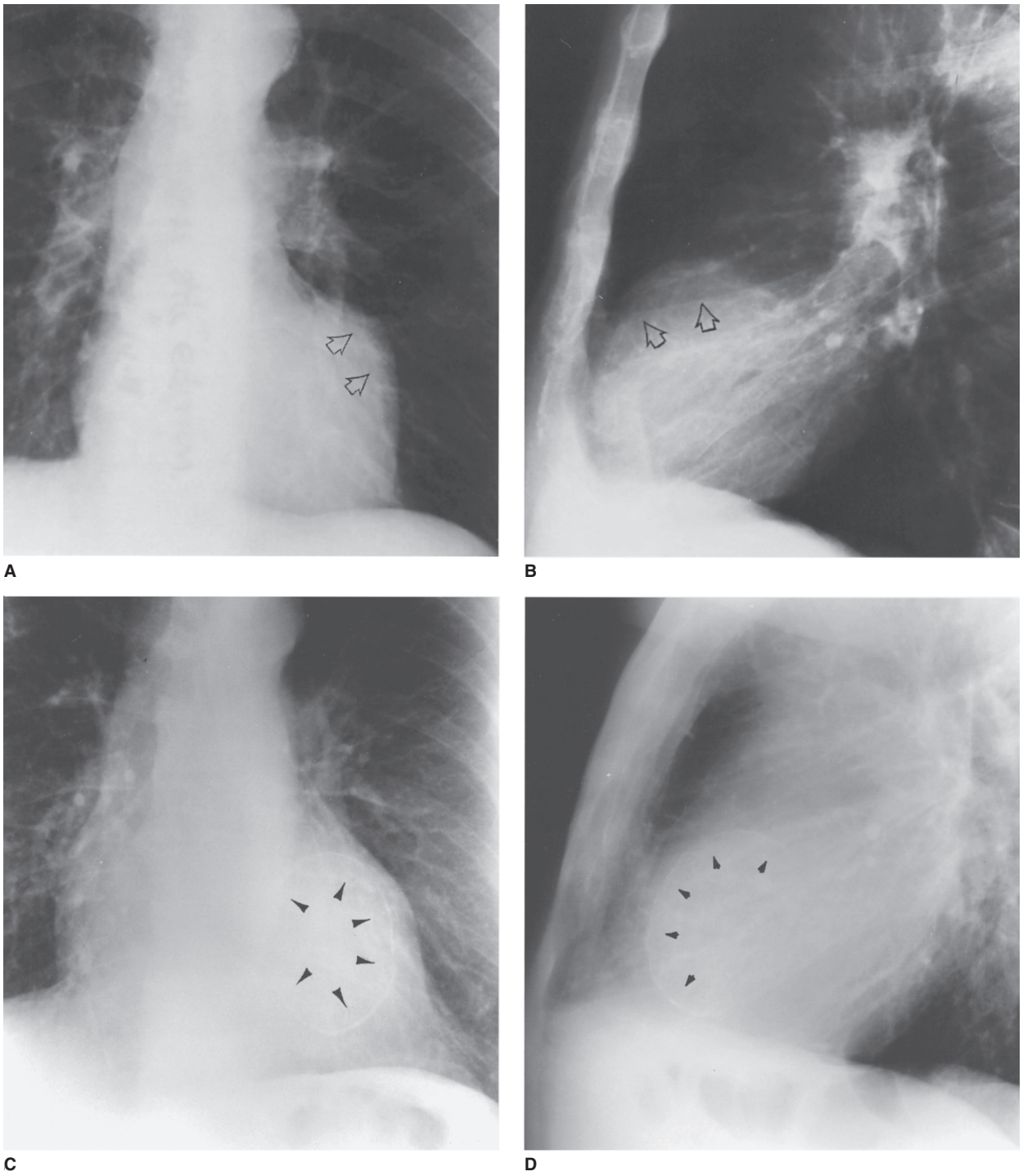


FIGURE 14–14. Left ventricular aneurysms. **A.** Posteroanterior (PA) view shows a localized bulge (*arrows*) along the left cardiac border representing a left ventricular (LV) aneurysm from the anterolateral wall. **B.** Lateral view shows a double density with sharp borders anteriorly and superiorly (*arrows*). This is the LV aneurysm that casts a shadow on the normal right ventricle (RV). Fluoroscopically, it is easy to confirm its origin and to separate it from the RV by rotating the patient under direct vision. **C.** PA view of a second patient, a 69-year-old man, shows total calcification of an anterolateral apical LV aneurysm (*arrows*). **D.** Lateral view shows the same (*arrows*).

FIGURE 14–15. Characteristic appearance of a patient with congenital absence of the pericardium. The heart is normal; however, the cardiac contour is markedly abnormal with elevation of the heart and in particular the cardiac apex. There is a broad band of lucency between the inferior cardiac border and the left hemidiaphragmatic silhouette, caused by normal left lung parenchyma beneath the heart that moves into place below the heart because of the absence of an inferior pericardial tether.

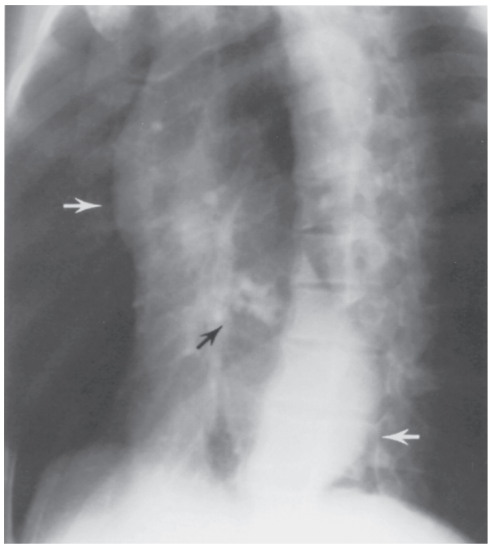
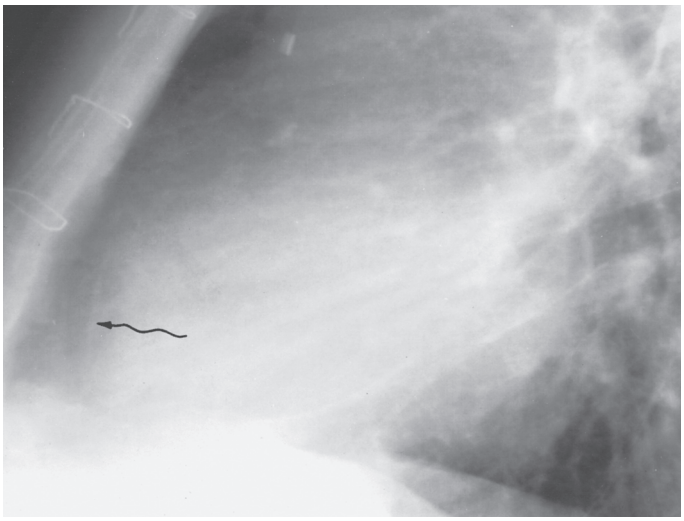


FIGURE 14–16. Left anterior oblique view of a patient with valvular aortic stenosis. The dilated ascending aorta (*upper white arrow*) is immediately above the flat anterior border of a normal right ventricle. The *black arrow* points to the calcified aortic valve. The *lower white arrow* marks the enlarged left ventricle.

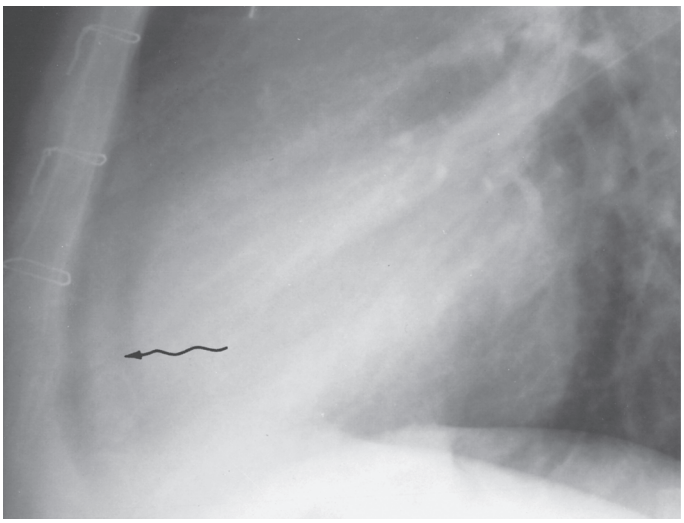
setting, decreased flow with increased pulmonary lucency is the hallmark of right heart failure (see Fig. 14–8); striking cephalization of the pulmonary vasculature is typical for left-sided decompensation (see Figs. 14–9A and 14–13B).

Left-Sided Heart Failure

Acute Left-Sided Heart Failure Left-sided heart failure is a common complication of myocardial infarction, dilated cardiomyopathy, systemic hypertension, and both stenosis and insufficiency of the mitral and aortic valves. The pulmonary vascular changes associated with acute LV failure are usually not discernible for two reasons: (1) the resulting severe pulmonary edema obscures the pulmonary vasculature and (2) the redistribution of PBF secondary to acute left-sided heart failure is usually relatively mild. The combination of alveolar pulmonary edema and a normal-sized heart is the hallmark of acute left-sided heart failure[16] (see Fig. 14–13A). The interstitial fluid may distribute in a classical butterfly pattern.[23]



A



B

FIGURE 14–17. Developing pericardial effusion in 2 weeks. **A.** A magnified view of the retrosternal area showing the hairlike normal pericardium (*arrow*) sandwiched between the subepicardial fat stripe interiorly and the mediastinal fat stripe exteriorly. The maximal width of normal pericardium is 2 mm. **B.** The same patient 2 weeks later, with moderate pericardial effusion. The pericardial cavity now measures more than 1 cm in width (*arrow*). Sternal wires are visible in both images.

Chronic Left-Sided Heart Failure Chronic left-sided heart failure is typically characterized by gross cardiomegaly, striking cephalization of the pulmonary vasculature, and interstitial pulmonary edema or fibrosis with multiple distinct Kerley B lines. Pulmonary hemosiderosis, ossification, or both may result from long-standing severe postcapillary PH (see Fig. 14–13B–E).

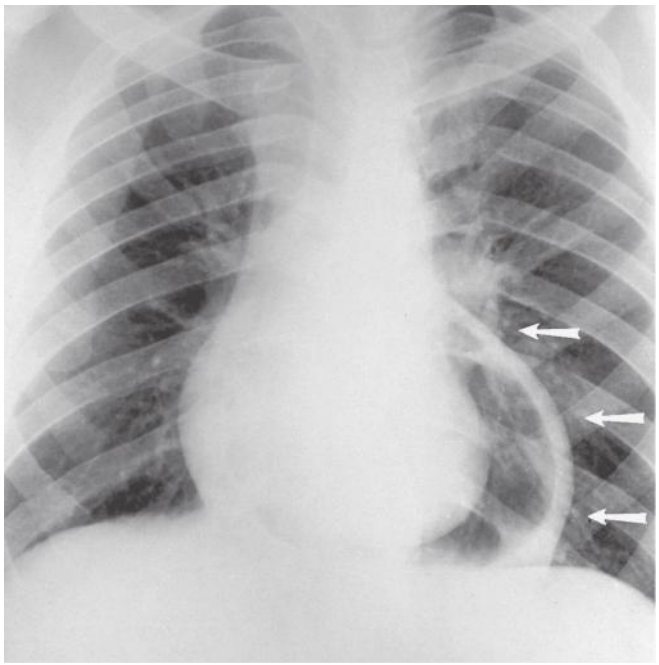


FIGURE 14–18. Traumatic constrictive-effusive pericarditis in a young man. After emergent pericardiocentesis and injection of air, a radiograph was taken in the supine position. Air is confined to the left side of the pericardium. Note the markedly thickened parietal layer (*arrows*). Contrast this appearance with that of congenital absence of the pericardium shown in Figure 14–11.

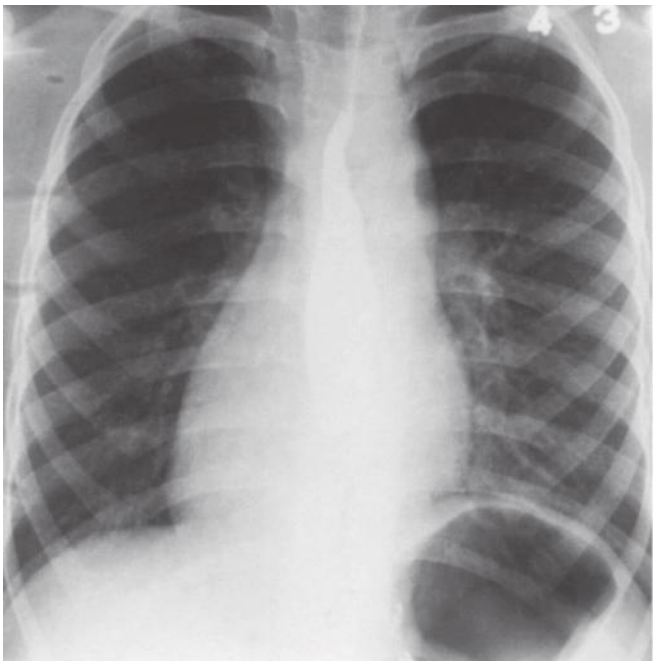


FIGURE 14–20. Posteroanterior view of a patient with dextrocardia and situs solitus. Note that the aortic arch and the stomach air bubble are both on the left (*situs solitus*) and the apex of the ventricles is pointing to the right inferiorly. This patient had the typical combination of congenitally corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis. He was cyanotic. The pulmonary vascularity appears decreased.

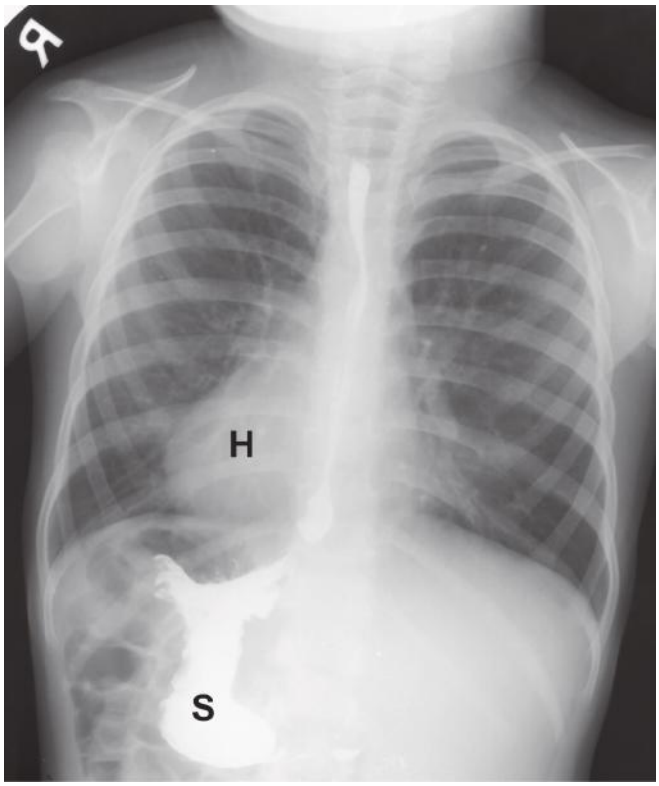


FIGURE 14–19. Frontal radiograph in a patient following barium swallow. There is dextrocardia (H) and situs inversus, which is established by the presence of the stomach (S) on the right and the liver on the left.

Isolated Right-Sided Heart Failure

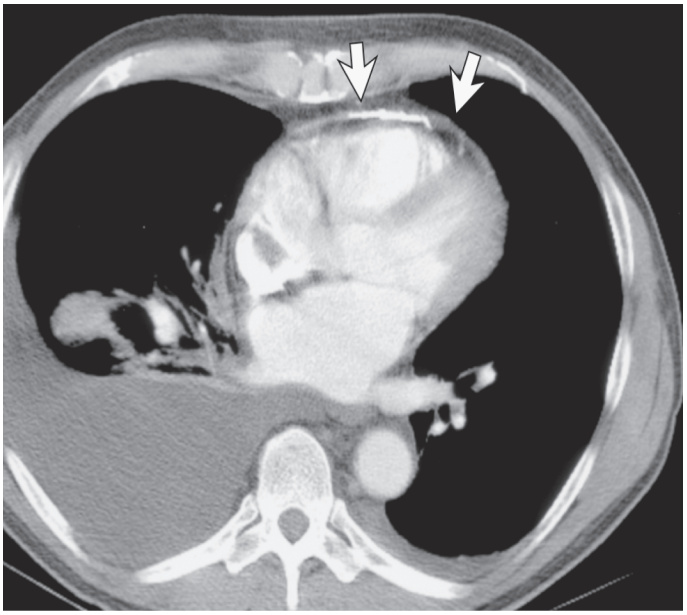
Acute Right-Sided Heart Failure Acute right-sided heart failure may result from massive pulmonary embolism. The typical radiographic signs are rapidly developing centralization of the pulmonary vasculature and dilatation of the right-sided cardiac chambers and vena cava. In addition, the lungs may show localized or lateralized oligemia (see Fig. 14–9C). Eventually, opacities in either or both lungs may develop as a result of pulmonary infarction.

Chronic Right-Sided Heart Failure Chronic right-sided heart failure has many causes, including PH, severe chronic obstructive lung disease, hypervolemia, recurrent pulmonary thromboembolic disease, congenital pulmonary stenosis, and Ebstein anomaly. Diffusely decreased pulmonary vascularity with unusually lucent lungs is seen in patients with right heart failure without PH (see Fig. 14–8C). A centralized PBF pattern is encountered when the right-sided heart failure is secondary to precapillary PH (see Fig. 14–8A and B). A cephalized flow pattern with unusually lucent lungs is found in patients with right-sided heart failure secondary to long-standing severe left heart failure (see Fig. 14–8D). The degree of right-sided chamber enlargement is proportional to the severity of tricuspid regurgitation.

Combined Heart Failure

Right heart failure is caused most often by severe left heart failure. Postcapillary PH from left-sided heart failure results in precapillary PH, which in turn leads to right-sided pressure overload. This is exemplified by patients with severe MS leading to severe PH and secondary tricuspid valvular regurgitation. This results in right atrial enlargement that is manifest on the frontal radiograph (see Fig. 14–8D). Constrictive pericarditis may also present as bilateral heart failure (Fig. 14–21).

A



B

FIGURE 14–21. Biventricular failure in the setting of constrictive pericarditis. **A.** Frontal radiograph demonstrates a large right subpulmonic pleural effusion and pulmonary vascular cephalization, findings consistent with right and left ventricular failure, respectively. **B.** Computed tomography section at the midventricular level demonstrates thickening and calcification of the pericardium (*arrows*) and right-greater-than-left pleural effusions.

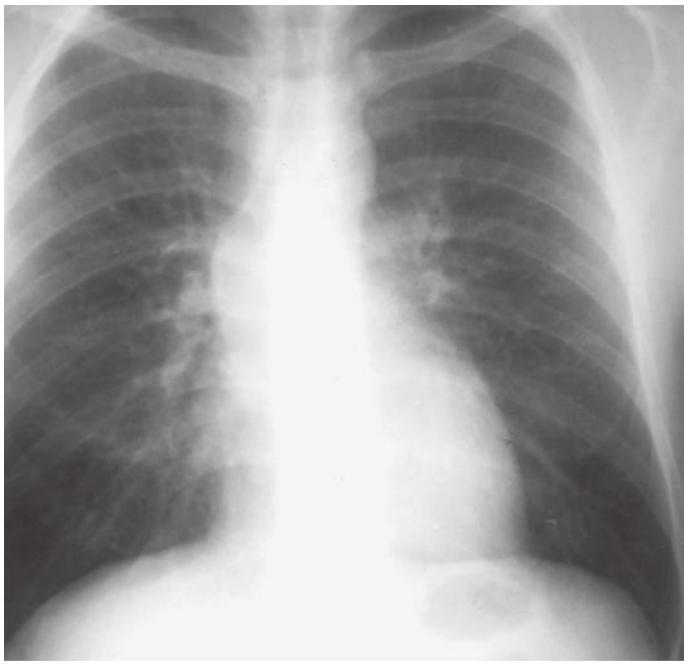


FIGURE 14–22. A 17-year-old boy with congenital aortic valve stenosis. Note the dilatation of the ascending aorta, increased convexity of the left ventricle, and normal pulmonary vascularity. The systolic aortic pressure gradient was 100 mm Hg.

OTHER ABNORMALITIES

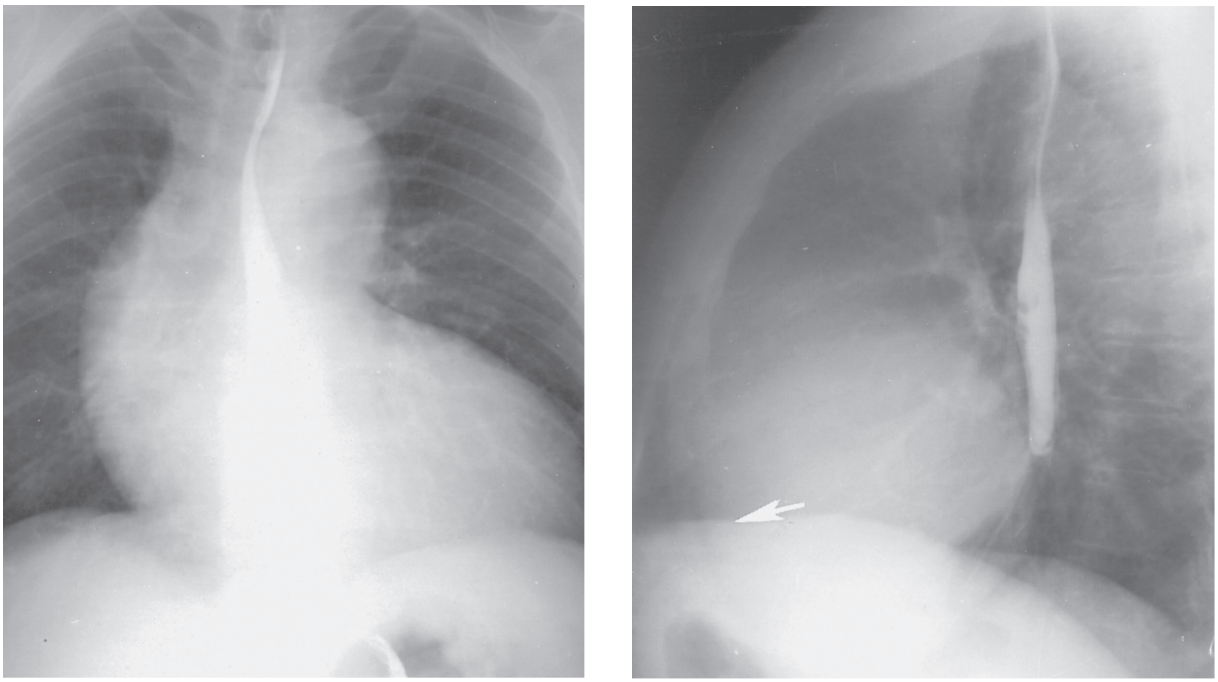
Great Vessels

The radiographic appearance of the great vessels often provides valuable information for the diagnosis of heart disease.[2,3,24,25] For example, whereas selective dilatation of the ascending aorta is the hallmark of valvular AS (Fig. 14–22), generalized dilatation of the entire thoracic aorta (Fig. 14–23) suggests AR, systemic hypertension, or both, depending on the size of the LV. In ASD and MS, the pulmonary trunk may be enlarged, and the aortic knob is usually small (see Fig. 14–7B). A leftward cardiac rotation occurs when an enlarged RV coexists with a normal-sized LV. When the heart rotates to the left, the aorta folds on itself in the midline and becomes inconspicuous. Meanwhile, the pulmonary trunk is brought laterally and looks larger than it actually is. Aortic aneurysm (Fig. 14–24) and dissection are frequently associated with hypertensive and atherosclerotic disease; heavy calcification of an ascending aortic aneurysm is suggestive of "luetic" aortitis secondary to syphilis (Fig. 14–25).

Prominence of the pulmonary trunk is a reliable secondary sign of RV enlargement (see Fig. 14–10; see also Fig. 14–7B), with the following exceptions: (1) ToF with RV hypertrophy but pulmonary trunk hypoplasia; (2) idiopathic dilatation of the pulmonary artery; (3) patent ductus arteriosus with dilated pulmonary trunk but normal RV; and (4) straight-back syndrome, pectus excavatum, and scoliosis with narrowed AP diameter of the chest. Under the latter conditions, the heart is compressed, displaced, and rotated to the left, giving rise to a falsely enlarged pulmonary artery.

In coarctation of the aorta, the engorged aortic knob and the poststenotic dilatation of the descending aorta can cause a *3 sign* on the aorta and an *E sign* on the barium-filled esophagus, both depicting the site of coarctation[26] (Fig. 14–26).

The abnormal size and distribution of both the pulmonary and systemic veins are important clues to the presence of certain conditions—for example, anomalous pulmonary venous connections, pulmonary arteriovenous fistulas, pulmonary varix, persistent left superior vena cava (SVC), and interruption of IVC with azygos continuation (see Fig. 14–1).



A B

FIGURE 14–23. Radiograph of a 45-year-old man with Marfan syndrome, severe aortic regurgitation, and proximal aortic dissection into the pericardial cavity. **A.** The posteroanterior view shows a huge left ventricle and aneurysmal dilatation of the ascending aorta. There is no sign of heart failure. **B.** The lateral view shows a small pericardial effusion (*arrow*). The esophagus is opacified in both views after a barium swallow.

Mediastinal Structures

The mediastinal organs are frequently affected by the cardiovascular structures because of their close spatial interrelationships. An enlarged LA not only displaces the esophagus and the descending aorta but also elevates and compresses the left mainstem bronchus. Radiographs acquired during a barium swallow were a common tool for assessing the secondary effects of left atrial enlargement. Widespread availability of echocardiography and CT have rendered this technique obsolete. A double aortic arch can compress both the trachea and the esophagus. Also, malignant processes can invade the heart and great vessels, causing cardiac tamponade or the SVC syndrome. Usually, these mediastinal changes are evident on the chest radiograph and should be recognized promptly.[24,25,27,28]

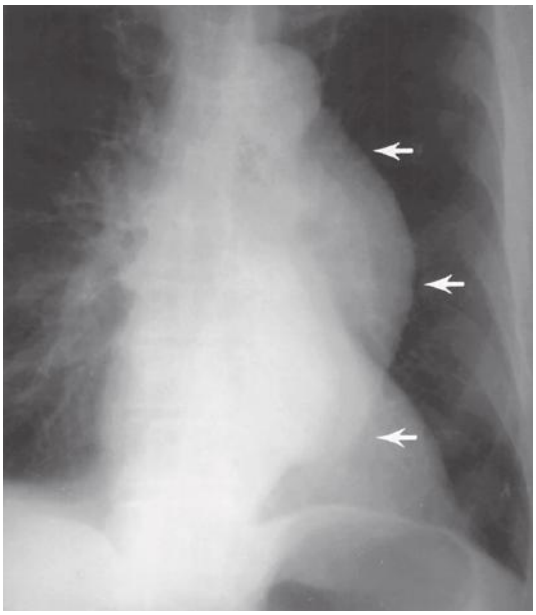


FIGURE 14–24. Posteroanterior view of a 77-year-old man showing a huge descending thoracic aortic aneurysm (*arrows*).

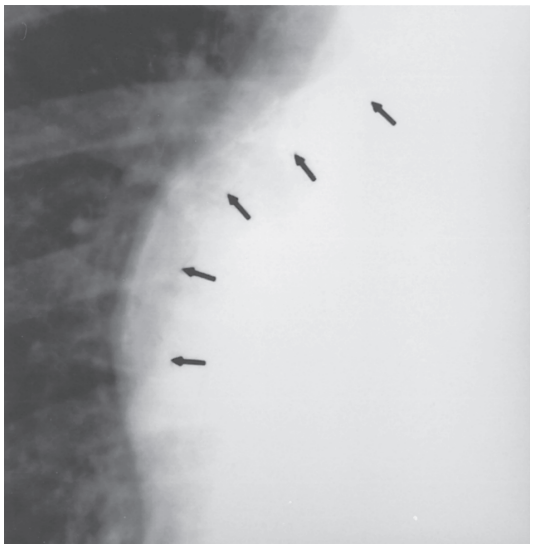
Pleura

A right-sided pleural effusion is often present with left heart failure. A bilateral hydrothorax suggests bilateral heart failure or a noncardiac etiology of the effusion. Heart failure is also known to be associated with a pseudotumor or *vanishing* tumor, representing an interlobar collection of pleural fluid (Fig. 14–27). As heart failure improves, the *pseudotumor* disappears.

Bones and Joints

Rib notching (see Fig. 14–26A and B) provides important clues to the diagnosis of coarctation of the aorta.[3,26] Notching of the ribs has many origins. Basically, any of the three major intercostal structures can enlarge, compress, and erode the lower borders of the ribs, producing areas of notching. They are intercostal arteries, veins, and nerves. Coarctation of the aorta represents the most common cause of rib notching as a result of dynamic dilatation and tortuosity of the arteries. SVC syndrome can produce a similar radiographic appearance, albeit through long-standing venous dilation. Neurofibromatosis also can produce rib notching through the compressive effect of numerous intercostal neurofibromas.

A



B

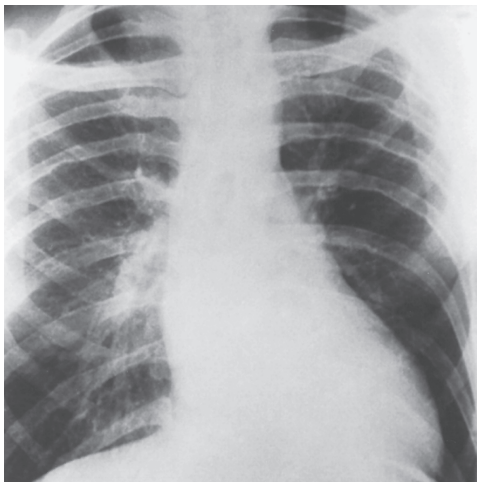
FIGURE 14–25. A 71-year-old woman with syphilitic aortitis. **A.** The posteroanterior radiograph shows a huge, calcified ascending aortic aneurysm (*arrows*). In addition, the entire aorta and the left ventricle are markedly dilated, compatible with severe aortic regurgitation. **B.** A magnified view of the ascending aorta provides a clearer view of the calcified aneurysm. Reproduced with permission from Chen JTT: The significance of cardiac calcifications, *Appl Radiol*. 1992;21:11-19.

Soft Tissues over the Chest

Severe edema in the soft tissues over the chest can be seen on radiographs in a setting of generalized anasarca (Fig. 14–28).

COMPARISON OF SERIAL STUDIES

To appreciate the acuteness or chronicity of a disease process or its response to therapy, one must carefully compare serial radiographs. As demonstrated in Fig. 14–8B, the heart can be considered neither enlarged nor failing if the baseline study made 3 years earlier in Fig. 14–8A were not available for comparison. Similarly, an enlarging heart with normal pulmonary vascularity is highly suggestive of pericardial effusion. Conversely, a shrinking heart in the presence of normal vascularity is compatible with resolution of a pericardial effusion (Fig. 14–29).



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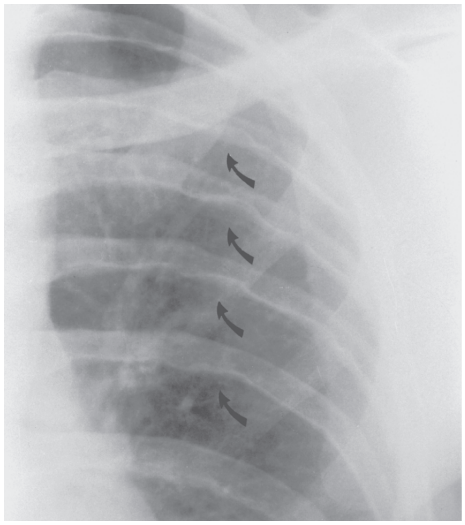

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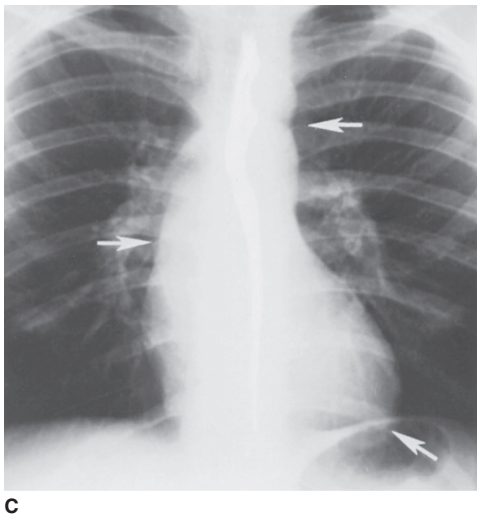
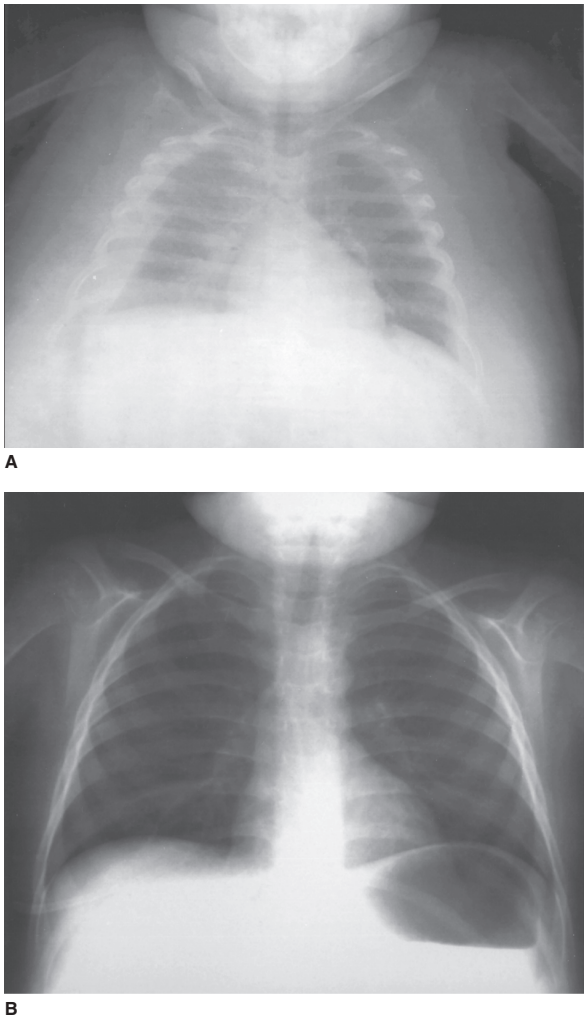


C

FIGURE 14–26. **A.** Posteroanterior (PA) view in a patient with coarctation of the aorta showing areas of rib notching bilaterally and left ventricular (LV) enlargement in the inferior and leftward direction. **B.** Magnified view of the left upper thorax of the same patient showing multiple areas of rib notching (*arrows*). **C.** PA view of another patient with aortic coarctation showing the *3 sign* of the deformed descending aorta and *E sign* on the barium-filled esophagus. The *upper arrow* points to the level of coarctation, and the *lower arrow* marks the apex of the enlarged LV. The *arrow* on the patient's right indicates the dilated ascending aorta.

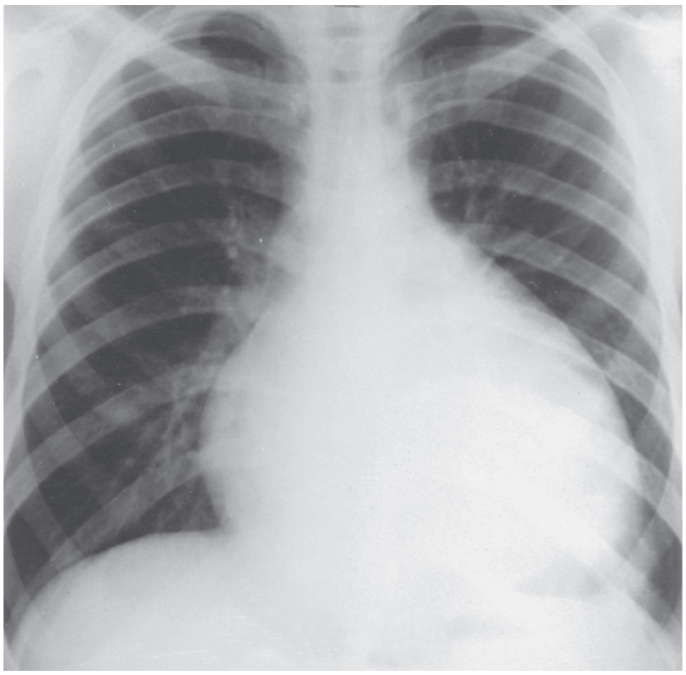
FIGURE 14–27. Patient with heart failure. Note the gross cardiomegaly, cephalization, interstitial pulmonary edema, and right-sided pleural effusion. Some of the fluid was loculated in the minor interlobar fissure, representing a pleural "pseudotumor" (*arrow*), which disappeared with improved cardiac function.



A

B

FIGURE 14–28. Radiograph of a child with nephrotic syndrome, which was treated successfully. **A.** The posteroanterior view during the worst period of disease shows general anasarca, pulmonary edema, and pleural effusion. Note the considerable soft tissue edema in the chest wall. **B.** With proper treatment, there was complete resolution of these abnormalities within 2 weeks.



A

B

FIGURE 14–29. Radiograph of a young man with acute pericarditis with effusion. **A.** The posteroanterior view shows a water bottle–shaped cardiomegaly, clear lungs, and normal pulmonary vascularity. **B.** Repeat film taken 5 days later shows an excellent response to therapy.

CLINICAL CORRELATION

The radiographic findings must be correlated with the clinical information and other laboratory parameters for a final conclusion. After gaining a thorough familiarity with the clinical context for the radiograph, reexamination of the image may reveal additional insights.

CARDIAC FLUOROSCOPY

Cardiac fluoroscopy explores the dynamic features of the organ that are discernible only in motion. However, it has been largely displaced by other imaging techniques, particularly two-dimensional echocardiography, MRI, and CT, and its use is limited to the cardiac catheterization laboratory, where it can assess the function of radiodense and echodense prosthetic valves and can guide the positioning of pacemakers or ICDs. With the emergence of transcatheter aortic valve replacement therapy, cardiac fluoroscopy has experienced a resurgence at some centers where it is preferred over transthoracic and transesophageal echocardiography for assessing the prosthesis.

The bileaflet St. Jude valve is used in both mitral and aortic positions. The valve is difficult to see radiographically but is readily detected under the fluoroscope or with CT. When the leaflets move sluggishly, thrombotic intravasation of the valve should be suspected. Rarely, one leaflet can dislodge and embolize distally, causing acute valvular regurgitation.[29]

The position of a pacemaker or ICD can be determined promptly under the fluoroscope during initial insertion and recorded on film. The subepicardial fat line overlies the myocardium and underlies the pericardium. If the pacing catheter is found within the fat stripe, it may have passed through the coronary sinus and entered one of the major cardiac veins. If the tip of the catheter is seen outside the fat stripe, however, it may have perforated the myocardium and thus be lying within the pericardium or beyond. Although the wires and electrodes of a transmediastinal pacemaker may look normal on the radiographs, minor breakage may be appreciated only in ventricular systole with the aid of fluoroscopy.

SUMMARY

Cardiac disease presents a broad array of manifestations on the chest radiograph. In spite of the proliferation of other cardiac imaging modalities that offer superior anatomic assessment through tomographic acquisition and display, the knowledgeable and disciplined observer can glean tremendous insights into altered anatomy and physiology The widespread availability, low cost, and ease of acquisition makes the use of cardiac radiography logical within an initial cardiac assessment, for assessing the status of assistive devices, and for monitoring dynamic processes during treatment, particularly when they result in altered pulmonary vascular physiology.

ACKNOWLEDGMENTS

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CHAPTER 15

ECHOCARDIOGRAPHY

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The term *echocardiography* refers to the evaluation of cardiac structure and function with images and recordings produced by ultrasound. The development of echocardiography is usually credited to Edler and Hertz in 1954.[1] In the past 30 years, it has become a fundamental component of the cardiac evaluation. Currently, echocardiography (*echo*) provides essential (and sometimes unexpected) clinical information and is the second most frequently performed diagnostic procedure.[2] The history of this technique has been closely linked with advances in computer processing, storage and miniaturization.

The first two decades of clinical echocardiography involved a one-dimensional (1D) time-motion (M-mode) recordings, performed from the precordial area to assess cardiac anatomy.[3] In the mid-1970s, a multielement linear-array scanner was created to produce anatomically correct, two-dimensional (2D) images of the beating heart.[4] This was followed by mechanical sector scanners[5] and ultimately by the present-day phased-array instruments.[6] After initial forays into three-dimensional (3D) ultrasound using reconstruction, 3D instruments capable of real-time volumetric imaging were developed, and 3D visualization is now routine.[7] This process of miniaturization permitted evolution from transthoracic echocardiography (TTE) to transesophageal echocardiography (TEE),[8] as well as handheld echographs that can be carried in a lab coat and devices incorporated into cardiac catheters to achieve intravascular images. Advances in image processing have led to the assessment of myocardial mechanics, including myocardial strain.[9] However, other technical developments, including the assessment of myocardial perfusion with contrast agents, have had a longer pathway to acceptance.[10]

Although efforts to use the Doppler principle to measure flow velocity by ultrasound were begun in the early 1970s,[11] clinical application of this technique as a partner to clinical echocardiography did not thrive until the work of Hatle in the early 1980s.[12] The combination with Doppler led to machines capable of also delineating flow and deriving hemodynamic data.[13] Pulsed and continuous-wave Doppler recordings soon were expanded to full 2D color-flow imaging. Most recently, Doppler velocity recordings have been obtained from myocardium itself, enabling measurement of tissue velocities and the derivation of values for regional strain.

PRINCIPLES OF ECHOCARDIOGRAPHY

PHYSICS AND INSTRUMENTATION

Sound is an energy form that travels through a medium as a series of alternating compressions and rarefactions of the molecules (Fig. 15–1). It is typically characterized by its wavelength, which is the distance between any two consecutive phases of the cycle (eg, peak compression to peak compression), and by its frequency, which is the number of wavelengths per unit time (customarily expressed as cycles per second, or Hertz [Hz]). The velocity of sound is the product of wavelength and frequency; thus there is an inverse relationship between these two characteristics: the greater the frequency, the shorter the wavelength. Ultrasound is sonic energy with a frequency more than the audible range of the human ear (> 20,000 Hz) and is useful for diagnostic imaging, because, like light, it can be directed as a beam that obeys the laws of reflection and refraction.[14] Thus an ultrasound beam travels in a straight line through a homogeneous medium. If the beam meets an interface of different acoustic impedance, however, part of the energy reflects, and the remaining attenuated signal is transmitted. The reflected energy, or echo, is used to construct an image (Fig. 15–2).

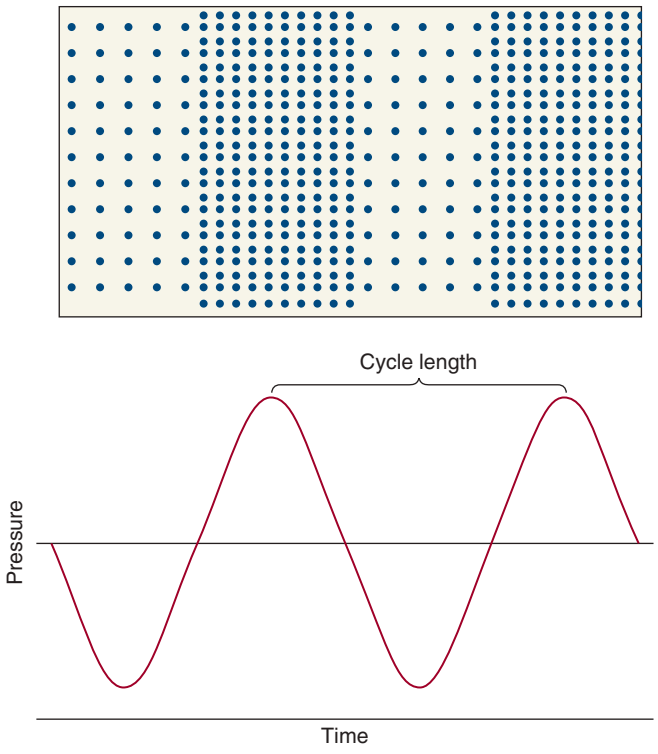


FIGURE 15–1. Sound energy results in alternating compression and rarefaction of particles in a conducting medium. This alternation, which can be plotted against time (or distance), conforms to a sine-wave pattern (*bottom panel*). Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

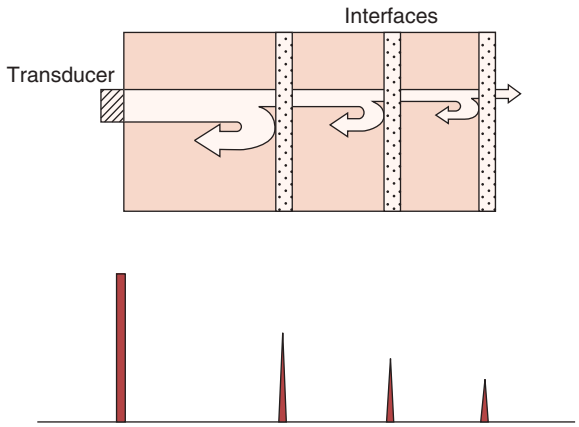


FIGURE 15–2. *Upper panel:* Attenuation of an ultrasound beam emitted from a transducer. There is reflection and progressive loss of energy at each interface encountered. *Lower panel:* The reflected wave fronts are recorded as signals of varying amplitudes (A mode) via the piezoelectric crystal. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

The transducer, which is responsible for both transmitting and receiving the ultrasound signal, consists of electrodes and a piezoelectric crystal, whose ionic structure results in deformation of shape when exposed to an electric current (Fig. 15–3). In the past, echographs have both transmitted and received signals of the same frequency. Recently, *harmonic imaging*, in which ultrasound energy is transmitted at a baseline (fundamental) frequency but then received at a higher multiple (harmonic) of that frequency (usually the first harmonic) has been implemented to enhance the signal-to-noise ratio. Harmonic imaging is based on the change in the ultrasound frequency of a transmitted wave induced by the interaction with a reflecting target. These harmonic signals, generated by the interaction of ultrasound and tissue, are analogous to the cresting of ocean waves (the tops of which move more rapidly than do the bases). These signals take some time (and distance) to develop, so structures close to the transducer do not generate much harmonic signal, so harmonic imaging minimizes near-field and reverberation artifacts. In addition, harmonic imaging has also been very useful in conjunction with echocardiographic contrast agents (discussed below), the cyclic expansion and constriction of which during ultrasound imaging produces a large amount of harmonic energy, exceeding that of myocardial tissue.[15] The net effect of harmonic imaging with echocardiographic contrast is a marked enhancement of the signal from the left ventricular (LV) cavity and/or the coronary microcirculation compared with that of the myocardium.

Ultrasound presents several unique technical difficulties. Sound energy is poorly transmitted through air and bone, and the ability to record adequate images depends on a thoracic window that gives the interrogating beam adequate access to cardiac structures. The degree to which ultrasonic energy is reflected depends on how perpendicular the interrogating beam is to the interface. When the ultrasound beam is directed parallel to the interface, little or no sound energy reflects to the transducer. Therefore, poor signal transmission, a nonorthogonal orientation of the ultrasound beam to the surface, and energy attenuation can cause failure to record signals from cardiac structures—a phenomenon referred to as *echo dropout*.[16] Conversely, some structures may be such strong ultrasonic reflectors, being extremely dense and usually perpendicular to the beam, that sufficient energy returns to the transducer to reflect and again transmit into the field. This phenomenon can lead to *reverberations*, or the reproduction of the echoes of anatomic structures

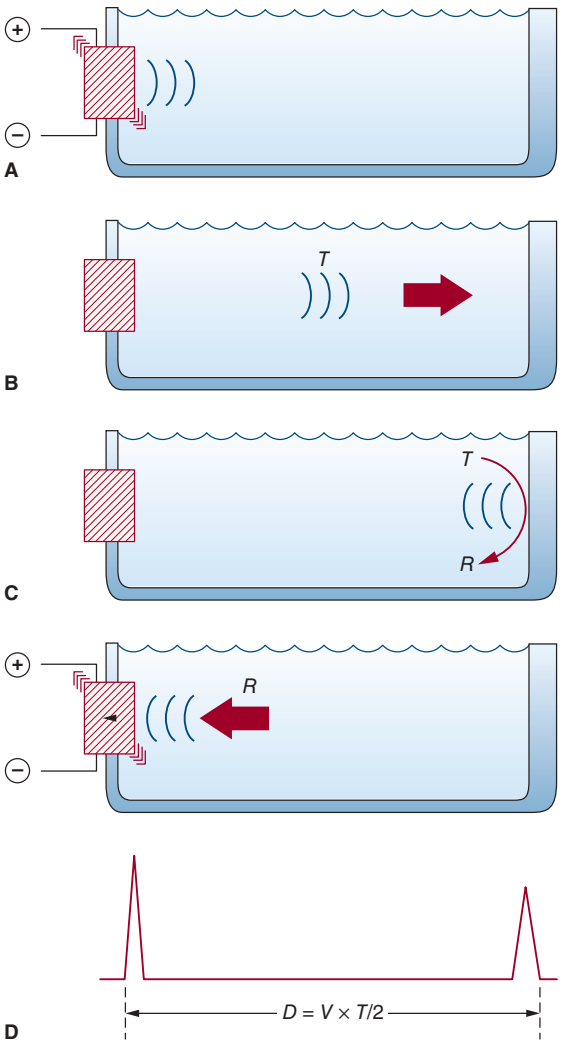


FIGURE 15–3. The basic principle of ultrasonic imaging. The piezoelectric crystal is activated, producing a transmitted pulse (T), which reflects off the interface. The reflected pulse (R) excites the crystal, producing an electric current. Because the velocity of the pulse is constant, distance can be calculated based on the transit time. (Because the pulse must travel back and forth from the interface, the time is divided by two.) Modified with permission from Weyman AE: *Principles and Practice of Echocardiography*, 2nd edition. Philadelphia: Lea & Febiger; 1994.

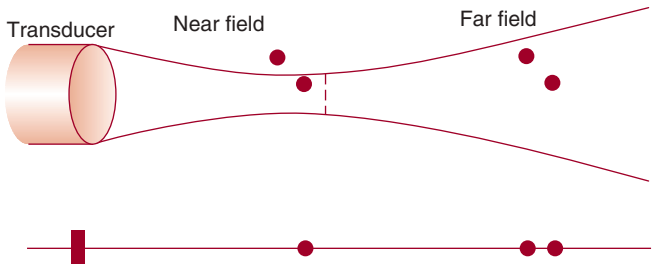


FIGURE 15–4. *Upper panel*: The transducer emits an ultrasonic beam that has a near field (where the beam is relatively focused) and a far field (where the beam width increases). *Lower panel*: B-mode diagram showing the effect of beam width. In the near field, the beam reflects off only one of two objects in close proximity to each other. In the far field, however, two similarly positioned objects are both within the beam width. Therefore, lateral resolution is compromised, and the objects' positions are misrepresented.

and myocardium. At this point, some ultrasonic energy reflects, some scatters, and some continues forward. The amplitude of the propagating signal is attenuated because of the reduction in energy at the interface (see Fig. 15–2). Electronic circuitry within the echograph measures the time interval required for the transit of the ultrasound beam from the transducer to the interface and back again. Because the velocity of sound in soft tissue is constant (~1540 m/s), the instrument can calculate the total distance traveled to and from the reflecting surface as the product of transit time and velocity of sound. Interface location is derived as one-half of the total transit distance, and a signal is depicted on an oscilloscope or video monitor at that point (see Fig. 15–3). The amplitude of ultrasonic energy reflected from each target interface is represented by the brightness of the signal that is displayed.

In the most basic forms of echocardiography, a single scan line produced by a piezoelectric crystal is passed through the heart (Fig. 15–5). At each structural interface, ultrasonic energy is reflected back and displayed at the appropriate distance as a signal, the amplitude of which represents the acoustic impedance or density of the material encountered. These signals are subsequently displayed as dots, the brightness of which is proportional to the amplitude of reflected ultrasonic energy. Accordingly, if repetitive B-mode scan lines are produced and swept across the screen over time, the movement of the heart [18] can be obtained as a time-motion (or M-mode) recording, providing dynamic cardiac images (see Fig. 15–5). In clinical use, the piezoelectric crystal within the transducer is activated by alternating electric current to transmit at a rate of approximately 1000 pulses/s. This same

at multiple locations within the image.[17] Finally, very dense targets lying on the periphery of a 2D-sector ultrasound beam may be recorded and displayed as if they were located along the central scan line (Fig. 15–4). This problem may be accentuated in the setting of strong reflectors that result in the formation of *side lobes*.[18]

The construction of a cardiac image from ultrasound signals is based on computation of the distance between an anatomic structure and the transducer (see Fig. 15–3). An ultrasound beam is produced by a handheld transducer positioned on the thorax and directed into the heart. This beam travels in a straight line until it reaches an interface between structures of different acoustic impedance, such as blood

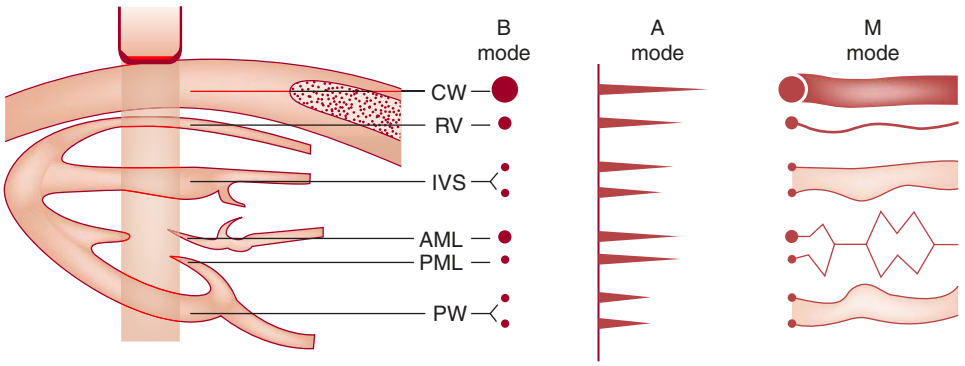


FIGURE 15–5. Formation of A-mode, B-mode, and M-mode echocardiograms. The transducer emits an ultrasound beam, which reflects at each anatomic interface. The reflected wave fronts can be represented as dots (B mode) or spikes (A mode). The dot brightness and spike magnitude vary with the amplitude of the reflected wave. If the B-mode scan is swept from left to right with time, an M-mode image is produced. AML, anterior mitral leaflet; CW, chest wall; IVS, interventricular septum; PML, posterior mitral leaflet; PW, posterior wall; RV, right ventricle. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

crystal also receives the returning echo reflections and actually spends most of the time (> 90%) in the *receive* rather than the *transmit* mode. Because it transmits ultrasound signals at 1000 pulses/second, M-mode echocardiography provides very high temporal resolution and is excellent for timing cardiac events or recording high-velocity motion. 2D echocardiography acquires multiple B-mode scan lines that are aligned in the appropriate anatomic location to form a wedge-shaped sector image that provides additional spatial information in either superoinferior or mediolateral directions.[18] High-quality images require optimal resolution—that is, the ability to distinguish two individual objects separated in space. Short wavelengths yield excellent resolution in echo imaging, because the shorter the cycle length, the smaller the object that will reflect the signal and be detected by the echo scanner. Because wavelength is inversely related to frequency, transducers that emit a high-frequency signal (≥ 3.5–7.0 MHz) yield high-resolution images. Because ultrasonic beams diverge as they propagate away from the transducer, the width of the beam can become sufficiently great to encompass multiple targets and decrease resolution (see Fig. 15–4). The degree of beam divergence is also less with high-frequency sonic energy than with low-frequency signals. The smaller wavelengths associated with high-frequency signals, however, are subject to greater reflection and scattering, with substantially higher attenuation as the beam propagates through tissue. The resultant attenuation is greater and leads to decreased sensitivity. Therefore, in clinical practice, echocardiographic examinations are performed using the highest-frequency transducer capable of sufficient penetration to obtain signals from all potential targets within the ultrasound field.

M-MODE ECHOCARDIOGRAPHY

The Standard M-Mode Examination

Despite the availability of 2D imaging, M-mode echocardiography remains a useful part of the ultrasound examination. Historically, the transducer was placed at the left parasternal area and rocked through the heart from apex to base (Fig. 15–6). However, more recently, the orientation of M-mode images have been directed from 2D images. Tissue typically reflects ultrasound at its surface (specular reflectors) and from internal inhomogenicity (backscatter), whereas blood is homogenous and does not produce reflections. At the mitral valve (MV) level (see Fig. 15–6C), MV excursion is well seen and is more easily recorded for the longer anterior leaflet. Diastolic mitral opening is bipeaked (M-shaped), with maximal opening during early diastolic filling at the E point, a subsequent reclosure downslope to the F point, and a reopening with atrial contraction at the A point before valve closure at the C point[19] (Fig. 15–7). When LV end-diastolic pressure is elevated, a shoulder (B bump) is often present between the A and C points (Fig. 15–8).

Assessment of Systolic Function by M-Mode Echocardiography

Measurements of the LV cavity dimension and wall thickness can be readily derived from M-mode recordings (Fig. 15–9) and are usually made according to the recommendations of the American Society of Echocardiography (ASE) at end diastole (the onset of the QRS complex) and end systole (the point of maximum upward motion of the LV posterior wall endocardium).[20] They are accurate if the beam is orthogonal to the long axis of the ventricle. By convention, left atrial dimension is measured at end systole, and aorta (AO) diameter is recorded at end diastole at the level of the base of the heart (see Fig. 15–9). During systole, opening of the aortic leaflets appears as a rhomboid produced by motion of the right coronary and (usually) the noncoronary aortic valve (AoV) cusps.

Although M-mode LV cavity dimensions are still used in guidelines,[21] their use to measure LV volumes and ejection fraction (EF) are based on several assumptions regarding LV geometry[22] and should be discouraged. Likewise, fractional shortening reflects the function of the LV in one chord and in one plane and can be misleading with asynchronous contraction.[23] *E-point to septal separation*, the distance between the anterior MV leaflet at its most anterior opening excursion (the E point) and the interventricular septum is a marker of LV enlargement (normal range < 8 mm).[24] The normal M-mode measurements are seen in Table 15–1.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Most current 2D scanners use a phased-array approach, where multiple ultrasonic crystals are used in concert to create individual B-mode scan lines (Fig. 15–10). The crystals are activated in a closely coordinated temporal sequence, so that the individual wavelets produced by each element merge to form a single beam, the direction of which is determined by the sequence of crystal firing (Fig. 15–11). The beam can be electrically swept throughout a 90-degree sector arc. A firing sequence can be used that results in dynamic focusing of the beam along its length to achieve minimal beam width and increased resolution.

Originally, echocardiographic data were displayed in analog form on a standard oscilloscope, transferred to a video monitor by a television camera, and hard-copied onto videotape or paper. Currently, computerized analog-to-digital scan conversion is standard, so the polar signals of individual scan lines are converted to a series of numerical gray-level values for individual boxlike picture elements (pixels) aligned along X-Y coordinates.[25] The ability of a digital step-gradation technique to reproduce the continuous gradation of analog methods is a function of the density of pixels in the matrix and the gray-level shades available. The digital format provides the opportunity for image processing, enhancement, and quantitation. Storage in digital format can avoid the image degradation inherent in videotape, provide random access and easy comparison of studies, enable rapid image transmission, and prevent deterioration with image copying and prolonged storage. Fully digital acquisition and storage of echocardiograms is now standard.

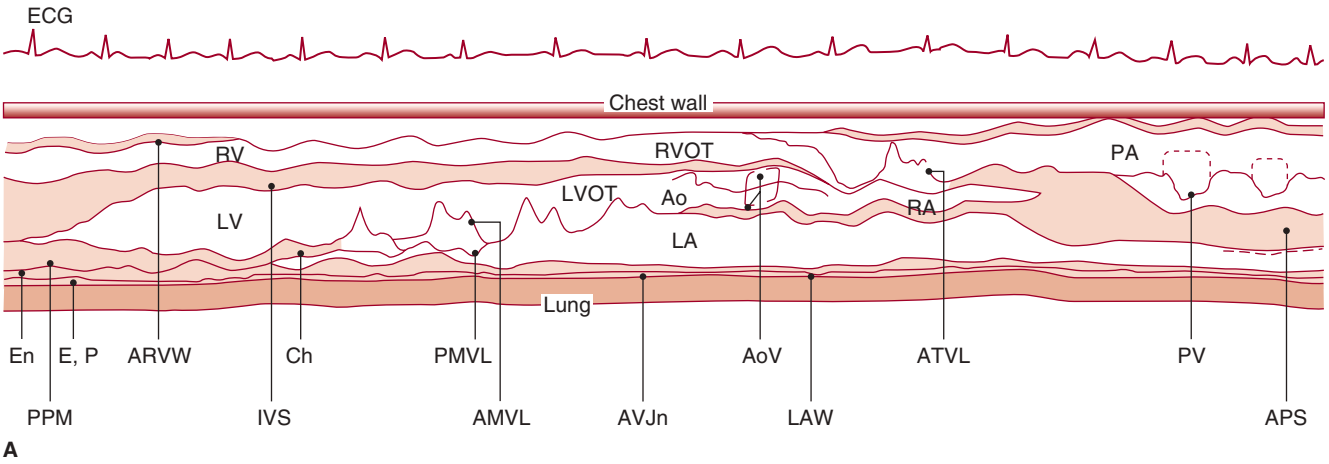
The Standard Two-Dimensional Examination

To help standardize the 2D examination, the ASE recommends that cardiac imaging be performed in three orthogonal planes:

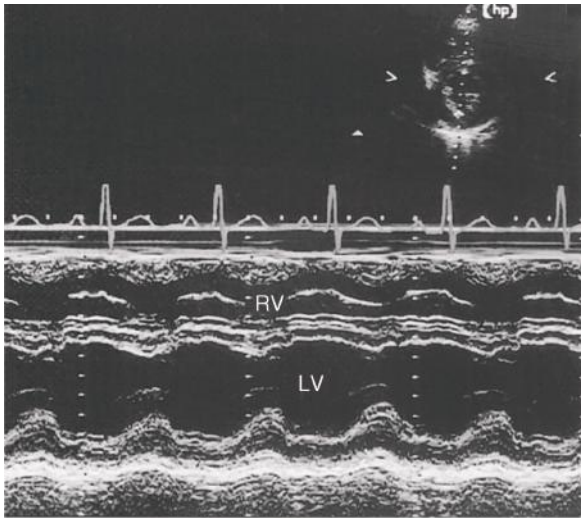
1. Long-axis (from AO to the apex), including parasternal and apical two- and three-chamber views
2. Short-axis (perpendicular to long axis)
3. Four-chamber (traversing both ventricles and atria through the mitral and tricuspid valves)[26] (Fig. 15–12).

The long and short axes are those of the heart, not the body. These three planes can be visualized using four basic transducer positions: parasternal, apical, subcostal, and suprasternal (Fig. 15–13). The four-chamber views are obtained from the apical and subcostal positions. To permit classification of off-axis images, an image obtained within 45 degrees of a basic orthogonal plane is identified with that orthogonal plane. Table 15–2 lists the standard transducer positions and TTE views. Anatomic drawings of the various imaging planes are seen in Fig. 15–13 through 15–20.

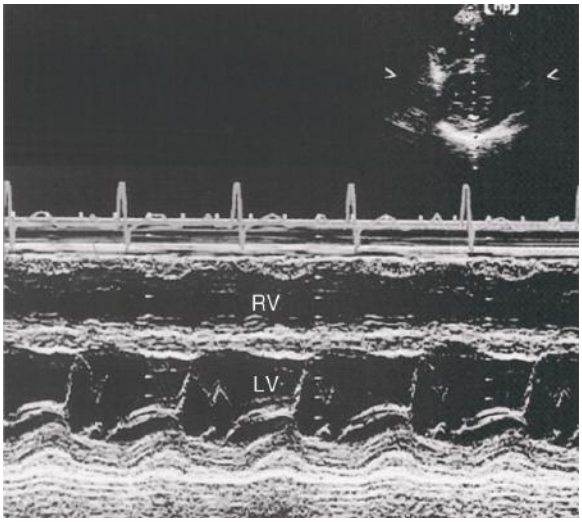
The echocardiographic examination may be performed with the operator either to the patient's left or right. The patient is in the left lateral decubitus position for most of the examination, with the head of the bed elevated 20 to 30 degrees. The echocardiographic examination is iterative and largely determined by the anatomic characteristics of the patient and manual manipulation of the transducer by the operator.



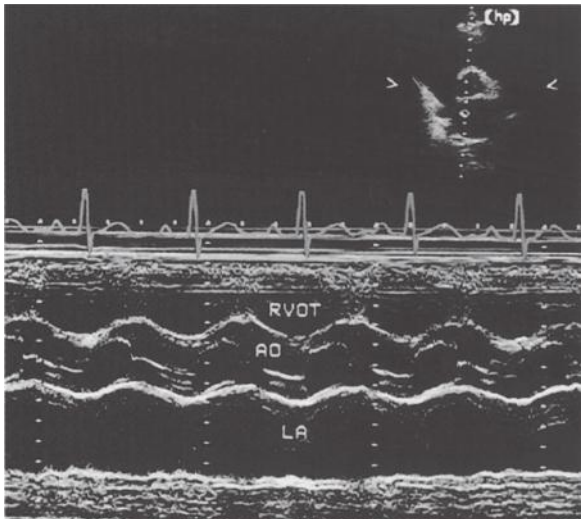
A



B



C



D

FIGURE 15–6. **A.** Diagram of an M-mode sweep from apex to base in a normal heart (parasternal view). **B.** to **D.** M-mode sweep from apex to base in a normal individual. aMVL, anterior mitral valve leaflet; Ao, aorta; AoV, aortic valve; APS, atriopulmonic sulcus; ARVW, anterior right ventricular wall; ATVL, anterior tricuspid valve leaflet; AVJ, atrioventricular junction; Ch, chordae tendineae; EN, endocardium; E,P, epicardial/pericardial interface; IVS, interventricular septum; LA, left atrium; LAW, left atrial wall; LV, left ventricle; LVOT, left ventricular outflow tract; PA, pulmonary artery; PMVL, posterior mitral valve leaflet; PPM, posterior papillary muscle; PV, pulmonic valve; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract. **A**, reproduced with permission from Felner JM, Schlant RC: *Echocardiography: A Teaching Atlas*. New York: Grune & Stratton; 1976.

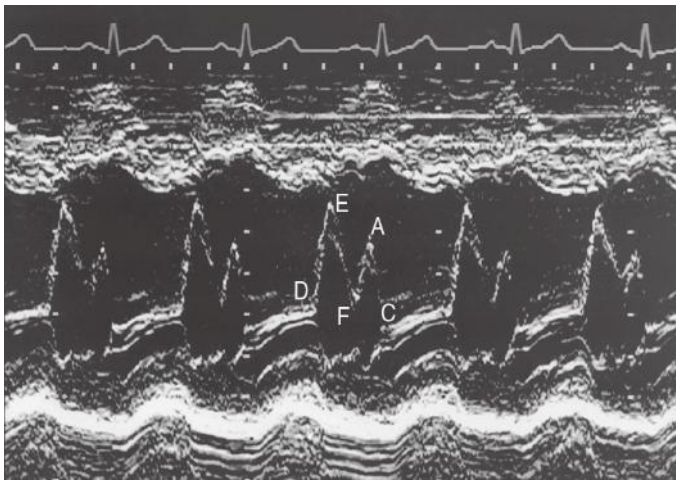


FIGURE 15–7. Standard M-mode image through the left ventricle at the level of the mitral valve. See text for discussion of nomenclature.

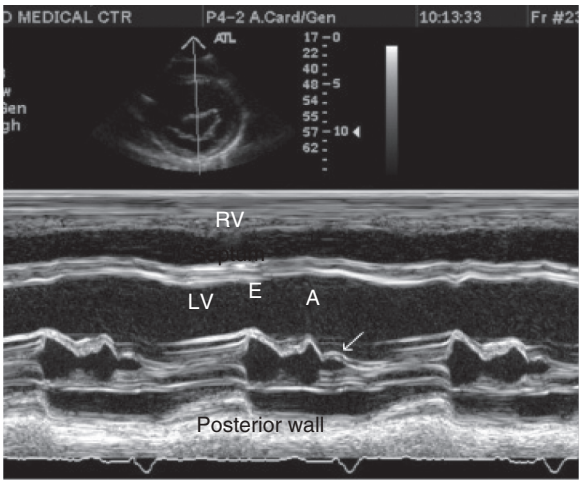


FIGURE 15–8. M-mode image through the mitral valve showing a B bump, suggesting high left ventricular diastolic pressure (*arrow*). The E-point septal separation is also increased. (Transducer is in the left parasternal position.)

Of paramount importance is the identification of a thoracic site (window) that enables transmission of the ultrasound signal to the heart. All of these considerations are fundamentally different from image acquisition by cardiac magnetic resonance, from which any imaging plane is obtainable.

The examination customarily begins with the transducer in the left parasternal position in the long-axis view (Fig. 15–14). This provides excellent images of the LV, aorta, LA, and the mitral and aortic valves. By angling the beam slightly rightward and inferiorly (right ventricular [RV] inflow view), the right atrium (RA), RV, and tricuspid valve (TV) are visualized (Fig. 15–15).

A 90-degree clockwise turn of the transducer produces the parasternal short-axis view. Slight axial angulation of the transducer enables visualization of the LV at various levels of the short axis, including the papillary muscle, mitral leaflets, and AoV (Fig. 15–16). With angulation toward the base, the LA, right heart structures, main pulmonary artery (PA), and occasionally the LA appendage are also recorded. The apical views are best acquired with the patient in a steep left lateral decubitus position and the transducer at the point of the apical impulse. The four-chamber view is obtained by turning the transducer so that both ventricles, atrioventricular valves, and atria are visualized (Fig. 15–17). In this view, the septal, apical, and lateral walls of the LV are visualized. Slight superior angulation of the transducer will add the

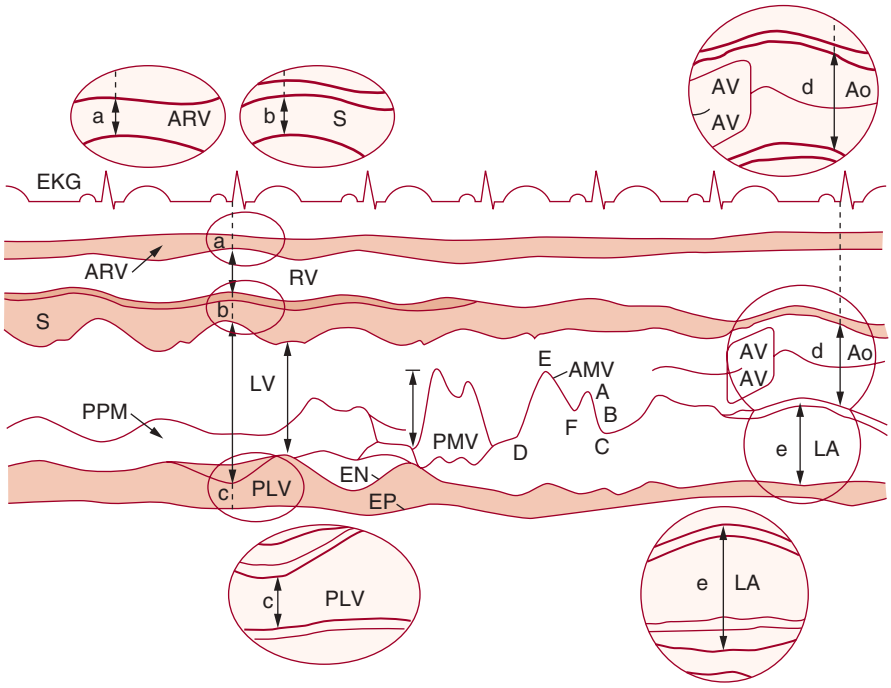


FIGURE 15–9. Recommended criteria for M-mode measurement of cardiac dimensions (see text for details). The figure and the elliptical inserts (a, b, c, d, and e) illustrate the leading-edge method. aMVL, anterior mitral valve leaflet; Ao, aorta; AoV, aortic valve; ARV, anterior right ventricular wall; EN, endocardium; EP, epicardium; LA, left atrium; LV, left ventricle; PLV, posterior left ventricular (wall); PPM, papillary muscle; PMVL, posterior mitral valve leaflet; RV, right ventricle; S, septum. Reproduced with permission from Sahn DJ, DeMaria A, Kisslo J, et al: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements, *Circulation*. 1978 Dec;58(6):1072-1083.

TABLE 15–1. Normal Values

	Mean ± Standard Deviation	Range	Mean ± Standard Deviation	Range
No. of patients	25	—	50	—
Age, years	10 ± 3	4–18	24 ± 0.6	1.10–2.53
BSA, m^2	1.33 ± 0.38	0.72–2.04	1.81 ± 0.34	1.10–2.53
$LVID_d$, mm	44 ± 6	32–50	50 ± 3	42–60
$LVID_s$, mm	28 ± 7	32–50	50 ± 3	22–43
FSLV	34 ± 4	25–42	33 ± 3	28–37
IVS thickness, mm	8 ± 2	5–10	9 ± 1	7–12
IVS excursion, mm	7 ± 1	5–9	9 ± 1	7–12
PW_d thickness, mm	7 ± 2	4–9	9 ± 1	7–12
PW_s thickness, mm	12 ± 3	8–17	16 ± 2	13–20
α thickening PW	0.70 ± 0.25	0.41–0.95	0.50 ± 0.19	0.32–0.69
PW excursion, mm	9 ± 2	7–14	11 ± 2	9–17
RVD_d supine, mm	—	—	15 ± 6	7–22
RVD_d left lateral, mm	—	—	20 ± 8	10–37
$Aorta_d$ mm	23 ± 4	15–27	28 ± 5	26–36
LAD_s mm	25 ± 5	20–31	27 ± 6	12–35

BSA, body surface area; FSLV, fractional shortening of left ventricle; IVS, interventricular septum; LAD, left atrial dimension; $LVID_d$, left ventricular internal diameter, end diastole; $LVID_s$, left ventricular internal diameter, end systole; PW, posterior wall; PWV, posterior wall velocity; RVD, right ventricular dimension.

Data from Felner JM, Schlant RC. *Echocardiography: A Teaching Atlas*. New York, NY: Grune & Stratton; 1976.

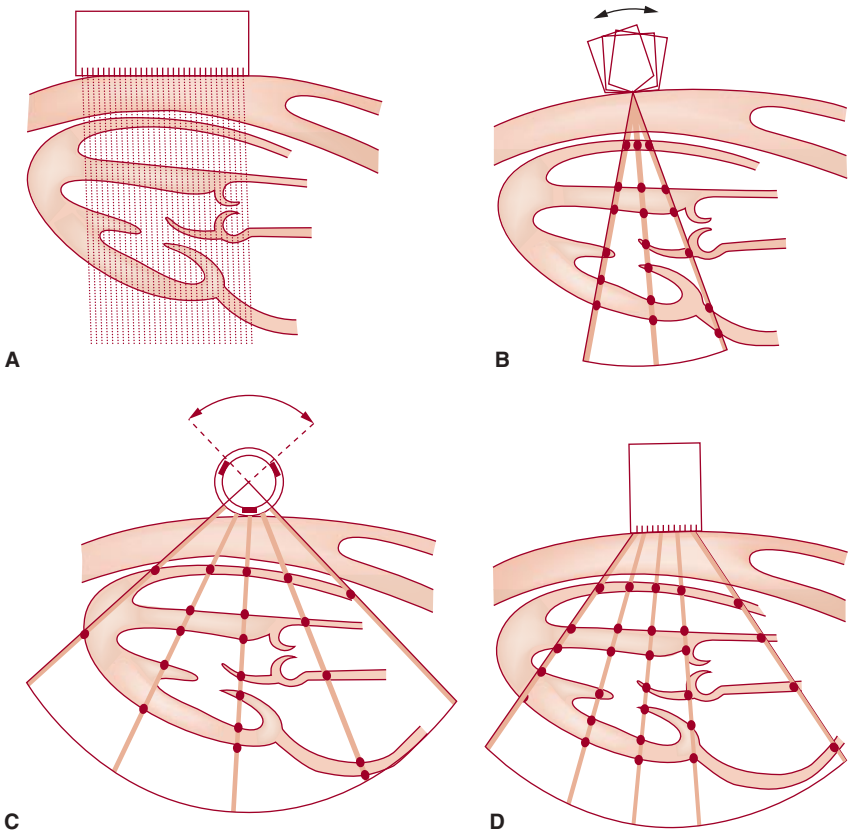


FIGURE 15–10. Phased-array scanner. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

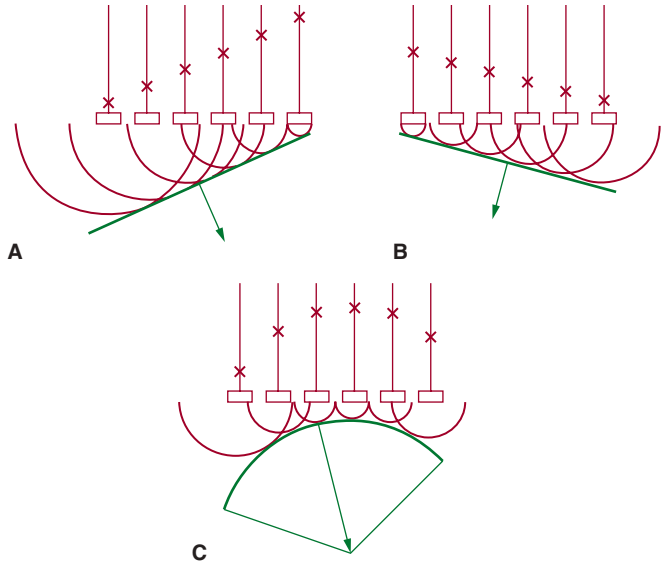


FIGURE 15–11. Electronic steering of a phased-array ultrasound beam. **A.** Elements are fired in sequence from left to right, resulting in a beam directed to the left. **B.** Elements are fired in sequence opposite to those in (**A**), producing a beam directed to the right. **C.** Elements are fired from the periphery toward the center, producing a beam that converges on a given focal point. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

AoV and proximal ascending aorta to the echocardiographic image (apical five-chamber view). From the four-chamber view, 90 degrees of counterclockwise transducer rotation produces the apical two-chamber view (Fig. 15–18A and B). This imaging plane demonstrates the LA and the inferior, apical, and anterior wall segments of the LV (the right heart structures are absent). If the transducer is rotated slightly further, a three-chamber view similar to the parasternal long-axis view is produced (Fig. 15–18C) and provides images of the posterior, apical, and anteroseptal LV wall segments, as well as the LA, AO, and mitral and aortic valves.

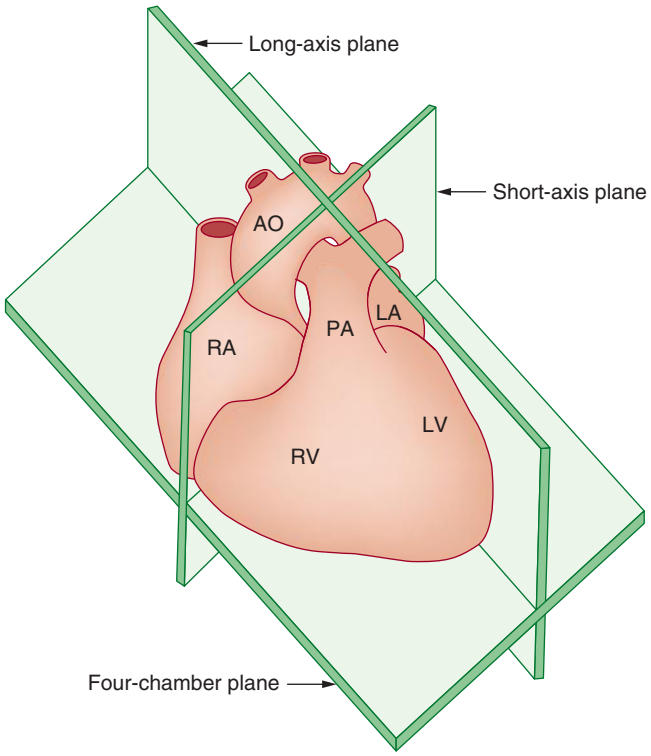


FIGURE 15–12. The three basic tomographic imaging planes used in echocardiography: long axis, short axis, and four chamber. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

To facilitate subcostal imaging, the patient is moved into a supine position. The subcostal four-chamber view is much like the apical four-chamber view (Fig. 15–19), but because the ultrasound beam is now more perpendicular to the interventricular and interatrial septa, subcostal imaging is often helpful in the examination of these structures. A 90-degree rotation of the transducer will record a subcostal short-axis view. The transducer can also be angled to image the RV outflow tract and PA as well as the inferior vena cava (see Fig. 15–19).

The long-axis suprasternal imaging plane is shown in Fig. 15–20. In adults, the LV is usually not visualized satisfactorily from the suprasternal position, but these imaging planes are well suited for examination of the thoracic aorta, PA, and great vessels. Normal values for 2D echocardiographic measurements are shown in Table 15–3.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Using a transducer with a matrix array of crystals, a pyramid-shaped ultrasound beam can be produced that can often encompass the entire heart from one transducer location and acquire an entire data set in a single cardiac cycle. Advances in processing have improved surface rendering and endocardial border definition (see Fig. 15–20C). 3D images can be valuable in exact quantification of cardiac volumes and EF, assessing congenital heart disease (CHD), and evaluating structures of complex geometry such as the RV.[27] Recent studies have shown an excellent correlation between real-time 3D echo and magnetic resonance imaging (MRI) in the measurement of regional and global LV volume and time-wall motion curves.[28] Real-time 3D TEE has been implemented and can provide valuable information regarding the evaluation of native, repaired, and prosthetic valves (see Fig. 15–20D and F).[29,30]

ASSESSMENT OF SYSTOLIC FUNCTION BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

2D echocardiography is the standard clinical approach for measuring cardiac chamber volumes and EF.[31-33] Numerous algorithms have been applied to calculate LV volumes by echocardiography (Fig. 15–21). Most algorithms assumed that the LV conforms to the shape of a prolate ellipsoid or a combination of geometric shapes and calculate volume by diameter-length or area-length formulas.[34] Multiple studies comparing LV volume calculated by area-length methods to those obtained by other techniques have yielded good correlations, with the best results obtained using biplane apical views.[35,36] Currently, the most commonly used algorithm to calculate LV volumes is based on the Simpson rule, which derives measurements by dividing the LV by parallel planes into a number of small segments and then summating the area of the individual disks. Although all modifications of the Simpson rule give good results, the optimal correlations have been achieved with a modification that separately quantifies the volume of the apex as an ellipsoid.[33,35]

Accurate calculations of LV volumes by echocardiography are critically dependent on high-quality images to delineate the endocardium and image the entire LV perimeter. Echocardiographic estimates of LV volumes underestimate those calculated by other techniques and are most accurate in the absence of significant alterations of LV size and contraction. Measurements are most accurate in images with superior

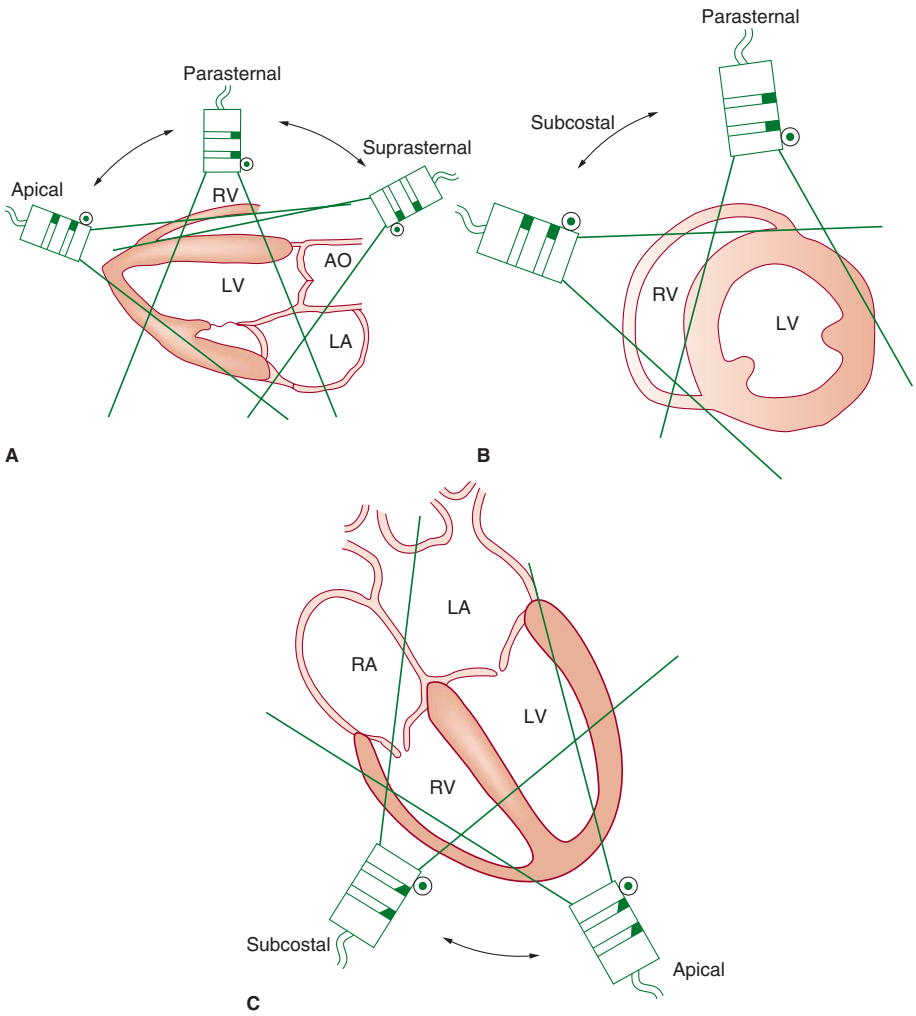
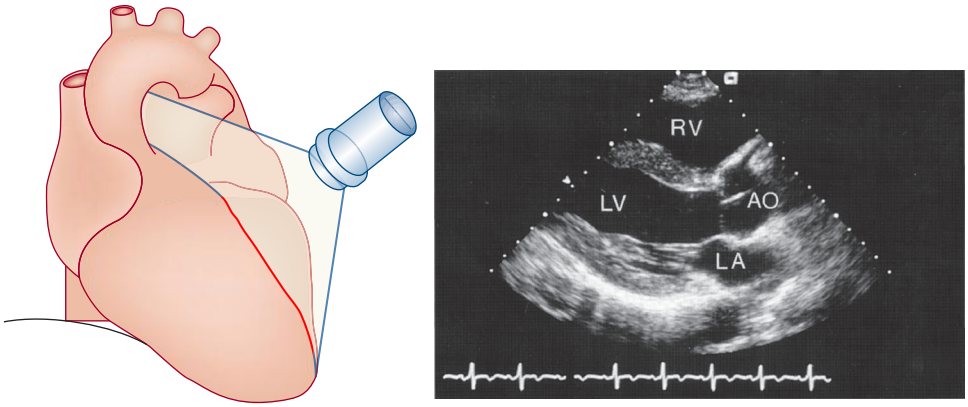


FIGURE 15–13. Visualization of the heart's basic tomographic imaging planes by various transducer positions. The long-axis plane (**A**) can be imaged in the parasternal, suprasternal, and apical positions; the short-axis plane (**B**) in the parasternal and subcostal positions; and the four-chamber plane (**C**) in the apical and subcostal positions. Reproduced with permission from Henry WL, DeMaria A, Gramiak R, et al: Report of the American Society of Echocardiography: nomenclature and standards in two-dimensional echocardiography, *Circulation* 1980 Aug;62(2):212-217.

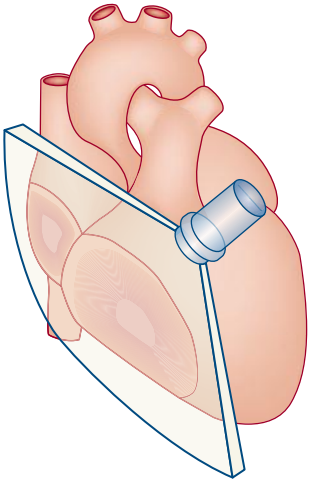
TABLE 15–2. Standard Two-Dimensional Echocardiographic Transducer Positions

Parasternal position	Five-chamber plane
Long axis	(Four-chamber plane angled superiorly to include the aorta)
Left ventricular long axis	Two-chamber plane
Right ventricular long axis	Three-chamber plane
Right ventricular outflow	Subcostal position
Short axis	Four-chamber plane
Short axis through the plane of the	Short axis through the plane of the
Cardiac base	Mitral valve
Mitral valve	Papillary muscles
Chordae tendineae	Cardiac base
Papillary muscles	Posteriorly directed planes through the venae cavae and atria
Apex	Suprasternal position
Apical position	Long axis (through the ascending and descending aorta)
Four-chamber plane	Short axis



A B

FIGURE 15–14. A. Orientation of the sector beam and transducer position for the parasternal long-axis view of the left ventricle. **B.** 2D image of the heart, parasternal long-axis view. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.



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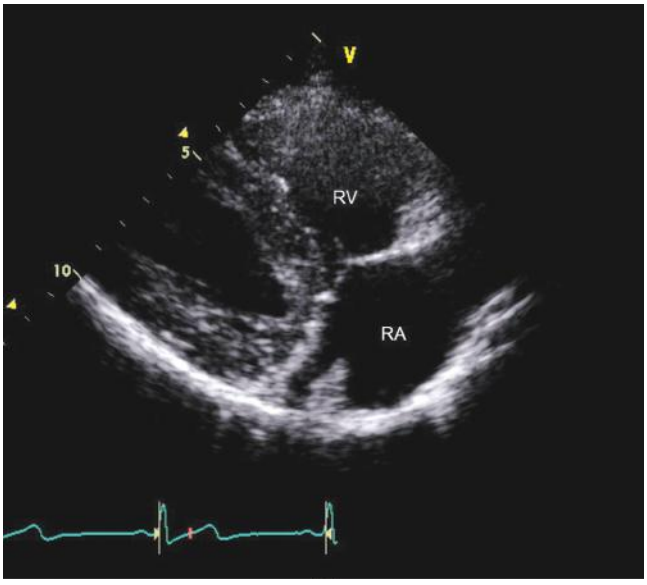


B

FIGURE 15–15. A. Orientation of the sector beam and transducer position for the parasternal RV inflow plane. **B.** Two-dimensional image of RV inflow plane. RA, right atrium; RV, right ventricle. **A**, reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

endocardial definition. Nevertheless, echocardiographic calculations of LV volumes have generally yielded correlation coefficients in excess of 0.75 as compared with radionuclide angiography, cineangiography, and autopsy studies, regardless of the algorithm used.[30-35]

Because of the 3D nature of the heart, 2D cut-planes are inevitably different between studies. Thus, the reproducibility of 2D echocardiography between individual studies has been limited, especially in comparison with MRI. Studies using 3D echocardiography have reported better reproducibility than 2D methods.

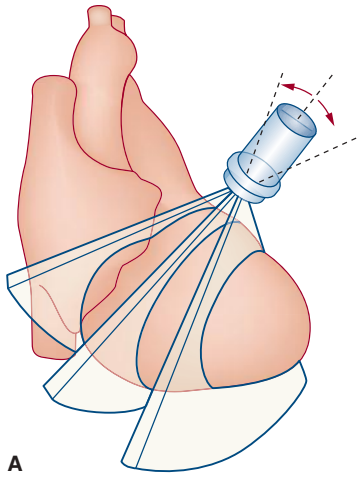
The use of 2D echo also presents limitations related to image quality. Several approaches have been used to improve contrast resolution of the echo signal and therefore better delineate the endocardial border. Greater enhancement of endocardial border delineation and improvement of the reliability of measures of LV size and contraction have been achieved using tissue harmonic imaging. LV opacification using echo contrast agents improves accuracy and reliability.[37] The available products vary by country, but in all jurisdictions, the technique remains underutilized. Images of the power spectrum of the Doppler signal produced by contraction/relaxation and colorization of the B-mode tissue image have been used to visualize the endocardial surface.[36] Another approach to quantitation of regional function is based on tissue Doppler or tracking of speckle patterns (Fig. 15–22). A variety of displays have been used to show the magnitude and time-course of contraction (Fig. 15–23). This technique has been valuable in the recognition of subtle abnormalities of LV contraction and regional disturbances of LV diastolic function.[38,39]

DOPPLER ECHOCARDIOGRAPHY: PRINCIPLES AND APPLICATIONS

THE DOPPLER PRINCIPLE

Using the principle first delineated by the physicist Johann Christian Doppler,[40] ultrasound can be used to determine the velocity and direction of blood flow by measuring the change in frequency produced when sound waves are reflected from red blood cells (RBCs). Thus information regarding the presence, direction, velocity, and turbulence of blood flow can be acquired by cardiac ultrasound.

The Doppler principle states that when a sound (or light) signal strikes a moving object, the frequency of that signal is altered, and the increase or decrease in frequency is proportional to the velocity and direction at which the object is moving (Fig. 15–24). If a stationary transducer



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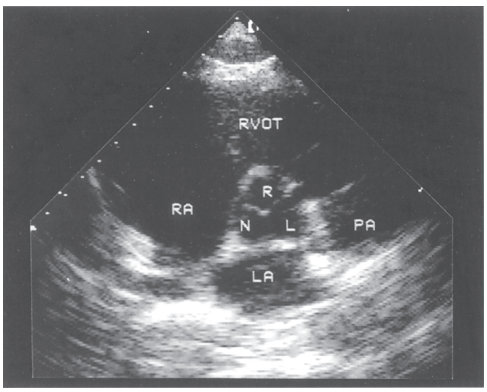

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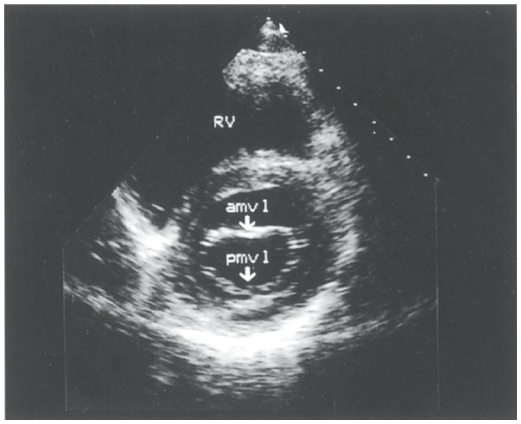

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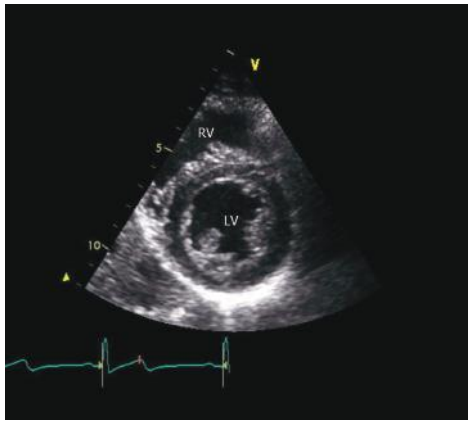

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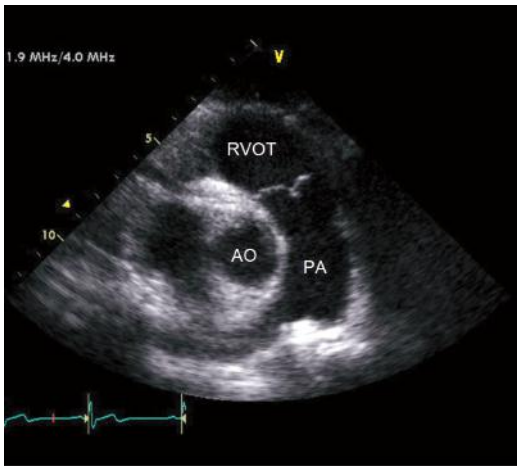
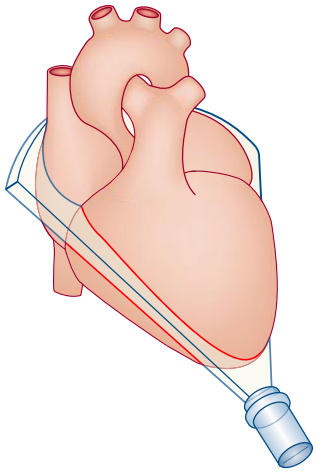


E

FIGURE 15–16. **A.** Orientation of various short-axis sector beams through the left ventricle obtained by angling the transducer in the parasternal position. **B.** Short-axis plane through the base of the heart. **C.** At the level of the mitral valve leaflets. **D.** At the papillary muscle level. **E.** Modified parasternal short axis plane through the RV outflow tract and pulmonary artery. aMVL, anterior mitral valve leaflet; L, left cusp of the aortic valve; LA, left atrium; LV, left ventricle; N, noncoronary cusp of the aortic valve, PA, pulmonary artery; PMVL, posterior mitral valve leaflet; RA, right atrium; R, right cusp of the aortic valve; RV, right ventricle; RVOT, right ventricular outflow tract. **A**, reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.



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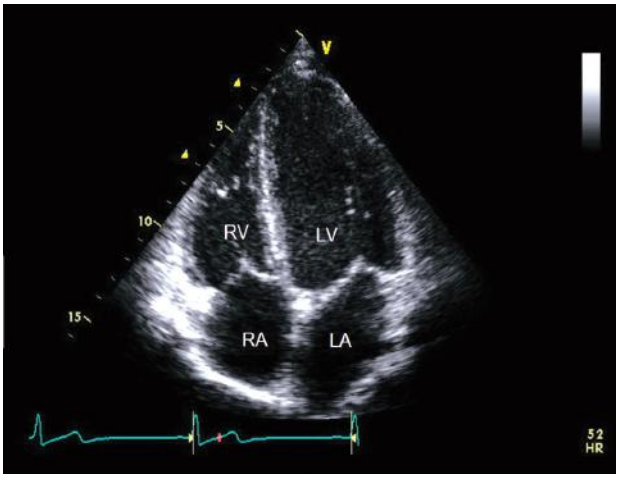


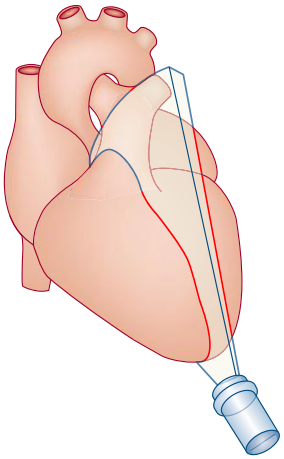
B

FIGURE 15–17. A. Orientation of the sector beam and transducer position for the apical four-chamber plane. **B.** Two-dimensional image of the apical four-chamber plane. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. **A**, reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

at the apex emits a sound wave with a transmitted frequency of f_o and the wave is reflected by nonmoving RBCs in an isovolumic phase of the cardiac cycle, the received frequency f_r will be identical to f_o. If the signal is reflected by RBCs that are moving toward the transducer, as through the MV in diastole, the returning waves will be compressed so that $f_r > f_o$. Conversely, if the target RBCs are moving away from the transducer, as in the outflow tract in systole, the returning sound waves will be elongated and the received frequency will be decreased. It is important to note that the magnitude of change in the received frequency is directly related to the velocity at which blood is flowing toward or away from the transducer.[41] If the velocity of sound and the angle θ between the direction of RBC flow and the beam path are known, then the velocity of the RBCs is described by the Doppler equation:

$$V = f_d\,(c)/2f_o\,(\cos\theta)$$

where f_d is the frequency shift recorded; f_o, the transmitted frequency; and c, the velocity of sound. Note that the denominator is doubled.



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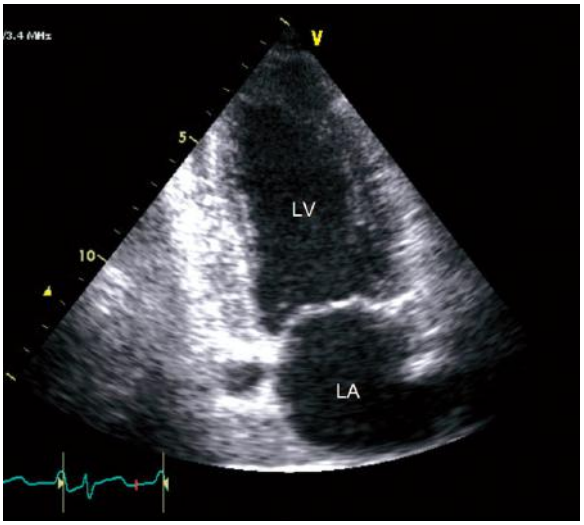

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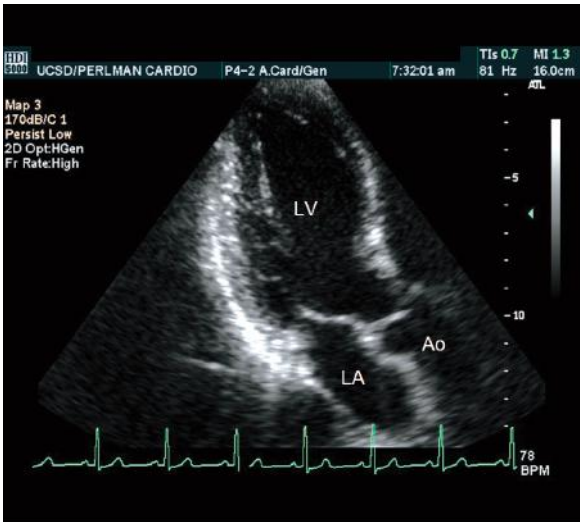
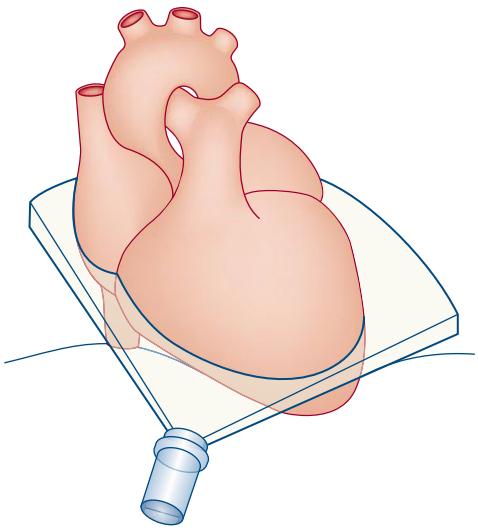


C

FIGURE 15–18. A. Orientation of the sector beam and transducer position for the apical two-chamber plane. **B.** Two-dimensional (2D) image of the apical two-chamber plane. **C.** 2D image of the apical three-chamber view. Ao, aorta; LA, atrium; LV, left ventricle. **A**, reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.



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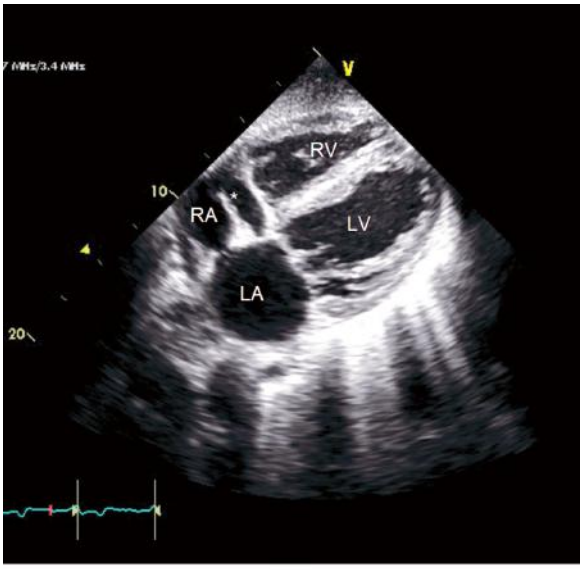

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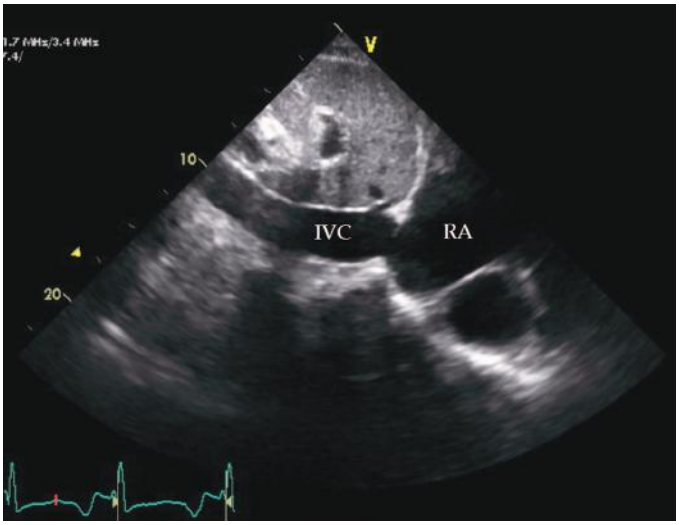

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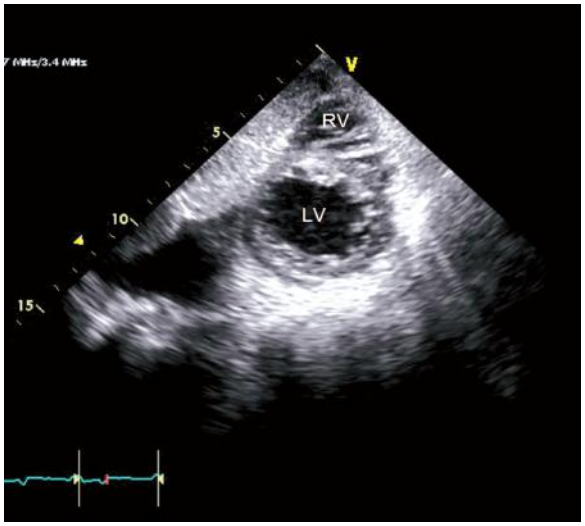


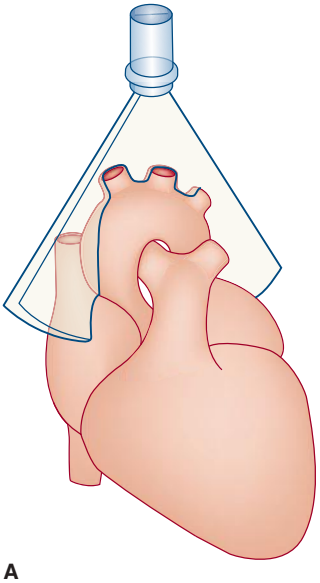
D

FIGURE 15–19. **A.** Orientation of the sector beam and transducer position for the subcostal four-chamber plane. **B.** Two-dimensional (2D) image of the subcostal four-chamber plane. **C.** Subcostal 2D image demonstrating the right atrium (RA) and inferior vena cava (IVC). **D.** 2D image of the subcostal short-axis plane. Asterisk, a prominent eustachian valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. **A**, reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

By measuring Doppler shift frequencies, the velocity and direction of blood flow can be calculated, displayed, and recorded.

The angle between the direction of blood flow and the course of the sound beam is the most important factor in Doppler ultrasound (Fig. 15–25). Velocity is a vectorial entity, having magnitude and direction, and Doppler best detects velocities parallel or near parallel to the interrogating signal. Because the relationship between velocity and the angle is a cosine function and the cosine of angles up to 20 degrees is 0.9, little error is introduced within this range.[41] However, considerable errors occur when the angle between the direction of blood flow and the course of the sound beam exceeds 20 degrees. Moreover, the angle of incidence in 3D space usually cannot be determined with certainty from 2D echocardiographic images. Therefore, it is crucial to position and direct the transducer so that the beam is as parallel to flow as possible. In clinical use, the frequency of transmitted ultrasound is in the range of 2 to 7 MHz, the velocity of sound in tissue is approximately 1540 m/s, and the Doppler shift frequency is relatively small (~1–4 kHz) as compared with the transmitted frequency. Because the Doppler shift frequencies are in the audible range, a speaker integrated into the Doppler echocardiography system can present them as an audible signal. Normal signals are tonal or musical.

Figure 15–26 shows the typical graphic pulsed Doppler pattern of normal systolic blood flow through the RV outflow tract into the PA, with flow velocity on the *y*-axis and time on the *x*-axis. The location and size of the area from which Doppler recordings are derived is determined by positioning a sample volume on the echo image. The absence of flow is represented by the zero or no-flow line, termed the *baseline*. By convention, flow toward the transducer is displayed above the baseline and flow away from the transducer is displayed below the baseline. The velocities above and below baseline represent flow toward



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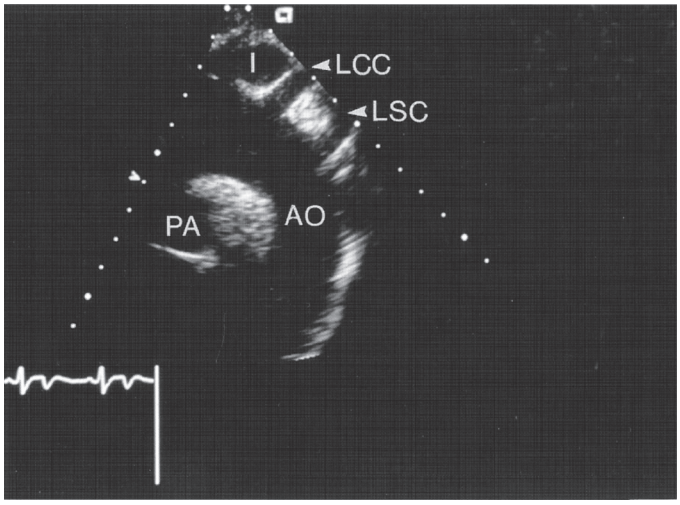

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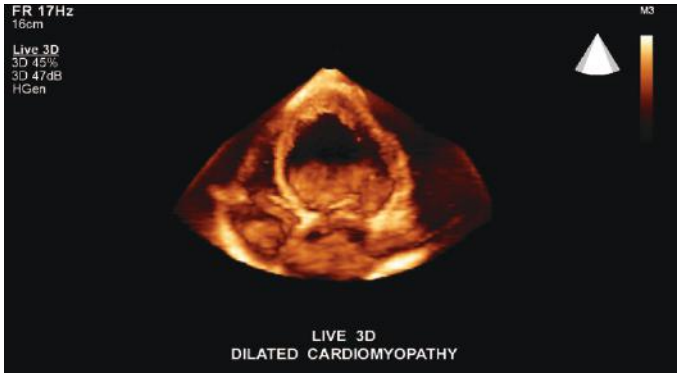

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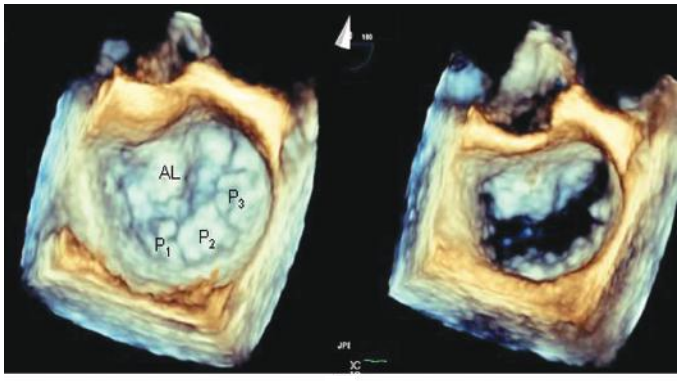

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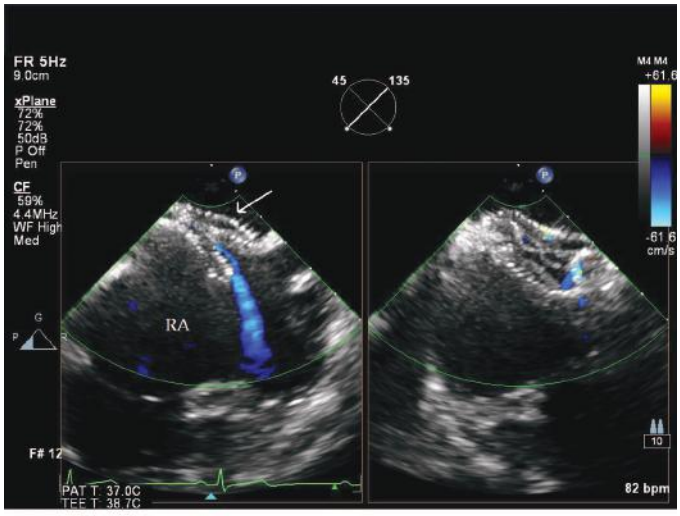

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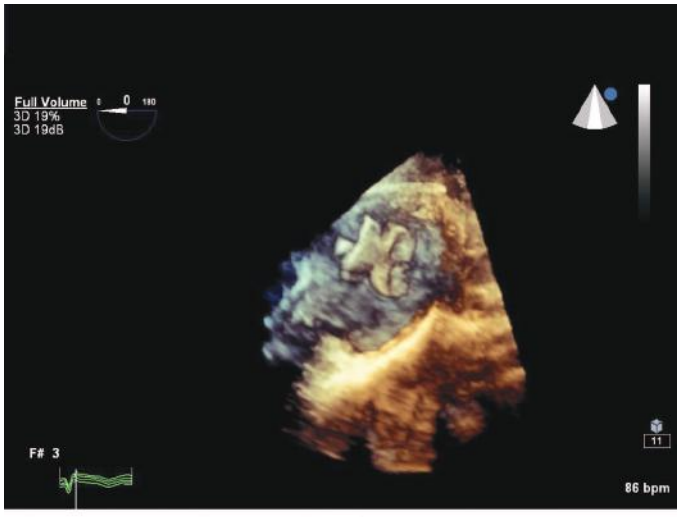

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FIGURE 15–20. **A.** Orientation of the sector beam and transducer position for long-axis plane through the aorta from the suprasternal position. **B.** Two-dimensional image of the suprasternal long-axis view of the thoracic aorta. **C.** Example of three-dimensional (3D) image in a case of dilated cardiomyopathy. **D.** 3D transesophageal image of the mitral valve during systole (*left*) and diastole (*right*). **E.** Simultaneous orthogonal transesophageal echocardiography images of a patent foramen ovale (PFO) occluder device (*arrow*). **F.** 3D transesophageal image of a PFO occluder device. AL, anterior mitral valve leaflet; Ao, aorta; I, innominate artery; LCCA, left common carotid artery; LSC, left subclavian artery; LV, left ventricle; P1/P2/P3, lateral/middle/medial scallops of the posterior mitral valve leaflet; PA, right pulmonary artery; RA, right atrium; RV, right ventricle. **D**, reproduced with permission from Perk G, Lang RM, Garcia-Fernandez MA, et al. Use of real time three-dimensional transesophageal echocardiography in intracardiac catheter based interventions, *J Am Soc Echocardiogr*. 2009 Aug;22(8):865-882.

TABLE 15–3. Cardiac Dimensions by Two-Dimensional Echocardiography

Cardiac Feature	Range	Mean	Index (cm/m^2)
Apical four-chamber view			
LV_d major	6.9–10.3 cm	8.6 cm	4.1–5.7
LV_d minor	3.3–6.1 cm	4.7 cm	2.2–3.1
LV_s minor	1.9–3.7 cm	2.8 cm	1.3–2.0
LV_d area	21.2–40.2 cm^2	31.2 cm^2	—
LV_s area	8.0–21.1 cm^2	14.2 cm^2	—
RV major	6.5–9.5 cm^2	8.0 cm	3.8–5.3
RV minor	2.2–4.4 cm^2	3.3–3.5 cm	1.0–2.8
RV_d area	12.0–22.2 cm^2	18.6–2.1 cm^2	—
RV_s area	5.4–14.6 cm^2	9.9 cm^2	—
LA major	4.1–6.1 cm	5.1 cm	2.3–3.5
LA minor	2.8–4.3 cm	3.5 cm	1.6–2.4
LA area	10.2–17.8 cm^2	14.7 cm^2	—
RA major (inf-sup)	3.5–5.5 cm	4.3–4.5 cm	2.0–3.1
RA minor	2.5–4.9 cm	3.7 cm	1.7–2.5
RA area	11.3–16.7 cm^2	13.8–14 cm^2	—
Apical two-chamber view			
LV_d major	6.8–9.4 cm	8.0 cm	—
LV_d minor	3.8–5.7 cm	4.6 cm	—
LV_d area	19.4–48.0 cm^2	35.6 cm^2	—
LV_s	8.9–27.0 cm	14.3 cm	—
Parasternal long-axis view			
LV_d	3.5–6.0 cm	4.8 cm	2.3–3.1
LV_s	2.1–4.0 cm	3.1 cm	1.4–2.1
RV	1.9–3.8 cm	2.8 cm	1.2–2.0
LA (A-P)	2.7–4.5 cm	3.6 cm	1.6–2.4
LA (S-I)	3.1–5.5 cm	4.4 cm	—
LA area	9.0–19.3 cm^2	13.8 cm^2	—
Ao	2.2–3.6 cm	2.9 cm	1.4–2.0
Parasternal short-axis view			
Ao	2.3–3.7 cm	3.0–2.3 cm	1.6–2.4
RVOT	1.9–2.2 cm	2.7 cm	—
RA	1.5–2.5 cm	1.9–2.2 cm	—
LA	2.6–4.5 cm	3.6 cm	1.6–2.4
LA area	7.2–13.0 cm^2	10.8 cm^2	—
LV_d (PM level)	3.5–5.8 cm	4.7 cm	2.2–3.1
LV_s (PM level)	2.2–4.0 cm	3.1 cm	1.4–2.2
LV_d area (PM level)	16.0–31.2 cm^2	22.2 cm^2	—
LV_s area (PM level)	5.2–13.4 cm^2	8.5 cm^2	—
LV_d (Ch. level)	3.5–6.2	4.8 cm	2.3–3.2
LV_s (Ch. level)	2.3–4.0	3.2 cm	1.5–2.2
LV_d area (Ch. level)	16.4–32.3 cm^2	22.5 cm^2	—
LV_s area (Ch. level)	6.1–16.8 cm^2	10.7 cm^2	—
Subcostal view			
IVC diameter		1.8 cm	—

Ao, aorta; Ch., chordal; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; LV_d, left ventricle, end diastole; LV_s, left ventricle, end systole; PA, pulmonary artery; PM, papillary muscle; RA, right atrium; RV, right ventricle; RV_d, right ventricle, end diastole; RVOT, right ventricular outflow tract; RV_s, right ventricle, end systole.

The values shown in this table represent a compilation of data from three sources: Schnittinger I, Gordon EP, Fitzgerald PJ, et al. Standardized intracardiac measurements of two-dimensional echocardiography. *J Am Coll Cardiol*. 1983; 5:934. Triulzi M, Weyman A. Normal cross-sectional measurements in adults. In: Weyman A, ed. *Echocardiography*. Philadelphia, PA: Lea & Febiger; 1982;497. Hagan AD, DiSessa TG, Bloor CM, et al. *Two-Dimensional Echocardiography: Clinical-Pathological Corrections in Adult and Congenital Heart Disease*. Boston, MA: Little, Brown; 1983;553.

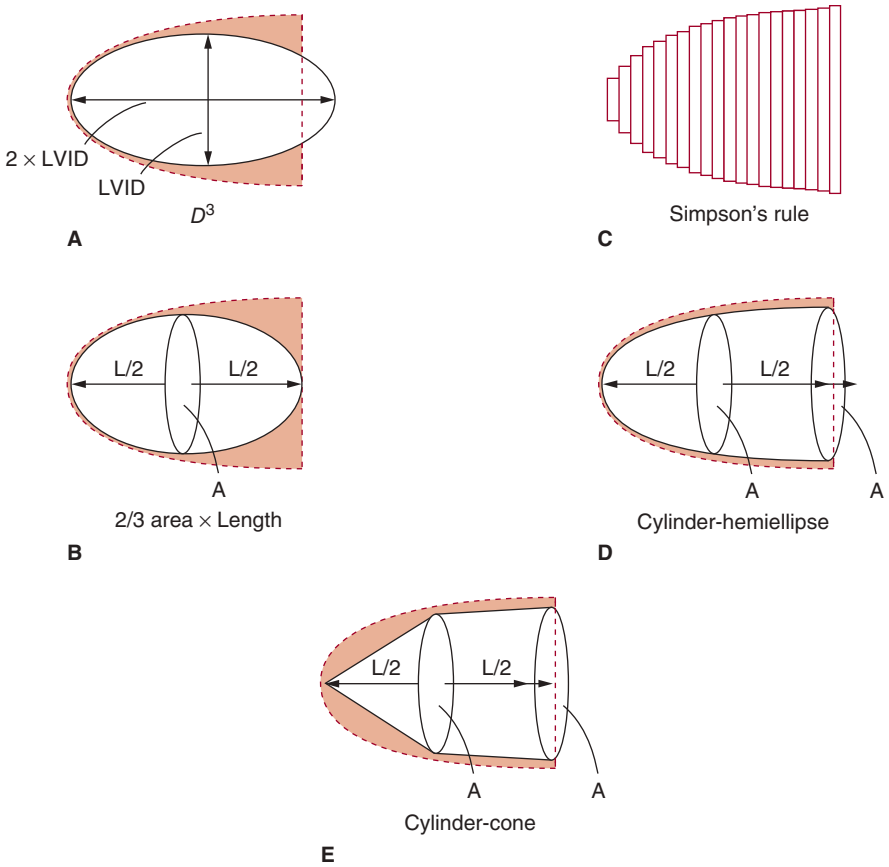


FIGURE 15–21. Various geometric models used to estimate left ventricular volume. **A.** D-cubed. **B.** Two-thirds area × length. **C.** Simpson rule. **D.** Cylinder-hemiellipse. **E.** Cylinder-cone. A, cross-sectional area; L, length of left ventricle major axis; LVID, left ventricular internal dimension (minor axis).

or away from the transducer, not forward or backward in the circulation. The sample volume almost invariably includes RBCs flowing at slightly different velocities. Even normal laminar blood flow in the great vessels varies in velocity across the lumen, because RBCs in the center of the vessel move at higher velocity than those exposed to viscous friction at the wall. Therefore, any returning Doppler-shifted signal contains a spectrum of velocities, each of which can be displayed by means of fast Fourier transform analysis. The graphic output of the Doppler signal displays the range of velocities within the sample volume site at any time in gray scale and the number of RBCs moving at any velocity as relative intensity. Normal laminar flow is characterized by a uniformity of velocity and direction of individual RBCs, and therefore a narrowly dispersed signal, whereas disturbed or turbulent flow is manifest by marked variability in velocity and direction and therefore a broad signal.

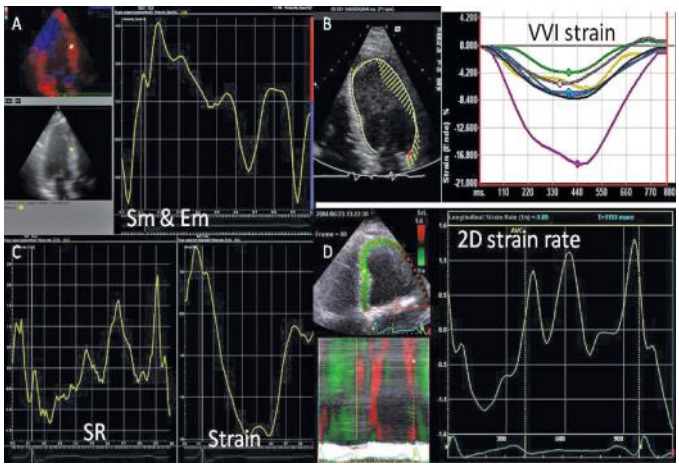


FIGURE 15–22. Methods for quantification of regional function, including tissue Doppler (**A**), velocity vector imaging (**B**), strain rate and strain derived from tissue Doppler (**C**), and strain rate–derived from speckle strain (**D**). Em, diastolic velocity; Sm, systolic velocity; SR, strain rate; VVI, velocity vector imaging.

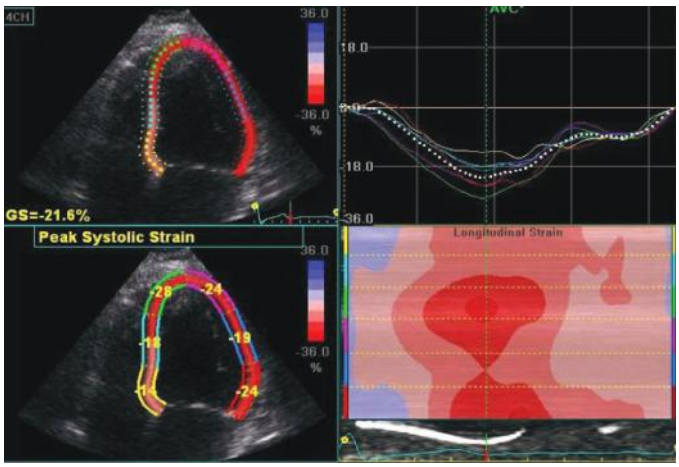


FIGURE 15–23. Speckle strain approach to the assessment of the magnitude and timing of strain in multiple segments, as well as averaging the longitudinal strain.

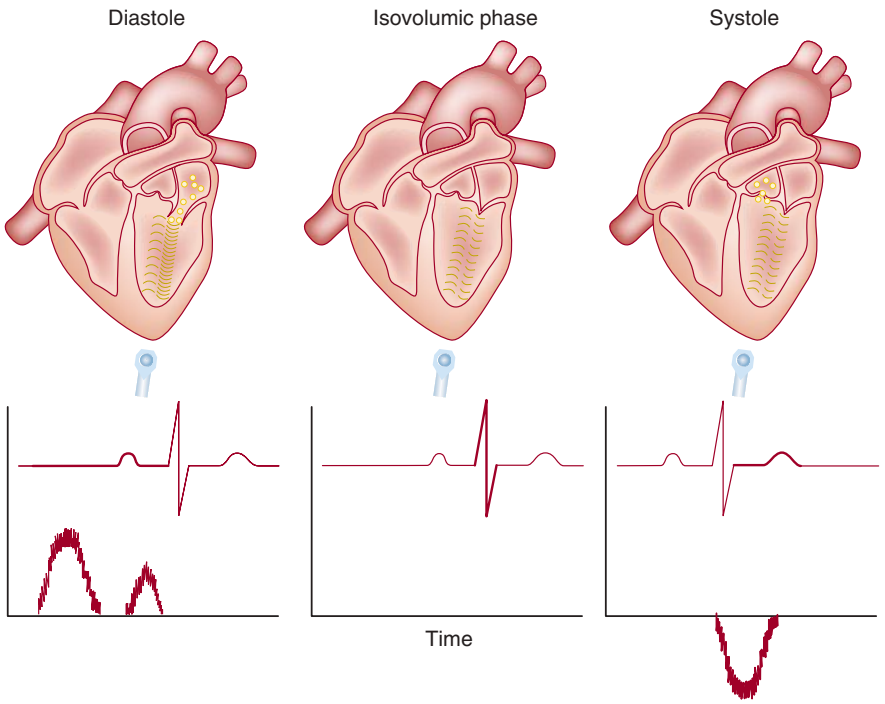


FIGURE 15–24. Basic principle of the Doppler shift. During diastole (*left panel*), an ultrasound beam directed toward the junction of the mitral and aortic annuli is reflected by red blood cells moving toward the transducer. The frequency of the received ultrasound is greater than that of the transmitted beam, and the spectral tracing is recorded above the baseline (ie, flow is toward the transducer). During the isovolumic phase (*middle panel*), both the mitral and aortic valves are closed and little flow occurs within the left ventricle. Therefore, there are no significant changes in the transmitted and received frequencies of the Doppler beam, and no spectral tracing is recorded. During systole (*right panel*), the transmitted beam is reflected by red blood cells moving away from the transducer. Therefore, the frequency of the received ultrasound is lower than that of the transmitted beam, and the spectral tracing is recorded below the baseline.

Echographs have now been modified to enable recording of the low-velocity, high-amplitude Doppler signals produced by moving tissue, as well as those of RBCs. The ability to assess tissue velocity provides an evaluation of transmural rate of contraction and relaxation.[42] Also, Doppler tissue recordings permit assessment of regional function and appear to be quite useful in the assessment of diastolic function (see The Standard Doppler Examination).[43]

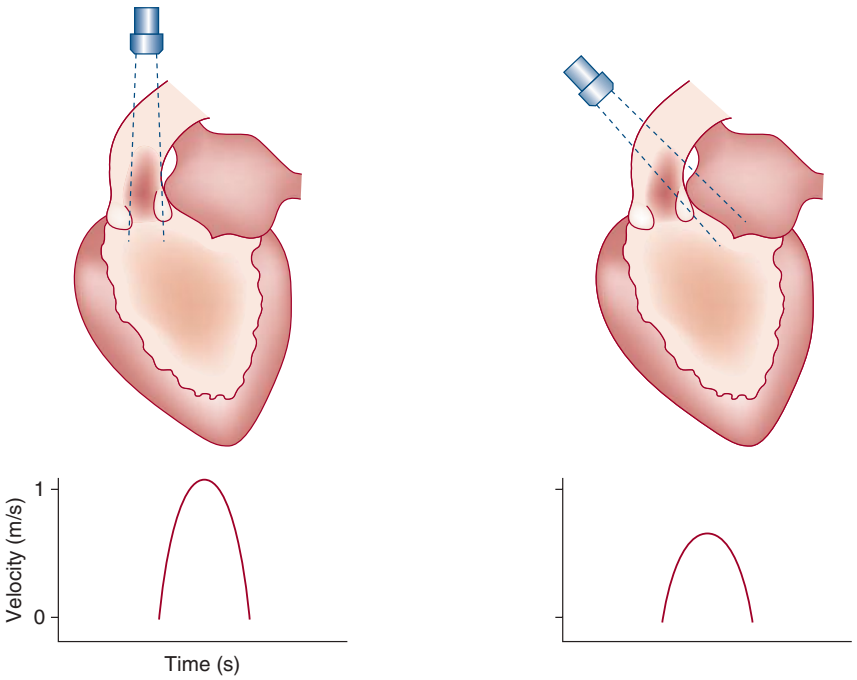


FIGURE 15–25. Effect of the angle of incidence on the velocity recorded with Doppler analysis. The true velocity is underestimated when the ultrasound beam is not parallel to the direction of blood flow. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

Doppler tissue recordings first provided the basis for the examination of myocardial deformation by echocardiography derived as regional myocardial strain measurements. This technique enabled assessment of the movement of an individual target relative to the movement of other targets in the tissue, not against the fixed reference of the transducer. Strain, which is the change in length divided by the original length could thereby be readily calculated. Such measurements are independent of overall cardiac movement and passive motion resulting from tethering to adjacent tissue and therefore enable the most accurate assessment of myocardial contractile performance. Several studies have documented the ability of strain measurements to identify impaired myocardial performance in the absence of other echo abnormalities in patients with hypertrophic cardiomyopathy, amyloid, and other conditions.[44] Most recently, the technique of tracking of the individual myocardial speckles of grayscale images has been developed, which can provide accurate measurements of strain independent of the orientation of the interrogating beam. Thereby, in conjunction with 3D imaging, maps of regional strain can be derived, as well as a global score for the entire left ventricle.

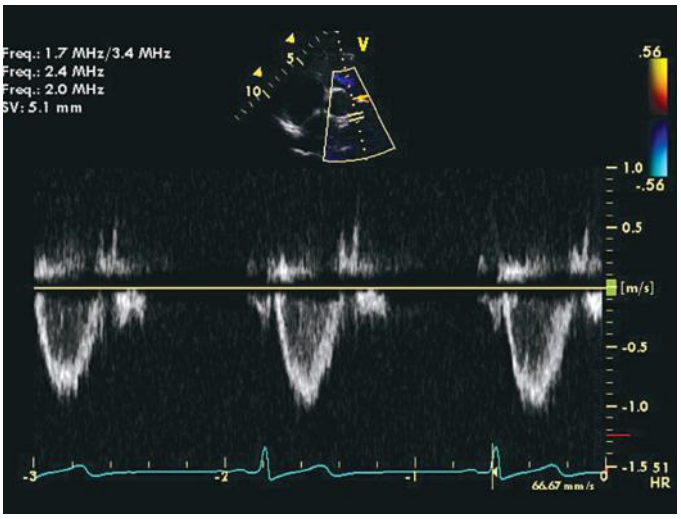


FIGURE 15–26. Doppler spectral envelope of normal blood flow through the right ventricular outflow tract (RVOT) during systole. The transducer is in the parasternal position and the sample volume is placed just proximal to the pulmonic valve.

CONTINUOUS- AND PULSED-WAVE DOPPLER

Time-velocity spectral recordings of blood flow are generally obtained with two types of Doppler interrogation: continuous and pulsed wave (Fig. 15–27).[11] In the continuous-wave (CW) mode, sound waves are both transmitted and received continuously. This requires two piezoelectric crystals in each transducer, one for transmitting and one for receiving. Because all flow velocities along the beam are recorded, CW Doppler cannot define individual signals at specific distances from the transducer—a problem referred to as *range ambiguity*. CW Doppler can accurately measure the direction and velocity of overall flow but cannot discern the precise site of origin of individual components within the signal (Fig. 15–28B).

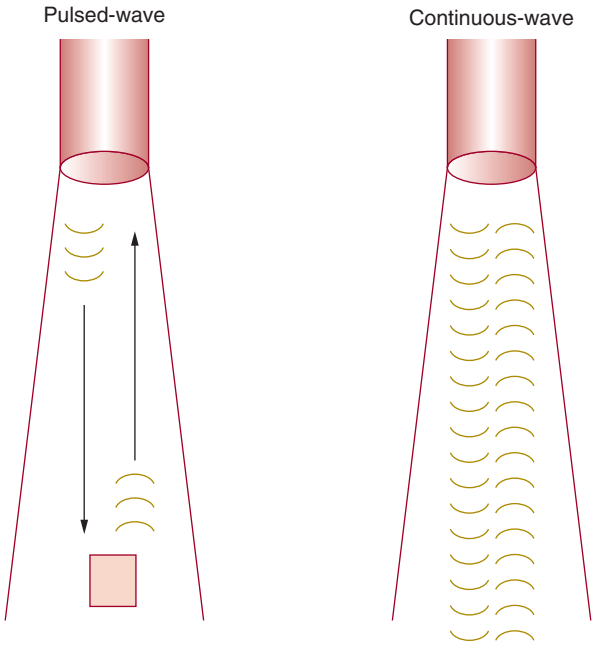
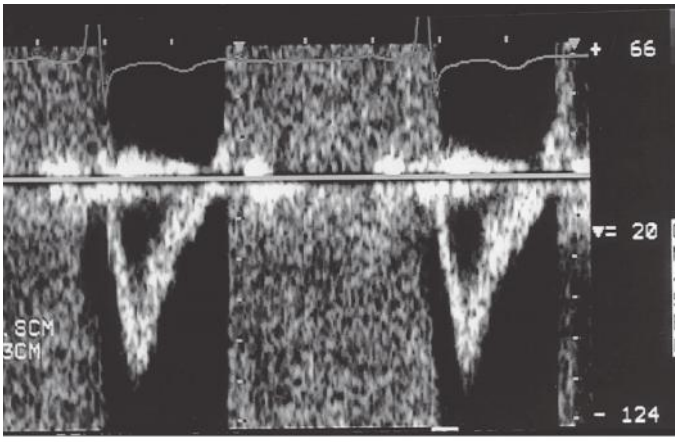


FIGURE 15–27. Pulsed-wave (PW) and continuous-wave (CW) Doppler. With PW, a single pulse of ultrasound energy is emitted, and its reflection from a sample volume is received before the following pulse is transmitted. With CW, there is continuous transmission and reception of ultrasound energy.

The problem of range ambiguity can be overcome by pulsed-wave Doppler (PWD). Short bursts of signal are transmitted from the transducer at a given pulse repetition frequency (PRF). The instrument then receives the signal for only a brief period: an interval that corresponds to the time required for sound energy to travel and return from a specific site along the beam path. The operator selects the location at which flow is to be examined by positioning a sample volume, and the instrument determines the period during which to receive the incoming reflected frequencies. With PWD only a single piezoelectric crystal is needed, and flow can be recorded in one small area within the heart or vasculature.[45] Unfortunately, pulsed Doppler techniques use intermittent sampling and are therefore susceptible to a problem of range ambiguity referred to as *aliasing*.[46] Aliasing is the erroneous representation of flow in the direction opposite to that in which it is actually occurring. To correctly record the velocity of blood flow by pulsed Doppler, the PRF must be at least double the Doppler shift frequency, a value known as the *Nyquist limit*. If the blood flow examined is of very high velocity or far from the transducer (requiring a long transit time), it may necessitate an unobtainably high PRF. In such cases, aliasing will



A

B

FIGURE 15–28. A. Pulsed-wave (PW) Doppler tracing from a patient with aortic regurgitation. The transducer is in the apical position and the sample volume is in the left ventricular outflow tract. A laminar envelope is seen during systole, whereas aliased flow is present during diastole because of high-velocity flow. **B.** Continuous-wave (CW) Doppler tracing through the left ventricular outflow tract (with transducer in the apical position). The maximal velocity of the aortic regurgitation is now measurable, but all other velocities along the Doppler beam are recorded as well.

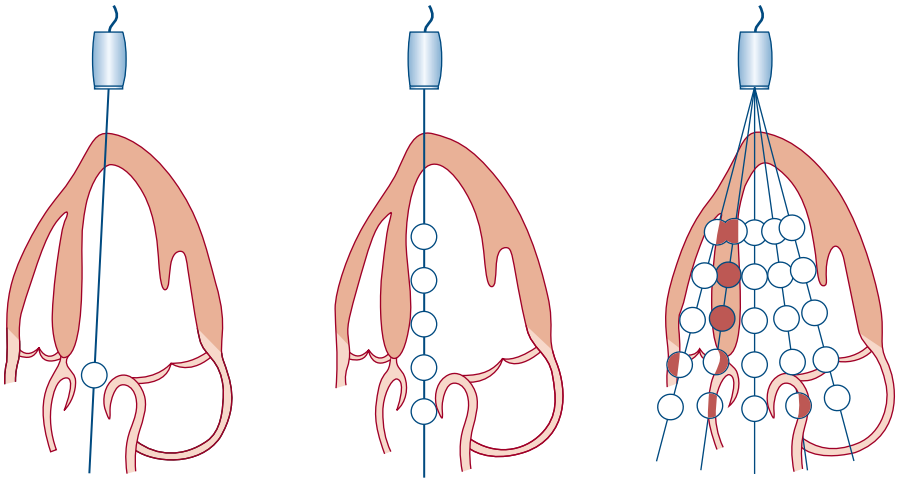


FIGURE 15–29. Simplified mechanism of color-flow Doppler imaging. Single-gate (*left*) or multiple-gate pulsed Doppler (*center*) can evaluate flow at points along a single ultrasound beam path. Color-flow imaging (*right*) assesses the velocity and direction of flow for multiple sample volumes along multiple beam paths and assigns a color indicative of velocity and direction at each sample volume site. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

occur as Doppler signals that depict flow at high velocity in ambiguous or opposite directions compared with actual flow (see Fig. 15–28A). An intermediate-mode, high-PRF Doppler is also available. This mode enables higher velocity recordings to be obtained at a compromise of depicting several sample sites simultaneously.

COLOR-FLOW DOPPLER

The major limitation of pulsed and CW Doppler (*spectral Doppler*) is that no spatial information regarding the size, shape, and 2D direction of flow is provided. An extension of PWD techniques, color-flow Doppler (CFD), provides real-time M-mode or 2D imaging of blood flow by presenting the velocity and direction of RBC movement as shades of color superimposed on gray-level 2D tissue structure. Standard pulsed Doppler yields flow signals from a single site along a single scan line. In CFD, rapid pulsed-wave interrogations are performed at multiple sites for multiple scan lines to create a spatially correct and dynamic display of moving blood within the heart and vasculature (Fig. 15–29). Doppler signals are presented as colors assigned to individual sites (Fig. 15–30). Blood flow moving toward the transducer is displayed in red, flow away from the transducer is displayed in blue, and increasing velocity is depicted in brighter shades of each color. The variance within each signal is calculated as a statistical marker of turbulence and is presented by adding green to the image (Fig. 15–31). Therefore, turbulent flow jets appear as a mosaic mix of colors. CFD also can be superimposed onto M-mode tracings (Fig. 15–32), often termed *color M-mode imaging*, and is helpful in clarifying the timing of flow phenomena.

NORMAL AND ABNORMAL FLOW DYNAMICS

Normal flow is laminar, with all RBCs exhibiting the same velocity and direction of flow. Most pathologic conditions, with the exception of atrial septal defects, involve disturbed or turbulent flow and share a common hydrodynamic basis for the resultant flow dynamics. Specifically, nearly all circulatory disturbances (stenosis, regurgitation, shunt) involve blood flow from a high-pressure chamber to a lower pressure chamber through a restricted orifice.[46] For example, aortic stenosis (AS) is a forward flow disturbance in which turbulent blood travels from a high-pressure LV to a lower pressure aorta through a restricted aortic orifice in systole. Aortic regurgitation (AR) is a retrograde flow disturbance in which turbulent blood regurgitates from a high-pressure aorta to a lower pressure left ventricle through a small regurgitant orifice in diastole. In each case, the pressure gradient results in a high-velocity jet coursing through a restricted orifice, reaching its maximal velocity at a site just distal to the orifice, designated the *vena contracta*, at which time shear forces produce vortices resulting in flow of varying direction and velocity (Fig. 15–33).

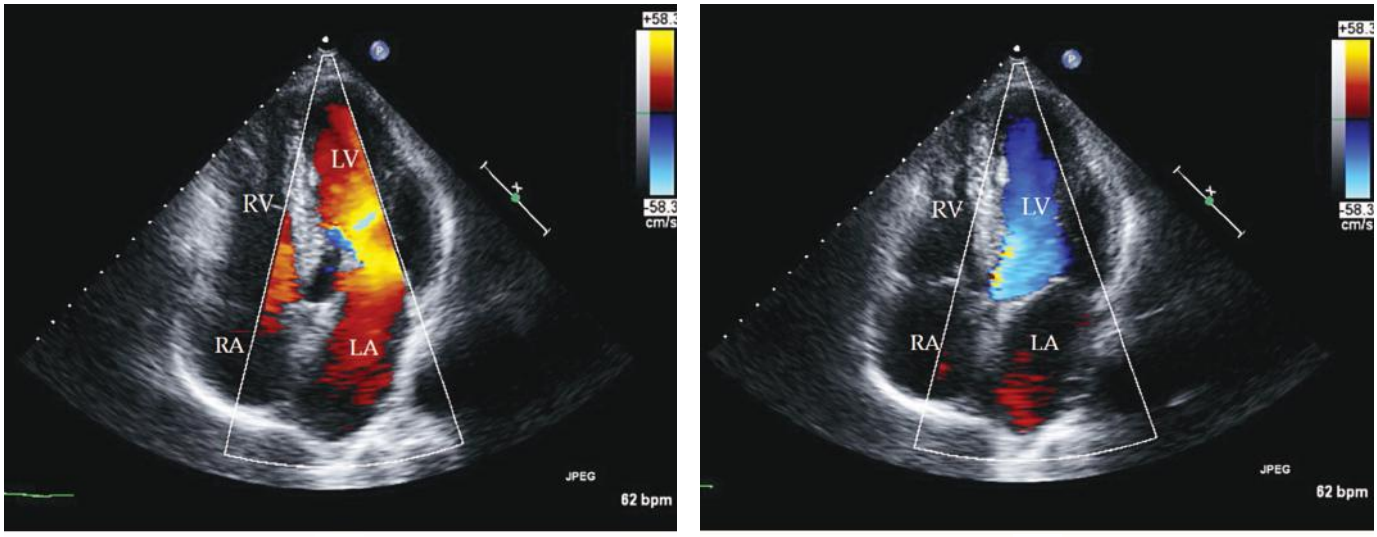


FIGURE 15–30. Apical four-chamber images with color-flow Doppler during diastole (**A**) and systole (**B**). Red flow indicates movement toward the transducer (diastolic filling); blue flow indicates movement away from the transducer (systolic ejection). LV, left ventricle; RA, right atrium; RV, right ventricle.

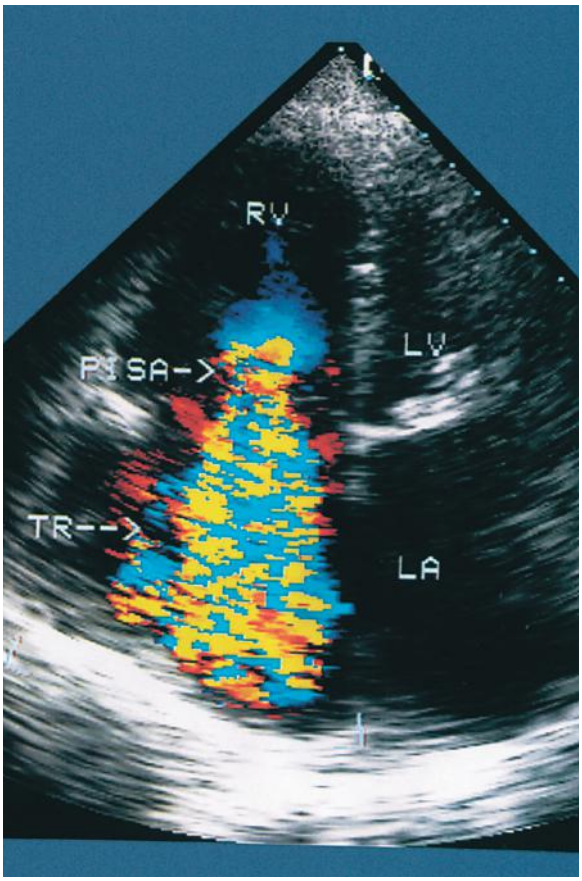


FIGURE 15–31. Apical four-chamber view of severe tricuspid regurgitation. The Doppler color jet of tricuspid regurgitation fills the right atrium. LA, left atrium; LV, left ventricle; PISA, proximal isovelocity surface area; RV, right ventricle; TR, tricuspid regurgitation.

In each case, the velocity of the jet is related to the pressure gradient across the orifice. On pulsed Doppler recordings, these hemodynamic abnormalities cause broadening of the spectral signal and aliasing. On CW recordings, high velocity represents the primary abnormality. By color-flow imaging, the disturbance is manifest by the increased variance and higher velocities in the signal.

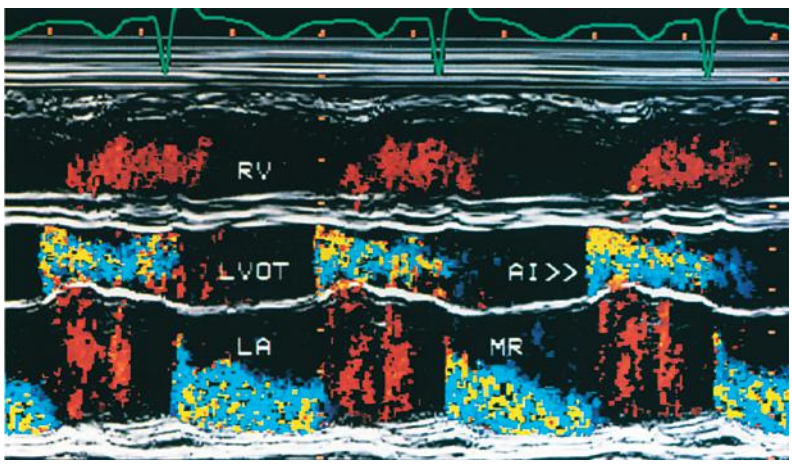


FIGURE 15–32. Color-flow Doppler superimposed on an M-mode image. The transducer is in parasternal position, and the cursor is directed through the left ventricular outflow tract (LVOT) and left atrium (LA). The patient under study has both aortic insufficiency (AI) and mitral regurgitation (MR). RV, right ventricle.

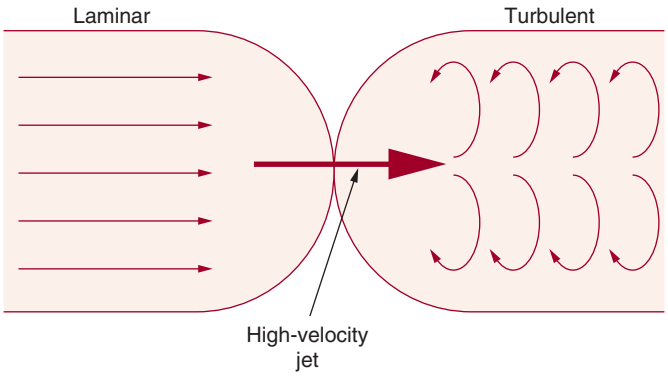


FIGURE 15–33. Flow characteristics through a stenotic orifice. Proximal to the stenosis, the flow is laminar. Near the point of maximal stenosis, the flow velocity is markedly increased. Turbulent flow is present distal to the stenosis.

THE STANDARD DOPPLER EXAMINATION

A clinical Doppler examination must be performed with full consideration of the different Doppler modalities available, the types of information each can provide, the multiple sites for flow interrogation, and the spectrum of pathologic lesions that produce flow disturbances. However, most echocardiographic examinations include screening for flow disturbances by CFD. Because Doppler signals are best recorded with the ultrasound beam parallel to flow, screening is typically performed in long-axis or apical views. Any flow disturbances visualized are subsequently examined by CW spectral recordings and, in most laboratories, by PWD. Although CW examination is typically reserved for flow disturbances, PWD may also be of value in quantifying flow dynamics in the setting of laminar flow. In this regard pulsed Doppler recordings obtained at the mitral, tricuspid, and aortic valvular orifices, PA, and pulmonary veins constitute part of a standard echocardiogram (see Fig. 15–26; Figs. 15–34 through 15–37). Finally, the usual Doppler examination will include tissue Doppler recordings from a region of interest placed in the septal and lateral mitral annulus in the apical four-chamber view.

Because the Doppler examination is usually performed with a long-axis or apical transducer orientation, diastolic filling is characteristically encoded in red and ejection in blue (see Fig. 15–30). Color aliasing is often observed at the levels of the mitral annulus and LV outflow tract as an abrupt change from bright red to bright blue or vice versa, usually in the center of the flow stream. Pulsed Doppler recordings of transmitral flow velocities are often recorded at the level of both the leaflet tips and annulus. Velocities are higher at the tips, whereas recordings at the annulus offer the ability to calculate flow through a cross-sectional area that is relatively uniform throughout the cardiac cycle. A sample volume positioned in the right upper pulmonary vein reveals systolic (S) and diastolic (D) flow velocities of nearly equal magnitude followed by a short, low-velocity reversal of flow into the pulmonary veins after atrial contraction (A) (see Fig. 15–36). Flow in the LV outflow tract is characterized by a progressive increase of velocity peaking in early systole, followed by a more gradual deceleration of flow (see Fig. 15–35). Examinations of the tricuspid and pulmonary valves give qualitatively similar results to those of the mitral and aortic valves (see Figs. 15–26 and 15–37). Normal values for forward flow velocity are given in Table 15–4. Velocity in normal individuals is highest in the aorta and is < 2 m/s.[45]

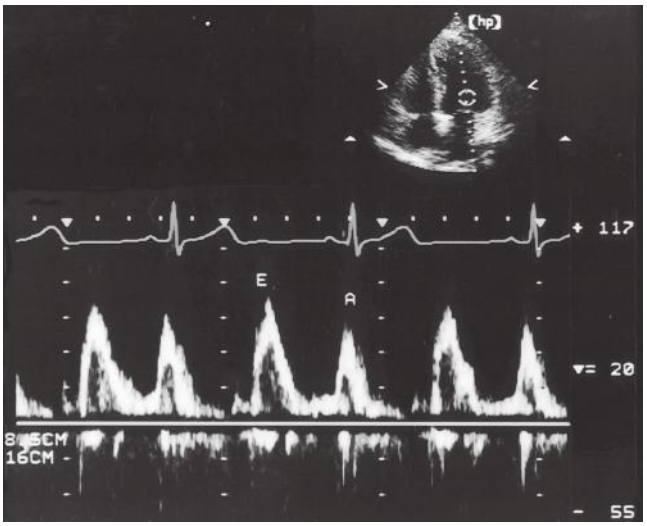


FIGURE 15–34. Normal pulsed-wave Doppler tracing from the left ventricular inflow tract, displaying the early rapid filling (E) and atrial contraction (A) phases of diastolic flow. The transducer is in the apical position and the sample volume is at the mitral leaflet tips.

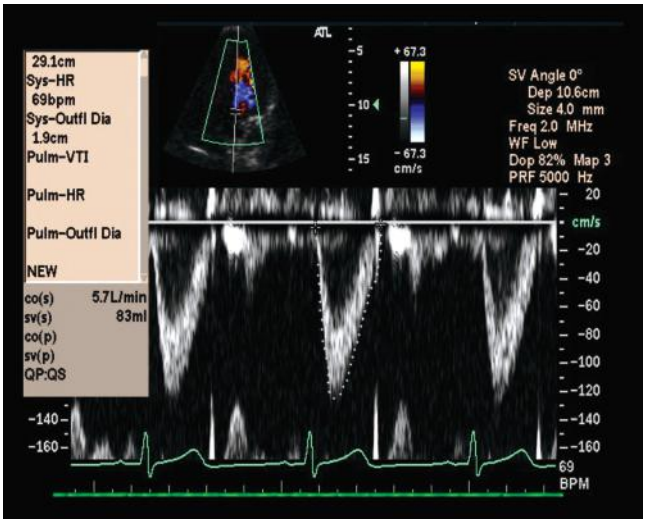


FIGURE 15–35. Normal pulsed-wave Doppler tracing with the sample volume in the left ventricular outflow tract (apical transducer position).

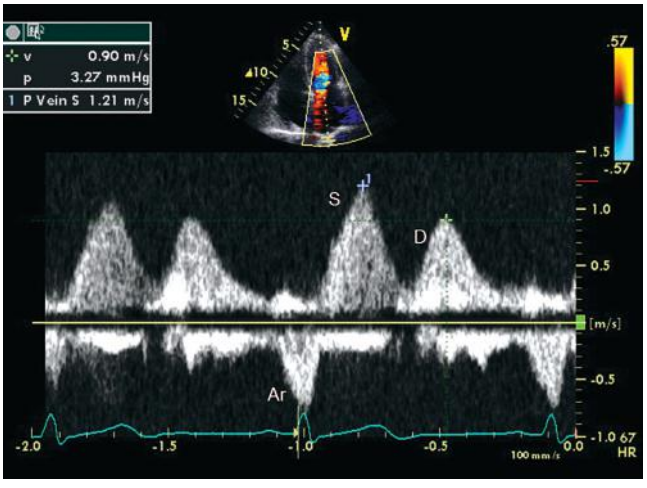


FIGURE 15–36. Pulsed-wave Doppler tracing from the right upper pulmonary vein (recorded from the apical transducer position). Flow toward the heart is biphasic, with peaks in systole (S) and diastole (D). A small amount of reversed flow is seen during atrial contraction (A_r).

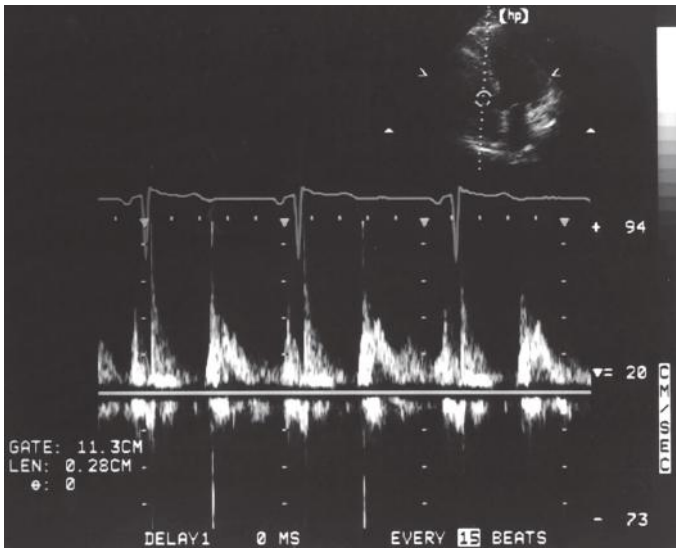


FIGURE 15–37. Pulsed-wave Doppler tracing from the right ventricle inflow tract (apical transducer position).

TABLE 15–4. Normal Intracardiac Doppler Velocities

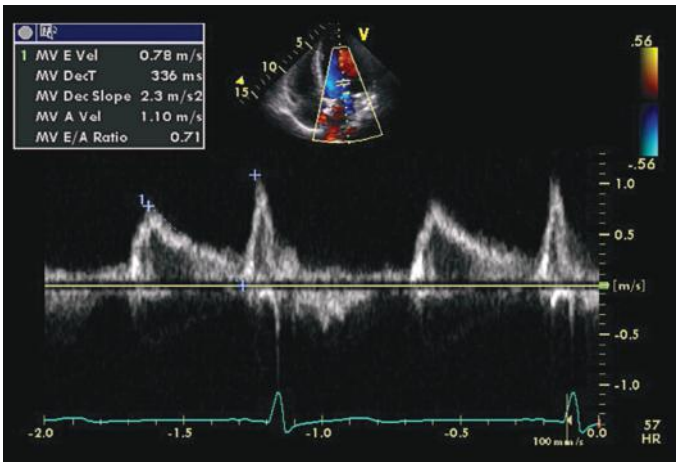
	Velocity (m/s)
Right ventricle	
Tricuspid flow	0.3–0.7
Pulmonary artery	0.6–0.9
Left ventricle	
Mitral flow	0.6–1.3
Aorta	1.0–1.7

Data from Hatle L, Angelsen B. *Doppler Ultrasound in Cardiology: Physical Principles and Clinical Applications*. 2nd ed. Philadelphia, PA: Lea & Febiger; 1984.

Other common measurements include the acceleration time, from the beginning of flow to peak velocity of flow in the ascending aorta or PA, and the deceleration time, from LV inflow peak E-wave velocity extrapolated to baseline zero velocity.

DOPPLER ASSESSMENT OF DIASTOLIC FUNCTION

There has been a great deal of interest in using mitral inflow velocity patterns to evaluate LV diastolic properties.[47-50] Transmitral filling velocities reflect the pressure gradient between the LA and LV during diastole (see Fig. 15–34).[47] In early diastole, pressure in the LV falls below that in the left atrium (LA), producing an increase in velocity due to rapid transmitral inflow (E wave). Flow decelerates as the pressures equilibrate in mid-diastole. In late diastole, LA contraction restores a small gradient, causing transmitral flow to accelerate to a second peak (A wave) that is normally lesser in magnitude than the E wave. In individuals in whom early relaxation is impaired, the transmitral pressure gradient is blunted, resulting in a decrease in both early filling and E-wave deceleration[48] (Fig. 15–38A). Conversely, in patients with marked increases of LA pressure and LV stiffness, early diastolic filling velocities are high, deceleration is rapid, and late filling after atrial contraction is markedly reduced. This is the so-called *restrictive pattern of LV filling* (Fig. 15–38B). Accordingly, an E-wave velocity that is substantially less than the A-wave velocity and is accompanied by a



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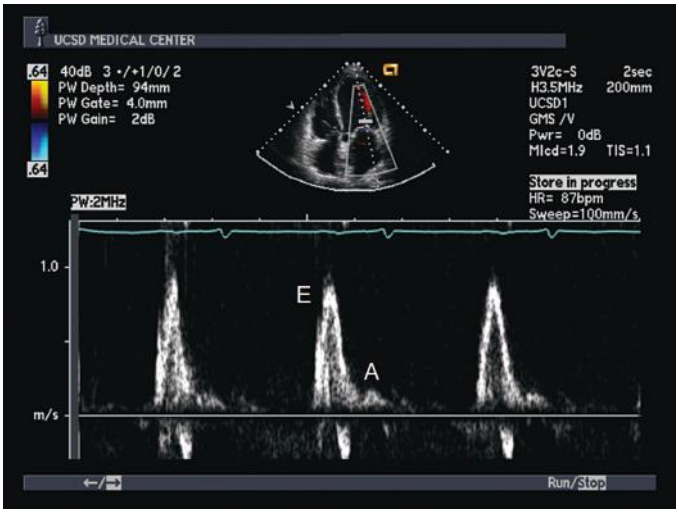

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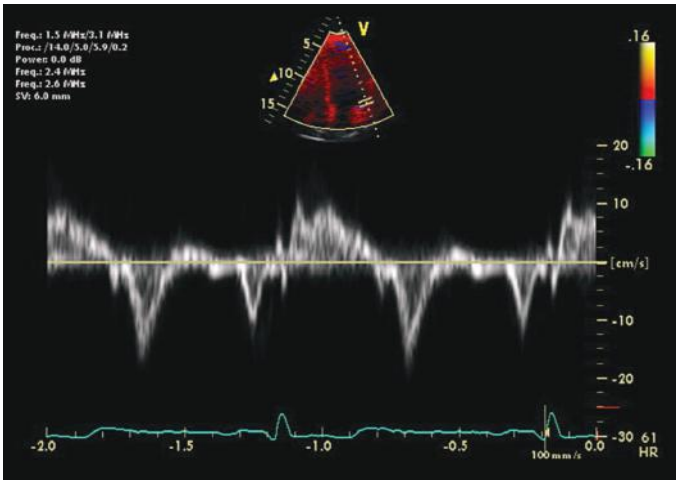

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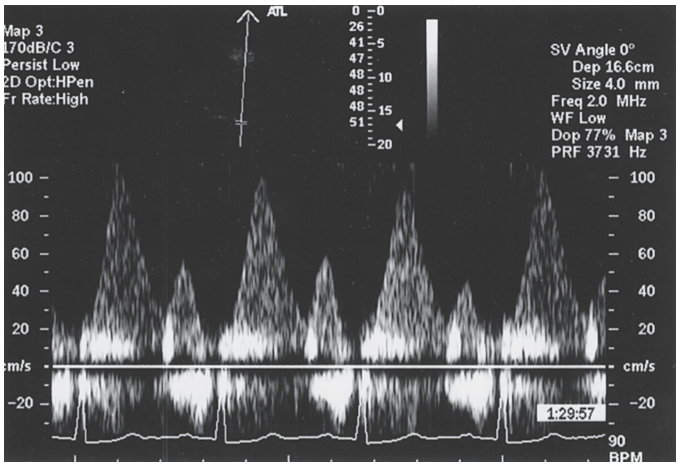

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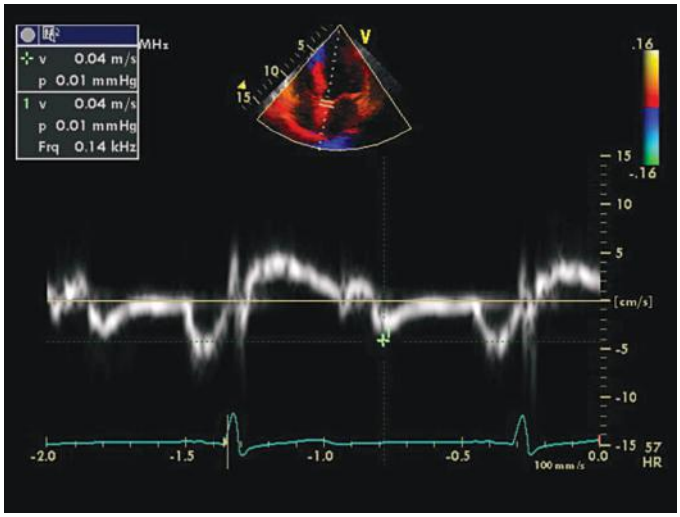

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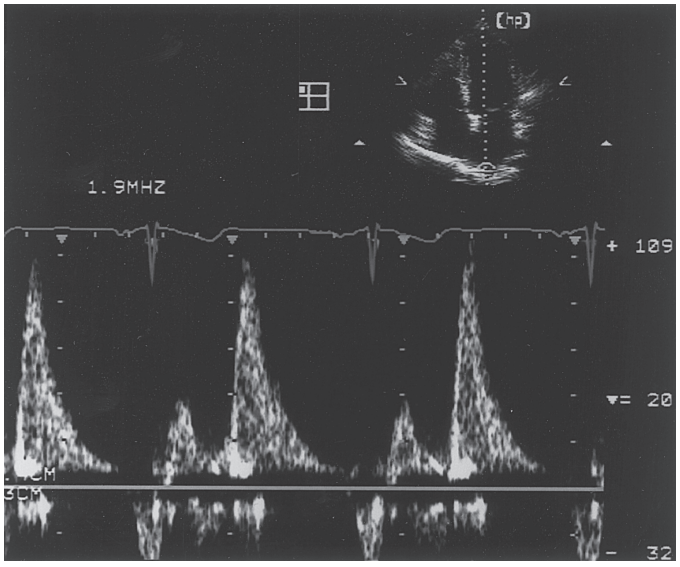
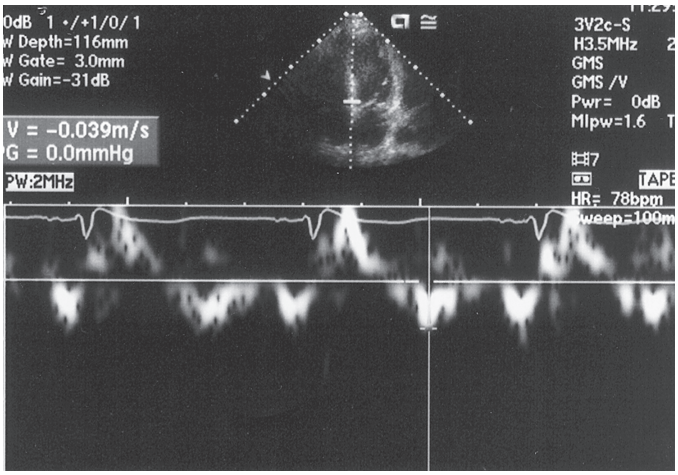


F

FIGURE 15–38. **A.** Pulsed-wave Doppler (PWD) tracing of diastolic relaxation abnormality (see text for details). **B.** PWD tracing of diastolic restrictive abnormality (see text for details). **C.** Tissue Doppler recording of normal lateral mitral annular motion (apical transducer position). Peak early diastolic annular velocity is 17 cm/s. **D.** PWD recording of pulmonary venous flow in mild diastolic dysfunction (abnormal relaxation). The S wave is prominent, whereas the D wave is small. **E.** Tissue Doppler image (septal mitral annulus) in mild diastolic dysfunction. Early diastolic velocity is blunted (4 cm/s). **F.** PWD recording of pulmonary venous flow in severe diastolic dysfunction. The S wave is small, whereas the D wave is prominent. (*continued*)



G

FIGURE 15–38. G. Tissue Doppler image in severe diastolic dysfunction. Both E_m and A_m velocities are abnormally low. A, atrial contraction; E, early rapid filling. (*continued*)

prolonged deceleration time represents evidence of impaired early diastolic relaxation by Doppler, whereas an increased E-wave velocity and decreased A-wave velocity (E/A ratio > 2.5:1 or 3:1) accompanied by a diminished deceleration time (< 160 milliseconds) is indicative of a noncompliant LV with markedly elevated LA pressures.[49] A restrictive pattern occurs with restrictive cardiomyopathy, advanced LV dysfunction of any cause, and/or in pericardial disease.[51]

These abnormal mitral inflow patterns are often useful in suggesting the presence of and characterizing diastolic dysfunction. Several variables other than diastolic function, however, are capable of influencing transmitral filling velocities. Transmitral Doppler filling dynamics are affected by the age of the patient, changes in heart rate,[52] respiration, and even the position of the Doppler sample volume within the MV orifice.[53] Transmitral inflow is sensitive to loading conditions, and reductions in LV preload can induce a striking decrease in early transmitral filling velocities independent of changes in diastolic properties. The influence of LV loading on transmitral filling is most striking when an increase in LA pressure caused by cardiac dysfunction obscures impaired relaxation by restoring early diastolic filling velocities, thus inducing pseudonormalization. Therefore, because Doppler transmitral filling dynamics have many limitations in assessing diastolic function, particular filling patterns should not be interpreted as pathognomonic findings of diastolic dysfunction but rather as components of a complete clinical and echocardiographic evaluation.

The addition of pulsed-wave tissue Doppler imaging (TDI) has significantly enhanced the noninvasive assessment of diastolic function. Although TDI can assess systolic performance, it is most often used to measure the motion of the mitral annulus away from the transducer during diastole. The diastolic pattern is similar to the pulsed-wave transmitral flow pattern, but the velocities are considerably less and in the opposite direction. The normal velocity of the early TDI motion (E_m; also abbreviated as e′) is 12 cm/s or greater at the lateral mitral annulus and 8 cm/s or more at the septal mitral annulus. In addition, the ratio of transmitral *E* velocity to E_m is normally in the range of 8 to 12.

In a young, healthy individual, the *E/A* ratio is generally between 1.5:1 and 2:1 (see Fig. 15–34). Because of high LV compliance, the *D* velocity is greater than the *S* velocity in the pulmonary venous Doppler tracing (see Fig. 15–36). With age, the LV compliance drops somewhat, so that by age 40 to 50 years, the *S* and *D* pulmonary venous velocities are similar. As mentioned, TDI E_m velocity is 12 cm/s or greater (Fig. 15–38C). In the setting of mild diastolic dysfunction, the *E/A* ratio is < 1, the *E* deceleration time is prolonged (*relaxation abnormality*; see Fig. 15–38A), and the pulmonary venous *S* wave is considerably larger than the *D* wave (*S/D* ratio > 1) (Fig. 15–38D). TDI shows blunting of the E_m wave with relative preservation of the later atrial component (A_m) (Fig. 15–38E).

As diastolic function worsens and LV filling pressures increase, a pseudonormal pattern occurs in the transmitral flow tracing (Fig. 15–39). Pulmonary venous and TDI are especially helpful in this case: If the *S/D* ratio is < 1 (except in the setting of a young individual), high LV filling pressure is likely present despite the seemingly normal E/A of > 1. Similarly, the presence of a low, blunted E_m velocity in the setting of a normal transmitral *E/A* ratio strongly suggests diastolic dysfunction and elevated LV filling pressure. In fact, the ratio of the E/E_m velocities correlates reasonably well with pulmonary capillary wedge pressure, and a ratio of > 15:1 reliably identifies an abnormal elevation of wedge pressure.[54] Of note, the Valsalva maneuver can be helpful in distinguishing pseudonormal and normal transmitral flow patterns. In normal individuals, both E and A velocities drop to a similar degree with Valsalva (ie, E/A remains > 1 following Valsalva). In pseudonormal states, however, the drop in preload caused by the Valsalva maneuver changes the transmitral pattern to that of mild diastolic

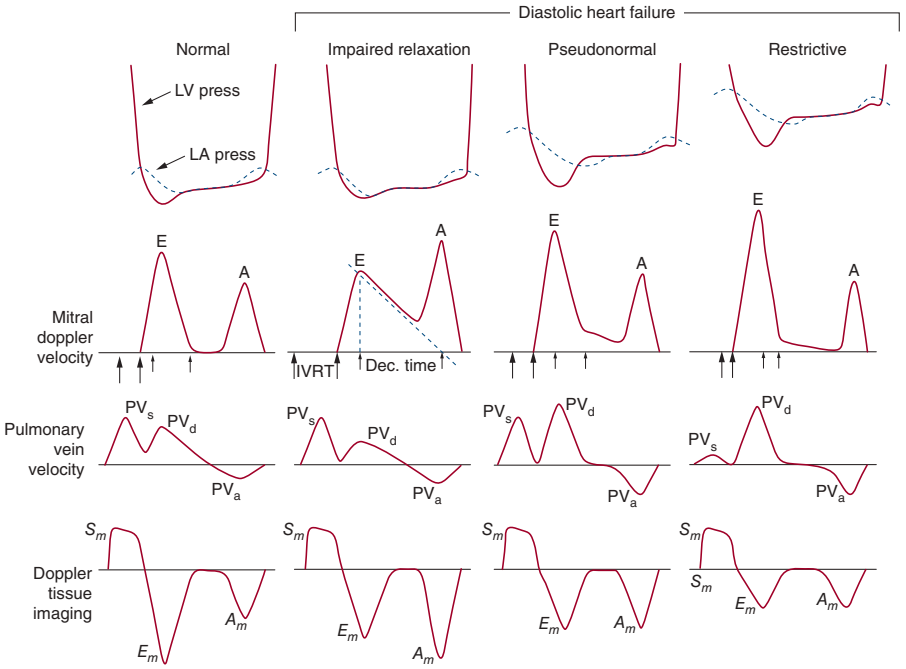


FIGURE 15–39. Doppler assessment of progressive diastolic dysfunction utilizing transmitral pulsed-wave Doppler, pulmonary venous Doppler, and mitral annular tissue Doppler imaging. A, atrial component of LV filling; A_m, myocardial velocity during LV filling produced by atrial contraction; Dec. Time, E wave deceleration time; E, early LV filling velocity; E_m, early diastolic myocardial velocity; IVRT, isovolumic relaxation time; PV_a, pulmonary vein velocity resulting from atrial contraction; PV_d, diastolic pulmonary vein velocity; PV_s, systolic pulmonary vein velocity; S_m, systolic myocardial velocity. Reproduced from Zile MR, Brutsaert DL: New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function, *Circulation*. 2002 Mar 19;105(11):1387-1393.

dysfunction (ie, reversal of E/A to < 1 following Valsalva, usually with a 50% reduction of E-wave magnitude). In atrial fibrillation, when an A wave is not present, assessment of diastolic function class is difficult, although E/e′ is still valid if averaged over sufficient cardiac cycles.

In severe diastolic dysfunction, transmitral flow demonstrates a restrictive pattern, with an abnormally high *E/A* ratio and a markedly shortened E wave deceleration time (see Fig. 15–38B). Concomitant pulmonary venous tracings show a very low *S* velocity and elevated *D* velocity (*S* << *D*) (see Fig. 15–38F). In some cases, the pulmonary venous atrial reversal wave can be prominent and prolonged. In this regard an abnormally prolonged duration of reversed pulmonary venous flow during atrial contraction accurately predicts elevated LV filling pressures.[47] TDI in severe LV diastolic dysfunction shows marked blunting of both E_m and A_m velocities (see Fig. 15–38G). An exception to this occurs in constrictive pericarditis, where early diastolic mitral annular motion is often preserved. Thus when transmitral and pulmonary venous Doppler suggest severe diastolic dysfunction, a normal TDI pattern suggests constrictive rather than restrictive physiology.

Many recent studies have demonstrated the importance of LA enlargement in the setting of diastolic dysfunction and elevated LV filling pressure. Indeed, left atrial enlargement appears to predict adverse cardiovascular outcomes in general, not just elevated LV diastolic pressure.[55] Clearly, the *E/A* ratio, pulmonary venous flow pattern, and mitral annular TDI are all load dependent and can often change quickly with medical intervention. However, LA volume increases over the long term in response to elevated pressure.[56] LA volume does not change significantly with short-term fluctuations in loading conditions. LA volume can be calculated relatively easily and should be normalized to body surface area. LA volume > 34 mL/m^2 is abnormal and signifies long-term diastolic dysfunction and elevated LV filling pressure.[7] An exception to this relationship occurs with atrial fibrillation: in this setting, LA volume is less predictive of cardiovascular events and elevated LV filling pressure.[55]

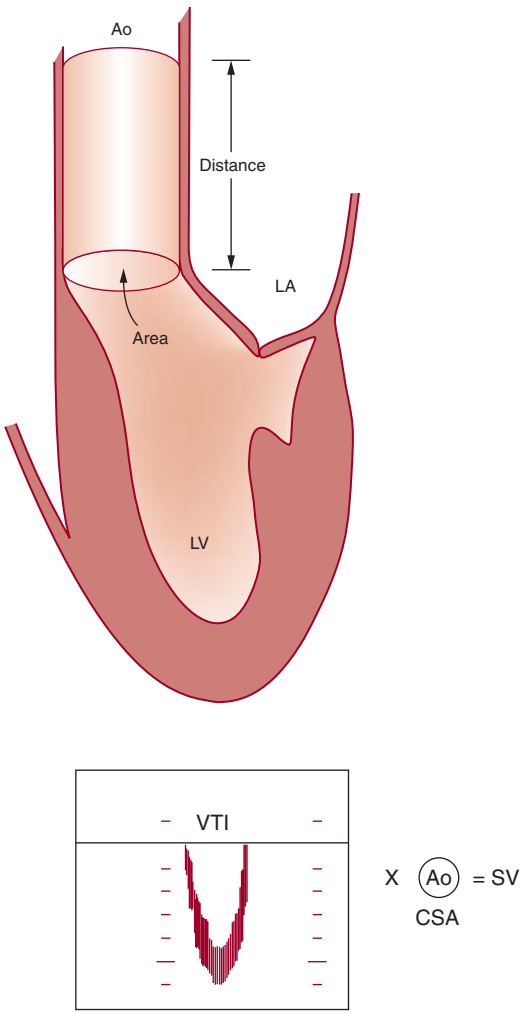


FIGURE 15–40. Calculation of stroke volume. Multiplying the cross-sectional area (CSA) of the blood column in the ascending aorta by the distance the column moves during a single cardiac contraction yields the stroke volume (SV). The velocity-time integral (VTI), expressed in units of length, represents the *stroke distance*. Modified with permission from Schlant RC, Alexander RW: *The Heart, Arteries, and Veins*, 8th ed. New York: McGraw-Hill; 1994.

DOPPLER ASSESSMENT OF SYSTOLIC FUNCTION AND CARDIAC OUTPUT

Doppler interrogation provides a unique and complementary noninvasive assessment of systolic function. Thus, LV systolic dysfunction often results in decreased aortic velocity and acceleration time. As discussed below, in the presence of mitral regurgitation (MR), the acceleration of the MR jet can provide information regarding contractile function.[57]

One of the most important applications of Doppler is in the calculation of the stroke volume.[58] The volume of flow through any orifice or tube can be calculated as the product of the cross-sectional area through which flow occurs and the velocity of that flow (Fig. 15–40). Measurements of anatomic cross-sectional area can be derived from echocardiographic images, whereas velocity can be determined by Doppler. Because the annulus of the aortic valve is nearly circular, its cross-sectional area can be estimated from a measurement of diameter as π (diameter/2)^2. In the PWD envelope recorded at the same level, the mean flow velocity through the orifice is calculated by integrating velocity over time (ie, by measuring the area under the Doppler curve). The product of this velocity-time integral, often called the *stroke distance*, with the cross-sectional area at the level of the Doppler interrogation provides the stroke volume.[58,59] The product of the stroke volume and heart rate then yields cardiac output. Doppler-derived measurements of cardiac output and stroke volume have been shown to correspond well with thermodilution, Fick, and angiographic calculations, but the correlation is not perfect.[58,59] Failure to provide an angle of < 20 degrees between flow and the interrogating beam can produce a large underestimation, as discussed previously. Recent advances may overcome some of the assumptions of the traditional calculation of stroke volume by this method. Multiple direct measurements of outflow tract area using 3D may avoid inaccuracies that arise from the assumption that the orifice is circular and constant in size. The assumption of uniform flow velocity throughout the cross-sectional area may be avoided by techniques using color flow Doppler.

Although stroke volume can theoretically be calculated at any valve annulus,[59] this is not always possible in clinical practice. Because the measurement of annular radius is squared in the computation of area, it is a potent source of error in Doppler stroke-volume analysis. Stroke-volume analysis through the mitral annulus is difficult; the shape of the annulus is elliptical rather than circular, and the cross-sectional area of the annulus probably changes slightly during diastole. Despite these limitations, measurements of stroke volume through the various cardiac valves are clinically useful and can be used to calculate pulmonary-to-systemic shunt ratios, regurgitant volumes,[60,61] and orifice areas of stenotic valves by the continuity equation, discussed in detail below.[62]

THE BERNOULLI EQUATION

An important application of Doppler echocardiography is the calculation of pressure gradients within the cardiovascular system using a modification of the Bernoulli equation.[63] This theorem states that the pressure drop across a discrete stenosis in the heart or vasculature occurs because of energy loss caused by three processes: (1) acceleration of blood through the orifice (*convective acceleration*), (2) inertial forces (*flow acceleration*), and (3) resistance to flow at the interfaces between blood and the orifice (*viscous friction*). Therefore, the pressure drop across any orifice can be calculated as the sum of these three variables (Fig. 15–41). The pressure gradient can be calculated from the velocities of blood proximal to and at the level of an orifice:

$$\text{Gradient} = 4[(\text{orifice velocity})^2 - (\text{proximal velocity})^2]$$

If the blood velocity proximal to the stenosis is low (< 1.5 m/s), this term can be ignored. The resulting modified equation states that the pressure gradient across a discrete orifice is equal to four times the square of the peak velocity (V) through the stenosis ($PG = 4V^2$).[63]

The modified Bernoulli equation can be used to calculate pressure gradients across any flow-limiting orifice and has been validated against invasive measurements.[64] If at least trivial valvular regurgitation is present, systolic gradients across the tricuspid valve and end-diastolic gradients across the pulmonic valve can be calculated.[65] If the RV diastolic pressure is known (or estimated as the right atrial or central venous pressure), peak RV and PA pressure (assuming pulmonic stenosis is absent) can be computed as follows[66]:

$$\text{Peak PA pressure} = 4(\text{TR velocity})^2 + \text{RA pressure}$$

End-diastolic PA pressure (PAD) also can be calculated:

$$\text{PAD} = 4(\text{end-diastolic pulmonary regurgitation velocity})^2 + \text{RA pressure}$$

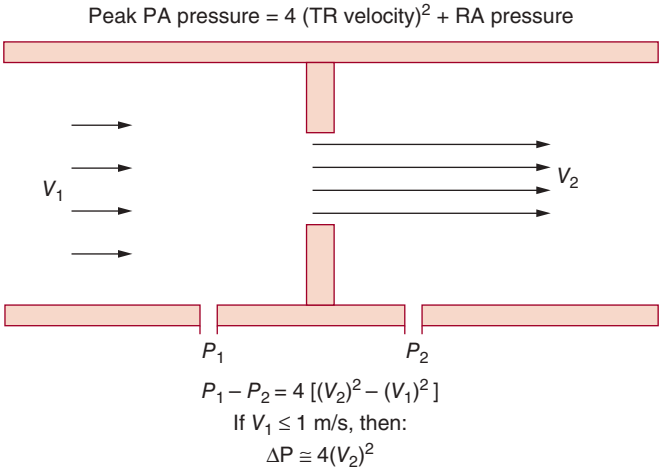


FIGURE 15–41. The modified Bernoulli equation. Pressure drop across a small orifice can be estimated as four times the square of the peak velocity (if the proximal velocity is < 1 m/s). V_1 and P_1, proximal velocity and pressure; V_2 and P_2, distal velocity and pressure. Modified with permission from Schlant RC, Alexander RW: *The Heart, Arteries, and Veins*, 8th ed. New York: McGraw-Hill; 1994.

In the presence of MR, a variety of calculations can be made. With measurement of peak systolic arterial pressure, systolic left atrial pressure can be estimated:

$$\text{LA systolic pressure} = \text{systolic blood pressure} - 4(\text{MR velocity})^2$$

Furthermore, the acceleration of the MR jet can be used to estimate LV systolic dP/dt. From the Bernoulli equation, the LA-to-LV pressure gradients at regurgitant velocities of 1 and 3 m/s are 4 and 36 mm Hg, respectively. Therefore, dP/dt can be calculated as 32 mm Hg divided by the time (in seconds) required for the mitral regurgitant jet to accelerate from 1 to 3 m/s. In the case of ventricular septal defects (VSDs) or aortopulmonary shunts, measurements of the peak systolic arterial pressure and the peak Doppler velocity across the defect allows calculation of the RV (or pulmonary arterial) systolic pressure.

THE CONTINUITY EQUATION

Although transvalvular pressure gradients can be calculated from CW Doppler recordings using the modified Bernoulli equation, gradients sometimes can be misleading in the evaluation of valvular stenosis. The transvalvular gradient is determined by both the size of the stenotic orifice and the stroke volume traversing it. Severe AS and accompanying LV systolic dysfunction may produce a low transvalvular gradient despite a small valve area, whereas coexistent AR may result in a large gradient with only mild AS. The calculation of orifice area by Doppler echocardiography uses the *continuity equation*, which is derived from the law of the conservation of mass and states that the product of cross-sectional area and velocity is constant in a closed system of flow (Fig. 15–42). Thus in the case of AS, the product of the area and velocity

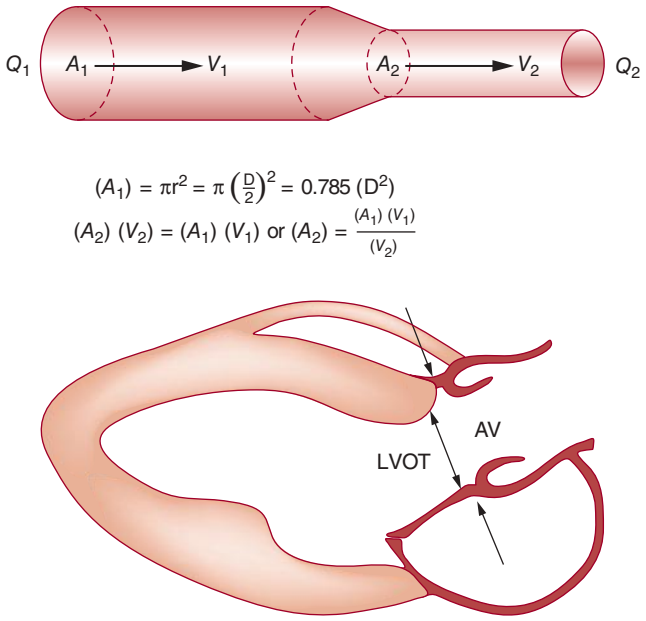


FIGURE 15–42. The continuity equation. In a closed system (*top*) with constant flow, $Q_1 = Q_2$. Therefore, $A_1 \times V_1$ must equal $A_2 \times V_2$. Determination of any three of the variables allows calculation of the fourth. Clinically (*bottom*), the area of the left ventricular outflow tract (LVOT) can be estimated and used to determine AV area. AV, aortic valve. V is usually incorporated as time-velocity integral (VTI), but mean or peak velocity have also been used. Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

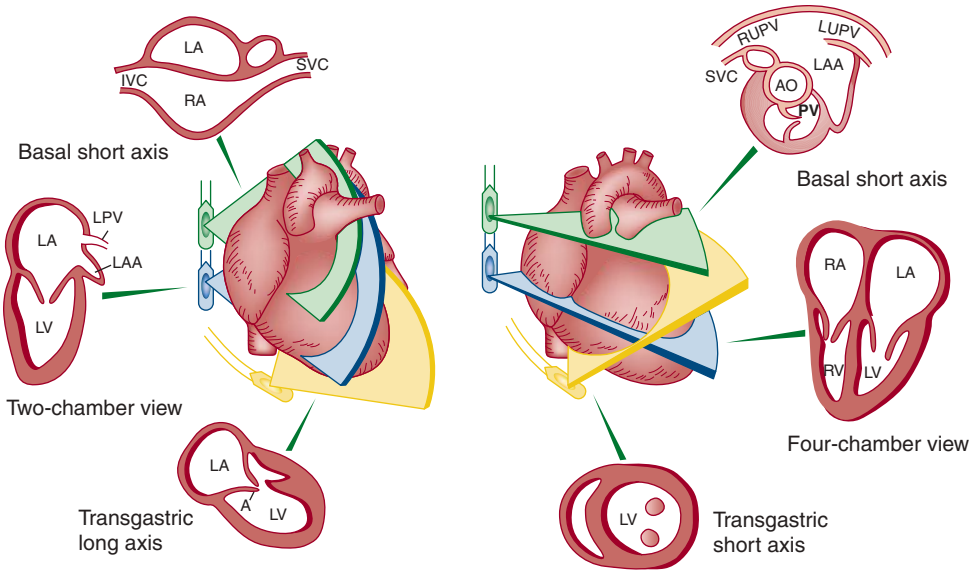


FIGURE 15–43. Standard transesophageal echocardiography imaging planes in transverse and longitudinal axes. Reproduced with permission from Fisher EA, Stahl JA, Budd JH, et al: Transesophageal echocardiography: procedures and clinical application, *J Am Coll Cardiol*. 1991 Nov 1;18(5):1333-1348.

of the left LV outflow tract equals the product of the area and velocity of the aortic valve orifice. Measurements of annular diameter and integrated velocity are derived by the standard volumetric approach, whereas the velocity across the stenotic orifice is derived by CW Doppler. The equation is then solved for the valve area.[62]

The most common pitfall is an inaccurate estimation of the cross-sectional area proximal to the stenosis. In addition, it is essential that blood velocity proximal to a stenosis be measured outside the area of flow acceleration. Finally, the continuity equation actually solves for the area of the vena contracta, which is usually just distal to the stenotic orifice. In general, however, this correlates well with the aortic valve area.

DETERMINANTS OF THE SIZE OF FLOW DISTURBANCES

Quantitative measurement of valvular regurgitation is possible using the proximal isovelocity surface area (PISA).[67] If the area of flow acceleration and body of the jet are visualized, measurement of the vena contracta using 2D or 3D CFD provides a marker of effective orifice area. Other CFD parameters are primarily qualitative, especially the area of turbulence recorded by CFD, which has multiple determinants.[68] Although the size of a flow disturbance is influenced by the orifice through which flow occurs, it is also determined by the size and compliance of the receiving chamber.[69] The pressure gradient operative in any flow disturbance is an important determinant of the spatial distribution or *spray area* of turbulence.[69] Finally, a number of technical factors can influence jet size, including instrument gain, the angle of incidence of the interrogating beam, the frequency and pulse repetition rate of the transducer, and the temporal sampling rate.[69] Therefore, measurements derived from the size of the turbulent jet recorded by color Doppler are at best semiquantitative and should not be expected to correlate with the volume of blood contained in the flow disturbance.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TTE usually defines cardiac anatomy and function satisfactorily, often obviating the need for further cardiac imaging. Occasionally, however, TTE does not provide complete or adequately detailed information. This is especially true in the evaluation of posterior cardiac structures (eg, LA, LA appendage, interatrial septum, aorta distal to the root), in the assessment of prosthetic cardiac valves, and in the delineation of cardiac structures < 3 mm in size (eg, small vegetations or thrombi). Echocardiographic imaging from the esophagus (TEE) is uniquely suited to these situations, because the esophagus is adjacent to the LA and the thoracic aorta for much of its course[70] and affords excellent access of the interrogating beam to these structures.

TECHNIQUE AND VIEWS

Current TEE probes are capable of multiplane imaging of the heart with full capabilities of pulsed-wave, CW, and color-flow Doppler. The latest generations of TEE transducers can also provide real-time 3D imaging, allowing visualization of cardiac structures and flow in the 3D space.[7] Images can be recorded from a variety of probe positions, but most commonly from the esophageal level, posterior to the cardiac base, and from the stomach (transgastric level), caudal to the heart (Fig. 15–43). TEE images are obtained in various planes through the heart (Figs. 15–44 through 15–47). It must be emphasized that, with the transducer in the esophagus, posterior structures appear at the top of the image. An apical-equivalent four-chamber and long-axis views of the heart with multiple intermediate planes are usually obtained; excellent visualization of the atria,

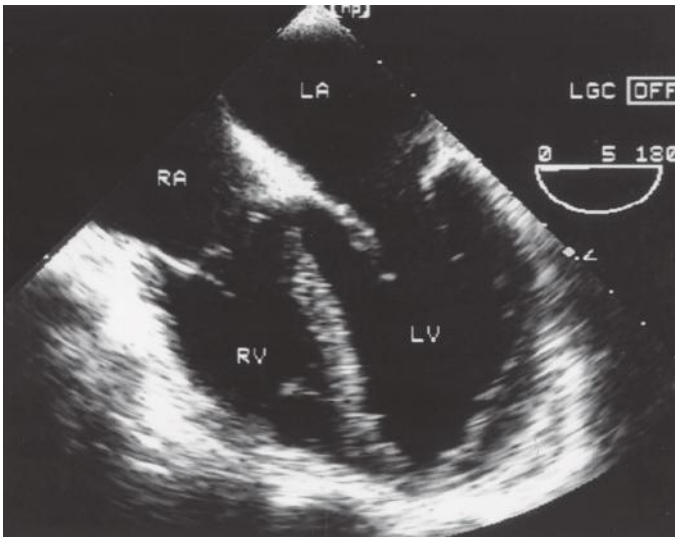


FIGURE 15–44. Transverse four-chamber transesophageal echocardiography plane. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

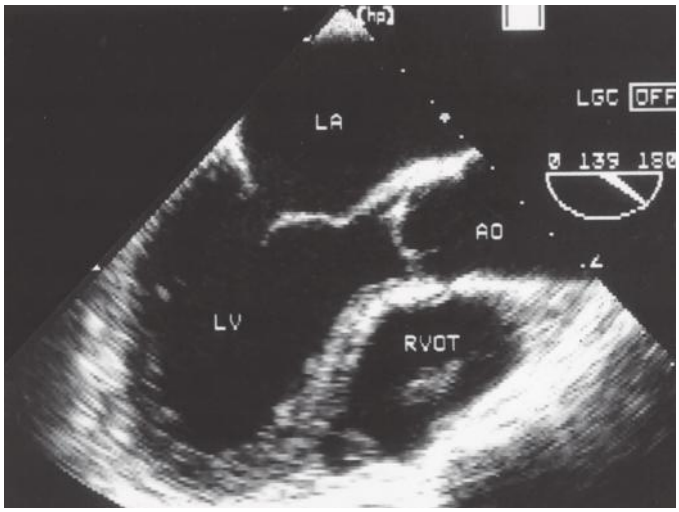
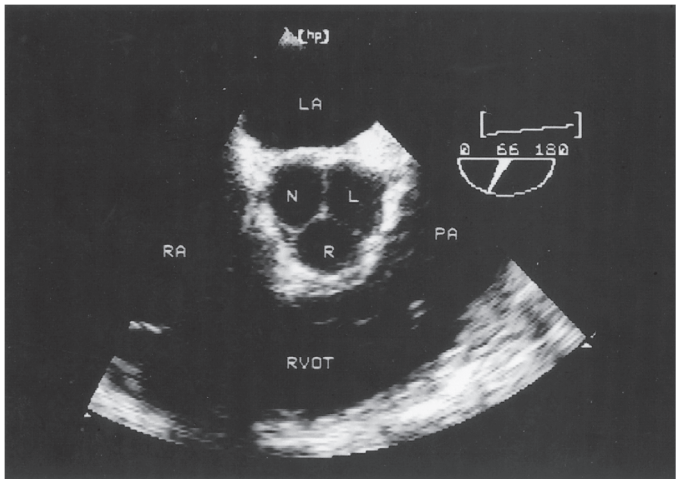


FIGURE 15–45. Modified longitudinal transesophageal echocardiography (TEE) plane (with transducer rotated to approximately 150 degrees), demonstrating a TEE apical three-chamber view. Ao, ascending aorta; LA, left atrium; LV, left ventricle.



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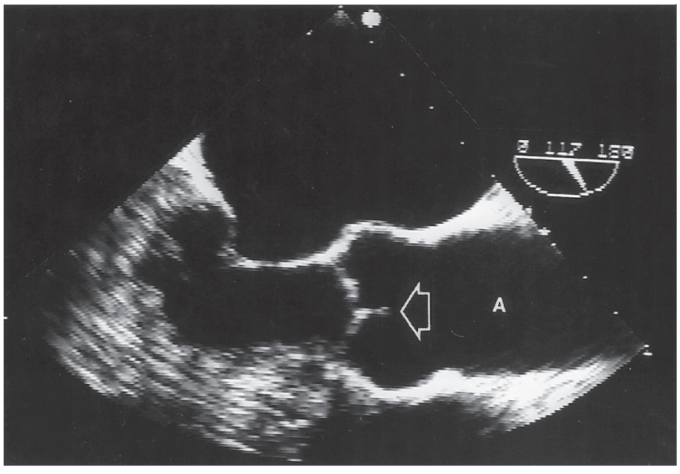
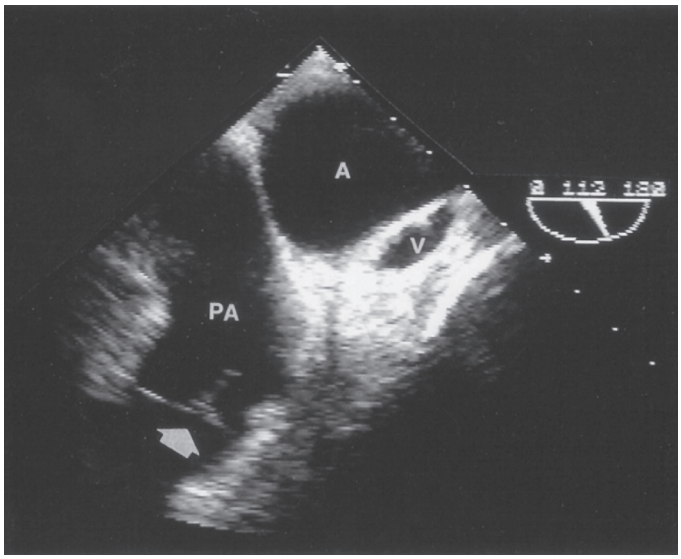


B

FIGURE 15–46. A. Modified short-axis view through the level of the aortic valve, demonstrating the left (*L*), right (*R*), and noncoronary (*N*) valvular cusps. **B.** Magnified longitudinal view of the aortic valve (*arrow*) showing the coaptation of the cusps and the sinuses of Valsalva. (*continued*)



C

FIGURE 15–46. C. Longitudinal image at level of the aortic arch, demonstrating the transverse aorta (*A*), the brachiocephalic vein (*V*), and the main pulmonary artery (*PA*). The pulmonic valve is visible as well (*arrow*). Ao, aorta; LA, left atrium; PA, pulmonary artery; RA, right atrium; RVOT, right ventricular outflow tract. **B**, reproduced with permission from Blanchard DG1, Kimura BJ, Dittrich HC, et al: Transesophageal echocardiography of the aorta, *JAMA*. 1994 Aug 17;272(7):546-551. (*continued*)

interatrial septum, cardiac valves, great vessels, and pulmonary veins can be acquired. Advancing the transducer into the stomach, a short-axis cardiac view is routinely obtained, with long-axis and apical views available to a variable degree. Lastly, on withdrawing the probe and aiming posteriorly, excellent imaging of the descending aorta and transverse arch can be achieved.

CLINICAL APPLICATIONS

With the improved imaging of cardiac structures at the base of the heart, less interference from the chest wall and lungs, and better

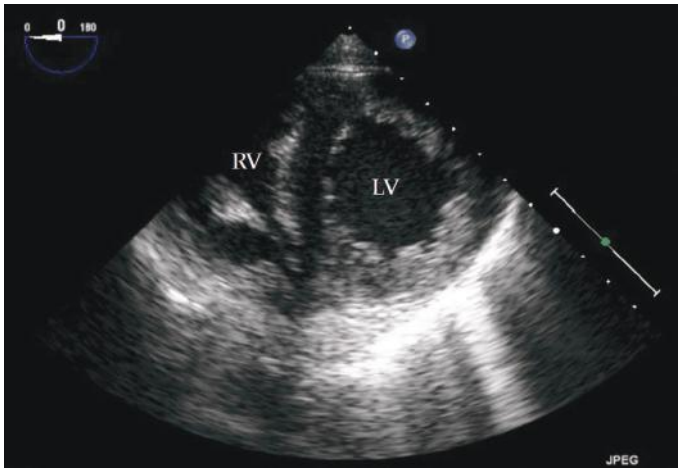


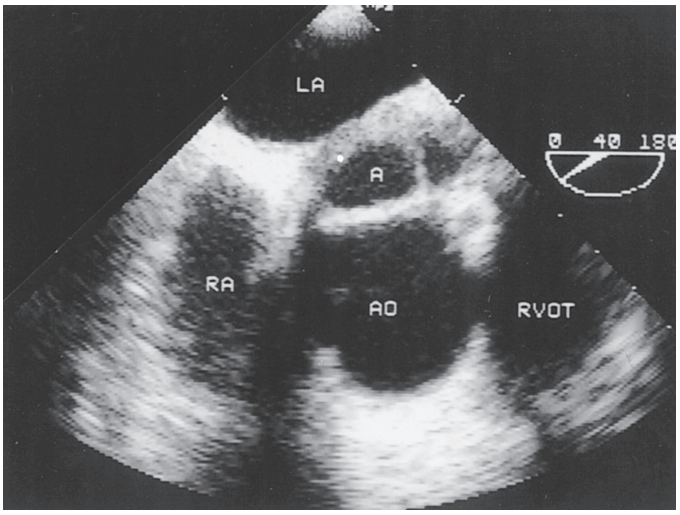
FIGURE 15–47. Short-axis transesophageal echocardiography plane through the left ventricle from transgastric position. The inferior wall is closest to the transducer, the anterior wall farthest. The interventricular septum is to the reader's left, the lateral wall to the right. LV, left ventricle; RV, right ventricle.

resolution with higher frequency transducers, TEE is an important adjunct to TTE for the diagnosis and management of a wide range of cardiac conditions. TEE is of value in patients with suspected or known endocarditis for the identification of valvular vegetations (particularly in prosthetic valves) and associated complications, such as chordal rupture, fistulas, perivalvular abscesses, and mycotic aneurysms,[71] because it is more sensitive and accurate than TTE[71] and provides further prognostic information (Fig. 15–48).

In addition, TEE imaging aids in the accurate assessment of native valvular heart disease when TTE is technically difficult or inconclusive. TEE is useful in identifying the mechanism of valvular regurgitation (Fig. 15–49), particularly in mitral and aortic regurgitation, and in further assessing the severity of regurgitant lesions with Doppler echocardiography. In MR, pulsed Doppler interrogation of the pulmonary veins (Fig. 15–50) is particularly helpful and more accessible with TEE, because systolic flow reversal is a specific marker of severe MR.[67] TEE can also be used to planimeter valve area in valve stenosis (AS with 2D; MS with 3D),[7,72] although in most clinical situations, this is usually better assessed hemodynamically with transthoracic Doppler echocardiography (see earlier). Another proven application of TEE is the evaluation of prosthetic valve dysfunction, particularly mechanical valves in the mitral position.[73] The areas behind prosthetic valves are usually hidden from view because of shadowing of ultrasound when transthoracic imaging is used. TEE is clearly superior to TTE imaging in the assessment of the mechanism and site of prosthetic regurgitation, its severity, associated infection, tissue ingrowth, or thrombosis (Fig. 15–51). The technique is also quite helpful in detection of diseases of the aorta, including dissection (Fig. 15–52), aneurysm, congenital malformations, and atherosclerosis (Fig. 15–53).[74] Because of its portability, accuracy, and short preparation and procedural times, TEE is recommended in suspected aortic dissection, particularly in unstable patients or in cases that are inconclusive on computed tomography (CT) angiography.[74]

Thromboemboli may originate from posterior cardiac structures such as the LA and LA appendage, atrial septal defect, patent foramen ovale (PFO), and aorta[75]; therefore, one of the applications of TEE is in the evaluation of possible cardiogenic embolization. The ability of TEE to visualize the LA appendage for possible thrombi is of particular value in this population as well as in patients with atrial fibrillation or flutter prior to cardioversion (Fig. 15–54). TEE can also detect spontaneous echo contrast signals in the LA or other chambers, which indicate low flow, appear to represent transient rouleaux formation, and predispose to thromboemboli (Fig. 15–55). In addition, TEE has provided unique real-time images of mobile, pedunculated, atherosclerotic debris in the thoracic aorta, many of which have been found to be thrombi[76] and appear to be significant risk factors for embolic events.[77,78] Although the optimal therapy for such plaques is not definitively established, warfarin may be helpful for selected patients.

Lastly, TEE has become an important tool to assist structural heart disease specialists and surgeons in various cardiac interventions. In the operating room, it is a method for the detection of cardiac ischemia and for the evaluation of valve function after repair or replacement. Cardiac surgeons often rely on intraoperative TEE for evaluation of cardiac anatomy and confirmation of success of surgical repair before closing the chest. In the catheterization laboratory, echocardiographic imaging has become essential in guiding interventional procedures such as transseptal catheterization, mitral valvuloplasty, closure of atrial and ventricular septal defects and the LA appendage, and percutaneous valve replacement or repair. The use of real-time 3D echo has proven of great value in facilitating these procedures and assessing their success.



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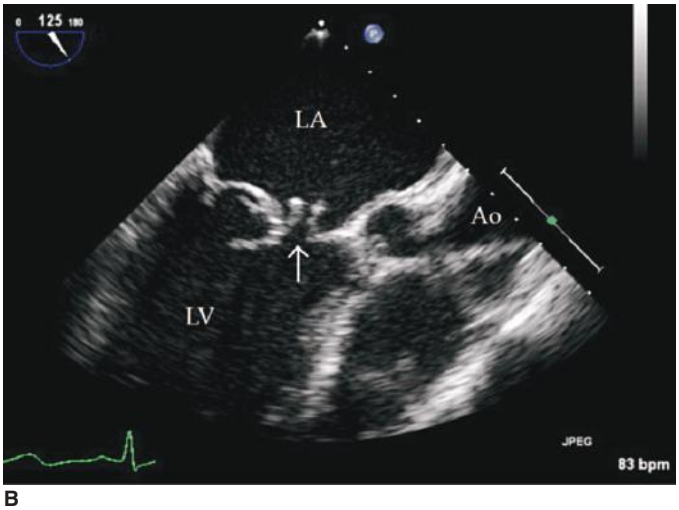

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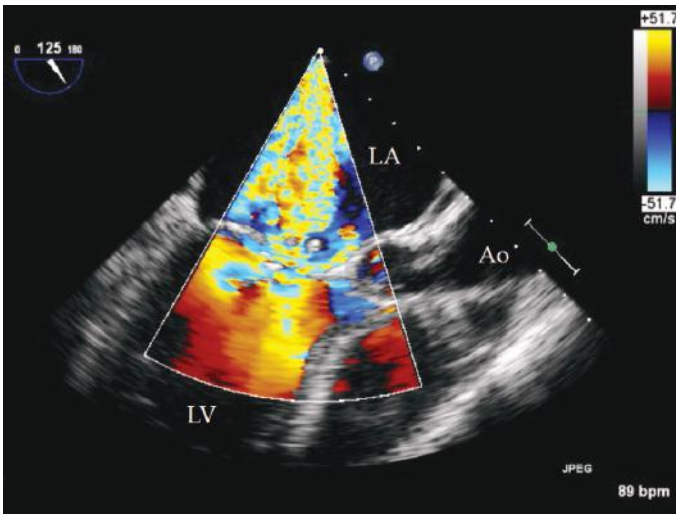
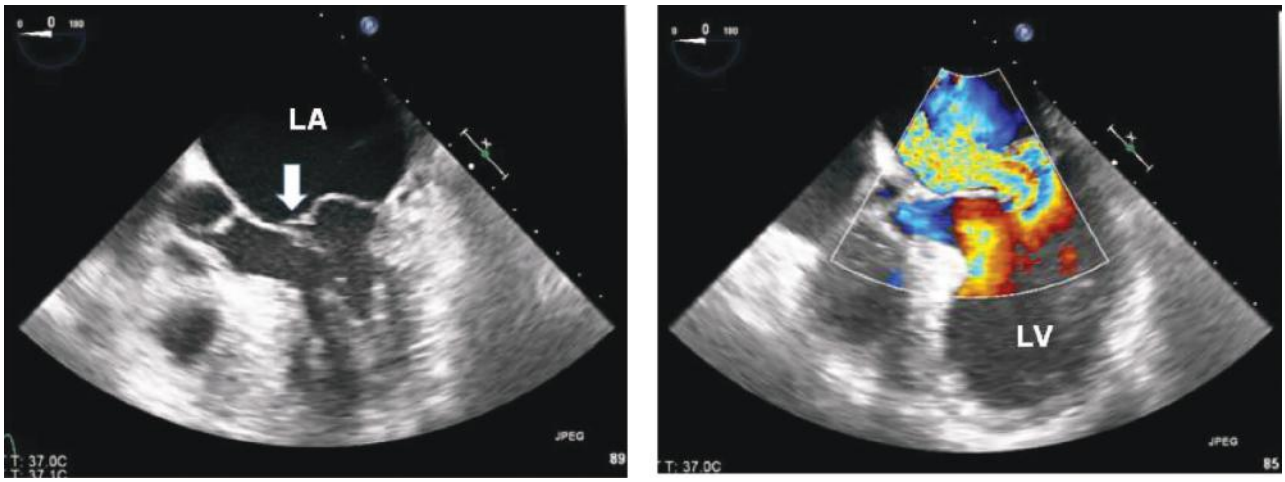


C

FIGURE 15–48. **A.** Short-axis transesophageal echocardiography (TEE) plane through the cardiac base. A large septated abscess cavity (A) is present between the aortic root (AO) and the left atrium (LA). **B.** Modified three-chamber TEE plane showing perforation of the anterior mitral valve leaflet (*arrow*) in a case of endocarditis. **C.** Color imaging reveals severe mitral regurgitation. LA, left atrium; LV, left ventricle; Ao, aorta.



A B

FIGURE 15–49. Transesophageal echocardiography image (five-chamber plane) demonstrating a flail posterior leaflet of the mitral valve (*arrow*), and the corresponding color Doppler showing severe mitral regurgitation into the left atrium (LA). LV, left ventricle.

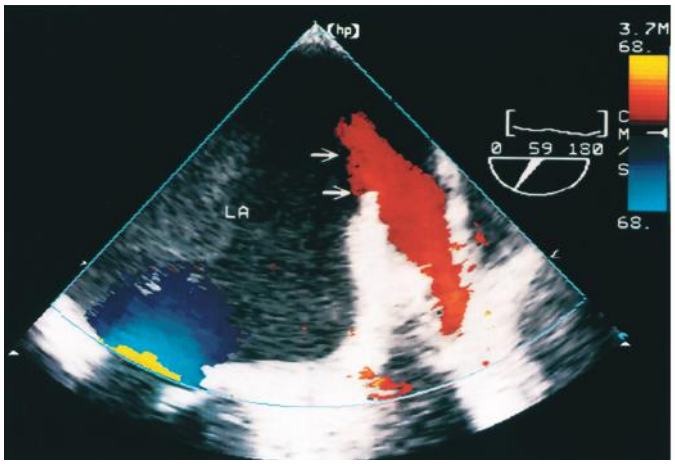


FIGURE 15–50. Transesophageal echocardiography image of pulmonary venous flow (*arrows*) entering the left atrium (LA) during diastole.

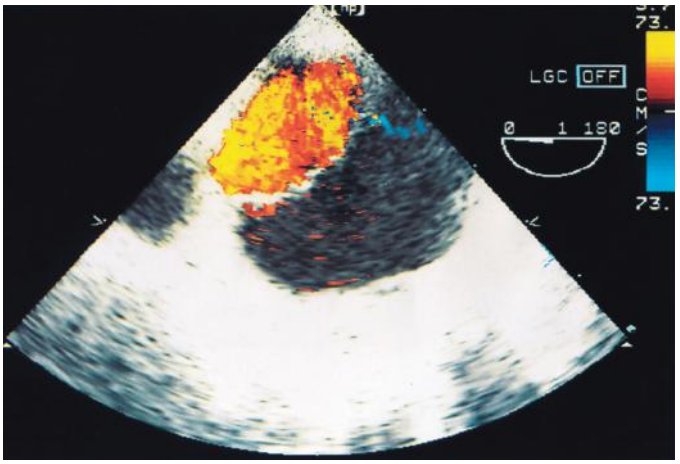


FIGURE 15–52. Transverse transesophageal echocardiography image of a descending aortic dissection. The true lumen is color-coded orange. The false lumen is mostly devoid of flow, but a small blue jet of communication between the two channels is present.

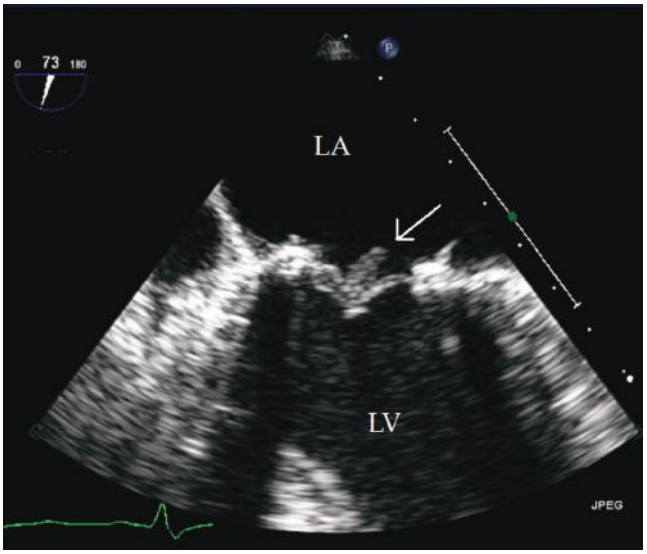


FIGURE 15–51. Transverse four-chamber transesophageal echocardiography image of an infective vegetation (*arrow*) on a porcine prosthesis in the mitral position. LA, left atrium; LV, left ventricle.

HANDHELD ECHOCARDIOGRAPHY

Recently, advances in electronic technology have led to the production of small, lightweight echocardiography units. These handheld devices can be carried to the clinic examination room or hospital bed, thereby facilitating bedside, point-of-care echo evaluation by the physician. The latest versions of these devices are small enough to fit in one's pocket.

Most studies have shown benefits from handheld scanning in the quick detection of significant cardiac pathology. It is clear that the sonographic and interpretive skills of the person performing the study are critical; however, it has been demonstrated that simple skills to evaluate overall cardiac function or pericardial effusion can be learned over a short period. It is probably true to say that this technology has been adopted more readily by noncardiologists than cardiologists. Issues exist about the quality of the studies, technical skills required, potential misdiagnosis or omission, added time commitment during clinic visits, and overall quality control.[79] To ensure adequate imaging

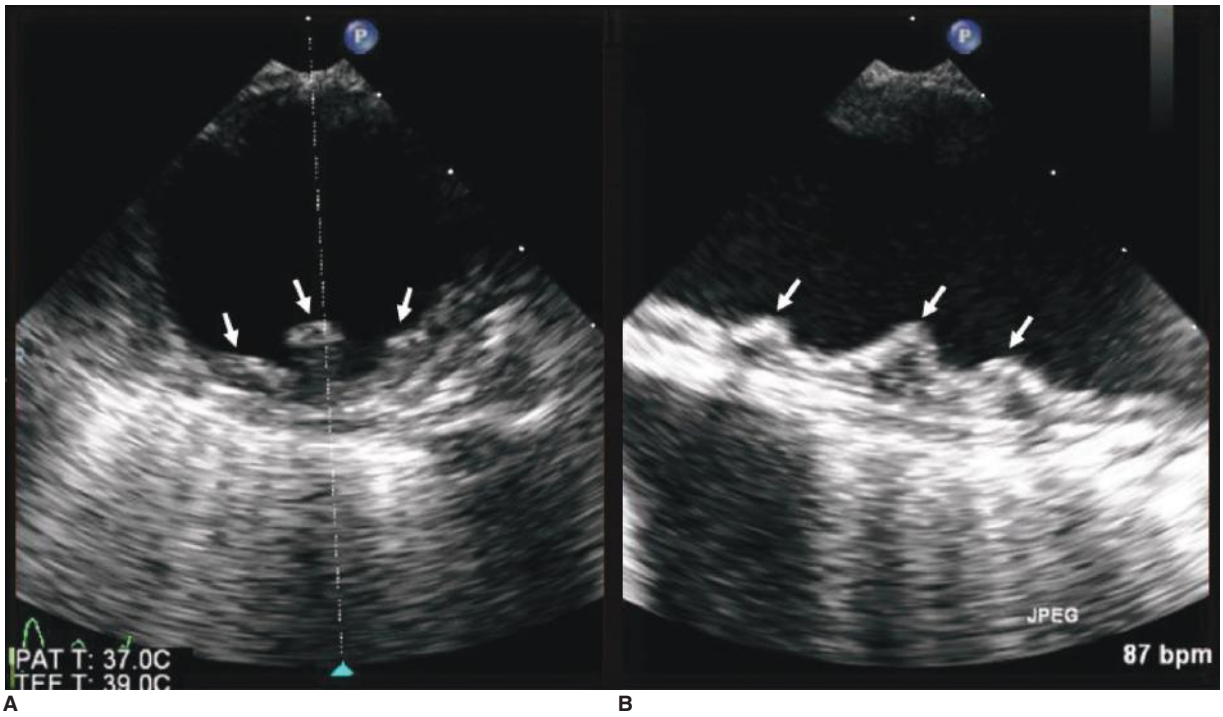


FIGURE 15–53. Transverse (**A**) and longitudinal (**B**) transesophageal echocardiography images of the descending aorta, demonstrating severe, extensive atherosclerosis (*arrows*).

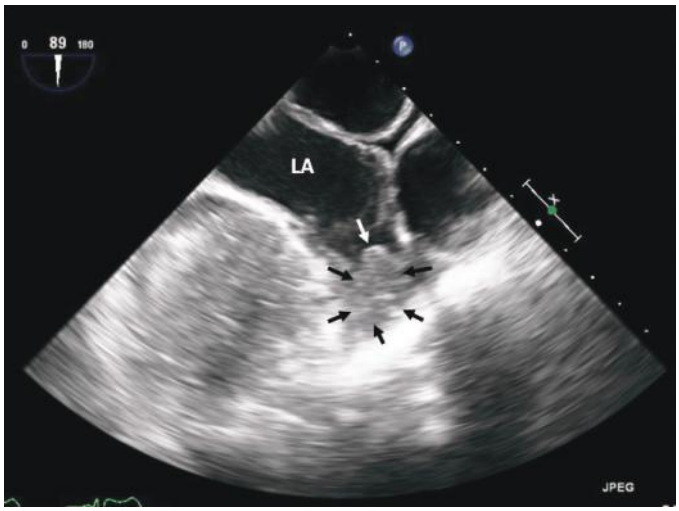


FIGURE 15–54. Transesophageal echocardiography image of a thrombus (*arrows*) within the left atrial appendage. This thrombus, as frequently the case, was not visible with transthoracic echocardiography. LA, left atrium.

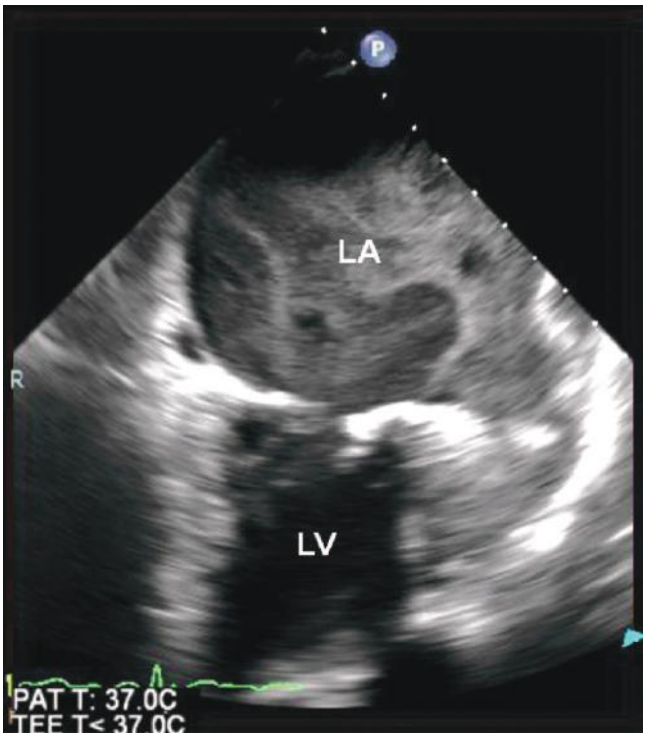


FIGURE 15–55. Transesophageal echocardiogram showing severe spontaneous contrast swirling in a severely enlarged left atrium, consistent with a very slow flow condition in the atrium. LA, left atrium; LV, left ventricle.

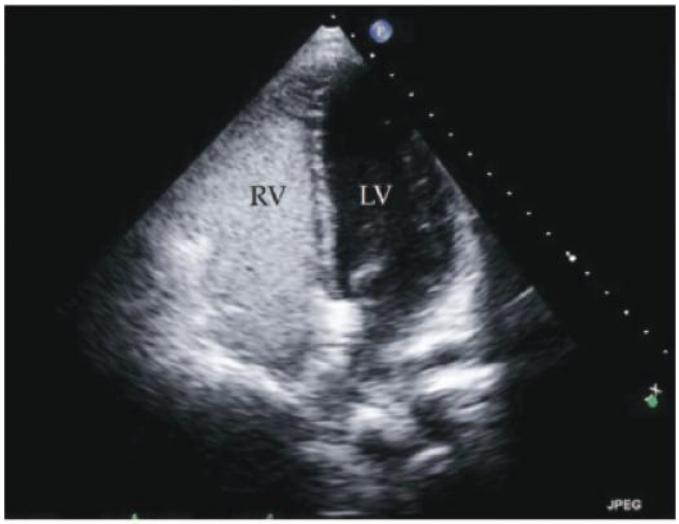
competency, the ASE had recommended that individuals performing handheld scanning have level 2 training in echocardiography.[80] More recently, a focused cardiac examination has been proposed for limited indications, mostly in hemodynamically unstable patients.[81]

A wide spectrum of opinion exists in this area. At present, most authorities view examinations with handheld echo devices as extensions of the stethoscope. Performed by a competent individual, the diagnostic capability of such an examination is superior to that of auscultation alone. Handheld ultrasound units can also provide clinically useful information by imaging the carotid arteries, the abdominal aorta, and the inferior vena cava. Importantly, when appropriately used and with good training, this approach can expedite diagnosis, decision making, and management of patients, and it can help triage patients for more complete echocardiographic examinations or other testing.[82]

CONTRAST ECHOCARDIOGRAPHY

Opacification of the right heart cavities with dense ultrasonic reflectance during intravenous contrast injection was first applied clinically in 1968. Subsequently, it became clear that the origin of the dense intracavitary echoes were microbubbles within the injectate that reflected the ultrasound and that any agitated liquid injected intravenously caused the effect. Because few room-air microbubbles with the diameter of pulmonary capillaries persist intact in blood for longer than 1 second before dissolving, agitated agents injected intravenously rarely cross the lungs and enter the left-sided cardiac chambers. Thus the presence of echocardiographic contrast entering left heart chambers after intravenous injection of an agitated liquid indicates the presence of a right-to-left shunt—either intracardiac or through a pulmonary arteriovenous fistula.

Identification of intracardiac shunts, particularly through a PFO in patients with unexplained cerebral ischemia (Fig. 15–56), remains a frequent indication for contrast echocardiography. Simple agitated normal saline solution remains the most commonly used contrast agent for such studies. It is important to mention that for contrast to cross the interatrial septum, the pressure in the RA has to be higher than in the LA, at least transiently. To facilitate this, a Valsalva maneuver or cough is performed in patients who do not readily show crossing of microbubbles across the septum. Although TEE provides excellent visualization of the interatrial septum and the mechanism of shunting, it is not the most sensitive technique to demonstrate a shunt, because the Valsalva maneuver is blunted because of the effect of sedation; a TTE with contrast is the preferred first echocardiographic screening for a PFO.[83] On the other hand, a pulmonary arteriovenous fistula manifests differently on a contrast study; contrast is seen in the left chambers after about five to six cardiac cycles from appearance of the contrast in the right heart, which represents the transit time in the pulmonary circulation. Furthermore, contrast appearance and intensity builds with time as opposed to a shunt through a PFO, where contrast in the left heart may occur earlier and intermittently, depending on the pressure difference between the atria.



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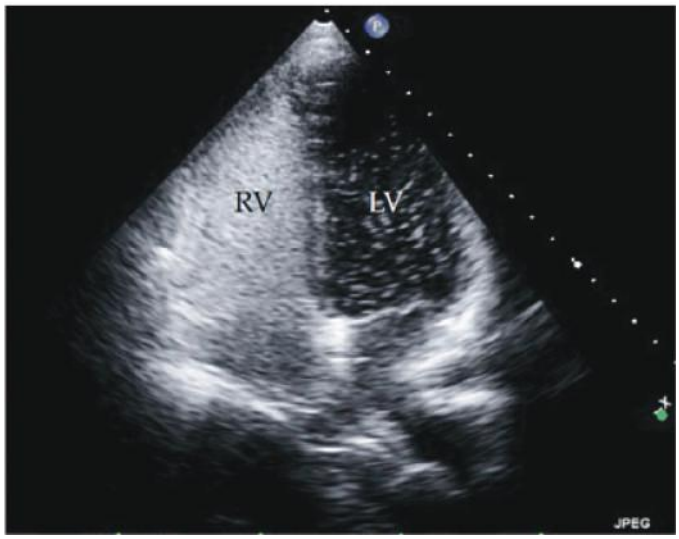


B

FIGURE 15–56. A transthoracic four-chamber view after an intravenous agitated saline injection opacifying the right heart completely and showing few microbubbles in the left atrium and ventricle. This shunting occurred early, with opacification of the right atrium within three beats, consistent with a shunt at the interatrial level. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Advances in microbubble technology over the past 25 years has allowed the production of smaller (~3 microns), more persistent bubbles, to achieve successful crossing of the pulmonary capillaries and echocardiographic opacification of the LV cavity and myocardium after intravenous administration.[84] This was accomplished by using a shell- or surface-modifying agent that inhibits the leakage of gas across the microbubble surface or by using a dense, high-molecular-weight gas with a reduced capacity to diffuse across the bubble shell. The clinically available ultrasonic contrast agents use fluorocarbon gases, which are dense and poorly soluble in blood, and shells made of albumin or liposomes. These microbubbles are capable of producing dense, high-intensity signals not only within the LV, but also within the myocardium after intravenous injection.[84] Numerous studies have documented the safety of the agents, particularly relative to the use of imaging agents in other modalities, such as angiography.[84]

Intravenous injection of stabilized solutions of microbubbles opacifies the LV in nearly all patients, thereby facilitating identification of the endocardial border. This capacity has found its greatest application in patients with technically difficult studies, particularly patients who are hospitalized and are instrumented in intensive care units.[85] Contrast enhancement of the LV allows interpretation of global and regional LV function. Various clinical applications of contrast echocardiography have been detailed by the ASE.[83-85,87,88] These include endocardial border definition at rest and during stress echocardiography,[86] where detection of the endocardium is of fundamental importance in recognizing abnormal contraction produced by ischemia, and evaluation of possible LV thrombi (Fig. 15–57).[84] Clinically, the impact of using contrast in either avoiding other diagnostic procedures, changing hemodynamically active drugs or anticoagulation was seen in 35% of hospitalized patients and was highest in surgical intensive care units (63%).[85] Contrast injections can also increase the accuracy of LV volume measurements and improve their reproducibility.[87] This may be needed in patients with valvular heart disease and in clinical trials. Contrast can also enhance Doppler signal, thus improving spectral recordings of tricuspid regurgitation and AS jets if suboptimal, facilitating the quantitation of valvular lesions and pulmonary hypertension (PH).[84]

In addition to contrast agents, novel imaging technology aimed at amplification of contrast signals are widely available. Harmonic imaging amplifies the ultrasonic backscatter from contrast microbubbles, which resonate in an ultrasonic field, relative to the returning signal from myocardium, which does not resonate (Fig. 15–58). Tissue harmonic imaging also decreases clutter and other artifacts, often improving endocardial definition (Fig. 15–59). Power Doppler

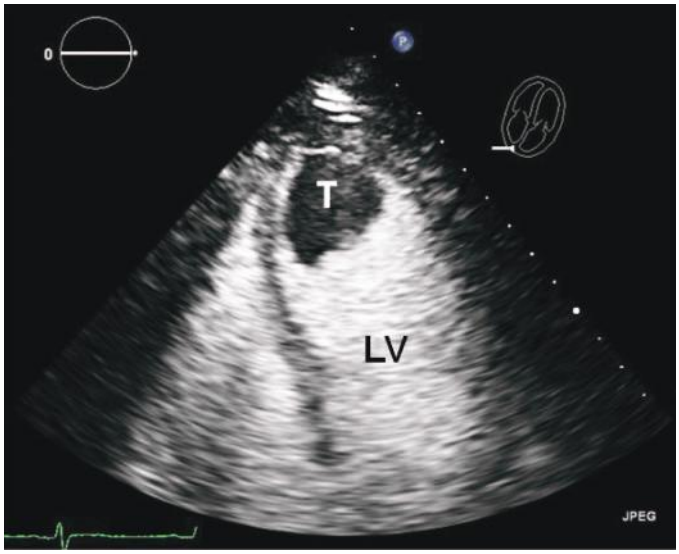


FIGURE 15–57. Large apical left ventricular thrombus seen after an intravenous injection of echocardiographic contrast. Thrombus does not enhance with echocardiographic contrast. LV, left ventricle; T, thrombus.

imaging is a method that correlates signals between successively transmitted pulses to derive images of moving blood or cardiac structures. Power Doppler techniques are especially well suited to detect the changing signals produced by movement and/or dissolution of contrast microbubbles.[36]

The microbubbles are sensitive to the transmitted energy (ie, mechanical index) by the ultrasound system and amenable to destruction. Thus for appropriate clinical visualization, a low mechanical index is usually used. However, the ability to disrupt bubbles can be the basis for the quantitation of blood flow by contrast. After destruction of all bubbles in an ultrasound field by a high-energy brief pulse, new blood with undestroyed bubbles progressively reenters the field until it is once again filled. It has been found that both flow velocity and volume are diminished in the presence of significant coronary stenoses and that the degree of reduction is proportional to the severity of the lesion.[88] Thereby, destroy/refill phenomena from myocardial contrast echo can be used not only to diagnose coronary artery disease (CAD) but also potentially to assess coronary flow reserve.

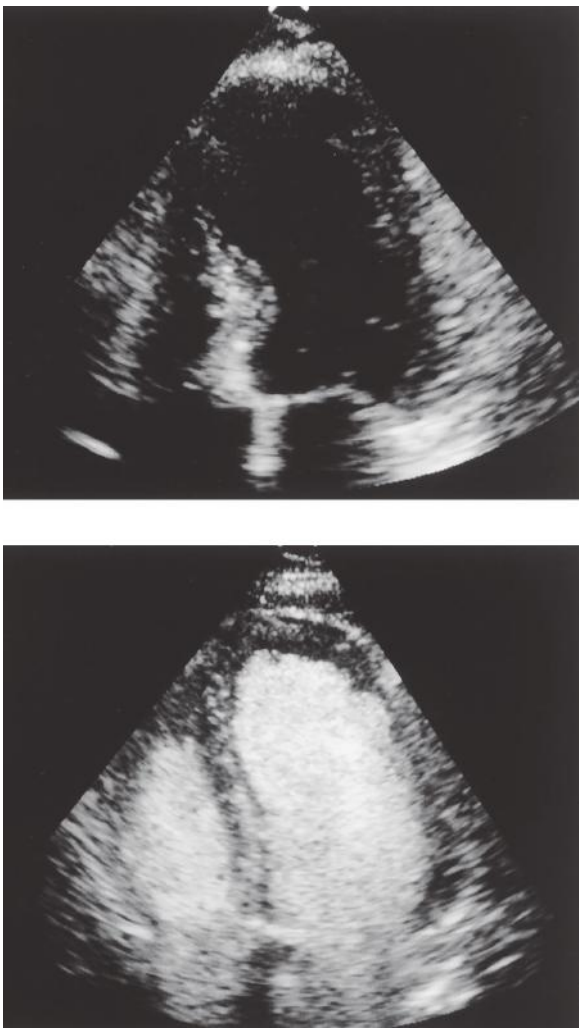


FIGURE 15–58. Harmonic imaging after intravenous injection of echocardiographic contrast. Endocardial border definition before injection is fair (*upper panel*) but is markedly improved with harmonic imaging after contrast injection (*lower panel*).

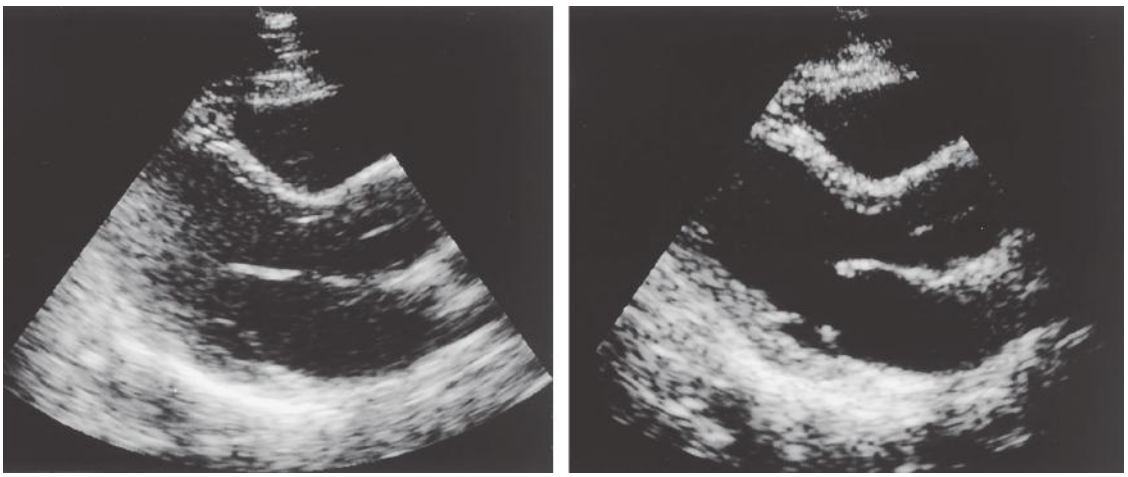


FIGURE 15–59. Tissue harmonic imaging. The *left panel* shows a parasternal long-axis view obtained with standard (fundamental) imaging. Endocardial definition is poor but is markedly enhanced with tissue harmonic imaging (*right panel*).

A number of trials indicate that myocardial contrast echocardiography can yield information regarding myocardial perfusion comparable to that obtainable by radionuclide techniques and can be valuable in delineating coronary artery stenoses.[89,90] However, the ability to obtain technically high-quality images is variable. Myocardial contrast echocardiography can identify infarct areas in acute myocardial infarction (AMI), document the absence of microcirculatory flow after epicardial coronary reperfusion (*no-reflow* phenomenon), and predict myocardial viability. The ability to delineate regional myocardial perfusion would be a major step forward in noninvasive imaging, but at the present time, echo contrast myocardial perfusion imaging remains an investigative tool.

DISEASES OF THE AORTA

The thoracic AO is best visualized from the left and right parasternal positions and from the suprasternal notch. The descending AO may also be imaged from subcostal and modified apical views. Normally, short-axis images of the AO yield a circular structure, whereas long-axis images exhibit two parallel linear walls.

AORTIC DISSECTION

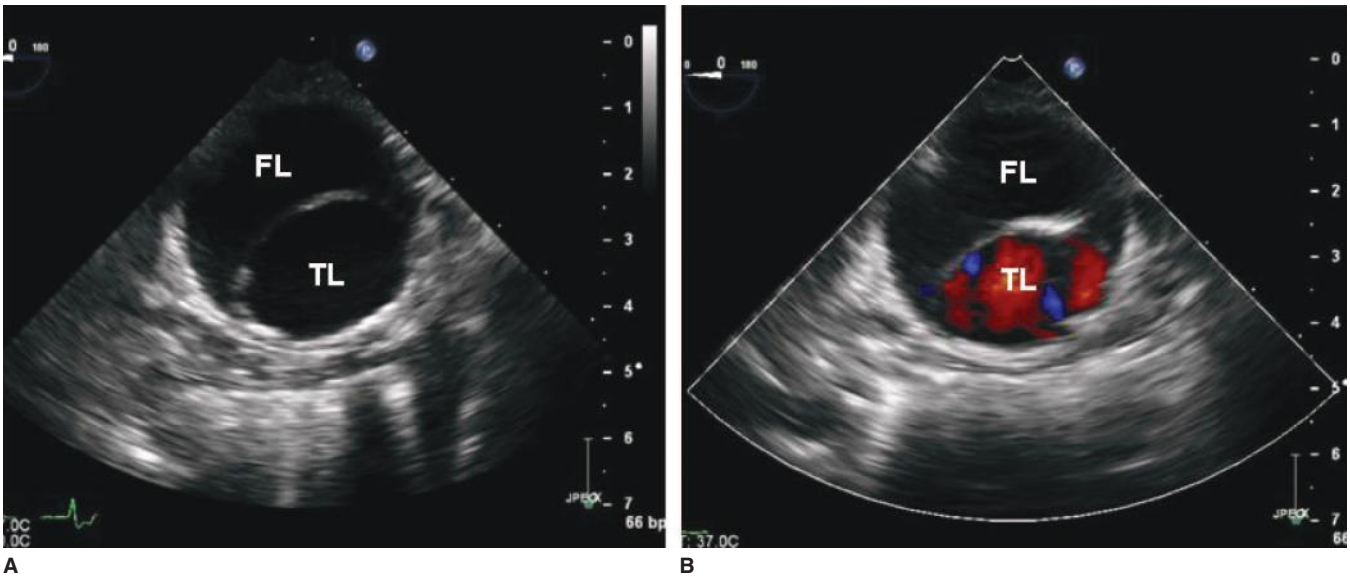
Echocardiography contributes significantly to the diagnosis and management of patients with suspected aortic dissection. Although TTE is a convenient screening test, it allows the evaluation of a limited portion of the aorta: the aortic root and proximal ascending aorta. The diagnostic findings of AO dissection include a dilated aorta with an intimal flap that presents as a thin, linear, mobile signal within the lumen. TTE is crucial in evaluating whether the AoV is involved with resultant AR, and whether there is an associated pericardial effusion—an ominous sign of dissection into pericardial sac. Transthoracic imaging is unreliable for detection of descending aortic dissection, but it occasionally visualizes the complete length of the thoracic aorta.

Among the noninvasive methods that exist to diagnose aortic dissection such as CT and MRI, TEE is a highly useful procedure because of its accuracy, portability, rapid procedural time, and ability to provide data regarding valvular regurgitation and LV function without the need for contrast injection.[74] These aspects are especially important in the postoperative patient (Fig. 15–60). Except for a short portion of the proximal aortic arch that is obscured by the bronchus, multiplane TEE provides excellent visualization of the entire thoracic aorta and high accuracy in detecting aortic enlargement, intimal tears, and false lumen thrombus (Fig. 15–61). CFD may reveal communications between true and false channels. TEE also appears useful for the diagnosis of aortic intramural hematoma, an increasingly recognized disorder that has a clinical prognosis similar to that of classic dissection. In this disorder, hemorrhage occurs within the aortic media, but an intimal tear (and a dissection flap) is absent. The finding of a curvilinear, asymmetric density within the aortic wall in a patient with typical symptoms of dissection strongly suggests a diagnosis of aortic intramural hematoma.[74]

FIGURE 15–60. Longitudinal transesophageal echocardiography view of an ascending aortic dissection in a patient with a porcine prosthetic valve in the aortic position (*large arrow*). The false (F) and true (T) lumens are separated by an intimal flap (*small arrow*).

AORTIC ANEURYSM

Aneurysms of the AO may be saccular or fusiform and are recognized as localized or circumferential areas of aortic enlargement, often with



A B

FIGURE 15–61. Transverse transesophageal echocardiography image of a descending aortic dissection. The true lumen (TL) is has flow by color Doppler whereas the false lumen (FL) is mostly devoid of flow or has very low flow.

thin walls. TTE is especially useful in detecting ascending aortic dilatation but can also visualize the aortic arch and descending thoracic and abdominal aortic aneurysms.[74]

Echocardiography has been used extensively to assess aortic pathology in patients with Marfan syndrome. The nature of the lesion is relatively specific in that there is symmetrical dilatation of the annulus, sinuses of Valsalva, and AO (Fig. 15–62A). Aortic leaflet coaptation may be compromised, leading to AR. Echocardiography is helpful in determining prognosis and timing of AO replacement.

Sinus of Valsalva aneurysms are also well visualized by both TTE and TEE. These lesions cause asymmetric dilatation of the AO and seem to affect the right coronary sinus most frequently. They are prone to rupture, often into the right heart (Fig. 15–62B). Doppler echocardiography in such settings demonstrates fluttering of the TV, a color jet crossing from the AO into the right heart throughout the cardiac cycle, and occasionally diastolic opening of the pulmonic valve (PV).

The aorta is susceptible to trauma, especially deceleration injuries. The versatility of TEE makes this a good choice for visualization of traumatic dissection (Fig. 15–63). Congenital aortic disease also can be detected with echocardiography. In these conditions, suprasternal and transesophageal imaging are often helpful. Supravalvular aortic stenosis is recognized as an *hourglass* narrowing or a discrete fibrous ridge just superior to the aortic valve leaflets, whereas coarctation of the aorta presents a more localized, abrupt luminal reduction in the descending aorta or distal portion of the aortic arch.

AORTIC ATHEROSCLEROSIS

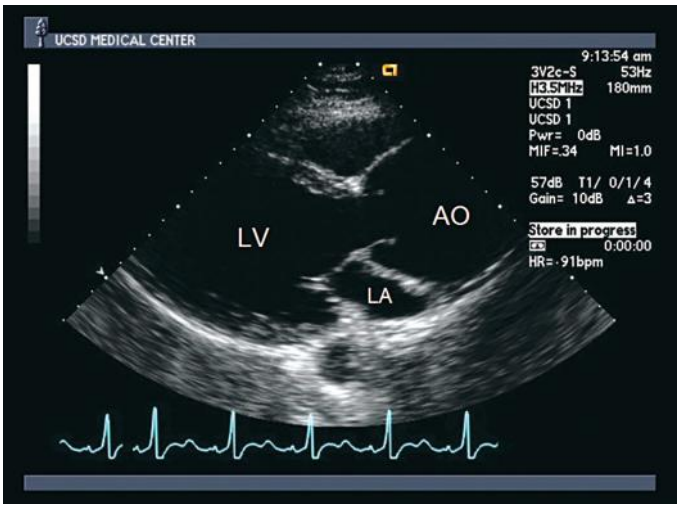
As mentioned in the section on TEE, several studies suggest that aortic atherosclerosis is an important cause of stroke and embolic events. Mobile and protruding intimal plaques have been detected by TEE (Fig. 15–64) in patients with stroke, a finding not previously appreciated by other imaging techniques. Optimal treatment for extensive aortic atherosclerosis is not definitively established, but statin therapy is a mainstay and warfarin may be useful in select patients.[91] When such plaques are present before cardiopulmonary bypass, prompt adjustment of cannula placement is indicated to avoid dislodging the aortic debris.

Penetrating aortic ulceration, which affects the descending AO and may mimic the clinical syndrome of acute aortic dissection, may also be diagnosed by TEE (see Fig. 15–64). A localized defect is visualized with protrusion of the ulcer into the vessel wall. Urgent surgery may be warranted in certain cases to avoid aortic rupture. Aortic tears induced by trauma are also accurately detected by TEE.

VALVULAR HEART DISEASE

AORTIC STENOSIS

The AoV is best imaged in the parasternal views (Fig. 15–65). The aortic cusps are thin, linear structures. All three can be visualized in the short-axis view and produce a triangular orifice during systolic opening. The long-axis view displays the right and usually the noncoronary cusps, which normally open to the walls of the aorta. Mild thickening and reduction of mobility is often observed in the elderly (aortic sclerosis) and is associated with an increased risk of CAD. In older adults, acquired AS is manifested by markedly thickened, often calcified, immobile AoV leaflets (Fig. 15–66), whereas doming leaflets suggests congenital AS (eg, bicuspid valve) and is usually encountered in younger patients. Subaortic stenosis may be caused by systolic anterior mitral motion as seen in hypertrophic cardiomyopathy, a subaortic



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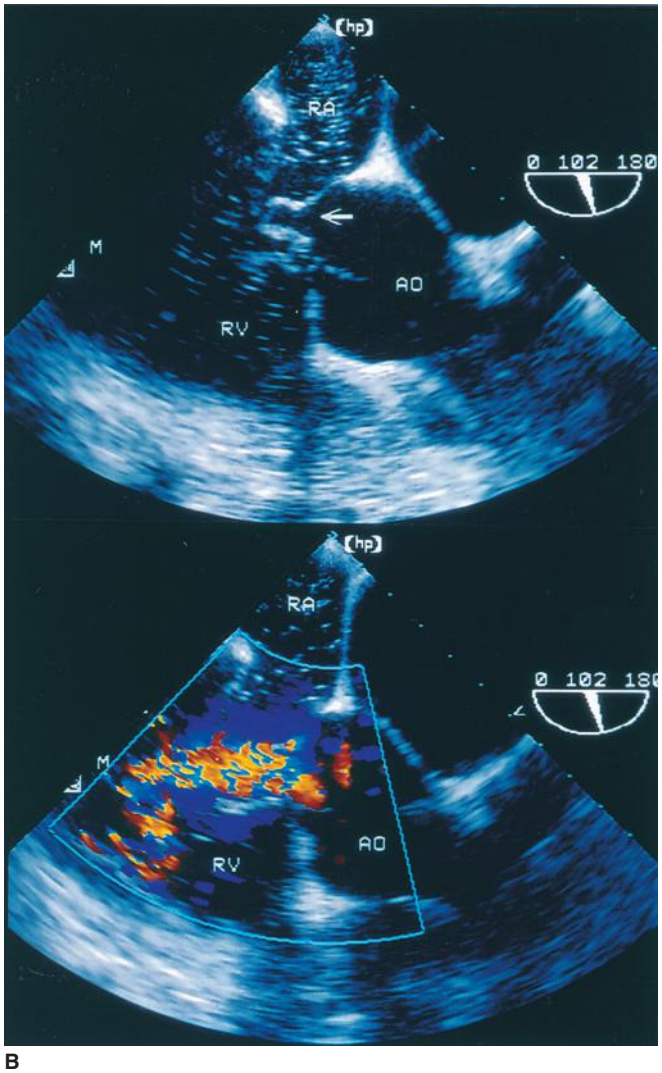


B

FIGURE 15–62. A. Parasternal long-axis plane demonstrating severe aortic root (AO) enlargement. **B.** Transesophageal echocardiography image of a ruptured sinus of Valsalva aneurysm. The *upper image* shows focal aneurysmal dilatation of the right coronary sinus with the appearance of a *windsock*. Color Doppler (*lower image*) reveals a high-velocity flow jet from the aorta into the right ventricle (RV). Agitated saline was injected intravenously to highlight right heart structures. LA, left atrium; LV, left ventricle.

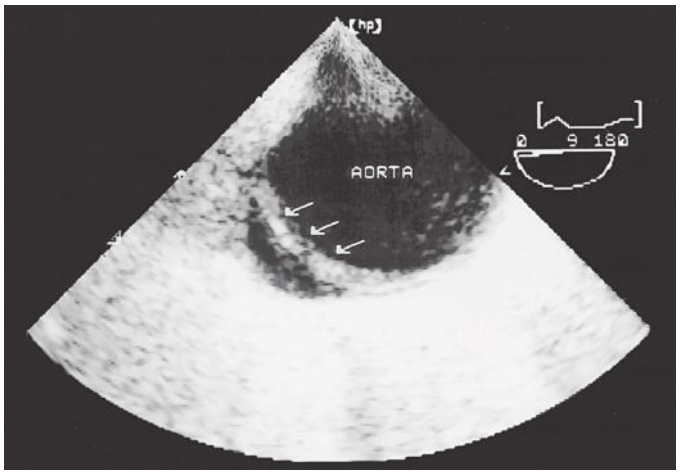


FIGURE 15–63. Transverse transesophageal echocardiography image of traumatic aortic disruption and partial transection (*arrows*) involving the distal portion of the aortic arch.

membrane, or (less commonly) a subaortic tunnel. Bicuspid valves exhibit an oval rather than triangular orifice (Fig. 15–67) in systole, while in diastole, a remnant raphe in the fused cusps may give the impression of a three-cusped valve. This distinction has relevance in the selection of patients for percutaneous valve replacement and may require clarification using TEE or other modalities.

Although the severity of stenosis can be assessed semiquantitatively by echocardiographic imaging, valvular calcification may shadow the leaflets or produce reverberations, obscure their motion, and overestimate the stenosis. Therefore, attempts to measure valve area by transthoracic planimetry have been unsuccessful, but multiplane TEE has been of greater value. Thus 2D-echocardiographic imaging accurately detects the presence and etiology of AS but not its severity. Likewise, CFD demonstrates turbulent flow through the AoV but provides no quantitative data of its severity. Doppler echocardiography with the use of the modified Bernoulli and continuity equations has now made

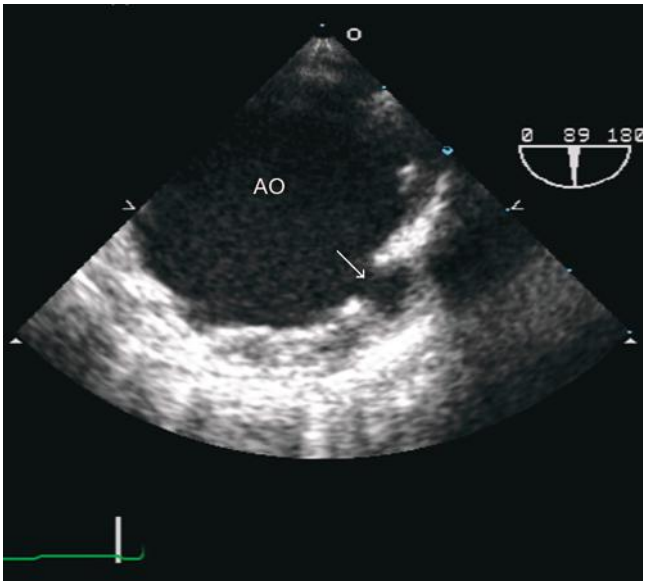


FIGURE 15–64. Transverse transesophageal echocardiography view of penetrating ulceration in the aortic arch. The mouth of the ulcer crater is visible (*arrow*).

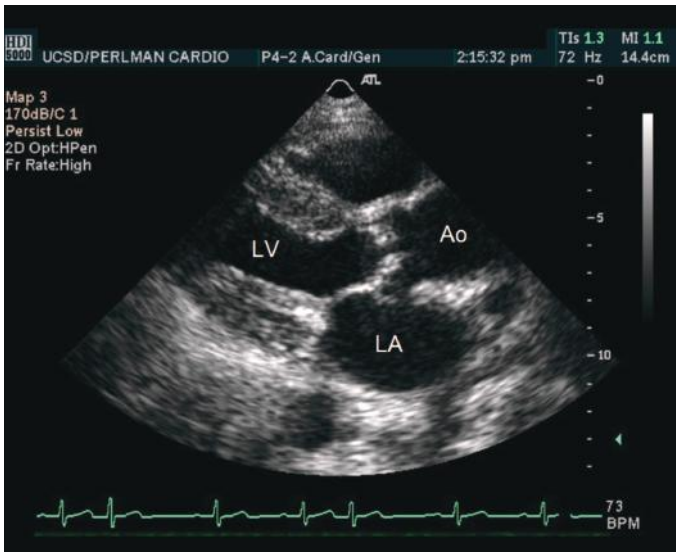


FIGURE 15–65. Parasternal long-axis plane demonstrating a thickened, stenotic aortic valve (AoV). Ao, aorta; LA, left atrium; LV, left ventricle.

noninvasive calculation of aortic gradients and valve area routine, and this has resulted in much less utilization of cardiac catheterization for the hemodynamic assessment of AS severity.

The cornerstone of the ultrasound evaluation of AS is CW Doppler interrogation through the AoV to evaluate the acceleration of blood velocity across the stenosis. A maximal gradient is calculated as 4∗[Peak AS velocity]^2, and a mean gradient is also derived (Fig. 15–68). The mean gradient by Doppler correlates well with the mean gradient at catheterization. Similarly, the maximal Doppler-derived gradient correlates closely with the peak *instantaneous* gradient measured at catheterization,[72] which is the physiologic maximal pressure difference between the LV and aorta. It is important to note that the "peak-to-peak gradient," commonly used in the catheterization laboratory, compares the highest pressures reached in the LV and aorta (even though neither simultaneous nor physiologic) and is uniformly lower than the peak instantaneous gradient recorded by Doppler. The maximal Doppler gradient does not correlate with the peak-to-peak catheterization gradient, and comparisons between the two should be avoided.

Several potential sources of error exist in the estimation of the transvalvular aortic gradient by CW Doppler recordings. It is imperative that Doppler signals from the stenotic jet be obtained with an angle of incidence of < 20 degrees, so as not to underestimate the velocity or gradient. For this purpose and because 2D techniques rarely reveal the precise direction of the jet, each Doppler examination must use all possible windows and angulations, choosing the window providing the highest velocity. Also, one must be careful to account for the proximal flow velocity in the Bernoulli equation if it is 1.5 m/s or greater. In the adult, CW Doppler can occasionally overestimate peak systolic pressure gradients, especially in patients with narrow ascending aortas. Lastly, in patients with concomitant dynamic LV outflow obstruction, it is usually difficult to separate the increased velocity caused by each of these conditions.

Using Doppler and echocardiographic imaging, an AoV area can be calculated using the continuity equation as noted earlier. Flow can be calculated by Doppler as cross-sectional area multiplied by blood velocity at a particular site. Because flow is constant in the LV outflow and through the aortic valve, an aortic valve area (AVA) can be derived as:

$$AVA = CSA_{LVO} * V_{LVO}/V_{AS}$$

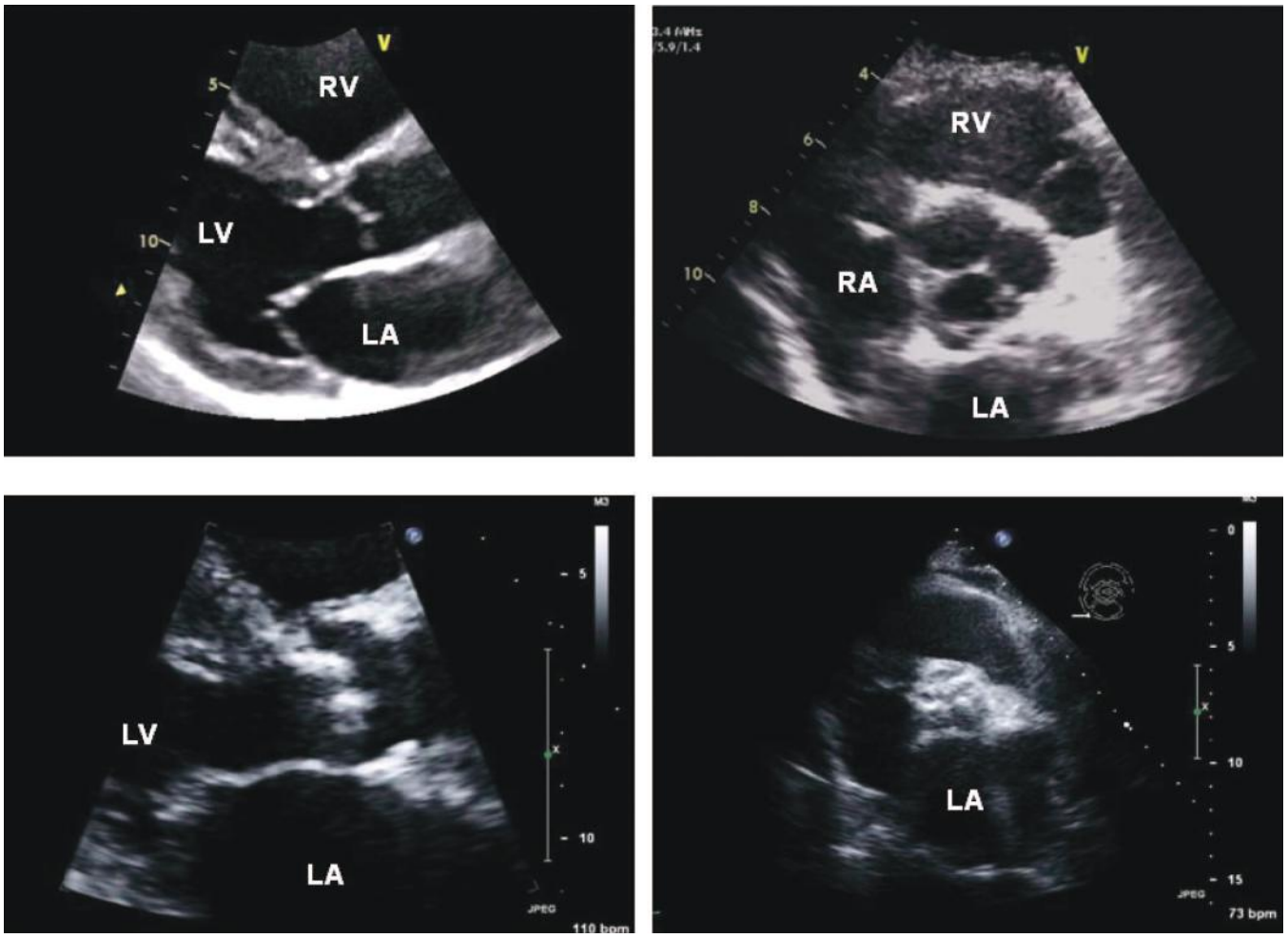
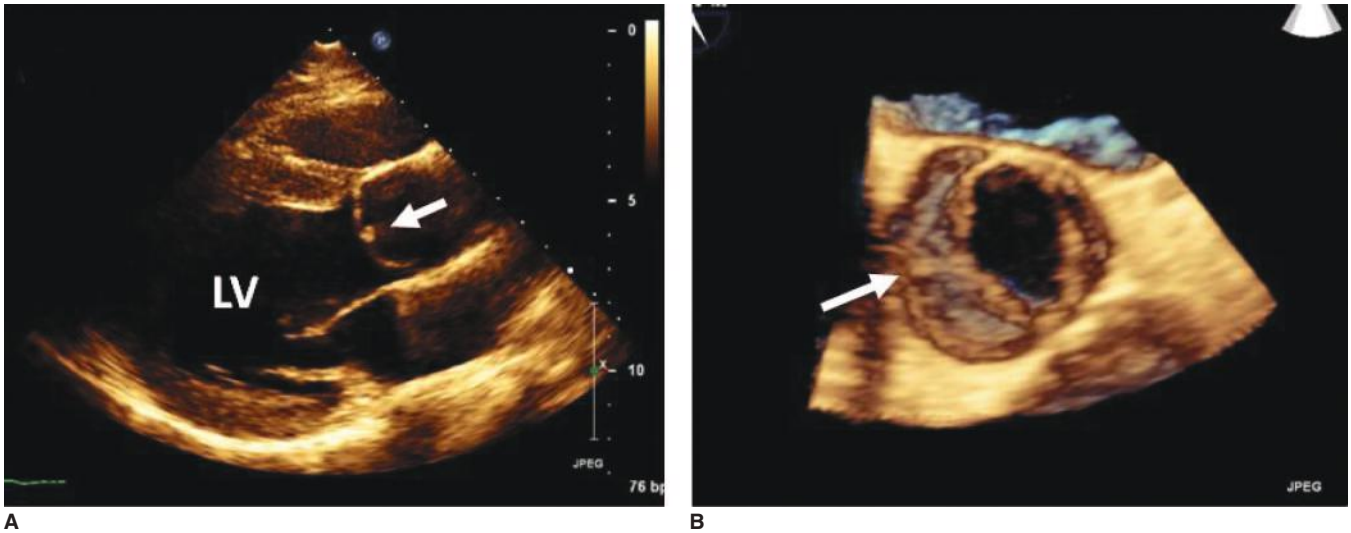


FIGURE 15–66. Transthoracic parasternal long- and short axis views depicting a normal aortic valve (*upper panels*) and a thickened, calcific aortic valve (*lower panels*). LA, left atrium; LV, left ventricle; RV, right ventricle.



A B

FIGURE 15–67. A. Parasternal long-axis image of a bicuspid aortic valve showing diastolic doming of the valve (*arrow*). **B.** A three-dimensional short-axis display of a bicuspid valve in systole viewed from the aorta showing the oval appearance of the open valve, and the fusion of the right and noncoronary cusps, with a remnant raphe (*arrow*).

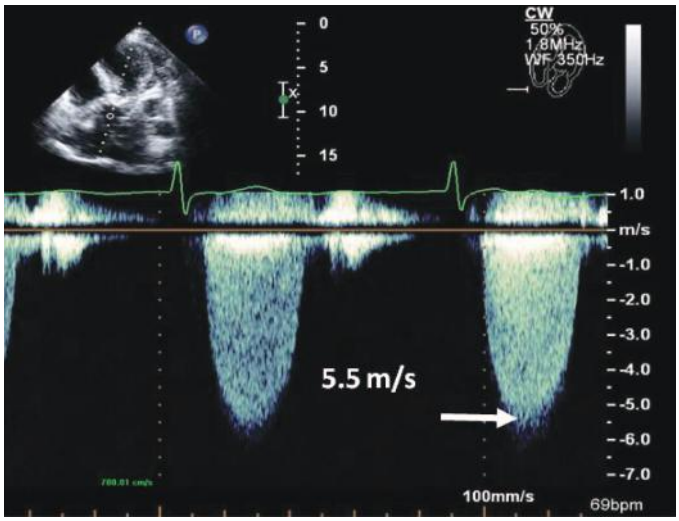


FIGURE 15–68. Continuous-wave Doppler tracing (from the apical transducer position) through the aortic valve in a case of severe aortic stenosis. The peak systolic velocity is 5.5 m/s, corresponding to a maximal instantaneous gradient of 121 mm Hg; the mean gradient was 80 mm Hg.

where CSA_{LVO} is cross-sectional area in the LV outflow derived from a diameter measurement assuming a circular geometry, V_{LVO} is the velocity in the LV outflow by pulsed Doppler, and V_{AS} is the velocity of the aortic stenosis jet by CW Doppler. Results from the continuity equation have correlated well with AoV area calculations based on catheterization data and the Gorlin formula.[72] Sources of errors include the measurements of each of the parameters involved, the position of the PW Doppler sample volume, and importantly the LV outflow diameter as it is squared to obtain the CSA. Particular attention to these details is essential for reliable measurements. For increased accuracy, particularly in low-flow AS, it is beneficial to internally verify stroke volume determinations in the LV outflow by corroborating measurements with estimated LV stroke volumes (LVend-diastolic volume* LV ejection fraction).[92] When atrial fibrillation is present, average of respective PW and CW Doppler measurements from several beats or matching of preceding R-R intervals for these two Doppler recordings is suggested for derivation of valve area.

In summary, a comprehensive Doppler echocardiographic examination in a patient with AS should establish both the presence and severity of disease. Doppler echocardiography provides a direct measurement of the maximal velocity and mean gradient through the valve, both having prognostic and management implications. The continuity equation should provide reliable estimates of AoV area, particularly needed in moderate or severe stenosis. Low-flow, low-gradient AS can be divided into patients with preserved EF and low EF. The former may represent nonsevere AS in small patients—a situation that may be clarified by indexing AVA to body surface area. Once this is excluded, the key to paradoxical low-flow, low-gradient AS is an LV stroke work index < 34 mL/m^2, reflecting a reduced stroke volume that explains the low gradient. In the setting of reduced EF, the distinction of true and "pseudosevere" AS may be elucidated by dobutamine stress echocardiography (see Stress Echocardiography)[93] or TEE imaging. In addition, dobutamine echocardiography is helpful in distinguishing high-risk patients with AS and severe LV dysfunction.

AORTIC REGURGITATION

In contrast to AS, the AoV leaflets are often anatomically normal by echocardiography in patients with AR. 2D and M-mode echocardiography often provide indirect evidence of the presence of AR, including signs of LV volume overload, diastolic fluttering of the anterior MV leaflet, aortic enlargement, and incomplete coaptation of the AoV leaflets. The important M-mode finding of premature diastolic closure of the MV before the onset of systole caused by elevated LV filling pressure from the regurgitant jet signifies acute, severe AR (Fig. 15–69).

Perhaps the most important contribution of echocardiographic imaging to the assessment of AR is in identifying its etiology and adaptation of the LV to the volume overload. Thickened cusps with restricted motion are observed in patients with acquired AS, whereas oval doming of two functional leaflets is seen in the presence of a bicuspid AoV (see Fig. 15–69), where associated AR is frequently eccentric. AR caused by infectious endocarditis can be identified by the presence of valvular vegetations (Fig. 15–70), whereas regurgitation caused by diseases of the aorta is manifest by anatomic changes of the aortic root or dissection. Less common etiologies of AR, such as those associated with subvalvular pathology or VSD, may also be recognized by echocardiographic imaging.

Doppler interrogation is necessary to obtain direct evidence of the presence and severity of AR. Screening is best performed with CFD and demonstrates turbulent flow in the LV outflow tract during diastole in virtually all views[67] (see Fig. 15–70). The jet extends from the AoV toward the LV and may be seen anywhere in the LV outflow tract. The estimate of severity most commonly derived from echocardiography is the width of the AR jet by CFD.[67] Conceptually, jets distributed over a small area of the LV outflow tract (LVOT) represent lesser degrees of AR than do jets that penetrate widely through the LVOT. A widely acceptable parameter of severity is the width of the AR jet just proximal to the valve, expressed as a percentage of the width of the LVOT; a jet occupying 50% or more of the outflow tract correlates with severe regurgitation by angiography.[67] This is provided that the jet is central, directed toward the middle of the LVOT. Therefore, assessment of the severity of AR by the size and shape of the flow disturbance is at best semiquantitative.

CW Doppler spectral recording of the jet yields a high-velocity diastolic signal directed toward the apex. Because AR jet velocity accurately reflects the diastolic pressure gradient between aorta and LV, it is maximum at the point of valve closure and decreases throughout diastole. The flow pattern of AR is distinct from that of mitral inflow, because it

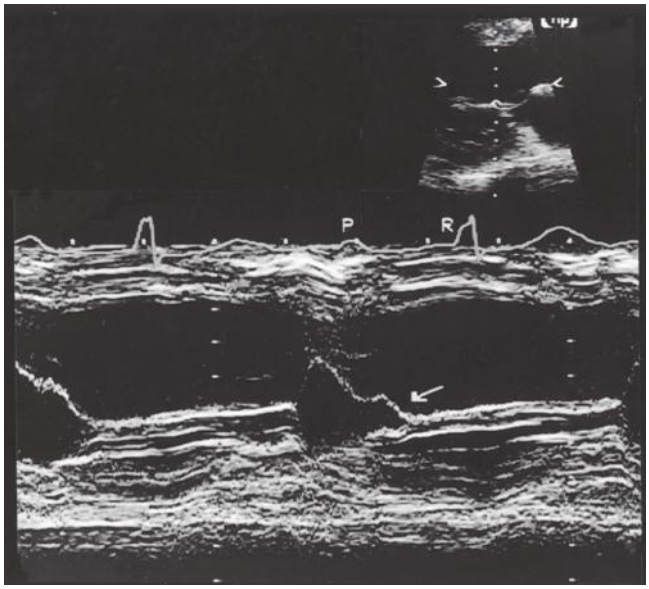


FIGURE 15–69. M-mode tracing (from the parasternal position) in a patient with acute severe aortic regurgitation. The mitral valve leaflets close (*arrow*) before ventricular contraction begins. P, p wave; R, QRS complex.

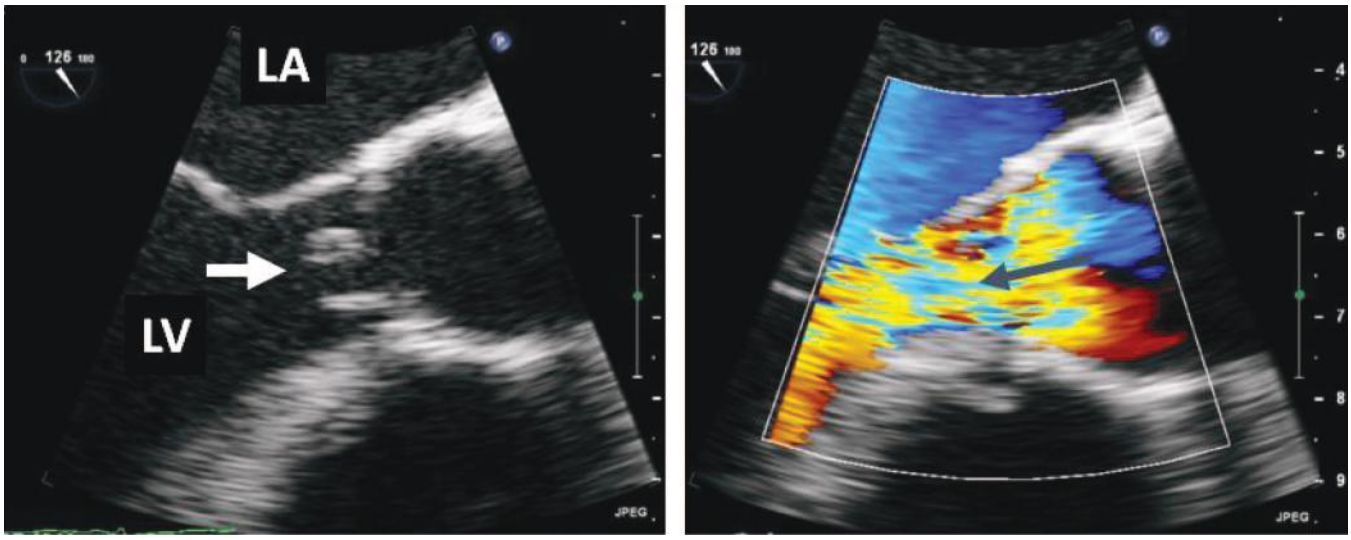


FIGURE 15–70. Transesophageal view depicting vegetations on the aortic valve (*white arrow*) and a flail aortic valve. Color Doppler shows severe aortic regurgitation, with the color jet occupying all of the left ventricle outflow tract. LA, left atrium.

has a higher velocity and begins immediately after AoV closure, with a much slower deceleration and without an increase in velocity after atrial contraction. A supportive parameter of AR severity is the deceleration rate of the jet recorded by CW Doppler (Fig. 15–71).[67] In the presence of mild degrees of AR, the transvalvular pressure gradient is maintained throughout diastole, creating a high-velocity jet with a minimal deceleration rate. Conversely, severe AR reduces aortic pressures and increases LV pressures in diastole, creating a rapid jet deceleration to a low velocity. Severe, acute AR can also cause diastolic MR through increased LV end-diastolic pressure. The most common approach to assessing the deceleration rate of the AR jet is by calculating the time required for the velocity to fall to one-half of the maximal pressure equivalent (pressure half-time). A pressure half-time of < 250 milliseconds identifies patients with severe degrees of AR. Application of the pressure half-time approach to quantifying AR must take into account both the volume of AR and LV compliance.

The AR volume can be estimated by comparing volumetric measurements of LV inflow and LV outflow calculated from annular velocity and cross-sectional area (derived from pulsed Doppler and 2D images, respectively).[67,94] This method depends on the absence of valvular stenosis and other regurgitant lesions. In the setting of AR, the volume ejected through the aortic annulus represents both systemic flow and regurgitant volume, whereas the volume coursing through the mitral annulus represents only systemic flow. Thereby, LV outflow exceeds LV inflow by the amount of the regurgitant volume. The presence of a significant, holodiastolic flow reversal in the aorta visualized by spectral Doppler is a reliable marker of severe AR (Fig. 15–72).

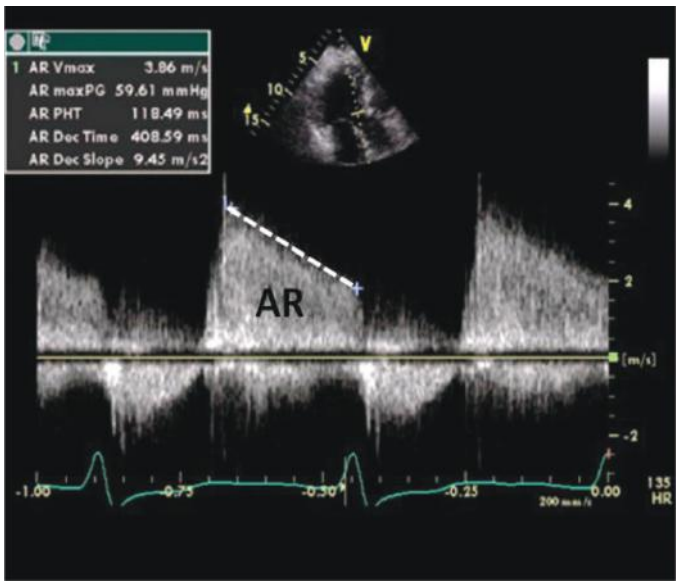


FIGURE 15–71. Continuous-wave Doppler tracing (from the apical transducer position) of severe aortic regurgitation (AR) showing a fast deceleration of the regurgitant jet. The pressure half-time of the AR envelope is approximately 120 ms.

FIGURE 15–72. Pulsed-wave Doppler tracing (from the suprasternal transducer position) in a case of severe aortic regurgitation. The sample volume is in the descending thoracic aorta, and holodiastolic flow reversal (*arrow*) is present.

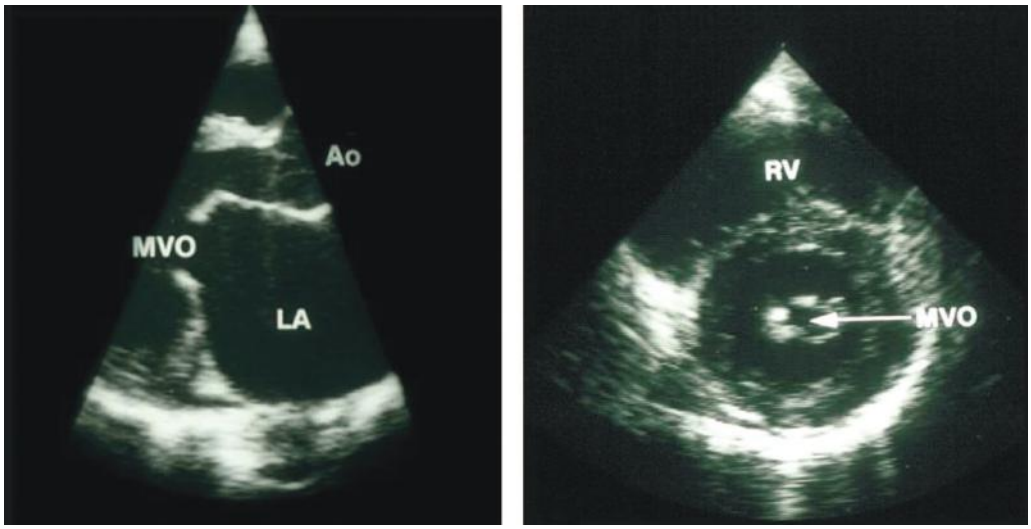


FIGURE 15–73. Parasternal long-axis and short axis views of typical rheumatic mitral stenosis. The left atrium (LA) is enlarged, mitral opening is limited, and *doming* of the anterior mitral leaflet is seen in the long axis view. The narrow mitral valve opening (MVO) is nicely depicted in short axis. Ao, aorta; RV, right ventricle.

Conventional echocardiographic imaging can provide evidence of the presence and extent of LV volume overload. Determination of the optimal timing of surgical intervention in patients with AR takes into account several factors, including AR severity, attributable symptoms, and LV size and function. Several criteria derived from echocardiographic recordings have been proposed to guide this decision.

MITRAL VALVE STENOSIS

Detection of *mitral stenosis* (MS) was one of the earliest clinical applications of echocardiography. In normal individuals, the MV leaflets are easily visualized as thin linear echoes that exhibit a wide bipeaked excursion as they open in early diastole and again in late diastole after atrial contraction. In contrast, the MV leaflets in rheumatic MS are thickened and often present bright, high-intensity reflections indicating calcification. Thickening, partial fusion and shortening of the chordal apparatus occur as well. There are varying degrees of commissural fusion restricting mitral leaflet separation, especially at the distal tips. This leads to a typical diastolic *doming* or a right-angle bend of the anterior MV leaflet, as high LA pressure creates a bulge in the leaflet's midportion (Fig. 15–73). The posterior leaflet actually may be pulled anteriorly during diastole because of commissural fusion with the longer anterior leaflet. The LA is nearly always enlarged in MS.

The effects of stenosis on MV motion is also nicely demonstrated with M-mode recordings (Fig. 15–74), depicting a characteristic decrease in the partial closure rate of the anterior mitral leaflet in early diastole (reduced E-F slope) caused by a persistent LA–LV pressure gradient and a slow rate of LV filling. The decrease of the E-F slope has been found to correlate grossly with the severity of MS. This finding without MS may occur whenever early diastolic filling is reduced.[19]

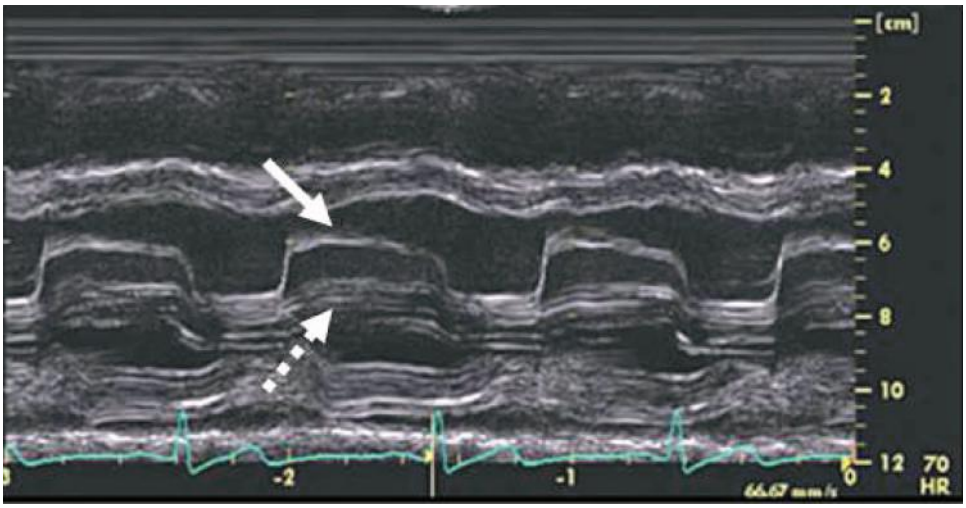


FIGURE 15–74. Parasternal M-mode image through the mitral valve in a patient with mitral stenosis. The abnormal motion of both the anterior (*solid arrow*) and posterior (*dashed arrow*) leaflets is shown. The downslope of the anterior mitral leaflet after early rapid diastolic filling is absent.

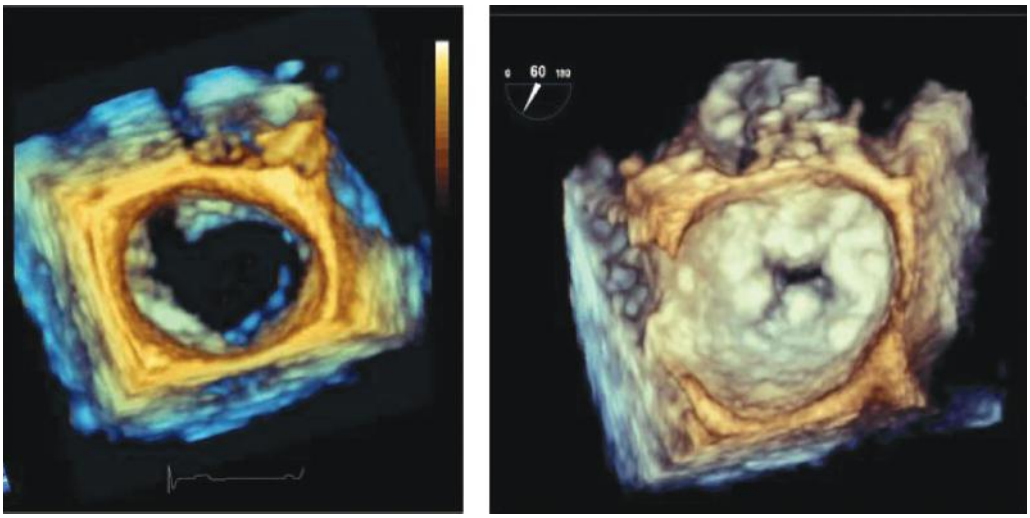


FIGURE 15–75. Three-dimensional transesophageal frames from the left atrial aspect depicting wide mitral valve opening of a normal mitral valve (*left*) and a severely stenotic valve (*right*).

The entire perimeter of the MV orifice can be visualized in the 2D parasternal short-axis view or by 3D echocardiography (Fig. 15–75). In the setting of MS, the thickened leaflets form a fish-mouth orifice, which occupies only a small portion of the cross-sectional area of the LV. Measurements of orifice area, obtained by planimetry of the orifice visualized in the parasternal short-axis view correlate well with those obtained by cardiac catheterization, provided that the degree of calcifications on echocardiography is not severe. It is crucial to identify the smallest cross-sectional area and obtain recordings with orthogonal beam orientation at that point to ensure that the plane position is at the valve tip, thus avoiding overestimation of orifice area.

Doppler examination provides important hemodynamic assessment of MS. Interrogation of mitral inflow with either PWD or CW Doppler (depending on velocity and Nyquist limit) reveals elevated diastolic velocities, with a reduction in the rate of deceleration in early diastole, yielding a pattern similar to the decreased E-F slope seen with M-mode in MS (Fig. 15–76). The maximal gradient across the MV can be calculated from the peak diastolic velocity using the Bernoulli equation. The mean transmitral gradient is commonly used to assess the severity of MS. In contrast to the mean gradient in AS, the mean gradient in MS is very dependent on the diastolic filling period and thus heart rate; the higher the heart rate (with the same stroke volume and degree of stenosis), the higher the mean gradient. Thus, heart rate should always be noted when evaluating the mean gradient in MS.

The Doppler technique can often provide an estimate of mitral valve area (MVA) by means of the "pressure half-time" method.[72] The pressure half-time represents the interval required for the transmitral velocity to decelerate from its highest point (E) to a velocity that yields one-half of the pressure equivalent (see Fig. 15–76). As the severity of MS increases, the rate of deceleration decreases, prolonging the pressure half-time. Derivation of MVA is performed by dividing an empiric constant of 220 by the pressure half-time. MVA with this method correlates well with values obtained during cardiac catheterization. The pressure half-time method is helpful in the majority of patients with MS. However, it has limitations: it cannot be used when the diastolic filling period is too short, when there is fusion of the early and late mitral inflow velocity in sinus rhythm, with concomitant significant AR, and in the presence of severely impaired LV relaxation. In these situations, the continuity equation can be used to derive a MVA as stroke volume through the mitral valve divided by the velocity-time integral of mitral inflow velocity.[72]

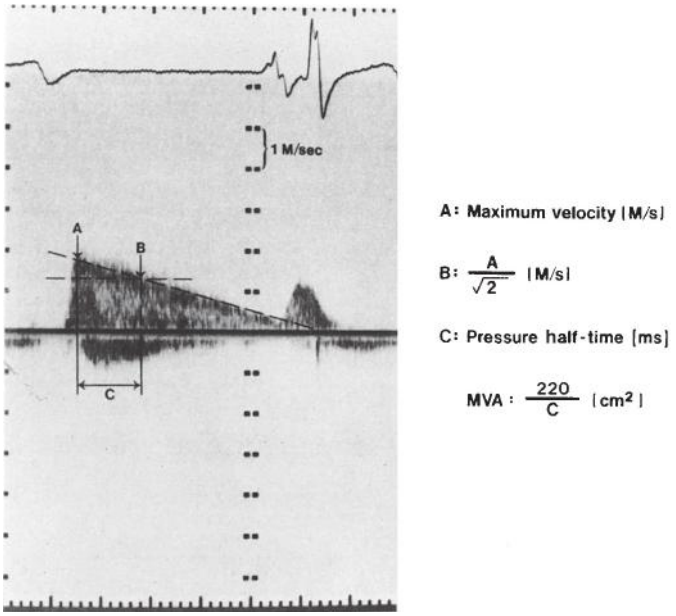


FIGURE 15–76. Pressure half-time method for calculation of mitral valve area (MVA). Reproduced with permission from Hagan AD, DeMaria AN: *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, 2nd edition. Boston: Little, Brown; 1989.

Echocardiography can help assess the feasibility and appropriateness of percutaneous balloon mitral valvuloplasty (vs surgery) to treat individual patients with predominantly isolated MS without significant mitral regurgitation.[95] An echocardiographic scoring system based on evaluation of mitral valvular thickening, calcification, mobility, and subvalvular involvement has been devised. Each variable is assigned a grade ranging from 1 (minimal involvement) to 4 (severe), with a maximal total score of 16. Although the prognostic capability of this method is limited, the outcome of balloon valvuloplasty in patients with higher scores, particularly > 12, is less satisfactory and involves a higher risk of complications than in patients with lower scores.[96]

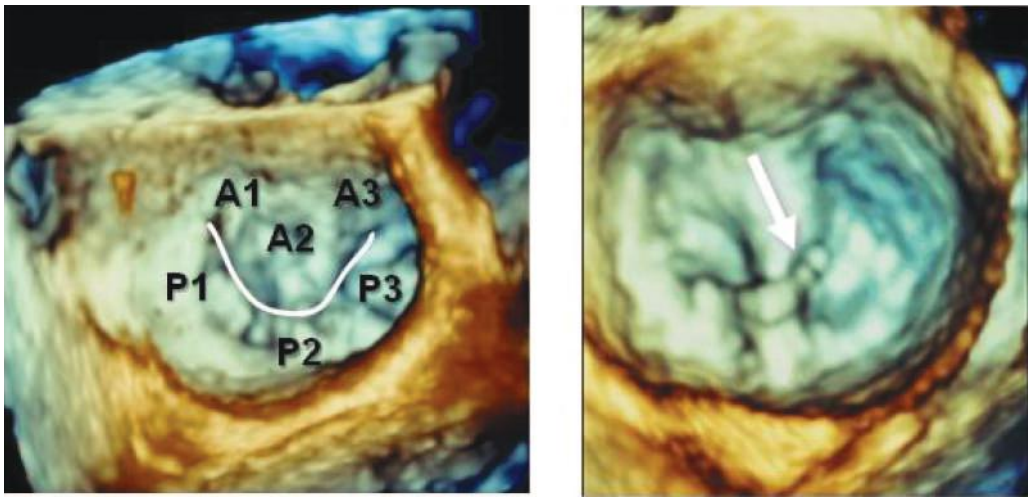


FIGURE 15–77. Nature and location of mitral pathology using three-dimensional echocardiography from the left atrial aspect depicting a normal mitral valve in systole (*left*) with its anterior (A) and posterior (P) scallops. The *right* panel shows a patient with fibroelastoic deficiency and a flail posterior (P2) scallop (*arrow*).

Therefore, echocardiographic analysis is an important part of the decision-making process before percutaneous balloon mitral valvuloplasty. Preprocedural TEE is also often performed to exclude the presence of left atrial thrombi. After valvuloplasty, echocardiography can identify complications, including MR and atrial septal defect.

Mitral Regurgitation

Although echocardiography is extremely accurate in the detection of mitral (and aortic) regurgitation, *quantitation* is more difficult. Imaging alone does not provide direct evidence of MR but usually reveals the underlying mechanism and etiology of the lesion. Thus 2D echocardiography reveals whether MR is primary (because of abnormalities of MV structure) or secondary caused by LV dysfunction, which results in displacement of the papillary muscles, tenting, and poor coaptation of the MV. 3D echocardiography has provided previously unparalleled opportunities to assess the nature and location of mitral pathology (Fig. 15–77). Primary abnormalities of the MV include thickened, restricted leaflets as seen in rheumatic disease, vegetations in infective endocarditis, flail mitral leaflets with torn chordae, and redundant leaflets with abnormal coaptation in MV prolapse. Imaging also provides evaluation of the cardiac adaptation to the volume overload. Enlargement of the LV and LA offers indirect evidence of the severity of MR. In cases of chronic, severe MR, 2D echocardiography can also discern the presence of depressed LV function.

Doppler echocardiography is the primary method for the detection and evaluation of severity of MR.[67] CFD is the primary method used and reveals a disturbed flow jet in the LA during systole. Spectral Doppler recordings provide several supportive indexes of severity. Similarly, an increase in transmitral filling velocities reflects increased forward flow into the LV and suggests a large regurgitant volume. An integrative approach of these findings is important in the overall evaluation of MR severity, because each of the methods can be affected by several factors.[67] Further specifics about the methods used in the overall assessment of MR are detailed below.

The most commonly applied method for the evaluation of MR is CFD. Three components of the regurgitant jet by CFD are important to consider (Fig. 15–78): flow convergence (zone of accelerated blood velocity on the LV side), the vena contracta (the width of the smallest area of the jet at the regurgitant orifice), and the jet area in the LA. Imaging of the LA in systole reveals a turbulent, mosaic jet of varying direction, size, and configuration. If the jet is central in the LA, a jet area that occupies more than 40% to 50% of the LA usually is consistent with severe MR, subject to the limitations discussed in the earlier section. Although jet area is important in evaluating MR severity, it is affected by several factors in addition to the regurgitant volume: the pressure gradient and compliance of the LA, the direction of the jet in

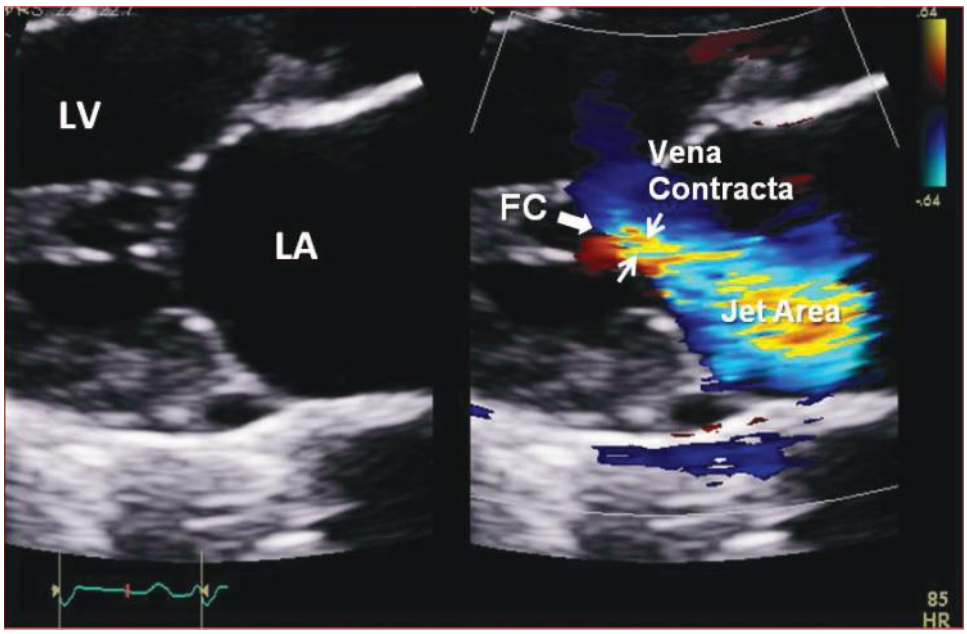


FIGURE 15–78. Transthoracic parasternal zoomed view depicting mitral regurgitation. The three components of a regurgitant jet are depicted: flow convergence (FC), vena contracta, and jet area. LA, left atrium; LV, left ventricle.

the receiving chamber, and technical limitations. Eccentric jets impinge on the wall of the LA (eg, in cases of MV prolapse and torn chordae tendineae), resulting in cross-sectional jet areas that are smaller than centrally directed flow disturbances of comparable regurgitant volume. This effect can lead to underestimation of the severity of regurgitation if one evaluates jet area alone. In these situations, considerations of flow convergence and vena contracta provide better evidence of MR severity. A vena contracta diameter, measured from the parasternal long axis, of at least 7 mm, usually denotes severe MR.

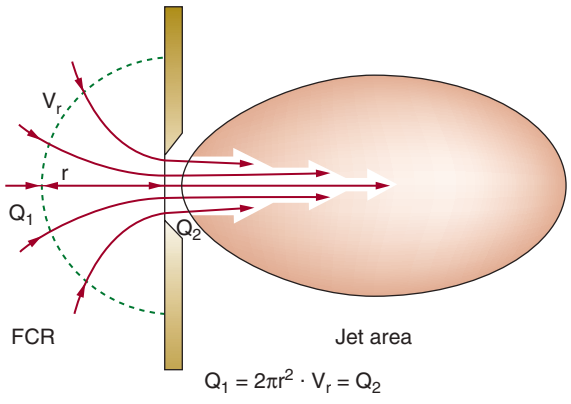
Color Doppler can also be used for quantitation of the severity of MR. This involves measurement of the zone of flow convergence proximal to the regurgitant orifice (PISA). The mechanism for this phenomenon is derived from the hydrodynamic principle that blood flow accelerates before passing through a small orifice under high pressure. If this increase in flow velocity exceeds the Nyquist limit, color aliasing occurs and the velocity aliasing border is equal to the Nyquist limit (Fig. 15–79). If one assumes that the aliasing border conforms to the geometry of a hemisphere around the mitral orifice, the instantaneous flow rate of blood through the orifice can be calculated as:

$$\text{Flow} = 2\pi r^2(V_r)$$

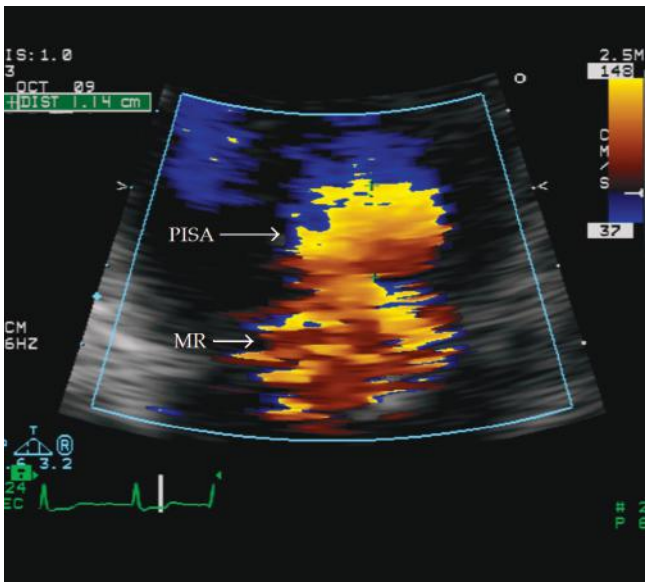
where r is the radius of the hemisphere shell (distance from alias border to orifice) and V_r is the velocity of blood at distance r (the Nyquist limit velocity). If the maximal calculated flow rate is divided by the peak regurgitant flow velocity (measured with CW Doppler), the regurgitant orifice area is then obtained.[67] The product of regurgitant orifice area and integrated velocity of the MR jet by CW yields regurgitant volume. The PISA method avoids the variables associated with jet size. Numerous studies have shown a correlation between both flow rate and regurgitant orifice area calculated by PISA and the severity of MR assessed by standard methods. In addition, flow convergence calculations have been applied to other valvular lesions, VSD, and prosthetic heart valves. The proximal flow convergence assumes a hemispheric geometry for the PISA signal and that the plane of the mitral leaflets is flat, representing two sources of potential error that can be exaggerated in eccentric jets and functional MR. An effective regurgitant orifice area of 0.4 cm^2 or more denotes severe MR.[67]

As in the case of AR, volumetric calculations of LV inflow and outflow by combined pulsed Doppler and 2D echocardiographic imaging techniques can be used to derive measurements of regurgitant volume. In the case of MR, transmitral filling represents both the systemic and regurgitant volumes, whereas aortic outflow represents only systemic flow. Therefore, mitral inflow should flow through the AoV, and the difference is the regurgitant volume.[67,94] Doppler of the MR jet can also be used to evaluate LV function (Fig. 15–80). Assuming a LA pressure close to zero, the downstroke of the MR jet is proportionate to the rate of increase of LV pressure (*dP/dt*) prior it aortic ejection. As the LV is "unloaded" by severe MR, this can be a marker of subclinical LV dysfunction, despite a normal ejection fraction.

TEE is useful for the assessment of MR, because the close proximity of the probe and its higher-frequency interrogating beam permit higher resolution of imaging of the valve with both 2D and 3D techniques, and imaging of regurgitant jets in greater detail than with TTE. It is usually reserved for technically difficult or inconclusive surface studies, or for better identifying the mechanism of MR. Eccentric jets and mitral valvular anatomy are visualized with high resolution. Because the regurgitant jets often appear larger with TEE than with TTE, one must avoid overestimation of MR severity with TEE. TEE often yields Doppler interrogation of the pulmonary veins that is superior to that



A



B

FIGURE 15–79. **A.** Proximal isovelocity surface area (PISA) concept and example. See text for details. **B.** Magnified view (from the apical four-chamber plane) of mitral regurgitation (MR) demonstrating color Doppler flow convergence proximal to the mitral valve (PISA). FCR, flow convergence region; Q, flow; r, radius of isovelocity hemisphere; Vr, velocity of flow at distance *r* from the orifice. **A,** Reproduced from Bargiggia GS, Tronconi L, Sahn DJ, et al. A new method for quantitation of mitral regurgitation based on color flow Doppler imaging of flow convergence proximal to regurgitant orifice, *Circulation*. 1991 Oct;84(4):1481-1489.

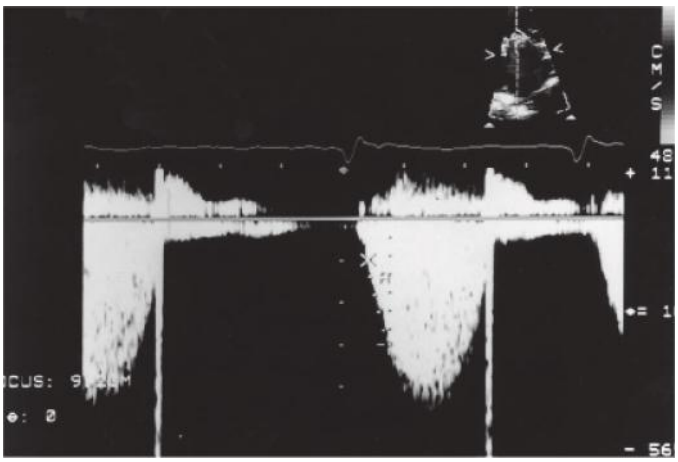


FIGURE 15–80. Continuous-wave Doppler spectral tracing of the mitral regurgitation jet from the apical window. The time between velocities of 1 and 3 m/s (0.07 s) indicates a dP/dt of 460 mm Hg/s.

of TTE, and several studies have shown that systolic reversal of flow into the pulmonary veins is a reliable sign of severe MR (Fig. 15–81).

Mitral Valve Prolapse

Echocardiography is the primary method for diagnosing MV prolapse. The classic findings in overt MV prolapse consist of mid- to late-systolic bulging of one or both mitral leaflets across the plane of the MV annulus into the LA (Fig. 15–82). The leaflets are often observed to be structurally abnormal, with thickening, elongation, and hooding. Mid- to late-systolic MR is sometimes present, often eccentric, and generally directed away from the prolapsing leaflet. The chordae tendineae may be thickened and elongated, the AO may be dilated (in associated diseases of the aorta), and the TV leaflets may prolapse as well. LV function is usually normal, but the LA and LV may be enlarged if MR is significant. The greater temporal resolution of M-mode over 2D echocardiography often yields striking evidence of abrupt mid-systolic posterior motion of the MV leaflets in prolapse patients (see Fig. 15–82C). Although such M-mode findings, which resemble a question mark on its side, are specific for MV prolapse, patients with classic MV prolapse occasionally may demonstrate diagnostic findings only with 2D imaging.

Although the diagnosis of classic, fully expressed MV prolapse is straightforward by echocardiography, identification of mild prolapse is more difficult, and no absolute diagnostic criteria currently exist. For prolapse to be present, the MV leaflets must cross the plane of the MV annulus after initial systolic coaptation. The MV annulus is not flat but rather saddle-shaped and reaches its nadir in the apical four-chamber view, and even normally coapting MV leaflets may appear to prolapse in this projection. Therefore, current criteria require that MV prolapse be diagnosed only when one or both of the mitral leaflets clearly bulge past the plane of the MV annulus in the parasternal long-axis view. Unfortunately, the degree to which the mitral leaflets must break the plane of the annulus is controversial. The greater the portion of the MV leaflets entering the LA, the more likely the diagnosis: a peak distance behind the annulus of 2 mm almost invariably establishes the presence of MV prolapse. The diagnosis of mild MV prolapse may be assisted by examination of the structure of the leaflets and chordae tendineae, because it has been demonstrated that patients with redundant or thickening valve leaflets (> 5 mm at midleaflet) are at increased risk for complications, including severe MR and infective endocarditis.

The implementation of real-time 3D TEE has provided important information regarding mitral and annular anatomy in patients with MV prolapse. The anterior and posterior mitral leaflets are divided into three segments each, and those involved in the prolapse, as well as the size of the annulus, can be identified. This along with overall evaluation of overall MV structure assist significantly in planning valve repair procedures.

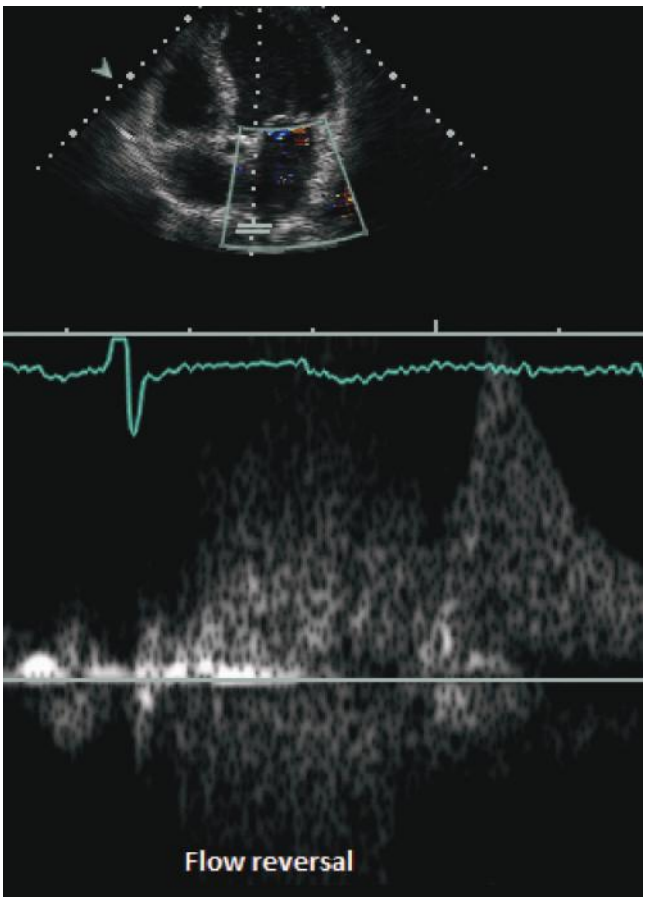


FIGURE 15–81. Pulmonary venous pulsed-wave Doppler in severe mitral regurgitation. The cursor is positioned at the pulmonary vein, and systolic flow reversal (ie, systolic flow into the pulmonary vein) is present.

Torn Chordae Tendineae

Rupture of chordae tendineae may occur spontaneously or in conjunction with MV prolapse or endocarditis. This can result in a flail mitral leaflet and severe MR. Although TTE often detects these lesions (Fig. 15–83), TEE is especially sensitive and accurate and often demonstrates free motion of the leaflet and ruptured chord into the LA, even when TTE is equivocal. As with MV prolapse, the MR jet in this condition is usually eccentric and directed away from the affected leaflet, often *hugging* the adjacent left atrial wall. Therefore, the jet's cross-sectional area may be misleadingly small. The evaluation of mitral valvular anatomy on TEE is also helpful in predicting the feasibility and success of valve repair surgery.

In the setting of ischemic heart disease, both LV enlargement and papillary muscle dysfunction (from infarction or transient ischemia) may cause MR. Both the MR and the contractile abnormality responsible for it are usually well visualized by 2D echocardiography. In rare cases, papillary muscle rupture (partial or complete) occurs in the post-infarction period.

Mitral Annular Calcification

The finding of mitral annular calcification is fairly common in adults and occurs more frequently with advancing age, concomitant hypertension, and renal disease. Although ultrasound cannot discern histology, calcification typically appears as thickened, extremely high-intensity (*bright*) signals (Fig. 15–84). The posterior portion of the mitral annulus is affected much more commonly, and calcification often extends into the posterior mitral leaflet, sometimes restricting its motion. The abnormality, best visualized in the parasternal long- and short-axis views, is seen as a bright calcific density at the junction of the posterior mitral leaflet and the annulus. In the short-axis view, the posterior band of calcification often appears crescentic. Although mitral annular calcification can be extensive, it rarely causes significant mitral inflow stenosis.

RIGHT-SIDED VALVULAR DISEASE AND PULMONARY HYPERTENSION

PULMONIC VALVE

Major structural abnormalities of the PV are relatively rare. *Pulmonic stenosis* (PS) is usually congenital in origin and resembles congenital AS in many respects. The stenotic valve does not open fully and

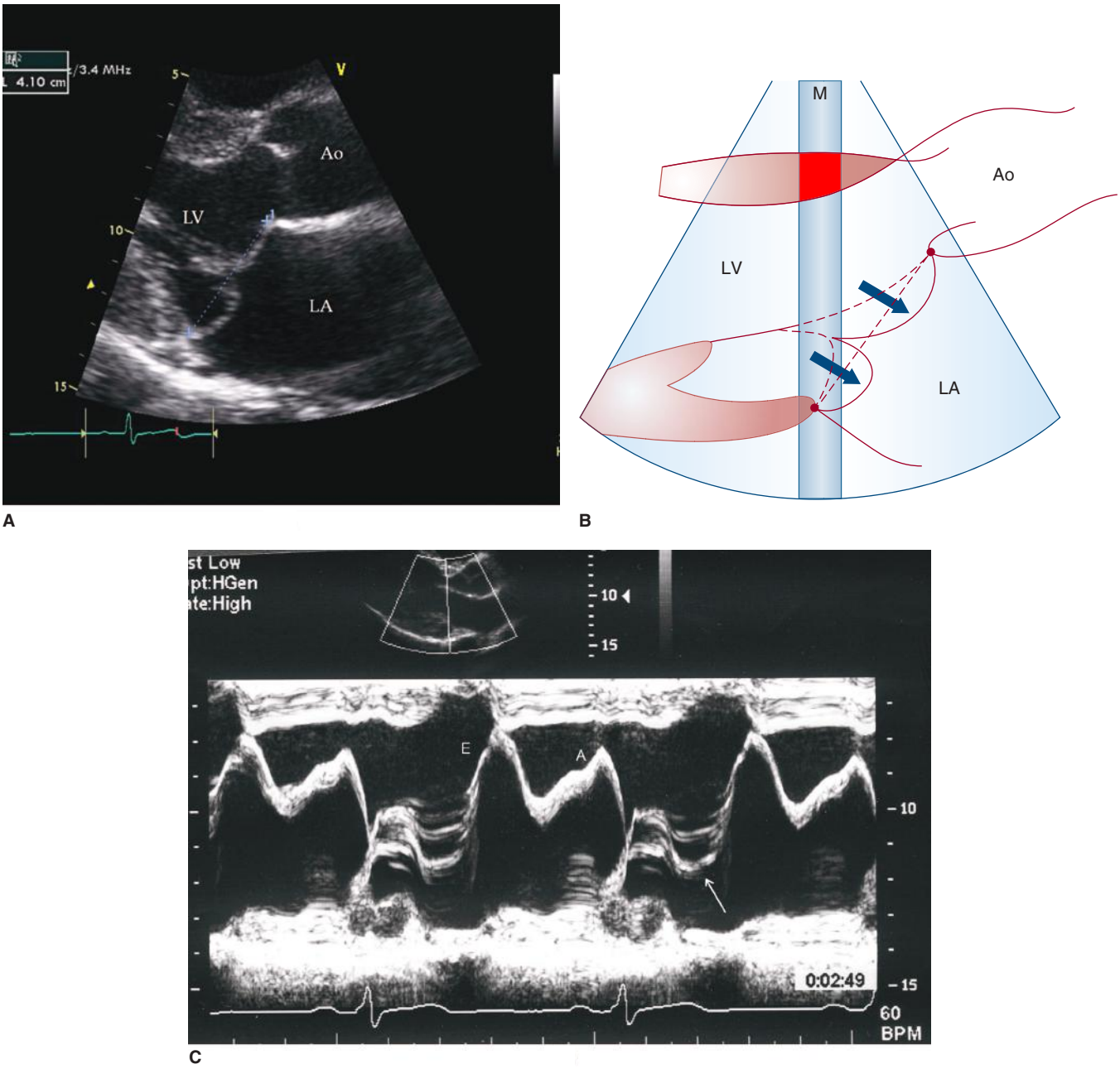
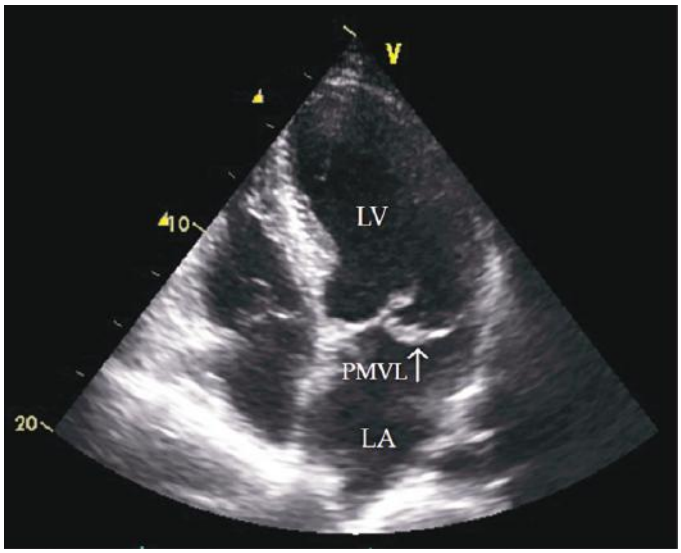


FIGURE 15–82. **A.** Parasternal long-axis plane through the mitral valve in late systole. The plane of the mitral annulus is drawn in a dotted line. The mitral valve leaflets prolapse past the level of the annulus into the left atrium (LA). **B.** Diagram of true mitral valve prolapse. The mitral leaflets clearly prolapse (*arrows*) posterior to the plane of the mitral annulus (*straight dotted line*). **C.** M-mode image through the plane of the mitral valve demonstrating posterior prolapse of the leaflets during systole (*arrow*). A, atrial component; Ao, aorta; LV, left ventricle; E, early diastolic filling; M, M-mode imaging beam. Reproduced with permission from Devereux RB, Kramer-Fox R, Kligfield P: Mitral valve prolapse: causes, clinical manifestations, and management. *Ann Intern Med.* 1989 Aug 15;111(4):305-317.

exhibits characteristic thickening and systolic doming on 2D imaging (Fig. 15–85). M-mode recordings of the PV often show a large a wave, because RV diastolic pressure is often so high and PA pressure so low that the atrial *kick* is sufficient to open the PV. Doppler interrogation reveals turbulent flow distal to the valve, and CW measurements can be used to calculate gradients and valve areas with the Bernoulli and continuity equations much as in AS.[72]

Although severe *pulmonic regurgitation* (PR) is rare, mild PR is common and appears as a flame-shaped flow disturbance in the *RV outflow tract* (RVOT) in diastole. Many individuals have trivial PR on color Doppler examination; this is a physiologic, normal variant (Fig. 15–86). Hemodynamically significant PR is uncommon; when present, it is usually caused by congenital heart disease, valvular tumors, endocarditis, or carcinoid heart disease (see Chap. 51). The echocardiographic grading of PR is semiquantitative, based on the density of the CW envelope, width of the jet at the valve, and flow reversal in the pulmonary arteries.[97] The PR pressure half-time by CW Doppler may be shorter with more severe PR. Measurements derived from the CW Doppler recording also provide estimates of PA end-diastolic pressure (PAEDP) using the Bernoulli equation, as follows:

$$\text{PAEDP} = 4(\text{PR end-diastolic velocity})^2 + \text{central venous pressure (CVP)}$$



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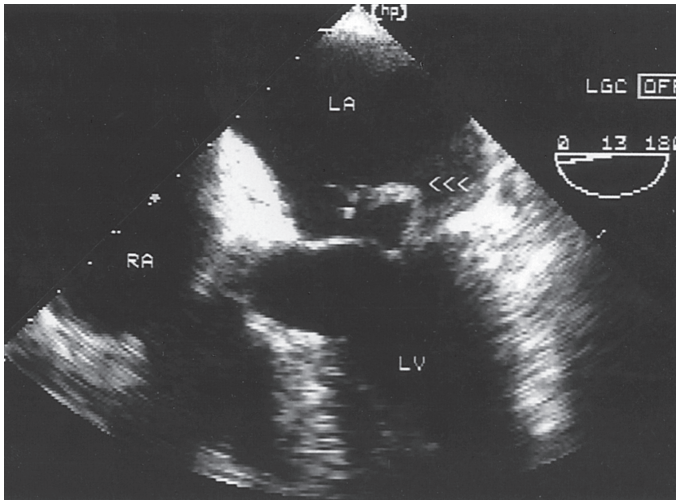


B

FIGURE 15–83. A. Apical four-chamber image of a flail posterior mitral valve leaflet (PMVL). The mitral valve is thickened and myxomatous. **B.** Transesophageal echocardiography image (transverse four-chamber plane) of a flail posterior mitral valve leaflet (*arrows*) secondary to ruptured chordae. LA, left atrium; RA, right atrium; LV, left ventricle.

TRICUSPID VALVE

Tricuspid stenosis (TS) is usually rheumatic in origin, and coexistent mitral and aortic valvular disease is the rule.[72] Congenital or acquired (nonrheumatic) causes of TS are quite uncommon. On rare occasions, TS may be caused by carcinoid heart disease or by leaflet adhesions to permanent pacemaker leads. Regardless of the etiology, diastolic doming of the valve leaflets suggests stenosis. CW Doppler interrogation is also helpful and mimics the findings of MS (high diastolic velocity with prolonged pressure half-time). The pressure half-time equation used to calculate the area of the MV orifice cannot be applied directly to the TV.

Tricuspid regurgitation (TR) is much more common than TS, and, like PR, is present to a mild degree in many normal individuals (see Chap. 51). Like MR, TR may be functional (due to annular enlargement or PH), or valvular (caused by endocarditis, rheumatic valvular disease, CHD [eg, the Ebstein anomaly], carcinoid heart disease, flail TR leaflet,

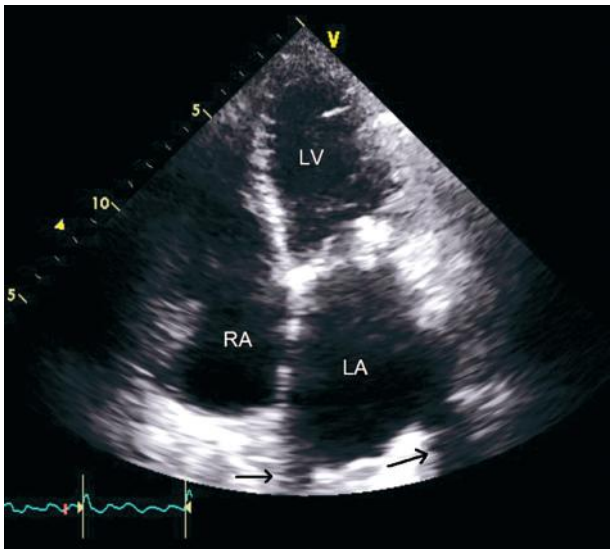


FIGURE 15–84. Apical four-chamber plane demonstrating calcification of the mitral annulus with ultrasonic shadowing posteriorly (*black arrows*). LA, left atrium; LV, left ventricle; RA, right atrium.

and TV prolapse).[98] The echocardiographic approach to TR therefore requires attention to valve abnormalities associated with TR (eg, annular size, incomplete leaflet coaptation, flail leaflet), RV enlargement and function, and PH. However, the accurate quantification of TR severity is difficult. In addition to color-flow mapping (which is semiquantitative), the examination should include the size of the proximal flow convergence zone (see Fig. 15–31), and hepatic vein Doppler (systolic flow reversal within the vein suggests severe TR) (Fig. 15–87).[98] Peak RV (and PA) pressure can be estimated using measurements of peak TR velocity by CW Doppler (see The Bernoulli Equation above). If intravenous echocardiographic contrast (usually, agitated saline will suffice) is needed to accentuate the TR Doppler jet and facilitate more accurate measurements of PA pressure, care should be taken to reset the Doppler gain as the signal may oversaturate.

RIGHT VENTRICULAR FUNCTION AND PULMONARY HYPERTENSION

RV enlargement and PH can be diagnosed and assessed by echocardiography (Fig. 15–88).[99] Because of the asymmetric and crescentic shape of the RV, accurate volume calculations are difficult with standard echocardiography, although 3D is promising in this respect. Nonetheless, 2D imaging provides useful general information regarding RV size and function. In an on-axis apical four-chamber view (with the imaging arc centered through the middle of the LV cavity), the RV should appear somewhat smaller than the LV; therefore, RV enlargement can be diagnosed qualitatively when the RV's cross-sectional area exceeds that of the LV. RV chamber area measurements in the apical four-chamber imaging plane can also be compared with standardized normal values. Measurements of RV wall thickness can be performed from the parasternal or subcostal view; a value of 5 mm is generally accepted as the upper limit of normal.

RV contraction involves both reductions in longitudinal and transverse dimensions—the latter attributable to both septal thickening and free wall shortening. The qualitative evaluation of RV systolic function should be complemented by quantitation of RV fractional area change (FAC) and/or longitudinal motion, including tricuspid annular excursion (TAPSE) and pulsed Doppler evaluation of RV free wall systolic

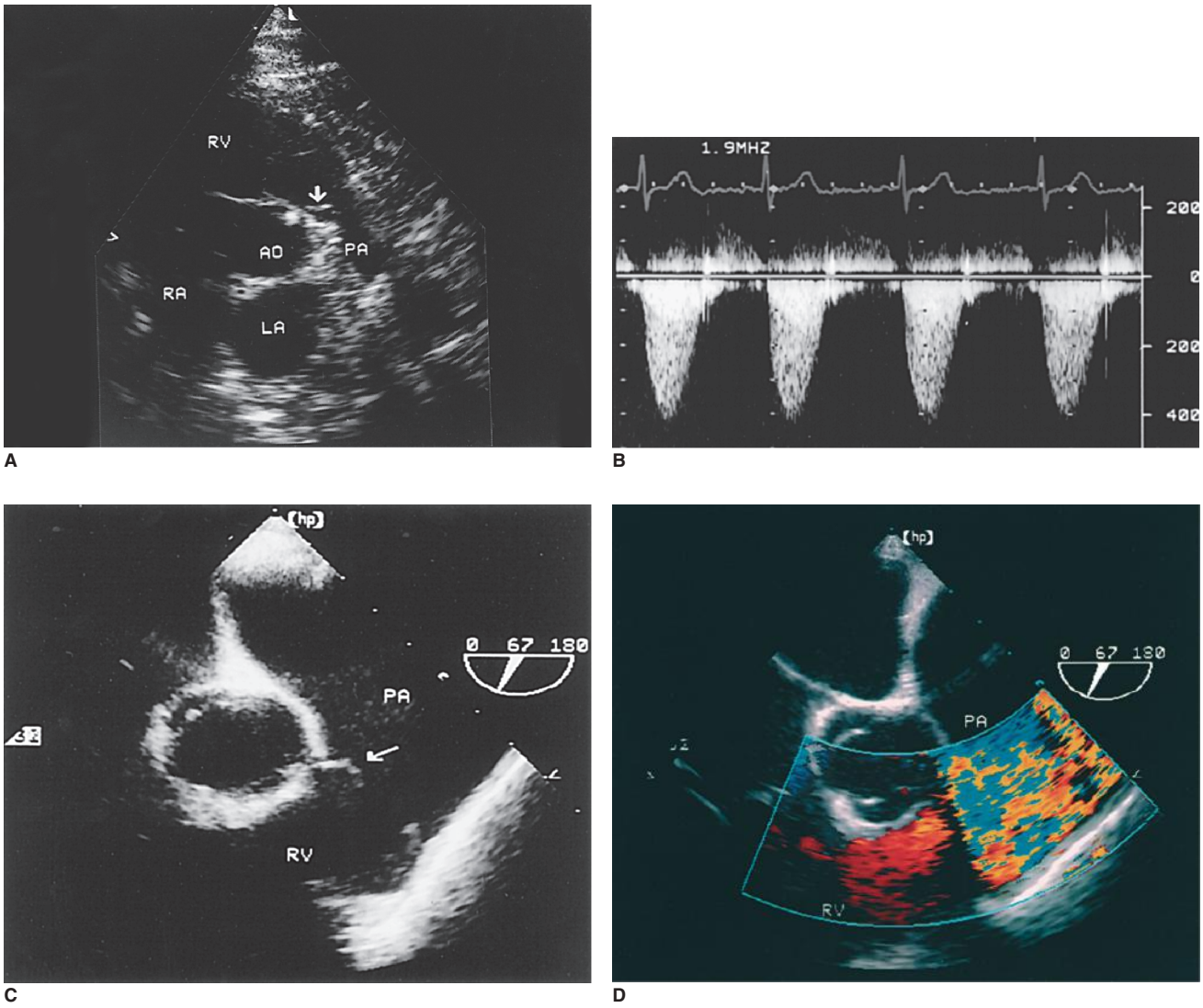


FIGURE 15–85. **A.** Pulmonic stenosis. The pulmonic valve leaflet is thickened and echo-reflective and does not open completely during systole (*arrow*). **B.** Doppler interrogation reveals increased flow velocity (4 m/s) through the valve orifice. **C.** Transesophageal image of pulmonic stenosis. The valve leaflets exhibit doming during systole (*arrow*). **D.** Transesophageal echocardiography image with color Doppler, showing high-velocity, turbulent flow in the main pulmonary artery. Ao, aorta; LA, left atrium; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

motion (RVs'). FAC is measured as the ratio of the difference in systolic to diastolic area to the diastolic area in the apical four-chamber view.

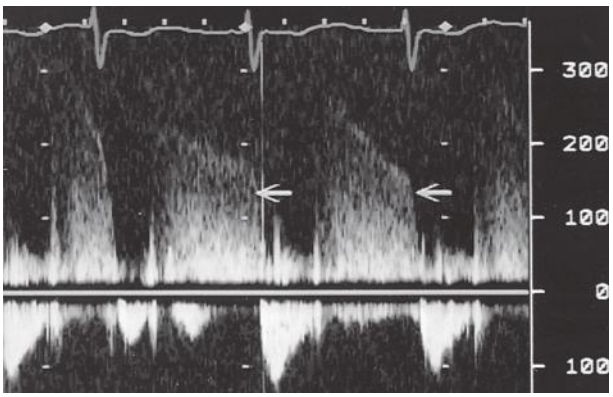
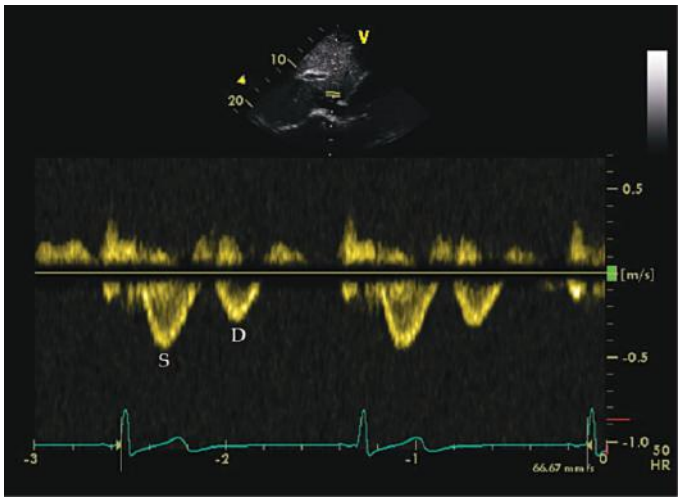


FIGURE 15–86. Continuous-wave Doppler tracing through the right ventricular outflow tract and pulmonary artery (left parasternal transducer position). Mild pulmonic regurgitation is present (*arrows*).

TAPSE is a measurement of the excursion of the tricuspid annular plane in the same view, and both are susceptible to inaccuracies related to image orientation. Motion of the RV free wall toward the interventricular septum should be roughly symmetric; asymmetric hypokinesis of the RV free wall indicates RV dysfunction.

RV volume overload can lead to chamber enlargement, and, in advanced stages, depressed RV systolic function. TR can result from or cause RV overload, and the TR Doppler velocity allows estimation of the peak RV systolic pressure. The interventricular septum also becomes abnormal in RV overload and tends to flatten or even bulge toward the LV (Fig. 15–89). The pattern of septal movement can help distinguish between volume and pressure overload. In pure volume overload, the RV diastolic pressure may equal or exceed that of the LV, whereas the systolic pressure of the LV greatly exceeds that of the RV. Therefore, the interventricular septum flattens during diastole and returns to its normal curvature during systole. With RV pressure overload, however, the abnormally high RV pressures persist through the entire cardiac cycle, and the interventricular septum remains deformed during both systole and diastole.



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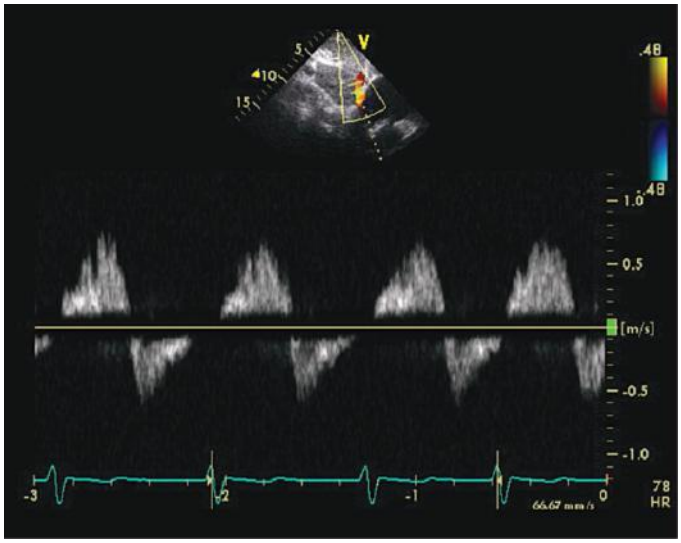
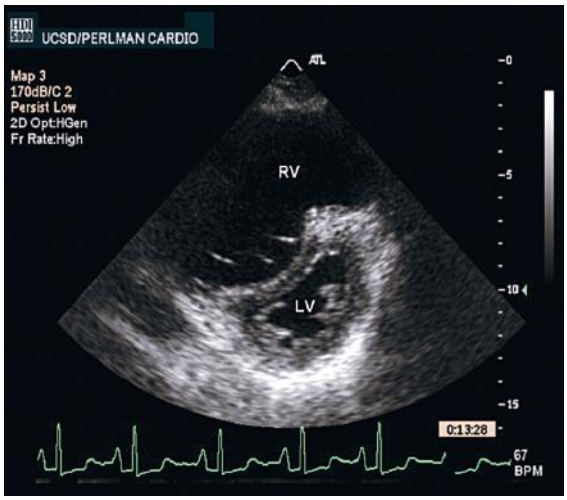


FIGURE 15–87. **A.** Pulsed-wave Doppler tracing of normal hepatic venous flow from the subcostal position. Systolic (S) and diastolic (D) velocities into the inferior vena cava are present. **B.** Pulsed-wave Doppler tracing in severe tricuspid regurgitation. There is systolic flow reversal into the hepatic vein.



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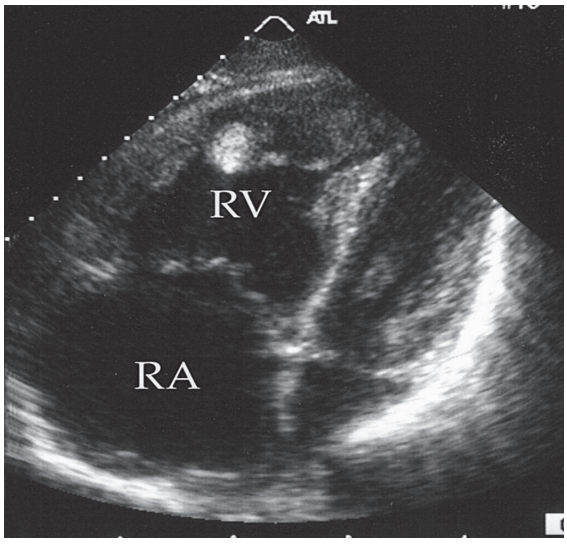


B

FIGURE 15–88. **A.** Parasternal short-axis view in severe pulmonary hypertension with marked enlargement of the right ventricle (RV). The left ventricle (LV) is small, and the interventricular septum is flattened. **B.** Apical four-chamber view in pulmonary hypertension. The right atrium (RA) and RV are much larger than the left-sided chambers.

The hallmark of PH by Doppler echocardiography is a high-velocity TR jet in the absence of PS. Peak TR jet velocity can be converted to peak systolic PA pressure as follows:

$$4(\text{TR velocity})^2 + \text{CVP}$$

where CVP = central venous pressure. In the setting of severe PH, the main PA and the inferior vena cava are often dilated to > 2.4 cm. M-mode examination is less widely used than formerly, but characteristic W-shaped motion of the pulmonic valve leaflets may be a valuable clue to PH if the TR signal is incomplete (Fig. 15–90). The mid-systolic closure of the valve and partial reopening in late systole (sometimes called the *flying W*) may be caused by elevated pulmonary vascular resistance and wave reflection within the PA. Characteristic PWD abnormalities in PH include a decrease in the velocity-time integral of flow through the pulmonic valve (secondary to depressed RV stroke volume) and a shortening of the acceleration time (measured from beginning of flow through the pulmonic valve to peak velocity). The acceleration time (in milliseconds) can be used to estimate the mean PA pressure as:

$$\text{Mean PA pressure} = 80 - (\text{acceleration time}/2)$$

Pulmonic regurgitation is also common in the setting of PH and is usually well recorded by pulsed Doppler. Cross-verification of multiple methods of estimating PA pressure is a good way of ensuring the accuracy of this measurement.[100]

RV hypertrophy and severe PH affect LV diastolic filling characteristics, possibly through septal effects (or by relative underfilling of the left ventricle). Diastolic abnormal relaxation patterns of LV filling (E < A) are common in severe PH, and LV diastolic function often returns to normal if PH is reversed.

PROSTHETIC CARDIAC VALVES

Echocardiography is a critically important tool in the evaluation and serial follow-up of mechanical and bioprosthetic valves. Unfortunately, the increased echo reflectivity of prosthetic valves (especially the mechanical models) causes extensive distal shadowing and reverberations that

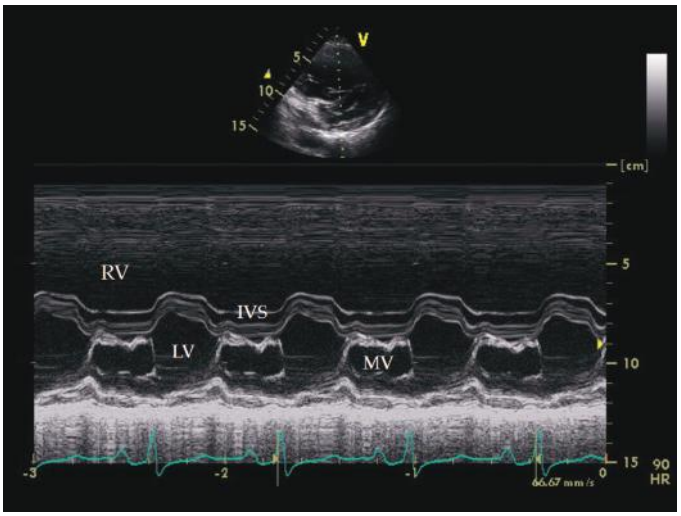


FIGURE 15–89. M-mode in severe pulmonary hypertension. The dimension of the right ventricle (RV) is larger than that of the left ventricle (LV). The interventricular septum (IVS) moves paradoxically (ie, toward the mitral valve [MV] during diastole rather than away).

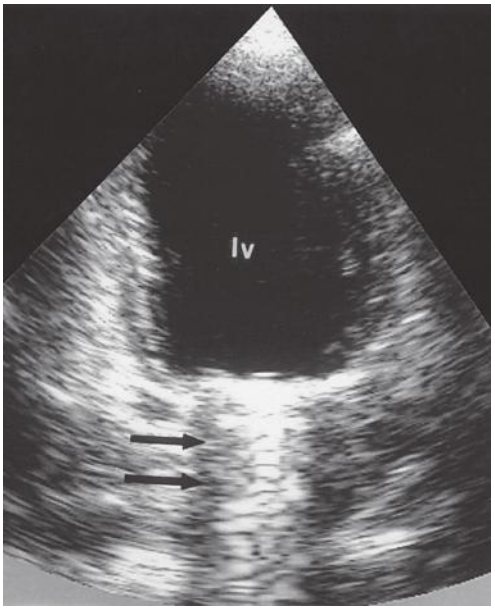


FIGURE 15–91. Apical two-chamber view of a mechanical prosthetic valve (mitral position) during systole. The left atrium is completely obscured by ultrasonic shadowing (*arrows*). LV, left ventricle.

markedly limit the utility of transthoracic 2D echocardiography (Figs. 15–91 and 15–92). TTE imaging may detect partial ring dehiscence, manifested as abnormal *rocking* motion of a prosthetic valve. TTE may also identify reduced movement of the valve disks or leaflets and may occasionally visualize adherent thrombi, tissue ingrowth, and vegetations. Leaflet thickening, detachment, and flail motion also may be visualized for bioprosthetic valves.

Doppler interrogation is the cornerstone of the echocardiographic assessment of prosthetic valvular function, stenosis, and regurgitation.[73] Color-flow imaging can document the presence, direction, and size of the forward flow stream. CFD can also detect regurgitant flow jets; but like 2D imaging, it is limited by acoustic shadowing distal to the prosthesis. Doppler color jets caused by prosthetic AR can be readily visualized from the transthoracic apical view, but jets produced by prosthetic mitral and tricuspid regurgitation are often obscured. Therefore, although detection of prosthetic regurgitation by transthoracic Doppler is usually feasible, quantitation is often difficult. A small flow signal shortly after valve closure may be observed frequently with prosthetic valves and is likely related to the blood caught behind the occluder as it closes.[101]

Doppler flow velocities and gradients through normal prosthetic valves vary depending on the type, position, and diameter of the prosthesis, and a wide range of transvalvular gradients has been reported with normally functioning prosthetic valves. Normal ranges have been reported for various valve types and can be used as a guide to recognize malfunction. These velocities and gradients are flow-dependent as well and therefore also relate to LV function. With aortic valve prostheses, peak systolic Doppler velocities may indicate higher systolic pressure

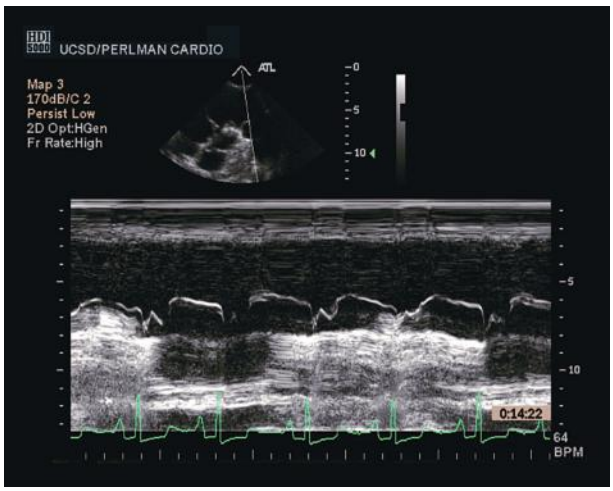


FIGURE 15–90. M-mode image of the pulmonic valve in severe pulmonary hypertension (parasternal transducer position). The A dip is absent, and a characteristic W-shaped motion of the leaflet is present during systole (the "flying W"), indicating partial closure of the valve during mid-systole followed by reopening before diastole.

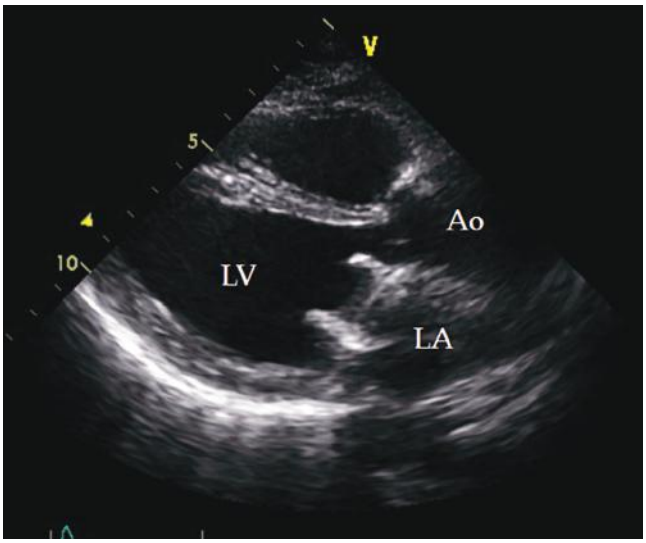


FIGURE 15–92. Parasternal long-axis view of a bioprosthetic valve in the mitral position (two of the three prosthetic valve struts are apparent). Ao, aorta; LA, left atrium; LV, left ventricle.

gradients than those actually found during cardiac catheterization, as a result of the phenomenon of pressure recovery. This problem is more prevalent with St Jude (bileaflet tilting disk) valves than with Medtronic-Hall (single tilting disk) and bioprosthetic valves. Because of these variabilities, an echocardiographic examination is warranted after prosthetic valve implantation to establish its baseline Doppler characteristics. Mean transvalvular gradients calculated by Doppler correlate reasonably well with direct catheter measurements.

TEE is a cornerstone of the diagnostic approach to prosthetic valve dysfunction and is especially useful for assessing mitral prostheses, because it overcomes the problem of left atrial shadowing and reverberation (Fig. 15–93).[73] TEE is extremely accurate in the detection of prosthetic regurgitation and impaired movement of the valve occluder, and it is the diagnostic procedure of choice in most cases of suspected prosthetic valve endocarditis. Small thrombi, tissue ingrowth, infected or sterile vegetations, and even sutures in the sewing ring can usually be visualized. Nearly all mechanical prostheses normally exhibit a small amount of regurgitation, which should not be misinterpreted as pathologic. TEE may also visualize thin, fibrinous strands sometimes attached to prosthetic valves; these structures appear to be a potential source of cardiogenic embolization. Prosthetic valve thrombosis is a potentially fatal medical emergency and TEE can assist in clinical decision making in this disorder.

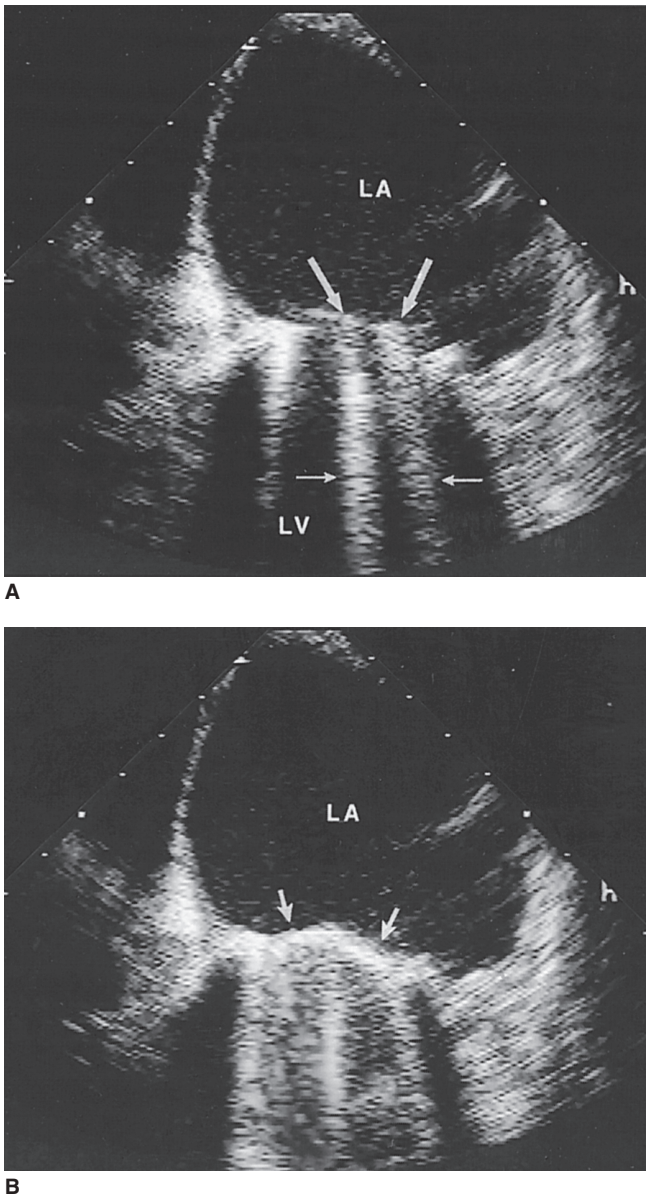


FIGURE 15–93. Transesophageal echocardiography images from a patient with a St Jude prosthetic valve in the mitral position. **A.** Diastolic image. The two struts of the open valve are seen (*large arrows*), as well as their ultrasonic shadows (*small arrows*). **B.** Systolic image. The two prosthetic leaflets are closed (*arrows*) and cast a dense ultrasonic shadow, obscuring the left ventricle (LV). LA, left atrium.

INFECTIVE ENDOCARDITIS

Infective endocarditis remains an all too common illness, with a significant risk of morbidity and mortality (see Chap. 67). Traditionally, the diagnosis is based on either the cumulative results of blood cultures, physical examination, and laboratory findings or on pathologic proof of infected valvular vegetations at surgery or autopsy. In newer clinical algorithms, however, echocardiography is important in the diagnosis of infective endocarditis, as well as detection of associated cardiac abnormalities and hemodynamic dysfunction, prognosis, and the need for surgery.[102] Vegetations can be visualized noninvasively in many cases of endocarditis and have become the echocardiographic hallmark of this disorder.[102] Thus, even though TTE cannot exclude endocarditis, abnormal findings may strongly suggest the disorder, even in the presence of negative blood cultures. Strategies for diagnosis have been devised based on a number of criteria,[103] and definite echocardiographic vegetations are designated as a major criterion. Both TTE and TEE are valuable in the detection of perivalvular abscesses and prosthetic-valve endocarditis. Although there is considerable debate concerning the most accurate diagnostic criteria for endocarditis, echocardiography has become one of the most commonly used techniques for the evaluation of potentially affected patients. Echocardiography (both TTE and TEE) is also useful for evaluation of patients with systemic lupus erythematosus complicated by Libman-Sacks endocarditis (see Chap. 100).

With 2D echocardiography, valvular vegetations typically appear as irregular, usually localized masses of varying echocardiographic density attached to valvular or perivalvular structures (Figs. 15–94 and 15–95) without significantly altering their mobility. The vegetations may be small or quite large and may attach directly to the valve leaflets or the supporting chordal apparatus.[102] Occasionally, vegetations may be attached to unusual structures, such as the atrial wall or the eustachian valve. Aggressive infections often cause perforation or distortion of the affected leaflet, leading to varying degrees of valvular regurgitation. This is distinctly different from most cases of nonbacterial thrombotic (marantic) endocarditis, where the valvular vegetations are usually nondestructive. In cases of infective endocarditis, the presence of vegetations by TTE increases the risk of heart failure, embolic events, and the ultimate necessity of valve replacement. That said, at least 20% of patients with proven native-valve endocarditis have unremarkable examinations. The sensitivity of TTE in prosthetic valve endocarditis is also low (~ 60%) because of technical limitations, especially in the detection of small vegetations.

TEE is significantly more sensitive than TTE for detection of infective vegetations and is extremely helpful for the diagnosis of perivalvular abscesses, mycotic diverticula, and prosthetic valve involvement. The technique is also useful for assessing valvular regurgitation, fistulas (Fig. 15–96), other hemodynamic complications of endocarditis, and risk of embolization.[102] Although a negative TEE examination cannot completely exclude infective endocarditis, it confers a relatively good prognosis in those cases where the diagnosis is eventually confirmed.

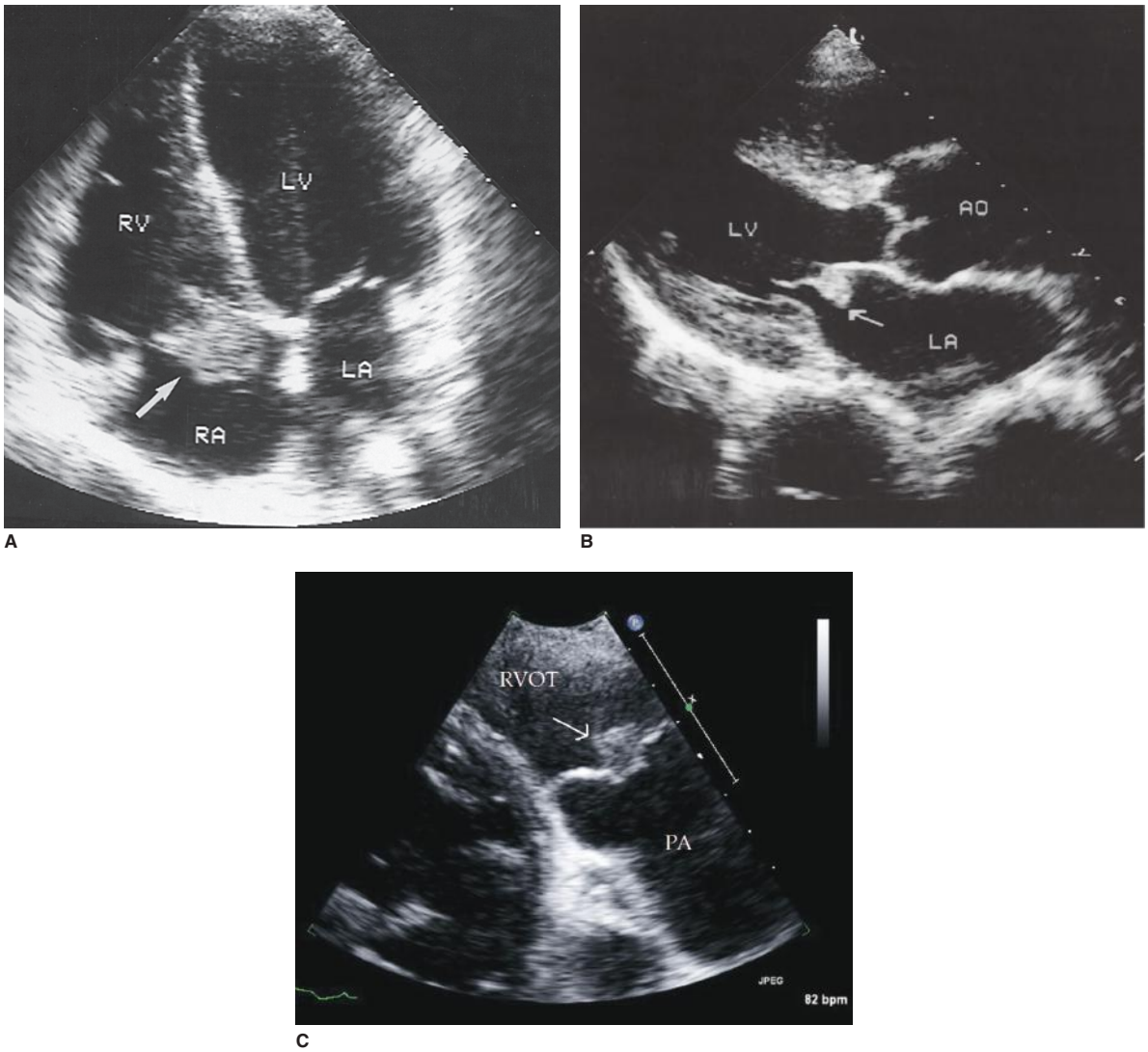


FIGURE 15–94. **A.** Apical four-chamber view demonstrating a large tricuspid valve vegetation (*arrow*). **B.** Parasternal long-axis view demonstrating a vegetation (*arrow*) on the anterior valve leaflet. **C.** Modified parasternal view demonstrating a vegetation (*arrow*) on the pulmonic valve. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract.

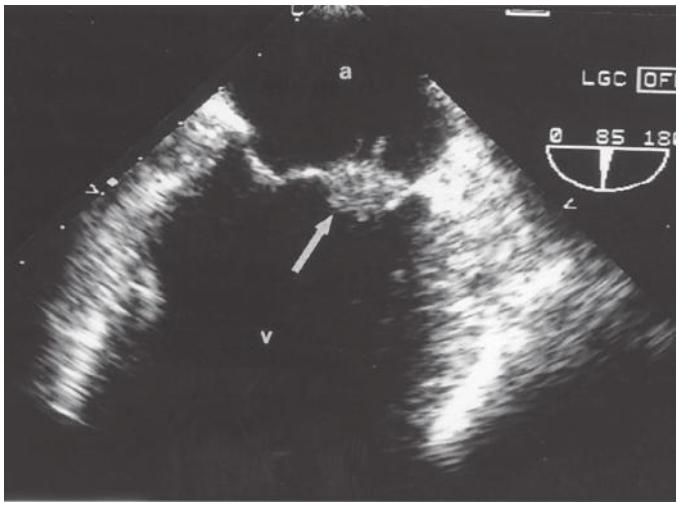


FIGURE 15–95. Longitudinal transesophageal echocardiography view of a large mitral valve vegetation (*arrow*). *a*, left atrium; *v*, left ventricle. Used with permission from William D. Keen, Jr., MD.

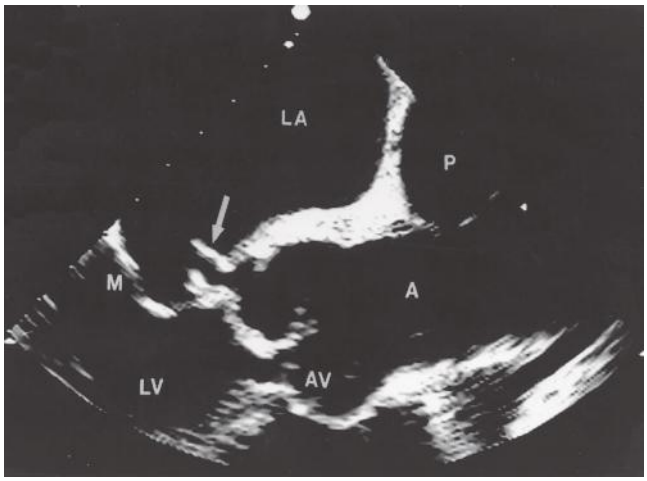


FIGURE 15–96. Longitudinal transesophageal echocardiography image demonstrating a fistula between the aorta (A) and left atrium (LA) in a patient with endocarditis. AV, aortic valve; LV, left ventricle; M, mitral valve; P, pulmonary artery. Reproduced with permission from Sobel JL, Maisel AS, Tarazi R, et al: Gonococcal endocarditis: assessment by transesophageal echocardiography. *J Am Soc Echocardiogr*. 1997 May;10(4):367-370.

The optimal use of TEE in suspected endocarditis remains controversial. A reasonable approach may be to perform TTE as the first screening test in patients with suspected endocarditis. If the study is technically difficult or equivocal, or detects vegetations in patients at high risk for perivalvular complications or hemodynamic compromise, TEE should be performed. If TTE is unremarkable or detects vegetations in patients at low risk for complications, TEE may not be necessary.[71] In high-risk patients (ie, with possible prosthetic valve involvement, congenital heart disease, or infection with virulent organisms), TEE is recommended, even if TTE is normal.[71]

Echocardiographic evaluation of suspected endocarditis has some pitfalls. It may be quite difficult to detect active vegetations in patients with preexisting valvular abnormalities such as calcification, myxomatous change, rheumatic involvement, and healed vegetations. Overreliance on echocardiography may cause mistakes. Therefore, echocardiographic results should be integrated with other clinical information to diagnose this disorder accurately[102] (see Chap. 67).

ISCHEMIC HEART DISEASE

ECHOCARDIOGRAPHY IN CORONARY HEART DISEASE

Cardiac ultrasound—because it is rapid, portable, noninvasive, and inexpensive—is especially well suited to the evaluation of ischemic heart disease. Although visualization of coronary artery structure and flow has been achieved by echocardiography, and the assessment of regional myocardial perfusion with contrast agents is feasible (but difficult), the primary application of echocardiography in patients with coronary heart disease is based on the detection of the effects of myocardial ischemia and/or infarction on LV structure and function.

Interruption of coronary flow or imposition of an oxygen demand that exceeds oxygen supply quickly leads to impaired systolic thickening and excursion of the affected myocardium. If flow is not restored, the affected myocardium may become akinetic or dyskinetic and eventually thinned and fibrotic. In addition, myocardial ischemia produces diastolic dysfunction, which may be detected by analysis of transmitral Doppler flow and myocardial Doppler.

2D imaging is the primary technique for the examination of LV size, wall thickness, myocardial thickening, and regional wall motion, because it enables visualization of all LV wall segments. Standard echocardiographic approaches can be used to calculate LV diastolic and systolic volumes, as well as EF. 3D echocardiographic techniques can be used to enhance the accuracy of volume calculations and regional strain patterns.

The echocardiographic manifestations of CAD consist of one or more of the following:

- Reduction in systolic thickening
- Abnormal segmental wall motion during systole or diastole
- Alterations in the acoustic properties of the myocardium
- Diminished regional blood flow (as measured during the LV myocardial phase after intravenous echo contrast injection)

These abnormalities may be expressed as a disturbance in global LV size and function, an increase in LV volume, and a decrease in left ventricular ejection fraction (LVEF) calculated by standard approaches. In addition, using the standard tomographic planes, the LV can be divided into 16 or 17 wall segments (Fig. 15–97). A 17-segment format has been presented more recently.[21] By grading the contraction of each of the various segments as hyperkinetic, normal, hypokinetic, akinetic, or dyskinetic, a semiquantitative wall motion score can be calculated as the mean numerical value for all segments. Wall motion scores of this kind have been used to assess prognosis in both AMI and chronic CAD. When LV dysfunction is detected echocardiographically, the specific coronary artery responsible can often be inferred based on the hypokinetic region(s). The echocardiographic findings of akinesis with segmental myocardial thinning can also be used to distinguish CAD from dilated cardiomyopathy, which typically manifests global hypokinesis and decreased wall thickness. There is overlap in the echocardiographic findings; severe ischemic disease may cause global hypokinesis, and nonischemic cardiomyopathy may sometimes cause heterogeneous dysfunction.

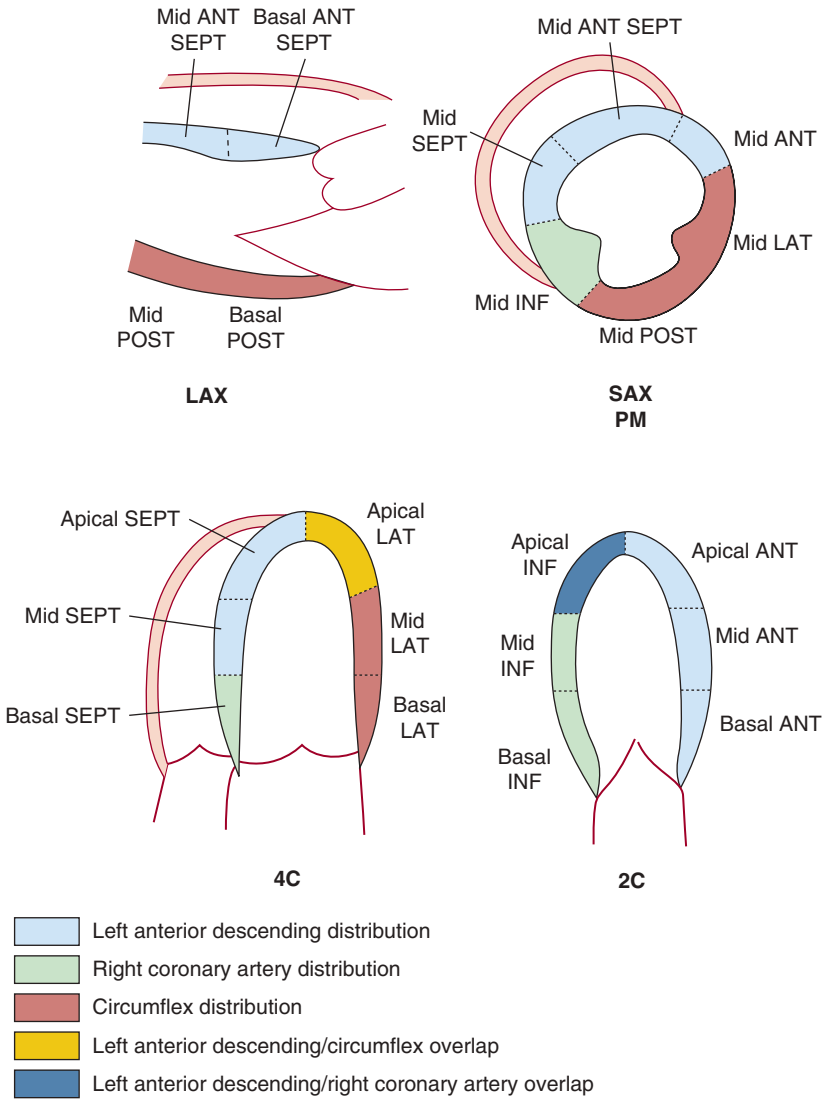


FIGURE 15–97. Sixteen-segment format for identification of left ventricular wall segments. Coronary arterial territories are also included. 2C, apical two-chamber; 4C, apical four-chamber; ANT, anterior; INF, inferior; LAT, lateral; LAX, parasternal long axis; POST, posterior; SAX PM, short axis at papillary muscle level; SEPT, septal. Reproduced with permission from Segar DS, Brown SE, Sawada SG, et al: Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. *J Am Coll Cardiol.* 1992 May;19(6):1197-1202.

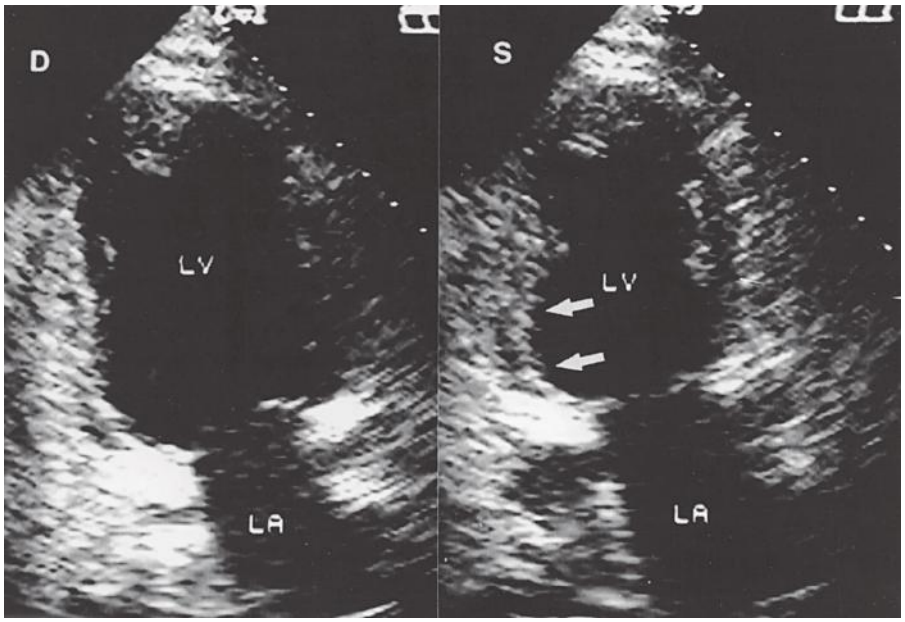


FIGURE 15–98. Diastolic (*left*) and systolic (*right*) images (apical two-chamber plane) from a patient with an inferior wall myocardial infarction. The inferobasal segment is dyskinetic (*arrows*). LA, left atrium; LV, left ventricle.

MYOCARDIAL INFARCTION AND POSTINFARCTION COMPLICATIONS

Cardiac ultrasound has achieved an important role in the evaluation of patients with AMI and is frequently used for diagnosis, quantitative functional assessment, risk stratification, and detection of complications (see Chap. 40). Echocardiography is valuable in excluding transmural infarctions, because these are almost always associated with regional akinesis or dyskinesis (Figs. 15–98 through 15–100).[104] Non-ST elevation infarctions are more difficult to diagnose with certainty. Echocardiography has been used to evaluate chest pain in the emergency department and appears to have a reasonable sensitivity and specificity in the diagnosis of MI.[105] Myocardial contrast echocardiography and LV strain imaging (discussed below) may help detect these smaller infarctions.

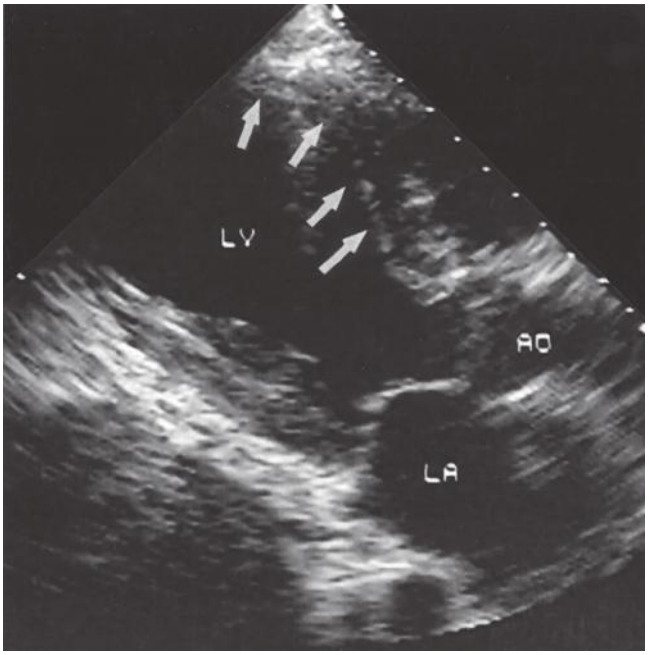


FIGURE 15–99. Parasternal long-axis view of a large anteroseptal myocardial infarction, with thinning and dyskinesis of the anteroseptal wall (*arrows*). Ao, aorta; LA, left atrium; LV, left ventricle.

Echocardiography is now the most commonly used approach to assess the effects of MI on LV function.[105] Ultrasound imaging studies of LV remodeling have demonstrated that infarct expansion occurs commonly with anterior infarctions, often beginning within the first 10 days, and conveys an adverse prognosis. Similarly, calculation of the wall motion score has identified a cohort of post–myocardial infarction patients at markedly increased risk for in-hospital complications. This prognostic marker appears superior to conventional clinical criteria in predicting events.

Echocardiography is probably of greatest value in assessing complications associated with AMI.[105] Most such complications are quickly detected by echocardiography. Severe LV dysfunction resulting in advanced heart failure or shock can be readily identified by echocardiography. In addition, aneurysm formation is usually quite apparent in ultrasonic images. By definition, postinfarction LV aneurysms are recognized as wide-mouthed, thin-walled myocardial segments that display dyskinetic expansion during systole. Aneurysms are a nidus for development of LV thrombi, which are covered in detail in the discussion of cardiac masses below. However, the presence of significant pericardial effusion on echocardiography in patients with hemodynamic compromise in the postinfarction period should suggest free wall rupture. If a free wall rupture is sealed off by clot and pericardial inflammation, a pseudoaneurysm is formed (Fig. 15–101). This lesion is distinguished from a true aneurysm by its highly localized nature and the presence of a narrow neck connecting it with the ventricle. Pseudoaneurysms frequently have multilayered thrombi within them and exhibit characteristic Doppler flow signals at the junction with the ventricle.[106] Because the risk of rupture is high, accurate diagnosis and prompt surgical repair of pseudoaneurysms is important.

Although postinfarction free wall rupture does not always lend itself well to echocardiographic detection, acquired defects of the interventricular septum are more commonly delineated by cardiac ultrasound.[105] Acquired VSDs often consist of a latticework of tissue rather than a discrete orifice, but nevertheless, echocardiographic images can depict absence of myocardium and distinct flow jets communicating between the left and right ventricles (Fig. 15–102). These color jets are typically high-velocity and aliased, coursing from the septum into the RV. The echocardiographic location of the defect and jet correlate well with the location by cineangiography, surgery, or autopsy.

MR is a common sequela of AMI; if severe, it may result in profound congestive heart failure and shock. Several mechanisms may be responsible for the occurrence of postinfarction MR, including dilation of the LV cavity and mitral annulus, papillary muscle dysfunction, and partial or complete rupture of a papillary muscle (Fig. 15–103). MR from papillary dysfunction may lead to eccentric color jets within the LA. Although the recognition and quantitation of MR occurring in the postinfarction period is no different from that of any other type of MR, guidelines differ as to the threshold for intervention.[107] TEE may play an important role in the identification and quantitative assessment of this complication, as well as in ensuring adequate operative repair.

In the setting of inferior wall infarction caused by occlusion of the proximal right coronary artery, RV myocardial infarction may occur.

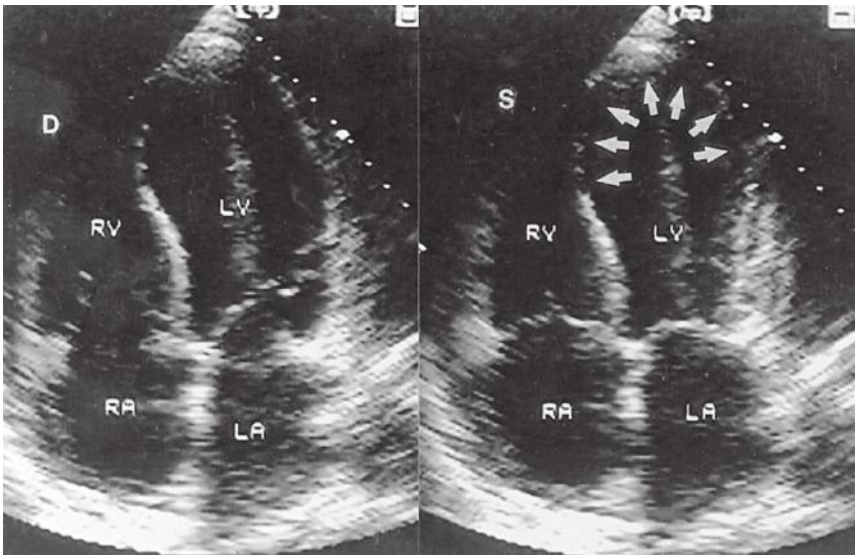


FIGURE 15–100. Apical four-chamber images of a large apical infarction. Diastole (D) is displayed on the left, systole (S) on the right. During systole, the base of the ventricle contracts, but the apex is dyskinetic (*arrows*).

The most specific echocardiographic sign of RV infarction is a regional wall motion abnormality, which is usually best visualized in the RV free wall (Fig. 15–104). RV infarction is typically accompanied by RV enlargement and TR; associated inferior or posterior LV wall motion abnormalities are virtually always present.

Pericarditis is a common complication of AMI, typically occurring during the acute phase of the illness and much less often in the late phases as part of the Dressler syndrome. Postinfarction pericarditis is not typically associated with marked echocardiographic abnormalities.

TEE has assumed a central role in the evaluation of patients with significant hemodynamic abnormalities in the postinfarction period. When TTE is technically suboptimal, transesophageal images can rapidly identify LV dyssynergy, valvular dysfunction, and other abnormalities associated with infarction. TEE may enable direct visualization of acquired VSDs when the lesion is not obvious or seen only as a disturbed flow stream in the RV with transthoracic imaging. Perhaps of greatest significance, TEE can provide definitive identification of a ruptured papillary muscle and a quantitative assessment of postinfarction MR.

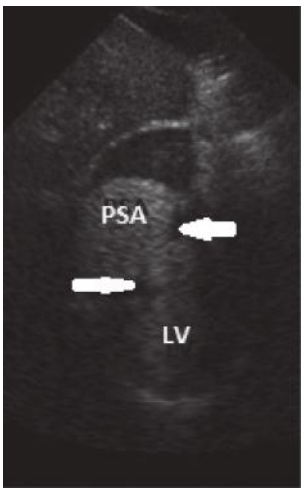


FIGURE 15–101. Subcostal two-chamber view demonstrating a pseudoaneurysm (PSA) at the apex of the left ventricle (LV). *Arrows* point to a narrow "neck."

Echocardiography has been used to evaluate the extent of reperfusion after thrombolytic or interventional therapy for AMI. LV systolic function assessed by 2D imaging improved within hours to days of successful thrombolysis. More recently, contrast echocardiograms obtained after intravenous or direct intracoronary injection have shown that reperfusion of the infarct-related epicardial coronary artery by angiography is not necessarily accompanied by evidence of normal flow in the downstream microcirculation. In addition, this *no-reflow* phenomenon on echocardiography heralds a poor prognosis, including failure of improvement of LV performance, as well as increased late complications.[108]

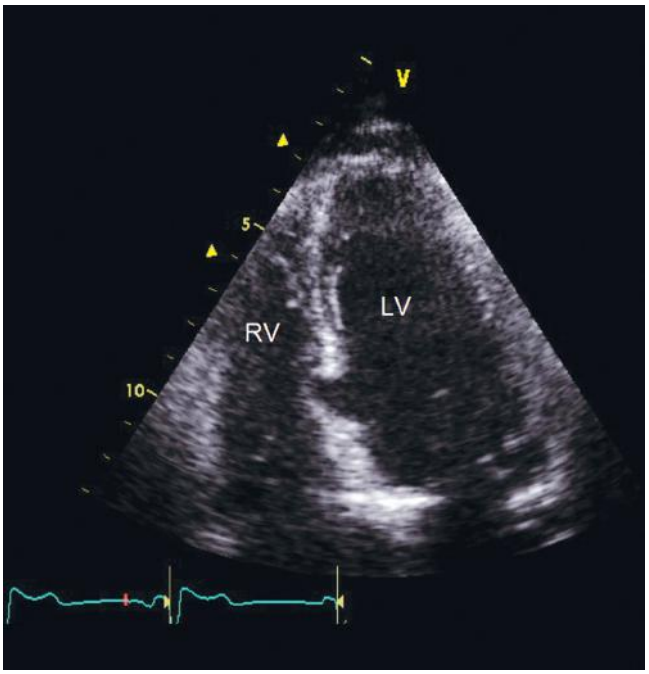
STRESS ECHOCARDIOGRAPHY

The combination of stress testing and echocardiography (stress echocardiography) has assumed an important role in the diagnosis of CAD. Its growth has been assisted by a number of technical advances, including side-by-side review of rest and stress images together in a cine-loop format, harmonic imaging, and LV opacification with intravenous echocardiographic contrast. The application of stress echocardiography is based on the concept that a stress-induced imbalance in the myocardial supply-to-demand ratio will produce regional ischemia and resultant abnormalities of regional contraction, which can be readily identified by echocardiography (Fig. 15–105). The location of wall motion abnormalities may be used to predict the stenosed coronary vessel(s), whereas the ratio of dyssynergic-to-normal myocardium can provide a quantitative assessment of LV ischemia.[109]

The types of stress used fall into two basic groups: exercise and pharmacologic. Exercise testing can be performed either on a treadmill or a stationary bicycle (either upright or supine). Echo imaging usually can be accomplished only before and after treadmill exercise, however, whereas bicycle exertion facilitates the acquisition of images during the exercise protocol. Thus far, treadmill has been the preferred exercise modality. Of importance, all postexertional images should be obtained within a 1-minute window after exercise to avoid missing inducible wall motion abnormalities provoked by stress.

Pharmacologic stress has the advantages of reducing the motion artifact of exercise, enabling continuous imaging throughout the protocol and assessing myocardial viability. Pharmacologic stress echocardiography can use vasodilator agents such as dipyridamole or adenosine, which induce a heterogeneity of myocardial perfusion in ischemic heart disease, or inotropic agents such as dobutamine, which increase myocardial oxygen demand and directly produce ischemia.[110] As with exercise stress, diagnostic criteria include induction of regional wall motion abnormalities and LV dilatation. Although the normal response to exercise is hyperkinesis, the most important comparison is between the thickening and speed of contraction on the rest and stress images, including variations in the degree of hyperkinesis as an ischemia signal may augment sensitivity at the cost of specificity. Dobutamine stress echocardiography appears particularly valuable in detecting myocardial viability.[111]

The safety and accuracy of stress echocardiography for the diagnosis of myocardial ischemia has been examined in several studies.[112] Both exercise and pharmacologic stress carry an extremely low risk of arrhythmia or infarction, but dobutamine can result in hypotension or *systolic anterior motion of the MV* (SAM) with resultant LV outflow obstruction. In general, stress echocardiography and nuclear scintigraphy yield similar results, although stress echocardiography may be



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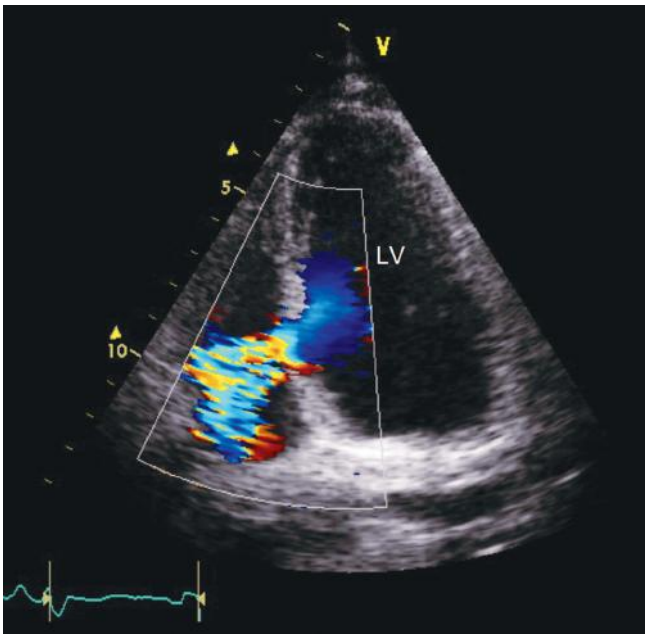


B

FIGURE 15–102. Modified apical four-chamber image of a ventricular septal rupture after myocardial infarction. With two-dimensional imaging (**A**), a defect is seen in the midseptum. With color Doppler imaging (**B**), a high-velocity color jet is seen entering the right ventricle (RV) through the septal rupture. LV, left ventricle.

slightly less sensitive and slightly more specific than scintigraphy. The two techniques are comparable in their accuracy of detecting CAD.[113] The most common clinical application of stress echocardiography is in the diagnosis of CAD in patients with an intermediate pretest probability, and it is clearly indicated where exercise electrocardiography (ECG) alone would be inaccurate because of baseline abnormalities (eg, left ventricular hypertrophy with repolarization abnormalities, paced rhythm, digoxin use in the preceding 2 weeks or ventricular preexcitation).[113] Left bundle branch block has traditionally been listed with the

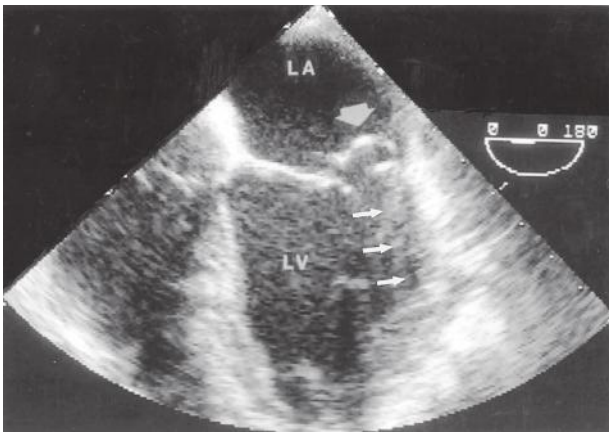
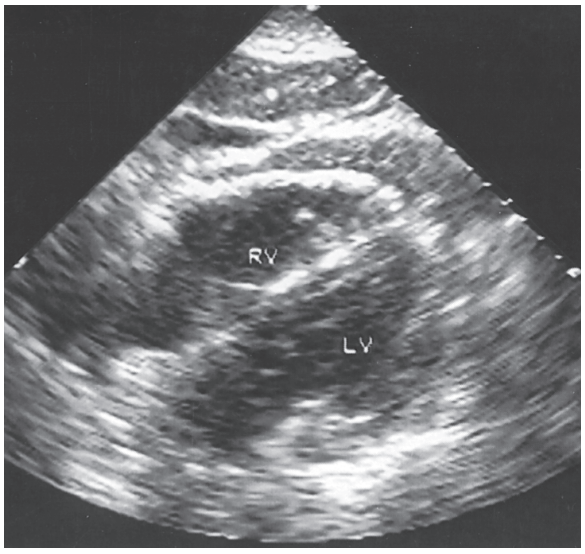


FIGURE 15–103. Transverse four-chamber transesophageal echography image of a posterolateral infarction causing posterior papillary muscle ischemia and partial rupture. The posterior mitral leaflet (*large arrow*) is poorly supported (but not actually flail) and prolapses into the left atrium (LA). The basal lateral wall segment (*small arrows*) of the left ventricle (LV) is dyskinetic.



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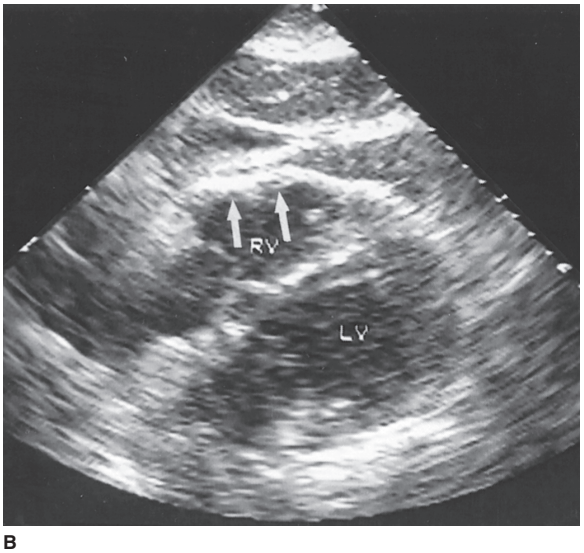

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FIGURE 15–104. Diastolic (**A**) and systolic (**B**) subcostal four-chamber images of right ventricular (RV) myocardial infarction. The RV free wall is dyskinetic (*arrows*) during systole (**B**).

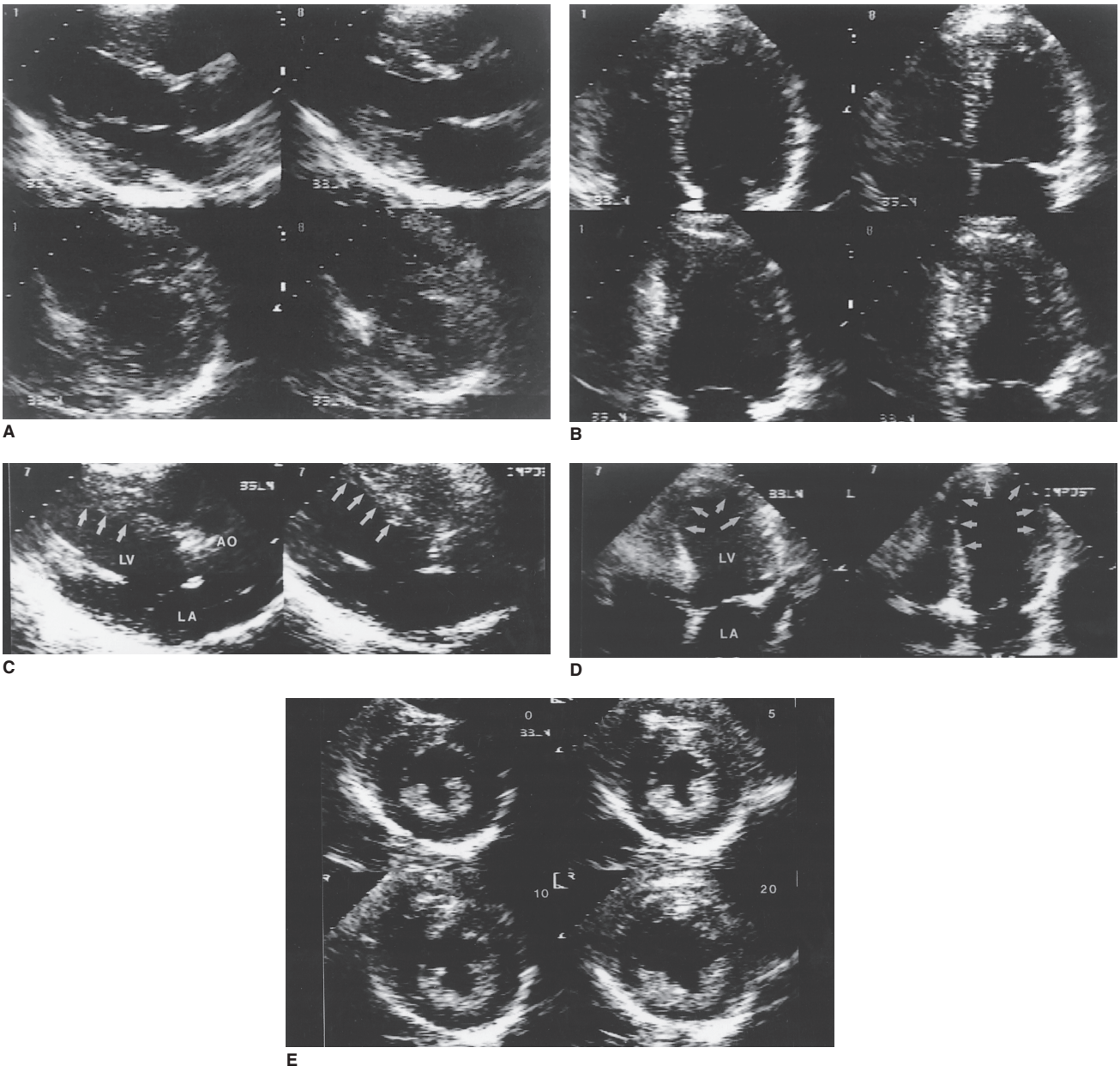


FIGURE 15–105. A. Parasternal views during diastole (*left*) and systole (*right*) from a normal individual. *Upper panels*: long-axis plane; *lower panels*: short-axis plane. **B.** Apical views during diastole (*left*) and systole (*right*) from a normal individual. *Upper panels*: four-chamber plane; *lower panels*: two-chamber plane. **C.** Parasternal long-axis views at peak systole before (*left*) and immediately after exercise (*right*). The anteroseptal wall moves normally at rest (*arrows*) but becomes dyskinetic with exercise. **D.** Apical four-chamber views at peak systole before (*left*) and immediately after exercise (*right*). The apical septal, apical, and apical lateral walls become dyskinetic with exercise, suggesting inducible ischemia in the left anterior descending artery territory. **E.** Parasternal short-axis views (all recorded at peak systole) during dobutamine echocardiography in a patient with three-vessel coronary artery disease. At baseline (*upper left panel*) the left ventricular systolic function is normal. With low-dose dobutamine (5 μg/kg/min; *upper right panel*), function improves. With 10 μg/kg/min, however (*lower left panel*), function is similar to that at baseline. At 20 μg/kg/min (*lower right panel*), systolic function deteriorates and the left ventricle dilates. This response suggests global ischemia induced by dobutamine infusion. Ao, aorta; LA, left atrium; LV, left ventricle.

latter group, but unless image quality is sufficient to assess thickening, assessment of the septum is difficult in this situation and vasodilator stress perfusion scintigraphy is easier and possibly more accurate. Stress echocardiography also adds independent prognostic information to exercise ECG, even in multivessel CAD. Dobutamine echocardiography may aid in the detection of ischemia in patients with cardiac transplantation and allograft vasculopathy (chronic rejection). In patients with known CAD, exercise echocardiography may facilitate localization and quantitation of ischemia, guide revascularization procedures, and assess the functional severity of coronary artery stenoses. Stress echocardiography can also demonstrate resolution of regional ischemia after successful coronary artery bypass surgery or angioplasty, although it is not routinely indicated in asymptomatic patients in such settings.

Stress echocardiography can play an important role in determining the prognosis of patients with CAD.[114] Both exercise and pharmacologic stress echocardiography appear superior to exercise ECG for identification of patients at high risk of recurrent ischemic events after MI. In addition, dobutamine stress echocardiography is useful in predicting perioperative ischemic complications in patients undergoing noncardiac surgery,[114] but careful patient selection is necessary to avoid inappropriate testing where it has strong negative predictive value. Contemporary guidelines recommend noninvasive testing only

in patients in whom the results of such testing would modify management, independent of the surgery or procedure planned (see Chap. 98).

In patients with chronic coronary heart disease, dobutamine stress echocardiography can identify hypokinetic yet viable myocardium and predict improvement in function after successful revascularization.[111] Functional improvement in a hypokinetic segment with low-dose dobutamine infusion that then progresses to hypokinesis or akinesis with higher dobutamine dose (the so-called *biphasic response*) correlates well with the presence of ischemic yet viable (*hibernating*) myocardium. Studies suggest that dobutamine stress echocardiography compares well with positron emission tomography and thallium single-photon emission computed tomography imaging in this regard. The assessment of viability (rather than scar) makes it inherently different from contrast-enhanced magnetic resonance. In addition, quantitation of regional myocardial blood flow using intravenous echo contrast agents may enhance the usefulness of stress echocardiography in the detection of both ischemia and viability.

There is evidence that exercise echocardiography can provide useful information regarding the hemodynamic status and functional severity of valvular heart disease.[115] Specifically, stress echocardiography has been used to assess the degree of obstruction in patients with MS and AS, and contractile reserve. In MS, the critical findings of exercise echocardiography pertain not so much to gradient (which is related to the heart rate), but to the development of PH with exercise. In AS, exercise testing can uncover hitherto inapparent symptoms in asymptomatic patients and dobutamine echo can distinguish true AS from pseudo-AS in patients with low-flow, low-gradient AS with low EF.

Stress echocardiography has many advantages over alternate diagnostic approaches such as radionuclide scintigraphy and coronary angiography. Nonetheless, as is true of all diagnostic modalities, stress echocardiography has certain limitations. High-quality ultrasound images may be difficult to acquire in some patients. Considerable expertise is required to interpret stress echocardiographic images accurately. Perhaps even more concerning, inappropriate use is prevalent with stress imaging, and careful patient selection remains an important cornerstone of a quality imaging service.[116]

THE CARDIOMYOPATHIES

The classification of cardiomyopathies is summarized in Chap. 57. In addition to descriptors of the individual pathophysiologic state, imaging is used to allocate patients into one of three morphologies: dilated, hypertrophic, or restrictive. Dilated cardiomyopathies are associated with myocyte loss and necrosis, a marked increase in LV volume, thinning of the myocardium, and profound systolic dysfunction. Hypertrophic cardiomyopathy (HCM) (see Chap. 59) is recognized by increased myocardial thickness, particularly involving the interventricular septum; preserved systolic function; and often subaortic stenosis induced by systolic anterior motion of the anterior MV leaflet. Restrictive cardiomyopathies may be caused by infiltration of the myocardium by abnormal substances or fibrotic tissue; these cause symmetrical degrees of wall thickening with modest or no diminution of systolic function and little change in cavity size. The role of echocardiography in the measurement of cavity size, wall thickness, and systolic function as the cornerstone of these evaluations is increasingly complemented by tissue characterization from cardiac MRI.

The early phases of dilated cardiomyopathy may be associated with subclinical LV dysfunction, apparent only with deformation imaging.[117] Strain is analogous to regional EF, whereas strain rate is analogous to regional *dP/dt*. These ultrasound measurements have been validated against MRI, which remains the gold standard for noninvasive assessment of LV strain. Strain and strain-rate imaging have shown promise in detecting ischemia and regional dysfunction in the setting of preserved EF[118] and, like tissue Doppler velocity, can be displayed graphically or as a 2D color-encoded parameter. Doppler-derived LV strain is susceptible to artifacts and has been replaced by a newer technique based on tracking the speckles that compose the ultrasound image (speckle strain).

HYPERTROPHIC CARDIOMYOPATHY

HCM is a primary abnormality of the myocardium, often transmitted in an autosomal-dominant pattern, and it involves abnormalities in genes that code for myocardial proteins. Unexplained LV hypertrophy with nondilated ventricular chambers is the cornerstone of this condition, occurring in the absence of another cardiac or systemic disease that would explain the magnitude of hypertrophy. LV hypertrophy may be concentric or involve any portion of the LV, but usually, it affects the septum disproportionately and includes myocyte disarray and scarring (see Chap. 59). The classic echocardiographic findings of HCM are hypertrophy, LVOT obstruction, and diastolic dysfunction (Fig. 15–106).

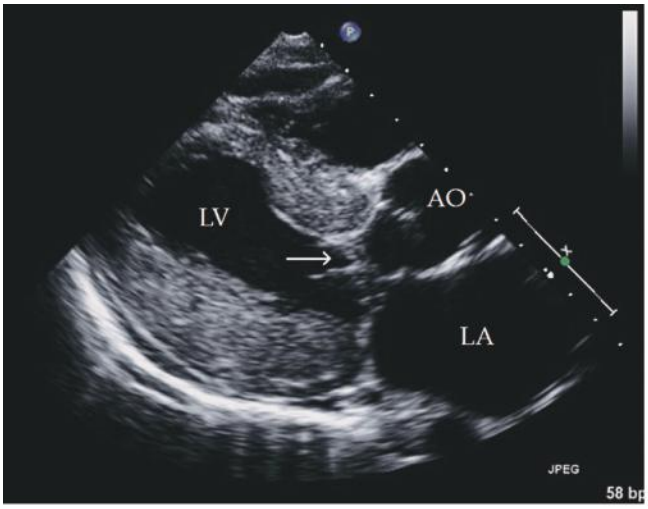
Left ventricular hypertrophy is often severe; the classic finding is *asymmetric septal hypertrophy*, defined as a disproportionate thickness of the interventricular septum compared with the posterobasal wall (ratio of > 1.3:1). Septal involvement is variable, ranging from the entire septum to thickening of the proximal, mid, or distal (apical) septum. Asymmetric hypertrophy of the proximal interventricular septum may lead to dynamic LVOT obstruction (hypertrophic obstructive cardiomyopathy), although this is not a specific marker for HCM. Although a thickness of > 30 mm is one of the risk factors considered in selecting patients for implantable cardiac defibrillator (ICD), nonmassive hypertrophy does not appear to correlate well with risk of sudden death.[119]

Outflow tract obstruction is evidenced by a Doppler gradient, systolic anterior motion of the MV (SAM), and premature aortic closure. Normally, Doppler interrogation of the LVOT produces a spectral tracing that peaks early in systole and has a maximum velocity < 1.7 m/s. The high-velocity systolic jet associated with LV outflow obstruction differs from valvular AS by a later systolic peak, creating a characteristic *saber-tooth* pattern (Fig. 15–107A). Similar Doppler patterns may be seen in hyperdynamic states if systolic obliteration of the hypertrophied LV causes localized areas of high flow velocity in the LV cavity. LV cavity obliteration produces a very late systolic rise in flow velocity (see Fig. 15–107B), distinct from LVOT obstruction.

SAM, which usually involves the anterior MV leaflet, results from contributions to this process from changes of LV morphology, papillary muscle position, and length of the mitral leaflets—the role of the Venturi effect in the LVOT is probably less important than previously thought. Because of disruption of mitral coaptation during systole, SAM is associated with MR of variable severity. SAM is not pathognomonic for HCM and can occur in other conditions involving hyperdynamic LV function (eg, hypovolemia, anemia) and/or anterior displacement of the annulus (eg, use of a rigid mitral ring in mitral repair).

Mid-systolic closure of the AoV (see Fig. 15–106E) is best seen on M-mode recordings, and it is probably a manifestation of the sudden pressure drop during mid and late systole caused by SAM. Mid-systolic aortic closure is not specific for HCM and can occur in MR, aortic dilatation, VSD, low cardiac output states, and discrete subaortic stenosis.

Diastolic dysfunction occurs in HCM resulting from abnormalities of myocardial relaxation and compliance. These may manifest as a typical relaxation abnormality—a reduced early diastolic (*E*) velocity, a prolonged deceleration slope of the E wave, and an increased velocity of the atrial systolic (*A*) component—but may also manifest as a pseudonormal LV filling pattern.[120]



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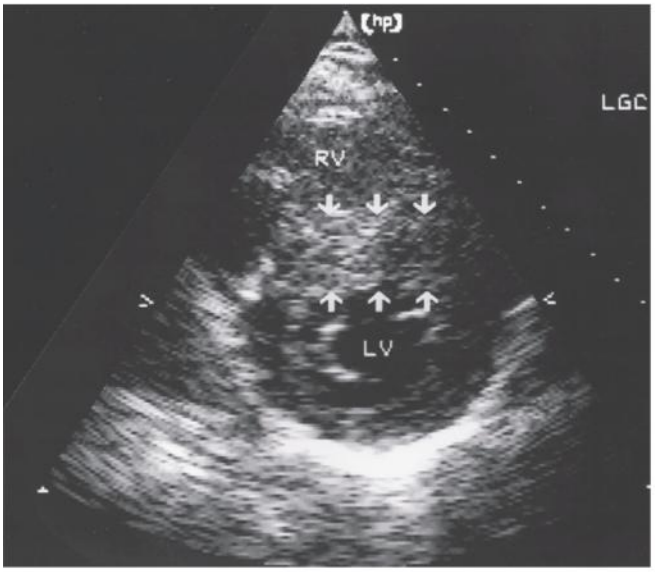

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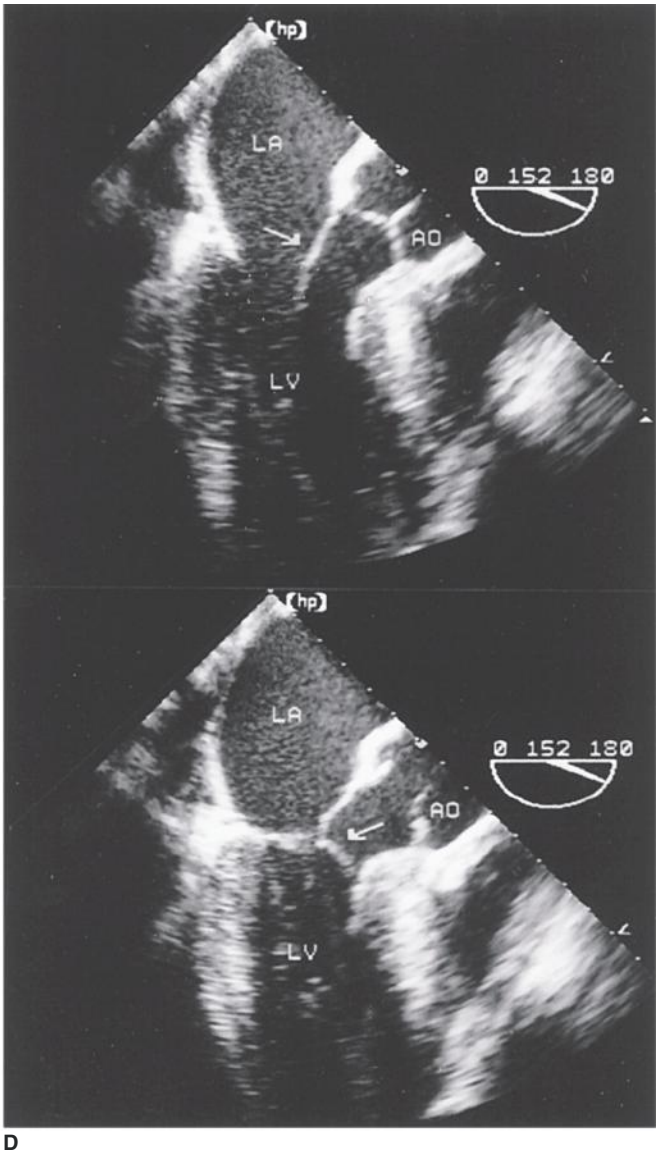

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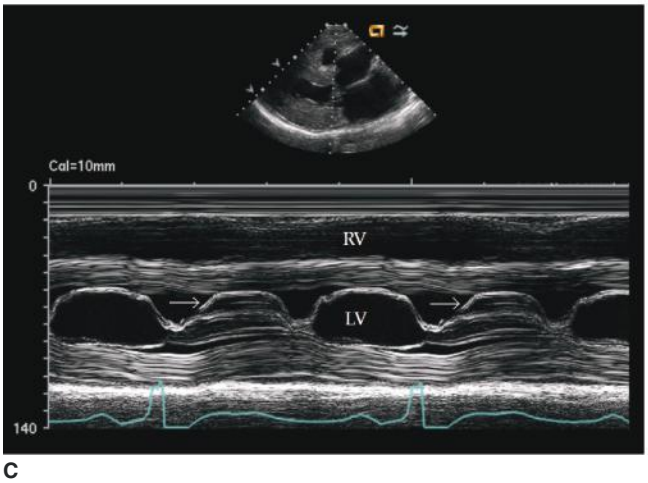

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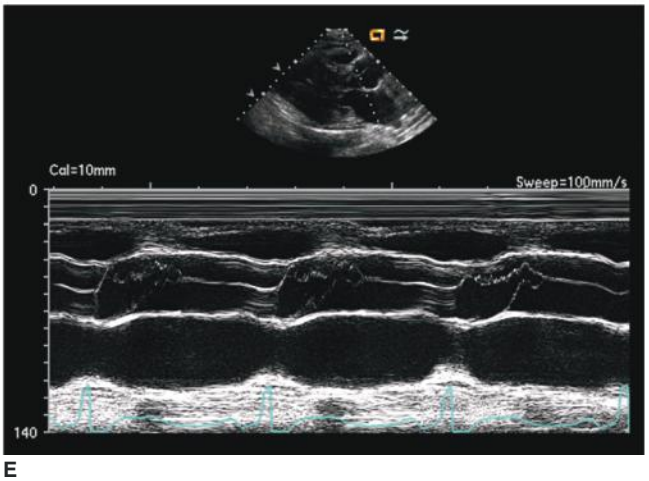
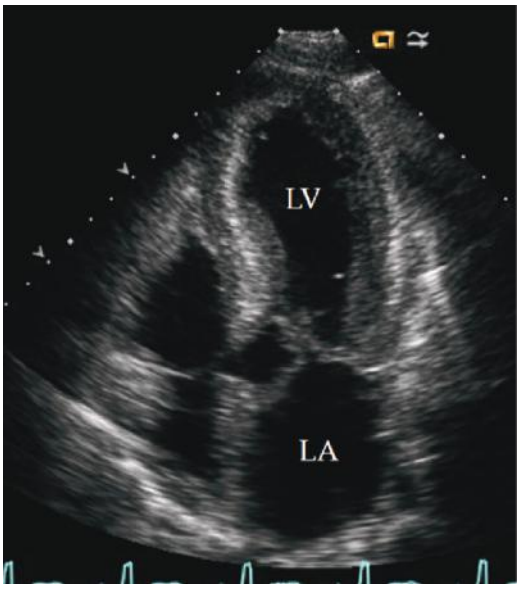


E

FIGURE 15–106. **A.** Parasternal long-axis view (during systole) of hypertrophic cardiomyopathy (HCM). Severe LV hypertrophy is present, as is systolic anterior motion of the anterior mitral valve leaflet (*arrow*). **B.** Parasternal short-axis view of HCM. Asymmetrical septal hypertrophy is present (*arrows*). **C.** Parasternal M-mode image from a patient with HCM, demonstrating systolic anterior motion of the anterior mitral valve leaflet (*arrows*). **D.** Transesophageal image of HCM. The anterior mitral valve leaflet appears normal during diastole (*upper panel*), but systolic anterior motion occurs during systole (*lower panel*). **E.** Parasternal M-mode tracing through the aortic valve. There is mid-systolic notching and partial closure of the aortic valve leaflets. (*continued*)



F

FIGURE 15–106. F. Apical four-chamber image of HCM during systole, demonstrating systolic anterior motion of the mitral valve. AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (*continued*)

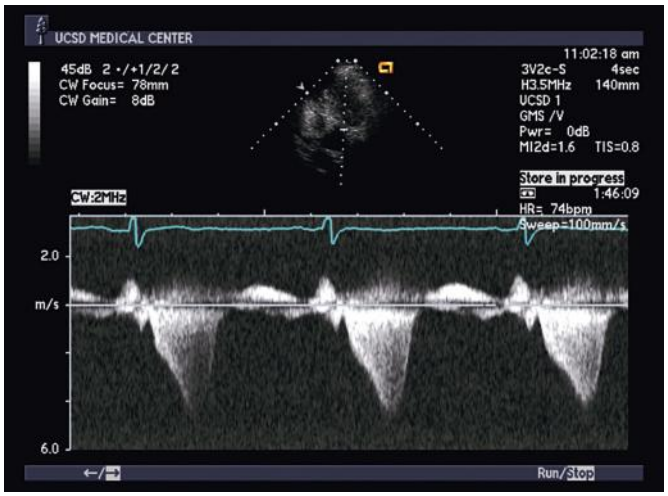
DILATED CARDIOMYOPATHY

In cases of *dilated cardiomyopathy* (DCM), the heart is typically greatly enlarged and systolic function is markedly depressed (see Chap. 58). Four-chamber dilatation is a common but not uniform finding, because some patients may have relatively preserved RV size. Marked LV enlargement and generalized dysfunction can also be caused by severe ischemic heart disease, chronic alcohol abuse, various infectious myocarditides, anthracyclines and other cardiotoxic agents, nutritional deficiencies, and hereditary myopathies. Severe ischemic disease is often segmental, whereas the LV dysfunction of DCM is usually global. The echocardiographic findings in DCM include an increased LV end-diastolic diameter and volume with decreased fractional shortening, thinning LV walls (Fig. 15–108A), increased E point-septal separation, LA enlargement, and limited mitral and AoV opening (caused by low stroke volume). Recognition of intracardiac thrombi—most often found in the LV apex—may require contrast LV opacification. M-mode imaging of the mitral leaflets may demonstrate a *B bump*, or notch just before systolic valve closure, indicating elevated LV diastolic pressure (see Fig. 15–8). Mitral annular dilatation and secondary MR are common.

Doppler echocardiography often reveals an abnormally low-velocity time integral in the LV outflow or inflow tracts. Diastolic MR caused by elevated LV diastolic pressure also may be present. Diastolic dysfunction is common, and PWD interrogation of mitral inflow may show an abnormal relaxation, restrictive, or pseudonormal pattern depending on LV diastolic pressures and loading conditions.[120] A restrictive pattern of mitral inflow Doppler confers a poor prognosis in patients with DCM. Diastolic tissue Doppler velocities of the mitral annulus are almost always abnormally diminished.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy may be idiopathic or secondary to infiltrative diseases such as amyloidosis, hemochromatosis, hypereosinophilic syndrome and Loeffler endocarditis, sarcoidosis, radiation toxicity, glycogen storage diseases, and Gaucher disease (see Chap. 61). Typical 2D echocardiographic features of these diseases include (1) a diffuse increase of ventricular thickness in the absence of marked ventricular



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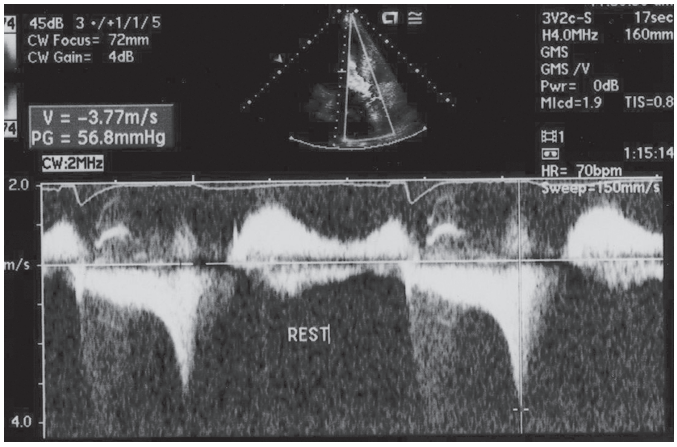
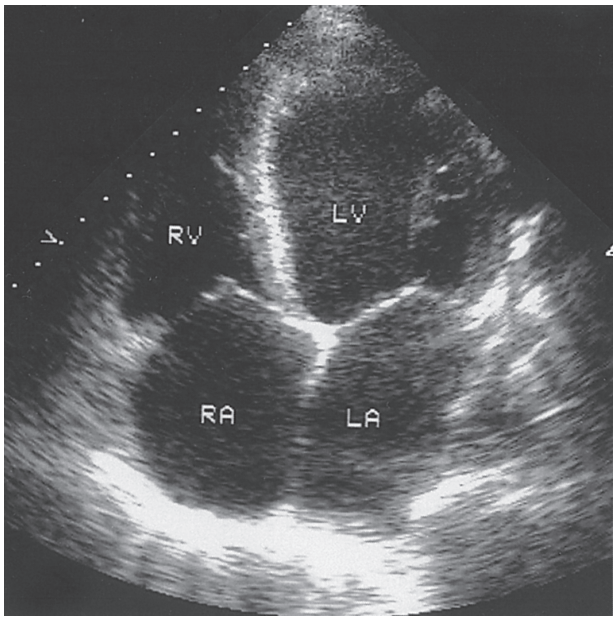


B

FIGURE 15–107. A. Continuous-wave Doppler tracing through the left ventricle (LV) outflow tract (from the apical transducer position) in hypertrophic obstructive cardiomyopathy. In comparison with valvular aortic stenosis, the rise in velocity is delayed (reflecting dynamic rather than fixed outflow obstruction). **B.** Continuous-wave Doppler tracing through the LV (from the apical transducer position) in LV hypertrophy with end-systolic LV cavity obliteration. The very late systolic rise in blood velocity is more consistent with obliteration than true LV outflow tract obstruction.

chamber dilation and (2) severe diastolic dysfunction and marked biatrial enlargement (Fig. 15–108B). EF is often modestly decreased, although myocardial deformation shows more substantial reduction, tissue Doppler of the mitral annulus is often markedly reduced—an e′ velocity < 5 cm/s should raise concerns about infiltration.

Amyloidosis is generally the most commonly encountered restrictive cardiac disease.[121] In addition to biventricular hypertrophy, advanced amyloidosis is also associated with diffuse thickening of the interatrial septum and cardiac valves. In advanced disease, depressed systolic function is also common. An abnormal *speckled* pattern or *ground glass* appearance of the myocardium has been described on 2D echocardiography, but this sign has become difficult to interpret in the era of harmonic imaging. More useful is the apical sparing pattern of myocardial strain.[122] A restrictive mitral inflow pattern on Doppler echocardiography is identified as a marker of advanced disease and poor prognosis. In addition to increased myocardial thickness, endocardial thickening and fibrosis as well as restricted atrioventricular leaflet motion are common features of Loeffler endocarditis and endomyocardial fibroelastosis. Intraventricular thrombi are also common in these processes.



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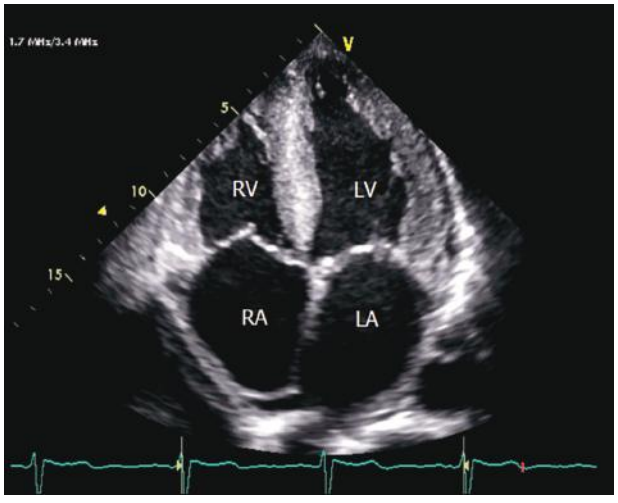


B

FIGURE 15–108. **A.** Apical four-chamber image of dilated cardiomyopathy. There is four-chamber enlargement as well as left ventricular (LV) spontaneous echo contrast. **B.** Apical four-chamber image of cardiac amyloid. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

OTHER CARDIOMYOPATHIES

Takotsubo cardiomyopathy (also called *stress cardiomyopathy* or *apical ballooning syndrome*) is a syndrome of sudden-onset chest pain associated with significant LV dysfunction but no occlusive coronary disease and only minor troponin elevations.[123] The current diagnostic criteria include (1) transient hypokinesis or akinesis in the LV midsegments with or without apical involvement, wall motion abnormalities that extend beyond a single coronary vascular distribution, and often, a stressful trigger; (2) the absence of obstructive coronary disease or acute plaque rupture; (3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or minor elevation in cardiac troponin; and (4) the absence of pheochromocytoma and myocarditis.[124] 2D echocardiography is well suited for evaluation in this setting and often shows dramatic apical ballooning with preservation (or hyperkinesis) of the LV basal segments (Fig. 15–109A and B). Long-term prognosis is generally—although not uniformly—good, but recurrences can occur.[123]

LV noncompaction is an uncommon form of cardiomyopathy that is characterized by a prominent noncompacted layer of myocardium lining the cavity of the left ventricle[125] (Fig. 15–109C and D). The LV apex is especially affected. Echocardiographic studies have suggested a prevalence of approximately 0.05% in the population, although recent reports suggest the prevalence may be higher.[126] The presence of a ratio of > 2.0 between the systolic thicknesses of the noncompacted and compacted myocardial layers is currently considered diagnostic of noncompaction.[127] The disorder may be accompanied by LV systolic dysfunction and heart failure, malignant arrhythmias, and thromboembolism. In addition, LV noncompaction can accompany congenital heart conditions, including Ebstein anomaly, ventricular septal defect, and congenital aortic valvular disease.

VENTRICULAR DYSSYNCHRONY AND CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy (CRT) has emerged as a potential means of both improving function and survival in patients with heart failure and left bundle branch block.[128] However, about 30% of patients do not show a beneficial response to CRT.[129] Although most benefit seems to be derived by improving mechanical dyssynchrony,[130] the use of various imaging methods to select patients for CRT remains unproven. Bax and coworkers[131] measured time to peak systolic velocity (from QRS onset) in the basal septal, anterior, lateral, and posterior segments and found that a difference of > 65 milliseconds between two opposing walls correlated strongly with a favorable response to CRT. However, in mid-2008, the multicenter Predictors of Response to CRT (PROSPECT) trial[132] showed that these indicators of dyssynchrony did not provide additional information about response to resynchronization therapy over and above the standard indicators for CRT (ie, LVEF < 35%, QRS > 130 milliseconds, and symptoms despite optimal medial therapy). Subsequently, based on results with speckle tracking of radial and circumferential planes,[133] recent studies have shown the best results to occur when the pacing lead is positioned in the segments of maximal delay.

CONGENITAL HEART DISEASE

ECHOCARDIOGRAPHIC IDENTIFICATION OF CONGENITAL CARDIAC ANOMALIES

Echocardiography and Doppler have had a major impact on the diagnosis and management of patients with CHD (see Chaps. 55 and 56). The long-term survival of patients with congenital heart lesions has added to small numbers of adult patients with unrecognized congenital lesions, to lead to a growing group of patients with *grown-up congenital heart disease*.[134] From isolated congenital lesions to complex, extensive cardiac malformations, echocardiographic imaging (often with 3D imaging and/or intravenous contrast injection) is able to delineate cardiac anatomy. TEE is an important adjunctive technique, and cardiac magnetic resonance, with its ability to align imaging planes independent of echo windows, is often used. Together, these noninvasive tests may obviate the need for cardiac catheterization and angiography.

The ultrasound diagnosis of a simple intracardiac shunt is usually straightforward, but the task of defining complex congenital cardiac abnormalities can be daunting. It is useful to remember a few basic anatomic rules;

- The venae cavae and pulmonary veins generally empty into the morphologic RA and LA, respectively.

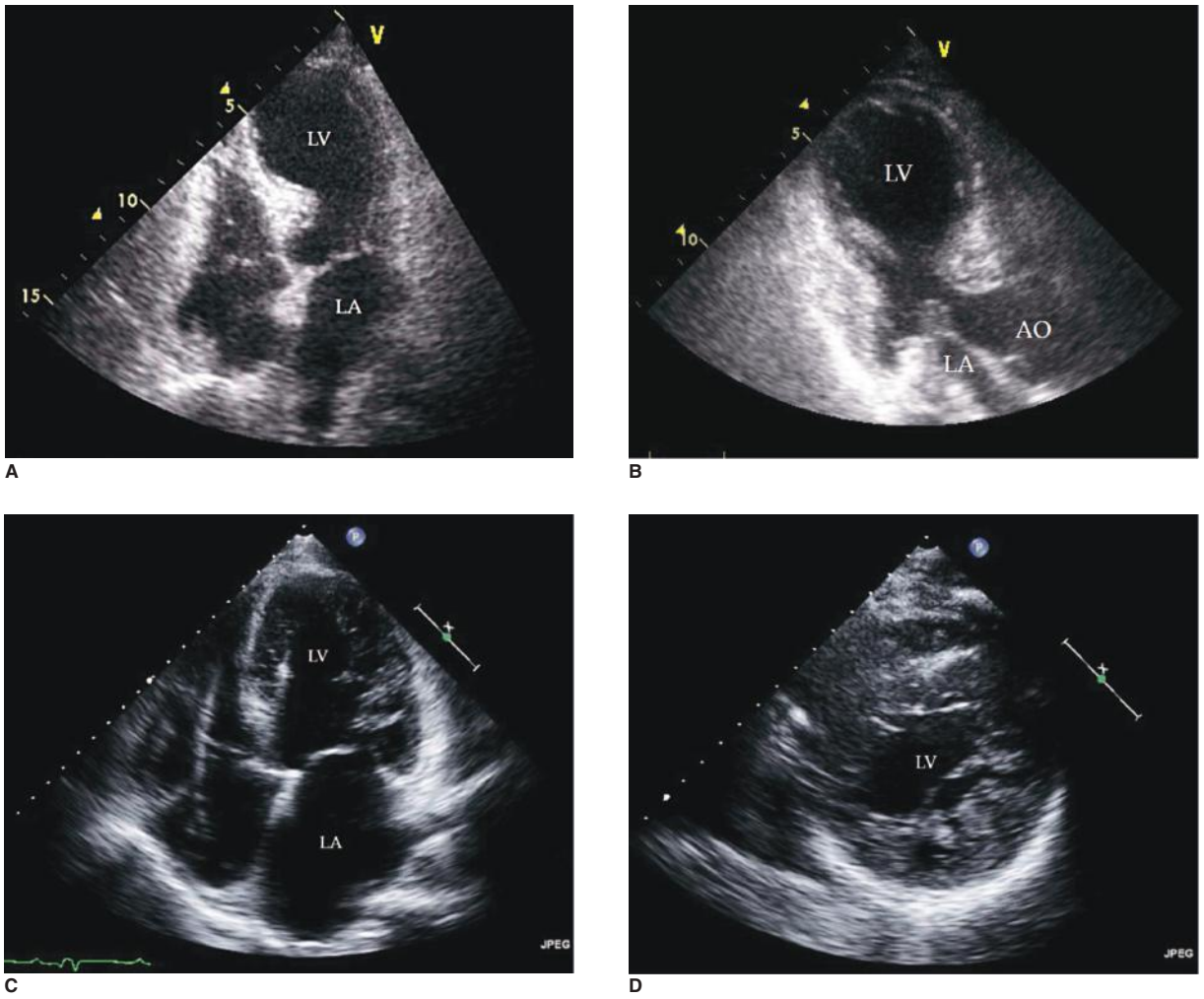


FIGURE 15–109. Takotsubo cardiomyopathy. Marked systolic apical ballooning with preservation of left ventricular basal function is shown in the apical four-chamber (**A**) and three-chamber (**B**) views. Left ventricular noncompaction. Extensive left ventricular trabeculation is present in the apical four-chamber (**C**) and parasternal short-axis (**D**) planes. A right ventricular pacing lead is also present in the apical four-chamber image. LA, left atrium; LV, left ventricle; AO, aorta.

- The atrioventricular valves uniformly follow their ventricles through embryologic development: A TV accompanies the morphologic RV and an MV accompanies the morphologic LV.
- The semilunar valves follow the great vessels. The aorta and PA can be distinguished, regardless of their position, by the bifurcation of the PA.

The RV has a moderator band, coarser trabeculations than the LV, an infundibulum that separates the inlet area from the RVOT, and a tricuspid atrioventricular valve. The tricuspid annulus is positioned slightly closer to the cardiac apex.

CARDIOVASCULAR SHUNTS

Atrial Septal Defect

Most secundum and primum *atrial septal defects* (ASDs) are easily visualized by echocardiography, but sinus venous defects are often difficult to detect without TEE. Often, the subcostal view provides the optimal imaging plane to detect lesions of the atrial septum.[135] Ostium secundum defects are the most common form of ASD—the localized absence of septal tissue in the midportion of the interatrial septum (Fig. 15–110A) may be difficult to see and contrast should be used if the diagnosis is suspected from physical examination, ECG, or unexplained atrial or RV enlargement. Lack of any interatrial septal tissue between the defect and the base of the interventricular septum characterizes an ostium primum defect (Fig. 15–110B). Although ostium secundum defects are usually isolated, ostium primum (or partial AV canal) defects are often accompanied by other lesions (Fig. 15–110C). Sinus venosus defects are strongly associated with partial anomalous pulmonary venous return (Fig. 15–111A). Rarely, the atrial septum may be completely absent (Fig. 15–112). With all but small ASDs, the RA is enlarged and RV volume overload is present, with a dilated RV and paradoxical septal motion.

Intravenous contrast injection generally demonstrates shunting across the ASD, frequently with bidirectional flow. Therefore, *negative jets* of unopacified flow from the LA into the contrast-filled RA may alternate with the appearance of contrast bubbles flowing through the defect into the LA. When an ASD is present, contrast should appear within one to five heart beats in the LA after entering the RA. Delayed appearance of contrast in the LA may indicate an intrapulmonary shunt rather than an ASD.

Color Doppler imaging can be useful for detecting flow through ASDs, but the pressure drop between atria often does not produce turbulence. Color inflow from the inferior vena cava and right-sided pulmonary veins may be prominent in normal subjects and should not

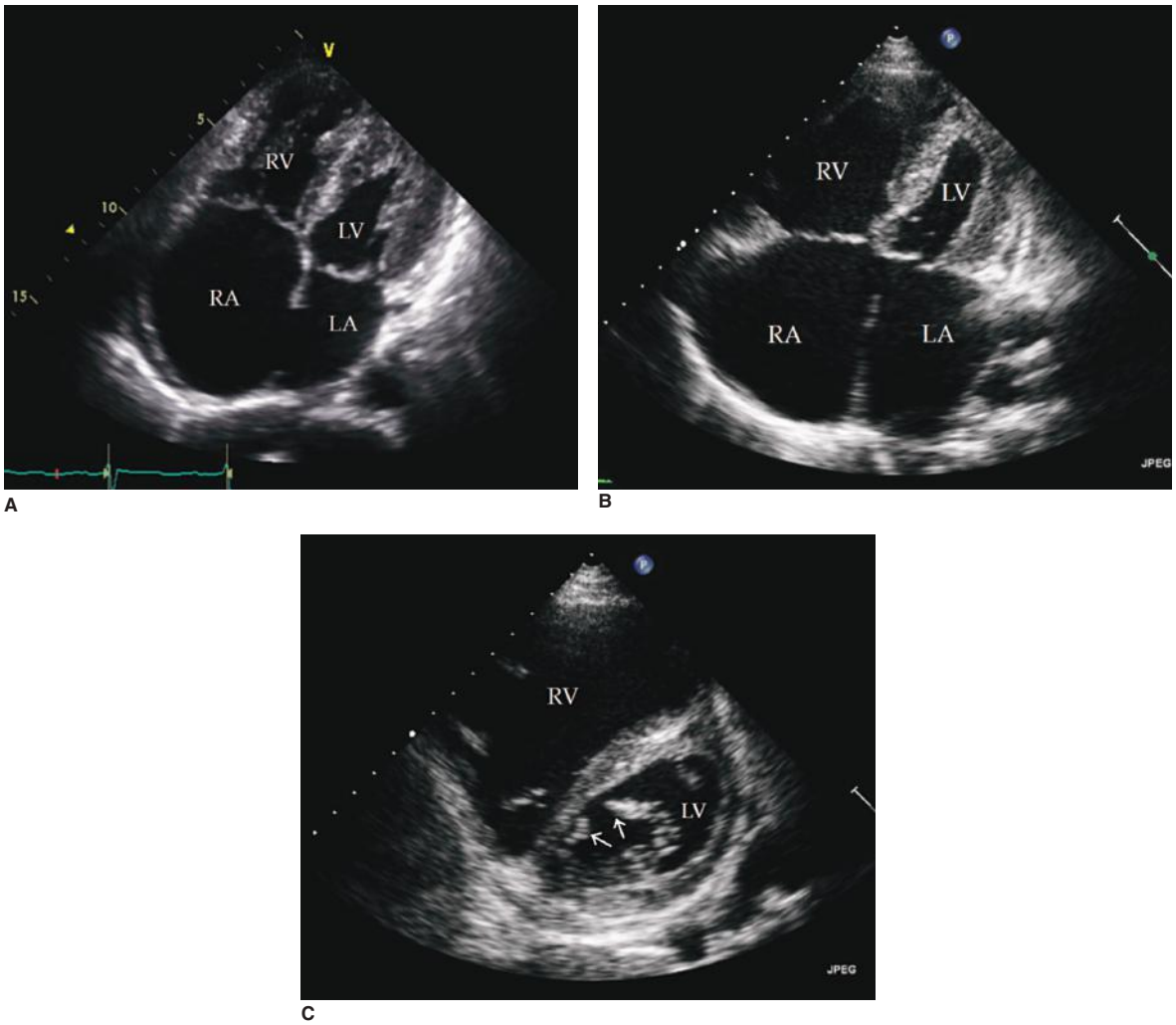


FIGURE 15–110. A. Modified apical four-chamber view of an ostium secundum atrial septal defect (ASD). A large defect is seen in the middle portion of the interatrial septum. The RA and RV are enlarged. **B.** Apical four-chamber view of a large ostium primum ASD. The RV and both atria are enlarged. **C.** Parasternal short-axis view in a case of ostium primum ASD, showing a cleft anterior mitral valve (*arrows*). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

be misinterpreted as a shunt. PWD recordings through an ASD usually reveal continuous flow, which peaks in late systole. Pulmonary-to-systemic flow ratios can be estimated in ASD (and VSDs) by comparing volumetric flow measurements through the LVOT and RVOT. With the advent of umbrella or *clamshell* devices that permit percutaneous closure of select ASDs, 3D, TEE and intracardiac echocardiography have assumed important roles in defining the cross-sectional dimensions and exact position of the ASD (Fig. 15–111B). TEE is also useful in confirming accurate placement of closure devices and subsequent correction of the interatrial shunt.

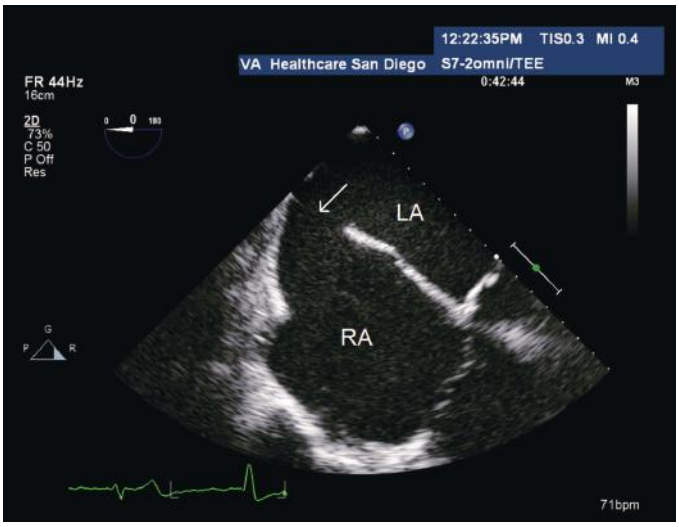
Ventricular Septal Defect

Ventricular septal defects (VSDs) may be classified as perimembranous, inlet, outlet, or trabecular. Echocardiography is useful for the detection and classification of VSDs; the defect itself is sometimes visible with 2D imaging alone (Fig. 15–113A), but smaller VSDs are easily missed. Complete absence of the interventricular septum (single ventricle) is quite rare (Fig. 15–113B). PWD or CW Doppler interrogation often reveals discrete areas of high-velocity flow across the interventricular septum. Measurement of the peak CW velocity through the shunt allows calculation of the interventricular pressure gradient (via the modified Bernoulli equation); subtraction of this gradient from the systolic blood pressure (in the absence of aortic stenosis) approximates the RV systolic pressure.

Overall, color-flow imaging is the most useful Doppler technique for the diagnosis of VSDs. Typically, a high-velocity systolic color jet is seen traversing the interventricular septum, but the velocity is lower with large defects and in the presence of PH (Fig. 15–114), in which case, reduction of the aliasing velocity should enhance the jet. The appearance of the color jet in the standard imaging planes can be used to determine the type of VSD. Use of agitated saline contrast should be used with caution in the setting of large shunts—cross-over of large bubbles to the systemic circulation has been linked to cerebrovascular symptoms. Accurate detection of other associated cardiac lesions (see Chap. 56) is especially critical before surgical intervention.

Patent Ductus Arteriosus

The ductus arteriosus originates just to the left of the PA bifurcation and inserts into the aorta slightly distal to and opposite from the ostium of the left subclavian artery. Given this posterior location, it is sometimes difficult to image a *patent ductus arteriosus* (PDA), but suprasternal imaging is of value (Fig. 15–115A and B), with the jet detected as



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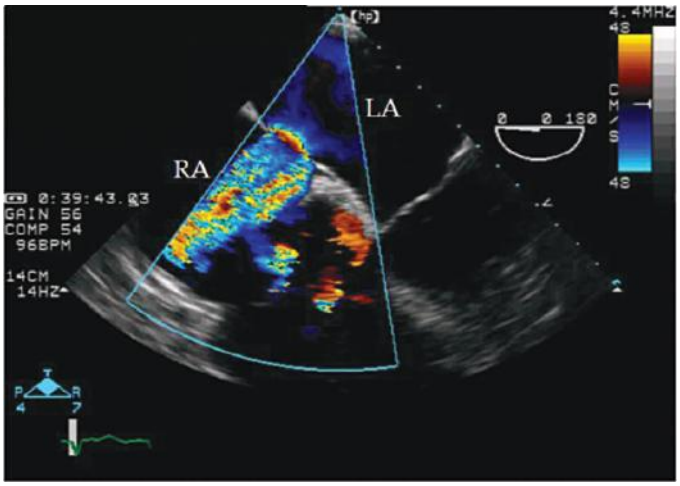


B

FIGURE 15–111. **A.** Transesophageal image of a sinus venosus atrial septal defect (ASD). The defect (*arrow*) is present in the superior and posterior portion of the interatrial septum. **B.** Transesophageal image of an ostium secundum ASD. Color-flow Doppler confirms a left to right shunt, and the size of the defect can be measured accurately. LA, left atrium; RA, right atrium.

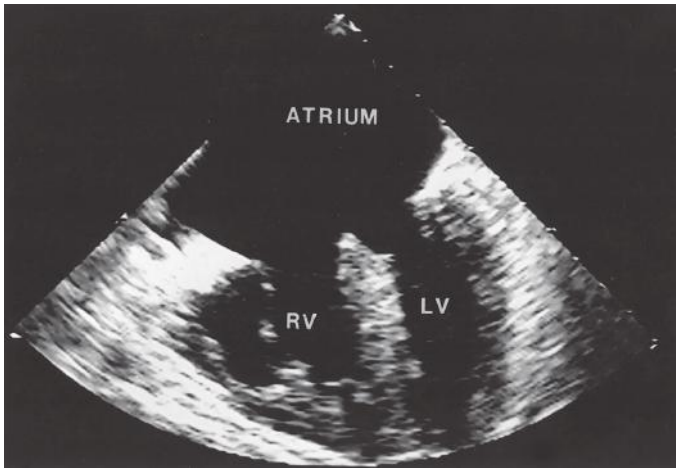
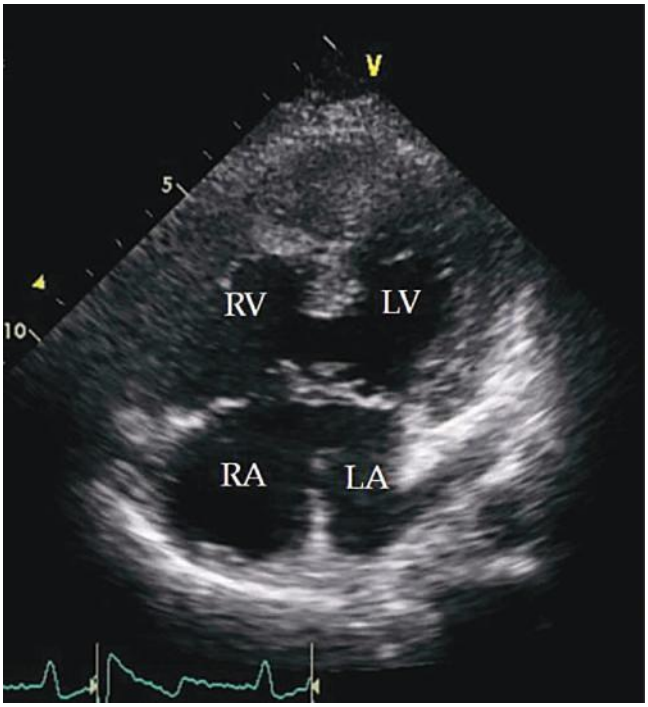


FIGURE 15–112. Transverse transesophageal image of single atrium. RV, right ventricle; LV, left ventricle. Reproduced with permission from Blanchard DG, Scott ED: Images in cardiovascular medicine. Single atrium. *Circulation*. 1997 Jan 7;95(1):273.



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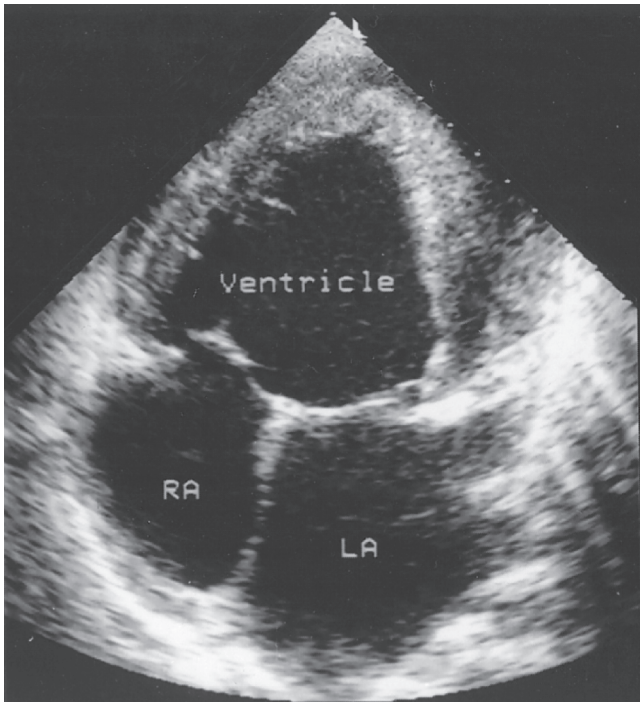


B

FIGURE 15–113. **A.** Apical four-chamber image of an inlet ventricular septal defect and an ostium primum atrial septal defect (complete AV canal defect). The ventricular septal defect (VSD) is situated more inferiorly than the typical position of a perimembranous VSD. **B.** Apical image of single ventricle. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

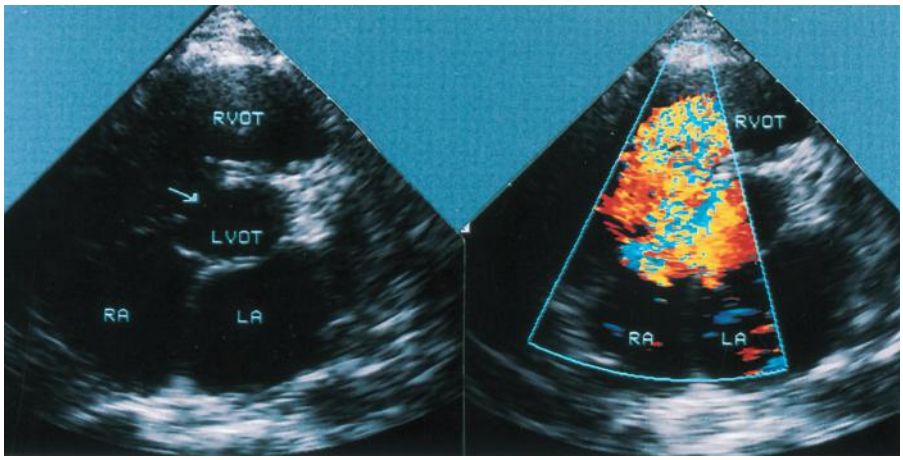
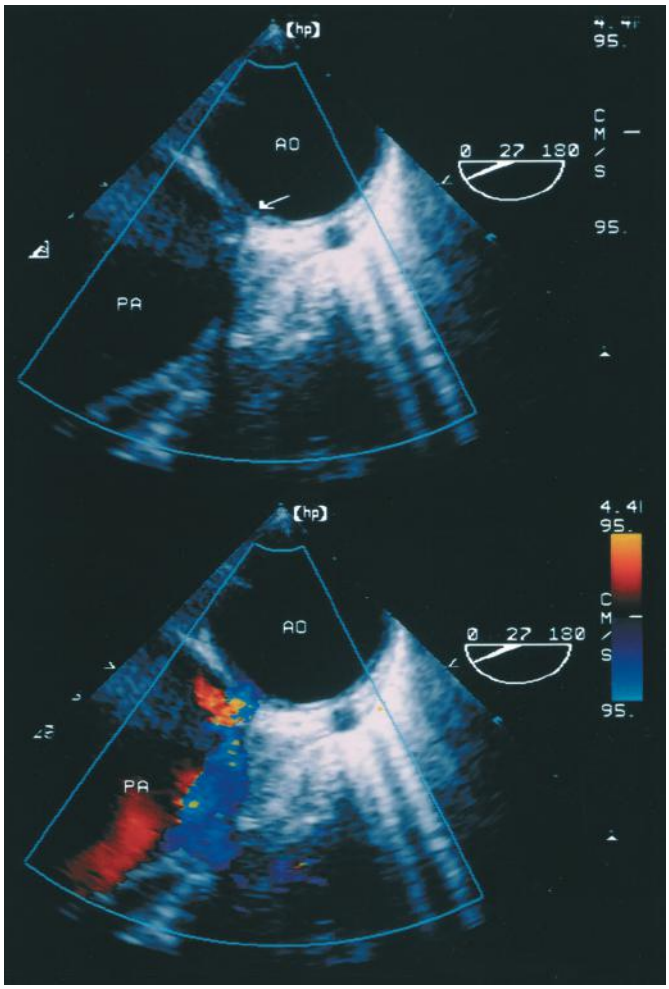


FIGURE 15–114. Parasternal short-axis images of a large perimembranous ventricular septal defect (VSD) (*arrow*) without (*left*) and with (*right*) superimposed color-flow Doppler. A large, turbulent color jet crosses the VSD during systole (*right*). LA, left atrium; LVOT, left ventricular outflow tract; RA, right atrium; RVOT, right ventricular outflow tract.



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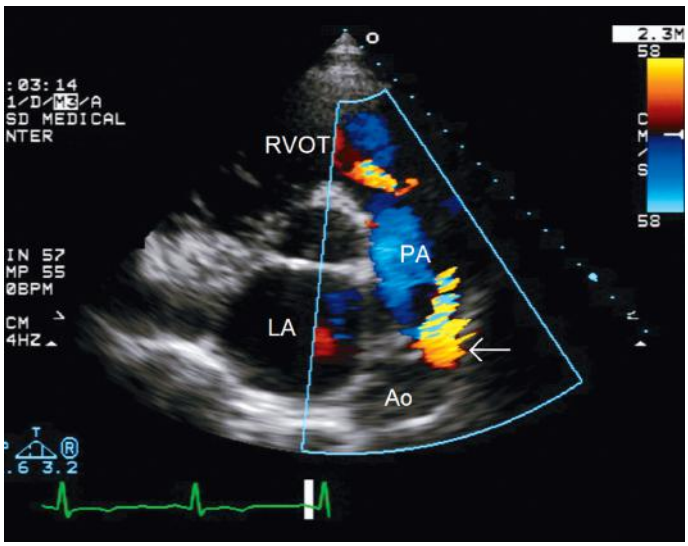


B

FIGURE 15–115. A. Transesophageal image of a patent ductus arteriosus. The upper panel shows a small communication (*arrow*) between the Ao and PA, which is confirmed with color-flow Doppler imaging (*lower panel*). **B.** Parasternal short-axis images at the AoV level. Color imaging reveals diastolic flow within the PA (*arrow*), consistent with a patent ductus arteriosus. Mild pulmonary regurgitation is also present. Ao, aorta; LA, left atrium; PA, pulmonary artery; RVOT, right ventricular outflow tract.

high-velocity diastolic flow entering the distal left region of the main PA and streaming anteromedially (see Fig. 15–115B). With large shunts, volume overload and subsequent dilation of the left ventricle occurs.

Aortopulmonary window is a much rarer shunt involving the great vessels, which presents as a communication anteriorly between the ascending AO and proximal PA. It is embryologically distinct from a PDA and more closely related to a truncus arteriosus defect.

VENOUS INFLOW ABNORMALITIES

Anomalous pulmonary venous return (APVR) may be partial or total. Partial APVR is present in 80% of sinus venosus ASD cases and is a feature of the scimitar syndrome. The usual finding on TTE is RV volume overload. TEE is useful in detecting these abnormal venous connections. In total APVR, the pulmonary veins may empty directly into the RA or into a common posterior chamber or vein. This structure and its connection with the RA may be visualized echocardiographically, along with the obligatory ASD.[136] In some cases, the collecting chamber posterior to the LA may mimic the appearance of *cor triatriatum*, an entity characterized by a membrane in the posterior LA that may obstruct pulmonary venous inflow, causing symptoms similar to those of MS (Fig. 15–116).

Persistent left superior vena cava occurs in 0.5% of the normal population. In most cases, the anomalous vein empties into the coronary sinus, which then drains into the RA (Fig. 15–117). Unless the coronary sinus is unroofed and drains into the LA, no shunting occurs. The typical echocardiographic finding is a large coronary sinus, which is especially well seen on transesophageal or parasternal transthoracic views. The diagnosis may be confirmed by intravenous contrast injection from the left arm, because this will opacify the coronary sinus shortly before filling the RA.

CONOTRUNCAL AND AORTIC ABNORMALITIES

Tetralogy of Fallot is one of the more common conotruncal abnormalities, and affected individuals may sometimes survive to adulthood without surgical intervention (see Chap. 56). The classic echocardiographic features include a large perimembranous VSD, an anteriorly displaced aorta that overrides the VSD, RV enlargement and dysfunction, and pulmonic stenosis (either infundibular, valvular, or supravalvular) (Fig. 15–118).[137] The VSD and aorta are well visualized

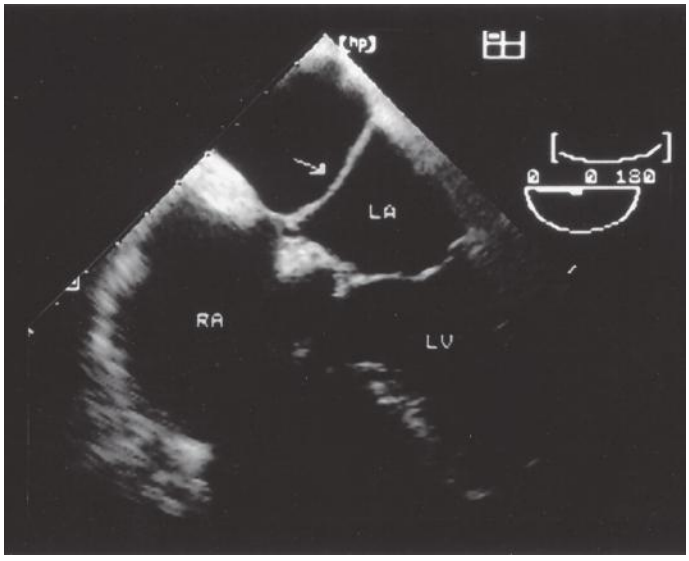


FIGURE 15–116. Transverse transesophageal image of cor triatriatum. A membrane (*arrow*) is present in the left atrium. LA, left atrium; LV, left ventricle; RA, right atrium.

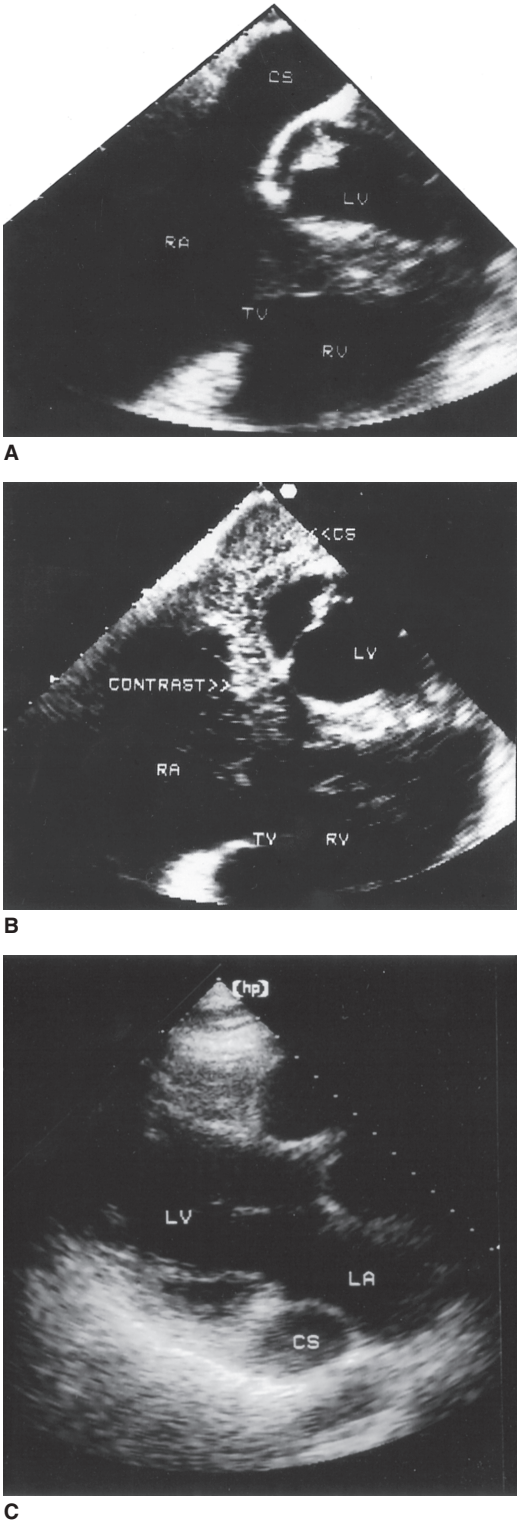
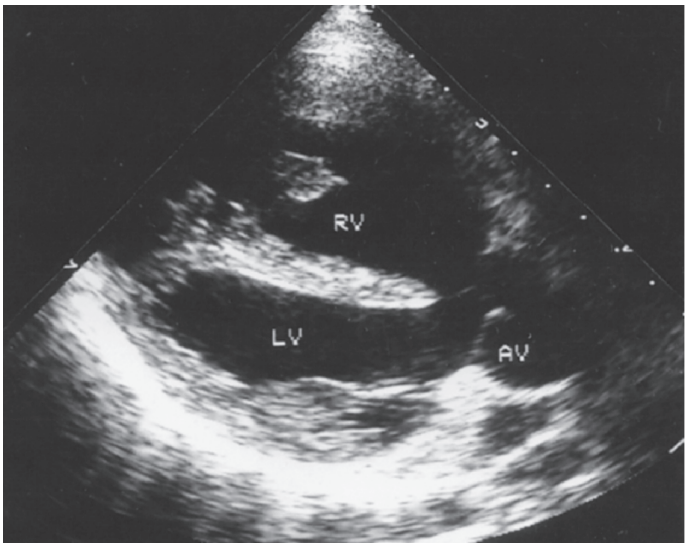


FIGURE 15–117. **A.** Transesophageal image (transverse plane) from a patient with persistent left superior vena cava. The coronary sinus (CS) is dilated. **B.** After injection of agitated saline into the left antecubital vein, contrast is seen entering the right atrium (RA) via the CS. LV, left ventricle; RV, right ventricle; TV, tricuspid valve. **C.** Transthoracic parasternal long-axis image of persistent left superior vena cava. The coronary sinus is dilated. **B**, reproduced with permission from Skorton DJ, Schelbert HR, Wolf GL, et al: *Marcus' Cardiac Imaging*, 2nd ed. Philadelphia: Saunders; 1996.



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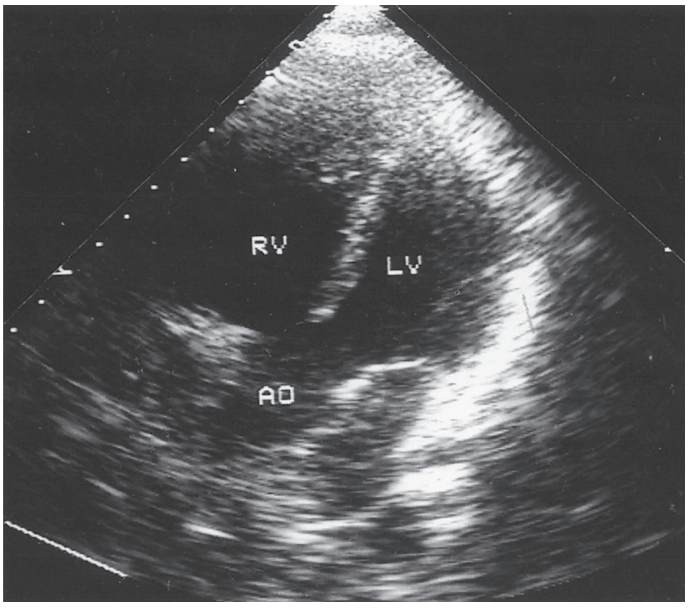


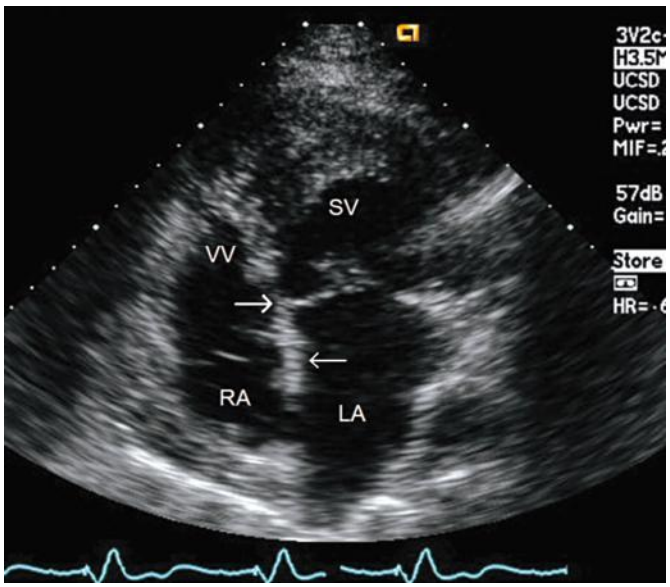
B

FIGURE 15–118. Parasternal long-axis (**A**) and apical four-chamber (**B**) images of tetralogy of Fallot. The right ventricle (RV) is enlarged, and a large ventricular septal defect is present. The aorta (Ao) overrides the interventricular septum. LV, left ventricle. Used with permission from Reinaldo W. Beyer, MD.

in the parasternal long-axis view, whereas the RVOT and proximal PA are best seen in the parasternal short-axis view at the base of the heart. Doppler interrogation can provide evaluation of the severity of pulmonic stenosis, before and after surgery. Echocardiography may aid detection of infants with tetralogy who will require early surgical intervention. Significant pulmonary regurgitation is a common problem in repaired tetralogy of Fallot in adults.

Although *double-outlet RV* (DORV) shares several clinical characteristics with tetralogy of Fallot—VSD and anterior aortic displacement are invariably present, and pulmonic valvular stenosis and ASD are common in both—it is morphologically distinct. Normal continuity of the posterior aortic wall with the anterior MV leaflet (always present in tetralogy of Fallot) is absent in DORV, and an interposed mass of fibrous tissue between the LA and the nearest great vessel is seen on 2D imaging. In addition, the great vessels may be transposed in DORV, resulting in a characteristic side-by-side appearance of the aorta and PA on parasternal short-axis images.

Echocardiography is a valuable tool for the detection, management, and postoperative follow-up of patients with *transposition of the great arteries*.[138] In D-transposition, the AO arises from the RV, the PA arises from the LV, and one or more obligatory shunts are present. With L-transposition, the morphologic right and left ventricles are switched, and associated anomalies such as VSD and pulmonic stenosis are common. In both types of transposition, the normal echocardiographic orientation of the great vessels on parasternal short-axis images (a sausage-shaped RVOT and PA draped over a circular AO) is no longer present, and the two great vessels are typically side by side and parallel (Figs. 15–119 and 15–120). In general, the AO is anterior



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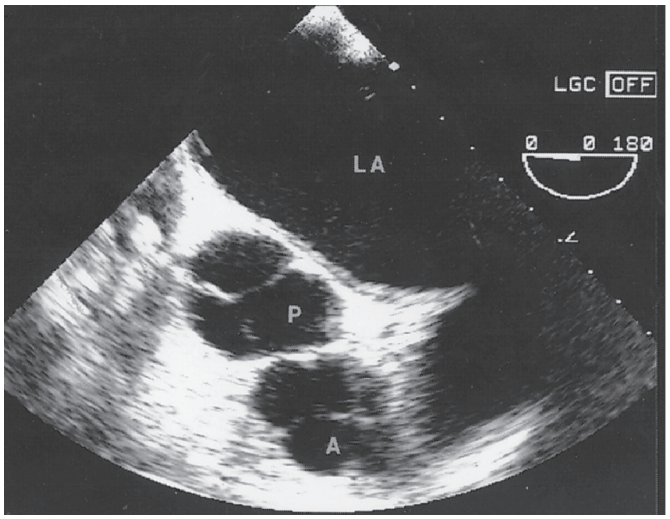

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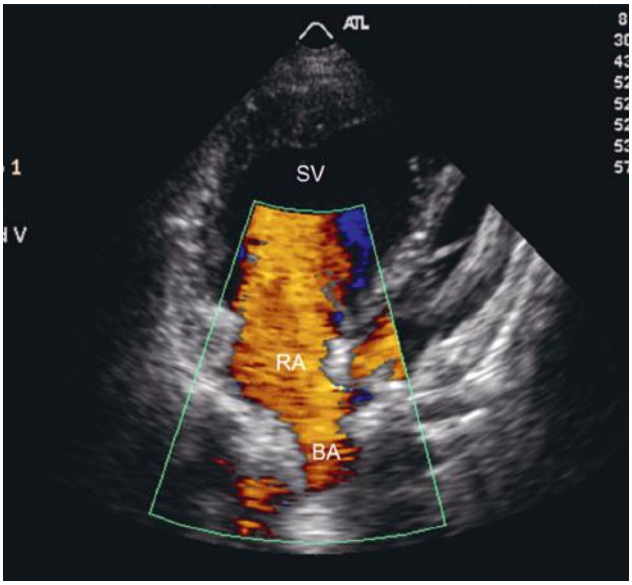
FIGURE 15–119. A. Apical four-chamber image of L-transposition (congenitally corrected). The morphologic LV and RV are inverted in position, whereas the atria remain intact. The *bold arrow* marks the annulus of the left-sided atrioventricular valve; the *thin arrow* marks the right-sided atrioventricular valve annulus. The left-sided annulus is displaced apically, identifying it as the tricuspid valve. Therefore, the systemic ventricle (SV) is a morphologic right ventricle, whereas the venous ventricle (VV) is a morphologic left ventricle. **B.** Transverse transesophageal image through the semilunar valves in L-transposition. The aortic valve (A) is anterior and to the left of the pulmonic valve (P). LA, left atrium; LV, left ventricle; RV, right ventricle.



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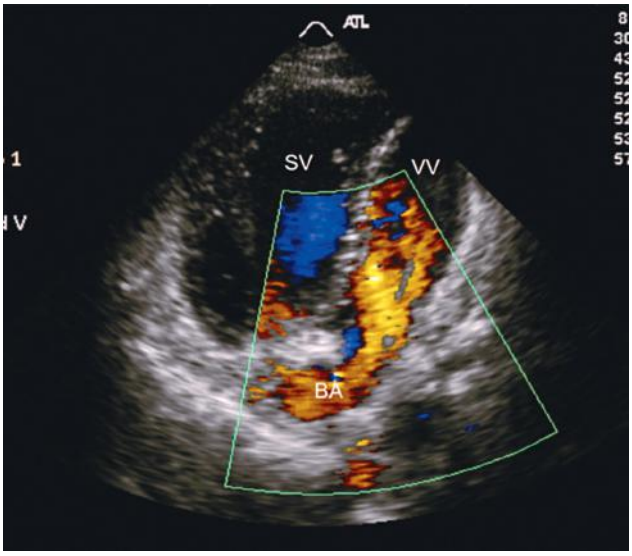

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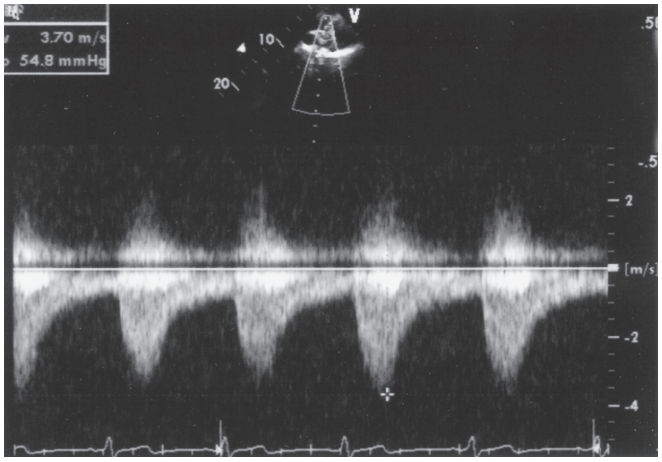
FIGURE 15–120. **A.** Modified apical image of D-transposition after baffle (Mustard) procedure. Pulmonary venous blood flows through a baffle (BA) to enter the right atrium (RA) and the systemic ventricle (SV), which is a morphologic right ventricle. The SV ejects into the aorta. There is no evidence of baffle stenosis. **B.** Modified apical image from the same patient showing vena caval blood flow through a BA into the left atrium and venous ventricle (VV), which is a morphologic left ventricle. The venous ventricle ejects into the pulmonary artery. Again, there is no evidence of baffle stenosis.

and to the right of the PA in D-transposition and anterior and to the left in L-transposition. Apical displacement of the tricuspid annulus is an important sign that helps define the anatomic position of the morphologic RV. Both TTE and TEE are an important part of continuing care after surgical repair or palliation of transposition (see Fig. 15–120).

Truncus arteriosus is a rare anomaly characterized by a large VSD, a single semilunar valve, and a single great vessel that divides into the ascending AO and PA. Ultrasound imaging can determine the anatomy of the great vessels and assist in defining the various subsets of truncus arteriosus.

Coarctation of the aorta (see Chap. 56) is associated with a bicuspid AoV and is best visualized from the suprasternal position. 2D imaging may identify the site of coarctation. Clear visualization of narrowing in the proximal descending AO with poststenotic dilatation is pathognomonic of coarctation. Doppler interrogation from the suprasternal notch demonstrates increased systolic velocity in the descending AO and may also reveal a persistent flow gradient throughout diastole in cases of severe coarctation (Fig. 15–121A). Color imaging may display flow acceleration proximal to the site of coarctation and aliasing distal to it (Fig. 15–121B). *Supravalvular AS*, either isolated or associated with Williams syndrome, is generally imaged best from the suprasternal and superior parasternal positions. Transesophageal imaging is also very helpful (Fig. 15–122E). Echocardiography reveals either an hourglass-shaped stenosis of the aorta above the sinuses of Valsalva, diffuse hypoplasia of the ascending aorta, or a focal fibrous ridge at the sinotubular junction (see Fig. 15–122E). Perhaps the most important message for adult cardiologists is that the disease is an aortopathy, and lifelong surveillance is mandatory.



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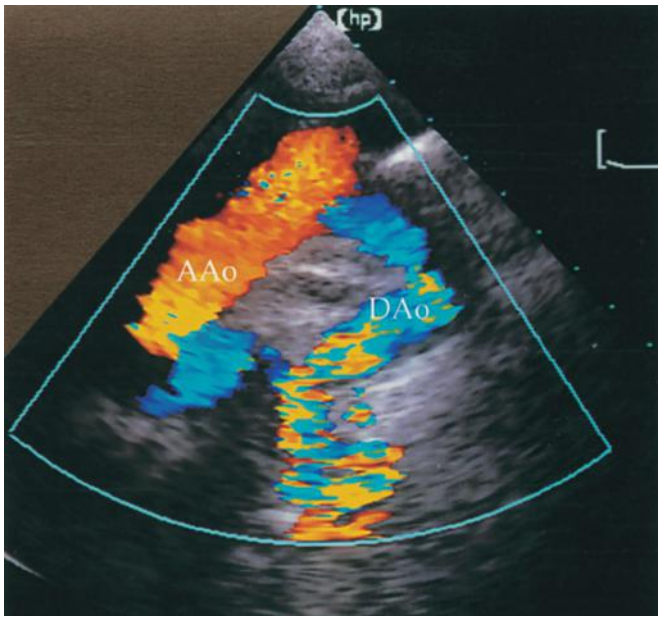

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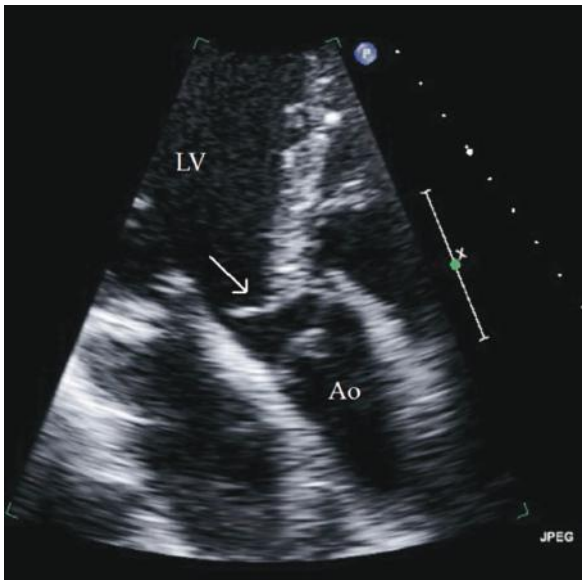
FIGURE 15–121. **A.** Continuous-wave Doppler tracing of the descending aorta (from the suprasternal position) in aortic coarctation. Peak systolic velocity is 3.7 m/s, and there is persistent flow during diastole, suggesting severe coarctation. **B.** Suprasternal image of aortic coarctation. The descending aorta (DAo) is focally narrowed and tortuous, and turbulent (aliased) flow is present distal to the site of coarctation.



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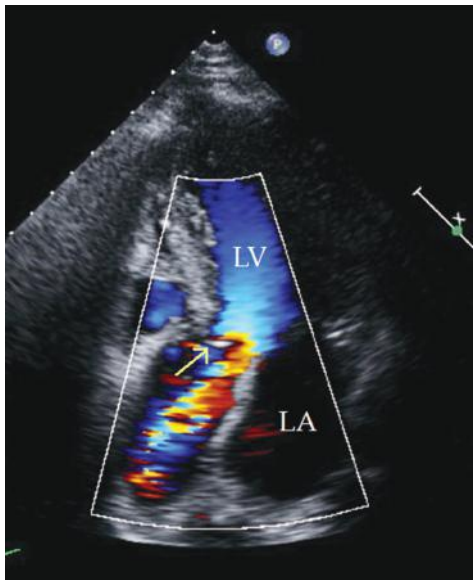

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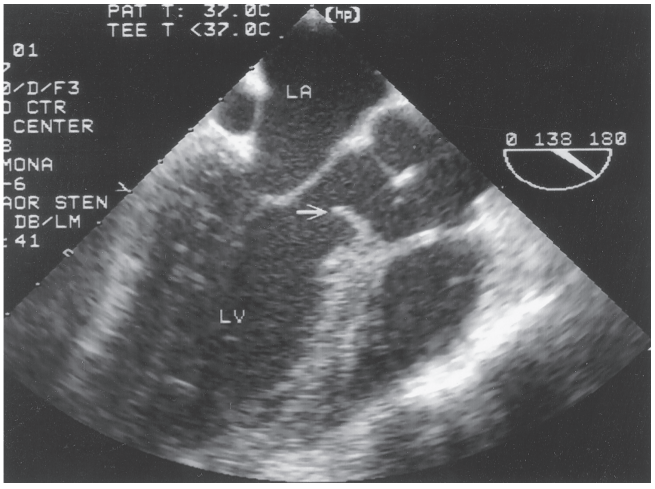

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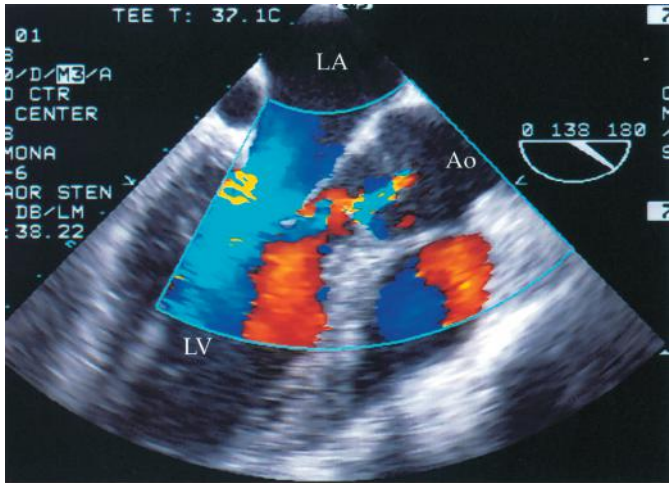

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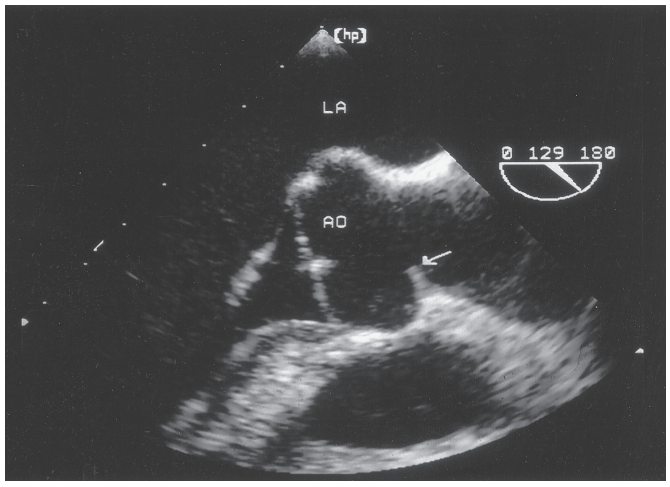

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FIGURE 15–122. Subvalvular and supravalvular aortic stenosis (AS). **A.** Apical three-chamber view of discrete subaortic stenosis (SAS). A fibrous ridge (*arrow*) is present in the left ventricular outflow tract. **B.** Apical five-chamber view of discrete SAS with color-flow Doppler, demonstrating aliasing and proximal flow convergence in the left ventricular outflow tract. **C.** Transesophageal image of discrete SAS. A fibrous ridge in the outflow tract of the LV is present (*arrow*). **D.** Transesophageal image with color-flow Doppler, demonstrating mild aortic insufficiency associated with discrete SAS. **E.** Transesophageal image of supravalvular AS. A fibrous ridge extends into the aortic lumen just above the sinus of Valsalva. Ao, aortic root; LA, left atrium; LV, left ventricle.

ABNORMALITIES OF THE VENTRICULAR OUTFLOW TRACTS AND SEMILUNAR VALVES

Right Ventricle

Infundibular stenosis is rare outside the setting of tetralogy of Fallot and is much less common than valvular PS. On 2D imaging, muscular hypertrophy is often visualized proximal to the PA, whereas Doppler interrogation reveals increased flow velocities through the infundibulum. PS is reasonably common and may be either isolated or associated with other congenital lesions. Typical echocardiographic features include thickening of the leaflets, restricted leaflet motion, systolic doming of the valve, and elevated systolic flow velocity on Doppler (see Fig. 15–85). The PV is best visualized in the parasternal short-axis view through the base (or a modified parasternal view of the RVOT). In children, the subcostal position frequently provides excellent visualization of the RVOT and PV. TEE can provide detailed images of the PV. In pulmonic stenosis, the valve leaflets may calcify over time, and poststenotic dilatation of the PA (particularly the left) is often present.

Left Ventricle

Subvalvular obstruction may be dynamic or fixed. HCM, which may present at any age, is discussed above. Discrete subaortic stenosis may be caused by a thin membrane in the LVOT, a fibromuscular ridge, or diffuse muscular narrowing of the outflow tract (see Fig. 15–122A–D). 2D echocardiographic imaging can distinguish these various forms of discrete subvalvular stenosis, and Doppler analysis permits estimation of the systolic gradient. Color-flow imaging demonstrates increased turbulence in the LVOT as well as aortic valvular regurgitation in approximately 50% of cases (see Fig. 15–122D). Apical views are sometimes more useful for detecting thin subaortic membranes. Subaortic fibromuscular ridges are sometimes associated with anomalous MV chordae connecting the papillary muscles or the anterior MV leaflet to the septum.

Bicuspid AoV is the most common congenital cardiac lesion in adults and is present in 1% to 2% of all individuals (see Chap. 56). Eccentric diastolic coaptation of the aortic cusps on M-mode is a useful clue to the presence of a bicuspid valve. However, M-mode findings are less accurate than 2D imaging, and the parasternal short-axis view is generally best for defining the fish-mouthed systolic aortic valvular anatomy (see Figs. 15–60 and 15–61). Bicuspid valves are best detected during systole. In equivocal cases, TEE is usually diagnostic (see Fig. 15–61). This disease is also associated with an aortopathy, and careful evaluation and surveillance of the thoracic aorta is necessary.

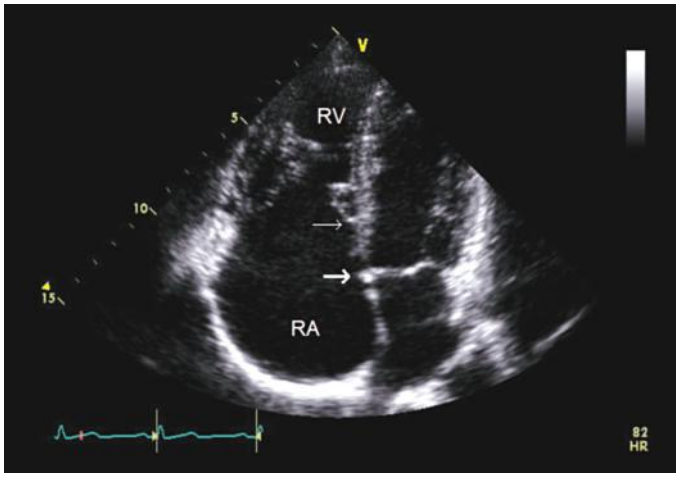


FIGURE 15–123. Ebstein anomaly, apical four-chamber view. The tricuspid valve annulus (*thin arrow*) is apically displaced in comparison to the mitral annulus (*thick arrow*). The right ventricle (RV) and right atrium (RA) are enlarged.

ABNORMALITIES OF THE VENTRICULAR INFLOW TRACT

Ebstein anomaly is a congenital deformity of the TV in which the leaflets are displaced into the RV (see Chap. 56). Associated findings include TR, right atrial enlargement, and ASD.[139] 2D imaging typically shows abnormal apical displacement of the septal leaflet insertion, with variable deformity of the leaflet (Fig. 15–123). The anterior leaflet originates from the tricuspid annulus but is elongated and often tethered to the RV free wall by abnormal chordal attachments. The tricuspid deformity and regurgitation are best visualized in the apical four-chamber view.

Atrioventricular valvular atresia is usually accompanied by hypoplasia of the corresponding ventricle. Echocardiographic images of tricuspid atresia characteristically show a small, nonfunctional RV, an interatrial communication of variable size, and a normally developed LV. Echocardiography is an important tool in the management of patients with tricuspid atresia after palliation with the Fontan procedure.

FETAL ECHOCARDIOGRAPHY

The average risk for significant heart disease in the fetus is approximately 0.4% to 0.8%. Fetal echocardiography has evolved over the past 20 years into a sophisticated method for intrauterine detection of cardiac abnormalities (Fig. 15–124). The technique has been advocated for the preterm diagnosis of CHD, especially in higher risk cases. Fetal echocardiography has successfully identified a variety of congenital lesions.[140] Prenatal detection of these lesions may improve prognosis and guide therapy.

FIGURE 15–124. Fetal echocardiogram (four-chamber view, with left heart on the viewer's left).

CARDIAC MASSES, THROMBI, AND TUMORS

NORMAL VARIANTS AND MASSES OF UNCERTAIN SIGNIFICANCE

When an abnormally localized accumulation of tissue reflectances appears on the echocardiogram, it is said to represent a mass. Echocardiographic masses may be caused by technical artifacts or anomalous structures, but they are of greatest significance in representing true lesions of the heart such as tumors, thrombi, and vegetations. Echocardiography remains the screening procedure of choice for the detection and evaluation of cardiac masses, and its high spatial and temporal resolution are particularly helpful for the delineation of small lesions such as vegetations and papillary fibroelastomas. Both 3D imaging and TEE may provide value in various circumstances, and cardiac magnetic resonance may be of value in tissue characterization.

A number of technical artifacts are capable of appearing as masses on echocardiogram. For example, side lobe signals, reverberations, and noise artifact may lead to accumulations of ultrasonic reflectance within the cavities or adjacent to the myocardium of the heart.[141] Such structures usually lack distinct borders, do not move appropriately through the cardiac cycle, lack identifiable attachments to endocardial surfaces, and cannot be visualized in all views and at all depth settings. The dissociation of fixed artifact location with adjacent cardiac motion is of diagnostic value.

Several benign normal variant findings can be observed during echocardiographic examination. Many adults manifest persistence of the eustachian valve (Fig. 15–125), a thin ridge of tissue at the junction of the inferior vena cava and RA. The eustachian valve appears as a long, linear, freely mobile structure in the RA at the mouth of the inferior vena cava and is nearly always benign. An additional embryonic remnant that may be seen in the posterior RA is the Chiari network, which typically appears as a weblike mobile structure. In some individuals, RV hypertrophy may produce significant enlargement of the RV moderator band coursing along the interventricular septum to the apex of the RV. Similarly, false chordae tendineae can occasionally be visualized as linear structures spanning the LV cavity attached to endomyocardium at both ends (Fig. 15–126).

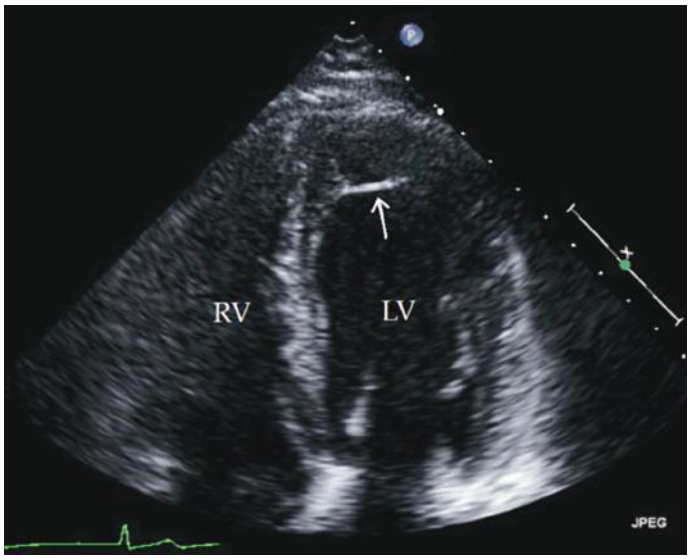


FIGURE 15–126. Apical four-chamber view demonstrating a false chord (*arrow*) in the apical region of the left ventricle (LV). RV, right ventricle.

A variety of foreign bodies and iatrogenically induced anatomic alterations may be visualized on echocardiogram and must be distinguished from pathologic lesions. Intracardiac catheters, pacemaker leads (Fig. 15–127), prosthetic valves or patches, and atrial suture lines after cardiac transplantation can be visualized during echocardiographic examination. These structures are usually easily recognized because of the highly reflective properties of the foreign material, which result in bright echoes, reverberations, and shadowing behind the structures. The avoidance of through-plane motion with 3D echocardiography makes this useful for the visualization of these structures, as well as attached material such as vegetations.

Several morphologic changes involving the interatrial septum are often considered under the classification of cardiac mass lesions of

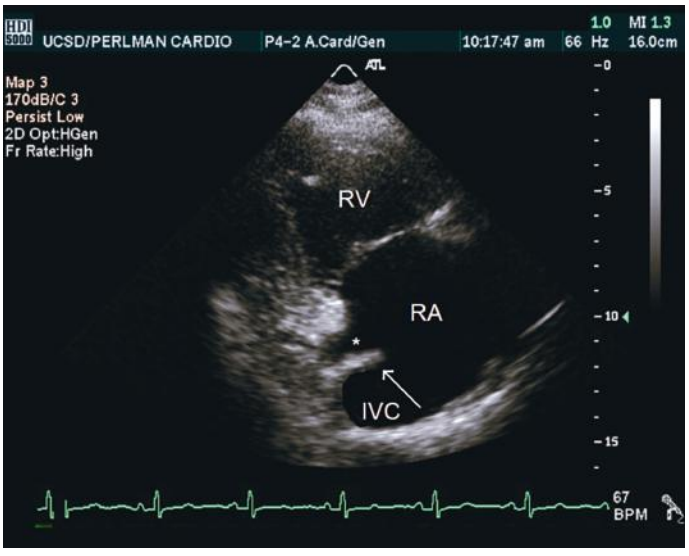


FIGURE 15–125. Right ventricular inflow view showing a prominent eustachian valve (*arrow*) at the junction of the inferior vena cava (IVC) and the right atrium (RA). Asterisk, ostium of the coronary sinus; RV, right ventricle.

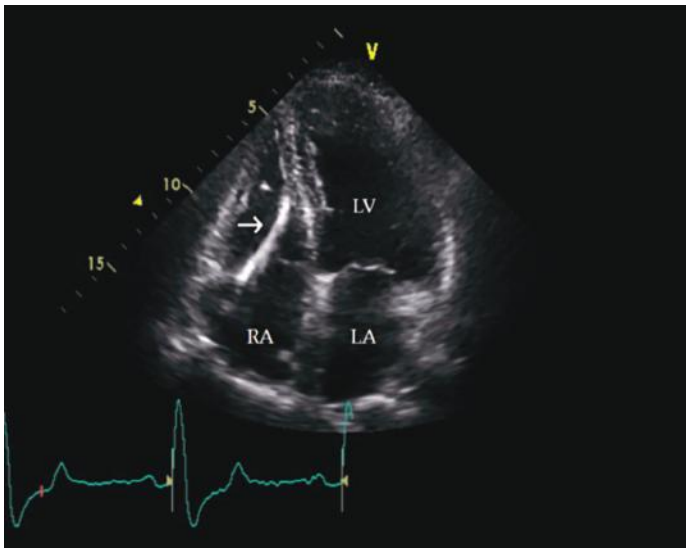
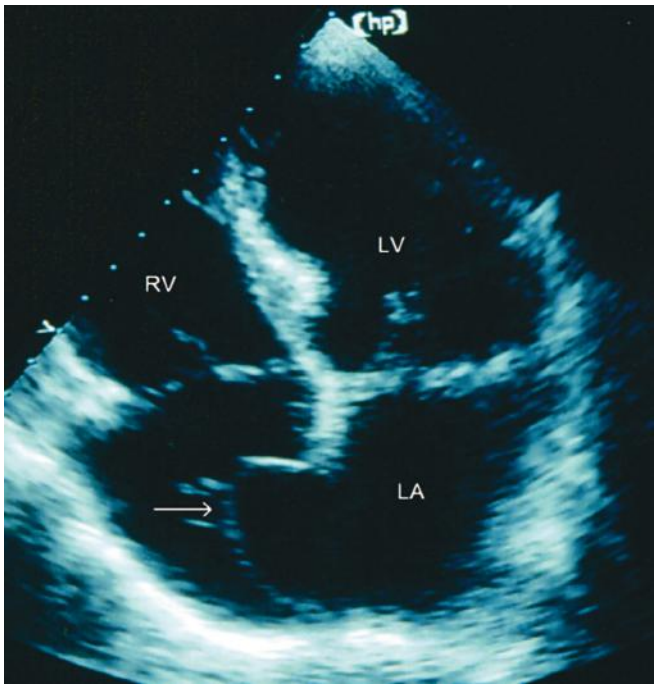


FIGURE 15–127. Apical four-chamber image demonstrating a pacemaker wire (*arrow*) in the right heart. LA, left atrium; LV, left ventricle; RA, right atrium.

uncertain significance. Aneurysms of the interatrial septum have been reported in approximately 1% of the population and are recognized on echocardiogram as a protrusion of the interatrial septum of at least 1.5 cm from its longitudinal plane dividing the left and RA (Fig. 15–128A). Interatrial septal aneurysms are often associated with a PFO and have been implicated as a source of cardiogenic emboli.[142] Interatrial septal aneurysms may be detected by TTE, but they are more readily imaged by the transesophageal approach.[142] Lipomatous hypertrophy appears as a highly reflective thickening of the interatrial septum that typically spares the foramen ovale, thereby creating a characteristic dumbbell-shaped echocardiographic appearance (Fig. 15–128B).

INTRACARDIAC THROMBI

Intracardiac thrombi may be visualized in any chamber of the heart and frequently result in embolic events. The major predisposing factors to intracardiac thrombi include localized stasis of flow, low cardiac output, and cardiac injury. In addition, migration of venous thrombi may also result in intracardiac clots. The appearance of intracardiac thrombi may vary considerably. Thrombi typically have identifiable borders and may be layered and homogeneous or heterogeneous, with areas of central liquefaction (Figs. 15–129 and 15–130). Contrast echocardiography may be of great value in delineating the presence of a thrombus if its occurrence cannot be definitively established on the nonenhanced recording.



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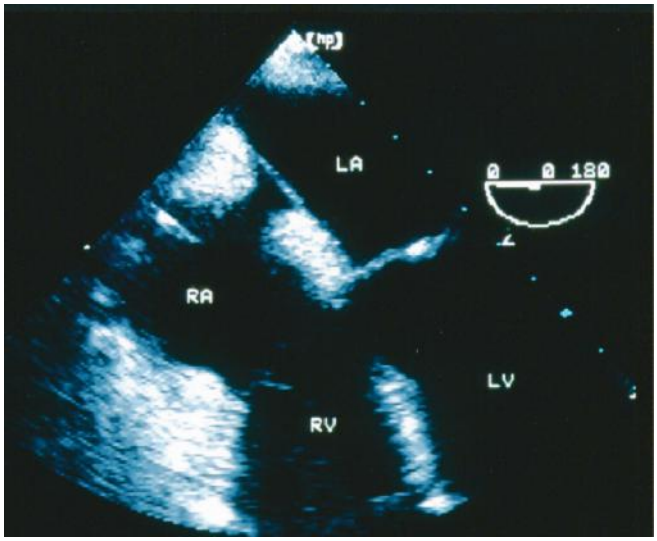

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FIGURE 15–128. **A.** Apical four-chamber image of a large interatrial septal aneurysm (*arrow*). **B.** Transesophageal image of lipomatous interatrial septal hypertrophy. The interatrial septum is markedly thickened, but the fossa ovalis is spared. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

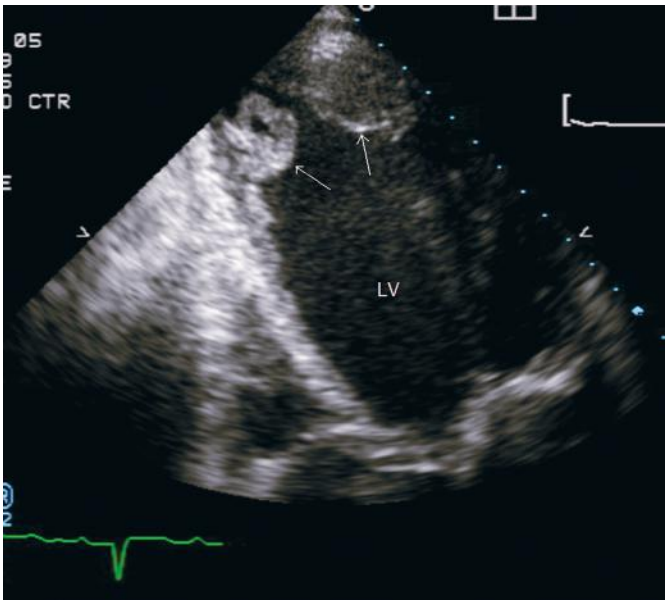


FIGURE 15–129. Magnified apical view demonstrating thrombi (*arrows*) in the apex of the left ventricle (LV).

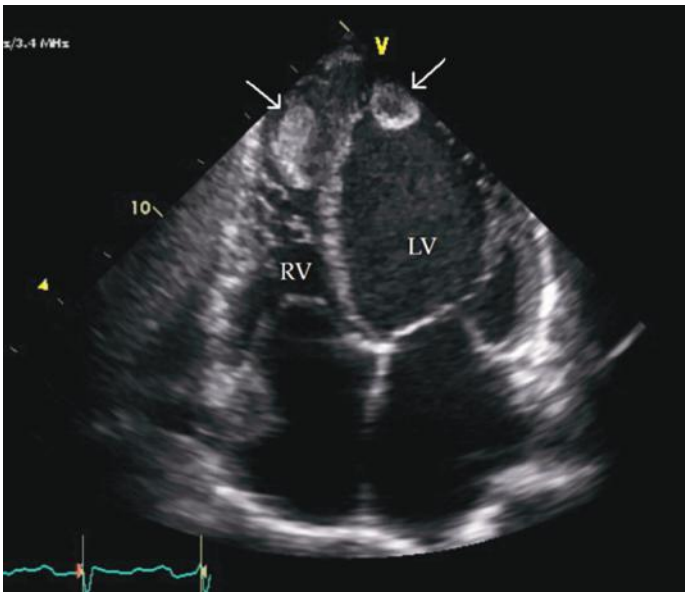


FIGURE 15–130. Apical four-chamber view demonstrating thrombi in the apices of both the right and left ventricles (*arrows*). LV, left ventricle; RV, right ventricle.

Right Heart

Thrombi within the right heart chambers may form locally or migrate from the venous circulation; they are found most commonly in the RA. As opposed to the laminar, relatively immobile nature of RA thrombi that form in situ, venous thromboemboli trapped in the RA tend to be serpentine and mobile. The potential for pulmonary embolism is high. Thrombi also can be seen within the main pulmonary arteries. RV thrombi are rare but may occur with RV infarction and endomyocardial fibrosis. Their appearance is similar to that of LV thrombi.

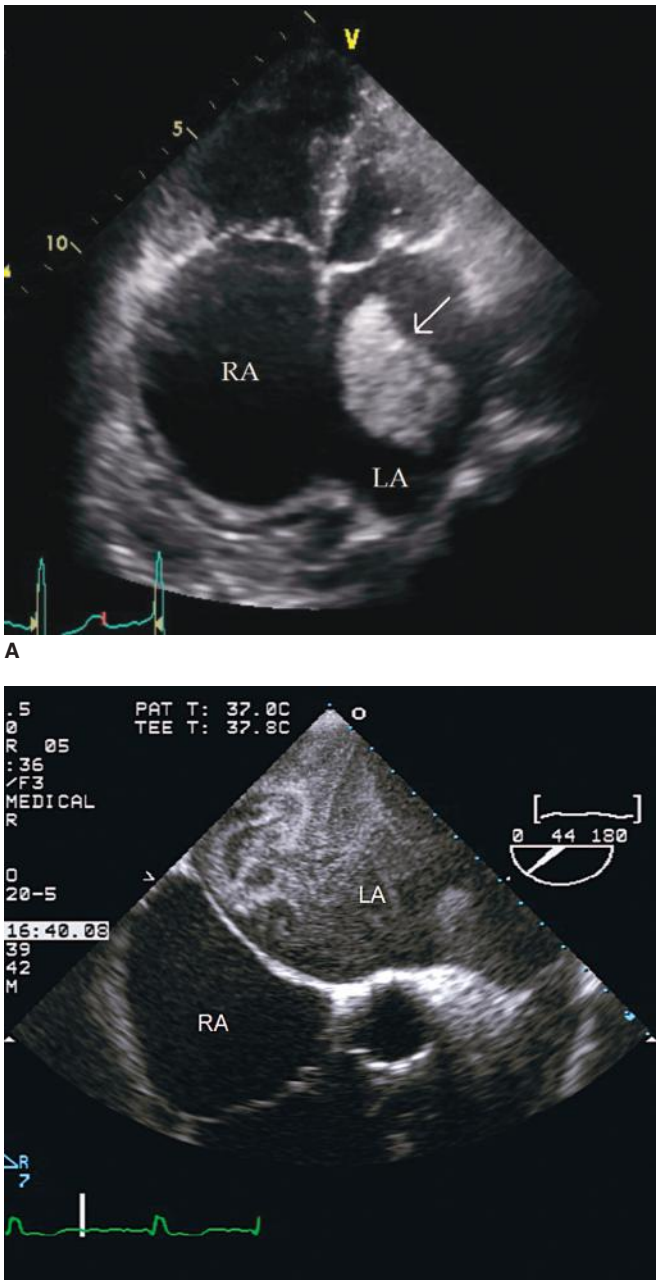
Left Atrium

LA thrombi occur in the setting of low cardiac output, mitral valvular disease, atrial fibrillation, and LA enlargement. Both TTE and TEE can detect thrombi within the main cavity of the LA (Fig. 15–131A), but TEE is clearly superior for visualizing thrombi within the LA appendage. TEE is the diagnostic procedure of choice to detect this lesion. LA thrombi appear as discrete masses, either fixed or mobile, and are usually of homogeneous echo density (see Fig. 15–52). Two sources of false-positive TEE for thrombus are normal pectinate muscles (which can be shown to be linear), and the atrial tissue separating the lobes of a multilobular appendage. LA thrombi are often accompanied by spontaneous echo contrast (or *smoke*) within the LA. This finding indicates stagnant blood flow. LA spontaneous echo contrast, like LA thrombus, has been associated with embolic events[143] and may be a marker of regional prothrombotic activity (Fig. 15–131B). On 2D imaging, the contrast signals are in constant motion and can be missed if gain settings are inappropriately low.

Left Ventricle

Most LV thrombi occur in settings of abnormal systolic contraction (DCM, AMI, and chronic LV aneurysm). LV thrombi have been reported in up to one-half of patients with large MIs and occur more frequently in anterior infarctions (up to 30%-40% of such patients). Most thrombi are located in the apex and thus are best visualized in the apical views (see Fig. 15–129). Cardiac magnetic resonance has shown that the sensitivity of echocardiography for apical thrombus is imperfect, and the use of echocardiographic contrast is prudent if this pathology is suspected.

LV thrombi may be laminar and fixed or protruding and mobile, and they may have a heterogeneous echo density (see Figs. 15–129 and 15–130). *Immature* thrombi are often filamentous, with irregular borders, whereas older thrombi tend to be echodense and fixed.[144] The echocardiographic characteristics of thrombi may influence the risk of cardiogenic embolization, because irregularly shaped, mobile, and protruding thrombi are more likely to embolize than laminar, immobile clots. True LV thrombi have a density distinct from the underlying myocardium, appear in multiple imaging planes, and move concordantly with the underlying myocardium.



A

B

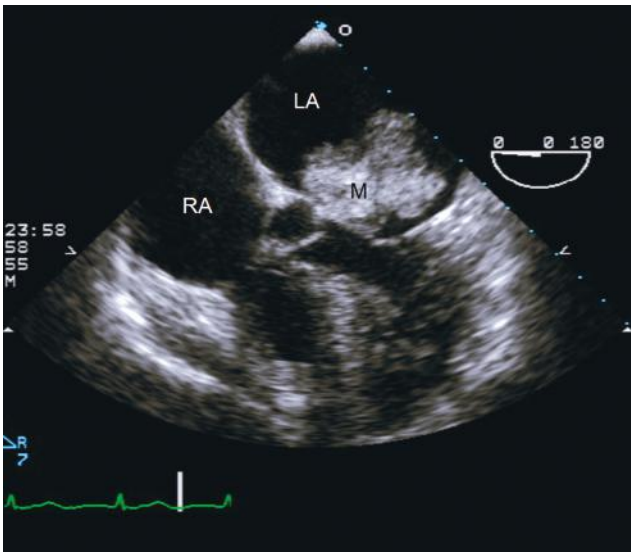
FIGURE 15–131. A. Apical four-chamber image of a large mobile ball thrombus (*arrow*) in the left atrium of a patient with severe mitral stenosis. **B.** Transesophageal image of spontaneous echo contrast (*smoke*) seen in an enlarged left atrium. The spontaneous contrast swirled on real-time imaging. LA, left atrium; RA, right atrium.

CARDIAC TUMORS

Although diagnosed infrequently, cardiac tumors often are included in the differential diagnosis of cardiac problems because of their protean clinical manifestations (see Chap. 101). Cardiac tumors may be intracavitary or intramural, and the location determines their echocardiographic appearance. Intracavitary tumors appear as sessile or mobile echo densities attached to the mural endocardium, whereas intramural tumors appear as localized thickening of the LV wall. The pericardium also may be involved with cardiac tumors, with or without the presence of concomitant effusion.

MYXOMAS

Myxomas are the most common primary cardiac tumors, accounting for approximately 25% of all such lesions.[145] Myxomas can occur in any cardiac chamber, but 75% are found in the LA.[145] On 2D imaging, myxomas usually appear as gelatinous, speckled, sometimes globular masses with frondlike projections (Fig. 15–132). Tissue heterogeneity is common, but calcification is rare. Myxomas are usually attached to the endocardial surface by a pedicle. Typically, they are attached to the interatrial septum. Large tumors are almost always mobile to some degree, and a sizable left atrial mass that appears fixed in position is



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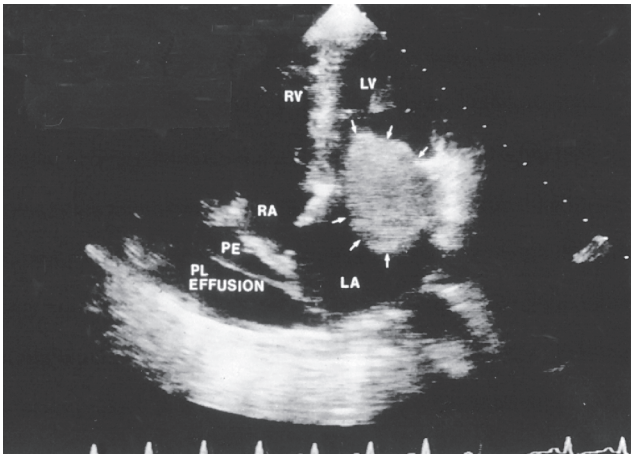


B

FIGURE 15–132. **A.** Transesophageal image of a large myxoma (M) in the left atrium (LA). **B.** Apical four-chamber image of a large left atrial myxoma (*arrows*), which is attached to the lateral wall of the atrium. LV, left ventricle; PE, pericardial effusion; PL, pleural; RA, right atrium; RV, right ventricle.

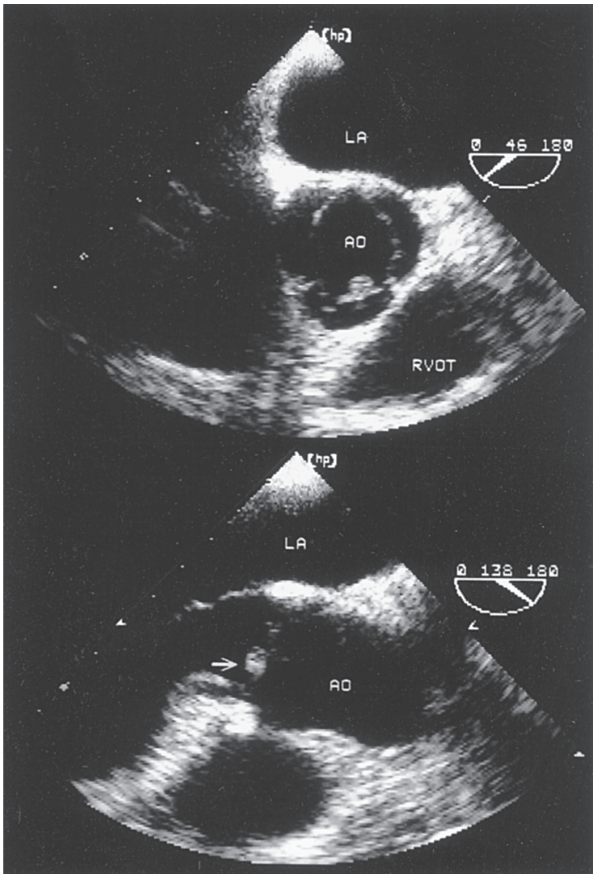
therefore less likely to be a myxoma. Large left atrial myxomas may move back and forth into the MV annulus during the cardiac cycle, entering the orifice in diastole and the LA in systole. Accordingly, Doppler interrogation may demonstrate either obstruction of flow, valvular regurgitation, or both. Most myxomas are visible on TTE, but TEE is superior for the delineation of tumor attachments and detection of small myxomas. Recently, it has been shown that contrast injection will intensify the signals from tumors, but not from thrombi, enabling the differential diagnosis.[146] Because approximately 5% of myxomas are biatrial, careful evaluation of the RA is mandatory.[145]

ADDITIONAL PRIMARY TUMORS

Benign

Rhabdomyomas are rare cardiac tumors associated with tuberous sclerosis. There is a strong tendency for multiple tumors to occur within an affected heart (90% of cases). Fibromas are found most often in children and affect the left ventricle most frequently. The tumor may grow within the myocardium rather than expanding into a cardiac chamber.

Papillary fibroelastomas are usually quite small in size (< 1 cm in diameter) and often grow on cardiac valves or chordae (Fig. 15–133A). Echocardiographic differentiation from vegetations can be difficult.



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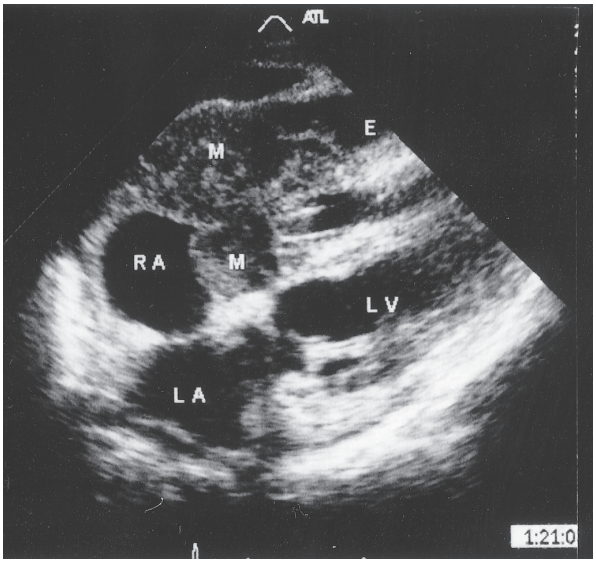


B

FIGURE 15–133. **A.** Transesophageal images of a surgically proven papillary fibroelastoma on the right coronary cusp of the aortic valve (*arrow*). The upper and lower panels show transverse and longitudinal planes through the aortic valve, respectively. **B.** Primary cardiac angiosarcoma (subcostal imaging plane). The tumor mass (M) is present in the right atrium (RA), and has extended through the atrial wall into the pericardial space. AO, aorta; E, pericardial effusion; LA, left atrium; LV, left ventricle.

Malignant

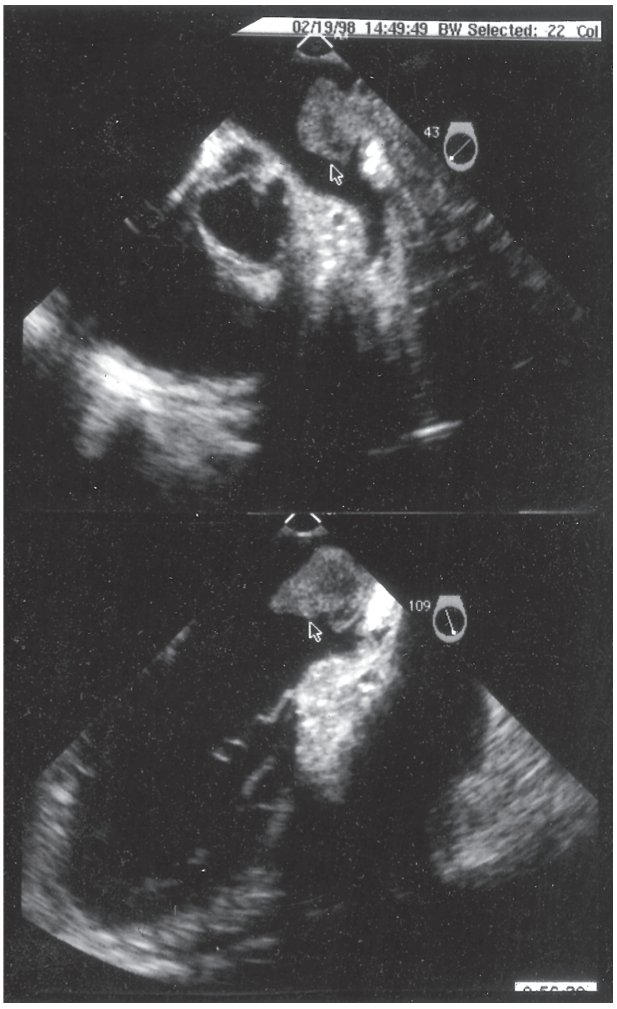
Primary malignant cardiac tumors are quite rare and confer a very poor prognosis. Angiosarcoma is the most common and occurs most often in the RA (Fig. 15–133B). Rhabdomyosarcoma is an additional primary cardiac malignancy. Echocardiography can be useful in monitoring response to therapy: its diagnostic utility is limited, because most findings are nonspecific.

METASTATIC AND SECONDARY TUMORS OF THE HEART AND PERICARDIUM

Metastatic tumors to the pericardium and heart occur 20 to 40 times more often than do primary cardiac tumors (see Chap. 101; Fig. 15–134A). Tumors that commonly metastasize to the heart and pericardium include breast and lung carcinoma, melanoma, and lymphoma (Fig. 15–134B and C). In these cases the tumor is often visible in the inferior vena cava and RA. Pericardial effusion is the most common echocardiographic manifestation in patients with cardiac metastases. Intracavitary and pericardial masses are easily visualized with 2D imaging, but intramural tumors are sometimes difficult to image. Echocardiographic findings are nonspecific, and metastatic tumors may be mistaken for primary cardiac neoplasms, vegetations, thrombi, or even prominent muscular trabeculations.

ADDITIONAL CARDIAC MASSES

The heart is rarely involved in echinococcal disease (< 2% of cases), but intracardiac or intrapericardial rupture of a cyst can lead to anaphylaxis and cardiac tamponade, respectively. Echocardiographic detection of a multiseptated cyst in the LV or interventricular septum suggests cardiac echinococcal disease. Simple pericardial cysts usually occur in the right costophrenic angle (posterior to the RA) and have a benign prognosis. The structures are nonseptated and fluid-filled; they do not compress the cardiac chambers.[147]



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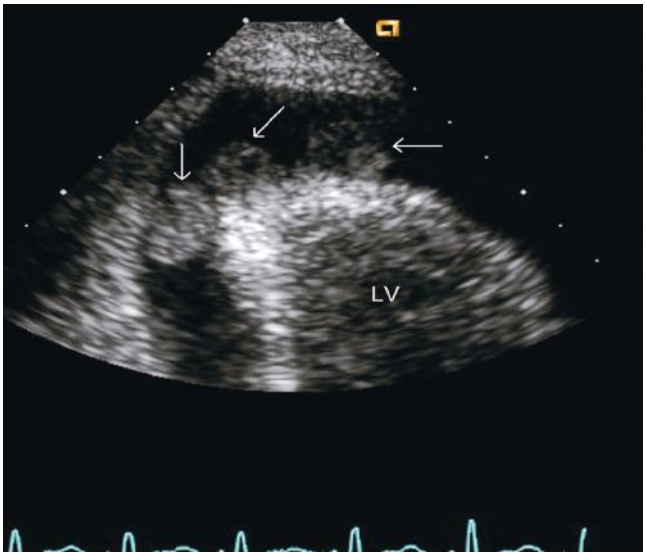

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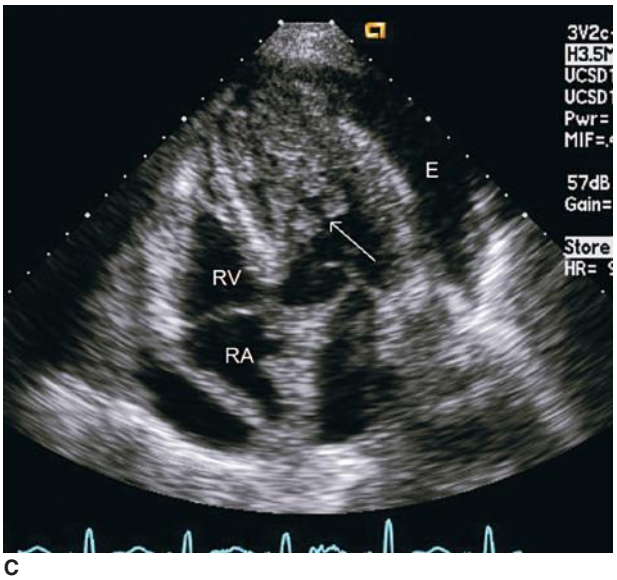


C

FIGURE 15–134. **A.** Magnified apical image showing several small metastatic tumors (*arrows*) on the epicardial surface. **B.** Transesophageal images from a case of metastatic lung carcinoma. The tumor (*arrows*) has entered the left atrium via contiguous spread through the left upper pulmonary vein. **C.** Apical four-chamber image of metastatic melanoma, with a large tumor (*arrow*) in the left ventricle and a malignant pericardial effusion (E). LV, left ventricle; RA, right atrium; RV, right ventricle.

PERICARDIAL DISEASE

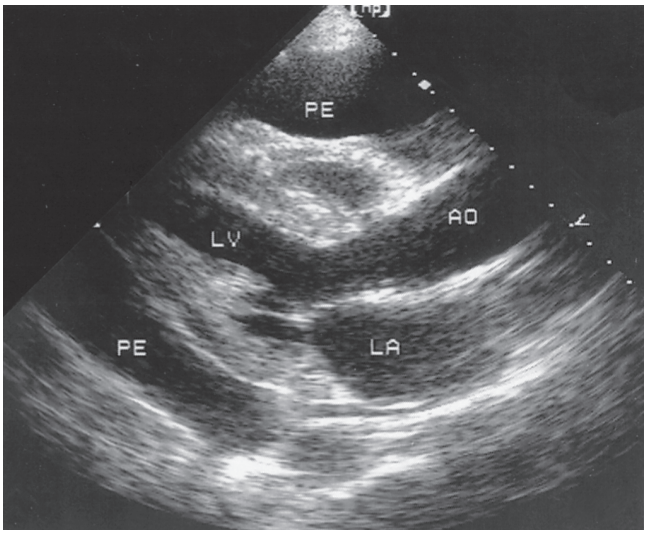
In normal subjects the pericardium is difficult to visualize because the pericardial cavity is only a potential space, and visceral and parietal pericardial layers appear as a single echo (see Chap. 66). In pericardial effusion, the fluid appears as a sonolucent area (or clear space) separating epicardium from pericardium. Pericarditis unaccompanied by pericardial effusion may be undetectable by echocardiography. Therefore, the evaluation of constrictive pericarditis by echocardiography primarily involves Doppler flow recordings.[148]

PERICARDIAL EFFUSION

Echocardiography is the diagnostic procedure of choice for detection of pericardial fluid (Fig. 15–135), and early M-mode studies demonstrated that volumes as small as 20 to 30 mL could be detected reliably. A sonolucent area between the epicardium and pericardium is diagnostic of a pericardial effusion. Although epicardial-pericardial separation may be seen during systole in normal cases, separation throughout the cardiac cycle is abnormal.

Echocardiography can be used to identify pericardial loculations, fibrous strands, and pericardial tumors, as well as to assess the size of effusions (Fig. 15–136). Pericardial effusions may be concentric or loculated. Pericardial tissue reflects on itself behind the LA between the pulmonary veins (the oblique sinus), and fluid in this area may be mistaken for aortic pathology. In general, small effusions are seen posteriorly rather than anteriorly on supine imaging. Moderate-sized (100-500 mL) nonloculated effusions are present both anterior and posterior to the heart. Large nonloculated effusions (> 500 mL) are circumferential and frequently allow free motion of the heart within the fluid-filled space.

The parasternal long-axis view is often helpful in differentiating between pericardial and pleural effusions. If these conditions coexist, the pericardium usually can be identified as a linear density separating



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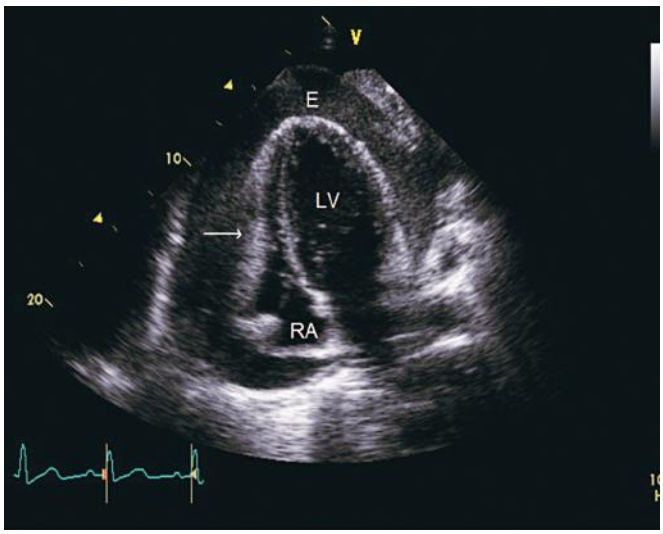

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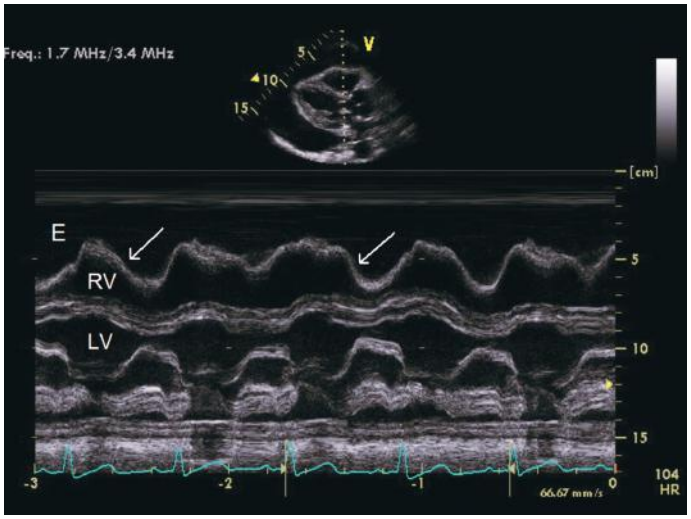

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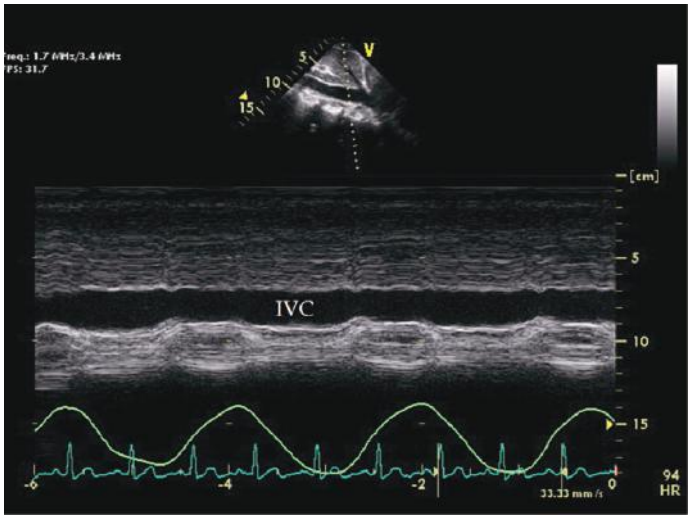


D

FIGURE 15–135. **A.** Large pericardial effusion (PE) on parasternal long-axis imaging. **B.** Right ventricular compression (*arrow*) in cardiac tamponade (apical four-chamber plane). **C.** Parasternal M-mode image of cardiac tamponade and right ventricular diastolic collapse. The right ventricular free wall (*arrows*) moves posteriorly toward the interventricular septum during diastole. **D.** Subcostal M-mode image of the inferior vena cava (IVC) in a patient with cardiac tamponade. The IVC is dilated and collapses only minimally with inspiration. Ao, aorta; E, effusion; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RV, right ventricle.

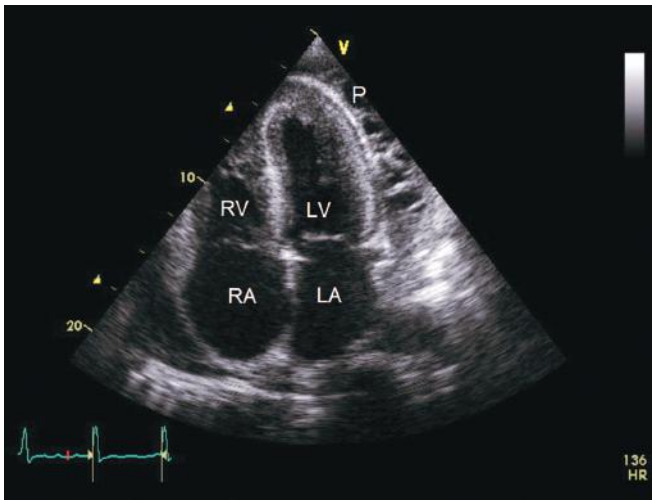


FIGURE 15–136. Apical four-chamber image in a case of malignant pericardial effusion (P). Numerous fibrinous strands are seen within the effusion. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

fluid in the two spaces. The descending aorta is a mediastinal structure; therefore, pericardial effusions will often separate the heart and descending aorta, whereas pleural effusions are seen inferior and posterior to the aorta (Fig. 15–137). In cases of large pleural effusions, atelectatic lung tissue also may be present. Subcostal views are often valuable and may yield the only satisfactory transthoracic images in postoperative or post-traumatic cases. The inferior vena cava also can be imaged in this view; if the vessel does not display inspiratory collapse > 50% of its maximum diameter, elevated RA pressure is present.

On parasternal images, an echolucent space is sometimes visualized anterior to the RV. Although this finding may represent pericardial fluid, it usually is caused by epicardial fat (without effusion) and has no pathologic significance.

CARDIAC TAMPONADE

Because the pericardium is a relatively noncompliant membrane that adapts slowly to volume changes, pericardial effusions (especially those that accumulate rapidly) may limit cardiac filling and cause cardiac tamponade. Echocardiography can help diagnose this condition by detecting morphologic signs of increased intrapericardial pressure as well as abnormal intracardiac flow patterns caused by tamponade and enhanced ventricular interdependence.

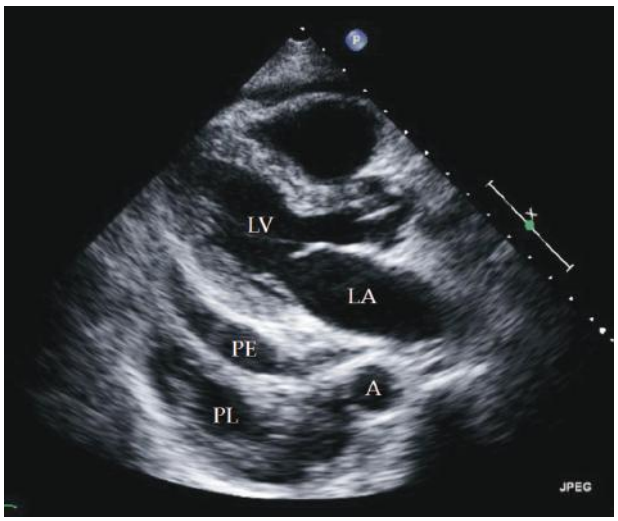


FIGURE 15–137. Parasternal long-axis view in a patient with both a pericardial (PE) and pleural (PL) effusion posterior to the heart. A, aorta; LA, left atrium; LV, left ventricle.

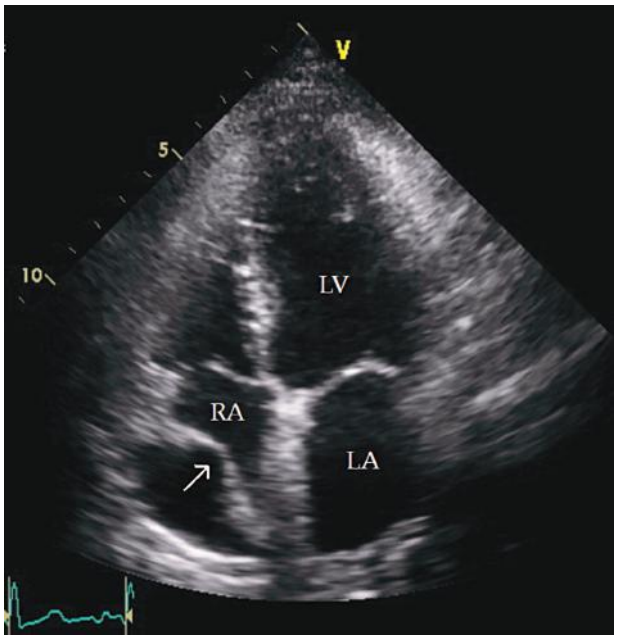


FIGURE 15–138. Right atrial collapse (*arrow*) in a patient with a small pericardial effusion. LA, left atrium; LV, left ventricle; RA, right atrium.

Because diastolic pressures are slightly lower in the right heart than the left, the RA and RV are usually the first chambers to exhibit evidence of increased intrapericardial pressure. High intrapericardial pressure can cause compression or collapse of right heart chambers. Invagination of the RA wall during atrial systole is a sensitive (but not specific) sign of tamponade (Fig. 15–138). Diastolic collapse or *buckling* of the RV free wall is a more specific sign of tamponade and can be visualized both on 2D and M-mode imaging (see Fig. 15–135B and C).

Doppler echocardiographic recordings in patients with tamponade demonstrate an exaggeration of the normal respiratory variation in ventricular inflow and outflow. Thus transmitral and LVOT velocities decrease significantly with inspiration, most likely because of enhanced ventricular interdependence and a marked decrease in the transmitral diastolic gradient during inspiration (Fig. 15–139). The latter is caused both by high intrapericardial pressure as well as leftward motion of the interventricular septum from increased RV filling. When echocardiography is used to direct pericardiocentesis to the site of greatest fluid accumulation, the risks associated with blind pericardial puncture are decreased. Please refer to Chap. 66 for a more detailed discussion.

CONSTRICTIVE PERICARDITIS

The diagnosis of constrictive pericarditis is sometimes difficult to establish, even by cardiac catheterization. 2D and M-mode echocardiography may provide evidence of thickened pericardial tissue by demonstrating increased reflectivity and multiple parallel moving echoes in the area of the pericardium (see Chap. 66). The criteria for pericardial thickening on echocardiogram are imperfect. Paradoxical septal motion may be seen on M-mode with constriction, as can an abnormal inspiratory interventricular septal *bounce* and limited diastolic motion of the posterior LV wall.

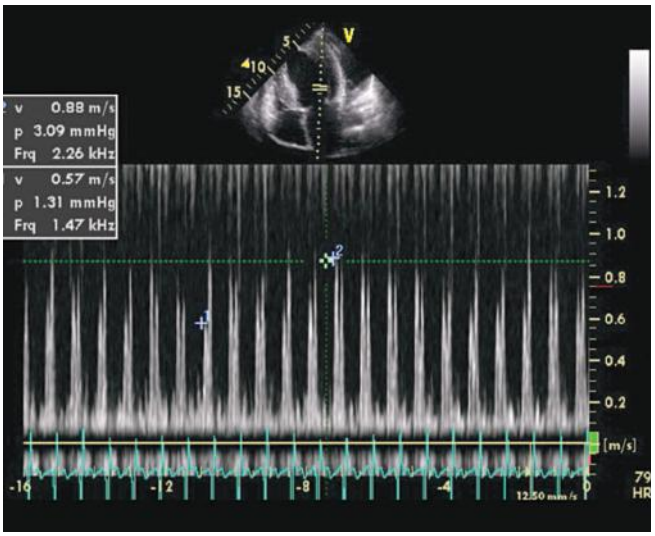
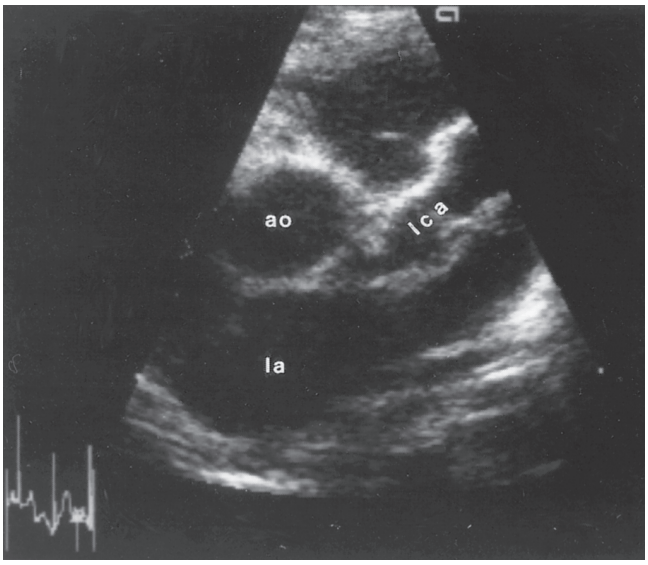


FIGURE 15–139. Pulsed-wave Doppler tracing of left ventricular inflow in cardiac tamponade (apical transducer position). Phasic respiratory variation in the peak E-wave velocity (which varies from 57 to 88 cm/s) is readily apparent; ideally this should be gathered with a respirometer.

The combination of Doppler with respirometry is useful for the evaluation of constrictive pericarditis.[149] As with cardiac tamponade, pericardial constriction produces exaggerated respiratory variation in the isovolumic relaxation time and in flow velocities within RV and LV, pulmonary veins, and hepatic vein. A respiratory variation of > 20% in peak mitral E velocity favors the diagnosis of constriction over restrictive cardiomyopathy, whereas little respiratory variation favors restrictive physiology. Unfortunately, exaggerated respiratory flow variation is not specific for pericardial constriction and also can be seen in chronic obstructive pulmonary disease and asthma. In these cases, Doppler examination of superior vena cava flow is useful; patients with asthma have increased flow toward the heart during inspiration, whereas limited forward flow is seen in constriction (the echocardiographic equivalent of Kussmaul sign). An important clue to constriction is the presence of large diastolic flow reversal in the hepatic veins with expiration. Both forms of diastolic dysfunction typically exhibit restrictive patterns on transmitral ($E > A$) and pulmonary venous ($S < D$) spectral flow recordings. Tissue Doppler imaging of the mitral annulus shows characteristic changes in constrictive physiology. First, the early diastolic velocity of the mitral annulus (e_m) remains normal, whereas it is abnormally low in restrictive cardiomyopathy. Second, because of pericardial tethering in pericardial constriction, there is a reversal of the usual pattern of higher lateral than septal annular velocities.



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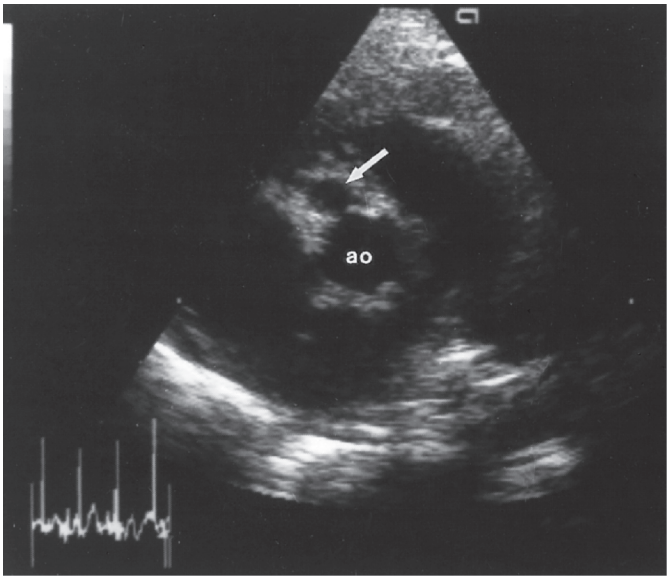


B

FIGURE 15–140. Parasternal short-axis images of coronary artery aneurysms associated with Kawasaki disease. **A.** The proximal left coronary artery (LCA) is diffusely dilated and aneurysmal. **B.** A proximal right coronary artery aneurysm (*arrow*) is shown. Ao, aorta, LA, left atrium. Used with permission from Victor Lucas, MD, and Paul Grossfeld, MD.

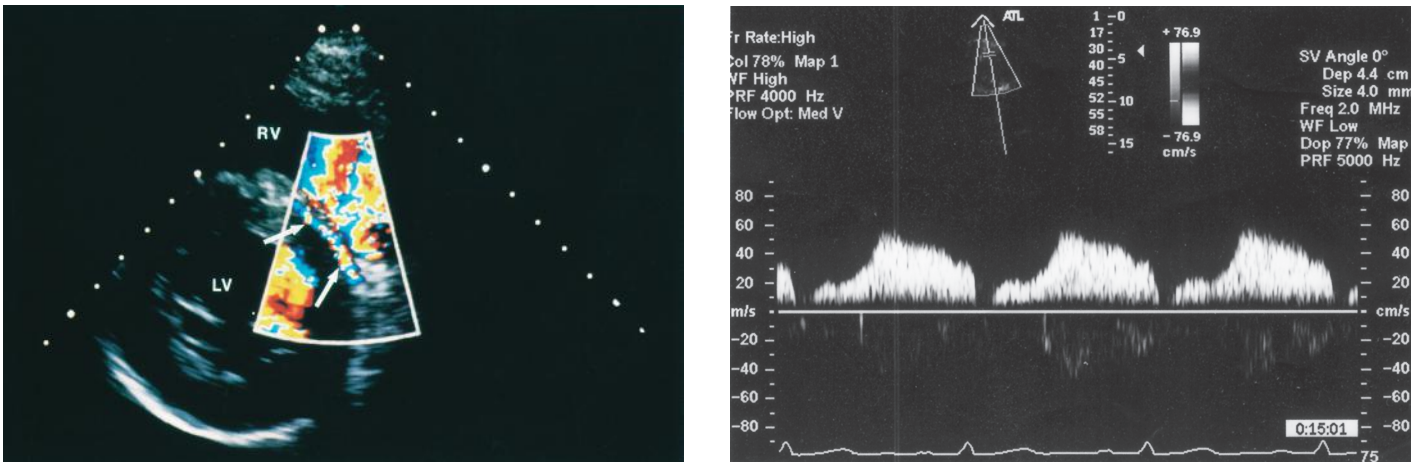
IMAGING OF THE CORONARY ARTERIES

The proximal segments of the left and right coronary arteries can be demonstrated by echocardiography. Color and spectral Doppler of the left anterior descending coronary artery are obtainable from TTE and TEE, and can be used to assess flow reserve, in conjunction with stress echocardiography.[150]

Transthoracic imaging has proven useful for the diagnosis and follow-up of patients with Kawasaki disease and coronary involvement (Fig. 15–140). However, their ability to distinguish normal from atherosclerotic coronary arteries is limited by the resolution of the technique being at the limit of vessel size and the vessels are circuitous and move vigorously, often coursing in and out of the beam path. Visualization of mid- and distal coronary arteries is problematic with both TTE and TEE. Figure 15–141A shows color flow within a septal coronary artery. Figure 15–141B shows a spectral Doppler recording of flow within the distal left anterior descending coronary artery (note the predominance of diastolic flow). These images were produced by an instrument using a fundamental frequency range of 5 to 7 MHz, rather than the more commonly used range of 2.5 to 5.0 MHz.

ACKNOWLEDGMENTS

We would like to Dr. Daniel G. Blanchard, who contributed to the previous version of this chapter in the 13th edition.



A B

FIGURE 15–141. A. Transthoracic short-axis image of a coronary artery within the interventricular septum (*arrows*). **B.** Pulsed-wave spectral Doppler tracing of flow within the distal left anterior descending artery. Diastolic flow is predominant. LV, left ventricle; RV, right ventricle. Used with permission from Ajit Raisinghani, MD.

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CHAPTER 16

MAGNETIC RESONANCE IMAGING OF THE HEART

W. Gregory Hundley, Christopher M. Kramer, and Javier Sanz

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INTRODUCTION

Over the past 30 years, cardiovascular magnetic resonance (CMR) imaging has evolved from a technique used to acquire static images of the heart and chest into a versatile imaging modality for assessing many physiologic variables pertinent to the evaluation of patients with cardiovascular (CV) disease. CMR-based methods accurately measure left and right ventricular (LV and RV, respectively) volumes, mass, and function and are able to characterize the presence and extent of myocardial infarction (MI) and viability. Hence, they now serve as "gold standard techniques" for assessing these metrics. Increasingly, CMR enables (1) assessments of myocardial perfusion in the investigation of ischemic heart disease; (2) differentiation of the etiology of nonischemic cardiomyopathies; and (3) characterization of congenital heart syndromes, pericardial disease, and cardiac masses. The purpose of this chapter is to review the use of CMR in these clinical situations. Also, several advantages (lack of ionizing radiation, ability to image in multiple tomographic planes, high spatial, temporal and contrast resolution, and reproducibility),[1] as well as disadvantages (primarily need for availability/operator-staff experience, less feasibility in claustrophobic patients, and potential hazards associated with the magnetic field) are discussed.

PHYSICAL PRINCIPLES AND INSTRUMENTATION

For the majority of magnetic resonance imaging (MRI)–related studies, image formulation relies on principles related to signals detected from hydrogen nuclei within the body. In a strong magnetic field, these hydrogen nuclei (or protons) align and "precess" (spin) about the *z*-axis of the field (along the bore of the scanner). Pulse sequences or small magnetic field pulses alter this precession by delivering nonionizing electromagnetic radiation that transfers energy to ("excites") protons and tilts them into the x-y plane to a degree determined by the flip angle. The subsequent relaxation of the protons to their original orientation within the magnetic field creates a signal that is detected by a radiofrequency receiver (or coil). Spatial variations in the magnetic field (magnetic gradients) enable identification of the physical location of these proton signals, which can then be processed into an image of their spatial distribution (Fig. 16–1). After excitation, relaxation of protons within the magnetic field is governed by the field strength and the T1 and T2 magnetic times, which are intrinsic properties of the tissue. T2* time refers to T2 after accounting for inhomogeneity of the magnetic field. Quantification ("mapping") of these times can be performed with appropriate sequences.

Most CMR studies are performed on scanners with field strengths of 1.5 Tesla (T) or 3T. In addition to the room housing the magnet (Fig. 16–2), there is a control room located just outside the scanner room housing the computer consoles to direct the scan acquisition as well as a small equipment room housing electrical and other scanner-related equipment. For CMR studies, additional equipment is required, including that for monitoring heart rate and blood pressure, injecting intravenous contrast, and delivering intravenous medications. As images are obtained, they are typically transferred to additional computer workstations for independent image analysis and interpretation.

Recommendations for acquisition,[2] reporting,[3] and analysis[4] of CMR images have been recently published to guide imagers on appropriate application of these techniques.

TECHNIQUES

Steady-state free precession (SSFP) cine "bright-blood" imaging forms the foundation and primary acquisition strategy for most CMR examinations.[5] This mode of acquisition provides high contrast-to-noise between

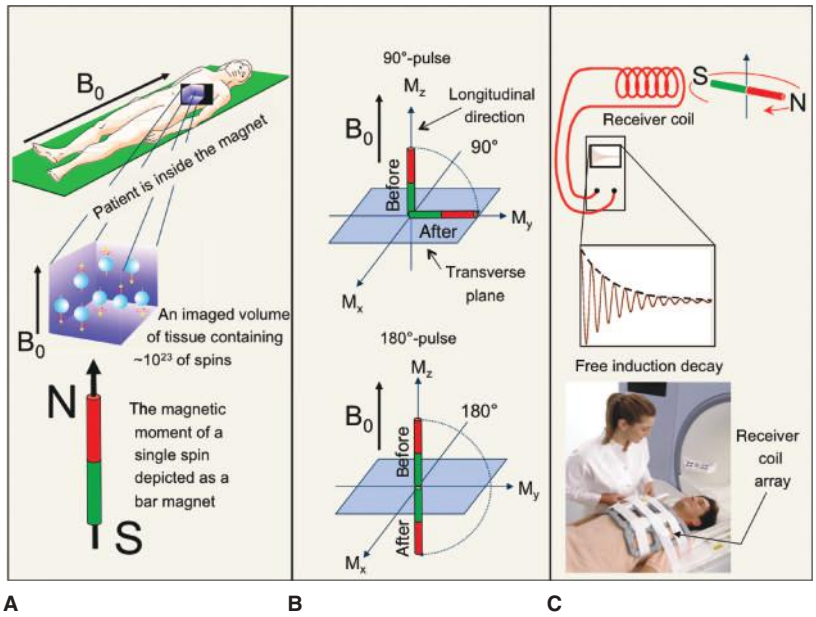


FIGURE 16–1. Basic operations of the magnetic resonance imaging scanner. **A.** The protons align parallel or antiparallel to the static magnetic field (Bo), creating a small net magnetization vector. While aligned to the magnetic field, the protons precess at a frequency proportional to the strength of the magnetic field (the Larmor frequency). **B.** Transmission of radiofrequency (RF) energy. Energy is transmitted to the rotating protons by an RF pulse at the Larmor frequency. RF pulses that result in a flip angle of 90 and 180 degrees are shown (*top* and *bottom*, respectively). The figures are presented in the rotating frame of reference, where the x-y axes are rotating at the Larmor frequency and thus appear stationary. **C.** Generation of the magnetic resonance (MR) signal. Rotation of the net magnetization vector into the transverse plane results in the creation of a time-varying magnetic field, which in turn induces an alternating current in the receiver coil array; this is the MR signal.

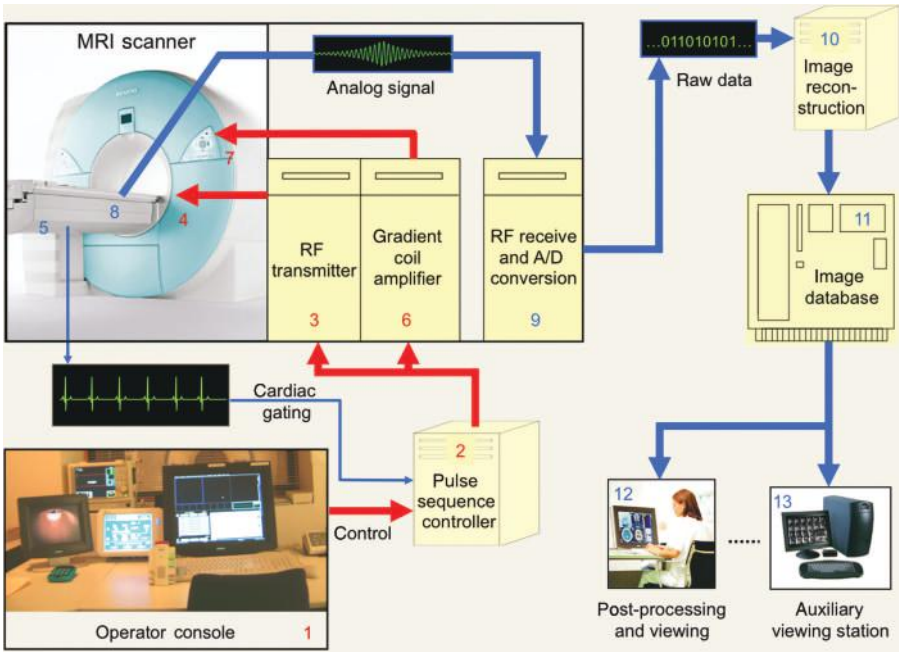


FIGURE 16–2. Components of the magnetic resonance imaging (MRI) scanner. For a cardiovascular magnetic resonance (CMR) study, the operator defines the type of examination and manipulates the imaging parameters from a control computer console using a graphical user interface (1). Software, known as a pulse sequence, is selected from a menu to acquire images that are appropriate for the diagnostic question. The precisely timed radiofrequency (RF) pulses, used to stimulate tissues, are generated by the pulse sequence controller (2), RF transmitter (3), and RF coil (4). For CMR, the electrocardiogram signal (5) from the patient is often used for timing. Spatial image information is encoded by the gradient coil amplifier (6) and gradient coil (7), which alter the net magnetic field (Bo) of the MRI scanner. The MR signal from the body is detected from fixed receiver coil arrays (8) that are built into the patient table and from flexible arrays that can be placed on top of the patient. These received signals, which are usually analog, are processed and digitized by an analog-digital (A/D) converter (9) and then passed to a computer dedicated to image reconstruction (10). The final images are then stored in a image database or picture archiving and communication system (11) and can undergo postprocessing at a work station (12) and interpretation at auxiliary viewing stations (13).

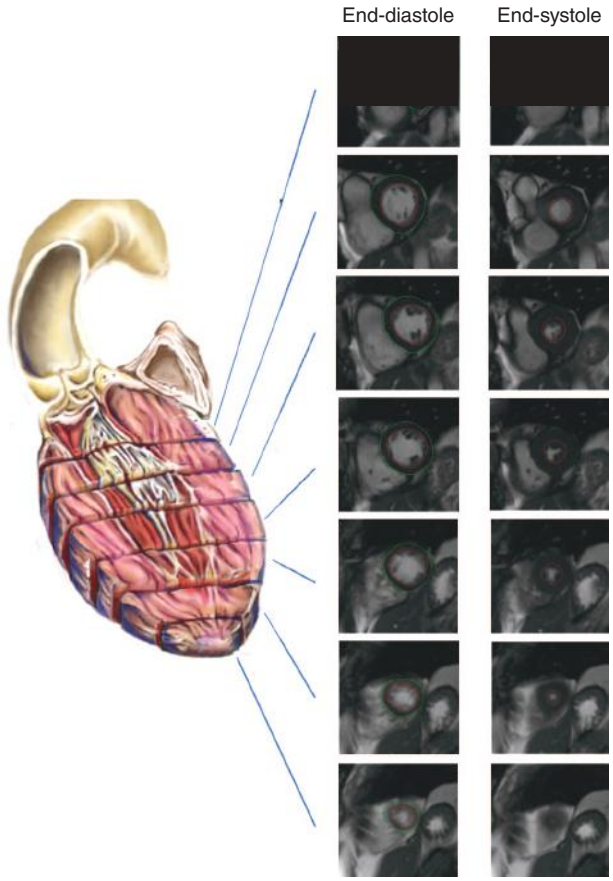


FIGURE 16–3. Cardiovascular magnetic resonance method to quantify left ventricular (LV) volumes, ejection fraction, and mass. The LV myocardium, cavity, mitral valve apparatus, and ascending thoracic aorta are depicted on the left. As shown on the right, a series of cine white blood images are acquired in short-axis planes positioned perpendicular to the long axis of the left ventricle. For each slice position, an end-diastolic frame and an end-systolic frame of the cine loop are displayed. On these images, the LV myocardial blood pool appears white and the myocardium gray. To calculate LV volumes, the area of the LV myocardial blood pool (red contour along the endocardial surface) is obtained. The LV volume is determined by summing the volume of all the slice positions (calculated for each slice by multiplying the area of each slice by the slice's thickness) spanning the cardiac base to the myocardial apex. The LV ejection fraction is calculated by subtracting the end-systolic volume from the end-diastolic volume and then dividing by the end-diastolic volume. Measurement of myocardial mass can be obtained by assessing the difference in the area bounded by the LV epicardial surface (green line) and endocardial surface (red line) and then summing myocardial volumes across the slices (and then multiplying by 1.05 g/cm^3 the assumed density of the LV myocardium). Image rendered by A.E. Hundley.

the dark myocardium and bright-blood pool[6] and allows for the visualization of cardiac anatomy as well as atrial and ventricular contraction/relaxation. Multiple studies have demonstrated the accuracy and reproducibility of cine CMR bright-blood imaging for measuring LV volumes, ejection fraction (EF), and regional systolic function.[1] To measure LV volumes, mass, and EF, short-axis images spanning the apex to the base of the heart are acquired throughout the cardiac cycle with slice thicknesses between 6 and 8 mm, with or without 2- to 4-mm gaps, and with temporal resolution ≤ 45 milliseconds[2] (Fig. 16–3). Analysis is performed with computer software that uses semiautomated techniques for tracing endocardial and epicardial contours at end-diastole and end-systole and the summation of disks methods for adding volumes together from all of the short-axis slices. Measurements made with this three-dimensional (3D) data set do not require geometric assumptions and are therefore less prone to error than are two-dimensional (2D) methods such as 2D echocardiography, especially in ventricles deformed by MI or cardiomyopathies. Interobserver and interscan reproducibility is high, allowing for reduced sample sizes in clinical trials in heart failure.[7,8] Similarly, CMR is a highly reproducible technique for measurement of RV volumes because of its 3D analysis nature.[9] The RV can be measured using short-axis views or stacked axial scans; the latter improves identification of the tricuspid valve plane and correlates better with pulmonary flow measures.[10]

Typically, long-axis images are also obtained in standard two-, three-, and four-chamber views. Most commonly, SSFP sequences are utilized; however, gradient-echo bright-blood images may also be acquired because these images are more sensitive to detect turbulent flow in the setting of valvular obstruction or regurgitation. Stress testing can be performed with SSFP cine in multiple planes at different stages of dobutamine ± atropine infusion. These cine bright-blood images may be acquired with high spatial and temporal resolution during 6- to 10-second breath-holds (known as a *segmented* acquisition), or at a slightly reduced spatial and temporal resolution in "real-time" that does not require electrocardiographic (ECG) gating or breath-holding. This latter technique is often used in those with arrhythmia or limited breath-holding ability.[11]

Additional CMR methods are available for quantifying abnormalities of regional LV systolic function that may not be evident on visual inspection of the images.[12] One such technique applies radiofrequency and gradient pulses to null the myocardium at end-diastole, resulting in the placement of "tissue tags" that can be tracked through the cardiac cycle to enable assessment of myocardial deformation and measurement of myocardial strain[13,14] (Fig. 16–4). In addition to quantifying myocardial deformation, tissue tags may be used to assess pericardial adherence in the setting of possible constriction and quantify myocardial deformation in cardiomyopathies. Another newly available method to quantify regional LV function involves cine displacement encoded echoes, which enable high temporal and spatial resolution strain analyses without application of tissue tags.[15] At present, these quantitative techniques are used primarily for research purposes because of their somewhat lengthy analysis times.

Morphologic imaging with "black-blood" and "bright-blood" imaging (Fig. 16–5) is useful for depicting cardiac anatomy. In spin echo black-blood images, the MRI signal of the spins from flowing blood is inverted, leaving the blood pool dark within the LV cavity. Once a staple of most CMR examinations, black-blood imaging has been

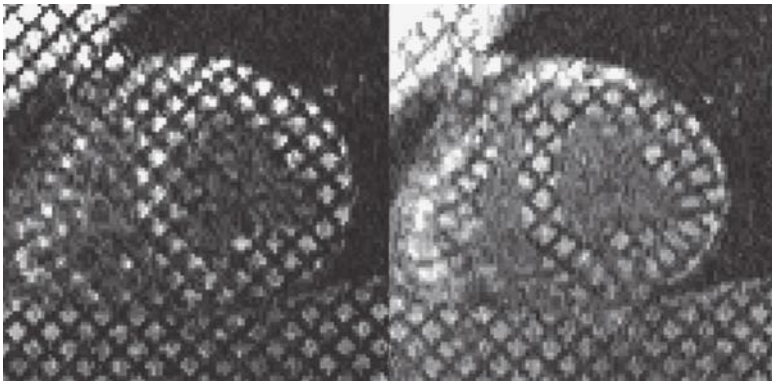


FIGURE 16–4. Short-axis end-diastolic (*left*) and end-systolic (*right*) gradient echo cine tagged images in a patient after acute anteroseptal myocardial infarction (MI). During systole, the tags deform and the boxes become trapezoids as the subendocardium shortens more than the subepicardium. Note the normal deformation of the tag stripes in the inferolateral wall at end-systole, whereas the rest of the myocardium shows little deformation from the MI.

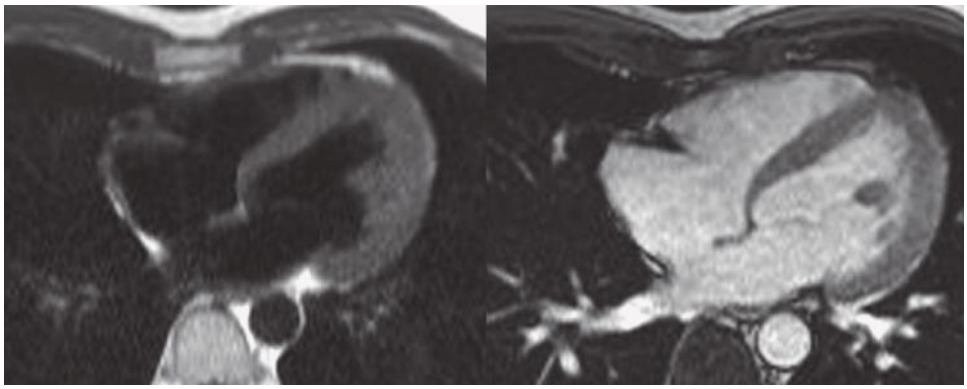


FIGURE 16–5. Axial back-blood half Fourier acquisition single-shot turbo spin echo (HASTE) image through the heart (*left*). Note that the blood within the cavities is black. Axial steady-state free precession–based bright-blood image through the heart in the same patient as on the left (*right*). With this pulse sequence, the blood appears white.

largely replaced by SSFP cine imaging because of its utility for assessing cardiac structure and function during the same acquisition. It is important to note that stationary SSFP images may be acquired in 3D view over a few minutes during free breathing with both respiratory and ECG synchronization. This has the advantage of providing a 3D data set that can be manipulated and viewed in any orientation, depicting both cardiac and extracardiac anatomy (Fig. 16–6), without the need for breath-holding or contrast.[16]

Tissue characterization with mapping or weighted imaging using assessments of T1, T2, or T2* relaxation is increasing in importance in CMR[17,18] (Fig. 16–7). High signal on T2-weighted imaging can demonstrate myocardial edema, such as in the setting of acute MI or myocarditis. Older T2-weighted imaging approaches are prone to artifacts and more recently, CMR protocols have used newer T2 mapping to overcome these limitations.[19] T1 of the myocardium can be measured by mapping with a modified Look-Locker inversion recovery, or MOLLI, sequence[20] or shorter versions of this approach, termed shMOLLI.[21] Native or precontrast T1 is measured before contrast infusion and then postcontrast T1 measures can be used to calculate the extracellular volume (ECV) fraction of the myocardium.[22] These techniques are increasingly used to differentiate causes of cardiomyopathy.[17] However, neither T1 nor T2 mapping are yet approved by the Food and Drug Administration (FDA) for clinical use. T2*-weighted imaging is sensitive to iron in the heart and can identify iron overload conditions and myocardial hemorrhage in the setting of acute MI.

Phase contrast (PC) imaging (also known as velocity-encoded cine, velocity mapping, or flow imaging) is used to display and quantify velocities and flow. It relies on the principle that precession frequency of protons is directly proportional to the velocity of a particle moving across a magnetic field gradient. If a magnetic gradient is created along the direction of blood flow, protons moving faster will be subjected to a stronger or weaker magnetic field and experience a proportional shift in their precession. Measurement of this shift therefore allows for the quantification of blood velocity along the direction of the gradient.[23] This is typically achieved by prescribing the acquisition perpendicular ("through-plane") to the expected direction of flow (ie, to the ascending aorta or pulmonary artery for quantification of systemic [aortic] or pulmonary forward cardiac outputs). PC sequences typically provide two reconstructions of the acquired data: a magnitude (or anatomic) image and a phase-difference reconstruction (velocity map) where the signal intensity of each voxel is rendered proportional to its velocity (Fig. 16–8). Accuracy is highest if the limit of measurable velocities is set close to but below the true velocity of blood. Using these sequences, flow is calculated by integrating changes in area and velocity throughout the cardiac cycle (see Fig. 16–8), and has been validated both in vitro and in vivo,[24] demonstrating very high accuracy. Newer 3D sequences (also known as four-dimensional PC or four-dimensional flow imaging) have been developed that enable the quantification of velocities in all directions[25]; however, these are not yet routinely used in clinical practice because of somewhat lengthy acquisition and processing times. Real-time PC sequences have also been developed that allow for acquisition during free breathing and without the need of ECG gating.[26]

Perfusion imaging has evolved significantly over the past 10 to 15 years.[27] In general, this is achieved by imaging the first-pass of a gadolinium-based contrast agent (GBCA) through the myocardium. It can be performed at rest (eg, to identify "tumor blush") and, for the purposes of stress testing, during vasodilator challenge to identify hypoperfusion associated with flow-limiting epicardial coronary artery stenoses.[28,29] Typically, images in three to five short-axis slices are acquired over 50 to 60 heartbeats. Images are assessed qualitatively for regions of low signal intensity consistent with hypoperfusion that

FIGURE 16–6. Axial (*left*), coronal (*middle*), and sagittal (*right*) reconstructions from a three-dimensional steady-state free precession data set.

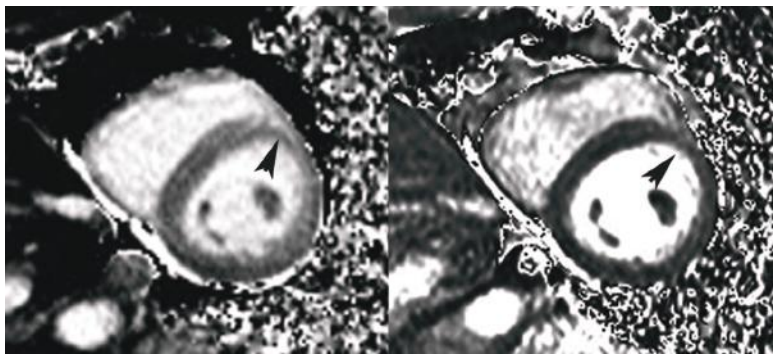


FIGURE 16–7. Short-axis T1 map in a patient with chest pain, troponin elevation, and normal coronary arteries with a recent viral infection and clinical diagnosis of myocarditis (*left*). There is higher T1 signal (brighter) in the anterior wall, which is also somewhat thinner. Short-axis T2 map in the same patient demonstrating bright signal (elevated T2) in the same region (*right*).

encompass at least the subendocardial one-third of the myocardial wall of at least five frames or heartbeats in duration (Fig. 16–9). Comparing rest and stress imaging with late gadolinium-enhanced (LGE) imaging (see below) can differentiate perfusion defects caused by ischemia from those cause by artifacts or MI.[30]

LGE refers to regions of scar and/or necrosis discriminated from normal tissue by prolonged retention of GBCAs as visualized on T1-weighted imaging.[31] An inversion recovery-based pulse sequence is used to optimize the differentiation of normal dark myocardial tissue from bright areas of fibrosis or scar.[32] These fibrotic areas appear bright as a result of retention of gadolinium, in turn because of increased volume of distribution as well as delayed washout of the contrast agent. LGE is considered the gold standard technique for detecting and sizing MI[31] (Fig. 16–10). However, LGE is not unique to infarct scar and can signify any cause of fibrosis or interstitial infiltration in cardiomyopathies, many of which have a unique pattern of LGE.[33]

Finally, magnetic resonance angiography (MRA), another important CV application, is typically performed using a 3D gradient echo acquisition during passage of a GBCA and is described in detail in Chap. 22.

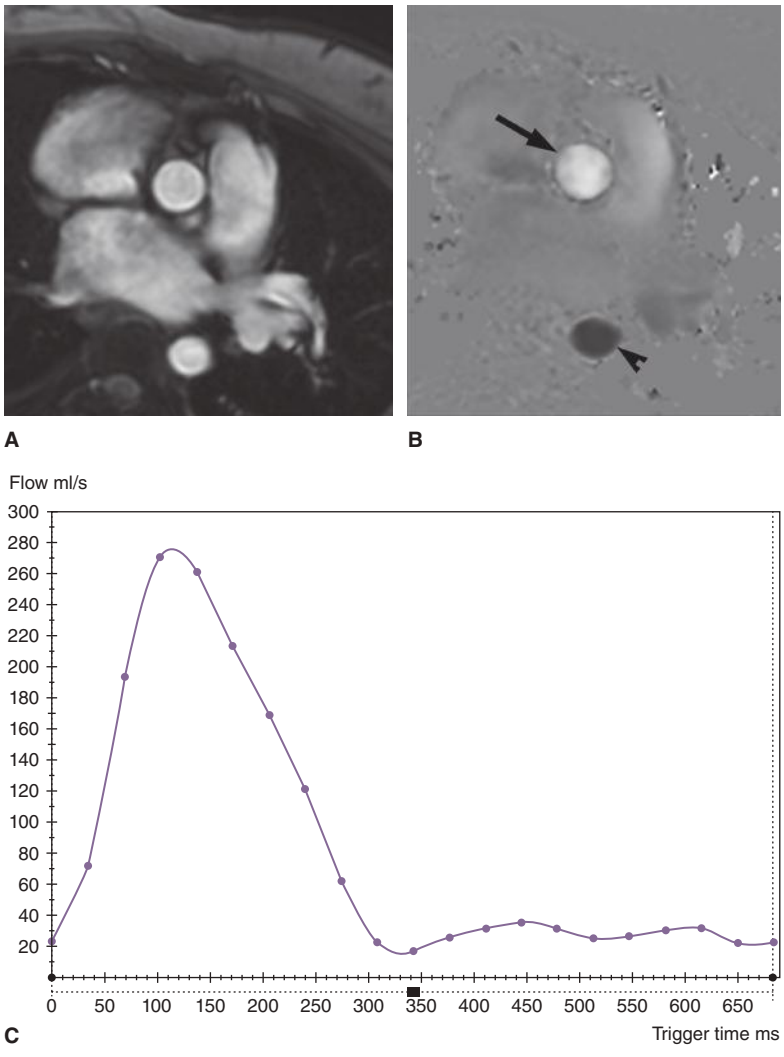


FIGURE 16–8. Magnitude image (**A**) and velocity map (**B**) of the ascending aorta as obtained with phase contrast. Note that flow moving in one direction through the plane is encoded in white (ascending aorta; *arrow*) whereas flow in the opposite direction is encoded in black (descending aorta, *arrowhead*). Integration of velocities and cross-sectional area allows for the quantification of flow (**C**).

SAFETY

METALLIC AND ELECTRONIC DEVICES

Although a relatively safe imaging modality, CMR does possess potential for serious and even lethal events. The magnetic field of clinical CMR scanners is 25,000 to 50,000 times stronger than that of the earth, and ferromagnetic metallic objects that come into close proximity with the field can be drawn toward the magnet in a projectile fashion. It is important to realize that the magnetic field is always "on," even when the scanner is not being used; therefore, all personnel involved in CMR operations need to be appropriately trained, and access to the CMR room and its vicinity must be severely restricted and adequately demarcated. Only MRI-compatible devices and materials (such as injections pumps or stretchers) may enter the magnet room, and individuals need to be appropriately screened.[34]

A CMR scanner may also pose danger to patients or personnel with implanted ferromagnetic or electronic devices. Aside from the potential for torque or pull by the magnetic field, the rapidly switching magnetic gradients can induce voltages in conducting materials, which in turn may heat surrounding tissues. In addition, depending on the sequence used, the magnetic field strength, and the specific device, changes in programming and functioning of implanted electronic devices may occur. Thus, the decision needs to be individualized for each patient to determine (1) whether the specific device is MRI-compatible and (2) at what field

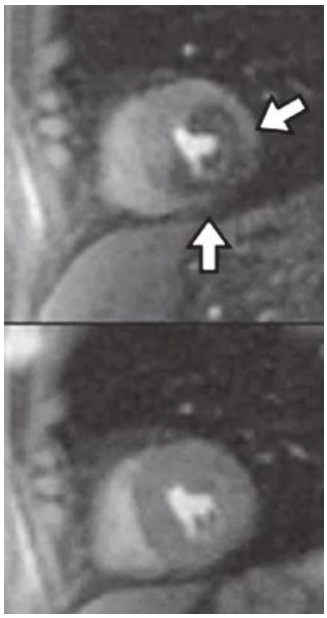


FIGURE 16–9. Hybrid gradient echo/echo planar first-pass contrast-enhanced perfusion images during vasodilator stress (*top*) and rest (*bottom*). At stress, there is a large perfusion defect in the anterolateral and inferolateral walls (*arrows*), whereas perfusion is normal at stress. This patient had two-vessel coronary artery disease (right and left circumflex) at subsequent cardiac catheterization.

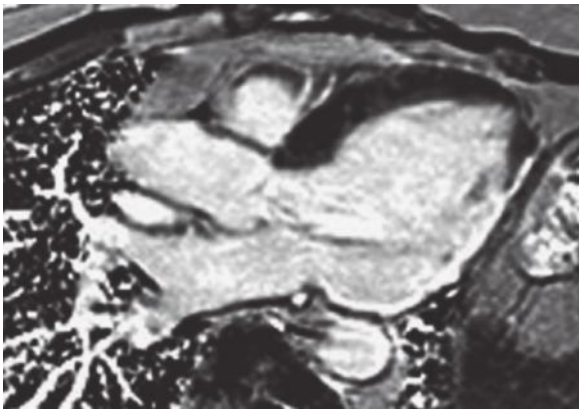


FIGURE 16–10. Three-chamber long-axis phase-sensitive inversion recovery late gadolinium-enhanced (LGE) image in a patient with a chronic inferolateral infarction. Note the wall thinning and near transmural LGE in that region.

strength it is compatible. As a general rule, objects located in soft tissues that can be easily harmed are the greatest concern; these include the orbits and the brain (typically aneurysm clips, of which most modern ones are MRI-compatible). The vast majority of orthopedic implants are safe. Regarding devices frequently encountered in cardiac patients, safety recommendations[35] are summarized in Table 16–1. All current coronary stents and prosthetic valves are safe and can be imaged immediately after implantation. Many other cardiac or vascular implants are nonferromagnetic and can also be scanned at any time, or are weakly ferromagnetic and a delay of 6 weeks before MRI is recommended to allow for endothelialization. Swan-Ganz catheters contain metal and are considered unsafe. Similarly, some medication patches contain metallic foil and may need to be removed before the procedure.

TABLE 16–1. Safety of Common Metallic Implants and Electronic Devices Commonly Found in Patients Undergoing Cardiovascular Magnetic Resonance at ≤3 Tesla

Safe at any Time	Safe at any Time or after 6 Weeks[a]	Unsafe
Valve prostheses/rings	Cardiac occluder devices	Pacemakers[b]
Coronary stents	Embolization coils	Defibrillators[b]
Retained epicardial leads	Peripheral stents	Retained intravenous leads
Sternotomy wires	Inferior vena cava filters	Swan-Ganz catheters
		Transdermal patches

[a]For weakly ferromagnetic devices, it is reasonable to wait 6 weeks after implantation; other devices can be scanned immediately after implantation.

[b]See text.

Although pacemakers and implantable cardioverter-defibrillators (ICDs) have been traditionally considered absolute contraindications for CMR, an increasing body of literature indicates that it is feasible to safely scan select patients with select devices, as long as strict protocols and monitoring are followed. In the absence of such protocols, MRI with pacemakers and ICDs should still be considered unsafe.[34] Some MRI-compatible pacemakers and, more recently, one ICD have become available, although not all of them allow performance of CMR.

NEPHROGENIC SYSTEMIC FIBROSIS

Although GBCAs were traditionally considered safe in patients with renal failure, an association between nephrogenic systemic fibrosis (NSF) and gadolinium use in advanced kidney disease was described in 2006. This led to a US FDA Black Box Warning related to the administration of GBCAs and NSF (a fibrosing disease primarily involving the skin and subcutaneous tissues, which can also affect internal organs). Symptoms typically include skin thickening and/or pruritus, with potential for contractures and joint immobility, and rarely, death through visceral fibrosis. The estimated incidence is 1% to 7% in those with an estimated glomerular filtration rate (eGFR) < 30 mL/min/m^2, and it is more common in patients on dialysis and with specific GBCAs.[36] GBCAs should be avoided in patients with eGFR < 30 mL/min/m^2 and in those with acute renal failure (where eGFR may be less accurate). Caution is recommended for those with eGFR between 30 and 40 mL/min/m^2 because of daily fluctuations in eGFR. For those patients on dialysis, prompt (within 2 hours) hemodialysis after the test should be considered to enhance elimination, although the benefit of this approach is unproven. Peritoneal dialysis is not considered effective.[36]

PREGNANCY AND LACTATION

There is no conclusive evidence that CMR can induce harm to the fetus; however, there is no solid data on its safety, either. Therefore, CMR is not recommended, although it can be performed after physician-patient discussion if the benefits are deemed to outweigh potential risks. The stage of the pregnancy plays no role in the decision.[34] The same applies to the use of GBCAs, which are known to cross the placental barrier and might be harmful to the fetus.[36] A very small amount of GBCA is excreted in the milk and it is considered safe to continue breastfeeding, although 12- to 24-hour interruption is occasionally recommended.[36]

OTHER

Magnetic gradients can cause peripheral stimulation that may be perceived as tingling. They also cause loud noises, so ear protection is systematically provided. The incidence of claustrophobia precluding CMR is approximately 4%; around half of these patients will be able to undergo the test with mild sedation.[37]

ISCHEMIC HEART DISEASE

CARDIOVASCULAR MAGNETIC RESONANCE STRESS TESTING

Appreciation of LV myocardial ischemia has traditionally depended on identifying abnormalities of LV myocardial perfusion, wall motion, metabolism, or epicardial coronary artery blood flow after experiencing some form of stress. CMR is unique in that with a single imaging modality one can identify abnormalities of LV myocardial perfusion or wall motion in a single test with a relatively high spatial resolution and without administration of any form of ionizing radiation (Fig. 16–11). Based on multimodality appropriate use criteria, stress CMR is considered appropriate for patients with high pretest probability for coronary artery disease (CAD) or intermediate pretest probability of CAD with an uninterpretable ECG or inability to exercise.[38] It is also appropriate for patients with an abnormal ECG who are intermediate to high risk as well as those with an abnormal or uncertain exercise ECG or those with obstructive CAD of uncertain significance noted on computed tomography (CT) or invasive coronary angiography.

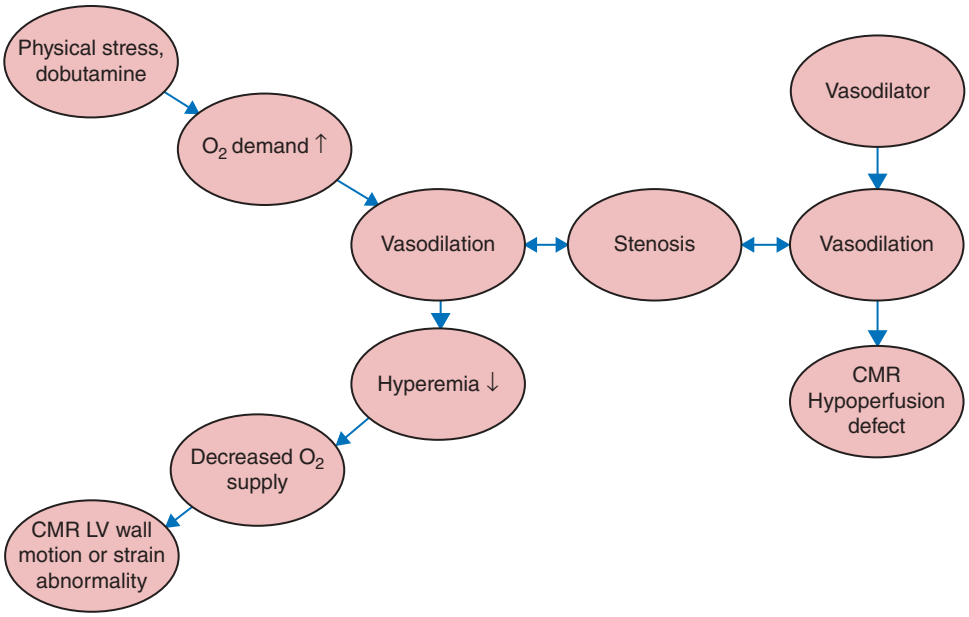


FIGURE 16–11. Mechanisms by which cardiovascular magnetic resonance (CMR) may appreciate functional evidence of epicardial coronary arterial stenoses. LV, left ventricular.

Imaging Suite and Environment

It is important to recognize that appropriate environmental conditions and safety procedures are required when seeking to perform CMR stress testing. Similar to stress testing environments used with other modalities, staff familiar with CV stress testing, including nursing personnel and physicians, should be present during and immediately after testing.[39,40] In regard to safety, medication carts and defibrillators should be secured outside of, but in close proximity to, the CMR scanning room, and if defibrillation during testing should be required, patients should be removed from the CMR room to deliver cardioversions. It is also important to note that specialized MRI-compatible equipment for assessing blood pressure, heart rate, oxygen saturation, and respiratory rate should be present in the MRI scanning room. Because the magnetic field alters the appearance of ST segments and T waves on the ECG once the patient enters the scanner, ECG tracings are used to monitor patients' rhythm and not to detect ST-segment changes associated with inducible ischemia. As such, many stress CMR facilities utilize near real-time image review to appreciate inducible ischemia (Fig. 16–12). As shown in Fig. 16–13, prior to CMR stress testing, a resting 12-lead ECG, intravenous access, pulse oximetry, and brachial blood pressure cuff are applied outside of the magnet room.[41]

In one of the largest studies of more than 1000 individuals undergoing dobutamine stress CMR, potential side effects were noted to occur in 6.4% of individuals (vasodilator stress CMR has an even better safety profile).[42] The side effects included sustained ventricular tachycardia (0.1%); nonsustained ventricular tachycardia (0.4%); paroxysmal atrial fibrillation (1.6%); transient second-degree atrioventricular block (0.2%); marked changes in systolic blood pressure, including elevations to greater than 240/120 mm Hg (0.5%); and substantial decreases of > 40 mm Hg (0.5%). Accordingly, personnel familiar with managing these conditions should be present.

Major events during CMR stress testing are usually associated with continued infusions of pharmacologic stress agents in the setting of concurrent myocardial ischemia. As such, near simultaneous viewing of images is recommended and a high level of attention is suggested so that termination of the stress procedure can occur once evidence of ischemia is present (see Fig. 16–12).

FIGURE 16–12. A photograph of a stress cardiovascular magnetic resonance (CMR) testing suite. The individual on the left (technologist) performs the scans, and the individual on the right (physician) reviews the stress image results in near real time. Through the window, the patient is seen in the CMR scanner with hemodynamic monitoring occurring during stress. Reproduced with permission from Chotenimitkhun R, Hundley WG: Pharmacological stress cardiovascular magnetic resonance. *Postgrad Med*. 2011 May;123(3):162-170.

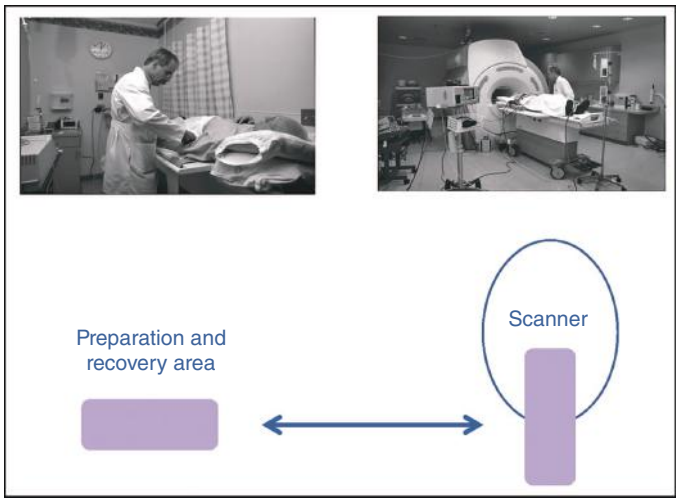


FIGURE 16–13. Images highlighting the preparation/recovery area (*left*) as well as the scanning facility (*right*). Note that by utilizing a preparation and recovery area, patient throughput in a cardiovascular magnetic resonance center is enhanced, because the scanning facility is not used for time-consuming, non–scan-related tasks such as insertion of intravenous catheters or placement of special monitoring equipment.

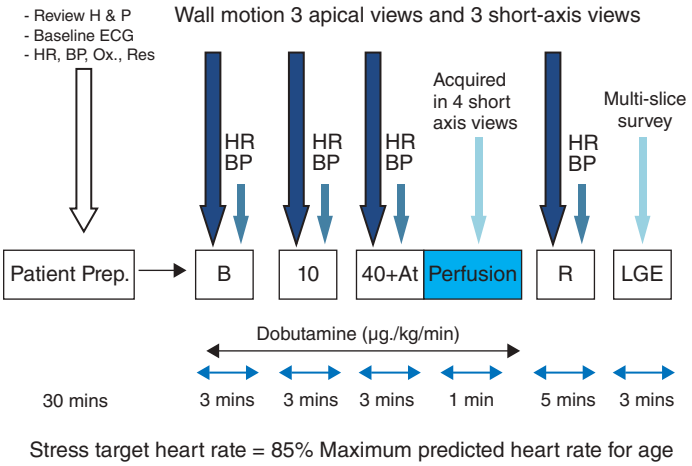
Dobutamine Stress

For dobutamine stress testing, baseline images are acquired in three standard long-axis and short-axis views at rest (Fig. 16–14). Dobutamine (in increasing doses up to 50 µg/kg/min) and atropine are then infused to achieve a heart rate response that is 85% of the maximum predicted heart rate response for age.[43] Optionally at intermediate stages, repeat wall motion images may be obtained. At peak stress or at the first sign of chest pressure consistent with angina, repeat wall motion and myocardial stress perfusion images are acquired (see Fig. 16–14).[39-43] The pharmacologic stress agents are then discontinued, and a recovery series of images is obtained. To interpret the test, the LV is divided into 17 segments according to the American Heart Association and American College of Cardiology.[44] Throughout testing, a four-point scoring system (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic) is used to assess wall motion within each segment. Myocardial ischemia is identified when a deterioration of ≥ 1 in a segment score occurs during the stress test (Fig. 16–15).

As shown in Table 16–2, the sensitivity and specificity of dobutamine stress CMR for detecting greater than 50% coronary arterial stenoses with wall motion analyses alone range from 78% to 96%.[45] It is important to recognize, however, that there are several situations in which dobutamine wall motion analyses alone may underappreciate the presence of inducible ischemia and functionally important CAD. To address these outstanding issues, several investigators have advocated for the incorporation of first-pass contrast-enhanced stress perfusion at peak heart rate response during intravenous dobutamine, and the acquisition of LGE images in the recovery phase of dobutamine and atropine administration (see Fig. 16–14). In 1493 patients referred for dobutamine stress with suspected or known CAD, the simultaneous identification of LV wall motion and myocardial perfusion abnormalities was associated with an increase in the hazard ratio for future CV events.[46] The results of myocardial perfusion stress testing were most evident in those individuals with resting LV wall motion abnormalities or underlying LVH (P =.02–.09)

These situations include those individuals with resting LV segmental wall motion abnormalities, the presence of prior MI and scar, those with left ventricular hypertrophy (LVH) or concentric remodeling, and finally those individuals who are older and exhibit a hyperdynamic response with a decline in systolic blood pressure during testing.[47].

In 278 individuals[48] aged 69 ± 8 years with preexisting or known risk factors for CAD who underwent simultaneous assessment of LV myocardial perfusion and wall motion after peak dobutamine infusion,



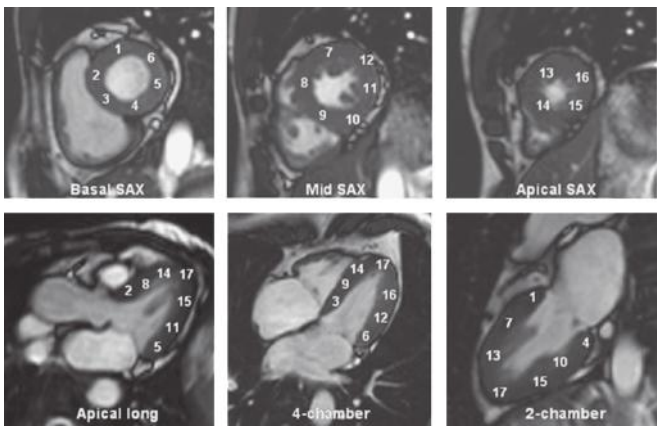


FIGURE 16–14. A. Dobutamine infusion protocol for cardiovascular stress testing. As shown, three apical and three short-axis views are acquired at baseline (B) over a 3-minute period. Also, heart rate (HR) and blood pressure (BP) are collected. Next, dobutamine is infused at 10 µg/kg/min, and the three apical and three short-axis views are repeated. At peak stress, a combination of dobutamine and atropine (At) are infused to achieve 85% of the maximum predicted heart rate response for age, and wall motion acquisitions are repeated. At this time, gadolinium first-pass perfusion images may be acquired. On completion of the peak stress image acquisitions, recovery images (R) are obtained prior to patient discharge. Also, if contrast was administered, late gadolinium-enhanced (LGE) images may be acquired. The total scan time for an individual with a negative stress test averages 25 minutes using this protocol. Ox, oxygen saturation; Res, respiratory rate. **B.** Cine magnetic resonance images of the left ventricle are displayed in three short-axis (*upper row*) and three long-axis (*lower row*) views. The left ventricular myocardium is divided into 17 segments as identified: 1 = basal anterior; 2 = basal anteroseptum; 3 = basal inferoseptum; 4 = basal inferior; 5 = basal inferolateral; 6 = basal anterolateral; 7 = midanterior; 8 = midanteroseptum; 9 = midinferoseptum; 10 = midinferior; 11 = midinferolateral; 12 = midanterolateral; 13 = apical anterior; 14 = apical septum; 15 = apical inferior; 16 = apical lateral; and 17 = apical cap. SAX, short axis. Reproduced with permission from Rerkpattanapipat P, Hundley WG: Dobutamine stress magnetic resonance imaging. *Echocardiography*. 2007 Mar;24(3):309-315.

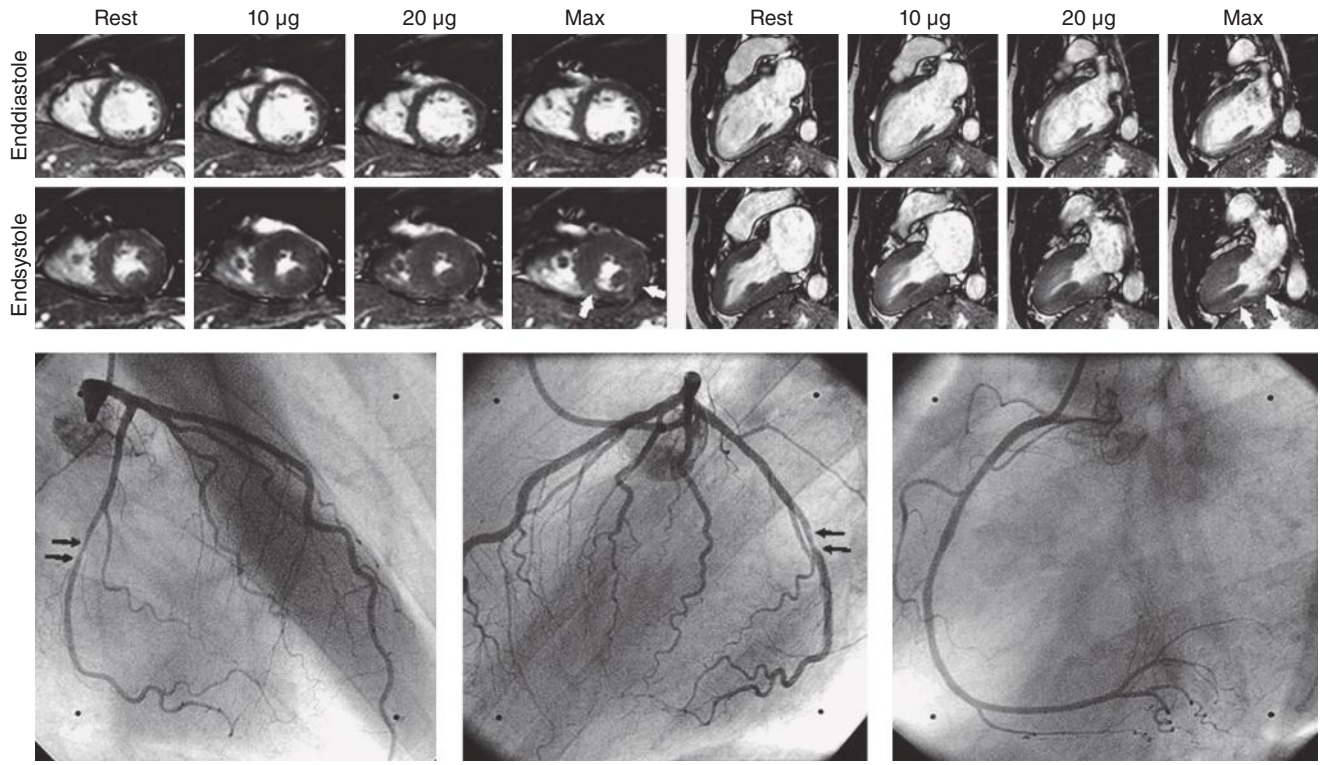


FIGURE 16–15. Positive dobutamine cardiac magnetic resonance (DCMR). DCMR cine images (short-axis and two-chamber view) of a patient with chest pain and suspected coronary artery disease (*top*). At rest and under increasing dobutamine, there is normal regional function. However, at maximum stress, an inferolateral wall motion abnormality is elicited. X-ray coronary angiography images demonstrating single-vessel left circumflex coronary artery disease (*bottom, black arrows*). Reproduced with permission from Paetsch I, Jahnke C, Fleck E, et al: Current clinical applications of stress wall motion analysis with cardiac magnetic resonance imaging. *Eur J Echocardiogr*. 2005 Oct;6(5):317-326.

60% of individuals with perfusion defects indicative of myocardial ischemia exhibited no inducible wall motion abnormalities. Among these participants, myocardial oxygen demand was lower in those who had both LV wall motion and perfusion abnormalities suggestive of ischemia (P =.03). Factors associated with the presence of perfusion defects without an inducible wall motion abnormality included a reduced LV end-diastolic volume index (LV preload) or increased concentric LV remodeling. The results of these studies demonstrate the limitations of LV wall motion assessments alone when evaluating patients referred for any form of dobutamine stress examinations

TABLE 16–2. Utility of Dobutamine Wall Motion Stress Cardiovascular Magnetic Resonance for Identifying ≥ 50% Coronary Arterial Luminal Narrowing

Author (Reference Number)	Patients (n)	Men (%)	Mean Age (years)	Dobutamine Dose (µg/kg/min)	Sensitivity (%)	Specificity (%)
Gebker et al (47)	455	65	64	40 + atropine	91	70
Hundley et al (39)	163	56	NS	40 + atropine	83	83
Korosoglou et al (258)	80	73	62	40 + atropine	83	91
Kuijpers et al (42)	194	67	62	40	96	95
Nagel et al (40)	208	71	60	40 + atropine	86	86
Paetsch et al (259)	79	66	61	40 + atropine	89	80
Paetsch et al (260)	150	83	61	40 + atropine	78	88
Pennell et al (261)	25	74	52	20	91	100
Schalla et al. (262)	22	80	60	40 + atropine	81	83
van Rugge et al (263)	45	82	61	20	81	100
van Rugge et al (264)	39	86	60	20	91	80
Wahl et al (265)	160	-	59	40 + atropine	89	84

Reproduced with permission from Charoenpanichkit C, Hundley WG: The 20 year evolution of dobutamine stress cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2010 Oct 26;12:59.

(CMR, echocardiography, radioisotope imaging) and point out the ability of simultaneous LV wall motion and perfusion assessments in these same situations.

Contractile Reserve and Viability

Although LGE techniques are widely used for identifying myocardial scar and thus infer viability, dobutamine stress CMR measures of LV myocardial contractile reserve remain important for assessing myocardial segments that have the potential to recover systolic function after successful epicardial coronary arterial revascularization.[49,50] Similar to the protocol utilized for myocardial ischemia, in those patients undergoing dobutamine viability studies, resting images are obtained prior to initiation of stress. After baseline imaging, low-dose dobutamine infusions in the range of 7.5 to 10 μg/kg/min are administered and repeat assessments of myocardial contractility are obtained. The first study[51] to publish comparisons of dobutamine stress CMR and ^{8}F-fluorodeoxyglucose positron emission tomography (PET) demonstrated that dobutamine-induced wall thickening was superior to resting LV end-diastolic wall thickness alone for predicting viable myocardium. In fact, dobutamine stress CMR had similar diagnostic accuracy relative to ^{8}F-fluorodeoxyglucose PET scanning.

A particular advantage of low-dose dobutamine infusions for assessing myocardial viability is that they can be administered to patients with reactive airways disease as well as those with renal dysfunction in whom the use of gadolinium may be contraindicated. In addition, there is some evidence that low-dose dobutamine stress CMR assessments of improvements in regional wall motion or radial thickening may be superior to the assessments of LGE, particularly in those individuals who have intermediate presence of LGE (Fig. 16–16; see also section on remote myocardial infarction).[50]

Vasodilator Stress

CMR perfusion imaging in general is accomplished after the administration of contrast agents that help to demonstrate discrepancies in LV myocardial perfusion between adjacent myocardial segments as well as absolute perfusion within a particular segment.[52] For the most part, GBCAs are utilized because of their ability to accentuate T1 relaxivity

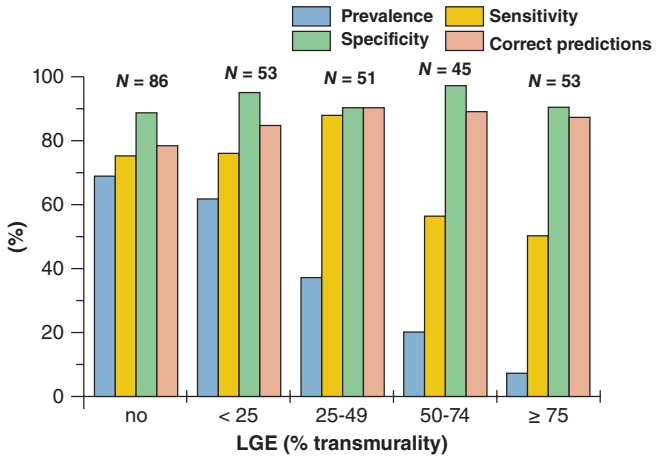


FIGURE 16–16. Transmurality of late gadolinium enhancement (LGE): subgroup analysis. Bars refer to the prevalence of recovery and sensitivity, specificity, and percentage of correct predictions by dobutamine cardiac magnetic resonance (DCMR) and are subgrouped with respect to LGE (cutoff: 25%). The specificity of DCMR remains high irrespective of the extent of LGE. The test retains high sensitivity in 25% to 49% LGE. Reproduced with permission from Wellnhofer E, Olariu A, Klein C et al: Magnetic Resonance Low-Dose Dobutamine Test Is Superior to Scar Quantification for the Prediction of Functional Recovery. *Circulation*. 2004 May 11;109(18):2172-2174.

in perfused myocardium as well as a relatively favorable safety profile for administration in those without severe chronic kidney disease.[53]

With CMR, myocardial perfusion may be assessed qualitatively (visual inspection), semiquantitatively, or by fully quantitative methods that assess the absolute perfusion of the agent.[54] Quantitative perfusion methods have been found very accurate and to vary inversely with the degree of coronary stenosis by quantitative coronary angiography. Importantly, both quantitative as well as qualitative perfusion assessments by CMR have demonstrated very high correlations with fractional flow reserve measures using cutoff values of < 0.75.[55] Overall, those studies using qualitative assessments may require larger amounts of gadolinium contrast in the 0.1 mmol/kg range to optimize visualization, whereas quantitative analysis may be achieved with much lower doses such as 0.05 mmol/kg. Although quantitative and qualitative analyses have similar accuracy on a per-patient basis, quantitative analysis of perfusion reserve identifies the extent of myocardial ischemia more accurately.[56]

Although intravenous adenosine or dipyridamole has traditionally been administered to accomplish vasodilator stress, regadenoson has been utilized in the CMR environment as well. This agent is beneficial for the study of those individuals with obstructive or reactive airways disease in that regadenoson will enhance endothelial independent vasodilation of the coronary microcirculation but not precipitate bronchial constriction associated with lung disease.[57]

The stress perfusion protocol includes a stress perfusion assessment, followed by evaluation of LV wall motion, rest perfusion, and LGE identification of myocardial injury/fibrosis. Utilizing this methodology, the sensitivities and specificities for identifying flow-limiting coronary arterial stenoses when compared to contrast coronary angiography have both exceeded 90%.[58] The high spatial resolution of this technology enables identification of subendocardial infarcts that can be distinguished from small areas of subendocardial hypoperfusion related to reduced myocardial microcirculatory blood flow (Fig. 16–17) resulting from flow-limiting epicardial coronary arterial stenoses. In addition, this particular technique is useful for identifying inducible ischemia in those individuals with preexisting concentric LVH or remodeling, reduced left ventricular ejection fraction (LVEF), or female gender (when body habitus can impede acquisition with other methodologies).

Across several meta-analyses, the overall sensitivity and specificity of CMR vasodilator perfusion tests for identifying flow-limiting coronary artery stenoses were 91% and 81%, respectively. In addition, in a relatively large meta-analysis,[59] reporting on 4721 vessels in 2048 patients, CMR vasodilator stress performed similarly to CT and PET and better than single-photon emission computed tomography (SPECT) or echocardiography using pooled sensitivity and specificity analyses for identifying functionally important CAD (Table 16–3). When compared with fractional flow reserve measures, CMR has been shown in multicenter initiatives to compare favorably and perhaps superiorly to existing radioisotope and radionuclide techniques.[60] Several comparative study results have suggested that CMR perfusion imaging could realistically be used as an alternative (with superior results) to SPECT imaging. This was most convincingly demonstrated in the recent single-center Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease CE-MARC study that directly compared CMR stress perfusion and LGE with SPECT.[61] In this study, CMR was found to have higher sensitivity and similar specificity to SPECT, using angiography stenosis severity as a study end point (Fig. 16–18). In addition, abnormal CMR stress perfusion abnormalities correlate with fractional flow reserve assessments obtained invasively.[55]

Prognosis

Beyond the identification of flow-limiting coronary stenoses or inducible ischemia, both CMR myocardial perfusion as well as CMR dobutamine

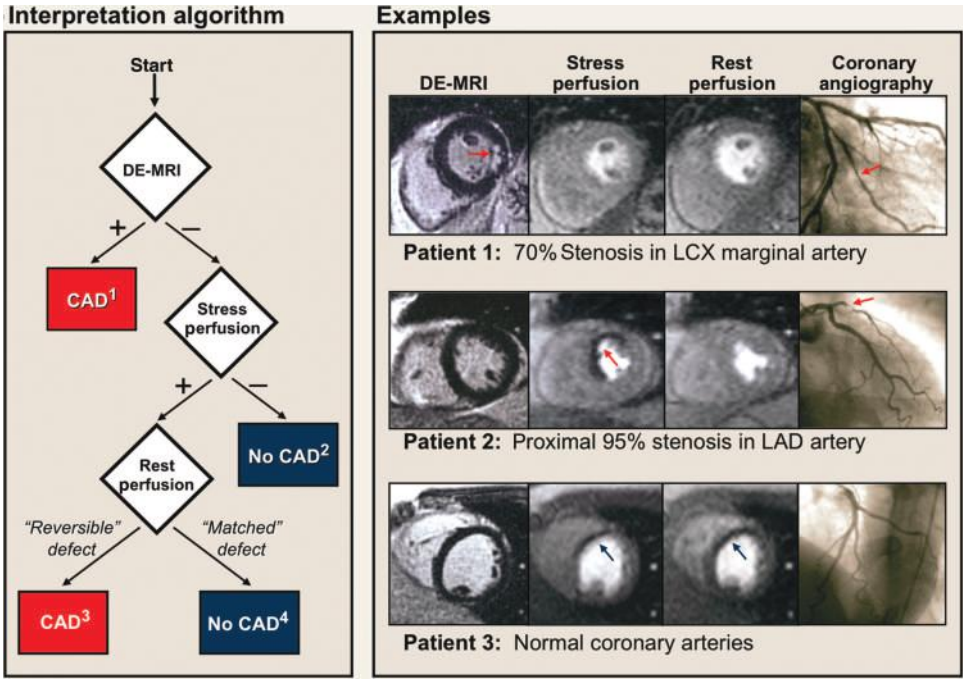


FIGURE 16–17. Interpretation algorithm for incorporating delayed enhancement magnetic resonance imaging (DE-MRI) with stress and rest perfusion MRI for the detection of coronary disease. **A.** Schema of the interpretation algorithm. (**1**) Positive DE-MRI study: Hyperenhanced myocardium consistent with a prior myocardial infarction (MI) is detected. Does not include isolated midwall or epicardial hyperenhancement, which can occur in nonischemic disorders. (**2**) Standard negative stress study: No evidence of prior MI or inducible perfusion defects. (**3**) Standard positive stress study: No evidence of prior MI, but perfusion defects are present with adenosine that are absent or reduced at rest. (**4**) Artifactual perfusion defect: Matched stress and rest perfusion defects without evidence of prior MI on DE-MRI. **B.** Patient examples. (*top row*) Patient with a positive DE-MRI study demonstrating an infarct in the inferolateral wall (*red arrow*) although perfusion-MRI is negative. The interpretation algorithm (step 1) classified this patient as positive for coronary artery disease (CAD). Coronary angiography verified disease in a left circumflex (LCX) marginal artery. Cine MRI demonstrated normal contractility. (*middle row*) Patient with a negative DE-MRI study but with a prominent reversible defect in the anteroseptal wall on perfusion-MRI (*red arrow*). The interpretation algorithm (step 3) classified this patient as positive for CAD. Coronary angiography demonstrated a proximal 95% left anterior descending (LAD) stenosis. (*bottom row*) Patient with a matched stress-rest perfusion defect (*blue arrows*) but without evidence of prior myocardial infarction on DE-MRI. The interpretation algorithm (step 4) classified the perfusion defects as artifactual. Coronary angiography demonstrated normal coronary arteries. Reproduced with permission from Klem I, Heitner JF, Shah DJ, et al: Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. *J Am Coll Cardiol*. 2006 Apr 18;47(8):1630-1638.

TABLE 16–3. Outcome Summary at Patient Level

Index Test	No. of Patients	TP	FP	FN	TN	Sensitivity	Specificity	PLR	NLR	DOR	AUC	Q*-Statistic
SPECT	533	162	67	58	246	0.74 (0.67–0.79)	0.79 (0.74–0.83)	3.13 (2.09–4.70)	0.39 (0.27–0.55)	9.63 (4.57–20.31)	0.82 (0.73–0.91)	0.75 (0.68–0.83)
ECHO	177	46	18	21	92	0.69 (0.56–0.79)	0.84 (0.75–0.90)	3.68 (1.89–7.15)	0.42 (0.30–0.59)	12.04 (5.25–27.65)	0.83 (0.74–0.93)	0.76 (0.68–0.85)
MRI	798	355	52	43	348	0.89 (0.86–0.92)	0.87 (0.83–0.90)	6.29 (4.88–8.12)	0.14 (0.10–0.18)	50.94 (32.45–79.97)	0.94 (0.92–0.96)	0.88 (0.85–0.90)
PET	224	73	18	14	119	0.84 (0.75–0.91)	0.87 (0.80–0.92)	6.53 (2.83–15.06)	0.14 (0.02–0.87)	47.26 (4.17–536.29)	0.93 NA	0.87 NA
CT	316	143	30	20	123	0.88 (0.82–0.92)	0.80 (0.73–0.86)	3.79 (1.94–7.40)	0.12 (0.04–0.33)	43.36 (20.26–92.78)	0.93 (0.89–0.97)	0.87 (0.82–0.92)

95% confidence interval in parentheses.

Reproduced with permission from Takx RAP, Blomberg BA, Aidi HE et al.: Diagnostic Accuracy of Stress Myocardial Perfusion Imaging Compared to Invasive Coronary Angiography With Fractional Flow Reserve Meta-Analysis, *Circ Cardiovasc Imaging*. 2015 Jan;8(1). pii: e002666.

AUC, area under the receiver operating characteristic curve; CT, computed tomography; DOR, diagnostic odds ratio; FN, false-negative; FP, false-positive; NA, not applicable; NLR, negative likelihood ratio; PET, positron emission tomography; PLR, positive likelihood ratio; SPECT, single-photon emission computed tomography; TN, true negative; TP, true positive.

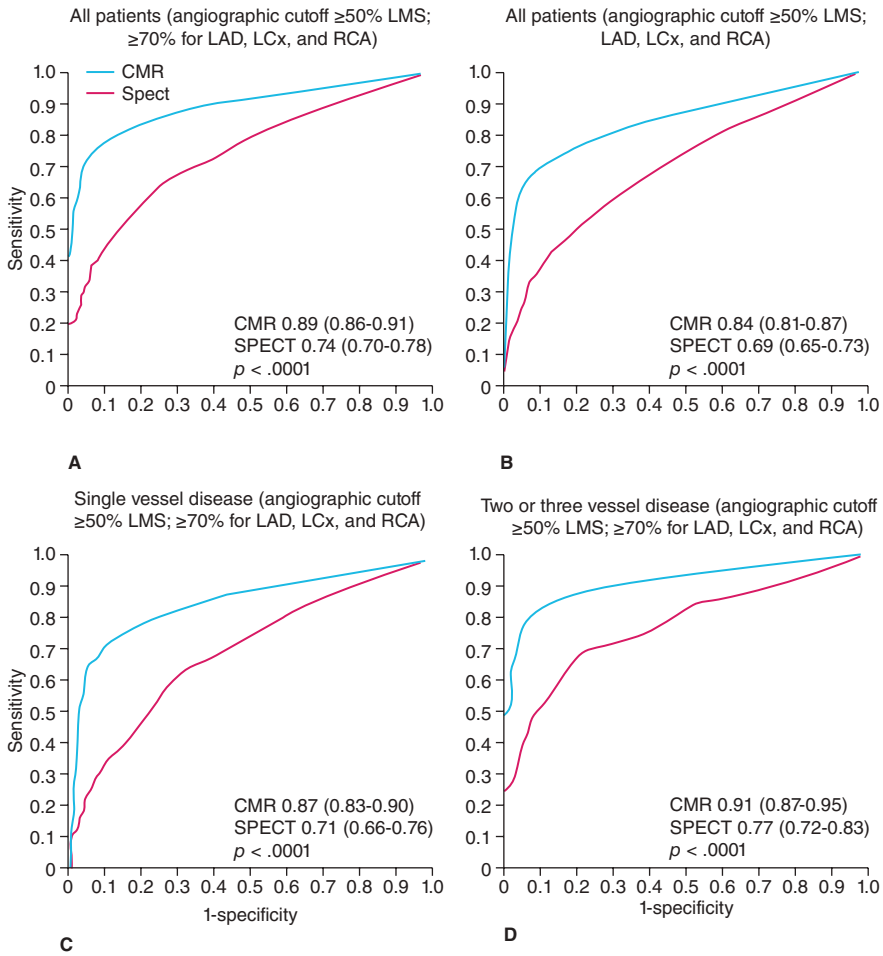


FIGURE 16–18. Results of the clinical evaluation of magnetic resonance imaging in coronary heart disease (CE-MARC) study. Stress magnetic resonance perfusion had higher diagnostic sensitivities for both single and multivessel coronary stenosis than single-photon emission computed tomography (SPECT). CMR, cardiac magnetic resonance; LAD, left anterior descending artery; LCx, left circumflex artery; LMS, left main stem; RCA, right anterior descending artery. Reproduced with permission from Daly C1, Kwong RY: Cardiac MRI for myocardial ischemia, *Methodist Debakey Cardiovasc J*. 2013 Jul-Sep;9(3):123-131.

wall motion stress are useful to determine cardiac prognosis.[62] In populations with chest pain presenting to the emergency department, CMR perfusion exhibits a sensitivity of 100% and specificity of 93% for predicting subsequent death from MI or detection of coronary stenosis after one year of follow-up.[63] In another study,[64] both adenosine myocardial perfusion as well as dobutamine CMR wall motion were evaluated in 513 patients subsequently followed for up to 3 years. Stress CMR using myocardial perfusion or wall motion analyses contributed to the incremental value over traditional risk factors for identifying those with an adverse cardiac prognosis. Normal perfusion studies were associated with an event rate of 0.7% at 2 years, whereas an abnormal study exhibited an event rate of 12.2% over the same time period. In a multivariable analysis including other risk factors for cardiac events, detection of perfusion abnormalities was associated with a 10-fold risk of future hard events. Similar results were found for dobutamine wall motion assessments.

A particular advantage for utilizing stress CMR for assessing myocardial perfusion or LV wall motion relates to the prognostic utility in women.[65,66] As shown in Fig. 16–19, stress CMR exhibits very high spatial resolution and fewer artifacts for imaging women relative to radioisotope techniques and importantly, CMR stress does not involve ionizing radiation exposure to breast tissue.

In a meta-analysis totaling 14 studies involving 12,178 individuals,[62] the negative predictive value for nonfatal MI and cardiac death of a normal CMR was 98.1% (with a 95% confidence interval of 97.3 to 98.8) during a main follow-up of 25.3 months. The corresponding annualized event rate after a negative test was 1.03%. These results demonstrate that CMR exhibits a relatively high negative predictive value for adverse cardiac events and the absence of inducible perfusion defects or wall motion abnormalities demonstrate a similar ability to identify low risk patients with known or suspected CAD.[62]

Health Care Expenditures and Utilization

Although clear algorithms for diagnosis and treatment of patients with chest pain at varying levels of risk for acute coronary syndrome (ACS) exist, there are less well-delineated criteria for those individuals presenting with chest pain at intermediate risk for ACS. An important series of studies from Miller and colleagues[67-69] has demonstrated the utility of stress CMR in chest pain observation units associated with emergency departments. Three recent studies involving more than 300 participants randomized to usual cardiac care versus a stress CMR implemented through chest pain observation units examined those presenting with intermediate-risk chest pain (preexisting CAD and MI, ECGs with T-wave inversions without ST-segment depression exceeding 3 mm or ST-segment elevation exceeding 1 mm). Participants managed through the CMR-guided pathways experienced on average a reduction in the cost of the initial visit of $588 and reduction of $1641

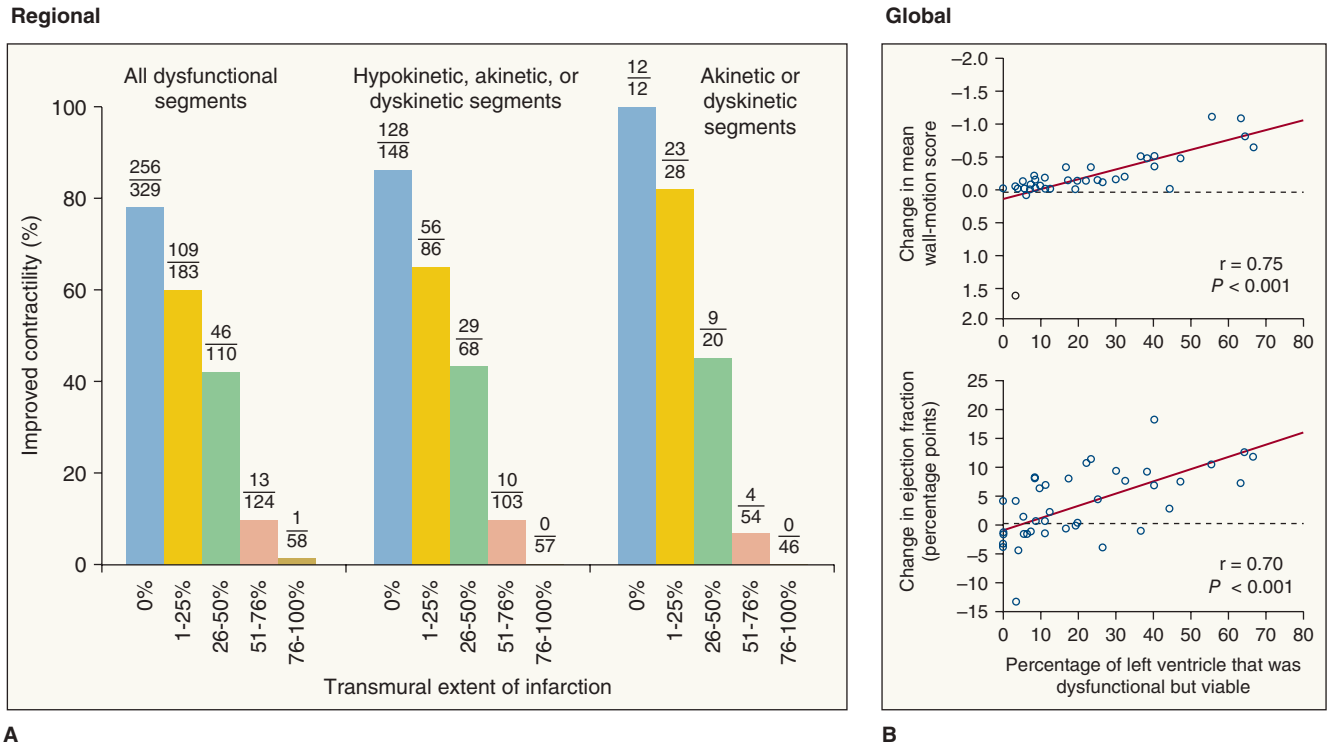


FIGURE 16–19. Importance of spatial resolution in stress perfusion imaging. Patient has an inducible perfusion defect limited to the subendocardial portion of the septal wall (*black arrow*) caused by an ostial stenosis (*white arrow*) of a septal branch of the left anterior descending coronary artery.

over the ensuing year (Fig. 16–20).[67-69] When examined further, the decreased utilization and costs associated with managing the patients using CMR results was related to fewer return visits to the emergency department, cardiac catheterizations, and percutaneous coronary artery revascularization procedures. Overall, patients experienced no difference in the 30 days or 1-year occurrence of MI or cardiac death. These important results highlight the potential benefits of using CMR stress perfusion for identifying those individuals presenting to the emergency department with chest pain at intermediate risk for ACS and in need of hospitalization as opposed to those who could be safely discharged to home.

MYOCARDIAL TISSUE CHARACTERIZATION

Today, perhaps the most widely used imaging method for identifying myocardial injury and fibrosis associated with MI is through CMR-based assessments of LGE.[70] LGE has several important uses in the setting of patients with suspected CAD. These include identification of the extent of acute and remote MI, prediction of recovery of myocardial contractility after successful coronary artery revascularization in chronic ischemic heart disease, characterization of prognosis, visualization of cardiac thrombus or microvascular obstruction and, when combined with T2 imaging methods, localization of the area of myocardial salvage.

Acute Myocardial Infarction

Triphenyltetrazolium chloride (TTC) histopathologic staining has been utilized to document the accuracy of the spatial extent and localization of LGE as it relates to infarcted myocardium.[71] In canine models, there

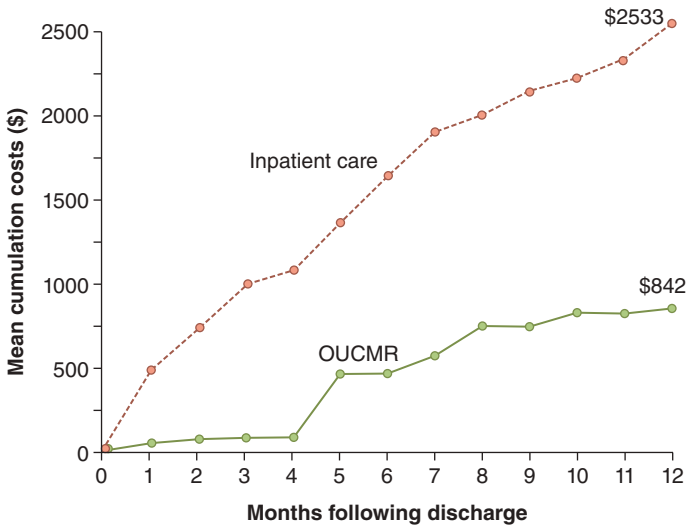


FIGURE 16–20. Cost accumulation by month following discharge among study groups, excluding the index hospital visit cost. Mean cumulative cost by study group after hospital discharge (*y* axis) is displayed by month of follow-up (*x* axis). Mean cumulative cost for a month is calculated as the sum of the costs across all patients up to and including that month divided by the number of patients. Observation unit cardiac magnetic resonance (OUCMR) participants had lower cost of care in the year after discharge from the index hospital visit ($P = .012$). Reduced cost was the result of fewer cardiac-related emergency department visits and cardiac-related hospitalizations, suggesting that an OUCMR strategy impacts care utilization after discharge. Reproduced with permission from Miller CD, Hwang W, Case D, et al: Stress CMR imaging observation unit in the emergency department reduces 1-year medical care costs in patients with acute chest pain: a randomized study for comparison with inpatient care. *JACC Cardiovasc Imaging*. 2011 Aug;4(8):862-870.

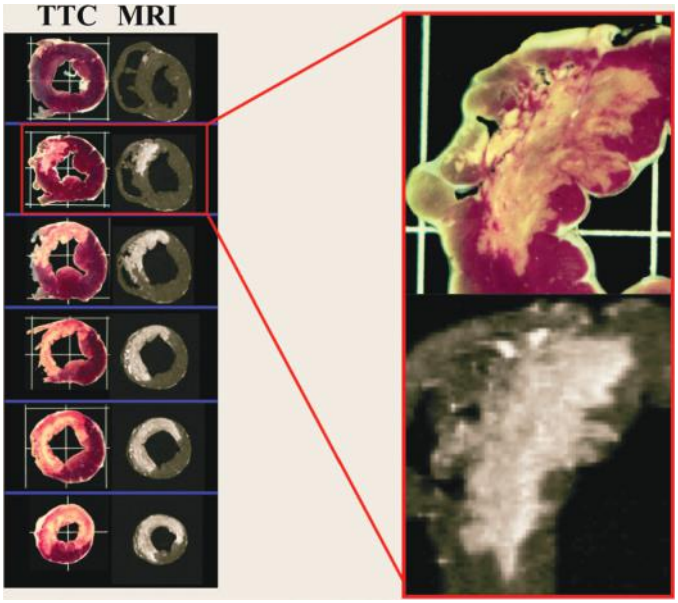


FIGURE 16–21. Comparison of ex-vivo, high-resolution, delayed enhancement magnetic resonance images (MRI) with acute myocardial necrosis defined histologically by triphenyltetrazolium chloride (TTC) staining. Note that the size and shape of the infarcted region (*yellowish-white region*) defined histologically by TTC staining is nearly exactly matched by the size and shape of the hyperenhanced (*bright*) region on the delayed enhancement image. Modified with permission from Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999 Nov 9;100(19):1992-2002.

have been high correlations between LGE and TTC-stained measures of infarcted myocardial segments (Fig. 16–21). The relatively high spatial resolution of LGE images enhances its sensitivity for detecting MI. CMR may be used to identify micro infarcts because of relatively small epicardial coronary artery branch occlusions or embolization of distal vessels related to percutaneous coronary artery revascularization procedures.[72] CMR has been shown to be more sensitive than both SPECT and PET imaging for detecting small infarcts.[73] In a large multicenter clinical trial of 282 patients, the sensitivity for detecting acute MI was 99%. Transmural extent of LGE can additionally predict the likelihood of functional recovery of stunned myocardium because there is an inverse relationship between transmurality and recovery of function.[74]

Remote Myocardial Infarction

In patients evaluated chronically (months to years) after MI, the assessment of transmural extent of infarction has also been shown to identify the likelihood of functional recovery of systolic thickening after percutaneous coronary artery revascularization procedures.[75] For those individuals with no LGE, recovery of function of resting segments with akinesis can approach 80%. Conversely, in those individuals with greater than 50% transmural extent of infarction, the likelihood of recovery of systolic thickening after coronary artery revascularization falls below 10%.

One potential difficulty in using this method to assess potential for recovery of systolic thickening occurs when the transmural extent of infarction ranges between 1% and 50%. In these situations, there is approximately a 40% to 60% chance of recovery of systolic thickening. As shown in studies by Wellenhoeffer and colleagues, the ability to identify those segments with a potential for systolic thickening after revascularization improves to nearly 90% through the identification of contractile reserve with low dose intravenous dobutamine (see Fig. 16–16).[50]

Microvascular Obstruction

In the setting of acute MI, the coronary artery microcirculation can be damaged to an extent such that no gadolinium may be temporarily delivered to specific areas within an infarct zone.[76,77] These areas have been shown histopathologically to be associated with microvascular obstruction caused by plugging of the small arterioles with thrombotic debris.[76,77] The characteristic image finding (Fig. 16–22) indicates a very dark central core nested within a relatively bright LGE region of myocardium consistent with acute/subacute necrosis. Often on the cine wall motion images, these areas display marked hypokinesis or akinesis. Postcontrast cine imaging can also be useful to differentiate microvascular obstruction from thrombus (see Cardiac Masses, below).

It is important to recognize that the presence of microvascular obstruction is associated with an adverse cardiac prognosis and very little opportunity for recovery of systolic thickening longitudinally over time.[78] In addition, the presence of microvascular obstruction has also been associated with adverse LV remodeling and worse patient outcomes.[78,79]

Myocardial Area at Risk and Salvageable Myocardium

In patients presenting with acute chest pain syndromes, it is important to recognize that edema imaging utilizing either T2-weighted or T2 mapping sequences may be combined with LGE techniques to identify the area at risk and salvageable myocardium as well as to differentiate stress-induced cardiomyopathies from actual MI.[80,81]

Prior to the administration of contrast, T2-weighted imaging or T2 mapping can be used to characterize the presence of myocardial edema. Abdel-Aty and colleagues[82] have demonstrated that edema imaging depicts acute ischemic injury often within the first 30 minutes from abrupt coronary artery occlusion and even before the development of LGE. Therefore, in the setting of an acute infarction, bright signal observed in T2 imaging techniques predicts the maximal area of myocardium that is at risk for necrosis.

Myocardial salvage relates to a term that defines the difference between the area at risk subtracted from the extent of necrosis as determined with LGE.[80,81] As shown in Fig. 16–23, edema involves the entire area of the myocardial wall, whereas the transmural spread of necrosis is variable and is identified with LGE imaging. In the situation where abrupt return of antegrade coronary flow is established or extensive collateral flow is present, the degree of myocardial salvage can be readily identified. Importantly, this region represents an area of risk of reinfarction in patients in whom inadequate coronary artery blood flow recurs.

Intramyocardial Hemorrhage

One complication associated with acute MI is the development of intramyocardial hemorrhage.[83] CMR is well suited to identify intramyocardial

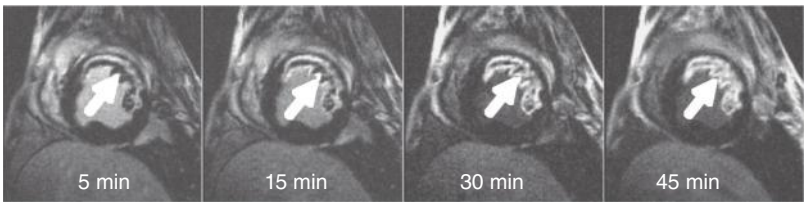


FIGURE 16–22. The *no reflow* phenomenon visualized by delayed enhancement magnetic resonance imaging. Labels refer to time after administration of gadolinium contrast. The subendocardial black zone surrounded by hyperenhancement corresponds to the region of no reflow (*white arrows*). This region can be distinguished from normal myocardium because it is encompassed in three-dimensional space by hyperenhanced myocardium or the left ventricular cavity and by the fact that it slowly becomes hyperenhanced over time. Reproduced with permission from Higgins CB, Roos Ad: *Cardiovascular MRI & MRA*. Philadelphia: Lippincott Williams & Wilkins; 2003.

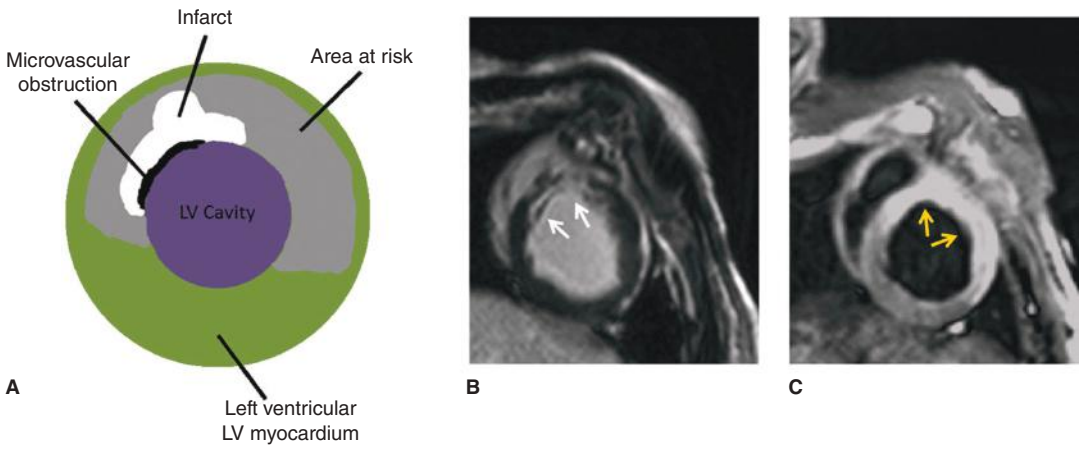


FIGURE 16–23. Three-part figure demonstrating cardiovascular magnetic resonance tissue characteristics associated with acute myocardial infarction (MI). **A.** Here is a cartoon representation of a short-axis view of the left ventricle. The cartoon demonstrates the left ventricular (LV) cavity (purple), LV myocardium (green), region of microvascular obstruction (dark rim), late gadolinium enhancement (LGE) associated with an infarct (white), and the myocardial area at risk (gray). **B.** Here is an example of a LGE short-axis plane where the normal LV myocardium is depicted as gray and the cavitary blood is depicted as white. The *white arrows* demarcate the bright signal intensity associated with LGE evidence of MI. In addition, the leftmost *white arrow* identifies dark signal intensity within the region of LGE associated with microvascular obstruction (MVO). Because of plugging of the coronary microcirculation, no gadolinium contrast is allowed to reach this area and hence the dark signal intensity associated with MVO. **C.** A T2-weighted black-blood image is displayed in a short-axis plane in the same location as **B.** In this image, the LV cavitary blood is dark and the normal LV myocardium is gray. The *yellow arrows* demonstrate increased signal intensity within the LV myocardium on the T2-weighted images, highlighting increased edema associated with the myocardial area at risk. Of note, one can subtract the region of infarction and MVO from the total myocardial area at risk and calculate the region of salvageable myocardium after successful coronary arterial revascularization in the setting of acute MI.

hemorrhage utilizing a combination of T2-weighted and T2*-weighted imaging, as well as LGE. T2*-weighted imaging is very useful to identify the presence of hemoglobin degradation products. These products produce a low signal intensity on T2*-weighted images. In a series of 98 individuals sustaining an MI, approximately one-fourth experienced hemorrhagic infarcts that were in turn associated with infarction transmurality, a larger MI size, and reduced LVEF.[83] In addition, those with myocardial hemorrhage experienced a greater increase in LV end systolic volume 4 months after the infarct relative to those without evidence of myocardial hemorrhage. These data suggest that the presence of myocardial hemorrhage identified by T2*-weighted imaging during CMR may predict adverse LV remodeling.

CARDIOMYOPATHIES

OVERVIEW

CMR is an extremely useful technique in the assessment of the heart failure (HF) patient.[1,5,84] The fact that SSFP cine CMR is considered the "gold standard" for measurement of LV and RV structure and function is especially important in cardiomyopathies. The pattern of LGE can be quite useful in differentiating causes of cardiomyopathies[33] (Fig. 16–24). T2-weighted imaging can be used to demonstrate myocardial edema, such as

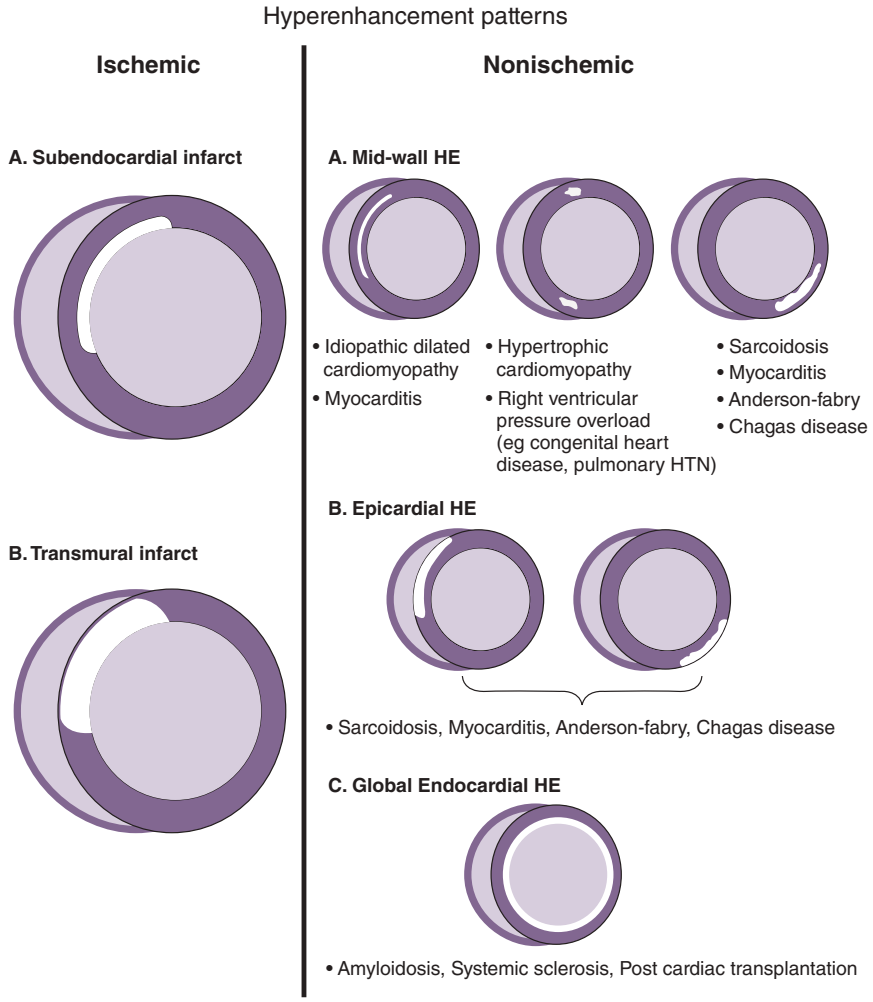


FIGURE 16–24. Patterns of late gadolinium-enhanced imaging seen in ischemic and nonischemic cardiomyopathies. HE, hyperenhancement; HTN, hypertension. Reproduced with permission from Edelman R, Hesselink J, Zlatkin M, et al: *Clinical Magnetic Resonance Imaging*, 3rd edition. New York: Elsevier Press; 2005.

in acute myocarditis.[85] T1 mapping techniques are being applied to help in the differential diagnosis of cardiomyopathies; some have characteristically high native T1[86] as well as high ECV fraction.[87] Native (or non-GBCA) T1 mapping is especially useful in patients with severe chronic kidney disease and risk of NSF.

ISCHEMIC CARDIOMYOPATHY

The first step in the evaluation of the patient with new-onset HF is to establish the underlying etiology and, importantly, to exclude ischemic heart disease as a potentially reversible cause. CMR is considered an appropriate technique for the evaluation of patients with new-onset HF.[88] The approaches to evaluating for ischemia are discussed in the preceding section of this chapter. In the setting of HF, stress CMR is considered appropriate in evaluating an ischemic cause.[88] SSFP cine imaging demonstrates LV dilatation and segmental LV dysfunction in a coronary distribution pattern. The presence of LGE in a coronary distribution can support the diagnosis of underlying CAD (Fig. 16–25), but its absence does not rule it out, because patients with extensive hibernating myocardium may not have LGE.[89] In a study by Soriano and colleagues of 71 patients with new-onset HF and systolic dysfunction, the sensitivity of the infarct pattern of LGE for ischemic cardiomyopathy as defined by the presence of obstructive CAD was 81%, whereas the specificity was 91%.[89] Patients without obstructive CAD may have evidence of LGE in an infarct pattern because of transient thrombotic occlusion of a nonobstructive artery, embolization, or spontaneous coronary dissection and thereby may be misclassified. This finding was noted in 13% of 63 patients with the diagnosis of dilated cardiomyopathy (DCM) with chronic HF.[90]

The presence and amount of LGE is prognostically important in the setting of CAD. One study of 195 patients found that the presence of any LGE was associated with an 8.3 hazard ratio for major adverse cardiac event (MACE) and a 10.9 hazard ratio for cardiac mortality.[91] In another study of 857 patients followed for 4.4 years on average, a scar index based on LGE was an independent predictor of all-cause mortality or cardiac transplantation, in addition to other well-known risk factors including LVEF and age.[92] The presence of scar is also a marker of poor response to cardiac resynchronization therapy (CRT), especially when the scar is located within the LV inferolateral wall at the site of the placement of the pacing lead within the cardiac vein.[93,94] CMR is considered an appropriate imaging examination in the evaluation of viability and in the evaluation of candidacy for CRT.[88]

DILATED CARDIOMYOPATHY

Cine imaging in DCM generally demonstrates global LV dysfunction or regional dysfunction in a pattern inconsistent with a territory subserved by a single epicardial coronary artery. The majority of patients with HF without obstructive CAD have no evidence of LGE.[90] As mentioned above, a minority of patients (13%) have LGE in an infarct pattern and may be misclassified as nonischemic.[90] Approximately one-fourth of patients with DCM will have evidence of mid-wall fibrosis[90] (Fig. 16–26). This may represent the chronic healing phase of myocarditis. In a study of 472 patients with DCM followed for 5.3 years, the 142 patients with mid-wall fibrosis had a hazard ratio of 3.0 for all-cause mortality and 5.2 for a composite end point of sudden cardiac death (SCD) and aborted SCD.[95] A study of 65 patients with DCM and LVEF ≤ 35% showed that the presence of LGE was associated with an eight-fold increase in HF, appropriate ICD firing, and cardiac death.[96] The presence of mid-wall fibrosis is also an independent predictor of mortality and morbidity of patients with DCM undergoing CRT.[97] In fact, in this study of 97 patients with DCM and 161 patients with ischemic cardiomyopathy, DCM patients with mid-wall fibrosis had a similar outcome to those with ischemic disease.[97] Thus, as with ischemic cardiomyopathy, the presence of fibrosis/scar is a marker of adverse outcome and lack of response to device therapy.

Hypertrabeculation can be seen in patients with DCM. A prospective CMR study of 162 patients with this disorder measured the amount of noncompacted myocardium relative to compacted myocardium.[98] Whereas LVEF and LGE were independent predictors of MACE-free survival, the amount of noncompacted myocardium had no effect above and beyond traditional factors (eg, LVEF) associated with adverse CV events.

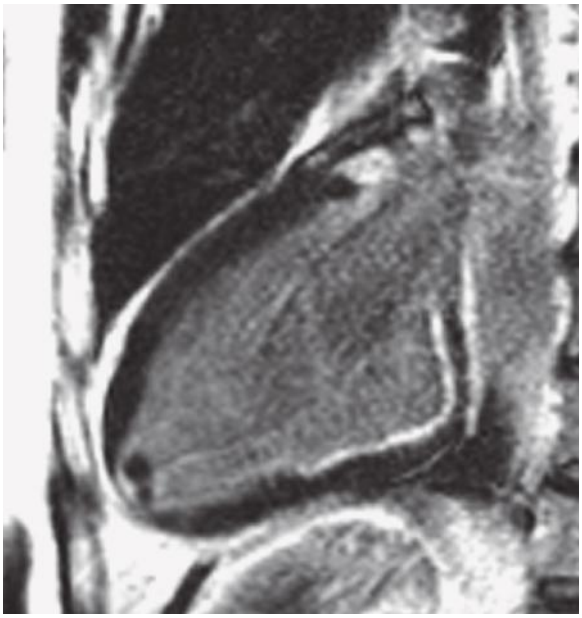


FIGURE 16–25. Late gadolinium-enhanced inversion recovery gradient echo image in a two-chamber long-axis orientation in a patient with systolic heart failure. Two areas of prior myocardial infarction are seen: a 1% to 25% transmural infarct in the basal to midinferior wall and a small apical infarct with an associated apical thrombus.

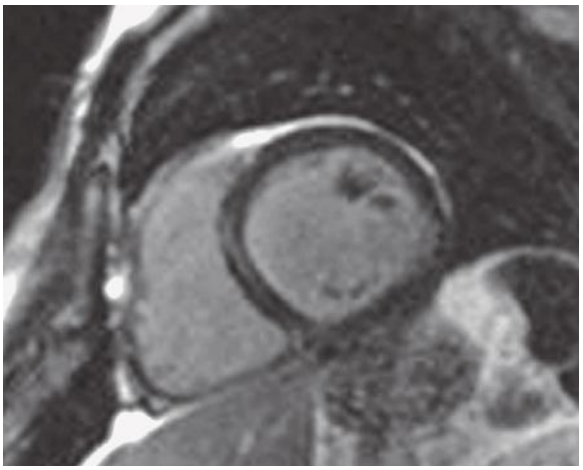


FIGURE 16–26. Late gadolinium-enhanced (LGE) inversion recovery gradient echo image in a basal short-axis orientation in a patient with systolic heart failure. A thin mid-wall stripe of LGE is seen in the septum.

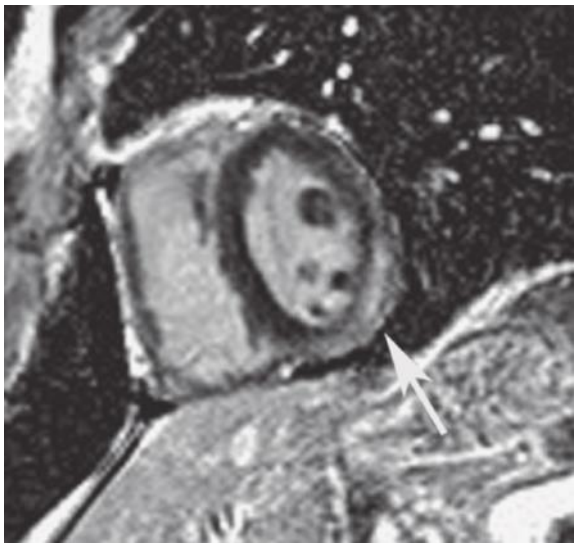


FIGURE 16–27. Late gadolinium-enhanced (LGE) inversion recovery gradient echo image in a basal short-axis orientation in a patient with clinical picture consistent with myocarditis. LGE is noted in the midwall and subepicardium in the inferolateral wall (*arrow*).

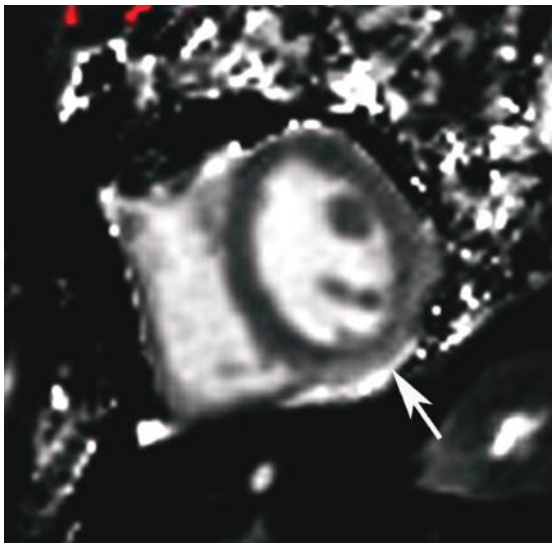


FIGURE 16–28. Native T1 map in the same patient as in the previous figure, demonstrating bright signal (high T1 values) in the subepicardium of the basal inferolateral wall.

MYOCARDITIS

A typical patient with acute myocarditis presents with chest pain, modest troponin elevation, and little or no evidence of angiographically detectable stenoses within epicardial coronary arteries. Cine imaging can demonstrate normal LV systolic function, regional dysfunction, or global dysfunction. The finding of LGE in the midwall and subepicardium of the LV is characteristic of viral myocarditis and has been validated against histopathology[33] (Fig. 16–27) The presence of LGE was shown to have a hazard ratio of 8.4 for mortality and 12.8 for cardiac mortality, independent of clinical symptoms in a study of 222 patients followed for 4.7 years.[99] Older studies suggested that early postcontrast T1-weighted enhancement of the myocardium could be a marker of inflammation in myocarditis.[100] In addition, T2-weighted imaging demonstrated that myocardial edema can be a diagnostic sign. The Lake Louise consortium in 2009 suggested that positivity of two of three techniques (early enhancement ratio, LGE, and/or increased T2 signal) may be a good diagnostic approach.[101]

However, the early enhancement ratio has lost favor because of lack of reproducibility, and T2-weighted imaging is being replaced by more quantitative T2 mapping. In addition, T1 mapping, both native and with contrast for measurement of ECV, is increasingly being used to make the diagnosis (Fig. 16–28). A study of 50 patients with suspected acute myocarditis and 45 age-matched controls showed that patients had higher T2 signal intensity ratios and native myocardial T1 than did controls.[87] In fact, a T1 cutoff of 990 milliseconds at 1.5T demonstrated a sensitivity, specificity, and diagnostic accuracy of 90%, 91%, and 91%, respectively. A combination of these techniques may more precisely identify acute myocarditis. In one recent study of 104 patients and 21 controls, a stepwise approach using LGE and myocardial ECV > 27% demonstrated an overall accuracy of 90%.[102] Diagnostic accuracy of the different techniques may depend on timing of clinical presentation. In a study of 61 patients with acute and 67 with chronic myocarditis showed that for acute myocarditis, diagnostic accuracy of native T1 was 99% as compared to 86% for LGE alone and 72% for increased T2-weighted signal.[103] In chronic myocarditis, LGE alone performed better than T1 mapping (94% vs 84% accuracy), but the combination of the two techniques performed even better, with a 98% overall accuracy.

HYPERTROPHIC CARDIOMYOPATHY

More sensitive than echocardiographic techniques, CMR can identify unusual sites of hypertrophy, particularly involving the cardiac apex.[104] It is the most accurate way of measuring LV mass in HCM, which is important because higher LV mass is associated with worse outcome.[105] Similarly to echocardiography, CMR is useful to identify systolic anterior motion of the mitral valve and characterize both LV outflow gradients and the severity of mitral regurgitation.

In addition to defining myocardial mass and assessing cardiac or valvular function, CMR can assess myocardial fibrosis. Approximately two-thirds of patients with HCM exhibit LGE with diffuse or "patchy" myocardial involvement, particularly at the RV septal insertion sites and in those walls with the greatest amount of hypertrophy (Fig. 16–29).

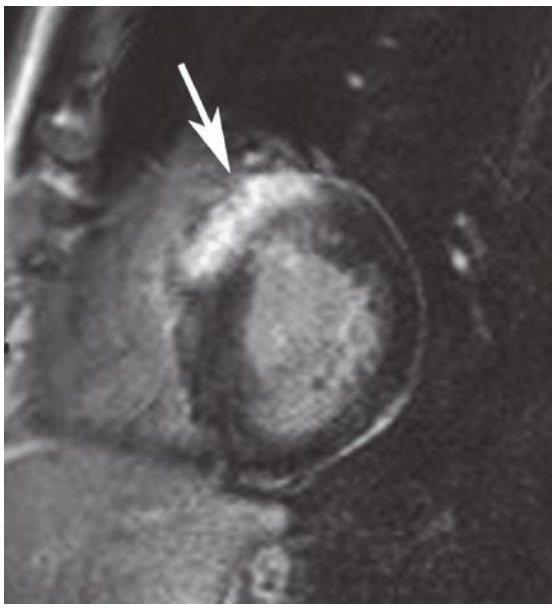


FIGURE 16–29. Late gadolinium-enhanced (LGE) inversion recovery gradient echo image in a basal short-axis orientation in a patient with hypertrophic cardiomyopathy. Mid-wall and subepicardial LGE is noted in the anteroseptum. The image also demonstrates asymmetric hypertrophy of the anterior wall and septum.

A number of studies have examined the relationship between the presence of LGE and outcome in HCM. Two prospective studies showed that LGE was associated with an increased risk of CV events. One study followed 243 HCM patients for 3 years for all-cause and cardiac mortality.[106] LGE was seen in 67% and demonstrated an odds ratio of 5.5 for all-cause mortality and 8.0 for cardiac mortality. Another group followed 217 patients for 3 years for a composite end point including CV death, unplanned CV admission, sustained ventricular tachycardia or ventricular fibrillation, or appropriate ICD discharge.[107] Sixty-three percent had LGE, which was associated with an odds ratio of 3.4 for the primary end point. A meta-analysis of 1063 patients pooled from four studies, including these latter two, followed for an average of 3.1 years, demonstrated that the presence of LGE had an odds ratio of 2.9 for cardiac death, 5.7 for HF death, and 4.5 for all-cause mortality, but only a trend for SCD.[108]

These studies treated LGE in a binary fashion, but more recently the extent of LGE has been shown to add discriminatory value. A single-center study of 711 patients followed for 3.5 years showed that 65% of patients had LGE and the extent was a univariate predictor of SCD risk but was not independent of LVEF.[109] A larger four-center study of 1293 patients followed for 3.3 years showed that LGE ≥ 15% of LV mass was associated with an independent two-fold increase in SCD event risk after adjusting for standard risk factors and LVEF.[110] In addition to the amount, the location and/or pattern of LGE may be more predictive of adverse outcome than the presence of LGE alone. The ongoing National Institutes of Health–funded natural history study HCMR-Novel Predictors of Prognosis in Hypertrophic Cardiomyopathy (NCT01915615) using CMR, genetics, and biomarker evaluation of 2750 patients with HCM is likely to offer further insight into identifying risk markers.[111]

AMYLOIDOSIS

In addition to the classic findings of biventricular hypertrophy and biatrial enlargement, and the possible presence of a pericardial effusion in cardiac amyloidosis, the existence of amyloid protein in the myocardial interstitium is associated with characteristic patterns of LGE resulting from abnormal gadolinium kinetics in the infiltrated myocardium[112] (Fig. 16–30). In 33 patients with diastolic dysfunction and features concerning for amyloid,[113] the pattern of circumferential subendocardial LGE had a sensitivity of 80% and specificity of 94% for identifying endomyocardial biopsy evidence of cardiac amyloid. When the volume of distribution of gadolinium is quantified using serial measures of T1 in the myocardium after gadolinium contrast infusion, it is markedly increased compared to normal controls.[114] In addition, the native T1 of myocardium is significantly longer in patients with amyloidosis as compared to that in age-matched individuals without amyloidosis[114] or in those with LVH resulting from aortic stenosis.[115]

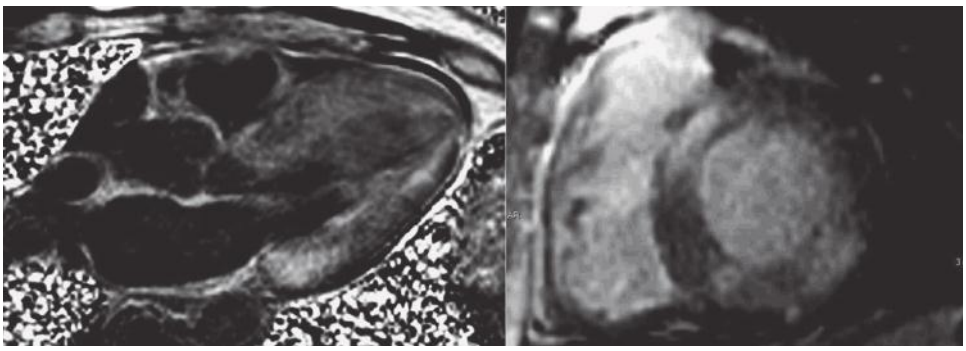
CMR is increasingly used to discriminate light chain (AL) amyloidosis from the transthyretin (ATTR) form of the disease. One group examined native T1 mapping in 85 ATTR patients and 79 AL patients compared with 52 normal subjects and 46 patients with HCM.[116] Compared to those with HCM, those with AL disease demonstrated the highest native T1, followed by those with ATTR, although the area under the receiver operating curve was similar for both forms of amyloidosis (0.84). The potential utility of native T1 is critically important because many amyloid patients have concomitant renal dysfunction and are not candidates for gadolinium caused by NSF concerns. Another study compared LGE findings in 46 patients with biopsy-proven AL and 51 with ATTR amyloidosis.[117] LGE was much more extensive in ATTR, with 90% demonstrating transmural LGE compared to only 37% in AL. These investigators developed an LGE scoring system that differentiated the two types with 87% sensitivity and 96% specificity.

LGE in amyloidosis has prognostic utility as well. In a study of 90 patients with suspected cardiac amyloidosis compared to 64 patients with hypertensive LVH, diffuse LGE predicted mortality with a HR of 5.5 in the amyloidosis patients.[118] A cohort of 250 patients (122 with ATTR, 9 asymptomatic mutation carriers, and 119 with AL) was followed for 2 years after LGE CMR.[119] A transmural pattern of LGE predicted death with a hazard ratio of 5.4 and remained independently predictive after adjustment for biomarkers and LV size and function. In a population of 100 patients with AL amyloidosis, ECV > 0.45 was also predictive of mortality, with a slightly lower hazard ratio of 3.8.[120]

SARCOIDOSIS

CMR can readily identify characteristic features of cardiac sarcoidosis, including biventricular dilation and dysfunction. There is a variable pattern of LGE seen with cardiac sarcoid with a classic pattern of midwall or epicardial LGE, but it can also present with subendocardial or transmural enhancement in almost any distribution (Fig. 16–31). One study of CMR in 58 patients with biopsy-proven pulmonary sarcoid found 19 patients with evidence of LGE, mostly in the basal and lateral myocardium, a higher prevalence than identified by standard Japanese Ministry of Health (JMH) guidelines.[121] Another study of 81 patients with extracardiac sarcoidosis followed on average for 21 months demonstrated a two-fold higher rate of cardiac involvement by CMR than by JMH guidelines,[122] suggesting the JMH criteria may be insensitive. Compared to those without, patients with LGE in the latter study had a nine-fold higher incidence of adverse events, although the difference did not reach statistical significance due to low numbers. In addition, T2 mapping may have a role in delineating activity of sarcoidosis. In a study of 28 patients with sarcoidosis, regions of LGE demonstrated decreased T2, which may reflect an inactive phase of the disease.[123]

With longer follow-up, LGE in sarcoidosis is demonstrating prognostic significance. In a study of 155 patients with systemic sarcoidosis followed for 2.6 years, the presence of LGE was associated with a hazard ratio of 31.6 for death, aborted SCD,



A B

FIGURE 16–30. Three-chamber long-axis (A) and short-axis (B) inversion recovery late gadolinium-enhanced (LGE) images in a patient with heart failure, concentric left ventricular hypertrophy, and left ventricular ejection fraction 25% demonstrating diffuse subendocardial LGE and signal nulling in the blood pool, all characteristic of amyloidosis, most likely the transthyretin variety.

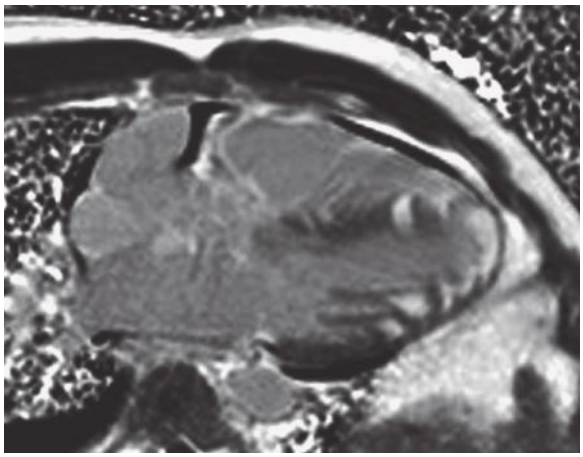


FIGURE 16–31. Long-axis phase-sensitive inversion recovery late gadolinium-enhanced (LGE) image in a patient with heart failure, paroxysmal ventricular tachycardia, and pulmonary sarcoidosis. Bands of dense LGE are seen in the septum and lateral wall as well as transmural apical LGE.

and appropriate ICD discharge.[124] In fact, no patient without LGE died of a cardiac cause despite LV dilatation and dysfunction. In another study of 106 patients with extracardiac sarcoid, cardiac involvement was identified by the presence of typical patterns of LGE in 32 patients. The presence of cardiac sarcoidosis/LGE was associated with more SCD and ventricular arrhythmias or appropriate ICD discharge.[125]

ANDERSON-FABRY DISEASE

Early CMR studies of Anderson-Fabry disease showed LGE related to the extent of LVH, typically located in the basal inferolateral wall and in the midwall or subepicardium.[126] T1 mapping in Anderson-Fabry disease demonstrates reduced native T1 in patients with phenotypic LVH compared to other hypertrophic diseases[127] and an intermediate reduction in native T1 before the onset of hypertrophy.[128] In the LVH-negative individuals, echo measures of systolic and diastolic function were impaired. CMR has been used to follow regression of LVH with enzyme replacement therapy in this disorder.[129]

CHAGAS DISEASE

A study of 51 patients with Chagas disease and CMR demonstrated cardiac involvement.[130] The patient group included 15 asymptomatic patients, 26 with clinical disease, and 10 with clinical disease and ventricular tachycardia. There was a stepwise increase in the prevalence of LGE in these groups (20%, 85%, and 100% respectively), and LV function was reduced proportionately to the extent of LGE.

NONCOMPACTION CARDIOMYOPATHY

The accurate diagnosis of left ventricular noncompaction cardiomyopathy (LVNC) by noninvasive imaging can be quite difficult because of substantial overlap between cardiac conditions. One group proposed CMR criteria of noncompacted to compacted layer thickness ratio of 2.3 to 1[131] and demonstrated a sensitivity of 86% and 99% in a study of 177 patients with and without cardiac disease (Fig. 16–32). When using these criteria, up to 43% of individuals who undergo CMR as part of screening studies such as the Multi-Ethnic Study of Atherosclerosis can meet imaging criteria.[132] Thus, ECG criteria and clinical criteria of symptomatic HF and LV dysfunction on imaging may need to be included to improve the specificity of diagnosis. Another group proposed a set of criteria in a study of patients with LVNC compared to those with DCM, HCM, and structurally normal hearts.[133] They found that a trabeculated LV mass greater than 20% of the LV mass was 94% sensitive and specific for the diagnosis of LVNC. LGE may be seen as well in LVNC, and its presence is specific but not sensitive in making the diagnosis.[134]

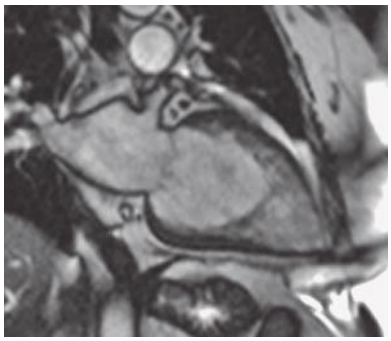


FIGURE 16–32. Two-chamber long-axis steady state free precession cine image in a patient with systolic heart failure. The apex is notable for extensive amount of noncompacted myocardium consistent with the diagnosis of noncompaction cardiomyopathy in this clinical setting.

IRON OVERLOAD CARDIOMYOPATHY

T2*-weighted imaging allows the measurement of cardiac iron deposition because there is an inverse relationship between T2* and iron concentration.[135] This mode of imaging has become quite important in iron overload states such as hemochromatosis and β-thalassemia major.[136] A T2* < 10 milliseconds is an important predictor of clinical HF[137] (Fig. 16–33). This application has been carefully validated and performed in a large number of international sites. Clinical trials of chelation therapies have used T2* imaging to track reductions in cardiac iron and concomitant improvements in LVEF.[138]

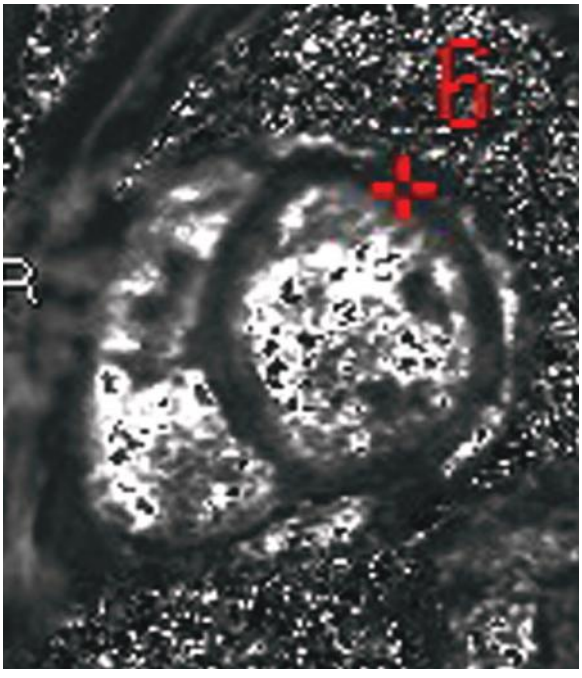


FIGURE 16–33. Basal short-axis T2* map in a patient with a history of multiple transfusions and systolic heart failure. The T2* is 6 milliseconds, which corresponds to the low ejection fraction noted on cine imaging in this patient.

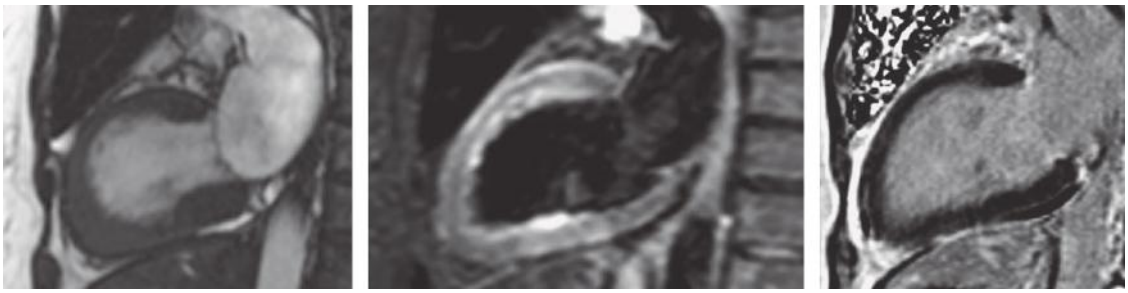


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FIGURE 16–34. End-systolic steady-state free precession two-chamber long-axis cine image from an elderly female with chest pain, troponin elevation, and normal coronary arteries (**A**). Note the midventricular bulging. T2-weighted image in the same orientation demonstrating bright signal in the mid anterior and midinferior walls consistent with myocardial edema (**B**). Phase-sensitive inversion recovery LGE image in the same orientation demonstrating absence of late gadolinium-enhanced (LGE) imaging (**C**).

TAKOTSUBO CARDIOMYOPATHY

Takotsubo or stress cardiomyopathy is a clinical syndrome characterized by chest pain and ECG changes that mimic an acute MI, generally occurs in older patients (more often women), and is typically provoked by underlying emotional or physical stress. Coronary angiography generally demonstrates no or minimal coronary atherosclerosis. Findings on CMR that corroborate this diagnosis are characteristic wall motion abnormalities (ballooning) involving the apex (82%), although midventricular (17%) and basal variants (1%) are also described.[139] In addition, there is generally no LGE but evidence of myocardial edema in the territory of the wall motion abnormality on T2-weighted imaging and/or T2 mapping (Fig. 16–34). Follow-up CMR generally shows normalization of LV function and inflammatory imaging markers.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

CMR is an important adjunct in making the diagnosis of arrhythmogenic RV cardiomyopathy.[140] Diagnostic findings in this disease include RV dilatation and global or regional dysfunction including focal RV systolic bulging or aneurysm as defined by SSFP cine imaging and are carefully assessed to meet ARVC Task Force for the diagnosis of right ventricular dysplasia/cardiomyopathy.[140] The finding of fatty infiltration within CMR images of the RV free wall is not part of the diagnostic criteria because this is a nonspecific finding. In certain cases, LGE of the RV free wall can be seen,[141] although this can be difficult to identify definitively because of the thin RV wall in this disorder.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart failure with preserved ejection fraction (HFpEF) is a heterogenous syndrome that is thought to cause up to 50% of cases of HF. A recent CMR study demonstrated that patients with HFpEF with invasively confirmed elevation in pulmonary capillary wedge pressure had a lower postcontrast T1 time corresponding with myocardial fibrosis.[142] However, ECV is less confounded than postcontrast T1 time by factors including imaging time after contrast and contrast dose.[18] One study demonstrated that patients with HFpEF had increased ECV as compared to systolic HF and controls and demonstrated a correlation between ECV and LV filling rate as a marker of diastolic dysfunction.[143] Studies such as these will help clarify the potential role of CMR in the diagnosis of HFpEF.

PERICARDIAL DISEASE

CMR imaging of pericardial disease in general is considered appropriate,[1,144] with evaluation for pericardial constriction being the most common indication.

CONSTRICTIVE PERICARDITIS

The hallmarks of this disease are increased pericardial thickness, pericardial inflammation, and ventricular interdependence. The pericardium can be visualized and measured in a number of sequences, although T1-weighted black-blood imaging is usually the standard,[145] where the pericardium appears as a hypointense linear structure surrounded by hyperintense fat layers (Fig. 16–35A). Although normal pericardial thickness is less than 1 mm or more, on CMR, 1 to 3 mm is considered normal because of limitations in spatial resolution,[145] and a thickness of 4 mm or more is considered abnormal.[2] Pericardial thickening may be focal or diffuse. It is important to realize that pericardial thickness may not be accurately quantified in the presence of an effusion (both are hypointense on black-blood imaging), that constriction can occur with normal pericardial thickness, and that increased thickness is not synonymous with constriction.

Pericardial inflammation and edema may be detected with T2-weighted imaging.[146] More commonly, inflammation is evaluated with postcontrast enhancement on T1-weighted black-blood imaging or standard LGE sequences (Fig. 16–35B). On histological validation, pericardial LGE is associated with chronic inflammation, granulation tissue, neovascularization, and fibroblast proliferation, while patients with absent LGE have thinner pericardium with more fibrosis and calcification.[147] Importantly, the presence of extensive LGE may identify a subgroup of patients in whom constrictive pericarditis can revert with anti-inflammatory therapy.[148,149]

Beyond anatomy and tissue characterization, CMR can provide information on the presence of constrictive physiology. Ventricular interdependence during respiration is studied with the use of real-time cine images. Marked inspiratory septal flattening can be seen in constriction (Fig. 16–35C and D) (and occasionally in the presence of significant tricuspid regurgitation), which can be helpful in the diagnosis and in the differentiation from restrictive cardiomyopathy.[150] Abnormal interdependence is typically assessed visually, although quantitative approaches have been proposed.[151] The availability of real-time PC imaging has enabled the study of respiratory variation in mitral and tricuspid inflow as another diagnostic tool.[152]

Additional features of pericardial constriction include tubular-shaped ventricles, abnormal diastolic septal bounce, atrial enlargement, dilated inferior vena cava and/or suprahepatic veins, and pleural or pericardial effusions. Application of myocardial tagging techniques often demonstrates lack of slippage between pericardium and epicardium, consistent with adherence. Pericardial calcification is not well seen on CMR and is better characterized with CT.[145]

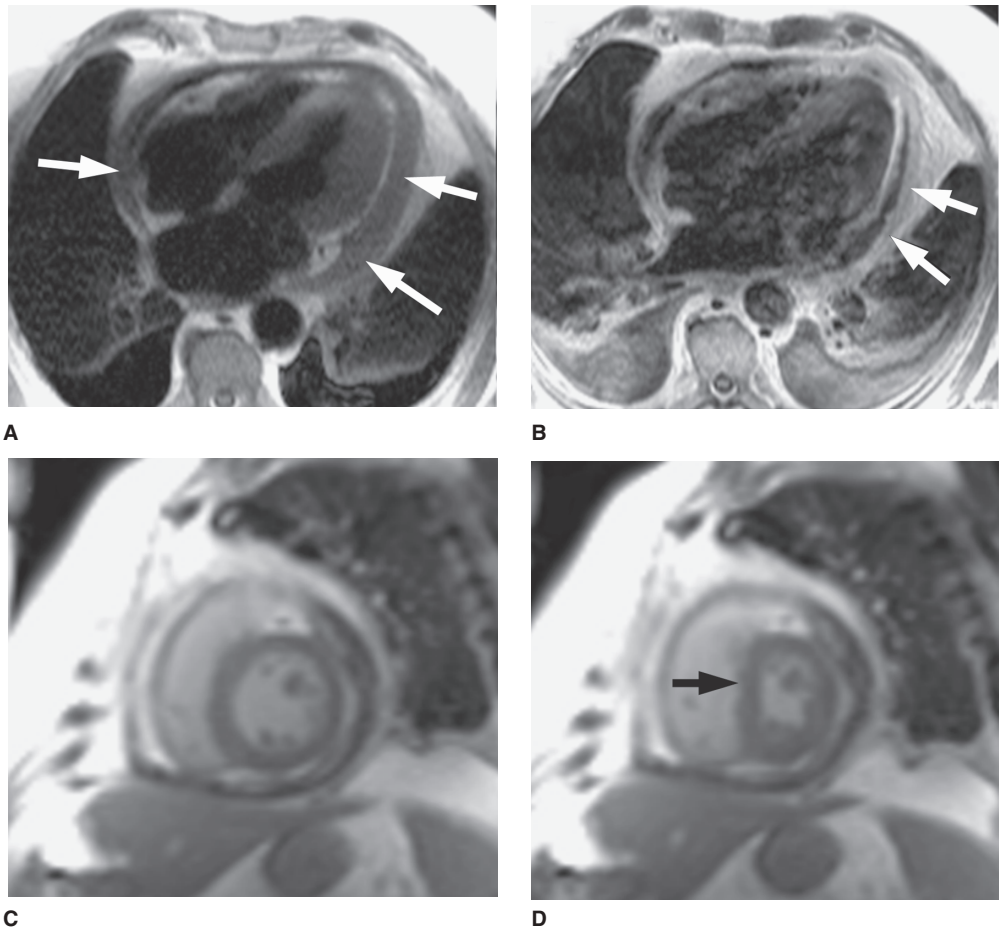


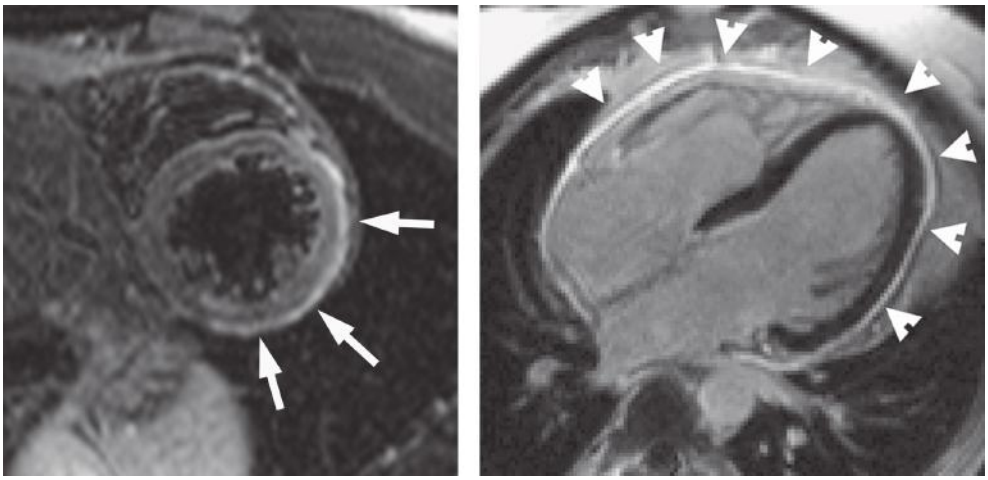
FIGURE 16–35. Patient with constrictive pericarditis. **A.** Four-chamber T1-weighted spin echo demonstrating markedly increased pericardium (dark band, *arrows*). **B.** Same image acquired after contrast showing pericardial enhancement (*arrows*). **C** and **D.** Expiratory and inspiratory, respectively—diastolic short-axis frames from a real-time cine acquisition during free breathing. Note the marked septal flattening during inspiration (*arrow*) consistent with increased ventricular interdependence.

OTHER PERICARDIAL DISEASES

Acute pericarditis can be diagnosed with CMR based on the presence of pericardial T2 hyperintensity and/or LGE[153] (Fig. 16–36). Using LGE to monitor inflammation, CMR-guided therapy has been associated with fewer relapses and decreased need for steroid therapy in recurrent pericarditis.[154] CMR is rarely used specifically for the evaluation of pericardial effusion or tamponade. However, CMR can depict loculated or small effusions that may be difficult to detect with ultrasound[145] and may also provide some gross fluid characterization. Uncomplicated fluid (transudate) is typically hyperintense on cine imaging and hypointense on T1-weighted black-blood imaging (although simple motionless fluid is also hyperintense on T2-weighted imaging, pericardial fluid often moves during the cardiac cycle and may be nulled like circulating blood). Exudates and (recent) hemorrhagic effusions become progressively less intense on cine images and more intense on T1-weighted imaging[145] (Fig. 16–37). Chylous effusions are particularly hyperintense on T1-weighted imaging.[155] Pericardial masses can also be characterized with CMR (see Cardiac Masses). Finally, congenital abnormalities such as pericardial diverticuli and partial or complete absence of the pericardium can also be depicted. The diagnosis of congenital pericardial absence relies on marked levorotation and hypermobility of the cardiac apex, together with lung interposition in the aortopulmonary recess.[156]

VALVULAR HEART DISEASE

The evaluation of valvular heart disease is not typically a primary indication for CMR, given the advantages of echocardiography: portability, high temporal and spatial resolution, excellent quantification of blood velocities, and reliable investigation of valve prostheses. Therefore, valve assessment in CMR is more often integrated into a protocol performed for a different reason such as the study of cardiomyopathy, aortic abnormalities, or congenital heart disease. Validation of CMR for valvular evaluation is somewhat limited, particularly for right-sided valves, although there is mounting evidence of not only diagnostic but also prognostic value (see below). Yet, as recommended by current practice guidelines, CMR is the best alternative to ultrasound in cases of discordant test results or when echocardiographic images are of limited quality.[1,144,157] The main advantage of CMR for assessing valvular heart disease is the ability to quantify the severity of stenosis and the magnitude of valvular regurgitation. Beyond one-time or serial determination of the impact of valvular abnormalities on chamber size and function[157] or the presence of concomitant myocardial fibrosis, the mainstays of valve assessment with CMR are the evaluation of valve morphology and function with cine sequences as well as flow velocities with PC imaging. Although the feasibility of prosthesis assessment (particularly biological) with CMR has been reported,[158] artifacts from



A B

FIGURE 16–36. Acute pericarditis depicted with cardiovascular magnetic resonance. Short-axis T2-weighted image demonstrating increased signal in the pericardium (*arrows*) indicative of edema and inflammation (**A**). Four-chamber long-axis inversion recovery late gadolinium-enhanced image displaying diffuse pericardial enhancement (*arrowheads*) (**B**).

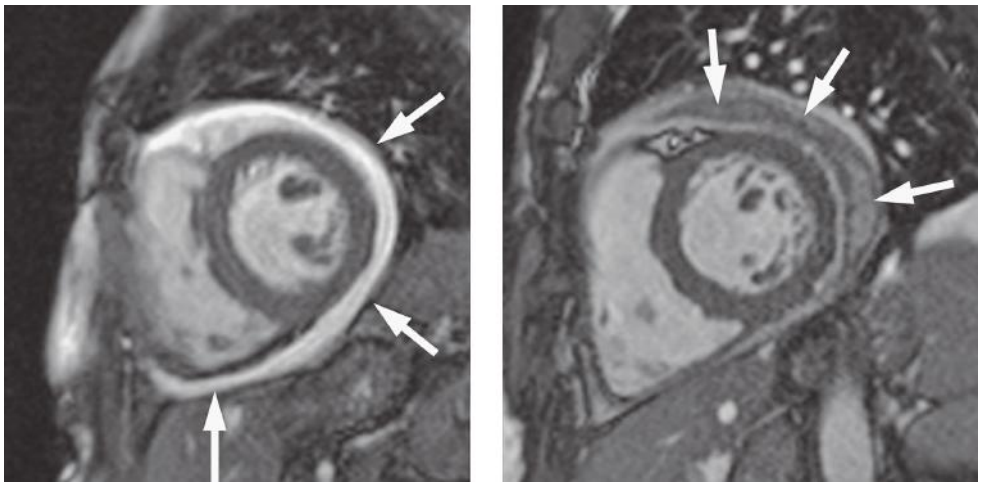
the metallic components of these devices often limit the ability to assess prosthetic leaflet mobility.

High-resolution cine images are typically obtained in standard or modified long-axis views as well as oblique planes parallel to the valvular annulus of interest,[2] the latter being particularly useful to demonstrate morphological variants[157] (Fig. 16–38). Valvular calcification can be depicted as persistently dark regions on the valvular apparatus, although CT is typically superior (see Chap. 17). The role of CMR in the evaluation of endocarditis is also limited because vegetations may be difficult to visualize due to their motion and the fact that they appear as signal voids (similar to calcification) on CMR (see Cardiac Masses).

As mentioned in the section on Techniques, flow turbulence leads to intravoxel phase dispersion and signal loss; thus, both stenotic and regurgitant jets appear dark on cine images (Fig. 16–39A). Although useful to identify the presence of a jet, the extent and appearance of jets are dependent on the sequence used, and thus one must take caution in using the size or extent of a CMR signal void to assess the severity of valvular stenosis or regurgitation.[159] Moreover, because dephasing is secondary to flow turbulence, laminar jets such as those observed with free regurgitation may be inconspicuous on cine imaging.

VALVULAR STENOSIS

There are two potential approaches for the evaluation of stenosis severity with CMR. The first one relies on the quantification of blood flow acceleration through the valve using PC imaging. Transvalvular gradients can be obtained by applying a modified Bernoulli equation (Fig. 16–40A), and valve area can be measured using the continuity equation in a fashion similar that used in Doppler ultrasound (see Chap. 15). Validation against echocardiography has been performed for both the mitral[160] and aortic[161] valves. It is important to note that CMR measures of peak velocity may be underestimated if the imaging



A B

FIGURE 16–37. Examples of pericardial effusion on short-axis cine images. Simple effusion (*arrows*) demonstrating high signal intensity (**A**). Complex effusion (*arrows*) with decreased signal intensity on steady-state free precession imaging (**B**).

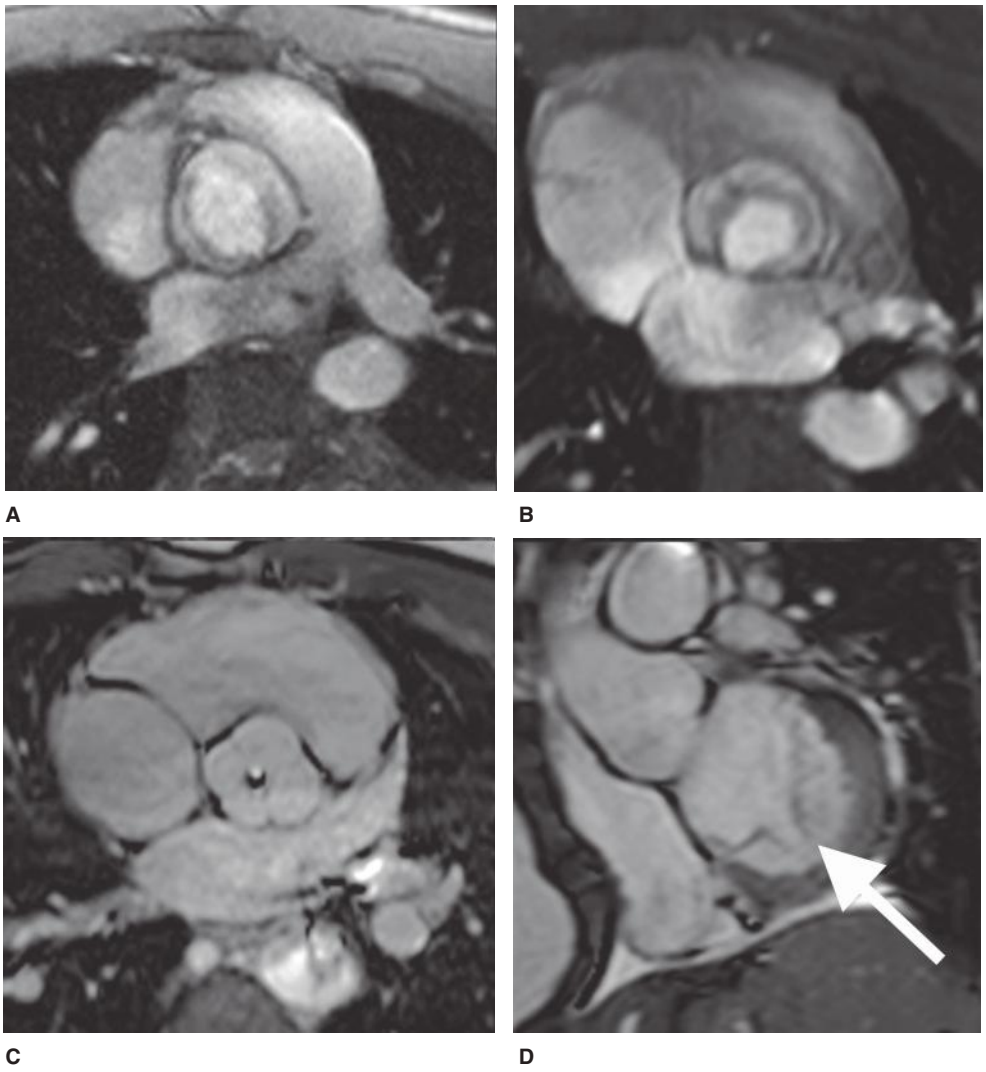


FIGURE 16–38. Cine steady-state free precession still frames demonstrating morphological valvular abnormalities. **A.** Bicuspid aortic valve. **B.** Unicuspid aortic valve. **C.** Quadricuspid aortic valve. **D.** Cleft of the posterior mitral leaflet (*arrow*).

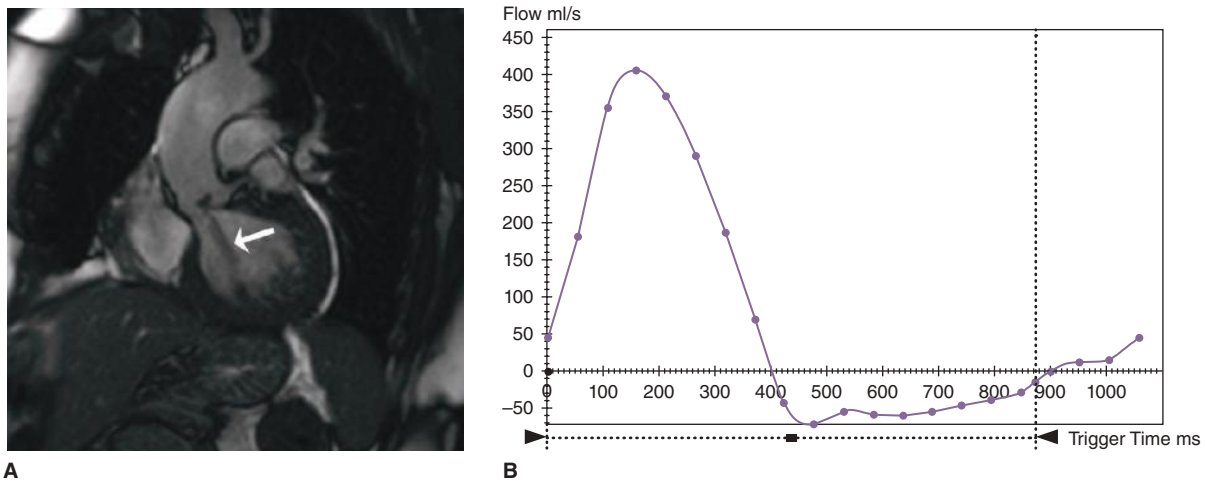


FIGURE 16–39. Cardiovascular magnetic resonance evaluation of valvular regurgitation. **A.** Diastolic steady-state free precession frame demonstrating a jet of aortic regurgitation (*arrowhead*). **B.** phase contrast flow curve. Regurgitant fraction is calculated as retrograde diastolic flow (area under the curve below the zero line) divided by systolic anterograde flow (curve above the zero line). In this case, regurgitant fraction was 23%.

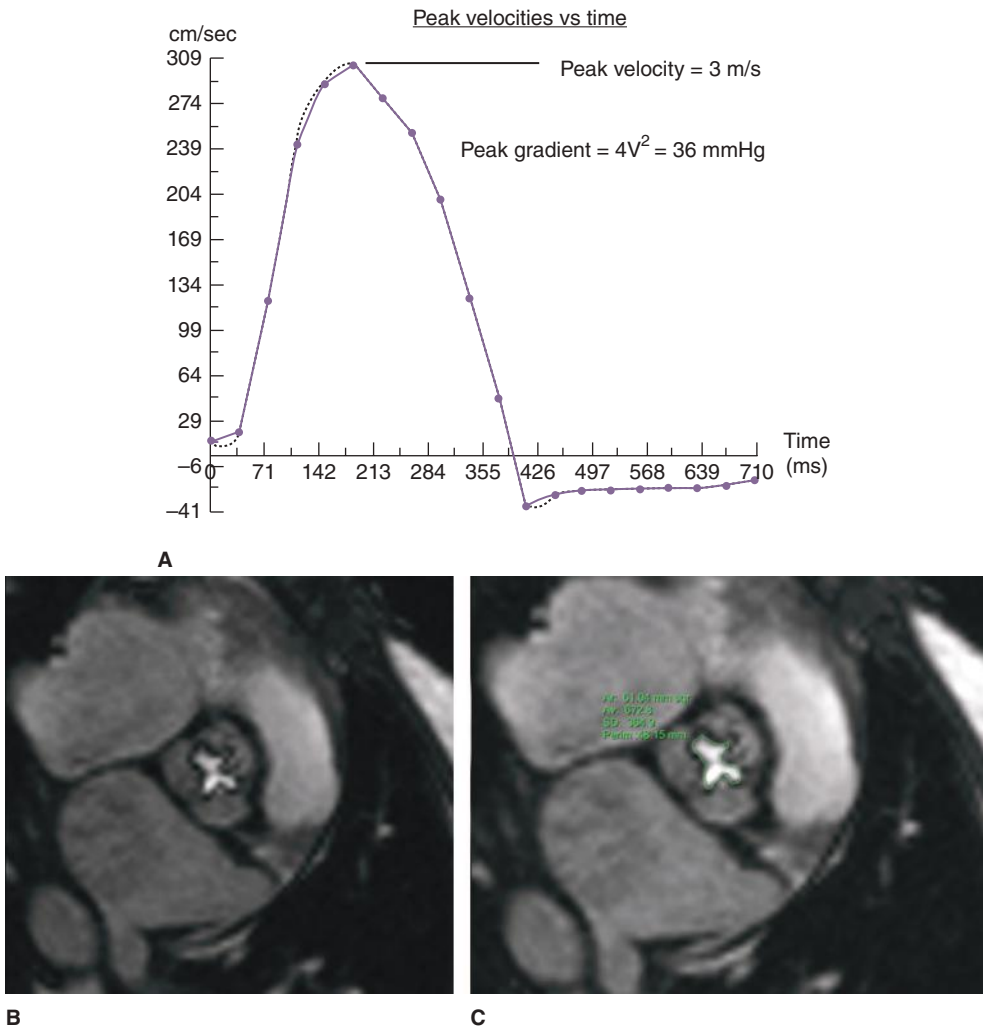


FIGURE 16–40. Cardiovascular magnetic resonance evaluation of valvular stenosis. **A.** Modified Bernoulli equation using peak velocity obtained from phase contrast imaging. **B.** Systolic cine steady-state free precession frame of a severely stenotic aortic valve stenosis. **C.** Severity can be measured by planimetry of valve area.

plane is not located at the site of maximal acceleration or the through-plane velocity encoding slice is not placed perpendicular to the maximal direction of flow.[159]

Planimetry of the stenotic orifice area can also be obtained to assess valve area (Fig. 16–40B and C). Compared to ultrasound as the reference standard, CMR has also demonstrated good accuracy in the aortic[162] and mitral[160] positions. Other evolving applications of CMR in aortic stenosis include the detection of localized fibrosis with LGE, which has demonstrated independent prognostic significance,[163] assessment of diffuse fibrosis with T1 mapping,[164] or planning transcutaneous valve interventions.[165]

VALVULAR REGURGITATION

High-resolution cine imaging in one of the long-axis orientations of the LV is helpful to demonstrate leaflet abnormalities such as prolapse, tethering, or systolic anterior motion.[2] Also using cine images, LV and RV stroke volumes can be calculated and are equal in normal conditions. In the presence of a single regurgitant valve, the difference between these two stroke volumes represents the regurgitant volume; however, this method is not reliable if more than one regurgitant lesion or other abnormalities such as intracardiac shunts are present. An alternative method that is used occasionally is direct planimetry of the regurgitant orifice on cine or PC images.[166,167]

Today, calculation of the regurgitant volume of blood or flow is more frequently performed using PC, alone or in combination with cine imaging. PC-based approaches for aortic or mitral regurgitation have also been found to be superior to transthoracic echocardiography in terms of reproducibility[168] and are increasingly used as the reference standard.[169] In semilunar valves, regurgitant volume is measured directly from the diastolic retrograde flow detected with PC in the ascending aorta or main pulmonary artery. The regurgitant fraction is then calculated as the ratio of retrograde volume to total systolic forward volume (see Fig. 16–39B). This approach has been validated in aortic[170] and pulmonary regurgitation,[171] and it has high interstudy reproducibility.[172] In the case of atrioventricular valves, flow can similarly be measured at the tricuspid or mitral levels, but this approach is usually considered unreliable.[173] The most accurate method is the quantification of regurgitant volume as the difference between the stroke volume calculated by volumetric analysis and that obtained with PC of the pulmonary artery or ascending aorta for tricuspid or mitral insufficiency, respectively. This method can be used in the presence of multiple regurgitant lesions. Measurement of mitral regurgitation has been validated against catheterization or Doppler echocardiography.[174,175]

TABLE 16–4. Cardiovascular Magnetic Resonance–based Severity of Valvular Regurgitation Based on Regurgitant Fraction

Severity	Regurgitant Fraction (%)
Mild	≤ 15
Moderate	16–25
Moderate to severe	26–48
Severe	> 48

Data from Gelfand EV, Hughes S, Hauser TH, et al: Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography. *J Cardiovasc Magn Reson*. 2006;8(3):503-507.

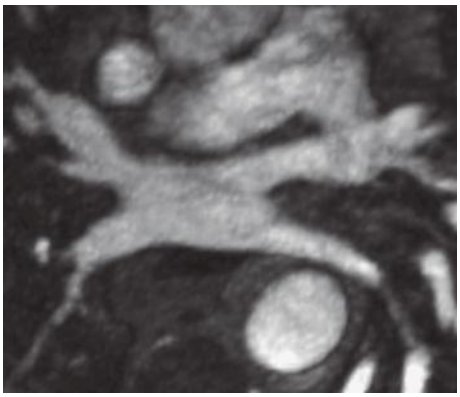


FIGURE 16–41. Maximum intensity projection of a left atrial magnetic resonance angiography demonstrating pulmonary vein anatomy.

From a diagnostic perspective, while echocardiographic thresholds are applied to the quantification of stenosis severity, CMR-specific cutoffs for regurgitation have been derived by optimization with ultrasound[176] (Table 16–4). Contemporary evidence additionally indicates the potential of these approaches to predict outcome and guide therapy. In a prospective, multicenter study of 113 patients with aortic regurgitation,[177] LV end-diastolic volume > 246 mL, regurgitant volume > 42 mL, and regurgitant fraction > 33% were independent predictors of guideline-based need for valvular replacement during a mean follow-up of 2.6 years. Another prospective, multicenter study of 103 patients with mitral regurgitation[178] demonstrated modest agreement between echocardiographic and CMR-derived severity, which was overall higher with ultrasound. However, in the 26 patients with repeated evaluation after valve surgery CMR regurgitant volume, but not echocardiographic severity, correlated strongly with reverse LV remodeling.

Ventricular assessment with CMR adds meaningful information in the assessment of valvular regurgitation. In the case of mitral insufficiency, quantification of LV end-systolic volume may demonstrate abnormal remodeling even in the presence of normal diameters.[179] Evaluation of LGE can demonstrate the relationships between scar characteristics and valvular dysfunction in ischemic mitral regurgitation.[180] Similarly, in patients with mitral valve prolapse, the presence of LGE in the LV inferobasal segment and papillary muscles has been linked to complex ventricular arrhythmias and possibly sudden death.[181] Also, T1-mapping techniques are being used to evaluate diffuse myocardial fibrosis in regurgitant disease.[182]

LEFT ATRIAL MAPPING

Noninvasive imaging with CMR or CT is often performed prior to pulmonary vein ablation for atrial fibrillation (AF).[1,144] Currently, these technologies provide a "road map" for positioning catheters along the circumference of the pulmonary vein ostia during the ablation procedure, although the impact of this approach on procedure duration or success remains uncertain.[183,184] Contrast-enhanced MRA is the cornerstone of left atrial mapping with MRI, but it can be replaced and/or complemented with cine imaging, 3D SSFP, or (particularly in the presence of a stenosis) PC. These sequences can provide clinically relevant information regarding not only anatomy but also left atrial function and structural remodeling.

LEFT ATRIAL AND PULMONARY VEIN ANGIOGRAPHY

Contrast-enhanced MRA is able to accurately depict the number, location, orientation, and dimensions of the pulmonary veins, demonstrating frequent anatomic variants such as a common left trunk or a right middle vein[185] (Fig. 16–41). Although no longer a frequent complication in the era of antral (rather than ostial) ablation, MRA is also well suited to detect pulmonary vein stenosis.[186] While the spatial resolution of CT angiography is superior, CMR provides comparable anatomic information without exposure to ionizing radiation, and is associated with similar procedural success.[187] Several newer study results suggest that left atrial volume,[188] left atrial sphericity,[189] and pulmonary vein size[190] are features that have been associated with higher recurrence rates of arrhythmia after ablation are obtainable during the same examination used to acquire the pulmonary vein angiographic data.

OTHER

Left atrial function can be studied using cine images. Reduced passive emptying (likely a reflection of increased ventricular end-diastolic pressure) has also been associated with risk of arrhythmia recurrence.[191] Although more commonly done with echocardiography, the evaluation of left atrial strain with cine CMR is feasible and has been validated.[192] Reduced strain has been associated with a prior history of stroke,[193] and with arrhythmia recurrence after ablation.[194] Beyond its association with AF, reduced left atrial function is also a risk marker for incident HF[195] or for impaired prognosis once HF develops.[196]

Regarding left atrial appendage characterization with CMR, increased size has been related to higher stroke prevalence.[197] Four different appendage morphologies have been described and were linked to different thromboembolic risk in one large series of patients referred for ablation,[198] although this association could not be replicated in a subsequent larger study.[199] Detection of left atrial appendage thrombus with CMR appears accurate when compared with transesophageal echocardiography,[200] although CMR has not been as extensively validated as CT.

A rapidly evolving field is the study of left atrial structural remodeling through visualization of atrial fibrosis with LGE. This application is more challenging than ventricular LGE resulting from the thin atrial walls. Also, these assessments require experienced operators; yet with appropriate expertise, the technique is feasible and has good intraobserver and interobserver reproducibility.[201]

In limited histological validation studies, atrial wall LGE correlates with fibrosis.[202] The amount of LGE is typically expressed as a percentage of left atrial wall (Utah classification): stage I < 10%, stage II ≥ 10% to 19%, stage III ≥ 20% to 29%, and stage IV ≥ 30%. A recent prospective, multicenter, observational study[203] evaluated the relationship

between baseline atrial fibrosis and arrhythmia recurrence in 272 patients referred for ablation. There was a progressive increase in recurrence rates across fibrosis categories, suggesting a potential role of CMR in identifying patients unlikely to benefit from intervention.[204] Furthermore, LGE can evaluate completeness of postablation lesions, a factor also associated with arrhythmia-free survival.[205] Additionally, more extensive left atrial LGE is associated with reduced atrial function,[206] appendage thrombus,[207] and prior history of stroke.[208]

CARDIAC MASSES

CMR can be considered the best modality for noninvasive characterization of cardiac masses[1,144] and may depict lesions not visualized on echocardiography.[209,210] The exception would be very small and mobile masses such as vegetations. These may be beyond the spatial resolution of the technique and/or averaged out of the image in segmented acquisitions, and they are usually detected more readily with transthoracic or transesophageal echocardiography. The CMR imaging protocol typically involves a combination of cine, black-blood, first-pass contrast-enhanced imaging, tagging, and LGE imaging.[2] This provides comprehensive information regarding mass number, location, morphology, chamber invasion, and tissue characterization. The latter combines signal intensity on T1- and T2-weighted images (typically in reference to normal myocardium), presence of perfusion, and fibrosis/necrosis within the mass.

THROMBI

In a study of 361 patients with ischemic cardiomyopathy referred for ventricular reconstruction surgery,[211] CMR as well as transthoracic and transesophageal echocardiography all had high specificity for the identification of thrombi. However, respective sensitivities were 88%, 23%, and 40%, indicating that many thrombi may be missed with echocardiography (even with the use of contrast), particularly if mural and/or small.[209,212] Regarding CMR techniques, LGE is able to detect thrombi that may be missed on cine imaging[213] (see Fig. 16–25); thus, when there is concern of potential cardiac thrombi, a contrast-enhanced examination should be considered. Most thrombi are chronic and appear isointense on T1-weighted and iso/hypointense on T2-weighted imaging in comparison with the myocardium. However, subacute thrombi may appear hyperintense on both T1- and T2-weighted imaging (caused by increase in paramagnetic methemoglobin and free water from erythrocyte lysis, respectively).[214] Clots do not usually perfuse, but some chronic, organized thrombi may develop neovascularization and demonstrate first-pass contrast enhancement and LGE.[214] In addition, as opposed to tumors, thrombi are typically hyperintense and hypointense with short and long inversion times, respectively (Fig. 16–42).

TUMORS

The main strength of CMR in the evaluation of cardiac masses is probably the ability to differentiate between cardiac thrombi from tumors. Features supporting the diagnosis of thrombus include location in the LV adjacent to areas of scar or the left atrial appendage, homogenous appearance, lack of mobility, isointensity or hypointensity on T2-weighted imaging, and absence of perfusion or LGE. Features consistent with tumor include large size, signs of infiltration, hyperintensity on T2-weighted imaging, evidence of perfusion and LGE, and accompanying pericardial or pleural effusions.[210,213,215] However, performing LGE imaging with different inversion times or a

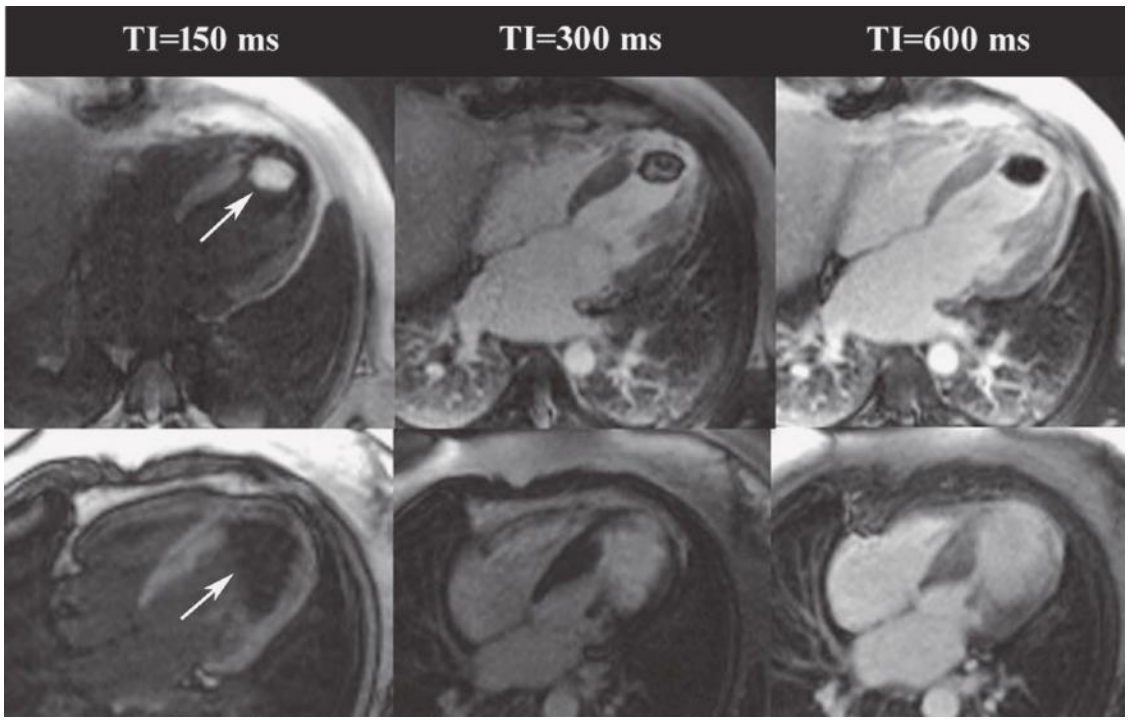


FIGURE 16–42. Comparison between an apical thrombus (*upper row; arrow*) and an apical tumor (*lower row; arrow*) with different inversion times (TI). Thrombus is hyperintense with short TI and hypointense with long TI, whereas the opposite is observed tumor.

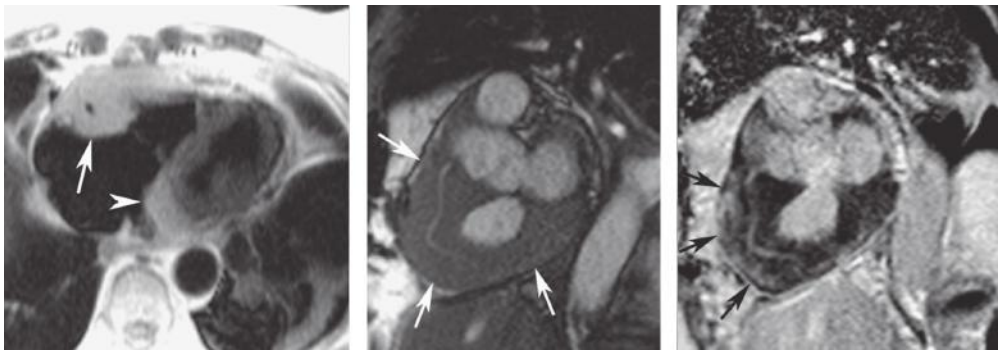


FIGURE 16–43. Cardiac lymphoma. **A.** Axial black-blood imaging demonstrating involving the right and left atrioventricular grooves (*arrow* and *arrowhead,* respectively). **B.** Short-axis cine imaging displaying the lymphoma in the right atrioventricular groove (*arrows*) surrounding the right coronary artery. **C.** Short-axis late gadolinium-enhanced (LGE) image demonstrating LGE in the mass (*arrows*).

"TI-scout" has the best accuracy to distinguish between both entities[213] (see Fig. 16–42).

Although less accurate, CMR can also help differentiate benign versus malignant neoplasms. Larger sizes, invasion of adjacent structure(s), presence of pleural or pericardial effusions, prominent perfusion, or positive LGE (Fig. 16–43) are all features seen more common in malignancy.[210,213] A few specific characteristics may be helpful in identifying individual tumors.[214] High signal intensity on T1-weighted images, besides the presence of recent hemorrhage (see above), can also be caused by fat. Together with signal reduction with fat suppression techniques, hyperintensity on T2-weighted imaging, and lack of perfusion/LGE, CMR allows for the straightforward diagnosis of lipoma (Fig. 16–44). Another rare tumor that is typically hyperintense on T1-weighted imaging is metastatic melanoma. Tumors have increased signal intensity on T2-weighted imaging in the presence of high water content, such as in cystic or highly vascular lesions. Pericardial cysts are typically noted in the right cardiophrenic space, are characteristically bright on T2-weighted imaging (Fig. 16–45) because of the proteinaceous fluid contained within, and lack perfusion or LGE. Beyond these examples, the diagnosis of a specific tumor often requires histological confirmation.

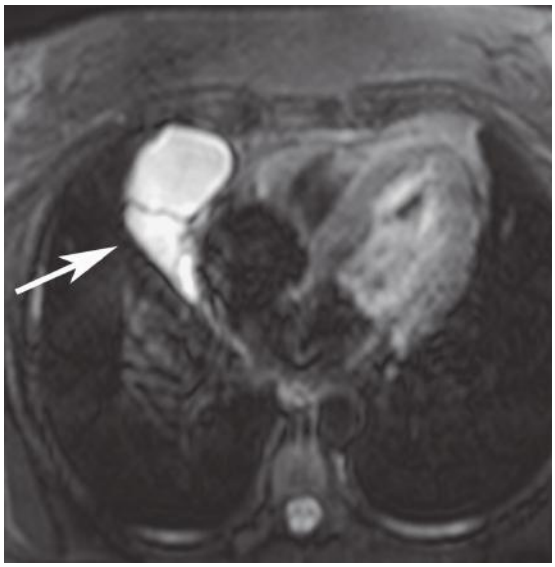


FIGURE 16–45. T2-weighted spin echo image demonstrating a pericardial cyst in the right cardiophrenic angle (*arrow*).

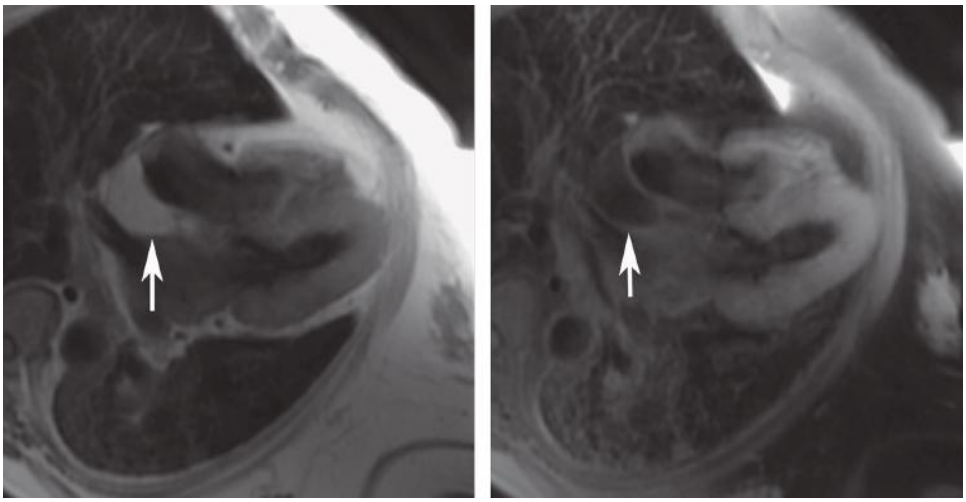


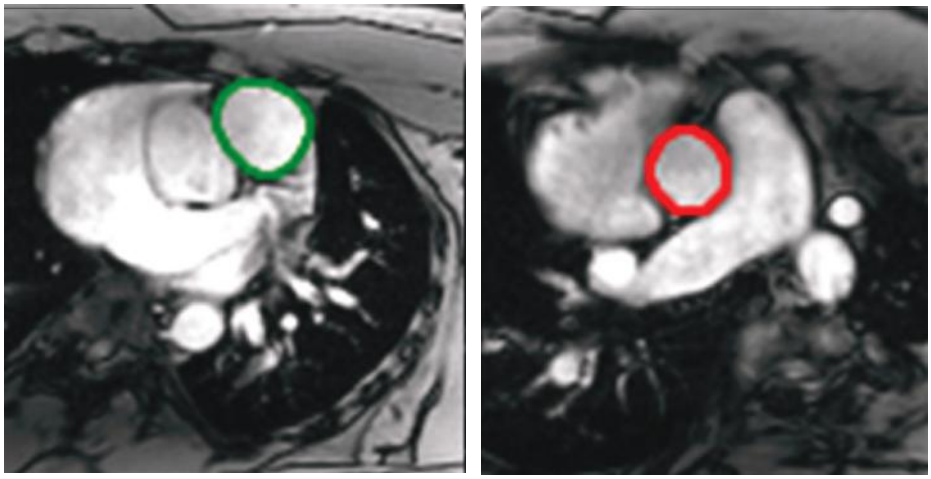
FIGURE 16–44. T1-weighted spin echo image in patient with a lipoma of the interatrial septum. On standard images, the lipoma is hyperintense (**A**; *arrow*). After the application of a fat suppression pulse, signal is nulled (*arrow*) confirming the fatty composition of the tumor (**B**).

CONGENITAL HEART DISEASE

Initially, cardiac congenital abnormalities are most frequently identified with transthoracic echocardiography. The role of CMR is typically reserved for cases of complex disease and evaluation of the great vessels or when information derived from ultrasound is insufficient for complete characterization.[216] CMR is also an attractive modality when serial follow-up is needed after surgical repair of extracardiac structures, particularly in younger individuals.[1,144,217] Comprehensive review of the many different types of congenital malformations of the heart and great vessels or detailed descriptions of specific CMR protocols are beyond the scope of this chapter. The interested reader is referred to other resources[217,218] (see also Chap. 56).

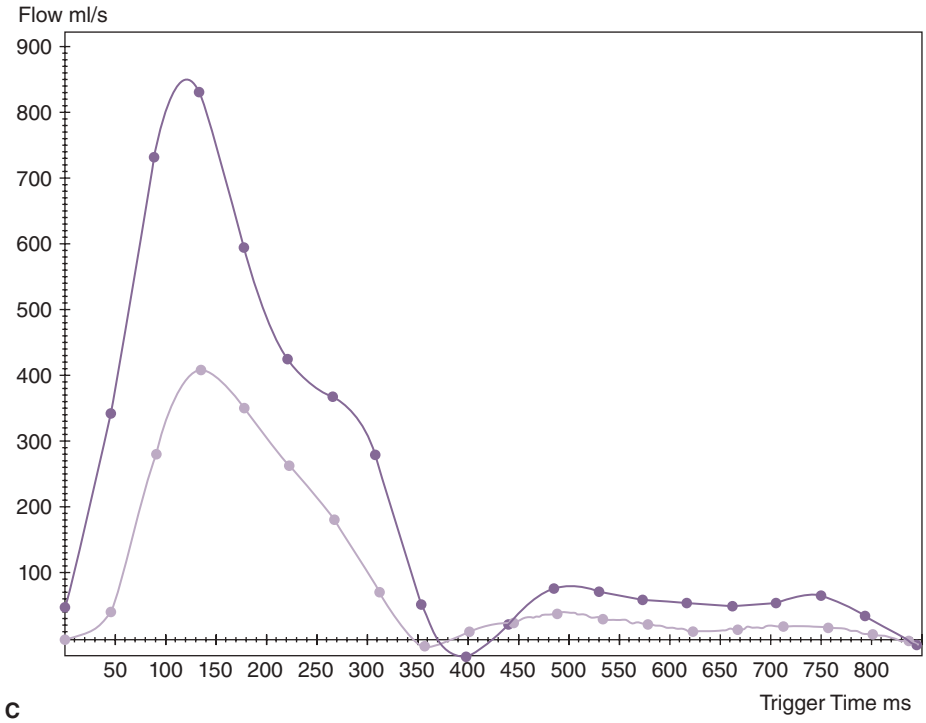
Although dependent on the specific indication, several sequences are commonly used. Breath-hold acquisitions are preferred but may not be possible in infants and young children. General anesthesia may be needed for pediatric examinations when children cannot comply with the examination (typically before age 7 years). Cine imaging is often performed in standard and modified views to obtain measurements of LV; importantly, RV size and function; and to visualize cardiac valves, shunts, or conduits. A fundamental component is the quantification of Qp/Qs using PC imaging; the most common approach is to measure systemic output at the ascending aorta and pulmonary output at the main pulmonary artery (Fig. 16–46), although other locations can be investigated such as the inferior and superior vena cavae or the right and left main pulmonary arteries. PC-derived Qp/Qs is superbly accurate and has been extensively validated.[219,220] Other potential applications of PC imaging include evaluation of valvular heart disease, characterization of differential lung perfusion, and quantification of gradients across narrowed vessels or grafts.

For the evaluation of anatomy, a 3D SSFP sequence is often used and can also document anomalous coronary origin.[2] This sequence can



A

B



C

FIGURE 16–46. Quantification of the Qp/Qs with phase imaging of the pulmonary artery (**A**) and aorta (**B**) in a patient with a shunt. The Qp/Qs (**C**) in this case was 2.1.

replace or complement contrast-enhanced 3D MRA (see Chap. 22), which is usually performed during breath-holding. Alternatively, time-resolved MRA techniques (see Chap. 22) allow for the dynamic visualization of contrast passage through the CV system.[221] Black-blood imaging can be used to evaluate areas with metallic prosthetic materials that typically cause a larger artifact in bright-blood sequences; yet, stents may be better evaluated with CT angiography. Finally, LGE can be performed to demonstrate myocardial scar, and T1 mapping techniques for quantification of diffuse fibrosis are being actively explored.[222]

SIMPLE SYSTEMIC-TO-PULMONARY SHUNTS

Intracardiac shunts such as atrial and ventricular septal defects rarely require CMR for evaluation. The exception may be sinus venosus atrial septal defect, which can be more difficult to detect on echocardiography and cause unexplained RV dilatation. The main role of CMR is usually to provide accurate and noninvasive quantification of RV size/function and shunt severity. Ostium secundum septal defects that are amenable to percutaneous intervention can be adequately identified and measured using en face views (Fig. 16–47) and CMR can provide relevant information such as additional communications or anomalous pulmonary veins.[223] CMR is more useful in the identification of extracardiac shunts. Anomalous pulmonary vein drainage can be easily depicted using MRA and severity of shunt calculated.[224]

PREDOMINANTLY OBSTRUCTIVE LESIONS

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is one of the most common indications for CMR in congenital heart disease, particularly after repair. CMR offers accurate determination of RV size and function, severity of pulmonary regurgitation, patency and dimensions of conduits and/or native arteries, and presence and extent of myocardial scar. In patients with corrected TOF and need for pulmonary valve replacement, single-center data and large prospective registries have shown associations of CMR-based biventricular ejection fraction and RV hypertrophy with major events, whereas data on volumes have been controversial.[225,226] Regional wall motion abnormalities and/or aneurysms, common in the RV outflow tract (Fig. 16–48), also contribute to systolic dysfunction

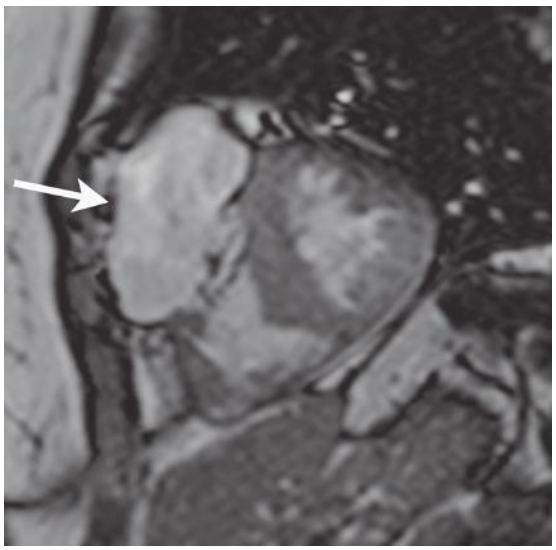


FIGURE 16–48. Cine steady-state free precession end-systolic frame in a patient with repaired tetralogy of Fallot, demonstrating an aneurysm (*arrow*) in the right ventricular outflow tract.

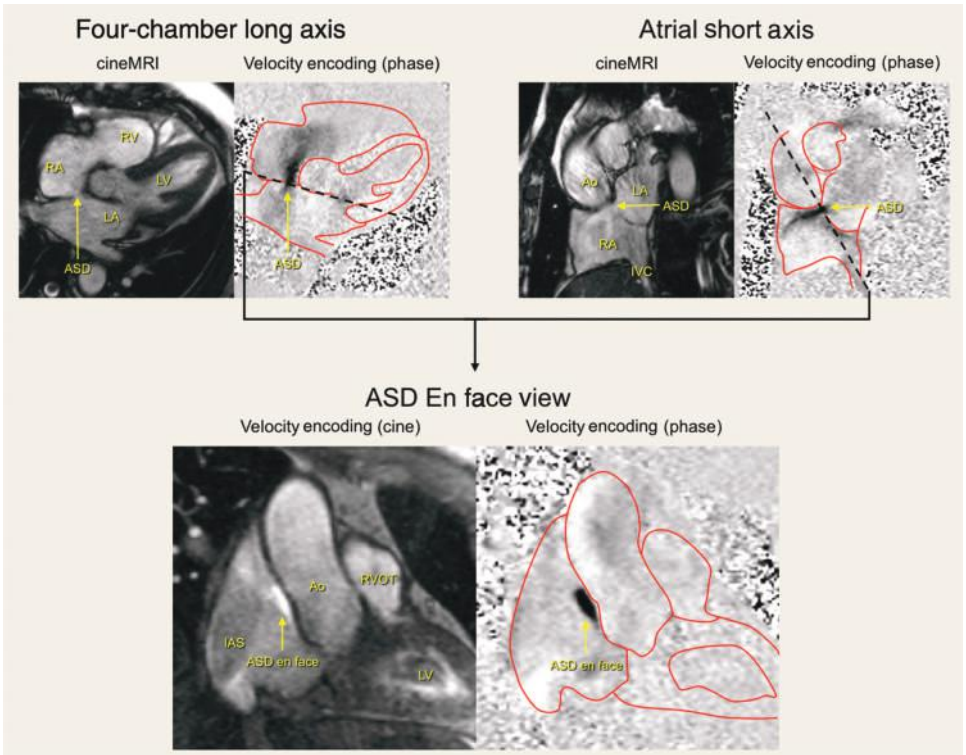


FIGURE 16–47. Visualization of secundum atrial septal defect (ASD). *Top*: Cine magnetic resonance image and in-plane phase contrast (PC) imaging in the four-chamber (*left*) and short-axis (*right*) views, demonstrating the anatomic defect and flow through the ASD (*arrows*). *Bottom*: Cine and PC en face views of the ASD (*arrows*). Ao, Aorta; ASD, atrial septal defect; IAS, interatrial septum; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

and exercise intolerance.[227] CMR is well suited for serial imaging of RV or LV size and function[228] and can help guide the timing of surgical replacement of the pulmonary valve; RV volumes can be normalized if surgery is performed while RV end-diastolic volume < 160 mL/m^2 and end-systolic volume < 80 mL/m^2.[229] PC is used to quantify the severity of pulmonary regurgitation, rule out residual shunts, and detect pulmonary artery end-diastolic forward flow (indicative of restrictive physiology), and it can be performed also in main pulmonary branches to evaluate differential pulmonary regurgitation and/or perfusion.[230] Contrast-enhanced MRA can depict stenosis of the pulmonary artery, its branches, or a ventriculoarterial conduit; aortic root dilatation; or, particularly prior to surgical repair, the presence of systemic-to-pulmonary collaterals or a patent ductus arteriosus. Finally, the presence of LGE is another common finding in the RV outflow tract and has been associated with adverse markers such as RV dilatation and dysfunction, decreased functional class, and arrhythmias.[231]

Coarctation of the Aorta

The extent and anatomic severity of aortic coarctation can be accurately depicted with black-blood sequences, 3D SSFP or, particularly, contrast-enhanced MRA (Fig. 16–49). The hemodynamic severity of the coarctation can be determined measuring peak velocity and gradient with PC imaging (see Valvular Heart Disease).[232] However, peak gradient may be reduced in the presence of extensive collateral circulation, which can be depicted anatomically with MRA or functionally with PC. The latter is acquired both at the proximal and distal descending aorta. In normal conditions flow in both locations should be similar or slightly lower distally; however, when there is significant collateral circulation, distal flow actually increases and the difference is proportional to the severity of the coarctation.[232] This index, and particularly the combination of the smallest cross-sectional area on MRA and flow deceleration in the distal aorta, provides the best diagnostic accuracies for the identification of significant stenosis or need for intervention.[233] Serial imaging after repair is recommended to rule out complications such as restenosis or aneurysms that can be readily identified with CMR.[234]

FIGURE 16–49. Contrast-enhanced three-dimensional magnetic resonance angiography in a patient with aortic coarctation and prominent collateral circulation.

ABNORMAL CARDIAC CONNECTIONS

Transposition of the Great Arteries

D-loop transposition of the great arteries (TGA) is the most common form and requires surgical correction (Fig. 16–50), and the most important role of CMR is the evaluation of potential postoperative complications. Goals of CMR include evaluation of ventricles, residual shunts, baffles/conduits, ischemia, and fibrosis with a combination of cine imaging, PC, contrast first-pass imaging, 3D SSFP and/or MRA, stress perfusion, and LGE.[234] In the case of atrial switch, the most common late complication is the progressive dilatation and dysfunction of the systemic RV, which can be serially evaluated with CMR. Also, an inadequate RV response to dobutamine stress has been linked to adverse events.[235] LGE in the systemic RV can occur and is associated with systolic dysfunction, arrhythmias, and functional deterioration.[236] In cases of arterial switch, stenoses tend to be most frequent in the RV outflow tract and pulmonary branches, particularly the right one if the pulmonary is positioned anterior to the ascending aorta (LeCompte maneuver). Other potential complications include stenoses of ventriculoarterial conduits, dilatation of the neoaortic root, or obstruction of the reimplanted coronary arteries.[237]

L-loop or congenitally corrected TGA is less common and does not have abnormal circulation. However, just like in D-loop TGA after atrial switch, the most common late complication is the failure of the systemic (congenitally right) ventricle. As described above, an abnormal response to stress or the presence of LGE may be markers of impaired prognosis.[235,236]

Single-Ventricle Physiology

Single-ventricle or univentricular heart physiology may result from a number of complex anomalies, including hypoplastic left heart syndrome. The standard palliative repair is the deviation of systemic flow directly to the lungs (Fontan circulation). CMR is possibly the best available technique today for evaluation of ventricular status

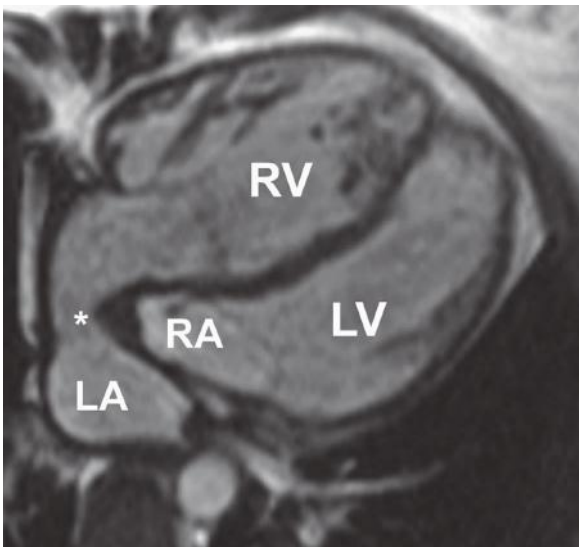


FIGURE 16–50. Cine steady-state free precession frame in a four-chamber view in a patient with D-transposition and an atrial baffle correction. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

and central circulation before and after Fontan.[238] Retrospective and prospective randomized data have shown that CMR can replace invasive catheterization prior to Fontan on many instances, with similar short-term and long-term outcomes.[239,240] The presence and extent of systemic-to-pulmonary collaterals is an important determinant of postoperative course and can be characterized anatomically and functionally both before and after surgery.[241] CMR can also be used to evaluate the different conduits and anastomosis of the Fontan stages,[242] which may occlude or narrow partly because of increased systemic venous pressure and associated blood stasis and thrombosis. Indexed ventricular end-diastolic volume has been associated with transplant-free survival,[243] and the extent of LGE has been linked to ventricular dilatation, hypertrophy, and dysfunction, as well as arrhythmias.[244]

PULMONARY HYPERTENSION

The use of CMR for pulmonary hypertension (PH) is not advocated in clinical guidelines/recommendations with the exception of PH associated with congenital heart disease.[234] The main role of CMR is the quantitative evaluation of RV performance, although flow imaging of the great arteries, pulmonary MRA, and LGE imaging are also important in disease characterization. One of the potential applications of CMR is the determination of underlying etiology when it is uncertain. Quantification Qp/Qs can identify the presence of an unsuspected shunt (see section on Congenital Heart Disease). MRA has good diagnostic accuracy to detect chronic thromboembolism,[245] although CT and, particularly, ventilation/perfusion scintigraphy are typically favored for this application. Other findings can raise suspicion for alternative etiologies.

A number of parameters have demonstrated discriminatory ability to detect the presence of PH. These include, among others, biventricular volumes, function, mass, and geometry (Fig. 16–51); LGE; and pulmonary artery size, stiffness, mean blood velocity, and flow vortices.[246-249] However, none of these parameters is considered accurate to justify routine use.[250] CMR-based approaches for the quantification of pulmonary hemodynamics have also been developed; the most extensively validated estimates pulmonary vascular resistance using RV ejection fraction and pulmonary artery mean velocity,[251,252] with preliminary data suggesting potential prognostic value.[253] Other CMR indices have been linked to reduced survival and include increased RV volumes and decreased RV ejection fraction or stroke volume.[254,255] CMR can also be used to track serial changes in ventricular volumes and function, assessing the effects of therapy or progressive deterioration, which also portends poor outcomes.[254,256] Finally, reduced pulsatility of the pulmonary artery is similarly associated with increased mortality.[257]

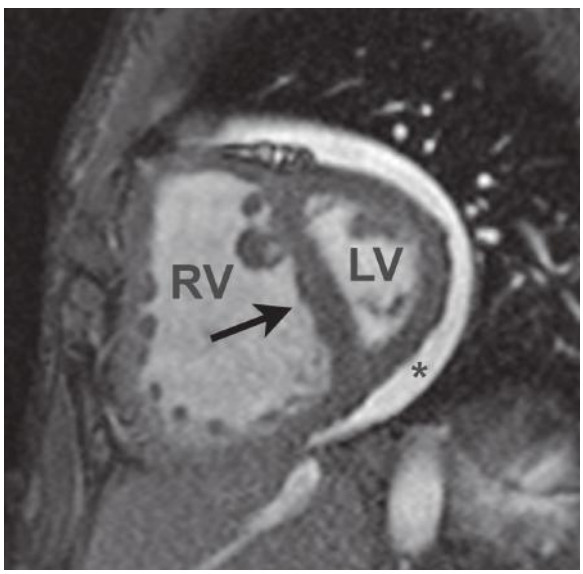


FIGURE 16–51. Cine steady-state free precession end-systolic frame in a patient with severe pulmonary hypertension, demonstrating severe right ventricular enlargement and hypertrophy as well as interventricular septal flattening (arrow). A pericardial effusion is also noted (asterisk). LV, left ventricle; RV, right ventricle.

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CHAPTER 17

COMPUTED TOMOGRAPHY OF THE HEART

Amir Ahmadi, Jagat Narula, and Jonathon Leipsic

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SUMMARY / 493

Computed tomography (CT) is a technique that can fully evaluate both cardiac structure and function. Recent advances in imaging allow for evaluation of not only relatively stationary anatomy, such as the thoracic aorta, but also rapidly moving structures, such as the myocardium and coronary arteries. This imparts the ability to noninvasively evaluate for significant coronary artery disease (CAD), myocardial and pericardial abnormalities, and aortic pathology. When combined with electrocardiographic (ECG) gating, freeze-frame images of the heart can be obtained, eliminating most of the motion artifact. This is particularly important in contrast-enhanced CT angiography of the coronary arteries and in quantification of coronary artery calcium. Advances in spatial and temporal resolution and image reconstruction software have also helped in the evaluation of such cardiac structures as coronary veins, saphenous vein grafts, atria, ventricles, and pulmonary arteries and veins, helping precisely define their spatial relationships within the cardiovascular system and allowing for a comprehensive assessment of a variety of cardiovascular disease processes. This chapter details the current and future role of cardiac CT for the assessment of cardiovascular physiology and pathology.

TECHNICAL CONSIDERATIONS

Advancements in CT technology have made it possible to noninvasively image the beating heart. Multidetector computed tomography (MDCT) scanners produce images by rotating an x-ray tube around a circular gantry through which the patient advances on a moving table. Improvements in gantry rotation speeds and the development dual source and large detector technologies have reduced effective temporal resolution to less than 100 milliseconds. The coronary arteries move independently throughout the cardiac cycle and even at slow heart rates exhibit significant translational motion of up to 60 mm/s for the right coronary artery (RCA) and 20 to 40 mm/s for the left anterior descending (LAD) and circumflex coronary arteries (Fig. 17–1).[1,2] Image acquisition of less than 50 milliseconds is truly required to completely avoid cardiac motion artifacts.[1]

With MDCT systems, temporal resolution may be further improved by selecting specific partial image sector data from different heartbeats and detector rings to reconstruct a complete 240-degree image data set. With retrospective gating, several thousand images can be acquired during a single cardiac study, allowing one to choose images with the least amount of motion-related distortion prior to final image reconstruction.

MDCT scanners using retrospective gating can increase exposure approximately 13-fold.[3] Prospective gating during either spiral or nonspiral acquisitions uses ECG-gated image triggering only at specific temporal locations in the cardiac cycle, thereby significantly reducing radiation exposure to more than 3 mSv, with reports as low as less than 1 mSv.[4] Gating works relatively well at slow heart rates (ie, < 60 beats/min), where the R-R interval is greater than 1000 milliseconds and the fastest imaging protocols may be used. However, at faster heart rates, a 200-millisecond acquisition effectively covers most of the cardiac cycle, thus removing any potential benefit from gating the image acquisition.

EVALUATION OF MYOCARDIAL FUNCTION

Both ventricles are equally well visualized by contrast cardiac computed tomography angiography (CCTA). The combination of ECG gating and image postprocessing permits the reconstruction of multiple data sets at predetermined percentages of the R-R interval throughout the entire cardiac cycle (Fig. 17–2). This multiphase image reconstruction can be displayed in cine mode as in echocardiography or cardiac magnetic resonance (CMR) imaging. Therefore, end-systolic and end-diastolic images can be obtained to assess ventricular volumes and function (see Fig. 17–2).

Both ventricles are well visualized by MDCT, allowing excellent spatial separation between the two structures. Delineation of the epicardial and endocardial surfaces allows accurate and reproducible measurement of left ventricular (LV) and right ventricular (RV) wall thickness and myocardial mass.[5] LV hypertrophy can be quantified and serially assessed.

Cardiac CT can assess left and right heart hemodynamics as well as regional myocardial wall motion and thickening.[6,7] The cine mode is used to acquire multiple gated images of the RV and LV during maximal contrast enhancement (see Fig. 17–2).[7] This affords accurate and reproducible quantification of LV and RV end-diastolic and end-systolic volumes for the calculation of ejection fraction (EF).[7] Cardiac CT is comparable to first-pass radionuclide angiography for the calculation of left ventricular ejection fraction (LVEF) in patients with myocardial infarction (MI).[8]

MDCT allows for precise measurements of LV volumes and overall function, which have a close correlation with echocardiography.[5,9-11] Compared with CMR, the current gold standard for cardiac functional evaluation, MDCT is an adequate alternative.[9] Furthermore, MDCT is also a valuable tool in estimating LV wall thickness and mass and revealing segmental wall motion abnormalities, demonstrating good overall agreement with echocardiography and CMR.[5,9-11]

Ventricular remodeling can be assessed by CT in a method similar to that used by gated blood-pool radionuclide angiography and

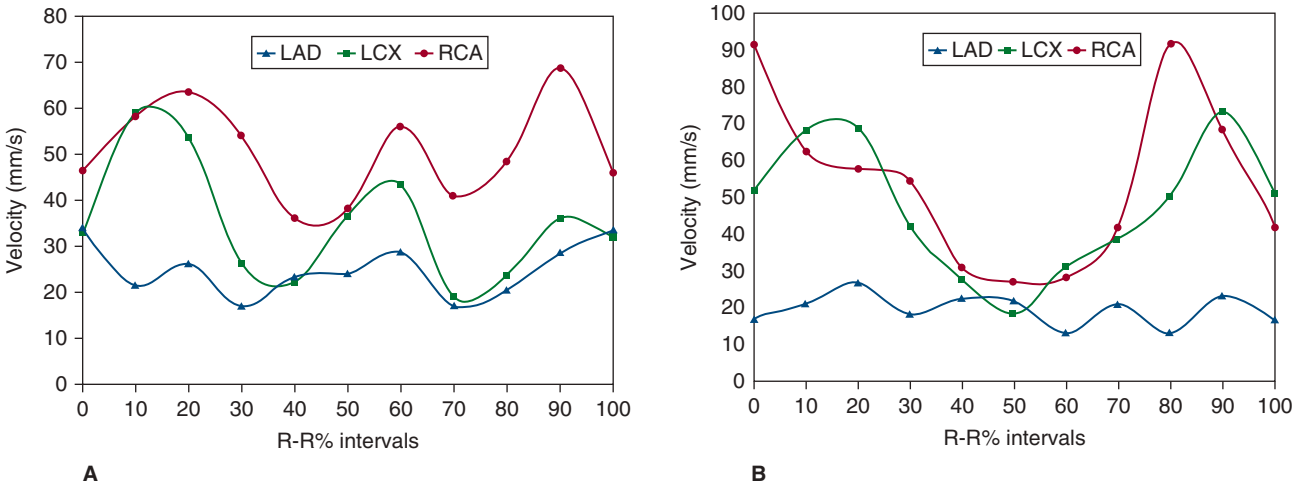


FIGURE 17–1. Coronary artery velocity varies substantially throughout the cardiac cycle, depending on whether the heart rate is relatively slow (72 beats/min) (**A**) or fast (89 beats/min) (**B**). The greatest motion occurs in the right coronary artery (RCA), followed by the left circumflex (LCX) and left anterior descending (LAD) coronary arteries. **A.** A biphasic pattern of rest is found during end-systole (at 40%-50% of the R-R interval) and mid-diastole (at 70%-80% of the R-R interval). **B.** A monophasic rest period pattern was found near end-systole (at 40%-60% of the R-R interval). Reproduced with permission from Lu B, Mao SS, Zhuang N et al: Coronary artery motion during the cardiac cycle and optimal ECG triggering for coronary artery imaging, *Invest Radiol*. 2001 May;36(5):250-256.[1]

echocardiography. Computed tomography angiography (CTA) can identify wall thinning and impaired LV thickening in an area of previous MI and delineate anterior and posterior LV aneurysms and associated mural thrombus (Fig. 17–3).[5,12]

RV volume and functional assessment by MDCT is feasible and has good correlation with both radionuclide ventriculography and CMR[5,11] (Fig. 17–4). CT acquisition protocols can be altered to more favorably opacify the right heart when RV volumes are needed by using a triphasic injection where the initial contrast injection is followed by a blend of saline (60%) and iodinated contrast (40%). When valvular surgery is considered, CT can delineate the important parameters of LV chamber size, wall thickness, and LVEF.[5,12] Congestive heart failure or left atrial enlargement can be complicated by left atrial thrombi. It has been recently suggested that CT could be used as an alternative to transesophageal echocardiography in detecting intra-atrial thrombus.[13]

EVALUATION OF CORONARY ARTERY DISEASE

CORONARY ARTERY CALCIFICATION

The presence of coronary artery calcification (CAC) is clearly indicative of coronary atherosclerosis,[14,15] serving as a marker for CAD; but importantly, the severity of angiographic coronary artery stenosis is not directly related to the total CAC. CAC is thought to begin early in life, but it progresses more rapidly in older individuals who have further advanced atherosclerotic lesions.[16] Calcification is an active, organized, and regulated process occurring during atherosclerotic plaque development where calcium phosphate in the form of hydroxyapatite precipitates in atherosclerotic coronary arteries in a fashion similar to that observed in bone mineralization.[17,18] Although lack of calcification does not categorically exclude the presence of atherosclerotic plaque, calcification occurs exclusively in atherosclerotic arteries and is not found in normal coronary arteries.

The presence and extent of histologically determined plaque area has been compared with the total calcium area in individual coronary arteries derived from autopsied hearts.[14] A strong linear correlation exists between total coronary artery plaque area and the extent of CAC as found in individual hearts ($r = 0.93$, $P < .001$) and in individual coronary arteries ($r = 0.90$, $P < .001$).

Detection of Coronary Artery Calcification

MDCT imaging protocols vary among different camera systems and manufacturers. Generally, 40 consecutive images, 2.5- to 3-mm thick, are acquired per cardiac study. Calcified lesions are defined as two or three adjacent pixels with a tomographic density of either greater than 90 or greater than 130 HU. Effective pixel size for a reconstruction matrix of 512 × 512 pixels with a common field of view of 26 cm is 0.26 mm^2. Calcium scoring is usually based on the traditional Agatston method (ie, initial density of > 130 HU). As with electron beam computed tomography (EBCT) scoring, the total coronary artery calcium score (CACS) is calculated as the sum of each calcified plaque over all the tomographic slices.

Noninvasive techniques, such as exercise treadmill testing and myocardial perfusion imaging, aim to identify patients with abnormal coronary flow reserve either secondary to abnormal microvasculature or advanced epicardial CAD. However, unlike CT, which can detect coronary atherosclerosis at its earliest stages, these techniques can identify only patients with advanced CAD who manifest myocardial ischemia. Although the presence and extent of ischemia can accurately identify asymptomatic individuals at high risk for cardiac events, the very low prevalence of a positive test result (< 5%) precludes the use of these methodologies as primary screening tests for the early detection and treatment of CAD (Fig. 17–5).[19,20]

Several studies emphasize the effectiveness of selectively combining stress myocardial perfusion imaging with CT in the anticipated small (10%) number of asymptomatic patients who will have a high (≥ 400) CACS so as to specifically identify those with silent myocardial ischemia.[20,21] This testing strategy may prove to be optimal based on the known prognostic value of perfusion imaging and the superior sensitivity of CT over the former for detecting preclinical CAD.

Coronary Artery Calcification: Prognostic Implications

Traditional risk factor assessment is routinely used to identify individuals who are at increased risk for developing cardiovascular disease based on standard clinical criteria.[22] Given that the development of symptomatic cardiovascular disease occurs almost exclusively in patients with atherosclerosis, it seems advantageous, for the purposes of risk assessment, to use a technique that directly characterizes the

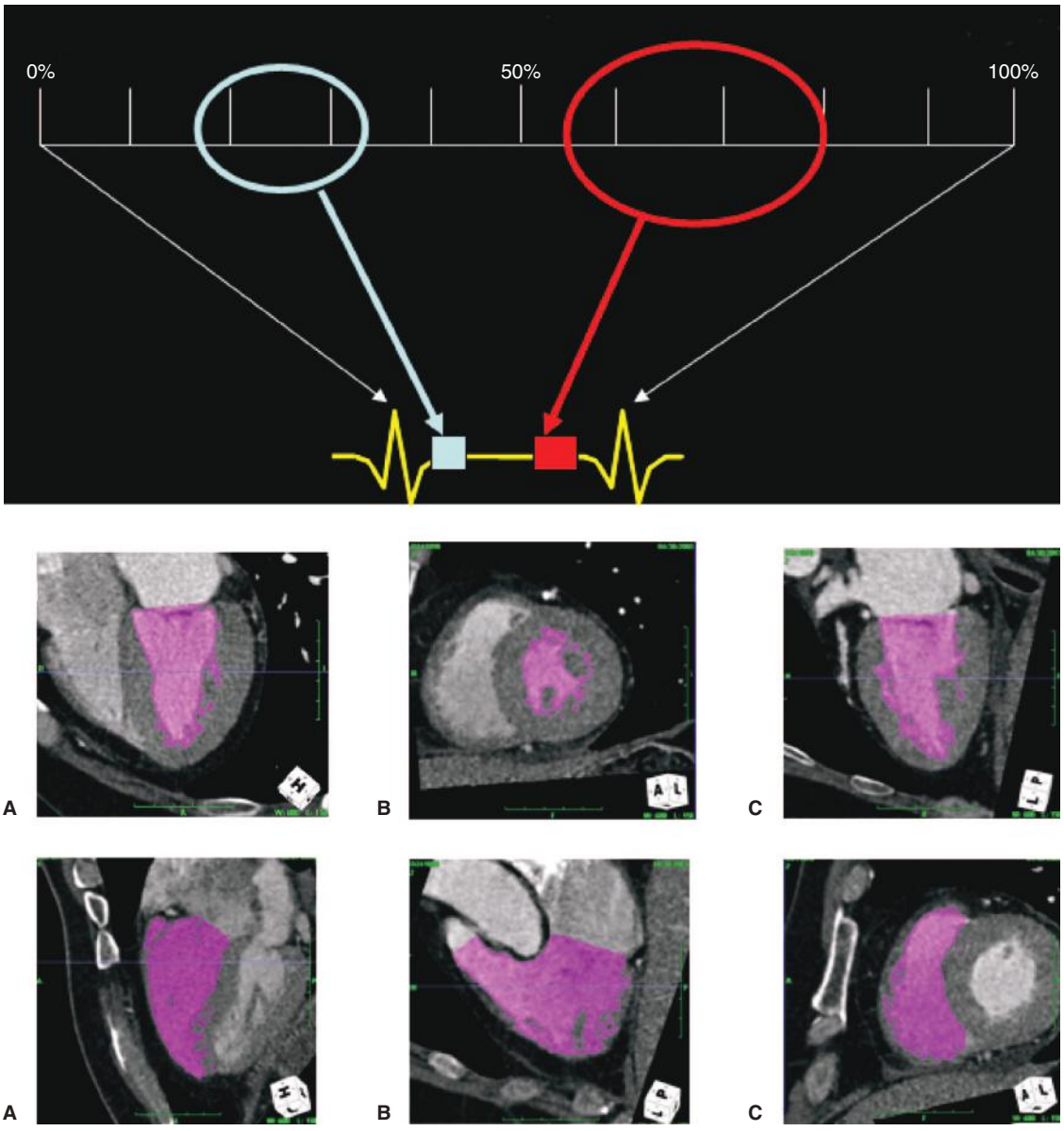


FIGURE 17–2. Evaluation of cardiac function. *Upper panel:* A diagram showing the division of the cardiac cycle into 10% intervals. The two ovals cover the two regions of the cardiac cycle where the motions are the most still. The *light blue oval* covers the mid- to end-systolic phase, and the *red oval* covers the mid- to end-diastolic phase. *Middle panel:* Images generated by an automatic contrast and contour detection software for quantitative functional evaluation. The three views are four chamber (**A**), short axis (**B**), and two chamber (**C**) of the left ventricle. *Lower panel:* Images generated by the same software for right ventricular ejection fraction calculation. The three views are four chamber (**A**), right ventricle outflow (**B**), and short axis (**C**).

presence and severity of atherosclerotic burden rather than estimating its presence through indirect measures. For example, although there is a clear relationship between the number of cardiac risk factors and the presence and extent of CAC, 40% of men and 30% of women without risk factors in one series had CAC, whereas 26% of men and 36% of women with more than three traditional risk factors did not have any CAC.[23] Importantly, this study and others have confirmed that CAC allows for much more accurate risk stratification than do other risk factors.

The likelihood of plaque rupture and the development of acute cardiovascular events is related to the total atherosclerotic plaque burden.[24,25] There is a direct relationship between the CAC severity, the extent of atherosclerotic plaque, and the presence of silent myocardial ischemia. Many studies have now demonstrated an increased risk of cardiac events in asymptomatic patients who have extensive atherosclerosis and silent ischemia,[19,26,27] Therefore, the CACS could be useful for risk assessment of asymptomatic individuals and potentially guide therapeutics.

Several studies in both symptomatic[28,29] and asymptomatic[30-34] patients have studied whether the extent of CAC can predict subsequent patient outcomes. In 422 symptomatic patients followed for 30 ± 12 months,[28] cardiac events were 10-fold higher in patients with a CACS above the 75th percentile for age (9.5%) versus patients with a CACS below the 25th percentile (0.9%). These results were also adjusted for age, gender, and race. Another study of 288 symptomatic patients referred for coronary angiography[29] showed that patients with a CACS of more than 100 had a 3.2-fold higher relative risk of death or MI than those with a lower CACS.

Large trials have reported an approximately 10-fold increased risk with the presence of CAC.[34,35] In one of the largest observational trials

FIGURE 17–3. A single frame from a contrast-enhanced cine computed tomography demonstrates thrombus in a left ventricular aneurysm. Also note that the wall of the aneurysm is calcified.

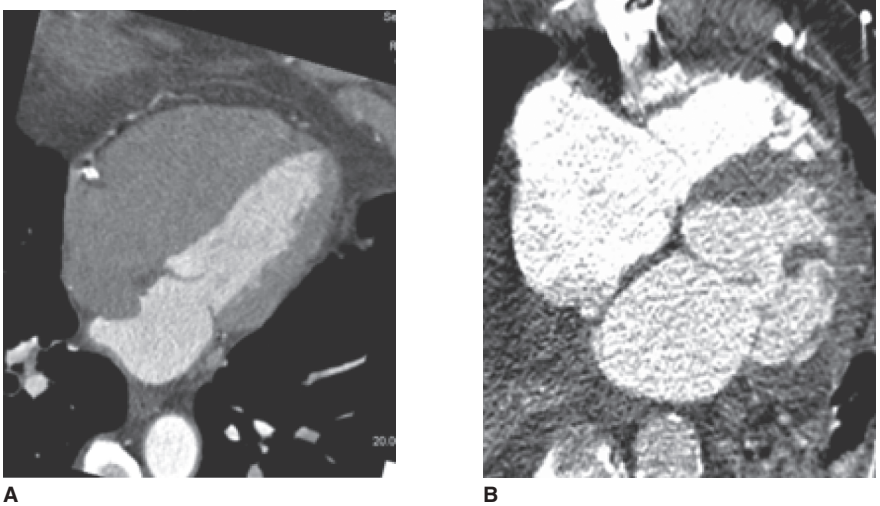
to date, Shaw and colleagues[36] reported all-cause mortality in 10,377 asymptomatic patients (4191 women and 6186 men) who had a baseline CAC and were then followed for 5.0 ± 3.5 years. Most patients had cardiac risk factors including a family history of CAD (69%), hyperlipidemia (62%), hypertension (44%), and current cigarette smoking (40%). The CACS was a strong independent predictor of mortality, with 43% additional predictive value contained within the CACS beyond risk factors alone. Mortality significantly increased with increasing CACS.

Similarly, in a younger cohort of asymptomatic persons, the 3-year mean follow-up in 2000 participants (mean age, 43 years) showed that coronary calcium was associated with an 11.8-fold increased risk of incident coronary heart disease ($P < .002$) in a Cox model controlling for the Framingham risk score.[37] The Rotterdam Heart Study[38] investigated 1795 asymptomatic participants (mean age, 71 years) who had CAC and measured risk factors. During a mean follow-up of 3.3 years, the multivariate-adjusted relative risk of coronary events was 3.1 for calcium scores of 101 to 400, 4.6 for calcium scores of 401 to 1000, and 8.3 for calcium scores greater than 1000 compared with calcium scores of 0 to 100.

Multiple studies have demonstrated that the relationship between CAC and outcomes is similar in men and women and across different ethnic groups.[39-43] Each of these studies demonstrated that the area under the curve to predict coronary artery events is significantly higher with CAC than either Framingham or Prospective Cardiovascular Munster (PROCAM) risk stratification. Studies comparing predictive capacity of conventional and newer biomarkers for prediction of cardiovascular events consistently demonstrate that adding a number of newer biomarkers (such as C-reactive protein, interleukins, and other proposed risk stratifiers) only changes the C statistic by 0.009 ($P = .08$).[39,40,44] Small changes such as these in the C statistic suggest limited or modest improvement in risk discrimination. However, CAC scanning has been shown to markedly improve the C statistic, suggesting robust improvement in risk discrimination.

In another study, 9715 individuals underwent CAC imaging and were followed for a mean of 14.6 years. A warranty period was defined as less than a 1% mortality rate. It was demonstrated that the warranty period in patients with CAC score of 0 and low and intermediate risk was almost 15 years with no significant differences regarding age and sex. A CAC score of 0 was associated with a vascular age of 1, 10, 20, and 30 years less than the chronological age of individuals between 50 and 59, 60 and 69, 70 and 79, and 80 years of age and older, respectively. CAC was the strongest predictor of death when compared to both Framingham Risk Score and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[45]

Overall, CAC score appears to provide complementary prognostic information to that obtained by the Framingham risk model or other risk assessment methods. Furthermore, multiple studies consistently demonstrate that CAC scanning confers more precise risk prediction than other alternatives such as C-reactive protein or carotid intimal-medial thickness.[39,40,44]



A B

FIGURE 17–4. Evaluation of the right ventricular (RV) function. **A**. Maximum intensity projection (MIP) image of a four-chamber view of a heart. The study was performed with normal saline chaser. No contrast enhancement is noted in the RV, allowing optimal evaluation of the right coronary artery (RCA), intracardiac shunts, and atrial septal aneurysm (as shown in this case). **B**. MIP image of a four-chamber view of a heart. This study was performed without saline chaser, and the timing of the study was suboptimal for the assessment of the left heart and coronary arteries. Overenhancement of the RV with contrast leads to difficulty in the assessment of the RCA. There is also significant beam-hardening artifact from the sternal wire.

Coronary Artery Calcification Progression

Much interest has been directed at using CAC to measure plaque burden and then remeasuring at some point after treatment is applied to assess for progression of disease.[46] Callister and coworkers[47] performed one of the first studies to demonstrate a relationship between cholesterol lowering and atherosclerosis progression. There was a significant net increase in mean calcium volume score among individuals not treated with cholesterol-reducing medications (mean change, 52% ± 36%; $P < .001$). There was a graded response depending on the low-density lipoprotein (LDL) reduction with statin therapy, with those treated to LDL less than 120 mg/dL demonstrating an average diminution of coronary calcium (7% ± 23%) and

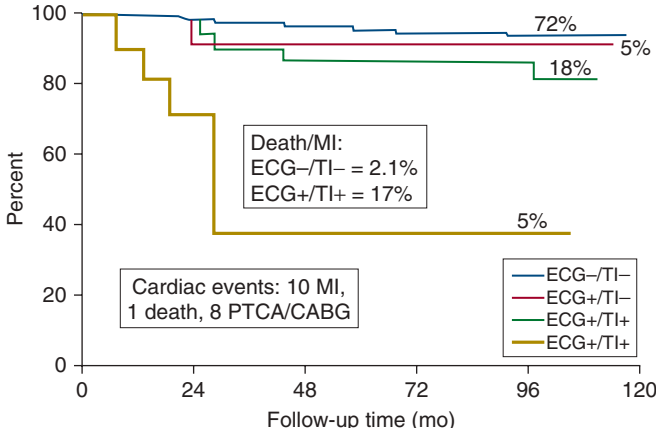


FIGURE 17–5. Kaplan-Meier survival curves based on exercise electrocardiogram (ECG) and thallium 201 (TI) scan results. The highest event rate (17%) is observed in patients with ischemia (+) by both tests. The percentages of patients with each test combination are shown above the curves. CABG, coronary artery bypass grafting; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty. Reproduced from Blumenthal RS, Becker DM, Moy TF, et al. Exercise thallium tomography predicts future clinically manifest coronary heart disease in a high-risk asymptomatic population, *Circulation*. 1996 Mar 1;93(5):915-923.[19]

those treated less aggressively (LDL > 120 mg/dL) showing a calcium volume score increase of 25% ± 22% ($P < .001$ for comparison with aggressively treated patients).

The Multi-Ethnic Study of Atherosclerosis (MESA) measured baseline CACSs and repeated this measurement after 3.5 years in 5756 patients. Of these, 2948 patients (51%) had a CACS of 0 at onset and were followed for development of incident positive CACS. The percentage developing positive scores was 16%. Another 2808 patients had a detectable CACS at baseline and were followed for progression. Their average rate of progression was 17.5 Agatston units per year. Risk factors associated with CAC progression were older age, male sex, white race/ethnicity, hypertension, higher body mass index, diabetes mellitus, and family history of heart attack. The associations that persisted after adjustment for baseline CAC were body mass index, family history of MI, diabetes mellitus, microalbuminuria, and blood glucose level.[48]

A new post hoc analysis[49] of eight intravascular ultrasound (IVUS) studies that assessed the effect of medical therapies on serial changes in coronary atheroma burden suggests that there is a paradoxical relationship between calcification of the coronary artery and atheroma volume among individuals treated with statin therapy. This study demonstrates that high-intensity statin therapy promotes coronary calcification despite inducing regression of overall coronary atheroma volume. One interpretation of such results could be that the increase in coronary calcification among patients treated with a statin might be suggestive of coronary plaque stabilization. Therefore, the interpretation of results demonstrating CAC progression in a setting of high-intensity therapy could change from plaque progression to plaque stabilization.

COMPUTED TOMOGRAPHY ANGIOGRAPHY

Anatomical Assessment of Coronary Arteries

Assessment of Native Coronary Arteries The explosive growth of cardiovascular imaging over the past few decades has facilitated the noninvasive detection of CAD. CCTA has the ability to accurately detect luminal stenosis in the coronary arteries and characterize coronary artery plaques. Advances in MDCT technology have resulted in high spatial and temporal resolution capable of detecting coronary atherosclerosis approximating that seen with invasive catheter-based coronary angiography. However, invasive coronary angiography (ICA) carries procedural risk (0.1%-0.2%), as well as high procedural cost.[50] It has been estimated that approximately up to 40% of patients who undergo coronary angiography have normal angiograms, and many patients with CAD do not require revascularization procedures.[51-53] CCTA has the potential to obviate the need for invasive procedures in select patients by demonstrating the absence of significant CAD, as well as improve risk stratification through detection of coronary atherosclerosis, assessment of ventricular function, and provision of information on cardiac structure.

Image Acquisition MDCT scanners produce images by rotating an x-ray tube around a circular gantry through which the patient advances on a moving table. Pitch is the speed of the table relative to the speed of the gantry rotation, which allows each cross-sectional level of the heart to be imaged during more than one cardiac cycle. The number of image slices acquired during each gantry rotation (4–320) determines the overall duration of the MDCT scan. Developments in MDCT technology have led to the rapid advancement from four-slice MDCT machines in 1998 to 64 slices in 2004 and 256-slice and 320-detector row scanners in 2007. The latest technology contains 0.5-mm-wide detector elements yielding a maximum of 16-cm *z*-axis coverage. This configuration allows three-dimensional (3D) volumetric whole heart imaging during the diastole of one R-R interval, which opens the possibility of CCTA usage in the settings of higher heart rates and even arrhythmia.[54] This progression is ongoing, with 640-detector row scanners now citing even less radiation and scanning time, as well as improved image quality.[55]

Cardiac CT is performed with ECG gating in either prospective or retrospective mode. ECG gating synchronizes image acquisition with the cardiac cycle. The optimal phase or interval for image analysis is the period during which the heart is the least mobile (usually end-diastole) and therefore the least degraded by motion artifact. Prospective ECG gating entails scan initiation at a defined interval after the R wave, continues for a prespecified duration, and then stops until the same optimal period is reached in the subsequent cardiac cycle, at which time scanning resumes. Retrospective ECG gating uses continuous acquisition of images throughout the cardiac cycle. The images from multiple consecutive heartbeats are then reconstructed at various percentages of the R-R interval (eg, from 0%-90% of an R-R cycle at 10% intervals). With retrospective gating, several thousand images can be acquired during a single cardiac study, allowing the interpreting physician to select the images with the least amount of motion-related distortion prior to final image reconstruction. Gating is the most advantageous at relatively slower heart rates (< 60 beats/min), where the R-R interval is more than 1000 milliseconds and the fastest imaging protocols may be used.

The coronary arteries move independently throughout the cardiac cycle and, even at relatively slower heart rates (ie, < 70 beats/min), exhibit significant translational motion of up to 60 mm/s for the RCA and 20 to 40 mm/s for the LAD and circumflex coronary arteries (Fig. 17–6).[1,2] The velocity of coronary artery motion increases significantly with increasing heart rates. Image acquisition of less than 50 milliseconds is truly required to completely avoid cardiac motion artifacts.[1] Cardiac motion is minimized with the use of oral and/or intravenous β-blockers prior to scanning, thereby reducing the heart rate and prolonging the time during the cardiac cycle at which coronary artery velocity is low. For individuals without contraindication to β blockade, these drugs are the medication of choice because they not only decrease the heart rate through the reduction of sympathetic tone, but may also reduce the number of premature atrial or ventricular beats, which adversely affect the overall quality of the images. Another

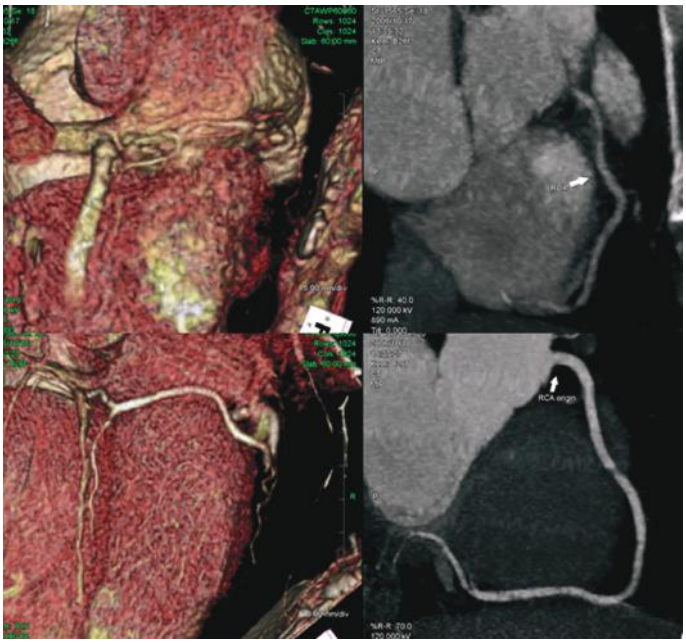


FIGURE 17–6. Cardiac motion artifact. *Top left panel*: Three-dimensional (3D) rendering image of a heart with significant motion artifact affecting the interpretation of the distal right coronary artery (RCA). This patient was scanned with a dual-source computed tomography (CT) (temporal resolution of 83 ms), and the heart rate in the time of the scan was 105 beats/min. *Top right panel*: Maximum-intensity projection (MIP) image of the same patient showing significant transitional motion artifact in the proximal and mid RCA. *Bottom left panel*: 3D rendering image of a heart without motion artifact showing the distal RCA. The heart rate was 75 beats/min, and the patient was scanned with a dual-source CT. *Bottom right panel*: MIP image of the same patient showing only slight transitional motion artifact in the mid RCA.

crucial element for obtaining high-quality coronary images is to maximally dilate coronary vessels with nitroglycerin through the use of sublingual tablets or spray (Fig. 17–7). Respiratory motion is excluded by performing the scan during a breath-hold.

Coronary CTA requires the intravenous administration of an iodinated contrast medium. Approximately 50 to 100 mL of contrast medium is necessary for adequate coronary artery enhancement. The accurate timing of image acquisition relative to the contrast injection is a major determinant of overall image quality. A test bolus or bolus tracking technique is used to optimize this timing by determining the amount of time necessary to peak enhancement in the aorta.

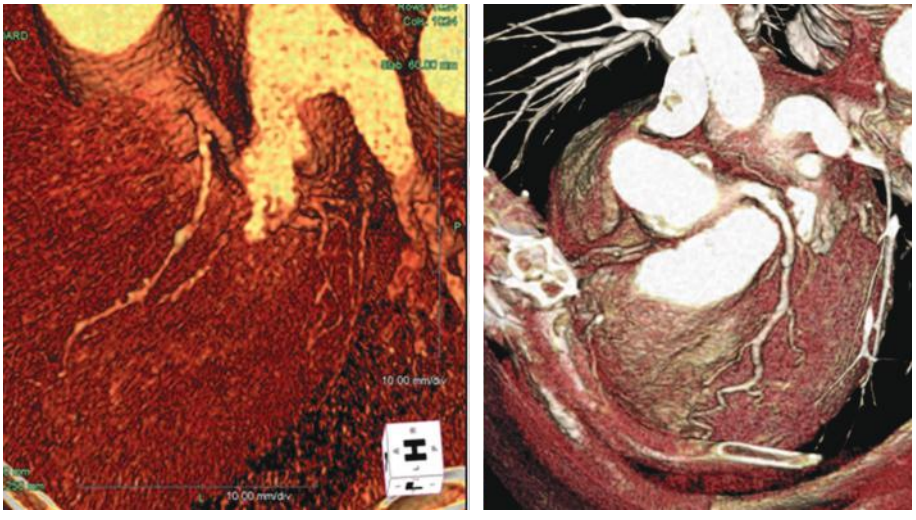
Advancements in MDCT technology have led to shorter scan times, reduced breath-hold duration, smaller intravenous contrast injections, and decreased motion-related artifacts, resulting in lower radiation exposure and improved diagnostic accuracy.

Image Interpretation The coronary vasculature on CCTA is evaluated through axial images, multiplanar (coronal, sagittal, or oblique) reformations, and 3D data sets constructed from specific phases during the cardiac cycle (Fig. 17–8). Maximum-intensity projection images allow the evaluation of longer segments of the coronary vessels but can be limited by overlapping structures adjacent to the artery of interest. Curved multiplanar reformations are reconstructed on a plane to fit a curve and allow display of the entire vessel in a single image. 3D volume-rendered images are useful for selecting images with the least motion artifact and for assessing the relationships among different anatomic structures (Fig. 17–9).

The spatial resolution of the image depends on the size of the 3D pixels or volume elements (voxels) that constitute the image. Slice thickness affects the spatial resolution of CCTA. Temporal resolution is determined by the speed of rotation of the gantry around the patient. A temporal resolution of 50 milliseconds or less is desirable for coronary artery imaging. The 64-slice MDCT scans have a spatial resolution of 0.4 mm and temporal resolution of 83 to 165 milliseconds, which limits the sensitivity and diagnostic accuracy for detecting stenosis in vessels less than 1.5 mm in diameter.[56,57] In comparison, invasive angiography has both a superior spatial resolution of 0.2 mm and a temporal resolution of 5 to 20 milliseconds, whereas magnetic resonance angiography has decreased spatial resolution (0.7 mm) compared with MDCT but a better temporal resolution of 20 milliseconds.[56]

Diagnostic Accuracy of Cardiac Computed Tomography Angiography Although there is still room for improvement in terms of image quality and elimination of artifacts, the diagnostic performance of the CCTA is now well established. A meta-analysis including nine studies totaling 566 patients using scanners with 64 or fewer detectors revealed a per-patient pooled sensitivity of 95% (95% confidence interval [CI] 90%–98%) and specificity of 90% (95% CI 87%-93%) in detecting acute coronary syndrome (ACS) in comparison with ICA.[58] Another meta-analysis including 16 studies and 1119 patients found sensitivity and specificity of 96% (95% CI 93%-98%) and 92% (95% CI 89%-94%), respectively.[59] Both studies demonstrate higher diagnostic accuracy for ACS with CCTA than with other previously studied modalities, including exercise treadmill, stress magnetic resonance imaging (MRI), stress nuclear imaging, and stress echocardiography.

Multiple trials have assessed the diagnostic accuracy of 64-slice CCTA compared with ICA.[60-64] Subsequent meta-analyses have found that in patient-based analysis for the detection of obstructive CAD (> 50% stenosis), 64-slice MDCT had a pooled sensitivity of 94% to 100%, a specificity of 89% to 100%, a positive predictive value of 93% to 97%, and a negative predictive value of 93% to 100%.[65-68] These



A **B**

FIGURE 17–7. Effect of optimal coronary vasodilation with nitroglycerin. **A**. Three-dimensional (3D) rendering image showing only the portion of the left anterior descending (coronary artery; LAD) with evidence of calcified plaques in mid LAD. The study was performed without nitroglycerin. **B**. 3D rendering image of the same patient who was given an oral sublingual nitroglycerin prior to the scan. In contrast to the image on the left, there is a significant improvement of the LAD with clear showing of all the side branches and the mid to distal portion of the vessel.

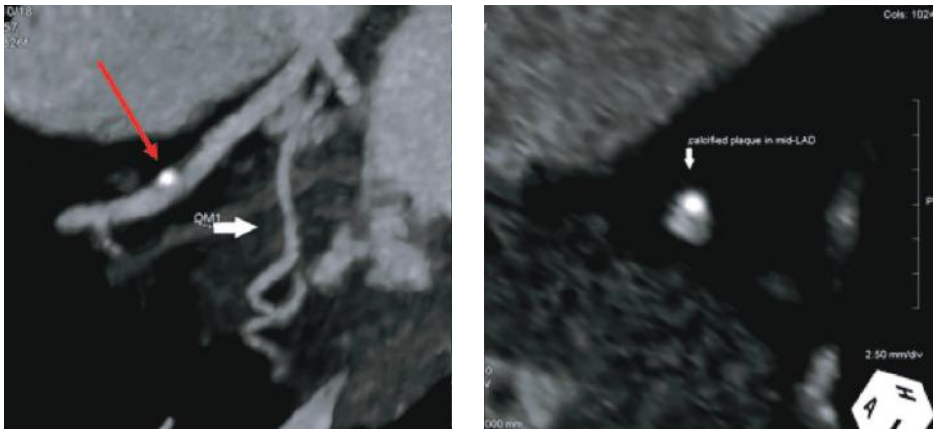


FIGURE 17–8. Evaluation of coronary atherosclerosis. **A**. Longitudinal maximum-intensity projection view of the mid left anterior descending (coronary artery) showing a calcified plaque. **B**. Axial multiplanar reconstruction view of the same nonobstructive plaque.

observational results suggest that CCTA has good diagnostic accuracy for the detection of obstructive CAD. This was corroborated by two ensuing multicenter prospective clinical trials: Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY)[69] and Coronary Artery Evaluation Using 64-Row Multidetector CT Angiography (CORE-64).[70] The ACCURACY trial enrolled 230 patients with chest pain, who underwent both CCTA and ICA. In a patient-based model, the ability of CCTA to detect obstructive CAD (>70% stenosis) had a sensitivity of 94%, specificity of 83%, positive predictive value of 48%, and negative predictive value of 99%.[69] The high negative predictive value of CCTA makes 64-slice MDCT a valuable tool in the exclusion of obstructive CAD. Therefore, CCTA is useful in the risk stratification of symptomatic patients and can reduce the need for invasive diagnostic coronary angiography in patients without obstructive CAD. A recent scientific statement from the American Heart Association (AHA) on CCTA concluded that "CT coronary angiography is reasonable for the assessment of obstructive disease in symptomatic patients (class IIa, Level of Evidence: B)."[71]

In particular, CCTA is an accurate tool in the assessment of chest pain in patients with intermediate risk of CAD or in patients with uninterpretable or equivocal stress tests.[72] Other important clinical roles of MDCT include the assessment of congenital heart disease, suspected coronary anomalies, and significant CAD as a cause of new-onset heart failure.

Cardiac Computed Tomography Angiography, Plaque Composition, and Noninvasive Identification of High-Risk Plaques In contrast to ICA, CCTA can assess the composition of the vessel wall, in addition to characterizing the degree of narrowing of the coronary artery lumen. MDCT can detect coronary plaque extent, distribution, location, and composition. Necropsy and coronary IVUS studies have shown that ICA consistently underestimates the amount of atherosclerotic plaque.[73,74]

Most ACS are caused by atherosclerotic plaque rupture, causing sudden luminal thrombosis. Pathological and anatomical features of high-risk or vulnerable plaques have been reviewed extensively in the literature[75] and in Chap. 32.

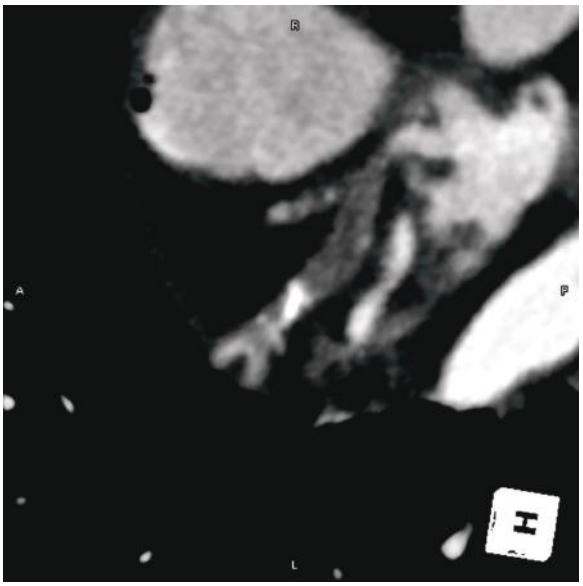
These features include presence of large necrotic core, thin fibrous cap, positive remodeling (PR), spotty calcifications (SC), and perivascular inflammation.[76] Some of these features are identifiable in vivo utilizing various invasive and noninvasive imaging modalities such as IVUS, optical coherence tomography (OCT) and positron emission tomography (PET).[77-85] In the past decade, noninvasive identification of such features using CCTA has been a major focus of research.

A study by Leber and colleagues[86] assessed the capability of 64-slice CT to detect and quantify coronary plaques compared with IVUS. For the detection of coronary plaque, 64-slice MDCT had a sensitivity of 84% and specificity of 91%. In addition, 64-slice MDCT showed good correlation with IVUS in determining the mean plaque area (r = 0.73) and mean lumen area (r = 0.81).

In 2007, Motayama and Narula[77] compared the CCTA plaque features of 38 patients with ACS to 33 patients with stable angina. Presence of PR, low attenuation plaque (LAP) (< 30 HU), and SC were associated with plaque rupture and ACS. In a prospective study by the same authors,[87] 1059 patients were followed for 27 months after the initial CCTA. The copresence of LAP and PR was associated with a 22.5% chance of ACS, whereas absence of these features was associated with 0.5% event rates. There were no significant differences in the degree of stenosis between the plaques that led to ACS and those that did not. The long-term follow-up (10 years) of this study[88] showed that ACS occurred in 23.0% of patients with two high-risk features, 10.7% of patients with one high-risk feature, 1.6% of patients with no such features, and 0.6% of patients without any plaque (log-rank $P < .0001$). The other CT finding suggestive of plaque vulnerability, the so-called "napkin ring" sign, was reported for the first time in 2010.[78] It was defined as a coronary plaque with a napkin ring–like attenuation pattern and SC (Fig. 17–10). The circumferential outer rim (red dashed line) of noncalcified plaque has a higher CT attenuation in both the noncontrast **(A)** and contrast-enhanced **(B)** images as compared to the attenuation within the central part of the plaque. These features of the "napkin ring" sign most likely identify a very similar histological pattern as the thin cap fibroatheroma. The "napkin ring" sign has also been shown to be predictive of events in a study of 895 patients[80] who had a CCTA and were followed for up to 5 years thereafter. Patients with plaques with no high-risk features had no events, whereas there was a 40% event rate for patients with lesions with the following three high-risk features: "napkin ring" sign, PR, and LAP.

Diagnostic Accuracy of Cardiac Computed Tomography Angiography for the Evaluation of Acute Coronary Syndrome The diagnostic accuracy of CCTA for the clinical diagnosis of ACS has been investigated in several studies that included more than 3000 patients presenting with acute chest pain to the emergency department.[89-92] In a prospective study by Rubinshtein and colleagues,[89] 58 patients (mean age, 56 years; 36% women) with chest pain and initially negative biomarkers in the absence of new ECG changes underwent 64-slice MDCT. Twenty-three patients were found to have obstructive CAD (> 50% luminal narrowing) on CCTA. Of these 23 patients, 20 were subsequently diagnosed with ACS. Thus, 64-slice MDCT was found to have a sensitivity of 100%, specificity of 92%, positive predictive value of 87%, and negative predictive value of 100% for diagnosing ACS in emergency department patients presenting with chest pain. Normal and nonobstructive CCTA results were predictive of a low rate of major adverse cardiovascular events (2.8%) and a favorable outcome during a 15-month follow-up period.[89]

The Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT)[90] study was a larger prospective trial evaluating the role of CCTA in patients presenting to the hospital with



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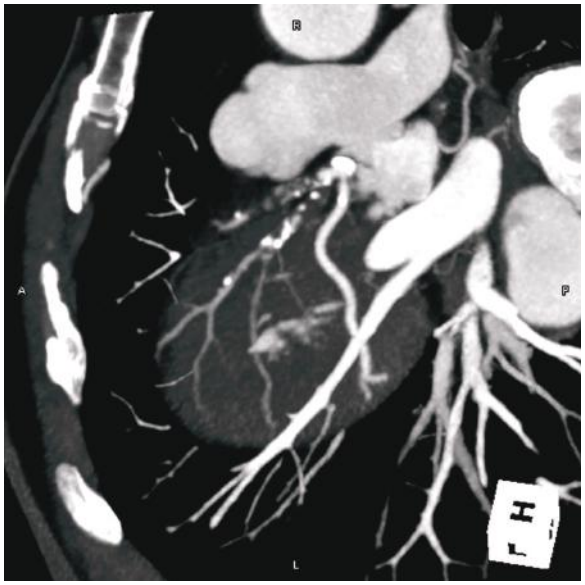

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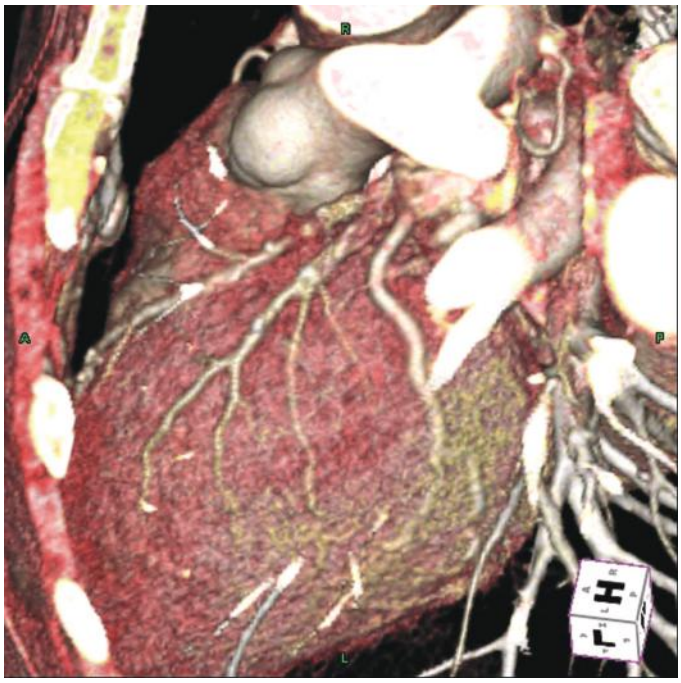


C

FIGURE 17–9. **A.** Three-dimensional volume rendering image of severe proximal left anterior descending (coronary artery; LAD) disease. **B.** Maximum-intensity projection (15-mm thickness) of the same heart showing diffuse proximal LAD and diagonal branch stenoses. **C.** Multiplanar reconstruction of the same heart focusing on the proximal LAD stenosis demonstrating total occlusion of the vessel segment with in situ thrombus (~ 20 HU).

possible ACS. Overall, 368 patients (mean age, 53 years; 61% men), were studied from a lower risk population. For CCTA, sensitivity and negative predictive value for ACS were both 100% and 100%, respectively.[93] In addition, this study demonstrated that CCTA independently predicts risk for ACS and has additive value for assessing risk in patients presenting with chest pain, when used in combination with traditional risk factors and clinical estimates of the probability of ACS.[93]

All trials demonstrated that absence of any coronary atherosclerosis by CCTA, which was observed in about half of the population, has an excellent negative predictive value (NPV) for presence of ACS. However, presence of significant stenosis by CCTA was only moderately diagnostic for ACS. In combination with the low prevalence of ACS in the acute chest pain population in the emergency department (2%-8%),[11] CCTA reveals a low positive predictive value (PPV) for ACS (~ 35%-50%).

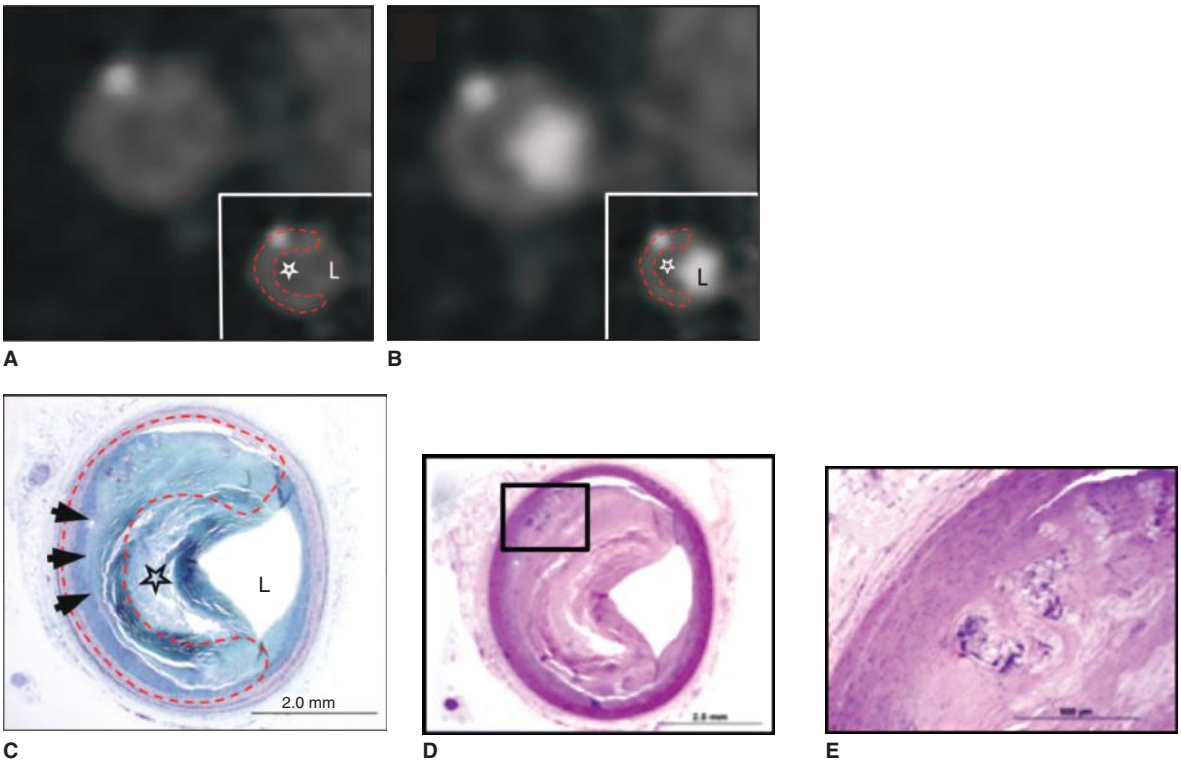


FIGURE 17–10. The cross-sectional computed tomography (CT) images show a coronary plaque with napkin ring–like attenuation pattern and spotty calcification. The circumferential outer rim (*red dashed line*) of the noncalcified plaque has a higher CT attenuation in both the noncontrast (**A**) and contrast-enhanced (**B**) images (44.0 ± 8.8 HU, range 23.0-61.0 HU vs 48.6 ± 5.8 HU, range 34.0-60.5 HU; respectively) as compared to the attenuation within the central part of the plaque (27.9 ± 4.2 HU, range 20.7-36.4 HU and 31.0 ± 6.6 HU, range 19.0-44.0 HU on noncontrast and contrast-enhanced images; respectively). The corresponding histological section (panels **C**, **D**, and **E**) revealed a late fibroatheroma, with spotty calcification (**E**). The lesion is characterized by a necrotic core (*star*), which is consistent with the low attenuation core of the plaque and a significant amount of fibrous plaque tissue, which is consistent with the high attenuation rim on the CT images (*red dashed line*). HU, Hounsfield units; L, lumen. Reproduced with permission from Maurovich-Horvat P, Hoffmann U, Vorpahl M, et al: The napkin-ring sign: CT signature of high-risk coronary plaques? *JACC Cardiovasc Imaging*. 2010 Apr;3(4):440-444.[76]

In order to improve the PPV, different strategies have been pursued[94]:

1. Assessment of plaque morphology. As mentioned earlier, CCTA has the potential to visualize select high-risk plaque features. Even though the assessment of such features is not part of current routine clinical practice, a plaque morphology-based score developed by Motayama and Narula resulted in a PPV of 100% for ACS and could potentially enhance the diagnostic accuracy of CCTA in the setting of acute chest pain.[2]
2. Assessment of LV function. It has been demonstrated that the identification of regional wall motion abnormalities incrementally improves the diagnostic accuracy of CCTA for ACS.[95] However, this comes at the expense of higher radiation exposure.
3. Physiologic assessment of coronary artery disease by CT perfusion (CT) or CT FFR see below. Functional testing, including rest and stress myocardial perfusion, is possible using CT, but stress testing is not recommended in the acute setting considering the potential adverse effects of stressing a patient with ACS. Similar to the nuclear literature, an incremental value of assessing rest myocardial perfusion by CT has been observed, particularly in improving PPV.[96,97]

In summary, the absence of coronary atherosclerosis on CCTA, as observed in 50% of the acute chest pain population, has a NPV of close to 100%. On the other hand, presence of significant stenosis, even though superior to clinical risk score such as thrombolysis in myocardial infarction (TIMI),[98] has a moderate diagnostic accuracy for ACS. Additional assessment of plaque morphology, LV function or physiological assessment of CAD with CT perfusion and CT FFR might prove beneficial in improving diagnostic accuracy of CCTA for the assessment of acute chest pain.

Effectiveness of Cardiac Computed Tomography Angiography in the Emergency Department Because CT has an excellent NPV and can be conducted in a timely manner, it has been hypothesized that CT may allow for rapid assessment of acute chest pain in the emergency department and lead to safe rapid discharge. Based on this hypothesis, three large clinical trials have been conducted.

Litt and colleagues[99] performed the largest trial of these series. A total of 1370 patients with acute chest pain in the emergency department were enrolled and randomized into CCTA versus standard of care in 2:1 fashion in the American College of Radiology Imaging Network–Pennsylvania Department of Health (ACRIN-PA) study. The results met the prespecified safety threshold of below 1% for missed ACS or death during the 30 days follow-up in the CCTA group. Importantly, this study was positive regarding its primary end point establishing CTA as a safe alternative to traditional ischemia testing, such as myocardial perfusion imaging and exercise echocardiography, in a cost-effective and time-efficient fashion.

Both Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT)[100] and the ROMICAT II[101] trials demonstrated that the CCTA-based strategy resulted in a shorter length of stay without lower safety (2.9 vs 6.2 hours for time to diagnosis [CT-STAT] and 23 vs 31 hours for time to hospital discharge [ROMICAT II] for CCTA vs control strategy). These findings were supported by other studies, indicating that the rate of direct discharge from the emergency department increased to about 50% by using a CCTA strategy while a typical rate of 15% to 25% is observed for standard of care.[99-101]

Prognostic Value of Cardiac Computed Tomography Angiography CCTA yields independent prognostic information in addition to clinical risk factors

in patients with suspected or known CAD.[102] In 100 patients referred for cardiac evaluation, the cardiac event rate in the year following CCTA was 0% in patients without evidence of CAD, 8% in patients with nonobstructive CAD, and 63% when obstructive lesions were present.[102] In patients with chest pain, CCTA can identify obstructive lesions, such as proximal LAD stenosis, as well as the number of vessels with moderate to severe stenosis, which predict an increased risk for all-cause mortality.[103]

In a meta-analysis of 11 studies, including a total of 7335 mostly symptomatic patients with suspected CAD followed for a median of 20 months, the presence of any greater than 50% stenosis at CCTA was associated with a 10-fold higher risk of cardiovascular events. In addition, the finding of any CAD inferred a 4.5-fold risk, and each coronary segment involved increased the risk of adverse outcomes by 23%.[104] In the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry, 27,125 patients underwent CCTA and were followed for a mean follow-up time of 22.5 months. Multivariable analysis demonstrated CCTA measures of CAD severity and LVEF have independent prognostic value. Incorporation of CAD severity had incremental value for predicting all-cause death over routine clinical predictors and LVEF in patients with suspected obstructive CAD.[105]

In a more recent analysis of 17,793 patients from the CONFIRM registry, the majority of whom had chronic chest pain, the number of proximal segments with mixed or calcified plaques and the number of proximal segments with 50% or more stenosis were the CCTA parameters with the strongest predictive value for all-cause mortality at a median follow-up of 2.3 years.[106] Evidence of the more long-term prognostic value of CCTA is beginning to accumulate. Hadamitzky and colleagues[107] followed up 1584 patients for a median of 5.6 years and described annual rates of major adverse cardiac events (MACE) of 0.2% for patients with no CAD and 1.1% in patients with obstructive CAD. In another recent study reporting on a median 6.9-year follow-up period in 218 patients, annual MACE rates were 0.3%, 2.7%, and 6.0% in patients with normal CCTA, nonobstructive CAD, and obstructive CAD, respectively.[108]

While CCTA is shown to be an extremely powerful prognostic tool, it shown only to improve prognostication for asymptomatic populations with intermediate CACS and is not incremental to CACS for asymptomatic patients with lower or higher CACS levels.[109]

CCTA has also shed light on the important prognostic value of nonobstructive coronary artery disease. Lin and colleagues[110] evaluated 2583 primarily symptomatic (85%) adults (mean age 52.7 years; 58% women) without known CAD or obstructive disease (50% stenosis) on 64-slice coronary CTA. Over a mean follow-up period of 3.1 years, it was demonstrated that the extent of nonobstructive CAD has a strong association with risk for all-cause mortality. The presence of any plaque increased the risk factor–adjusted mortality risk (hazard ratio [HR], 1.98), and risk was increased with multivessel nonobstructive disease (HR of 4.75 for three-vessel nonobstructive disease and HR of 5.12 when five or more segments were involved). Of importance, the increased risk from nonobstructive CAD was also seen in patients with low Framingham Risk Scores (FRS), a patient subset that does not typically qualify for aggressive primary cardiovascular preventive therapies. Similarly, the presence of any plaque demonstrated an improvement in the net reclassification index when compared with risk estimates using the FRS alone. Ahmadi and colleagues[111] similarly demonstrated in 1102 consecutive symptomatic patients with nonobstructive (< 50%) CAD on coronary CTA, nonobstructive disease independently predicted all-cause mortality. Moreover, mortality incrementally increased according to the type of nonobstructive disease present (mortality given in parentheses): purely calcified plaque (1.4%), partially calcified plaque (3.3%), or noncalcified plaque (9.6%) ($P < .001$). On the same note, one of the analyses of the CONFIRM registry demonstrated that patients with two or more noncalcified or partially calcified plaques have a prognosis similar to that of patients with one or two obstructive plaques. However, patient with up to seven calcified nonobstructive plaques had an excellent prognosis with a less than 3% event rate in 2.3 years.[112]

In summation, the data available to date suggest that (1) the warranty period of a negative coronary CT angiogram appears to extend to at least 5 years, (2) the presence of any CAD and the burden of atherosclerotic changes at CCTA is strongly predictive for MACE and all-cause mortality in those with stable chest pain, and (3) plaque morphology by CT confers incremental prognostic information beyond that provided by percent stenosis alone.

Use of Cardiac Computed Tomography Angiography versus Other Modalities in Evaluation of Patients with Stable Coronary Artery Disease Three recent randomized prospective studies have evaluated the role of CCTA compared to other commonly used noninvasive modalities for the evaluation of patients with stable CAD.[113-115]

In a multicenter European study,[113] 475 patients with stable chest pain and low prevalence of CAD underwent CCTA and stress myocardial perfusion imaging by single-photon emission computed tomography (SPECT) or positron emission tomography, as well as ventricular wall motion imaging by stress echocardiography or CMR for detection of obstructive (> 50%) CAD. CCTA had the highest diagnostic accuracy; the area under the receiver operating characteristics curve was 0.91 (95% CI, 0.88-0.94), with sensitivity of 91%, and specificity 92%.

In the Scottish Computed Tomography of the Heart Trial (SCOT-HEART)[114,116] a total of 4146 patients assessed for new-onset chest pain were randomized to CTA in addition to standard care or to standard care alone. The standard care included documentation of the clinical history of angina pectoris and objective demonstration of exercise-induced myocardial ischemia through exercise stress testing. At 6 weeks, use of CTA reclassified the diagnosis of coronary heart disease in 27% of patients and the diagnosis of angina in 23% of patients. Use of CTA increased the certainty of attributing the patient's symptoms to angina caused by CAD compared with usual care alone (relative risk [RR] 1.79, 95% CI 1.62-1.96). The certainty of diagnosing CAD was also significantly improved (RR 2.56, 95% CI 2.33-2.79). Adding CTA to usual care changed planned investigations and treatment options and was associated with a trend toward a reduction in fatal and nonfatal MI.

The PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial[115] randomized a total of 10,003 patients and no prior diagnosis of CAD to a strategy of initial anatomical testing with CCTA or to functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography). The study showed no difference in the primary end point, a composite rate of death, MI, major procedural complications or hospitalization for chest pain. However, select secondary end points, including level of radiation exposure and rate of subsequent procedures that did not reveal significant heart disease, favored CCTA.

Assessment of Coronary Bypass Grafts Saphenous vein grafts are relatively easier to image with CCTA (because of their larger diameter and decreased mobility) compared with native coronary arteries. CCTA has high diagnostic accuracy for evaluating arterial and venous bypass graft stenosis. The diagnostic efficacy of 64-slice MDCT in detecting angiographically significant stenosis in bypass grafts has been demonstrated by several studies, yielding sensitivity and specificity ranging from 97%

to 100% and specificity ranging from 89% to 100%.[117-120] However, the assessment of bypass graft stenosis has several important limitations, namely the image artifacts caused by surgical clips and the presence of extensive coronary calcification in the native coronary arteries. These limitations can particularly hinder the evaluation in distal runoff vessels and nongrafted native coronary arteries.[118,120] The percentage of un-interpretable segments can be as high as 31% with 16-slice MDCT[121] but is significantly reduced to approximately 2% or less with 64-slice MDCT.[120] Furthermore, the percentage of segments of native coronary vessels that cannot be evaluated may be less relevant in the clinical decision-making process because the most extensively calcified vessels are often bypassed.

Therefore, CCTA may be clinically useful for the evaluation of coronary bypass grafts and coronary anatomy in symptomatic patients.[119,120] In the case of reoperation or revascularization, coronary CTA may provide critically important information on the status and anatomic location of the bypass grafts. The AHA Scientific Statement on CCTA states, "It might be reasonable in most cases to not only assess the patency of bypass graft but also the presence of coronary stenoses in the course of the bypass graft or at the anastomotic site as well as in the native coronary artery system (class IIb, Level of Evidence: C)."[71] In summary, CCTA using 64-slice MDCT may be appropriate in properly selected patients by providing diagnostic information on the overall patency of the bypass grafts and the presence of significant stenosis without exposure to an invasive diagnostic approach.

Assessment of In-Stent Restenosis The partial volume effect, or imaging artifacts, caused by the metallic stents limits the overall visibility of the inner lumen of a deployed stent and can potentially reduce the diagnostic accuracy of CCTA for the noninvasive evaluation of in-stent restenosis. Stent location, heart rate, and stent diameter are also important determinants of accuracy and feasibility (Fig. 17–11). The feasibility of stent visualization is approximately 95%, with the remaining 5% being unevaluable or uninterpretable because of the aforementioned factors.[122] A systematic review of CCTA with 16-slice or more MDCT revealed moderate sensitivity (85%) and high specificity (97%) for the detection of coronary in-stent restenosis when compared with ICA.[123] Similarly, a study exclusively comparing 64-slice MDCT with ICA found a sensitivity of 87% and specificity of 98% for the identification of significant in-stent restenosis by CCTA.[122] In addition, CCTA has the ability to identify stent gaps, which may represent stent fracture or overlap failure and are often associated with in-stent restenosis.[124] A new method of substraction CCTA with a long breathhold (25 seconds) using a 320-row scan was recently shown to improve the diagnostic accuracy of CCTA in detecting in-stent restenosis from 62.7% to 89.5% as compared to ICA[125] (Fig. 17–12).

Evaluation of Coronary Anomalies Anomalies of the coronary arteries are reported in 0.3% to 1% of the general population.[126] Approximately 20% of coronary anomalies can be hemodynamically significant and manifest as arrhythmias, syncope, MI, or sudden death.[127,128] An interarterial course between the pulmonary artery and aorta is the coronary anomaly most commonly associated with sudden cardiac death (Fig. 17–13).[129]

The diagnosis of coronary artery anomalies has previously required ICA; however, in up to 50% of patients, the coronary artery anomalies may be incorrectly classified during invasive angiography.[130] This misclassification may result from the difficulty in delineating the precise vessel path within a complex 3D geometry using a relatively restricted two-dimensional (2D) view. Coronary CTA has been shown to accurately depict the anomalous vessel origin, its subsequent course, and the relationship to the great vessels.[128] Two studies comparing CCTA and ICA found that invasive angiography was able to detect 80% of the anomalous origins but only 53% of the anomalous coronary courses[131] and resulted in a precise anatomic diagnosis in only 55% of patients.[132] In a multicenter coronary artery CT registry, CCTA was able to unequivocally demonstrate the origin and the course of the anomalous artery in all patients with equivocal findings on ICA.[133] Demonstrating the precise course of an anomalous coronary artery is crucial for determining proper therapeutic options. Therefore, CCTA may be preferable to invasive angiography for the diagnosis of coronary anomalies given its superior diagnostic accuracy.

Physiologic Assessment of Coronary Artery Lesions by Cardiac Computed Tomography Angiography

Rationale While there is ongoing debate among cardiologists as to whether coronary anatomy or physiology is more important in determining prognosis and impacting treatment decisions, anatomic and

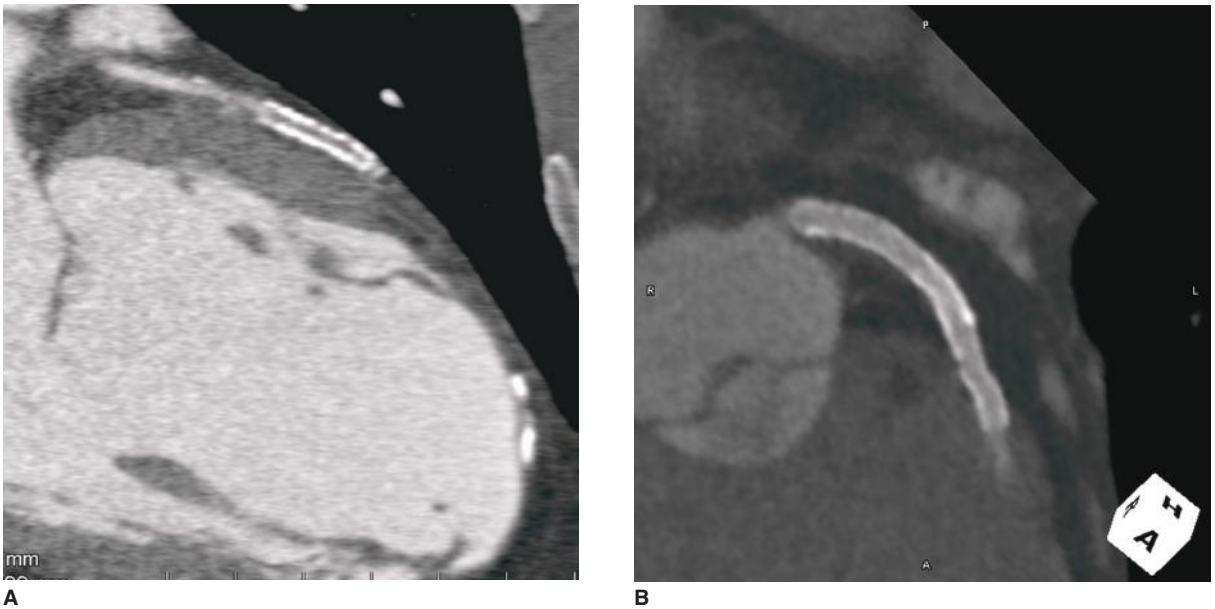


FIGURE 17–11. Evaluation of coronary stents. (**A**) Occluded stent in the proximal left anterior descending (coronary artery). (**B**) Multiplanar reconstruction of widely patent stents without evidence of in-stent restenosis.

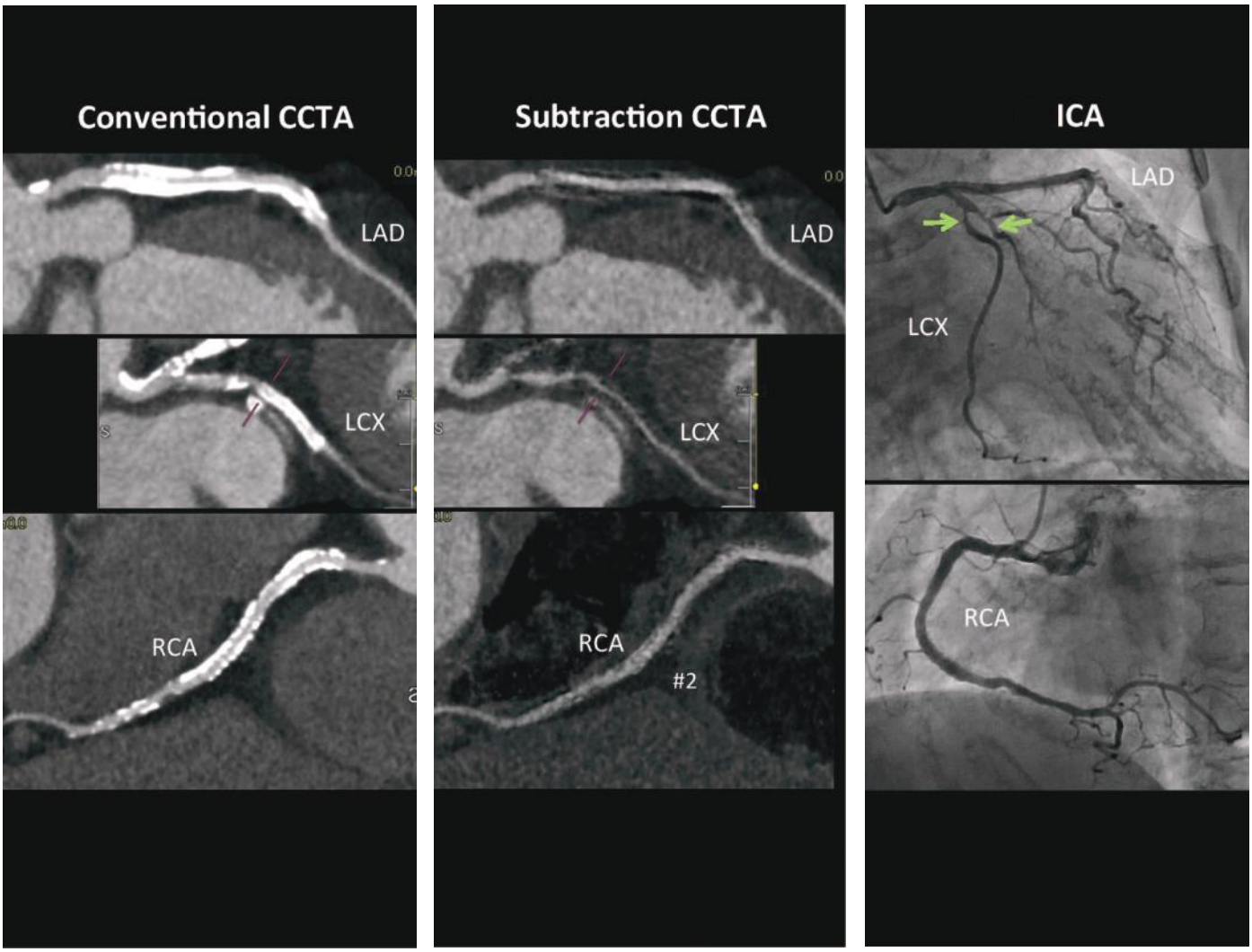


FIGURE 17–12. A 78-year-old woman with multivessel coronary artery disease and multivessel PCI. **A.** Conventional cardiac computed tomography angiography (CCTA) for evaluation of CCTA with no evaluable segment in the left circumflex artery (LCX). **B.** Subtraction CCTA demonstrating evaluable segments in all three arteries. **C.** Invasive coronary angiography (ICA) confirming the findings of subtraction CCTA in all three vessels. LAD, left anterior descending (artery); RCA, right coronary artery.

functional testing for CAD are often complimentary. Even though the degree of stenosis is one of the factors that partially predicts the presence or absence of ischemia, the association between coronary anatomy and ischemia is poor. For instance, there are lesions causing Ischemia WithOut significant Stenosis (IWOS) and there are lesions that cause significant Stenosis WithOut Ischemia (SWOI).[134,135] Therefore, an ideal diagnostic test would possess the technology that not only can give accurate assessment of the burden of atherosclerosis, location and composition of each plaque, but also determine the physiological consequence of each lesion in the form of presence or absence of ischemia. Two such techniques are computed tomography perfusion (CTP) and CT FFR. They have allowed us to evaluate both coronary anatomy and physiology.

Techniques for Computed Tomography Myocardial Perfusion Imaging In order to assess both coronary anatomy and myocardial ischemia using CTP, two separate CT acquisitions are required: one for vasodilator induced stress myocardial perfusion imaging (MPI) and one for rest MPI and coronary CTA.[136] While heart rate is required for the rest acquisition, it is not as stringent for stress perfusion MPI because coronary opacification is not necessary or assessed. Typically, a delay ranging from 10 to 30 minutes is currently employed between acquisitions to allow for CT contrast washout and/or reversal of the effects of the pharmacological vasodilator used. For the stress perfusion, peak hyperemia may be achieved with adenosine, dipyridamole, or regadenoson. Regadenoson has can be used with a single injection that results in several minutes of hyperemia. A clinical example of CTP is demonstrated in Fig. 17–14.

Stress-rest perfusion and rest-stress protocols yield similar clinical results. However, rest–stress protocols could lead to more cost effectiveness testing, because the stress portion could be avoided in the rest-stress protocol if no stenosis were identified in the rest images.

Any modern scanner with 64 or more detectors can be used to perform CT MPI, although there are unique considerations for each specific CT platform. Most important is the *z*-axis coverage. In the 64 MDCT platforms, which require image acquisition over multiple heartbeats, the use of this technique results in nonhomogenous myocardial contrast enhancement resulting from the slight differences in acquisition time of each slab. Even though such heterogeneity does not impact the clinical value of the test, the sufficient *z*-axis coverage in 320 MDCT eliminates this issue by allowing for a single beat acquisition.

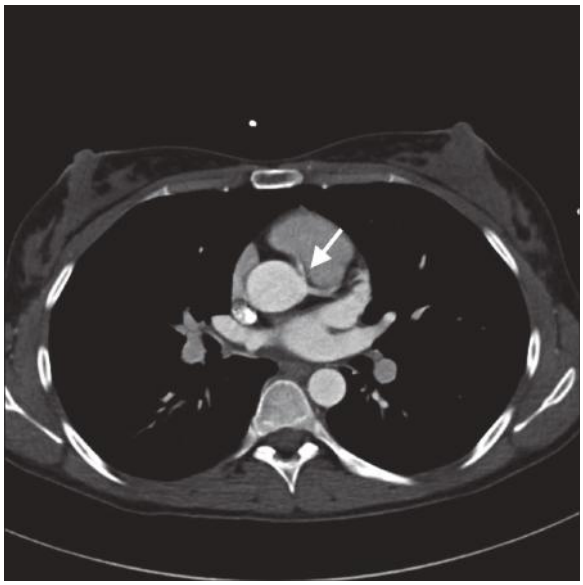


FIGURE 17–13. Anomalous right coronary artery. A 37-year-old woman with atypical chest pain who underwent coronary computed tomography angiography to exclude coronary artery disease. Note the right coronary artery (*arrowhead*) arising to the left of midline from the left sinus of Valsalva taking interarterial course.

Another important consideration is the estimated effective radiation dose delivered to the patient. Estimated effective dose is significantly dependent on scanner technology and acquisition protocol.[137] An axial acquisition with prospected ECG gating, as well as reduction in the tube voltage (kV) in nonobese patients and use of a single data set utilizing either a test bolus or bolus tracking are some of the techniques that could lead to reduction in effective radiation dose.

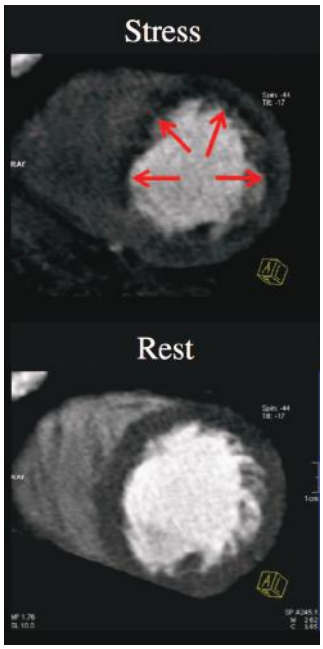


FIGURE 17–14. Example of stress-induced computed tomography perfusion defect involving the anterior, anteroseptal, and lateral walls (*top image*). The rest perfusion images demonstrated a small defect in the anterior wall. Collectively, these findings were consistent with severe ischemia and the patient was found to have severe stenosis of the left anterior descending and left circumflex coronary arteries. Reproduced with permission from Hulten E, Ahmadi A, Blankstein R: CT Assessment of Myocardial Perfusion and Fractional Flow Reserve. *Prog Cardiovasc Dis*. 2015 May-Jun;57(6):623-631.[132]

After raw data acquisition, CTP images should be reconstructed with a smooth filter and beam-hardening correction, when available. For optimal image display of myocardial perfusion, the grayscale window width and level are set at approximately 300/150[138] and multiplanar reformat images are viewed using thick slices (6-8 mm) and average intensity projection of each slab.

Clinical Evidence for Computed Tomography Myocardial Perfusion Imaging Single-center studies on 64 MDCT were first reported in 2009[139,140] and demonstrated a per-vessel sensitivity and specificity of 86% to 93% and 74% to 91% for CTA-CTP in comparison to ICA-SPECT. These results were followed by other single-center, observational studies evaluating CTP, which demonstrated an accuracy of CTP similar to that of both invasive angiography and functional imaging.[141-148]

The multicenter, international study Coronary Artery Evaluation using 320-row multidetector computed tomography angiography and myocardial perfusion (CORE 320) followed the previously mentioned single-center studies. This study evaluated 381 patients who underwent CTP and CTA using the 320 MDCT, as well as SPECT MPI and invasive angiography. CTA ≥ 50% demonstrated a sensitivity of 94% and specificity of 64% for detecting obstructive lesions causing defects on myocardial perfusion imaging. There was a modest improvement in specificity with the addition of CTP to CTA.[149] The presence of stenosis by CTA had an area under the curve of 0.82 (0.78–0.85), which improved to 0.87 (0.84–0.89) with the addition of CTP. A subsequent multicenter trial has been conducted using regadenoson for CTP in comparison with SPECT incorporating a variety of different vendors' CTA.[150,151] This study demonstrated that addition of CTP increased the accuracy of CTA for detecting a reversible perfusion defect on SPECT could be improved from 0.69 to 0.85.

Fractional Flow Reserve Computed Tomography: the Fundamentals Recent advances in the field of computational fluid dynamics (CFD) and advanced imaging-based modeling have allowed for noninvasive calculation of FFR based on static CT images. As applied to typically acquired coronary CT angiograms, these technologies enable noninvasive calculation of FFR without modification of image acquisition protocols, additional imaging or radiation, or need for vasodilators. The details of methods used in calculation of FFR CT have been described elsewhere.[152,153]

In general, by using the "Navier-Stokes Equations" of CFD and based on the relationship of mass conservation and momentum balance, coronary artery flow and pressure can be obtained.[136,153-155] Because blood is an incompressible fluid, it can be treated as a newtonian fluid with a relatively constant viscosity in larger vascular beds such as coronary arteries. Clinical evaluation of a true vascular territory such as coronary arteries requires a numerical method to estimate the principle equations and generate a solution, which must be solved simultaneously over many time intervals in a single cardiac cycle, using CFD methods.[153] Definition of flow boundaries is necessary for construction of the 3D model of coronary arteries and aorta and solving flow equations. These boundaries include the vessel lumen, the root of aorta as the inlet, and the thoracic aorta and the coronary arteries as the outlets.[156] Myocardial wall volume and mass extracted from the coronary CTA data are used to calculate the overall coronary flow under the resting conditions. Total coronary resistance can be calculated using the coronary flow. Using a simulation model of the effect of adenosine on reducing the peripheral resistance of the coronary microcirculation down-stream to the epicardial coronary arteries, maximum hyperemia state is estimated in the FFR CT model.[157] FFR CT can then be obtained by solving the equations of blood flow for velocity and pressure.[153] Figure 17–15 demonstrates a clinical example of FFR CT with invasive FFR correlation.

Clinical Evidence for Fractional Flow Reserve Computed Tomography to Date FFR CT technology has been shown to be more accurate than CTA in

predicting lesion-specific ischemia, as determined by invasive FFR. To date, three separate multicenter prospective studies have examined the performance of FFR CT using invasive FFR as the gold standard.

The prospective, multicenter international Diagnosis of ISChemia-Causing Stenoses Obtained Via Non-invasivE FRactional FLOW Reserve (DISCOVER-FLOW) trial[158] was the first study to evaluate the accuracy of FFR CT in a prospective fashion. In this study, it was demonstrated that in 103 patients who underwent CTA and invasive FFR measurement, FFR CT was superior to CTA as a predictor of lesion-specific ischemia with higher accuracy, specificity, PPV, and NPV in both per-patient and per-vessel analyses.[158] Specifically, there was a significant improvement in accuracy of CCTA by FFR CT among the 50% to 69% stenosis group. Moreover, it was shown that in the scans with motion artifact, calcium artifact or low signal-to-noise ratio, FFR CT performed significantly better than CTA.

The Determination of Fractional Flow Reserve from Anatomic Computed Tomographic Angiography (DEFACTO) trial[159] was a multicenter study of 252 patients and 407 vessels were investigated by both FFR CT and invasive FFR. The primary end point was to assess the diagnostic accuracy of FFR CT compared to that of invasive FFR. The primary end point of the study was set as having the lower bound of the confidence interval for diagnostic accuracy to be more than 70%, because this represents a 15% increase in diagnostic accuracy over stress echocardiography or MPI when compared to invasive FFR. The per-patient diagnostic accuracy for FFR CT plus CT was 73% (95% CI, 67%-78%), which did not meet the prespecified primary end point. Although the performance of FFR CT did not meet the criteria for the prespecified primary end point, DEFACTO confirmed the superiority of FFR CT over CT alone for the determination of lesion-specific ischemia. The diagnostic accuracy of CTA alone was 64% (95% CI, 58%-70%), and FFR CT showed 9% absolute improvement in the diagnostic accuracy. Importantly, there was a significant improvement in the evaluation of intermediate severity lesions causing 30% to 70% luminal narrowing. DEFACTO also represents the first large-scale demonstration of patient-specific computational models to assess for lesion-specific ischemia from CT images.

The Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) trial is the third multicenter prospective study that has evaluated the diagnostic performance of FFR CT using invasive FFR as a gold standard.[160] This study evaluated the diagnostic accuracy of an updated iteration of FFR CT and for the first time compared the FFR CT accuracy to ICA in predicting invasive FFR. Two hundred fifty-four patients had a clinically indicated CCTA before ICA. Diagnostic accuracy of FFR CT, CTA, and ICA were compared to invasive FFR. This study compared FFR CT with CCTA and ICA against the reference standard of invasive FFR in patients with CCTA stenosis of 30% to 90%. The area under the receiver-operating characteristic curve of FFR CT was 0.90 (95% CI, 0.87-0.94) versus 0.81 (95% CI, 0.76-0.87) for coronary CTA (P = .0008). The per-patient and per-vessel sensitivity, specificity, PPV, and NPV of FFR CT were superior to CTA for detecting lesion-specific ischemia. FFR CT was also superior in diagnostic accuracy for lesion-specific ischemia compared to diameter stenosis by ICA.

Following the validation of the diagnostic accuracy of FFR CT, it was then necessary to assess the potential impact FFR CT may have on clinical practice and patient outcomes. The Prospective LongitudinAl Trial of FFR CT: Outcome and Resource IMpacts study (PLATFORM) trial was published in the *European Heart Journal* in 2015. PLATFORM is a multicenter, prospective consecutive cohort study conducted in 11 European sites with a total of 584 patients. The aim of the PLATFORM trial was to compare the accuracy and clinical outcomes of a CCTA/FFR CT–guided approach to assessing stable

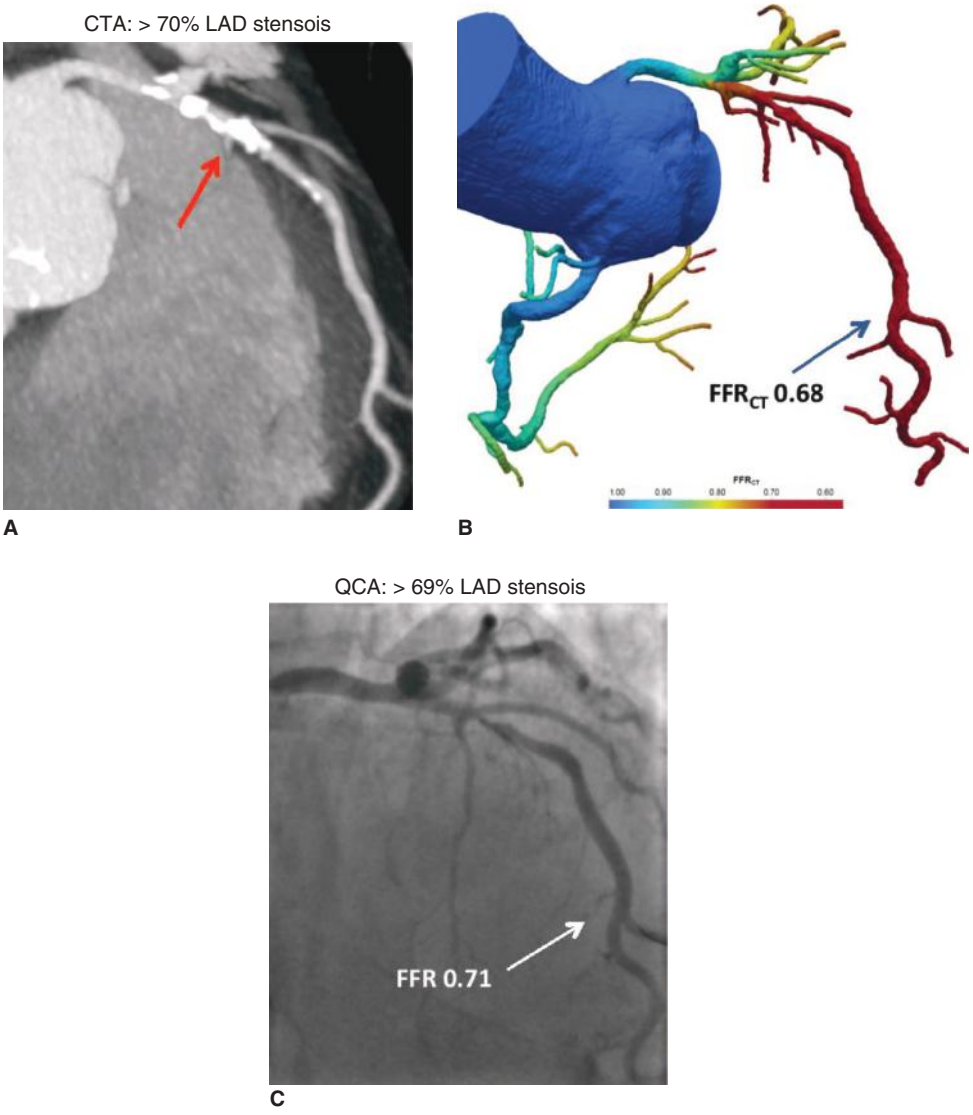


FIGURE 17–15. Evaluation of a lesion by fractional flow reserve (FFR) computed tomography (CT). **A.** Cardiac computed tomography angiography (CTA) finding of heavily calcified left anterior descending (artery; LAD) lesion of > 70% stenosis. **B.** FFR CT of the same lesion demonstrating its clinical significance. **C.** Invasive angiography and FFR of the same lesion, showing its clinical significance by quantitative coronary angiography (QCA).

patients at intermediate risk (20%-80%) of obstructive CAD. Importantly, there were two separate arms of the trial. One arm aimed to evaluate the potential role of CTA/FFR CT as a gatekeeper to the coronary angiography by comparing the rate of nonobstructive disease at the time of ICA in those who simply underwent ICA when referred as compared to those who only underwent ICA following a an abnormal CT/FFR CT assessment. The second, noninvasive arm, compared a noninvasive strategy of CTA/FFR CT to a traditional noninvasive assessment, with any chosen ischemia test. The primary end point was the rate of nonobstructive CAD (< 50%) at ICA in the cohort planned for ICA, where CCTA/FFR CT was used as a gatekeeper compared to the arm of direct ICA. The secondary accuracy end point was the rate of nonobstructive CAD at ICA in the noninvasive cohort with standard noninvasive testing as gatekeeper to ICA compared to CCTA/FFR CT as gatekeeper. The clinical outcomes' end point was the rate of MACE and vascular complications as well as resource utilization, change in quality of life, and cumulative radiation exposure. MACE was defined as all-cause mortality, nonfatal MI, and unplanned urgent revascularization.[161]

With respect to the primary end point, the rate of nonobstructive CAD in the standard of care invasive cohort was 73.3% compared to only 12.4% in the CCTA/FFR CT arm ($P < .0001$). An impressive 61% of CCTA/FFR CT patients had ICA canceled with no resultant adverse events; however, the reported follow-up period was short at 90 days.[161]

The comparison of radiation exposure between the groups in PLATFORM was suboptimal. The CCTA radiation exposure was calculated for each individual case or inferred using the median measured value. For all other modalities, predetermined standard values were used; 7 mSv for ICA, 15 mSv for PCI, and 14 mSv for MPI.[161] The use of standardized values instead of measured values reduces the robustness of the radiation dose comparison, which showed a significantly lower dose in the usual care arm (5.8 mSv) versus the FFR CT arm (8.8 mSv) in the noninvasive cohort. No difference was shown in the invasive cohort with respect to radiation dose.

A cost-effectiveness analysis of the PLATFORM trial demonstrated that among patients in the invasive strategy arm the use of CCTA/FFR CT as a gatekeeper to ICA was considerably less expensive than the usual care arm ($7,343 vs $10,734; $P < .0001$). By trial design, 100% of patients in the ICA usual care arm proceeded to coronary angiography compared with 61% in the FFR CT arm. Importantly, despite the lower rate of ICA, the rate of coronary revascularization was comparable between the two strategies (28% vs 32%). This important cost analysis seems to suggest that FFR CT is not only more accurate than traditional stress testing for lesion-specific ischemia by FFR but that it is also a cost effective method to determine which patients will benefit from ICA and revascularization.

In the noninvasive arm of the trial despite the higher rates of ICA (18% vs 12%) and revascularization (10% vs 5%) in the FFR CT cohort, the 90-day cost of care was not significantly different than that in the usual care group ($2,679 vs $2,137; $P = .26$). Interestingly, there was a greater improvement in quality of life scores in the FFR CT group (19.5 vs 11.4; $P = .04$), which one could hypothesize may reflect more appropriate physiologically guided revascularization.[162]

Association of Plaque Morphology on Computed Tomography Angiography and Invasive Fractional Flow Reserve: An Emerging Concept in Coronary Atherosclerosis As mentioned above, the relationship between FFR and luminal stenosis is not perfect,[163] because there are numerous examples of IWOS and SWOI seen in day-to-day clinical practice and have been reported in various studies.[134,135] Features other than the degree of luminal stenosis, such as lesion length, entrance angle, exit angle, size of the reference vessel, and absolute flow relative to the territory supplied were originally thought to explain the lesions with IWOS and SWOI.[164] Recently, it has been shown that the presence of high-risk plaque features, especially large LAP, a CTA surrogate for necrotic core, is a strong predictor of FFR-verified ischemia independent of degree of luminal stenosis.[165,166] Local impairment of the vessel to dilate at the site of a large necrotic core may contribute to ischemia independent of the degree of luminal narrowing. A once nonsignificant stenosis with impaired local vasodilatory ability could cause significant functional stenosis when the adjacent segments dilate at the time of maximal hyperemia. The reason for such local inability of vessel to dilate at the site of large necrotic core could be related to reaching the Glagovian limit caused by the presence of significant positive remodeling, presence of significant local endothelial dysfunction at the site of large necrotic core,[134,167-169] or disruption of the local signaling mechanism between intima and smooth muscle cells that is essential for vasodilatation resulting from the presence of large necrotic core.[135] As a result, FFR-negative lesions are more likely to be devoid of both large necrotic core and severe stenosis. Therefore, FFR may indirectly be a sensitive (but not specific) detector of stenotic plaques with large volume necrotic core.[135] This might also explain the favorable prognosis associated with negative FFR, given the excellent prognosis of lesions without large necrotic core on CTA.[135]

EVALUATION OF STRUCTURAL HEART DISEASE

AORTIC VALVE DISEASE

Minimally invasive transcatheter heart valve interventions have revolutionized the historical paradigm for the treatment of valvular heart disease. Since the first transvenous transcatheter aortic valve replacement (TAVR) performed by Alain Cribier in 2002, TAVR has seen rigorous validation and now broad clinical adoption being considered the first-line treatment for high-and extreme-risk patients with severe symptomatic aortic stenosis.[170-174] In fact, the technique is seeing even further growth in clinical integration in the intermediate-risk population.[175] Along with its rapid adoption in clinical practice the pretreatment planning has also undergone significant transformation from its early days where sizing and device selection were largely dependent on 2D echocardiography. MDCT is now the primary noninvasive imaging tool for the evaluation of patients prior to TAVR and includes annular sizing, aortic root assessment, provision of coplanar angles to guide implantation, evaluation of suitability of vascular access, and screening for procedural complications.[176]

Annulus and Root Assessment

The word *annulus* comes from the Latin word meaning "ring." In reality, though, the aortic annulus is an almost uniformly noncircular structure. This was, however, underappreciated historically because of the limitations of 2D imaging. As a result, early transcatheter heart valve (THV) selection, which was performed with 2D echocardiography, often resulted in deploying a valve that was too small for the annulus, often leading to significant paravalvular regurgitation following valve deployment.[171,172,177,178] MDCT, with its isotropic voxels and resulting comparable spatial resolution in all reconstructed planes, affords a robust platform to characterize the 3D complex anatomy of the aortic annulus in a granular and reproducible fashion[176] (Figs. 17–16 and 17–17).

The concept of the virtual basal ring, immediately below the hinge point of the aortic valve cusps, was first described by Piazza and colleagues in 2008 as the anatomical correlate of the aortic annulus given that there is no well demarcated anatomical landmark otherwise

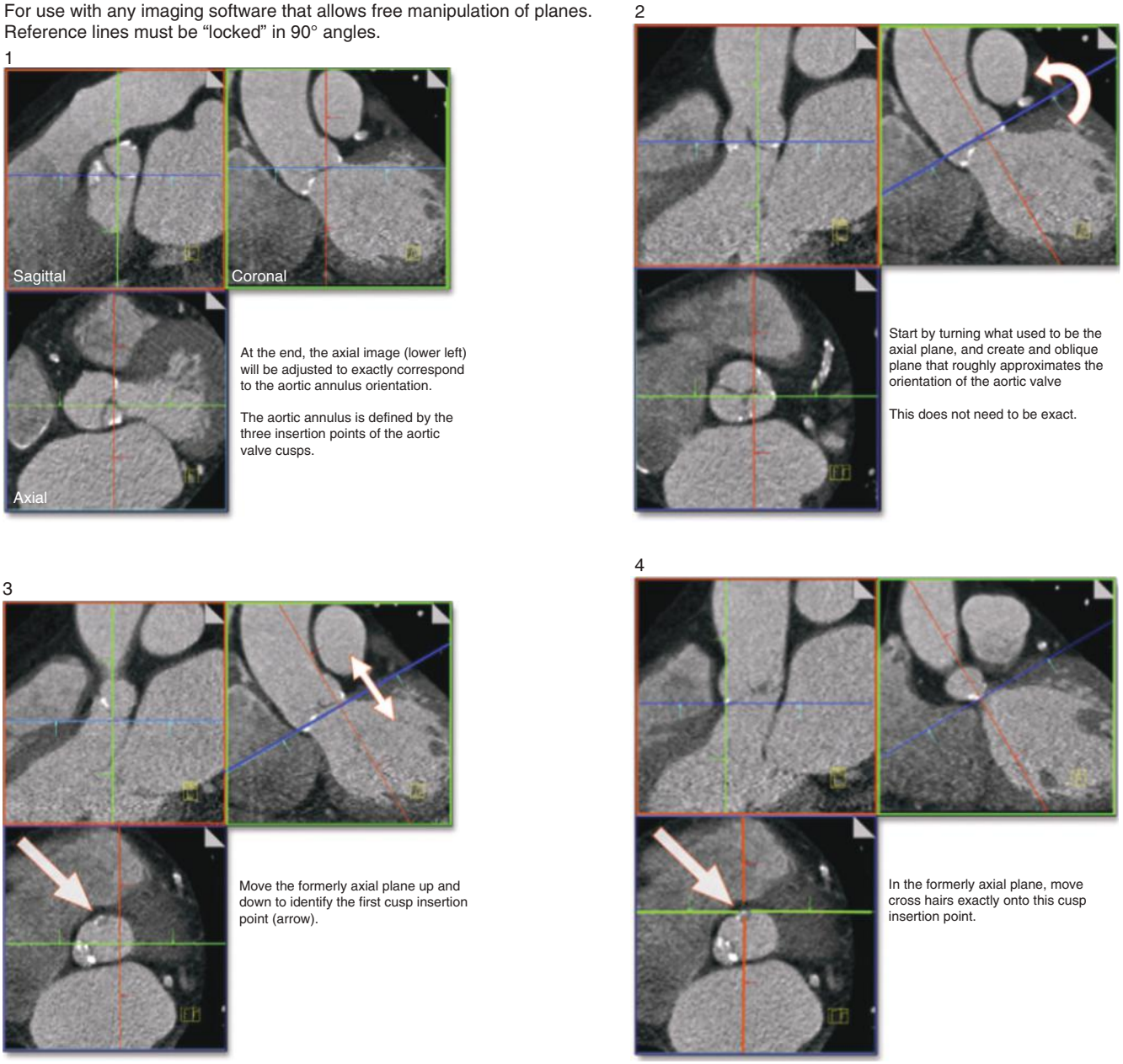


FIGURE 17–16. A method to create the aortic annulus plane in computed tomography. Reproduced with permission from Achenbach S, Schuhbäck A, Min JK, et al: Determination of the aortic annulus plane in CT imaging-a step-by-step approach, *JACC Cardiovasc Imaging*. 2013 Feb;6(2):275-278.[228]

present.[179] This basal ring can be easily generated in its true short axis using standardized multiplanar reformatting in either a manual or facilitated fashion (see Fig. 17–16). Once generated, various measurements of the annulus can be performed that facilitate device sizing and selection. These include but are not limited to the short and long axes, the perimeter, and the area. In the very early days of CT integration into TAVR practice, it was shown that the mean annular diameter and area measurements[178,180] were the most reproducible across readers and work station platforms. The perimeter, which has been subsequently integrated into THV sizing, was not as stable because of the lack of contour smoothing algorithms across all work stations until recently. Establishing the most reproducible measurements was, however, only a first step toward CT integration. Initial sizing was on the basis of 2D diameters and measurements such as area and perimeter were confounding to the proceduralist and imager.

Sizing algorithms using CT 3D measurements began to appear in 2012. Willson and colleagues proposed area-based sizing for the balloon-expandable Edwards Sapien XT (Edwards Lifesciences, Irvine, CA) with a recommended threshold of 5% to 20% area oversizing to help mitigate the risk of paravalvular regurgitation. This threshold of oversizing needs to be greater for the self- expanding device (Corevalve, Medtronic) given the lower radial force of the device to obviate significant paravalvular regurgitation. Initial experiences with CT sizing for this device were consistently performed on a stable CT work station solution with perimeter smoothing available and as such perimeter has become the default measurement for sizing this device. The degree of oversizing recommended based on perimeter is approximately 15% to 30%.[173,181] Importantly, these measurements are performed in late systole when the annulus is the largest. Some have argued the perimeter is impervious to the dynamism of the

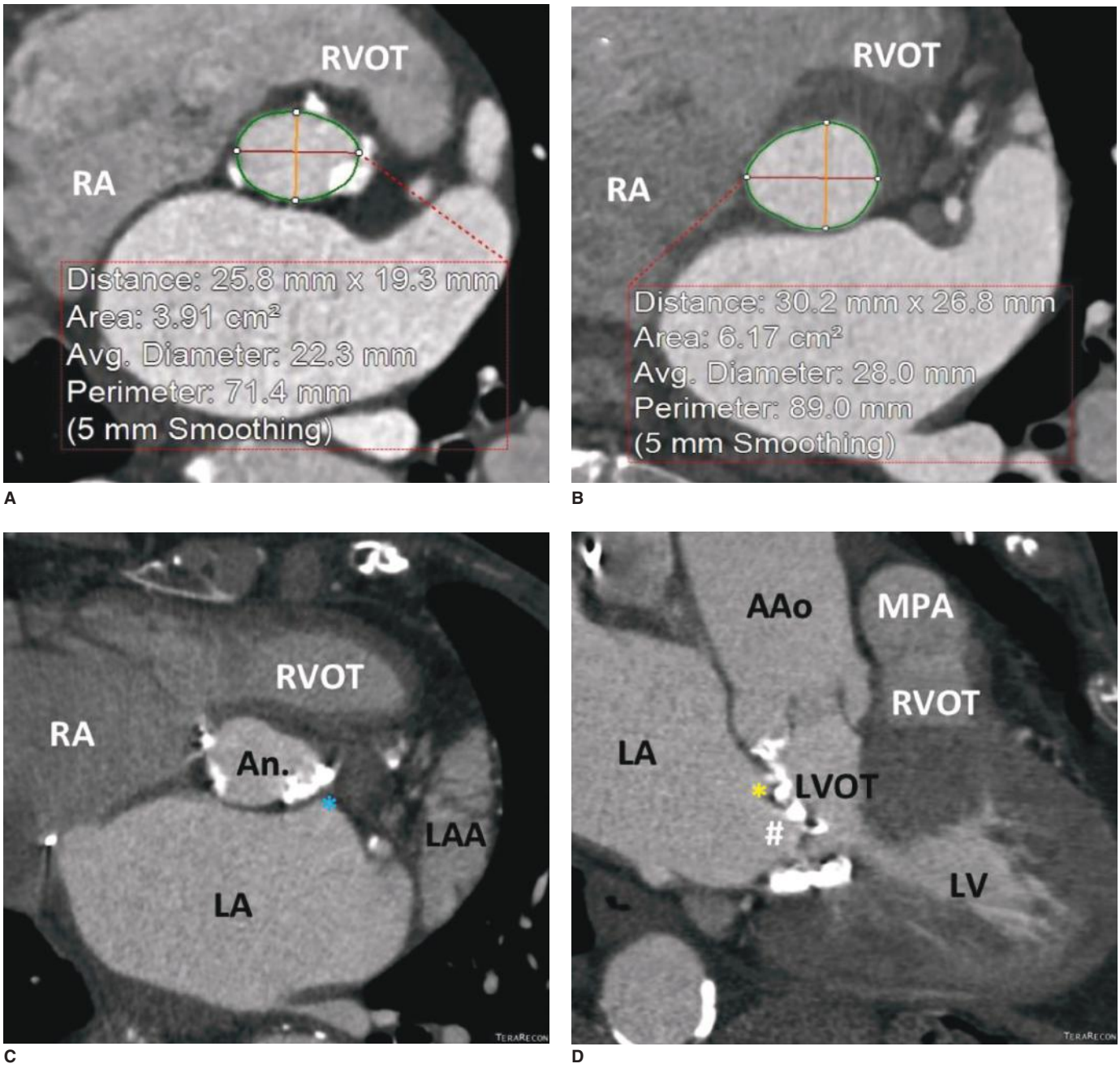


FIGURE 17–17. **A.** Moderate annular calcium in an 89-year-old female patient. Annular measurement should traverse any annular calcium in order to maintain a "harmonic" elliptical configuration. **B.** A large annular area measurement in an 85-year-old male patient reflecting noncircular geometry of the annulus. **C.** An 84-year-old female patient with severe aortic stenosis and moderate annular calcium (*). **D.** Same patient with additional subannular (*) and left ventricular outflow tract (LVOT) (#) calcification. AAo, ascending aorta; An, aortic annulus; LAA, left atrial appendage; MPA, main pulmonary artery; RA; right atrium; RVOT, right ventricular outflow tract.

cardiac cycle[182]; however, these data are primarily derived from bench phantom work and with data derived from cardiac CT, suggesting that the perimeter of the annulus changes throughout the cardiac cycle. This is not surprising because the annulus not only undergoes conformational change but also experiences a degree of stretch. Blanke and coworkers noted that the annular perimeter changes approximately 7% as compared to annular area, which undergoes closer to 15% change over the course of the cardiac cycle.[183,184] These data have been reproduced by others, supporting the importance of consistently measuring the annulus in systole or at least being aware of the dynamic changes in the cardiac cycle when using diastolic measurements for sizing with a systolic sizing algorithm.[185,186] Given the dynamism of the annulus throughout the cardiac cycle, it is still recommended that retrospective ECG gating be performed with peak tube current in late systole.

Sizing Algorithms

Current sizing algorithms for THVs being used in practice are based on systolic area and perimeter measurements of the aortic annulus from MDCT. Typically, the goal of device selection is to place a THV that is larger than the native annulus to help reduce the risk of non-apposition and paravalvular regurgitation.[177,178,187-190] The degree of

oversizing recommended varies between device platforms and depends on the radial force of the selected device. Balloon-expandable devices, although associated with greater risk for annular injury, require less oversizing to control paravalvular regurgitation while balancing with the potential risk of annular injury that can occur more frequently with these devices. From an imaging perspective, there are important CT findings beyond annular size that are important to identify to help guide the procedure.

Subannular and extensive annular calcium has been shown to be associated with increased frequency and severity of paravalvular regurgitation.[191] In addition, in a multicenter registry of patients who experienced annular rupture, Barbanti and colleagues showed that subannular calcification, particularly below the noncoronary cusp,[192] is associated with an increased risk of annular rupture, particularly in conjunction with oversizing greater than 20% by area.[192,193] The identification and evaluation of the subannular zone is now routine and helps determine device sizing and often the type of THV used (Fig. 17–18).

MDCT is also extremely helpful in reducing the risk of coronary occlusion during TAVR. Coronary occlusion is said to occur in 0.66% of TAVR procedures and is associated with a poor clinical outcome. The mechanism of coronary occlusion relates to the native aortic valve leaflet being displaced up toward the coronary ostium. In the early days of TAVR, angiography was the only modality that allowed for prediction of coronary occlusion preemptively and its performance in doing so was modest. CT allows for accurate assessment of both the height of the coronaries as well as the size and capacity of the sinus of Valsalva.[194] In 2013, a registry was published highlighting the preprocedural anatomical findings that help predict the risk of occlusion. The authors collected 42 cases concerning patients who experienced coronary occlusion and had undergone a contrast-enhanced CTA in advance of the procedures. The authors were able to match 27 of these patients to patients who did not experience rupture. They found that left main height of less than 12 mm in conjunction with shallow of Valsalva mean diameter (cusp to commissures) of < 30 mm was associated with an over five-fold increased risk of coronary occlusion (Fig. 17–19). In addition, a sinus of Valsalva–to–annular ratio of less than 1.25 was also strongly predictive of an increase risk.

Fluoroscopic Angle Prediction with Multidetector Computed Tomography

In TAVR, the proceduralist seeks to use a fluoroscopic angle that allows for the profiling of all three aortic cusps in a single plane. This allows for appropriate device deployment to ensure adequate positioning and reduce the burden of paravalvular aortic regurgitation (PAR). This angle selection can be performed at the time of the procedure through repeated angiographic root injections and perhaps 3D rotational angiograms.[195-197] Although this may be effective, it requires repeated contrast injections and at times rapid pacing while the spin is being performed, which somewhat limits these techniques. MDCT can provide coplanar angles for valve deployment that correlate with the angles obtained at the time of the procedure. From experience, the aortic root is typically angled in an RAO caudal fashion with rotation to more carinal angulation extending to the LAO direction. There are, in fact, innumerable angles falling on this S-shaped curve that are coplanar to the root of the aorta, however, because of the limited number of feasible working angles in the hybrid operating room. It has largely become convention to provide angulation at straight AP and some varying degrees of caudal or cranial angulation as well as at least on LAO angle. Preprocedural angle prediction with CT have been shown to correlate well with rapidly paced 3D rotational angiography performed at the time of the procedure[195] when the patient is positioned in a similar fashion for the CT and the ICA.

Reducing the Frequency of Root Injury

Annular injury, manifesting as uncontained or contained root rupture, is a feared complication of transaortic valve implantation (TAVI). Prior to routine integration of cardiac CT, there was the impression that this was a random event associated with balloon-expandable THVs. Through a registry of patients undergoing MDCT prior to TAVI, certain patient- and procedure-related predictors have been identified.[192,193] This registry highlighted that subannular calcification, particularly moderate/severe in grade, was much more common in those patients who experienced annular injury as compared to those who did not. In addition, the authors found that oversizing the annular area by greater than 20% resulted in an incrementally elevated risk. Building on these findings, Hansson performed a more elaborate analysis on the pattern and distribution of calcium using an advance postprocessing algorithm.[192] This analysis confirmed the importance of left ventricular outflow tract (LVOT)/subannular calcification but importantly highlighted that it is really the immediate subannular calcium within 2 mm of the annulus that drives the increased risk. In addition, although most clinical reports have suggested that rupture most commonly occurs below the left main (LM) in an area of relative annular weakness, the calcification is most commonly seen below the noncoronary cusp. These findings have impacted clinical practice with the subannular space now very much being a part of the clinical report and guiding device size selection with the goal of ensuring that annular oversizing is more modest in its presence. Unfortunately, while subannular calcification is an accepted driver of annular rupture, it is also a well-accepted mechanism of paravalvular regurgitation. Protruding nodules of calcification, by preventing THV apposition, often result in PAR, which further complicates device sizing. The appropriate device type and size in the setting of such subannular calcification remains uncertain, but it is imperative that the CT imager understand these potential pitfalls and carefully interrogate and report on the subannular space.

MDCT for Valve in Transcatheter Aortic Valve Replacement

THV deployment within a failing surgical bioprosthesis is becoming an increasingly common procedure for those patients deemed to be at high or excessive surgical risk (Fig. 17–20). This treatment has been shown to be effective at relieving surgical aortic valve replacement (SAVR) valve regurgitation and stenosis with good 30-day and intermediate-term outcomes.[198,199] Although this procedure has shown great promise in its early days, it is not without limitations or complications. Increased THV gradients is the most common complication, with malpositioning probably the second. Although less common, mechanical occlusion of the coronary ostia is a feared complication associated with a high mortality. The role of MDCT in the preprocedural assessment of patients prior to valve-in-valve (VinV) therapy is evolving. Sizing of the THV for the procedure is largely determined by the type and size of the failing surgical valve, with CT being limited to guide device selection in the setting of unknown surgical valve history and to assess the extent of pannus when present. The most important clinical role at present for CT in VinV is to help mitigate the risk of coronary occlusion.

To use anatomical imaging with MDCT to reduce the risk of coronary occlusion with VinV, one must first have an understanding of the mechanism of coronary occlusion with this procedure (which is different than with native TAVI). With native TAVI, coronary occlusion occurs when the native aortic valve leaflet is displaced by the THV and occludes a typically low left main coronary artery. On the other hand, with VinV, the surgical aortic valve leaflets are displaced and wedged between the THV and the surgical bioprosthetic valve struts resulting in the formation of a covered stent in the root of the aorta. If the surgical aortic prosthetic stent struts do not extend

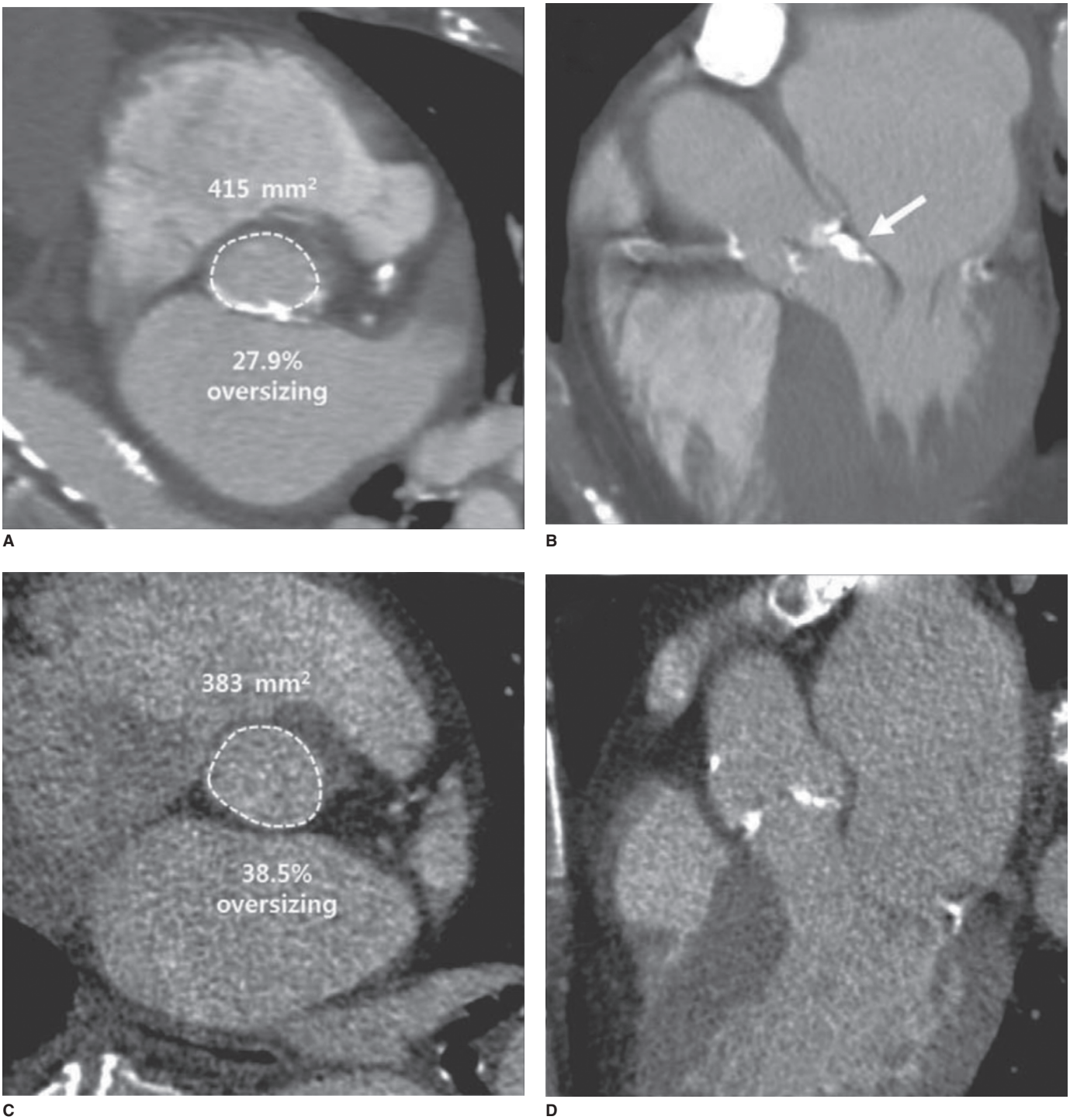


FIGURE 17–18. Case examples of two patients who underwent transcatheter aortic valve replacement (TAVR) with a 26-mm (**A**, **B**) and a 23-mm (**C**, **D**) SAPIEN XT valve. In these cases, significant annular area oversizing (27.9% and 38.5%, respectively) resulted in different outcomes. The case showed in **A** and **B** (multidetector computed tomography double-oblique transverse and coronal projections, respectively) with severe left ventricular outflow tract (LVOT) calcification (*white arrow*) experienced annular rupture during TAVR complicated by procedural death. The second case (**C** and **D**) displays an absence of LVOT calcification and, despite comparable prosthesis oversizing, this patient underwent an uneventful TAVR. Reproduced with permission from Barbanti M, Yang TH, Rodes Cabau J et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement, *Circulation*. 2013 Jul 16;128(3):244-253.[181]

above the coronary ostia, if the sinuses are capacious, and if the surgical valve is centrally positioned coronary occlusion rarely occurs. If, however, the sinuses are shallow and the SAVR valve is canted toward the coronary ostium, then the risk of occlusion is much higher. Importantly, with the anatomical detail afforded by MDCT, one can assess for these at-risk features, including the angulation and positioning of the SAVR valve, which is less easily done with other imaging modalities. Simple modeling of a ring the size of the THV is planned to be implanted at the level of the SAVR valve tips, integrating the tilting/canting of the valve, allowing for an estimation of the risk of coronary occlusion. This methodology allows for the determination of a measure referred to as a "the virtual ring to coronary

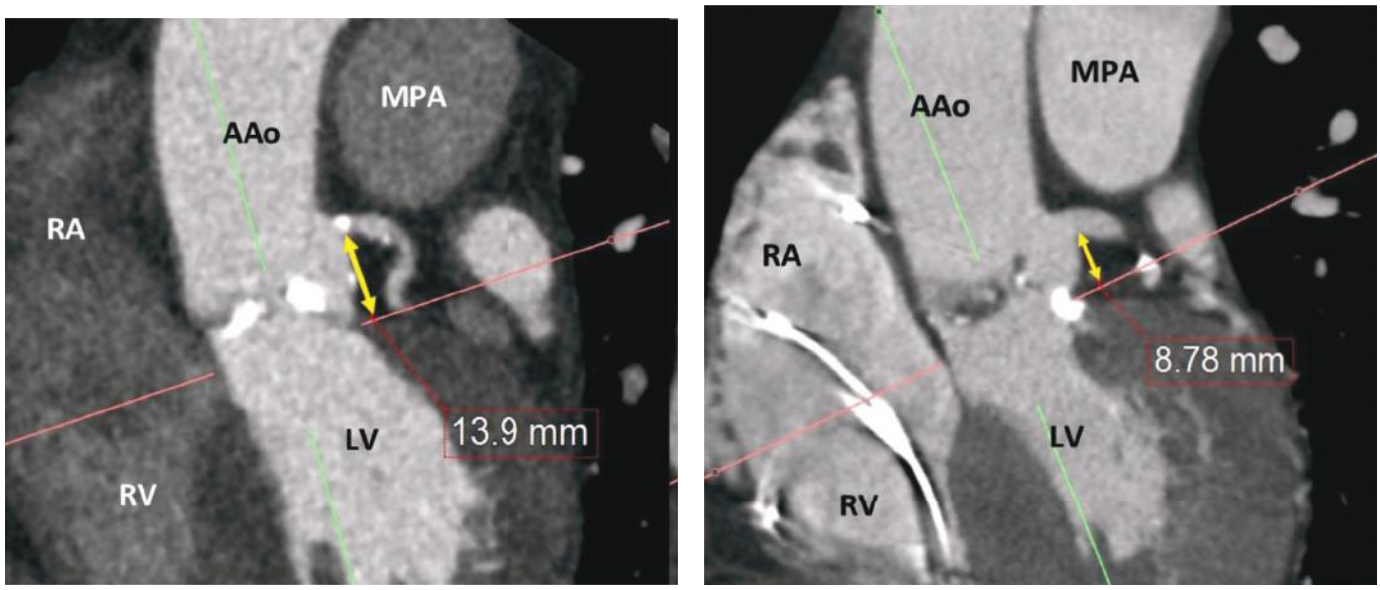


FIGURE 17–19. A. Left main coronary artery craniocaudal height measured perpendicular to the annular plane. A height greater than 12 mm is less frequently associated with coronary occlusion. **B.** Low left main coronary artery height in an 85-year-old female patient with severe aortic stenosis undergoing computed tomography planning pretranscatheter aortic valve replacement. Increased risk of coronary occlusion results from a combination of low left main ostial height, as well as moderate to severe annular, subannular, and left ventricular outflow tract calcium. AAo, ascending aorta; LV, left ventricle; MPA, main pulmonary artery; RA; right atrium; RV, right ventricle.

ostial distance," or the VTC. Although not yet broadly validated, thresholds of less than 3 mm, 3 to 6 mm, and greater than 6 mm have been proposed as VTC measurement cutpoints to discriminate the risk of coronary occlusion.[200]

BEYOND THE AORTIC VALVE

The success story of TAVR has resulted in a significant amount of interest in the development and validation of transcatheter solutions for other valvular diseases. Given the incidence of mitral regurgitation and the frequency that patients with functional mitral regurgitation in particular are not considered surgical candidates, transcatheter mitral valve replacement (TMVR) has become one of the hottest topics in structural heart disease.[201-204] To date, there have been six devices implanted in humans showing promising feasibility and many more undergoing animal testing. Given the years of validation of MDCT to support TAVR, the role of MDCT in TMVR has been evident from day one. Cardiac CT allows for a 3D and granular assessment of the saddle-shaped mitral annulus. In addition, using commercially available postprocessing, the annulus can be reconstructed in a highly reproducible fashion. CT has also allowed us to propose the concept of the D-shaped annulus, truncating the anterior peak at the level of the fibrous trigones, which has been shown to be more conducive for appropriately measuring for device sizing[200,205,206] (Fig. 17–21). Cardiac CT is also able to provide procedural guidance providing coplanar angles of deployment[207] similar to TAVR. In the mitral position, the coplanar curve is much steeper than the aortic annular curve. This results in many angles requiring an excessively caudal angulation for use in the hybrid operating room. This is commonly the case to generate an angle coplanar to the commissure-commissure line, with angles parallel to the septal-lateral line being achievable. Puncture site localization is also more complex than with TAVR as deploying the device along an axis oriented perpendicular to the 2D mitral annular plane is very important to ensure device sealing and avoid device migration. As a result, the appropriate access point is commonly not the true apex frequently anterior and anterolateral with substantive interpatient variability.[206] CT is also very helpful in determining the appropriateness of other anatomical parameters for the varied transcatheter mitral valve devices. Nodular or extensive mitral annular calcification poses challenges for use of most of the current devices. In addition, the capture and sealing mechanisms are varied among the devices, with some having a tether to the apex and others using barbs/tabs to engage a posterior shelf commonly seen in FMR.

In a fashion to TAVR, cardiac CT has been shown to be helpful in identifying patients at risk for TMVR-related complications. Annular rupture and coronary occlusion are not of concern, but rather with TMVR, there is a significant concern regarding LVOT obstruction. THVs in the mitral position protrude into the LV cavity, resulting in displacement of the anterior mitral valve leaflet toward the basal septum, leading to remodeling of the outflow tract by elongating the outflow tract into the LV.[206] We have proposed that this remodeled LVOT be referred to as the "neo-LVOT," which can be routinely modeled using basic 3D work station algorithms; these integrate the device size and its positioning into a "postimplant CT," which will allow a better understanding of the remodeling of the LVOT that will develop following the procedure.[208] Clearly, this modeling has many limitations, including an assumption of postimplant device positioning and its inability to predict dynamic LVOT obstruction related to the native mitral valve. In the future, more advance dynamic 3D models from CT, integrating CFD or other computational/simulated approached may allow for a more thoughtful approach to the prediction of the risk of LVOT obstruction post-TMVR.

EVALUATION OF PERICARDIAL DISEASE

CT scanning provides excellent visualization of the pericardium and associated lung and mediastinal structures. The low density of epicardial and extrapericardial fat outlines the pericardium and serves

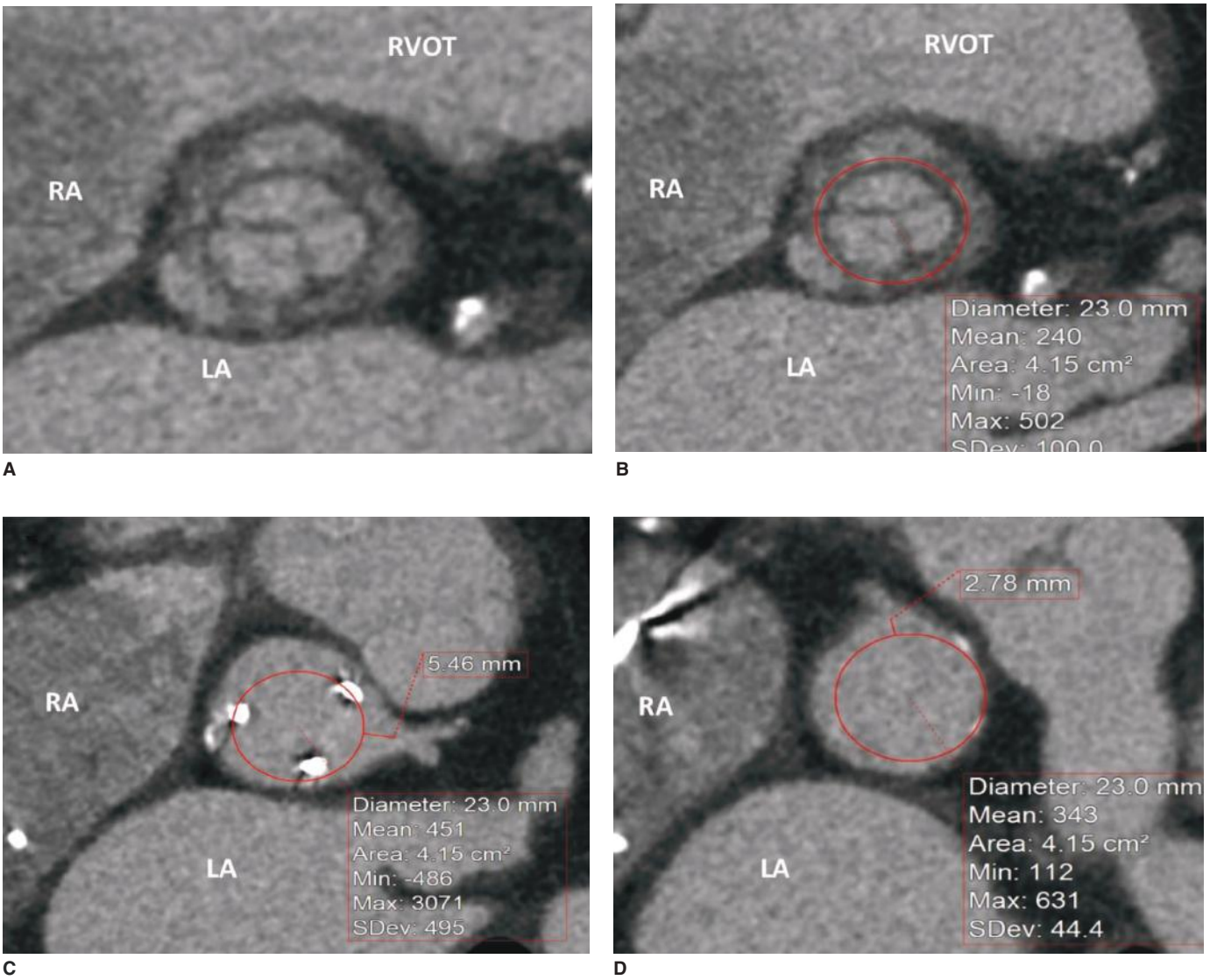


FIGURE 17–20. A. An 84-year-old man with a failed bioprosthetic aortic valve for consideration of transcatheter aortic valve in valve replacement. **B.** A simulated 23-mm valve is placed at the base of the in situ aortic valve. **C.** The simulated ring is propagated cranially to the level of the left main coronary artery ostium. A transverse distance of 5.46 mm confers an intermediate risk of coronary artery occlusion. Note the relative tilt of the simulated prosthesis compared to the radio-opaque posts of the in situ valve. **D.** Transverse distance to the right coronary artery origin of 2.78 mm confers a high risk of coronary artery occlusion. LV, left ventricle; RA; right atrium; RVOT, right ventricular outflow tract.

as a natural contrast. Therefore, even minimal (4-5 mm) pericardial thickening and calcification is easily detected.[209] CT can be useful particularly when visualization of the pericardium is suboptimal with echocardiography. Contrast-enhanced CT can elucidate inflammation of the pericardium and can be diagnostic for pericarditis in the appropriate clinical setting.[210] In addition, cardiac CT can readily detect pericardial effusion and hematoma and may help distinguish different processes within the pericardial space based on density or attenuation.[211] Cine mode images of the right atrium and RV can also detect diastolic collapse when pericardial tamponade is present.[212] Enlargement of the superior and inferior vena cavae can be identified when either tamponade or constriction is present.[194] Furthermore, cardiac CT is useful in accurately diagnosing constrictive pericarditis and differentiating it from similar conditions, such as restrictive cardiomyopathy. A pericardial thickness of more than 4 mm in a patient with abnormal rapid early LV diastolic filling is diagnostic of pericardial constriction.[213]

Congenital abnormalities such as absence of the pericardium or pericardial cyst can also be evaluated with cardiac CT.[214] CT is currently one of the best techniques for defining the location and extent of pericardial tumors and diagnosing metastatic involvement of the pericardium from mediastinal tumors.[215]

EVALUATION OF CONGENITAL HEART DISEASE

Cardiac CT and MRI have been increasingly used for the assessment of congenital heart disease. Both modalities can be rendered into 3D images that are useful in clarifying the often complex anatomic relationships in patients with congenital heart disease. MRI may be of limited use in critically ill patients because of its relatively long scan time, and it is contraindicated in patients with history of severe claustrophobia and with metallic implants. Despite these limitations, MRI is still preferred over MDCT because it does not involve ionizing radiation or nephrotoxic

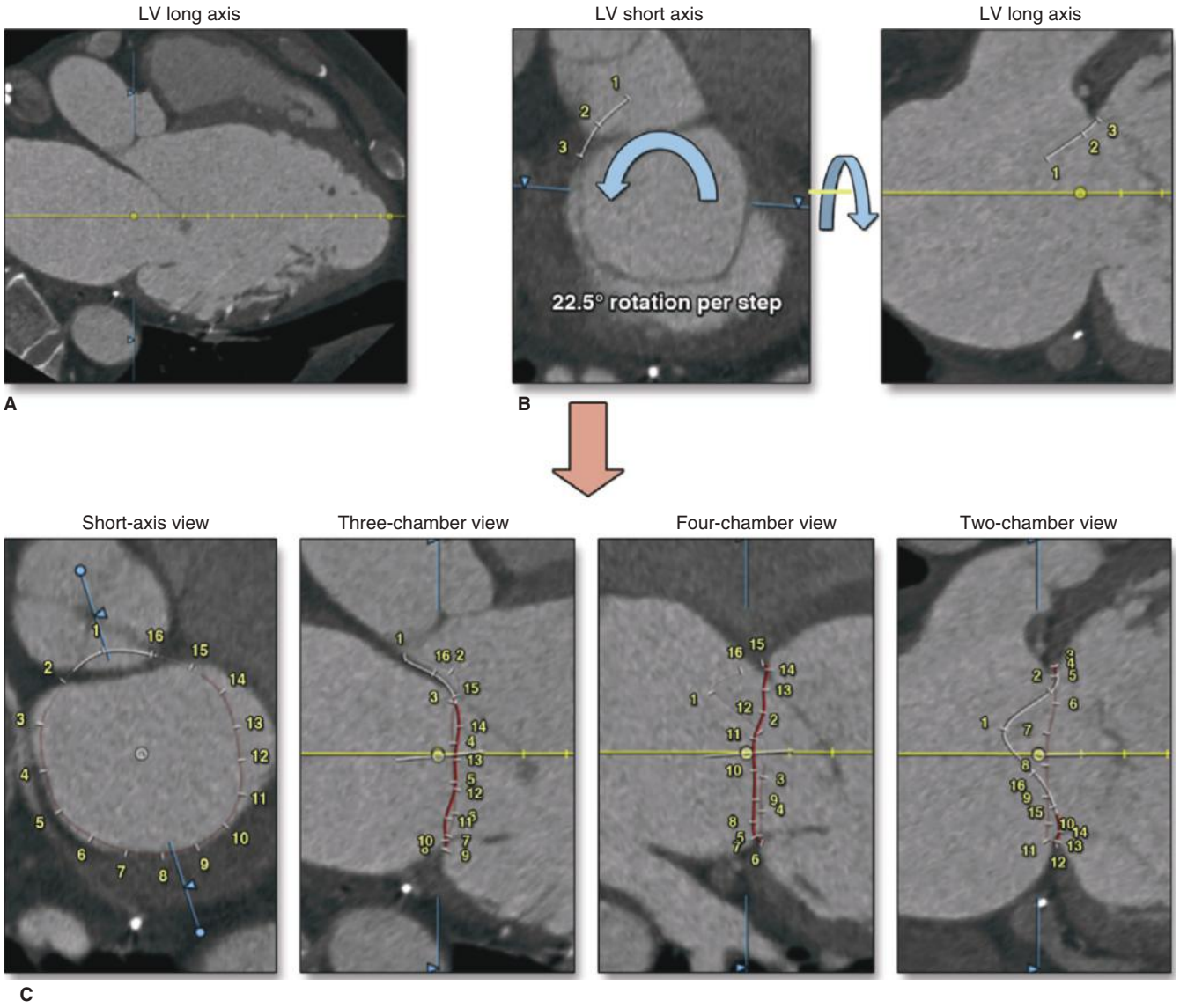


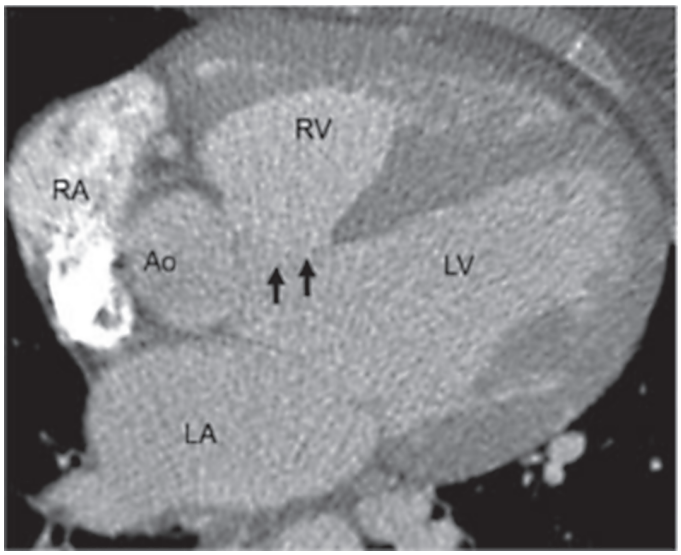
FIGURE 17–21. Mitral valve annulus evaluation. **A.** The saddle-shaped mitral annulus is manually segmented by placing 16 seeding points along the insertion of the posterior mitral leaflet and along the contour of the fibrous continuity while rotating the long-axis view by 22.5° in a stepwise fashion. **B.** (3mensio Structural Heart version 7.0, Pie Medical Imaging, Maastricht, the Netherlands). The *yellow line* denotes the orientation of the left ventricular (LV) long axis. **C.** The fully segmented saddle-shaped annulus in standard views. The *blue line* on the short-axis view indicates the orientation of the long-axis view, the *red line* depicts the posterior aspect of the saddle-shaped annulus, and the *white line* indicates the anterior aspect of the saddle-shaped annulus.

contrast agents and allows the precise quantification of flow with superior tissue characterization. However, advances in CT image quality, decreases in radiation dose, and the provision of accurate functional information have helped make CT a viable alternative. Furthermore, MRI most often requires significant sedation in children (often necessitating intubation), which is not necessary with the fast study times of CT.

Anomalies of the aortic arch, patent ductus arteriosus, tetralogy of Fallot, and abnormal arteriovenous connections can all be carefully evaluated with cardiac CCTA (Fig. 17–22).[216] The high spatial resolution of MDCT also permits the evaluation of the atrioventricular valves in conditions such as Ebstein anomaly and tricuspid and mitral valve atresia.[217] MDCT can also be used to accurately quantify intracardiac shunts as well as cardiac masses.[218,219] Both atrial and ventricular septal defects can be detected and analyzed with CCTA (Fig. 17–23). MDCT evaluation has been used prior to closure device implantation.[220] Arrhythmogenic RV cardiomyopathy is accurately diagnosed based on the characteristic CT findings of an enlarged RV, with a scalloped appearance, trabeculations with low attenuation characteristics, and abundant epicardial adipose tissue.[221]

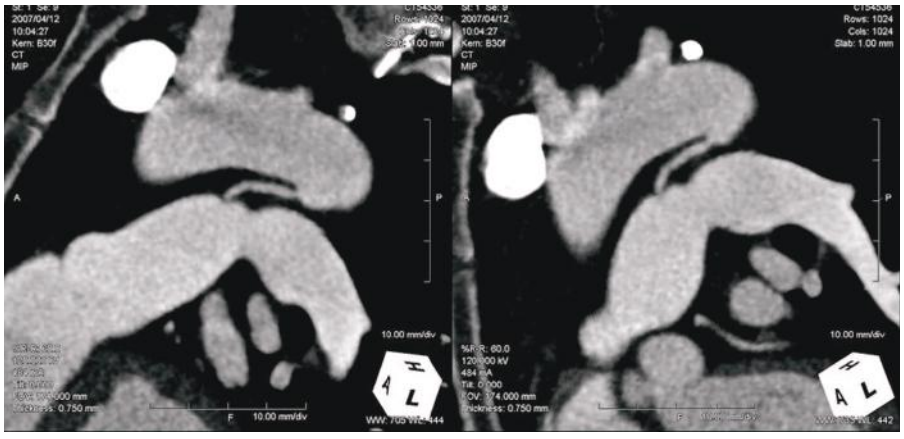
The development of four-dimensional (4D) capability has accelerated over the past few years. The heart is a dynamic organ best understood when studied throughout the cardiac cycle. Hence, the development of 4D CT cine angiography (time being the fourth dimension) is a milestone in the clinical application of this technology. It is ideally suited for the complex dynamic dilemmas frequently encountered in congenital heart disease.

In conclusion, the application of CT in evaluating congenital heart disease is feasible and appropriate. In selected cases, CT may be a valuable alternative to MRI for both structural and functional delineation of the anatomic abnormality.



A

B

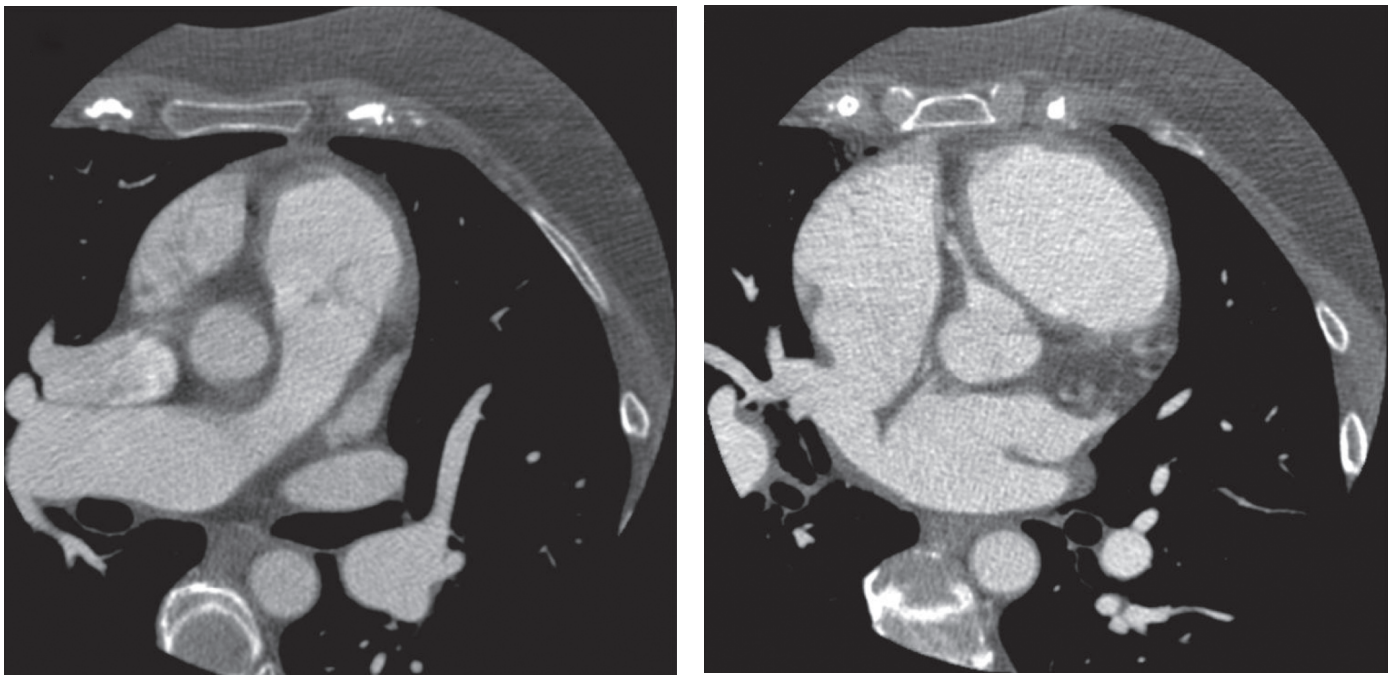


C

FIGURE 17–22. A patient with tetralogy of Fallot with large ventricular septal defect (*black arrows*), overriding aorta (Ao), and thickened right ventricle (RV) (**A**). Three-dimensional rendering (**B**) and corresponding maximum-intensity projection (**C**) images of a patent ductus arteriosus. Cardiac computed tomography is helpful in defining the anatomy in most forms of congenital heart disease. LA, left atrium; LV, left ventricle; RA, right atrium.

EVALUATION OF CARDIAC TUMORS

Cardiac neoplasms are rare and have a reported prevalence of 1 to 3 per 10,000 patients in autopsy series.[222] The most common primary cardiac neoplasm is myxoma, which accounts for more than half of all cases.[222] Although the majority of these tumors are benign, there is a 10% mortality associated with myxomas, a 30% mortality with nonmyxoma benign tumors, and 100% mortality within 3 years in all patients with malignant cardiac tumors.[223] In addition, the clinical course can be complicated by arrhythmias or ventricular dysfunction caused by mass effect or tamponade, which makes prompt diagnosis and management imperative. Echocardiography is usually the first diagnostic test,



A B

FIGURE 17–23. Sinus venosus atrial septal defect (ASD) and partial anomalous pulmonary venous return. Transverse axial images from a cardiac computed tomography angiogram in a 45-year-old patient with shortness of breath. At the level of the right pulmonary artery (**A**) there is evidence of the right upper lobe pulmonary vein draining in to the super vena cava. More caudally (**B**) a connection between the right atrium and left atrium is apparent in keeping with a sinus venosus ASD.

particularly in patients with tumor-related cardiac symptoms, such as tamponade, heart failure, or systemic emboli. However, CT has expanded the diagnostic capabilities of imaging beyond that of echocardiography. The presence and extent of intracardiac tumors can be well defined with either MDCT or EBCT. In the evaluation of cardiac tumors, MDCT can help differentiate benign from malignant masses and delineate metastatic tumor within the myocardial wall.[224] Given the precise anatomic information afforded by MDCT, presurgical assessment of cardiac neoplasms with MDCT may assist in determining the resectability of tumors and allow planning for the reconstruction of cardiac chambers.

DISEASES OF THE GREAT VESSELS AND PULMONARY VASCULATURE

Conventional CT is widely used for diagnosing thoracic aortic aneurysms and dissections.[225,226] With the introduction of MDCT scanners, thousands of images can be acquired within a single breath-hold, and a complete study of the thoracic aorta can be completed in only 10 to 15 seconds. After scan acquisition, 3D reconstructions are produced, which can be rotated and analyzed in multiple views. EBCT can also acquire rapid CT images with elimination of aortic pulsation as a cause of potential artifact.[227]

Aortic dissection is readily diagnosed with CTA with greater than 90% accuracy (Fig. 17–24).[226] In a study comparing MDCT, MRI, and 2D echocardiography, CT and MRI were shown to be superior to echocardiography in diagnostic accuracy.[228] CTA can also be used in monitoring of the expansion of thoracic aortic aneurysm over time.[226] In addition, MDCT can diagnose atherosclerotic disease of the aorta, aortic intramural hematoma, penetrating aortic ulcer, sinus of Valsalva aneurysm, and coarctation of the aorta.[225,226]

In patients undergoing repeat coronary artery bypass surgery, MDCT scanning has several advantages. CTA may guide the surgical approach by defining the position of the sternum to the RV, establishing patency of existing grafts, and visualizing the aorta, thereby avoiding unnecessary trauma and bleeding.[229]

MDCT[230] can diagnose acute and chronic pulmonary thromboembolism (Fig. 17–25). CTA of the pulmonary arteries has replaced nuclear ventilation/perfusion scans as the primary imaging study in the diagnosis of acute pulmonary embolism.[231] The cross-sectional view of the main and proximal right and left pulmonary arteries provides clear delineation of the proximal extent of the thrombi, which is essential for successful surgical treatment.[232] Accurate measurement of pulmonary artery size may also help to estimate the severity of pulmonary hypertension.[233]

Triple rule-out (TRO) CTA can evaluate the coronary arteries, pulmonary arteries, aorta, and intrathoracic structures in select patients presenting with acute chest pain of unclear etiology.[72] Standard 64-slice MDCT scanners can provide high-quality TRO CTA studies by tailoring the injection of iodinated contrast to provide simultaneous high levels of arterial enhancement in the coronary arteries and aorta (> 300 HU) and in the pulmonary arteries (> 200 HU).[234] Radiation exposure is minimized by limiting the imaging window to include from the aortic arch down through the heart, rather than encompassing the entire chest. In addition, the same imaging parameters, such as prospective gating and current modulation, used in CCTA are incorporated into the TRO CTA to limit ionizing radiation doses to between 5 and 9 mSv. New dual-source and whole-heart single-beat scanners allow for further optimization of the timing of image acquisition to

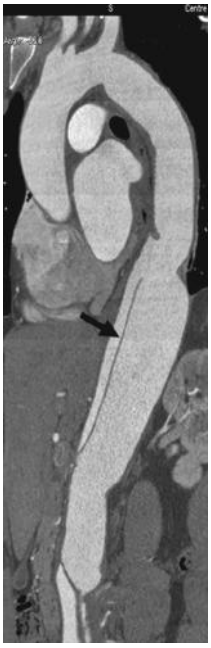


FIGURE 17–24. An aortic dissection starting in the descending thoracic aorta and extending down to right iliac artery.

allow for straightforward evaluation of both vascular beds with ECG synchronization. When used in the emergency department in appropriately selected patients, TRO CTA can eliminate the need for further diagnostic testing in more than 75% of patients.[234]

Lastly, CTA can be used for the noninvasive evaluation of the coronary veins prior to lead placement for a biventricular pacemaker or to assess the pulmonary vein anatomy prior to pulmonary vein isolation with radiofrequency ablation for the treatment of atrial fibrillation.[72] CTA can also be used in the evaluation of the symptomatic patient after atrial fibrillation ablation to exclude the presence of pulmonary vein stenosis, which can be rapidly progressive and may require further intervention in the postprocedural period.[180]

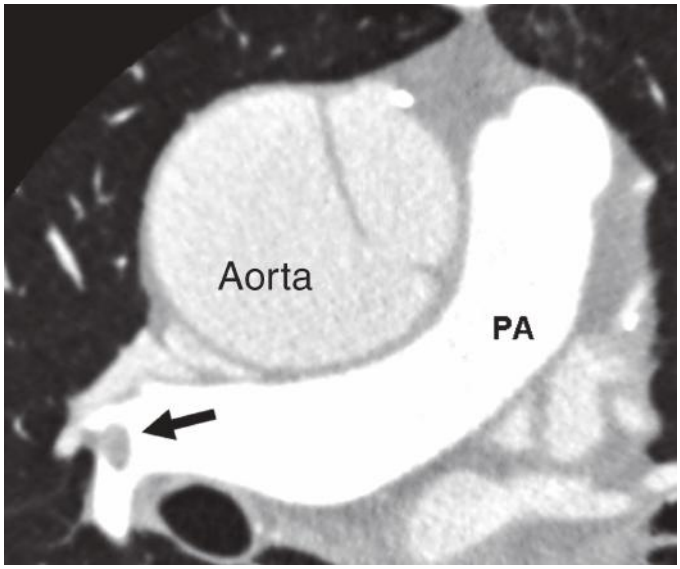


FIGURE 17–25. Patient with both an aortic dissection evidenced in a dilated aorta and a small pulmonary embolism (*black arrow*) in the left pulmonary artery (PA).

RADIATION DOSE IN CARDIAC COMPUTED TOMOGRAPHY

The main historical limitation of MDCT has been the radiation exposure, which used to be two to four times the radiation dose of diagnostic ICA. However, with multiple advancements in technology, there are several effective means of reducing the radiation dose during CCTA to 1 to 3 mSv. The most significant, and routinely available, radiation reduction strategy (up to 79%) can be achieved through prospective ECG-gated or sequential CCTA image acquisition, which involves the use of axial scanning with the tube current on only during prespecified portions of the cardiac cycle, eliminating tube current (milliampere) during nonimaging portions of the cardiac cycle (ie, systole).[3,235] Additionally, radiation exposure can be further minimized by approximately 46% to 53% by decreasing the tube voltage in nonobese (body mass index < 30 kg/m^2) patients from 120 to 100 kVp.[236,237] More recently, new iterative reconstruction algorithms have been introduced and validated for use in cardiac CT to allow for significant noise reduction, enabling an uncoupling of tube current and image noise and thereby allowing for significant tube current and dose reduction.[238] All major CT vendors offer similar algorithms, making them the standard algorithm for coronary CT angiography, Finally, new scan acquisition modes employing fast helical pitch technique afforded by dual source dual detector technology allow for rapid scan acquisition and significant dose reduction as a result.[239] Implementation of one or more of these strategies has been shown to consistently reduce radiation exposure to less than 15 mSv[240] and can even achieve radiation doses as low as 1 to 3 mSv in suitable patients.

SUMMARY

Coronary CTA has undergone significant development and evolution in the past 15 years, since its first description in clinical medicine. From its infancy with 2.5-mm slice acquisition, temporal resolution of 250 milliseconds, and *z*-axis coverage of 2 cm, modern cardiac CT scanners now offer spatial resolution of 0.5 mm, temporal resolution up to 67 milliseconds, and 16-cm whole heart coverage. In addition to improvements in scanner technology, new CT scan acquisition protocols and software algorithms allow the performance of coronary CTA at significantly lower estimated effective radiation dose exposures than were previously achievable.

The clinical utility of cardiac CT has grown exponentially in conjunction with these technological improvements. While coronary calcium scoring has seen an explosion in validation data, the diagnostic accuracy of coronary CTA is now well established and is considered the noninvasive gold standard for detection and exclusion of anatomical obstructive coronary artery disease; this is supported by large-scale robust prognostic data. Recent multicenter randomized clinical trials have shown coronary CT to be a viable alternative to traditional stress testing in the setting of stable chest pain with higher diagnostic certainty. Also, it is associated with lower nonobstructive disease incidence at the time of invasive angiography and a significant trend toward lower rates of downstream MI. Similarly, in the acute setting, coronary CTA has been shown to allow for more rapid discharge than traditional algorithms in a safe and cost-effective fashion. Evolving new applications for the adjudication of the hemodynamic significance of stenosis such as CT myocardial perfusion and FFR CT are now being used in clinical practice. Evaluation of plaque morphology and identification of high-risk plaque features and their prognosis is enhancing the understanding of mechanism of acute events in CAD and might prove very useful clinically in the near future.

Finally, the field of structural heart disease interventions are now increasingly dependent on the spatial resolution and unparalleled anatomical evaluation noninvasively offered by cardiac CT.

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CHAPTER 18

NUCLEAR CARDIOLOGY

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OVERVIEW

Nuclear cardiology is an integral part of routine cardiovascular practice. This chapter provides a synopsis of nuclear cardiology procedures and the published evidence of their role in the diagnosis, risk assessment, and management of patients with suspected or known coronary artery disease (CAD). In the technical section, the focus is on single-photon emission computed tomography (SPECT) since positron emission tomography (PET) is the subject of Chapter 19. Guidelines and appropriate use criteria combine SPECT and PET, and considerations of the applications are similar; therefore, the clinical portions of this chapter discuss both approaches. While nuclear cardiology has a broad potential role in molecular imaging, myocardial perfusion imaging (MPI) with SPECT and PET makes up the vast majority of current clinical nuclear cardiology procedures; hence, MPI is the primary subject of this chapter. In the chapter, CAD generally refers to the presence of an obstructive stenosis, in contradistinction to coronary atherosclerosis, which is used to denote the presence of any atherosclerotic plaque in the coronary arteries. The term *nuclear MPI* will be used when the discussion refers to both SPECT and PET-MPI approaches.

HISTORICAL PERSPECTIVES IN NUCLEAR CARDIOLOGY

The roots of nuclear cardiology began with the assessment of radioactivity transit times in the central circulation in the 1920s,[1] followed by clinical assessment of cardiac output in the late 1940s.[2] The Anger

scintillation camera, the imaging device still used today for the majority of all nuclear cardiology procedures, ushered in the practical clinical use of nuclear cardiology in the late 1960s by providing images of the cardiac distribution of radioactivity. The commercial availability of thallium-201 (^{201}Tl) in 1976 initiated the broad application of clinical MPI. In the early 1980s, SPECT, using a rotating Anger camera detector, became widely available, increasing the ability to localize and quantify regional myocardial perfusion defects. In 1990, technetium-99m (^{99m}Tc)-sestamibi was approved for use in the United States, followed shortly thereafter by ^{99m}Tc-tetrofosmin. The higher myocardial count rates of the ^{99m}Tc agents made it possible to perform electrocardiogram (ECG)-gated SPECT-MPI by obtaining images from the different parts of the cardiac cycle (gated SPECT). By 2003, more than 90% of SPECT-MPI used gated SPECT, providing routine objective clinical assessments of rest and stress myocardial perfusion and function.[3] PET scanning became available in the early 1980s and its application for myocardial viability using 18F-Fludeoxyglucose (FDG) and MPI with 13N-ammonia and 15O-H_2O was described soon thereafter. In the early 1990s, rubidium-82 (^{82}Rb), a generator-produced PET radiopharmaceutical, became available broadening clinical adoption of PET-MPI as well as opening the possibility of dynamic SPECT-MPI to quantify bloodflow.

There has been an evolution over time of the applications of clinical nuclear cardiology, roughly corresponding to the decades since its introduction. In the 1970s, nuclear cardiology procedures were validated for the detection of CAD, and their application was developed in conjunction with the concepts of Bayesian analysis. In the 1980s, first reports of the prognostic application of MPI appeared, followed by reports of its incremental value for risk stratification in a variety of patient subsets in the 1990s. Coupled with this growing body of supporting evidence, the establishment of the American Society of Nuclear Cardiology (ASNC) led to a period of marked growth of the field. In the decade of the 2000s, the concept of predicting benefit from revascularization for improving referral to coronary angiography emerged. In the current decade, with the imperative to reduce the growing costs of medical care, the focus of interest has turned to assessing the value of nuclear cardiology as it impacts medical care and improves patient outcomes.

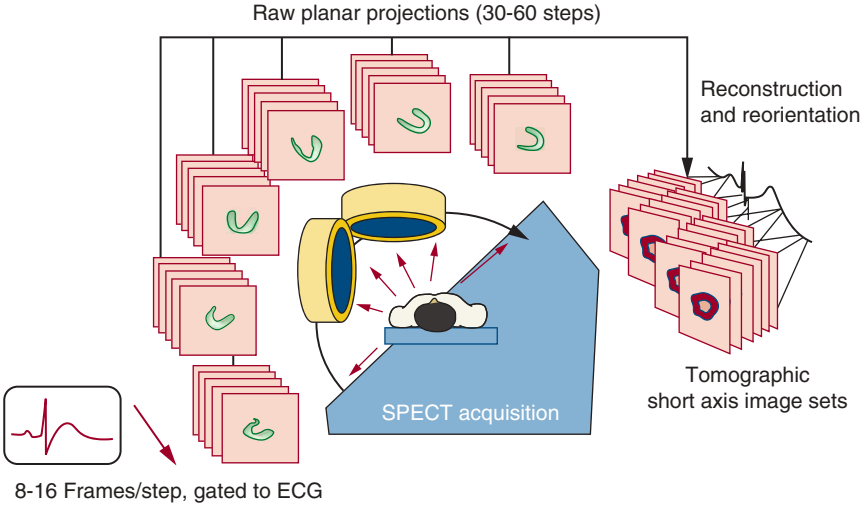

FIGURE 18–1. Schematic representation of electrocardiogram (ECG)-gated perfusion single-photon emission computed tomography (SPECT) acquisition and processing.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY–MYOCARDIAL PERFUSION IMAGING

BASIC CONCEPTS OF GATED SPECT-MPI

SPECT-MPI is performed using a scintillation camera and an intravenously injected radiopharmaceutical that distributes to the heart in proportion to regional myocardial perfusion. Various standardized SPECT-MPI protocols are used for imaging at rest and after exercise or pharmacologic stress. For SPECT, conventional scintillation camera detectors rotate to cover a 180-degree arc around the patient in a semicircular or elliptical fashion, collecting a series of planar *projection images* at regular angular intervals. The three-dimensional (3D) distribution of radioactivity in the myocardium is then mathematically *reconstructed* from the two-dimensional projections, and the resulting data are displayed in series of slices in the short-axis, vertical long-axis, and horizontal long-axis orientations. For gated SPECT (Fig. 18–1), the feature that distinguishes it from nongated SPECT is that the projection images are acquired in 8 to 16 phases of the cardiac cycle based on ECG triggering (*gating*). Reconstruction of a summation of the frames is used to assess myocardial perfusion, and reconstruction of each of the separate phases is used to evaluate ventricular function. Recently, solid-state detector cameras with new acquisition geometries have been introduced that do not require detector rotation around the patient and offer the potential for reducing the time and the patient radiation dose associated with SPECT-MPI.[4,5]

RADIOPHARMACEUTICALS

The radiopharmaceuticals used for SPECT-MPI and their properties (Table 18–1) share the characteristic that they are accumulated in viable myocardium in proportion to regional myocardial blood flow (Fig. 18–2) (see Table 18–1). The concept that CAD can be detected with this approach is based on the ability to detect a reduction in myocardial perfusion in a region supplied by a significantly stenosed vessel when compared with a normal region during hyperemia. The relationship between the quantitative degree of coronary artery narrowing and the maximal hyperemic response was first elucidated by Gould in 1974.[6] Resting myocardial perfusion is normal until the luminal diameter narrowing of a coronary artery exceeds 90% to 95%. With maximal coronary hyperemia produced by dipyridamole, Gould demonstrated a progressive decrease in the hyperemic response associated with increasing degrees of stenosis above a threshold of 50% diameter narrowing.

Since the work of Gould, it has become widely recognized that multiple factors beyond focal percent stenosis can also affect the degree of hyperemia achievable in diseased vessels. These include stenosis length, myocardial mass distal to the stenosis, plaque composition, diffuse atherosclerosis, nonatherosclerotic microvascular disease, and endothelial dysfunction.[7,8] In general, a significant reduction in maximal hyperemia is usually present when stenosis severity exceeds 70%.[9] However, when compared to assessment of fractional flow reserve (FFR), considered the gold standard only 35% of vessels visually assessed as having 50% to 70% stenosis manifest a decrease in maximal hyperemia.[10] With quantitative coronary angiography, only one-third of vessels with more than 50% stenosis manifest normal hyperemic response.[11]

The ability of nuclear MPI to assess the hyperemic response is related to the degree of extraction of the myocardial perfusion tracer

TABLE 18–1. Available Single-Photon Emission Computed Tomography Radiopharmaceuticals

Radiopharmaceutical	Isotope Half-Life (hours)	Energy (keV)	Protocol	Injected Dose (mCi)	Radiation Dose (mSv)
^{99m}Tc-sestamibi OR	6	140	Stress only	5–12	1–3
^{99m}Tc-tetrofosmin			Stress/rest or rest/stress	5–12/15–36	5–13
^{201}Tl	73.1	69–83	Stress/redistribution (or rest/redistribution)	2.5–3.5	11–15

employed during its first pass through the myocardium. The amount of the injected tracer in the myocardium at the time of imaging (net extraction) is a function of the proportion extracted by the myocardium (extraction fraction) and the amount retained at the time of imaging. With the exception of oxygen-15 water, which is generally used only for research purposes, all available nuclear radiopharmaceuticals manifest a roll-off in extraction as coronary flow reaches high levels. Because moderate stenoses may produce a decrease in flow only at very high flow rates, the net extraction is one of the most important characteristics of perfusion tracers. Figure 18–2 illustrates the net extraction of the various SPECT and PET myocardial perfusion tracers. Figure 18–3 illustrates a highly extracted and retained PET tracer (Flurpiridaz-F18) and compares it to ^{99m}Tc-sestamibi.[12]

Thallium-201

The monovalent cation thallium is a potassium analog that is avidly extracted from the blood by myocardial cells. A cyclotron-generated radionuclide with a half-life of 73 hours, ^{201}Tl emits photons at 69 to 80 keV (90% abundance) and at 167 keV (10% abundance). Because of its relatively long half-life of 73 hours, the absorbed radiation dose per unit injected is much higher with ^{201}Tl than with ^{99m}Tc agents. For the same radiation dose to the patient, approximately one-tenth as much radioactivity with ^{201}Tl can be injected compared with ^{99m}Tc, making imaging times longer and generally providing lower information density ("counts") in the clinical images. ^{201}Tl has superior physiologic properties for MPI compared with the ^{99m}Tc agents. Unlike the ^{99m}Tc agents, with ^{201}Tl, the linear relationship between myocardial blood flow and ^{201}Tl uptake is more maintained during hyperemic stress up to high levels of flow (approximately > 3 mL/min/g) before the previously noted roll-off in uptake occurs[13] (see Fig. 18–2). Unbound within the myocardial cells, ^{201}Tl redistributes over time[14,15]; its initial distribution is proportional to regional myocardial perfusion, and at equilibrium, the distribution of ^{201}Tl is proportional to the regional potassium pool, which represents viable myocardium.[16] By virtue of these properties, myocardial perfusion defect reversibility can be imaged at multiple times with a single injection of ^{201}Tl. The mechanisms of ^{201}Tl redistribution include differential washout rates between hypoperfused but viable myocardium and normal zones, and washin from the blood to initially hypoperfused zones. For practical purposes, the time it takes for ^{201}Tl to reach its ultimate distribution in viable myocardium varies, such that delayed redistribution imaging (at 24 hours rather than 3-4 hours) is commonly used to gain the greatest amount of information from thallium studies regarding defect reversibility and myocardial viability.[17,18]

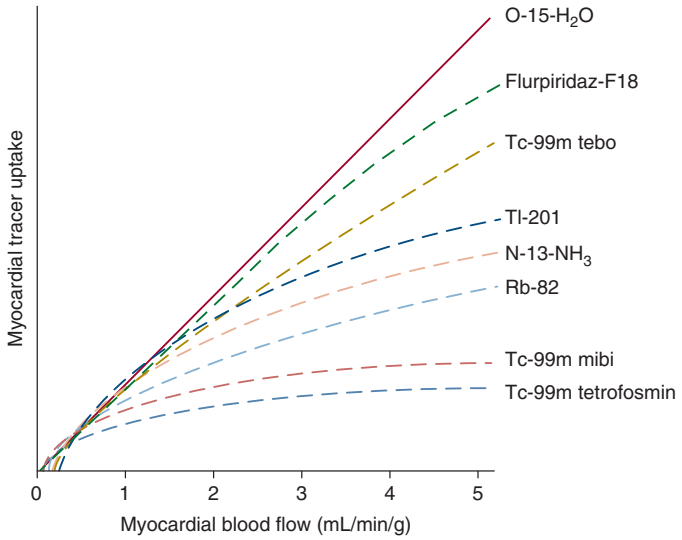

FIGURE 18–2. Relationship between tracer uptake and myocardial blood flow: theoretical considerations. O-15-H_2O, oxygen-15 water; N-13-NH_3, nitrogen-13 ammonia; tebo, teboroxime; mibi, sestamibi; Rb, rubidium; Tc-99m, technetium-99m, Tl-201, thallium-201.

The washout rate of ^{201}Tl is a function of the concentration gradient between the myocardial cell and the blood. Hyperinsulinemic states drive thallium into cells, leading to reduced blood ^{201}Tl concentrations and slowing redistribution; thus carbohydrates are avoided prior to and for 4 hours following ^{201}Tl injection.[13] An inverse relationship between the degree of coronary stenosis and subsequent redistribution of ^{201}Tl (ie, late redistribution) has been reported.[18] Late redistribution of ^{201}Tl—that is, defect reversibility seen on 24-hour imaging and not seen on standard 4-hour redistribution imaging—was reported to be common with standard ^{201}Tl SPECT stress/4-hour/late redistribution protocols.[19] 24-hour imaging was also shown to detect a substantially greater number of viable segments than stress/reinjection protocols ($P < .0001$).[17]

^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin

^{99m}Tc is produced from a molybdenum-99 generator, has a half-life of 6 hours, and emits monoenergetic gamma rays at 140 keV. The greater count rates achieved clinically with ^{99m}Tc agents compared to ^{201}Tl result in, improved image quality. Following extraction from the blood, ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are quickly bound by mitochondria, and only a limited amount of myocardial washout (or washin) occurs over time.[13,20] Thus, with these tracers, separate rest and stress injections are required to evaluate perfusion defect reversibility. A drawback of both perfusion tracers is that they exhibit a greater roll-off of extraction with increasing coronary flow and lower net extraction by the myocardium than thallium.[21] Another drawback of the ^{99m}Tc tracers is their gastrointestinal excretion, resulting in greater hepatic and gastrointestinal uptake than thallium, not infrequently interfering with inferior myocardial wall visualization, particularly after rest injection.[13]

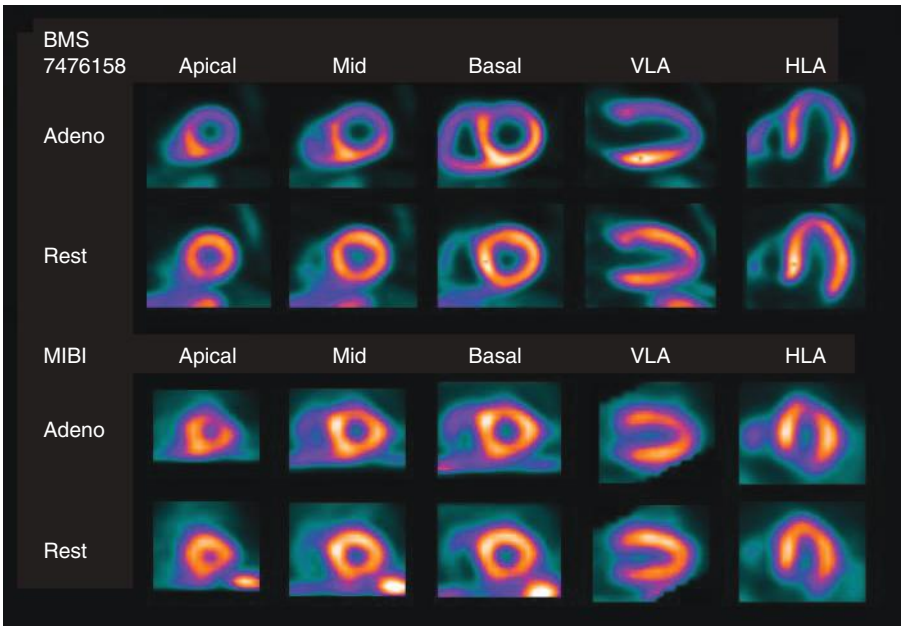

FIGURE 18–3. Case example of adenosine (Adeno) PET myocardial perfusion imaging study from the Lantheus Medical Imaging phase II clinical trial to evaluate flurpiridaz-F18 as a myocardial perfusion imaging agent. The subject is an 87-year-old woman with shortness of breath and prior percutaneous coronary intervention. Positron emission tomography perfusion images using flurpiridaz-F18 (*top two rows*) show a large severe reversible defect in the left anterior descending (LAD) coronary artery territory, in contrast to the ^{99m}Tc–sestamibi (MIBI) SPECT images (*bottom two rows*) in which the reversible defect is much smaller. Invasive coronary angiography revealed a 100% occlusion resulting from in-stent restenosis in the LAD. HLA, horizontal long axis; VLA, vertical long axis; BMS, Bristol-Myers Squibb.

From a practical standpoint, a main advantage of the ^{99m}Tc agents is greater flexibility than provided by ^{201}Tl. Because of their mitochondrial binding, they do not require that imaging commence immediately after the stress injection for maximal sensitivity in detecting perfusion defects. In contrast, with ^{201}Tl, imaging must be performed soon after stress testing (recommended to begin within 10-15 minutes) because rapid redistribution can cause mild perfusion defects to become undetectable by the time imaging begins. ^{99m}Tc sestamibi or tetrofosmin, imaging can commence as late as 2 hours after injection. Additionally, when patient motion, soft tissue attenuation, or other artifact is considered to be responsible for the production of a perfusion defect, image acquisition can simply be repeated (eg, in the prone position[22]), without concern that defects may no longer be detectable due to redistribution of the tracer.

SPECT-MPI STRESS PROTOCOLS

Patient Preparation for Stress Imaging: Anti-Ischemic Medications and Caffeine-Containing Compounds

In general, for purposes of diagnosis or initial risk stratification, stress nuclear MPI is performed with the patient off anti-ischemic medications,[23] because these medications may limit the development of ischemia during the stress test. When feasible, use of beta-blockers or long-acting calcium channel blockers should be discontinued for 48 hours before and long-acting nitrates should be discontinued for 12 hours before stress imaging.[23] With respect to exercise, lower peak heart rates would be achieved in patients on beta-blockers, reducing sensitivity for detection of hemodynamically significant CAD. It has also been shown that patients with normal exercise SPECT-MPI who achieve less than 80% to 85% maximum predicted heart rate (MPHR) are at greater prognostic risk than those who achieve maximal workload.[24,25] With respect to pharmacologic stress, it has been[26] reported that compared with SPECT-MPI performed off cardiac medications, dipyridamole SPECT-MPI performed on medications was associated with smaller reversible perfusion defects and a marked lowering of overall sensitivity for detecting disease in individual vessels (62% vs 92%).[27] Another study has demonstrated that acute beta blockade reduces the size of adenosine stress myocardial perfusion defects and doubles the likelihood of false-negative studies (14.3% vs 28.6%).[28] Although *initial risk stratification* studies are generally performed *off cardiac active medications*, potentially useful clinical information regarding ischemia in daily life can be derived from exercise or pharmacologic SPECT-MPI performed on cardiac medications.[23]

With respect to caffeine, patients should be off of compounds containing caffeine or theophylline as well as cardiac-active medications prior to vasodilator stress testing.[29] In general, discontinuation of caffeine-containing medicines, foods, or beverages for 24 hours prior to use of adenosine or dipyridamole and 12 hours prior to use of regadenoson is recommended.[23,30] Methylxanthines, such as theophylline or caffeine, block adenosine binding and can reduce the coronary vasodilation effects of adenosine, regadenoson, or dipyridamole, leading to false-negative stress perfusion studies. In a recent multicenter randomized study, patients underwent two regadenoson stress MPI procedures, once with and once without caffeine prior to regadenoson administration. In the scan in which the patients had received caffeine prior to regadenoson stress, there was a shift of the MPI results to a lower ischemia category in a majority of patients, and the number of reversible segments decreased by 60%.[31] The results of this study were added to the regadenoson package insert in 2011.[32] Given variations in the amount of caffeine in coffee, tea, and various foods as well as interindividual variations in the half-life of caffeine in the blood, abstinence from caffeine for the longer period for all agents (24 hours) would be preferred. A recent study found residual serum caffeine in 8% of participants despite careful instruction prior to the study.[42]

The recommendations are that even patients avoid caffeine for 24 hours prior to their study, in case there is a need for using pharmacologic stress. If a patient fails to achieve 85% of MPHR during exercise, regadenoson can be injected prior to tracer injection while the patient is still exercising or immediately after, as discussed below provided the patient is off of caffeine.[33,36] Regarding supplementing an inadequate exercise test with regadenoson, injecting regadenoson during a slow walk recovery and verifying the absence of ischemic ST changes prior to injecting regadenoson may provide a greater margin of safety than injecting regadenoson at peak exercise stress.[36] Of note, even in patients referred for pharmacologic stress, 50% to 60% of patients are able to undergo adequate exercise stress allowing the measurement of exercise capacity and avoiding stress pharmacologic drug costs and side effects.[34,35] Dipyridamole-containing medications should be held for 48 hours prior to adenosine or regadenoson stress, because they can potentiate the effects of the vasodilator stress agents.

EXERCISE STRESS PROTOCOLS

Exercise stress is preferred over pharmacologic stress for use with SPECT-MPI in patients who can exercise adequately because it allows assessment of exercise capacity, heart rate (HR), and blood pressure

(BP) responses (including HR reserve and HR recovery); symptoms; and ST-segment response (although such ST changes may occur with pharmacologic stress). This provides additional clinical information that can be useful in clinical decision making.[23,37] For exercise SPECT-MPI, the tracer is injected at maximal stress. Exercise is continued for an additional 1 minute at peak workload to ensure that the myocardial tracer uptake reflects distribution of blood flow at the time of maximum flow achieved. Unless contraindicated, exercise stress testing should be maximal, terminated by symptoms and not based on the HR achieved. If less than 85% of age-adjusted MPHR (220 – age) is achieved and unless there is clear clinical or ECG evidence of ischemia, the stress is considered inadequate, and switching to pharmacologic stress should be considered. When the exercise duration is less than 3 minutes on the Bruce protocol (or give or more metabolic equivalents [METs]), a normal SPECT is associated with a much greater event rate than in those with greater exercise capacity, similar to that seen in patients deemed unable to exercise.[38] Postexercise stress imaging routinely commences 15 minutes after stress, but , as noted above, with the ^{99m}Tc perfusion tracers imaging can begin up to 2 hours after stress injection. The advantage of starting imaging earlier is that it increases the opportunity to observe stress-induced wall motion abnormalities ("stunning") during gated SPECT acquisition.[39] Initiating image acquisition too early, before the patient has not fully recovered from stress, potentially introduces artifactual defects related to increased depth of respiration very early after stress, causing the heart to gradually move cephalad during the early portion of SPECT acquisition. ("upward creep of the heart")[40]

PHARMACOLOGIC STRESS PROTOCOLS

Vasodilator Stress (SPECT or PET)

For patients who cannot achieve an adequate level of exercise (≥ 85% of MPHR[23]) pharmacologic stress testing is the preferred approach to stress.[41] The preferred pharmacologic stress agents for SPECT- and PET-MPI are coronary vasodilators: adenosine, regadenoson, or dipyridamole (Table 18–2). These agents provide a three- to five-fold increase in coronary flow. Dipyridamole blocks the cellular reuptake of adenosine, increasing the extracellular adenosine concentration. Increased extracellular adenosine results in coronary vasodilation. Regadenoson is a selective A_{2A} adenosine receptor agonist, approved for clinical use in the United States in 2008 questioning on the day of the study.[42] The diagnostic accuracies of SPECT-MPI using exercise or vasodilator stress have been found to be equivalent, despite the higher coronary flow rates associated with the vasodilators.[43] In patients who have taken dipyridamole-containing medications in the 48 hours prior to testing, adenosine or regadenoson administration should be avoided, because it could result in overstimulation of adenosine receptors.[30]

Vasodilator stress is frequently associated with chest discomfort and shortness of breath, even in normal subjects, and thus, unlike exercise, with vasodilator stress, these symptoms are not considered to indicate the presence of ischemia. Vasodilator stress frequently causes an increase in HR and a decrease in BP. With adenosine and dipyridamole, these changes are mild, but with regadenoson, the HR increase has been reported to be more marked.[29] The clinical assessment and hemodynamic responses to vasodilators are not useful in identifying patients in whom the pharmacologic effects of adenosine or dipyridamole may have been blocked by caffeine. HR may increase with vasodilator stress even though myocardial blood flow increase may be blunted, and conversely, failure of HR or BP to change with adenosine stress does not imply lack of myocardial perfusion response.[44] However, it has been shown that resting tachycardia and failure to mount a reflex tachycardia in response to vasodilator stress are associated with an increase in mortality risk.[45,46]

Dipyridamole Infusion Dipyridamole is usually infused at 140 μg/kg/min for 4 minutes (total dose 0.56 mg/kg), but some investigators have recommended increasing the dose by 50%.[43] The maximal effect occurs approximately 3 to 4 minutes after end of the infusion, and hyperemia persists for approximately 20 to 30 minutes. Mild transient adverse effects are common, including chest pain, shortness of breath, dizziness, and flushing. Severe adverse effects are rare, being noted in only 1 of 10,000 patients.[47] Persistent side effects or significant adverse events after dipyridamole, adenosine, or regadenoson stress can usually be reversed by intravenous aminophylline, usually 50 to 100 mg intravenously over 30 to 60 seconds. Because of the potential adverse effect of severe bronchospasm, dipyridamole is *contraindicated* for asthmatics.

Adenosine Infusion Adenosine is infused intravenously (140 μg/kg/min), usually over 4 to 6 minutes, with radiopharmaceutical administration at 2 to 3 minutes of infusion.[43,48] Transient side effects occur more frequently than with dipyridamole,[43] but because of the brief duration of action (approximately 13 seconds), reversal with aminophylline is rarely used. With adenosine, there is an increased incidence of transient advanced atrioventricular (AV) block. Adenosine is considered *contraindicated* for patients with second- or third-degree AV block, sick sinus syndrome, or bronchospasm.

Regadenoson Selective A_{2A} receptor agonists have the potential for reducing the high frequency of uncomfortable systemic adverse effects and the risk of bronchoconstriction in asthmatics that are associated with adenosine and dipyridamole (Fig. 18–4). At the time of this writing, regadenoson is the only selective A_{2A} adenosine receptor agonist to receive US Food and Drug Administration (FDA) approval, based on the results of two phase III studies that demonstrated equivalency

TABLE 18–2. Pharmaceutical Stress Agents

Stress Agent	Half-Life	Dose	Infusion Protocol	Inhibitors/Antidote
Regadenoson	2–4 min[a]	0.4 mg	10 s	Methylxanthines
Adenosine	< 10 s	140 μg/kg/min	4–6 min	Methylxanthines
Dipyridamole	40 min	140 μg/kg/min	4 min	Methylxanthines
Dobutamine	2 min	5–40 μg/kg/min	Increase every 3 min up to 40 μg/kg/min, often with atropine	Beta-blockers

[a]Intermediate half-life 30 minutes; terminal half-life 120 minutes; methylxanthines are caffeine, theophylline, and aminophylline.

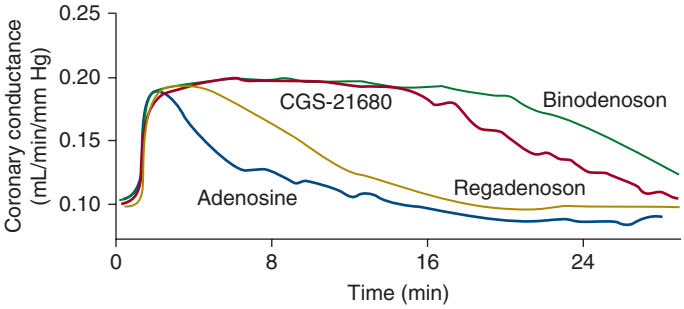

FIGURE 18–4. Time course of changes in coronary conductance caused by regadenoson (yellow), binodenoson (green), CGS-21680, a selective adenosine receptor agonist (red), and adenosine (blue). Reproduced with permission from Gao Z, Li Z, Baker SP, et al: Novel short-acting A2A adenosine receptor agonists for coronary vasodilation: inverse relationship between affinity and duration of action of A2A agonists. *J Pharmacol Exp Ther*. 2001 Jul;298(1):209-218.

to adenosine for the detection of reversible perfusion defects.[29] Regadenoson has become the most commonly used vasodilator stress agent used in the United States. Unlike adenosine and dipyridamole, which require infusions and weight-based dosing, regadenoson is injected over a 10-second period with a fixed dose (0.4 mg) in a prefilled syringe, without requiring an infusion pump.[30] Side effects have been reported to be better tolerated than adenosine.[29] The radiopharmaceutical is injected over 10 to 20 seconds after intravenous injection of regadenoson.[30] The peak effect is seen approximately 1 minute after injection, and peak blood flow lasts for approximately 2 minutes. There is a three-phase washout period with this agent, such that side effects can be more prolonged than with adenosine. Because of the longer physiologic effect of regadenoson, reversal of side effects with aminophylline is more commonly necessary with regadenoson than with adenosine.

Regadenoson is considered *contraindicated* for patients with second- or third-degree AV block or sinus node dysfunction unless a functioning pacemaker is present.[30] A large phase IV study (999 patients) has reported the safety of regadenoson in patients with stable chronic obstructive pulmonary disease or asthma, but appropriate resuscitative measures should be available in case bronchospasm should occur.[30,49] Regadenoson is well tolerated in patients with renal impairment, but there is increased frequency of diarrhea in patients with end-stage renal disease.[50-52] High-grade AV block/asystole may be the result of a vasovagal response, so atropine should be administered if no response to aminophylline is observed.[53] The regadenoson and adenosine package inserts were undated in 2014 to reflect that regadenoson and adenosine may lower the seizure threshold, and that if seizures occur, aminophylline is not recommended because it may prolong regadenoson- and adenosine-related seizures.[32]

Vasodilator Stress with Low-Level Exercise with SPECT-MPI It has become increasingly common to combine vasodilator stress with low-level exercise.[54] With dipyridamole, low-level exercise is begun after the end of dipyridamole infusion, and with adenosine, low-level exercise is performed during the infusion. With regadenoson, low-level exercise is started before injection, allowing the vasodilator and tracer to be injected during exercise or the regadenoson can be added to inadequate exercise as described above.[55-57] Exercise even at low levels reduces splanchnic blood flow and, thereby, hepatic uptake of ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin, facilitating early postinfusion imaging with these tracers (as early as 10-15 minutes following injection) compared to the 1-hour delay required when adjunctive exercise is not performed. Another key benefit of adjunctive exercise is a marked reduction in the frequency and severity of adverse effects from the vasodilator stress agents, possibly due to the increased attention to the task of walking inpatients who usually have reduced exercise capacity. Being able to perform low-level exercise also provides additional prognostic information.[58,59] Given all of these advantages, it is widely recommended that low-level exercise be combined with vasodilator stress for MPI when possible, with the exception of patients with left bundle branch block (LBBB) or paced rhythm in whom it is preferable not to have the increased HR associated with exercise.

Use in LBBB and Right Ventricular Pacing With exercise stress, patients with LBBB frequently demonstrate reversible defects in the septal wall in the absence of CAD. Because of the relationship between the increase in HR and the presence of perfusion defects without CAD in LBBB and paced ventricular rhythms, vasodilator stress is preferred over exercise in these patients; the vasodilator stress protocols are performed without adjunctive low-level exercise.[23] Stress modalities that do not increase HR as markedly as exercise, such as vasodilator stress without walking, are generally considered preferable in LBBB patients.[60] HR increases more with regadenoson stress than with adenosine; however, it has been reported that this does not result in an increase in perfusion defects in the left anterior descending (LAD) coronary artery or septal territories.[61] With exercise SPECT-MPI, the perfusion defect associated with LBBB in the absence of LAD CAD most commonly involves the interventricular septum with sparing of the apex of the left ventricle, a pattern that would be uncommon for LAD CAD.[27] Myocardial perfusion defects in the inferior and apical walls have also been reported in the absence of CAD in patients with prolonged right ventricular (RV) pacing.[43] Despite the high heart rate associated with regadenoson, no increase in the false-positive rate has been shown with this agent.

Dobutamine Stress (SPECT and PET)

An alternative to vasodilator stress is inotropic stress with dobutamine. At present, dobutamine stress is usually reserved for patients with asthma, patients with chronic obstructive pulmonary disease with bronchospasm, or patients who have ingested caffeine close to the time of testing. With the increased use of regadenoson, which has fewer contraindications, dobutamine stress nuclear MPI has markedly decreased in many nuclear laboratories. Dobutamine stress results in a lower-rate pressure product than exercise and a lower peak coronary blood flow with vasodilator stress. Adverse effects, including ventricular ectopy, are more common than with the vasodilator stress. The protocol used is the same as that used for dobutamine stress echocardiography. As with echocardiography, atropine is commonly used in addition to dobutamine if the maximal predicted heart rate is not achieved (> 85%).

SPECT-MPI IMAGING PROTOCOLS

Stress ^{99m}Tc-Sestamibi or ^{99m}Tc-Tetrofosmin Protocols

A variety of protocols can be used with these agents, including 2-day stress/rest, same-day rest/stress, same-day stress/rest, and dual-isotope. Because uptake and radiation dosimetry of these compounds are similar, the recommended acquisition protocols for these tracers are the same. After intravenous injection, the myocardial distribution of these agents does not change significantly over time. Therefore, in contrast to ^{201}Tl, which redistributes into viable myocardium, separate rest and stress injections are needed with ^{99m}Tc-sestamibi or ^{99m}tetrofosmin SPECT (Fig. 18–5)[43] to assess reversibility of perfusion defects. With these agents, if imaging artifact is suspected on supine images, additional prone

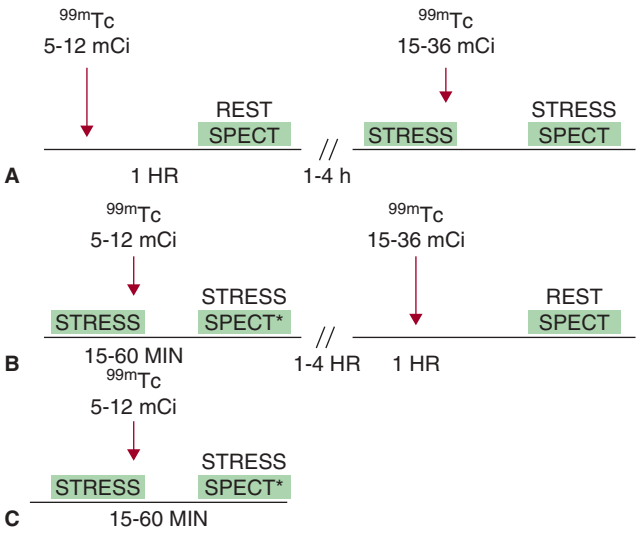

FIGURE 18–5. Same-day rest/stress (**A**), same-day stress/rest (**B**) and stress-only (**C**) technetium-99m (^{99m}Tc)-sestamibi or ^{99m}Tc-tetrofosmin protocols. An *asterisk* indicates where attenuation correction or imaging in multiple positions is recommended. SPECT, single-photon emission computed tomography.

imaging can be performed to increase the specificity of SPECT-MPI (Fig. 18–6).[22,43,62]

The most common ^{99m}Tc agent protocol is same-day low-dose rest/high-dose stress (see Fig. 18–5A).[43] The protocol takes approximately 2 to 4 hours. Compared to a stress-first protocol, there is a reduction in stress-defect contrast, because approximately 15% of the radioactivity observed at the time of stress imaging comes from the preexisting resting injection. Additionally, the protocol always involves two injections, not allowing for elimination of the rest if the stress is normal. An advantage of the rest/stress sequence is that the resting images can be inspected prior to stress testing, enabling the identification of patients with unexpected rest perfusion defects. For application in patients with acute chest pain, the protocol has the advantage of allowing for image assessment for perfusion defect on the resting scan prior to exercise and for cancellation of stress if unexpected perfusion defect is present.

The same-day low-dose stress/high-dose rest sequence (see Fig. 18–5B) has the advantage of optimal perfusion defect contrast, with no contribution from a prior rest injection. An important advantage is that the sequence allows for cancellation of the rest portion of the test if the stress images are normal. (see Fig. 18–5C).[43] The resultant "stress-only" protocol reduces the overall radiation dose of the SPECT-MPI procedure by 75% and reduces the overall time of the study for the patient by a similar amount. The principal drawback of this approach is that the count rates associated with the low dose stress images are low. In obese patients, in whom a low-dose injection may result in inadequate image quality, a 2-day stress/rest protocol may be preferred. Both stress and rest studies are obtained after injection of standard doses of ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin. Viability assessment with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin may be improved by the administration of nitroglycerin prior to the rest-injection study.[43,64]

Stress ^{201}Tl Protocols

As noted, unlike ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin, which are fixed within the myocardial cells, ^{201}Tl redistributes over time. This property has important implications for acquisition protocols. Initial poststress image acquisition should be started promptly (within 15 minutes) because early ^{201}Tl redistribution can decrease sensitivity for CAD if poststress imaging is delayed. The initially described stress/redistribution protocol is still commonly used (Fig. 18–7). It was later reported that reinjection with a small dose of ^{201}Tl could improve detection of perfusion defect reversibility.[65,66] Sublingual nitroglycerin prior to ^{201}Tl reinjection may further improve assessment for defect reversibility. If unexpected, nonreversible defects are found at 4-hour imaging (see Fig. 18–7A), additional 24-hour imaging has been reported to improve detection of defect reversibility.[17,18] If late redistribution imaging is performed, a separate rest injection prior to this late imaging should not be given, because resting hypoperfusion could result in incorrect information regarding myocardial viability.

Dual-Isotope Protocols

Because of the increased radiation burden associated with the dual-isotope approach, its use is not recommended unless both ischemia and viability testing are needed. A rest ^{201}Tl/stress ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin dual-isotope SPECT protocol (see Fig. 18–5B),[48] takes advantage of the Anger camera's ability to collect data in different energy windows. It is usually performed with separate rest/stress acquisitions and can include redistribution thallium images either before the stress study (see Fig. 18–7B) or at 24 hours (after stress) (see Fig. 18–7B) if a rest defect is present. An alternative rapid "reverse dual" protocol (stress thallium/rest ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin) using lower radionuclide doses and camera systems capable of faster acquisitions has been reported, allowing the use of ^{201}Tl as the stress agent (preferable because of superior net extraction compared with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin) while maintaining a relatively low radiation burden for the patient.[67]

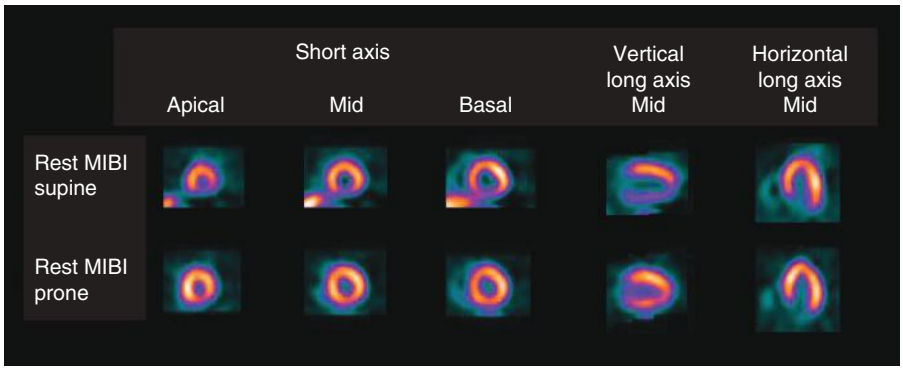

FIGURE 18–6. Rest sestamibi (MIBI) single-photon emission computed tomography (SPECT) images in the supine position (*top*) and prone position (*bottom*) in a 55-year-old patient with a low likelihood of coronary artery disease. Prone images are normal, demonstrating that the apparent inferior wall perfusion defect on the supine images is secondary to soft tissue attenuation. Normal wall motion was noted on gated SPECT-myocardial perfusion imaging (MPI). Gated resting MPI: end-diastolic volume 55 mL, end-systolic volume 35 mL, and ejection fraction 55%. Reproduced with permission from Germano G, Berman DS: *Clinical Gted Cardiac SPECT*. Armonk: Futura; 1999.[62]

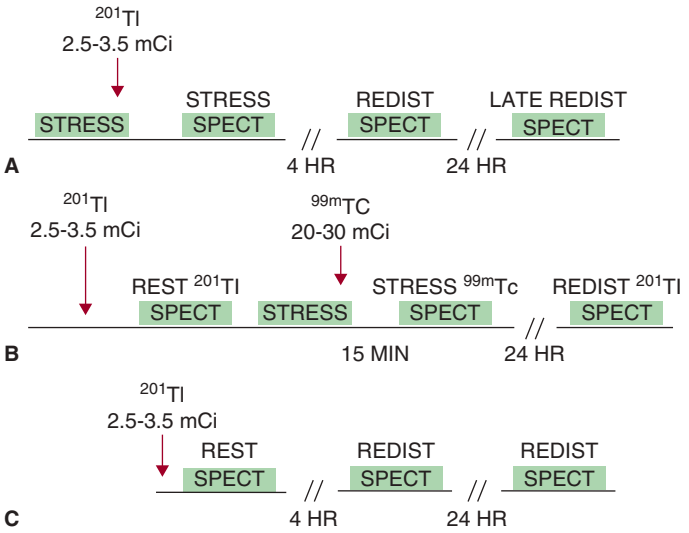

FIGURE 18–7. Thallium-201 (^{201}Tl) protocols. **A.** Stress/reinjection/late redistribution. **B.** Resting thallium-201 (^{201}Tl)/technetium-99m (^{99m}Tc)-sestamibi or ^{99m}Tc-tetrofosmin dual-isotope single-photon emission computed tomography (SPECT) myocardial perfusion imaging protocol. Most commonly, only rest and stress imaging are performed. When resting defects are present, redistribution imaging is recommended. **C.** Rest/redistribution myocardial viability protocol. REDIST, redistribution.

Stress-Only Imaging

Standard myocardial perfusion SPECT imaging protocols traditionally have consisted of a rest acquisition first followed by a second acquisition after exercise or pharmacologic stress. As noted above, stress-first protocols offer the opportunity to maximize the number of studies with stress-only imaging, resulting in several potential benefits.[87-90] The rest study is not performed when stress imaging is not clearly normal; thus there is reduced imaging time, lower radiation exposure, and lower cost.[88] In addition, a 40% lower radiation exposure to nuclear cardiology staff has been reported.[91]

Limitations of the stress-only protocol are that transient ischemic dilation (TID) and stunning (decrease in ejection fraction [EF] or wall motion on poststress compared with rest imaging or development of poststress worsening of wall motion) cannot be assessed.[88] The approach can also result in a higher false-positive rate than rest/stress imaging because failure of a minor defect to change between rest and stress can be used to identify artifact. The use of attenuation correction or two-position imaging is of greater importance for the stress-only protocol; they increase the percentage of normal stress images and thus reduce the percentage of patients who have to return for rest imaging.[88] A challenge for implementation is the need for real-time review of the stress images to decide if rest imaging is required. Automated quantitative analysis can be a useful aid in making this determination. Because patients undergoing pharmacologic stress are, as a group, at higher risk, it has been suggested that the stress-only approach may be more appropriate for patients who can exercise. It is not used in patients with known or expected resting perfusion defects.[88] Multiple studies have documented that normal stress-only MPI studies are associated with the same excellent prognosis as normal rest/stress MPI studies.[89,92-94]

SPECT Myocardial Viability Protocols

Although PET and MRI are considered superior for viability assessment, rest/redistribution ^{201}Tl SPECT-MPI is the optimal SPECT approach for assessment of myocardial viability[14] (see Fig. 18–7C; Fig. 18–8). Theoretically, the effectiveness of ^{201}Tl SPECT-MPI for viability assessment could be improved by administration of nitroglycerin prior to the rest injection. Importantly, 24-hour imaging may show additional redistribution compared to 4-hour imaging,[17,43] because, as noted above, in the setting of a critical coronary stenosis with reduced resting blood flow, the time to complete redistribution may be delayed. Stress-redistribution and late imaging for assessment as well as dual-isotope protocols can also be used to assess myocardial viability as discussed above.

Rest ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin can also be used for assessment of myocardial viability. However, they are not considered optimal, because unlike ^{201}Tl, they reflect only myocardial perfusion and do not redistribute into the potassium pool. These agents underestimate viability in the presence of myocardial hibernation with resting hypoperfusion. To assess hypoperfused but viable myocardium with these agents, administration of nitroglycerin prior to rest injection is recommended.[64,68]

TECHNICAL AND RADIATION DOSE CONSIDERATIONS

New Generation of SPECT-MPI Instrumentation

Dramatic advances in cardiac SPECT instrumentation have been introduced to clinical practice in the recent years, allowing both a decrease in imaging time and a reduction in patient radiation dose. These developments include innovative designs of the gantry dedicated to cardiac imaging, new photon detectors, and new collimators.[69,70] In parallel, software reconstruction methods incorporating resolution recovery and computed tomography (CT)–based attenuation correction have been developed, which allow further reduction in imaging time or radiation dose.[71] Two hardware vendors have introduced compact cardiac scanners with cadmium-zinc-telluride (CZT) detectors, coupled with high-sensitivity collimation (multipinhole or high-sensitivity, parallel-hole—focusing on the myocardium). It is estimated that more than 300 of such high-efficiency cardiac scanners were in use worldwide as of 2015, and the number is increasing by about 100 per year. The new scanners can achieve simultaneous improvement in sensitivity (five to eight times higher than with conventional MPI SPECT) and in image resolution (up to two times higher). To date, these new techniques have been utilized primarily to dramatically reduce the routine scan time. With faster imaging, patient comfort is markedly improved,

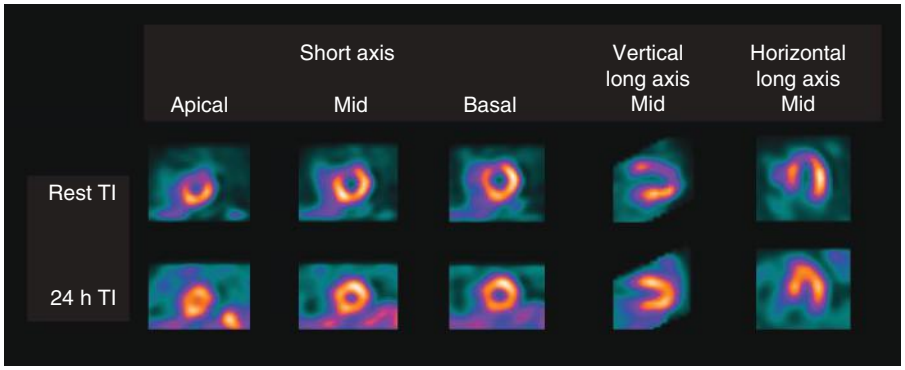

FIGURE 18–8. Rest and 24-hour redistribution thallium-201 (^{201}Tl) single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) of a 75-year-old man with atypical angina showing a large amount of resting ischemia in the left anterior descending (LAD) artery. Coronary angiography subsequently revealed a 95% proximal LAD stenosis. Of note, the left ventricle was larger at rest than at the time of redistribution imaging. The stress SPECT-MPI study was canceled in this patient because of the unexpected perfusion defect.

and motion artifacts are reduced. However, these systems also allow low-dose (~ 4-6 mSv)[72] stress/rest or rest/stress imaging at fast imaging times or ultra-low radiation dose (~ 1 mSv) stress-only scans at standard imaging times (10-12 minutes).[73-75]

Two-Position Imaging

One of the most difficult problems in interpretation of SPECT-MPI is the differentiation of artifactual from true perfusion defects. Soft-tissue attenuation and patient motion are the two major sources of artifact. Imaging the patient in two different positions decreases both types of artifacts. Regarding soft-tissue attenuation, shifting of attenuating organs occurs between supine and prone positions, particularly involving the breast and the diaphragm, the latter determining the position of subdiaphragmatic structures. Imaging the patient in the prone position with the nuclear detector rotating underneath the patient, as well as the standard supine imaging, decreases the frequency of attenuation artifacts in the inferior wall and breast and also decreases motion artifact (see Fig. 18–6).[76] However, prone imaging alone may create artifactual anteroseptal defects caused by the more pronounced sternal attenuation in this position.[43] As a consequence, combined prone and supine imaging (two-position imaging) with the sestamibi or tetrofosmin has been described. With two-position SPECT, perfusion defects are considered present only when they are seen on the images in both positions.

Patients with inferior wall defects on supine SPECT-MPI but normal on prone SPECT-MPI were shown to have as low a risk of subsequent cardiac events, as patients with normal supine-only studies.[76] Visual analysis of prone and supine images has demonstrated improved interobserver agreement as compared to supine-only analysis.[77] A quantitative method for computer-based interpretation of combined supine and prone sestamibi SPECT images has recently been reported.[22] With this approach, supine and prone images are compared to their respective normal databases, and only regions found concordantly abnormal by both positions are considered abnormal. The combined quantitation has demonstrated an increase in the normalcy rate without a loss of sensitivity. Regarding motion artifact, two-position imaging decreases false-positive findings, because motion artifact, occurring at the same time and to the same degree in two separate acquisitions, is unlikely.

With the more recently available CZT detector instrumentation, additional novel protocols have been developed with two rapid sequential scans in two patient positions (supine-upright[78] or supine-prone[79]—depending on the scanner). As with the conventional camera systems, two-view imaging provides improved differentiation of true perfusion defects from artifacts with these systems. With one of the systems using a multipinhole technology, the addition of prone imaging may allow for detection of position-related artifacts, which may occur with limited field-of-view gantry of the new scanners.[80] In the other system using a standard semiupright position, the use of an additional supine acquisition reduces artifact in the same manner as it does with the conventional systems.[77]

Attenuation Correction

Several manufacturers offer hardware and software implementation of attenuation correction protocols for SPECT and PET-MPI. Attenuation correction is considered mandatory for PET-MPI because of more pronounced attenuation effects in positron emission. Several reports have compared the diagnostic accuracy of attenuation-corrected and non–attenuation-corrected SPECT-MPI using a variety of commercially available approaches. In general, these studies have demonstrated improved specificity with no change in overall sensitivity by visual analysis[81,82] and overall improvement in accuracy for detection of obstructive coronary artery disease by automated computer analysis in a large cohort.[83] Despite these considerations, attenuation correction is not yet widely used for SPECT-MPI, because of the increased cost and complexity of the attenuation correction hardware, the potential for imaging artifacts resulting from misregistration of attenuation maps, additional radiation dose and imaging time, and the lack of a common approach to its commercial implementation by vendors.[84] These difficulties—with the exception of the misregistration artifact—are lessened with the use of hybrid SPECT/CT or PET/CT systems. With these systems, attenuation correction is routinely applied. By observing both attenuation-corrected and non–attenuation-corrected images, misregistration artifacts are reduced. The SPECT/CT or PET/CT approaches offer the important benefit of providing the capability to assess coronary artery calcium (CAC) and myocardial perfusions in a single examination. Recently, methods for automated alignment for attenuation correction CT scans or even calcium CT scans with MPI images have been developed by vendors,[85,86] which may allow further improvement of clinical protocols.

Minimizing Radiation Dosimetry/Best Practices

The As Low As Reasonably Achievable (ALARA) Principle highlights the goal to minimize radiation dosimetry in all patients while maintaining high-quality imaging. In 2010, ASNC set an initial goal to decrease the radiation dose in at least 50% of SPECT and PET-MPI studies to 9 mSv or less.[95] Table 18–3 lists best practices that can help achieve this goal and/or minimize each patient's effective radiation dose.[95-97] The standard rest/stress ^{99m}Tc-based study is associated with an 11-mSv radiation dose. The annual background radiation dose is 3 to 4 mSv.[98]

Stress/rest protocols are preferred because they allow the potential for performance of stress-only SPECT if stress studies are normal. Stress-only ^{99m}Tc studies decrease the radiation dose by approximately 75%. Furthermore, as noted above, ultra-low radiation dose (~1 mSv) stress-only scans at standard imaging times (10-12 minutes) can now be achieved with CZT detector systems.[73-75] ^{99m}Tc-based protocols are preferred over ^{201}Tl protocols due to more favorable radiation dosimetry. For example, a stress-only ^{99m}Tc-based study with a standard camera is associated with approximately a 2.5-mSv dose compared with an 11- to 15-mSv dose of a stress ^{201}Tl study. Dual-isotope (rest ^{201}Tl/stress ^{99m}Tc) protocols are the highest radiation dose protocols; therefore, they should be avoided unless combined perfusion and viability imaging is needed. Because of the very short half-life of each of the PET-MPI tracers, rest/stress PET-MPI is associated with a very low radiation dose of approximately 2 to 3 mSv. Figure 18–9 includes the comparison of radiation stress scan doses from various MPI techniques, including those achievable with latest generation equipment for SPECT-MPI.

TABLE 18–3. Minimizing Radiation Dosimetry/Best Practices

Use stress/rest protocols instead of rest/stress protocols. Use stress-only protocols if stress normal.
Use weight-based dosing.
Use recommended radiopharmaceutical doses (see Table 18–1).
Avoid ^{201}Tl protocols (^{99m}Tc-based protocols are preferred).
Avoid dual-isotope (rest ^{201}Tl/stress ^{99m}Tc) protocols.
Use positron emission tomography when available.
Use newer high-efficiency solid-state single-photon emission computed tomography cameras with high-sensitivity crystal material.
Use advanced reconstruction software.

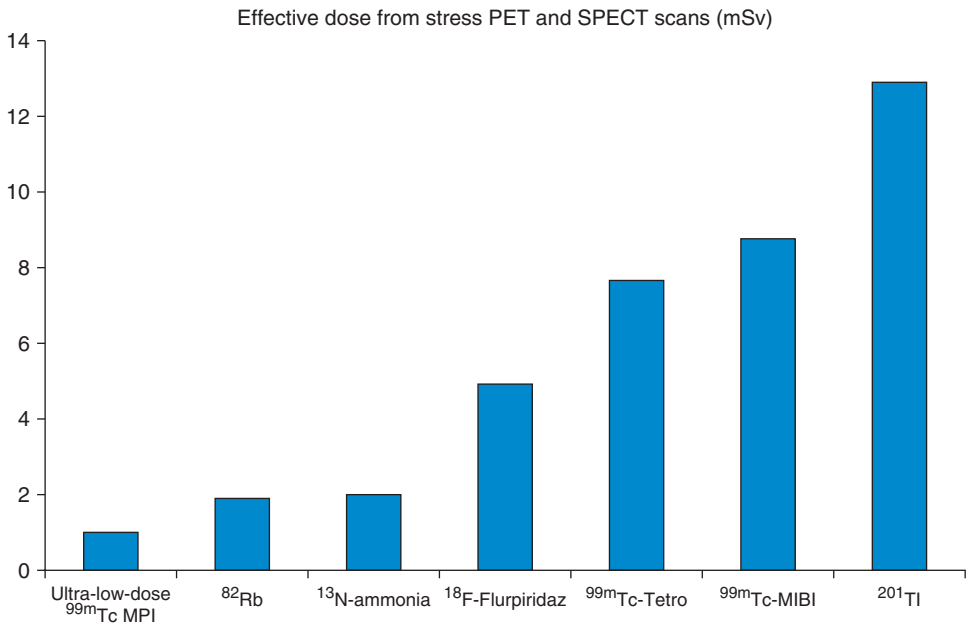

FIGURE 18–9. Effective radiation doses delivered to an adult patient for typical injected activities in one stress myocardial perfusion positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scan (standard and ultra-low-dose protocols). Activities are 40 mCi for ^{82}Rb, 20 mCi for ^{13}N-ammonia, 7 mCi for ^{18}F-Flurpiridaz, 30 mCi for ^{99m}Tc-tetrofosmin or ^{99m}Tc-MIBI, 3.5 mCi of ^{99m}Tc-MIBI for ultra-low-dose protocol with high-efficiency-MPS[73,74] and 2.5 mCi for ^{201}Tl.[409-414] MPS, myocardial perfusion scintigraphy; MIBI, sestamibi.

BASICS OF INTERPRETATION OF SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY–MYOCARDIAL PERFUSION IMAGING

The interpretation of SPECT and PET-MPI is performed by visual or computer-based quantitative methods.

PERFUSION DEFECTS

Perfusion defects are characterized by their type as well as their extent and severity. The various defect types are illustrated in Fig. 18–10 for stress and rest SPECT-MPI and in Fig. 18–11 for rest SPECT-MPI viability patterns. These perfusion defect patterns also apply to SPECT-MPI. Figure 18–11A illustrates the pattern seen in hibernating myocardium. The distribution of SPECT abnormalities provides information regarding the location of coronary artery stenoses. Representative examples of SPECT defect locations associated with individual coronary artery stenoses are illustrated in Figs. 18–12 and 18–13.

Visual Semiquantitative Segmental Scoring

Semiquantitative perfusion scoring systems standardize the visual interpretation of scans and provide global indices for overall assessment of extent and severity of perfusion abnormality. Furthermore, they are more systematic and reproducible than simple qualitative evaluation.

Seventeen-Segment Model The 17-segment scoring system for SPECT- and PET-MPI is used as recommended for all noninvasive cardiac imaging modalities by the American Heart Association in 2002, (Fig. 18–14).[99] Segmental assignment is based on three short-axis slices (four distal [apical], six middle, and six basal) representing the entire left ventricle (LV), with the apical segments visualized in a midventricular long-axis image. Each of the 17 segments has a distinct descriptor and is scored for defect severity using a five-point system (0 = normal; 1 = mild [equivocal]; 2 = moderate; 3 = severe reduction of a radioisotope; and

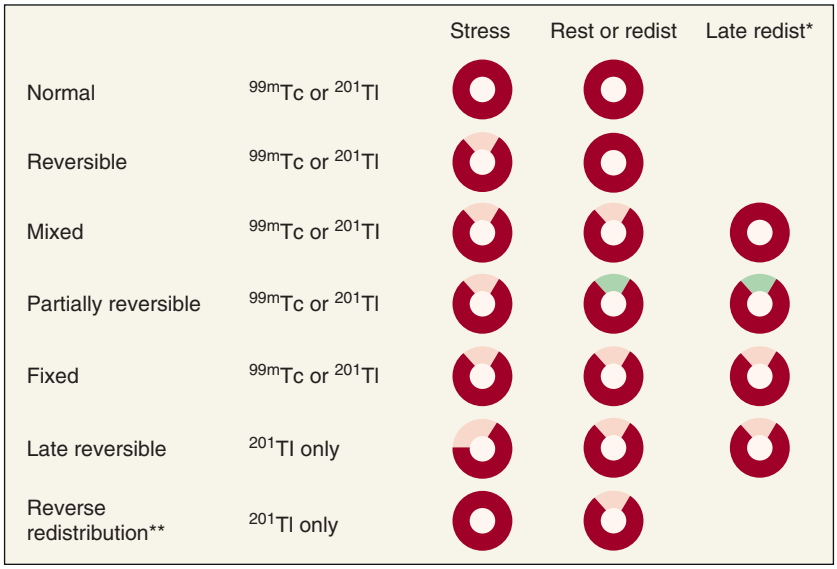

FIGURE 18–10. Patterns of stress/rest or redistribution (redist) single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) defects. Red represents normal tracer update; pink represents a definite perfusion defect; green represents less severe but still definite perfusion defect (seen in the partially reversible defect example). *Single asterisk* indicates redistribution (redist) or reinjection image. *Double asterisk* indicates stress/redist or rest/redist. ^{99m}Tc, technetium-99m–sestamibi or –tetrofosmin; ^{201}Tl, thallium-201.

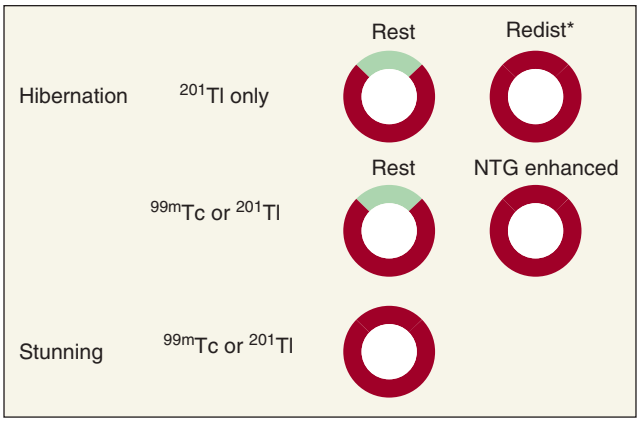

FIGURE 18–11. SPECT patterns of perfusion defects associated with myocardial viability and resting regional contractile abnormality. Green represents perfusion defect. The *asterisk* indicates 4- or 24-hours redistribution (Redist). NTG, nitroglycerin; ^{201}Tl, thallium-201.

4 = absence of detectable tracer uptake).[23,27] Severe reversible perfusion defects with scores of 3 or 4 (see Fig. 18–12 *second row* and *bottom row*; see Fig. 18–13 *second row* and *bottom row*) can be reported as consistent with a critical (≥ 90%) coronary stenosis.[27] The differences between the 17- and the previously described 20-segment models are that with 17-segment scoring, the smaller size of the distal (apical) short-axis slice is accounted for by four versus six segments and the apex is one rather than two segments, more accurately reflecting the size of these segments.

Summed Scores Segmental scoring systems lend themselves to the derivation of summed segmental scores as global indices of perfusion.[23,100] The overall extent and severity of perfusion defects is reflected by the summed stress score (SSS), the summed rest score (SRS), and the summed differences score (SDS), with the latter defined by SSS – SRS and measuring the degree of reversibility. Risk groups may be defined using SSS categories (Table 18–4).[23,27]

Percent Myocardium Abnormal We subsequently describe expression of overall perfusion defects as percent myocardium involved (percent stress, percent reversible, and percent fixed) and now routinely use this approach for clinical reporting and prognostic publications.[25] The conversion of summed scores to percent myocardium is accomplished by dividing the summed scores by the worst segmental score possible in the specific model used (68 for 17 segments, 80 for 20 segments) and multiplying by 100. The benefits of this approach are that it provides a measure with intuitive implications (percent myocardium hypoperfused) not possible with the unitless summed scores, it can easily be applied with scoring systems using varying numbers of segments (eg, 17, 20, 14, 12), and it is applicable to quantitative methods that directly measure these abnormalities as percent myocardium (see Table 18–4). In general, risk groups by the percent stress abnormal, which correlate with SSS risk groups, are as follows: % to 1%, normal; 2% to 4%, borderline/equivocal; 5% to 9%, mildly abnormal; 10% to 14%, moderately abnormal; and 15% or more, severely abnormal.[25,27,101,102] When converted to percent myocardium abnormal, the prognostic implications of the 17- and 20-segment scoring systems have been shown to be equivalent.[103]

Quantitative Analysis

A variety of commercial software packages are available to assist in image interpretation, and the various quantitative measurements they can provide are summarized in Table 18–5. With respect to myocardial perfusion assessment, these computer approaches generally operate by automatic determination of the amount of radioactivity observed at rest and stress within each voxel or small zone of the myocardium, scaling this amount by the maximal amount of radioactivity in the myocardium (normalization) and then comparing this scaled amount to the lower limit of normal. The perfusion defect size (extent) represents the proportion of voxels below the normal limit, which would correlate best with the number of visually abnormal segments. The total perfusion deficit (TPD) in another application assesses both the proportion of voxels below normal limits and the degree by which they are abnormal and would correlate best with the summed segmental scores. The change between rest and stress is also assessed providing information about perfusion defect reversibility. It is possible to automatically register and subtract the rest images from the stress images or serial stress or rest studies from previous studies, resulting in a "change" image without requiring comparison to protocol specific normal limits. The change image reflects the amount of regional perfusion change.[104] The results are most commonly displayed using polar maps. Figure 18–15 displays polar maps associated with the various scan abnormalities shown in Figs. 18–12 and 18–13. The major clinical value of the quantitative analysis packages is in providing an objective assessment of the presence and magnitude of perfusion defects. It further gives the reader a "second expert" opinion, which is of importance even for experts; given the subjective nature of visual assessment. Quantitative assessment of serial studies is also more reproducible than expert visual assessment.[105,106] Moreover, it is also highly useful in facilitating decision making in individual patients regarding the need to perform a rest scan following a stress study or to simply perform a stress-only procedure. Recent developments in

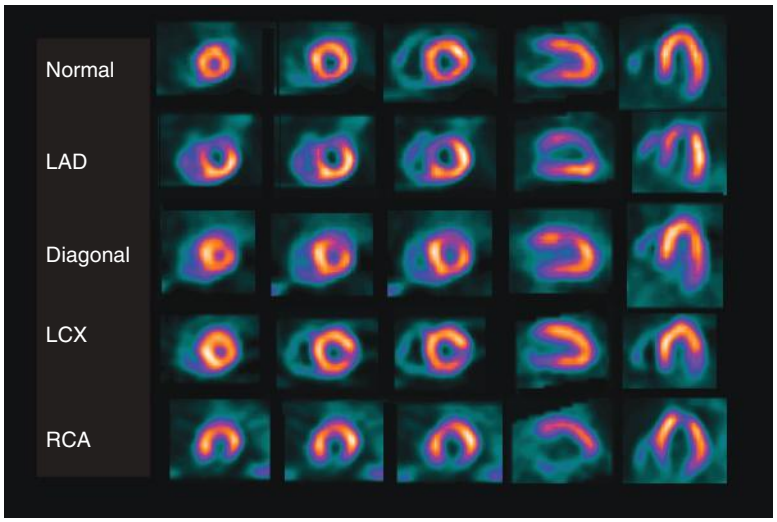

FIGURE 18–12. Examples of typical stress perfusion patterns corresponding to normal (*top*) and various single-territory abnormalities. Coronary angiographic findings in these patients were as follows: left anterior descending (LAD) coronary artery, proximal 95% stenosis; diagonal, occluded proximal first diagonal artery; left circumflex coronary artery (LCX), occluded first marginal artery branch; and right coronary artery (RCA), mid-95% stenosis. All patients had no evidence of myocardial infarction and normal single-photon emission computed tomography myocardial perfusion imaging at rest. From left to right, the images represent apical short axis, mid short axis, basal short axis, mid vertical long axis, and mid horizontal long axis. These patients show the typical distributions of perfusion defects associated with the specific coronary arteries involved.

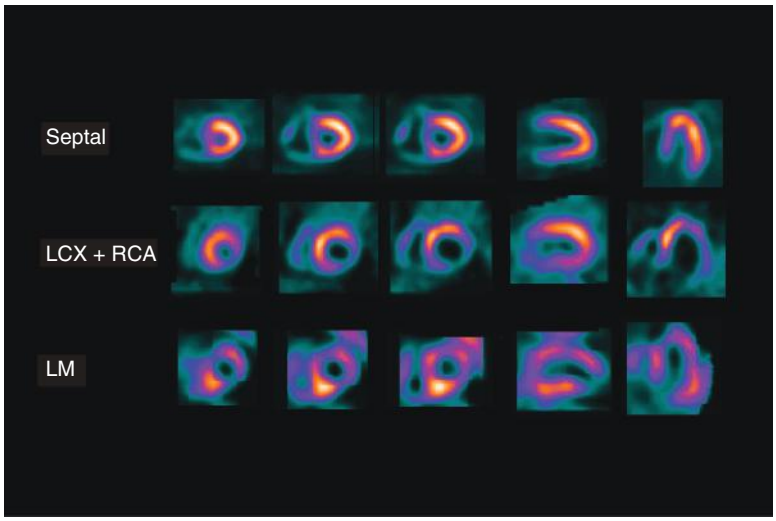

FIGURE 18–13. Stress single-photon emission computed tomography myocardial perfusion imaging images demonstrating more complex patterns associated with known coronary lesions in patients with normal resting perfusion images and no history of prior myocardial infarction. Septal refers to trapped septal perforator coronary artery (septal) in a patient with critical left anterior descending coronary artery (LAD) stenoses proximal and distal to the septal perforator takeoff and patent LAD internal mammary graft. Left circumflex coronary artery (LCX) plus right coronary artery (RCA) refers to occlusion of proximal LCX and proximal RCA. Left main (LM) refers to subtotal LM coronary artery stenosis.

computer-based quantitative analysis of SPECT-MPI have been shown to provide equal or greater accuracy in detecting CAD than expert visual assessment.[37] The results of quantitative analysis have been shown to be prognostically useful and may complement information derived from visual analysis alone.[107,108] These computer-based quantitative programs do not currently take into account artifacts (eg, patient motion); therefore, the final interpretation currently always includes visual verification and, if necessary, modification.[3,27]

The quantitative MPI discussed thus far assesses with SPECT- or PET-MPI the presence and magnitude of regional myocardial perfusion abnormalities by comparison with more normal zones. This is called relative quantitation. With PET, the high count rates allow quantitation of the first-pass arrival of the radiotracer, permitting assessment of absolute myocardial perfusion in milliliters/gram/minute as well as myocardial flow reserve, comparing rest and stress perfusion. With this approach each segment or region is can be assessed on its own, avoiding the reliance on comparison to perfusion of a normal area.

Overall Scan Assessment Based on Perfusion Findings

The final scan interpretation should express whether perfusion scan is abnormal and the degree to which it is abnormal. Summed stress scores 0-1 are considered normal, 2-3 borderline/equivocal, 3 probably abnormal and 4 or more definitely abnormal. For percent myocardium abnormal or TPD, 2-3% is considered equivocal, 4% probably abnormal, and 5% or greater definitely abnormal. There is general agreement that the category of "borderline" or "equivocal" is needed for circumstances in which the interpreting physician is uncertain whether mild perfusion defects are attributable to true perfusion abnormality or to imaging artifact. The use of the terms "probably or "definitely" abnormal are optional.

VENTRICULAR FUNCTION

It is currently recommended that ECG gating be performed with all SPECT - and PET-MPI protocols, whether ^{201}Tl or ^{99m}Tc tracers are used.[109] Gated MPI allows the assessment of a variety of ventricular function parameters, adding diagnostically and prognostically important information to MPI examinations.[110] Regional wall motion or thickening is most commonly assessed by semiquantitative visual analysis, using the same segmental system used for perfusion defect assessment. Automatic computer-based methods quantify global function parameters, including left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), end-systolic volume (ESV), and diastolic function. Regional LV myocardial wall motion and thickening can also be quantified from rest gated MPI images. Gating of both the rest and the poststress acquisition provides the ability to detect stress-induced stunning by detecting inducible region wall motion abnormalities poststress.[39] Gated images are also useful for distinguishing true perfusion defects from attenuation artifacts. Also, LV dyssynchrony can be quantified by measuring the onset of contraction of each myocardial sample point relative to the cardiac cycle; this is done by taking the first Fourier harmonic of its temporal displacement curve, the phase angle of which forms the basis for all of the synchrony measurements.[111] Phase information from all LV sample points can be pooled together into a phase histogram, the parameters of which offer a global measure

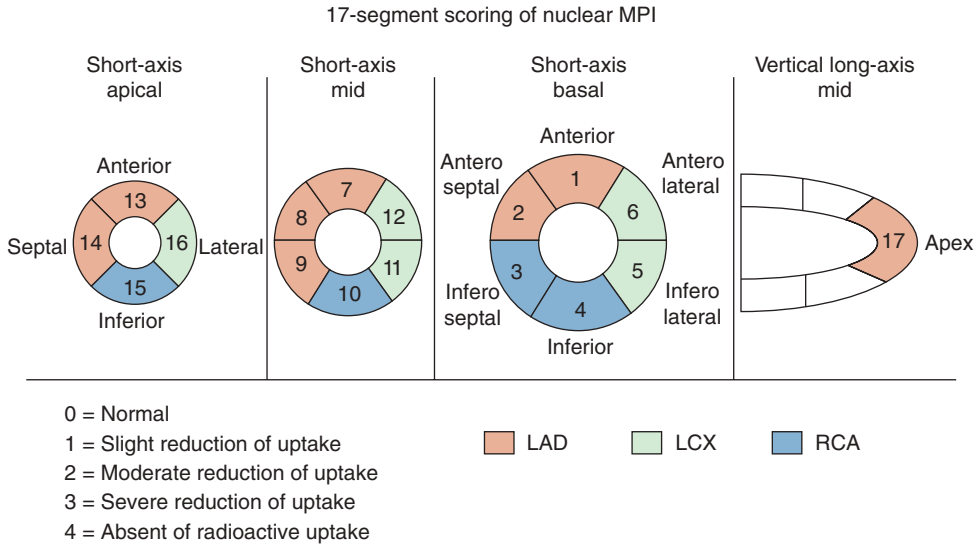

FIGURE 18–14. Nuclear myocardial perfusion 17-segment scoring (diagrammatic representation of segmental division of the tomography slices and assignment of the segments to the individual coronary arteries using the 17-segment model). LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery. Reproduced with permission from Imaging guidelines for nuclear cardiology procedures, part 2. American Society of Nuclear Cardiology. *J Nucl Cardiol*. 1999 Mar-Apr;6(2):G47-G84.[99]

TABLE 18–4. Definitions of Summed Perfusion Scores and Percent Myocardium Hypoperfused

Summed stress score (SSS)[a]	Sum of the segmental scores at stress	Amount of infarcted, ischemic, or jeopardized myocardium
Summed rest score (SRS)[a]	Sum of the segmental scores at rest	Amount of infarcted or hibernating myocardium
Summed difference score[a] (SDS)	SSS – SRS	Amount of ischemic or jeopardized myocardium
	20-Segment	17-Segment
Percent total	= SSS × 100/80	= SSS × 100/68
Percent ischemic	= SDS × 100/80	= SDS ×100/68
Percent fixed	= SRS × 100/80	= SRS × 100/68

[a]Reflects the extent and severity of perfusion abnormality/ischemia.

Data from Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003 Jun 17;107(23): 2900-2907.[25]

TABLE 18–5. Quantitative Measurements Possible with Gated Myocardial Perfusion Single-Photon Emission Computed Tomography

Type	Parameter	Comment
Perfusion	Perfusion defect extent	Expressed as percent of LV myocardium
	Perfusion defect severity	Related to the degree of hypoperfusion in the defect area
	Total perfusion deficit	Takes into account defect extent and severity; expressed as % of LV myocardial perfusion deficit
	Segmental scores and summed scores (poststress, rest, reversibility)	Summed scores depend on specific myocardial model chosen; usually 0–4 with 17-segment model
	Change	Accounts for difference between two image sets (eg, stress/rest; study 1 vs study 2); expressed as percent of the myocardium
Function (global)	LV ejection fraction	
	LV end-systolic and end-diastolic volumes	
	PFR; time to PFR	LV diastolic function
Function (regional)	Wall motion and wall thickening	
Other	LV contraction histogram	LV contraction phase/ dyssynchrony
	Lung:heart ratio	Ratio of uptake in lung and LV
	Transient ischemic dilation ratio	Ratio of LV cavity volume poststress vs at rest
	LV myocardial mass	Estimates of LV shape (global or regional)
	LV eccentricity, shape index	

LV, left ventricular; PFR, peak filling rate.

Data from Sandler MP: *Diagnostic Nuclear Medicine*, 4th edition. Philadelphia: Lippincott Williams & Wilkins; 2003.

of intraventricular dyssynchrony. Moreover, regional contraction differences (eg, between the lateral and the septal LV wall) can be measured, similarly to what is done in echocardiography.[111-113] Stress-induced wall motion abnormalities on gated SPECT-MPI are a sign of exercise-induced stunning and a marker of severe CAD.[180]

Quantitation of ventricular function and volumes with gated SPECT and PET-MPI can be performed by a variety of algorithms.[114-116] The approaches are fully 3D and based on the automatic detection of endocardial and epicardial surface points.[117-119] In validation studies published to date of LVEF by gated SPECT,[3] the agreement between gated SPECT and other standard measurements of LVEF has been shown to be very good to excellent. Although LVEF measured by the various quantitative algorithms correlate highly, the thresholds for abnormality are different depending on the method used.[120,121] With some methods, the normal threshold for the global LVEF measured by gated SPECT-MPI images is slightly lower than that measured using other imaging modalities (~ 45%), principally because of the use of only eight gating intervals.[3] Sixteen-frame gating reduces underestimation of LVEF. Sex-based normal limits for LVEF and LV volumes and volume indices have been reported.[122] Fully automated scoring of SPECT-MPI LV wall motion and thickening can outperform experienced observers in the detection of CAD.[123]

TRANSIENT ISCHEMIC DILATION OF THE LV

In addition to perfusion defects, several nonperfusion abnormalities can be observed with nuclear MPI, including size and shape of the LV, transient ischemic dilation (TID) of the LV,[124,125] RV myocardial uptake,[126] RV size, and abnormalities of lung uptake or other abnormal extracardiac activity. TID is considered present when the LV cavity appears to be significantly larger in the poststress images than at rest.[124,125] It may represent true changes in LV size or may actually be an apparent cavity dilation secondary to diffuse subendocardial ischemia (obscuring the endocardial border). The latter would explain why TID may be seen for several hours following stress, when true cavity dilation would most likely no longer be present. The correlation between LV TID and lung uptake is weak, suggesting that there may be different pathophysiologic mechanisms for each, and their measurements may be complementary in assessing the extent and severity of CAD for risk sidered to represent severe and extensive ischemia and has been shown to be highly specific for critical stenosis (> 90% narrowing) in vessels supplying a large portion of the myocardium (ie, proximal left anterior descending or multivessel 90% lesions).[124,125] It has also been shown to improve the detection of severe coronary disease when combined with perfusion measures.[128] Dipyridamole or adenosine-induced TID has similar implications as those associated with exercise.[129] Figure 18–16 illustrates an example of TID on SPECT-MPI from a patient with severe left main CAD. TID can easily be measured by the quantitative gated nuclear MPI algorithms. TID ratios are typically calculated from the summed (nongated) rest and stress images. The upper limit of normal for the TID ratio with on stress nuclear-MPI depends on the stress type and the imaging protocol used.[130] With exercise stress, the upper limit of normal for TID has been reported to be 1.14 to 1.19 for same-day rest/stress ^{99m}Tc imaging and 1.22 for dual-isotope imaging.[128,131] With vasodilator stress, for reasons that are not completely understood, the upper limit of normal to consider TID to be present is higher, approximately 1.14 to 1.19 for same-day rest/stress ^{99m}Tc imaging and 1.36 with dual-isotope SPECT.[129,132,133] When unaccompanied by a stress perfusion defect, TID is less specific for severe CAD.[168]

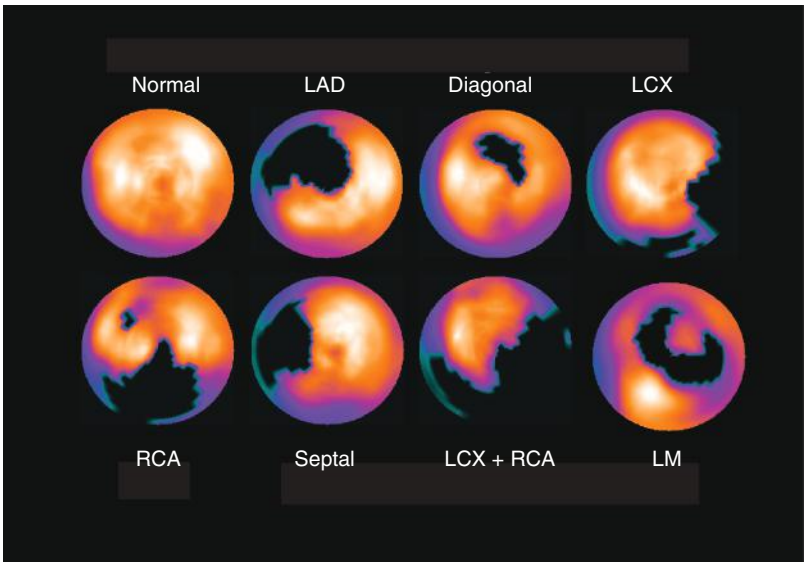

FIGURE 18–15. Quantitative stress polar maps of stress myocardial perfusion imaging demonstrating typical vascular perfusion pattern. Black represents regions of quantitative perfusion defect when compared to normal limit files. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main; RCA, right coronary artery.

INCREASED LUNG UPTAKE

Increased lung uptake of thallium reflects increased pulmonary capillary wedge pressure. Nonischemic causes of increased pulmonary capillary wedge pressure, such as mitral regurgitation and mitral stenosis, are also associated with increased pulmonary thallium uptake. Increased thallium lung uptake after exercise has been shown to have incremental prognostic information over myocardial perfusion defect assessment.[134] Prognostic value of increased pulmonary uptake of ^{99m}Tc-sestamibi has recently been reported.[135]

MARKERS OF HIGH RISK ON NUCLEAR MPI

A number of patient characteristics, clinical and ECG stress test findings, and stress MPI findings have been found to be associated with increased patient risk of adverse events (Table 18–6). Clinical high-risk markers tend to be related to patient age, rest ECG abnormalities, diabetes mellitus, presenting symptoms, functional capacity, and prior CAD. Stress test markers of risk include ability to perform exercise, exercise duration, stress-related BP and HR responses, ECG changes, and clinical response in terms of symptoms. MPI high-risk markers include the presence of extensive reversible or fixed defects and direct evidence of the presence of significant LV dysfunction. Hence, for any MPI result, the estimated risk of the patient is increased in proportion to the degree to which other higher risk markers are present. Consideration of markers beyond those provided by assessment of perfusion defects is particularly important in the case in patients found to have normal stress perfusion and function, but with TID, LV enlargement, or severe ST-segment changes.

Chronotropic incompetence, defined as a low percentage of HR reserve achieved [(peak HR – rest HR)/(220 – age – rest HR) × 100], with less than 80% considered abnormal, has been shown to be a powerful predictor of cardiac death and all-cause mortality in patients undergoing exercise SPECT-MPI.[37,136,137] Inability to achieve 80% of HR reserve has been shown to be a more powerful predictor of cardiac death than failure to reach 85% of MPHR.[137] Also, patients with normal SPECT-MPI but abnormal HR reserve achieved have been shown to be at as high a risk of overall mortality as patients with abnormal SPECT-MPI but normal HR reserve achieved. Impaired chronotropic response to vasodilator stress with ^{82}Rb PET has been reported to be independently predictive of CAD mortality—adding to perfusion defect assessment.[46] Recently, it has also been shown that exercise capacity, chronotropic incompetence, and abnormal heart rate recovery are independent predictors of cardiac death and add incremental value in risk prediction over risk factors and comprehensive SPECT-MPI assessment.[37]

SOURCES OF ARTIFACT

As with any diagnostic test, quality control is critical to effective clinical application of nuclear-MPI. Artifactual perfusion defects have a variety of causes, the most common of which are patient motion, breast and diaphragmatic attenuation, reconstruction artifacts caused by adjacent or superimposed extracardiac radioactivity, and poor count statistics.[109] With both SPECT and PET-MPI, several technical artifacts can affect the accuracy of LVEF measurement. LVEFs can be overestimated in analyzing images of small hearts,[121] because of the limitations of spatial resolution. In patients with left ventricular hypertrophy (LVH), LVEF may be underestimated because of failure to accurately determine the endocardial border in the presence of the large muscle mass. Marked arrhythmia results in a falsely low LVEF measurement. Sources of artifact on PET-MPI are further discussed in Chapter 19. As noted below, from SPECT two-view imaging—in supine/prone or upright/supine positions—reduces both attenuation and motion artifacts. With hybrid SPECT/CT or PET/CT systems, misregistration of perfusion and attenuation correction images is a major source of artifact.

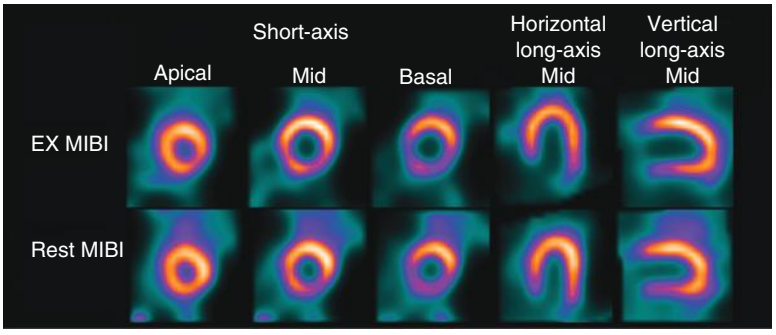

FIGURE 18–16. Exercise myocardial perfusion single-photon emission computed tomography in a 67-year-old man with new-onset atypical chest pain. Exercise (EX)/rest ^{99m}Tc sestamibi imaging shows a mild (borderline) inferolateral reversible perfusion defect; however, transient ischemic dilation was present (ratio, 1.44). Invasive coronary angiography revealed severe left main stenosis.

ASSESSMENT OF MYOCARDIAL VIABILITY

Assessment of myocardial viability with the myocardial perfusion tracers applies to segments with contractile dysfunction.[27] Viability is considered present if the degree of uptake at rest, redistribution, or following nitrate-augmented rest injection[138] is normal or nearly normal. Various patterns of viability associated with regional wall motion abnormality in these studies are shown in Fig. 18–11. The presence of normal or near-normal tracer uptake in an abnormally contracting segment predicts improvement in ventricular function with successful revascularization. A dysfunctional segment or region with severely reduced or absent uptake of radioactivity

TABLE 18–6. Markers of High Risk

Clinical and Demographic	Stress Test	SPECT
Diabetes mellitus (especially insulin dependence, more so in women)	Severe ST-segment depression	TID
Resting ECG abnormalities: atrial fibrillation, LBBB, RBBB, other block (first-or second-degree, hemiblocks), LVH with repolarization, PVCs	Inability to perform exercise/Type of stress performed	Lung uptake
Increasing age	Exercise-induced hypotension	Stress-induced stunning
Increased resting HR	High Duke Treadmill Score	Reduced EF
Dyspnea as presenting symptom	Stress-induced ventricular dysrhythmias	Severe and/or extensive defects
Typical angina	Tachycardic response to stress	Increased RV tracer uptake
Functional capacity		
Presentation with unstable angina	Exercise duration	Akinetic-dyskinetic LV segments
History of prior CAD (especially prior myocardial infarction)	Chronotropic incompetence	LV enlargement
	Blunted HR response to adenosine	
	Inability to perform exercise	

CAD, coronary artery disease; ECG, electrocardiogram; EF, ejection fraction; HR, heart rate; LBBB, left bundle branch block; LV, left ventricular; LVH, left ventricular hypertrophy; PVC, premature ventricular contraction; RBBB, right bundle branch block; RV, right ventricular; SPECT, single-photon emission computed tomography; TID, transient ischemic dilation.

on a viability study is considered to be nonviable. Areas with moderate reduction of counts in these conditions are usually partially viable, and patients in this group have a variable response in terms of improvement after revascularization. When perfusion defects are seen at rest and not after redistribution (with ^{201}Tl) or after separate tracer injection following administration of nitroglycerin, SPECT-MPI is commonly interpreted as showing *resting ischemia* and considered to represent regions of critically reduced blood flow to viable myocardium,[63] generally requiring rapid consideration of revascularization. The use of F-18 fluorodeoxyglucose (FDG) to assess myocardial viability is described in Chapter 19.

CLINICAL APPLICATIONS OF NUCLEAR MYOCARDIAL PERFUSING IMAGING

The principles underlying the efficient use of stress nuclear techniques and the optimal use of the test results are discussed below. The most common applications are identifying inducible ischemia in patients with suspected disease, assessing the likelihood that a patient with known CAD has ischemia, evaluating patients prior to noncardiac interventions, and assessing the magnitude of ischemia for prognostic purposes. The section that follows explores these applications and discusses the evidence for the use of SPECT and PET-MPI in specific patient populations commonly encountered in clinical cardiology settings. Evidence for SPECT is emphasized below, because PET is covered in Chapter 19.

SELECTING THE APPROPRIATE PATIENTS FOR DIAGNOSIS OF OBSTRUCTIVE CAD USING STRESS NUCLEAR MPI

Central to appropriate patient selection for nuclear imaging and the interpretation of test results for purposes of establishing the diagnosis of obstructive CAD is the assessment of an individual patient's pretest likelihood of CAD based on demographic, clinical, and historical information. Bayes' theorem underlies the selection of SPECT- or PET-MPI for diagnostic testing (see Chap. 19). For a given test result, the post-test likelihood is a function of three variables: patient pretest likelihood of disease and the test sensitivity and specificity. The degree to which the test result alters the post-test likelihood is directly affected by the pretest likelihood of disease. For any test with less than 100% sensitivity and specificity, the greatest shift in post-test likelihood of disease occurs in patients with an intermediate pretest likelihood of CAD. As a benchmark, for a test with sensitivity and specificity of 90%, a patient with a pretest likelihood of 50%[139] will have a post-test likelihood of 10% (*low*) with a normal test result and a 90% likelihood (*high*) with an abnormal test result. For purposes of assessing the post-test likelihood of CAD when using SPECT- or PET-MPI, the patient's pretest likelihood takes into account all available information, including age, sex, symptoms, risk factors, the degree of coronary atherosclerosis if known (eg, from a coronary artery calcium [CAC] score), and the results of the non-nuclear stress testing components of the examination (eg, the duration of exercise and degree of ST-segment depression).

The pretest likelihood or risk assessment is conventionally estimated from published nomograms or by using available computerized programs. Recent data, however, suggest that the commonly used approaches to assessing the pretest likelihood of CAD, based on the work of Diamond and Forrester,[139] may not be applicable in the types of patients currently being referred for noninvasive testing. From a contemporary series, Cheng and coworkers reported that the Diamond-Forrester criteria markedly overestimated pretest likelihood of CAD in patients referred for coronary computed tomography angiography (CCTA).[140] In 8106 patients from the COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) registry with nonanginal angina, atypical angina, or typical angina, the Diamond-Forrester pretest likelihood of angiographically significant CAD was 51%; however, the observed frequency of 50% or more stenosis on coronary CTA in these patients was 18%. This overestimation of CAD likelihood was confirmed in the recent PROMISE trial. In the patients in the coronary CT arm of the trial, the pretest likelihood of obstructive CAD was 53% while the abnormal was present in >= 50% stenosis on coronary CTA was 10.7%. As noted below, the overestimation of the pretest likelihood of obstructive CAD is likely a principal factor in the recently observed low frequency of abnormal SPECT-MPI studies.[141]

Diagnostic Accuracy of SPECT and PET-MPI

The accuracy of diagnostic testing for CAD has been defined on the basis of sensitivity and specificity as compared to an anatomic stenosis standard of either a 50% or 70% diameter-narrowing determined by invasive coronary angiography. A large meta-analysis of 86 studies reported 10,870 patients and examined the diagnostic accuracy of exercise or pharmacologic stress MPI for detecting significant CAD.[142] Pooling studies published between January 2002 and October 2009, the authors found that SPECT performed without attenuation correction or gating (63 studies) had a sensitivity of 87% and a specificity of 70%. The addition of gating information increased specificity to 78% (19 studies), and the use of attenuation correction further increased specificity to 81% (12 studies).

Several meta-analyses have compared the sensitivity and specificity of SPECT versus PET-MPI techniques. McArdle and colleagues reported on a comparison of the two modalities limiting the SPECT

studies to those that used attenuation correction and gating, thus allowing for comparison of contemporary techniques.[143] Pooling 15 PET and 8 SPECT studies (1344 and 1755 patients), the authors reported, for PET, a pooled sensitivity of 90% (confidence interval [CI], 0.88-0.92) and specificity of 88% (CI, 0.85-0.91) and, for SPECT, a sensitivity of 85% (CI, 0.82-0.87) and specificity of 85% (CI, 0.82-0.87). The area under the summary receiver-operating characteristic curves were 0.95 and 0.90 for PET and SPECT ($P < .0001$), respectively. This study was limited by interstudy heterogeneity and likely the differential referral patterns for each modality. Parker and coworkers performed a bivariate meta-analysis to compare the sensitivity and specificity of PET versus SPECT stress MPI using a 50% stenosis or more threshold to define obstructive CAD.[144] The authors identified 117 studies, including 108 evaluating SPECT-MPI, 4 evaluating PET-MPI, and 5 evaluating both modalities. A significantly higher pooled mean sensitivity was found with PET (93% [95% confidence interval or CI, 88%-96%]) compared with SPECT (88%) [95% CI, 86%-90%] ($P = .035$). No significant difference in specificity was present between PET (81% [95% CI, 67%-90%]) and SPECT (76% [95% CI, 72%-79%]) ($P = .39$). In a multicenter European cohort of 475 symptomatic patients undergoing CCTA and nuclear MPI (Evaluation of Integrated CAD Imaging in Ischemic Heart Disease [EVINCI]) trial, the diagnostic accuracy of detection of obstructive CAD was higher for PET than for SPECT-MPI.[145] For PET-MPI, the diagnostic accuracy, sensitivity, and specificity were 85%, 81%, and 89%, respectively. By comparison, for SPECT-MPI, the diagnostic accuracy, sensitivity, and specificity were 70%, 73%, and 67%, respectively. Given the physiological basis of these tests, a more relevant comparison would be based on FFR by invasive angiography as a gold standard. As part of a comparison of multiple modalities (SPECT, PET, stress echocardiography, CT, or magnetic resonance [MR]), to invasive FFR 37 studies were identified (n = 2048 patients).[146] Using FFR as a gold standard, PET had a lower negative likelihood ratio compared to SPECT (PET 0.14 [95% CI, 0.02-0.87]; SPECT 0.39 [95% CI, 0.27-0.55]) with a greater positive likelihood ratio (PET 7.43 [95% CI, 5.03-10.99]; SPECT 3.76 [95% CI, 2.74-5.16]). PET, MR, and CT perfusion performed similarly in excluding abnormal FFR, whereas MR and PET had similar positive likelihood ratios that were greater than that of CT. SPECT and stress echocardiography were inferior to the three other modalities with respect to both metrics.[146]

Referral or Partial-Verification Bias

A major limitation in assessing the diagnostic accuracy of nuclear MPI to detect CAD is that the decision to perform the gold standard test—catheter-based coronary angiography—after nuclear testing strongly influenced by the MPI result, thereby biasing the population available for the analysis of test accuracy. This is referred to as past test referral bias or verification bias. The referral to invasive angiography is largely driven by the presence of ischemia, particularly the extent and severity of perfusion abnormalities, as well as anginal symptoms, ECG changes, and other clinical factors. This referral pattern results in an overestimation of test sensitivity and a reduction in test specificity, with the most dramatic change occurring in specificity.[147] Importantly, only a small proportion of patients with normal or low-risk MPI findings proceed to invasive coronary angiography, resulting in more variability in specificity measures than in sensitivity. In the extreme case—catheterization in all abnormal MPI but none in normal MPI—test sensitivity and specificity would approach 100% and 0%, respectively. For example, Miller and colleagues reported that in a large series from the Mayo Clinic that the uncorrected SPECT specificity was less than 10% in men, because the referral for invasive angiography in patients having SPECT-MPI is strongly affected by the SPECT results.[148] Adjustments for referral bias have been described.

Normalcy Rate

The normalcy rate has been suggested as surrogate for assessing test *specificity* without requiring the angiographic standard; thus, it is not being affected by the marked post-test referral bias associated with assessment of specificity based on invasive coronary angiographic stenosis.[147] The normalcy rate is defined as the percentage of patients with normal test results in a population with a low (< 10%) pretest risk of CAD. The 2003 American College of Cardiology (ACC)/American Heart Association (AHA)/ASNC guidelines reported a normalcy rate for SPECT-MPI of 91%. Even in obese patients, normalcy rates for SPECT-MPI of greater than 90% have been reported when attenuation correction or combined supine/prone imaging is used.[22,149] This measure of "specificity" has limitations that the patients being tested—generally those who would not be appropriate for testing—are much "healthier" than the patients. Potentially fewer artifacts might occur in these patients (eg, they might be less likely to move during the study), and they are likely to have higher quality images (eg, greater coronary blood flow leading to greater radiopharmaceutical uptake). Thus, normalcy rate is likely to overestimate true test specificity.

RISK ASSESSMENT OF THE PATIENT WITH KNOWN OR SUSPECTED CAD

Principles of Risk Stratification

The first of the prognostic studies concerning exercise MPI was published by Brown and coworkers in 1983, based on a small cohort of only 100 patients.[150] In 1986, Ladenheim and colleagues reported a landmark study involving the follow-up of 1689 diagnostic patients undergoing exercise ^{201}Tl MPI.[151] This approach of prognostic accuracy of stress MPI overcame many of the limitations of diagnostic accuracy that have been previously discussed, improving separation of low- to high-risk patient subsets. Both the number of perfusion defects and the severity of perfusion defects were shown to be related to adverse cardiac outcomes in an exponential fashion, with extent and severity of ischemia as independent predictors of outcome (Fig. 18–17). When PET-MPI is used, measurements of myocardial flow have been shown to add information over perfusion defects.

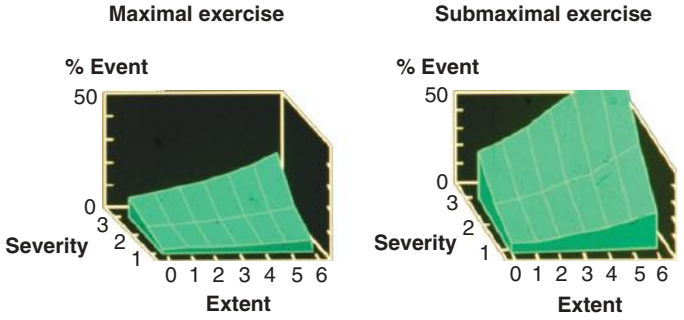

FIGURE 18–17. The extent of myocardial ischemia, ranging from 0 to 6 myocardial zones (*x* axis); the severity of defects, ranging from none (score of 0) to severe (score of 3) on the *y* axis; and the frequency of cardiac events on the orthogonal *z* axis, shown both for patients achieving more than 85% of maximal predicted heart rate (ie, "maximal" exercise) and those achieving less than 85% of maximal predicted heart rate ("submaximal"). The extent and severity of ischemia were both independently correlated to cardiac event rates. Thus, a patient who had extensive ischemia that was also severe in one or more zones had a considerably higher event rate compared to a patient who had extensive ischemia but without severe ischemia. For any given degree of ischemia, the event rate was approximately three-fold higher if the patient could only exercise sub-maximally. Reproduced with permission from Ladenheim, M.L., et al., Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. *J Am Coll Cardiol*. 1986 Mar;7(3):464-471.[151]

These early results led to a *risk-based approach* for the application of MPI to patients with known or suspected CAD with stable symptoms. In a risk-based approach, the focus is not on predicting the presence of CAD but on identifying patients at risk for specific, potentially preventable adverse events. Subsequent management then focuses on reducing the risk of these outcomes, whether cardiac death, nonfatal myocardial infarction (MI), or CAD progression. A major goal of management of stable ischemic heart disease (SIHD) patients following stress MPI is adherence and, as needed, intensification of guideline-directed medical therapy.[152] For the high-risk, invasive diagnostic, and therapeutic procedures are limited to patients who are most likely to benefit from them. This approach has been extensively evaluated using registry data for both SPECT and PET-MPI.

Risk Thresholds For the purposes of risk assessment, it has been proposed that low risk be defined as a less than 1% annual cardiac mortality rate and intermediate risk be defined by the range of 1% to 3% per year.[153] Because the mortality risk for patients undergoing revascularization is 1% or more (see Chaps. 20 and 44), symptomatic patients with a less than 1% annual mortality risk would not appear to be candidates for revascularization to improve survival. The values of these risk thresholds vary according to the population being tested.

Risk Stratification in Patients with Suspected or Known CAD

Incremental Prognostic Value The clinical value of SPECT- or PET-MPI for prognostic assessment of CAD results from the incremental or added prognostic information yielded overall data available prior to the test (clinical, historical, and stress data), as first demonstrated by Ladenheim and colleagues.[154] The incremental prognostic value of SPECT- and PET-MPI has since been documented extensively, including a broad spectrum of patient subsets.

Event Risk after a Normal Scan Extensive literature exists documenting the risk of adverse events following a normal stress SPECT-MPI. A normal scan is generally associated with a less than 1% annual risk of cardiac death or MI but in higher risk cohorts this risk can be about 2% per year or higher. A meta-analysis of the prognostic value of a normal stress perfusion scan (n = 29,788) revealed that the annual risk of MI or cardiac death after a normal stress MPI is 0.5% (95% CI, 0.3%-0.7%).[155] This low event rate is critical in applying nuclear test information to risk stratification, because in the absence of significant or limiting symptoms, it implies that patients with normal perfusion scans can be managed conservatively. Such an approach requires careful follow-up for signs of clinical worsening and treatment of cardiac risk factors and related symptoms (see Chap. 32). Increasingly, many studies are using all-cause death as an end point, and the degree of comorbidity impacts the annual mortality rates. Thus, the all-cause mortality rates following a normal MPI are expectedly higher than that of cardiac-specific end points.[156]

The risk of cardiac events is consistently lower in patients with normal than in those with abnormal SPECT-MPI but there are multiple subsets of patients with a normal scan in which the absolute risk is not low. There is a strong temporal component as well in the assessment of risk. A study examining predictors of risk and its temporal characteristics in a series of 7376 patients with normal stress SPECT-MPI identified the following as markers of increased risk and shortened time to a hard event—use of pharmacologic stress, known CAD (Fig. 18–18A), diabetes mellitus (in particular, female diabetics), and advanced age.[24] Hence, a dynamic temporal component of risk was present, and the existence of a *warranty* period for specific patient groups was defined (Fig. 18–18B). The warranty period of a normal scan was further examined by Acampa and colleagues, who documented the importance of diabetes and reduced LVEF (< 45%) in identifying those with a slightly higher CAD event risk and shorter warranty period.[157] Increased risk after normal SPECT has also been reported in patients with dyspnea as the presenting symptom.[158] The importance of exercise duration has also been reported. In 6069 patients with a normal SPECT-MPI study followed for a mean of 10.2 years, the all-cause mortality rate rose progressively as the exercise duration associated with the SPECT study declined. Patients who could not exercise for more than 3 minutes had a mortality rate that was comparable to that of patients requiring pharmacologic stress.[59] In a subsequent study, of 12,232 patients with a normal exercise SPECT-MPI study followed for a mean of 11.2 years, hypertension, smoking, diabetes, and exercise capacity were significant predictors, beyond age, of long-term mortality (Fig. 18–19). Combining these predictors, the mortality rates ranged from 0.2% per year in patients exercising 9 minutes or more and with none of these CAD risk factors to 1.6% per year in patients exercising less than 6 minutes and having two or more of these risk factors.[159] Thus, the lower risk and more functional the patient, the lower the expected annual event rates following a normal MPI. The converse is also true—that the annual event rates are increased in higher risk cohorts including those of advanced age or with known cardiovascular disease, impaired LVEF, and/or functional impairment. By comparison, patients with normal SPECT-MPI who performed some exercise at the time of stress MPI (combined low-level exercise with

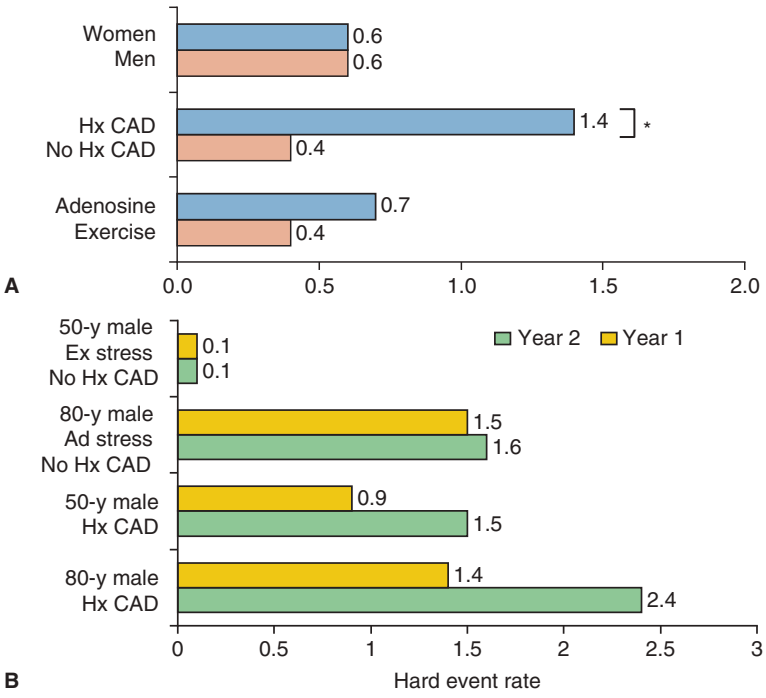

FIGURE 18–18. A. Annual rates of hard events, defined as cardiac death and nonfatal MI, in patients after normal single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). The following subgroups are shown: women versus men, patients with or without history (Hx) of coronary artery disease (CAD), and patients undergoing adenosine (Ad) versus exercise (Ex) stress. **B.** A significant risk is noted in the patients with a Hx of CAD, as demonstrated by the rates of hard events in the first and second years of follow-up after normal SPECT-MPI. Four examples are given: a 50-year-old man undergoing Ex stress with no Hx of CAD, an 80-year-old man undergoing Ad stress with no Hx of CAD, a 50-year-old man with a Hx of CAD, and an 80-year-old man with a Hx of CAD. In patients with no Hx of CAD, the event rates in the first and second years after SPECT-MPI are not different; however, the event rate for normal SPECT-MPI goes up significantly with increased patient risk. In patients with previous CAD, the event rates in the second year after SPECT-MPI were greater than those in the first year, and there is additional increase in the event rate with clinical risk. *Asterisk* indicates $P < .001$. Reproduced with permission from Hachamovitch R, Hayes S, Friedman JD, et al: Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan. *J Am Coll Cardiol*. 2003 Apr 16;41(8):1329-1340.[24]

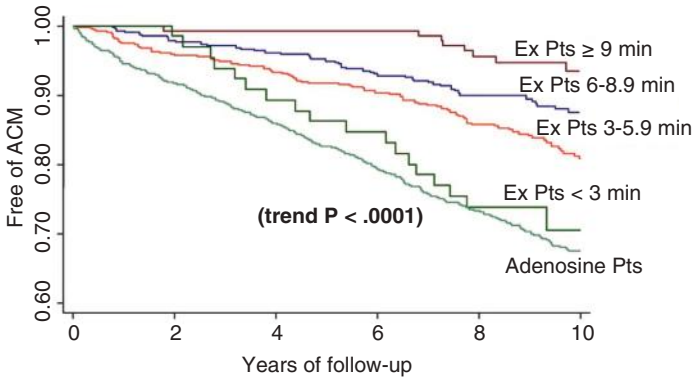

FIGURE 18–19. Comparison of survival in the propensity-matched exercise and adenosine patients, with the exercise patients divided according to exercise duration. Mortality rate increased progressively as exercise duration diminished. There was no statistical difference in mortality rate among patients unable to exercise more than 3 minutes and patients undergoing adenosine single-photon emission computed tomography ($P = .65$). Reproduced with permission from Rozanski A, Gransar H, Min JK, et al: Long-term mortality following normal exercise myocardial perfusion SPECT according to coronary disease risk factors. *J Nucl Cardiol*. 2014 Apr;21(2):341-350.

pharmacologic stress) have been reported to have event rates that are intermediate between those who underwent exercise SPECT-MPI and those who had pharmacologic SPECT-MPI without exercise.[160]

The contextual nature of risk requires some consideration of expected population mortality and cardiac event risk. As an example, from a study of elderly patients aged 75 to 84 years and 85 years or older, the annual cardiac mortality rates were 1.0% and 3.3%, respectively. Although these rates are not low, they are lower than the expected cardiac mortality rates for individuals of these ages in the US population (1.5% and 4.8%, respectively; $P < .05$ vs normal SPECT-MPI patients).[161]

The importance of stress-only SPECT protocols has been emphasized in the preceding portions of this chapter. The low risk associated with a normal rest/stress SPECT-MPI has been reported in patients studied with the stress-only protocols. In the largest study to date, Chang and coworkers reported all-cause mortality rates over a 4.5-year median follow-up in 16,854 consecutive patients with a normal gated stress SPECT (stress-only protocol in 8034 patients, 8820 both stress and rest imaging),[93] finding lower annualized unadjusted mortality rate after a stress-only protocol compared to a stress-rest protocol (2.6% vs 2.9%; $P = .02$). The very low risk associated with a stress-only protocol has been confirmed and extended by other authors.[92,162,163]

In some patients, extensive CAD may be *missed* because of balanced reduction of flow.[164] The latter would lead to a severe underestimation of the extent of ischemia by SPECT-MPI.[165] However, many of the patients with normal SPECT-MPI found subsequently to have high-risk anatomic lesions had abnormal ancillary markers on their SPECT study (eg, TID,[129] a rest-to-poststress decrease in LVEF, increased lung tracer uptake, or small perfusion defect below threshold to be considered abnormal).[165] A recent study of 580 patients with normal or minimal perfusion abnormalities on stress SPECT-MPI (SSS < 4) who underwent invasive angiography within 2 months after SPECT reported that the finding of TID, abnormal EF response, or SSS of more than 0 were predictors of the small proportion (7.2%) who were found to have high-risk angiographic findings. Use of a coronary calcium (CAC) scan can be very helpful in identifying underlying atherosclerotic disease risk as discussed later in the chapter. When the CAC score is high (400 Agatston units or higher), a normal stress MPI would not exclude significant CAD, as the score would indicate a high likelihood of obstructive CAD. Kaminek and colleagues reported that, in patients with known CAD, a combined approach of SPECT-MPI perfusion-function assessment and CAC improves the identification of multivessel CAD.[166] In general, when nonperfusion abnormalities are present in patients with otherwise normal SPECT-MPI, they are by themselves insufficient to warrant proceeding to invasive coronary angiography. PET-MPI, through the assessments of absolute rest and stress myocardial blood flow and coronary flow reserve (CFR), can improve risk detection and a greater understanding of the burden of obstructive CAD, functionally limiting mild epicardial CAD, or coronary microvascular dysfunction.[167]

Event Risk with a Borderline/Equivocal Scan As noted in the interpretation section, in some patients semiquantitative visual scoring or quantitative analysis results in a study being neither completely normal (percent myocardium abnormal = 0) nor definitely abnormal (percent myocardium abnormal ≥ 5%). In these circumstances, the scan is interpreted as "borderline" or "equivocal." The equivocal SPECT-MPI study is associated with an increased risk compared to the normal scan. In a study of 18,200 patients followed for a mean of 2.7 years for cardiac death, a significant increase in risk was found in patients with equivocal stress SPECT scans ($P < .001$) (Fig. 18–20).[102] In a recent study of prognostic assessment using a CZT camera, significantly increased risk of cardiac events was noted in patients with hypoperfusion below the threshold to be considered abnormal.[168] In a recent report of a subset of a large database studying patients with angiographically identified high-risk obstructive CAD following a borderline/equivocal SPECT-MPI study, the presence of a score greater than 0 (but lower than the abnormal threshold of ≥ 5%) was a variable associated with a higher than expected event rate.[169] Thus, for purposes of risk assessment, the scan category of "equivocal" or "borderline" should not be interpreted as being completely normal. Nonetheless, the "equivocal" or "borderline" scan result should not by itself prompt referral to invasive coronary angiography, because a preponderance of patients in this scan category do not have significant CAD.

Event Risk with Abnormal Scan The relationship of varying extent and severity of perfusion abnormalities with cardiac outcomes has been reported in numerous, diverse patient subsets.[103,153,170,171] Consistently, increasing perfusion scan abnormality is associated with an increasing risk of cardiac events, and this risk is further increased in patients with reduced LVEF.

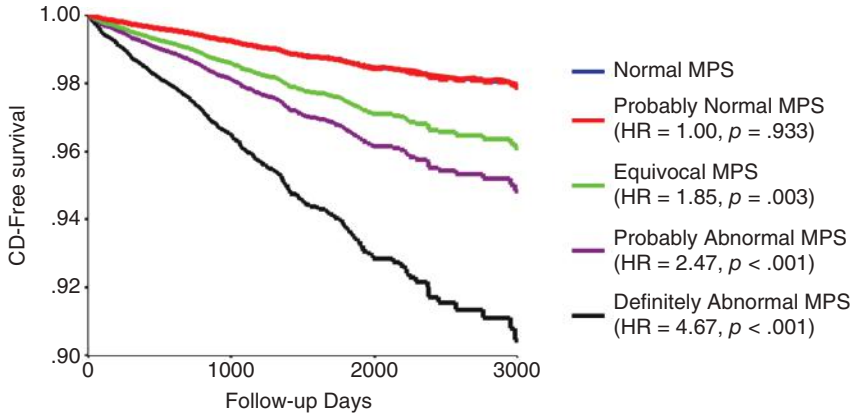

FIGURE 18–20. Risk-adjusted cardiac death (CD)–free survival as a function of the clinical myocardial perfusion single-photon emission computed tomography (MPS) certainty category (global χ^2 of the final model = 957.2, $P < .001$). This is adjusted for age, gender, type of stress, symptoms (angina/shortness of breath [SOB], history of coronary artery disease (prior myocardial infarction/revascularization), diabetes, hyperlipidemia, and ischemic electrocardiographic response. Reproduced with permission from Abidov A, Hachamovitch R, Hayes SW, et al: Are shades of gray prognostically useful in reporting myocardial perfusion single-photon emission computed tomography? *Circ Cardiovasc Imaging*. 2009 Jul;2(4):290-298.[102]

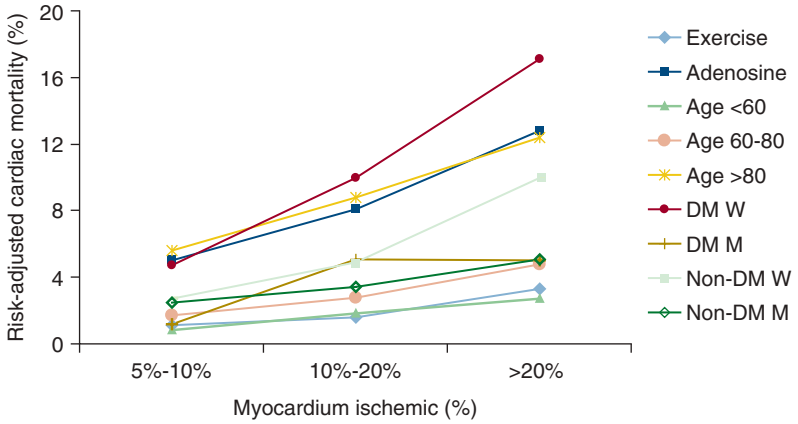

FIGURE 18–21. Rates of risk-adjusted cardiac mortality as a function of percent myocardium ischemic (5%-10%, 10%-20%, and > 20%) in medically treated patients (exercise vs adenosine stress; patients aged < 60, 60-80, and > 80 years; diabetic men vs women; and nondiabetic men vs women). Although predicted cardiac mortality increases with increasing percent myocardium ischemic, the rates at any level of ischemia vary widely as a function of clinical information. DM, diabetes mellitus; M, men; W, women. Data from Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003 Jun 17;107(23):2900-2907.[25]

The severity of perfusion defects correlates with the degree of stenosis, and extent of perfusion defect correlates with the amount of myocardium subtended by the stenosed vessels.[151] As described above, the percent myocardium abnormal, as estimated by 17-segment scoring or quantitative assessments such as TPD, combines the assessments of both extent and severity of perfusion abnormality and the general categories of abnormality have been described.[25,27,101] Illustration of how these parameters affect risk in various patient subsets is shown in Fig. 18–21. Annual cardiac event rates generally range from 0.7% to 6.7% for patients with normal, mild, moderate, and severely abnormal perfusion scans, with significant variability associated with each level of defect extent and severity; depending on the pretest likelihood of CAD.[25] Findings similar to those observed with ^{99m}Tc-sestamibi have been described with ^{201}Tl and ^{99m}Tc-tetrofosmin SPECT as well as in a multicenter PET registry.[155,172]

Importance of Prescan Data As noted, prescan information adds incrementally to SPECT data for predicting outcomes. For all groups of patients, risk assessment in an individual patient is improved by taking into account findings other than those of the scan. The presence of high-risk clinical or historical markers identifies a subset of patients at greater risk *for any level of scan abnormality* (see Fig. 18–21).[25,101,173,174] Additionally, for any degree of perfusion defect, the risk of adverse events after SPECT-MPI is greater in patients with higher clinical risk, including atrial fibrillation,[174] diabetes,[175,176] advanced age,[161] reduced LVEF, dyspnea,[158,177] high CAC scores, known CAD, reduced functional capacity, and inability to exercise.

Mildly Abnormal SPECT-MPI The presence of a mildly abnormal scan (5-9% myocardium) usually implies the presence of CAD but a moderately elevated risk of cardiac event. However, the risk is higher in a variety of subgroups with significant comorbidities and presentations, as mentioned above. The need to take into account all risk predictors is of particular importance in this patient group. A highly important consideration is that with SPECT-MPI or PET-MPI (unless absolute blood flow is being assessed), detection of abnormality is spatially relative, that is, perfusion defects are detected by their comparison to other myocardial regions. Thus, SPECT or PET-MPI without absolute flow measurements may underestimate the extent of hemodynamically significant CAD. Although patients with mildly abnormal SPECT-MPI results have an elevation in cardiac event risk, generally optimal medical therapy approaches are the mainstay in this patient subset, with referral to invasive angiography limited to patients with refractory symptoms.

Moderately to Severely Abnormal SPECT-MPI As discussed earlier, this category of scan abnormality is associated with high levels of patient risk and even greater in patients with high-risk cardiovascular comorbidities, increased LV size/reduced LV function, extensive scar, or reduced LVEF. As discussed later, patients in this SPECT- or PET-MPI category with extensive ischemia are identified as those in whom knowledge of coronary anatomy may define clinical management. This patient subset benefits from revascularization as opposed to guideline-directed medical management alone, as is discussed in detail later in this chapter.

Added Value of LV Function and Size Using Gated SPECT or PET Assessment of LV function on gated SPECT or PET-MPI provides incremental value over perfusion in assessing prognosis. Poststress LVEF and LV ESV provide incremental information over the perfusion defect assessment in the prediction of cardiac death.[178] In a report of 6713 patients, using separate criteria for EF and ESV for men and women, Sharir and coworkers reported that perfusion (percent myocardium ischemic), function (LVEF), and LV volumes (ESV) provide incremental prognostic information regarding cardiac death and hard events[122] (Fig. 18–22), with particularly high event rates noted among women with reduced

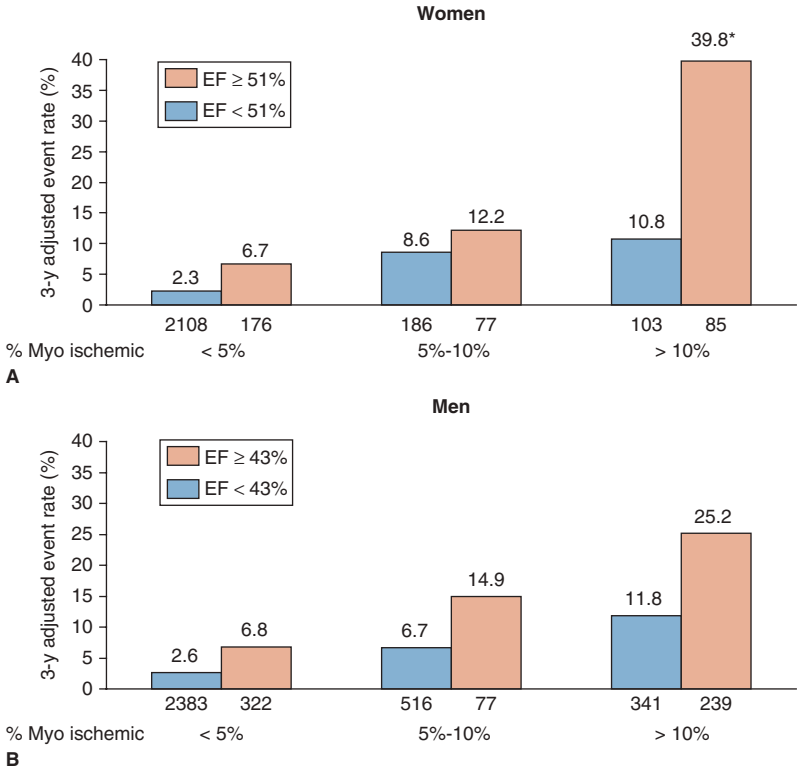

FIGURE 18–22. Three-year adjusted cardiac hard event rates in women (**A**) and men (**B**) as a function of the amount of ischemia (percent myocardial [myo] ischemic) and sex-specific normal/abnormal ejection fraction (EF). Reproduced with permission from Sharir T, Kang X, Germano G, et al: Prognostic value of poststress left ventricular volume and ejection fraction by gated myocardial perfusion SPECT in women and men: gender-related differences in normal limits and outcomes. *J Nucl Cardiol*. 2006 Jul;13(4):495-506.[122]

LVEF and more than 10% myocardium ischemic. A subsequent study reported that SPECT-MPI determined ischemia and gated LVEF added incrementally to each other for the prediction of adverse events.[179]

Other important information that can be derived from gated SPECT-MPI and are related to risk has not been widely included in literature reporting the prognostic assessment (see Table 18–6). These include regional or global stunning. (31, 180) TID of the LV[124,125,129] and pulmonary uptake of radioactivity.[134] Extensive *reversibility of resting* ^{201}*Tl perfusion defects* (as determined by 24-hour ^{201}Tl imaging after rest ^{201}Tl/stress ^{99m}Tc-sestamibi SPECT-MPI) has been shown to be predictive of a higher mortality rate than would be predicted by rest or stress perfusion defect abnormalities alone.[181] As noted below, with the most commonly performed PET-MPI approach—^{82}Rb PET—unlike SPECT, imaging is performed during as opposed to after pharmacologic stress. Any fall in EF is considered abnormal and has been associated with critical coronary stenosis.[182]

As noted above, PET-MPI offers an important characteristic that is not provided by current SPECT-MPI—the quantitation of absolute rest and stress myocardial blood flow and CFR. These absolute flow measurements provide added value in risk assessment as discussed below. Furthermore, they provide an ability to recognize when there has been inadequate vasodilation stimulus caused by caffeine intake by the patient—detected as no increase in flow between rest and stress. Of importance, from a diagnostic perspective, a completely normal PET-MPI study, including normal CFR, has been reported to essentially exclude the presence of high-risk epicardial CAD.[167] In addition, CFR and maximally myocardial blood flow provide assessments of overall myocardial blood flow and thus evaluation for focal epicardial coronary stenosis as well as diffuse epicardial disease and microvascular disease or microvascular dysfunction. This capability of PET flow measurements provides information that is complementary to the invasive assessment of FFR, allowing the identification of diffuse epicardial disease and microvascular dysfunction. These have their own prognostic and therapeutic implications beyond those associated with assessment of an individual epicardial coronary lesions.[183,184]

SEX-BASED DIFFERENCES IN THE PROGNOSTIC VALUE OF SPECT-MPI

Recent guidelines for cardiac imaging in women have been published by the AHA.[185] In women, because of breast tissue artifact, false-positive SPECT-MPI examinations are most notable in the anterior and anterolateral segments of the heart and are more common with ^{201}Tl than with the ^{99m}Tc agents.[185] Improved accuracy has been reported with use of the ^{99m}Tc agents as well with combined acquisition of gated EF and wall motion imaging and prone imaging and the use of validated attenuation correction algorithms.[185,186]

Regarding prognosis, pooled data involving more than 7500 women noted annual rates of cardiac death or nonfatal MI of 0.4% for those with low-risk or normal SPECT-MPI.[187] High-risk MPI findings elevated a woman's risk by nearly 10-fold, with annual rates of major cardiac events of 6.3% for all women and 10.9% for diabetic subsets of women.[187] With separate criteria for abnormality of ventricular function in women, there was similar prognostic content of combined perfusion and function information from gated SPECT in men and women.[122]

Coronary vascular dysfunction (often termed coronary microvascular disease [CMD] or dysfunction) has been proposed as a mechanism for mislabeled "false-positive" stress testing results in women, suggesting that some of these studies may represent true perfusion abnormalities without significant epicardial coronary stenosis. Evidence suggests that these SPECT- and PET-MPI perfusion findings may be associated with increased near-term risk of major cardiac events.[188] Multiple reports suggest that prognostically important CAD states not involving epicardial, obstructive CAD occur more frequently in women than in men and that PET-MPI could be useful for detecting this process. A current active field of investigation is to more clearly define the types of CMD and the prevalence of mild epicardial CAD stenosis or high-risk atherosclerotic plaque features (eg, expansive or positive remodeling), in women which may also influence CFR findings.

PET-MPI IN RISK ASSESSMENT

For PET-MPI, the past decade has witnessed a surge in publications. Along with the assessment of incremental prognostic value, risk stratification, and test performance in various patient subgroups and the role of change in LVEF, the impact of CFR on patient outcomes has also been extensively reported. As recently summarized,[189] a large number of studies have evaluated the prognostic value of stress PET-MPI.[182,190-195] As described for SPECT-MPI, the risk of a normal stress PET is very low, with risk increasing as a function of the extent and severity of perfusion defects.[182,190,191,193,194]

A recent meta-analysis assessing the prognostic value of stress PET perfusion identified 20 eligible studies (7 prospective) included a median sample size of 551 patients (interquartile range [IQR] 232-1291) with follow-up ranging from 1.0 to 7.3 years for clinical outcomes.[196] These included four studies using NH_3, fifteen using Rb^{82}, and one combining patients who underwent either. These studies were published between 1993 and 2013. The authors reported that similar to SPECT, a significant increase in risk of cardiac death was present in patients with > = 10% ischemic myocardium (summary hazard ratio [HR] 1.66, 95% CI 1.51-1.82) or scarred (fixed defect) myocardium (HR 1.83, CI 1.70-1.96). Furthermore, analyses revealed that an SSS of 4 or more (> = 6%) and a CFR less than 2 identified significant associations with major adverse cardiovascular events (HR, 95%, CI 2.30 [1.53-3.44] and 2.11 [1.33–3.36]), respectively].

A recent multicenter registry evaluated the prognostic value of stress PET-MPI in 7061 patients with known or suspected CAD who underwent a rest/stress ^{82}Rb PET drawn from four sites.[194] Risk-adjusted analyses revealed that over a median follow-up of 2.2 years, stress PET results added incremental value over preimaging data for the prediction of cardiac death. Compared to normal studies, mild, moderately, and severely abnormal studies were associated with HRs of 2.3 (1.4-3.8), 4.2 (2.3-7.5), and 4.9 (2.5 to 9.6; all $P < .001$), respectively. A study comparing the prognostic value of stress PET by sex was also reported from a subset of 6037 patients in this multicenter effort.[190] In this study, men had greater likelihood of CAD and more frequently had PET abnormalities. Men had a higher mortality rate during follow-up (5-year mortality: 6.0% vs 3.7%, $P < .001$; 115 vs 54 deaths). PET results added incremental value in both men and women and had numerically similar adjusted HRs (women 1.81 [1.54-2.14]; men 1.71 [1.52–1.94]). Hence, stress cardiac PET was prognostically valuable for both women and men. This registry has also been used to ascertain and compare the prognostic implications of PET-MPI in normal, overweight, and obese patients.[197] Body mass index (BMI) as is grouped in three patient categories: normal (< 25 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥ 30 kg/m^2, with a mean BMI of 30.5 ± 7.4 kg/m^2). PET results defined by a percent myocardium abnormal were categorized into normal (0%), mild (1%-9.9%), moderate (10%-19.9%), and severe (≥ 20%). In 6037 patients, a normal PET-MPI was associated with an excellent prognosis with very low annual cardiac death rates in normal (0.4%), overweight (0.4%), and obese (0.2%) patients. Furthermore, in all three BMI-defined categories, greater abnormality of PET-MPI results were associated with increased patient risk. Similarly, PET-MPI results added incremental prognostic value and enhanced risk stratification in all patient subgroups.

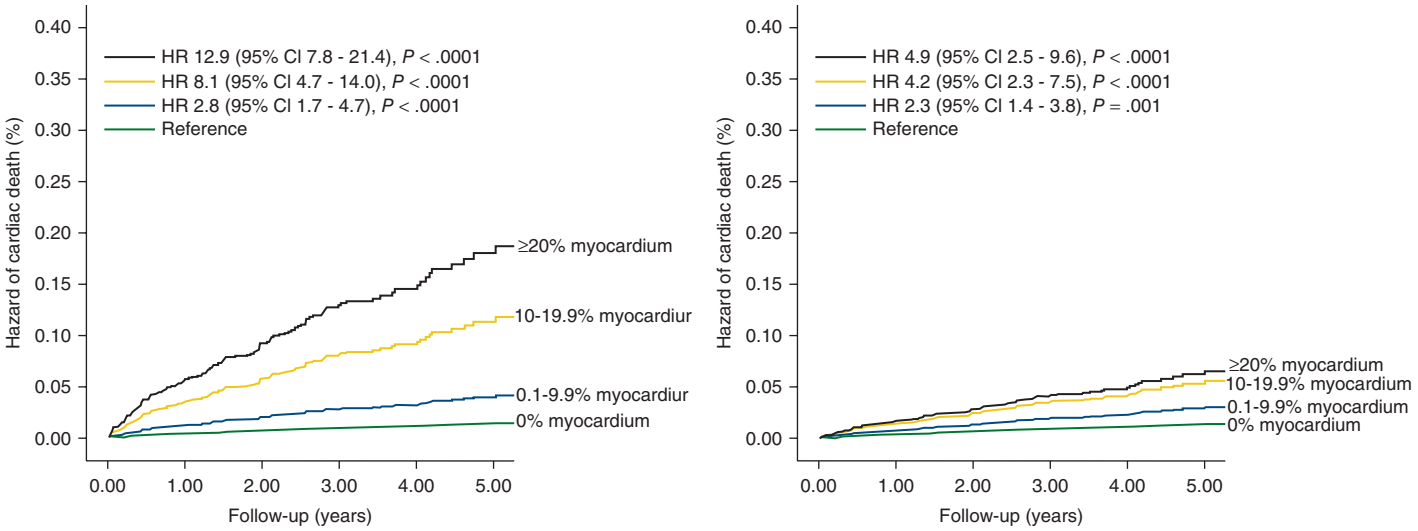

FIGURE 18–23. Unadjusted (*left*) and adjusted (*right*) hazard curves of cardiac mortality stratified by percent myocardium abnormal show increasing separation of risk over time across different amounts of abnormal positron emission tomography (PET) perfusion. Compared to a normal PET study, patients with mild, moderate, and severe PET perfusion defects have progressively greater hazard ratios (HRs). Reproduced with permission from Dorbala S, Di Carli MF, Beanlands RS, et al: Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. *J Am Coll Cardiol*. 2013 Jan 15;61(2):176-184.[194]

As noted above, one of the advantages of cardiac stress PET compared to stress SPECT is the acquisition of peak stress, rather than poststress image data. Hence, PET-MPI provides a rest LVEF, peak stress LVEF, and an LVEF reserve (stress LVEF–rest LVEF). The independent and incremental prognostic implications of rest and peak stress LVEF have been reported.[182,192,194,198] The prognostic value of the LVEF reserve information was first investigated by Dorbala and colleagues[182] in 985 consecutive patients who underwent gated rest/vasodilator stress ^{82}Rb PET. Over a mean follow-up of 1.7 years, the unadjusted annualized rates of cardiac death or nonfatal MI were greater in patients with an LVEF reserve less than 0% than with an LVEF reserve greater than 0% (2.1% vs 5.3%, $P < .001$). Multivariable survival modeling revealed that after adjustment for clinical, historical, and resting EF data, the LVEF reserve added incremental prognostic value for the prediction of both the end point of cardiac death or nonfatal MI and for all-cause mortality (Fig. 18–23).

In the MPI literature, the terms *coronary blood flow* and *coronary flow reserve,* or CFR, have been used interchangeably with the terms *myocardial blood flow* and *myocardial flow reserve*. A distinct clinical advantage afforded by the use of PET-MPI over SPECT-MPI is the ability to capture accurate, validated, and reproducible measures of rest and stress absolute flow and flow reserve on a per-vascular territory and global LV basis, as discussed in Chapter 19. The first large study examining the prognostic implications of impaired vasodilator function relative to indices of PET myocardial perfusion, Murthy and coworkers[192] examined a cohort of 2783 consecutive patients referred for stress PET who were followed up for a median of 1.4 years (IQR 0.7-3.2 years), with cardiac death as the primary end point. After adjustment for multiple factors, including rest LVEF, SSS, and LVEF reserve, compared to the highest tertile of CFR, the lowest tertile had a HR of 5.6 (95% CI, 2.5-12.4) and the middle tertile had a HR of 3.4 (95% CI, 1.5-7.7) (Fig. 18–24).[192] Similarly, Ziadi and colleagues[195] evaluated the added prognostic information provided by CFR using Rb^{82} PET-MPI in 677 patients who were followed for adverse events (median follow-up ~ 1 year). In a Cox model adjusted for pre–PET-MPI data, CFR was an independent predictor of the end point of cardiac death or MI (HR 3.3; 95% CI, 1.1-9.5; $P < .029$). This relationship persisted after adjustment for stress perfusion data.

Murthy and colleagues extended this work in an investigation of sex-related differences in 405 men and 813 women.[199] This cohort was identified on the basis of having no prior history of CAD and no evidence of CAD-associated perfusion defects on their PET studies. A threshold for abnormality of CFR was less than 2.0. In both men and women, a CFR less than 2.0 was a frequent finding (51% and 54%, equivalence $P = .0002$). Patients were followed over a median 1.3 years (IQR 0.5-2.3 years) for major adverse cardiac events (cardiac death, nonfatal MI, late revascularization, or hospitalization for heart failure). In both sexes, CFR was incrementally predictive of major adverse cardiac events (HR, 0.80 [95% CI, 0.75-0.86] per 10% increase in CFR; $P < .0001$). This finding shows an inverse relationship with higher CFR equating to lower risk and vice versa. Interestingly, the authors also reported that in a subgroup of 404 patients without evidence of CAC and with normal stress perfusion imaging in both sexes, a CFR of less than 2.0 was common (44% of men vs 48% of women). Future work is needed to identify its putative role as a therapeutic target.

An additional report focused on examining the prognostic significance of CFR among diabetics as compared to nondiabetics.[200] In this report, PET-assessed CFR was performed in a total of 1172 diabetic and 1611 nondiabetic patients who were followed up for a median of 1.4 years (IQR 0.7-3.2 years) for occurrence of cardiac death. An impaired CFR was defined as that falling below the median value and was associated with an adjusted 3.2- and 4.9-fold increase in cardiac death risk in diabetics and nondiabetics ($P < .0004$). CFR findings had a profound impact on risk assessment among diabetic patients without prior CAD—those with a reduced CFR experienced risk equivalent to nondiabetic patients with CAD while those with preserved CFR had a level of risk similar to that of patients without CAD or without diabetes; both of which were similar to patients with normal PET-MPI and LVEF (Fig. 18–24).[200] These data support an integral role for CFR in assessing risk. Even in patients without CAD and with normal LV function, after adjusting for multiple confounders, impaired CFR was associated with both the occurrence of a positive troponin and with major downstream adverse events.[201]

INTEGRATING CLINICAL DATA WITH NUCLEAR MPI RESULTS FOR RISK ASSESSMENT

A challenge facing clinicians attempting to apply nuclear MPI results to patient care is to distill all information reported after SPECT-MPI—clinical, historical, stress test, perfusion, and function data—for risk of

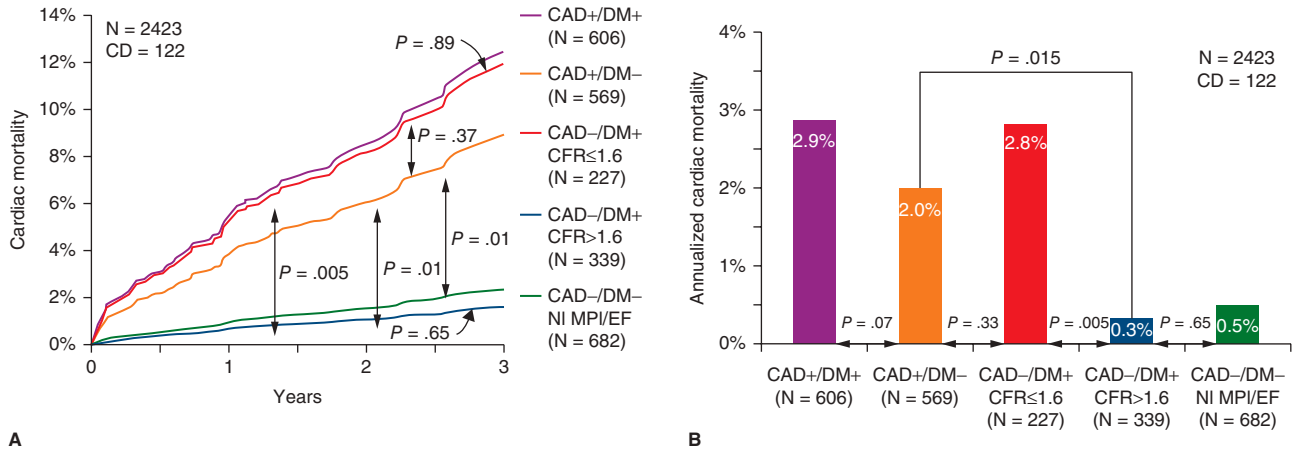

FIGURE 18–24. Adjusted and annualized cardiac mortality among patients with diabetes mellitus (DM) or coronary artery disease (CAD). Cardiac mortality among patients with DM or CAD. In (**A**), adjusted cardiac mortality survival curves in CAD patients (prior myocardial infarction or revascularization), patients without DM (orange), DM patients without CAD but with compromised CFR (red), DM patients without CAD and preserved CFR (blue), and patients without DM or CAD with normal perfusion and left ventricular function (green). In (**B**), annualized cardiac mortality rates are plotted. Data for patients with CAD and DM are also presented for comparison (purple). CD, cardiac death; EF, ejection fraction; MPI, myocardial perfusion imaging; NI MPI, normal myocardial perfusion imaging. Reproduced with permission from Murthy VL, Naya M, Foster CR, et al: Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation*. 2012 Oct 9;126(15):1858-1868.[200]

adverse events for an individual patient or likelihood of obstructive CAD as discussed above. Accurate final estimates of risk must incorporate all relevant prognostic factors. Ideally, validated prognostic assessments can be developed integrating all available sources of information, including nuclear MPI results, and be incorporated into nuclear MPI reporting.

Incorporating non-nuclear variables obtained at the time of testing in risk assessment is particularly difficult with pharmacologic stress because prognostically important variables used in exercise testing, such as exercise duration and exertional chest pain, are not components of pharmacologic stress testing protocols. To test the potential of a multivariable integration of findings into a single score, a score was developed in 5873 patients studied by adenosine stress who experienced 387 cardiac deaths on follow-up (6.6%).[58] The authors derived a complex score taking into account all significant variables, including age, percent myocardium ischemic, percent myocardium fixed, diabetes, dyspnea as the presenting symptom, resting HR, peak HR, and ECG findings. Separate scores were calculated for therapeutic choices of medical therapy or revascularization (Fig. 18–25). The results of this study, although not in common clinical use, point the way to how test results may be analyzed in the future. In this regard, improvement in prediction of obstructive coronary disease and post-MPI revascularization has been recently demonstrated by deriving integrated scores by machine learning from imaging and clinical features.[202,203] With the increased applications of machine learning methods and computer-assisted test analysis and reporting, application of these comprehensive assessments—which have the potential of systematically taking into account all available information—may become practical tools to improve the clinical interpretation and reporting of nuclear MPI studies.

Estimating the True Prognostic Value of Nuclear MPI and Post-Test Referral Bias

Although there is compelling evidence that SPECT- and PET-MPI are effective in the prognostic stratification, current data on risk stratification by nuclear MPI may underestimate the strength of this modality because of a prognostic counterpart to the verification bias described earlier. Most prognostic analyses performed to date are comprised of patients undergoing follow-up medical management and without documentation of the adequacy of guideline-directed care. Moreover, many survival analyses also censor revascularized patients at the time of their invasive procedure with varying physician practices of prompt or delayed referral to coronary revascularization. The rationale for censoring of revascularized patients is the traditional viewpoint that surgical intervention improved outcome. This practice is less commonplace today because current randomized trial evidence does not support risk reduction with coronary revascularization as compared to medical therapy.[152,204] Thus, there is a varied relationship between the test results and the referral to revascularization.[205] The result is a potential underestimation of the prognostic value of SPECT-MPI; the patients at the highest risk, with the most abnormal test results, are removed from the population being studied.[173,205,206]

The reduction in observed event rates resulting in this referral bias in medically treated patients with severe amounts of ischemia on SPECT-MPI[206] has been quantified. Thus, reported event rates in observational studies limited to medically treated patients may be high risk but underestimate the true risk in these patients; the patients with the greatest ischemic risk were referred for revascularization and censored from the

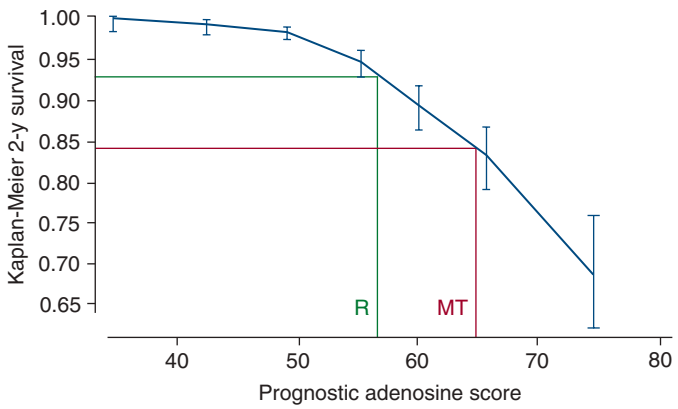

FIGURE 18–25. Relationship between prognostic adenosine score and 2-year Kaplan-Meier survival free of cardiac death. With lower scores, patient risk is relatively low with narrower confidence intervals. As scores increase, particularly over 50, risk increases more rapidly and confidence intervals increase as well. The orthogonal lines represent a specific example of an 80-year-old man with exertional shortness of breath who demonstrated 30% myocardium ischemic and 0% myocardium fixed on no-walk adenosine myocardial perfusion imaging. Using the adenosine score, early revascularization (R, green) would be predicted to have a 93% 2-year survival and medical therapy (MT, red), an 84% survival. Reproduced with permission from Hachamovitch R, Hayes SW, Friedman JD, et al: A prognostic score for prediction of cardiac mortality risk after adenosine stress myocardial perfusion scintigraphy. *J Am Coll Cardiol*. 2005 Mar 1;45(5):722-729.[58]

prognostic studies. Moreover, the quality of medical management is quite disparate, and the relative adherence to SIHD guidelines is unknown.[152] Statistical techniques may be applied in observational cohorts that may yield insight into the potential for stress MPI to define candidates and guide management of SIHD patients.[25,58,205]

NUCLEAR MPI AND CLINICAL DECISION MAKING: ASSESSMENT OF CARDIAC RISK VERSUS POTENTIAL SURVIVAL BENEFIT FROM REVASCULARIZATION—RANDOMIZED TRIALS AND OBSERVATIONAL FINDINGS IN SIHD

The paradigm of the application of nuclear MPI to patient risk assessment conceptually yields a series of strata, representing the spectrum of risk and where along the continuum of risk patient undergoing nuclear-MPI falls after consideration of clinical, historical, stress test, and nuclear MPI results. Beyond risk stratification, optimal selection of patient treatment should be based on reasonable estimates of potential patient benefit with respect to a relevant and important end point with one treatment option versus an alternative. Moreover, the current evidence on the potential benefit of stress MPI should be considered in light of the randomized trial evidence and guideline-directed medical therapy approaches, which largely support equipoise on the use of surgical revascularization even for those with moderate to severe ischemia.[152]

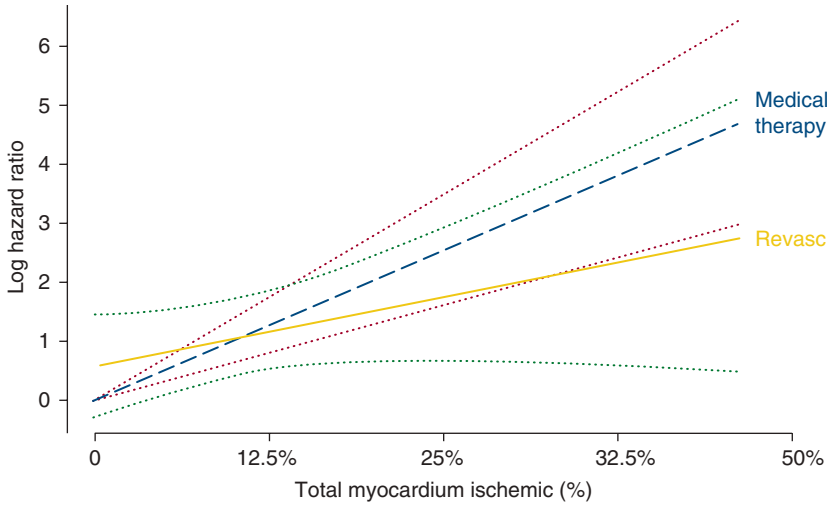

FIGURE 18–26. Relationship between percent myocardium ischemic and log of the hazard ratio in 10,647 patients treated either with medical therapy (*dashed line*) or early revascularization (< 60 days after single-photon emission computed tomography myocardial perfusion imaging; *solid line*) based on multivariable modeling. In the setting of little or no ischemia, medical therapy is associated with superior survival; with increasing amounts of ischemia, a progressive survival benefit with revascularization over medical therapy is present. Ninety-five percent confidence intervals are shown by the closely dotted lines. Reproduced with permission from Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003 Jun 17;107(23):2900-2907.[207]

Identifying Optimal Post-MPI Patient Management

Evidence is evolving that beyond identifying patient risk, a principal role of nuclear MPI in a testing strategy is the identification of patients who may accrue a *clinical benefit* in terms of risk reduction with a specific therapeutic approach. Observational evidence is available from registry data and randomized trials regarding the impact of stress MPI for medical management decisions of patients with SIHD.[207-211] With regard to the observational evidence on a survival benefit with coronary revascularization, a study of 10,627 patients without prior MI or revascularization underwent stress SPECT-MPI reported a survival benefit for patients undergoing medical therapy versus revascularization in the setting of no or mild ischemia, whereas patients undergoing revascularization had an increasing survival benefit over patients undergoing medical therapy when moderate to severe ischemia was present (> 10% of the total myocardium ischemic) (Fig. 18–26).[25] Furthermore, the roles of stress perfusion and gated SPECT-MPI EF in identifying this observational benefit have also been compared.[179] Although EF, percent myocardium ischemic, and the percent myocardium fixed are all predictors of cardiac death, the first is by far the best predictor of cardiac mortality. Conversely, only inducible ischemia identified patients who would benefit from revascularization compared with medical therapy (Fig. 18–27). With increasing amounts of ischemia, increasing survival benefit for revascularization over medical therapy was found, across all values of EF. A subsequent study by the same investigators examined this relationship in a large cohort of 13,969 patients both with and without prior CAD who were followed-up for an average of 8.7 years after MPI. As previously described, patients without prior CAD (n = 8791) had improved survival with revascularization in the setting of significant ischemia, as did patients with prior revascularization but no prior MI (n = 1542). However, as an overall group, patients with prior MI (n = 3216) did not show benefit with early revascularization as a function of the extent of ischemia (Fig. 18–28). However,

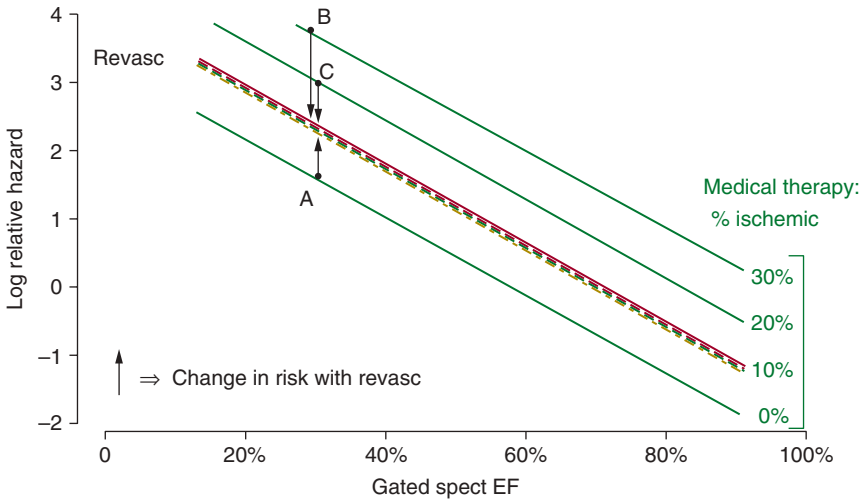

FIGURE 18–27. Relationship between gated single-photon emission computed tomography (SPECT) ejection fraction (EF) and log of the hazard ratio in 5366 patients based on multivariable modeling. *Solid lines* represent predicted survival for 0%, 10%, 20%, and 30% myocardium ischemic in medically treated patients. *Dashed lines* represent predicted survival for patients treated with revascularization for all values of percent myocardium ischemic. Overall, risk increased with decreasing ejection fraction (EF). For any value of EF, however, risk also increases as percent myocardium ischemic increases, indicating an incremental value for percent myocardium ischemic over EF. Compared with risk in patients treated medically, risk in patients undergoing early revascularization (revasc) was independent of the percent myocardium ischemic present (as evidenced by a *single dashed line* representing survival after revascularization for all degrees of ischemia). Risk in early revasc patients was similar to the risk of medically treated patients with 10% myocardium ischemic, throughout the range of EF. Reproduced with permission from Hachamovitch R, Rozanski A, Hayes SW, et al: Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? *J Nucl Cardiol*. 2006 Nov;13(6):768-778.[208]

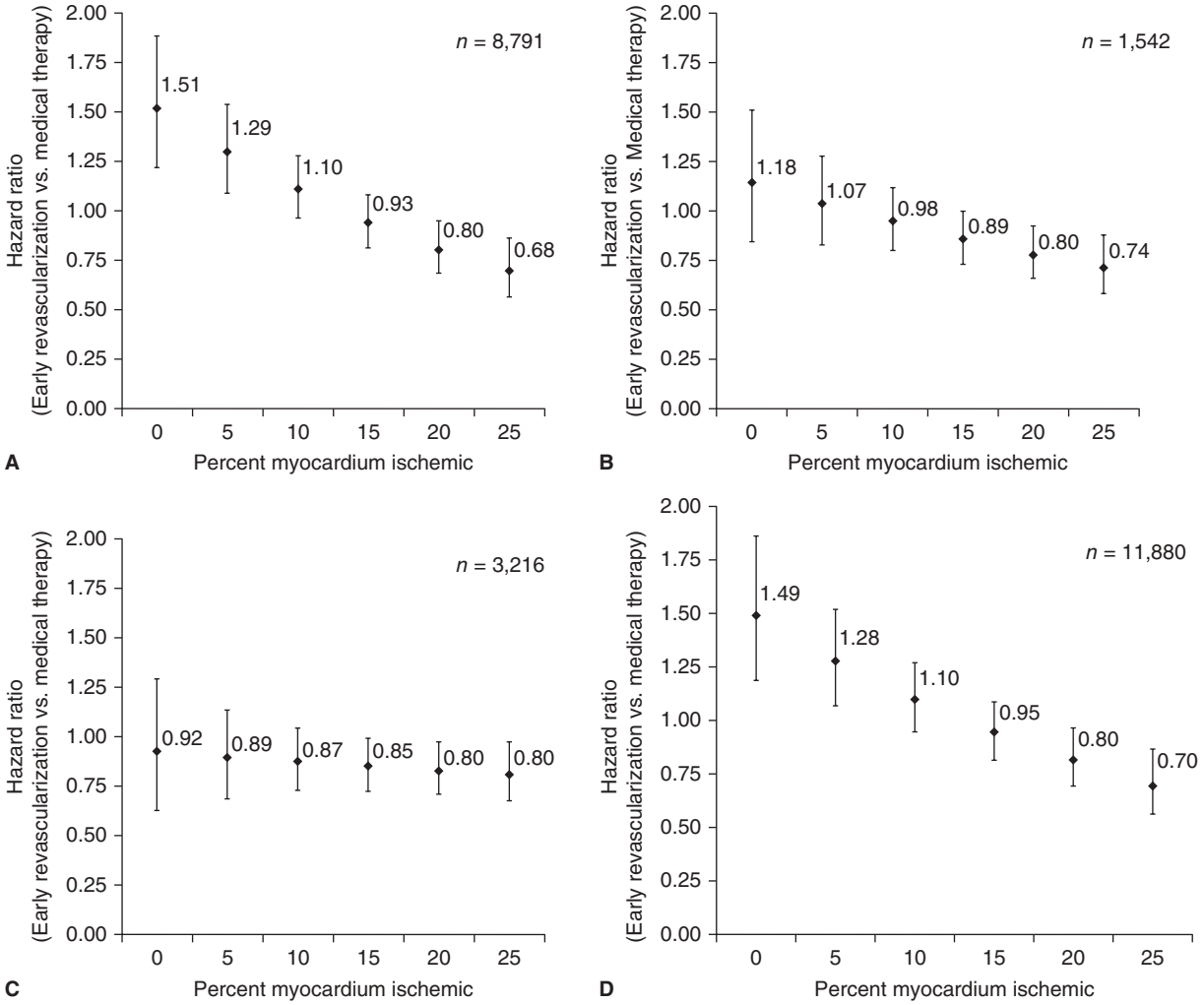

FIGURE 18–28. Hazard ratios (with 95% confidence intervals) for death with early revascularization versus medical therapy at specific values of single-photon emission computed tomography–measured ischemia (percent myocardium ischemic) based on Cox proportional hazards survival modeling. (**A**) Patients with no prior coronary artery disease, (**B**) patients with prior revascularization but no prior myocardial infarction (MI), (**C**) patients with prior MI (with or without prior revascularization), and (**D**) patients with < 10% fixed defect. *P* values as per Cox proportional hazards model. Reproduced with permission from Hachamovitch R1, Rozanski A, Shaw LJ, et al: Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy, *Eur Heart J*. 2011 Apr;32(8):1012-1024.[209]

patients with more than 10% to 15% of their myocardium ischemic, but with less than 10% of their myocardium with fixed defects, had a survival benefit with revascularization compared to medical therapy alone. These observational findings suggest that it was patients with extensive scar in whom ischemia did not identify a survival benefit.[209,212]

The value of MPI-assessed ischemia to identify patients who may benefit from revascularization has been assessed in other observational patient cohorts. In 5200 patients who were age 75 years or older, increasing ischemia was associated with increasing survival with early revascularization. Of interest, the threshold of ischemia at which this survival benefit appeared to be present was higher (≥ 15%) than observed in the previously described.[213] Sorajja and colleagues extended these results in a series of 826 asymptomatic diabetic patients without known CAD who had undergone stress SPECT-MPI. Improved post-MPI survival with revascularization during follow-up was limited to those patents with high-risk SPECT treated with coronary artery bypass grafts (CABGs).[214] Finally, a recent study of asymptomatic patients with history of prior revascularization, no benefit with revascularization was found, despite the presence of significant ischemia.[215] This observational survival benefit was striking in higher risk patients (ie, elderly, requiring adenosine stress, women, and diabetics). Thus, in assessing treatment options in an individual patient, cardiac risk factors, comorbidities, coincidental anatomic findings, and EF all have to be considered along with ischemia to determine the potential advantages of a specific therapeutic strategy.

Observational studies, such as those discussed above, are primarily intended for hypothesis generation and have significant limitations. These include concerns regarding generalizability and dependency on risk adjustment techniques. Use of the latter does not obviate the impact of selection biases, unmeasured covariates, and other factors, on the results of the study.[156] For instance, to what degree the intensity of medical therapy in these studies is equivalent to that used in clinical trials is uncertain. However, these studies are effectiveness studies—treatment received by patients was dictated by clinical practice. Hence, they may better represent patients seen in practice and changes in practice over time than in randomized trials.

These results from single-site observational series have been recently extended by the results of prospective randomized clinical trials of SIHD.[204,216] Shaw and coworkers[210] reported several important results from the nuclear substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. First, in this subset of COURAGE patients, the addition of percutaneous coronary intervention (PCI) to optimal medical therapy (OMT) resulted

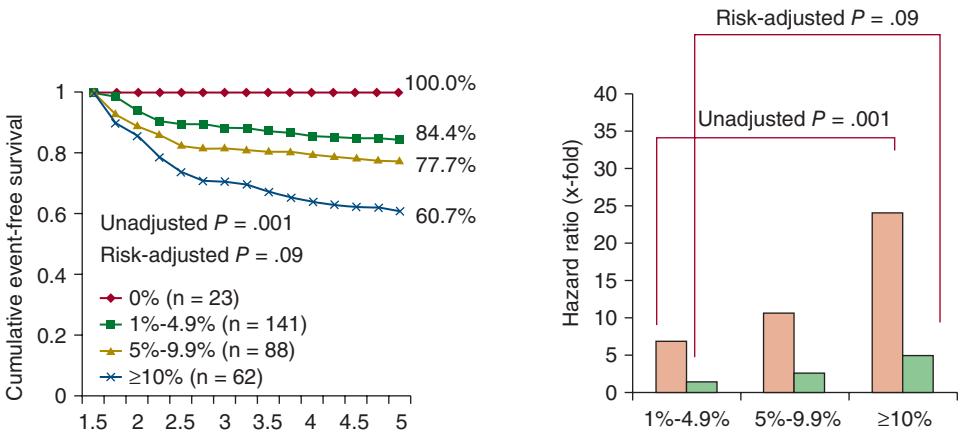

FIGURE 18–29. Kaplan-Meier survival for patients by residual ischemia after 6 to 18 months of percutaneous coronary intervention plus optimal medical therapy or optimal medical therapy alone (*left*). Overall event-free survival rates were 100%, 84.4%, 77.7%, and 60.7% for 0%, 1% to 4.9%, 5% to 9.9%, and 10% ischemic myocardium, respectively ($P = .001$). In a risk-adjusted Cox model (controlling for randomized treatment), this difference was not significant ($P = .09$). Unadjusted (brown bars) and risk-adjusted (green bars) hazard ratios for the extent and severity of residual ischemia at 6 to 18 months of follow-up (*right*) are shown. Reproduced with permission from Shaw LJ, Berman DS, Maron DJ, et al: Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy, *Circulation*. 2008 Mar 11;117(10):1283-1291.[210]

in more effective reduction of ischemia and angina symptoms than OMT alone. The reduction in ischemia was documented by comparing pretreatment (baseline) MPI to repeat stress MPI 1 year after. Importantly, regardless of treatment assignment, the magnitude of residual ischemia determined by follow-up SPECT-MPI was proportional to the risk of death or MI, and patients with a greater than 5% reduction in ischemia, measured quantitatively by the TPD at stress minus the TPD at rest, had a reduced rate of death or MI (Fig. 18–29).[210] Importantly, this substudy within the COURAGE trial was powered to examine an ischemia reduction and not for clinical events. Accordingly, this significant univariable analysis was not statistically significant in adjusted analyses.

An additional study from the COURAGE trial evaluated the results of site-interpreted MPI in 1381 patients randomized to OMT alone versus PCI and OMT who had baseline MPI studies.[217] Using the results of interpretation of defect extent using a six-segment model, researchers found no difference in rates of death and MI in patients with three segments or more with ischemia versus those patients with less than three segments. Furthermore, patient risk did not increase with worsening extent of ischemia, suggesting a failure to risk stratify. Importantly, this report is unique in reporting the results of MPI interpretation and outcomes from numerous sites in the United States and Canada. The results suggest the possibility that differences between "expert" reads to a variety of readers with varying experience affect outcomes.

The most recent study from COURAGE examined 621 patients with baseline quantitative MPI data and quantitative anatomic data to determine the predictive value of these two measures on patient outcomes (end point of death, MI, and non–ST-segment elevation acute coronary syndromes [ACS]) in medically treated patients as well as to determine whether either of these factors could identify which patients would benefit from one therapeutic approach versus another.[218] The authors found that both with and without risk adjustment, coronary anatomic burden and LVEF were significantly associated with patient outcomes. Neither ischemia nor treatment assignment was predictive, although a significant interaction between ischemic burden and coronary artery anatomy was present. Most importantly, however, neither coronary anatomy nor ischemic burden was predictive of which treatment option would be predictive of improved survival.

Finally, the nuclear substudy from Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) included data from SPECT-MPI studies performed 1 year after enrollment in 1505 patients randomized to medical therapy versus medical therapy with revascularization.[211] Thus, the ability to compare reductions in MPI abnormalities following intercurrent randomized treatment was not possible because of a lack of data collection in the prerandomization setting. However, comparing 1-year MPI results in patients who received revascularization plus medical therapy had smaller total defect size and lower percent myocardium ischemia when compared to those receiving medical therapy alone. At 1 year after randomization, 59% of revascularized patients had ischemia compared to 49% with OMT alone ($P < .001$). Furthermore, 4-year risk of death and MI increased with more severe and extensive MPI defects.[211] As was the case in the COURAGE nuclear substudy, the relationship between treatment, MPI results, and outcomes was not statistically significant. Although there are statistical power issues in the randomized trial comparisons for clinical effectiveness, these data support the main SIHD trial findings, such as from COURAGE and BARI 2D, that revascularization reduces angina and ischemic findings as compared to medical therapy for patients with SIHD. However, no differences in long-term event reduction were reported for either trial when comparing PCI versus medical therapy.

There is little published data evaluating the ability of stress PET-MPI to observationally identify which patients may accrue a survival benefit with revascularization with medical therapy compared to optimal medical therapy (OMT) alone. In a study of 2223 patients followed for a median of 3.6 years after PET-MPI, Taqueti and colleagues examined the association of post-MPI treatment, the amount of ischemia present, and post-test patient outcomes.[219] Cox proportional hazards modeling adjusting for multiple potential confounders, including a propensity score to correct for nonrandomized treatment allocation ($P < .0001$), revealed significant interactions between ischemia and the use of revascularization (ie, survival increased with the use of revascularization for patients with more extensive and severe ischemia) and between CFR and the number of anti-ischemic medications used ($P = .01$). As with SPECT, these findings are observational and hypothesis generating, thus further investigations are necessary.

STRESS MPI IN THE SIHD CLINICAL PRACTICE GUIDELINES

Applications of nuclear MPI in SIHD are included in the recent ACCF/AHA clinical practice guidelines on SIHD[152] as well as in the European Society of Cardiology (ESC) guidelines for management of stable CAD.[220] They are also covered in the ACCF/AHA multimodality appropriate use criteria (AUC), as discussed below. The ACCF/AHA SIHD guideline assigned a class Ib level of evidence to exercise MPI for patients with an intermediate to high pretest risk who have an ECG for which the exercise response cannot be interpreted and a class Ia for those unable to exercise. An exercise stress MPI in this same subset with an intermediate to high risk in the presence of an interpretable ECG was assigned a class IIa level of evidence. More details on these indications are also provided in the AUC section and in the sections on specific patient cohorts. With regards to ischemia-guided management, the SIHD clinical practice guideline recommend initiation of guideline-directed medical therapy as the initial post-test treatment strategy. However, they also provide variable

recommendations for revascularization, including consideration of patient preferences and clinical factors, as well as the high-risk stress test findings.[152,220] In general, the index approach for most patients is OMT with invasive angiography limited to those failing to improve symptoms following treatment intensification. In the ESC guidelines, consideration of revascularization is limited to patients with more than 10% ischemic myocardium.[220] However, as discussed above, there is no randomized trial evidence to demonstrate a therapeutic risk reduction with revascularization as compared to OMT in patients with moderate to severe ischemia (ie, > 10% ischemic myocardium). Current randomized trials fail to support such a threshold benefit and the lack of consistent recommendations across the guidelines reflects the variable evidence base. The ongoing International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial is examining this primary aim with enrollment of about 5000 patients with moderate to severe ischemia on stress imaging. Patients are being randomized to a routine invasive strategy with cardiac catheterization followed by revascularization when appropriate plus OMT or to a conservative strategy of OMT. In the latter group, catheterization and revascularization are reserved for those who fail OMT. Additional SIHD and other MPI trials using MPI are discussed in the special patient population sections below.

POST-MPI RESOURCE UTILIZATION AND COST-EFFECTIVENESS FINDINGS

A number of investigators have examined the relationship between SPECT-MPI and subsequent patient management. Overall, there is a clear relationship present in patients with normal scans; only a small proportion undergoes early post–SPECT-MPI cardiac catheterization, usually as a result of clinical symptomatology.[100,161,208,209,221-225]

As first shown by Hachamovitch and coworkers, the extent and severity of reversible defects shown by the SPECT-MPI result are the dominant factors driving subsequent resource utilization[25] (Fig. 18–30). Importantly, even among the patients at greatest post-MPI risk—patients with high postexercise treadmill test likelihood of CAD and moderate to severe MPI abnormalities—only about half the patients were referred to catheterization. These findings, coupling MPI results to catheterization rates and potential underuse of catheterization, have been confirmed by this group and other authors.[100,161,208,209,221-225] Regarding the cost-effectiveness of this approach, Shaw and colleagues,[225] in a multicenter study of 11,249 patients, extended these results to show that a strategy of SPECT-MPI with selective subsequent catheterization produced a substantial reduction (31%-50%) in costs for all levels of pretest clinical risk compared with a direct catheterization approach (Fig. 18–31), with essentially identical outcomes as assessed by cardiac death and MI rates. Importantly, in the SPECT-MPI strategy, rates of revascularization, rates of cardiac catheterization after normal SPECT-MPI, and the frequency of normal coronary angiographic findings were significantly reduced.[225]

A recent prospective, multicenter study, the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease (SPARC), examined referral rates to catheterization and use of medical therapy after clinically ordered SPECT, PET, and CTA in patients from 40 sites.[223] In a cohort of 1703 patients with no prior CAD and intermediate to high pretest likelihood of CAD, the authors found that referral rates to catheterization mimicked those in previous studies; after the most abnormal test results, 38% to 61% of patients were not referred to catheterization (Fig. 18–32). Additionally, about half these patients with significant abnormalities did not receive medical therapy. Although there were significant increases in the use of aspirin and beta-blockers post-testing, the change in use of lipid-lowering agents was not significant. Furthermore, only one in five patients were on all three of these medications, most were on one or two of them, and there was no increase in the proportion of patients with increased number of medications after testing (Fig. 18–33). The study did not examine the root cause of these results, but they do suggest that additional studies are needed and, perhaps, postnoninvasive utilization of resources may need to be considered as a quality metric.

The data are robust on the cost consequences that follow the above discussion on post-testing resource consumption testing patterns. Although the older nuclear MPI literature is replete with cost-effectiveness analysis, more contemporary evidence has also recently been reported. In a report including a large number of Medicare beneficiaries (n = 282,830), 180-day costs of stress MPI were compared to those of CCTA.[226] An index testing strategy of CCTA was associated with higher rates of follow-up coronary angiography and revascularization procedures and, as a result, had higher total health care spending ($P < .001$). The costs for stress MPI were about $4200 lower over 6 months when compared to CCTA.

Similarly, in another report from the SPARC registry, 1703 patients with suspected CAD were enrolled and underwent CCTA (n = 590), stress PET-MPI (n = 548), or stress SPECT-MPI (n = 565).[227] In this registry, stress PET-MPI patients had the highest risk, with 2-year mortality of 5.5%, followed by stress SPECT-MPI (1.7%), and lowest with CCTA (0.7%). The stress PET-MPI patients had the highest costs at $6647 at 2 years, with costs of $4909 for CCTA and $3695 for stress SPECT-MPI. In a decision analytic model, the incremental cost-effectiveness ratio for CCTA versus SPECT was $11,700 per life year saved. These results support that risk is a prominent factor impacting resource consumption patterns and costs following testing; that is, when comparing the cost-effectiveness of tests, risk adjustment is of paramount importance.

The Cost Effectiveness of Noninvasive Cardiac Testing (CeCAT) trial studied 898 patients referred

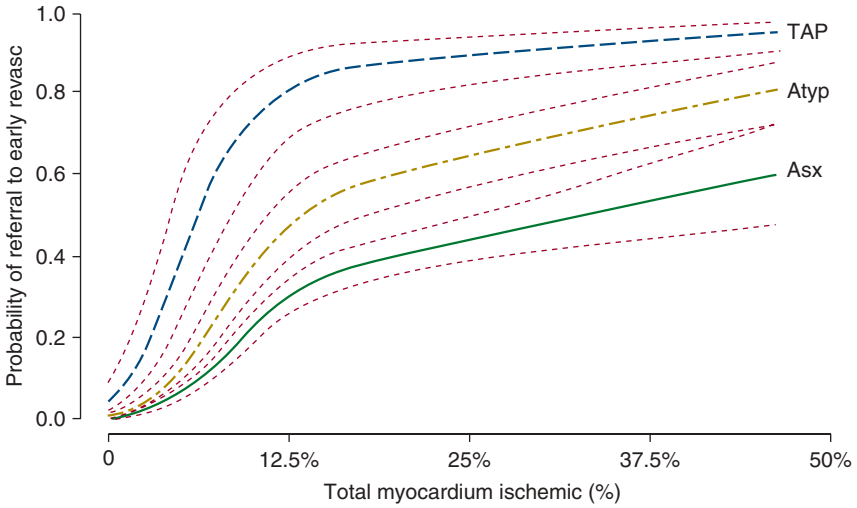

FIGURE 18–30. Relationship between percent myocardium ischemic and probability of referral to early revascularization (revasc; < 60 days post–single-photon emission computed tomography– myocardial perfusion imaging). Results are based on multivariable modeling in 10,647 patients. In this study, percent myocardium ischemic was most strongly associated with referral to revascularization (83% of all information used for decision making). Furthermore, patients' presenting symptoms also influenced this process as evidenced by greater likelihood of referral at any level of ischemia with typical versus atypical versus asymptomatic patients. Atyp, atypical; Asx, asymptomatic; TAP, typical angina pectoris. Reproduced with permission from Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003 Jun 17;107(23):2900-2907.[207]

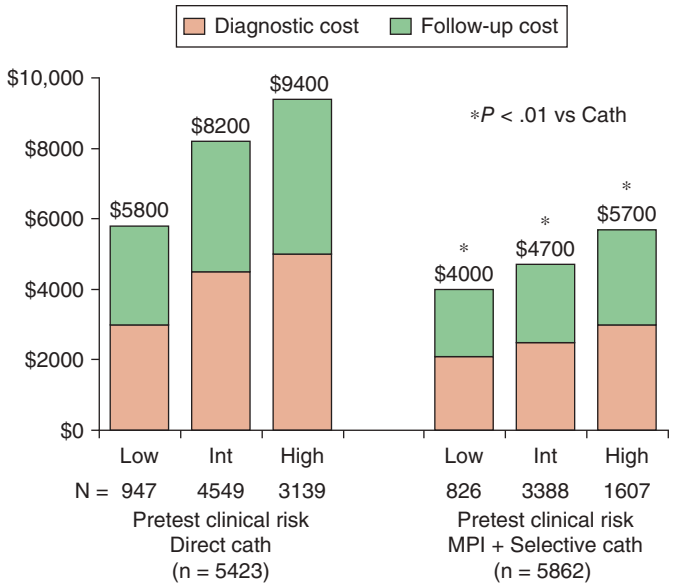

FIGURE 18–31. Comparative cost between screening strategies using direct catheterization (Cath) and myocardial perfusion imaging (MPI) with selective Cath. Low, Int, and High represent low-, intermediate-, and high-risk subsets of the patients with stable angina. Shown are the initial diagnostic costs (brown bars) and follow-up costs including costs of revascularization (green bars). A 30% to 41% reduction in costs was noted in each category. Hard event rates were similar in the two strategies, but the revascularization rate was twice as high in the direct Cath group. Adapted with permission from Shaw LJ, Hachamovitch R, Berman DS, et al: The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group, *J Am Coll Cardiol*. 1999 Mar;33(3):661-669.[225]

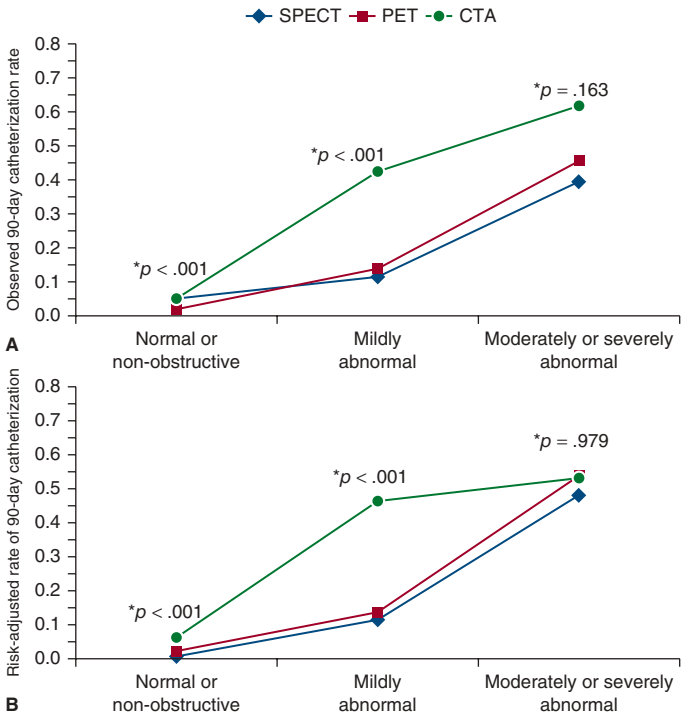

FIGURE 18–32. Observed (**A**) and predicted (**B**) rates of referral for cardiac catheterization after normal/nonobstructive, mildly abnormal, or moderately to severely abnormal within 90 days of single-photon emission computed tomography (SPECT), positron emission tomography (PET), or computed tomography angiography (CTA) in patients from the study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease study. Both unadjusted and adjusted catheterization rates significantly increased with worsening abnormal results in all three modalities. Results of statistical testing of differences in catheterization rates between modalities within study result categories are indicated by *asterisks*. Reproduced with permission from Hachamovitch R, Nutter B, Hlatky MA, et al: Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease), *J Am Coll Cardiol*. 2012 Jan 31;59(5):462-474.[223]

for nonurgent coronary angiography who were randomized in a 1:1:1:1 basis to SPECT, cardiac magnetic resonance (CMR), stress echocardiography (echo), or catheterization (cath). The study was designed to study the noninvasive tests as a gatekeeper to invasive coronary angiography, evaluating mortality and costs.[228] CMR was associated with a higher mortality rate as compared to the other modalities, and the mortality rates in the other groups were not significantly different from the mortality rate in the cath group. Overall, the frequency of cath was reduced by 20% to 25% in the noninvasive testing arms. Stress SPECT-MPI was economically superior to the other noninvasive tests and to cath, with a more than 70% probability of being cost effective (in bootstrap simulations) when compared to stress CMR imaging and echocardiography. The 2-year costs for stress SPECT-MPI were lower than those for invasive coronary angiography. The costs for stress echocardiography were actually higher than for coronary angiography, which the authors attribute to the relatively high risk of the population being studied.

A synthesis of the cost data underscores the importance of pretest risk in assessing cost effectiveness. As expected, as risk increases, there are greater treatment intensity and greater costs of care. Cost-effectiveness of the various noninvasive and invasive approaches depends to a large extent on the risk of the patients being tested.

COMPARATIVE EFFECTIVENESS

A recent large comparative effectiveness trial compared stress testing, which was predominantly MPI, to coronary CT angiography. Sponsored by the National Institutes of Health (NIH)–National Heart, Lung, and Blood Institute (NHLBI), the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) evaluated 10,003 symptomatic patients who were randomized to an initial

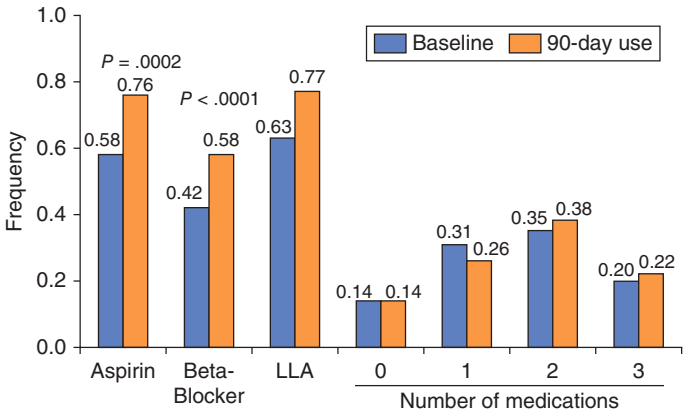

FIGURE 18–33. Frequency of aspirin, beta-blocker, and lipid-lowering agent use and the proportion of patients taking none, one, two, or three of these agents before versus 90 days after single-photon emission computed tomography, positron emission tomography, or coronary computed tomography angiography in patients with moderately to severely abnormal imaging results and no prior coronary artery disease. Results from the Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease. The *P* values indicate differences in baseline versus 90-day medication use. Reproduced with permission from Hachamovitch R, Nutter B, Hlatky MA, et al: Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease), *J Am Coll Cardiol*. 2012 Jan 31;59(5):462-474.[223]

strategy of CCTA versus functional testing (67% nuclear MPI, 23% stress echocardiography, and 10% exercise ECG).[229] Although all enrollees were symptomatic, the majority (78%) had atypical symptoms with the result being a low risk cohort with a low rate of CAD events. The primary end point was death, ACS, or major procedural complication, which occurred in approximately 3% of randomized patients at 2 years of follow-up. The primary end point was similar by randomization strategy with an HR of 1.04 (95% CI, 0.83-1.29; $P = .75$). Similarly, the Scottish COmputed Tomography of the HEART Trial (SCOT-HEART) randomized 4146 patients with suspected CAD to CCTA or standard of care arms. In both arms, stress testing was usually performed.[230] The results of this trial do not provide information regarding comparative effectiveness with MPI directly, because only about 10% of the patients in the standard of care arm underwent MPI.

To provide value, MPI must be applied in a population with at least intermediate risk or likelihood of CAD. Notably, the PROMISE trial provided evidence that the pretest likelihood of obstructive CAD and of risk is overestimated by current clinical algorithms. The event rate in the population was substantially lower than expected based on historical data. Whereas the mean pretest likelihood of obstructive CAD by the Diamond-Forrester classification was 53.3 ± 21.4%, the observed prevalence of 50% stenosis or more on CCTA in the CCTA arm was only 10.7% and the prevalence of abnormality on stress testing was only 11.7%. A change in true likelihood of CAD according to age, sex, and symptoms, since the time of the initial descriptions by Diamond and Forrester, may have occurred over time, accounting for these observations. In this regard, recent findings in 39,515 patients undergoing SPECT-MPI over an 18-year period have shown a dramatic fall in the frequency of abnormal SPECT-MPI procedures, despite a rise in the apparent pretest likelihood of CAD (Fig. 18–34). These observations suggest the need to use new algorithms for assessing pretest likelihood of CAD and of risk inpatients considered for referral to noninvasive testing. To this end, the recently described CONFIRM risk score developed by Min and colleagues provides an easily applied approach, which has been validated in patients undergoing coronary CTA and SPECT-MPI studies.[231]

AUC FOR OPTIMAL PATIENT SELECTION

The ACC, in conjunction with multiple professional organizations, has developed AUC for applications of testing in cardiology. Such AUC play a complementary role along with clinical practice guidelines. The documents were developed to guide health care coverage decisions and are now mandated by many private payers in the United States. Use of the AUC or similar approaches will be required for Medicare coverage beginning in 2018.[232] The initial AUC were published for cardiac radionuclide imaging, which were then updated.[233,234] Recently, a multimodality AUC document was published and replaced prior published documents.[235] Although the recent document includes multimodality criteria including exercise ECG, stress echocardiography, stress magnetic resonance imaging, CCTA, and stress nuclear MPI, we will highlight the criteria directly relevant to stress SPECT and PET-MPI. Of note, the AUC considers the assessments of SPECT and PET-MPI as the same.

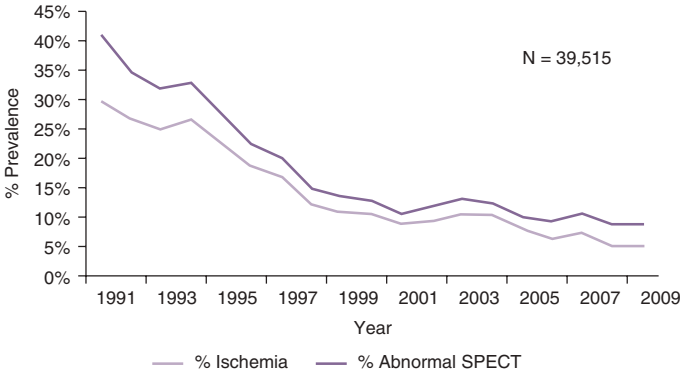

FIGURE 18–34. Year-by-year prevalence of abnormal and ischemic single-photon emission computed tomography (SPECT)–myocardial perfusion imaging studies between 1991 and 2009 among 39,515 patients tested at Cedars-Sinai Medical Center. Reproduced with permission from Rozanski A1, Gransar H, Hayes SW, et al: Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. *J Am Coll Cardiol*. 2013 Mar 12;61(10):1054-1065.

In the multimodality AUC for detection and risk assessment in SIHD, three principal scenarios are discussed and rated based on AUC categories: suspected SIHD, known SIHD, and preoperative cardiac assessment.[235] Each modality is rated individually, and the ratings of each procedure were accomplished by evaluating the evidence within the modality and not as a comparison between the modalities. The multimodality AUC categorizes indications for cardiac imaging as appropriate, maybe appropriate, or rarely appropriate. Moreover, the term maybe appropriate also indicates that some of the patients within a given indication will be candidates for MPI. Further, the term *appropriate* does not mandate testing but supports that a large proportion of patients within a given indication will be candidates for nuclear MPI. Importantly, the term *rarely appropriate* does not prohibit testing but implies that only a limited number of patients within a given indication will be candidates for nuclear MPI. For nuclear MPI, rarely appropriate indications largely include low-risk or asymptomatic patients. Several published reports have examined the proportion of appropriate indications based on patient referrals to an SPECT-MPI laboratory.[234,236-238] From the largest series, Hendel and coworkers[239] presented data on 5928 patients, with 71%, 15%, and 14% of the studies being categorized as appropriate, maybe appropriate, or rarely appropriate, respectively. The most common rarely appropriate indications were (1) asymptomatic low-risk patients, (2) asymptomatic patients less than 2 years postrevascularization, (3) evaluation of chest pain in low-probability patients with interpretable ECG who were able to exercise, (4) asymptomatic patients (or patients with stable symptoms) with known CAD less than 1 year after angiography or prior abnormal stress nuclear study, and (5) preoperative assessment prior to low-risk surgery. These five indications accounted for 12% of all studies and 92% of the studies that were considered inappropriate. By reducing utilization of inappropriate or rarely appropriate studies, considerable cost savings could be achieved. From a recent meta-analysis in 22 studies in 23,343 patients, the proportion of rarely appropriate testing was 15%.[240] This analysis also indicated that rarely appropriate MPI had a 59% reduced odds of being abnormal ($P < .0001$) when compared to patients with appropriate indications for MPI.

Decision support tools have been developed for use of the AUC and can guide improvements in appropriate referral patterns and reduce unwarranted testing patterns. Lin and colleagues published findings following the introduction of an AUC decision support tool, noting an increase appropriate use (pre: 49% to post: 61%, $P = .02$) and marked reductions in inappropriate use (pre: 22% to post: 6%).[241]

Reports examining clinical outcomes based on AUC are limited.[242,243] From one series of 1511 patients, the relative hazard for CAD death or MI was elevated nearly four-fold for patients with abnormal MPI when those tested with appropriate or maybe appropriate indication were compared to patients with a rarely appropriate indication ($P = .006$). A smaller study of 280 patients demonstrated that appropriate studies are more likely to result in abnormal results requiring subsequent revascularization compared to rarely appropriate and may be appropriate stress studies.[244] These studies provide evidence of greater risk stratification by testing when used in patients with an appropriate indication than in patients with rarely appropriate indications.

USE OF SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY–MYOCARDIAL PERFUSION IMAGING IN SPECIFIC PATIENT POPULATIONS

A principal strength of nuclear cardiology is that large databases have been accumulated resulting in evidence documenting the effectiveness of SPECT and PET-MPI for risk stratification of appropriately selected patients, comprising the full spectrum of patients with suspected or chronic CAD. This evidence has resulted in many class I indications for the use of stress SPECT and PET-MPI.[23] Several specific lines of evidence are described in the following sections. In this section, we highlight the evidence supporting each of the AUC indications. Of note, the AUC considers the assessments of SPECT and PET-MPI as the same.[235,245]

SYMPTOMATIC PATIENTS WITH NORMAL RESTING ECG ABLE TO EXERCISE

Symptomatic patients with normal resting ECGs represent a large subgroup commonly encountered in clinical practice in whom the use of nuclear MPI is applied. The radionuclide AUC report regarding radionuclides states that it is appropriate to refer symptomatic patients with interpretable ECG who are able to exercise for stress MPI testing if they have an intermediate or high pretest likelihood of CAD but inappropriate if they have a low pretest likelihood.[246] However, in symptomatic patients with a low pretest probability of CAD, interpretable ECG, and ability to exercise, stress nuclear MPI is considered rarely appropriate.

Several studies have examined the added value of exercise SPECT-MPI over clinical and exercise treadmill test (ETT) data in these patients.[154,247,248] The Mayo Clinic group demonstrated that although SPECT-MPI yielded incremental value over clinical and ETT data for the prediction of left main or three-vessel disease, the yield was modest and not cost-effective.[248] A study from Cedars-Sinai of 3058 patients with normal resting ECGs then showed that selective use of SPECT-MPI in patients with intermediate to high post-ETT CAD likelihood yielded significant risk stratification, statistical incremental value, and cost-effectiveness in predicting hard events.[247] Results from the What is the Optimal Method of Ischemia Elucidation in Women (WOMEN) Trial have shown that the ETT alone without imaging is sufficient in symptomatic women who are able to exercise. A total of 824 symptomatic women capable of exercise and without a prior CAD diagnosis were randomized to an index exercise ECG or exercise SPECT-MPI.[249] The trial revealed similar 2-year outcomes (death, ACS, or heart failure hospitalization) for women randomized to the ETT-alone arm compared and in the exercise SPECT-MPI arm (2-year event rate: 1.7% for exercise ECG arm vs 2.3% for the exercise SPECT-MPI arm; HR 1.3 [95% CI, 0.5-3.5; P = .59]). These results reveal a low risk of 2-year CAD outcomes and support the utility of the exercise ECG as an initial test for evaluation of women capable of exercising and with a normal resting ECG. Of note, in both men and women, patients achieving 10 METs of exercise on ETT have been shown to have excellent prognosis and low likelihood of moderate to extensive ischemia, potentially obviating the need for stress nuclear MPI.[250]

SYMPTOMATIC PATIENTS WITH INDETERMINATE OR INTERMEDIATE-RISK TREADMILL TEST RESULT

An important appropriate indication for nuclear MPI are those for the diagnostic or risk evaluation following an ETT with indeterminate stress test findings or intermediate post-ETT risk. MPI has been shown to be most effective in risk stratification and governing management of patients with intermediate Duke treadmill score (DTS), derived from exercise-induced chest pain, ST-segment changes, and exercise duration.[222] Similar results were shown in subsequent multicenter studies reporting event rates and catheterization rates.[23] Similar findings have been reported for stress ^{82}Rb myocardial perfusion PET.[251]

Patients with LVH commonly have indeterminate exercise ECG results. Exertional ST-segment depression is frequently seen without significant CAD. SPECT-MPI has been shown to be as effective in patients with LVH as in patients without LVH for identifying obstructive disease and for risk stratification. It has been reported that patients with LVH and a low-risk SPECT-MPI had less than a 1% annual risk of cardiac death or MI, whereas the annual cardiac death or MI rates ranged from 4.9% for patients with mildly abnormal scans to 10.3% for those with moderately to severely abnormal SPECT-MPI.[252] Of note, in patients with hypertrophic cardiomyopathy, stress perfusion defects are commonly seen in the absence of significant disease (Fig. 18–35). Indications within the AUC and SIHD clinical practice guidelines support nuclear testing in symptomatic patients with uninterpretable or intermediate exercise ECG response.[23,235,245]

SYMPTOMATIC PATIENTS UNABLE TO EXERCISE

The SIHD clinical practice guideline simplified the criteria defining a patient unable to exercise and categorized patients into those with limitations in physical functioning or disabling comorbidity.[245] Patients may be categorized as unable to exercise if they are challenged with performing moderate household, yard, or recreational work. In addition, patients with disabling comorbidities are also those unable to exercise and include patients who are frail, of advanced age, marked obesity, with peripheral arterial disease, chronic obstructive pulmonary disease, or orthopedic limitations. These groups form a large proportion of patients who will be referred and have appropriate indications for nuclear MPI.

In patients unable to exercise, guidelines support pharmacologic stress imaging is useful as the initial test in symptomatic male and female patients with intermediate or high pretest likelihood of CAD.[23,185,246]

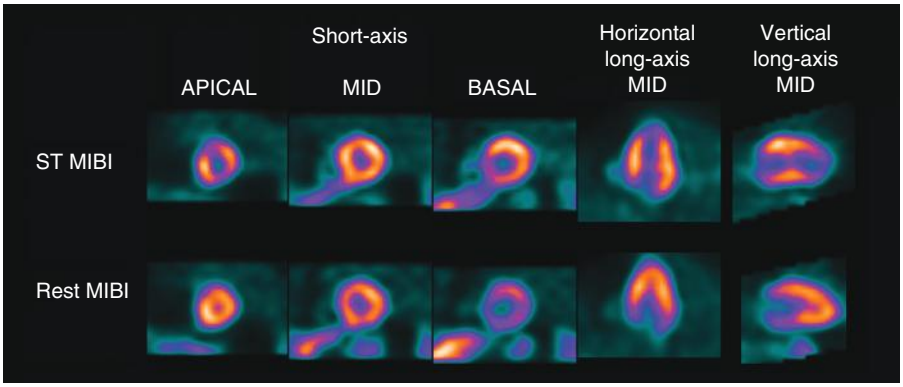

FIGURE 18–35. Exercise stress (ST)/rest myocardial perfusion single-photon emission computed tomography (SPECT) in a 68-year-old man asymptomatic man apical variant hypertrophic cardiomyopathy. The patient had multiple risk factors for coronary artery disease and presented with ST-T wave changes on resting electrocardiogram. SPECT demonstrated large, severe reversible defect in an apparent left anterior descending (LAD) coronary artery distribution. Invasive coronary angiography revealed a mid-LAD 50% stenosis with a fractional flow reserve of 0.87.

Consistent with other functionally disabled cohorts, the overall expected risk of major adverse cardiac events in these patients is elevated.[253] As reported by the recent AHA consensus statement on cardiac imaging in women, functionally impaired patients (eg, < 5 METs of exercise) have at least a 2% per year risk of coronary heart disease death or MI, ranking them as having intermediate risk with event rates equivalent to patients with established coronary heart disease.[185] In multivariable models, the need for pharmacologic stress (as opposed to exercise) is itself an incremental predictor of adverse outcomes,[24] with event rates that are at least 50% higher than in an exercising population. Event rates are higher when patients undergoing pharmacologic stress are unable to perform adjunctive low-level exercise.[58] Despite higher event rates observed for patients with a normal resting ECG and an intermediate to high CAD likelihood but inability to exercise, vasodilator stress SPECT-MPI has been shown to be effective for CAD risk stratification.[58,101,174] Recent evidence has reported prognosis in patients with a normal stress MPI over a long period of follow-up.[159] With mean of 11 years of follow-up, the overall annualized rate of all-cause mortality was 0.8%, with values varying based on risk factors, resting heart rate, and LVEF. The annual all-cause mortality rates were 1.6% per year for patients with multiple risk factors and exercising less than 6 minutes. Conversely, very low all-cause mortality rates (0.2%) were reported for patients with high exercise capacity (> 9 minutes) and for those without risk factors. Indications within the AUC and SIHD clinical practice guidelines support the use of nuclear testing in symptomatic patients unable to exercise.[23,235,245]

Recently, an arm exercise protocol was applied in a large veteran population with lower extremity disability.[254] Results from this report revealed that arm exercise capacity and HR responses provided added risk information to the prognostic value of MPI findings. Although not routinely performed, the use of arm exercise testing provides valuable functional information that may be supplemental to MPI data and is not available when applying pharmacologic stress. Exercise METs during arm testing ($P < .001$), 1-minute HR recovery ($P < .001$), and the delta heart rate measures ($P < .001$) were independently predictive of cardiovascular mortality.

SYMPTOMATIC PATIENTS WITH A HIGH PRETEST LIKELIHOOD OF CAD

Patients with high pretest likelihood of CAD are excellent candidates for SPECT-MPI. In these patients, the amount of ischemia can be helpful in selecting patients for referral to invasive coronary angiography and for consideration of revascularization. The ACC AUC support nuclear MPI in high-likelihood patients who have an interpretable or uninterpretable ECG as well as in patients able or unable to exercise.[246] Supporting this, in a consecutive series of 1270 patients with a high likelihood of CAD (ie, > = 0.85), the annual rate of cardiac death or MI was 1.3% for normal SPECT-MPI, which was found in more than 60% of patients. In this cohort, moderate to severe ischemia (in 10% of the myocardium) is associated with an annual risk of CAD death or MI of 5%, based on a recent meta-analysis.[255]

ASYMPTOMATIC PATIENTS

Asymptomatic patients (without chest pain or ischemic equivalents) with multiple risk factors frequently have an intermediate high-risk global risk score but are largely not considered appropriate candidates for MPI. Appropriate indications for MPI are limited to patients without these symptoms who are being evaluated for arrhythmias or syncope (in the patient with an intermediate to high global risk score).[235] AUC in this category include patients with sustained ventricular tachycardia or fibrillation, exercise-induced ventricular tachycardia, or frequent premature ventricular contractions.

Other asymptomatic groups considered as intermediate to high risk include diabetics (see Asymptomatic Patients with Diabetes Mellitus), patients with peripheral arterial disease, and siblings of patients with premature CAD. These subsets of asymptomatics have a maybe appropriate indication for nuclear MPI.[235] In a study examining asymptomatic siblings of patients with manifest CAD, a cohort acknowledged to be at increased risk for developing CAD, a relative risk of 4.7 for experiencing an adverse cardiac event was reported for individuals with an abnormal scan,[256] and the presence of both an abnormal exercise ECG and abnormal perfusion scan yielded a relative risk of 14.5. As predicted by Bayesian principles, however, the routine use of any test for detection of CAD in an asymptomatic population with low risk/low prevalence of CAD will be associated with high cost-effectiveness ratios and low positive predictive values. The overall risk of these patients is not as great as in the symptomatic cohort.[257,258] As discussed later, strategies using initial coronary atherosclerosis assessment using CAC scanning followed by selective SPECT-MPI may prove to be clinically effective and cost effective for identifying asymptomatic patients at risk and guiding their therapy (as noted later in Asymptomatic Patients with Diabetes Mellitus and after CAC Scanning).[259-261] Although considered appropriate in asymptomatic high-risk patients, the use of nuclear MPI in asymptomatic patients with intermediate risk is considered maybe appropriate if the rest ECG is uninterpretable, and it is considered rarely appropriate in asymptomatic patients with low risk, interpretable ECG, and ability to exercise.[235]

ASYMPTOMATIC PATIENTS WITH DIABETES MELLITUS

SPECT-MPI has been reported to be effective in risk stratification of patients with diabetes.[101,173,176,262] In a study comparing 1271 patients with diabetes to 5862 without, SPECT-MPI risk-stratified patients in both groups, but risk-adjusted event-free survival was worse in patients with diabetes than in those without.[263] These findings were confirmed in a multicenter series.[176] A large single-center study reported that 59% of asymptomatic diabetics have abnormal stress SPECT-MPI studies, including 20% with a *high-risk* scan defined by a high SSS.[264] A further study by this group showed that ECG Q waves and/or evidence of peripheral artery disease identified the most suitable diabetic candidates for screening with SPECT-MPI.[265] Subsequent studies have reported that the frequency of abnormal SPECT-MPI in asymptomatic diabetic patients is not high.[266] The Diagnostic Imaging in Asymptomatic Diabetics (DIAD) trial suggested that imaging of asymptomatic diabetics is not effective. In DIAD, 1123 patients were randomized to adenosine SPECT-MPI or nonimaging approaches. Although 22% of asymptomatic diabetic patients had ischemia by adenosine SPECT-MPI at baseline[266] at 5-year follow-up, there was no significant difference in adverse cardiac outcomes between patients randomized to the imaging and nonimaging approaches. Based on these findings, atherosclerosis testing may be a more effective approach as the initial screening tool of diabetics,[259,260,267] reserving SPECT-MPI for those who have extensive coronary atherosclerosis. As with other patient cohorts, the level of exercise achieved has an important impact on the prognostic implications of SPECT-MPI findings.[268]

PATIENTS WITH LBBB AND VENTRICULAR PACING

Current guidelines support nuclear MPI in symptomatic patients with LBBB.[269] As previously discussed, pharmacologic stress without adjunctive exercise is recommended in these patients. Vasodilator stress SPECT-MPI has been shown to be an excellent predictor of cardiac events in LBBB patients.[270] Regarding patients with ventricular pacemakers, expert consensus is that these patients can be

appropriately risk stratified by vasodilator SPECT-MPI, similar to patients with LBBB.[23] The SIHD guidelines give a class I indication for the use of pharmacologic stresses nuclear MPI in the patients with LBBB regardless of the ability to exercise to an adequate workload.[269] Due to the problem of septal PD without symptomatic CAD, coronary CTA may be a preferred in these patients.[131]

PATIENTS WITH ATRIAL FIBRILLATION

In asymptomatic patients with new-onset atrial fibrillation, the use of stress SPECT-MPI has been reported to provide risk-stratification information. A large observational report in 16,048 patients on the prognostic value of SPECT-MPI in patients with atrial fibrillation showed that the annual rate of cardiac death in patients with normal SPECT-MPI was 1.6% per year for those with atrial fibrillation and 0.4% for the cohort without atrial fibrillation ($P < .001$).[174] Of interest, in patients with atrial fibrillation, even patients with only mildly abnormal SPECT-MPI were at much higher risk than those without atrial fibrillation (6.3% vs 1.2% per year, respectively; $P < .0001$). Nonetheless, recent AUC consider MPI in asymptomatic patients with atrial fibrillation as a maybe appropriate indication.[235,246]

ELDERLY PATIENTS

With the increased longevity of the US population and the age-related increase in CAD prevalence, large numbers of elderly patients are undergoing diagnostic and/or prognostic assessment for CAD. The DTS has been reported to be less effective in risk stratification of elderly patients than in younger patients.[271] The Mayo Clinic group reported that exercise SPECT-MPI provides effective risk stratification in elderly men and elderly women. A cohort of 247 patients 75 years of age or older who were undergoing SPECT-MPI were followed for a median of 6.4 years for cardiac death. Although the DTS was not associated with the risk of cardiac death, MPI-measured SSS was significantly associated with cardiac death and classified 49% of patients as low risk and 35% of patients as high risk, with annual cardiac mortality rates of 0.8% and 5.8%, respectively. More recently, a report on 5200 elderly patients who underwent stress SPECT-MPI and had a 2.8 (± 1.7)-year follow-up reported that both MPI measured ischemia and fixed defect added incrementally over pre-MPI data in both adenosine and exercise stress patients. Furthermore, in a subset of patients who underwent gated SPECT-MPI, EF and perfusion data added incrementally to each other, further enhancing risk stratification. Importantly, modeling of all-cause death in a subset of 684 patients with extended follow-up (6.2 ± 2.9 years) revealed that after risk adjustment, an interaction between early treatment and ischemia was present such that increasing ischemia was associated with increasing survival with early revascularization, whereas in the setting of little or no ischemia medical therapy had improved outcomes.[213] While the elderly patients with normal SPECT-MPI had a risk of cardiac death that was greater than 1% per year, the risk in these patients was lower than that of the age-matched general population.

Pharmacologic stress testing is increasingly being applied in the elderly, who frequently are unable to exercise adequately, and this group makes up a high proportion of patients undergoing pharmacologic stress imaging. Consistent with data on other functionally impaired patients, elderly patients undergoing pharmacologic stress SPECT-MPI have higher cardiac event rates than patients undergoing exercise stress across the spectrum of test results. Risk stratification by SPECT-MPI has also been reported with dobutamine stress MPI, in the elderly with similar results to those of vasodilator stress.[272] Given the frequent finding of high CAC score in the elderly, it is likely that nuclear-MPI studies will remain preferred to coronary CTA in this group.

PATIENTS WITH CHRONIC KIDNEY DISEASE

It has long been recognized that chronic kidney disease (CKD) is associated with high cardiovascular morbidity and mortality. This increased cardiovascular risk associated with CKD is in part related to hypertension and dyslipidemia,[273] as well as to activation of both inflammatory mediators and the renin-angiotensin system.[273,274] The cardiovascular mortality rate in CKD patients is 15 to 30 times the age-adjusted cardiovascular mortality rate in the general population.[273,275,276]

Successful risk stratification of these patients by SPECT-MPI results has been reported in numerous reports.[277-281] Hakeem and coworkers followed 1652 patients who underwent stress SPECT-MPI for more than 2 years, finding that stress perfusion defects on SPECT-MPI and CKD were independent and incremental predictors of cardiac death after accounting for baseline data, risk factors, LV dysfunction, type of stress used, and symptom status. For any MPI result (normal or abnormal) cardiac mortality is far greater in CKD patients, and the risk increases with increasing degrees of renal failure.[279] Nuclear-MPI may be the noninvasive test of choice in symptomatic patients with CKD. Then, because the asymptomatic CKD patient is at high risk, nuclear-MPI use would be classified as maybe appropriate by the AUC. In patients with functional disability, nuclear MPI would be appropriate in patients being evaluated for kidney transplantation.[235] However, it remains uncertain which CKD patients are optimal candidates for nuclear MPI and how clinicians can optimally use the test results to enhance patient outcomes.

Nuclear MPI has a distinct advantage over the use of CMR imaging and CCTA for risk assessment of the CKD patient, because there is no organ toxicity associated with injection of the radionuclide tracers. CMR with gadolinium contrast is contraindicated in these patients due to the risks of nephrogenic systemic fibrosis in renal failure patients. With CCTA, the nephrotoxicity of the iodinated contrast results in this study being contraindicated unless the patient is on dialysis. Even in the dialysis patient, the high CAC scores commonly found in the renal failure patient can reduce the diagnostic and prognostic value of the coronary CTA study.

AFRICAN AMERICAN AND OTHER RACIAL AND ETHNIC PATIENT SUBSETS

The rate of cardiac death or MI in African Americans with a normal SPECT-MPI is approximately 2% per year,[23] likely a result of higher risk burden.[188] In a multicenter series, 2-year cardiovascular death and MI were compared in 1993 African American and 464 Hispanic patients as compared with 5258 white, non-Hispanics undergoing stress ^{99m}Tc-tetrofosmin SPECT-MPI.[172] Moderate to severely abnormal SPECT-MPI occurred more often in ethnic minority patients (see Chap. 109). The prognostic results noted a 1.4- to 1.6-fold and 2.3- to 5.6-fold higher risk of hard events in African American and Hispanic patients compared with white patients, respectively, with mild and moderate to severely abnormal SPECT-MPI findings ($P < .0001$ vs whites), likely caused by a higher degree of comorbidity.

OBESE PATIENTS

SPECT-MPI remains a highly useful test for diagnosis and prognosis in obese patients, although excess soft tissue attenuation can make scan interpretation more difficult. For obese patients, the ^{99m}Tc agents are considered preferable to ^{201}Tl because of the higher photon energy of ^{99m}Tc. Attenuation correction hardware and software, combined with quantitation and ECG gating has been shown to have significantly higher specificity and normalcy rates without

loss of sensitivity for detection of CAD in obese patients when compared with studies without attenuation correction.[282,283] Combined supine and prone ^{99m}Tc-sestamibi stress SPECT-MPI acquisitions, without attenuation correction, have been shown to have equally high sensitivity, specificity, and normalcy rates among normal weight, overweight, and obese patients, and have been reported in a large clinical series.[149] Furthermore, these investigators reported that when a quantitative approach to analysis of supine, prone, and combined supine/prone acquisitions was used, the combined supine/prone approach increased the specificity in identifying CAD without significant reduction in sensitivity. This approach was also successfully applied to combined supine/upright imaging of obese patients with new cameras.[168]

Regarding prognostic assessment of obese patients, a large study demonstrated that SPECT-MPI is highly effective in risk stratification across weight groups. Normal SPECT-MPI studies were associated with a low risk of events in all weight categories. Interestingly, there was an inverse relationship between weight and risk of cardiac death in the patients with abnormal scans or known CAD.[284] Most SPECT imaging tables have weight limits (often 300 lb [136.1 kg]). Recently, two-position imaging using a high-efficiency CZT parallel-hole SPECT-MPI system with a weight limit of 542 lb has been studied in obese patients. With this system, SPECT-MPI was shown to have high accuracy for the identification of patients with 50% or more stenosis on invasive coronary angiography, with excellent image quality even in morbidly obese patients (Fig. 18–36).[168] PET imaging is considered to be superior to conventional SPECT-MPI in obese patients because of the robust attenuation correction and the higher photon energy associated with positron emissions (see Chap. 19). However, in morbidly obese patients who cannot fit in the PET gantry, the new cameras with solid-state detectors may of particular importance.[285]

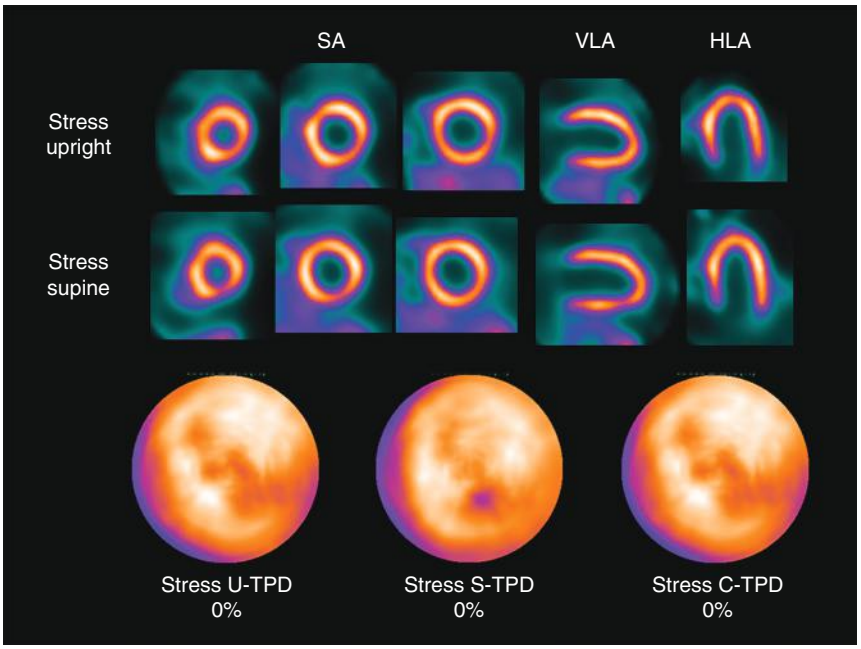

FIGURE 18–36. Case example of high single-photon emission computed tomography–myocardial perfusion image quality obtained with a cadmium-zinc-telluride camera using moving detectors in a 48-year-old man with body mass index of 60. C-TPD, combined total perfusion deficit; HLA, horizontal long axis; SA, short axis; S-TPD, supine total perfusion deficit; U-TPD, upright total perfusion deficit; VLA, vertical long axis. Reproduced with permission from Nakazato R, Slomka PJ, Fish M, et al: Quantitative high-efficiency cadmium-zinc-telluride SPECT with dedicated parallel-hole collimation system in obese patients: results of a multi-center study. *J Nucl Cardiol*. 2015 Apr;22(2):266-275.[168]

PATIENTS WITH PRIOR TESTING

After CAC Scanning

Evidence supports the use of the CT-derived CAC score as a means to evaluate asymptomatic patients for detection of early, subclinical coronary atherosclerosis.[286,287] This application has been included in the ACCF/AHA guidelines.[287] Given the known relationship between CAC and risk, the finding of high CAC burden raises patient risk to intermediate or high levels, resulting in consideration that ischemia testing might be warranted. When the CAC exceeds 400, the rate of an ischemic SPECT-MPI is elevated to at least the intermediate range, and has been reported to be as high as 47%.[287-289] Regarding the frequency of indication for this application, CAC scores of 400 or more were found in 9.9% asymptomatic subjects aged 45 to 84 years in the Multi-Ethnic Subclinical Atherosclerosis (MESA) study and in the Heinz Nixdorf study, 9.6% of patients in the 45- to 75-year age range had these scores.[290]

Subset analyses have suggested that a lower threshold might be appropriate in higher risk patients, including type 2 diabetics with or without the metabolic syndrome, patients with a family history of premature coronary heart disease, and patients with multiple risk factors.[260,261,286,291] In these cohorts, a greater frequency of ischemic SPECT-MPI was reported at a CAC score of 100 or greater. In patients with the metabolic syndrome, the frequency of an ischemic SPECT-MPI was 15% for CAC of 100 to 400, equivalent to patients with normal metabolic status with CAC 400 or more.[291] Anand and colleagues[260] prospectively enrolled 510 asymptomatic, type 2 diabetics who underwent CAC and SPECT-MPI. Data from this series revealed that the rate of abnormal SPECT-MPI (including both fixed and reversible defects) was 0% (n = 15) for CAC of 10 or less, 18% (n = 38) for CAC 11 to 100, 23% (n = 70) for CAC 101 to 400, 48% (n = 29) for CAC 401 to 1000, and 71% (n = 28) for CAC greater than 1000. Similar results were reported for patients with a family history of premature coronary heart disease, with a greater frequency of ischemic SPECT-MPI when CAC is 100 or greater.[261] Consideration of a lower threshold for referral to SPECT-MPI after CAC scoring thus appears reasonable for diabetic and metabolic syndrome patients as well as in patients without metabolic abnormalities when combined risk factors and symptoms indicate a relatively high pretest likelihood of CAD.[286] In general, patients with a normal nuclear MPI and extensive CAC have been shown to be at low risk for short-term cardiac events[243]; however, increased risk over time in patients with normal SPECT-MPI and increasing CAC has been shown in a large series of patients undergoing both examinations.[93]

The multimodality AUC have addressed the use of stress nuclear MPI in patients with prior CAC scanning and consider it appropriate or maybe appropriate, depending on the time between CAC scanning and consideration of MPI.

After CCTA

CCTA is increasingly used for detection of CAD and assessment of patients with suspected or known CAD. Although highly accurate for the detection of anatomic coronary stenosis, CCTA is limited in the assessment of the functional significance of stenosis. It has been well established that assessment of

percent stenosis even by invasive coronary angiography is limited in this regard. In the FAME trial, 65% of stenosis in the 50% to 69% stenosis category by visually interpreted coronary angiography had FFR greater than 0.8 as did 20% of lesions in the more than 70% stenosis category.[10] With respect to percent stenosis on CCTA and ischemia, similar findings have been reported. In a recent study assessing the use of a functional assessment of CCTA (FFR CT) for predicting invasive FFR, the accuracy of using a greater than 50% stenosis on CCTA for predicting the results of invasive FFR was 65%; stenosis by CCTA had 83% sensitivity and 60% specificity with respect to invasive FFR. The low specificity of CCTA for ischemia can result in an increase in unnecessary invasive coronary angiograms.

Nuclear MPI plays an important role in selected patients following CCTA. The relationship between the degree of stenosis on CCTA and the finding of an ischemia on SPECT-MPI has been evaluated in a small series of patients.[292] Ischemia was rare in patients with less than 50% stenosis on CCTA (6%). A progressive increase in the frequency of SPECT-MPI ischemia in the corresponding vascular territory was observed in the 5% to 69%, 70% to 89%, and greater than 90% stenosis categories.

Figure 18–37 illustrates the circumstances in which nuclear MPI might be considered after CCTA and for those in whom it should not. Consideration of testing for ischemia would not be considered in patients with less than 25% stenosis or for patients whose maximal stenosis is in the 25% to 49% range; further testing is not recommended, unless there are compelling reasons to suspect ischemia. In patients with lesions in the 50% to 69% range—the category considered by CCTA reporting guidelines to be "borderline," further testing is generally recommended. CCTA has been shown to frequently overestimate the percent stenosis seen on invasive coronary angiography; therefore, further testing for ischemia in patients with 70% to 89% stenosis is also reasonable, approximately one-half of which are have ischemia.

The multimodality AUC have extensively addressed the use of nuclear MPI in patients with prior CCTA. If CCTA is performed within 90 days, stress MPI is considered appropriate in each of the following categories, concordant with the above discussion: for patients with obstructive CAD (presumably to confirm ischemia and assess its magnitude); in patients with "uncertain" results, specified as equivocal or borderline results where obstructive CAD remains a concern; or when there is a coronary stenosis or anatomic abnormality of unclear significance. Recent data suggests that adding CT perfusion or CT- based fractional flow reserve may provide this functional information (340, 342).

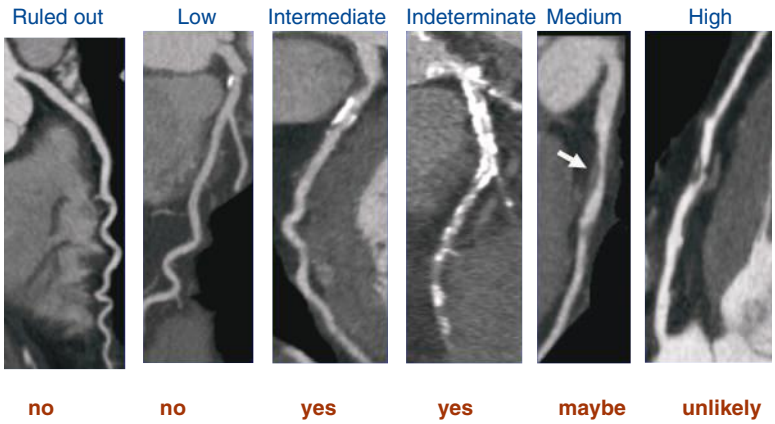

FIGURE 18–37. Curved multiplanar reconstructions of coronary computed tomography angiography (CCTA) from patients representing different levels of risk based on CCTA findings (likelihood of epicardial stenosis as cause of symptoms; *top*) and possible subsequent management (usefulness of nuclear myocardial perfusion imaging; *bottom*).

PATIENTS WITH A PRIOR REVASCULARIZATION

For patients with prior testing, the AUC statement categorizes patients as being evaluated for early MPI (within 90 days) and late MPI (> 90 days) after an index/prior test. For patients being considered for early nuclear MPI following an index procedure, a prior exercise ECG or anatomic evidence of obstructive CAD is considered an appropriate indication for MPI. In general, minimal evidence is available to guide the indications for follow-up testing even late after testing in patients without a change in symptoms and, as such, many indications are categorized as maybe or rarely appropriate.[235] If the patient has new or worsening symptoms, the AUC support the use of nuclear MPI. The evidence for follow-up MPI is detailed below.

After PCI

In the BARI 2D and the COURAGE trials, it has been shown that the rates of ischemia were much lower at 1 year of follow-up in patients in the revascularization arms than in patients in the OMT.[210,211] In the BARI 2D trial, this was observed for both PCI and CABG (0.017 and 0.032) compared to the medical therapy arm.[211]

However, these findings do not imply that routine testing of patients after revascularization is appropriate. By the multimodality AUC, MPI is appropriate for patients with recurrent symptoms, for those with incomplete revascularization, or when additional intervention is being considered.[235] Nuclear-MPI abnormalities after PCI may detect restenosis, periprocedural myocardial injury, side-branch compromise, de novo disease, or functionally significant angiographic disease in nonrevascularized vessels. As part of a staged procedure, SPECT-MPI can assess the remaining ischemic burden after the initial PCI.

Post-PCI, SPECT-MPI has been extensively used for the detection of silent or minimally symptomatic restenosis. Based on literature reviews and a meta-analysis,[293,294] several statements can be made regarding use of nuclear-MPI for this application. It is superior to ETT and can detect silent restenosis. However, post-PCI patients undergoing SPECT-MPI have a low overall annual event rate, suggesting no need for *routine* testing, despite the predictive value of abnormal SPECT-MPI for adverse events. Because of the relatively low prevalence of clinically significant silent restenosis in the era of drug-eluting stents, poststent SPECT-MPI is rarely appropriate in the asymptomatic patient for purposes of assessing stent patency.[23,246] Importantly, from a Bayesian perspective, testing these patients with a low prevalence of ischemia would result in a low yield with false positives outnumbering true positives. However, the AUC do state that risk assessment of the asymptomatic patient after PCI is appropriate if there is incomplete revascularization and additional revascularization is possible based on the angiographic findings.[246] It is noteworthy that AUC do not cover all conceivable appropriate applications. For example, the AUC did not consider patients with extensive silent ischemia who undergo PCI. The general consensus is that repeat SPECT-MPI testing after PCI would be appropriate in these patients even in the absence of clear symptoms, if the results of PCI were uncertain or when there is clinical suspicion of restenosis.

Recently, the results of the Basel Stent Kosteneffektivitäts Trial LATE IMAGING study were reported regarding the use of SPECT-MPI at 5 years post-PCI.[262] The majority of the 339 trial enrollees were asymptomatic at the time of the

4-year SPECT scan. Patients with symptomatic or silent ischemia at time of MPI had a higher relative hazard for cardiac events. The presence of ischemia remote from the stented territory was independently predictive of events. These trial findings indicate that follow-up use of MPI late after PCI may risk stratify even asymptomatic patients. This application has a maybe appropriate designation in the AUC. Routine testing of the asymptomatic patient less than 2 years after PCI is considered rarely appropriate.

After CABG

Nuclear testing has become central in the assessment of the post-CABG patient. It is known that more than 50% of vein grafts are projected to become occluded by 10 years after surgery; hence, there is an intermediate likelihood of vein graft disease.[293] Thus, a 5-year cutoff point to evaluate the post-CABG patient may be appropriate (depending on the number and type of grafts placed).[293,295-297] In post-CABG patients with new symptoms, nuclear MPI can identify the presence and extent of ischemia and is considered appropriate at anytime after surgery. In asymptomatic patients, nuclear MPI is considered appropriate 5 or more years after CABG. However, only routine nuclear MPI testing of the asymptomatic patient less than 5 years after CABG is considered rarely appropriate.

PREOPERATIVE RISK ASSESSMENT IN PATIENTS PRIOR TO NONCARDIAC SURGERY

A large body of literature exists examining the utility of perioperative cardiac testing with stress MPI in adult patients prior to noncardiac surgery and has been synthesized in a recent ACC clinical practice guideline.[298] The guideline acknowledges that assessment of LV function and/or jeopardized myocardium provides an accurate method to complement clinical preoperative risk assessment prior to noncardiac surgery; importantly, however, the guideline does not recommend routine use of preoperative imaging, but rather its selective use in only very limited clinical situations.

This guideline highlighted a stepwise approach for evaluation of patients in the preoperative setting, beginning with an index assessment of functional capacity in patients with an elevated risk, defined as a risk of perioperative death or MI of 1% or more (see Chap. 98). This risk is based on combined surgical and patient characteristics.

Then, regarding exercise testing, exercise testing with imaging, and pharmacological stress imaging, the guideline recommends that in high-risk patients with excellent functional capacity (> 10 METs), it is reasonable to forgo further exercise testing with cardiac imaging. In patients with elevated risk and unknown functional capacity, it considers it reasonable to perform exercise testing, and then in those with moderate to good functional capacity (≥ 4 METs), to forgo further exercise testing with imaging. Only in patients with elevated risk and poor functional capacity (< 4 METs) does it consider it reasonable to perform exercise or pharmacological testing with cardiac imaging to assess for ischemia, and only then if it will change management. This guideline approach defines additional use of coronary angiography and guideline-directed medical therapy for those with abnormal stress MPI findings. Guidance on appropriate stress MPI candidates was also published in the recent AUC stating that it is appropriate prior to intermediate-risk or vascular surgery *only* if the patient has poor functional capacity and at least one clinical risk factor (eg, prior CAD, heart failure, or cerebrovascular disease; diabetes; renal insufficiency).[246]

ASSESSMENT OF THERAPY: SERIAL TESTING

In patients with no change in symptoms, the need for repeat testing and the appropriate interval for this retesting have not been fully explored. In this regard, the nuclear substudy of the COURAGE trial[210] provided landmark "proof of principle" data, addressing how serial SPECT testing may predict clinical outcomes This COURAGE substudy was performed in 314 patients who underwent both prerandomization and 6- to 18-month postrandomization SPECT-MPI. The prerandomization study was performed with patients off of cardiac medications (eg, β-blockers, calcium channel blockers), and the follow-up study was performed with the patients on their medications. The amount of ischemia in the prerandomization SPECT-MPI was similar between patients assigned to PCI and OMT versus OMT alone. Some patients in the OMT-alone group demonstrated dramatic improvement in ischemia (Fig. 18–38). Patients in the PCI plus OMT group more frequently demonstrated significant ischemia reduction (> 5%) when compared with patients receiving OMT alone (33% vs 19%, respectively; $P = .0004$). Importantly, the frequency of subsequent adverse events over a 4-year period was directly proportional to the amount of residual ischemia measured on the 6- to 18-month postrandomization SPECT-MPI study (see Fig. 18–29). Although this study

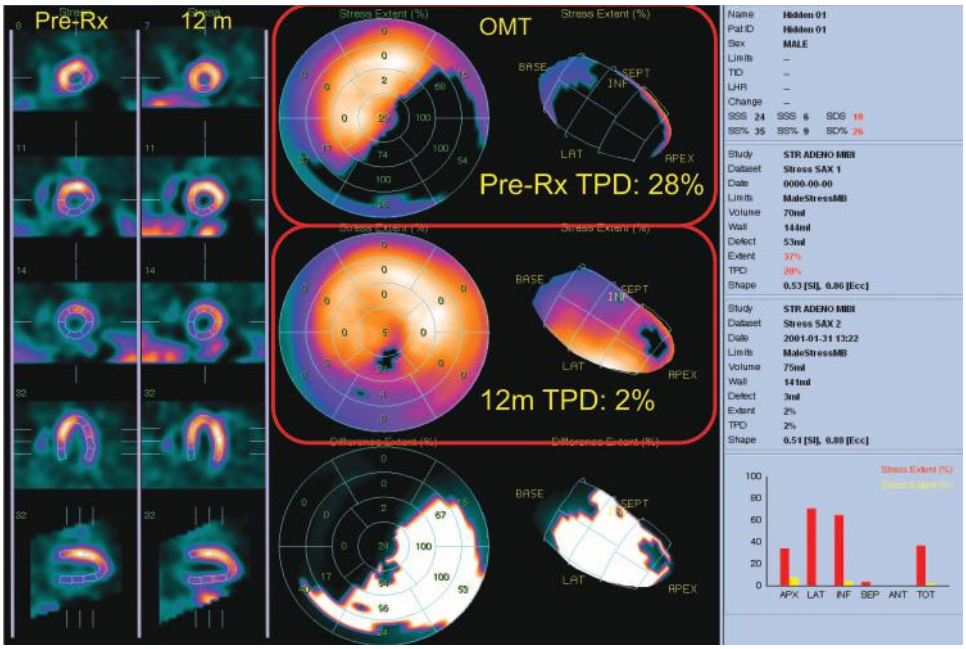

FIGURE 18–38. An illustrative case of a patient enrolled in the nuclear substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. The pretreatment stress images are in the first column, whereas the 12-month follow-up images are in the second column. A severe and extensive perfusion defect is seen in the pretreatment study with near complete resolution on the posttreatment study. The polar plots for the first and second studies are also noted in the center of this slide. The stress total perfusion defect (TPD) for the baseline study was 28% of the myocardium, whereas after 12 months of aggressive medical intervention, the second study demonstrated a dramatic decline in TPD to only 2%. OMT, optimal medical therapy; Rx, treatment.

was not designed to prove that ischemia reduction directly reduces adverse CAD events, it nevertheless provides supportive evidence that serial imaging of ischemia before and after implementation may be useful in defining patient risk.

There is no consensus regarding whether serial testing should be performed with the patients receiving medical therapy, as it was in the COURAGE nuclear substudy, or off antianginal medications. If the purpose of repeat testing is to assess the effects of therapy on ischemia in daily life, then repeat testing would be performed *on* medications (see Fig. 18–38).

The appropriate interval between serial SPECT-MPI studies in clinical practice is discussed in the recent AUC.[246] If the patient has new or worsening symptoms after MPI, repeat stress MPI is appropriate; however, routine repeat testing is not appropriate at any time. Early imaging following abnormal stress imaging within 90 days following the index test is considered a maybe appropriate criterion, as a means of evaluating the response to medical therapy.

PATIENTS WITH CORONARY STENOSIS OF UNCLEAR PHYSIOLOGICAL SIGNIFICANCE

For patients who are being considered for revascularization and are found to have coronary stenosis that is of uncertain significance regarding hemodynamic significance, either exercise or pharmacological stress nuclear MPI has a class I indication in the SIHD guidelines.[299]

ASSESSMENT OF CONGESTIVE HEART FAILURE AND IDENTIFICATION OF MYOCARDIAL VIABILITY

Because of the mortality rate, increasing prevalence of heart failure, and need to tailor therapy to the etiology or the stage of the condition, testing of patients with heart failure will remain common. Various radionuclide methods may be useful in initial staging of congestive heart failure (CHF; measurement of EF and ventricular volumes), ruling out CAD as an etiology, identifying myocardial hibernation, and determining the likelihood of response to interventional therapies. The 2013 ACCF/AHA guideline for the management of heart failure[300] summarized the recommendations for the use of imaging in the heart failure patient. Based on this statement, the clinical applications where imaging may play a role include:

1. Repeat measurement of LVEF in patients who have had a significant change in their clinical status, received treatment that may impact cardiac function, or are under consideration for device therapy (class I, level of evidence C)
2. Imaging to detect ischemia and viability in patients with de novo heart failure, known CAD, and no angina, unless the patient is not eligible for revascularization (class IIa, level of evidence C)
3. Viability assessment prior to revascularization in select situations is reasonable in the heart failure patient with CAD (class IIa, level of evidence B)
4. Radionuclide ventriculography for the assessment of LVEF and LV volumes when echocardiography is inadequate (class IIa, level of evidence C)

Multimodality AUC for imaging in heart failure were also published in 2013.[301] For the evaluation for an ischemic etiology for heart failure, stress nuclear MPI is considered to be appropriate for the evaluation of ischemia in patients with or without angina/anginal equivalent. This was based on the heart failure guidelines giving the use of MPI to define the likelihood of CAD in patients with heart failure and LV dysfunction a class IIb evidence level C irrespective of symptoms. In patients with a known ischemia etiology for their heart failure who are revascularization candidates, stress nuclear MPI to assess the magnitude of ischemia. Viability assessment is considered appropriate in patients with LVEF of less than 30%. In patients considered or followed up for implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) devices, radionuclide ventriculography can be used in the evaluation of patients who require a documentation of LVEF.[300,301] In the setting of (re)evaluation of known heart failure, stress nuclear MPI is considered appropriate in the setting of new angina/ischemic equivalent or for the presence of new or worsening heart failure symptoms.[301] In the heart failure guidelines, repeat measurement of LVEF and LV remodeling are considered useful with a change in clinical status, after a clinical event, or received treatment that may impact cardiac function.[300]

DETECTING CAD AS THE ETIOLOGY OF CHF

Because CAD represents the largest etiology of CHF and because the therapy of CAD is so distinct from that of the general management of patients with CHF from other etiologies, ruling out CAD as the cause of CHF is of clinical importance. If a patient with CHF is found to have no abnormalities of myocardial perfusion at stress (percent myocardium ischemic < 5%), the likelihood of CAD as the cause of CHF can be considered low.[23] However, the possibility of balanced reduction of flow masking severe and extensive CAD in a patients with ischemic cardiomyopathy, as mentioned above, must be considered. CCTA and CMR with delayed enhancement likely could be preferable in this regard: the former providing direct coronary assessment and the latter providing assessment of MI (even small) and concomitantly allowing for assessment of multiple other heart failure etiologies.

IDENTIFYING CHRONICALLY STUNNED OR HIBERNATING MYOCARDIUM

In patients with CAD and CHF, repetitive stunning or myocardial hibernation are important causes of LV dysfunction that might improve with revascularization. Although 18F-FDG PET is preferred over SPECT in detecting these conditions, SPECT-MPI protocols using ^{201}Tl are effective in distinguishing viable but nonfunctioning myocardium from nonviable myocardium.[138] As noted above, late redistribution ^{201}Tl imaging improves detection of regions of severely hypoperfused but viable myocardium,[18,19] and nitroglycerin-augmented technetium agent protocols might be employed. Myocardium subjected to acute or chronic ischemia may remain viable and demonstrate prolonged alterations in regional and global LV function that can be improved with revascularization.[138] Consequently, the distinction of ventricular dysfunction caused by fibrosis from that arising from viable myocardium has important implications for patients with low LVEF. Failure to identify patients with these potentially reversible causes of heart failure may lead to progressive cellular damage, worsening CHF, and death.[138] When available, assessment of myocardial viability directly by 18F-FDG PET (Chap. 19) or indirectly by late enhancement of scarring by CMR would be preferable to SPECT-MPI viability testing.

PREDICTING IMPROVED PATIENT SURVIVAL IN ISCHEMIC CARDIOMYOPATHY

The demonstration of viable myocardium in patients with CAD and LV dysfunction is commonly used to identify patients with enhanced survival with revascularization but with particularly poor prognosis with medical therapy. A meta-analysis of observational studies based

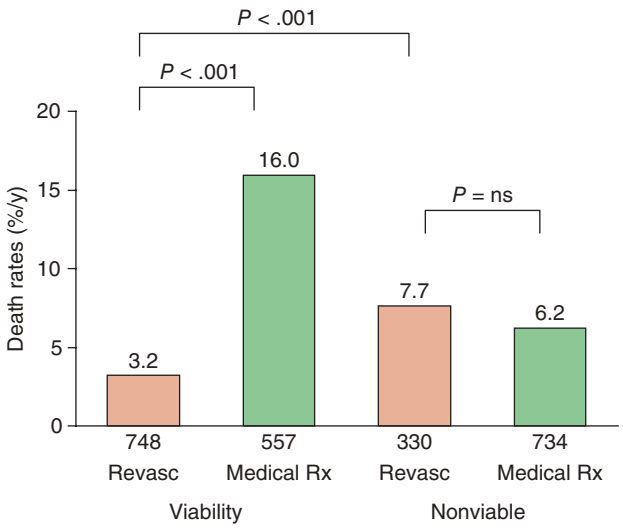

FIGURE 18–39. Meta-analysis of studies examining rates of death in patients undergoing revascularization (revasc) versus medical therapy (Rx). When viability was present by noninvasive testing, a significant reduction in cardiac death rates was present in patients undergoing revascularization compared with those undergoing medical therapy. No such difference was present in patients without viability. Furthermore, patients with viability undergoing revascularization had a significantly lower cardiac death rate compared to patients without viability. Reproduced with permission from Allman KC, Shaw LJ, Hachamovitch R, et al: Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis, *J Am Coll Cardiol.* 2002 Apr 3;39(7):1151-1158.[302]

on either radionuclide or echocardiographic assessments that dichotomized patients into groups with or without myocardial viability suggests that only patients with extensive viability have survival improvement with CABG compared with medical therapy[302] (Fig. 18–39).

The PET and Recovery Following Revascularization (PARR-2) study was a randomized trial that assessed the use of FDG PET scanning[303] in patients with heart failure, known or suspected CAD, and LVEF of 35% or less. It also served to illustrate that the ability of a test to affect outcomes is dependent on several factors, ranging from the intrinsic measurements possible with the test to the manner in which test results change therapy. In this study, 430 patients in nine centers were randomized to a management plan assisted by FDG PET (n = 218) or standard care (n = 212), with specific recommendations regarding the use of FDG PET information for revascularization decisions. The outcome was a composite of cardiac death, MI, or recurrent hospital stay for cardiac cause within 1 year. In the overall trial, there was a trend for benefit for FDG PET–assisted management in the HR for the composite outcome in the PET versus standard of care arm ($P = .15$). Importantly, however, when adherence to imaging recommendations was considered, in patients in whom the PET treatment recommendations were followed, the HR was significant ($P = .19$). These findings illustrate the general concept that test results can have a beneficial effect on outcome only if the test appropriately changes therapy. A post-hoc analysis was performed comparing a subgroup of patients studied in five hospitals with greater experience in and access to the use of the PET-assisted strategy in the PARR-2 trial.[304] There was a significant reduction in cardiac events in the patient population studied at the five sites with expertise in the performance and application of PET ($P = .005$) that had not been seen in the overall trial (Fig. 18–40).

In contrast to the prior observational studies, several substudies of the recent NIH-NHLBI–sponsored Surgical Treatment for Ischemic Heart Failure (STICH) trial have reported negative findings with respect to viability and ischemia testing in predicting revascularization benefit in patients with CAD and severe LV dysfunction. The STICH trial assessed the benefits of CABG in 1212 patients with CAD and EF less than 35%. The initial viability substudy reported the results of viability testing accomplished in 618 (51%) of enrolled patients. This testing was performed with SPECT-MPI in approximately two-thirds and with dobutamine echocardiography in the remaining one-third.[305] The SPECT studies included (1) stress/redistribution/reinjection or rest/redistribution ^{201}Tl or (2) nitrate-augmented ^{99m}Tc rest sestamibi or tetrofosmin protocols. PET or CMR assessments of myocardial viability were not used. Myocardial viability was defined as the presence of 11 or more of 17 segments demonstrating viable myocardium. The presence of substantial amounts of viable myocardium was associated with improved survival in the overall cohort (HR 0.64, 95% CI, 0.48-0.86; $P = .003$); however, it was not predictive of a benefit in survival with CABG compared to OMT ($P = .53$). In a subsequent report, 399 patients in STICH who also underwent assessments of stress-induced ischemia were evaluated. Inducible ischemia in these patients with severe LV dysfunction did not identify patients with worse prognosis or those with greater benefit from CABG over OMT.[212] In a further assessment, in 267 patients randomized to surgical ventricular reconstruction plus CABG compared CABG alone, the presence of viability was not associated with a mortality benefit from the addition of the ventricular reconstruction.

Numerous methodological criticisms, however, have called question to the validity of the STICH results.[306] The study was only a substudy, containing only half of the STICH patients. The assessment mixed the patients having SPECT and dobutamine echocardiography. Viability was not analyzed as a continuous variable, and myocardial hibernation was not reported; that is, the presence of viability in regions with myocardial dysfunction was not addressed. Patients were not randomized on the basis of the viability test results. Compared with PARR-2, the STICH patient population was at lower risk, already being considered appropriate for CABG, having more single-vessel disease, infrequent previous CABG, low incidence of renal dysfunction, and predominantly no clinical heart failure. In contrast, in PARR-2, physicians were uncertain about revascularization decisions and, therefore, needed viability assessment; that is, viability testing was considered clinically indicated. Furthermore, only 19% of patients in the STICH substudy were considered to have nonviable myocardium. More advanced (or alternative) ischemia and viability imaging modalities (ie, using PET and CMR) were not evaluated. Thus, the STICH results need to be interpreted cautiously. Assessments of myocardial viability remain of particular importance in patients with very high surgical risk, in whom assessments of potential benefit of revascularization in heart failure symptoms or survival are crucial factors in clinical decision making. A similar important application of viability assessment is in guiding decision making regarding coronary revascularization versus cardiac transplantation in patients with severe ischemic cardiomyopathy.

ACUTE CORONARY ISCHEMIC SYNDROMES

EVALUATION OF PATIENTS WITH ACUTE CHEST PAIN

Almost 8 million individuals are evaluated each year for acute chest pain in the emergency department (ED).[307] Despite standardized protocols and high vigilance, between 2% and 6% of patients are erroneously discharged with missed MI,[308] with higher mortality rates than patients who are hospitalized. For patients with normal or nondiagnostic initial ECGs and negative troponin levels on presentation to the ED, an important clinical problem is to distinguish those with ACS requiring hospital admission from those who may be safely discharged. Noninvasive imaging has become part of the standard of care in assessing patients with low to intermediate risk of an ACS in the ED.

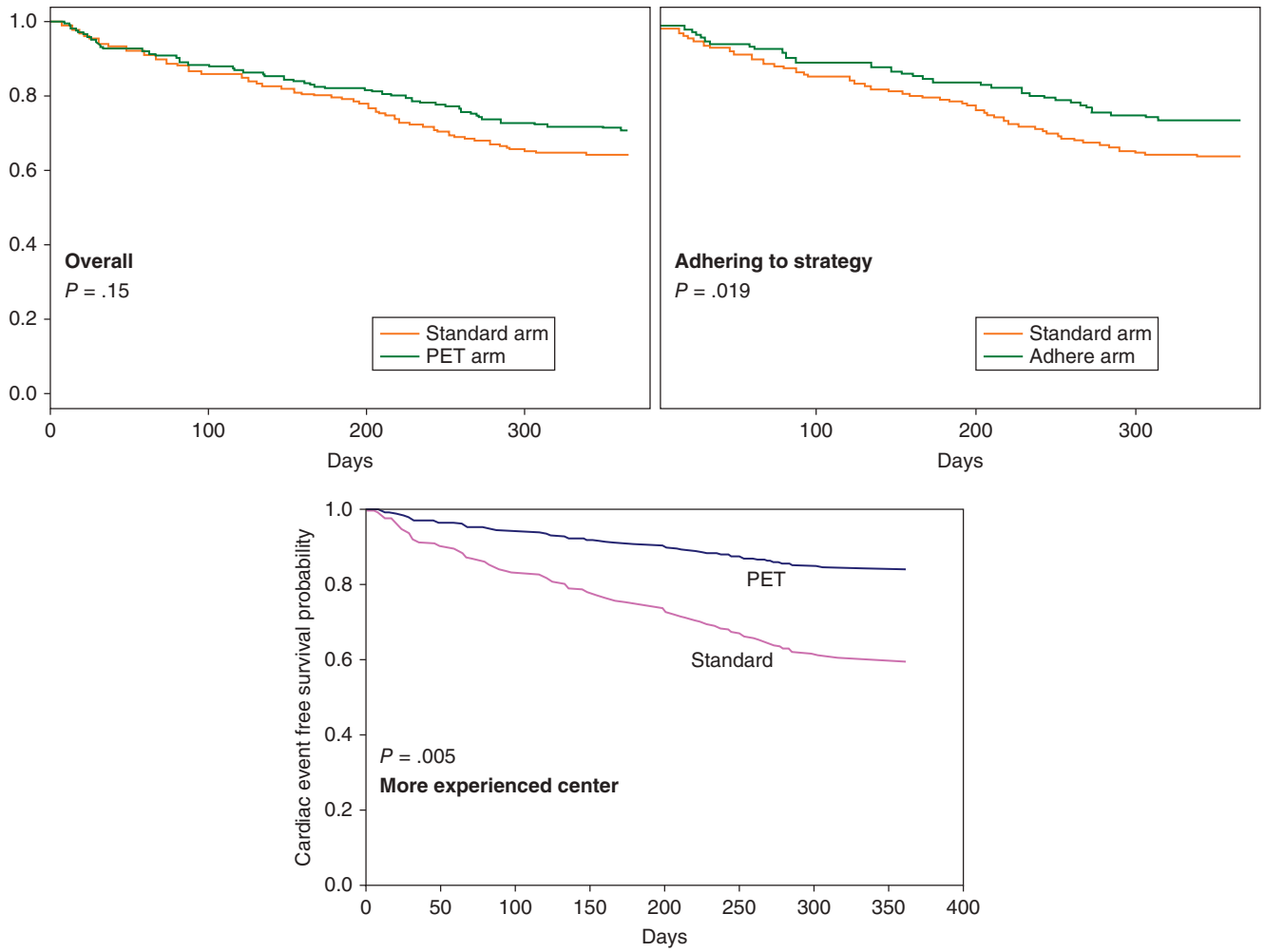

FIGURE 18–40. Influence of adherence to strategies and expertise on impact of FDG-positron emission tomography (PET) on patient outcomes as shown in two publications from the PET and Recovery Following Revascularization (PARR-2) study. The *top two* graphs illustrate composite outcome of cardiac death, myocardial infarction, and recurrent hospital stay for cardiac cause within 1 year. In the overall trial (*left*), no survival benefit was shown. In the subset in which the planned therapeutic strategy of the trial based on PET viability results was followed (*right*), a significant survival benefit in the PET arm was seen. When patients who were tested in a center with greater experience with FDG-PET were assessed (*lower* graph), an even greater survival benefit in the PET arm was shown. Top two graphs: Reproduced with permission from Beanlands RS, Nichol G, Huszti E, et al: F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2), *J Am Coll Cardiol*. 2007 Nov 13;50(20):2002-2012.[303]

Use of SPECT-MPI in the Evaluation of Acute Chest Pain

Rest or rest/stress ^{99m}Tc sestamibi or tetrofosmin SPECT-MPI is commonly used for this purpose. Because of the very strong relationship between an acute MI and acute closure of a coronary artery, a normal rest MPI alone, without stress imaging, provides strong evidence of the absence of MI. A 99% negative predictive value of rest SPECT-MPI alone for MI was reported in several studies beginning in the mid-1990s.[307] A prospective, randomized, controlled multicenter trial reported a reduction in hospitalizations when rest SPECT-MPI was incorporated into an ED evaluation strategy of patients presenting with suspected ACS (ERASE Trial).[309]

When the radiopharmaceutical is injected after pain has subsided and the SPECT-MPI study is normal, stress SPECT-MPI studies are commonly used to further rule out an ACS—as unstable angina might be associated with normal rest perfusion (Fig. 18–41).

Based on extensive literature documenting safety of maximal exercise testing in low-risk ED with a normal ECG and normal serial enzymes (4-6 hours apart), stress SPECT-MPI as the first MPI examination has recently been studied. In a large initial study, Duvall and colleagues[312] reported the safety and prognosis of stress-only SPECT-MPI studies performed in 2340 patients and compared these to findings in 1805 patients having rest/stress studies (Fig. 18–42). The patients in the stress-only group were younger and had a lower risk profile. All-cause death was 0.5% (11 patients) in the stress-only group. Even higher frequency of stress-only procedures in a similar population has been reported in a study comparing SPECT-MPI to CCTA by the same authors[313] in which 939 patients were studied in the ED with SPECT-MPI and 75.4% had stress-only procedures (43.6% pharmacologic). Another recent study comparing an approach of MPI versus CCTA studying 310 patients with SPECT reported the use of stress-only MPI in 24%, stress/rest in 24%, and rest-first imaging in 52%.[314] In both studies, a normal stress SPECT-MPI study was safe and associated with a very low cardiac event rate.

Comparative Use of CCTA and Standard of Care (Most Commonly Including SPECT-MPI) in the Evaluation of Patients with Acute Chest Pain

Three large randomized clinical trials have evaluated the application of CCTA to patients with suspected ACS in the ED in comparison to a standard of care approach. In all of these studies, the patients evaluated were defined as being in a low to intermediate group regarding

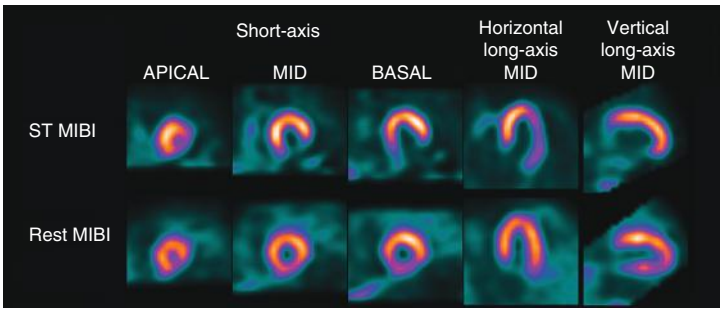

FIGURE 18–41. Case example illustrating value of stress testing when rest myocardial perfusion imaging is normal in the acute chest pain patient. Shown are adenosine stress/rest myocardial perfusion single-photon emission computed tomography images in a 55-year-old man with multiple risk factors for coronary artery disease presenting to the emergency department with 2 days of chest discomfort at rest. Rest sestamibi (MIBI) demonstrated minimal (borderline) perfusion defect in the inferior wall. Stress imaging revealed evidence of severe and extensive ischemia in the inferior and inferolateral wall (41% of the left ventricle). Coronary angiography revealed an occluded right coronary artery that was successfully stented.

the likelihood of having an ACS at the time of their ED visit. The first of these was the Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) trial comparing CCTA to rest/stress SPECT-MPI.[315] In 16 centers, 699 patients were randomly assigned to CCTA (n = 361) or MPI (n = 338) because the index noninvasive test. CCTA resulted in a 54% reduction in time to diagnosis (2.9 vs 6.3 hours) compared with MPI ($P < .0001$). Costs of care were 38% lower ($P < .0001$). The diagnostic strategies had no difference in major adverse cardiac events after normal index testing (0.8% in the CCTA arm vs 0.4% in the MPI arm, $P = .29$). The American College of Radiology Imaging Network–PA (ACRIN-PA) trial[316] evaluated 1392 low- to intermediate-risk patients (thrombolysis in myocardial infraction, or TIMI, score: 0-2) presenting to the ED to CCTA or the physician elected-traditional approach to standard care in a 2:1 ratio. Fifty-eight percent of patients in the standard care arm had stress imaging. Patients evaluated with coronary CTA had a shorter mean hospital stay and were also discharged more rapidly (total length of stay of 18 vs 25 hours; $P < .0001$) and more frequently (50% vs 23%) than patients undergoing the standard care evaluation.[316] The Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) II trial[317] randomly assigned patients 40 to 74 years of age with symptoms suggestive of ACS but without ischemic ECG changes or an initial positive troponin test to early CCTA or to standard evaluation in the ED. Only 25% of the 499 patients in the standard care arm had SPECT-MPI. The rate of ACS among 1000 patients with a mean age of 54 ± 8 years (47% women) was 8%. Compared with standard evaluation, in the CCTA group, the mean length of hospital stay was reduced by 7.6 hours ($P < .001$). A higher proportion of patients were discharged directly from the ED (47% vs 12%, $P < .001$). There were no undetected ACS and no significant differences in major adverse cardiovascular events at 28 days. The cumulative mean cost of care was similar in the CCTA group and the standard-evaluation group ($4289 and $4060, respectively; $P = .65$).

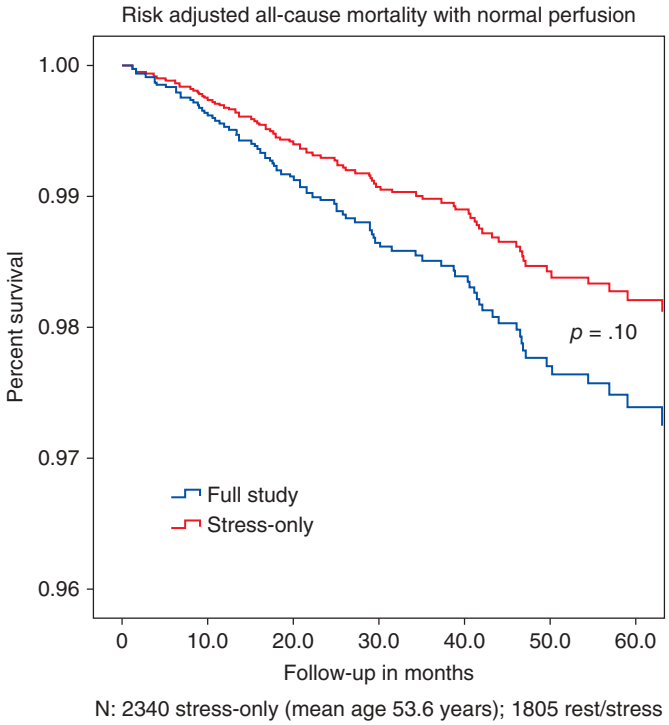

FIGURE 18–42. Risk-adjusted all-cause mortality with normal perfusion an average follow-up of 3 years with normal myocardial perfusion imaging in the stress-only cohort and full study cohort. At 1 year, there were 11 all-cause deaths in the stress-only group (0.5%). Reproduced with permission from Duvall WL, Wijetunga MN, Klein TM, et al: Stress-only Tc-99m myocardial perfusion imaging in an emergency department chest pain unit, *J Emerg Med*. 2012 Jun;42(6):642-650.[312]

As noted, another recent randomized trial compared coronary CTA and SPECT-MPI approaches with protocols in which stress-only imaging was used. In 598 patients with chest pain in the ED, the coronary CTA study was associated with more rapid time to diagnosis, shorter hospital stay, and lower costs. However, when stress-only imaging was performed (24%), these outcomes assessments were comparable between SPECT and CCTA.[314]

The results of these studies show that coronary CTA is of value when compared to an approach using SPECT-MPI in the ED—making coronary CTA the preferred study for some patients. Importantly, however, there are multiple settings of chest pain in the ED in which SPECT-MPI would be preferred. These include patients with known dense coronary calcification and elderly patients in whom dense coronary calcifications are likely; patients with prior bypass surgery, possibly with prior PCI, and known ischemic cardiomyopathy; and with contraindications to CCTA. Both approaches are effective. Local expertise in the performance and interpretation of these two examinations and the availability of the examinations are additional factors that would favor one approach over the other in an individual patient.

Assessment of imaging in patients with suspected ACS was part of the AUC for cardiac radionuclide imaging.[318] In patients with acute chest pain presenting with *possible ACS*, rest/stress nuclear MPI was considered appropriate in the settings found in Table 18–7. In patients with elevated troponin without additional evidence of ACS, rest/stress MPI was also considered appropriate. The AUC also address settings in which nuclear imaging might be appropriate for risk assessment within 3 months of an ACS. Routine testing after primary PCI, including asymptomatic patients prior to discharge or prior to cardiac rehabilitation, was considered inappropriate. The only settings listed as appropriate were to evaluate for inducible ischemia in post-ACS patients without prior coronary angiography. Patients with incomplete revascularization were not specifically addressed. Stress MPI is commonly used in these patients to assess for inducible ischemia. The indication for this could be considered under the category of patients with prior coronary angiography with "coronary stenosis or anatomic abnormality of uncertain significance," which is given an appropriate category.

TABLE 18–7. Detection of Coronary Artery Disease: Symptomatic

Acute Chest Pain		
Indication		Appropriate Use Score (1–9)
1.	• Possible ACS • ECG: no ischemic changes or with LBBB or electronically ventricular-paced rhythm • Low-risk TIMI score • Peak troponin: borderline, equivocal, minimally elevated	A(8)
2.	• Possible ACS • ECG: no ischemic changes or with LBBB or electronically ventricular-paced rhythm • High-risk TIMI score • Peak troponin: borderline, equivocal, minimally elevated	A(7)
3.	• Possible ACS • ECG: no ischemic changes or with LBBB or electronically ventricular-paced rhythm • Low-risk TIMI score • Negative peak troponin levels	A(8)
4.	• Possible ACS • ECG: no ischemic changes or with LBBB or electronically ventricular-paced rhythm • High-risk TIMI score • Negative peak troponin levels	A(8)
5.	• Definite ACS	I(1)
6.	**Acute Chest Pain (Rest Imaging Only)** • Possible ACS • ECG: no ischemic changes or with LBBB or electronically ventricular-paced rhythm • Initially troponin negative • Recent or ongoing chest pain	A(7)

ACS, acute coronary syndrome; CAD, coronary artery disease; ECG, electrocardiogram; LBBB, left bundle branch block; LV, left ventricular; LVF, left ventricular function; PET, positron emission tomography; RNA, radionuclide angiography; RVF, right ventricular function.

Adapted with permission from Hendel RC, Berman DS, Di Carli MF, et al: ACCF/ASNC/ACR/AHA/ASE/ SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *J Am Coll Cardiol*. 2009 Jun 9;53(23):2201-2229.[318]

RADIONUCLIDE ANGIOGRAPHY

Radionuclide angiography (RNA) can be performed by either equilibrium or first-pass methods, with assessments of LVEF, RV EF, LV regional wall motion, and LV volumes and LV diastolic function. Equilibrium RNA uses ECG-gated acquisition, in which each frame corresponds to a specific portion (interval or gate) of the cardiac cycle, identified relative to the R wave on the patient's ECG. Because of the use of a multiple gated acquisition (MUGA), the term *MUGA scan* has also been applied to this technique. The cardiac cycle is divided into 16 to 64 intervals, and data from multiple cardiac cycles are averaged to ensure adequate count statistics. With the equilibrium approach, a blood-pool tracer (usually ^{99m}Tc-labeled red blood cells) is used. With the first-pass approach, imaging was performed only during the initial transit of radioactivity through the central circulation. Both techniques can be performed during exercise as well as at rest.

Because of the ability to image the blood-pool radiopharmaceuticals for a substantial time period, SPECT acquisition is also practical with equilibrium RNA. It has been shown that equilibrium blood-pool SPECT acquisition and processing are essentially the same as for SPECT-MPI and thus can be easily adopted in the laboratory where SPECT-MPI is performed. Methods for automatically assessing LVEF from gated blood-pool SPECT have been developed and validated.[319] Because the SPECT approach avoids the overlap of cardiac chambers inherent in planar imaging, it enhances assessment of regional function and may well become the method of choice for RNA. Techniques for assessing regional asynchrony from the gated blood-pool SPECT have been described and may be of use in predicting the benefit from cardiac resynchronization therapy (Fig. 18–43). Synchrony of contraction can be assessed using gated blood-pool SPECT,[320,321] with potential application as an aide to determining the need for cardiac resynchronization therapy; however, in recent reports, SPECT-MPI has been more commonly used for this application, as discussed later.

ROLE OF RNA IN CHRONIC CAD

Early in the application of nuclear cardiology, the use of RNA was common. Transthoracic echocardiography has now become the standard in the settings in which RNA was previously used. The principal application of RNA remains the measurement of LVEF.[23] This measurement can be used in a variety of settings such as defining the need for specific therapy, including angiotensin-converting enzyme inhibitors, automatic ICDs, and surgical ventricular restoration; guiding the use of cardiotoxic chemotherapy; and documenting severe reduction of LVEF prior to admission into heart failure trials. RNA can be of value as an arbiter of LVEF when the result of echocardiograph or other methods are uncertain or discordant.

For the detection and management of patients with CAD, exercise RNA played a prominent role in the past, but is now rarely used, predominantly because of advances in stress echocardiography and the ability of gated SPECT-MPI to assess ventricular function as well as myocardial perfusion.

SPECIAL APPLICATIONS OF RNA

Assessment of Anthracycline Cardiotoxicity

While echocardiography has become the more common test for this application, RNA can be used in for evaluating the effects of doxorubicin and other anthracyclines on LV function in patients with suspected cardiotoxicity.[322] In an early report, Schwartz and colleagues demonstrated that patients with normal LVEF that had not decreased by more than 15% did not develop cardiotoxicity with continued doxorubicin therapy; however, once EF decreased to less than 45% or by more than 15%, continued doxorubicin therapy was commonly associated with irreversible cardiac failure. In a subsequent report of a large high-risk population from the same group, guidelines were established for the use of continued doxorubicin therapy.[323] In a group of 70 high-risk patients in whom these guidelines were strictly followed, 2.9% developed subsequent CHF that responded to therapy. Of 212 high-risk patients in whom the recommendations were not closely followed, 21%

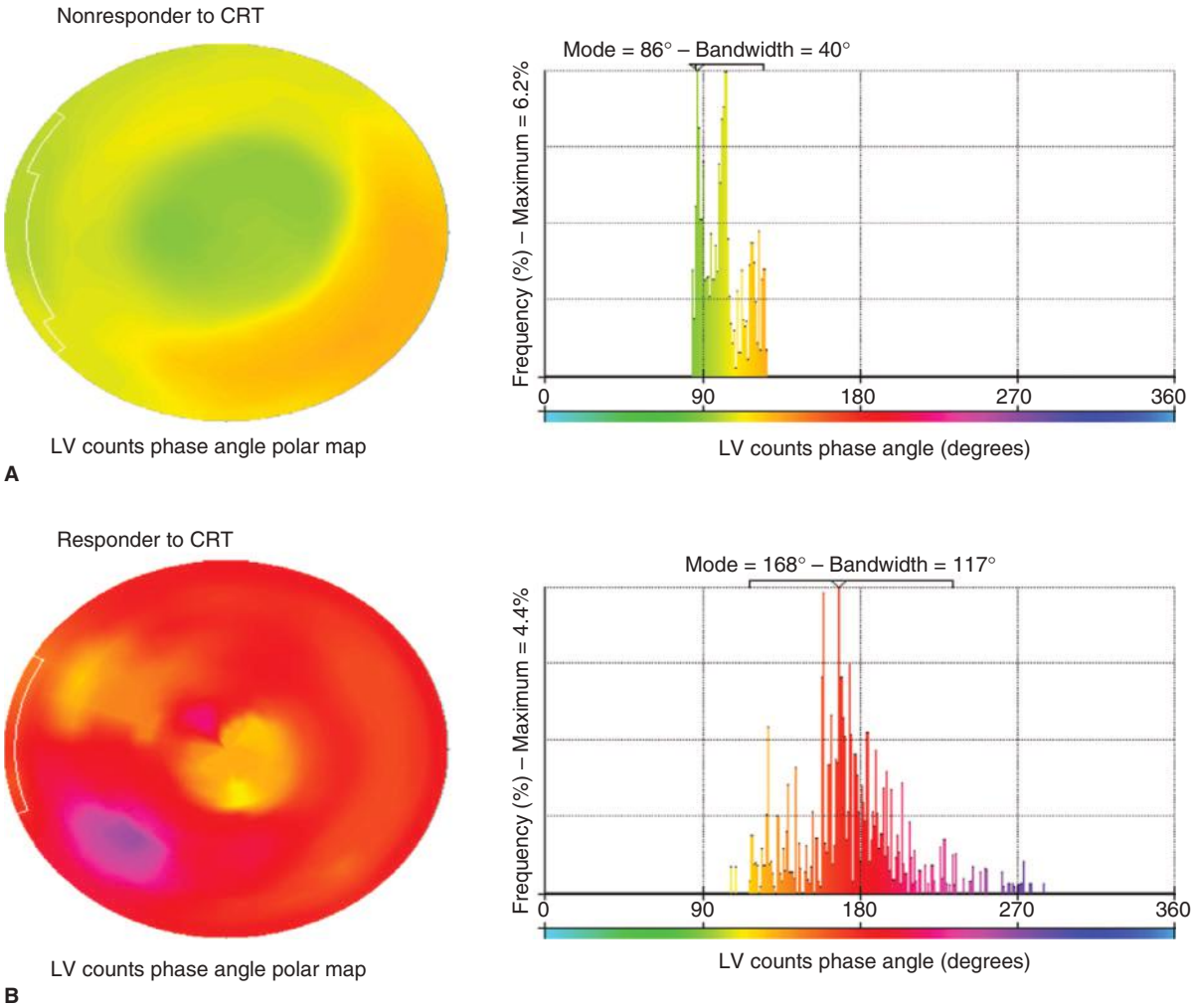

FIGURE 18–43. A. Example of a patient without left ventricle (LV) dyssynchrony on gated myocardial perfusion single-photon emission computed tomography (SPECT). Synchronous contraction pattern is reflected by homogeneous phase angle distribution of polar map (*left*) and narrow highly peaked histogram (*right*). At the 6-month follow-up, no improvement in New York Heart Association (NYHA) functional class was observed, and LV ejection fraction remained unchanged (32% at baseline vs 33% at 6-month follow-up). **B.** Example of a patient with extensive LV dyssynchrony on gated myocardial perfusion SPECT. LV dyssynchrony is indicated by heterogeneous phase-angle distribution of polar map (*left*) and wide histogram (*right*). At the 6-month follow-up, NYHA functional class improved from 3 to 2, with increase in LV ejection fraction from 21% to 33%. CRT, cardiac resynchronization therapy. Reproduced with permission from Boogers MM, Van Kriekinge SD, Henneman MM, et al: Quantitative gated SPECT-derived phase analysis on gated myocardial perfusion SPECT detects left ventricular dyssynchrony and predicts response to cardiac resynchronization therapy, *J Nucl Med*. 2009 May;50(5):718-725.[353]

developed CHF ($P < .001$ vs the strict-guideline group), which was usually moderate to severe.

CARDIAC COMPUTED TOMOGRAPHY: COMPLEMENTARY ROLE WITH NUCLEAR CARDIOLOGY

The physiologic assessments of nuclear cardiology and the anatomic assessments of CCTA provide complementary information. Their sequential use of the complementary testing in settings in which the initial test left clinically uncertainty regarding the clinical question being asked is useful. Although recent developments in CCTA have demonstrated that CCTA alone may increasingly be used to assess both the presence and the functional significance of CAD, to date they are not widely applied clinically. Furthermore, stress nuclear imaging remains the dominant initial imaging method. Thus consideration of the clinical value of combined testing of the physiologic and anatomic processes, whether combined or in sequential fashion, remains important. Which type of test might be optimal as the initial test depends on the clinical subset of patients being studied. In asymptomatic patients, there has been dramatic growth in the evidence base supporting the use of CAC scanning with noncontrast CT to assess subclinical atherosclerosis (see Chap. 17). As discussed above, in patients with extensive CAC, usually defined by a threshold of 400 Agatston units or more, assessment with nuclear MPI for the presence and extent of myocardial ischemia can help guide patient management for adding anti-ischemic therapy and consideration of the need for revascularization. Also, as noted above, after CCTA, nuclear MPI may play a role in further risk stratification if the results of the CCTA are not definitive regarding patient management.

The evaluation of symptomatic patients with suspected CAD is the most common application of nuclear MPI. However, in recent years, CCTA has become increasingly utilized as the initial diagnostic test in these patients. CCTA has emerged as the noninvasive method with the highest accuracy for prediction of anatomic stenosis by invasive coronary angiography, with sensitivity in the range of 95%, higher than that associated with all other noninvasive testing.[324-326] Furthermore, when compared to nuclear MPI, CCTA is less likely to fail to detect CAD in a patient with high-risk

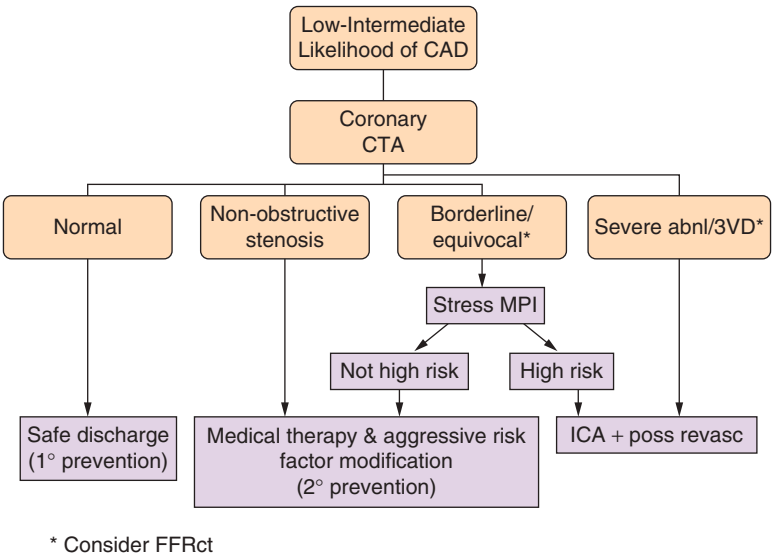

FIGURE 18–44. Coronary computed tomography angiography approach to diagnosis and management of coronary artery disease (CAD) in symptomatic patients with an intermediate pretest likelihood of CAD. The *asterisk* indicates that fractional flow reserve by computed tomography should be considered. Abnl, abnormal; revasc, revascularization; 3VD, triple vessel disease. Data from Schuijf JD, Bax JJ, Shaw LJ, et al: Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography. *Am Heart J.* 2006 Feb;151(2):404-411.

anatomy unless quantitative myocardial perfusion flow reserve assessment is employed (167). A large number of studies have demonstrated high prognostic accuracy of CCTA measures across a broad spectrum of presentations of suspected CAD (327-330). The mortality rate in patients with entirely normal CCTA studies is extremely low.[327] With each degree of increasing anatomic abnormality, including nonobstructive disease, significant increases in mortality were observed.[327] A long "warranty period" for patients with a normal study has been described: the annual event rate of patients with a normal CCTA study has been reported in multiple studies to be less than 0.25%. Thus, CCTA is likely to increase in application as an initial test in symptomatic patients with suspected CAD. When CCTA is used as the initial test, there is a selective use of nuclear MPI in patients in whom management is unclear after the CCTA study. The role of nuclear MPI in an "initial CCTA" strategy is illustrated in Fig. 18–44. Nuclear MPI also plays a role in other circumstances when the results of coronary CTA are indeterminate regarding therapeutic options (eg, in the post-PCI or post-CABG patient).

In patients with a high likelihood of CAD or in those with known CAD, physiologic testing with nuclear MPI has generally been preferred over the anatomic approach. The limitations of stenosis assessment alone in guiding the management of stable CAD patients has been discussed above, based on results from the COURAGE and BARI 2D trials. Furthermore, in these patients, extensive coronary calcification is common and may obscure the accurate interpretation of stenosis by CCTA.

In patients in whom nuclear MPI is the initial test, cardiac CT often plays a complementary role (Fig. 18–45). In patients with normal MPI results, CAC scanning can be useful in detecting subclinical atherosclerosis and guiding patient management. A drawback of stress imaging without anatomic assessment in patients with an intermediate likelihood of CAD is that the methods detect only patients with hemodynamically significant lesions and fail to identify patients with subclinical atherosclerosis in whom aggressive medical and lifestyle modification might prevent subsequent cardiac events. Although SPECT-MPI assessment of ischemia is an excellent test of short-term prognosis, CAC scanning may be a better test of long-term prognosis.[331] More than a decade ago, it was recognized that high CAC scores are common in patients with normal SPECT-MPI.[332] By combining CAC scanning with nuclear MPI, patients with normal MPI and nonobstructive CAD can be identified and afforded effective preventive therapies. The use of CAC scanning in conjunction with nuclear MPI can also be an aid in increasing certainty in interpretation and accuracy in prediction of hemodynamically significant stenosis in the presence of borderline MPI abnormalities or when there is discordance between the nuclear MPI results and clinical or ECG responses to stress (Fig. 18–46). The coupling of CAC scanning with SPECT or PET-MPI by hybrid scanning would likely increase the effectiveness of nuclear MPI as a first choice approach to management of the patient with suspected SIHD. How CCTA would fare regarding "value" when compared to hybrid CAC/SPECT or PET-MPI imaging has not been studied and would be of great interest.

CCTA is often more definitive than CAC scanning in guiding management of patients with borderline or discordant MPI results as well as in patients with mild degrees of ischemia. The decision to proceed to invasive angiography can be aided by CCTA, which might rule in or out the presence of high-risk anatomic findings. The incremental prognostic value of SPECT-MPI and CCTA has recently been reported in a study of 1295 patients undergoing both studies in sequential fashion.[333] Thus, clinical strategies are likely to emerge in which selected patients may benefit from both nuclear MPI and CCTA studies.

HYBRID SPECT/CT AND PET/CT

With the advent of hybrid SPECT/CT and PET/CT systems, assessment of both coronary anatomic and physiologic can be made as a routine in a single study. As noted above, with such systems, nuclear MPI is routinely coupled with CAC scanning, allowing assessment of and management of coronary atherosclerosis that might not be detected by ischemia testing alone. Coupling of MPI and CCTA in the same setting with these systems has also been described.[334] Several studies have evaluated hybrid PET-MPI/CCTA with respect to prediction of

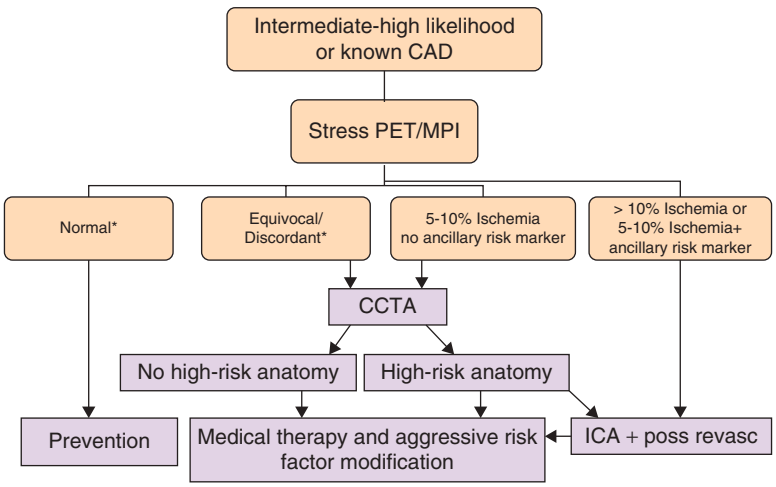

FIGURE 18–45. Myocardial perfusion imaging (MPI) approach to diagnosis and management of coronary artery disease (CAD) in symptomatic patients with an intermediate-to-high pretest likelihood of CAD or known CAD. The *asterisk* indicates that there may be benefit from coronary artery calcium scanning to assess underlying subclinical atherosclerosis. CCTA, coronary computed tomography angiography; ICA, invasive coronary angiography; PET, positron emission tomography. Data from Schuijf JD, Bax JJ, Shaw LJ, et al: Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography. *Am Heart J.* 2006 Feb;151(2):404-411.

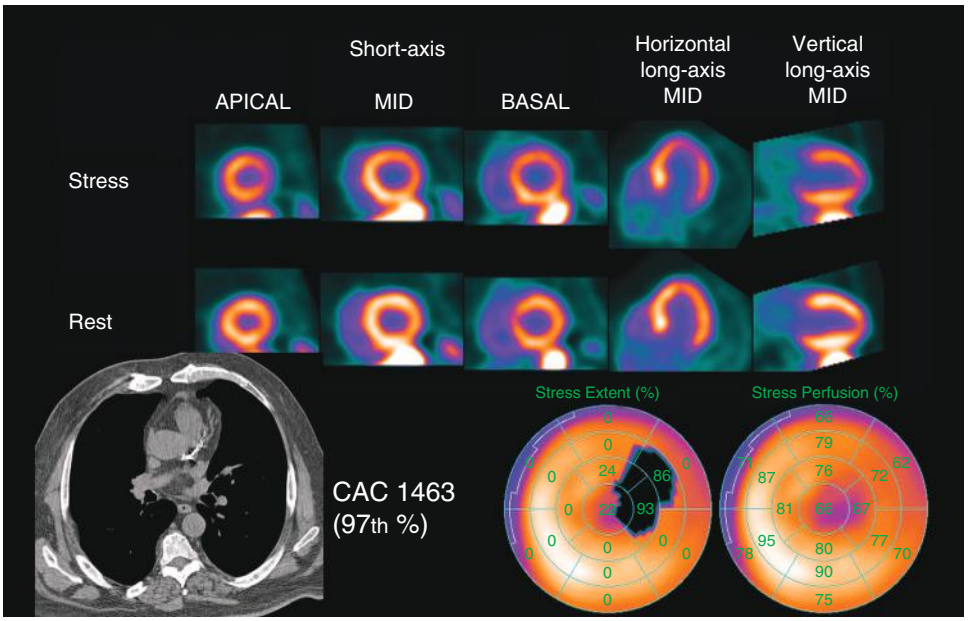

FIGURE 18–46. Case example of combined single-photon emission computed tomography (SPECT)–myocardial perfusion imaging (MPI) and coronary artery calcium scanning (CAC). The patient was a 57-year-old man. The SPECT-MPI study was considered probably abnormal based on the perfusion study alone. The finding that the CAC score was 1463 (97th percentile adjusted for age, gender, and ethnicity) resulted in increased observer certainty in interpreting the study as abnormal. %, percentile.

hemodynamically significant stenosis defined by invasive angiography in combination with FFR[335,336] and have demonstrated higher accuracy of the combination than with either modality alone. Because it is difficult to predict in advance whether a patient will need both studies, the practicality and cost-effectiveness of the routine combination of the two studies remains in question. If a single test provides sufficient information to accurately guide patient management, the routine performance of the both tests would have resulted in unnecessary radiation.

COMBINED ANATOMY AND FUNCTION FROM CORONARY CTA

The recently described method for estimating FFR from the resting CT—FFR CT—also allows the potential to assess both the presence and the physiologic significance of coronary stenosis. Three multicenter studies have demonstrated improved prediction of invasive FFR by the combination of FFR CT with coronary CTA.[339-341] Computed tomography perfusion (CTP) has been described as a method for assessing myocardial perfusion at the time of CCTA, accomplished through acquisition of an additional contrast CT study during vasodilator stress. Improved accuracy in detection of functionally significant stenosis using CTP has been reported.[342] A recent meta-analysis of FFR CT and CTP has reported that these methods improve the specificity of CCTA for detecting hemodynamically significant stenosis as defined by FFR.[343] Their combination in a single setting may expand the clinical use of CCTA for the combined purpose of assessing anatomic and functionally significant CAD. Applications of these methods could affect both the choice of initial testing and reduce the need for the sequential performance of testing with CCTA and nuclear perfusion techniques.

FUTURE OF NUCLEAR CARDIOLOGY

The past decade has seen new developments in noninvasive imaging technology and improvements in existing modalities. The options for imaging in known or suspected CAD include echocardiography, CMR, multidetector CT, and PET as alternative or complementary modalities to stress SPECT-MPI. Each modality is likely to play an important clinical role for the foreseeable future. In many patients, these tests will be used in combination to most effectively guide patient management decisions. The ability of myocardial perfusion SPECT to provide standardized procedures that are not highly technologist dependent and provide objective quantization assessments of myocardial perfusion and function with equipment of only moderate expense offers a strength likely to sustain this approach for many years. Over a longer time frame, echocardiography, CT, and CMR may increasingly be used for many of the applications for which SPECT is commonly used today. During this time, however, opportunities for growth of molecular imaging methods both in SPECT and in PET are likely to be developed as growth areas for the field of nuclear cardiology. Although the basic SPECT camera has had little fundamental change over several decades, entirely new SPECT approaches have been introduced recently, offering the potential to increase both sensitivity (reducing imaging time or radiation dose) and resolution.[5,344,345]

RECENT CARDIAC SPECT APPLICATIONS

Assessment of LV Dyssynchrony: Guidance for CRT

Accurate assessment of ventricular dyssynchrony may improve the selection of patients who benefit from CRT. Because of the four-dimensional nature of the image data sets, gated SPECT can be used to assess ventricular dyssynchrony.[347,348] Studies have shown that an assessment of intraventricular dyssynchrony can be effectively performed by means of phase analysis on gated SPECT-MPI[111,112,349-351] or gated blood-pool SPECT, the latter also allowing the assessment of interventricular dyssynchrony.[320,321,352] Studies have reported that responders and nonresponders from CRT therapy can be distinguished by phase analysis.[350,353,354] Patients with broad dispersion of phase angles are more likely to respond to CRT (see Fig. 18–43). In small single-center trials, sensitivity and specificity for predicting response to CRT have been reported as 70% and 74%,[350] 83% and 81%,[353] and 77% and 56% respectively.[352] In comparison to tissue Doppler imaging by echocardiography, the SPECT-MPI methods have the advantage of providing true 3D onset of contraction data for the entire LV. Additionally, the methods of analysis are automatic, thus providing high reproducibility. Prospective trials are needed to compare the value of MPI versus echocardiography in predicting benefit from CRT as well as to determine whether this assessment is superior to the standard criterion of prolonged QRS duration for selecting patients for CRT. Other potential applications include guiding CRT LV lead placement toward the site of latest mechanical activation,[355,356] and risk stratification and disease process identification in various populations such as patients with known or suspected CAD,[357] hypertension, nonischemic cardiomyopathy with narrow QRS and mildly decreased LVEF,[358] ICDs,[359] or end-stage renal disease.[360] Because of intrinsic differences between published SPECT-MPI methods, algorithm-specific thresholds are recommended for clinical applications.[361]

Cardiac Amyloidosis

With the aging of the population, cardiac amyloidosis is becoming increasingly more prevalent and is now recognized as an under-recognized cause of heart failure. The diagnosis is often suspected in patients with heart failure and an apparent increase in LV mass by echocardiography, without clear explanation such as hypertensive heart disease with LVH or known hypertrophic cardiomyopathy.[362,363] Although endomyocardial biopsy may be required for a definitive diagnosis, it is not used indiscriminately, and noninvasive approaches leading to the diagnosis are of great clinical use.

Hot-spot (infarct-avid) imaging methods for detecting acute MI were among the earliest techniques in nuclear cardiology. The most common of these techniques was the use of ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP)—a standard bone scanning agent—for direct imaging of active calcification occurring in the presence of myocardial necrosis.[23] With improvements in enzymatic diagnosis of myocardial necrosis and with the development of CMR as a method for imaging MI, ^{99m}Tc-PYP is no longer used for acute MI.

^{99m}Tc-pyrophosphate is a bone scanning agent that tracks active calcification and was previously used to detect myocardial infarct.[356] More than 30 years ago, it was noted that ^{99m}Tc-PYP cardiac uptake was seen in cardiac amyloidosis, demonstrating a characteristic pattern of diffuse, intense myocardial uptake.[174] After the initial reports, it became recognized that many patients with biopsy-proven cardiac amyloidosis did not have abnormal ^{99m}Tc-PYP scans, and for 20-plus years, the method was considered highly specific (because of its characteristic pattern) but not sensitive for cardiac amyloidosis and was not widely used clinically.

Further understanding of the relationship between ^{99m}Tc-PYP and cardiac amyloidosis has led to the ^{99m}Tc-PYP scan now playing an important part in the diagnosis of this disease.[364] There are two major types of cardiac amyloidosis: light-chain amyloidosis (AL), associated with a plasma-cell dyscrasia, and transthyretin-related amyloidosis (ATTR), also referred to as senile amyloidosis or wild type, often occurring in the elderly or less commonly representing a familial process (see Chap. 61).The two types of cardiac amyloidosis have different treatments. For AL, a rapidly progressive and almost uniformly fatal disease, chemotherapy or liver transplantation is used. More supportive therapies are used for the more indolent ATTR. Further study of ^{99m}Tc-PYP in cardiac amyloidosis revealed that the characteristic diffuse uptake pattern was seen in ATTR amyloidosis but not in AL, explaining its apparent low sensitivity.[363,365,366] In a recent study, Bokhari and colleagues showed that a 1.5 heart:contralateral lung ratio in ^{99m}Tc PYP imaging accurately distinguished AL (< 1.5) from ATTR (> 1.5) amyloidosis.[365] Characteristic patterns of delayed enhancement on CMR are observed in both forms of cardiac amyloidosis.

With respect to the method of imaging ^{99m}Tc-PYP for cardiac amyloidosis, planar imaging is standard and is performed 90 minutes after injection. However, because it may be difficult to distinguish cardiac ^{99m}Tc-PYP uptake from residual ^{99m}Tc-PYP in the blood pool, cardiac SPECT may also be performed. The use of a dual-isotope approach, with ^{201}Tl and ^{99m}Tc-PYP, is useful for interpretive certainly regarding the presence and location of the myocardial ^{99m}Tc-PYP uptake.

In terms of clinical application, ^{99m}Tc-PYP imaging, therefore, now plays a central role in the evaluation of cardiac amyloidosis. It becomes part of the standard evaluation of patients with heart failure and unexplained increase in LV mass by echocardiography. CMR is the initial test of choice, being sensitive for both ATTR and AL cardiac amyloidosis. In a proposed diagnostic algorithm for cardiac amyloidosis, Falk and coworkers recommend CMR for initial testing along with assessment for the presence of plasma-cell dyscrasia.[367] If CMR is positive and a plasma cell dyscrasia is present, AL is likely and would be confirmed by endomyocardial biopsy. If the CMR is suggestive of cardiac amyloidosis but no plasma cell dyscrasia is found, ^{99m}Tc-PYP imaging is performed. If the pyrophosphate scan is negative, other etiologies of hypertrophic cardiomyopathy or infiltrative cardiomyopathy are evaluated.[367] Conversely, if the pyrophosphate scan is positive, it implies the presence of ATTR, and this finding leads to genotyping and endomyocardial biopsy. ^{99m}Tc-PYP imaging is also useful if CMR is contraindicated or if it is negative or equivocal and a high clinical suspicion remains present for amyloidosis, then PYP imaging would again be of value if a plasma-cell dyscrasia is ruled out.[367] The noninvasive testing with CMR and/or ^{99m}Tc-PYP is not considered definitive, and in most settings, the endomyocardial biopsy is used to establish the diagnosis. Serial scanning with ^{99m}Tc-PYP has not been found to be useful. A recent study by Castano and colleagues showed no significant changes of uptake over an 18-month period, despite significant clinical progression.[368]

Cardiac Sarcoidosis

Other applications of nuclear cardiology beyond MPI imaging are currently common with PET, as discussed in Chapter 19. Among these, the most common is the use of FDG imaging for diagnosis and guiding patients with known or suspected cardiac sarcoidosis.[369,370]

Metaiodobenzylguanidine Imaging: Neuronal Dysregulation in Heart Failure

^{123}I-metaiodobenzylguanidine (*m*IBG), a single-photon emitting analog of norepinephrine (NE), has extensively been used for almost a quarter of century for the assessment of neuronal dysregulation in patients with heart failure.[371-373] It is currently approved for use by the FDA for imaging of myocardial innervation; however, reimbursement for this application is not currently in place, resulting in low rates of its clinical use. Semiquantitative measures[374-376] reveal reduced myocardial *m*IBG uptake in heart failure that has a strong association with the likelihood of adverse outcomes such as ventricular arrhythmias and cardiac and all-cause mortality.[377-381] *m*IBG imaging can also verify resolution of neuronal dysfunction in response to treatment with neurohumoral agents or device therapy for heart failure.[382-388] Discordance between the extent of *m*IBG tomographic defect and the myocardial perfusion deficit determines the likelihood of unstable arrhythmias associated with sudden cardiac death and the need for ICD.[389-393]

The Pathophysiologic Basis of mIBG Imaging in Heart Failure Neuronal dysregulation plays an important role in the pathogenesis of heart failure (Fig. 18–47). NE synthesis in presynaptic sympathetic neurons and its release into the synaptic left are substantially increased in the failing heart. Although NE reuptake from the cleft into the neurons is increased through human norepinephrine transporter 1 (hNET1), it gradually fails to keep pace with the increasing NE spill, because of oxidative stress–mediated reduction in the efficiency of the reuptake mechanism. NE excess in the synaptic clefts leads to postsynaptic sarcolemmal adrenoceptor desensitization and contributes to myocardial remodeling. Increased NE content of the synaptic cleft is also reflected in increased circulating NE levels. Increased release and disproportionately lower reuptake results in 50% lower neuronal NE stores in heart failure. Because *m*IBG is a structural and functional analog of NE, radiolabeled *m*IBG has been employed to track the NE metabolism in failing hearts.

*m*IBG is taken up by the hNET1 with even higher affinity than NE (K_m = 0.31 μM and 1.8 μM, respectively). However, it binds poorly to the adrenergic receptors, exerts only minimal sympathomimetic effects,[394,395] and is not catabolized by monoamine oxidase (MAO) or catechol-O-methyl transferase (COMT).[396,397] Injected *m*IBG is

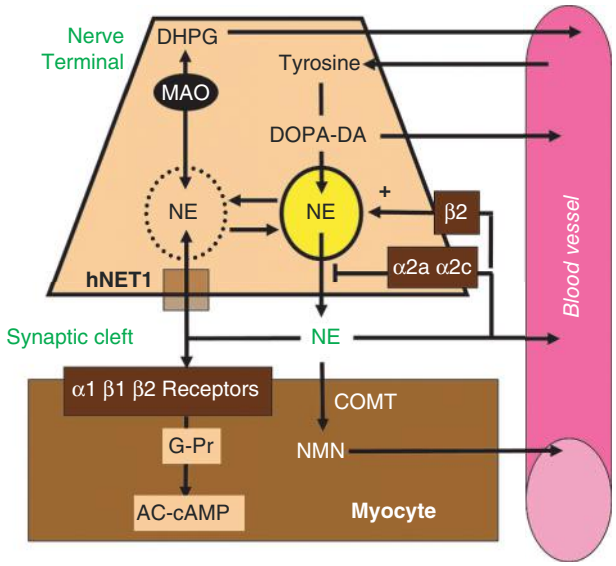

FIGURE 18–47. NE synthesis in presynaptic neuron, storage, release, reuptake via hNET1 and the pathophysiological basis of *m*IBG imaging. In the myocardial presynaptic nerve terminal, tyrosine is converted to dihydroxyphenylalanine (DOPA) and subsequently to dopamine (DA), from which NE is synthesized and stored in intraneuronal vesicles. NE released into the synaptic cleft activates postsynaptic adrenoceptors. NE in the synaptic cleft also activates presynaptic a-receptors (a_{2a}–,a_{2c}) which increase release of NE. The most important mechanism for the termination of NE action in the synaptic cleft is active reuptake into the presynaptic neuron through human NE transporter (hNET-1), while some NE diffuses into the plasma. Part of reabsorbed NE within the neuron is degraded by monoamine oxidase (MAO). NE that penetrates the postsynaptic myocyte may be partly inactivated by catechol O-methyltransferase (COMT) and returns to the circulation through normetanephrine (NMT). The myocyte membrane has a(1a, b, d)– and b(1-3)–adrenergic receptors. Adrenergic receptors interact with stimulatory G protein, leading to activation of effector pathways through conversion of ATP to cAMP. In heart failure incessant exposure of b_1-adrenoceptor to supraphysiologic NE amounts causes blunting of receptor responsiveness by decreasing the number of receptors on the myocyte membrane and uncoupling the receptor from its transducing G protein. In the nerve terminal, there is increased release of NE and decreased efficiency of NE reuptake due decrease in hNET1 sites, contributing to decrease in NE store size and increase in NE turnover. Metaiodobenzylguanidine (*m*IBG) is a guanethidine analog that has storage, transport, and uptake characteristics similar to those of NE in sympathetic neurons; radiolabeled mIBG tracks the NE metabolism in failing hearts. Consequently, with the NE analogue- *m*IBG in heart failure patients, there is decreased uptake in and washout from the nerve terminal, which correlate with the degree of sympathetic dysfunction, clinical severity of disease, and relatively poor prognosis. Modified with permission from Narula J, Sarkar K. A conceptual paradox of MIBG uptake in heart failure: Retention with incontinence. *J Nucl Cardiol*. 2003 Nov-Dec;10(6):700-704.

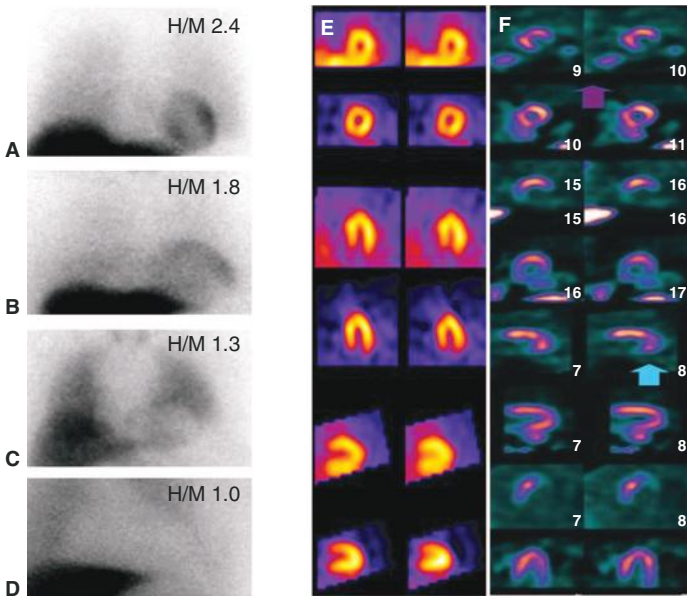

FIGURE 18–48. Being a norepinephrine (NE) analog, *m*IBG replicates the same behavior as that of NE. **A.** From synapse mIBG is taken up by the presynaptic neurons; because the ventricular myocardium is rich in sympathetic innervation, it shows prominent *m*IBG uptake. With each cycle of neuronal stimulation and NE release, a small amount of *m*IBG reenters the cleft and leaks into the vascular compartment to be transported to the kidneys unchanged for excretion. In heart failure (HF) patients, increased sympathetic outflow and decreased hNET1 efficiency results in faster clearance of neuronal *m*IBG. The images are quantified as heart-to-mediastinum uptake ratio (H/M) and shows faster washout of *m*IBG activity between 15 minutes and 4 hours, with consequently lower uptake ratio in the late images. Normal washout is 10% to 20% and the H/M ratio greater than 1.6; faster washout and low H/M are associated with increased occurrence of adverse events such as HF progression, ventricular arrhythmogenicity, and cardiac death. Parts **B–D** demonstrate progressively worsening HF with lower *m*IBG uptake and higher washout rates; all patients were symptomatic with NYHA class II to IIB and demonstrated progressively worsening H/M ratio. Parts **E** and **F** demonstrate single-photon emission computed tomography images; *m*IBG and ^{99m}Tc-tetrofosmin in a patient without heart disease (**E**) and an ischemic HF patient (**F**). Each display alternates between rows of *m*IBG and myocardial perfusion image slices. There is uniform uptake of both tracers in all myocardial walls of the normal patient. The HF patient has a perfusion defect in the basal inferolateral wall, consistent with a prior myocardial infarction (MI). The associated innervation defect is much larger, involving most of the surrounding inferior and lateral walls and apex (eg, arrow). This pattern of innervation/perfusion mismatch (ie, abnormal innervation in a region with preserved perfusion) is common in patients with MI and has been associated with increased susceptibility to ventricular arrhythmic events. Image courtesy of GE Healthcare.

taken up from the synapse into the neuron by the hNET1 pathway and stored in NE vesicles. With each cycle of neuronal stimulation, a small amount of *m*IBG reenters the synapse with the release of NE and diffuses back into the vascular compartment to be excreted unchanged by the kidneys. Normally, approximately 1% of the intravenously injected dose of *m*IBG localizes to the myocardium.[398] In heart failure, with increased sympathetic outflow,[399] and quantitative reduction in NE uptake sites,[400] there is more rapid clearance of neuronal *m*IBG. This is represented by higher washout rate in terms of the percentage reduction in *m*IBG activity between early (15-minute) and late (4-hour) images. Accordingly, late images show lower myocardial retention of *m*IBG and are assessed as a lower myocardium-to-background (usually mediastinal) uptake ratio. Lower *m*IBG retention at 4 hours, as evidenced by a heart-to-mediastinum (H/M) ratio of less than 1.6) and high levels of myocardial washout (> 40%-50% over the 4 hours) are associated with increased occurrence of adverse events such as heart failure progression and cardiac death (Fig. 18–48).[375]

***m*IBG Imaging for Prognostic Assessment** The following three studies provide the state-of-art description of the value of mIBG imaging.

1. ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study provided prospective validation of the independent prognostic value of *m*IBG scintigraphy in assessment of patients with heart failure.[401] The ADMIRE-HF study prospectively evaluated *m*IBG imaging for identifying symptomatic heart failure patients most likely to experience cardiac events. A total of 961 subjects with New York Heart Association (NYHA) functional class II/III heart failure and LVEF less than 35% underwent *m*IBG myocardial imaging and MPI and were then followed up for up to 2 years. Time to first occurrence of NYHA functional class progression, potentially life-threatening arrhythmic event, or cardiac death was compared with H/M less than1.60, and 25% of patients experienced events. The HR for H/M greater than 1.60 was 0.40; HR for individual event categories were 0.49, 0.37 and 0.14 for heart failure progression, arrhythmic events, and cardiac death, respectively. Significant contributors to the multivariable model were H/M,

LVEF, brain natriuretic peptide (BNP), and NYHA functional class, wherein *m*IBG imaging provided incremental discriminatory value beyond BNP and LVEF. In a subsequent substudy, 777 patients from ADMIRE-HF without ICD at the time of index *m*IBG were evaluated. There were 75 all-cause deaths. After adjusting for multiple factors, the H/M ratio analyzed as a continuous variable added incremental prognostic value and enhanced reclassification for survival. Although the H/M ratio did not identify individual patients with enhanced survival with ICD implantation, it identified the absolute benefit gained by ICD use, in groups as assessed by the number of lives saved per 100 treated, suggesting it may play a role in optimizing the cost-effectiveness of ICD placement.[402]

2. The pooled analyses of independent cohort studies from Japan (the largest user of *m*IBG imaging) confirmed the long-term prognostic value of cardiac *m*IBG uptake in patients with heart failure independently of other markers, including NYHA class, BNP, and LVEF. In addition, they demonstrated that categorical assessments could be used to define meaningful thresholds for lethal event risk. Six prospective heart failure cohort studies were updated, and the individual data sets were combined for the patient-level analysis. The database consisted of 1322 patients with heart failure followed up for a mean interval of 78 months; lethal events were observed in 326 patients with the mortality rate of 5.6%, 11.3%, and 19.7% at 1, 2, and 5 years, respectively. Multivariate Cox proportional hazard model analysis for all-cause mortality identified age, NYHA class, H/M, and LVEF as significant independent predictors. The receiver operating characteristic (ROC)-determined threshold of H/M (1.68) reported progressively decreasing 5-year survival rates with decreasing H/M; all-cause annual mortality rates were greater than 7% for H/M less than 1.25, and less than 2% annually for (heart-to-mediastinum ratio) HMR of 1.95 or more. Addition of H/M to the clinical information resulted in a significant net reclassification improvement of 0.175. The discriminatory value of H/M was observed at every level of LVEF.
3. To verify previous observations using a rigorous clinical trial methodology, a retrospective review and prospective quantitative reanalysis was performed on a series of *m*IBG scans acquired during a 10-year period in Europe from 290 heart failure patients. Major cardiac events occurred in 26% patients, wherein the mean H/M ratio was 1.51 ± 0.30 for the event group as compared to 1.97 ± 0.54 for the no event group.[43] With an optimum H/M ratio threshold of 1.75, the 2-year event-free survival was 95% for greater, and 62% for H/M ratio less than 1.75. Logistic regression showed H/M and LVEF to be the only significant predictors.

From European and USA studies in 636 heart failure patients, all-cause mortality, cardiac mortality, arrhythmic events and cardiac transplantation during follow-of 37±20 months deaths, cardiac deaths, arrhythmic events, and heart transplants occurred in 13, 11, 5 and 9%, respectively. In multivariate analysis, late H/M was an independent predictor for all event categories, except for arrhythmias. In the European study, the highest event proportions for cardiac transplant and cardiac death were in patients with H/M ratios in the lowest quartile (≤ 1.45), whereas the lowest proportions were for those in the highest H/M ratio quartile (≥ 2.18).[403] In contrast, the highest proportion of arrhythmic events was among patients in the second quartile (1.46-1.74), representing those with only mild to moderate neuronal dysfunction. This observation was confirmed in the ADMIRE-HF, where the highest arrhythmic event rate (nonfatal and fatal) was in subjects with H/M between 1.30 and 1.59.[401] The potential for use of *m*IBG imaging as a cost-effective noninvasive means to individualize heart failure treatments to optimize patient outcomes is both unproven and untapped.[371]

NEW SPECT RADIOPHARMACEUTICALS

Radionuclide imaging has an inherent advantage over other cardiac imaging techniques for assessment of myocardial metabolic and biochemical processes. Although they can examine a wide variety of biochemical processes both PET and SPECT radiopharmaceuticals must go through the standard FDA phase I, II, and III steps prior to commercial availability a highly costly process. For SPECT, two new tracers are in clinical trials using iodine-123 (^{123}I). From a radiochemistry standpoint, ^{123}I is an excellent radionuclide, because, unlike the more commonly used ^{99m}Tc, it is easily incorporated into a wide variety of physiologically important compounds by a halogen exchange reaction in which the iodine replaces a methyl group. From a physical standpoint, ^{123}I has favorable half-life (13 hours), photon energy (159 keV), and radiation exposure characteristics, all nearly as favorable as those of ^{99m}Tc for gamma camera imaging. ^{123}I-MIBG is the only I-123 labeled compound currently available for routine cardiac applications in the United States.

Fatty Acid Imaging

Although radionuclide imaging of fatty acids has been studied for decades, it is not yet in common use, with the exception of one SPECT radiopharmaceutical β-methyliodophenyl pentadecanoic acid (BMIPP), which is in clinical use in Japan. BMIPP is a modified branched-chain fatty acid first introduced by Knapp and coworkers.[404] This tracer appears to have *ischemic memory* properties offering unique capability for the assessment of previously severely ischemic myocardium. Discordant myocardial fatty acid uptake/perfusion findings, with less BMIPP uptake than rest ^{201}Tl, have been described in patients who have had a recent episode of severe ischemia, with BMIPP representing the previously ischemic zone and the ^{201}Tl the infarcted zone.[405] This finding likely represents a persistent metabolic abnormality out of proportion to the perfusion abnormality at the time of injection. Dilsizian and colleagues recently reported a phase II study in which 32 patients with ischemia by exercise ^{201}Tl SPECT were studied by BMIPP SPECT injected with BMIPP at a mean of 6.2 hours after exercise in 21 patients and a mean of 24.9 hours after exercise in 11 patients (Fig. 18–49). More than 90% agreement was observed between the studies for presence of abnormality. In a clinical study

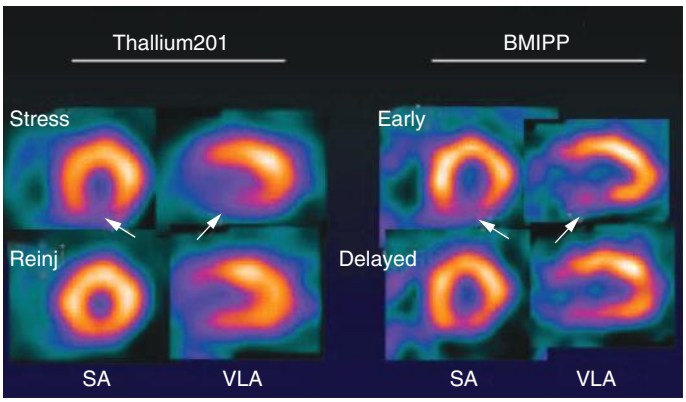

FIGURE 18–49. Thallium-201 stress and reinjection (Reinj) images (*left*) after treadmill exercise in the short-axis (SA) and vertical long-axis (VLA) single-photon emission computed tomography. Thallium images demonstrate a severe reversible inferior defect (*arrows*) consistent with exercise stress–induced ischemia. A similar defect is seen (*right*) on the early β-methyliodophenyl pentadecanoic acid (BMIPP) images in the same tomographic cuts (*arrows*), with BMIPP injected 22 hours after the stress-induced ischemia. The defect on the delayed BMIPP image is less prominent than on the early image. These image data suggest that BMIPP detects prolonged postischemic suppression of fatty acid metabolism for up to 22 hours after stress-induced ischemia. Reproduced with permission from Dilsizian V, Bateman TM, Bergmann SR, et al: Metabolic imaging with beta-methyl-p-[(123)I]-iodophenyl-pentadecanoic acid identifies ischemic memory after demand ischemia. *Circulation*. 2005 Oct 4;112(14):2169-2174.[406]

from Japan of 111 patients with possible acute coronary syndrome, BMIPP SPECT 1 to 5 days after pain was more sensitive for abnormality in the zone of the culprit vessel than ^{201}Tl (74% vs 38%, respectively; $P < .05$). These findings suggest that a possible clinical application of BMIPP would be assessment of patients presenting several hours to days after a possible severe ischemic episode, potentially providing direct evidence of the recent severe ischemia at a time when perfusion had returned to normal.[406]

MOLECULAR IMAGING

The current explosion of information in cell biology has led to initial formulations of numerous imaging agents with specific molecular targets. Perhaps the greatest future potential of the discipline of nuclear cardiology lies in molecular imaging because of the ability of the radiotracer technique to assess minute tracer concentrations in vivo. SPECT and PET methods are thousands of times more sensitive than ultrasound, magnetic resonance imaging, or CT methods.[407] Although most work has occurred with PET in this regard (Chap. 19), molecular SPECT tracers have also been developed. For example, indium-111 antimyosin antibody,[407] is highly specific for myocardial necrosis and has been shown to be useful in the assessment of myocarditis[407] and the necrosis associated with cardiac transplant rejection.[407] The full commercialization of this molecular imaging agent, however, was not pursued. The most promising of the molecular imaging SPECT radiopharmaceuticals has been ^{99m}Tc-annexin, an agent that allows imaging of apoptosis by specific binding to the exteriorized phosphatidylserine molecules, normally only found in the inner leaflet of the cell membrane and that become exteriorized during apoptosis.[408] Initial clinical trials with this agent demonstrated high sensitivity for MI. Other clinical settings in which this agent could prove useful as a myocardial imaging agent include myocarditis, transplant rejection, and possibly CHF. Multiple PET radiopharmaceuticals for imaging specific molecular targets are described in the Chapter 19.

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CHAPTER 19

POSITRON EMISSION TOMOGRAPHY IN HEART DISEASE

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QUANTITATIVE MYOCARDIAL PERFUSION IMAGING: THE BASIS OF PERSONALIZED CORONARY CARE

OVERVIEW: MYOCARDIAL PERFUSION AND METABOLISM—NOW AND AT THE BEGINNING

Low coronary blood flow may cause acute coronary syndromes, angina pectoris, heart failure, arrhythmias, and even death, as reviewed in detail in Chap. 34. The capacity for increased coronary blood flow is associated with cardiovascular health, and its variations may reflect our emotional states and lifestyles, including the foods we eat—even our most recent meal. Intense risk factor treatment prevents or stabilizes atherosclerosis, thereby preserving coronary blood flow, which is the most basic vital sign of life on which blood pressure, heart rate, and respiration depend. Assessing, maintaining, or restoring coronary blood flow are the objectives of all coronary procedures and most cardiac diagnostic testing. Next to "heart," the commonest critical word in cardiovascular practice is "ischemia," implicitly referring to low myocardial perfusion.

Coronary blood flow is a personalized, vital sign of individual status. When severely depressed, similar to blood pressure, it heralds imminent adverse events in an individual, not just a statistical probability of adverse outcome as do risk factors or the diagnosis of coronary artery disease (CAD). Advanced imaging technology and an extensive research literature document its measurement and relevance. Yet quantitative assessment of myocardial perfusion or coronary blood flow remains largely unused and unmeasured in clinical practice; its use is restricted to a research tool in a small number of academic centers where it usually has limited impact on clinical decisions. However, in view of revascularization trials failing to improve event-free survival in patients with CAD or reduced left ventricular (LV) function, quantitative perfusion and metabolic imaging should play a larger role in selecting patients optimally benefiting from revascularization.

How does the "now" of coronary blood flow in acute coronary syndromes relate to "the beginning" of the four-chambered mammalian heart already evolved 200 million years ago? A stem mammal (eg, *Morganucodon watsoni*) was a 1-inch long weasel-like animal during dinosaurs' domination for 250 million years.[1] The Chicxulub asteroid impact[2] and associated Deccan volcanism blocked the sun, causing the end-Cretaceous mass extinction of most life.[3,4] However, small mammals survived,[5] radiating into multiple open niches and large sizes, reflecting adaptability to extreme demands and environments that required an extraordinary heart and cardiovascular system before large brains and facile limbs evolved. As documented in humans,[6] canines,[7] and swine,[8] the branching coronary artery tree of mammals is structured in mathematically exact arterial size and length for myocardial mass.[6,7]

This arterial size-length-mass relationship and the branching structure of the coronary arterial tree are precisely related to coronary blood flow by a power equation for minimum energy loss. This relationship is mediated by normalized wall shear force to distribute efficiently the

oxygenated coronary blood to myocardium[6] while preserving capacity for high demands of coronary blood flow or coronary flow reserve (CFR).[9,10] The same equation characterizes the observed the mother-daughter relationship of coronary arterial branch diameters.[6] This power equation may even explain some of the different manifestation of CAD in women compared to men as addressed in Chapter 34. The heart's phasic contraction and relaxation is the oldest, most developed mechanism for pumping its own fuel supply and systemic needs. Evolutionary functional demands drove coronary physiology, thence anatomy, to its current essential role for understanding and managing coronary artery disease addressed in this chapter on clinical quantitative myocardial perfusion by positron emission tomography (PET).

Cellular metabolism and contractile proteins evolved for survival even earlier than physiology or coronary blood flow.[11,12] One of many such mechanisms is myocardial metabolism that switches from aerobic metabolism of fatty acids when there is adequate supply of oxygenated coronary blood to anaerobic metabolism of glucose when coronary blood flow is impaired or hypoxic.[13] Under such adverse circumstances, the flow-deprived myocardium "hibernates" or stops contracting but remains "alive or viable" for potential return of normal contractile function when coronary blood flow is restored. Transient severely impaired coronary blood flow may temporarily stop or "stun" myocardial contraction after the low-flow episode is over, with slow contractile recovery over hours to days after normal blood flow is restored. PET metabolic or viability imaging drives optimal personalized management of such patient with advanced coronary artery disease and impaired left ventricular function as addressed in this chapter.

Although current literature provides many excellent supporting papers and reviews,[14-42] quantitative myocardial perfusion and metabolism remain at the edges of mainstream cardiology despite their value in relation to myocardial ischemia (see Chap. 34). Consequently, this chapter on PET takes a different approach. Rather than providing a detailed summary of the literature on the current "average" use of cardiac PET perfusion imaging, this chapter emphasizes two major themes developed in the two leading centers prominent in developing clinical cardiac PET—the David Geffen School of Medicine at the University of California at Los Angeles and the McGovern Medical School, University of Texas–Houston.

First, we use quantitative PET to elucidate complex but clinically relevant coronary pathophysiology and integrate its complexity into comprehensive decisional "smart" analytical displays to guide binary clinical decisions personalized for individuals. Second, we demonstrate, by case examples, how quantifying myocardial perfusion and metabolism drives personalized assessment of CAD, its severity, and its management, including invasive procedures and revascularization for individuals or for optimally determining average group treatment outcomes. For conceptual simplicity, the term *coronary blood flow* is used interchangeably with *myocardial perfusion* because of their physiologic interchangeability of mechanisms and consequences while having slightly different units of cc/min versus cc/min/g due to different measurement methodology.

Each case illustrates a major class of clinical conditions uniquely addressed by PET, providing personalized insight so that clinical readers and patients can see its value in the delivery of individually tailored cardiovascular practice and not just as a remote research tool capable of generating bulk data without personalized relevance. Although somewhat unconventional, our approach provides the vision for readers, cardiologists, and patients to see what can and should be the optimal, objective, and personalized mechanism for establishing and managing CAD. The quantitative, personalized data from PET allows for individualized decisions about the intensity of therapy recommended—lifestyle changes alone or combined with medical therapy with or without revascularization. In essence, PET provides quantitative data highly specific for each individual's personalized coronary care with a scientific and technically valid basis that physicians and patients themselves visually readily understand with a corresponding powerful influence on their management.

WHY CARDIAC POSITRON EMISSION TOMOGRAPHY FOR MYOCARDIAL PERFUSION?

Diagnostic Sensitivity and Specificity

The diagnostic sensitivity and specificity of PET for the diagnosis of CAD are 90% to 95% and 88% to 95%, respectively, and are higher than those for single-photon emission computed tomography (SPECT) at 85% and 85%, respectively.[24,25,43,44] The area under the receiver-operating characteristic for PET was 0.95 compared to 0.90 for SPECT, a significant difference ($P < .0001$).[24] This greater diagnostic accuracy of PET versus SPECT results from better resolution and attenuation correction of PET.

However significant, these comparisons fail to demonstrate the enormous differences between these two technologies for several reasons. In these studies, the reference gold standard for defining CAD to which PET and SPECT were compared was visually interpreted angiographic percent diameter stenosis. The variability of visually estimated percent diameter stenosis; its poor correlation with coronary blood flow or myocardial perfusion; and failure to account for diffuse narrowing, complex anatomy, or arterial remodeling contravene the validity of the angiogram as a reference for identifying or assessing either anatomic or physiologic severity of stenosis or diffuse disease.[16,31,37-41] When compared to objective automated quantitative coronary analysis (QCA) of angiographic severity of discrete coronary artery stenosis, diagnostic sensitivity and specificity of PET perfusion images approaches 95%.[34]

However, even QCA remains limited as a gold standard of severity of CAD[16,31,37-41] for several reasons. The coronary angiogram fails to quantify the essential and more basic physiologic function of the coronary arteries now shown to define severity for guiding management.[16,31,39] Diffuse epicardial atherosclerosis cannot be measured. Epicardial endothelial function or small-vessel disease may profoundly affect coronary blood flow but is not accounted for on angiogram. Moreover, coronary blood flow relates to the arterial diameter raised to the fourth power so that small changes in arterial size that cannot be measured accurately on arteriogram markedly alters coronary blood flow. Finally, the varying diameters and irregularities over different lengths, angles, and shapes affect coronary blood flow but are not reliably accounted for on anatomic images. The computed tomography (CT) angiogram with best resolution of 0.5 mm has a large uncertainty at each arterial border that precludes projecting or calculating blood flow capacity in 3- to 5-mm diameter coronary arteries because the flow-diameter to the fourth power relation magnifies the uncertainty of arterial dimensions.[39] Coronary anatomic-functional relationships are detailed further in Chap. 34 on coronary blood flow and myocardial ischemia.

Fractional flow reserve (FFR), measured by trans-stenotic invasive pressure wire during cardiac catheterization, was originally validated and compared to CFR by quantitative PET perfusion imaging.[45] Although FFR has advanced cardiovascular science from anatomic characterization to one based on the physiologic severity of stenosis to guide percutaneous coronary intervention (PCI),[46,47] FFR is also an inadequate reference standard because of the substantial discordance between FFR and CFR by invasive technologies and also by quantitative and relative myocardial perfusion by PET.[48,49] Moreover, FFR was low or discordant with the absence of visually significant stenosis when all arteries were interrogated as opposed to measuring FFR in only arteries with stenosis visually severe enough to be considered for PCI.[50]

While offering a major advantage over SPECT imaging, relative PET perfusion images fail to utilize PET capacity for absolute quantification of perfusion in cc/min/g and absolute CFR. Such quantitative measurements move PET into the highest level of assessing CAD in order to personalize the physiologic severity of CAD that is unmatched by any other technology. To date, all trials of elective revascularization fail to reduce myocardial infarction (MI) or cardiovascular death, despite relief of angina.[51-54] Consequently, simply diagnosing CAD should no longer be considered the primary, or even an adequate goal of diagnostic testing, because establishing evidence-driven physiologic severity is now the optimal scientific basis for revascularization versus medical management alone.

The evidence-driven goal of diagnostic testing now requires objectively identifying those patients with quantitative physiologically severe CAD of sufficiently high risk in whom revascularization would reduce the risk for MI or mortality, while also relieving angina.[35-39] Quantitative assessment of perfusion provides comprehensive personalized quantification of physiologic severity of CAD, integrating information from each individual coronary artery and its secondary and tertiary branches to delivery an integrated gold standard. Within the confines of biologic and methodological variability, quantitative perfusion defines the flow through a coronary artery as a vital sign essential for survival, just like blood pressure, where a defined low range may bode illness.

As addressed in Chap. 34, randomized trials are needed to determine the threshold at which coronary perfusion or pressure is so low such that the risk of adverse events is high enough to justify revascularization as a means to improve outcomes. However, a deep truth resides in individual cases, representative of the variations of CAD, where quantitative PET provides unique insights and management guidance as the basis for its current clinical use. The cases also illustrate the need for more advanced interventional trials than have been completed to date that lack adequate low flow thresholds having high enough risk for optimal benefit from revascularization.

THE CORONARY FLOW CAPACITY MAP: COMPLEXITY MADE SIMPLE FOR PERSONALIZED PATIENT DECISIONS

Three measures of coronary blood flow, or myocardial perfusion, quantify its profound effects in all the manifestations of CAD. Rest and stress myocardial perfusion in cc/min/g and coronary flow reserve (CFR) as the ratio of stress perfusion to rest perfusion on a regional pixel basis are the final common pathways of coronary anatomy and physiology on patient outcomes. Myocardial perfusion is commonly heterogeneous regionally and temporally associated with multiple, interacting mechanisms that may contravene some providers' preference for a simple, binary, positive or negative, one-result-fits-all test to guide management. Rather than a diagnostic limitation of methodology or biological variability, these three perfusion measurements provide rich insights into the reality of heterogeneous coronary pathophysiology essential for individualized management when integrated to provide a valid binary directive—"complexity made knowledgeably simple." These insights for individual personalized management provide an equally rational basis for randomized trials of "group" management or revascularization based on quantitative physiologic severity of CAD.

Accordingly, at the outset, we account for and incorporate these three measures into a coronary flow capacity map color-coded for severity from healthy young volunteers to patients having angina and significant electrocardiogram (ECG) changes during dipyridamole stress PET imaging.[55-57] After we demonstrate its clinical utility, later sections address the technical details of quantifying myocardial perfusion. Figure 19–1 orients topographic PET images derived from tomographic views as previously described.[16,31,37,40,48,55-57]

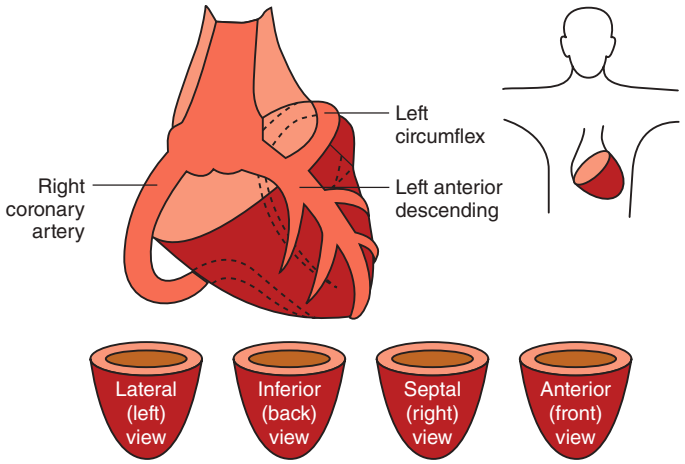


FIGURE 19–1. Orientation of positron emission tomography (PET) images. The perfusion images are viewed as if looking through a patient's body at the left ventricle (LV) first through the left side at the left lateral wall, then through the back, then the right side through the right heart at the septum of the LV and finally through the chest at the anterior wall of the LV. These topographic views are as if the heart were held in one's hand and rotated around in the lateral, inferior, right, and anterior views. They visually integrate the acquired tomographic slices to topographic views that avoid the spatial distortion of bull's eye or pie views of the heart. These topographic displays parallel views of the heart as seen on a cine angiogram or a surgeon's open chest view.

Stress flow and CFR require integrated interpretation caused by frequent discordance of rest and stress flow, as seen in Fig. 19–2. High rest flow (A, white) caused by a high pressure-rate product, anxiety, medications, or female sex,[41] either separately or cumulatively (proportionately higher than stress flow) may cause low CFR (A, blue) that alone erroneously implies flow-limiting stenosis. Alternatively, CFR may be high (B, white or red) with no ischemia despite low flow at rest and stress (B, blue) because of beta-blockers, physical conditioning, increased vagal tone, or CAD with low stress flow erroneously suggesting ischemia if it is considered alone without CFR. By plotting values for each pixel of stress flow in cc/min/g on the horizontal axis and CFR on the vertical axis (C), all three perfusion measures for each pixel are accounted for in the coronary flow capacity map panel (D, red) because CFR is the ratio of stress to rest flow. Caffeine, beta-blockers, inadequate vasodilator stress, and diffuse or small-vessel disease may lower stress perfusion in cc/min/g to apparently low ischemic levels; therefore, measuring rest flow and CFR commonly provides essential diagnostic information for correct clinical interpretation from the coronary flow capacity map.

The coronary flow capacity map plot is color-coded red for stress flow and CFR in 241 young healthy volunteers with no risk factors, no medical conditions, no measurable blood caffeine, and no measurable urinary cotinine as an objective test for smoking as previously reported.[40,45,56,57] The lower limit of red is the mean minus one standard deviation (SD) of CFR and stress flow for this group. Blue indicates the optimal stress flow and CFR thresholds for patients with angina, ECG changes, and/or a regional stress defect during dipyridamole stress PET imaging. Green indicates for patients with either angina or ECG changes but not both during stress imaging with a regional stress defect. Orange indicates for patients with CFR and stress flow at the lower one SD of the healthy volunteers. Yellow indicates for the upper one SD above the patients with angina or ST changes during stress imaging. The orange-to-yellow transition is halfway between these SD limits.

Each color-coded pixel is then mapped to its original position and displayed as the coronary flow capacity map in four projections (lateral, inferior, septal, and anterior views) showing coronary flow capacity

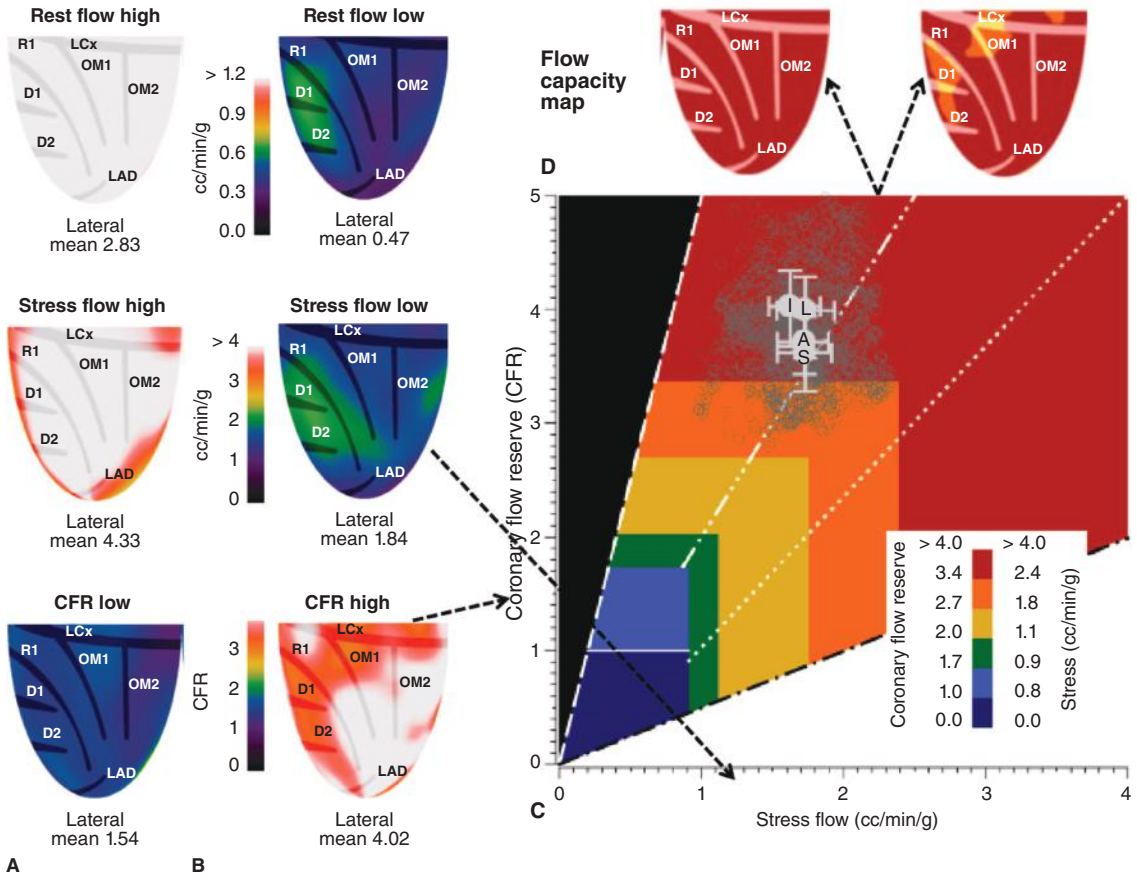


FIGURE 19–2. Integrating stress perfusion in cc/min/g and coronary flow reserve (CFR). (A) High rest and stress flows in cc/min/g (myocardial perfusion) with low CFR due to high rest flow. (B) Low rest and stress flows with high CFR (C) Integration of all flow data by plotting stress flow on horizontal axis and CFR on vertical axis for each pixel of stress flow and CFR images for color coding for ranges of values listed below. (D) Coronary flow capacity map accounting for spatial distribution of integrated stress flow and CFR with percent of the left ventricle within color-coded ranges. Red, healthy young volunteers with no risk factors; blue, patients with angina, electrocardiogram (ECG) ST depression > 1 mm Hg, and/or a regional stress defect during dipyridamole stress; dark blue, myocardial steal wherein stress flow falls below rest flow associated with collaterals beyond arterial occlusion or subtotal stenosis; green, either angina or ECG changes with stress defect but not both; orange, patients with risk factors but no known clinical coronary artery disease (CAD); yellow, patients with documented CAD by angiogram or a coronary event without angina or ECG changes during dipyridamole stress. The color bar scales show ranges of flow in cc/min/g and CFR. (A and B) Each pixel of the stress flow images and the CFR images are plotted on the color-scale graph, assigned a color corresponding to their quantitative values, and back-projected into their position in the topographic map. The color bar on the plot shows the thresholds of stress flow and CFR at each color transition (not combined stress flow–CFR values for pixels in the images).

comparable to that in young healthy volunteers within the distribution of the coronary arteries (D). The specific ranges of stress perfusion in cc/min/g and CFR for each color used for all PET perfusion images in this chapter are detailed in Fig. 19–3.

Complete relevant perfusion information in a single clinical case involve five sets of different data in four views involving 6720 pixels spatially distributed over a total of 20 different image views. Each of these views has 5 continuous variables (rest-stress uptake, rest-stress flow and CFR) color coded into 7 ranges from healthy young volunteers to patients with overt ischemia during dipyridamole stress as in Figs. 19-3 and 19-4. The rest and stress relative images (A) are abnormal with subtle differences between the distal anterior region (green) and the distal septum (yellow) that are difficult to interpret, inconsistent with a single left anterior descending coronary artery (LAD) territory and providing little insight into the detailed regional severity and size of abnormal stress perfusion.[57] Rest perfusion and stress perfusion images (B) are proportionately larger and more severe than the relative perfusion defects but are complicated by spatial heterogeneity of both rest and stress perfusion. The CFR display (B) reflects the rest-stress perfusion heterogeneity into better defined normal or abnormal regions but still fails to define the subtle differences between the distal septum and the distal anterior regions on the relative images. Visually interpreting or simply quantifying the

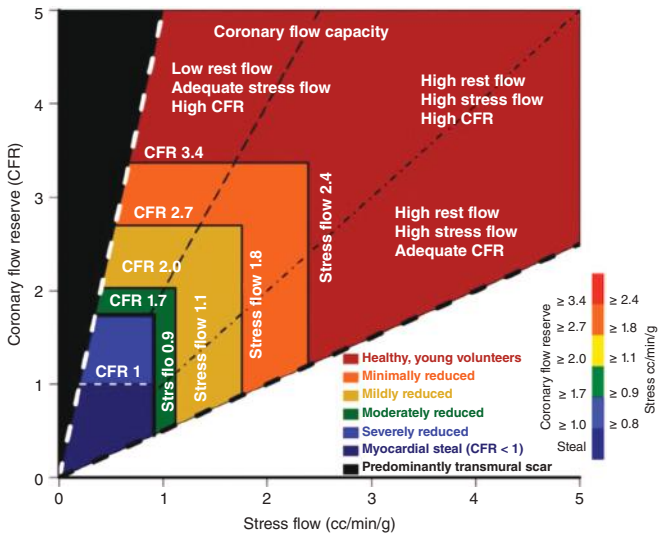


FIGURE 19–3. Ranges of stress flow and coronary flow reserve (CFR) for color-coding of the coronary flow capacity map. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow–CFR values for pixels in the images). Color codes are the same as in Figure 19–2. Adapted with permission from Johnson NP, Gould KL: Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging*. 2012 Apr;5(4):430-440.[57]

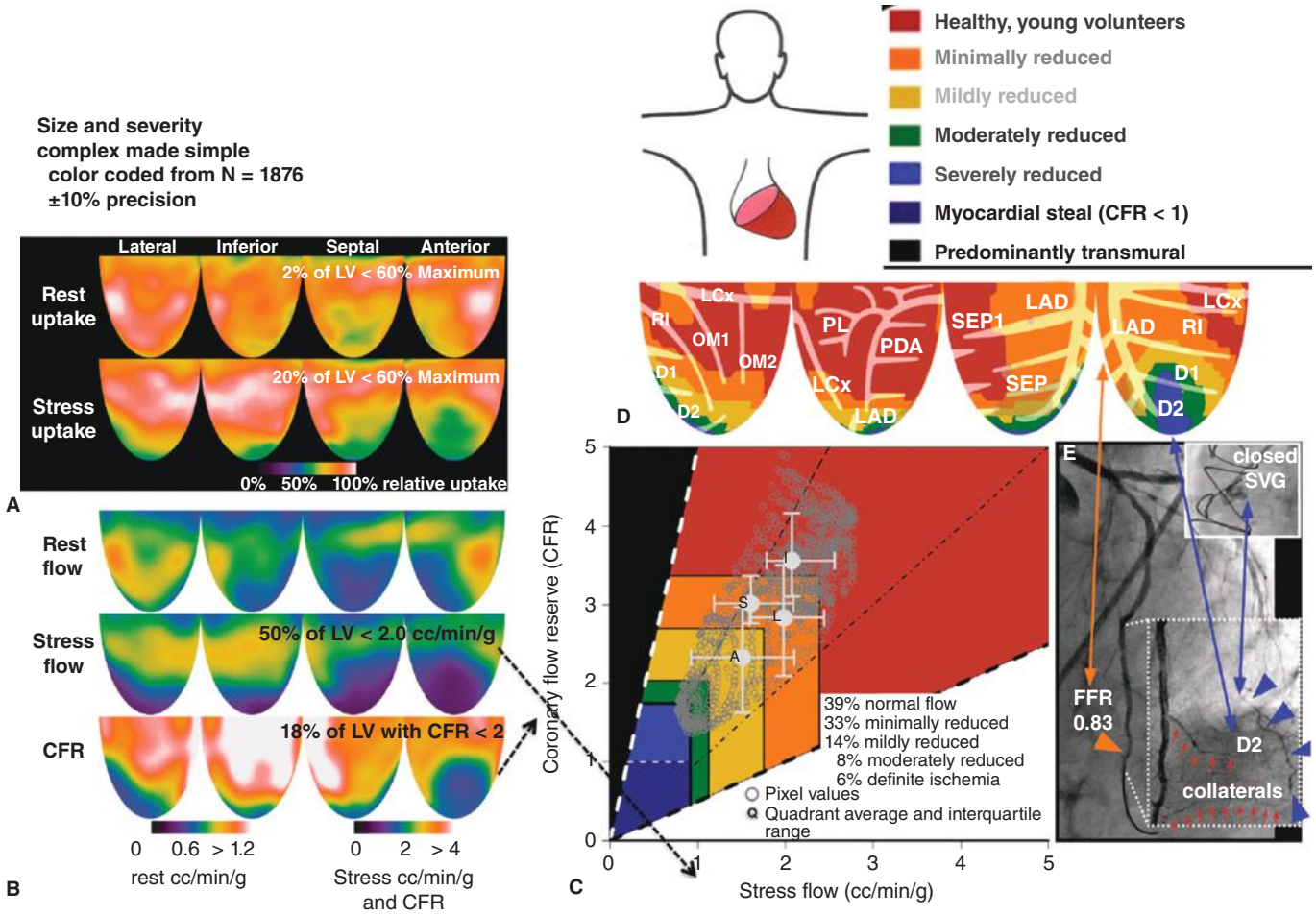


FIGURE 19–4. Integration of quantitative perfusion images. (**A**) Rest-stress relative images. (**B**) rest-stress perfusion in cc/min/g and CFR. (**C**) Pixel plot of stress perfusion and CFR for color coding each pixel (**D**) Coronary flow capacity map made by projecting each color coded pixel back to its original position in the topographic image. The percent of LV in each of the color coded groups are printed out on the pixel plot. The angiogram inset has arrows relating the angiogram to corresponding locations on the coronary flow capacity map. Color codes are the same as in Figs. 19-2 and 19-3. Reproduced with permission from Johnson NP, Gould KL: Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging*. 2012 Apr;5(4):430-440.[57]

6720 pixels spatially distributed in the 20 different views is difficult or limited for even an experienced reader.

However, based on the color-coded pixel graph (C), the coronary flow capacity map (D) integrates all these data into a single four-view color-coded image for the entire range of flows from active ischemia (blue) to flow in healthy young volunteers (red), accounting for all the flow data in a particular patient.[57] The map demonstrates preserved flow capacity (red) in left circumflex coronary artery (LCX) and right coronary artery (RCA) distributions, minimally reduced flow capacity on the proximal LAD distribution tapering to mild (yellow) diffuse narrowing in the distal LAD and thence to the moderate (green) border zones around a small severe stress defect (blue) in the distribution of a small distal diagonal branch off the patent but diffusely narrowed distal LAD. The small apical defect shows myocardial steal, indicating an occluded collateralized distal diagonal branch. The PET findings are confirmed by the angiogram inset done as part of a research protocol because the defect is too small and distal to warrant PCI.

CLINICAL PET CASES: PERSONALIZED TO QUANTIFY SEVERITY FOR GUIDING MANAGEMENT

The following fourteen cases visually demonstrate the principles and personalized management for the wide range of manifestations of CAD for which PET uniquely drives patient management as examples seen daily at the Weatherhead PET Imaging Center for Preventing and Reversing Atherosclerosis. The clinical power of cardiac PET illustrated in these cases requires knowledge of coronary physiology and myocardial ischemia addressed in the chapter on coronary blood flow and myocardial ischemia (Chap. 34). Here, to begin, quantitative PET is integrated with coronary physiology as comprehensive analytical displays of complex perfusion data made knowledgeably "simple" for clinical use in both physician and patient understanding. Later sections address technical aspects of measuring myocardial perfusion by PET.

Case 1: Coronary Flow Capacity in Multivessel Complex CAD

A 63-year-old man with 6 months of mild stable angina (Fig. 19–5)[47] illustrates the complex data inherent in all quantitative perfusion imaging that is integrated into a "simple," easily understood image for clinical decisions by validated directive software based on a large patient database detailed in a later section. Figure 19–5 displays relative myocardial perfusion images of rubidium (Rb)-82 at rest (A) and during dipyridamole stress (B). With the arterial input function as detailed later, stress perfusion in cc/min/g (C) and CFR (D) for every pixel in every topographic image in each of four topographic views are plotted (E), color-coded and back-projected to the coronary flow capacity map (F).

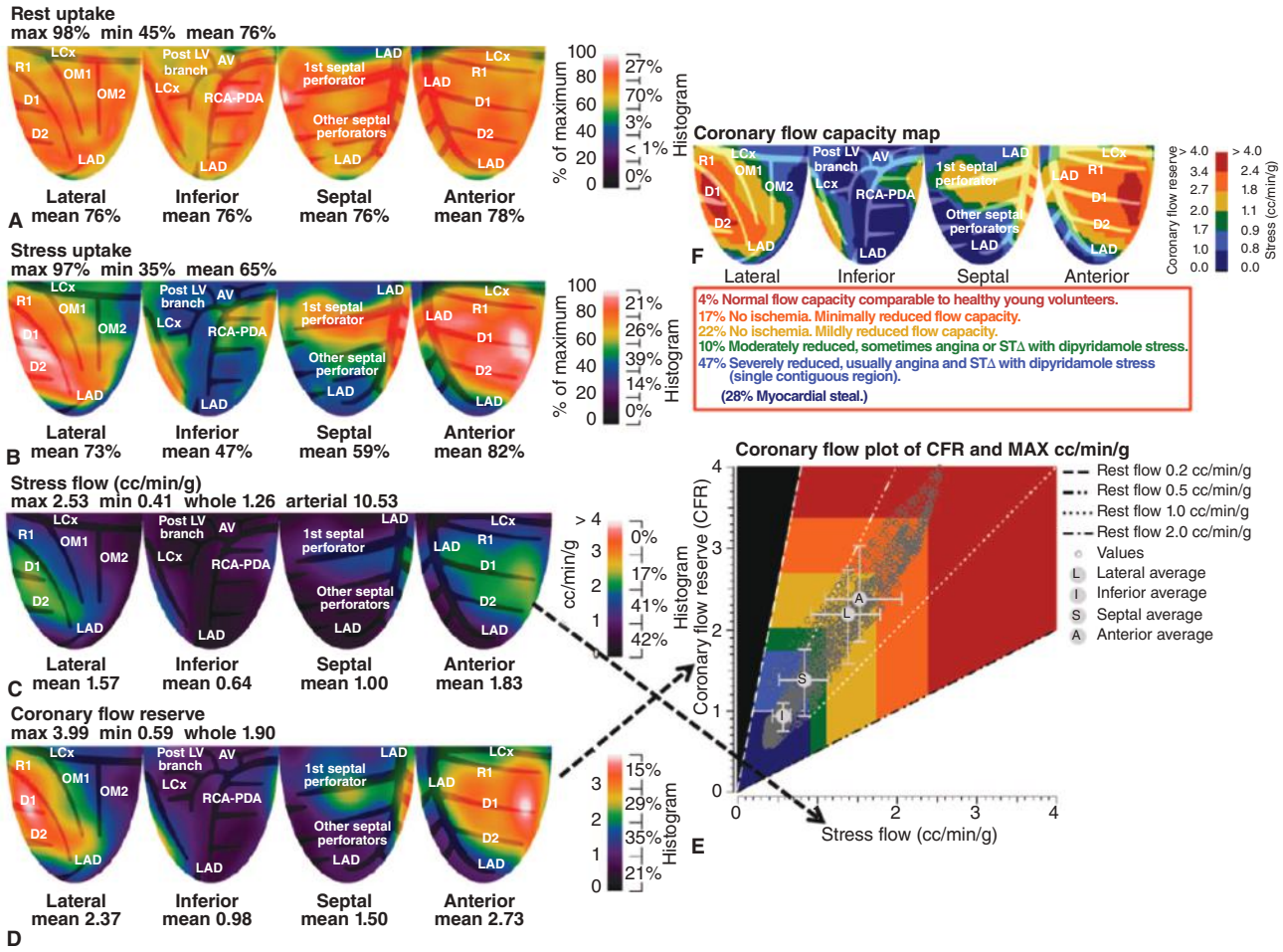


FIGURE 19–5. Case 1. Coronary flow capacity in multistenosis complex coronary artery disease. (A) Rest relative uptake. (B) Stress relative uptake. (C) Stress perfusion in cc/min/g. (D) Coronary flow reserve (CFR. (E) Plot of stress perfusion and CFR. (F) Coronary flow capacity map. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

For the patient whose images are depicted in Fig. 19–5, the coronary flow capacity map (F) shows occlusion or subtotal stenosis of the mid LAD, of the RCA, and of the distal LCX. Coronary flow capacity is severely reduced in 47% of the LV, of which 28% of LV shows myocardial steal in the central area of the stress defect, a typical pattern indicating collaterals beyond occlusions or subtotal stenosis. There is a more proximal moderate or "intermediate" LAD stenosis involving the first septal perforator (yellow, 22% of LV) with further reduced border zones (green, 10% of LV). The diagonals and ramus intermedius distributions have only minimally reduced (orange, 17% of LV) or good (red, 4% of LV) coronary flow capacity. Because of the definitive images of complex multivessel disease, the patient was scheduled for coronary artery bypass graft (CABG) surgery with preoperative coronary angiography confirming the PET findings. He has done well over the following 3 years with a good flow capacity on follow-up PET.

Case 2: Saved from Unnecessary CABG Surgery

A 76-year-old asymptomatic man with preserved left ventricular ejection fraction (LVEF) had PET for a second opinion after CABG surgery was recommended following abnormal SPECT imaging and angiography reported to show the following stenoses: 70% left main; 80% LAD; 80% first diagonal; 70% first obtuse marginal; and 70% and 80% serial stenoses in the RCA. In Fig. 19–6, his rest-stress relative uptake images show no stress defect but only a small inferoapical motion artifact from the inferior apex recoiling briefly into the most inferior image plane during systole. The inferior apex is outside this lowest imaging plane during diastole, lasting two-thirds of the contraction cycle, thereby acquiring less activity. It normalized on electrocardiogram (ECG)-gated systolic images. As the coronary flow capacity map shows, 69% of the LV has flow capacity comparable to that of healthy young volunteers, with 21% of the LV having minimal reduction (orange) and 10% with mildly reduced flow capacity consistent with age and mild, diffuse, nonobstructive, calcific CAD with coronary flow capacity well above the low ischemic flows that would be coded green or blue if present. The patient was advised against CABG surgery and did not have it performed. After the PET, the prior angiogram on which the recommendation for bypass surgery was based was obtained for review by the author K. Lance Gould (KLG). It showed luminal irregularities, mild nonobstructive coronary artery disease, and arterial lip dividers at branch points with no significant stenosis that were overinterpreted by the prior cardiologist. The SPECT images were false positives.

Case 3: Missed Severe CAD with Normal Treadmill Test

A 62-year-old asymptomatic man with risk factors but no known CAD recently had a normal ECG exercise stress test, and he underwent PET

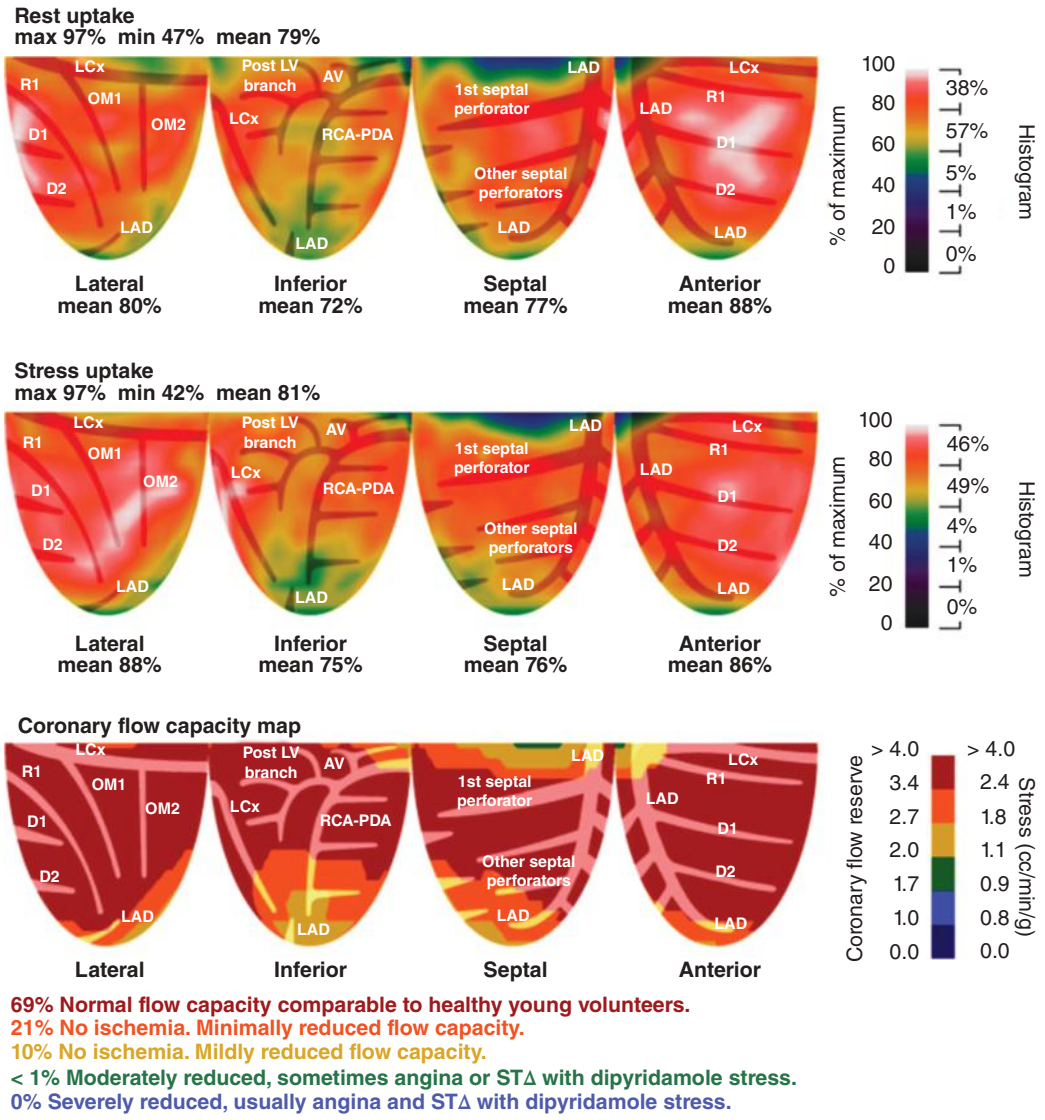


FIGURE 19–6. Case 2. Saved from unnecessary coronary bypass surgery. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

in a research protocol. He had a history of back pain related to activity thought to be the result of degenerative disc disease that he experienced during his normal treadmill stress test. His relative myocardial uptake images in Fig. 19–7 show a large, severe, anterior, septal and apical stress-induced defect involving 55% of the left ventricle in the distribution of the LAD proximal to the first septal perforator and wrapping around the apex and up the distal inferior wall.

Absolute myocardial perfusion capacity was severely reduced, with myocardial steal in 37% of the LV indicating occlusion just distal to the first septal perforator. The proximal LAD had additional proximal moderately severe stenosis involving the first septal perforator (green, 10% of LV) with small-vessel or diffuse disease of distal the RCA supplying posterior perforators (yellow, 23%). The left circumflex had preserved coronary flow capacity (red, 14% of LV) with mild diffuse disease tapering to yellow distally (orange, 17% of LV). The CT scan done for attenuation of PET data shows moderate coronary calcification in the left anterior descending and right coronary arteries. Gated PET perfusion images showed normal left ventricular contraction with an ejection fraction (EF) of 73% at stress. Based on the PET scan, medical therapy and coronary angiography with revascularization were recommended due to the size and severity of the rest-stress PET abnormalities. An angiogram confirmed the PET findings, for which his cardiologist had CABG carried out.

Case 4: Complex Post PCI Perfusion—Septal Perforator Caged by LAD Stent

A 58-year-old man with atypical chest discomfort, separate episodes of dyspnea—at night or inconsistently while walking—had PET as part of a research protocol. His baseline coronary flow capacity map in Fig. 19–8A shows a severe stress defect typical of a severe stenosis of the LAD proximal to the first septal perforator and wrapping around the apex. An angiogram confirmed these findings, and PCI was done with a proximal stent. The post-PCI PET showed a residual small, severe, basal septal, stress defect comprising 4% of the LV in the distribution of the first septal perforator caged by the LAD stent. In our experience, most coronary branches caged by stents have reduced coronary flow capacity even when open on post-PCI angiogram.

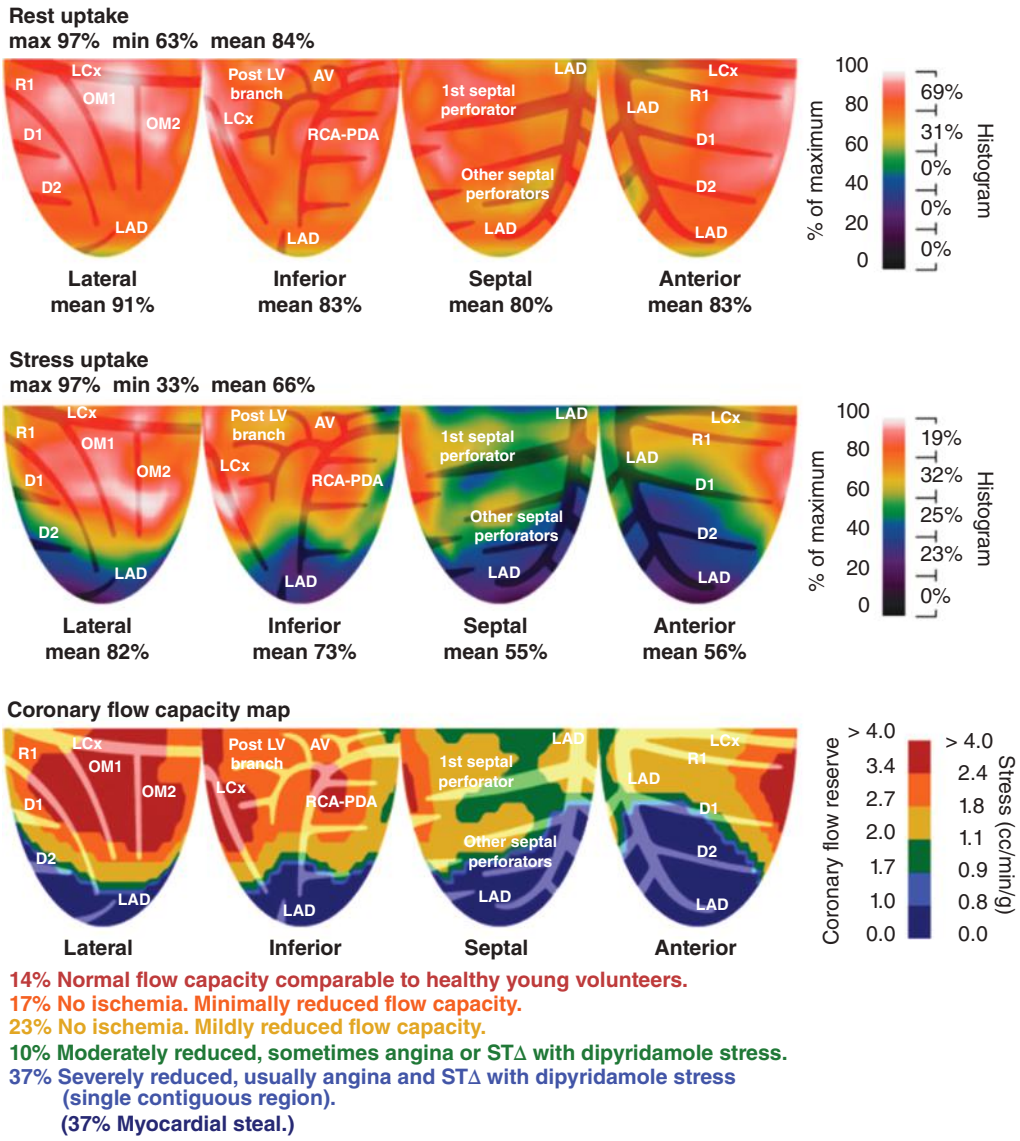


FIGURE 19–7. Case 3. Missed severe coronary artery disease with normal treadmill test. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

Case 5: Normal Relative Myocardial Uptake Images Miss Severe Diffuse CAD

A 56-year-old man with mild stable angina had a PET scan as part of a research protocol. During dipyridamole stress he had angina with 1 mm ST depression with normal relative uptake images in Fig. 19–9. Despite completely normal relative stress images (A), stress perfusion in cc/min/g (B) and CFR (C) were severely reduced to low flow ischemic levels caused by severe diffuse CAD. The histogram color bars to right of each image show color-coded severity and percent of the LV in each range of severity. He developed angina and greater than 1 mm ST depression at 5 minutes (early stage 2) of the Bruce protocol. An angiogram confirmed severe diffuse disease with superimposed visually estimated 70% stenosis in all three epicardial arteries. He underwent bypass surgery, after which his symptoms resolved and treadmill duration increased to 7 minutes without angina but with still with greater than 1 mm ST depression. At follow up PET, global stress flow increased from 1.25 to 2.0 cc/min/g reflecting improved coronary flow capacity but still limited by residual diffuse CAD at the borderline threshold for ischemia.

Case 6: Complex Post-PCI Angiogram with Question of Left Main

A 52-year-old physically active asymptomatic man had PET for a second opinion for CABG surgery. He had a prior PCI with two stents to the LAD, with a moderate estimated 50% to 55% diameter left main stenosis that was not stented. Treadmill exercise stress testing and myocardial perfusion imaging were reported as normal; however, the patient developed nonsustained supraventricular tachycardia in recovery from exercise, leading his cardiologist to recommend coronary bypass surgery (given the moderate left main disease on angiography). In Fig. 19–10, rest relative uptake is normal (A). Stress relative uptake (B) and the coronary flow capacity map (C) show the following:

1. A severe stress defect in the distribution of left circumflex proximal to its the first obtuse marginal (OM) branch (blue on the flow capacity map)
2. A severe stress defect in the distribution of the first diagonal branch off the LAD (blue on the flow capacity map)

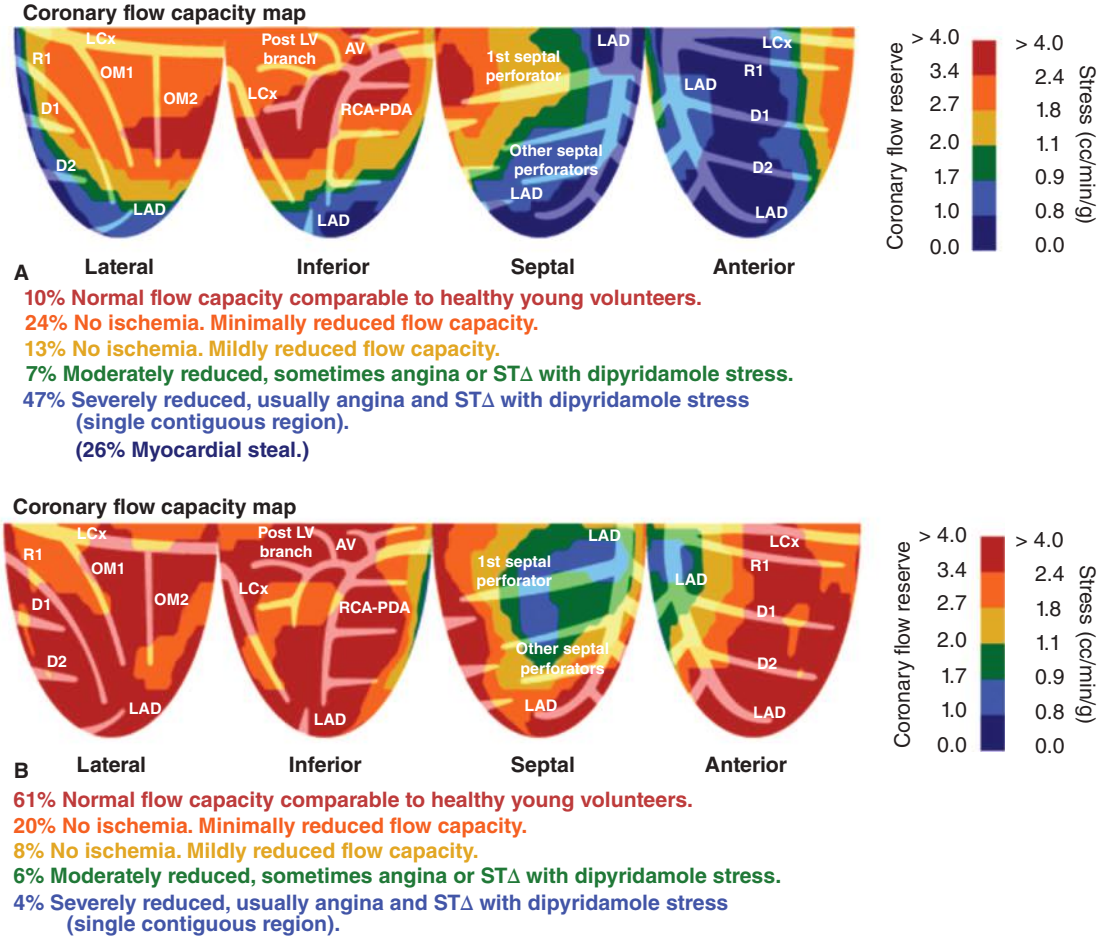


FIGURE 19–8. Case 4. Complex post–percutaneous coronary intervention (PCI) perfusion–septal perforator caged by left anterior descending artery stent. (**A**) Before PCI. (**B**) After PCI. The color bars on the right of the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

3. Mildly reduced but adequate coronary flow capacity of the proximal LAD and first septal perforator above low flow ischemic levels (yellow on the flow capacity map) tapering to more severely reduced flow at the apex (green on the flow capacity map) consistent with severe diffuse narrowing
4. Mildly reduced but adequate flow capacity above ischemic levels in the ramus intermedius distribution anterior to the lateral stress defect caused by the first OM stenosis
5. Excellent high flow capacity in the RCA distribution

Objective computer analysis and review of the angiogram by KLG measured the left main as a 52% diameter stenosis with diffuse LAD narrowing with moderate stenosis of the OM1-LCX and first diagonal branch (D1). The left main stenosis alone did not severely limit flow capacity. However, the cumulative effects of the left main in sequence with diffuse disease and downstream moderate anatomic stenosis severely reduced flow capacity heterogeneously. The PET results suggested that bypass surgery was appropriate and also helped elucidate appropriate bypass targets (LAD with its diffuse narrowing, the large D1, and OM1 with branches on either side of the ramus). In the absence of symptoms, the patient was reluctant to have bypass surgery but after reviewing the PET with him and his cardiologist with the high risk of cumulatively severe CAD, CABG was performed with patient doing well at follow-up 9 years later.

Case 7: Left Main Stenosis with Patent RCA

A 49-year-old man had PET as part of a research protocol. Nine years previously, he had a prior ascending aorta graft for type A aortic dissection complicated by severe aortic regurgitation. The left main coronary artery had been reattached to the graft. He followed an intense exercise regimen consisting of 1 hour on the elliptical and 30 minutes on the bicycle five times weekly without symptoms or limitation of exercise, except over the prior week when he felt that "something was not quite right." After rest and dipyridamole stress images were completed (Fig. 19–11), he developed hypotension, deep ST depression, and cardiac arrest. He was supported by advanced cardiac life support to the catheterization laboratory, with subsequent extracorporeal membrane oxygenation. An angiogram showed a severe stenosis at the anastomosis of the left main to the aortic graft that was stented open. He recovered fully with normal brain function and normal EF.

Case 8: Left Main Stenosis with Occluded RCA

A 69-year-old man with poorly controlled risk factors, right bundle branch block, and past angiogram showing an occluded RCA had mild exertional angina for 3 years. Although his angina was variable, he thought that perhaps it had slightly worsened over the prior 3 weeks; however, he was reluctant to have an angiogram. Dipyridamole stress led to severe angina, 3-mm ST depressions, and blood pressure falling

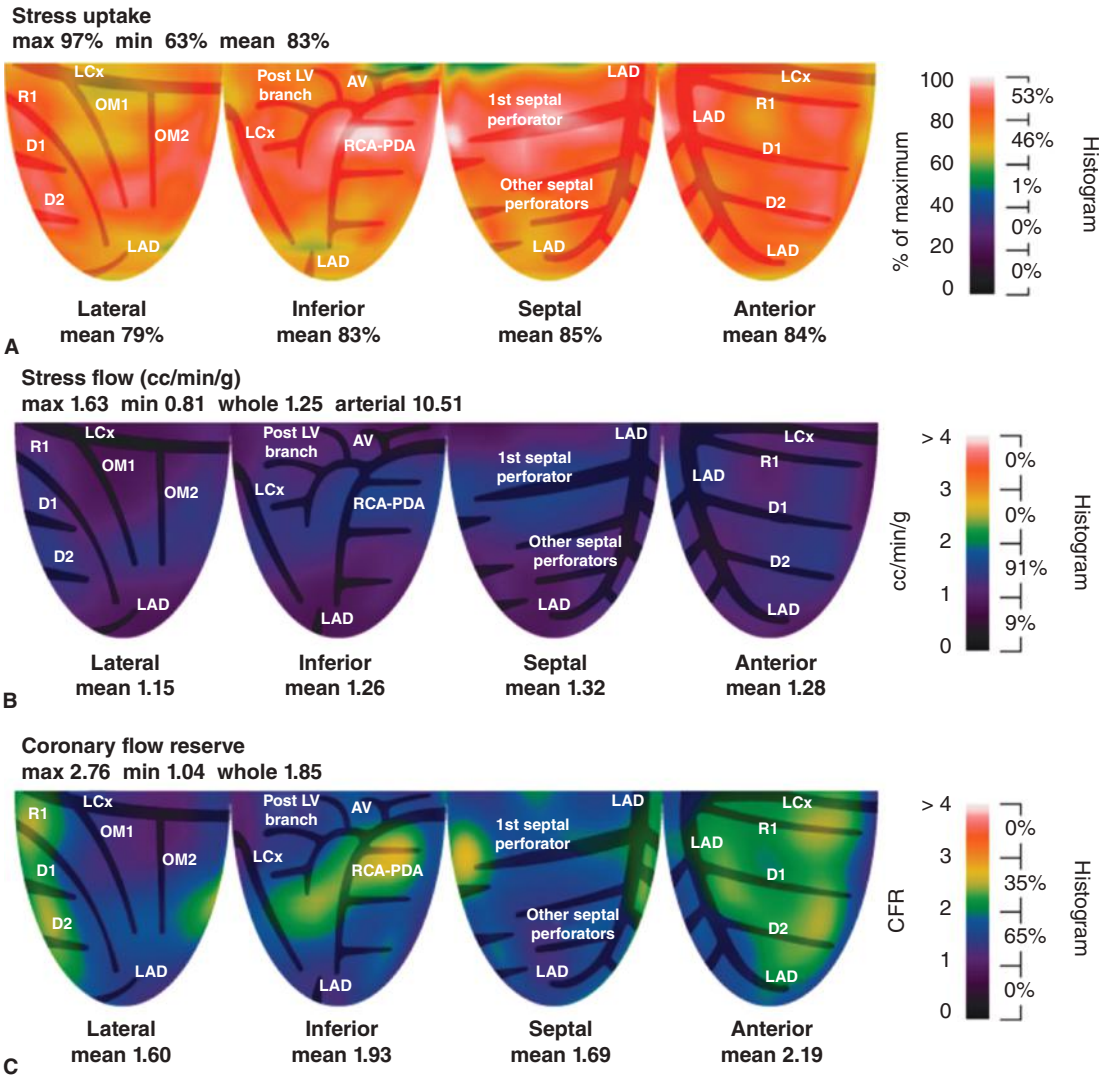


FIGURE 19–9. Case 5. Normal relative myocardial uptake images with severe diffuse coronary artery disease. (**A**) Stress relative uptake. (**B**) Stress perfusion in cc/min/g. (**C**) Coronary flow reserve (CFR).

from 126/78 to 90/56 mm Hg, requiring early imaging and termination of stress with intravenous aminophylline, metoprolol, and nitroglycerin resolving these stress effects. The relative images in Fig. 19–12 show mild perfusion heterogeneity or small mild separate stress defect with no severe large regional perfusion defect. However, the stress flow, CFR, and coronary flow capacity map show severely reduced stress perfusion to low ischemic flow levels. Angiogram confirmed a severe stenosis of the left main coronary artery and an occluded RCA; he underwent successful CABG surgery.

Case 9: Abnormal Relative Stress Image But Adequate Absolute Perfusion

A 60-year-old man had known angiographic occlusion of the LCX with extensive collaterals and variable angina over the prior 10 years, depending on adherence to exercise and healthy living. After a half year of unhealthy high-stress living, his exertional angina worsened, leading to a follow-up PET scan (Fig. 19–13). While there is stress perfusion abnormality on the relative perfusion images, the flow capacity map shows only mildly to moderately reduced flow capacity in a small lateral region with good flow capacity in the remaining myocardium. The collaterals supplying collaterals to the LCX distribution were sufficiently well developed to prevent myocardial steal. Collateral perfusion improves with regular exercise, as well as low-fat and low-carbohydrate foods by complex mechanisms, including lowering the postprandial lipid surge that inhibits endothelial function.[58-63] Accordingly, an angiogram was avoided, and return to healthy habits resolved his angina.

Case 10: Progression of Diffuse CAD, Compromising Collateral Supply

A 69-year-old asymptomatic man with total occlusion of the RCA by angiogram and poor risk-factor control had a baseline PET as part of a research protocol (Fig. 19–14A). The baseline coronary capacity map showed a severe perfusion defect comprising 13% of the LV (blue) with the central 7% revealing myocardial steal (dark blue) associated with collateral perfusion. Although he was still asymptomatic 6 years later, protocol follow-up PET in Fig. 19–14B showed a larger, severe defect comprising 23% of the LV (blue) with an additional 9% border zones (green) and 13% central steal (dark blue). In the rest of the myocardium outside the severe stress defect, the best coronary flow capacity (red) had declined from 56% to 16% of the LV, with a corresponding increase in the areas of mildly reduced flow capacity (yellow) from 10% to 26% of the LV. Therefore, this enlarging stress defect in the RCA distribution was likely the result of progressive diffuse disease in the

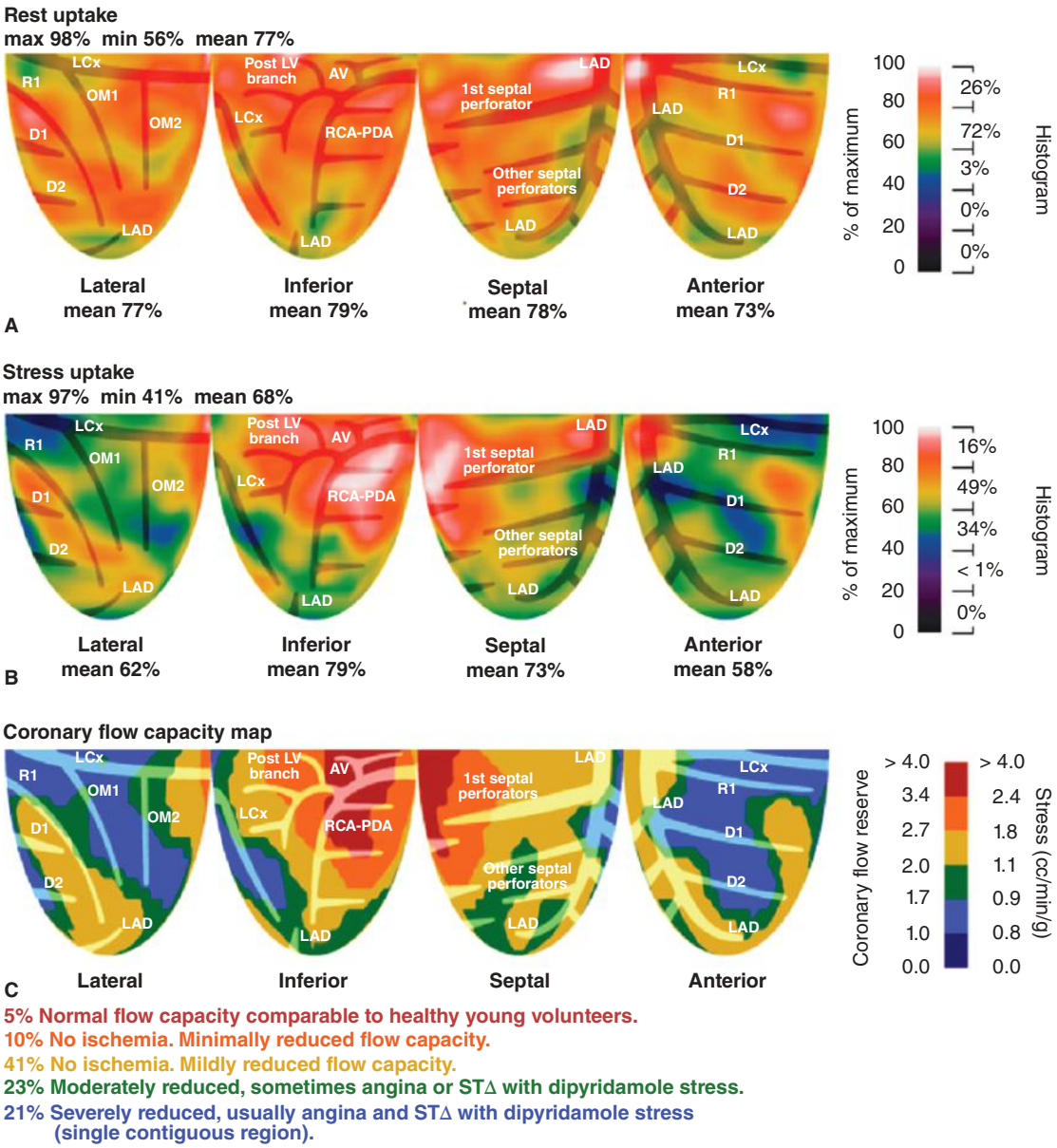


FIGURE 19–10. Case 6. Complex post–percutaneous coronary intervention angiogram with question of left main. (**A**) Rest relative uptake. (**B**) Stress relative uptake. (**C**) Coronary flow capacity map. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

other coronary arteries supplying the collaterals to the totally occluded RCA. Accordingly, coronary angiography confirmed the PET findings but could not quantify the diffuse CAD. Attempted PCI of the occluded RCA was not successful. Because the patient was asymptomatic with good LV function, coronary bypass surgery was not indicated after the failed PCI of the chronically occluded RCA.

Case 11: Severe Angina at High Coronary Flow—Abnormal Adenosine A1 Receptor?

A 66-year-old man had continued intermittent atypical chest pain before and after PCI, with two stents to the LAD. Rather than perform another angiogram, his cardiologist requested PET for assessing progression of his CAD (Fig. 19–15). He developed moderately severe rest chest pain during initial rest perfusion imaging; rest imaging was normal and symptoms resolved spontaneously. Consequently, repeat rest imaging was followed by regadenoson stress imaging. All rest and stress images were normal. Stress perfusion and CFR showed extraordinarily high coronary flow capacity. However, at these very high flows, at the end of image acquisition, the patient developed extreme chest pain (the worst he had ever had), requiring intravenous aminophylline and metoprolol as well as two sublingual nitroglycerin for relief. There were no ECG changes. EF on ECG-gated PET perfusion images increased from 75% to 78% with normal wall motion. The high flows argued against either coronary spasm or microvascular disease. Regadenoson is considered to be a specific adenosine A2 agonist mediating coronary arteriolar vasodilation with weak affinity for the adenosine A1 receptor mediating cardiac pain. In this case, regadenoson triggered severe cardiac pain without ischemia, suggesting aberrant A1 receptor activation by possibly binding regadenoson, or a high density of partially activated A1 receptors, thereby causing severe angina despite high coronary flow mediated by A2 receptor agonism.

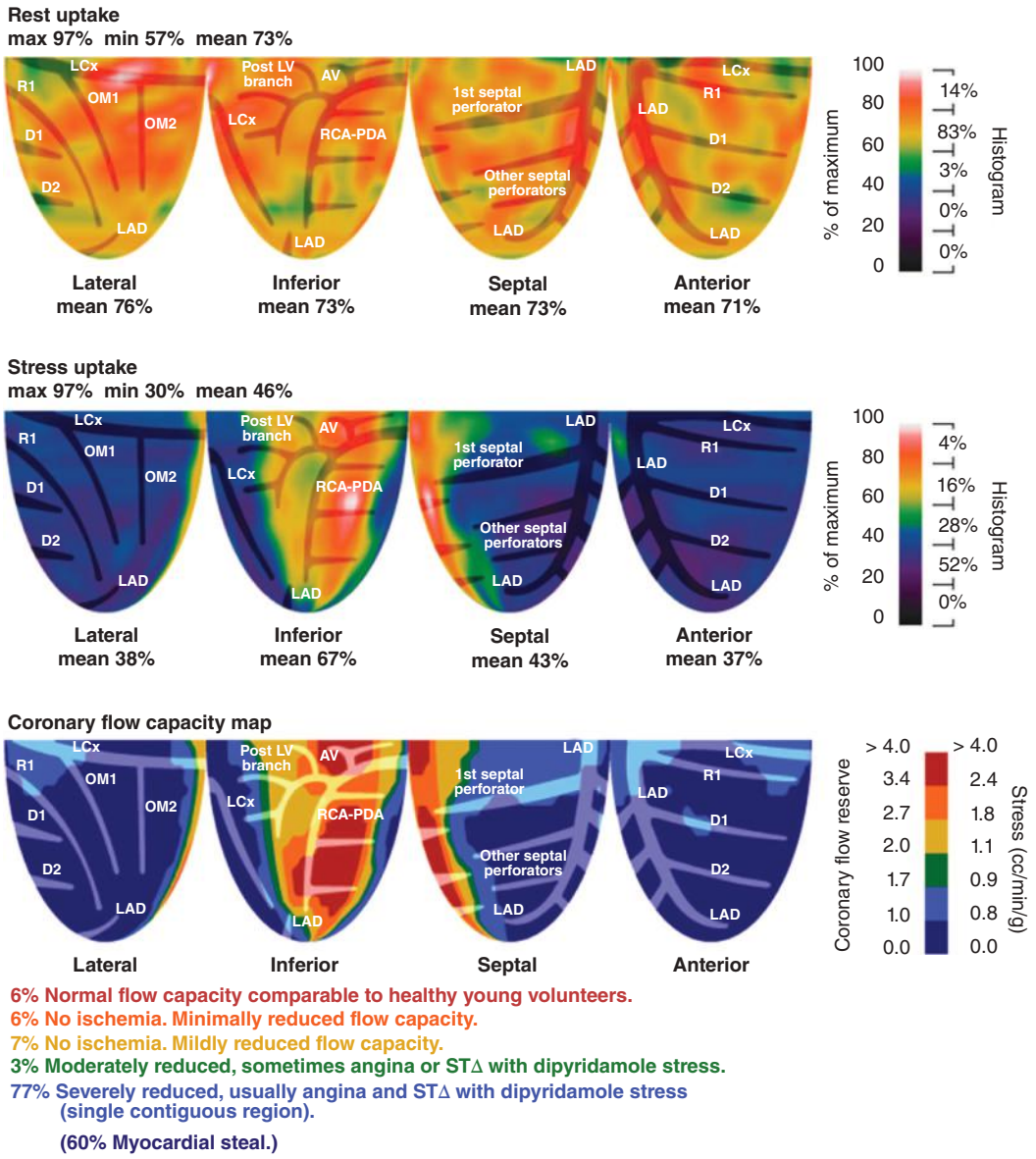


FIGURE 19–11. Case 7. Left main stenosis with patent right coronary artery. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

Case 12: Abnormal Relative Stress Images That Miss Diffuse CAD

A 72-year-old asymptomatic man had routine follow-up PET scan with abnormal stress test 15 years previously leading to angiogram then demonstrating a chronic total occlusion of the LAD. He had no PCIs at that time, and he remained asymptomatic. Fifteen years later, PET relative images (Fig. 19–16), showed a mid-anterior stress defect distal to the first septal perforator and first diagonal branches. The coronary flow capacity map showed myocardial steal, indicating collateral flow with diffuse underlying disease not apparent on relative images. With stability of a known occlusion for 15 years, stability of diffuse disease, absence of symptoms, and preserved LV function, the patient elected for continued medical treatment.

Case 13: Severe Microvascular Dysfunction Without Obstructive CAD

A 78-year-old woman presented with angina manifest as jaw and arm pain for 11 years at rest and exertion that had progressed to limit her walking to 100 feet. She has hypertension and hyperlipidemia. Five coronary angiograms over the years showed no obstructive CAD. She was referred for dipyridamole PET-CT scan with images shown in Fig. 19–17. Relative stress perfusion images were normal (A). Global stress flow of 1.66 cc/min/g and CFR of 1.99 are moderately impaired without angina or ECG changes during dipyridamole stress. CT for attenuation correction showed no coronary calcium, and EF was 70% on gated perfusion images. These findings indicated microvascular dysfunction without calcific coronary atherosclerosis.

Case 14: Saved from Unnecessary Coronary Angiogram

A 43-year-old asymptomatic woman requested a second opinion and PET scan after a cardiologist recommended coronary angiography because of a positive ECG stress test performed at routine physical examination followed by a positive SPECT myocardial perfusion imaging reported to show mild anterior ischemia. Her PET images

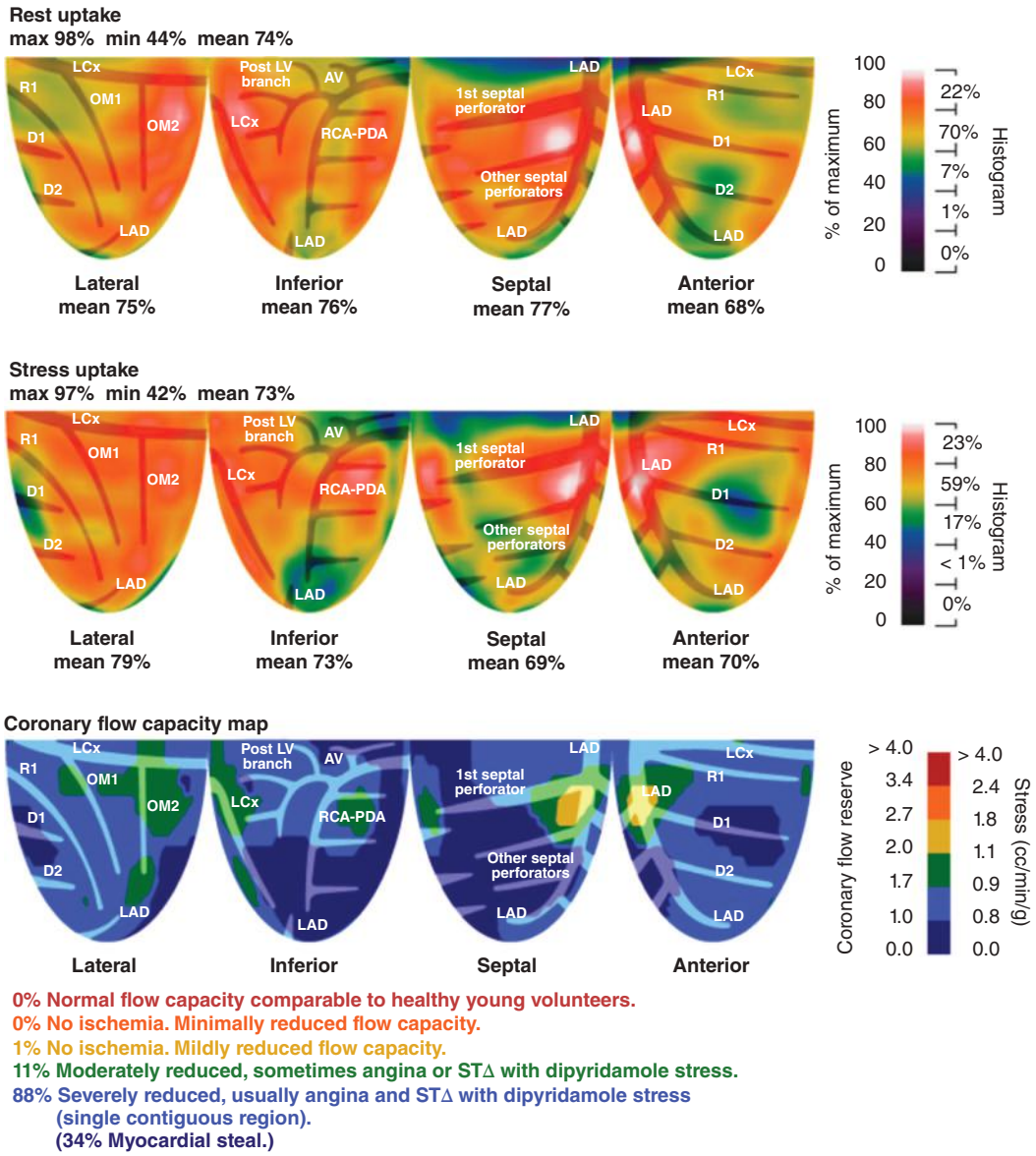


FIGURE 19–12. Case 8. Left main stenosis with occluded right coronary artery. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

(Fig. 19–18) were normal with CFR of 3.9 and a coronary flow capacity map showing uniformly high-flow capacity comparable to that in young healthy volunteers.

CLINICAL PATIENT GROUPS AND THE COLOR-CODED RANGES FOR THE CORONARY FLOW CAPACITY MAP

The case examples demonstrate the power of quantitative perfusion, CFR, and coronary flow capacity for virtually every manifestation of CAD, whereas the coronary flow capacity map correlates with high statistical certainty with large classes of healthy young subjects and patients with clinical and subclinical CAD (Fig. 19–19 and Table 19–1). This extensive validation of the coronary flow capacity map serves to personalize management of CAD or forms the basis for randomized trials of intervention versus medical management by identifying patients with sufficiently large, physiologically severe CAD to optimally benefit from revascularization.[31,37,40]

HETEROGENEOUS MYOCARDIAL PERFUSION: SIMPLIFYING NATURE'S COMPLEXITY

Resting and stress perfusion are variable in different regions of the heart because of differences in regional endothelial function, wall stress and thickness, regional workload, spatially variable systolic compression and relaxation, differing regional metabolic demands, and multiple control mechanisms as reviewed in the chapter on coronary blood flow (Chap. 34). This regional perfusion variability, or perfusion heterogeneity, is profoundly influenced by risk factors, early subclinical and clinically manifest coronary atherosclerosis, medications, emotions and emotional stress, physical activity or training, and food (even a single recent meal). Perfusion heterogeneity is commonly more

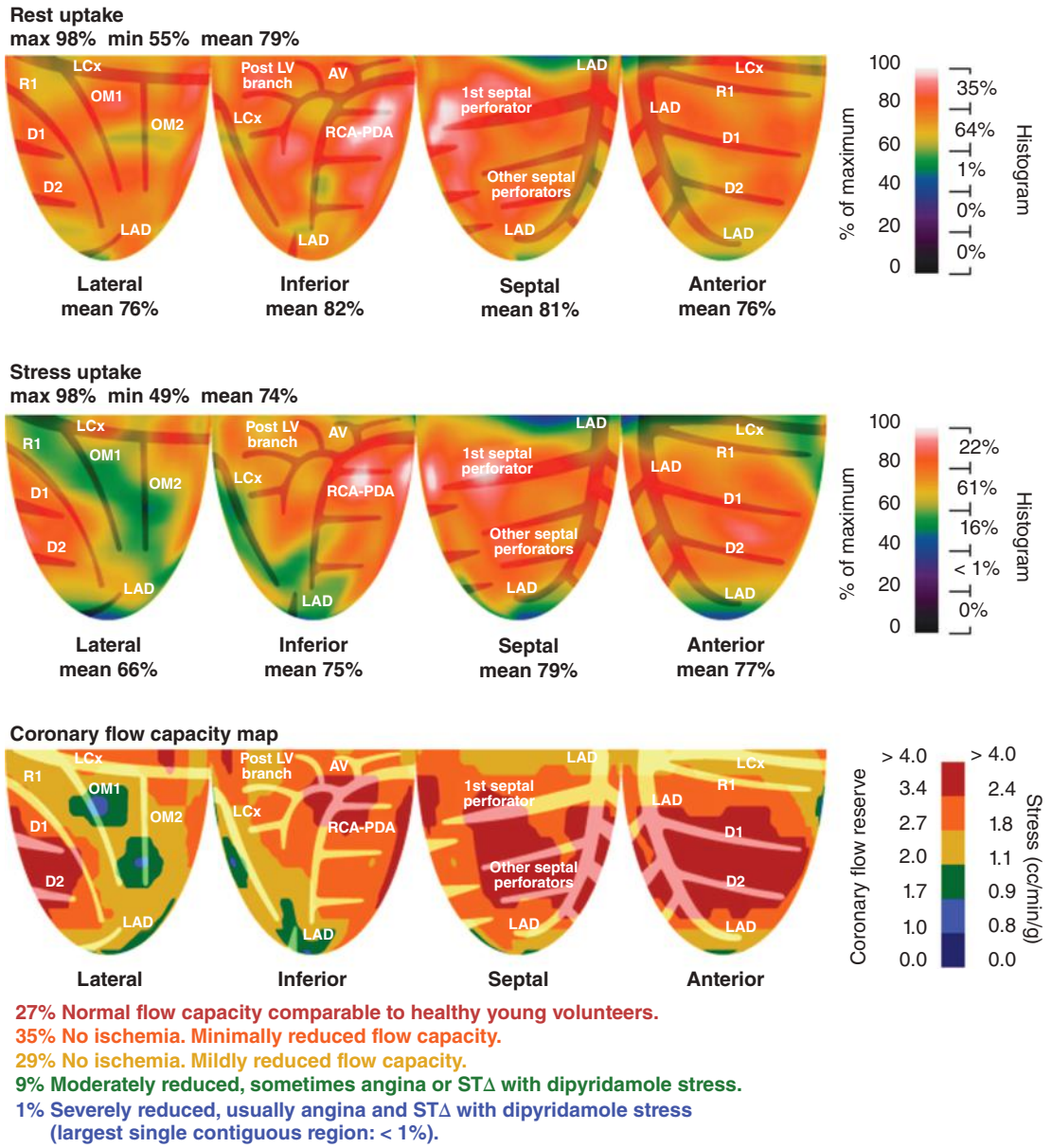


FIGURE 19–13. Case 9. Abnormal relative stress image but adequate absolute perfusion. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

prominent in resting perfusion, as in Fig. 19–20 (A with only lateral and inferior views) because vasodilatory stress substantially overrides autoregulation and many resting control mechanisms (B). Consequently, CFR (C) may show apparent severe regional perfusion defects (blue and green) caused by localized high rest perfusion or may show regional high CFR values (red) caused by low resting flow regions.

The coronary flow capacity map integrates the regional variations in color-coded ranges of perfusion for the entire range of people from healthy young volunteers to patients having angina and significant ECG changes during dipyridamole stress. The percentage of the LV with low stress perfusion in cc/min/g (> 5% or approximately 10% in B) or with low CFR (18% in C) as stand-alone metrics overestimates severity compared to the coronary flow capacity map, accounting for both stress flow and CFR together that shows only mildly reduced flow capacity diffusely (yellow and orange) caused by mild, nonobstructive, calcific CAD. Perfusion heterogeneity provides important clinical insights into endothelial dysfunction and heterogeneous distribution of coronary atherosclerosis rather than being a limitation of quantitative perfusion of the technology. Overprocessing or oversmoothing images to eliminate perfusion heterogeneity destroys essential data that reveal important insights into coronary pathophysiology.

TYPES OF STRESS FOR QUANTITATIVE PERFUSION IMAGING

Quantitative perfusion imaging requires acquisition of the first-pass blood activity of the radionuclide perfusion tracer. Treadmill exercise precludes imaging this first-pass arterial input because of patient motion and the vertical position of PET scanners with horizontal gantries for supine patient positioning. Although supine exercise is reported for quantitative PET imaging,[26,38,42] pharmacologic stress is the standard using either arteriolar vasodilators or dobutamine, as listed in Table 19–2, with their differing biological effects. Dipyridamole and adenosine are the oldest, best established for achieving near-maximum hyperemia and a CFR of 4.0 or higher in healthy volunteers required

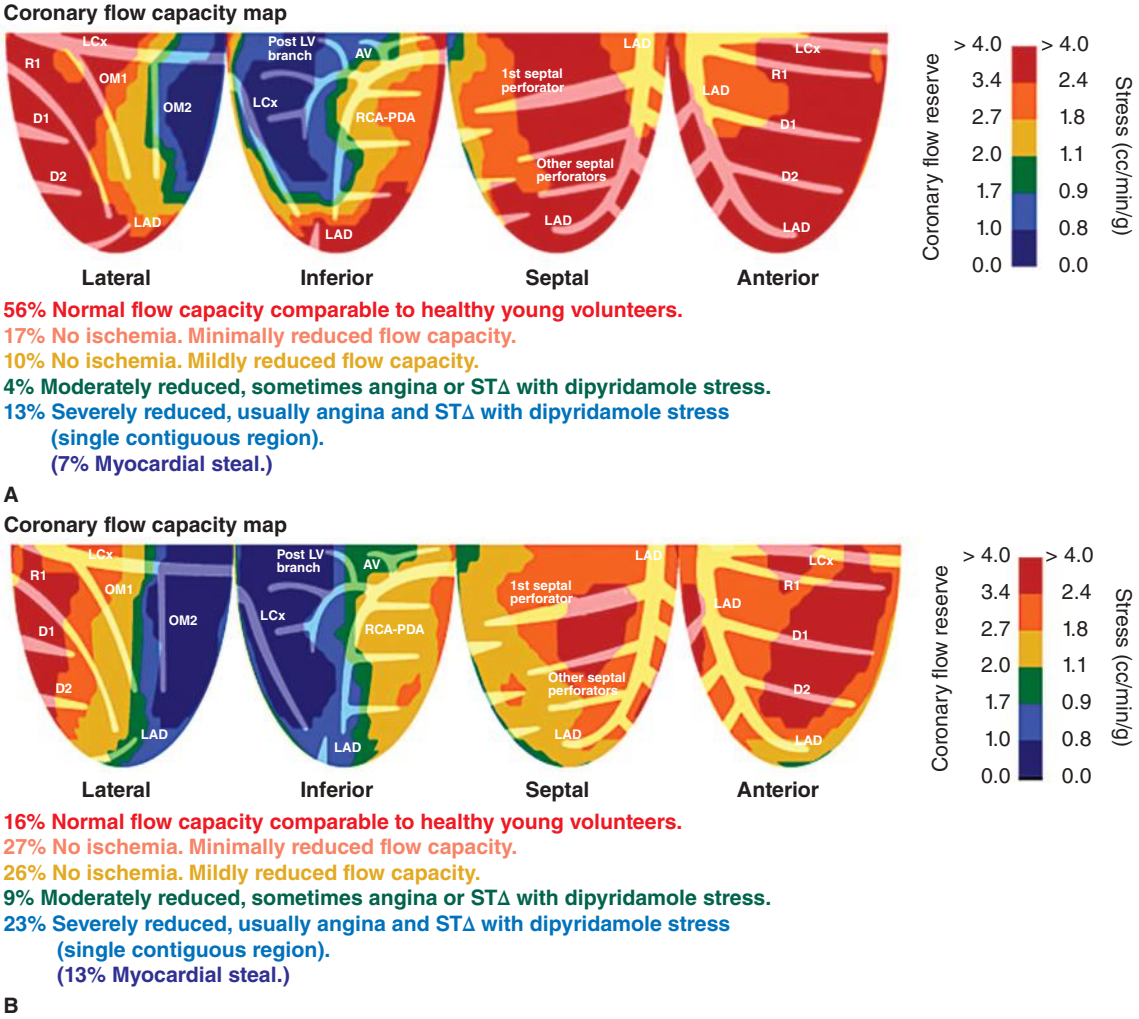


FIGURE 19–14. Case 10. Progression of diffuse coronary artery disease compromising collateral supply. (**A**) Baseline coronary flow capacity map. (**B**) Follow-up 5 years later. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

for the optimal diagnosis or assessment of the physiologic severity of CAD.

Residual blood caffeine inhibits the hyperemic effects of these vasodilators, thereby invalidating diagnostic accuracy as shown in Fig. 19–21. The baseline coronary flow capacity map shows no clinically significant abnormality after withholding caffeine for 24 hours but with residual blood caffeine levels of 1.0 μg/mL. After 48 hours of abstinence from caffeine and no measurable blood caffeine level, repeat rest-dipyridamole PET caused a large severe perfusion defect involving 25% to 30% of the left ventricle in an RCA or LCX distribution with a minimum CFR of 0.69 indicating myocardial steal with stress perfusion reduced to 69% of rest perfusion. Myocardial steal is associated with collaterals beyond an occluded artery corresponding in this case to a chronic asymptomatic occlusion of a dominant RCA on angiogram.

The recent adenosine A2 agonist, regadenoson, is marketed for vasodilator stress myocardial perfusion imaging. When used according to the protocol recommended by the manufacturer, the maximum stress flow and CFR with regadenoson is only 80% of stress perfusion with dipyridamole in patients undergoing sequential stress imaging with both agents.[64] Inadequate or submaximal vasodilator stress reduces the relative size and severity of stress perfusion defects compared to their size and severity with maximum hyperemia induced by dipyridamole or adenosine. The relative PET images for Case Y in Fig. 19–22 show a large dipyridamole-induced stress defect caused by a chronic asymptomatic LAD occlusion. The regadenoson stress defect in the same patient is substantially smaller and less severe, thereby failing to quantify size and severity.

Submaximal stress has the opposite misleading effect on absolute perfusion by eliciting lower stress flow in cc/min/g compared to maximum stress, thereby erroneously appearing to reflect diffuse disease. In Case Z of Fig. 19–22, relative stress images (A, red) are both normal. However, stress perfusion in cc/min/g (B, blue) is moderately reduced to approximately 1.1 cc/min/g (by the right stress flow color bar scale) also indicated by the coronary flow capacity map (C, yellow by the color bar scale of combined stress flow of 1.1 cc/min/g and CFR of approximately 2.0). With dipyridamole, stress perfusion is 2.0 cc/min/g and the flow capacity is high (C, red). In a systematic study on the time course of regadenoson stress perfusion by PET using Rb-82, maximum perfusion occurred 55 seconds after the 10-second regadenoson infusion, achieving 90% of dipyridamole stress perfusion.[64] Therefore, injecting radionuclide at 55 seconds after the 10-second regadenoson infusion produces greater hyperemia and was associated with better quantification of size and severity of stress-induced perfusion defects

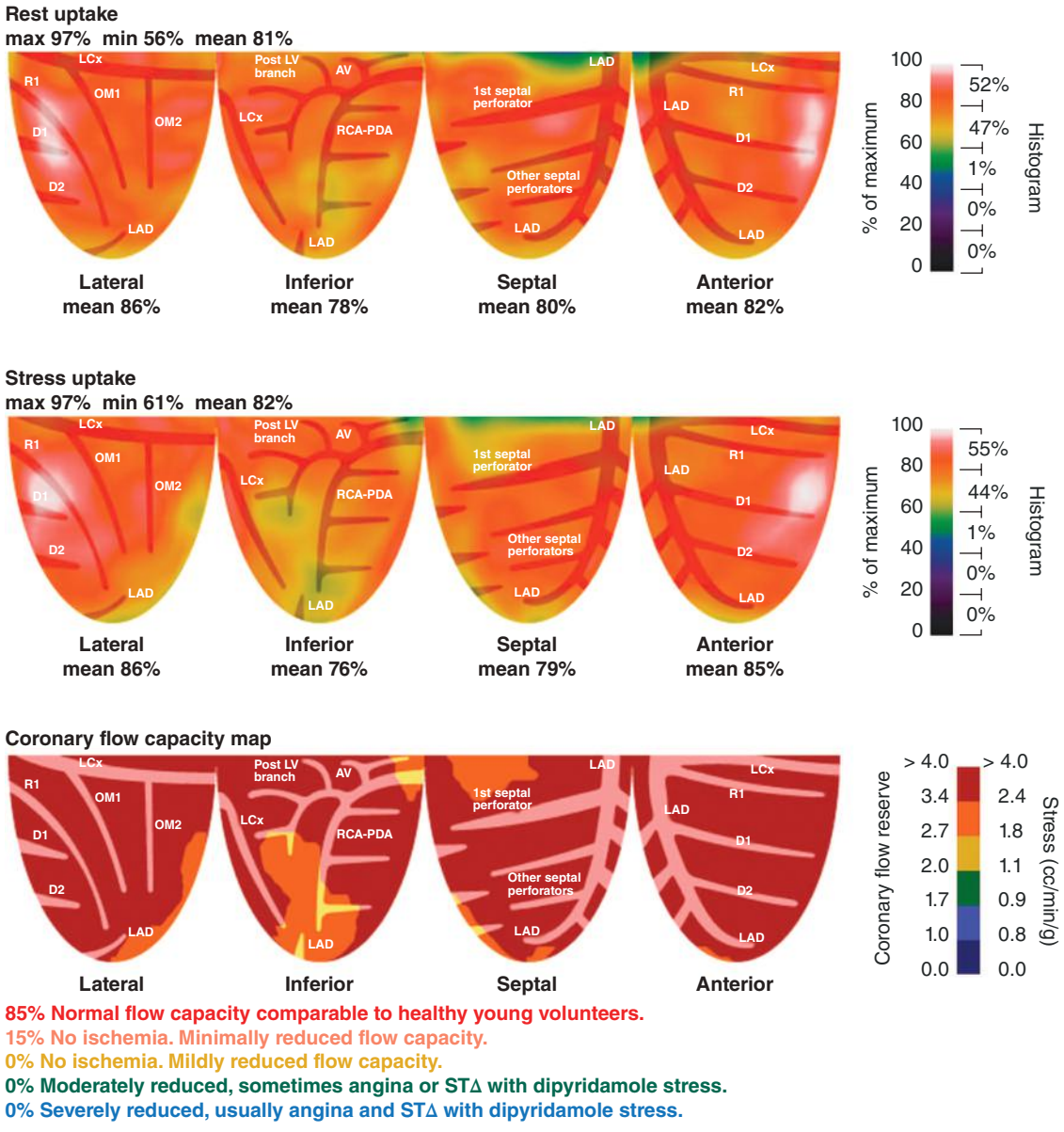


FIGURE 19–15. Case 11. Severe angina at high coronary flow—abnormal adenosine A1 receptor function. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

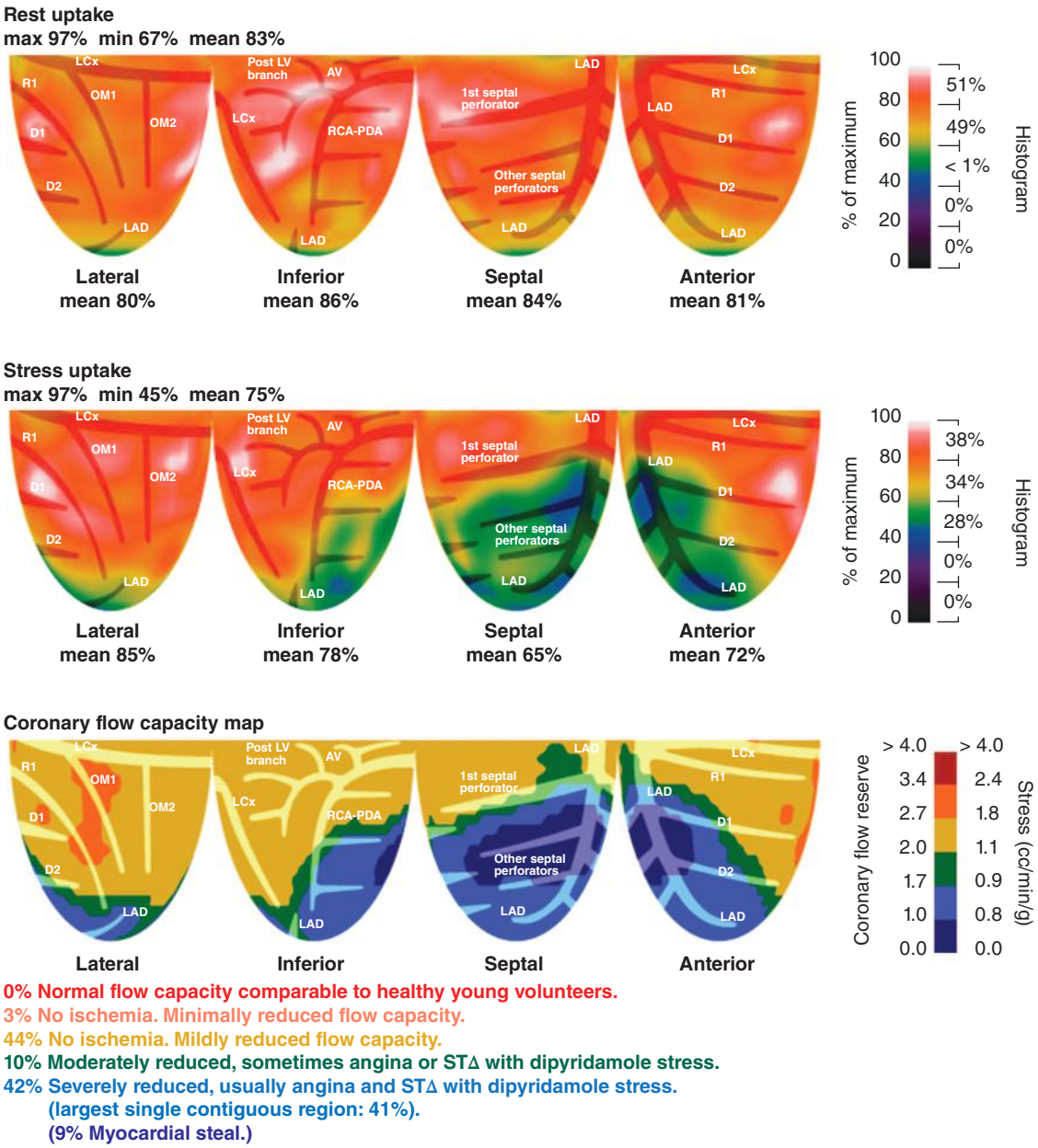
but not the same as dipyridamole. Finally, regadenoson has more adverse events than adenosine.[65]

TECHNICAL COMPONENTS OF QUANTIFYING MYOCARDIAL PERFUSION

Measuring myocardial perfusion in cc/min/g using radionuclides requires three components: the time-integrated arterial blood concentration of activity, the myocardial tissue activity, and the equation or model for calculating perfusion from these measured components (Fig. 19–23). Radiolabeled microspheres used in experimental animals are 100% trapped in the myocardium so that the model calculation of perfusion is a simple ratio with resulting units of cc/min/g. Radionuclides used clinically are variably trapped in myocardium with decreasing myocardial trapping or "extraction" declining as perfusion increases.

The model for calculating flow from the measured arterial input function and myocardial uptake for the common clinical radionuclides employ a correction term for this flow-dependent extraction, E, in Fig. 19–23. The extraction fraction is expressed as a fraction of 1.0 for 100% extraction-like microspheres. At resting perfusion levels, the extraction for nitrogen (N)-13 ammonia is about 0.80 or 80% falling to about 55% at maximum stress perfusion; for Rb-82, the resting extraction is about 65% falling to 35% at maximum stress perfusion (Table 19–3).

The extraction correction for each radionuclide can be determined in two ways. The extraction-perfusion relation can be experimentally determined in animals and inserted into the equation with the remaining two unknowns, arterial input and myocardial uptake activities, measured by the scanner for each pixel or specified region with perfusion in cc/min/g displayed regionally. The other method uses multicompartmental curve fitting of the arterial input and myocardial activities over time to account for extraction as part of the flow model



0% Normal flow capacity comparable to healthy young volunteers.
3% No ischemia. Minimally reduced flow capacity.
44% No ischemia. Mildly reduced flow capacity.
10% Moderately reduced, sometimes angina or STΔ with dipyridamole stress.
42% Severely reduced, usually angina and STΔ with dipyridamole stress.
(largest single contiguous region: 41%).
(9% Myocardial steal.)

FIGURE 19–16. Case 12. Abnormal relative stress images that misses diffuse coronary artery disease (CAD). There is severely reduced stress flow with myocardial steal associated with an collateralized occluded left anterior descending artery distal to the first septal perforator (blue) and diffuse CAD of the collateral supply arteries (yellow) not seen on relative images. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

equations to calculate perfusion in cc/min/g. The latter approach requires acquiring serial 10- to 15-second images for the first usually 2 minutes followed by serial images every 30 to 60 seconds for at least 5 minutes in order to construct time activity curves of arterial input and myocardial activity with time. Each of these common radionuclides has a specific acquisition protocol and flow model.

RADIONUCLIDES FOR QUANTIFYING MYOCARDIAL PERFUSION

PET radionuclides for myocardial perfusion imaging (see Table 19–3) have differing biological behavior, availability, and clinical advantages and disadvantages. The partially extracted radionuclides, cyclotron-produced N-13 ammonia and generator-produced Rb-82, are the most widely used with the largest literature as recently reviewed.[31] The positron ranges and extraction or retention fraction vary with their definition and how they are measured. Each has a specific flow model incorporating the arterial input function, myocardial uptake, and flow-dependent extraction or retention, as described below. Both provide accurate measures of myocardial perfusion but with differing operational advantages and disadvantages.

Nitrogen-13 ammonia has a smaller positron range, associated sharper images, and a longer half-life that is less demanding of scanner performance suitable for three-dimensional (3D) cardiac imaging; the first-pass bolus for arterial input has much lower activity than Rb-82. On the other hand, it requires an on-site or nearby cyclotron, close coordination of patient imaging with the cyclotron run, and slower

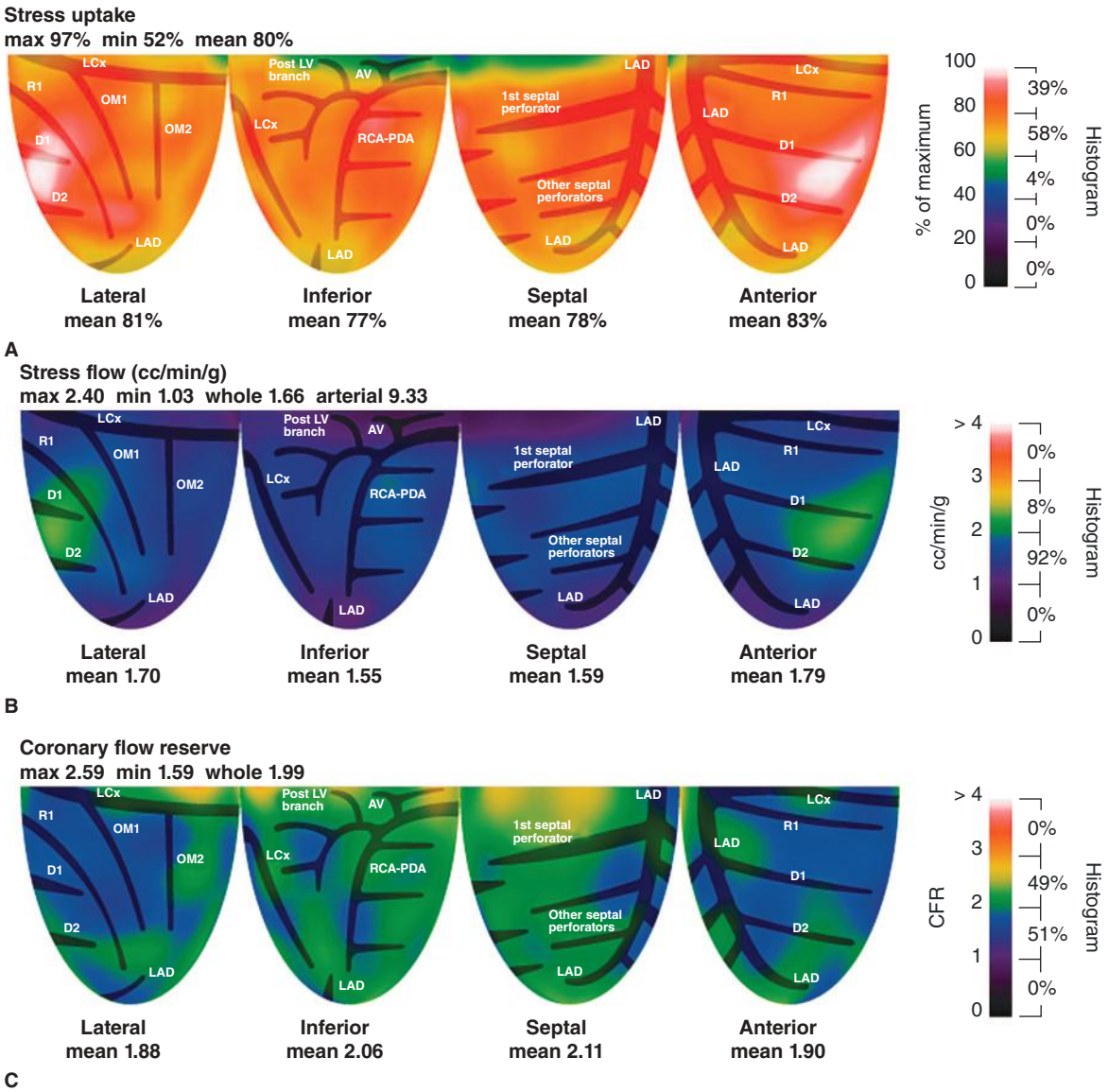


FIGURE 19–17. Case 13. Severe microvascular dysfunction without obstructive coronary artery disease. (A) Stress relative uptake. (B) Stress perfusion in cc/min/g. (C) Coronary flow reserve (CFR).

patient throughput because of the longer half-life of N-13 (10 minutes) requiring decay time between rest and stress images.

Rubidium-82 has the most user-friendly generator source of the PET radionuclides, a short half-life permitting rapid serial rest-stress imaging or serial stress-stress images for research protocols, and a well-validated "simple" two-image acquisition protocol. However, the images are lightly less sharp than N-13 ammonia, although the small difference have no clinical consequences. The full dose of 40 to 50 mCi of Rb-82 for the first-pass arterial input requires high scanner performance optimal with two-dimensional (2D) imaging but not feasible with 3D scanners that, therefore, require half-dose Rb-82 to avoid saturating the scanner as discussed in a later section. The radiation dose for both radionuclides are similar at 1 to 2 mSV per image, compared to three times that dose from the CT attenuation scan of a PET-CT scanner.

Oxygen-15 produced by an on-site cyclotron requires the arterial input function and myocardial uptake but is 100% extracted by myocardium, an important theoretical advantage over the partially extracted radionuclides. However, myocardial uptake imaging is challenging because of its high concentration in the blood pool that requires subtraction of the blood-pool counts from the original image to visualize the myocardium. This subtraction requires acquiring a second set of images after a single inhalation of 40 to 50 mCi of oxygen (O)-15 carbon monoxide. Therefore, the imaging and processing protocol for the O-15 flow model for is substantially more complex than the partially extracted tracers such as N-13 ammonia and Rb-82.[50] Oxygen-15 has a short half-life of (2 minutes); thus, an on-site cyclotron is necessary. Because of its very short half-life and more complex processing, the images are somewhat noisy with greater variability, which is suboptimal for routine clinical applications and regional perfusion needed for clinical decisions. However, in experienced sites, it has provided important research data, particularly for validating in humans other radionuclides more suitable for clinical use such as Rb-82.[66]

F-18 flurpiridaz is a new perfusion tracer not yet approved by the US Food and Drug Administration.[67] F-18 has a longer half life (110 minutes) than N-13 or Rb-82. Its first-pass extraction is reportedly 90%, and it requires its own specific flow model. However, the frequent claim that any one of the radionuclides is better than another because of higher extraction, as for O-15, fails to acknowledge that all of these perfusion

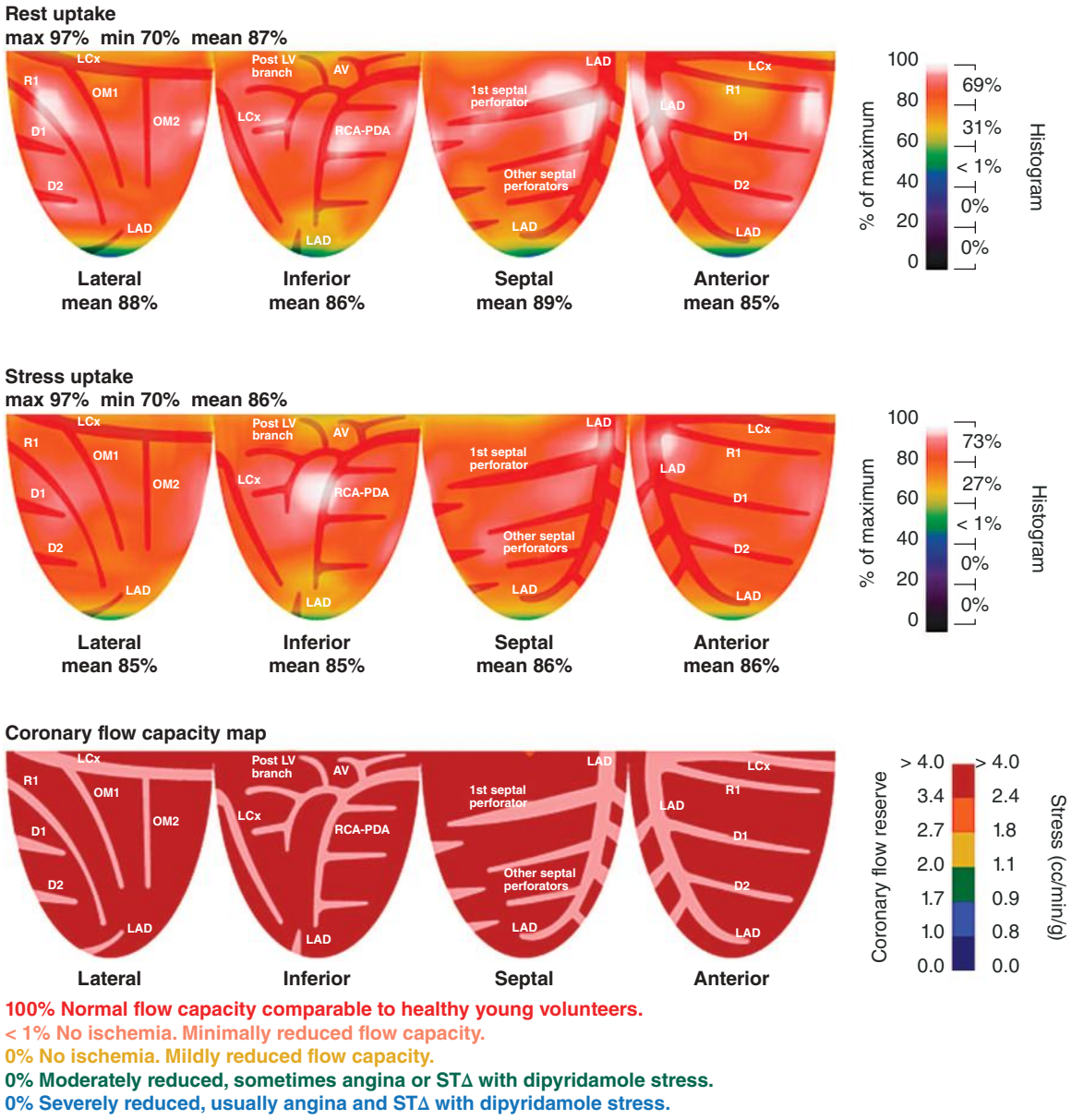


FIGURE 19–18. Case 14. Saved from unnecessary coronary angiogram. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

tracers work well for measuring perfusion; the extraction characteristics are inherently incorporated into the specific flow model for each radionuclide. The disadvantage of F-18 flurpiridaz is its long half-life, which complicates quantitative timely sequential rest-stress quantitative imaging as well as requiring a nearby cyclotron. As addressed below, the primary source of variability in cc/min/g among the different perfusion tracers resides in the arterial input acquisition, not the radionuclide or details of flow models.

FLOW MODELS FOR CALCULATING MYOCARDIAL PERFUSION IN CC/MIN/G

There are two basic flow models for calculating myocardial perfusion in cc/min/g (Fig. 19–24). After intravenous injection of radionuclide, the arterial activity rises rapidly, peaks, and then falls as the systemic circulation dilutes its concentration after intravenous injection. The spreading out of the arterial input activity is caused by cardiac output or systemic circulation diluting the activity concentration and dispersing it over time by multilength pathways or transit times through the lungs. Significant myocardial uptake begins as the broadened arterial pulse of activity passes into the coronary arteries off the aortic root.

The primary data needed for perfusion in cc/min/g are the area under the time-integrated curve of the arterial input activity and the "instantaneous" myocardial uptake at completion of the arterial input function. For Rb-82, the myocardial uptake is flat after the first 2 minutes, so that a single high-quality 5-minute image is obtained representing the "instantaneous" myocardial uptake. As indicated above and in Fig. 19–24, the multicompartmental model acquires serial short images to construct arterial input and myocardial time activity curves that account for flow-dependent extraction from the time activity curves best fit to the compartmental model equation for calculating

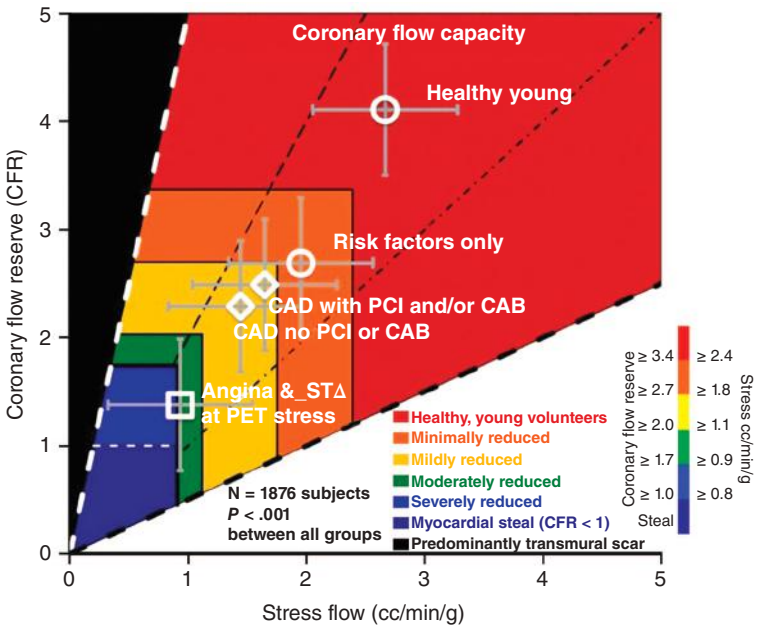


FIGURE 19–19. Clinical patient groups and the color-coded ranges for the coronary flow capacity map as in Figure 19–2. CAB, coronary artery bypass surgery; CAD, coronary artery disease; CFR, coronary flow reserve; PCI, percutaneous coronary intervention. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

perfusion. A variation of this approach uses the experimental extraction-flow relation entered into the equation to simplify the best fit of the time activity curves for solving the equation for perfusion in cc/min/g.

The "simple" or "retention" flow model for Rb-82 acquires a single, early phase, 2-minute first-pass arterial input image followed by a 5-minute myocardial uptake image (or a 10-minute myocardial image for N-13 ammonia), as in Fig. 19–24 and Fig. 19–25. Flow in cc/min/g is calculated using an experimentally determined extraction correction (the exponential term of Fig. 19–24).[68] All flow models use iterative solutions for calculating perfusion in cc/min/g.

An extensive literature addresses the several variations in radionuclides, flow models, and acquisition protocols for quantitative myocardial perfusion, supporting whichever one available is the "best" for that facility. Although "best" at any facility implies that its methodology is objectively selected and optimized, needing no change or critical internal comparison to alternatives, the method used at most sites is usually driven by convenience, prior experience, preexisting facilities, prior expertise in a given method, and particularly funding support. Established research PET facilities with on-site cyclotron generated radionuclides typically have physicists developing the more complex multicompartmental flow models and serial image acquisition protocols. Other PET sites that are primarily clinical may use

TABLE 19–1. Color Coding for Quantitative Stress Flow in cc/min/g, Coronary Flow Reserve (CFR), and Clinical Classification of Subjects Undergoing PET Perfusion Imaging

Quantitative change in flow capacity	Normal	Normal	Minimal	Mild	Moderate	Severe	Steal
Stress flow (cc/min/g)[a]	≥ 2.39[b]	≥ 2.39[c]	< 2.39 & ≥ 1.76[c]	< 1.76 & ≥ 1.12[c]	< 1.12 & ≥ 0.91[d]	< 0.91 & ≥ 0.8[e]	< 0.8
CFR[a]	≥ 3.37	≥ 3.37	< 3.37 & ≥ 2.7	< 2.7 & ≥ 2.03	< 2.03 & ≥ 1.74	< 1.74 & ≥ 1.0	< 1.0
Clinical group in Refs. 56 and 57	Young volunteers	Patients with normal flow and CFR	Patients with none of three[f]	Patients with none of three[f]	Patients with one of three[f]	Patients with two or three of three[f]	Patients with three of three[f]
Group ID in Ref. 57	1	2	3	4	5	6	Part of 6
Number of PETs in clinical group	241	258	610	108	163	120	77 (part of 6)
Minimum stress flow (mean)[a]	2.55 ± 0.56	2.58 ± 0.57	1.80 ± 0.35	1.36 ± 0.16	0.97 ± 0.25	0.85 ± 0.32	Minimum, 0.4 ± 0.2
Minimum CFR mean[a]	3.79 ± 0.81	3.69 ± 0.73	2.69 ± 0.49	2.1 ± 0.29	1.71 ± 0.35	1.46 ± 0.50	Minimum 0.7 ± 0.2
Stress flow mean ± SD whole heart	2.71 ± 0.58	2.78 ± 0.59	1.99 ± 0.34	1.51 ± 0.16	1.18 ± 0.26	1.23 ± 0.37	Not applicable
CFR mean ± SD whole heart	4.02 ± 0.85	3.94 ± 0.77	2.91 ± 0.51	2.26 ± 0.30	1.93 ± 0.40	1.97 ± 0.59	Not applicable

[a]Minimum quadrant average.

[b]N = Normal 125 health volunteers younger than 40 years of age.

[c]N = 840 patients with none of three dipyridamole stress abnormalities.

[d]N =302 patients with one of three stress abnormalities, $P < .001$ versus normals.

[e]N = 193 patients with two or three of three stress abnormalities, $P < .001$ versus normal or AUC = 0.98.

[f]Three dipyridamole stress abnormalities:

1. Angina requiring aminophylline reversal, nitroglycerin, and/or intravenous metoprolol.

2. ST change ≥ 1 mm new with stress, resolving after stress.

3. Relative stress defect ≥ 10% of left ventricle with ≤ 60% of maximum relative update.

PET, positron emission tomography; SD, standard deviation.

Reproduced with permission from Gould KL, Johnson NP: Quantitative Coronary Physiology for Clinical Management: the Imaging Standard. *Curr Cardiol Rep*. 2016 Jan;18(1):9.

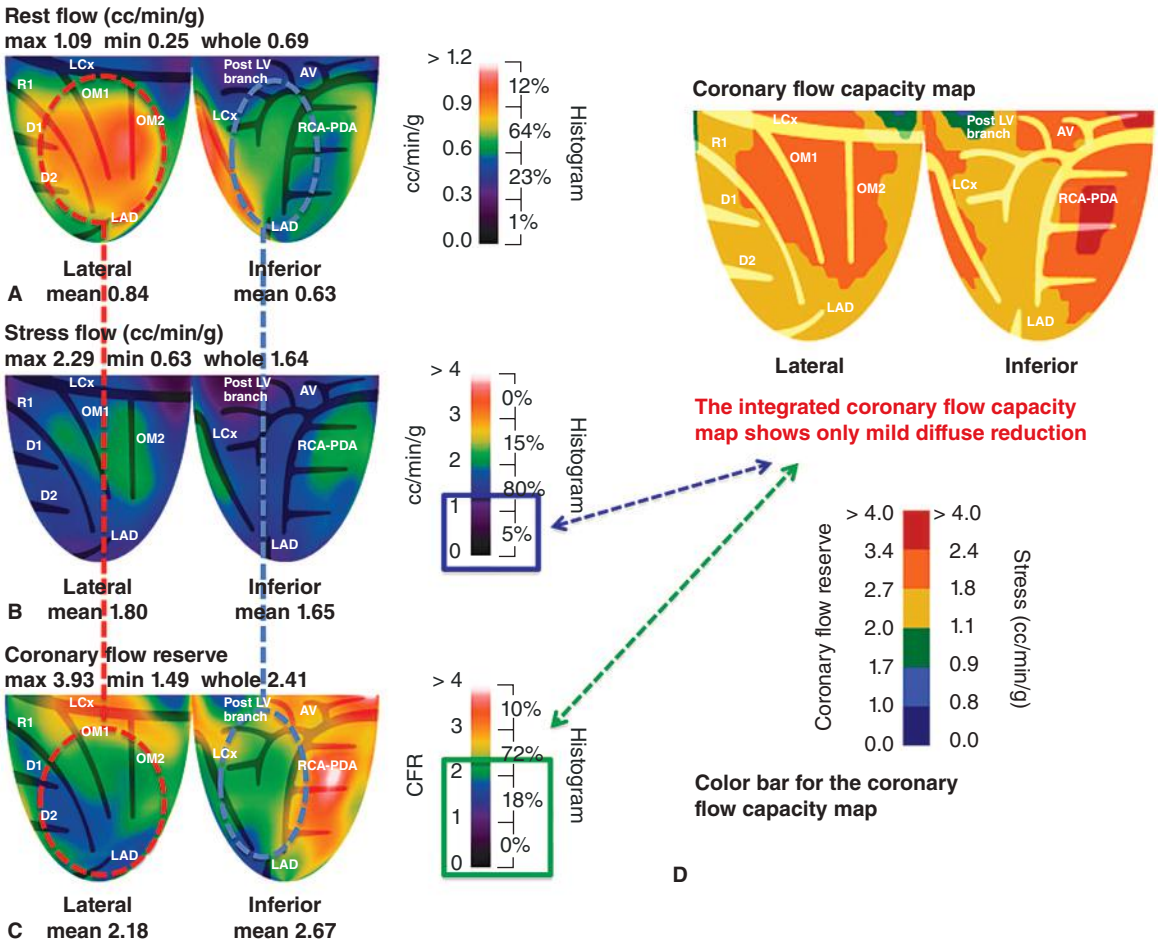


FIGURE 19–20. Regional heterogeneity of stress perfusion and coronary flow reserve (CFR) integrated by the coronary flow capacity map. (**A**) Rest perfusion in cc/min/g. (**B**) Stress perfusion. (**C**) Coronary flow reserve (CFR). (**D**) Coronary flow capacity map. Stress flow is low in about 10% (well over 5%) of the left ventricle (LV) and CFR is low in 18% of LV. However, their integration on the coronary flow capacity map accounting for rest flow heterogeneity shows only mild diffuse reduction, indicating mild diffuse nonobstructive coronary artery disease. The color bar below the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

the "simple" or simpler "retention" flow models for Rb-82 that are more widely available with simpler facility requirements.

Direct comparison of the various models experimentally,[68] theoretically,[69] or clinically[32,33,70] show that the "simple model" provides perfusion in cc/min/g comparable to multicompartmental models (Fig. 19–26) with less variability than multicompartmental models.[32,69] In experimental animals, the simple model using a single arterial input image (A) correlated tightly with the compartmental model using serial images to construct time activity curves and with perfusion by radiolabeled microspheres (B).[68] In patients, the simple model for Rb-82 (C) and 13-N ammonia (D) provided "higher sensitivity for detection and localization of abnormal flow and myocardial perfusion reserve… without the computational complexity and sensitivity to noise—of the multicompartmental model."[32]

The variability of stress perfusion of flow models parallels their complexity because the assumptions necessary to calculate flow introduce

TABLE 19–2. Pharmacologic Stress Imaging[a]

	Adenosine or Dipyridamole	Dobutamine	Exercise
Blood pressure	Falls	+	+++
Heart rate	+	++	+++
Cardiac output	+	++	+++
Coronary blood flow	+	++	++
Neural sympathetic vasoconstriction	±	++	+++

[a]Generalized average effects of different pharmacologic stress for myocardial perfusion imaging on blood pressure, heart rate, cardiac output, coronary blood flow, and neural-mediated sympathetic coronary vasoconstriction.

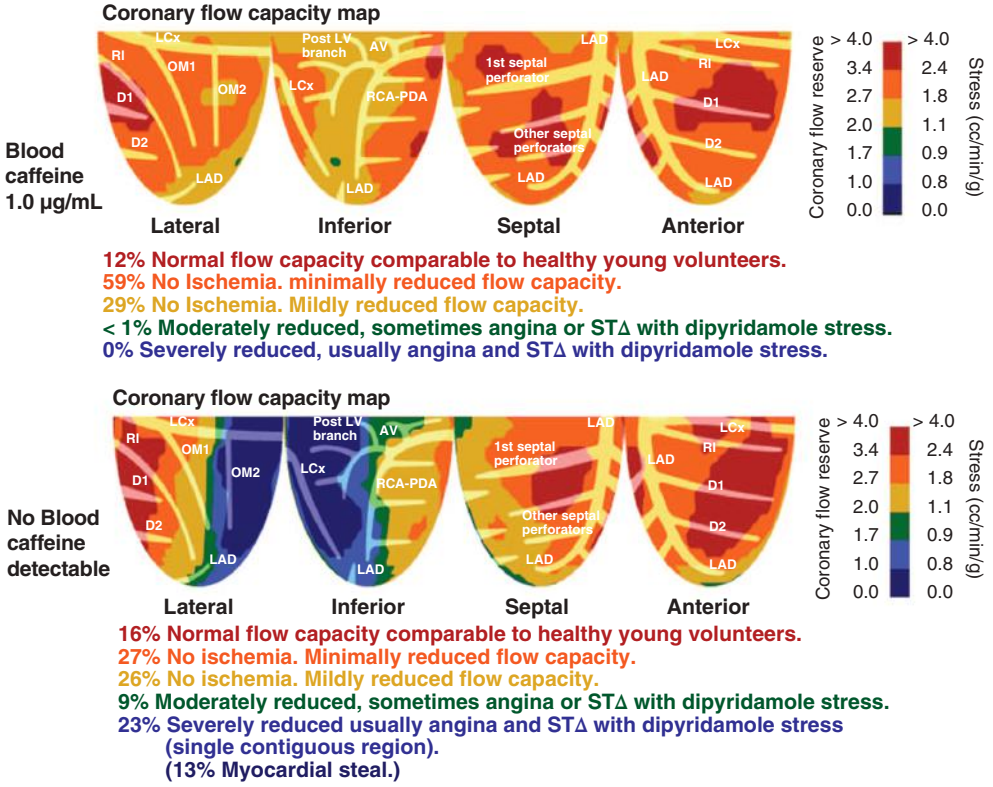


FIGURE 19–21. Effect of caffeine on vasodilator stress perfusion imaging. Inadequate stress may fail to detect or quantify even severe coronary stenosis. The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

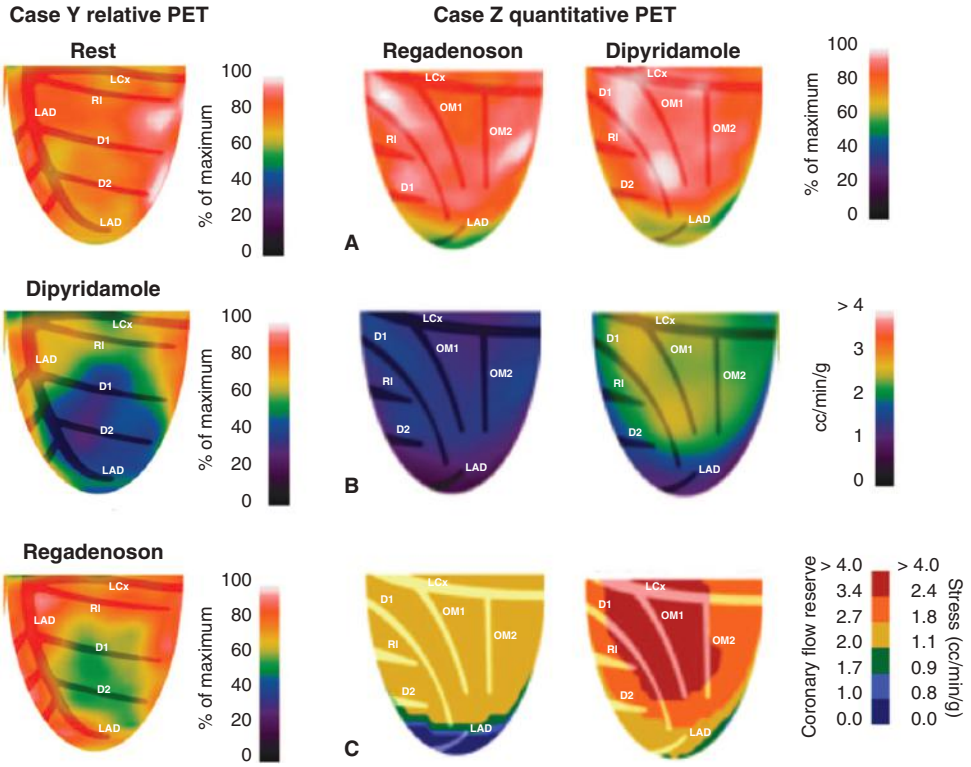


FIGURE 19–22. Regadenoson stress compared to dipyridamole stress perfusion imaging. Case Z (**A**) stress relative uptake. (**B**) Stress perfusion in cc/min/g. (**C**) Coronary flow capacity map. The suboptimal stress of the standard regadenoson protocol may fail to quantify physiologic severity of coronary stenosis as in Case Y or may falsely suggest diffusely reduced coronary flow capacity (yellow) in Case Z resulting from poor stimulus for increasing coronary blood flow compared to dipyridamole (red and orange). The color bar on the right of the map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

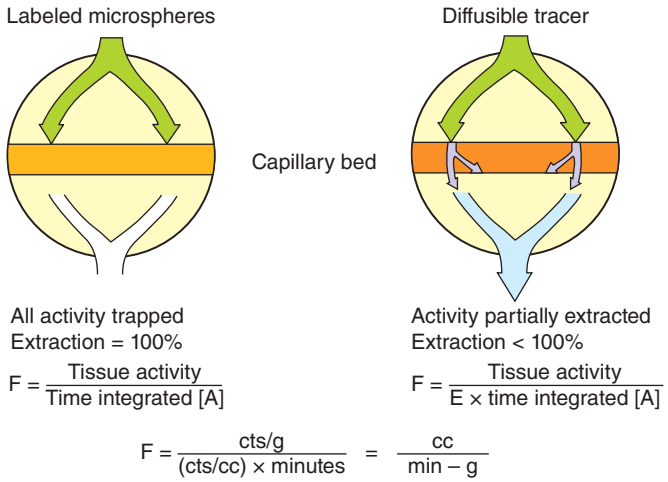


FIGURE 19–23. Principle of measuring myocardial perfusion in cc/min/g. [A], time-integrated arterial blood activity of the tracer; cts, radioactivity of the tracer; E, extraction fraction by the myocardium of the radionuclide tracer from blood; F, flow; g, gram of myocardium; min, minute; tissue activity, activity of myocardium.

TABLE 19–3. Radionuclides Used for Positron Emission Tomography Perfusion Imaging

Radionuclide	Half-Life	Dose (mCi)	Positron Range (mm)	Extraction (%) Rest	Extraction (%) Maximum Flow
F-18 flurpiridaz	110 min	6–10	0.2–0.65	94	94
N-13 ammonia	10 min	5–20	0.57–1.4	80	55
O-15	2 min	10–30	1.5–1.9	100	100
Rb-82	76 s	20–50	1.7–4.3	65	35

noise that their greater mathematical or theoretical precision fails to overcome. For example, the most complex distributive model developed to date had greater variability than standard versions for this reason and proved less clinically useful than simpler versions.[71] However, most of the variability among different flow models does not result from the equations for calculating perfusion. Rather, the greatest variability in absolute perfusion is caused by variable arterial input imposed by short, noisy, serial images using back-projected regions of interest (ROIs)[72] as discussed below.

As a result of differences in PET scanners, radionuclides, acquisition protocols, and flow models, rest and stress perfusion in cc/min/g may be different among different PET centers. However, the ranges of CFR (myocardial perfusion reserve) are more comparable among different PET facilities because the ratio of stress to rest flow for CFR cancels out the acquisition and modeling factors; this leads to variations in the absolute perfusion in the numerator and denominator of this ratio.[33] Complete integrated quantification of stenosis or diffuse CAD requires both CFR and stress flow in cc/min/g; therefore, reducing variability of absolute perfusion in cc/min/g is essential as reviewed below.

THE ARTERIAL INPUT FUNCTION: THE ACHILLES HEEL OF QUANTITATIVE PERFUSION IMAGING

An extensive literature addresses all the components of quantitative perfusion imaging—scanners, radionuclides, imaging protocols, myocardial resolution, partial volume correction, flow models, and software—except one, the arterial input function. A single, excellent, unique recent editorial[73] on the topic related to a detailed study of the issue,[72] emphasizing the paucity of literature on this critical but neglected component of quantitative perfusion.

For multicompartmental flow models, the short, serial images of the first-pass arterial activity are so noisy that an ROI cannot be reliably located directly on the aorta, left atrium (LA), or LV cavity for the arterial input function. For the same reason, the arterial ROI cannot be placed to avoid spillover activity from the immediately adjacent superior vena cava, right atrium, and pulmonary artery or its major branches having the highest activity after intravenous injection. Multicompartmental models based on these noisy, short, serial images therefore require locating the arterial ROI on late myocardial images just superior to the estimated atrioventricular ring at the base of the LV and back projecting it onto the early-phase noisy serial images. The position of this back-projected ROI is assumed to be the LA from which the arterial input curve is obtained.

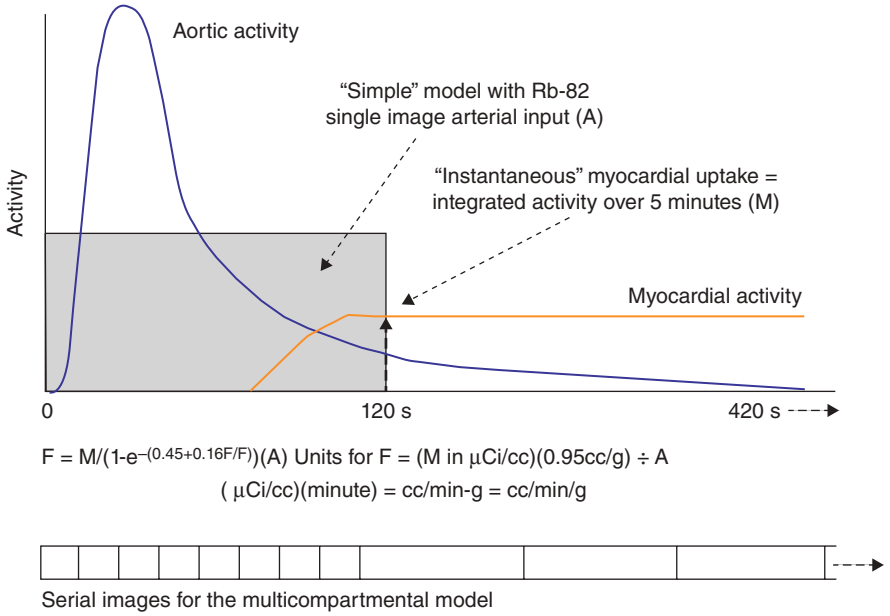


FIGURE 19–24. Schematic of arterial input function, myocardial uptake, and flow model for determining myocardial perfusion in cc/min/g using the "simple" retention model and serial imaging for the multicompartmental model. (A), time-integrated blood arterial radionuclide activity; cc, cubic centimeter; cts, radionuclide activity; F, flow; g, gram of myocardium; min, minute; $(1\text{-}e^{-(0.45+0.16F/F)})$ = flow-dependent extraction fraction correction of radionuclide uptake by myocardium. The time-integrated arterial input curve can be obtained by a single early 2-minute arterial phase, high-quality image acquired as the Rb-82 is infused intravenously. The "instantaneous" myocardial activity at the end of this arterial phase image is closely approximated by the following 5-minute myocardial phase image because Rb-82 is trapped in the myocardial potassium space and remains constant during this interval. In contrast, multicompartmental models acquire short (15 s) serial images during the early arterial phase that have low activity and statistical noise that precludes directly locating the optimal region of interest for the optimal, reproducible arterial input function needed for accurate reproducible quantitative perfusion measurements.

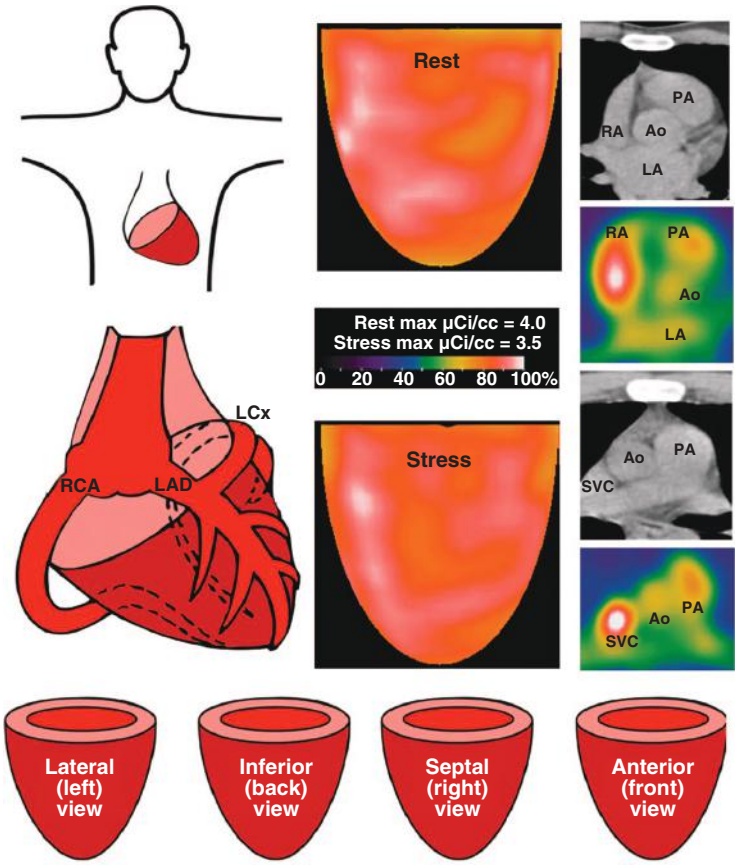


FIGURE 19–25. Components of myocardial perfusion in cc/min/g using Rb-82 from the arterial input and myocardial uptake images. Ao, aorta; LA, left atrium; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; SVC, superior vena cava. The color bar shows relative activity as a percent of maximal at 100%. Reproduced with permission from Sdringola S, Johnson NP, Kirkeeide RL, et al: Impact of unexpected factors on quantitative myocardial perfusion and coronary flow reserve in young, asymptomatic volunteers. *JACC Cardiovasc Imaging*. 2011 Apr;4(4):402-412.[55]

However, cardiac position, translation, and motion vary greatly during the cardiac and respiratory cycle at rest; movement of still several centimeters more occurs during the tachycardia and tachypnea that accompany the administration of vasodilator stress.[74-77] In a systematic study, an ROI located on late myocardial images back-projected onto first-pass images were outside the LA or aortic root for significant portions of the cardiac cycle in a substantial number of patients,[72] thereby giving erroneous perfusion values. Moreover, this study demonstrated that each individual has a personally optimal ROI in central either LA or aorta that avoids spillover from high-activity adjacent structures containing venous blood. No single ROI site was optimal for all patients or even for rest and stress in the same patient.

An arbitrary fixed ROI in the LA or aortic root, particularly back-projected from late myocardial images, yielded erroneous arterial inputs (Fig. 19–27) and perfusion values in 50% or more of all patient studies (Fig. 19–28). Erroneous location of arterial ROI may cause profound life-threatening errors of quantitative perfusion imaging illustrated in Fig. 19–29. Incorrect ROI location that fails to capture the true arterial activity may cause the arterial input function to be too low, with resulting erroneously high perfusion measurements (A) compared to the true arterial input (B) proven by the angiogram.

The commonly unrecognized great strength of the single 2-minute arterial input image of the simple model resides in its high-quality arterial images that allow optimal selection of the most reliable arterial input and therefore perfusion measurements. Arterial ROI selection is so critical that the details of venous or pulmonary artery anatomy adjacent to arterial input anatomy for perfusion imaging need review because they are not widely understood. Fig. 19–30 views the supine patient through the left side where the scanner tomographic planes are rotated counterclockwise and viewed from the feet looking toward the head in traditional radiologic views. Tomographic planes in this schematic labeled A, B, and C correspond to the CT and PET image planes of Fig. 19–31.

In Fig. 19–31, the high-activity venous blood in the superior vena cava, right atrium, right ventricle, and pulmonary arteries is immediately adjacent to the LA and aortic root. In addition, the heart recoils downward and medially during systole and also moves inferiorly with inspiration, all motions that are greatly increased with the tachycardia and tachypnea during vasodilator stress over 2- to 3-centimeter ranges.[74-77] A fixed back-projected ROI from late myocardial images is therefore commonly not over the optimal central LA or aorta site but may be over high-activity venous structures or low-activity lung.[72]

With semiautomated software, the high-quality 2-minute arterial images allow rapidly placing five to eight ROIs over pulmonary artery, aorta, right ventricle, and LV sites, as well as several LA sites. The high activity in the pulmonary artery and right ventricle bracket the upper range of activity for selecting ROIs with no spillover from high-activity venous blood structures. Of all possible ROI sites for measuring arterial activity, the LA or aorta site with the highest activity without spillover from adjacent venous blood activity is the best arterial input activity for that image personalized for that patient. The optimal ROI may be different at rest conditions compared to stress is the same patient. These conclusions are based on repeated serial quantitative PET perfusion imaging for test-retest precision, day-to-day variability, and multiple ROIs in the same subject in more than 200 volunteers or patients and more than 6000 patients having clinical, protocol, and follow-up quantitative PET at the Weatherhead PET Center for Preventing and Reversing Atherosclerosis of the University of Texas at Houston.[16,31,37,39,40,48,55,57,64,72,74-77] In this PET center, the technicians are highly skilled with every ROI checked for any potential errors, complete with perfusion, CFR, and coronary flow capacity maps within 3 to 5 minutes after image reconstruction by KLG.

Dedicated mathematical models focusing on the details and mathematical precision of complex multicompartment models largely overlook variability of the arterial input function resulting from heart translation and motion during the cardiac cycle.[74-77] These arterial input errors may cause errors in perfusion measurements that are greater than what could be ascribed to the flow models.[74-77] The simple retention models appear to have the greatest ease of application for routine clinical use with the least variability.[32,33,68-77] However, there is not, and will likely will not be, a standardized protocol given the wide range of radionuclides, protocols, and flow models already in place. Nevertheless, as discussed below, for all the different approaches there is a relatively simple standard of performance for accuracy of whichever tracer, protocol, or flow model used that makes quantitative perfusion a universal measure, a universal vital sign, such as blood pressure, regardless of the specific technology used to measure it.

THE UNIVERSAL STANDARD OF PERFORMANCE FOR QUANTITATIVE MYOCARDIAL PERFUSION

The standards to which we adhere are based on well-established physiologic facts of maximal and minimal myocardial perfusion proven in experimental models and in humans long before cardiac PET or magnetic resonance imaging (MRI) even existed. In experimental models and healthy young humans, CFR is 4.0 or higher was established in humans as early as 1973[78] followed by confirmatory invasive measurements[79-83] and reconfirmed by later PET literature recently summarized

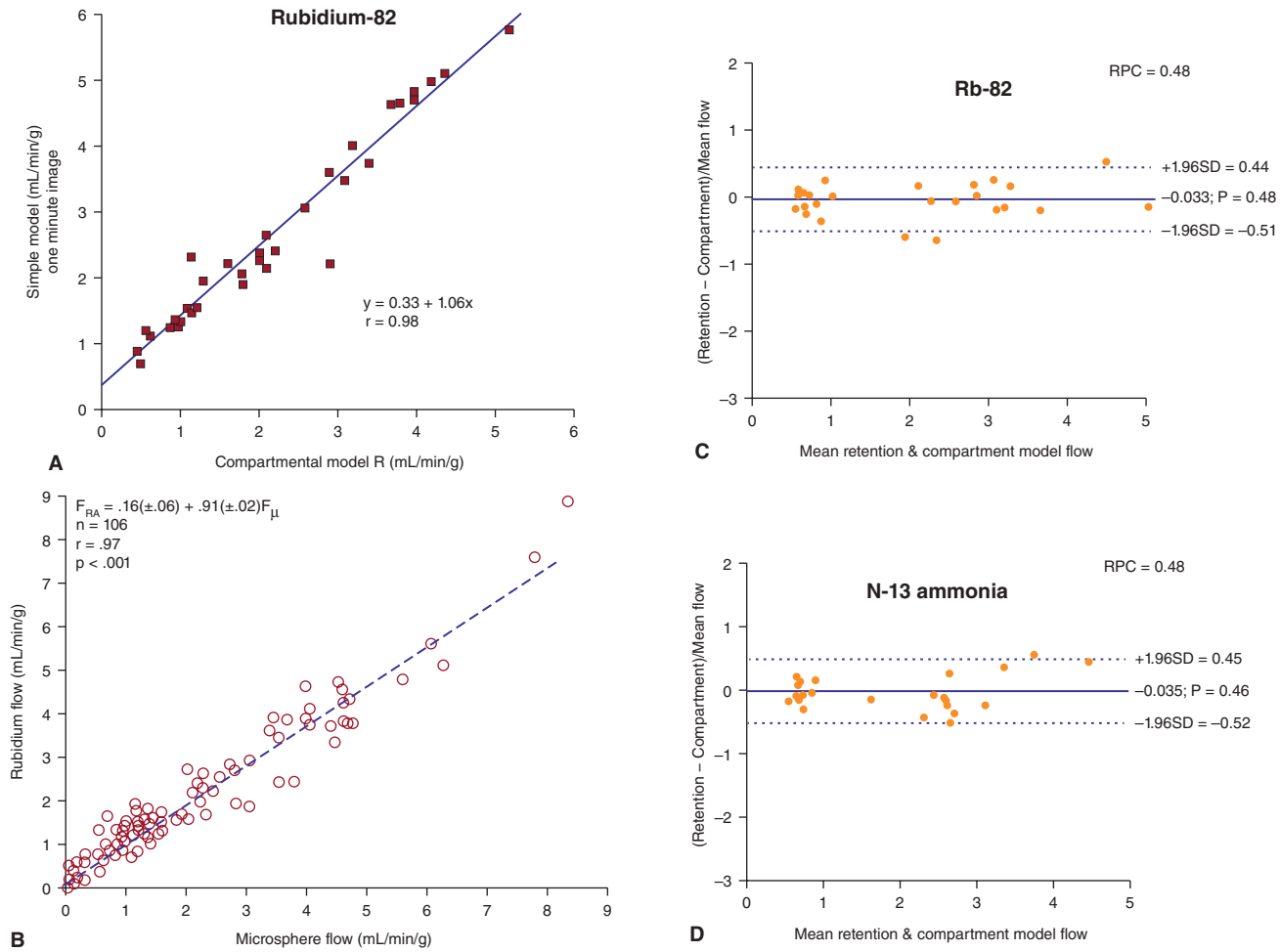


FIGURE 19–26. Myocardial perfusion by the "simple" or "retention" model for Rb-82 compared to (**A**) multiple serial images for compartmental analysis by curve fitting to solve the flow equations and (**B**) microspheres in experimental animals. (**C**) Bland Altman plots for comparison of the retention model to the multicompartmental model for Rb-82 and (**D**) for N-13 ammonia. **A** and **B**, adapted with permission from Yoshida K, Mullani N, Gould KL: Coronary flow and flow reserve by PET simplified for clinical applications using rubidium-82 or nitrogen-13-ammonia. *J Nucl Med*. 1996 Oct;37(10):1701-1712.[68] **C** and **D**, reproduced with permission from Renaud JM, DaSilva JN, Beanlands RS, et al: Characterizing the normal range of myocardial blood flow with ^{82}rubidium and ^{13}N-ammonia PET imaging. *J Nucl Cardiol*. 2013 Aug;20(4):578-591.[32]

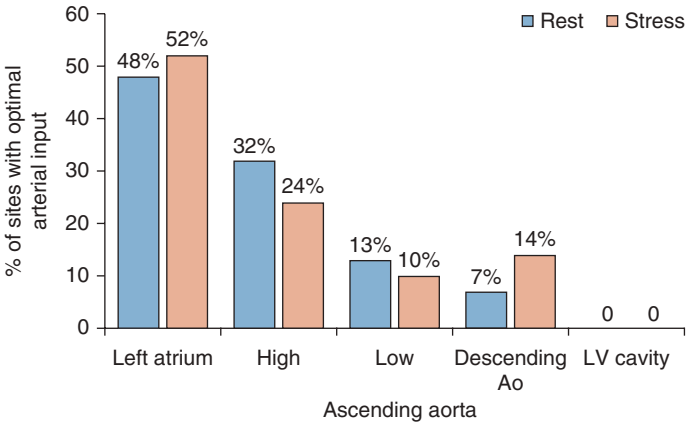


FIGURE 19–27. Percent of anatomic sites with optimal arterial input function (highest arterial input without spillover). For approximately half of patients, the left atrium has the optimal highest arterial activity without spillover from adjacent structures containing venous blood such as the subclavian vein, right atrium, or superior vena cava. However, in many other patients the aorta is the optimal arterial region of interest (ROI) site. Every patient has to have an individually optimal arterial ROI site for accurate repeatable quantitative perfusion measurements as described in the text. Ao, aorta; LV, left ventricle. Data from Vasquez AF, Johnson NP, Gould KL: Variation in quantitative myocardial perfusion due to arterial input selection. *JACC Cardiovasc Imaging*. 2013 May;6(5):559-568.[72]

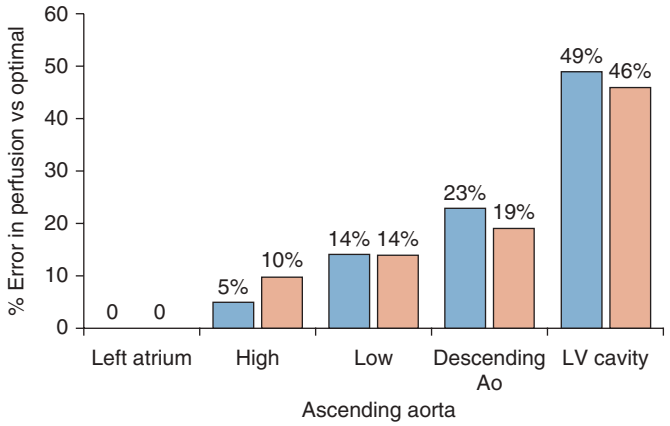


FIGURE 19–28. Mean percent error in perfusion at fixed site versus optimal region of interest (ROI) site for each individual first-pass 2-minute image. Effect of incorrect ROI selection on arterial input function and quantitative perfusion measurements expressed as the mean percent error in perfusion at fixed site versus optimal ROI site for each individual. Ao, aorta; LV, left ventricle. Data from Vasquez AF, Johnson NP, Gould KL: Variation in quantitative myocardial perfusion due to arterial input selection. *JACC Cardiovasc Imaging*. 2013 May;6(5):559-568.[72]

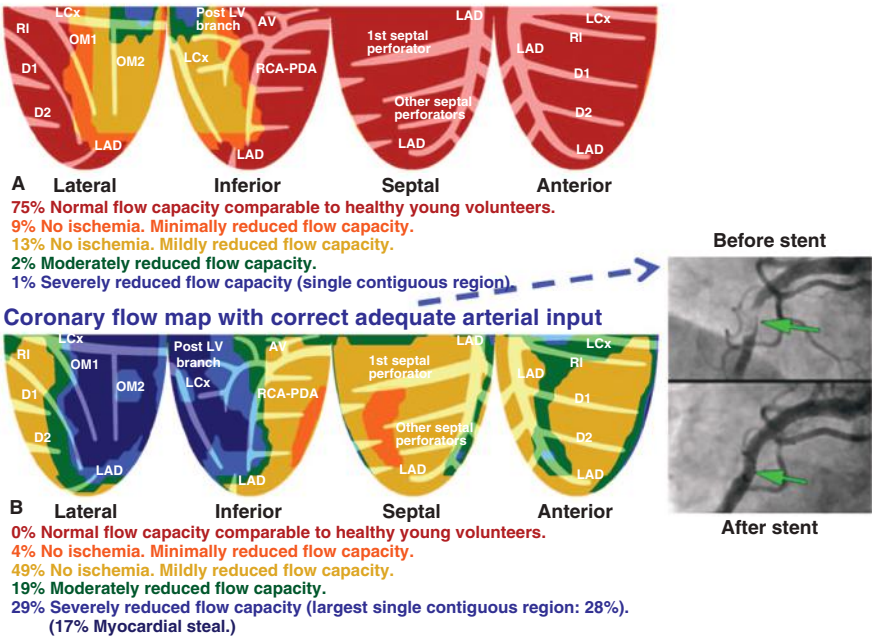


FIGURE 19–29. The region of interest (ROI) back-projected from late myocardial images causes an incorrect arterial input function that falsely lowers arterial input with falsely high flow and therefore falsely mild stenosis on the coronary flow capacity map (A) compared to the correct arterial input, correct severely low coronary flow capacity indicating severe stenosis (B) confirmed by coronary angiogram. Reproduced with permission from Vasquez AF, Johnson NP, Gould KL: Variation in quantitative myocardial perfusion due to arterial input selection. *JACC Cardiovasc Imaging*. 2013 May;6(5):559-568.[72]

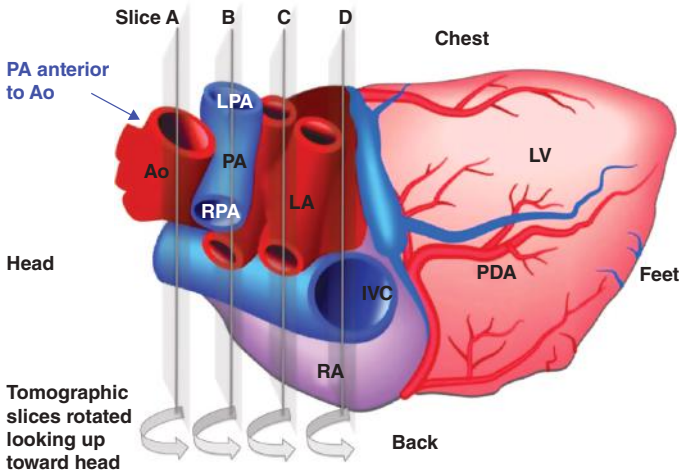


FIGURE 19–30. Anatomic orientation of tomographic planes for optimal region of interest (ROI) selection to obtain optimal arterial input function: looking at the right side of the patient lying on back. This schematic shows closely adjacent arterial and structures containing high activity venous blood after intravenous radionuclide injection (pulmonary artery [PA] and branches, subclavian vein, superior vena cava, right atrium [RA]). Consequently, high-quality, early, first-pass, 2-minute arterial phase images are required to identify the optimal anatomic site for arterial ROI that is highest of possible sites but without spillover from venous blood as bracketed by PA and right ventricle activity. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PDA, posterior descending coronary artery, RPA, right pulmonary artery. Slices A, B and C correspond to the computed tomography and early phase arterial positron emission tomography images of Fig. 19–31.

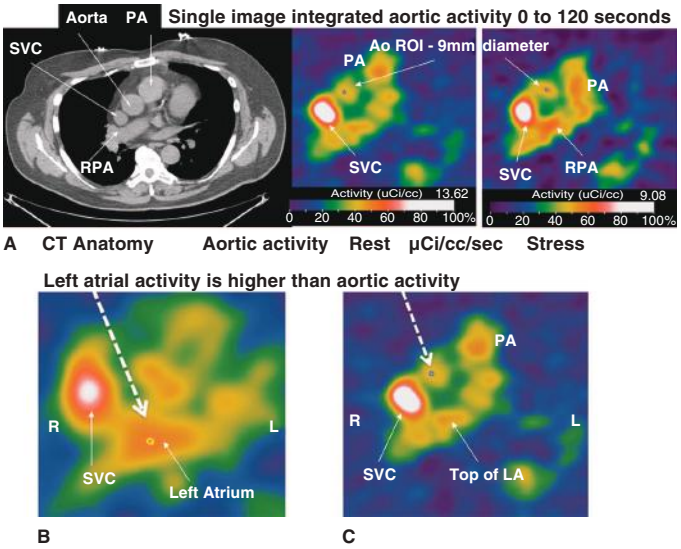


FIGURE 19–31. Computed tomography scan of anatomy and positron emission tomography images of the arterial input function for the simple model. Ao, aorta. LA, left atrium; PA, pulmonary artery; RPA, right pulmonary artery branch; SVC, superior vena cava. Region of interest selection for arterial activity in the tomographic views correspond to the planes A, B, C, and D of Fig. 19–30. The LA in slice C has the highest activity without contamination from the right PA seen in slice A (top right) and higher than the top of LA in slice C (lower right).

for 14,962 individuals previously reported.[31] For healthy young volunteers without risk factors and no detectable blood caffeine, CFR by PET averaged 4.2 ± 0.8; absolute stress perfusion in cc/min/g, 2.9 ± 0.5 cc/min/g[45]; and transmural myocardial scar perfusion, 0.2 cc/min/g.[31,40,57]

Accordingly, for the many variations in PET protocols for quantifying myocardial perfusion to define physiologic severity, the simple standard performance test combining measurement accuracy and clinical coronary pathophysiology to ensure correct clinical decisions is the capacity to measure (1) rest perfusion of 0.2 cc/min/g in transmural scar in at least five patients to test low perfusion accuracy and (2) regional and global CFR of 4.0 or higher and stress perfusion of 2.9 cc/min/g or higher on two sequential rest-stress PET perfusion studies in the same subject with ± 15% variability for at least 15 young healthy volunteers with no risk factors and no measurable blood caffeine levels.[40,55]

THE PET SCANNER

Most cardiac PET literature is based on using 2D scanners, initially with rotating rod attenuation correction and more recently PET-CT scanners with CT attenuation correction. At present, only 3D PET-CT scanners are manufactured largely for cancer applications. The CT attenuation correction of the PET-CT scanner may provide slightly better reconstructed resolution with sharper images than does rotating rod attenuation correction. However, this small difference has little clinical impact. PET-CT also detects coronary calcification that is useful clinically for identifying clinical or subclinical coronary atherosclerosis, but also incurs two to three times the radiation dose as does the rotating rod.

2D scanners have lead septa and in-plane reconstruction algorithms that reduce random coincidences and allow first-pass acquisition of full dose 50 mCi of Rb-82 with high-quality, high-count arterial and myocardial images without scanner saturation. 3D scanners lack septa and therefore have greater sensitivity acquiring more counts that, however, include high random coincidences. Therefore, the first-pass arterial activity of full dose Rb-82 (40-50 mCi) saturates the scanner or shuts down acquisition of 3D scanners and some older 2D scanners (Fig. 19–32), thereby precluding quantitative perfusion measurements.

Therefore, for 3D scanners, the dose of Rb-82 has to be reduced to 20 to 25 mCi infused slowly over 30 to 60 seconds. Higher doses cause lower noise equivalent counts rate by 50% (Fig. 19–33).[74,84] Although studies from a site experienced in 3D PET for cardiac PET with Rb-82 report adequate quality images, primarily global perfusion measurements are reported or used clinically as guides to the angiogram on which clinical decisions rely without demonstrating regional perfusion for clinical guidance shown in the examples above. For N-13 ammonia or F-18 radionuclides that are given in lower doses of 10 to 20 mCi, scanner saturation is not an issue with either 2D or 3D PET scanners.

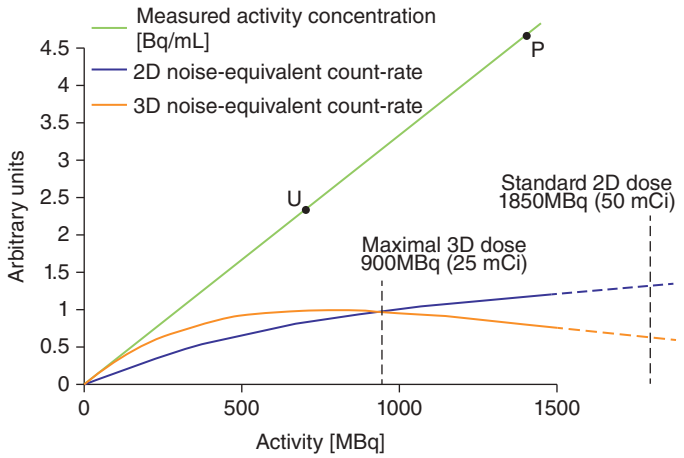


FIGURE 19–33. Noise equivalent counts for increasing dose of Rb-82 for two-dimensional (2D) and three-dimensional (3D) positron emission tomography–computed tomography scanners with adequate acquisition at 25 mCi for the 3D scanner compared to 50 MCi for the 2D scanner. At 50 mCi dose, the 3D scanner saturates and cannot acquire the arterial region of interest activity accurately, thereby precluding quantitative perfusion measurements. Reproduced with permission from deKemp RA, Yoshinaga K, Beanlands RS: Will 3-dimensional PET-CT enable the routine quantification of myocardial blood flow? *J Nucl Cardiol*. 2007 May-Jun;14(3):380-397.[84]

Most PET scanners have sufficiently comparable reconstructed resolution as to constitute little differentiation among them for cardiac PET. However, the order of magnitude better resolution of PET over SPECT at heart depth in the chest is a powerful advantage for PET, as illustrated in Fig. 19–34. For SPECT imaging of an unmoving static

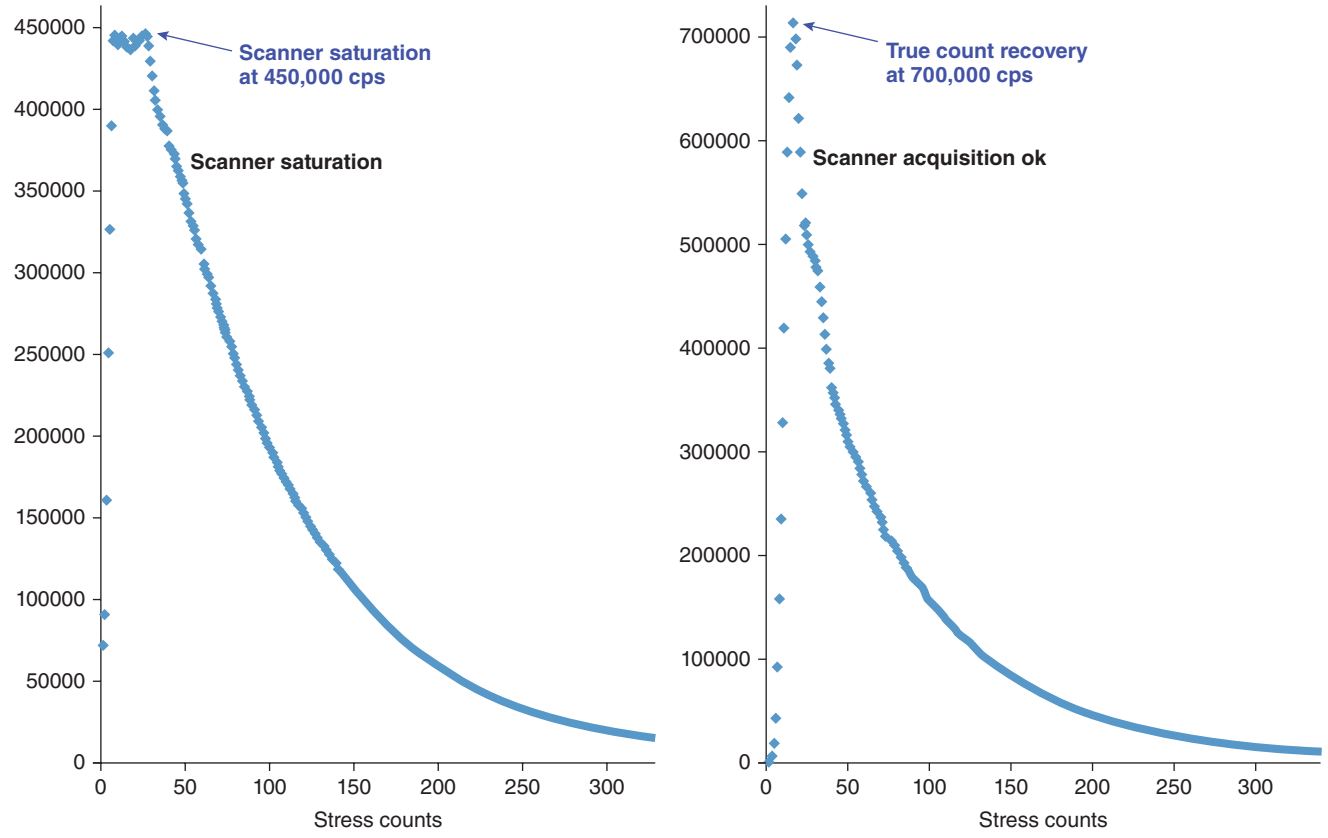


FIGURE 19–32. Scanner saturation during the first pass arterial activity of Rb-82.

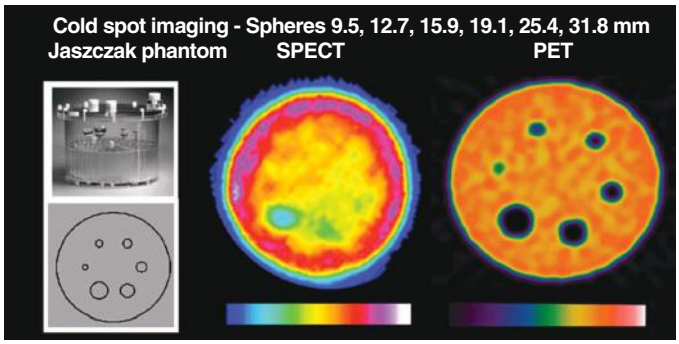


FIGURE 19–34. Positron emission tomography (PET) resolution compared to single-photon emission computed tomography (SPECT) resolution in the static Jaszczak phantom. The SPECT images identifies only the large 3-cm diameter defect with no activity as compared to PET that detects the smallest 9-mm defect. In addition, the SPECT image shows a 50% attenuation of central activity (see relative activity color bar) whereas PET shows uniform activity present in the body of the phantom.

Jaszczak phantom under ideal imaging conditions, any negative defect having no activity that is smaller than 3 centimeters in diameter fails to be detected. In addition on the SPECT images, attenuation also reduces activity recovery in the center of the 20-cm phantom by 50%, thereby creating attenuation artifacts. In contrast, PET imaging sees all the abnormal cold spots with no central attenuation less.

The final critical component of the scanner is software to display and shift attenuation or emission data in order to achieve correct coregistration (Fig. 19–35). Despite alignment by external body markers in this case, both rest and stress helical CT images do not coregister with the emission data, thereby causing severe abnormalities that are misregistration artifacts. However, the cine CT shifted to achieve correct coregistration provides accurate size and severity of a mild to moderate medium sized stress defect in the distribution of a chronically occluded collateralized ramus intermedius coronary artery on angiogram.

With both rotating rod and CT attenuation data, misregistration is common in 20% to 40% of all cases because of cardiac position changing within the chest attenuating structures differentially at rest and stress even with the patient body position unchanged compared to external markers.[74-77] This misregistration may cause gross

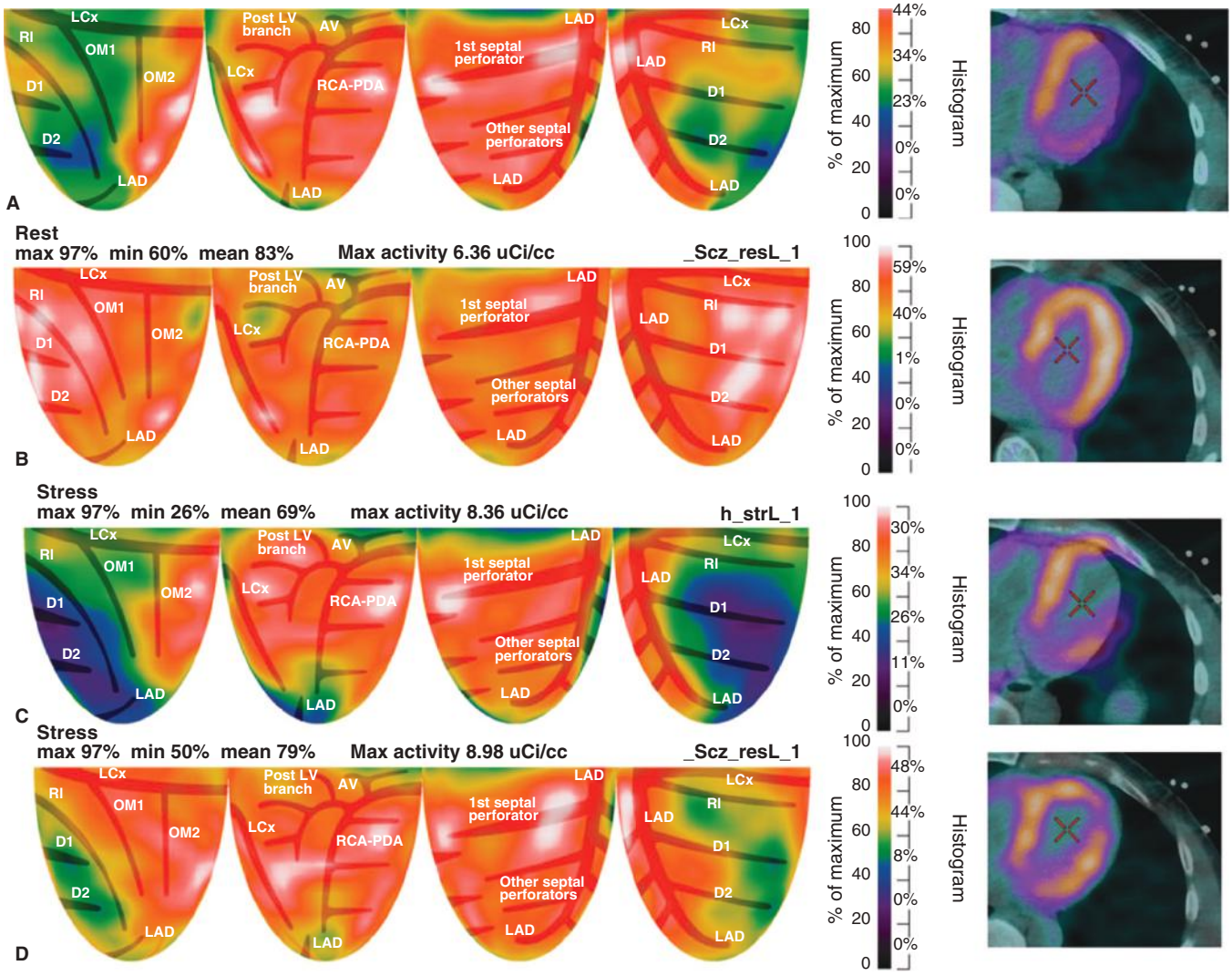


FIGURE 19–35. Effect of misregistration of emission and transmission data for attenuation correction, causing apparent perfusion defects that are artifacts compromising clinical validity. (**A**) Rest relative uptake images reconstructed with helical computed tomography (CT) data misregistered with emission data. (**B**) The same rest relative images reconstructed with cine CT data shifted to achieve correct coregistration. (**C**) Stress relative uptake images reconstructed with helical CT data misregistered with emission data. (**D**) The same stress relative images reconstructed with cine CT data shifted to achieve correct coregistration.

artifactual abnormalities or reduce accuracy of quantitative perfusion measurements.[74-77]

Over the breathing and heart cycles, cine CT for attenuation correction averages the Hounsfield density units of chest attenuating structures, diaphragm, and heart motion over several breathing and heart cycles.[58-61] The resulting cumulative or averaged attenuation data are more comparable to the 5-minute emission image acquisition. In contrast, a short helical CT attenuation scan at some point in the cardiac or respiratory cycle or breath-hold may not coregister with the emission data acquired over 5 minutes with multiple cardiac and breathing cycles. In Weatherhead PET Center at the University of Texas at Houston, every case is checked for misregistration and corrected in order to ensure optimal perfusion quantification even in the absence of relative perfusion defects.

Standard CT attenuation correction incurs a higher radiation dose than does rotating rod attenuation correction. Accordingly, modifying the CT dose for lower resolution suitable for attenuation correction and using a single poststress CT scan reduces total dose for a rest-stress study to approximately 7 to 8 mSv.[77]

COMPLEXITY MADE SIMPLE: QUANTITATIVE MYOCARDIAL PERFUSION FOR PERSONALIZED CORONARY CARE

Coronary blood flow is a determinant of survival and quality of life. As a basic vital sign, its accurate measurement should guide cardiovascular management (Fig. 19–36[31]) based on physiologic knowledge and careful technology serving to eliminate inappropriate procedures and maximize patient outcomes. Of the single views of 12 different cases in Fig. 19–36, the coronary flow capacity maps definitively identified and quantified patients with excellent flow capacity, those with risk factors only, those with mild to moderate focal and/or diffuse CAD optimally managed medically, and those requiring angiography or potentially appropriate revascularization.

MYOCARDIAL METABOLIC AND VIABILITY IMAGING: THE BASIS FOR PERSONALIZED REVASCULARIZATION DECISIONS

CHRONIC LOW CORONARY BLOOD FLOW SYNDROMES AND MYOCARDIAL VIABILITY

Just as acutely reduced coronary blood flow causes acute coronary syndromes, chronically reduced coronary blood flow causes "chronic coronary syndromes"—hibernating myocardium, stunned myocardium, or ischemic cardiomyopathy. For these syndromes, the physiologic severity of coronary artery stenosis by perfusion imaging is not the question addressed in the prior section on physiologic severity of coronary stenosis. The distinction characterizing these chronic coronary syndromes is usually chronic total coronary occlusion with collateral perfusion or chronic subtotal occlusion with low forward coronary flow.

Myocardial perfusion for these conditions remains essential for interpreting the metabolic images. Equally important for clinical decisions, quantitative perfusion also provides valuable information on the flow capacity of surrounding donor coronary arteries supplying the collaterals at risk from stenosis or diffuse disease of the supply arteries feeding the collaterals. Collateral steal during vasodilator stress is integral to quantifying the interaction of supply arteries, the region supplied by collaterals, and the "viability" of this region.

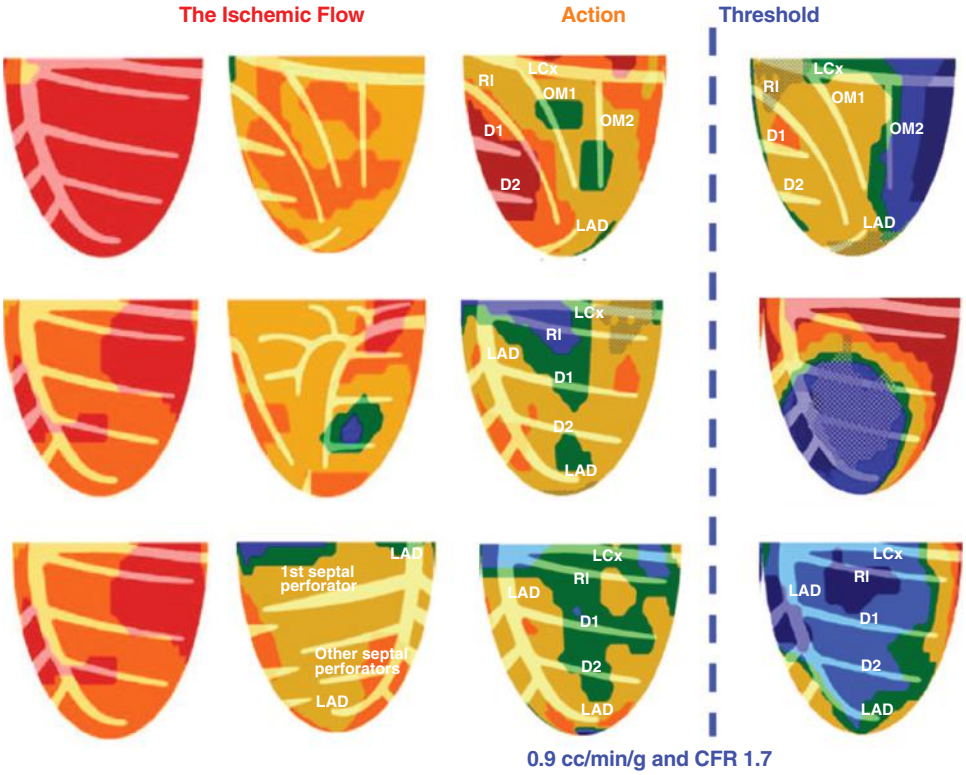


FIGURE 19–36. Complexity made simple—quantitative myocardial perfusion to guide management of coronary artery disease (CAD). Single views of the coronary flow capacity map from 12 different patients covering the ranges of perfusion abnormalities from healthy young volunteers to severe CAD to the right of the dashed blue threshold line of coronary blood flow capacity severity associated with angina and significant electrocardiographic changes during dipyridamole stress potentially appropriate for revascularization. Adapted with permission from Johnson NP, Gould KL: Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging*. 2012 Apr;5(4):430-440.[57]

CLINICAL MYOCARDIAL METABOLISM

With adequate oxygenated coronary blood flow, the myocardium preferentially metabolizes fatty acids aerobically as its primary source of energy for contraction. Following a high-sugar or a high-carbohydrate meal, the myocardium adapts by switching a substantial portion of its energy requirements for contraction to aerobic glucose metabolism. Ischemia resulting from low blood flow or hypoxia interrupts aerobic metabolism of either fatty acids or glucose. The myocardium then switches to anaerobic metabolism of glucose with production of lactic acid because complete metabolism to carbon dioxide requires an adequate supply of oxygenated coronary blood flow.

Under conditions of reduced coronary flow or hypoxia, the myocardial shift to anaerobic metabolism of glucose can provide only limited energy for contraction as a result of the accumulation of lactic acid, impeding further anaerobic metabolism of glucose and impeding LV contraction. Although this low-level fuel source from anaerobic metabolism of glucose at low coronary perfusion may inhibit regional contraction, it provides sufficient metabolism to maintain noncontracting myocardial cell integrity for prolonged periods of hours to even years, at least in some patients. The dysfunctional myocardium recovers aerobic metabolism and contractile function on restoration of adequate oxygenated blood flow, hence the term *hibernating myocardium*.

Sustained metabolic activity for production of high-energy phosphate is fundamental for survival of functionally compromised myocardium. Maintenance of cell membrane integrity and transmembrane ion concentration gradients depends on sustained ATP production and availability. As demonstrated in both human and animal investigations, chronic segmental myocardial dysfunction is associated with profound alterations of fuel substrate metabolism.[85-87] Selection of fuel substrates shifts from free fatty acid to the more energy-efficient glucose with an increase in regional anaerobic glycolysis. This transcriptionally regulated shift in regional substrate usage and metabolism has been referred to as "recapitulation of the fetal gene program."[88] Regionally increased glucose uptake is therefore considered a hallmark of reversibly dysfunctional myocardium that is readily identifiable with 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET) imaging. Such imaging is clinically useful for risk assessment and for predicting postrevascularization regional and global LV function or long-term survival.

The noninvasive study of the myocardium substrate's metabolism with PET extends beyond coronary perfusion and delivery of products necessary for metabolism. Energy-generating substrate oxidation relates to external cardiac work, myocardial efficiency, myocardial changes in energy needs, and substrate availability by shifting its metabolism among substrates in normal healthy myocardium. A wide spectrum of radionuclide probes is available for imaging these metabolic shifts, ranging from radiolabeled myocardial fatty acid, glucose, lactate, and amino acid metabolism to neuronal control and activity.

The radioligand 18F-FDG is the most important and widely used for clinical applications. As a glucose analog, it tracks the initial transport of glucose from blood into cells and its phosphorylation to glucose-6-phosphate as the initial metabolic step of transformation of exogenously derived glucose. Because phosphorylated 18F-FDG cannot be metabolized further, it is metabolically trapped in the cell and accumulates in tissue in proportion to rates of exogenous glucose utilization. However, the radiotracer 18F-FDG is not cell specific for myocardium. It also traces glucose utilization in different organs such as skeletal muscle and brain as well as in tumors and inflammatory processes. Therefore, 18F-FDG is clinically useful for imaging regional myocardial metabolism and for identifying inflammatory disease of the cardiovascular system.

DEFINITIONS OF MYOCARDIAL VIABILITY, HIBERNATING, AND STUNNED MYOCARDIUM

The term *viable* is rather broad because, by definition, it also applies to normally contracting myocardium with adequate perfusion as well as ischemic myocardium with normal resting contraction without scar. The term *potentially reversible contractile dysfunction* is a more accurate term but is seldom used in clinical cardiology. By common use, *myocardial viability imaging* implies poorly contracting myocardium caused by chronic or transient low myocardial perfusion that recovers contractile function with restoration of normal perfusion. Although improved segmental contractile function following revascularization serves as a measure of *myocardial viability*, more definitive clinical outcome measures include postrevascularization improvements in global LV function, in heart failure symptoms, and in long-term survival.

Mechanisms of reversible contractile dysfunction include *myocardial hibernation* and *myocardial stunning*. *Myocardial hibernation* is a response to chronically reduced resting myocardial blood flow, where the myocardium downregulates its energy expenditures for contractile work so that the diminished energy demand matches the diminished energy supply. Associated with this downregulation, the myocardium switches substrate selection from fatty acid to glucose as a more oxygen-efficient substrate to accommodate the reduced supply of coronary perfusion that is available.

Alternatively in animal experiments, hibernation may result from severe reductions in CFR without occlusion associated with increased glucose extraction, leading to a secondary decrease in resting blood flow due to the efficiency of aerobic glucose metabolism.[89,90] Findings in patients with ischemic cardiomyopathy support the latter mechanism where the extraction of 18F-FDG and, thus, of glucose, increases with declining CFR. Rates of glucose extraction were found to be highest at flow reserves of about 1.2.[91] In hibernating myocardium, importantly, energy-producing cellular processes are maintained, although at a lower level, with high-energy phosphates expended mostly for the maintenance of transmembrane ion concentration gradients and for facilitation of basic cell maintenance rather than active contraction.[92]

Myocardial stunning is the myocardial response to a transient ischemic episode caused by a severe but transient decline in coronary flow or an increase in cardiac work without adequate flow increase (demand-induced ischemia). Following the ischemic episode, blood flow promptly recovers but contractile dysfunction of the postischemic myocardium initially persists (ie, "stunning") and recovers only gradually over subsequent hours, weeks, or months.[93,94] In this scenario, repeated ischemic episodes interrupt the recovery of contractile function, leading to chronic impairment of contractile function despite normal resting coronary blood flow. A distinct feature of "repetitive" or "chronic stunning" is therefore the relatively well-preserved coronary flow at rest, which differs from the diminished resting coronary flow in "hibernating myocardium." Apart from hibernation, regional flow reductions may also reflect scar tissue and infarcted myocardium with irreversible loss or impairment of contractile function. As summarized in Table 19–4, the diagnostic challenge is therefore to identify the potential reversibility of functionally impaired myocardium with diminished blood flow.

In patients, hibernation likely coexists with stunning in dysfunctional but viable myocardium. The delicate balance between supply and demand, although at a lower level, combined with the severe impairment in flow reserve renders "hibernating" myocardium susceptible to temporary increases in demand as, for example, related to physical and mental stress during daily life so that ischemia and stunning are superimposed

TABLE 19–4. Definition of Terms Used for Assessing Myocardial Viability: Low Ejection Fraction (EF) or Left Ventricular (LV) Change Better After Percutaneous Coronary Intervention (PCI)/Coronary Artery Bypass (CAB)

Hibernating myocardium

- Severe chronic ischemia
- Reduced LV function
- Reduced perfusion at rest

Stunned myocardium

- Severe transient ischemia
- Reduced LV contraction
- Normal perfusion at rest
- Large severe stress defect

Cardiomyopathy: no defects, low LV ejection fraction

on hibernation.[91,93,95] This possibly accounts for the "incomplete adaptation to ischemia" and for progressive loss of viable tissue.[96]

IMAGING MYOCARDIAL VIABILITY

Imaging Perfusion and 18F-FDG Uptake

Regional increases in myocardial glucose utilization are most reliably identified by comparing the myocardial 18F-FDG uptake with myocardial perfusion. Resting myocardial perfusion is typically acquired first followed by assessment of 18F-FDG uptake. 18F-FDG is administered intravenously with image acquisition beginning 1 hour later. The F-18 glucose analog, F-18 fluorodeoxyglucose (FDG) is taken up by viable myocardium in the LV regions of low resting perfusion, thereby imaged as a perfusion-FDG mismatch.[97] This perfusion-FDG "abnormal mismatch" pattern of high 18F-FDG uptake in regions of low resting relative perfusion is the hallmark of hibernating myocardium.

Stress myocardial perfusion imaging after the rest perfusion image before 18F-FDG imaging may add clinically useful diagnostic information. Although not essential for the assessment of viability, rest-stress perfusion imaging can delineate the extent and severity of epicardial coronary artery disease and provide explanations for increases in myocardial 18F-FDG uptake in normally perfused but dysfunctional regions of myocardium. A stress-induced perfusion defect reflects a regional impairment in myocardial flow reserve and identifies the dysfunctional myocardium as chronically stunned. Furthermore, stress perfusion images aid in identifying possible reasons for impairments in LV function. Different from ischemic cardiomyopathies with regional stress-induced perfusion defects, myocardial perfusion in nonischemic idiopathic dilated cardiomyopathy is characteristically homogeneous both at rest and during vasodilator stress.

PATTERNS OF PERFUSION: 18F-FDG IMAGES

Figure 19–37 illustrates the four basic clinical perfusion-FDG image patterns in topographic simple 3D format as in the prior section of this chapter:

- Normal perfusion and normal FDG or "normal match" of healthy subjects or patients with low EF caused by nonischemic cardiomyopathy (A)
- Abnormal perfusion and abnormal FDG or "abnormal match" of myocardial scar (B)

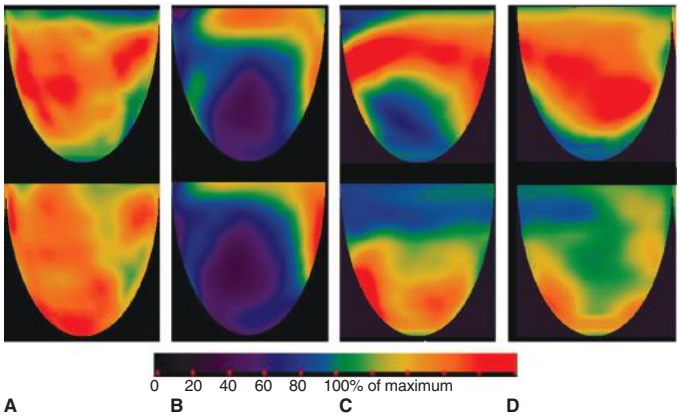


FIGURE 19–37. Single topographic views of left ventricle with patterns of relative perfusion and 18F-FDG images. The color bar scales the relative activity with red being 100% of relative maximum activity. (**A**) Normal perfusion and normal 18F-FDG or "normal match." (**B**) Abnormal perfusion and abnormal 18F-FDG or "abnormal match" of myocardial scar. (**C**) Abnormal perfusion and normal 18F-FDG or "abnormal mismatch" of hibernating myocardium. (**D**) Normal perfusion and low 18F-FDG uptake or "reverse mismatch" of adequately perfused myocardium metabolizing fatty acids rather than glucose.

- Abnormal perfusion and normal 18F-FDG or "abnormal mismatch" of hibernating myocardium in the distal half of the LV (C)
- Normal perfusion and low FDG uptake or "reverse mismatch" of adequately perfused myocardium metabolizing fatty acids rather than glucose (D)

In C, the base of the LV also shows a "reverse mismatch" with normal perfusion and preferential fatty acid metabolism. There is no 18F-FDG uptake proximal to the chronic LAD occlusion with distal hibernating myocardium demonstrating low perfusion and high 18F-FDG uptake.

Despite carbohydrate loading, some patients may have normally perfused LV regions that preferentially metabolize fatty acids with no 18F-FDG uptake thereby causing a "normal reverse mismatch" pattern (see Fig. 19–37D). Finally, nonischemic cardiomyopathy with poor contractile function has normal perfusion and 18F-FDG images with a "normal match" 18F-FDG–perfusion pattern as in a normal heart with a reduced EF. Commonly, patients may have combinations of all these patterns in different regions of the LV, particularly diabetic patients with myocardial transmural scar, substantial border zones of nontransmural scar, hibernating myocardium, and/or ischemia with a component of diabetic cardiomyopathy as well.

Tomographic Display and Analysis of Perfusion and Metabolism Images

Transaxially acquired perfusion and metabolism images are reoriented into short- and vertical- and horizontal long-axis slices, using the same reorientation parameters for both (Figs. 19–38 to 19–41). Visual assessment of myocardial radiotracer concentrations employs the standard 17-segment model and grades segmental radiotracer activity concentrations separately for the perfusion and 18F-FDG images on a four-point scale, where 1 is normal; 2, mildly reduced; 3, moderately reduced; and 4, severely reduced or absent radiotracer activity.[98] Differences in segmental radiotracer uptake between perfusion and metabolism images of at least one grade are considered "segmental metabolism perfusion-mismatches." The sum of segments with mismatch scores represents the extent of potentially reversible dysfunctional myocardium. The sum of all segmental mismatch scores serves as a measure of the combined extent and severity of the "mismatch myocardial region" or the amount of viable myocardium.

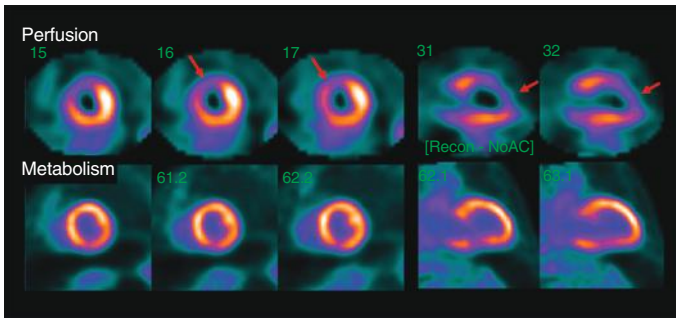


FIGURE 19–38. Myocardial viability with positron emission tomography myocardial perfusion and 18F-FDG imaging. Selected short- and vertical long-axis images of myocardial perfusion and 18F-FDG uptake. Perfusion is severely reduced in the anterior wall while 18F-FDG uptake is fully preserved, consistent with a perfusion metabolism mismatch and viable myocardium.

Semiquantitative information on regionally increased 18F-FDG uptake relative to blood flow is available through polar or topographic map analysis of the PET 18F-FDG and perfusion images as in Fig. 19–42. The analysis approach defines myocardial regions with the highest relative flow-tracer uptake as "normal" as the reference for normalizing the 18F-FDG polar maps. "Mismatches" between metabolism and perfusion are identified by subtracting the perfusion from the normalized metabolism polar maps (regional differences) (see Fig. 19–42). Regional count differences are compared to a database of normal values and predetermined thresholds defined as "mismatches" of 18F-FDG uptake relative to perfusion. Accordingly, the quantitative image analysis approach generates a map of the geographic distribution and the total amount of viable (perfusion defect metabolism mismatch), nonviable (perfusion defect metabolism match), and normal myocardium (no perfusion defect normal metabolism match). Based on postrevascularization outcomes in regional wall motion, differences of more than two SDs from the normal indicate potential reversibility of wall motion impairment.[99] Importantly, the approach identifies those myocardial regions with increased extraction of 18F-FDG and thus of glucose relative to blood flow as an indication of persisting energy-producing metabolic processes that are essential for cell survival and identification of myocardial viability likely to benefit from improved coronary blood flow.

Evaluation of Glucose Metabolism, Only Without Perfusion Imaging

Some laboratories employ 18F-FDG imaging only for the assessment of reversible contractile dysfunction. Myocardial segments with normal

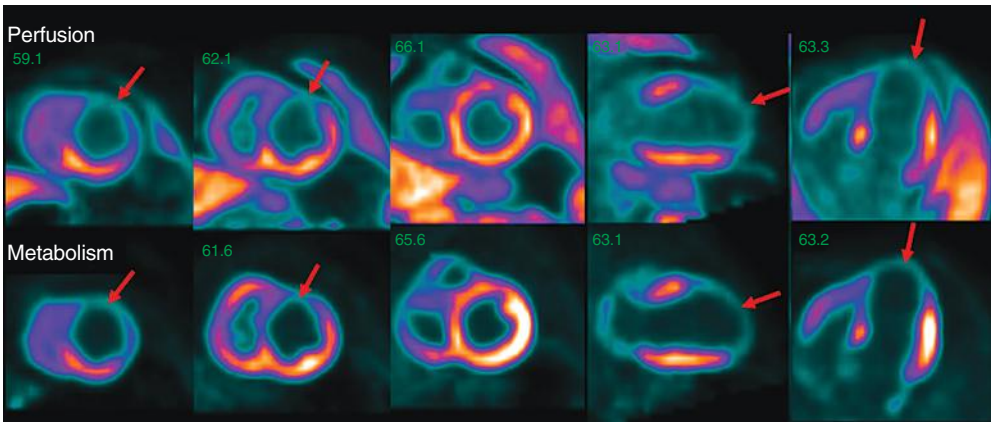


FIGURE 19–39. Myocardial viability with positron emission tomography myocardial perfusion and 18F-FDG imaging. On the selected reoriented views, perfusion is severely reduced in the anterior wall, the apex, the distal inferior wall, and the interventricular septum. On the 18F-FDG images, metabolic activity is decreased in proportion to blood flow, consistent with a perfusion metabolism match and absence of myocardial viability, reflecting scar tissue.

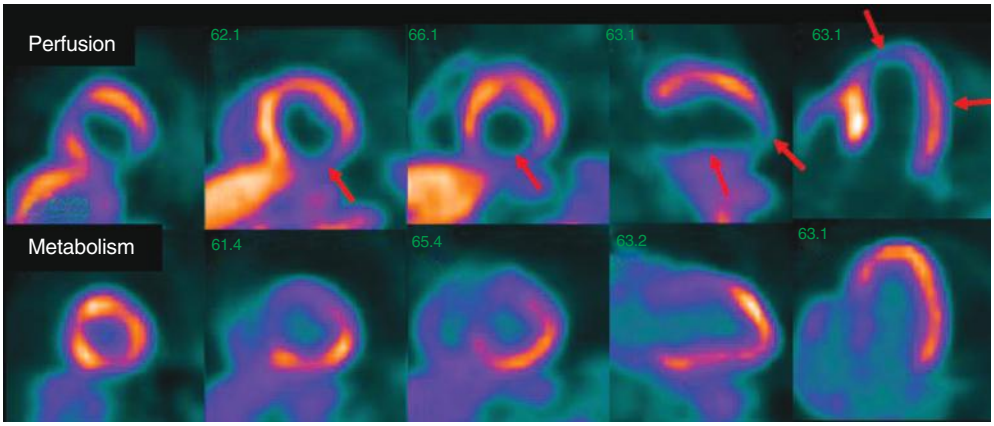


FIGURE 19–40. Myocardial viability with positron emission tomography myocardial perfusion and 18F-FDG imaging. The short-axis and vertical and horizontal long-axis images reveal an extensive moderate to severe perfusion defect in the distal anterior wall, the apex, and the inferior and inferolateral walls. Metabolic activity as shown on the 18F-FDG images is preserved throughout the hypoperfused myocardium, consistent with a large perfusion metabolism mismatch and thus myocardial viability. Note the low 18F-FDG uptake in apparently normally perfused myocardium, related to the patient's fasting prior to the study, leading to suppression of 18F-FDG uptake in normal myocardium.

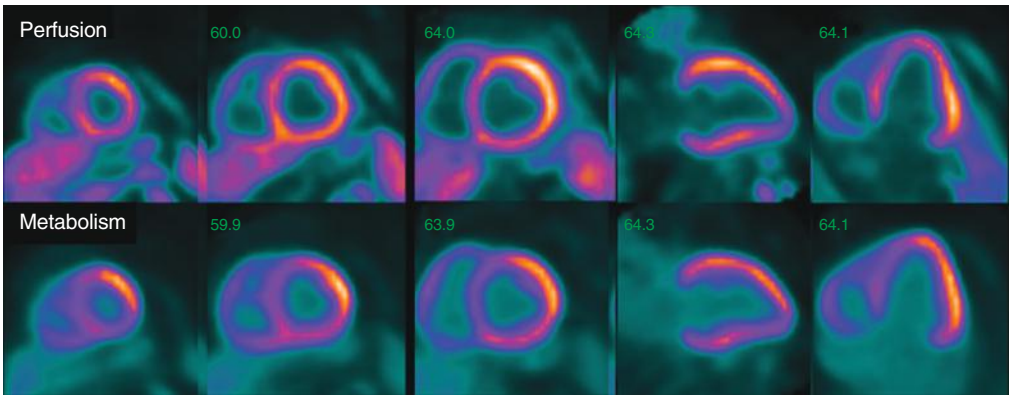


FIGURE 19–41. Positron emission tomography myocardial perfusion and 18F-FDG images in a patient with idiopathic dilated cardiomyopathy. Note the enlarged left ventricle with homogeneous perfusion and glucose uptake.

or only mildly reduced (ie, < 50%) 18F-FDG uptake are considered reversibly dysfunctional, whereas segments with more severe reductions in 18F-FDG uptake (usually > 50%) are considered to be irreversibly dysfunctional.[100-103] Acquisition of gated 18F-FDG images affords assessments of regional myocardial systolic thickening as an additional parameter of viability.[103]

Although relatively high predictive accuracies for identifying reversibly and irreversibly dysfunctional myocardial segments have been reported,[101,104] imaging 18F-FDG only may be diagnostically limited. Dysfunctional myocardial regions with only mild matched perfusion and metabolism defects that do not recover function following revascularization are identified as viable by 18F-FDG imaging only.[105] Conversely, in regions with more severe reductions in 18F-FDG uptake, defined by the 18F-FDG–only approach as "nonviable," the 18F-FDG uptake may substantially exceed regional flow and, thus, reflect the presence of viable myocardium. Moreover, the variability of 18F-FDG uptake in normal myocardium (ie, low or no uptake because of fasting, fatty food, or diabetes), frequently limits accurate identification of "viable myocardium" without characterization of perfusion. Importantly, it is the regionally increased extraction fraction of glucose as the hallmark of "myocardial viability," which can be determined only by relating 18F-FDG uptake to myocardial perfusion.[91]

Absolute rates of glucose utilization have little value for predicting postrevascularization outcomes[100] because of substantial heterogeneity of functional cellular compromise and injury in hypoperfused myocardial regions, lack of adequate control normal regions or patients, assumptions in the metabolic models, and lack of standardized protocols for quantifying myocardial glucose consumption.

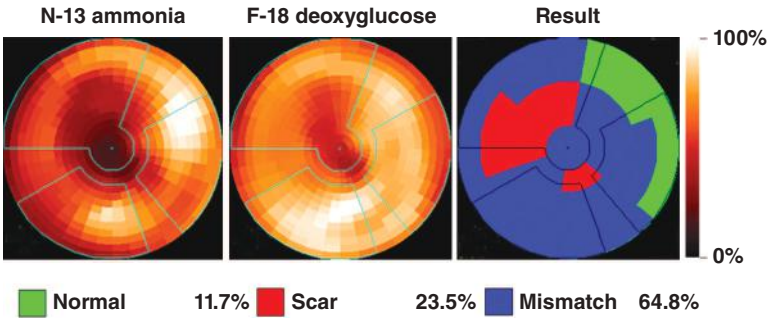


FIGURE 19–42. Polar map analysis of perfusion (N-13 ammonia) and glucose uptake (18F-FDG) images. Note the extensive perfusion defect in the interventricular septum and anterior wall associated with reduced 18F-FDG uptake. The "results" polar map delineates an extensive perfusion metabolism mismatch (segments in blue), a perfusion metabolism match (shown in red, reflecting scar tissue) with well-preserved 18F-FDG uptake and perfusion in the lateral and inferior wall, consistent with normal myocardium shown in green. Images derived with "Munich Heart" software package.

PRE-PET PATIENT PREPARATION AND STANDARDIZATION OF STUDY CONDITIONS

In view of these complex adaptive metabolic pathways, the preceding preparation in the 24 hours before and at the time of the 18F-FDG PET scan is essential for clinically reliable results. This pre-PET preparation is largely due to the myocardium's ability to shift its energy needs among several fuel substrates including free fatty acid, glucose, and lactate. Selection of fuel substrates depends on their concentrations in blood, adequate oxygenated coronary blood flow, prior carbohydrate or fatty food, and hormonal influences. Complicating factors include diabetes mellitus, insulin resistance, and elevated blood catecholamine concentrations, frequently present in heart failure patients. Standardization of study conditions for perfusion metabolism imaging seeks to maximize myocardial glucose utilization and, thus, 18F-FDG uptake for diagnostic assessment of viability. High carbohydrate meals in the 24 hours before the 18F-FDG PET are necessary to precondition myocardium toward glucose metabolism and inhibit fatty acid metabolism. For resting perfusion-FDG imaging without stress, high-carbohydrate food can be eaten up to 2 hours before the scan. For combined vasodilator stress imaging with 18F-FDG after the stress perfusion image, patients should fast for four hours before the study. At the PET scan, several standardization protocols are available:

1. Oral glucose loading. After an approximate 5-hour fasting period, oral glucose (50-100 g) is administered orally about 1 hour prior to the 18F-FDG injection. Besides suppressing circulating free fatty acid levels, glucose loading raises plasma glucose concentrations and stimulates insulin secretion.
2. Administration of the antilipolytic agent acipimox. Acipimox diminishes lipolysis and, therefore also circulating free fatty acid levels. It also increases glucose levels caused by prior carbohydrate ingestion.
3. Euglycemic-hyperinsulinemic clamping.[90] This entails continuous infusion of insulin with coinfusion of glucose at rates to maintain the plasma glucose concentrations within the range of normal. Among the standardization approaches, glucose clamping most consistently produces high-quality diagnostic 18F-FDG images. However, it is so labor intensive that its use has remained confined to investigational settings.

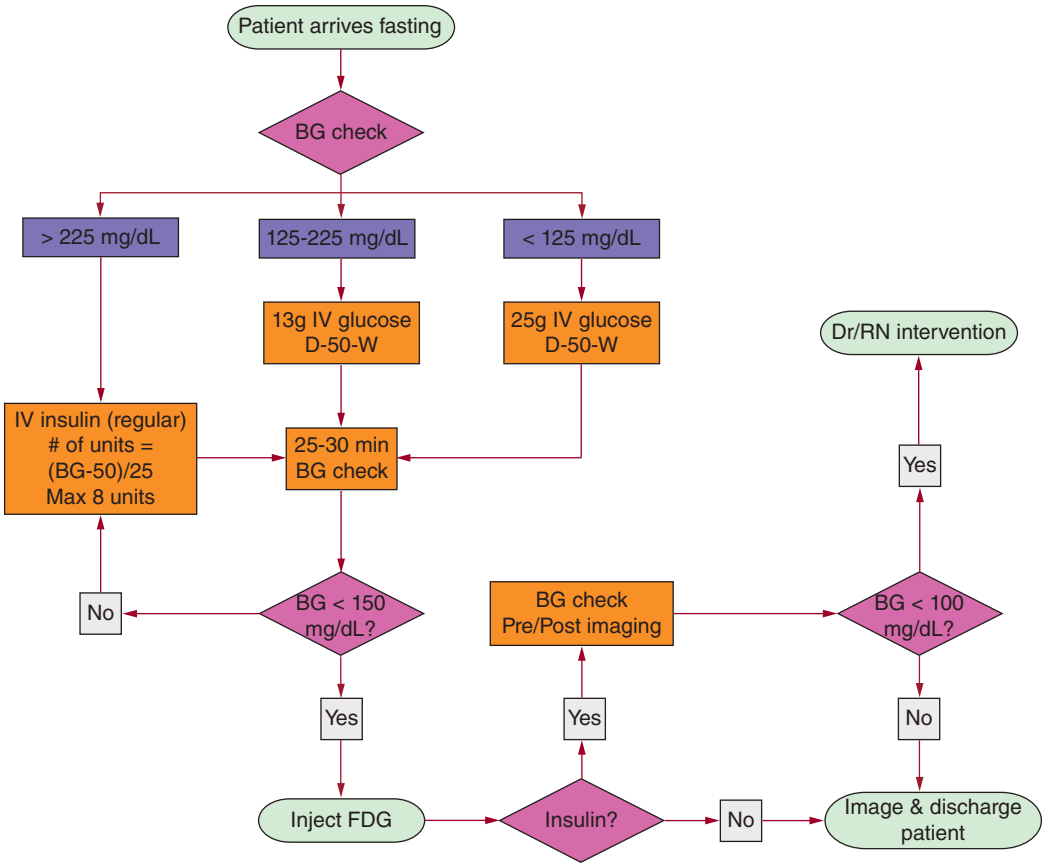


FIGURE 19–43. Protocol for intravenous glucose and insulin to optimize myocardial 18F-FDG imaging. The dose of glucose and insulin vary depending on fasting blood sugar at the time of PET imaging as shown. In this 18F-FDG protocol, a baseline finger stick blood sugar determines the next step. If the blood sugar is more than 225 mg/dL the patient is given iv regular insulin according to the sliding scale where number of units equals (blood sugar – 50)/25 with a maximum of 8 units. If the blood sugar is 125 to 225 mg/dL, 13 grams of glucose from a vial of dextrose 50 g in water is given IV. If the blood sugar has fallen to less than 150 mg/dL in 25 to 30 minutes, 18F-FDG is injected IV. If the baseline blood sugar is less than 125 mg/dL, 25 g from the D-50-W vial is given IV and blood sugar checked 25 to 30 minutes later. If the blood sugar is less than 150 mg/dL, FDG is injected IV. After IV injection of 18F-FDG, test myocardial images are obtained at 25 to 30 minutes. Test myocardial uptake images are continued for up to 1½ hours until good myocardial uptake images with blood pool clearing are obtained. After final image acquisition, if insulin was given, blood sugar is checked after imaging; if less than 100 mg/dL, the physician or nurse decides whether or not to give more IV glucose for stabilization before leaving the positron emission tomography (PET) laboratory. If no insulin is given, the patient is discharged from the PET laboratory. BG, blood glucose by fingerstick; D-50-W dextrose 50 g in water; Dr/RN Intervention, physician or registered nurse makes all decision to give insulin or more IV glucose based on the fingerstick blood glucose levels before and after FDG imaging.

4. Hybrid approach. After high-carbohydrate foods during the preceding 24 hours, a modified relatively simple insulin semiclamp can be easily applied clinically according to the protocol in Fig. 19–43 with excellent results in 98% of cases (protocol B[106]). Just prior to the PET 18F-FDG study, measure fingerstick blood sugar to determine the need for intravenous glucose and insulin to enhance myocardial uptake of 18F-FDG for optimally differentiating viable myocardium from scar. The loading dose of intravenous glucose and addition of regular insulin intravenously depends on the baseline blood glucose as in Fig. 19–43. The aim is a controlled intravenous glucose load followed by a decreasing blood glucose indicating adequate response to native or exogenous injected insulin, thereby ensuring myocardial uptake of FDG.

COMPLEX CASES MANAGEMENT DRIVEN BY PET PERFUSION AND VIABILITY IMAGING

The following cases show progressively complex cases in whom PET perfusion–18F-FDG imaging guided management, particularly revascularization procedures versus medical management.

Case 15: Primarily Hibernating Myocardium with Minimal Nontransmural Scar

A 75-year-old diabetic woman with daily moderate to severe resting and exertional angina was referred for rest/viability PET to determine treatment of an occluded LCX, occluded RCA artery, and severe LAD-diagonal disease. Resting perfusion images (Fig. 19–44) showed large, severe, contiguous, anterior, apical, lateral, and inferior perfusion defects involving 60% of the LV in the distribution of the mid LAD, mid LCX, and RCA coronary arteries. 18F-FDG metabolic images showed myocardial uptake of 18F-FDG, indicating viability of essentially the entire heart with only a small distal inferior nontransmural scar comprising 3% of the LV taking up less 18F-FDG. ECG-gated PET perfusion images showed EF reduced to 36%. The PET viability scan suggested that surgical revascularization was appropriate because of the large area of underperfused, viable, hibernating myocardium comprising 56% of the LV.

Case 16: Transmural Scar, Hibernating Myocardium, and Low EF in Multivessel Distribution

The 65-year-old man with images in Fig. 19–45 was referred for PET because of recent abnormal ECG and 6-month history of exertional,

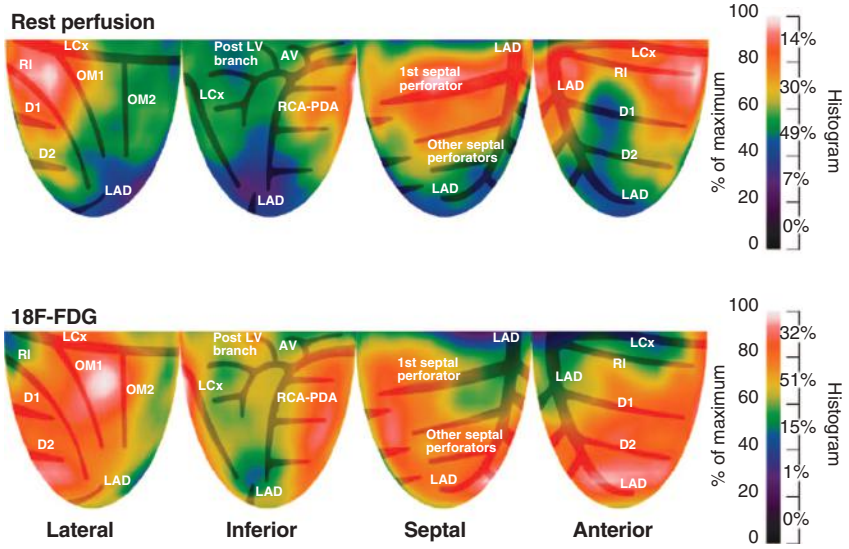


FIGURE 19–44. Case 15. Patient with primarily hibernating myocardium with minimal nontransmural scar. Relative rest perfusion and 18F-FDG images are color coded by the scale for relative myocardial uptake. The histogram on the right side of the color scale gives the percent of the left ventricle in each range of relative uptake.

epigastric discomfort, chest pain, and throat tightness, all provoked by dyspnea. He had two prior percutaneous coronary interventions with drug-eluting stents to the LAD in 2005 and the third obtuse marginal in 2007; the most recent pharmacologic SPECT nuclear stress test demonstrated normal perfusion images.

The relative rest and stress PET images showed a large, severe, lateral, apical, mid-anterior, and distal inferior, resting scar or hibernating myocardium involving 60% to 70% of the left ventricle in the distribution of the left circumflex, mid-posterior descending, and mid-left anterior descending coronary arteries. After dipyridamole, the defect was minimally worse, indicating fixed scar or viable, low-flow, hibernating myocardium.

The viability 18F-FDG images showed substantial mismatch with active FDG uptake in anterior, septal, and apical regions, indicating hibernating, viable, hypoperfused myocardium in mid to distal LAD and RCA distributions comprising approximately 30% of the LV. The lateral LV had a predominantly transmural scar comprising 25% of the LV with an additional 10% of the anterior, anterolateral wall, apex, and

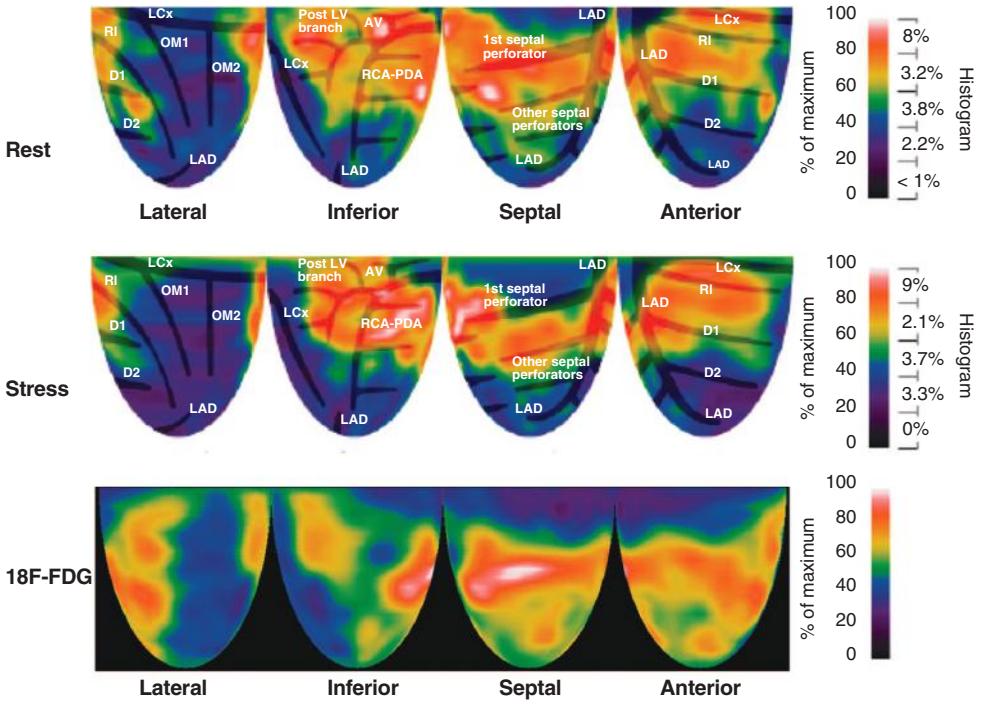


FIGURE 19–45. Case 16. Patient with transmural scar, hibernating myocardium, and low ejection fraction. Relative rest and stress myocardial perfusion and 18F-FDG images are color coded by the scale for relative myocardial uptake. For the rest stress relative perfusion images, the histogram on the right side of the color bar scale gives the relative activity as percent of maximum (100%) and percent of the left ventricle in each range of relative perfusion.

basal inferior wall being viable and hibernating in the distribution of a large first OM branch. Therefore, cumulatively, 40% of the LV was metabolically viable, underperfused, hibernating, and akinetic, but it was potentially salvageable by revascularization of the LAD and OM coronary arteries. Approximately 25% of the LV was fixed scar and 35% was normally perfused.

Absolute myocardial perfusion combining CFR and maximal cc/min/g showed severely reduced perfusion in the large defect and normal perfusion in the basal regions. In the transmural scar, resting and stress perfusion were 0.2 cc/min/g and minimum CFR was 0.8, indicating myocardial steal with border zones of mixed hibernating myocardium, scar, and myocardial steal associated with collaterals in the OM distribution. Gated PET perfusion images showed abnormal LV contraction with severe, anterior, apical and lateral hypokinesis and an EF of 40%. Based on the PET scan, coronary arteriography with revascularization procedures are indicated because of the size and severity of the rest-stress-FDG PET findings. After bypass surgery, the EF increased to 53% with residual apical hypokinesis and resolution of symptoms.

Case 17: Complex Mix of Transmural Scar, Border Zone Nontransmural Scar, and Hibernating and Ischemic Myocardium in Multivessel Distribution

The 82-year-old man whose images are shown in Fig. 19–46 was referred for follow-up PET after a prior abnormal rest stress PET study 22 years previously demonstrated an occluded collateralized LAD. He was asymptomatic, and no intervention was performed at that time. He remained asymptomatic until 6 months prior to the current follow-up PET, when he developed leg weakness, fatigue, and dyspnea during walking without chest pain.

Relative PET images showed a moderate-sized, severe, anterior, resting perfusion defect involving 15% of the LV in the distribution of a distal diagonal branch. In addition, there was a large, severe, lateral resting perfusion defect involving 20% of the LV in the distribution of the mid-LCX distal to the first OM branch. After adenosine, the anterior defect was slightly larger in the proximal border zones, indicating predominantly nonviable myocardium with a small proximal border zone of viable myocardium with reduced CFR. The lateral resting defect was also larger, indicating viable ischemic border zones with reduced coronary flow capacity. 18F-FDG images showed separate small transmural scars each comprising 10% of LV (anterior) and 8% of LV (basal lateral), cumulatively comprising 18% of the LV as scar. Approximately 27% of the LV was viable and ischemic or viable and hibernating, with the remaining 55% of myocardium having severe diffusely reduced stress flow and CFR but above ischemic levels.

In the transmural scar, minimum rest and stress perfusion was 0.26 cc/min/g and minimum CFR was 0.65, indicating myocardial steal that may be seen in the border zones of scar. Gated PET perfusion images showed abnormal LV contraction with anterior and lateral akinesis with the EF of 41% at rest falling to 24% during adenosine stress. These results indicated severe dysfunction resulting from severe regional abnormalities on the relative images and severe diffuse CAD on the perfusion images (not shown in Fig. 19-46), more apparent than on the relative images. Based on the PET perfusion and 18F-FDG viability images, coronary angiography and revascularization were recommended (1) to salvage approximately 30% of the myocardium that was viable, ischemic, and underperfused and (2) to improve CFR in the remaining approximately 55% of LV with flow-limiting stenosis or diffuse disease.

Case 18: Scar Replaced by Endogenous Stem Cells with Recovery of LV Function

A 69-year-old man whose images are shown in Fig. 19–47 had an anterior MI in 1996 at age 49 years while hunting in the Alaska wilderness. An angiogram 1 week later showed an occluded LAD proximal to the first septal perforator and first diagonal with an EF of 25% to 30% without significant obstructive disease of the left circumflex or right

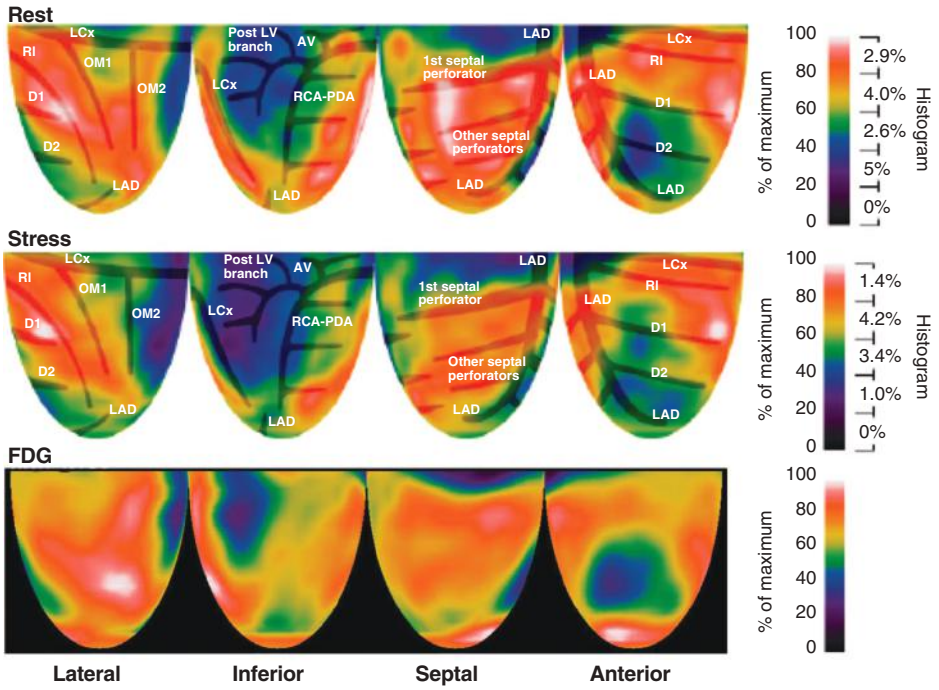


FIGURE 19–46. Case 17. Patient with a complex mix of transmural scar, border zone nontransmural scar, and hibernating and ischemic myocardium. Relative rest and stress myocardial perfusion and FDG images are color coded by the scale for relative myocardial uptake. For the rest stress relative perfusion images, the histogram on the right side of the color bar scale gives the relative activity as percent of maximum (100%) and percent of the left ventricle in each range of relative perfusion.

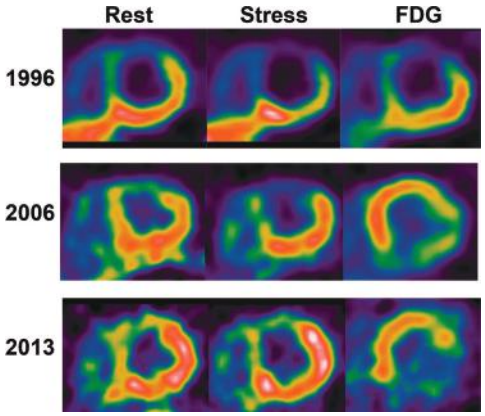


FIGURE 19–47. Case 18. Patient with myocardial scar replaced by endogenous stem cells with recovery of left ventricular function. Relative rest and stress myocardial perfusion and FDG images are color coded for relative activity as in the prior figures.

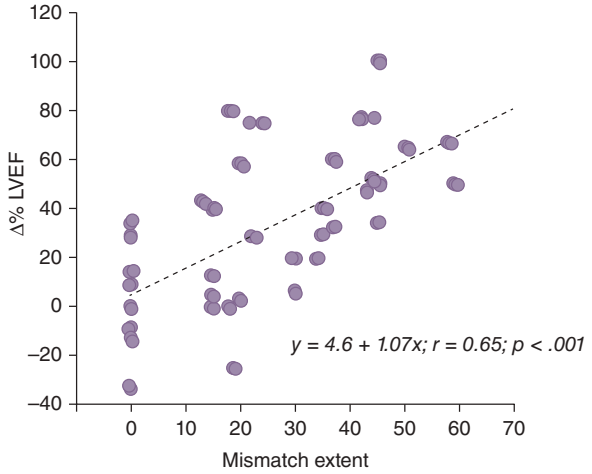


FIGURE 19–48. Postrevascularization improvement in global left ventricular function, change in myocardial blood flow and extent of viable myocardium. LVEF, left ventricular ejection fraction. Data from Schoder H, Campisi R, Ohtake T, et al. Blood flow-metabolism imaging with positron emission tomography in patients with diabetes mellitus for the assessment of reversible left ventricular contractile dysfunction. *J Am Coll Cardiol*. 1999;33:1328-1337.

coronary arteries. Follow-up PET perfusion and 18F-FDG viability imaging showed a large anterior, septal, and apical myocardial scar with insignificant FDG uptake. Treated for heart failure and with vigorous risk-factor management, he remained stable with an EF increasing to 42% in 2002. Follow-up PET imaging in 2006 showed normal 18F-FDG uptake throughout the LV, a normal resting EF of 61%, and a large severe stress-induced perfusion defect during dipyridamole perfusion imaging. PET imaging remained unchanged up to 2013. He received PCI of the LAD, and he underwent implantable cardioverter-defibrillator (ICD) placement because similar patients with recovered LV function had experienced sudden death. Several years later, while lifting 300-lb farm equipment, the man had wide complex tachycardia that electrophysiology determined was probably aberrantly conducted atrial fibrillation; he had an internal shock with no sequelae and no recurrence.

This spontaneous LV recovery prior to any procedures and without exogenous stem cell therapy was so striking that heparinized blood was analyzed for endogenous stem cells. The results showed massive numbers of circulating CD133–/CD34+ stem cells comprising 5% of mononuclear cells compared to 0.03% in a normal control. Repeat blood analysis for circulating stem cells 6 months later showed the same finding. The electrophoretic migration of these cells showed them to be "sticky," indicating a subtype of CD 133–/CD34+ cells not previously identified in the literature. This unknown endogenous CD+34 cell type was associated with striking LV recovery of myocardial scar replaced by normally functioning myocardium over 10 years.

CLINICAL OUTCOMES RELATED TO MYOCARDIAL VIABILITY

Segmental perfusion-metabolism patterns accurately predict improved postrevascularization segmental contractile function. Based on a pooled analysis of 24 clinical investigations in 756 patients, perfusion-metabolism imaging identified myocardial viability with a weighted average sensitivity of 92% and specificity of 63%.[107] Corresponding positive and negative predictive values are 74% and 87%, respectively. Although postrevascularization segmental wall motion provides a measure (or gold standard) of the diagnostic accuracy of perfusion-metabolism imaging, changes in the global LV function are more powerful clinical measures of benefit. Pooled data from three investigations indicate average sensitivities and specificities of 83% and 64%, respectively, for at least a 5% postrevascularization increase in LVEF with positive and negative predictive values of 68% and 80%, respectively.[107]

The degree to which LV function recovers after revascularization depends on the amount of "viable myocardium." To achieve at least a 5% increase in the LVEF requires the presence of "viability" in about 15% to 25% of the LV.[108-110] These thresholds are based on 18F-FDG and SPECT Tc-99m perfusion data. These thresholds may be lower when the extent of viable myocardium is determined from the higher spatial resolution PET perfusion-metabolism images. Postrevascularization improvements in LV function correlate linearly with the extent of viable myocardium (Fig. 19–48).[111,112] A larger perfusion-metabolism mismatch is associated with a correspondingly greater postrevascularization improvement in LV function.

Available evidence suggests that the risk of cardiac death relates to the amount of viable myocardium.[108-112] This finding has been corroborated by two key observations from a prospective study of 260 patients with ischemic heart disease and severely diminished LV function over a mean follow-up period of 2.1 years after a PET perfusion-metabolism study.[113] First, the incidence of cardiac death in patients with clinically significant perfusion-metabolism mismatch of greater than 20% of the LV was significantly lower in those patients who received revascularization than in those treated with medical therapy alone (28% vs 15%; $P < .05$). Second, the risk of death rose in proportion to the amount of viable myocardium in patients with a mismatch greater than 20%. Importantly, small amounts of viable myocardium of less than 7% to 10% of the LV were not associated with an increased risk of death, implying that small amounts of viable myocardium insufficient for a postrevascularization improvement in global LV function do not require revascularization for risk reduction (Fig. 19–49).[114]

Another study of 648 consecutive patients with reduced LV function demonstrated a direct relationship between extent of viable myocardium and the benefits of revascularization.[115] Revascularization conferred a statistically significant benefit for all-cause death in patients with PET a perfusion-metabolism mismatch greater than 10% of the LV myocardium. The survival benefit depended on the extent of viable myocardium and was greatest for mismatch greater than 15%.

The only randomized trial to date, the Positron emission tomography And Recovery following Revascularization (PARR-2) trial,[116] showed no overall mortality advantage of 18F-FDG–guided revascularization compared to standard of care, including aggressive medical therapy and revascularization.[116] However, this negative result

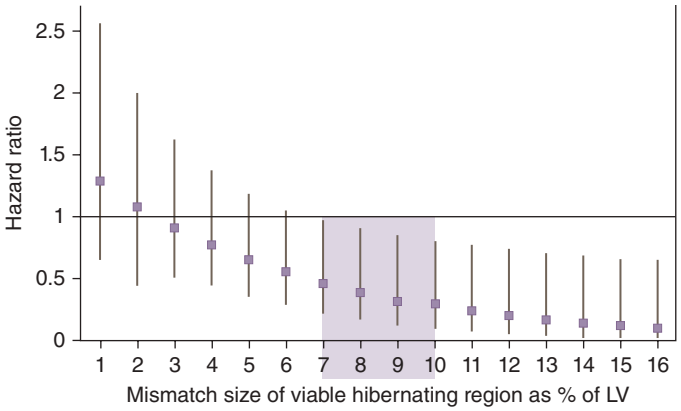


FIGURE 19–49. Risk of a major cardiac event (including cardiac death, nonfatal myocardial infarction, cardiac transplantation, or hospitalization for cardiac reasons) and amount of viable myocardium (defined as mismatch size). LV, left ventricle. Reproduced with permission from D'Egidio G, Nichol G, Williams KA, et al: Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. *JACC Cardiovasc Imaging*. 2009 Sep;2(9):1060-1068.[114]

may have been the result of 30% nonadherent crossovers, wherein revascularization decisions were made contrary to what would have been recommended by 18F-FDG PET results (Fig. 19–50). In fact, in a per-protocol treatment analysis, the patients who underwent 18F-FDG PET–guided revascularization had a significantly better composite outcome comprised of cardiac death, MI, heart transplant, heart failure, or cardiac-driven hospitalization within 1 year) than did patients with non-FDG PET–guided revascularization (see Figure 19–49).[114] For the 182 patients with EF less than 35% and mismatch of 10% or greater, those who received revascularization had a composite outcome that was 40% or lower than the composite outcome for patients without revascularization (see Fig. 19–49).[98] Nonetheless, for resting perfusion defects comprising small regions of the LV, 18F-FDG imaging–guided decisions are not likely to reduce mortality.

Global LV Function

Most studies have reported statistically significant postrevascularization increases in LVEF in patients with viability as compared to no or only minimal improvements in LVEF in patients without viable myocardium.[107] Only a few investigators did not observe such significant improvements in LV function following revascularization.[117,118] Yet these studies still report significant improvements in the response of the LV to exercise and improvements in overall exercise capacity following surgical revascularization. Distinct from the more conventional perfusion-metabolism imaging performed at rest only, these studies identified myocardial viability and its extent from stress perfusion images (when the rest perfusion images were normal) and combined these results with 18F-FDG images at rest to report stress-induced myocardial ischemia. Successful revascularization rectifies the cause of stress-induced ischemic myocardial dysfunction or "stunning" and thus restores the normal functional response to stress.

Revascularization of viable myocardium may lead to reversal of LV remodeling.[119] Ventricular remodeling is known to occur after a non-Q wave MI or, in the absence of a prior infarction, in the presence of dysfunctional, but viable myocardium.[120] The end-diastolic and end-systolic volumes of the LV progressively increase, LVEF declines, and the LV becomes more spherical. Revascularization of reversibly dysfunctional viable myocardium can reverse the remodeling process; follow-up studies 7.6 months after revascularization revealed significant decreases in LV volumes (both in end-diastole and end-systole), an increase in LVEF, and a less spherical shape of the LV.[119]

It is important to emphasize that despite the presence of myocardial viability, even involving an adequate amount of the LV, surgical revascularization may not always be followed by a functional improvement or reversed remodeling of the LV. Fixed subendocardial scar with normal adequate perfused subepicardium as after PCI for acute coronary syndromes may show reduced perfusion with good 18F-FDG uptake but fail to improve function after revascularization. LV function may also fail to improve after revascularization in markedly enlarged LVs with advanced remodeling.[121,122] Increased LV end-systolic volumes or dimensions predicted failure to recover LV function.[121] Large myocardial regions with severely reduced perfusion require longer times for improvement in contractile function after revascularization, sometimes as long as 12 to 18 months.[119,123,124] Finally, myocardial viability may not persist indefinitely but may progress to scar tissue formation.[125,126] In patients with PET demonstrated myocardial viability, for example, LV function failed to improve when revascularization was delayed by an average of 35 days.[126] Hence, there may be a basis for revascularization as soon as possible to avert irreversibility that precludes improvement of LV function after late revascularization.

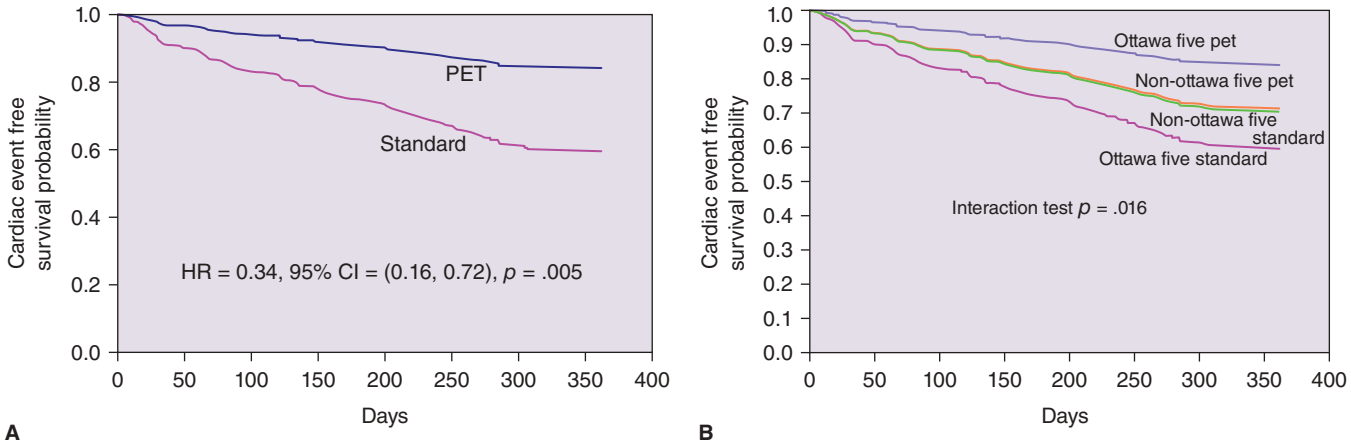


FIGURE 19–50. Positron emission tomography (PET)-guided treatment of patients with ischemic cardiomyopathy. An initial outcome report for the multicenter PAAR trial failed to observe a significant benefit of PET viability assessment (as delineated in **B** as the non-Ottawa FIVE PET). However, in a post-hoc analysis of the clinical trial data, adherence of treatment to PET findings, as done in the OTTAWA-FIVE PET, demonstrated a clear benefit of PET-guided over standard care treatment. As shown in **A,** the cardiac event-free survival was significantly higher in patients with PET-guided treatment as compared to patients with standard care.

Heart Failure Symptoms and Physical Activity

Revascularization of viable myocardium in ischemic cardiomyopathy was also associated with relief of congestive heart failure symptoms.[127] In one study, 81% of patients in New York Heart Association (NYHA) heart failure classes 3 and 4 had improved to class 1 or 2 one year after CABG as compared to an improvement in heart failure symptoms in less than 20% of patients without viable myocardium.[128] Postsurgical improvements in physical activity are related to the amount of viable myocardium with improved physical exercise during daily life prior to and 24 months after CABG.[128] Expressed in metabolic equivalents (METs), the level of physical activity increased by an average 107% in patients with a greater than 18% mismatch as compared to an only 34% increase in patients with a mismatch less than 5% in size.

MYOCARDIAL VIABILITY IN EARLY POSTINFARCTION AND REPERFUSED MYOCARDIUM

Patterns of myocardial perfusion and glucose utilization differ early after an acute MI. In early postinfarction patients without reperfusion, studied within 72 hours of onset of acute symptoms, 50% of regional flow defects were associated with concordantly reduced 18F-FDG uptake; 18F-FDG uptake was preserved or enhanced in the remainder of flow defects.[129] Viability in these patients was associated with residual anterograde flow through the infarct vessel.[130] Contractile function in segments with matching flow and glucose metabolism defects failed to improve on follow-up, whereas some improvement in contractile function was observed in half of the segments with initially persistent metabolic activity.

Persistent 18F-FDG uptake with subsequent improvement in regional contractile function has been reported in some early postinfarction patients, whereas in other patients, regional 18F-FDG activity concentrations in postischemic myocardium were lower than regional flows, a pattern referred to as *reversed mismatch*.[131,132] The size of regions with diminished 18F-FDG uptake exceeds that of contrast enhancement on MRI.[131] Importantly, oxidative metabolism rates determined with C-11 acetate in reverse mismatch regions were not significantly lower than in remote myocardium, and thus were normal, suggesting a possible shift in substrate selection as the reason of the reduced 18F-FDG uptake. Of interest, relative flows in reversed mismatch regions were similar to those in remote myocardium while relative flows in mismatch regions were significantly reduced. This observation raises the question whether flow in reversed mismatch regions had recovered more rapidly than glucose utilization rates and thus accounted for the observed flow metabolism pattern, whereas in mismatch myocardial regions, the recovery of myocardial blood flow was substantially delayed.

Postinfarction Inflammation and Regeneration

Because 18F-FDG uptake is not specific to myocardium, increases in radiotracer uptake in reperfused myocardium may also reflect accumulation of leukocytes in postinfarction myocardium as the result of recruitment of inflammatory cells as active participants in infarct healing and regeneration.[133,134] Indeed, regional increases in 18F-FDG uptake in reperfused myocardium in early postinfarction patients have been demonstrated when radiotracer uptake in remote myocardium had been effectively suppressed by prolonged fasting.[133,135] Although the findings did not fully exclude the possibility of increased uptake in injured myocardium, studies with a novel radiotracer targeting the chemokine receptor CXCR4 as a "central regulator of infarct healing and regeneration" unequivocally demonstrated the postinfarction inflammatory process in early post infarction patients.[136] Thus, increased 18F-FDG uptake in acutely reperfused myocardium may reflect the inflammatory process, the presence of viable myocardium, or both.

Cardiac Disorders Potentially Mimicking Patterns of Perfusion and Metabolism in CAD

Transient apical ballooning, called *Takotsubo (stress) cardiomyopathy*, may mimic an acute coronary syndrome; it affects predominantly postmenopausal women and accounts for 1% to 2% of patients with troponin-positive acute coronary syndromes but with angiographically normal coronary vessels. It has been referred to as *neurogenic myocardial stunning*[137] because it frequently follows a stressful event. Wall motion is typically impaired and perfusion severely diminished in the apical portion of the LV.[137,138] MRI frequently does not show abnormal enhancement, whereas 18F-FDG uptake in the affected myocardial regions is typically reduced in proportion to blood flow (Fig. 19–51). Regionally 18F-FDG uptake may be increased when patients are studied after suppression of 18F-FDG uptake in normal myocardium with prolonged fasting.[137] The changes observed during the acute phase are fully reversible when wall motion, perfusion, and metabolism were examined several weeks later (see Fig. 19–51).[139,140] Finally, *isolated left ventricular noncompaction* may also cause regional myocardial perfusion defects that may or may not be associated with relative increases in regional 18F-FDG uptake.[137,141]

RISK ASSESSMENT AND STRATIFICATION

Assessment of myocardial viability has become clinically important in patients with ischemic cardiomyopathy with severely impaired LV function because of its independent prediction of cardiac risk and on outcomes of treatment. A meta-analysis of long-term follow-up data in 3088 ischemic cardiomyopathy patients in 24 clinical investigations with an average LVEF of 30 ± 8% found the presence of myocardial viability to be associated with a 16% annual mortality in patients treated medically as compared to an only 6.2% annual mortality of patients without viable myocardium (Fig. 19–52).[142]

Surgical revascularization of patients without viable myocardium remained without significant effect on annual mortality (7.7%) but was

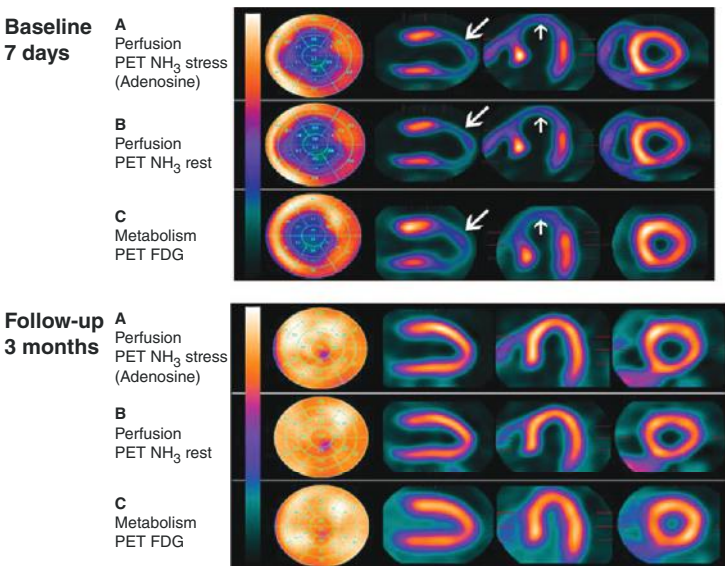


FIGURE 19–51. Positron emission tomography stress and rest perfusion and 18F-FDG metabolism images in a patient with Takotsubo (stress) cardiomyopathy at baseline (7 days after the acute event) and 3 months later. Note the severe and extensive fixed perfusion defect involving the apical half of the left ventricle associated with concordantly reduced 18F-FDG metabolic activity (*upper panel*) with complete restoration of myocardial perfusion in metabolic activity at follow-up (*lower panel*). Reproduced with permission from Ghadri JR, Dougoud S, Maier W, et al: A PET/CT-follow-up imaging study to differentiate takotsubo cardiomyopathy from acute myocardial infarction. *Int J Cardiovasc Imaging*. 2014 Jan;30(1):207-209.[141]

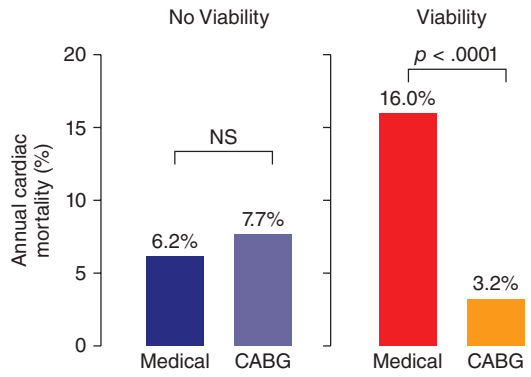


FIGURE 19–52. Meta-analysis of outcome data in patients with viability assessment and medical treatment or surgery revascularization (coronary artery bypass graft [CABG]) as reported by Allman KC and colleagues.[142] Note the high annual mortality in patients with viable myocardium treated medically as compared to the significantly lower mortality of patients after surgical revascularization. In patients without myocardial viability, annualized mortality rates are similar for patients treated medically or with surgical revascularization. Adapted with permission from Allman KC, Shaw LJ, Hachamovitch R, et al: Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol*. 2002 Apr 3;39(7):1151-1158.[142]

associated with a significantly lower annual mortality of only 3.2% in patients with viable myocardium. Revascularization thus substantially reduced the annual mortality of patients with viable myocardium in these studies by as much as 80% in the meta-analysis. Although most studies in the meta-analysis were retrospective, the findings nevertheless strongly suggest that viable myocardium, in ischemic cardiomyopathy with severely depressed LV function, signifies a high risk of cardiac death that is significantly reduced by revascularization.

In response to shortcomings of that meta-analysis, especially the inclusion of retrospective data, the STICH (Surgical Treatment of IsChemic Heart failure) trial attempted to prospectively answer the question whether "coronary artery bypass grafting (CABG) improves survival in patients with ischemic left ventricular dysfunction compared to aggressive medical therapy."[143] In a subgroup of 601 of 1212 patients enrolled in the STICH trial, viability was assessed with SPECT Tc-99m perfusion imaging or with low-dose dobutamine stress echocardiography.[144] Although the viability substudy revealed a significantly lower mortality for patients with than without viability (37% vs 51%; $P < .003$), this difference was no longer significant after adjustments were made for baseline variables. The failure of the STICH substudy to demonstrate survival benefit of patients with myocardial viability and surgical revascularization may be ascribed to the limitation of SPECT imaging and lack of radionuclides specific for and proven to identify viable myocardium and its quantitative extent. In contrast, 18F-FDG PET has shown essential for predicting benefit from revascularization.[145,146]

INDICATIONS FOR PERFUSION-METABOLISM IMAGING

Patients with ischemic cardiomyopathy, severe LV dysfunction, and congestive heart failure symptoms will benefit most from the assessment of myocardial viability. Presence or absence of myocardial viability can substantially contribute to treatment planning. Therapeutic options in these patients include aggressive medical management, revascularization, and cardiac transplantation. Presence of viable myocardium in amounts sufficient for a possible postrevascularization improvement in LV function favors stratification of patients to revascularization provided, of course, that the coronary anatomy is suitable for bypass grafting. Demonstration of viability in these patients not only indicates the high risk of cardiac death if treated medically but also favorably affects the surgical risk-to-benefit ratio, considering the high perioperative risk of these patients.

In patients considered initially for cardiac transplantation, surgical revascularization based on demonstration of extensive amounts of viable myocardium resulted in substantial improvements in LV function and congestive heart failure symptoms together with long-term survival rates that were comparable to those of patients following cardiac transplantation.[147] Even if the coronary anatomy is unsuitable for bypass grafting, the presence of viability is predictive of a more favorable outcome with beta-blocker treatment or with cardiac resynchronization therapy.[148-152] Finally, evaluation of early postinfarction patients for myocardial viability can also aid in deciding on interventions seeking to salvage myocardium compromised by ischemia.[130]

REST-STRESS QUANTITATIVE PERFUSION, MYOCARDIAL SCAR, AND VIABILITY

Large severe relative resting perfusion defects with uptake below 20% to 30% of maximum are most commonly transmural scar by FDG PET. Quantitative perfusion in such defects is commonly 0.2 cc/min/g or less as in the case examples above that may increase somewhat with stress, the hyperemia of scar tissue, or a thin layer of subepicardial myocardial cells. For such very large severe resting perfusion defects, if clinical circumstances indicate, 18F-FDG PET may show substantial viability or more commonly scattered subepicardial foci of viability. For less severe to moderate relative resting perfusion defects, quantitative perfusion may range to near normal, indicating a corresponding range of nontransmural scar. Resting defects with perfusion of about 0.4 cc/min/g or higher suggest sufficient viable myocardium that 18F-FDG PET may not add substantial new information. However, with the high risk of bypass surgery, definitive 18F-FDG imaging is indicated.

With resting perfusion in the range of 0.2 to 0.4 cc/min/g, the clinical question is whether this average transmural perfusion represents viable under perfused transmural hibernating myocardium or fixed nontransmural scar comprised of fixed subendocardial scar with nonischemic adequately perfused subepicardium at resting conditions. Similarly, the mean transmural uptake of 18F-FDG may reflect either mean transmural viable myocardium or the average of no uptake in subendocardial scar with intense subepicardial uptake. In many patients, these possibilities are mixed heterogeneously with transmural scar, border zone nontransmural scar, hibernating, stunned, ischemic, normally perfused myocardium, and primary diabetic or hypertensive cardiomyopathy in the same patient. In these circumstances, combined quantitative rest-stress perfusion and 18F-FDG imaging may be necessary as described above for comprehensively assessing the proportion of viable ischemic, scarred, or normally perfused myocardium in specific arterial distributions for guiding management as in the cases above.

MYOCARDIAL CELLULAR POTASSIUM SPACE, INJURY, AND VIABILITY

Myocardial cell membranes normally maintain high intracellular potassium concentrations compared to the extracellular fluid, thereby maintaining the resting membrane potential of the myocardial cells (Fig. 19–53).[153] Myocardial injury causes potassium to leak out of the cell with an injury current reducing the resting membrane potential manifest as ST-segment elevation on the AC-coupled ECG. However, some intracellular potassium may be retained with a reduced membrane potential associated with potential cell recovery. Restoration of oxygenated coronary blood flow restores normal potassium trapping, normal resting membrane potential, and

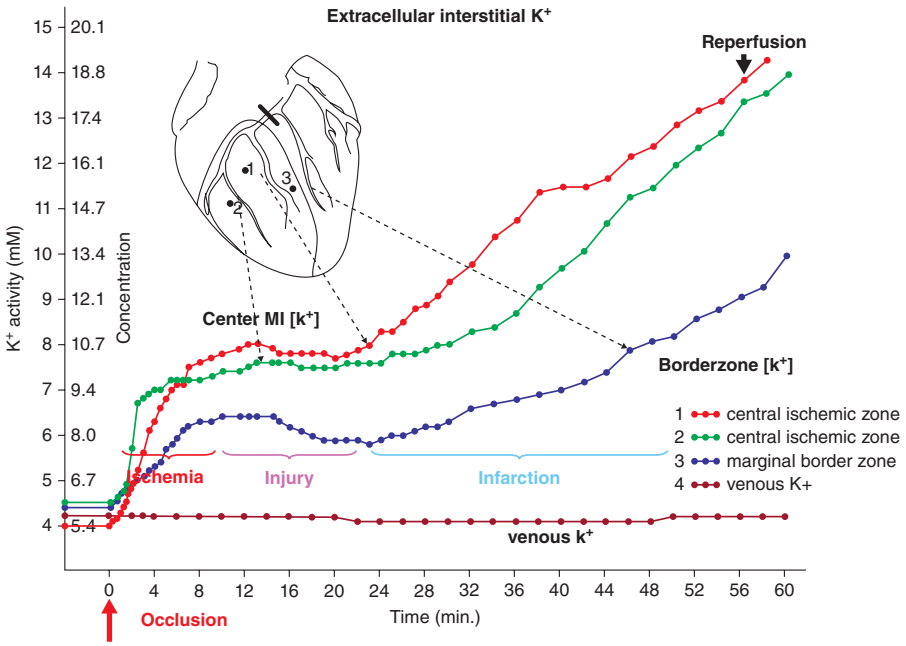


FIGURE 19–53. Loss of myocardial potassium cell trapping after acute experimental coronary occlusion. Adapted with permission from Hill JL, Gettes LS: Effect of acute coronary artery occlusion on local myocardial extracellular K+ activity in swine. *Circulation*. 1980 Apr;61(4):768-778.[153]

some Rb-82 leaking out of the myocardial cells. However, myocardium that fails to trap Rb on standard static 5-minute images is usually scar, the size of which relates to the EF (Fig. 19–54) and adverse outcomes.[155,156] However, 18F-FDG uptake may identify viable myocardium in select cases and remains the definitive modality for assessment of myocardial viability.

As for all perfusion radionuclides, the clinical question is whether residual average transmural trapping of perfusion tracers and perfusion indicates the average of subendocardial scar with subepicardial perfusion or low mean transmural perfusion to viable myocardium. Of course, 18F-FDG images pose the same question. Both experimental infarction and pathology of human infarction indicate that the extent of subendocardial infarction or ischemia is nearly always greater than the extent of subepicardial infarction or injury. For large regions of viability, 15% to 20% of LV, associated with benefit from revascularization, the fine distinction between subendocardial and subepicardial extent of infarction or injury is likely less important than the overall proportion of the LV at risk.

normal contraction. However, with ongoing injury caused by low blood flow ischemia, cell necrosis follows with irreversible loss of all potassium trapping.

The positron emitting potassium analog, Rb-82, follows the distribution of the cellular potassium space of viable myocardium. It is therefore not trapped in myocardial scar associated with severe perfusion defects.[154-157] Residual activity in resting perfusion defects indicates residual myocardium with intact potassium space that traps Rb-82 as a perfusion tracer. Initial Rb uptake may leak back out or wash out of injured myocardium to some extent while 18F-FDG is still trapped, indicating some viability. Therefore, the rate of potassium washout may not reflect viability because myocardium taking up 18F-FDG may show

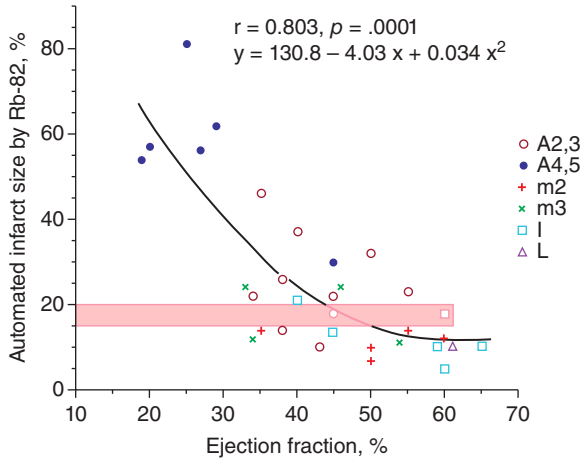


FIGURE 19–54. Size of myocardial scar by perfusion imaging with Rb-82 compared to ejection fraction. The red zone indicates the average size of cardiac scar where ejection fraction begins to fall. Reproduced with permission from Yoshida K1, Gould KL: Quantitative relation of myocardial infarct size and myocardial viability by positron emission tomography to left ventricular ejection fraction and 3-year mortality with and without revascularization. *J Am Coll Cardiol*. 1993 Oct;22(4):984-997.[154]

ALTERNATIVE NON-PET VIABILITY IMAGING

Identification of Viable Myocardium with Perfusion Imaging at Rest with SPECT and Tc-99m-Labeled Flow Tracers

Perfusion in functionally impaired myocardial regions contains information on potential reversibility of wall motion. Blood flow at rest closely follows the distribution of normal myocardium; accordingly, it decreases in proportion to the amount of fibrosis and scar tissue. Transmural tissue concentrations of flow tracers correlate inversely with the transmural amount of fibrosis and scar tissue on histopathologic analysis.[158] Accordingly, regional flow reductions closely and quantitatively correlate to the amount of fibrosis and scar tissue. For assessments of potentially reversible contractile dysfunction, myocardial segments with flow reductions of less than 50% (ie, < 50% transmural scar tissue) are defined as "viable," whereas more severe flow reductions (> 50%) are defined as "nonviable." The approach identifies potentially reversible regional wall motion abnormalities with a sensitivity and specificity of 82% and 57%, respectively.[107] Assessment of perfusion alone does not identify a key feature of viable myocardium (ie, the enhanced extraction of glucose) and defines regions with severe flow reductions as nonviable even though comparison studies with PET have shown that myocardial viability can be associated with more severely reduced flows.[159] This limitation likely accounts for the only moderately high negative and predictive accuracies of SPECT imaging (ie, 72% and 71%, respectively).[107]

Contrast-Enhanced MRI for the Assessment of Myocardial Scar Tissue

Late gadolinium contrast enhancement on MRI indicates the presence of scar tissue. In patients with ischemic cardiomyopathy, the approach identifies the transmural extent of scar tissue. Nonenhancing myocardial tissue is considered to be normal or, less precisely, to be "viable." Generally, myocardial segments with less than 50% transmural scar tissue improve contractile function after restoration of blood flow, whereas the likelihood of a postrevascularization improvement in contractile function declines with increasing transmurality of late contrast enhancement.[160] Analogous to the resting perfusion approach, the late enhancement does

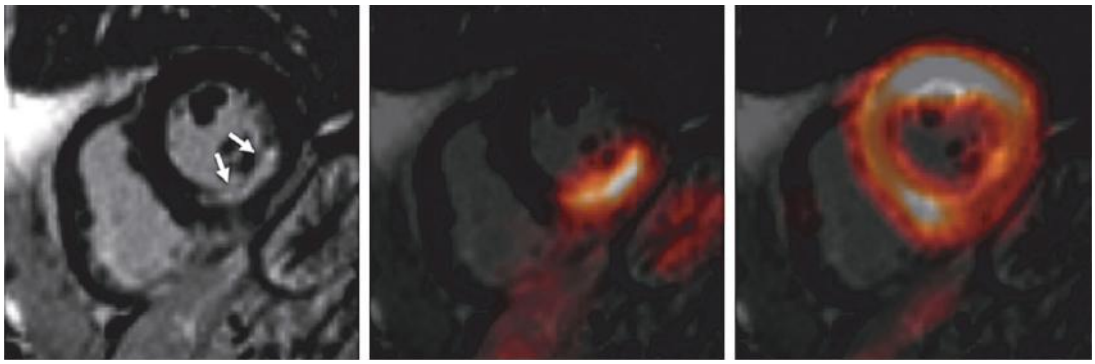


FIGURE 19–55. Positron emission tomography/magnetic resonance imaging (PET/MRI) for identifying scar tissue and viable myocardium in an early postinfarction patient. Subendocardial scar tissue (*left panel, arrows*) associated with 18F-FDG activity in the adjacent mid-myocardial layer (*center panel*) on hybrid 18F-FDG PET and late gadolinium enhancement MRI. N-13 ammonia myocardial perfusion images obtained after reperfusion demonstrate an only mild perfusion defect (*right panel*). The regionally enhanced 18F-FDG uptake likely reflects viable myocardium, although postischemic inflammation cannot be excluded. Reproduced with permission from Rischpler C, Nekolla SG1, Kunze KP, et al: PET/MRI of the heart. *Semin Nucl Med*. 2015 May;45(3):234-247.

not differentiate between normal and ischemic or viable myocardium. Sensitivity and specificity are 84% and 64%, respectively.[107]

However, it is possible to distinguish between normal and viable myocardium in nonenhancing regions by hybrid 18F-FDG PET/MRI.[135] In early postinfarction patients, wall motion was more likely to improve in nonenhancing myocardial segments on MRI with persistent 18F-FDG uptake than without (Fig. 19–55). Hybrid PET/MRI could thus enhance the diagnostic accuracy of the late contrast enhancement MRI approach because it would identify presence and amounts of viable and of normal myocardium in nonenhancing regions as well presence and extent of irreversibly injured (scar) tissue. As an additional and important aspect of MRI, its high spatial resolution offers predictive information based on wall-thickness measurements. Severe reductions in end-diastolic wall thickness (ie, < 7 mm) were highly accurate in predicting irreversible wall motion impairment with a 92% negative predictive accuracy.[107]

Thallium-201 Rest Redistribution for Cell Membrane Integrity

Cell membrane integrity, and thus, preserved transmembrane ion concentration gradients in functionally compromised myocytes serve as another measure of reversibility that can be evaluated with thallium (Tl)-201 rest and redistribution imaging. Like Rb-82, Tl-201 is a potassium analog reflecting potassium trapping in the myocyte. The initial, early postinjection myocardial images depict the distribution of myocardial blood flow while delayed (4 hours or more) "redistribution images" reflect the equilibrium of the cation Tl-201 between myocardium and blood and thus the myocardial potassium pool. Although highly predictive in patients with only moderately reduced LV function,[107] its accuracy is limited in patients with severely depressed LV function, because of low signal-to-noise ratios resulting from low myocardial and high blood radiotracer activities, limiting the certainty with which redistribution can accurately be identified.[161-164]

Contractile Reserve by Low-Dose Dobutamine Stimulation

Persistence of contractile reserve serves as another marker of potentially reversible contractile dysfunction. Wall motion responses to inotropic stimulation with intravenous low-dose dobutamine infusion, assessed by 2D echocardiography, cine CT, or gated MRI, accurately predict postrevascularization outcomes of regional myocardial wall motion and global LV function, including changes in the LV volumes, both in end-diastole and the end-systole and thus, in LV remodeling.[107]

Identification of Myocardial Viability by Reversibility of Stress Perfusion Defects

Stress-induced perfusion defects on myocardial perfusion imaging with SPECT have been considered as indicators of reversible contractile dysfunction. However, in patients with ischemic cardiomyopathy and severely impaired LV function, stress-rest myocardial perfusion imaging has proved to be of limited accuracy in distinguishing between reversible and irreversible contractile dysfunction (Fig. 19–56).[165] Possible reasons for this limitation include impairments in CFR in "remote" myocardium resulting from multivessel macrovascular and/or microvascular disease, so that pharmacologic stress fails to selectively induce more severe perfusion defects. Rather, assuming that the perfusion reserve is uniformly diminished throughout the LV myocardium, the relative distribution of myocardial blood flow during rest and stress remains relatively constant so that a perfusion defect appears "fixed" despite the presence of viable myocardium.[166]

IMAGING INFLAMMATION AND INFECTIONS OF THE CARDIOVASCULAR SYSTEM BY POSITRON EMISSION TOMOGRAPHY

CARDIAC SARCOID

Sarcoidosis is a granulomatous disease that most often affects the lymphoid and respiratory systems. The cardiovascular system is the third most often affected organ system, although its involvement frequently remains undiagnosed. Several etiologies have been proposed and explored, although the underlying etiology of sarcoidosis still awaits full clarification; sarcoidosis has been defined as a "multisystem disorder of unknown cause(s)."[167]

The presence of sarcoidosis is histologically confirmed by demonstration of noncaseating epithelioid granulomas. Involvement of the cardiovascular system is frequently underestimated because cardiac sarcoidosis remains clinically silent in as many as 50% of patients. Different from the 5% to 10% incidence reported previously, more recent use of advanced diagnostic imaging techniques such as CT and MRI has raised the incidence to about 40%[168]; nearly 50% of patients with cardiac involvement are asymptomatic. Importantly, however, cardiac complications account for about 50% of all deaths in sarcoidosis patients.

According to autopsy findings in patients with cardiac sarcoidosis, the LV free wall including the papillary muscles, together with the

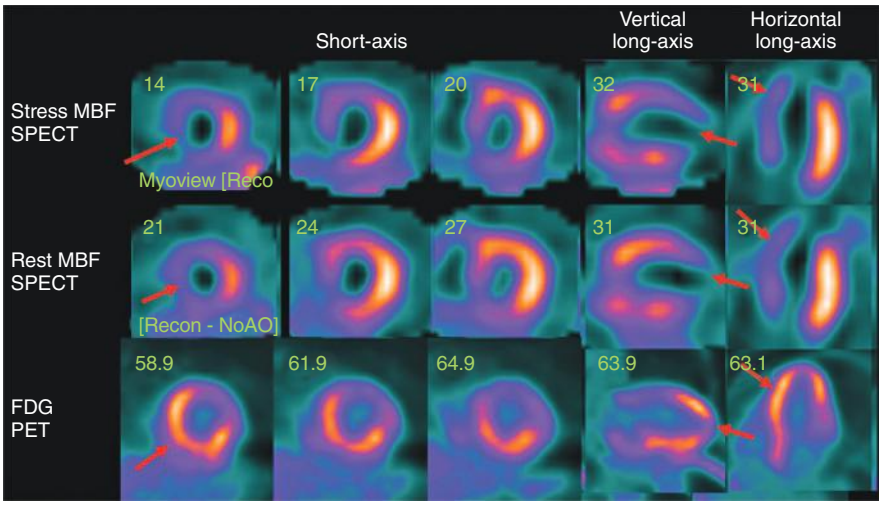


FIGURE 19–56. Stress and rest single-photon emission computed tomography (SPECT) myocardial perfusion (*upper* and *middle panel*) and 18F-FDG metabolic images (*bottom panel*) in a patient with ischemic cardiomyopathy. The *arrows* point to the defects or abnormalities of perfusion and F18-FDG images. The large and severe perfusion defect in the anterior wall and the interventricular septum is predominantly fixed but is associated with increased 18F-FDG uptake, consistent with viable myocardium. PET, positron emission tomography.

immediately adjacent myocardium, the interventricular septum, and the right ventricular myocardium are affected most frequently.[169] The inflammatory regions preferentially reside in the more basal portions of the LV myocardium and typically exhibit granulomatous noncaseating lesions; with progression of the active inflammatory process, there is myocardial repair with increased fibrosis and formation of scar tissue. Clinicopathologic correlations have found no statistically significant associations of the site of inflammation and clinical findings. However, small sarcoid lesions appear to be associated with fewer clinical symptoms or cardiac findings, whereas more extensive involvement tends to be associated with left ventricular dysfunction and heart failure.[169]

Perfusion and Metabolism Imaging in Cardiac Sarcoid

The diagnosis of cardiac sarcoidosis has remained challenging because it depends on the histologic demonstration of noncaseating granulomas in myocardium. In the absence of myocardial biopsy data, a diagnostic algorithm is employed that includes presence of histologically confirmed systemic sarcoidosis together with clinical signs of cardiac involvement. The now modified Japanese Ministry of Health and Welfare (JMHW) 2006 guidelines consist of major and minor criteria.[170] Major criteria include advanced atrioventricular block, basal thinning of the interventricular septum, positive myocardial 18F-FDG uptake, and depressed LVEF to less than 50%. Minor criteria include abnormal ECG, abnormal echocardiogram (regional wall motion abnormality), myocardial perfusion defect (Tc-99m SPECT or Rb-82 or N-13 ammonia PET), gadolinium-enhanced MRI, and an abnormal endomyocardial biopsy (interstitial necrosis or moderate monocyte infiltration). Two or more major criteria or only one major and at least two minor criteria are required for the diagnosis of cardiac sarcoid.

Detection of inflammatory sarcoid lesions strongly depends on adequate suppression of 18F-FDG uptake in normal myocardium. It requires careful patient preparation prior to PET/CT imaging in order to shift the myocardium's substrate selection from glucose to free fatty acid, thereby reducing accumulation of 18F-FDG in normal myocardium. Among several approaches, prolonged fasting for 16 to 20 hours has been proven most effective in consistently suppressing 18F-FDG uptake.[171-173] The fasting approach can be supplemented with intravenous unfractionated heparin 15 minutes prior to 18F-FDG injection in order to further raise circulating free fatty acid levels,[174] although a true incremental effect on the suppression of myocardial 18F-FDG uptake remains uncertain.

The study protocol typically includes assessment of myocardial perfusion at rest and of myocardial and whole-body 18F-FDG uptake (the latter for identifying extracardiac sarcoid as a major criterion). Myocardial perfusion is preferably assessed with PET/CT either with N-13 ammonia or Rb-82 but can also be evaluated with SPECT myocardial perfusion imaging with Tc-99m labeled radiotracers of blood flow. Perfusion defects indicate the presence of scar tissue as evidence of the postinflammatory myocardial repair process. 18F-FDG images are typically acquired 60 to 120 minutes after the radiotracer administration. They include dedicated cardiac and whole-body or only chest 18F-FDG images for identifying the inflammatory activity as well as the presence or absence of systemic sarcoidosis. As an alternative clinically more practical approach, especially when searching for active inflammation as the target of treatment, metabolism imaging is performed first for identifying presence or absence of acute inflammatory lesions in the myocardium and evidence of systemic sarcoidosis; myocardial perfusion images are then obtained the following day as needed.

Patterns of Myocardial Perfusion and Glucose Imaging in Sarcoid

Patterns of myocardial 18F-FDG uptake are defined as (1) no uptake, (2) mild diffuse uptake, (3) focal on diffuse uptake, and (4) focal uptake (one or more foci of increased uptake; Fig. 19–57). Absence of focally enhanced 18F-FDG uptake effectively rules out the presence of moderate- to large-sized inflammatory sarcoid granuloma, although small lesions as reported from autopsy studies in patients with systemic sarcoid may remain undetected. Diffuse myocardial 18F-FDG uptake poses several diagnostic challenges. It may be related to insufficient suppression of 18F-FDG uptake in normal myocardium, but it has also been attributed to a diffuse nonsarcoid inflammation of the myocardium.

Most consistent with cardiac sarcoid are one or more myocardial foci of intensely increased 18F-FDG uptake (see Fig. 19–57). Their location does not follow the distribution of coronary vessels; they preferentially locate in the more basal portions of the LV myocardium—that is, the basal segments of the inferior ventricular septum and the inferior and the lateral walls, as well as the right ventricular wall. Occasionally, focally enhanced 18F-FDG uptake may be observed selectively

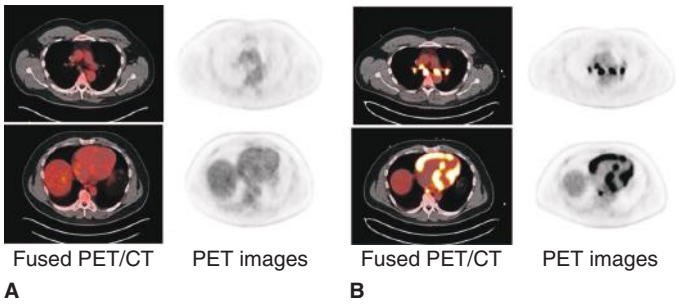


FIGURE 19–57. Imaging of cardiac sarcoid with 18F-FDG positron emission tomography (PET) in two patients with suspected cardiac sarcoid. The axial PET-only and PET/computed tomography (CT) images of the mediastinum (*upper row*) and the left ventricle (*lower row*) are shown. In the patient in **A,** myocardial 18F-FDG is completely suppressed and no abnormally increased 18F-FDG uptake is seen. In contrast, in the patient in **B,** multiple foci of intensely increased 18F-FDG uptake are seen in the mediastinum (consistent with mediastinal lymph node involvement) and throughout the left and right ventricular myocardium, consistent with cardiac sarcoid associated with systemic sarcoid.

in papillary muscles; while possibly related to cardiac sarcoid, such selective uptake may also represent a normal variation.

While the diagnosis of cardiac sarcoid is predicated on the presence of systemic sarcoid, recent observations have provided evidence for sarcoidosis limited to the cardiovascular system. Necropsy findings in patients with sudden death from cardiac sarcoid have failed to detect gross extracardiac disease in 10 of 25 (40%) with cardiac sarcoid lesions.[175] Observations with 18F-FDG PET in patients with suspected cardiac sarcoid but without apparent clinical evidence of systemic sarcoid are similar[176]; in 25 patients with focally enhanced myocardial 18F-FDG and flow defects, only 13 revealed involvement of mediastinal lymph nodes on whole-body 18F-FDG PET, whereas the remaining 12 (48%) patients were without evidence of extracardiac sarcoidosis.

Addition of myocardial perfusion imaging increases the sensitivity of identifying cardiac sarcoid.[168] Perfusion defects correspond to scar tissue after healing of the acute inflammatory process. The incidence of regional perfusion defects varies between clinical investigations—possibly for technical reasons (SPECT vs PET perfusion imaging)—but also because of differences in patient populations. Early acute inflammatory stages of the disease exhibit abnormally increased 18F-FDG, whereas more advanced stages are associated with tissue fibrosis and scar formation and, consequently, with perfusion defects. Therefore, depending on the stage of the granulomatous disease, cardiac sarcoid may be associated with focally increased 18F-FDG uptake only, reflecting the acute inflammatory process; with flow defects only, reflecting myocardial scar tissue; or with both, regionally increased 18F-FDG uptake and reduced flow, reflecting a combination of both.

Diagnostic Accuracy of PET for Sarcoid

Estimates of the diagnostic accuracy of perfusion-metabolism imaging are limited because histopathologic evidence of myocardial noncaseating inflammatory lesions as the gold standard is frequently missing. The diagnostic yield of endomyocardial biopsies has remained low (in the range of 30% to 35%).[177] The diagnosis of cardiac sarcoid is further complicated because it is predicated on histopathologic proof of systemic sarcoid as defined by the JMHW criteria.[170] For example, in 118 patients without CAD, 38 patients met the JMHW criteria for cardiac sarcoid, although only 16 (or 42%) had abnormal cardiac findings on PET imaging.[178,179] Among 20 patients with perfusion defects and increased 18F-FDG uptake, endomyocardial biopsy findings were positive in only 9 (45%) patients.

Overall, the presence of cardiac sarcoid as established by JMHW criteria correlates poorly with that by cardiac PET/CT as well as that by endomyocardial biopsy findings. Some of the disparity among diagnostic strategies also relates to shortcomings of the JMHW criteria, which require the presence of systemic sarcoidosis while sarcoid disease may in fact be limited to the cardiovascular system in some patients. As another reason for the diagnostic disparities is that the current diagnostic criteria do not consider the possibility of focally increased myocardial 18F-FDG uptake due to nonsarcoid inflammatory processes.

Focal Myocardial 18F-FDG Uptake Unrelated to Cardiac Sarcoid: Differential Diagnosis

The pattern of focally increased myocardial 18F-FDG uptake is not specific for cardiac sarcoid but also occurs in other types of granulomatous and nongranulomatous inflammatory processes of the myocardium as, for example, in tuberculous myocarditis,[180] Epstein-Barr virus myocarditis,[181] or Chagas disease (Fig. 19–58).[182] In a retrospective study of 29 patients with suspected myocarditis, focally increased 18F-FDG uptake was observed in nearly half of the patients with histopathologically confirmed myocarditis (lymphocytic cell infiltrates associated with myocyte necrosis).[183]

Apart from myocardial inflammatory processes, interpretation of perfusion and 18F-FDG images should include consideration of potentially alternate causes of focally enhanced myocardial 18F-FDG uptake. Regional increases in myocardial 18F-FDG uptake may be related to postischemic myocardium after strenuous exercise in patients with epicardial coronary artery disease[184,185] or following an ischemic injury (Fig. 19–59). Stress-related, postischemic regional increases

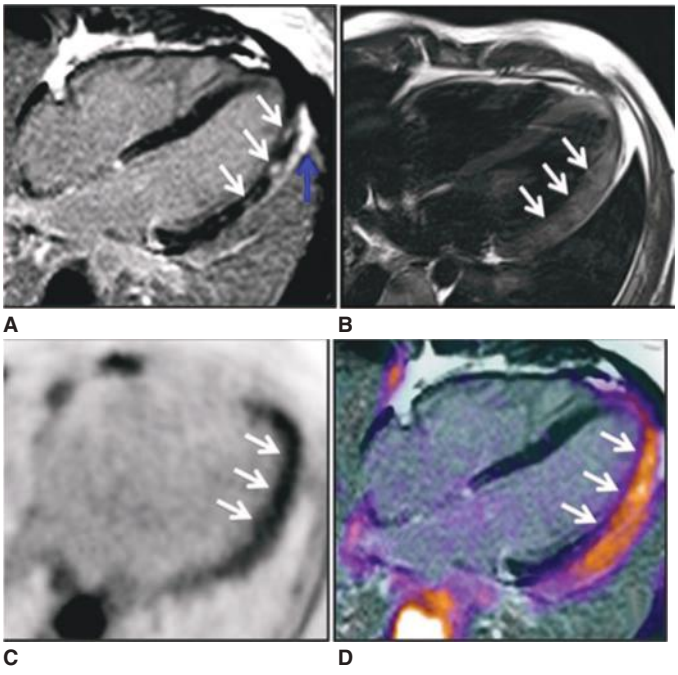


FIGURE 19–58. Acute myocarditis caused by Epstein-Barr virus infection in a 27-year-old man, imaged with hybrid positron emission tomography (PET)/magnetic resonance imaging (MRI). There are intramyocardial nodules (**A**) and diffuse subepicardial late gadolinium enhancement associated with subepicardial edema on T2-weighted images (**B**). Intense 18F-FDG uptake is noted in the anterolateral wall (**C**), corresponding in location to the late enhancement regions on MRI (**D**). Reproduced with permission from von Olshausen G, Hyafil F, Langwieser N, et al: Detection of acute inflammatory myocarditis in Epstein Barr virus infection using hybrid 18F-fluoro-deoxyglucose-positron emission tomography/magnetic resonance imaging. *Circulation*. 2014 Sep 9;130(11):925-926.[181]

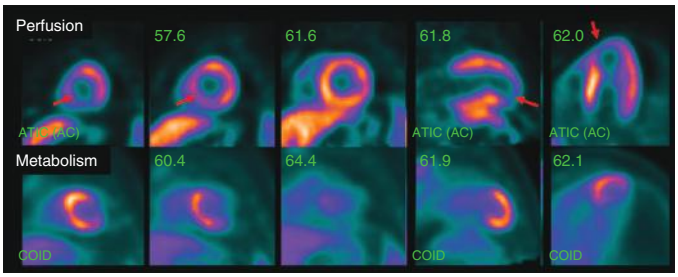


FIGURE 19–59. Positron emission tomography (PET) N-13 ammonia perfusion and glucose metabolism images in a patient with systemic sarcoid and with ventricular tachycardia referred for evaluation of cardiac sarcoidosis. Perfusion is severely reduced in the distal anterior wall, the apex, and the distal inferior wall, suggestive of obstructive disease of the left anterior descending coronary artery. 18F-FDG activity is selectively increased in the region of the perfusion defect, most likely consistent with myocardial viability. No evidence of systemic sarcoidosis was seen on the whole-body 18F-FDG PET/computed tomography (CT) images; the perfusion metabolism mismatch corresponds in location to the distal left anterior descending coronary artery. Further evaluation of the patient revealed obstructive coronary artery disease. 18F-FDG uptake in normal myocardium is absent as a result of prolonged fasting.

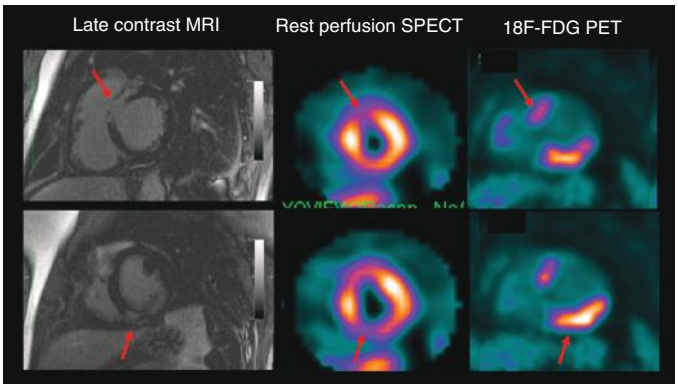


FIGURE 19–60. Late gadolinium-enhanced magnetic resonance imaging (MRI), positron emission tomography (PET) myocardial perfusion, and 18F-FDG images in a patient with cardiac sarcoid. Regions of late enhancement are seen in the anterior septum and the inferolateral wall (*arrows*) and correspond to regional flow defects on the N-13 ammonia perfusion images. Focal increases of 18F-FDG uptake in both flow defect regions are consistent with active inflammation. SPECT, single-photon emission computed tomography.

in 18F-FDG uptake may persist for as long as 24 hours or more but typically correspond in location to the distribution of a coronary artery, whereas sarcoid lesions typically reside in the more basal portions of the left ventricle and are unrelated to coronary vascular territories.

The known physiologic heterogeneity of myocardial 18F-FDG uptake can complicate the image interpretation. Myocardial 18F-FDG uptake in normal individuals is more prominent in the posterior lateral wall[186,187] ; activity concentrations are on average about 10% higher than in the anterior and anterior septal wall after standard glucose loading prior to PET/CT imaging and may be as high as 20% when patients are imaged after prolonged fasting.

Primary and secondary cardiac tumors may also account for focal or regional increases in myocardial 18F-FGD uptake. Primary cardiac tumors are rare, and most are benign. Secondary cardiac tumors are 40 to 100 times more frequent than are primary tumors.[188] They are seen in cancer of the lung, breast, and kidneys and in melanoma, lymphoma, and leukemia. As compared to the mild to moderate 18F-FDG uptake in benign cardiac tumors, malignant cardiac tumors characteristically exhibit intense 18F-FDG activity.[174,189] Differentiation of cardiac tumors from inflammatory processes may be possible with radiolabeled amino acids as has been shown for cardiac metastases of serotonin-producing neuroendocrine tumors with 18F fluoro-L-dopa.[190] However, it is probably clinically accomplished best by structural characterization with contrast CT or MRI.[191]

Cardiac MRI contributes to the diagnosis of cardiac sarcoid.[177,192] The myocardial distribution of late gadolinium enhancement is characteristically "noncoronary" and primarily involves the subepicardial and mid-myocardial layers with sparing of the endocardium, a pattern distinctly different from that of ischemia and infarction (Fig. 19–60). Based on comparison studies, MRI appears to be more specific but less sensitive than 18F-FDG PET for the detection of cardiac sarcoid.[193] Furthermore, findings on PET and MRI can differ. Of 21 patients, 8 patients were positive on either PET or MRI, while 8 patients were positive on both yet with frequently disparate locations of PET and MRI lesions. Late contrast enhancement of MRI reflects scar tissue and edema as compared to active inflammation on 18F-FDG PET so that interpatient and intrapatient disparities likely reflect different stages of the inflammatory process. Use of MRI may, however, be limited in patients with cardiovascular implanted electronic devices (CIEDs).

It is uncertain whether the intensity of regional 18F-FDG uptake can be used as a diagnostic markers of cardiac sarcoid. Besides the level of inflammation, the apparent intensity of 18F-FDG uptake depends on the size of the inflammatory lesion with lower activity in smaller lesions. Some evidence suggests that standard uptake values (SUVs) or coefficients of variance, an index of the heterogeneity of the myocardial 18F-FDG uptake, improves the interpretive certainty and, possibly, yield associations with specific electrocardiographic abnormalities. It is also possible to assess the abnormal, sarcoid-related 18F-FDG uptake more quantitatively. Analogous to the metabolic tumor volume and the total lesion glycolysis, widely used with oncologic PET studies, the cardiac metabolic volume and the cardiac metabolic activity can be estimated from the total volume of increased 18F-FDG uptake (using threshold values for defining the extent and, thus the total volume of abnormal 18F-FDG uptake) and the intensity of 18F-FDG uptake, derived from average SUV (intensity of 18F-FDG uptake corrected for the dose of activity injected and body weight).[179,194]

Predictive Value of FDG PET/CT and Therapeutic Implications in Sarcoid

PET perfusion-metabolism imaging in cardiac sarcoid contains predictive information on cardiac death and risk of sustained ventricular tachycardia. One investigation reports an annual event rate of 7.3% in patients without focal 18F-FDG uptake that increases to 18.4% with either a flow defect or focal 18F-FDG uptake and, even further to 31.9% when both flow defects and focally increased 18F-FDG uptake are present.[178] Semiquantitative indices of the total 18F-FDG uptake such as cardiac metabolic volume and cardiac metabolic activity similarly contain predictive information and appear to be useful for estimating treatment responses.

18F-FDG PET/CT defines the target of therapy and aids in monitoring treatment responses.[195] Besides antiarrhythmic treatment and ICD implantation, immunosuppression with corticosteroids is the treatment of choice. It is associated with decreasing lesional 18F-FDG uptake on repeat imaging (Fig. 19–61).[196] In one study, the cardiac metabolic volume decreased in five of seven patients by an average of 88% during steroid treatment[194]; in another study, therapy-induced decreases in the cardiac metabolic volume were associated with moderate improvements in the LVEF.[179]

INFECTIVE ENDOCARDITIS

The modified Duke criteria remain the diagnostic gold standard of infective endocarditis[197] (see Chap. 67 on endocarditis). Major criteria include positive blood cultures, evidence of endocardial involvement, echocardiographic evidence for infective endocarditis, and new-onset

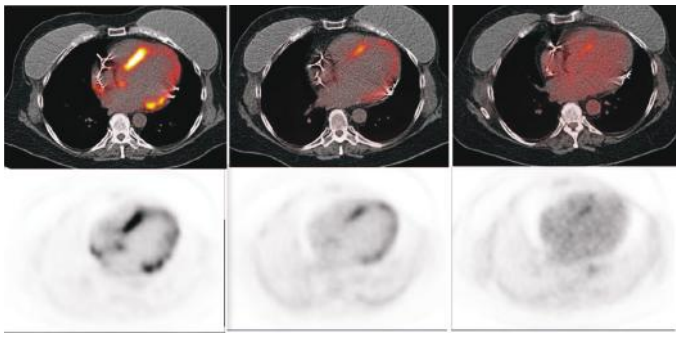


FIGURE 19–61. Response of inflammatory cardiac sarcoid to immunosuppressive treatment demonstrated by serial 18F-FDG imaging. Positron emission tomography (PET)/computed tomography (CT) fusion images are shown in the *upper row* and PET-only images in the *lower row*. Note the intensely increased 18F-FDG activity in the interventricular septum and the posterior lateral wall at baseline (*left panel*) and the progressive decline in abnormal 18F-FDG activity with treatment.

valvular regurgitation. Minor criteria include a predisposition for infective endocarditis, persistent fever despite antimicrobial treatment, vascular phenomena, immunologic phenomena, and microbiological evidence. The criteria are highly specific for infective endocarditis, but their sensitivity is low, so that infective endocarditis and its downstream complications may remain undetected or are recognized only late in the course of the disease. Early diagnosis is, however, critical for initiating aggressive and prolonged antibiotic treatment and, if indicated, valvular surgery in order to reduce morbidity and improve overall survival.

There is now substantial evidence that 18F-FDG PET/CT contributes to the identification of infective endocarditis (including infection of prosthetic valves, CIEDs, pacemakers, and ICDs), endovascular devices and prosthetic vascular grafts and, importantly, detection of downstream septic emboli.

FDG PET/CT Imaging of Infective Endocarditis

Transthoracic or transesophageal echocardiography detects valvular infections and abscesses with a sensitivity of 75% to 85%; both are considered "major criteria."[197,198] Vegetations and abscesses of native and prosthetic valves can be visualized with 18F-FDG PET/CT, though with a lower and clinically insufficient sensitivity (about 40%) and a specificity of about 70% to 100%.[199,200] They are typically seen as small foci of mildly to intensely increased 18F-FDG activity in the region of the mitral or aortic valve (Fig. 19–62) and do not invariably correspond to findings on echocardiography. In one investigation in 30 patients with definite prosthetic valve infection, for example, findings by echocardiography and 18F-FDG PET/CT agreed in only half of the patients; in nearly half of the remaining patients, focally increased 18F-FDG uptake was seen in the valve area without corresponding vegetations on echocardiography, possibly because of an early stage of disease[200] and when echocardiography may still be negative. Conversely, absence of abnormal 18F-FDG uptake effectively ruled out the presence of prosthetic valve infection in that study so that the authors proposed to include PET/CT as a major criterion for the diagnosis of infective endocarditis. The feasibility of 18F-FDG PET/CT for visualizing infected endovascular leads has also been explored but has remained of limited accuracy because of low signal intensity.[201]

Clinically more promising has been use of 18F-FDG PET/CT for diagnosing infections of cardiovascular implantable electronic devices. According to the Consensus on Transvenous Lead Extraction,[202] removal of devices is indicated when one of three criteria is present: (1) infection of device (or generator) pocket, (2) lead endocarditis, and (3) persistent or recurrent bacteremia. Several studies have reported

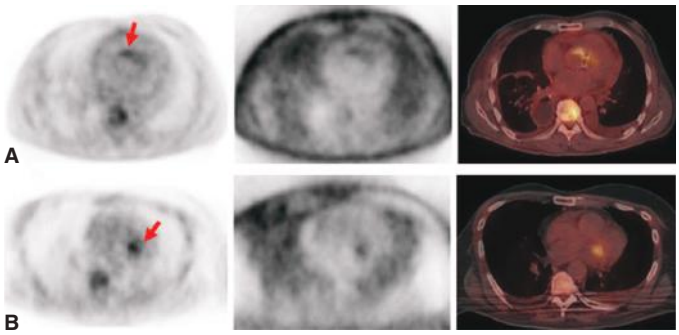


FIGURE 19–62. 18F-FDG positron emission tomography (PET)/computed tomography (CT) imaging of infective endocarditis: PET attenuation corrected (*left*) and nonattenuation corrected images (*center*) together with fused PET/CT images (*right*) are shown in two patients. **A.** The patient is a 65-year-old man with definite endocarditis by modified Duke criteria; the focally increased 18F-FDG activity (*arrow*) corresponds to infection of the mitral valve. **B.** The PET findings in a 70-year-old man with *Staphylococcus aureus* bacteremia and possible endocarditis. The focally increased 18F-FDG activity (*arrow*) corresponds to an infected mitral valve. Reproduced with permission from Kouijzer IJ, Vos FJ, Janssen MJ, et al: The value of 18F-FDG PET/CT in diagnosing infectious endocarditis. *Eur J Nucl Med Mol Imaging*. 2013 Jul;40(7):1102-1107 .[199]

sensitivities ranging from 76% to 100% for detecting device infections with 18F-FDG PET/CT.[201,203] Abnormally increased 18F-FDG uptake in patients with device infections is frequently seen in the pocket around the generator, over intravascular leads, superficially in skin and subcutaneous tissues, and within the region of the heart (Fig. 19–63). Evidence of infection on 18F-FDG PET/CT led to device extraction in 24 of 27 patients in one study.[203] Negative findings on 18F-FDG PET/CT may also prove useful as they may aid in deciding against device extraction.

Limitations of Endocarditis Imaging Despite the promise of 18F-FDG PET/CT for visualizing the site of endocarditis (native and prosthetic valves),

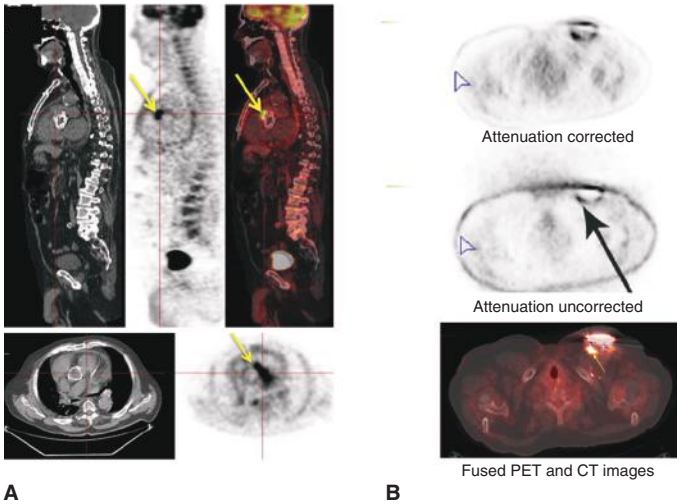


FIGURE 19–63. 18F-FDG positron emission tomography (PET)/computed tomography (CT) images of infective endocarditis. **A.** Focally increased 18F-FDG activity in an infected transcatheter aortic valve implantation as seen on the sagittal and axial images in the *left panel*. **B.** Axial 18F-FDG PET/CT images of an infected generator pocket. The focally increased activity in the left anterior chest wall on the attenuation corrected image (*top*) is also seen on the nonattenuation corrected images and is therefore not an image artifact. Fused PET/CT images are shown in the *bottom panel*. **A**, reproduced with permission from Saby L, Laas O, Habib G, et al: Positron emission tomography/ computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. *J Am Coll Cardiol*. 2013 Jun 11;61(23):2374-2382. **B**, reproduced with permission from Sarrazin JF, Philippon F, Tessier M, et al: Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. *J Am Coll Cardiol*. 2012 May 1;59(18):1616-1625.[203]

limitations remain. One is the frequently small size of infectious lesions, at least relative to the spatial resolution of the PET imaging system. A second one is the low intensity of the radiotracer activity relative to background activity (ie, 18F-FDG activity concentrations in blood and myocardium), and thus, a low signal-to-noise ratio. Approaches to enhance the signal strength include delayed image acquisition after radiotracer administration in order to allow more time for clearance of radiotracer from blood and suppression of radiotracer uptake in normal myocardium by prolonged fasting in order to suppress myocardial glucose uptake.[171] Delaying the time of image acquisition from the standard 1 to 3 hours substantially after the radiotracer administration improved the detection of device infections (especially of infected endovascular leads).[203]

As a third limitation, increased radiotracer uptake in noninfected tissues or structures adjacent to valves or prostheses may lead to falsely positive interpretations, especially in patients with recent device or prosthesis implants when postsurgical reactive tissue inflammation is associated with increased 18F-FDG uptake. A comparison study found no abnormal 18F-FDG uptake in patients with remote device implants without evidence of infection, only mild 18F-FDG uptake in patients with recent device implants (4-8 weeks) without device infection but focally intense 18F-FDG uptake in patients with suspected infection of device implants.[203] Prosthetic vascular grafts, when combined with valve replacements, may also represent sites of endocarditis and demonstrate intense 18F-FDG uptake[204,205] but may also be associated, even when not infected, with persistent but only mildly to moderately increased radiotracer uptake.[206]

Assessment of Septic Emboli and Metastatic Infections

Investigations have established the clinical value of 18F-FDG PET/CT for identifying septic emboli and downstream infectious metastases. Their detection with conventional approaches (ultrasound, CT, and MRI) has remained challenging and is of limited effectiveness. Although frequent in infectious endocarditis, as many as 30% to 40% of downstream infections persist without localizing signs or symptoms but will significantly affect clinical outcomes. Timely detection of septic emboli and metastatic infection is thus critical for initiating aggressive prolonged antibiotic treatment together, if needed, with draining of infected abscesses, in order to avoid relapses of infectious endocarditis and reduce mortality. In one investigation in 111 patients with gram-positive bacteremia, whole-body 18F-FDG PET/CT uncovered focally abnormal radiotracer uptake in 65 patients (58.6%).[207] Of these, 53 were true positives for metastatic infections as verified by ultrasound, CT, or MRI. Forty percent of the patients had more than one lesion. There were 46 true negative patients overall; the study reported a sensitivity and specificity of 100% and 87%, respectively. Other investigators have confirmed the high sensitivity and specificity of 18F-FDG PET/CT for the detection of septic emboli and metastatic infections in patients with definite infectious endocarditis by the Duke criteria.[199,200,208,209] Sites most often affected include the lung (in right-sided infective endocarditis), the bones, the colon, the spleen, and the brain. Metastatic infections of brain, myocardium, and kidneys may remain undetected because of physiologically high 18F-FDG uptake and thus high background activities.

VASCULAR INFLAMMATION AND ATHEROSCLEROSIS

Inflammation is a hallmark of several vascular disease entities and, because of the avidity of inflammatory cells for 18F-FDG, can be identified with PET. Vascular imaging with PET in arteritis of the large vessels is clinically useful while its clinical role in atherosclerotic disease remains to be fully determined.

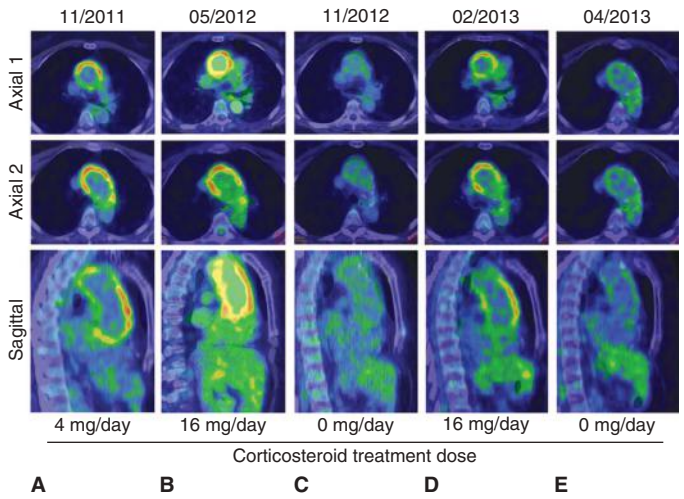


FIGURE 19–64. Imaging of inflammatory aortitis and response to treatment in a patient with an aneurysmal ascending aorta and aortic arch. Note the intense the increased circular activity on the axial images of the ascending aorta (axial 1) and the aortic arch (axial 2) and the changes in metabolic activity in response to different doses of steroids with subsequent recurrence of activity and successful steroid retreatment. Reproduced with permission from Bruls S, Courtois A, Nusgens B, et al: 18F-FDG PET/CT in the Management of Aortitis. *Clin Nucl Med*. 2016 Jan;41(1):28-33.

Large-Vessel Vasculitis

Among inflammatory diseases of the great arteries, *giant cell arteritis* and *Takayasu's arteritis* have been studied most with PET/CT. Monocytes and macrophages avidly accumulate and retain 18F-FDG[210] and represent the "biological" substrate of enhanced 18F-FDG uptake in the walls of the great arteries in patients with inflammatory vascular diseases (Fig. 19–64). Patients with suspected arteritis are studied in the fasting state with acquisition of whole-body PET and PET/CT, beginning in most investigations at 45 minutes after intravenous 18F-FDG administration.[211] Longer time intervals are preferable to allow more time for vascular uptake and for clearance of radiotracer from blood, producing higher signal-to-background ratios with improved detection of vascular 18F-FDG uptake.[212] Uptake in the arterial wall is graded visually on a three-point scale, where 1 is minimal or no uptake; 2, mild but definite; and 3, intense. A total vascular score, as the sum of all regional scores throughout the arterial system, can be obtained and be used for estimating progression or regression of vascular inflammation on serial PET imaging.[213]

Diagnostic Performance Case reports and investigations with only small patient numbers limit an accurate assessment of the diagnostic performance of PET and PET/CT 18F-FDG imaging in patients with arteritis. Pooled findings in 90 patients with clinically documented giant cell arteritis or Takayasu's disease (based on the presence of least three of the classification criteria established by the American College of Rheumatology),[214,215] in four investigations, indicate a weighted average sensitivity of 81% and specificity of 86%.[211,213,216]

Some, but not all studies, report a correlation between the vascular 18F-FDG uptake and serum inflammatory markers. In one study, the intensity of vascular 18F-FDG activity was found to correlate with serum C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR).[211] The diagnostic sensitivity of vascular imaging appears to be related to levels of serum markers of inflammation and, thus, to the inflammatory activity. As suggested in one study, the sensitivity declines when CRP is less than 10 mg/L or the ESR is less than 12 mm/h.[211]

Clinical Indications Vascular imaging with 18F-FDG PET/CT may prove useful for establishing the diagnosis of vasculitis, especially in patients with nonspecific symptoms as, for example, fever of unknown origin or polymyalgia rheumatica, which frequently coexists with giant cell arteritis. Furthermore, it delineates the spread of active disease throughout the great vessels. Although relatively infrequent, aortic aneurysms and dissections are complications of giant cell arteritis; complications of Takayasu's arteritis include arterial stenoses but also aneurysms, most often involving the aortic root and leading to valvular insufficiency.[217] Delineation of the extent of vascular involvement may therefore draw attention to possible sites of downstream vascular complications. Finally, the intensity of vascular 18F-FDG uptake serves as a measure of the degree of inflammation and of its response to therapy. The vascular 18F-FDG uptake declines with successful corticosteroid treatment, parallels symptomatic improvement (see Fig. 19–64),[218] and, as suggested by one investigation, reflects the treatment response more accurately than contrast-enhanced MRI.[218]

Atherosclerosis and Plaque Imaging

General Considerations Increased 18F-FDG uptake in the large arteries, including, in declining order, the ascending aorta and the aortic arch, the abdominal aorta, and the carotid arteries, but also the iliac and femoral arteries, is frequently observed in patients undergoing whole-body PET and PET/CT imaging for cancer diagnosis and staging. Unlike the diffuse vascular uptake seen in arteritis, 18F-FDG uptake in atherosclerosis is characteristically more heterogeneous and often focal.[219-222] Studies combining PET with contrast CT or even MRI angiography have reported increased 18F-FDG accumulation in the carotid arteries of patients with recent cerebral vascular ischemic events[223,224] or in patients with carotid artery stenoses scheduled for endarterectomy.[225]

Consistent with findings in animal experiments,[226] vascular 18F-FDG uptake correlates quantitatively with lesional concentrations of macrophages, especially of the activated proinflammatory type.[224,225] Potentially vulnerable or unstable atherosclerotic plaques are typically bulky in size, have a thin fibrous cap, exhibit a large necrotic core (≥ 25% of the plaque area) and are rich in macrophages.[227] Rupture appears related to the severity of plaque inflammation and, thus, the degree of macrophage invasion. The magnitude of 18F-FDG (ie, macrophage concentration) might thus serve as a "marker" of potential plaque instability.[225]

Methodological Aspects of Imaging of Vascular 18F-FDG Uptake Fusion of PET and CT images allows for easy localization of vascular radiotracer uptake and its extent and intensity. Regions of vascular 18F-FDG uptake typically coexist with regions of vascular calcification but rarely overlap.[220] Focal increases in 18F-FDG uptake are more prevalent than are calcifications in younger patients, whereas vascular calcifications are more prevalent in older patients.[220] Vascular radiotracer uptake is identified by its higher than blood activity and can be quantified by peak activity (counts/pixel/min) or by SUVs.[225,228,229] The target-to-background ratio (TBR) is a more quantitative measure of 18F-FDG uptake in the arterial wall because it is corrected for activity in blood.[230]

Repeat measurements over longer time periods reveal considerable changes in focal vascular 18F-FDG uptake. When reexamined after an 8- to 26-month period, vascular calcifications had remained relatively stable, but 48% of the initially observed regions of increased 18F-FDG had resolved while 32% of all lesions at follow-up had newly developed.[231] Although attributable to some extent to methodology-related differences, the lesion variability likely reflects the dynamic nature of atherosclerosis with healing of inflamed lesions and development of new inflammatory lesions. The incidence of vascular 18F-FDG uptake in patients with atherosclerotic disease is still undetermined.

Aortic aneurysms, especially of the abdomen, frequently reveal intense 18F-FDG activity. On histopathologic comparison studies, 18F-FDG activity concentrations correspond to accumulation of adventitial inflammatory cells often associated with decreased numbers of vascular smooth muscle cells, suggesting that 18F-FDG–rich abdominal aortic aneurysms might be prone to rupture.[232] Observations in a relatively small number of patients with abdominal aortic aneurysms appear to support this possibility; intense 18F-FDG uptake was associated with unfavorable outcomes including rupture, death, and surgical repair.[233] Other studies have pointed to cyclic patterns of 18F-FDG uptake in aortic aneurysms where diameter increases are preceded by low 18F-FDG uptake.[234] Future studies are thus needed to clarify the potential value of 18F-FDG uptake in guiding therapeutic strategies, especially in asymptomatic patients with abdominal aortic aneurysms that by size criteria might qualify for surgical (or endovascular) repair.[234,235]

Coronary Arterial Plaques Visualization of 18F-FDG uptake in atherosclerotic plaques of the coronary circulation faces formidable technical challenges for several reasons: the limited spatial resolution of PET relative to the size of the coronary vessels, cardiac and respiratory motion, and high background activity (ie, accumulation of 18F-FDG in the myocardium). Gated image acquisition for both cardiac and respiratory motion may thus become necessary for visualizing coronary arterial plaques and for quantification of 18F-FDG activity. Despite the inherently limited spatial resolution of PET, visualization of coronary plaques has become possible, especially because they are most frequently located in the larger sized proximal segments of the coronary arteries. Indeed, recent observations have confirmed such a possibility and have shown 18F-FDG avid lesions in the coronary vessels.[220] In 25 patients with CAD, PET/CT images in patients with acute coronary syndrome revealed high 18F-FDG activity in the culprit coronary lesion (Fig. 19–65).[236]

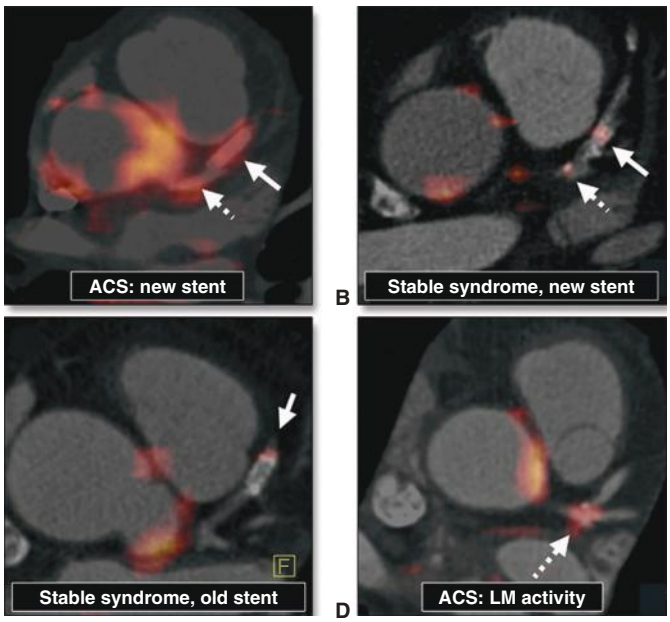


FIGURE 19–65. 18F-FDG positron emission tomography (PET)/computed tomography (CT) images of coronary arterial 18F-FDG uptake. Intense 18F-FDG uptake is seen in the left main coronary artery and the stented culprit lesion in a patient with acute coronary syndrome (**A**). Uptake is less intense in another patient with stable coronary artery disease and a recent stent placement (**B**), whereas only mild uptake is seen in a patient with coronary artery disease and an old stent (**C**). Mild 18F-FDG uptake is noted in the trifurcation of the left main coronary artery in a patient with acute coronary syndrome (**D**). Reproduced with permission from Rogers IS, Nasir K, Figueroa AL, et al: Feasibility of FDG imaging of the coronary arteries: comparison between acute coronary syndrome and stable angina. *JACC Cardiovasc Imaging*. 2010 Apr;3(4):388-397.[236]

Clinical Implications Vascular 18F-FDG uptake has been associated with an increased incidence of cardiovascular events. Investigations in cancer patients undergoing whole-body 18F-FDG PET/CT have reported statistically significant associations among large artery 18F-FDG uptake, traditional risk factors for cardiac disease, and adverse cardiovascular events.[237,238] More definitive support for a predictive value of vascular 18F-FDG uptake comes from an investigation in 513 patients who had undergone whole-body 18F-FDG PET/CT for cancer surveillance.[239] Patients enrolled were free of cancer, were at least 30 years of age and were without known cardiovascular disease. Over a median 4.2-year follow-up, 44 cardiovascular events occurred (ischemic stroke or transient ischemic attacks, acute coronary syndrome, coronary, carotid or peripheral revascularization, new-onset angina, peripheral arterial disease, heart failure, and cardiac death). The incidence of adverse events was related to the intensity of vascular 18F-FDG uptake (TBR in the ascending aorta). Abnormally high 18F-FDG uptake (TBR > 2.2) was associated with a 4.71-fold higher risk of a cardiovascular event than was low uptake (TBR ≤ 1.84). Of interest, cardiovascular events occurred earlier in patients with higher and more intense vascular 18F-FDG uptake.

18F-FDG uptake in large arteries can serve as imaging biomarker of the atherosclerotic inflammatory activity. In fact, local vessel inflammation as visualized with 18F-FDG correlates with serum inflammatory biomarkers.[240] Vascular 18F-FDG imaging may therefore prove useful for monitoring responses to anti-inflammatory and plaque-stabilizing interventions. The enhanced 18F-FDG uptake in atherosclerotic vessels also serves as a surrogate end point for assessing anti-inflammatory effects of drugs. Lipid-lowering with statins has been associated with significant reductions in vascular 18F-FDG uptake,[230] an effect that is dose dependent without, however, directly and significantly correlating with changes in plasma LDL cholesterol levels, corroborating a pleotropic anti-inflammatory effect of statins.

Active Mineral Deposition and Calcification of Atherosclerotic Plaques 18F sodium fluoride (18F-NaF) has recently emerged as another tool for probing the pathophysiology of atherosclerosis. Initial observations with this bone-imaging agent in oncologic patients reported focal increases in 18F activity throughout the large arteries. They were most prominent to in the femoral arteries, and, in declining order, the abdominal aorta and the thoracic aorta. Almost invariably, they were associated with vascular calcifications on CT.[241] In another study, vascular 18F-NaF lesions were found to be more intense than 18F-FDG lesions; increased 18F-NaF uptake colocalized with vascular calcifications as compared to only 14.5% of 18F-FDG sites. Importantly, 18F-FDG sites generally did not colocalize with 18F-NaF sites; in only 6.5% of all sites were both radiotracers present.[242] Vascular 18F-NaF uptake appears to be associated with cardiovascular events, coronary artery disease and the Framingham cardiac risk score.[243]

The findings reported in both the large arterial vessel and the coronary vessels studies imply that 18F-FDG and 18F-NaF target atherosclerotic plaques but different aspects and, probably, different phases of dynamic plaque biology. Lesional 18F-FDG uptake likely precedes uptake of 18F-NaF as an indicator of active calcification.[244] Vascular uptake of either radiotracer may reflect potential plaque instability—one as a consequence of high inflammation and the other as a consequence of plaque rupture and active mineral deposition.

FUTURE DEVELOPMENTS OF PET/CT FOR INFLAMMATION AND INFECTIONS OF THE CARDIOVASCULAR SYSTEM

The clinical utility of metabolic imaging of the cardiovascular system with PET and, especially with hybrid PET/CT, has considerably grown in recent years. Initially confined to the identification and characterization of myocardial viability, metabolic imaging now includes assessments of inflammatory processes of the heart and the vasculature and monitoring of response to various therapies. Much of the knowledge gained through metabolic imaging with PET has remained in the domain of basic and clinical research; if applied to human cardiovascular disease, it will likely lead to important insights into mechanisms of human cardiovascular disease and meet specific diagnostic needs and challenges. Judging from recent developments in PET radionuclide imaging, much of the current and future growth will be driven by progress in cancer research and through translation of basic science findings to human cardiovascular disorders. Moreover, the ever-increasing availability and use of multimodality imaging will likely accelerate further current developments in PET radionuclide imaging.

FINANCIAL SUPPORT AND RELATIONS WITH INDUSTRY

KLG received internal funding and is salaried solely from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis. KLG is the 510(k) applicant for HeartSee, a software package for quantifying absolute flow using cardiac positron emission tomography. All royalties will go to a University of Texas scholarship fund. The University of Texas has a commercial, nonexclusive agreement with Positron Corporation to distribute and market HeartSee in exchange for royalties. However, KLG retains the ability to distribute cost-free versions to selected collaborators for research. Additionally, KLG has financial research support from Volcano Corporation (maker of FFR pressure wires) for the multicenter study DEFINE_FLOW, Clinical Trials number NCT02328820.

HS has no financial relationships to disclose.

JN has no financial relationships to disclose.

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CHAPTER 20

CARDIAC CATHETERIZATION, CARDIAC ANGIOGRAPHY, AND CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

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CARDIAC CATHETERIZATION

In 1929, Werner Forssman, a resident surgeon at Eberswalde in Germany, inserted a urologic catheter into his right atrium from a left antecubital vein cut down he had performed on himself using a mirror. After walking downstairs to the radiology suite, the position of the catheter tip was verified by a roentgenogram. This was the beginning of cardiac catheterization: the insertion and passage of small plastic catheters into arteries, veins, the heart, and other vascular structures to obtain angiographic images of coronary arteries and cardiac chambers and to measure hemodynamic data (pressure and flow) in the heart. Cardiac angiography images not only diagnose coronary artery disease but are used to visualize abnormalities of the aorta as well as the pulmonary and peripheral vessels.

Equally important, the modern cardiac catheterization laboratory is a therapeutic theater of operations for catheter-based interventions (eg, stent implantation, atherectomy, thromboaspiration), collectively called percutaneous coronary intervention [PCI]) or catheter-based treatment of structural heart disease (Table 20–1). Figure 20–1 shows a typical modern cardiac catheterization laboratory.

TABLE 20–1. Diagnostic and Therapeutic Interventional Procedures That May Accompany Coronary Angiography

Diagnostic Procedures	Comment
Central venous access (femoral, brachial, internal jugular, subclavian)	Access for emergency medications or fluids, temporary pacemaker
Hemodynamic assessment	
Left heart pressures (aorta, left ventricle)	Routine for all studies
Right and left heart combined pressures	Not routine for coronary artery disease; mandatory for valvular heart disease; CHF, right ventricular dysfunction, pericardial diseases, cardiomyopathy, intracardiac shunts, congenital abnormalities
Transseptal or LV puncture	Valvular heart disease
Intracoronary pressure/flow	Coronary lesion assessment
Left ventricular angiography	Routine for all studies; may be excluded with high-risk patients, left main coronary or aortic stenosis, severe CHF, renal failure
Internal mammary artery and saphenous vein bypass graft selective angiography	Routine for coronary bypass conduit assessment
Pharmacologic studies	
Ergonovine/acetylcholine	Specialized studies for suspected coronary vasospasm
IC/IV/sublingual nitroglycerin	Routine for all coronary angiography
Inhaled nitric oxide	Evaluation of pulmonary vasoreactivity
Aortography	Routine for aortic insufficiency, aortic dissection, aortic aneurysm, with or without aortic stenosis, routine to locate bypass grafts not visualized by selective angiography
Renal and peripheral vascular angiography	For renovascular hypertension and peripheral vascular disease
Cardiac pacing and electrophysiologic studies	Arrhythmia evaluation
Therapeutic interventional procedures	
Coronary artery disease	Percutaneous coronary interventions (eg, stenting, rotablator, thrombus aspiration)
Valvular heart disease	Balloon catheter valvuloplasty, TAVR, Mitra-Clip
Atrial septal defect/PFO	Atrial septal defect/PFO closure
HOCM	Transcoronary ablation of septal hypertrophy (TASH)
Arrhythmia	Electrophysiologic catheter ablation
Arterial access site closure devices	Available for patients prone to access site bleeding

Abbreviations: CHF, congestive heart failure; HOCM, hypertrophic obstructive cardiomyopathy; IC, intracardiac; LV, left ventricular; PFO, patent foramen ovale, TAVR, transaortic valvular replacement.

INDICATIONS AND CONTRAINDICATIONS

The principal indications for cardiac catheterization are summarized in Table 20–2. In general, cardiac catheterization is an elective diagnostic procedure and should be deferred if the patient is not prepared either psychologically or physically. For urgent procedures, especially if the patient is unstable from a suspected cardiac cause such as acute myocardial infarction, catheterization must proceed. In the event of decompensated congestive heart failure requiring cardiac catheterization for diagnosis and potential treatment, rapid medical management in the catheterization laboratory may be an expeditious option, whereby endotracheal intubation, left ventricular (LV) support device insertion, and vasopressors can be instituted rapidly before angiography and revascularization. Relative contraindications to cardiac catheterization

FIGURE 20–1. The modern catheterization laboratory. 1 AP imaging C-arm, with the image intensifier above the patient and the x-ray tube below; 2 lateral imaging C-arm with the x-ray system to the patient's right; 3 the lateral plane imaging intensifier on the patient's left side; 4 table pad position for patient's head; 5 contrast media power injector; 6 angiographic and hemodynamic monitors; 7 crash cart; 8 pressure transducer holders; 9 table controls for integrated intravascular ultrasound and coronary hemodynamics system; 10 control panel for x-ray images; 11 table controls for movement of x-ray system; 12 undertable lead shield; and 13 foot pedal controls for fluoroscopy and cineangiography imaging. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

include fever, anemia, electrolyte imbalance (especially hypokalemia predisposing to arrhythmias), or other systemic illnesses needing stabilization (Table 20–3).

TABLE 20–2. Indications for Cardiac Catheterization

Indications	Procedures
Suspected or known coronary artery disease	
Angina: New onset, unstable, stable refractory to medical treatment, atypical	LV, COR
Ischemia: positive stress test, evaluation before major surgery, atypical chest pain of coronary spasm	LV, COR, ERGO
Myocardial infarction, unstable angina postinfarction, failed thrombolysis	LV, COR, RH
Shock	LV, COR, RH
Mechanical complications (ventricular septal defect, rupture of wall, or papillary muscle)	LV, COR, RH
Sudden cardiovascular death	LV, COR, R + L
Valvular heart disease	LV, COR, R + L, AO
Congenital heart disease (before anticipated corrective surgery)	LV, COR, R + L, AO
Aortic dissection	AO, COR
Pericardial constriction or tamponade	LV, COR, R + L
Cardiomyopathy	LV, COR, R + L, BX
Initial and follow-up assessment for heart transplant	LV, COR, R + L, BX

Abbreviations: AO, aortography; BX, endomyocardial biopsy; COR, coronary angiography; ERGO, ergonovine provocation of coronary spasm; ETT, exercise tolerance test; LV, left ventriculography; RH, right heart oxygen saturations and hemodynamics (eg, placement of Swan-Ganz catheter); R + L, right and left heart hemodynamics.

TABLE 20–3. Contraindications to Cardiac Catheterization

Absolute contraindications
Inadequate equipment or catheterization facility
Relative contraindications
Acute gastrointestinal bleeding or anemia
Anticoagulation (or known uncontrolled bleeding diathesis)
Electrolyte imbalance
Infection/fever
Medication intoxication (eg, digitalis, phenothiazine)
Pregnancy
Recent cerebral vascular accident (> 1 mo)
Renal failure
Uncontrolled congestive heart failure, high blood pressure, arrhythmias
Uncooperative patient

PREPARATION OF THE PATIENT FOR CARDIAC CATHETERIZATION

The procedure should be explained to the patient (and family) in simple terms describing what will take place and the reason for each step of the procedure. The operator (preferably) or the assistant, usually a physician, obtains consent. The operator should explain the risks for routine cardiac catheterization to the patient and family. The incidence of major risks of stroke, death, and myocardial infarction is approximately 0.1%. The minor risks of vascular injury, allergic reaction, bleeding, hematoma, and infection range from 0.04% to 5% and should be discussed.

Certain patient groups are at higher risk for complications (Table 20–4). Patient information should be tailored to the specific individual and the associated clinical problems (Table 20–5). Patients with diabetes mellitus, renal insufficiency, or previously reported hypersensitivity to iodinated contrast media constitute groups who need special consideration. For diabetic patients, the dose of neutral protamine Hagedorn (NPH)

TABLE 20–4. Conditions of Patients at Higher Risk for Complications of Catheterization

Acute myocardial infarction
Advanced age (> 75 y)
Aortic aneurysm
Aortic stenosis
Congestive heart failure
Diabetes
Extensive three-vessel coronary artery disease
Left ventricular dysfunction (left ventricular ejection fraction < 35%)
Obesity
Prior cerebral vascular accident
Renal insufficiency
Suspected or known left main coronary stenosis
Uncontrolled hypertension
Unstable angina

TABLE 20–5. Conditions Requiring Special Preparations for Cardiac Catheterization

Condition	Management
Allergy	Treat potential hypersensitivity
Prior contrast studies	Contrast premedication, iso-osmolar contrast
Iodine, seafood	Contrast reaction algorithm, patient discussion
Premedication allergy	Hold premedication
Lidocaine	Use bupivacaine
Patients receiving anticoagulation	Defer procedure or use radial approach
(INR > 1.5)	Vitamin K
	Fresh-frozen plasma
	Hold heparin or administer protamine
Diabetes	Hydration, urine output greater than 50 mL/h
	Hold metformin for 48 h, caution for use of protamine in patients receiving NPH insulin (protamine reaction)
Decreased renal function	If renal insufficiency, consider postponing catheterization
	Metformin usage (prone to CIN)
	Consider urgency and risk of lactic acidosis
	Limit contrast volume, IV hydration, ensure high urine output
Electrolyte imbalance (K^+, Mg^{2+}, or Mg^{++})	Defer procedure, correct electrolytes
Arrhythmias	Defer procedure, administer antiarrhythmics
Anemia	Defer procedure, identify and control bleeding site, consider transfusion
Dehydration	Hydration

Abbreviations: CIN, contrast-induced renal failure; INR, international normalized ratio; NPH, neutral protamine Hagedorn.

insulin should be cut by 50% because overnight fast with their normal morning dose of insulin causes hypoglycemia. Patients receiving NPH insulin are also at higher risk for protamine reactions. Some diabetic patients who receive an antihyperglycemic agent, such as metformin, are at risk for lactic acidosis, particularly patients with chronic renal failure. There is no evidence that withholding metformin for 48 hours before a catheter procedure in patients with normal renal function provides any clinical benefit.

TECHNIQUES OF VASCULAR ACCESS

Traditionally, femoral access has been the most commonly used technique in the United States. Because of familiarity, training, and the potential need for large-diameter interventional equipment, the femoral artery approach is often preferred to the radial artery approach. However, in recent years, most large laboratories routinely use radial artery access as their preferred diagnostic and interventional approach because of significantly fewer access-related complications and in some studies better late outcomes. The discussion of the radial technique will follow the femoral approach, although many operators familiar with current clinical data would advocate a "radial first" method when possible.

PERCUTANEOUS FEMORAL ARTERY PUNCTURE

In brief, the femoral artery at the inguinal ligament is palpated. After general localization, the proposed puncture site should be verified by fluoroscopy using the tip of a metal clamp. The clamp should be near the medial edge of the middle of the head of the femur (Fig. 20–2). Palpation identifies the center line of the artery, and the needle is advanced at a 30-degree angle to the vessel, puncturing only the front wall. The guidewire is then advanced through the needle, and the needle is exchanged for a valved sheath. A more detailed explanation of percutaneous femoral puncture technique can be found elsewhere.[1-3]

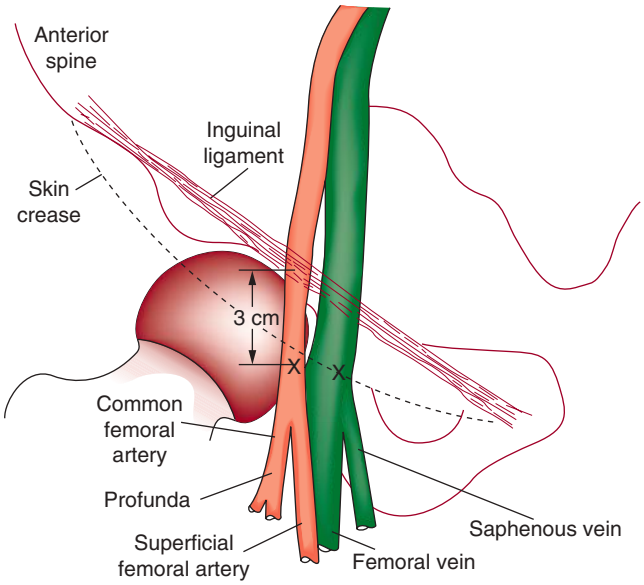
PERCUTANEOUS FEMORAL VEIN PUNCTURE

The femoral vein is located approximately 1 cm medial to the femoral artery (FA). The procedure for femoral vein percutaneous entry is similar to that for the FA, with only minor differences. Because venous pressure is low, it may be difficult to detect back bleeding from the needle on entry. A syringe may be attached to the Seldinger needle and gently aspirated during needle advancement. Once in the vein, the remainder of the venous sheath placement is completed in the same fashion as described for the femoral arterial sheath insertion.

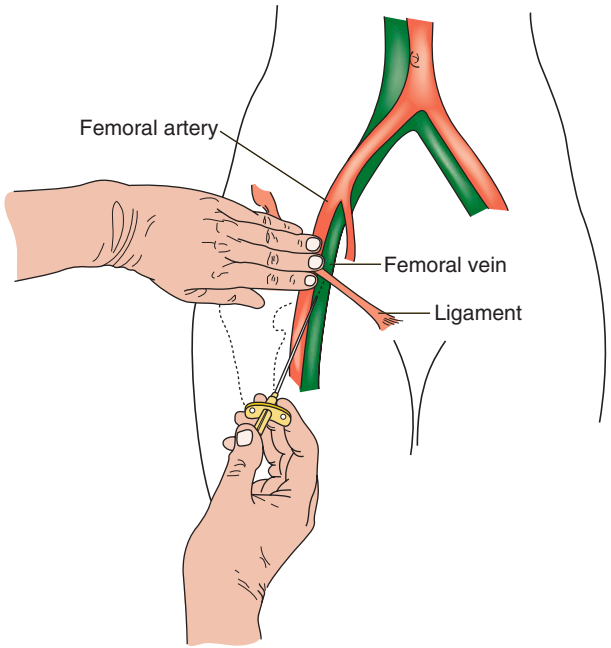
RADIAL ARTERY CATHETERIZATION

The radial artery approach is associated with reduced bleeding complications and increased patient satisfaction and laboratory/hospital workflow. In patients with claudication, chronic arterial insufficiency, diminished or absent pulses, or bruits over the iliofemoral area, radial access should be the preferred method. The radial approach is favored for several additional reasons: (1) the radial artery is easily accessible and is not located near significant veins or nerves; (2) the superficial artery location permits rapid and secure compression band hemostasis; (3) the radial artery access provides the most secure hemostasis in fully anticoagulated patients; (4) because of the collateral flow to the hand through the ulnar artery, the rare case of radial artery occlusion is generally well tolerated; and (5) patient comfort is enhanced by the ability to sit up and walk immediately after the procedure.

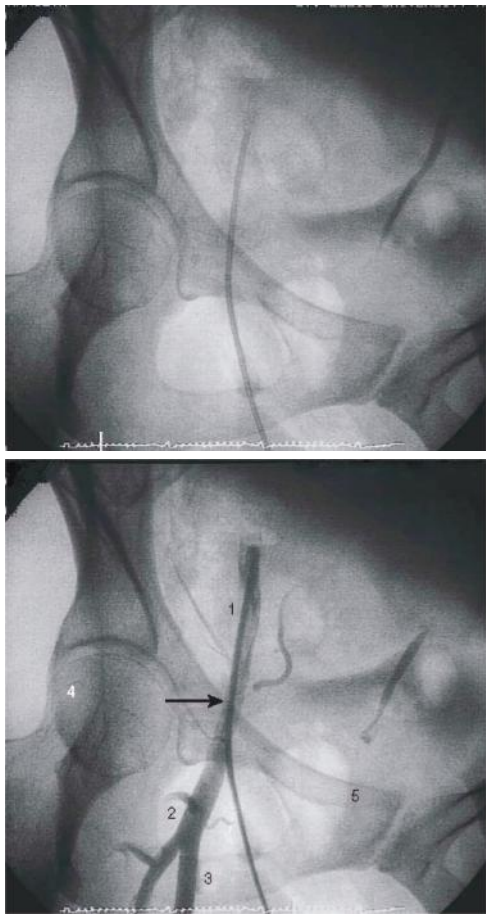
Patients with a normal Allen test (Fig. 20–3) are candidates for the radial approach with 4- to 6-Fr sheaths and catheters. Small or female patients are more likely to have spasm of the radial artery, but this can be treated effectively with the use of intra-arterial nitroglycerin or verapamil. Specially coated hydrophilic sheaths reduce spasm on sheath insertion and removal. Arterial puncture using a short 22-gauge micropuncture needle or cannula system, a 0.021-inch guidewire, and a radial artery sheath system (10 cm) is performed in a manner similar to FA puncture. Ultrasound imaging facilitates radial artery access (Fig. 20–4). Studies have demonstrated improved first-pass rates, reduced number of attempts, and lower times to achieve success when using ultrasound compared with palpation alone.[4] After the puncture, the 0.021-inch guidewire is inserted, followed by the arterial sheath. Once the sheath is inserted, 5000 units of intravenous heparin is given. Many laboratories use an antispasm "cocktail" of nitroglycerin (250–500 mcg) or verapamil (2.5–5.0 mg) given through the sheath. Although most procedures are performed from the right wrist because of the laboratory setup, the use of the left radial artery approach in some patients (especially those < 5'5" tall) provides easier manipulation of the standard preformed Judkins shapes with minimal effort. The left arm should be brought over the abdomen so that the operator can work from his or her usual position on the right of the patient. Figure 20–5 shows radial artery access technique. After vascular access has been secured, angiographic and hemodynamic data are obtained, as discussed below.



A



B



C

FIGURE 20–2. **A.** Anatomy relevant to percutaneous catheterization of the femoral artery (FA) and vein. The right FA passes underneath the inguinal ligament, which connects the anterior-superior iliac spine and public tubercle. The arterial skin nick (indicated by *X*) should be placed approximately 1 1/2 to 2 fingerbreadths (3 cm) below the inguinal ligament and directly over the FA pulsation. The venous skin nick should be placed at the same level but approximately one fingerbreadth medial. **B.** Femoral vein puncture with the needle at a 30- to 45-degree angle aiming medially toward the umbilicus. **C.** Femoral artery landmarks. *Top*, Angiogram of sheath in the femoral artery in the anteroposterior projection. *Bottom*, Correct positioning is seen relative to angiographic landmarks. 1, common femoral artery; 2, bifurcation of profunda; 3, superficial femoral artery; 4, midpoint of femoral head; 5, iliac-symphysis pubis ridge (inguinal ligament line). Upper limit of common femoral artery is lower margin of the inferior epigastric artery. **A**, reproduced with permission from Baim DS, Grossman W. Percutaneous approach including transseptal and apical puncture. In: Baim DS, Grossman W, eds. Grossman's *Cardiac Catheterization, Angiography, and Intervention*. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **B**, reproduced with permission from Tilkian AG, Daily EK. Cardiovascular Procedures: *Diagnostic Techniques and Therapeutic Procedures*. St Louis: Mosby;1986. **C**, reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

A

Oxymetry + Plethysmography
The clamp sensor is applied to the thumb

Type	Radial artery compression: Start	Radial artery compression: After 2 min.		
A	Oxymetry +	Oxymetry +	No damping of pulse tracing immediately after radial artery compression	15%
B	+	+	Damping of pulse tracing	75%
C	–	+	Loss of pulse tracing followed by recovery of pulse tracing within 2 minutes	5%
D	–	–	Loss of pulse tracing without recovery within 2 minutes	5%

B

FIGURE 20–3. **A.** Method of checking patency of palmar arch, the modified Allen Test. **B.** Pulse waveforms for the Barbeau's oximetric test. Method: 1. The radial and ulnar arteries are simultaneously occluded while the patient makes a fist; 2. The hand is opened, appearing blanched; and 3. The ulnar artery is released, and the hand observed for change in color. Satisfactory palmar arch flow is present if color returns to palm in 5 to 15 seconds. A reverse Allen test can also be performed by occluding the ulnar artery. The Barbeau oximetric method involves using the pulse oximeter; the pulse wave is displayed with both arteries open. The radial artery is then compressed and the pulse wave observed. Four grades of wave forms were defined: type A, no change in pulse wave; type B, a damped but distinct pulse wave with recovery; type C, loss of phasic pulse waveform with recovery within 2 minutes; type D, loss of pulse waveform without recovery. Radial cannulation can proceed with either type A or B and not recommended for type C or D.

ACCESS SITE HEMOSTASIS

After the catheterization procedure has been completed and the catheters removed, the sheath is flushed. The femoral sheath should be removed when the activated clotting time is less than 180 to 200 seconds.

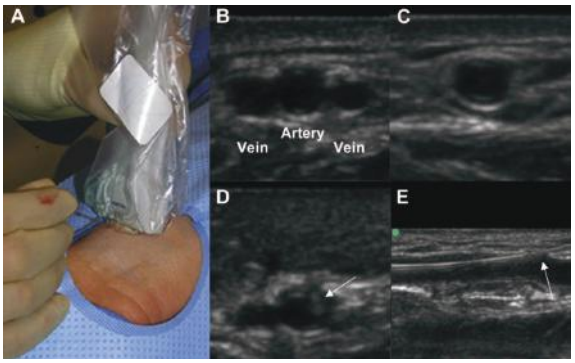


FIGURE 20–4. Ultrasound access. Technique for ultrasound-guided radial access. **A.** Position of draped ultrasound probe over radial artery. **B.** Visualization of radial artery and veins. **C.** Compression closes radial veins to reveal pulsatility of artery. **D.** Visualization of the needle tip (*arrow*) compressing and puncturing the artery. **E.** Confirmation of the wire position (*arrow*) in the radial artery in the longitudinal plane. Reproduced with permission from Seto AH, Roberts JS, Abu-Fadel MS, et al: Real-time ultrasound guidance facilitates transradial access: RAUST (Radial Artery access with Ultrasound Trial). *JACC Cardiovasc Interv*. 2015 Feb;8(2):283-291.[4]

Protamine may be used to reverse active or poorly controlled bleeding. Caution should be used in giving protamine to patients receiving NPH insulin, who may have higher likelihood of a protamine reaction.

To remove the FA sheath, gentle pressure is applied over the puncture site while the sheath is removed, taking care not to crush the sheath and *strip* clot into the distal artery. Firm downward pressure is applied for 15 to 30 minutes, periodically evaluating distal pulses. After manual hemostasis is achieved, a clear adhesive bandage is used to cover the wound. Large dressings are generally ineffective to prevent bleeding and obscure the puncture site. Additional methods to secure postprocedure femoral arterial hemostasis include mechanical pressure clamps and a variety of vascular closure devices (VCDs), which reduce the time to hemostasis and allow for early ambulation. VCDs are helpful in anticoagulated patients and patients with back pain or in those who cannot lie flat. The advantages and disadvantages of VCDs are summarized in Table 20–6. All VCDs should be used after imaging of the iliofemoral artery and avoided in patients with peripheral vascular disease or low arterial puncture (at or below the femoral bifurcation). Patients at high risk for femoral arterial complications may benefit from a VCD; such patients are listed in Table 20–7.

For radial artery hemostasis, a plastic bracelet with a pressure pad (or inflatable bladder) is placed around the wrist during sheath removal. With pressure over the puncture site, the sheath is gently withdrawn and the radial band compression increased. With the inflatable wrist band, the pressure can be set just above that producing

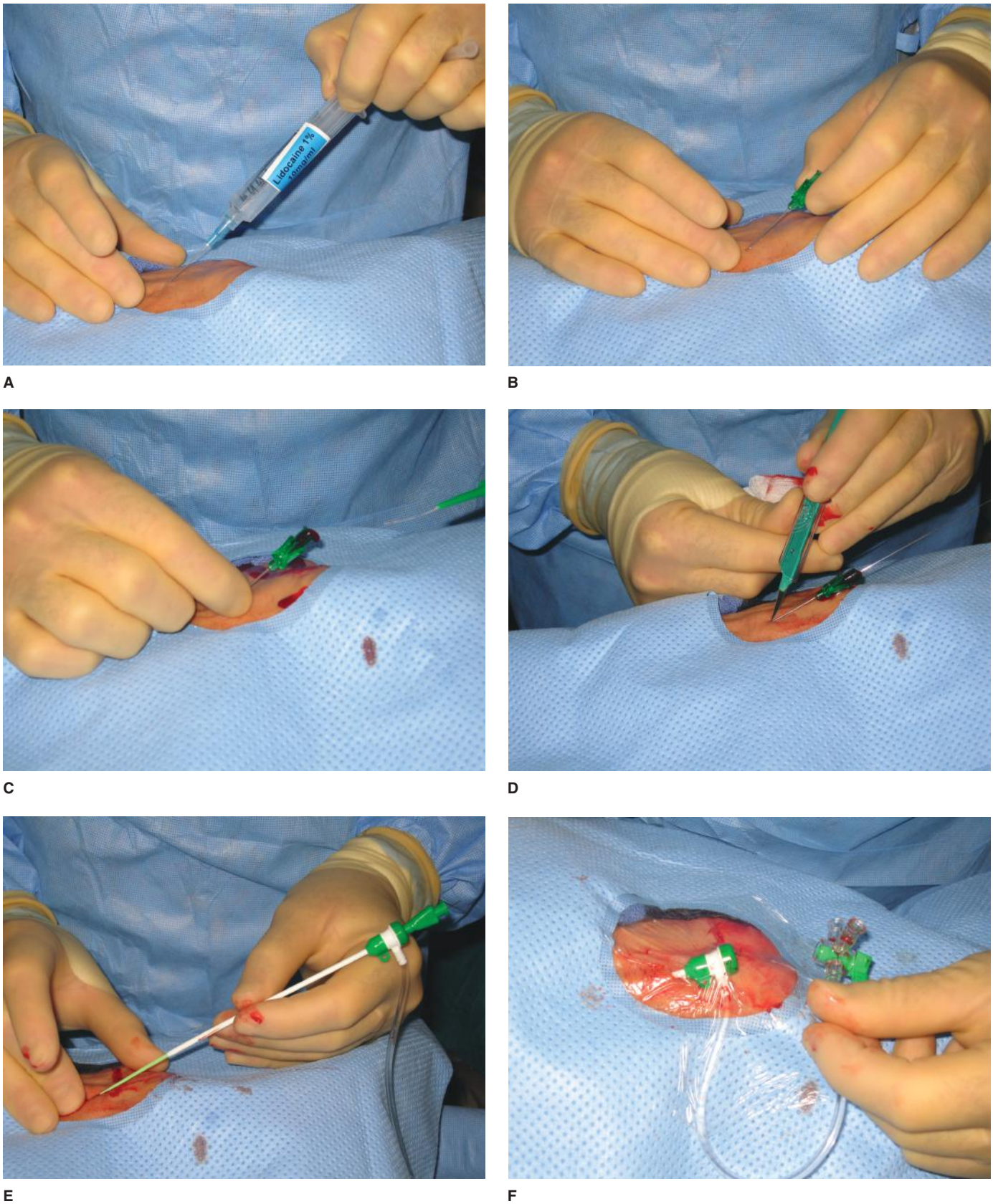


FIGURE 20–5. Radial artery access technique. **A.** After preparation and positioning wrist, lidocaine is given over puncture site. **B.** Micropuncture needle inserted. **C.** Guidewire advanced through micropuncture needle. **D.** Small skin incision to ease sheath advancement. **E.** Sheath advancement. **F.** Secured sheath in right wrist.

TABLE 20–6. Closure Devices

Device	On the Market	Mechanism	Advantages	Disadvantages	Sheath Sizes
Angio-Seal (St Jude Medical, St Paul, MN)	1997 to present	Collagen and suture mediated	Secure closure, long track record	Intra-arterial component, possible thromboembolic complications, infection/inflammation related to plug, concern over restick	6 and 8 Fr
Perclose (Abbott Vascular, Redwood City, CA)	1997 to present	Suture mediated	Secure closure	Intra-arterial component, steep learning curve, device failure may require surgical repair	5 to 8 Fr
StarClose (Abbott Vascular, Redwood City, CA)	2005 to present	Nitinol clip	No intra-arterial component	Adequate skin tract, calcium needed to prevent device failure	5 to 6 Fr
MynxGrip (Access Closure, Mountain View, CA)	2007 to present	PEG hydrogel plug	No intra-arterial component, potential use in PVD	Possible intra-arterial injection of sealant, increased minor complications	5 to 7 Fr
Vascade, Catalyst (Cardiva Medical, Sunnyvale, CA)	2013 to present	Extravascular collagen plug	No permanent intra-arterial component	Prolonged dwell time, need for adjunctive manual compression (catalyst)	5 to 7 Fr
Exoseal (Cordis, Bridgewater, NJ)	2014 to present	Passive extravascular Polyglycolic acid plug	No intra-arterial component	Passive closure	5 to 7 Fr
Axera (Arstasis, Redwood City, CA)	2011 to present	Controlled arteriotomy	No foreign material, hemostasis by hydrostatic pressure only against angled arteriotomy	Controlled dissection, limited by calcium	5 to 6 Fr
FISH (Morris Innovative, Bloomington, IN)	2007 to present	Intraluminal deployment of small intestinal mucosa	Active closure, possibly outside the cath lab	Approved for diagnostic cases only	5 to 8 Fr

Abbreviations: PEG, polyethylene glycol; PVD, peripheral vascular disease.

leaking, allowing good blood flow and delivery of hemostatic factors to the puncture site (a technique called patent hemostasis). The patient is checked 1 to 2 hours later and the bracelet is removed. The patient can be discharged 2 to 4 hours later. Figure 20–6 shows this common method of radial artery hemostasis.

EQUIPMENT IN THE CATHETERIZATION LABORATORY

The modern catheterization laboratory is a marvelous center of technologic development with sophistical x-ray imaging systems, image display monitors, pressure transducer systems, and a variety of disposable catheters, manifolds, and equipment to make the procedure quick and safe. Figure 20–7 shows the cardiac catheterization laboratory with its major components.

CATHETERS FOR ANGIOGRAPHY AND HEMODYNAMICS

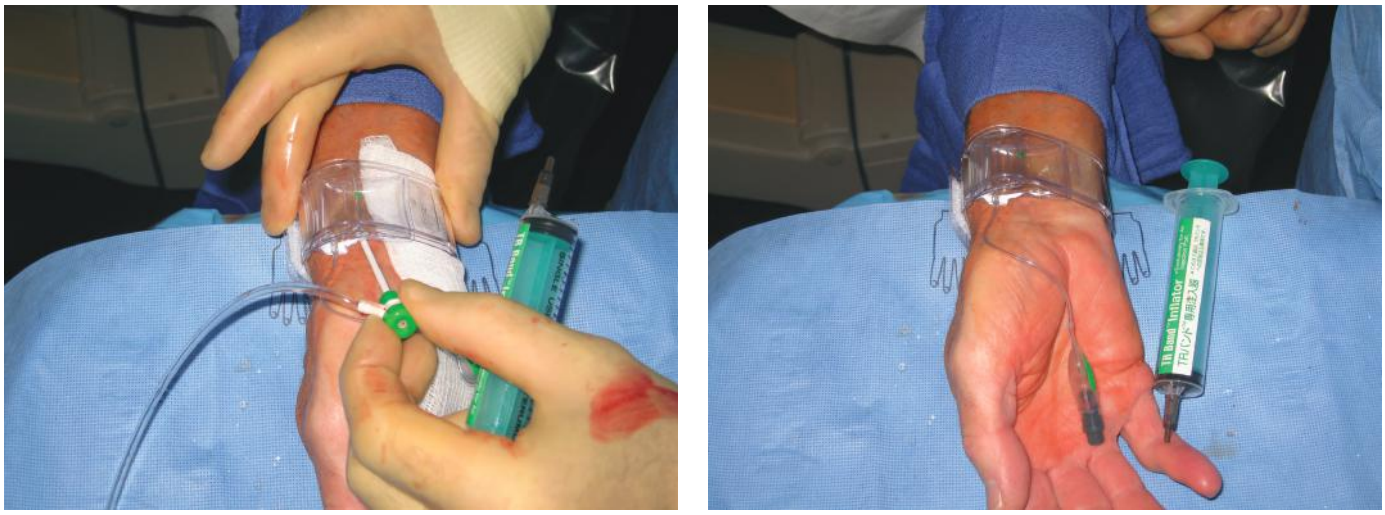
The choice of catheters for coronary angiography depends on the approach (radial or femoral access) and physician preferences. Numerous shapes and sizes of catheters are available. Basic, routine catheters that are preshaped for normal anatomy are useful for both the radial and femoral approaches. There is an array of unique "universal" (one catheter for both left and right coronary artery) shapes for the radial approach, designed to aid the angiographer through difficult aortic anatomy (Fig. 20–8).

Judkins-Type Coronary Catheters

The Judkins catheters have unique preshaped curves and tapered end-hole tips. The Judkins left coronary catheter has a double curve. The length of the segment between the primary and secondary curve determines the size of the catheter (ie, 3.5, 4.0, 4.5, or 5.0 cm). The proper size of the left Judkins catheter is selected depending on the length and width of the ascending aorta. The ingenious design of the left Judkins catheter permits cannulation of the left coronary artery without any major catheter manipulation except the slow advance of the catheter under fluoroscopic control. The catheter tip follows the ascending aortic border and falls into the left main coronary ostium, often with an abrupt jump. A left 4-cm Judkins catheter is appropriate for most adult patients. The Judkins right coronary catheter is sized by the length of the secondary curve and comes in 3.5-, 4.0-, and 5.0-cm sizes. The 4.0-cm catheter is

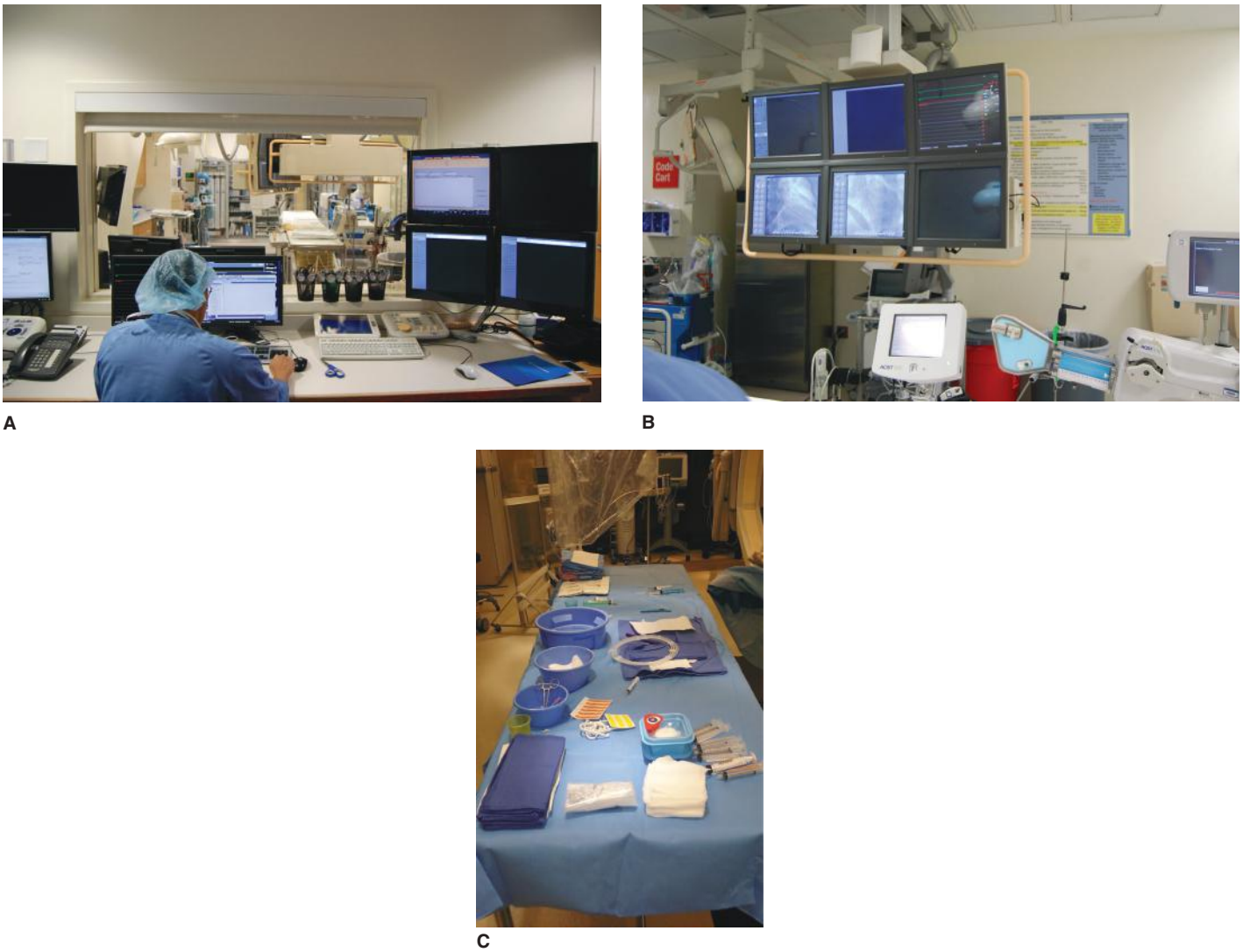
TABLE 20–7. Patients Who May Benefit from a Vascular Closure Device

Obese patients
Patients with hypertension
Elderly
Women
Patients with aortic regurgitation
Patients who suffer from coagulopathy or those receiving anticoagulant or antiplatelet agents
Patients with back pain
Patients desiring early ambulation and discharge



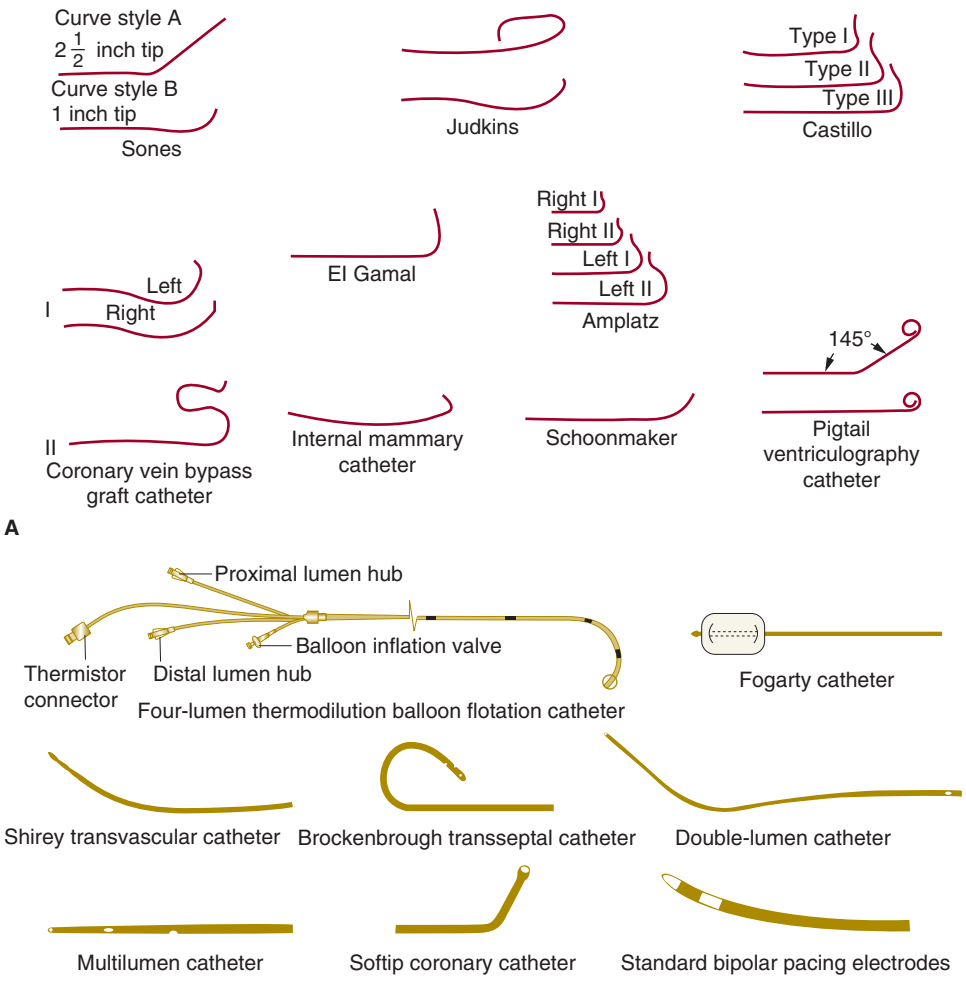
A B

FIGURE 20–6. Radial hemostasis band. **A.** Terumo pressure band applied, pressure pad inflated, and sheath removed. **B.** Final wrist hemostasis band in place.



A B C

FIGURE 20–7. The cardiac catheterization laboratory. **A.** The view from the control room into the laboratory. **B.** The image monitor bank showing the hemodynamic and angiographic display monitors. **C.** The back table holding the sterile supplies used during the procedure.



C

FIGURE 20–8. **A.** Catheters in common use for selective coronary arteriography, ventriculography, and right heart catheterization. **B.** Universal-shaped catheters commonly used for radial artery catheterization. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

adequate for most cases. The right Judkins catheter is advanced into the ascending aorta (usually in the left anterior oblique [LAO] projection) with the tip directed caudally.

Amplatz-Type Catheters

The left Amplatz-type catheter is a preshaped half circle with the tapered tip extending perpendicular to the curve. Amplatz catheter sizes (left 1, 2, and 3, and right 1 and 2) indicate the diameter of the curve. In the LAO projection, the tip is advanced into the left aortic cusp. Further advancement of the catheter causes the tip to move upward into the left main trunk. It is necessary to advance the Amplatz catheters slightly to disengage the catheter tip upward and out of the left main ostium. If the catheter is pulled instead of first being advanced, the tip moves downward and into the left main or circumflex artery. Amplatz catheters have a higher risk of coronary dissection than Judkins-style catheters. The right Amplatz (modified) catheter has a smaller but similar hook-shaped curve. The catheter is advanced into the right coronary cusp. Like Judkins right catheters, the catheter is rotated clockwise for 45 to 90 degrees. The same maneuver is repeated at different levels until the right coronary artery (RCA) is entered. After coronary injections, the catheter may be pulled, advanced, or rotated out of the coronary artery.

Multipurpose Catheters

These catheters are mostly gently curved catheters with an end hole and two side holes placed close to the tapered tip. The multipurpose catheter can be used for both left and right coronary intubation and left ventriculography.

Universal Coronary Catheters

The radial artery technique uses Judkins catheters and several uniquely shaped "universal" catheters (eg, JACKY, TIGER, SARAH; see Fig. 20–8) designed to cannulate both the left and right arteries (and ventriculography by some, a practice to be avoided). Although multiple-tip side holes permit ventriculography, the small diameter and high-pressure jet of power-injected contrast has been known to perforate the heart. The pigtail catheter is safer.

Ventriculography Catheters

The safest and most commonly used ventriculographic catheter is the pigtail catheter. This catheter has a tapered tip, preshaped to make a full circle 1 cm in diameter. Five to 12 side holes are located on the straight portion of the catheter above the curve. A multipurpose catheter can be used for ventriculography, but a high-pressure contrast jet from the end hole often produces ventricular tachycardia; rarely, myocardial tissue contrast staining or perforation occurs. The new operator should concentrate on mastering a few types of catheters and gain extensive experience in using them effectively.

Right Heart Catheters

A balloon-tipped flotation catheter (see Fig. 20–8A) is the most widely used for right heart catheterization. The balloon tip allows the catheter to float through the right side of the heart safely and easily in most cases. The balloon *wedges* in the distal pulmonary artery (PA) to measure pressure transmitted backward through pulmonary capillaries (hence the name *pulmonary capillary wedge pressure*) from the left atrium, and reflecting LV filling pressures. Thermodilution cardiac output measurements are exclusive to this type of catheter. The balloon-tipped catheter can be introduced through any venous access route. The balloon is inflated with air. The balloon-tipped catheters do not provide good torque control. Thus right heart catheterization in patients with right atrial (RA) enlargement, right ventricular (RV) dilation, pulmonary hypertension, or tricuspid regurgitation may be difficult from the femoral vein approach.

THE FLUOROSCOPIC IMAGING SYSTEM

Passage of catheters and acquisition of angiographic data requires a high-resolution image-intensifier television system with digital cineangiographic capabilities. The components are mounted on a U or C arm, which is a support with the radiograph tube beneath the patient and the image intensifier above. Rotation of the arm allows viewing over a wide range of different angles. Some laboratories have two systems perpendicular to each other (called *biplane*) and use a double monitoring system, providing simultaneous visualization of the heart from two different angles.

THE PHYSIOLOGIC MONITOR AND RECORDING SYSTEM

During catheterization, it is necessary to monitor and record electrocardiographic and hemodynamic signals. Digital recording systems record and archive physiologic data with the ability to display several pressure or electrocardiographic signals simultaneously. Computations of derived cardiac parameters are also a function of these systems.

CONTRAST POWER INJECTOR

A high-pressure contrast media injector is needed to administer a large bolus (20–50 mL) of contrast media into the left ventricle at a rate of 12 to 15 mL/s; pulmonary arteries, at 10 to 25 mL/s; or aortic arch, at 20 to 30 mL/s. When properly set and flushed, the power injector can be used to inject contrast into the coronary arteries (at a rate of 3–8 mL/s). Some injector systems also incorporate a pressure transducer and have replaced traditional manifolds with stopcocks.

RESUSCITATION EQUIPMENT AND DEFIBRILLATOR

Every cardiovascular laboratory is equipped with an emergency crash cart containing emergency drugs, oxygen, airways, suction apparatus, and other emergency equipment. A defibrillator should be charged and ready for use during a procedure.

STERILE EQUIPMENT AND SUPPLIES

The angiographer works from a sterile pack or tray that contains the various supplies needed to perform the procedure. The pack will contain syringes and needles, local anesthetic, basins for flushing solutions, small drapes and towels, clamps, scalpels, pressure manifolds and connecting tubing, and the like.

RADIOGRAPHIC CONTRAST MEDIA

CHARACTERISTICS OF CONTRAST MEDIA

All contrast media contain three iodine molecules attached to a fully substituted benzene ring. Traditional high-osmolar contrast agents (> 1400 mOsm) were ionic monomers with sodium or meglumine as the cation. These were frequently (10%) associated with peripheral arterial vasodilatation, transient myocardial dysfunction, and osmotic diuresis resulting in reduced circulating volume and blood pressure. As a result, they are now rarely used for intravascular procedures. Modern radiographic contrast media include nonionic monomeric agents (and one ionic dimeric agent), which have approximately the same viscosity and iodine concentration but less than 50% of the

TABLE 20–8. Properties of Radiographic Contrast Agents

Quality	High	Low	Low	Iso-osmolar
Osmolality	> 1500	600	600–1000	280
Ionicity	Ionic	Ionic	Nonionic	Nonionic
No. of benzene rings	Monomer	Dimer	Monomer	Dimer
Name	Diatrizoate Iothalamate	Ioxaglate	Iohexol Iopamidol Ioversol Iopromide Iomeprol	Iodixanol
Viscosity	Low	Low	Intermediate	High
Ratio (iodine/osmotically active particles	1.5	3	3	6

osmolality of the high-osmolar agents. The advantages of the nonionic, low-osmolar agents include less hemodynamic loading, patient discomfort, binding of ionic calcium, depression of myocardial function and blood pressure, and fewer anaphylactoid reactions. Currently, nonionic, low-osmolar agents are routine for nearly all patients, and are especially helpful in patients with poor LV function, renal disease, diabetes, or prior reactions to contrast media. Iodixanol is a nonionic, iso-osmolar dimer that is particularly well tolerated and used selectively in patients with peripheral arterial procedures and prior contrast reactions. All media are excreted predominantly by glomerular filtration with a normal half-time of excretion of 20 minutes. Table 20–8 lists properties of radiographic contrast agents, and Table 20–9 provides a summary of contrast agents used in the catheterization laboratory.

CONTRAST MEDIA REACTIONS

There are three types of contrast allergies (Table 20–10): (1) minor cutaneous and mucosal manifestations, (2) smooth muscle and minor anaphylactoid responses, and (3) major cardiovascular and anaphylactoid responses.

TABLE 20–9. Contrast Agents in the Catheterization Laboratory

Contrast Type	Chemical Name	Trade Name	Manufacturer
High-osmolar ionic	Diatrizoate	Renografin	Bracco
	Diatrizoate	Hypaque	Amersham
	Iothalamate	Conray	Mallinckrodt
	Metrizoate	Isopaque	Winthrop
Low-osmolar nonionic	Iopamidol	Isovue	Bracco
	Iohexol	Omnipaque	Amersham
	Ioversol	Optiray	Mallinckrodt
	Ioxilan	Oxilan	Guerbet
Low-osmolar ionic dimer	Ioxaglate	Hexabrix	Mallinckrodt
Isoosmolar nonionic dimer	Iodixanol	Visipaque	Amersham

Reproduced with permission from Klein LW, Sheldon MW, Brinker J, et al: The use of radiographic contrast media during PCI: a focused review: a position statement of the Society of Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2009 Nov 1;74(5):728-746.[5]

TABLE 20–10. Anaphylactoid Reactions to Contrast Medium

Cutaneous and mucosal
Angioedema
Flushing
Laryngeal edema
Pruritus
Urticaria
Smooth muscle
Bronchospasm
Gastrointestinal spasm
Uterine contraction
Cardiovascular
Arrhythmia
Hypotension (shock)
Vasodilatation

Major reactions involving laryngeal or pulmonary edema often are accompanied by minor or less severe reactions. Although some reactions to a pretest contrast dose may be violent (but rarely life-threatening), pretesting has been found to be of no value in determining who will have an adverse reaction. Although definitive data are lacking on the true effectiveness of premedication to prevent allergic reactions, patients reporting allergic reactions to contrast media should be pretreated with prednisone and diphenhydramine. The routine for the laboratories may vary, but common dosages include 60 mg of prednisone the night before and 60 mg of prednisone the morning of, along with 50 mg of oral diphenhydramine given at the time of call to the catheterization laboratory. Additional routine treatment of patients with prior allergic reactions with an H_2 blocker (eg, cimetidine) does not appear to have any benefit.

CONTRAST-INDUCED RENAL FAILURE

Dehydrated patients or those with diabetes or renal insufficiency are at risk for contrast-induced nephropathy (CIN). Advanced precautions to limit CIN include hydration, minimizing contrast delivered, and maintenance of large-volume urine flow (> 200 mL/h). These patients should be hydrated intravenously the night before the procedure. After the contrast study, intravenous fluids should be liberally continued unless intravascular volume overload is a problem. Furosemide, mannitol, and calcium channel blockers are not helpful in reducing CIN. No pharmacologic regimen has been demonstrated to perform better than volume loading with normal saline. A decreased urine output after the procedure that is unresponsive to increased intravenous fluids indicates that renal insufficiency is probable. All types of contrast agents (ionic, nonionic, low-osmolar, iso-osmolar) are associated with a similar incidence of CIN.[5,6]

COMPLICATIONS OF CARDIAC CATHETERIZATION

Table 20–11 lists the major and minor complications of cardiac catheterization. For diagnostic catheterization, analysis of the complications in more than 200,000 patients indicates the incidence of risks as follows: death (< 0.2%), myocardial infarction (< 0.05%) stroke (< 0.07%),

TABLE 20–11. Complications of Cardiac Catheterization

Major
Cerebrovascular accident
Death
Myocardial infarction
Ventricular tachycardia, fibrillation, or serious arrhythmia
Other
Aortic dissection
Cardiac perforation, tamponade
Congestive heart failure
Contrast reaction/anaphylaxis/nephrotoxicity
Heart block, asystole
Hemorrhage (local, retroperitoneal, pelvic)
Infection
Protamine reaction
Supraventricular tachyarrhythmia, atrial fibrillation
Thrombosis/embolus/air embolus
Vascular injury, pseudoaneurysm
Vasovagal reaction

serious ventricular arrhythmia (< 0.5%), and major vascular complications (thrombosis, bleeding requiring transfusion, or pseudoaneurysm; < 1%)[7] (Table 20–12). Vascular complications are highest with the brachial approach and lowest with the radial technique. Risks are higher in well-described subgroups and with all therapeutic interventions, with rates increasing with increasing complexity of the procedure.

COMPLICATIONS OF ARTERIAL ACCESS

The most common complication from femoral catheterization is hemorrhage and local hematoma formation, increasing in frequency with the increasing size of the sheath, the amount of anticoagulation, and obesity. Other common complications (in order of decreasing frequency) include retroperitoneal hematoma, pseudoaneurysm, arteriovenous (A-V) fistula, arterial thrombosis, stroke, sepsis with or without abscess formation, and cholesterol or air embolization. The frequency of these complications is increased in obese patients; high-risk procedures; critically ill elderly patients with extensive atheromatous disease; patients receiving anticoagulation, antiplatelet, and fibrinolytic therapies; and concomitant interventional procedures. A retroperitoneal hematoma, a potentially life-threatening complication, should be suspected in patients with hypotension, tachycardia, pallor, a rapidly falling hematocrit post-catheterization, or lower abdominal or back pain. This complication is associated with high femoral arterial puncture and full anticoagulation. Pseudoaneurysm is a complication associated with low femoral arterial puncture (usually below the head of the femur). With ultrasound imaging techniques, the pseudoaneurysm can easily be identified and nonsurgical closure performed. Manual compression of the expansile growing mass guided by Doppler ultrasound with or without thrombin or collagen injection is an acceptable therapy for femoral pseudoaneurysm. Compared with the femoral approach, the radial approach is associated with significantly lower rates of vascular complications.

TABLE 20–12. Incidence of Major Complications of Diagnostic Catheterizations

	Percent
Death	0.11
Myocardial infarction	0.05
Neurologic	0.07
Arrhythmia	0.38
Vascular	0.43
Contrast	0.37
Hemodynamic	0.26
Perforation	0.03
Other	0.28
Total (patients)	1.98

Data from Noto TJ, Johnson LW, Krone R, et al: Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). Cathet Cardiovasc Diagn. 1991;24:75-83 and Uretzky BF, Weinert HH: *Cardiac Catheterization: Concepts, Techniques, and Applications*. Walden: Blackwell; 1997.

PROTAMINE REACTIONS

Protamine is sometimes used to reverse the systemic effects of heparin. Minor protamine reactions may appear as back and flank pain or flushing with peripheral vasodilation and low blood pressure. Major protamine reactions simulate anaphylaxis. Although rare, major reactions involve marked facial flushing and vasomotor collapse, which may be fatal. The incidence of major protamine reactions in patients with NPH insulin-dependent diabetes is 27%, compared with 0.5% in patients with no history of insulin use. It is recommended that diabetic patients on NPH insulin and patients with allergies to fish undergoing cardiac catheterization do so without use of protamine or, when necessary, that protamine be administered cautiously in anticipation of a major reaction.

COMPLICATIONS OF RIGHT HEART CATHETERIZATION

Right heart catheterization may be complicated by arrhythmia caused by stimulation of the RV outflow tract, which may result in atrioventricular block, or rarely, right bundle branch block (Table 20–13). Significant but transient ventricular arrhythmias occur in more than

TABLE 20–13. Complications of Right Heart (Pulmonary Artery) Catheterization

	Major	Minor
Access	Pneumothorax	Hematoma
	Hemothorax	Thrombosis
	Tracheal perforation (subclavian route)	
Sepsis	Cellulitis	
Intracardiac	Right ventricular perforation	Ventricular arrhythmia
	Heart block (right bundle branch block)	
	Pulmonary rupture	
	Pulmonary infarction	
	Tricuspid regurgitation	
	Dislodgement of pacemaker leads	

30% of patients undergoing right heart catheterization and are terminated when the catheter is readjusted. Sustained ventricular arrhythmias have been reported, especially in unstable patients or those with electrolyte imbalance, acidosis, or concurrent myocardial ischemia. In patients with left bundle branch block, a temporary pacemaker may be needed if right bundle branch block occurs during right heart catheterization.

CARDIAC ANGIOGRAPHY

Cineangiography is the term used to describe the x-ray photographing of cardiac and vascular structures. This term persists even though radiographic images are now acquired and stored electronically on digital computer imaging media rather than on cine film. Angiographic images are the visual representation of the vascular conduits and networks connected to internal structures (organs) and, at times, predict cardiovascular function. Angiography is the primary method of defining coronary anatomy in patients, providing an anatomic map of the site, severity, and the shape and distribution of stenotic coronary lesions. In addition, the vessel size or diameter, presence of intracoronary thrombus, and extent of diffuse atherosclerotic diseases can be assessed. The mass of myocardium served by various diseased arteries and an approximate index of coronary flow and identification of collateral vessels may be obtained by astute angiography. By using provocative maneuvers, the presence of coronary spasm can be ascertained. The functional significance of a coronary stenosis can be assessed by measuring coronary flow or pressure directly, using information obtained both at rest and during maximal coronary vasodilatation. Successful angiography requires a completed chain of actions beginning with the positioning of the patient on the table, acquiring the angiographic image, recording and storing the digital image data, and finally displaying the images for review and analysis. A full discussion of assessing the functional significance of coronary angiographic lesions is provided later in this chapter.

Left ventriculography is often part of a coronary angiographic study. Contrast opacification of the contracting ventricle enables one to make a visual analysis of wall motion. Ventricular systolic and diastolic volumes and ejection fraction can be calculated. Examination of the LV wall motion helps identify viable myocardium. For research purposes, LV wall motion can be further evaluated by the addition of stress such as atrial pacing, pharmacologic agents, or exercise. LV angiography also documents the degree of mitral regurgitation.

CORONARY ARTERIOGRAPHY

Expertise in performing coronary arteriography is achieved by training in an active laboratory and performing hundreds of coronary arteriograms under close supervision. In this way, the physician can gain needed skills and an appreciation of the potential hazards of coronary arteriography and coronary interventions. The American College of Cardiology/American Heart Association (ACC/AHA) appropriate use recommendations for the indications of diagnostic catheterization are provided in Appendix 20–1.

IMAGING TECHNIQUES AND PITFALLS

Appreciating the techniques of cannulating coronary arteries and grafts will provide better angiographic information needed for accurate diagnosis and therapies.

The nomenclature of coronary angiographic imaging is based on the position of the image intensifier relative to the patient. The image intensifier is directly over the patient collecting the x-rays from the source under the patient (Fig. 20–9 and Table 20–14). The x-ray source and image intensifier are connected on a C-shaped armature and move in unison in opposite directions around the patient. The body surface of the patient that faces the observer determines the specific view. This relationship holds true whether the patient is supine, standing, or rotated.

The various positions are:

Anteroposterior (AP) position: The image intensifier is directly over the patient with the beam traveling perpendicular back to front (ie, from posterior to anterior) through the patient lying flat on the radiograph table. An oblique view is achieved by turning the left/right shoulder forward (anterior) to the camera (image intensifier) or in the catheterization laboratory, rotating the image intensifier toward the shoulder.

Right anterior oblique (RAO) position: The image intensifier is to the right side of the patient.

LAO position: The image intensifier is to the left side of the patient.

Cranial/caudal position: This nomenclature refers to image intensifier angles in relation to the patient's long axis.

Cranial: The image intensifier is tilted toward the head of the patient.

Caudal: The image intensifier is tilted toward the feet of the patient.

Cranial views are best for the left anterior descending artery, and caudal views are best for the circumflex artery. Cranial and caudal views are used to *open* overlapped coronary segments that are foreshortened or obscured in regular views.

THE LEFT CORONARY ARTERY: COURSE AND BRANCHES

The ostium of the left coronary artery originates from the left sinus of Valsalva near the sinotubular ridge. The anterior descending artery is usually best visualized in a cranially angulated RAO view. If the orientation of the anterior descending artery is unusually superior, a caudally angulated LAO view or a straight lateral view may be helpful. The circumflex coronary artery travels in the A-V groove, after its right-angle origin from the left anterior descending artery. Its course is quite variable. The artery may terminate in one or more large, obtuse marginal branches coursing over the lateral to posterolateral LV free wall. The circumflex may continue as a large artery in the interventricular groove. In 10% to 15% of cases, the circumflex gives rise to a posterior descending artery (Fig. 20–10). The artery that supplies the major posterior descending artery is commonly referred to as the dominant artery. The circumflex artery in the A-V groove is best seen in either caudally angulated LAO or RAO views (see Fig. 20–10).

THE RIGHT CORONARY ARTERY: COURSE AND BRANCHES

The RCA ostium normally is located in the right sinus of Valsalva. It may be high near the sinotubular ridge or above it, in the midsinus, or occasionally low near the aortic valve. The artery commonly courses upward from the plane of the aortic valve and then travels in the right A-V groove to reach the posterior LV wall (Fig. 20–11). Along the way, several vessels arise. The conus branch and sinus node arteries branch first, followed by small RV branches, then a large branch that courses over the right ventricle. The right coronary continues to become the posterior descending artery before reaching the crux of the heart (junction of the interventricular and interatrial septa). The posterior descending artery sends branches at right angles into the posterior interventricular groove, providing the perforating branches to the basal and posterior one-third of the septum. An RCA that supplies the major posterior descending branch has been referred to as a

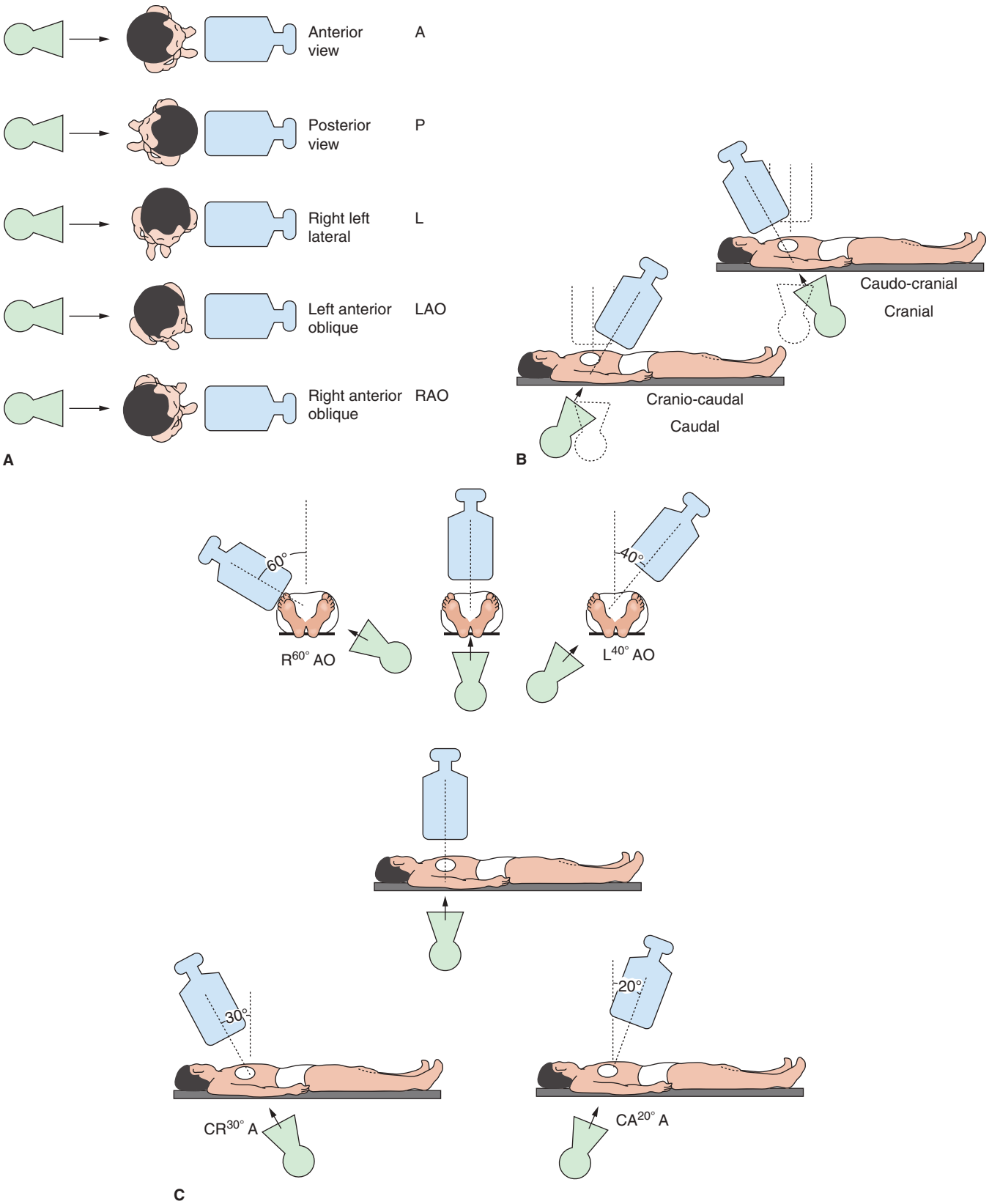


FIGURE 20–9. Nomenclature for radiographic projections. The *small black arrowheads* show the direction of the x-ray beam. **A.** Anterior (*A*), posterior (*P*), lateral (*L*), and oblique (*O*). **B.** If the intensifier is tilted toward the feet of the patient, a caudal (CA) view is produced. If the intensifier is tilted toward the head of the patient, a cranial (CR) view is produced. **C.** CR and CA oblique views. Reproduced with permission from Paulin S: Terminology for radiographic projections in cardiac angiography. *Cathet Cardiovasc Diagn*. 1981;7(3):341–344.

TABLE 20–14. Angiographic Views for Specific Coronary Artery Segments

Coronary Segment	Origin/Bifurcation	Course/Body
Left main	AP	AP
	LAO cranial	LAO cranial
	LAO caudal[a]	
Proximal LAD	LAO cranial	LAO cranial
	RAO caudal	RAO caudal
Mid-LAD	LAO cranial	
	RAO cranial	
	Lateral	
Distal LAD	AP	
	RAO cranial	
	Lateral	
Diagonal	LAO cranial	RAO cranial, caudal, or straight
	RAO cranial	
Proximal circumflex	RAO caudal	LAO caudal
	LAO caudal	
Intermediate	RAO caudal	RAO caudal
	LAO caudal	Lateral
Obtuse marginal	RAO caudal	RAO caudal
	LAO caudal	
	RAO cranial (distal marginals)	
Proximal RCA	LAO	
	Lateral	
Mid-RCA	LAO	LAO
	Lateral	Lateral
	RAO	RAO
Distal RCA	LAO cranial	LAO cranial
	Lateral	Lateral
PDA	LAO cranial	RAO
Posterolateral	LAO cranial	RAO
	RAO cranial	RAO cranial

[a]Horizontal hearts.

Abbreviations: AP, anteroposterior; LAD, left anterior descending artery; LAO, left anterior oblique; PDA, posterior descending artery (from RCA); RAO, right anterior oblique; RCA, right coronary artery.

dominant RCA. The posterior descending artery usually stops before reaching the apex, but it may curl around the apex in association with a short anterior descending artery. After giving rise to the posterior descending artery, the RCA becomes intramyocardial at the crux, giving rise to the A-V node artery. The LV branches of the RCA are variable and cover the same area as the posterolateral branches of a large circumflex system. The proximal portion of the RCA is well seen in standard RAO and LAO views. However, because of its horizontal orientation, the origin and length of the posterior descending artery, well seen in the RAO view, is foreshortened in the LAO view. Thus cranial angulation provides a better view of the patent ductus arteriosus.

INTERPRETATION OF THE CORONARY ARTERIOGRAM

Every coronary arteriogram should be reviewed in a systematic fashion. The entire LV surface and septum should be adequately supplied with vessels. No gaps should exist. If significant vessels are missing, an occluded or anomalous artery should be suspected. Vessels with foreshortening or overlap should be examined in other angled views to better visualize and resolve the region in question.

ANGIOGRAPHIC ASSESSMENT OF CORONARY ARTERY DISEASE

An angiographic lumen narrowing or stenosis may be caused by a number of conditions such as atherosclerosis, vasospasm, dissection, thrombus, or angiographic artifact (Fig. 20–12). The operator must appreciate that unlike computed tomographic angiography (CTA), the angiogram is a lumenogram and does not permit visualization of the vessel wall to demonstrate atherosclerosis. The grading of a stenosis is most commonly reported as the percentage reduction in the diameter of the narrowed vessel site compared to the adjacent unobstructed vessel segment. Although the diameter stenosis is calculated in the projection where the greatest narrowing is seen, an exact percent narrowing is impossible because many stenoses have an eccentric morphology and a two-dimensional image does not accurately reflect the importance of only the worst luminal dimension. In fact, the severity of stenotic lesions should be classified in one of four groups: normal, minimal, moderate, or severe narrowing. It should be noted that the stenotic lumen is compared with a nearby unobstructed lumen, which indeed may have diffuse atherosclerotic disease and thus appears *angiographically* normal but may still be diseased. This fact explains why postmortem examinations report much more plaque than is seen on angiography. The angiographic *normal* adjacent proximal segments may be larger than distal segments, explaining the large disparity between several observer estimates of stenosis severity. Also note that area stenosis is always greater than diameter stenosis and assumes the lumen is circular, whereas in reality the lumen is usually eccentric. For nonquantitative reports, the length of a stenosis may be simply mentioned (eg, left anterior descending [LAD] artery proximal segment stenosis diameter 25%, long or short). Other features of a coronary lesion (eg, eccentricity, distribution of calcifications, true diseased segment length) may not be appreciated by angiography and require intravascular ultrasound (IVUS) or optical coherence tomography (OCT) imaging (Fig. 20–13). Because of the subjective nature of visual lesion assessment, there is a ± 20% variation between readings of two or more experienced angiographers, especially for lesions narrowed by 40% to 70%. Different angiographers may interpret the same angiographic image quite differently, and the same angiographer may render a different interpretation at a time remote from the first reading. In addition, there may be disagreement about the number of major vessels with 70% stenosis approximately 30% of the time. The correspondence between angiographic diameter narrowings of 40% to 75% and abnormal physiology and myocardial ischemia is poor. For such lesions, noninvasive (stress testing) or direct physiologic measurements (intracoronary pressure or flow, specifically at this time fractional flow reserve [FFR]) of impaired flow rather than intravascular imaging with ultrasound or OCT should be used to validate decisions for revascularization.

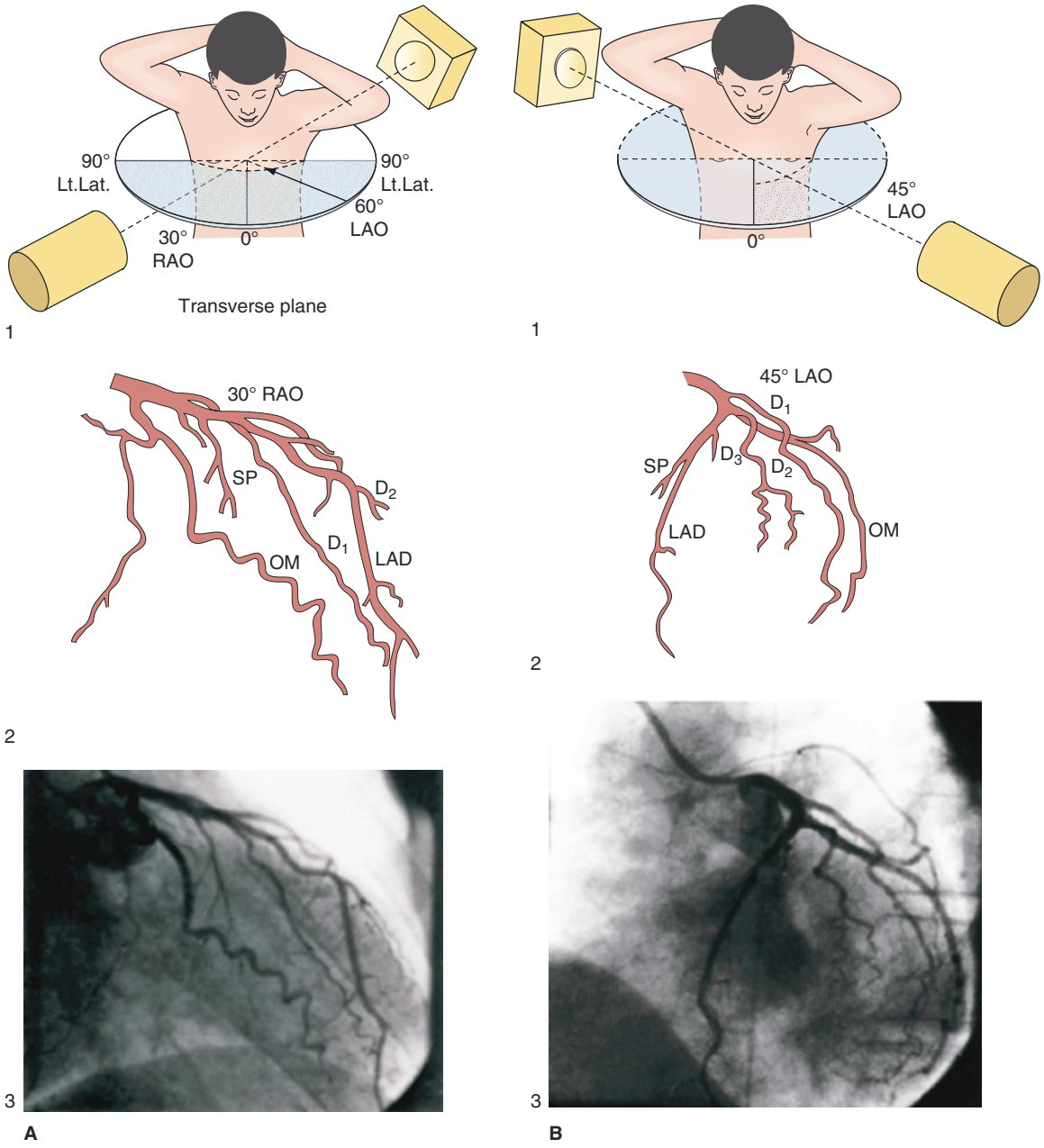


FIGURE 20–10. Diagrammatic representations of the standard right anterior oblique (RAO) and left anterior oblique (LAO) views (**A**) without cranial angulation and (**B**) with cranial angulation of the left coronary artery, the direction of the x-ray beam, and the position of the overhead image intensifier. In the RAO view, most of the left coronary artery is well visualized in this projection, but there is considerable overlap of the middle left anterior descending (LAD) artery and the diagonal branches. When the left main, circumflex, and diagonal branches have a leftward initial course, the long axis of these arterial segments is projected away from the image intensifier, preventing optimal visualization from the RAO view. The image intensifier is placed anteriorly in an RAO position relative to the patient. Diagrammatic representation of the LAO left coronary angiogram and the direction of the x-ray beam in this view. The value of this view depends in large part on the orientation of the long axis of the heart. When the heart is relatively horizontal, the LAD coronary artery and diagonal branches are seen end-on throughout much of the course. In this illustration, the longitudinal axis is an intermediate position and there is moderate foreshortening of the anterior descending and diagonal branches in their proximal portions. The LAO projection is frequently inadequate to visualize the proximal LAD and its branches: the left main segment, which is directed toward the image tube and therefore foreshortened, and the proximal circumflex coronary artery, which may be obscured by overlapping vessels, as in this illustration. The LAO projection is frequently used to visualize the distal LAD and its branches, the midcircumflex coronary artery in the arteriovenous groove, and the distal right coronary artery that is filling via collaterals from the left coronary artery. The image intensifier is above the patient in an LAO position. The left coronary angiogram in the 45-degree LAO with 30 degrees of cranial angulation and the direction of the x-ray beam used to produce this view. This is the most valuable view of the left coronary artery in most patients. Foreshortening of the left main and proximal left anterior descending and diagonal branches present in the LAO view is usually overcome by cranial angulation of the image intensifier. OM, obtuse marginal.

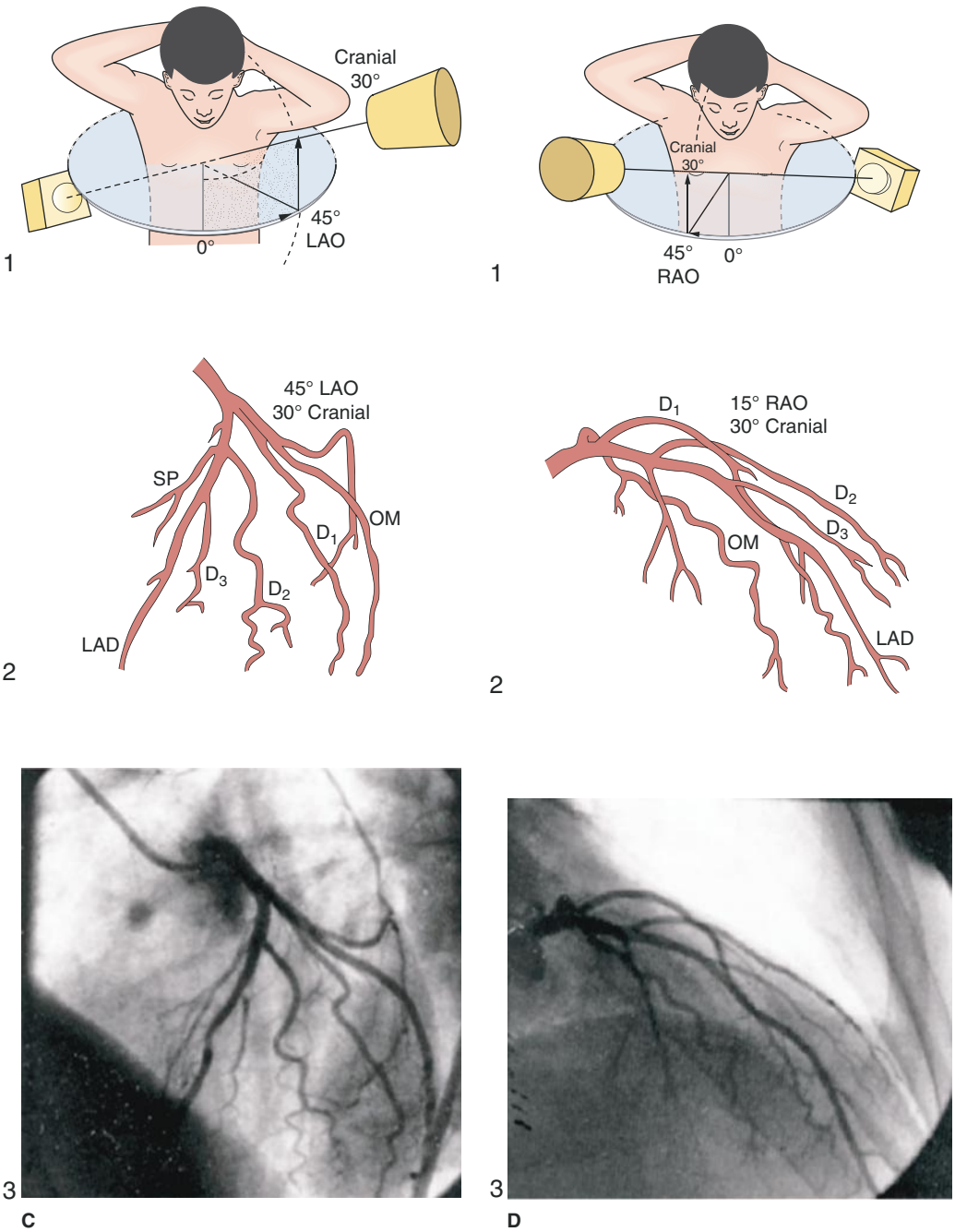


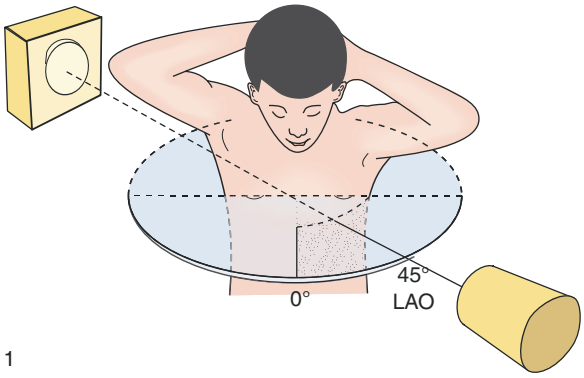
FIGURE 20–10 (*Continued*)

QUANTITATIVE ANGIOGRAPHIC ASSESSMENT

The degree of coronary stenosis is usually a visual estimation of the percentage of diameter narrowing using the proximal assumed normal arterial segment as a reference. The ratio of normal-to-stenosis artery diameter, widely used in clinical practice, is inadequate for a true quantitative methodology. The intraobserver variability may range between 40% and 80%, and there is frequently a range as wide as 20% on interobserver differences. Quantitative methodologies include digital calipers, automated or manual edge detection systems, or densitometric analysis with digital angiography and are principally used for research where consistency of imaging is required.[8]

INTRAVASCULAR ULTRASOUND OR OPTICAL COHERENCE TOMOGRAPHIC IMAGING IN THE ASSESSMENT OF CORONARY ARTERY NARROWINGS

IVUS generates a tomographic, cross-sectional image of the vessel and lumen (see Fig. 20–13). IVUS is inherently different from physiologic measurements. IVUS provides only anatomic information, including plaque characteristics, lesion length, and lumen dimensions. It is complementary to both angiography and physiology, allowing a more thorough investigation of the disease within the vessel wall. By better determining plaque characteristics, IVUS also is useful in guiding selection of interventional equipment, such as the need for plaque debulking.



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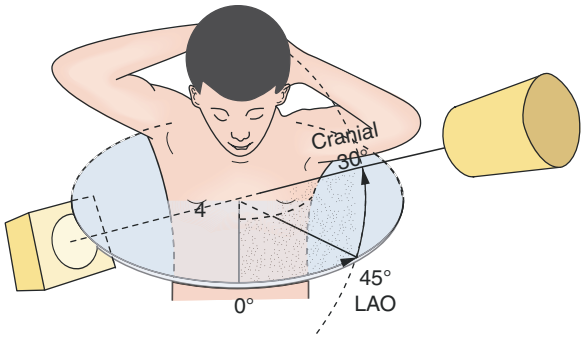

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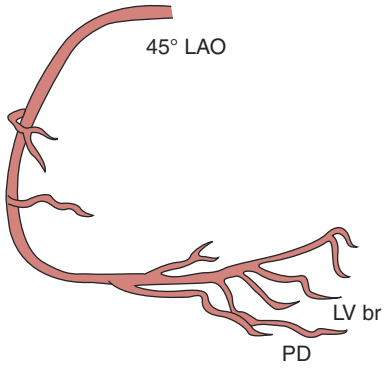

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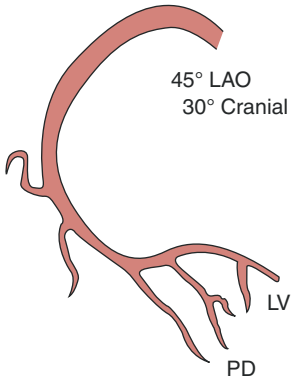

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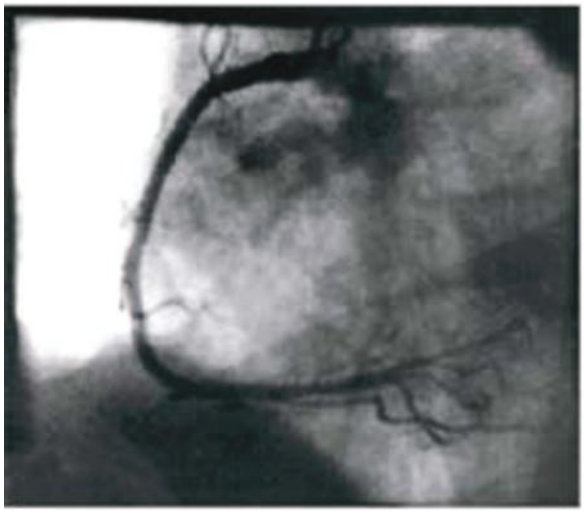

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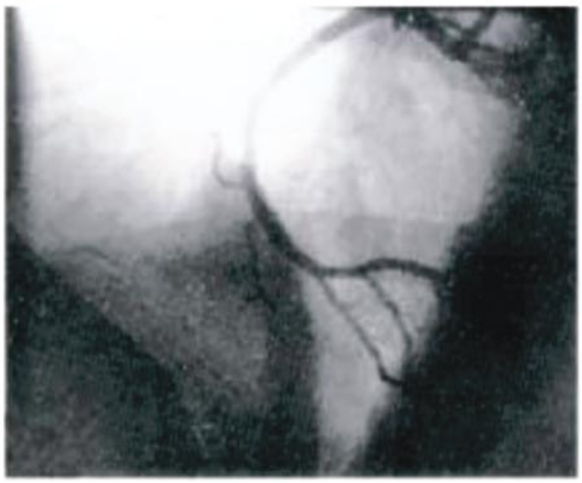
A



3

B

FIGURE 20–11. Diagrammatic illustration of the direction of the x-ray beam and the right coronary artery in the 45-degree left anterior oblique (LAO) projection. This view is excellent for visualizing the proximal mid- and distal right coronary artery in the atrioventricular groove, because the direction of the x-ray beam is perpendicular to these arterial segments. Ostial lesions of the right coronary artery are now well visualized if the proximal right coronary artery takes an anterior direction from the aorta and therefore originates in a direction parallel to the x-ray beam. This usually can be overcome by turning to a more severe left oblique projection. The posterior descending and left ventricular (LV) branches of the right coronary artery, which pass down the posterior aspect of the heart toward the apex, are severely foreshortened because the long axis of these vessels is in the same direction as the x-ray beam. The proximal posterior descending branches can be visualized by cranial angulation of the overhead intensifier or from a right oblique view. The image intensifier is in the standard LAO position. Lesions in the posterior descending or LV branches can be well visualized. When the right coronary artery originates anteriorly from the aorta, the proximal portion of the vessel is frequently well seen in this projection.

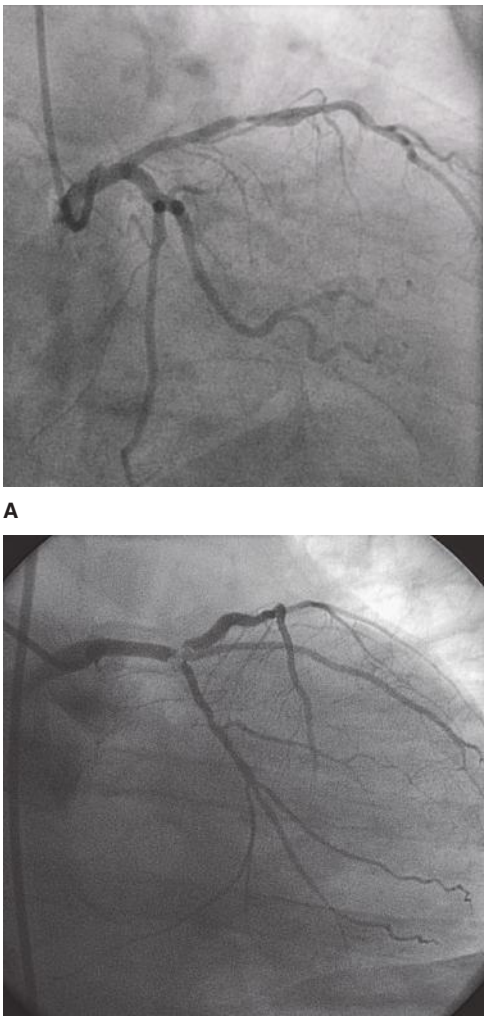


FIGURE 20–12. **A.** Left anterior descending artery in the right anterior oblique (with cranial angulation) view of high-grade lesion in its midportion. **B.** Cineangiographic frame of left main coronary stenosis shows critical narrowing requiring immediate revascularization.

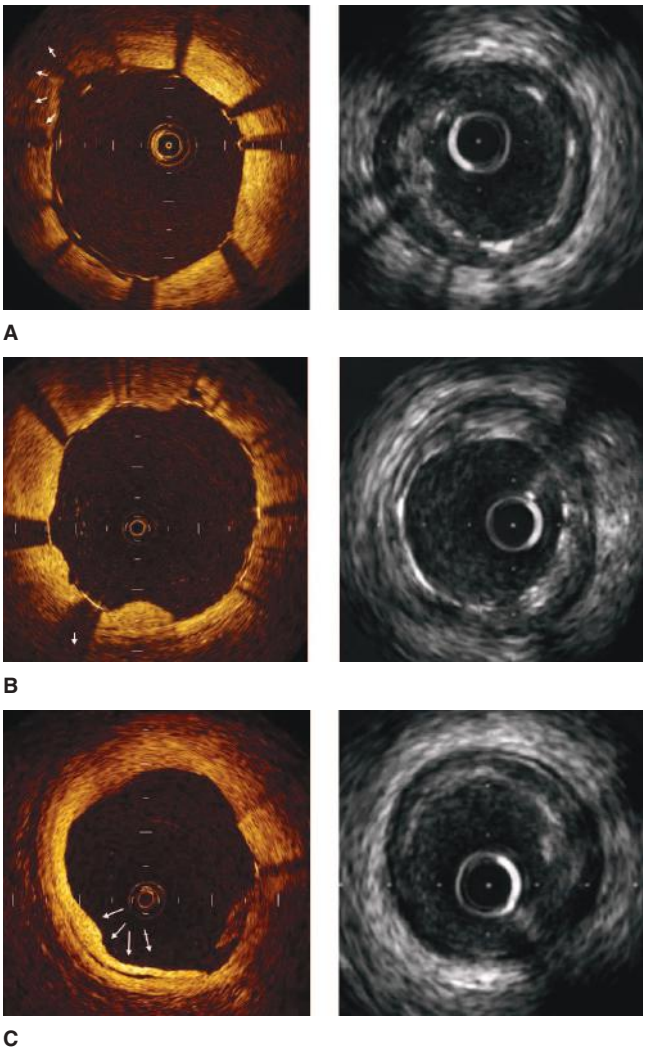


FIGURE 20–13. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) imaging of the coronary artery. **A.** Images showing unopposed stent struts by OCT (left) and IVUS (right). Light is blocked by metal struts creating radial line shadows. On IVUS struts are bright white spots of high reflectance. **B.** OCT images of tissue protrusion between the asymmetrically distributed stent struts. This small change in tissue is not well seen by IVUS because of lower resolution of tissue. **C.** OCT showing linear lucency of coronary artery dissection (*arrows*). The IVUS image also shows separation of the internal layers from the media.

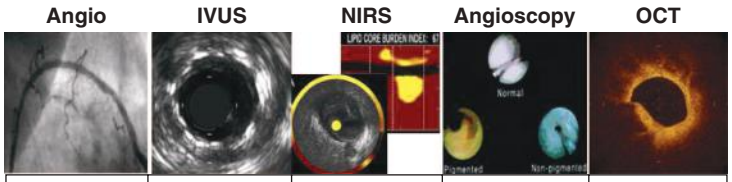
Intracoronary OCT is a catheter-based optical imaging modality, providing high-resolution cross-sectional images of the coronary wall. OCT is an interferometric technique, employing near-infrared light. By analyzing the coherence of the light reflections, the OCT imaging catheter permits structual imaging with 10- to 20-mcm level of resolution. The OCT catheter is nearly identical to an IVUS catheter except that the fiberoptic imaging core replaces the ultrasound imaging core. The catheter is introduced into the artery over a guidewire exactly like the IVUS catheter. Images are acquired during rapid automated pullback after an injection of saline or contrast to displace blood and clear the viewing field. Compared to IVUS, OCT has superior resolution to evaluate certain features of the vulnerable plaque, such as plaque rupture, intracoronary thrombus, thin-capped fibroatheroma, and macrophages within the fibrous caps. For stent placement, OCT can visualize stent malapposition and tissue protrusion after stenting and neointimal hyperplasia at late follow-up. One drawback of OCT in comparison to IVUS is its shallow depth of penetration (1–2 mm), limiting assessment of plaque composition. Figure 20–13 show examples of OCT in coronary artery interventions. OCT may replace IVUS for certain applications, such as assessing stent deployment. Figure 20–14 compares coronary imaging modalities that can be used in the catheterization laboratory today.

The ACC/AHA recommendations for IVUS/OCT imaging and FFR are provided in Appendix 20–2.

ANGIOGRAPHICALLY ESTIMATED CORONARY BLOOD FLOW (TIMI FLOW)

Myocardial blood flow has been assessed angiographically using the thrombolysis in myocardial infarction (TIMI) score for qualitative grading of coronary flow. TIMI flow grades 0 to 3 have become a standard description of angiographic coronary blood flow in clinical trials. In acute myocardial infarction trials, TIMI grade 3 flows have been associated with improved clinical outcomes. The four grades of flow are described as follows.[9]

1. Flow equal to that in noninfarct arteries (TIMI-3)
2. Distal flow in the artery less than noninfarct arteries (TIMI-2)
3. Filling beyond the culprit lesion but no antegrade flow (TIMI-1)
4. No flow beyond the total occlusion (TIMI-0)



	Angio	IVUS	NIRS	Angioscopy	OCT
Resolution (μm)	100–200	80–120	=	< 200	10–15
Probe size (μm)	N/A	700	1000	800	140
Contact	No	Yes	Yes	Yes	Yes
Ionizing radiation	Yes	No	No	No	No
Other	Lumen only	N/A	N/A	Surface only	Plaque character

FIGURE 20–14. Comparison of coronary imaging devices in the catheterization laboratory. angio, coronary angiography; IVUS, intravascular ultrasound imaging; NIRS, near infrared spectroscopy; OCT optical coherence tomography. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 3rd edition. Philadelphia: Elsevier; 201.

The quantitative method of TIMI flow uses cineangiography with 6-Fr catheters and filming at 30 frames per second is described elsewhere.[9] The TIMI frame count can further be quantitated for the length of the left anterior descending coronary artery for comparison to the two other major arteries; this is called the corrected TIMI frame count. The TIMI frame count method provides valuable information relative to clinical responses after coronary interventions.

COLLATERAL CIRCULATION

The opacification of a totally or subtotally (99%) occluded vessel from antegrade or retrograde filling is defined as *collateral filling*. Advances in the ability to open chronically occluded total occlusions have made the appreciation and visualization of collateral pathways a key to the success of this new approach. It is useful but difficult to establish the size of the recipient vessel exactly, whether the collateral circulation is ipsilateral (eg, same side filling, proximal RCA to distal RCA collateral supply) or contralateral (eg, opposite side filling, LAD to distal RCA collateral supply). Identification of exactly which region is affected by collateral supply will influence decisions regarding management of stenoses in the artery feeding the collateral supply. Collateral vessel evaluation is important for making decisions regarding which vessels might be protected or lost during coronary angioplasty.

PITFALLS AND ARTIFACTS IN CORONARY ARTERIOGRAPHY

There are a number of pitfalls and artifacts that make the performance and interpretation of coronary arteriography unreliable.

Short Left Main or Double Left Coronary Orifices

When the left main orifice is very short or absent, selective injection of the anterior descending or circumflex arteries may be done. The absence of circumflex or anterior descending artery filling, either primarily or through collaterals from the RCA, may indicate that the artery was missed by subselective injection or have an anomalous location.

Ostial Lesions

Contrast opacification of the aorta may obscure the origins of the left or right coronary artery ostium. The aortocoronary orifices need to be seen on a tangent with the opacified aortic sinuses. Some contrast reflux from the orifices is needed to fully opacify the ostium to see whether an ostial narrowing is present. Catheter pressure damping may indicate that there an ostial stenosis but may reflect the acute upward angle of the catheter into the wall of the coronary artery with transient tip occlusion.

Myocardial Bridges

The anterior descending, diagonal, and marginal branches occasionally run an intramyocardial course. The overlying myocardium may compress the artery during systole. If the coronary artery is not viewed carefully in diastole, this bridging may give the appearance of a stenosis.

Foreshortening

Foreshortening is the viewing of a vessel in plane with its long axis. Vessels seen on end cannot display a lesion along its length. When possible, arteries that are seen coming toward or away from the image intensifier should be viewed in angulated (cranial/caudal) views. The dense opacification of vessel segments seen end-on-end may produce the appearance of a lesion in an intervening segment.

Coronary Spasm

Coronary spasm can appear as an angiographic narrowing, provoked by mechanical stimulation, acetylcholine, cold pressor testing, or hyperventilation. Definitive diagnosis is demonstrated by relief of the narrowing either spontaneously or by nitrate administration. Intracoronary acetylcholine has also been used as a provocative test for coronary spasm. Its effectiveness is comparable to that of methylergonovine. In patients with one episode of variant angina per day, the hyperventilation provocative test is nearly as effective as methylergonovine in causing vasospasm. The end point of a pharmacologic provocative test is focal coronary narrowing, which can be reversed with intracoronary nitroglycerin. In patients with documented ST-segment elevation with chest pain and a normal coronary angiogram, provocative tests are unnecessary.

Catheter-induced spasm should be suspected when the vessel appears normal except at a location near the catheter tip, which causes mechanical stimulation. In most laboratories, the practice of giving intracoronary nitroglycerin (100–200 μg) before angiography is used to eliminate catheter-related spasm. Spontaneous coronary artery spasm may also present as an atherosclerotic narrowing. When this is suspected, an angiogram is obtained before and after administration of nitrates.

Totally Occluded Arteries or Vein Grafts

Absence of vascularity in a portion of the heart may indicate total occlusion of its arterial supply. Collateral channels often permit visualization of the distal occluded artery. Vessels filled solely by collaterals are under low pressure and may appear smaller than their actual lumen size. This finding should not exclude the possibilities for surgical anastomosis.

TABLE 20–15. Radiographic Appearance of Anomalous Origin of the Left Main Coronary Artery from the Right Sinus of Valsalva

Course of Anomalous Left Main Coronary	DOT	Eye	LAD Length	Septal Arising from LMCA
Septal	–	+ (upper CFX) (lower LMCA)	Short	Yes
Anterior	–	+ (upper LMCA) (lower CFX)	Short	No
Retroaortic	+(posterior)	–	Normal	No
Interarterial	+(anterior)	–	Normal	No

Abbreviations: +, present; –, absent (posterior and anterior are in reference to the aorta root); CFX, circumflex coronary artery; LAD, left anterior descending coronary artery; LMCA, left main coronary artery

Anomalous Coronary Arteries

Coronary arteries may arise from anomalous locations, or a single coronary artery may be present. Only by ensuring that the entire epicardial surface has an adequate arterial supply can one be confident that all branches have been visualized. Misdiagnosis of unsuspected anomalous origin of the coronary arteries is a potential problem for any angiographer. Because the natural history of a patient with an anomalous origin of a coronary artery may be dependent on the initial course of the anomalous vessel, it is the angiographer's responsibility to define accurately the origin and course of the vessel. It is an error to assume a vessel is occluded when in fact it has not been visualized because of an anomalous origin. It is often difficult even for experienced angiographers to delineate the true course of an anomalous vessel. For the most critical anomaly, the anomalous left main artery originating from the right cusp, a simple *dot-and-eye* method for determining the proximal course of anomalous artery from an RAO ventriculogram, an RAO aortogram, or selective RAO injection is proposed (Table 20–15). The RAO view best separates the normally positioned aorta and PA. Placement of right-sided catheters or injection of contrast in the PA is unnecessary and often misleading. Figure 20–15 diagrams the four common pathways of anomalous left coronary arteries. Alternative imaging modalities such as magnetic resonance imaging angiography or CTA can provide information on the course of anomalous coronary arteries and their relationship to surrounding structures.

Complications of Coronary Arteriography

Minor complications of coronary angiography include local arterial complications, arterial occlusion or stenosis, hematoma formation, false aneurysm, and infection. Major complications are potentially lethal and include thromboembolic events or depression of myocardial function caused by infarction or acute ischemia.

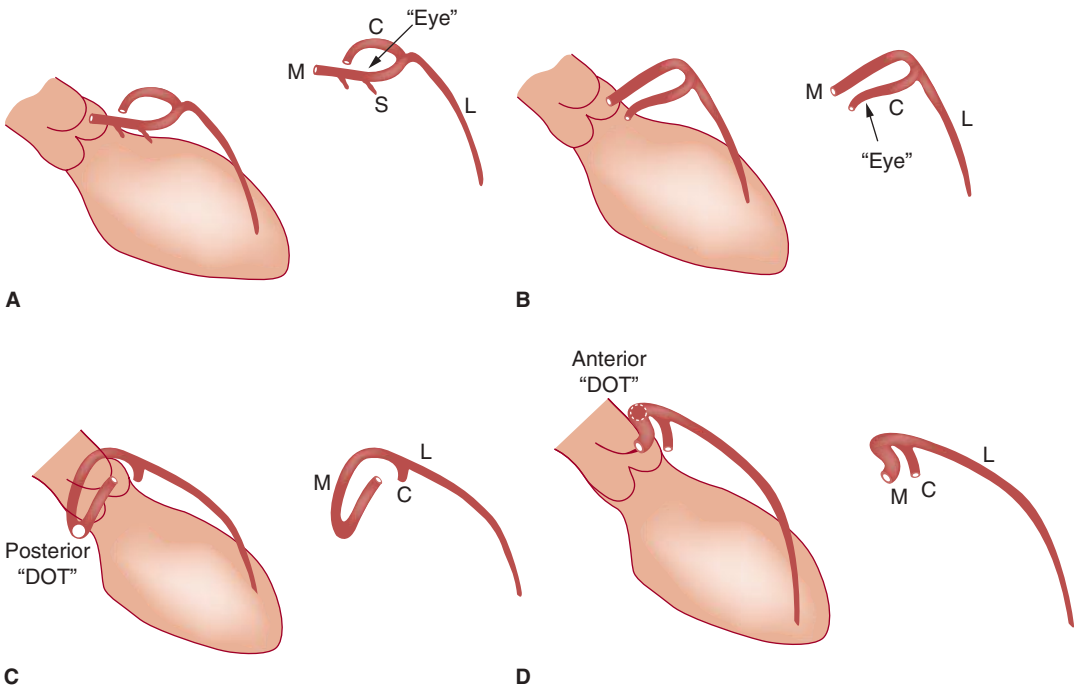


FIGURE 20–15. A. Diagram of septal course of anomalous left coronary artery. **B.** Diagram of anterior course of anomalous left coronary artery. **C.** Diagram of retroaortic course of anomalous left coronary artery. **D.** Diagram of interarterial course of left main coronary artery. C, circumflex; L, left anterior descending artery; M, left main; S, septals. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

LEFT VENTRICULOGRAPHY

Left ventriculography is the standard method for evaluating LV function in the cardiac catheterization laboratory. The normal pattern of LV contraction is a uniform and almost concentric inward movement of all points along the endocardial surface during systole. Harrison introduced the term *asynergy,* which has been used to indicate a disturbance of the normal contraction pattern. The Ad Hoc Committee for Grading of Coronary Artery Disease of the American Heart Association has recommended that five RAO segments and two LAO LV segments be defined and characterized as to wall motion (Fig. 20–16).

VENTRICULAR WALL MOTION ANALYSIS

There are three distinct types of asynergy (see Fig. 20–16B):

1. *Hypokinesia:* a diminished but not absent motion of one part of the LV wall (also called weak or poor contraction)
2. *Akinesia:* total lack of motion of a portion of the LV wall (ie, no contraction)
3. *Dyskinesia:* paradoxical systolic motion or expansion of one part of the LV wall (ie, an abnormal bulging outward during systole)

There are several methods for analyzing LV wall motion. A point system based on the regional severity of abnormal wall motion from the Coronary Artery Surgery Study is used to produce a wall motion score reflecting overall LV function. The RAO and LAO left ventriculograms are divided into five segments. Points are assigned as follows: normal contraction = 1, moderate hypokinesis = 2, severe hypokinesis = 3, akinesis = 4, and aneurysm/dyskinesis = 5. A normal score is 5. Higher scores indicate more severe wall motion abnormalities. Some methods of determining regional wall motion abnormality use computer planimetry, which is available currently on most advanced radiograph systems.

INDICATIONS FOR LEFT VENTRICULOGRAPHY

It is necessary to:

1. Identify LV function for patients with coronary artery disease, myopathy, or valvular heart disease.
2. Identify ventricular septal defect (VSD).
3. Quantitate degree of mitral regurgitation.
4. Quantitate mass of myocardium for regression of hypertrophy or other similar research studies.

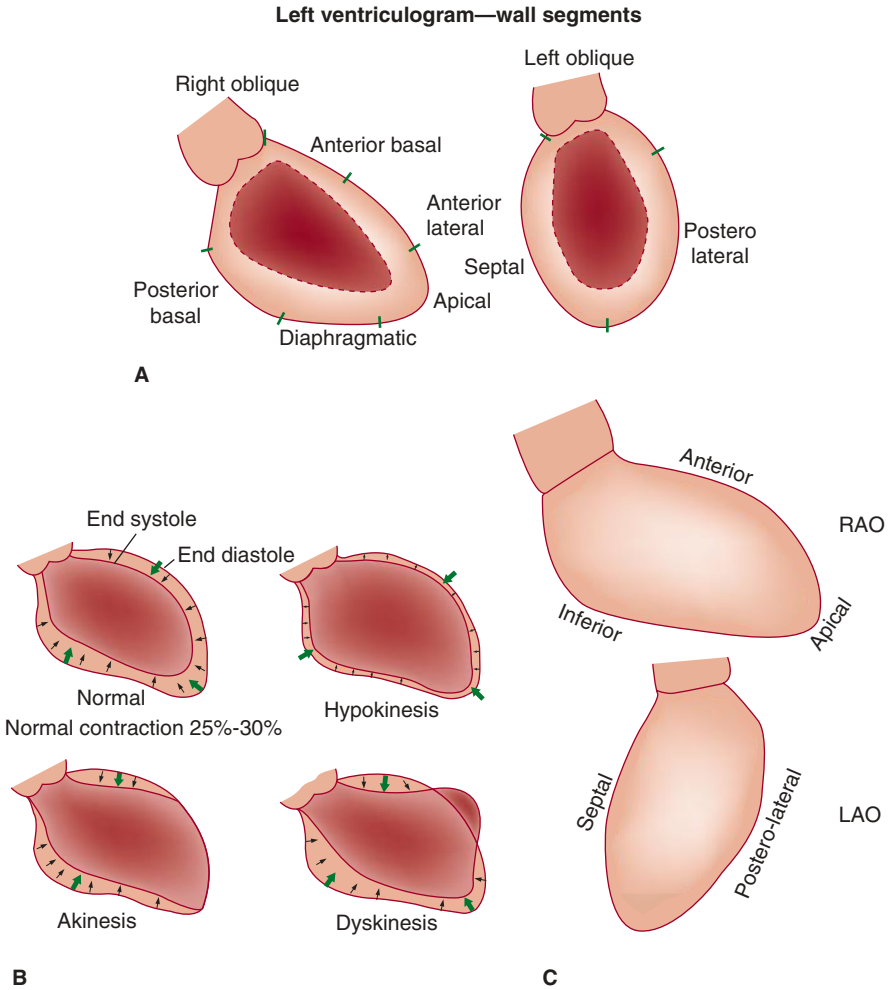


FIGURE 20–16. A. Left ventricular wall silhouette in right anterior oblique (RAO) and left anterior oblique (LAO) views. **B.** Types of ventricular asynergy. **C.** Diagrammatic representation of the zones of the left ventricular inner wall in the RAO above and (LAO below left ventriculograms. **A,** and **B,** reproduced with permission from Herman MV, Heinle RA, Klein MD, et al: Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. N Engl J Med 1967:227:225.

VENTRICULOGRAPHY TECHNIQUES

Catheters

The two most common ventriculography catheters are the pigtail and multipurpose side-hole catheters. The multipurpose catheter should be positioned freely in the LV chamber so that the high-pressure contrast jet does not produce ventricular tachycardia, contrast injection in the myocardial tissue (contrast staining), or perforation. The pigtail catheter (and halo-modified pigtail) is safer and produces less ectopy, contrast staining, and perforation than a multipurpose catheter.

Left Ventriculography Views

Standard left ventriculographic views are (1) a 30-degree RAO that visualizes the high lateral, anterior, apical, and inferior LV walls and (2) a 45- to 60-degree LAO, 20 degrees of cranial angulation that best identifies the lateral and septal LV walls.

The LAO with cranial angulation provides a view of the interventricular septum, projected on edge and tilted downward to give the best view of VSDs and septal wall motion. An elongated RAO view, which is useful for seeing the RV infundibulum and supracristal VSD, is obtained by a 30-degree axial RAO and 40 degrees of cranial angulation. The main PA and its bifurcation are seen in the frontal position with 30 degrees of cranial angulation; a steep LAO position with marked cranial angulation is also used.

ANGIOGRAPHIC ASSESSMENT OF VALVE REGURGITATION

Aortic regurgitation is qualitatively assessed by large volume contrast opacification of the aortic root. Contrast reflux into the left ventricle is then gauged against the opacification of the left ventricle over the following five beats after injection. Mild, moderate, and severe grades of aortic regurgitation are determined by visualization of contrast in the ventricle lasting only two beats, four beats with increased density, or a density equal to the ventriculogram.

For the aortic valve, contrast injections made low in the aortic root serve to quantify aortic regurgitation. In mild degrees of aortic regurgitation, a fine regurgitant jet or puff is noted. Opacification is limited to the LV outflow tract, clearing with each systole (grade 1), or faint, persistent, incomplete opacification of the LV cavity (grade 2) occurs. In grades 3 and 4, no distinct jet is seen, and dense complete opacification of the left ventricle occurs either progressively or in one or two diastolic cycles, and LV density exceeds aortic density in the severe case.

For the mitral valve, LV injection in the RAO view detects and quantifies mitral regurgitation. The angiographic criteria for grading mitral regurgitation are highly subjective. Mild grades 1 and 2 mitral regurgitation have a narrow-to-moderate width regurgitant jet of slight to moderate density with minimum-to-moderate opacification of the left atrium clearing quickly. Grades 3 and 4 have no well-defined jet with intense and persistent left atrial (LA) opacification. The left atrium appears denser than the left ventricle or aorta in grade 4 mitral regurgitation. If there is associated mitral valve prolapse, shown best in a lateral projection, all or a portion of one or both leaflets balloons may appear above the mitral annulus in systole. A normal mitral valve may be transiently regurgitant if ectopic beating occurs.

The angiographic quantitation of valvular regurgitation is shown in Table 20–16.

RIGHT VENTRICULOGRAPHY

The RV volume is estimated by applying the Simpson rule or the area-length method to the cavity silhouettes after biplane angiography. The end-diastolic volume of the right ventricle in normal persons is 81 ± 12 mL/m^2. The opacified LA shadow is represented as an ellipsoid, so the LA volume also can be calculated in the biplane mode; the normal LA maximal volume is 63 ± 16 mL with a mean volume of 35 ± 8.7 mL. Indications for right ventriculography include documentation of tricuspid regurgitation, RV dysplasia for arrhythmias, pulmonary stenosis, abnormalities of pulmonary outflow tract, and RV-to-LV shunts.

COMPLICATIONS OF VENTRICULOGRAPHY

Cardiac arrhythmias, especially ventricular tachycardia and ventricular fibrillation, require immediate cardioversion. Intramyocardial *staining*, injection of contrast into the myocardium, is generally transient and of no clinical importance unless it is deep or perforating (emergency pericardiocentesis may be required). Arrhythmias and staining are more common with end-hole catheters than pigtail catheters. Embolism from thrombi or air may occur. These events are minimized with careful catheter and injection syringe preparation and flushing. Contrast-related complications including allergic-type vasomotor collapse may occur during this procedure.

TABLE 20–16. Angiographic Quantitation of Valvular Regurgitation

	Mitral Regurgitation		Aortic Regurgitation
+	Mild LA opacification; clears rapidly, often jet-like	+	Small regurgitant jet only; LV ejects contrast each systole
++	Moderate LA opacification, < LV	++	Regurgitant jet faintly opacifies LV cavity; not cleared each systole
+++	Diffuse contrast regurgitant; LA opacification = LV; LA significantly enlarged[a]	+++	Persistent LV opacification = aortic root density; LV enlargement[a]
++++	LA opacification > LV, persistent; systolic pulmonary vein opacification may occur; often marked LV enlargement[a]	++++	Persistent LV opacification > aortic root concentration; often marked LV enlargement[a]

[a]Chronic regurgitation.

Abbreviations: ++, mild; ++, moderate; ++++, severe; LA, left atrium; LV, left ventricle.

OTHER CARDIOVASCULAR ANGIOGRAPHIC STUDIES

ASCENDING AND ABDOMINAL AORTOGRAPHY

For abdominal aneurysms, a lateral projection is commonly needed, especially if stent graft repair of abdominal aortic aneurysm is being considered. Evaluation of peripheral lower extremity disease requires identification of iliac bifurcation and common FA patency before selective injections. The contraindications of abdominal aortography are the same as those of thoracic aortography.

PULMONARY ANGIOGRAPHY

Pulmonary angiography, the visualization of vascular abnormalities of the lung vessels (eg, intraluminal defects representing pulmonary emboli, shunts, stenosis, A-V malformation, and anomalous connections), should be preceded by the measurements of right heart pressures.

PERIPHERAL VASCULAR ANGIOGRAPHY

Digital subtraction angiography is the method of choice for identifying peripheral vascular disease. However, cineangiography can provide satisfactory information if the filming time, frame rates, and contrast dosages are properly established. Cineangiography is also helpful to detect the speed of vessel opacification and collateral filling. Based on clinical signs and symptoms of arterial insufficiency to the legs, suspected obstructions of vessel are often screened with noninvasive studies (ie, ankle brachial index) before angiography is performed. Small-diameter (4- to 5-Fr) catheters are satisfactory. Reduced volume of contrast (10–20 mL over 1–2 seconds) is injected during filming with panning down the artery, following the course to the most distal locations. Angulated views may be necessary to open bifurcations and overlying vessels that obscure the vessel origin. When possible, angiographic filming should extend at least to the ankle. Iso-osmolar contrast agents are less painful than low or high osmolar media for peripheral angiography.

The area most frequently involved in peripheral atherosclerotic disease is the distal superficial FA at the abductor canal. The calf (tibial) and knee (popliteal) arteries are the next most commonly involved vessels after the superficial FA. Disease in the deep FA (femoral profunda) is rare. Pathways of collateralization are often rich and varied in patients with chronic distal FA disease, especially in total occlusions of the superficial FA that reconstitutes at or below the knee, close to the branching trifurcation of the tibial and deep peroneal arteries. Determining the level of reconstitution of collateralized vessels and distal runoff is crucial in determining the feasibility of revascularization.

RENAL ARTERIOGRAPHY

Selective renal arteriography evaluates the renal artery origins and vasculature. Selective arterial injections provide the most detail and are easily obtained with a JR4 catheter. For screening aortography, the renal artery origins usually arise at L1 vertebra (just below the T12 ribs). The 30-degree ipsilateral oblique projection often provides the best view of the renal artery ostia in a majority of patients. Acutely angled takeoffs of the renal artery may require specially shaped catheters or an arm approach. Atherosclerotic disease of the renal artery usually involves the proximal one-third of the renal artery and is seldom present without abdominal atherosclerotic plaques. Delayed imaging to see the nephrogram is essential to exclude accessory renal arteries and to screen for presence of severe parenchymal disease. In a manner similar to that for assessing coronary stenoses of uncertain significance, measurement of a pressure gradient across ostial proximal lesion is recommended to determine the need for intervention.

GENERATION OF THE X-RAY IMAGE

Cardiac angiography uses a complex series of radiographic x-ray elements, transforming energy into a visual image. The x-ray image generation chain can be simplified into three major components: (1) the x-ray generator, (2) the x-ray tube, and (3) the image intensifier. The details of x-ray equipment should be familiar to all personnel working in a catheterization laboratory.

X-RAY GENERATOR

The generator provides the power source necessary to accelerate the electrons through the x-ray tube. The duration of x-ray exposure is similar to the shutter speed on a regular camera. During the cardiac *photographic* examination, the exposure usually is set fast enough to stop blurring as a result of heart movement. During selective coronary arteriography, the shorter the exposure time, the better the image. Exposure times of 3 to 6 milliseconds reduce movement blur. Most modern generators are capable of delivering adequate power while providing precise and automatically adjusted exposure timing. Current generators are equipped with either multiple-phase (alternating on/off) or short/long pulse widths that are automatically adjusted for correct exposure. Manual settings, which are operator selected, are limited to film frame rates (eg, 15, 30, or 60 frames per second).

X-RAY TUBES

The function of the x-ray tube is to convert electrical energy, provided from the generator, to an x-ray beam. Electrons emitted from a heated filament (cathode) are accelerated toward a rapidly rotating disk (anode) and at contact undergo conversion to x-radiation (Fig. 20–17). This process generates extreme heat. The heat capacity of an x-ray tube is a major limiting factor in the design of x-ray tubes. Only 0.2% to 0.6% of the electrical energy provided to the tube eventually is converted to x-rays. In addition to the exposure times (controlled by the generator system) and the size of the imaging field (controlled by the x-ray tube), two other factors of the x-ray determine the quality of x-ray for proper image exposures.

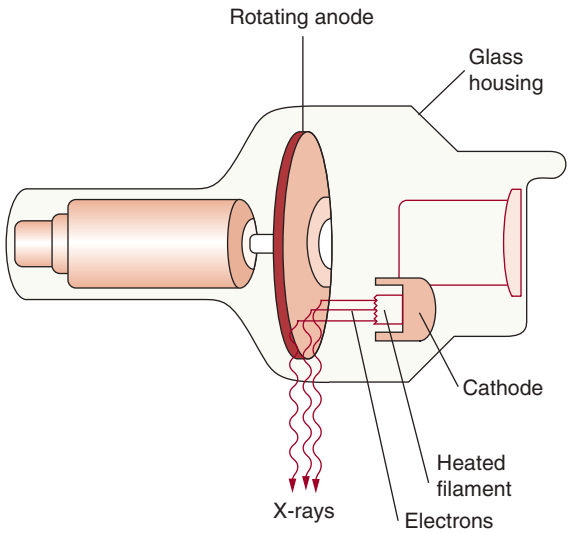


FIGURE 20–17. X-ray generation. Reproduced with permission from Baim D, Grossman W: *Grossman's Cardiac Catheterization, Angiography and Intervention*, 6th edition. Philadelphia: Lippincott Williams & Wilkins; 2000.

Electrical Current

Electrical current is the number of photons (electrical particles) generated per unit of time. The greater the electrical current, the greater the number of photons delivered, resulting in improved image resolution. If the photon delivery is marginal, the resulting image may be *mottled* or have a spotty appearance. Increasing the milliamperage will improve this result, but the level of milliamperage is limited by the heat capacity of the x-ray tubes. Also, increasing the number of milliamperes markedly increases radiation exposure and scatter to patient and catheterization personnel.

Level of Kilovoltage

Kilovoltage is the energy spectrum (wavelengths) of the x-ray beam. The higher the level of kilovoltage, the shorter the wavelength of radiation and the greater the ability of x-rays to penetrate target tissue. Increased kilovoltage is especially important in obese patients. To obtain better images through more tissue, a higher kilovolt level is required. Unfortunately, a high kilovolt level also will produce lower resolution because of wide scatter. There is also greater radiation exposure to patients and laboratory personnel. Modern radiographic equipment currently allows for variability of the amperage and voltage to attain optimal quality radiographic images. An automatic exposure control system sets exposure times to incorporate changes in voltage (kV) and amperage (mA), providing the desired images at the best exposures possible.

Image Intensifier and Detector

After the x-rays have penetrated the body, the partially absorbed beams are cast in a shadow fashion on the input screen of the image intensifier or flat panel detector. The image intensifier converts the invisible x-ray image into a visual image. Each x-ray photon hits the phosphorus-covered plate of the intensifier, resulting in a light particle that is detected, the position and intensity of which are noted. The sum of all events produces an image for video. Image intensifiers are equipped with various-sized image fields that alter the image resolution. In general, the smaller the image field size, the sharper the resolution, but the higher the radiation dose. Smaller input screen diameters (5- to 7-inch screens) are better suited for coronary angiography because of their enhanced resolution. For more detailed work, such as percutaneous transluminal coronary angioplasty and other coronary interventions, 5-inch fields are commonly used by some operators. In contrast, for large-area examinations (ie, left ventriculography, aortography, or peripheral angiography), field diameters of 9 to 11 inches are used, with the known trade-off of loss of resolution for small structures.

Modern image intensifiers are predominantly of a flat panel construction, eliminating many of the artifacts associated with tube-like intensifiers used in earlier x-ray systems. The x-ray image is now generated in a digital format, which lends itself to easier analysis. Digital angiography converts the x-ray image into a quantitative information format for storage and display on a computer. Digital imaging permits the contrast image to be amplified or enlarged or contrast adjusted. One image can be subtracted from another.

RADIATION SAFETY

The catheterization laboratory environment should be made as safe as possible for the staff and patients. Standards for radiation protection (from the Society for Cardiac Angiography and Intervention) include four basic principles:

1. The less exposure, the less chance there is of absorbed energy biologic interaction.
2. No known level of ionizing radiation is a permissible dose or absolutely safe.
3. Radiation exposure is cumulative. There is no washout phenomenon.
4. All participants in the cardiac catheterization laboratory have voluntarily accepted some degree of radiation exposure, but they are obliged to minimize and reduce risks to other personnel and themselves.

The primary x-ray beam, emanating from the undertable x-ray tube upward through the patient and onto the image intensifier, exposes all subjects to radiation in a dose geometrically inverse to the distance from the source. Radiation scatter occurs in all directions from the patient and is increased when the angle of the x-ray tube is set obliquely (Fig. 20–18). Acrylic shields and table-mounted lead aprons reduce exposure from x-ray scatter. Fluoroscopy generates approximately one-fifth the x-ray exposure of cineangiography. Complex catheterization procedures inherently have an increased total radiation exposure that should be considered as a limiting boundary for procedures requiring extensive intracardiac manipulation, such as coronary interventions, percutaneous heart valve replacements, or electrophysiology studies.[10] Practices to ensure radiation dose limitation should be routinely used. Although no known threshold for radiation exposure exists to define specific risks, the National Council on Radiation Protection and Measurements indicates that no dose of more than 3 rem (roentgen equivalent man) should be allowed over a 3-month period.

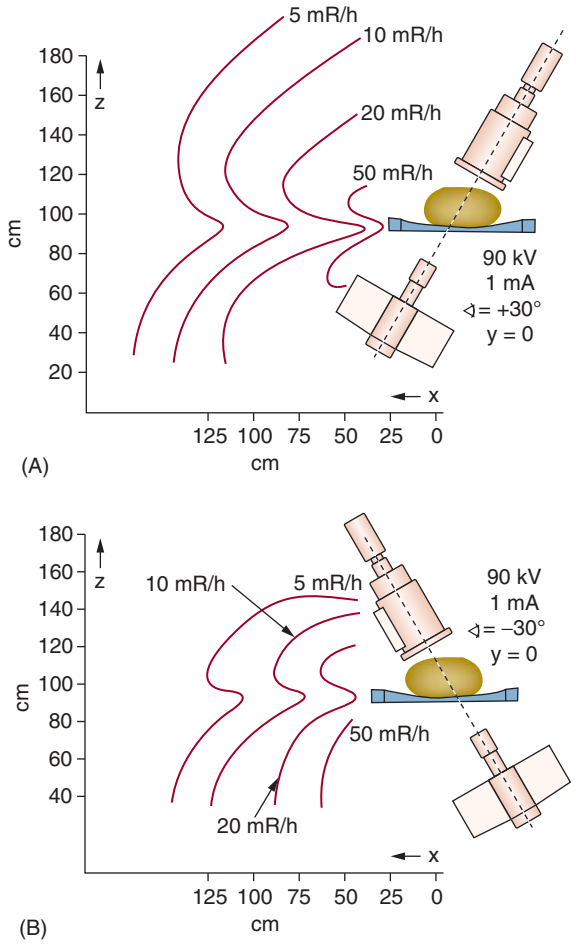


FIGURE 20–18. Isoexposure curves representing ranges of relative exposure in the position usually occupied by the operator performing an angiographic procedure from the right arm. **A.** 30-degree left anterior oblique. **B.** 30-degree right anterior oblique. Reproduced with permission from Balter S, Sones FM Jr, Brancato R: Radiation exposure to the operator performing cardiac angiography with U-arm systems. *Circulation*. 1978 Nov;58(5):925-932.

TABLE 20–17. Definitions of Radiation Units

Roentgen (*R*) is the measure of ionization delivered to a specific point (exposure). One chest radiography equals 3 to 5 mR.
Radiation absorbed dose (*rad*) is the amount of radiation energy deposited per unit mass of tissue. The amount of absorbed dose per given exposure is dependent on tissue type. For example, for soft tissue, 1 R = 1 rad; for bone, 1 R = 4 rad (ie, greater absorption).
Radiation equivalent dose in man (*rem*) is used to express the biological impact of a given exposure. For x-radiation, 1 rad = 1 rem.

The eyes, gonads, and red bone marrow have a whole-body limit of 5 rem per year; any specific organ, such as the thyroid or skin, has a yearly limit of 15 rem. The maximal permissible dose, or *safe* exposure, for catheterization laboratory personnel is 100 mrem per week monitored by an unshielded left collar badge. Definitions of radiation units are provided in Table 20–17.

HEMODYNAMIC DATA FROM THE CARDIAC CATHETERIZATION LABORATORY

In conjunction with angiographic data gathered during the cardiac catheterization, hemodynamic information is recorded from catheters inside vascular structures. Hemodynamic data include pressure measurements, blood flow, and blood oxygen saturation measurements. An excellent review of hemodynamic data and pressure waveforms is available elsewhere.[11,12]

PRESSURE MEASUREMENTS

Blood within the heart or vessels exerts pressure. A pressure wave is created by cardiac muscular contraction and is transmitted from the vessel or chamber along a closed, fluid-filled column (catheter) to a pressure transducer, converting the mechanical pressure to an electrical signal that is displayed on a video monitor. Cardiac pressure waveforms are cyclical, repeating the pressure change from the onset of one cardiac contraction (systole) to the onset of the next contraction. An examination of the cardiac cycle and corresponding pressures will provide an understanding of basic hemodynamics in the cardiac catheterization laboratory. The collection of hemodynamic data for cardiac catheterization is an integral part of every procedure. A predetermined plan for data collection facilitates simultaneous pressure measurements across the heart, concentrating on the aortic and mitral valves, which are affected most commonly by disease. Different hemodynamic measurements for specific clinical situations are necessary. In conjunction with pressure measurements, cardiac output can be measured using the thermodilution technique or by application of the Fick principle (oxygen consumption) method. To measure suspected cardiac shunts, arterial, vena caval (superior and inferior), RA (high, middle, and low right atria), RV, RV outflow tract, and PA oxygen saturations are collected.

Pressure wave fidelity depends on quality components that can transmit the pressure wave to a transducer without signal distortion. If the heart rate is 60 to 120 beats/min, the fundamental frequency of the basic wave is 1 to 2 per second. The higher frequency sine wave components of the pressure wave then occur at frequencies of up to 10 to 20 Hz. Modern pressure transducers have sufficient frequency capabilities to minimize phase lag and amplitude distortion. Pressure systems should be set for optimal damping to minimize overshoot or undershoot of the waveform. A high natural frequency is obtained by using a bubble-free, saline solution–filled system of minimum length whose catheter and connector tubing have stiff walls and wide bores.

THE FEMORAL ARTERY AND LEFT VENTRICULAR PRESSURE

The most common pressure measurements include systemic pressure and LV pressure. The FA sheath is often used to compare aortic pressure (AoP) with LV pressure to assess the aortic valve. A delay in pressure transmission and overshoot of the systolic pressure compared with centrally measured AoP are characteristic of FA pressure measurements. The LV pressure should be examined for waveform characteristics to ensure all side holes are beneath the aortic valve and that the catheter system is flushed to permit accurate interpretation of the diastolic LV waveform.

RIGHT HEART PRESSURES

Right heart hemodynamics are easily obtained with a balloon-tipped flotation catheter. Blood oxygen saturations in the inferior vena cava, right atrium, and PA are collected to screen for cardiac shunts. RA, RV, PA, and pulmonary capillary wedge (PCW) pressures are measured and cardiac output estimated by thermodilution. If necessary, during right heart pressure catheter pullback, the LV pressure can be compared with RV pressure to identify constrictive/restrictive physiology.

THE PULMONARY CAPILLARY WEDGE PRESSURE

PCW pressure closely approximates LA pressure. PCW pressure overestimates LA pressure in patients with acute respiratory failure, chronic obstructive lung disease with pulmonary hypertension, pulmonary vein stenosis, or LV failure with volume overload. Discrepancies between LA and PCW may be caused, in part, by different types of catheters: balloon-tipped flotation catheters are soft with small lumens, and LA pressure catheters (eg, Brockenbrough or Mullins-type sheath) are stiff with large lumens. In most patients, the PCW is sufficient to assess LV filling pressure. However, in patients with mitral valvular disease or mitral valve prostheses, the most accurate method is direct LA pressure measurement by transseptal puncture. PCW pressure can be identified from adequate pressure waveforms and confirmed by oximetry. The best location of the PCW pressure has been questioned, but for practical purposes, any of the four locations (left or right upper lobes or left or right lower lobes) within the pulmonary tree are generally acceptable. In patients with high PA pressures (> 50 mm Hg), an inflated balloon should not be left in place for more than 10 minutes because prolonged balloon inflation may cause pulmonary infarction or damage to the PA. Care should be taken not to inflate a balloon vigorously in distal portions of the lung, where the balloon may tear a small pulmonary vessel. Complications of PA catheterization are similar to those of right heart catheterization (see Table 20–13).

COMPUTATIONS FOR HEMODYNAMIC MEASUREMENTS

Once the hemodynamic data have been obtained, computations are made to clarify and enhance quantitation of cardiac function. Although these calculations are most commonly performed by the computerized hemodynamic system in the catheterization laboratory, knowledge of the calculations involved is critical to a thorough understanding of the pathophysiology. The most often used computations involve quantitation of cardiac work, flow resistance, valve areas, and amount of shunting. Specific derivations and applications of these formulas can be found elsewhere.[1-3]

1. Cardiac output (CO) using the Fick principle (O_2 consumption) is calculated as follows:

$$CO = \frac{O_2 \text{ consumption (mL/min)}}{AVo_2 \text{ difference (mL } O_2/100 \text{ mL blood)} \times 10}$$

In 1870, Adolph Fick expounded a theory for the measurement of flow: "The total uptake or release of a substance by an organ is the product of the blood flow to the organ and of the arteriovenous concentration of the substance." Using total oxygen consumption of 300 mL/min, arterial blood oxygen content of 19 mL/100 mL of blood, and mixed venous blood oxygen content of 14 mL/100 mL of blood, the cardiac output, in liters per minute, is equal to the oxygen consumption divided by the arteriovenous oxygen difference (A-Vo_2) multiplied by 10 (to convert the latter to liters). With these data in this case, the cardiac output equals 6.0 L/min. Oxygen consumption is measured from a metabolic *hood*; it also can be estimated as 3 mLO_2/min/kg or 125 mL/min/m^2. A-Vo_2 is calculated from arterial-mixed venous (PA) O_2 content, where O_2 content = saturation × 1.36 × hemoglobin concentration. For example, if the arterial saturation is 95%, the PA saturation is 65%, the hemoglobin concentration is 13.0 g/dL, and the O_2 consumption is 210 mLO_2/min (70 kg × 3 mLO_2/min/kg), then the cardiac output is:

$$\frac{210}{(0.95-0.65)\times 1.36\times 13.0\times 10} = \frac{210}{53} = 3.96 \text{ L/min}$$

2. Cardiac index (CI, L/min/m^2)

$$CI = \frac{CO \text{ mL/beat}}{BSA\ (m^2)}$$

where CO = cardiac output and BSA = body-surface area.

3. Stroke volume (SV, mL/beat)

$$SV = \frac{CO\ (mL/min)}{HR\ (beats/min)}$$

where *HR* = heart rate.

4. Stroke index (SI, mL/beat/m^2)

$$SI = \frac{SV\ (mL/beat)}{BSA\ (m^2)}$$

5. Stroke work (SW, g · m)

$$SW = (\text{mean } LV \text{ systolic pressure} - \text{mean } LV \text{ diastolic pressure}) \times SV \times 0.0144$$

6. Pulmonary arteriolar resistance (PAR, Wood units)

$$PAR = \frac{\text{mean pulmonary} - \text{mean LA pressure}}{\text{arterial pressure (or mean PCW)}}{CO}$$

7. Total pulmonary resistance (TPR, Wood units)

$$TPR = \frac{\text{mean pulmonary arterial pressure}}{CO}$$

8. Systemic vascular resistance (SVR, Wood units)

$$SVR = \frac{\text{mean systemic} - \text{mean right arterial pressure artial pressure}}{CO}$$

Resistance calculations follow the form of Ohm's law

$$R = \Delta p/\dot{Q}$$

where R = resistance; Δp = mean pressure differential across the vascular bed; = blood flow. Resistance units (mm Hg/L/min) are also called *hybrid resistance units* or Wood units. To convert Wood units to metric resistance (dynes × s × cm^{-5}), multiply by 80.

CALCULATION OF VALVE AREAS

Valvular or vascular obstruction produces a pressure gradient across a stenosis or vascular conduit/chamber narrowing. A pressure gradient is defined as the pressure difference across an area of valvular or vascular obstruction (such as a stenosis or an occlusion). The pressure gradient is influenced by physiologic variables such as rate of blood flow (eg, cardiac output, coronary blood flow); resistance to flow; proximal chamber pressure and compliance; and anatomic variables, such as shape and length of valve orifice, tortuosities of the vessels (for arterial stenosis), or multiple or serial lesions (for both cardiac valves and arterial stenosis). In addition, pressure measurements may be influenced by artifactual variables, including miscalibrated pressure transducers; pressure leaks on catheter manifold or connecting tubing; pressure tubing type, length, and connectors; air in system; catheter sizes (especially small diameters); and fluid viscosity.

VALVE AREA FORMULAS

A valve area can be calculated from standard hemodynamic data with the following formula:

$$\text{Area } (cm^2) = \frac{\text{value flow (mL/s)}}{K \times C \times \sqrt{MVG}}$$

where *MVG* = mean valvular gradient (mm Hg); *K* (44.3) = a derived constant by Gorlin and Gorlin and *C* = an empiric constant that is 1 for semilunar valves and tricuspid valve and 0.85 for mitral valve. Valve flow is measured in milliliters per second during the diastolic or systolic flow period.

For mitral valve flow:

$$\frac{CO\ (mL/min)}{(\text{diastolic filling period})\ (HR)}$$

For aortic valve flow:

$$\frac{CO\ (mL/min)}{(\text{systolic ejection period})\ (HR)}$$

CALCULATING AORTIC VALVE AREA

The method of calculating aortic valve area (AVA) from data obtained at catheterization for a patient with aortic stenosis (Fig. 20–19) is as follows, assuming CO = 4000 mL/min and HR = 60 beats/min.

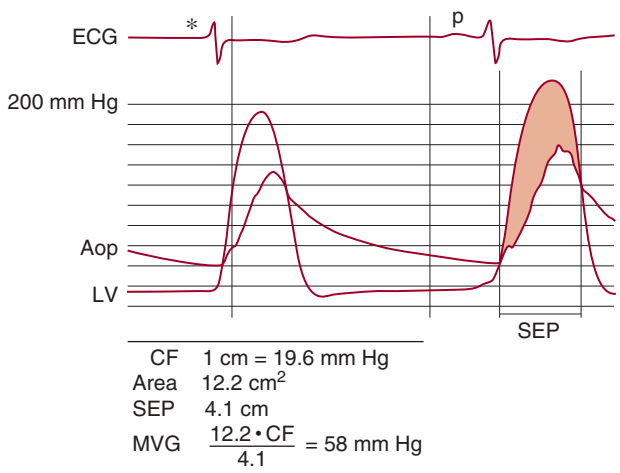


FIGURE 20–19. Aortic valve area is determined from the planimetered area of the aortic valve gradient. The aortic valve gradient area (shaded area) is bounded by the systolic ejection period (SEP). AoP, aortic pressure; CF, correction factor or scale factor; LV, left ventricular pressure (scale 0-200 mm Hg); MVG, mean value gradient. See text for details. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

1. Planimeter aortic-LV pressure gradients (area = 12.2 cm^2) and measure systolic ejection periods (SEPs = 4.1 cm). Next convert cm to time and convert planimetered area to mean systolic pressure gradient. SEP of 4.1 cm/beat at paper speed of 100 mm/s = 0.41 s/beat. Mean valve gradient (MVG) = (area × scale factor)/SEP (scale factor: 1 cm = 19.6 mm Hg [directly measured paper calibration lines of 200 mm Hg])

$$\text{MVG} = 12.2\ \text{cm}^2 \times \frac{19.6\ \text{mm Hg/1 cm}}{4.1\ \text{cm}} = \frac{239}{4.1} = 58\ \text{mm Hg}$$

2. Compute aortic valve flow.

$$\text{Flow} = \frac{\text{CO}}{\text{SEP} \times \text{HR}} = \frac{4000\ \text{mL/min}}{0.41\ \text{s/beat} \times 60\ \text{beats/min}} = \frac{4000}{24.6} = 126.6\ \text{mL/min}$$

3. Compute AVA.

$$\text{AVA} = \frac{\text{Aortic value flow}}{1.0 \times 44.3\sqrt{\text{MVG}}} = \frac{162.6}{44.3 \times \sqrt{58}} = \frac{162.6}{44.3 \times 7.6} = \frac{162.6}{336.6} = 0.48\ \text{cm}^2$$

Although the mean pressure gradient is used in the Gorlin formula, the peak-to-peak systolic pressures difference has been used to estimate valve area. The peak-to-peak systolic gradient is not equivalent to mean gradient for mild and moderate stenosis but often approximates mean gradient for severe stenosis. When using the FA and LV pressure to compute mean pressure gradient, the delay in FA pressure transmission and augmented wave reflection and amplification of the FA artificially increases the mean gradient. For most accurate measurements, a double-lumen pigtail catheter is widely available. Transseptal cardiac catheterization also can be performed to obtain LV pressure (via crossing mitral valve). AVA can also be estimated closely by a simplified formula as cardiac output divided by the square root of the LV–Ao peak-to-peak pressure difference. For example, if peak-to-peak gradient = 65 mm Hg and CO = 5 L/min, then a simplified valve area = 0.63 cm^2.

$$\frac{5\ \text{L/min}}{\sqrt{65}} = \frac{5\ \text{L/min}}{8} = 0.63\ \text{cm}^2$$

The simplified formula for valve area differs from the Gorlin formula by 18% ± 13% in patients with bradycardia (< 65 beats/min) or tachycardia (> 100 beats/min). The Gorlin equation at low flow states overestimates the severity of valve stenosis. In low flow states (CO < 2.5 L/min), the Gorlin formula should be modified to use the mean transvalvular gradient with new empirically derived constants.

CALCULATIONS FOR MITRAL VALVE AREA

To calculate the most accurate valve area, use the direct LA pressure from transseptal measurement. Transseptal catheterization should be performed to confirm large pressure gradients, especially for suspected prosthetic mitral stenosis. The PCW pressure overestimates LA pressure (transseptal catheterization) in patients with prosthetic mitral valves (Fig. 20–20). Overestimation is caused, in part, by large *v* waves increasing the phase delay, making correction and alignment of pressure tracings difficult. However, if the PCW pressure–LV pressure tracings show no significant gradients, transseptal catheterization is unnecessary. Mitral valve area from the following data is calculated below, assuming CO = 3500 mL/min and HR = 80 beats/min.

1. Planimeter LV-PCW areas (area = 9.46 cm^2) and measure diastolic filling period (DFP = 3.4 cm). Next convert cm to time and planimetered area to mean diastolic pressure gradient.

   DFP of 3.4 cm/beat at paper speed of 100 mm/s = 0.34 s/beat

   Mean valve gradient (MVG) = (area × scale factor)/DFP (scale factor: 1 cm = 3.9 mm Hg [directly measured paper calibration lines of 40 mm Hg])

$$\text{MVG} = 9.46\ \text{cm}^2 \times \frac{3.9\ \text{mm Hg/1 cm}}{3.4\ \text{cm}} = 10.85\ \text{mm Hg}$$

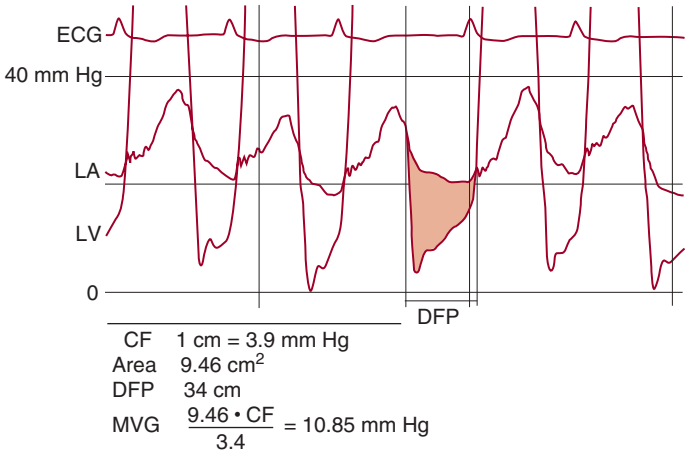


FIGURE 20–20. Hemodynamic tracing used to calculate mitral valve area. The shaded area is the diastolic mitral valve gradient surrounded by the diastolic filling period (DFP). CF, correction factor or scale factor; LA, left atrial pressure; LV, left ventricular pressure (scale 0–40 mm Hg); MVG, mean value gradient. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

2. Compute mitral valve flow.

$$\text{Flow} = \frac{\text{CO}}{\text{DFP} \times \text{HR}} = \frac{3500 \text{ mL/min}}{0.34 \text{ s/beat} \times 80 \text{ beats/min}}$$
$$= \frac{3500}{0.34 \times 80} = \frac{3500}{27.2} = 128.7 \text{mL/min}$$

3. Compute mitral valve area.

$$\text{MVA} = \frac{\text{Mitral value flow}}{0.85 \times 44.3\sqrt{10.85}} = \frac{128.7}{0.85 \times 44.3 \times 3.3}$$
$$= \frac{128.7}{124.3} = 1.0 \text{ cm}^2$$

CARDIAC OUTPUT TECHNIQUES

THERMODILUTION TECHNIQUE

A multiple-lumen, balloon-tipped flow-directed thermistor catheter is placed in the PA. Ten milliliters of room-temperature normal saline solution is injected rapidly (< 4 seconds) through a second lumen into the right atrium. As the injectate-blood mixture initially passes from the right ventricle, the PA blood temperature drops maximally and then progressively rises in a beat-to-beat disappearance slope as the residual injectate-blood mixture is washed out of the right ventricle. The recirculation phase is negligible. The area under the time-temperature curve is electronically integrated, and the cardiac output is computed by the Stewart-Hamilton formula. Because there is no gold standard for cardiac output, the results have been compared with the dye-dilution and Fick techniques and have correlated well, except in low cardiac output states, where the Fick method is preferable. If severe tricuspid or pulmonary regurgitation or significant left-to-right shunting is present, the indicator (temperature loss) is attenuated and the downslope of the temperature curve is prolonged, so the thermal dilution cardiac output will be unreliable. In general, when one uses thermal dilution, a true directional change in cardiac output is reflected by an observed change of ±10%. Thermodilution is inaccurate in patients with low cardiac output. Significant variations among cardiac output techniques occur in patients with low cardiac output or in those with aortic or mitral regurgitation.

THE FICK METHOD OF CARDIAC OUTPUT

The Fick method most often uses an assumed oxygen consumption value or less frequently a metabolic hood to measure oxygen consumption. The Fick calculation is described above.

INTRACARDIAC SHUNTS

A *shunt* is the term for transit of blood through an abnormal communication between the left and right heart chambers or great vessels. The direction of blood flowing through the shunt may be left to right, right to left, or sometimes bidirectional. In the absence of shunting, the pulmonary blood flow (right heart output) is equal to the systemic blood flow. A left-to-right shunt increases the amount of blood to the right heart and increases pulmonary blood flow, now equal to the sum of the systemic blood flow plus shunt flow. With a right-to-left shunt, the amount of blood shunted from the right side to the left is added to that normally ejected into the systemic circulation. Systemic blood flow is then greater than pulmonary blood flow by the amount of the shunt.

OXIMETRY FOR CARDIAC SHUNTS

An increase in the oxygen content of blood from the chambers of the right side of the heart in excess of the normal variation in oxygen content on serial sampling is used as evidence of a left-to-right shunt. Oxygen content can be expressed as volumes percent (vol% = mL O_2/100 mL blood) or can be expressed from percent oxygen saturation where content is calculated from the hemoglobin concentration, assuming a constant relationship for oxygen-carrying capacity (1.36 mL O_2/g hemoglobin). Thus, an oxygen step-up from the superior vena cava (SVC) to the right atrium of more than 1.9 vol% indicates shunting into the right atrium, and a step-up from the right atrium to the right ventricle of 0.9 vol% or more and a step-up from the right ventricle to the PA of 0.5 vol% or more indicates a left-to-right shunt at the RV and PA levels, respectively. By these criteria, false-positive results are rare, but false-negative results can occur in patients with small shunts. In an anemic or polycythemic patient, the detection of shunting is best reflected by the step-up in percentage oxygen saturation rather than the step-up in volume percent, because the latter depends on the hemoglobin concentration. Studies show that sensitivity in detecting left-to-right shunts is improved if numerous serial paired blood samples are withdrawn in rapid succession for oximetry. Assuming an arterial saturation of 95%, a 9% saturation increase between the SVC and the right atrium indicates a large atrial shunt, a 5% saturation increase between the right atrium and the right ventricle indicates a ventricular shunt, and a 3% saturation increase between the right ventricle and the PA indicates a PA shunt. The rise in oxygen saturation step-up for a given left-to-right shunt is related to the saturation of mixed venous blood (MVB). For example, if the MVB is 85%, a 5% step-up represents a 2:1 shunt; if MVB is 75%, a 10% step-up is needed; if the MVB is 65%, a 15% step-up indicates a 2:1 shunt. Left-to-right shunts of less than 20% of pulmonary flow are not detectable by oximetry. Desaturation of arterialized blood samples from the left heart chambers and aorta suggests a right-to-left shunt. In determining the site of the right-to-left shunt, sequential sampling can be made from the left atrium, left ventricle, and aorta (Table 20–18). MVB is assumed to be fully mixed PA blood. If there is a left-to-right shunt, MVB is measured one chamber proximal to the step-up. In the case of an atrial septal defect, the mixed venous oxygen content is computed from the weighted average of vena caval blood (ie, as the sum of three times the superior vena cava plus one inferior vena cava oxygen content and divided by four). When pulmonary venous blood is not collected, PVO_2 (pulmonary vein) percentage saturation is assumed to be 95%. The oximetric technique has some well-known limitations, which include inability to detect small shunts, poor blood oxygen mixing, and inaccuracies with high flow states.[13]

TABLE 20–18. Oxygen Saturation Values for Shunt Detection

Level of Shunt	Significant Step-Up Different[a] O_2 Saturation
Atrial (SVC/IVC to right ventricle)	7
Ventricular	5
Great vessel	5

[a]Difference distal-proximal chamber. For example, for atrial septal defect:

Abbreviations: IVC, inferior vena cava; SVC, superior vena cava.

SHUNT CALCULATIONS

The Fick or left-sided indicator dilution methods of cardiac output determination are used to measure systemic flow. Using the Fick method, the following formulas apply:

1. Systemic flow,

$$Q_s(\text{L/min}) = \frac{O_2 \text{ consumption(mL/min)}}{(\text{arterial} - \text{mixed venous})\ O_2 \text{ content}}$$

2. Pulmonary flow,

$$Q_P\ (\text{L/min}) = \frac{O_2 \text{ consumption (mL/min)}}{(\text{pulmonary venous} - \text{pulmonary arterial})\ O_2 \text{ content}}$$

Thus, the effective pulmonary blood flow (EPB)

$$O_{EPB} = \frac{O_2 \text{ consumption (mL/min)}}{(\text{pulmonary venous} - \text{mixed venous})\ O_2 \text{ content}}$$

The effective pulmonary blood flow is that volume of blood, which after returning to the right atrium, actually reaches the pulmonary capillaries.

It follows that

$$L \rightarrow R \text{ shunt} = Q_P - Q_{EPB}$$

and

$$R \rightarrow L \text{ shunt} = Q_S - Q_{EPB}$$

If arterial blood is fully saturated, then there is no $R \rightarrow L$ shunt, because arterial O_2 content is equal to pulmonary venous O_2 content and $Q_S = Q_{EPB}$.

The shunt ratio is defined as Q_p/Q_s. Shunt ratios of more than 1.5 are associated with anatomic defects that often require closure.

3. Example calculations for a simple left-to-right shunt in a patient with an atrial septal defect (ASD) using data obtained at catheterization are as follows:

Assume Hgb = 14.1 g/dL, O_2 consumption = 225 mL O_2/min and oxygen saturation data as follows:

a. Compute O_2 content.

$$\text{Arterial } O_2 \text{ content} = 0.98 \times 1.36 \text{ mL } O_2/\text{g} \times 14.1 \text{ g/dL} \times 10$$
$$= 188 \text{ mL } O_2/\text{L}$$

Mixed venous O_2 content (use estimate of mixed venous oxygen saturation):

$$\frac{3\text{SVC} + 1\text{IVC}}{4} \text{(for mixed venous oxygen saturation)}$$
$$\frac{(.71 + .71 + .71 + .70)}{4} = 0.71$$

$$71 \times 1.36 \text{ mL } O_2/\text{g} \times 14.1 \text{ g/d} \times 10 = 136 \text{ mL } O_2/\text{L}$$

$$\text{Pulmonary artery } O_2 \text{ content} = (0.81 \times 1.36 \text{ mL } O_2/\text{g} \times 14.1 \text{ g/dL} \times 10)$$
$$= 155 \text{ mL } O_2/\text{L}$$
$$\text{Pulmonary vein } O_2 \text{ content} = (0.98 \times 1.36 \text{ mL } O_2/\text{g} \times 14.1 \text{ g/dL} \times 10)$$
$$= 188 \text{ mL } O_2/\text{L}$$

b. Compute systemic flow [Equation (1)].

$$\frac{225 \text{ mL } O_2/\text{min}}{(188 - 136) \text{ mL } O_2/\text{L}} = \frac{225}{52} = Q_S = 4.3 \text{ L/min}$$

c. Compute pulmonary flow

$$\frac{225 \text{ mL } O_2/\text{min}}{(188 - 155) \text{ mL } O_2/\text{L}} = \frac{225}{33} = Q_P = 6.8$$

d. Compute,

$$\frac{Q_P}{Q_S} = \frac{6.8}{4.3} = 1.6$$

and the $L \rightarrow R$ shunt is 6.8 L/min − 4.3 L/min or 2.5 L/min.

If absolute flows are not required, the Q_P/Q_S ratio can be determined using saturations only as follows:

$$\frac{Q_P}{Q_S} = \frac{SA_{O_2} - MV_{O_2}}{PV_{O_2} - PA_{O_2}}$$

where SA_{O_2} = systemic arterial O_2 saturation; PV_{O_2} = pulmonary venous O_2 saturation; MV_{O_2} = mixed venous O_2 saturation; PA_{O_2} = pulmonary artery O_2 saturation.

Using saturation data from the example of left-to-right shunt:

$$\frac{Q_P}{Q_S} = \frac{98 - 71}{98 - 81} = \frac{27}{17} = 1.6$$

NORMAL HEMODYNAMIC WAVEFORMS

NORMAL RIGHT HEART PRESSURE WAVES

Simultaneous RV and RA pressures (Fig. 20–21) demonstrate the correspondence of the atrial contraction *a* wave and the *v* wave (caused by venous return to the right atrium while the tricuspid valve is closed) to the RV pressure tracing. Following the *a* wave is the X descent and

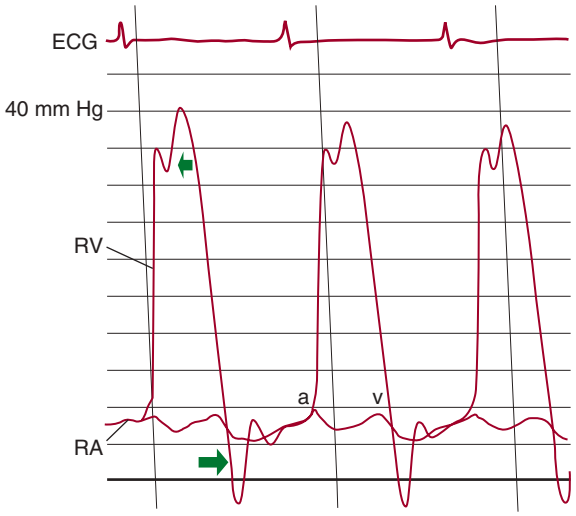


FIGURE 20–21. Right atrial (RA) and right ventricular (RV) tracings in a normal patient. Notch of ringing or overshoot on RV pressure rise (*closed arrow*). Ringing and overshoot of decline in RV pressure at early diastole (*open arrow*). a, atrial wave; v, ventricular filling wave. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

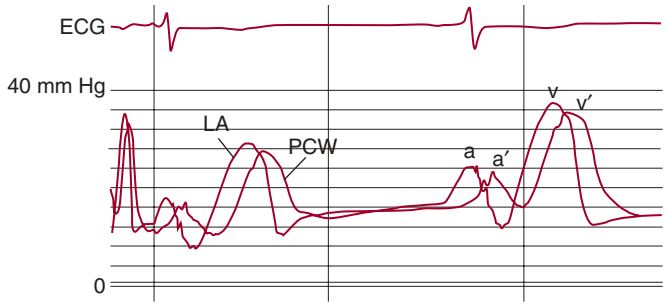


FIGURE 20–22. Simultaneous left atrial (LA) and pulmonary capillary wedge (PCW) tracings. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

following the *v* wave is the normal Y descent. These features may be altered in the presence of disease or obscured in patients who have atrial arrhythmias. The notch (*closed arrow*) on the top of the RV tracing is the *ringing* (underdamping) of a fluid-filled catheter. This rebound or ringing also is evident on the early diastolic part of the pressure wave (*open arrow*, bottom of same beat). In general, RA *a* waves are bigger than *v* waves. In the left atrium, *v* waves are more prominent than *a* waves. RA pressure can be markedly altered by respiration.

SIMULTANEOUS PULMONARY CAPILLARY WEDGE AND LEFT ATRIAL PRESSURE

The simultaneous PCW pressure and the LA pressure measured through a transseptal Brockenbrough catheter (Fig. 20–22) demonstrate the delay of PCW pressure relative to LA pressure by approximately 100 to 150 milliseconds, representing the transit of pressure through the pulmonary circuit. The acceptable correspondence between PCW and LA pressures permits clinical use of PCW pressure.

NORMAL FEMORAL ARTERIAL AND CENTRAL AORTIC PRESSURES

The femoral arterial pressure measured through the side arm of the femoral arterial sheath is matched against LV pressure in the pigtail catheter 1 Fr size smaller (Fig. 20–23). These pressures normally correspond closely with only a slight overshoot of the more peripheral FA pressure. Note the phase lag and normal overshoot of the arterial pressure compared with the LV pressure. The timing of upstroke of the pressures distinguishes the central aortic (first tracing rising) from FA pressure. The left panel of Fig. 20–23 shows high-fidelity aortic and LV pressures measured from two transducers on a single catheter.

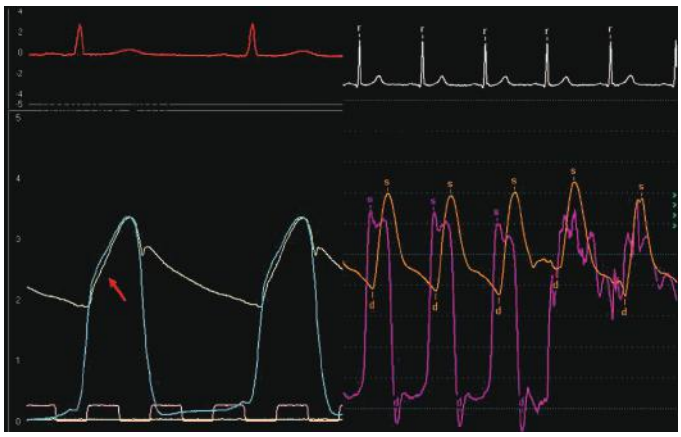


FIGURE 20–23. *Left*, Simultaneous Ao and LV recorded from a micromanometer high-fidelity dual transducer catheter. Note small impulse gradient of a normal LV outflow tract. *Right*, Simultaneous hemodynamic tracings of femoral artery (FA) pressure, taken through the side arm of the 8 Fr sheath and central aortic (Ao) pressures. Ao pressure is obtained through the 7-Fr pigtail catheter. The overshoot of the FA pressure (*arrow*) and lag in the pressure upstroke are the normal characteristics for the femoral tracings. Reproduced with permission from Kern MJ, Lim MJ, Sorajja P: *The Cardiac Catheterization Handbook*, 6th edition. Philadelphia: Elsevier; 2016.[1]

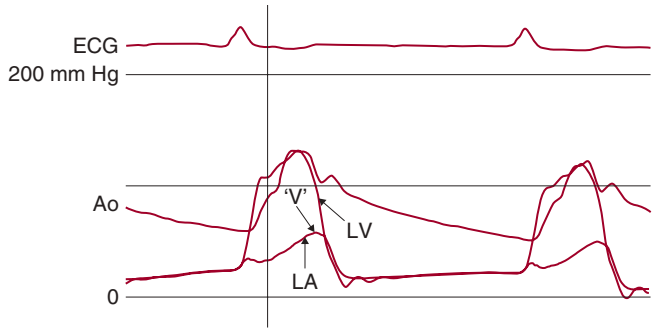


FIGURE 20–24. Left ventricular (LV) and left atrial (LA) pressures showing large V wave of severe mitral regurgitation.

PATHOLOGIC HEMODYNAMIC WAVEFORMS

LARGE PULMONARY CAPILLARY WEDGE/LEFT ATRIAL *v* WAVES

The *v* wave on an LA or PCW pressure tracing usually is associated with significant mitral regurgitation (Fig. 20–24). However, large *v* waves are neither highly sensitive nor specific for mitral regurgitation. Large *v* waves also may be present with mitral stenosis with or without mitral regurgitation or any condition in which the left atrial volume (eg, VSD or LA pressure relationship [the stiffness or compliance] is increased [such as in rheumatic heart disease, postcardiac surgery, and infiltrative heart diseases]).

AORTIC–LEFT VENTRICULAR GRADIENTS

Both aortic stenosis (Fig. 20–25) and hypertrophic obstructive cardiomyopathy (Fig. 20–26) produce large pressure gradients across the LV outflow tract. Specific characteristics of the pressure waveforms differentiate the pathology that generates the gradient.

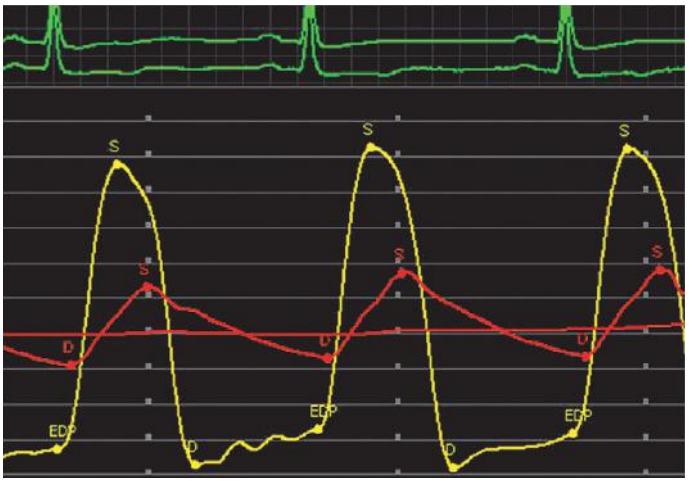


FIGURE 20–25. Simultaneous left ventricular (LV) (*yellow*) and aortic (*red*) pressure from dual lumen pigtail catheter across the aortic valve demonstrating large pressure gradient and characteristic features of slow aortic upstroke of delayed LV ejection of the stenosis.

FIGURE 20–26. Hemodynamic tracings of patient with hypertrophic obstructive cardiomyopathy. *Left side* of tracing shows large intracavitary gradient, and on pullback from distal left ventricle (LV) to mid/proximal LV, the gradient disappears, consistent with proximal-LV cavity (ie, subvalvular) obstruction.

Hypertrophic obstructive cardiomyopathy produces asymmetric septal wall thickening of heart muscle that can produce obstruction to outflow, increasing with increasing contraction. Figure 20–26 depicts simultaneous LV and AoP, showing a large aortic–LV gradient (LV pressure = 180 mm Hg; AoP = 100 mm Hg). On pullback of the LV catheter from the distal LV to a position just beneath the aortic valve, the Ao–LV gradient disappears (see the LV pressure matching with AoP).

LEFT ATRIAL–LEFT VENTRICULAR GRADIENTS

Simultaneous LV and PCW pressures demonstrate a mitral valve gradient throughout diastole. The *a* wave is absent in this patient in atrial fibrillation. As can be seen, mitral valve gradients are strongly influenced by heart rate. Large *v* waves in the PCW tracing represent LV pressure transmitted backward through an incompetent mitral valve. The *v* wave (up to 60 mm Hg) occurs on the downstroke of the LV pressure in a patient with mitral regurgitation (Fig. 20–27).

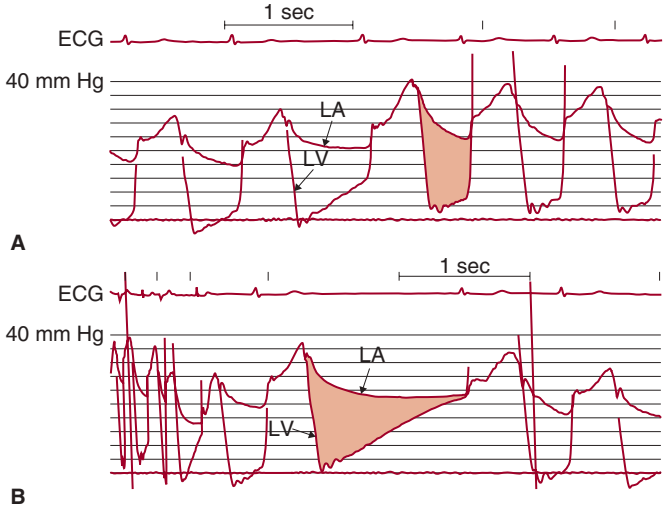


FIGURE 20–27. Influence of heart rate (diastolic period) on mitral valve gradient. The mitral stenosis gradient changes with heart rate (RR interval). **A.** Short RR interval is associated with gradient (shaded area) of 22 mm Hg. **B.** Long RR interval has a mean gradient of 29 mm Hg. When computing mean valve area in atrial fibrillation, average 10 beats. LA, left atrial pressure; LV, left ventricular pressure. Reproduced with permission from Kern MJ, Aguirre F: Interpretation of cardiac pathophysiology from pressure waveform analysis: mitral valve gradients: Part I, *Cathet Cardiovasc Diagn.* 1992 Aug;26(4):308-315.

PHYSIOLOGIC MANEUVERS IN THE CATHETERIZATION LABORATORY

EXERCISE

Exercise evaluation of cardiac function is helpful to relate symptoms to hemodynamic changes, especially for patients with valvular heart disease (eg, mitral stenosis). Hemodynamics are measured at rest and during peak exercise using bicycle ergometry, repeated leg or arm lifts, and occasionally arm bicycle ergometry. Commonly measured responses to exercise include minute ventilatory capacity, oxygen extraction, heart rate, cardiac output, ventricular volume and filling pressures, and metabolic substrate utilization (eg, glucose concentration without lactate production). Exercise may be dynamic or isometric. Measurement of each type demonstrates different features of LV function. Dynamic exercise measures the ability of the cardiovascular system to supply oxygen in keeping with increased metabolic demands. Oxygen consumption and workload increases should be parallel until the maximal oxygen consumption for the patient is reached. Dynamic exercise in the cardiac catheterization laboratory requires simultaneous right and left heart pressure measurements during exercise (eg, treadmill device mounted on the catheterization table). The patient's oxygen consumption also is measured by artery and vein oxygen saturations and is compared with the normal hemodynamic responses. Supine exercise in the catheterization laboratory differs from normal upright exercise in four ways—larger ventricular volumes, lower heart rate and diastolic arterial pressure, higher pulmonary and intracardiac filling pressures, and lower increase in stroke volume.

Isometric exercise consists of skeletal muscle contraction without shortening. Isometric exercise commonly is performed using a hand grip with a graded hand dynamometer. Measurements of hemodynamics and ventricular function are obtained during sustained hand grip at a predetermined range (15%–50% of the maximal hand-grip contraction) for a period of 3 to 4 minutes.

VALSALVA, MUELLER, AND OTHER PHYSIOLOGIC MANEUVERS

The Valsalva maneuver is performed by having the patient forcibly expire against a closed glottis and straining as if having a bowel movement. The magnitude of the Valsalva can be quantitated by measuring the pressure against which the patient must expire. The Valsalva maneuver can be performed safely and without complications by almost every type of patient. The four phases of the normal Valsalva maneuver (strain, hypotension, release, and pressure overshoot) may be absent in patients with specific cardiac diseases (congestive heart failure, coronary artery disease, and obstructive cardiomyopathy). In addition, the hemodynamics demonstrated for different types of valvular lesions may be more pronounced during the Valsalva maneuver because of changes in ventricular filling.

The Mueller maneuver is performed by inspiring against a closed glottis, and it is considered the inverse or opposite of the Valsalva maneuver. The subject inhales and the force of inhalation is measured with a manometer, usually 30 to 60 mm Hg for 30 seconds. Hemodynamic alterations of the Mueller maneuver include increased RV filling, increased period of diminished filling as a result of the collapse of the venae cava at thoracic inlets, increasing LV afterload with increase in LV end-diastolic and end-systolic volumes, diminished stroke volume, reduced cardiac output, and reduced ejection fraction. This maneuver is used to augment right-sided heart murmurs and to decrease the physical findings of obstructive cardiomyopathy by a reduction in LV outflow gradient. A reduction in the intensity of the systolic murmur in patients with echocardiographic evidence of anterior mitral valve leaflet motion also can be demonstrated with this maneuver.

Pharmacologic and physiologic stress on LV performance can be obtained in the catheterization laboratory by cold pressor testing, hyperventilation, or pharmacologic stimuli such as dobutamine, nitroglycerin, or any nitrates.

TRANSSEPTAL HEART CATHETERIZATION

Retrograde left heart catheterization for aortic or mitral stenosis or prosthetic valve dysfunction may not be suitable or possible in all patients. Transseptal access across the thin atrial septal membrane at the fossa ovalis into the left atrium and left ventricle is an established and safe technique in experienced hands.[14]

INDICATIONS

Conditions that require direct LA or LV measurement of pressure, such as mitral stenosis, pulmonary venous disease, left intraventricular gradient, aortic stenosis, or hypertrophic cardiomyopathy, require transseptal access. This procedure is needed for mitral balloon valvuloplasty or mitral clip for regurgitation, deployment of atrial septal defect closure devices, or hemodynamic assessment of prosthetic aortic or mitral heart valve dysfunction.

CONTRAINDICATIONS

Transseptal catheterization should not be performed in patients who cannot lie flat or fully cooperate; are anticoagulated; have a low platelet count or other hemostatic abnormalities, LA or RA thrombus, atrial myxoma, inferior vena cava mass, or obstruction. It should be considered carefully in patients with distorted cardiac anatomy secondary to congenital heart disease, dilated aortic root, marked atrial enlargement, or thoracic skeletal deformity.

ENDOMYOCARDIAL BIOPSY

Endomyocardial biopsy is a common procedure in the catheterization laboratory. Monitoring cardiac transplant rejection and anthracycline cardiotoxicity are the two major indications for endomyocardial biopsy. Other indications include diagnosis for secondary causes of cardiomyopathy, myocarditis (when there is a history of congestive heart failure in the preceding 6 months), and differentiation between restrictive and constrictive cardiomyopathies. The two major contraindications to endomyocardial biopsy are anticoagulation and anatomic abnormality precluding bioptome placement. Complications of endomyocardial biopsy include access site–related events (3%), biopsy-related events (3%), arrhythmia (1%), conduction abnormalities (1%), perforation (0.7%), and death (0.4%). All complication rates are higher for patients with cardiomyopathy compared with heart transplant recipients.

PERICARDIOCENTESIS

Pericardiocentesis may be required for diagnosis and management of acute and chronic pericardial effusions. In cardiac tamponade, this is a lifesaving technique. A sufficient degree of operator skill is necessary to prevent damage to the heart and pericardium. Pericardiocentesis usually is preceded by echocardiographic confirmation of pericardial fluid. However, in cases in which a large pericardial effusion is known or suspected with hemodynamic compromise in which tamponade is acute, echocardiographic assessment is not required and may be detrimental by delaying needed intervention. A Seldinger puncture technique is used from a subxiphoid approach to access the pericardial space, verify the position by echo-contrast or hemodynamics, and introduce a catheter to drain the pericardial effusion. Although monitoring of pericardial pressure is not essential for elective procedures, it is important to document evidence of cardiac tamponade and resolution of pericardial pressure restricting cardiac output.

LEFT VENTRICULAR HEMODYNAMIC SUPPORT DEVICES

In patients with hypotension, mitral regurgitation, multivessel disease, or decreased LV function, hemodynamic support may need to be instituted before the procedure begins. There are three principal types of LV hemodynamic support devices; intra-aortic balloon counterpulsation pump, LV-aortic centripetal pump (Impella) and LA-FA pump (Tandem Heart, a variation of full RA-FA cardiopulmonary support).

INTRA-AORTIC BALLOON COUNTERPULSATION PUMP

Intra-aortic balloon pump (IABP) counterpulsation involves positioning a 30- to 50-mL balloon in the descending aorta that inflates in diastole and deflates in systole to increase coronary blood flow and decrease myocardial afterload and oxygen demand.[15] Augmented diastolic blood pressure typically produces a substantial increase in mean arterial blood pressure. LV end-diastolic pressures decrease during IABP counterpulsation, with a preservation or increase in LV stroke volume and ejection fraction. LV demand is reduced by the reduction in afterload. Coronary perfusion occurs predominantly during diastole when the balloon is inflated, causing a rise in the AoP. IABP diastolic pressure augmentation can increase coronary flow in unobstructed coronary vessels but has little effect on flow across significant stenoses. Kern and colleagues[16] showed that IABP counterpulsation augmented coronary flow velocity proximal but not distal to a high-grade stenosis. After a successful angioplasty of a stenotic lesion in the same vessel, the IABP augmented coronary flow velocity across the entire vessel. The IABP increases diastolic flow velocity more in patients with a basal systolic blood pressure of less than 90 mm Hg.

Impella Left Ventricular Support Device

The Impella LV support device is an alternative to the IABP and complete cardiopulmonary support (heart-lung machine). The Impella 2.5 is a minimally invasive, catheter-based cardiac assist device that directly unloads the left ventricle, reduces myocardial workload and oxygen consumption, and increases cardiac output and coronary and end-organ perfusion.

The Impella 2.5 is inserted into the left ventricle over a 0.018" stiff guidewire through the FA and across the aortic valve.The tip of the catheter has a “pigtail” that facililates safe positioning in the left ventricle. The impeller motor draws blood into the cannula and expels it into the aorta, thereby generating pressure and flows up to 2.5 L/min, a significant increase over the the IABP (0.2–0.4 L/min). A 13-Fr femoral sheath is required for insertion of the Impella 2.5. Peripheral vascular disease and aortic valve disease are contraindications to the Impella.

Unloading of the left ventricle by the Impella increases aortic and intracoronary pressure, hyperemic flow velocity and coronary flow velocity reserve, and decreased microvascular resistance. The Impella-induced increase in coronary flow, probably results from both an increased perfusion pressure and a decreased LV volume-related intramyocardial resistance.

Clinical trials comparing the IABP with the Impella 2.5 have demonstrated improvements in hemodynamic parameters but no improvements in survival or main adverse coronary events (MACE). Based on its relative ease of use and high level of circulatory support, the Impella is a powerful device for use in selected patients for high-risk PCI or refractory shock.

The TandemHeart Pump System

The TandemHeart percutaneous ventricular assist device is designed for short-term mechanical LV support. The TandemHeart involves the placement of a 21-Fr catheter inserted into the left atrium from the femoral vein via a transseptal puncture. Blood is withdrawn from the left atrium by an external centrifugal pump and infused into the FA via a 14- to 19-Fr catheter. The TandemHeart can provide up to 4.5 L/min of cardiac support. As with the IABP and Impella, iliac-femoral angiography must be performed prior to canula insertion. Compared with the IABP, the TandemHeart has been shown to improve hemodynamic parameters in two small trials. However, there is a higher rate of complications with its use, including bleeding, tamponade, and vascular complications. The complexity of its insertion (30–45 minutes) and higher complication rate compared with the Impella or IABP likely will limit the role of the TandemHeart to critcally ill patients with aortic valve disease or refractory cardiogenic shock.

INDICATIONS AND CONTRAINDICATIONS

The indications and contraindications of LV support devices are listed in Table 20–19. In high-risk or unstable patients, an LV support pump may be inserted before catheterization depending on the degree of hemodynamic compromise anticipated during or after the procedure.

COMPLICATIONS OF LEFT VENTRICULAR SUPPORT DEVICES

Complications of LV support devices are principally related to vascular access, bleeding, leg ischemia, and thrombosis when patients are insufficiently anticoagulated.

TABLE 20–19. Indications and Contraindications to Left Ventricular Support Devices

Indications	Contraindications
Acute myocardial infarction, complicated by hypotension or cardiogenic shock	Severe peripheral vascular disease
Refractory unstable angina	Severe aortic incompetence
Hemodynamic stabilization prior to left main revascularization	Active bleeding
	Patients with contraindication to anticoagulation
Complications of acute myocardial infarction—acute myocardial regurgitation or VSD	Thrombocytopenia (< 50,000)
Weaning from cardiopulmonary bypass	Acute stroke
High-risk cardiac percutaneous revascularization	
Bridge to cardiac transplantation	
High-risk noncardiac surgery in coronary patients	
Refractory arrhythmias or induced arrhythmias during EP study	
Right ventricular failure (right-sided Impella or ECMO)	

Abbreviations: ECMO, extracorporeal membrane oxygenator; VSD, ventricular septal defect.

CARDIAC CATHETERIZATION IN HEART TRANSPLANT PATIENTS AND ADULTS WITH CONGENITAL HEART DISEASE

TRANSPLANTATION

Cardiac transplant patients have unique problems that may include altered anatomic relationships, absence of anginal pain, contrast allergic reactions, and high sensitivity to infection, all of which must be considered in the approach to this unusual patient population. Routine yearly follow-up of the transplant patient typically includes cardiac catheterization, coronary angiography, and assessment of LV function; PA pressures; and endomyocardial biopsy.

Angiography in the heart transplant patient must account for the transplanted heart that is rotated clockwise. Thus, the right coronary ostium is anterior and the left coronary ostium is located in a more posterior plane than in the normal heart. In addition, a suture ridge in the lower ascending aorta at the site of the aortic anastomosis may be encountered, causing the Judkins catheter to snag or bend as it is advanced. The anterior position of the right coronary ostia may be better engaged using an anterior-posterior or slightly rightward oblique view. These patients are generally preload-dependent, and thus the recommended administration of intracoronary nitroglycerine before angiographic studies may result in a significant drop in blood pressure. Of course, one of the important contributions of angiography in the transplant heart is the detection of allograft vasculopathy. IVUS is used to quantify this pathology.

CONGENITAL HEART DISEASE

Adults with corrected congenital heart disease are encountered with increasing frequency by the adult cardiac catheterization physician. Detailed knowledge of previous cardiac surgery, catheterization, and echocardiographic findings is necessary for the performance of a complete and accurate catheterization. Residual hemodynamic and electrophysiologic abnormalities must be identified in these patients to maintain long-term survival. Among the most commonly encountered problems are those of VSDs and conditions resulting in cyanosis. VSDs may occur at the muscular septum or the site of an old patch in corrected hearts. Great vessel shunts may occur from collateral supply, especially in those patients with repaired cyanotic heart disease or incompletely occluded shunts. Cyanosis in these individuals may result from persistent left SVC to left atrium shunting with or without coronary sinus or septal defect, right pulmonary A-V fistula (Glenn anastomosis), acquired lung disease, or a combination of the above conditions.

Careful hemodynamic and oximetric measurements are important to examine cardiac or extracardiac shunting. Both right and left PAs must be sampled for oxygen saturations during the oximetry run. Patients with cyanosis are placed on 100% oxygen to identify cardiac causes of cyanosis from noncardiac causes. Large-format image intensifiers (9-inch screen) or biplane angiography may be needed to display both ventricles simultaneously. Coronary artery abnormalities may occur and contribute to ventricular dysfunction in the adult with congenital heart disease. The late natural history of coronary atherosclerosis in corrected forms of congenital heart disease is unknown. It is recommended that any patient older than 35 years with evidence of ventricular dysfunction undergo coronary arteriography. Patients with complex congenital heart disease—such as tetralogy of Fallot with an overriding Ao, ventricular septal defect, and pulmonary stenosis or truncus arteriosus (common arterial trunk with VSD)—may have abnormally large aortic roots requiring modified coronary catheters. Single coronary arteries or anomalous origins of the left coronary from the right coronary artery may be part of the truncus arteriosus

(a common pulmonary and aortic outflow tube) and transposition of the great vessels (switching of PA and aorta).

CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS TO ASSESS CORONARY STENOSES

The rationale for measuring coronary blood flow and pressure arises from the failure of angiographic or any anatomic imaging modality to accurately predict the ischemic potential of a stenosis. For the intermediately narrowed angiographic stenosis (30%–80% diameter stenosis), the visual identification of ischemia is largely guesswork. This limitation of angiography has been documented repeatedly by poor correlations to stress testing (approximately 60% accuracy) and is attributable to the anatomic complexity of the atherosclerotic lumen.

Coronary angiography produces a two-dimensional silhouette image of the three-dimensional vascular lumen. Angiography does not provide vascular wall detail sufficient to characterize plaque size, length, and eccentricity. The eccentric lumen produces conflicting degrees of angiographic narrowing when viewed from different angulations, causing uncertainty related to lumen size and its impact on coronary blood flow. Moreover, there are at least six morphologic features that determine resistance to flow, most of which cannot be measured with the angiogram or even IVUS (Fig. 20–28).

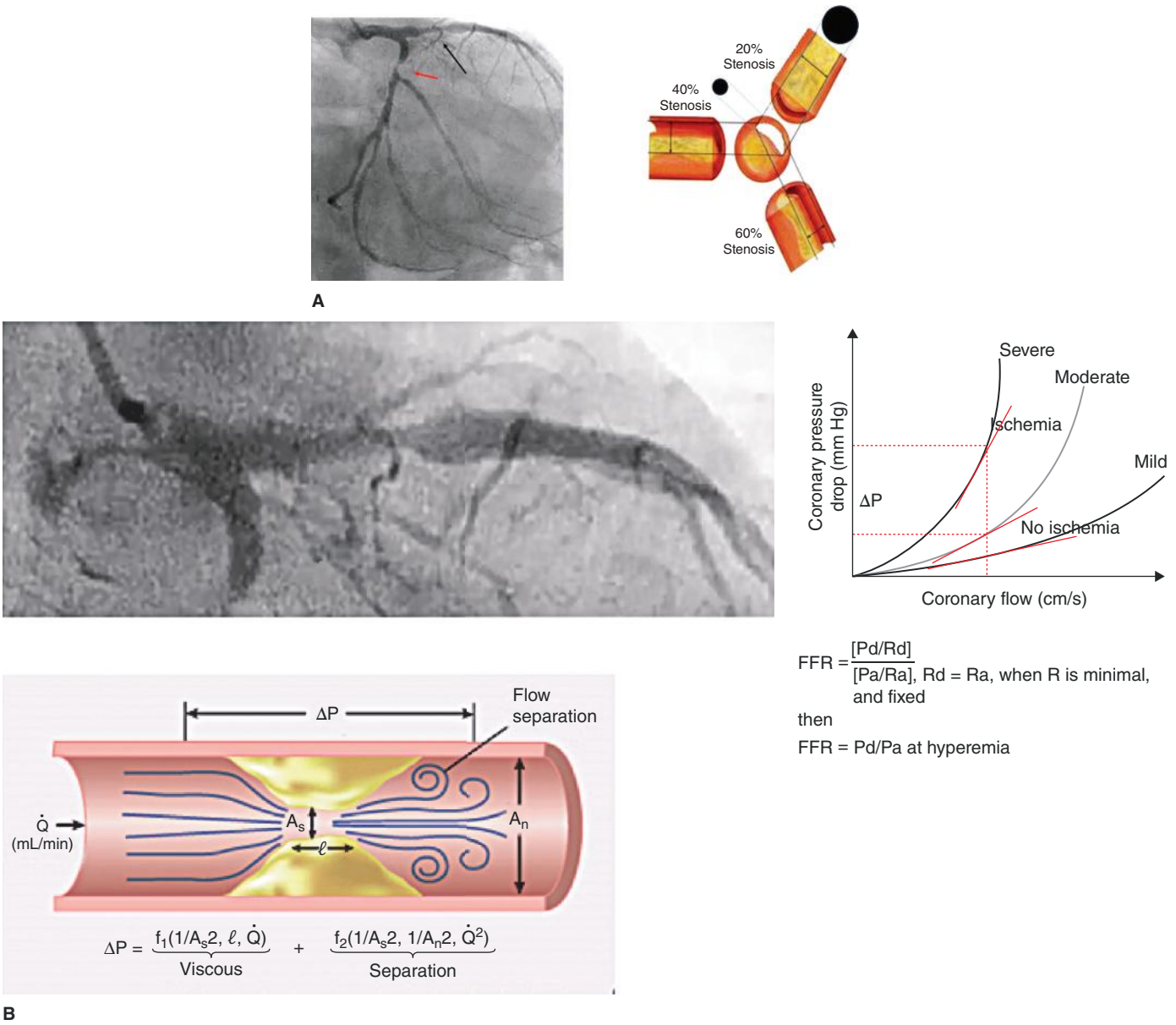


FIGURE 20–28. **A.** *Left*, cineangiographic frame showing the left coronary artery with a severe lesion in the circumflex artery (*red arrow*) and moderate lesioin in the LAD (*black arrow*). *Right,* diagram of eccentric lesion with three different angiographic projections in which the lumen may be assessed as mild, moderate, or severe depending on which projection is accepted. Because of the two-dimensional image projection, the severity of some lesioins, especially those in the intermediate range, do not reflect the flow impairment and thus require fractional flow reserve for accurate assessment. **B.** Coronary pressure and flow measurements and the relationship determines the ischemic potential of a stenosis. *Top left*, cineangiogram frame showing stenosis. There are seven features that contribute to resistance to flow, length being only one. *Bottom left,* diagram of a stenosis and factors that equate the change in pressure to two factors of viscous friction and energy loss due to flow separation, right translesional pressure drop compared to change in flow (horizontal). For each severity of flow, the pressure-flow relationship becomes steeper.

In contrast to the anatomic approach, a physiologic approach to lesion assessment examines the specific hemodynamic responses of flow across a stenosis. Such an approach has now been determined in clinical trials to improve outcomes after PCI, making physiologic lesion assessment a best practice to support the decision to proceed with PCI. There are two coronary physiologic tools available in the catheterization laboratory: (1) coronary pressure wire and microcatheter systems and (2) Doppler and thermodilution flow wires (which are principally research tools to study the microcirculation).[17-19]

CORONARY BLOOD FLOW AND RESISTANCE

Coronary blood flow can increase from a resting level to a maximum depending on increases in myocardial oxygen demand or in response to neurogenic or pharmacologic hyperemic stimuli. The ratio of maximal-to-basal flow is coronary flow reserve (CFR), or coronary vasodilatory reserve (CVR). Resistance to flow increase occurs at three levels: epicardial conduits (R1), precapillary arterioles (R2), and intramyocardial resistance (R3). Normally, large epicardial vessel resistance (R1) is trivial. Most coronary flow is regulated by the myocardial precapillary arteriolar resistance vessels (R2). In a normal artery supplying normal myocardium, CFR can exceed three. However, several conditions, including LV hypertrophy, myocardial ischemia, and diabetes, can affect the microcirculatory resistance R3, blunting the maximal absolute increase in coronary flow. Increased R3 resistance may also be associated with increased resting flow above the expected level for myocardial oxygen demand at rest, also resulting in reduced coronary flow reserve (Fig. 20–29).

Significant atherosclerotic stenosis produces epicardial conduit resistance. In parallel with resistance to flow, viscous friction, flow separation forces, and flow turbulence at the site of the stenosis produce pressure loss at the stenosis. The pressure loss increases with increasing coronary flow along an exponential pressure-flow relationship of the specific coronary stenosis resistance[18] (Fig. 20–30). In response to the loss of perfusion pressure and flow to the distal microcirculation bed, precapillary resistance vessels (R2) dilate to maintain satisfactory basal flow appropriate for myocardial oxygen demand. However, there exists an absolute poststenotic myocardial perfusion pressure threshold below which myocardial ischemia occurs. The hemodynamic significance of a given stenosis can be measured by the pressure-flow relationship using sensor angioplasty guidewires.[19]

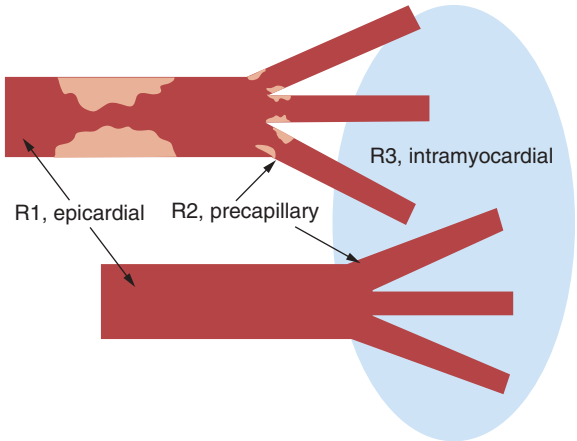


FIGURE 20–29. Coronary circulation. R1, R2, R3, epicardial, arteriolar, and microvascular resistance, respectively.

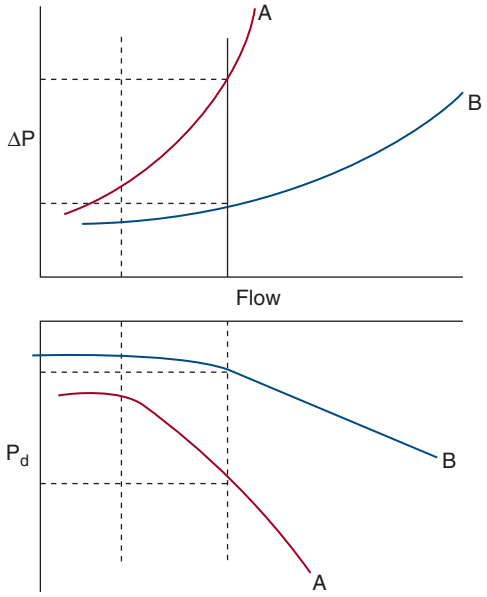


FIGURE 20–30. Coronary pressure–flow relationships for two stenoses of the same angiographic severity. *Top,* ΔP versus coronary flow. *Bottom,* Absolute distal coronary pressure P_d versus flow. Increasing flow produces marked loss of P_d as well as an increase in ΔP. The loss of P_d in absolute terms determines myocardial perfusion pressure (P_d venous pressure) and the potential for inducible ischemia. ΔP, pressure gradient (aortic-distal coronary pressure); P_d, distal coronary pressure.

PRESSURE-DERIVED FRACTIONAL FLOW RESERVE OF THE MYOCARDIUM

FFR is the preferred method for in-laboratory coronary stenosis assessment (Fig. 20–31). This pressure-derived ratio is an easily measured surrogate of coronary blood flow and has proven to be the most useful adjunctive test in the catheterization laboratory. It is derived from fairly straightforward principles. Myocardial perfusion is primarily dependent on coronary blood flow as determined by the interaction between the driving pressure and the three major coronary vascular resistances.

$$\text{Flow} = \Delta\text{Pressure}/\text{Resistance}$$

Pijls and colleagues[20,21] as well as De Bruyne and coworkers[22] defined the FFR as the ratio of coronary blood flow through a stenotic artery compared with the normal blood flow in the theoretical absence of the stenosis. Stated another way, FFR represents that fraction of normal maximum flow that remains despite the presence of an epicardial lesion.

$$FFR = \text{Myocardial flow } (Q_s) \text{ across stenosis}/\text{Myocardial flow } (Q_n) \text{ without stenosis}$$

$$FFR = Q_s/Q_n = (P_d - P_v/R_s)/(P_a - P_v/R_n)$$

If the myocardial bed resistances are induced pharmacologically to maximal hyperemia and remain constant, then the resistances of the vessels become equivalent. The poststenotic hyperemic coronary artery pressure is linearly related to flow and represents the maximal achievable perfusion available in that vessel.

$$FFR = (P_d - P_v)/(P_a - P_v)$$

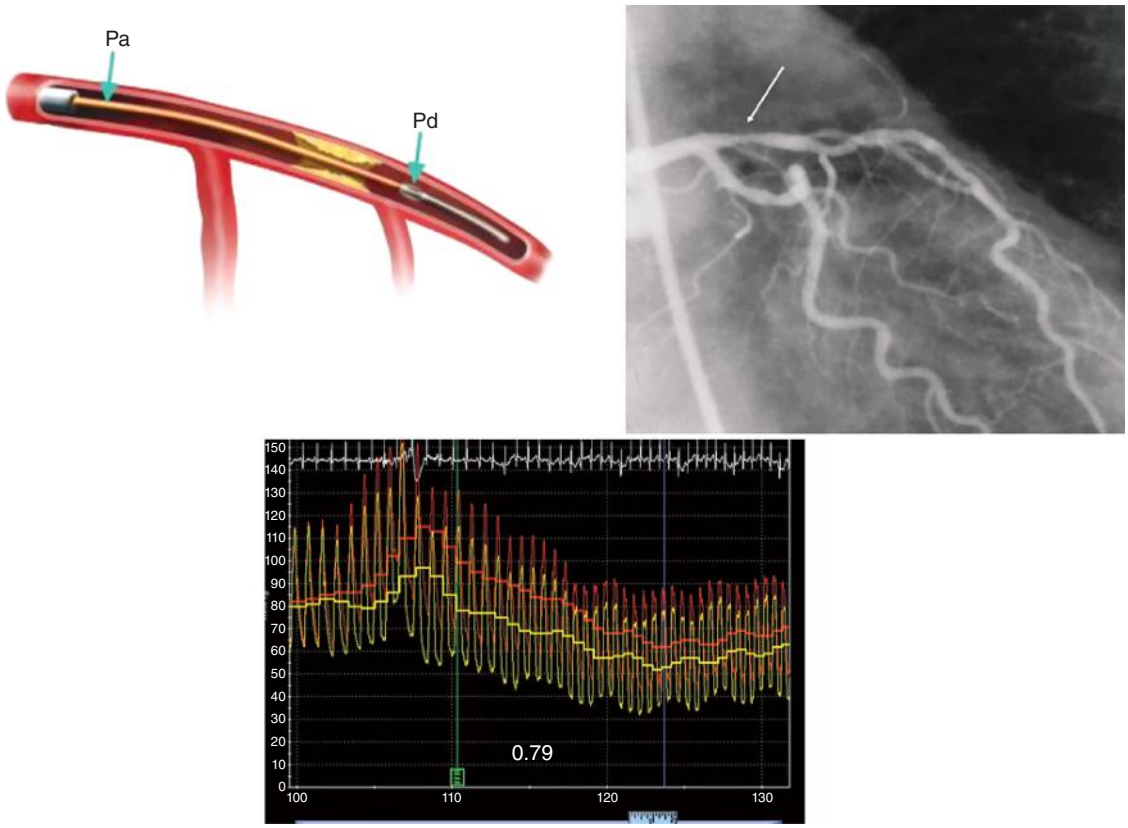


FIGURE 20–31. Method of measuring fractional flow reserve (FFR). *Top,* Diagram of coronary artery and pressure wire across stenosis (*middle*). *Bottom,* FFR tracing phasic and mean pressure signals used to measure FFR, calculated as the ratio of distal coronary pressure (Pd) to aortic pressure (Pa) at maximal hyperemia, which is equal to 0.79, the point of lowest Pd/Pa ratio.

where P_a = mean aortic pressure, P_d = mean distal coronary pressure, and P_v = mean venous or RA pressure. For daily clinical practice, assuming P_v is negligible relative to P_a, FFR can be easily estimated by a simplified ratio of pressures and expressed as:

$$FFR = P_d / P_a$$

An FFR value of 0.6 means that the maximum myocardial flow across the stenosis is only 60% of what it should be without the stenosis. An FFR of 0.9 after PCI means that the maximum flow to the myocardium is 90% of a completely normal vessel.

The concept of FFR has been thoroughly examined in both experimental and clinical studies. Unlike most other physiologic indexes, FFR has a normal value of 1.0 for every patient and every coronary artery. Despite findings in animal studies defining an effect of heart rate and arterial pressure, human studies did not show significant changes in FFR with changes in heart rate, blood pressure, or contractility.[22] FFR has a high reproducibility and low intraindividual variability. Moreover, FFR, unlike CFR, is independent of sex or coronary artery disease risk factors such as hypertension and diabetes and has less variability with common doses of adenosine. FFR reflects both antegrade and collateral myocardial perfusion rather than merely transstenotic pressure loss (ie, a stenosis pressure gradient). Because it is calculated only at peak hyperemia, FFR is also differentiated from CFR by being largely independent of basal flow, driving pressure, heart rate, systemic blood pressure, or status of the microcirculation (Fig. 20–32). The FFR, but not the resting pressure or hyperemic pressure gradient, is strongly related to provocable myocardial ischemia, demonstrated by comparisons to different clinical stress testing modalities in patients with stable angina.

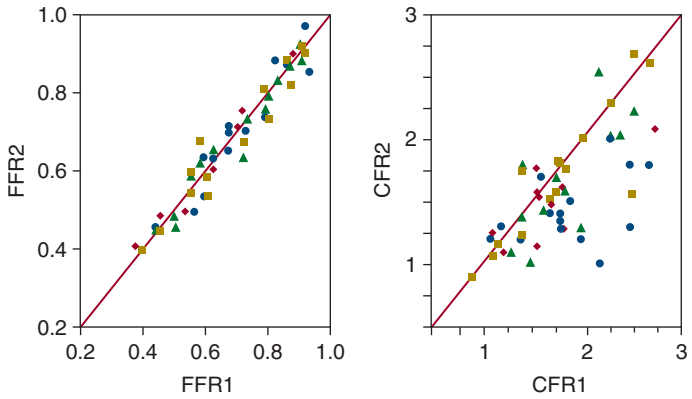


FIGURE 20–32. Reproducibility of fractional flow reserve (FFR) versus coronary vasodilatory reserve (CVR) for changing heart rate, blood pressure, and contractility. Circles, contractility; diamonds, mean arterial pressure; FFR, fractional flow reserve; squares, duplicate measurement; triangles, heart rate. Reproduced with permission from de Bruyne B, Bartunek J, Sys SU, et al: Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation.* 1996 Oct 15;94(8):1842-1849.[22]

CORONARY FLOW VELOCITY RESERVE

Coronary flow velocity reserve is used to study the microcirculation. Because CFR is the result of flow through both the conduit and the microvascular bed, CFR is useful for coronary lesion assessment only when normal. For this reason, FFR is the preferred in-laboratory technique for physiologic lesion assessment.

The coronary flow velocity of red blood cells moving past the ultrasound emitter/receiver on the end of a 0.014-inch Doppler-tipped angioplasty guidewire can be determined from the frequency shift, defined by the Doppler equation as the difference between the transmitted and returning frequency:

$$V = (F_1 - F_0) \times (C) / (2F_0) \times (Cos\ \emptyset)$$

where V = velocity of blood flow, F_0 = transmitting (transducer) frequency, F_1 = returning frequency, C = constant for the speed of sound in blood, and Ø = angle of incidence.

Volumetric flow is the product of vessel area (cm^2) and flow velocity (cm/s), yielding a value in cm^3/s. Absolute Doppler flow velocities represent changes in volumetric coronary flow when the vessel cross-sectional area remains constant over the measurement period. Compared with volumetric measurements, velocity may underestimate the volumetric flow reserve in some vessels which demonstrate intact endothelial mediated vasodilation. CFR is the ratio of maximal hyperemic-to-basal mean flow velocity in the target vessel obtained distal to the stenosis. As stenosis severity increases, hyperemic flow becomes attenuated, and CFR decreases.

CFR measures the capacity of the two-component system of the R1 coronary artery resistance and the R2 vascular resistance to achieve maximal blood flow in response to a given hyperemic stimulation. Normal CFR in young patients with IVUS-demonstrated normal arteries commonly exceeds 3.0.[23] In patients with chest pain undergoing cardiac catheterization with angiographically normal vessels, the normal CFR is 2.7 ± 0.6,[24] suggesting some degree of patient to patient variability and distal microvascular disease. The values for CFR associated with nonobstructed coronary arteries in patients with chest pain syndromes, in patients with transplanted hearts, and in normal arteries in patients with obstructive coronary artery disease elsewhere are 2.8 ± 0.6, 3.1 ± 0.9, and 2.5 ± 0.95, respectively.[24] The incidence of impaired coronary vasodilatory reserve of less than 2.0 in 450 angiographically normal coronary arteries from 220 patients undergoing evaluation for chest pain or cardiac transplant follow-up angiography is approximately 12%.[24]

FACTORS INFLUENCING CORONARY FLOW RESERVE

Unlike FFR, CFR is subject to variations in hemodynamics that may alter resting flow and limit maximal hyperemic flow. In patients with a nonuniform microcirculation, such as those with myocardial infarction, CFR cannot be used for assessment of lesion severity. Tachycardia increases basal flow; therefore, CFR is reduced by 10% for every 15 heart beats.[23] Increasing mean arterial pressure reduces maximal vasodilatation, thus reducing hyperemia with less alteration in basal flow. CFR may be reduced in patients with essential hypertension or aortic stenosis. In some patients with moderate coronary artery disease, the stenotic configuration and surrounding vessel segments are subject to vasomotor stimuli. Thus vasoconstrictor, neurologic, or humoral influences, endothelial dysfunction, and extracardiac vasoconstrictor stimuli may produce dynamic or episodic ischemia-related symptoms with activities of daily life such as exercise, emotional stress, or adrenergic stimulation. The variability in CFR in nonobstructed arteries may also be due to age.[25] Table 20–20 lists pathologies associated with impairment of the microcirculation.

TABLE 20–20. Pathologies Impairing the Microcirculation

Abnormal vascular reactivity
Abnormal myocardial metabolism
Abnormal sensitivity toward vasoactive substances
Coronary vasospasm
Myocardial infarction
Hypertrophy
Vasculitis syndromes
Hypertension
Diabetes
Recurrent ischemia

Reproduced with permission from Baumgart D, Haude M, Liu F, et al: Current concepts of coronary flow reserve for clinical decision making during cardiac catheterization. *Am Heart J.* 1998 Jul;136(1):136-149.[25]

METHOD OF SENSOR GUIDEWIRE USE

After diagnostic angiography or during angioplasty, the sensor guidewire is passed through an angioplasty Y connector attached to a guiding catheter. Intravenous (IV) heparin or bivalirudin is administered for anticoagulation. Intracoronary (IC) nitroglycerin (100–200 μg) is also given before the guidewire is advanced into the artery to minimize the risk of guidewire-induced spasm.

For FFR, the guidewire is advanced in the guide catheter to the coronary ostium, and the sensor pressure is matched to the guide catheter pressure. The wire is then advanced into the artery beyond the stenosis. Baseline pressure is recorded. Coronary hyperemia with IC or IV adenosine is induced, while both guide catheter and sensor wire pressures are continuously recorded. FFR is computed as the ratio $pressure_{distal}$ to $pressure_{aorta}$ at maximal hyperemia (Fig. 20–33). Pressure signal artifacts may be reduced by careful attention to technique.

For flow velocity, the sensor tip is advanced at least 5 to 10 artery-diameter lengths (> 2 cm) beyond the stenosis to measure reestablished laminar flow. Resting flow velocity data are recorded. Induction of coronary hyperemia by IC or IV adenosine is performed with continuous recording peak hyperemic flow velocity. CFR is computed as maximal

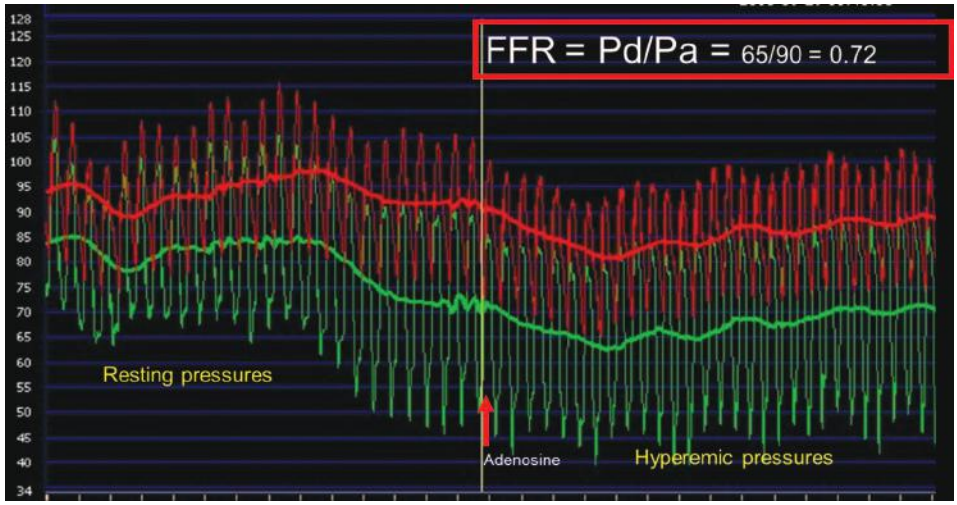


FIGURE 20–33. Pressure signals used to calculate fractional flow reserve (FFR). Screen from FFR monitor showing colored signals of Pa (*red*) and Pd (*green*) for FFR of 0.72. Mean aortic pressure (Pa) and distal coronary pressure (Pd) are recorded at rest and then during hyperemia induced by adenosine (in this case intracoronary; *arrow*). The nadir of distal pressure is used for the FFR calculation.

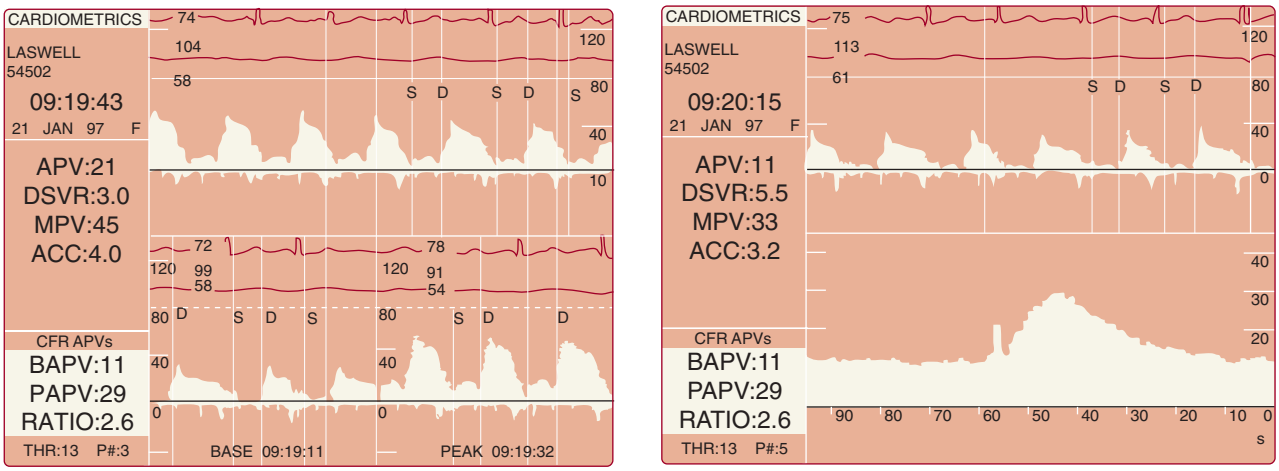


FIGURE 20–34. **A.** Coronary flow velocity signals obtained in a normal circumflex artery (CFX) of a patient undergoing angioplasty of the right coronary artery. The top half represents continuous flow-velocity signals in real time. The electrocardiogram, aortic pressure, and spectral flow signals are provided from top to bottom. The scale is 0 to 120 cm/s. S and D periods are demarcated by the electrocardiogram. **B.** The trend plot of the continuous flow velocity measurement is shown in the right-hand panel on the lower tracing. After intracoronary adenosine administration, average peak velocity increased from 11 to 29 cm/s, producing a coronary flow reserve of 2.6. The duration of hyperemia is 45 seconds. The trend velocity scale is 0 to 40 cm/s. The time base is 90 seconds. D, diastolic; S, systolic. Reproduced with permission from Kern MJ, de Bruyne B, Pijls NH: From research to clinical practice: current role of intracoronary physiologically based decision making in the cardiac catheterization laboratory. *J Am Coll Cardiol*. 1997 Sep;30(3):613-620.

hyperemic to basal average peak velocity (Figs. 20–34 and Fig. 20–35). Poor Doppler signal acquisition may occur in 10% to 15% of patients even within normal arteries. As in transthoracic echo-Doppler studies, the operator must adjust the guidewire's position (sample volume) to optimize the velocity signal. Several different tip orientations interrogating the maximal velocity spectra are necessary.

The safety of IC sensor-wire measurements has been excellent, as reported by Qian and coworkers[26] in 906 patients. Complications included severe transient bradycardia after IC adenosine (1.7%), coronary spasm during passage of the Doppler guidewire (1%), and ventricular fibrillation during the procedure (0.2%). All complications could easily be managed medically.

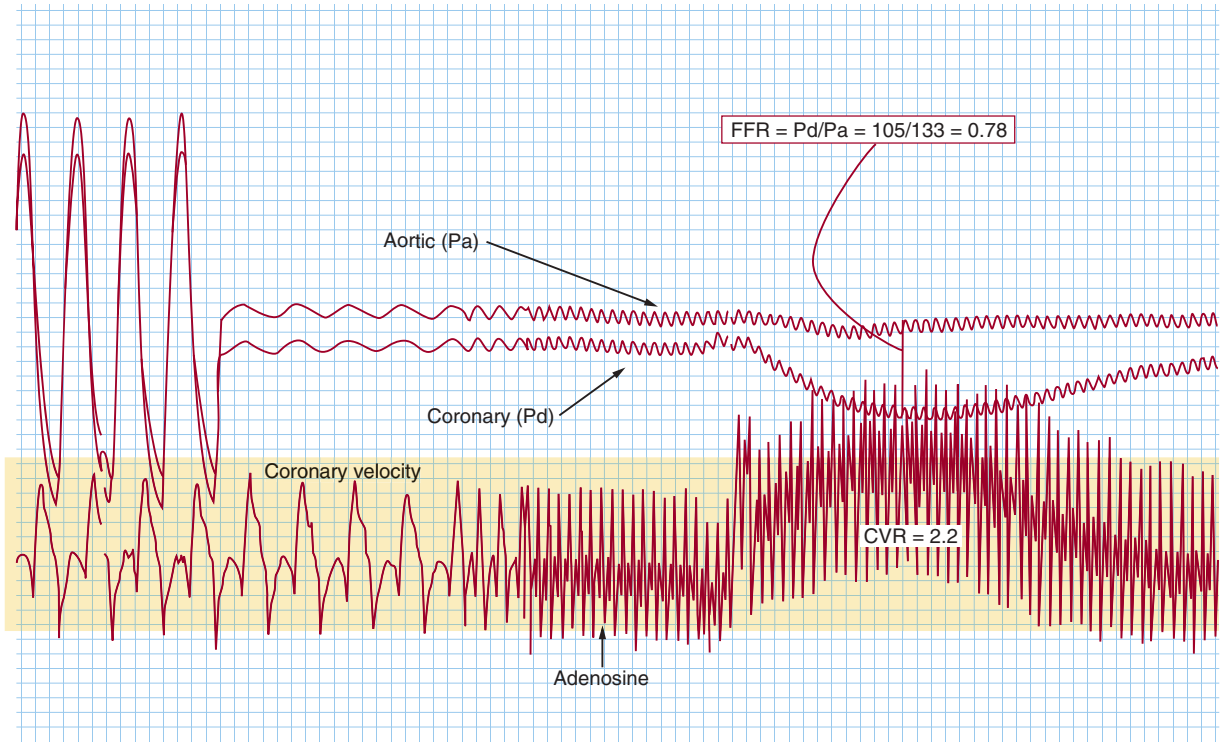


FIGURE 20–35. Phasic and mean pressure signals used to measure fractional flow reserve (FFR), calculated as the ratio of distal coronary pressure (Pd) to aortic pressure (Pa) at maximal hyperemia, which is equal to 0.78 in this example. For reference to coronary flow, a velocity signal is shaded and shown at the bottom to identify the time of maximal hyperemia. The velocity signal is only available in combined sensor wire studies. CVR, coronary vasodilatory reserve. Used with permission from Dr. Bernard de Bruyne.

COMBINED PRESSURE AND FLOW MEASUREMENTS

Recent advancements in technology allow a more complete evaluation of the coronary circulation with either a single wire equipped with pressure and velocity sensors or with pressure and thermodilution sensors. With combined measurements beyond a stenosis, a clinician can acquire relevant hemodynamic data regarding the physiological condition of the entire coronary circulation and its clinical implications for treatment.

Presently, there are two methods used for these calculations. The first method combines simultaneous measurement of the phasic pressure and Doppler velocity distal to a stenosis with a dual-sensor guidewire. Using distal pressure and velocity during hyperemic conditions, a hyperemic stenosis resistance (HSR) (by velocity, v) index is calculated as $HSR_v = \Delta P/v$, where ΔP = hyperemic pressure gradient (P_aP_d); v = average peak velocity at hyperemia.[27-29] This index purportedly provides a refined physiologic measurement quantifying the impediment to maximal flow caused exclusively by the stenosis. Like FFR, HSR_v has a normal reference value ($HSR_v = 0$) and is independent of basal hemodynamic conditions, with high reproducibility and low variability.[27] An HSR_v value greater than 0.8 mm Hg/cm/s is the threshold for prediction of reversible ischemia when compared with noninvasive stress testing.[27] HSR_v had a higher diagnostic accuracy than either pressure (FFR) or flow velocity (CFR) alone, especially in cases where outcomes of FFR and CFR do not agree.[30]

The second method for calculating CFR is measurement of thermodilution flow, as assessed by the inverse of the arrival (transit) time of a room-temperature saline bolus to the distal coronary artery segment (Fig. 20–36).[31] By measuring the mean transit time at rest and comparing it with the mean transit time at peak hyperemia, a thermodilution CFR can be calculated. The ability to measure distal pressure and estimate flow using the thermodilution technique with a single wire also allows independent assessment of the microvasculature by calculating the index of microcirculatory resistance (IMR) as the product of P_d and the hyperemic mean transit time.[32] Although principally a research tool, the simultaneous measurement of FFR, CFR, IMR, and HSR permits a unique characterization of the epicardial and microvascular resistances. The significant features of available physiologic measurements in the catheterization laboratory are listed in Table 20–21 and Appendix 20–3.

TABLE 20–21. Characteristics of Physiologic Measurements in the Catheterization Laboratory

Characteristic	FFR	IFR	CVR	HSR
Ischemic threshold range	0.75–0.80	≤ 0.89	< 2.0	> 0.8
Normal value	1.0	1.0	Variable	0
Epicardial lesion specific	Yes	Yes	No	Yes
Independent of hemodynamics	Yes	Yes	No	Yes
Reproducibility	+++	+++	+	++
Spatial resolution	+++	+++	+	++
Assesses microvascular integrity	–	–	+++	+++
Assess both stenosis and microvasculature	–	–	–	+++
Pressure-flow curves	–	–	–	+++

Abbreviations: CVR, coronary velocity reserve; FFR, fractional flow reserve; IFR, instantaneous wave-free ratio; HSR, hyperemic stenosis resistance.

BASAL FLOW ASSESSMENT OF CORONARY STENOSIS: THE INSTANTANEOUS WAVE-FREE RATIO

In a search to simplify the physiologic lesion assessment methods and increase user acceptance, Sen et al[33] have described an adenosine-independent index of stenosis severity. Using coronary wave intensity analysis, they identified a wave-free period during which there are no forward- or backward-traveling pressure waves in the epicardial vessels.[34] Importantly, they identified that during the wave-free period the intracoronary resistance is naturally constant (but not always minimal) at rest, similar to the mean coronary resistance (over the entire cardiac cycle) achieved under hyperemia. The Pd/Pa ratio calculated during this wave-free period is called the instantaneous wave-free ratio (iFR).

Sen et al[33] showed in 157 lesions that iFR had good correlation to FFR (r = 0.90, $P < .001$). The correlation was maintained (r > 0.85) in a

FIGURE 20–36. Thermodilution-derived transit time curves at baseline and during maximal hyperemia.

variety of subgroups analyzed, including different coronary anatomies, single versus multivessel disease, IC versus IV adenosine, diabetics, smokers, and hypertensives. The iFR also showed excellent diagnostic efficiency with an area under the curve of the receiver operating characteristic curve of 0.93. The overall diagnostic accuracy to predict an FFR cutoff of 0.80 was 88%, which may be as high as 95% when accounting for variability in serial FFR measurements. The iFR was highly reproducible, with a mean difference between repeated measures of 0.0005 ± 0.002; this compared to a historical FFR cohort with mean difference between repeated measures of 0.01 ± 0.04.[33]

Unfortunately at this time, iFR can only be computed from proprietary software provided by the Volcano Corp. Moreover, in a larger multicenter study of 1593 lesions, iFR had only an accuracy of 80% to predict the FFR.[35] Whether a hyperemia-free index can accurately determine the ischemic potential of the coronary stenosis is conceptually appealing but fundamentally challenging and is a controversial concept currently being tested in several large outcome studies.

PHARMACOLOGIC HYPEREMIC STIMULI

Most indices of stenosis severity are assessed using measurements obtained during maximal coronary flow or hyperemia. Hyperemia is most commonly achieved with IV or IC adenosine (50–100 μg in the RCA or 100–200 μg in the left coronary artery[36] (Table 20–22). Alternative IV hyperemic agents include IV adenosine triphosphate (ATP) (140 mcg/kg/min), regadenoson 400 mcg IV bolus, and rarely IV dopamine (10–40 mcg/min × 2-minute increments). Less commonly used agents include IC ATP (50–100 mcg), and rarely used agents are IC papaverine (10–15 mg) and IC nitroprusside (50–100 mcg).[37]

CLINICAL APPLICATIONS OF CORONARY BLOOD FLOW AND PRESSURE MEASUREMENTS

PHYSIOLOGIC CRITERIA

Coronary physiologic measurements associated with several major clinical outcomes are supported by numerous studies and are summarized in Table 20–23. The recommendation for use of physiologic measurements during invasive procedures is provided in Appendix 20–4.

TABLE 20–23. Catheter-Based Anatomic and Physiologic Criteria Associated with Clinical Outcomes

Application	IVUS	CVR	FFR	iFR
Ischemia detection	< 3–4 mm^2	< 2.0	≤ 0.75–0.80	≤ 0.89
Deferred angioplasty	—	> 2.0	> 0.80	> 0.89
Multivessel FFR-guided PCI			> 0.80	
End point of stenting	> 9 mm^2 > 80% reference area, full apposition	—	> 0.94	—

Abbreviations: CVR, coronary vasodilator reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

FRACTIONAL FLOW RESERVE AND VALIDATION BY ISCHEMIC STRESS TESTING

Strong correlations exist between myocardial stress testing and FFR or CFR. An FFR of less than 0.75 identified physiologically significant stenoses associated with inducible myocardial ischemia, with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%). Uniquely, FFR of less than 0.75 has been compared against a composite of three stress tests performed on the same patients before and after PCI, overcoming limitations of each individual stress test. An abnormal CFR (< 2.0) corresponded to reversible myocardial perfusion imaging defects with high sensitivity (86%–92%), specificity (89%–100%), predictive accuracy (89%–96%), and positive and negative predictive values (84%–100% and 77%–95%, respectively).[38]

Magnetic resonance myocardial perfusion imaging (MRMPI), with IV adenosine (140 mcg/kg/min) and a first-pass 0.1-mmol/kg gadolinium bolus, has been shown to correlate well with FFR in detecting reversible ischemia. When tested against an FFR of less than 0.75 in 103 patients with angina (300 coronary artery segments), MRMPI had a high sensitivity (91%), specificity (94%), positive predictive value (91%), and negative predictive value (94%) for detecting functionally significant coronary heart disease.[39] A summary of ischemic stress testing and coronary physiologic measurements is provided in Table 20–24.

TABLE 20–22. Pharmacological Hyperemic Agents for Fractional Flow Reserve Measurements

	Adenosine	Adenosine	Regadenoson	NTP	Papaverine
Route	IV	IC	IV	IC	IC
Dosage	140 mcg/kg/min	60-100 mcg LCA 20-30 mcg RCA	0.4 mg	50-100 mcg	15 mg LCA 10 mg RCA
Half-life	1-2 min	30-60 sec	2-4 min (up to 30 min)	1-2 min	2 min
Time to Max Hyperemia	< 1-2 min	5-10 sec	1-4 min	10-20 sec	20-6 sec
Advantage	Gold Standard	Short action	IV bolus	Short action	Short action
Disadvantage	↓ BP, chest burning	AV Block, ↓ BP	↑ HR, long action, ?redose	↓ BP	Torsades, ↓ BP

Abbreviations: AV, atrioventricular; BP, blood pressure; HR, heart rate; IC, intracoronary; IV, intravenous; LCA, left coronary artery; LCA, left coronary artery.

TABLE 20–24. Physiologic Measurements and Noninvasive Stress Test Results

Index	Reference	Reference No.	N	Ischemic Test	BCV	Accuracy %
FFR	Pijls	40	60	X-ECG	0.74	97
	de Bruyne	44	60	X-ECG/SPECT	0.72	85
	Pijls	29	45	X-ECG/SPECT/pacing/DSE	0.75	93
	Bartunek	45	37	DSE	0.68	90
	Abe	46	46	SPECT	0.75	91
	Chamuleau[a]	47	127	SPECT	0.74	77
	Caymaz	48	40	SPECT	0.76	95
	Jimenez-Navarro	49	21	DSE	0.75	90
	Usui	50	167	SPECT	0.75	79
	Yanagisawa	51	167	SPECT	0.75	76
	Meuwissen	52	151	SPECT	0.74	85
	de Bruyne[b]	53	57	MIBI-SPECT post MI	0.78	85
	Samady[b]	54	48	MIBI-SPECT post MI	0.78	85
H-SRv	Meuwissen	36	151	SPECT	0.80	87

[a]Multivessel disease.

[b]Myocardial infarction.

Abbreviations: BVC; best cutoff value (defined as the value with the highest sum of sensitivity and specificity); DSE; dobutamine stress echocardiography; SPECT; single-photon emission computed tomography, X-ECG; exercise ECG.

Modified with permission from Kern MJ: Coronary physiology revisited : practical insights from the cardiac catheterization laboratory. *Circulation*. 2000 Mar 21;101(11):1344-1351.

CLINICAL OUTCOMES OF PERCUTANEOUS CORONARY INTERVENTION BASED ON FRACTIONAL FLOW RESERVE

Three prospective randomized trials have demonstrated the safety and efficacy of using FFR to guide PCI, forming the evidence supporting FFR for daily use in the catheterization laboratory.

1. The DEFER Trial[40] randomized 325 patients with stable ischemic heart disease and an intermediate angiographic lesion. FFR was performed on all the lesions and PCI was performed if FFR was less than 0.75. Those lesions with an FFR of 0.75 or more were then randomized to either PCI or medical therapy (ie, deferral of angioplasty). The patients receiving PCI for an FFR of less than 0.75 comprised a reference group. All patients were followed for 5 years (Fig. 20–37). The results showed that it was safe to defer PCI on lesions determined to be nonischemic by FFR and continue medical therapy only for CAD.
2. The FAME Trial[41] (Fractional Flow Reserve versus Angiography for Guiding Coronary Intervention) was a prospective randomized trial that enrolled 1005 patients with multivessel coronary artery disease (at least two vessels with a 50% angiographic stenosis). Patients were randomized to one of two revascularization strategies, either (1) an angiographically guided PCI group where drug-eluting stents were deployed in all lesions identified or (2) an FFR-guided group having a stent placed in only those lesions producing an FFR of 0.80 or less. The

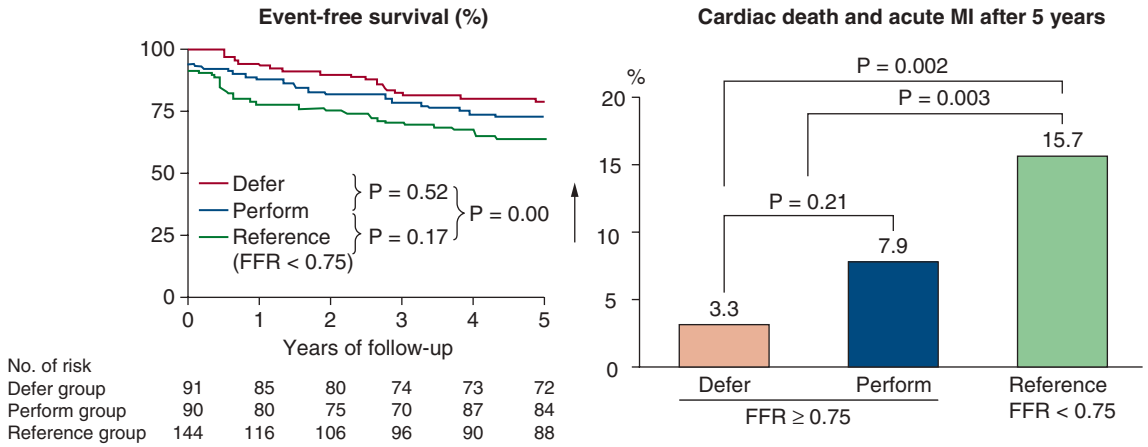


FIGURE 20–37. DEFER 5-year follow-up event rates. *Top*, Kaplan-Meier survival curves for freedom from adverse cardiac events during 5 years follow-up for the three groups. *Bottom*, Cardiac death and acute myocardial infarction rate in the three groups after a follow-up of 5 years. Reproduced with permission from Pijls NH1, van Schaardenburgh P, Manoharan G, et al: Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007 May 29;49(21):2105-2111.[40]

primary end point was the combined end point of death, nonfatal myocardial infarction, and repeat revascularization at 1 year (Fig. 20–38). The results showed that FFR guided–PCI had fewer myocardial infarction/death events than angiographically guided PCI.

3. The FAME 2 Trial[42] (Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease) enrolled 1220 patients with angiographic disease in one, two, or three vessels that was suitable for PCI. All patients with lesions with FFR of 0.80 or less were randomized to either PCI or medical therapy. A composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization during a 2-year follow-up was the primary end point (Fig. 20–39). The results showed that FFR-guided PCI had dramatically fewer events over the first year and was also cost-effective compared to optimal medical management alone for stable ischemic patients.

These studies are discussed in detail below.

The DEFER trial examined the outcome of deferring revascularization of a coronary stenosis based on a nonischemic FFR value. The DEFER study randomized 325 patients scheduled for PCI into three groups and reported the 5-year outcomes.[40] If FFR was greater than 0.75, patients were randomly assigned to the deferral group (n = 91, medical therapy for coronary artery disease [CAD]) or the PCI performance group (n = 90, PCI with stents). If FFR was less than 0.75, PCI was performed as planned and patients were entered into the reference group (n = 144). Complete follow-up was obtained in 98% of patients. Overall, the event-free survival was not different between the deferred and performed group (80% and 73% respectively, P = .52), and both were significantly better than in the reference group (63%, P = .03). The composite rate of cardiac death and acute myocardial infarction in the deferred, performed, and reference groups was 3.3%, 7.9%, and 15.7%, respectively (P = .21 for deferred vs performed and P = .003 for reference vs both of the deferred and performed groups) (see Fig. 20–37). The percent of patients free from chest pain on follow-up was not different between the deferred and performed groups. The 5-year risk of cardiac death or myocardial infarction in patients with nonischemic FFR was less than 1% per year and was not decreased by stenting. Treating patients guided by FFR is associated with a low event rate, comparable to event rates in CAD patients with normal noninvasive testing.

The superior outcome of FFR-guided PCI for patients with multivessel CAD was reported by Tonino et al[41] for the FAME I study. These investigators addressed the hypothesis that a physiologically guided

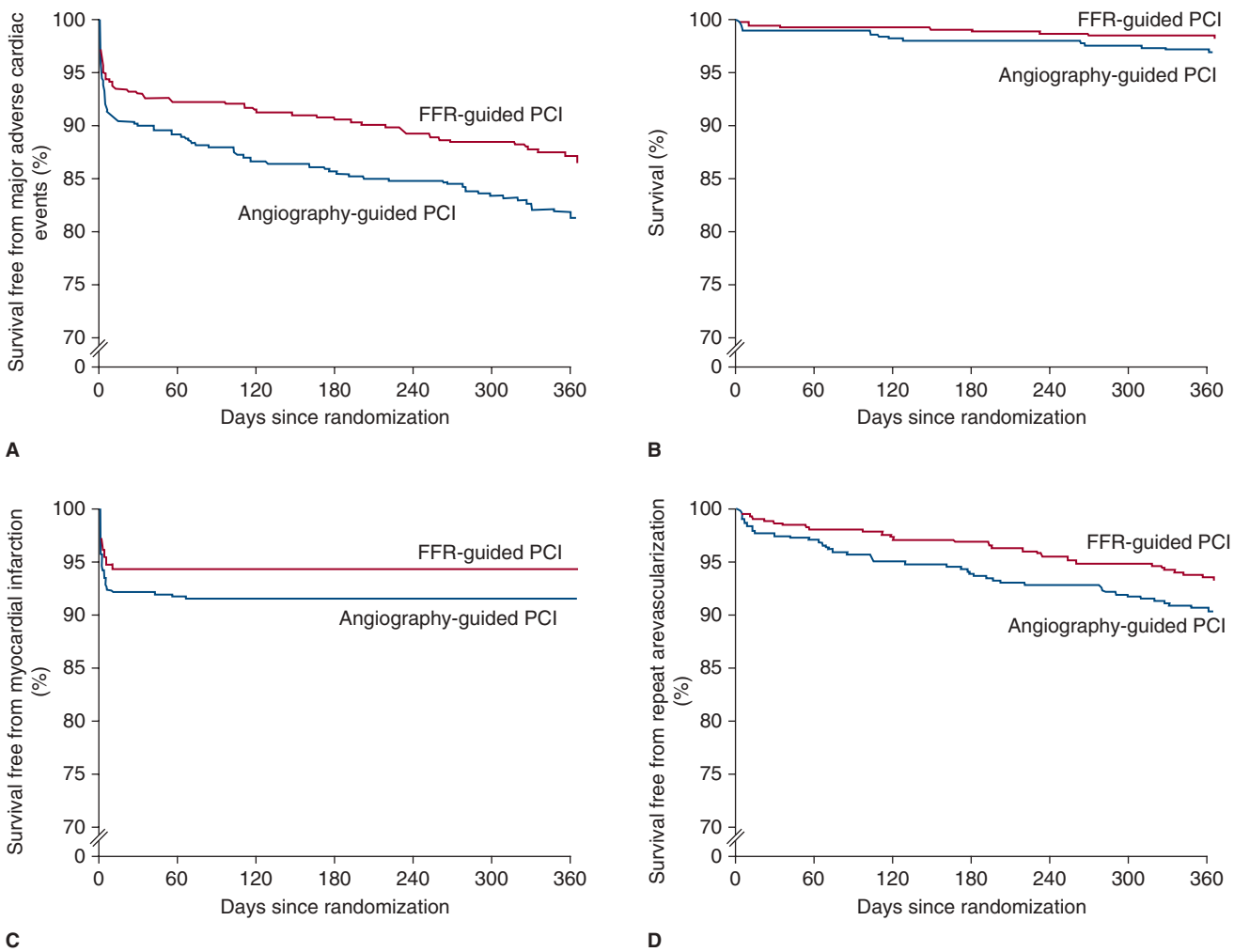
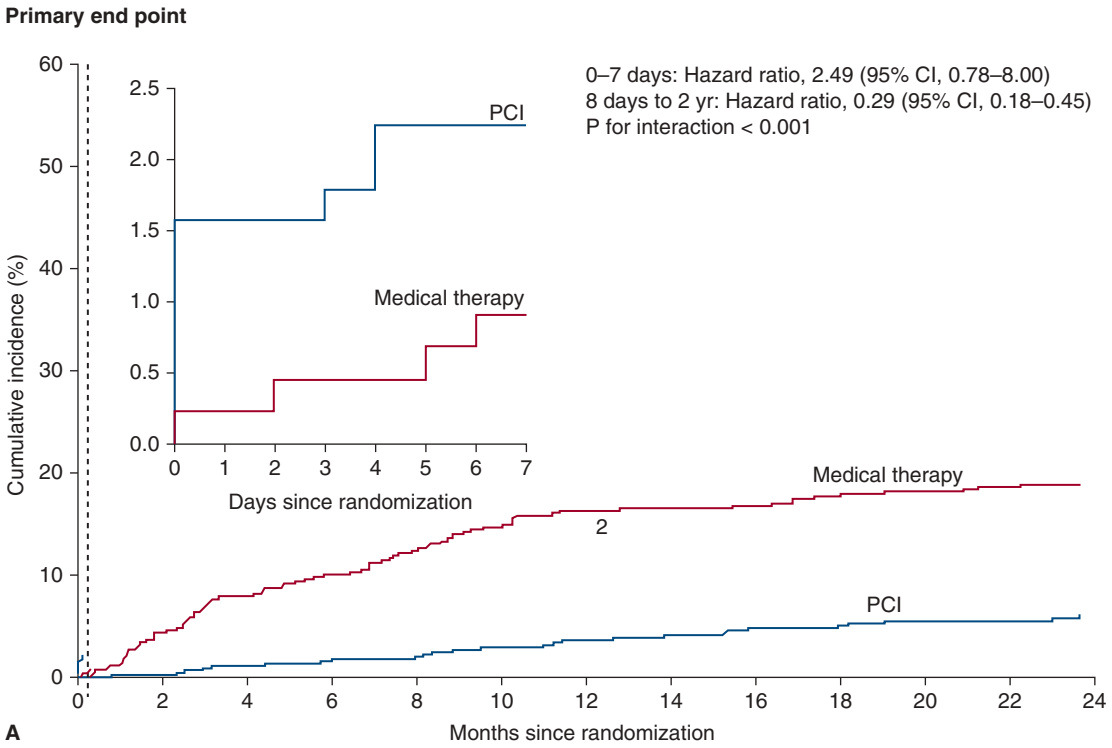


FIGURE 20–38. Kaplan Meier survival curves for the 1-year follow-up of the FAME patients. **A**. Event-free survival for major adverse cardiac events was significant at 1 year. No differences in event-free survival for death (**B**), myocardial infarction (MI) (**C**), or coronary artery bypass grafting/percutaneous coronary intervention (PCI) (**D**). FFR, fractional flow reserve. Reproduced with permission from Tonino PA, De Bruyne B, Pijls NH, et al: Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009 Jan 15;360(3):213-224.[41]



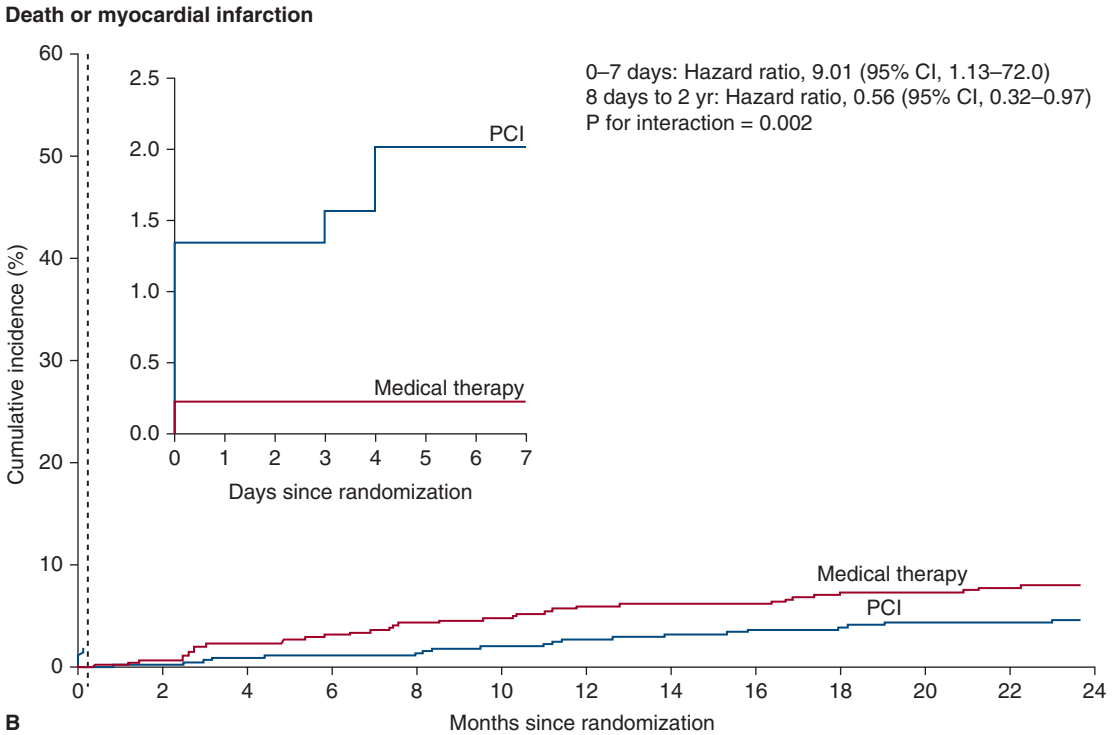


FIGURE 20–39. FAME 2 Study comparing optimal medical therapy (OMT) to percutaneous coronary intervention (PCI) plus OMT. Two-year followup. Landmark analysis excluding the first 7 days after PCI demonstrated that fractional flow reserve–guided PCI had a significantly lower rate of the primary endpoint (death, MI, or urgent revascularization) **(A)** and a lower rate of death or MI **(B)**. Reproduced with permission from De Bruyne B, Fearon WF, Pijls NH, et al: Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014 Sep 25;371(13):1208-1217.

PCI approach (FFR-PCI) was superior to a conventional angiographic guided PCI (angio-PCI) in patients with multivessel CAD. A total of 1005 patients with multivessel CAD undergoing PCI with drug-eluting stents were randomized to one of the two strategies. Operators selected all indicated lesions in advance of randomization for stenting by visual angiographic appearance (> 50% diameter stenosis). For the FFR-PCI group, all lesions had FFR measurements and were only stented if the FFR was 0.80 or less. The primary end points of death, myocardial infarction, repeat revascularization (coronary artery bypass grafting [CABG] or PCI) were obtained at 1 year. Of the 1005 patients, 496 were assigned to the angio-PCI group, and 509 were assigned to the FFR-PCI group. Clinical characteristics and angiographic findings were similar in both groups. The Syntax (Synergy between PCI with Taxus and Cardiac Surgery) scores for gauging risk in multivessel disease involvement were identical at 14.5, indicating low-intermediate risk patients.

Despite identifying in advance three angiographically indicated lesions per patient for stenting, compared with the angio-PCI group, the FFR-PCI group used fewer stents per patient (1.9 ± 1.3 vs 2.7 ± 1.2, $P < .001$), less contrast (272 vs 302 mL, $P < .001$), had lower procedure cost ($5332 vs $6007, $P < .001$), and shorter hospital stay (3.4 vs 3.7 days, $P = .05$). More importantly, at 1-year follow-up, the FFR-PCI group had with fewer MACE (13.2% vs 18.4%, $P = .02$), fewer combined deaths or myocardial infarction (7.3% vs 11%, $P = .04$), and a lower total number of MACE (76 vs 113, $P = .02$) compared with the angio-PCI group (see Fig. 20–38).

The precise mechanisms of reduced end points in the FFR-guided arm of FAME are not known but are likely associated with fewer implanted stents having fewer procedure-related early (eg, side-branch occlusion, additional troponin release) and late stent complications (eg, subacute thrombosis, restenosis). This study is a clinical validation of FFR outcomes and has important implications for managing CAD patients.

The FAME 2 study demonstrated that optimal medical therapy in addition to FFR-guided PCI in patients with stable CAD results in improved outcomes when compared to optimal medical therapy (OMT) alone. FAME 2 examined 764 lesions with an angiographic stenosis greater than 50% with an FFR of less than 0.80 (mean of 0.68 ± 0.15). The study was stopped early because of an excess incidence of MACE in the OMT group. Although 50% of events were urgent revascularization, the other 50% were NSTEMI, STEMI, or unstable angina with electrocardiographic changes of ischemia. A landmark analysis (see Fig. 20–39) suggested a higher rate of acute coronary syndromes in the medical therapy arm starting 1 week after randomization. This data strongly suggest that lesions with abnormal FFR values have better long-term prognosis with revascularization than those with abnormal FFR values receiving continued medical therapy. FFR-guided PCI also is a cost-effective alternative to optimal medical management for stable angina.[43]

ASSESSMENT OF THE LEFT MAIN STENOSIS

Numerous studies of FFR support its use in equivocal left main disease (Table 20–25). Most recently, Hamilos M et al[44] examined FFR and 5-year outcome in 213 patients with an angiographically equivocal left main coronary artery stenosis in a large multicenter prospective trial. When FFR was 0.80 or more, patients were treated medically or another stenosis was treated by coronary angioplasty (nonsurgical group; n = 138). When FFR was less than 0.80, CABG surgery was performed (surgical group; n = 75). The 5-year survival estimates were 90% in the nonsurgical (FFR ≥ 0.80) group and 85% in the surgical (FFR < 0.80) group ($P = .48$). The 5-year event-free survival estimates were 74% and 82% in the two groups, respectively ($P = .50$) (Fig. 20–40). Of note, only 23% of patients with a diameter stenosis of more than 50% had a hemodynamically significant left main by FFR. FFR appears helpful in identifying patients with intermediate left main disease suitable for surgical revascularization or continued medical therapy, with excellent survival and low event rates.

TABLE 20–25. Studies with Fractional Flow Reserve to Assess Intermediate Left Main Coronary Stenoses

Study	Year of Publication	Definition of Intermediate LMCA Stenosis	FFR Cutoff Value	Total Number of Patients		Revascularization	Mean FU (months)
				Total	Deferred		
Bech et al.[7]	2001	40–60%	< 0.75	54	24	30 (CABG)	29 ± 15
Jiménez-Navarro et al.[9]	2004	30–50%	0.75	27	20	7 (6 CABG, 1 PCI)	26 ± 12
Legutko et al.[10]	2005	30–60%	< 0.75	38	20	18 (12 CABG, 5 PCI, 1 OMT)	24 ± 12
Lindstaedt et al.[12]	2006	40–80%	< 0.75[a]	51	24[b]	27[c] (CABG)	29 ± 16
Courtis et al.[13]	2009	30–60%	< 0.75[a]	142	82	60 (54 CABG, 6 PCI)	14 ± 11
Hamilos et al.[14]	2009	30–70%	< 0.80	213	138	75 (CABG)	36 (6-99)
Total	2009	—	—	525	308	217	—

[a]Revasularization was recommended for FFR < 0.75. For FFR between 0.75 and 0.80, additional clinical data used to proceed with revascularization.

[b]22 patients with FFR > 0.75 and 2 patients with FFR between 0.75 and 0.80.

[c]21 patients with FFR < 0.75 and patients with FFR between 0.75 and 0.80.

CABG = coronary artery bypass surgery; FFR = fractional flow reserve; FU = duration of follow-up; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

Abbreviations: CABG, coronary artery bypass surgery; FFR, fractional flow reserve; FU, duration of follow-up; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

Reproduced with permission from Mallidi J, Atreya AR1, Cook J, et al: Long-term outcomes following fractional flow reserve-guided treatment of angiographically ambiguous left main coronary artery disease: A meta-analysis of prospective cohort studies. *Catheter Cardiovasc Interv*. 2015 Jul;86(1):12-18.

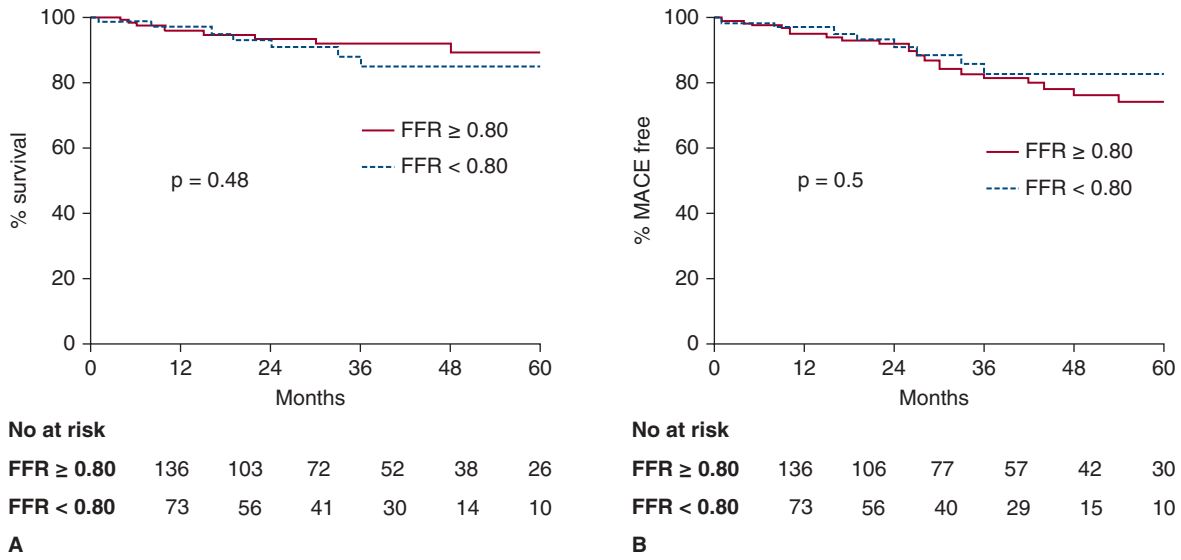


FIGURE 20–40. Kaplan–Meier mortality curves showing percent survival (**A**) and major adverse cardiac events (MACE; **B**) in the two study groups. There is no difference between the nonsurgical and surgical groups. FFR, fractional flow reserve. Reproduced with permission from Hamilos M, Muller O, Cuisset T, et al: Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation*. 2009 Oct 13;120(15):1505-1512.[44]

Although the frequent presence of downstream distal CAD theoretically limits the accuracy of left main FFR, several laboratory, animal, and human models of CAD have demonstrated that the impact is modest. Disease of one of the major side branches (ie, the LAD), must be very severe and very proximal to have a significant effect on left main FFR.[45,46]

SERIAL LESION ASSESSMENT

Fundamental to an accurate FFR is the condition of minimal and fixed microvascular resistance that is achieved during maximal hyperemia. When there are two (or more) consecutive or serial stenoses, the first stenosis limits maximal flow across the downstream lesions, whereas all downstream stenoses limit the maximal flow across the more proximal lesion. Thus, the interaction between the stenoses prevents us from using the simple FFR ratio (P_d/P_a) for each stenosis individually. The extent to which both stenoses influence each other is somewhat unpredictable. However, the simple FFR across all lesions can assess the summed result of any group of stenoses.

Pijls and DeBruyne[47,48] demonstrate nicely the effect of increasing the severity of the distal lesion on the serial FFR measurements in an experimental model. As the distal lesion becomes more severe with a larger gradient, the FFR of the proximal lesion becomes less severe (ie, FFR goes up). This experiment confirms the adverse interaction between serial lesions when attempting to use simple FFR alone. The method of serial lesion assessment by pressure wire can be found elsewhere.[47]

ACUTE CORONARY SYNDROMES AND FRACTIONAL FLOW RESERVE

The predictive ability of FFR in acute coronary syndrome has several limitations:

1. The microvascular bed in the infarct zone may not have uniform, constant, or minimal resistance.
2. The severity of stenosis may evolve as thrombus and vasoconstriction abate.
3. FFR measurements are not meaningful when normal perfusion has not been achieved.

Thus, a negative (≥0.80) FFR has limited diagnostic utility in the infarct-related artery during the first 24 to 48 hours after acute coronary syndrome, whereas a positive (≤0.80) value still identifies a stenotic lesion. FFR has demonstrated value in nonculprit remote lesion assessment and in target lesion assessment during the recovery phase of MI.[49,50]

A normal FFR is indicative of reversal of myocardial perfusion defects in patients with prior myocardial infarction. De Bruyne et al[50] examined FFR in 57 patients who had sustained a myocardial infarction more than 6 days before investigation. Sensitivity and specificity of an FFR of 0.75 to detect abnormal scintigraphic imaging were 82% and 87%, respectively; the concordance between FFR and scintigraphy was 85% ($P < .001$). An FFR of more than 0.75 distinguished patients after myocardial infarction with negative scintigraphic imaging (Fig. 20–41). Similar findings relating FFR of infarct-related arteries in patients early after myocardial infarction to reversible perfusion defects by myocardial contrast echocardiography has been reported by Samady and colleagues[51] (Fig. 20–42).

COLLATERAL CIRCULATION

The collateral circulation can be described by intracoronary pressure and flow relationships. Ipsilateral collateral flow and contralateral arterial responses have been described in numerous studies using both pressure and flow to provide new information regarding mechanisms, function, and clinical significance of collateral flow in patients and provide new insights into coronary artery disease. The reader is referred to excellent works elsewhere for details.[52,53]

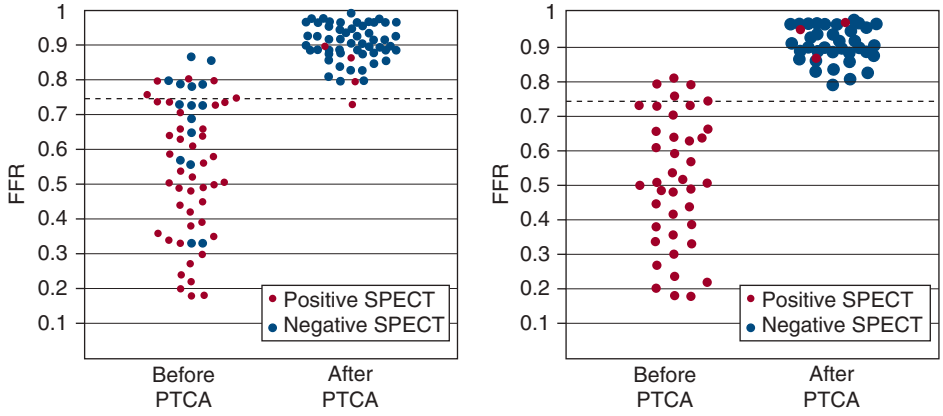


FIGURE 20–41. Values of fractional flow reserve (FFR) before and after angioplasty for myocardial infarction according to results of sestamibi single-photon emission computed tomography (SPECT) myocardial perfusion imaging in patient population as a whole (**A**) and in patients with truly positive and truly negative SPECT imaging (**B**). PTCA, percutaneous transluminal coronary angioplasty. Reproduced with permission from De Bruyne B, Pijls NH, Bartunek J, et al: Fractional flow reserve in patients with prior myocardial infarction. *Circulation*. 2001 Jul 10;104(2):157-162.[50]

SUMMARY

Measurements of coronary physiology strongly complement coronary luminography and permit exploration of the coronary microcirculation, collateral flow, myocardial infarction physiology, and mechanisms of interventions for CAD. The evaluation of CAD in the cardiac catheterization laboratory necessitates that the operator define ischemia producing coronary lesions. Angiography alone is often insufficient and not specific enough to characterize an individual coronary stenosis. A coronary stenosis that does not produce an "ischemic" FFR has been shown to have a favorable long-term outcome when treated with medical therapy. In these patients, outcomes are not significantly improved with coronary revascularization. PCI of only those lesions that are physiologically significant by FFR has been prospectively demonstrated clinically and shown economically superior results over angiographically guided PCI in patients with multivessel CAD. FFR has been proven to be an accurate detector of the ischemic potential of a stenosis and an invaluable adjunct to the modern-day catheterization laboratory.

ACKNOWLEDGMENTS

We would like to thank Dr. Spencer King, who contributed to the previous version of this chapter in the 13th edition.

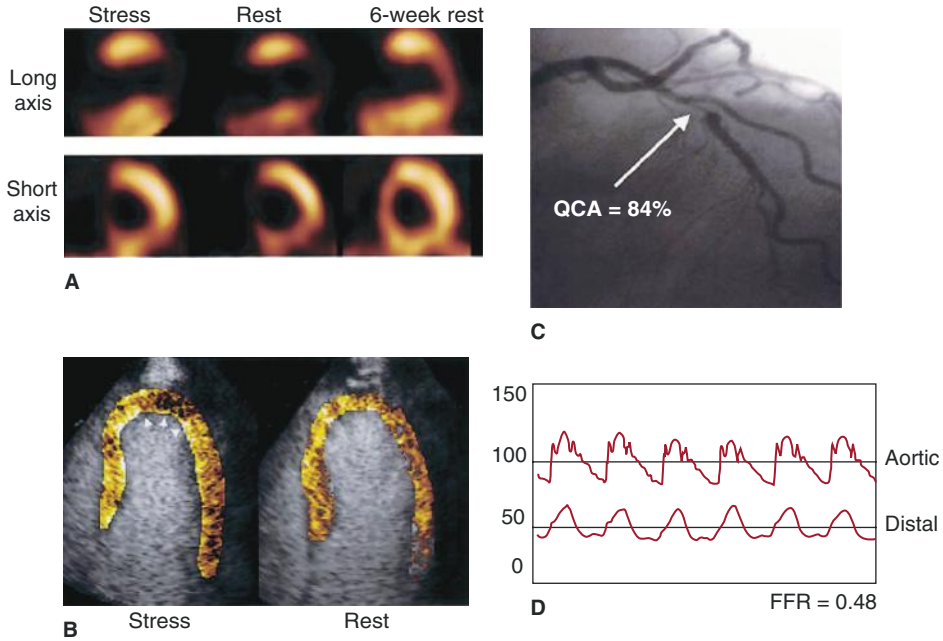


FIGURE 20–42. **A.** Baseline rest and dipyridamole (DP)-stress vertical long-axis single-photon emission computed tomography (SPECT) images and 10-week follow-up rest images are shown from a patient with anterior myocardial infarction who received thrombolytic therapy. When DP stress is paired with initial rest images, there is a fixed perfusion defect in the anteroapical wall. When DP stress is paired with the delayed rest images, SPECT is reclassified as reversible. **B.** Rest and post-DP stress myocardial contrast echocardiography images from the apical four-chamber view of the same patient demonstrate an apical-lateral perfusion defect during DP that was not present at rest, indicating reversibility. **C.** Angiogram of the patient showing an 84% lesion in the left anterior descending coronary artery. **D.** Fractional flow reserve (FFR) tracings showing an FFR of 0.48. QCA, quantitative coronary angiography. Reproduced with permission from Samady H, Lepper W, Powers ER et al: Fractional flow reserve of infarct-related arteries identifies reversible defects on noninvasive myocardial perfusion imaging early after myocardial infarction. *J Am Coll Cardiol*. 2006 Jun 6;47(11):2187-2193.[51]

Appendix 20–1. Appropriate Indications for Diagnostic Catheterization

- Suspected acute coronary syndrome
  - Cardiogenic shock due to suspected acute coronary syndrome
  - STEMI or suspected STEMI
  - Unstable angina/NSTEMI
  - Suspected ACS with newly diagnosed LV wall motion abnormality or newly diagnosed resting myocardial perfusion defect
- Suspected CAD
  - High pretest probability (asymptomatic or symptomatic, with or without prior noninvasive testing)
  - High-risk findings on noninvasive testing
  - Baseline LV dysfunction
  - Equivocal or discordant findings on noninvasive testing in a symptomatic patient
- Known CAD
  - Intermediate or high-risk noninvasive findings, with symptoms
  - High-risk noninvasive findings, asymptomatic
- Arrhythmias
  - Resuscitated cardiac arrest with return of spontaneous circulation
  - VF or sustained VT with or without symptoms
- Valvular disease
  - Preoperative assessment before valvular surgery
  - Pulmonary hypertension out of proportion to the severity of valvular disease
  - Conflicting noninvasive impression of severity with clinical impression
  - LV dysfunction out of proportion to the severity of valvular disease
- Pericardial diseases
  - Suspected pericardial tamponade
  - Suspected or clinical uncertainty between constrictive vs. restrictive physiology
- Cardiomyopathy
  - Known or suspected cardiomyopathy with or without heart failure
  - Reevaluation of known cardiomyopathy
  - Change in clinical status or cardiac examination or to guide therapy
- Pulmonary hypertension or intracardiac shunt evaluation
  - Known or suspected intracardiac shunt with indeterminate shunt anatomy or shunt fraction
  - Suspected pulmonary hypertension
  - Pulmonary vascular vasodilator responsiveness study
- Pretransplant or posttransplant
  - With or without endomyocardial biopsy

Adapted from ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 Appropriate Use Criteria for Diagnostic Catheterization. *J Am Coll Cardiol*. 2012;59:1995–2027.

Abbreviations: CAD, coronary artery disease; LV = left ventricular; NSTEMI, non-ST elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Data from Patel MR, Bailey SR, Bonow RO, et al: ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 May 29;59(22):1995-2027.

Appendix 20–2. Appropriate Indications for Fractional Flow Reserve and Intravascular Ultrasound

Indication	Appropriate Use Score (1-9): Unexpected Angiographic Finding or No Prior Noninvasive Testing	Prior Testing = No Ischemic Findings	Prior Testing = Concordant[a] Ischemic Findings
FFR for Lesion Severity			
• Angiographically indeterminate severity left main stenosis (defined as 2 or more orthogonal views contradictory whether stenosis > 50%)	A(7) I(3) A(7)	A(7) 1(2) U(6)	A(7) U(5) A(7)
• Nonobstructive disease by angiography (non-left main) < 50%	A(7)	A(7)	1(3)
• Angiographically intermediate disease (non-left main) 50% to 69%			
• Angiographically obstructive significant disease (non-left main) ≥ 70% stenosis			
IVUS for Lesion Severity			
• Angiographically indeterminate left main stenosis (defined as 2 or more orthogonal views contradictory whether stenosis > 50%)	A(7) I(3) u(5)	A(7) 1(3) U(5)	A(7) U(6) U(6)
• Nonobstructive disease by angiography (non-left main) < 50%	u(4)	U(5)	I(3)
• Angiographically intermediate disease (non-left main) 50% to 69%			
• Angiographically obstructive significant disease (non-left main) ≥ 70% stenosis			
IVUS—Examination of Lesion or Artery Morphology			
• Coronary lesions or structures difficult to characterize angiographically (e.g., aneurysm, extent of calcification, stent fracture, stent apposition, stent expansion, dissections) or for sizing of vessel before stent placement			A(8)

[a]Concordance refers to noninvasive imaging studies demonstrating evidence of abnormal myocardial perfusion that is in the same distribution as a coronary artery stenosis or degree of valvular disease that is similar to clinical impression.

From SCCT/SCMR/STS. 2012 Appropriate use criteria for diagnostic catheterization. *J Am Coll Cardiol*. 2012;59:1995-2027.

Abbreviations: A, appropriate; FFR, fractional flow reserve, I, inappropriate; IVUS, intravascular ultrasound; U, uncertain.

Reproduced with permission from Patel MR, Bailey SR, Bonow RO, et al: ACCF/SCAI/AATS/AHA/ ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 May 29;59(22):1995-2027.

Appendix 20–3. Comparison and Derivations of Intracoronary Physiologic Measurements

Fractional Flow Reserve (FFR):

Derivation: FFR = Q_{sten}/Q_{normal} at maximal hyperemia. Q = flow, sten = stenotic artery, normal = theoretic same artery without stenosis.

$Q_{sten} = P_{sten}/Resistanc_{esten,}$

$Q_{normal} = P_{aorta}/Resistanc_{esten,}$ then $Q_{sten}/Q_{normal} = P_{sten}/P_{aorta}$

Hence FFR = $P_{distal\ to\ stenosis}/P_{aorta,}$

[for complete derivation includes venous pressure Pv as FFR = $P_{distal\ to\ stenosis}$ - Pv/P_{aorta} –Pv, see reference 2]

Unique features:

- Nonischemic threshold range > 0.75–0.80
- Normal value of 1.0 for every artery and every patient
- Epicardial lesion specific
- Linear relation with relative maximum blood flow
- Independent of hemodynamic alterations
- Value that accounts for total myocardial blood flow, including collaterals
- Highly reproducible
- High spatial resolution (pressure pullback recording)

Coronary Flow Velocity and Reserve:

Derivation: CFVR = $Q_{hyperemia}/Q_{base}$. Q = velocity if cross-sectional area unchanged during hyperemia

Unique features:

- Nonischemic threshold range of CFR > 2.0
- Coronary flow reserve in nonobstructed vessels assesses microvascular integrity
- Complements invasive coronary studies of endothelial function
- Accurate estimation of volumetric flow when vessel cross-sectional area available
- Valuable for blood flow research studies

Combined Pressure and Flow Velocity Measurements:

Derivation: HSR = P_{aorta} -$P_{distal\ to\ stenosis}/Q_{hyperemic}$

Derivation: IMR= $P_{distal\ to\ stenosis}/(1/mean\ transit\ time_{hyperemic})$

- Separate assessment of stenosis and microvascular resistances
- Allows construction of pressure-flow curves (assessment of compliant lesions, hemodynamic gain after percutaneous coronary intervention)

Stenosis Resistance Index:

- Normal value of 0
- Lesion specific
- Highly reproducible, high sensitivity
- Useful in cases of discordance between coronary flow reserve and FFR

Modified with permission from Kern MJ, Samady H: Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol*. 2010 Jan 19;55(3):173-185.

Appendix 20–4. Applications of Fractional Flow Reserve in the Catheterization Laboratory

A. Applications Supported by Percutaneous Coronary Intervention (PCI) Guidelines
   1. Fractional Flow Reserve (FFR): Recommendations[a]
   2. FFR is reasonable to assess angiographic intermediate coronary lesions (50%–70% diameter stenosis) and can be useful for guiding revascularization decisions in patients with stable ischemic heart disease. (Class IIa, Level of Evidence: A)
   3. Assessing the success of PCI in restoring flow reserve and to predict the risk of restenosis. (Class IIb, Level of Evidence: C)
   4. Evaluating patients with anginal symptoms without an apparent angiographic culprit lesion. (Class IIb, Level of Evidence: C)
   5. Routine assessment of the severity of angiographic disease in patients with a positive, unequivocal noninvasive functional study is not recommended. (Class III, Level of Evidence: C)

B. Clinical Applications of FFR
   1. Determination of one or more culprit stenoses (either serially or in separate vessels) in patients with multivessel disease
   2. Evaluation of ostial or distal left main and ostial right lesions, especially when these regions can not be well visualized by angiography
   3. Guidance of treatment of serial stenoses in a coronary artery
   4. Determination of significance of focal treatable region in vessel with diffuse coronary artery disease
   5. Determination of prognosis after stent deployment
   6. Assessment of stenosis in patients with previous (nonacute, > 6 days) myocardial infarction
   7. Assessment of lesions in patients with treated unstable angina pectoris
   8. Assessment of the collateral circulation

C. Clinical Applications of Combined Coronary Pressure and Doppler Flow Velocity Under Study
   1. Assessment of intermediate stenosis
   2. Assessment of the microcirculation
   3. Identification of lesion compliance (change of pressure-velocity relationship)

[a]Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–e651.

Abbreviations: FFR, fractional flow reserve.

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CHAPTER 21

CORONARY INTRAVASCULAR IMAGING

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Intravascular imaging continues to play a vital role in advancing our understanding of the pathophysiology of coronary artery disease (CAD) and in the development of novel cardiovascular drugs and device therapies.[1-7] Grayscale intravascular ultrasound (IVUS) was introduced more than 25 years ago and has been an integral component of the clinical decision-making process in the catheterization laboratory. Contemporary percutaneous coronary intervention (PCI) techniques mostly derived from initial IVUS observations showing that high-pressure balloon inflation was required to adequately appose metallic stents to the vessel wall and prevent thrombosis. Intravascular imaging has also evolved with time. IVUS technologies have added features such as tissue characterization by means of radiofrequency data analysis to facilitate evaluation of the atherosclerotic plaque. This technique allows a more sophisticated assessment of changes in plaque characteristics over time beyond simplistic measurements of plaque dimensions.[8] However, the relative poor image resolution of IVUS and physical limitations of sound have hampered a broader clinical and research application of intravascular imaging. The introduction of infrared light-based imaging technologies such as optical coherence tomography (OCT), which offers image resolution 10 times greater than that of IVUS, has allowed interventional cardiologists to explore the vascular microenvironment for the first time, whereas near-infrared spectroscopy (NIRS) has enabled more reliable assessment of plaque composition and detection of the lipid component.[9] Other emerging invasive imaging techniques such as Raman spectroscopy photoacoustic imaging, near-infrared fluorescence imaging, and time-resolved fluorescence spectroscopy are currently undergoing preclinical evaluation; they are expected to have clinical applications in the near future and provide additional information about plaque morphology and pathophysiology (Fig. 21–1). These intravascular imaging technologies and their clinical and research applications are discussed in more detail below.

RATIONALE FOR INTRAVASCULAR IMAGING

Coronary x-ray angiography has retained the gold standard status in coronary imaging for more than four decades. Angiography depicts arteries as a planar silhouette of the contrast-filled lumen and provides a quick road map of the coronary circulation. Importantly, angiography does not provide visualization of the vessel wall and is not suitable for assessment of atherosclerosis. Essentially, angiography provides assessment of lumen dimensions and is used to localize and estimate the severity of obstructive coronary disease. Angiographic disease assessment is based on the comparison of the stenotic segment with the adjacent, "normal-appearing" coronary, which is often an incorrect assumption because of the diffuse nature of atherosclerosis. Angiography image interpretation is flawed by large inter- and intraobserver variability and usually underestimates the severity of the disease and vessel dimensions. Although quantitative coronary analysis (QCA) has reduced visual errors, the ability of arteries to enlarge to compensate for plaque growth makes angiography an unreliable method of assessing atherosclerosis burden.[10] Vessel foreshortening and overlapping side branches, particularly in disease involving bifurcations, are important practical limitations of angiography and QCA. Despite the use of multiple views, characterization of eccentric lesions by angiography remains a challenge. Finally, angiographic assessment of balloon angioplasty results is hampered by the presence of contrast-filled dissection and intraplaque channels, and determination of proper stent apposition is not possible. Three-dimensional angiography at the time of the contrast injection may provide an accurate and precise assessment of the luminogram. This may address some of the limitations of conventional angiography but still does not allow visualization of the arterial wall and plaque burden. These limitations of angiography can be minimized by the intravascular tomographic visualization of lumen and vessel wall architecture. Intravascular imaging plays an essential complementary role in the catheterization laboratory, enabling more definitive assessment of angiographically intermediate disease, of vessels with aneurysmal dilatation, ostial stenoses, or disease located at branching points or in the left main (LM), as well as tortuous or calcified segments and eccentric plaques, complex disease morphology, intraluminal filling defects, thrombus, dissection, and lumen dimensions after coronary intervention.

IMAGING TECHNOLOGIES

INTRAVASCULAR ULTRASOUND

Basic Principles

The final graphic image display is a result of reflected ultrasound waves that are converted to electrical signals and sent to an external processing system for amplification, filtering, and scan conversion. After leaving the transducer, the beam remains parallel for a short distance (*near*

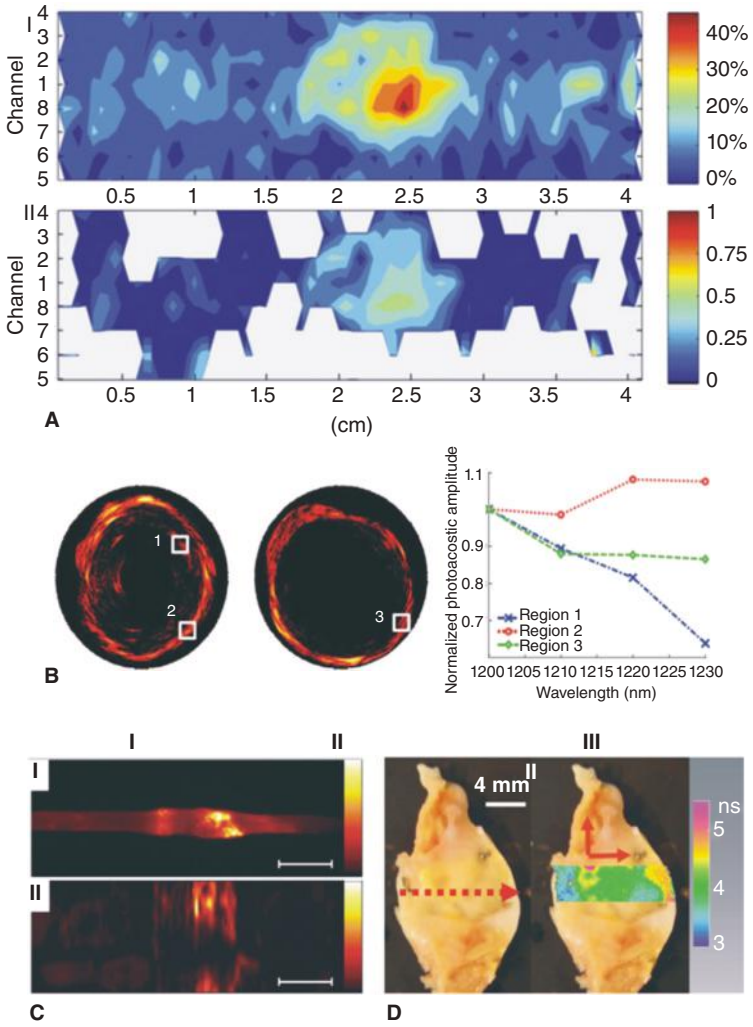

FIGURE 21–1. Emerging intravascular imaging techniques. **A.** Spread-out plots of the compositional characteristics of the plaque estimated by an intravascular Raman spectroscopy catheter. The first panel portrays the distribution of the total cholesterol (in *y*-axis the number of the sensors used to scan the vessel); the yellow-red color corresponds to increased cholesterol. The second panel provides estimation of the nonesterified cholesterol, which was measured when the total cholesterol was greater than 5%. **B.** Intravascular photoacoustic images of a diseased (I) and a normal (II) aorta. The unique photoacoustic characteristics of different tissues (eg, lipid tissue [1], normal vessel wall [2], and media-adventitia [3]) allow identification of the plaque's composition (III). **C.** Fluorescence reflectance imaging (I) and NIRF images obtained by an intravascular near-infrared fluorescence (NIRF) catheter in a stented rabbit aorta (II). An activatable NIRF agent has been used to mark the cysteine protease activity before pullback. An increased activity was noted at the edges of the stent (indicated with a white-yellow color), suggesting inflammation of the vessel wall. **D.** A carotid atherosclerotic plaque assessed by time-resolved spectroscopy (TRFS) imaging. TRFS allows evaluation of the biochemical composition of superficial plaque that is portrayed in a color-coded map (red corresponds to fibrotic plaque, the yellow color to fibrolipid and the cyan to normal endothelium) (II). Reproduced with permission from Bourantas CV, Garcia-Garcia HM, Naka KK, et al: Hybrid intravascular imaging: current applications and prospective potential in the study of coronary atherosclerosis. *J Am Coll Cardiol*. 2013 Apr 2;61(13):1369-1378.[241]

field; better image quality) and then begins to diverge (*far field*). The length of the near field is expressed by the equation $L = r^2/\lambda$, where L is the length of the near field, r is the radius of the transducer, and λ is the wavelength. After encountering a transition between different materials (eg, the interface between blood and the intimal arterial layer), the beam will be partially reflected and partially transmitted, depending on tissue composition and differences in mechanical impedance between materials. Calcium produces nearly complete backscattering of the signal and is displayed as a bright image with a characteristic acoustic shadowing. Ultimately, grayscale IVUS imaging is formed by the envelope (amplitude) of the radiofrequency signal (Fig. 21–2).

The quality of ultrasound images can be described by *spatial resolution* and *contrast resolution*. Spatial resolution is the ability to discriminate small objects and is determined in *axial* (parallel to the beam; primarily a function of wavelength) or *lateral* (perpendicular to the beam; a function of wavelength and *aperture*). Axial resolution is approximately 100 μm, and lateral resolution reaches 200 to 250 μm in conventional IVUS systems (20-45 MHz) (Table 21–1). *Contrast resolution* is the distribution of the gray scale of the reflected signal and is often referred to as dynamic range. An image of low dynamic range appears as black and white with a few levels of gray; images at high *dynamic range* are often softer.

Catheter Designs

The IVUS equipment consists of a catheter incorporating a miniaturized transducer and a console to reconstruct and display the image. Lately, IVUS consoles have been incorporated into the catheterization laboratory equipment for easier operation. Current catheters range from 2.6 to 3.2 French (Fr) in size and can be introduced through conventional 6-Fr guide catheters. The Opticross catheter (Boston Scientific) is the only mechanical system that is compatible with a 5-Fr guiding catheter; Eagle Eye Platinum electronic phased-array IVUS

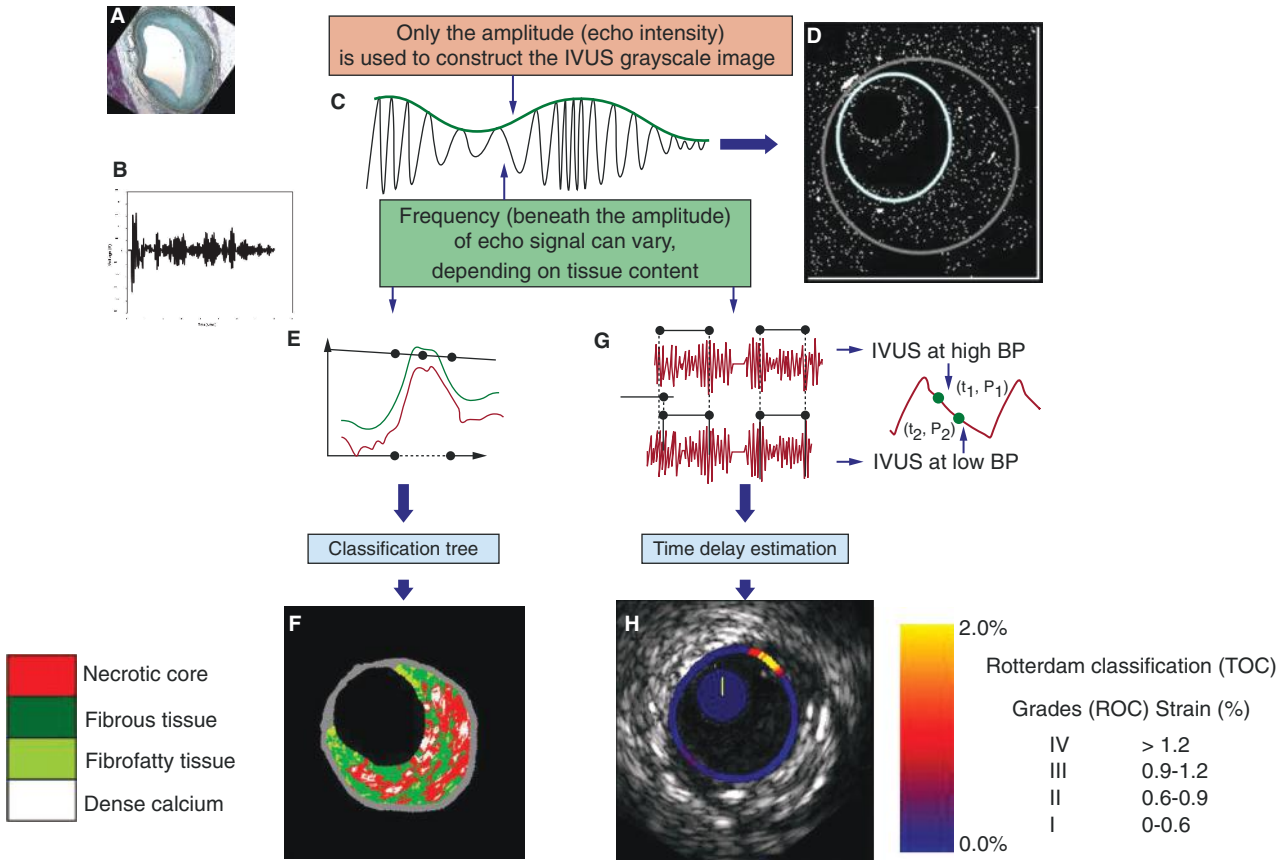

FIGURE 21–2. The ultrasound signal is generated in a piezoelectric crystal (*) that transmits and receives sound waves (**A**). Ultrasound reflected by the tissue deforms crystal generating radiofrequency (RF) signal (**B**). Grayscale intravascular ultrasound (IVUS) is derived from the amplitude of RF signal, discarding information beneath the peaks of the signal (**C**). Changes in the electric field of the piezoelectric crystal caused by ultrasound reflection is used to generate a gray image (**D**). IVUS RF analysis uses several additional spectral parameters to identify four plaque components (**E**). Plaque components that are identified are dense calcium (white), fibrous (green), fibrofatty (greenish-yellow), and necrotic core (red) (**F**). IVUS palpography takes advantage of RF signals generated by the artery being deformed by blood pressure (BP). Using analysis of RF signals at "low" and "high" BP, the strain (deformation) in the inner layer of atheroma is determined (**G**). This strain is quantified and superimposed on the IVUS image at the lumen–vessel wall boundary (**H**). Note that high strain (yellow) is found at the shoulders of the eccentric plaque.

catheters (Volcano Corporation) are also 5—Fr guide catheter compatible. Rotational, mechanical IVUS catheters operate at frequencies between 30 and 45 MHz, and electronic phased-array systems operate at a center frequency of approximately 20 MHz. Higher ultrasound frequencies are associated with better image resolution. At 30 MHz, the wavelength is 50 μm, yielding a practical axial resolution of approximately 150 μm. But increasing the frequency beyond 60 MHz has been limited because of decreased tissue penetration.[11] The mechanical

TABLE 21–1. Comparison of Time-Domain Optical Coherence Tomography, Fourier-Domain Optical Coherence Tomography and Intravascular Ultrasonography

Specifications	TD-OCT	FD-OCT	IVUS
Axial scan/second	5000–10,00	~ 100,000	
Lines/frame	~ 200	~ 500–1000	
Maximum frame rate (frames/second)	20	~ 200	30
Maximum pullback speed (mm/s)	3	20–40	1
Scan diameter (FOV) (mm)	6.8	~ 6–10	5–19
Axial resolution (μm)	15	10–15	65–150
Lateral resolution (μm)	90	20–40	200–250
Tissue penetration (mm)	1.5–3.0	2.0–3.5	4–10
Balloon occlusion	Highly recommended	No	No
Coronary infusion required	Yes; Ringer's lactate with occlusion balloon	Yes; iodine contrast	No

FD-OCT, Fourier domain optical coherence tomography; FOV, field of view; IVUS, intravascular ultrasound; TD-OCT, time-domain optical coherence tomography.

probes rotate a single piezoelectric transducer at 1800 rpm, yielding 30 images per second. Electronic systems have up to 64 transducer elements in an annular array that are activated sequentially to generate the cross-sectional image.[11] In general, whereas electronic catheter designs are slightly easier to set up and use, mechanical probes offer superior image quality and have a better crossing profile. Images may be recorded on videotape or digitally with both systems. Electronic IVUS catheters have the ability to display blood flow in color to facilitate distinction between lumen and wall boundaries.

Autoregressive spectral analysis of IVUS backscattered data has been incorporated into conventional IVUS systems to facilitate image interpretation of different tissue components (see Fig. 21–2). This function displays different plaque components in a color-coded scheme according to tissue signal properties (necrotic core in red, dense calcium in white, fibrous in dark green, and fibrofatty in light green).[12] In a postmortem validation study, radiofrequency analysis demonstrated sensitivity and specificity for detection of necrotic core of 92% and 97%, respectively.[12] The initial algorithm was validated using the mechanical rotating single-element IVUS system, but the first commercially available IVUS backscattering image analysis, named virtual histology (IVUS-VH), was built on the electronic 20-MHz IVUS platform. Lately, rotational mechanical IVUS systems have also integrated a backscattering regression algorithm.[13]

IVUS-VH imaging has been extensively used in clinical trials to monitor progression of atherosclerosis and to predict plaque growth, providing for the first time evidence that plaque composition carries significant prognostic information.[14-18] Nevertheless, reports have raised concerns about the efficacy of this approach to characterize plaque composition, especially in complex calcified lesions and in stented segments, highlighting the need to develop alternative imaging modalities for more reliable assessment of the composition of the plaque.[19,20]

IVUS-based imaging has been used to assess the mechanical properties of the plaque and in particular its deformability using the analysis of radiofrequency signals at different diastolic pressure levels, normalized to a pressure difference of 2.5 mm Hg per frame. This allows the construction of a "strain" image, in which harder (low strain) and softer (high strain) regions of the coronary arteries can be identified, with radial strain values ranging between 0% and 2%[21] (see Fig. 21–2). Postmortem coronary arteries were investigated with histology and IVUS palpography. The sensitivity and specificity of palpography to detect vulnerable plaques was reported to be 88% and 89%, respectively.[21] Although preliminary studies have provided evidence about the ability of palpography in detecting high-risk plaque, a substudy of the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, which investigated the value of IVUS in identifying lesions that will progress and cause cardiovascular events, showed that palpography did not provide additional prognostic information.[22] This technology has currently limited applications in the research arena.

Examination Technique

The IVUS procedure is performed using standard guide catheters (≥ 5 Fr) under full anticoagulation with an activated clotting time of more than 250 seconds. After intracoronary infusion of nitroglycerin (100-200 μg) to minimize vasospasm, the rapid-exchange IVUS catheters are introduced in the coronary over a standard 0.014-in guidewire. Mechanical IVUS systems require infusion of heparinized saline through a dedicated port to clear air bubbles inside the sheath covering the transducer before inserting the catheter in the guide catheter. The IVUS catheter should be advanced under fluoroscopic guidance approximately 10 mm distal to the segment of interest. The operator should realize that the distal marker in mechanical systems at the tip of the catheter is a radiopaque marker and not the ultrasound probe. If possible, the catheter should be advanced beyond 10 mm and retracted slowly to straighten the catheter shaft, which may have built up some slack during insertion, to minimize nonuniform rotation distortion (NURD) artifacts. Motorized pullback devices should be used to withdraw the catheter at a constant speed (most frequently at 0.5 mm/s) to allow proper examination of the entire coronary artery and calculation of distances. During pullback, the record function should be activated to allow storage of images with concomitant voice narration of interesting findings for off-line detailed analysis. Unless coronary ischemia ensues, the catheter should be withdrawn up to the aortic coronary junction and the guide catheter should be retracted slightly to allow imaging of the coronary ostium. Side branches visualized by angiography or ultrasonography are useful landmarks to facilitate interpretation and comparisons in sequential examinations.

Safety

IVUS has been performed safely in a large number of subjects enrolled in research studies with no apparent increase in the incidence of adverse effects. The rate of complications associated with IVUS images was investigated in 2207 patients from 28 centers (including 915 patients studied for diagnostic purposes).[23] A total of 87 patients (3.9%) had complications judged to be unrelated to IVUS imaging, and 63 patients (2.9%) had transient vasospasm. In nine patients (0.4%), complications were judged to be related to the IVUS procedure, including five acute vessel occlusions, three dissections, and one embolism. In 14 patients (0.6%), complications were judged to have an "uncertain" relationship to IVUS. Major events (acute myocardial infarction [MI] or emergency bypass surgery) occurred in 3 of 9 and 5 of 14 of these patients, respectively. The complication rate was higher in patients with unstable angina or acute MI and in patients undergoing intervention compared with diagnostic IVUS.

Another report comprising 718 IVUS "examinations" performed at 12 centers reported a 1.1% rate of complications without adverse clinical consequences. There were four cases of transient vasospasm; two dissections; and two guidewire entrapments. All complications occurred in patients with unstable angina undergoing PCI. In 7085 IVUS studies from 51 centers, vasospasm occurred in 3% of patients.[24] Major complications (dissection, thrombosis, ventricular fibrillation, and refractory spasm) occurred in 10 (0.14%). There was only one major event.

The safety of multivessel IVUS imaging has been investigated in the PROSPECT and the Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology (PREDICTION) studies. These studies utilized three-vessel IVUS imaging to assess plaque characteristics and predict atherosclerotic disease progression and future cardiovascular events in patients admitted with an acute coronary syndrome (ACS). In these high-risk populations, the complications caused by IVUS imaging were 1.6% in the PROSPECT study and only 0.6% in the PREDICTION study.[15,25]

Limitations and Image Artifacts

The echogenicity and texture of different tissue components may exhibit comparable acoustic properties. The similar appearance of different materials represents an inherent limitation of all gray-scale IVUS systems. For example, an echolucent intraluminal image may represent thrombus, atheroma with a high lipid content, retained contrast, or an air bubble.

Most mechanical limitations of IVUS imaging are specific to the construct of each system. NURD is specific to mechanical catheters and arises from friction of the transducer in the coronary or guiding catheter or from a poor connection of the IVUS catheter in the motor drive

unit, which causes a typical "onion skin" image appearance. Common causes of NURD are tortuosity; severely stenotic segments; small guide lumen size; and guide catheters with sharp secondary curves, slack in the catheter shaft, or tightened hemostatic valve. The *ring-down* artifact, however, is specific to electronic systems and is caused by transducer oscillations that obscure the near-field image.[26] The *side lobe* artifact is an intense reflection that comes from strong reflectors such as calcium and stent struts. This usually follows the circumferential sweep of the beam. The presence of the side lobes may mask the actual lumen edge or may also be taken as tissue prolapse or dissection flaps. *Reverberation* is another artifact that comes from strong reflectors and is concentric repetitions at equidistant locations of the same image.

An eccentric or nonperpendicular position of the IVUS catheter produces geometric distortions and an artificially elliptical appearance of the cross-sectional image, leading to overestimation of the lumen area.[26] The speed of catheter pullback is also prone to errors, which may lead to incorrect assessment of the length of the segment of interest. In non–sheath-based catheters (electronic system), the pitfalls of automatic pullback are greater and include the presence of catheter slack outside the patient and friction in the coronary artery and guiding catheter during pullback. Sheath-based, mechanical catheter systems allow more uniform pullbacks during image acquisition and more precise length measurements.[27] The accuracy of four IVUS pullback systems was evaluated in 180 patients (45 in each group) who had been treated with a single stent of known length ranging from 8 to 33 mm. The correlation between the actual versus IVUS-measured stent lengths was 0.92 for Cardiovascular Imaging Systems (CVIS), 0.83 for Galaxy (both from Boston Scientific Corporation, IVUS Technology Center, Fremont, CA), 0.63 for Endosonics Track-Back, and 0.69 for Volcano Model R-100 (both from Volcano Corporation, Rancho Cordova, CA) pullback devices.[27] The pullback speed is least accurate at the beginning of an imaging run (in the distal artery) and most accurate in the proximal artery. In battery-powered pullback devices, the battery charge should be verified at the beginning of the procedure to ensure uniform pullback speed. Ideally, the same pullback device and catheter should be used in repeated longitudinal studies. Finally, one should realize that intravascular imaging only assesses a single coronary segment at a time.

OPTICAL COHERENCE TOMOGRAPHY

Basic Principles

OCT evolved from optical one-dimensional, low-coherence reflectometry, which uses a Michelson interferometer and a broadband light source. The addition of transverse B-scans by James Fujimoto in 1991 enabled a two-dimensional imaging of the retina.[28] Intravascular OCT uses a single optical fiber that both emits and records light reflection. The image is formed by the backscattering of light from the vessel wall based on "echo time delay" with measurable signal intensity. The speed of light (3×10^8 m/s) is much faster than that of sound (1500 m/s), thus requiring interferometry techniques because direct signal quantification cannot be achieved on such a time scale. The interferometer uses a fiberoptic coupler similar to a beam splitter, which directs half of the beam to the tissue and the other half to the reference arm. The reference arm of the first-generation, time-domain OCT system (TD-OCT), consists of a mirror that moves to produce variable, yet known echo delays. The second-generation intravascular OCT systems use a fixed mirror with a variable frequency light source or "swept laser." This method, termed Fourier-domain OCT (FD-OCT), allows the simultaneous detection of reflections from all echo time delays, making the system significantly faster. There are two types of FD-OCT systems that differ in their method of data extraction from the interferometer: optical frequency domain imaging (OFDI), also known as swept-source OCT, and spectral domain OCT. OCT images are formed by the reflected signal returning from the tissue and reference arms "interferes" in the fiber coupler and are detected by a photodetector.

As the fiberoptic rotates, multiple axial scans (A-lines) are continuously acquired to generate the cross-sectional vascular image. Bandwidths in the near-infrared spectrum with central wavelengths ranging from 1250 to 1350 nm are used for intravascular applications. Longer wavelengths would provide deeper tissue penetration but would be limited by absorption and the refractive index caused by protein, water, hemoglobin, and lipids. Thus, the image depth of current OCT systems ranges from 1 to 3 mm into the vessel wall. The axial resolution, which is determined by the light wavelength, ranges from 12 to 20 μm. The lateral resolution in catheter-based OCT is typically 20 to 90 μm (see Table 21–1).

Catheter Designs

The first clinically available OCT systems used time-domain (TD) technology (M2 and M3 OCT Imaging Systems, LightLab Imaging Inc., Westford, MA). The newer systems are based on frequency domain technology. TD-OCT system consists of a single-mode fiberoptic wire (ImageWire), which is able to rotate inside a fluid-filled polymer sheath. An over-the-wire low-pressure occlusion balloon catheter (Helios Goodman, Advantec Vascular Corp.) with distal flush ports is used to infuse saline or Ringer's lactate at approximately 0.5 mL/s to displace blood during imaging acquisition.

The St. Jude C7XR (FD-OCT) was the first OFDI-OCT system and is approved for clinical use in most countries, including the United States. It is equipped with a tunable laser light source, with the fiber encapsulated within a rotating torque wire built in a rapid exchange 2.6-Fr catheter compatible with 6-Fr guides. Recently, St. Jude introduced an updated version Optis that is able to acquire 180 frames per second, enabling more accurate axial imaging resolution. Lunawave (Terumo Corporation, Tokyo, Japan) has also developed an FD-OCT system, which has a 2.6-Fr shaft.

Examination Technique

General principles of intravascular imaging also apply to OCT. Standard guide catheters (≥ 6 Fr) are used, patients must receive full anticoagulation, the image wire or catheter should be advanced under fluoroscopy guidance approximately 10 mm distal to the segment of interest, and the image is acquired after intracoronary infusion of intracoronary nitroglycerin. Despite its guidewire-like profile, the OCT ImageWire is not designed to be advanced into the coronary artery as a stand-alone device. Thus, a conventional angioplasty guidewire (0.014 in) should be inserted first and exchanged to the ImageWire using the Helios or a microcatheter with an inner diameter larger than 0.019 in. Proper OCT imaging requires a blood-free environment because any amount of residual red blood cells causes signal attenuation. In TD-OCT, this is achieved by the inflation of the occlusion balloon proximal to the segment of interest. After advancing the ImageWire into the distal coronary segment, the occlusion balloon is pulled back and repositioned in a healthy proximal segment. Before inflating the Helios balloon at 0.4 to 0.7 atm using a dedicated inflator, injection of Ringer's lactate at 0.5 mL/s should be started using an injector pump with a warming cuff. Infusion rates can be increased to up to 1.0 mL/s until blood is completely cleared. In TD-OCT systems, the pullback speed can be adjusted from 0.5 to 3.0 mm/s.

FD-OCT is built in rapid-exchange, 6-Fr–compatible, catheter-based systems that are advanced into the coronary segment over a standard

0.014-in guidewire. These systems can acquire 100 to 180 image frames per second, reaching pullback speeds up to 18 to 40 mm/s with the potential to scan epicardial coronary vessels that are 4 to 6 cm long in less than 3 seconds, with the use of a single, high-rate (~ 4 mL/s) bolus injection of contrast (see Table 21–1).[29] For nonocclusion techniques, iodinated contrast media are preferred over saline or Ringer's lactate because of the advantage of high-viscosity solutions in completely removing blood. Before introducing the catheter, a small amount of iodine contrast must be purged into the covering sheath to clear air bubbles and prevent blood entry. The activation of the pullback is automatic as the blood is cleared from the lumen and triggers recording of images, which are stored electronically. The pullback system also has a function to readvance the fiber within its cover sheath. The fast pullback speed does not allow voice recording during imaging acquisition of FD-OCT systems.

Safety

The OCT imaging technique has been adopted in many centers across Europe and Japan, and various centers have presented large series of patients imaged by OCT without major complications. The applied energy in intravascular OCT is relatively low (output power in the range of 5.0-8.0 mW) and is not considered to cause functional or structural damage to the tissue. Safety concerns thus seem mainly dependent on the mechanical properties and need for blood clearance for image acquisition. Studies comparing OCT with IVUS suggest that TD-OCT is safe and can be performed with success rates at least comparable to those of IVUS. The most frequent complication in 76 patients imaged with TD-OCT using the occlusive OCT technique were transient chest discomfort, bradycardia or tachycardia, and ST-T changes on electrocardiography (ECG), all of which resolved immediately after the procedure. Similar transient events were also seen during IVUS imaging procedures. Neither hemodynamic instability nor ventricular tachyarrhythmia was observed.[30] In addition, in a multicenter registry, the acute complications associated with OCT were assessed in 468 patients. TD-OCT was performed using a nonocclusive flush technique in 45.3% of the patients with a mean contrast volume of 36.6 ± 9.4 mL (M2 and M3). Transient chest pain and QRS widening or ST-segment depression or elevation were observed in 47.6% and 45.5% of patients, respectively. Major complications were rare; they included five (1.1%) cases of ventricular fibrillation caused by balloon occlusion or deep guide catheter intubation, three (0.6%) cases of air embolism, and one (0.2%) case of vessel dissection. There were no cases of coronary spasm or major cardiovascular events (MACE) during or within the 24-hour period after OCT examination.[31] The more recent nonocclusive FD-OCT technique has led to an important reduction in the image acquisition time (3-4 seconds) and in the rate of chest pain and ECG changes during image acquisition. The safety and feasibility of the larger catheter-based FD-OCT systems has been examined in numerous small scale studies, which demonstrated that FD-OCT is safer to TD-OCT as it is associated with a low risk of complications.[32,33] In the study of Lehtinen and colleagues, the procedural success of FD-OCT was 87.4%, whereas the complication rate was 17.4% (chest pain in 10.9% of the cases, myocardial ischemia in 2.6%, and minor bleeding in 4.8%). In contrast, in the study of Imola and coworkers, which included 90 patients who underwent FD-OCT to assess lesion severity and the final results poststent implantation, none of the studied patients experienced major complications (ie, death, MI, emergency revascularization, embolization, life-threatening arrhythmia, coronary dissection, prolonged and severe vessel spasm, or contrast-induced nephropathy).[32,33]

Recently, Taniwaki and colleagues reported the safety and feasibility of multimodality three-vessel intravascular imaging in the Integrated Biomarkers Imaging Study (IBIS) 4.[34] This study included 103 patients admitted with a ST-elevation MI who had serial IVUS and IVUS-VH imaging at baseline and 13 months follow-up. OCT and IVUS-VH were feasible in the vast majority of the cases at both baseline (OCT: 89.9%; IVUS-VH: 85.7%) and follow-up (OCT: 86.6%; IVUS-VH: 84.8%). Failure of OCT imaging was mainly caused by poor vessel flushing and difficulty of advancing the OCT catheter to the distal vessel; IVUS-VH imaging failure was mainly caused by the inability to gate the ECG or to advance the catheter into the distal vessel. A low complication rate was reported (1.9% at baseline; 1.1% at follow-up); all the events (one ventricular fibrillation, and one dissection at baseline and one ventricular fibrillation at 13 months follow-up) were caused by OCT imaging. There were no differences in the MACE between patients who had PCI with and without multimodality intravascular imaging at 2 years follow-up (16.7% vs 13.3%, $P = .39$). These findings suggest that multimodality intravascular imaging is feasible and safe, even in high-risk patients.

Limitations and Image Artifacts

Some image artifacts are common to both OCT and IVUS. NURD can result in focal image loss or shape distortion, but this seems to occur less frequently in OCT than in IVUS imaging, perhaps as a result of the smaller profile and simplified rotational mechanics of OCT wires. Sew-up artifact is the result of rapid artery or imaging wire movement in one frame's imaging formation, leading to misalignment of the lumen border. Eccentricity intraluminal position of the ImageWire may lead to wider distances between A-lines and consequently decrease lateral resolution. This effect has been dubbed the "merry-go-round." Some catheters have reflecting surface; the reflections may bounce off of multiple facets of the catheter, resulting in one or more circular lines; this artifact is called as multiple reflection artifact. Similarly, one can notice the reflection from metallic stent struts aligning toward an eccentrically positioned ImageWire ("sunflower" effect). The saturation artifact occurs when light reflected from a highly specular surface (usually stent struts) produces signals with amplitudes that exceed the dynamic range of the data acquisition system. Although these artifacts are common to all intravascular imaging technologies, others are specific to OCT imaging. The attenuation artifact occurs when the catheter is against the vessel wall. In this case, the light beam is attenuated as it passes along the surface of the artery wall, and thus the vessel wall may appear as a signal poor region below the luminal surface.[35] The foldover artifact is seen when the vessel is larger than the ranging depth; in this occasion the vessel may appear to fold over in the image. Residual blood produces light attenuation and may defocus the beam if the red blood cell density is high. This reduces the brightness of the vessel wall. Residual blood does not appear to affect area measurements in OCT images with a clearly defined lumen-wall interface.[35] The operator should be aware that residual blood can mimic the OCT appearance of thrombus. Foldover artifact is specific to the new generation of FD-OCT systems and is the consequence of the "phase wrapping" or "alias" along the Fourier transformation when structure signals are reflected beyond the field of view. This can occur at the site of bifurcations or in large vessels. Air bubbles can form within the silicon lubricant used to reduce friction between the sheath and the optic fiber in TD-OCT systems, causing light attenuation (Fig. 21–3).

OTHER INTERVASCULAR IMAGING MODALITIES

Near-Infrared Spectroscopy

Another imaging modality able to detect necrotic core invasively is NIRS. To this aim, the 3.2-Fr NIRS catheter approved by the US Food and Drug Administration is used. This catheter is compatible

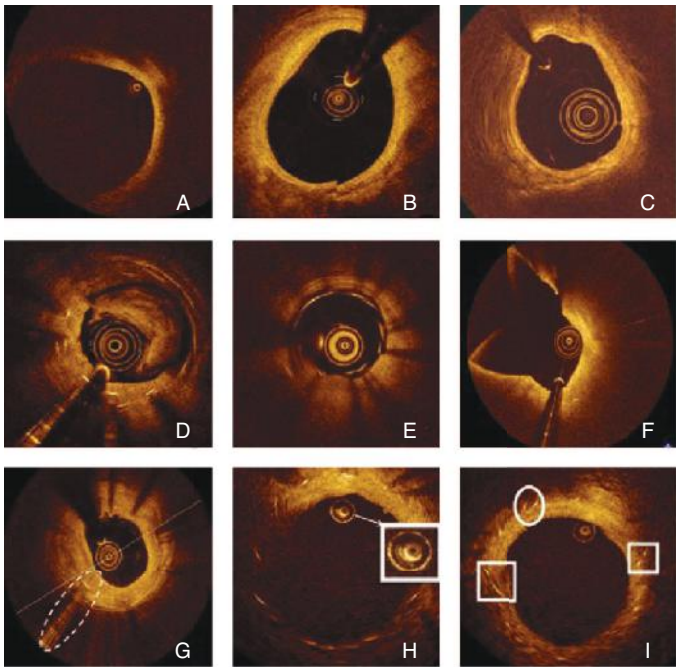

FIGURE 21–3. Cross-sectional optical coherence tomography images of human coronary arteries depicting the most frequently observed artifacts. **A.** Vessel "out-of-screen." **B.** Sew-up artifact resulting in misalignment of the image. **C.** Nonuniform rotational distortion, usually produced by a tight bend or by an imperfection in the torque wire or sheath that interferes with rotation speed. **D.** Incomplete intracoronary blood displacement causing light attenuation. **E.** The presence of blood inside the image catheter sheath. **F.** Foldover artifact observed in a large vessel bifurcation. **G.** Saturation artifact; some scan lines have a streaked appearance. **H.** Light attenuation caused by air bubbles within the silicon lubricant used to reduce friction between the sheath and the optic fiber in time-domain optical coherence tomography systems. The box is indicating a magnified view of the sheath and the optic fiber. **I.** Eccentric intraluminal location of the ImageWire can distort stent reflection (circle), causing struts to align toward the imaging wire ("sunflower effect," *left box*) or appear elongated ("merry-go-round," *right box*).

with a conventional 0.014-in guidewire, contains a rotating (240 Hz) NIRS light source at its tip, and is pulled back by a motor drive unit at 0.5 mm/s. The catheter's ability to detect lipid core plaques (LCPs) has been validated successfully in a human autopsy study in which the device algorithm prospectively identified LCP with a receiver operator characteristic area of 0.80 (95% confidence interval [CI], 0.76-0.85).[36] Nevertheless, a more extensive validation suggested that NIRS may be superior to IVUS in detecting lipid-rich plaques, but it has limited accuracy in characterizing their phenotype and detecting fibroatheroma (FA) and thin-cap fibroatheroma (TCFA).[9] Other significant limitations of NIRS that have considerably reduced its application in the clinical arena are its inability to quantify plaque burden; visualize lumen and outer vessel wall; and assess plaque characteristics associated with increased vulnerability such as plaque erosion, neovascularization, and microcalcification.

To overcome these limitations, combined NIRS-IVUS imaging has been proposed. Recently, a combined NIRS-IVUS catheter has been designed that enables simultaneous acquisition and coregistration of the NIRS and IVUS data. The /TVC) imaging system (InfraReDx, Burlington, MA) incorporates a monorail catheter that can be inserted through a 6-Fr guide and over a 0.014-in guidewire. The catheter has an entry profile of 2.4 Fr and a shaft profile of 3.6 Fr and includes a mechanical rotating IVUS probe operating at 40 MHz that is pulled back at a speed of 0.5 mm/s using an automated pullback device. NIRS imaging is performed by a NIRS probe located at the tip of the catheter that acquires 30,000 chemical measurements per 100 mm. Each measurement interrogates 1 to 2 mm^2 of a tissue at a depth of 1 mm. The output of NIRS is the chemogram that is a map of the measured probability of the presence of lipid-rich tissue presented as a two-dimensional image with pullback position on the *x*-axis, rotation on the *y*-axis (as if the artery were cut longitudinally and laid flat). Yellow color indicates regions with a high probability of lipid-rich tissue, whereas red regions suggest a low probability. A measure of the lipid burden is the lipid core burden index, which ranges from 0 to 1000, and gives a semiquantitative summary of the lipid core within the scanned segment. The block chemogram is the summary of the chemogram that display the presence of the lipid tissue in 2-mm intervals. The TVC system also provides a composite view of the coregistered NIRS and IVUS data, allowing comprehensive assessment of the association between plaque burden and composition (Fig. 21–4).

Histology-based studies have shown that combined NIRS-IVUS imaging allows more accurate characterization of the composition of the plaque[9,37] while several in vivo studies have examined the reproducibility of NIRS imaging and provided robust data that this enables a consistent assessment of plaque compositional characteristics. Over the last years numerous studies have implemented this technology to assess the implications of lipid-lowering therapies on the compositional characteristics of the plaque and its role in identifying high-risk plaques and culprit lesions.[18,38-43]

Emerging Imaging Modalities

Raman Spectroscopy Raman spectroscopy relies on the spectral analysis of the Raman scattering by a tissue after being illuminated with a laser beam. The laser light is scattered between molecules, and finally the energy of the photons is changed resulting in a different frequency of the backscattered light. The Raman spectra is unique for a given molecule and therefore it can be used to assess the chemical composition of the plaque and differentiate esterified from nonesterified cholesterol (see Fig. 21–1A). A significant limitation of Raman spectroscopy is the increased noise, generated within the fibers of the imaging catheters, which interferes with the Raman spectra. Modification of the initial prototypes and utilization of high-wave number Raman spectroscopy can potentially overcome this limitation and enable its application in the study of atherosclerosis.[44,45]

Intravascular Photoacoustic Imaging Intravascular photoacoustic (IVPA) imaging involves irradiation of the vessel wall by short laser pulses with a length of several nanoseconds. The absorbed laser light transfers the optical energy to the tissue, which causes a transient pressure rise[46] that propagates through the tissue as an acoustic wave and can be detected with an ultrasound transducer. The time interval between tissue irradiation and acoustic wave detection enables localization of the source and depth-resolved imaging. Studies have demonstrated that IVPA can detect the composition of the plaque and in particular lipid component as well as plaque features associated with increased vulnerability, such as intraplaque hemorrhage and inflammation (see Fig. 21–1B).[47]

Limitations of IVPA include its inability to assess the luminal, outer vessel wall and plaque dimensions; the vessel geometry the distribution of the plaque; and the fact that optimal image quality requires blood clearance and prolonged timing. With the advent of high-speed lasers, the time for imaging is becoming compatible with clinical application.

Near-Infrared Fluorescence Imaging Near-infrared fluorescence (NIRF) imaging caries a great potential for the study of vascular inflammation. It relies on the use of activatable markers that have the ability to bind molecules associated with plaque vulnerability and fluorescence when they irradiated by near-infrared light (see Fig. 21–1C). Advances in molecular biology have enabled detection of fibrin, of plaque's inflammation, and identification of neovascularization.[48] Recently, a two-dimensional rotational NIRF catheter has been designed that is pulled

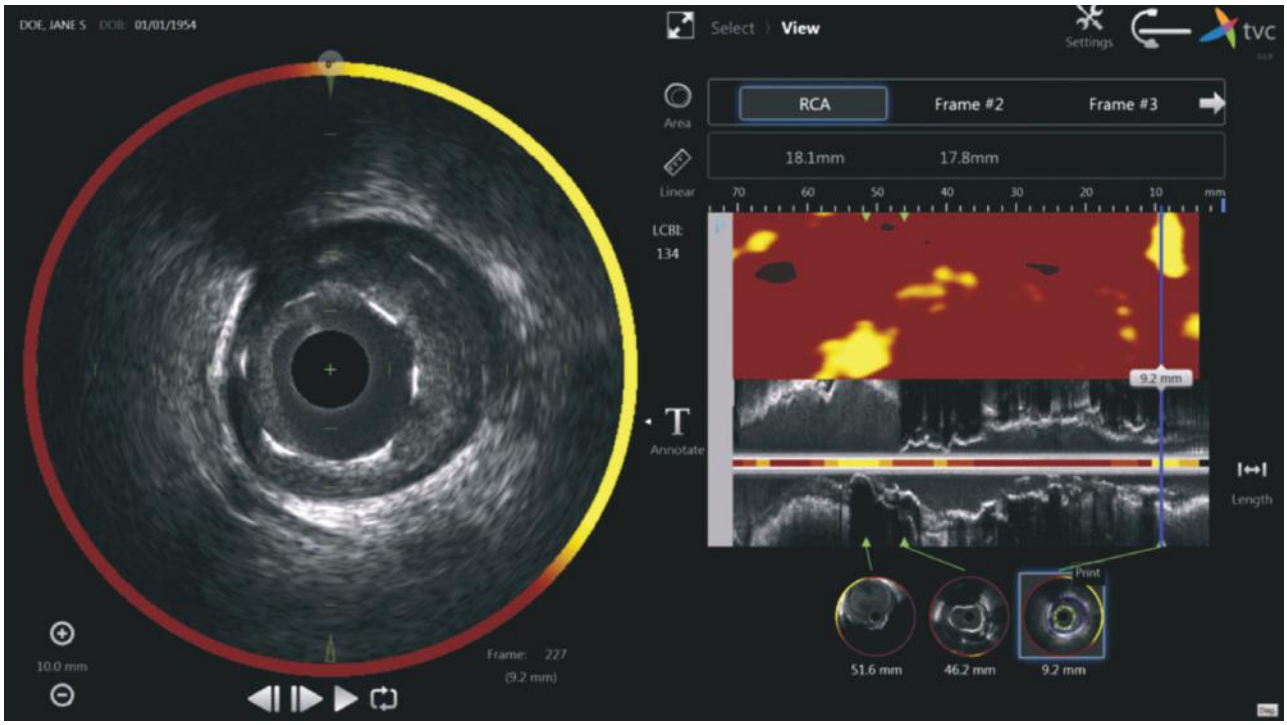

FIGURE 21–4. Output of the combined near-infrared spectroscopy–intravascular ultrasound TVC imaging system (Infraredx, Burlington, MA). RCA, right coronary artery.

back by an automated pullback device at a constant speed, enabling generation of a spread out plots of the coronary plaque inflammation and assessment of vessel wall biology.[49] This design enables in vivo detection of different molecules such as thrombin; matrix metalloproteinases 2 and 9; and cathepsin K, D, and S, and permits assessment of plaque biology, inflammation, and neorevascularization.

Significant limitations of this modality are (1) that it requires injection of an activatable agent; (2) that it cannot provide depth-resolved information, and (3) assess the lumen, outer vessel wall, and plaque dimensions and composition.

Time-Resolved Fluorescence Spectroscopy Time-resolved (lifetime) spectroscopic (TRFS) imaging using pulsed ultraviolet light appears able to provide information about the compositional characteristics of the plaque. It relies on the assessment of the time required to resolve the fluorescence emitted after molecules being excited by light. The compositional characteristics of the plaque (ie, the lipid component, macrophages, elastin, and collagen) have different fluorescence properties; thus TRFS has a value in assessing plaque composition and inflammation (see Fig. 21–1D).[50]

Recent technological advances in fluorescence lifetime imaging have enabled adaptation of these techniques for intravascular scanning.[51,52] Experimental studies have shown that TRFS measurements enable detection of diseased segments, visualization of pathological changes in the superficial plaque (~ 250-300 μm depth), and characterization of the phenotype of the plaque and differentiation of TCFA from FA.

CHARACTERIZATION OF ATHEROSCLEROSIS

NORMAL CORONARY ARTERY STRUCTURE

Understanding of the structure of a normal coronary artery is essential to identify its pathologic conditions. The arterial wall of coronary arteries is composed of three layers. The innermost tunica intima is in direct contact with the blood and is constituted by an endothelial cell monolayer resting on a basement membrane. Aging of human arteries is associated with the presence of smooth muscle cells in the tunica intima. These cells produce extracellular matrix molecules, leading to intimal layer thickening. This process is not necessarily associated with pathologic lipid accumulation and atherosclerosis formation. The second layer, the tunica media, is separated from the tunica intima by the internal elastic membrane (IEM) and is formed by concentric layers of smooth muscle cells. The adventitia is the outermost arterial layer, which is separated from the media by the external elastic membrane (EEM) and contains fibroblasts and mast cells, collagen fibrils, vasa vasorum, and nerve endings. At the take-off from the aorta of the right and LM coronary arteries, the media and the adventitia show multiple layers of elastic lamellae as the artery transitions into a muscular artery.

The normal coronary architecture can be assessed using intravascular imaging. The circulating blood elements may assist IVUS image interpretation and differentiate the lumen from the vessel wall because these produce characteristic speckles in the image. However, the appearance of blood speckles depends on the flow velocity and may have increased intensity in case of slow blood flow, causing it to have a similar appearance as the vessel wall. The reported normal value for intimal thickness in young subjects is typically 0.15 ± 0.07 mm. Thus, the thin tunica intima poorly reflects ultrasound and is not visualized as a separate layer. The media is typically less echogenic than the intima, but it may appear thick because of signal attenuation and weak reflectivity of the IEM. A monolayer appearance is a common finding in normal coronary arteries, but a trilayered appearance by IVUS suggests the presence of intimal thickening.[53] A trilaminar appearance depends not only on the age but also on the histologic characteristics of the vessel. The adventitia has the strongest echo signal, which is used as a reference to determine plaque components. Importantly, the IVUS beam penetrates beyond the adventitial layer, allowing visualization of the perivascular structures, including the cardiac veins and the pericardium.

In contrast, the normal coronary artery wall (< 1.5 mm thick) appears as a three-layer structure on OCT, but imaging beyond the adventitial layer is not possible. The normal thickness of the tunica intima is approximately 4 μm, which is beyond the resolution capacity of current OCT systems. The first visualized layer is indeed the internal elastic lamina (IEL) (not seen by IVUS), which despite its less than 3-μm thickness, generates a 20-μm signal-rich band. The relatively thick media (> 100 μm) can be visualized easily by OCT,[35] which is depicted as a low-intensity band between the IEL and external elastic lamina (EEL). Whereas the EEL produces a signal-rich band, the adventitia produces a signal-rich band with heterogeneous texture on OCT images.

ATHEROMA

A number of studies have demonstrated the ability of IVUS and OCT to differentiate coronary atheroma components (Figs. 21–5 and 21–6). However, it should be stressed that in vivo intravascular imaging is fundamentally different from ex vivo histology and that specific histologic plaque components cannot be assessed by conventional clinical imaging. A detailed description of atherosclerosis development and composition is beyond the scope of this chapter (see Chap. 32). In brief, an atheroma is formed by an intricate sequence of events, not necessarily in a linear chronologic order, that involves extracellular lipid accumulation, endothelial dysfunction, leukocyte recruitment, intracellular lipid accumulation (foam cells), smooth muscle cell migration and proliferation, expansion of extracellular matrix, neoangiogenesis, tissue necrosis, and mineralization at later stages. The ultimate characteristic of an atherosclerotic plaque at any given time depends on the relative contribution of each of these features.[54] Thus, the pathologic intimal thickening (PIT) is rich in proteoglycans and lipid pools, but no trace of necrotic core is seen. The earliest lesion with a necrotic core is the FA, and this is the precursor lesion that may give rise to symptomatic heart disease. TCFA is a lesion characterized by a large necrotic core containing cholesterol clefts. The overlying fibrous cap is thin and rich in inflammatory cells, macrophages, and T lymphocytes with few smooth muscle cells. A cutoff value for cap thickness of less than 65 μm has been suggested by histology studies to define a thin cap vulnerable coronary plaque.[55]

Based on tissue echogenicity, not necessarily histologic composition, atheromas have been classified into four categories by grayscale IVUS: (1) soft plaque (lesion echogenicity less than the surrounding adventitia), (2) fibrous plaque (intermediate echogenicity between soft [echolucent] atheromas and highly echogenic calcified plaques), (3) calcified plaque (echogenicity higher than the adventitia with acoustic shadowing), and (4) mixed plaques (no single acoustical subtype represents > 80% of the plaque)[26] (see Fig. 21–5).

IVUS-VH can potentially identify all of the previously mentioned plaque types.[56] Figure 21–7 outlines the VH plaque and lesion types that are proposed based on the histological data.

Intravascular ultrasound-derived thin-cap fibroatheroma (IDTCFA) using IVUS-VH has been defined as a lesion fulfilling the following criteria in at least three consecutive frames: (1) necrotic core of 10% or more (2) without evident overlying fibrous tissue and (3) plaque burden of 40% or more. Here, thin cap is defined as all fibrous caps of less than 200 microns, which is the limit of IVUS resolution. In this study, 62% of patients had at least one IDTCFA in the interrogated vessels. Patients with ACS had a significantly higher incidence of IDTCFA than did stable patients (P = .018). Finally, a clear clustering pattern was seen along the coronaries, with 66.7% of all IDTCFAs located in the first 20 mm. This distribution of IDTCFAs is consistent with previous clinical studies, with a clear clustering pattern from the ostium demonstrating a nonuniform distribution of vulnerable plaques along the

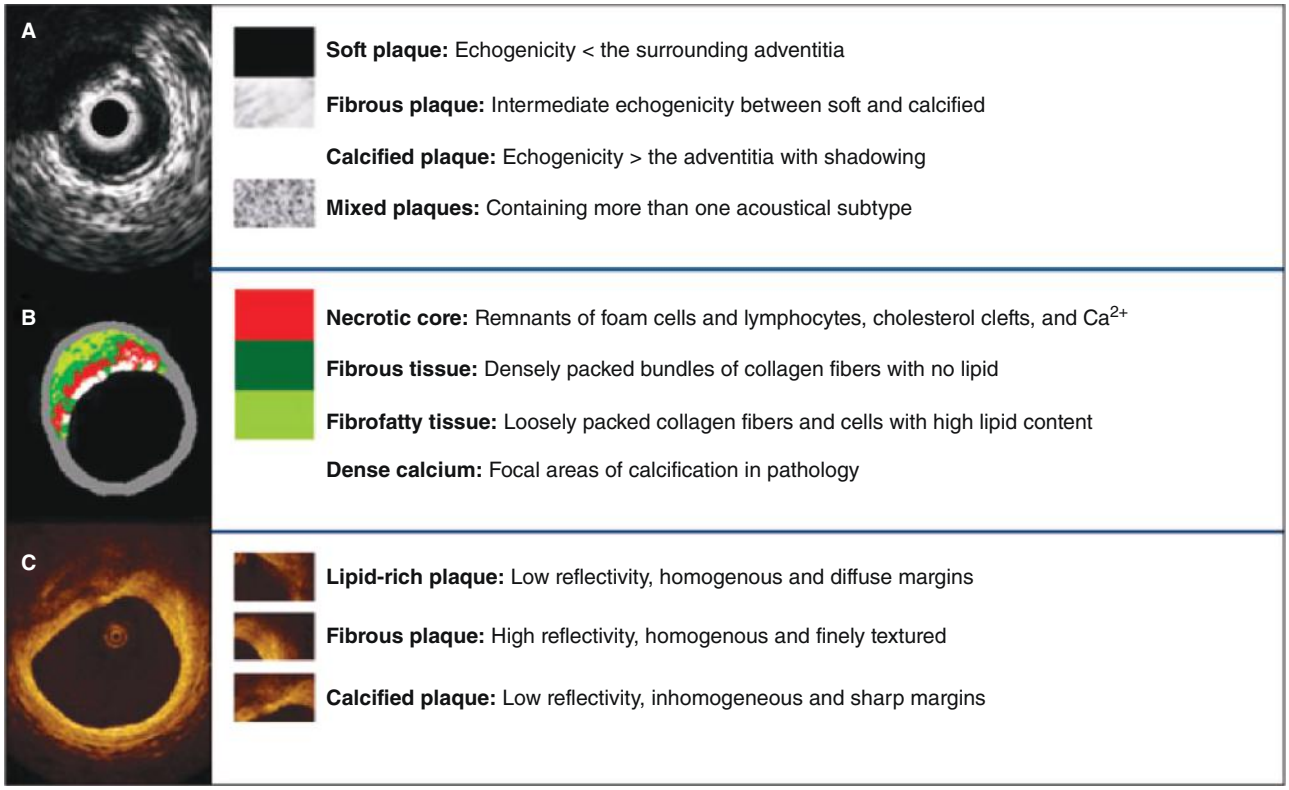

FIGURE 21–5. **A, B,** and **C** are corresponding images of the same coronary plaque. By gray scale, atherosclerotic plaque can be classified into four categories: soft, fibrous, calcified, and mixed plaques (**A**). Virtual histology (**B**) is able to detect four tissue types: necrotic core, fibrous, fibrofatty, and dense calcium. At the bottom, optical coherence tomography (**C**) is showing the different plaque types that can be detected with this technique.

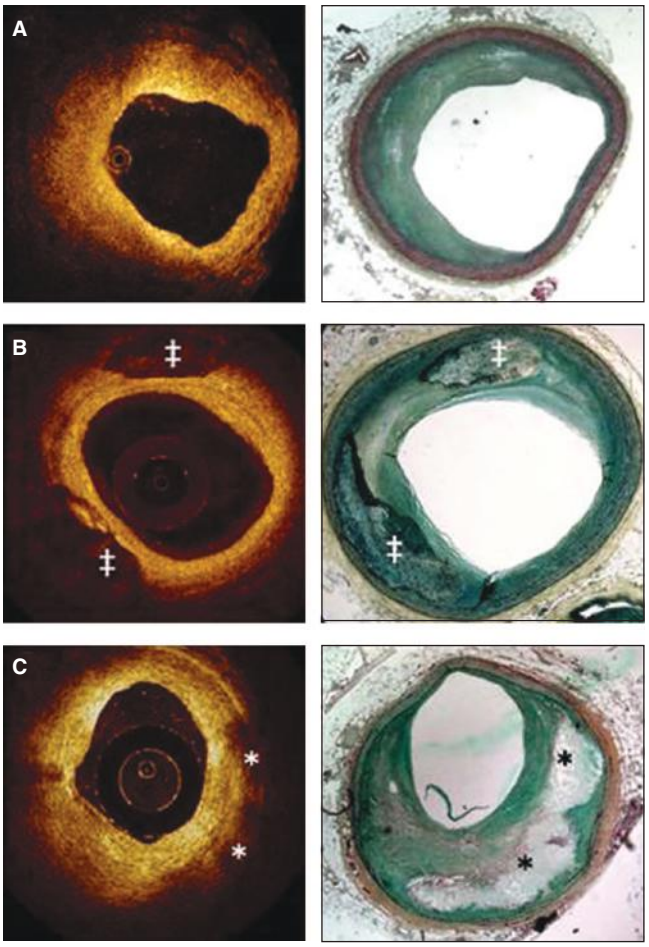

FIGURE 21–6. Correlation between optical coherence tomography and histology. **A.** Fibrotic plaque: characterized by high signal (high backscattering) and low attenuation (deep penetration). **B.** Predominantly calcified plaque: calcified regions have a sharp border, low signal, and low attenuation, permitting deeper penetration. **C.** Lipid-rich plaque: the lipid core has a diffuse border. Light attenuation results in poor tissue penetration (in contrast to calcified regions). The overlying fibrotic cap can be readily measured; in this case, a thick cap (> 200 μm) is present. ‡Calcified region; *lipid core. Used with permission from C.Y. Xu and J. M. Schmitt, LightLab Imaging.

coronary tree.[57] Rioufol and colleagues reported that patients presenting with ACS had a significantly higher prevalence of plaque ruptures even in nonculprit vessels, supporting the concept that atherosclerosis is a multifocal process.[58] Of note, the plaque burden and the mean necrotic core areas of the IDTCFAs detected by IVUS-VH were also similar to previously reported histopathologic data (55.9% vs 59.6% and 19% vs 23%, respectively).[59]

The frequency and distribution of IDTCFA identified in patients with ACS (n = 105) and stable angina pectoris (SAP; n = 107) in a three-vessel IVUS-VH study have been reported by Hong and coworkers.[60] There were 2.5 ± 1.5 in ACS and 1.7 ± 1.1 in SAP TCFAs per patient ($P < .001$). A total of 76 patients with ACS and 58 with SAP had multiple ID-TCFA ($P = .009$). Presentation of ACS was the only independent predictor for multiple IDTCFA ($P = .011$). A total of 83% of IDTCFA were located within the first 40 mm of the coronary.

Although a 2-mm depth might be sufficient to image the entire plaque in most diseased vessels, OCT cannot serve as a routine method to assess deeper arterial wall structures such as the adventitia. Ex vivo validations have also shown that OCT is superior to conventional and integrated backscatter IVUS for characterization of coronary atherosclerotic plaque composition.[19,61] In vivo, OCT is able to identify most of the architectural features identified by IVUS and may be superior for the identification of lipid pools, calcification, and thrombus.[62] A study comparing OCT with histopathology reported 41% plaque misclassification mostly caused by a combination of incomplete image penetration and the inability to distinguish calcium deposits from lipid pools.[63] An ex vivo OCT investigation classified 357 diseased carotid and coronary segments as fibrous, fibrocalcific, and lipid-rich plaques. Fibrous plaques were characterized as homogeneous, signal-rich regions; fibrocalcific plaques as signal-poor regions with sharp borders; and lipid-rich plaques as signal-poor regions with diffuse borders (see Figs. 21–5 and 21–6). The comparison with histology showed a sensitivity and specificity ranging from 71% to 79% and 97% to 98% for fibrous plaques; 95% to 96% and 97% for fibrocalcific plaques; and 90% to 94% and 90% to 92% for lipid-rich plaques, respectively.[64]

Numerous OCT-based studies confirmed the findings of IVUS-based imaging reports, demonstrating a higher prevalence of lipid-rich plaques in the proximal segment of the coronary arteries[65,66] and in patients with ACS than in patients with SAP.[62,67,68] Patients with renal impairment, diabetic patients, and patients with metabolic syndrome appear to have coronary plaques with an increased lipid component compared to patients without a metabolic syndrome/renal failure. In addition, patients with renal failure also had an increase in calcific tissue component.[69-71]

DETECTION OF CALCIFICATION

The presence, depth, and circumferential distribution of calcification are important factors for selecting the type of interventional device and estimating the risk of vessel dissection and perforation during PCI. On IVUS, calcium appears as bright echoes that obstruct the penetration of ultrasound (acoustic shadowing) (see Fig. 21–5A). IVUS detects only the leading edge of calcium and cannot determine its thickness. Thus, calcification on IVUS is usually described based on its circumferential angle (arc), longitudinal length, and depth. Calcification can be located deeper in the arterial wall or in the surface of the plaque in close contact with the lumen wall interface. As mentioned above, calcium can produce reverberations or repeated reflections at reproducible distances. IVUS has shown significantly higher sensitivity than fluoroscopy in the detection of coronary calcification.[72] Virtual histology, compared with histology, has a predictive accuracy of 96.7% for detection of dense calcium.[12]

In contrast to ultrasonography, light penetrates calcium well, and OCT can depict calcification within plaques as well-delineated, low-backscattering heterogeneous regions (see Figs. 21–5 and 21–6). In addition to circumferential angulation, depth, and longitudinal length, OCT can quantify calcium burden. A histology-based study that compared the accuracy of IVUS and OCT in assessing the calcific burden has demonstrated that OCT allows more accurate estimation of the calcium component than IVUS, which significantly underestimates its extent.[73]

Superficial microcalcifications can also be identified on OCT images as small calcific deposits separated from the lumen by a thin tissue layer. A sensitivity of 96% and a specificity of 97% to detect calcified nodules by OCT compared with histology have been reported.[64]

ARTERIAL REMODELING

Arterial remodeling refers to a continuous process involving positive or negative changes in vessel size measured by the EEM cross-sectional area (CSA). *Positive remodeling* occurs when there is an outward increase in EEM. *Negative remodeling* occurs when the EEM decreases in size (shrinkage of the vessel).[26] The magnitude and direction of

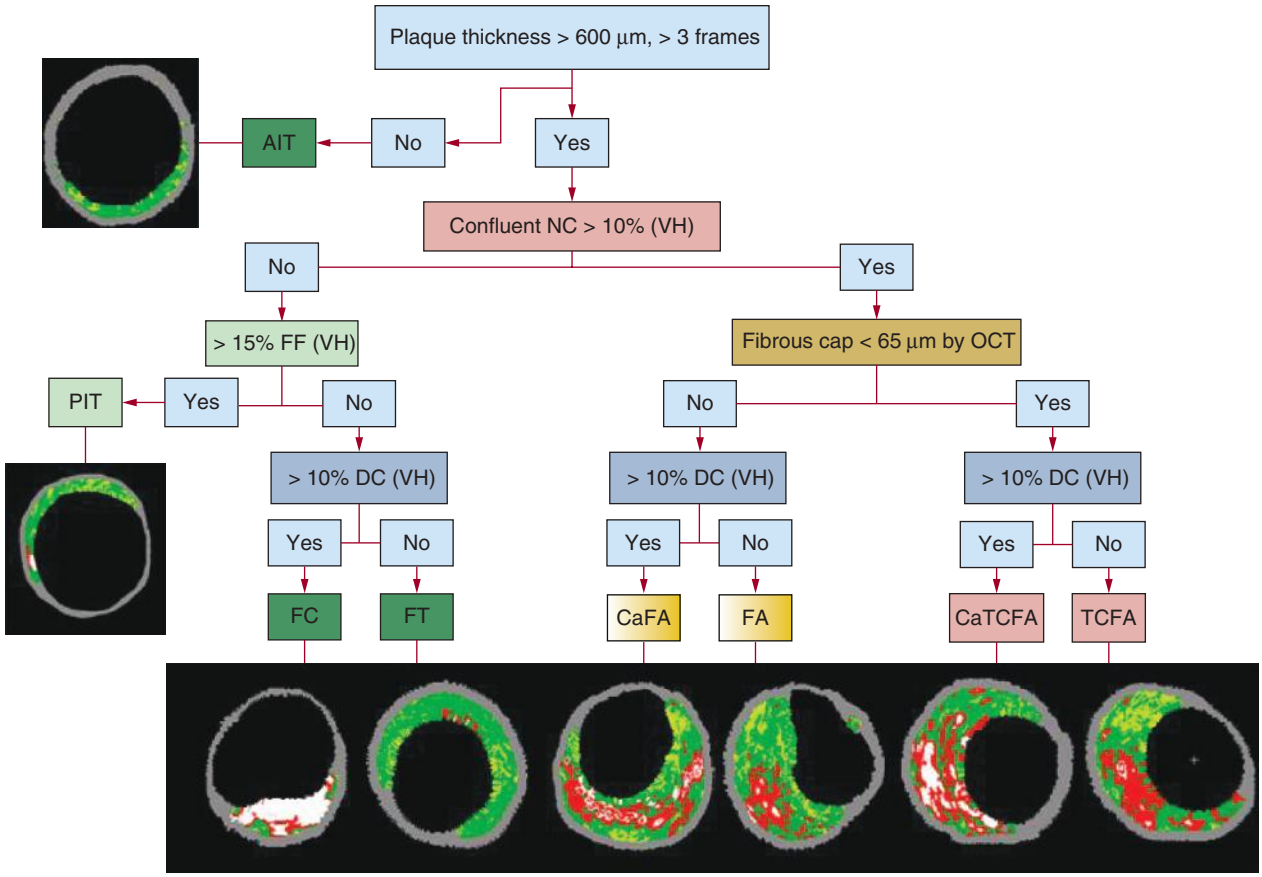

FIGURE 21–7. Plaque classification using optical coherence tomography (OCT) and intravascular ultrasound virtual histology (IVUS-VH). AIT, adaptive intimal thickening; CaFA, calcified fibroatheroma; CaTCFA, calcified thin cap fibroatheroma; DC, dense calcium; FA, fibroatheroma; FC, fibrocalcic (tissue); FF, fibrofatty (tissue); FT, fibrotic (tissue); NC, necrotic core; PIT, pathologic intimal thickening; TCFA, thin-cap fibroatheroma.

remodeling can be expressed by the following index: EEM CSA at the plaque site divided by EEM CSA at the reference "nondiseased" vessel. Whereas positive remodeling demonstrates an index above 1.0, negative remodeling has an index below 1.0. Direct evidence of remodeling can only be demonstrated in serial studies showing changes in the EEM CSA over time because remodeling may also be encountered at the "normal-appearing" reference coronary segment.[26]

Whether this phenomenon, which was first described by Glagov,[74] is an independent process or an adaptive response to compensate for plaque growth is still debated. The limitation of angiography in determining disease burden and stenosis severity is largely caused by vessel remodeling. Detection of remodeling is extremely important during PCI to define plaque burden and the appropriate size of devices. The limited penetration of light into tissue poses significant limitations for appropriate assessment of remodeling by OCT.

Pathologic studies have also suggested a relationship between positive vessel remodeling and plaque vulnerability. Vessels with positive remodeling showed increased inflammatory marker concentrations, larger lipid cores, a paucity of smooth muscle cells, and medial thinning.[75,76] Several IVUS studies have linked positive vessel remodeling with culprit and ruptured coronary plaques.[77] Positive remodeling has been observed more often in patients with an ACS than in those with stable CAD,[78] and it has been identified as an independent predictor of MACE in patients with unstable angina. Plaques exhibiting positive remodeling also more often demonstrate thrombus and signs of rupture.[79] The pattern of remodeling has also been correlated with plaque composition; soft plaques exhibit often positive remodeling, whereas fibrocalcific plaques have more often negative or constrictive remodeling.[80] Similar findings have been observed in studies using IVUS-VH analysis, a technique developed specifically for tissue characterization. Positive remodeling was directly correlated with the presence and size of the necrotic core and inversely associated with fibrotic tissue. NIRS-IVUS imaging based studies have also revealed a direct association between positive remodeling and lipid component.[37,81] A recent meta-analysis of the PROSPECT study has shown that not only positive remodeling, but also negative remodeling predicted lesions, that cause cardiovascular events at follow-up.[82]

VULNERABLE PLAQUE AND THROMBI

ACS are often the first manifestation of coronary atherosclerosis, making the identification of plaques at high risk for complication an important component of strategies to reduce deaths associated with atherosclerosis. Our current understanding of plaque biology suggests that approximately 60% to 80% of clinically evident plaque rupture originates within an inflamed TCFA.[2,83] Plaque ruptures occur at sites of significant plaque accumulation but are often not highly stenotic by coronary angiography because of positive vascular remodeling.[84-86] The transition to plaque rupture has been characterized by the presence of active inflammation (monocyte or macrophage infiltration), thinning of the fibrous cap (< 80 µm), development of large lipid necrotic core, endothelial denudation with superficial platelet aggregation, and intraplaque hemorrhage.[87] The remaining plaques that cause ACS contain calcium nodules (~ 10%) or have none of the pathologic features described (~ 20%). Superficial plaque erosion explains at least a portion of the latter events, particularly in women and individuals

with diabetes, and occurs in plaques that are rich in proteoglycans and smooth muscle cells, as well as in individuals with a PIT or a FA phenotype.[88]

In addition, most plaque ruptures are silent without clinical manifestations, and repetitive healed ruptures may contribute to stable progression into obstructive disease.[89,90] Although plaque characteristics do not yet influence current therapeutic guidelines, the available clinical imaging modalities, IVUS and OCT, have the ability to identify some of the pathologic atheroma features described above (see Figs. 21–5 and 21–6). The clinical implications of plaque rupture appear to depend on the anatomical characteristics of the plaque. A recently published analysis demonstrated that OCT plaque characteristics enable detection of the lesions that are likely to rupture, whereas IVUS imaging appears able to predict which of the ruptured plaque will cause cardiovascular events.[91,92] Ruptured TCFA have more thrombus and a thinner fibrous cap compared to the nonruptured TCFA. IVUS analysis demonstrated that the ruptured plaques causing events have smaller lumen area and increased plaque burden compared to the plaques having a silent rupture.

The preferential localization of atherosclerosis is somewhat puzzling. The entire vasculature is exposed to systemic injury from insults such as high lipoproteins, hypertension, cigarette-smoking metabolites, inflammation, high insulin and glucose levels, and oxidative stress. Nevertheless, pathologic, angiographic, and more recently IVUS and OCT studies have shown that plaque rupture occurs more often in the proximal 40-mm segment of the left coronary arteries.[66,93,94] In the LM coronary artery, plaque ruptures are more often observed in the distal segment or at the bifurcation.[95] Several IVUS and OCT studies revealed that up to 79% of the patients with ACS also have a ruptured plaque in another nonculprit lesion.[58,90,91]

IVUS has also been used to assess the natural evolution of ruptured plaques. IVUS studies have suggested that up to 50% of the ruptured plaques detected in a first ACS event heal with medical therapy without significant change in plaque size.[96] One study revealed complete healing of plaque rupture in 29% of patients treated with statins and incomplete healing in untreated patients.[97]

Thrombus represents the ultimate pathologic feature leading to ACS. Thrombus is usually recognized as an echolucent intraluminal mass, often with a layered or pedunculated appearance by IVUS.[26] Whereas fresh or acute thrombus may appear as an echodense intraluminal tissue that does not follow the circular appearance of the vessel wall, older, more organized thrombus has a darker ultrasound appearance. However, none of these IVUS features is a hallmark for thrombus, and one should consider slow flow (fresh thrombus), air, stagnant contrast or black hole, an echolucent neointimal tissue observed after drug-eluting stents (DES), and radiation therapy as differential diagnoses.[26]

Although OCT images do not currently have the tissue penetration to quantify large lipid cores and evaluate remodeling, their high resolution allows precise visualization and quantification of the thin fibrous cap, allowing accurate detection of ruptured plaques.[35,98] As already discussed, OCT is highly sensitive and specific for characterizing different types of atherosclerotic plaques. In particular, studies have shown the ability of OCT to detect macrophage infiltrate (at least in vitro), detect plaque erosion, and not only identify but also characterize thrombus composition.[35,99] These findings position OCT as the ideal tool for unraveling the complex pathophysiology of atherosclerosis progression and plaque rupture.

The prevailing hypothesis that ruptured *fibrous caps* have less than a 65-μm thickness[55] derives from seminal postmortem investigations. OCT has revealed that patterns of fibrous cap thickness in ruptured plaques vary widely in vivo. The average cap thickness was 90 μm in patients presenting with ST-segment elevation myocardial infarction (STEMI) triggered by exertion. In contrast, ruptured fibrous cap thickness averaged 50 μm in 57% of STEMI patients who experienced symptoms at rest[27] (Fig. 21–8). The incidence of TCFA was 83% in a clinical study comparing OCT, IVUS, and angioscopy, and only OCT was able to estimate the fibrous cap thickness (mean, 49 ± 21 μm).[100,101] OCT has also been used to monitor the thickness of the fibrous cap over time, with several studies showing an increase in cap thickness in patients taking lipid-lowering medications.[3,102,103]

The large size of macrophages and the high lipid content of foam cells yield strong optical signals, allowing OCT to detect *macrophage infiltration* in the fibrous cap as bright spots.[35] Histology-based studies have showed that OCT allows accurate detection of the macrophages in the fibrous cap but it has a low sensitivity and specificity in the remaining plaque.[104] In vivo OCT studies have suggested higher macrophage density in unstable versus stable patients and at sites of plaque rupture versus nonruptured sites.[105]

The interface between lipid and fibrous tissue causes a high superficial backscattering border, allowing OCT to accurately identify the presence of a *necrotic core*. However, light is highly absorbed by lipids, leading to low or no signal beyond the necrotic core, making determination of the extent of the lipid pool difficult to quantify.

Overall, OCT possesses diagnostic advantages compared with both IVUS and angioscopy in the assessment thrombus in culprit lesions, but previous studies were conducted in a selected population with a high pretest probability of thrombosis.[98,106,107] OCT was compared with IVUS and angioscopy for the assessment of the culprit lesion morphology in patients with ACS. Plaque rupture, detected by OCT in 73% of patients, was significantly higher than that detected by both angioscopy (47%; $P = .035$) and IVUS (40%; $P = .009$). Intracoronary thrombus was observed in all cases by OCT and angioscopy but was identified in only 33% by IVUS.[98] Furthermore, the ability of OCT to distinguish between white, low-backscattering thrombus from red, high-backscattering thrombus, has been demonstrated in a postmortem study (Fig. 21–9).[99]

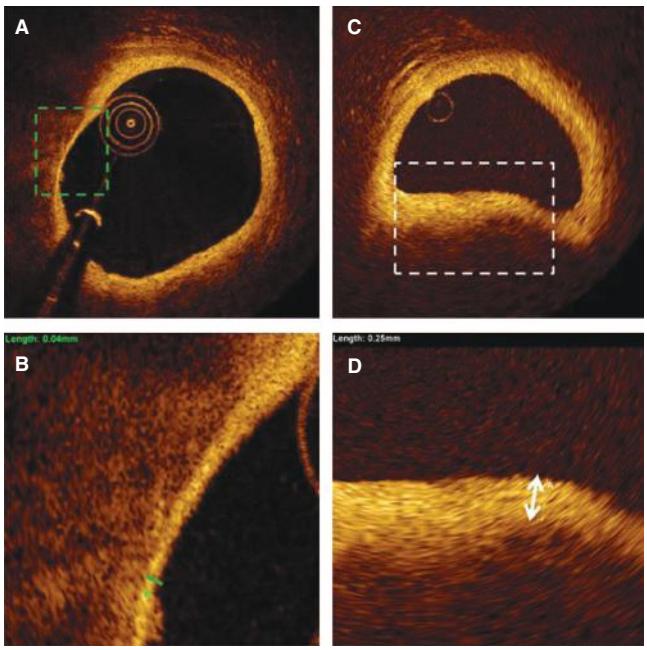

FIGURE 21–8. Representative cross-sectional optical coherence tomography images showing atherosclerotic plaque with different fibrotic cap thicknesses. **A.** Thin fibrotic cap, measuring 40 μm (indicated with green arrow in the magnified view **B**). **C.** Thick fibrotic cap, measuring 250 μm indicated with white arrow in the magnified view **D**).

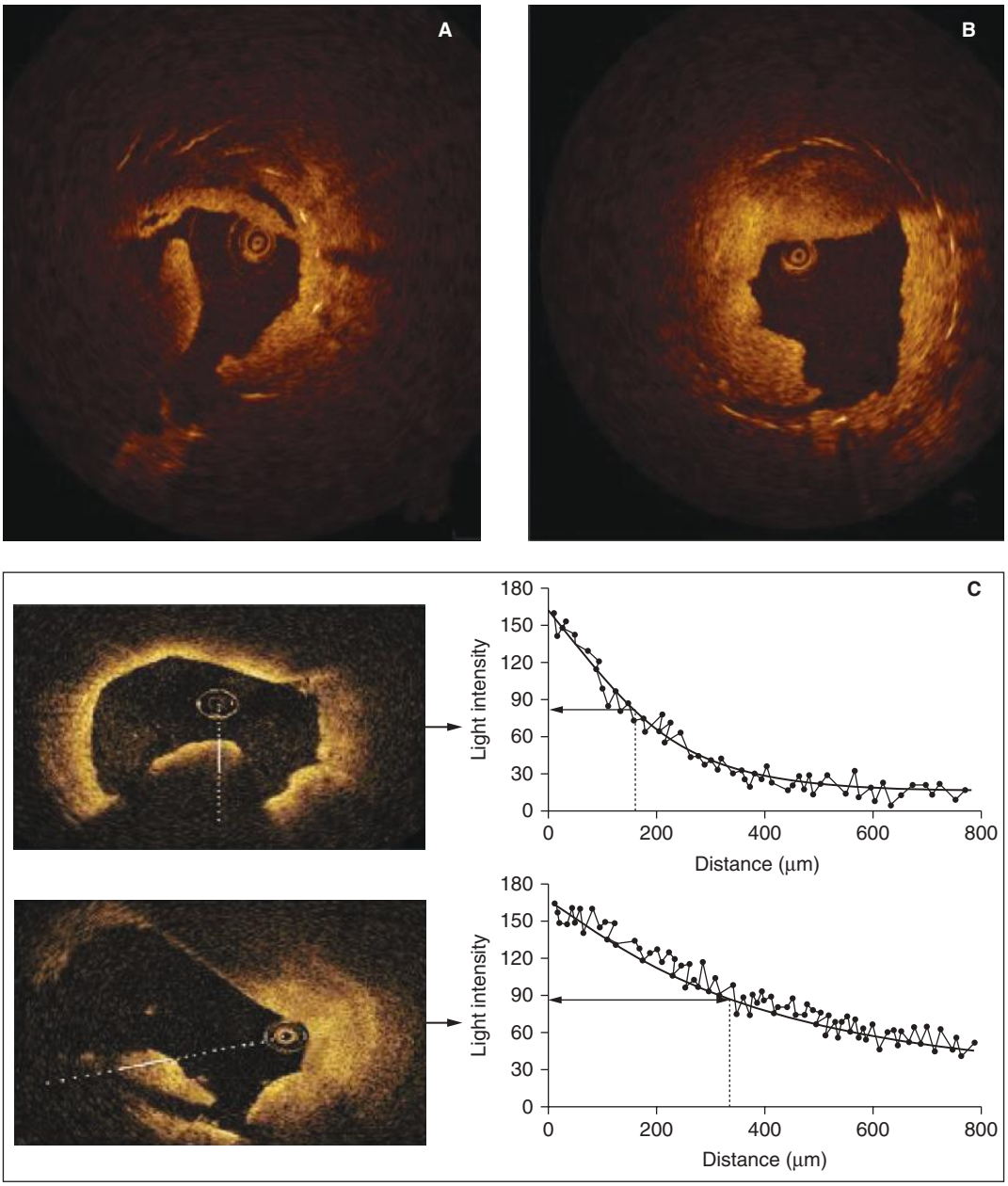

FIGURE 21–9. Red (**A**) and white (**B**) thrombus seen by optical coherence tomography imaging. **C.** A comparison of light attenuation of red thrombus (*upper panel*) and white thrombus (*lower panel*). Note the sharper decrease in light intensity in red thrombus. Reproduced with permission from Kume T, Akasaka T, Kawamoto T, et al: Assessment of coronary arterial thrombus by optical coherence tomography. *Am J Cardiol*. 2006 Jun 15;97(12):1713–1717.[99]

CLINICAL APPLICATIONS: DIAGNOSTIC

DETERMINATION OF THE SEVERITY AND EXTENT OF ATHEROSCLEROSIS

The estimation of the severity and extent of atherosclerosis remains one of the main diagnostic clinical applications of intravascular imaging because angiography and noninvasive methods lack spatial and temporal resolution for accurate coronary disease assessment. Standards for acquisition, measurement, and reporting of IVUS have been proposed in a clinical expert consensus document.[26] Similarly, a recent expert opinion report proposed standards for diagnostic assessment of atherosclerosis by OCT.[32] Cross-sectional measurements are essentially the same for both IVUS and OCT. *Luminal area stenosis* describes the relative decrease in luminal CSA at the site of disease, in percentage, compared with lumen CSA in a "normal-appearing" reference segment in the same coronary. The lumen area relative to the reference lumen area is analogous to the angiographic definition of diameter stenosis. *Proximal* and *distal reference lumen areas* are calculated at sites with the largest lumen located before large side branches and within 10 mm proximal and distal to the plaque, respectively. The image analyst should be aware of potential poststenotic dilatation of the vessel wall when using these measurements to guide clinical decisions. The *minimal lumen area* (*MLA*) describes the smallest lumen CSA area along the length of the target lesion. Because most vessels depict an oval rather than a perfect circular shape, *maximum lumen diameter* and *minimal lumen diameters* are calculated along a vector passing through the lumen center at the reference segments. Reference vessel lumen diameter is essential to guide section of interventional devices. Measurements of distances (*length*) are based on the automated pullback

speed during image acquisition. Disease length can be calculated based on the number of seconds or frames between the first and last image frames depicting the atherosclerotic plaque.

Calibration represents an essential step in any image quantification. Current IVUS digital systems provide automated calibration without the need for manual adjustments. Older mechanical IVUS systems required manual calibration, which was based on a predefined calibration grid displayed in the cross-sectional image. The imperatives of accurate image calibration remain valid for OCT images. The size of the OCT image is calibrated by adjusting the feature called the *z-offset*, which represents the zero-point setting of the system. Given the high resolution of OCT images, z-offset must be fine-tuned before image quantification, particularly when performing strut-level analysis. In the current LightLab TD-OCT system, the catheter diameter acts as a reference for optimal z-offset determination within an image frame. The four marks or fiduciaries should align to fit the outer surface of the catheter. If the catheter is not well visualized, calibration is performed in a frame where the catheter is in contact with the vascular surface by adjusting the fiduciaries to align the vessel wall. Corrections are typically made in the first 10 mm of the pullback image. The operator should monitor these patterns throughout the entire pullback because additional adjustments may be necessary. In the C7-XR LightLab FD-OCT catheters, calibration is adjusted automatically and the semitransparent catheter around the optic fiber facilitates manual calibration when needed.

Quantification of Luminal Dimensions

Comparisons of luminal geometry at the site of disease versus a reference "nondiseased" segment remain the cornerstone of clinical decision making in the catheterization laboratory. Clinical IVUS units have integrated automated contour detection algorithms to facilitate online measurements, which should be performed at the leading edge of luminal boundaries (Fig. 21–10).[26] Measurements are determined by planimetry in cross-sectional images, and longitudinal views may help orient the operator. The similar ultrasound appearance of blood and soft plaques may render lumen detection in single-image frames inaccurate, requiring evaluation of dynamic images to properly differentiate moving blood speckles from the arterial wall.

Blood is displaced by saline or iodine contrast during OCT imaging acquisition, leading to a clear, well-characterized interface between the lumen and the vessel wall. This allows fully automated and real-time lumen contour detection with high precision, requiring minimal, if any, operator interference.

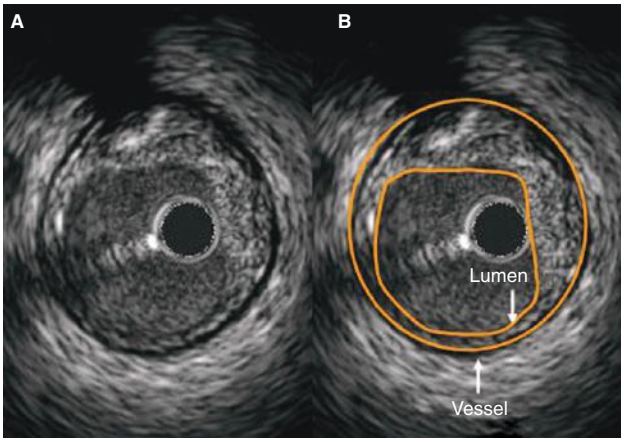

FIGURE 21–10. A. A grayscale cross-sectional area. **B.** The vessel and lumen contours have been traced. The vessel contour is also called the external elastic membrane contour.

Assessment of Atheroma Burden Quantification of atheroma or plaque area in IVUS images is performed by subtracting the lumen area from the EEL area. Hence, the IVUS-defined atheroma area is a combination of plaque plus the media area. The atheroma area can be calculated in each frame (cross-sectional image), and total atheroma volume (TAV) can be calculated based on the pullback speed during image acquisition. The atheroma volume can be reported as the percent of the volume of the EEM occupied by atheroma, namely the percent atheroma volume (PAV). Parameters commonly used to report the extent of the coronary atherosclerosis in research protocols are shown in Fig. 21–11.

In the presence of a large plaque burden (> 1.5-mm thick), OCT may fail to visualize the entire circumference of the IEL. Consequently, the plaque burden cannot be measured in many lesions. Unlike IVUS, OCT can visualize the IEL and therefore can distinguish the atherosclerotic plaque from the muscular media. Measurements are performed between the inner lumen border and the media, which corresponds to the "true" histologic area of the atheroma.

Assessment of Ambiguous Anatomy on Angiography

The three-dimensional and dynamic nature of the coronary vasculature cannot be fully appreciated by planar angiography. Frequently, defining the proper angiographic angulation that provides a straight, nonforeshortened view of the target coronary segment without overlapping of other vessels may be a challenge in the catheterization laboratory. As discussed previously, determination of disease severity by angiography is hampered by the diffuse nature of atherosclerosis and its most common eccentric growth in the vessel wall. Hence, lesions may appear more stenotic in one orthogonal view than in the other, making clinical decisions difficult. The so-called "intermediate lesion" is the more prevalent phenotype in the coronary tree. The American Heart Association/American College of Cardiology/Society for Angiography and Interventions (AHA/ACC/SCAI) guidelines define an intermediate coronary lesion as a plaque producing a 30% to 70% stenosis on angiography.[108] These plaques represent a heterogeneous group of coronary lesions, which can be hemodynamically flow limiting or not. The IVUS minimum luminal cross-sectional area (MLA) proved to be a good morphometric surrogate of coronary physiology. In 73 patients studied preintervention, an MLA of 4.0 mm^2 or more had a diagnostic accuracy of 89% in predicting a coronary flow reserve above 2.0. Likewise, IVUS has been correlated with noninvasive single-photon emission computed tomography (SPECT).[109] A 4-mm^2 MLA by IVUS had 88% sensitivity and 90% specificity to discriminate the SPECT (+) group from the SPECT (–) group. Over the past years, several studies have examined the value of IVUS in detecting hemodynamic significant lesions using FFR as a gold standard and demonstrated that IVUS has a moderate accuracy in identifying obstructive stenoses.[110-113] Reports have recently explored the accuracy of OCT-derived metrics in detecting flow-limiting stenoses and showed that OCT had also a moderate—although a slightly better than IVUS—accuracy in detecting hemodynamic significant lesions.[110,114,115]

The limited value of intravascular imaging in detecting flow-limiting lesions should be attributed to the fact that the hemodynamic implications of a stenosis depends not only on the MLA but also on the length of the stenosis and the physiology of the microvascular bed, which cannot be assessed by imaging techniques.

Intravascular imaging can have a role, however, in assessing hazy lesions,[116,117] detecting spontaneous dissection,[118] identifying the causes of stent failure (ie, stent fracture, in-stent restenosis, stent underexpansion, neoatherosclerosis, stent malapposition), and planning further treatment.[119-121]

$$TAV = (EEM_{CSA} - Lumen_{CSA})$$

$$TAV_{norm} = \Sigma \frac{EEM_{CSA} - Lumen_{CSA}}{\text{Number of analyzed frames per patient}} \times \text{Mean/median no. of analyzed frames in the population}$$

$$\%\ \text{Change in TAV} = \frac{\text{TAV (follow-up)} - \text{Baseline}}{\text{TAV (baseline)}} \times 100$$

$$PAV = \frac{\Sigma\,(EEM_{CSA} - Lumen_{CSA})}{\Sigma\,EEM_{CSA}} \times 100$$

FIGURE 21–11. Parameters commonly used to report the extent of the coronary atherosclerosis. CSA, cross-sectional area; EEM, external elastic membrane; norm, normalized; PAV, percent atheroma volume; TAV, total atheroma volume.

Aneurysmal and Large Vessels

A true aneurysm cannot be determined by angiography because its definition requires expansion of all three layers of the vessel wall with an increased in EEM and lumen area more than 50% larger than the proximal reference segment. Pseudoaneurysm is characterized by disruption of the EEM, usually observed after PCI or plaque rupture. IVUS is extremely useful not only to differentiate between true and pseudoaneurysmal formation but also to evaluate vessel sizes and the presence of lumen stenosis, which is often masked by the aneurysm.[122] On the other hand, OCT is not suitable to evaluate aneurysmal disease in vessels larger than 3 mm in diameter, given its limited imaging depth.

There is robust evidence that intravascular imaging can provide useful information in patients with an intermediate LM obstruction. Abizaid and colleagues followed 122 patients with moderate LM stenosis for 1 year and found that a smaller minimal lumen diameter (MLD) measured by IVUS, was associated with a worse outcomes (event rate 60%, for patients with MLD < 2.0 mm, 24% for MLD 2.0-2.5mm, 16% for MLD 2.5-3.0 and 3% for MLD > 3 mm). In contrast to angiographic indices, IVUS-derived MLD was an independent predictor of cardiac events in multivariable model (odds ratio [OR] 0.17, 95% CI: 0.05-0.59; $P = .005$).[123] In another study, an IVUS-determined MLD of 2.8 mm and an MLA of 5.9 mm^2 had the highest sensitivity and specificity (93% and 98% for MLD; 93% and 95% for MLA, respectively) for detecting hemodynamically significant LM stenosis compared with FFR.[124] Based on this study, the LITRO study has been recently conducted that examined the value of IVUS in deferring PCI in patients with an intermediate LM stenosis. Three hundred fifty-four patients with an intermediate LM disease were included in the study; patients underwent PCI if they had a MLA of 6 mm^2 or less while those with a MLA of greater than 6 mm^2 were left untreated. At 2 years follow-up, there was no differences in the event rate in the patients who underwent LM revascularization and those who were left untreated (87.3 vs 94.3; $P = 0.3$).[125] Of note, this study was conducted in a Caucasian population and it is unclear whether this criterion can be applied in other ethnicities. Recently, a Korean report that included 55 patients with isolated LM disease who had IVUS and FFR imaging has shown that the IVUS-derived MLA that predicted hemodynamic significant stenosis was considerably smaller in this population (4.8 mm^2 for FFR < 0.80).[126]

Data about the role of OCT in assessing LM disease are limited. A. Erglis (personal communication, 2009) compared FD-OCT with IVUS to visualize the LM and showed that OCT may have a value in this setting. However, future studies are required to determine the role of OCT to determine lesion severity and guide LM PCI.

Ostial and Bifurcation Disease

The continuous dynamic variation in the three-dimensional anatomical configurations of coronary bifurcations poses significant challenges to planar coronary imaging modalities. Intravascular imaging plays an important role in evaluating the severity and distribution of atheroma in the bifurcation segment. IVUS has been used to identify and characterize aorto-ostial disease, but OCT remains limited for this anatomical indication because of the difficulty to clear the blood. The concept of "plaque shift" to explain side-branch occlusion during intervention in the main branch is not supported by IVUS, and necropsy studies that have shown plaques most commonly located in the opposite side of side branches.[127] Three-dimensional OCT has recently attracted attention for the evaluation of the bifurcation lesions because it appears able to provide a comprehensive assessment of the coronary anatomy. Thus, it can facilitate rewiring and procedural planning and assessment of the final results, detect carina shift, and evaluate the extent of the stenosis at the ostium of the side branch.[128-130]

Diffuse and Cardiac Allograft Disease

Most clinical adverse events in transplant patients occur after 1 year. The cumulative incidence of cardiac events per patient year is 0.9% within the first year, increasing to 1.9% by 5 years. Cardiac events account for 3.8% of the deaths by the end of the first year, increasing to 18% of total mortality by 7 years after heart transplantation. After the first year of transplantation, 36% (20 of 55) of the patients die because of CAD.[131] MI is usually silent because the heart is denervated. Therefore, there is a need for screening for early detection of coronary atherosclerosis. The presence of obstructive coronary disease in angiography is a predictor of any cardiac event (OR 3.44; $P < .05$), as well as a predictor of cardiac death (OR 4.6; $P < .05$). A pathologic study reported 10 patients who died or underwent retransplantation within 2 months of coronary angiography. One-fourth of the patients had intermediate lesions or atheromatous plaques. Fresh or organizing thrombus was most often associated with discrete lesions and accounted for all complete occlusions. The authors concluded that transplant CAD has a heterogeneous histologic and angiographic appearance, with angiographic underestimation of disease in some patients. Numerous reports have demonstrated that IVUS-derived plaque characteristics provide useful prognostic information in this vulnerable population.[132,133] In a study that included 143 patients who underwent three-vessel IVUS investigation at 1 and 12 months after transplantation rapid change in intimal thickness (≥ 0.5 mm was defined as rapidly progressive vasculopathy) was found at 1 year, in 37% of the patients, and a new lesion was found in 47% of them. At 5.9 years, patients with rapid progression had a higher mortality rate than their counterparts (26% vs 11%; $P = .03$). The combined end point of death and MI was also more frequently seen in patients with rapid progression (51% vs 16%; $P < .0001$).[133] In a more recent report an increase in the media-intima thickness greater than 0.35 mm and not of 0.5 mm was an independent predictor of MACE.[132] Accordingly, many active transplant centers have incorporated IVUS imaging into their post-transplant surveillance to estimate prognosis, but there is no consensus on how frequently IVUS should be performed. IVUS has been also used to assess novel therapies in heart transplantation recipients. Eisen and colleagues randomized 634 patients to receive 1.5 mg/d of everolimus (209 patients), 3.0 mg/d of everolimus (211 patients), or 1.0 to 3.0 mg/d of azathioprine per kilogram of body weight (214 patients) in combination with cyclosporine, corticosteroids, and statins. The primary efficacy

end point was a composite of death, graft loss or retransplantation, loss to follow-up, biopsy-proven acute rejection of grade 3A, or rejection with hemodynamic compromise. At 1 year, IVUS showed that the average increase in maximal intimal thickness was significantly smaller in the two everolimus groups than in the azathioprine group.[134] The value of OCT to assess allograft disease has been recently investigated in small-scale studies. Ichibori and coworkers assessed with OCT coronary plaque characteristics in 45 patients (155 vessels) who have undergone heart transplantation and demonstrated that neovessels are seen more often in segments with an increased intima-media thickness, suggesting that neovessels may play a role in transplant coronary artery vasculopathy.[135] In addition, Dong and colleagues used OCT to study the coronary anatomy of 48 patients and showed that patients with transplant coronary artery vasculopathy have an increased intima-medial thickness and macrophage accumulation.[136] Finally, Cassar and coworkers used OCT to demonstrate that patients with coronary artery vasculopathy have lesions with vulnerable plaque characteristics (ie, TCFA phenotype, microchannels, macrophages, thrombus, and intimal laceration).[137]

CLINICAL APPLICATIONS: INTERVENTIONAL

The use of intravascular imaging to guide PCI is heterogeneously distributed across the world, varying from more than 60% of use in Japan to less than 20% in Europe and United States. The explanation for such disparity is multifactorial but likely involves local reimbursement practices for the procedure, differences in clinical practice and training, and a relative lack of scientific evidence.

PREINTERVENTIONAL IMAGING

Intravascular imaging provides the only means (1) to accurately determine the vessel size, disease severity, character, extent, as well as location and (2) to guide therapeutic decision making in the cardiac catheterization laboratory. The main limitation of intravascular imaging is that despite the extreme miniaturization of IVUS and FD-OCT catheters, these probes may occlude vessels with severe stenoses, which may disturb image acquisition and interpretation. The additional information provided by IVUS on lesion composition, eccentricity, and length may change treatment strategies in up to 20% of cases.[138] As discussed previously, the presence, depth, and circumferential distribution of calcification are very important factors for selecting the type of interventional device.[139]

NON–STENT-BASED PERCUTANEOUS CORONARY INTERVENTIONS

Contemporary PCI techniques are essentially based on stents, but balloon angioplasty remains an integral step of the procedure. In addition, atherectomy and plaque modification strategies remain necessary in some procedures. Thus, understanding the mechanisms and the proper utilization of these techniques remains important in the modern era. The importance of intravascular imaging is likely amplified in non–stent-based interventions with the goal of maximal luminal gain and minimal risk of dissection and vessel perforation. Selection of the device size can be based on measurements of the total vessel (EEM) diameter, although a more conservative approach matching the balloon size to that of lumen diameter of the distal reference segments is most routinely performed in practice. The landmark Clinical Outcomes with Ultrasound Trial (CLOUT) study showed that mid-wall dimensions measured by IVUS can be safely used to for balloon sizing.[140] In this study, angioplasty was initially performed using angiography-defined balloon sizes; then repeat angioplasty was performed guided by IVUS imaging. This study showed that 73% of the lesions needed larger balloons even after achieving an "optimal" angiographic result and a success rate of IVUS-guided angioplasty of 99% without increased rates of dissections or ischemic complications. These findings have been confirmed in other studies.

Modifications of the dilatation strategy based on IVUS results include changes in balloon diameter, length, type, and inflation pressure. IVUS is also critical to define circumferential and longitudinal extension of plaque fracture or dissection and to guide the need for further intervention. Dissections can be classified into five categories: (1) intimal, (2) medial, (3) adventitial, (4) intramural hematoma (an accumulation of blood within the medial space, displacing the IEM inward and EEM outward), and (5) intrastent.[26] The severity of a dissection can be quantified according to depth, circumferential extent (in degrees of arc), length, size of residual lumen (CSA), and CSA of the luminal dissection.[141] Additional descriptors of a dissection may include the presence of a false lumen, the identification of mobile flap(s), the presence of calcium at the dissection border, and dissections in close proximity to stent edges. In a minority of patients, the dissection may not be apparent by IVUS because of scaffolding by the imaging catheter or because the dissection is located behind calcium.

IVUS studies have also been performed to define predictors of restenosis after balloon angioplasty. One of the main contributions of intravascular imaging to this field was the realization that negative remodeling, not neointimal hyperplasia, was the most important mechanism of long-term failures of nonstented coronary interventions, namely restenosis. This was initially demonstrated in the peripheral vessels and later reported in the coronary circulation.[142] These studies revealed that more than 70% of lumen loss was attributable to the decrease in EEM area; the neointima accounted for only 23% of the loss.

Although stand-alone atherectomy coronary intervention is not used in modern practice, these techniques still play a role in plaque modification and facilitate stent deployment. The use of IVUS during atherectomy results in a more aggressive strategy, leading to a greater plaque removal and a larger lumen diameter.[143] The adjunctive use of IVUS-guided directional coronary atherectomy (DCA) before stenting was proposed in the Stenting after Optimal Lesion Debulking (SOLD) registry[144] but the Atherectomy before Multilink Improves Lumen Gain Outcome (AMIGO) randomized trial failed to show a benefit in terms of angiographic restenosis of DCA followed by coronary stenting compared with coronary stenting alone.[145] Although DCA technologies have been removed from the US market, rotational atherectomy remains a niche technique to facilitate stent delivery in patients with severe coronary lesion calcification. IVUS can detect calcification, define the location and extent of calcification, and help define the need for the use of rotational atherectomy in clinical practice.[146,147] However, vessel calcification impacts delivery of the IVUS catheter and the quality of images, which hinders preintervention IVUS utilization in many cases.

STENT-BASED PERCUTANEOUS CORONARY INTERVENTIONS

Stents have become standard in virtually every PCI. IVUS has played a critical role in the establishment of modern stent deployment techniques. IVUS provides cross-sectional views of the stent, enabling unique assessment of expansion, apposition, vessel dissection, and residual untreated disease that cannot be properly defined by angiography. The pioneer report of Colombo and coworkers revealing a mean residual stenosis of 51% after angiography-guided stent deployment and a high prevalence of incomplete stent apposition significantly altered the understanding of optimal stent deployment and prevention of subacute thrombosis. After balloon inflations at higher pressures

(typically 18-20 atm), use of a larger balloon, or both, the operators were able to reduce the residual stenosis to 34%, which likely led to a 0.3% rate of subacute thrombosis without the need for systemic post-procedure anticoagulation.[148] However, restenosis remained an important limitation of the bare metal stent (BMS), affecting approximately 20% to 40% of patients.

"The bigger the better" adage that has dominated the interventional cardiology approach for decades[125] derived from angiography assessment of lumen gain and late loss, but it also suggests the importance of IVUS to optimize stent expansion and maximize lumen gain without the risk of vascular complication. The landmark Multicenter Ultrasound Stenting in Coronaries (MUSIC) registry helped defined IVUS criteria for optimal stenting and was based on three variables: (1) complete apposition of the stent over its entire length, (2) symmetric stent expansion defined by the ratio of minimal to maximal lumen diameter of 0.7 or above, and (3) in-stent minimal lumen area 90% or greater of the average area of distal and proximal references or 100% or greater of the lumen area of the reference segment with the smallest lumen area.[149] The subgroup of patients that met the criteria had a record 8% rate of restenosis after BMS implantation. However, the criteria are difficult to achieve in real practice. In the Optimal Stent Implantation Trial, stents were postdilatated at 18 atm, and only 60% reached the MUSIC criteria. In the Angiography Versus Intravascular Ultrasound Directed (AVID) stent placement trial, the more liberal goal of in-stent lumen CSA 90% or larger of the distal reference area was not achieved in more than 70% of 225 patients.[150] Other adaptations to the criteria have been suggested, including (1) an 80% average reference area and a 90% lumen area of the reference segment with the smallest area, (2) a minimal in-stent lumen area of 9 mm^2 or larger, and (3) a ratio of stent area to reference EEM area of 0.55 or above. However, these commonly used IVUS end points based on a predefined stent-to-reference ratio are also difficult to achieve.

Several prospective clinical studies have been conducted to test the hypothesis that IVUS guidance of stent deployment improves outcomes, but the results were conflicting. Can Routine Ultrasound Influence Stent Expansion? (CRUISE) was a large observational substudy involving 538 patients from the Stent Anticoagulation Regimen Study (STARS), a randomized, multicenter trial testing different antithrombotic regimens that compared angiographic versus ultrasound guidance on a center-by-center basis. The study showed improvement in the rates of target vessel revascularization after 9 months in patients treated at centers using the IVUS-guided approach.[151] In the Optimization with ICUS (OPTICUS) study, IVUS- and angiography-guided approaches resulted in similar rates of both angiographic restenosis and need for target vessel revascularization.[152] The Thrombocyte Activity Evaluation and Effects of Ultrasound Guidance in Long Intracoronary Stent Placement (TULIP) study suggested that routine IVUS guidance for stent deployment was likely to be of benefit only in patients at high risk for restenosis.[153] A large retrospective study including 884 patients compared outcomes of IVUS-guided versus a propensity-score matched population undergoing DES implantation with angiographic guidance alone.[154] The study showed that IVUS guidance during DES implantation reduced both DES thrombosis and the need for repeat revascularization.

However, the focus of contemporary interventional cardiology has shifted toward improving the safety rather than efficacy of DES because these devices have virtually eliminated the problem of restenosis but have been associated with late in-stent thrombosis. IVUS studies were important to provide a morphologic analysis of the local biologic effects of the implantation of DES. Initial IVUS studies were essentially to confirm suppression of neointimal hyperplasia by DES.[155,156] These studies also revealed the occurrence of new late, incomplete stent apposition, which has been anecdotally associated with in-stent thrombosis. The first randomized control studies investigating the prognostic implications of IVUS-guided PCI in DES era failed to demonstrate improved outcomes in the IVUS-guided group.[157,158] The Angiography Versus IVUS Optimization (AVIO) study was the first well-designed clinical study that examined the role and prognostic value of IVUS-guided PCI. In this study, prespecified criteria were suggested to define optimal stent deployment in the IVUS guided group. According to the AVIO criteria, the average EEM diameter at the proximal and distal reference segment was used to select the diameter of the noncompliant balloon for postdilation and optimal stent deployment was defined as a greater than 80% minimum lumen area of the predicted area of the noncompliant balloon. Two hundred eighty-four patients with complex lesions (long lesions, chronic total occlusions, bifurcations, small vessels ≤ 2.5 mm) were randomized to IVUS and conventional PCI and were followed for 2 years. Although at postprocedure, the MLD was higher in the IVUS-guided group (2.70 ± 0.46 vs 2.51 ± 0.46mm; $P = .0002$), there were no differences in the clinical outcomes at 2 years follow-up.[157] Similar were the results of the study conducted by Kim and colleagues, who focused on long lesions: 543 patients with lesions greater than 28 mm were randomized to IVUS and angiography-guided PCI. At 1 year of follow-up, there was no difference in the major adverse cardiovascular event rate between the two groups (4.5% vs 7.3%; $P = .16$).[158]

Nevertheless, the results of meta-analyses and of the large-scale Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) registry have provided cumulative evidence that IVUS-guidance is related with better clinical outcomes in the DES-era.[159-163] Possible explanation of this controversy was the small number of patients included in the first studies, which were not sufficiently powered to demonstrate the prognostic benefit of IVUS guidance. Indeed, the recently published IVUS Guidance on Outcomes of Xience Prime Stents in Long Lesions (IVUS-XPL)—the first appropriately sized randomized study—confirmed this hypothesis. In this study 1400 patients with long lesions (> 28 mm) were randomized to IVUS and angiography-guided PCI.[164] IVUS guidance was associated with a lower incidence of MACE at 1 year of follow-up (2.9% vs 5.8%; $P = .007$), which was attributed to a lower incidence of target lesion revascularization (2.5% vs 5.0%; $P = .02$).

IVUS-guidance seems also to be useful in the treatment of chronic total occlusions. IVUS can be used to identify the entry site in stumpless chronic total occlusions and optimize stent deployment. A recent report has shown that IVUS-guided stent implantation in chronic total occlusion is associated with a lower incidence of late lumen loss (0.28 ± 0.48 mm vs 0.46 ± 0.68 mm; $P = .025$) and in-stent restenosis (3.9% vs 13.7%; $P = .021$) compared to angiography-guided PCI,[165] while another study that included 402 patients with chronic total occlusions who were randomized to IVUS- or angiography-guided treatment has demonstrated a lower MACE rate in the IVUS-guided group (2.6% vs 7.1%; $P = .035$).[166] On the other hand, the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) MI registry has shown that IVUS-guided PCI in patients admitted with a STEMI is not associated with better clinical outcomes compared to angiography-guided PCI.[167]

The use of IVUS to guide stent implantation in LM PCI has been evaluated in two propensity matched analyses.[168,169] Park and colleagues compared clinical outcomes in 402 propensity matched patients who had LM PCI under angiographic or under IVUS guidance with bare metal or drug-eluting stents. At 3 years of follow-up, the patients who had IVUS-guided PCI had lower mortality (4.7% vs 16%; $P = .048$) compared to those having angiography-guided PCI.[168] In the study of Hernandez and coworkers, 1010 propensity matched patients who had LM PCI under

IVUS or angiographic guidance were followed for 3 years. Lower event rate was noted in the IVUS-guided group (death-MI-revascularization: 14.4% vs 22.2%; $P = .006$; cardiac death-MI-revascularization: 11.7% vs 16%, $P = .04$).[169] The benefit of the IVUS guidance can be attributed to the optimal stent deployment in the IVUS group. Indeed, Kang and colleagues have recently demonstrated that stent underexpansion in LM PCI is associated with an increased incidence of restenosis and cardiovascular events at 2 years follow-up.[170]

The concept of OCT-guided PCI has been tested prospectively in the ILUMIEN I study.[171] In this study, 418 patients with stable angina and non-STEMI underwent OCT and FFR-guided PCI. The use of OCT changed procedural planning in 55% of the cases. At the end of the procedure, OCT imaging indicated further intervention in 25% of the patients. OCT guidance resulted in a low event rate at 30 days (death: 0.25%; MI: 7.7%; repeat PCI: 1.7%). In the ILUMIEN II study, the clinical outcomes were compared in patients undergoing OCT- and IVUS-guided PCI.[172] This matched pair analysis of the patients included in the ILUMIEN I and ADAPT-DES study compared stent expansion, stent malapposition, and edge dissection and demonstrated no significant differences in the two groups. The clinical benefit of OCT-guidance over angiography-guided PCI has been examined in a small propensity matched analysis including 670 patients.[173] Although OCT-guidance appeared to be associated with a better clinical outcomes in this study, further research and convincing data from randomized control trials are required before advocating the prognostic value of OCT-guided PCI.

Small-scale studies have demonstrated that the combined NIRS-IVUS catheter allows accurate prediction of lesions associated with an increased incidence of periprocedural MI caused by distal embolization and that an embolic protection device may reduce this risk.[174] Recently, Erlinge and coworkers have shown that thrombus aspiration devices reduce the lipid content at the culprit lesion site. They aspirate not only thrombus but also calcium, macrophages, and lipids; thus they can potentially reduce the risk of no reflow.[175] However, the recently published Coronary Assessment by Near-infrared of Atherosclerotic Rupture prone Yellow (CANARY) failed to demonstrate a prognostic benefit of an embolic protection device in lipid-rich plaques, and therefore the role of NIRS-IVUS imaging in guiding PCI is under question.[176]

Diseased bypass grafts have been a challenge for both interventionists and cardiac surgeons. Intravascular imaging is important to guide stent size selection and define the extent of disease. IVUS has also been used to monitor outcomes after treatment of vein grafts with DES. The Compassionate Use of Sirolimus-Eluting Stent (SECURE) study included 76 patients (94 lesions) with graft disease treated with a sirolimus-eluting stent (SES), and 14 patients had IVUS follow-up performed at 8 months. Overall, the percentage of intimal hyperplasia was 11.8 ± 16.5%, and 50% of the patients with graft SES had less than 1% intimal hyperplasia.[177] In the setting of a randomized trial, 75 patients with graft disease (96 lesions) who received either sirolimus-eluting or bare metal stents (Reduction of Restenosis In Saphenous Vein Grafts with Cypher Sirolimus-Eluting Stent [RRISC] study), were assessed by IVUS at 6 months. The SES showed smaller neointimal hyperplasia volume compared with the BMS (1.3 vs 24.5 mm^3; $P < .001$). In the SES group, there was greater intimal hyperplasia at overlapping sites compared with nonoverlapping segments.[178]

ASSESSMENT OF COMPLICATIONS AFTER PERCUTANEOUS CORONARY INTERVENTIONS

Dissection

Many interventional cardiologists prefer to use angiography alone to manage intraprocedural complications. However, IVUS can be instrumental in many unanticipated circumstances. The presence of significant persistent flow-limiting lesions or dissections has been linked to higher likelihood of stent thrombosis.[179] These findings are often angiographically occult or appear as areas of indistinct haziness at the vessel border. In this scenario, IVUS distinguishes patients who require further intervention to treat uncovered dissections from those who have minimal lumen compromise and a short dissected segment and can be managed conservatively. In 201 stent patients, IVUS detected 31 segments with persistent angiographic haziness; 15 of them had significant lumen obstruction, and 14 had significant wall injury. IVUS is useful to detect the extent of post-PCI dissection, often revealing a greater length than is evident from angiography, which may be helpful in guiding vessel salvage and ensuring that the full length of dissection is covered by the stent. Finally, during treatment of dissections, IVUS may be very helpful in differentiating between the true and false lumen. OCT represents an optimal imaging tool to evaluate coronary dissection and in a recent report Radu and colleagues explored the natural history of edge dissections in 57 patients (63 lesions) undergoing PCI.[180] Twenty-two non–flow-limiting edge dissections were identified immediately after stent implantation. At 1 year of follow-up, most of the dissections were completely healed. No stent thrombosis or target lesion revascularization was reported, indicating that non–flow-limited edge dissections are associated with good prognosis. On the other hand, in the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI II) study, the presence of a dissection more than 200 μm at the distal edge of the stent was an independent predictor of stent failure and MACE.[181]

Thrombosis

Intravascular imaging can play an important role in both prevention and diagnosis of stent thrombosis. Stent underexpansion, incomplete wall apposition, and vessel dissection—features easily identified by intravascular imaging—have been associated with an increased risk of stent thrombosis.[182] The minimum stent CSA (4.3 ± 1.6 mm^2 vs 6.2 ± 1.9 mm^2; $P < .001$) and the degree of stent expansion (0.65 ± 0.18 vs 0.85 ± 0.14; $P < .001$) were significantly smaller in patients with versus those without DES thrombosis. The same study also showed that residual edge disease—defined as edge lumen CSA smaller than 4 mm^2 and a plaque burden greater than 70%—was associated with a risk of thrombosis.[183]

OCT studies have been proven useful in understanding the mechanisms of stent thrombosis and reports have shown that suboptimal stent expansion, stent fracture, neoatherosclerosis, and delayed arterial healing and stent malapposition are common causes of stent thrombosis in the DES era.[119-121,184]

Restenosis

Unlike restenosis after balloon angioplasty or atherectomy, IVUS studies have shown that in-stent restenosis is essentially a result of neointimal hyperplasia. Predictors of stent restenosis have been identified by multivariate analyses and include a small reference vessel and lumen size, a larger plaque burden, and a small in-stent lumen area. Although the prevalence of restenosis has decreased dramatically with DES, maximizing luminal gain remains an important approach in preventing restenosis. The receiver operating characteristic curve identified a poststenting minimum stent CSA of 5 mm^2 for the SES and 6.5 mm^2 for the BMS, which were associated with lumen CSA larger than 4 mm^2 at 8 months of follow-up.[185] Others have shown that the highest restenosis rate was observed in lesions with a stent area smaller than 5.5 mm^2 and a stent length larger than 40 mm after deployment of an SES.[186]

Intravascular imaging is also essential to guide therapy of in-stent restenosis because mechanical problems related to stent deployment

procedures contribute to approximately 25% of in-stent restenosis.[187] Stent fracture has been reported as a cause of stent restenosis in the modern era of long stent implantation, which may be identified by intravascular imaging.[188] Intravascular imaging has shown that characteristics of neointimal hyperplasia may differ between bare metal and drug-eluting stents. Neointimal hyperplasia in the DES may have a more echolucent nonhomogeneous appearance compared to that in the BMS.[189] In addition, diffuse in-stent restenosis is common after the use of the BMS, but the pattern of restenosis associated with the DES is most frequently focal. One of the most common variables used to report restenosis is percentage of intimal hyperplasia volume in the stent segment.[190] This variable normalizes the intimal hyperplasia to the stent length, allowing a comparison of different stent types (BMS vs DES), as well as different drug types (ie, SES vs PES). The percentage of intimal hyperplasia, however, minimizes the impact of focal restenosis. The use of IVUS-VH to assess in-stent restenosis in metal stents is hampered by the following factors: lack of validation of the technique in this context, misclassification of the stent struts as "dense calcium" surrounded by necrotic core, and the potential interference of the superficial stent struts on the backscattering of the tissue behind them.

OCT has been used to evaluate the restenotic tissue based on structure, lumen shape, and the presence of microvessels and intraluminal material with low inter- and intraobserver variability. The qualitative definition of tissue backscatter is influenced by the position of the OCT catheter relative to the vessel wall.[191] Tissue with low and high backscatter and variable optical properties are often observed in the same vessel, suggesting that "restenosis" after DES might have a heterogeneous composition. Histologic analysis of human atherectomy specimens has also shown heterogeneous tissue components, including proteoglycan-rich tissue, organized thrombus, atheroma, inflammation, and fibrin.[191,192] Restenosis presenting with unstable angina symptoms was more frequently associated with an irregular lumen shape and intraluminal material suggestive of thrombus.[191]

Neoatherosclerosis is a common cause of very late stent failure and is characterized by the accumulation of lipid-laden foamy macrophages with or without necrotic core or calcification formation. Histology studies have showed that OCT allows reliable detection of neoatherosclerotic lesion characteristics and is regarded today as the gold standard for the in vivo identification of these lesions.[119,193] The exact mechanisms that regulate neoatherosclerotic lesion formation are yet unclear. However, it appears that endothelial dysfunction, delayed vascular healing, the local endothelial shear stress patterns, and a chronic inflammatory response to the DES polymer contribute to the generation of the neoatherosclerotic lesions.[119] Several OCT-based studies have explored the neoatherosclerotic lesion distribution in different stent types,[194,195] and in different study populations[196,197] and investigated the association between neointima characteristics and neoatherosclerotic lesion formation.[198] Nakazawa and colleagues[199] have shown that in-stent neoatherosclerosis occurs early in the first generation of DES as compared to BMS and that no differences in the prevalence of neoatherosclerosis were seen between the first and second generation (Fig. 21–12).[200] A recent meta-analysis of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) study has shown that neoatherosclerotic lesion formation is related to atherosclerotic disease progression in the native coronary arteries, suggesting that these processes are regulated by the same pathophysiological mechanisms.[201]

RESEARCH APPLICATIONS

Intravascular imaging has played an important role in the understanding of atherosclerosis disease in humans and translation of novel therapies to the clinical arena.

DRUG EFFECTS ON ATHEROSCLEROSIS

The initial observations about a positive continuous relationship between coronary heart disease and cholesterol levels led to the conduction of a number of IVUS-based studies that evaluated the effect of different lipid-lowering drugs on atheroma size. Changes in plaque characteristics may be a more relevant end point to predict the risk of vascular thrombosis than plaque progression or regression of mild to moderate disease, but imaging tools to accurately evaluate plaque characteristics were not available until recently. Other limitations of using conventional grayscale IVUS to assess the natural history of atherosclerosis should be enumerated, including (1) use of catheterization, an invasive procedure, which is required for serial imaging; (2) only a segment of the coronary tree can be studied; (3) plaque composition is not obtained; and (4) there is no direct evidence linking changes in coronary plaques and clinical events.

The efficacy of lowering low-density lipoprotein cholesterol (LDL-C) with inhibitors of hydroxymethylglutaryl coenzyme A reductase (statins) is unequivocal; however, the change in atheroma size by statins is not constant across all IVUS studies. There are many potential explanations for these discrepancies in IVUS studies such as drug properties, dose, and duration of treatment. In early studies such as the German Atorvastatin Intravascular Ultrasound (GAIN) study, atheroma volume was not reduced by atorvastatin despite the reduction in LDL-C (86 vs 140 mg/dL) at 12 months. In contrast, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study showed that LDL-C levels were further lowered by atorvastatin versus pravastatin (110 vs 79 mg/dL), which was associated with an increase of 2.7% of atheroma volume in pravastatin-treated patients and in a 0.4% reduction in atheroma volume in atorvastatin-treated patients.[202] The clinical significance and the accuracy of IVUS for such measurements are still debatable, but these results were statistically significant. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study showed that the lower the LDL-C and C-reactive protein values, the greater the reduction in clinical events and atheroma progression.[203]

The first study showing regression of plaque size was the A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial.[204] At 24 months, treatment with 40 mg/d of rosuvastatin resulted in lowering of LDL-C to 60.8 mg/dL and elevation of high-density lipoprotein cholesterol (HDL-C) by 14.7%. These lipid effects were associated with statistically significant, albeit small, reductions in PAV (0.79%) and TAV (6.8%).

OCT has also been used to evaluate the effect of statin therapy on coronary fibrous cap thickness in patients with ACS.[205] This pilot study showed that lipid-lowering therapy for 9 months after STEMI increases the fibrous cap thickness. Although fibrous cap thickness increased in both the statin treatment group (151 ± 110 to 280 ± 120 μm) and the control group (153 ± 116 to 179 ± 124 μm), the magnitude was greater in the statin treatment group. The EASY-FIT (Effect of AtorvaStatin therapy on FIbrous cap Thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography) study that recently compared aggressive treatment with 20 vs 5 mg of atorvastatin has also shown that the patients on the higher dose of atorvastatin exhibited an statistical significant increase in the thickness of the fibrous cap at 12 months follow-up (69% vs 17%; $P < .001$).[3]

IVUS studies have also demonstrated coronary plaque modification in HDL-treated patients. The infusion of synthetic HDL-C particles containing the variant apolipoprotein, apoA-I Milano, complexed with phospholipids (ETC-216) reduced the PAV by –1.06% (3.17%; $P = .02$ compared with baseline) in the combined ETC-216 group at 5 weeks. On the contrary, in the placebo group, PAV increased by 0.14% (3.09%;

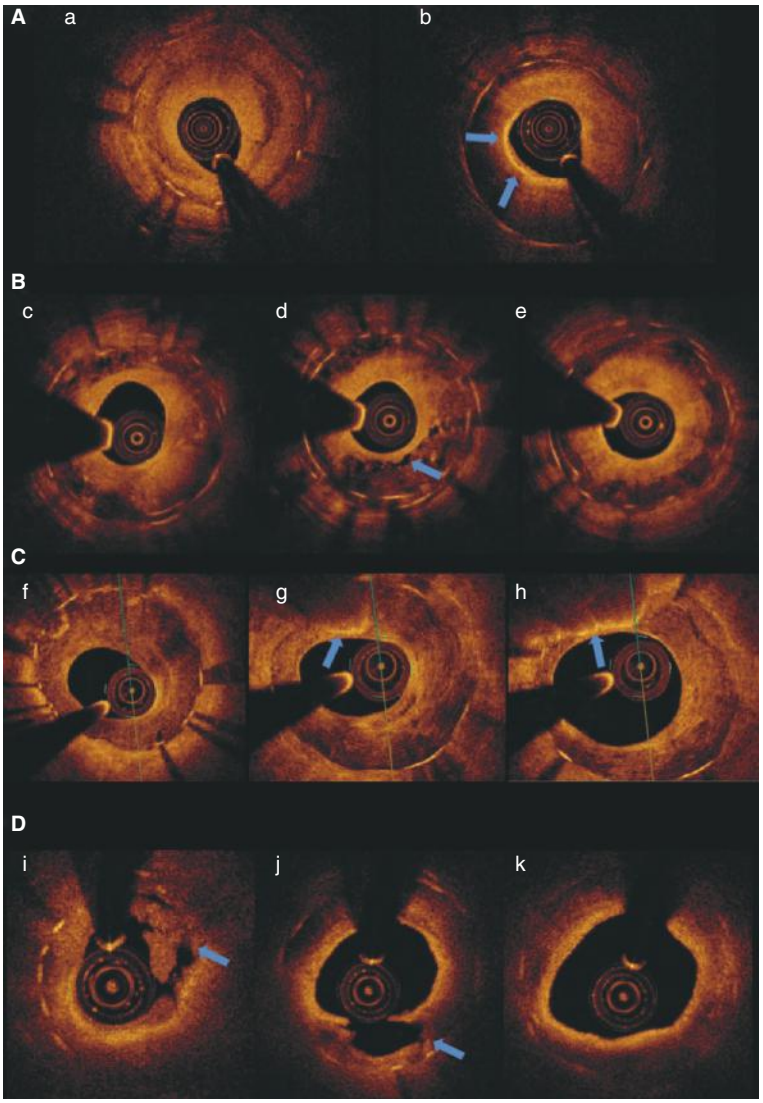

FIGURE 21–12. Clinical assessment of stented coronary arteries by optical coherence tomography (OCT) showing different neointimal tissues. **A.** A 55-year-old male patient presented with unstable angina 9 years after percutaneous coronary intervention to the left anterior descending artery with a durable polymer paclitaxel-eluting stent. OCT showed diffuse high-grade in-stent restenosis. In the distal stented segment there is a homogeneous high signal intensity lesion close to the luminal surface with signal poor region in the middle of the neointima (*a*). This appearance may indicate neointima hyperplasia with smooth muscle cell growth and accumulation of lipid or extracellular matrix such as proteoglycan, or a healed lesion secondary to thrombotic event. The proximal stented segment (*b*) shows an area of plaque with superficial high signal intensity (*arrows*), which may represent macrophage accumulation, and deeper there is high signal attenuation, which may indicate granulation tissue or the accumulation of lipid or fibrin. **B.** In-stent restenosis 4 years after durable polymer sirolimus-eluting stent implantation in the proximal right coronary artery (RCA). OCT demonstrates focal restenosis with heterogeneous and layered pattern tissue (*c–e*). The relatively well-demarcated borders and the lack of signal attenuation (*d*) indicate that this is likely granulation tissue with overlying neointimal hyperplasia that is rich in smooth muscle cells. The signal dropout (*arrow in d*) represents neovascularization. **C.** A 58-year-old male patient presented with stable angina 7 months after implantation of a durable polymer everolimus-eluting stent. OCT imaging showed focal in-stent restenosis. There is a heterogeneous signal intensity in the neointima with low attenuation (*f–h*), which is likely to indicate proteoglycan-rich neointima or granulation tissue or fibrin deposition. Cross-sections (*g*) and (*h*) show focal signal-rich regions with attenuation (*arrows*) that indicates neoatherosclerosis characterized by macrophage clusters. **D.** A 67-year-old patient admitted with stent thrombosis in the RCA 3 years following durable polymer drug-eluting stent implantation. OCT imaging after thrombus aspiration showed concentric restenosis distally with a signal-rich region close to the luminal surface accompanied by signal attenuation (*i–k*) and evidence of plaque rupture (*arrow in j*). The most-distal stented segment (*i*) exhibits severe eccentric restenosis with residual intraluminal thrombus (*arrow in i*). These frames show that stent thrombosis was caused by in-stent plaque rupture from neoatherosclerosis. Reproduced with permission from Otsuka F, Byrne RA2, Yahagi K, et al: Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015 Aug 21;36(32):2147-2159.[119]

$P = .97$ compared with baseline).[206] In the Effect of Reconstituted High-Density Lipoprotein on Atherosclerosis: Safety and Efficacy (ERASE) study, 60 patients were randomly assigned to receive four weekly infusions of placebo (saline), 111 to receive 40 mg/kg of reconstituted HDL (CSL-111), and 12 to receive 80 mg/kg of CSL-111. The latter was discontinued because of liver function test abnormalities. Within the treated group, the percentage change in atheroma volume was –3.4% with CSL-111 ($P < .001$ vs baseline) and was –1.6% ($P = .48$ between groups) for the placebo group. It is still unclear what the future holds for these therapeutic agents.[207]

Patients with human deficiency of cholesteryl ester transfer protein (CETP) have elevated circulating levels of HDL-C. This has led to investigation on CETP inhibition as a novel and potentially effective approach to elevate HDL-C. In the Investigation of Lipid Level Management Using Coronary Ultrasound To Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE)

trial, the PAV (primary efficacy measure) increase was similarly low in patients receiving atorvastatin monotherapy compared with those receiving the combined torcetrapib–atorvastatin therapy after 24 months (0.19% vs 0.12%, respectively).[208]

The enzyme acyl–coenzyme A:cholesterolacyltransferase (ACAT) esterifies cholesterol in a variety of cells and tissues. Inhibition of ACAT1 by blocking the esterification of cholesterol could prevent the transformation of macrophages into foam cells and slow the progression of atherosclerosis, and inhibition of ACAT2 would be expected to decrease serum lipid levels. In the ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) study, the change in PAV was similar in the pactimibe (100 mg/d) and placebo groups (0.69% and 0.59%, respectively; $P = .77$).[209]

Systolic blood pressure has been shown to be an independent predictor of plaque progression by IVUS.[210] A randomized study of patients with CAD and a diastolic blood pressure below 100 mm Hg treated with placebo or antihypertensive therapy using either 10 mg/d daily of amlodipine or 20 mg/d of enalapril showed that patients treated with amlodipine had a reduction in plaque size and a reduction in cardiovascular events at 24 months compared with those given placebo.[210] The PERindopril's Prospective Effect on Coronary aTherosclerosis by IntraVascular ultrasound Evaluation (PERSPECTIVE) study, a substudy of the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial, evaluated the effect of perindopril on coronary plaque progression in 244 patients. There were no differences in changes in IVUS plaque measurements detected between the perindopril and placebo groups, indicating that this treatment had no effect on the plaque burden.[211]

Several recent reports have shown serial changes of plaque composition in patients treated with various statin treatments. In one of them, patients with SAP (n = 80) treated with fluvastatin for 1 year had significant regression of plaque volume and changes in atherosclerotic plaque composition with a significant reduction of fibrofatty volume ($P < .0001$). This change in fibrofatty volume had a significant correlation with the change in LDL-cholesterol level ($r = 0.703$; $P < .0001$) and change in high-sensitivity C-reactive protein (hsCRP) level ($r = .357$; $P = .006$).[212] Of note, the necrotic core did not change significantly. In a second study, Hong and colleagues randomized 100 patients with stable angina and ACS to either rosuvastatin 10 mg or simvastatin 20 mg for 1 year. Overall, necrotic core volume significantly decreased ($P = .010$), and fibrofatty plaque volume increased ($P = .006$) after statin treatments. Particularly, there was a significant decrease in necrotic core volume ($P = .015$) in the rosuvastatin-treated subgroup. By multiple stepwise logistic regression analysis, the researchers showed that the only independent clinical predictor of decrease in necrotic core volume was baseline HDL-C level ($P = .040$; OR, 1.044; 95% CI, 1.002-1.089).[213]

The Integrated Biomarkers and Imaging Study-2 (IBIS-2) compared the effects of 12 months of treatment with darapladib (an oral Lp-PLA2 inhibitor, 160 mg/d) or placebo in 330 patients.[14] End points included changes in necrotic core size (IVUS-VH) and atheroma size (grayscale IVUS). Background therapy was comparable between groups, with no difference in LDL-C at 12 months (placebo, 88 ± 34; darapladib, 84 ± 31 mg/dL; $P = .37$) In the placebo-treated group, however, the necrotic core volume increased significantly, but darapladib halted this increase, resulting in a significant treatment difference of −5.2 mm^3 ($P = .012$). These intraplaque compositional changes occurred without a significant treatment difference in TAV.

NIRS and NIRS-IVUS have also been used to investigate the effect of statins on the compositional characteristics of the plaque. In the Reduction in Yellow Plaque by Intensive Lipid Lowering Therapy (YELLOW) study, NIRS and IVUS imaging were used to assess the effect of aggressive lipid lowering treatment in plaque burden and composition in flow limiting lesions.[39] In this study, NIRS and IVUS imaging were performed at baseline and at 7 weeks follow-up in lesions with a FFR of less than 0.80 in 87 patients who were randomized to aggressive lipid therapy with rosuvastatin 40 mg/d or standard of care lipid therapy. A significant reduction (by 24%) in the lipid component and an increase in the elastic membrane area by 9% in the intensive treatment group was noted at 2 months follow-up, whereas in the standard of care group, the change in the lipid component was increased by 5.4% and the external elastic membrane by 3%.

On the other hand, the Integrated Biomarkers Imaging Study 3 (IBIS-3) that included 103 patients who underwent coronary angiography for clinical purposes and had serial single vessel NIRS-IVUS imaging at baseline and at 12 months of follow-up failed to demonstrate an effect of the treatment with rosuvastatin on the lipid component (lipid core burden index, 44.9 at baseline vs at 12 months 46.1, $P = .80$; max 4 mm lipid core burden index, 201.9 vs 206.8, $P = .72$) at 1 year of follow-up.[18]

PREDICTIVE VALUE OF INTRACORONARY IMAGING

The potential value of IVUS in the prediction of adverse coronary events was evaluated in an international multicenter prospective study, the PROSPECT study. The PROSPECT trial was a multicenter, natural history study of patients with ACS. All patients underwent PCI in their culprit lesion at baseline followed by angiography and IVUS-VH of the three major coronary arteries. Within a follow-up period of 3.4 years, 104 new lesions were developed in the nontreated vessels (11.6%). Interestingly, most of the nontarget lesion–related cardiovascular events were unstable, progressive angina (92%) and only 8% were acute thrombotic cardiovascular events. Of the 104 new lesions, 55 were studied by IVUS-VH at baseline.[15] An IDTCFA with a minimum lumen area of 4 mm^2 or less and a large plaque burden (≥ 70%) had a 18.2% likelihood of causing an event within 3 years. Similar were the results of the VH-IVUS in Vulnerable Atherosclerosis (VIVA) study, which included 170 patients admitted with stable angina or an ACS who had IVUS-VH imaging in the nonculprit vessel at baseline during the index procedure and were followed for 2 years.[16] During follow-up, 16 cardiovascular events occurs in the nontreated vessels. Similarly to what it has been shown in the PROSPECT study, IDTCFA (hazard ratio [HR] 8.16; $P = .007$), plaque burden > 70% (HR 7.48; $P < .001$), and MLA less than 4 mm^2 (HR 2.91; $P = .036$) were associated with cardiovascular events.

IVUS-based imaging has also been used to assess the implication of the local hemodynamic forces on atherosclerotic evolution. Fusion of conventional angiography and IVUS has been used to reconstruct coronary anatomy, perform blood flow simulation, and assess the endothelial shear stress (ESS) and its effect on plaque phenotype morphology and evolution.[214-216] Several OCT-based and IVUS-based reconstruction studies have shown that low ESS promotes atherosclerotic evolution and the formation of vulnerable high-risk lesions in native arteries and stented vessels.[217-220] The recently reported PREDICTION study is the largest prospective large-scale trial that examined the implications of ESS on plaque growth and future cardiovascular events.[221] This study included 509 patients who were admitted for an ACS and underwent three-vessel IVUS examination at baseline and at 6 months follow-up. The baseline IVUS and angiographic data were used to reconstruct the coronary anatomy and evaluate the ESS distribution. Low ESS, which appeared to promote plaque growth, and baseline plaque burden were the only independent predictors of future revascularizations, with a positive predictive value of 41%.

The efficacy of OCT in predicting lesions that are prone to progress and cause cardiovascular events has been assessed in a small-scale

study that included 53 patients with CAD who had PCI and OCT imaging at baseline and repeat coronary angiography at 7 months follow-up. During this time interval 13 non–flow-limiting lesions showed disease progression at follow-up. Compared to lesions that did not progress, these that they progressed had a higher incidence of intima laceration (61.5% vs 8.9%; $P < .01$), thrombi (30.8 vs 1.8%; $P < .01$) microchannels (76.9% vs 14.3%; $P < .01$), macrophages (61.5% vs 14.3%; $P < .02$) and an increased lipid component (100% vs 60.7%; $P < .01$). This study provided for the first time evidence that plaque microfeatures and the presence of inflammation, indicated by the presence of macrophages, may facilitate prediction of lesions that will progress and cause cardiovascular events.[222]

VASCULAR RESPONSE TO ENDOVASCULAR DEVICES

Metallic Stents

IVUS has been extensively used as a surrogate end point in stent trials, primarily to assess the effectiveness of devices as it relates to neointimal proliferation. IVUS was an essential investigational tool during initial clinical testing of the DES,[155,156] confirming the dramatic suppression of neointimal proliferation, revealing new patterns of restenosis, and establishing intravascular imaging metrics of stent optimization as described above.

Intravascular imaging is now focused on the evaluation of surrogate safety end points. "Vascular healing" represents a complex array of vascular responses to DES implantation, including reendothelialization, tissue coverage, thrombus and fibrin deposition, and strut apposition. In particular, stent-strut coverage and apposition have been linked to the risk of stent thrombosis.[120] Histology has revealed that IVUS does not have the adequate resolution to detect small amounts of tissue coverage.[223] Contemporary DES clinical trials such as OCT for DES Safety (ODESSA), Optical Coherence Tomography in Acute Myocardial Infarction (OCTAMI), and Optical Coherence Tomography Drug Eluting Stent Investigation (OCTDESI) trials have selected these variables as their primary end point, and larger studies such as Limus Eluted from A Durable versus ERodable Stent coating (LEADERS) and Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) have integrated OCT substudies. Light, in a manner similar to ultrasound, reflects from the metal surface and hides the abluminal stent face. For the quantification of strut malapposition, the distance between the luminal surface of the strut and the vessel wall needs to be measured, accounting for the additional thickness of the polymer and drug coating.[224] Malapposition is then declared if the measured distance is longer than the strut-polymer thickness. Some images of struts protruding in the lumen are obviously related with malapposition; others may represent a well-apposed, but not embedded, strut. This is particularly critical in the research environment, where a "quantitative strut-level analysis" should be performed for accurate data evaluation (Fig. 21–13).

Bioresorbable Scaffolds

Bioresorbable scaffolds (BRS) constitute a novel approach for the treatment of CAD. These devices have the ability to provide a transient support to the vessel wall, deliver the antiproliferative drug, and then disappear, allowing the vessel to return to its natural state. The unique advantages of these devices have been appreciated from their first applications in the clinical and research arena and attracted the attention of the industry and scientific communality.[225,226] Today, numerous BRS with different properties and design have been developed and are available in the clinical arena or undergoing clinical or preclinical evaluation.

Intravascular imaging has played a pivotal role in understanding the properties, advantages, and limitations of these devices.[227] Serial IVUS imaging has provided unique insights about the resorption process in the first-generation BRS (ie, the ABSORB BVS 1.0, the AMS 1.0, and DREAMS) and the causes of the high late lumen loss noted in the first clinical trials (ie, late vessel recoil caused by inadequate lumen support by the BRS and neointima formation).[228] To address these limitations, the second-generation BRS with delayed resorption were introduced

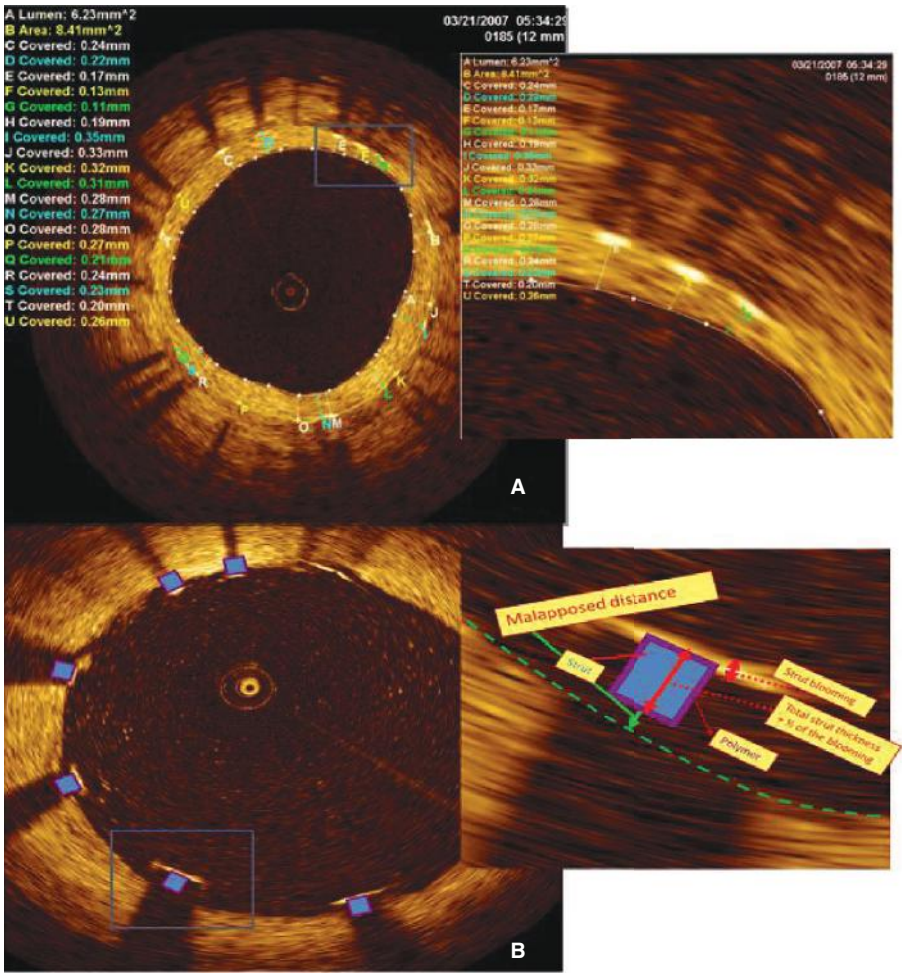

FIGURE 21–13. A. The *upper panels* show cross-sectional optical coherence tomography (OCT) image with lumen contours and strut-level quantitative analysis (*detailed left panel*) of a stented segment with neointimal hyperplasia. **B.** The *lower panels* show cross-sectional OCT image of various levels of stent-strut apposition. Note that the strut located at the 7 o'clock position is malapposed (also shown in details in the *left panel*). Malapposition is defined when the measured distance from the surface of the blooming to the lumen contour is larger than the total thickness of the stent strut + polymer + half of the blooming. The stent surface is, theoretically, located at half the distance of the blooming. The *box* represents the stent strut. In this particular case, the total estimated strut thickness is 164 µm (strut thickness = 132 µm + polymer = 16 µm + half of the blooming = 18 µm). The measured distance is 200 µm, confirming a 36-µm malapposition. Because of the eccentric wire position, strut blooming is elongated on the struts distant from the wire (5 and 7 o'clock positions), also known as the "merry-go-round" effect.

that provided prolonged radial support and incorporated a drug elution that reduced the neointima response.[229,230]

Apart from IVUS, OCT with its high imaging resolution has been used to study the vessel wall response to BRS. In the ABSORB BVS, struts appear as black central cores framed by light-scattering borders that permit complete imaging of their distribution and their position with regard to the vessel wall. OCT has been used to assess the resorption process, understand the mechanisms of scaffold expansion[230] and the vascular edge response following device implantation;[231] and identify acute strut fractures caused by excessive postdilation of the scaffold, which constitute one of the causes of early scaffold failure.[232] Moreover, OCT has allowed us to appreciate the healing response following BRS implantation and assess the neointima burden and its composition. Serial OCT studies have demonstrated that following ABSORB BVS implantation a thick layer of fibromuscular tissue develops that shield the underlying potential high-risk plaque, leading to its passivation (Fig. 21–14).[233,234] The long-term—5-year follow-up—OCT imaging data have shown complete scaffold resorption, and plaque sealing while IVUS analysis has showed plaque regression.[235,236]

Computational fluid dynamic studies performed in models reconstructed from OCT and x-ray imaging data have demonstrated that BRS implantation affects the local hemodynamic forces, as the protruded struts disturb flow, creating flow disturbances and recirculation zones behind the struts.[237] This creates a low ESS environment that promotes neointima proliferation which seals the underlying high risk plaques.[238] The developed neotissue appears to create a smooth luminal surface that normalizes the ESS. Therefore, the treated segment at long-term follow-up has a low-risk plaque phenotype (as all the high-risk lesions are covered by the developed neointima) and is exposed to a normal atheroprotective ESS environment.[239,240] These favourable imaging findings have attracted attention and, recently the PROSPECT ABSORB study has commenced (NCT02171065) that aims to investigate the potential role of ASBORB BVS in sealing future culprit lesions.

FUTURE DIRECTIONS

The future of intravascular imaging relies on the development of hybrid intravascular imaging modalities that would enable complete and comprehensive evaluation of plaque pathology and physiology. Advances in signal processing and the miniaturization of medical devices have enabled the design of hybrid-dual probe catheters that combine two imaging modalities with complementary strengths and permit simultaneous visualization of plaque morphology and bioogy.[241] Apart from the NIRS-IVUS catheter that has already been presented in previous sections and has applications in the clinical setting, several other prototypes have been recently introduced that are currently undergoing preclinical evaluation. These include the combined IVUS-OCT,[242-244] OCT-NIRS,[245] IVUS-IVPA,[246,247] OCT-NIRF,[248-251] IVUS-NIRF,[252,253] TRFS-IVUS,[51,52] and the combined three-probe NIRS-OCT-IVUS catheters (Fig. 21–15).[254] These modalities are anticipated to allow detailed evaluation of plaque characteristics and thus more precise assessment of the effect of new treatment on the compositional characteristics of the plaque, detection of high-risk vulnerable lesions that are prone

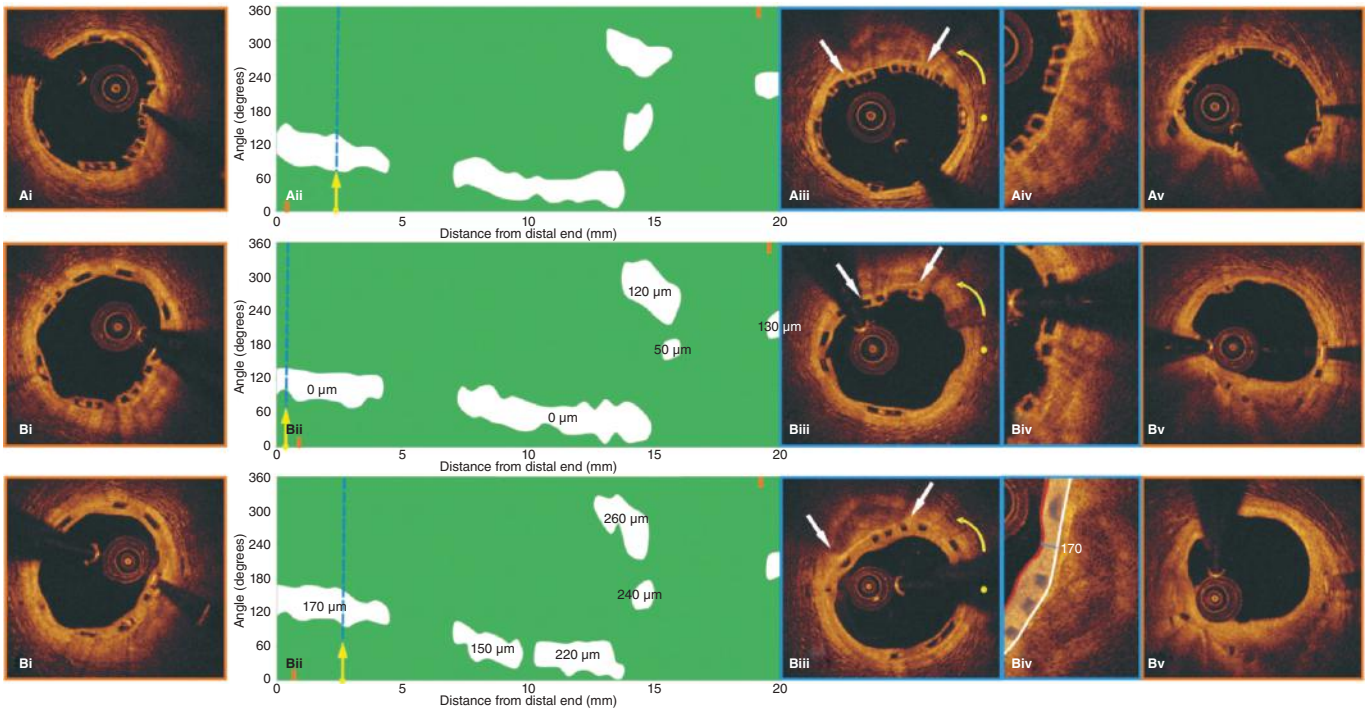

FIGURE 21–14. Spread-out plots of a scaffolded coronary segment at baseline at 6- and 24-month follow-up. The *x* axis represents the distance from the distal end of the scaffold, and the *y* axis represents the circumferential segment (angle) where the different plaque components are located. Fibrotic tissue is indicated with green and calcific with white. The orange markers, at the spread-out plots at baseline (*Aii*) and follow-up (*Bii, Cii*), correspond to the axial position of the metallic markers and are shown in panels *Ai, Bi, Ci* (proximal markers) and in panels *Av, Bv,* and *Cv* (distal markers). The blue dashed lines indicate the location of the frames shown in panels *Aiii, Biii,* and *Ciii.* The yellow spot in these panels denotes the zero-degree location in the spread-out scaffold plots and the *yellow arrow* the counterclockwise direction followed to evaluate the circumferential location of the detected tissues. The *white arrows* correspond to the lateral extremities of the detected calcific tissue. As is shown in *panels Aiii, Aiv, Biii, Biv, Ciii*, and *Civ*, the neointima (minimum thickness: 110 µm at 6 months and 210 µm at 24 months of follow-up, respectively) developed after scaffold implantation gradually increased and sealed the calcific tissue at follow-up. Reproduced with permission from Bourantas CV1, Serruys PW, Nakatani S, et al: Bioresorbable vascular scaffold treatment induces the formation of neointimal cap that seals the underlying plaque without compromising the luminal dimensions: a concept based on serial optical coherence tomography data. *EuroIntervention*. 2015 Nov;11(7):746-756.[234]

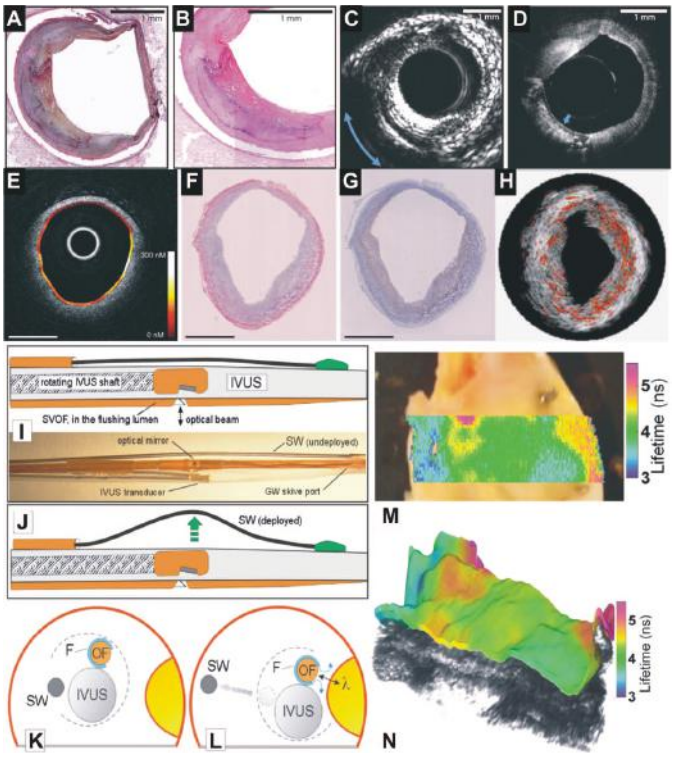

FIGURE 21–15. Hybrid intravascular imaging modalities. Output of the combined intravascular ultrasound–optical coherence tomography (IVUS-OCT) catheter. Panels (**A**) and (**B**) illustrate a histological cross-section obtained from a human coronary artery (stained with Movat's pentachrome and hematoxylin and eosin, respectively). A calcified superficial plaque spanning from 6 to 9 o'clock is noted. Panels (**C**) and (**D**) portray the corresponding IVUS and OCT images obtained during examination with a 4F hybrid IVUS-OCT system that allows simultaneous image acquisition and reliable assessment of plaque characteristics. Output of the combined OCT–near-infrared fluorescence (NIRF) imaging catheter (**E**). OCT illustrates an eccentric plaque extending from 2 to 10 o'clock, while NIRF imaging demonstrates increased inflammation (indicated with a white-yellow color). Hematoxylin and eosin staining of the corresponding histological cross section confirms the presence of an eccentric plaque (**F**) whereas immunohistochemistry shows an increased cathepsin B concentration within the plaque (**G**). Combined IVUS–intravascular photoacoustic (IVPA) imaging (**H**). IVPA enables detection of the lipid tissue (portrayed in an orange color) while IVUS allows assessment of the lumen and the plaque. Hybrid IVUS–time-resolved spectroscopy (TRFS) imaging (**I–N**). The catheter incorporates (1) a sheathed IVUS mechanical rotating probe, (2) a side-viewing optical fiber (SVOF/OF in views **K, L**) placed in a 0.7-mm water-flushing lumen that occupies the position of the IVUS monorail guidewire (GW), and (3) a steering wire (SW) that is connected to the distal end of the catheter and can be pushed forward to steer the device toward the luminal surface of the region of interest (**J, L**). Panels (M) and (N) portray the output of combined TRFS high resolution ultrasound imaging of a carotid atherosclerotic plaque. TRFS allows evaluation of the molecular composition of the superficial plaque (the red corresponds to fibrotic plaque, the yellow color to fibrolipid and the cyan to normal endothelium) (**M**). By overlaying the TRFS onto the ultrasound image, it is possible to coregister the intima biochemical features with the underlying plaque morphology and microstructure (**F**). **A-D, E-G, I-N**, reproduced with permission from Bourantas CV, Garcia-Garcia HM, Naka KK, et al: Hybrid intravascular imaging: current applications and prospective potential in the study of coronary atherosclerosis. *J Am Coll Cardiol*. 2013 Apr 2;61(13):1369-1378. **H**, reproduced with permission from Bourantas CV, Garcia-Garcia HM, Diletti R, et al: Early detection and invasive passivation of future culprit lesions: a future potential or an unrealistic pursuit of chimeras? *Am Heart J*. 2013 Jun;165(6):869-881.[241]

to progress and cause cardiovascular events, and evaluation of lesion severity and procedural planning. For example, the combined IVUS-OCT catheter carries a great clinical potential because IVUS can be used to plan stent implantation and OCT to evaluate the final results poststent implantation, and there is hope that it will constitute the ideal modality for guiding PCI in the future in complex cases. Whether these modalities will improve clinical outcomes especially in the BRS era is expected to be investigated by future studies.

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CHAPTER 22

MAGNETIC RESONANCE IMAGING AND COMPUTED TOMOGRAPHY OF THE VASCULAR SYSTEM

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Imaging of the vasculature has evolved greatly in the past 20 years. Although the current gold standard remains invasive x-ray angiography, noninvasive modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) are becoming routine for the evaluation of patients with vascular diseases. In many instances, either MRI or CT has replaced x-ray angiography as the imaging modality of choice in the assessment of patients with suspected vascular disease because of the ever-increasing image quality, the noninvasive application, the ease and comfort for patients, and the clinical versatility of both CT and MRI. In addition to evaluating the degree of luminal stenosis, MRI and CT can now noninvasively detect the presence and composition of atherosclerotic plaques in various arterial beds. This chapter provides a comprehensive and state-of-the-art overview of the clinical indications for MRI and CT in the evaluation of vascular diseases, focusing on both angiographic and plaque-based assessments. It also introduces emerging molecular imaging approaches for the assessment of disease activity.

ANGIOGRAPHY

TECHNIQUES/PHYSICS

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) can be divided into two categories: nonenhanced MRA and contrast-enhanced MRA (CE-MRA).[1] Nonenhanced MRA can be obtained by detecting the effect of blood flow on either the signal amplitude (time of flight [TOF]) or on the phase of moving protons (phase contrast [PC]). TOF angiography relies on differences in signal amplitude between in-slice stationary protons and protons in blood flowing into the slice. In-slice stationary protons become relatively saturated with repeated excitation pulses and produce low signal intensity, whereas inflowing blood protons have not experienced these excitation pulses, are not saturated, and generate high signal intensity. Two-dimensional (2D) or three-dimensional (3D) datasets can be acquired. Limitations of TOF imaging are long acquisition times and the need to position sections orthogonal to the direction of flow. In addition, slow flow or turbulent flow can lead to signal loss. PC angiography derives image contrast from differences in phases accumulated by stationary and moving spins in a magnetic field gradient. Phase data can be used to reconstruct velocity-encoded flow-quantification images or MRA images. With velocity-encoded imaging, phase amplitude is directly proportional to flow velocity, allowing for quantitative assessment of flow velocity and direction. This can assess flow and pressure gradients across stenoses in the carotid arteries, peripheral arteries, and renal arteries, as well as coarctation of the aorta. This technology also permits visualization of thoracic aortic dissection. However, clinical applications are hampered by the long acquisition times required for velocity-encoded imaging.

Other nonenhanced MRA sequences include electrocardiogram (ECG)-gated fast spin echo (FSE or turbo spin echo) and sequences based on steady-state free precession (SSFP). ECG-gated FSE has a shorter imaging time than TOF imaging and is sensitive to slow flow. It has therefore been used to assess peripheral and collateral vessels.[2] Image contrast with SSFP sequences stems from the T2/T1 ratio, which is high in blood compared to other tissues. SSFP sequences produce bright blood imaging without reliance on blood inflow. Both arteries and veins have high signal intensities with balanced SSFP sequences; therefore venous signal must be nulled, for example, by saturation bands or spin labeling. SSFP sequences are increasingly being used to evaluate the thoracic aorta and coronary arteries.

First-pass CE-MRA with gadolinium-based contrast agents has gained widespread acceptance because of shorter acquisition times compared to noncontrast MRA. The strong increase of luminal signal intensity after intravenous injection of T1-shortening contrast agents such as gadolinium chelates allows for fast angiographic acquisitions with 3D gradient echo sequences.[3] These techniques give an accurate evaluation of intra- and extracranial, thoracic, abdominal, and peripheral vessels. In many centers, CE-MRA has widely replaced conventional x-ray angiography for the evaluation of peripheral arterial vessels.[4] However, a disadvantage of CE-MRA is the association between gadolinium-based contrast agents and nephrogenic systemic fibrosis.[5] Nephrogenic systemic fibrosis is a rare but life-threatening condition involving the deposition of collagen in the skin and other organs. The etiology of this condition is not fully understood, but gadolinium-based contrast agents have been associated with its development in patients with renal failure (eGFR < 30 mL/m^2). Different gadolinium contrasts agents have been divided into low, medium, and high risk for causing this condition by the European Medicines Agency. High-risk agents include the linear chelates of gadolinium, and these are contraindicated in patients with an eGFR less than 30 mL/m^2, acute renal impairment, and perioperative liver transplantation, as well as in neonates. Low-risk agents include newer cyclic preparations of gadolinium. These are considered safe in patients with an eGFR of more than 30 mL/m^2, and they can be used in patients with an eGFR below this threshold if the benefit of undergoing contrast MRI outweighs the risk. The volume of contrast agent used in this case should be minimized and repetition within 7 days avoided.[6] In addition, recent research has identified gadolinium deposition in the brain and bones of patients who have undergone contrast enhanced MR, although the clinical implications of this finding remain unclear.[7]

Technical advances, such as synchronization of the arrival of contrast agent with magnetic resonance (MR) acquisition,[8] moving bed technology for multistation studies,[9] parallel imaging,[10] and k-space sharing methods[11] have dramatically reduced acquisition times and paved the way for whole-body MRA. Whole-body MRA is well suited for repeated clinical examinations in patients with systemic diseases such as vasculitis or atherosclerosis. Whole-body MRA (Fig. 22–1) is feasible and accurate for simultaneous evaluations from the carotid down to lower limb arteries.[12] Compared with invasive angiography, the sensitivity and specificity of whole-body MRA for the detection of significant arterial stenosis were both 96%, similar to the accuracy of single-station MRA.[13] However, intracranial and coronary artery imaging still requires dedicated acquisitions. MR scanners at high field strength 3.0 Tesla [T] are now widely available, but have both advantages and drawbacks for angiographic studies. On one hand, the intrinsic higher signal-to-noise ratio of tissues at 3 T allows shorter scan times and improved spatial resolution. On the other hand, higher field strengths increase field inhomogeneity, cause disturbances in the electrocardiogram and increase acoustic noise and susceptibility artefacts.[14] Until recently, these artifacts rendered SSFP imaging particularly challenging, although this has recently been improved with the development of advanced shimming and parallel imaging techniques. Further research aimed at improving image quality at a wide range of field strengths (≥ 3.0 T) is therefore ongoing. In the future, ECG and respiratory gating will also become less important for cardiovascular imaging as new free breathing techniques are developed.[15]

FIGURE 22–1. Whole-body magnetic resonance angiography using coronal three-dimensional, T1-weighted, gradient recalled echo, fast low-angle shot imaging. Images were obtained with a rolling table platform and five contiguous stations in a 31-year-old volunteer. The arterial signal is improved with venous compression. Modified with permission from Herborn CU, Ajaj W, Goyen M, et al: Peripheral vasculature: whole-body MR angiography with midfemoral venous compression--initial experience. *Radiology*. 2004 Mar;230(3):872-878.

In summary, recent technical advances in MR technology have dramatically reduced acquisition times and allowed for larger spatial coverage. These advances have led to more widespread adoption of MRA for the clinical assessment of the cardiovascular system.

Computed Tomography Angiography

CT technology has advanced rapidly since its inception in the 1970s. CT acquires a 3D volume of data that can then be manipulated using postprocessing software. In step-and-shoot mode, the scanner acquires a single data set before moving, where as in helical (spiral) mode the scanner moves constantly as it rotates. Helical scanning is now used for most applications, initially with single-detector CT and now with multidetector CT (MDCT) systems.[16] Wide-volume multidetector scanners are capable of acquiring a longer length of data in each rotation, thus reducing scanning time and potential motion artifact while increasing coverage.

CT angiography (CTA) involves the injection of iodinated contrast agents to opacify the blood vessels. A variety of iodinated contrast agents are now available with different chemical compositions and iodine concentrations. Care must be taken using iodinated contrast in patients with a history of contrast allergy. For such patients, if the benefit of the scan outweighs the risk, then the scan should be performed under close medical supervision and monitoring with rapid access to treatments for anaphylaxis. Nonionic, low, or isoosmolar iodinated contrast should be used for high-risk patients. Pretreatment with steroid and antihistamine can be considered; however, the evidence for this is uncertain. Renal impairment is a relative contraindication to the use of iodinated contrast, which may be nephrotoxic. ECG gating allows acquisition of CT data in diastole when the heart is still. It is essential for coronary artery imaging and is also useful for imaging the thoracic aorta where motion artifact may be mistaken for an aortic dissection. In retrospective ECG gating, there is radiation exposure throughout the cardiac cycle, and individual phases of the cardiac cycle are reconstructed from these data. Newer prospective ECG gating involves radiation exposure only at predefined portions of the cardiac cycle, and thus substantially reduces radiation dose.

The resolution of current generations of CT scanners is excellent (0.35–0.4 mm^3 with 64-MDCT). More recent advances in CT hardware include wide-volume detectors, dual source systems, new detectors, and faster gantry rotation times. Advances in CT software include iterative or model-based reconstruction algorithms, "partial scan" reconstructions, tube current/voltage optimization, and dose modulation. Dual-energy imaging harnesses the difference in tissue attenuation between images acquired with two different energy spectra. Dual-energy images can be acquired coincidentally with a dual-source scanner or with

two separate acquisitions with a single-source scanner. This can be used to provide additional information on material composition and potentially reduce the effect of calcium blooming artifacts.[17] Ongoing advances in CT imaging means that radiation doses will continue to fall. This is an important concern because of the association between cumulative radiation exposure and the lifetime risk of cancer.[18]

CTA is therefore a rapid and widely available noninvasive technique to assess the cardiovascular system, offering excellent spatial resolution. However, these benefits must be weighed against the risks of radiation exposure, and all attempts possible should be made to keep radiation dose "As Low As Reasonably Achievable," or ALARA.

PRACTICAL APPROACH

CT and MRI scanners are now widely available in the vast majority of hospitals in the developed world. Often these are located in radiology departments, so that close collaboration is required between radiologists and cardiologists as well as vascular surgeons, cardiothoracic surgeons, and pulmonologists. CT and MRI are both performed in the outpatient and inpatient settings although the shorter duration of CT scans and the ability to monitor patients closely within the scanner make it more suitable for imaging in emergency situations. Although emergency imaging is possible with MRI, this is complicated by the need for MRI-compatible monitoring and life-support equipment. Prior to CT or MRI, patients should be screened for potential risk for allergy or contrast-induced nephropathy as discussed above. In order to perform contrast-enhanced imaging, an intravenous catheter should be inserted, ideally into an antecubital fossa vein.

Magnetic Resonance Imaging

Prior to entering the restriction zone around the MRI scanner, patients should be screened for potential contraindications to MRI scanning such as the presence of orbital metal foreign bodies or implanted devices, stents, or clips that are MRI incompatible. The patient is positioned on the scanner bed with the receiver (+/– transmit) coil positioned over the area to be imaged. Appropriate coil selection and positioning can improve image signal-to-noise ratio. Because of the high acoustic noise of most MRI sequences, ear plugs and/or headphones may be required. The patient can also be provided with an alert buzzer to allow them to contact staff if required. If cardiac images are to be acquired, then ECG leads are also attached.

Computed Tomography Imaging

Patients are positioned on the scanner bed, which moves through the scanner gantry. If cardiac images are to be acquired, ECG leads are also attached. Initial low-dose 2D images (called "localizers") are acquired, which are used to plan the scan. The scanner tube voltage and current should be optimized to the individual patient in order to obtain diagnostic images at the lowest possible radiation dose. Similarly the scan range should cover only the area of interest. Depending on the indication, both noncontrast, contrast-enhanced, and delayed images can be acquired. Contrast-enhanced images can be obtained using either a specific time delay after the contrast injection or using bolus tracking, where the attenuation density in a specific region must reach a target value before the scan commences. Manual triggering of contrast-enhanced images may also be used, particularly for patients with challenging contrast hemodynamics. Specifics of imaging individual vascular beds are discussed further below. Images are reconstructed using filtered back projection, iterative, or model-based reconstruction algorithms, and a 3D volumetric data set is produced for assessment.

Having reviewed the different imaging approaches to noninvasive angiography, the subsequent sections will focus on how these can be applied to different vascular territories within the body: the carotid arteries, the aorta, the peripheral arteries, and the pulmonary arteries.

CAROTID ARTERIES

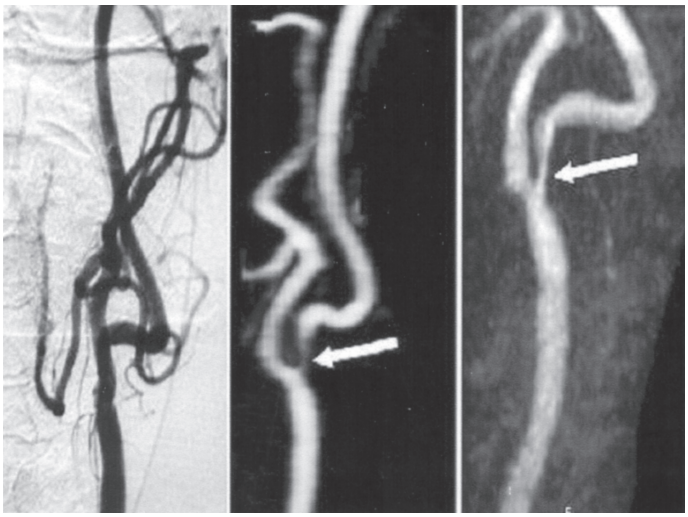
Stroke represents the third leading cause of death in the United States, accounting for 600,000 cases each year. The risk of stroke associated with carotid stenosis has been evaluated in several trials. The North American Symptomatic Carotid Endarterectomy Trial (NASCET),[19] the European Carotid Surgery Trial (ECST),[20] and the Veterans Affairs Trial (VAT)[21] demonstrated that carotid endarterectomy reduced recurrent stroke in symptomatic patients with severe stenosis (70%–99%) of the ipsilateral carotid artery (see Chap. 95). Therefore, carotid endarterectomy is recommended if the morbidity of surgery is reasonably low (< 6%). Symptomatic patients with moderate stenosis (50%–69% in NASCET) still benefited from surgery, although the overall gains were more modest. For asymptomatic patients with severe carotid stenosis, carotid endarterectomy significantly reduced the 5-year stroke rate in selected subgroups with the highest risk. Carotid artery stenting is an alternative approach for patients at high surgical risk, in whom outcomes are similar after 10 years of follow-up.[22,23] In most of the original surgical trials, intra-arterial digital subtraction angiography (DSA) was the gold standard assessment of stenosis severity. However, the risk of thromboembolic complications from DSA means that noninvasive imaging modalities are now favored, such as Doppler ultrasonography, MRA, and CTA.[24]

Magnetic Resonance Angiography of Carotid Arteries

MRA has emerged as one of the noninvasive methods of choice for carotid imaging, providing accurate assessment of carotid stenosis without the use of ionizing radiation and the problem of calcium blooming observed with CT. Before the advent of CE-MRA, TOF acquisitions were used to image the carotid arteries, demonstrating good agreement with DSA.[25] However, TOF acquisitions are sensitive to turbulent flow, can overestimate stenoses, and have long acquisition times, increasing potential motion artifacts. Although TOF MRA remains useful for patients with contraindications to MRI contrast, such as renal insufficiency, CE-MRA has become the technique of choice for imaging the carotid arteries. Image acquisition needs to be synchronized with the arterial phase of the contrast bolus in order to prevent venous enhancement. Unlike TOF MRA, vascular contrast is less sensitive to turbulent flow, particularly in cases of high-grade stenosis; moreover, a large volume from the aortic arch to the circle of Willis (Fig. 22–2) can be obtained in less than 1 minute. CE-MRA demonstrates high sensitivities and specificities for the evaluation of carotid artery stenosis (Table 22–1) and is currently the most accurate noninvasive imaging for carotid stenosis.[26,27] Although CE-MRA offers two to three times lower spatial resolution than DSA or CTA, this is likely to improve with new technologic developments, such as high field strengths,[28] parallel imaging techniques, and the use of blood-pool contrast agents that remain in the circulation longer.[29]

Computed Tomography Angiography of Carotid Arteries

With the advent of MDCT, the whole length of the carotid artery, from the aortic arch to the circle of Willis, can be imaged with high spatial resolution in a true arterial phase, limiting adjacent venous enhancement (Fig. 22–3). CTA demonstrates higher sensitivities and specificities than TOF MRA, but lower than those for CE-MRA for the evaluation of the degree of carotid stenosis (see Table 22–1).[30] Although spatial resolution is higher than for MRA, the lower specificity of CTA can be explained by the difficulty in evaluating the degree of



A B C

FIGURE 22–2. Severe stenosis (*arrows*) of left internal carotid artery in a 72-year-old patient evidenced with contrast-enhanced magnetic resonance angiography (**B**) and 3D time-of-flight magnetic resonance angiography (**C**). Stenosis was not detectable with conventional digital subtraction angiography in this projection (**A**). Reproduced with permission from Anzalone N, Scomazzoni F, Castellano R, et al: Carotid artery stenosis: intra-individual correlations of 3D time-of-flight MR angiography, contrast-enhanced MR angiography, conventional DSA, and rotational angiography for detection and grading. *Radiology*. 2005 Jul;236(1):204-213.[27]

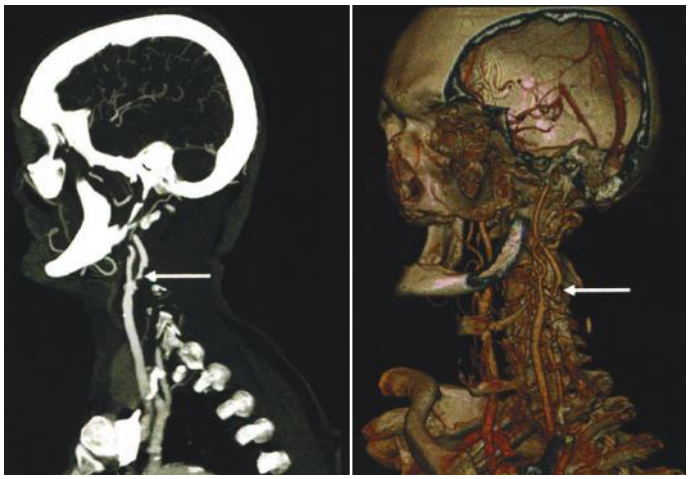
luminal stenosis in the presence of extensive calcification. Dual-energy imaging might potentially reduce this calcium "blooming" artifact and aid assessment of plaque composition. CTA can also be used to assess carotid artery stents for stent integrity and in stent restenosis.[31]

In summary, MRA and CTA of the carotid arteries are readily accessible, and their accuracy is now considered sufficient to outweigh the risks associated with invasive DSA. A combination of screening with Doppler ultrasound followed by MRA or CTA in patients with hemodynamically significant stenosis or poor ultrasound image quality has become clinically routine.

AORTA

Aortic Dissection

Aortic dissection is a life-threatening disease in which early diagnosis and treatment is critical for survival (see Chap. 93).[32] The yearly incidence of aortic dissection is 10 to 20 cases per million. Misdiagnosis



A B

FIGURE 22–3. Contrast-enhanced computed tomography of the supra-aorta and intracranial vessels. Maximum-intensity projection (**A**) and volume-rendering technique (**B**) both reveal a complex ulcerated atherosclerotic plaque of the proximal right internal carotid artery associated with a high-grade stenosis (*arrows*). Used with permission from B. Ertl-Wagner, Ludwig-Maximilians-University, Munich, Germany.

can have fatal consequences because untreated patients with type A aortic dissection have mortality rates as high as 25% at 24 hours and 75% by 2 weeks.[33] Retrograde invasive aortography was the first accurate method for the diagnosis of aortic dissection. It requires the presence of an intimal flap and two distinct lumens, with an overall sensitivity of 88% and specificity of 94% for the detection of aortic dissection.[34,35] Major drawbacks are the time required for the procedure and the complications associated with instrumenting an already damaged aorta. Invasive angiography has now been superseded by noninvasive imaging techniques that have greatly improved the early diagnosis and management of aortic dissection.

CTA is now the mainstay for the diagnosis of acute aortic syndromes. It is a rapid, noninvasive diagnostic test that is routinely available on a 24-hour basis. An initial nonenhanced CT is performed in order to identify intramural hematoma that would otherwise be obscured by intravenous contrast. Intramural hematoma appears as a crescent of high attenuation within the wall of the aorta or, less often, as localized thickening of the aortic wall with internal displacement of intimal calcifications. CTA using iodinated contrast can then be performed. If aortic root or thoracic aorta involvement is suspected, ECG-gated images of the thoracic aorta should be acquired, in order to minimize

TABLE 22–1. Magnetic Resonance Angiography and Computed Tomography Angiography of the Carotid Arteries[a]

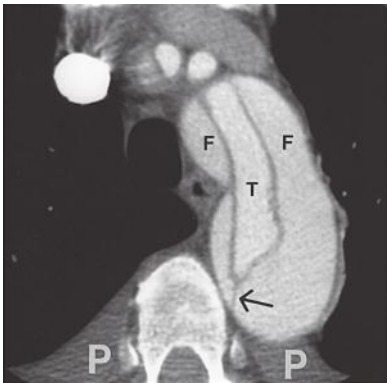
References	Technique	Patients (No.)	Sensitivity (%)	Specificity (%)
Wardlaw et al 2006[24]	TOF MRA	2541	88	84
Debrey et al 2008	TOF MRA	1422	91	88
Debrey et al 2008	CE-MRA	1422	99	100
Wardlaw et al 2006[24]	CE-MRA	2541	94	93
Menke et al 2009	CE-MRA	974	94	93
Wardlaw et al 2006[24]	CTA	2541	76	94

[a]Sensitivity and specificity of MRA and CTA for the detection of significant carotid artery stenoses (> 70%). The table presents results of a selection of meta-analyses in comparison to conventional angiography.

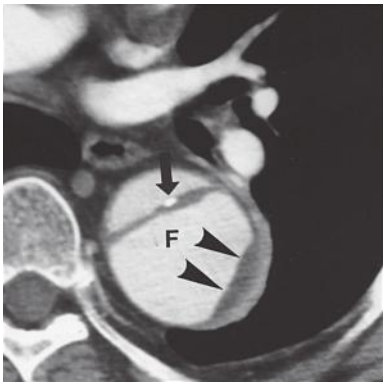
Abbreviations: CE-MRA, contrast-enhanced magnetic resonance angiography; CTA, computed tomography angiography; MRA, magnetic resonance angiography; TOF MRA, time-of-flight magnetic resonance angiography.

motion artifacts that can mimic the presence of dissection.[36] CTA has a sensitivity of 83% to 95% and a specificity of 87% to 100% for the diagnosis of acute aortic dissection.[37] It can visualize the intimal flap, extent of dissection, patency of the false lumen, size of the aorta, branch vessel involvement, presence of pericardial fluid, and evidence of end-organ ischemia, and it can potentially identify other unexpected causes for the patient's symptoms. Limitations of CTA for the evaluation of aortic dissection include the inability to obtain hemodynamic information, as may be necessary when there is concomitant aortic regurgitation.

MRA is an accurate and reliable alternative imaging technique for the diagnosis of aortic dissection. Acquisition times have been significantly shortened by implementation of faster and stronger gradients in recent MR systems. The thoracic aorta and major aortic branches can now be imaged in a few seconds with 3D CE-MRA[38] (Fig. 22–4) or in a few minutes using noncontrast bright-blood sequences such as steady-state gradient echo sequences. As with invasive angiography, the diagnosis of aortic dissection is based on visualization of an intimal flap and two distinct aortic lumens. Velocity-encoding sequences can help to differentiate true and false lumens and to determine whether aortic side branches are perfused by the true or false lumen. Black-blood sequences offer high spatial and contrast resolution and are well suited for the analysis of the aortic wall. They can identify intramural aortic hematoma as a crescentic aortic wall thickening (≥ 5 mm) without intimal flap or tear. Of all the imaging techniques, MRI has the highest sensitivity and specificity for detecting aortic dissection (98%).[39] However, the use of MRI for the detection of aortic dissection is limited by its lack of availability in urgent situations and the difficulty in monitoring and managing critically ill patients in the MRI scanner.



A



B

FIGURE 22–4. Contrast-enhanced computed tomography images of aortic dissection. Images from a 69-year-old woman demonstrate an acute dissection at the level of the aortic arch (**A**). The outer false lumen (F) wraps around the true lumen (T). (**B**) Images from a 59-year-old man with chronic dissection of the thoracic aorta. Eccentric flap calcification is present along the true lumen side of the flap. The false lumen contains thrombus (*arrowheads*) and is larger than the true lumen. Reproduced with permission from LePage MA, Quint LE, Sonnad SS, et al: Aortic dissection: CT features that distinguish true lumen from false lumen. *AJR Am J Roentgenol*. 2001 Jul;177(1):207-211.[37]

Transesophageal echocardiography, like CTA and MRA, has demonstrated high accuracy for the diagnosis of aortic dissection and is an alternative diagnostic technique.[40] Because there is a clear time-dependent mortality rate in patients with aortic dissection who do not receive treatment, decisions about which imaging technique to use should take into account availability in an emergency.

Aortic Aneurysm

Thoracic Aortic Aneurysm Thoracic aortic aneurysms (TAAs) are typically discovered in asymptomatic patients (see Chap. 93), with symptoms occurring in the setting of either a complication of the disease (ie, rupture or dissection) or when these complications are imminent.[32] The most frequent etiologies of TAAs include degenerative aneurysms, bicuspid aortic valve disease, and aneurysms associated with connective tissue disease (eg, Marfan syndrome). Patients with bicuspid aortic valve disease or connective tissue disease should undergo screening at regular intervals for the presence of associated aortopathy. The risk of complications depends mainly on TAA diameter, location, and etiology. Thresholds for preventive surgical interventions have been defined accordingly. When the diameter of the ascending aorta is more than 55 mm for degenerative aneurysm and more than 50 mm for aneurysm associated with bicuspid aortic valve or Marfan disease, surgery is recommended. These thresholds can be lowered in case of rapid expansion of TAA (> 5 mm/y) or in select connective tissue diseases (eg, Loeys-Dietz syndrome). Expression of aortic diameters indexed to body surface area is preferred, in particular when body surface area is outside the normal range.

CTA and 3D CE-MRA perform equally well in depicting the thoracic vascular anatomy, particularly the relationship of aortic aneurysms to branch vessel origin and the extent of aneurysm.[41] Acquisitions should be performed in diastole and with breath holding to limit motion artifacts in the ascending aorta. CT can combine noninvasive evaluation of coronary arteries and imaging of the thoracic aorta. 3D CE-MRA has demonstrated a diagnostic accuracy of 100% for assessing the size and extent of the aneurysm and its relationship to aortic branches, compared with conventional angiography and surgical exploration.[42] A disadvantage of MRA is the inability to assess calcification at operative sites. CE-MRA should be complemented by cross-sectional black-blood imaging of the aortic wall to determine the presence of an intraluminal thrombus. In addition, the presence of inflammation, such as in mycotic aneurysm or aortitis, might be suspected when delayed enhancement is detected in the aortic wall and surrounding soft tissues. The aortic valve is frequently involved in ascending aortic aneurysms. Cine SSFP sequences of the valve can help to determine whether the aortic valve is bicuspid and either stenotic or regurgitant. Before surgical intervention involving the descending aorta is undertaken, care should be observed to identify the origin of the artery of Adamkiewicz with MRA to avoid spinal complications after surgery.[43] Both MRI and CT can be used to monitor the size of thoracic aneurysms and dissections following surgical repair or conservative management. In these scenarios, the need for repeat imaging often favors MRI, given the absence of ionizing radiation.

Abdominal Aortic Aneurysm The abdominal aorta is the most frequent arterial location of aneurysms, with abdominal aortic aneurysms (AAA) usually being defined as a maximal aortic diameter of 30 mm or more. The prevalence of asymptomatic AAAs in men and women over the age of 60 years is evaluated at 4% to 8% and 0.5% to 1.5%, respectively, and increases with age. AAAs share common risk factors with

atherosclerosis, except diabetes. At least 15,000 deaths in the United States are caused by ruptured AAAs annually. Once an AAA ruptures, mortality is high (80%–90%). In contrast, elective repair is associated with a low rate of complications (2%–3%). Screening strategies have therefore been developed to identify patients with large AAAs (> 55 mm in diameter), who might benefit from elective repair. Ultrasonography remains the most cost-effective imaging technique for detection and follow-up of abdominal AAA expansion. Main indications for CTA and MRA are preoperative evaluation of AAAs and follow-up of patients who have had open or endovascular repairs. Preoperative assessment of AAAs before open or endovascular repair should include determination of the maximum transverse diameter; the relation of the AAA to the renal arteries; the length, diameter, and angulation of the normal-caliber aorta below the renal arteries before the aneurysm (ie, the infrarenal neck); the presence of iliac or hypogastric aneurysms; and serious occlusive disease in the iliac or renal arteries.

CTA represents the preferred imaging modality for preoperative evaluation of AAAs before open or endovascular surgery because it allows precise assessment of each of the aforementioned parameters. It provides a volumetric acquisition that allows for multiplanar and 3D reconstructions to be generated perpendicular to the long axis of the aneurysm, resulting in greater accuracy of the measurements of aneurysmal size.[44] As with other indications of CT, the limitations of CTA are the need for ionizing radiation and iodinated contrast. In addition, extensive calcification can preclude accurate diameter determination of the iliofemoral arteries.

MRI represents an alternative to CTA for the preoperative evaluation of AAA, particularly in cases of renal insufficiency or advanced arterial calcification, although attention should be paid to the risk of developing nephrogenic systemic fibrosis following gadolinium administration in patients with the former. Angiography can be obtained either with nonenhanced TOF sequences that require long acquisition times or, more rapidly, with CE-MRA using fast gradient echo sequences (Fig. 22–5). Accurate dimensions of the aneurysm can be determined with multiplanar reconstructions,[45] and MRA can also assess extension into the iliac and renal arteries and the presence of concomitant renal artery stenosis. Delayed axial acquisitions can be used to evaluate for intraluminal thrombus.[46] CT and MRI can also be used to assess outcomes following endovascular repair, in particular for evidence of endoleak (persistent blood flow within the aneurysm sac), which is a common complication. One approach is to perform CT and abdominal x-ray imaging at 1, 6, and 12 months postrepair and then annually. However, this involves substantial cumulative radiation exposure and repeated iodinated contrast exposure. More recent protocols therefore recommend the increased use of ultrasound rather than CT; MRA can be considered as an alternative to CT when ultrasound assessment is nondiagnostic.[47]

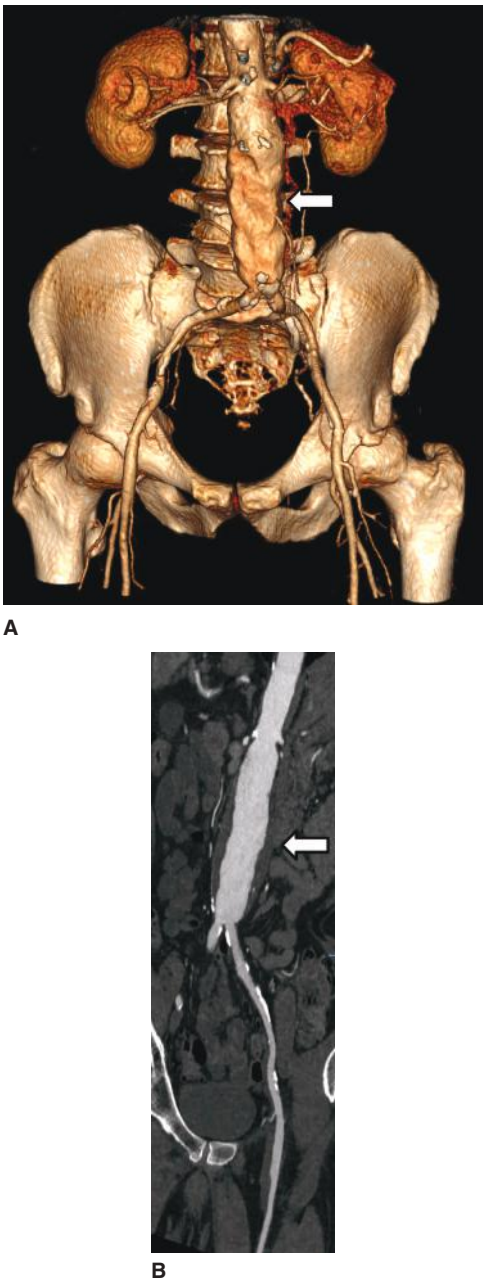


FIGURE 22–5. Contrast-enhanced computed tomography angiogram from an asymptomatic 65-year-old man with an infrarenal abdominal aortic aneurysm with mural thrombus. (**A**) Three-dimensional reconstruction and (**B**) curved planar reconstruction of the aorta to the femoral artery. Used with permission from M.C. Williams, Royal Infirmary of Edinburgh and University of Edinburgh, Edinburgh, United Kingdom.

PERIPHERAL VESSELS

The most common initial investigation in patients presenting with suspected peripheral vascular disease is the ankle brachial pressure index. This is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery. An ankle brachial pressure index of 0.90 or less should then prompt further investigation to confirm a diagnosis of peripheral artery disease. This is commonly performed with either CT or MRA[48] (see Chap. 96).

Magnetic Resonance Angiography of Peripheral Vessels

MRA is indicated for the preoperative evaluation of patients with lower limb ischemia. Similar to invasive angiography, MRA can depict the location and degree of stenosis of the peripheral arteries. TOF angiography was the first technique used to evaluate the peripheral arteries,[49] but has been supplanted by CE-MRA owing to shorter acquisition times (a few seconds) and greater accuracy with reported sensitivities of 96% to 98% and a specificity of 96% for the detection of significant stenoses (Table 22–2).[50] The high degree of agreement between MRA and conventional angiography has led to surgical planning based on MRA alone (Fig. 22–6). CE-MRA is also suitable for the evaluation of lower extremity bypass grafts and has been found to be 100% sensitive and specific in this setting.[51] For CE-MRA, the beginning of the acquisition should be perfectly synchronized with the arrival of the contrast bolus to avoid venous enhancement.

TABLE 22–2. Magnetic Resonance Angiography and Computed Tomography Angiography of the Peripheral Arteries[a]

References	Technique	Patients (No.)	Sensitivity (%)	Specificity (%)
Jens et al 2013	CE-MRA	1404	93	94
Menke et al 2010	CE-MRA	1022	85	96
Koelemay et al 2001	CE-MRA	1090	94	90
Jens et al 2013	CTA	673	96	95
Met et al 2009	CTA	957	95	96

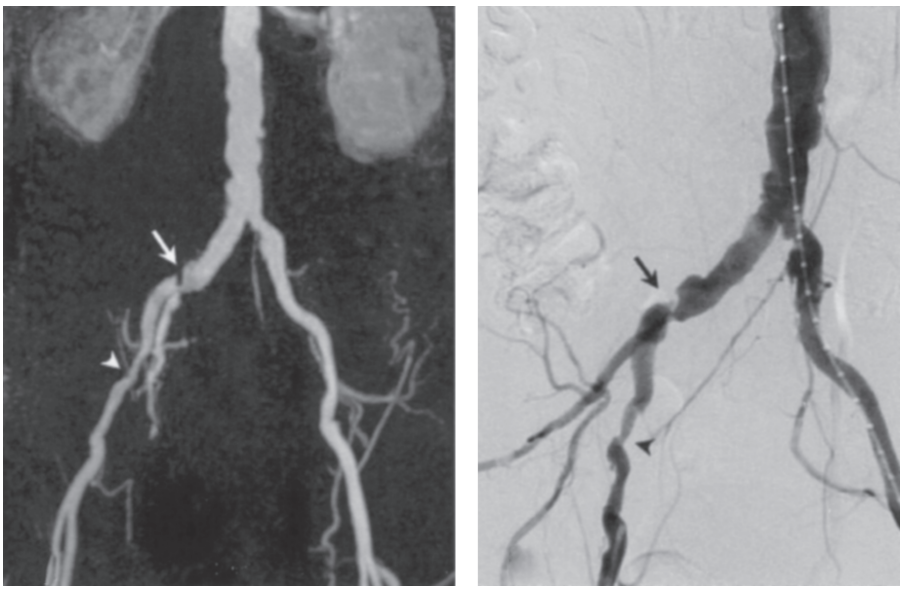
[a]Sensitivity and specificity of magnetic resonance angiography and CTA for the detection of significant stenoses of peripheral arteries (> 50%). The table presents results of a selection of meta analyses in comparison to conventional angiography.

Abbreviations: CE-MRA, contrast-enhanced magnetic resonance angiography; CTA, computed tomography angiography.

Early detection of renovascular disease has been previously hampered by the lack of an adequate noninvasive diagnostic modality. CTA and CE-MRA were found to be more accurate than ultrasound scanning or captopril renal scintigraphy for the diagnosis of renal artery stenosis.[52] Sensitivity and specificity values for the diagnosis of renal artery stenosis with CE-MRA range from 82% to 100% and 64% to 100%, respectively. In addition, PC-MRA also provides functional information such as the velocity profile of renal arterial flow.[53] MRA can also be used to image the splanchnic vessels; in particular CE-MRA, and true fast imaging with steady-state precession (true-FISP) provide excellent spatial resolution and signal-to-noise.[54,55]

Computed Tomography Angiography of Peripheral Vessels

The diagnostic accuracy of CTA for the evaluation of peripheral vessels compares well with MRA and invasive angiography. Shorter acquisition times, thinner slices, and higher spatial resolution have enabled rapid scanning of the whole vascular tree with small volumes of iodinated intravenous contrast (Fig. 22–7). The main clinical indications of CTA for imaging the lower extremities include the evaluation of arterial and aneurysmal disease, patency and integrity of bypass grafts, traumatic arterial injury, and acute ischemia.[56] More recently, CTA of the peripheral vasculature has been widely incorporated into the assessment of patients considered for percutaneous valve replacement (eg, transcatheter aortic valve replacement [TAVR]) or other percutaneous procedures.[57] Here, it can assess whether peripheral access is feasible but also help to measure the aortic valve annulus, the height of the coronary arteries above the valve, and the degree of calcification in the left ventricular outflow tract. Studies using CTA in peripheral vascular disease report sensitivity and specificity rates of greater than 95% for the detection of stenosis (see Table 22–2).[58] Once more this diagnostic accuracy is limited in the presence of severe and diffuse calcifications,[59] although CTA seems of particular use in the evaluation of calf vessels of patients with proximal occlusions, outperforming conventional



A B

FIGURE 22–6. A 67-year-old man suffering from intermittent claudication. Both contrast-enhanced magnetic resonance angiography (**A**) and digital subtraction angiography (**B**) show significant stenosis in the right common iliac artery (*arrow*) and in the right external iliac artery (*arrowhead*). Reproduced with permission from de Vries M, de Koning PJ, de Haan MW, et al: Accuracy of semiautomated analysis of 3D contrast-enhanced magnetic resonance angiography for detection and quantification of aortoiliac stenoses. *Invest Radiol*. 2005 Aug;40(8):495-503.

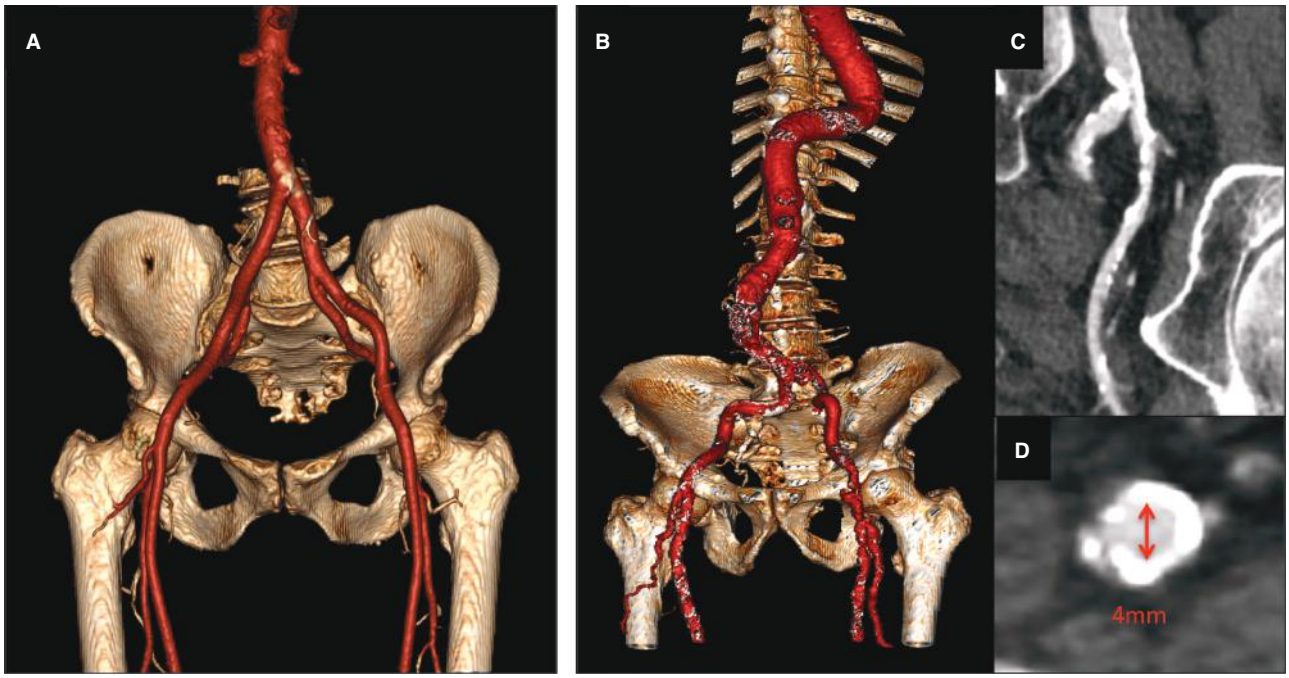


FIGURE 22–7. Computed tomography angiography of the peripheral vasculature in two patients being considered for transcatheter aortic valve replacement (TAVR). Maximum intensity projections of the vessels are displayed in relation to the bony structures of the pelvis. A 75-year-old man with good caliber peripheral vessels and minimal calcification (**A**) was felt to have suitable peripheral vessels and underwent successful TAVR using the femoral approach. By contrast a 68-year-old man was found to have small-caliber vessels (minimum 4.5 mm) with severe tortuosity and extensive near-circumferential calcification on a maximum intensity projection (**B**) and on angiographic images in the long-axis (**C**) and short-axis (**D**) views of the vessel. He was felt not suitable for a peripheral approach and instead underwent transaortic TAVR. Used with permission from M.R. Dweck and M.C. Williams, Royal Infirmary of Edinburgh and University of Edinburgh, Edinburgh, United Kingdom.

invasive angiography.[60] For the evaluation of renal and mesenteric arterial stenoses, the diagnostic accuracy of CTA is similar to that MRA.[52]

PULMONARY ARTERIES

Although pulmonary x-ray angiography is the gold standard for the diagnosis of pulmonary embolism (PE), it is invasive, can yield false-positive results, and is associated with a 1% risk of major procedural complications and a mortality of 0.5%.[61] It is now rarely performed in most centers. Instead a variety of noninvasive tests are preferred, including CTA and MRA, alongside clinical probability scores, plasma D-dimer concentrations, lung scintigraphy (ventilation/perfusion), and compression venous ultrasonography of the legs (see Chap. 109).

Computed Tomography Angiography of Pulmonary Arteries

CT pulmonary angiography (CTPA) is now the mainstay for the diagnosis of PE in many centers. CTPA (Fig. 22–8) has been proven to be an accurate, safe, noninvasive, rapid, and cost-effective technique for the direct detection and demonstration of intraluminal PE.[62,63] In addition to the identification of pulmonary artery thrombus, CTPA can also provide information on secondary right heart strain.[64] The sensitivity of spiral CT is on the order of 90% for central, lobar, or segmental PE (Table 22–3). The advent of MDCT provides the ability to analyze subsegmental PE, although the clinical importance of this finding remains uncertain.[65] Current guidelines for the diagnosis of PE recommend CTPA alongside clinical probability assessment and D-dimer measurement.[66,67] Low- or intermediate-risk patients should undergo D-dimer testing in order to avoid unnecessary CTPA, whereas high-risk or hemodynamically unstable patients should undergo direct imaging. Patients with a negative CTPA and clinical suspicion of venous thrombosis can be considered for compression venous ultrasonography. CT venography is no longer recommended because of the significant dose of radiation involved and lack of additional value compared to ultrasound.[67] More recently, dual-energy CT assessments of lung perfusion have demonstrated potential in improving the diagnosis of acute and chronic PE.[68,69] However, the utility of these novel techniques will need to be balanced against the added radiation exposure.

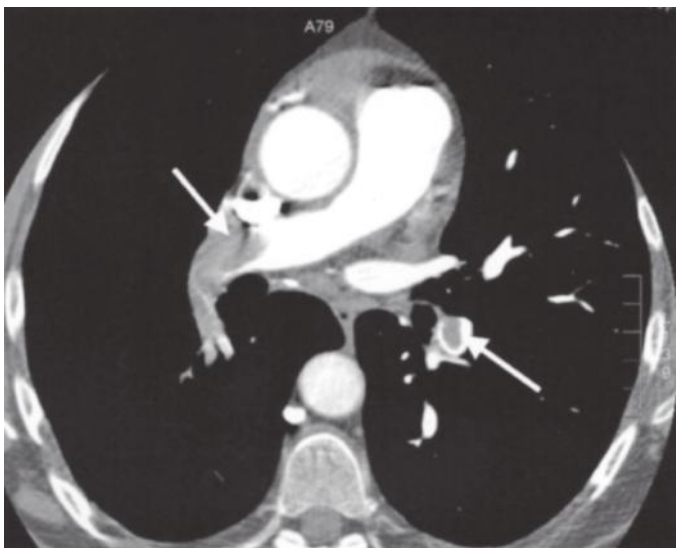


FIGURE 22–8. Pulmonary computed tomography angiography (CTA) acquired with a 16-detector computed tomography scanner in a 61-year-old woman with a high clinical probability of pulmonary embolism. CTA reveals large thromboembolic clots (*arrows*) on both sides confirming a massive pulmonary embolism. Used with permission from G. Le Gal, University Hospital, Brest, France.

TABLE 22–3. Magnetic Resonance Angiography and Computed Tomography Angiography of the Pulmonary Arteries[a]

References	Technique	Patients (No.)	Sensitivity (%)	Specificity (%)
Pleszewski et al 2006	MRA	48	82	100
Ohno et al 2004	MRA	48	83	97
Oudkerk et al 2002	MRA	118	77	98
Stein et al 2006[63]	CTA	824	83	96
Stone et al 2003	CTA	25	57	94
Perrier et al 2001	CTA	299	70	91

[a] Sensitivity and specificity of MRA and CTA for the detection of thromboembolic events in the pulmonary vasculature. The table presents results of a selection of clinical trials in comparison to conventional invasive angiography.

Abbreviations: CTA, computed tomography angiography; MRA, magnetic resonance angiography.

Magnetic Resonance Angiography of Pulmonary Arteries

MRA of pulmonary arteries can be acquired with several techniques. Large pulmonary arteries can be imaged using TOF sequences,[70] although CE-MRA is now preferred. 3D CE-MRA can be acquired in a single breath-hold (Fig. 22–9) because of the development of short time-resolved 3D gradient echo sequences and parallel acquisition techniques.[71] A number of clinical studies have reported high sensitivities and specificities for the detection of central PE compared with conventional pulmonary angiography (see Table 22–3). However, the sensitivity for the detection of smaller peripheral emboli is lower.[72] In addition, MRI sequences have been developed to allow for the evaluation of lung ventilation in addition to perfusion sequences,[73] whereas a combined one-stop MRI approach for PE and deep venous thrombosis also seems feasible.[74] However, the high frequency of inconclusive MRAs and its lack of availability in an emergency setting currently limits the clinical application of this approach.[66,71]

Coronary artery angiography is covered in Chapter 16. Please refer to it.

ATHEROSCLEROTIC PLAQUE IMAGING

Atherosclerosis is characterized by accumulation of lipids, inflammatory cells, and connective tissue within the arterial wall. It is a chronic, progressive disease with a long asymptomatic phase. The first pathologic abnormality is the fatty streak, caused by accumulation of lipids and macrophages in the subendothelial space. These streaks can be observed in the aorta from as early as the second decade of life,[75] and they develop over time into mature atherosclerotic plaques consisting of a central lipid core covered by an endothelialized fibrous cap containing vascular smooth muscle cells and connective tissue. As the plaque grows, the affected vessel expands outward so that the lumen diameter and thus blood flow are preserved in a process known as *positive remodeling*.[76] Consequently, even large plaques can be accommodated without producing symptoms that would result from luminal stenosis. Eventually, the artery can expand no further, and the plaque begins to encroach into the lumen of the vessel, hindering blood flow and causing angina at times of high demand. Atherosclerotic plaques

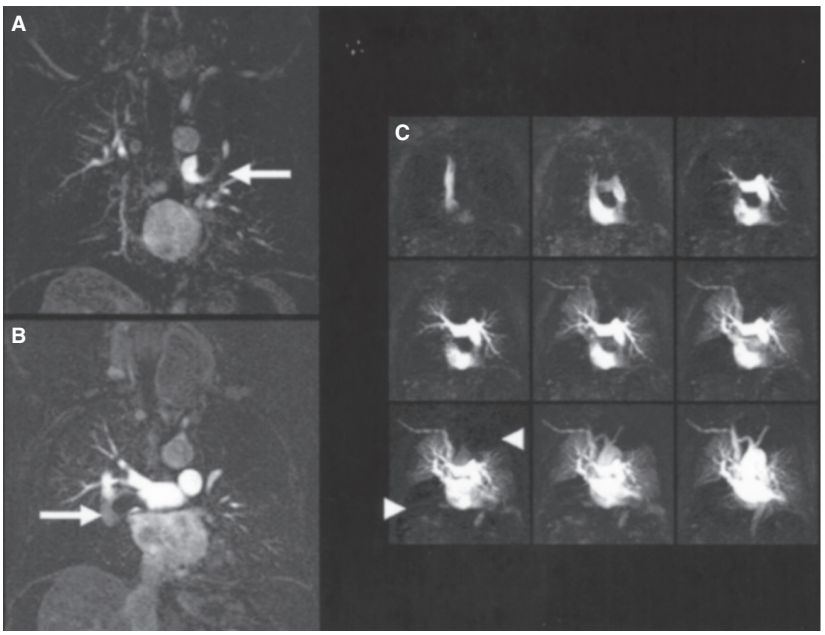


FIGURE 22–9. Three-dimensional, contrast-enhanced, high-resolution magnetic resonance angiography (MRA) of the pulmonary vasculature in a 55-year-old patient (**A, B**) revealing large thromboembolic clots in the central pulmonary artery tree on both sides (*arrows*). Using time-resolved MRA perfusion techniques and acquiring one data set every 1.1 seconds, significant perfusion defects in the upper left and right lower lobe become visible (**C**, *arrowheads*). Used with permission from K. Nikolaou, Ludwig-Maximilians-University, Munich, Germany.

can remain quiescent for years. However, they can become life threatening when they initiate clot formation in the vessel lumen, disturbing blood flow or allowing emboli to break off and lodge in the downstream circulation.[77] Most commonly, this occurs with sudden fibrous cap rupture, which exposes the thrombogenic, tissue factor–rich lipid core to circulating blood. Alternatively, plaque erosion of the endothelium overlying the fibrous cap can lead to the formation of a platelet-rich thrombus and adverse clinical events. Endothelial erosion is thought to account for approximately 30% of plaque rupture events overall and seems particularly common in women.[78] The processes leading to plaque erosion are less well characterized than those implicated in plaque rupture. Both forms of plaque disruption invariably lead to local platelet accumulation and activation at the site of rupture. This may trigger the clotting cascade, with thrombus formation and, if extensive, complete vessel occlusion. However, symptoms are not invariable after fibrous cap disruption; indeed, subclinical plaque rupture appears common with up to 70% of obstructive coronary plaques containing histologic evidence of previous rupture and subsequent repair.[79] This is particularly likely to occur if high blood flow through the vessel prevents the accumulation of a large occlusive thrombus, as frequently occurs in the carotid system. Additionally, the body's natural fibrinolytic pathways can lead to resolution of some thrombi, allowing subsequent healing of the cap and overlying endothelium. Whether and how a plaque becomes symptomatic is determined by its macroscopic structure, its microscopic composition, and the thrombogenicity of the blood. Plaques that precipitate plaque rupture usually have several key characteristics, consisting of a thin fibrous cap (< 65 μm) with few smooth muscle cells and a heavy infiltrate of inflammatory cells, principally macrophages, microcalcification, and a large necrotic core accounting for more than half of the volume of the plaque. Each of these characteristics therefore represents a potential imaging target for identifying *high-risk plaques*. Although prospective data have suggested that the majority of these so-called high-risk lesions either heal or rupture subclinically rather than causing myocardial infarction,[80] such plaques rarely exist in isolation and can serve as a marker of patients with advanced and active atheroma. On this basis, interest persists in identifying these lesions as a means of pinpointing patients at high risk of cardiovascular events. A limitation, however, is that these same plaque characteristics are not necessarily associated with plaque erosion.

Here we will briefly review how CT, MRI, and hybrid imaging platforms might be used to investigate atherosclerotic plaque, focusing on (1) their ability to assess plaque burden, high-risk plaque characteristics, and increased disease activity and (2) how these techniques might improve patient risk stratification and our understanding about the pathogenesis and progression of atherosclerosis.

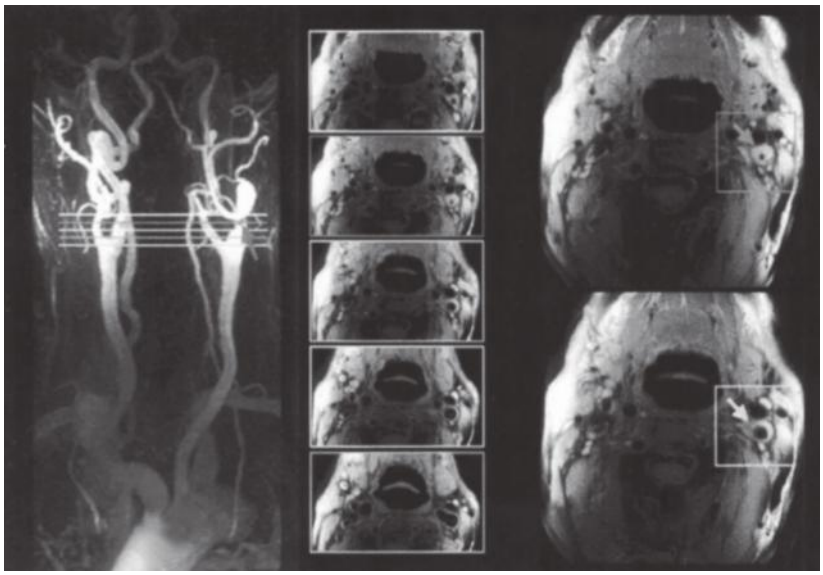


FIGURE 22–10. Carotid magnetic resonance angiography (MRA) showing a severe stenosis of the left internal carotid artery (*arrow, left panel*). MRA was obtained with a contrast-enhanced, 3D, fast gradient echo and carotid-aortic arch-phased array coil. A large atherosclerotic plaque is detected on corresponding cross-sections of the left internal carotid artery using magnetic resonance black-blood sequences (*middle panels*; magnified views, *right panels*). Reproduced with permission from Fayad ZA, Fuster V: Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. *Circ Res*. 2001 Aug 17;89(4):305-316.[81]

MAGNETIC RESONANCE PLAQUE IMAGING

Atherosclerotic plaque MRI relies on the same fundamental principles as other MRI techniques, making use of differences in relaxation times (T1 and T2) and proton density to generate soft-tissue contrast and to provide detailed information about atherosclerotic plaque composition. This is increasingly being applied to the large and relatively immobile carotid arteries and thoracic aorta, with intensive research aimed at transferring these techniques into the coronary vasculature (Fig. 22–10).

Plaque Burden

Simple measures of the atherosclerotic plaque burden in different vascular beds can provide powerful prognostic information, presumably on the basis that the more plaques a patient has the more likely one will rupture or erode and cause an event. MRI can effectively image atherosclerotic plaque using high-resolution, black-blood, FSE sequences. Preparatory pulses are added in order to null signal in the blood pool (hence the black blood) and to improve contrast between the plaques and surrounding tissue. Measurements of plaque thickness in 2D and plaque volume in 3D can then be performed, providing quantification of the atherosclerotic plaque burden.

In the aorta, these measurements demonstrate a close correlation with transesophageal echography[81] and with increasing number of cardiovascular risk factors.[82,83] Similar approaches have been used to measure plaque thickness and the plaque volume in the carotid arteries,[84] providing measures of atherosclerotic burden that predicts major adverse cardiovascular outcomes.[85] Translating these approaches in to the coronary arteries has proved more challenging. The first description was in 2000 when black-blood, breath-held, single-slice imaging was used by Fayad et al to obtain high resolution, cross-sectional images of individual coronary plaques.[86] Measurement of plaque thickness was then possible and found to be increased in patients with established ischemic heart disease versus control subjects[86] and again associated with cardiovascular risk factors.[87] Such measurements are of course prone to sampling error, whilst the ability to measure plaque burden across the entire coronary vasculature remains elusive.

Carotid MRI plaque burden assessments using MRI have proved useful in assessing the efficacy of lipid-lowering therapies and their ability to induce atherosclerotic plaque regression. Indeed, the excellent reproducibility of these measurements means that relatively few patients are required in order to demonstrate treatment efficacy. This was demonstrated in a recent study comparing high- and low-dose statin regimens where improved atheroma burden reduction was demonstrated with the former using only 29 and 22 patients per group.[88,89]

Similar black-blood imaging techniques and wall thickness measurements can be used to identify positive remodeling. Indeed, identification of positive remodeling in the aorta and carotids has been shown to identify patients with an increased risk of future adverse cardiovascular outcomes.[85] Moreover, positive remodeling is also detectable with MRI in the coronary arteries, although the relationship between this MRI finding and prognosis is yet to be established.[90]

Plaque Composition

A key advantage of MRI of the vasculature is the soft-tissue contrast it provides, potentially allowing detailed examination of the composition of individual atherosclerotic plaques. As with other approaches, this is much easier in the carotid versus the coronary arteries. Yuan et al[91,92] demonstrated that multicontrast MRI of human carotid arteries had a sensitivity of 85% and specificity of 92% for the identification of the lipid necrotic core. MRI is also useful in detecting intraplaque hemorrhage, a process believed to play a key role in triggering plaque rupture and growth.[93] T2*-weighted sequences have been used to accurately image intraplaque hemorrhage in carotid atherosclerotic plaques,[94] which in a prospective study was associated with accelerated plaque expansion over 18 months.[95] Plaque hemorrhage and luminal thrombosis can also be detected on T1-weighted imaging as high-intensity plaques,[96] with a recent meta-analysis of 689 patients demonstrating a six-fold increase in cerebrovascular events in patients with high-intensity carotid plaque.[97] Importantly, T1-weighted imaging has also been successfully used in the coronary arteries, again with prognostic implications. Indeed, a recent large study demonstrated high-intensity plaques in 159 out of 568 patients with known or suspected coronary artery disease. Forty-one of these subjects subsequently developed a coronary event with the presence of a high intensity plaque acting as an independent predictor on multivariate analysis (hazard ratio, 3.96; confidence interval, 1.92–8.17).[98]

Late gadolinium enhancement detects regions of extracellular expansion in the myocardium and in carotid atheroma similarly identifies areas of interstitial edema, angiogenesis, and fibrosis. In particular, late enhancement toward the adventitia relates to regions of inflammation and angiogenesis on histology[99] and in a retrospective study localized to the culprit lesions of patients who had suffered a recent stroke. Late gadolinium enhancement can also improve visualization of the atherosclerotic fibrous cap, allowing estimation of the carotid cap thickness and the size of its necrotic core.[100] Importantly, this approach can also be used to identify regions of carotid plaque rupture or ulceration[101] that may or may not be clinically apparent.[102] Attempts have been made to use this technology in the coronary arteries, with early studies showing that the presence of coronary late gadolinium enhancement correlated with the severity of atherosclerosis.[103]

Macrophages play a pivotal role in the destabilization of atherosclerotic plaques, secreting locally abundant quantities of fibrous cap–degrading matrix metalloproteinases, proinflammatory cytokines, and tissue factor.[104] These cells can be imaged using iron oxide contrast agents that have superparamagnetic properties on T2*-weighted sequences. After injection of ultra-small superparamagnetic particles of iron oxide (USPIO), these particles are removed from the circulation by the reticuloendothelial system and accumulate in macrophages present in atherosclerotic plaques. The distortion in the MRI signal that this causes can then be used to estimate the macrophage burden in these areas.[105] Kooi et al[106] studied 11 symptomatic patients scheduled for carotid endarterectomy with USPIO-enhanced MRI and found a 24% decrease in signal intensity in the culprit vessel on T2*-weighted sequences with histological evidence of USPIO uptake in 75% of these plaques postsurgery. The USPIO signal also appears to be modifiable with drug therapy, with high-dose statins inducing a stronger decrease in USPIO carotid plaque uptake than does lower-intensity statin therapy.[107] Current limitations of ferumoxtran-enhanced MRI are the obligatory 36-hour delay after injection before imaging[108] and the artifact on T2*-weighted sequences.

In summary, because of the absence of ionizing radiation, MRI is an excellent imaging technology for the noninvasive detection and serial monitoring of atherosclerotic plaque volumes. High image quality and sensitivity to small changes in plaque size mean that there is little variance between measurements, permitting the use of small sample sizes in comparative mechanistic studies. In addition, MRI can be used to investigate features of plaque composition, including the presence of plaque hemorrhage, angiogenesis, and macrophage burden. In the future, we are likely to see an expansion in molecular MRI contrast agents targeting specific disease processes, similar to current nuclear techniques, but with added potential as drug delivery agents.[109-111]

CT coronary plaque imaging including assessments of plaque burden are covered in Chapter 16. Please refer to it.

POSITRON EMISSION TOMOGRAPHY AND DISEASE ACTIVITY

Anatomic imaging with x-ray angiography, MRI, and CTA can identify arterial stenoses and plaque composition, but these techniques do not inform about disease activity. This is potentially important given that patients with metabolically active disease and more rapid progression are more likely to have events than patients with inactive stable atheroma.[112] Positron emission tomography (PET) is a molecular imaging technique that is highly sensitive in its ability to detect the activity of specific disease processes that have been targeted with specially designed radiotracers. PET imaging has a very high sensitivity but low spatial resolution. As a result, it is generally performed on hybrid PET/CT or PET/MRI systems that combine the functional information of PET with the anatomic detail of CT or MRI.

Arterial inflammation is a key driver of atherosclerosis and in particular the precipitation of acute plaque rupture and adverse cardiovascular events. The radiopharmaceutical agent 18F-fluorodeoxyglucose (18F-FDG) is a glucose analog and identifies cells with high glucose utilization. These include macrophages, which use substantially more glucose than neighboring cell types in the vasculature,[113] particularly in hypoxic conditions.[114] The 18F-FDG uptake in the arterial wall was first noted in the aorta of patients undergoing PET imaging for cancer staging.[115] Since these early studies, it is now established that 18F-FDG uptake is generally greater in symptomatic carotid plaques compared with asymptomatic lesions.[116] Also, the arterial 18F-FDG signal is linked to levels of inflammatory biomarkers[117,118] and the number of components of the metabolic syndrome,[119] and it appears to identify patients with an adverse prognosis.[120,121] More recently, it has been demonstrated that arterial 18F-FDG uptake can be reduced by drug therapy (Fig. 22–11). Indeed, 18F-FDG-PET is increasingly being used as an end point in trials assessing the anti-inflammatory effects of novel antiatherosclerosis drugs in the carotid arteries and thoracic aorta.[122-124] Studies using this tracer in the coronary arteries have had mixed results, predominantly because glucose is also the predominant energy source of the myocardium, with uptake in the heart muscle often obscuring coronary activity.[125,126] This has led to interest in more specific PET markers of inflammation[127,128] and tracers targeting other disease processes of interest.

In addition, 18F-fluoride is a PET tracer increasingly being used to measure the activity of calcific processes in the vasculature.[129,130] 18F-Fluoride preferentially binds regions of vascular microcalcification activity.[131] These are beyond the resolution of CT, a technique that instead detects macroscopic calcium deposits. The difference is

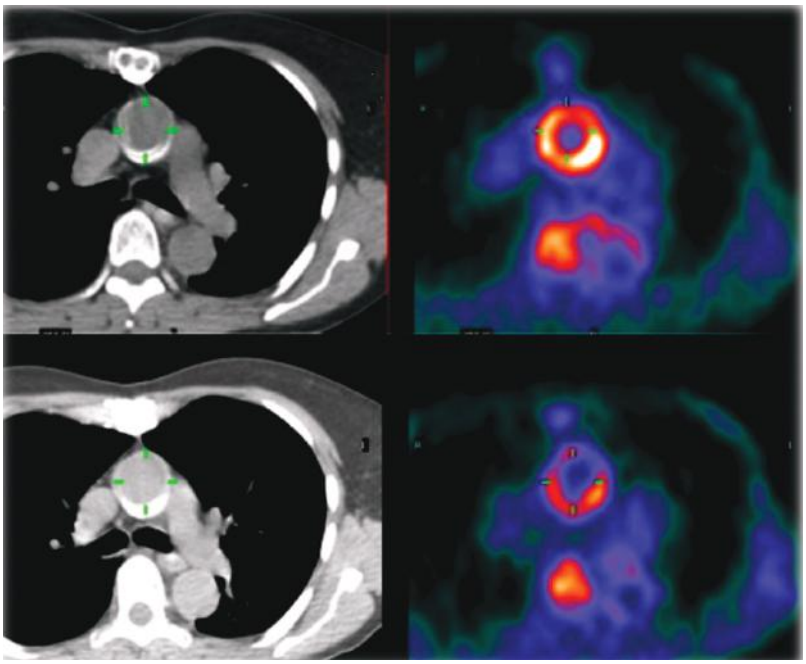


FIGURE 22–11. 18F-Fluorodeoxyglucose positron emission tomography/computed tomography image of aorta before (*top*) and during (*bottom*) antiatherosclerosis therapy. Note reduction in fluorodeoxyglucose uptake in the aortic wall under statin treatment. Used with permission from J. Rudd, Division of Cardiovascular Medicine, University of Cambridge, Cambridge, United Kingdom.

potentially important given that macroscopic calcium imparts stability to the plaque, whereas microcalcification is consistently associated with high-risk coronary lesions and increased risk of rupture.[132] Two clinical trials have explored 18F-fluoride uptake in the coronary vasculature, demonstrating that unlike 18F-FDG, 18F-fluoride uptake can be readily detected in these vessels with excellent signal-to-noise (Fig. 22–12). In the first trial increased tracer uptake localized to individual plaques and in so doing identified high-risk patients with increased Framingham risk scores.[133] The second demonstrated that the plaques with increased 18F-fluoride activity had multiple high-risk characteristics including a large necrotic core, microcalcification, and positive remodeling. Perhaps most interestingly, this same study demonstrated that in patients post–myocardial infarction, 18F-fluoride localized to the exact site of plaque rupture, the culprit plaque, in 37 of the 40 subjects recruited. These studies indicate that 18F-fluoride can identify patients with increased metabolic activity in their coronary arteries and at least retrospectively appears to identify the individual lesions responsible for coronary events.[126] The ability of this marker of disease activity to prospectively identify patients at risk of myocardial infarction is currently being tested in a large prospective multicenter study (PREFFIR clinicaltrials.gov NCT02278211).

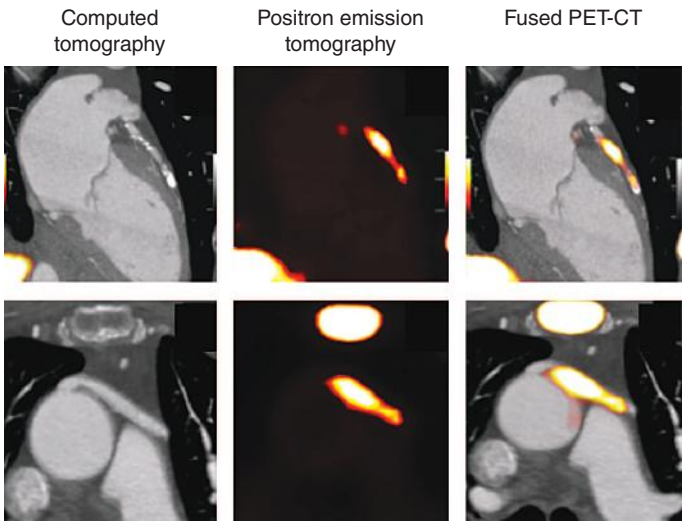


FIGURE 22–12. 18F-Fluoride positron emission tomography/computed tomography (PET/CT) of the left anterior descending artery (*top row*) and a saphenous vein graft (*bottom row*). Individual contrast enhanced CT angiograms (*right*) and PET images (*center*) are shown alongside fused PET/CT images (*left*). Note the focal regions of increased 18F-fluoride activity as a marker of microcalcification activity and the different distribution to calcium deposits identified on CT.

CONCLUSIONS

Noninvasive methods such as MRA and CTA are increasingly being used to assess vascular disease at different sites in the body. CTA plays a major role in pulmonary and coronary imaging, whereas in the iliofemoral and carotid arteries, MRA is generally preferred. More generally, noninvasive imaging is undergoing rapid evolution, allowing us to investigate plaque burden, plaque composition, and disease activity in great detail and potentially within a single scan. The challenge will be to translate these exciting advances in to clear-cut improvements in the clinical care offered to patients with cardiovascular disease.

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SECTION 4

Systemic Arterial Hypertension

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CHAPTER 23

EPIDEMIOLOGY OF HYPERTENSION

Nathan D. Wong and Stanley S. Franklin

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Elevated blood pressure (BP) is the top attributable cause of mortality globally, responsible for some 7.5 million deaths annually, approximately 12.8% of all deaths, and accounts for 57 million disability-adjusted life years.[1] Global prevalence of elevated BP in 2008 was approximately 40%, being highest (46%) in the World Health Organization African region and lowest in the Americas, around 35% overall for both men and women. Approximately one billion persons throughout the world have uncontrolled hypertension, an increase from 600 million in 1980.

Hypertension is the most prevalent chronic condition in the United States and the most common one reason for an office visit to a physician. It accounts for the most drug prescriptions and is one of the most important risk factors for heart disease and stroke.[2] This chapter reviews the epidemiology of hypertension—how it is defined and classified, the extent of its prevalence, treatment, and control, and its relation to cardiovascular and other consequences.

CLASSIFICATION AND SUBTYPES OF HYPERTENSION

Hypertension can be quantified on the basis of a large number of epidemiologic studies showing that the distribution of BP in the population is continuous, although the curve is skewed at the higher levels of BP. The unimodal distribution of BP implies that hypertension is unlikely to be the result of a single physiologic process or gene and perhaps most importantly suggests that any BP level used to define hypertension is arbitrary.

Hypertension can be classified in different ways—helpful for its diagnosis and clinical management (Fig. 23–1). The two principal divisions are severity (the height of the BP) and underlying cause (primary or essential hypertension vs secondary hypertension). A third major component is age: the pathophysiology of hypertension in younger and older people is quite different.

The original subdivision of hypertension according to its severity was *benign* and *malignant*. Although malignant hypertension carries a prognosis that is equivalent to that of other malignant diseases (if untreated), the term *benign* for less severe forms of hypertension is a misnomer and is no longer used. Malignant hypertension is now relatively uncommon in Western countries, but it does still occur and when present it requires urgent treatment, which can dramatically alter its natural history.

In hypertensive patients, either or both the systolic and diastolic BP are elevated, but most common are elevations in systolic BP, and in particular, the most common circumstance is isolated systolic hypertension where the systolic is elevated, but the diastolic normal, occurring predominantly in older persons. Isolated diastolic hypertension can also occur and is the most common hypertensive subtype in younger persons. Hypertension can also be the result of the measurement method used; traditional methods of classification have all been based on office or clinic BP measurements, but with the wider use of out-of-office BP measurement, office measurements can be shown to significantly over- or underestimate the BP level during daily life. In most hypertensive patients, the BP is higher in the office than at other times, a phenomenon referred to as the *white coat effect* and that is usually defined as the difference between the office pressure and the average daytime pressure.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) 7 classification for hypertension[2] has continued the definition of hypertension as a BP at or above 140/90 mm Hg for adults age 18 years or older. The classification is based on the average of two or more seated BPs, properly measured with well-maintained equipment, at each of two or more visits to the office or clinic. Hypertension has been divided into stages 1 and 2, as shown in Table 23–1. JNC 7 has defined normal BP as less than 120 and less than 80 mm Hg. What JNC-6 previously labeled as normal (120–129 mm Hg systolic BP or 80–84 mm Hg diastolic BP) and high normal (130–139 mm Hg systolic BP or 85–89 mm Hg diastolic BP) are now combined into a single group renamed as *prehypertension*, to increase awareness to these individuals with an intermediate level of risk that may progress to definite hypertension. The more recent American Heart Association/American College of Cardiology/Centers

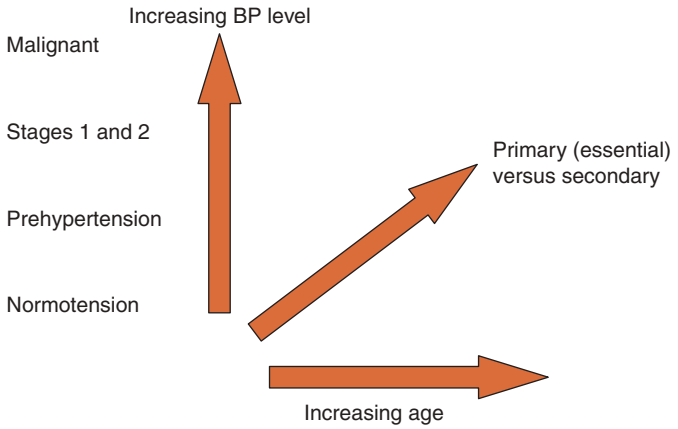

FIGURE 23–1. Three-dimensional classification of hypertension according to severity (height of the blood pressure), etiology (primary vs secondary), and age. BP, blood pressure.

for Disease Control and Prevention Science Advisory[3] "An Effective Approach to High Blood Pressure Control" has retained the JNC-7 cutoff points for stages 1 and 2 hypertension, as well as the goal levels that were recommended for treatment, as has the recent clinical practice guidelines from the American Society of Hypertension and International Society of Hypertension.[4]

PREHYPERTENSION

It is estimated that approximately 15% of BP–related deaths from coronary heart disease (CHD) occur in individuals with BP in the prehypertensive range.[5] JNC 7 officially defined prehypertension (systolic BP of 120–139 mm Hg or diastolic BP of 80–89 mm Hg) based on data mainly from the Framingham Heart Study. It showed (1) that people who have BP in the prehypertensive range have a higher risk of heart disease and stroke than do people with BPs below this level, with 18% of those with BPs of 120–129/80–84 mm Hg and 37% of those with BPs of 130–139/85–89 mm Hg progressing to clinical hypertension within only a few years,[6] and that (2) the lifetime risk of hypertension approaches 90%,[7] warranting the importance of the concept of prehypertension to help motivate physicians and patients alike to promote lifestyle modifications to prevent or delay the transition to clinical hypertension. Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2006 in persons without cardiovascular disease (CVD) or cancer shows a prevalence of prehypertension of 36.3%, higher in men than in women, and associated with adverse cardiometabolic risk factors.[8] A recent meta-analysis of 17 prospective cohort studies comprising 591,664 participants showed that compared with optimal blood pressure (< 120/80 mm Hg), those with prehypertension had a 43% higher risk of incident CHD (hazard ratio [HR], 1.43; 95% confidence interval [CI], 1.26–1.63) a risk that was higher in Western subjects (relative risk [RR], 1.70; 95% CI, 1.49–1.94) than in Asian subjects (RR, 1.25; 95% CI, 1.12–1.38), with 24.1% of CHD attributable to prehypertension in Western subjects versus 8.4% in Asian subjects.[9] A similar analysis by the same group involving 19 prospective studies showed prehypertension to be associated with a 66% greater risk of stroke; even those in the lower range of prehypertension (systolic BP 120–129 mm Hg or diastolic BP 80–84 mm Hg) had a significant 44% increased risk.[10] Importantly, prehypertension has been recently shown to be associated with abnormalities of cardiac structure and function, specifically increased left ventricular remodeling and impaired diastolic function[11]; inflammatory factors including C-reactive protein, interleukin-6, and tumor necrosis factor-alpha[12]; as well as increased arterial stiffness in older persons.[13]

ISOLATED SYSTOLIC HYPERTENSION

In many older adults, systolic BP tends to rise as diastolic BP falls. When the average systolic BP is at least 140 mm Hg or more and diastolic BP is less than 90 mm Hg, the patient is classified as isolated systolic hypertensive. The increased pulse pressure (systolic-diastolic) and systolic pressure predict risk and determine treatment.[14] The transition of hypertensive subtypes from isolated diastolic hypertension being most common in younger persons to isolated systolic hypertension being the most common subtype in those aged 60 and over, accounting for more than 90% of hypertension in those aged 80 and over, has been described from data from the NHANES (Fig. 23–2).[15]

Isolated systolic hypertension can also occur in the young. High systolic pressure in younger persons may be the result of two changes: a high stroke volume and increased arterial stiffness. In contrast to essential hypertension, which raises both systolic and diastolic pressures, peripheral resistance is not increased.[16] In long-term follow-up of 31 years, younger and middle-aged adults with isolated systolic hypertension had higher relative risk than those with high-normal BP.[17]

ISOLATED DIASTOLIC HYPERTENSION

More commonly seen in younger adults, a systolic BP of less than 140 mm Hg accompanied by a diastolic BP of 90 mm Hg or more defines isolated diastolic hypertension. This represents more than half of hypertension under the age of 40 years (see Fig. 23–2).[15] Diastolic pressure is generally thought to be the best predictor of risk in patients younger than age 50 years[18]; an analysis of data from the Framingham Heart Study also concluded that

TABLE 23–1. JNC Classification of Blood Pressure Stages

JNC VI					JNC 7			
Category	SBP (mm Hg)		DBP (mm Hg)		Category	SBP (mm Hg)		DBP (mm Hg)
Optimal	< 120	and	80	→	Normal	< 120	and	80
Normal	120–129	and	80–84		Prehypertension	120–139	or	80–89
High-normal	130–139	or	85–89					
Hypertension								
Stage 1	140–159	or	90–99		Stage 1	140–159	or	≥ 90
Stage 2	160–179	or	100–109	→				
Stage 3	≥ 180	or	≥ 110		Stage 2	≥ 160	or	≥ 100

Abbreviations: DBP, diastolic blood pressure; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP, systolic blood pressure.

Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003 Dec;42(6):1206-1252

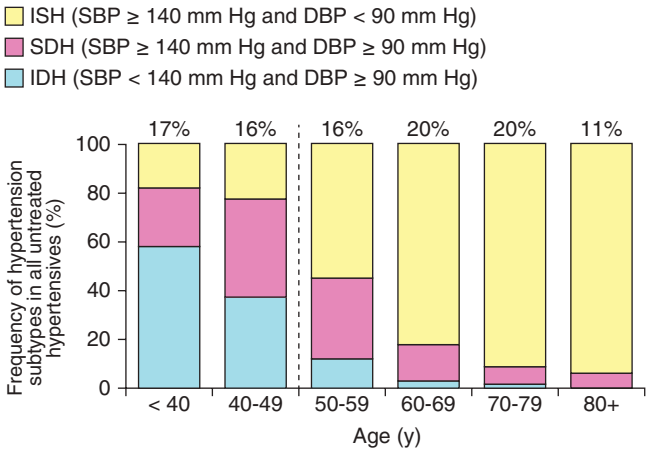

FIGURE 23–2. Distribution of hypertensive subtypes in the untreated hypertensive population by age (National Health and Nutrition Examination Survey [NHANES III]). Numbers at top of bars represent the overall percentage distribution of untreated hypertension by age. Reproduced with permission from Franklin SS, Jacobs MJ, Wong ND, et al: Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension*. 2001 Mar;37(3):869-874.

isolated diastolic hypertension may evolve into systolic and diastolic hypertension.[19] The US NHANES survey also showed that obesity was associated with isolated diastolic hypertension in all age groups and both genders—but most frequently in young adults.[20] Thus, any patients in whom isolated diastolic hypertension is diagnosed should be carefully followed.

WHITE COAT HYPERTENSION

In approximately 15% to 30% of people with stage 1 hypertension, BP is elevated only persistently in the presence of a health care worker, particularly a physician. When measured elsewhere, including while at work, the BP is not elevated. When this phenomenon is detected in patients who are not taking medications, it is referred to as *white coat hypertension* or *isolated office hypertension*. The commonly used definition is a persistently elevated average office BP of 140/90 mm Hg or more and an average awake ambulatory reading of less than 135/85 mm Hg (Fig. 23–3).[21] Although it can occur at any age, it is more common in women, older adults, nonsmokers, and those with recently diagnosed hypertension; a misdiagnosis of a person with white coat hypertension as being truly hypertensive can result in his or her being penalized for employment and consideration for insurance, as well as possibly being subjected to lifelong antihypertensive treatment.[22] This assertion was recently confirmed by Ogedegbe et al in a study in which patients with white coat hypertension reported significantly higher levels of state anxiety compared with other hypertension diagnostic categories.[23] Its magnitude can be reduced (but not eliminated) by the use of stationary oscillometric devices that automatically determine and analyze a series of BPs over 15 to 20 minutes with the patient in a quiet environment in the office or clinic. Although white coat hypertension has been generally thought to have a benign prognosis, a recent meta-analysis of 14 studies comprising 29,100 patients showed that cardiovascular mortality and morbidity in subjects with white coat hypertension is slightly higher than normotensive controls but well below the cardiovascular risks associated with sustained hypertension.[24] All patients should be followed indefinitely with office and out-of-office measurements of BP. Treatment with antihypertensive drugs may lower the office BP but does not change the ambulatory measurement. This pattern of findings suggests that drug treatment of white coat hypertension is less beneficial than treatment of sustained hypertension.

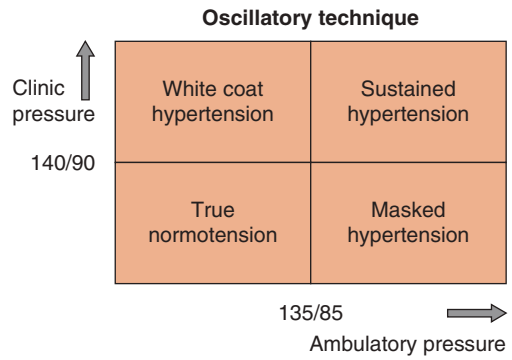

FIGURE 23–3. Classification of white coat and masked hypertension according to clinic and ambulatory blood pressures.

MASKED HYPERTENSION

The mirror image of white coat hypertension, *masked hypertension* is defined as a normal office BP (< 140/90 mm Hg) together with an elevated daytime BP (≥ 135/85 mm Hg) (see Fig. 23–3). It is present in approximately 10% to 40% of patients not receiving antihypertensive treatment. Also, persons with prehypertension are more likely to have masked hypertension and can even develop target organ damage before transitioning to established sustained hypertension. Twenty-four–hour ambulatory BP monitoring is the standard for diagnosing masked hypertension, but home BP monitoring can also be used. Importantly, reliance on in-office BP values to initiate treatment can result in up to a third of persons remaining at increased risk resulting from masked hypertension.[25] Masked hypertension is associated both with target organ damage[26] and an adverse prognosis,[27] and it has been detected both in subjects who have not been diagnosed or treated for hypertension and in patients on antihypertensive treatment.[28] The Dallas Heart Study also recently showed a two-fold greater risk of future cardiovascular events in those with masked hypertension compared to those who were normotensive.[29] Importantly, masked hypertension is more common in older persons; those with mental stress; smokers, and those with metabolic syndrome, diabetes, chronic kidney disease, and obstructive sleep apnea. Thus, there is an underdiagnosis of clinical hypertension in such persons, thus emphasizing an even greater importance for the use of 24-hour ambulatory BP measures in these individuals.[28] Furthermore, persons with masked hypertension frequently present with elevated nocturnal BP and a nondipping pattern that predicts worse cardiovascular outcomes; this again can only be diagnosed with 24-hour ambulatory BP monitoring.[30]

PSEUDOHYPERTENSION

The term *pseudohypertension* is misleading; it suggests a false elevation of diastolic BP when in actuality it is low. This condition represents wide pulse pressure isolated systolic hypertension in the elderly. It frequently occurs with diabetes and diabetic kidney disease and is associated with extensive calcification of many large arteries, including the brachial and elastic aorta. These conditions are obviously associated with severe CVD risk. Differential diagnosis must exclude benign white coat hypertension, which is a frequent finding in the elderly and is best diagnosed with ambulatory BP monitoring. Indeed, with the advent of 24-hour ambulatory BP measurement, description of cases of pseudohypertension have largely disappeared from the literature—except for false inclusion in textbooks.[31]

ORTHOSTATIC OR POSTURAL HYPOTENSION

This condition is defined as a reduction of systolic BP of at least 20 or 10 mm Hg in diastolic BP within 3 minutes of quiet standing.[32] An alternative method is to detect a similar decline during head-up tilt at 60 degrees. This may be asymptomatic or accompanied by symptoms of light-headedness, faintness, dizziness, blurred vision, and cognitive impairment.[33] If chronic, the fall of BP may be part of pure autonomic failure or a complication of diabetes. The major life-limiting failure is inability to control the level of BP, especially in those patients with orthostatic hypotension who concomitantly have supine hypertension. In these patients, there are great and swift changes in pressure so that the patients faint as a result of profound hypotension on standing and have very severe hypertension when supine. Often the heart rate is fixed as well. The supine hypertensive person is subject to serious consequences, such as left ventricular hypertrophy[34] and stroke.[35,36]

HYPERTENSIVE CRISES: URGENCY, EMERGENCY, AND MALIGNANT HYPERTENSION

A hypertensive crisis can present as urgency or emergency that requires immediate medical treatment.[37] A hypertensive urgency is defined as having two or more readings where the systolic is elevated at 180 mm Hg or higher or diastolic of 110 mm Hg or higher, without associated organ damage, and may or may not be accompanied by symptoms such as severe headache, nosebleeds, shortness of breath, or severe anxiety. This is distinguished from a hypertensive emergency where target organ damage has occurred (eg, chest pain, shortness of breath, back pain, numbness/weakness, change in vision, difficulty speaking) requiring the individual seek immediate emergency medical assistance.[38] Malignant hypertension is defined as the presence of elevated BP in association with bilateral retinal hemorrhages and/or exudates, with or without papilledema. Although there have been substantial improvements in the general management of hypertension, there is no good evidence of reduction in its prevalence.[39] However, in the absence of retinopathy, a hypertensive emergency is based on the criteria of acute elevated BP accompanied by damage to one of many target organs. Its importance lies in the fact that if untreated, it has a 5-year survival rate of 1%.[40] It is still relatively uncommon in developing countries,[41] but its prevalence may be increasing with the global increase in hypertension prevalence.[39] It can result from essential or secondary hypertension. Treatment of malignant hypertension has a dramatic effect on survival, and the first article demonstrating the benefits of antihypertensive drugs was based on patients with malignant hypertension.[42]

CLASSIFICATION BY CAUSE

In more than 95% of cases of hypertension, no single and reversible cause can be detected, and the terms *essential* and *primary* hypertension have been used. The former term was introduced because it was thought that a higher-than-usual level of BP was needed to maintain perfusion of vital organs.

In approximately 5% of cases there is a definable cause of the hypertension.[2] Table 23–2 shows a list adapted from JNC 7.[2] From an epidemiologic point of view, the two most important conditions on the list are chronic kidney disease and sleep apnea. Although chronic kidney disease is certainly a major cause of hypertension, it is often difficult to decide whether the hypertension or the kidney disease came first, because a vicious cycle can develop where one condition exacerbates the other. In practice, however, this distinction is of little consequence, because most forms of chronic kidney disease are not reversible. The most common curable form of hypertension is renal artery stenosis, which has two principal causes: (1) fibromuscular disease in children and young adults and (2) atherosclerosis in middle-age and older patients.

TABLE 23–2. Secondary Forms of Hypertension

Condition
Chronic kidney disease
Renal artery stenosis
Primary aldosteronism and other causes of mineralocorticoid excess
Sleep apnea
Cushing disease
Coarctation of the aorta
Drug-induced hypertension
Obstructive uropathy
Pheochromocytoma
Thyroid/parathyroid disease

Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003 May 21;289(19):2560-2572

Sleep apnea is emerging as one of the major causes of hypertension that is of epidemiologic significance. Support for a causal association between sleep-disordered breathing and hypertension includes physiological mechanisms involving vascular dysfunction secondary to altered sympathovagal balance and insulin resistance. Also, respiratory disturbances accompanied by hypoxemia and sympathetic activation can trigger acute surges in BP.[43] A population survey showed that 2% of women and 4% of men have sleep apnea, which was defined as having an apnea-hypopnea index (AHI) score of five or more and daytime sleepiness.[44] The prevalence of an AHI of 5 or more increases with age, reaching a maximum prevalence in a population at approximately the age of 70 years.[45] Both sleep apnea and hypertension are common, and unsurprisingly there are many individuals who have both conditions. Furthermore, both are closely linked to obesity (particularly central obesity, as seen in the metabolic syndrome), so there is a cluster of related syndromes: hypertension, sleep apnea, diabetes, and the metabolic syndrome. Thus, approximately 60% of sleep apnea patients are hypertensive,[46] and, conversely, approximately 25% of hypertensive patients have sleep apnea.[47,48] One issue is the causal link between sleep apnea and hypertension. The largest study of this is the Sleep Heart Health Study, which is a prospective study of the relationship between sleep apnea and cardiovascular morbidity. In an initial cross-sectional study of 6132 subjects age 40 years or older,[49] there was a dose-response relationship between the AHI score and the prevalence of hypertension, although some of it was attributable to the effects of increased body mass index. A prospective follow-up of this cohort, restricted to the 2470 individuals without hypertension, showed *effect sizes almost identical to that of the* cross-sectional analyses: (1) an odds ratio of 2.19 in the age-, sex-, and ethnicity-adjusted models and an (2) odds ratio of 1.51 in a model that was further adjusted for body mass index. However, given the smaller sample in the prospective analysis, this did not quite reach statistical significance.[50] The Wisconsin Sleep Cohort Study, however, did find a consistent dose-response relationship, even after controlling for age, sex, body mass index, and antihypertensive medications.[51]

TABLE 23–3. Differences Between Hypertension in Younger and Older Patients

Factor	Younger (< 60 y)	Older (≥ 60 y)
Blood pressure increase	Systolic and diastolic	Systolic
Major cause	Hormonal	Mechanical
Hemodynamic change	Increased peripheral resistance	Increased arterial stiffness
Sleep apnea	Yes	No
Treatment threshold	140/90 mm Hg	7 higher in younger subjects

CLASSIFICATION BY AGE

There is a fundamental difference between the genesis of hypertension in younger and older patients (Table 23–3). The most obvious difference is that in younger patients, whatever the underlying etiology of the hypertension (with a few exceptions noted below), both systolic and diastolic BPs are raised, whereas in people aged 60 years and older, the diastolic BP starts to fall (Fig. 23–4), but there is a marked increase of systolic BP. The underlying hemodynamics are also different: in younger patients, the characteristic changes are an increased peripheral resistance with a normal cardiac output, whereas in older patients, the reason for the selective increase of systolic BP is increased arterial stiffness.[52] This has two consequences. First, when the left ventricle pumps into a stiffened aorta, there will be a higher systolic BP because the stiffer vessel will be less able to accommodate the stroke volume. Second, the velocity of the arterial pulse wave traveling out to the peripheral vessels will be increased. Just like a wave resulting from a stone dropped in a pool, the wave is reflected when it reaches the periphery, so that the pressure waves in the circulation will be a combination of the outgoing and reflected waves. In younger people, where the pulse wave velocity is low, the reflected wave arrives relatively late and coincides with the diastolic downslope of the incident wave, so that it has no effect on the systolic or diastolic pressure. But in older individuals, it returns earlier and forms a second or late systolic peak, which augments the height of the systolic pressure. Another difference concerns the physiologic measurements. In younger patients, the increased peripheral resistance is a result of active vasoconstriction that is mediated hormonally, particularly by the sympathetic nervous system and the renin-angiotensin system. In older patients with systolic hypertension, hormonal mediation is less important and the changes are mostly mechanical (eg, loss of elastin fibers in the media of the arterial wall).[52] The affected vessels (principally the aorta and central elastic vessels) dilate and stiffen. The effects of increased aortic stiffness may be bidirectional; that is, hypertension will itself increase arterial stiffness, so there may be a vicious cycle.[53]

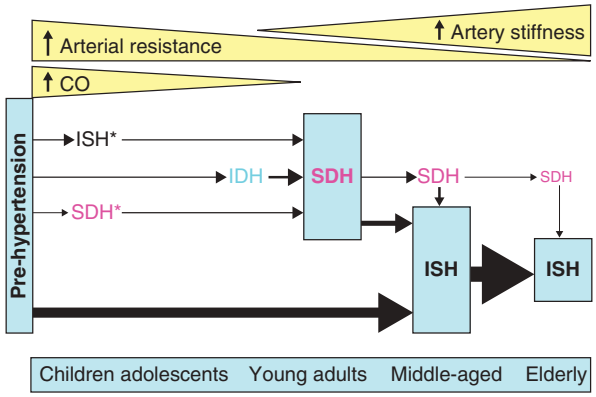

FIGURE 23–4. Pathways in the development of hypertension according to age. ISH, isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic and diastolic hypertension. Reproduced with permission from Sorof JM: Systolic hypertension in children: benign or beware? *Pediatr Nephrol.* 2001 Jun;16(6):517-525. From Sorof JM. Systolic hypertension in children: benign or beware? *Pediatr Nephrol.* 2001;16(6):517-525.

Treatment thresholds are also different. In younger patients, it is clearly established that starting drug treatment when the pressure exceeds 140/90 mm Hg is beneficial. This may also be true in older patients, but the clinical trials that have investigated the benefits of treatment have almost all used an initial systolic BP of 160 mm Hg or greater as an entry criterion and have not lowered the pressure to below 140 or 150 mm Hg.[54] Thus, the benefits of treatment in older patients with systolic pressures below 160 mm Hg remain unproven. Of interest, however, the recently reported Systolic Blood Pressure Intervention Trial (SPRINT) of 9361 persons with diabetes with a mean age of 68 years did show treatment to a target of less than 120 mm Hg systolic BP compared to less than 140 mm Hg (achieved 121.4 vs 136.2 mm Hg) did result in a 25% reduced risk of the composite cardiovascular end point, with a trend toward greater benefit of treatment in those 75 years of age or older. Interpreting the SPRINT study results should be in the context of its use of an automated device for measuring BP that eliminated the white coat effect to obtain a more accurate estimate of cardiovascular risk.[55]

There is some evidence that in the very old (age 85 years or older), mortality may be higher in patients with the lowest BPs[56] and that lowering the diastolic pressure with treatment may actually increase mortality.[57] The benefit or harm of treating very old patients is currently being evaluated.[58]

PREVALENCE OF HYPERTENSION

In the United States, an estimated 80 million adults, or 32.6% overall aged 20 years and older, have hypertension. The overall age-adjusted prevalence in 2009–2012 is 44.9% and 46.1% among non-Hispanic black men and women, respectively; 32.9% and 30.1% among non-Hispanic white men and women, respectively; and 29.6% and 29.9% among Hispanic men and women, respectively.[59] There is a direct age-related prevalence of hypertension, being less than 10% in those aged 20 to 34 years and increasing to more than 75% in those aged 75 years and older (Fig. 23–5). Since 1988–1994, there has actually been an increase in prevalence of hypertension among most gender-ethnic groups (Fig. 23–6), with non-Hispanic black women having the highest prevalence (42.9%) in 2007–2012. Overall during this time period, 82.7% were aware of their condition and 76.5% were currently being treated, but only 54.1% were under control. Non-Hispanic blacks tend to be most aware of their condition, with Hispanics least likely to be treated or controlled (Fig. 23–7).

Surveys in Europe show much higher rates of hypertension, with an overall prevalence of 44% reported in Europe.[60] A comparison of seven European countries' data found the highest rate in Germany (55%) and the lowest in Italy (38%), with France, England, Spain, and Sweden all showing a prevalence between these two extremes. The prevalence in Canada is very similar to that in the United States (27%).[61] The reasons for these wide differences are unknown but do not appear to be because of differences in measurements or sampling rates. In Egypt, the rate is also approximately 25%, whereas in China, where much of the population is still rural, the rate is lower (14%) but is increasing rapidly.[61]

More recently, a large analysis in 199 countries examining current levels and trends in systolic BP that involved 5.4 million subjects, a global average systolic BP in 2008 was noted to be 128.1 mm Hg in men and 124.4 mm Hg in women. In this study, women in some East African and West African countries had the highest mean systolic BPs of at least 135 mm Hg, whereas men living in the Baltic and East African and West African countries had mean systolic BP at least 138 mm Hg.

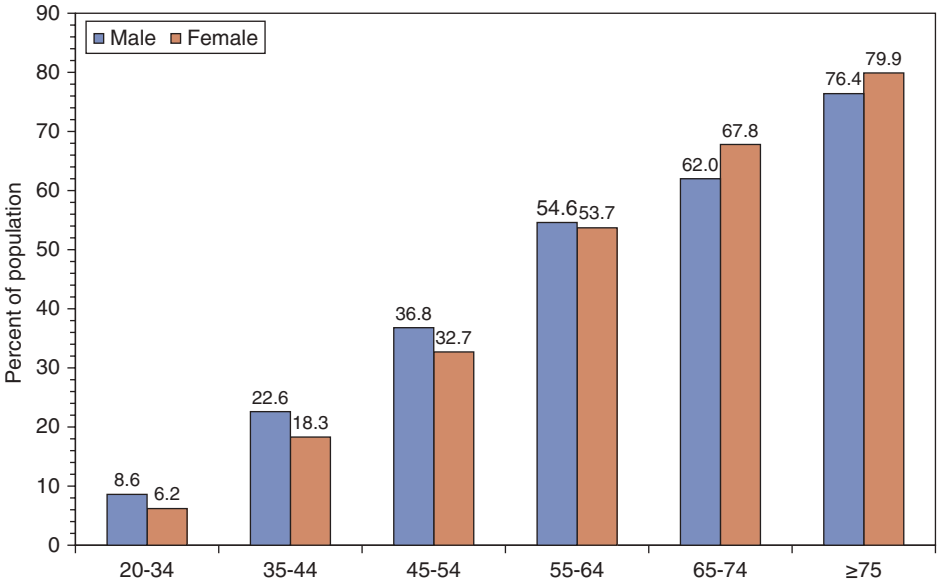

FIGURE 23–5. Prevalence of hypertension according to age and gender in US adults: National Health and Nutrition Examination Survey 2009–2012. Reproduced with permission from National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Among higher income countries, those in Western Europe had the highest systolic BP. They also noted the greatest decreases in systolic BP between 1980 and 2008 to have occurred among women in Western Europe and Australasia (≥ 3.5 mm Hg) and among men in North America (2.8 mm Hg). Increases in systolic BP during this period, however, were noted in Oceania, East Africa, and southern and Southeast Asia.[62]

AFRICAN AMERICANS

In the United States, hypertension is significantly more prevalent in African Americans than in whites. In the most recent NHANES 2009–2012 survey,[59] the prevalence in African American men was 44.9%, whereas in white men it was 32.9%. In this same survey, in women the prevalence was 46.1% for African Americans and 30.1% for whites. The 40-year incidence of hypertension in someone aged 45 is also higher for blacks (92.7%) than for whites (86.0%).[63] A big issue here is whether the higher prevalence is genetic or environmental. Although the prevalence is higher than in whites in other countries (eg, Brazil),[64] there is a large body of literature showing that the rates of hypertension in Africans living in traditional rural societies are relatively low but increase markedly when they move to cities.[65]

A huge effort has already been made to try to understand the reasons for the higher prevalence of hypertension in African Americans, almost all of which has made the underlying assumption that there is some genetically determined physiologic difference. However, it appears human hypertension is determined by several genes; genetic factors probably do not account for more than 50% of hypertension.[66] A recent comparative study involving large surveys of BP in populations of European versus African descent outside the United States indicated a lower range of hypertension prevalence in blacks (14%–44%) than in whites (27%–55%).[67] One of the most powerful pieces of evidence that environmental factors are important in the development of hypertension is a series of epidemiologic studies showing that when people move from a traditional rural setting to an urban westernized lifestyle, their BP goes up. For example, the Luo study from Kenya[65] showed those who had moved to Nairobi had higher pressures than people living in the villages, even if they had only been in the city for a month, and others reported the same pattern for other countries in sub-Saharan Africa.[68] Socioeconomic status, which is strongly associated with ethnicity in the United States, affects the prevalence of hypertension, particularly in African Americans.[69] Harburg first showed that BP in African Americans living in the inner city was highest in those people living in the worst-off neighborhoods.[70,71] A more recent analysis of the Atherosclerosis Risk in Communities (ARIC) study by Diez-Roux et al[72] found that "neighborhood" effects were independently related to BP after controlling for other risk factors. In four US communities, people living in the neighborhoods with the lowest median house prices tended to have the highest blood pressure. This was most pronounced in the one community (Jackson, Mississippi) that was largely African American.

HISPANIC AMERICANS

One of the fastest-growing segments of the US population is Hispanics (Latinos), who are overtaking African Americans as the largest minority group. Most recent NHANES data from 2009–2012 show a prevalence of hypertension of 29.6% and 29.9% in Hispanic men and women,

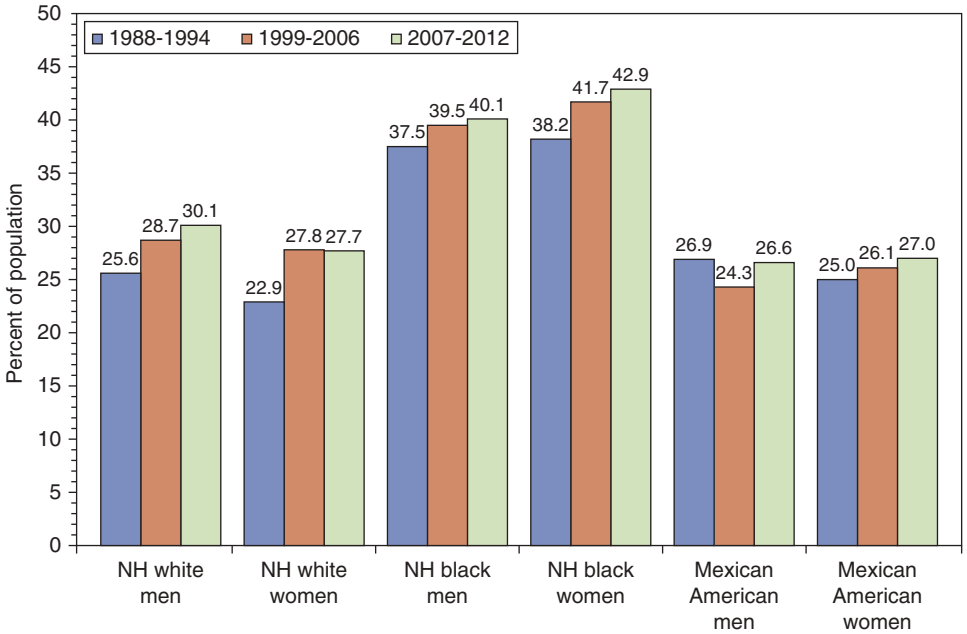

FIGURE 23–6. Prevalence of hypertension according to ethnicity and year in US adults: National Health and Nutrition Examination Survey. Reproduced with permission from National Center for Health Statistics and National Heart, Lung, and Blood Institute.

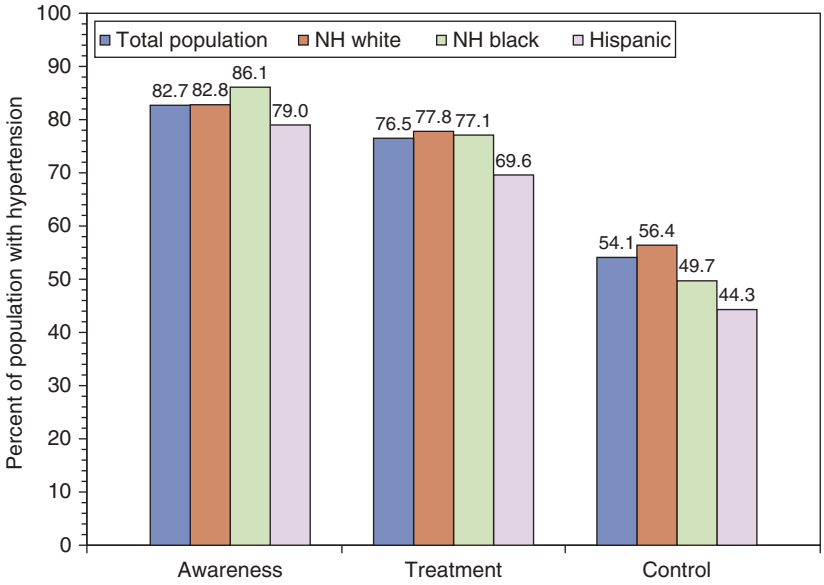

FIGURE 23–7. Awareness, treatment, and control of hypertension according to ethnicity: National Health and Nutrition Examination Survey 2009–2012. Reproduced with permission from National Center for Health Statistics and National Heart, Lung, and Blood Institute.

respectively. Many are recent immigrants, and they tend to be of relatively low socioeconomic status. If psychosocial factors are so important in determining the socioeconomic status gradient of disease, one might expect that Hispanics would also have higher mortality rates than whites. Surprisingly, this does not appear to be the case. For example, death rates in women in 2013 from CHD and stroke are lowest in Hispanics (61.3 and 27.6 per 100,000, respectively) compared to blacks (94.7 and 45.9 per 100,000, respectively) or whites (75.0 and 34.5 per 100,000, respectively).[59] There are two major subgroups of Hispanics in the United States: those from Mexico and Latin America, who are predominant in states such as Texas and California, and those of Caribbean origin, who are mostly in the Northeast and Florida. However, they can be classified mainly into those of Mexican, South American, Central American, Cuban, Puerto Rican, or Dominican backgrounds. As shown from recently published data from the Hispanic Community Health Study/Study of Latinos, enrolling more than 16,000 participants among four major US communities, the prevalence of hypertension appears to vary greatly according to background and gender being lowest among South American women (17.2%) and highest in Dominican men (34.3%). Those of Cuban, Puerto Rican and Dominican background had overall higher prevalences of hypertension than those of Mexican, South American, or Central American background.[73] Some early studies suggested that, despite higher rates of obesity and diabetes in Mexican Americans, they have a lower all-cause and cardiovascular mortality than whites,[74] leading to what has been called the *Hispanic paradox*. However, the highly regarded San Antonio Heart Study found just the opposite—namely, that mortality from CVD is approximately 60% higher in Mexican Americans than whites.[75] The authors attribute the contrary findings of the earlier studies to underreporting of deaths in Mexican Americans.

ASIAN AMERICANS

Only recently have national data on the prevalence of hypertension and other risk factors become available in Asian Americans from NHANES. In 2011–2012, 25.6% of non-Hispanic Asian adults aged 20 and older were defined to have hypertension.[76] Earlier, the Multiethnic Study of Atherosclerosis showed the prevalence of hypertension to be similar in Chinese (39%) and whites (38%), lower than in African Americans (60%) and Hispanics (42%).[77] National data on self-reported hypertension from 2004–2006 have previously shown the percentage of people ever being told they had hypertension to be lowest in Chinese (17%) and Koreans (17%) as compared to Filipinos (27%) and Japanese (25%).[78]

RISK FACTORS FOR DEVELOPMENT OF HYPERTENSION

Although there is a dramatic age-related increase in the prevalence of hypertension, several important cardiovascular risk factors, including family history and genetic factors, educational/socioeconomic status, greater weight, physical inactivity, tobacco use, psychosocial stressors, diabetes, and diet (including dietary fat, higher sodium intake, lower potassium intake, and excessive alcohol) also relate to the likelihood of hypertension.[59] In fact, risk prediction models such as those developed by the Framingham Heart Study includes age, sex, systolic BP, diastolic BP, body mass index, smoking, and parental history of hypertension and predicts the development of hypertension over 25 years,[79,80] although underestimating risk, perhaps because there are additional factors not included in the model that may attribute to development of hypertension.

Age is probably the factor most strongly associated with hypertension and the powerful age-related increase in hypertension prevalence has been described above (see Fig. 23–5). More than 75% of persons older than 75 years of age have hypertension, making it the most predominant risk factor for CVD in older adults. In those free of hypertension at age 55, 93% of men and 91% of women will develop hypertension by age 80.[7] Systolic BP rises monotonically with age, whereas diastolic BP increases to about age 50, plateaus, and then decreases throughout the remainder of the life span. Increased arterial stiffness and decreased compliance is a major contributor to this increase in systolic BP and corresponding decrease in diastolic BP among most Western nations.[13]

Next to age, increasing weight may be the largest contributor to the development of hypertension; more than 42% of those with a body mass index of 30 kg/m^2 or greater have hypertension, compared to 28% in those who are overweight (body mass index, 25 to less than 30 kg/m^2) and only 15% in those with a body mass index less than 25 kg/m^2.[81] Of interest, increases in hypertension prevalence of 13% in men and 24% in women among US adults from 1988–1994 to 1999–2004 are almost completely explained by corresponding increases in body mass index, which when adjusted for, nearly completely diminish the increase in hypertension.[82] In addition, the Coronary Artery Risk Development in Young Adults (CARDIA) study showed those young adults who maintained a stable body mass index did not have increases in blood pressure over 15 years, but those whose body mass index increased by 2 kg/m^2 or more had significant increases in BP during the same period.[83]

Key lifestyle factors, in particular cigarette smoking and sodium intake, are important risk factors for hypertension. Cigarette smoking has an acute effect on increasing blood pressure, primarily through stimulation of the sympathetic nervous system with adverse effects on arterial stiffness and wave reflection. Also, hypertensive smokers are more likely to develop severe hypertension, including malignant and renovascular hypertension.[84] It has been shown the incidence of hypertension is increased in those who smoke 15 or more cigarettes per day.[85] A 14-year longitudinal study of more than 5000 Japanese

male workers showed smoking to be associated with the onset of both hypertension and systolic hypertension,[86] and a large Chinese cohort of 38,520 subjects showed both current smoking and previous cigarette smoking to be associated with an increased risk of hypertension, with a log-linear dose response relation found between duration of smoking and hypertension as well.[87]

Dietary sodium is implicated by numerous genetic, epidemiological, migrational, and intervention studies to contribute to increasing BP in the population, and higher salt intake is likely to contribute to CVD mainly through its effects on BP but also independently by increasing arterial stiffness and albuminuria.[88] The INTERSALT study, probably among the best known of such studies, involved 10,079 persons and found a strong positive relation between sodium intake and BP, with an increase of 6 g/d in salt intake estimated to elevated systolic BP 9 mm Hg over 30 years.[89] More recently, both the European Prospective Investigation into Cancer (EPIC-Norfolk) and International Population Study on Macronutrients and BP (INTERMAP) studies confirm these relationships.[90,91] Also, a recent Japanese study of 4523 participants shows higher versus lower sodium intake to be associated with a significant 25% greater risk of developing hypertension over approximately 3 years.[92] There is also strong evidence that salt reductions of 4.4 g/d for at least 4 weeks can lower systolic and diastolic BP by 4 and 2 mm Hg, respectively.[93]

Other predisposing factors to hypertension include gender. Men have a higher prevalence until about the sixth decade of life, after which a higher prevalence in women emerges and continues for subsequent decades; more women than men are affected by hypertension, mainly because of their longer life span. Race/ethnicity is also a major factor; as demonstrated above, African Americans have among the highest prevalences of hypertension compared to other major ethnic groups, and Mexican Americans have prevalences that are similar to that of whites. Excessive alcohol use and intake of an omnivorous as opposed to vegetarian diet also appears to be related to an increased likelihood of hypertension.[59]

HYPERTENSION AND CARDIOVASCULAR RISK

The Prospective Studies Collaboration data from numerous observational epidemiologic studies provide persuasive evidence of the direct relationship between BP and CVD. This meta-analysis aggregated data across 61 prospective observational studies that together enrolled 958,074 adults with 12.7 million person-years at risk, during which there were about 56,000 vascular deaths[94]; there were strong, direct relationships between average BP and vascular mortality. These relationships were evident in middle-age and older individuals (Fig. 23–8). Importantly, there was no evidence of a BP threshold; that is, vascular mortality increased progressively throughout the range of BP, including the prehypertensive range, down to a systolic pressure of 115 mm Hg and a diastolic pressure of 75 mm Hg. Between the ages of 40 and 70 years, each 20–mm Hg increment of systolic pressure (and 10–mm Hg of diastolic pressure) is associated with a doubling in the risk of stroke, with the slope of the lines relating BP and risk attenuated in older people.

RELATIVE CONTRIBUTION OF BLOOD PRESSURE MEASURES TO CARDIOVASCULAR RISK

A continuing debate in the field of hypertension is the relative importance of the different components of the arterial pressure wave in determining cardiovascular risk. There are four candidates: systolic BP, diastolic BP, pulse pressure, and mean arterial pressure. An additional issue is whether the traditional brachial artery pressure should be used or the central aortic pressure. For many years, the diastolic pressure reigned supreme, and most of the early hypertension treatment trials

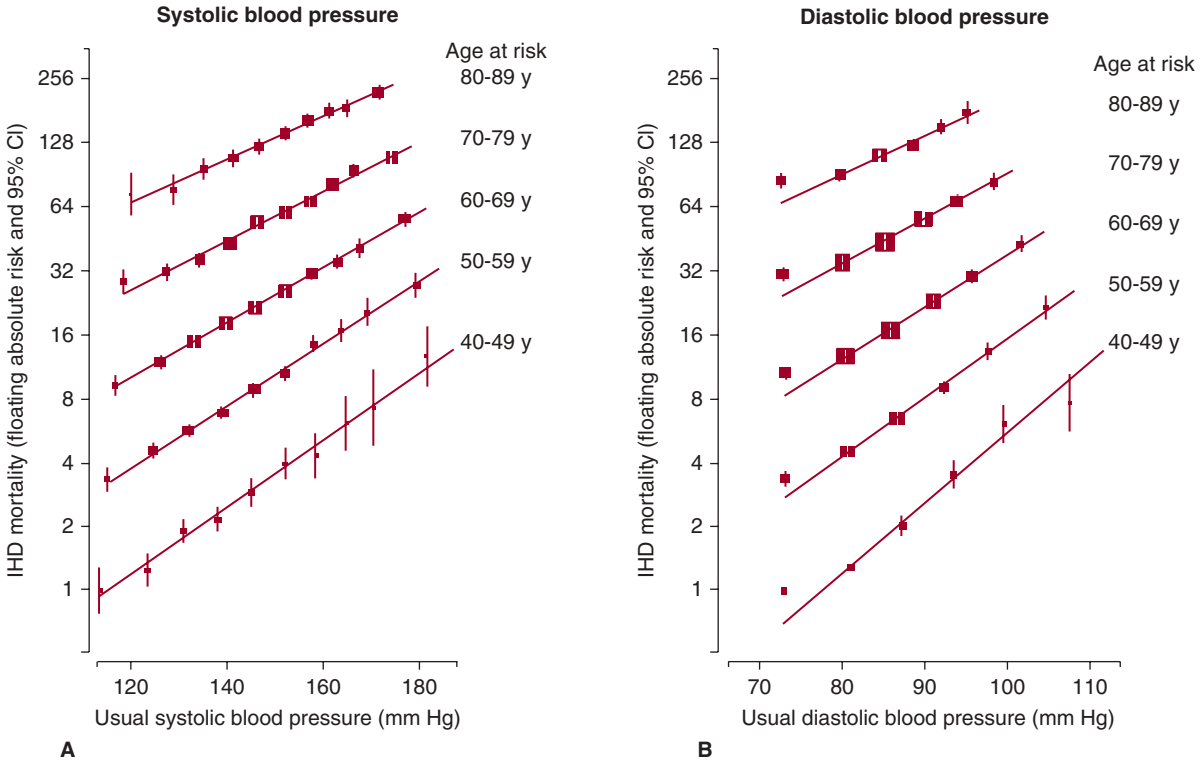

FIGURE 23–8. Relation of systolic blood pressure and diastolic blood pressure to ischemic heart disease mortality by age group. Reproduced with permission from Lewington S, Clarke R, Qizilbash N, et al: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002 Dec 14;360(9349):1903-1913.

used a high diastolic pressure as an entry criterion. This was reinforced by the publication of an analysis by MacMahon and coworkers[95] based on pooled data from 420,000 subjects, which showed a log-linear relationship between diastolic pressure and the risk of stroke and myocardial infarction. Although the importance of systolic pressure was never in doubt, it gained precedence over diastolic pressure with the publication of a series of epidemiologic studies showing not only that a high systolic pressure was the best predictor of risk in the elderly, but also that a low diastolic pressure was associated with increased risk.[96] An analysis by Franklin and coworkers[18] examined the Framingham Heart Study data and provided an elegant solution to this apparent paradox. In subjects younger than age 50 years, the best predictor of risk was a high diastolic pressure, but in those older than age 60 years, systolic pressure was the best predictor, and the relationship between diastolic pressure and risk was now negative, so that a low diastolic pressure was related to higher risk.

INCREASED PULSE PRESSURE

It is well known that systolic pressure increases steadily with age, but after the age of 50 years diastolic pressure starts to fall. A number of studies suggest that pulse pressure may be the best predictor of risk in the elderly. In the JNC 7, however, which is still the official guideline for the evaluation and management of hypertension,[2] there is no mention of pulse pressure as a predictor. Over the past 20 years, there have been multiple observational studies and controlled trials showing the value of pulse pressure as an important risk factor for CVD. This was clearly shown by an analysis of the Multiple Risk Factor Intervention Trial (MRFIT) data, which found that the highest risk group was patients who had a systolic pressure above 160 mm Hg and a diastolic pressure below 80 mm Hg.[97] The Framingham Heart Study using the combination of mean arterial pressure and pulse pressure together, rather than any single BP component separately (systolic BP, diastolic BP, mean arterial pressure, or pulse pressure) improved the fit monotonically for predicting CVD collectively or CHD, heart failure, and stroke separately.[98] Indeed, introducing the interaction terms pulse pressure multiplied by mean arterial pressure further improved the fit over the main effects of the two-component models, indicating that the effect of one BP component on risk varied accordingly to the level of the other. When pulse pressure, a measurement of stiffness, was combined with mean arterial pressure, a measurement of resistance, one could relate the two major physiologic components of hydraulic load to clinical outcome; single BP components cannot do this (Fig. 23–9).

Furthermore, there was evidence of a diastolic J-curve of increased CVD risk in individuals with isolated systolic hypertension and low diastolic BP (ie, < 70 mm Hg), which occurred in about 30% of untreated persons of at least 60 years of age in the NHANES survey.[99] There was a three-fold greater prevalence of CVD events from the highest to the lowest strata in untreated isolated systolic hypertension. Advanced age, female sex, and diabetes mellitus, but not treatment status, were associated with the low diastolic BP and widened pulse pressure. Most recently, in a follow-up of more than 45,000 subjects in the international Reduction of Atherothrombosis for Continued Health (REACH) registry, increasing pulse pressure quartile, after adjustment for mean arterial pressure, BP medication, and other risk factors was associated with increased risk of myocardial infarction, nonfatal stroke, cardiovascular hospitalization, and the composite CVD end point.[100] Moreover, the European Society of Hypertension has recognized widened pulse pressure as a distinct risk factor that is separate from elevated systolic BP in older individuals.[101]

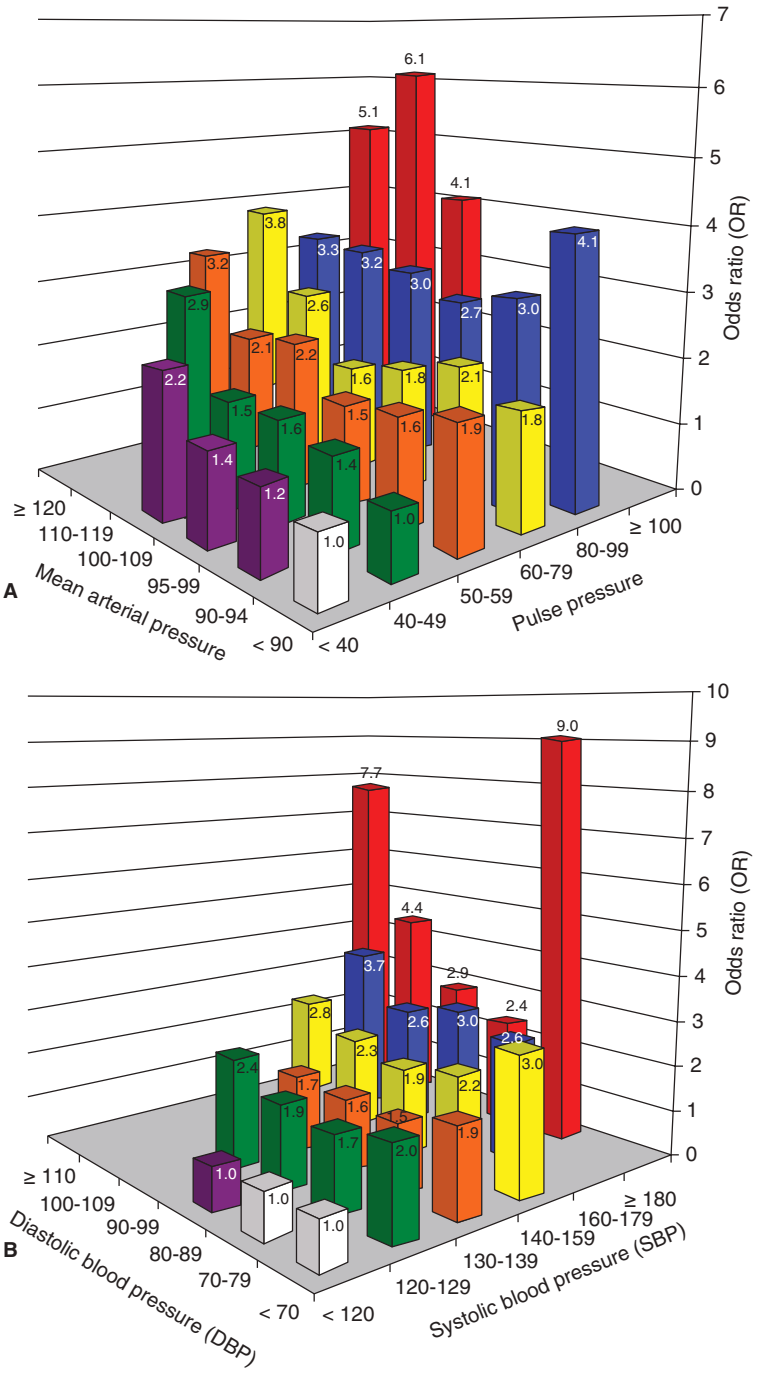

FIGURE 23–9. A. Odds for the likelihood of a cardiovascular event with combined pulse pressure (PP) and mean arterial pressure (MAP) categories in a 6 × 6 cross-classification three-dimensional bar graph, adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend. An interaction term of PP × MAP improved the model fit. **B.** Odds for the likelihood of a cardiovascular event with combined systolic blood pressure (SBP) and diastolic blood pressure (DBP) categories in a 6 × 6 cross-classification three-dimensional bar graph, adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend. An interaction term of SBP × DBP improved the model fit. Reproduced with permission from Franklin SS, Lopez VA, Wong ND, et al: Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009 Jan 20;119(2):243-250.

IMPACT OF LOW DIASTOLIC BLOOD PRESSURE

These findings support the point that a very low diastolic pressure in combination with a very high systolic pressure is associated with high risk. There are at least two explanations for this, which we may call *direct* and *indirect*. Taking the direct explanation first, it is possible that a very low diastolic pressure might impair coronary artery perfusion, which takes place during diastole. If this were the case, we should expect the adverse outcomes resulting from a low diastolic pressure to be ischemic cardiac events—but not strokes. The indirect explanation is that the low diastolic pressure is not harmful per se but is a marker for generalized CVD or, more particularly, increased arterial stiffness. It is generally accepted that the age-related increase of systolic and decrease of diastolic pressure that is seen in the brachial artery is largely the result of accelerated wave reflection found in stiff arteries.[102] Indeed, the Framingham Heart Study quoted above[99] and followed by a second study from the same group would support stiff arteries as a major cause of low diastolic BP.[103] This community-based study showed that persons with an initial CVD event and persistent isolated systolic hypertension in combination of diastolic BP of less than 70 mm Hg versus diastolic BP 70 to 89 mm Hg, had increased risk for recurrent CVD events; this included not only CHD as well as heart failure and stroke. Moreover, these findings support wide pulse pressure in combination with low diastolic BP as important risk factors, largely independent of antihypertensive treatment status.[103]

MEAN ARTERIAL PRESSURE

Mean arterial pressure is typically defined as diastolic pressure plus one-third of the pulse pressure, measured directly by oscillometric devices, although the numbers are rarely displayed. In an analysis of three intervention studies in older patients, Blacher and coworkers[96] found that pulse pressure, but not mean arterial pressure, predicted cardiovascular outcomes. However, in younger patients, mean arterial pressure is more important, especially in the prediction of stroke[104] in a study using ambulatory BP monitoring. One explanation for this finding may be that the patient with the high pulse pressure has increased arterial stiffness and is effectively being hit with a "double whammy": the high systolic pressure in the central aorta increases the afterload on the heart, and the low diastolic pressure impairs coronary perfusion. The reason why mean arterial pressure is a better predictor of stroke may be that it is closer to diastolic than to systolic pressure, and it has been shown that the relationship between diastolic pressure and stroke is steeper than for coronary events.[95]

CENTRAL VERSUS PERIPHERAL ARTERIAL PRESSURE

The arterial pressure wave in the brachial artery looks very different from the waves recorded at more proximal sites, where the damage to target organs, such as the heart and brain, occurs, and it is now possible to estimate the central aortic pressure indirectly from measurements made noninvasively from peripheral sites such as the radial artery. In older patients with stiff arteries, the central aortic systolic pressure is similar to the brachial pressure, whereas in younger subjects with compliant arteries, it is substantially lower.[101] As shown above, different drugs have different effects on pulse pressure, and recent studies show that similar differences occur in their effects on central pressure.[105] There are, however, many different methods for measuring arterial stiffness,[106] and there is disagreement regarding which is the most reliable. Some have been shown to predict cardiovascular events,[107,108] and it is likely that such measurements may become part of routine clinical practice in the future.

COMPLICATIONS OF HYPERTENSION

Hypertension promotes complications in the brain, heart, and kidneys through two related mechanisms, both of which involve the effects of increased pressure on the arteries. The first is the effects on the structure and function of the heart and arteries, and the second is the acceleration of the development of atherosclerosis. The former is directly the result of the BP, whereas the latter requires an interaction with other risk factors for CVD, most importantly cholesterol. Thus, strokes are closely related to the direct effects of BP, whereas CHD is related to atherosclerosis, depending more on the combination of the effects of hypertension with other risk factors; therefore, the relationship between BP and events is steeper for stroke than for CHD events.

Stroke, CHD, left ventricular hypertrophy, peripheral arterial disease, heart failure, and chronic kidney disease are principal complications of hypertension. The 36-year follow-up data from the Framingham Heart Study show that while the relative impact of hypertension is greatest for stroke and heart failure (RRs, 2.6–4.0), because overall incidence of CHD is greater than that for stroke or heart failure, the absolute impact of hypertension on CHD is greatest, even though the RR is lower (2.0–2.2).[109] A recent meta-analysis has further emphasized the importance of increasing risk above normotensive levels, showing that starting at a systolic BP/diastolic BP of 115/75 mm Hg, CVD mortality doubles with each increment of 20/10 mm Hg throughout the BP range.[110] Even compared to individuals with BPs of less than 120/80 mm Hg, those with BP levels of 130 to 139 mm Hg systolic or 85 mm Hg diastolic have a three-fold greater risk of CVD events.

CORONARY HEART DISEASE

The Prospective Studies Collaboration of 61 studies[110] found strong log-linear relationships between both systolic and diastolic pressure and the risk of CHD events in five deciles of age, ranging from 40 to 49 to 80 to 89, such that for each 20–mm Hg increase of systolic pressure, there was a two-fold increase of risk over a range from 115 to 180 mm Hg. For diastolic pressure, the risk doubled with a 10–mm Hg increase over a range of 75 to 100 mm Hg. There is an also an additive effect between various risk factors; for instance, the relation between systolic pressure and CHD risk is much steeper in patients whose cholesterol is high than in patients in whom it is normal.[111] This relationship has been reported in several countries, although the slope of the line relating BP and risk is shallower in countries where the overall risk of CHD is low, such as Japan.[112] The relationship between risk and BP in individuals who have already had an myocardial infarction is different and has been reported to be J-shaped for the first 2 years after the myocardial infarction (ie, there is a paradoxical increase of risk in those with the lowest BP [eg, < 110/70 mm Hg]); however, with longer follow-up, there is a positive relationship.[113] The increased mortality at lower levels of pressure may be an example of reverse causality; that is, the pressure is low because of extensive damage to the heart. A history of hypertension per se does not necessarily lead to an increased mortality after an myocardial infarction, but it does predict reinfarction.[114]

The official recommendation for the treatment of hypertensive patients with CHD is that the target BP should be 140/90 mm Hg; whether further reduction is beneficial or harmful is controversial. The J-curve hypothesis was postulated on the basis of observations suggesting that if diastolic pressure was lowered below a certain level (~85 mm Hg), there was a paradoxical increase of events.[115] The proposed explanation was that because coronary artery perfusion occurs during diastole, excessive reduction in combination with diseased coronary arteries would result in ischemia. Subsequent work supported this idea, because the J-curve was seen for myocardial infarction but not with

stroke, where the adage that the lower the BP, the better still holds. A recent analysis of the International Verapamil-Trandolapril Study (INVEST) trial,[116] which compared two drug regimens in post–myocardial infarction patients, confirmed that there was an increased risk of all-cause mortality and myocardial infarction. Again, there was no such relationship for strokes. Data from the Framingham Heart Study also support the idea of a J-curve phenomenon, but only in patients with previous myocardial infarctions and in the presence of a high systolic pressure as well as a low diastolic pressure.[117] This would be consistent with the results of the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial,[118] which randomized normotensive patients with documented CHD to amlodipine, enalapril, or placebo, and found that although both active drugs lowered the blood pressure, amlodipine resulted in a lower rate of recurrent events than either placebo or enalapril. The BPs at entry to the study were 129/78 mm Hg, and there was a 5–mm Hg reduction with treatment. Consequently, at the present time, it would seem prudent to avoid excessive reductions of diastolic pressure in patients with known CHD, particularly if the systolic pressure is high. In practice, however, there is approximately a 3 mm Hg decrease in SBP for each 1 mm decrease in DBP in elderly persons with antihypertensive therapy; thus, there is no evidence of increased cardiovascular risk until DBP reach levels below 65-70 mm Hg.

HEART FAILURE

Heart failure is now the leading cause of hospitalization for people age 65 years and older in the United States, and unlike other complications of hypertension, its prevalence has been increasing over the past 30 years.[119] For a 40-year-old man or woman, the "remaining lifetime risk" of developing heart failure is approximately 20%.[120] BP is a major contributor to heart failure with a two-fold greater risk in hypertensive versus normotensive men and three-fold greater risk in hypertensive versus nonhypertensive women; 90% of people with new cases of heart failure in the Framingham Heart Study had a history of previous hypertension.[121] It has been estimated that the percentages of heart failure resulting from hypertension are 59% in women and 39% in men, substantially higher than the population attributable risks for myocardial infarction resulting from hypertension, which are only 13% and 34%, respectively. This risk is much more strongly related to systolic than diastolic pressure.[122] Treatment of hypertension in older people reduces the incidence of heart failure by approximately 50%.[105] The good news is that the incidence of heart failure is now decreasing in women (but not men), whereas survival has improved in both sexes.[123]

Over recent decades, it has become apparent that approximately half of the patients who present with classic signs and symptoms of heart failure appear to have a normal ejection fraction of more than 50% on echocardiography. This group has been described as having diastolic dysfunction, diastolic heart failure, or heart failure with preserved ejection fraction. Diastolic heart failure is thought to be responsible for as many as 74% of cases of heart failure in hypertensive patients.[124] The Framingham Heart Study,[125] showed in a study of 73 heart failure patients that half had normal systolic function—and about 75% of those with and without normal systolic function had a history of hypertension. Mortality was high in both groups but higher in those with systolic heart failure. It is generally accepted wisdom that hypertensive patients develop ventricular hypertrophy and heart failure because the increased arterial pressure places an excessive burden on the heart (afterload). Why should the same explanation not apply to diastolic heart failure? Patients with diastolic heart failure have been found to have stiffer aortas than normal,[126] which may result in accelerated wave reflection from the periphery and a combined increase of central aortic systolic pressure and reduced diastolic pressure. The latter will lead to decreased coronary artery perfusion during diastole and hence impair myocardial relaxation.

CEREBROVASCULAR DISEASE

Stroke is the third most common cause of death throughout the world after CHD and cancer. Approximately 80% of strokes are ischemic, 15% are hemorrhagic, and 5% are caused by subarachnoid hemorrhage.[127] As with coronary events, there is a strong log-linear relationship between both systolic and diastolic pressure and stroke, although the relationship is steeper for strokes than for CHD events and much stronger for systolic than diastolic pressure.[128] Approximately 60% of patients who present with strokes have a past history of hypertension, and in those who are hypertensive, approximately 78% have not had their BP adequately controlled.[129] Of all the risk factors for stroke, hypertension has the highest relative risk (4.0 at 40–50 years, falling to 2.0 at ages 70–80 years), and the highest population attributable risk (40% at ages 40–50 years and 30% at ages 70–80 years). Also, stroke incidence is approximately three times greater in persons with stage 2 systolic hypertension (160 mm Hg or greater) and 50% higher in those with stage 1 systolic hypertension (140–159 mm Hg) compared to those with lower BP. In a recent report from the Northern Manhattan Study among 1750 participants aged at least 60 years, after adjustment for diastolic BP and other risk factors, even those with a systolic BP of 140 to 149 mm Hg had a 70% greater risk (HR, 1.7; 95% CI, 1.2–2.6) of stroke compared to those with a systolic BP of less than 140 mm Hg, suggesting a benefit for using the lower cutoff point.[130] The Prospective Studies Collaboration analyzed data from 45 prospective studies of 450,000 individuals and found a five-fold difference in stroke risk over a range of diastolic pressure from 75 to 102 mm Hg.[131] Global risk algorithms for the prediction of stroke have been developed by the Framingham Heart Study and the Cardiovascular Heath Study[132] and indicate systolic pressure to be the principal predictor, with other predictors being serum creatinine, diabetes, left ventricular hypertrophy by electrocardiogram, age, atrial fibrillation, and history of heart disease. Moreover, hypertension also indirectly raises risk of stroke through its role as an important risk factor for atrial fibrillation and left atrial enlargement, which both relate directly to stroke risk.[133,134]

The different subtypes of stroke have somewhat different relationships with BP. A large proportion of cerebral infarcts are classified as lacunar infarcts, which are the result of lesions in small arteries penetrating the deeper layers of the cerebral cortex, and approximately 70% of patients who experience these are hypertensive.[135] The characteristic pathology is a destructive lesion of the vessel wall, termed *lipohyalinosis*, which is distinct from both atherosclerosis and the remodeling of arteries that occurs in other vascular beds. Infarcts of the large cranial and extracranial arteries are more related to atherosclerosis, and only 50% of patients with this type of stroke are hypertensive (despite being the most important risk factor).[136] Cardioembolic strokes are being increasingly recognized, and atheromatous plaques that protrude from the aorta are an independent risk factor for ischemic strokes.[137] Cerebral hemorrhage also shows a very strong relationship with hypertension and, particularly concerning, with discontinuation of antihypertensive medications.[137]

The decline in the death rate from strokes since the 1960s has received a lot of publicity, and because BP is such an important risk factor for stroke, it is tempting to think that better hypertension control can take the credit. There are, however, reasons why this may not be the case. First, the decline of stroke mortality preceded the widespread use of antihypertensive medications.[138] Second, attempts to correlate the decline of mortality with improved BP control rates have been unsuccessful,[139] suggesting that changes in socioeconomic status might be

more important. However, since the publication of the guideline on BP management from committee members of the JNC 8 recommending a higher cutoff point of less than 150/90 mm Hg for control of BP in persons aged 60 and over, this is renewed concern that this may have a deleterious effect on overall BP control in the very population (older persons) at increased risk of stroke.[140]

BP typically rises acutely after a stroke, and it is postulated that this helps to maintain cerebral perfusion in the infarct's *penumbra* zone.[141] This forms the rationale for avoiding excessive reduction of BP immediately after a stroke.

Treatment of hypertension reduces stroke rates by 35% to 44%[142]; this has been shown in both younger patients with systolic and diastolic hypertension and in older patients with isolated systolic hypertension.[105] Recent data from the Hypertension in the Very Elderly Trial (HYVET) suggests that treatment of patients older than age 85 years leads to a statistically significant 39% reduction in the risk of death from stroke. Although shy of statistical significance, the primary end point of fatal and nonfatal stroke was reduced by 30% in the active treatment group.[58] There is general agreement that the reduction of BP is more important than which drugs are used to lower it, but there are some minor differences. β-Blockers are less effective than other drugs for preventing stroke,[142] and there is some evidence that angiotensin-receptor blockers may be more effective.[143]

CHRONIC KIDNEY DISEASE

The Multiple Risk Factor Intervention Trial showed systolic BP of greater than 140 mm Hg to be associated with a five- to six-fold greater risk for end-stage renal disease (ESRD) compared to systolic BP of less than 117 mm Hg. Risk of developing ESRD is graded and continuous; even high normal BP has two-fold greater risk of developing ESRD compared to those with optimal BP.[144] A Japanese study of nearly 100,000 men and women found a progressive relationship between the height of the BP and the risk of developing ESRD during a 17-year follow-up period, such that there was an increased risk even in patients with high normal BP, in comparison with those whose pressure was optimal (< 120/80 mm Hg).[145] Hypertensive patients whose BP is not well controlled are more likely to show a deterioration of renal function.[146] In a large pooled cohort study of more than 500,000 individuals from the Asia-Pacific region followed for a median of 6.8 years, systolic BP was the strongest risk factor for renal death with each standard deviation increase in systolic BP (19 mm Hg) associated with a more than 80% higher risk (HR, 1.84; 95% CI, 1.60–2.12).[147] A study of post–myocardial infarction patients found that there was a steep and linear relationship between glomerular filtration rate (GFR) and cardiovascular death.[148] In addition, hypertensive patients with mildly impaired renal function (estimated GFR < 60 mL/min) have an increased prevalence of target organ damage, such as left ventricular hypertrophy, increased carotid intima-media thickness, and microalbuminuria.[149] Moreover, compared to those with normal BP, masked hypertension as identified by ambulatory BP readings in the Chronic Renal Insufficiency Cohort was recently shown to be associated with reduced estimated GFR in those with chronic kidney disease (CKD).[150] In addition, higher BP variability has also been shown to be associated with poor renal outcomes as indicated by incident ESRD in persons with hypertension in the large Antihypertensive Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT).[151] The importance of these considerations to cardiologists is, first, that CKD is an important consequence of hypertension, and, second, it is associated with a marked increase in cardiovascular risk. In the case of patients on hemodialysis, the risk is 10 to 30 times higher than in the general population, and a task force of the American Heart Association has recommended that patients with CKD should be considered as being in the highest risk group for cardiovascular disease.[152] There are two main effects of CKD on the arteries: (1) increased prevalence of atherosclerosis and (2) remodeling of the arteries and increased stiffness, which has been related to increased mortality.[107]

As highlighted by JNC 7,[2] the dramatic decline in death rates from CHD and stroke that we have witnessed in the past 30 years has not been paralleled by any decline of ESRD, which has been showing a relentless increase.[2] Many of these incident cases have been attributed to poorly controlled hypertension and the others mostly to diabetes. Renal disease and diabetes are the two conditions where JNC 7[1] and other guidelines, such as those from the National Kidney Foundation,[153] have proposed lower thresholds for treatment (130/80 vs 140/90 mm Hg) than in other hypertensive patients, so one would think that the relationship between BP and clinical outcomes should be particularly tight in these conditions.

PERIPHERAL ARTERIAL DISEASE

Hypertension is a major risk factor for peripheral vascular disease. This is important for two reasons: first, it causes debilitating symptoms, and second, it is a marker of high risk for cardiovascular events.[154] The accepted definition is an ankle brachial BP index of less than 0.9 (the ratio between the systolic pressure in the ankle and the brachial artery). This test was performed in the latest NHANES examination, and in adults older than age 40 years, the prevalence was 4.3%.[155] It is strongly associated with the risk factors of atherosclerotic disease—hypertension, smoking, cholesterol, diabetes, and, most importantly, age. In a study of the Framingham Offspring, the strongest risk factor for peripheral vascular disease was age (odds ratio [OR], 2.6/10 y), followed by hypertension (OR 2.2), and smoking (OR 2.0).[156] Peripheral arterial disease (intermittent claudication) also varies three- to four-fold across systolic BP quintiles.[17] Moreover, a recent report involving electronic health records from more than 4 million adults in the United Kingdom noted a 20–mm Hg higher than usual systolic BP to be associated with a 63% higher risk of peripheral arterial disease (HR, 1.63; 95% CI, 1.59–1.66)—more reliably than CHD.[157] The detection of peripheral vascular disease should prompt a search for atherosclerotic disease in other vascular beds, because 60% of patients with it have significant coronary disease, cerebrovascular disease, or both, whereas 40% of patients with coronary or cerebrovascular disease also have peripheral vascular disease.[158]

RISK STRATIFICATION FOR HYPERTENSION

Although current US guidelines suggest treatment for all persons younger than 80 years of age with a BP of at least 140/90 mm Hg, not all persons with hypertension have the same risk for CVD and therefore the appropriateness of a single target level of BP regardless of level of risk could be questioned. In fact, analysis of US adults with hypertension in NHANES using Framingham risk assessment showed that 24% of subjects were actually at low risk (< 10% 10-year risk of CVD), 21% intermediate risk (10%–20%), 23% high risk (> 20%), and 32% had prior CVD. These data show 55% of US adults with hypertension to be at high risk (> 20% 10-year risk of CVD or with preexisting CVD), but such an approach may underestimate persons at significant long-term risk. The addition of European algorithms that include those with metabolic syndrome, diabetes, or CKD as high risk would raise this proportion to 80%.[159] Current European Society for Hypertension guidelines have such a risk stratification algorithm identifying persons at successively lower levels of BP to be at high or very high risk according to the accompanying number of risk factors, diabetes, and/or presence of target organ damage (Table 23–4).[160]

TABLE 23–4. European Society for Hypertension Risk Stratification Algorithm[a]

Other Risk Factors, Asymptomatic Organ Damage, or Disease	Blood Pressure (mm Hg)			
	High-normal SBP 130–139 or DBP 85–89	Grade 1 Hypertension SBP 140-159 or DBP 90–99	Grade 2 Hypertension SBP 160-179 or DBP 100–109	Grade 3 Hypertension SBP ≥ 180 or DBP ≥ 110
No other risk factors		Low risk	Moderate risk	High risk
One to two risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
Three or more risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Organ damange, CKD stage 3, or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4, or diabetes with organ damage/risk factors	Very high risk	Very high risk	Very high risk	Very high risk

[a]According to blood pressure level and the accompanying number of risk factors, diabetes, and/or presence of target organ damage.

Adapted with permission from Mancia G, Fagard R, Narkiewicz K, et al: 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2013 Jul;34(28):2159-2219.[160]

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

HYPERTENSION AWARENESS TREATMENT AND CONTROL

AWARENESS

The NHANES surveys have for decades provided estimates of the prevalence of hypertension and have asked participants if they have been diagnosed as having hypertension. The proportion of hypertensive subjects who are aware of their condition has improved since 1988 to 1991 when it was 69.2%[161] to 82.7% in 2009–2012 in adults aged 20 and older,[162] with both awareness and treatment greater in older people and in non-Hispanic blacks (87%) compared to Hispanics (77.7%). It has also been shown that awareness, treatment, and control of hypertension varies by region of the United States, being highest in the southeastern United States.[163]

In countries in which health care systems are less well developed, the level of awareness of hypertension is much lower. In China, 35.6% of city dwellers were aware of their condition in 1991, but only 13.9% of those living in rural areas were aware of their condition.[61]

TREATMENT AND CONTROL

The usual definition of BP control is a level less than 140/90 mm Hg. Since 2003–2004, when only 39.4% of persons with hypertension were under control, latest data from 2011–2012 show the control rate now at 51.8%, with a corresponding improvement in treatment rates from 65.0% to 74.5%. Importantly, among those taking prescription medication, BP control rates improved from 65.0% to 74.5% during this period. However, medication use among persons with hypertension is still highly variable, ranging from only 44.5% in those aged 18 to 39 years to 82.2% in those aged 60 years and older. Moreover, treatment rates among non-Hispanic black adults are highest (77.4%) compared to whites (76.7%), Hispanics (73.5%), and Asians (lowest, at 65.2%). Despite the relatively decent treatment rates among non-Hispanic blacks and Hispanics, data show they are 40% more likely to have uncontrolled BP than whites.

In the United States, approximately 52% of hypertensive persons are taking medications, whereas in the Europe the numbers are much lower: In Germany, where the prevalence of hypertension is very high (55%), only 26% of patients are taking antihypertensive medication.[60] In other countries, the rate is even lower. In China, in 1991, the control rate was 4% in urban areas and 1% in rural areas. In Egypt, the control rate is 8%.[61] However, surveys based on health care programs rather than the general population give a more optimistic picture. The 2003 Health Plan Employer Data and Information Set (HEDIS) report stated that BP control rates ranged from 58.6% for Medicaid to 62.2% for commercial plans, but studies based on ambulatory care practices have quoted figures in the range of 30% to 50%.[59] In clinical trials, control rates of up to 70% can be obtained[164]; the crucial ingredients here are likely to be the use of rigid treatment protocols and the fact that the participants are likely to be compliant.

The public health implications of poor BP control are enormous. It has been estimated that controlling BP to the JNC target levels could prevent 19% of CHD events in men and 31% in women.[165] Importantly, in a recently published systematic review and meta-analysis, involving 123 clinical trials comprising 613,815 subjects, every 10–mm Hg reduction in systolic BP was noted to significantly reduce the risk of major cardiovascular events by 20%, CHD by 17%, and stroke by 27%, with an overall significant 13% reduction in all-cause mortality. However, there was no benefit seen with renal failure.[166]

FACTORS RELATED TO POOR BLOOD PRESSURE CONTROL

Although hypertension treatment has increased over the years, treatment still remains suboptimal, with control affected not only by age, severity of hypertension, and presence of comorbidities (eg, resistant patients are often older and have isolated systolic hypertension and CVD), but also by nonadherence, inaccurate measurements, and failure to recognize a white coat effect. Physicians' therapeutic inertia, involving an insufficient or inappropriate combination of agents, is also an important factor.[7]

Treatment and control rates also vary according to risk group and comorbidity. We have previously demonstrated treatment for hypertension to be lowest (58%) in those categorized as low risk and highest

TABLE 23–5. Factors Related to Poor Control of Hypertension

Patient	Physician	Health Care System
Older age	Therapeutic inertia	Poor availability of care
Resistant hypertension	Inappropriate choice of drugs	
Poor adherence	Lack of knowledge	
Poor access to care		

(75%) in those classified as high risk according to Framingham global risk scores, but the reverse is seen with control of BP, being highest (80%) in those at low risk and lowest (< 50%) in high-risk persons.[167] Moreover, in persons with known CVD, control rates are poor with elevations in systolic BP being the main problem, and often being more than 20 mm Hg from goal. Higher risk persons or those with cardiovascular comorbidities are also typically older, and thus isolated systolic hypertension becomes the predominant issue and with increased arterial stiffness is more difficult to control, even with polypharmacy.

Barriers to adequate BP control are also related to other factors involving the patient, the health care provider, and the health care system.[168] Table 23–5 lists some of the more important reasons.

It is often typical to blame the patients for the poor rates of BP control, on the grounds that they are not taking their prescribed medications. One survey found that 70% of physicians attributed treatment failures to poor compliance by their patients, whereas 81% of patients thought their compliance was good.[169] One recent report[170] notes dropout rates of up to 15% in the first year and 25% in the second year of treatment. By the end of 2 years, 25% to 33% of patients are no longer compliant with the treatment regimen. Thus this report indicates that compliance decreases with years of treatment; because control of hypertension requires a lifelong adherence to medication, this is clearly an important factor in morbidity and mortality caused by sustained BP elevations. It has also been shown that in patients receiving triple therapy, that use of a fixed-dose combination plus one pill results in better adherence and even lower risk of cardiovascular events compared to taking three separate pills.[171]

Another major factor is therapeutic inertia, a concept that was first put on the map by Berlowitz and coworkers[172] who surveyed Veterans' Affairs (VA) clinics and found that 40% of hypertensive patients had BPs in excess of 160/90 mm Hg, despite an average of six annual visits. Increases in medications were prescribed in only 7% of visits. This state of affairs is not likely to be a result of physicians' ignorance about the goals of treatment. In a survey conducted at about the same time as the Veterans' Affairs study, 97% of physicians knew that the goal BP was 140/90 mm Hg.[173] Knowledge does not necessarily dictate behavior, however. In another study of 21 primary care physicians in the United States[174] who were also familiar with the guidelines, the systolic pressure of their hypertensive patients was above 140 mm Hg at 93% of visits. A more recent study[175] surveyed clinical records of 7253 hypertensive patients from family practices in the South and quantified therapeutic inertia as the proportion of visits during which the BP was more than 140 mm Hg systolic or 90 mm Hg diastolic, with no increase in medication. The main finding was a linear relationship between the therapeutic inertia scores and the degree of BP control. For the highest quintile of therapeutic inertia (ie, the least likely to increase antihypertensive medications), the control rate was 25% at the first visit and 6% at the last visit. In contrast, for the lowest therapeutic inertia quintile, the control rate increased from 53% to 75%. In addition, a recent clinical trial showed intervention consisting of an outreach coordinating raising patient and provider awareness of unmet BP goals, as well as arranging BP-focused primary care visits and treatment decision support to reduce clinical inertia, although this did not result in differences in BP changes compared to the usual care group.[176] Also, a large study of 28 US-based physician organizations showed care management processes involving physician education efforts to improve medication fill compliance, systematic processes for screening or assessing patients for hypertension, and maintaining a list of hypertensive patients with clinical data were shown to result in improvement in BP control.[177]

In a recent review of BP control rates in the United States, achieved both in different health care systems and in clinical trials, Krakoff[178] suggested four types of intervention that might improve national rates of control: (1) providing education and feedback to providers (which would include attention to therapeutic inertia), (2) making greater use of nonphysician providers, (3) wider use of electronic medical records, and (4) self-monitoring of BP. Probably the best example of a large health care system's implementation of a large-scale hypertension program derives from Kaiser Permanente Northern California. Using a comprehensive hypertension registry, developing and sharing performance metrics, using evidence-based guidelines, medical assistant visits for BP checks, and a single-pill combination therapy, hypertension control improved from 43.6% in 2001 to 80.4% in 2009, in comparison to the national average where control improved from only 55.4% to 64.1%.[179]

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CHAPTER 24

PATHOPHYSIOLOGY OF HYPERTENSION

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More than 1 *billion* individuals worldwide, including at least 70 million Americans, have high blood pressure (BP) warranting some form of treatment.[1–4] Higher-than-optimal BP is the largest contributor to global mortality, and approximately 9.4 million deaths per year are attributed to uncontrolled hypertension.[2–4] As life expectancy continues to increase, hypertension will become an even more important medical and public health issue because BP typically increases with aging in most industrialized countries. In the United States, 50% of people 60 to 69 years of age and approximately 75% of people 70 years or older have hypertension.[3] In some nonindustrialized populations, however, BP does not rise with increasing age, and only a small fraction of the population develops hypertension. This suggests that predisposing environmental factors play a major role in causing hypertension and that an increase in BP with aging is not inevitable when these factors are absent.

A direct positive relationship between BP and cardiovascular disease (CVD) risk has been observed in men and women of all ages, races, ethnic groups, and countries, regardless of other risk factors for CVD.[1] Observational studies indicate that death from CVD increases progressively and linearly as BP increases above 115 mm Hg systolic and 75 mm Hg diastolic.[1] For every 20–mm Hg increase in systolic BP or 10–mm Hg increase in diastolic BP, there is a doubling of mortality from both ischemic heart disease and stroke in all age groups from 40 to 89 years of age.[5]

Despite major advances in our understanding of its pathophysiology and the availability of many drugs that can effectively reduce BP in most hypertensive subjects, hypertension continues to be the most important modifiable risk factor for CVD.

HYPERTENSION CLASSIFICATION

BP is a variable, quantitative trait with a nearly normal distribution. In industrialized societies, where there is typically higher dietary sodium and increasing body weight with age, the BP distribution is skewed slightly to the right.

BP classification is determined through analysis of observational and experimental data (clinical trials) regarding the relationship of BP and cardiovascular risk. Several organizations provide BP or hypertension classifications based largely on measurements obtained in a single encounter ("office" BPs). Classifications based on home BP monitoring and 24-hour ambulatory BP monitoring will likely be common in the future.[6]

The cutoff points for BP classification are generally driven by evidence from clinical trials and represent recommended levels for initiation of pharmacological therapy, goal BP, and recommended levels for initiation of nonpharmacological therapy. The levels for initiation of drug therapy and goal BP have traditionally been the same BP level.

The most commonly cited and used BP classifications are the 2003 Seventh Report of the United States Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[7] (Table 24–1) and the 2013 European Society of Cardiology/European Society of Hypertension Guidelines for the Management of Hypertension[8] (Table 24–2). The JNC guidelines will, in the future, be replaced by guidelines from the American College of Cardiology/American Heart Association.[9]

Results of the Systolic Blood Pressure Intervention Trial (SPRINT)[10,11] will have an impact on upcoming guidelines, including the classification of BP. The SPRINT protocol called for treating participants over age 50 with systolic BP of 130 to 180 mm Hg and high cardiovascular risk to goal systolic BP of 140 or 120 mm Hg. Based on a clear benefit for the systolic BP goal of 120 mm Hg, we anticipate that the threshold for initiation of pharmacological therapy and the goal systolic BP may be reduced compared to previous guidelines.

PRIMARY (ESSENTIAL) HYPERTENSION

Primary (essential) hypertension accounts for about 95% of all cases of hypertension and has been traditionally defined as high BP for which an obvious secondary cause (eg, renovascular disease, aldosteronism, pheochromocytoma, or gene mutations) cannot be determined.

TABLE 24–1. JNC 7 Classification of Blood Pressure for Adults Ages 18 Years and Older[a]

Category	Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)
Normal[b]	< 120	and	< 80
Prehypertension	120–139	and	81–89
Hypertension[c]			
Stage 1	140–159	or	90–99
Stage 2	≥ 160	or	≥ 100

[a]This classification assumes that patients are not taking antihypertensive drugs and are not acutely ill. When systolic and diastolic pressures fall into different categories, the higher category should be used to classify the individual's blood pressure status. Isolated systolic hypertension is defined as systolic blood pressure of 140 mm Hg or above and diastolic blood pressure below 90 mm Hg and staged appropriately.

[b]Normal blood pressure with respect to cardiovascular disease risk is below 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.

[c]Based on the average of two or more readings taken at each of two or more visits after an initial screening.

Abbreviations: JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

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Although primary hypertension is heterogeneous, some of the main causes of high BP are known. For example, overweight and obesity may account for 65% to 75% of the risk for primary hypertension, as discussed later in this chapter. Sedentary lifestyle, excess intake of alcohol or salt, and low potassium intake are also known to increase BP in some patients. Thus, identified causes can be often found in patients classified as having primary hypertension.[12]

This chapter discusses basic concepts of circulatory regulation, the physiologic mechanisms involved in short- and long-term BP control, and the pathophysiologic changes that can lead to secondary hypertension as well as primary hypertension. We also review interactions of genetic and environmental factors that influence intermediate phenotypes such as activity of the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), endothelial factors, oxidative stress, and natriuretic hormones. These, in turn, influence vascular resistance, cardiac output, renal excretion of salt and water, and therefore BP.

TABLE 24–2. European Classification of Blood Pressure Levels[a]

Category	Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)
Optimal	<120	and	<80
Normal	120-129	and / or	80-84
High normal	130-139	and / or	85-89
Grade 1 hypertension	140-159	and / or	90-99
Grade 2 hypertension	160-179	and / or	100-109
Grade 3 hypertension	≥180	and / or	≥110
Isolated systolic hypertension	≥140	and	<90

[a]According to the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.

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BASIC CONCEPTS OF CIRCULATORY CONTROL

RELATIONSHIP OF TISSUE BLOOD FLOW AND CARDIAC OUTPUT REGULATION

Discussion of cardiac output (CO) regulation often begins with the well-known formula *cardiac output = stroke volume × heart rate*. This equation describes mathematically the determinants of cardiac pumping but does not elucidate another major factor that normally controls CO—the venous return (total tissue blood flow), which is the amount of blood available for the heart to pump.

Figure 24–1 illustrates the relationship between CO and tissue blood flows; it is obvious that CO, in the steady state, is equal to the sum of the blood flows in the body's tissues and organs. Removing one kidney, for example, decreases venous return to the heart by approximately 10% (assuming that total flow to both kidneys is approximately 20% of the CO). Decreased CO would also occur with amputation of an arm or a leg or removal of any other tissue from the body. Conversely, increased CO occurs when additional tissue is added to the body during normal growth, weight gain, or pregnancy. These examples illustrate that CO is determined not only by the pumping ability of the heart but also by the peripheral circulation. Except when the heart is severely weakened and unable to adequately pump the venous return, CO (total tissue blood flow) is determined mainly by the metabolic needs and other special requirements of the body's tissues and organs; the heart plays a permissive role is controlling CO and intrinsic and neurohumoral mechanisms normally allow the heart to effectively accommodate large changes in venous return.

This conceptual framework helps to explain changes in CO during exercise (when metabolic activity and skeletal muscle blood flow are increased), after eating a large meal (which increases metabolic activity and gastrointestinal blood flow), and in pathophysiologic conditions such as hypertension in which CO and tissue blood flows are usually normal unless metabolic demands of the tissues are altered.

The importance of tissue blood flow regulation in determining CO can also be illustrated by considering the chronic effects of vasodilators and vasoconstrictors. In most cases, CO changes very little even when there are high levels of circulating vasoconstrictors (eg, angiotensin II

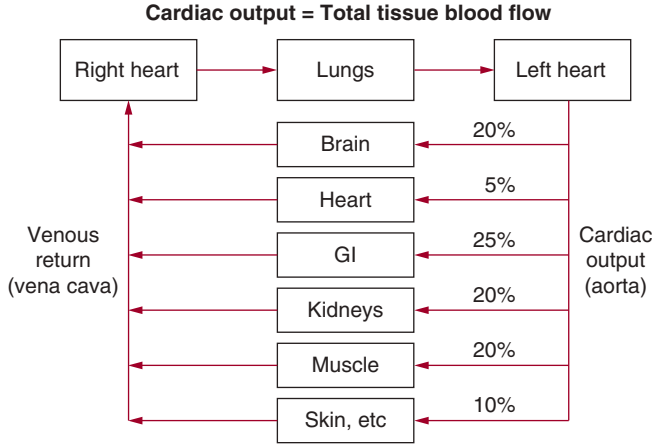

FIGURE 24–1. Relationship between cardiac output, peripheral blood flow regulation, and venous return. GI, gastrointestinal.

[Ang II]) or vasodilators (eg, calcium channel blockers). If CO regulation is the sum of all local blood flow regulations, why is CO not significantly altered in these conditions?

To answer this question, consider one of the most fundamental principles of circulatory function—the ability of each tissue to *autoregulate* its own blood flow according to the metabolic needs and other functions of the tissue.[13–15] Administration of a powerful vasoconstrictor, such as Ang II, may cause a transient decrease in tissue blood flow and CO but usually has little long-term effect if tissue metabolic rate is unchanged. Likewise, vasodilators cause only short-term changes in tissue blood flow and CO if they do not alter tissue metabolism.

Therefore, consideration of tissue blood flow control is important for understanding CO regulation. Local tissue blood flow regulation involves short- and long-term mechanisms. Acute control occurs within seconds or minutes as a result of constriction or dilatation of the vasculature. After administration of a vasoconstrictor that does not alter tissue metabolic rate, there is a transient decrease in tissue supply of nutrients and oxygen and accumulation of metabolic waste products. This, in turn, causes vasodilation and return of tissue blood flow toward normal. In tissues where blood flow regulation is not determined mainly by metabolic needs, such as the kidney, some vasoconstrictors, such as Ang II, may cause small, sustained decreases in blood flow that barely reduce CO. Other short-term controls, such as the *myogenic response*, also alter vascular resistance in response to changes in BP and help to autoregulate tissue blood flow.[16]

Long-term blood flow regulation takes place over days or weeks and involves structural changes in the blood vessels, such as thickening of vessel walls and decreased numbers of capillaries (rarefaction) in some tissues when BP is chronically elevated. When tissues grow, additional blood vessels are generated (*angiogenesis* or *vasculogenesis*) to provide the required blood flow and metabolic substrates for the tissues. Together, the short- and long-term mechanisms maintain the required levels of blood flow in each tissue to ensure normal function. Thus, in most physiologic conditions, excluding those associated with impaired cardiac pumping ability, CO reflects mainly the combined actions of multiple control mechanisms for blood flows in the body's tissues and organs.

In conditions such as heart failure or when large increases in cardiac output are needed to meet the metabolic demands of the body's tissues, such as exercise, various factors that alter cardiac pumping also play a major role in regulating cardiac output.

BLOOD FLOW REGULATION IN HYPERTENSION

The main function of the circulation is to provide adequate blood flow to each tissue to meet its requirements. This is achieved by a combination of local tissue controls that regulate vascular tone as well as overall adjustments of the circulation that influence cardiac pumping and vascular tone.[13,17] For example, during intense exercise, local conditions (eg, accumulation of metabolites or decreased levels of oxygen and nutrients) in skeletal muscles cause intense vasodilation that permits adequate blood flow to match the increased metabolic requirements of the muscles. Although decreased peripheral vascular resistance tends to decrease BP, this is usually offset by multiple neurohumoral changes (eg, sympathetic stimulation) that tend to elevate BP.

If decreased vascular resistance continues for several days, such as occurs with anemia or with opening a large arteriovenous fistula, additional adjustments take place that cause salt and water retention by the kidneys and increased blood volume or even hypertrophy of the heart if the stimulus lasts for several weeks. Thus, multiple factors that control the circulation, including those that influence CO, BP, blood volume, and others, normally work in concert to provide adequate tissue blood flow.

These same mechanisms also operate in hypertension. However, one of the important characteristics of many, but not all, hypertensive patients is that they have increased total peripheral vascular resistance (TPR). In most instances, however, tissue blood flows are approximately the same in normotensive and hypertensive subjects and are regulated at a level that is adequate for the tissue needs.[18] The elevated TPR observed in many patients with hypertension appears to be an autoregulatory response that helps to maintain normal tissue blood flow despite increased BP rather than a primary cause of the hypertension. Thus, the hemodynamic pattern often (but not always) observed in nonobese subjects with primary hypertension is normal blood flow, normal oxygen consumption, and elevated vascular resistance.[18]

Cerebral blood flow, for example, shows a normal value of about 50 mL/min/100 g per tissue weight in primary hypertension. Coronary blood flow is elevated in essential hypertension in proportion to the increase in myocardial hypertrophy. Blood flow per unit weight of heart muscle is usually normal, however, with a value of about 80 mL/min/100 g per tissue weight. Splanchnic blood flow is slightly reduced in essential hypertension, having a typical value of about 750 mL/min/m^2 of surface area compared with about 800 mL/min/m^2 in normotensive subjects. Skin blood flow is also normal in individuals with primary hypertension.

Renal blood flow may be increased, normal, or decreased in primary hypertension. These seemingly disparate observations, however, should be interpreted with regard to the special functional needs of the kidney and the conditions under which renal blood flow is studied. For example, increased dietary protein, high sodium intake, and excess weight gain all are associated with increased renal blood flow. Nephron loss, which may occur with prolonged, uncontrolled hypertension and diabetes, leads to reduction in renal blood flow. Impaired renal blood flow is also related to the cause of hypertension in some individuals.

Although resting skeletal muscle blood flow is usually normal in primary hypertension, several differences in blood flow regulation have been noted. For example, the ability of skeletal muscle blood vessels to dilate in some patients with primary hypertension is impaired. This reduced blood flow "reserve" in hypertension is probably a result of structural limitations imposed by blood vessel hypertrophy and of endothelial dysfunction and impaired release of nitric oxide (NO).

In general, the maximal level of exercise, as quantified by oxygen uptake, is depressed in proportion to the severity of hypertension. BP is high before exercising and increases even further during exercise. In the presence of impaired vasodilation, elevated BP boosts blood flow through the skeletal muscle but it also increases cardiac afterload, which limits CO and exercise performance. At each level of exercise below maximum, however, CO and skeletal muscle blood flow are generally identical to flows seen in normotensive subjects.[18] These flows are achieved at higher vascular resistances and higher BPs; the resistance and BP effects cancel each other to yield a normal blood flow in most tissues.

In obese hypertensive patients, resting skeletal muscle blood flow per gram of tissue weight may be elevated compared with lean individuals. However, increased muscle blood flow during exercise is attenuated and forearm-reactive hyperemia after temporary occlusion of the brachial artery is less in obese than in lean normotensive subjects.[19] Thus, although obesity-associated hypertension may be associated with increased resting blood flow, flow reserve is often reduced.

In older hypertensive individuals, total tissue blood flow (ie, CO) may be reduced compared with flow in younger individuals. This is perhaps not surprising if one considers that lean muscle mass usually decreases with aging. Because CO represents total tissue blood flow, decreased muscle mass and decreased physical activity characteristic of older hypertensive patients also are associated with reduced CO and decreased total body oxygen consumption.

ARTERIAL PRESSURE AND REGIONAL BLOOD FLOW REGULATION

Adequate tissue blood flow in response to normal daily activities requires adequate BP. When a person with normal autonomic reflexes begins to exercise, skeletal muscle vascular resistance is reduced, but muscle blood flow and CO increase markedly and BP remains relatively constant. In persons with autonomic dysfunction, exercise also decreases skeletal muscle vascular resistance, but BP decreases and muscle blood flow and CO increase only modestly because of impaired autonomic reflexes. Therefore, exercise is not well tolerated and syncope may occur.

When CO is inadequate to meet normal tissue needs, as in heart failure or severe hypovolemia, strong activation of the SNS, the RAAS, and other hormonal factors produce vasoconstriction that may override normal flow regulation in some organs, such as skeletal muscle and skin. This keeps BP from falling too low and provides adequate blood flow to the vital organs, especially the brain and the heart.

BASIC PRINCIPLES OF BLOOD PRESSURE REGULATION

The major function of BP is to provide the driving force that moves blood through the vascular system to supply the needs of the tissues. Consequently, BP regulation is a complex physiologic function that depends on integrated actions of multiple cardiovascular, renal, neural, endocrine, and local tissue control systems.

BP varies throughout the day depending on the activity of the body, environmental influences, and the responses of multiple BP control systems. Hypertension is usually considered to be a disorder of the average level at which BP is regulated during resting conditions, although there is increasing interest in other measures of BP, including peak arterial pressure, lability of BP, nighttime and daytime BP, responses of BP to stress, and so forth.[20] Many of the cardiovascular derangements associated with hypertension, such as cardiac and vascular hypertrophy, arise as compensatory mechanisms for hypertension, and reducing BP can largely reverse these changes if they have not progressed too far.

The multiple local, hormonal, neural, and renal systems that regulate BP are often discussed in terms of how they influence cardiac pumping or vascular resistance because of the well-known formula *mean arterial pressure = CO × TPR*. This mathematical description of BP (with addition of factors that influence vascular capacity and transcapillary exchange) adequately explains short-term BP regulation but is inadequate when discussing abnormalities of long-term BP regulation, such as hypertension.

To illustrate this point, consider the changes in BP, CO, and extracellular fluid volume after a 25% increase in TPR caused by closure of a large arteriovenous (AV) fistula. In this case, cardiac pumping ability is not directly altered and TPR is chronically increased by 25%. One might assume that BP would also rise because of increased TPR. However, there are no detectable changes in mean arterial pressure a few days after AV fistula closure despite a sustained increase of TPR.[21] Likewise, increasing TPR by amputation of a limb or hypothyroidism (which reduces metabolic rate of the tissues and increases vascular resistance) or decreasing TPR by creating an AV fistula, anemia, or hyperthyroidism fails to have a significant long-term effect on mean arterial pressure (Fig. 24–2).[21] To explain BP regulation in these circumstances, we introduce two other concepts: (1) time dependency of BP control mechanisms and (2) the necessity of maintaining balance between intake and output of water and electrolytes and the role of BP in maintaining this balance.

Feedback Control Systems for Blood Pressure Are Time Dependent

The effectiveness of BP control systems can be expressed in terms of *feedback gain*, which is defined as the amount of "correction" by the control system divided by the remaining "error" after a perturbation. For example, if a disturbance initially increases BP from 100 to 150 mm Hg and a control system returns BP to 125 mm Hg, the correction would be –25 mm Hg, and the remaining error would be +25 mm Hg. Therefore, the feedback gain would be –25/+25, or –1.0, indicating a *negative feedback* that corrects one half of the initial disturbance. The higher the feedback gain, the more powerful the control system.

BP control systems are often considered as if they were static, and time dependency is usually not discussed. Short-term mechanisms are often emphasized to a greater degree than long-term controls, probably because they have been studied much more extensively and are easier to explain, even though most cardiovascular disorders, including hypertension, involve abnormalities of long-term regulation.

If we examine the maximal feedback gains of several BP controllers, it is obvious that their quantitative importance is highly time dependent. Figure 24–3 shows the response of some of the major control systems after a sudden change in BP, as might occur with rapid blood loss. Three important neural control systems begin to function powerfully within seconds: (1) the arterial baroreceptors, which detect changes in BP and send appropriate autonomic reflex signals back to the heart and blood vessels to return the BP toward normal; (2) the chemoreceptors, which detect changes in oxygen or carbon dioxide in the blood and initiate autonomic feedback responses that influence BP; and (3) the central nervous system (CNS), which responds within a few seconds to ischemia of the vasomotor centers in the medulla, especially when BP falls below about 50 mm Hg. Each of these nervous control mechanisms works rapidly and can have potent effects on BP. Also note, however, that the feedback gains of these systems decreases with time, as a disturbance of BP is maintained.

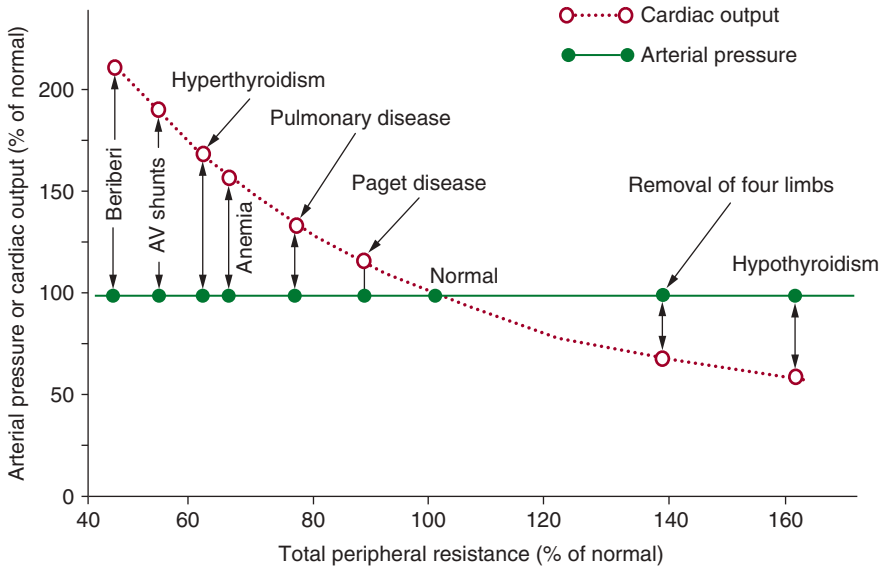

FIGURE 24–2. Failure of changes in total peripheral vascular resistance (TPR) to cause chronic changes in arterial pressure in several clinical conditions in which the kidneys are functioning normally. In each case, there is a reciprocal relationship between TPR and cardiac output but no long-term effect on arterial pressure. Reproduced with permission from Guyton AC, Hall JE: *Textbook of Medical Physiology*, 11th ed, Philadelphia: Elsevier; 2006.

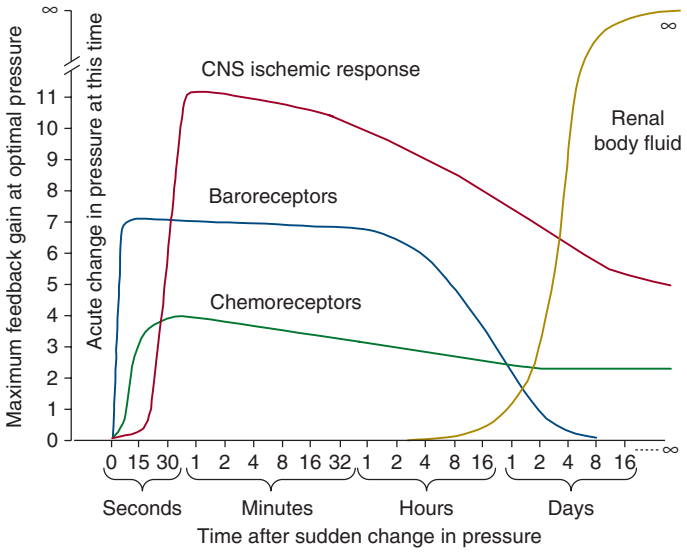

FIGURE 24–3. Time dependency of blood pressure (BP) control mechanisms. Approximate maximum feedback gains of various BP control mechanisms at different time intervals after the onset of a disturbance to BP. CNS, central nervous system. Reproduced with permission from Guyton AC, Hall JE: *Textbook of Medical Physiology*, 11th ed, Philadelphia: Elsevier; 2006.

Within a few minutes or hours after a BP disturbance, additional controls react, including (1) a shift of fluid from the interstitial spaces into the blood in response to decreased BP (or a shift of fluid out of the blood into the interstitial spaces in response to increased BP); (2) the RAAS, which is activated when BP falls too low and suppressed when BP increases above normal; and (3) multiple vasodilators systems (not shown in the figure) that are suppressed when BP decreases and stimulated when BP increases above normal.

Most of the BP regulators are *proportional* control systems. This means that they can partly correct a BP abnormality. The arterial baroreceptor reflex system, for example, has a proportional feedback gain of approximately 2.0 during acute changes in BP and therefore buffers about two-thirds of a sudden change in the BP.

There is one BP control system, the renal–body fluid feedback system, with *near infinite feedback gain* if it is given enough time to operate.[21,22] Thus, the renal–body fluid feedback control mechanism does not stop functioning until the BP returns nearly all the way back to its original control level, as discussed below.

LONG-TERM BLOOD PRESSURE REGULATION BY RENAL–BODY FLUID FEEDBACK

Figure 24–4 shows the conceptual framework for understanding long-term control of BP by the renal–body fluid feedback. Extracellular fluid volume is determined by the balance between intake and excretion of salt and water by the kidneys. Even temporary imbalances between intake and output can lead to a changes in extracellular volume and potentially changes in BP. During steady-state conditions, there must be balance between intake and output of salt and water; otherwise, there would be continued accumulation or loss of fluid leading to circulatory collapse.

A key mechanism for regulating salt and water balance is *pressure natriuresis* and *diuresis*, the effect of increased BP to raise sodium and water excretion.[21,23] Under most conditions, this mechanism stabilizes BP and body fluid volumes. For example, when BP increases above the renal set point, because of increased TPR or increased cardiac pumping, this also increases sodium and water excretion via pressure natriuresis. As long as fluid excretion exceeds fluid intake, extracellular fluid volume continues to decrease, reducing venous return and cardiac output until BP returns to normal and fluid balance is reestablished.

An important feature of pressure natriuresis is that hormonal and neural control systems can amplify or attenuate the basic effects of

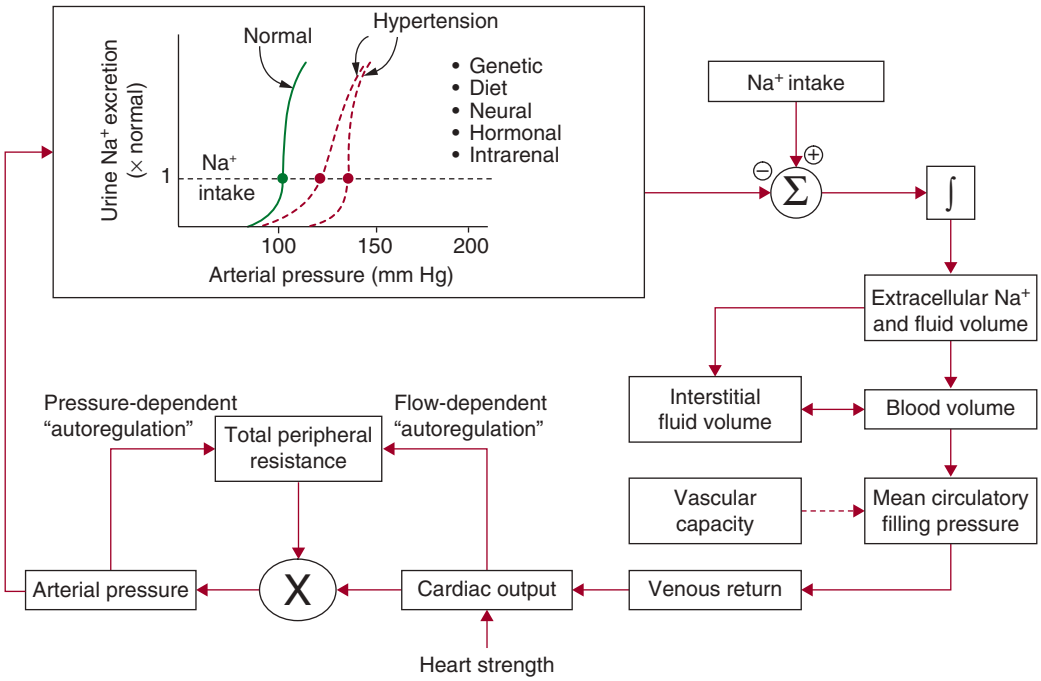

FIGURE 24–4. Basic elements of renal-body fluid feedback mechanism for long-term regulation of blood pressure. A key component of this feedback is the effect of arterial pressure on urine sodium excretion, called pressure natriuresis/diuresis. The *red dashed lines* show altered pressure natriuresis in salt-sensitive and salt-resistant hypertension. Increased arterial pressure may cause secondary increases in total peripheral resistance via pressure-dependent or flow-dependent "autoregulation" in various tissues. Increased vascular capacity tends to reduce mean circulatory filling pressure.

BP on sodium and water excretion.[12] For example, during chronic increases in sodium intake, only small changes in BP occur in most people. One reason for this insensitivity of BP to changes in salt intake is decreased formation of antinatriuretic hormones such as Ang II and aldosterone, which enhance the effectiveness of pressure natriuresis and allow sodium balance to be maintained with little or no increase in BP. On the other hand, overactivation of these antinatriuretic systems can reduce the effectiveness of pressure natriuresis, thereby necessitating greater increases in BP to maintain sodium balance.[12]

Another important feature of pressure natriuresis is that it continues to operate until BP returns to nearly the original set point. In other words, it acts as part of a *near infinite gain* feedback control system.[22] As far as we know, it is the only feedback system for BP regulation that displays near infinite feedback gain, and this property makes it a dominant long-term BP controller.

Figure 24–5 illustrates the near infinite gain characteristic of the renal–body fluid feedback system. In this case, BP is increased without a change in pressure natriuresis, as would occur with increased TPR because of closure of an AV fistula, coarctation of the aorta *below* the kidneys (aortic coarctation *above* the kidneys causes hypertension), or other changes that increase TPR without influencing renal vascular resistance. The peripheral constriction initially increases BP from point A to point B, but the rise in BP cannot be sustained; as long as pressure natriuresis is unaltered, sodium excretion will increase above intake, thereby reducing extracellular fluid volume and CO until BP eventually returns to normal. In fact, normal BP is the only point at which sodium and water balance can be maintained if pressure natriuresis is unaltered. Likewise, disturbances that decrease TPR or alter cardiac function without influencing renal pressure natriuresis have no long-term effect on BP.[21,22]

In all types of human or experimental hypertension studied thus far, there is a shift of pressure natriuresis that appears to sustain the hypertension. In some cases, abnormal pressure natriuresis is caused by intrarenal disturbances that alter renal hemodynamics or increased tubular reabsorption. In other cases, altered kidney function is caused by extrarenal disturbances, such as increased SNS activity or excessive formation of antinatriuretic hormones that reduce the kidney's ability to excrete sodium and water and eventually increase BP. Consequently, effective treatment of patients with hypertension requires interventions that reset pressure natriuresis toward normal BP either by directly increasing renal excretory capability (eg, with diuretics), or by reducing antinatriuretic influences (eg, with RAAS blockers) on the kidneys.

RENAL MECHANISMS OF HYPERTENSION AND SALT SENSITIVITY

Severe kidney disease has long been recognized as with a cause as well as a consequence of hypertension. However, the importance of more subtle renal dysfunction in the pathogenesis of essential hypertension has not been widely appreciated, partly because there are no obvious renal defects in many patients with primary hypertension. Measurements commonly used to evaluate kidney function, such as glomerular filtration rate (GFR), renal blood flow, serum creatinine, and sodium excretion are often within the normal range in the early stages of hypertension before kidney damage occurs. On the other hand, TPR is often increased in hypertensive subjects, leading many to conclude that vasoconstriction is the cause of increased BP. However, as discussed previously, increased TPR may be an autoregulatory response to increased BP in many hypertensive subjects and in the absence of altered kidney function does not cause sustained hypertension.

An observation that points toward abnormal kidney function as a key factor in hypertension is that most models of experimental hypertension and monogenic forms of human hypertension are caused by obvious insults to the kidneys that alter renal hemodynamics or tubular reabsorption. For example, constriction of the renal arteries (eg, Goldblatt hypertension), compression of the kidneys (eg, perinephritic hypertension), or administration of sodium-retaining hormones (eg, mineralocorticoids or Ang II) are all associated with initial reductions in GFR or increases in renal tubular reabsorption prior to development of hypertension. Likewise, in monogenic human hypertension, the common pathway to hypertension appears to be increased renal sodium reabsorption caused by mutations that directly increase renal electrolyte transport or the synthesis/activity of antinatriuretic hormones. As BP increases, the initial renal changes are often obscured by compensations that restore kidney function toward normal. Increased BP then initiates a cascade of cardiovascular changes

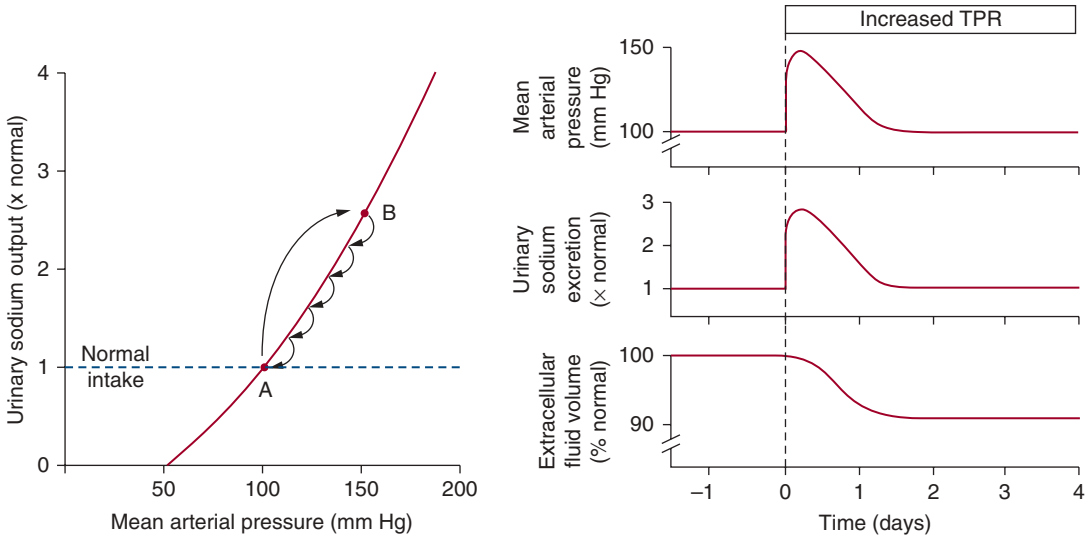

FIGURE 24–5. Long-term effects of increased total peripheral resistance (TPR), such as that caused by closure of a large arteriovenous fistula, with no change in the renal-pressure natriuresis relationship. Blood pressure (BP) is initially increased from point A to point B, but elevated BP cannot be sustained because sodium excretion exceeds intake, reducing extracellular fluid volume until blood pressure returns to normal and sodium balance is reestablished. Reproduced with permission from Hall JE: The kidney, hypertension, and obesity. *Hypertension*. 2003 Mar;41(3 Pt 2):625-633.

TABLE 24–3. Renal Causes and Characteristics of Salt-Sensitive and Salt-Insensitive Hypertension[a]

Causes	Blood Pressure	Pressure Natriuresis	Renal Blood Flow	Glomerular Filtration Rate	Plasma Renin Activity	Glomerular Injury[b]
Salt-sensitive hypertension						
Decreased kidney mass	↑, ↔	Decreased slope	↓	↓	↓	Yes
Decreased glomerular capillary filtration coefficient (K_f)	↑	Decreased slope	↑	↓, ↔	↑, ↔	Yes
Increased distal and collecting tubule reabsorption	↑	Decreased slope	↑	↑	↓	Yes
Salt-insensitive hypertension						
Increased preglomerular resistance	↑	Parallel shift	↓, ↔	↓, ↔	↑, ↔	No[c]

[a]The changes shown in the table are those predicted to initially occur after the initial disturbances (causes). With chronic changes in arterial pressure and glomerular hydrostatic pressure, injury to the kidney may lead to secondary reductions in glomerular filtration rate and renal blood flow.

[b]Glomerular injury is predicted to occur secondary to hypertensive stimuli that cause chronic increases in glomerular hydrostatic pressure or hyperfiltration of surviving nephrons.

[c]Increased preglomerular resistance attenuates transmission of increased blood pressure to the glomerulus and protects against hypertension-induced glomerular injury. Severe increases in preglomerular resistance, however, can cause nephron ischemia and glomerular injury.

that may be more striking than the initial disturbance of kidney function. For this reason, the importance of renal dysfunction in causing hypertension has often been underestimated. However, one aspect of kidney function that is abnormal in all types of experimental and clinical hypertension is renal pressure natriuresis.[12,21]

The general types of renal abnormalities that can alter pressure natriuresis and cause chronic hypertension include increased preglomerular resistance, decreased glomerular capillary filtration coefficient, reduced numbers of functional nephrons, and increased tubular reabsorption (Table 24–3). Some of these kidney abnormalities increase salt sensitivity of BP, whereas others cause salt-*insensitive* hypertension.

INCREASED PREGLOMERULAR RESISTANCE

Generalized Increases in Preglomerular Resistance Cause Salt-Insensitive Hypertension

Examples of generalized increases in preglomerular resistance are those caused by suprarenal aortic coarctation or constriction of one of the renal arteries and removal of the contralateral kidney (eg, one-kidney, one-clip Goldblatt hypertension). Immediately after constriction of the renal artery or aortic coarctation, renal blood flow decreases, renin secretion increases, and sodium excretion transiently decreases. Within a few days, sodium excretion returns to normal, and sodium balance is reestablished (Fig. 24–6). If sodium intake is normal, renin secretion also returns to normal in the established phase of hypertension. At this point, most indices of renal function are nearly normal, including BP distal to the stenosis if the constriction is not too severe. The rate at which renal function returns to normal and time course for development of hypertension depend the severity of the stenosis, sodium intake, and the rate of Ang II formation.[21,24]

How do these experimental models relate to human hypertension, other than the obvious conditions of aortic coarctation or renal artery stenosis? Presumably, functional or pathologic increases in preglomerular resistance at other sites besides the main renal arteries, such as the interlobular arteries or afferent arterioles, could increase BP through the same mechanisms as activated by clipping the renal artery. For example, widespread structural increases in afferent arteriolar resistance (eg, nephrosclerosis) or functional increases in resistance caused by excessive activation of the SNS or high levels of catecholamines

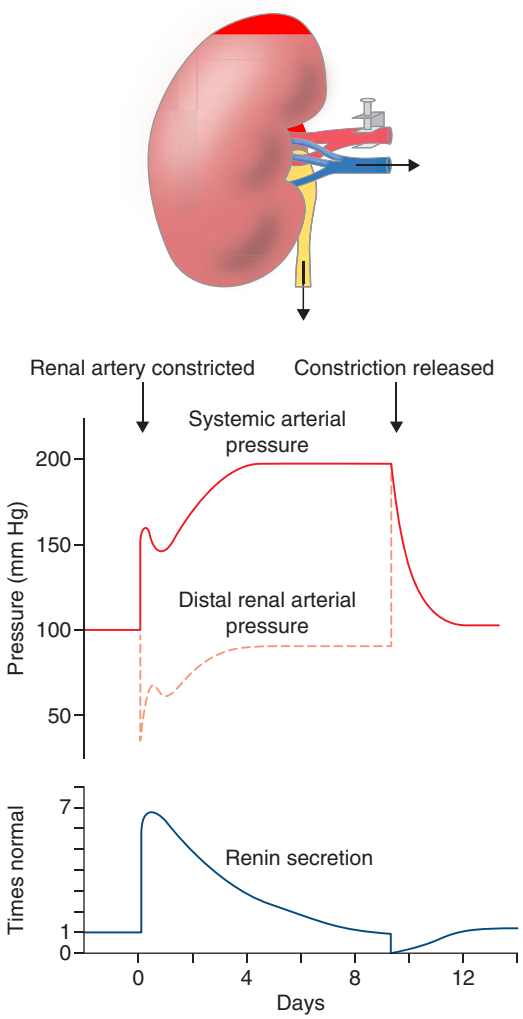

FIGURE 24–6. Effects of constriction of the renal artery of a sole remaining kidney. Renal artery pressure distal to the constriction, renin secretion, and sodium excretion rate return to nearly normal after a few days. Reproduced with permission from Hall JE: *Guyton and Hall Textbook of Medical Physiology*, 13th ed. Philadelphia: Elsevier; 2016.

(eg, pheochromocytoma) would also cause hypertension through the same mechanisms as constriction of the main renal artery.

Some patients with primary hypertension have nearly the same characteristics seen in the one-kidney, one-clip Goldblatt model of hypertension, including nearly normal GFR and plasma renin activity, a parallel shift of pressure natriuresis to higher BP, and a relatively salt-insensitive form of hypertension.[21,24] Thus, primary hypertension in some patients may be caused by functional or pathologic increases in preglomerular resistance. This is almost certainly the case in patients who have severe atherosclerotic lesions in the renal blood vessels.

Patchy Increases in Preglomerular Resistance Cause Salt-Sensitive Hypertension

In the two-kidney, one-clip Goldblatt model of hypertension and in patients with a stenosis in only one renal artery, there is a nonhomogeneous increase in preglomerular resistance with ischemia occurring in nephrons of the clipped or stenotic kidney; nephrons in the contralateral nonclipped or nonstenotic kidney have normal or increased single-nephron blood flow and GFR. Whereas the underperfused clipped kidney secretes large amounts of renin, the untouched kidney secretes very little renin.[12]

An important distinction between a generalized increase in preglomerular resistance and patchy, nonhomogeneous increases in preglomerular resistance is the evolution of renal injury associated with hypertension. When there is a generalized, homogeneous increase in preglomerular resistance, the glomeruli are protected from the damaging effects of increased BP. In the two-kidney, one-clip model, however, the glomeruli of the untouched kidney are subjected to the effects of increased BP. With prolonged hypertension, pathologic changes in the untouched kidney add to the impairment of overall renal excretory capability. At this stage, removal of the clipped kidney only partially restores BP to normal. However, removal of the contralateral untouched kidney and unclipping the stenotic kidney usually normalizes BP. Thus, chronic exposure to high BP in the untouched kidney causes structural changes as well as functional changes that contribute to the progression of hypertension.

The relevance of experimental models of nonhomogeneous increases in preglomerular resistance to human hypertension is obvious when there is stenosis of only one renal artery with the contralateral kidney being initially unaffected. Also, some patients with primary hypertension may have patchy nephrosclerosis within each kidney. In these instances, the ischemic nephrons secrete large amounts of renin, and the nonischemic nephrons may initially have increased single-nephron GFR. The combined effects of hypertension and hyperfiltration, however, may eventually damage the nephrons that were not initially ischemic, leading to progressive nephron loss.

DECREASED GLOMERULAR CAPILLARY FILTRATION COEFFICIENT

Reducing the glomerular capillary filtration coefficient (K_f) initially lowers GFR and sodium excretion while stimulating renin release and causing dilation of afferent arterioles via a macula densa feedback.[12,21] The sodium retention and increased Ang II formation increase BP, which then helps to restore GFR and renin release toward normal. After these compensations, the main persistent abnormalities of kidney function are reduced filtration fraction, increased glomerular hydrostatic pressure, and increased renal blood flow. BP is often salt sensitive when reductions in K_f are severe.

Compensatory increases in BP and glomerular hydrostatic pressure, which offset a decrease in K_f and restore sodium excretion to normal, may also lead to additional renal dysfunction over a period of years by causing further glomerular injury; the gradual injury and loss of glomeruli further reduce K_f and elicit additional increases in BP to maintain normal water and electrolyte balances. Such a sequence may initiate progressive kidney damage, worsening of hypertension, and greater salt sensitivity of BP.

The clinical counterparts of this sequence may be found in hypertension caused by glomerulonephritis or by other conditions that cause thickening and damage to the glomerular capillary membranes, such as chronic diabetes mellitus.[12]

NEPHRON LOSS

A factor that contributes to BP salt sensitivity in some hypertensive patients is loss of functional nephrons. Complete loss of nephrons (eg, surgical reduction of kidney mass or unilateral nephrectomy) in the absence of other abnormalities may not lead to significant hypertension.[12] In contrast, loss of functional nephrons because of ischemia or infarction of renal tissue usually induces hypertension that initially is caused by increased renin secretion and Ang II formation and then is eventually mediated by additional abnormalities, such as immunologic and renal injury, in the established phase of the hypertension.[25]

Reductions in nephron number might be expected to impair renal excretory capability and cause hypertension regardless of whether the loss was associated with renal ischemia. Yet, experimental studies show that surgical removal of large amounts of the kidney, to the point that uremia occurs, rarely causes severe hypertension as long as sodium intake is normal.[21,26] Figure 24–7 shows the effect of surgically reducing kidney mass on salt sensitivity in dogs. As long as sodium intake was normal, surgical reduction of kidney mass by 25%, or even as much as 70%, did not markedly alter BP.[26] However, after loss of kidney mass, BP became exquisitely sensitive to changes in sodium intake, and with high sodium intake, BP increased by approximately 40 mm Hg.

The reason hypertension often does not develop with nephron loss is that glomerular filtration and tubular reabsorption capability are proportionally reduced so that balance between filtration and reabsorption can be maintained without major adaptive changes in BP.

Reducing the number of functional nephrons, however, makes the kidneys susceptible to additional insults that impair their function or to additional challenges of sodium homeostasis. Thus, hypertension associated with excess mineralocorticoids is much more severe after reducing

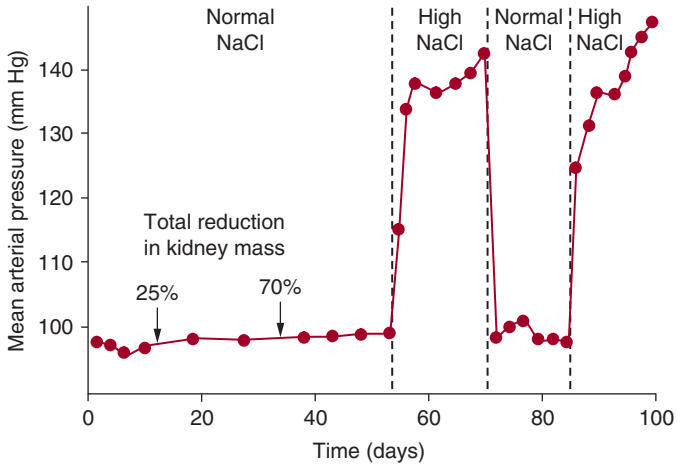

FIGURE 24–7. The effect of reducing kidney mass on salt sensitivity of blood pressure (BP) in dogs. Note that as long as sodium chloride intake was normal, surgical reduction of kidney mass by 25% or even 70% did not markedly alter arterial pressure. However, after loss of kidney mass, BP became exquisitely sensitive to high sodium chloride intake. Reproduced with permission from Langston JB, Guyton AC, Douglas BH, et al: Effect of changes in salt intake on arterial pressure and renal function in partially nephrectomized dogs. *Circ Res.* 1963;May;12(5):508-512.

kidney mass. Likewise, the kidney's ability to increase sodium excretion in response to the additional challenge of high sodium intake is accompanied by much larger increases in BP when kidney mass is reduced.[12,21]

After loss of entire nephrons, the surviving nephrons must excrete greater amounts of sodium and water to maintain balance. This is achieved by increasing GFR and decreasing reabsorption in the remaining nephrons, resulting in increased sodium chloride delivery to the macula densa and suppression of renin release. This, in turn, impairs the kidney's ability to further decrease renin secretion during high sodium intake, and BP becomes salt sensitive.

Nephron loss may also initiate compensatory changes that damage surviving nephrons. For example, over long periods of time, renal vasodilation and increased single-nephron GFR may lead to glomerulosclerosis and reductions in K_f. These pathologic changes, in addition to the loss of functional nephrons, may eventually impair pressure natriuresis sufficiently to cause substantial hypertension.

With normal aging, especially after age 40 to 50 years, there is gradual nephron loss that is accelerated by renal diseases, such as glomerulonephritis, diabetes mellitus, or long-standing hypertension. Thus, even though hypertension may not begin with nephron loss, chronic elevations in glomerular pressure and other metabolic abnormalities that are often associated with hypertension may eventually cause progressive nephron loss that amplifies the hypertension and makes BP more salt sensitive.

Nephron Loss by Partial Renal Infarction Causes Salt-Sensitive Hypertension

The experimental model of surgical reduction of kidney mass discussed above should not be confused with the model of partial renal infarction hypertension produced by tying off branches of the renal artery, the so-called *5/6 ablation* model. This model is usually produced by removing one kidney and obstructing two of the three branches of the renal artery of the remaining kidney. In the infarction model, hypertension develops even without a high sodium intake because of ischemia of surviving nephrons, activation of the RAAS, and immune-mediated injury of the kidney.[25] The 5/6 renal ablation hypertension is a model of severe patchy renal ischemia with characteristics similar to that described for the two-kidney, one-clip Goldblatt model or nonhomogeneous patchy glomerulosclerosis. The clinical counterpart of this model occurs with partial renal infarction caused by septic emboli, thrombus, trauma, or sometimes after corrective surgery for renal artery stenosis.

INCREASED RENAL TUBULAR SODIUM REABSORPTION

Factors that increase renal tubular sodium reabsorption, such as excessive levels of mineralocorticoids or Ang II, can also cause hypertension. The severity of hypertension depends on the degree to which tubular reabsorption is stimulated and on other factors, such as the functional kidney mass and sodium intake.[12,21] With nephron loss or high sodium intake, the hypertensive potency of mineralocorticoids or Ang II is greatly enhanced.

Excessive Distal and Collecting Tubule Reabsorption Causes Salt-Sensitive Hypertension

One feature of hypertension caused by increased distal or collecting tubular reabsorption is that it is usually salt sensitive, with increased sodium intake exacerbating the hypertension. Increased reabsorption at sites beyond the macula densa, such as the distal tubules and collecting tubules, elicits chronic increased sodium chloride delivery to the macula densa, which, in turn, suppresses renin secretion.[12,21,23] Reduction of renin secretion to *very low* levels, characteristic of disorders associated with excessive distal or collecting tubular reabsorption, prevents further suppression of Ang II formation during high sodium intake, making BP salt sensitive.

Another feature of hypertension caused by increased tubular reabsorption (as occurs with excess aldosterone secretion) is that it is often associated with extracellular volume expansion. However, the initial volume expansion and increased CO usually subside because of pressure natriuresis and TPR increases because of the vascular autoregulatory mechanisms discussed previously. When increased tubular reabsorption is also associated with marked peripheral vasoconstriction, such as occurs with very high levels of Ang II, the degree of volume expansion depends on the relative effects of the vasoconstrictor on the peripheral blood vessels and the kidneys.[21,23] With severe peripheral vasoconstriction and decreased vascular capacitance, relatively small amounts of volume retention can lead to substantial hypertension.

Reduced Responsiveness of the Renin-Angiotensin-Aldosterone System Increases Salt Sensitivity of Blood Pressure

Figure 24–8 shows the importance of changes in Ang II formation in maintaining BP relatively constant during variations in salt intake from a very low level of 5 mmol/d up to 80, 240, and 500 mmol/d for 8 days at each level.[27,28] In normal dogs with a functional RAAS, there were only small increases in BP associated with this 100-fold range of sodium intakes. However, when Ang II was infused at a low level that initially had little effect on BP but prevented Ang II from being suppressed as sodium intake was raised, BP became very salt sensitive. After blockade of Ang II formation, BP also became salt sensitive, although pressure was maintained at a much lower level, especially

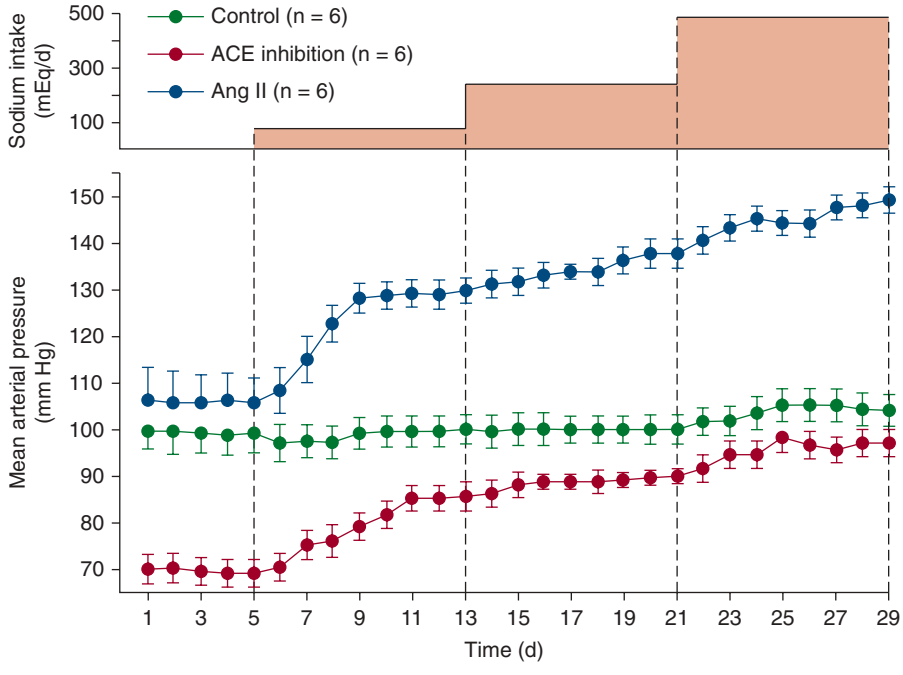

FIGURE 24–8. Changes in mean arterial pressure during chronic changes in sodium intake in normal control dogs, after angiotensin-converting enzyme (ACE) inhibition, or after angiotensin Ang II infusion (5 ng/kg/min) to prevent Ang II from being suppressed when sodium intake was raised. Reproduced with permission from Hall JE, Guyton AC, Smith MJ, et al: Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. *Am J Physiol.* 1980 Sep;239(3):F271-F280.

when sodium intake was low.[28] Thus, one of the major functions of the RAAS is to permit wide variations in intake and excretion of sodium without large fluctuations in BP that would otherwise be needed to maintain sodium balance.

As discussed previously, focal nephrosclerosis or patchy preglomerular vasoconstriction, as occurs with renal infarction, leads to increased renin secretion in ischemic nephrons and very low levels of renin release by overperfused nephrons.[12] Thus, in ischemic, as well as overperfused, nephrons, the ability to adequately suppress renin secretion during high salt intake is impaired.

Another cause of reduced responsiveness of the RAAS is increased distal and collecting tubular sodium reabsorption as occurs with mineralocorticoid excess or mutations that increase distal and collecting tubule reabsorption (eg, Liddle syndrome). In these conditions, excess sodium retention causes almost complete suppression of renin secretion, resulting in an inability to further decrease renin release during high sodium intake. Consequently, BP becomes very salt sensitive.

SIGNIFICANCE OF SALT SENSITIVITY

Salt sensitivity of BP in humans is a quantitative phenotype, rather than following a bimodal categorization of *salt sensitive* or *salt insensitive*, and there is considerable heterogeneity of BP responses to changes in sodium intake in normotensive and hypertensive individuals.[29–31]

Assessment of BP salt sensitivity in clinical studies is challenging. Although various methods have been used to assess salt sensitivity, none are widely used in clinical practice. Most salt-sensitivity protocols involve short-term changes in sodium intake, usually over a few days. Weinberger et al[31] defined salt sensitivity as a 10 mm Hg or greater change in mean BP from the level measured after a 4-hour infusion of 2 L of normal saline compared with the level measured the morning after 1 day of a low-sodium (10 mmol) diet and administration of three doses of furosemide. With this definition, 51% of hypertensive and 26% of normotensive subjects were found to be salt sensitive.[31] However, the repeatability of salt sensitivity in the same persons over long periods of time (years) is unclear, and it is not known whether short-term BP responses reliably predict the long-term effects of changes in salt intake. Measuring BP during prolonged changes in dietary sodium intake in outpatient protocols and clinical trials provides a more relevant assessment of BP salt sensitivity. However, chronic studies of salt sensitivity in humans lasting more than a few days are rare.

Clinical observations indicate that many demographic and pathophysiologic conditions are associated with salt sensitivity. Older individuals are usually more salt sensitive than young people, and blacks are often more salt sensitive than whites. However, there are many exceptions to these generalizations, and considerable heterogeneity exists in the BP responses to changes in salt intake.

Genetic factors independent of ethnicity have also been linked to BP salt sensitivity, especially monogenic disorders that increase distal and collecting tubule sodium reabsorption or that cause excess secretion of sodium-retaining hormones (eg, mineralocorticoids).[32] Also, diabetes mellitus, renal diseases that cause nephron loss, and abnormalities of the RAAS are all associated with increased BP salt sensitivity.[29,33] Many of these examples appear to share two common pathways to salt sensitivity of BP: loss of functional nephrons or reduced responsiveness of the RAAS.

Salt Sensitivity and Target Organ Injury

Some studies suggest that salt sensitivity predicts which patients are at greatest risk for hypertensive target organ injury. Salt-sensitive hypertension is often associated with glomerular hyperfiltration and increased glomerular hydrostatic pressure (see Table 24–3); together, the hypertension and renal hyperfiltration promote glomerular injury and may eventually cause loss of nephron function. Clinical studies support this concept and demonstrate that whereas salt-sensitive individuals typically have increased glomerular hydrostatic pressure and albumin excretion when given a salt load, salt-resistant individuals have lower glomerular hydrostatic pressure and less urinary albumin excretion.[34]

There is also evidence that salt-sensitive subjects die earlier than salt-resistant individuals. Weinberger et al[35] followed patients for more than 20 years and found that normotensive individuals with increased salt sensitivity died almost at the same rate as hypertensive individuals and much faster than salt-resistant individuals who were normotensive. Whether increased mortality was related to BP effects of salt or to other effects is still unclear. It is also not known whether chronic high salt intake, lasting over many years, may cause a person who is initially "salt insensitive" to become "salt sensitive" as a consequence of gradual renal injury.

NEUROHUMORAL AND IMMUNE MECHANISMS OF HYPERTENSION

Although impaired renal-pressure natriuresis plays a central role in hypertension, not all disorders of pressure natriuresis originate within the kidneys. Inappropriate activation of multiple antinatriuretic hormone systems (eg, Ang II, aldosterone) that normally regulate sodium excretion or deficiency of natriuretic influences (eg, atrial natriuretic peptide [ANP], NO) on the kidneys can impair pressure natriuresis and cause chronic hypertension. Likewise, excessive SNS activation plays a major role in elevating BP in many hypertensive patients. The following sections discuss some of the neural, hormonal, and autacoid mechanisms that contribute to long-term BP regulation, their actions on the kidneys, and their potential roles in hypertension.

THE SYMPATHETIC NERVOUS SYSTEM

The SNS is a major short- and long-term controller of BP. Sympathetic vasoconstrictor fibers are distributed to almost all regions of the vasculature, as well as to the heart and kidneys, and activation of the SNS can raise BP within a few seconds by causing vasoconstriction, increased cardiac pumping capability, and increased heart rate. Conversely, sudden inhibition of SNS activity can decrease BP to as low as half normal in less than 1 minute. Therefore, changes in SNS activity, caused by various reflex mechanisms, CNS ischemia, or by activation of higher centers in the brain, provide powerful and rapid, moment-to-moment regulation of BP.

The SNS also plays an important role in long-term BP regulation and in the pathogenesis of hypertension, in large part by activation of the renal sympathetic nerves.[12,36] There is extensive innervation of the renal blood vessels, juxtaglomerular apparatus, and renal tubules, and excessive activation of these nerves promotes sodium retention, increased renin secretion, and impaired renal-pressure natriuresis. Except for extreme circumstances, such as severe hemorrhage or other conditions associated with marked circulatory depression, activation of the renal sympathetic nerves is usually not great enough to cause major reductions in renal blood flow or GFR. However, even mild increases of the renal sympathetic activity stimulate renin secretion and sodium reabsorption in multiple segments of the nephron, including the proximal tubule, the loop of Henle, and distal segments.[12,36] Thus, the renal nerves provide a mechanism by which various reflex mechanisms and higher CNS centers may contribute to long-term BP regulation.

The preganglionic neurons that synapse with the renal sympathetic postganglionic fibers are located in the lower thoracic and upper

lumbar segments of the spinal cord and receive multiple inputs from various regions of the brain, including the brainstem, forebrain, and cerebral cortex. These complex neural circuits provide multiple pathways by which neural reflexes and higher CNS centers can influence renal SNS activity and chronic BP regulation.

Evidence for a role of the renal nerves in hypertension comes from multiple studies showing that renal denervation (RDN) reduces BP in some models of experimental hypertension.[12,36] For example, complete RDN attenuates the development of hypertension in spontaneously hypertensive rats as well as in obese hypertensive dogs.[36–38] RDN may delay or attenuate increased BP in other forms of experimental hypertension, although some studies have not found an important role for the renal nerves in several forms of secondary hypertension. In Ang II hypertension, for example, *decreased* renal sympathetic activity appears to attenuate the rise in BP.[39]

Human primary hypertension is often associated with increased renal sympathetic activity. In obese humans with resistant hypertension, catheter-based radiofrequency RDN lowered office BP for up to 24 months.[36,40] When 24-hour ambulatory BP was measured in a subgroup of patients, reductions in BP after RDN averaged –11/–7 mm Hg systolic/diastolic, although a recent trial failed to find a major effect of RDN on BP, compared to sham controls.[41] However, these patients were already on at least three antihypertensive medications, including blockers of the RAAS, which may mediate at least part of the effect of the renal nerves on BP, and the extent of RDN was not verified. It appears that even under optimal conditions the usual radiofrequency method causes only 40-50% ablation of the renal nerves.[37,42] Increased efficacy of renal denervation (up to 75% ablation of the renal nerves) can be achieved if the radiofrequency ablation procedure is performed in the branches of the main renal artery close to the kidneys.[43] Longer periods of follow-up will be needed to determine if the renal nerves eventually regrow and reinitiate increases in BP, as has been observed in experimental animal models of RDN.

Whether RDN will prove to be an effective therapy for patients who are resistant to the usual pharmacological treatments remains to be determined. Although the mechanisms that activate renal sympathetic nerves in primary hypertension or in most experimental models are still unclear, we briefly discuss three that have attracted the interest of many researchers.

Role of Baroreceptor Reflexes in Hypertension

The importance of the arterial baroreceptors in buffering moment-to-moment changes in BP is clearly evident in baroreceptor-denervated animals in which there is extreme BP variability during normal daily activities.[44] After baroreceptor denervation, BP increases to high levels or decreases to low levels with normal daily activities, although the average 24-hour mean arterial pressure is not markedly altered.

Although the arterial baroreceptors clearly provide a powerful means for acute BP regulation, their role in long-term BP regulation is controversial. Some studies suggest that the baroreceptors reset within a few days to the level of BP to which they are exposed and are reset to higher BP in chronic hypertension.[44] To the extent that resetting of baroreceptors occurs, this would attenuate their potency as a long-term controller of BP.

Other experimental studies, however, suggest that the baroreceptors do not completely reset and may contribute to chronic BP regulation. With prolonged increases in BP, the baroreflexes may contribute to *reductions* in renal sympathetic activity and promote sodium and water excretion, attenuating the increase in BP.[45] Thus, impairment of baroreflexes may cause increased lability of BP in hypertension and may fail to attenuate the increase in BP caused by other disturbances. However, there is currently little evidence that primary disturbances of baroreceptor function play a major role in *causing* chronic hypertension.

Chronic activation of the baroreceptors by electrical stimulation of the carotid sinus reduces BP in experimental hypertension.[46] In humans with hypertension that was resistant to drug treatment, electrical stimulation of baroreceptors also significantly reduced BP.[47] However, the primary role of arterial baroreceptors in hypertension, as in normotension, is to buffer deviations in BP from the set-point determined by renal pressure natriuresis.

Increased BP lability associated with baroreflex dysfunction, however, is accompanied by periodic large increases in BP that may cause gradual renal injury and eventually lead to chronic hypertension. Studies in experimental animals show, for example, that baroreceptor-denervated animals have significant structural changes in the kidneys, including glomerular injury.[48]

Does Chronic Stress Cause Hypertension by Sympathetic Nervous System Activation?

Acute physiologic stresses, including pain, exercise, exposure to cold, and mental stress, can all lead to increased SNS activity and transient hypertension. It is also widely believed that chronic stress may lead to long-term increases in BP. Support for this concept comes largely from a few epidemiologic studies showing that air traffic controllers, lower socioeconomic groups, and other groups who are believed to lead more stressful lives also have increased prevalence of hypertension.[49] There is limited evidence, however, for a direct cause-and-effect relationship between psychosocial stress and chronic hypertension. Nevertheless, many researchers believe that stress is an important cause of hypertension in humans.

Obesity

Excess weight gain appears to be a major cause of human primary hypertension. The mechanisms responsible for obesity hypertension are closely linked to increased renal SNS activity.[12,50–52] Obese persons have elevated SNS activity in various tissues, including the kidneys and skeletal muscle, as assessed by microneurography, tissue catecholamine spillover, and other methods. Studies in experimental animals and humans indicate that combined α- and β-adrenergic blockade markedly attenuates hypertension associated with obesity.[50,53] Moreover, bilateral renal denervation greatly attenuates sodium retention and hypertension in obese dogs and obese patients with primary hypertension.[37,40] Thus, obesity increases renal sodium reabsorption, impairs pressure natriuresis, and causes hypertension partly by increasing renal SNS activity, as discussed in more detail later in this chapter.

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The RAAS is perhaps the most powerful hormone system for regulating body fluid volumes and BP as evidenced by the effectiveness of various RAAS blockers in reducing BP in normotensive and hypertensive subjects. Although the RAAS has many components, its most important effects on BP regulation are exerted by Ang II and aldosterone.

Ang II is a powerful vasoconstrictor and helps maintain BP in conditions associated with acute volume depletion (eg, hemorrhage), sodium depletion, or circulatory depression (eg, heart failure). The long-term effects of Ang II on BP, however, are closely intertwined with volume homeostasis through direct and indirect effects on the kidneys.[27,54,55]

When the RAAS is fully functional, sodium balance can be maintained over a wide range of intakes with minimal changes in BP (see Fig. 24–8). Blockade of the RAAS, with Ang II–receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors, increases

renal excretory capability so that sodium balance can be maintained at reduced BP.[28] However, blockade of the RAAS also makes BP salt sensitive. Thus, the effectiveness of RAAS blockers in lowering BP is greatly diminished by high salt intake. Conversely, reducing sodium intake or addition of a diuretic improves the effectiveness of RAAS blockers in reducing BP.

Inappropriately high levels of Ang II reduce renal excretory capability and impair pressure natriuresis, thereby necessitating increased BP to maintain sodium balance. The mechanisms that mediate the potent antinatriuretic effects of Ang II include direct and indirect effects to increase tubular reabsorption as well as renal hemodynamic effects.[27,28]

Ang II Stimulates Renal Sodium Reabsorption

Physiologic activation of the RAAS usually occurs as a compensation for conditions that cause volume depletion or underperfusion of the kidneys, such as sodium depletion, hemorrhage, or heart failure. Increased Ang II formation helps restore renal perfusion by causing salt and water retention, which helps prevent reductions in BP. Ang II causes salt and water retention by increasing renal sodium reabsorption through stimulation of aldosterone secretion, by direct effects on epithelial transport, and by hemodynamic effects.

Ang II–mediated constriction of efferent arterioles reduces renal blood flow and peritubular capillary hydrostatic pressure and increases peritubular colloid osmotic pressure as a result of increased filtration fraction.[27] These changes, in turn, increase the driving force for fluid reabsorption across tubular epithelial cells. Reductions in renal medullary blood flow caused by efferent arteriolar constriction or by direct effects of Ang II on the vasa recta may also enhance reabsorption in the loop of Henle and collecting ducts.[27]

Ang II also directly stimulates tubular sodium reabsorption. This effect occurs at low Ang II concentrations and is mediated in by actions on the luminal and basolateral membranes.[12,27,56] In the proximal tubules, Ang II stimulates Na^+-H^+ exchange on the luminal membrane and increases sodium-potassium ATPase activity as well as sodium bicarbonate cotransport on the basolateral membrane (Fig. 24–9).[12;27;56] These effects are partly mediated by inhibition of adenyl cyclase and increased phospholipase C activity.

Sodium reabsorption in the loop of Henle, macula densa, and distal nephron segments is also stimulated by Ang II. At physiologic concentrations, Ang II increases bicarbonate reabsorption in the loop of Henle and stimulates Na^+-K^+-2 Cl transport in the medullary thick ascending loop of Henle.[12,27,56] Ang II stimulates multiple ion transporters in the distal parts of the nephron, including H^+-ATPase activity, as well as epithelial sodium channel activity in the cortical collecting ducts.[12,27,56]

Renal Hemodynamic Effects of Ang II

Ang II is a powerful renal vasoconstrictor but in most physiologic conditions, the constriction is confined mainly to the *postglomerular efferent* arterioles. For example, efferent arteriolar constriction by Ang II acts in concert with other autoregulatory mechanisms, such as tubuloglomerular feedback and myogenic activity, to prevent excessive reductions in GFR when kidney perfusion is threatened.[27] In these cases, administration of ARBs or ACE inhibitors may actually reduce GFR further, even though renal blood flow is preserved. The impairment of GFR after RAAS blockade is caused, in part, by inhibition of the constrictor effects of Ang II on efferent arterioles as well as reduced BP.

The weak constrictor action of Ang II on preglomerular vessels is related, in part, to selective protection of these vessels by autacoid mechanisms such as prostaglandins (PGs) or endothelial-derived NO.[27] When the ability of the kidneys to produce these autacoids is impaired by treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or

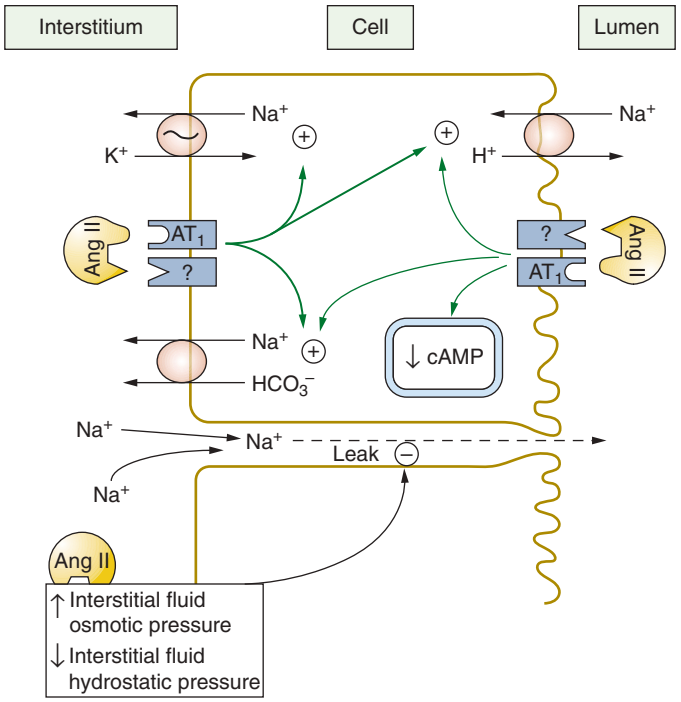

FIGURE 24–9. Angiotensin Ang II increases proximal tubular reabsorption by binding to receptors on the luminal and basolateral membranes and stimulating Na^+/H^+ antiporter, Na^+/HCO_3 cotransport, and Na^+/K^+ adenosine triphosphatase (ATPase) activity. Ang II also increases reabsorption by increasing interstitial fluid colloid osmotic pressure and decreasing interstitial fluid hydrostatic pressure. Reproduced with permission from Hall JE, Brands MW, Henegar JR: Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. *J Am Soc Nephrol*. 1999 Apr;10 Suppl 12:S258-S265.

by chronic vascular disease (eg, atherosclerosis), increased Ang II may reduce GFR by constricting afferent arterioles.

Blockade of Ang II May Attenuate Glomerular Injury in Overperfused Kidneys

RAAS blockade is often beneficial when nephrons are hyperfiltering, especially if Ang II is not appropriately suppressed. For example, in diabetes mellitus and certain forms of hypertension associated with glomerulosclerosis and nephron loss, Ang II blockade decreases BP, efferent arteriolar resistance, and glomerular hydrostatic pressure, and it attenuates glomerular hyperfiltration.[54] Clinical and experimental studies indicate that RAAS blockers are more effective than other antihypertensive agents in preventing glomerular injury, even with similar reductions in BP.[57–59] This appears to be partly caused by a greater reduction in glomerular hydrostatic pressure as a result of vasodilation of efferent arterioles after RAAS blockade.

Mechanisms of Ang II–mediated Target Organ Injury

Ang II has been suggested to cause injury to the kidneys and other organs through direct actions in addition to hemodynamic effects. Although clinical and experimental studies have demonstrated greater renal protective effects of RAAS blockers compared with other antihypertensive drugs, efferent arteriolar vasodilation and decreased glomerular hydrostatic pressure may have contributed to these beneficial effects. In studies in which BP was measured very accurately, using 24-hour telemetry, the renal protective effects of RAAS blockade appear to be largely a result of reductions in BP.[60]

An observation that is difficult to reconcile with the concept that Ang II directly mediates target organ injury, independent of BP, is the finding that physiologic activation of the RAAS is not associated with

vascular or renal injury as long as the BP is not elevated. For example, sodium depletion does not cause renal, cardiac, or vascular injury despite marked increases in renal Ang II levels. Also, elegant studies in genetically engineered mice indicate that chronic Ang II infusion does not cause cardiac hypertrophy and fibrosis in the absence of increased BP.[61] For example, when large amounts of Ang II were infused into WT mice that received transplanted kidneys from AT1 receptor knockout mice (ie, AT1 receptors were present in the heart and other organs but not in the kidneys), Ang II infusion did not chronically increase BP or cause cardiac hypertrophy and fibrosis.[61] However, when AT1 receptors were present only in the kidneys and not in the heart or other organs, Ang II infusion caused chronic hypertension as well as cardiac hypertrophy and fibrosis.[61] These observations indicate that in the absence of hypertension, Ang II does not cause cardiac hypertrophy or fibrosis. Thus, the hemodynamic effects appear to account for most of the target injury that occurs in Ang II–dependent hypertension.

Aldosterone and Mineralocorticoid Receptor Blockade in Hypertension

Aldosterone, the primary mineralocorticoid in humans, is a powerful sodium-retaining hormone and has important effects on renal-pressure natriuresis and BP regulation. The primary sites of actions of aldosterone on sodium reabsorption are the principal cells of the distal tubules, cortical collecting tubules, and collecting ducts where aldosterone stimulates sodium reabsorption and potassium secretion. Aldosterone binds to intracellular mineralocorticoid receptors (MRs) and activates transcription by target genes, which, in turn, stimulate synthesis or activation of the Na^+-K^+-ATPase pump on the basolateral epithelial membrane and activation of amiloride-sensitive sodium channels on the luminal side of the epithelial membrane.[62] These effects are termed *genomic* because they are mediated by activation of gene transcription and require 60 to 90 minutes to occur after aldosterone administration.

Aldosterone may also exert rapid *nongenomic* effects on the cardiovascular and renal systems. Aldosterone increases the sodium current in principal cells of the cortical collecting tubule through activation of the amiloride-sensitive channel and stimulates the Na^+-H^+ exchanger in a few minutes after application.[62,63] In vascular smooth muscle cells, aldosterone stimulates sodium influx by activating the Na^+-H^+ exchanger in less than 4 minutes. The putative membrane receptor and the cell-signaling mechanisms responsible for these rapid nongenomic actions of aldosterone have not been identified, especially with physiologic levels of aldosterone. Thus, the importance of the nongenomic effects of aldosterone on long-term regulation of renal-pressure natriuresis and BP are still unclear.

The overall effects of aldosterone on pressure natriuresis are similar to those observed for Ang II. With low sodium intake, increased aldosterone helps prevent sodium loss and reductions in BP. Conversely, during high sodium intake, suppression of aldosterone helps prevent excessive sodium retention and attenuates increased BP.

Excess aldosterone secretion reduces the slope of pressure natriuresis so that BP becomes salt sensitive. Consequently, increasing plasma aldosterone 6- to 10-fold causes marked hypertension when sodium intake is normal or elevated but has little effect on BP when sodium intake is low.[21,64]

The role of aldosterone and activation of MRs in human hypertension has been a topic of considerable interest. Some investigators suggest that hyperaldosteronism or excess activation of MRs may be more common than previously believed, especially in patients with hypertension that is resistant to treatment with the usual antihypertensive medications. For example, the prevalence of primary aldosteronism is reported to be almost 20% among patients referred to specialty clinics for resistant hypertension. Many of these patients, however, are overweight or obese.[65]

Regardless of the prevalence of primary aldosteronism, MR antagonism may provide an important therapeutic tool for preventing target organ injury and reducing BP in hypertension.[65,66] For example, MR antagonism attenuated sodium retention, hypertension, and glomerular hyperfiltration in obese dogs fed a high-fat diet even though plasma aldosterone concentration was only slightly elevated.[67] However, even mild increases of plasma aldosterone may increase BP when accompanied by high sodium intake and volume expansion because aldosterone greatly enhances salt sensitivity of BP. In obese patients, there may be enhanced sensitivity to the effects of aldosterone because of increased abundance of epithelial sodium channels (ENaCs), which would amplify the effects of MR activation on sodium reabsorption and BP. It is also possible that glucocorticoids may contribute to MR activation in obese patients. There is also evidence that obesity may activate MR independently of the aldosterone or glucocorticoids.[68]

THE ENDOTHELIN SYSTEM

Endothelin (ET) peptides are derived from a 203–amino acid peptide precursor, preproendothelin, which is cleaved after translation to form proendothelin.[69] A converting enzyme located within the endothelial cells cleaves proendothelin (or big endothelin) to produce ET.[70,71] Although all three members of the ET family of peptides—ET-1, ET-2, and ET-3—are expressed in the cardiovascular system, ET-1 is the predominant isoform.

ET-1 is the most powerful vasoconstrictor produced in humans, and its levels are increased in hypertension.[72,73] Although tissue concentrations of ET-1 have been reported to be elevated in some forms of hypertension, circulating levels of ET-1 are typically not elevated in patients with essential hypertension or most forms of experimental hypertension unless renal failure, endothelial damage, or atherosclerosis are present.[72–75] Circulating ET-1 levels, however, do not reflect the local vascular production of the peptide. Indeed, ET-1 acts in a paracrine fashion, regulating nearby vascular smooth muscle cells.

ET-1 Receptor Subtypes and Physiological Actions

ET-1 can either elicit a hypertensive effect by activating ET type A (ET_A) receptors in the kidneys or an antihypertensive effect via ET type B (ET_B) receptor activation. Thus, the ability of ET-1 to influence BP regulation is highly dependent on where ET-1 is produced and which ET receptors are activated (Fig. 24–10). ET-1 receptor binding sites have been identified throughout the body, with the greatest numbers of receptors in the kidneys and lungs.[75,76] Although the biochemical and molecular nature of ET-1 is well characterized, its physiologic importance in regulating renal and cardiovascular function has yet to be fully elucidated.

ET-1 produces vasoconstriction, impairs renal-pressure natriuresis, and increases BP via ET_A receptor activation. ET_A receptors are located primarily on vascular smooth muscle cells and mediate ET-1 vasoconstriction and cellular proliferation in various disease states.[75,76]

ET-1, via ET_A receptor activation, exerts multiple actions within the kidney that, if sustained chronically, could contribute to the development of hypertension and progressive renal injury. ET-1 decreases GFR and renal plasma flow through stimulation of vascular smooth muscle and mesangial cell contraction. Long-term effects of ET-1 on the kidney include stimulation of mesangial cell proliferation and extracellular matrix deposition, as well as vascular smooth muscle hypertrophy in renal resistance vessels.[75,76]

Expression of ET-1 is greatly enhanced in several animal models of severe hypertension with renal vascular hypertrophy and in models of progressive renal injury.[77–80] In addition, treatment with ET receptor antagonists attenuated the hypertension and small artery morphologic

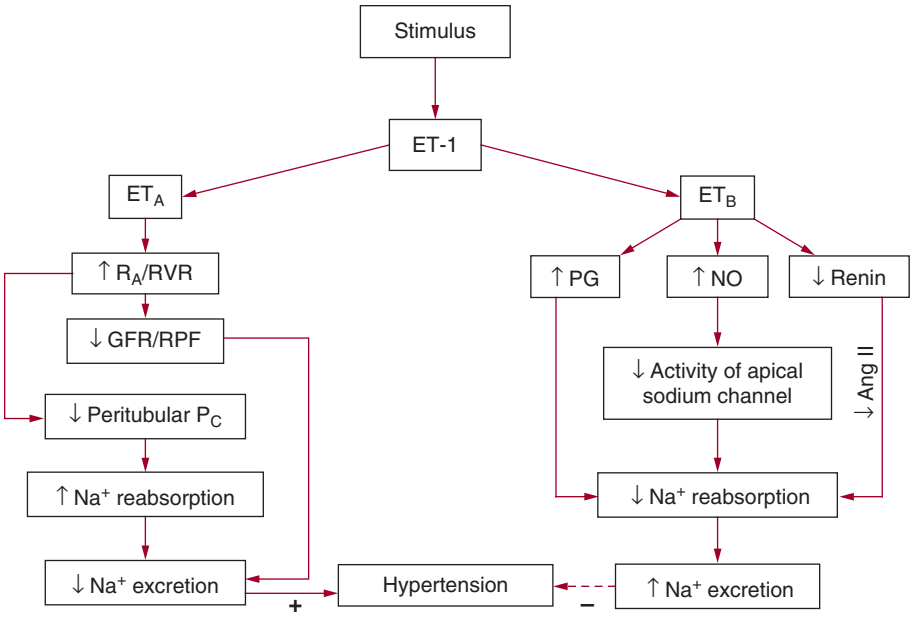

FIGURE 24–10. Summary of the pro- and antihypertensive actions of endothelin-1 (ET-1). The ability of ET-1 to influence blood pressure (BP) regulation and renal-pressure natriuresis is highly dependent on where ET-1 is produced and which renal ET receptor type is activated. ET-1 can elicit a prohypertensive antinatriuretic effect by activating ET_A receptors in the kidneys. Activation of renal ET_A receptors increases renal vascular resistance (RVR), which decreases renal plasma flow (RPF) and glomerular filtration rate (GFR), and enhances sodium reabsorption by decreasing peritubular capillary hydrostatic pressure (Pc). The net effect of renal ET_A receptor activation is decreased sodium excretion and increased BP. Conversely, ET-1 can elicit an antihypertensive natriuretic effect via ET_B receptor activation. Activation of the renal ET_B receptor leads to enhanced synthesis of nitric oxide (NO) and prostaglandin (PG) E_2 and suppression of the renin–angiotensin system. The net effect of renal ET_B receptor activation is increased sodium excretion and decreased BP.

changes and improved kidney function in these models.[77–84] ET_B receptors are located on multiple cell types throughout the body, including endothelial cells and renal epithelial cells. ET_B activation causes vasodilation, enhances pressure natriuresis, and decreases BP. Although much attention has been given to ET_A receptor activation in the pathophysiology of cardiovascular and renal disease, several studies indicate an important antihypertensive role for ET_B receptor. The most compelling evidence for a major role of ET_B receptors in regulating BP comes from reports that transgenic mice deficient in ET_B receptors develop severe salt-sensitive hypertension and that pharmacologic antagonism of ET_B receptors produces significant hypertension in rats.[85–87]

Bagnall et al reported that ablation of ET_B receptors exclusively from endothelial cells produced endothelial dysfunction but did not cause hypertension.[88] In contrast to models of total ET_B receptor ablation, the BP response to a high-salt diet was unchanged in endothelial cell-specific ET_B receptor knockouts compared with control mice. These findings suggest that ET_B receptors in nonendothelial cells are important for BP regulation. Supporting this concept is the finding that collecting duct ET_B knockout mice on a normal sodium diet were hypertensive and a high-sodium diet worsened the hypertension.[89] These findings provide strong evidence that the intrarenal effect of ET_B receptor activation on the collecting duct is an important physiologic regulator that increases renal sodium excretion and reduces BP. These effects of collecting duct–derived ET on BP and sodium excretion appear to be mediated by NO.[90]

ET-1 and Salt-Sensitive Hypertension

Several lines of evidence suggest that ET-1 may contribute to salt-sensitive hypertension. Dahl salt-sensitive (DS) rats placed on a high-sodium diet develop attenuated pressure natriuresis, hypertension, and progressive renal injury.[77,78] Evidence suggests that ET-1, acting via an ET_A receptor, may play a role in mediating the renal injury of DS hypertension. Prepro-ET-1 mRNA and vascular responsiveness to ET-1 are increased in the renal cortex of DS rats compared with Dahl salt-resistant (DR) rats, and a positive correlation between ET-1 generation in the renal cortex and the extent of glomerulosclerosis has been reported in DS hypertensive rats.[77] Acute infusion of a nonselective ET_A-ET_B receptor antagonist directly into the renal interstitium improved renal hemodynamic and excretory function in DS rats but not in DR rats. Moreover, chronic blockade of ET_A receptors attenuated hypertension and proteinuria and ameliorated glomerular and tubular damage associated with high salt intake in DS rats.[78] An important unanswered question is whether the beneficial effect of ET_A blockade in reducing renal injury is mediated through lower BP or through direct renal mechanisms.

Renal ET-1 synthesis is enhanced in various animal models of chronic hypertension including Ang II hypertension, deoxycorticosterone acetate (DOCA) hypertension, and placental ischemic-induced hypertension.[79–82] Hypertension in these models is markedly attenuated or completely abolished by ET_A receptor antagonists.

Role of Endothelin in Human Hypertension

Several selective and mixed endothelin receptor antagonists have been developed and utilized in clinical trials for therapy in renal disease, systemic and pulmonary arterial hypertension, and heart failure.[91,92] Although ET-1 clearly plays a significant role in the pathogenesis of some forms of experimental hypertension, especially salt-sensitive models, its role in human primary hypertension is unclear. Bosentan, a combined ET_A-ET_B receptor antagonist, significantly lowered BP in a large double-blind clinical trial, indicating that ET system helps maintain BP in human hypertension.[93] However, the magnitude of the BP reduction by bosentan was almost the same as that observed in normotensive humans. This observation suggests that ET may not play a major role in raising BP in most patients with essential hypertension, although bosentan blocks both ET_A and ET_B receptors, and antagonism of antihypertensive ET_B receptors may have masked an important role of ET on BP via ET_A receptor activation.

In another study, 6 weeks of darusentan, a selective ET_A receptor antagonist, was effective in lowering both systolic and diastolic BP.[94] There are currently no clinical studies that directly compare selective and mixed ET receptor antagonism in the treatment of hypertension, although both approaches clearly reduce BP. Therefore, the importance of ET-1 in human essential hypertension deserves further investigation.[93]

Role of Endothelin in Pulmonary Arterial Hypertension

Although the importance of ET-1 in essential hypertension remains unclear, ET-1 appears to play an important role in pulmonary arterial hypertension (PAH). PAH is characterized by a progressive increase in pulmonary vascular resistance resulting from vascular remodeling, vasoconstriction, and cellular proliferation.[94] Depending on the severity of the disease, PAH may progress to right ventricular failure and death. Studies in animal models of PAH and in humans suggest that ET-1 plays an important role in mediating the vascular remodeling, vasoconstriction,

and cellular proliferation associated with PAH.[92] Macitentan, a nonselective $ET_{A/B}$ receptor antagonist with beneficial effects in experimental PAH has been recently tested in a Phase III clinical Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial in patients with PAH. Macitentan significantly reduced morbidity and mortality in patients with PAH. Clinical trials utilizing other $ET_{A/B}$ receptor antagonists have also reported beneficial effects in PAH patients.[95] Thus, ET-1 receptor antagonists have proven to be efficacious in treating patients with PAH.

NITRIC OXIDE

Vascular NO is mainly produced from l-arginine by endothelial NO synthase (eNOS). Three distinct genes encode NOS isozymes that catalyze production of NO from l-arginine.[96] These include neuronal NOS (nNOS or NOS-1), cytokine-inducible NOS (iNOS or NOS-2), and endothelial NOS (eNOS or NOS-3). Production of NO from l-arginine by NOS also requires the presence of various cofactors, including tetrahydrobiopterin (BH_4), flavin adenine dinucleotide, flavin mononucleotide, calmodulin, and iron protoporphyrin IX. Tonic release of eNOS-derived NO by the vascular endothelium plays a major role in regulating vascular function, and nNOS and NOS-derived NO from renal epithelial cells regulate sodium transport and renal hemodynamics.[96] Long-term inhibition of NO synthase (NOS) causes sustained hypertension associated with impaired renal-pressure natriuresis.[97] The magnitude of the increase in BP during NO inhibition depends on sodium intake, indicating that NO also regulates sodium balance and renal-pressure natriuresis.

Nitric Oxide Enhances Pressure Natriuresis

Deficiency of NO synthesis impairs pressure natriuresis by several mechanisms, including hemodynamic and tubular effects, each of which may be modulated by processes that are intrinsic or extrinsic to the kidneys (Fig. 24–11). For example, reductions in NO synthesis may decrease renal sodium excretory function by increasing renal vascular resistance directly or by enhancing renal vascular responsiveness to vasoconstrictors such as Ang II or norepinephrine.[98–101] Reductions in NO synthesis also increase renal tubular sodium reabsorption via direct effects on tubular transport and through changes in intrarenal physical factors, such as renal interstitial hydrostatic pressure (RIHP) and medullary blood flow.[98–101] Inhibition of NO synthesis reduces RIHP and urinary sodium excretion.[101]

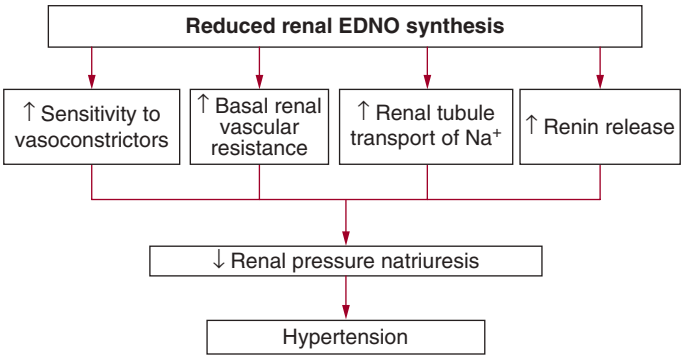

FIGURE 24–11. Renal mechanisms whereby reduced nitric oxide (NO) synthesis decreases pressure natriuresis and increases blood pressure. Decreased endothelial-derived nitric oxide (EDNO) synthesis impairs renal sodium excretory function by increasing basal renal vascular resistance, enhancing the renal vascular responsiveness to vasoconstrictors such as Ang II or norepinephrine, or activating the renin–angiotensin system. Reductions in NO synthesis also impair sodium excretory function either by directly increasing tubular reabsorption or by altering intrarenal physical factors, such as renal interstitial hydrostatic pressure or medullary blood flow.

Salt-Sensitive Hypertension Caused by Impaired Nitric Oxide Production

Several lines of evidence suggest that impaired NO synthesis plays an important role in the pathogenesis of salt-sensitive hypertension.[101] Increased renal NO production or release, as evidenced by increased urinary excretion of NO metabolites or the NO second messenger, cyclic guanosine monophosphate, has been reported to be essential for maintenance of normotension during a dietary salt challenge. Prevention of this increase in renal NO production resulted in salt-sensitive hypertension. Genetic models of hypertension such as DS rats have impaired pressure natriuresis associated with NO deficiency. Stimulation of NO production with chronic l-arginine supplementation normalizes the blunted pressure natriuretic response in DS rats as a result of improvement in the kidney's ability to generate increased RIHP in response to increased renal perfusion pressure.[101]

Evidence suggests that NO synthesis is impaired in some vascular beds in human primary hypertension. The extent to which these changes are secondary to increased BP or reflect important mechanisms for the pathogenesis of hypertension, however, remains unclear.

OXIDATIVE STRESS

Increased levels of reactive oxygen species (ROS) may play a role in initiation and progression of cardiovascular dysfunction associated with hyperlipidemia, diabetes mellitus, and hypertension.[102,103] In some forms of hypertension, increased ROS appear to be derived mainly from nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, which could serve as a trigger for uncoupling endothelial NOS by oxidants.[103] Four members of the NADPH oxidase (Nox) enzyme family have been identified as important sources of ROS in the vasculature: Nox1, Nox2, Nox4, and Nox5. Multiple factors control the expression and activity of these enzymes and of their regulatory subunits such as p22phox, p47phox, Noxa1, and p67phox.

ROS produced by migrating inflammatory cells or vascular cells have distinct effects on different cell types.[104] These effects include endothelial dysfunction, increased renal tubule sodium transport, cell growth and migration, inflammatory gene expression, and stimulation of extracellular matrix formation. ROS, by affecting vascular and renal tubule function, can also impair renal-pressure natriuresis, alter systemic hemodynamics, and raise BP (Fig. 24–12).[105]

Considerable evidence supports a role for ROS in various animal models of hypertension.[105] The DS rat, for example, has increased

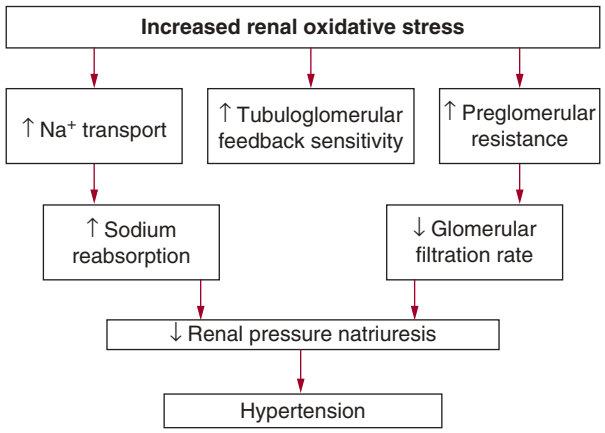

FIGURE 24–12. Renal mechanisms whereby reactive oxygen species impair pressure natriuresis and increase blood pressure. An increase in renal oxidative stress impairs renal-pressure natriuresis by increasing renal vascular resistance or enhancing tubuloglomerular feedback, both of which decrease the glomerular filtration rate. Renal oxidative stress also reduces sodium excretion by direct effects to increase renal tubular reabsorption.

vascular and renal superoxide production and increased levels of H_2O_2. Renal expression of superoxide dismutase is decreased in kidneys of DS rats, and long-term administration of Tempol, a superoxide dismutase mimetic, significantly decreases BP and attenuates renal damage. Another salt-sensitive model, the stroke-prone spontaneously hypertensive rat, has elevated levels of superoxide and decreased total plasma antioxidant capacity. Superoxide production is also increased in the DOCA-salt hypertensive rat and treatment with apocynin, an NADPH oxidase inhibitor, decreases BP. ROS also appear to play an important role in chronic Ang II hypertension. Ang II is a potent stimulus of NADPH oxidase and long-term administration of Tempol significantly decreases the chronic BP response to Ang II.[105,106]

Although elevated production of ROS is believed to play an important role in hypertension, clinical studies on chronic antioxidant therapy have failed to confirm this hypothesis.[107,108] An imbalance between total oxidant production and the antioxidant capacity in human primary hypertension has been reported in some, but not all, studies. Equivocal findings in human studies are partly caused by the difficulty of assessing oxidative stress. Measurement of ROS in tissues is a challenge because of their low levels and relatively short half-lives.[107,108] Most human studies have found that chronic antioxidant therapy with vitamin E and C supplementation has little or no effect on BP.[107,108]

VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor (VEGF or VEGF-A) has numerous physiological actions, including inducing endothelial cell permeability, proliferation, angiogenesis, lymphogenesis, and vasodilation.[109] VEGF belongs to a family of secreted glycoproteins, including VEGF-B, -C, and -D and placenta growth factor (PlGF). VEGF signaling is mediated via two receptors, VEGFR1/Flt1 and VEGFR2/Flk1. Drug therapies that specifically target VEGF inhibit tumor angiogenesis and have been highly beneficial in treating various cancers. Despite their clinical benefit, the safety of these targeted agents is of special concern especially for longer term treatment. Importantly, VEGF inhibitor therapy has been associated with hypertension and control of BP after administration of these drugs remains a challenge.[110]

Although hypertension appears to be one of the most common side effects of VEGF inhibitors, the pathophysiologic mechanisms underlying increases in BP have not been fully elucidated.[110,111] Because the endothelium is a major target for VEGF actions, it is likely that decreases in production of endothelium-derived relaxing factors such as NO and PGs or enhanced production of vasoconstricting factors such as thromboxane and ET-1 play a role in the hypertensive response to drugs that block the VEGF-pathway.[112] Facemire and colleagues reported that administration of a specific antibody against the major VEGF receptor, VEGFR2, to normal mice caused a rapid and sustained increase in BP that was associated with significant reductions in expression of endothelial and neuronal NOS in the kidney.[112] They also reported that L-NAME administration abolished the difference in BP between the vehicle- and anti-VEGFR2–treated groups. These findings suggest that VEGF, acting via VEGFR2, plays a critical role in influencing basal levels of BP control by enhancing NOS expression and NO activity. Moreover, the results suggest that reducing NO production or availability may be one mechanism underlying hypertension caused by antiangiogenic agents targeting VEGF.

Although the exact physiologic mechanisms whereby VEGF inhibition leads to hypertension are still unclear, in all forms of hypertension examined to date, including experimental models and human essential hypertension, there is a hypertensive shift in the renal-pressure natriuresis relationship. In the study of Facemire and colleagues, the anti-VEGFR2 antibody caused a rightward, parallel shift in the chronic pressure natriuresis relationship.[112] The parallel shift in the chronic pressure natriuresis relationship is consistent with the idea that increased preglomerular vascular resistance may be involved in mediating the hypertension.

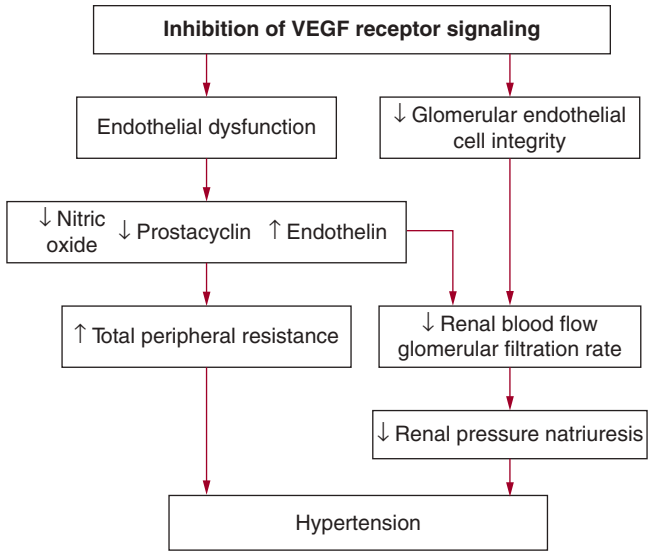

FIGURE 24–13. Potential mechanisms whereby inhibitors of vascular endothelial growth factor (VEGF) receptor signaling raise blood pressure (BP). Blockade of VEGF receptors results in endothelial dysfunction, leading to decreased production of endothelium-derived relaxing such as nitric oxide and prostaglandin or enhanced production of vasoconstrictor factors such as thromboxane and endothelin. Inhibitors of VEGF signaling may also result in alterations in glomerular structure and function. These changes may elevate BP by reducing renal blood flow and GFR and impairing the kidney's ability to excrete sodium and water (depicted by a decrease in the pressure-natriuresis relationship).

The altered pressure natriuresis relationship in response to blockade of VEGF receptors may be the result of endothelial dysfunction, leading to decreases in production of endothelium-derived relaxants such as NO (Fig. 24–13). Supporting this possibility is the fact that the hypertension in response to the anti-VEGFR2 antibody was associated with significant reductions in expression of endothelial and neuronal NOS in the kidney. These changes tend to reduce renal blood flow and GFR and impair the kidney's ability to excrete sodium and water. Unfortunately, the effect of the anti-VEGFR2 antibody on renal hemodynamics was not reported in the study of Facemire and colleagues.[112]

Another important endothelial-derived factor that may play a role in mediating the hypertension produced by VEGF inhibition is the vasoconstrictor ET-1. Kappers et al published the results of a series of clinical, animal, and in vitro studies suggesting a strong correlation between ET-1 and the hypertension associated with sunitinib, an orally active multitarget receptor tyrosine kinase inhibitor that inhibits phosphorylation of the VEGF receptor.[113] Verdonk et al also investigated the relationship between disturbed angiogenic balance, BP, and ET-1 in pregnant women with a high (≥ 85) or low (< 85) sFlt1/PlGF ratio. Plasma ET-1 levels were increased in women with a high ratio.[114] In addition, plasma ET-1 correlated positively with sFlt1, an endogenous inhibitor of VEGF that is elevated in preeclamptic women. Finally, the hypertension seen with the multitarget RTKI ABT-869 (known to target the VEGF receptor) is prevented by pretreatment with the selective ET_A receptor antagonist atrasentan.[115] Thus, another potential mechanism whereby VEGF blockade could increase BP is by enhancing ET-1 synthesis. However, the relative importance of the ET system in mediating increases in BP in response to VEGF pathway inhibitors remains to be determined.

Another potential mechanism for impaired pressure natriuresis after inhibition of VEGF is altered glomerular structure and function (see Fig. 24–13). VEGF and VEGF receptors are highly expressed in

the kidney. VEGF is expressed in glomerular podocytes, and VEGF receptors are present on endothelial, mesangial, and peritubular capillary cells. Signaling between endothelial cells and podocytes is thought to be important for maintenance of the filtration function of the glomerulus, and inhibitors of VEGF signaling has been shown to alter glomerular structure and function.

In summary, current evidence suggests that VEGF may have important physiologic roles in adult humans. Results from VEGF neutralization studies in animals and clinical trials in humans have demonstrated significant endothelial dysfunction and hypertension, implicating VEGF in maintaining normal endothelial function and BP regulation in adults. Further elucidation of the mechanisms whereby VEGF achieves this important physiological function could provide new drug targets to minimize the risk of significant hypertension and proteinuria in patients treated with VEGF pathway inhibitors.

ATRIAL NATRIURETIC PEPTIDE

ANP is a 28–amino acid peptide synthesized and released from atrial cardiocytes in response to stretch. ANP enhances sodium excretion through extrarenal and intrarenal mechanisms.[116] ANP increases GFR but has little effect on renal blood flow. However, an increase in GFR is not a prerequisite for ANP to enhance sodium excretion. ANP may also inhibit renal tubular sodium reabsorption directly by inhibiting active tubular transport of sodium or indirectly via alterations in medullary blood flow, physical factors, and hormones such as Ang II and aldosterone.[116–119]

Atrial Natriuretic Peptide Enhances Pressure Natriuresis and Lowers Blood Pressure

Plasma levels of ANP are elevated in numerous physiologic conditions associated with enhanced sodium excretion.[116–119] Acute blood volume expansion consistently elevates circulating levels of ANP. Some, but not all, investigators report that chronic increases in dietary sodium intake also increase circulating levels of ANP. Infusions of exogenous ANP at rates that result in physiologically relevant plasma concentrations, comparable to those observed during volume expansion, elicit significant natriuresis, especially in the presence of other natriuretic stimuli, such as high renal perfusion pressure. Long-term physiologic elevations in plasma ANP also enhance renal-pressure natriuresis and reduce BP.[120] ANP has been shown to buffer renin-dependent hypertension.[121]

Blockade of the Atrial Natriuretic Peptide System Produces Salt-Sensitive Hypertension

Genetic mouse models that exhibit altered expression of ANP or its receptors (NPR-A, NPR-C) have provided compelling evidence for a role of ANP in chronic regulation of renal-pressure natriuresis and BP.[122] Whereas transgenic mice overexpressing ANP are hypotensive relative to their WT litter mates, mice harboring functional disruptions of the ANP or NPR-A genes are hypertensive. ANP gene knockout mice develop salt-sensitive hypertension in association with failure to adequately suppress the RAAS. Although these findings suggest that genetic deficiencies in ANP or its receptors could play a role in the pathogenesis of hypertension, the role of ANP in human hypertension remains unclear.[123]

Inadequate renin and Ang II suppression in obese hypertensive men was associated with a relative ANP deficiency.[124] Burnett and colleagues found that human hypertension is characterized by a lack of activation of the antihypertensive cardiac hormones ANP and brain natriuretic peptide.[120] Moreover, several studies have found ANP gene variants to be associated with hypertension.[118] Although these studies suggest a potential role for ANP deficiency in hypertension, further studies are necessary to determine the role of ANP in human hypertension.

INNATE AND ADAPTIVE IMMUNITY

A strong association between innate or adaptive immune system activation with renal inflammation, reduced pressure natriuresis, and hypertension has been demonstrated in several experimental models, including Ang II, aldosterone, salt-sensitive, and spontaneously hypertensive rodent models.[125–130] An important characteristic commonly observed in these models is increased infiltrating immune cells, including macrophage and T lymphocytes, in the kidneys. In support of a role for T cells in the pathogenesis of hypertension are studies demonstrating that treatment with mycophenolate mofetil attenuates hypertension in association with reduced renal cortical T-cell infiltration in DS rats.[126]

T cells also play an important role in Ang II hypertension. RAG1$^{-/-}$ mice have an attenuated BP response to Ang II, which is fully restored with adoptive transfer of T cells.[131,132] Harrison and colleagues have proposed that Ang II increases T-cell activation and infiltration into perivascular fat.[131,132] T cells produce cytokines and release other mediators such as ROS that may affect smooth muscle cells and the endothelium of adjacent blood vessels. In support of this hypothesis, etanercept, a TNF-α antagonist, has been reported to prevent Ang II–induced increases in BP and vascular superoxide production.[133]

T cells contain components of the RAAS such as the Ang I-converting enzyme, renin, the renin receptor, and angiotensinogen. Hoch et al recently reported that T cells can produce Ang II and that AT_1 receptors are expressed within the T cell, suggesting an intracrine RAS.[134] They also demonstrated that Ang II has direct actions on T-cell function, including activation, expression of tissue-homing markers, and production of tumor necrosis factor-alpha (TNF-α). These authors proposed that that T-cell production of Ang II, superoxide, and TNF-α could contribute to inflammation in other settings in which T cells accumulate such as in arthritis, transplant rejection, and experimental myocarditis.

Crowley and colleagues examined the importance of activation of Ang II type 1 receptors (AT_1R) on hematopoietic cells in mediating Ang II-dependent hypertension by utilizing bone marrow chimeras deficient only in hematopoietic AT_1R. They reported that Ang II hypertension was exaggerated in the mice with bone marrow–specific AT_1R deficiency, suggesting a protective role for Ang II-stimulated hematopoietic cells.[135]

A subset of T cells called T-regulatory cells (CD4+CD25+Foxp3+ cells) has an important role to suppress autoreactive T cells and promote immune tolerance.[135] T-regulatory cell function is impaired in human autoimmune disorders associated with hypertension. T-regulatory cells are reduced in the renal cortex of Ang II-hypertensive animals and adoptive transfer to increase T-regulatory cells reduces BP in association with reduced renal inflammatory cytokines. These findings support the concept that impaired T-regulatory function may contribute to the pathogenesis of hypertension in autoimmune disorders.

The role of self-antigens in promoting hypertension by activating the adaptive immunity has been recently examined. Agonistic antibodies directed to adrenergic and angiotensin receptors and immunoglobulin G (IgG) and IgM autoantibodies are elevated in primary and secondary forms of hypertension. Utilizing a murine model of systemic lupus erythematosus (SLE), characterized by a multiorgan inflammation in response to self-antigens and autoantibody (antinuclear) production, Ryan and colleagues showed that depleting B cells before the development of SLE with the administration of anti-CD20 antibody reduced

formation of autoantibodies, decreased tumor necrosis factor-α expression, and ameliorated hypertension.[136] These data suggest that development of autoimmunity and the resultant increase in renal inflammation are important underlying factors in the hypertension that occurs during SLE.

Th17 cells represent a newly characterized subset of T cells that produce the cytokine IL-1. IL-17 is elevated in several experimental models of hypertension such as Ang II and placental ischemia induced hypertension. Chronic infusion of IL-17 induced hypertension and endothelial dysfunction in mice and placental oxidative stress and hypertension in pregnant rats.[137] To investigate the role of IL-17 in Ang II hypertension, Harrison and colleagues examined the chronic effects of Ang II in IL-17a$^{-/-}$ and wild-type mice.[138] These mice exhibited a similar initial increase in BP as wild-type mice in response to Ang II; however, after 7 days, BP dropped in IL-17a$^{-/-}$ mice. The Ang II-induced hypertension was reduced and aortic T-cell infiltration observed in wild-type mice was abolished in IL-17a$^{-/-}$ mice, as were increases in vascular oxidative stress and endothelial dysfunction.

Although there are a growing number of experimental studies in variety of animal models suggesting an important role for the immune system in the pathogenesis of hypertension, comparable studies in humans are limited. Thus, the importance of the immune system and inflammatory cytokines in the pathogenesis of primary and secondary human hypertension remains an important unanswered question.

SECONDARY CAUSES OF HYPERTENSION

In a small percentage of patients, the clinical features, history, and physical examination point to a specific cause of increased BP, and the hypertension is therefore said to be *secondary*. Some types of secondary hypertension have a definite genetic basis, and others are associated with specific neurohormonal or kidney disorders. In some instances, hypertension is caused by drugs or treatments that the patient receives. Nearly all forms of secondary hypertension, however, are characterized by impaired renal function or altered activity of the SNS or hormones that impair the ability of the kidneys to excrete salt and water.

Table 24–4 lists some of the most frequently diagnosed causes of secondary hypertension, including those caused by drugs that either themselves increase BP or exacerbate underlying disorders that contribute to hypertension. These drugs include NSAIDs, oral contraceptives, glucocorticoids, and sympathomimetics. This chapter discusses only a few of the more common causes of secondary hypertension.

TABLE 24–4. Some Secondary Causes of Hypertension

A.	Renal parenchymal disease
	Acute and chronic glomerulonephritis
	Chronic nephritis (eg, pyelonephritis, radiation)
	Polycystic disease
	Diabetic nephropathy
	Hydronephrosis
	Neoplasms
B.	Renovascular
	Renal artery stenosis or compression
	Intrarenal vasculitis
	Suprarenal aortic coarctation
C.	Renoprival (renal failure, loss of kidney tissue)
D.	Endocrine disorders
	Renin-producing tumors
	Cushing syndrome
	Primary aldosteronism
	Pheochromocytoma (adrenal or extraadrenal chromaffin tumors)
	Acromegaly
E.	Pregnancy-induced hypertension
F.	Sleep apnea
G.	Increased intracranial pressure (brain tumors, encephalitis)
H.	Exogenous hormones and drugs (partial list)
	Glucocorticoids
	Mineralocorticoids
	Sympathomimetics
	Tyramine-containing foods and monoamine oxidase inhibitors
	Apparent mineralocorticoid excess (eg, licorice)
	Nonsteroidal anti-inflammatory drugs
	Cyclosporine
	Excess alcohol use
	Drug abuse (eg, amphetamines, cocaine)

RENOVASCULAR HYPERTENSION

Renovascular hypertension, although accounting for only about 5% of all hypertension, is one of the most common causes of secondary hypertension. The pathophysiology of renovascular hypertension is related to reductions in renal perfusion that result from stenosis of the main renal artery, one of its branches, or stenosis/injury of other smaller preglomerular blood vessels and glomeruli. The majority of renal vascular lesions reflect either fibromuscular dysplasia or atherosclerosis.[139,140] The predominant lesion found in the main renal artery or its branches in patients older than 50 years of age is atherosclerotic disease. More subtle functional (constriction) or structural changes in smaller blood vessels (eg, afferent arterioles, glomeruli), however, are difficult to detect clinically and can contribute to increased BP.

Renovascular hypertension may be unilateral or bilateral and may result in homogeneous or nonhomogeneous ischemia of nephrons. As discussed earlier in the chapter, there are some important differences in the pathophysiology of homogeneous compared with nonhomogeneous renal ischemia. Experimental counterparts of these two clinical forms of renovascular hypertension can be found in the one-kidney, one-clip and the two-kidney, one-clip models of Goldblatt hypertension, respectively.

Renal Artery Stenosis in a Single Remaining Kidney

In the one-kidney, one-clip model of Goldblatt hypertension and in patients with stenosis of a single remaining kidney, there is a fairly homogeneous reduction in perfusion of all nephrons, leading to an elevation of BP that is proportional to the severity of the stenosis. In experimental one-kidney, one-clip Goldblatt hypertension, BP increases rapidly after clipping the renal artery and remains stable as long as the stenosis does not worsen. Moreover, the BP returns to normal when the stenosis is removed.

Renal artery constriction, if severe enough to reduce renal perfusion pressure below the range of autoregulation (~70 mm Hg), initially decreases renal blood flow, GFR, and sodium excretion while increasing renin secretion. However, if the stenosis is not too severe,

sodium excretion returns to normal, and if sodium intake is normal and adequate volume is available, renin secretion also returns to nearly normal in the established phase of hypertension.[24,141] At this point, the hypertension is stable and most indices of renal function are relatively normal, including pressure distal to the stenosis.

Increased Ang II accounts for most of the rapid increase in BP after stenosis of the renal artery. However, even after blocking the RAAS, BP still increases (although more slowly) until renal perfusion pressure returns to nearly normal. This increase in renal perfusion pressure, at the expense of systemic arterial hypertension, permits normal excretion of sodium and water to be maintained. As long as sodium intake is normal, activation of the RAAS serves mainly to increase the rate at which BP is elevated. In the established phase of hypertension, blockade of the RAAS causes only small reductions in BP, similar to the decreases observed in normal subjects after Ang II blockade.[142]

The importance of volume expansion in elevating BP in one-kidney, one-clip Goldblatt hypertension depends on sodium intake. Whereas with normal or high sodium intake, significant extracellular volume expansion occurs, a low-sodium diet converts this model of hypertension from one that is volume dependent to one that is highly Ang II dependent. When the stenosis is severe and adequate renal perfusion cannot be restored even with increased systemic arterial pressure, renin secretion continues to increase, as does BP, leading eventually to malignant hypertension and renal failure. Thus, the ability to return renal perfusion pressure to normal, or nearly normal, by volume retention or activation of the RAAS is critical to maintaining homeostasis when there is renal artery stenosis in a single remaining kidney.

The same sequence as described above occurs when there are widespread homogeneous increases in preglomerular resistance caused by bilateral renal artery stenosis or aortic coarctation above both renal arteries.[21,24]

Nonhomogeneous Nephron Ischemia

In patients with nonhomogeneous increases in preglomerular resistance or in the two-kidney, one-clip model of Goldblatt hypertension, the pathophysiology of hypertension is more complicated. Nonhomogeneous nephron ischemia may be a result of stenosis of one renal artery and normal perfusion of the contralateral kidney or of patchy increases in preglomerular resistance within the kidneys, with some nephrons being underperfused and others having normal or increased blood flow. Thus, these forms of hypertension are characterized by ischemia of some nephrons and normal or increased blood flow in adjacent nephrons or in the nonstenotic kidney.

In experimental models with unilateral renal artery stenosis, the ischemic nephrons (or the entire underperfused kidney in the case of a unilateral renal artery stenosis) are exposed to reduced perfusion pressure, secrete more renin, and excrete less sodium and water than kidneys with normal blood flow. In contrast, the nonischemic nephrons (or nonstenotic kidney) are exposed to increased renal perfusion pressure, decreased renin secretion, and increased sodium excretion. However, even with increased perfusion pressure, the function of the nonischemic nephrons (or unclipped, nonstenotic kidney) is impaired because of increased circulating Ang II, which exerts an antinatriuretic effect and helps sustain hypertension.

The higher BP experienced by the nonstenotic kidney may eventually damage its nephrons, which then sustains increased BP even after correction of the stenosis in the other kidney. However, correction of the stenosis plus nephrectomy of the nonstenotic kidney usually normalizes BP.[143]

Administration of ACE inhibitors or ARBs as a treatment for renovascular hypertension may improve structure and function of the nonstenotic kidney but in some cases may also produce shrinkage of the stenotic kidney, resulting in fibrosis and deterioration of its function. This is partly a result of decreased BP, which may reduce renal perfusion pressure distal to the lesion to a level below the range of autoregulation. Blockade of the RAAS also dilates efferent arterioles, which contributes to a decline in GFR in the stenotic kidney. In some patients with severe renal vascular lesions, administration of ACE inhibitors or ARBs may cause severe decreases in renal function, especially when there is also volume depletion because of concomitant use of diuretics. Therefore, renal function should be monitored frequently after administration of RAAS inhibitors in patients suspected of having renovascular hypertension. Fortunately, these effects appear to be reversible upon cessation of ACE inhibition or ARB, and in many patients, the beneficial BP lowering effects of RAAS blockade can be achieved without precipitating further loss of kidney function.

ADRENAL CORTEX HYPERTENSION

Aldosterone normally exerts nearly 90% of the mineralocorticoid activity of the adrenocortical secretions. However, cortisol, the major glucocorticoid secreted by the adrenal cortex, can also provide significant mineralocorticoid activity in some conditions. Aldosterone's mineralocorticoid activity is about 3000 times greater than that of cortisol, but the plasma concentration of cortisol is nearly 2000 times that of aldosterone. Normally, the renal MR is "protected" from activation by cortisol as a result of 11β-HSD2, which converts active cortisol into inactive cortisone. However, when 11β-HSD2 activity is reduced or when cortisol levels are very high, the MR may be activated by cortisol.

Primary Aldosteronism (Conn Syndrome)

Primary aldosteronism, also called *Conn syndrome* in honor of Jerome Conn who first described this condition in 1955, results from hypersecretion of aldosterone in the absence of a known stimulus. The excess aldosterone secretion almost always comes from the adrenal cortex and is usually associated with a solitary adenoma or bilateral hyperplasia of the adrenal cortex. *Secondary aldosteronism* refers to increased aldosterone secretion as a result of a known stimulus, such as increased Ang II. This is the most common form of aldosteronism seen in clinical practice and occurs in various conditions associated with increased renin secretion, such as congestive heart failure, sodium depletion, or renal artery stenosis.

Primary aldosteronism may occur as a result of an aldosterone-producing adenoma (APA) or unilateral or bilateral adrenal hyperplasia (BAH).[144] The effects of excess aldosterone were discussed earlier, but the most important actions with regard to chronic BP regulation are increased sodium reabsorption, increased potassium secretion by the principal cells of the renal tubules, and increased hydrogen ion secretion by the intercalated cells of the renal tubules. These effects cause expansion of extracellular fluid volume, hypertension, suppression of renin secretion, hypokalemia, and metabolic alkalosis—hallmarks of primary aldosteronism. Most of these effects are highly salt sensitive, and low sodium intake greatly attenuates the hypertension and hypokalemia associated with primary aldosteronism.

Diagnosis of primary aldosteronism is made by a multistep process that ends with adrenal venous sampling.[145] APA and BAH together account for more than 95% of primary aldosteronism. Patients with APA are often treated by surgical removal of the adenoma whereas those with BAH are treated pharmacologically with MR antagonists.[144] With wider screening for primary aldosteronism, approximately 70% of cases of aldosterone excess appear to be caused by BAH, with APA comprising most of the remainder.[144]

In most studies of unselected patients, the classic form of primary aldosteronism was found in less than 1% of hypertensive patients.[123]

Some adrenal glands in patients with primary aldosteronism may have varying degrees of hyperplasticity, and the term *idiopathic hyperaldosteronism* (IHA) was coined to describe this condition. Clinically, APA and IHA are difficult to distinguish, although patients with APA often have more severe hypertension and hypokalemia than those with IHA.

Measurements of the aldosterone-renin ratio have been used in an attempt to define more subtle cases of primary aldosteronism.[123,146] This approach has led to the suggestion that excess aldosterone secretion may account for as much as 5% to 10% of essential hypertension. However, there is considerable debate about whether patients with increased aldosterone-renin ratios truly have primary aldosteronism. In many of these patients, the major reason for the increased aldosterone–renin ratio is the low level of renin, rather than excess aldosterone secretion.[123]

Increased Arterial Pressure and "Escape" from Sodium Retention during Hyperaldosteronism

Although aldosterone is a powerful sodium-retaining hormone, sodium excretion eventually returns to match sodium intake even in patients with APA and very high levels of aldosterone. This "escape" from sodium retention is secondary to increases in extracellular fluid volume and pressure natriuresis.[64] After extracellular fluid volume increases 5% to 15% above normal, BP also increases 15 to 25 mm Hg, and the elevated BP returns renal output of salt and water to normal despite excess aldosterone (Fig. 24–14). The importance of pressure natriuresis in permitting aldosterone escape was demonstrated experimentally by servo-controlling renal perfusion pressure; when renal perfusion pressure was servo-controlled, aldosterone infusion caused continued sodium retention and progressive increases in cumulative sodium balance and extracellular fluid volume, resulting in severe circulatory congestion and edema.[64] Failure of the kidneys to escape from aldosterone-induced sodium retention also occurs in patients with heart failure who, because of a severely weakened heart, cannot increase BP sufficiently to reestablish salt and water balance.

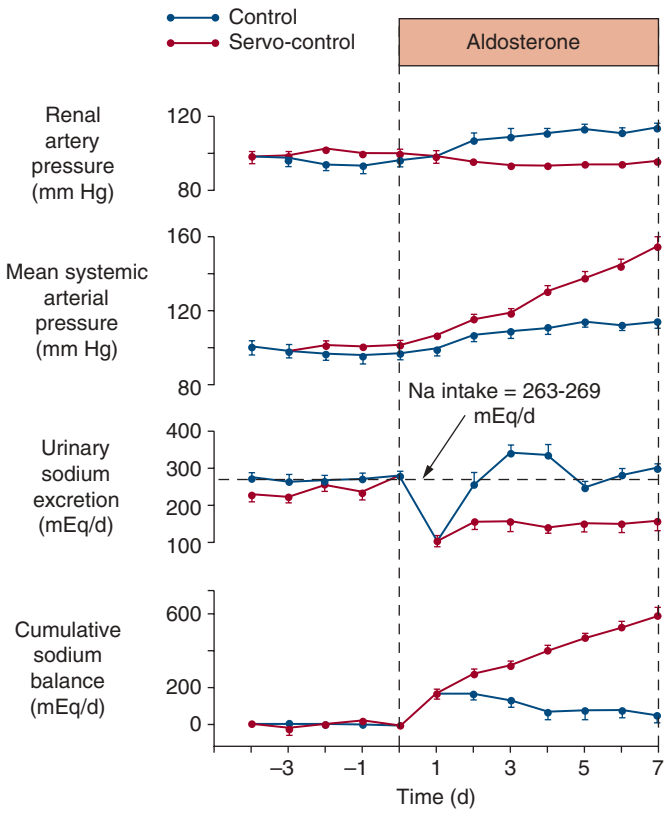

FIGURE 24–14. Effects of chronic aldosterone infusion when renal perfusion pressure was servo-controlled (*red lines*) or allowed to increase (*blue lines*). When renal perfusion pressure was prevented from increasing, "escape" from sodium retention did not occur, and cumulative sodium balance and systemic arterial pressure continued to increase. Data from Hall JE, Granger JP, Smith MJ Jr, et al: Role of renal hemodynamics and arterial pressure in aldosterone "escape". *Hypertension*. 1984 Mar-Apr;6(2 Pt 2):I183-I192.

Sustained Hypokalemia and Metabolic Alkalosis with Hyperaldosteronism

Excess aldosterone not only increases secretion of potassium ions by the principal cells of the renal tubules but also stimulates transport of potassium from the extracellular fluid into most cells of the body. This shift of potassium from the extracellular to intracellular fluid accounts for a significant part of the hypokalemia in hyperaldosteronism.

Excess aldosterone secretion also stimulates secretion of hydrogen ions in exchange for sodium as well as bicarbonate reabsorption in the intercalated cells of the renal collecting tubules and collecting ducts. This decreases hydrogen ion concentration in the extracellular fluid causing metabolic alkalosis.

Patients with IHA often have a milder form of aldosteronism than those with APA, although there may be overlap in severity of the clinical features of these two groups. In patients with APA, plasma aldosterone concentration is not usually increased in response to upright posture because of marked suppression of renin secretion and insensitivity of the aldosterone-secreting adenoma to Ang II. In contrast, patients with IHA usually have a significant increase in aldosterone concentration during upright posture, suggesting that adrenal sensitivity to Ang II is maintained.[147] These differences between IHA and APA in adrenal responsiveness to RAAS activation have been used to discriminate between these two forms of primary aldosteronism.

Cushing Syndrome (Glucocorticoid Excess)

Cushing syndrome is characterized by excess secretion of glucocorticoids. Hypertension occurs in approximately 80% of patients with Cushing syndrome and is difficult to control.[148] The morbidity associated with cortisol excess is substantial, and risk for death is largely due to excess cardiovascular events, including heart attack and stroke.

Cushing syndrome may be caused by administration of excess cortisol (eg, for treatment of various inflammatory disorders) or by excess endogenous cortisol secretion. The most common cause of endogenous cortisol excess is overproduction of adrenocorticotropic hormone (ACTH) from a pituitary adenoma, a condition referred to as *Cushing disease*. Increased ACTH causes adrenal hyperplasia and stimulates cortisol secretion. Cushing disease may also occur as a result of ectopic secretion of ACTH by tumors outside the pituitary, such as an abdominal carcinoma.

ACTH-independent hypercortisolism may also be caused by adenomas of the adrenal cortex. Primary overproduction of cortisol by the adrenal glands, independent of ACTH, accounts for approximately 20% to 25% of cases of Cushing syndrome and is usually associated with suppressed ACTH levels caused by cortisol-induced feedback inhibition of ACTH secretion from the anterior pituitary gland. Administration of large doses of dexamethasone, a synthetic glucocorticoid, can be used to distinguish between ACTH-dependent and ACTH-independent Cushing syndrome. In patients with overproduction of cortisol because of an ACTH-secreting pituitary adenoma or hypothalamic-pituitary dysfunction, even large doses of dexamethasone usually do not suppress ACTH secretion. In contrast, patients with primary adrenal overproduction of cortisol (ACTH independent) usually have low or undetectable levels of ACTH. However, the dexamethasone test may occasionally give an incorrect diagnosis because

some ACTH-secreting pituitary tumors respond to dexamethasone with suppression of ACTH secretion.

Glucocorticoids modulate a wide variety of cell processes and the precise mechanisms by which hypercortisolism causes hypertension are incompletely understood. One potential mechanism is activation of the MR; the high levels of cortisol in Cushing syndrome may overwhelm the ability of the renal 11β-HSD2 to convert active cortisol into inactive cortisone at the MR receptor so that cortisol stimulates the MR and causes sodium retention, volume expansion, hypertension, and hypokalemia. High levels of cortisol may also increase the responsiveness to various pressor stimuli, including Ang II and norepinephrine.[149]

Studies in experimental animals suggest that excess cortisol may also raise BP through mechanisms that may be at least partially independent of activation of classical glucocorticoid or MR.[150] Most of the available evidence, however, suggests that sodium retention plays a key role, although the precise mechanisms that lead to sodium retention are incompletely understood.

Other Forms of Adrenocortical Hypertension

There are several other rare forms of adrenocortical hypertension, as discussed in Genetic Causes of Hypertension (below). Some of these genetic disorders include familial hyperaldosteronism, glucocorticoid-remediable aldosteronism, deoxycorticosterone-secreting tumors, and the syndrome of apparent mineralocorticoid excess (AME) where glucocorticoids activate the MR because of a deficiency of 11β-HSD2. The clinical characteristics of these conditions are similar to those observed with primary increases in aldosterone secretion.

PHEOCHROMOCYTOMA

Although rare, occurring in only 0.05% of hypertensive patients,[49,151] pheochromocytoma can provoke fatal hypertensive crises if unrecognized and untreated. Pheochromocytoma can arise from neuroectodermal chromaffin cells, which are part of the sympathoadrenal system. The chromaffin cells have the capacity to synthesize and store catecholamines and are normally found mainly in the adrenal medulla. Although most chromaffin cell tumors are found in the adrenal medulla, as many as 15% to 30% may be extraadrenal, located along the sympathetic chain or, rarely, in other sites.[49,151]

The symptoms and severity of hypertension associated with pheochromocytoma are highly variable, depending on the secretory pattern and amount of catecholamines released.[151,152] With tumors that continuously release large amounts of catecholamines, there may be sustained hypertension with few paroxysms or sudden bursts of very high BP. Tumors that are less active may have cyclical release of catecholamines that induce paroxysms of hypertension.

The clinical presentation also depends on whether the predominant catecholamine secreted is norepinephrine or epinephrine. Whereas norepinephrine produces α-adrenergically mediated vasoconstriction with diastolic hypertension, epinephrine produces β-adrenergically mediated cardiac stimulation with mainly systolic hypertension and tachycardia, along with sweating, tremors, and flushing. Patients with predominantly epinephrine-secreting tumors sometimes have hypertension alternating with hypotension, and approximately 5% of patients with pheochromocytoma remain normotensive.[49]

Pheochromocytoma patients often have decreased blood volume, consistent with the potent peripheral vasoconstrictor effects of norepinephrine, which reduces vascular capacitance. Orthostatic hypotension is common among patients with pheochromocytoma and is related not only to decreased blood volume but perhaps also to desensitization of adrenergic receptors secondary to the chronic excess of catecholamines.

Although a high level of circulating catecholamine is the ultimate cause of hypertension in pheochromocytoma, BP is often only modestly correlated with plasma catecholamine levels. However, periodic bursts of catecholamine release may cause moderate to severe hypertension and lead to target organ injury. Consequently, diagnosis and effective treatment of pheochromocytoma are essential.

PREECLAMPSIA

Preeclampsia is a complex maternal syndrome characterized by multiple disorders, including proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms; however, it is most identifiable by the development of new-onset hypertension (systolic BP ≥ 140 mm Hg/diastolic BP ≥ 90 mm Hg) after the 20th week of gestation.[153] Progression of the disease may lead to eclampsia, in which seizures develop in association with a high risk of fetal and maternal mortality. Despite being a leading cause of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia have not yet been fully elucidated. Hypertension associated with preeclampsia remits after delivery, implicating the placenta as a central culprit in the disease.[154,155]

Although numerous factors, including genetic, immunologic, behavioral, and environmental factors, have been implicated in the pathogenesis of preeclampsia, reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles appears to play a key role.[154,155] Placental ischemia is thought to cause widespread activation or dysfunction of the maternal vascular endothelium, which results in enhanced formation of ET-1, thromboxane, superoxide, increased vascular sensitivity to Ang II, and decreased formation of vasodilators such as NO and prostacyclin. These endothelial abnormalities, in turn, cause hypertension by impairing renal function while increasing TPR.

One of the most intensely studied pathways in preeclampsia is that related to VEGF signaling.[154,155] VEGF and PlGF, besides their role in angiogenesis, are also important in the maintenance of proper endothelial cell function and health. This signaling pathway came to prominence with the discovery of elevated circulating and placental levels of the soluble form of the VEGF receptor, fms-related tyrosine kinases (sFlt)-1 in preeclampsia.[156] sFlt-1 is a circulating soluble receptor for both VEGF and PlGF, which when increased in maternal plasma leads to less circulating free VEGF and free PlGF, thus preventing their availability to stimulate angiogenesis and maintain endothelial integrity. In the kidney, this inactivation of free VEGF is believed to cause endotheliosis and proteinuria. In addition, sFlt-1 administration to pregnant rats decreases free VEGF and free PlGF in the blood and produces hypertension and proteinuria.[157] Moreover, recombinant VEGF 121 infusion lowers BP and improves renal function in rats with placental ischemia-induced hypertension and elevated levels of sFlt-1.

There is also growing evidence for an important role of ET-1 in the pathophysiology of preeclampsia.[158] Multiple studies have examined circulating levels of ET-1 in normal pregnant and preeclamptic cohorts and found elevated levels of plasma ET-1 in the preeclamptic group, with some studies indicating that the level of circulating ET-1 correlates with the severity of disease symptoms, though this is not a universal finding. ET-1, however, is produced locally, and plasma levels typically do not reflect tissue levels of the peptide. Animal studies have shown that a myriad of experimental models of preeclampsia (placental ischemia, sFlt-1 infusion, TNF-α infusion, and AT1-AA infusion) are associated with elevated tissue levels of ET-1.[158] Finally, the fact that hypertension in pregnant rats, induced by placental ischemia or

chronic infusion of sFlt-1, TNF-α, or AT1-AA can be attenuated by ET_A receptor antagonism, strongly suggests that ET-1 may be a final common pathway linking factors produced during placental ischemia to elevations in BP.[158]

Unfortunately, effective treatments for patients with preeclampsia remain elusive. In light of the recent developments in our understanding of the pathophysiology of preeclampsia, treatment strategies aimed at improving endothelial dysfunction, safely lowering BP, and reducing maternal and perinatal morbidity should be further explored.

GENETIC CAUSES OF HYPERTENSION

GENE VARIANTS AND HUMAN PRIMARY HYPERTENSION

With the development of superb tools for genetic studies and sequencing of the human genome, there has been great enthusiasm for the possibility that genetic causes of primary hypertension can be identified.[159] Proponents of the genetic basis for primary hypertension have implied that advances in genetics will offer unparalleled insights into the pathophysiology of hypertension and development of more effective individualized treatments for hypertension. However, despite great effort, there has been limited success in identifying genes that cause human primary hypertension. The success that has been achieved thus far has been mainly identification of rare monogenic forms of hypertension. A detailed discussion of this topic is beyond the scope of the chapter, but others have discussed some reasons why the "geneticism of hypertension" approach has had limited success.[160]

When one considers the complexity of the multiple neural, hormonal, renal, and vascular mechanisms that contribute to short- and long-term BP regulation, it is perhaps not surprising that finding a few variant genes (alleles) to account for a substantial portion of BP variation has been challenging. The complexity of the problem is further amplified by the fact that genetic components of BP variation are likely to be mediated not by only single-gene variations but also by polymorphic genetic differences, complex interactions among several genes, and interaction among genetic and environmental factors. The observation that hypertension does not occur with significant frequency in multiple populations living in nonindustrialized regions of the world suggests that environmental influences play a major role in the development of common forms of hypertension.

What is the evidence that gene variants play a major role in human primary hypertension? Multiple studies provide evidence that the closer the genetic relatedness, the greater the similarity of BP.[161,162] For monozygotic twins (with genetic similarity of 100%), the correlation coefficient for systolic BP has ranged from 0.5 to 0.8 (average, 0.6); for dizygotic twins, it has ranged from 0.19 to 0.46 (average, 0.35); and for nontwin siblings (genetic similarity of around 50%), the correlation coefficient has averaged around 0.23. There is also a better correlation of BP values in biologic children than in adopted children. However, the importance of shared family environment is also evident from the BP correlations observed in genetically unrelated adopted siblings.

Comprehensive familial analyses that include other relatives in addition to twins suggest that environment may contribute to as much as 30% of BP variance, and genetic factors may contribute 40% to 50% of BP variance.[161,162] However, despite the use of sophisticated mathematical models for these calculations, the possibility of nonlinear gene-environmental interactions makes it difficult to quantify the precise roles of genes and environment in BP variation.

Hypertension has been suggested to result from the additive effects of multiple variant genes acting in concert to elevate BP. Each gene variant is presumed to have a relatively weak impact on BP but may produce significant hypertension when they act together in the presence of the necessary environmental conditions. This *polygenic* model also applies to other complex diseases (eg, diabetes or cancer) in which multiple genes and environmental factors may play a role in the development of the disease.

Although the hypertension research literature is replete with studies showing associations of gene polymorphisms and BP, the genetic alterations that contribute to primary hypertension remain unknown.[161] Most of these genetic studies have produced mixed results, even for widely studied polymorphisms such as the ACE insertion or deletion and angiotensinogen polymorphisms. All of the polymorphisms studied thus far show weak associations, if any, with BP, and many of the early studies showing statistically significant associations have not been confirmed. Large-scale genome-wide association studies, in which hundreds of thousands of common genetic variants are genotyped and analyzed for BP association, have shown limited success in identifying genes that contribute to hypertension.[163–165] At best, the gene variations discovered thus far explain only a tiny part of the BP variation found in humans.

Epigenetic modification of gene expression may help to explain some of the "missing heritability" of human BP variation.[166,167] Epigenetics is the study of heritable changes in gene expression caused by factors that orchestrate changes in DNA expression without altering the underlying DNA sequence.[166,167] Nucleic acid methylation, histone modification, nucleosome positioning, transcriptional control with DNA-binding proteins and noncoding RNAs, and translation control with microRNAs and RNA-binding proteins could potentially contribute to epigenetic changes in gene expression. Evidence from rodent studies suggests that some epigenetically influenced phenotypes (eg, obesity, insulin resistance) may even be passed on to more than one generation of offspring.[168] However, the importance of epigenetic changes in contributing to human primary hypertension is still unclear and is a rapidly emerging area of investigation.[169]

MONOGENIC DISORDERS THAT CAUSE HYPERTENSION

At least 10 monogenic disorders have been identified that have either high or low BP as part of the phenotype.[170,171] Table 24–5 shows some of the monogenic disorders associated with high BP. An interesting feature of these genetic disorders is that they increase either electrolyte transport in the renal tubule or the synthesis or activity of mineralocorticoid hormones. The final common pathway to hypertension in these disorders appears to be increased renal sodium reabsorption. Monogenic hypertension, however, is rare, and all of the known forms together account for less than 1% of human hypertension.

Familial Hyperaldosteronism Type I

Also called *glucocorticoid remediable aldosteronism*, familial hyperaldosteronism type I (FH-I) is an inherited autosomal dominant trait caused by a chimeric gene derived from a meiotic mismatch and unequal crossing between the promoter of the 11β-hydroxylase (*CYP11B1*) controlled by the structural portion of the aldosterone synthase gene (*CYP11B2*).[172] This causes aldosterone secretion to be regulated by ACTH. Because ACTH is suppressed by glucocorticoids, administration of glucocorticoids is effective in reducing aldosterone secretion in patients with FH-I.

Patients with FH-I exhibit many of the same characteristics as those with primary aldosteronism, including elevated aldosterone, hypokalemia, volume expansion, metabolic alkalosis, and low plasma renin. Although some patients with FH-I have severe hypertension, others have only moderate hypertension or may even be normotensive.[173] The

TABLE 24–5. Known Genetic Causes of Hypertension

Genetic Disorder	Age of Onset	Pattern of Inheritance	Aldosterone Level	Serum Potassium Level	Treatment[a]
AME2[b,c]	Childhood	Autosomal recessive	Low	Low to normal	Spironolactone, dexamethasone
Liddle syndrome[d]	Third decade of life	Autosomal dominant	Low	Low to normal	Amiloride, triamterene
Gordon syndrome[e]	Second or third decade of life	Autosomal dominant	Low	High	Thiazide diuretic, low-sodium diet
FH-I (GRA)[f]	Second or third decade of life	Autosomal dominant	High	Decreased in most cases; marked decrease with thiazides	Glucocorticoids
FH-II[b]	Middle age	Autosomal dominant	High	Low to normal	Spironolactone, eplerenone
DOC oversecretion caused by CAHb[g]	Childhood	Autosomal recessive	Low	Low to normal	Glucocorticoids
Activating MR mutation exacerbated by pregnancy[h]	Second or third decade of life	Unknown	Low	Low to normal	Delivery of fetus

[a]Treatment for underlying mechanisms; other forms of treatment, including different antihypertensive medications, might be needed to adequately control blood pressure.

[b]Excess production of nonaldosterone mineralocorticoids.

[c]Apparent mineralocorticoid excess caused by either licorice ingestion or ectopic ACTH secretion.

[d]Increased activity of sodium channels.

[e]Increased activity of NaCl cotransporter in the distal tubule.

[f]Familial hyperaldosteronism.

[g]CAH, DOC-producing tumors.

[h]Increased activity of MRs.

Abbreviations: ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; CAH, congenital adrenal hyperplasia; DOC, deoxycorticosterone; FH-I, familial hyperaldosteronism type I; FH-II, familial hyperaldosteronism type II; GRA, glucocorticoid-remediable aldosteronism; MR, mineralocorticoid receptor.

reasons for this wide range of BP in patients are unclear but could be related to variable expression of the chimeric gene or to other differences in genetic background that would place their inherited BP in the low or normal range in the absence of the FH-I mutation. The final BP could therefore be the combined result of the low or normal inherited BP, the hypertensive effect of the FH-I mutation, and other environmental factors such as salt intake. Patients with FH-I respond well to both thiazide diuretics and MR antagonists such as spironolactone or eplerenone.

Familial Hyperaldosteronism Type II

Familial hyperaldosteronism type II (FH-II) is a rare disease in which hypertension is caused by excessive secretion of aldosterone that is not suppressed by glucocorticoid administration, distinguishing it from FH-I.[174] Patients with FH-II have the same clinical symptoms as patients with primary hyperaldosteronism caused by bilateral adrenal hyperplasia. The genetic abnormality causing FH-II has been localized to chromosome 7p22.[174] Although hypertension in FH-II is unresponsive to glucocorticoids, MR antagonists are effective in reducing BP and correcting the metabolic disturbances.

Congenital Adrenal Hyperplasia

This disorder describes a group of syndromes caused by defects in cortisol biosynthesis. Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder. When 21-hydroxylase (*CYP21A2*) is deficient, the most common cause of CAH, patients are normotensive.[175,176] When 11β-hydroxylase (*CYP11B1*) and 17 β-hydroxylase (*CYP17*) are deficient, production of deoxycorticosterone, which has mineralocorticoid activity, is increased, leading to hypertension. Defects in *CYP11B1* and *CYP17* cause inhibition of cortisol production with subsequent reduction in feedback inhibition of ACTH secretion by the anterior pituitary and hypothalamus. Increased ACTH secretion then stimulates production of steroid precursors proximal to the blocked step, leading to excessive levels of deoxycorticosterone.

Both forms of CAH are associated with early-onset hypertension and hypokalemia. Signs of androgen excess distinguish the two disorders; whereas 11β-hydroxylase deficiency causes virilization in girls and precocious puberty in boys, 17α-hydroxylase deficiency causes sex hormone deficiency, primary amenorrhea, and delayed sexual development in girls and ambiguous genitalia in boys. Genetic diagnosis of both conditions relies on testing for mutations that either severely depress or abolish enzyme activity. Both conditions can be effectively treated by administering glucocorticoids that normalize ACTH secretion and ACTH-mediated buildup of cortisol precursors proximal to the enzymatic deficiency, including deoxycorticosterone.

Liddle Syndrome

This is an autosomal dominant form of monogenic hypertension that results from mutations in the amiloride-sensitive ENaC. Several mutations that result in the elimination of 45 to 75 amino acids from the cytoplasmic carboxyl terminus of β- or γ-subunits of the channel have been reported. Mutations that increase ENaC activity, in turn, cause excessive distal and collecting tubule sodium reabsorption and hypertension.[177,178]

Liddle syndrome is characterized by the early onset of hypertension with hypokalemia and suppression of plasma renin activity and aldosterone. Suppression of aldosterone and lack of responsiveness to MR antagonists differentiates this syndrome from primary aldosteronism. Hypertension and the hypokalemia vary in severity, depending on salt intake, and can be treated with amiloride or triamterene, specific inhibitors of ENaC.

Apparent Mineralocorticoid Excess

AME is an autosomal recessive form of monogenic hypertension that results from a mutation in the renal-specific isoform of the 11β-hydroxysteroid dehydrogenase gene.[179] This enzyme normally converts cortisol to the inactive metabolite cortisone and "protects" the MR from being activated by cortisol. The renal epithelial MR receptor in the distal and collecting tubules has a similar affinity for aldosterone and cortisol, and cortisol concentrations are normally much higher than aldosterone. Therefore, deficiency of 11β-hydroxysteroid dehydrogenase allows the tubular MR to be occupied and activated by cortisol, causing sodium retention, low renin, low aldosterone, and a form of hypertension that is salt sensitive.

A nongenetic form of the AME syndrome occurs in persons ingesting large amounts of licorice, which contains glycyrrhetinic acid, an inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase. Both forms of AME are effectively treated with MR antagonists such as spironolactone or eplerenone.

Pseudohypoaldosteronism Type II

Also called *Gordon syndrome*, pseudohypoaldosteronism type II is a rare Mendelian form of hypertension that is salt sensitive and associated with hyperkalemia (despite normal GFR), hyperchloremia, metabolic acidosis, and suppressed plasma renin and aldosterone levels. The disorder is caused by mutations in two genes encoding the serine/threonine protein kinases WNK1 and WNK4.[180]

The phenotypes of excessive salt retention and hypertension are caused by loss of normal inhibition or to constitutive activation of the renal tubular NaCl cotransporter by mutant WNK1 or WNK4 genes; thiazide diuretics, which inhibit distal nephron NaCl reabsorption, are especially effective in reducing BP in patients with pseudohypoaldosteronism type II. The mutant WNKs may also have a direct effect on the renal outer medullary potassium channel, the major potassium secretory channel in the distal nephron, because hyperkalemia is another major feature of pseudohypoaldosteronism type II.[175,180] The fact that hyperkalemia is invariably present in pseudohypoaldosteronism type II is often used to distinguish it from other monogenic forms of hypertension.

Mineralocorticoid Receptor Activating Mutation

This monogenic disorder is caused by a substitution of leucine for serine at codon 810 of the MR.[181] This mutation alters the shape and the specificity of the MR and eliminates the usual requirement for the 21-hydroxyl group of aldosterone to interact with the MR. This explains why other steroids, such as progesterone, activate the MR and why spironolactone, which is normally an MR antagonist, acts as an MR agonist in this disorder. Thus, treatment of these patients with spironolactone or increased levels of progesterone, as occurs in pregnancy, worsens the sodium retention, hypokalemia, and hypertension.

PATHOPHYSIOLOGY OF PRIMARY (ESSENTIAL) HYPERTENSION

Widespread human primary (essential) hypertension appears to be associated with industrialization. Nearly all studies of industrialized populations have demonstrated that BP and the prevalence of hypertension increase with age.[1] Hunter-gatherers living in nonindustrialized societies, however, rarely develop hypertension or progressive increases in systolic and mean pressures that occur in the majority of individuals living in industrialized societies.[182] This observation suggests that environmental factors play a major role in increasing BP in many patients with primary hypertension. This does not, however, imply that genetic factors are unimportant in primary hypertension. Genetic variation is responsible for differences in baseline BP that result in normal BP distribution in a population. When hypertension-producing environmental factors are added to the population baseline BP, the normal distribution is shifted toward higher BP. Moreover, variations in the impact of environmental factors flatten the BP curve and cause even greater variability in the overall population BP.

What are the factors that cause BP to increase in the majority of people as they age in industrialized societies? How do they affect the physiologic controllers of BP? As discussed earlier, many of the long-term BP controllers either directly or indirectly influence renal function. In patients with primary hypertension, there is a resetting of renal-pressure natriuresis so that sodium balance is maintained at higher BP.[12,21] In some individuals, this resetting is related to increased renal tubular reabsorption because of abnormalities intrinsic to the kidneys or to altered neurohumoral control of the kidneys. In other instances, resetting of pressure natriuresis is associated with renal vasoconstriction and reductions in GFR, as a result of intrarenal mechanisms or of nervous and hormonal mechanisms acting on the kidneys. After hypertension is established, many of these changes are difficult to detect because increased BP often returns renal function to normal.

Some of the key environmental factors that affect BP include excess weight gain, high sodium intake, and excess alcohol intake.

EXCESS WEIGHT GAIN IS A MAJOR CAUSE OF PRIMARY HYPERTENSION

Current estimates indicate that more than 1.4 *billion* people in the world are overweight or obese.[183] In the United States, more than 67% of adults are overweight, and one-third of the adult population is obese, with body mass indices (BMIs) above 30.[184] Population studies show that excess weight gain is a good predictor for development of hypertension, and the relationship between BMI and systolic and diastolic BP is nearly linear in diverse populations throughout the world.[50,185] Risk estimates from the Framingham Heart Study, for example, suggest that approximately 78% of primary hypertension in men and 65% in women can be ascribed to excess weight gain.[186] Clinical studies indicate that maintenance of a BMI less than 25 kg/m^2 is effective in primary prevention of hypertension and that weight loss reduces BP in most hypertensive subjects.[187,188]

One question often raised is why some overweight or obese persons are not hypertensive by the usual standards (ie, BP > 140/90 mm Hg) if obesity is a major cause of hypertension. Perhaps this is not surprising if one considers that BP is normally distributed and that excess weight gain shifts the frequency distribution of BP toward higher levels (Fig. 24–15). However, even obese individuals who are considered "normotensive"

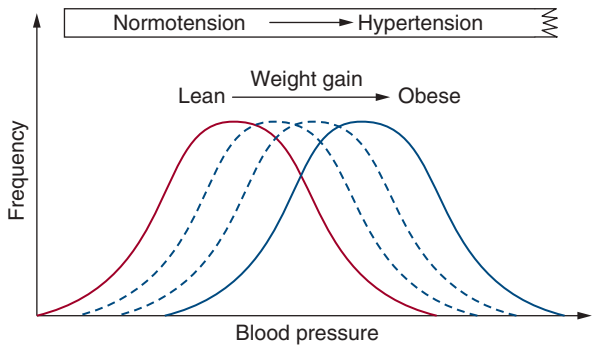

FIGURE 24–15. Effect of weight gain to shift the frequency distribution of blood pressure (BP) to higher levels. Not all obese subjects have BP in the hypertensive range (> 140/90 mm Hg), but excess weight gain increases BP above the baseline level for an individual.

TABLE 24–6. Hemodynamic, Neurohumoral, and Renal Changes in Experimental Obesity Caused by a High-Fat Diet and in Human Obesity

Model	Arterial Pressure	Heart Rate	Cardiac Output	Renal Sympathetic Activity	Plasma Renin Activity	Na^+ Balance	Renal Tubular Reabsorption	Glomerular Filtration Rate[a]	Insulin Resistance
Obese rabbits (high-fat diet)	↑	↑	↑	↑	↑	↑	↑	↑	↑
Obese dogs (high-fat diet)	↑	↑	↑	↑	↑	↑	↑	↑	↑
Obese humans	↑	↑	↑	↑	↑	↑	↑	↑	↑

[a]The glomerular filtration rate changes refer to the early phases of obesity before major loss of nephron function has occurred.

have higher BP than they would at a lower body weight, and weight loss lowers BP in normotensive as well as hypertensive obese subjects.[189]

Adipose tissue distribution is also important. Most population studies that have investigated the relationship between obesity and BP have measured BMI rather than visceral or retroperitoneal fat, which appear to be better predictors of increased BP than subcutaneous fat.[190]

Although the importance of obesity, especially excess visceral fat, is well established as a cause of primary hypertension, the pathophysiologic mechanisms involved are only beginning to be elucidated. Table 24–6 summarizes some of the changes in hemodynamics, neurohumoral systems, and renal function that occur with excess weight gain in humans and experimental animals.

Mechanisms of Impaired Renal Pressure Natriuresis in Obesity Hypertension

Increased renal tubular sodium reabsorption plays a major role in initiating the rise in BP associated with excess weight gain, and obese individuals require higher than normal BP to maintain sodium balance. Three mechanisms appear to be especially important in increasing sodium reabsorption and impairing renal-pressure natriuresis in obesity hypertension: (1) increased SNS activity, (2) activation of the RAAS, and (3) physical compression of the kidneys by fat accumulation within and around the kidneys and by increased abdominal pressure (Fig. 24–16). Also, CKD may, over a much longer time, amplify the BP effects of these mechanisms and make obesity-associated hypertension more difficult to control and less easily reversed by weight loss.[189,191]

Sympathetic Nervous System Activation in Obesity Hypertension

Several observations in experimental animals and in humans indicate that increased SNS activity contributes to obesity hypertension[50,52]: (1) SNS activation, especially renal sympathetic activity, is increased in obese subjects; (2) pharmacologic blockade of adrenergic activity lowers BP to a greater extent in obese compared with lean individuals; and (3) renal denervation markedly attenuates sodium retention and hypertension associated with a high-fat diet in experimental animals.

Increased SNS activity appears to be highly differentiated in obesity. For example, cardiac sympathetic activity may not be substantially elevated, but SNS activity is usually increased in kidneys and skeletal muscles of obese subjects.[192] Obesity-induced SNS activation is usually not sufficient to cause vasoconstriction in most tissues, such as the kidneys or skeletal muscle, but does contribute to renin secretion and increased renal tubular sodium reabsorption.[50,52]

Current evidence indicates that the chronic BP effects of SNS activation in obesity are mediated mainly by renal nerves. Bilateral RDN greatly attenuated sodium retention and hypertension in obese dogs fed a high fat diet.[8,37] Similar results were observed in obese humans with resistant hypertension in which catheter-based radiofrequency RDN lowered office systolic BP by 25 to 30 mm Hg and diastolic BP by 10 to 12 mm Hg for up to 24 months.[40] Although a recent trial failed to find a major effect of RDN on BP in obese resistant hypertensive subjects,[41] compared to sham controls, these patients were already on at least three antihypertensive medications, including blockers of the RAAS, which may mediate part of the effect of the renal nerves on BP.

Several potential mediators of SNS activation in obesity have been suggested, including (1) hyperinsulinemia; (2) Ang II; (3) increased levels of free fatty acids; (4) impaired baroreceptor reflexes; (5) activation of chemoreceptor-mediated reflexes associated with sleep apnea and intermittent hypoxia; and (6) cytokines released from adipocytes

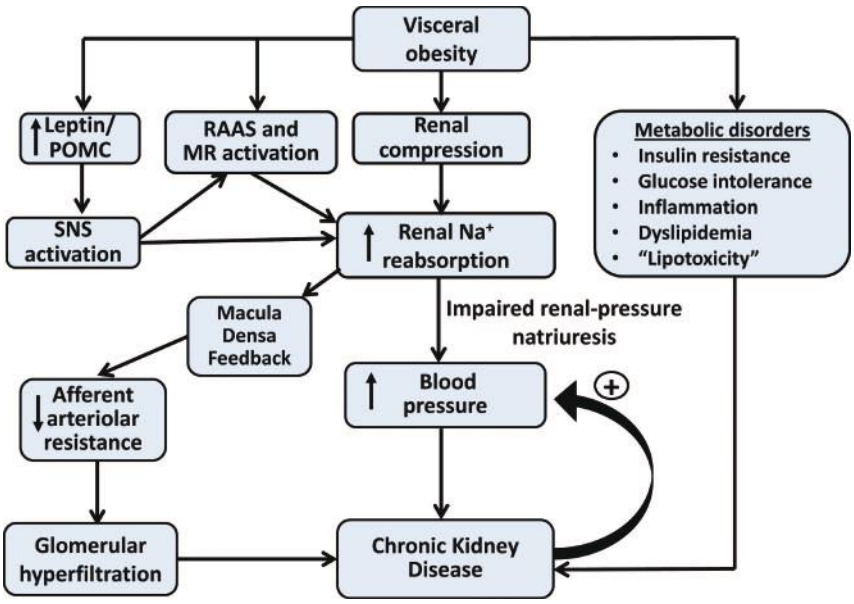

FIGURE 24–16. Summary of mechanisms by which obesity causes hypertension and renal injury. Visceral obesity increases blood pressure by activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), as well as by physical compression of the kidneys from the fat surrounding the kidneys. These effects increase renal sodium reabsorption and impair pressure natriuresis. SNS activation may be caused by, in large part, the effects of leptin, which acts on proopiomelanocortin (POMC) neurons in the hypothalamus and brainstem. Obesity-induced hypertension and glomerular hyperfiltration may cause renal injury, especially when combined with dyslipidemia, hyperglycemia, and other metabolic disorders. Renal injury then exacerbates the hypertension and makes it more difficult to control. MR, mineralocorticoid receptor.

(ie, "adipokines") such as leptin, TNF-α, and IL-6. Although the importance of most of these factors is still uncertain, leptin and the CNS proopiomelanocortin pathway may contribute to obesity-induced SNS activation and hypertension (Fig. 24–17).

Leptin is released from adipocytes and acts on the hypothalamus and other regions of the brain to reduce appetite and increase SNS activity.[51] In rodents, increasing plasma leptin concentration to levels comparable to those found in severe obesity not only increases SNS activity but also increases BP.[193,194] Moreover, the hypertensive effects of leptin are enhanced when NO synthesis is inhibited,[195] as often occurs in obese subjects with endothelial dysfunction.

Another observation that points toward leptin as a potential mechanism of obesity hypertension is the finding that leptin-deficient, obese mice and obese mice with mutations of the leptin receptor usually have little or no increase in BP compared with lean control subjects.[50] Similar results have been found in obese children with leptin gene mutations who have early-onset morbid obesity but normal BP. Moreover, children with leptin gene mutations did not have hypertension despite having other characteristics of the metabolic syndrome, including severe insulin resistance, hyperinsulinemia, and hyperlipidemia.[196] These observations suggest that the functional effects of leptin may be important in linking obesity with SNS activation and hypertension.

Leptin's stimulatory effect on SNS activity appears to be mediated by activation of proopiomelanocortin (POMC) neurons in the hypothalamus and brainstem; these neurons release α-melanocyte stimulating hormone, which then activates melanocortin 4 receptors (MC4R) in second-order neurons in the hypothalamus and brainstem. Deletion of leptin receptors specifically in POMC neurons completely abolished the hypertensive effects of leptin.[197] Also, antagonism of the MC4R or genetic deletion of MC4R completely abolished leptin's chronic BP effects.[198,199] These findings indicate that activation of POMC neurons and subsequent stimulation of the MC4R mediate most of the effects of leptin to activate SNS activity and raise BP.[50,200]

Studies in humans also suggest that MC4R activation may contribute to obesity-induced hypertension. The prevalence of hypertension is markedly lower in MC4R-deficient humans compared with control subjects despite severe obesity and associated metabolic disorders.[201] Moreover, subcutaneous administration of an MC4R agonist for 7 days caused significant increases in BP similar to those observed in rodents. Thus, in humans and rodents, chronic activation of the MC4R increases BP, and the presence of a functional MC4R system appears to be necessary for obesity to increase SNS activity and BP.[201]

Renin-Angiotensin-Aldosterone System Activation in Obesity

Obese subjects, especially those with visceral obesity, often have mild to moderate increases in plasma renin activity, angiotensinogen, ACE activity, Ang II, and aldosterone levels.[50,189] Activation of the RAAS in obese subject occurs despite sodium retention, volume expansion, and hypertension, all of which would normally tend to suppress renin secretion and Ang II formation.

An important role for Ang II in stimulating renal sodium reabsorption and in mediating obesity hypertension is supported by studies in experimental animals demonstrating that Ang II receptor blockade or ACE inhibition blunts sodium retention, volume expansion, and increased BP during the development of obesity.[50,189] Unfortunately, there have been no large-scale clinical studies comparing the effectiveness of RAAS blockers in obese and lean hypertensive patients, although small clinical trials have shown that both ARBs and ACE inhibitors are effective in lowering BP in obese hypertensive patients.[202,203]

Antagonism of MR also provides an important therapeutic tool for lowering BP and attenuating target organ injury in obesity hypertension. Antagonism of MR in obese dogs, for example, markedly attenuated sodium retention, hypertension, and glomerular hyperfiltration.[67] Moreover, this protection against hypertension occurred despite marked increases in plasma renin activity, suggesting that combined blockade of MR and Ang II might be especially effective in treating patients with obesity hypertension. The observation that MR antagonism attenuated glomerular hyperfiltration may also have important implications for renal protection in obesity, although studies in obese humans are limited. Administration of the MR antagonists also provides significant antihypertensive benefit in resistant obese patients, although there was no correlation between plasma aldosterone levels and BP responses to MR blockade.[65,204] The reductions in BP caused by MR antagonism in obese patients with resistant hypertension occurred despite concurrent therapy with ACE inhibitors or ARBs, calcium channel blockers, and thiazide diuretics, suggesting that MR activation in obesity may occur independently of Ang II–mediated stimulation of aldosterone secretion.[205]

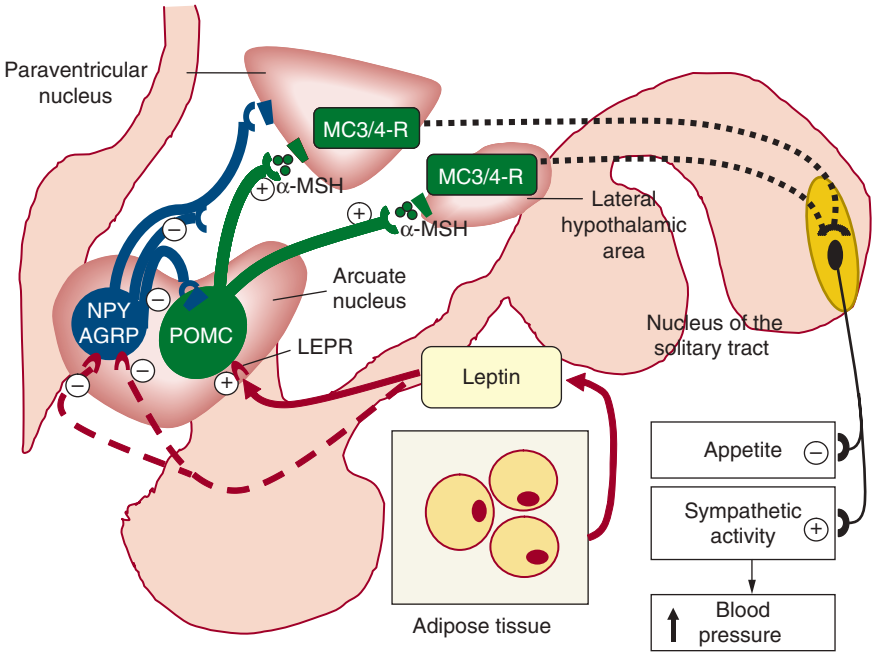

FIGURE 24–17. Possible link of increases in adiposity with leptin and its effects on the hypothalamus to initiate sympathetic activation and hypertension. Within the hypothalamus, one of the key pathways of leptin's action on appetite, renal sympathetic nervous system activity (RSNA), and arterial pressure is stimulation of the proopiomelanocortin (POMC) neurons in the arcuate nucleus. These neurons send projections to the paraventricular nucleus and lateral hypothalamus, releasing α-melanocyte–stimulating hormone, which then acts as an agonist for melanocortin 4 receptors (MC4Rs). These neurons then send projections to the nucleus of the solitary tract (NTS) to effect changes in appetite, RSNA activity, and blood pressure. Leptin may also stimulate POMC neurons in the NTS. MC4R activation in the dorsal motor nucleus of the vagus, rostral ventrolateral medulla, and the spinal cord intermediolateral nucleus may also contribute to obesity-induced increases in RSNA and arterial pressure.

Renal Compression Caused by Visceral Obesity

Visceral obesity initiates several changes that lead to compression of the kidneys, increased intrarenal pressures, impaired renal-pressure natriuresis, and hypertension.[50] For example, intra-abdominal pressure increases in proportion to abdominal diameter,

reaching levels as high as 35 to 40 mm Hg in some individuals.[206] In addition, retroperitoneal adipose tissue often encapsulates the kidney and penetrates the renal hilum into the renal medullary sinuses, causing additional compression and increased intrarenal pressures.[191,207] Obesity also causes changes in renal medullary histology and increased extracellular matrix that could exacerbate intrarenal compression and hypertension.[208] Although these physical changes in the kidneys cannot account for the initial increase in BP that occurs with rapid weight gain, they may help to explain why visceral obesity is much more closely associated with hypertension than subcutaneous obesity.

Glomerular Injury and Nephron Loss in Obesity Hypertension

Obese patients often develop proteinuria, frequently in the nephrotic range, followed by progressive loss of kidney function.[191,207] The most common types of renal lesions observed in renal biopsies are of obese subjects are focal and segmental glomerular sclerosis and glomerulomegaly.[209]

Animals placed on a high-fat diet for only a few weeks have significant structural changes in the kidneys, including enlargement of the Bowman space, glomerular cell proliferation, increased mesangial matrix, and increased expression of glomerular TGF-β.[210] These early changes, which occur with only modest hypertension, no evidence of diabetes, and only mild metabolic abnormalities, may be the precursors of more severe renal injury as obesity is sustained.

Population studies indicate that obesity increases the risk of chronic kidney disease even after adjustment for hypertension, diabetes, or preexisting renal disease.[211,212] Moreover, obesity also amplifies the effect of other primary renal insults, even those that are usually considered to be relatively benign, such as unilateral nephrectomy. Obesity also exacerbates the deleterious effects of other kidney insults, including unilateral nephrectomy, kidney transplantation, unilateral renal agenesis, and IgA nephropathy.[207,213] Thus, obesity exacerbates the loss of kidney function in patients with preexisting glomerulopathies and weight loss may lessen the impact of renal injury from other causes.

Gradual loss of kidney function, as well as hypertension and diabetes that commonly coexist with obesity, may lead to progressive impairment of kidney function, increases in salt sensitivity, and progressive increases in BP (Fig. 24–18). Thus, renal injury in obese subjects not only makes the hypertension more severe but also more difficult to control with antihypertensive drugs. Early control of hypertension and effective weight management are crucial in preventing injury to the kidneys and other in obese patients.

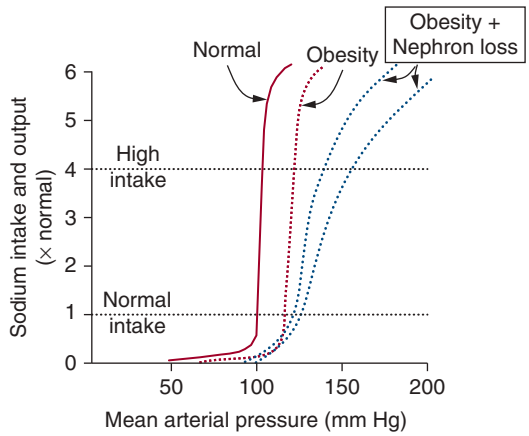

FIGURE 24–18. Effect of obesity to shift renal pressure natriuresis curve to higher arterial pressure. With chronic obesity lasting for many years, there may be a gradual loss of nephron function, further impairment of pressure natriuresis, increasing salt sensitivity, and higher arterial pressures.

WHAT IS THE ROLE OF METABOLIC SYNDROME OR INSULIN RESISTANCE IN PRIMARY HYPERTENSION?

Dyslipidemia, hyperinsulinemia, and hyperglycemia often occur concurrently with hypertension, leading to the proposal of a unique pathophysiologic condition that is often called the *metabolic syndrome*. Definitions of the metabolic syndrome generally include disordered glucose homeostasis or measures of insulin resistance, dyslipidemia, hypertension, and obesity.[214]

Some researchers suggest that a defect in insulin action (ie, insulin resistance) is the main cause of all the CVD risk factors that constitute the different versions of the metabolic syndrome.[215] Broadly defined, insulin resistance refers to a subnormal tissue response to a given concentration of insulin or an impairment of insulin's action of overall glucose homeostasis.[216] Other analyses of the metabolic syndrome, however, have questioned whether insulin resistance and hyperinsulinemia are, in fact, the underlying causes of this complex cluster of cardiovascular risk factors.[217,218]

Hyperinsulinemia Does Not Cause Hypertension in Humans

Evidence supporting a role for hyperinsulinemia in hypertension comes mainly from epidemiologic studies showing correlations between insulin resistance, hyperinsulinemia, and BP and from short-term studies indicating that insulin has sympathetic effects that, if sustained, could theoretically increase BP.[219] However, chronic hyperinsulinemia, in the absence of obesity, does not raise BP in dogs or humans (see Hall et al[220–222] for reviews). For example, chronic insulin infusions did not increase BP even when there was preexisting impairment of renal function caused by a 70% reduction of kidney mass[222] and did not enhance the hypertensive effects of other pressor substances such as norepinephrine or Ang II.[220,223] Chronic hyperinsulinemia also did not increase BP in insulin-resistant obese dogs that were resistant to the vasodilator effects of insulin.[223] Multiple studies in humans have also shown that chronic insulin treatment does not raise BP, and patients with severe hyperinsulinemia as a result of insulinoma are not hypertensive.[220,224] These observations suggest that hyperinsulinemia per se is insufficient to cause chronic hypertension.

Does Insulin Resistance Cause Hypertension Independent of Hyperinsulinemia?

Insulin resistance has also been suggested to cause hypertension by increasing TPR through mechanisms that are independent of hyperinsulinemia. However, several disorders associated with severe insulin resistance in humans and experimental animal models are not associated with hypertension. For example, experimental models of obesity caused by mutations of the leptin gene or the leptin receptor or by mutations of the MC4R have severe insulin resistance and many of the characteristics of the metabolic syndrome but do not have increased BP compared to WT control subjects.[50,198] Likewise, humans with leptin gene mutations have severe insulin resistance but no indication of SNS activation or hypertension.[196]

Several reports indicate that antihyperglycemic agents that increase insulin sensitivity, such as the thiazolidinediones, also lower BP. However, these drugs also influence the expression of multiple genes by binding to the peroxisome proliferator-activated receptor-γ, a nuclear receptor. Thiazolidinediones also inhibit L-type calcium channels and reduce BP in renovascular hypertension that is not associated with insulin resistance or hyperinsulinemia.[225] Therefore, the BP-lowering effects of these drugs are likely related to other actions besides improvement of insulin sensitivity.

Although a direct causal relationship between insulin resistance and hypertension has not been established, abnormalities of glucose and

lipid metabolism associated with insulin resistance may, over many years, lead to vascular and renal injury and contribute indirectly to increased BP. However, the importance of these effects in the absence of diabetes is still unclear.

Does Hypertension Cause Insulin Resistance?

It also has been suggested that insulin resistance is secondary to peripheral vascular changes that occur in hypertension.[226] However, most models of secondary hypertension, such as renovascular hypertension, are characterized by increased peripheral vascular resistance and vascular rarefaction but are not associated with development of insulin resistance (see Hall et al[216,221] for reviews). These observations indicate that hypertension per se is not a primary cause of insulin resistance.

Although insulin resistance and hypertension are often closely correlated, much of the available evidence suggests that this association is largely a consequence of obesity that causes both insulin resistance and high BP through parallel mechanisms. There is little doubt that obesity, especially visceral obesity, is a major cause of the entire cluster of CVD risk factors associated with the metabolic syndrome. Importantly, all of the disorders associated with the metabolic syndrome can be reversed in most patients with weight loss.

Until more effective antiobesity drugs are developed, the impact of obesity on hypertension and related cardiovascular, renal, and metabolic disorders is likely to become even more important as the prevalence of obesity continues to increase. In the meantime, effective BP control is essential in treating patients with metabolic syndrome and preventing CVD. Weight reduction is an essential first step in the effective management of most patients with metabolic syndrome and hypertension, and more emphasis should be placed on lifestyle modifications that help patients to maintain a healthier weight and prevent CVD.

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CHAPTER 25

DIAGNOSIS AND TREATMENT OF HYPERTENSION

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INTRODUCTION

Hypertension, elevated systemic arterial pressure, is a recognized risk factor and cause of fatal and nonfatal cardiovascular and renal disease that has become a public health problem worldwide.[1,2] Furthermore, treatment of hypertension with widely available antihypertensive drugs is highly effective for long-term prevention of cardiovascular disease as demonstrated in well-controlled randomized clinical trials.[3] On a global basis, it has been predicted that treating hypertension will have the greatest impact over the next decade in preventing premature cardiovascular mortality.[4]

BLOOD PRESSURE CLASSIFICATION

The diagnosis of hypertension has, in the past, been based on measurements in the office or clinic. Clinic blood pressures have been the basis for assessing response to treatment in the large randomized clinical trials that have provided the evidence for establishing the effectiveness of antihypertensive drug treatment. However, the development of technologies for accurate measurement of arterial pressure outside the clinic and during usual activity through 24-ambulatory blood pressure monitoring and home blood pressure assessment has led to expansion of the terms used to define hypertension. Table 25–1 provides current classification of hypertensive disorders as recommended in recent guidelines.

Based on clinic measurements alone, patients may be classified by the height of the pressure: optimal or normal pressure, prehypertension overlapping with high-normal pressure, and definite hypertension. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) further subdivided definite hypertension into stage I, 140–159/90–99 mm Hg, and stage II, more than 160/100 mm Hg.[5] The panel report for JNC 8 suggested that, for older patients, a cutoff of 150 mm Hg systolic pressure was more consistent with evidence from clinical trials.[6] This conclusion has been questioned and remains controversial.[7] However, results from two recently conducted studies, Systolic Blood Pressure Intervention Trial (SPRINT) and Secondary Prevention of Small Subcortical Strokes (SPS3) may influence selection of lower thresholds for defining hypertension in future guidelines.[8,9] Although the terms *prehypertension* and *hypertension* are widely used, it is important to recognize that that they can misrepresent the risk associated with a verbal diagnosis compared with the risk associated with a given level of pressure. The risk of a systolic pressure of 139 mm Hg is the same as that for 141 mm Hg, yet the former may be labeled as "prehypertension" and the latter as "hypertension."

With the introduction and implementation of 24-hour ambulatory blood pressure monitoring and systematic home blood pressure monitoring, have come the recognition that blood pressure measured out-of-the office/clinic may differ substantially from office/clinic pressure. White coat hypertension and masked hypertension are now widely recognized and confer different predictions for future cardiovascular risk.[10] The risk of white coat hypertension is nearly that of normal blood pressure, but the risk of masked hypertension is nearly or equal to that of sustained hypertension (elevated pressure both in and out of the clinic).[11] The importance of out-of-office blood pressures for accurate prognosis is now supported by several national and international guidelines.[12-15]

EPIDEMIOLOGY

PREVALENCE

National and international surveys indicate that hypertension is highly prevalent in adult populations throughout the world and is increasing in relation to increased overweight and, all too often, reduced daily exercise. In the United States, the prevalence of hypertension has been nearly constant at about 30% over the past several years as recorded in National Health and Nutrition Examination Survey (NHANES) results, but awareness, treatment, and control have steadily increased; however, they may be reaching a plateau (Fig. 25–1).[16] In the recent survey, hypertension prevalence was similar in adult men and women (~ 25%), but higher in black (self identified African Americans ~ 40%)

TABLE 25–1. Glossary: Classification of Hypertension in Adult Patients

Definition	Blood Pressure Range (mm Hg)	Comment
Normal (optimal pressure)	< 120/80	All guidelines
Prehypertension	120–139/80–89	JNC 7
High-normal pressure	130–139/85–89	EHS
Hypertension	≥ 140/90	All guidelines
Resistant hypertension	≥ 140/90	On treatment with three or more antihypertensive drugs, usually including a diuretic
White coat hypertension	Clinic pressures ≥ 140/90 and 24-hour ABP < 130/80 or home blood pressures < 135/85	Untreated
White coat effect	Clinic pressures ≥140/90 and 24-hour ABP < 130/80 or home blood pressures < 135/85	Treated patients
Masked hypertension	Clinic pressures < 140/90 and 24-hour ABP > 130/80 or home blood pressures > 135/85	Untreated patients
Masked resistant hypertension	Clinic pressures < 140/90 and 24-hour ABP > 130/80 or home blood pressures > 135/85	Treated patients
Essential hypertension	As defined by either clinic or out-of-office measurement	No identifiable cause is found
Identifiable or secondary hypertension	As defined by either clinic or out-of-office measurement	An identifiable cause has been found; see Table 25–2

Abbreviations: ABP, ambulatory blood pressure; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

than white groups (~ 25%). Hypertension in children may be increasing due to higher rates of overweight[17] and underdiagnosed based on age related criteria.[18] Young adults with higher and increasing blood pressures may be at greater risk for eventual cardiovascular disease as indicated by coronary artery calcification.[19] These consideration imply that in the United States, hypertension, despite higher detection rates, will continue to be a major challenge for effective prevention of cardiovascular disease in the next decades.

CONSEQUENCES OF HYPERTENSION: PATHOLOGY

Hypertension is the direct cause or contributing cause of a wide range of cardiovascular and renal pathology. Stroke "brain attacks" may result from cerebral hemorrhage or to thromboembolism with brain infarction. The source of emboli may be the carotid arteries, aorta, or cardiac thrombi. Intracerebral arteriosclerosis may be the cause of cerebral infarction, as well. Coronary artery disease with myocardial infarction is all too common in hypertensive patients, who often have the presence of other coronary risk factors. Multiple infarcts may lead to congestive heart failure with low ejection fraction (systolic heart failure). The increased left ventricular afterload of sustained hypertension induces left ventricular hypertrophy with reduced compliance and the syndrome of heart failure with preserved systolic function.[20] This syndrome may result in repeated episodes of pulmonary congestion; bilateral renal artery stenosis should be considered as well in this setting.[21] Left ventricular hypertrophy adds a burden to left atrial contraction. Dilation of this chamber is a risk factor for atrial fibrillation, for which hypertension is a definite risk factor.[22,23]

Hypertension contributes to atherosclerosis in many arteries: the carotid arteries, aorta, renal arteries, and peripheral arteries. Hypertension, usually when sustained at very high pressures, is linked aortic dissection. Hypertension also participates in the formation of atherosclerotic aortic aneurysms.

Renal pathology due to hypertension (nephrosclerosis) may occur alone, but often accompanies chronic renal disease which is diabetic nephropathy.

CARDIOVASCULAR RISK OF HYPERTENSION AND BENEFIT OF TREATMENT

Follow-up surveys relating eventual cardiovascular disease with initial or baseline measurement of blood pressure have invariably shown a high degree of correlation between level of pressure and future disease-related events for untreated patients.[1] The benefit of antihypertensive drug treatment has now been firmly established by randomized clinical trials that have been summarized in meta-analyses and other studies.[24,25] The relative benefit of blood pressure reduction appears to be similar, irrespective of the pretreatment level of pressure. However, the absolute benefit (eg, in the number to treat needed to prevent a single event) varies widely, being much lower in persons with higher pressure and risk, compared to the large fractions of those with minimal elevations of pressure and overall lower cardiovascular risk profiles.[26] Neither age nor choice of antihypertensive drug class affects the relative benefit of antihypertensive treatment.[27]

Recent clinical trials and meta-analyses have focused on goals of treatment to be achieved by antihypertensive drug therapy for maximum benefit. Is less than 140/90 mm Hg sufficient or is a lower goal (< 120 mm Hg) achievable and beneficial? For nondiabetic hypertensive patients, the SPRINT trial provides compelling evidence that lower is better. The usual goal group had a baseline systolic pressure of 140 mm Hg that fell to 136 mm Hg after 1 year. The intensive treatment group, with a similar baseline systolic pressure had a fall to 121 mm Hg with a highly significant 25% reduction in the primary outcome, a 27% reduction in death from any cause, and a 43% reduction in cardiovascular deaths (Fig. 25–2).[8] With regard to diabetic hypertensive patients, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, designed similarly to SPRINT, failed to demonstrate a significant benefit with regard to its primary outcome for the low goal cohort, which had an on-treatment systolic pressure of 119 mm Hg, compared to the usual goal 1-year pressure of 134 mm Hg. However, in subgroup analysis, stroke rate was 47% ($P < .01$) lower in the low-goal group.[28] Furthermore, the low-goal group of ACCORD had a significant 13% ($P = .02$) reduction in new atrial fibrillation or new atrial P-wave abnormalities compared to the usual goal group.[29] The SPS3 trial compared usual, 130 to 139 mm Hg and a low goal (< 130 mm Hg systolic pressure) in hypertensive participants included because of a recent lacunar stroke. The primary event rate (stroke) for the lower goal target was 19% ($P = .08$) lower than for the usual care group.[9] The optimal on-treatment blood pressure for prevention of a second stroke was 120–129/65–70 mm Hg with higher rates above and below this range.[30] The results of these recent trials are highly likely to be influential in development of new guidelines for treatment of hypertension.

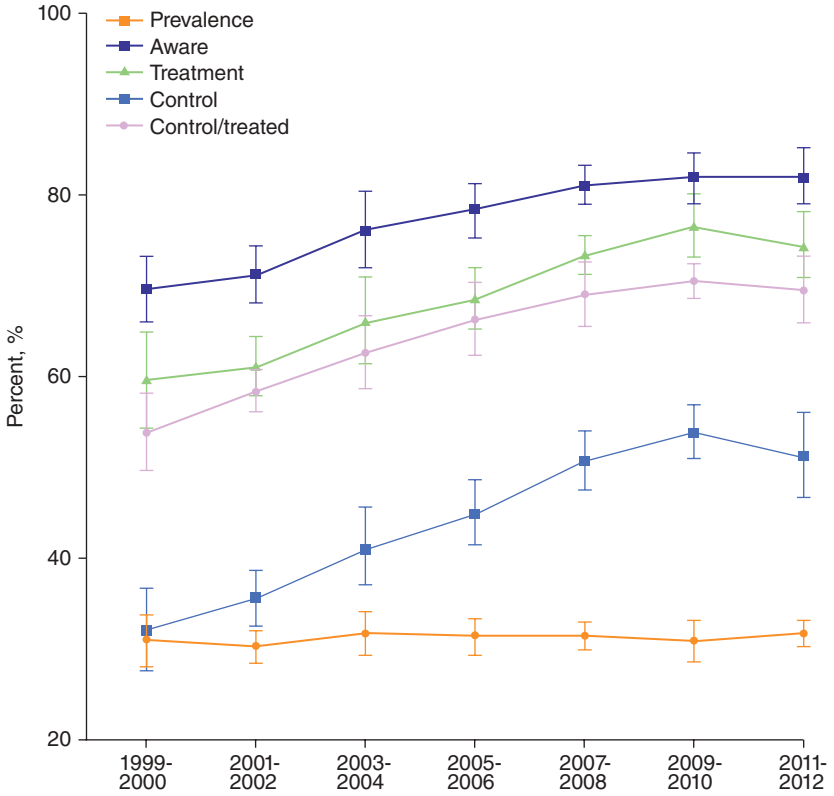
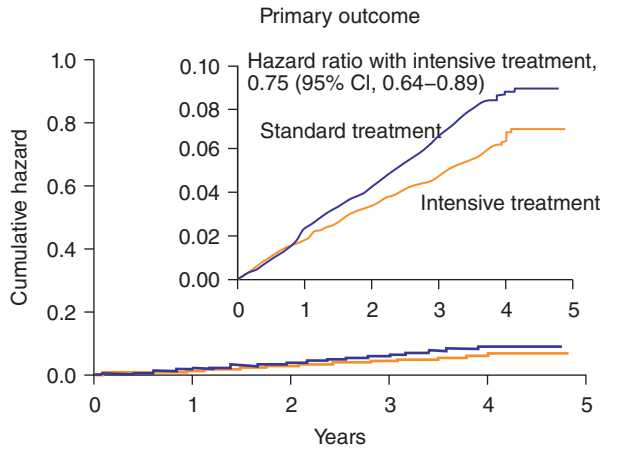


FIGURE 25–1. The percentages are shown (mean and 95% confidence intervals) for hypertension prevalence, awareness, treatment, control, and proportion of treated patients controlled (control/treated) among adults at least 18 years of age in National Health and Nutrition Examination Survey (NHANES) 1999-2012 at 2-year increments. All trend lines showed a significant increase over time ($P \leq .0015$) except for prevalent hypertension ($P = .32$). Reproduced with permission from Egan BM, Li J, Hutchison FN, et al: Hypertension in the United States, 1999 to 2012: progress toward Healthy People 2020 goals. *Circulation*. 2014 Nov 4;130(19):1692-1699.

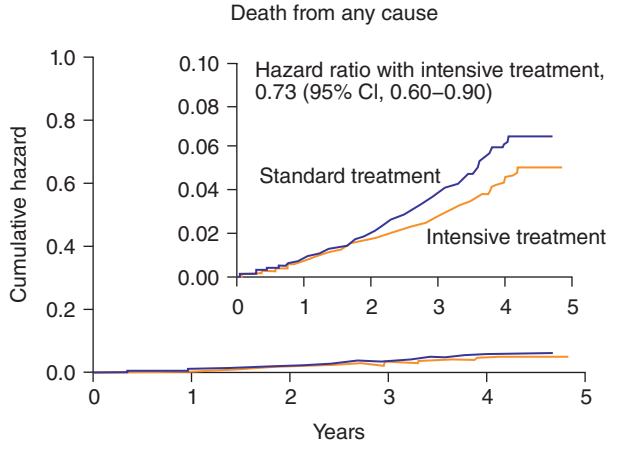
TABLE 25–2. Initial Evaluation of Hypertensive Patients

General Assessment	Status
Clinic blood pressure	Average of two or more
Out-of-office blood pressure	Ambulatory or home monitoring
Cardiovascular risk factors (status)	Diabetes, lipids, smoking, body mass index
History or symptoms of cardiovascular and renal disease	History of angina, dyspnea, palpitations, claudication, stroke
Current cardiac, renal, metabolic status	Serum creatinine, fasting blood sugar or $HgbA_1C$, Na, K, Ca
Identifiable hypertension	See Table 25–3
Specific	
A 55-year old male factory worker referred from a screening site with no complaints. His father was hypertensive.	
Assessment	**Status**
Clinic blood pressure	140–150/80–90 mm Hg
Out-of-office blood pressure	Home average: 137/90 mm Hg
Cardiovascular risk factors-status	Metabolic syndrome, body mass index 30, 20% overweight, high-density lipoprotein cholesterol 40, low-density lipoprotein cholesterol 140
History or symptoms of cardiovascular and renal disease	None; normal sleep
Current cardiac, renal, metabolic status	Electrocardiogram normal
Identifiable hypertension	No signs on examination; normal urinalysis, serum creatinine, Na, K, thyroid-stimulating hormone, Ca
Classification	
International Classification of Diseases, 10th revision: essential hypertension I10	



No. at risk					
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

A



No. at risk					
Standard treatment	4683	4528	4383	2998	789
Intensive treatment	4678	4516	4390	3016	807

B

FIGURE 25–2. Primary outcome and death from any cause. Shown are the cumulative hazards for the primary outcome (a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) (**A**) and from death from any cause (**B**). The inset in each panel shows the same data on an enlarged *y* axis. CI, confidence interval. Reproduced with permission from SPRINT Research Group, Wright JT Jr, Williamson JD, et al: A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015 Nov 26;373(22):2103-2116.

INITIAL EVALUATION OF HYPERTENSIVE PATIENTS

Most hypertensive patients are initially identified during office or clinic visits when seen for checkups or nonemergent symptoms. Some are found at community screening programs and then referred for medical assessment. Hypertension is mostly a silent disorder. The goals for initial evaluation are:

- Estimating the average blood pressure
- Considering the overall cardiovascular risk status
- Determining presence or absence of target organ pathology
- Some assessment for identifiable hypertension

TABLE 25–3. Identifiable (Secondary) Hypertension

Diagnosis	Comments	Clinical Findings
Overweight- obese	Associated with sleep apnea, diabetes, and metabolic syndrome	Elevated body mass index and waist circumference
	Most prevalent	
Sleep apnea syndrome	Treatable with weight reduction and nocturnal continuous positive airway pressure	History of snoring, apneic periods as noted by partner
	Most, but not all, overweight	
Adrenal causes: pheochromocytoma	Pheochromocytoma	History of symptoms, family history of endocrine disease, unusual blood pressure pattern
Adrenal causes: steroid-related	Primary aldosteronism	Hypokalemia, cushingoid appearance
	Other forms of mineralocorticoid excess	
	Cushing's syndrome	
Renovascular causes	Atherosclerotic renal artery disease	Upper abdomen bruit
	Fibromuscular dysplasia	
	Aortitis, Takayasu-type syndromes	
Chronic renal diseases	Polycystic kidney disease	Enlarged kidneys, history of chronic renal disease
	Diabetic nephropathy	
	Glomerular kidney diseases	
	Other renal diseases	
Coarctation of the aorta	With or without association with Turner's syndrome	Reduced femoral pulses
Rare genetic disorders	Congenital adrenal hyperplasia, 11-OH hydroxylase deficiency	Hypokalemia, early-onset hypertension, family history
	Apparent mineralocorticoid excess syndrome: 11-OH dehydrogenase deficiency	
	Glucocorticoid remediable aldosteronism	
	Liddle's syndrome	
	Gitelman's syndrome	
Therapeutic drug-related causes of hypertension	Glucocorticoid treatment: Cushing's- like	History is crucial with a complete review of current illnesses and medications
	Nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, vascular endothelial growth factor inhibitors	
Nontherapeutic drug related hypertension	Diet pill excess: phenylethanolamines	Questions about use of these drugs or agents
	Ephedrine: "energy" preparations	Screens for illicit substances, alcohol level
	Cocaine and related sympathomimetic substances	Hypokalemia for licorice excess
	Licorice-related apparent mineralocorticoid excess	

- Beginning the process of education that will lead to the patient's recognition and collaboration in long-term reduction in risk (ie, adherence and prevention)

Hypertensive emergencies will be dealt with separately in a later section. This section will focus on those examinations and tests performed for outpatients (Table 25–2).

MEDICAL HISTORY

A careful and well-focused medical history is the foundation for initial appraisal of the five goals stated above. For overall cardiovascular risk, use of tobacco and presence or absence of diabetes and/or lipid status are crucial. Target organ status includes assessment of neurologic function for history of stroke or transient ischemic attacks, cardiac and coronary artery disease (ie, angina or dyspnea), renal function, and symptoms of peripheral vascular disease (claudication). Clues to presence of identifiable may be detected: symptoms of sleep apnea syndrome or rare disorders suggested by unusual symptoms or family history. The initial history can be the setting of discussion about lifestyle issues of exercise and diet as well as considering value of antihypertensive drug treatment. Use of one of the many now available risk estimators may aid in portraying the patient's potential for future cardiovascular disease.[31]

PHYSICAL EXAMINATION

The physical examination profiles a risk profile of its own with measurement of weight and height and calculation of body mass index. Waist circumference is helpful as a clue to the metabolic syndrome. Target organ pathology may be revealed if there are carotid bruits or signs of peripheral artery disease. The chest examination may be abnormal because of signs of congestion or effusion. Cardiac auscultation can be useful for signs of left ventricular hypertrophy, abnormal rhythm, or heart failure. Diminished peripheral pulses indicate peripheral arterial occlusive disease. Clues to identifiable hypertension, such as abdominal bruit or signs of endocrine disease, may be detected. Neurologic status with regard to signs of a previous stroke is important.

BLOOD PRESSURE MEASUREMENT: CLINIC

Clinic blood pressures should be as accurate and unbiased as possible.[32] Patients should be seated comfortably. An appropriate cuff size is necessary; large adult cuffs are mandatory for most large or obese patients. There is growing recognition that automated devices, such as the BpTRU Omron or Welch Allyn units, are more likely to be accurate when compared to the stethoscope and hand-inflated cuff.[33,34] Furthermore, automated devices can take multiple readings. Some record measurements and transmit them to the electronic record system. Often the first measurement is higher than subsequent ones, so that several pressures are needed to establish the average.[35] Blood pressures should be taken in both arms when seated, also in the standing position, especially in older patients and in those with dizziness, to unmask orthostatic hypotension.[36]

Blood Pressure: Central Aortic Pressure

Brachial artery pressures are measured using the upper arm cuff and a sensor that detects sounds (auscultation) or pulse waves, oscillometry.[32] Brachial artery pressures fail to duplicate central aortic pressures, which are closer to intracarotid and renal artery pressures (those arteries nearest to the brain, heart, and kidneys, which are the target organs for hypertension-related cardiovascular disease). Central aortic pressures can only be measured directly by aortic catheterization. However, indirect methods have been developed that rely on mathematical models of the brachial pressure waveform transformed to estimated central aortic pressure. Cross-sectional studies suggest that central aortic pressures correlate better with target organ damage than brachial artery pressures.[37] Some recommend that use of central aortic pressure estimation be expanded for use in both the initial and subsequent evaluation of hypertensive patients. Those with lower central aortic pressures during treatment compared to brachial pressures may require less medication for control of their hypertension.[38] Whether measurement of central aortic pressure will be valuable for predicting benefit in reduction of event-based outcomes in randomized trials is uncertain at this time.

BLOOD PRESSURE MEASUREMENT: OUT-OF-OFFICE—AMBULATORY AND HOME MONITORING

Ambulatory blood pressure measurement, a noninvasive fully automated technique in which multiple blood pressure measurements are recorded over an extended period (typically 24 hours), has gained acceptance in several national and international guidelines.[12-14,39] Prospective studies have documented that the average level of ambulatory blood pressure predicts risk of morbid events better than clinic blood pressure.[40] Normal 24-hour ambulatory blood pressure values for adults (nonpregnant) are less than 130/80 mm Hg (< 135/85 mm Hg when awake during the day and < 120/75 mm Hg, when sleeping, during the night).[41] The normal fall in systolic and diastolic pressure during sleep is 10% to 20%. Those with a normal nocturnal fall have been labeled "dippers," and those with either no fall or an increase in pressure during sleep are labeled as "nondippers" or "reverse dippers."

Ambulatory blood pressure monitoring is valuable for determining whether the patient's usual pressure, in "real life," is either higher or lower than the clinic pressure. When the clinic pressure is high, but ambulatory pressure is normal, the diagnosis of white coat hypertension (or white coat effect) can be made (see Table 25–1). The risk of future cardiovascular events in people with white coat hypertension is nearly the same as in those with normal pressure but may be slightly higher when the clinic pressure is in the high normal range.[42,43] Trials have not yet established to determine whether antihypertensive treatment of white coat hypertension is beneficial. Prognosis is best related to nocturnal average pressures. Dippers have a better outlook than nondippers.

Normal or high normal pressures measured in the clinic may not accurately predict out-of-office pressures. Masked hypertension refers to the finding that either ambulatory or home pressures are elevated, despite normal or high-normal pressures in the clinic. Criteria for masked hypertension are given in Table 25–1. In contrast to white coat hypertension, masked hypertension is associated with increased target organ pathology, notably left ventricular hypertrophy and carotid artery thickening.[44] It is expected that antihypertensive drug therapy will be effective in preventing cardiovascular events, as is the case with sustained hypertension. However, definitive clinical trials for masked hypertension are not yet available.

Home blood pressure monitoring is becoming a more widely used strategy for classification of hypertension and for monitoring response to treatment.[45] In fact, the first prospective study demonstrating that out-of-office measurement provides superior prediction of cardiovascular disease was performed with a self-recording device that required manual inflation, not suitable for measurements during sleep.[46] Subsequent studies have confirmed the value of home monitoring.[47,48] Home pressure monitoring has the limitation that nocturnal pressures are not measured. However, the predictive accuracy home

monitoring is superior to that of clinic measurement and nearly that of 24-hour ambulatory monitoring. Devices for home monitoring are now widely available and distributed in several national surveys of developed nations. Some devices are linked to telemetry strategies for transmission to provider's offices for review and feedback. Home blood pressure monitoring can be combined with self-titration of medication that may reduce the need for unnecessary clinic visits.[49] This approach is effective lowering blood pressure compared with usual office-based care.[50]

USE OF THE LABORATORY FOR BIOCHEMICAL TESTING AND IMAGING

There is general agreement that in the absence of clues to identifiable hypertension, efficient use and appropriate selection of laboratory resources can be confined to those needed to define cardiovascular risk, target organ pathology and establish a baseline for treatment. The following are suggested:

- Urinalysis
- Multichannel blood test to include serum creatinine, Na, K, HCO_3, calcium, and glucose (fasting)
- Serum lipids: total cholesterol, high-density lipid cholesterol, low-density lipid cholesterol, triglycerides
- Electrocardiogram

The value of echocardiography and nuclear or echo-based exercise stress testing is unclear for asymptomatic hypertensive patients. The results of the above tests combined with blood pressure measurement can be used to calculate a comprehensive risk value using one of the currently available formulas, some of which include C-reactive protein or other biomarkers.[31]

THE SEARCH FOR IDENTIFIABLE HYPERTENSION

A comprehensive discussion of this spectrum is far beyond the scope of this chapter. What is most important is that clinicians be aware of those forms of identifiable hypertension that are most likely to be found in their practices and the initial findings that suggest their presence. These are summarized in Table 25–4.

FOLLOW-UP EVALUATIONS

After the initial assessment, the importance of appropriate follow-up reassessment is crucial. In clinical trials, intervals of 3 to 6 months between clinic visits are often used. However, in ordinary practice, the constraints of travel time, demands of employment, and other responsibilities compete with medical needs. A survey of hypertension care in the United Kingdom found that, for those with clinic pressures of at least 150 mm Hg systolic pressure, increased cardiovascular event rates were related to (1) failure to intensify treatment, (2) delays of more than 1.4 months for intensification, and (3) delays in follow-up of more than 2.7 months after intensification.[51] In general, the higher the blood pressure, the greater the need for shorter intervals between revisits.[5] Home blood pressure monitoring is becoming widely available, and communication between provider and patient can be achieved by telephone or computer. The development of telemetry/telemedicine as a strategy for management of hypertension is being explored to increase adherence to medication, reduction of blood pressure to goal, and minimizing the need for office or clinic visits.[49]

TABLE 25–4. Antihypertensive Drug Classes

Drug Class	Examples of Widely Used Agents
Thiazide-type diuretics	Hydrochlorothiazide, chlorthalidone
Potassium-sparing agent–mineralocorticoid receptor blocker	Spironolactone, eplerenone
Potassium-sparing agent (sodium epithelial channel blocker)	Triamterene, amiloride
Loop diuretics	Furosemide, bumetanide, torsemide
Angiotensin-converting enzyme inhibitors	Lisinopril, enalapril, etc
Angiotensin receptor blockers	Losartan, valsartan, irbesartan
Direct renin inhibitor	Aliskiren
Beta-receptor blockers	Metoprolol, atenolol, carvedilol, nebivolol
Combined alpha-/beta-blockers	Labetalol, carvedilol
Alpha-receptor blockers	Doxazosin, terazosin, prazosin
Dihydropyridine calcium channel blockers (DHP CCBs)	Nifedipine, amlodipine, felodipine
Non-DHP CCB blockers	Diltiazem, verapamil
Direct vasodilators	Hydralazine, minoxidil
Central antiadrenergic agents	Clonidine, reserpine (partial), methyldopa
Peripheral adrenergic neuron depletors	Reserpine (partial), guanethidine

TREATMENT OF HYPERTENSION

This section will summarize treatment of arterial hypertension in the clinic, where this therapy is most often prescribed. Such treatment also occurs in the emergency department, where the presentation may be a true hypertensive emergency or, now more often, a life-threatening event[52]—or one of lesser risk in which hypertension is part of a more complex picture, a hypertensive urgency.

GOALS FOR TREATMENT

The rationale for treatment of hypertension is to prevent future cardiovascular and renal disease. There are two components to treatment: improvement in lifestyle patterns and prescription of antihypertensive drugs. The minimum goal as reflected in several guidelines has been to achieve clinic pressures of less than 140/90 mm Hg (systolic/diastolic).[5,53] A recent advisory from panel members of the JNC 8 process, on the basis of a conservative examination of trial evidence, accepted a higher goal of less than 150/90 mm Hg for older patients.[6] This view is controversial and has been criticized as too permissive and could result in failure to treat some who might benefit.[54,55] Publication of the SPRINT trial, for nondiabetic hypertensive patients, provides the basis for a lower goal for systolic pressure—in the range of 120 to 130 mm Hg.[8] For diabetic hypertensives, best available evidence suggests a goal of about 135 mm Hg systolic pressure.[28,56,57] It is unknown, at present, whether antihypertensive drug treatment will provide effective prevention for those with office/clinic hypertension, but normal pressures outside the office (white coat hypertension) as documented by either 24-hour ambulatory blood pressure monitoring or home pressure monitoring. However, lifestyle improvement is recommended for those who are overweight, underexercised, smoke, or otherwise have risky habits.

LIFESTYLE INTERVENTION

For those with pretreatment clinic blood pressures in the range of 140 to 150 mm Hg, lifestyle improvement may be effective in achieving the desired goal. Weight reduction, avoiding a high dietary salt intake, adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, and increased exercise may be effective. In 6- to 12-month studies of those with stage 1 hypertension, the DASH diet, lowered blood pressures 6 to 8 mm Hg systolic and 3 to 4 mm Hg diastolic more than controls.[58] Reduced fat intake may also be beneficial for lowering low-density lipid cholesterol and serum triglycerides.[59] Smoking cessation, while having no effect on blood pressure, is nonetheless mandatory for cardiovascular prevention.

ANTIHYPERTENSIVE DRUG TREATMENT: OVERVIEW

The value of antihypertensive drug therapy for prevention of fatal and nonfatal cardiovascular disease has been firmly established by well-controlled randomized clinical trials. At present, there is an abundant array of drug classes to be prescribed to achieve control of hypertension (see Table 25–4). A fairly small fraction of people with hypertension, about 15% to 20%, can be often controlled with a single drug class, as is the case with younger patients. Most with higher average pressures will require two or more drug classes to achieve current goals.

The most effective two-drug combinations consist of a renin-system blocking agent (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin-receptor blocker [ARB]) and a thiazide-type diuretic or a renin system blocker and a calcium channel blocker (CCB). When the two-drug combination is not fully effective, adding the third component will often be successful (ie, renin system blocker, diuretic, and CCB). The benefit of adding a drug class appears to be substantially greater than up-titrating dosage with a single drug class.[59]

Resistant Hypertension

When blood pressure remains above treatment goals, despite combining drugs from three classes, it is referred to as "resistant" hypertension. Despite a substantial increase in control of hypertension in many countries, resistant hypertension still has a prevalence of 20% to 30%.[60] Frequently, apparent resistant hypertension is caused by a lack of adherence to prescribed medication. This lack may result from a variety of causes, such as limited health knowledge, unavailable primary care facilities, inability to pay, or lack of insurance. A large white coat effect may obscure the much lower average pressures at home, so that pseudo–resistant hypertension is present. Use of 24-hour ambulatory blood pressure monitoring or home pressure monitoring is justified when the white coat effect is suspected. Conversely, out-of-office monitoring of blood pressure may reveal masked hypertension for which more intensive antihypertensive treatment is necessary to prevent target organ pathology.[61]

Identifiable hypertension may be present in resistant hypertension, such as bilateral renal artery stenosis or primary aldosteronism.[62] Treatment of definite resistant hypertension may include maximizing drug doses as well as addition of alternate drug classes and counseling to increase adherence.[60,63] Even when primary aldosteronism is not confirmed, addition of spironolactone may be effective in drug treatment of resistant hypertension.[64] Minoxidil or high-dose nifedipine has also been shown to be effective for treatment of definite resistant hypertension, if these drugs are tolerated.[65,66]

True resistant hypertension conveys increased risk of future cardiovascular disease leading to exploration of interventional modalities: baroreflex activation therapy (BAT)[67] and bilateral renal denervation (RDN).[68] BAT requires neck surgery with planting of stimulating electrodes on either right, left, or both carotid sinus nerves. Substantial reduction in blood pressure has been reported in small series. At this time, it remains a research intervention with an uncertain future because of the small size of series and practical considerations.[69] RDN has been extensively evaluated in uncontrolled series and in randomized trials compared to sham procedures. Results have been inconsistent. Meta-analyses of RDN compared to various comparison groups in trials and a large registry have reported that RDN was not significantly more effective than use of antihypertensive drug treatment in the comparison groups.[70,71] RDN is approved for treatment of resistant hypertension in some countries, but health authorities in the United States, Canada, and the United Kingdom consider the procedure to be a research intervention.

Hypertensive Emergencies

A hypertensive emergency is defined by rapid increase in blood pressure linked to an immediate threat to target organs: aortic dissection, pulmonary congestion, symptomatic coronary heart disease, progressive renal disease, stroke, or encephalopathy.[52,72] A distinct form of cerebral edema, posterior leukoencephalopathy, has been associated with hypertensive emergencies explaining the encephalopathy that may cause loss of vision, altered mental status, and seizures.[73] Although there is no blood pressure threshold for the diagnosis of hypertensive emergencies, most end-organ damage is noted with systolic blood pressures exceeding 220 mm Hg or diastolic blood pressures exceeding 120 mm Hg. The condition is usually related to a rapid increase in pressure from already high levels in established hypertension, perhaps related in poor adherence to antihypertensive medications. However, abrupt increases in pressure with threat to target organs may appear without prior warning as in some patients with pheochromocytoma or some forms of renal disease (eg, scleroderma renal crisis). The medical history should include queries about use of nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, and substance use. Alcohol withdrawal syndromes may mimic hypertensive encephalopathy. Cocaine or diet pill overdose may raise pressure quickly and even cause cerebral hemorrhage. In hypertensive emergencies in these patients, immediate but monitored reduction of pressure, often accomplished with parenteral medications, is essential to prevent long-term damage.

In addition to very high arterial pressure, people with hypertensive emergencies may have signs of (1) increased intracranial pressure (papilledema, retinal hemorrhages, and exudates), (2) aortic dissection, and (3) pulmonary congestion. The electrocardiogram may show left ventricular enlargement, and the chest x-ray will indicate congestion. Often, renal function will be impaired with proteinuria and microscopic hematuria.

Patients with a hypertensive emergency must be treated in an emergency department or intensive care unit with rapid-acting, controllable medications and continued monitoring to achieve reduction in arterial pressure until stable or the immediate threat is dealt with (eg, proximal aortic dissection requiring surgery). Intravenous medications are usually required to reduce pressure to the range of 150–160/less than 110 mm Hg within a few hours. The medications, described below, are to be considered for intravenous use in achieving the therapeutic goal. Once blood pressure reduction to a safe range has been achieved, patients can be transitioned to oral medications, usually two- or three-drug combinations. Close follow-up and adjustment of medications in the clinic are necessary to achieve long-term control of hypertension in patients admitted for hypertensive emergencies, regardless of the cause.

Sodium nitroprusside is the drug of choice for most hypertensive emergencies because it has an immediate onset of action and can be titrated quickly and accurately. The duration of effect is 1 to 2 minutes. Thiocyanate levels must be followed in patients who have hepatic or renal insufficiency to prevent toxic buildup.

Parenteral labetalol is another first-line agent for hypertensive emergency. Its onset of action is 5 to 10 minutes, and the duration of action is about 3 to 6 hours. Labetalol can be used safely in most patients, but caution should be exercised in patients who have severe bradycardia, congestive heart failure, or bronchospasm.

Nicardipine is a dihydropyridine CCB administered parenterally by continuous infusion for hypertensive crises. The onset of action of this drug is 5 to 10 minutes, and the duration of action is 1 to 4 hours after discontinuing the infusion. Nicardipine is contraindicated in patients with heart failure.

Esmolol is a cardioselective β-blocker with a short duration of action. It reduces systolic blood pressure and mean arterial pressure, as well as heart rate, cardiac output, and stroke volume. There is a notable decrease in myocardial oxygen consumption. Peak effects are generally seen within 6 to 10 minutes after a bolus dose, and the effects resolve 20 minutes after discontinuing the infusion.

Fenoldopam is the first selective dopamine-1 receptor agonist approved for in-hospital short-term management of severe hypertension up to the first 48 hours of treatment. Fenoldopam is a good choice in these patients because of the improvement in renal perfusion, diuresis, and lack of production of toxic metabolites. Tolerance develops to fenoldopam after 48 hours.

Phentolamine is available for intravenous use and is an alpha-receptor adrenergic antagonist that is valuable for treating a hypertensive emergency in patients with pheochromocytoma. When tachycardia occurs in this setting, a rapid beta-blocker, such as esmolol or intravenous metoprolol, can be given to control heart rate.

Intravenous nitroglycerine may be considered when the clinical picture indicates significant myocardial ischemia. This is used as a temporizing step in stabilizing a patient who will most often be prepared for a cardiac intervention.

Intravenous furosemide, a rapidly acting loop diuretic, may be useful in management of acute pulmonary congestion associated with severe hypertension. Duration of action is short, a few hours, so that repeated dosing may be needed.

Hypertensive Urgencies

A hypertensive urgency is defined as the presence of a very high blood pressure (eg, > 180/110 mm Hg) in the absence of the characteristics of a hypertensive emergency, as described above. Although the blood pressure may be markedly elevated, the major problem can be another critical medical event, such as myocardial ischemia or stroke.[72] Some may seek emergency care because of high pressures, without any associated symptoms. The increased use of home blood pressure monitoring may account, in part, for this emerging pattern. The role of anxiety or pain in those patients without cardiac or cerebrovascular disease needs study. In the absence of other medical problems that require emergency care, immediate management of hypertensive urgencies is problematic. Often, without specific treatment, blood pressure will fall substantially and patients can be discharged from the emergency department within a few hours. The role of antihypertensive medication for hypertensive emergencies is entirely uncertain with regard to future risk. Although several drugs may rapidly lower pressure, there is a risk of hypotension as well. When the patient is asymptomatic and clinically stable, outpatient management with close follow-up is appropriate. Long-term blood pressure control is essential, but the reduction can be achieved over a period of weeks. Patient education to achieve understanding of the real risk of elevated blood pressure, value of daily medication, and periodic follow-up is crucial because those with hypertensive urgencies are at greater risk for long-term cardiovascular pathology.[74]

Properties of Antihypertensive Drug Classes

This section will provide an overview and concise description of the currently used antihypertensive drug classes.

Diuretic Drugs

Thiazide-Type Diuretics The thiazides and related drugs (eg, chlorthalidone, indapamide) have been the mainstay of antihypertensive drug treatment since the 1960s as single agents or in effective two-drug combinations together with (1) potassium-sparing diuretics and (2) beta-receptor blockers, ACEIs, and ARBs. Adverse reactions to these drugs are well characterized, the most frequent being hypokalemia and elevated uric acid. The latter may be a cause of gout. Hypercalcemia may occur with thiazide diuretics and might result from underlying hyperparathyroidism. Chlorthalidone was used in several of the early clinical trials; it has the advantage of a longer duration of action compared to hydrochlorothiazide and may be slightly more effective, but it is also more likely to elicit hypokalemia.[75]

Potassium-Sparing Diuretics The two available mineralocorticoid receptor antagonists, spironolactone and eplerenone, may be valuable for treatment of primary aldosteronism or for thiazide-related hypokalemia. When renal function is normal, these drugs infrequently cause hyperkalemia at usual doses. Spironolactone has been found to be effective for resistant hypertension, often in combination with several other drugs including renin system blockers (ACEIs, ARBs, or direct renin antagonists). In this setting, careful monitoring for hyperkalemia is necessary.[76]

Amiloride and triamterene block the sodium epithelial channel of the distal renal tubule. This channel mediates the action of aldosterone, so that these agents can also correct the hypokalemia of thiazide-type diuretics. They have very little effect on blood pressure.

Loop-Active Diuretics Furosemide, bumetanide, torsemide, and ethacrynic acid are diuretics whose site of action is proximal to the thiazide site. They are more effective than thiazides when renal function is impaired. Their adverse reactions are similar to those of the thiazides, except for the lack of hypercalcemia. In general, the loop diuretics are preferred in the presence of congestive heart failure. The unique feature of ethacrynic acid is the lack of a sulfur group, so that it may be used for those infrequent patients with allergic reactions to both the thiazides and furosemide. The loop diuretics are often given together with renin system blockers for effective combinations in those with reduced glomerular filtration rates. Combining a loop diuretic with a thiazide-type diuretic (eg, furosemide and metolazone) may be effective for refractory edema, but very close monitoring for hypokalemia or hyponatremia is required.[77]

Renin System Blockers

Angiotensin-Converting Enzyme Inhibitors The ACEIs were the first renin system blockers to become widely used antihypertensive drugs, most often in combination with thiazide-type diuretics. This combination is highly effective for sustained reduction in blood pressure and usually well tolerated. The ACEIs are also kininase inhibitors that may account for characteristic adverse effects: dry cough (5%–10%) and rare occurrence of urticarial angioedema reactions (swelling of the lips or tongue) that can be fatal. When used in renal disease with proteinuria, most often diabetic nephropathy, ACEIs reduce urinary protein excretion and may retard progression of renal impairment. Similarly, ACEIs may be beneficial for retardation of renal impairment in African Americans with chronic renal disease.[78] ACEIs, like all renin system blockers, may reduce aldosterone secretion when

the renin-angiotensin-aldosterone system is normal but not when primary aldosteronism is present.

Angiotensin II Receptor Antagonists The ARBs block the angiotensin II, type 1, receptor that mediates vasoconstriction by vascular smooth muscle and also stimulation of adrenal aldosterone production. The effects of ARBs are similar to those of the ACEIs except that kinin potention is absent. Cough with use of ARBs is not different from placebo administration in controlled blinded trials or when ARBs are given to patients with ACEI cough.[79,80] An ARB has been shown to significantly lower blood pressure in prehypertensives for a year, preventing new hypertension in comparison with placebo.[81] At the end of the trial, most people had an increase in pressure to pretreatment levels but some remained at lower levels. A small fraction of hypertensives will have full control of hypertension when taking ARBs, but these drugs are most effective in combination with a thiazide type diuretic or a CCB.

Direct Renin Inhibitors Aliskiren is a direct-acting renin inhibitor that is an effective antihypertensive agent that, as monotherapy, has a similar effect on blood pressure as an ARB.[82] Like the other renin system blockers, aliskiren is more effective in combination with either a thiazide diuretic or CCB. ACEIs or ARBs increase plasma renin activity and lower aldosterone in those with normal renin systems. Unlike ACEIs or ARBs aliskiren reduces the assay of plasma renin activity and serum aldosterone. The differences in the effects of the renin system blockers is important when testing the renin system for identifiable hypertension. Blockade of the renin system with two or three drugs is not recommended because of the risk of hyperkalemia and lower glomerular filtration rate.[83,84]

Calcium Channel Blockers

Dihydropyridine Calcium Channel Blockers There are many dihydropyridine calcium channel blockers (DHP CCBs). Several either have prolonged duration of action (eg, amlodipine) or have been formulated in long-acting delivery systems (eg, nifedipine ER), so that they are effective when given once daily. The hemodynamic effect of these agents is to reduce peripheral resistance with minimal reflex increase in heart rate—and with minimal effects on the renin-angiotensin system. DHP CCBs are widely used and are effective as monotherapy but often combined with renin system blocker for greater effectiveness (eg, benazepril and amlodipine). The first-pass intestinal absorption of CCBs is increased by concurrent intake of grapefruit or natural grape fruit juice; the most effect has been found with felodipine.[85-88] The increased levels of felodipine may be sufficient to lower blood pressure, a possible adverse effect in elderly patients. The major adverse effect for this class is pedal or ankle edema that can be bothersome and occasionally, severe. Prolonged use of DHP CCBs may lead to gingival hyperplasia, requiring dental care.

Non–Dihydropyridine Calcium Channel Blockers Diltiazem and verapamil are like DHP CCBs blockers of the L-channel of smooth muscle and cardiac tissue. They are effective antihypertensive agents, often given together with inhibitors of the renin system. However, their antihypertensive effect overlaps that of the thiazide-type diuretics with little additive potential. These two drugs differ from the DHP CCBs by inhibiting cardiac AV conduction, so can be used for management of supraventricular arrhythmias. They should not be combined with beta-receptor blockers because of the risk of bradycardia. These drugs are usually well tolerated, but they may cause edema. Verapamil can cause bothersome constipation.

Antiadrenergic Drugs Used for Hypertension

Beta-Receptor Blockers At one time, beta-receptor blockers, especially when combined with thiazide-type diuretics, were a major component of antihypertensive drug treatment and play an important role in several clinical trials. The effectiveness of beta-blockers either as monotherapy or in combination with a diuretic, for prevention of cardiovascular disease in the absence of coronary artery disease (especially for stroke), has been questioned, particularly now that combinations of renin system blockers and either diuretics or CCBs have become available.[89,90] However, the value of beta-blockers for management of coronary heart disease, especially angina, remains well accepted.[91] In general, the most used beta-receptor blockers have a long duration of action, are more selective $beta_1$-blockers with no $beta_2$-blocking action, and have no sympathomimetic effect. Beta-receptor blockers combined with alpha-blockers (carvedilol, labetalol) or agents with vasodilator activity (nebivolol) are now available. Whether they more effective for treatment of hypertension with coronary artery disease remains uncertain.

Adverse effects of beta-blockers are well known and include bradycardia, fatigue, bronchospasm, or worsening of asthma (for beta-blockers with $beta_2$-receptor blocking (eg, propranolol or timolol). Cold fingers, simulating Raynaud's phenomenon, may occur.

Alpha-Receptor Blockers The prototype alpha-receptor blocker is prazosin, which produces vasodilation by blocking vascular alpha receptors. This drug has a relatively short duration of action; terazosin (twice a day) or doxazosin (once a day) are preferable. The alpha-blockers may be combined with a beta-blocker as combined antiadrenergic receptor antagonism for persons with highly variable blood pressure associated with tachycardia. Like the alpha-receptor blocker, phenoxybenzamine, doxazosin may be used to treat hypertension associated with pheochromocytoma. The alpha-receptor blockers are effective for reducing symptoms of prostatism, so they offer a "two for one" benefit for men with hypertension and bothersome prostatic enlargement. However, doxazosin was associated with increased occurrence of heart failure in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), so that careful monitoring for signs of heart failure is warranted when this drug is used.[92]

Centrally Acting Antiadrenergic Drugs and Neuron Depletor Methyldopa is considered safe for use in pregnancy-related hypertension, including preeclampsia, but has been superseded by recently developed drugs; see section on Pregnancy and Hypertension, below. Clonidine, an alpha-receptor agonist, acts within the brain and may also reduce peripheral neuron release by presynaptic inhibition. As an oral preparation, clonidine must be given two to three times daily; withdrawal overshoot hypertension is a risk of missed doses. The transdermal therapeutic system for transcutaneous delivery of clonidine over a 7-day period may be useful for nonadherent patients or those who cannot take oral medication.[93,94]

Direct Vasodilators

Hydralazine, a direct-acting vasodilator, may release nitric oxide release as part of its action. This drug has a short duration of action and must be give three times daily for effectiveness; no long-acting formulation is available. Adverse reactions to hydralazine include fluid retention, tachycardia, and drug-induced lupus erythematosus.

Minoxidil is a very potent vasodilator with a longer duration of action so that it can be given once or twice daily. Minoxidil opens the ATP-potassium channel of vascular smooth muscle cells.[65] This drug may reduce blood pressure in highly resistant hypertension, when alternatives fail. However, edema and tachycardia need management, usually with a loop diuretic (eg, furosemide) and a beta-blocker. Hair growth caused by minoxidil when used to treat hypertension may be disfiguring, so that adherence to treatment is problematic. High-dose nifedipine has reduced the need for minoxidil for treatment of resistant hypertension.[95]

MANAGEMENT OF HYPERTENSION FOCUSED ON SPECIFIC ISSUES

ETHNIC STATUS

The prevalence and severity of hypertension is not entirely uniform in comparing populations with different ethnic status as reflected in national surveys. The ongoing NHANES has examined prevalence of hypertension in several categories, as self reported: non-Hispanic white (white), non-Hispanic black (black), Hispanic, other (American Indian, Native Alaskan, Asian or Pacific Islander), and other race not specified. Prevalence of hypertension was about 25% for non-Hispanic whites and Hispanic groups but about 35% for non-Hispanic (black) groups.[96] In the United States, the prevalence of hypertension has been relatively constant in the past decade, but increasing fractions of all groups are being treated (64%–77%) and controlled (64%–77%).[97] An increase in use of multidrug combinations has paralleled increased control.[98] The most recent assessment found that treatment rates were 77% in non-Hispanic whites, 75% in non-Hispanic blacks, but 68% in Mexican Americans. For both non-Hispanic whites and non-Hispanic blacks, the fraction for being controlled on treatment is about 45%. Evidence from the large randomized trial comparing a thiazide-type diuretic, chlorthalidone, with an ACEI, lisinopril, or the CCB, amlodipine, as initial and continuing first-drug treatment indicates that black hypertensives have better control of blood pressure and equal or lower event rates given the diuretic, compared with the other two agents.[99] This pattern is consistent with observations that black hypertensives may be more salt sensitive, on average, compared to nonblack populations. However, other dietary factors may be relevant as black hypertensives had greater blood pressure reductions than nonblacks when given the DASH diet.[100] Treatment goals for nondiabetic black hypertensives, with blood pressures below 140/90 mm Hg, are supported by the results of the SPRINT trial, in that reduction of the primary event rate (25%) was similar for blacks and nonblacks.[8]

DIABETES AND HYPERTENSION

Diabetes, largely type 2, is present in 10% to 20% of the adult US population, with higher fractions in older age groups. A prospective survey conducted in several communities in the United States reported that beta-receptor blockers may significantly increase the incidence of type 2 diabetes, but diuretics and ACEIs had no discernable effect.[101] For those with diabetes, the benefit-to-risk ratio for beta-blockers should be considered when hypertension occurs with or without coronary heart disease. It is well established that the concurrence of diabetes and hypertension confers a two- to three-fold greater risk of future cardiovascular disease compared to hypertension alone.[102,103] There had been general acceptance of the need to control hypertension in persons with diabetes; the predicted goals for such treatment had been less than 130/80 mm Hg for office pressures.[5] However, the results of the ACCORD trial combined with several large prospective surveys support a goal of about 135/85 mm Hg for office pressures.[28,56] The value of renin system–blocking drugs, particularly the ACEIs and ARBs may be additive to blood pressure reduction for diabetics for prevention of renal disease and reduction of microalbuminuria or proteinuria. It has been suggested that diabetic hypertensives are relatively resistant to antihypertensive drug treatment,[104] but the experience from ACCORD indicates that currently available drugs in combination at appropriate doses can achieve treatment goals well below 140 mm Hg systolic pressure.

ELDERLY, OLDER PATIENTS

Antihypertensive drug treatment is effective for prevention of cardiovascular disease in healthy elderly populations, age 80 and above, as evidenced by the Hypertension in the Very Elderly Trial (HYVET).[105] In the SPRINT trial, intensive treatment aimed at a goal of less than 120 mm Hg systolic pressure was more effective in those older than 75 years of age, approximately 25% of the trial, compared to those 50 to 75 years of age.[8] However, many older patients are more likely to be less healthy that those enrolled in HYVET or SPRINT. Often, coronary heart disease with or without heart failure, previous stroke, cognitive dysfunction, and other chronic conditions are present, affecting optimal decisions for best outcomes.[106] Orthostatic hypertension may be asymptomatic until increased medication is given to achieve lower goals.[36] Risk of falls and serious fractures may occur with intensive treatment of more frail elderly.[107]

Choice of antihypertensive drugs for elderly patients should take into account that the beneficial clinical trials were based on either a diuretic[108,109] or CCB[110] as initial treatment. Beta-receptor blockers, useful for angina, nonetheless may not be as effective for prevention of stroke as ARBs (Losartan Intervention for Endpoint (LIFE) trial).[111] Also, they have potential for bradycardia and exacerbation of obstructive pulmonary disease. No matter which drugs are chosen, careful monitoring for adverse reactions is necessary to maintain full function and quality of life.

CORONARY HEART DISEASE

In aging populations with highly prevalent risk factors, smoking, diabetes, and lipid disorders, coronary heart disease and hypertension are often clustered together. The management of acute coronary syndromes will be covered elsewhere. The focus of this section is treatment of hypertension with established coronary artery disease, either as angina or following an acute syndrome, but without heart failure. A recent comprehensive guideline is addressed to management of hypertension in coronary heart disease[91] The value of diuretics, beta-receptor blockers, and ACEIs for hypertension with angina is strongly supported. The role of the DHP CCBs is less clear, although these drugs can be effective for angina when added to beta-receptor blockers.[112] Verapamil or diltiazem, the non–DHP CCBs, may be effective when beta-blockers cannot be given. ARBs may be helpful for those who cannot tolerate ACEIs, usually because the ACEIs have caused bothersome cough or angioneurotic edema.[80]

STROKE, CEREBROVASCULAR DISEASE

Once a stroke has occurred or there is evidence of cerebrovascular disease, antihypertensive drug therapy still has an important role for preventing additional pathology. One trial has reported that the combination of an ACEI and diuretic is effective for preventing the second stroke.[113] Apart from elevated blood pressure, per se, as a risk factor for recurrent stroke or stroke in persons with transient ischemic attacks, intervisit blood pressure variability has recently be identified as contributing, independently to risk as.[114] A review suggests that CCBs may reduce interindividual blood pressure variability, compared to beta-blockers and ACEIs and thereby have an additive benefit for treating hypertension in poststroke patients.

Carotid artery stenosis, another manifestation of generalized atherosclerosis, is often found in hypertensive patients, detected by the finding of a carotid bruit or by screening with carotid artery ultrasound. Whether or not screening of asymptomatic patients is beneficial is uncertain at this time.[115] Those with asymptomatic carotid stenosis

and hypertension should receive treatment until the usual goals are met. When symptoms occur implying imminent risk of stroke, it less clear that aggressive reduction of arterial pressure is desirable[116] until a successful carotid intervention occurs.

CHRONIC RENAL DISEASE

Hypertension is well associated with chronic renal disease of various types with and without proteinuria. Diabetic nephropathy is the most likely form to be encountered, but the glomerular diseases, adult polycystic kidney disease, and others may be seen. The goals for treatment of hypertension in chronic kidney disease are both to slow deterioration of renal function and to minimize risk of cardiovascular disease, as recommended in several evidence-based guidelines. However, the optimal goal for on-treatment blood pressure remains uncertain. Increased risk of progression to end-stage renal disease is related to the height of systolic pressure, but it is inversely related to diastolic pressure in older patients.[117] Ambulatory blood pressure monitoring is helpful in defining risk in chronic renal disease.[118] This may be the result of the greater importance of nocturnal hypertension in chronic renal disease.[119] Aggressive treatment of hypertension in nondiabetic renal disease is supported by clinical trial evidence.[120] ACEIs and ARBs can reduce proteinuria in diabetic and nondiabetic renal diseases and, in some studies, retard progression of renal deterioration. Treatment of persons with minimal proteinuria or microalbuminuria with ACEIs may prevent either the appearance of increased protein excretion.[121]

Goals for antihypertensive treatment for chronic renal disease have, in recent guidelines, been set well below 140/90 mm Hg for clinic pressure.[122] However, recent large trials fail to support the lower goal, so the lower goal remains controversial.[8,123,124] Greater use of ambulatory blood pressure monitoring to assess nocturnal pressures might resolve this issue for the future.[125]

POST-TRANSPLANT HYPERTENSION

Hypertension often occurs following solid organ transplantation. Multiple mechanisms participate in blood pressure elevation, including the effects of immunosuppressive drugs: steroids and the calcineurin inhibitors cyclosporine or tacrolimus.[126-128] Hypertension may be slightly less prevalent with tacrolimus compared to cyclosporine.[129] Treatment of hypertension following organ transplantation is recommended, with prominence given to the value of CCBs and lack of support for ACEIs and ARBs.[130]

HYPERTENSION IN PATIENTS WITH CANCER

Occurrence of cancer in hypertensive patients is all too frequent and as the benefits of antihypertensive therapy reduce fatal cardiovascular disease, more survive to older age, when cancer incidence increases. Management of hypertension in many of those with cancer who remain fully active need not be any different than from treatment of those without cancer. However, incidence of new hypertension or worsening of previous hypertension in cancer patients may result from chemotherapy with the vascular endothelial growth factor (VEGF) inhibitors typified by bevacizumab. The incidence of new hypertension with these agents varies from 20% to 70%,[131] with some evidence of a dose-related effect.[132] Abrupt and life-threatening increases in arterial pressure caused by the VEGF inhibitors have been reported, including cardiac toxicity and posterior leukoencephalopathy, as seen in malignant hypertension.[133] A consensus panel has recommended that patients with cancer who receive VEGF inhibitors have assessment of overall cardiovascular risk and close monitoring of their blood pressure to detect and treat incident hypertension or, if already on antihypertensive medication, a significant increase in pressure. Retrospective reviews of series of patients with VEGF inhibitor–related hypertension indicate that the usual antihypertensive agents, especially ACEIs and CCBs, are effective, but diuretics may less so.[134,135] Because these patients are often taking a variety of medications for control of cancer and hypertension, thorough familiarity with potential adverse effects and drug interactions is crucial for optimal management by the oncologist and cardiologist.

RHEUMATOLOGIC DISEASE

Hypertension is often found in patients with various forms of arthritis or the disorders of connective tissue. As in those without rheumatologic disease, presence of hypertension nearly doubles risk of future cardiovascular disease.[136] In part, the associations may only be the concurrence of essential hypertension with the other disease, as in rheumatoid arthritis and dermatomyositis. Use of steroids or NSAID therapy for the rheumatologic diseases should be recognized as possible aggravating elements. Use of the tumor necrosis factor antagonists has been associated with a nearly two-fold higher incidence of hypertension in a prospective study.[137] However, several specific diseases have a more specific link. Scleroderma renal crisis describes rapid development of severe hypertension with renal impairment and, pulmonary congestion in patients with scleroderma. The skin manifestations may be of brief duration and unrelated to the severity of the hypertensive emergency. Renin system blockers have been highly effective in reversing the high renin clinical picture by lowering blood pressure and, perhaps, by ameliorating the cutaneous disorder as well.[138] Nephritis due to systemic lupus erythematosus may be associated with hypertension. ACEIs initiated before onset of renal disease may delay onset of the nephropathy.[139] The use of high-dose glucocorticoids for treatment of systemic lupus erythematosus may contribute to the severity of hypertension in this disease. Polyarteritis nodosa may involve renal artery branches with or without infarction and produce hypertension with activation of the renin-angiotensin system that is, de facto, renovascular hypertension. The intense renal arterial inflammation may respond to steroid therapy with lessening of the hypertension; an exception to the rule that steroids frequently cause blood pressure elevations.

COGNITIVE IMPAIRMENT

Hypertension in older patients has been associated with increased risk of cognitive impairment and dementia.[140] Imaging studies have indicated correlation between cognitive impairment and signs of cerebral microvascular pathology. Prospective surveys of cognitive function have been conducted within the framework of several randomized trials of therapy for prevention of cardiovascular events. A meta-analysis supports the view that antihypertensive drug treatment does not significantly increase likelihood of dementia or cognitive impairment.[141] It has been suggested that ACEIs that cross the blood-brain barrier may be more effective in preventing cognitive impairment than those that enter the brain to a lesser extent.[142] In the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) trial comparing an ACEI with an ARB, there was no difference between the two with regard to rates of cognitive impairment during the study.[143]

PREGNANCY AND HYPERTENSION

Hypertension occurring anew during pregnancy may be a spontaneous occurrence without previous hypertension and without features of preeclampsia (gestational hypertension); may be accompanied by new

proteinuria with or without edema (preeclampsia); or may be characterized by seizures (eclampsia).[144] Preeclampsia may be associated, not only with proteinuria (> 300 mg/24 h), but thrombocytopenia, abnormal liver function tests, and impaired renal function (the HELLP syndrome). Those with hypertension prior to pregnancy are considered to have chronic hypertension, but pressure may fall to normal levels in the first and second trimesters of gestation. Occasionally, hypertension first appears immediately after delivery (postpartum hypertension). With exception of chronic hypertension, hypertension in pregnancy or shortly after delivery is usually gone about 6 weeks after delivery. Close monitoring of blood pressure during pregnancy is necessary and use of home blood pressure monitoring may be helpful.[145] Ambulatory blood pressure monitoring has been explored and may be helpful when additional studies are available.[146]

Goals and strategy for treating hypertension in pregnancy differ from the usual pattern for nonpregnant women.[144] Optimal care requires effective collaboration between specialties, including the internist, cardiologist, nephrologist, and high-risk obstetrician. Current guidelines suggest that new hypertension not be treated with antihypertensive drugs if clinic pressures are less than 160/105 mm Hg without any complications. For women with treated hypertension before pregnancy, pressure should be kept in the range of 120–160/80–105 mm Hg. However, the range of drug classes suitable for treating hypertension in pregnancy is a restricted one, excluding the renin system blockers, because of risk of fetal damage,[147,148] as well as the mineralocorticoid receptor blockers, spironolactone, and eplerenone. Recommended drugs are methyldopa, labetalol, and nifedipine because these have acceptable evidence of safety in pregnancy.

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CHAPTER 26

THE METABOLIC SYNDROME

Michael A. Via and Jeffrey I. Mechanick

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INTRODUCTION

The metabolic syndrome (MetS) is a theoretic construct from clustering of interrelated processes to better represent complex pathophysiology into actionable and effective clinical decision making. Specifically, the rationale and practical utility of MetS is to facilitate early diagnosis, risk stratification, and management of cardiometabolic risk factors. This topic is relevant but also remains controversial because many aspects remain unproven. Nevertheless, the core principle is that the value of MetS is related to the impact of residual risk (total risk minus the aggregate of known specific risk factors) on cardiovascular disease (CVD). A recent consensus statement has advanced the discussion and relevance of MetS by proposing different subtypes and severity levels in the context of a public health care model.[1]

Energy homeostasis is coordinated by hormone signal pathways that integrate the metabolic activities of multiple tissues and organ systems. Insulin resistance disrupts metabolic efficiency, thereby driving many chronic metabolic diseases, including type 2 diabetes (T2D), atherosclerosis, hypertriglyceridemia, hepatosteatosis, polycystic ovary syndrome, and obesity. Informally, insulin resistance may also be classified as prediabetes. As a common pathophysiologic pathway, insulin resistance affects and is affected by metabolism in adipose tissue, skeletal muscle, vascular endothelium, bone, liver, kidneys, pancreatic islets of Langerhans, hypothalamic nuclei, and the immune system.

In general, the diagnosis of MetS is based on the complex of increased adiposity/obesity, hypertension, hypertriglyceridemia, and insulin resistance.[1] The prevalence of MetS varies depending on the specific definition used (Table 26–1)[2-7] but has nevertheless increased substantially over the past few decades in parallel to the rise in obesity. This rise is associated with modern (westernized) lifestyles, food preferences and availability, agricultural changes, environmental exposures, and other related epigenetic factors. Depending on the specific criteria used, approximately 20% to 35% of various reported worldwide adult populations have MetS (Table 26–2), substantially increasing the risk of atherosclerotic disease.[8]

The etiology of MetS is not clear but is thought to be related to adipose tissue pathology, insulin resistance, inflammation, other processes, or combinations of these. Accumulation of fat in adipose and nonadipose tissue, a core feature of MetS, results in obesity in many cases, which is defined by a body mass index (BMI) above 30 kg/m^2 in Caucasians (a BMI of 25–29.9 kg/m^2 corresponds to "overweight"), but cutoff points as low as 25 to 27 kg/m^2 in various Asian regions (with varying BMI cutoff points in the 23–26.9 kg/m^2 range for overweight).[9] Even these definitions can be modified by a blurring of the overweight-obesity demarcations through the incorporation of weight-related complications or other anthropometrics, such as waist circumference (WC).[10] Additionally, a subset that comprises about 10% of the obese population does not demonstrate signs of insulin resistance or inflammation. These people with obesity have been described as metabolically healthy,[11] although the true healthy nature of these people is highly debatable.[12,13] In fact, the vast majority of people with obesity, unhealthy or healthy, have some degree of insulin resistance, are at risk for associated metabolic diseases, and have increased mortality.[7] In this sense, BMI may still serve as a predictor of adverse outcomes and should not be entirely abandoned, although because of the overlap of obesity, insulin resistance, and MetS, better predictive and treat-to-target parameters based on risk are needed.

Currently, the diagnosis of MetS is based on a set of commonly measured metabolic markers: abdominal girth (WC), hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein (HDL) levels. However, debate still exists over the relative weighting of each of these measures in a predictive model for morbidity and mortality risk. Definitions given for MetS vary among major organizations based on different interpretations of the scientific evidence as well as expert consensus/opinions (see Table 26–1), but common to each of these is a constellation of metabolic disturbances centered on insulin resistance and obesity.

Cardiovascular risk is nearly doubled in people with MetS and further increases as people acquire more of the defining criteria. Moreover, quality of life is substantially reduced and the risk of other weight-related complications rises in the presence of MetS. If we stipulate that MetS is a complex pathophysiological state, then it makes sense that a multifaceted approach to treatment, rather that a singular intervention, can reduce these risks and lead to improved quality of life.[5,6]

COMPONENTS OF METABOLIC SYNDROME

The observation that specific metabolic factors—obesity, hypertension, insulin resistance, and dyslipidemia—commonly occur together and influence cardiovascular risk was first proposed by Reaven et al[2] nearly three decades ago. Since this seminal observation, a number of organizations have recognized the aggregate risk of MetS, although they differ slightly in the specific definition of the syndrome.

A decade after the first proposed version of MetS, the World Health Organization (WHO) affirmed the classification of clustered metabolic disorders that impart high risk of atherosclerotic disease.[3] The WHO definition of MetS emphasized the importance of abdominal obesity as a marker of impaired metabolic function and includes measures of insulin resistance in the presence of at least two other metabolic criteria to qualify as having MetS. Shortly after this publication, the European Group for the study of Insulin Resistance (EGIR) emphasized the contribution of insulin resistance to MetS.[14]

TABLE 26–1. Diagnostic Criteria for Metabolic Syndrome

			Defining Criteria				
Organization	Reference Year	Requirements for Diagnosis	Adiposity	Blood Pressure/ Hypertension	High Serum Triglycerides	Low Serum HDL	Hyperglycemia/Insulin Resistance
American Heart Association/ National Heart, Lung, and Blood Institute	2005[2]	Three of five criteria	Men: WC ≥ 102 cm Women: WC ≥ 88 cm	≥ 130/85 mm Hg or medication use	≥ 150 mg/dL	Men: < 40 mg/dL Women: < 50 mg/d Or medication use	Serum glucose > 100 mg/dL or medication use
International Diabetes Federation	2005[3]	Adiposity plus two of four other criteria	Increased WC	≥ 130/85 mm Hg or medication use	≥ 150 mg/dL	Men: < 40 mg/dL Women: < 50 mg/d Or medication use	Serum glucose > 100 mg/dL
American Association of Clinical Endocrinologists	2003[4]	Insulin resistance plus any of the other criteria	BMI ≥ 25 kg/m^2	≥ 130/85 mm Hg	≥ 150 mg/dL	Men: < 40 mg/dL Women: < 50 mg/dL	Impaired fasting glucose or impaired glucose tolerance, excluding T2D
National Cholesterol Treatment Program	2001[5]	Three of five criteria	Men: WC ≥ 102 cm Women: WC ≥ 88 cm	≥ 130/85 mm Hg	≥ 150 mg/dL	Men: < 40 mg/dL Women: < 50 mg/dL	Serum glucose > 100 mg/dL
European Group for the Study of Insulin Resistance	1999[6]	Insulin resistance plus any two of the other four criteria	Men: WC ≥ 94 cm Women: WC ≥ 80 cm	≥ 140/90 mm Hg or medication use	≥ 150 mg/dL	< 39 mg/dL	Fasting plasma insulin > 75th percentile; impaired fasting glucose; or impaired fasting glucose excluding T2D
World Health Organization	1998[7]	Insulin resistance plus any two of the other four criteria	Waist-to-hip ratio— Men: ≥ 0.9 in Women: ≥ 0.85 in Or BMI ≥ 30 kg/m^2	≥ 140/90 mm Hg	≥ 150 mg/dL	Men: < 35 mg/dL Women: < 39 mg/dL	Impaired glucose tolerance; impaired fasting glucose; or reduced insulin sensitivity

Abbreviations: BMI, body mass index; T2D, type 2 diabetes; WC, waist circumference.

The 2002 report of the National Cholesterol Education Program (NCEP) reiterates these concepts of abdominal obesity, hypertension, and insulin resistance that yield a proinflammatory and prothrombotic state and enhance the risk of atherosclerotic disease.[4] The NCEP stresses the importance for addressing each individual factor to diminish cardiovascular risk.

The American Heart Association (AHA), in conjunction with the National Heart, Lung, and Blood Institute (NHLBI), recognizes the atherogenic properties associated with the pattern of dyslipidemia of the MetS and proposes the use of a low threshold to pharmacologically treat elevated low-density lipoprotein (LDL) cholesterol.[15]

More recently, the International Diabetes Federation (IDF) added several other biomarkers of impaired energy homeostasis that can be considered in the diagnosis of MetS.[16] These adjunct criteria include markers of adiposity such as plasma leptin and adiponectin concentration, hepatic fat content, apolipoprotein B, LDL particle size, endothelial dysfunction, urinary microalbumin levels, and markers of systemic inflammation and thrombosis.

The minor differences in emphasis and in measurement of each component for the diagnosis of MetS (see Table 26–1) highlight the true syndromic nature of this condition. Individuals may vary in their presentation and may be included or excluded depending on the exact definition utilized. Overall, atherosclerotic risk rises in association with severity of MetS.[17,18] The practical decisions of diagnosis and clinical intervention should take into consideration the continuum of risk imposed by MetS.

The term *residual risk* compliments the concept of the MetS. Specifically, residual risk describes the remaining increased potential for atherosclerotic CVD, after the treatment of a specific risk factor, such as using cholesterol-lowering agents with dyslipidemia.[19] Factors that contribute to residual risk include lifestyle factors, such as eating patterns and nutrient content, endocrine-disrupting compounds (EDCs), physical activity, sleep hygiene, and others. Fundamentally, as a driver of atherosclerotic disease, lifestyle components of MetS pose a tantalizing public health issue.[15]

TABLE 26–2. Reported Worldwide Prevalence of Metabolic Syndrome

Country	Year	Reported Prevalence of Metabolic Syndrome	Definition of Metabolic Syndrome
United States	2010	22%	NCEP
United States	2010	37%	AHA/NHLBI
South Korea	2012	22%	NCEP
Iran	2004	33%	NCEP
Nigeria	2014	28%–31%	WHO, NCEP, or IDF
Spain	2010	22%	WHO
India	2004	46%	NCEP

Abbreviations: AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

EPIDEMIOLOGY

Since the first description of MetS, prevalence has been increasing in parallel with increases in obesity and T2D. According to the 2001-2010 National Health and Nutrition Examination Survey, the prevalence of MetS in the United States is 22% using NCEP criteria and 37% using AHA/NHLBI criteria.[8] In contrast, the MetS prevalence using NCEP criteria is 28% in Mexican Americans and 24% in African Americans.[20] These differences highlight important cultural and biological variables when evaluating MetS on a population scale within a particular region.

Worldwide, different regional populations demonstrate similar, as well as unique phenotypic expressions and related epidemiologies of MetS. For instance, the prevalence of MetS is 22% in South Korea using NCEP criteria,[21] the same as in the United States. But in Iran, the prevalence of MetS is higher at 33% by NCEP criteria (and 18% by WHO criteria).[22] In Nigeria, the prevalence is 28% to 31%, based on NCEP, WHO, or IDF criteria.[23] A cohort of German autoworkers demonstrated a surprisingly low prevalence of 11% by WHO criteria.[24] A cohort study in Catalonia, Spain, demonstrated a 22% prevalence of MetS by WHO criteria.[25] And finally, the prevalence of MetS in India has been reported as high as 46%.[22] The consistently high but varying prevalence of MetS on a global scale raises many important questions about specific drivers, both biological and cultural; the dominant role of lifestyle; and the overarching relevance of and need for transculturalizing evidence-based recommendations from one region to another to improve clinical outcomes.[26]

PATHOGENESIS OF METABOLIC SYNDROME

LIFESTYLE AND ENVIRONMENTAL FACTORS

Sedentary Behavior

The modern-day western lifestyle is largely responsible for the high prevalence of MetS in many populations, as well as the rapidly rising prevalence in populations undergoing economic, demographic, nutritional, and cultural transitions.[22] Along these lines, modification of the multiple drivers and contributing factors within modern living can reduce specific and residual risks. Among these, sedentary behavior figures prominently.[17] Physical activity has multiple effects on metabolism, including activation of brown fat, improvement in insulin sensitivity, as well as modulation of endothelial function and adipose tissue function.[27,28] Shifts in internal energy use among highly active individuals may also contribute to more efficient carbohydrate processing and reduced insulin resistance.[29] Additionally, gene activation following physical activity can influence insulin resistance and mitochondrial function.[30] Interventional studies consistently demonstrate great reduction in the prevalence and severity of MetS within highly active subjects.[17] Most notably, trials that incorporate increased physical activity demonstrate a 29% to 58% reduction in incidence of T2D among at risk subjects.[31]

Modern Agriculture

The potential adverse metabolic effects of modern agricultural techniques, food processing, and the resultant food chain in the United States with respect to nutrient content and endocrine disruptors are only just becoming clarified but still not without controversy. For example, the use of corn for animal feed rather than grass for beef production or seeds for poultry yields a higher n-6 fatty acid content, which may have proinflammatory effects.[32] Maintaining livestock in small cages promotes adipose tissue growth, potentially raising saturated and n-6 fatty acid and lowering n-3 fatty acid content in the animals.[32] The use of antibiotics among livestock may also lead to increased adipose tissue mass and saturated fat content.[33]

The early harvesting of fruits and vegetables, which allows for ease of transportation, reduces micronutrient and antioxidant content. The use of industrial fertilizers can affect nitrogen and phosphorus content, although the metabolic effects of these changes are not fully understood. High amounts of corn and soy production yield a vast array of derivative food products, including *trans*-fatty acids, peroxidized fatty acids, and high-fructose corn syrup. These compounds are commonly added to processed foods and can promote insulin resistance, hepatosteatosis, and atherosclerosis.[34]

Endocrine Disruptors

A number of man-made industrial chemicals have properties that allow interruption of normal hormone signaling either through molecular mimicry of natural hormones, blockade of hormone activity, or by affecting hormonal synthesis, transport, binding, or catabolism. Animal models and population exposure studies identify specific EDCs, such as pesticides, plasticizers, preservatives, and artificial sweeteners, among other chemicals that hinder glucose metabolism and cause insulin resistance.[35-38]

EDCs have multiple entry points in the food chain and many are retained within individuals because of lack of clearance pathways. However, the degree to which EDCs contribute to the high prevalence of MetS is presently unclear. Considering the seemingly endless introduction of novel industrial chemicals, the pathophysiologic effects on metabolism and range of chemicals that act as EDC may never be fully understood. A prudent approach of minimizing exposure has been recommended.[39]

Fructose

Prior to the industrial production of sugars, dietary fructose was relatively scarce; natural sources of fructose included fruits (which contained only small amounts), honey (which was relatively unavailable), and agave extract (which was not widely consumed). Now, the high content of fructose within industrially produced sugars, such as sucrose and high-fructose corn syrup, makes this inefficiently metabolized monosaccharide highly available.

Fructose enters energy metabolism downstream of important regulatory steps and without hormonal control.[40,41] Nearly all consumed fructose is taken up and metabolized by hepatocytes, leading to fatty acid synthesis and hepatosteatosis.[42]

Multiple longitudinal and cross-sectional studies demonstrate a strong association among high fructose intake and the development of obesity, MetS, and/or vascular disease.[43-46] These associations are corroborated in several controlled trials demonstrating increased insulin resistance and increased circulating triglyceride levels after 3 to 6 months of increased fructose consumption compared to isocaloric diets containing starch and low in fructose.[47-49]

Sleep Hygiene

Many studies demonstrate that a reduced amount of sleep, generally 6 hours or less per night, is associated with increased insulin resistance, hypertension, and obesity.[50] One large study demonstrated that reduced time of slow-wave sleep was specifically associated with increased waist circumference.[51] Quality of sleep can also affect metabolism. Shift workers, with frequent changes in circadian patterns have higher rates of obesity and T2D compared to the general population. Insulin resistance also worsens in the presence of obstructive sleep apnea. Current trends over the past 50 years demonstrate a 1.5- to 2-hour reduction

in time spent sleeping each night, which may further contribute to the rising prevalence of MetS.[52]

Other Factors

The rising use of certain antidepressant and other psychotropic medications that affect metabolic control within the hypothalamus leads to insulin resistance and weight gain. Even the widespread use of antibiotics may influence metabolism through alteration of intestinal microbiota.[53] The average American adult is given one to two prescriptions for antibiotics annually, which has been associated with the development of obesity.[53] Macrolides confer the greatest risk, perhaps reflecting a greater effect on intestinal microbiota.[53,54]

Behavioral patterns related to nutrition also contribute to the development of MetS. The shift in practice from breastfeeding newborns and infants to formula feeding that has occurred over the past century is associated with insulin resistance in the mother and risk of obesity in the child.[55,56] Population survey data demonstrate that the reduced time dedicated to food preparation is also associated with the development of obesity, insulin resistance, and MetS.[57,58] In some cases, the effect culture has on nutritional choices can be detrimental for insulin resistance.[26] One example is the high intake of rice among specific cultures, representing high dietary carbohydrate intake. Many of these behavioral factors can be modified within individuals at risk for MetS. However, given their wide acceptance as part of modern culture and lack of immediate benefit or repercussions, change is difficult.

BIOLOGICAL FACTORS

At the cellular and molecular levels, each of the MetS components has the potential to synergistically influence one another. These simultaneous mechanistic processes alter multiple aspects of metabolism, contribute to specific risk factors, create residual risk, and ultimately generate MetS. In other words, the biological complexity of metabolic pathophysiology translates into various expressions of MetS in susceptible people.

Metabolic Pathways

It is useful to view a common starting pathway as the accumulation of fat in adipose and/or nonadipose tissue (Table 26–3), which increases systemic inflammation and insulin resistance. Pancreatic β-cell dysfunction ensues via degeneration or transformation to inactive cells.[59] Impaired insulin signaling leads to further accumulation of fat mass.[60]

Reduced release and reduced activity of glucagon-like peptide-1 (GLP-1) by L-cells of the distal ileum worsens insulin resistance and drive further increases in adipose tissue.[61] Nutrient sensing within the paraventricular nucleus of the hypothalamus becomes impaired and resistance to leptin develops within the arcuate nucleus.[62] Adiponectin production within adipose tissue is also diminished, which further promotes insulin resistance.[63]

Lipoprotein metabolism is affected by this process. Insulin resistance reduces endothelial and adipose lipoprotein lipase activity, yielding elevated triglycerides.[64] Hepatic lipoprotein synthesis shifts to produce small, dense LDL particles that enter the circulation and are highly atherogenic.[65] Circulating free fatty acids further drive insulin resistance through oxidative stress and accumulation of intracellular derivatives such as ceramides.[66] Visceral fat stores increase, leading to hepatosteatosis and fat accumulation within the pancreas, promoting insulin resistance and β-cell dysfunction.[67,68]

Within the vascular endothelium, insulin resistance also impairs nitric oxide (NO) synthase activity, which diminishes NO production, affecting vasodilation and leading to the development of essential hypertension.[69] Low circulating adiponectin and resistance to leptin induce increased expression of endothelin-1, further driving vasoconstriction and promoting hypertension.[69]

High levels of circulating lipid particles naturally oxidize and are taken up by macrophages that become activated.[70] Free fatty acids also bind toll-like receptor 4 on macrophage cell surfaces.[71] Both processes trigger the release of inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin (IL)-1, and IL-6. These cytokines promote the degradation of insulin receptor substrate-1, a downstream mediator of insulin activity, further driving insulin resistance.[70]

This narrative describing an interconnected cascade of dysregulated energy metabolism provides a candidate molecular basis for MetS as a true emergent syndrome, greater in risk than the aggregate of its individual components. Hence, interventions should target multiple aspects within these processes to mitigate network-based mechanisms (represented by residual risk) involved in the development of MetS.

TABLE 26–3. Areas of Fat Accumulation in Obesity

Class of Fat Deposit	Examples
Peripheral adipose tissue	Extremities
Central adipose tissue	Abdomen
Ectopic adipose tissue	Pericardial, perinephric
Nonadipose tissue	Visceral tissues, skeletal muscle, liver

Genetic and Epigenetic Effects

Very few genes have been identified that specifically confer risk of MetS.[72] This finding is consistent with the relatively unchanged human gene pool over the past century, despite significant increases in the prevalence of obesity and MetS during this time. However, epigenetic phenomena secondary to behavioral and environmental factors have great potential to influence the development of obesity and MetS. One example is the observation that children born to women with obesity prior to bariatric surgery are more likely to develop obesity than their younger siblings born after bariatric surgery and weight loss.[73]

A number of animal studies demonstrate the effect of diet on metabolic regulatory genes through methylation of DNA or methylation/acetylation of histones.[74] For example, leptin gene methylation increases following the consumption of a high-fat diet.[75] Also, hypothalamic proopiomelanocortin gene methylation increases following the consumption of a diet high in fat and sucrose.[76,77] These epigenetic changes can persist in animal models for at least three generations.[78]

Following moderate intense physical activity, skeletal muscle glucose transporter-4 expression is enhanced, promoting insulin sensitivity.[79] Also, there is increased hexokinase and lipoprotein lipase expression, increasing glucose and fatty acid metabolism,[80,81] respectively. In addition, there is activation of peroxisome proliferator-activated γ coactivator-1α, a nuclear receptor cofactor expressed in skeletal muscle that induces expression of genes involved in mitochondrial function.[82]

While specific mechanisms are being worked out, the epigenetic changes that result from modern behaviors over the past several generations are likely to contribute to the increasing prevalence of MetS.

DIAGNOSTIC STRATEGIES

The high prevalence of MetS should trigger aggressive case finding in a large portion of the general population.[1] Signs of obesity, weight gain, hypertension, hyperlipidemia, and hyperglycemia can be early markers

TABLE 26–4. Diagnosis of Metabolic Syndrome

Component of Metabolic Syndrome	Clinical Signs	Diagnostic Tests
Insulin resistance	Acanthosis nigricans, elevated serum glucose	Fasting glucose, 2-hour postprandial glucose, hemoglobin A1C, fasting insulin, oral glucose tolerance test
Hypertension	Elevated blood pressure	Sphygmomanometry
Hyperlipidemia	Elevated triglycerides, Low HDL	Fasting lipid panel (HDL, LDL, triglycerides), adjunct serum lipids including Lp(a), ApoB
Obesity	Increased waist size, increased adiposity	Weight, body mass index, waist circumference
Inflammation		Serum C-reactive protein

Abbreviations: ApoB, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a).

of MetS. People with a family history of T2D, hypertension, and CVD should also be evaluated for MetS. Additionally, the presence of other conditions associated with insulin resistance, such as polycystic ovary syndrome, hepatosteatosis, obstructive sleep apnea, or gestational diabetes, should raise suspicion for MetS. Assigning a diagnosis of MetS to an individual emphasizes the decision to intervene (Table 26–4).

PREVENTIVE CARE

The annual risk of T2D is approximately 2.5% when stratified by fasting glucose.[83] In people with obesity and MetS, the annual risk of T2D is nearly 5%, although annual regression of hyperglycemia is about 10%, emphasizing the need for intensive lifestyle changes as part of a preventive care paradigm.[83] By virtue of its syndromic nature, this preventive care approach to individuals at high risk for MetS should follow the same treatment strategies for MetS. The intensity of intervention should parallel the severity of each MetS component.[1] A striking theme among the major clinical trials investigating individual criteria of MetS is that early, intensive intervention is best at reducing adverse outcomes, especially with the intention of atherosclerotic risk reduction (Table 26–5).[31,84-88]

TABLE 26–5. Prevention and Treatment of Metabolic Syndrome: Therapeutic Interventions

Physical activity	30 minutes daily, moderate intensity: 5 days per week
Dietary pattern	Low-carbohydrate pattern: Mediterranean, NND, Ornish, DASH diets
Pharmacology	Agents that improve insulin sensitivity, lower cholesterol, address hypertension, and induce weight loss
Procedural interventions	Intragastric balloon, duodenal sleeve insertion, bariatric surgery

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; NND, New Nordic Diet.

THERAPEUTIC STRATEGIES

LIFESTYLE INTERVENTION

Once the diagnosis of MetS is made, aggressive interventions should be adopted that in the form of lifestyle changes, pharmacology, or procedures. In early MetS, when the severity of component risks are mild, lifestyle interventions should be implemented that minimize refined carbohydrates, avoid processed foods; favor meats that are lean; and contain large amounts of fruits, vegetables, and fish. Debate continues over the ideal diet, but beneficial dietary pattern examples include the Mediterranean diet, the New Nordic diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Ornish diet. The use of very low carbohydrate diets, such as the Atkins diet, can also be considered. The most important consideration for dietary intervention is the ability of the individual to maintain this new lifestyle over the long term.[89]

DIETARY PATTERNS

The Mediterranean Diet

The relatively low prevalence of atherosclerotic disease in the Mediterranean region prompted interest in the metabolic health benefits of the local diet.[90] There are many types of Mediterranean diets with varying degrees of pork, meat, and wine consumption, depending on the region and specific culture. The key features of this general lifestyle are subject to debate but likely to include a high polyphenol content, a diversity of fruits and vegetables, and healthy protein sources.[91]

Numerous observational studies demonstrate reduced rates of obesity, T2D, and CVD in people consuming a Mediterranean diet.[91] In a large randomized controlled trial, subjects assigned to the Mediterranean diet had the greatest weight loss, as well as significant reduction in LDL, triglycerides, fasting serum glucose, and fasting plasma insulin levels, compared to subjects assigned to a very low carbohydrate diet or a low-fat diet.[92] In another randomized trial, individuals on the Mediterranean diet demonstrated a 30% reduction in cardiovascular events and cardiovascular mortality over 6 years, compared to subjects assigned a low-fat diet.[93] Additionally, there was a 30% reduction in the incidence of T2D among subjects on the Mediterranean diet in this trial.[94]

The content of the Mediterranean diet provides a nutritional basis that addresses many of the molecular mechanisms of MetS. Approximately 30% of calories are derived from carbohydrates in the form of whole grains and fruits, which are high in fiber and in polyphenols. At least three to four fruits are consumed daily. Additionally, three to four servings of vegetables are consumed daily. These are comparable to the recommended fruit and vegetable intake given by the Institute of Medicine, which suggests six to eight total servings daily.[95]

Another 35% to 40% of the total calories of the Mediterranean diet are in the form of fats and oils. Sources include high amounts of olive oil, nuts, cheese, poultry, and fish. These foods are generally rich in n-3 fatty acid content and low in saturated fats. There is a low content of red meat and minimal amounts of refined grains and simple sugars.

A moderate amount of wine consumption is included in most of the Mediterranean diets, which may provide metabolic benefits. A recent randomized trial demonstrated improved fasting blood glucose, reduced fasting insulin, and increased HDL levels in subjects already on the Mediterranean diet that were provided red wine with dinner.[96] These benefits, possibly related to the higher polyphenol content in red wine, were not observed in individuals provided white wine or water. Many other small trials corroborate these results that moderate red wine consumption, defined as zero to one servings of wine daily for women and one to two servings daily for men, may confer clinical benefits in obesity and MetS.[95,97]

Other Dietary Patterns

The Ornish and New Nordic diets are similar to the Mediterranean diet in that they contain high amounts of fruits, vegetables, legumes, and nuts, with minor differences in animal and fish protein sources. A recent large randomized study demonstrates that after 6 months of follow-up, subjects with obesity assigned the New Nordic diet had greater weight loss, reduced fasting serum glucose by 5 mg/dL, reduced fasting insulin, and reduced fasting triglyceride levels by 18 mg/dL, compared to those assigned a western diet.[98] Studies of the Ornish diet are limited in that they are observational in nature. Still, cohort studies of subjects on the Ornish diet demonstrate reduced fasting glucose and hemoglobin A1c levels, as well as reduced total LDL content and shifts to larger LDL particle size.[99,100]

PHARMACOLOGIC INTERVENTION

Insulin Resistance

Although they are not approved by the US Food and Drug Administration, several agents that improve glucose metabolism and potentially reduce insulin resistance are effective treatments for people with MetS. In the Diabetes Prevention Program, the use of metformin reduced the incidence of T2D by 27% in subjects with insulin resistance and increased BMI.[31] In comparison studies focusing specifically on people with MetS, the use of metformin is similar in efficacy to intensive lifestyle interventions and has been shown to reduce weight, fasting serum glucose, triglyceride, and LDL levels.[101] In people taking antipsychotic medication, metformin has been shown to protect against obesity and MetS, with greater efficacy than lifestyle changes alone.[102] Through effects on glucose and lipid metabolism within the liver, metformin can improve hepatosteatosis that is commonly present in people with MetS.[103] Metformin use is also associated with reduced TNFα and increased adiponectin levels when administered to adolescents with obesity, and it raises endothelial NO production, which mitigates MetS development.[104,105] Because of the relative low cost, long history of use, and favorable safety profile, metformin is a first-line agent in the treatment of MetS.

In addition, agents that more directly influence insulin sensitivity can be considered. The GLP-1 receptor analog liraglutide is presently approved for the treatment of obesity and T2D. The class of drugs achieves supraphysiologic plasma GLP-1 activity; serves to supplement the relatively low GLP-1 activity in MetS; and exerts a plurality of beneficial effects, such as improved insulin sensitivity, improved pancreatic β-cell function, activation of central controls of satiety, and reduced hepatic glucose release.[106] Together, these effects lead to weight loss and reduced insulin resistance, which can lead to improved outcomes, although direct confirmatory data are lacking.[106]

Acarbose, an α-glucosidase inhibitor, acts to slow the hydrolysis and absorption of dietary carbohydrates. The use of acarbose in T2D is limited by a relatively low efficacy on serum glucose reduction. However, the preventive use of acarbose in people with obesity and insulin resistance reduces the incidence of T2D by approximately 20%.[107] A post-hoc analysis of subjects with MetS included in this study demonstrates a reduction in the incidence of T2D by 38%.[107]

Pioglitazone and rosiglitazone (thiazolidinediones) activate peroxisome proliferator-activated receptor (PPAR)-γ, which enhances insulin signaling, especially in adipose and muscle tissues. Although these agents have the potential to improve both insulin resistance and lipid profiles in individuals with MetS,[108] concerns about their safety and potential for weight gain may limit their utility in MetS.

Inhibitors of sodium glucose cotransporter type 2 have been approved for treatment of T2D. Mechanistically, these agents prevent reuptake of glucose in the proximal collecting tubules, lowering the renal glucose threshold and promoting glucose excretion within urine.[109] In addition to minimizing hyperglycemia, these agents induce weight loss, increase GLP-1 levels and may preserve normal pancreatic β-cell function.[110] All of these effects would be beneficial in MetS, although studies addressing this specific use have not been conducted. An observed reduction of cardiovascular events with the use of empagliflozin in T2D demonstrates the therapeutic potential for this class of agents.[111]

Weight Loss Pharmacotherapy

Drugs that are directed specifically for weight loss may also be beneficial in the treatment of MetS. In general, currently available weight-loss agents induce a modest weight reduction of 3% to 5% that is maintained over 1 to 2 years of follow-up.[112,113] Lorcaserin reduces appetite through modulation of serotonin receptors within the hypothalamus.[112] The combination of phentermine and topiramate also reduces appetite, although there are concerns for use in patients with underlying CVD resulting from tachycardia induced by phentermine.[113] The combination of Wellbutrin and naltrexone affects both appetite regulation and reward pathways. These agents demonstrate similar degrees of modest weight reduction, although to date, improvements in cardiovascular events and other outcomes have not been demonstrated.

The use of orlistat, a pancreatic lipase inhibitor, may also be beneficial in MetS because of effects of modest weight loss and decreased lipid absorption. Clinical trials of orlistat demonstrate reduced fasting glucose levels, triglycerides, and blood pressure, as well as improvements in hepatosteatosis.[114] These benefits should be weighed against the potential adverse effect of loose bowel movements and malabsorption of fat-soluble vitamins.[115]

Rapid development of novel therapeutic agents for the treatment of obesity continues. Potential targets include ghrelin inhibition, peptide YY analogs, and inhibition of the Dyrk family of proteins involved in the nutrient-sensing cascade.[116]

Hypertension

The treatment targets for hypertension with MetS should be a systolic blood pressure of 120 mm Hg or less.[117] Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers demonstrate the greatest protection from atherosclerotic and renal disease and may be protective against the development of T2D.[87] Agents from either of these classes should be considered as first-line therapy for hypertension in the setting of MetS.[118]

Hyperlipidemia

Treatment targets for hyperlipidemia with MetS should involve lowering LDL cholesterol (< 100 mg/dL)[1,4] while also addressing severe hypertriglyceridemia. The LDL reduction achieved by statin therapy significantly reduces cardiovascular risk in MetS. PCSK-9 inhibitors are presently approved for individuals with familial hypercholesterolemia or those with atherosclerotic disease unable to achieve therapeutic targets with statins. Ezetimibe can be considered as an adjunct to statin therapy, although its LDL-lowering effect is only modest in comparison.

Colesevelam deserves special attention in the case of MetS. This bile acid sequestrant lowers LDL cholesterol by approximately 18% and slows dietary carbohydrate absorption, which lowers serum glucose levels and insulin requirements.[119] Several randomized trials demonstrate reduced incidence of T2D with the use of colesevelam.[120,121] In a trial of men with MetS already taking statins, colesevelam treatment increased insulin sensitivity and reduced fasting serum glucose by 6 mg/dL, postprandial serum glucose by 17 mg/dL, and LDL cholesterol by 22 mg/dL.[119]

Treatment of hypertriglyceridemia is also beneficial. Several large trials suggest pharmacologic intervention in individuals with triglyceride levels greater than approximately 200 mg/dL and HDL levels less than approximately 35 mg/dL can reduce the risk of cardiovascular events.[122-124] Fibrate medications reduce circulating triglycerides through activation of PPAR-α, which increases lipoprotein lipase activity and reduces hepatic triglyceride synthesis. Administration of concentrated long-chain n-3 fatty acids can also reduce hypertriglyceridemia. However, preventive cardiovascular effects of long-chain n-3 supplementation are not consistently demonstrated in clinical trials.[125-127]

PROCEDURAL INTERVENTION

Several surgical and nonsurgical procedures have been developed and approved for the treatment of obesity, but they also mitigate the severity of MetS components. Approved bariatric surgical procedures include the Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), biliopancreatic diversion with or without duodenal switch (BPD), and laparoscopic gastric banding (LGB). Approved nonsurgical procedures include the insertion of a gastric balloon or a duodenal sleeve (endoluminal barrier).[128] Other nonsurgical procedures are being tested and hold promise, including vagal nerve stimulation.[129]

Surgically induced changes in the gastrointestinal tract affect energy physiology, insulin resistance, hypertension, hyperlipidemia, and other weight-related complications.[130] Additionally, many of the factors contributing to MetS improve and the risk of cardiovascular events and mortality is reduced.[131] In people undergoing RYGB, SG, or BPD, insulin resistance improves in the immediate postoperative period, signifying the predominance of improved energy regulatory hormone signaling well before weight loss occurs.[132] Following LGB, insulin resistance declines in association with weight loss.[132] The significant improvement and possible resolution of T2D is also substantially higher following RYGB, SG, and BPD, when compared to LGB.[133-135] These observations suggest that the metabolic benefits of RYGB, SG, and BPD may confer additional improvement to people with MetS.

At present, bariatric surgery is approved for people with BMI of (1) at least 40 kg/m^2 or (2) at least 35 kg/m^2 in the presence of T2D, CVD, or other weight-related complications. Special consideration should be given to people with obesity and MetS, in whom bariatric surgical procedures can drastically alter their risk of atherosclerotic disease and T2D.[136] In the case of people with MetS and mild obesity, defined as a BMI ranging from 30 to 35 kg/m^2 (or just over the BMI cutoff for Asians), clinical evidence is mounting for reduction in the incidence of T2D following bariatric surgery.[137]

Evidence for the reduction in atherosclerotic risk or improvement in components of MetS would be expected at the levels of weight loss associated with nonsurgical procedures for obesity. Specifically, results from current published trials demonstrate reductions in hemoglobin A1C (0.4%–1.6%), LDL, triglycerides, and blood pressure following endoscopic bariatric procedures or gastric electrical stimulation.[128,129]

CONCLUSION

The worldwide epidemic of noncommunicable diseases, especially obesity and diabetes, places a large portion of the population at risk for atherosclerotic CVD. Through complex pathophysiologic mechanisms, the emergence of MetS places those individuals at even greater risk. Clinical interventions should be multifaceted, applied early, and in proportion to the severity of metabolic dysregulation. Changes in lifestyle are the most important approach, with a special focus on beneficial behaviors that can be maintained for the long term. The use of medications to improve insulin sensitivity, induce weight loss, control blood pressure, and address dyslipidemia in concert can mitigate the risk of atherosclerotic disease. Procedural interventions such as bariatric surgery are generally more effective than medication therapy and should be considered in appropriate individuals. The constellation of interwoven etiologies and effects of MetS necessitates a comprehensive, patient-centered clinical approach in a preventive care paradigm.

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CHAPTER 27

OBESITY AND CARDIOVASCULAR DISEASE

W. Timothy Garvey and Jeffrey I. Mechanick

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INTRODUCTION

Prevalence rates of obesity rates have increased sharply worldwide over the past 30 years.[1] Worldwide, the proportion of adults with a body mass index (BMI) of 25 kg/m^2 or greater increased between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women.[2] Prevalence has increased substantially in children and adolescents in developed countries to the point where 23.8% of boys and 22.6% of girls were overweight or obese in 2013.[2] In the United States, data from the National Health and Nutrition Examination Survey (NHANES) show that roughly two out of three US adults are overweight or obese, more than one-third are obese, and 17% of children are obese.[3,4] This has created a global health crisis with a profound impact on morbidity, mortality, and health care costs largely attributable to weight-related complications.

In recent years, accumulating scientific evidence has confirmed that obesity is a chronic disease with interacting genetic, environmental, and behavioral determinants resulting in serious complications.[5,6] In addition, exciting advances have occurred in all three treatment modalities for obesity: lifestyle intervention; pharmacotherapy; and weight-loss procedures, including bariatric surgery.[6-10] Clinical trials have established the efficacy of lifestyle and behavioral interventions in the treatment of obesity, and refinements in surgical approaches and improved preoperative and postoperative care have improved outcomes of bariatric surgery. Importantly, there are now five weight-loss medications approved by the US Food and Drug Administration (FDA) for chronic management.[6-9] These new therapeutic tools together with advances in our scientific understanding of obesity have led to the development of rational medical care models and evidence-based therapeutic approaches with the goal of improving patient health.

PATHOPHYSIOLOGY OF OBESITY: A CHRONIC DISEASE

OBESITY IS A CHRONIC DISEASE

The pathophysiology of obesity produces excess adiposity sufficient to impair health and results from an imbalance between caloric intake and energy expenditure in favor of fat accretion. In 2012, the American Association of Clinical Endocrinologists (AACE) published a position statement designating obesity as a disease.[5] Subsequently, following a proposition submitted by AACE together with multiple other professional organizations, the American Medical Association (AMA) also recognized obesity as a chronic disease in June, 2013.[11] Like many other chronic diseases, genetic factors constitute a substantial component of disease risk[12] that can explain 50% to 60% of individual variation in body weight in monozygotic/dizygotic twin studies. Monogenic forms of the disease are rare, such as in families with leptin or leptin receptor mutations or deletion of the *SNORD116* gene cluster in patients with Prader-Willi syndrome. Susceptibility to obesity in the majority of individuals results from the inheritance of multiple genes with each allele conferring a very small relative risk for the disease. Genome-wide association studies have identified more than 100 susceptibility loci for obesity.[13] Particularly strong association signals have been detected for the fat mass- and obesity-associated gene (*FTO*) and the melanocortin-4 receptor (*MC4R*) gene, but even these variants confer odds for obesity of less than 1.7.[14,15] The multiple susceptibility genes interact with each other and with the environment, behavior, and biological factors to produce individual variation in the risks of obesity, as illustrated in Fig. 27–1. The development of excess adiposity is a complex process; however, those individuals who inherit larger subsets of obesity susceptibility genes will tend to be more overweight in any given environment.[16,17] Progressive weight gain is not a lifestyle choice and cannot be viewed in terms of a simple thermodynamic equation of greater energy in than energy out. Rather, gene-environment interactions generate a human biological and behavioral interface unique to each individual that not only determines body weight but also explains individual variation in the net effect on body weight for any given amount of food intake or physical activity. To this point, among monozygotic twin pairs, the intra-twin changes in body weight are highly correlated in response to overfeeding[18] and underfeeding[19] of the same number of calories, such that if one member of the twin pair lost a greater or lesser amount of weight, so too did the corresponding twin. Thus, the genetic background and/or the common shared environment determined differences in the amount of weight gained or lost in response to an identical degree of caloric excess or deficit.[20]

Obesity fulfills the three essential criteria for a disease established by the AMA (report 4 A-05 of the AMA Council on Scientific Affairs), which are (1) characteristic signs or symptoms, (2) an impairment in normal functioning of some aspect of the body, and (3) a process that

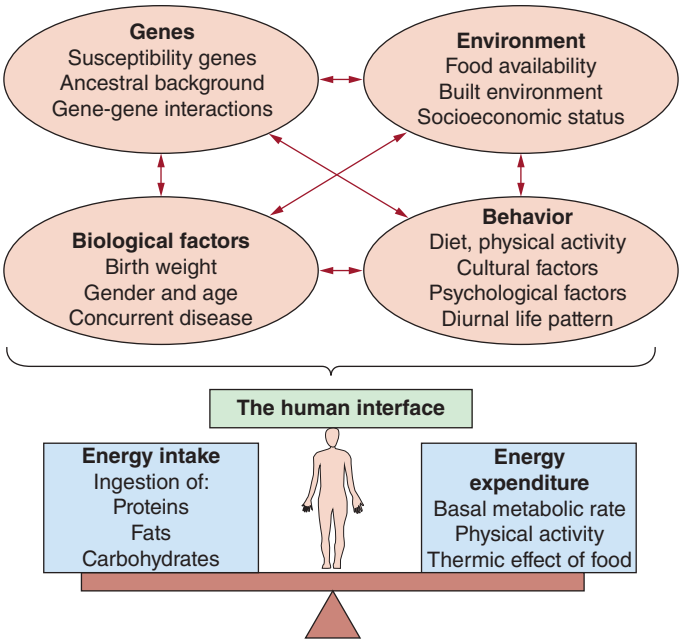

FIGURE 27–1. Pathophysiology of obesity as a chronic disease.

results in harm or morbidity. A defining sign of obesity is an excess of adipose tissue widely measured as BMI, calculated as weight in kilograms divided by height in meters squared (Table 27–1). There are two salient examples of pathophysiology that contribute to an understanding of the obese state: hypothalamic dysfunction and cardiometabolic risk.

DEFECTS IN HYPOTHALAMIC REGULATION OF APPETITE

Homeostatic dysregulation in the hypothalamus adversely affects appetite and satiety as they respond to peripheral hormones that register fuel storage and availability. With obesity, these mechanisms drive an increase in appetite producing a positive energy balance, which generates and maintains a higher body weight.[21,22] By way of illustration, this pathophysiology is fully operational in response to weight loss when compensatory changes in hypothalamic processes result in increased hunger and energy storage, driving weight regain back to the previous high level of body weight.[21] As shown in Fig. 27–2, following a weight-loss intervention, secretion of ghrelin from the stomach is increased above baseline both before and after meals. Ghrelin stimulates neuropeptide Y (NPY) and Agouti-related peptide neurons in the arcuate nucleus of the hypothalamus, causing release of NPY, which activates orexigenic neural pathways leading to an increase in appetite. At the same time, hormones from the gastrointestinal tract and pancreas (eg, leptin, cholecystokinin, glucagon-like peptide-1, amylin, and peptide YY) are reduced below baseline levels.[21] These latter hormones circulate to the hypothalamus and stimulate proopiomelanocortin-expressing neurons in the arcuate nucleus to produce α-melanocyte-stimulating hormone (MSH). The α-MSH binds upstream MC4R receptors to activate anorexigenic neural pathways, resulting in suppression of appetite. The fall in these satiety-producing hormones has an additional effect to stimulate appetite. Furthermore, in response to weight loss, resting energy expenditure rates are decreased, and the energy that muscles use for any given amount of work is also decreased (ie, increased muscle energy efficiency). These energetic changes also promote weight regain.[23] Finally, psychological food preferences become oriented to food of greater caloric density with high fat and sugar content.

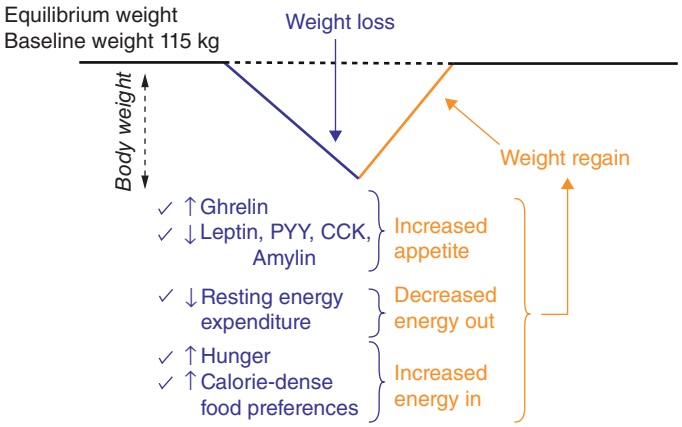

FIGURE 27–2. The pathophysiology of obesity protects against weight loss and maintains a high body weight. CCK, cholecystokinin; PYY, peptide YY.

TABLE 27–1. Classification of Overweight and Obesity by Body Mass Index and Waist Circumference

	Body Mass Index		Waist	
Classification	Measurement (kg/m²)	Comorbidity Risk	Waist Circumference and Comorbidity Risk	
			Men: ≤ 40 in Women: ≤ 35 in	Men: > 40 in Women: > 35 in
Underweight	< 18.5	Low but other problems		
Normal Weight	18.5–24.9	Average		
Overweight	25–29.9	Increased	Increased	High
Obese class I	30–34.9	Moderate	High	Very high
Obese class II	35–39.9	Severe	Very high	Very high
Obese class III	≥ 40	Very severe	Extremely high	Extremely high

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All of these factors promote weight regain and help to maintain a degree of excess adiposity that is harmful to health. In this sense, obesity protects obesity in that hypothalamic set points protect the obese state and resist efforts to reduce adiposity. This makes it challenging for people to maintain a healthy weight. To maintain weight loss, individuals must adhere to therapeutic behaviors or take weight-loss medications that oppose these pathophysiological adaptations (ie, recalcitrant set points) as well as other factors favoring weight regain.

DYSFUNCTIONAL ADIPOSE TISSUE AND THE CARDIOMETABOLIC DISEASE PROCESS

The second dysfunctional aspect of the obese state is adipose tissue itself and the role it plays affecting other organ systems. The BMI is used to estimate overall adiposity; however, an important consideration is the distribution of body fat, which can have significant implications for disease risk. With increases in body weight, accumulation of intra-abdominal fat is central to the pathophysiology of cardiometabolic disease.[24] Cardiometabolic disease risk represents a spectrum of disease manifestations due to common underlying pathophysiological mechanisms that begins with insulin resistance, progresses to the clinically identifiable high risk states of metabolic syndrome (MetS) and prediabetes, and finally to type 2 diabetes mellitus (T2D), cardiovascular disease (CVD), or both in individual patients.[25] Based on animal models, primarily murine, and human studies, fat accumulation in visceral adipose tissue is accompanied by an influx of macrophages, the production of proinflammatory cytokines (eg, interleukin-6 [IL-6]), adipocyte insulin resistance, and the dysregulated secretion of adipokines such as adiponectin and resistin.[26-29] Altered levels of circulating adipokines affect metabolism in various organs (eg, liver, muscle, vascular wall), and this helps produce the MetS trait complex. For example, serum adiponectin levels are decreased, which exacerbates systemic insulin resistance and promotes atherogenesis through loss of adiponectin's effect to suppress foam cell formation.[30]

Another aspect of dysfunctional fat is the diminished ability to store lipid. This causes a redistribution of fat to the intra-abdominal compartment and the accummulation of lipid within muscle cells and hepatocyes, which further exacerbates insulin resistance at the level of these organs and contributes to abnormal glucose tolerance. Generalized obesity can exacerbate insulin resistance by augmenting lipid accumulation in muscle, liver, and the visceral compartment, and thus it further impels progression of cardiometabolic disease toward the end-stage manifestations of overt T2D and CVD.[31] Obesity alone, however, is not a prerequisite for cardiometabolic disease, and it is not sufficient as a cause of such disease because even lean individuals can be insulin resistant, and obese indivuals can be insulin sensitive with no manifestations of MetS.[25] Nevertheless, weight loss in overweight/obese individuals with insulin resistance and cardiometabolic disease represents highly effective therapy. These principles and the spectrum of cardiometabolic disease are illustrated in Fig. 27–3.

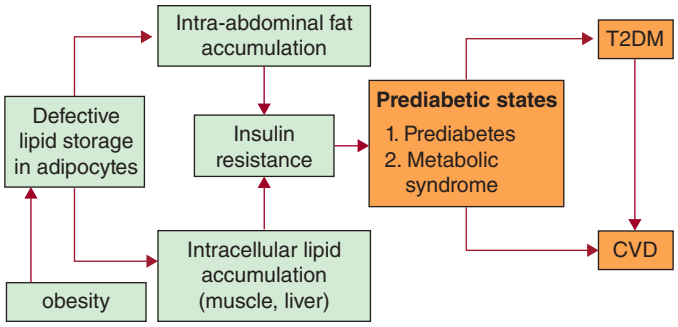

FIGURE 27–3. The spectrum of cardiometabolic disease. Insulin resistance represents the initial lesion beginning early in life. This includes insulin resistance in adipocytes and defective capability for lipid storage, with accumulation of lipid in muscle and liver cells and in the intra-abdominal depot. There is the eventual transition to the clinically identifiable high-risk states of prediabetes and metabolic syndrome. These individuals are then at high risk for developing type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) events, or both. Thus, the operant pathophysiological mechanisms give rise to both metabolic and vascular disease components.

OBESITY, CIRCADIAN RHYTHMS, SLEEP, AND CARDIOMETABOLIC RISK

Lifestyle plays a central role in the expression of the obese state comprising not only dietary patterns, physical activity, and stress, but other factors as well, including sleep hygiene and the emerging science of chronobiology.[32] Hierarchical regulatory levels ultimately determine circadian changes in appetite, energy consumption, adipocyte function, and body composition. These grossly consist of (1) photic entrainment by the retinal-hypothalamic pathway, (2) oscillators in the suprachiasmatic nuclei of the hypothalamus (master clock), (3) neuronal and hormonal (eg, glucocorticoid) coordination of peripheral clocks (eg, gastrointestinal, pulmonary, and fat), (4) transcription-translation feedback loops involving clock genes (eg, Clock, Bmal1, Per1-3, Cry1-2, Chrono, Rev-erbα, and Rorα), and many downstream clock-controlled genes.[32] Food intake also entrains circadian rhythmicity via nutrients (eg, glucose, amino acids, sodium, ethanol, caffeine, thiamin, and retinoic acid), hormones (eg, glucagon, leptin, and ghrelin), cellular energy signals, and various transcription factors.[32] Chronodisruptors that are associated with obesity include frequent flying, shift work, disturbed eating patterns, and certain macronutrient distributions (eg, high fat).[32] Considering the increased risk of myocardial infarction from 6:00 a.m. to noon, it is not surprising that there may be chronobiological mechanisms mediating the association of obesity with CVD.[33]

Potential targeted interventions addressing chronodisruptor-related weight gain include healthy dietary patterns, structured and consistent sleep-wake cycles, decreasing artificial light exposures, and improved sleep hygiene, with pharmacological modalities currently under investigation.[32,34] More specifically, disrupted sleep during critical weight gain periods in young adulthood, as well as short sleep durations (< 6–9 hours/night) and other causes of sleep debt (eg, television/computer screen time and long commuting hours), affect appetite and energy balance (via hormones, such as insulin, cortisol, ghrelin, leptin, NPY, and orexin). Poor sleep hygiene is associated with obesity, T2D, CVD, and total mortality, and it should be targeted therapeutically.[35-41]

Obesity markedly augments risk of obstructive sleep apnea, which interrupts normal sleep with periods of hypoxia. This establishes a vicious cycle whereby progressive weight gain exacerbates sleep apnea and sleep apnea promotes further weight gain.[38,42] Obstructive sleep apnea adversely affects psychological health causing fatigue and depression, metabolic health by predisposing to metabolic syndrome and T2DM, and cardiovascular health as an independent risk factor for refractory hypertension, stroke, and CVD.[43-47] The therapeutic options for obstructive sleep apnea include continuous positive airway pressure therapy and weight loss.[48,49] Severity of sleep apnea is quantified by the apnea-hypopnea index (AHI), which reflects the average number of apneic/hypopneic episodes per hour during a polysomnography study.[45] Weight loss, whether achieved by lifestyle therapy[49] or obesity medications,[49] can dramatically improve both AHI scores and symptomatology; however, therapeutic benefits are most predictably achieved with at least 10% weight loss.[48,50]

RELATIONSHIP BETWEEN OBESITY AND CARDIOVASCULAR DISEASE

The association between obesity and CVD has been extensively investigated using the end points of CVD events, CVD mortality and all-cause mortality, which are interrelated given that CVD is the most common cause of death in many societies. Numerous epidemiological cohort studies have reported a U-shaped or J-shaped relationship between mortality and BMI. In all studies, there is an optimal range of BMI above and below which increasing or decreasing BMI values begin to be associated with increasing rates of CVD events and mortality. The controversy essentially involves BMI in the overweight range (25–29.9 kg/m^2). When compared with lean subgroups (18.5–24.9 kg/m^2), various studies have reported that the overweight subgroup is associated with either increased, decreased, or unchanged rates of CVD and mortality rates.[51-55] Therefore, the optimal BMI with respect to mortality has not been identified over a range that includes both normal and overweight individuals, and it is affected by gender, ethnicity, age, and body fat distribution. One criticism of studies reporting that overweight status is associated with reduced mortality versus the lean subgroup is the confounding effects of reverse causality where preexisting diseases in the lean subjects both increase mortality and cause weight loss (eg, cigarette smoking and cancer).[55,56] The Prospective Studies Collaboration conducted a meta-analysis assessing the association between BMI and mortality in 894,576 participants in 57 prospective studies and observed that mortality was lowest at BMI 22.5 to 25 kg/m^2.[57] Above this range, each 5 kg/m^2 higher BMI was on average associated with about 30% higher overall mortality, including significant increments in mortality risk within the overweight subgroup. BMI below 22.5 kg/m^2 was associated with greater overall mortality, largely resulting from respiratory disease and lung cancer.

It is important to consider that the association between BMI and CVD is largely explained by its association with other risk factors, such that independent risk conferred by BMI is usually minimized in multivariate analyses. For example, when adjusted for waist circumference or the presence of MetS, BMI is no longer a significant independent risk factor for CVD or becomes a much weaker predictor.[25,58-60] Cardiometabolic disease risk (ie, risk for both CVD and T2D) conferred by BMI and MetS traits has been examined in the Atherosclerosis Risk in Communities Study (ARIC) over a 20-year follow-up.[61] Regarding overall survival, coronary heart disease cumulative incidence, and stroke cumulative incidence, the presence of MetS was more predictive of outcomes than BMI status as shown in Fig. 27–4. Subjects with MetS at baseline had higher risks of CVD outcomes than metabolically healthy individuals with no MetS traits regardless of BMI status. BMI status as lean, overweight, and obese did not substantially affect risk in patients with the MetS or in metabolically healthy subjects having no MetS traits. Risk for T2D was somewhat different (see Fig. 27–4). In the metabolically healthy subgroup, cumulative rates of T2D remained low; however, the relative risk did increase with progressive increases in BMI from lean to overweight to obese. Among patients with the MetS, cumulative incidence rates of T2D where much higher and the rise in BMI produced a much greater effect to augment cumulative incidence. Notably, lean unhealthy subjects with MetS displayed a more than two-fold increase in cumulative diabetes when compared with obese metabolically healthy individuals. Thus, weight gain against an insulin-sensitive background (ie, metabolically healthy) exerts a relatively small effect to increase cumulative incidence of T2D but can significantly augment T2D risk in insulin-resistant patients with MetS.[61]

Regarding congestive heart failure (CHF), the presence of overweight or obesity may be protective against mortality, referred to as the *obesity paradox*. Elevations in BMI are associated with increased risk of developing CHF in part by predisposing to hypertension, T2D, sleep apnea, and CVD. However, once patients present with CHF, the presence of overweight and/or obesity has been observed to be protective regarding risks of future CVD mortality and hospitalizations when compared with lean individuals.[62-64] Again, better outcomes in overweight or obese subjects may reflect reverse causality resulting from processes that both lower body weight and increase mortality (eg, cardiac cachexia and cigarettes).

THE DIAGNOSIS OF OBESITY

BODY MASS INDEX: THE ANTHROPOMETRIC COMPONENT OF THE DIAGNOSIS OF OBESITY

The BMI is widely used in the screening, diagnoses, and classification of patients with obesity. The criteria established by the World Health Organization in 1998[65] are shown in Table 27–1. BMI values 18.5 to 24.9 kg/m^2 are indicative of lean individuals, BMIs 25 to 29.9 kg/m^2 overweight, and BMIs of 30 kg/m^2 or more represent obesity categorized as obese class I (BMI 30–34.9), obese class II (BMI 35–39.9), or obese class III (BMI ≥ 40). The BMI values are used in conjunction with waist circumference measurements as an addition indicator of comorbidity risk. These criteria were soon thereafter adopted by the National Institutes of Health,[66] which promulgated their widespread application in epidemiology and medicine. In South Asian, East Asian, and Southeast Asian populations, health is adversely affected at lower levels of BMIs, and alternate criteria have been advocated, with BMIs of 18.5 to 22.9 kg/m^2 indicative of normal weight, 23 to 24.9 kg/m^2 overweight, and 25 or more kg/m^2 obese.[67] Waist circumference cutoff points to indicate increased risk of cardiometabolic disease also exhibit regional and ethnic variations.[68]

BMI is an anthropometric measure that interrelates the height and weight of individuals, and, therefore, is only an indirect measure of adiposity of total body fat mass. BMI incorporates lean mass, fat mass, bone mass, and fluid status, all of which can vary independently from fat mass. BMI will overestimate adiposity in athletes with high muscle mass and in patients with edema and will underestimate adiposity in elderly patients with sarcopenia. For this reason, patients with elevated BMI measurements must be clinically evaluated to confirm excess adiposity.

WEIGHT-RELATED COMPLICATIONS: THE CLINICAL COMPONENT OF THE DIAGNOSIS OF OBESITY

Another limitation of BMI is that it does not indicate the impact of excess adiposity on the health of individual patients.[69] The adverse effect of excess adiposity on health is manifest by the development of weight-related complications and the emergence of risk factors for those complications. Although the likelihood of weight-related complications generally increases as a function of progressive obesity, there can be a poor correlation between BMI and the development of complications. Patients with obesity need not have weight-related complications and can be free of disease-related morbidity and mortality, as illustrated in Fig. 27–4. Therefore, individuals who meet the anthropometric criterion for overweight or obesity must then undergo a clinical evaluation for the presence or absence of weight-related complications.[7,69] The identification of complications and their severity are important for two reasons in patients with overweight or obesity. First, the presence and severity of complications or relevant risk factors will indicate the need for more aggressive therapy to improve the health of individual patients. Second, because these complications can be

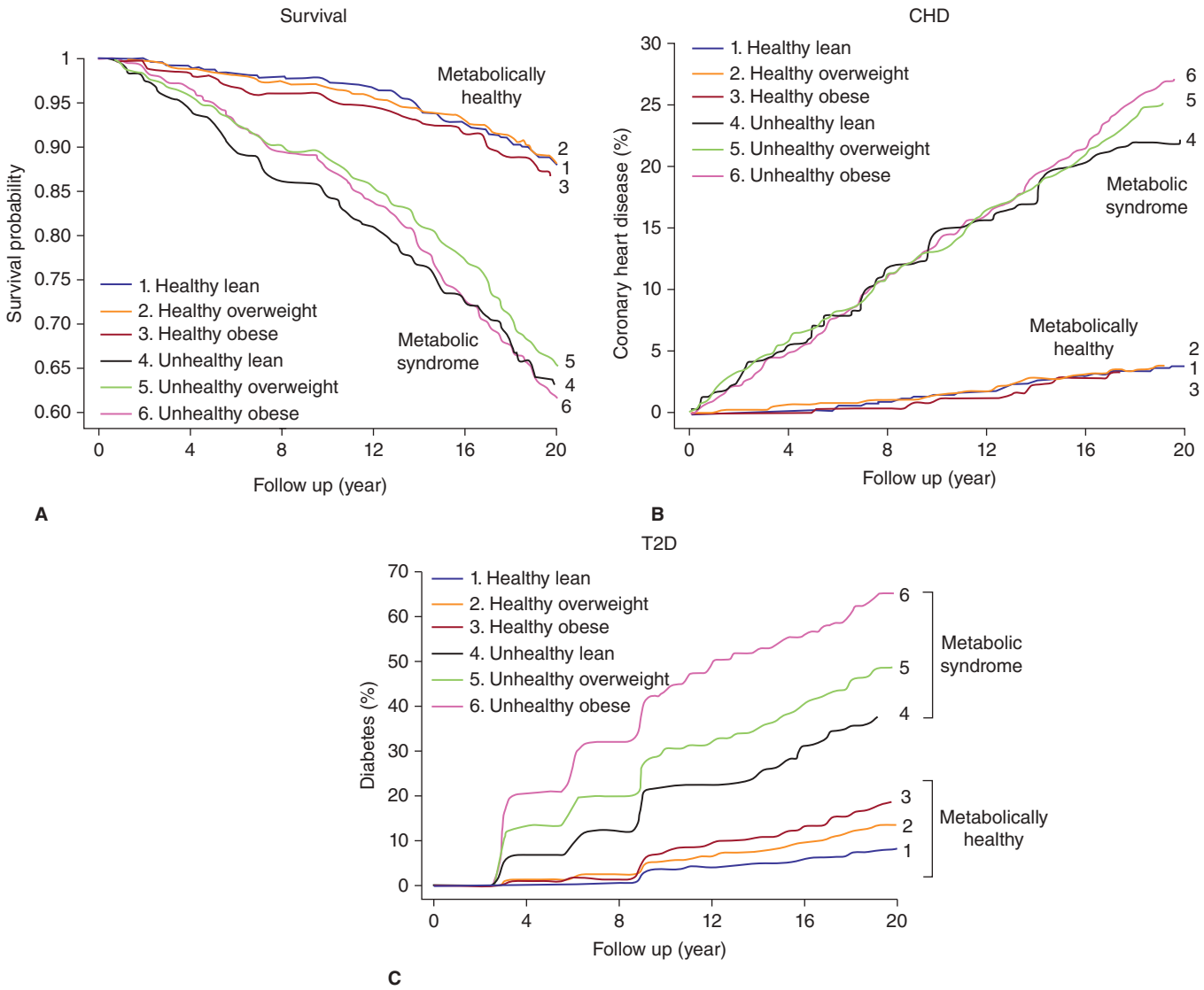

FIGURE 27–4. Survival probability (**A**), and cumulative incidence of coronary heart disease (CHD) as myocardial infarction or coronary death (CHD) (**B**), and type 2 diabetes (T2D) (**C**) according to cardiometabolic health and body mass index status (lean, overweight, obese) in subjects from the Atherosclerosis Risk in Communities study. Metabolically healthy have no metabolic syndrome traits. Metabolic syndrome determined using ATP III criteria. Adapted with permission from Guo F, Garvey WT: Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: Stability of metabolic health status in adults. *Obesity (Silver Spring)*. 2016 Feb;24(2):516-525.[61]

improved or reversed by weight-loss therapy, the evaluation will establish therapeutic targets for weight loss and the integration of these goals as desired outcomes into the therapeutic plan. From this perspective, the goals of weight-loss therapy are to improve the health of patients with obesity by treating and preventing weight-related complications. This is consistent with the "complications-centric" approach to obesity management advocated by the AACE.[5,69,70]

The evaluation for the presence and severity of weight-related complications represents the clinical component of the diagnostic evaluation for obesity.[69] Health care professionals should screen patients for common weight-related complications as illustrated in Table 27–2. The identification of complications does not involve an extensive or extraordinary degree of testing but can be ascertained in the course of an initial patient evaluation consisting of medical history, review of systems, physical examination, and laboratory studies. In the initial evaluation, the clinician will need to (1) pay particular attention to the relevant aspects of the history and examination and (2) conduct an obesity-focused review of systems assessing potential symptomatology of weight-related complications. In many cases, the information gathered in the initial examination is sufficient for the diagnosis of certain weight-related complications. For other complications, the initial information augments the degree of suspicion and additional testing consistent with standards of care is then necessary to confirm the diagnosis and for staging the severity of the complication. Depending on the expertise of the clinician, referral may be indicated for further evaluation and treatment of specific complications.

IMPACT OF WEIGHT LOSS ON CARDIOVASCULAR DISEASE AND CARDIOVASCULAR DISEASE RISK FACTORS

EFFECTS OF WEIGHT LOSS ON CARDIOVASCULAR DISEASE RISK FACTORS

Weight loss, whether due to lifestyle therapy, weight-loss medications, or bariatric surgery, has been shown to (1) enhance insulin sensitivity; (2) improve hepatic steatosis and reduce intracellular lipid content

TABLE 27–2. Screening and Diagnoses of Weight-Related Complications in Patients with Overweight/Obesity—the Clinical Component of the Diagnosis

Weight-Related Complication Checklist	Clinical Evaluation	Clinical Data	Diagnosis
☑ Prediabetes	Laboratory	Fasting glucose; HbA1c	Fasting glucose 100–125 mg/dL; 2-hour OGTT glucose 140–199 mg/dL; HbA1c 5–7–6.4%
	Family history	Positive for diabetes	
☑ Metabolic syndrome	Examination	Waist circumference, blood pressure,	Waist circumference ≥ 40 inches in men and ≥ 3 5 inches in women; BP ≥ 130/85 mmHg; fasting glucose ≥ 100 mg/dL; triglycerides ≥ 150 mg/dL; HDL-c ≤ 40 mg/dL in men and 50 in women
	Laboratory	Fasting glucose, triglycerides, HDL-c	
	Family history	Positive for diabetes and/or cardiovascular disease	
☑ Type 2 diabetes	ROS	Symptoms of hyperglycemia	Overtly elevated glucose (≥ 200 mg/dL); repeat fasting glucose ≥ 126 mg/dL; 2-hour OGTT glucose ≥ 200 mg/dL; HbA1c ≥6.5%
	Laboratory	Fasting glucose; HbA1c;	
	Family history	Positive for diabetes	
☑ Hypertension	Examination	Elevated BP	Repeated measurements ≥ 140/90 mmHg (without other risk factors)
☑ Dyslipidemia	Laboratory	Lipid panel (total cholesterol, HDL-c, triglycerides, LDL-c, non-HDL-c)	Triglycerides ≥ 150 mg/dL; HDL-c ≤ 40 mg/dL in men and 50 in women; LDL-c ≥ 100 or 130 mg/dL lipoprotein subclasses, apolipoprotein B-100 may further define risk
☑ Nonalcoholic fatty liver disease	Examination	Firm or enlarged liver	Elevated hepatic transaminases; abnormal imaging (eg, ultrasound, magnetic resonance imaging, elastography); liver biopsy
	Laboratory	Liver function tests (see Metabolic syndrome)	
☑ Polycystic ovary syndrome	Examination	Hirsutism, ovarian cysts	Elevated androgen levels; oligo- or chronic anovulation; polycystic ovaries
	ROS	Hirsutism, menstrual irregularities, infertility	
	Laboratory	Androgen levels, LH/FSH (see Metabolic syndrome)	
☑ Obstructive sleep apnea	Examination	Neck circumference	Polysomnography needed to complete diagnosis
	ROS	Positive symptoms	
☑ Osteoarthritis	Examination	Joint tenderness, crepitance, structural changes	Radiographic imaging may be needed to complete diagnosis
	ROS	Joint pain, decreased function	
☑ Urinary stress incontinence	ROS	Urge or stress incontinence	Urine culture, urodynamic testing may be needed to complete diagnosis
☑ GERD	ROS	Esophagitis symptoms	Endoscopy, esophageal motility study may be needed to complete diagnosis
☑ Disability	Examination	Decreased mobility	Functional testing may be helpful
	ROS	Impaired function daily activities	
☑ Depression/stigmatization	ROS	Symptoms of depression, binge eating disorder	Psychological testing and evaluation may be needed to complete diagnosis
☑ Obesity secondary to hormonal disorder	Examination	Hyper-/hypothyroid manifestations; hypercortisolism manifestations	Thyroid-stimulating hormone for suspected hypothyroidism; saliva/serum/urine cortisol for hypercortisolism, if clinical findings or symptoms present
	ROS	Symptoms of hyper-/hypothyroidism, hypercortisolism	
	Laboratory	Hormonal testing	
☑ Iatrogenic obesity (eg, secondary tomedications)	History	Review current medications and medication history	Follow-up following withdrawal of offending medication and/or substitution with weight-neutral alternative

Abbreviations: BP, blood pressure; FSH, follicle-stimulating hormone; Hb, hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LH, luteinizing hormone; OGTT, oral glucose tolerate test; ROS, review of symptoms.

in skeletal muscle as well as liver; (3) prevent or delay progression to T2D, particularly in high-risk patients with prediabetes or MetS; (4) effectively reduce CVD risk via improvements in blood pressure and lipids; and (5) improve biomarkers of CVD risk, including C-reactive proteins, IL-6 and other markers of inflammation, fibrinogen levels, and serum adiponectin concentrations.[71] Thus, weight loss is perhaps the most effective therapeutic approach for treating and preventing the progression of cardiometabolic disease (see Fig. 27–3) via improvements in the core physiological processes that confer risk of future T2D and CVD events.

Three major randomized clinical trials, the Diabetes Prevention Program,[72] the Finnish Diabetes Study,[73] and the Da Qing Study,[74] all demonstrated the impressive efficacy of lifestyle/behavioral therapy to prevent T2D. In these studies, lifestyle modifications generally involved reductions in caloric intake by 500 to 1000 cal/d, behavioral interventions, and increases in physical activity. The Diabetes Prevention Program study randomized subjects with impaired glucose tolerance to ordinary care, metformin, and lifestyle intervention subgroups, and after 4 years, lifestyle modification reduced progression to T2D by 58% and metformin by 31%, compared with placebo. Subjects achieved approximately 6% mean weight loss at 2 years and approximately 4% weight loss at 4 years in the lifestyle intervention arm, and there was a progressive 16% reduction in T2D risk with every kilogram of weight loss.[75] With observational follow-up after termination of the study,

there was still a significant reduction in the cumulative incidence of T2D in the lifestyle treatment group at 10 years, despite the fact that BMI levels had equalized among the three treatment arms.[72] In addition to the reductions in T2D, there was also evidence in the Da Qing Study that CVD events and mortality were reduced after 23 years when comparing the combined subgroups treated with diet and exercise compared with the controls.[76]

Hypertension is an established consequence of overweight and obesity. It is therefore not surprising that one of the associated benefits of weight reduction is lowering blood pressure. A meta-analysis of eight studies involving more than 2100 participants who were randomized to either a weight-reducing diet or a control intervention demonstrated that weight loss led to decrements in blood pressure of 4.5/3.2 mm Hg together with a 4.0-kg decrease in body weight compared with the control groups after follow-up of 6 to 36 months.[77] The results of this meta-analysis are consistent with earlier analyses suggesting that BP decreased by 1.2/1.0 mm Hg for every kilogram of weight lost. A weight-reducing diet based on the Dietary Approaches to Stop Hypertension (DASH) plan with a lower sodium intake and moderate or no alcohol intake has been shown to be an effective nonpharmacologic approach to reduce blood pressure.[78]

The dyslipidemia associated with obesity and insulin resistance is characterized by elevations in triglyceride levels (eg, 150–400 mg/dL); reduced high-density lipoprotein (HDL) cholesterol; and increased concentrations of small, dense low-density lipoprotein (LDL) particles.[79] Hypertriglyceridemia is largely due to excess production of large triglyceride-enriched very low-density lipoprotein (VLDL) particles by the liver, and it is responsive to alterations in macronutrient composition, increased physical activity, and restriction of alcohol. Because carbohydrates can drive hepatic VLDL production, ingested carbohydrates, particularly sugars and refined carbohydrates, should be reduced and replaced with unsaturated fats and protein.[80] Weight loss has additional beneficial effects on lipids and lipoproteins. Weight loss of 5% to 10% has been shown to amplify the benefits of changes in macronutrient composition resulting in a 20% decrease in triglycerides, a 15% reduction in LDL cholesterol, and an 8% to 10% increase in HDL cholesterol. However, greater degrees of weight loss can achieve progressive improvements in dyslipidemia. Meta-analyses have reported that for every kilogram of weight loss, triglyceride levels decrease about 1.9% or 1.5 mg/dL.[81] Furthermore, there are beneficial effects of weight loss on LDL subclasses characterized by reductions in small, dense LDL particle concentrations and an increase in medium and large LDL particles, coupled to a mean increase in LDL particle size and reductions in total LDL particle concentration.[82,83]

STAGING AND STRATIFICATION OF CARDIOMETABOLIC DISEASE RISK

The prevalence of overweight and obesity can approximate 70% of the population in some societies, and not all obese patients are insulin resistant with cardiometabolic disease. The presence of overweight/obese subjects with no MetS risk factors (metabolically healthy obese) has been well documented, and these individuals exhibit lower rates of future T2D, CVD events, and mortality.[25,84-87] Therefore, estimates of cardiometabolic disease risk can be used to identify patients at greatest risk for future T2D and CVD in order to target more aggressive weight-loss therapy to those individuals who will receive the greatest benefit.

The clinician should evaluate patients for MetS and prediabetes, because this effectively identifies individuals at high risk for future T2D and CVD. However, MetS and prediabetes have high specificity but low sensitivity for identifying patients with insulin resistance and cardiometabolic disease,[86,88] and these entities alone will not identify significant proportions of at-risk patients. Various indices using information from history and physical examination, such as the American College of Cardiology (ACC)/American Heart Association (AHA) Omnibus risk estimator,[89] Framingham Coronary Heart Disease Risk Score,[90] the Reynolds Risk Score,[91] or commercial products that use clinical laboratory assays, can be used to stage risk in insulin resistant patients whether or not they meet diagnostic criteria for MetS or prediabetes.

Another approach to cardiometabolic disease risk stratification for the patient with obesity is the Cardiometabolic Disease Staging system (CMDS)[25,92] shown in Fig. 27–5. CMDS defines five stages of risk that are based on established physiological and epidemiological observations. These are (1) the presence of the metabolically healthy obese with no MetS traits (stage 0); (2) the fact that patients with one or two risk factors are at increased risk of T2D and CVD even if they do not meet criteria for MetS or prediabetes (stage 1); (3) the documented risk conferred by the presence of having only one of the risk states of MetS or impaired fasting glucose or impaired glucose tolerance (stage 2); (4) the augmented risk for T2D and CVD in patients having both MetS and prediabetes (stage 3); and (5) patients with end-stage cardiometabolic disease who have either T2D (a cardiovascular disease risk

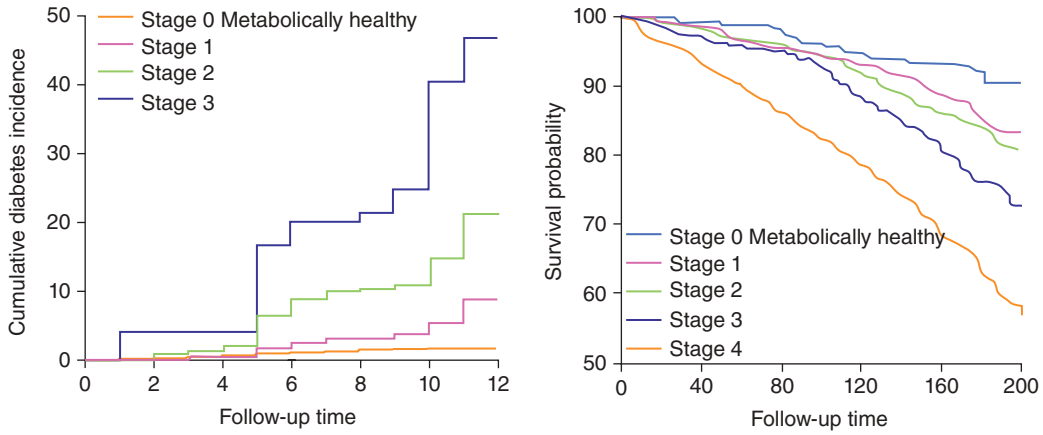

FIGURE 27–5. Cardiometabolic disease staging (CMDS) quantitatively stratifies risk for type 2 diabetes (left) and survival probability (right) using available clinical information. Cumulative rates of incident diabetes were generated from the CARDIA study cohort and survival probability using data from NHANES III. The system can be used to guide aggressiveness of weight loss therapy and optimize benefit/risk ratio for interventions. Adapted with permission from Guo F, Moellering DR, Garvey WT: The progression of cardiometabolic disease: validation of a new cardiometabolic disease staging system applicable to obesity. *Obesity (Silver Spring)*. 2014 Jan;22(1):110-118.[25]

equivalent) and/or CVD (stage 4). Advancement of CMDS stage 0 to 4 was validated to predict increasing risk of diabetes using data from the national Coronary Artery Risk Development in Young Adults (CARDIA) cohort, as well as all cause and CVD mortality using NHANES data.[25,92] Thus, CMDS utilizes information that is readily available to the clinician in the context of routine clinical practice to quantitatively stratify risk of both T2D and CVD.

EFFECTS OF WEIGHT LOSS ON CARDIOVASCULAR DISEASE EVENTS AND MORTALITY

It is difficult to assess an independent effect of weight loss on CVD events and CVD mortality for several reasons: (1) the confounding effect of treatment targeted to risk factors can affect mortality (eg, statins, angiotensin-converting enzyme inhibitors); (2) the need to include only intentional weight loss in cohort studies and exclude unintentional weight loss; (3) studies that largely do not differentiate between patients with obesity with and without CVD risk factors, which could be the basis of heterogeneity in the response to weight loss; and (4) the need for long-term interventions and follow-up. Weight loss produces improvements in CVD risk factors as indicated by improvements in blood pressure, lipids, glycemia, waist circumference, and various biomarkers. However, the question remains whether these effects translate into reductions in CVD events and mortality.

There are few, if any, long-term randomized clinical trials (RCTs) assessing effects of weight loss on CVD events and/or mortality as a predetermined primary outcome measure. Most RCTs involve short-term lifestyle interventions and do not demonstrate significant reductions in mortality when compared with control groups. One example is the Action for Health in Diabetes (Look AHEAD) study in patients with T2D randomized to intensive lifestyle therapy versus standard care, which prespecified mortality as an outcome. Although weight loss improved glycemia, lowered blood pressure, and improved lipids, the Look AHEAD study was discontinued prematurely because lack of effect of the intensive lifestyle intervention on mortality compared with standard care.[93] However, two meta-analyses of relevant RCTs have demonstrated that lifestyle-induced weight loss was associated with decreased mortality and CVD outcomes.[94,95] Large cohort studies have shown that intentional weight loss is associated with reduced mortality, particularly in subjects with weight-related complications such as T2D,[96,97] including long-term follow-up following a lifestyle intervention in the Da Qing study[77] and following bariatric surgery in case-control cohort studies such as the Swedish Obese Subjects study[98] and a study involving Veterans Affairs Medical Centers.[99] The data suggest that weight loss of more than 15% body weight is more likely to be associated with efficacy in this regard. Cardiovascular outcome trials assessing all four weight-loss medications (see below) approved by the FDA between 2012 and 2014 are ongoing or planned.

TREATMENT OF OBESITY

Treatment of patients with obesity incorporates three therapeutic modalities: lifestyle therapy, pharmacotherapy, and bariatric surgery.[6-9]

LIFESTYLE THERAPY

Lifestyle therapy is the cornerstone of therapy for patients with obesity. It can constitute the sole approach to treatment, but it must also accompany treatment using weight-loss medications or bariatric surgery. The components of lifestyle therapy include a reduced-calorie healthy meal plan, a prescription for increased physical activity, and a package of behavioral interventions that are designed to promote adherence with the meal plan and physical activity. Lifestyle therapy is most effective for weight loss when delivered as a structured program with flexibility to accommodate the personal and cultural preferences of patients. The components of a structured lifestyle intervention can be delivered by a multidisciplinary team consisting of primary or specialty medical care professionals, health educators, dietitians, nurses, exercise trainers, and psychologists, and it may involve a variety of venues in the clinic and in the community. Commercial programs featuring meal substitutes or delivered meals and interventions using remote technologies (telephone, text, Internet) have also been shown to be effective.

Reduced Calorie Healthy Meal Plan

The most important aspect of lifestyle therapy is a reduction in caloric intake, amounting to a 500- to 1000-kcal/d deficit in most instances. This can be achieved in the format of a healthy meal plan that provides all needed micronutrients and avoids processed foods. Examples of healthy meal plans include low carbohydrate, low fat, low glycemic index, DASH, Mediterranean, and vegetarian. The macronutrient composition is less important than the patient's ability to adhere with the diet. Therefore, the meal plan should be individualized and selected to be compatible with the personal and cultural preferences of the patient. The use of meal substitutes in the form of shakes and bars add structure to the diet and have been shown to be effective. The patient should also be instructed in approaches to portion control and stimulus control.

Increased Physical Activity

A physical activity prescription can modestly increase caloric expenditure and is particularly helpful for maintaining lean body mass during weight loss and in helping sustain weight loss over a longer interval. The physical activity program optimally includes aerobic exercise, which should begin at a low level allowing the patient to increase the intensity and duration of the exercise over time. Ideally, the patient will achieve at least 150 minutes per week of moderately intense aerobic exercise accomplished in three to five sessions.[100] The combination of aerobic and resistance exercise provides better outcomes than either form of exercise per se. Therefore, a resistance exercise program should be added consisting of single-set repetitions targeting the major muscle groups two to three times per week. A final component of a physical activity program is to reduce sedentary behavior and increase active leisure activity. The physical activity prescription should be compatible with patient preferences and take into account any health-related or physical limitations.

Behavioral Therapy

Lifestyle therapy in patients with overweight or obesity should include behavioral interventions that enhance adherence to prescriptions for a reduced-calorie meal plan and increased physical activity. RCTs have not only demonstrated the efficacy of lifestyle therapy programs that include behavioral interventions but have underscored those practices that are most likely to be associated with success.[73-75,101] Effective practices include self-monitoring of weight, food intake, and physical activity. Patient education is also advantageous pertaining to obesity, nutrition, and physical activity, which can be delivered face-to-face, in group meetings, or using remote technologies (telephone, texting, and Internet). The program should also feature clear and reasonable goal setting, strategies for stimulus control, and systematic approaches for problem solving and stress reduction. Other components can include cognitive restructuring (ie, cognitive behavioral therapy), motivational interviewing, behavioral contracting, and mobilization of social support structures. Obesity can often be associated with depression,

disordered eating (eg, binge eating disorder), anxiety, and other psychiatric disorders, which can impair the effectiveness of lifestyle interventions. For this reason, psychological counseling and psychiatric care may be necessary. The behavior intervention package is effectively accomplished by a multidisciplinary team that can include combinations of the following: dietitians, nurses, health educators, physical activity trainers or coaches, and clinical psychologists. As with the meal plan and physical activity components, behavioral lifestyle intervention should be tailored to a patient's ethnic, cultural, socioeconomic, and educational background.

WEIGHT-LOSS MEDICATIONS

Since 2012, there have been four new weight-loss medications approved for the chronic treatment of obesity by the FDA.[6-9] These medications are in addition to orlistat (120 mg), approved in 1999, which was the only preexisting medication for long-term pharmacotherapy and the only one currently permitted in Europe and many other countries. The newer medications include lorcaserin, phentermine/topiramate extended-release (ER), naltrexone ER/bupropion ER, and high-dose liraglutide (3 mg). The availability of these new medications has greatly expanded treatment options for patients with obesity and has led to more robust approaches to patient management.[7] All these medications are approved in the United States as adjuncts to lifestyle modification in overweight patients with BMIs of 27 to 29.9 kg/m^2 having at least one weight-related comorbidity (generally taken to be diabetes, hypertension, or dyslipidemia), or obese patients (BMI ≥ 30 kg/m^2) whether or not comorbidities are present. Orlistat is the only approved long-term drug for obese adolescents aged at least 12 years, while all others are only approved for adult patients. Orlistat acts as a lipase inhibitor in the gut to impair digestion and absorption of ingested lipids. The other approved weight-loss medications act on the mechanisms regulating appetite and satiety, helping to combat the pathophysiological adaptations that drive and sustain weight gain. In clinical trials, the addition of pharmacotherapy to lifestyle promotes greater weight loss and sustains weight loss for a greater period of time than that attributable to lifestyle interventions alone. The available data, which only encompass 2 years or fewer of follow-up, demonstrate that these pharmacotherapies sustain weigh loss even when patients randomized to lifestyle plus placebo are regaining weight (Table 27–3).

Although studies of the recently approved weight-loss medications have not yielded long-term results, it is important to consider that obesity is a lifelong disease and requires long-term management. Given the need to maintain weight loss, clinical experience needs to be developed in using medications to sustain weight loss over the patient's lifetime. Postmarketing cardiovascular outcome trials are planned or ongoing for the four new weight-loss medications, and these studies should provide information pertinent to longer duration of therapy.

SURGERY

Bariatric surgery is the most effective method for treating class II and III obesity[102,103] and can be considered in patients with (1) BMIs of 35 kg/m^2 or more and associated comorbidities or (2) BMIs of 40 kg/m^2 whether or not accompanied by comorbidities, particularly after failure of lifestyle modification and medical therapies. Bariatric surgery can provide substantial weight loss (15% to more than 40%), but this varies by procedure.[103] The most common performed procedures are Roux-en-Y gastric bypass (RYGB), adjustable gastric banding, sleeve gastrectomy, and biliopancreatic diversion with or without duodenal switch. Many patients achieve long-term weight loss; however, it is not uncommon for patients to gradually regain weight over time.[104] Sustained weight loss also depends on ongoing lifestyle therapy, patient reeducation in terms of active lifestyle changes, and long-term medical follow-up.

A few key studies help highlight outcomes of bariatric surgery. Adams and colleagues examined the association of RYGB surgery with

TABLE 27–3. Pharmacotherapy for Weight Loss in Patients with Obesity

Weight Loss Medication	Dose	Mechanism	Side Effects	Warnings and Contraindications
Approved for Short-Term Therapy (≤ 3 Months)				
Phentermine (Adipex-P, Suprenza)	30 mg/d by mouth	Sympathomimetic amine	Restlessness, insomnia, dry mouth	Pregnancy; cardiovascular disease; hyperthyroidism; glaucoma; agitated states; abuse potential
Approved for Chronic Management of Obesity				
Orlistat (Xenical)	120 mg tid by mouth with meals	Gastrointestinal lipase inhibitor	Fat malabsorption,	Pregnancy, fat-soluble vitamin deficiency; malabsorption, oxalate stones; cholestasis
Phentermine/ Topiramate ER (Qsymia)	Escalate to 7.5 mg/46 mg once a day by mouth; maximum dose 15 mg/92 mg	Sympathomimetic amine/anti-convulsant, carbonic anhydrase inhibitor, gabaminergic	Paresthesia, dysgeusia, dry mouth, insomnia,	Pregnancy; glaucoma, hyperthyroidism, fetal toxicity, suicidality; cognitive impairment; metabolic acidosis
Lorcaserin (Belviq)	10 mg twice a day by mouth	5-HT$_{2C}$ serotonin receptor agonist	Headache, nausea, fatigue	Pregnancy, serotonin syndrome, (avoid other SSRIs), cognitive impairment, psychiatric disorders, euphoria at high doses; suicidality; priapism
Naltrexone ER/ Bupropion ER (Contrave)	Escalate to 8 mg/90 mg two pills twice a day by mouth	Opioid receptor antagonist/ dopamine-norepinephrine reuptake inhibitor	Nausea, headache, fatigue	Pregnancy, seizure risk, glaucoma, uncontrolled hypertension, chronic opioid use, suicidality, increase in blood pressure/pulse
Liraglutide 3 mg (Saxenda)	Escalate to 3 mg/d subcutaneous injection	Glucagon-like peptide-1 receptor agonist	Nausea, vomiting, diarrhea, constipation,	Pregnancy, medullary thyroid cancer, MEN type II, increased pulse, acute pancreatitis, suicidality, acute gallbladder disease

Abbreviations: 5-HT, 5-hydroxytryptamine; MEN, multiple endocrine neoplasia; SSRI, selective serotonin reuptake inhibitor.

weight loss, T2D, and other health risks 6 years after surgery.[102] Weight-loss maintenance was superior in severely obese patients (BMI ≥ 35 kg/m^2) undergoing RYGB compared with nonsurgical controls, with 76% of patients maintaining at least a 20% weight loss over 6 years. RYGB was also associated with higher rates of diabetes remission and lower cardiovascular disease risk over 6 years. The Swedish Obese Subjects (SOS) study involved patients receiving any one of several bariatric procedures and matched conventionally treated obese controls (lifestyle intervention, behavior modification, or no treatment).[103] The mean reported body weight changes after 2, 10, 15, and 20 years were –23%, –17%, –16%, and –18% in the surgery group, and 0%, 1%, –1%, and –1% in the conventionally treated care group, respectively.[105] Compared with standard care, bariatric surgery reduced overall mortality and decreased the incidence of diabetes, CVD events, and cancer. However, Cooper and colleagues demonstrated that weight regain is a common complication following RYGB surgery.[104] In this study, the mean weight regain for all patients was 23.4% of maximum weight loss (mean 6.9 ± 4.9 years after surgery). Furthermore, more than one-third of patients experienced excessive weight regain (≥ 25% of lost weight).

SUMMARY: A COMPLICATIONS-CENTRIC OBESITY CARE MODEL

Within the past decade there have been improvements in all three therapeutic modalities for obesity treatment: evidence-based lifestyle interventions, the new medications, and more refined bariatric surgery procedures. This has prompted the development of rational guidelines for how to best to use these tools to achieve the best outcomes while balancing efficacy, safety, and costs. While emphasizing the health benefits of weight loss, these guidelines can be viewed as falling along a continuum from a more BMI-centric approach, with a goal of losing a given amount of weight, to a complications-centric model focused on preventing and treating weight-related complications.[6,7] The BMI-centric approach is best illustrated by the obesity treatment guidelines set forth by the NHLBI in 1998,[66] as shown in Table 27–4. Under these guidelines, appropriate treatment was defined in terms of patients' initial BMI, with those having a BMI of 25 to 26.9 kg/m^2 receiving dietary, physical activity, and behavior interventions and pharmacotherapy and surgery being added in a stepwise manner for those with progressively higher BMIs. Although this approach does make some allowances for comorbidities, it depended largely on BMI as the major determinant and indication for appropriate treatment.

At the other end of the spectrum from the traditional NHLBI approach is the complications-centric approach developed by the AACE[69,70] shown in Fig. 27–6. In this model, weight loss becomes a therapeutic tool for the treatment of obesity-related complications, to a large extent independent of patients' degree of general adiposity or BMI. This approach targets more aggressive therapies to those who will derive the greatest benefits from weight-loss therapy, namely those patients with weight-related complications, thereby optimizing benefit/risk, outcomes, and cost effectiveness. Therapy begins with evaluating patients for the presence and severity of obesity-related cardiometabolic or biomechanical complications, followed by identifying therapeutic targets for improvement in existing complications. Lifestyle modification is recommended for patients without complications regardless of their BMI; for those with BMIs of 27 kg/m^2 or more and complications, therapeutic options expand to include medications, and, for those with BMIs of 35 kg/m^2 or more, bariatric surgery. Targets for improvement in complications should be monitored, and intensification of all modalities (lifestyle, medication, and surgery) should be implemented if necessary—along with direct treatment of complications—to achieve the desired outcomes.

The evidence-based ACC/AHA/The Obesity Society (TOS) practice guidelines published in 2014 update the earlier NHLBI guidelines and were developed, using a formal and rigorous evidence review process, to provide guidance on five specific critical questions.[106] The ACC/AHA/TOS clinical practice guidelines and accompanying treatment algorithm generally advocate a sequential approach, recommending that individuals who have never participated in a comprehensive lifestyle management program should be encouraged to do so before considering weight loss medications or bariatric surgery. By comparison, the AACE algorithm does not stipulate that a stepwise, sequential approach is strictly necessary and indicate that the aggressiveness of initial therapy should be determined by the presence and severity of weight-related complications and their adverse impact on the health of the patient.

In all guidelines, obesity is recognized as a chronic disease, and therapy is directed at improving the health of the patient. As our scientific understanding of obesity has progressed, it has become clear that obesity is not a lifestyle choice and its treatment is not a cosmetic enterprise. The new perspective of obesity as a disease mandates that

TABLE 27–4. National Heart, Lung, and Blood Institute (NHLBI) Obesity Treatment Guidelines

	Body Mass Index (BMI) Category (all values in kg/m^2)				
Treatment	25–26.9	27–29.9	30–34.9	35–39.9	≥40
Diet, physical activity, and behavior	Appropriate NHLBI guidelines	+	+	+	+
Pharmacotherapy	No	With comorbidities	+	+	+
Surgery[a]	No	No	No[a]	With comorbidities	+

[a]US Food and Drug Administration–approved lap band surgery for patients with BMI of at least 30 kg/m^2 and one weight-related medical condition (February, 2011).

Abbreviations: **+,** clinically indicated for consideration; **No,** not indicated.

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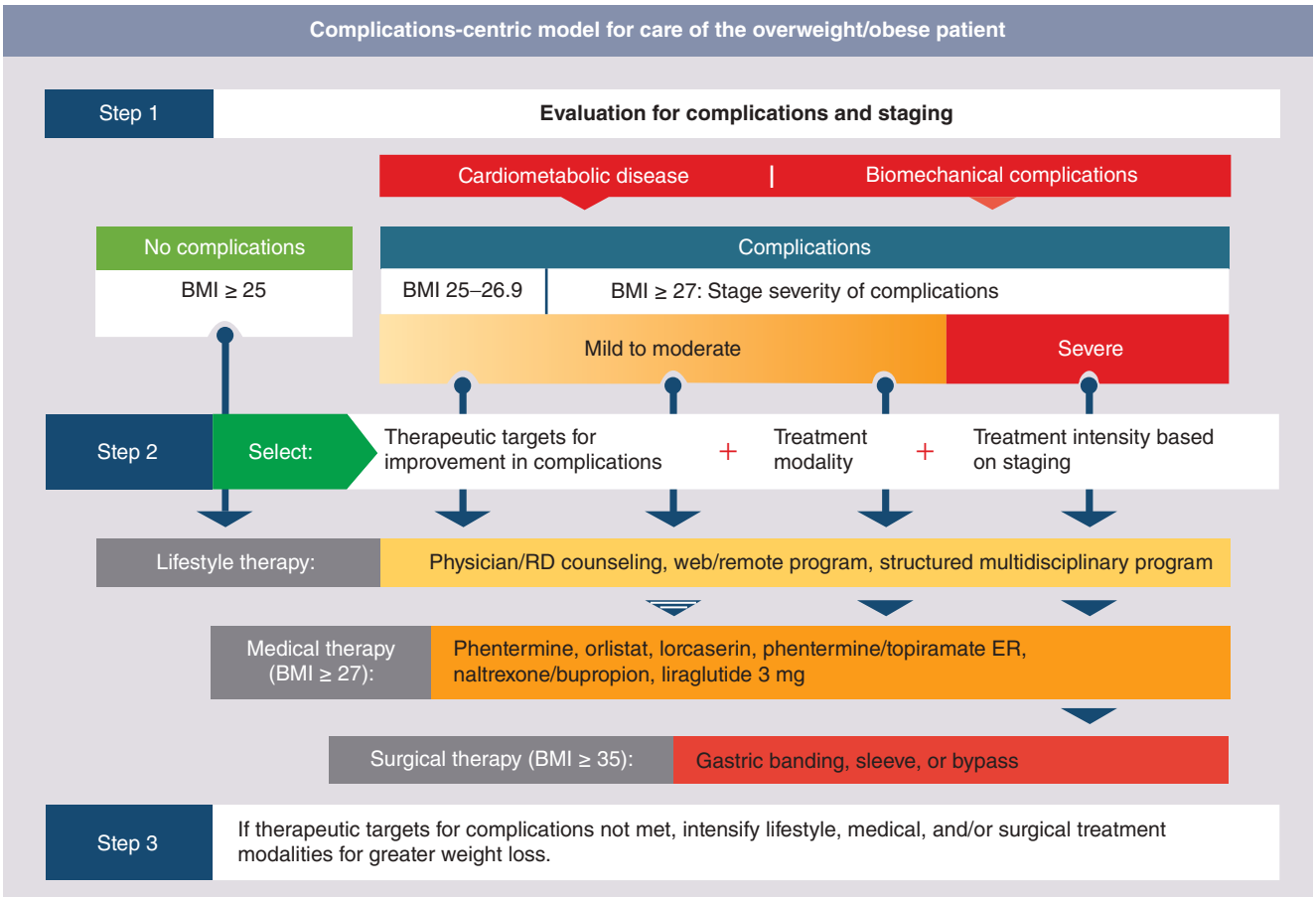

FIGURE 27–6. The American Association of Clinical Endocrinologists Complications-Centric Algorithm for care of the patient with overweight/obesity. Reproduced with permission from Garber AJ, Abrahamson MJ, Barzilay JI, et al: Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. *Endocr Pract*. 2016 Jan;22(1):84-113.

we bring the full force of our medical care model for prevention and treatment. An increasing effort is being expended in the development of new treatments and therapeutic approaches. With increased access to current and emerging therapies, we will be able to effectively combat the rising worldwide problem of obesity and mitigate the burden of patient suffering and social costs of the lifelong disease.

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CHAPTER 28

DIABETES AND CARDIOVASCULAR DISEASE

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Cardiovascular disease continues to be a major cause of morbidity and mortality in patients with diabetes and prediabetes and is expected to exponentially increase over the next 30 years. The global burden of cardiovascular disease has emerged not only in the developed world but also in low- and middle-income countries. As a result, the major focus in type 1 diabetes patients and type 2 diabetes patients is the prevention of the development of cardiovascular disease. Recently, the American Diabetes Association (ADA) published their recommendations for practice regarding cardiovascular disease risk management in *Diabetes Care* in January 2016.[1]

DIAGNOSIS OF DIABETES

The universally recognized criteria for the diagnosis of prediabetes and diabetes are as follows: (1) a normal glycated hemoglobin should be less than 5.7%, (2) a glycated hemoglobin of 5.7% to 6.4% is considered prediabetes, and (3) a level of 6.5% or higher on two separate occasions indicates diabetes.[1] Prediabetes can be diagnosed by a fasting plasma glucose of 100 mg/dL or more (impaired fasting glucose), a postglucose load of 140 to 199 mg/dL (impaired glucose tolerance), or both. Other recognized criteria include a fasting plasma glucose greater than 126 mg/dL or a 2-hour postprandial glucose of greater than 200 mg/dL during an oral glucose tolerance test involving a glucose solution containing the equivalent of 75 grams of glucose dissolved in water. Diabetes can also be diagnosed in the patient who has a random plasma glucose of greater than 200 mg/dL with classic symptoms of hyperglycemia.

With regard to classification and diagnosis of diabetes, a number of important classification issues need to be clarified. Apart from the classification in type 1 and type 2 diabetes, gestational diabetes is the diagnosis of diabetes in the absence of overt diabetes made in the second or third trimester of pregnancy.

The new recommendations also identified patients who are at increased risk for diabetes and who require testing. These include patients who were overweight or obese with a body mass index (BMI) of greater than 25 kg/m^2 or in the case of Asian Americans of 23 kg/m^2 or higher. Recommendations for screening for diabetes have now expanded to screening of children and adolescents who are overweight or obese. With regard to gestational diabetes, patients are tested in the first prenatal visit with risk factors. At 28 weeks of gestation, there is a test for gestational diabetes in pregnant women who are not previously known to have diabetes. It is recommended that women with a history of gestational diabetes are considered to have prediabetes and should receive lifestyle interventions for the prevention of diabetes.

The prevalence of diabetes is higher in developed countries than in developing countries, but the developing world will be hit the hardest by the diabetes epidemic in the future. Increased urbanization, westernization, economic growth in developing countries have already contributed to a substantial rise in diabetes by promoting overweight, obesity and decreased physical activity. Although diabetes is most common among the elderly in many populations, prevalence rates are rising among young populations in the developing world.

GLYCEMIC VARIABILITY

Patients with similar mean glucose or glycosylated glycated hemoglobin values can have markedly different daily glucose profiles depending on the numbers and duration of glucose excursions. In 1970, Service and colleagues described the metric Mean Amplitude Glucose Excursions (MAGE) using hourly blood glucose sampling for 48 hours.[2] It is known that the MAGE calculated from continuous glucose monitoring data corresponds to the originally developed value. A strong relationship between glucose variability and oxidative stress ($r = 0.86$; $P < .001$) was observed.[3] Furthermore, Marling and coworkers found that the number of excessively variable days using a naive Bayes classifier may be a reliable way to assess the glycemic variability of continuous glucose monitoring (CGM) data.[4] This measurement closely mirrors 90-day changes in serum 1.5 anhydroglucitrol. Actuation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemic is observed in patients with type 2 but not in type 1 diabetes.[5]

EPIDEMIOLOGY

Globally, diabetes mellitus is a major threat to human health. The number of people with diabetes has increased alarmingly since 1985 and the rate of new cases is escalating. In 1985, an estimated 30 million people worldwide had diabetes and this figure is expected to rise to almost

TABLE 28–1. Clinical Evaluation of Risk Factors for the Development of Cardiovascular Disease in Diabetic Patients

Cigarette smoking
Assess pack-years
Blood pressure
Duration (if known), current and previous medications, assess presence of orthostatic hypertension
Serum lipids and lipoproteins
Dietary habits, alcohol intake, amount of exercise and whether aerobic
Family history of dyslipidemia, eruptive xanthoma, lipemia, retinalis, xanthelasma, thyroid function tests
LDL, HDL, cholesterol, fasting triglycerides
Spot albumin/creatinine ratio (in micro- and macroalbuminuria)
Serum creatinine
Do not rely on dipstick protein, because negative results may reflect lack of sensitivity of test
Glycemic status
Duration of diabetes; family history of diabetes; vascular, renal, and retinal complications
Laboratory: FPG, hemoglobin A1c every 3 months: diagnosis FPG > 126 × 2, hemoglobin A1c > 6.5%[126]: impaired fasting glucose 110–126 × 2. When in doubt, have patient undergo 2-hour oral glucose tolerance test.

FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

350 million by 2025.[6] In the United States in 2012, the unadjusted prevalence of diabetes was 12.3% (95% confidence interval [CI], 10.8%-14.1%). Within the diabetes population, 25.2% (95% CI, 21.1%-29.8%) were undiagnosed.[7]

Diabetes mellitus, whether type 1 or type 2, is a very strong risk factor for the development of coronary artery disease (CAD) and stroke[6] (Table 28–1). Diabetes accelerates the natural course of atherosclerosis in all groups of patients and involves a greater number of coronary vessels with more diffuse atherosclerotic lesions (Fig. 28–1). Cardiac catheterizations in diabetic patients have shown significantly more severe proximal and distal coronary heart disease (CHD). In addition, plaque ulceration and thrombosis have been found to be significantly higher in diabetic patients. Cardiovascular complications include CHD, peripheral artery disease, nephropathy, retinopathy, cardiomyopathy, and possible neuropathy (involvement of vasa vasorum). These observations underscore the heightened risks of a diabetic patient of developing vascular disease and compel the physician to monitor and correct all risk factors (see Table 28–1). By understanding the mechanisms underlying all these risks, physicians will be poised to prevent them.

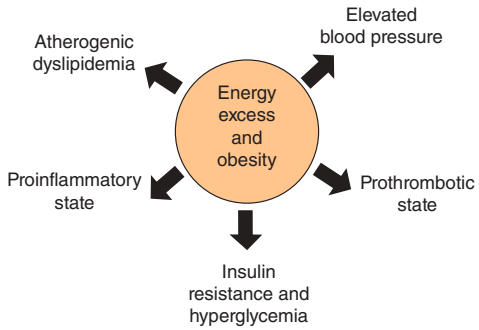


FIGURE 28–1. Relationships between energy excess/obesity and risk factors of the metabolic syndrome. Reproduced with permission from Grundy SM: Metabolic syndrome update, *Trends Cardiovasc Med*. 2016 May;26(4):364-373.[12]

METABOLIC SYNDROME

The metabolic syndrome is considered to be an aggregation of various established cardiovascular risk factors. Multiple attempts have been made to define the metabolic syndrome encompassing what each investigator deems the relevant clusters. The most widely used definitions come from the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III and the World Health Organization (WHO).[8,9] Other definitions from the International Diabetes Federation and American Association of Clinical Endocrinologists (AACE) have also been proposed.[10,11] Figure 28–1 outlines the relationship between energy excess and obesity and risk factors for the metabolic syndrome.[12]

COMPLICATIONS OF DIABETES

MICROVASCULAR COMPLICATIONS

Renal

Nephropathy occurs in 40% of patients with type 1 and type 2 diabetes. Risk factors include poor glycemic control, hypertension, and ethnicity (blacks, Mexicans, Pima Indians).[13] Table 28–2 summarizes the key points for the assessment of renal status in a diabetic patient. The earliest clinical finding of diabetic kidney disease is microalbuminuria, which may occur at a time when renal histology is essentially normal (Fig. 28–2). The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed that the development and progression of microalbuminuria can be prevented through strict glycemic control.

TABLE 28–2. Evaluation of Renal Status

Urine albumin and protein
Yearly screen for microalbumin in type 1 and type 2 diabetes; microalbumin-to-creatinine ratio collected in a spot urine, ideally first morning urine specimen (normal < 30 mg/g creatinine); must rule out other diseases that cause proteinuria
If urine albumin/creatinine is greater than 300 mg/g in first morning specimen, macroalbuminuria is present and is usually not reversible with angiotensin-converting enzyme (ACE) inhibitors; nephrology consult
Nephrotic syndrome: urine protein greater than 3 g/d; nephrology consult
Other reasons to consult nephrologists are diabetic patients with increasing creatinine from 1.4 to > 2.0 mg/g, elevated creatinine and symptoms of uremia, microalbuminuria not responding to ACE inhibitor
Urinalysis
Red cells, pyuria, casts require nephrology consult
Blood pressure evaluation
If hypertension is present, exclude secondary causes, including with advancing renal insufficiency
Treatment with an ACE inhibitor is preferred first choice even in African Americans (except if precluded by hyperkalemia or other complications)
Blood urea nitrogen, serum creatinine, and glomerular filtration rate
Yearly creatinine clearance should be obtained with 24-hour urine collection and serum creatinine; most accurate way to estimate kidney function without using a radioisotope

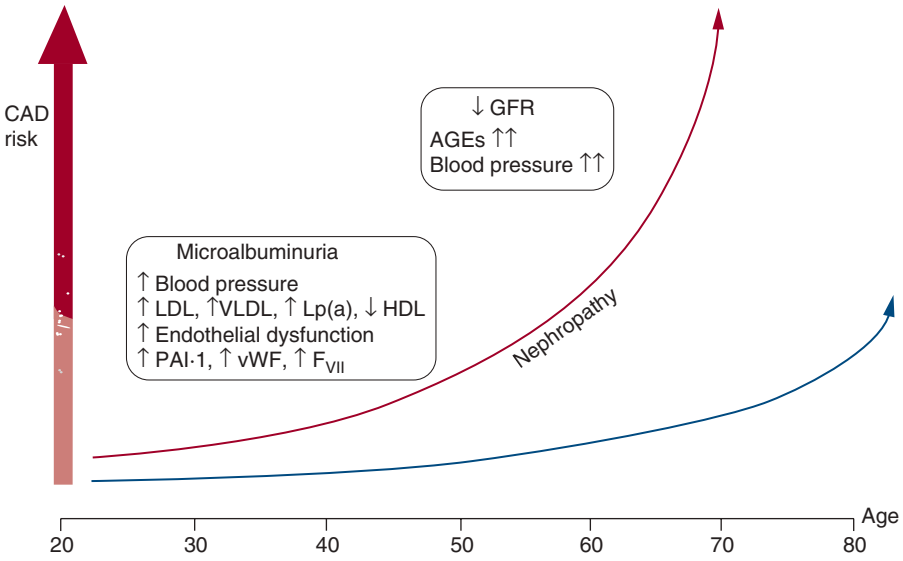


FIGURE 28–2. Coronary artery disease (CAD) risk in patients with diabetes mellitus**.** A subset of genetically predisposed patients develops diabetic nephropathy. In these patients, the risk of CAD increases dramatically. AGE, advanced glycosylation end-product; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); PAI, plasminogen activator inhibitor; VLDL, very-low-density lipoprotein; vWF, von Willebrand factor.

There is insufficient evidence to recommend angiotensin-converting enzyme (ACE) inhibitors in normotensive patients without microalbuminuria. Nonetheless, physicians should still recommend screening on at least a yearly basis, because the risk-to-benefit ratio of diagnosing microalbuminuria justifies treatment with an ACE inhibitor, if not for renal disease alone, then for reducing the incidence of myocardial infarction (MI).

Clinical trials evaluating angiotensin receptor blockers (ARBs), including losartan and irbesartan, have demonstrated a significant renal protective effect in the diabetic patient with nephropathy. There were no differences between the ARB and usual care groups with regard to cardiovascular outcomes.[14]

An optimal approach toward diabetic nephropathy combines control of hypertension, preferably with an ACE inhibitor or ARB, glycemic control, sodium restriction, and adjustment of protein intake.

If increasing macroalbuminuria occurs or if renal insufficiency is progressive despite these measures, the patient should be referred to a nephrologist. It is strongly recommended that renal arteriography be avoided. Dietary protein restriction in patients who have progressive renal insufficiency will reduce accumulation of nitrogen-containing waste products and can have a beneficial influence on progression of renal insufficiency.

Renal Hyperfiltration

Glomerular hyperfiltration is the hallmark of early renal hemodynamic disturbance and is an independent predictor of the development and progression of diabetic nephropathy in hypertensive type 2 diabetes when only microalbuminuria is present.[15] SGLT-2 inhibitors appear to delay progression to albuminuria in type 2 diabetic patients with chronic kidney disease.[16-19]

Ophthalmologic

Diabetic retinopathy is the most prevalent microvascular complication, affecting nearly 50% of the diabetic population at a given time and eventually occurring in all diabetic patients. Diabetes remains the leading cause of visual loss in adults. Visual loss from diabetes occurs either as a result of proliferative retinopathy or macular edema.[20]

MACROVASCULAR MANIFESTATIONS

Coronary Heart Disease

CHD is strongly associated with type 2 diabetes mellitus and is the leading cause of death regardless of the duration of disease. There is a two- to fourfold increase in the relative risk ratio of cardiovascular disease in type 2 diabetes patients compared to the general population. This increase is particularly disproportionate in diabetic women when compared with diabetic men. The protection that premenopausal women have against CHD is not seen if they suffer from diabetes. The degree of hyperglycemia and the duration of hyperglycemia are strong risk factors for the development of microvascular and macrovascular complications. Even impaired glucose tolerance increases cardiovascular risk, although there is minimal hyperglycemia.[21]

The first detectable sign of a problem in people genetically prone to develop type 2 diabetes is insulin resistance, which can be seen as long as 15 to 25 years before the onset of diabetes. Several atherogenic factors are associated with insulin resistance, which can start the atherosclerotic process years before clinical hyperglycemia ensues. It is unclear whether the compensatory hyperinsulinemia plays a role in atherosclerosis generation in insulin-resistant patients. A number of prospective studies have shown an association between fasting or postprandial hyperinsulinemia and the future development of CHD.

Hyperglycemia itself plays an important role in enhancing the progression of atherosclerosis in type 2 diabetes. The threshold above which hyperglycemia becomes atherogenic is not known but may be in the range defined as impaired glucose tolerance (ie, fasting plasma glucose level < 126 mg/dL with 30-, 60-, or 90-minute plasma glucose concentrations > 200 mg/L and a 2-hour plasma glucose level of 140 to 200 mg/dL during an oral glucose tolerance test). An important Mendelian randomization study strongly suggests that not only is type 2 diabetes mellitus directly causal for CHD but that longer term studies are needed to demonstrate a benefit of glucose lowering on CHD outcomes.[22]

ACUTE CORONARY SYNDROMES

Diabetic patients represent a high-risk group for developing and surviving acute MI. In particular, patients with type 1 diabetes have a worse outcome than do patients with type 2 disease, and diabetic women have almost twice the risk of mortality of diabetic men. Reperfusion therapy is the cornerstone of the management of acute MI. In a meta-analysis of the major trials comparing thrombolytic therapy to percutaneous coronary intervention (PCI), diabetic patients had significantly higher 30-day mortality when compared with nondiabetic patients (9.4% vs 5.9%; $P < .001$).[23] The advantages of angioplasty over thrombolytic therapy in the diabetic population are comparable to those observed in the nondiabetic patients.

New treatment strategies are emerging. The use of insulin and glucose infusion for at least 24 hours after admission followed by intensive long-term insulin was compared with usual care in the Diabetes Mellitus Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) trial.

A total of 620 diabetic patients were randomized, and the trial demonstrated a 30% reduction in mortality at 12 months for the group treated under the intensive program.[24]

However, the follow-up DIGAMI-2 trial, which compared three strategies—intensive insulin infusion followed by long-term insulin therapy, intensive insulin infusion followed by long-term standard glucose control, and regular metabolic control—in 1253 patients was unable to show a difference in short- and long-term mortality and morbidity between any of the arms. DIGAMI-2 concluded that intensive glucose control was of great importance in the peri-ischemic period irrespective of the strategy used to achieve it.[25]

The use of antiplatelet therapy is the mainstay of management of acute coronary syndromes in diabetic patients. With the advent of newer antiplatelet drugs, there have been recommendations for greater utilization of prasugrel and ticagrelor. The evidence suggests that there is no heterogeneity in the response to newer agents and strategies based on diabetes status[26-31] (Table 28–3[32]). The optimal strategy and regimen in diabetic patients is still elusive and remains the question of ongoing trials focused on limiting the thrombotic burden and not increasing the risk of major bleeding.

Chronic Coronary Artery Disease

The association between CHD and diabetes is strong and has led to screening strategies in diabetic patients even before they are symptomatic. In addition, diabetic patients often are unaware of myocardial ischemic pain, and so silent MI and ischemia are markedly increased in this population. There is a heightened concern for the development of sudden cardiac death in those with diabetes. Therapeutic modalities in diabetic patients with CHD revolve around standard therapy with aspirin, β-blockers, calcium channel blockers, and nitrates.

Epidemiologic evidence from the Bezafibrate Infarction Prevention Study registry shows almost a 50% reduction in mortality for type 2 patients with chronic CHD who were treated with β-blockers, compared with controls. Other randomized trial evidence has demonstrated that diabetes is a strong predictor of death and that diabetic patients may benefit more from β-blocker therapy than do nondiabetics. In general, β-blockers are extremely well tolerated, and masking or prolonging of hypoglycemic symptoms appears to be highly infrequent, particularly with cardioselective β blockers.[33]

Novel therapies have been tested to address the increased ischemic burden experienced by diabetic patients with CAD. Ranolazine has

TABLE 28–3. Main Outcomes Measures According to Diabetic Status from Recent Randomized Trials Investigating the Effects of Oral Anti-P2Y12 Agents in Patients with Acute Coronary Syndrome

Study	Primary End Point	n	Standard Treatment: % of Events	Active Treatment: % of Events	HR (95% CI)	*P*-value for Interaction
CURE (placebo vs clopidogrel)	1-year CV death, nonfatal MI or stroke	No DM:9,722	9.9	7.9	0.78 (0.71-0.86)	.31
		DM:2,849	16.7	14.2	0.83 (0.71-0.96)	
PCI CLARITY (placebo vs clopidogrel in STEMI)	30-day CV death, recurrent MI or stroke	No DM:1,555	5.3	2.9	0.51 (0.30-0.87)	.93
		DM:282	10.1	6.0	0.61 (0.24-1.53)	
CURRENT-OASIS 7 (standard-dose clopidogrel vs double-dose clopidogrel; low-dose aspirin vs high-dose aspirin)	30-day CV death, MI, or stroke	No DM:13,418	Standard-dose clopidogrel:	Double-dose clopidogrel:	0.98 (0.81-1.20)	.32
		DM:3,844			0.86 (0.68-1.13)	.62
		No DM:13,418	3.9	3.9	0.95 (0.76-1.10)	
		DM:3,844	6.1	5.2	1.01 (0.76-1.25)	
			Low-dose aspirin	Low-dose aspirin		
			4.0	3.8		
			5.6	5.7		
CURRENT-OASIS 7 PCI subgroup (standard-dose clopidogrel vs double-dose clopidogrel; low-dose aspirin vs high-dose aspirin)	30-day CV death, MI, or stroke	No DM:13,418	Standard-dose clopidogrel:	Double-dose clopidogrel:	0.84 (0.71-1.00)	.87
		DM:3,844			0.89 (0.68-1.18)	.22
		No DM:13,418	4.2	3.5	0.92 (0.77-1.10)	
		DM:3,844	5.6	4.9	1.12 (0.85-1.48)	
			Low-dose aspirin	Low-dose aspirin		
			4.0	3.7		
			5.0	5.6		
TRITON-TIMI 38 (clopidogrel vs prasugrel)	15-month CV death, nonfatal MI, or nonfatal stoke	No DM:10,462	10.6	9.2	0.86 (0.76-0.98)	.09
		DM:3,146	17.0	12.2	0.70 (0.58-0.85)	
PLATO (clopidogrel vs ticagrelor)	1-year CV death, MI, or stroke	No DM:13,951	10.2	8.4	0.83 (0.74-0.93)	.49
		DM:4,662	16.2	14.1	0.88 (0.76-1.03)	

CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HR; hazard ratio; MI, myocardial infarction; STEMI, ST-segment elevation MI.

Reproduced with permission from Patti G, Proscia C, Di Sciascio G: Antiplatelet therapy in patients with diabetes mellitus and acute coronary syndrome. *Circ J.* 2014;78(1):33-41.[32]

been studied widely and has recently been shown to lower the weekly angina frequency when compared to placebo (3.8 vs 4.3 episodes per week; $P = .008$) as well as the use of sublingual nitroglycerin in the Type 2 diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) trial.[34]

Diabetes-Related Cardiomyopathy

Diabetes-related cardiomyopathy is a term used by clinicians to encompass the multifactorial etiologies of diabetes-related left ventricular failure characterized by both systolic and diastolic function.[35] The Framingham Heart Study showed that men with diabetes who have congestive heart failure were twice as common as their nondiabetic counterpart and that females with diabetes had a fivefold increase in the rate of congestive heart failure. The spectrum of heart failure ranges from asymptomatic to overt systolic failure. Diabetes complicated by hypertension represents a particularly high-risk group for the development of congestive heart failure.[36] Diastolic dysfunction is exceedingly common (> 50% prevalence in some studies) and may be linked to diabetes without the presence of concomitant hypertension.

The etiology of impaired left ventricular function may involve any of the following mechanisms: (1) coronary atherosclerotic disease, (2) hypertension, (3) left ventricular hypertrophy, (4) obesity, (5) endothelial dysfunction, (6) coronary microvasculature disease, (7) autonomic dysfunction, and (8) metabolic abnormalities.

Echocardiographic studies confirm that diastolic abnormalities occur in young diabetic patients who have no known diabetic complications.[37] Presently diabetic cardiomyopathy is included under the umbrella of heart failure with preserved left ventricular ejection fraction (HFpEF), which is characterized by coronary microvascular endothelial dysfunction related to hyperglycemia, hyperinsulinemia, and lipotoxicity and leading to a restrictive picture.[38] Patients will have impaired diastolic dysfunction, and valvular, coronary, and hypertensive causes should be excluded. The management of HFpEF is diuretic therapy and usually includes β-blockers and ACE inhibitors, but evidence for this is sparse.

Once CHD develops in the diabetic patient, the heart failure with preserved left ventricular systolic dysfunction (HFrEF) that ensues responds to all the same therapies as in the nondiabetic population. The findings of the Heart Outcomes Prevention Evaluation (HOPE) trial suggest that early initiation of ACE inhibition retards the progression to overt congestive heart failure.[39]

Cerebrovascular Disease

Compared to nondiabetic subjects, the mortality from stroke in diabetic patients is almost threefold higher. The small paramedial penetrating arteries are the most common sites of cerebrovascular disease. In addition, diabetes increases the likelihood of severe carotid atherosclerosis. Diabetic patients are likely to suffer increased brain damage with carotid emboli that would result in a transient ischemic attack in a nondiabetic individual.[40]

MOLECULAR AND ENZYMATIC MECHANISMS

The spectrum of metabolic disturbances associated with diabetes and insulin resistance extends beyond hyperglycemia and includes dyslipidemia, hypercoagulability, and inflammation.

ADIPOKINES

Adipose tissue is an active organ that produces multiple adipokines,[41] which play an important role in the development and progression of atherosclerosis. Table 28–4 shows the prominent adipokines with their actions.

TABLE 28–4. Adipokines

Adipokine	Actions
Adiponectin	• Antiinflammatory and antiatherogenic properties • Low levels characteristic of persons at increased risk of diabetes • Decreases foam cell formation • Decreases uptake of oxidized low-density lipoprotein • Decreases monocyte adhesion to endothelial cells • Decreases expression of adhesion molecules • Decreases proliferation and migration of VSMCs
Leptin	• Regulates energy intake and expenditure • Enhances cellular immune responses • Increases blood pressure levels
Angiotensinogen and angiotensin II	• Vasoconstrictive • Enhances the formation of foam cells • Stimulates intracellular adhesion molecule-1, vascular cell adhesion molecule-1, MCP-1, and M-CSF expression in the cells of the vessel wall • Increases monocyte–macrophage platelet activity in the vessel wall • Endothelial dysfunction
Tumor necrosis factor	• Expression of adhesion molecules on the surface of the endothelial cells and VSMCs
Plasminogen activator inhibitor-1	• Inhibits the breakdown of fibrin clots • Promotes thrombus formation

MCP, monocyte chemotactic protein; M-CSF, monocyte colony-stimulating factor; VSMCs, vascular smooth muscle cells.

ENDOTHELIAL DYSFUNCTION

The normal endothelium regulates vasomotor tone, and keeps the coagulation cascade in balance. Insulin resistance, itself, appears to be an endothelial dysfunction risk equivalent.

In healthy endothelium, the stimulation of insulin receptors activates the phosphoinositol-3 kinase (PI3-K) pathway. The production of nitric oxide by endothelial cells stimulated by this pathway leads to a host of anti-inflammatory and antithrombotic effects which are antiatherogenic. The endothelial dysfunction of insulin resistance is a result of decreased levels of nitric oxide and thus impaired blood flow because of a downregulation of the PI3-K pathway.[42]

A parallel pathway downregulates the production of endothelin-1. In response to hyperglycemia, endothelial cells secrete endothelin-1, which induces proatherogenic effects such as vasoconstriction, increased vascular permeability, and vascular smooth muscle cell (VSMC) proliferation. Elevated glucose levels stimulate the production of interleukin-6 by endothelial cells and monocytes and increased proteoglycan synthesis by VSMCs.

VASCULAR SMOOTH MUSCLE CELL MIGRATION AND PROLIFERATION

The insulin receptors on VSMCs are structurally and functionally similar to those in skeletal muscle and adipocytes. Insulin signaling in VSMCs initiates proatherogenic cellular events such as proliferation and migration. Insulin acts synergistically with other atherogenic

growth factors such as platelet-derived growth factor to promote the proliferation and migration of bovine aortic smooth muscle cells.

MONOCYTE/MACROPHAGE ADHESION AND MIGRATION

Circulating monocytes are important inflammatory cells involved in the immune response. Insulin and insulin-like growth factor-1 receptors are present on circulating monocytes and macrophages. Defective insulin signaling is implicated in macrophage foam cell formation.[43] Under conditions of insulin resistance, the protective effect of insulin to reduce macrophage apoptosis may be lost. Macrophage apoptosis in atherosclerotic lesions may contribute to further monocyte recruitment by the release of cytokines and may thus accelerate the development of the vascular lesion and contribute to plaque rupture.

INSULIN RESISTANCE

The insulin resistance syndrome is a composite of dyslipidemia, hypertension, and hypercoagulability.[44] It is only now being recognized that insulin resistance is the predominant defect in more than 90% of type 2 diabetes patients and the major pathologic mechanism for the susceptibility to premature cardiovascular disease. Insulin resistance and hyperinsulinemia accelerate the development of atherosclerosis. Hyperinsulinemia is an independent risk factor when adjusted for lipid profile, hypertension, and family history. Studies of multiple ethnic groups show increased carotid intima-medial thickness (a reliable marker for coronary disease) in subjects with insulin resistance. Impaired glucose tolerance can increase the risk of heart disease. Because insulin resistance precedes clinically diagnosed type 2 diabetes by 10 to 15 years in as many as 90% of patients, this extensive period of atherogenic exposure may account for the higher rates of cardiovascular disease in type 2 diabetics.[45,46]

Although the euglycemic-insulin clamp remains the gold standard for the measurement of insulin resistance, simpler formulas are used clinically to quantify insulin resistance, or IR, using the Homeostasis Model Assessment (HOMA IR = Serum Insulin × Serum Glucose/22.5).[45] Insulin resistance as assessed by HOMA (HOMA-IR) also has been shown to be predictive of cardiovascular disease. In long-term follow-up of type 2 diabetic patients, insulin resistance was independently predictive of cardiovascular disease, with a one-unit increase in HOMA-IR associated with a 5.4% increased risk of cardiovascular disease.[45] The Insulin Resistance and Atherosclerosis Study (IRAS) also demonstrated the relationship between insulin resistance and atherosclerosis in the carotid artery.

MANAGEMENT OF DIABETES AND ITS COMPLICATIONS

DIET AND LIFESTYLE MODIFICATION

There have been major advances in our understanding of the role of lifestyle modification in diabetic patients.

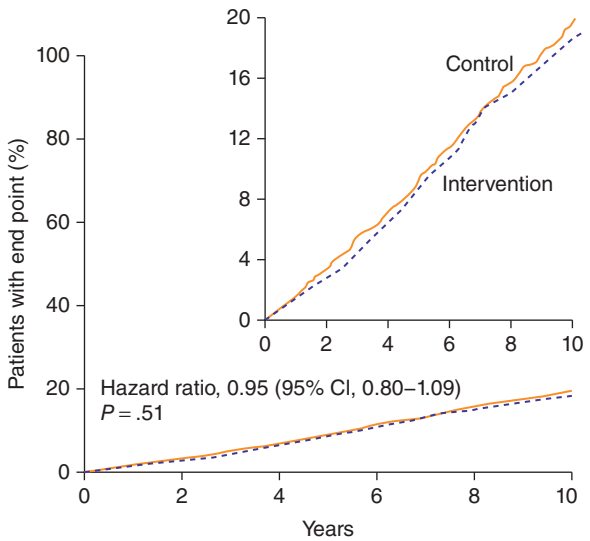
Benefits of Modest Weight Loss

The current approach to managing type 2 diabetes is to focus on modest weight loss in the range of 5% to 10% of initial weight. The concomitant reductions in low-density lipoprotein (LDL) cholesterol and systolic blood pressure along with improvements in glycated hemoglobin have real and sustained cardiovascular benefits.[47] Weight loss is an important therapeutic strategy in all overweight or obese individuals who have type 2 diabetes or are at risk for developing diabetes.[48] The primary approach for achieving weight loss, in the vast majority of cases, is therapeutic lifestyle change, which includes a reduction in energy intake and an increase in physical activity. A moderate decrease in caloric balance (500-1000 kcal/d) will result in a slow but progressive weight loss (1-2 lb/wk). For most patients, weight-loss diets should supply at least 1000 to 1200 kcal/d for women and 1200 to 1600 kcal/d for men. In selected patients, drug therapy to achieve weight loss as an adjunct to lifestyle change may be appropriate. However, it is important to note that regain of weight commonly occurs on discontinuation of medication.

Physical activity is an important component of a comprehensive weight management program. Regular moderate-intensity physical activity enhances long-term weight maintenance. Regular activity also improves insulin sensitivity, glycemic control, and selected risk factors for cardiovascular disease (ie, hypertension and dyslipidemia), and increased aerobic fitness decreases the risk of CHD. Initial physical activity recommendations should be modest, based on the patient's willingness and ability, gradually increasing the duration and frequency to 30 to 45 minutes of moderate aerobic activity, 3 to 5 days per week, when possible. Greater activity levels of at least 1 hour per day of moderate (walking) or 30 minutes per day of vigorous (jogging) activity may be needed to achieve successful long-term weight loss. The American College of Sports Medicine now recommends that resistance training be included in fitness programs for adults with type 2 diabetes.[49] Resistance exercise improves insulin sensitivity to about the same extent as aerobic exercise.

Look-Ahead

The National Institutes of Health–sponsored The Action for Health in Diabetics (Look Ahead) trial of weight reduction and exercise in over 5000 type 2 diabetic patients sought to evaluate the role of modest weight loss and an exercise program on major cardiovascular events with at least 8 years of follow-up (Fig. 28–3).[50] The trial was halted prematurely in September 2012 because of futility bringing into question whether lifestyle provides adequate cardioprotection in type 2 diabetes. The surrogate markers appeared favorable with a greater rate of modest weight loss in the intervention arm (4.7% vs 2.1% of initial weight was lost by year 8; $P < .001$) and with more than one-fourth of patients



No. at risk						
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

FIGURE 28–3. Cumulative hazard curves for the primary composite end point in Look-AHEAD. Reproduced with permission from Look AHEAD Research Group, Wing RR, Bolin P, et al: Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013 Jul 11;369(2):145-154.[50]

in the intervention group losing at least 10% of initial weight in the long-term. The real challenge in interpreting Look-AHEAD is that the control group was aggressively treated for cardiovascular risk through marked cointervention of evidence-based therapies.

PREDIMED

The Mediterranean diet, originally coined by Ansel Keys, is rich in fruits, vegetables, and olive oil, with the addition of chick peas, bulgur, couscous, lentils, and fava beans. It is very limited in the consumption of red meat and eggs. Emerging evidence has shown that adoption of the Mediterranean diet has positive effects on the progression of type 2 diabetes and on cardiovascular outcomes. Shia and colleagues first showed that rates of type 2 diabetes development and progression can be markedly reduced.[51] The transformational Prevención con Dieta Mediterránea (PREDIMED) study in Spain demonstrated a 52% reduction (95% CI, 0.27-0.86) in the development of type 2 diabetes mellitus in primary prevention cohort[52] (Fig. 28–4). At present, the evidence for the preventive effects of the Mediterranean diet in type 2

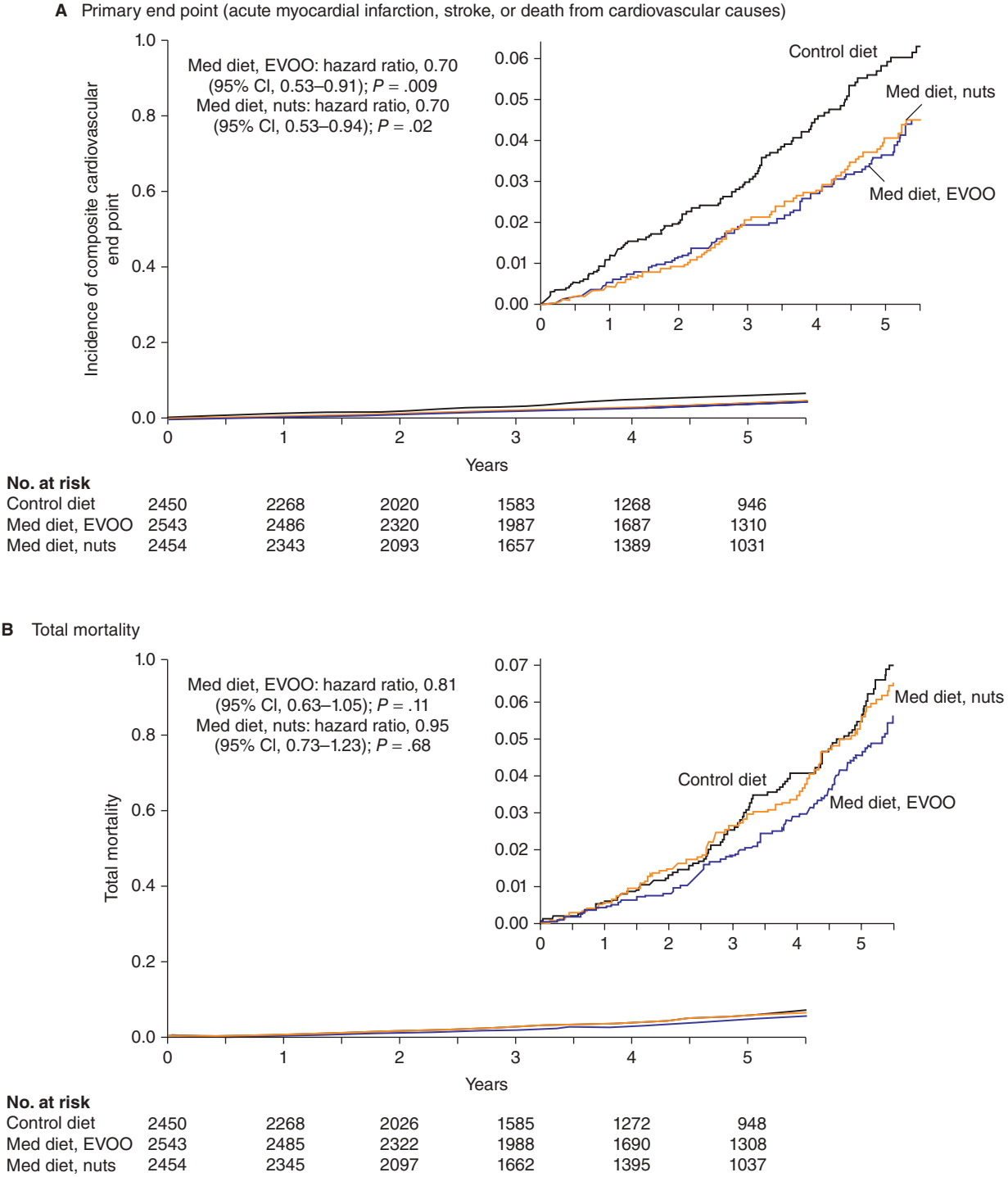


FIGURE 28–4. Kaplan-Meier estimates of the incidence of outcome events in the total study population. EVOO, extra virgin olive oil; Med, Mediterranean diet. Reproduced with permission from Estruch R, Ros E, Salas-Salvadó J, et al: Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013 Apr 4;368(14):1279-1290.[52]

diabetes mellitus is rather limited. A case-control Italian study of 144 type 2 diabetes mellitus patients with peripheral arterial disease (PAD) matched to 288 age and sex matched type 2 diabetes mellitus controls showed that a diet with a greater adherence to Mediterranean diet was associated with a lower (by 50%) incidence of PAD.[53]

STENO-2 demonstrated that a comprehensive multifactorial strategy (including lifestyle and pharmacologic interventions) to reduce cardiovascular risk in type 2 diabetic patients with microalbuminuria was highly effective (hazard ratio [HR] 0.47; 95% CI, 0.24-0.73) when compared to usual care after a mean time of 7.8 years. The number needed to treat to prevent a major cardiovascular event was only five patients. The approach included targets of glycated hemoglobin less than 6.5%, blood pressure less than 130/80 mm Hg, total cholesterol less than 175 mg/dL, and triglycerides below 150 mg/dL. Patients were prescribed aspirin and an ACE inhibitor or ARB. This study validates the multidisciplinary approach to the cardiovascular care of the diabetic patient.[54]

DYSGLYCEMIA

Glycemic Control

The ADA has increased the recommendation for premeal blood glucose targets to 80 to 130 mm/dL from 70–130 mm/dL. The ADA has also promoted the utilization of CGM into practice and laid out a plan to educate on CGM.[1]

Prevention or the Delay of Type 2 Diabetes

Patients with an impaired glucose tolerance tests or glycated hemoglobin of 5.7 to 6.4% should be recommended for intensive diet and physical activity intervention with a target loss of body weight of about 7%. Metformin should be considered for those with a BMI of more than 35 mg/m^2 who are under the age of 60 or in women with prior gestational diabetes. Recommended lifestyle intervention is for 7% weight loss with diet and moderate intensity physical activity of at least 2.5 hours per week.

Dysglycemia Management

Patients with type 1 diabetes (generally caused by viral illness or autoimmunity) are treated with insulin. A cardiologist should know that such a patient will require an average of 0.5 units of insulin/kg body weight per day (half of this is basal insulin [0.25 units/kg] and the other half is bolus insulin (0.25 units/kg), if divided in three boluses injections given before each meal. The patient will need to be managed by an endocrinologist who can work collaboratively with the cardiologist because cardiovascular disease and diabetes are inextricably intertwined.

Glycemic control in type 1 diabetics is associated not only with lower rates of microvascular complications as observed in type 2 diabetes but also with reductions in cardiovascular events. One of the major distinctions between type 1 and type 2 diabetes is the timing of initiation of insulin therapy and the types of insulin therapy that are provided. Patients with type 1 diabetes are prescribed a balanced individualized diet and exercise program and are often treated with multiple-dose insulin (known as MDI injections), which include the use the insulin analogs.

Patients with type 2 prediabetes or diabetes are managed by first teaching them lifestyle changes, including a Mediterranean diet and carbohydrate counting with an aerobic exercise program at last four times a week. The training is shared between an endocrinologist and a certified diabetes nurse or nutritionist educator, either of whom should be a CDE. The target glycated hemoglobin is generally 6.5% AACE or less than 7% (ADA, European Association for Study of Diabetes [EASD]) unless higher as dictated by a personalized patient-centered approach, which is discussed. In some cases, glycated hemoglobin of 8.5% is acceptable with a patient who is elderly, has multiple comorbidities, limited resources, and an anticipated short life span. We offer two algorithms for the management of type 2 diabetes from ADA and from AACE. The AACE algorithm has gained more traction as it is more pragmatic. Metformin is generally the first drug to be used, with add-ons depending on the circumstances of each patient. Basal insulin and eventually basal and bolus insulin before meals is generally required in most, but not all, patients. Mindful eating and lifestyle changes are of critical importance. It is best to refer most patients to an endocrinologist for consultation because the algorithm can be daunting to a busy cardiologist or internist, and a nuanced personalized approach is strongly recommended[1] (Figs. 28–5 and 28–6).

More recently, Inzucchi and colleagues have reviewed their valuable patient-centered approach to the management of type 2 diabetes.[55] With the ADA guideline for a target glycated hemoglobin of 7%, factors that would lead a clinician to aim to a higher target in decision making were the following: risks potentially associated with hypoglycemia and other drug effects, disease duration, life expectancy, important comorbidities, established vascular complications, patient attitude and expected treatment effects, and resources and support system. There are some patients with multiple such factors in whom a glycated hemoglobin of 8.5% might be reasonable to prevent untoward outcomes (Fig. 28–7).

Hypoglycemia

One of the most important aspects of glycemic control is not only to prevent microvascular events but also to avoid hypoglycemia. Once a hypoglycemic episode has occurred, patients should be reevaluated for their treatment strategy. Patients who are elderly should have ongoing cognitive assessment to make sure that they are aware of hypoglycemia. Hypoglycemia is associated with a greater risk of dementia and cognitive impairment.[56] In the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) and The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials, severe hypoglycemia was associated with increased overall mortality.[57,58]

Antidiabetic Medications

The Use of Insulin In patients with type 2 diabetes, the use of insulin is largely related to the duration of type 2 diabetes. As patients survive longer with diabetes given the optimization of medical therapy, there is a greater likelihood that patients will eventually require insulin in order to maintain their target glycated hemoglobin. It is important to remember that type 2 diabetes is a progressive disease and that eventually patients will require more intensive medical therapy, including insulin.

Insulin is used in the management of type 1 diabetes mellitus or type 2 diabetes mellitus as monotherapy or in combination with oral agents. Insulins currently available are synthetic human insulins or analogs of human insulin, which differ in their rate of absorption and duration of action. There are also products that are mixtures rapid short-acting and intermediate-acting insulins (Table 28–5). Purified animal insulins are no longer used.

Basal insulin can be initiated at 10 units per day or 0.1 to 0.2 units per kg/d. Then basal insulin is adjusted 10% to 15% or two or four units once or twice weekly to reach the fasting blood glucose target. Although this is not the topic of this chapter, it is important to note that working closely with the endocrinologists will allow cardiovascular specialists to be more involved in the care of their patients, including those for whom insulin is prescribed. When more complex insulin regimens are used beyond basal insulin strategies, combination of insulin with oral antidiabetic drugs is common.

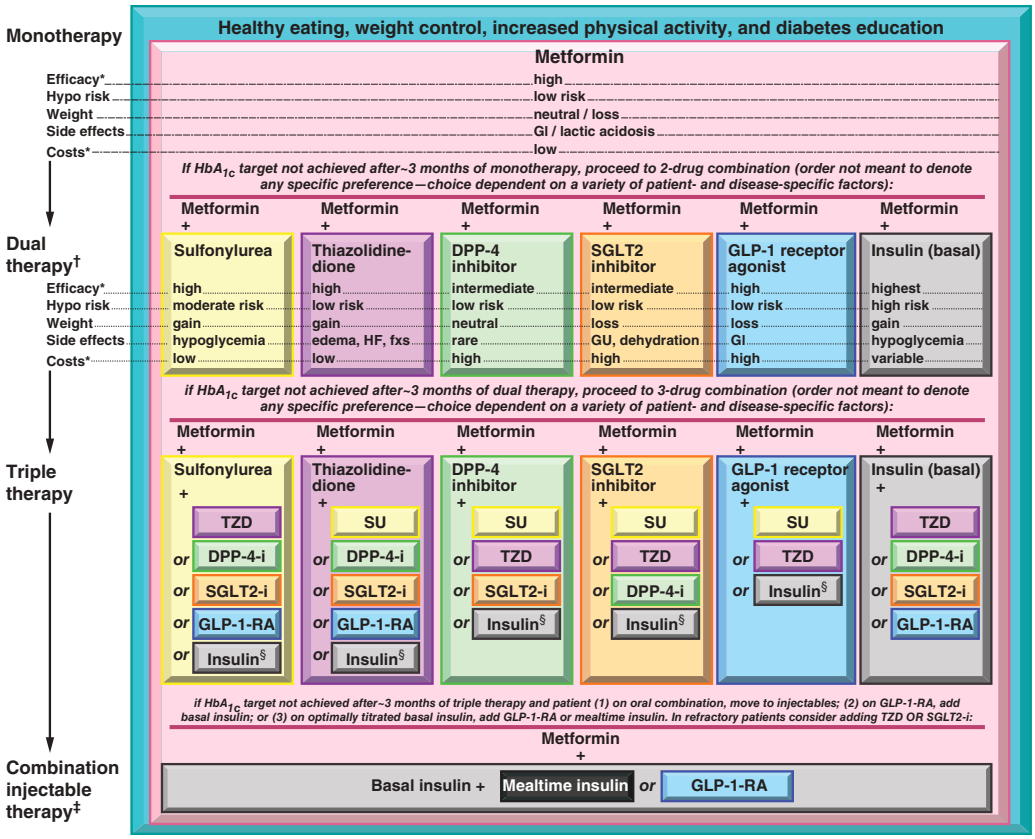


FIGURE 28–5. American Diabetes Association algorithm for type 2 diabetes. fx, factor; GI, gastrointestinal; GU, genitourinary; HF, heart failure; SU, sulfonylurea; TZD, thiazolidinedione. Reproduced with permission from Inzucchi SE, Bergenstal RM, Buse JB, et al: Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015 Jan;38(1):140-149.[1]

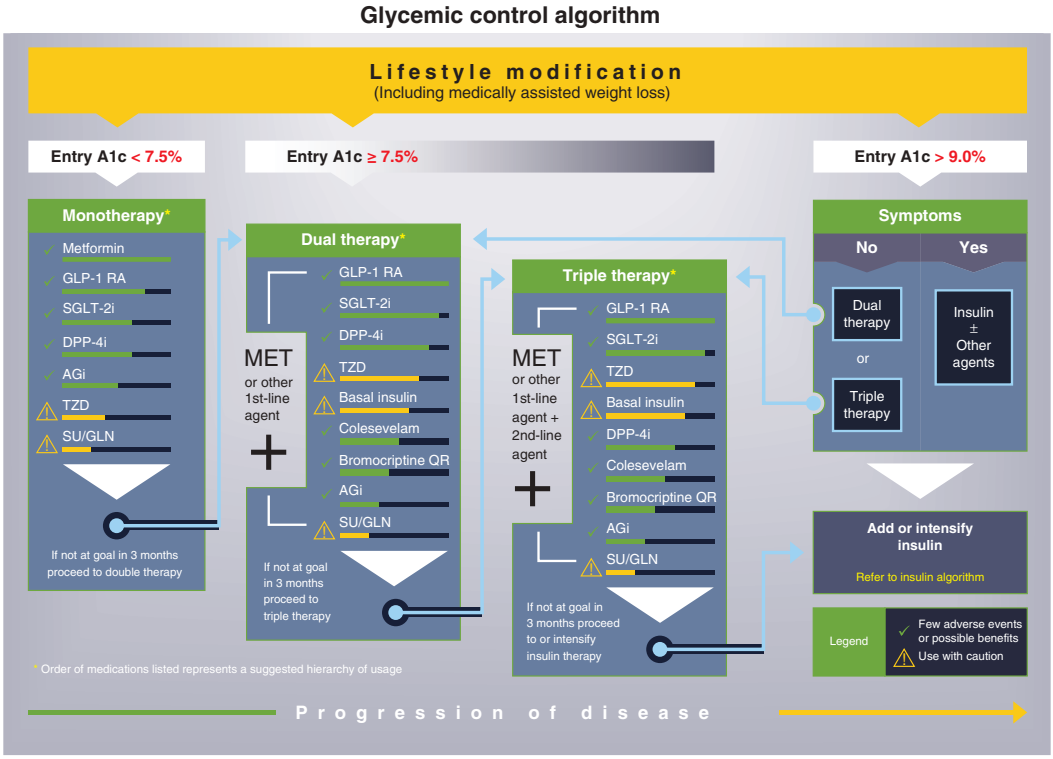


FIGURE 28–6. American Association of Clinical Endocrinologists/American College Endocrinology (AACE/ACE) comprehensive diabetes management algorithm. GLN, glinide; GLP, glucagon-like peptide; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione. Reproduced with permission from Garber AJ, Abrahamson MJ, Barzilay JI, et al: AACE/ACE comprehensive diabetes management algorithm 2015, *Endocr Pract*. 2015 Apr;21(4):438-447.

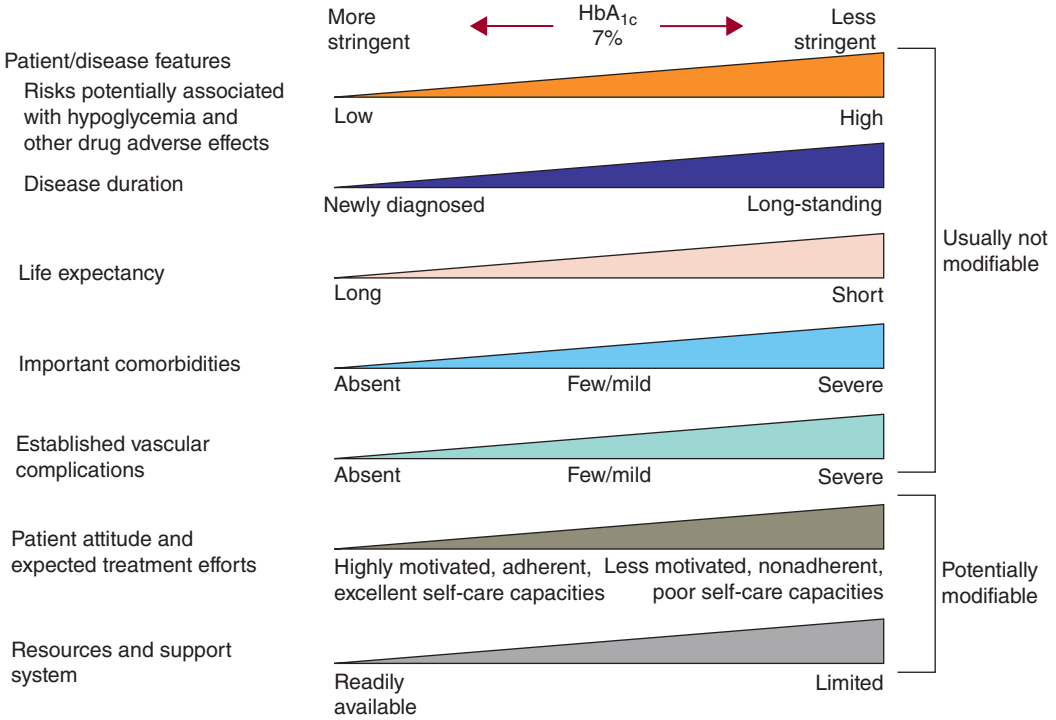


FIGURE 28–7. Patient-centered approach to the management of hyperglycemia. Reproduced with permission from Ismail-Beigi F, Moghissi E, Tiktin M, et al: Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. *Ann Intern Med*. 2011 Apr 19;154(8):554-559.

Use of Insulin Pumps and Continuous Glucose Monitoring Systems Insulin pumps are devices with a subcutaneous catheter that deliver continuous subcutaneous insulin infusion. One or more basal rates are preprogrammed by the user, and boluses are taken as needed whenever carbohydrates are ingested. The catheter is changed every 2 to 3 days, and abdominal infusion sites are most commonly used. In a motivated patient, better glycemic control can be achieved with continuous subcutaneous insulin infusion—compared with multiple subcutaneous insulin injections—because continuous subcutaneous insulin infusion can provide multiple basal rates of insulin.[59]

CGM systems that use a glucose sensor to provide up to 3 days of CGM in the subcutaneous tissue are available. The record shows glucose patterns and trends that can help in the recognition and prevention of hypoglycemia, hyperglycemia, postprandial glucose excursions, nocturnal hypoglycemia, and the effects of exercise. However, "normal" interstitial glucose values may be lower than realized, including some values in the "hypoglycemic range." Also, the CGM systems may not always read the glucose concentrations consistently and accurately. A recent comprehensive consensus document reports on the use of CGM systems in type 1 and type 2 diabetes. More trials are needed in type 2 diabetes. Insulin delivery can be integrated with digital technology to change insulin dosing and avoid hypoglycemia.

Multiple other agents are used in the management of diabetes. Table 28–6 outlines the various oral agents used to control glycemia in diabetes. The ominous octet described by Defronzo dictates that multiple agents tackling the various pathophysiological defects are necessary to managing type 2 diabetes[60] (Fig. 28–8).

Metformin Metformin[61] has been used in Europe for several decades but has been marketed in the United States since 1995. The mechanism of action of metformin is to decrease hepatic glucose output by inhibiting glucose-6-dehydrogenase activity and stimulating the insulin-induced component of glucose uptake into skeletal muscle and adipocytes and decrease the intestinal absorption of glucose.

The starting dose for metformin is 500 mg orally with dinner. A sustained-release preparation is preferred for once-daily dosing and should be uptitrated weekly to two, three, and four 500-mg tablets at dinner. Because of its mechanism of action, there is minimal risk of hypoglycemia. This drug should be used with caution and at reduced dosing in renal disease and not at all in renal failure or potential hypoxic states, such as congestive heart failure and severe pulmonary disease, because of the risk of lactic acidosis.

Thiazolidinediones Thiazolidinediones (TZDs)[62,63] induce peroxisome proliferator-activated receptor (PPAR)-γ binding to nuclear receptors in muscle and adipocytes, allowing insulin-stimulated glucose transport. Three PPARs have been identified to date: PPARα, PPARδ (also known as PPARβ), and PPARγ. After ligand binding, PPARs change their conformation to permit the recruitment of one or more coactivator proteins. The first mechanism, transactivation, is DNA-dependent and consists of binding PPAR components with target genes and heterodimerization with the retinoid X receptor. The second mechanism, transrepression, interferes with other transcription factor pathways that are not DNA-dependent. The protein kinase C signaling pathway functions as a molecular switch that dissociates with transactivation and transrepression properties of PPARα. PPARα resides mainly in the liver, heart muscle, and vascular endothelium; when it is activated, it controls genes that regulate lipoprotein levels and confers anti-inflammatory effects. PPARγ is located mainly on adipocytes, but it is also found in pancreatic beta cells, vascular endothelium, and macrophages.

Thiazolidinediones and Cardiovascular Outcomes The TZDs have come under increased scrutiny because of the association with edema and weight gain. What is clear after a number of key trials is that there are likely differences between the two approved PPAR agents, pioglitazone and rosiglitazone.[64] Pioglitazone and rosiglitazone have significantly different effects on plasma lipids.[65,66] Pioglitazone compared with rosiglitazone is associated with significant improvements in LDL particle concentration, LDL particle size, triglycerides, and high-density

TABLE 28–5. Insulins

Drug Name Generic/Brand Name	Onset of Action	Time to Peak Activity	Duration of Action	Side Effects
Rapid-Acting Insulin				Sweating, dizziness, skin reaction on injection site, headaches, worsening of diabetic retinopathy, hypoglycemia, weight gain
				?Mitogenic effects
Lispro (generic) Humalog	10–30 min	30 min–2 h	3–5 h	
Aspart (generic) NovoLog	10–30 min	30 min–2 h	3–5 h	
Glulisine (generic) Apidra	10–30 min	30 min–2 h	3–5 h	
Afrezza (inhaled insulin)	10–30 min	~ 53 min	2.6 h	May cause throat pain or irritation and cough, hypoglycemia, weight gain
				?Mitogenic effects
Short-Acting Insulin				Headache, hunger, dizziness, sweating, irritability, rapid breathing, muscle pain or cramps, hypoglycemia, weight gain
				?Mitogenic effects
Regular (generic) Humulin R	30–60 min	2–3 h	6–8 h	
Regular (generic) Novolin R	30–60 min	2–3 h	6–8 h	
Intermediate-Acting Insulin				Sweating, shaking, fast heartbeat, hunger, blurred vision, dizziness, tingling in hands/feet, hypoglycemia, weight gain
				?Mitogenic effects
NPH (generic) Humulin N	2–4 h	4–10 h	Up to 20 hours	
NPH (*generic*) Novolin N	2–4 h	4–10 h	Up to 20 hours	
Long-Acting Insulin				Dizziness, chills, blurred vision, weakness headache fainting, hypoglycemia, weight gain
				?Mitogenic effects
Detemir (generic) Levemir (U-100)	1–3 hours	varies	up to 24 hours	
Glargine (generic) Lantus (U-100)	1–3 hours	0	24+ h	
Glargine (generic) Toujeo (U-300)	6 hours	0	24+ h	
Glargine (generic) Basaglar (U-100)	1–3 hours	0	24+ h	
Degludec (generic) Tresiba (U-100 and U-200)	1–3 hours	0	24+ h	
Premixed Insulin				Redness; itching or swelling at site of injection; nausea; sweating; tiredness; weakness; nervousness; trembling; numbness or tingling of the lips, fingers, or tongue; hypoglycemia; weight gain
				?Mitogenic effects
Humalog Mix 75/25; 50/50	10–30 min	1–4 h	Up to 20 h	
NovoLog Mix 70/30	10–30 min	1–4 h	Up to 20 h	
Humulin 70/30, 50/50	30–60 min	3–12 h	Up to 20 h	
Novolin 70/30	30–60 min	3–12 h	Up to 20 h	
Ryzodeg 70/30 (degludec/aspart), starting dose of 10 units subcutaneously once daily for type 2 diabetes mellitus)	10–30 min	30 min–2 h	24+ h	

lipoprotein (HDL) cholesterol. When it comes to the TZDs, it is essential to balance the risk and benefits. Clearly, patients with chronic heart failure are not candidates for TZD therapy.

The pivotal outcomes trial of pioglitazone, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), did not provide as clear a picture as the surrogate outcomes trials.[67] This large trial of over 5000 diabetic patients with established macrovascular complications were randomized to pioglitazone 45 mg/d or placebo. The primary end point, which included MACE but also leg amputation, peripheral and coronary revascularization, and acute coronary syndromes, did not demonstrate any difference. However, a key secondary end point of death, MI, and stroke showed a 16% relative risk reduction in favor of pioglitazone (HR 0.84; 95% CI, 0.72-0.98; P = .027). The potential reduction in cardiovascular events associated with pioglitazone is supported by a large randomized, placebo-controlled trial of pioglitazone in patients after stroke or transient ischemic attack. With 4.8 years of follow-up the rate of MI or stroke was significantly reduced in the pioglitazone arm 9.0% versus 11.8% (HR 0.76; 95% CI, 0.62-0.93).[68]

TABLE 28–6. Type 2 Diabetes Drugs

Drug Name Generic/Brand Name	Dosage	Expected A1c Reduction (%)	Mechanism of Action	Side Effects	Advantages	Cardiovascular Safety
Biguanides		1.0–1.5	Activate AMP-kinase, decreases hepatic glucose production, decreases intestinal absorption of glucose	Diarrhea, abdominal cramping, lactic acidosis, vitamin B_{12} deficiency	Extensive experience, no hypoglycemia, decreases cardiovascular events (UKPDS)	Schramm et al. Mortality and cardiovascular associated with different insulin secretagogues compared to with metformin. *Eur Heart*. 2011;32:1900.
Metformin (*generic*) Glucophage HCl	500 mg qd to 1000 mg bid to 850 mg tid					
Metformin (*generic*) Riomet (liquid)	500 mg/5 mL bid					
Extended release						
Glucophage XR	500, 850, 1500 mg once daily at dinner					
Glumetza	500, 1000 mg once daily at dinner					
Fortamet	500, 1000 mg once daily at dinner					
Sulfonylureas		1.0–1.5	Closes K_{ATP} on β-cell plasma membranes, increases insulin secretion	Hypoglycemia, increased weight, abdominal pain, diarrhea, muscle weakness, headache ?Possible cardiovascular effects	Extensive experience, decreased microvascular risk (UKPDS)	Monami et al. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized trials. *Diabetes Obes Metab*. 2013;15:938.
Glimepiride (*generic*) Amaryl	1, 2, 4 mg once daily					
Glizide (*generic*) Glucotrol	5, 10 mg once daily					
Glucotrol XL (extended release)	2.5, 5, 10 mg once daily					
Glyburide (*generic*) DiaBeta	1.25, 2.5, 5 mg once daily					
Glyburide (*generic*) micronized tablets	1.5, 3, 4.5, 6 mg once daily					
Glynase PresTab	1.5, 3, 6 mg once daily					
Meglitinides		0.5–1.0	Closes K_{ATP} on β-cell plasma membranes, increases insulin secretion	D	Decreased postprandial glucose excursions, dosing flexibility	Ajjan RA, Grant PJ. The cardiovascular safety of rosiglitazone. *Exp Opin Drug Safety*. 2008;7:367.
Nateglinide (*generic*) Starlix	60, 120 mg tid with meals					
Repaglinide (*generic*) Prandin	0.5, 1.2 mg tid with meals					
Thiazolidinediones		1.0–1.5	Activates the nuclear transcription factor PPAR-γ, increases insulin secretion and sensitivity	Edema/heart failure, weight gain, headache, myalgia, osteoporosis	No hypoglycemia, durability, increased HDL-C; decreased triglycerides (pioglitazone) ?decreased cardiovascular disease events (PROactive, pioglitazone)	EXSCEL (NCT01144338)

(*continued*)

TABLE 28–6. Type 2 Diabetes Drugs (*Continued*)

Drug Name Generic/Brand Name	Dosage	Expected A1c Reduction (%)	Mechanism of Action	Side Effects	Advantages	Cardiovascular Safety
Pioglitazone (*generic*) Actos	15, 30, 45 mg one daily					
Repaglinide (*generic*) Avandia	2, 4, 8 mg once daily or divided					
GLP-1 Receptor Agonist		1.0–1.5	Activates GLP-1 receptors, increases insulin secretion (glucose-dependent), decreases glucose secretion (glucose-dependent), slow gastric emptying, increases satiety	Diarrhea, nausea, vomiting, headaches, dizziness, increased sweating, indigestion, constipation, increased heart rate, occasional acute pancreatitis, C-cell hyperplasia/medullary thyroid tumors in rodents	No hypoglycemia, decreases weight, increases postprandial glucose excursions, decreases some cardiovascular risk factors	LEADER (NCT01179048)
Exenatide (*generic*) Byetta (immediate release)	5, 10 mcg (prefilled pen) bid					
Exenatide (*generic*) Bydureon (extended release)	2 mg once/week					
Linglutide (*generic*) Victoza	0.6, 1.2, 1.8 mg (prefilled pen) once daily					
Albiglutide (*generic*) Tanzeum	30, 50 mg (prefilled pen) once/week					
Dulaglutide (*generic*) Victoza	0.75, 1.5 mg once/week					REWIND (NTC01394952)
DPP-4 Inhibitors		0.5–1.0	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations, increases insulin secretion (glucose-dependent), decreases glucagon secretion (glucose-dependent)	Stomach discomfort, diarrhea, sore throat, stuffy nose, upper respiratory infection	No hypoglycemia, well tolerated	EXAMINE CAROLINA SAVOR-TIMI 53 TECOS
Alogliptin (*generic*) Nesina	6.25, 12.5, 25 mg once daily					
Linagliptin (*generic*) Tradjenta	5 mg once daily					
Saxagliptin (*generic*) Onglyza	2.5, 5 mg once daily					
Sitagliptin (*generic*) Januvia	25, 50, 100 mg once daily					
Alpha-Glucosidase Inhibitors		0.5–1.0	Inhibits intestinal α-glucosidase, slows intestinal carbohydrate digestion/absorption	Flatulence, upset stomach, diarrhea, constipation	No hypoglycemia, decreases postprandial glucose excursions ?Decreases cardiovascular death events (STOP-NIDDM), nonsystemic	
Acarbose (*generic*) Precose	25, 50, 100 mg tid with meals					
Miglitol (*generic*) Glyset	25, 50, 100 mg tid with meals					

(*continued*)

TABLE 28–6. Type 2 Diabetes Drugs (*Continued*)

Drug Name Generic/Brand Name	Dosage	Expected A1c Reduction (%)	Mechanism of Action	Side Effects	Advantages	Cardiovascular Safety
SGLT2 Inhibitors		0.5–1.0	Inhibits SGLT2 in the proximal nephron, blocks glucose reabsorption by the kidney, increasing glucosuria	Genitourinary infections, including mycotic infections; polyuria; volume depletion/hypotension/dizziness; increased LDL-C; increased creatine (sometimes transient), osteoporosis (Invokana)	No hypoglycemia, decreases weight, decreases blood pressure, effective at all states of type 2 diabetes, significant reductions in cardiovascular death (empagliflozin)	
Canagliflozin (*generic*) Invokana	100, 300 mg once daily					
Dapagliflozin (*generic*) Farxiga	5, 10 mg once daily					
Empagliflozin (*generic*) Jardiance	10, 25 once daily					EMPA-REG OUTCOME
Dopamine-2 Agonist		0.5–1.0	Activates dopaminergic receptors, modules hypothalamic regulation of metabolism, increases insulin sensitivity	Dizziness, syncope, nausea, fatigue, rhinitis	No hypoglycemia ?Decreases cardiovascular disease events (Cycloset Safety Trial)	Charmathi et al. Timed bromocriptine-QR therapy reduced progression of cardiovascular disease and dysglycemia in subjects with well-controlled type 2 diabetes mellitus. *J Diabetes Res*. Epub 2015 Apr 28.
Bromocriptine (*generic*) quick release Cycloset	Initial: 0.8 mg daily Maintenance: 1.6–4.8 mg daily					
Amylin mimetics		0.5–1.0	Activates amylin receptors, decreases glucagon secretion, slows gastric emptying, increases satiety	Nausea, hypoglycemia, vomiting, headache, stomach ache, weight loss, fatigue	Decreases postprandial glucose excursions, decreases weight	Wysham et al. Effect of pramlintide as an adjunct to basal insulin on markers of cardiovascular risk in patients with type 2 diabetes. *Curr Med Res Opin*. 2008;24:79.
Pramlintide (*generic*) Symlin	1.5 mL Symlin Pen 60 (1000 mcg/mL) for 30, 45, and 60 mcg[1] 2.7 mL Symlin Pen 120 (1000 mcg/mL) 60 and 120 mcg[1]					

Dosage is tid for meals with at least 30 g of cholesterol.

The evidence for a cardioprotective effect of rosiglitazone is not apparent. In fact, the meta-analysis by Nissen and Wolski created a media firestorm by reporting a 4% excess in MI and a 60% excess for cardiovascular death for patients treated with rosiglitazone compared with an active comparator in type 2 diabetes mellitus.[69] This meta-analysis was highly criticized for a number of reasons, including pooling trials for which cardiovascular end points were relatively rare, with a great deal of heterogeneity between trials. What was most controversial is that it lead to the publishing of an interim analysis of the Rosiglitazone Evaluated for Cardiac Outcome and Regulation of glycemia in Diabetes (RECORD) trial.[70] Eventually, RECORD was published.[71] The trial randomized over 4000 patients in an open-label design. After a mean follow-up of 5.5 years, the addition of rosiglitazone to a combination of metformin and sulfonylurea was found to be noninferior to metformin and sulfonylurea alone a combination of metformin and sulfonylurea for the combination of cardiovascular hospitalization or cardiovascular death (HR 0.99; 95% CI, 0.85-1.16). Heart failure causing admission to hospital or death was increased in the rosiglitazone group (HR 2.10; 95% CI, 1.35-3.27). At present, rosiglitazone is rarely used.

Sulfonylureas Sulfonylureas[72] are the oldest class of treatment for type 2 diabetes mellitus. The mode of action is by stimulating β-cell insulin secretion.

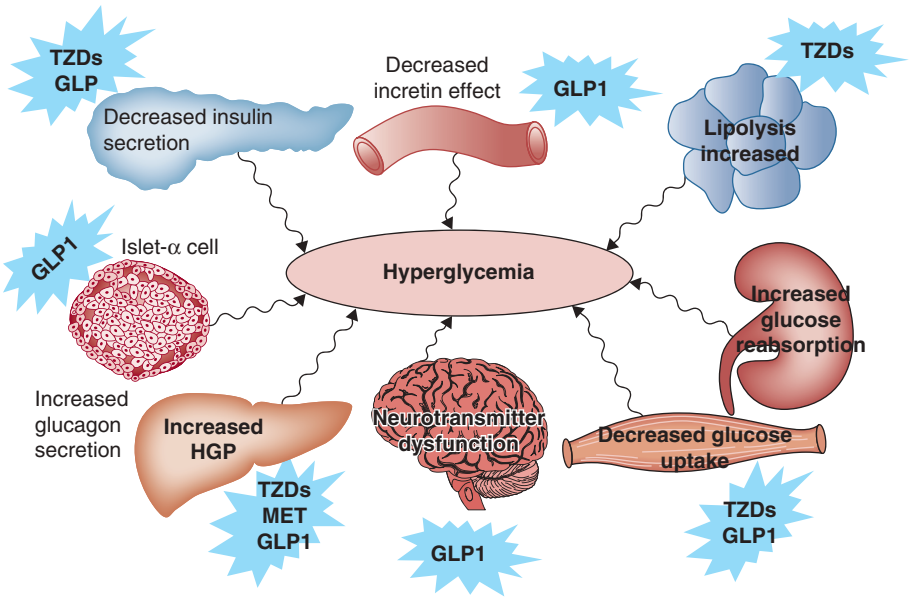


FIGURE 28–8. Ominous octet mechanism of action of hypoglycemic agents. Reproduced with permission from Defronzo RA: Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009 Apr;58(4):773-795.[60]

The beta-cell sulfonylurea receptor (SUR) is functionally linked to an ATP-sensitive K^+ channel (K^+-ATP) on the cell membrane. In the basal state, the K^+-ATP channel shifts K^+ from the inside of the β cell to the extracellular space and maintains the resting potential of the beta-cell membrane. When the sulfonylurea binds to the SUR, K^+ efflux diminishes and the membrane depolarizes. This depolarization opens a voltage-dependent calcium channel in the same membrane, which enables extracellular calcium to enter the cell. The resultant increase in intracellular calcium triggers insulin-containing secretory granule exocytosis.

The first-generation sulfonylureas have a long half-life and bind ionically to plasma proteins, making them easily displaced. The major concern with these agents is hypoglycemia. The second-generation sulfonylureas have a shorter half-life and bind to plasma proteins nonionically, making them less easily displaced from proteins and available for binding to receptors. Commercially available second-generation sulfonylureas are glyburide (1.25-20 mg/d), glipizide (2.5-40 mg/d), and glimepiride (1-8 mg/d). Sulfonylureas decrease the glycated hemoglobin by 1% to 2%.

Incretins The newer agents available for the treatment of type 2 diabetes mellitus belong to the class of incretin hormones[73] (see Table 28–6). The two key incretins are GLP-1 and glucose-dependent insulinotropic peptide (GIP), both secreted in the small intestine by the L cells and K cells, respectively. Both GLP-1 and GIP are decreased in type 2 diabetes mellitus, and when given pharmacologically to animals, these hormones stimulate beta-cell proliferation and can prevent or delay the onset of diabetes.

Exenatide is a synthetic peptide that is a GLP-1 agonist (incretin mimetic). It potentiates insulin secretion and decreases glucagons secretion postprandially. Exenatide delays gastric emptying and promotes satiety, resulting in weight loss. Liraglutide, another in this class, has also been approved as an antiobesity drug by demonstration of over 9% weight loss in the SCALE trial in nondiabetic patients.[74]

Dipeptidyl Peptidase IV Inhibitors The enzyme dipeptidyl peptidase IV (DPP-IV) rapidly degrades GLP-1 and GIP to inactive forms and include the following agents: sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin. DPP-IV inhibitors retard peptide degradation of these incretins, allowing therapeutic efficacy.[75] The DPP-IV inhibitors are given orally and are weight neutral.[76]

In head-to-head comparisons, exenatide has been shown to reduce weight and postprandial triglyceride levels when compared to a DPP-4 inhibitor.[77]

Cardiovascular Benefits of GLP-1 and DPP-IV Inhibitor Agents For the GLP-1 agonists, weight loss may be a key to improved cardiovascular effects. Indirect benefits can arise through reductions in blood pressure and inflammatory markers. There are GLP-1 receptors in the cardiac myocytes, and treatment with GLP-1 has been shown to improve myocardial function in rat and dog heart failure models.[78-81]

DPP-IV compounds are not associated with either weight gain or reduction and hold promise by enhancing meal time levels of GLP-1 and GIP.[82] The risk of hypoglycemia is very low. Because hypoglycemia has been linked to acute cardiovascular events, the DPP-IV inhibitors may provide an additional margin for safety.

Over the past 2 years, a number of important studies of a newer class of drugs, the incretin therapies, have emerged. This includes three important studies of a DPP-4 inhibitors and one for a GLP agonist in the treatment of patients with type 2 diabetes at cardiovascular risk. Overall, these trials of incretin drugs that are currently reported have shown a neutral effect on the primary end point of cardiovascular mortality, nonfatal MI, and nonfatal stroke.

The SAVOR TIMI-53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR Trial)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial), evaluating saxagliptin, showed a hazard ratio of 1.0 for primary cardiovascular events out to about 2 years.[83] The EXAMINE (EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome) trial, with alogliptin in acute coronary syndrome patients, showed an HR of 0.96 with a 95% CI that encompassed unity.[84] The TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) trial, presented at the ADA in June 2015, evaluated the use of sitagliptin and showed an HR of 0.98.[85]

A GLP-1 agonist has also now reported their first trial. The ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial with lixisenatide showed an HR of 1.02 for primary cardiovascular events (95% CI, 0.89-1.17).[86]

In light of the SAVOR trial finding of about a 25% increase in heart failure hospitalization with saxagliptin over placebo, a cardiovascular safety concern has been considered. Recent evidence suggests that this signal was only apparent in the SAVOR trial with the other three outcome trials showing no significant increase in heart failure.[87] This issue is not fully resolved at present, and recent studies suggest that the link between heart failure and antidiabetic drugs may be tightly linked to weight gain.[88-90]

SGLT Inhibitors The SGLT-2 inhibitors block renal glucose resorption in the proximal tubule, thereby increasing urinary glucose excretion. One drug in this class has now reported cardiovascular end points, empagliflozin, which is associated with weight loss and significant reductions in glycated hemoglobin comparable to other oral antihyperglycemic agents, as well as reductions in systolic blood pressure.[91]

The EMPA-REG trial was conducted to examine the long-term effects of empagliflozin versus standard of care on cardiovascular morbidity and mortality in type 2 diabetes.[92] This was a randomized, double-blind, placebo-controlled trial that was conducted at 590 sites

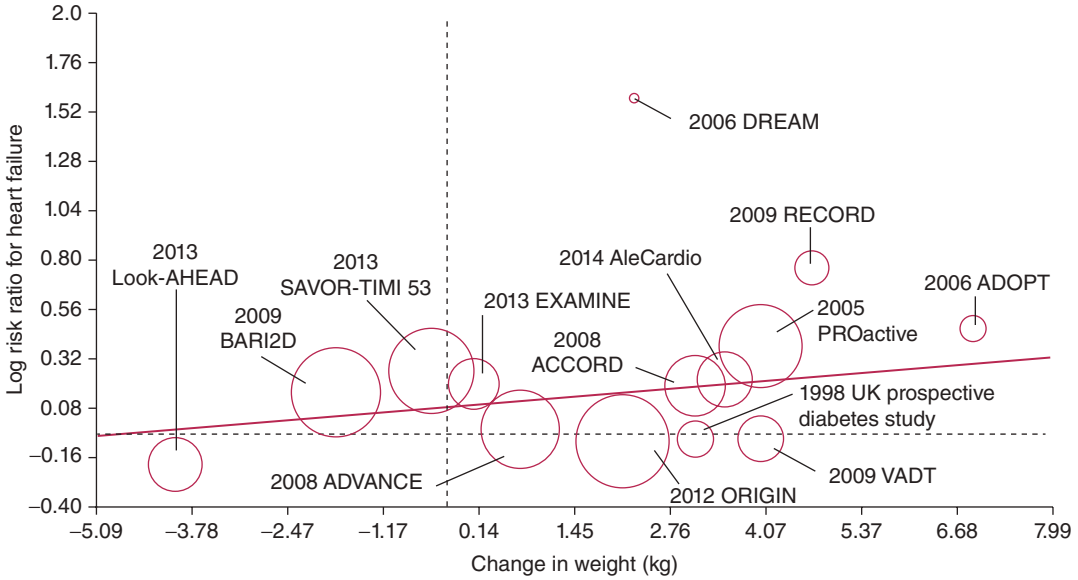


FIGURE 28–9. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomized controlled trials. HGP, hyperglycemia; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione. Reproduced with permission from Udell JA, Cavender MA2, Bhatt DL, et al:Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2015 May;3(5):356-366.[90]

in 42 countries. Patients were screened for the trial, and 7020 patients were randomized either to placebo or two doses of empagliflozin 10 mg daily or 25 mg daily in a 1:1:1:1 allocation. At least 691 patients would experience a primary adjudicated event of cardiovascular death, nonfatal MI, and nonfatal stroke. Patients were included if they had a BMI of less than 45 kg/m^2 and a glycated hemoglobin of 7% to 10% with a history of established cardiovascular disease. Patients were excluded if their estimated glomerular filtration rate was less than 30 mm/m. The primary end point was a three-point MACE of cardiovascular death, nonfatal MI, and nonfatal stroke. The trial recruited about 72% males with an average glycated hemoglobin of 8.1%. About one-half of the patients who were on insulin therapy and the mean BMI in the trial was about 30.7. Only 10% of the patients had a history of cardiac failure prior to enrollment in the study.

The glycated hemoglobin in the trial was not statistically different between the treatment and placebo groups after long-term follow up of about 4 years. Patients in the first 12 weeks of the study had to stay on their current therapy, so those randomized to placebo had a slightly elevated glycated hemoglobin but by the end of the trial patients were treated to a target glycated hemoglobin of about 7%. The overall mean glycated hemoglobin achieved was closer to 8%. With regard to other important biomarkers, empagliflozin was associated with no difference in heart rate, diastolic blood pressure, or LDL cholesterol. At a median follow-up of 2.6 years, empagliflozin was associated with a reduction in systolic blood pressure of approximately 4 mm Hg, a reduction in waist circumference of approximately of 2 cm, and a reduction in weight of 2 kg. For the primary end point of the study, the HR overall was approximately 0.85 with no significant differences overall between the two doses of empagliflozin. When comparing placebo to empagliflozin overall, there is about 15% reduction in primary events, which just met statistical significance at *P* value of .04 (see Fig. 28–3). However, there were significant reductions in cardiovascular death (HR 0.62; 95% CI, 0.49-0.77; $P < .0001$) and a significant reduction in the hospitalization for heart failure (HR 0.065; 95% CI, 0.50-0.85; $P = .0017$). The drug was safe and well tolerated, and the only significant safety issue was a three-fold increase in the rates of genital infections. This was observed in both males and females. The number of confirmed cases of hypoglycemia was no different at about 28% in both the placebo and treatment arms. The number of patients experiencing diabetic ketoacidosis was not significantly different at about 0.1% overall.

For patients treated with empagliflozin over placebo, the number needed to treat it at 3 years to prevent one death is approximately 39 patients. This compared very similarly to the number needed to treat (NNT) for simvastatin to prevent one death in the Scandinavian Simvastatin Survival Study (4S) after 5 years of treatment.[92] The EMPA-REG study will likely transform the care of patients with type 2 diabetes and will lead empagliflozin to now be the first- or second-line agent in diabetic patients with established cardiovascular disease. Table 28–2 summarizes the different classes of drugs used in the treatment of type 2 diabetes. This combined with Fig. 28–10 provides algorithm that are approved by the ADA. What is clear in the light of EMPA-REG and the relative safety of the DPP-4 inhibitors is that sulfonylureas are likely to be will be relegated to fourth or fifth line use.

Results of Large Cardiovascular Outcome Trials Evaluating the Role of Glucose Control For type 1 diabetes, the DCCT trial provides concrete evidence for the cardiovascular benefits of an intensive insulin program.[93] Even after the publication of ACCORD, ADVANCE and VADT (Veterans Affairs Diabetes Trial), the question of whether glucose management reduces macrovascular events in type 2 diabetes remains unclear (Tables 28–7 and 28–8).

For type 2 diabetes mellitus, the UKPDS program played a major role in establishing that optimal glycemic targets decreased long-term microvascular complications. Currently, the ADA guidelines, target glycemic control at glycated hemoglobin level less than 7% without causing significant hypoglycemia.

With the publication of ACCORD, ADVANCE, VADT, STENO-2 Mortality, and UKPDS-10 years, there is a greater wealth of evidence, but the question of glycemic control and macrovascular outcomes remains confusing.[94-97]

The ACCORD trial is a pivotal randomized study sponsored by the National Heart Lung and Blood Institute (NHLBI), including over 10,000 individuals with type 2 diabetes mellitus and established cardiovascular disease or additional cardiovascular risk factors. In one part of the trial, the comparison between tight glycemic control to keep

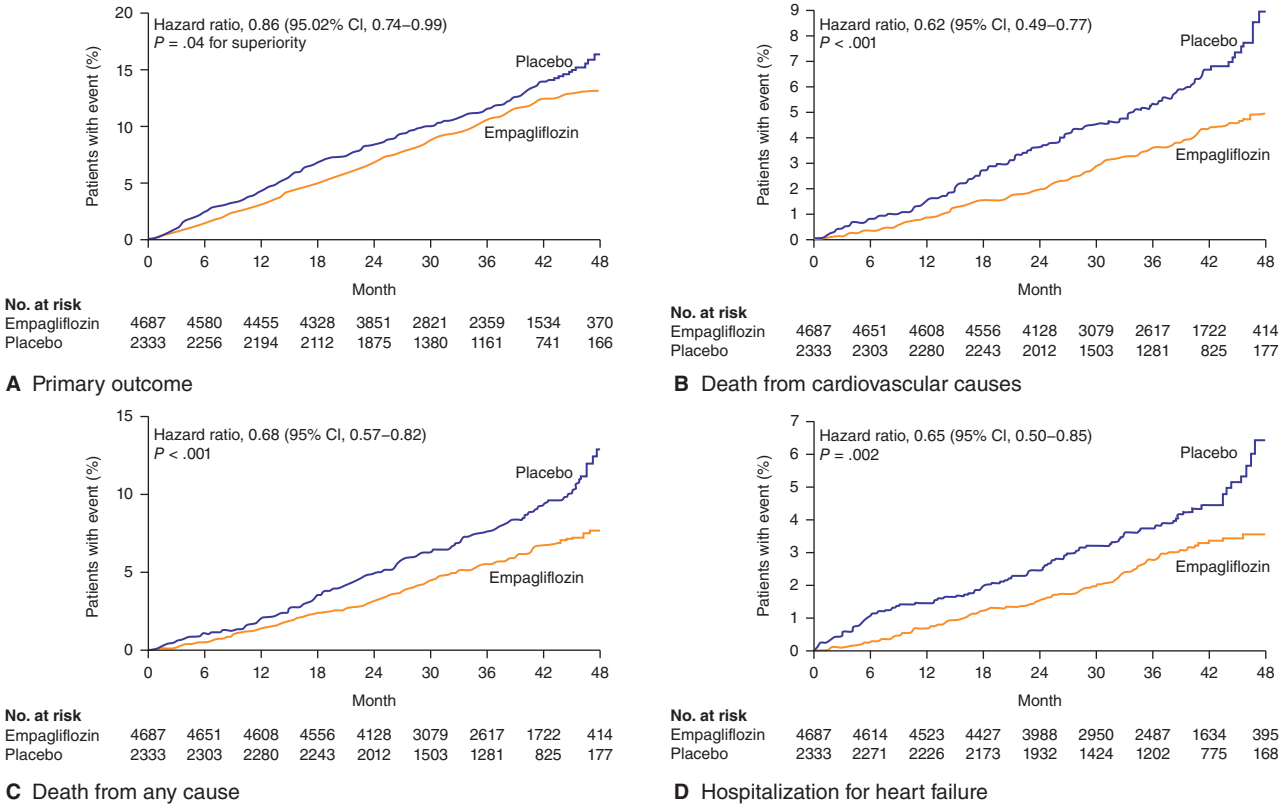


FIGURE 28–10. Cardiovascular outcomes in the EMPA-REG trial. Reproduced with permission from Zinman B, Wanner C, Lachin JM, et al: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015 Nov 26;373(22):2117-28.[92]

TABLE 28–7. Glycemic Control

Trial	Treatment	Primary Outcome	Events Control Group	Events Treatment Group	Relative Risk Reduction (%)	Number Needed To Treat	*P*
Type 1 Diabetes Mellitus							
DCCT *n* = 1441 Patients free of cardiac disease, hypertension, and dyslipidemia	Intensive glycemic control versus conventional therapy	Macrovascular events	40/730 (5.5%)	23/711 (3.2%)	42%	43	.08
Type 2 Diabetes Mellitus							
UKPDS *n* = 3867 Patients with newly diagnosed diabetes mellitus	Sulfonylurea or insulin versus conventional therapy	Diabetes-related outcomes	438/1138 (38.4%)	963/2729 (35.2%)	8.3%	31	.029
UKPDS *n* = 3277 At 10-year follow-up	Intensive glycemic control versus conventional therapy	Mortality	(19.6%)	(16.8%)	14%	7	.01
ACCORD	Intensive glycemic control versus conventional therapy	MACE	371/5123 (7.2%)	352/5128 (6.9%)	40%	NA	.16
ADVANCE *n* = 11140	Intensive glycemic control versus conventional therapy	MACE	1116/5569 (20.0%)	1009/5571 (18.1%)	10%	NA	.37
VADT *n* = 1791	Intensive glycemic control versus conventional therapy	MACE	264/899 (29.4%)	235/892 (26.3%)	11%	Na	.12

DCCT, Diabetes Control and Complications Trial Research Group; MACE, major adverse cardiovascular events; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study.

TABLE 28–8. Recent Trials Examining the Effect of Glycemic Control on Macrovascular Outcomes

	UKPDS	ACCORD	ADVANCE	VADT
Diabetes duration (y)	Newly diagnosed	10 (median)	8 (mean)	11.5 (mean)
Mean age (y)	53	62	66	60
History of vascular events (%)	Not reported in detail, probably low	35	32	40
Duration of intervention (y)	10	3.5	5	6
Postintervention follow-up	10 years	None	None	None
Primary outcome	Three composite endpoints	Nonfatal MI, nonfatal stroke, CVD death	Microvascular + macrovascular complications	Nonfatal MI, nonfatal stroke, CVD death, CHF hospitalization, revascularization
Medication	A: Sulfonylurea/insulin-based B: Metformin-based in obese subjects	All oral drugs and insulin possible	Primarily sulfonylurea-based, other oral drugs possible	All oral drugs and insulin possible
Achieved HbA1c in active vs control group, median exception for ADVANCE mean (%)	Medication A: intervention period 7.0 vs 7.9; follow-up 7.7 v. 7.7 Medication B: intervention period 7.4 vs 8.0; follow-up 8.0 vs 8.0	6.4 vs 7.5	6.5 vs 7.3	6.9 vs 8.4
Hazard ratio for primary outcome (*P*-value or 95% CI)	Medication A: MI 0.85 ($P = .014$) Medication B: MI 0.67 ($P = .005$)	0.90 (0.78-1.04)	Macrovascular 0.94 (0.84-0.87 (0.73-1.04) 1.06)	
Hazard ratio for death	Medication A: 0.87 ($P = 0.006$) Medication B: 0.73 ($P = 0.002$)	1.22 (1.01-1.46)	0.93 (0.83-1.06)	1.07 (0.80-1.42)

CHF, chronic heart failure; CVD, cardiovascular disease; MI, myocardial infarction.

Reproduced with permission from Rönnemaa T: Intensive Glycemic Control and Macrovascular Disease in Type 2 Diabetes - A Report on the 44th Annual EASD Meeting, Rome, Italy, September 2008. *Rev Diabet Stud*. 2008 Fall;5(3):180-183.

hemoglobin glycated hemoglobin levels below 6.0% versus conventional control (glycated hemoglobin between 7% and 7.9%) and the reduction of combined cardiovascular events (death by cardiovascular causes, nonfatal MI, and cerebrovascular accident) was investigated. ACCORD was stopped prematurely because of a 22% excess in total mortality in the treatment group at 3.5 years. A higher incidence of hypoglycemia, weight gain, and fluid retention was also observed in the intensive treatment group when compared to the conventional treatment group. The investigators suggest that the higher mortality in the aggressively treated group might be associated with the intensity and time to glycated hemoglobin levels decrease and/or changes in the treatment regimen with changes in drug types and dosages, eventual interaction of the different classes of drugs used in high doses and their side effects, as well as the combination of all of these factors with the clinical characteristics of each patient.

The mechanism for this mortality excess remains unclear, but there was a trend for a 10% reduction in major cardiovascular events overall with lower incidence of nonfatal MI (respectively, 3.6% vs 4.6%, CI 0.62-0.92; $P = .004$) with aggressive treatment.

Evidence from updated meta-analyses indicates that, for CV death, there is no difference between the intensive (< 7.0% glycated hemoglobin) and usual care strategies.[98] In long-term studies that combine UKPDS, ACCORD, and VADT, MI was reduced by about approximately 15% over the long term. Apart from this modest reduction in MI rates, there was no significant benefit of a more intensive lowering of glycated hemoglobin with regard to cardiovascular macrovascular end points. One meta-analysis of 27,000 participants with 2370 major cardiovascular events, including hospitalization or death from heart failure, showed no important differences between the more intensive arm compared to the less intensive arm.[99]

DYSLIPIDEMIA

Lipid disorders constitute one of the cornerstones in the cardiovascular management of diabetic patients. Many factors influence the lipid profile in these patients, including glycemic control, whether the diabetes is type 1 or type 2, and the presence of diabetic nephropathy.

In type 1 diabetes mellitus, the major determinant of the lipid profile is the level of glycemic control. LDL is moderately increased, triglycerides are markedly increased, and HDL is decreased when the level of glycemic control is impaired. For patients with type 2 diabetes, lipid abnormalities are related not only to hyperglycemia but also to the interplay of the insulin-resistant state. Patients with type 2 diabetes may have normal LDL levels but elevated levels of the very-low-density lipoprotein (VLDL) triglycerides moiety and reduced HDL levels. The expected elevation in VLDL triglyceride is usually no more than 100%.

Low-Density Lipoprotein Cholesterol

Although LDL levels in patients with controlled type 1 or type 2 diabetes may be normal, the atherogenic properties of LDL are increased.[100] There is glycosylation of both apoprotein B and the phospholipid component of LDL, which changes LDL clearance and susceptibility to oxidative modifications. Glycosylation of apoprotein B occurs mainly in the LDL receptor-binding area and is directly related to glucose levels.

As a result, there is impairment in the LDL receptor-mediated uptake, and therefore clearance of LDL. Glycosylation also makes LDL more susceptible to oxidative modification. The product generated by the combined glycosylation and oxidation of LDL is more atherogenic than is either glycosylated or oxidized LDL alone. Such LDL molecules are taken up more easily by the aortic intimal cells and macrophages, resulting in the formation of foam cells.

Type 2 diabetic patients with insulin resistance have LDL particles that are small and rich with triglycerides but have little cholesterol in them (small, dense LDL). These LDL particles increase the risk of CHD independent of the total LDL level, probably because of their increased susceptibility to oxidative modification. Therefore, even though LDL levels may be normal in these patients, high levels of small, dense LDL may contribute to the increased risk of CHD in such patients.

High-Density Lipoprotein Cholesterol

A low HDL level is a strong risk factor for the development of CHD in the diabetic patient. There is decreased production and increased catabolism of HDL in diabetes. The decreased HDL production is a result of decreased lipoprotein lipase activity. The failure of lipoprotein lipase to efficiently catabolize VLDL results in reduced availability of surface components for HDL production. By contrast, increased catabolism of HDL results from the hypertriglyceridemia of diabetes, producing triglyceride-rich HDL_2 that is prone to catabolism by liver enzymes.

Dyslipidemia Management

It is recommended that diabetic patients have a lipid profile performed at or around the age of 40 and every 1 to 2 years thereafter. The frontline primary management strategy remains lifestyle modification with reduction of saturated fats and cholesterol. This specifically involves increase in viscous fiber and plant sterols increase combined with weight loss.

Low-Density Lipoprotein Lowering

Statin Therapy Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors—statins—are the frontline therapy in lowering LDL cholesterol levels in type 2 diabetes patients without having an adverse effect on glycemic control.

The management of diabetic patients with lipid abnormalities is a unique challenge to the cardiologist. Important evidence from large randomized trials of lipid-lowering therapies is based on subgroup analyses in which diabetic patients represented less than 10% of all the patients enrolled; however, more recently studies have been done exclusively in diabetic patients. The 4S study enrolled 202 diabetic patients with a prior history of CHD.[101] Although this number was too small, the comparison of simvastatin with a placebo showed almost a 50% reduction in coronary events in favor of simvastatin (45% vs 23%; *P* = not significant). Similar trends were observed in the Cholesterol and Recurrent Events (CARE) Trial, which compared pravastatin with a placebo in secondary prevention. In the CARE trial, the baseline mean LDL concentration in diabetic patients was 136 mg/dL. LDL was reduced 27% in the group receiving pravastatin, which translated into a 25% reduction in coronary events over 5 years compared with that of the control group.[102] The Heart Protection Study (HPS), with a subgroup of 5963 diabetic patients, showed a 28% reduction in total CHD (nonfatal MI and CHD death), nonfatal and fatal strokes, coronary and noncoronary revascularizations, and major vascular events (total CHD, total stroke, or revascularizations) with simvastatin therapy.[103]

In the trials of statin therapy with hyperlipidemia, the relative benefit appears similar between diabetic patients and nondiabetic patients. The CARDS (The Collaborative Atorvastatin Diabetes Study) trial showed that among 2838 diabetic subjects with at least one heart disease risk factor, but without elevated cholesterol levels, randomized to atorvastatin versus placebo and followed up for 3.9 years, statin therapy was associated with a 37% reduction in the primary composite end point of CHD death, fatal MI, hospitalized unstable angina, resuscitated cardiac arrest, coronary revascularization, and stroke.[104]

The Deutsche Diabetes Dialysis (4D) Study, in contrast, studied 1255 diabetic patients on maintenance hemodialysis, but was unable to show a significant reduction in CHD death, on fatal MI, and on stroke with atorvastatin compared with placebo.[105]

Once patient is on statin therapy, LDL determinations are recommended for improving adherence to therapy but not for monitoring the effect of therapy.

- Secondary prevention: For patients with diabetes and known cardiovascular disease, high-intensity statin therapy is recommended according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines of 2013.[106]
- Primary prevention: For patients with diabetes under the age of 40 with one additional cardiovascular risk factor or those age 40 to 75 without any cardiovascular risk factors, moderate to high intensity statins are recommended.

In a pooled analysis from the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering) trials, patients with prediabetes treated with high-intensity compared to low-intensity statins were more likely to develop new onset diabetes over 5-years (HR 1.20, 95% CI; 1.04-1.37).[107]

Ezetimibe The recent publication of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial has brought ezetimibe back into focus as a potential add-on therapy to statins for acute coronary syndrome patients.[108] There were 4933 diabetic patients enrolled of the over 18,000 total sample size, and they enjoyed even greater benefit in cardiovascular reduction compared to non-diabetic patients (ezetimibe in diabetics; HR 0.86; 95% CI, 0.78-0.94), whereas without diabetes, ezetimibe reduced MACE by only ~ 2%; HR 0.98; 95% CI, 0.92-1.04; *P*-interaction = .02). The use of ezetimibe will likely increase, at least in the acute coronary syndrome population with diabetes.

PCSK-9 Inhibitors Proprotein convertase subtilisin/kexin type 9 (PCSK-9) antibodies hold the promise of significant isolated LDL-lowering of around 60% and have been approved in the United States (alirocumab, evolocumab) for patients who are unable to reach target LDL levels on statins alone either for lack of optimal LDL lowering or because of statin intolerance at higher doses.[109,110] They work by binding to LDL receptors, leading to their degradation and reduction in serum LDL levels. At present there are no specific differences in the efficacy and safety of these compounds between diabetic and nondiabetic patients.

High-Density Lipoprotein and Triglycerides

The addition of niacin and fibrates to statin has not been shown to provide any additional cardiovascular benefit in the following trials.

AIM-HIGH/ HPS-2 The use of niacin to raise HDL, particularly in diabetic lipid disorders has been attractive. However, in the setting of combination therapy with statins, niacin has failed to improve cardiac end points in two major trials: the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE).[111,112] There remains some controversy about these negative results: namely, the rather reduced follow-up in AIM-HIGH and the use of laropiprant in combination with niacin in HPS-2.

The hypertriglyceridemia of diabetes can be treated effectively with fibric acid derivatives without an adverse effect on glucose metabolism. These drugs cause a drop of 5% to 15% in LDL levels in patients with normal triglyceride levels, but in patients with hypertriglyceridemia, LDL levels go up. This elevation probably is caused by the catabolism of the atherogenic LDL particle, resulting in less atherogenic LDL. Fibrate therapy also made a lot of sense prior to the reports from pivotal randomized trials. At present, the use of fibrates for isolated hypertriglyceridemia in individual cases remains an option.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial studied 9795 patients with diabetes at risk for CHD, and showed that fenofibrate was not associated with a difference in the primary composite end point of CHD death or nonfatal MI compared with placebo at 5 years of follow-up.[113] The treatment effect differences, however, may have been attenuated as a consequence of the more frequent use of statins as lipid-lowering therapy in the placebo arm.

The ACCORD lipid trial did not demonstrate any reduction in cardiovascular events when fenofibrate was combined with simvastatin.[114] Fenofibrate in combination with simvastatin did reduce postprandial triglyceride levels thus raising the question of targeted use in diabetic dyslipidemia.[115,116]

HYPERTENSION

The presence of hypertension in diabetic patients significantly increases their risk of micro- and macrovascular complications. It is estimated that 11 million Americans have both diabetes and hypertension. This "deadly duo" definitely march together.[117] Furthermore, hypertension in diabetic patients has been linked with numerous other vascular complications such as nephropathy, retinopathy, the development of cerebrovascular disease, and significant decline in cognitive function in middle-aged diabetic hypertensive patients.

Hypertension Management

Hypertension and Blood Control Current guidelines suggest the following goals for the management of blood pressure in patients with diabetes: systolic blood pressure of less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg, which represents liberalization compared to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) targets.[118] This was on the heels of the ACCORD Blood Pressure trial and the (The International Verapamil-Trandolapril Study) subgroup analysis suggesting that a target blood pressure of 140 mm Hg was adequate when compared to more aggressive targets.[119,120]

Lifestyle modification is frontline therapy with weight loss and a Dietary Approaches to Stop Hypertension (DASH) diet remaining the cornerstone of management. Most diabetic patients will require multiple drug therapies with an ACE-inhibitor or ARB included across the board.[1] An important practice-related strategy is to give at least one of the antihypertensives at night. This has conferred additional cardiovascular benefit.[121]

The UKPDS demonstrated no advantage of captopril over atenolol in reducing macrovascular complications.[122] Clearly, this illustrates the significant role lowering of blood pressure plays in reducing adverse events independent of the agent used. The role of further blood pressure reduction even when high-risk patients such as diabetic patients are in the normal range needs to be delineated further. The Hypertension Optimal Treatment (HOT) study showed that the risk of major cardiovascular events in diabetic patients was halved if they had a target diastolic pressure of 80 mm Hg of less compared with those with a diastolic pressure of 90 mm Hg or less (P for trend = .005).[123] There was a lower but still significant decrease in the risk of silent MI and approximately a 30% risk reduction in the rate of stroke in the 80 mm Hg or less group compared with the 90 mm Hg or less group.

The HOPE trial evaluated over 9000 high-risk patients with evidence of vascular disease or diabetes in a randomized trial comparing ramipril with placebo over a 5-year period.[124] A total of 3578 of these patients had diabetes. This study demonstrated a 22% reduction in primary cardiovascular end points of death, MI, and stroke in favor of ramipril. The beneficial effect of ramipril was observed over all predefined subgroups. Interestingly, there was a 30% reduction in the diagnosis of new diabetic patients in the ramipril-treated arm.

In recent years, therapy with dual renin–angiotensin–aldosterone system (RAAS) inhibition has been suggested as a routine practice, particularly in diabetic patients. On the other hand, data from Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ON-TARGET), which evaluated a combination of ramipril and telmisartan demonstrated a worsening of major renal outcomes despite a reduction in proteinuria compared with monotherapy.[125]

ANTIPLATELET THERAPY

For men over the age of 50 and women over the age of 60 with at least one additional major cardiovascular risk factor, it is recommended that aspirin therapy at 81 mg daily be instituted as a primary prevention statin strategy for type 1 and type 2 diabetic patients, However, for patients who are under the age of 50 for men and 60 for women with no additional major risk factors, aspirin therapy is not recommended.[1]

BARIATRIC SURGERY

In patients with severe/morbid obesity, bariatric surgical options, such as gastric bypass and gastroplasty, may be appropriate and allow significant improvement in glycemic control with reduction or discontinuation of medications. Commonly used bariatric procedures include the Roux-en-Y gastric bypass with a less invasive gastric sleeve or vertical sleeve gastrectomy (Fig. 28–11).

Emerging evidence from large scale randomized trials from both Mingrone and Schauer indicate that for patients with a BMI of more than 35 kg/m^2 with type 2 diabetes, bariatric surgery may be a viable option.[126,127] In the Schauer study from the Cleveland Clinic, the glycated hemoglobin target was achieved in only 5% of those on intensive medical therapy compared to 38% for the gastric bypass group and 24% for the sleeve gastrectomy group out to 3 years. Both surgical groups were statistically superior to intensive medical therapy alone with respect to important biomarkers (Fig. 28–12).

Bariatric procedures are not only reducing glycated hemoglobin levels but also the number of antidiabetic drugs required. Approximately 72% of patients treated with bariatric surgery have near or complete stabilization of glycemic control at 2 years in the SOS (Swedish Obese Subjects) study.[128] Interestingly, the highest rates of remission after bariatric surgery tend to be in patients with higher serum insulin levels with a shorter duration of diabetes.

It is important to fully evaluate the patient for existing or risk for cardiovascular disease and improve glycemic control preoperatively so as to decrease the risk of complications. It is important to counsel patients on the risks of surgery, including mortality, depression, hypoglycemia, nutritional deficiencies, osteoporosis, and weight regain over the long-term. Very little data are currently available on the long-term consequences of surgery for weight loss in people with diabetes. The potential benefits should be weighed against short- and long-term risks.

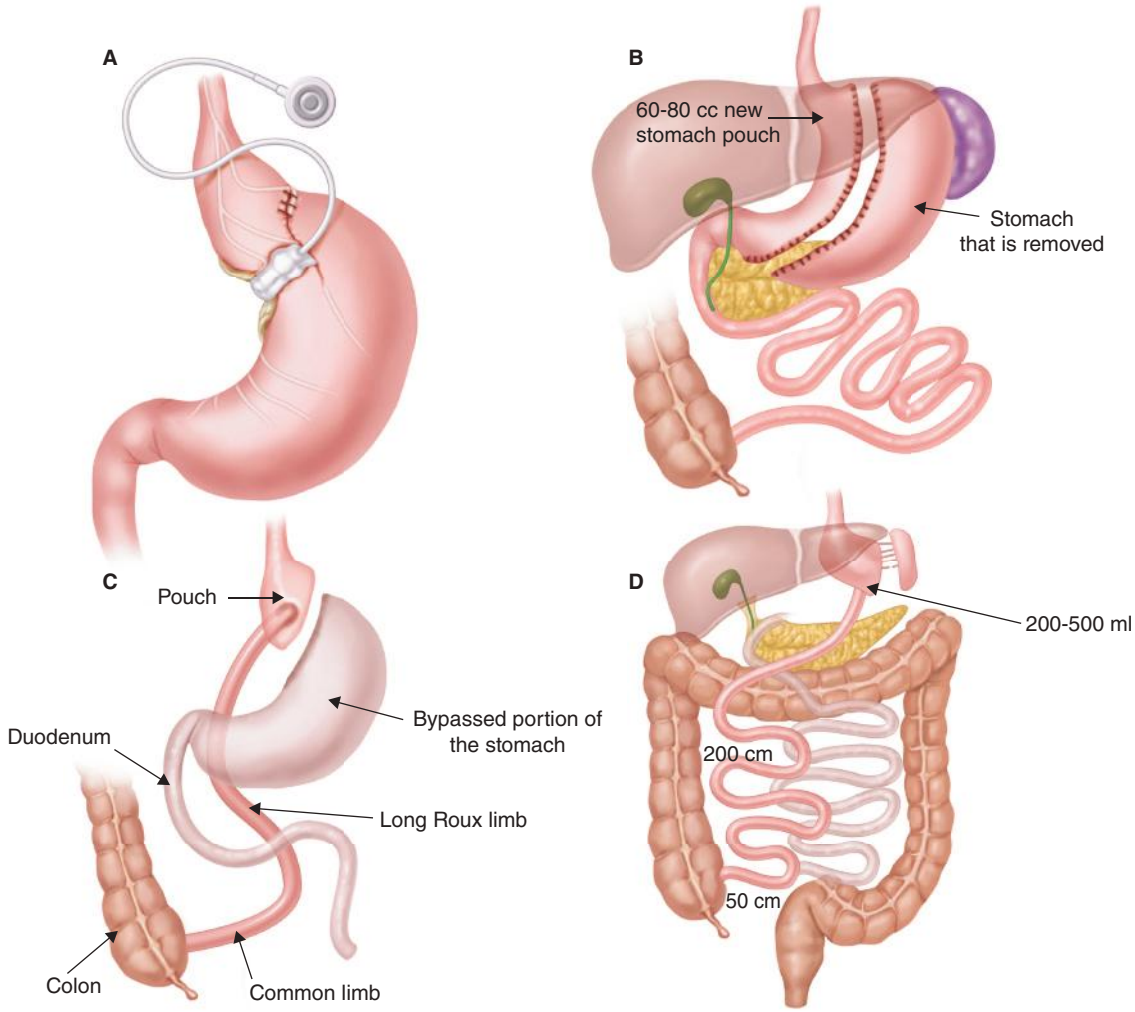


FIGURE 28–11. Different types of bariatric surgery. This figure outlines the different types of bariatric surgery performed in the United States.

NEWER THERAPIES

Islet Cell Transplants

Whole-pancreas transplants have successfully restored insulin secretion in people with advanced diabetes but are usually limited to those who are also undergoing kidney transplantation. In 2000, Shapiro and colleagues developed the Edmonton Protocol for islet transplantation, which used a larger quantity of islet cells with drugs that were less toxic to the immune system.[129] This method infuses islet cells through a small tube into the portal vein of the liver. Patients whose islet cells fail to continue secreting insulin can be retransplanted. Islet cell transplants are still experimental and are available to people who are willing to participate in a study protocol. Also, only a small percentage of islet cell transplant recipients achieve normal blood glucose levels. It is unclear whether the islet transplants will stop or reverse secondary complication related to diabetes. It is also unclear whether islet cell transplantation will ultimately extend a patient's long-term survival. As of 2008, data from the Collaborative Islet Transplant Registry (CITR) indicates that 71% of adults with type 1 diabetes receiving islet cell transplants were insulin dependent at 1 year, 52% at 2 years, and 23% at 3 years.[130]

Pancreas Transplantation

Ten percent of pancreas transplantations are performed in nonuremic patients with very labile and problematic diabetes.[131] The negative aspect of whole-pancreas transplantation is the need for immunosuppression, which increases the risk of viral and fungal infections and some types of malignancy. Recipients of a pancreas transplant alone have an average 1-year pancreas graft survival rate as high as 78% to 83%.

Successful pancreas transplantation will reverse the thickening of glomeruli and tubular basement membranes, as well as the increase in mesangial volume. Motor sensory and autonomic neuropathy are reversed within 12 to 24 months after transplantation.

Artificial Pancreas

The closed-looped artificial pancreas is being aggressively developed. Russell, Damiano, and colleagues in Boston have shown that compared to an insulin pump, a wearable, automated bionic pancreas delivering both insulin and glucagon was able to improve glycemic targets with less frequent episodes of hypoglycemia over a 5-day period in 20 adults and 32 adolescents with type 1 diabetes mellitus.[132]

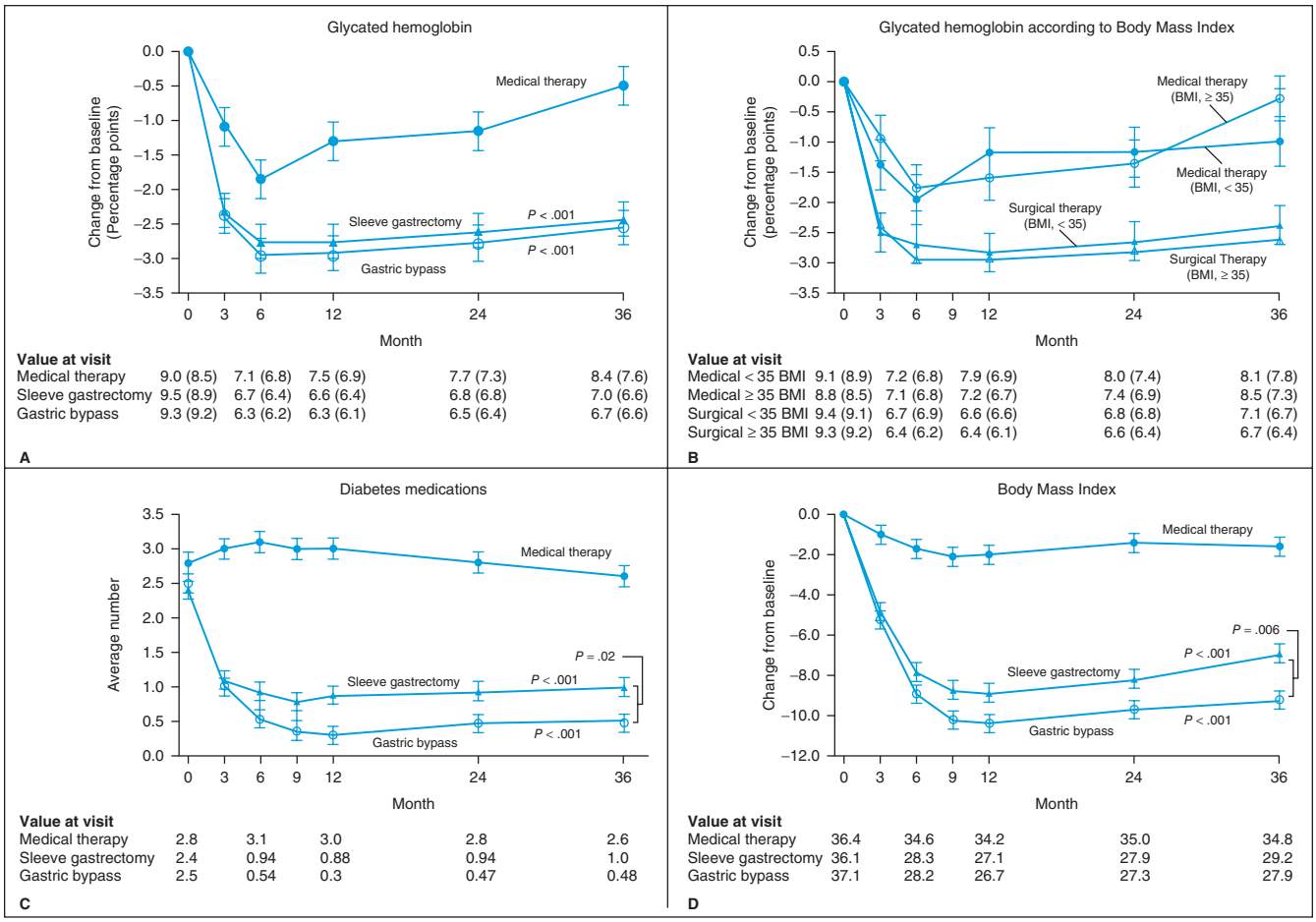


FIGURE 28–12. STAMPEDE, with mean changes in measures of diabetes control from baseline to 3 years. BMI, body mass index. Reproduced with permission from Schauer PR, Bhatt DL, Kirwan JP, et al: Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. *N Engl J Med*. 2014 May 22;370(21):2002-2013.[127]

Another collaborative ongoing series of studies led by Kovatchev and collaborators from Charlottesville, Virginia and other centers, uses a smartphone app that receives data from a CGM and gives commands via Bluetooth to an insulin pump. These two devices are being actively studied both in inpatient and ambulatory settings.[133]

Gene Therapy

Type 1 diabetes mellitus is caused by T-cell–mediated destruction of pancreatic insulin-producing beta cells. Tian and colleagues found a novel way to restore central tolerance in nonobese diabetic mice using hematopoietic stem cells retrovirally transduced to express a protective form of the major histocompatibility complex class II β chain.[134] As a result, autoreactive T cells will be killed in the thymus and never get to the pancreatic beta cells. Central tolerance refers to mechanisms of tolerance acting in the thymus or bone marrow, in contrast to peripheral tolerance, which occurs in immune cells after they have left the primary lymphoid organs. Preclinical studies must be completed before stem cells can be successfully given to humans with type 1 diabetes mellitus. Some drugs may be synthesized so that they exert their effect only within the areas of inflammation. One example is an engineered transforming growth factor-1β that can become activated locally within areas of beta-cell inflammation.

Mechanical Closed-Loop Sensors

Mechanical closed-loop systems are currently under development.[135] They consist of a continuous glucose sensor and an insulin pump that can either infuse insulin subcutaneously or directly into the portal circulation. Such a device would not require immune suppression but would be potentially subject to mechanical breakdowns. In theory, these devices could provide both "basal" and synchronized "bolus" insulin requirements. One such device tested in 10 type 1 diabetic patients was implanted without complications. However, the system's success was limited by pump slowdowns due to insulin precipitation and limited sensor longevity (average of 9 months).[136]

Stem Cells

Stem cells are a potential source of beta cells, which may restore the deficient beta-cell mass found in diabetes,[137] and are the "holy grail" for the treatment of type 1 diabetes. This concept would assume the source of beta-cell destruction could be abated. Ianus and colleagues found an extrapancreatic source of pancreatic beta cells in bone marrow–derived cells in a mouse model. Pancreatic endocrine and exocrine cells both originate from epithelial cells from early gut endoderm. A second source of stem cells is in the pancreas from progenitor epithelial cells in the pancreatic duct. Much more work is required to translate the potential that stem cells have to produce insulin on demand clinically.

Stem cell therapy is in the research pipeline and the reader is referred to several articles for more data.[138-140]

A central theme of current research is that inhibition of tumor growth factor-β signaling an adult murine beta cells can promote beta-cell replication.[141] Stem cell differentiation and transdifferentiation from alpha or

delta cells may be possible. Also, autoimmunity needs to be harnessed. We must stay tuned for further developments in this exciting area.

CORONARY REVASCULARIZATION

The management of diabetic patients with CHD entails both pharmacologic and revascularization strategies. Over the past several years, there have been many advances in the medical management of the diabetic patient with CHD. Aspirin, β-blockers, statins, and ACE inhibitors are routinely administered. These agents may provide clinical benefit not only by treating ischemia, but also by stabilizing atherosclerotic plaque and inhibiting endovascular thrombosis, thereby preventing acute coronary events.

Coronary revascularization procedures have become a mainstay of therapy for CHD patients, providing both symptomatic relief and mortality reduction in certain anatomic subsets. Several studies have attempted to rationalize the use of different revascularization techniques by comparing them to medical therapy and to each other in various clinical settings.

The evaluation of coronary revascularization in diabetic patients was enriched by a number of important trials important trials CARDIA (The Coronary Artery Revascularisation in Diabetes), VACARDS,[142,143] SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery), and FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease). The SYNTAX program consisted of a randomized trial of patients with three-vessel or left main disease comparing PCI with paclitaxel-eluting stents versus coronary artery bypass graft (CABG) as well as two parallel registries of patients ineligible for PCI or CABG respectively. In the SYNTAX trial about 28% or 452 of the 1800 patients had diabetes.[144] At 12-months of follow-up, the only difference between PCI and CABG for diabetic patients was the excess of repeat revascularization in the PCI arm (20.3% vs 6.4%; $P < .001$). As expected, when compared to nondiabetic patients, the 12-month rate of death, MI, or stroke was higher for the diabetic cohort (10.2% vs 6.8%). Interestingly, when moving across the spectrum of non-diabetes to metabolic syndrome to insulin-treated diabetes, the 12-month major adverse cardiovascular and cerebrovascular events (MACCE) rate for CABG was consistent at between 12% and 14%, whereas, the MACCE rates for PCI progressed from 15% in nondiabetes to 30% in insulin-treated diabetes. The SYNTAX investigators intend to follow the patients for up to 5 years.

Another important aspect of the SYNTAX program was the derivation and evaluation of the SYNTAX scoring system for grading the complexity of CAD. Simply, the SYNTAX score is the summation of the points assigned for each individual lesion in the coronary tree (divided into 16 segments). The percent stenosis is not included, but rather the scoring is assigned according to occlusive versus degrees of nonocclusive disease, and the complexity of a given lesion (eg, bifurcation lesion) is factored into the score. Based on angiographic criteria, the investigators demonstrated that patients with higher scores and, therefore, more complex disease, were more likely to benefit from CABG surgery over PCI. This is based on the observation that not all three-vessel and left main disease are equivalent.

The CARDIA trial evaluated diabetic patients with multivessel disease exclusively to either drug-eluting stent (DES)-PCI or CABG. This 500-patient trial was underpowered to detect important clinical differences in death, MI, or stroke at 12 months. In a noninferiority analysis, the primary event rate was greater in the PCI arm (11.6 vs 10.2%; P = not significant), but this failed to meet statistical significance. PCI was not proven to noninferior to CABG because of wide 95% confidence intervals. As in SYNTAX, there was an excess in repeat revascularization in the PCI arm. CARDIA set the stage for the FREEDOM trial, which will have 1900 subjects with a mean follow-up 3.8 years. FREEDOM, in 2012,[145] reported that the primary outcome (composite of all-cause mortality, nonfatal MI, or nonfatal stroke) was more likely to occur at 5 years in the PCI group as opposed to the CABG group (26.6% vs 18.7%, respectively; $P = .005$). The percent-year rates of nonfatal MI and all-cause mortality were greater in the PCI arm (13.9% vs 6.0%; $P < .001$ for nonfatal MI and 16.3% vs 10.9%; $P = .049$) for all-cause mortality, and the rate of nonfatal stroke was significantly lower in the PCI-DES arm (2.4% vs 5.2%; $P = .03$). Given the findings from COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and from BARI 2D (The Bypass Angioplasty Revascularization Investigation 2 Diabetes), FREEDOM had strict medical management targets for both strategies. FREEDOM led to a class 1 indication for CABG in diabetic patients with multivessel CAD when using the heart team approach.[146]

See Chap. 44, which reviews the trials of PCI versus CABG in detail.

Newer Generation Drug-Eluting Stents

By the time that FREEDOM reported, we witnessed the advent of second- and later generation DES platforms. New evidence suggests that later generation stents have closed the gap between CABG and PCI in diabetic patients.[147] The TUXEDO (The Taxus Element versus Xience Prime in a Diabetic Population) trial and meta-analysis that included patients from 68 randomized controlled trials showed, for example, using cobalt-chromium everolimus-eluting stents may be promising.[148] From BARI to ARTS to FREEDOM the point estimate for mortality remains unchanged, so that it would be a mistake to continue to test the CABG versus PCI hypothesis without first demonstrating that systemic therapy with optimal medical management can be improved to the point where nontarget lesions are no longer an issue.

Comprehensive Meta-Analysis of PCI versus CABG

One major meta-analysis by Hlatky and colleagues from the early percutaneous transluminal coronary angioplasty, or PTCA, and bare metal stent (BMS) era reported on their findings. The diabetes subgroup appeared to fare better with CABG when 5-year findings were pooled.[149] Verma and coworkers reported on the 5-year survival benefit of CABG over PCI in diabetic patients with multivessel CAD showing little difference between BMS-PCI and DES-PCI. The increased risk of stroke after CABG was significant and consistent with the FREEDOM findings.[150]

Screening Asymptomatic Diabetic Patients—DIAD

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial publication answered an important question in the diabetes and CAD field: namely, what is the role of routine screening for myocardial ischemia in asymptomatic diabetic patients?[151] For many years, the American Heart Association had advocated for optimal management of coronary risk factors as frontline therapy. Colleagues from the ADA felt strongly for routine stress testing in these patients. Over 1000 patients asymptomatic patients were randomized to undergo myocardial perfusion imaging or no screening. After 5 years, there was no difference in the rates of nonfatal MI or cardiac death between the two arms (relative risk reduction 12%; 95% CI, 78%-56%). The DIAD trial demonstrated a very low rate of significant ischemia in the screening arm (about 6% with moderate to large perfusion defects) and a very high adherence to a robust medical risk factor modification program. In fact, the excellent medical therapy in DIAD is responsible for a very low 5-year primary event rate. The National Institutes of Health-funded ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial will address what

is the best therapy for patients with moderate to large perfusion defects if they were to be treated aggressively in an adequately powered trial? If there is no benefit to revascularization in these patients then there is no rationale to screen for ischemia. Further analysis from BARI 2D may help address this issue.

Coronary Revascularization Compared to Optimal Medical Therapy in Less Aggressive CAD

About one-third of the patients randomized in the COURAGE trial were diabetic.[152] The trial demonstrated no difference in the 5-year MACE rate. This required further confirmation. BARI 2D was a multicenter NHLBI-sponsored study to address two important question.[153] First, it addressed the question of whether diabetic patients with relatively mild or no symptoms could be treated with deferred (optimal medical therapy [OMT] alone) compared with prompt revascularization on top of OMT. The important feature was that patients were randomized postcatheterization with anatomy defined and required at least one lesion to be amenable for revascularization. It is critical to emphasize that the decision to undertake PCI or CABG was left to the discretion of the investigators with the caveat that patients with multivessel and more extensive disease were more likely to undergo CABG. Second, BARI 2D addressed the question of whether treatment with an insulin-sensitizing strategy was superior to a strategy of insulin provision with a target glycated hemoglobin of less than 7.0% in both arms. Patients with left main disease or creatinine greater than 2.0 mg/dL were excluded.

In the end, 2368 patients were enrolled at 60 international sites with 1605 in the PCI versus OMT strata and 763 in the CABG versus OMT strata (see Fig. 28–12). As expected, 93% of patients with single-vessel disease were enrolled in the PCI stratum and conversely, 55% of triple-vessel disease patients were enrolled in the CABG stratum. The primary outcome measures of the trial demonstrated no difference in 5-year mortality for either of the comparison of OMT versus prompt PCI (12.2% vs 11.7%; $P = .97$) or the comparison of an insulin-sensitizing versus an insulin-providing strategy (11.8% vs 12.1%; $P = .89$). Similarly, the rates of MACE between the two principle comparisons did not differ.

BARI 2D was an important contribution because two key conclusions can be drawn. One, patients with diabetes mellitus who are asymptomatic or have mild symptoms can be first treated with OMT alone. By 5 years, 40% of these patients will require a deferred revascularization procedure. Two, when OMT is applied, the target of glycated hemoglobin of 7% can be achieved by an individualized approach. Patient adherence, polypharmacy, weight gain, and edema are all factors that will factor into the antidiabetic strategy employed. The TZDs were safe in BARI 2D with a high prescription of rosiglitazone observed.

DIABETES PREVENTION

Increasing evidence suggests that an atherogenic prediabetic state exists prior to the development of diabetes. In the San Antonio Heart Study, patients converting to overt diabetes had significantly higher blood pressure, BMI, waist circumference, triglyceride levels, and lower HDL cholesterol levels at baseline compared to nonconvertors.[154]

Investigators from Finland conducted a randomized trial of 522 middle-aged, overweight subjects with impaired glucose tolerance (350 women, mean age: 55 years).[155] Patients were randomized to a control group or an intervention group that consisted of individualized counseling aimed at reducing weight, total intake of fat, and intake of saturated fat, and increasing intake of fiber and physical activity. Over 4 years of follow-up, the cumulative incidence of diabetes was 11% in the intervention group and 23% in the control group (58% reduction; $P < .001$). The authors concluded that type 2 diabetes indeed could be prevented with an intensive lifestyle modification program.

The Diabetes Prevention Program evaluated more than 3000 nondiabetic subjects with impaired fasting, and postglucose loading plasma glucose levels and showed that when compared to placebo, a lifestyle intervention reduced the incidence of developing diabetes by 58% (95% CI interval, 48%-66% and NNT of 7).[156] Metformin reduced the incidence by 31% (95% CI interval, 17%-43%; NNT of 14). When compared head to head, the intervention group fared better than did the metformin group.

Trials with antidiabetic agents in preventing type 2 diabetes have had limitations: the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial has randomized 5269 patients with either impaired glucose tolerance or impaired fasting glucose in a factorial design to ramipril and/or rosiglitazone to determine whether such therapy prevents the onset of new type 2 diabetes. Rosiglitazone therapy led to a highly significant reduction in incident diabetes (HR 0.04, 95% CI 0.35-0.46; $P < .0001$); however, the use of rosiglitazone has fallen off because of safety concerns.[157,158] The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, the largest diabetes prevention clinical trial to date, showed a modest reduction of 14% in the development of type 2 diabetes with valsartan but not nateglinide in 9150 subjects who have impaired glucose tolerance and are at high cardiovascular risk.[159,160]

EARLY DETECTION OF CARDIOVASCULAR DISEASE IN THE DIABETIC PATIENT

The significant increase in major microvascular and macrovascular complications makes it important to begin screening for diabetes at an age younger than 45 years.[161] It has become necessary to implement aggressive screening strategies to be able to identify populations at the highest risk of developing diabetes.[162]

Current measures of cardiovascular surveillance for CAD in asymptomatic diabetic patients focus on routine stress testing in accordance with the ACC/AHA guidelines. Exercise testing in diabetic patients is more likely to be accurate when combined with echocardiography or radionuclide imaging.[163] Diabetic patients are less likely to have an appropriate blood pressure and heart rate response to exercise and less likely to experience any pain corresponding to ST-segment changes caused in part by autonomic dysfunction. The AHA recommends that the finding of subclinical CAD should prompt clinicians to initiate more aggressive preventative measures. The DIAD study has shown that the prevalence of silent ischemia in the diabetic population is not insignificant, but the annual cardiac event rate is less than 1% overall at 4.8 years of follow-up and that routine screening for inducible coronary ischemia did not reduce cardiovascular events.[164]

NOVEL STRATEGIES FOR EARLY DETECTION AND RISK PREDICTION

There are a number of strategies aimed at identifying subclinical atherosclerosis in diabetic patients. Two strategies that have the best evidence include coronary artery calcium (CAC) and ankle brachial index determination (ABI). CAC imaging has been shown to provide incremental predictive value over traditional cardiovascular risk factors.[165] The ABI is a cost-effective technique for screening that is underutilized three-dimensional carotid ultrasound and not carotid media thickening is showing promise in large cohort studies.[166] Other strategies as measuring for cardiac autonomic dysfunction through assessment of

heart rate variability and QT index may provide incremental prognostic value in predicting mortality.[167]

FUTURE DIRECTIONS

On the clinical front, there are still many challenges in the prevention and management of diabetic cardiovascular complications. The focus on a multidisciplinary approach to diabetic cardiovascular disease is critical because we are dealing with a chronic, systemic illness. Glycemic control appears to be the mainstay of long-term diabetes management. Thus, development of better therapies and devices (eg, gene therapy, stem cell therapy, artificial pancreas, closed-loop pumps, islet and pancreatic transplants) for achieving and maintaining glycated hemoglobin at not only less than 7%—but in the normal range of less than 6%—will be a primary goal in the next decade. The first antidiabetic trial to demonstrate a benefit both in cardiovascular mortality and heart failure hospitalization, EMPA-REG, was recently reported and is a potential transformational development. The results of cardiovascular outcomes trials with SGLT-2 agents are anxiously awaited. The superiority of CABG over PCI with DES in FREEDOM led to a class 1 recommendation for the treatment of multivessel CAD. Strategies to reduce the increased risk of periprocedural stroke in CABG remains an important challenge for the next decade because the diabetic population with CAD ages and a focus on quality of life will prevail. Significant improvement in OMT with aggressive LDL-lowering agents will potentially alter the need for coronary revascularization down the road. Finally, the role of cell-based therapies in the management of diabetic atherosclerotic vascular disease needs to be addressed within the context of all other advances.

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CHAPTER 29

HYPERLIPIDEMIA

Robert S. Rosenson and Scott M. Grundy

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LIPOPROTEIN METABOLISM AND ATHEROSCLEROSIS

The major lipids of plasma, cholesterol and triglyceride, are transported in molecular complexes called lipoproteins. The basic structure of all lipoproteins is similar. They contain a core of neutral lipid (triglyceride and cholesterol ester) that is surrounded by a polar coat containing nonesterified cholesterol, phospholipid, and proteins (called apolipoproteins) (Fig. 29–1). The major categories of lipoproteins consist of low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), high-density lipoprotein (HDL), and chylomicrons. These lipoproteins vary in size and density (Fig. 29–2). Because lipoproteins can be separated by electrophoresis, they also have been named according to their migration relative to serum proteins. LDL is called beta lipoprotein, VLDL is pre-beta lipoprotein, and HDL is alpha lipoprotein.

The primary function of lipoproteins is to transport triglycerides and cholesterol.[1-5] The major forms of triglyceride-rich lipoproteins (TGRLs) are chylomicrons (Fig. 29–3)[6,7] and VLDLs (Fig. 29–4). Chylomicrons are synthesized in the liver from dietary fat. They are secreted into the circulation for transport of lipids to tissues. In the circulation, chylomicron triglyceride undergoes hydrolysis by an enzyme, lipoprotein lipase (LPL), located on the surface of capillary endothelial cells; fatty acids released during lipolysis are taken up by adipose tissue and muscle. In addition, the liver synthesizes triglyceride from fatty acids and incorporates it into VLDL particles. VLDL triglyceride likewise undergoes lipolysis, releasing fatty acids for adipose tissue and muscle. Following triglyceride lipolysis, an intermediate lipoprotein, called a VLDL remnant, is formed. A portion of VLDL remnants is removed by the low-density lipoprotein receptor (LDLR), but most VLDL is converted through intermediate lipoproteins to LDL. The latter is removed from the circulation by LDLRs that are located on the surface of liver cells.[8,9]

Circulating lipoproteins contain multiple proteins, called apolipoproteins.[10-15] The major apolipoprotein of LDL and VLDL is called apo B-100.[16] VLDL also contain apo Cs and apo Es[13,17,18]; these apolipoproteins are smaller than apo B-100. LDL contains only apo B-100. LDLRs recognize apo B-100, and to a lesser extent, apo Es. Apo C-II is required for activation of LPL, whereas apo C-III interferes with LPL activity[13,19] (Fig. 29–5).

Following ingestion of dietary fat, the intestine also forms triglyceride- rich lipoproteins (TGRLPs) called chylomicrons. The triglyceride of chylomicrons follows a metabolic path similar to that of VLDL-triglyceride. Chylomicrons interact with LPL and release fatty acids, which go mainly to adipose tissue for reesterification into triglyceride. The major apolipoprotein of chylomicrons is apo B-48, which is a truncated version of apo B-100.[16] Apo B-48 is not recognized by LDLRs. Removal of most chylomicron-triglyceride results in a chylomicron remnant, which is then removed by the liver. The removal pathway is not fully understood.

An elevated plasma LDL is designated a major risk factor for atherosclerotic cardiovascular disease (ASCVD). Several lines of evidence support a strong association: animal studies, genetic forms of elevated LDL, epidemiological associations, and randomized controlled trials (RCTs) of LDL-lowering therapies.[20]

The biological mechanisms whereby elevated LDL produces atherosclerosis have been extensively studied.[4,21-26] Circulating LDL particles filter into the arterial intima, where they are retained by interstitial proteoglycans. Through processes not fully understood, LDL undergoes structural modifications that render it susceptible to macrophage attack. Macrophages ingest modified LDL particles and are thereby transformed into lipid-rich foam cells.

Steps in progression of atherosclerosis have been studied in detail.[27-33] The major stages of atherogenesis are summarized in Fig. 29–6.[33] Accumulation of large numbers of foam cells gives rise to fatty streaks. Some foam cells die and release their cholesterol esters into the interstitium, and over time the core of extracellular lipid expands. Later, smooth muscle cells from the medium began to produce fibrous connective tissue. This tissue forms a covering of the fatty streak; here the lesion is called a fibrous plaque (fibroatheroma). Continuous filtration of LDL

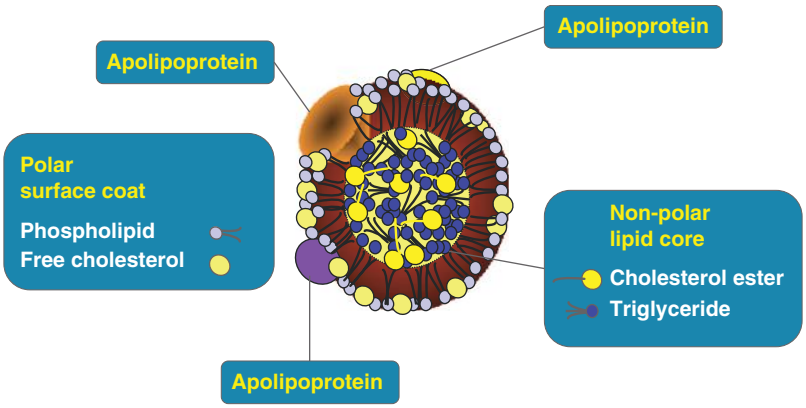

FIGURE 29–1. Lipoprotein structure. Because cholesterol and triglycerides are hydrophobic lipids that are insoluble in plasma, intravascular transport cannot occur with these lipids in their free state. Consequently, cholesterol esters and triglycerides are packaged into spherical lipoprotein particles that span a wide range of particle size and density. Lipoprotein particles are configured so that the outer surface is polar and the inner core is nonpolar. The surface of lipoprotein particles is composed of a phospholipid monolayer, nonesterified cholesterol, and various apolipoproteins. The core of lipoprotein particles contains variable amounts of cholesterol ester and triglycerides. Reproduced with permission from Davidson MH, Toth PP, Maki KC: *Therapeutic Lipidology*. Totowa: Humana Press; 2007.

into the arterial wall leads to several steps to plaque progression; after many years, atheromas degenerate into complicated lesions, become unstable, and are prone to rupture.

When rupture occurs, plaque material discharges into the lumen of the artery, producing thrombosis and cardiovascular events.[34-37] At any stage of this process, LDL-lowering therapy reduces plaque progression and decreases the likelihood of plaque rupture and acute ASCVD events.[38]

A unique form of LDL is called lipoprotein(a) [Lp(a)].[39-42] This is an LDL particle in which apo B is covalently linked to another protein named apolipoprotein(a) [apo(a)]. Metabolism of Lp(a) is illustrated in Fig. 29–7.[43] The structure of apo(a) is genetically variable. This variability determines the size of the Lp(a) particle. Apo(a) is structurally related to plasminogen. It contains a variable number of "kringle IV" repeats, each of which consists of 114 amino acids. The greater the number of repeats, the lower is the plasma concentration of Lp(a). Considerable evidence exists of Lp(a) carries atherogenic potential equal to or even greater than LDL.

There is growing evidence that VLDL, like LDL, is atherogenic.[7,44-50] For this reason, many investigators favor combining LDL and VLDL into a single fraction of *atherogenic lipoproteins*. This can be done in either of two ways. First, the cholesterol (C) content of both LDL-C and VLDL-C can be combined; this fraction is named non-HDL cholesterol (non–HDL-C).[51-53] Because LDL and VLDL contain apo B-100 (Fig. 29–8),[54] some investigators favor measurement of total apo B-100 over non–HDL-C.[55-57] But there is a high correlation between non–HDL-C and apo B,[58] so either can be used as a surrogate for atherogenic lipoproteins. Non–HDL-C has the advantage that it is more readily available in clinical practice and is less expensive than apo B. Nonetheless, apo B may be more informative for treatment decisions such as titration of statins or lowering atherogenic lipoprotein concentrations with combination therapy.

Chylomicrons seemingly are not atherogenic. Native chylomicrons likely are too large to filter into the arterial wall. There is a minimal amount of triglyceride in atherogenic lesions. On the other hand, chylomicron remnants may promote atherosclerosis.[59-63] Normally, chylomicron remnants are rapidly removed from the circulation; consequently plasma levels are very low. In some circumstances, however, concentrations of chylomicron remnants can be relatively high.[64] When this occurs, chylomicron remnants may contribute to atherosclerosis.[65]

HDLs do not contain apo B. Instead, HDL particles are held together by apo A-I and apo A-II.[66] HDLs are considered antiatherogenic (Fig. 29–9),[67] but under some circumstances HDL apo A-I may be proatherogenic (Fig. 29–10).[68] It has been conventionally believed that the reason is an absence of apo B; however, HDL have multiple potentially atheroprotective properties. High levels of HDL-C nonetheless are associated with reduced risk of ASCVD.[69,70] Whether an elevation of HDL is actually protective against ASCVD or instead is a marker for reduced risk is uncertain.[71] Although the epidemiologic evidence for an inverse association is strong, to date no convincing RCTs have demonstrated that raising HDL-C levels prevents ASCVD events. Nonetheless, the search for efficacious HDL-raising drugs continues to be active.[72] If HDL is truly antiatherogenic, therapies that enhance these atheroprotective pathways are being explored. Various possibilities have been proposed and continue to be investigated.[68,73]

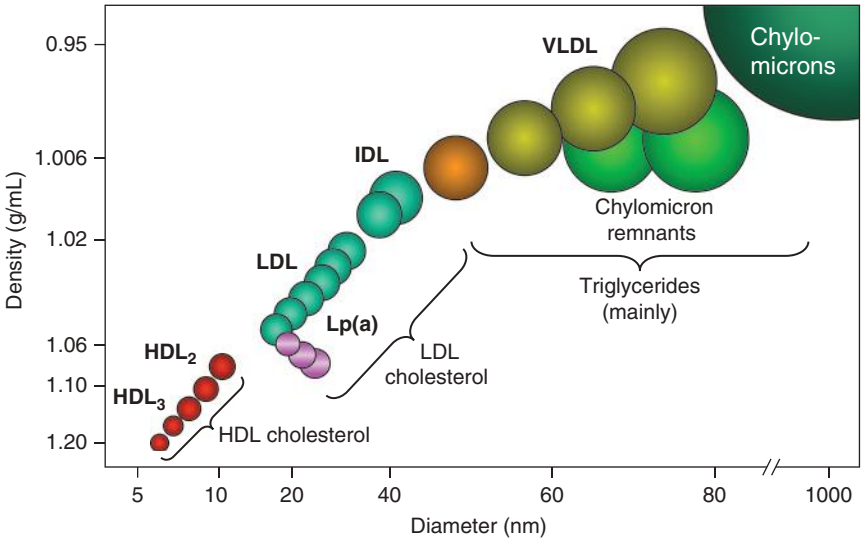

FIGURE 29–2. Spectrum of lipoprotein particles. Cholesterol and triglycerides are lipid measures used to infer the amount of various lipoprotein particles. HDL, high-density lipoprotein, IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein, Lp(a), lipoprotein a, VLDL, very-low-density lipoprotein.

DEFINITION OF HYPERLIPIDEMIA

The two main categories of hyperlipidemia are hypercholesterolemia and hypertriglyceridemia. Neither has a precise definition. In the past, they were defined according to their gaussian distribution. This approach no longer holds, because of their graded associations with atherosclerotic disease. The National Cholesterol Education Program (NCEP),[20] identified multiple levels of LDL-C based on their association with ASCVD; a modification of this classification, including values for non–HDL-C, is shown in Table 29–1.

Hypertriglyceridemia likewise is subdivided into normal, borderline high, high, and very high (Table 29–2).[20]

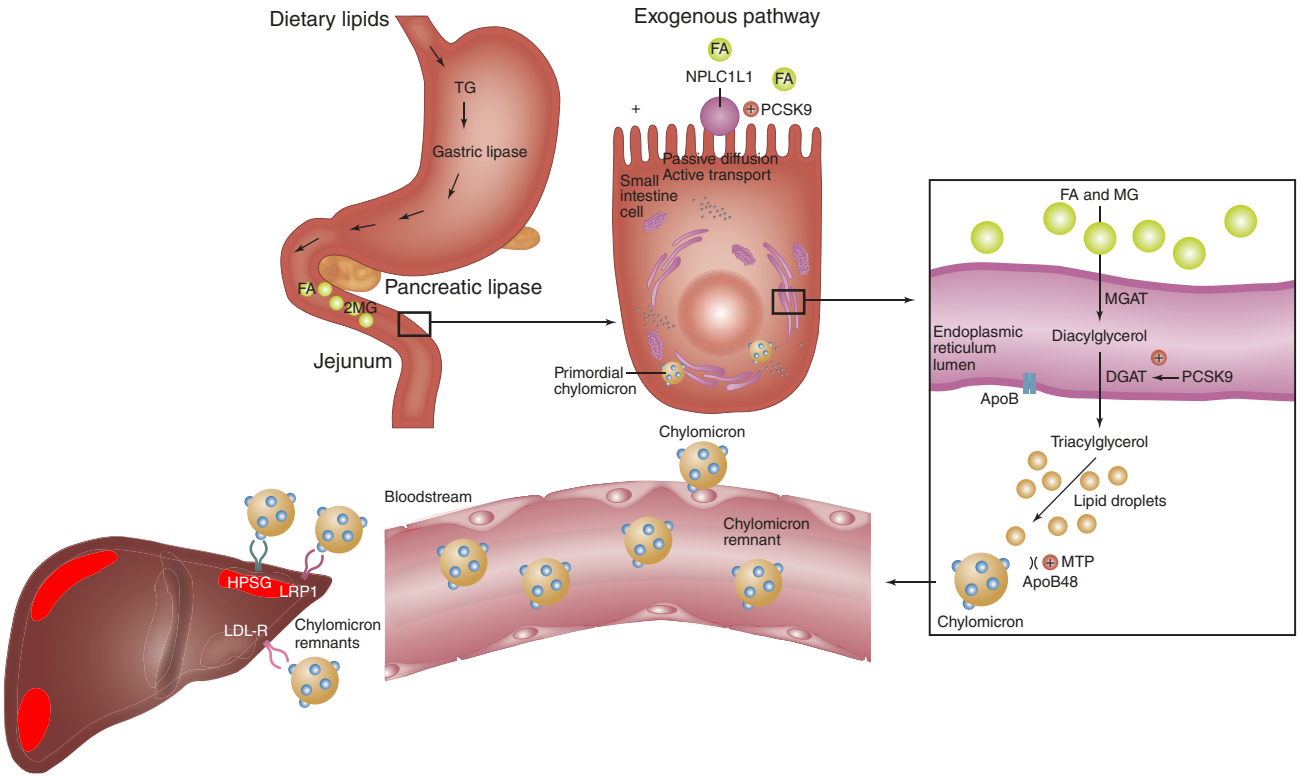

FIGURE 29–3. Intestinal synthesis and hepatic synthesis and metabolism of triglyceride-rich lipoprotein, with chylomicrons and exogenous pathway of lipoprotein biogenesis. FA, fatty acid; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kinexin 9; TG, triglyceride; ApoB, apolipoprotein B; LDC-R, low density lipoprotein receptor; MG, monoglyceride; HSPG, heparin sulfate proteoglycan; NPLC1L1, Niemann-Pick C1-like. Reproduced with permission from Rosenson RS, Davidson MH, Hirsh BJ, et al: Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014 Dec 16;64(23):2525-2540.[7]

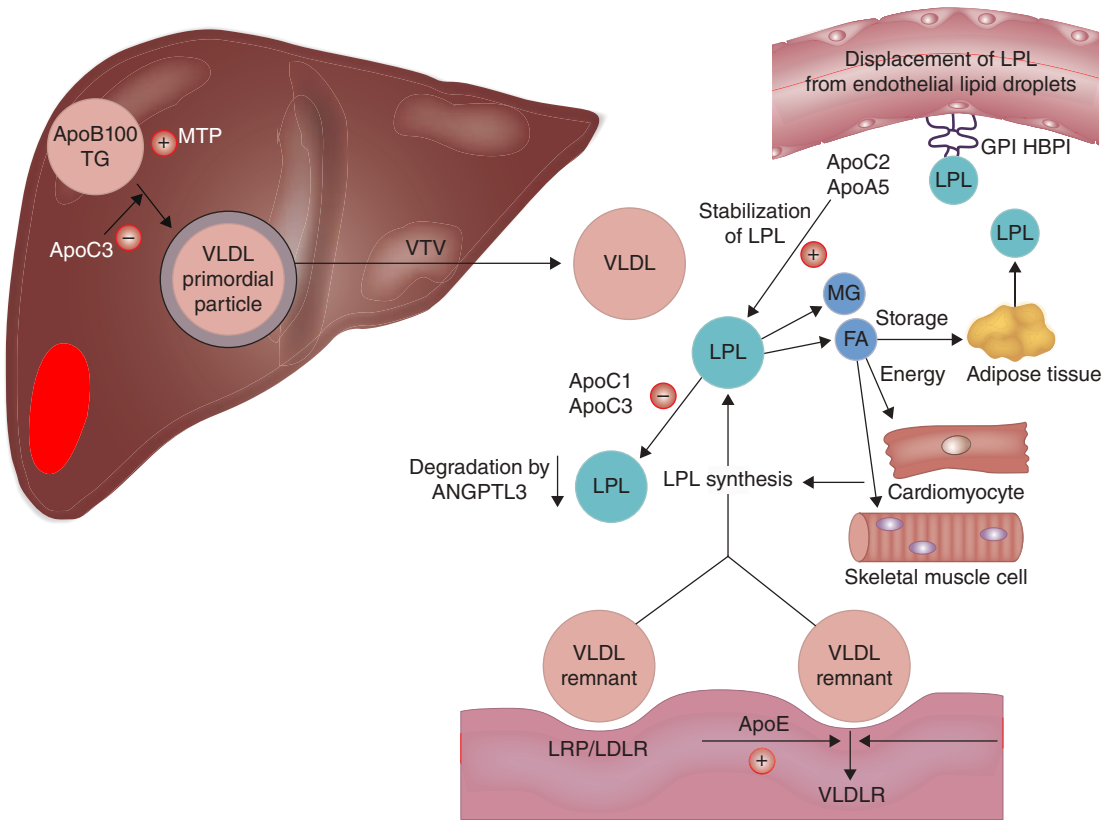

FIGURE 29–4. Very-low-density-lipoprotein (VLDL) and endogenous pathway of lipoprotein biogenesis. FA, fatty acid; LDL, low-density lipoprotein; MTP, microsomal triglyceride transfer protein. Reproduced with permission from Rosenson RS, Davidson MH, Hirsh BJ, et al: Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014 Dec 16;64(23):2525-254.[7]

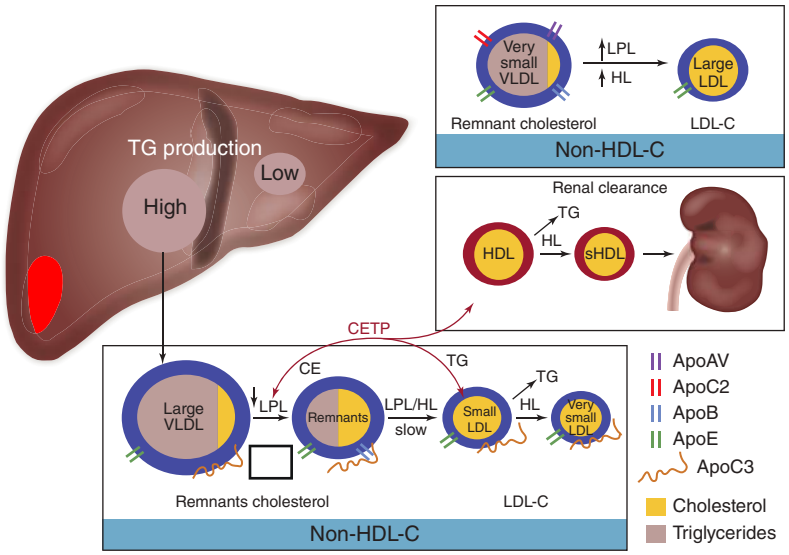

FIGURE 29–5. Apolipoprotein C-III and triglyceride-rich lipoprotein metabolism. CTEP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein. Reproduced with permission from Rosenson RS, Davidson MH, Hirsh BJ, et al: Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014 Dec 16;64(23):2525-2540.[7]

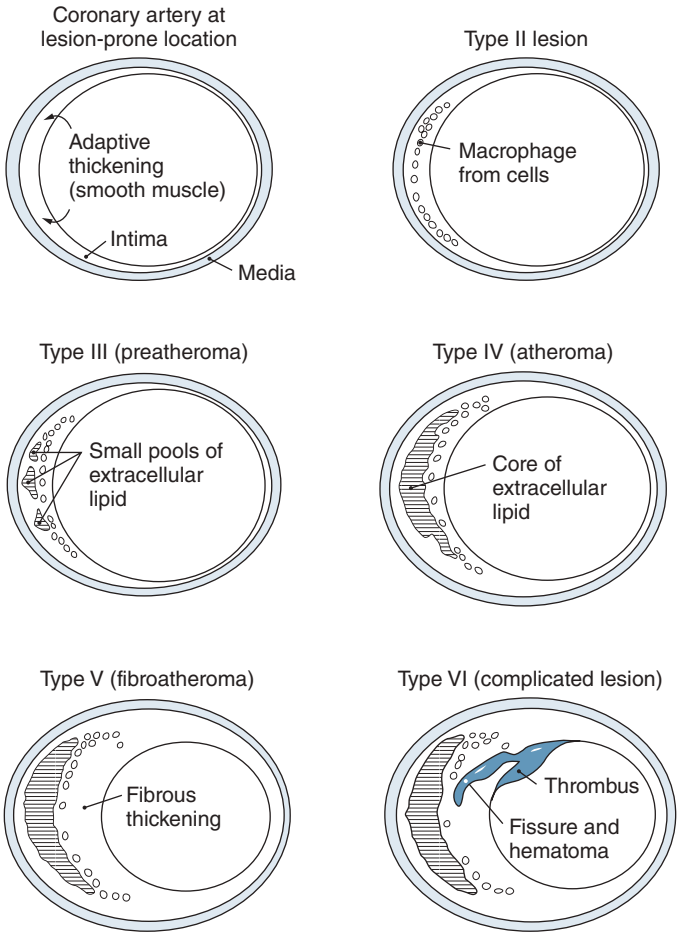

FIGURE 29–6. Atherogenesis. The progression of atherosclerosis is depicted from the earliest stages (*top left*) to the most advanced (*bottom right*), culminating in plaque rupture and associated thrombosis. Originally from Stary HC, Chandler AB, Dinsmore RE, et al.[33] Reproduced with permission from Stocker R, Keaney JF Jr: Role of oxidative modifications in atherosclerosis. *Physiol Rev*. 2004 Oct;84(4):1381-1478.

Borderline-high levels are commonly associated with obesity or diabetes. High levels are often found in persons with a genetic predisposition to hypertriglyceridemia. Most people with a high triglyceride concentration have elevations of VLDL-triglyceride; less commonly they have a condition called *dysbetalipoproteinemia*, which signifies an excess of cholesterol-enriched VLDL remnants.[10] When fasting triglycerides occur in the very high range, chylomicrons typically are present.[10] Excessively high levels of chylomicrons signify an increased risk of acute pancreatitis.

The term *combined hyperlipidemia* indicates an increase concentration of both cholesterol and triglycerides. It can be present under several circumstances (eg, combined elevations of LDL and VLDL, dysbetalipoproteinemia, or very high triglycerides).

GENETIC HYPERLIPIDEMIAS

GENETIC HYPERCHOLESTEROLEMIAS

Several genetic defects have been identified to underlie hypercholesterolemia. In most cases, these are associated with high levels of LDL-C (Table 29–3).[74] They can be briefly summarized.

LDL receptor deficiency, or LDLR deficiency, is an autosomal dominant genetic disorder accompanied by very high levels of LDL-C and premature atherosclerotic disease.[75-77] This was the first genetic cause of hypercholesterolemia identified and typically is called *familial hypercholesterolemia (FH)*. Most people carry mutations in the *LDLR* gene, which is responsible for encoding the LDLR protein. This protein is located mainly on the surface of liver cells, which removes LDL from the circulation. It does this by binding to apo B-100 molecules of LDL particles. LDLR deficiency can occur in two forms: heterozygous or homozygous. In the heterozygous form, one allele of the *LDLR* gene is defective or absent. A large number of different mutations have been found in the *LDLR* gene, many of which produce very high LDL-C levels. When these mutations are present in heterozygotes, only half the normal number of LDLRs is expressed and LDL-C levels are approximately doubled. In homozygous form of LDLR deficiency, both alleles are absent or defective, and LDL-C levels are approximately increased by a factor of four. Classic estimates were that heterozygous FH occurs in about one in 500 persons; homozygous FH occurs only one in a million persons. In some populations, the prevalence of both forms can be higher. Patients with heterozygous FH commonly develop premature ASCVD, most often between the ages of 30 to 60 years, and estimates are that it accounts for at least 2% of premature myocardial infarctions (MIs). Homozygous FH leads to very premature disease, often in the teens or earlier. Another clinical feature of FH is the presence of cholesterol deposition in tendons (xanthomas) of the hands, elbows, knees, and feet, especially the Achilles tendon. Deposition of cholesterol in the skin about the eyes is called xanthelasma; in individuals with hypercholesterolemia, this finding suggests but is not pathognomonic of FH. The same is true for corneal arcus.

Familial defective apo B-100 (FDB) is a genetic defect in apo B-100 that causes moderate to severe hypercholesterolemia.[78-80] It results from a mutation in a single amino acid (Arg-Gln at position 3500 of the apo B molecule); this mutation reduces the ability of LDL to bind to the LDLR. It is relatively common (1/500 to 1/1000) in central Europe but much less common in other populations. FDB is accompanied by increased risk of ASCVD, but apparently less so than with LDLR deficiency.

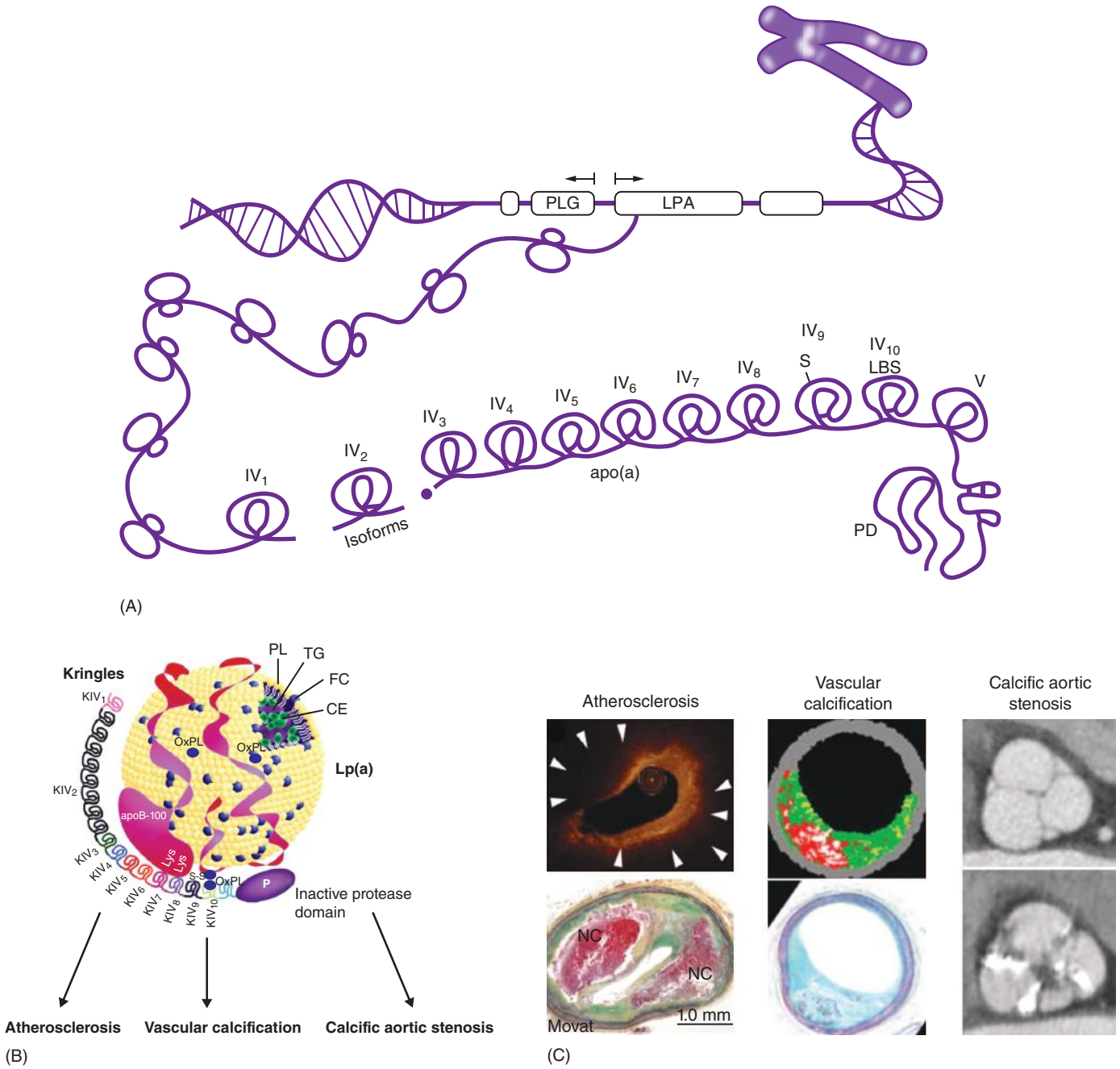

FIGURE 29–7. Summary of pathological consequences of elevated lipoprotein(a) [Lp(a)]. **A.** Genetic architecture of apo(a). The genes for plasminogen (PLG) and apo(a) (LPA) are depicted on chromosome 6. LPA is transcribed into apo(a) consisting of kringle domains KIV1-KIV10, KV, and a protease-like domain, with variable number of tandem KIV2 repeats that determine apo(a) isoform size. A strong lysine binding site (LBS) is present in KIV10. **B**, Structure of Lp(a) and its content of oxidized phospholipids. Lp(a) consists of apo(a) covalently bound to apoB-100 through a disulfide bone in KIV9. Oxidized phospholipids (OxPL) are present within the lipid phase as well as covalently bound to Lp(a). **C**, Cardiovascular diseases associated with elevated Lp(a) include atherosclerosis (*left*), vascular calcification (*middle*) and aortic stenosis (*right*). Left panels depict optical coherence tomography (OCT) imaging of a thin fibrous cap atheroma "vulnerable plaque" with large necrotic cores (NC) and hemorrhage. The corresponding histologic specimen is shown below the OCT image. The overlying fibrous cap (FC) is thin (70 µm) and heavily infiltrated by macrophages. The middle panels depict intravascular ultrasonographic (IVUS) images using "virtual histology," show fibrous (dark green) and fibrofatty (light green) necrotic core (red) and calcified (white) tissue. The corresponding histologic specimen is shown below the IVUS image. The right panels depict a noncalcified tricuspid aortic valve (*top*) and the presence of aortic valve calcifications using multislice computed tomography. Figure from manuscript number CDTY-D-15-00241R1 (Experimental Animal Models Evaluating the Causal Role of Lipoprotein(a) in Atherosclerosis and Aortic Stenosis) by Yeang C, Cotter B, Tsimikas S). **A** reproduced with permission from Leibundgut G, Scipione C, Yin H, et al: Determinants of binding of oxidized phospholipids on apolipoprotein (a) and lipoprotein (a). *J Lipid Res*. 2013 Oct;54(10):2815-2830. **B** reproduced with permission from Rao F, Schork AJ1, Maihofer AX, et al: Heritability of Biomarkers of Oxidized Lipoproteins: Twin Pair Study. *Arterioscler Thromb Vasc Biol*. 2015 Jul;35(7):1704-1711. **C** (*left)* reproduced with permission from Otsuka F, Joner M1, Prati F, et al: Clinical classification of plaque morphology in coronary disease. *Nat Rev Cardiol*. 2014 Jul;11(7):379-389; **C** (*middle*) reproduced with permission from König A, Margolis MP, Virmani R, et al: Technology insight: in vivo coronary plaque classification by intravascular ultrasonography radiofrequency analysis. *Nat Clin Pract Cardiovasc Med*. 2008 Apr;5(4):219-229; **C** (*right*) Reproduced with permission from Tops LF, Wood DA, Delgado V, et al: Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *JACC Cardiovasc Imaging*. 2008 May;1(3):321-330.

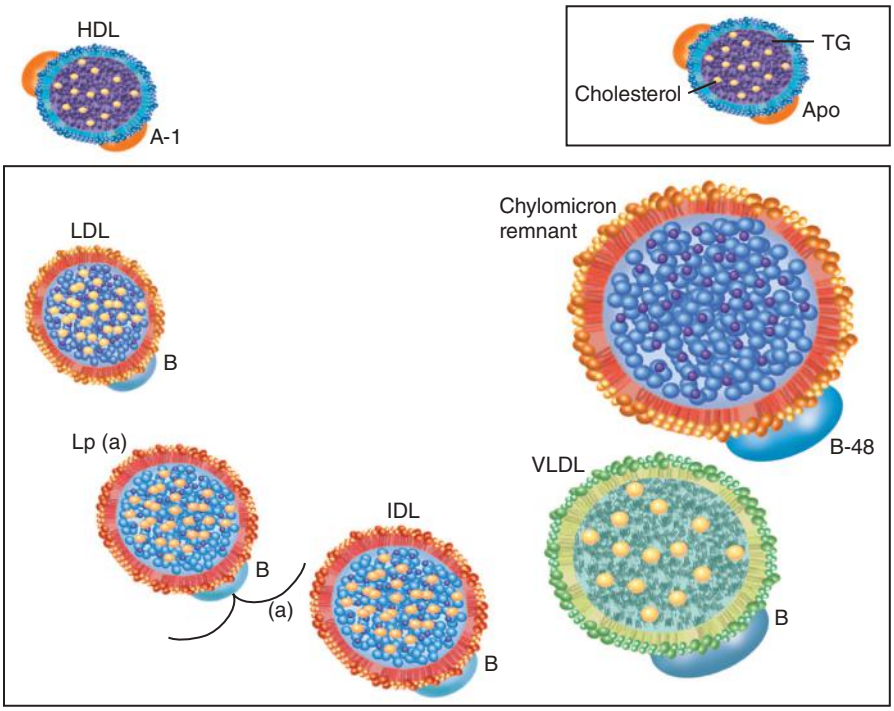

FIGURE 29–8. Non–high-density lipoprotein (HDL). Non–HDL-cholesterol (HDL-C), a derived variable, is the sum of all cholesterol carried within atherogenic lipoproteins. One molecule of full-length apolipoprotein B (known as apo B-100) is present on all atherogenic lipoproteins, except for chylomicron remnants, whose defining shorter B-48 isoform is undetectable by common laboratory methods. Given these biochemical interconnections, concentrations of apo B and non–HDL-C are highly correlated. Apo B reflects the total particle number, whereas non–HDL-C integrates their total cholesterol content. However, correlation of both apo B and non–HDL-C with a third variable, namely low-density lipoprotein cholesterol (LDL-C), is more erratic. Box in upper right shows a "generic lipoprotein." IDL, intermediate-density lipoprotein; Lp(a), lipoprotein(a); TG, triglyceride; VLDL, very-low-density-lipoprotein. Reproduced with permission from Rosenson RS, Hegele RA2, Gotto AM, et al: Integrated Measure for Atherogenic Lipoproteins in the Modern Era: Risk Assessment Based on Apolipoprotein B. *J Am Coll Cardiol*. 2016 Jan 19;67(2):202-204.[54]

Autosomal recessive hypercholesterolemia (ARH) is a recessive disorder characterized by very high levels of LDL-C, xanthomatosis, and premature ASCVD.[81,82] It results from mutations in the ARH protein's phosphotyrosine binding domain, needed for internalization of LDL into the liver. ARH protein functions as an adapter that couples the LDL receptor to the endoplasmic reticulum. A defect in the protein impairs the normal function of the LDL receptor and results in severe hypercholesterolemia.

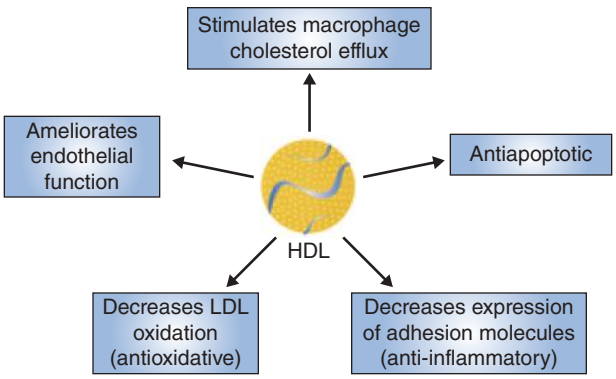

FIGURE 29–9. Particles of high-density lipoprotein (HDL) and/or its main protein constituent, apolipoprotein A-I, have diverse antiatherosclerotic influences. LDL, low-density lipoprotein. Reproduced with permission from Rosenson RS, Brewer HB, Ansell BJ, et al: Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nat Rev Cardiol*. 2016 Jan;13(1):48-60.[68]

Sitosterolemia is a rare autosomal recessive disorder that manifests hypercholesterolemia, tuberous and tendon xanthomas, and in some patients, premature ASCVD.[83,84] Metabolic abnormalities include hyperabsorption of cholesterol and sitosterol and decreased biliary secretion of these sterols. Severe hypercholesterolemia commonly occurs in affected children and is called *pseudo–homozygous familial FH*. As children grow older, serum cholesterol levels typically return to normal. Plasma sitosterol levels are several-fold elevated. Sitosterolemia results from mutations in two ATP-binding cassette transporter (ABC transporter) proteins that are encoded by *ABCG5* and *ABCG8* genes.[84,85] In the liver, these transporters pump cholesterol and sitosterol into bile; with mutations, both sterols are retained in the liver and whole body. Retention of sitosterols leads to tissue accumulation, resulting in xanthomas and accelerated atherosclerosis.

Autosomal dominant hypercholesterolemia caused by gain-of-function mutations in the proprotein convertase subtilisin/kinexin 9 (PCSK9) gene is another form of hypercholesterolemia, which has recently been discovered. This is characterized by missense variants in PCSK9. PCSK9 is a circulating protein that promotes degradation of the LDLR (Fig. 29–11).[74] A gain-of-function mutation in PCSK9 causes autosomal dominant hypercholesterolemia.[86,87] The discovery of this mutation was critical for the development of a new class of drugs for treatment of elevated LDL-C—namely PCSK9 inhibitors.

GENETIC FORMS OF HYPERTRIGLYCERIDEMIA

Genetic abnormalities affecting all types of TGRLP have been identified. These include VLDL, VLDL remnants, chylomicrons, and their combinations. These various hypertriglyceridemias sometimes become clinical manifest only when associated with conditions that lead to VLDL overproduction (ie, obesity and diabetes). Each category will be reviewed.

Familial hypertriglyceridemia is defined by the presence of elevated triglyceride levels in a single family.[88] Available evidence suggests that impaired catabolism of VLDL underlies this condition.[89,90] The most common abnormality found consists of heterozygous variants of LPL.[91,92] Other lipolytic defects also may exist. When such abnormalities occur in obese patients, production of VLDL-TG is enhanced, which worsens hypertriglyceridemia.[90] Whether familial hypertriglyceridemia is associated with ASCVD has been uncertain. But the most definitive long-term follow-up of families with familial hypertriglyceridemia strongly suggests that risk of ASCVD mortality is in fact increased.[93]

Familial combined hyperlipidemia is said to be present when different lipoprotein phenotypes (eg, hypercholesterolemia, hypertriglyceridemia, or combined hyperlipidemia) occur in different members of the same family.[88] To date, no single genetic defect has been identified to account for this condition. Most likely, it is a polygenic disorder.[94] Familial combined hyperlipidemia is more frequently accompanied by premature ASCVD than is familial hypertriglyceridemia.[95] Obesity and/or type 2 diabetes are common in familial combined hyperlipidemia; thus, a component of the abnormal lipoprotein patterns likely

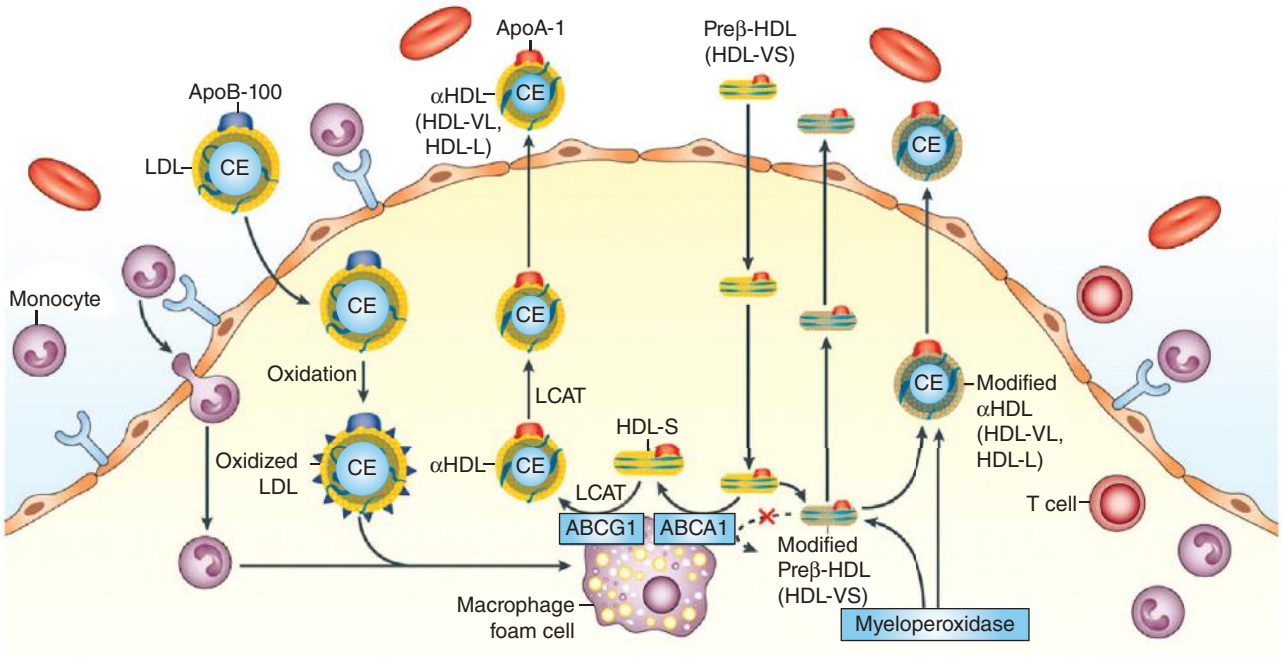

FIGURE 29–10. Dysfunctional high-density lipoprotein (HDL). In the absence of myeloperoxidase activity, preβ-HDL (HDL-VS) binds to the ABCA1 transporter and initiates the efflux of cholesterol from macrophage foam cells with the concomitant conversion of preβ-HDL (HDL-VS) to HDLα4 (HDL-S). Oxidation of apoA-I on multiple residues by the proinflammatory enzyme myeloperoxidase might limit the capacity of HDL or apoA-I to mediate cholesterol efflux from macrophages and thus promote the development of experimental and human atherosclerosis. ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; apoA-I, apolipoprotein A-I; apoB-100, apolipoprotein B-100; CE, cholesteryl ester; HDL-L, large HDL particle; HDL-S, small HDL particle; HDL-VL, very large HDL particle; HDL-VS, very small HDL particle; LCAT, lecithin–cholesterol acetyltransferase; LDL, low-density lipoprotein. Reproduced with permission from Rosenson RS, Brewer HB, Ansell BJ, et al: Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nat Rev Cardiol*. 2016 Jan;13(1):48-60.[68]

results from overproduction of apo B–containing lipoproteins by the liver.[96,97] Another cause of apparent overproduction of apo B in this disorder could result concomitant LDLR deficiency.[98]

A disorder closely related to familial combined hyperlipidemia is called *hyperapobetalipoproteinemia*.[99,100] It is characterized by elevations in apo B, small LDL particles, and frequent ASCVD. Like familial combined hyperlipidemia, where apo B levels are typically increased, the lipid phenotype of hyper–apo B is variable. In some affected families, triglycerides and/or cholesterol are elevated. It is generally believed that the production of apo B is increased,[101] although the actual mechanism has not been determined.

Familial dysbetalipoproteinemia denotes accumulation of cholesterol-enriched remnants of VLDL and chylomicrons.[102,103] Patients with this disorder frequently show xanthoma striatum palmare (orange or yellow discoloration of palmar creases) and tuberoeruptive xanthomas over the elbows and knees. They carry increased risk of ASCVD, notably coronary heart disease (CHD) and peripheral arterial disease. Dysbetalipoproteinemia typically results from less-common isoforms of apo E. There are three apo E isoforms—E2, E3, and E4. Frequencies of apo E alleles in the general population are 7% for E2, 79% for E3, and 14% for E4 (http://www.alzgene.org/meta.asp?geneID=83). Persons who are homozygous for E2 (E2:E2) are those most likely to show dysbetalipoproteinemia. The E2 isoform appears to be a poor ligand for the LDLR, leading to accumulation of remnant lipoproteins. There is also impaired conversion of VLDL remnants to LDL, which results in excess cholesterol-enriched remnants. The presence of the E2:E2 pattern does not necessarily lead to hyperlipidemia. Most patients who manifest hyperlipidemia have a concomitant condition that causes overproduction of lipoproteins, such as obesity and/or type 2 diabetes.[104] The presence of approximately equal elevations in plasma cholesterol and triglycerides suggests a diagnosis of dysbetalipoproteinemia.

TABLE 29–1. LDL and Non–HDL-C CVD Risk-Associated Treatment Thresholds

Category	LDL-C (mg/dL)	Non–HDL-C (mg/dL)
Very high	> 190	> 220
High	160–189	190–219
Borderline high	130–159	160–189
Borderline low	100–129	130–159
Low	70–99	100–129
Very low	< 70	< 100

HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol.

TABLE 29–2. Categories of Triglycerides

Category	Concentration Range (mg/dL)
Normal	< 150
Borderline high	150–199
High	200–499
Very high	> 500

TABLE 29–3. Phenotypic Consequence of DNA Sequence Variation in Genes Targeted by Pharmacological Therapies

					Anticipated Efficacy: Effect of DNA Variant on			Anticipated Adverse Events: Effect on DNA Variant on
Drug(s)	Genes Targeted by Drugs	Effect of Drugs on Target Gene Function	DNA Sequence Variants in Target Gene	Frequency of DNA Sequence Variant(s)	Gene Function	Plasma Biomarkers	CHD Risk	Pleiotropic Phenotypes
Statin	HMGCR	Reduce	Gene score of three variants	Those above median in gene score	Reduce	↓ 2.0–3.0 mg/dL LDL-C	↓ 5.2%–5.3%	
			rs12916 T	60% frequency	Reduce mRNA expression	↓ 3.0 mg/dL LDL-C	↓ 4%	↑ 0.3 km/m^2 body mass index ↑ 6% risk for T2D
			rs17238484 G	77% frequency	?	↓ 2.3 mg/dL LDL-C	?	↑ 0.3 km/m^2 body mass index ↑ 2% risk for T2D
Ezetimibe	NPCTL1	Reduce	Gene score of five variants	Those above median in gene score	Reduce	↓ 2.3–2.4 mg/dL LDL-C	↓ 4.4%–4.8%	None identified yet
			Null mutations	1 in 650 cumulative carrier frequency	Reduce	↓ 12 mg/dL LDL-C	↓ 4.9%	
Alirocumab Evolocumab	PCSK9	Reduce	Y142X and C679K	2.9% carrier frequency in blacks	Reduce	↓ 3.5% LDL-C	↓ 4.9%	None identified yet
Anacetrapib	CETP	Reduce	D442G	6% carrier frequency in East Asians	Reduce	↑ 2 mg/dL HDL-C for T2D	Unknown	↑ 70% risk for AMD
Evacetrapib	CETP	Reduce	D442G	32% minor allele frequency in whites	Reduce	↑ 3.4 mg/dL HDL-C for T2D	↓ 4%	↑ 39% risk for AMD
Antiserum oligonucleotide	*APOC3*	Reduce	R19X rvS2+ 1G → A fwS3 + ↑G → T A43T	1 in 150 cumulative carrier frequency	Reduce	↓ 39% TG ↑ 22% HDL-C ↓ 16% LDL-C	↓ 40%	None identified yet

AMD, age-related macular generation; CHD, coronary heart disease; DNA, deoxyribonucleic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger ribonucleic acid; TG, triglycerides; T2D, type 2 diabetes.

Reproduced with permission from Kathiresan S: Developing medicines that mimic the natural successes of the human genome: lessons from NPC1L1, HMGCR, PCSK9, APOC3, and CETP. *J Am Coll Cardiol*. 2015 Apr 21;65(15):1562-1566.[138]

This diagnosis can be confirmed by detection of the E2:E2 genotype through genetic analysis.

Familial chylomicronemia is characterized very high triglyceride levels consequent to accumulation of chylomicrons in plasma. It results from a defect in lipolysis of chylomicron triglycerides. The most common cause is a genetic deficiency in LPL.[105] Other causes of defective lipolysis are deficiencies in apo C-II[106,107] and mutations in GPIHBP1.[108] Apo C-II is required for activation of LPL. GPIHBP1 is a glycosylphosphatidylinositol-anchored protein of capillary endothelial cells; it binds LPL in the subendothelial spaces and shuttles it to the capillary lumen, where it can hydrolyze the triglyceride of chylomicrons. In patients with any of these genetic disorders, high-fat diets produce severe chylomicronemia and predispose to acute pancreatitis. Mechanisms underlying development of pancreatitis are unknown. Other clinical features of the chylomicronemia syndrome include eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and cognitive impairment.[109]

Familial type V hyperlipoproteinemia is characterized by very high triglycerides in both VLDL and chylomicrons and present in multiple family members.[90,110-112] This lipoprotein pattern may represent a severe form of familial hypertriglyceridemia.[90] Many affected patients are obese or have type 2 diabetes. In them, overproduction of VLDL-TG and defective clearance of TGRLP are reported.[90,113] This dual defect in metabolism of TGRLP likely accounts for elevations in both VLDL and chylomicrons. The defect in catabolism of TGRLP may be caused by a variety of catabolic abnormalities.[114]

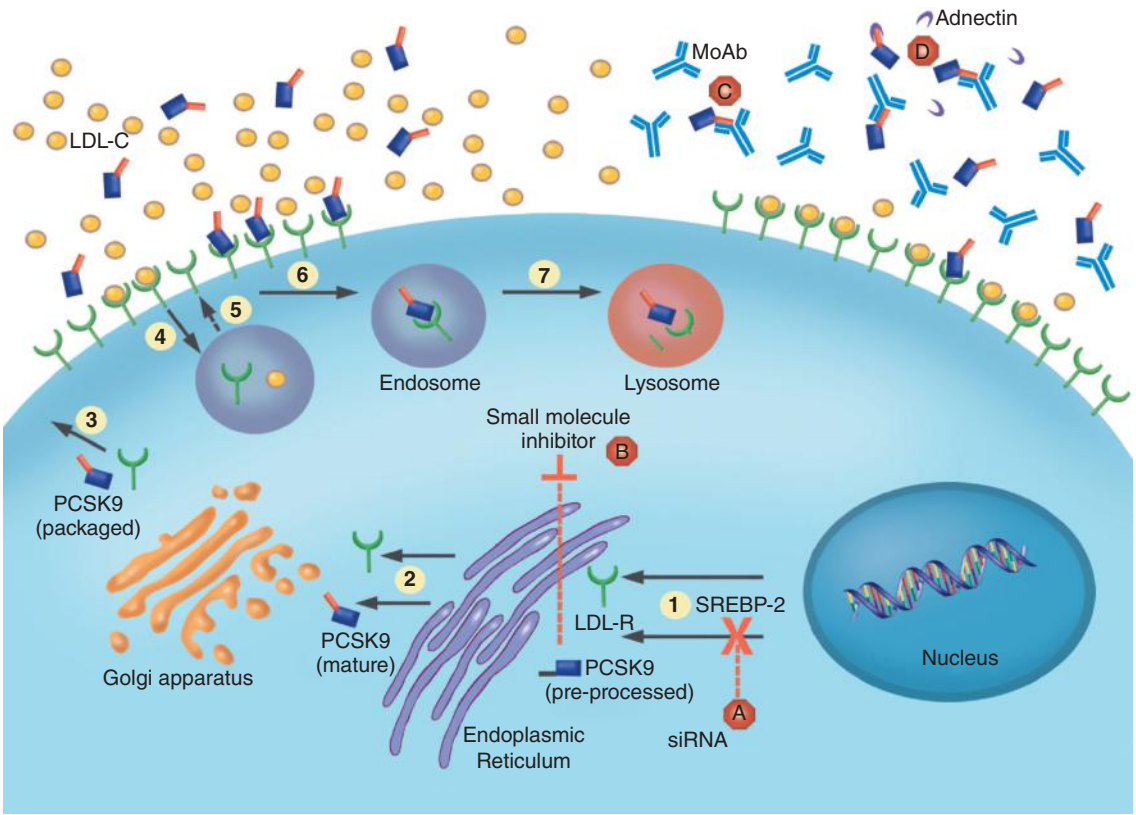

FIGURE 29–11. Proprotein convertase subtilisin/kinexin 9 (PCSK9) and low-density lipoprotein (LDL) metabolism. LDL-R, LDL receptor. Reproduced with permission from Giugliano RP, Sabatine MS: Are PCSK9 Inhibitors the Next Breakthrough in the Cardiovascular Field? *Am Coll Cardiol*. 2015 Jun 23;65(24):2638-2651.[74]

Familial hypoalphalipoproteinemia is characterized by several genetic causes of low HDL-C. These include *apo A1 deficiency, apo A1 structural mutations, Tangier disease (homozygous deficiency of adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1)*, and *lecithin-cholesterol acyl transferase (LCAT).*[115-117] *Apo A1 deficiency* can result from mutations in the *apo A1* gene.[116,118] Affected patients show very low HDL-C levels and often have corneal opacifications, planar xanthomas, and sometimes, premature atherosclerosis. One notable structural variant of apo A1, among others, is called *apo A-I Milano*[119]; most affected individuals are heterozygous for this mutation. They nonetheless usually have very low HDL-C levels. Even so, they do not manifest premature ASCVD. *Tangier disease* is a genetic disorder having near absence of HDL-C, reduced LDL-C, and mild elevations of triglyceride.[115,116,120] Affected patients are characterized by enlarged, yellow/orange tonsils, hepatosplenomegaly, and peripheral neuropathy. Some patients have premature ASCVD. The molecular defect in Tangier disease is a mutation in the *ABC1* gene. ABC1 on the surface of cells appears to initiate the first step of reverse cholesterol transport; its deficiency reduces the availability of cholesterol for formation of HDL. Premature atherosclerosis has been observed in some affected patients. *Genetic LCAT deficiency* is accompanied by extremely reduced HDL-C concentrations.[121-123] LCAT is required for conversion of nonesterified cholesterol to cholesterol esters. In the absence of cholesterol esters, normal HDL particles cannot form. Persons with LCAT deficiency have corneal opacification, anemia, and progressive renal disease.

Abetalipoproteinemia is a rare disease characterized by an absence of lipoproteins containing apo B-48 and apo B-100.[124,125] It is an autosomal recessive disorder caused by a mutation in microsomal triglyceride transfer protein (MTP).[126,127] The absence of MTP prevents the incorporation of triglyceride into apo B-containing lipoproteins, thereby preventing their secretion in plasma. There is a fat malabsorption caused by an inability to form chylomicrons. A parallel defect in the liver prevents the formation of VLDL, which eliminates both VLDL and LDL from the circulation. These defects lead to an absence of apo B-48 and apo B-100 in the circulation. Patients with abetalipoproteinemia are subject to serious side effects, notably, steatorrhea and a failure to thrive; fat-soluble vitamin deficiency, including vitamin E, neurological disease (degeneration of the spinocerebellar and dorsal column tracts, retinitis pigmentosa; hepatic steatosis; and cirrhosis.[128,129]

Familial hypobetalipoproteinemia is characterized by very low (but not absent) LDL-C levels. A precise lower cut point to define a very low LDL-C is not well defined. Many cases exhibit truncating mutations in apo B-100.[130-134] However, in the majority of those with LDL-C in the low range, truncations of apo B seemingly are not present; beyond apo B truncations, other causes of very low LDL-C have not been identified.[135] A potential side effect of hypobetalipoproteinemia is development of a fatty liver; this is secondary to failure to adequately mobilize triglycerides into VLDL.[136]

GENETIC VARIANTS AFFECTING LIPOPROTEIN PATHWAYS AND ASCVD

Lipid and lipoprotein levels are influenced by multiple conditions that may influence atherosclerosis risk by mechanisms that are partly unrelated to lipoprotein metabolism. Some examples include diabetes, cigarette smoking, hormonal replacement therapy, and many others. More than 100 variants are associated with changes in various lipid and lipoprotein parameters. The mechanisms of many other lipid loci are not fully understood. Recent efforts have evaluated polymorphisms in specific lipoprotein pathways that are associated with ASCVD. Genetic risk scores of these variants support the concept that hyperlipidemia is

often polygenic or polygenic with environmental influence. Mendelian randomization has been used to infer causality of a genome-wide association trait involved in lipoprotein metabolism with ASCVD.[137] This approach has been used in the identification of established and emerging pathways of interest, to stratify responders and nonresponders to lipid-modifying therapy, to explore the genetic basis for adverse reactions and drug elimination pathways, and to provide support for the investigation of pharmacological inhibitors of a selected pathway. The phenotypic consequences of DNA sequence variation in genes targeted by pharmacological agents is summarized in Table 29–3.[138,139]

LDL Receptor (LDLR)

Rare LDLR mutations have been shown to contribute to increased risk of MI in individual families,[140,141] whereas more common variants at nearly 50 loci have been associated with MI risk in the general population.[142-146] About 2% of individuals with early-onset MI (≤ 50 years in males and ≤ 60 years in females) carry an *LDLR* mutation.[146] More severe LDLR mutations were associated with higher MI risk in the National Heart, Lung, and Blood Institute's exome sequencing project. Carriers of rare nonsynonymous mutations had a 4.2-fold increased risk of MI versus non-MI controls, and carriers of null alleles had a higher 13-fold risk of MI. These associations with MI presumably are mediated through elevations of LDL-C.

Although mutations in *LDLR* have been emphasized loss-of-function and increased CHD risk, *LDLR* sequence noncoding variants have been shown to be protective. In an Icelandic population, a splice variant in *LDLR* (rs72658867-A, c.2140+5G>A) and an intronic variant (rs17248748-T) are associated with lower non–HDL-C levels and lower CAD risk.[147] The splice variant alters the *LDLR* reading frame and increases mRNA expression of *LDLR* that was unrelated to increased expression in wild-type *LDLR*.

HMG-CoA Reductase (HMGR)

Hydroxymethyl-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase (HMGR) is the rate-limiting step in cholesterol biosynthesis, Inhibition of HMGR increases *LDLR* synthesis. The magnitude of HMG-CoA reduction with statins results in a correlative reduction in cardiovascular events.[148] In an analysis of randomized trials of statin therapy, a genetic risk score based on 27 genetic variants was used to stratify the risk of both incident and recurrent CHD events.[149] The benefit of statin therapy on incident and recurrent coronary events increased across the low (13%), intermediate (29%), and high (48%) genetic risk categories. The high genetic risk participants had larger absolute risk reduction, resulting in a threefold decrease in the number needed to treat to prevent one CHD event in primary prevention trials.

The mendelian randomization principle has been used to investigate the mechanism underlying the risk of type 2 diabetes observed in randomized controlled trials of statins.[150,151] Single nucleotide polymorphisms (SNPs) in the *HMGCR HMGCR* rs1723848-G allele and rs12916 were associated with weight gain and incident type 2 diabetes.[152] These data suggest a genetic basis for weight gain and type 2 diabetes in 2% to 6% of patients treated with statin therapy.

Proprotein Convertase Subtilisin Kinexin 9 (PCSK9)

The genetics of *PCSK9* have identified missense and nonsense loss-of-function variants that are associated with lower LDL-C levels and lower rates of MI (see Table 29–3).[139,153] *PCSK9* variants were associated with a 35 mg/dL lower LDL-C concentration and a 49% lower CHD risk in African Americans—and a 13 mg/dL lower LDL-C and 18% lower CHD risk in whites. These associations support the concept that lifelong lower levels of LDL-C are accompanied by lower risk of CHD. Thus, every 1 mmol/L lower LDL-C level is associated with a 54% lower CHD risk. This risk is twofold greater than anticipated from meta-analysis of statin-based RCTs[154] and supports the concept that the duration of low LDL-C levels influences long-term risk.

Niemann-Pick C1-Like1 (NPC1L1)

Niemann-Pick C1-like1 (NPC1L1) is expressed in the small intestine, where it functions as a transporter of dietary cholesterol from the intestinal lumen to the enterocytes.[155,156] The Myocardial Infarction Genetics Consortium Investigators identified 15 naturally occurring inactivating mutations that were associated with an average LDL-C level that was 12 mg/dL lower than in noncarriers.[157] Carrier status for an inactivating mutation was associated with a 53% relative reduction in the risk of CHD (carrier frequency 0.04% vs 0.09% in controls). The effects of inhibiting *NPC1L1*, *HMGCR*, or both on CHD events were examined in a mendelian randomization study.[158] *NPC1L1* polymorphisms were associated with a 2.4 mg/dL lower LDL-C and 4.8% lower risk of CHD, whereas the group with *HMRCR* polymorphisms had a 2.9 mg/dL lower LDL-C and 5.3% lower risk of CHD. Individuals with *NPC1L1* and *HMGCR* polymorphisms had an additive 5.8 mg/dL lower LDL-C and larger 10.8% lower risk of CHD. This 2 × 2 genetic analysis provides support for NPC1LI as a valid target for pharmacological intervention in combination with statin therapy, which was recently supported by the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial).[159]

Cholesteryl Ester Transfer Protein (CETP)

Cholesteryl ester transfer protein (CETP) variants located near or in the *CETP* gene at 16q13 were associated with higher levels of HDL-C and lower risk of incident MI.[160,161] SNP rs708272 in the *CETP* gene was associated with a per-allele increase in HDL-C levels of 3.1 mg/dL and a corresponding 24% lower risk of future MI (age-adjusted hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.62-0.94). Concordant effects on HDL-C and incident MI were also observed at the *CETP* locus for rs4329913 and rs7202364. In a meta-analysis, the CETP polymorphism was associated with lower LDL-C levels of 1.2 mg/dL. Based on these genetic studies, it would be anticipated that CETP is a valid therapeutic target; however, pharmacological inhibition with multiple agents has not reduced CHD risk.[162,163] Several explanations for the failed trials include off-target toxicity with torcetrapib and lack of LDL-C lowering with dalcetrapib. In contrast, anacetrapib lowered LDL cholesterol by about 28% in ACCELERATE (A Study of Evacetrapib in High-Risk Vascular Disease), but this trial was terminated after 2 years based on the futility analysis (https://investor.lilly.com/releasedetail.cfm?ReleaseID).

A pharmacogenomics approach has been proposed for the identification of individuals who derive benefit versus harm from CETP inhibition. In the dal-Outcomes trial, polymorphisms in the *ADCY9* gene on chromosome 16 were associated with reductions in cardiovascular events.[164] Among patients with genotype AA at rs1967309, there was a 39% reduction in the composite cardiovascular end point with dalcetrapib compared with placebo. In contrast, patients with genotype GG had a 27% increase in events with dalcetrapib versus placebo. Surprisingly, the GG genotype was associated with slightly lower LDL-C levels. These data have been replicated in dal-PLAQUE with carotid intima-medial thickness. This pharmacogenomic approach to CETP inhibition has been suggested as strategy to investigate whether dalcetrapib may prove an effective target for the prevention of atherosclerotic cardiovascular events among individuals with the certain variants in ADCY9. The mechanism for the participation of ADCY9 in dalcetrapib-associated cardiovascular risk remains uncertain.

Triglyceride-Rich Lipoprotein (TGRL)

The genetic architecture for triglycerides in the population is comprised of rare large-effect variants, common small-effect variants, and environmental influences.[7,165] Variants associated with common, complex traits such as plasma triglyceride range from common (> 1:20), to low (1:200 to 1:20), to rare (< 1:200). Approximately 50% of interindividual plasma triglyceride variability is estimated to come from DNA sequence variants (Table 29–4).

Elevated triglyceride levels have been associated with increased risk of cardiovascular events; however, the causality of TGRL has been challenging because of the associations with other major cardiovascular risk markers. As will be discussed in the following sections, mendelian randomization studies provide evidence that mutations in apo V5, LPL, and apo C-III are associated with increased risk of MI.

Apolipoprotein A5 (APOA5)

Apo A5 is involved in multiple stages of TGRL metabolism, including VLDL production, TGRL remnant clearance, and regulation of LPL activity.[166] Genome-wide association studies have shown that polymorphisms in or near the apo A5 locus are associated with nonfasting TG levels. *APOA5* genetic variants associate with incident CHD that is in direct relation to the increase in elevated nonfasting TG and remnant cholesterol.[167-169] Carriers of rare nonsynonymous mutations in *APOA5* had higher plasma triglyceride levels and were at 2.2-fold increased risk of MI.[146]

Apolipoprotein C3 (APOC3)

Two mendelian randomization studies have established a central role for apo C3 in TGRL and CHD risk.[170,171] *APOC3* variants are strongly associated with triglyceride levels. Approximately 1 in 150 individuals carried any of four protein-altering or splice-site variants of *APOC3*.[170] Heterozygous carriers of any of these four *APOC3* mutations had 39% lower plasma triglyceride levels, 46% lower circulating plasma *APOC3*, and 40% lower risk of CHD. In two general populations studies from Denmark that included data from 75,725 participants, participants with nonfasting triglyceride levels of less than 90 mg/dL had a 57% lower incidence of cardiovascular disease than those with levels of 350 mg/dL or more.[171] Loss-of-function mutations in one allele for *APOC3* was associated with lower triglyceride levels and lower ischemic vascular disease risk that were similar to the first study (44% nonfasting triglycerides and 41% for ischemic vascular disease).

Adipokine Angiopoietin-Like 3 and 4 (ANGPTL3)

Angiopoietin-like protein 3 (ANGPTL3) renders LPL and endothelial lipase more susceptible to proteolytic inactivation by proprotein convertases. In ANGPTL3-knockout mice, circulating triglycerides and HDL-C are elevated.[172-174]

Individuals with distinct nonsense mutations in *ANGPTL3* exhibit low plasma levels of LDL-C, triglycerides, and HDL-C or a phenotype referred to as familial combined hypolipidemia (FHBL2).[175] *ANGPTL3* polymorphisms are most strongly associated with triglyceride level (polymorphism rs2131925, change of 4.9 mg/dL per allele) but also LDL-C (rs2131925, change of 1.6 mg/dL). In a study of 115 FHBL2 individuals carrying 13 different mutations in the *ANGPTL3* gene (14 homozygotes, 8 compound heterozygotes, and 93 heterozygotes) and 402 controls, carriers of two mutant alleles had nondetectable plasma levels of *ANGPTL3* protein, whereas heterozygotes exhibited a reduction ranging from 34% to 88% depending on the genotype.[176]

ANGPTL4 is a secreted protein induced in adipose tissue that inactivates LPL in the subendothelial space.[177] Loss-of-function variants in *ANGPTL4* (E40K, T266M) are associated with increased LPL activity and low triglycerides.[178] In the Atherosclerosis Risk in Communities Study (ARIC), carriers of one or two copies of the 40K variant had age- and sex- adjusted lower levels of triglycerides (–19 mg/dL), LDL-C (–5 mg/dL) and higher HDL-C (+4 mg/dL). Carriers also had a 37% adjusted reduced risk of CHD.

TABLE 29–4. Genetic Triglyceride Variants: Phenotypic Consequences of DNA Sequence Variation in Genes Targeted by Pharmacological Agents

Gene	rsID	Protein	Effect of Variant on Protein Function	Effect of Mutation on LPL Activity	Lipid Phenotype Association	CHD Risk	Allele Frequency in Whites	Allele Frequency in Blacks	Reference Number[a]
LPL	rs1801177	D36N	Loss	Decrease	↑ TG	↑	2%	5%	385
	rs328	S474X	Gain	Increase	↓ TG	↓	11%	7%	
APOA5	rs662799	Promoter -1131T→C	Loss	Decrease	↑ TG	↑	8%	Rare	Sarwar N
ANGPTL4	rs116843064	E40K, T266M	Loss	Increase	↓ TG	↓	1.6%	0.1%	178
APOC3	Multiple	R19X, IVS2 + 1 G→A, IVS3 + 1 G→T, A43T	Loss	Increase	↓ TG	↓	0.7% (collective for all four mutations)	0.7% (collective for all four mutations)	Pollin TI, et al. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute 171

[a]Sarwar N, et al. *Lancet*. 2010;375:1634-1639.

Pollin TI, et al. *Science*. 2008;322:1702-1705.

TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. *N Engl J Med*. 2014;371:22-23.

CHD, coronary heart disease, LPL, lipoprotein lipase, TG, triglycerides.

Reproduced with permission from Rosenson RS, Davidson MH, Hirsh BJ, et al: Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014 Dec 16;64(23):2525-2540.[7]

SECONDARY CAUSES OF DYSLIPIDEMIA

DIABETES

Patients with type 2 diabetes commonly manifest atherogenic dyslipidemia (diabetic dyslipidemia).[179] When this occurs, it is essentially part of the metabolic syndrome. Dyslipidemia is usually the result of accumulation of ectopic fat in the liver.[180] The causes of hepatic ectopic fat are attributed to overnutrition, obesity, and insulin resistance.[180,181] Two major responses to ectopic fat are overproduction of VLDL-triglyceride[182,183] and increased expression of hepatic lipase.[184] VLDL particles in type 2 diabetes are particularly enlarged and enriched with triglycerides.[185] Elevated hepatic lipase contributes to the low HDL-C characteristic of diabetic dyslipidemia.[186,187] LDL particles in diabetic dyslipidemia are typically small and dense.[179]

Another factor contributing to diabetic dyslipidemia may be a decrease in expression or activity of LPL.[188,189] This possibility accords with early studies showing that patients with type 2 diabetes have a decreased clearance of TGRL.[190,191]

Occasionally, persons with type 2 diabetes will present with severe hypertriglyceridemia and chylomicronemia. Most of these have poor glycemic control and reduced circulating insulin. Two factors likely contribute. First, they have an elevation of nonesterified fatty acids (NEFAs) caused by lack of insulin to suppress NEFA release from adipose tissue. This elevation drives an overproduction of VLDL-triglyceride. Lack of insulin further reduces LPL, which reduced clearance of TGRL. It should be noted, however, that poor glycemic control per se usually does not cause chylomicronemia. One study strongly suggests that chylomicronemia can be explained by a combination of insulin deficiency and a familial form of hypertriglyceridemia.[191] Insulin deficiency in type 1 diabetes also can result in chylomicronemia when it coexists with a genetic hypertriglyceridemia.

NEPHROTIC SYNDROME

The characteristic lipid abnormality in patients with the nephrotic syndrome is hypercholesterolemia. This abnormality has been attributed to low levels of serum albumin (or low oncotic pressure). The response to hypoalbuminemia was early proposed to be overproduction of apo B–containing lipoproteins by the liver.[192-194] On the other hand, elevated LDL-C levels could be secondary to reduced clearance of LDL from the circulation. Isotope kinetic studies have noted both patterns of response in patients with nephrotic syndrome.[195-197] The overproduction of LDL can readily be explained by response to reduced oncotic pressure when plasma albumin levels are low. On the other hand, the observed reduction in clearance of LDL suggests downregulation of LDLRs. Another cause of increased LDL-C with nephrotic syndrome appears to be an overloading of LDL particles with cholesterol.[195] This could result from prolonged circulation of LDL particles in plasma. But in addition, this abnormality may be secondary to increased plasma levels of cholesterol ester transfer protein, which is been reported in nephrotic syndrome.[198]

An elevation of LDL-C is not the only lipid abnormality seen many patients with nephrotic syndrome. In fact, there can be a concomitant increase in plasma triglycerides. The latter response appears to be secondary to decrease clearance of TGRL.[193,195] A decrease clearance of these lipoproteins may be the result of a loss of apo C-II in the urine.[199] Apo C-II is required for activation of LPL; therefore, its deficiency in VLDL particles could contribute to lipolysis of VLDL triglyceride.[200]

A persistent question has been whether the hyperlipidemia associated with nephrotic syndrome can promote development of ASCVD. Long-term follow-up of large numbers of nephrotic patients is not available; nonetheless, limited evidence supports the atherogenic potential of nephrotic syndrome.[201,202]

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a risk factor for ASCVD.[203] Mechanisms are believed to be multifactorial, including various components of the metabolic syndrome (ie, dyslipidemia, prothrombotic state, proinflammatory state). Several patterns of dyslipidemia are reported. The most common is hypertriglyceridemia.[204] Evidence supports a defective clearance of triglyceride from the circulation, most likely secondary to defective triglyceride lipolysis.[205,206] A high ratio of apo C-III:apo C-II has been implicated in reduced lipoprotein lipase activity.[205-207] Reduced levels of HDL also are common.[208] Although elevated LDL-C is typically not present in CKD, the demonstration that LDL-lowering therapy reduces risk for ASCVD implicates LDL as one factor.[209] Because of the likelihood of many factors contributing to ASCVD in CKD, the quantitative contribution of dyslipidemia to cardiovascular disease is uncertain.

HYPOTHYROIDISM

Hypothyroidism has long been known to raise serum LDL-C levels.[210] The mechanism for this response is not well understood, but most likely there is a decreased expression of LDLRs.[211-213] Clinical experience mandates that all patients with hypercholesterolemia or other dyslipidemia be tested for hypothyroidism. Many hypothyroid patients are asymptomatic and may go undetected if their thyroid-stimulating hormone values are not measured.[214] Not only can hypothyroidism cause hypercholesterolemia, it can unmask other forms of latent dyslipidemia.[215-217] Another reason to test for hypothyroidism is because it predisposes to severe myopathy when statins are used for treatment of hypercholesterolemia.[218] A long-debated issue is whether hypothyroidism (or subclinical hypothyroidism) predisposes to ASCVD. The data are conflicting, but several reports suggest a greater risk.[219-224]

HUMAN IMMUNODEFICIENCY VIRUS

Dyslipidemia is higher among human immunodeficiency virus (HIV)-infected patients than among uninfected persons, occurring in over one-third of patients.[225] Dyslipidemia is a major risk factor for CHD and cerebrovascular events (Data Collection on Adverse Events of Anti-HIV Drugs [DAD] Study Group). Changes over time in risk factors for cardiovascular disease and use of lipid-lowering drugs in HIV-infected individuals and impact on MI.[226-230]

Statins have a number of drug-drug interactions that affect choice of specific statin and dosing in HIV-infected patients.[231] A number of these drugs are commonly used in HIV-infected patients, particularly HIV and hepatitis C, and treatment with protease inhibitors and cobicistat.[232] In addition, comorbid conditions that may affect the use and dosing of statins such as chronic liver and kidney diseases are more common among persons with HIV.[233-235] Thus, HIV-infected patients may be at higher risk for inappropriate statin prescription (contraindicated agent or higher than recommended dose) and toxicity. Despite this, there are scant data regarding patterns of statin use and dosing among HIV-infected patients.

MEDICATIONS

Androgens

In hypogonadal men, testosterone replacement has little effect on serum lipoproteins.[236] However, there is evidence that testosterone increases the activity of hepatic lipase, which can reduce HDL-C.[237-239]

This effect could explain the reduction of HDL-C that occurs during puberty in body.[240-242] Anabolic steroids more potently raise hepatic lipase activity and cause marked reduction in HDL-C.[243]

An important question relates to the role of testosterone in causing the differences in body fat distribution between men and women.[244] Men characteristically exhibit accumulation of adipose tissue mainly in the upper body subcutaneous and visceral regions. In women, fat is located predominantly in the lower body. This difference in body fat distribution may contribute to the higher cardiovascular risk in men. In women with polycystic ovarian disease, testosterone levels are elevated, which may account for their male-pattern of body fat distribution.[245] On the other hand, low testosterone levels have been found to associate with upper body obesity,[246] so the role of testosterone in determining body fat distribution is uncertain.

Estrogens

It is well known that women are at lower risk for ASCVD. Many investigators have speculated that estrogens protect against cardiovascular disease. A considerable body of research indicates that estrogens lower LDL-C and raise HDL-C.[247] LDL-C levels commonly rise after the menopause, most likely due to decrease in LDLR activity.[248,249] Occasionally, estrogen replacement can cause severe hypertriglyceridemia.[250-252] This may be more likely in women with an underlying hypertriglyceridemia. The mechanisms for this response are not well understood, but most likely represent a defect in triglyceride lipolysis.

Retinoids

It is well known that use of oral retinoids for treatment of skin diseases, such as acne, can induce hypertriglyceridemia.[253] In some cases, severe hypertriglyceridemia can occur and can be accompanied by acute pancreatitis.[254]

LIFESTYLE INFLUENCE ON LIPOPROTEINS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

ASCVD rates vary in different countries.[255] Difference in diet seeming contributes importantly to this variability.[256-263] Besides the composition of the diet, obesity, physical activity levels, and cigarette smoking are risk factors.[264,265] Diet composition, obesity, and physical active influence LDL-C levels and other lipoproteins.

DIETARY LIPIDS

Dietary fats have been extensively studied for their effects on lipoproteins.[266] Dietary cholesterol as well as saturated and *trans* fatty acids are LDL-raising nutrients.[20] In populations with high intake of these saturated fatty acids, LDL-C levels are raised by 10% to 15%.[267,268] In contrast, unsaturated fatty acids (monounsaturated and polyunsaturated) do not raise LDL-C levels.[269-271] Therefore, these fats can be used in the place of saturated fatty acids.[272] High-carbohydrate diets, in contrast, cause mild-to-moderate increases in VLDL and reduce HDL-C levels.[273,274] Because of these effects, monounsaturated fatty acids may be preference for carbohydrate as a replacement of saturated fatty acids.[273] A diet high in monounsaturated fatty acids is characteristic of the traditional Mediterranean diet.[275,276]

Populations having high intakes of saturated fats and cholesterol are at increased risk for ASCVD, compared to those with lower intakes.[277-279] Several smaller RCTs indicate that unsaturated fats reduce CHD events when substituted for saturated fats.[280-282]

CARDIOPROTECTIVE FOODS AND FOOD PATTERNS

Much epidemiologic evidence indicates that certain foods other than dietary fats offer some protection against ASCVD. Among these foods are fruits and vegetables, fish, nuts, seeds, perhaps modest alcohol consumption, and low sodium/high potassium intakes.[265,283-289] Also, some natural foods, such as tree nuts and peanuts, legumes, whole grains rich in soluble fiber such as oats and barley, and cocoa products such as chocolate, have been reported to reduce plasma cholesterol.[290] Furthermore, high intake of soluble fiber will reduce cholesterol levels.[291,292] Finally, plant sterols/stanols and intake of about 2 g/d will lower serum cholesterol by about 10%.[293-297] None of these factors has undergone rigorous a RCT, but epidemiologic data are highly suggestive of benefit. But in the case of n-3 fatty acids, an RCT from Japan found that eicosapentaenoic acid incrementally lowered risk of major coronary events when given in combination with a statin.[298] Another impressive RCT examined influence of Mediterranean-type diet on CHD risk.[299] This diet was rich in virgin olive oil or mixed nuts; it was reported to reduce risk for ASCVD.[299]

OBESITY, OVERNUTRITION, AND METABOLIC SYNDROME

Obesity in the general population is associated with increased risk of ASCVD and other disorders. Among the latter are hypertensive cardiovascular disease, type 2 diabetes, fatty liver disease, gallstone disease, obstructive sleep apnea, and certain forms of cancer (colon, breast, and endometrial). Excess body weight can be defined as *overweight* (body mass index [BMI] 25-29 kg/m^2) and *obesity* (BMI ≥ 30 kg/m^2). According to the Centers for Disease Control and Prevention (CDC), more than one-third (34.9% or 78.6 million) of US adults are obese. In addition, more than one-third of American adults (35.7%) and 17% (12.5 million) of American children and teens are clinically obese. The CDC notes that non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%). Moreover, obesity is higher among middle-age adults (age 40-59 years; 39.5%) than among younger adults (age 20-39 years; 30.3%) or older adults (≥ age 60 years; 35.4%).

Obesity denotes an excess of adipose tissue, which is a storage tissue for triglycerides. It is a strong indicator of chronic ingestion of greater intakes of nutrient energy (calories) than needed to maintain normal body weight. Ingestion of excess calories is at the core of metabolic abnormalities associated with obesity.[181] The primary function of adipose tissue is to safely store excess triglycerides and to protect vital tissues from nutrient overload. In some obese individuals, adipose tissue efficiently serves this function and prevents the metabolic consequences of caloric overload. But in others, adipose tissue becomes overloaded with triglyceride and cannot mount an adequate defense against overnutrition.

Fat (triglycerides) can be stored in either upper body or lower body adipose tissue pools.[181] Lower body fat occurs predominantly in subcutaneous adipose tissue in the gluteofemoral region. This appears to be a preferable location for fat storage, because the metabolic consequences of gluteofemoral obesity tend to be minimal.[300] It is a common storage site for triglyceride in women. In contrast, men usually store excess fat in the upper body (abdominal obesity). Here fat storage can occur in either subcutaneous or visceral pools. Upper body obesity is accompanied by greater nutrient overload in other issues. The latter is called ectopic fat.[180]

Dangers for cardiovascular disease overnutrition fall under the category of metabolic syndrome. The latter includes the following features: atherogenic dyslipidemia (elevated triglycerides and total apo B; reduced HDL-C; and small, dense LDL particles), dysglycemia

(prediabetes or diabetes), elevated blood pressure, a proinflammatory state, and a prothrombotic state.[301] Most patients, but not all, with the metabolic syndrome exhibit abdominal obesity. Nonobese individuals with metabolic syndrome most likely have genetic susceptibility to metabolic syndrome, and minimal overnutrition elicits the condition. Even in obese persons with the syndrome, susceptibility factors other than triglyceride-storage capacity most certainly contribute development of metabolic risk factors.[302]

An essential defect in the metabolic syndrome appears to be the accumulation of ectopic fat in skeletal muscle, liver, and possibly the heart and pancreatic beta cells. In muscle, ectopic fat contributes to insulin resistance and type 2 diabetes.[180] In the liver, it predisposes to nonalcoholic fatty liver as well as to atherogenic dyslipidemia.[180,300,303] In beta cells, ectopic fat may impair insulin secretion.[304] And in the heart, it may lead to systolic or diastolic dysfunction.[305,306]

A clinical diagnosis of the metabolic syndrome can be made in accord with a clinical definition (Table 29–5).[307]

The risk factors of this definition include increased blood pressure, dyslipidemia (increased triglycerides and lowered HDL-C), increased fasting glucose, and abdominal obesity (increased waist circumference). This diagnosis harmonized previous recommendation from the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute. Any three of five abnormal findings constitute a diagnosis of the metabolic syndrome. A single set of cut points are used for all components except waist circumference, for which different national or regional thresholds for waist increased circumference were recommended.

Several meta-analyses or studies in large cohorts have been carried out to determine risk of CHD or stroke in patients with metabolic syndrome.[308-313] All of these studies reveal that patients with the syndrome are at higher risk for ASCVD events or mortality than are those without the syndrome. Epidemiological studies show that obesity itself is an underlying risk factor for ASCVD,[314,315] and this risk appears to be mediated largely through the metabolic syndrome.

TABLE 29–5. Criteria for Clinical Diagnosis of Metabolic Syndrome

Measure	Categorical Cut Points
Elevated waist circumference	≥ 40 inches (102 cm) in males
	≥ 35 inches (88 cm) in females
Elevated triglycerides	≥ 150 mg/dL (1.7 mmol/L)
(drug treatment for elevated triglycerides is an alternate indicator)	
Reduced HDL-C	< 40 mg/dL (1.0 mmol/L) in males
(drug treatment for reduced HDL-C is an alternate indicator)	< 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
(antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	
Elevated fasting glucose	≥ 100 mg/dL
(drug treatment of elevated glucose is an alternate indicator)	

HDL-C, high-density lipoprotein cholesterol.

In patients with this syndrome, risk for ASCVD events is increased 1.5- to 2-fold, and for total ASCVD mortality, the risk is increased in the range of 1.5-fold.

PHYSICAL INACTIVITY

Epidemiological data indicate that physical activity offers some protection against ASCVD.[316] Vigorous physical activity can lower triglycerides, raise HDL-C, overall improve the metabolic syndrome, and may protect against ASCVD in other ways.[317-319]

CIGARETTE SMOKING

Cigarette smoking is a major cause of ASCVD worldwide. All prevention strategies should emphasize smoking prevention or cessation as a component of lifestyle intervention.[255] It lowers HDL-C and creates a dysfunctional HDL particle.[320]

LIPID-LOWERING DRUGS AND REDUCTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

STATINS

Statins inhibit cholesterol synthesis in the liver, which increases LDLRs, and increased LDLR activity promotes removal of LDL and VLDL remnants from the circulation. Depending on the dose and agent chosen, statins can reduce LDL-C levels by 25% to 55%. These powerful cholesterol-lowering drugs reduce risk of ASCVD events in both primary and secondary prevention.[148,321,322] RCTs, carried out up to 5 years, demonstrate risk reductions of 25% to 45%; long-term treatment likely reduces risk even more.[323] When drugs are indicated for risk reduction, statins are first-line treatment.

BILE ACID RESINS

Bile acid resins include cholestyramine, colestipol, and colesevelam. These agents bind bile acids in the intestine. They reduce the return of bile acids to the liver and reduce feedback inhibition on the conversion of cholesterol into bile acids.[324] This change reduces hepatic cholesterol concentrations and stimulates the synthesis of LDLRs. The net result is a reduction of LDL-C levels of 15% to 25%, depending on the dose of drug given. A major RCT revealed that treatment of hypercholesterolemia with cholestyramine reduces the risk of ASCVD.[325] The use of bile acid resins is limited by the fact that they are less efficacious than statins and are often accompanied by constipation and other gastrointestinal side effects. These agents have been shown to enhance LDL lowering when given with statins; however, no large-scale clinical trials have ever tested the efficacy of this combination.

EZETIMIBE

Ezetimibe inhibits intestinal absorption of cholesterol and lowers LDL-C by 15% to 25%.[326] It is largely safe and very well tolerated. There are no large monotherapy prevention trials with ezetimibe. However, in one large secondary prevention study, addition of ezetimibe to maximal dose statins incrementally reduced risk of ASCVD events.[159] In another study, the combination of ezetimibe and simvastatin was significantly lowered cardiovascular events in persons with CKD.[327]

MONOCLONAL ANTIBODY INHIBITORS OF PCSK9

Monoclonal antibody inhibitors of PCSK9 are a new class of LDL-lowering drugs. They bind PCSK9 from the circulation and thereby prevention the action of PCSK9 to promote degradation of LDL receptors.[328,329] As a result, more LDLRs are expressed by the liver, and serum LDL-C levels are reduced.[330,331] US Food and Drug Administration (FDA)–approved PCSK9 inhibitors are evolocumab[330,331] and alirocumab.[332] Another agent (bococizumab) is under investigation. These drugs must be given systemically once or twice a month. They cause marked incremental reductions of LDL-C even when given with statins. To date, they appear to be safe and have not been reported to cause myopathy. Interim reports from RCTs indicate that they enhance risk reduction in high-risk patients treated with statins.[333,334] Meta-analysis of several smaller trials further suggest ASCVD benefit.[335]

MIPOMERSEN

Mipomersen is an RNA antisense agent that targets the messenger RNA for synthesis of apo B. It reduces the hepatic secretion of apo B–containing lipoproteins and thus lowers VLDL and LDL.[336] Mipomersen has been approved by the FDA for treatment of homozygous FH. The agent is given weekly by injection. Because it inhibits the secretion of lipoproteins, development of fatty liver is a risk; this appears to be its major side effect. Outcome RCTs have not been carried out.

LOMITAPIDE

Lomitapide is an inhibitor of MTP.[337,338] This protein delivers triglyceride into VLDL particles and reduces their secretion into the circulation. Both VLDL and LDL levels are reduced. High doses markedly lower serum lipoprotein, but this causes retention of triglyceride in the liver (fatty liver). Recent investigations show that low doses of lomitapide produce a substantial reduction of LDL levels with lesser risk of fatty liver.[339] The FDA has approved lomitapide for treatment of homozygous FH.

FIBRATES

Fibrates (eg, gemfibrozil and fenofibrate) are primarily triglyceride-lowering agents that also lower VLDL-C. They also mildly reduce LDL-C and raise HDL-C. They are useful in patients with severe hypertriglyceridemia to reduce risk of acute pancreatitis. They also seemingly lower risk of ASCVD, but considerably less than do statins. In a meta-analysis of all fibrates trials, average risk of CHD morbidity was lowered by approximately 10%.[340] This was not enough to document, on the other hand, when meta-analysis was carried out in subgroups of patients with hypertriglyceridemia, CHD was reduced by of approximately 25%.[341] In addition, in large RCTs, significant reduction in risk was found during monotherapy with gemfibrozil[342,343]; they are thus an alternative for patients who are statin intolerant. Although subgroup analysis favors use of fibrates in patients with hypertriglyceridemia, a major RCT is required to provide convincing evidence that the combination is beneficial.

NIACIN

Niacin is similar to fibrates in that it reduces triglycerides and increases HDL-C. It also can be more efficacious in lowering LDL-C; reductions in the range of 10% to 15% can be obtained. One monotherapy, secondary prevention RCT showed that niacin reduces CHD events and total mortality.[344,345] Niacin further appears to reduce subclinical atherosclerosis when combined with a statin.[346,347] On the other hand, in large secondary prevention RCTs, combining with maximal statin therapy did not further lower ASCVD events.[348,349] Niacin can cause a variety of side effects—flushing, skin rashes, rises in liver transaminases, gastrointestinal upset, and elevations of plasma glucose; many people cannot tolerate niacin for long periods.[350] In a recent clinical trial, niacin plus simvastatin increased risk in the Chinese population.[351] On the other hand, patients who can tolerate niacin but not statins may find the former useful when combined with ezetimibe.[352]

CETP INHIBITORS

CETP inhibitors inhibit CETP.[353] The protein transfers cholesterol ester HDL from VLDL and LDL; this raises HDL-C. From HDL-C to very-low-density or low-density lipoproteins (VLDL or LDL). As a result, HDL-C levels are increased, whereas VLDL-C and LDL-C are decreased. This exchange theoretically could be beneficial by raising HDL-C, the so-called good cholesterol. However, to date three RCTs with CETP inhibitors have failed to show an ASCVD risk reduction. One inhibitor, torcetrapib, gave an increase in total mortality, and the trial was discontinued.[162] Trials with two other CETP inhibitors, dalcetrapib and evacetrapib, were discontinued before completion because of futility.[354] A fourth drug, anacetrapib, continues to be evaluated in clinical trials.[355]

LDL APHERESIS

LDL apheresis is an extracorporeal method for the removal of circulating apo B–containing lipoproteins, including LDL, Lp(a), and VLDL. There are multiple apheresis methods, including dextran sulphate cellulose adsorption, heparin-induced extracorporeal LDL cholesterol precipitation, immunoadsorption, and double filtration plasma pheresis of lipoproteins.[356] The procedure is performed weekly or biweekly depending on the rate at which LDL-C levels return to baseline after therapy. LDL apheresis lowers LDL-C acutely by 50% to 76%.[357,358] However, the time-averaged LDL-C reduction is about 30% after 6 months and 38% after 18 months in the absence of statin therapy.[359] Larger LDL-C reductions may be observed in patients with higher baseline lipid levels, who appear to have a relatively greater response to this therapy.[360] The most frequent adverse effects include hypotension, anemia, nausea, flushing, and headache. Venous access is necessary, and many patients require construction of an arteriovenous fistula or a central venous port that increases the risk of long-term complications.[356]

Clinical outcomes studies with LDL apheresis are limited, and no study has demonstrated significantly improved survival with LDL apheresis. In an observational study of 130 patients with heterozygous FH who were treated with either LDL apheresis plus statin therapy (n = 43) or statin therapy (n = 87), there was a significantly lower rate of total coronary events (nonfatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and death from CHD) in the LDL apheresis group (10% vs 36%, respectively) at 6 years.[361]

STATIN INTOLERANCE

Statin intolerance is the inability to tolerate statins at the recommended dosage to reduce cardiovascular events caused by adverse symptoms, signs or laboratory studies that result in interruption, discontinuation dose reduction of the statin therapy.[362] The major cause of statin intolerance includes adverse muscle complaints, with far less common reports of cognitive impairment and peripheral neuropathy. A crucial component of assessment of statin intolerance is dechallenge and rechallenge of statin therapy at a reduced dosage or selection of an alternate statin with different pharmacodynamics and

pharmacokinetic properties.[363,364] Consensus statements differ with respect to the number of statins that require rechallenge, but this process is essential because 60% to 70% of individuals tolerate reintroduction of a statin on blinded rechallenge.[365]

STATIN-ASSOCIATED ADVERSE MUSCLE COMPLAINTS

Although the main concern with statins is the risk of rhabdomyolysis, this is a rare occurrence that affects 0.1% of patients.[363,364] Terminology relating to statin-associated adverse muscle events is variable and has changed over time. According to the 2014 National Lipid Association Statin Muscle Safety Task Force:[363]

- **Myalgia:** A symptom of muscle-discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK) level. Myalgia symptoms can be described as flu-like symptoms.
- **Myopathy:** Muscle weakness (not due to pain), with or without an elevation in CK level
- **Myositis:** Muscle inflammation
- **Myonecrosis:** Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal that has been adjusted for age, race, and sex:
  - Mild: 3- to 10-fold elevation in CK above baseline
  - Moderate: 10- to 50-fold elevation in CK above baseline
  - Severe: 50-fold or greater elevation in CK above baseline or an absolute level of 10,000 U/L or more
- **Clinical rhabdomyolysis:** Myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of least 0.5 mg/dL [44 μM/L])

Adverse events with statins is derived from large clinical trials of statin therapy and from observational studies of statins in clinical use.[366] However, experience in clinical practice suggests that muscle side effects are more common, resulting in discontinuation of statin therapy.[367] Differences in selection criteria in randomized trials from clinical practice may limit the ability to generalize their results to the adverse event profiles seen in a broader population of patients.[368]

Risk Factors for Statin-Associated Adverse Muscle Events

Statin Characteristics The ability to cause muscle injury varies among statins. Myositis has been reported in less than 0.5% percent, but the frequency increases at higher doses. With simvastatin, the incidence in clinical trials, in which patients were carefully monitored and potential interacting drugs were prohibited, was 0.02% at 20 mg/day, 0.07% at 40 mg/day, and 0.3% at 80 mg/day.[369] In one clinical trial, simvastatin 80 mg/day was accompanied by a 10-fold increase in rhabdomyolysis when compared to simvastatin 20 mg/day.[370] Other clinical trials have reported more common adverse muscle events than simvastatin 80 mg/d.[351,371] Thus, simvastatin 80 mg/day is not recommended.

The risk of adverse muscle events appears to be lowest with fluvastatin.[372] Pravastatin also has a low risk of myonecrosis as demonstrated with pravastatin (40 mg/day) in an analysis of more than 112,000 patient-years of experience in three large controlled trials.[373] In addition to this difference in direct toxicity, pravastatin, fluvastatin, and pitavastatin are also less likely to be involved with drug interactions since they are not extensively metabolized by CYP3A4 (Table 29–6).

Preexisting Neuromuscular Disorders Underlying neuromuscular disorders may become clinically manifest after initiation of statin therapy.[363] In some cases, statins can cause new neuromuscular disorders. However, others involve increased risk of toxicity in patients with known underlying neuromuscular disorders or the development of clinically manifest disease in patients who had likely had preclinical disease before statins were initiated.

Hypothyroidism and Other Disorders Enhanced susceptibility to statin-associated myopathy occurs in patients with hypothyroidism, acute or chronic renal failure, and obstructive liver disease. Hypothyroidism may predispose to the development of statin-associated myopathy that "unmasks" hypothyroid myopathy. In addition, hypothyroid patients who are pharmacologically euthyroid have higher rates of statin-associated adverse muscle complaints.[374]

Patient Characteristics Genetic factors may increase the risk of statin myopathy. A genome-wide association study found that common variants of the *SLCO1B1* gene, which encodes the organic anion transporting polypeptide 1B1 (OATP1B1) that mediates hepatic uptake of most statins, substantially increased the risk of adverse muscle complaints and myonecrosis (mild to severe) than in patients treated with simvastatin.[371] A subsequent randomized trial of statins found an association between a specific *SLCO1B1* variant (SLCO1B1*5) and an increased risk of myalgias and myonecrosis.[375]

Certain ethnic populations have an increased risk of statin muscle adverse events. Simvastatin prescribing information recommends caution when doses above 20 mg daily are used in Chinese patients who are also receiving niacin and states that such patients should not be treated with simvastatin 80 mg daily in combination with niacin.[351] In a large randomized trial in which all patients were treated with simvastatin 40 mg daily, participants from China had a higher rate of adverse muscle symptoms, including myonecrosis, than patients from Europe (1.3 vs 0.4 events per 1000 patients per year).

Other patient factors associated with an increased risk of statin-associated adverse muscle events include advanced age (> 75 years), frailty, female sex, small body frame, acute or decompensated liver disease, and severe renal disease.[363,376]

Concurrent Drug Therapy The increase in susceptibility to myopathy is substantially greater in patients receiving concurrent therapy with a number of drugs, particularly those that inhibit cytochrome P450 3A4 (CYP3A4) (see Table 29–6) gemfibrozil and peroxisome proliferator-activated receptor (PPAR)-alpha agonists.[231] Concurrent use of a drug or drug class that is independently considered a risk factor for myopathy (ie, glucocorticoids, cyclosporine, daptomycin, zidovudine) may further increase risk. The uptake, metabolism, and clearance of each statin is different, and therefore each statin is subject to different types of drug interactions (see Table 29–6).

Exercise Unaccustomed vigorous exercise in those on statins may increase the risk of muscle injury. However, the association has not been consistently observed across trials.[377,378] Clinical judgment is necessary in interpreting elevated CK levels in patients on statins. CK elevations can be related to hypothyroidism or muscle injury during sports (eg, running, hockey, impact or collision sports), and patients who engage in high-impact sports should be advised to have a CK measured before engaging in particularly high-intensity exercise that day. Although there have been concerns about the effects of statin therapy on exercise tolerance even in asymptomatic individuals, no statistically significant differences were reported in muscle strength, muscle endurance, or aerobic performance.[379] In contrast to these results, a smaller trial conducted in less fit patients found that treatment with simvastatin diminished exercise-associated improvements in aerobic fitness and muscle mitochondrial content.[380]

Time Course of Muscle Events The onset of muscle symptoms is usually within weeks to months after the initiation of statin therapy but may occur at any time during treatment. Myalgias and myopathy resolve and serum CK concentrations return to normal over days to weeks after discontinuation of the drug.

TABLE 29–6. Statins and Cytochrome 3A4 Drug Interactions: Predicted versus Observed Fold Increases in Various Statins and Enzymes Systems[a]

		Predicted Fold Increase in AUC from Inhibition of Composite Pathways				
Statin	**Perpetrator Drug**	**BRCP (Intestine)**	**CYP3A4 (Intestine)**	**OAT1B1**	**CYP3A4 (liver)**	**Clinically Predicted Fold Increase in AUC**
Simvastatin	Cyclosporine		1.67	4.5 (56)	1.0 (0.09)	7.5
	Telithromycin		1.67	1.2 (0.2)	2.0 (1.6)	4.0
	Posaconazole		1.67	NI	1.7 (0.9)	4.0
	Cyclosporine	1.72 (174)	1.45	3.2 (103)	NA	8.0
	Lopinavir/ritonavir	NA, low solubility	1.45	1.9 (2.3) 1.1 (0.14)	1.0 (0.16)	2.9
	Clarithromycin	NI	1.45	2.0 (2.7)	1.1 (0.4)	3.2
	Itraconazole	NI	1.45	NI	1.0 (0.4)	1.45
Fluvastatin		**BRCP (intestine)**		**OAT1B3**	**CYP2C9**	
	Cyclosporine	1.72 (100)		1.8 (19)	NI	3.2
	Fluconazole	NI		NI	1.7 (9.9)	1.7
Statin	Precipitating drug	BRCP (intestine)	Active uptake (OATP1B1:NTCP:OATP1B3) ($f_e = 0.38{:}21{:}0.11 = 0.7$)	OAT3	Overall predicted fold increase in AUC	Clinically observed fold increase in AUC
Rosuvastatin	Cyclosporine	2.0 (100)	3.2 (56)	NI	6.4	7.1
	Gemfibrozil	NI	1.5 (OATP1B) (2.0)	1.2 (2.1)	1.8	1.9
	Lopinavir/ritonavir	No effect–low solubility	1.5 (OATP1B) (1.9 if all inhibited (2.3)	NA	1.5 (1.9)	2.1
	Atazanavir/ritonavir	2.0 (25)	1.6 (OATP1B) (3.5)	NA	3.2	3.1
		Efflux (intestine)	**OATP1B1**	**OAT3**		
Pravastatin	Cyclosporine	2.9	2.0 (103)	NI	5.8	3.82
	Clarithromycin	NI	1.6 (2.7)	NI	1.6	2.1
	Gemfibrozil	NI	1.3 (0.9)	1.4 (2.6)	2.1	2.0
			OAT			
Pitavastatin	Cyclosporine		4.2 (39)		4.2	4.55
	Erythromycin		1.5 (0.7)		1.5	2.8
	Gemfibrozil		1.5 (0.8)		1.5	1.45

AUC, area under the curve; BRCP, breast cancer–resistant protein; CYP3A4, cytochrome P450 isozyme 3A4; DDI, drug-drug interaction; IC50, half maximal inhibitory concentration; Ki, reversible inhibition constant; NA, not applicable; NI, not an inhibitor; OAT; organic antion transporter; OATP.\, organic anion transporting peptide.

[a](number), ratio of $_{\text{inlet max, unbound}}$/IC50.

Modified with permission from Elsby R, Hilgendorf C, Fenner K: Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. *Clin Pharmacol Ther*. 2012 Nov;92(5):584-598.

Diagnosis of Statin-Associated Adverse Muscle Events

The diagnosis of symptomatic and more severe statin-associated muscle events with laboratory abnormalities (ie, elevated serum CK) is based on a temporal association for both onset with initiation of statin therapy and resolution with statin withdrawal. Definitions of the categories of statin-associated adverse muscle events are provided in Table 29–7.

However, some patients report muscle symptoms from statin therapy without an elevation in serum CK. Distinguishing among these is typically based on a careful history and trials of cessation and reintroduction of statin therapy. Even with this, in some patients it will be difficult to be certain whether muscle symptoms result from statin therapy. A scoring system has been proposed for statin-associated symptoms,[363] but this tool has not yet been validated (Table 29–8).

Management of Statin-Associated Adverse Muscle Events

Patients with significant muscle toxicity from a statin should discontinue therapy. Based on clinical experience, in the absence of clinical symptoms, a CK level more than 10 times the upper limit of normal that is believed to be caused by a statin is an indication for discontinuing the medication. Patients should drink large quantities of fluids to facilitate renal excretion of myoglobin. If a patient requires a statin and experiences adverse muscle events other than rhabdomyolysis, once symptoms have resolved and the CK has returned to baseline off statin therapy, we suggest the following approach.

If switching statin therapy is unsuccessful, initiate alternate-day (or less frequent) dosing with careful monitoring. Patients with a history of statin-induced rhabdomyolysis should generally not be treated with another statin because of the risk of recurrent myonecrosis and acute kidney injury.[381]

TABLE 29–7. Definitions of Statin-Associated Adverse Muscle Events

- Myalgia—unexplained muscle discomfort often described as "flu-like" symptoms in normal CK level. The spectrum of myalgia complains includes:
  - Muscle aches
  - Muscle soreness
  - Muscle stiffness
  - Muscle tenderness
  - Muscle cramps with or shortly after exercise (not nocturnal cramping)
- Myopathy—muscle weakness (not attributed to pain and (not necessarily associated with elevated CK)
- Myositis—muscle inflammation
- Myonecrosis—muscle enzyme elevations of hyperCKemia
  - Mild > 3-fold greater than baseline untreated CK levels or normative upper limit that are adjusted for age, race, and sex
  - Moderate ≥10-fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race, and sex
  - Severe ≥50-fold above baseline CK levels or normative upper limit that are adjusted for age, race, and sex
- Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine ≥0.5 mg/dL (clinical rhabdomyolysis)

Abbreviation: CK, creatine kinase.

Reproduced with permission from Rosenson RS, Baker SK2, Jacobson TA, et al: An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol*. 2014 May-Jun;8(3 Suppl):S58-S71.

TABLE 29–8. Statin Muscle Adverse Symptom Clinical Index

Clinical symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Nonspecific asymmetric, intermittent	
Temporal pattern	
Symptom onset < 4 weeks	3
Symptom onset 4–12 weeks	2
Symptom onset > 12 weeks	1
Dechallenge	
Improves on withdrawal (< 2 weeks)	2
Improves on withdrawal (2–4 weeks)	1
Does not improve on withdrawal	0
Challenge	
Same symptoms recur on challenge < 4 weeks	3
Same symptoms recur on challenge 4–12 weeks	1
Statin myalgia clinical index score	
Probable	9–11
Possible	7–8
Unlikely	< 7

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COGNITIVE IMPAIRMENT

Statin therapy has been associated with case reports of cognitive impairment. However, prospective analysis of cognitive impairment in controlled clinical trials has been limited. A randomized trial of pravastatin versus placebo did not show an association with cognitive impairment in 5777 white adults 70 years of age or older with existing vascular disease or at high risk for vascular disease because of smoking, hypertension, or diabetes.[382] This study was restricted to white participants and limited by the inclusion of a select population of older, high-risk, clinical trial participants. Additionally, incident cognitive impairment was not reported.

TYPE 2 DIABETES

Statin therapy is associated with a small increased risk of type 2 diabetes mellitus, which is more pronounced among nondiabetes patients treated with high-intensity compared with low- to moderate-intensity statin therapy.[151] The mendelian randomization principle was used to investigate the mechanism underlying the glucose-raising effect of statins. Single SNPs in the *HMGCR* gene, rs17238484 and rs12915, were used to explore the association of incident and prevalent type 2 diabetes. The rs172348484G allele was associated with a 1.62% higher plasma insulin concentration (95% CI 0.53-2.72; P = .04), 0.23% high plasma glucose concentration and 0·30 kg (95% CI: 0·18-0·43) higher body weight. These polymorphisms explained 2% of 6% of the risk of type 2 diabetes.[150-152,383] It is important to note that the decreased risk of ASCVD with statins usually trumps the small increased risk of type 2 diabetes.

CHOLESTEROL-LOWERING THERAPY

LDL-C AND NON–HDL-C AS MAJOR TARGETS OF THERAPY

Most guidelines identify LDL as the primary atherogenic lipoprotein—and therefore the dominant target of cholesterol-lowering therapy.[20,384] But growing evidence indicates that VLDL is similarly atherogenic.[20,385] Many investigators thus contend that combining LDL-C and VLDL-C into non–HDL-C is preferable to LDL-C alone.[386] Non–HDL-C can also be called *atherogenic cholesterol*. The major apolipoprotein of LDL and VLDL is apo B; for this reason, the measurement of total apo B thus is an alternative to non–HDL-C.[56] The measurement of total apo B can be converted to the total lipoprotein particle number for apo B–containing lipoproteins; this conversion is possible because there is one apo B molecule per lipoprotein particle. According to several reports, total apo B (or lipoprotein particle number) is a better predictor of ASCVD than is LDL-C.[320,387-395] Moreover, a few reports claim that apo B is superior to non–HDL-C in prediction of ASCVD.[55,396,397] But other investigators report that non–HDL-C is superior to apo B.[53,398,399] Regardless, the difference in predictive power between the two is small.

CHOLESTEROL-LOWERING THERAPY IN SECONDARY PREVENTION

Efficacy of Therapy

Many RCTs document that statin therapy reduces risk of recurrent cardiovascular events in patients with established ASCVD.[20,322,400-402] Risk reduction occurs regardless of baseline LDL-C (or non–HDL-C) levels. Several RCTs report that risk reduction with statin therapy extends to LDL-C ranges of 70 to 80 mg/dL.[403-409] Statin treatment reduces strokes as well as CHD, as shown in several RCTs, and particularly, in one trial designed to test effects on stroke.[410] Based on RCT evidence, it is reasonable to maximize statin therapy in patients with established CHD.

A critical question is whether further cholesterol lowering beyond maximal statin therapy will give additional risk reduction. Recent American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines[411] concluded that RCT evidence is insufficient to justify adding other nonstatin drugs to statin therapy. Nonetheless, it may be worthwhile to review their potential. Examples include bile acid resins, ezetimibe, nicotinic acid, fibrates (eg, fenofibrate), and n-3 fatty acids.

Until recently, the only agent systematically tested as an add-on drug was nicotinic acid. As mentioned, adding nicotinic acid to statin therapy failed to achieve additional risk reduction for ASCVD.[348,349] This was true even though previous studies showed that adding nicotinic acid to statins favorably reduced carotid atherosclerosis in imaging studies.[347] Even so, in the light of large outcome trials, nicotinic acid cannot be considered a first-line, add-on drug in secondary prevention.

Fenofibate, a fibrate, resembles nicotinic acid in that it lowers VLDL and LDL and raises HDL-C.[412] Among fibrates, fenofibrate is preferred over gemfibrozil when used with statins because it is accompanied by a lower risk of severe myopathy.[413] Nonetheless, in one recent study in patients with diabetes, the combination of statin plus fenofibrate failed to reduce ASCVD risk more than statin alone.[414] Still, in meta-analysis of results in hypertriglyceridemic patients from this study, combination therapy showed a strong trend toward greater benefit compared to statin alone.[415] This result accords with subgroup meta-analysis of hypertriglyceridemic in all fibrate trials; together, they showed greater risk reduction were used compared to placebo.[341] A similar favorable trend from fibrate therapy was not found in subgroups without hypertriglyceridemia. In sum, meta-analysis supports the concept that adding fenofibrate to statin therapy is an option for high-risk patients with hypertriglyceridemia.

Many providers add -3 fatty acids to statin therapy on the belief that additional risk reduction will be achieved. In two secondary prevention trials, adding n-3 fatty acids to statin treatment, however, did not produce additional benefit.[416,417] But in contrast, in the JELIS [Japan Eicosapentaenoic acid (EPA) Lipid Intervention Study] trial,[298] adding eicosapentaenoic acid to statins in patients with ASCVD caused a reduction in cardiovascular events. Thus, the benefit of adding n-3 fatty acids to statin therapy remains open to question. Some investigators prefer n-3 fatty acids in combination with statins to treat hypertriglyceridemia because they do not raise the risk of severe myopathy.

Another potential add-on drug is ezetimibe. This agent was combined with a statin in the IMPROVE-IT trial.[159] The combination of maximal simvastatin therapy plus ezetimibe significantly reduced recurrent ASCVD events in patients who had recent acute coronary syndromes compared with simvastatin alone. The addition of ezetimibe reduced LDL-C levels to well below 70 mg/dL, which was the approximate level attained by simvastatin alone. This study makes several important points. First, it undercuts any notion that statins are the only cholesterol-lowering drug that can reduce ASCVD events. Second, it supports the concept of "the lower, the better" for atherogenic cholesterol in patients with established ASCVD. And third, it reinforces the *cholesterol hypothesis* by showing that a drug that uniquely lowers cholesterol levels will decrease risk.

Hot on the heels of the IMPROVE-IT trial was approval of PCSK9 inhibitors by US and European regulatory agencies. Monoclonal antibodies against PCSK9 free up LDLRs and dramatically reduce serum LDL-C levels.[418] Recent reports[333,334] further document a striking reduction in LDL-C when PCSK9 inhibitors are combined with statins in high-risk patients. They further showed preliminary data in which this combination enhanced reduction of CHD and stroke.

Cholesterol Goals in Secondary Prevention

There are two ways to approach the question of cholesterol goals in secondary prevention. First, the meta-analysis of the Cholesterol Treatment Trialists' (CTT) Collaboration[322] showed that for every mmol/L lowering of LDL-C there was an approximate 22% reduction in relative risk of ASCVD events (see Fig. 29–11). On average, for every 1% reduction in LDL-C, risk is reduced by 1%. This means that a 50% reduction in LDL-C should reduce risk by 50%. For simplicity, this meta-analysis supported the concept of "the more, the better" for LDL-C reduction. The 2014 ACC/AHA guidelines implicitly accepted this conclusion when it recommended high-intensity statins in patients with ASCVD. For example, treatment with either atorvastatin 80 mg/day or rosuvastatin 20 mg/day should achieve a "more-the-better" goal of 50% reduction of LDL-C. Based on the IMPROVE-IT trial, an even greater reduction of LDL-C (eg, ≥ 60%), attained by adding ezetimibe to a high-intensity statin, could be recommended by the same rationale.

An alternate approach to a cholesterol goal can be based on a meta-analysis of statin trials that examines maximal risk reduction that can be achieved by cholesterol lowering.[419] The results of this analysis showed "the lower, the better" for cholesterol lowering. That is, the lowest levels of LDL-C (or non–HDL-C) were accompanied by the lowest risk of future ASCVD events. This relationship held to an LDL-C of less than 50 mg/dL. Similar results were obtained for non–HDL-C. This "lower-is-better" relationship is supported by the IMPROVE-IT trial. At the least, an LDL-C goal for secondary prevention can be reasonably set at less than 70 mg/dL, but based on IMPROVE-IT, a case can made for a still lower goal. In the future, RCTs with PCSK9 inhibitors may call for a very low goal for atherogenic cholesterol levels.

CHOLESTEROL-LOWERING THERAPY FOR PRIMARY PREVENTION

Optimal Cholesterol Levels in Primary Prevention

There is no simple answer to the question of what is the optimal LDL-C (or non–HDL-C) for primary prevention. Several epidemiological studies indicate that CHD risk is progressively lower for a total cholesterol down to 150 mg/dL.[420,421] This level corresponds to an LDL-C of about 100 mg/dL.[20] Genetic epidemiology further demonstrates that lifetime levels of LDL-C of approximately 100 mg/dL are accompanied by a low lifetime risk of CHD.[153,422,423] Moreover, RCTs with cholesterol-lowering drugs show that reducing LDL-C concentrations to near 100 mg/dL or below produce significant reduction in ASCVD rates.[20,424] Based on these congruent lines of evidence, the Adult Treatment Panel (ATP) III[20] defined an LDL-C level of less than 100 mg/dL as being optimal, whereas 100 to 129 mg/dL was called near optimal. On the other hand, this so-called optimal level may not be the most efficacious level for high-risk patients, who may benefit from still further cholesterol lowering.

Selection of Patients for Drug Therapy in Primary Prevention

Three methods have been used for selection of patients for initiation of cholesterol-lowering drugs. These are (1) 10-year risk for ASCVD based on multiple-risk-factor algorithms (global risk assessment), (2) lifetime risk based on single major risk factors, and (3) 10-year risk based on imaging for subclinical atherosclerosis. Each approach can be briefly reviewed for its strengths and weaknesses.

Ten-Year Risk Estimates Based on Multiple-Risk-Factor Algorithms These algorithms have been developed from various test cohorts. The most widely used in the United States is that derived from a population in Massachusetts, the Framingham Heart Study.[425] The Framingham cohort included several thousand subjects studied over many years.

Recently, the National Heart, Lung and Blood Institute commissioned the creation of a new algorithm based on five cohorts, including Framingham. This algorithm is currently sponsored by the AHA and the ACC. It was published in 2013 and will be called the 2013 ACC/AHA risk algorithm.[426] It can be accessed online (http://tools.acc.org/ASCVD-Risk-Estimator/).

Similarly, QRISK is an ASCVD risk assessment tool developed in the United Kingdom that derives from a large prospective, open-cohort study.[427] The derivation cohort for this algorithm included 1.28 million individuals (35-74 years and free of diabetes and ASCVD). The validation study contained 610,000 subjects from 160 practices. A comparison study indicated that the Framingham study overpredicts risk compared to QRISK by about 35%.[427] This algorithm is available online (http://qrisk.org/). A major strength of QRISK lies in its much larger size compared to US algorithms.

In essence, multiple–risk factor algorithms use population averages to predict risk in individual patients. When applied in guidelines, they assume that individuals resemble population means. A major limitation of this approach is that risk in individuals can vary substantially from the population mean. This is particularly so in older persons who exhibit wide variability in atherosclerotic burden. Moreover, population risk tends to decline over time, as suggested by QRISK versus Framingham.[427] Consequently, population-risk algorithms derived in the past tend to overestimate current risk. This is illustrated by recent reports showing that application of the ACC/AHA algorithm overestimates population risk when tested in more recently studied cohorts.[428-433] A risk algorithm developed in one country does not necessarily hold in another; for example, various studies have shown that Framingham algorithms overestimate CHD risk in several countries.[434]

Lifetime Risk Assessment Based on Algorithms and on Individual High-Risk Conditions If lifetime risk estimates were to be reliable, they would have utility for deciding on treatment strategies. Online estimates for lifetime risk are provided by both 2013 ACC/AHA (http://tools.acc.org/ASCVD-Risk-Estimator/) and QRISK (http://www.qrisk.org/lifetime/). These are not as reliable as 10-year risk estimates because long-term risk is not as well substantiated. An alternate and simpler approach is to identify higher risk conditions and to use these as a guide to lifetime risk reduction (Table 29–9).

TABLE 29–9. High-Risk Conditions

Diabetes[a]
Metabolic syndrome[b]
Chronic kidney disease[c]
Heavy cigarette smoking[d]
Persistent hypercholesterolemia[e]
Persistent hypertension[f]

[a]Diabetes in a person > 40 years should be considered a high-risk condition; for younger patients risk depends on clinical judgment.

[b]Metabolic syndrome defined by Adult Treatment Panel (ATP) III criteria (x).

[c]Chronic kidney disease equates to an estimated glomerular filtration rate < 30 mg/min.

[d]Habitual cigarette smoking is inability to stop smoking.

[e]Persistent hypercholesterolemia is a low-density lipoprotein cholesterol of ≥ 160 mg/dL.

[f]Persistent hypertension is failure to achieve a systolic blood pressure ≥ 140 mm Hg.

Any of these conditions carry a relatively high lifetime risk, as can be shown by risk algorithms. The presence of higher risk conditions makes 10-year risk assessment unnecessary. Most such patients deserve serious consideration of statin treatment. Use of this strategy will shift drug administration to an earlier age than will current 10-year risk algorithms. Practical considerations make RCTs testing lifetime therapies unrealistic. But RCTs have been carried out in persons with each high-risk condition, and they show efficacy for shorter term risk.[435,436] RCTs demonstrating efficacy of cholesterol-lowering therapy has been documented in patients with diabetes,[437] metabolic syndrome,[438-440] CKD,[327] cigarette smoking,[441] hypertension,[442] and hypercholesterolemia.[443] Therefore, lifetime risk reduction is almost certain when used in patients with higher risk conditions.

Ten-Year Risk Assessment Based on Atherosclerosis Imaging A major drawback of global risk algorithms is that they place excessive weight on age as a risk factor. In essence, age is used as a surrogate for progressive atherosclerosis. The impact of age on estimated risk is so powerful that most men over 60 and most women over 70 are recommended for statin therapy.[411] Atherosclerotic burden increases with age in the population as a whole; yet many older individuals have little or no atherosclerosis. They will not benefit from taking statins. One way to improve identification of individuals without atherosclerotic burden is to measure subclinical atherosclerosis. The most readily available and intensively studied modality for atherosclerosis imaging is coronary artery calcium (CAC).[444,445] Measurement of CAC in older individuals who are at relatively low risk by global risk assessment will uncover a substantial portion who are devoid of coronary atherosclerosis.[446,447] Recent studies show that actual 10-year risk for clinical CHD when CAC is zero is very low (see Table 29–9).[448] In the absence of CAC, statin treatment is not needed.[449]

Atherosclerosis imaging may be particularly useful under the following circumstances: absence of high-risk conditions (Table 29–10), estimated 10-year risk for ASCVD in the range of 5% to 19% by global risk assessment,[426] presence of emerging risk factors in otherwise lower risk individuals (see Table 29–10), and statin intolerance in persons without ASCVD. As shown in Table 29–10, individuals with a zero CAC Agatston units are virtually free of CHD after 10 years.[448] These individuals will not need statin therapy. If CAC scores are in the range of 1 to 99 Agatston units, risk is borderline, and statins are optional. The decision should be made on a variety of factors previously considered. At higher CAC scores (> 100 Agatston units), use of statins is reasonable.

Risk Classification for Primary Prevention

The following are classifies risk categories that can be applied to primary prevention.

TABLE 29–10. Predicted 10-Year Risk for Coronary Heart Disease (CHD) According to Age and Coronary Artery Calcium (CAC)

CAC Score (Agatston Units)	10-year Risk for CHD (45–54 years)	10-year Risk for CHD (> 75 years)
Zero	1%	1%
1–99	4%	7%
≥ 100	17%	18%

- *High risk*. ATP III guidelines categorized patients according to absolute risk. These guidelines pointed out that patients with established ASCVD have a 10-year risk of recurrent events exceeding 20%. Patients who exceeded this risk but had no history of ASCVD were said to have *CHD risk equivalents*. This nomenclature is no longer used, but identifying those at *high risk*, whose risk is as high as ASCVD patients and who deserve more intensive cholesterol-lowering therapy, may still be useful.
- *Moderately high risk*. There is no agreement at present on what constitutes moderately high risk. At this level, risk is high enough to justify cholesterol-lowering drugs, but it is less than that of patients with ASCVD. The ACC/AHA guidelines set a 10-year risk for statin consideration of 7.5% or more. The National Institute of Health and Care Excellence (NICE) guidelines recommend a threshold of ≥ 10%. In neither of the recent guidelines was an upper boundary set, and *moderately high risk* and *high risk* were not distinguished. In this document, *moderately high risk* will be defined as a 10-year risk of ASCVD of 7.5% to 19% and thus will be distinguished from *high risk*. This distinction may be useful in selection of intensity of statin therapy.
- *Higher lifetime risk*. At the next lower level, some patients can be said to be at relatively low 10-year risk but a higher lifetime risk (ie, 35%-50%). One way to identify these patients is through a multiple risk factor algorithm—available from the ACC/AHA (http://tools.acc.org/ASCVD-Risk-Estimator/) or QRISK (http://www.qrisk.org/lifetime/). Another way to identify a high lifetime risk in current lower risk individuals is through the presence of higher risk conditions (see Table 29–10). Among these are persistently high LDL-C levels (≥ 160 mg/dL), and especially those with very high LDL-C (≥ 190 mg/dL).

Cholesterol Goals in Primary Prevention

There are two reasons to establish goals for atherogenic cholesterol in primary prevention. The first is to prevent ASCVD events in the short-term (eg, 10 years) and second is the need to prevent events over a lifetime. Table 29–11 poses a strategy to achieve these aims.

For high-risk individuals, whose 10-year risk is equivalent to that of a patient with established ASCVD (ie, ≥ 20%), cholesterol lowering should be as intense as in ASCVD patients. Accordingly, the goal can be either a 50% reduction in LDL-C levels, or alternatively, a target non–HDL-C of less than 100 mg/dL (LDL-C < 70 mg/dL). For most patients, a high-intensity statin can be justified. If the goals of therapy are not achieved, a nonstatin add-on agent can be considered. If only a moderate-intensity statin can be tolerated, consideration can be given to adding ezetimibe or bile acid resin.

For those at moderately high risk (ie, 10-year risk in the range of 7.5%-19%), the use of a high-intensity statin is an option, as recommended by ACC/AHA guidelines, or a moderate-intensity statin, as proposed by NICE. At this risk level, atherogenic cholesterol should be reduced by at least 40%, or alternatively, to achieving an LDL-C goal of less than 100 mg/dL (or a non–HDL-C goal of < 130 mg/dL).

For lower risk individuals whose lifetime risk is high (eg, 35%-50%), the LDL-C likewise should be reduced to less than 100 mg/dL. The same goal should be set for patients with was very high LDL-C. In both cases, the aim is to slow progression of atherosclerosis so as to reduce lifetime risk.

TABLE 29–11. Number Needed to Treat with Cholesterol-Lowering Drugs to Prevent One ASCVD Event over 10 Years

Estimated 10-Year Risk for ASCVD	Number Needed to Treat
5%	50
7.5%	33
10%	25
12.5%	20
15%	17
17.5%	14
20%	12
22.5%	11
25%	10

ASCVD, atherosclerotic cardiovascular disease.

PHYSICIAN-PATIENT DISCUSSION

The decision to initiate a lifetime of statin therapy should not be taken lightly. For therapy to be successful, the patient becomes a key partner in the treatment regimen. Before starting a statin, several issues should be discussed or considered as options. These can be reviewed briefly.

Adherence to Therapy

Discontinuation of prescribed statin is a common issue in clinical practice. It has been shown that failure to sustain statin therapy results in higher rates of ASCVD after MI. Poor adherence to statins can be attributed to many factors, among which are health system factors, provider behavior, and patient behavior.[450] The first step in overcoming failure to adhere is to review strategies for maintaining compliance in patient discussion.

Consideration of Drug Side Effects

Most patients tolerate statins and other cholesterol-lowering drugs without significant side effects. As mentioned before, some patients complain of a variety of side effects of statins: statin-associated adverse muscle events, hyperglycemia, cognitive dysfunction, and neuropathy. Statins also can increase plasma glucose, which may cross the threshold for categorical diabetes. This may be alarming, but is not a serious side effect. Unfortunately, many patients have a preconceived anticipation of drug side effects and often blame various symptoms on their drug. If complaints arise, physicians should thoroughly discuss symptoms and make an effort to separ ate real from imagined statin intolerance. By encouragement, it is often possible to successfully restart and maintain statin therapy. For those who cannot tolerate statins, a variety of strategies, as discussed before, can be used to achieve a satisfactory cholesterol lowering.

Alternatives to Statin or Add-on Drugs

Statins are first-line cholesterol-lowering therapy, but if they are not tolerated, other ways to achieve cholesterol goals can be considered. Efforts should be doubled to start and maintain lifestyle modification, which can lower cholesterol levels by 10% to 15% (NCEP 2002). Both bile acid resins and ezetimibe can lower LDL-C by 15% to 25%. Ezetimibe plus a moderate-intensity statin will reduce cholesterol levels as much as high-intensity statins. Fibrates and niacin are alternative add-on drugs for patients with hypertriglyceridemia. Finally, in patients with severe hypercholesterolemia, PCSK9 inhibitors may be an option for patients who are statin intolerant, especially in those with ASCVD or very high LDL-C levels.

Cost-Effectiveness

With introduction of generic statins, drug costs have declined greatly. But for some patients, overall cost of therapy is a significant issue. Expenses mount with regular monitoring for response, clinical management of side effects, and time and expense of travel to provider locations. In patients who are at borderline risk, these factors deserve consideration as to whether to institute statin therapy.

Number Needed to Treat

Some physicians find the number need to treat (NNT) to be useful in discussions with patients. NNT is the number of people needed to treat to prevent one ASCVD event over a given period of time. Periods of time may be 5 years (the duration of most RCTs), 10 years (the usual absolute risk projection), or a lifetime. Table 29–11 illustrates the NNT for statins therapy at different 10-year risk estimates for moderate-intensity and high-intensity statins.

The NNT for a lifetime of therapy will be much lower, depending the age at which statin therapy is started. A low lifetime NNT constitutes the strongest rationale for a lifetime of statin therapy in primary prevention.

Emerging Risk Factors

Most patients who have persistent major risk factors deserve consideration for statins (see Table 29–11); they have a relatively high lifetime risk. In addition, some investigators use emerging risk factors in risk assessment (Table 29–12).[451]

The most commonly used factor is C-reactive protein.[424] Others include low HDL-C, hypertriglyceridemia, family history of premature ASCVD, elevated fibrinogen, prediabetes, and elevations of Lp(a). Although measurements of any or all of these emerging risk factors are not routinely recommended by guideline committees, they are an option for patients whose indications for statins are borderline.

Elderly Patients

Current cholesterol guidelines place high emphasis on use statins in older persons. This is because risk assessment algorithms give heavy weight to age is a risk factor. Unfortunately, these algorithms become less reliable advancing age.[452] This places a greater responsibility on clinicians who care for older persons. One solution to this dilemma is to measure subclinical atherosclerosis. For example, older individuals who are free of CAC have a very low risk for future ASCVD events. On the other hand, if CAC levels are high, the clinician is justified in advocating statin therapy. In addition, if an older person has long-standing, major risk factors, statin therapy is warranted. There is little doubt that high-risk, older persons will benefit from statins treatment; this is been adequately demonstrated in RCTs.[453,454]

TABLE 29–12. Emerging Cardiovascular Risk Factors

- Lipid markers (triglycerides, HDL-C, Lp(a), apolipoprotein, particle size)
- Inflammatory markers (C-reactive protein, fibrinogen, interleukin-6, leukocyte count)
- Prothrombotic markers (fibrinogen, PAI-1, von Willebrand factor, D-dimer)
- Dysglycemic markers (prediabetes, hemoglobin A1c, insulin)
- Renal markers (creatinine, uric acid)
- Family history of premature ASCVD

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol Lp(a), lipoprotein a; PAI-1, plasminogen activator inhibitor-1.

Statins in Women

The benefit of statin therapy for women having ASCVD is well documented.[154] Their utility for primary prevention has been questioned[455-458] (http://tinyurl.com/7ywndqe). At comparable ages, women generally have lower absolute risk than men. Therefore, close attention should be given to absolute risk estimates when contemplating statin usage and women. Some of the factors that favor statin therapy include diabetes, heavy cigarette smoking, multiple risk factors (eg, metabolic syndrome), hypercholesterolemia, and a strong family history of premature ASCVD.

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SECTION 6

Cigarette Smoking and Cardiovascular Disease

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CHAPTER 30

EPIDEMIOLOGY OF SMOKING AND PATHOPHYSIOLOGY OF CARDIOVASCULAR DAMAGE

Sunil K. Agarwal, Petra Maslov, Jagat Narula, and Valentin Fuster

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This chapter provides an epidemiological overview of cigarette smoking and its impact on health with a focus on cardiovascular diseases. Although smoking-related pathophysiological changes are discussed in all relevant chapters, this chapter aims to provide a synopsis of smoking-related pathological changes in the cardiovascular system. As health care providers striving to improve cardiovascular health, we are uniquely positioned to promote smoking cessation through counseling and clinical support for both primary and secondary prevention. Chapter 31 discusses the clinical management of patients to prevent and mitigate the adverse effects of smoking. The seriousness, resources, and political will to counterbalance the strong interest and position of the smoking industry may be catching up after a lag of almost half a century. There are growing concerns about (1) an increase in the total number of smokers worldwide with population growth despite a reduction in smoking rates, (2) an increasing prevalence of smoking among young adults and in developing countries, and (3) an increasing uptake of electronic cigarettes (e-cigarettes) ahead of research examining its health effects.

TRENDS IN PREVALENCE OF SMOKING

TOBACCO CONTROL: A LONG AND ARDUOUS JOURNEY

Although the Surgeon General's report in 1957 concluded that cigarette smoking is associated with an increased risk of lung cancer, it was not until publication of the landmark 1964 Surgeon General's report that the adverse relationship between cigarette smoking and cardiovascular disease was seriously recognized. The Surgeon General's report concluded that cigarette smoking is strongly associated with myocardial infarction and coronary heart disease deaths, and it laid the foundation for tobacco control.[1] Unfortunately, health care providers, professional societies, civic bodies, and governments have also played negative or timid roles, largely attributed to smoking industry's exploitation of the natural skepticism and probabilistic nature inherent in scientific evidence, serious conflicts of interest, and lack of a strong public will. Smoking has claimed more than 20 million lives with premature deaths in the United States alone since the publication of the 1964 report.

The annual per capita cigarette consumption in the United States was at its peak in early 1960s, with a prevalence of about 45% in 1965. Through concerted efforts over more than half a century, the cigarette consumption in the United States has declined to half of its peak prevalence rates—to about 18% in 2012.[2] Multiple factors, including an improved understanding of the adverse effects of secondhand smoke, and policy measures such as ban of broadcast advertising, increased public awareness, and the increase in taxes on cigarettes have played an important role in this epidemiological transition (Fig. 30–1). Despite years of progress, cigarette smoking still remains the leading cause of preventable cardiovascular morbidity and mortality across the globe.

GLOBAL BURDEN OF CIGARETTE SMOKING

Globally, about one billion individuals smoke (Fig. 30–2B). The majority (about 800 million) are males. Although the prevalence of smoking has declined over the past few decades, the total number of smokers has increased globally owing to population growth (Fig. 30–2A).

The worldwide prevalence of smoking is highly variable by country and region, suggesting a heavy influence of socioeconomic and cultural currents as well as national policies. In 2012, the prevalence of smoking among adults was 49% in eastern Europe; 45% in China; 36% in Japan; 28% in western Europe; 23% in India; and about 18% in Australia, the United States, and Canada[3] (Fig. 30–3). In China, an increase in cigarette use from 1.5 trillion cigarettes in 1998 to 2.5 trillion in 2016 is disturbing. Tobacco control in China is complex: the state acts as a regulator but also simultaneously owns the Chinese National Tobacco Company, the world's largest tobacco company by volume.[4] Strong surveillance systems reporting trends at frequent regular intervals will be necessary on a global platform to inform policy and decision making. For instance, a rapid rise in smoking is predicted among men in Africa and among both genders in eastern Mediterranean, based on recent surveillance data calling for action.[5]

The prevalence of smoking had decreased by about 1% to 2% annually from 1980 through 2005. Unfortunately, after many years of steady decline, the annualized rate of decline has plateaued; it didn't change for males for the year 2012.[3]

When considering differences by age groups, the highest prevalence of smoking worldwide in year 2012 was seen in male aged 44- to 49-year (41% prevalence), and females aged 50- to 54-year (8.7% prevalence) (Fig. 30–4). There is a disproportionately high burden of smoking among males compared to females in countries such as China and India. This is also reflected in the recent estimates of deaths attributable to smoking in China; of the nearly 1 million deaths in 2010, 840,000 were among males in contrast to 130,000 among females.[6] A high burden of smoking among adolescents and young adults (more than 150 million smokers were 25 years or younger) remains a major concern and challenge.[3] During 2012, the prevalence of smoking among 20- to 24-year-old males was above 50% in eastern Europe, Russia, Indonesia, 41% in China, 37% in Japan, 28% in Latin

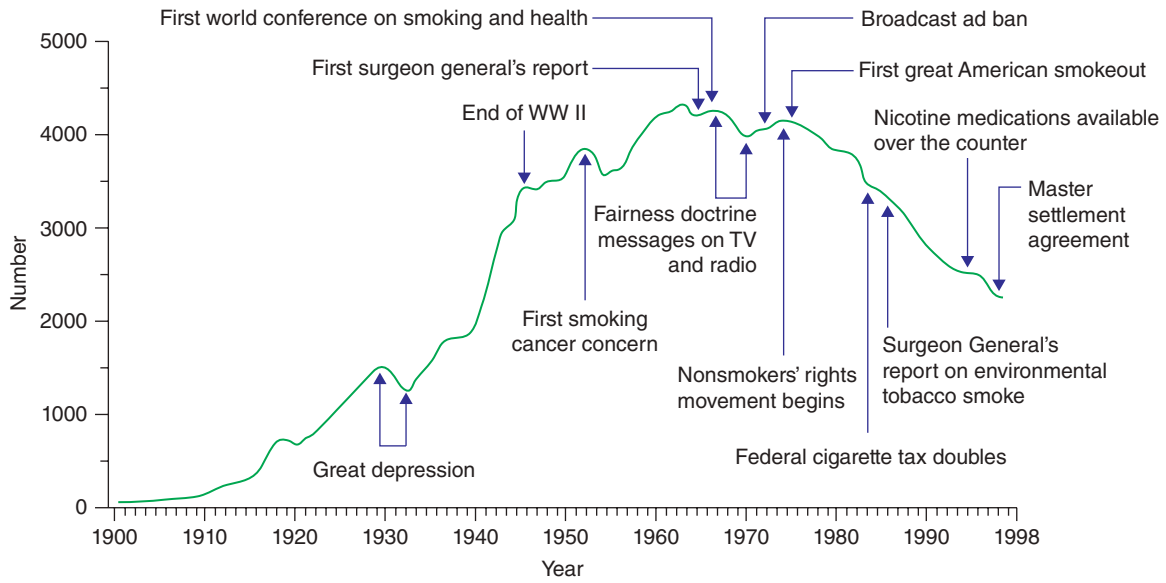

FIGURE 30–1. Annual adult per capita cigarette consumption and major smoking and health events—United States 1990-1998. ad, advertising; WWII, World War II. Reproduced with permission from Centers for Disease Control and Prevention (CDC): Tobacco use—United States, 1900-1999, *MMWR Morb Mortal Wkly Rep*. 1999 Nov 5;48(43):986-993.

America, 24% in Pakistan, 21% in Australia, 19% in Canada and the United States, and 13% in India.

US SMOKING PREVALENCE AND TRENDS

According to the Behavioral Risk Factor Surveillance System (BRFSS) survey, the prevalence of smoking among United States adults has declined by 25%, with only 17.9% smokers in 2013 as compared to 24.1% smokers in 1998.[7] There are important differences in the smoking prevalence by states/regions in the United States. Similarly, US population-based survey data (National Health and Nutrition Examination Survey [NHANES]) for 2011-2012 showed a much higher smoking prevalence among people 20 to 49 years of age (23.1%) compared to those 50 years of age and older (16.3%).[7]

There is significant heterogeneity in smoking prevalence by race/ethnicity and gender. Although smoking rates did not differ by gender among Asians residing in the United States; they were slightly and different among non-Hispanic white men compared to non-Hispanic white women. The smoking rate among Hispanic men (16%) is almost two times higher than it is among Hispanic women (8.3%) (Fig 30–5).

Among various cardiovascular risk factors, however, there has been progress toward reducing smoking rates. Cigarette smoking prevalence is still high and seems to have stagnated recently around 18%. A larger change in smoking prevalence has been seen among US high school students: 15.7% in 2013 compared to 36.4% in 1997.

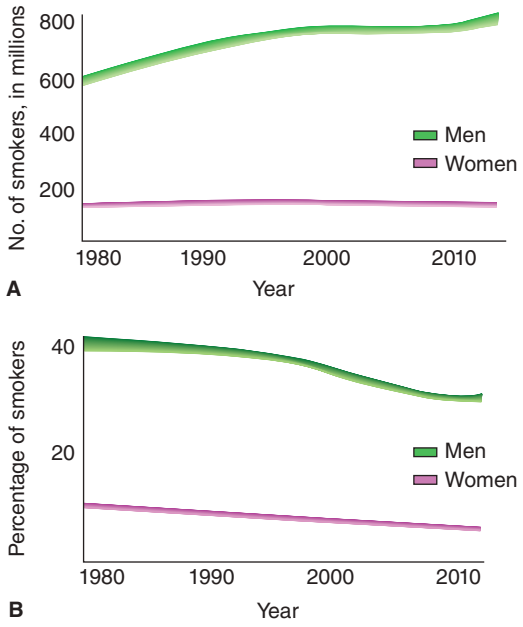

FIGURE 30–2. **A.** Global number of smokers among men and women, 1990-2012. **B.** Global prevalence of smokers among men and women, 1990-2012. Both **A** and **B** available from Institute of Health Metrics and Evaluation. http://vizhub.healthdata.org/tobacco/#. (Accessed October 20, 2016).

HEALTH EFFECTS OF SMOKING

About 5 to 6 million yearly deaths worldwide and about 0.5 million in the United States are attributable to cigarette smoking each year. This estimate is projected to increase to more than 10 million in a few decades.[8,9] In countries such as China, noncommunicable diseases account for 84% of all deaths in 2010 compared to 74% in 1990; sadly, 16.5% of these deaths are attributable to smoking.[10] About one in ten cardiovascular deaths worldwide is still attributed to smoking.[11]

In 1990, smoking was the third-ranked risk factor after childhood malnutrition and indoor pollution from biofuels for loss of disability-adjusted life years (ie, sum of years of life lost and years lived with disability [DALY]). With improvement in nutrition and clean fuel availability, in 2010, it has become the second most common contributor to loss of DALYs 6.3% (95% confidence interval, 6.2-7.7).[12] Smoking is the highest contributor to loss of DALYs in males worldwide and both males and females in many developing countries.

A loss of about a decade of life expectancy is estimated because of smoking throughout adulthood among both men and women in

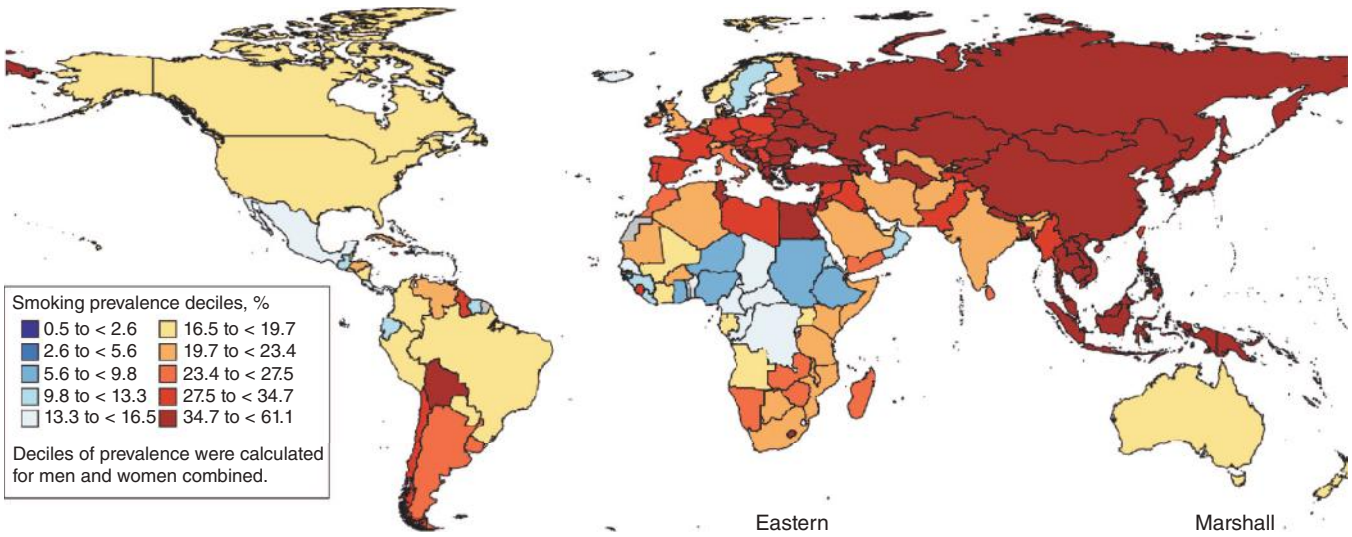

FIGURE 30–3. Age-standardized prevalence of smoking in 2012. Reproduced with permission from Institute for Health Metrics and Evaluations.

various countries, including the United Kingdom, the United States, Japan, and India (Fig. 30–6).[8] Importantly, people who have smoked cigarettes since early adulthood but stopped at 30, 40, or 50 years of age gain back 10, 9, and 6 years of life expectancy, respectively.[8] The US societal costs of cigarette smoking per year are around $289 billion; this includes about $151 billion in lost productivity caused by premature deaths and remaining as direct health care costs.[7]

SMOKING AND CARDIOVASCULAR DISEASES

Smoking has been associated with increased and accelerated atherosclerosis and acute plaque rupture and all cardiovascular end points, including myocardial infarction, stroke, and peripheral arterial disease.[13] While smoking causes incremental and independent risk with other risk factors such as hypertension and diabetes on coronary and cerebral vasculature, its prominent role in peripheral vasculature and small-vessel disease has been appreciated: fivefold increased risk of peripheral arterial disease and abdominal aortic aneurysm compared to a 1.5- to 2-fold increased risk of ischemic heart disease and stroke.[14] A linear and independent relationship of smoking duration and intensity has been reported, with an increase in arterial stiffness measured using brachial-ankle pulse wave velocity.[15]

The availability of low-cost and high-fidelity genetic analysis has opened new vistas of expansion to our understanding of the genetic basis of smoking behavior such as finding a few genes localized to the substantia nigra, brain area associated with reward and addition as well as end-organ damage.[16]

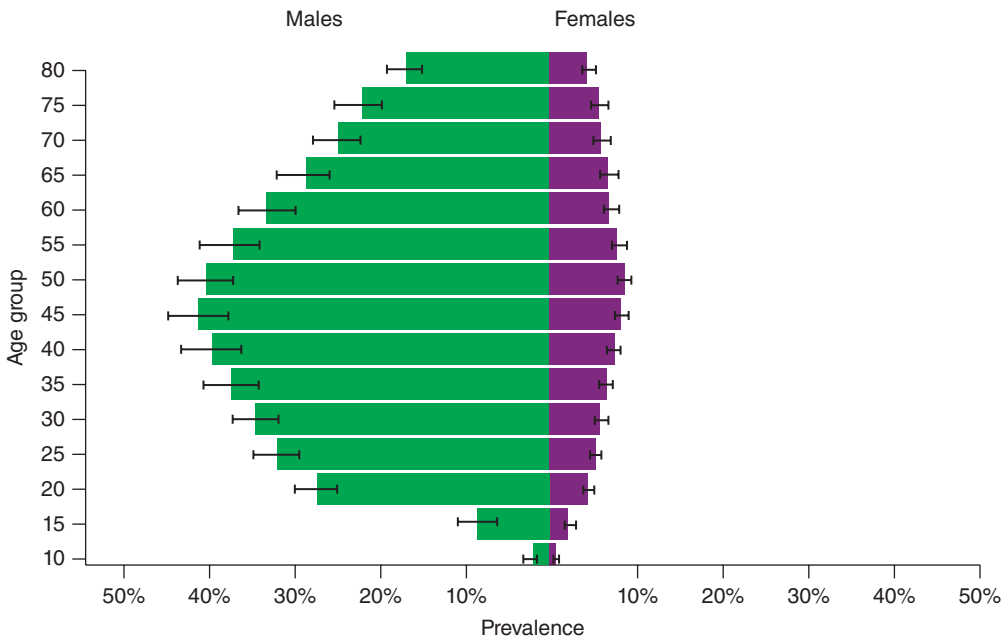

FIGURE 30–4. Prevalence of smoking by gender and age group globally in year 2012. Available from Institute of Health Metrics and Evaluation. http://vizhub.healthdata.org/tobacco/#. (Accessed October 20, 2016).

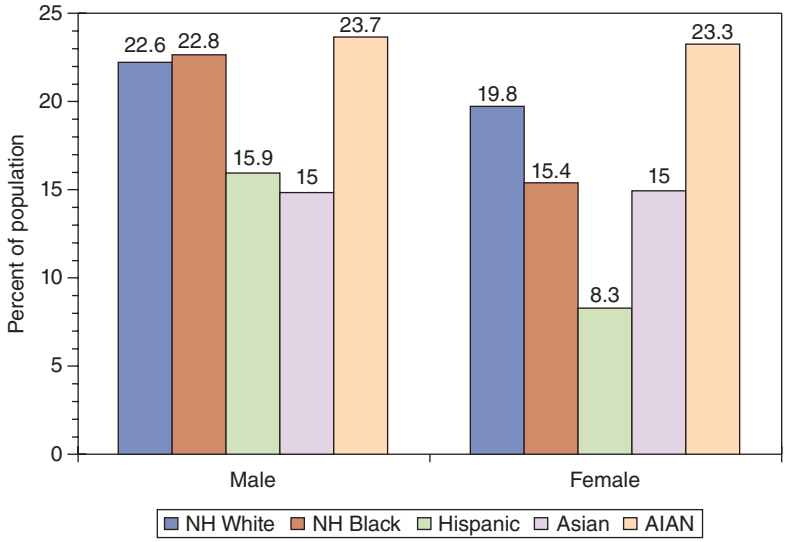

FIGURE 30–5. Prevalence (%) of current smoking for adults age 18 years or older by race/ethnicity and sex (National Health Interview Survey, 2010-2012). All percentages are age adjusted. Includes both Hispanics and non-Hispanics. AIAN, American Indian or Alaska Native; NH, non-Hispanic. Data from the Centers for Disease Control and Prevention/National Center for Health Statistics, Health Data Interactive.

PATHOGENESIS

Cigarette smoking is intimately (Fig. 30–7) involved in development and progression of cardiovascular disease. Cigarette smoke is a mixture of more than 5000 toxic chemicals[17] and 10^{15} to 10^{17} free radicals.[18,19] It is conventionally divided in two chemically different phases: a tar phase and a gas phase.[20] The tar or particulate phase is material that is trapped when the smoke steam is passed through the glass-fiber (cigarette) filter. The cigarette filter retains 99.9% of all particles of greater than 0.1 μm. Nicotine is a major chemical component of particulate phase of cigarette smoke.[21] The gas (or vapor) phase consists of the material that passes through the cigarette filter.[21] The common chemical components of the gas phase include carbon monoxide (CO), acetaldehyde, formaldehyde, acrolein, nitrogen oxides, and carbon dioxide. Both phases are high in reactive oxygen species (ROS).[22] Despite the presence of multitude of constituents in both phases, only three constituents (ie, nicotine, CO, and ROS) have been shown to play a role in the initiation and progression of cardiovascular disease.[23]

Cigarette smoke affects various cell lines and acts through several pathophysiological mechanisms.[24-29] These mechanisms include, but are not limited to, hemodynamic changes, cardiac remodeling, inflammation, endothelial dysfunction, thrombosis, and changes in glucose and lipid metabolism. The central role in the cigarette smoking–related cardiovascular pathogenesis belongs to oxidative stress. Most of the molecular changes associated with cigarette smoking are triggered by high concentration of oxidizing chemicals inhaled by smokers with the cigarette smoke.

The net effect of various endogenous chemicals from cigarette smoke such as oxidative free radicals and nicotine, together with inflammatory molecules and endogenous-produced ROS released by activated inflammatory cells, is disruption of cardiovascular homeostasis leading to hemodynamic changes, endothelial dysfunction, inflammation, thrombosis and plaque progression, and abnormalities in lipid and glucose metabolism.[19]

HEMODYNAMICS

Nicotine from cigarette smoke is the major culprit for hemodynamic changes caused by cigarette smoking. It is a strong sympathomimetic drug that stimulates release of catecholamines from the adrenal medulla and local sympathetic neurons.[25] Via sympathetic stimulation, nicotine leads to an increase in cardiac contractility, acute and chronic increase in heart rate up to 7 to 10 beats per minute,[25] and elevation in systolic blood pressure up to 5 to 10 mm Hg from baseline.[23] Interestingly, a large study using mendelian randomization selecting genes associated with smoking heaviness to overcome the observational nature of studies did not find any relationship with hypertension, and it hypothesized that a lower body mass index among smokers may be nullifying adverse effects of smoking on blood pressure.[30] The study did find an important relationship between smoking and higher heart rate.

The net result is increased myocardial oxygen demand that can predispose individuals to myocardial ischemia. In long-term smokers with coronary artery disease, cigarette smoking causes coronary vasoconstriction. Smoking-induced coronary vasoconstriction can be prevented with α adrenergic blocker phentolamine and potentiated with the β-blocker propranolol, suggesting that the α-adrenergic pathway is the main mechanism of smoke-related cardiac hemodynamic changes.[24] CO is another component of cigarette smoke that has been implicated in cigarette smoke–induced hemodynamic changes. By binding to hemoglobin, CO reduces the oxygen-carrying capacity of hemoglobin, resulting in relative hypoxemia and subsequent dilation of coronary arteries.[31] However, this increase in coronary blood flow is lower than required to keep up with nicotine-mediated increased sympathetic drive toward the heart. A combination of nicotine-induced increased oxygen demands on one side and CO-associated reduced oxygen availability on the other side, may lower the threshold for angina onset in smokers.[32]

ENDOTHELIAL DYSFUNCTION

Cigarette smoking–induced endothelial dysfunction is an important factor in coronary hemodynamic disturbances and the progression of atherosclerosis. Endothelium is an active regulator of the vascular tone through the release of nitric oxide (NO), prostacyclin, tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1.[23] Endothelium-dependent vasodilation in coronary and peripheral vessels is diminished in smokers when compared to nonsmokers. The primary mechanism by which smoking leads to vascular and endothelial

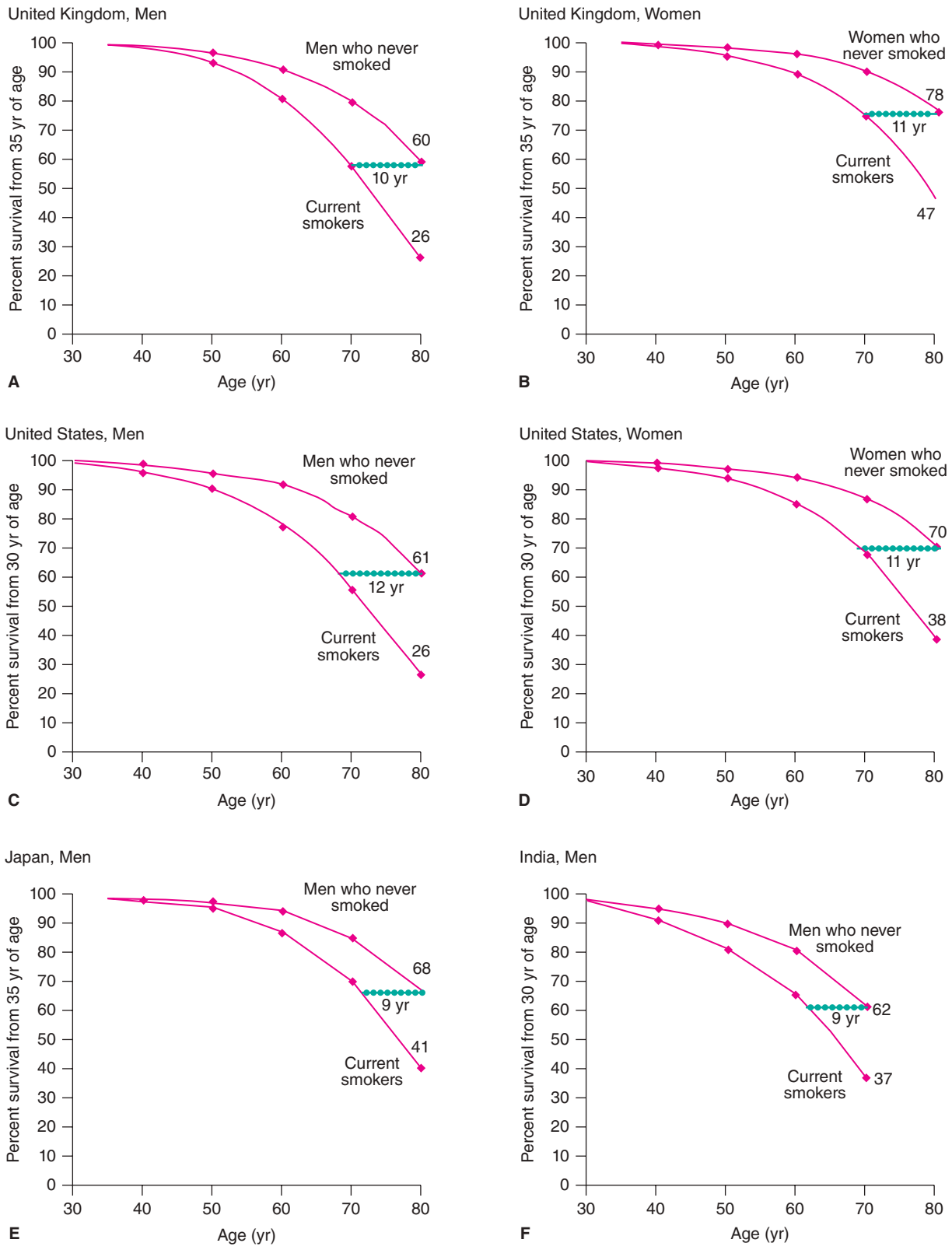

FIGURE 30–6. Loss of a decade of life expectancy caused by smoking through adulthood. Shown are probablities of survival from 30 or 35 years of age (current smokers vs persons who never smoked, linked by dots representing 1 year each) among UK men and women, US men and women, Japanese men, and Indian men. Reproduced with permission from Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. *N Engl J Med*. 2014 Jan 2;370(1):60-68.[8]

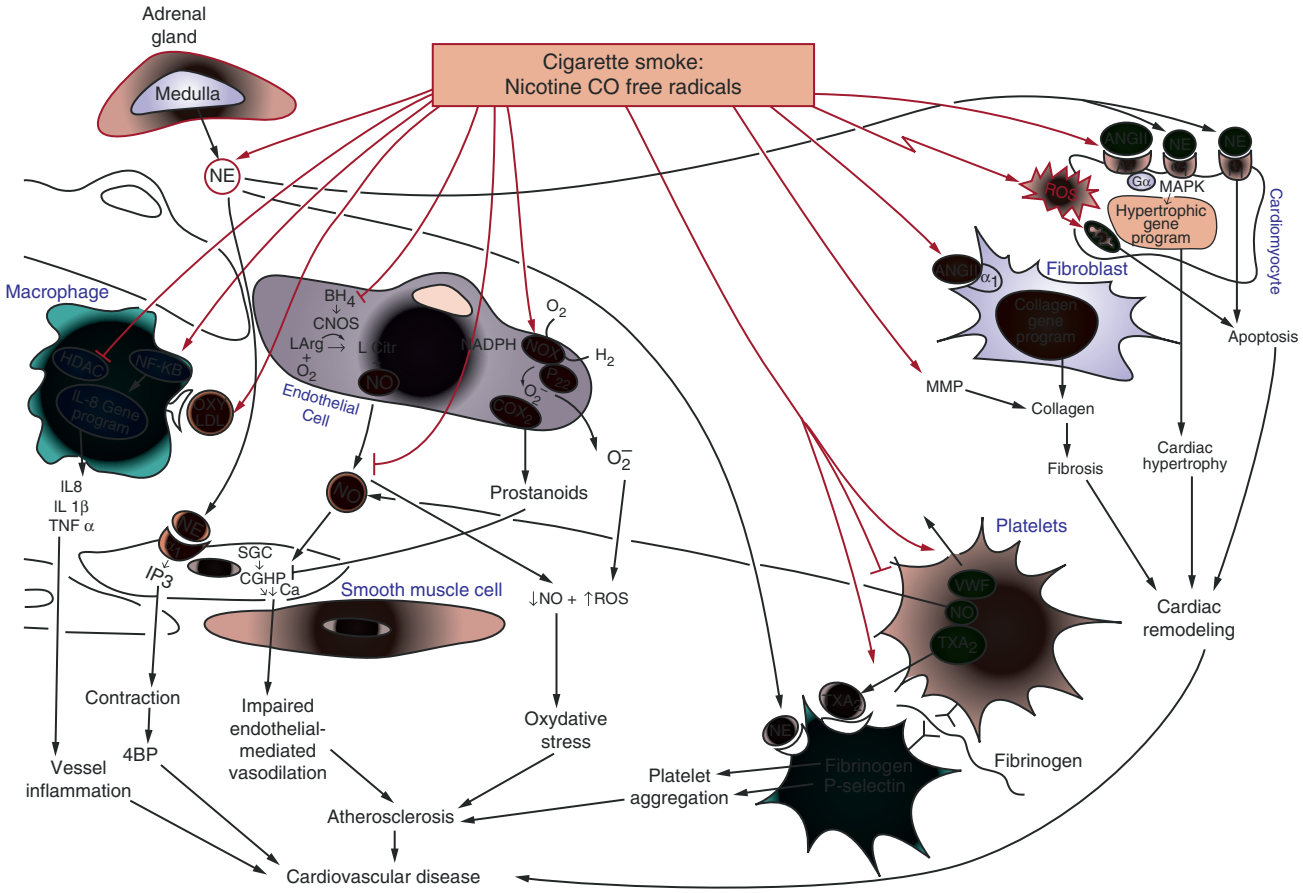

FIGURE 30–7. Schematic representations of pathways linking cigarette smoking with development and progression of cardiovascular disease. NE, norepinephrine; NO, nitric oxide.

dysfunction is thought to be suppression of endothelial nitric oxide synthase (eNOS) expression and subsequent decreased bioavailability of NO caused by oxidant chemicals from cigarette smoke.[33] NO is synthesized by eNOS when L-arginine is transformed to L-citrulline in the presence of oxygen, and cofactors such as calmodulin, tetrahydrobiopterin (BH4), and reduced nicotinamide adenine dinucleotide phosphate.[26] The main role of endothelial NO is vasodilation and increased blood flow. However, NO also participates in various vascular functions such as inhibition of platelet aggregation and adhesion, inhibition of leukocyte adhesion, and reduction of smooth muscle proliferation.[26] Therefore, deficiency of NO participates in initial phases of plaque formation and atherosclerosis pathogenesis. Biomolecular pathways behind decreased NO production in endothelial cells caused by smoking-related oxidative stress are complex and involve several different components of the cigarette smoke such as free radicals, ROS, and reactive aldehydes. Free radicals from cigarette smoke oxidize and deplete BH4 in vascular endothelial cells, an important cofactor of eNOS, resulting in uncoupling of eNOS and production of superoxide anions (O_2) instead of NO.[26] Another mechanism by which oxidative stress affects endothelium-mediated vasodilation is direct degradation of NO by oxidant chemicals from inhaled cigarette smoke. If vitamin C is administered to smokers, it may reverse endothelial-mediated vasodilation, thus providing additional support that pathogenesis of endothelial dysfunction caused by smoking involves oxygen-derived free radicals from cigarette smoke.[34] Chronic application of nicotine decreases the bioavailability of endogenous NO by producing superoxide anions and impairs vasodilation of pial vessels.[35]

PROTHROMBOTIC STATE

Cigarette smoking has been shown to promote a prothrombotic state through several mechanisms. These mechanisms include alterations in platelet activity as well as alterations in antithrombotic and prothrombotic factors, including fibrinolytic factors and platelet-mediated pathways.[20,36]

Once atherosclerotic plaque is formed, its vulnerability for rupture depends on the amount of its lipid content, thickness of the fibrous cap, size of its necrotic core, the rate of plaque progression,[37] recruitment of inflammatory cells, and intraplaque hemorrhage.[38] Smokers are shown to have higher extracellular content in their plaque[39] and lower activity of n-prolyl-4-hydroxylase,[40] a key enzyme in arterial wall collagen metabolism that could contribute to thinning of the fibrous cap in the atherosclerotic plaque of smokers. Furthermore, cigarette smoking leads to increased activity of matrix metalloproteinases (MMPs) involved in degradation of extracellular matrix proteins within atherosclerotic plaque.[41] Taken together, most of pathologic changes associated with highly vulnerable plaque and plaque rupture[37] are potentiated by smoking.[38] Moreover, cigarette smoke accelerates biopathological pathways such as platelet activation and aggregation that occur after plaque rupture. Platelets isolated from smokers have shown to exhibit an increased spontaneous and stimulated aggregation compared to nonsmokers.[42] Not only does smoking decrease endothelial NO production, it also leads to diminished bioavailability of platelet-derived NO and decreased platelet sensitivity to NO.[28,29,43] Both mechanisms promote platelet activation and adhesion, making

smokers' platelets more thrombogenic. In addition to impaired NO release from platelets, cigarette smoke also triggers the release of thromboxane A_2, a potent vasoconstrictor, and inhibits coronary endothelial release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation.[24] Cigarette smoking exposure has also been related to different clot dynamics that are more resistant to thrombolysis compared with clots of nonsmokers.[38] An increased level of circulating von Willebrand factor, an important ligand of platelet binding, has been demonstrated in smokers compared to nonsmokers.[44,45] Furthermore, cigarette smoking is associated with increased concentration of fibrinogen[46,47]; increased expression of tissue factor that contributes to thrombosis after plaque rupture[48]; and reduced basal production of tPA,[33] which is an essential regulator of plasminogen-plasmin transformation. Lower level of activated plasmin leads to diminished lysis of fibrin and propagation of thrombus. As previously mentioned, CO from cigarette smoke causes relative hypoxemia, which compensatory leads to increase in the number (and mass) of erythrocytes in the circulation which increases blood viscosity.[31] An increased blood viscosity may mildly increase predisposition to thrombosis and atherosclerotic plaque formation.

PROINFLAMMATORY EFFECTS

Chronic vascular inflammation mediated by cigarette smoking may play an important role in progression of atherosclerosis.[49] The exact molecular-pathogenic mechanisms by which smoking induces vascular inflammation are not completely established. Nonetheless, the role of several proinflammatory cytokines as well as activation and interaction between leukocytes and endothelial cells is well recognized in this process. Smoking increases the peripheral leukocyte count by 20% to 25%[50] and promotes leukocyte adhesion to endothelial cells within the blood vessel wall, starting an initial inflammatory step in atherosclerosis.[51] One of the proposed biochemical pathways that links cigarette smoking to vascular inflammation is enhanced expression of soluble vascular cell adhesion molecule-1; intercellular adhesion molecule-1; and E-selectin, which leads to increased leukocyte-endothelial cell interaction.[52] Increased levels of multiple proinflammatory markers have been associated with smoke exposure; these include C-reactive protein, cytokines such as the interleukins (ILs) IL-1β and IL-6, and tumor necrosis factor-α (TNF-α).[27] It has been shown that cigarette smoking induces release of proinflammatory cytokines in macrophages[53] and lymphocytes by activation of NF-κB and post-translational modification of histone deacetylase.[49] Free radicals in cigarette smoke in synergy with inflammatory cytokines (IL-1β and TNF-α) present in the serum of smokers increase the activity of nicotinamide adenine dinucleotide phosphate oxidase within endothelial cells, leading to generation of superoxide anion and induction of cyclooxygenase-2 (COX-2) expression via the p38 mitogen-activated protein kinase (MAPK)/Akt pathway.[27] COX-2 induces production of prostanoids, which diffuse toward endothelial cells and attenuate vasodilation by decreasing the activity of soluble guanylate cyclase and production of cyclic guanosine monophosphate (cGMP).[54]

CARDIAC REMODELING

Smoking has been associated with left ventricular hypertrophy and left atrial enlargement in animal models.[55,56] Smokers exhibit higher level of activation of MMPs that degrade elastin and collagen in the extracellular matrix. Within myocardium, increased MMP activity leads to breakdown of the supporting fibrillary collagen and ventricular wall thinning.[57] Smoke-related ROS stimulate fibroblasts to proliferate and induce myocardial cell apoptosis, leading to cardiac fibrosis and remodeling.[58] Cigarette smoking–induced cardiac remodeling has also been linked to increased activation of MAPKs by either norepinephrine (NE), which is increased in smoker's serum, or directly by free radicals from cigarette smoke.[57] Within the heart, NE can lead to myocyte hypertrophy by binding to α_1-adrenergic receptors or apoptosis by binding to β_1-adrenergic receptors.[59] Nicotine increases the expression of angiotensin-converting enzyme and production of angiotensin II,[60] which has an important role in cardiac remodeling through stimulation of hypertrophic gene program within cardiomyocytes as well as through stimulation of fibroblast proliferation within myocardium.

LIPID METABOLISM

Multiple studies have demonstrated that cigarette smoking enhances atherosclerosis at least in part by altering the lipid profile. Cigarette smoking lowers serum high-density lipoprotein (HDL), but it increases triglycerides, cholesterol, and low-density lipoprotein (LDL).[61] More important, smokers have higher levels of oxidized LDL which is involved in pathogenesis of atherosclerosis.[62] Exposure of human plasma to cigarette smoke causes oxidative modification of plasma LDL that is actively taken up by the macrophages and forms foam cells in the culture.[62] In addition to this, smoking increases hepatic lipase activity, which leads to production of small dense LDLc and small dense HDLc. First, LDLc has toxic effects on endothelium and promotes release of even more ROS. Second, HDLc has no protective antiatherogenic effects, which are normally attributed to HDL.[63] A nicotine-induced increase in circulating catecholamines induces lipolysis and release of plasma-free fatty acids.[23,64]

GLUCOSE METABOLISM

Cigarette smoking increases the risk of development of diabetes mellitus type 2.[65] A dose-response relationship has been found between the smoking and the incidence of diabetes mellitus in both men and women.[66] Data from the Cancer Prevention Study have shown that there is a 45% higher diabetes rate among smokers than among men who had never smoked. Higher levels of HbA1C have been found in smokers with diabetes as compared to nonsmokers with diabetes. Smoking also increases requirements for insulin and causes insulin resistance in nondiabetics.[67] Studies have also shown increased risk of microvascular complications of diabetes such as diabetic neuropathy and faster progression of renal disease.[68] There has been a debate about whether possible weight gain associated with quitting smoking is associated with increased risk, too.[69] Although confounding in observational studies makes it difficult to test this relationship further, the increased risk of weight gain after cessation ameliorates with duration of smoking cessation.[69] The pathogenesis of smoking and glucose metabolism is not well understood, but nicotine appears to have central role in this process.[19,70] Nicotine stimulates cathecholamine release from the adrenal medulla and sympathetic nervous system, which may lead to insulin resistance. It also increases the release of corticosteroids, which are known hyperglycemic hormone.[23]

SECONDHAND SMOKE

Despite early warnings seen in the Surgeon General's report in 1972, awareness about the adverse health implications of exposure secondhand exposure to cigarette smoke gained significant momentum around early 2000, from multiple epidemiological studies supporting it.[71] Contrary to intuition, the adverse effect of brief secondhand

smoke exposure is significant.[72] A higher coronary calcium score has been reported among never smokers who are exposed to secondhand smoke.[73] A higher amount of ammonia, nicotine, and other carcinogens is released in sidestream smoke.[74] These studies have shaped the policies restricting and banning smoking in public places and gained public support for such efforts. According to NHANES, the secondhand smoke exposure among nonsmoking adults in the United States has decreased from 37.6% in 2005-2008 to 25.5% in 2009-2012.

Exposure to cigarette smoke from parental smoking during childhood was associated with a higher risk of developing carotid atherosclerotic plaques and higher carotid intima media thickness during adulthood, even 25 years after last exposure among Cardiovascular Risk in Young Finns Study participants.[75,76] An improvement in respiratory health as measured by symptoms, spirometry measures, and markers of inflammation was seen among bar workers after passage of smoke-free legislation in Scotland.[77] Importantly, a decrease in cardiovascular morbidity and mortality has been seen immediately following workplace ban of cigarette smoking even among people who never smoked.[78]

ELECTRONIC CIGARETTES

Invented in the early 2000s by a Chinese pharmaceutical company and patented in 2004, e-cigarettes deliver a nicotine-containing vapor when a solution of nicotine with humectant solution (glycerol or propylene glycol) and flavoring is heated by a battery-powered atomizer (Fig. 30–8).[79] Their purported use, also reflected in the US patent application, is to be a substitute for quitting smoking.

Currently, there are no appropriately powered randomized controlled trials with e-cigarettes examining the efficacy of smoking cessation.[80] Also, studies looking at long-term safety of e-cigarettes are lacking. Among current smokers who are motivated to quit smoking, there was modest success (7.3% abstinence at 6 months) with nicotine e-cigarettes, although this was no different than with using the nicotine patch (5.8% abstinence at 6 months).[81] However, when using the population-based studies in the absence of good randomized controlled trials, e-cigarette users are associated with a 28% lower relative odds of quitting compared to nonusers.[82] There were no meaningful individual side effects reported with this study with nicotine e-cigarettes over the short duration of follow-up.

There are growing concerns about their use due to absence of studies showing either safety or efficacy. Importantly, e-cigarettes can circumvent the regulations created to control active smoking and second hand smoke exposure such as taxation, advertisement bans, and ban in smoke free zones. Their potential for use among adolescents as bait and switch to regular cigarettes, and their continued use among current smokers using them with the intent to quit remain serious concerns. For instance, among high school students, use of e-cigarettes tripled in 2014 to 2 million (13.4%) from 0.67 million (4.5%) in year 2013.[83] Because of a lack of evidence supporting the safety or efficacy of e-cigarettes at this time, e-cigarettes companies cannot advertise them as an alternative for smoking cessation or for therapeutic purposes in the United States. On the one hand, sale of nicotine-containing e-cigarettes is unauthorized in countries such as Canada, and they have been banned in Brazil, Norway, and Singapore.[80] On the other hand, large tobacco companies have been acquiring and/or launching e-cigarette companies/subsidiaries, and there is growing advertisement and increasing public awareness about their presence.[80]

OPPORTUNITIES FOR CARDIOVASCULAR PRACTITIONERS

The details of various pharmacological and nonpharmacological options for quitting smoking are discussed in Chapter 31. The majority of the hospitals in the United States have met the Joint Commission of Accreditation of Healthcare Organizations (JCAHO) smoking ban standards.[84] Although it is pleasing to note that smoking rates among physicians are less than 2%, a high smoking rate of 25% among licensed practical nurses needs action in the health care settings.[85] Addition of smoking cessation support at the population level has been shown to reduce the cessation success to 20% per year compared to 5% in an unaided setting.[86] In a retrospective analysis of over 2000 patients who underwent percutaneous coronary intervention (PCI) from 1999 to 2009 at Olmsted County, Minnesota, smoking cessation rates at 6 to 12 months were around 50% and did not change over a decade.[87] The odds of cessation were 2.6 times higher among those who had presented with myocardial infarction and three times among those who participated in cardiac rehabilitation, and cessation was associated with better prognosis.[87] Similarly, a cessation rate of about 60% was seen in Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial participants and those who continued to smoke had 1.8 times higher risk of death/myocardial infarction/stroke as compared to those who had quit.[88] It is a big challenge and opportunity for us that less than one in three of the current smokers hospitalized with acute coronary syndrome (ACS) remains abstinent

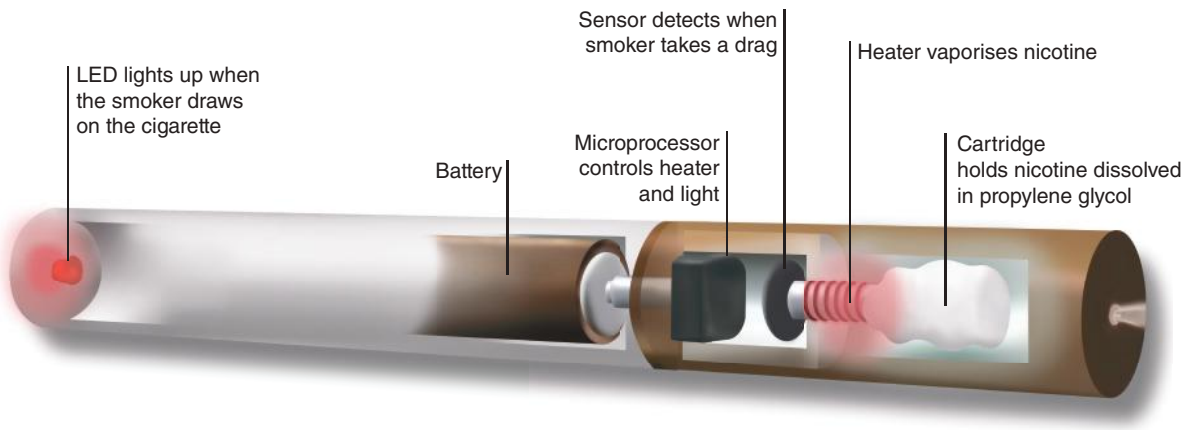

FIGURE 30–8. Mechanism and design of an e-cigarette. LED, light-emitting diode. Redrawn from http://electronicdesignmanufacturing.com/blog/e-cigarette-engineering.

following discharge. Smokers have worse outcomes than nonsmokers after PCI and those who quit smoking after PCI had less anginal episodes at 1 year follow-up than those who continued.[89] In a recent study of patients presenting with ACS, varenicline was associated with an abstinence rate of 47.3% versus 32.5% in the placebo group at 6 months.[90] At the same time, it is sobering to see that in non-ACS patients recruited from community and a long-term cohort in Wisconsin, with lower number of average cigarette smoked per day than previous studies, there was no difference in smoking cessation with randomization to varenicline versus nicotine patch versus combination nicotine replacement with a cessation rate at 1 year of about 25%.[91] Not offering smoking cessation counseling to those in need of help may be considered downright unethical and should be the focus of every clinical encounter.[92] Individualized treatments based on genetics or markers of metabolism may be more effective and safe; further studies are needed in this direction.[93] Individual level incentives to quit smoking have been shown to have a higher rate of success than usual care and should be considered by employers and health insurance companies.[94] At the level of health care systems, advice from health care workers, use of technology with automated text-based reminders, and individual and group counseling should be strongly considered. The cost-effectiveness of such low-cost interventions needs to be examined.

POLICY AND SMOKING RATES

The Framework Convention on Tobacco Control (FCTC) of the World Health Organization (WHO) created in 2004 has had a steady progress in many countries. However, the goal of a tobacco-free world by the year 2040, with a smoking prevalence rate below 5% without prohibition, requires a turbo-charged approach involving the WHO, United Nations, and national and global investments.[95]

To this effect, the most common and successful step that has been used is tobacco taxes (Fig. 30–9). About 20% decrease in cigarette consumption has been reported with a 50% increase in inflation-adjusted tobacco price[96] (see Fig. 30–9). Tobacco taxes have proven to be more effective among younger adults, and among poor or less educated groups.[8] However, a rapid growth in income and purchasing power parity in developing countries and availability of low-priced alternatives such as "bidis" is a challenge. The lower excise tax in the low-income countries makes cigarettes cheaper than in developed countries. However, cigarettes may be cheaper in developing countries after due adjustment for purchasing power parity and may replace "bidis" with increase in purchasing power in countries such as India.[8] Additionally, organized smuggling of cigarettes with a raise in excise remains another challenge that will require stricter tax administration.[8]

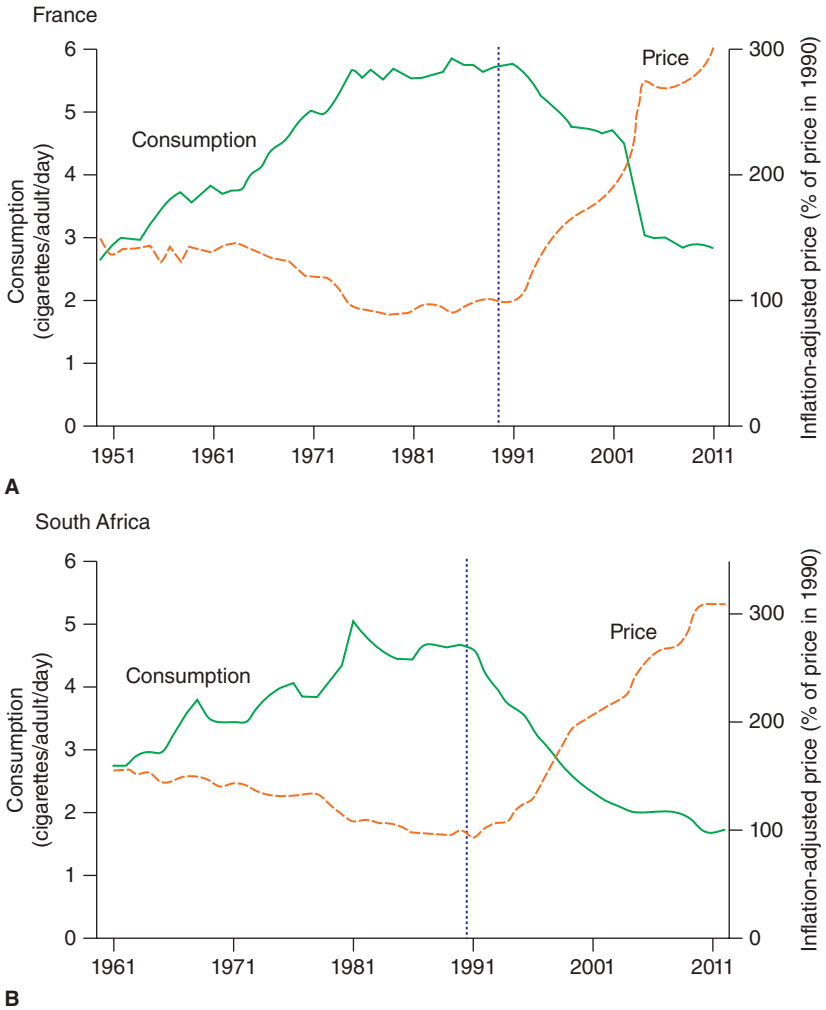

FIGURE 30–9. Changes in the inflation-adjusted cigarette price and its consumption in France and South Africa. Reproduced with permission from Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. *N Engl J Med*. 2014 Jan 2;370(1):60-68.[8]

Profits from tobacco manufacturing exceeded 50 billion US dollars in 2012,[97] and beyond industry's lobbying effort for keeping a check on excise taxes, the major portal for more than half a century has been influence and use of mass media. Although a complete or partial ban on tobacco advertisements remains a strong tool to reduce smoking rates, comprehensive bans may be needed to prevent industries use of media for advertisement.[8]

Legislative developments to protect individuals from secondhand smoke, research to continue to study the influence of various interventions in reduction in smoking rates, and understanding the counterforces such as smoking industry and human behavior will be important. Separation and empowerment of regulatory bodies in stages where manufacturing is state-owned such as in China, the largest cultivator of tobacco in the world with doubling of production since 1978, will remain a difficult and critical task ahead.[10] Large-scale philanthropy and international organizations such as WHO have played important critical roles to control/reduce rapid rise in smoking, with programs such as "towards a smoke free China" supported by Bloomberg Initiative and pressures on Chinese delegation by WHO FCTC.[10] Focus on high "growth markets" such as Europe, the Middle East, and Africa will be equally important while focusing on China, where 40% of the world cigarette is consumed. Beyond policy changes, simple low cost and scalable interventions such as those involving community health care workers, and use of mobile health platforms such as mobile phone texts need to be examined for efficacy, process evaluation, and cost-effectiveness.[86]

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CHAPTER 31

PREVENTING AND MITIGATING SMOKING-RELATED HEART DISEASE

Sara Kalkhoran and Stanton Glantz

SMOKING CESSATION AMONG CURRENT SMOKERS / 860
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The reductions in cigarette smoking prevalence over the second half of the 20th century and beginning of the 21st century represent one of the major medical and public health advancements of this time. Decreases in smoking rates, in conjunction with improvement in treatment of other cardiovascular risk factors such high cholesterol and blood pressure and advancements in the treatment of heart disease, have contributed to substantial declines in rates of death from heart disease.[1,2] Despite this progress, tobacco use remains a major preventable cause of morbidity and mortality worldwide. Both active smoking and passive exposure to secondhand smoke increase the risk of cardiovascular disease, malignancy, and pulmonary diseases. As a result, effective strategies for reducing health risks from smoking should address both smoking cessation and reduction of exposure to secondhand smoke.

SMOKING CESSATION AMONG CURRENT SMOKERS

Smoking cessation is an important component of both primary prevention and secondary prevention of cardiovascular disease. Despite this and the US Public Health Service recommendation that all patients be asked about their tobacco use status on a regular basis,[3] tobacco use screening occurs in only two-thirds of outpatient physician office visits.[4] Even though 69% of smokers are interested in quitting and over half report having made a quit attempt in the past year,[5] only 21% of adult current tobacco users received tobacco cessation counseling and 8% received tobacco cessation medication during outpatient visits.[4] This situation highlights the importance of screening by health professionals to capture individuals interested in tobacco cessation and assist them in quitting. This screening is particularly important because physician advice to quit smoking is associated with increased smoking cessation compared to no advice to quit or usual care, with higher cessation seen with more intensive advice compared to minimal advice.[6] Interventions led by other members of the health care team, such as nurses, have also been associated with increased smoking cessation.[7] It is important that screening be incorporated into all clinical encounters, including by cardiologists and other specialists, not only to identify and assist patients who are ready to stop smoking, but also to encourage those who are not yet ready to move toward making the decision to quit.

OVERALL AND CARDIOVASCULAR BENEFITS OF SMOKING CESSATION

The risk of overall mortality is greatly reduced for patients who quit smoking.[8,9] Smoking cessation before the age of 30 years eliminates nearly all of the risk of death from smoking-related disease, and even those who quit when they are older gain years of life compared to those who continue to smoke.[10,11] This fact highlights both the importance of encouraging smokers to quit early as well as encouraging quitting among all smokers, no matter how old they are.

In addition to contributing to long-term development of atherosclerosis, smoking (and secondhand smoke exposure) has immediate effects (within minutes) on endothelial function[12,13] and platelet activation[9] and so can trigger a cardiac event. The risk of cardiac events begins to drop immediately after quitting and declines rapidly. The heart rate drops 20 minutes after quitting, and in a year, half the excess risk of a myocardial infarction is gone.[14] The risk of myocardial infarction and other cardiac events drops 15% to 20% by a month after implementing comprehensive smoke-free laws to protect people from secondhand smoke.[15,16] Smoking cessation should be used as a first-line therapy for people with heart disease.

Among patients with coronary heart disease, a systematic review of 20 studies found an overall 36% reduction in risk of mortality among those who quit smoking compared to those who continued to smoke.[17] A meta-analysis of 12 cohort studies found that the odds of death after myocardial infarction was nearly halved among those who quit smoking compared to those who continued smoking,[18] and one study found that the risk of repeat coronary events in patients who quit smoking after their first myocardial infarction decreased to that of nonsmokers 3 years after cessation.[19] In patients with a previous myocardial infarction or stable angina followed for a mean of 8 years, risk of sudden cardiac death was significantly increased in current smokers compared to those who had never smoked, while there was no significant difference between former smokers and "never" smokers.[20] In patients with left ventricular dysfunction, quitting smoking was associated with decreased morbidity and mortality within 2 years.[21] Such improvements are comparable to benefits from treatment with medications such as beta-blockers or angiotensin-converting enzyme inhibitors.[22]

SCREENING FOR TOBACCO USE

The US Public Health Service recommends the "5As" model for smoking cessation intervention, in which providers (1) *ask* patients about tobacco use to identify current users, (2) *advise* tobacco users to quit, (3) *assess* patient interest in and willingness to quit, (4) *assist* patients interested in quitting with counseling and/or pharmacotherapy, and (5) *arrange* for follow-up to monitor progress (Fig. 31–1). Although current smokers report high rates of being asked about tobacco use (88%), fewer report being advised to quit (66%), and even fewer being asked if they wanted to quit (43%).[23] If smokers are not properly identified, those interested in cessation cannot be connected with resources that can help them with their quit attempt. Therefore, screening should be incorporated into all outpatient and hospital encounters.

Adequate follow-up with patients interested in quitting is important for prevention of relapse. Although most relapse to smoking occurs

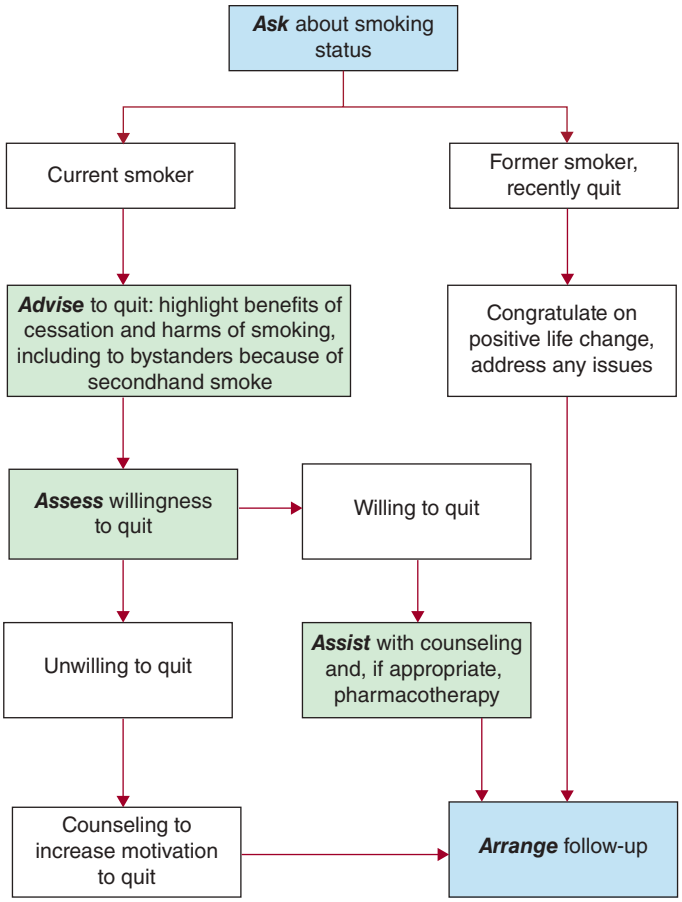

FIGURE 31–1. Algorithm for implementing the 5As for smoking cessation. Adapted with permission from Fiore MC, Jaén CR, Baker TB, et al: al. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services. Public Health Service; 2008.[3]

within the first week of quitting,[24] relapse does occur in those who have been abstinent from cigarettes for much longer periods of time,[25] making it important to monitor patients for at least 6 months after they quit.

TREATMENT FOR SMOKING CESSATION

Both pharmacotherapy and counseling are effective treatments for smoking cessation, with success highest when they are combined.[26] Such a combination of methods can address both a smoker's physical addiction to nicotine (by managing withdrawal symptoms) as well as the habit of smoking. Symptoms of nicotine withdrawal include cravings, as well as a number of nonspecific symptoms including irritability, depressed mood, restlessness, sleep disturbance, trouble concentrating, and increased appetite. Withdrawal symptoms have a variable time course, with resolution within 10 days in some[27] but longer in others,[28] particularly for cravings, which can persist for over 6 months after quitting.[25]

Pharmacologic Therapy for Smoking Cessation

Various prescription and nonprescription medications approved by the US Food and Drug Administration (FDA) are available to assist patients in their quit attempt, provided patients do not have contraindications to their use.[3] This includes nicotine replacement therapy (NRT), varenicline, and bupropion (Table 31–1). They are all first-line treatments for smoking cessation, and choice of agent should take into consideration patient preferences, medical comorbidities, and potential drug-drug interactions.

Nicotine Replacement Therapy Nicotine is the addictive drug in cigarettes and other tobacco products, and nicotine withdrawal is what triggers many of the symptoms smokers suffer after quitting. NRT, which provides patients with nicotine to manage cravings and nicotine withdrawal symptoms, comes in a variety of forms. Types of NRT include patches, gum, lozenges, inhalers, and nasal sprays. The nicotine patch is a long-acting form of nicotine replacement with a slow onset of action, providing a steady dose of nicotine throughout the day, whereas the gum, lozenge, inhaler, and nasal spray are short-acting forms of replacement that provide more rapid relief of cravings and withdrawal symptoms. Each type of NRT is associated with significantly increased smoking cessation compared to control (either placebo or no NRT), and use of a combination of NRT products (ie, use of a nicotine patch in conjunction with a short-acting form of nicotine) is associated with increased smoking cessation compared to a single type of NRT.[29] Therefore, for highest efficacy, the nicotine patch should be combined with a short-acting form of NRT.

With respect to treatment duration, a randomized clinical trial of different durations of nicotine patch treatment (8, 24, or 52 weeks) found higher rates of smoking abstinence at 24 weeks in those still using nicotine patches, but no significant difference was seen at 52 weeks.[30] This result suggests that, while nicotine patch treatment can continue longer than 8 to 10 weeks, evidence does not support extending treatment past 24 weeks. For timing of treatment initiation, there is some evidence that starting nicotine patches prior to a patient's quit day is associated with increased smoking cessation compared to starting after the quit day. However, no difference was seen with nicotine gum or lozenges.[29] Thus, it is not necessary to wait until the quit date to initiate treatment with nicotine patches.

It is important to note that, while clinical trials have demonstrated efficacy of NRT when used as part of an organized cessation effort, unsupervised NRT bought over the counter is associated with significantly less quitting than use of no smoking cessation aids (odds ratio [OR] 0.68, confidence interval [CI] 0.49-0.94).[31] Thus, patients using NRT should be followed and encouraged to maintain their quit attempt. Such combinations of counseling and NRT can be accomplished through telephone quitlines, which also provide certain types of NRT to eligible callers.

A network meta-analysis of 21 randomized controlled trials found an increase in all cardiovascular disease events (relative risk [RR] 2.29, 95% CI 1.39-3.82) with NRT compared to placebo, but no significant difference in major adverse cardiovascular events (RR 1.95, CI 0.92-4.30).[32] In one study of patients who had acute coronary syndrome, there was no significant difference in death, myocardial infarction, repeat revascularization, or rehospitalization for angina, congestive heart failure, or arrhythmia after one year in those who received NRT compared to those who did not.[33] In any event, the risks associated with NRT are much lower than the risks of continued smoking.

Varenicline Varenicline is a partial nicotinic receptor agonist that is taken daily by mouth, starting the week prior to a patient's quit date and continuing for a total of 12 weeks. Varenicline is associated with two to three times higher odds of smoking cessation compared to placebo,[34] and extension of varenicline treatment for an additional 12 weeks has also been associated with increased continuous abstinence from cigarettes.[35] Thus, treatment can be continued for a total of 6 months. A 2015 randomized controlled trial of varenicline for smoking cessation among patients hospitalized with acute coronary syndrome found higher point prevalence of smoking abstinence at 24 weeks in those taking varenicline compared to placebo (47.3% vs 32.5%, $P = .012$) and higher continuous abstinence rates (35.8% vs 25.8%, $P = .05$).[36]

Varenicline has a number of safety concerns, including a boxed warning for serious neuropsychiatric events such as agitation, hostility, depressed mood, changes in behavior or thinking, and suicidal

TABLE 31–1. First-line Prescription and Nonprescription Medications for Smoking Cessation

Medication	Mechanism of Action	Available Doses	Method of Use	Duration of Use	Potential Side Effects	Availability	Relative Risk for Cigarette Abstinence (compared to control)
Nicotine patch	Provides a steady dose of nicotine throughout the day transdermally	If smoking > 10 cigarettes/day: • 21 mg for 6 weeks, then • 14 mg for 2 weeks, then • 7 mg for 2 weeks If smoking ≤ 10 cigarettes/day: • 14 mg for 6 weeks, then • 7 mg for 2 weeks	• Can be worn for 16 or 24 hours • Changed daily	8–10 weeks, can be extended	• Redness/irritation at patch site • Sleep disturbance • Headache • Nausea • Dizziness	Prescription or OTC	1.64 (1.52–1.78)[a]
Nicotine gum	Provides short-acting nicotine through oral absorption	If smoke first cigarette within 30 minutes of waking: • 4 mg gum every 1–2 hours for 6 weeks, then every 2–4 hours for 3 weeks, then ever 4–8 hours for 3 weeks If smoke first cigarette after 30 minutes of waking: • 2 mg gum every 1–2 hours for 6 weeks, then every 2–4 hours for 3 weeks, then ever 4–8 hours for 3 weeks	• Chew until feel tingling, then keep the gum between cheek and gum • Repeat when tingling disappears, stop when no longer tingling (~30 minutes) • Avoid eating or drinking for 15 minutes before and while chewing the gum • Use at least 9 pieces/day for the first 6 weeks; do not exceed 24 pieces/day	12 weeks, can be extended	• Mouth, tooth, or jaw problems • Nausea • Heartburn • Hiccups	Prescription or OTC	1.49 (1.40–1.60)[a]
Nicotine lozenge	Provides short-acting nicotine through oral absorption	If smoke first cigarette within 30 minutes of waking: • 4 mg lozenges every 1–2 hours for 6 weeks, then every 2–4 hours for 3 weeks, then ever 4–8 hours for 3 weeks If smoke first cigarette after 30 minutes of waking: • 2 mg lozenges every 1–2 hours for 6 weeks, then every 2–4 hours for 3 weeks, then ever 4–8 hours for 3 weeks	• Place lozenge into mouth and allow it to dissolve slowly, moving from side to side • Avoid eating or drinking for 15 minutes before and during using the lozenge • Use at least 9 lozenges/day for the first 6 weeks; use no more than 5 lozenges in 6 hours or 20 lozenges/day	12 weeks, can be extended	• Mouth irritation • Sore throat • Nausea • Heartburn • Hiccups	Prescription or OTC	1.95 (1.61–2.36)[a]
Nicotine inhaler	Provides short-acting nicotine through oral/pharyngeal absorption after inhalation	• Use 6–16 cartridges (each containing 10 mg of nicotine of which 4 mg is delivered) per day for 12 weeks; can gradually taper for additional 6–12 weeks	• Inhale or puff into mouth and back of throat • Cartridges last for about 20 minutes of puffing	12–24 weeks	• Mouth or through irritation • Cough	Prescription only	1.90 (1.36–2.67)[a]
Nicotine nasal spray	Provides short-acting nicotine through nasal mucosa	• 1–2 sprays (each 50-μLspray contains 0.5 mg nicotine) per nostril per hour (1 dose = 1 spray in each nostril) for 8 weeks, followed by discontinuation of 4–6 weeks	• Tilt head back slightly and pump spray into the nostril; repeat for other nostril • Do not sniff, swallow, or inhale while spraying • Maximum of 10 sprays (5 mg nicotine) per hour or 80 sprays (40 mg nicotine) per day	12–14 weeks	• Nasal irritation • Throat irritation • Sneezing • Watery eyes • Runny nose • Coughing	Prescription only	2.02 (1.49–2.73)[a]

(*continued*)

TABLE 31–1. First-line Prescription and Nonprescription Medications for Smoking Cessation (*Continued*)

Medication	Mechanism of Action	Available Doses	Method of Use	Duration of Use	Potential Side Effects	Availability	Relative Risk for Cigarette Abstinence (compared to control)
Varenicline	Nicotinic receptor partial agonist	• 0.5 mg tablets daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily for total of 12 weeks	• Start 1 week prior to quit date • Take after eating with a full glass of water	12–24 weeks	Serious side effects: • Depression, suicidal ideation, changes in behavior, hostility, agitation, cardiovascular events Other adverse reactions: • Nausea • Abnormal dreams • Constipation • Flatulence • Vomiting	Prescription only	2.27 (2.02–2.55)[b]
Bupropion	Norepinephrine and dopamine reuptake inhibitor and releasing agent	• 150 mg tablets daily for 3 days, then 150 mg twice daily for total of 12 weeks	• Start 1 week prior to quit date	12 weeks	Serious side effects: • Suicidal thoughts and behaviors • Contraindications: • Seizure disorder • Current or past bulimia or anorexia nervosa Other adverse reactions: • Insomnia • Dry mouth • Rhinitis • Dizziness • Anxiety • Nausea • Constipation	Prescription only	1.62 (1.49–1.76)[c]

Abbreviations: OTC, over the counter.

[a]Data obtained from Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T.[29]

[b]Data obtained from Cahill K, Stead LF, Lancaster T.[34]

[c]Data obtained from Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T.[41]

ideation or behavior. A 2015 systematic review and meta-analysis of 39 randomized controlled trials found no significant increase in suicide or attempted suicide, suicidal ideation, depression irritability, aggression, or death in those taking varenicline compared to those taking placebo.[37] Additionally, a retrospective cohort study of 164,766 patients in England found a decrease in depression and self-harm in patients taking varenicline compared with those taking NRT.[38] Nevertheless, patients should be closely monitored after initiation of varenicline for onset of neuropsychiatric events.

Studies on the cardiovascular safety of varenicline have yielded mixed results. A network meta-analysis of 18 randomized controlled trials comparing varenicline versus placebo found no significant difference in

all cardiovascular disease events (RR 1.30, 95% CI 0.79-2.23) or major adverse cardiovascular events (RR 1.34, CI 0.66-2.66),[32] while another meta-analysis reported an increase in serious adverse cardiovascular events in those using varenicline (Peto OR 1.72, 95% CI 1.09-2.71).[39] One possible explanation for the difference in results of these two studies is the statistical approach (random effects meta-analysis vs Peto method). In a third meta-analysis conducted by the FDA, no statistically significant increase in major adverse cardiac events within 30 days of discontinuation of varenicline treatment versus placebo was found (hazard ratio [HR] 1.96, 95% CI 0.79-4.82).[40] In this study, the overall incidence of major adverse cardiovascular events was low in both the varenicline group (0.31%) and the placebo group (0.21%).

Bupropion Bupropion is approved both for the treatment of depression and for smoking cessation. It is started a week prior to a smoker's quit date and continued for 7 to 12 weeks. Bupropion is associated with greater smoking cessation than placebo/control in a recent meta-analysis.[41] However, whether this is true in all patient populations is unclear. A study of smokers hospitalized with acute myocardial infarction found that although bupropion was well tolerated, it did not increase smoking cessation compared to placebo.[42]

Like varenicline, bupropion carries a boxed warning for neuropsychiatric reactions and suicidal thoughts and behaviors. A meta-analysis of 33 trials found (1) increased incidence of serious adverse events (defined as a life-threatening event; an event leading to hospitalization, death, disability, or permanent damage; or an event requiring intervention to prevent such an outcome) in individuals treated with bupropion compared to control (RR 1.30, 95% CI 1.00-1.69) and (2) no significant increase in psychiatric serious adverse events (RR 0.60, 95% CI 0.28-1.28).[41] A network meta-analysis found no significant difference associated with bupropion treatment versus placebo in cardiovascular disease events and significantly decreased major adverse cardiovascular events in those treated with bupropion.[32]

Combination Therapy As discussed above, treatment with a combination of long-acting and short-acting NRT is associated with increased smoking cessation compared to a single type of NRT.[29] A randomized controlled trial found that varenicline combined with NRT was associated with higher tobacco abstinence at 12 weeks and 6 months compared to varenicline alone.[43] Another randomized controlled trial found that treatment with both varenicline and bupropion for 12 weeks was associated with significantly greater smoking cessation than treatment with varenicline alone at 12 weeks (OR 1.49, 95% CI 1.05-2.12) and 26 weeks (OR 1.52, 95% CI 1.04-2.22)—but not at 52 weeks (OR, 1.32, 95% CI 0.91-1.91).[44] Participants receiving combination therapy, however, reported more anxiety and depressive symptoms. Combination bupropion and NRT treatment is not associated with a significant different in smoking cessation compared to NRT alone.[41] While combining different forms of NRT is a recommended, effective strategy for smoking cessation, combination of NRT with bupropion has not proven to be effective, and while combination varenicline and NRT has shown some promise of efficacy at 6 months, further studies on long-term efficacy and safety are needed.

Other Pharmacotherapy Other medications, although not FDA-approved for smoking cessation in the United States, have been studied for smoking cessation. Nortriptyline, a tricyclic antidepressant, has been associated with increased smoking cessation compared to placebo.[41] However, given the association between tricyclic antidepressants and cardiac disease, this drug should be avoided in patients with underlying heart disease. Clonidine, an α2-agonist, has been shown in a meta-analysis of six studies to be associated with significantly increased smoking cessation. However, only one of the individual trials had a statistically significant result.[34] Cytisine, a nicotine receptor partial agonist, has been associated with increased smoking cessation compared to placebo in combined results from two trials.[34] Although it is marketed in some European countries, it is not currently approved for smoking cessation in the United States.

Behavioral Interventions and Other Therapies for Smoking Cessation

Counseling delivered by telephone, either through telephone quitlines or other sources, is also associated with smoking cessation,[45] as are some mobile phone–based interventions,[46] printed self-help materials,[47] and interactive, tailored Internet-based interventions.[48] Motivational interviewing, which consists of counseling to improve an individual's motivation to and interest in undergoing behavioral change, has also been associated with increased smoking cessation compared to brief advice or usual care.[49] In individuals using pharmacotherapy for smoking cessation, the addition of behavioral support through in-person or telephone contact is also associated with increased smoking cessation compared to control groups.[50]Assistance via telephone is available from state telephone quitlines toll-free at 1-800-QUIT-NOW (1-800-784-8669). Support through text messaging can also be found through the National Cancer Institute's Smokefree TXT program, which is available at smokefree.gov/smokefreetxt, or by texting the word QUIT to 47848 from a mobile phone.

Acupuncture, acupressure, or laser therapy has not been associated with long-term smoking cessation compared with sham interventions.[51] Studies on hypnotherapy for smoking cessation, either compared to no intervention or other interventions, have not found a consistent long-term benefit.[52]

HEALTH EFFECTS OF SMOKING REDUCTION

Cigarette smoking, even at low levels, is associated with an increased risk of cardiovascular disease.[53-55] The dose-response relationship between smoking and cardiovascular disease is highly nonlinear, with more rapid increases in risk at low levels of exposure and flattening of the curve at higher levels of exposure.[53] In fact, smoking as few as five cigarettes a day is associated with higher risk of death from ischemic heart disease.[55] Smoking a few cigarettes a day should not be promoted as a long-term use pattern, and complete cessation should be encouraged in all patients.

Smoking reduction has been associated with improved levels of biomarkers associated with cardiovascular disease in some studies[56,57] but not in others.[58] It is not clear whether improvements in these biomarkers also results in improvements in risk of smoking-related disease. Statistically significant improvement in systolic and diastolic blood pressure and heart rate have been seen with smoking reduction,[57] but a randomized controlled trial of smoking reduction found no difference in angina, quality of life, or adverse events in those assigned to the reduction group.[58] A study in Denmark found that although there was a decreased risk of myocardial infarction among individuals who had stopped smoking (HR 0.71, 95% CI 0.59-0.85), smoking reduction by at least 50% had no significant association with myocardial infarction (HR 1.15, 95% CI 0.94-1.40).[59]

Smokers should be encouraged to quit cigarettes entirely, particularly because smoking even a few cigarettes still carries significant increased cardiovascular risks compared to quitting cigarettes altogether.

PROTECTION FROM SECONDHAND SMOKE EXPOSURE

Exposure to secondhand smoke significantly increases the risk of myocardial infarction and other cardiac events. Indeed, heart disease accounts for about 90% of all secondhand smoke–attributable deaths.[16] All patients should be instructed to make their homes smoke-free and

avoid exposure to secondhand smoke. Doing so not only reduces exposure to smoke and the associated health risks, but smoke-free homes also facilitate smoking cessation.

Laws making workplaces and restaurants and bars smoke-free covered half of the US population in 2015.[60] Several meta-analyses have evaluated the impact of smoke-free laws on hospitalization for cardiovascular disease.[15,61-63] The most recent of these meta-analyses,[62] which included 31 studies with estimates for 47 locations, found an overall 12% reduction in hospitalizations for acute coronary events (RR 0.88, 95% CI 0.85-0.90) after implementation of smoke-free laws. Greater reductions were seen for locations with comprehensive legislation (workplaces, restaurants, and bars) compared to partial legislation (14% for comprehensive vs 8% for partial). Studies have also found reduction in mortality from cardiovascular disease after implementation of smoke-free laws.[64-67] A meta-analysis of the association between smoke-free legislation and hospital admission for cerebrovascular accidents and found a 19% decrease in hospitalizations following implementation of comprehensive smoke-free laws (RR 0.81, 95% CI 0.70-0.94; five studies).[15] A study found a 32% reduction in stroke mortality (RR 0.68, 95% CI 0.54-0.85) in Ireland after implementation of a national ban on smoking in workplaces; this mortality reduction was seen only for those age 65 and older.[67] Furthermore, a decrease in calls to ambulances was seen after implementation of a smoke-free law in Colorado.[68] This evidence that smoke-free laws reduce cardiovascular disease events highlights the importance of asking nonsmokers, especially those with cardiovascular disease, about secondhand smoke exposure and give strong advice to have smoke-free homes and automobiles if they do not already, which extends the protection of laws into their home environment.

In addition to the benefits of smoke-free laws and policies for reducing secondhand smoke exposure in workplaces, public places, and homes, these regulations have also been associated with increased smoking cessation and decreased cigarette consumption among current smokers[69,70] and with increases in voluntary smoke-free laws in homes and cars.[71] Smoke-free laws promote both increased protection from secondhand smoke and decreased active smoking.

GLOBAL BURDEN OF TOBACCO USE

There is great variability in the prevalence of cigarette smoking worldwide. Although tobacco control policies have played a substantial role in reducing smoking prevalence in places such as the United States and United Kingdom, smoking rates remain high in many parts of the world, particularly among men. For example, over half of men in Indonesia, Russia, and China currently smoke,[72] compared to fewer than 19% of men in the United States.[73] The World Health Organization's Framework Convention on Tobacco Control (FCTC), the first global public health treaty, adopted in 2003 and implemented in 2005, emphasizes the importance of promoting public health through implementation of policies, including smoke-free environments to protect people from secondhand smoke and provide an environment that helps people stop smoking; elimination of tobacco advertising and promotion; increased taxes to reduce demand for cigarettes; and education of the public on the risks of smoking, such as with large graphic warning labels on tobacco products.[74] Although the FCTC has accelerated implementation of smoke-free laws[75] and strong health warning labels,[76] only about half of nations report 100% smoke-free restaurants and even fewer in private workplaces.[77] As of 2016, the United States was one of the few countries that had not ratified the FCTC, and the United States lags behind the rest of the world in several areas, notably strong graphic warning labels on tobacco products, restrictions on advertising and promotion, and tobacco taxation. More comprehensive smoking laws are needed worldwide to ensure the maximum health benefits conferred to both smokers and nonsmokers by such tobacco control legislation.

ELECTRONIC CIGARETTES

Electronic cigarettes (e-cigarettes), a type of electronic nicotine delivery systems, are battery-powered devices that heat a solution of humectants such as propylene glycol or glycerol, generally with nicotine and/or flavorings, to form an aerosol that is inhaled by the user. E-cigarettes are relatively new products, so their long-term health effects are unknown. Additionally, as of January 2016, e-cigarettes were not regulated by the FDA. Although many smokers report using e-cigarettes to quit smoking, randomized controlled trials on efficacy for smoking cessation have been limited and their results have been equivocal.[78,79] As currently being used in the real world, e-cigarettes are associated with significantly less quitting than NRT or no cessation aids.[80] Data from three studies[81-83] suggest that specific e-cigarette use patterns (daily use of high nicotine delivery devices, which represents the minority of users in these studies) may be associated with increased quitting; as e-cigarette product types and use patterns continue to evolve, this association should continue to be studied. Nevertheless, e-cigarettes should not be recommended as effective smoking cessation aids until there is evidence that, as promoted and used, they assist smoking cessation.[80,84]

A policy statement by the American Heart Association in 2014 encourages the inclusion of e-cigarette use in tobacco screening questions.[85] Use of e-cigarettes by patients may signal readiness to quit cigarettes, and thus clinicians should be prepared to support patients in their quit attempts and to discuss evidence-based practices for smoking cessation, including counseling, NRT, or stop-smoking pharmacotherapy, with these patients.[84]

RECOMMENDATIONS AND CONCLUSIONS

Clinicians should screen all patients for use of tobacco products and exposure to secondhand smoke. Once patients who use tobacco use are identified, they should be advised to quit and educated about the various health benefits of quitting, which begin to develop soon after abstinence. Patients should be guided to evidence-based resources to assist them in their quit attempts, including both counseling (either from clinicians themselves or through resources such as in-person tobacco counselors, telephone counselors through state quitlines, or mobile-based counseling through text messaging) and medications. Follow-up with patients should occur shortly after a plan for cessation is established—to ensure that the patients are not having problems with obtaining medications or counseling support; that they are not experiencing any side effects from treatment; and to provide continued support and encouragement, particularly soon after the quit attempt, when risk of relapse is highest.

Cigarette smoking remains a major cause of cardiovascular and all-cause mortality. The risk of smoking-induced cardiovascular diseases decreases soon after smoking cessation regardless of how old people are when they quit. Counseling and pharmacotherapy are both effective aids for smoking cessation, and their combination is more effective than either alone. Comprehensive smoke-free policies both protect nonsmokers from secondhand smoke exposure and encourage smoking cessation and implementation of smoke-free homes among current smokers, which, in turn, not only protects people from exposure to secondhand smoke but supports cessation.

Smoking cessation should be considered an important therapeutic intervention for people with heart disease and implemented as part of routine clinical care for these patients.

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SECTION 7

Atherosclerosis and Coronary Heart Disease

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CHAPTER 32

ATHEROTHROMBOSIS: DISEASE BURDEN, ACTIVITY, AND VULNERABILITY

Erling Falk and Valentin Fuster

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Atherosclerosis with thrombosis superimposed, *atherothrombosis*, is the main cause of coronary heart disease (CHD), peripheral artery disease, and large-artery stroke.[1-3] The development of thrombosis-prone atherosclerotic plaques, also known as high-risk or vulnerable plaques,[4] in the coronaries and other arteries is the leading cause of death and severe disability, not only in affluent countries, but also worldwide.[5,6]

Causal and modifiable risk factors for atherosclerotic cardiovascular disease are well known (eg, smoking, dyslipidemia, high blood pressure, diabetes) and account for most heart attacks in both sexes.[7] However, for unknown reasons, the individual susceptibility to these risk factors varies greatly, and consequently, their predictive value is limited.[8,9] Most first heart attacks occur among people with average or only slightly elevated risk factor levels.[10-12] Recurrent events still occur despite lowering of these levels,[13,14] indicating that we need both better detection and better treatment of those who are destined for a heart attack. Better detection of at-risk individuals may be achieved by visualizing the diseased arterial wall rather than just assessing risk factors for getting the disease.[15-17] The prospect for atherosclerosis-based risk assessment will be discussed in the concluding section.

ATHEROGENESIS AND PLAQUE DEVELOPMENT

Atherosclerosis is a chronic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development,[18-20] predominantly at sites characterized by low and oscillatory endothelial shear stress (bifurcations, inner wall of curvatures) and preexisting intimal thickenings.[21,22] The speed of disease progression varies greatly, but it usually takes decades to develop the advanced atherosclerotic lesions responsible for clinical disease. Plaques are very heterogeneous in size and composition, even plaques located next to each other and exposed for the same systemic risk factors (Fig. 32–1). Most plaques remain asymptomatic (subclinical disease), some become obstructive (stable angina), and a few, if any, become vulnerable and lead to atherothrombotic events such as a fatal heart attack or a disabling stroke.

ENDOTHELIAL CELLS

The endothelium, located at the interface between the blood and the arterial wall, plays a key role in the development of atherosclerosis.[22] In lesion-prone areas, apoprotein B–containing lipoproteins extravasate into intima, where they are retained and modified (eg, oxidized) into cytotoxic, proinflammatory, chemotaxic, and proatherogenic molecules.[23] The overlying endothelium becomes activated and mediates transendothelial trafficking of leukocytes, especially monocytes but also T cells and a few mast cells, primarily via upregulated adhesion molecules.[18,19]

MACROPHAGES

Monocyte-derived macrophages play a key role in the initiation, progression, and destabilization of atherosclerotic plaques.[18-20,24,25] Some macrophages perform beneficial scavenger functions, cleaning up intima for toxic lipid-rich waste products, and others are destructive and accelerate the development of a destabilizing necrotic core and a rupture-prone fibrous cap as described below. Consequently, macrophage number and function within atherosclerotic plaques are obvious putative markers of disease activity. However, because atherosclerosis is a protracted and smoldering inflammatory disease in which the advanced and potentially symptomatic lesions are dominated by fibrosis, extracellular lipids, necrosis, and calcification (Fig. 32–2),[26] the macrophage density is usually low, and macrophages rarely occupy more than a small percentage of the plaque.[27] In fact, advanced atherosclerosis is a smoldering inflammatory disease without much inflammation.

SMOOTH MUSCLE CELLS

When intimal damage occurs, vascular smooth muscle cells (SMCs) modulate into a synthetic phenotype and perform fibroblast-like functions. They migrate, proliferate, and synthesize extracellular matrix, including collagen, and thus confer stability to plaques.[28] Analogous to scar contraction, collagen-rich plaques tend to contract and aggravate luminal narrowing. If the vascular SMCs vanish, healing and repair are compromised and the macrophage-mediated destructive processes will prevail.

CELL REPLICATION AND DEATH

During atherogenesis, some cells proliferate and others die by apoptosis or necrosis. The rate of cell proliferation is low and predominantly

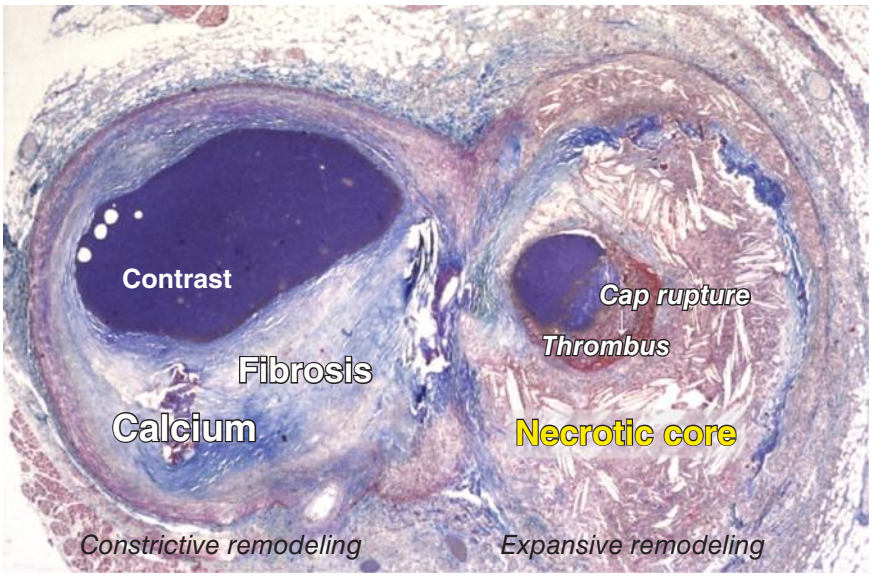


FIGURE 32–1. Heterogeneity of atherosclerotic plaques. Cross-section of a coronary artery cut just distal to a bifurcation. The plaque to the left (circumflex branch) is fibrotic with a dense calcification, whereas the plaque to the right (marginal branch) contains a large lipid-rich necrotic core covered by a thin fibrous cap that is disrupted with mural thrombosis. The lumen contains contrast medium injected postmortem. Trichrome, staining collagen blue and thrombus red.

confined to inflammatory cells.[29] Apoptosis is also most common in inflammatory cells, but its rate is more difficult to determine because of defective clearance of dead cells in advanced lesions.[30-32] Death of macrophage foam cells and SMCs are believed to play important pathogenetic roles in the formation of a necrotic core and thinning of the overlying fibrous cap, respectively.[25,30-32]

CIRCULATING PROGENITOR CELLS

Subsets of mononuclear cells in the blood, termed *endothelial progenitor cells* and *smooth muscle progenitor cells*, form colonies in cell culture with endothelial or SMC-like features, respectively.[33,34] These circulating cells, assumed to originate solely or mainly from the bone marrow, have been claimed to home and differentiate into bona fide endothelial and smooth muscle cells in atherosclerotic lesions and thus promote healing and repair.[35,36] However, more recent data question this theory. First, the putative endothelial progenitor cells identified in clinical studies have been shown to give rise to colonies composed of inflammatory and immune cells, rather than endothelial cells, in vitro.[37,38] Second, new mouse studies using improved techniques to track endothelial and SMC origin in atherosclerotic plaques have found that both cell types are derived from local sources with rare, if any, contributions from the blood.[39-41] Thus, rather than differentiating into endothelial or smooth muscle cells, the so-called *progenitor cells* in the blood might influence the progression of atherosclerosis by paracrine signaling, as appears to be the case for neovascularization (angiogenesis).[42]

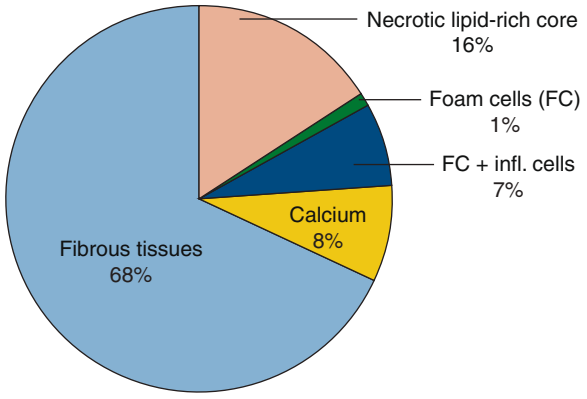


FIGURE 32–2. Average composition of advanced coronary plaque. Pie diagram illustrating the average composition of advanced atherosclerotic plaques (> 75% stenosis by histology) in the coronary artery tree in fatal myocardial infarction.[26] Hypocellular tissues (fibrosis, calcium, and necrosis) constitute by far the most voluminous plaque components.

VULNERABLE AND THROMBOSED PLAQUES

The great majority of symptomatic coronary thrombi (~75%) are caused by *plaque rupture*.[20] Plaque rupture with mural thrombosis (with or without plaque hemorrhage) is also a common cause of episodic but asymptomatic progression to severe stenosis.[43,44] The remaining thrombi are caused by less well-defined mechanisms, of which so-called *plaque erosion* is the most common type.[20] Plaque rupture is a more frequent cause of coronary thrombosis in men (~80%) than in women (~60%) but, except for sex and menopause, no other risk factors have consistently been connected with a particular mechanism of thrombosis.[20] By inference, there are two major types of vulnerable plaques, rupture-prone and erosion-prone, that are presumed to look like the corresponding thrombosed plaques, just without rupture and thrombosis.[45]

PLAQUE RUPTURE

The prototype of a presumed rupture-prone plaque contains a large and soft lipid-rich necrotic core covered by a thin and inflamed fibrous cap (Fig. 32–3).[25,45] Associated features include big plaque size, expansive positive remodeling mitigating luminal obstruction (mild stenosis by angiography), neovascularization (angiogenesis), plaque hemorrhage, adventitial inflammation, and a *spotty* pattern of calcifications (Fig. 32–4). Although the macrophage density in ruptured caps is high,[25,45] whole-plaque macrophage density rarely exceeds a small percent because ruptured caps are tiny (Fig. 32–5).

PLAQUE EROSION

Vulnerable plaques of the erosion-prone type are heterogeneous and defined only by their fate (thrombosis, mostly mural) (Fig. 32–6).[20,45] The surface endothelium is missing, but, whether it vanished before or after thrombosis remains unknown. No distinct morphologic features have been identified, but in general, eroded plaques with thrombosis are scarcely calcified, rarely associated with expansive remodeling, and only sparsely inflamed.[20,45] So, irrespective of plaque type, it is a misconception that vulnerable plaques are heavily inflamed.

LOCATION AND NATURAL HISTORY

Vulnerable plaques, plaque rupture, and thrombosed plaques tend to cluster in *hot spots* within the proximal segments of the major coronary arteries,[46-48] and rarely more than one or a few such lesions exist

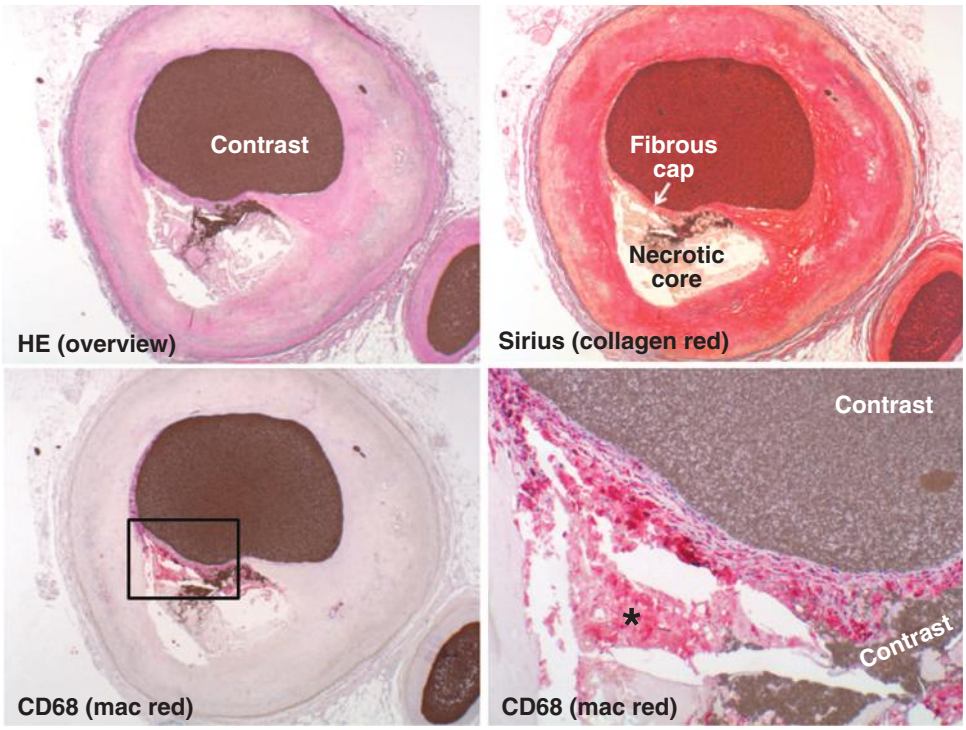


FIGURE 32–3. Inflamed thin-cap fibroatheroma (TCFA). Coronary TCFA composed predominantly of hypocellular fibrous tissue and acellular necrotic core. Penetration of contrast medium injected postmortem from the lumen into the necrotic core reveals fibrous cap rupture. Immunohistochemistry visualizes abundant macrophages (mac) within the thin fibrous cap but virtually nowhere else. Beneath the cap, dead macrophages without nuclei are seen within the necrotic core (*asterisk*). The cap contains very few smooth muscle cells (not shown). HE, hematoxylin and eosin.

simultaneously.[49,50] The natural history of vulnerable plaques such as speed of development, lifetime (persistency), and fate, is, however, unknown.

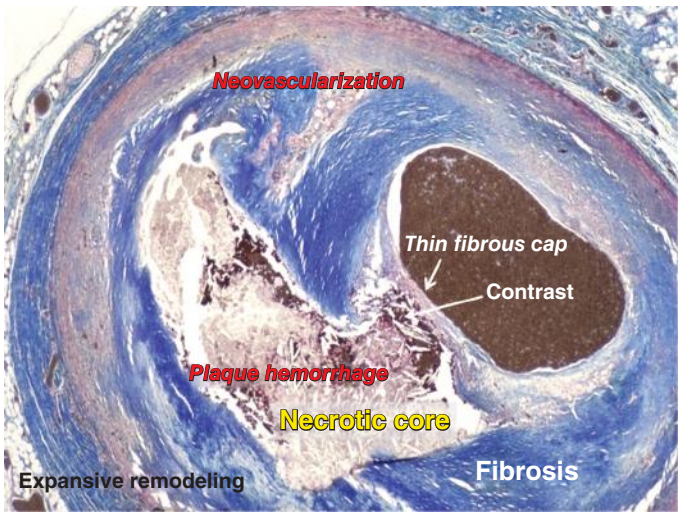


FIGURE 32–4. Coronary thin-cap fibroatheroma (TCFA). A TCFA containing a soft and destabilizing necrotic core devoid of supporting collagen and separated from the lumen only by a thin fibrous cap. Such a plaque is presumed to be rupture-prone and, if correct, constitutes the most common type of vulnerable plaques. In this case, postmortem contrast injection provided proof of vulnerability; the contrast has penetrated from the lumen into the necrotic core, indicating the presence of a disrupted fibrous cap. The contrast followed a path bordered by extravasated erythrocytes (plaque hemorrhage). Trichrome, staining collagen blue (necrotic core not stained).

DETERMINANTS OF PLAQUE VULNERABILITY

Plaque rupture requires the presence of a lipid-rich necrotic core covered by a thin fibrous cap. The size of the necrotic core and the thickness of the fibrous cap appear to be the two major structural determinants of vulnerability (Fig. 32–7).

NECROTIC CORE

During atherogenesis, atherogenic lipoproteins are retained within intima, modified, and accumulate, predominantly deeply in the abluminal part of intima.[51,52] Some of these *pools* of lipids seem to attract macrophages that secrete proteolytic enzymes and engulf lipid until they die, leaving behind a soft and destabilizing lipid-rich cavity containing cholesterol crystals and devoid of supporting collagen and cells, the *necrotic core*.[20,45] Such a plaque is called an *atheroma* or *fibroatheroma*.[53,54] Later on, extravasation of erythrocytes into the necrotic core may expand it (see Neovascularization and Plaque Hemorrhage).

FIBROUS CAP

The fibrocellular part of the plaque located between the necrotic core and the lumen is called the *fibrous cap*. It is extremely thin in coronary plaque rupture.[25,45] Assessed by microscopic examination postmortem, ruptured caps were usually less than 65 μm thick.[54] Assessed by optical coherence tomography in vivo, the mean thickness was only 49 μm.[55] If the fibrous cap is thin, the plaque is called a *thin-cap fibroatheroma* (TCFA).[54,56] In TCFA, the necrotic core occupies approximately 23% of plaque area.[56] Thin fibrous caps are usually heavily inflamed (macrophage density ~14%), particularly those that have ruptured (macrophage density ~26%),[56] but because they are thin, their ability

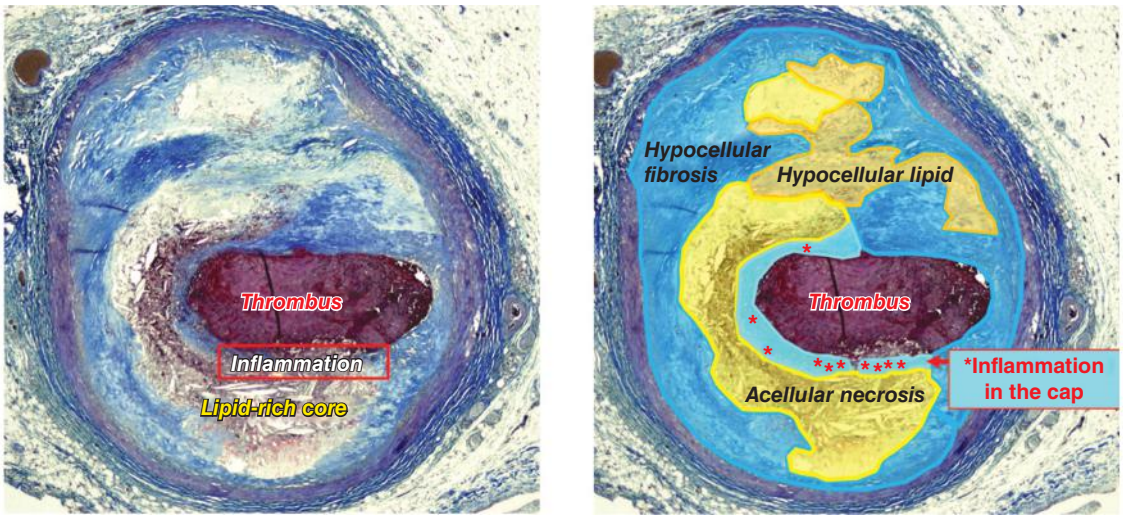


FIGURE 32–5. Ruptured coronary plaque with thrombosis. The thin cap is heavily inflamed, whereas the remainder of the plaque is not. Macrophages (*asterisk*) cluster in the cap next to the rupture site. The majority of the plaque consists of acellular lipid-rich core and hypocellular fibrosis and lipid pools.

to accommodate macrophages are limited (see Fig. 32–5). Apoptosis is common at the site of fibrous cap rupture, usually confined to macrophages because the vascular SMCs already have vanished when rupture occurs.[31,56] With their ability to synthesize extracellular matrix, including collagen, SMC apoptosis is associated with impaired healing and repair, increasing the risk of plaque rupture.

CAP INFLAMMATION

Atherosclerosis is an innate inflammatory disease in which smoldering inflammatory activity is not confined to just a few atherosclerotic lesions but is present, more or less, in all such lesions throughout the body.[18,19] In contrast, vulnerable plaques are relatively rare,[49] and inflammation may play a causal role in plaque rupture only if located

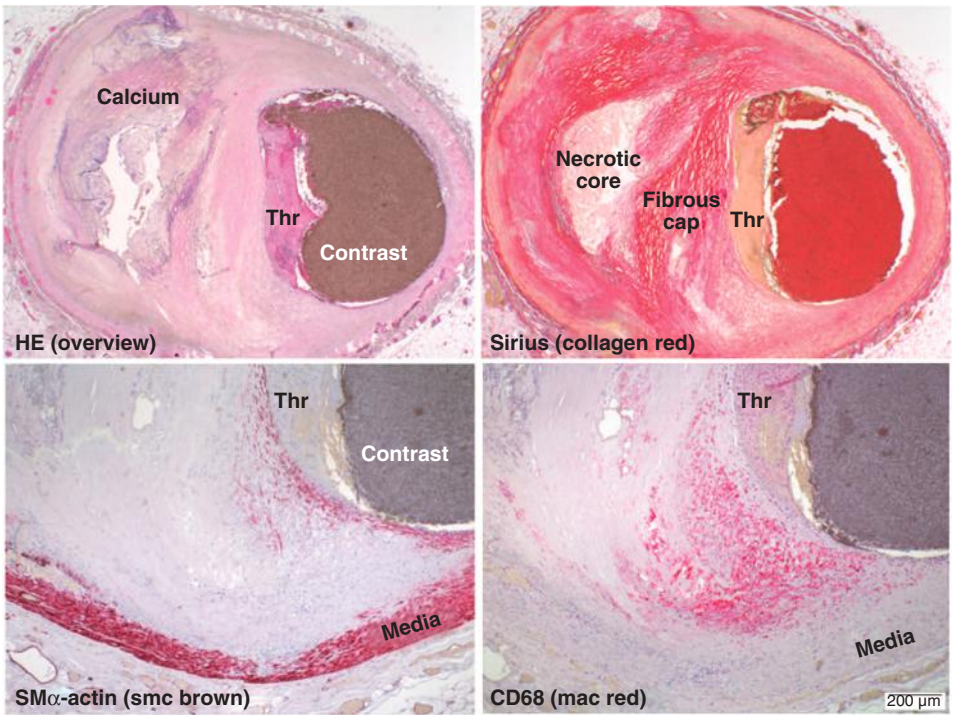
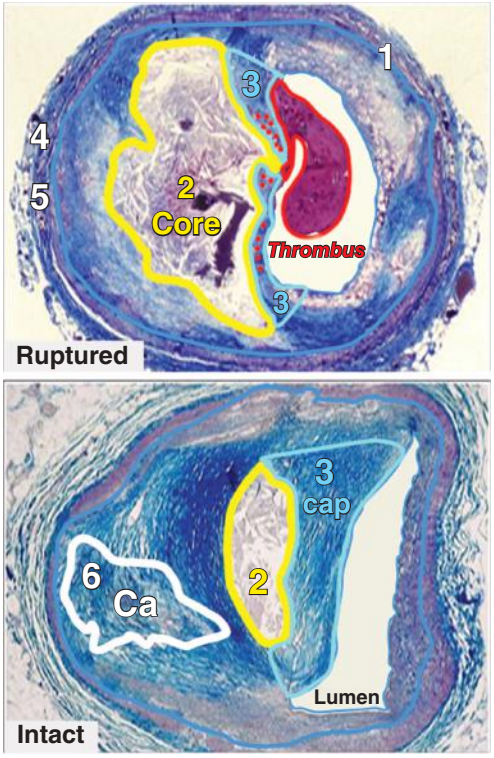


FIGURE 32–6. Thrombosis not caused by plaque rupture. Coronary artery containing a nonruptured plaque with mural thrombosis (*Thr*), so-called *plaque erosion.* The endothelium between the plaque and the thrombus is missing, but no other morphologic features characterize this type of thrombosed plaques and their vulnerable precursors. The plaque is rich in smooth muscle cells (*smc*), but not macrophages (*mac*), just beneath the thrombus. Focal mac accumulation is seen at the shoulder region of the plaque but not located within a thin cap (ie, this plaque morphology is not permissive for plaque rupture). HE, hematoxylin and eosin; SMα, smooth muscle α.



Coronary plaque rupture

1. Plaque size↑
- Paradoxical remodeling (stenosis↓)

2. Necrotic core↑
- ~34% of plaque area*
- ~3.8 mm² and ~9 mm long*

3. Fibrous cap
- Thinkness↓, ~23 μm (95% < 65 μm)*
- Macrophages (•)↑, ~26% of cap*
- Smooth muscle cells↓
- Apoptosis↑
- Thrombus

4. Neovascularization↑
- Intraplaque hemorrhage↑

5. Perivascular inflammation↑

6. Calcification ↓ and "spotty" ↑

FIGURE 32–7. Plaque rupture and determinants of vulnerability. For comparison, a ruptured plaque with thrombus (*top*) and an intact and stable plaque (*bottom*) are depicted, and vulnerable plaque features are listed to the right. By inference, vulnerable plaques of the rupture-prone type are presumed to look like plaque rupture except for an intact cap without thrombus. Data from Kolodgie FD, Burke AP, Farb A, et al. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol*. 2001 Sep;16(5):285-92.

within a thin fibrous cap (ie, the microstructure of the plaque needs to be permissive for rupture). Thus, although plaque inflammation may be useful as a marker of disease activity,[45] it is probably not useful as a stand-alone marker for plaque vulnerability (see Figs. 32–5 and 32–7).

PLAQUE SIZE AND EXPANSIVE REMODELING

During atherogenesis, the artery tends to remodel in such a way that the luminal obstruction caused by some plaques is attenuated (*expansive remodeling*) and by others accentuated (*constrictive remodeling*). Although vulnerable plaques of the rupture-prone type (TCFA) usually are big, they often appear nonobstructive by angiography because of local expansive remodeling and extension of the disease to the adjacent reference segments judged to be normal by angiography.[25,45,57,58] In contrast, plaques responsible for stable angina usually are smaller but nevertheless are often associated with more severe luminal narrowing by angiography because of concomitant constrictive remodeling.[59] The reasons for the different modes of remodeling remain to be defined, but recent clinical observations indicate that diabetes is accompanied by inadequate compensatory remodeling.[60]

NEOVASCULARIZATION AND PLAQUE HEMORRHAGE

Angiogenesis and inflammation often coexist at the base of advanced plaques.[61] The new microvessels rarely originate from the lumen but usually originate from vasa vasorum in adventitia.[62] They lack supporting cells and are fragile and leaky, giving rise to local extravasation of plasma proteins and erythrocytes.[63-65] Such intraplaque bleeds are common[66] and may expand the necrotic core, causing rapid progression of the lesion.[67] Another common source of plaque hemorrhage is extravasation of blood through a ruptured fibrous cap.[50] Neovascularization and inflammation are dynamic processes that disappear with plaque regression induced by cholesterol-lowering in animals.[68,69]

SPOTTY CALCIFICATION

Focal calcifications in atherosclerotic plaques are very common and increase with age.[70] At autopsy, the amount of coronary artery calcium (CAC) correlates poorly with luminal narrowing but strongly with plaque burden.[71] Apoptotic cells, extracellular matrix, and necrotic cores may calcify; healed ruptured plaques are often heavily calcified; and microcalcifications have been described in the fibrous cap.[72,73] The pathogenesis and clinical significance of these different forms of calcifications are, however, poorly understood. Nonatherosclerotic calcifications of coronary arteries are exceedingly rare except in chronic renal failure, where Mönckeberg medial calcific sclerosis may be seen.[74]

ATHEROTHROMBOSIS IN NONCORONARY ARTERIES

Atherosclerosis is a generalized, multifocal arterial disease. However, compared with other arteries, the coronary arteries are in general the most susceptible to atherosclerosis and its thrombotic complications.[75,76] Therefore, if atherosclerosis is present in noncoronary arteries, the coronary arteries will usually also be diseased, irrespective of symptoms.[77] The CHD risk equivalent concept introduced in the previous prevention guidelines included symptomatic disease in noncoronary arteries, carotid stenosis of more than 50%, ankle-brachial blood pressure index less than 0.9, and abdominal aortic aneurysm.[78] Asymptomatic carotid bruit is also associated with high CHD risk.[3,79]

Similar to coronary atherosclerosis, plaque rupture is by far the most common cause of symptomatic thrombosis in carotid atherosclerosis,[80,81] but the thrombus is more often nonocclusive and prone to embolize, often prolonged because of slow-healing plaque ulceration.[82] Intraplaque hemorrhage is common. Carotid plaques, including those that rupture, are rarely heavily inflamed.[83,84] The critical thickness for a rupture-prone cap is greater for carotid plaques than for the much smaller coronary plaques, but a relatively thin cap is most critical for rupture in both arteries.[82,85] In one study, the mean fibrous cap thickness in carotid plaque rupture was found to be nearly three times greater than in coronary plaque rupture (72 ± 15 μm vs 23 ± 17 μm; mean ± standard deviation [SD]), and the macrophage density within ruptured caps was lower (13.5% ± 10.9% vs 26% ± 20%).[82]

ATHEROSCLEROSIS IMAGING: BURDEN, ACTIVITY, AND VULNERABILITY

The individual susceptibility to risk factors and atherosclerosis varies greatly, explaining the well-known limitations of risk factors as prognostic tools.[8-11] However, an alternative and potentially much more

rewarding approach to finding those at highest risk for atherothrombotic events is at hand. It is not based only on risk factors for getting atherosclerosis, but it also incorporates direct and indirect evidence for already having diseased arteries without knowing it (subclinical atherosclerosis), capturing the overall impact of all risk and susceptibility factors combined, known as well as unknown.[86] Subclinical atherosclerosis can be detected by imaging, and its severity and extent (burden), progression rate (activity), and thrombosis-risk (vulnerability) can be assessed.[15-17,45,86]

BURDEN OF ATHEROSCLEROSIS

The number and severity of stenoses determined by coronary angiography are signs of atherosclerosis with diagnostic, therapeutic, and prognostic implications.[87-89] However, most acute coronary events originate from angiographically nonobstructive plaques, probably because they are much more numerous.[25,45,90-93] An irregular lumen and/or filling defects indicating plaque disruption and/or thrombosis are associated with worse outcomes.[94] In contrast to coronary *luminography*, CAC detected by computed tomography (CT) imaging reveals the diseased arterial wall directly and correlates strongly with plaque burden.[71,95] The total amount of CAC (usually expressed as the *Agatston score*) is a strong predictor of coronary events and provides prognostic information beyond that provided by traditional risk factor scoring.[96]

Contrast-enhanced CT angiography not only visualizes the lumen but also the arterial wall. Because the strong relationship between the CAC score and coronary events is mediated predominantly by coexisting noncalcified or less calcified vulnerable plaques, total or noncalcified plaque burden detected by CT angiography may prove to be an even better marker of risk than the CAC score.[58,97]

Intravascular ultrasound (IVUS) can detect and localize plaque as well as quantitate plaque burden, but it requires selective catheterization and motorized pullback in the arteries of interest. Serial examinations of well-defined coronary segments have been used to monitor the speed of plaque progression (or regression) over time in patients with established CHD.[98]

DISEASE ACTIVITY

Imaging inflammation in atherosclerosis serves two different purposes: detecting vulnerable patients (systemic activity) or vulnerable plaques of the rupture-prone type (focal activity). Because atherosclerosis is an innate inflammatory disease, inflammatory activity is not confined to just a few atherosclerotic lesions but is present, more or less, in all such lesions throughout the body.[18,19] In contrast, vulnerable plaques are relatively rare,[49] and inflammation plays a causal role in plaque rupture only if the microstructure of the plaque is permissive for rupture (TCFA) (see Fig. 32–5), as described in Plaque Vulnerability.

With its high sensitivity, positron emission tomography (PET) imaging using fluorine-18-fluorodeoxyglucose (FDG) has evolved as a promising method for the detection of arterial inflammation when combined with higher-resolution CT or magnetic resonance imaging to help localizing the signal to the arterial wall.[99-101] With adequate suppression of myocardial FDG uptake using a low-carbohydrate, high-fat diet rather than a fasting protocol, coronary FDG uptake was recently identified in a large proportion of cancer patients undergoing invasive coronary angiography because of suspected or manifest ischemic heart disease.[102]

In carotid atherosclerosis, proof-of-concept studies, focusing on symptomatic or stenotic carotid plaques, have documented a positive correlation between FDG uptake and macrophage density.[103,104] Other studies have revealed widespread FDG uptake in asymptomatic plaques and arterial segments unlikely to harbor vulnerable plaques, and FDG uptakes among different arteries in the same person correlate strongly.[99,100] In asymptomatic persons undergoing ultrasound screening for carotid artery disease, as many as 30% of ultrasound-defined atherosclerotic arteries and 10% of normal arteries accumulated FDG,[105] supporting the current understanding that FDG-defined inflammation may be used to assess systemic disease activity unrelated to plaque vulnerability. Arterial inflammation defined by FDG-PET imaging appears to be dynamic and modifiable by a healthier lifestyle and short-term statin treatment.[106-108] In a population of stable cancer patients, extensive arterial FDG accumulation was associated with recent and/or near-term cardiovascular events,[109] supporting the "vulnerable patient" concept.[110] Contrast-enhanced magnetic resonance imaging is also able to detect plaque inflammation, but its sensitivity is much lower than that of nuclear imaging.[111]

PLAQUE VULNERABILITY

Inflammation is not common in plaque erosion and not enough to make a vulnerable plaque of the most common type, the TCFA, where the microstructure of the plaque needs to be permissive for plaque rupture (see Figs. 32–3 through 32–5).[25,45] No distinct morphologic feature characterizes the erosion-prone type of vulnerable plaque (see Fig. 32–6).[4] Consequently, useful targets for imaging of erosion-prone plaques remain elusive. In contrast, the TCFA has a distinct microstructure, including a large necrotic core covered by a thin and inflamed fibrous cap, and other characteristic plaque features are common, such as a big-size, expansive remodeling, neovascularization (angiogenesis), and a spotty pattern of calcification (see Fig. 32–7).[25,45]

Although inflammation most likely plays a causal role in plaque rupture, it does not necessarily imply that inflammation also is a useful target for the detection of plaques assumed to be rupture-prone, such as TCFA. A unique feature of TCFA is the location of inflammation within the plaque rather than the overall severity of plaque inflammation. In coronary TCFA, the macrophage density within the thin and disrupted fibrous cap is high (~14%),[56] but the whole-plaque macrophage density is only 2.0% ± 1.9% (mean ± SD) versus 1.1% ± 1.5% in "stable" fibroatheromas.[27] These low values and the substantial overlap, indicated by the large SDs, probably preclude the use of plaque inflammation as a useful standalone marker of vulnerability (see Fig. 32–5).

Coronary CT angiography may not only visualize the lumen and detect obstructive and nonobstructive plaques, it may also quantify calcified and noncalcified plaque burden. Furthermore, coronary CT angiography may also provide additional prognostic information by detection of higher-risk plaques characterized by large plaque volume, low CT attenuation, napkin-ring sign, expansive remodeling, and spotty calcification.[112,113]

Many catheter-based technologies have been developed or are under development for the assessment of coronary atherosclerosis and vulnerable plaques, including conventional grayscale IVUS, virtual histology IVUS and other ultrasound-based tissue characterization modalities, optical coherence tomography, angioscopy, near-infrared spectroscopy, intracoronary magnetic resonance imaging, thermography, and vascular profiling.[114-117] Because vulnerable coronary plaques of the rupture-prone type (TCFA) are relatively large, not numerous, and often cluster proximally in the major coronary arteries, their detection in patients undergoing percutaneous coronary interventions might be feasible.[49]

THE VULNERABLE PATIENT

Although vulnerable (thrombosis-prone) coronary plaques must exist, the critical question is whether timely identification and targeted

treatment of such lesions are possible and can reduce the risk for a future atherothrombotic event. Despite major advancements in imaging technology that allow visualization of plaque features assumed to confer vulnerability, the clinical benefit of searching for vulnerable plaques remains to be documented.[118] Considering the multifocal nature of atherosclerosis and the complex interaction between plaque size, plaque composition, local flow disturbances, and the actual susceptibility to thrombosis, trying to predict the fate and the clinical impact of a particular plaque may be futile.[118,119] Atherosclerosis is a systemic disease calling for a systemic approach, focusing on cardiovascular risk factors and the overall burden of disease to ensure appropriate identification and treatment of those who are at highest risk, the so-called *vulnerable patients*.[110,120]

CONCLUSION

Thrombosis-prone atherosclerotic plaques, also known as high-risk or vulnerable plaques, are the main cause of death and severe disability worldwide. Although causal risk factors are known and constitute important therapeutic targets, their usefulness in risk assessment and finding people at risk for an atherothrombotic event is limited. Most heart attacks and strokes occur in people who are not identified as being at particular high risk by conventional risk factor scoring. Atherothrombotic events are, however, always preceded by a long preclinical phase in which subclinical atherosclerosis evolves and can be detected by noninvasive imaging, offering unique opportunities for timely and individualized preventive care. The utility of such an imaging-based approach in the primary prevention of atherothrombotic events is being evaluated in the Progression of Early Subclinical Atherosclerosis (PESA) study[15] and the BioImage study.[16]

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CHAPTER 33

CORONARY THROMBOSIS: LOCAL AND SYSTEMIC FACTORS

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ROLE OF SYSTEMIC FACTORS IN THE REGULATION OF CORONARY THROMBOSIS / 889

SUMMARY / 891

The formation of an acute thrombus on a ruptured coronary atherosclerotic lesion, obstructing coronary blood flow and reducing the oxygen supply to the myocardium, leads to the onset of acute coronary syndromes (ACS). These thrombotic episodes largely occur in response to atherosclerotic lesions that have progressed to a high-risk inflammatory or prothrombotic stage. Although they are distinct from one another, the atherosclerotic and thrombotic processes appear to be closely related, causing ACS through a complex, multifactorial process called *atherothrombosis*. ACS represents a spectrum of ischemic myocardial events that share similar pathophysiology; these include unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI), ST-segment elevation myocardial infarction (STEMI), and sudden cardiac death.

Atherosclerosis is a systemic disease involving the intima of large and medium-sized arteries, including the aorta, carotids, coronaries, and peripheral arteries, that is characterized by intimal thickening caused by the accumulation of cells and lipids (Fig. 33–1).[1] Lipid accumulation results from an imbalance between the mechanisms responsible for the influx and efflux of lipids into the arterial wall.[2] Secondary changes may occur in the underlying media and adventitia, particularly in advanced disease stages. The early atherosclerotic lesions might progress without compromising the lumen because of compensatory vascular enlargement (Glagovian remodeling).[3] Importantly, the culprit lesions leading to ACS are usually mildly stenotic and therefore barely detected by angiography.[4] These high-risk, rupture-prone lesions usually have a large lipid core, a thin fibrous cap, and a high density of inflammatory cells (particularly at the shoulder region, where disruptions most often occur).

Recent evidence has highlighted the importance of lesion neovascularization and blood extravasation in plaque destabilization and plaque growth.[5-7] Leaky vasa vasorum with the subsequent red blood cell extravasation has been postulated as a major source for intraplaque cholesterol deposition. This change in composition, characterized by increased extracellular cholesterol within the lipid core and excessive macrophage infiltration, increases the vulnerability of the atherosclerotic lesions. In fact, postmortem studies have shown a strong correlation between macrophage infiltration and increased vasa vasorum in human atherosclerotic lesions. Preexisting vasa vasorum in the adventitia is thought to spread into the intima, prompting intimal neovascularization.[6] A recent study using optical coherence tomography has associated vasa vasorum increase with fibrous plaque volume and intraplaque neovessels with plaque vulnerability.[8] These observations suggest that imaging for microvasculature could become a new biomarker for plaque vulnerability. On the other hand, inhibition of plaque neovascularization could be seen as a potential new therapeutic intervention to prevent plaque disruption.

Inflammation is another important process that affects plaque progression, vulnerability, and subsequent thrombus formation. Inflammation could be considered as the link between atherosclerosis and thrombosis. In fact, the relationship of inflammation and atherothrombosis could represent different faces of the same disease. Most of the studies on inflammation and cardiovascular disease have been based on the effects of inflammatory cyto/chemokines without paying the deserved attention to their cellular sources. Recent studies are bringing light to the key role played by leukocytes and platelets as sources of proinflammatory cytokines. Inflammatory cells (monocyte/macrophages, T cells, and mast cells) are present in the core and shoulder of atherosclerotic lesions. Many of the cells exhibit signs of activation and release inflammatory cytokines and matrix metalloproteinases (MMPs) that affect each step of atherosclerosis from lesion formation, to progression, to disruption and ACS. The circulating monocytes are recruited within the subendothelial space in response to the synthesis and exposure of adhesive proteins (eg, selectins, monocyte chemotactic protein [MCP]-1) triggered by the early accumulation of lipids. The internalized monocytes release inflammatory mediators that maintain the monocyte recruitment favoring lesion progression. The presence of growth factors, such as the macrophage colony-stimulating factor, facilitates the replication of these cells and their transformation into macrophages. Several factors, such as netrin-1 and vascular cell adhesion molecule-1, or VCAM-1, are responsible for their retention in the lesions. The attenuation of the proatherogenic state, as occurs in conditions characterized by high-density lipoprotein (HDL)-raising or low-density lipoprotein (LDL)-lowering by statins, seems to facilitate the efflux of the wall macrophages. Whether it is due to reduced levels of the retaining factors or systemic lipid lowering is not clear yet.[9]

The monocyte/macrophage system includes the most representative cells of the *innate immunity* via the scavenger and Toll-like receptors. Innate immunity does not require "previous education" but only recognizes a few hundred antigens. Monocytes, dendritic cells, and mast cells are the major players in the innate immunity (Fig. 33–2). Mast cells are inflammatory by releasing histamine, leukotrienes, interleukin (IL)-6, and interferon (IFN)-gamma. Dendritic cells are responsible for antigen presentation via human leukocyte antigen (HLA) molecules CD80/86 and CD40. Monocytes are divided into two major types according to their expression of CD14 and CD16. Those expressing CD14+/CD16$^-$, also known as "classic" or Mon 1, are the most abundant subtype. They express CCR2 (receptor for MCP-1), CD62L, CD64, and CD115, but not CXCR1, and they perpetuate the inflammatory status by releasing reactive O_2 species, tumor necrosis factor (TNF), IL-1, and other inflammatory cytokines. A second subtype is the CD14+/CD16++, Mon 3, also called "nonclassic" or resident. These do not express CCR2 or CD64 but express CXCR1 (receptor for fractalkine). They release transforming growth factor-beta, CD-36, CD163, and the angiogenic factor vascular endothelial growth factor. They are less

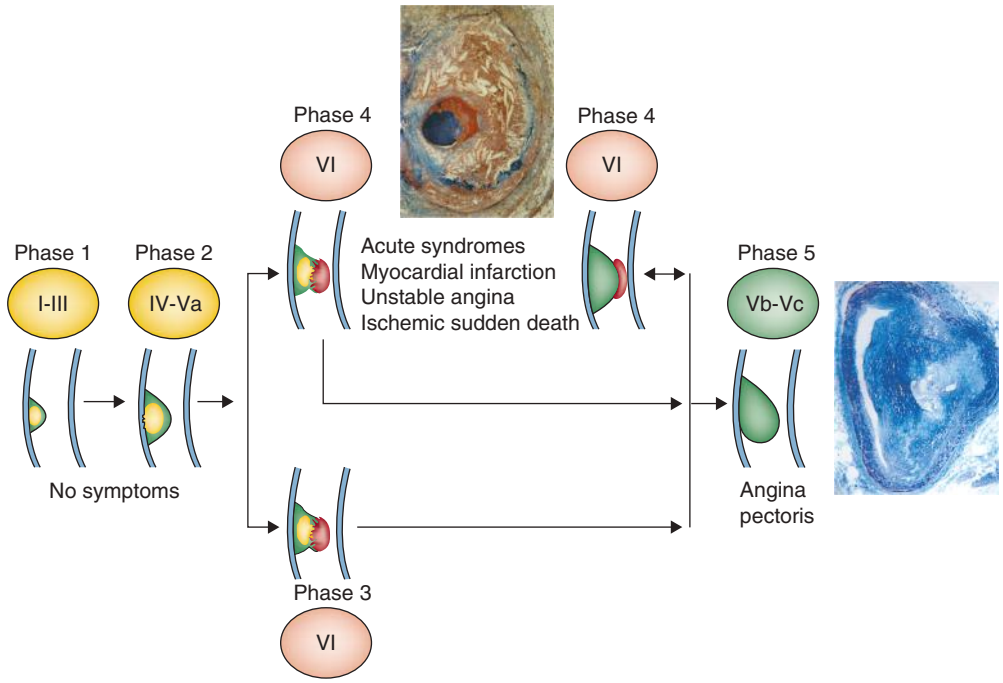


FIGURE 33–1. Simplified diagram of the evolution of coronary atherosclerosis. Phases and morphology of lesion progression.

inflammatory and responsible for metabolic tissue repair. A recently described subtype is the CD14++/CD16+, Mon 2, also called intermediate. These express high levels of CCR2, CX3CR1, and CDS115, but not CD62. Their role is still not well understood, although they may play an inflammatory role.[9,10]

The *acquired immunity* is more modern from an evolutionary view. It is very specific and recognizes millions of antigens but requires "previous education." This makes it similar to vaccines, which require weeks of prior generating antibodies. It is involved in the interactions between lymphoids with the dendritic and lymphatics of the atherosclerotic lesions.[11] Lymphoids, CD4, and the helper T cells are involved in cellular responses while lymphocyte B is responsible for antibody release. Among the T-lymphocytes, the Th1, and 17 lineages release IFN-gamma while regulatory T cells (Treg) are anti-inflammatory (Fig. 33–3). The possibility of modulating the adaptive immune system may be seen as a novel therapeutic target to treat atherosclerosis.[12] Studies are ongoing into the development of vaccines that could effectively interfere with the proportion of pro- and anti-inflammatory cells

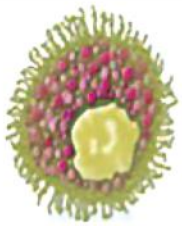
Monocytes		Dendritic cells	Mast cells	Activated platelets
				
Ly6C/GR-1 positive TLRs Proteases Redox species TNF IL-1 Cytokines	Ly6C/GR-1 negative TGF-β CD36 SR-A CD163 VEGF	HLA molecules CD80/86 CD40	Histamine Leukotrienes Chymase IL-6 Interferon	CD40L RANTES MRP-8/14 PDGF TGF-β
Pro-inflammatory	**Anti-inflammatory?**	**Antigen presentation**	**Inflammatory**	**Hemostasis**

FIGURE 33–2. Major cell players involved in innate immunity. Note the two subsets of monocytes; the Ly6C/GR-1 considered proinflammatory and Ly6C/GR1 negative are anti-inflammatory. The dendritic cells play a key role in the antigen presentation, triggering the response of the adaptive immunity. Activated platelets play also a key role via the release of several inflammatory substances. Ly6C/GR-1, lymphocyte antigen 6 complex, locus C1; TLRs, toll-like receptors; TNF, tumor necrosis factor; IL-1, interleukin-1; TGF, tumor necrosis factor; CD36, cluster differentiation 36; SR-A, scavenger receptor A; CD163, cluster differentiation163; VEGF, vascular endothelial growth factor; HLA, human leukocyte antigen; CD80/86, Cluster differentiation80/86 CD40, cluster differentiation40; IL-6, interleukin-6; CD40L, cluster differentiation40 ligand; RANTES, regulated on activation, normal T expressed and secreted; MRP-8/14, migration inhibitory factor-related protein 8/14; PDGF, platelet derived growth factor.

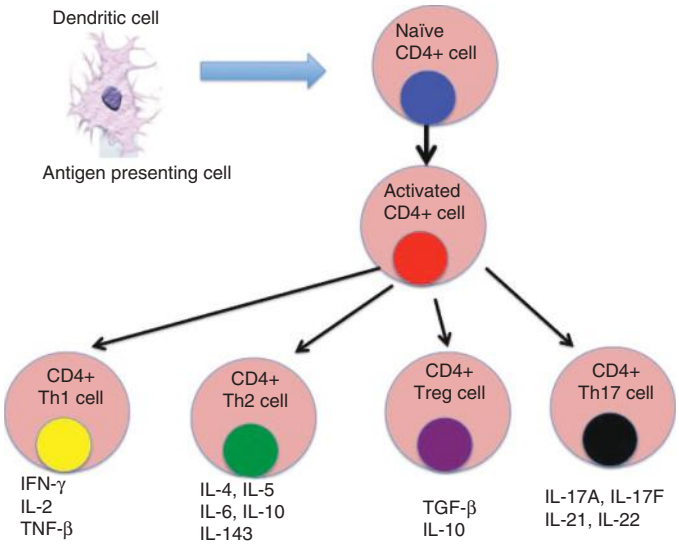


FIGURE 33–3. Normal physiology of the adaptive immune response. The antigen-presenting cells (APCs, dendritic cells and macrophages) activate the CD4+ cells by binding MHC-2 to the T-cell receptor of the CD4+ naïve cells. The combination of APCs with another activators (CD80 and/or CD86 molecules) trigger the differentiation of the helper T cells (Th) into the different subsets shown in the figure and the pattern of cytokine released by each differentiated cell. CD, cluster differentiation; Th1 cell, type 1 T cells; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; Treg cell, regulatory T cell; Th2 cell, type 1 T cells; Th17 cell, type 1 T cells; MHC-2, major histocompatibility complex class 2.

in the lesions and the secretion of protective antibodies while affecting the general host defense.[13] T cells constitute 10% of all cells in human lesions. Seventy percent of T cells are described to be CD4+ and the remainder CD8+. Most of the CD4+ cells are T helper 1 (Th1) and a major source of INF-gamma and TNF and thus estimated to be inflammatory. Other T cells, including Th2, Treg, Th17, and natural killer T cells, account for 85% of the total monocyte in the atherosclerotic lesions, while only 10% to 15% could be considered anti-inflammatory.

Inflammation is beginning to be a potential therapeutic target for atherosclerosis without significant success so far.[11,12] One of the major problems for anti-inflammatory strategies as treatment for atherosclerosis is that, so far, all the considered "anti-inflammatory" approaches have also affected plasma lipid levels (eg, statins). Recent advances in the understanding of the pathophysiology of the inflammatory pathways may lead to more success. In fact, several ongoing trials with specific anti-inflammatory interventions—the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (NCT01327846) studying canakinumab and the cardiovascular inflammation reduction trial (CIRT) (NCT 02576067) studying low-dose methotrexate—are testing the effectiveness of this novel approach.

Chronic inflammatory diseases are associated with an increased risk of cardiovascular disease. The role of inflammation as an important proatherosclerotic factor is illustrated by the increased cardiovascular risk exhibited by chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, as well as with infections such as periodontal disease and human immunodeficiency virus (HIV).[3,14,15] There is an abundance of evidence, mostly from imaging studies, supporting an association between inflammation and calcium deposition, but the question still unanswered is whether inflammation precedes calcification or rather calcification triggers inflammation.[16]

Platelets also play an important role in the inflammatory environment. Although formerly, platelets were suggested to be passive players because they are organelles lacking nuclei, currently we know that they are very active, being important not only in thrombosis itself but also in perpetuating the inflammatory environment. Platelets secrete various vasoactive chemokines and cytokines. These include CD40L; thrombospondin; platelet-activating factor; regulated on activation, normal T-cell expressed and secreted (RANTES); epithelial-derived neutrophil-activating peptide 78 (ENA-78); macrophage inflammatory protein (MIP); and hemokine (C-X-C motif) ligand 4 (CXCL4), with autocrine and paracrine effects. Also very important is the notion that free cholesterol, a major component of atherosclerotic plaques, is one the most inflammatory substances triggering the recruitment of more macrophages. Therefore, inflammation plays a dual role in atherothrombosis both at the vascular and circulating levels.[17]

A reliable, noninvasive imaging tool able to detect early atherosclerotic disease and characterize lesion composition would be clinically advantageous. Although magnetic resonance imaging (MRI) has been widely tested for plaque composition analysis, other imaging techniques, such as computed tomography (CT) and radionuclide imaging (positron emission tomography [PET]),[18-22] have recently been used for this enterprise.

All the molecular knowledge gathered on the biochemical and molecular processes involved in the genesis and progression of atherosclerosis have been incorporated into the imaging techniques generating the concept of molecular imaging for a more specific and better characterization of atherosclerotic lesions. Studies from the multi-ethnic study of atherosclerosis (MESA) trial suggest adding coronary artery calcium to the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines to improve subjects statin eligibility for statin therapy.[23]

Growing thrombi on atherosclerotic vessels may occlude the lumen locally or embolize and be washed away by the blood flow to occlude distal vessels. However, thrombi may be physiologically or spontaneously lysed by mechanisms that block thrombus propagation. Thrombus size, location, and composition are regulated by local fluid dynamic conditions (mechanical effects), the thrombogenicity of exposed substrate (local molecular effects), the relative concentration of fluid phase and cellular blood components (local cellular effects), and the efficiency of the physiologic mechanisms of control of the system, mainly fibrinolysis. Similarly, the size and stability of the thrombus are major modulators of the severity of the ACS.[1,7]

CELLULAR AND MOLECULAR MECHANISMS IN THROMBUS FORMATION

Although several decades ago the endothelium was viewed as a simple barrier separating the fluid phase of the blood from the highly thrombogenic smooth muscle vascular wall, today we know that the endothelium is a critical player in the maintenance of the normal function of the arterial bed. The endothelium (endothelial cells) constantly secretes substances (eg, hormones, growth factors) into the vascular lumen to maintain vascular tone and to avoid abnormal platelet adhesion or activation and clot formation. When the endothelium is damaged and cannot perform this crucial task, it is dysfunctional. Endothelial dysfunction, as well as a discontinuity of the endothelial integrity, triggers a series of biochemical and molecular reactions aimed at preventing excessive blood loss and repairing the vessel wall. Vasoconstriction and platelet adhesion at the site of injury combine to form a hemostatic aggregate as the first step in vessel wall repair and the hemostasis. A few platelets may interact with injured and dysfunctional endothelium and release growth factors that stimulate intimal hyperplasia. Several layers of platelets may be deposited on the lesion with mild injury and may or may not evolve to become a mural thrombus (Fig. 33-4). The release of platelet growth factors may contribute significantly to accelerated intimal hyperplasia, as occurs in the coronary vein grafts within the first postoperative year. With severe injury and exposure of components

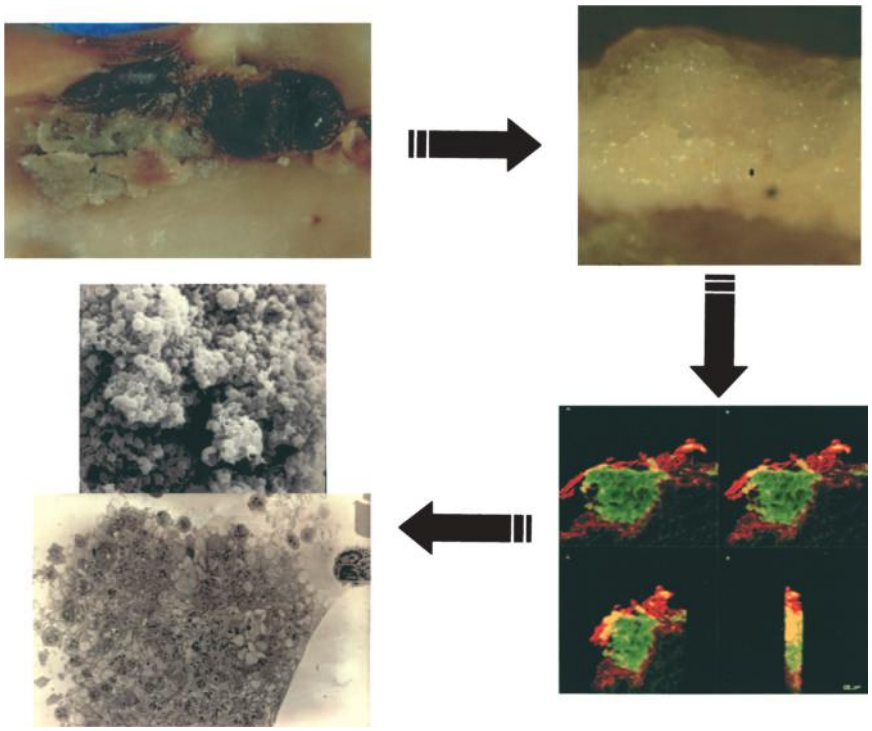


FIGURE 33–4. Images of thrombosis—from naked eye observation to immunohistochemistry (*green*, platelets; *red*, fibrinogen) and electronic microscopy (*top*, scanning; *bottom*, transmission).

of deeper layers of the vessel, as in spontaneous plaque rupture and in angioplasty, marked platelet aggregation with mural thrombus formation follows. Vascular injury of this magnitude also stimulates thrombin formation through both the intrinsic (surface-activated) and extrinsic (tissue factor [TF]–dependent) coagulation pathways (see Fig. 33–3).

PLATELETS

Platelets are anucleated cells (2 μm in diameter) that are devoid of genomic DNA but contain messenger RNA and have the capability of synthesizing proteins. They are cytosolic fragments of bone marrow–derived megakaryocytes and they have a life span of 7 to 10 days under normal conditions. Plaque rupture facilitates the interaction of the inner plaque components with the circulating blood.[24] Among these components, TF exhibits a potent activating effect on platelets and coagulation. There is now understanding of the biochemical events involved in platelet activation. At the site of vascular lesions, circulating von Willebrand factor (vWF) binds to the exposed collagen that subsequently binds to the glycoprotein (GP) Ib/IX receptor on the platelet membrane. Under pathological conditions and in response to changes in shear stress, vWF can be secreted from the storage organelles in platelets or endothelial cells, reinforcing the activation process. Although GP Ib/IX–vWF interaction is enough to promote binding of platelets to subendothelium, it is highly transient, resulting in rapid dislocation of platelet from the site of injury. GP VI binding to matrix collagen has slower binding kinetics, but when initiated, it promotes a firm adhesion of platelet to the vessel surface.[25] Figure 33–5 shows mechanisms and agonists involved in platelet adhesion, activation, and aggregation.[26] Finally, both GP Ib/IX and GP VI also regulate platelet-leukocyte adhesion and thereby are implicated in other vascular processes, such as inflammation and atherosclerosis.[27-29] Exposed matrix from the vessel wall and thrombin generated by activation of the coagulation cascade, as well as epinephrine and adenosine diphosphate (ADP), are powerful platelet agonists. Each agonist stimulates the discharge of calcium and promotes the subsequent release of its granular content. Platelet-related ADP and 5-hydroxytryptamine (5-HT) stimulate adjacent platelets, further enhancing the process of platelet aggregation. Arachidonate, which is released from the platelet membrane by the stimulatory effect of collagen, thrombin, ADP, and 5-HT, promotes the synthesis of thromboxane A_2 (TXA_2) by the sequential effects of cyclooxygenase (COX) and thromboxane synthetase. TXA_2 not only promotes further platelet aggregation but is also a potent vasoconstrictor (Fig. 33–6; see also Fig. 33–5). The initial recognition of damaged vessel wall by platelets involves (1) adhesion, activation, and adherence to recognition sites on the thromboactive substrate (extracellular matrix [ECM] proteins such as vWF, collagen, fibronectin, vitronectin, and laminin); (2) spreading of the platelet on the surface; and (3) aggregation of platelets to form a platelet plug or white thrombus.

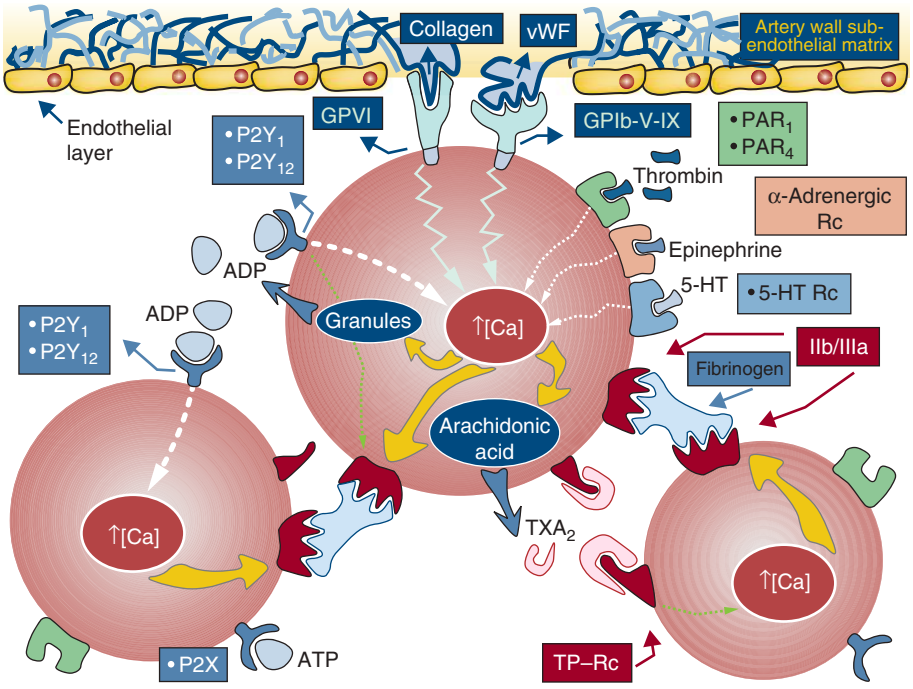


FIGURE 33–5. Mechanisms and agonists involved in platelet adhesion, activation, and aggregation. ATP, adenosine triphosphate; GP, glycoprotein; 5-HT, 5-hydroxytryptamine; PAR, protease-activated receptor; TP, thromboxane receptor, TXA, thromboxane; vWF, von Willebrand factor. Reproduced with permission from Ibanez B, Vilahur G, Badimon J: Pharmacology of thienopyridines: rationale for dual pathway inhibition. *Eur Heart J Suppl*. 2006;8(Suppl G):G3-G9.

Figure 33–5 shows the processes implicated in the formation of a thrombus on a plaque disruption.[26] The efficiency of platelet recruitment depends on the underlying substrate and local geometry (local factors). A final step involving the recruitment of other blood cells also occurs; erythrocytes, neutrophils, and occasionally monocytes are found on evolving mixed thrombus.

Platelet function depends on the adhesive interaction of several compounds. Most of the GPs on the platelet membrane surface are receptors for adhesive proteins. Many of these receptors have been identified, cloned, sequenced, and classified within large gene families that mediate a variety of cellular interactions (Table 33–1). The most abundant is the integrin family, which includes GP IIb/IIIa, GP Ic/IIa, the fibronectin receptor, and the vitronectin receptor, in decreasing order of magnitude. Another gene family present in the platelet membrane glycocalyx is the leucine-rich GP family represented by the GP Ib/IX complex, receptor for vWF, on unstimulated platelets that mediates adhesion to subendothelium and GP V. Other genes include the selectins (such as GMP-140) and the immunoglobulin domain protein (HLA class I antigen and platelet/endothelial cell adhesion molecule 1. Unrelated to any other gene family is GP IV (IIIa) (see Table 33–1).

TABLE 33–1. Platelet Membrane Glycoprotein Receptors

Glycoprotein Receptor	Function	Ligand
GP IIb/IIIa	Aggregation, adhesion at high shear rate	Fg, vWF, Fn, Ts, Vn
Receptor Vn	Adhesion	Vn, vWF, Fn, Fg, Ts
GP Ia/IIa	Adhesion	C
GP Ic/IIa	Adhesion	Fn
GP IcN/IIa	Adhesion	Ln
GP Ib/IX	Adhesion	vWF, T
GP V	Unknown	Substrate T
GP IV (GP IIIb)	Adhesion	Ts, C
GMP-140 (PADGEM)	Interaction with leukocytes	Unknown
PECAM-1 (GP IIa)	Unknown	Unknown

Abbreviations: C, collagen; Fg, fibrinogen; Fn, fibronectin; Ln, laminin; PECAM-1, platelet endothelial cell adhesion molecule 1; Ts, thrombospondin; Vn, vitronectin; vWF, von Willebrand factor.

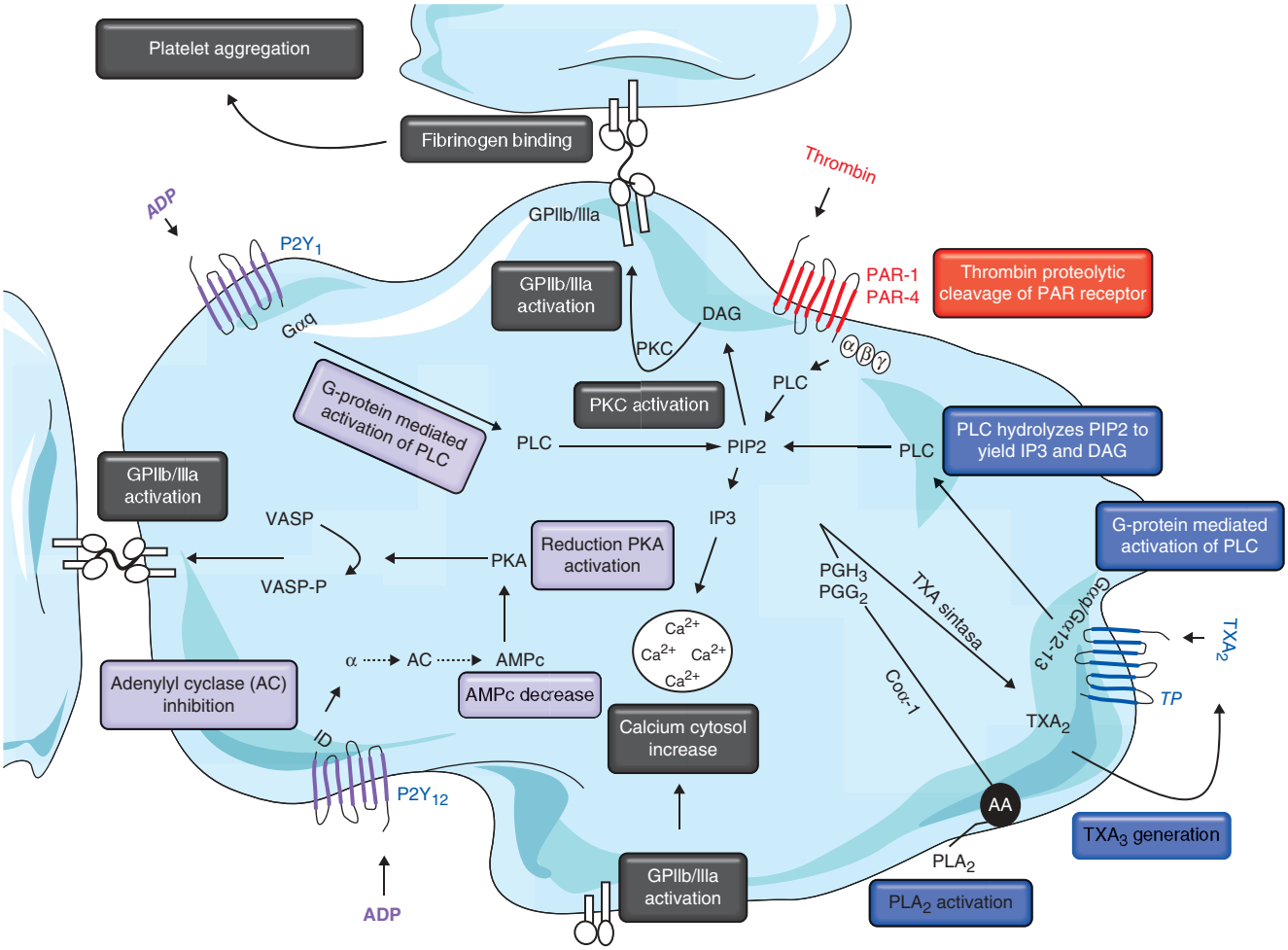


FIGURE 33–6. Signal transduction mechanisms of platelet activation and aggregation. AA, arachidonic acid; ADP, adenosine diphosphate AMP, adenosine 3′5′-cyclic monophosphate; ATP, adenosine triphosphate; DG, diacylglycerol; Gs, Gi, Gp, Gq, guanine nucleotide-binding regulatory proteins; 5HT, 5-hydroxytryptamine; IP3, inositol 1,4,5-triphosphate; PGI2, prostacyclin; PIP2, phosphoinositol diphosphate; PKCi and PKCa, protein kinase C, inactivated and activated; PLA2, phospholipase A2; PLC, phospholipase C; IIb/IIIa, receptor glycoprotein for adhesive protein ligands (mainly fibrinogen and vWF); TXA_2, thromboxane A_2. Reproduced with permission from Badimon L, Vilahur G: Thrombosis formation on atherosclerotic lesions and plaque rupture. *J Intern Med.* 2014 Dec;276(6):618-632.[17]

Randomly distributed on the surface of resting platelets are about 50,000 molecules of GP IIb/IIIa. The complex is composed of one molecule of GP IIb (disulfide-linked large and light chains) and one of GP IIIa (single polypeptide chain). It is a Ca^{2+}-dependent heterodimer, noncovalently associated on the platelet membrane. Calcium is required for maintenance of the complex and for binding of adhesive proteins. On activated platelets, the GP IIb/IIIa is a receptor for fibrinogen, fibronectin, vWF, vitronectin, and thrombospondin.

The GP Ib/IX complex consists of two disulfide-linked subunits (GP Ibα and GP Ibβ) tightly (not covalently) complexed with GP IX in a 1:1 heterodimer. GP Ibβ and GP IX are transmembrane GPs and form the larger globular domain. The elongated, protruding part of the receptor corresponds to GP Ibα. The major role of GP Ib/IX is to bind immobilized vWF on the exposed vascular subendothelium and initiate adhesion of platelets. GP Ib does not bind soluble vWF in plasma; apparently, it undergoes a conformational change on binding to the ECM and then exposes a recognition sequence for GP Ib/IX. The cytoplasmic domain of GP Ib/IX has a major function in linking the plasma membrane to the intracellular actin filaments of the cytoskeleton and functions to stabilize the membrane and to maintain the platelet shape.

Thrombin plays an important role in the pathogenesis of arterial thrombosis. It is one of the most potent known agonists for platelet activation and recruitment. In addition, thrombin is critical in the maintenance of the fibrin mesh. The thrombin receptor has 425 amino acids with seven transmembrane domains and a large NH_2-terminal extracellular extension that is cleaved by thrombin to produce a "tethered" ligand that activates the receptor to initiate signal transduction.[27] Thrombin is a critical enzyme in early thrombus formation, cleaving fibrinopeptides A and B from fibrinogen to yield insoluble fibrin, which effectively anchors the evolving thrombus. Both free and fibrin-bound thrombin are able to convert fibrinogen to fibrin, allowing propagation of thrombus at the site of injury (Fig. 33-7).

Therefore, platelet activation triggers intracellular signaling and expression of platelet membrane receptors for adhesion and initiation of cell contractile processes that induce shape change and secretion of the granular contents. The expression of the integrin IIb/IIIa ($\alpha IIb\beta_3$) receptors for adhesive GP ligands (mainly fibrinogen and vWF) in the circulation initiates platelet-to-platelet interaction. The process is perpetuated by the arrival of platelets from the circulation. Most of the GPs in the platelet membrane surface are receptors for adhesive proteins or mediate cellular interactions. vWF has been shown to bind to platelet membrane GPs in both adhesion (platelet-substrate interaction) and aggregation (platelet-platelet interaction), leading to thrombus formation, as seen in perfusion studies conducted at high shear rates.[28] Ligand binding to the different membrane receptors triggers platelet activation with different relative potencies. Great interest in the platelet ADP receptors (P2Y, P2X) has recently been generated because of available pharmacologic inhibitors. The P2Y1 receptor is responsible for inositol trisphosphate formation through activation of phospholipase C, leading to transient increase in the concentration of intracellular calcium, platelet shape change, and weak transient platelet aggregation.[29,30] Pharmacologic data have revealed an essential role for the P2Y1 receptor in the initiation of platelet ADP-induced activation, TXA_2 generation, and platelet activation in response to other agonists. The P2Y12 receptor is responsible for completion of the platelet aggregation response to ADP. There are several signaling molecules downstream of P2Y12 activation, including cAMP, vasodilator-stimulated phosphoprotein dephosphorylation, phosphoinositide 3-kinase, and Rap1B. Pharmacologic approaches have shown a role for the P2Y12 receptor in dense granule secretion, fibrinogen-receptor activation, P-selectin expression, and thrombus formation, identifying it as a central mediator of the hemostatic response. Both P2Y12 and P2Y1 are indirectly involved in platelet P-selectin exposure and formation of platelet-leukocyte conjugates, which leads to leukocyte-TF exposure.[31-35] Although not activated by ADP, platelets possess a third purinergic receptor (P2X1), which is a fast adenosine triphosphate (ATP)-gated calcium channel receptor mainly involved in platelet shape change. Figure 33–8 shows in detail the platelet purinergic receptors. The most recent advances in antiplatelet therapy related to the inhibition of the P2Y12 receptors are focused on the availability of faster acting and reversible inhibitors.[36,37]

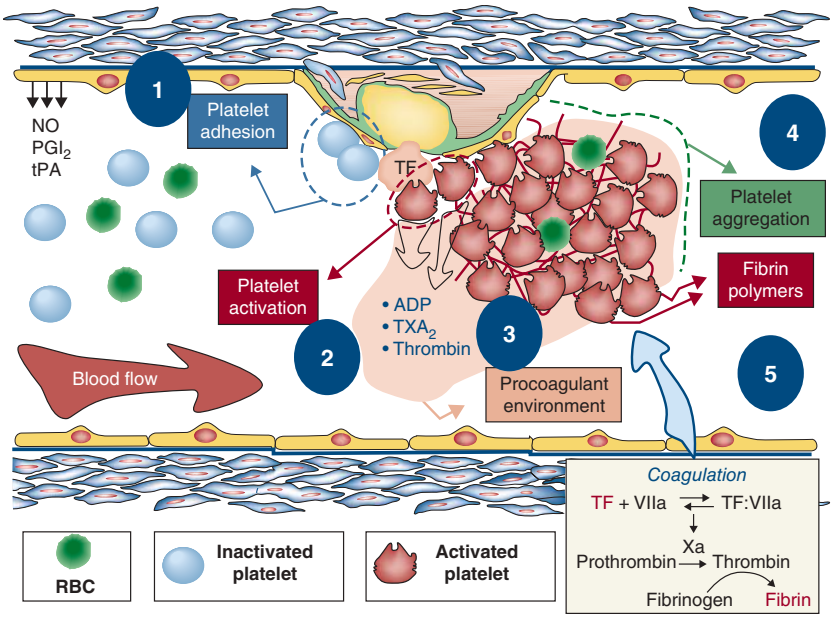


FIGURE 33–7. Mechanism involved in thrombus formation. Healthy endothelium (*left*) presents antithrombotic properties because it is able to release vascular protective substances such as nitric oxide (NO), prostacyclin (PGI_2), tissue plasminogen activator (tPA), and tissue factor pathway inhibitor (TFPi). On the contrary, dysfunctional endothelium (*right*) not only favors platelet adhesion, activation, and aggregation but also promotes vascular lipid deposition, macrophage migration, and tissue factor (TF) expression (activation of the coagulation cascade). After platelet adhesion, activation is characterized by platelet shape change. Activated platelets secrete different agonists, prompting activation of circulating platelets and a procoagulant environment. This prothrombotic milieu favors thrombus formation and the subsequent clinical manifestations. ADP, adenosine diphosphate; RBC, red blood cell; TXA_2, thromboxane A_2. Reproduced with permission from Ibanez B, Vilahur G, Badimon J: Pharmacology of thienopyridines: rationale for dual pathway inhibition. *Eur Heart J Suppl*. 2006;8(Suppl G):G3-G9.

Dual antiplatelet therapy, with aspirin, a platelet COX-1 inhibitor, and P2Y12 receptor blocker, remains a major drug strategy to prevent ischemic event occurrence in patients with ACS and in patients undergoing coronary stenting. The new P2Y12 receptor blockers, prasugrel and ticagrelor, have been shown to have an enhanced benefit on the prevention of atherothrombotic events when compared with clopidogrel in patients with ACS. However, despite these improvements, there are still a significant number of events still taking place. A recent article reported the antithrombotic effects of the synergistic inhibition of both P2Y1 and P2Y12 ADP receptors; given the intravenous formulation of this agent, the authors suggested that this dual inhibitory agent could serve as a promising strategy in the initial phases of ACS.[37] Other strategies focusing on additional targets have been investigated. One of these potential targets is thrombin. Thrombin is not only the most potent agonist

of platelet aggregation and degranulation but also plays a major role in the conversion of fibrinogen into fibrin and the maintenance of the formed thrombus. Thrombin activates platelets by cleaving platelet protease activated receptors (PARs). The thrombin effect on platelets is mostly mediated via PAR-1 and PAR-4. Blockade of PAR-1 receptor blockade by specific inhibitors, such as vorapaxar, results in the inhibition of thrombin-induced platelet signaling and in platelet function inhibition.[38]

COAGULATION SYSTEM

During plaque rupture, flowing blood interacts with inner components of the lesions, TF being among them. In addition to the TF located in the plaques, there is robust evidence of the existence of a bloodborne circulating TF. Such circulating TF is found in monocytes and small microparticles (MPs). It has been shown that leukocytes may transfer TF-enriched MP platelets by the Cd15 and platelet P-selectin interaction. These interactions contribute to a high local TF concentration in the disrupted area. One issue yet to be clarified is the individual contribution of the TF from the plaque versus the contribution of systemic TF to thrombus formation.[1,7]

The blood coagulation system involves a sequence of reactions integrating zymogens (proteins susceptible to activation into enzymes via limited proteolysis) and cofactors (nonproteolytic enzyme activators) into three groups: (1) the contact activation (generation of factor XIa via the Hageman factor), (2) the conversion of factor X to factor Xa in a complex reaction requiring the participation of factors IX and VIII, and (3) the conversion of prothrombin to thrombin and fibrin formation[39] (Fig. 33–9).

Citrate is calcium Quelant frequently used in studies of platelet–vessel wall interaction. Its anticoagulant properties are based on its action over calcium. It not only blocks the coagulation cascade because the coagulation reactions do not proceed further than the activation of factor XI because of their dependence on Ca^{2+} but also inhibits platelet activation because of the central role of calcium in platelet activation (see Fig. 33–5). Platelets may provide the membrane requirements for the activation of factor X, although the participation of cells of the vessel wall (in exposed injured vessels) has not been excluded. As such, endothelial cells in culture have been shown to support the activation of factor X. Factor VIII forms a noncovalent complex with vWF in plasma, and its function in coagulation is the acceleration of the effects of IXa on the activation of X to Xa. Absence of factor VIII or IX produces the hemophilic syndromes (see Fig. 33–10).

The TF pathway, previously known as the extrinsic coagulation pathway, through the TF–factor VIIa complex in the presence of Ca^{2+} induces the formation of Xa. A second TF-dependent reaction catalyzes the transformation of IX into IXa. TF is an integral membrane protein that serves to initiate the activation of factors IX and X and to localize the reaction to cells on which TF is expressed. Other cofactors include factor VIIIa, which binds to platelets and forms the binding site for IXa, thereby forming the machinery for the activation of X, and factor Va, which binds to platelets and provides a binding site for Xa. The human genes for these cofactors have been cloned and sequenced. In physiologic conditions, no cells in contact with blood contain active TF, although cells such as monocytes and polymorphonuclear leukocytes can be induced to synthesize and express TF.[40]

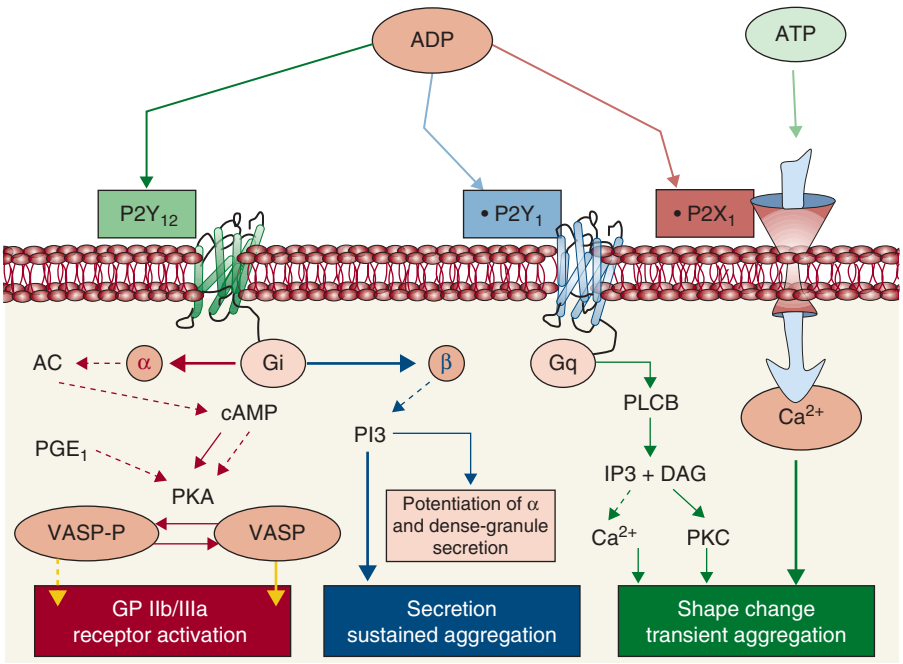


FIGURE 33–8. P2Y platelet receptors. P2Y receptors can be clearly divided into two subgroups: the Gq-coupled subtypes P2Y1 and the coupled to Gi P2Y12. P2Y1 that is responsible for platelet shape change and calcium mobilization is coupled to Gq and activates phospholipase Cβ (PLCβ) that is responsible for the formation of inositol (1,4,5)-trisphosphate (IP3) and diacylglycerol (DAG), an activator of protein kinase C (PKC). IP3 causes calcium mobilization from internal stores. The P2Y12 receptor couples primarily to Gαi2 inhibition of adenylyl cyclase (AC). The subsequent decrease in cAMP production leads, in turn, to a reduction in the activation of specific protein kinases (PKA), which can no longer phosphorylate the vasodilator-stimulated phosphoprotein (VASP); VASP phosphorylation is crucial for glycoprotein (GP) IIb/IIIa receptor inhibition. The subunit βγ activates phosphatidylinositol 3-kinase, which is an important signaling molecule for P2Y12-mediated platelet-dense granule secretion and GP IIb/IIIa receptor activation. Finally, P2X1 is a gated cation channel protein activated by adenosine triphosphate (ATP). This activation leads to increase intraplatelet calcium, platelet shape change, and a transient and weak platelet aggregation response. ADP, adenosine diphosphate. Reproduced with permission from Ibanez B, Vilahur G, Badimon J: Pharmacology of thienopyridines: rationale for dual pathway inhibition. *Eur Heart J Suppl*. 2006;8(Suppl G):G3-G9.

Activated Xa converts prothrombin into thrombin. The complex that catalyzes the formation of thrombin consists of factors Xa and Va in a 1:1 complex. This activation results in the cleavage of fragment 1.2 and formation of thrombin from fragment 2. The interaction of the four components of the "prothrombinase complex" (Xa, Va, phospholipid, and Ca^{2+}) enhances the efficiency of the reaction.

Activated platelets provide a procoagulant surface for the assembly and expression of both intrinsic Xase and prothrombinase enzymatic complexes.[41] These complexes respectively catalyze the activation of factor X to factor Xa and prothrombin to thrombin. The expression of activity is associated with the binding of both of the proteases factor IXa and factor Xa and the cofactors VIIIa and Va to procoagulant surfaces. The binding of IXa and Xa is promoted by VIIIa and Va, respectively, such that Va and likely VIIIa provide the equivalent of receptors for the proteolytic enzymes. The surface of the platelet expresses the procoagulant phospholipids that bind coagulation factors and contribute to the procoagulant activity of the cell.

Thrombin acts on multiple substrates, including fibrinogen, factor XIII, factors V and VIII, and protein C in addition to its effects on platelets. It plays a central role in hemostasis and thrombosis. The catalytic transformation of

fibrinogen into fibrin is essential in the formation of the hemostatic plug and in the formation of arterial thrombi. Thrombin binds to the fibrinogen central domain and cleaves fibrinopeptides A and B, resulting in the formation of fibrin monomer and polymer formation. The fibrin mesh holds the platelets together and contributes to the attachment of the thrombus to the vessel wall.

The new orally active anticoagulants (NOACs) are focused on the inhibition of the TF pathway, clearly proving the importance of TF in the onset of thrombotic events. The NOACs can be divided into two major classes according to their mechanism of action. Direct thrombin inhibitors, such as dabigatran, that block thrombin activity but not its generation, and factor Xa inhibitors that block the activation of factor Xa, suppressing the in vivo thrombin generation (however, they are not able to inhibit the thrombin already generated). Rivaroxaban, apixaban, and most recently edoxaban are the major exponents of coagulation factor Xa inhibitors. It is not the scope of this chapter to expand on the clinical efficacy of these antithrombotic agents; they are discussed in other chapters.

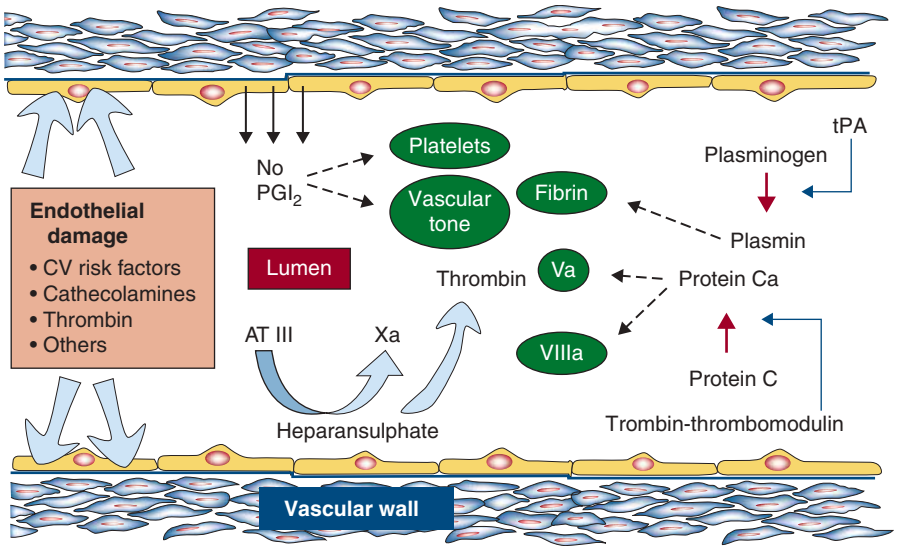


FIGURE 33–10. Simplified diagram of the physiologic anticoagulation system. AT, antithrombin; CV, cardiovascular; NO, nitrous oxide; tPA, tissue plasminogen activator.

New techniques that permit the retrieval of thrombus from ACS patients allow a better characterization of the thrombus formed in vivo on atherosclerotic plaques. Recent data obtained by thromboaspiration of coronary occlusive thrombi (manifested as STEMI) indicate that the recruitment of platelets is an early and fast event as thrombi more than 6 hours old show a significant reduction in the platelet number and an increased in coagulation products. Of interest, older intracoronary thrombi are still capable of recruiting systemic inflammatory cells.[42]

SPONTANEOUS FIBRINOLYSIS

The control of the coagulation reactions occurs by diverse mechanisms, such as hemodilution and flow effects, proteolytic feedback by thrombin, inhibition by plasma proteins (eg, antithrombin III [ATIII]), endothelial cell–localized activation of an inhibitory enzyme (protein C), and fibrinolysis (Fig. 33–10). Although ATIII readily inactivates thrombin in solution, its catalytic site is inaccessible while bound to fibrin; it may still cleave fibrinopeptides even in the presence of heparin. Thrombin has a specific receptor in endothelial cell surfaces, thrombomodulin, which triggers a physiologic anticoagulation system. The thrombin-thrombomodulin complex serves as a receptor for the vitamin K–dependent protein C, which is activated and released from the endothelial cell surface. Thrombin generated at the site of injury binds to thrombomodulin, an endothelial surface-membrane protein, initiating activation of protein C, which in turn (in the presence of protein S) inactivates factors Va and VIIIa and limits thrombin effects. Loss of Va decreases the role of thrombin formation to negligible levels. Thrombin stimulates successive release of both tissue plasminogen activator (tPA) and plasminogen-activator inhibitor type 1 (PAI-1) from endothelial cells, thus initiating endogenous lysis through plasmin generation from plasminogen by tPA with subsequent modulation through PAI-1. Thrombin therefore plays a pivotal role in maintaining the complex balance of initial prothrombotic reparative events and subsequent endogenous anticoagulant and fibrinolytic pathways. The pivotal role of thrombin in the different mechanisms exposed here is represented in Fig. 33–11.

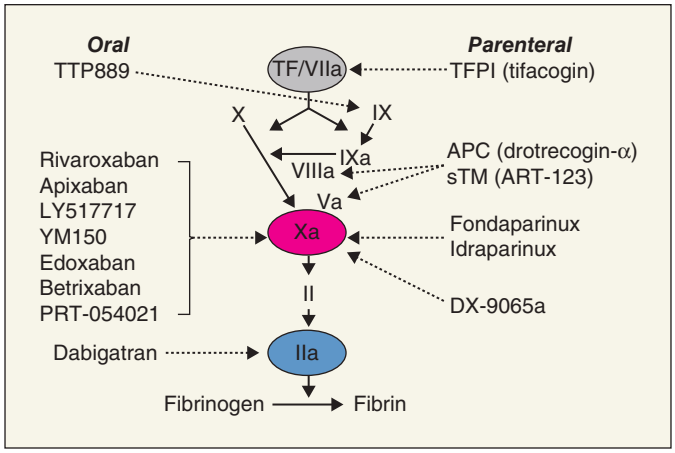


FIGURE 33–9. Simplified diagram of the tissue factor pathway with specific inhibitor at the different steps of the cascade. The underlined compounds are those approved by the Food and Drug Administration. APC, antigen-presenting cell; FFR, active site-inhibited factor VIIa; LMWH, low-molecular-weight heparin; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

Endogenous fibrinolysis, a repair mechanism, involves catalytic activation of zymogens, positive and negative feedback control, and inhibitor blockade (see Fig. 33–10). Blood clotting is blocked at the level of the prothrombinase complex by the physiologic anticoagulant-activated protein C and oral anticoagulants. Oral anticoagulants prevent post-translational synthesis of γ-carboxyglutamic acid groups on the vitamin K–dependent clotting factors, preventing binding of prothrombin and Xa to the membrane surface. Activated protein C cleaves factor Va, rendering it functionally inactive.

ROLE OF LOCAL FACTORS IN THE REGULATION OF CORONARY THROMBOSIS

The cellular and molecular mechanisms of platelet deposition and thrombus formation after vascular damage are modulated by the type of injury, the local geometry at the site of damage (degree of stenosis), and local hemodynamic conditions.[43,44] Similarly, three major factors also determine the vulnerability of the fibrous cap: (1) circumferential wall stress, or cap "fatigue"; (2) lesion characteristics (location, size, and consistency); and (3) blood flow characteristics.

EFFECTS DERIVED FROM THE SEVERITY OF VESSEL WALL DAMAGE

Exposure of deendothelialized vessel wall, native fibrillar collagen type I bundles with a rough surface, or atherosclerotic plaque components at similar blood shear rate conditions lead to increasing degrees of platelet deposition. Thromboplastin or TF, readily available in the atherosclerotic intimal space exposed by endothelial loss, contributes to the high thrombogenicity of atherosclerotic plaques.[45,46] Overall, it is likely that when injury to the vessel wall is mild, the thrombogenic stimulus is relatively limited, and the resulting thrombotic occlusion is transient, as occurs in UA. On the other hand, deep vessel injury secondary to plaque rupture or ulceration results in exposure of collagen, TF, and other elements of the vessel matrix, leading to relatively persistent thrombotic occlusion and myocardial infarction (MI).

It is likely that the nature of the substrate exposed after spontaneous or angioplasty-induced plaque rupture determines whether an unstable plaque proceeds rapidly to an occlusive thrombus or persists as nonocclusive mural thrombus. The analysis of the relative contribution of different components of human atherosclerotic plaques (fatty streaks, sclerotic plaques, fibrolipid plaques, atheromatous plaques, hyperplasic cellular plaque, and normal intima) to acute thrombus formation has shown that the atheromatous core is up to six-fold more active than the other substrates in triggering thrombosis.[43] The atheromatous core remained the most thrombogenic substrate when the various components were normalized by the degree of irregularity, as defined by the roughness index. Therefore, ruptured plaques with a large atheromatous core are at high risk of leading to ACS. The plaque TF content is directly related to its thrombogenicity.[46] As proof of concept, we showed that local tissue blockade of TF by treatment with TF pathway inhibitor significantly reduces thrombosis.[46,47] Recently, the use of active site–inhibited recombinant FVIIa (FF-rFVIIa) has been shown to significantly reduce thrombus growth on severely damaged vessels.

Monocytes and macrophages are key to the development of vulnerable plaques. The vulnerable plaques (AHA type IV and Va), commonly composed of an abundant lipid core separated from the lumen by a thin fibrotic cap, are particularly soft and prone to disruption.[48] A high density of activated inflammatory cells has been detected in the disrupted areas of atherectomy specimens from patients with ACS. These cells are capable of degrading ECM by secreting proteolytic enzymes, such as MMPs.[49,50] In addition, T cells isolated from rupture-prone sites can stimulate macrophages to produce metalloproteinases and may predispose to the disruption of lesions by weakening their fibrous caps. Leukocytes, their enzymes, and their activation, play a critical role in plaque vulnerability and rupture.[51,52] Links between the activity of the leukocyte enzyme myeloperoxidase (MPO) and features of vulnerable plaque have been reported.[53] MPO has been implicated in endothelial cell loss or denudation and development of a prothrombotic environment. LDL has been shown to downregulate the expression of lysil-oxidase (LOX) in vascular wall cells. LOX is an enzyme that contributes to the maturation of the elastin and collagen fibrils of the ECM. Its decrease is associated with increased permeability of the vascular wall and hence may contribute to plaque destabilization. Cell apoptosis and MPs with procoagulant activity and postulated apoptotic origin have also been linked to inflammation and thrombosis.[54-56] Resident smooth muscle cells also play a role in the thrombogenic status of the atherosclerotic lesions. Aggregated LDL is able to induce TF expression in smooth muscle cells by inhibiting sphingomyelinase. The expression of TF in smooth muscle cells strongly depends on the expression of the LDL receptor–related protein LRP.[54]

Macrophages are suggested to play a key role in inducing plaque rupture by secreting proteases capable of destroying the ECM that provides physical strength to the fibrous cap. Recently, it has been showed that macrophage-mediated matrix degradation by matrix MMPs can induce plaque rupture. MMP-9 enhances elastin degradation and induces significant plaque disruption when overexpressed by macrophages in advanced atherosclerotic lesions of apo $E^{-/-}$ mice.[57] Other MMPs have also been implicated in different stages of atherosclerotic plaque progression.[58] In addition to secreting proteases and increasing the likelihood of plaque rupture, lipid-rich macrophages within the atherosclerotic plaque undergo apoptosis, expressing TF and increasing the thrombogenic status of the vascular lesions.[59] Plaque vulnerability and thrombogenic status can be reduced by long-term treatment with lipid-lowering agents.[60]

Epidemiological and retrospective studies have suggested an important protective effect of HDL against cardiovascular disease. Preclinical evidence and small human studies suggest that acute treatment with recombinant apo A-I Milano or other HDL-targeting interventions can induce acute plaque stabilization representing a promising approach for high-risk patients.[61-64] However, the lack of benefit seen in the most recent randomized clinical trials targeting HDL (eg, AIM-HIGH, ACCORD, HPS-2) has generated a cloud on the postulated benefits effect of HDL. Those failures, despite attaining significant increases in HDL, have initiated an important discussion on the physiological value of the quality versus quantity of HDL. Major criticisms of the design and the selected population for the trials have to be taken into account before totally disregarding the protective benefits of "functional" HDL as those raised by exercise, diet, and so on. These failures have supported the existence of a "dysfunctional" HDL. Several cardiovascular risk factors, such as preexistent coronary artery disease, diabetes, inflammation, and so on, are associated with this dysfunctional HDL.[65-67]

EFFECTS DERIVED FROM GEOMETRY

Platelet deposition is directly related to the degree of stenosis in the presence of the same degree of injury, indicating a shear-induced platelet activation.[68] In addition, analysis of the axial distribution of platelet deposition indicates that the apex, not the flow recirculation zone distal to the apex, is the segment of greatest platelet accumulation. These data suggest that the severity of the acute platelet response to plaque disruption partly depends on the sudden changes in geometry after rupture. Interestingly, hemodynamic effects play a role in the regulation of the thrombotic response in different arteries. In the absence of atherosclerotic changes in the porcine normolipemic model, the dilatation of carotid and coronary arteries in the same animal produced significantly different levels of platelet deposition in the arterial beds, with the coronaries triggering a significantly greater deposition than the carotids.[68] Also, it has been shown in apolipoprotein E–deficient (apo $E^{-/-}$) mice that whereas lowered shear stress induces larger lesions with a vulnerable plaque phenotype, vortices with oscillatory shear stress induce stable lesions.[69]

Spontaneous lysis of thrombus does occur, not only in UA but also in acute MI. In these patients as well as in those undergoing thrombolysis for acute infarction, the presence of a residual mural thrombus predisposes to recurrent thrombotic vessel occlusion. Two main contributing factors for the development of rethrombosis have been identified. First, because platelet deposition increases with increasing degrees of vessel stenosis, residual mural thrombus encroaching into the vessel lumen may result in an increased shear rate, which facilitates the activation and deposition of platelets on the lesion. Second, a fragmented thrombus appears to present one of the most powerful thrombogenic surfaces. A gradual increase in platelet deposition in the area of maximal stenosis may be followed by an abrupt decrease in platelet deposition, probably because of spontaneous embolization of the thrombus or platelet deaggregation.[70] Such an episode can

be immediately followed by a rapid increase in platelet deposition, suggesting that the remaining thrombus is markedly thrombogenic. In fact, platelet deposition is increased two to four times on residual thrombus compared with deeply injured arterial wall, and thrombus continues to grow during heparin therapy. However, it is inhibited by specific antithrombin treatment.

A specific antithrombin such as r-hirudin (a recombinant molecule that blocks both the catalytic site and the anion-exosite of the thrombin molecule) is capable of significantly inhibiting the secondary growth. Thus, after lysis, thrombin becomes exposed to the circulating blood, leading to activation of the platelets, coagulation, and further thrombosis. The antithrombin activity of heparin is limited for three main reasons: (1) a residual thrombus contains active thrombin bound to fibrin, which is thus poorly accessible to the large heparin-ATIII complexes; (2) a platelet-rich arterial thrombus releases large amounts of platelet factor 4, which may inhibit heparin; and (3) fibrin II monomer, formed by the action of thrombin on fibrinogen, may also inhibit heparin. Conversely, molecules of hirudin and other specific antithrombins are at least 10 times smaller than the heparin-ATIII complex and have no natural inhibitors and therefore have greater access to thrombin bound to fibrin. These findings clarify the clinical observations in patients with acute MI undergoing thrombolysis, which have shown that residual stenosis is partly related to residual nonlysed thrombus. The effects of different antithrombotic treatment regimens on thrombus formation triggered by a residual mural thrombus have been evaluated, and specific thrombin inhibition has been shown to be the most effective method of slowing the progression of thrombus growth compared with aspirin, heparin, or both.[71]

The fact that a clear predilection exists for lesion formation at arterial branch points strongly indicates the important influence of local hemodynamics and rheologic conditions on atherosclerosis. Furthermore, vascular cell gene expression profiles are also modulated by acute changes in flow profiles.[72,73]

ROLE OF SYSTEMIC FACTORS IN THE REGULATION OF CORONARY THROMBOSIS

The severity of coronary thrombosis and associated ACS is modulated by the magnitude or stability of the formed thrombus. In addition, successive events of plaque disruption and asymptomatic thrombus formation have been postulated to be responsible for the rapid progression of disease in certain patients. When a plaque ruptures, in addition to the local factors mentioned above, systemic factors modulate, predispose, or lead to ACS. In fact, current knowledge supports the concept that rupture of atherosclerotic plaques happens more frequently than initially thought. This disruption occurs in an asymptomatic fashion and thus remains clinically unnoticed. Postmortem evidence has demonstrated the existence of repeated and healed thrombotic episodes within the same lesion.[74] This plaque rupture without a superimposed thrombus suggest that in addition to local factors implicated in coronary thrombosis, other circulating systemic factors modulate coronary thrombosis (Table 33–2). This knowledge led to the concept of vulnerable patient as a composite of vulnerable plaque plus vulnerable blood.[75-79]

One-third of ACS cases, particularly those involving ischemic sudden cardiac death, develop without plaque disruption but just superficial erosion of a markedly stenotic and fibrotic plaque. Under such conditions, thrombus formation seems to depend on the hyperthrombogenic state triggered by systemic factors (Table 33–3). Indeed, systemic factors—including elevated LDL, decreased HDL, cigarette smoking, diabetes, and dysregulated hemostasis—are associated with increased thrombotic complications. Our group has reported an increased blood thrombogenicity associated with hyperlipemia as well as diabetes; more importantly, the effective management of these risk factors normalized this increased blood thrombogenicity.[80,81]

TABLE 33–2. Factors Implicated in Thrombus Formation

	Plaque Disruption	Rheology	Blood Thrombogenicity
Coronaries	+++	++	+
Carotids	++	+	++
Peripherals	+	++	+++

As stated above, TF is a major local player in the vulnerability and thrombogenicity of atherosclerotic plaques. TF is highly expressed in atherosclerotic plaques, and its content has been related to plaque thrombogenicity. More recent is the knowledge of the existence of a bloodborne pool of TF that may play a critical role in the propagation of thrombosis. Moreover, it has been reported that polymorphonuclear leukocytes might be involved in the transport of circulating TF to platelets. High plasma levels of TF antigen and TF-positive MPs with procoagulant activity have been reported in patients with ACS.[81,82] It seems that bloodborne TF plays an important role in the blood thrombogenicity and in the thrombotic complications of plaque disruption and erosion. Our group has found increased levels of circulating TF activity to be associated with cardiovascular risk factors. Our group has found high levels of circulating TF activity in certain pathological conditions characterized by high rate of thrombotic complications (diabetes, hyperlipidemia, and smoking). In addition, we have found that patients with improvement in glycemic control showed a reduction in circulating TF,[83] suggesting that circulating TF may be the mechanism of action responsible for the increased thrombotic complications associated with the presence of these cardiovascular risk factors. Figure 33–12 shows the possible cellular sources of circulating bloodborne TF. C-reactive protein (CRP) has been implicated in various aspects of cardiovascular disease. It has been shown that a circulating isoform of CRP (mCRP) enhances platelet deposition and thrombus growth in contrast to the

TABLE 33–3. Factors Modulating Thrombus Formation

Local Fluid Dynamics	Nature of the Exposed Substrate	Systemic Thrombogenic Factors
Shear stress	Degree of injury (mild vs severe arterial injury)	Hypercholesterolemia
Tensile stress	Composition of atherosclerotic plaque	Catecholamines (eg, smoking, cocaine, stress)
	Residual mural thrombus	Smoking
		Diabetes
		Homocysteine
		Infections (*Chlamydia pneumoniae*, *Helicobacter*, cytomegalovirus)
		Hypercoagulable state (Fg, vWF, TF, FVII)
		Defective fibrinolytic state (and so on)

Abbreviations: Fg, fibrinogen; FVII, factor VII; TF, tissue factor; vWF, von Willebrand factor.

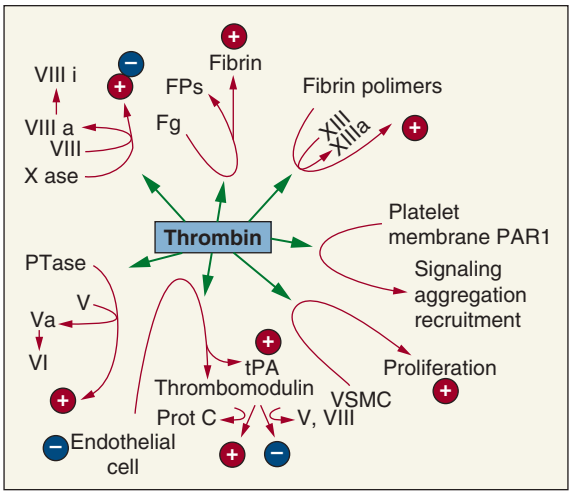


FIGURE 33–11. Role of thrombin in different pathways of coagulation. Thrombin plays a critical role in the maintenance of physiological fibrinolysis system but also in thrombosis. Fg, fibrinogen; FPs, fibrinopeptides; PAR1, protease-activated receptor 1; PTase, prothrombinase; tPA, tissue plasminogen activator; VSMC, vascular smooth muscle cell.

native form of CRP.[84] In addition, CRP seems to be a direct mediator of neovessel formation of high-risk plaques.[85]

Thrombogenic systemic factors can be modulated by controlling the cardiovascular risk factors and by dietary and pharmacologic strategies. The development of additional novel therapeutic approaches depends on the increasing knowledge of the pathogenesis of ACS.

Atherosclerosis and inflammation could represent different faces of the same disease. Currently, it is well known that inflammatory circulating markers correlate with cardiovascular events and the severity of the disease. Several inflammatory markers are being postulated as having a significant prognostic value for recurrent cardiovascular events. Therefore, given the role of inflammation on atherosclerosis, it is plausible that drugs directed against inflammation (eg, COX-2 inhibitors and nonsteroidal anti-inflammatory drugs [NSAIDs]) could render a positive impact in the prevention of cardiovascular events. However, several studies associated a significant increase in cardiovascular events with the use of COX-2 inhibitors. At that time, it was thought that NSAIDs did not have the same association with cardiovascular events and could even be protective; however, it has been demonstrated that NSAIDs also seem to have a negative impact in patients with cardiovascular disease.[86,87] Therefore, it is clear that the best approach to treating inflammation in patients with cardiovascular disease is an aggressive management of all the cardiovascular risk factors (eg, statins, angiotensin-converting enzyme inhibitors, hypoglycemic agents, antiplatelets). Interestingly, the use of these therapeutic interventions has been demonstrated to not only offer significant benefits but also to reduce the systemic levels of proinflammatory markers. This emphasizes the idea that atherothrombotic disease and inflammation could be two faces of the same disease rather than two different entities. As stated above, the infusion of recombinant Apo A-I Milano is able to stabilize atherosclerotic plaques. Interestingly, this effect is not restricted to the vessel wall because systemic markers of inflammation are downregulated.[88]

The antithrombotic agents presently used in clinical practice can be subdivided into three categories, according to their mechanism of action: fibrinolytics, inhibitors of the intrinsic coagulation cascade, and antiplatelet agents. Among the novel antithrombotic strategies that are reaching clinical research are the inhibitors of the TF:FVIIa pathway, direct factor Xa inhibitors, and direct thrombin inhibitors (DTIs). The newly generated understanding of the role of TF in atherothrombosis has suggested the inhibition of its pathway as a new antithrombotic approach. The biochemistry of TF and the clotting cascade has identified TF:VIIa, factor Xa, and thrombin as potential targets. Several direct and specific antagonists to each of these targets have been developed and are being investigated in the clinical arena. Specific anti-TF antibodies, recombinant forms of endogenous TF pathway inhibitors, inhibitors of factor VIIa, and inhibitors of factor Xa may afford at least a theoretical advantage over therapies that target more "downstream" components of the coagulation cascade.

DTIs inhibit thrombin by directly binding to exosite 1 or the active site of thrombin. DTIs produce a predictable anticoagulant response because they exhibit minimal binding to plasma proteins or cellular elements and inhibit fibrin-bound thrombin as well as fluid-phase thrombin. The intravenous DTIs approved in the United States by the Food and Drug Administration (FDA) for anticoagulation in patients with heparin-induced thrombocytopenia are the recombinant hirudin, lepirudin, and argatroban. An oral DTI, dabigatran, has been tested in a large clinical trial recruiting more than 18,000 patients. The results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study have been recently reported. Two doses of dabigatran were tested against warfarin in patients with atrial fibrillation. The low dabigatran dose (110 mg) resulted in similar results in thromboembolic event prevention, but it was associated with significantly lower hemorrhagic episodes. The high dose of dabigatran (150 mg) was associated with significantly lower thromboembolic events but similar rates of major hemorrhages.[90] In addition, the REDEEM (Dabigatran vs Placebo in patients with acute coronary syndromes) Trial studied the safety and indication for efficacy of the combination of dabigatran and dual antiplatelet therapy in patients with a recent MI. The results showed a dose-dependent increase in bleeding events and significant reduction in the coagulation activity.[91,92]

Another way to interfere with thrombin generation is the possibility of inhibiting the activation of FX. Selective factor Xa inhibitors effectively block coagulation because factor Xa is positioned at the start of the common pathway of the extrinsic and intrinsic coagulation systems (see Fig. 33–9). The indirect factor Xa inhibitor fondaparinux was the first of the selective factor Xa inhibitors to receive FDA approval for the prevention and treatment of venous thromboembolism. Several direct FXa inhibitors—rivaroxaban, apixaban, and edoxaban—have been approved

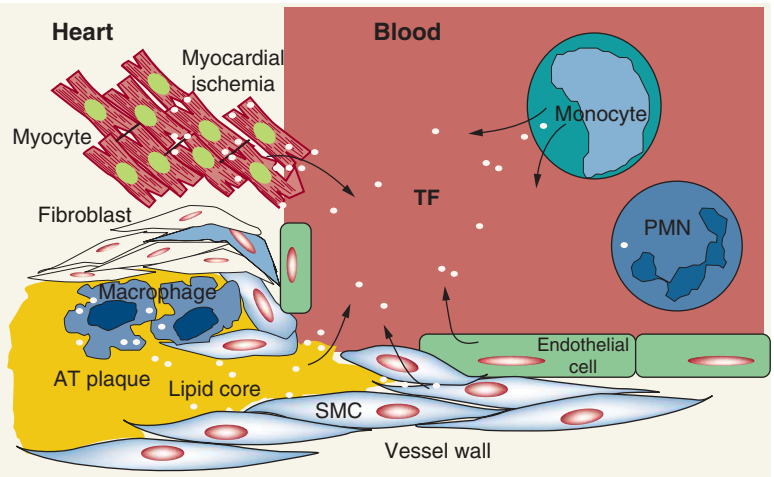


FIGURE 33–12. Suggested sources of circulating tissue factor (TF). AT, antithrombin; PMN, polymorphonuclear leukocyte; SMC, smooth muscle cell.

by the FDA for the prevention of stroke in patients with nonvalvular atrial fibrillation. Their action is exerted selectively toward factor Xa, contrary to the action of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), which act on a number of coagulation factors. UFH has equipotent activity against factors IIa and Xa but also acts on factors IXa, XIa, and XIIa in an antithrombin-dependent manner. LMWHs, which are prepared by chemical or enzymatic depolymerization of UFH, have relatively more antifactor Xa than antifactor IIa activity. Figure 33–9 shows the site of action of the different drugs targeting the coagulation cascade.

The effectiveness and safety of the new oral anticoagulants suggesting the possibility of their use in the prevention of ACS, combined with the increasing incidence of atrial fibrillation in today's aging population, has generated a major clinical dilemma.[93] The ATLAS ACS 2–TIMI 51 (NCT 00809965) investigated the effects of rivaroxaban (2.5 and 5.0 mg twice a day) in acute coronary syndromes receiving a low dose of aspirin and randomized based on the investigator's intent to administer a thienopyridine. Rivaroxaban reduced the risk of composite end point (cardiovascular death, MI, and stroke). These benefits were associated with an increased risk of major bleeding and intracranial hemorrhage but not fatal bleeding.[94] Similarly, apixaban was also studied in ACS patients receiving dual antiplatelet therapy in the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial (NCT 00831441). The results showed increased bleeding complications without reductions in ischemic events.[95] What is the best therapeutic intervention in those patients with atrial fibrillation undergoing stent deployment? Or what should be done in patients with stents being diagnosed with atrial fibrillation? There is not a clear suggestion from any of the guidelines; simply it is recommended to balance the risk of thrombosis and the risk of bleeding prior making a therapeutic decision. Several ongoing trials are being developed to investigate this question.

Other approaches, still in early preclinical phase, are inhibitors of GP Ib receptor (anti-vWF), inhibitors of vWF-collagen binding (saratin), and inhibitors of the ADP receptor P2T and PAR-1,[96] among others.

SUMMARY

The formation of a thrombus within a coronary artery with obstruction of coronary blood flow and reduction in oxygen supply to the myocardium produce the several types of ACS. These thrombotic episodes largely occur in response to atherosclerotic lesions that have progressed to a high-risk inflammatory or prothrombotic stage by a process modulated by local and systemic factors. Although distinct from each other, these atherosclerotic and thrombotic processes appear to be closely related as the cause of ACS through a complex multifactorial process called *atherothrombosis*. The cellular and molecular mechanisms at play in the formation, growth, and stabilization of a coronary thrombus are being thoroughly investigated, and many of the activation pathways and receptor-ligand interactions have been identified. Inflammation has been revealed as a great player in the systemic and diffuse pattern of atherothrombotic disease. Strategies combining dietary, pharmacologic-medical, and interventional-surgical therapies have shown considerable success in the prevention and treatment of major cardiovascular events. These regimens focus on inhibiting the various pathways involved in thrombus generation. Novel strategies based on the knowledge of the biochemistry of platelet aggregation and the coagulation processes as well as the geometric conditions encountered in the circulation are presently in different stages of development and clinical trials. Advances in noninvasive imaging techniques will help to identify plaques at risk and reduce the clinical impact of atherothrombosis.

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CHAPTER 34

CORONARY BLOOD FLOW AND MYOCARDIAL ISCHEMIA

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OVERVIEW

Low coronary blood flow causes acute coronary syndromes, angina pectoris, myocardial infarction, impaired left ventricular function, heart failure, arrhythmia, and death. High coronary blood flow capacity associates with cardiovascular health with its variations, reflecting our emotional states, lifestyles, and food, even the postprandial lipid surge of the last meal, all documented to alter coronary blood flow and risk factors, symptoms, and outcomes of coronary artery disease. The mammalian heart evolving from 200 million years ago—coronary blood flow, human gender evolution, fluid dynamic equations, coronary pressure flow measurements, quantitative perfusion imaging, diagnostic tests, coronary artery disease in women versus men, and how poor coronary flow is optimally treated—constitutes a highly integrated conceptual continuum, a syncytium of knowledge immediately relevant to current cardiovascular medicine and patient well-being.

Resurgent interest in coronary blood flow related to myocardial "ischemia" derives in part from substantial disconnects in cardiovascular medicine. Immediate percutaneous coronary intervention (PCI) in acute coronary syndromes (ACS) reduces myocardial infarction and cardiovascular mortality.[1] However, all elective revascularization trials driven by "ischemia" on diagnostic testing fail to reduce myocardial infarction or cardiovascular deaths despite relief of angina[2-9] (Fig. 34–1).

This disconnect even reaches into the legality of fully informed consent wherein "cardiologists (95%) in this sample did not inform the patient that PCI would not lower the risk of death or MI [myocardial infarction], or that the symptom benefit is gone after 5 years."[10,11] This issue is particularly relevant in view of only half of procedures being classified as appropriate out of 145,000 elective PCIs of the National Cardiovascular Data Registry.[12]

Moreover, the rationale for all diagnostic tests, prognosis, treatment, and procedures for coronary artery disease (CAD) invokes coronary blood flow that is not measured, used clinically, and poorly understood. Finding "ischemia" for the diagnosis of CAD should no longer be the sole, the primary, or even an adequate goal of diagnostic testing because most CAD is best treated medically for optimal outcomes. The essential evidence driven goal of "diagnostic" testing now requires identifying objectively those patients with quantitative physiologically severe CAD of sufficiently high risk that revascularization reduces myocardial infarction or mortality in addition to relief of angina.

These disconnects in cardiovascular medicine require us to rethink the term *ischemia* because its specific definition or rather many potential definitions highlights the core issues of CAD, how it is quantified and for what goal—diagnosis, progression/regression, medical

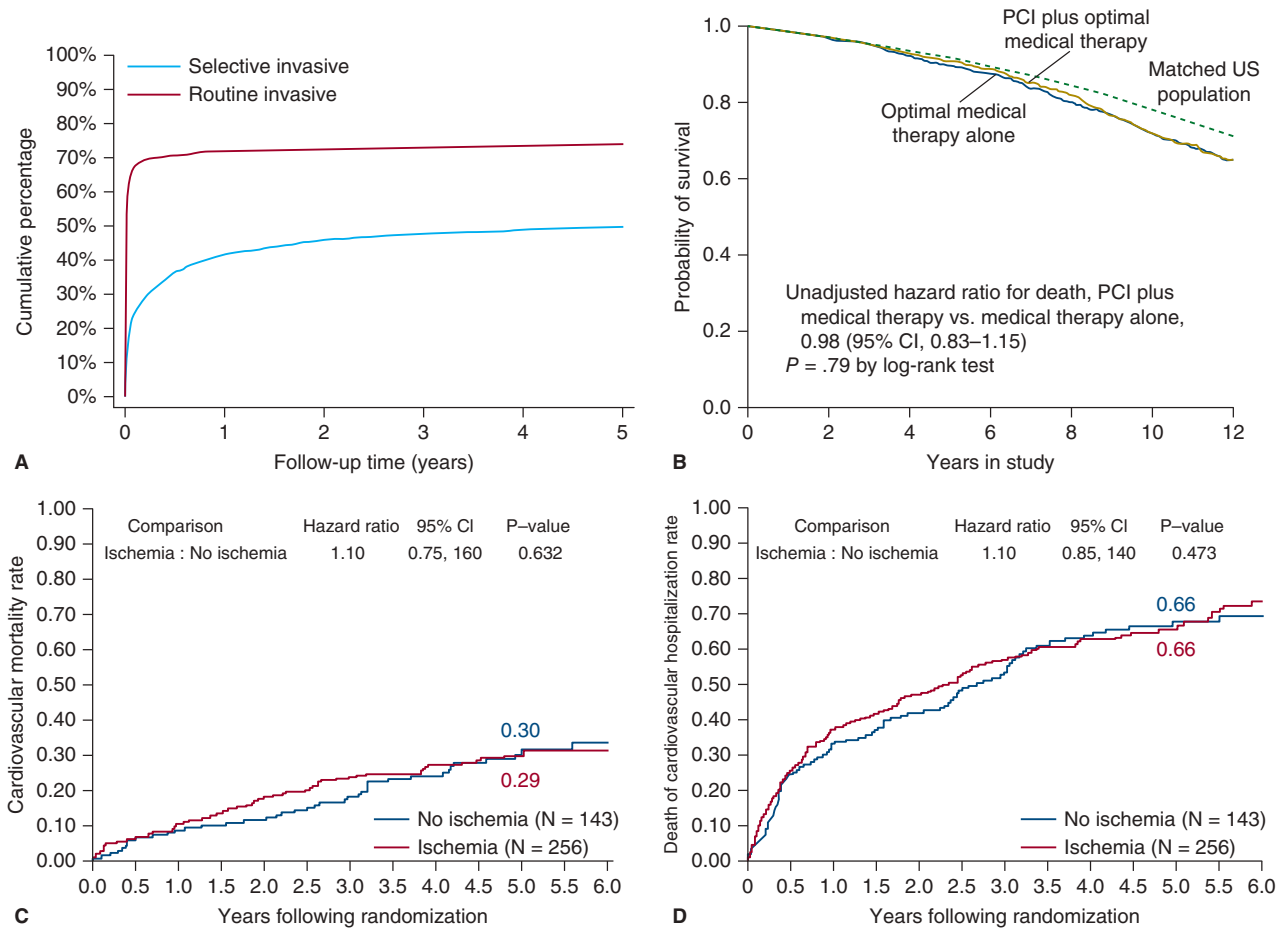


FIGURE 34–1. Outcomes after coronary revascularization in (**A**) acute coronary syndromes (ACS), stable coronary artery disease at 12-year follow-up of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (**B**), cardiovascular mortality (**C**) and all-cause mortality or cardiovascular hospitalization (**D**) in the Surgical Treatment for Ischemic Heart Failure (STICH) trial with (red line) and without (blue line) ischemia by single-photon emission tomographic perfusion imaging. CI, confidence interval; PCI, percutaneous coronary intervention. (A) reproduced with permission from Fox KA, Clayton TC, Damman P, et al: Reproduced from Fox KA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol*. 2010 Jun 1;55(22):2435-2445. (B) reproduced with permission from Sedlis SP, Hartigan PM, Teo KK: Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease. *N Engl J Med*. 2015 Nov 12;373(20):1937-1946. C, data from Velazquez EJ, Lee KL, Deja MA, et al: Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011 Apr 28;364(17):1607-1616. D, reproduced with permission from Panza JA, Holly TA, Asch FM, et al: Inducible myocardial ischemia and outcomes in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol*. 2013 May 7;61(18):1860-1870.

treatment, or revascularization. This chapter addresses these disconnects by integrating coronary blood flow, myocardial ischemia, coronary pathophysiology, angiographic anatomy, diagnostic testing, and treatment trials into a rational synthesis for clinical practice.

MYOCARDIAL ISCHEMIA—WHICH OF MULTIPLE MEANINGS FOR WHAT PURPOSE?

Myocardial ischemia, *reversible ischemia*, or its absence, is considered or invoked in virtually every aspect of every patient evaluated for CAD. Diagnostic test reports, clinical history, verbal discussion, risk stratification, long-term prognosis, clinical decisions, management, and outcomes all utilize or report evidence of *ischemia* (or not). It is associated with adverse outcomes as the basis for treatment or interventions intended to prevent ischemia and associated coronary events. *Myocardial ischemia* is an emotionally loaded, general term conjuring up a sense of life-threatening badness or "cardiovascular evil" that demands immediate action.

These associations are explicitly formalized in the concept of the *ischemic cascade* embedded in clinical practice as relentless progression demanding intervention. In restricted circumstances, such as ACS, this view has some statistical or trial justification with proven modest reduction of myocardial infarction or death by immediate PCI.[1] However, in many other circumstances, the diagnosis of *ischemia* carries no such adverse risk, thereby misguiding management with no benefit[2-12] and possibly more potential patient harm than benefit from revascularization in some circumstances.

The wide range of meaning for *myocardial ischemia* is obvious when trying to define or quantify it as one or more of the specific conditions listed in Fig. 34–2. Each of these definitions is a physiologic end point or measurement having greater or lesser importance and effectiveness for optimal patient outcomes depending on their severity, rate of development, their different combinations together, and clinical circumstances. Therefore, actionable use of the term *myocardial ischemia* requires defining a specific measurement, its severity, its time course, and trial evidence of treatment or interventions that alter symptoms, cardiac function, and coronary events or survival resulting from those quantitative measures of *ischemia*, guiding treatment.

Traditional textbooks or training approaches to *myocardial ischemia* start with the process, procedures, and paradigm of clinical cardiology. This traditional training paradigm of clinical cardiology typically begins with the prevalence and demographics of CAD, pathology of

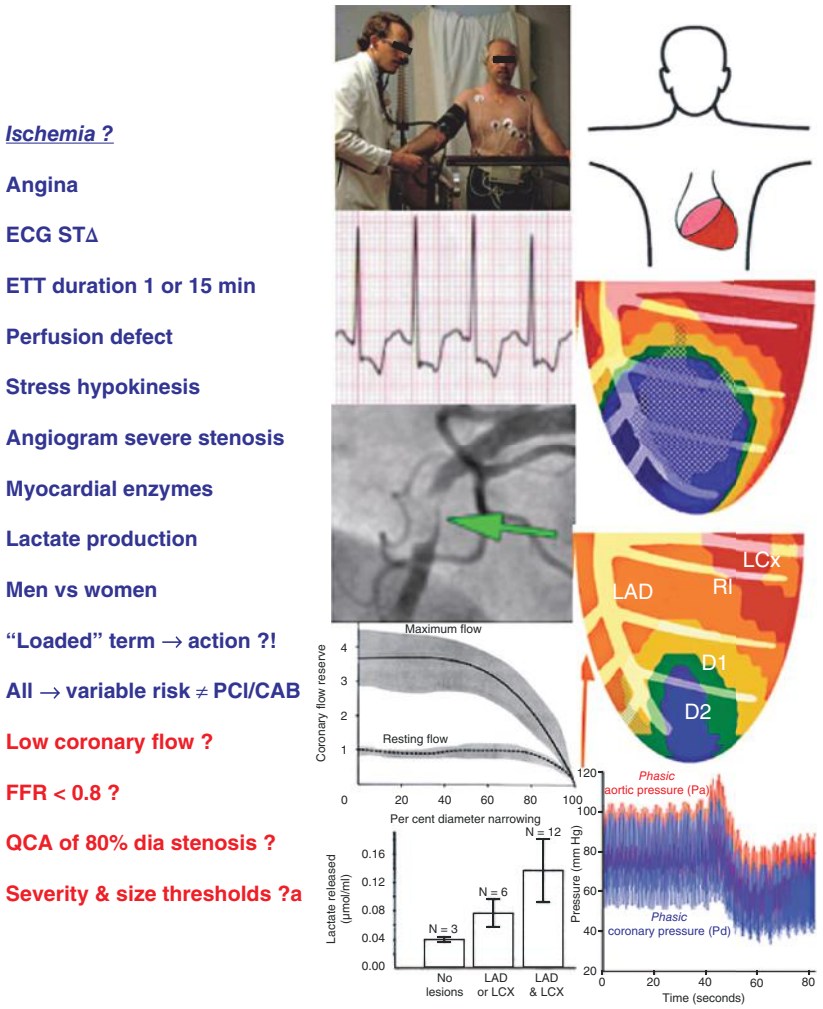


FIGURE 34–2. Definitions of myocardial ischemia or clinical associations. Insets: treadmill exercise test, ST segment depression, angiogram, coronary flow reserve, myocardial lactate production, Positron emission tomography perfusion images with large and small stress defects and coronary and aortic pressures for fractional flow reserve (FFR). ECG, electrocardiogram; QCA quantitative coronary angiogram; dia, diameter stenosis.

atherosclerosis, plaque rupture, elements of the ischemic cascade, noninvasive diagnostic tests, their sensitivity and specificity, and risk stratification. This is followed by details of medical treatment and invasive interventions for assumed benefit. Alternatively, particularly in medical school, the training paradigm starts with pure basic physiology as separate, primary, commonly experimental knowledge independent of and somewhat unrelated to cardiology practice.

MYOCARDIAL ISCHEMIA—TRADITION VERSUS TRIALS

The traditional *myocardial ischemia* paradigm imbues generations of cardiologist in the processes and procedures of cardiovascular medicine as the standard of community care with expected benefit by patients and physicians reinforced to some extent by fee-for-service–oriented tests and procedures. However, the failure of randomized revascularization trials to reduce myocardial infarction or coronary deaths compared to medical treatment alone in "stable CAD" challenges this training and practice paradigm.[2-8] Whether defined clinically, symptomatically, or by any diagnostic test for CAD, this well-documented failure to reduce myocardial infarction or mortality requires rethinking the meaning and use of the term *myocardial ischemia*—its definition, quantification, time course, pathophysiologic meaning, management, its invasive and invasive testing, outcomes, and therefore cardiology textbooks and training.

The science of randomized trials drives a sharp edge into tradition versus change, into group statistics versus individual personalized medicine, and into the economics or business versus evidence-based practice of cardiovascular medicine. This chapter on myocardial ischemia addresses this edge by changing the traditional training-practice paradigm to reorient the reader's mindset. We start with the outcomes of randomized revascularization trials—success and failures, that biting edge, the purpose of cardiovascular medicine. Trial outcomes provide a powerful lesson on coronary pathophysiology with insights into the mechanisms and quantitative measures of *ischemia* thence leading directly into the critical role of quantitative coronary blood flow (myocardial perfusion) to assess physiologic severity of CAD for binary clinical decisions, diagnostic testing, interventions and management of ACS or chronic stable CAD

MYOCARDIAL ISCHEMIA—MINDSET BASED ON PATIENT OUTCOMES

Clinical training, practice, and research require a new mindset based on benefit to patients proven in randomized trials rather than the traditional clinical or pure physiology paradigms that assume patient

benefit without objective scientific basis. These trials provide clear evidence for an integrated conceptual chain from outcomes to treatment, to measures of severity, its time course, its relevant pathophysiology, its quantitative methodology, and routine diagnostic testing. Clinical coronary pathophysiology is essential for integrating this outcomes driven chain of reasoning toward evidence-based personalized management. Within the continuum of coronary pathophysiology, randomized revascularization trials divides our approach to myocardial ischemia into two parts—ACS and nonacute or stable CAD.

Accordingly, we start with ACS as manifestations of ischemia caused by low coronary blood flow for which revascularization reduces coronary events and mortality[1] without preangiogram noninvasive testing or invasive quantitative measurements. Our beginning with the outcomes of intervention trials in acute syndromes reveals profound pathophysiologic insights into noninvasive cardiac testing and management of "stable CAD"—indeed, the entire current paradigm of cardiovascular practice and economics or "business" of medicine. Diagnosis of CAD has been and will substantially remain the goal for all noninvasive testing and diagnostic angiograms. However, randomized trials and advanced imaging technology are driving "diagnostic" testing for *ischemia* toward a more advanced purpose beyond just diagnosis to the primary guide for invasive procedures and revascularization. This reasoning requires us to rethink *ischemia* because its specific definition or rather many potential definitions highlights the core issues of CAD, how it is quantified for what goal—diagnosis, progression/regression, medical treatment, or revascularization.

ACUTE CORONARY SYNDROMES

ACS now account for 70% to 80% of PCIs, with the remainder for nonacute or stable CAD.[13,14] ACS are categorized as unstable angina or myocardial infarction with ST elevation (STEMI) or without ST elevation (NSTEMI). In randomized trials, acute revascularization improves left ventricular (LV) function, reduces death, subsequent myocardial infarction, and long-term mortality,[1] illustrated in Figure 34–1. Immediate primary PCI gives the best outcomes without preangiogram diagnostic tests, imaging, or intravascular diagnostic measurements.

The definitions or measures of ischemia in these syndromes provide lessons in clinical pathophysiology relevant to stable CAD and diagnostic testing. STEMI is defined by elevated cardiac specific enzymes with ST elevation on electrocardiogram (ECG) and acute onset of symptoms. Coronary angiogram typically shows a severe coronary stenosis or thrombus and regional LV dysfunction. Unstable angina typically has acute onset of definite chest pain and or typical associated symptoms, commonly with nonspecific ECG changes without diagnostic enzyme rise.

However, even in these acute syndromes for which acute PCI reduces myocardial infarction and mortality, the actionable definition of ischemia is not unique or singular. Acute characteristic symptoms in one case, cardiac enzymes in another, acute ECG changes in another, all indicating ischemia or injury as commonly used interchangeably with benefit by revascularization. These different manifestations or criteria of *ischemia* reflect a more basic commonality—reduced coronary blood flow reflecting anatomically and physiologically severe coronary artery stenosis, thrombosis, and spasm.

Other than ECG and cardiac enzymes for characteristic ACS, the coronary angiogram with potential PCI is indicated without requiring preangiogram diagnostic testing or measures of severity because clinical ACS documents severity sufficient to benefit by PCI reducing myocardial infarction or death. For less clear clinical manifestations or for nonacute CAD, diagnostic testing for quantitative anatomic or physiologic severity becomes the essential guide for revascularization. Therefore, stenosis severity in ACS establishes a severity threshold for which revascularization definitively reduces myocardial and mortality. Quantifying that threshold and the pathophysiology leading to ACS provide insight into quantitative severity by "diagnostic tests" in stable CAD for which intervention might provide similar benefit that is not yet demonstrated in intervention trials in stable CAD.

The schematic of Fig. 34–3 illustrates the pathophysiologic sequence of recurrent subclinical plaque ruptures leading to an ACS.[15-17] Eighty-nine percent of acute fatal coronary events result from a series of preceding, subclinical, small plaque ruptures that heal with progressive narrowing to a severe stenosis; the final plaque rupture that was previously subclinical finally occludes the small remaining lumen with myocardial infarction. Most of these subclinical small plaque ruptures heal and stabilize without occluding the relatively large lumen before the final plaque rupture occludes the evolving narrowed artery. A large nonstenotic lumen with an initial single occlusive plaque rupture explains only 11% of fatal infarctions at pathologic examination.[15]

Intracoronary optical coherence tomography–intravascular ultrasound (OCT-IVUS) in ACS demonstrates severe focal lumen narrowing averaging 72% ± 13% diameter stenosis (DS) superimposed on varying severity of diffuse disease.[16] The OCT-IVUS finding confirms in patients the high-risk severe stenosis superimposed on diffuse disease in ACS. This progression to severe stenosis by serial plaque ruptures may develop over days, weeks, months, or years, thereby explaining the continuum of clinical manifestations from ACS to chronic "stable" CAD of varying severity.[18-22]

The anatomic and physiologic severity of CAD associated with ACS defines that severity threshold at which revascularization may reduce myocardial and mortality in nonacute CAD. Extrapolating these thresholds to cardiac testing and management of chronic "stable" CAD requires conceptual integration with coronary pathophysiology, coronary blood flow (or myocardial perfusion), stenosis pressure gradients, the quantitative coronary angiogram, and specific definitions of *ischemia* as the basis for managing CAD.

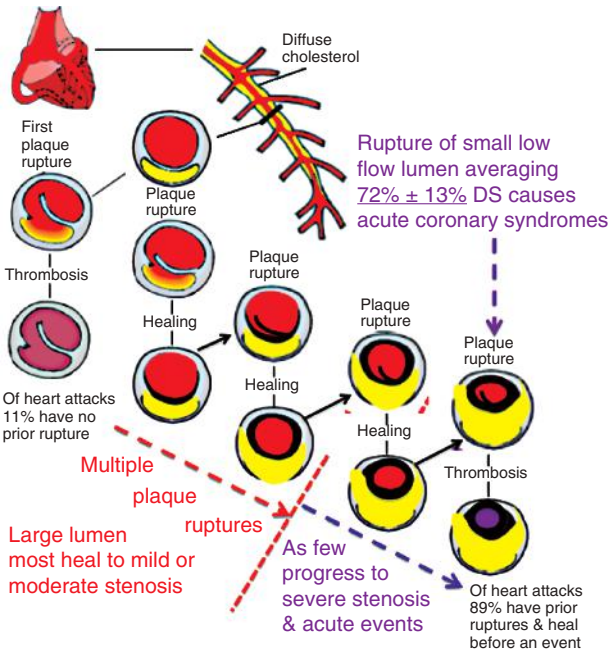


FIGURE 34–3. Schematic of anatomic and pathophysiologic evolution of acute coronary syndromes. DS, diameter stenosis.

CORONARY BLOOD FLOW AT ANATOMIC SEVERITY OF ACUTE CORONARY SYNDROMES

In contrast to anatomic stenosis severity by OCT-IVUS in ACS, coronary blood flow in ACS has not been defined because the clinical circumstances demand immediate intervention. However, coronary blood flow for comparable anatomic severity has been documented in several different ways: (1) comparable stenosis of in vivo experimental models where coronary blood flow is measured, (2) quantitative myocardial perfusion during stress positron emission tomography (PET) imaging in patients having angina and significant ECG changes comparable to ACS, (3) quantitative perfusion in a large study of patients with and without CAD with and without revascularization for comparative ranges of perfusion, and (4) precise fluid dynamic modeling of stenosis and diffuse narrowing in simulations of pressure flow behavior of the entire coronary artery tree.

EXPERIMENTAL CORONARY STENOSIS

Experimental models link severity of coronary blood flow with precise anatomic stenosis comparable to that measured by OCT-IVUS at ACS. Because of high coronary bed resistance at resting conditions, coronary artery stenosis does not cause enough resistance to affect resting flow until 85% to 90% DS as in Figs. 34–4 and 34–5.[23] However, the reserve capacity to increase flow begins to fall at 65% to 70% DS. This reserve capacity or coronary flow reserve (CFR) is the ratio of absolute stress flow to rest flow in absolute units of cc/min for arterial flow or cc/min/g for myocardial perfusion, also called myocardial perfusion reserve (MPR). Because of the extensive literature on fluid dynamic, experimental, and clinical data, we use the terms *CFR* and *MPR* interchangeably here with specific units of flow in cc/min or perfusion in cc/min/g as appropriate.

The term *maximal hyperemia* of coronary flow for quantifying CFR derives from the initial experimental vasodilatory stimulus—reactive hyperemia that is the marked rapid rise in coronary blood flow to maximum after transient coronary occlusion for 10 to 20 seconds. As addressed in a later section on control of coronary blood flow, this basic physiologic phenomenon of maximal hyperemia occurs after every systolic contraction and after every balloon deflation at PCI with little awareness of its physiologic significance.

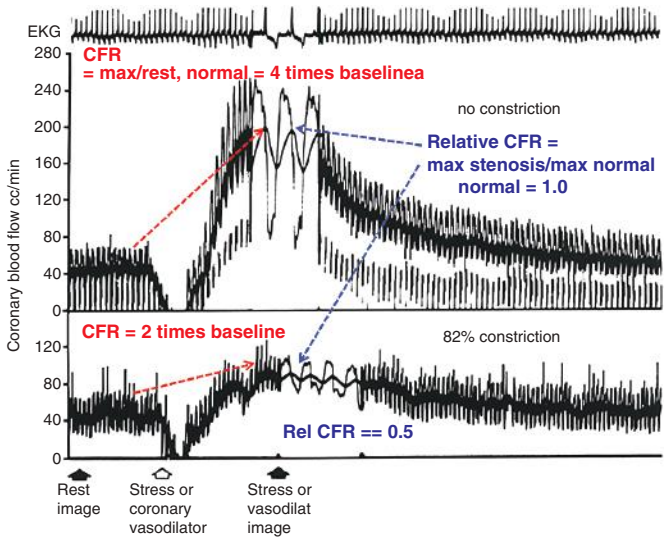


FIGURE 34–4. Coronary flow at rest and at maximal hyperemia with and without coronary artery stenosis. Reproduced with permission from Gould KL, Lipscomb K, Hamilton GW: Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974 Jan;33(1):87-94.[23]

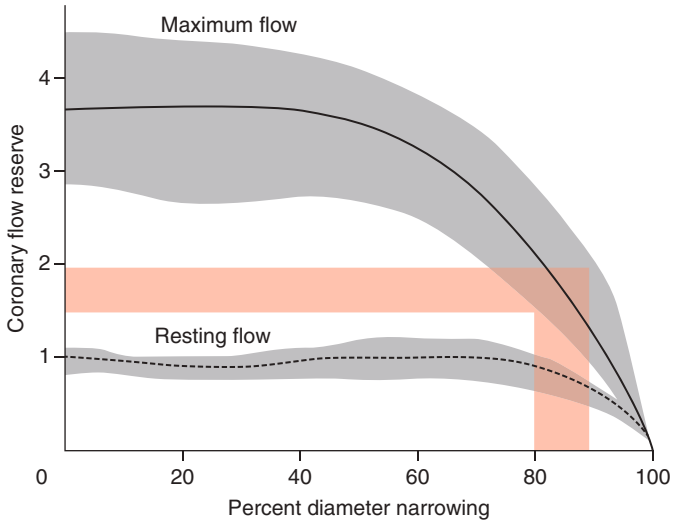


FIGURE 34–5. Coronary flow reserve for progressive percent diameter stenosis. The gray zone marks the limits of data. The red zones correspond to anatomic severity observed in acute coronary syndromes by intracoronary optical coherence tomography–intravascular ultrasound. Reproduced with permission from Gould KL, Lipscomb K, Hamilton GW: Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974 Jan;33(1):87-94.[23]

Experimentally and clinically, maximal hyperemic flow for determining CFR is achieved pharmacologically by arteriolar vasodilating drugs such as contrast media in early experiments, followed by dipyridamole, adenosine, ATP, and regadenoson. Dobutamine is an alternative sympathomimetic stressor producing near-maximal hyperemia for determining CFR. Although exercise increases coronary blood flow, it cannot be measured during upright treadmill exercise that precludes obtaining the arterial input function required for quantitative myocardial perfusion imaging. Although similar for most diagnostic purposes, vasodilator, exercise, and sympathomimetic stressors have some differences that are clinically relevant, as reviewed in the chapter on PET imaging (Chap. 19).

Progressive coronary narrowing reduces CFR with little change in resting flow until an approximately 80% to 90% DS on high-resolution cut film angiograms with a measured resolution of 10 to 11 line pairs per millimeter and/or by a mechanical stenosis caliper. At this severe stenosis, resting flow falls but some residual CFR capacity remains on pharmacologic vasodilator stimulus as seen in Fig. 34–5 in the vertical red zone.[23] Stenosis severe enough to reduce resting perfusion does not elicit all remaining reserve vasodilator capacity because of a remarkable self-regulating mechanism that protects subendocardial perfusion by mechanisms further explained in the later section on myocardial steal.

At such severe stenosis reducing resting perfusion, any increase in vasodilator-mediated increased coronary flow causes a proportionately greater severe fall in coronary perfusion pressure, thereby reducing subendocardial perfusion more than subepicardial perfusion causing subendocardial ischemia, angina, and ST depression on ECG. The coronary control mechanisms that prevent invoking maximal vasodilatory capacity thereby prevent the fall in perfusion pressure and associated subendocardial ischemia. When exercise or pharmacologic vasodilation forces greater vasodilation than stable resting conditions, this protective control is overridden with ensuing subendocardial ischemia.

The red zones of Fig. 34–5 highlight the anatomic severity, 80% to 90% DS, and the physiologic severity at which rest flow falls below normal

resting demands to potentially "ischemic" flow levels. While in the same severe range, the experimental stenosis of 80% to 90% DS appears somewhat worse than the average 72% ±13% DS superimposed on a large burden of diffuse disease observed by OCT-IVUS, causing low enough coronary flow for ACS.[16] The experimental models of isolated stenosis do not have the underlying diffuse disease observed by OCT-IVUS in ACS. Therefore, a 72% DS superimposed on diffuse disease would expect to have an effect on coronary flow comparable to a more severe isolated stenosis of 80% to 90% diameter narrowing without underlying diffuse disease.[24-26]

At such severe stenosis, the anatomic severity parallels severe flow reduction in both experimental, clinical correlations, and fluid dynamic models. Regardless of the mechanical cause of stenosis—structural narrowing, plaque rupture or hemorrhage, thrombosis, or spasm—ACS result from low coronary flow caused by severe stenosis commonly superimposed on diffuse disease in varying proportions. Consequently, the experimental anatomic severity would be expected to be somewhat worse than clinical stenosis superimposed on diffuse disease for a given limitation on CFR or stress flow. For less severe stenosis superimposed on predominantly diffuse disease, the discordance between anatomic severity or percent DS and coronary flow capacity becomes more common as reviewed further below.

CLINICAL QUANTITATIVE PERFUSION IMAGING OF CAD SEVERITY

In a large series of patients with angina, significant ECG changes and severe regional perfusion defects during dipyridamole infusion, the quantitative stress perfusion was 0.91 cc/min/g and CFR 1.7 shown in Fig. 34–6.[27] This low flow threshold causing ischemia in patients compares to the threshold of CFR and percent DS at which resting flow falls in the experimental model of Fig. 34–5 and compares to the 72% DS superimposed on diffuse disease seen in ACS.[16]

In a large clinical study (N = 1674), the low flow threshold of 0.9 cc/min/g and CFR of 1.7 associates with angina, ECG changes, and a severe regional stress defect (Fig. 34–7).[25-28] In these same patients, the relative severity of stress perfusion defects at this ischemic low flow was 0.59. These thresholds at which angina and ST changes develop are substantially lower than in patients without angina or ST changes during dipyridamole stress either with or without revascularization, shown by the red zones of Fig. 34–7.[25-28] ECG-gated PET perfusion images typically show associated impaired regional LV contraction or fall in ejection fraction compared to resting baseline. Importantly, global CFR and stress perfusion in cc/min/g were reduced in parallel with, but less severe than, the regional stress defects, thereby indicating a substantial burden of diffuse CAD underlying the worst flow-limiting stenosis.

Regardless of the mix of regional stenosis or diffuse disease causing these low-stress flows, the thresholds of perfusion in cc/min/g and CFR correlate closely with angina and significant ST changes. Most patients with angina and ECG changes had predominantly severe regional stress perfusion abnormalities superimposed on diffusely reduced stress perfusion reflecting diffuse disease, consistent with OCT-IVUS findings and pathology studies. A significant minority of these patients had severe regional stress perfusion abnormalities with good global flow capacity throughout the remainder of the heart, indicating little diffuse narrowing. Another significant minority had less severe relative regional stress defects superimposed on severely reduced global stress perfusion, indicating relatively more severe diffuse flow-limiting disease, as reviewed in the chapter on PET imaging (Chap. 19).

FLUID DYNAMIC MODELS OF STENOSIS AND DIFFUSE NARROWING

Correlating or predicting physiologic severity from angiographic anatomy, or vice versa, is limited by the modest but real limited resolution and variability of clinical angiographic anatomy and myocardial perfusion measurements. In addition, standard angiography does not account for effects of diffuse CAD. Experimental stenosis with high-resolution angiograms, accurate flow meter measurements, and absence of diffuse disease provide accurate enough data to confirm the applicability of theoretical fluid dynamic equations for stenosis in the absence of diffuse disease.[23,29-32] However, clinical OCT-IVUS observations,[16-22] pathology findings,[15] and quantitative perfusion in

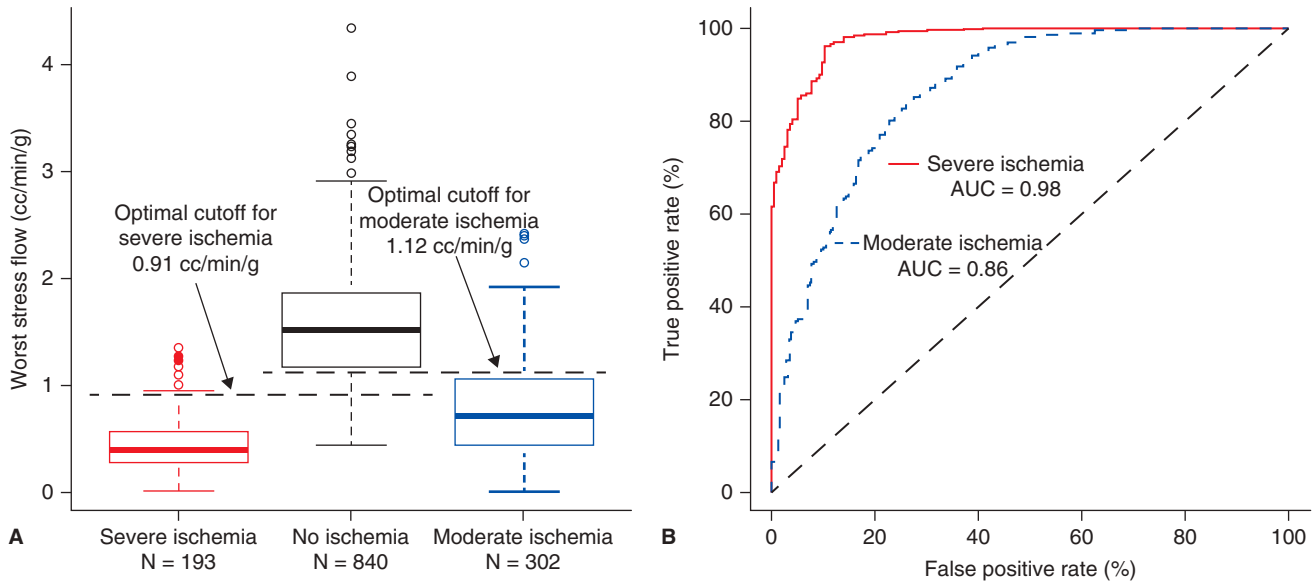


FIGURE 34–6. Regional myocardial perfusion in cc/min/g in patients having a severe stress perfusion defect, angina requiring aminophylline reversal, and/or 1 mm or greater ST depression during dipyridamole stress. Severe (red line) indicates two or all of these criteria. Moderate (blue line) indicates electrocardiogram changes or angina but not both. AUC, area under the true positive versus false positive correlations. Reproduced with permission from Johnson NP, Gould KL: Physiological basis for angina and ST-segment change PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. *JACC Cardiovasc Imaging*. 2011 Sep;4(9):990-998.[27]

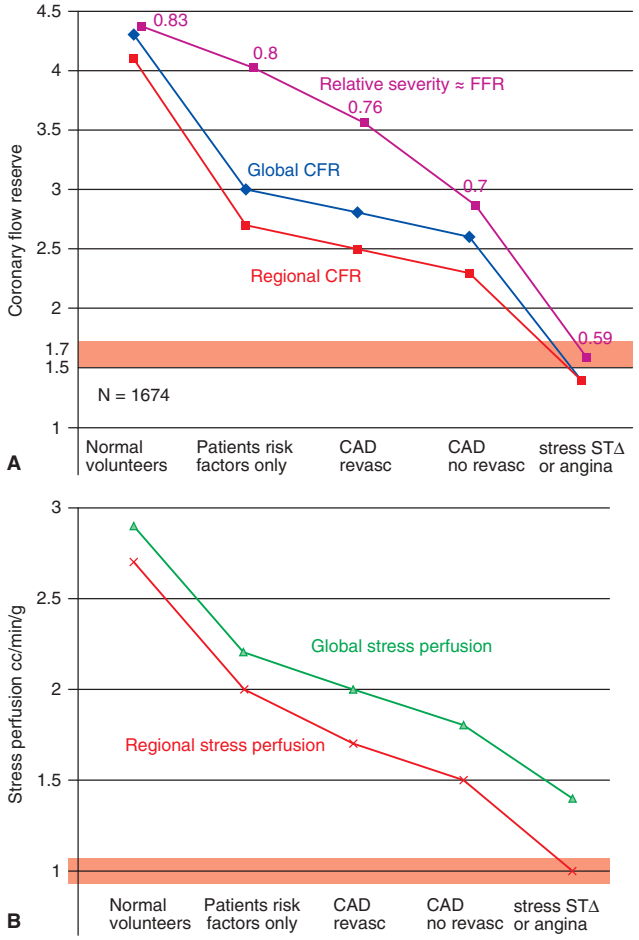


FIGURE 34–7. Coronary flow reserve (CFR) and relative stress defect severity (**A**) and stress perfusion in cc/min/g (**B**) in healthy normal volunteers without risk factors, patients with risk factors only, patients with documented coronary artery disease (CAD) by coronary event or angiogram with and without revascularization, and patients having angina and electrocardiogram changes during dipyridamole stress as reported for Figure 34–6. The red line indicates CFR in the regional stress defect in the distribution of the worst stenosis. The blue line indicates global CFR due to diffuse coronary artery disease. The purple indicates relative severity on the primary radionuclide uptake images using rubidium-82. The red line of B indicates regional stress perfusion in cc/min/g in the distribution of the worst stenosis and the green line indicates global stress perfusion due to diffuse coronary artery disease. The red shaded zone highlight the ranges of severe low CFR and stress perfusion associated with angina and ST changes during dipyridamole stress. FFR, fractional flow reserve. (A) reproduced with permission from Gould KL, Johnson NP2, Kaul S, et al: Patient selection for elective revascularization to reduce myocardial infarction and mortality: new lessons from randomized trials, coronary physiology, and statistics. *Circ Cardiovasc Imaging*. 2015 May;8(5).[26]

patients[24-29] illustrated in Figs. 34–3 and 34–7 indicate the critical role of diffuse CAD underlying most focal stenosis.

In the absence of a clinical or experimental anatomic measure of diffuse disease cumulatively throughout the entire coronary artery tree, fluid dynamic simulations of stenosis and diffuse narrowing in Fig. 34–8[24,26] provide important insights consistent with clinical observations. These precise computer models of stenosis and diffuse narrowing are based on the dimensions and vascular bed sizes reported for the human branching coronary artery tree.[33-36] The model accounts for interacting viscous pressure loss of diffuse narrowing and vortex shedding or turbulent flow caused by segmental stenosis in varying proportions. The calculated CFR and stress flows match the experimental model for stenosis. They also correlate reasonably with clinical anatomic and physiologic quantification of stenosis with minimal diffuse narrowing evidenced by good global CFR and stress flow in patients.

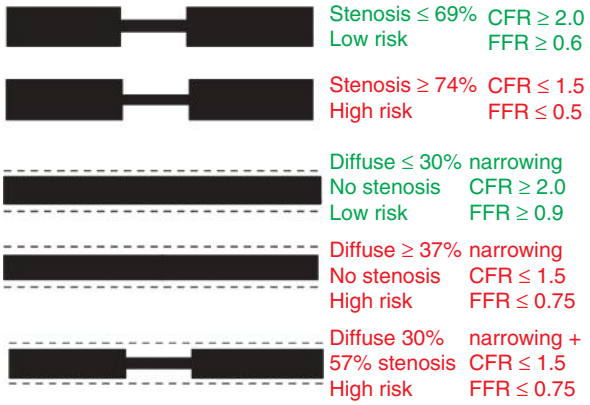


FIGURE 34–8. Computer models of stenosis and calculated coronary flow reserve (CFR) and fractional flow reserve (FFR) based on fluid dynamic analysis of the entire branching coronary artery tree with and without stenosis or diffuse narrowing. Green indicates mild to moderate low-risk stenosis and/or diffuse narrowing. Red indicates severe high-risk stenosis and/or diffuse narrowing as explained in the text. Reproduced with permission from Gould KL, Johnson NP2, Kaul S, et al: Patient selection for elective revascularization to reduce myocardial infarction and mortality: new lessons from randomized trials, coronary physiology, and statistics. *Circ Cardiovasc Imaging*. 2015 May;8(5). pii: e003099.[26]

Coronary flow is a function of the arterial radius raised to the fourth power. Consequently, in Fig. 34–8, the small stenosis diameter change from 69% to 74% DS reduces CFR from 2.0 associated with low risk to 1.5 associated with high risk in large clinical studies reviewed in detail subsequently. Diffuse 30% diameter narrowing reduces CFR to 2.0 associated with low risk. With minimal further diffuse narrowing to only 37% diameter, diffuse narrowing reduces CFR to 1.5 and high risk of coronary events in clinical studies reviewed below. A modest stenosis superimposed on mild diffuse narrowing reduces CFR to low levels associated with high risk where either alone causes no significant high-risk reduction in CFR.

Even for these precise computer models of stenosis, the difference in DS is not visually obvious and diffuse narrowing cannot be seen in the absence of a "normal" reference. As subsequently addressed, the resolution of clinical angiograms is not adequate to quantify such small anatomic differences between high-risk and low-risk physiologic severities of stenosis. Consequently, anatomy-derived predictions of physiologic severity incur such poor accuracy and imprecision as to preclude their reliably guiding clinical decisions on revascularization procedures based on physiologic severity of CAD.

These separate streams of data associated with stenosis severity at ACS suggest a critical threshold of CFR and stress perfusion resulting from physiologically severe high-risk CAD that may benefit from revascularization. This threshold also may also serve to prevent unnecessary procedures incurring greater risk than medically treated disease, thereby leading to nonacute CAD, diagnostic tests, and physiologically guided treatment trials.

NONACUTE CORONARY ARTERY DISEASE

In contrast to ACS,[1] revascularization trials in nonacute CAD have not reduced myocardial infarction or mortality,[2-12] illustrated in Fig. 34–1. However, randomized trials of intervention guided by fractional flow reserve (FFR) provide important insights on physiologic severity.[37-41] Although not definitive for reducing myocardial infarction or mortality by classical intention to treat analysis, the Multicenter Randomized Study to Compare Deferral Versus Performance of PCI (DEFER)[37] and Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trials[38-41] provide additional strong support confirming physiologic stenosis severity as the potential optimal guide to revascularization or medical treatment.

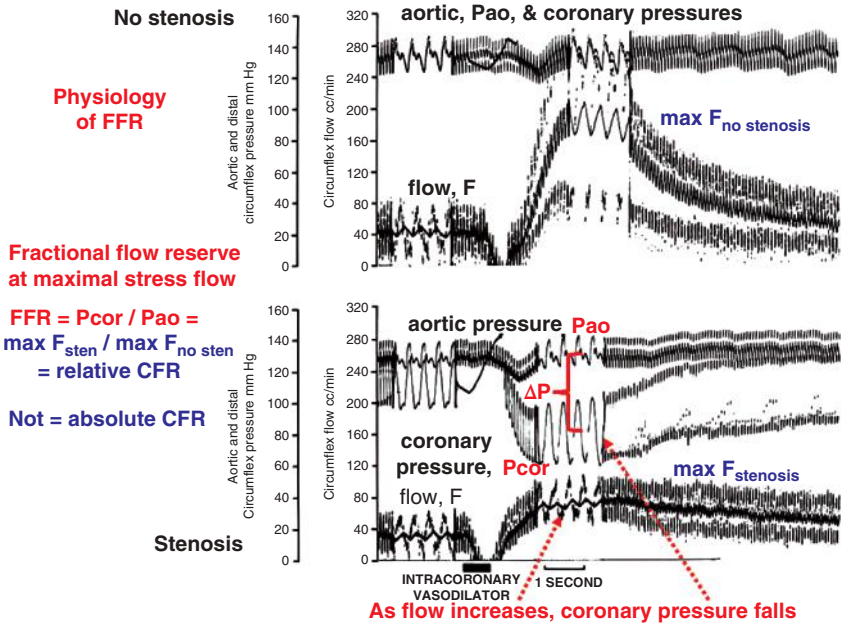


FIGURE 34–9. Coronary blood flow and aortic and coronary pressures at resting baseline and maximal hyperemia with and without stenosis. CFR, coronary flow reserve; max F, maximum flow with and without stenosis; FFR, fractional flow reserve; Pao, aortic pressure; Pcor, coronary pressure. Adapted with permisison from Lipscomb K, Gould KL: Mechanism of the effect of coronary artery stenosis on coronary flow in the dog. *Am Heart J*. 1975 Jan;89(1):60-67.

FFR was first introduced 23 years ago as a potential clinical tool. It has spurred a major evolution in cardiology from angiogram anatomy to coronary physiology as the scientific basis for assessing stenosis severity to guide revascularization.[42] As used clinically, FFR is calculated as the ratio of pressure distal to a stenosis to aortic pressure during maximal pharmacologic hyperemia, typically intracoronary or intravenous adenosine,[42] as illustrated in experimental pressure-flow recordings of Fig. 34–9.[25,43] FFR is comparable to relative CFR (relCFR) but not absolute CFR derived from perfusion in cc/min/g, the consequences of which incur discordances addressed later. The FAME 1 trial[38,39] showed that FFR-guided PCI reduced major adverse coronary events (MACE) compared to angiogram-guided intervention (Fig. 34–10).[38]

Based on traditional intention to treat analysis, the FAME 2 trial using FFR criteria of 0.8 for PCI showed no reduction in myocardial infarction or mortality compared to medical treatment in nonacute CAD[40,41] (Fig. 34–11). However, Landmark Analysis beginning 1 week after the PCI excluded procedure-related events in the first 7 days to show significantly reduced MACE in the PCI versus medical treated group after the first postprocedure week. Therefore, for an FFR threshold of 0.8, the reduced MACE after the first week following PCI was balanced out by an increased risk of MACE (factor of nine) associated with the procedure within the following week. Consequently, PCI had no net benefit on reducing risk of MACE. Because greater stenosis severity associates with higher risk of MACE,[44] the data suggest that at a lower more severe threshold than 0.8, PCI might potentially reduce MACE more than the reported risk of the procedure, thereby providing net benefit at long-term follow-up by intention-to-treat analysis.

The original reports on FFR in patients (DEFER)[37] used a threshold of 0.65 that has increased to 0.8 over the ensuing years, likely related to its application in multivessel disease that includes diffuse disease but lacking trial evidence. Figure 34–12 documents the continuum of severity and risk from meta-analysis of FFR measurements compared to MACE outcomes.[44] Severity-driven risk is an established general concept, but quantification of physiologic severity by FFR versus risk provides important new insights. The intercept of the severity-risk–benefit curves at the black dot of Fig. 34–12 defines the threshold at which the benefit of PCI balances the risk of the disease: here 0.67 from all reports on PCI outcomes at the time of analysis.

In Fig. 34–12, choosing an FFR threshold at the intercept, or at severities close to it on either side of the intercept, would have little net benefit or harm because of the overlap of the probability ranges for severity risk curves. At thresholds further toward lower FFR and greater physiologic severity, the benefit of revascularization can be more readily detected if it exists. Note that the relative severity of PET perfusion images at 0.59 associated with stress angina and ECG changes in Fig. 34–7 compare to the severity of FFR in Fig. 34–12 expected to have net reduction in MACE over medical treatment.

The evidence-driven scientific basis for management of CAD has evolved from anatomic angiographic to physiologic severity of CAD, incurred by widening use of pressure-based, FFR-guided elective interventions. However, FFR has some limitations, was derived from the original concepts of CFR, and has been validated by quantitative PET absolute perfusion in cc/min/g. As for most science, each major advance establishes a springboard for the next step—here FFR leading to quantitative myocardial perfusion to guide CAD management. Evolving physiologic severity to guide management beyond FFR will likely parallel remaining dominance of the coronary angiogram in CAD management. However, transcatheter therapeutics have and will increasingly rely on physiologic severity rather than the past dominant role of the angiogram. The current major gap in cardiovascular medicine/interventions is absence of randomized revascularization trials with myocardial infarction or mortality end points guided by integrated, comprehensive, quantitative physiologic severity of stenosis and diffuse CAD based on combined stress perfusion and CFR.

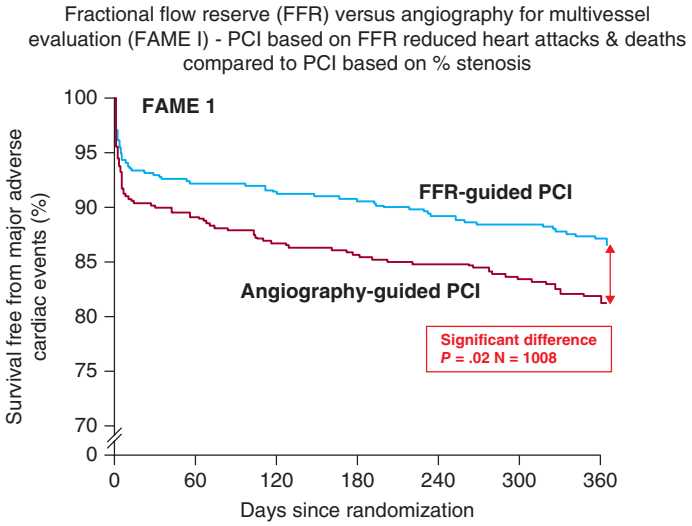


FIGURE 34–10. Survival free from major adverse events in patients with angiogram-guided percutaneous intervention (PCI; red line) compared to fractional flow reserve (FFR)–guided PCI (blue line) of the FAME 1 randomized trial. Reproduced with permission from Tonino PA, De Bruyne B, Pijls NH, et al: Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009 Jan 15;360(3):213-224.[38]

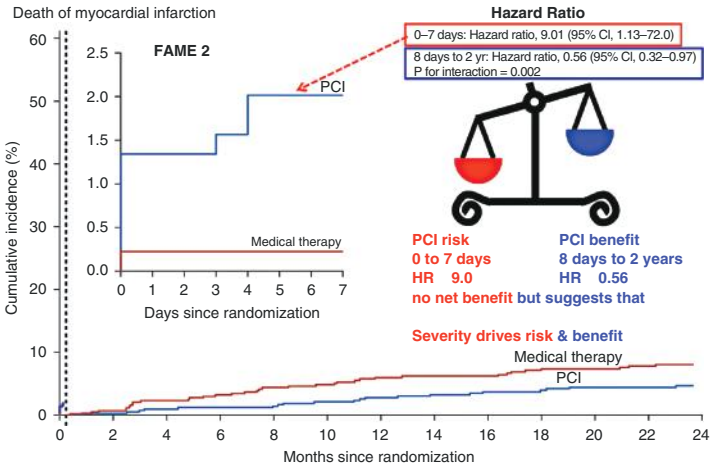


FIGURE 34–11. Cumulative major adverse coronary events in patients with fractional flow reserve–guided percutaneous coronary intervention (PCI) (blue line) compared to medical treatment (red line) within the first week after the procedure (inset) and after the first week up to 24 months follow-up. See text for red and blue icon of the balance scales. Reproduced with permission from De Bruyne B, Fearon WF, Pijls NH, et al: Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014 Sep 25;371(13):1208-1217.[41]

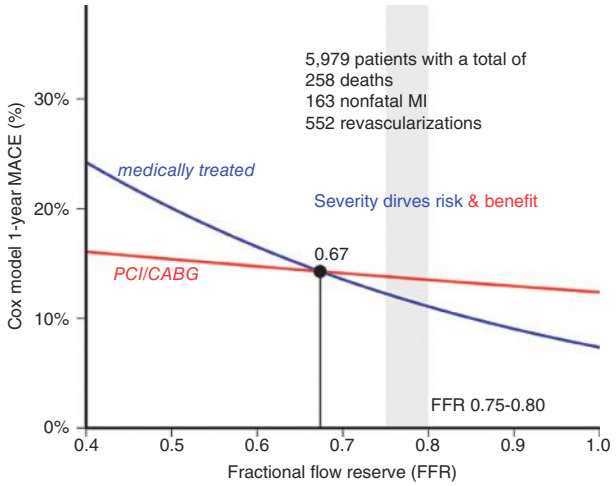


FIGURE 34–12. Meta-analysis showing the continuous relation of fractional flow reserve and major adverse coronary events (MACE) with medical treatment (blue line) and revascularization (red line). See text for blue and red groups of patients. Reproduced with permission from Johnson NP, Tóth GG, Lai D, et al: Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol*. 2014 Oct 21;64(16):1641-1654.[44]

THE CORONARY ANGIOGRAM AND RISK

Because anatomic severity by OCT-IVUS at ACS defines critical physiologic stenosis severity underlying ACS, why has the coronary angiogram severity failed to identify patients for whom revascularization also reduces myocardial infarction or mortality in nonacute CAD? Early and recent literature shows a severity risk relation as in Fig. 34–13. Panel A from old literature shows *average* angiographic percent DS related to subsequent occlusion at follow-up angiogram[45,46] regardless of clinical events and obviously not accounting for deaths. Panel B shows recent data with similar power curves relating the angiographic SYNergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) score to mortality at different follow-up intervals.[47] These correlations of average percent DS with outcomes confirm a severity-risk continuum as for FFR in Fig. 34–12.

However, angiographic severity to guide revascularization has not identified patients for whom these procedures reduce myocardial infarction or mortality. There are three possible reasons: (1) revascularization procedures do not benefit any severity of nonacute CAD; (2) the percent DS threshold guiding procedures is not severe enough with insufficient risk to benefit from the procedures; and (3) resolution of the clinical angiogram is inadequate to define the critical different between high-risk, low-low capacity stenosis and mild to moderate low-risk, adequate flow stenosis.

In view of beneficial intervention in ACS, the latter two alternatives likely answer the question above as illustrated in Fig. 34–14.[28] The PET scan shows a severe large-stress defect leading to the angiogram and stenting with follow-up angiogram. Quantitative analysis of the angiogram reported an average 83% DS tapering stenosis seen visually. The computer simulations in panels A, D, and E are precise simulated stenosis of 67% DS, 75% DS, and 83% DS with their fluid dynamically calculated CFR associated with low or high risk. Panels B and C are the angiogram of a plastic stenosis model of 67% DS filled with contrast media without heart motion or other factors degrading angiogram quality.

The limited resolution of the angiogram[34] with loss of border resolution makes it look worse than its true 67% DS associated with adequate CFR associated with low risk. In this critical range, even precise simulated stenosis from 67% to 83% DS is not readily distinguished visually and certainly not quantifiable by automated quantitative angiographic analysis. At the critical threshold of 75% to 83% DS associated with low CFR and high risk, the angiogram cannot identify those patients with physiologically severe stenosis who may benefit from revascularization more than the risk of the procedure.

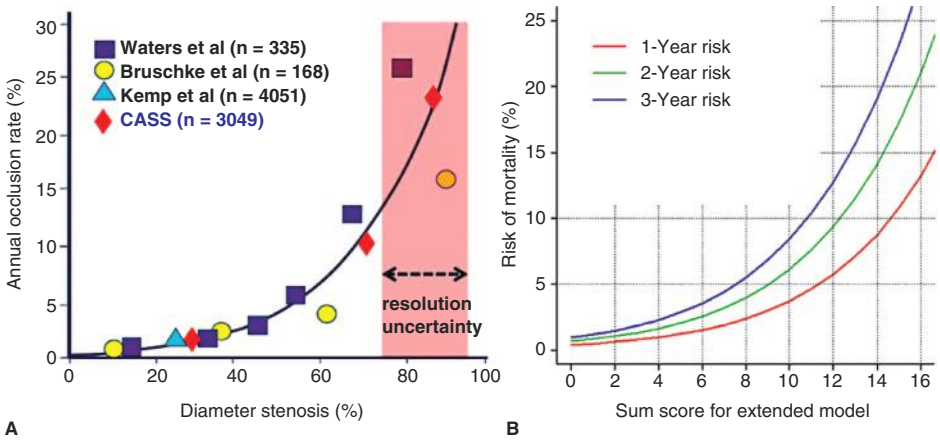


FIGURE 34–13. Percent diameter stenosis at baseline angiogram compared to annual rate of total occlusion on follow-up angiogram (**A**) and mortality compared to angiogram SYNTAX score (**B**). CASS, Coronary Artery Surgery Study; SYNTAX, SYNergy Between PCI With TAXUS and Cardiac Surgery. (A) data from Alderman EL, Corley SD, Fisher LD, et al: Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. *J Am Coll Cardiol*. 1993 Oct;22(4): 1141-1154.[45] (B) reproduced with permission from Iqbal J, Vergouwe Y, Bourantas CV, et al: Predicting 3-year mortality after percutaneous coronary intervention: updated logistic clinical SYNTAX score based on patient-level data from 7 contemporary stent trials, *JACC Cardiovasc Interv*. 2014 May;7(5):464-470.[47]

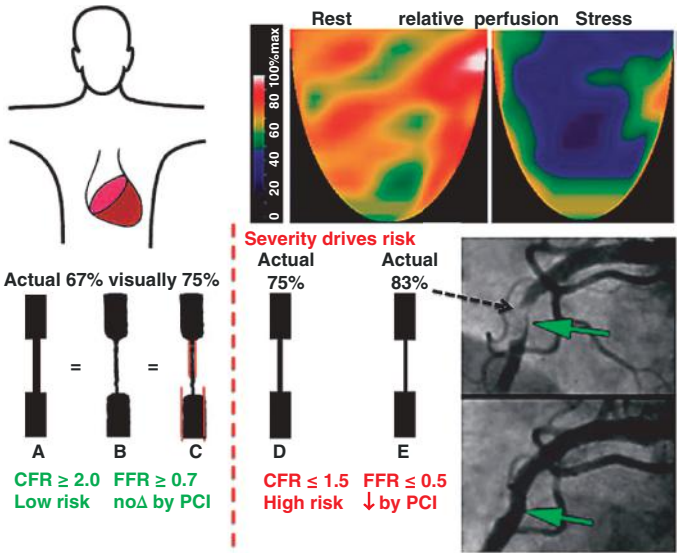


FIGURE 34–14. Rest and stress positron emission tomography perfusion images showing a severe stress defect (blue) with angiogram before and after percutaneous coronary intervention (PCI). Inset: Simulated stenosis fluid dynamic models (**A, D, E**) and angiogram of stenosis phantom (**B, C**). See text for green and red coronary flow reserve (CFR) and fractional flow reserve (FFR) categories. Reproduced with permission from Gould KL, Johnson NP, Kaul S, et al: Patient selection for elective revascularization to reduce myocardial infarction and mortality: new lessons from randomized trials, coronary physiology, and statistics. *Circ Cardiovasc Imaging*. 2015 May;8(5).[26]

Finally, in past and current trials, it is likely that patients with objectively measured stenosis of 67% to 83% DS shown here would not be randomized to medical treatment or revascularization because of preexisting bias that those randomized to medical management would suffer unethical withholding beneficial treatment. The same bias now applies to the FFR threshold of 0.8 despite the fact that angiographic severity or FFR as now used does not identify patients for whom revascularization reduces myocardial infarction or mortality despite reducing angina as discussed above.

QUANTITATIVE MYOCARDIAL PERFUSION AND RISK

An extensive literature documents the relation of CFR and cardiovascular risk as recently reviewed[25,26] and confirmed in a large patient cohort (Fig. 34–15).[48,49] Global CFR by PET reflecting the global burden of diffuse and segmental CAD in a large cohort of patients showed high risk for global CFR less than 1.5 compared to low risk for global CFR greater than 2.0 and intermediate risk for CFR between these values, as in Panel A. In this nonrandomized study, PCI or coronary artery bypass (CAB) in patients with global CFR over 2.0 had no benefit over medical treatment on mortality, as in Panel B. For global CFR less than 1.5, PCI had no benefit over medical treatment as expected for severe diffuse CAD. However, patients with global CFR less than 1.5 undergoing CAB had significantly better survival than medical treatment. Although the data are not definitive in the absence of a randomized trial, they are consistent with the quantitative severity-risk relations discussed above, all leading to a unifying synthesis on physiologic severity of stenosis and diffuse disease for guiding management of CAD.

THE UNIFYING CONCEPT—QUANTITATIVE PHYSIOLOGIC SEVERITY

This overview derived from ACS benefited by revascularization establishes the relevance of coronary blood flow and clinical coronary pathophysiology, stenosis pressure gradients, and quantitative diffuse disease in management of CAD. Figure 34–16 (central illustration) summarizes the concept for the various measures of severity outlined above.[50] The continuum of quantitative severity versus risk likely explains in part the failure of all trials using all of these technologies to identify those patients having physiologically severe enough CAD to benefit optimally with revascularization or medical treatment alone. In the severity-risk continuum, less severity associates with procedural risk higher than risk of the disease and therefore patient harm. Progressively greater severity associates with higher risk most likely to benefit from revascularization over the risk of the procedure plus risk of medical management. Of course, there is no randomized trial to prove this view, and there may not be one given the general unwillingness to randomize patients with more severe disease on the left of the curves intersection (the red dot).

DISCORDANCES AMONG CORONARY FLOW, STENOSIS PRESSURE GRADIENT, AND ANATOMIC SEVERITY

Although FFR has had a profound beneficial influence on moving the scientific basis for assessing coronary stenosis from angiogram anatomy to physiologic severity, it has several clinically important limitations. It requires invasive coronary pressure measurements at coronary angiogram that commonly bypasses physiologic measurements. By increasing costs of the cardiac catheterization and potentially

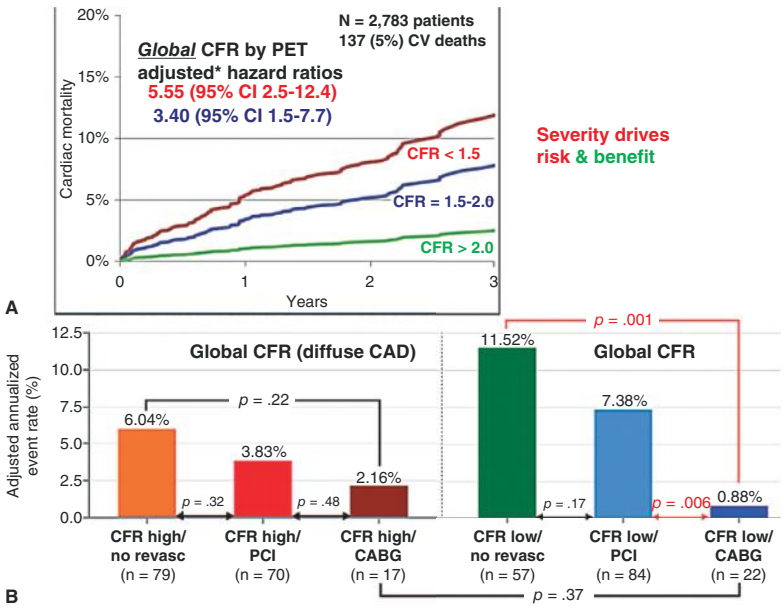


FIGURE 34–15. Global coronary flow reserve (CFR) by positron emission tomography (PET) perfusion imaging and cardiac mortality (**A**) and outcomes in relation to revascularization by percutaneous coronary intervention (PCI) or coronary bypass graft surgery (CABG) (**B**). See text for red and green phases. CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular. (A) reproduced with permission from Murthy VL, Naya M, Foster CR, et al: Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011 Nov 15;124(20):2215-2224.[48] (B) reproduced with permission from Taqueti VR, Hachamovitch R, Murthy VL, et al: Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation*. 2015 Jan 6;131(1):19-27.[49]

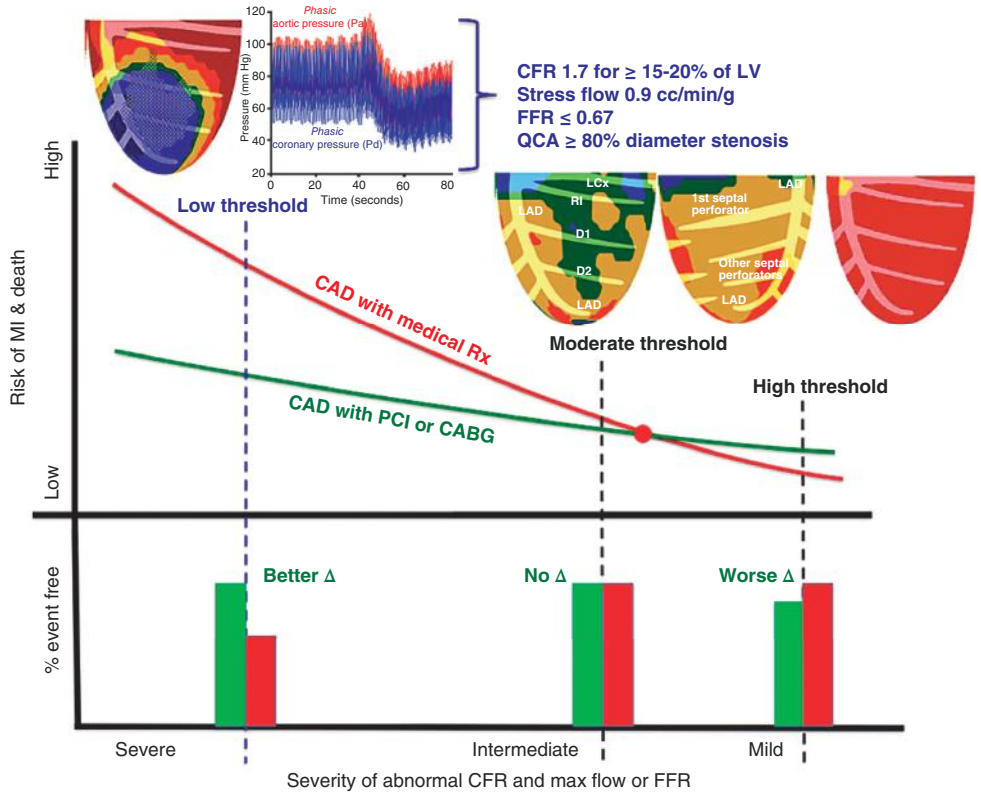


FIGURE 34–16. Conceptual synthesis of the continuous relation of coronary artery disease (CAD) severity to risk of myocardial infarction (MI) or death with revascularization compared to medical treatment (Rx) alone. Severity thresholds are indicated for stress positron emission tomography perfusion images and for fractional flow reserve (FFR) from aortic and coronary pressures. CFR, coronary flow reserve; LV, left ventricle; QCA, quantitative coronary angiogram. Reproduced with permission from Gould KL, Johnson NP, Kaul S, et al: Patient selection for elective revascularization to reduce myocardial infarction and mortality: new lessons from randomized trials, coronary physiology, and statistics. *Circ Cardiovasc Imaging*. 2015 May;8(5).[26]

reducing revenues by eliminating stent procedures, it is not widely considered as economically favorable for slim catheterization laboratory margins. Scientifically, FFR discordance with CFR by flow velocity wires or by quantitative PET perfusion imaging shown in Fig. 34–17[33] is an unresolved issue for which measurement should guide PCI. The discordances are comparable in both invasive pressure-flow velocity correlations as well as correlations between relative CFR, analogous to FFR, versus absolute CFR by quantitative PET imaging.[25,33] These discordances arise primarily from FFR, reflecting relative as opposed to absolute CFR derived from quantitative perfusion in cc/min/g.

For example, consider the orange region of Fig. 34–17,[33] where vasodilatory capacity is preserved with CFR of 3.0 associated with a large pressure gradient and FFR less than 0.8. Such high flow capacity is associated with low risk on medical treatment as in Fig. 34–15 and is well above ischemic flow levels at CFR of 1.7 in patients having angina and ST changes of Figs. 34–6 and 34–7. In this report relating CFR to FFR,[33] 19% of cases had high-flow, low FFR discordance typical of mild to moderate focal stenosis with high flow capacity preserved by minimal diffuse or small-vessel disease, the orange region of Fig. 34–17. At the opposite end of the continuum, 21% of patients fell into in the yellow region of Fig. 34–17 with severely reduced CFR and an FFR greater than 0.8. This discordance is caused by severe diffuse disease reducing CFR without significant focal stenosis, causing a stenosis gradient with high FFR. As in Fig. 34–15, such low global CFR or stress perfusion associates with high-risk disease for which bypass surgery may reduce risk of myocardial infarction and mortality despite high FFR but requires randomized trials.

FFR has similar discordance with angiographic severity separately from the issue of precise angiographic quantification of stenosis. Inclusion criteria for FAME 1[38,39] and FAME 2[40,41] trials were an angiogram stenosis of visual moderate severity for which FFR was measured to guide PCI randomized to medical treatment. Many other patients without visual moderate stenosis on angiogram had FFR

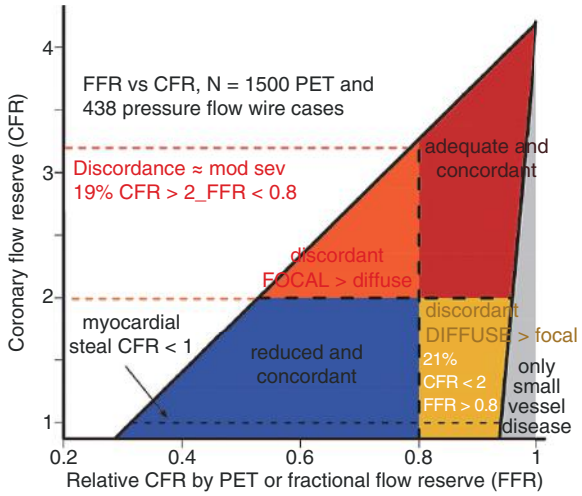


FIGURE 34–17. Discordance between fractional flow reserve (FFR) and coronary flow reserve (CFR) by pressure-flow velocity wires and by absolute CFR derived from perfusion in cc/min/g versus relative CFR by positron emission tomography (PET) analogous to the relative flow reserve by pressure-based FFR. See text for details. Reproduced with permission from Johnson NP, Kirkeeide RL, Gould KL: Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? *JACC Cardiovasc Imaging*. 2012 Feb;5(2):193-202.[33]

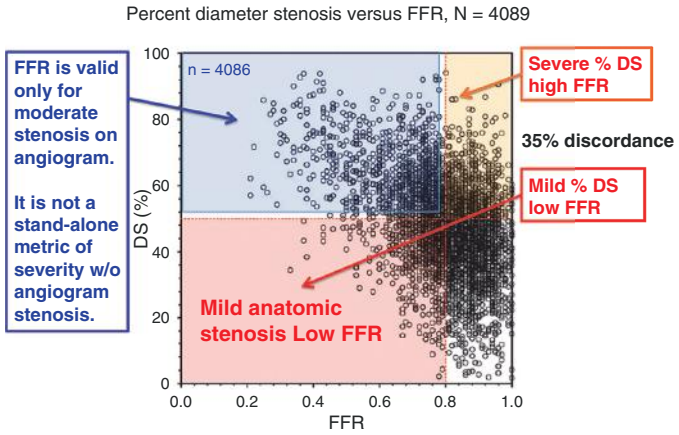


FIGURE 34–18. Percent diameter stenosis (DS) on angiogram compared to fractional flow reserve (FFR) for all patients without selection for visual angiographic severity. The blue shaded area indicates concordance of low FFR with severe percent DS. The red shaded area indicates discordance with low FFR and mild percent stenosis. The yellow shaded area indicates discordance with high FFR and severe stenosis. There was discordance of either type in 35% of the patients. See text for red and blue phases. Reproduced with permission from Toth G, Hamilos M, Pyxaras S, et al: Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J*. 2014 Oct 21;35(40):2831-2838.[51]

measurements but were excluded from the FAME trials. For all patients including those with no significant visual stenosis on angiogram, FFR versus percent DS values are plotted in Fig. 34–18.[51]

The blue region shows concordance of severe percent DS with low FFR. However, it also indicates that FFR is not a stand-alone measure of severity. Rather, the validity of FFR to guide PCI depends on a visually moderate angiographic stenosis (ie, it depends on the angiogram). Patients in the red region of Fig. 34–18 had low FFR despite having visually mild or no stenosis on angiogram, likely as a result in part to diffuse disease proximal to the pressure wire measurement or preserved CFR with high stress perfusion causing low FFR. In either case, the low FFR may not indicate PCI for either diffuse disease or the non–flow-limiting stenosis. Patients in the yellow region had severe stenosis on angiogram with high FFR, likely the result of diffuse or small-vessel disease or blood caffeine that impaired coronary flow sufficiently to prevent a pressure gradient across the stenosis. This study reported an overall discordance of 35% between FFR and percent DS on angiogram separately from the limitations of resolution on quantitative angiographic analysis.

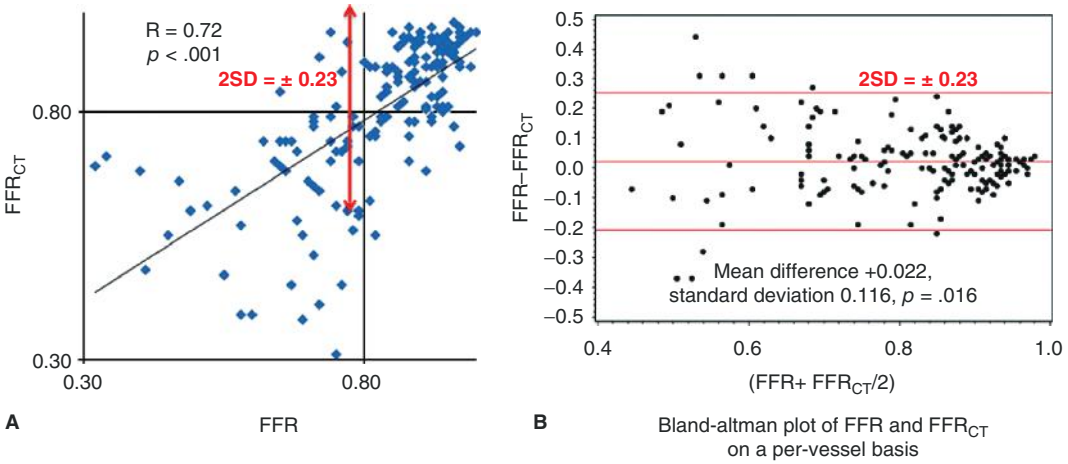
CORONARY ANATOMY TO PREDICT PHYSIOLOGIC SEVERITY

Thirty-four years ago, angiographic stenosis dimensions were first used to predict physiologic characteristics of stenosis in an in vivo experimental model. Good average correlations between pressure gradients and CFR were found using relatively simple fluid dynamic equations. However, the standard deviation or variability around the good mean correlations was sufficiently great to preclude reliable application to individuals. The most recent advanced technology using computed tomography (CT) angiograms and advanced computational fluid dynamics have also shown a comparable good (but not better) average correlation between CT predicted and measured FFR by pressure wire.

However, the wide standard deviation about this average good correlation is the same as the early years[32,34,52,53] that limits application to individuals for personalized clinical management, as illustrated in Fig. 34–19.[34,52] The Bland Altman analysis shows two standard deviations (SD) of ± 0.23 for 95% confidence intervals. Therefore, for a true measured FFR of 0.8, the FFR_{ct} could be 0.57 or 1.0, thereby explaining why the clinical trial of FFR_{ct} failed to achieve its target of predicting measured FFR.[52] The reasons include the limited resolution of CT[34] and real biological discordance between FFR and CFR.[25,33]

EXERCISE, CORONARY BLOOD FLOW, AND MYOCARDIAL ISCHEMIA

Exercise stress testing is embedded in cardiovascular medicine, particularly the Bruce treadmill protocol. Although the diagnostic sensitivity and specificity of ECG changes may be suboptimal, treadmill duration reflecting overall cardiovascular fitness associates with risk of clinically manifest cardiovascular disease as reviewed below. However,



For true FFR = 0.8 by pressure wire, the CT FFR may be 1.0 to 0.57 for 95% certainty. Therefore, CT predicted FFR fails to quantify severity.

FIGURE 34–19. Fractional flow rate (FFR) derived from the computed tomography (CT) angiogram by computational fluid dynamics compared to FFR from measured pressures (**A**) with its Bland Altman plot (**B**) showing two standard deviations (SD) of ± 0.23 FFR units. Red arrows show this SD spread about the FFR threshold of 0.8 for guiding PCI. Reproduced with permission from Koo BK, Erglis A, Doh JH, et al: Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol*. 2011 Nov 1;58(19):1989-1997.[53]

as a currently used component of randomized intervention trials, it does not identify patients for whom revascularization reduces myocardial infarction or mortality.[3-13] Consequently, the relation of exercise capacity to coronary blood flow projects directly into the definition of ischemia, anatomic versus physiologic severity, and their relative risks and treatment outcomes.

A basic limitation is lack of adequate data on quantitative myocardial perfusion during upright treadmill exercise most commonly used that precludes acquiring accurate arterial input and quantitative myocardial radionuclide uptake during treadmill exercise. Although substantially different exercise stress than the treadmill, supine exercise and dobutamine stress provide some limited insights into associated coronary blood flow. Recent reviews relate myocardial perfusion by quantitative PET using oxygen-15 water to heart rate (HR), mean arterial pressure (MAP), their pressure rate product (PRP), and associated estimated metabolic equivalents (METS) during supine bicycle exercise in healthy young conditioned volunteers.[54-56] At severe to maximal effort to the anaerobic threshold, HR was over 200 beats/min, MAP was approximately 120 mm Hg, PRP was approximately 20,000, and the myocardial perfusion was approximately 3.0 cc/min/g.

Although normalizing perfusion to PRP is not useful clinically, it serves here for estimating the maximum or ischemic perfusion threshold at high PRP workloads. As reported above,[54-56] normalizing perfusion of 3.0 cc/min/g to 20,000 PRP is 0.15 cc/min/g per 1000 PRP units in the healthy young volunteers.[54] For a convenient MAP of 100 mm Hg and HR of 60,[54] this maximum perfusion threshold is 0.15 × 6 or 0.9 cc/min/g per 6000 PRP units This threshold of 0.9 cc/min/g per 6000 PRP in healthy young conditioned volunteers establishes their limit of coronary blood flow at their limit of cardiac performance. In patients with CAD, the low-flow perfusion threshold associated with angina and significant ST depression is also 0.9 cc/min/g at PRP of 6000 (MAP 100, HR 60).[27] Therefore, patients with CAD are limited to much lower PRP workloads at the ischemia threshold of 0.9 cc/min/g at 6000 PRP,[27] which is the same threshold of 0.9 cc/min/g per 6000 PRP units for healthy young volunteers who achieve much higher PRP workload at maximum exercise effort.[54]

Therefore, patients with CAD during dipyridamole stress had angina, significant ECG changes, and severe regional perfusion defects at the same threshold, 0.9 cc/min/g per 6000 PRP[27] as healthy young volunteers at maximum exercise limits and PRP of 20,000.[54] This stress perfusion threshold in these clinical patients was the same for those with total occlusion and myocardial steal as for those with severe stenosis without total occlusion and no myocardial steal regardless of beta-blockers or other medications. Therefore, at whatever level of effort or PRP causing ischemia in patients or limiting cardiac performance in healthy young subjects, the normalized perfusion threshold appears to be 0.9 cc/min/g per 6000 PRP. A stress perfusion at this threshold or less will likely be associated with angina or ST changes in patients with CAD or associated with maximum cardiac performance in healthy subjects.

However, PRP is not a complete measure of coronary blood flow demand because it does not account for "contractility" that, however, has no standardized definition or quantitative measure. "Contractility" usually parallels HR and blood pressure; therefore, PRP remains a useful clinical approximation of metabolic and therefore coronary blood flow demand. *Myocardial oxygen consumption* is a more complete measure of myocardial demand accounting for "contractility" but is not readily measured routinely. Because of the high oxygen extraction from coronary artery blood, coronary blood flow closely parallels oxygen demand and supply thereby explaining in part the concept of a universal absolute perfusion threshold at which ischemia develops or maximal myocardial performance is reached. Finally, in patients, the area under the curve (AUC) of 0.98 for the threshold of 0.9 cc/min/g to predict angina and significant ST changes was not increased or improved by normalizing for PRP. Consequently, this threshold appears to be the observed universal threshold of myocardial perfusion below which ischemia develops or the limits of myocardial performance is reached.

Normalizing perfusion to PRP allows comparison of the perfusion threshold of ischemia or maximum cardiac performance at markedly different workloads, thereby minimizing differences among subjects; it therefore eliminates personalized clinical assessment for any specific single subject. Consequently, primary perfusion data without normalization to PRP are essential for assessing an individual's coronary flow capacity for personalized clinical decisions.

ISCHEMIC THRESHOLDS AND EXERCISE PRESSURE RATE PRODUCT

This observation thrusts coronary blood flow and exercise into varied conflicting definitions of ischemia best clarified by illustrative case examples. Consider a patient reaching PRP of 20,000 or higher at nine METS[54] and stage 4 of the Bruce treadmill protocol before getting angina and ST changes on ECG. Although diagnostic of ischemia and CAD, the good cardiovascular capacity associates with relatively low risk of adverse events with medical treatment.[57] Now consider a patient reaching PRP of 6000 at one METS in stage 1 of the Bruce treadmill protocol or dipyridamole stress with angina and ST changes on ECG; this patient is at high risk for adverse events.[57] Based on clinical data above, both patients likely have ischemia at the same normalized threshold of 0.9 cc/min/g per 6000 PRP but at markedly different exercise levels.

Although in one sense a universal physiologic measure of ischemia, this normalized perfusion threshold does not indicate the effort level for each patient at which such low perfusion caused ischemia. Ischemia at 20,000 PRP, nine METS, and stage 4 of the Bruce protocol is low risk, whereas ischemia at 6000 PRP,[57] one METS, and stage 1 of the Bruce protocol is high risk.[54] However, stress perfusion for the first patient above is high, well over the threshold causing angina and ECG changes during stress perfusion imaging and well over flows associated with high risk. Stress perfusion for the second patient is at the low-flow threshold that is associated with high risk. Thus, stress perfusion of 0.9 cc/min/g becomes an objective, quantitative, universal measure of high-risk ischemia by whatever stress is used.

Both of the above examples have ischemia, but the term fails to provide management direction. Moreover, for clinical practice and intervention trials, treadmill tests are largely viewed as positive or negative for ECG changes or angina. Treadmill duration is less often considered because variability is in part caused by many other factors, particularly deconditioning and musculoskeletal limitations or beta blockade that limits duration aside from restricted coronary blood flow, limiting exercise capacity.

Figure 34–20 shows a graph of this concept with stress flow in cc/min/g and CFR on the vertical axis and PRP on the horizontal axis derived from a large patient database[25,27,28] and the literature.[54] The large bold letters "X" in the graphs are *measured* thresholds of CFR and stress perfusion at which angina and significant ST change developed during dipyridamole stress perfusion imaging. The *measured* thresholds of stress flow and CFR for patients with total coronary occlusion with myocardial steal are similar to those with severe stenosis without occlusion, averaging 0.9 cc/min/g and CFR 1.4 at an average PRP of 21,000, and a normalized PRP of 0.26 cc/min/g per 6000 PRP. The solid lines plot *projected* stress flow and CFR at other levels of PRP based on the *measured* PRP for the patients having angina and ST changes at the *observed* CFR stress flow thresholds.

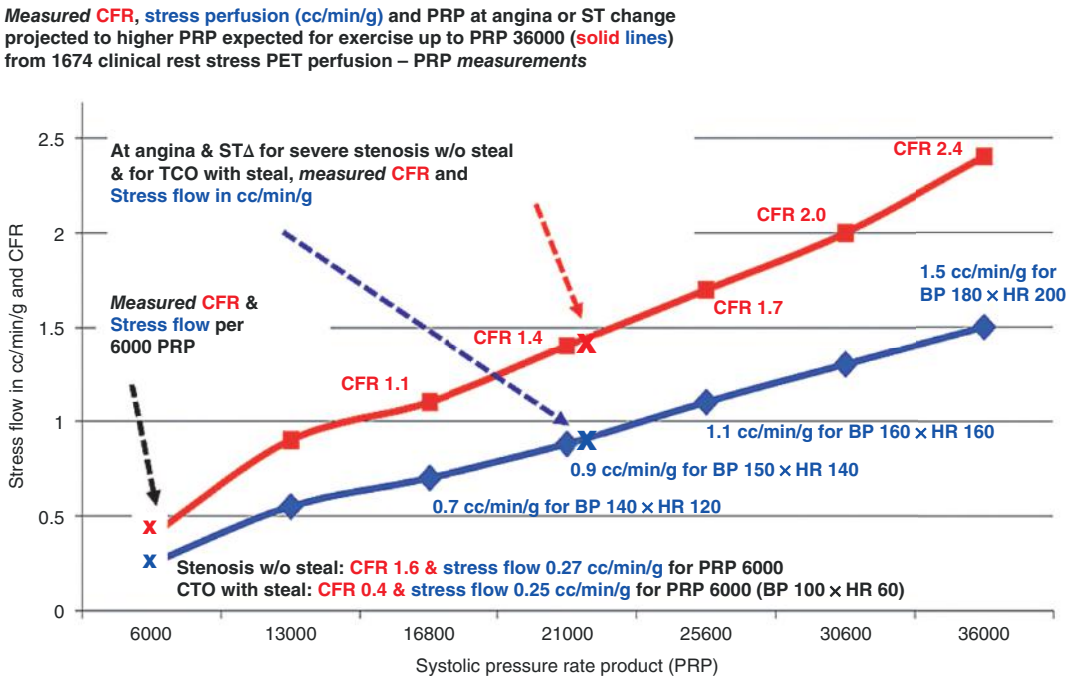


FIGURE 34–20. Coronary flow reserve (CFR) (red) and stress perfusion in cc/min/g (blue) compared to pressure rate product (PRP) extrapolated from measured values (large "X") in patients with angina and ECG changes during dipyridamole stress PET perfusion imaging. See text for red and blue text phrases. BP, blood pressure; HR, heart rate; CTO, chronic total occlusion.

The graph shows many different thresholds of stress perfusion or CFR for ischemia depending of the PRP demand. The choice or definition of ischemic flow threshold depends on what question is asked for what purpose. For diagnosis of CAD in active people, a stress threshold of 1.3 to 1.5 cc/min/g or higher and CFR of 2.0 or higher at a high PRP might be observed but does not associate with high risk[26,48,49] and therefore is best treated medically.[2-7] Therefore, *ischemia* is not necessarily synonymous with high-risk severity indicating revascularization. For quantifying severe high-risk CAD to guide revascularization, a flow threshold of 0.9 cc/min/g or below and CFR of 1.7 or below are documented critical thresholds for angina and ST depression during dipyridamole stress.[25-29] However, randomized revascularization trials are needed using patient selection based on integrated quantitative stress perfusion and CFR to identify more physiologically severe disease than current trials.[26]

In the original report of these thresholds for stress perfusion and CFR at which angina and ST developed,[27] normalizing the observed values by the corresponding PRP values did not improve the area under the probability curve separating the patients with and without angina and ECG changes. Because normalization of flows to PRP eliminates its value for assessing severity in an individual, as explained above, the observed 0.9 cc/min/g and CFR 1.7 at which angina and ST changes occurred during stress perfusion imaging are essentially objective quantitative, universal thresholds defining high-risk ischemia that may benefit from invasive procedures. Less severe stress abnormalities indicate reduced stress flow or CFR but not ischemic high-risk, low coronary flow capacity.

With low rest flow and low stress flow resulting from beta blockade with adequate CFR, patients usually have no angina or ST change with exercise despite very low stress flow. This reduced flow demand parallels reduced myocardial oxygen demand and reduced PRP at a given level of exercise that is the mechanism of beta-blocker relief of angina. With beta blockade, stress perfusion may be low because of low PRP for a given level of exercise and remaining CFR. As exercise intensity increases, this remaining CFR may be recruited until reaching the threshold of 0.9 cc/min/g per 6000 PRP units when angina and ST changes are likely to develop, limiting further exertion.

Therefore, with beta blockade in patients with CAD, CFR provides additional diagnostic insight over and above stress perfusion alone to help guide management. Patients with CAD on beta-blockers commonly have low stress perfusion but remaining CFR associated with no angina or ST changes at dipyridamole or exercise stress. Therefore, there is little basis for revascularization in such asymptomatic patients because revascularization trials show no reduction myocardial infarction or death.[1-8] However, if CFR is also low, below 1.7, the combined low CFR and low stress perfusion associate with severe CAD and high-risk angina and ST depression with stress for which revascularization my reduce adverse outcomes,[49] although remaining unproven in randomized trials.

Diagnosing CAD by an upper threshold of *ischemia*, physiologic or anatomic severity is the traditional role of diagnostic testing. However, current technology and knowledge suggest that it should not be the sole, primary or even an adequate goal of diagnostic testing because most CAD is best treated medically for optimal outcomes. The more advanced essential goal of diagnostic testing and specifically quantitative myocardial perfusion imaging is identifying those patients for whom revascularization optimally reduces myocardial infarction or mortality in addition to elective relief of angina.

EXERCISE, CORONARY BLOOD FLOW, AND TYPE 2 SUPPLY/DEMAND MYOCARDIAL INFARCTION

ACS during or within 1 hour of exercise is rare, occurring in 4% to 10% of ACS cases with highest prevalence in deconditioned subjects not doing regular exercise.[58] Even in this small percent of patients, ACS during exercise is not likely a simple supply/demand imbalance for several reasons. For fixed stable structural narrowing, habitual exercise would be expected to increase the frequency of exercise-induced ACS. However, in fact, risk of ACS during exercise decreases with increased

exercise frequency.[58] Therefore, ACS during exercise on a given day implies underlying progression, plaque disruption, sympathetic vasoconstriction, thrombosis associated with increased blood pressure, and tachycardia enhanced by sympathetic activity. Hence, the vast majority of ACS is driven by low flow caused by severe narrowing while the very small minority is driven by demand that exceeds significant flow-limiting stenosis. Undoubtedly, demand ischemia may cause arrhythmia and sudden cardiac death. However, there is strong evidence that benefits of exercise far override the small risk of incurring ACS during exercise.[58]

Lack of specific meaning of the term *ischemia* addressed earlier in this chapter also characterizes subcategories of myocardial infarction. In a 2014 review,[59] a type 1 myocardial infarction was defined "as secondary to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus leading to decreased myocardial blood flow or distal platelet emboli with consequent myocyte necrosis (acute coronary syndrome) (ACS)." A type 2 myocardial infarction was defined as "due to supply/demand mismatch, without plaque rupture, but also with myocardial necrosis evidenced by a rise and/or fall of cardiac biomarkers either—in addition to at least one of the other criteria for MI."[59] However, "several major expert opinion documents—none of these documents have defined specific criteria for T2MI [type 2 myocardial infarction] . . . and . . . the current 'gold-standard' definition for T2MI remains undetermined..."[59]

The review continues, "On the basis of the above criteria, T2MI is diagnosed in instances in which a supply/demand imbalance leads to myocardial injury with necrosis that is not caused by ACS, including arrhythmias, aortic dissection, severe aortic valve disease, hypertrophic cardiomyopathy, shock, respiratory failure, severe anemia, hypertension with or without left ventricular hypertrophy, coronary spasm, coronary embolism or vasculitis, and coronary endothelial dysfunction without significant coronary artery disease."[59] The term STEMI correlates with type 1 myocardial infarction, whereas NSTEMI correlates with type 2 myocardial infarction.[59]

These fine type 1 and type 2 distinctions have become even more blurred for several reasons. First, as reviewed earlier in this chapter, OCT-IVUS studies of ACS show on average severe stenosis of 72% diameter narrowing with complex morphology[16-19] not fitting any single pathophysiology corresponding to the type 1 and type 2 myocardial infarction categories. Second, pathology in people dying of myocardial infarction shows that about 90% have had serial small plaque ruptures that heal, leading to severe stenosis that lowers flow enough to cause infarction or a final plaque rupture or thrombosis occludes the stenosis.[15] Third, frequently elevated high-sensitivity troponins found with no ECG, functional, or clinical evidence of myocardial infarction further cloud the definitions, meaning, implications, future risk, and treatment. Fourth, trials of revascularization for ACS have reduced myocardial infarction and mortality irrespective of these fine distinctions.

Finally, even for the above definitions of type 2 myocardial infarction, exercise-demand myocardial infarction is very uncommon compared to the vast greatest proportion of coronary events occurring at rest, during sleep, or during minimal activity.[58,59] Therefore, the essential basis for coronary events is low coronary flow caused by severe stenosis, not supply/demand imbalance during exercise. As in the review above, a major criteria of type 2 myocardial infarction is absence of "significant coronary artery disease."[59] Of course, other pathologies cause myocardial infarction as listed above may constitute the true uncommon supply/demand imbalance without flow-limiting stenosis or diffuse CAD. However, of such cases, nearly always the problem is an excess demand in the face of underlying moderate to severe CAD, so that the proportional contribution of demand versus flow-limiting disease severity is moot and of little clinical or conceptual importance.

Quantitative myocardial perfusion provides a universal cohesive integrated view of the continuous spectrum of coronary events, such as OCT-IVUS and pathology, thereby avoiding artificial binary classifications that have proven poor guides to revascularization decisions. The threshold of stress flow at 0.9 cc/min/g and CFR of 1.7 associated with angina and significant ST depression during dipyridamole stress serve as a nearly universal measure of critical severity because the vast majority of acute coronary events occur during resting conditions or minimal activity for the wide mixed spectrum of pathologies reducing coronary blood flow.

CORONARY FLOW RESERVE AND STRESS PERFUSION IN CC/MIN/G—THE CORONARY FLOW CAPACITY MAP

Coronary blood flow and myocardial perfusion may be substantially heterogeneous, both globally and regionally and over time; the causes are normal, pathologic, or iatrogenic mechanisms that are multiple, complex, or interacting. Rather than viewed as an important useful insight into coronary pathophysiology, this heterogeneity is commonly viewed as a "diagnostic limitation" of methodology or biological variability, or competing diagnostic value of relative perfusion abnormalities versus CFR versus stress perfusion versus exercise or pharmacologic stress. However, the reality of heterogeneous rest and stress perfusion requires incorporating all of these measurements in order to quantify the wide range of complex coronary pathophysiology essential for individualized management decisions.

Rather than ignoring or selectively excluding such heterogeneity from clinical perfusion displays, quantitative data, or clinical interpretation, we account for and incorporate it into our image display as important physiologic information essential for optimal clinical value. Figure 34–21[28] illustrates the complex data inherent in all quantitative perfusion imaging. This complexity is then integrated into a "simple" easily understood image for clinical decisions by validated directive software based on a large patient database, further detailed in the chapter on PET imaging (Chap. 19). In Fig. 34–21, panel A displays

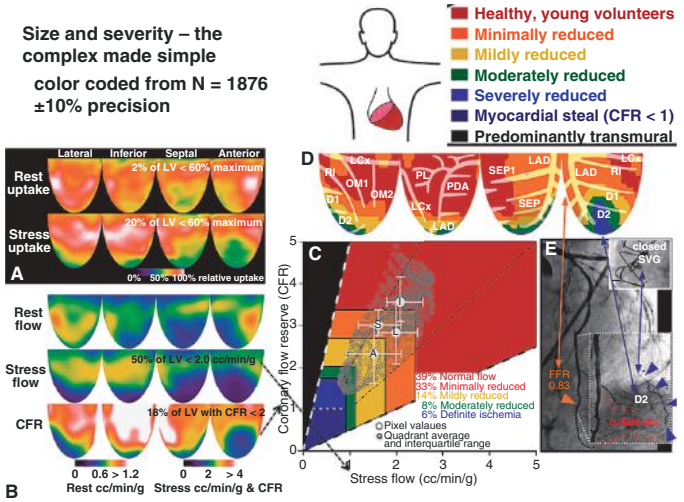


FIGURE 34–21. Positron emission tomography topographic images in lateral, inferior, septal, and anterior views of relative rubidium-82 myocardial uptake at rest and stress (**A**), rest and stress perfusion in cc/min/g and coronary flow reserve (CFR) (**B**), the plot of stress perfusion (horizontal axis) and CFR (vertical axis) color-coded for severity (**C**) as defined in the text. The open silver circles are CFR and stress perfusion for each pixel for its color-coded severity for both measurements. Each color-coded pixel is located back to its original spatial location and displayed as coronary flow capacity map color-coded for severity with percent of the left ventricle in each category of severity. Reproduced with permission from Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging*. 2012 Apr;5(4):430-440.[28]

relative myocardial perfusion images of rubidium-82 at rest and during dipyridamole stress. With the arterial input function for rest and stress (not shown), panel B displays rest and stress perfusion in cc/min/g and CFR for every pixel in every topographic image in each of four views of the human schematic figure. The CFR and stress perfusion for each pixel is then plotted on the graph with CFR on the vertical axis and stress perfusion on the horizontal axis in panel C.

The color codes correspond to clinical status of 1876 patients grouped according clinical status and CFR and stress perfusion in cc/min/g.[24,25,27,28,60] Red codes 125 young healthy volunteers under 40 years old without risk factors or blood caffeine.[60] Blue codes patients having angina, ECG changes, and/or a regional stress defect during dipyridamole stress PET imaging. Green codes for patients with either angina or ECG changes but not both during stress imaging. Orange codes for patients with CFR and stress flow at the lower one SD of the healthy volunteers. Yellow codes for the upper one SD above the patients with angina or ST changes during stress imaging. The orange to yellow transition is halfway between these SD limits. As documented in the chapter on PET imaging (Chap. 19), the color codes correspond to healthy young volunteers (red), patients with risk factors without known CAD (orange), patients with documented CAD with and without revascularization (yellow), patients with angina and/or ECG changes during dipyridamole stress as above (blue or green) and patients with myocardial steal (dark blue).[24,25,27,28,60]

Each color-coded pixel is then mapped to its original position and displayed as the coronary flow capacity map in four projections (lateral, inferior, septal, and anterior views) within the generic distribution of the coronary arteries as in panel D. For this patient's coronary flow capacity map, there is a small severe distal stress defect in the distribution of a small distal diagonal branch with myocardial steal associated with collaterals beyond an occlusion. The left anterior descending (LAD) artery distribution has good proximal CFR and stress flow (orange) tapering to mildly reduce levels (yellow) distally caused by diffuse disease without flow-limiting stenosis in the LAD distribution itself adjacent the severe stress defect (blue) caused by the small occluded distal diagonal. The left circumflex and right coronary artery distributions have the best coronary flow capacity (red). The angiogram inset confirmed all of these conclusions made from the coronary flow capacity map prior to angiogram.

Therefore, the easily understood, "simple" directive flow capacity map accounted for and integrated regionally complex heterogeneous perfusion data that are not readily interpreted from the primary perfusion displays. The coronary flow capacity map also provides an objective measure of percent of LV within each range of CFR and stress flow as a reflection of the LV mass at risk. A region comprising 15% of LV with stress flow at 0.9 cc/min/g and CFR at or below 1.7 may be a reasonable size threshold for revascularization based on the observation that 23% of LV infarcted starts to lower ejection fraction having adverse prognosis[61] and the CFR threshold of 1.5 associated with adverse coronary events.[48,49]

Figure 34–22 shows two topographic views of three common patterns of quantitative myocardial perfusion for which either CFR or stress perfusion alone fail to provide the needed definitive information for clinical management that is provided by both together. For efficiency of comparisons, only two of the four topographic views are displayed. In panel A, rest perfusion (first row) is very high, stress perfusion also high (second row) and CFR very low (third row) because of the high rest flow, as commonly seen with anxiety, high blood pressure, and in women. In panel B, rest perfusion is very low because of beta-blockers; stress flow is also low but CFR is excellent and well above the ischemic threshold.

For both cases A and B, the integrated coronary flow capacity map (fourth row) of Fig. 34–22 accounts for both CFR and stress perfusion scaled according to the color bar for both CFR and stress perfusion together. For these two examples, the red regions indicate coronary flow capacity of young, healthy volunteers without risk factors. With such common global perfusion heterogeneity, CFR alone or stress perfusion alone fails to characterize adequately the coronary blood flow of these examples as the basis of clinical management.

In panel C, the absolute rest and stress perfusion images in cc/min/g are so diffusely reduced as to preclude visual differentiation of scar from low rest or stress perfusion. However, the CFR display and the coronary flow capacity map all show fixed scar as well as reduced but adequate (orange and yellow) above low-flow ischemic levels outside the scar on the coronary flow capacity map. The coronary flow capacity map also scales perfusion for less than or equal 0.2 cc/min/g from the resting image as scar indicated by the hatched area within the low-flow blue zone. As detailed in Fig. 34–21, the red to orange to yellow to green to blue regions correspond to progressive lower combinations of reduced CFR and stress perfusion in 1876 patients as per the color bar beside the coronary flow capacity map.

Although they both quantify physiologic severity, CFR and stress perfusion are independent and complimentary, and both are necessary for definitive complete definition of severity. Stress perfusion alone fails to assess severity adequately in several common clinical circumstances. Stress perfusion alone cannot distinguish myocardial scar from a stress-induced perfusion defect or identify myocardial steal associated with collaterals, both of which require CFR or the resting image. Beta blockade may profoundly lower the stress flow to below the low-flow threshold that would cause angina or ECG changes without beta-blockers. This lowered threshold by beta blockade prevents angina or ECG changes at much lower stress flow than without beta-blockers. Such patients usually have very low stress perfusion but also low rest perfusion with resulting good CFR that prevents ischemia with activity.

CFR alone also fails to quantify severity when rest flow is high resulting from hypertension, anxiety, or gender with adequate stress perfusion and corresponding low CFR that causes no ischemia resulting from adequate stress perfusion. Thus, quantitative rest and stress perfusion and CFR are all needed, integrated into the coronary flow capacity map in order to define common clinical conditions. Integrated quantitative perfusion identifies and quantifies diverse components of myocardial scar with ischemic border zones, cardiomyopathy with low ejection fraction particularly with CAD, hibernating myocardium, diffuse CAD, mixed focal plus diffuse disease, endothelial dysfunction, caffeine nonresponders, beta blockade or other drugs that alter or lower stress flow, postprocedure patients, and occlusions with myocardial steal.

Although we use quantitative PET perfusion images to illustrate this essential clinical pathophysiology, any other technology providing corresponding CFR and absolute coronary flow documents the concepts. For example, Fig. 34–23 shows invasive measures of coronary flow capacity using intracoronary flow velocity wires during pharmacologic stress.[62] Coronary flow velocity reserve is plotted on the vertical axis with hyperemic flow velocity on the horizontal axis in panel A. The colors code for normal, mildly reduced and moderately reduced coronary flow capacity associated with risk of MACE in panel B. Although other technologies of MRI and CT perfusion may eventually provide such comprehensive physiologic data, PET remains optimal with the largest supportive literature and experience.[24-29,33,34,48-50,54-56,60,61]

DIFFUSE CORONARY ARTERY DISEASE—THE HIDDEN HIGH RISK

Figs. 34–3, 34–7, and Fig. 34–15 above indicate the essential component of diffuse CAD underlying most stenosis that carries high risk of adverse events that remains after revascularization. In the Surgical Treatment

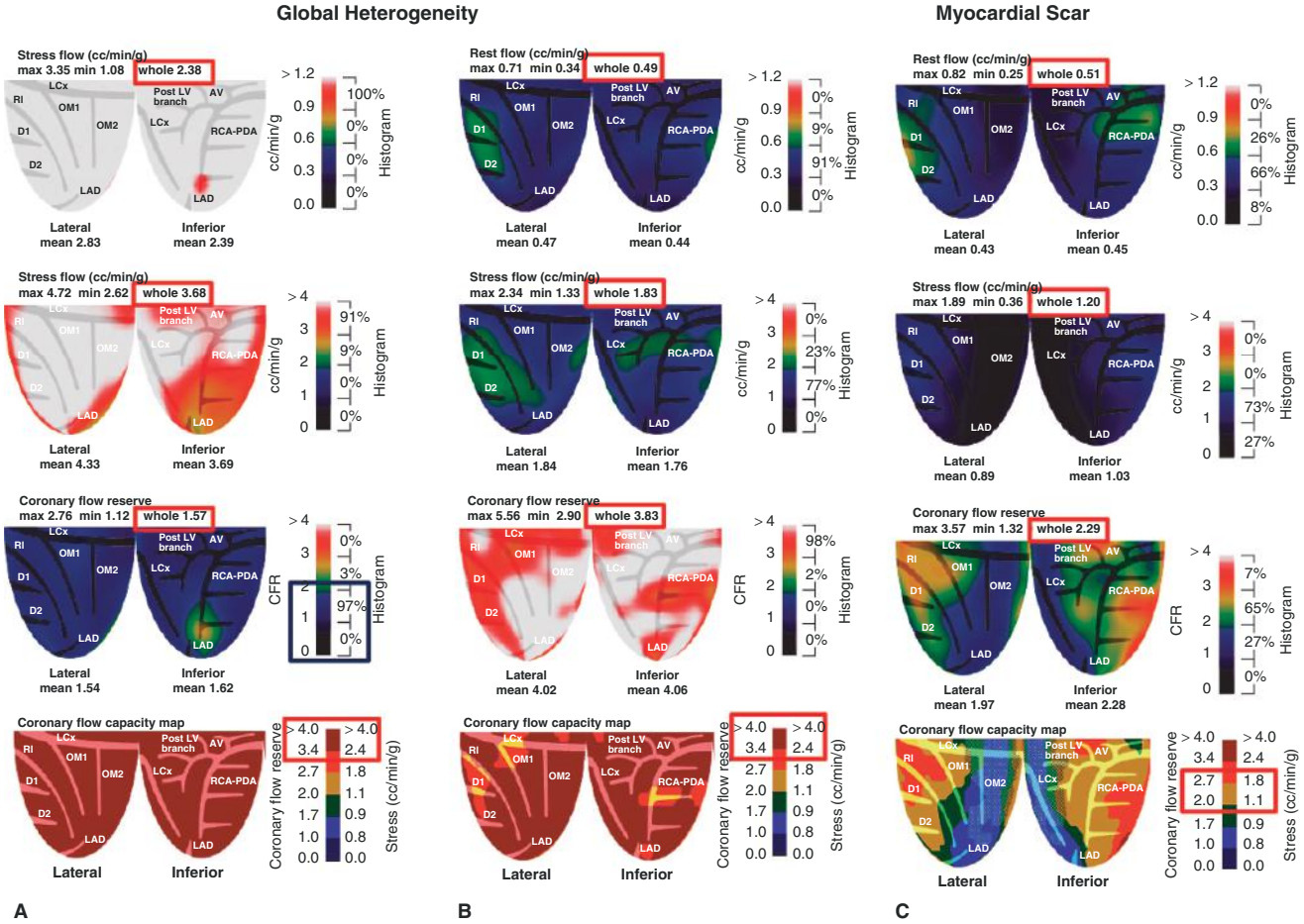


FIGURE 34–22. Coronary flow capacity maps in two of four views for three different patients. Patient A has high rest and stress flow discordant with very low coronary flow reserve (CFR) because of high rest flow. The discordance is quantitatively resolved by the normal flow capacity map. Patient B has very low rest and stress flow discordant with a high CFR caused by low rest flow resulting from beta blockade. The discordance is resolved by the normal coronary flow capacity map. Patient C has a fixed scar that cannot be separated from low rest or stress perfusion defects on rest or stress images alone. The CFR display and the coronary flow capacity map that account for all the perfusion data readily indicate scar from the remainder of myocardium with reduced but adequate flow capacity scar. The color bar to the right of each coronary flow capacity map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

for Ischemic Heart Failure (STICH) trial, CAB in three-vessel disease failed to lower mortality.[6,7] In meta-analysis of FFR-guided PCI, residual FFR after successful PCI is associated with subsequent risk of recurrent MACE.[44] In Fig. 34–24, the severe abnormality on the coronary flow capacity map of panel A on the same patient in Fig. 34–14 improved after successful PCI in panel B. However, the residual mildly diffusely reduced coronary flow capacity (yellow) in panel B indicates substantial diffuse remaining disease not seen on the angiogram but requiring intense medical management in order to prevent further progression, cause regression,[63,64] and reduce adverse events.[65,66] Failure to account for or quantify diffuse disease in randomized revascularization trials explains in part failure to reduce myocardial infarction or mortality resulting from residual diffuse disease.[26]

CORONARY BLOOD FLOW IN WOMEN

CAD in women is characterized by atypical chest pain, diffuse epicardial coronary atherosclerosis, microvascular dysfunction, inaccurate diagnostic tests, delayed or late ACS associated with high mortality, and differential responses to medical treatment or invasive procedures in women compared to men.[67,68] Although these differences are well described and likely related to hormonal influences, they remain without a systematic mechanistic explanation. However, coronary blood flow and associated fluid dynamics offer some insight into potential mechanisms as recently reported and summarized in Fig. 34–25.[69]

Coronary arteries in women are smaller than men[70-72] but myocardial perfusion is higher in women.[61] Accordingly, average endothelial shear is higher in women.[61,64] High endothelial shear stress inhibits low-density lipoprotein transport by reducing "leaky" endothelial cell junctions; inhibiting inflammation, platelet activation, and thrombosis; retarding oxidative processes; promoting mild stable uniform remodeling; and inhibiting focal atheroma, focal stenosis, and plaque instability.[69,73-78] These beneficial effects are mediated by high shear that upregulates endothelial nitric oxide (NO), NO synthase (eNOS) gene expression, eNOS phosphorylation, manganese superoxide dismutase (Mn-SOD) expression and downregulates endothelial NADPH oxidase, thereby decreasing superoxide ion and oxidative stress.[73-78] The later section on pressure-flow relationships reviews the fluid dynamic equations describing the arterial size, length, and regional LV mass relations that define the structure of the branching coronary artery tree for women compared to men.

These beneficial effects of high endothelial shear on inhibiting atheroma formation applied throughout the coronary artery tree of women

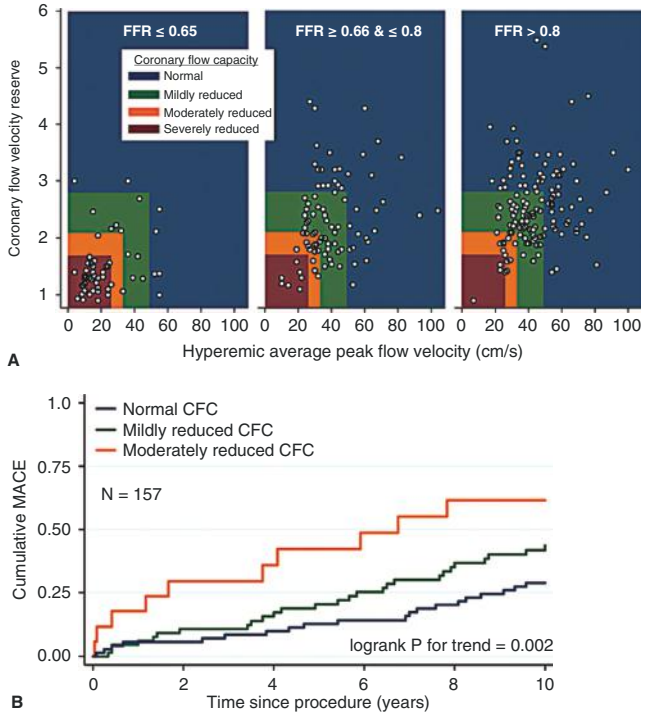


FIGURE 34–23. Coronary flow capacity (CFC) derived by intracoronary coronary flow velocity wires (**A**) color codes for severity correlated with major adverse coronary events (MACE) outcomes (**B**). FFR, fractional flow reserve. Reproduced with permission from Van de Hoef TP, Pinto ME, van Lavieren MA, et al: Diagnostic and prognostic implications of coronary flow capacity. *JACC Cardiovasc Interv*. 2015 Nov;8(13):1670-1680.[62]

may explain their average different manifestation of CAD. However, endothelial shear stress and its effects are a complex, heterogeneously varying regional, time-and age-related continuum with great individual differences. Consequently, for given risk factors, some women never get CAD, other develop it prematurely like men, others have delayed focal disease, and commonly in women coronary atherosclerosis is modified by high shear into diffuse disease without focal stenosis.

Shear effects on CAD in women may also explain their frequent atypical nonexertional angina because of diffuse coronary narrowing that relates linearly with flow (flow^1), thereby causing less pressure gradient, less subendocardial ischemia and less angina with exercise.[69] In contrast, with more focal stenosis in men, increased coronary flow with exercise associates with a stenosis pressure gradient proportional to flow raised to the second power (flow^2), thereby reducing coronary perfusion pressure with consequent subendocardial under perfusion and angina.

Late stenosis in women is superimposed on severe diffuse disease developing silently over their middle years to produce a large burden of atherosclerosis in small arteries that incurs higher risk than men who present earlier in life with primarily focal disease. With estrogen withdrawal, the partial protection of their high shear stress against atheroma formation is lost, leading to "accelerated" clinical manifestations caused by focal stenosis added to diffuse disease. The long "silent" period of developing diffuse coronary atherosclerosis in women may evolve a more lethal combination of diffuse plus late focal disease than commonly seen in men. Therefore, vigorous risk factor treatment is essential during this long latent period in order to reduce adverse outcomes.

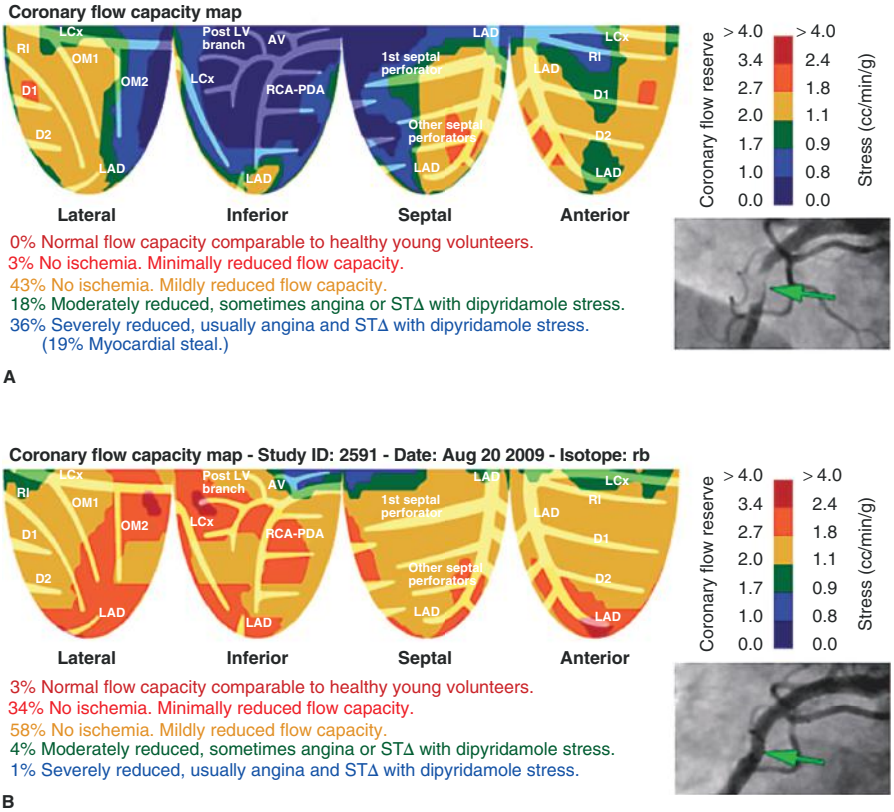


FIGURE 34–24. Coronary flow capacity map and angiogram before (**A**) and after percutaneous coronary intervention (**B**) with resolution of the severe regional stress defect (blue) but residual limited coronary flow capacity indicating diffuse coronary atherosclerosis (yellow). The color bar to the right of each coronary flow capacity map shows the thresholds of stress flow and CFR at each color transition (not combined stress flow—CFR values for pixels in the images).

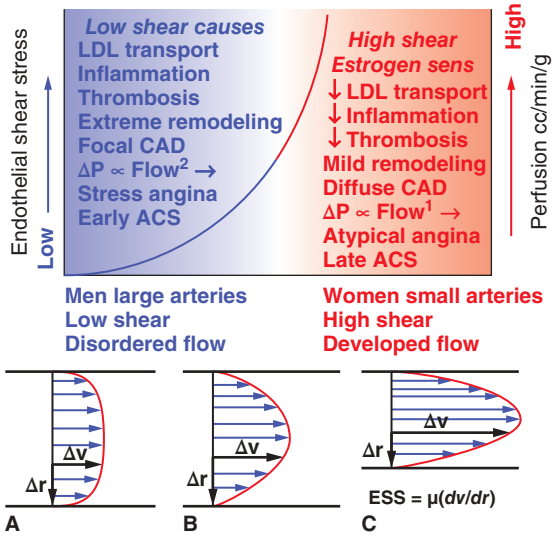


FIGURE 34–25. Schema of female and male manifestations of coronary artery disease (CAD) related to coronary artery diameter, coronary blood flow, blood flow profiles, and endocardial shear stress. ACS, acute coronary syndrome; LDL, low-density lipoprotein; ESS, endothelial shear stress. Reproduced with permission from Patel MB, Bui LP, Kirkeeide RL, et al: Imaging Microvascular Dysfunction And Mechanisms For Female Male Differences in Coronary Artery Disease. *JACC Cardiovasc Imaging*. 2016 Apr;9(4):465-482.[69]

PHASIC CORONARY BLOOD FLOW AND STENOSIS PRESSURE-FLOW RELATIONS

Having established the relevance of coronary blood flow and pathophysiology to clinical cardiology, let us now review other clinically pertinent aspects of coronary blood flow. Figure 34–26 shows recordings of coronary blood flow velocity, aortic and coronary pressures, and the coronary pressure gradient at resting conditions without stenosis (panel A), with moderate stenosis (panel B), and with severe stenosis (panel C) in a chronically instrumented canine model of coronary artery stenosis.[79] With no stenosis, systolic compression reduces systolic coronary flow. During isometric LV contraction in early systole, coronary pressure rises above aortic pressure because of a momentary reversal of the aortic gradient to negative values (red arrow) arising from the pressure wave caused by isometric contraction propagating backward through the coronary arteries before the aortic valve opens. For the moderate stenosis in (B), this reversed gradient with coronary pressure higher than aortic pressure in early systole is replaced by varying pressure gradient from zero in early systole at zero flow to 38 mm Hg during the maximum early diastolic flow. The phasic flow is more damped with the peak diastolic flow reduced.

At the severe stenosis in C, the phasic pressure gradient reaches 40 to 50 mm Hg while average rest flow velocity remains normal. However, the phasic pattern of coronary flow is lost with increased coronary flow during systole compared to low systolic flow in the absence of stenosis. This paradoxical increased coronary flow with severe stenosis is caused by the loss of regional systolic compression associated with the low coronary perfusion pressure and consequent subendocardial underperfusion and ischemia.

Figure 34–27 shows the same experimental stenosis model with a mild to moderate stenosis at resting baseline conditions in panel A with systolic compression reducing systolic flow and the momentary reversal of coronary pressure or aortic pressure during isometric systole.[79] With progressive vasodilation stress in panels B, C, and D, mean coronary flow velocity increases only modestly as the pressure gradient increases proportionately much more. The phasic pattern of coronary

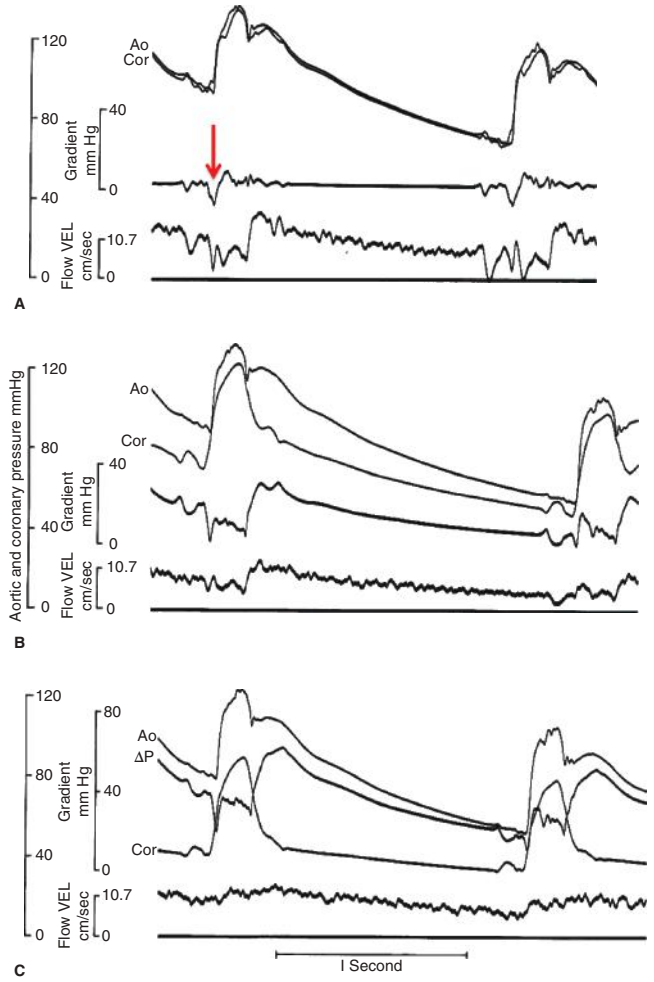


FIGURE 34–26. Coronary flow velocity and aortic and coronary pressures at resting conditions (A) during progressively mild (B) and severe (C) experimental stenosis. Red arrow indicates reverse pressure gradient, with early coronary pressure higher than aortic pressure.

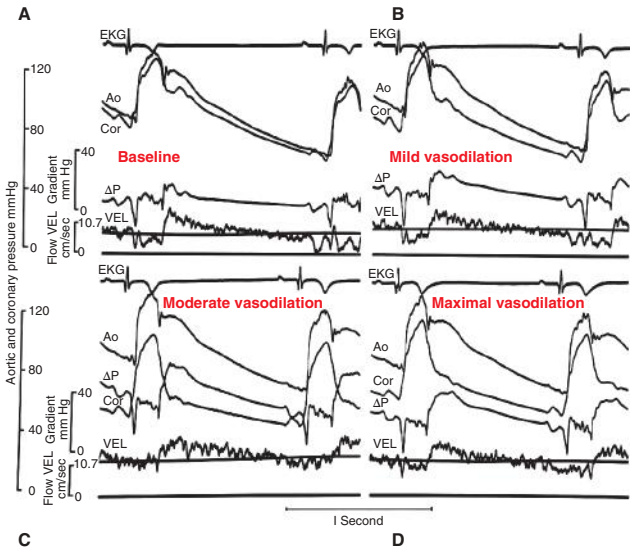


FIGURE 34–27. Coronary flow velocity and aortic and coronary pressures with a moderate stenosis at resting baseline (A), with initial mild vasodilator stress (B), with moderate vasodilator stress (C), and with maximal vasodilator stress (D). Reproduced with permission from Gould KL: Pressure-flow characteristics of coronary stenoses in intact unsedated dogs at rest and during coronary vasodilation. *Circ Res*. 1978 Aug;43(2):242-253.[79]

flow is damped with increased systolic flow compared to low systolic flow without stenosis. Thus, the phasic pattern of coronary blood flow during vasodilator stress parallels the phasic flow changes during progressive stenosis at resting conditions.

Figure 34–28 plots the phasic pressure gradient and flow velocities during a single cardiac cycle for a mild stenosis.[79] The highlighted regions of the phasic tracings and the dashed lines of the pressure-flow plot show the systolic deceleration and early diastolic acceleration of flow that distort the smooth diastolic pressure gradient flow relation fitting a characteristic quadratic fluid dynamic equation equation.[79] Deceleration or stopping coronary blood flow by systolic compression and early diastolic acceleration of coronary blood flow at high early diastolic pressure are associated with inertial pressure loss separately and independently from the pure diastolic pressure-flow characteristics of the stenosis.

Consequently, average coronary pressure gradient flow relations are somewhat different from the pure diastolic pressure gradient relations undistorted by systolic compression of the coronary vascular bed.

The schematic in Fig. 34–29 shows the fluid dynamic equations relating stenosis dimensions, coronary blood flow, pressure gradient, flow profiles, exit vortex shedding, and endothelial shear stress. The quadratic equation has a viscous pressure loss linearly proportional to flow and an exit separation loss proportional to flow squared. Both viscous and separation pressure losses are related to the arterial radius raised to the fourth power. Consequently, small changes in arterial diameter that are not visible or quantifiable on angiogram may have major effects on coronary flow or CFR incurring high or low risk. Figure 34–30 lists the consequences of the flow profile patterns on biologic behavior of the atherosclerotic coronary artery. High endothelial

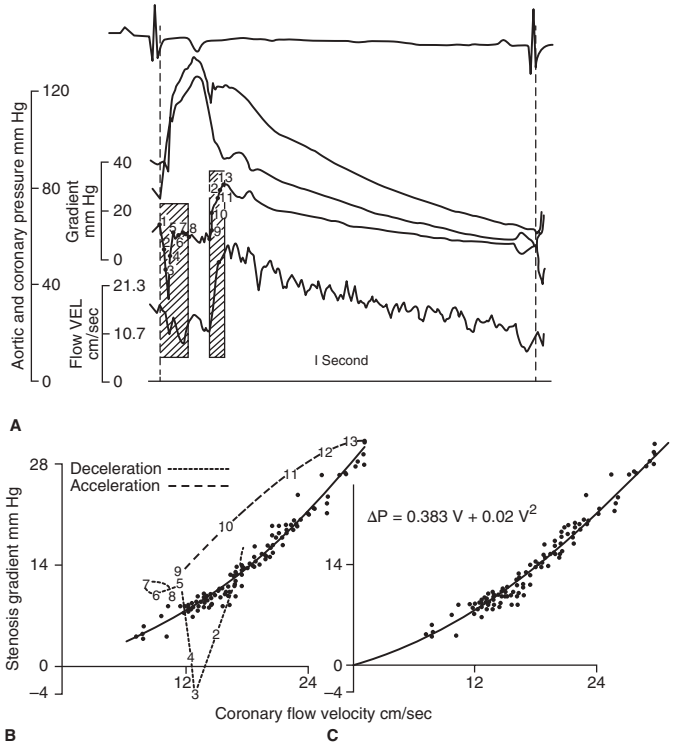


FIGURE 34–28. Coronary flow velocity and aortic and coronary pressures digitized and plotted for fitting to a quadratic equation characterizing the fluid dynamic severity. Shaded areas indicate deceleration and acceleration of coronary blood flow in early systole and early diastole, respectively, that are excluded from the pure diastolic pressure flow relation characterizing the stenosis. Reproduced with permission from Gould KL: Pressure-flow characteristics of coronary stenoses in intact unsedated dogs at rest and during coronary vasodilation, *Circ Res*. 1978 Aug;43(2):242-25.[79]

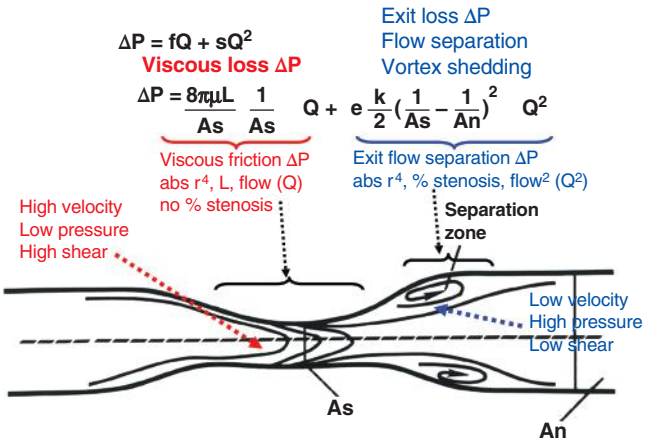


FIGURE 34–29. Schema of blood flow through a stenosis with fluid dynamic equation characterizing stenosis severity. μ, blood viscosity; ΔP, pressure gradient across the stenosis; An, cross-sectional area of the normal nonstenotic artery; As, cross-sectional lumen area of the stenosis. K, constant; L, stenosis length. ΔP, pressure gradient; Q flow, fQ, friction coefficient of flow; sQ, separation coefficient of flow squared.

shear stress has antiatherogenic effects, whereas low shear stress is atherogenic with implications for the different manifestations of CAD in women versus men addressed in the prior section on coronary blood flow in women.

These pressure-flow curves first defined in experimental stenosis[79] have been confirmed in patients[80-83] by pressure-flow velocity wires as in Fig. 34–31, with panel A showing diastolic pressure-flow velocity (p-v) plots fitting the quadratic fluid dynamic equation; panel B showing p-v plots for severe, moderate, and mild stenosis; and panel C showing p-v plots of a severe stenosis before and after PCI.[81] All current invasive and noninvasive quantification of physiologic stenosis severity using FFR and stress perfusion imaging to guide management are based on these experimental models, classical fluid dynamic equations, and early confirmation in patients. The discordances between CFR, FFR, and/or stress perfusion noted above arise from choosing one of these measures alone that inadequately defines the actual physiologic complexity of CAD over the wide range of clinical conditions. Consequently, complete invasive pressure flow relations are currently being acquired in the DEFINE FLOW (Distal Evaluation of Functional

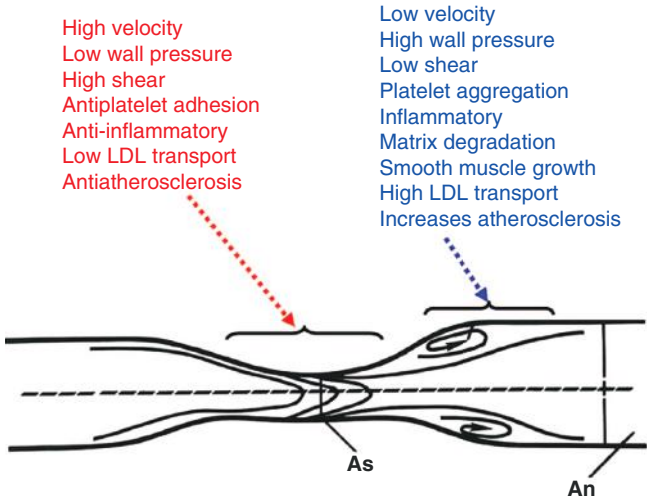


FIGURE 34–30. Schema of flow through a stenosis with biological changes associated with different section of the stenosis. LDL, low-density lipoprotein.

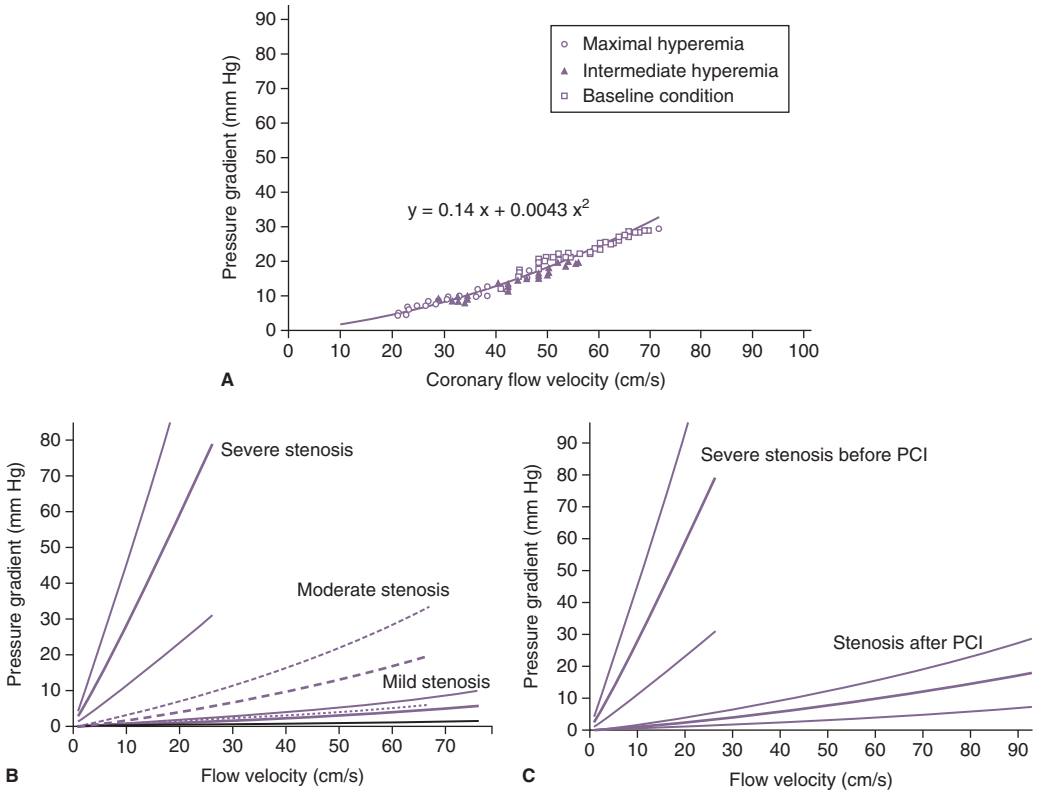


FIGURE 34–31. Coronary flow velocity and pressure gradient relations for different severities of stenosis, before and after percutaneous coronary intervention in a patient demonstrating the classic quadratic fluid dynamic equation originally observed in experimental models in vivo. Reproduced with permission from Marques KM, Spruijt HJ, Boer C, Westerhof N, Visser CA, Visser FC. The diastolic flow-pressure gradient relation in coronary stenoses in humans. *J Am Coll Cardiol*. 2002 May 15;39(10):1630-1636.[72]

performance with Intravascular sensors to assess the Narrowing Effect—Combined pressure and Doppler FLOW velocity measurements) trial to resolve the implications of FFR-CFR discordance for management decisions (ClinicalTrials.gov NCT02328820).

Fluid dynamic equations tell an even more profound story than quantifying coronary artery stenosis clinically. The arterial size, length, and branching tree structure of the mammalian heart can be explained or described by equations derived from three different starting points: (1) minimal energy loss for coronary blood flow distribution, (2) adaptive arterial size to normalize wall shear stress, and (3) parent-to-child branching arterial size for downstream mass.[35,36,72] All three derivations confirm the same equation now validated in clinical and animal studies as follows: arterial cross-sectional area = (K) flow$^{0.67}$, where flow is proportional to mass that is proportional to the sum of branch lengths beyond each point along the length of the artery on clinical coronary arteriograms defining K, as in Fig. 34–32A.[35]

Remarkably, this equation for women is different than for men (Fig 34–32B). Women have smaller arteries and men have larger arteries[72] than predicted by the original equation derived from both male and female patients in equal proportion.[35] The data indicate that women do not adapt to wall shear stress with increased arterial size as much as men. Women thereby maintain higher wall shear stress than men with corresponding antiatherosclerotic benefits summarized in Figs. 34–25 and 34–30. Thus, the mammalian heart of 200 million years ago, coronary blood flow, human gender evolution, fluid dynamic equations, pressure-flow measurements, CFR, FFR, quantitative perfusion imaging, diagnostic tests, CAD in women versus men, and their differential optimal treatment comprise a highly integrated conceptual continuum, a syncytium of knowledge immediately relevant to cardiovascular medicine and patient survival.

REACTIVE HYPEREMIA—THE RESPONSE TO EVERY BALLOON DEFLATION AT PERCUTANEOUS CORONARY INTERVENTION

After brief 10- to 20-second coronary occlusion, coronary flow increases dramatically for a longer time than the occlusion. This flow response to brief occlusion is called reactive hyperemia, shown in Fig. 34–33A.[84] The volume of flow repayment is four times greater than the flow deficit during occlusion so that flow repayment to the myocardium is four times the flow debt. Consequently, during reactive hyperemia coronary, the oxygen content of coronary venous blood may double or triple because of unextracted oxygen not needed by the myocardium.

This surplus flow after transient occlusion is far more than needed to repay myocardial flow or oxygen demands as shown in Fig. 34–33B where the coronary is perfused with deoxygenated blood for the same time period of occlusion. Flow payback after perfusion with deoxygenated blood exactly matches the flow debt. The excess flow payback after brief occlusion is therefore caused by mechanisms other than oxygen payback, particularly autoregulation discussed below. Reactive hyperemia occurs after the brief systolic compression of every heart cycle, contributing to the rapid rise in coronary blood flow early in diastole in Figs. 34–26, 34–27, and 34–28.

The factors controlling coronary blood flow include myocardial metabolism, autoregulation, shear-mediated vasodilation, contractile compression, endothelial function, perfusion pressure, and direct or indirect sympathetic and parasympathetic neural mechanisms, as briefly outlined below. Thus, reactive hyperemia reflects all the complex interacting control mechanisms for coronary blood flow

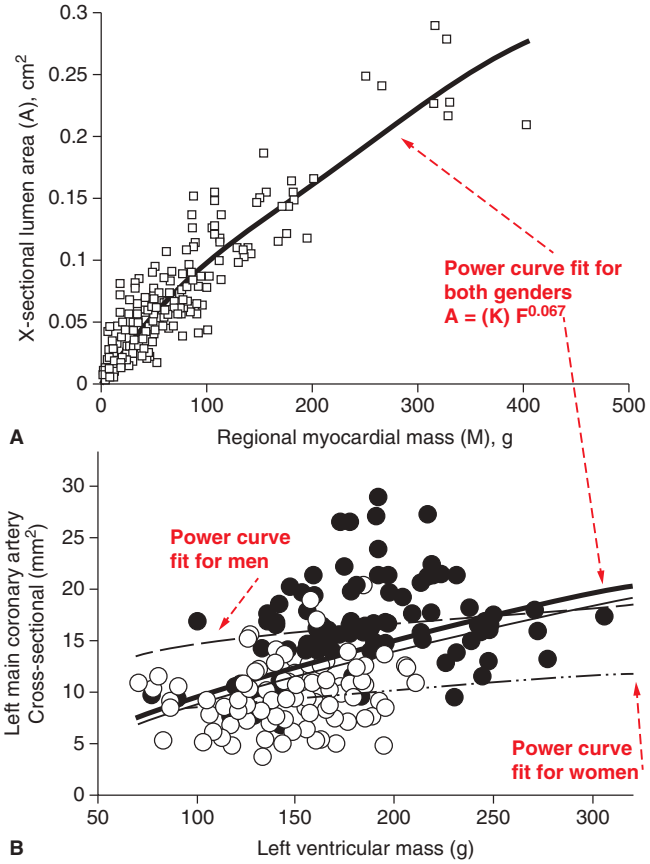


FIGURE 34–32. Regional mass compared to cross-sectional arterial lumen area on clinical coronary angiogram with the fitted power curve relating area to flow describing the size, length, and branching structure of the human coronary artery tree originally reported for both genders (**A**) and subsequently in different patients for women compared to men (**B**). (A) reproduced with permission from Seiler C, Kirkeeide RL, Gould KL: Basic structure-function of the epicardial coronary vascular tree—the basis of quantitative coronary arteriography for diffuse coronary artery disease. *Circulation*. 1992 Jun;85(6):1987-2003.[35] (B) reproduced with permission from Marques KM, Spruijt HJ, Boer C, Westerhof N, Visser CA, Visser FC. The diastolic flow-pressure gradient relation in coronary stenoses in humans. *J Am Coll Cardiol*. 2002 May 15;39(10):1630-1636.[72]

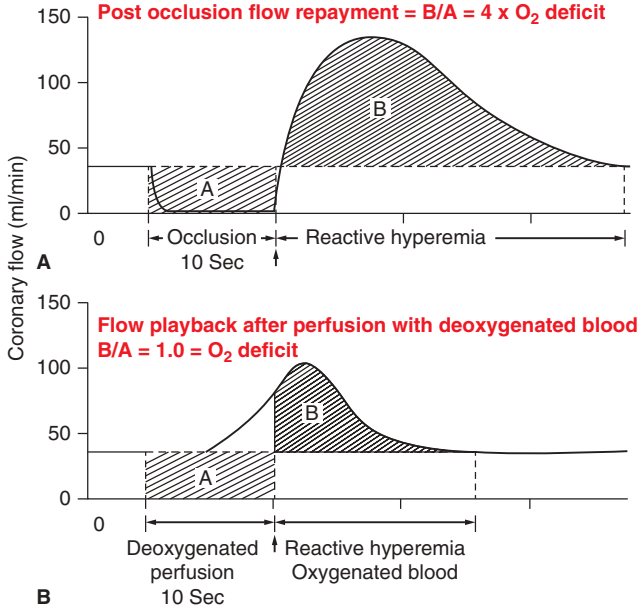


FIGURE 34–33. Reactive hyperemia of coronary blood flow after 10-second occlusion (**A**) and after 10-second infusion of deoxygenated blood (**B**). The shaded areas labeled A indicate the flow times the duration-flow volume debt. The shaded areas labeled B indicate the flow times the duration-flow volume response or payback flow volume after the occlusion. Reproduced with permission from Kelley KO, Gould KL: Coronary Reactive Hyperemia after Brief Occlusion and After Deoxygenated Perfusion. *Cardiovasc Res*. 1981 Nov;15(11):615-622[84]

optimized for evolutionary survival. It occurs after every systolic contraction and immediately after every balloon deflation at PCI, generally without cognizance of its physiologic significance for coronary blood flow or its profound, elegant, complex, interacting control mechanisms already evolved in the mammalian heart before dinosaurs ruled the earth. The asteroid creating the Chixulub crater and Deccan volcanism ended their rule, thereby making way for this extraordinary pulsatile, self-fueling pump to support mammalian evolution to the mobility, dexterity, and mental capacity for writing this sentence in Hurst's *The Heart* some 66 million years later.

MYOCARDIAL STEAL—MEANING AND MECHANISMS

INTRAMYOCARDIAL STEAL AND SUBENDOCARDIAL ISCHEMIA

Intramyocardial steal, also called subendocardial-subepicardial steal, is common, manifest as stress-induced ST depression on ECG and usually angina with reduced average transmural perfusion in cc/min/g to the ischemic threshold of 0.9 cc/min/g. It results from several interacting mechanisms, revealing profound insights into the exquisite regional control of coronary blood flow by ATP release from red blood cells in local regions of myocardial hypoxia in response to delayed subendocardial hyperemia by stenosis and fall in coronary pressure associated with increased flow during vasodilator stress.

Delayed Subendocardial Hyperemia

As listed in Table 34–1, the subendocardium has higher wall tension then the subepicardium and consequently greater oxygen demands.

TABLE 34–1. Characteristics of Subendocardium and Subepicardium

Variable	Subendocardium	Subepicardium
Wall stress	++	+
O_2 consumption	++	+
Myocardial pO_2	—	++
Perfusion pressure	—	++
Saturated VO_2, ATP content	—	++
Lactate production	++	-
Capillaries recruited	+++	+
Flow reserve	+	+++
Vascular resistance	+	++
Systolic compression	+++	+
Diastolic flow increase	+	++
Normal mean flow	++	++
Tachycardia CBF fall	+	+++
Stenosis → CBF fall	—	-
Stenosis → pressure fall	—	-

Abbreviations: ATP, adenosine triphosphate; CBF, coronary blood flow; high (+, mild; ++, moderate; +++, marked); low (-, mild; –, moderate; —, marked); O_2, oxygen; pO_2, partial oxygen pressure; VO_2, oxygen saturation.

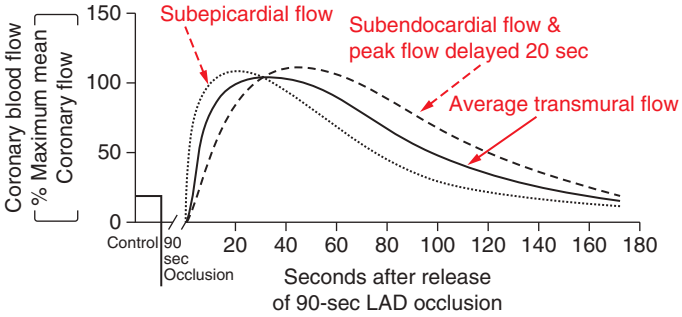


FIGURE 34–34. Transmural distribution of coronary blood flow during reactive hyperemia after transient occlusion in an experimental preparation without stenosis. LAD, left anterior descending (artery). Reproduced with permission from Downey HF, Crystal GJ, Bashour FA. Asynchronous transmural perfusion during coronary reactive hyperemia. *Cardiovasc Res*. 1983 Apr;17(4):200-206.[85]

Compared to the subepicardium, the subendocardial perfusion is limited by systolic compression, lower perfusion pressure, greater diastolic tissue pressure, and longer perfusion distances compared to subepicardium. Consequently, subendocardial arterioles are more dilated and more capillaries are recruited with less remaining vasodilatory reserve, oxygen extraction is greater with lower tissue pO_2, lower ATP levels, potential lactate production rather than utilization, and lower saturation of coronary venous blood.

The normal reactive hyperemia after systolic compression with rapid rise in early diastolic flow is delayed to the subendocardium as in Fig. 34–34.[85] Even a delay of a few seconds during tachycardia further compromises subendocardial perfusion. Coronary artery stenosis further impairs the early rapid diastolic perfusion to subendocardium, especially with tachycardia, thereby explaining subendocardial ischemia and ST depression during exercise tachycardia. Similarly, LV hypertrophy with a thickened LV wall, especially aortic stenosis, impairs rapid diastolic perfusion to subendocardium during tachycardia even without coronary stenosis.

Low Coronary Pressure Caused by Increased Flow during Vasodilator Stress

As flow increases through a stenosis, the pressure gradient increases and distal coronary pressure falls, thereby impairing subendocardial perfusion more than the subepicardium. As in Fig. 34–35, myocardial perfusion is relatively well maintained at coronary perfusion pressures down to 37 to 40 mm Hg.[86] However, as perfusion pressure falls further to 28 mm Hg, subendocardial perfusion falls by 50% or more while subepicardial perfusion is maintained. This subepicardial to subendocardial perfusion gradient is called intramyocardial steal because of the superficial appearance of perfusion being "stolen away" from the subendocardium by the subepicardium. However, the term is a misnomer because blood flow is not withdrawn from one region by another region. The intramyocardial gradient is caused by subendocardial perfusion falling more than subepicardial perfusion at low perfusion pressures. Figure 34–36[87] shows preservation of contractile function at a perfusion pressure of 38 mm Hg in an experimental model consistent with Fig. 34–35 relating perfusion pressure and subendocardial perfusion.

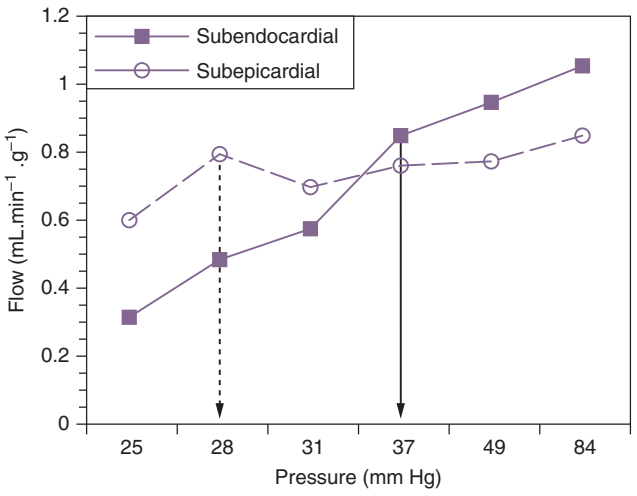


FIGURE 34–35. Subendocardial and subepicardial perfusion as a function of coronary perfusion pressure. Reproduced with permission from Hoffman JIE, Buckberg GD. The myocardial oxygen supply:demand Index revisited. *J Am Heart Assoc*. 2014 Jan 21;3(1):e000285.[86]

Why Does Remaining Coronary Flow Reserve with Severe Stenosis Lower Resting Coronary Blood Flow?

Counterintuitively, coronary flow increases with vasodilator stress even after severe stenosis reduces resting coronary blood flow, as first reported in 1975.[88] Holding back this potential increased reserve flow capacity that maintains adequate perfusion pressure appears superficially to be an astonishing teleological adaptation for maintaining subendocardial perfusion. However, in reality, the explanation is not teleological intelligence of the coronary arteries but rather their exquisite regional control of coronary blood flow by ATP release from red blood cells in a hypoxic environment, as detailed in the next section of control mechanisms for coronary blood flow. As epicardial perfusion pressure and flow falls because of stenosis, the subendocardium vasodilates maximally as a result of ATP release from red blood cells that prevents ischemia up to a limit. At that level of epicardial perfusion pressure and flow, the subepicardium sees higher pressure and flow, thereby not vasodilating maximally.

With added pharmacologic vasodilator stress, the epicardial flow increases, the pressure gradient across the stenosis increases, and perfusion pressure falls, thereby making the subendocardium ischemic. With pharmacologic arteriolar vasodilation distal to a stenosis with

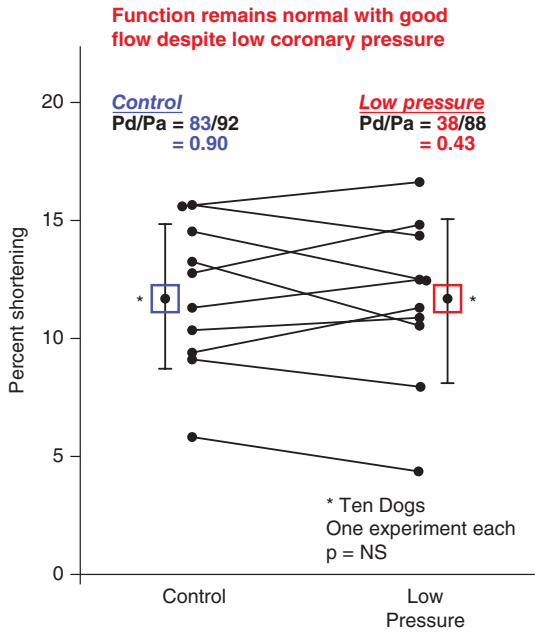


FIGURE 34–36. Left ventricular contraction at baseline and at low coronary perfusion pressure during constant normal resting coronary blood flow. Pa, aortic pressure in mm Hg; Pd, distal coronary pressure in mm Hg. Reproduced with permission from Smalling RW, Kelley K, Kirkeeide RL, et al: Regional myocardial function is not affected by severe coronary depressurization provided coronary blood flow is maintained. *J Am Coll Cardiol*. 1985 Apr;5(4):948-955.[87]

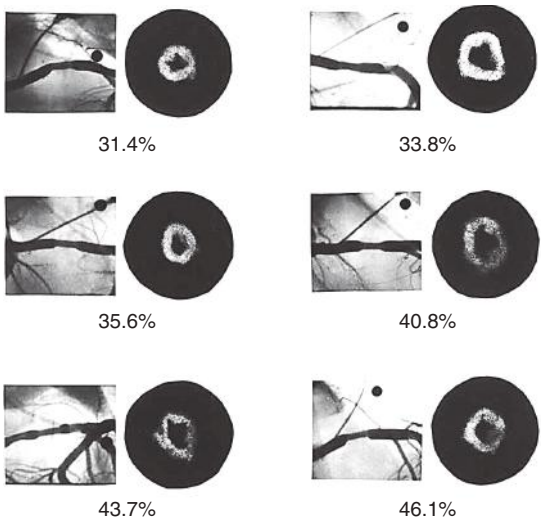


FIGURE 34–37. Angiogram of mild percent diameter stenosis and left ventricular cross-sectional perfusion images of thallium-201 during dipyridamole stress imaged postmortem by laying the cross-sectional slices of the left ventricle on a gamma camera. Reproduced with permission from Gould KL. Assessment of Coronary Stenoses by Myocardial Perfusion Imaging During Pharmacologic Coronary Vasodilatation. IV. Limits of Stenosis Detection by Idealized, Experimental, Cross-Sectional Myocardial Imaging. *Am J Cardiol*. 1978 Nov;42(5):761-768.[89]

increase transmural perfusion, paradoxically subendocardial perfusion falls with ischemia as epicardial coronary blood flow increases—hence the misnomer *intramyocardial steal*. Reversing the vasodilator stress or beta blockade lowers epicardial coronary artery flow, lowers the pressure gradient, increases perfusion pressure, and relieves subendocardial ischemia. Thus, the remaining coronary flow reserve with severe stenosis lowering resting flow is regional subepicardial flow reserve that has no stimulus for vasodilation because it has adequate pressure and perfusion.

Figures 34–37 and 34–38 demonstrate this subendocardial hypoperfusion during vasodilatory stress with progressive coronary artery stenosis in the first images of subendocardial underperfusion in an experimental model with postmortem imaging of cross-sectional LV

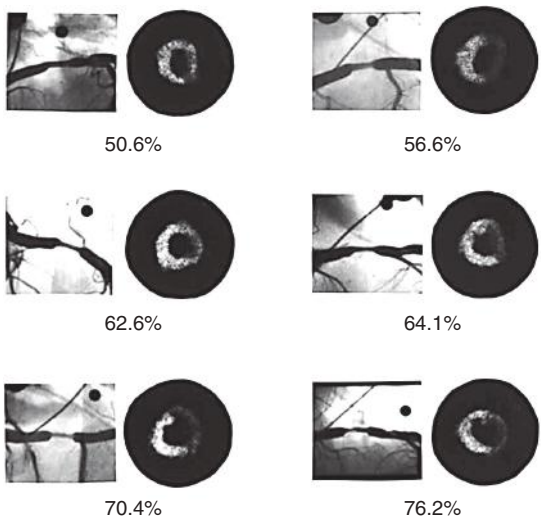


FIGURE 34–38. Angiogram of moderate to severe percent diameter stenosis and left ventricular cross-sectional perfusion images of thallium-201 during dipyridamole stress imaged postmortem by laying the cross-sectional slices of the left ventricle on a gamma camera. Reproduced with permission from Gould KL. Assessment of Coronary Stenoses by Myocardial Perfusion Imaging During Pharmacologic Coronary Vasodilatation. IV. Limits of Stenosis Detection by Idealized, Experimental, Cross-Sectional Myocardial Imaging. *Am J Cardiol*. 1978 Nov;42(5):761-768.[89]

slices before availability of in vivo tomographic myocardial perfusion imaging.[89] Even mild stenosis caused reduced subendocardial stress perfusion during vasodilator stress. With more severe stenosis, the stress perfusion abnormality extends transmurally. Earlier sections of this chapter establish that severely reduced average transmural perfusion associates with high risk of adverse events but mild to moderately reduced average transmural perfusion do not associate with high risk of adverse events. Consequently, the subtle milder subendocardial perfusion during stress caused by mild to moderate stenosis may establish a diagnosis but may not justify interventions in the absence of severe large transmural stress perfusion defects.

Does Intramyocardial Steal Negate the Observed Average Transmural Threshold for Ischemia of 0.9 cc/min/g?

The average transmural perfusion of 0.9 cc/min/g associated with angina and ST depression on ECG is a hard clinical correlation with severe epicardial stenosis. This average transmural threshold reflects a lower subendocardial and higher subepicardial perfusion than this average with a severe subendocardial to subepicardial perfusion gradient. Therefore, intramyocardial steal does not negate the average transmural flow threshold at which ischemia develops but rather reinforces this threshold at which angina and ST depression reflect subendocardial underperfusion and ischemia. Currently, subendocardial and subepicardial perfusion values are not routinely measured for clinical decisions by any technology. However, even if possible clinically, measuring subendocardial perfusion may not provide any additional critical information over the mean transmural stress perfusion that associates closely with high- or low-risk CAD regardless of subendocardium perfusion. With reduced but adequate mean transmural stress perfusion, subendocardial hypoperfusion may be present, but risk of adverse events is well defined by the mean transmural perfusion, thereby limiting the clinical value of quantifying subendocardial perfusion for clinical decisions.

COLLATERAL STEAL

Collateral steal refers to a fall in perfusion below resting levels in a region of myocardium supplied by collaterals beyond an occlusion or severe stenosis during vasodilator stress that increases perfusion in other regions of the left ventricle (Fig. 34–39). It therefore parallels intramural myocardial steal

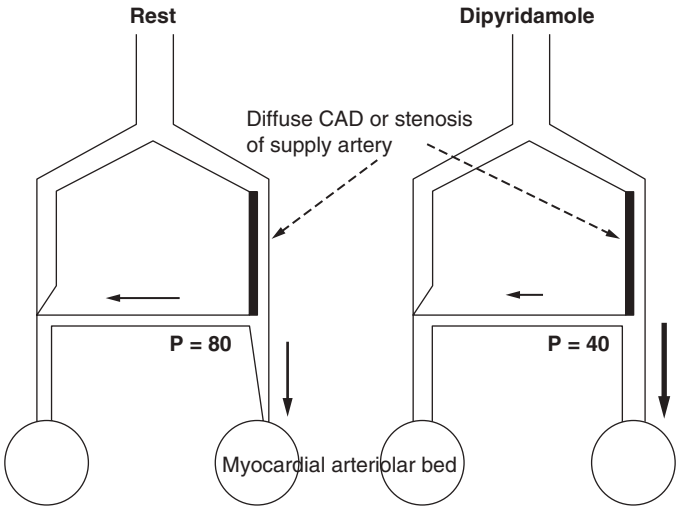


FIGURE 34–39. Schematic of collateral steal. At rest conditions, the coronary perfusion pressure to the collaterals is 80 mm Hg. With dipyridamole stress, the increased flow through a diffusely narrowed or stenotic supply artery causes decreased perfusion pressure to the collaterals, thereby reducing collateral perfusion to the vascular bed of the occluded artery. CAD, coronary artery disease.

except involves different regional distributions of the coronary arteries rather than an intramural perfusion gradient. Therefore, regional collateral steal can be imaged and quantified during vasodilator stress as indicating collateral perfusion. The pressure-flow mechanisms of collateral steal illustrated in Fig. 34–39 are similar to intramyocardial steal. With even moderate stenosis or mild diffuse CAD of the arteries supplying the collaterals, increased flow in the arteries supplying the collaterals causes the distal perfusion pressure in the supply artery to fall at the origin of the collaterals. This lowered perfusion pressure during vasodilator stress reduces collateral perfusion to below resting perfusion present before vasodilator stress, thereby potentially causing angina and ST depression. The fall in perfusion in the collateralized myocardium as perfusion in surrounding regions increases gives the appearance of the surrounding region "stealing" or shunting blood back out of the collateralized region. However, no such backward shunting occurs but rather perfusion in the collateralized area simply falls because of the lowered perfusion pressure resulting from high flows in the supply artery having even mild stenosis or diffuse narrowing. Stopping the vasodilator stress lowers blood flow in the supply artery, decreases the pressure gradient, increases collateral perfusion pressure and flow with relief of angina or ST changes. PET images of collateral seal are shown in the chapter on cardiac PET (Chap. 19).

BRANCH STEAL

The final form of myocardial steal in the absence of collaterals manifests as a base to apex longitudinal perfusion gradient with adequate or high stress perfusion at the base of the LV, tapering to low ischemic perfusion at the apex of the LV associated with angina and ST depression.[90,91] It is seen with severe diffuse three-vessel CAD with diffusely small-lumen arteries without occlusion or severe focal stenosis and without collaterals. The mechanism is falling pressure along the length of the artery as flow increases during vasodilator stress. With this longitudinally falling coronary perfusion pressure, the proximal artery branches have higher perfusion pressure than more distal branches, thereby providing lower resistance proximal localized vascular bed to which flow preferentially goes, thereby decreasing flow to the distal branches. This shunting of blood flow to proximal branches from distal branches is a true steal phenomenon with perfusion at the apex falling below resting levels, thereby causing ischemia. It is also readily imaged by PET, indicating severe diffuse CAD.[91]

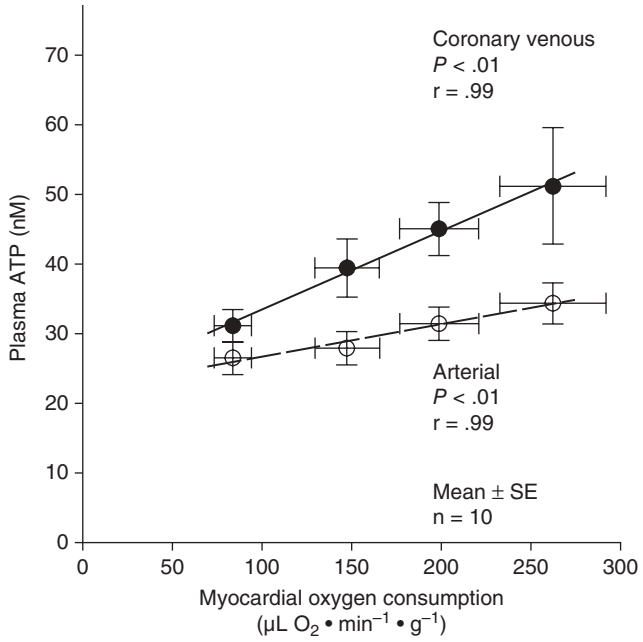


FIGURE 34–40. Plasma adenosine triphosphate (ATP) correlated with myocardial oxygen consumption in chronically instrumented exercising canines. Reproduced with permission from Farias M, Gorman MW, Savage MV, Feigl EO. Plasma ATP during exercise: possible role in regulation of coronary blood flow. *Am J Physiol Heart Circ Physiol*. 2005 Apr;288(4):H1586-H1590.[92]

CONTROL MECHANISMS REGULATING CORONARY BLOOD FLOW—THE HIERARCHY

MYOCARDIAL OXYGEN DEMAND AND CORONARY BLOOD FLOW

Of the many factors affecting coronary blood flow, the primary controller is metabolic demand that nearly instantaneously regulates regional coronary flow, even in small separate myocardial regions independently. Figs. 34–40 and 34–41 define the mechanism.[92,93] Myocardial oxygen demand regulates coronary blood flow via ATP release from oxygenated red blood cells at low myocardial pO_2.

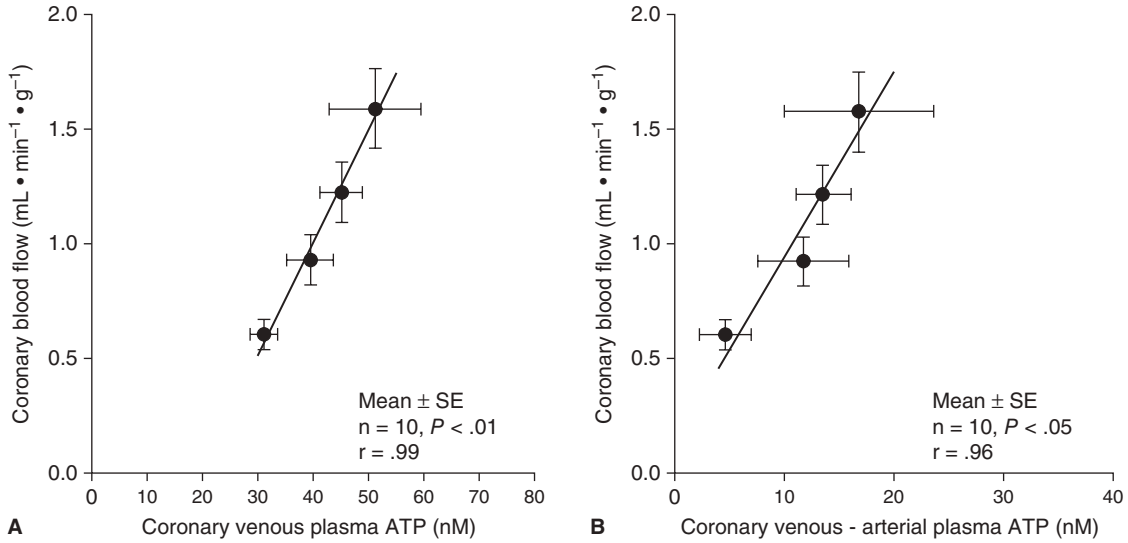


FIGURE 34–41. Coronary blood flow correlated with coronary sinus venous plasma ATP concentration (**A**) and coronary venous–arterial difference plasma ATP concentrations (**B**). Reproduced with permission from Farias M, Gorman MW, Savage MV, Feigl EO. Plasma ATP during exercise: possible role in regulation of coronary blood flow. *Am J Physiol Heart Circ Physiol*. 2005 Apr;288(4):H1586-H1590.[92]

This ATP acts on microvascular endothelium to cause arteriolar vasodilation and increased regional coronary blood flow. From a chronically instrumented model, plasma ATP in arterial and coronary venous blood correlate tightly with myocardial oxygen consumption during treadmill exercise shown in Fig. 34–40. Coronary blood flow correlates tightly with coronary venous plasma ATP (see Fig. 34–41A) and with the coronary venous-arterial difference in plasma ATP concentration (see Fig. 34–41B).

AUTOREGULATION OF CORONARY BLOOD FLOW

Coronary arterial smooth muscle inherently responds to changes in arterial pressure even with adequate arterial oxygenation and in the absence of myocardium or neural connections, as in Fig. 34–42.[94] A sudden rise in coronary pressure that initially increases coronary blood flow incurs coronary artery vasoconstriction that reduces flow back toward baseline. A sudden fall in coronary pressure that initially reduces coronary blood flow incurs vasodilation that increases flow back toward baseline. Autoregulation is a major component of reactive hyperemia after systolic contraction and after balloon occlusion at PCI.

CORONARY PERFUSION PRESSURE, CORONARY BLOOD FLOW, AND LV FUNCTION

Perfusion pressure in relation to coronary blood flow has been addressed in previous sections on FFR and phasic pressure flow relations. Despite major advances in clinical coronary pathophysiology derived from FFR, the relation of FFR or coronary pressure directly to ischemia manifest as angina, ECG changes or contractile remains poorly defined. Because of its invasiveness, the consequences of low FFR are all indirect, remote observations or associations with exercise tests, single-photon emission CT, or PET stress perfusion imaging done at a different time or as outcomes in trials. Although important, such remote associations do not elucidate pathophysiologic effects of low coronary pressure compared to coronary blood flow.

In the experimental model of Fig. 34–36,[25,87] coronary flow was held constant while mean coronary was decreased to an average of 38 mm Hg and an FFR of 0.43 or 43% of normal control pressure, or a 57% fall in perfusion pressure. Contractile function was maintained at perfusion pressure of less than half the normal control pressure. The data indicate that the heart is fairly tolerant of low pressure. By comparison, myocardial steal during dipyridamole stress that reduces resting myocardial perfusion to even 80% of resting levels typically causes angina, ECG changes, and regional dysfunction on ECG-gated perfusion PET images.[27,28] For quantitative PET perfusion imaging, coronary blood flow reduced by 57% below resting levels causes a very severe defect associated with regional contractile dysfunction, angina, and ECG changes not seen with a comparable 57% decrease in perfusion pressure.

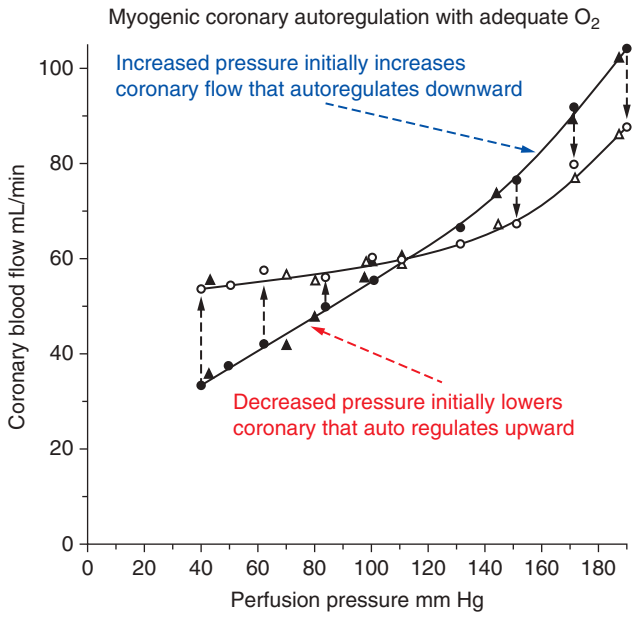


FIGURE 34–42. Coronary blood flow responses to transient changes in perfusion pressure in an experimental preparation in vivo. Reproduced with permission from Downey HF, Crystal GJ, Bashour FA. Asynchronous transmural perfusion during coronary reactive hyperemia. *Cardiovasc Res*. 1983 Apr; 17(4):200-206.[85]

MYOCARDIAL COMPRESSION OF CORONARY BLOOD FLOW

The phasic pressure flow recordings of Figs. 34–26, 34–27, and 34–28 and the reactive hyperemia of Figs. 34–33 and 34–34 show the effect of systolic compression on coronary blood flow, particularly associated with reduced diastolic perfusion time of tachycardia and limited rapid early rise of diastolic flow caused by coronary artery stenosis or LV hypertrophy.

ENDOTHELIAL CONTROL OF CORONARY BLOOD FLOW

Although it is only a thin cell layer lining the coronary arteries, the endothelium is a dynamic, active organ producing and responding to many vasoactive mediators, listed in Table 34–2. NO is the dominant endothelial mediator paralleling ATP from red blood cells and myogenic-mediated vasodilation. The great range and complexity of opposing influences indicate tremendous redundancy with interactions not readily measurable or by completely understood mechanisms. However, the end result of this endothelial complexity, its final common pathway, and the cumulative integrated measure of endothelial function, is simply coronary flow or perfusion, at rest and during stress, acutely or chronically.

Coronary atherosclerosis, diabetes, hypertension, hyperlipidemia, inflammation, age, gender, physical activity, food, stress, adiposity, medications, and other factors may affect coronary blood flow. Endothelium may mediate to some extent these effects on coronary blood

TABLE 34–2. Endothelial Mediation of Coronary Blood Flow

Stimulus	Epicardial Artery Dilation	Arteriolar Dilation Increased Flow
Flow shear	NO	NO
Exercise, pacing	NO	ATP, NO
Ischemia, hypoxia	NO	ATP, NO
Reactive hyperemia	Myogenic, NO	Myogenic, ATP, NO, PGI_2
Acetylcholine	Shear EDHF	Direct, shear, NO

Vasodilation, antithrombotic, antiproliferative:

Nitric oxide (NO), adenosine triphosphate (ATP), prostacyclin (PGI_2), endothelium-derived hyperpolarizing factor (EDHF), bradykinin, adrenomedullin, C-natriuretic peptide, plasminogen activator, protein C, tissue factor inhibitor, von Willebrand factor, transforming growth factor-beta, heparin sulfate.

Vasodilation, prothrombotic, proproliferative:

Endothelin-1, angiotensin II, thromboxane A2, oxidant radicals, prostaglandin, histamine, platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor, interleukins, plasminogen-activator inhibitor-1, fibrinogen, tissue factor, inflammatory markers, P- and E-selectin, intercellular adhesion molecule, vascular cellular adhesion molecule.

flow, but their mechanistic roles are poorly understood and cannot be directly manipulated for immediate or short-term diagnostic or therapeutic purposes. On the other hand, healthy living and good risk factor control generally improve endothelial function and coronary flow capacity, with reduced risk of atherosclerosis.

As a component of its complex molecular biology, arteriolar vasodilation with increased coronary blood flow also increases endothelial shear stress that normally triggers epicardial coronary artery vasodilation mediated by NO. However, with endothelial dysfunction, shear-induced epicardial vasodilation is lost or vasoconstriction occurs. Invasive assessment of endothelial dysfunction requires a coronary angiogram at control baseline and after intracoronary acetylcholine. Acetylcholine is an endothelial-dependent arteriolar vasodilator that increases coronary blood and endothelial shear stress, thereby inducing epicardial artery dilation on angiogram. However, with endothelial dysfunction, acetylcholine challenge that increases coronary flow induces epicardial artery vasoconstriction rather than vasodilation on clinical angiograms.[95,96] Endothelial dysfunction is typically very heterogeneous regionally and with time, where different coronary arteries and different parts of coronary arteries have differing degrees of endothelial dysfunction at different times. Coronary atherosclerosis, risk factors, or drugs that block NO inhibit epicardial artery vasodilation but have little inhibition of ATP-driven coronary arteriolar vasodilation caused by increased metabolic demands.[97]

Noninvasive assessment of endothelial dysfunction utilizes quantitative myocardial perfusion during cold pressor stress by immersing one hand in ice water.[98,99] Normally, cold pressor stress increases coronary blood flow. However, with endothelial dysfunction, coronary cold pressor stress causes epicardial and arteriolar vasoconstriction with reduced coronary blood flow that is associated with long-term development of CAD or adverse coronary events.[100] As another clinical example, with normal endothelial function, eating causes a rise in coronary blood flow. However, with risk factors or CAD, the postprandial lipid surge after a high-fat or high-carbohydrate meal worsens endothelial dysfunction that blocks endothelial-mediated vasodilation or causes vasoconstriction with decreased myocardial perfusion.[101,102] This mechanism partially explains postprandial exercise angina, whereas the same exercise while fasting causes no angina.

NEURAL CONTROL OF CORONARY BLOOD FLOW

Both sympathetic and parasympathetic neural networks enervate the coronary arteries, as listed in Table 34–3. The direct neural effect of parasympathetic stimulation is coronary vasodilation that would increase coronary blood flow but is overridden by the fall in systemic blood pressure and HR with reduced metabolic demand resulting in lowered coronary blood flow. Parasympathetic stimuli include carotid sinus massage, intravenous atropine, digoxin, the Bezold-Jarisch reflex from high osmotic intracoronary contrast media, and the parasympathetic reflex from pain. The direct neural effect of parasympathetic blockade is vasoconstriction that would lower coronary blood flow, but is overridden by metabolic demand from the unbalanced sympathetic drive that elevates HR and blood pressure, resulting in increased coronary blood flow.

The direct neural effect of beta-sympathetic blockade causes coronary vasoconstriction augmented by reduced metabolic demand from lowered HR and contractility resulting in decreased coronary blood flow. This neural effect explains why beta blockade may exacerbate coronary spasm and leg claudication. The direct neural effect of beta-sympathetic stimulation is vasodilation augmented by increased metabolic demand caused by beta-sympathetic–driven increased HR and contractility, resulting in increased coronary blood flow.

TABLE 34–3. Neural Control of Coronary Blood Flow

Parasympathetic	Direct Neural Effect	Secondary Metabolic Effect
Vagal stimulation	Vasodilation	↓HR, ↓BP, ↓CBF, vasoconstriction
Vagal blockade	Vasoconstriction	↑HR, ↑BP, ↑CBF, vasodilation
Clinical: carotid sinus pressure vagotonic, Bezold-Jarisch reflex, digoxin, ↓angina, atropine		
Sympathetic	Direct Neural Effect	Secondary Metabolic Effect
Beta blockade	Vasoconstriction	↓HR, ↓CBF, ↓contractility
Beta stimulation	Vasodilation (B2)	↑HR, ↑CBF, ↑contractility
Alpha blockade	Vasodilation	↓HR, ↓CBF, vasoconstriction
Alpha stimulation	Vasoconstriction	↑HR, ↑CBF, vasodilation
Clinical: exercise, catechols, beta-blockers, alpha-blockers		

Metabolic overrides neural control but alpha contraction limits vasodilation. Beta blockade may → unopposed alpha vasoconstriction → angina/claudication.

BP, blood pressure; CBF, coronary blood flow; HR, heart rate.

The direct neural effect of alpha blockade is coronary vasodilation that is overridden by reduced metabolic demand from reduced blood pressure, resulting in decreased coronary blood flow. The direct neural effect of alpha-sympathetic stimulation causes coronary artery vasoconstriction that is overridden by increased metabolic demand from sympathetically driven increased blood pressure, resulting in increased coronary blood flow. Both parasympathetic and sympathetic direct neural effects on coronary blood flow are usually overridden by metabolic demands but do limit the coronary blood flow response to metabolic demands.

CORONARY BLOOD FLOW AND MYOCARDIAL ISCHEMIA TO GUIDE MANAGEMENT OF CORONARY ARTERY DISEASE

Despite the deeply established relation between coronary blood flow and myocardial ischemia, their use and precise meaning in clinical practice remain surprisingly limited. Use of FFR to guide management has importantly expanded scientific focus from angiographic anatomy to coronary pathophysiology that now continues beyond FFR back to its origins—coronary blood flow. Although quantitative PET perfusion imaging is not commonly available, we use it here to demonstrate the principles and potential of quantitative coronary perfusion in clinical management. Any technology proven to quantify myocardial perfusion or coronary blood flow reliably and accurately will serve as in these examples and detailed in the chapter on PET imaging (Chap. 19). As for complexity or expense, a PET laboratory is simpler and less costly than a catheterization laboratory. Moreover, it requires a different physiologic mindset and corresponding physiologic knowledge and training, which is now lacking in most cardiac facilities and training programs. This review aims to improve this limited knowledge.

This chapter closes with vivid examples in Fig. 34–43[25] of current accurate physiologic quantification of coronary blood flow and pathophysiology to guide management of coronary artery disease. It is easily understood visually by invasive and noninvasive cardiologists, internists, family practitioners, and most importantly by patients. The quantitative images return to the basics of coronary blood flow to

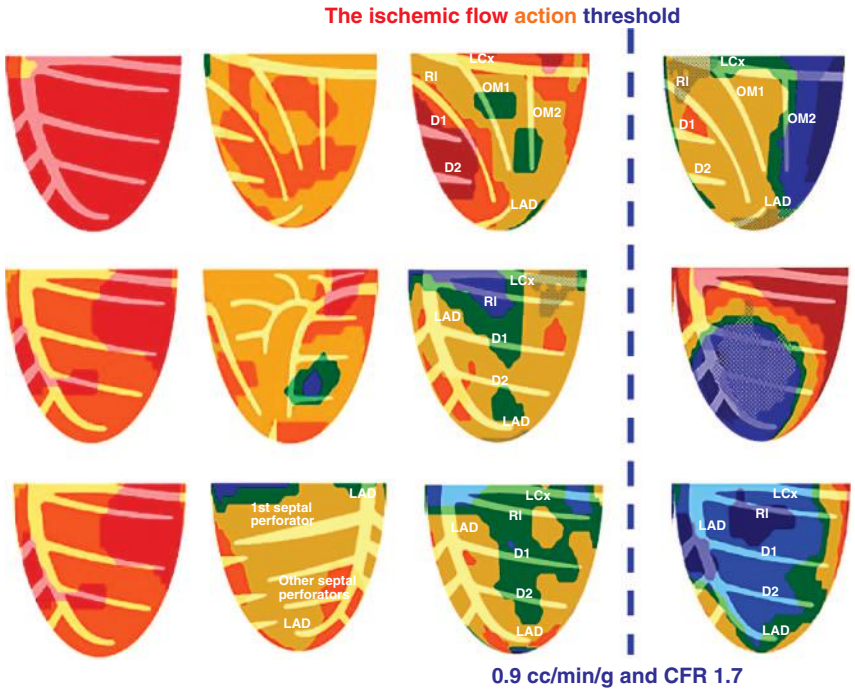


FIGURE 34–43. Coronary flow capacity maps from 12 separate cases showing the ranges of coronary flow reserve (CFR) integrated with stress perfusion in cc/min/g from healthy young volunteers and those with severe coronary artery disease. Reproduced with permission from Gould KL, Johnson NP, Bateman TM, et al: Anatomic versus Physiologic Assessment of Coronary Artery Disease: Role of CFR, FFR, and PET Imaging in Revascularization Decision-Making. *J Am Coll Cardiol*. 2013 Oct 29;62(18):1639-1653.[25]

define myocardial ischemia in universal terms of absolute flow in cc/min/g and CFR as essential vital signs even more basic than blood pressure and HR that depend on coronary blood flow.

As integrated biological, technical, and clinical complexity made simple by relevant knowledge, Fig. 34–43 shows coronary flow capacity maps from 12 separate cases (single views) representing the range of CAD: healthy young volunteers; the healthy middle aged; those only with risk factors; and those with documented CAD with or without segmental stenosis, diffuse disease, coronary events, or revascularization. The blue regions with stress perfusion of 0.9 cc/min/g or less and CFR of 1.7 or less for over 15% of the heart comprise our definition of "ischemia" requiring revascularization-based objective, measurable, universal terms of cc/min/g integrated with clinical circumstances and judgment. Less severe abnormalities comprise regionally reduced coronary flow capacity suitable for medical management that we do not call "ischemia," depending on clinical circumstances, experience and judgment.

Patients on the left of the blue dashed line are optimally treated medically without need for revascularization to achieve relief of symptoms and reduced myocardial infarction and death. Patients on the right of the blue dashed line are optimally treated with an angiogram and revascularization added to vigorous medical treatment to achieve the same goals. Of course, more randomized trials are needed but they will likely succeed in providing definitive proof only by patient selection based on quantitative myocardial perfusion or blood flow.

FINANCIAL SUPPORT AND RELATIONS WITH INDUSTRY

KLG received internal funding and is salaried solely from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis. KLG is the 510(k) applicant for HeartSee, a software package for quantifying absolute flow using cardiac positron emission tomography. All royalties will go to a University of Texas scholarship fund. The University of Texas has has the right to license the HeartSee software in exchange for royalties. However, KLG retains the ability to distribute cost-free versions to selected collaborators for research. Additionally, KLG has financial research support from Volcano Corporation (maker of FFR pressure wires) for the multicenter study DEFINE_FLOW, Clinical Trials number NCT02328820. HG and JN have no financial relationships to disclose.

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CHAPTER 35

NONOBSTRUCTIVE ATHEROSCLEROTIC AND NONATHEROSCLEROTIC CORONARY HEART DISEASE

David E. Winchester and Carl J. Pepine

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INTRODUCTION

Although obstructive coronary atherosclerosis and myocardial infarction tend to be predominant topics when discussing coronary heart disease, many other clinically relevant processes affect the coronary arteries. In this chapter, we will discuss a wide array of nonobstructive atherosclerotic and nonatherosclerotic coronary heart diseases. Our discussion will begin with pathology of the coronary artery intima and media, then move to diseases that affect the entire coronary, and conclude with physical abnormalities of the coronary arteries and mechanical disruption of coronary blood flow. Most of these diseases, however, can overlap and adversely interact. For example, coronary microvascular dysfunction (CMD) contributes to angina in patients with obstructive atherosclerosis, coronary spasm can occur at both micro and macro levels, and inflammatory disease can have an impact on the entire coronary tree.

NORMAL CORONARY ANATOMY AND FUNCTION

The normal arrangement of the coronary arteries is for the left main artery and right coronary artery to arise from the ascending aorta, 1 to 2 cm above the base of their respective coronary sinuses. The left main artery divides into anterior descending and circumflex branches, which travel in the interventricular and atrioventricular grooves, respectively. The right coronary artery also travels in the atrioventricular groove on the right side of the heart, typically terminating in the posterior descending artery in the inferior interventricular groove. Each vessel gives rise to branch vessels to create a comprehensive network of epicardial conduits. Vessels branch and decrease in size, from prearterioles to arterioles to capillaries. Myocardial blood flow is regulated mostly in the coronary microcirculation, where only small changes in arteriolar diameter can result in large changes in conductance and flow as predicted by Poiseuille's law (Fig. 35–1).[1] For example, a 20% reduction in arteriolar diameter results in a more than 100% increase in resistance and reduces blood flow by more than 50%.

The coronary arteries are lined by the intima (endothelial cells and internal elastic lamina), the media (vascular smooth muscle cells), and adventitia (eg, external elastic lamina, fibroblasts, vasa vasorum) (Fig. 35–2).[2] Many macrovascular diseases result from mechanical disruption of one or more of these layers, whereas microvascular diseases predominantly result from dysfunction of endothelial cells and/or vascular smooth muscle cells.

The endothelium functions as a mechanical barrier and also produces a variety of regulatory compounds. This layer also serves as the attachment point for surface molecules that attract or repel platelets, leukocytes, and soluble compounds in the blood. The elastic lamina act as a barrier and reinforces the structure of the coronary artery. Contractile tone of the smooth muscle layer regulates resistance to blood flow, thus controlling the volume and distribution of blood flow. This layer also proliferates in response to various disease states. Cells in the adventitial layer nourish the artery, secrete vasoactive substances, and provide the nervous system with feedback on its function.

CORONARY MICROVASCULAR DYSFUNCTION AND NONOBSTRUCTIVE ATHEROSCLEROSIS

Despite historical focus on the epicardial coronary macrovessels, the microvessels represent the predominant resistance within the coronary flow circuit and are innumerable in comparison to the epicardial vessels seen during invasive coronary angiography. Interest in and knowledge about diseases of the coronary microvessels has grown dramatically in the past few decades while clinical awareness and adequate treatment options have lagged. These disease processes also suffer from a lack of consistent terminology, leading to widespread use of catchall names such as *open artery ischemic heart disease*, *ischemic heart disease without obstructive coronary artery disease*, *microvascular angina*, and *cardiac syndrome X*. After a comprehensive review of the literature, Vermeltfoort and colleagues concluded that there was no consensus regarding the definition of cardiac syndrome X.[3] Thus we have recommended that this term not be used in favor of specific description of the clinical and microvascular findings.[4] A comprehensive understanding of coronary microvessels is vital (Fig. 35–3)[5] because in some cohorts, particularly women, angina without obstructive coronary artery disease (CAD) exceeds angina with obstructive CAD.

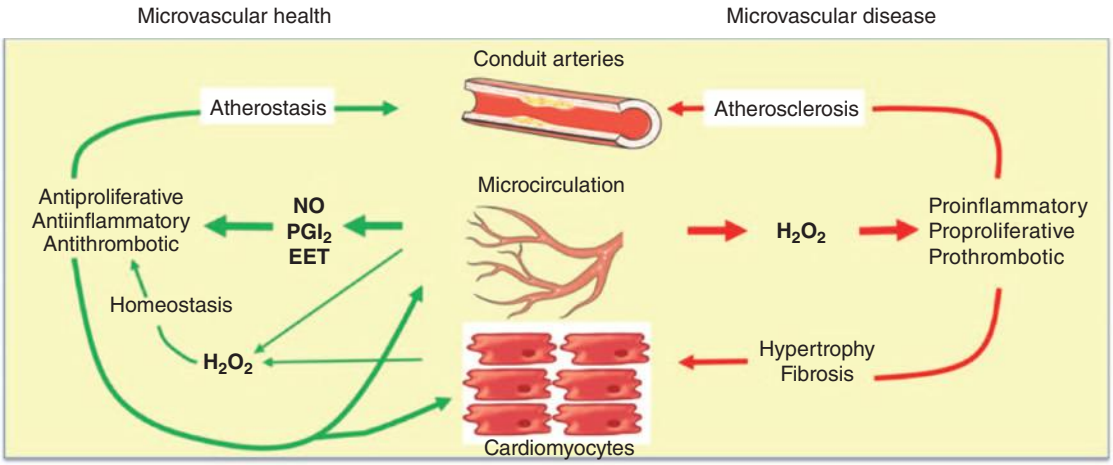


FIGURE 35–1. Regulators of coronary microvascular function. Healthy endothelium produces nitric oxide (NO) and prostacyclin (PGI_2), which are anti-inflammatory and promote homeostasis. Unhealthy endothelium produces hydrogen peroxide (H_2O_2), which promotes inflammation, proliferation, and atherosclerosis. EET, epoxyeicosatrienoic acids. Reproduced with permission from Gutterman DD, Chabowski DS, Kadlec AO, et al: The Human Microcirculation: Regulation of Flow and Beyond. *Circ Res*. 2016 Jan 8;118(1):157-172.[1]

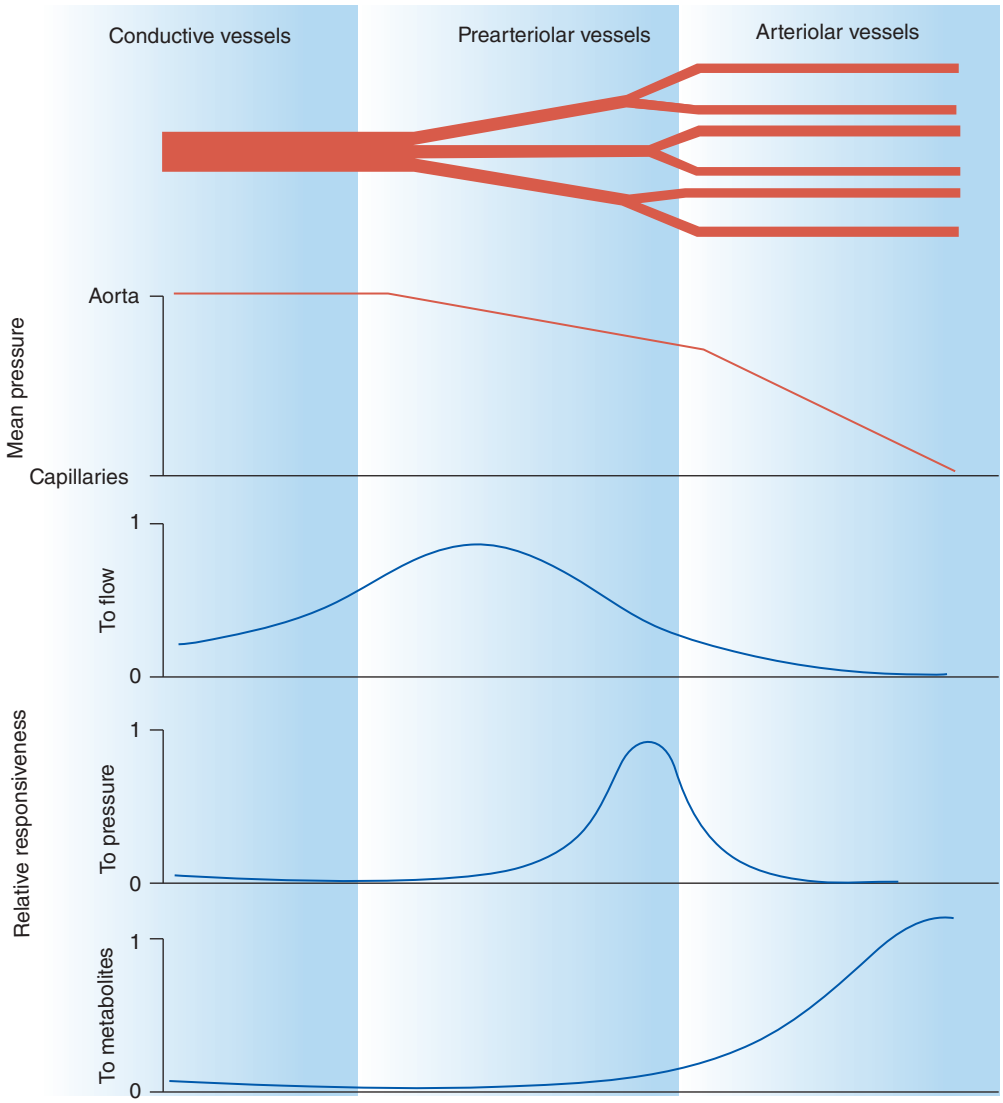


FIGURE 35–2. Components of the coronary circulation. The precapillary coronary tree consists of conductive, prearteriolar, and arteriolar vessels. Resistance in these vessels components is primarily responsive to flow, pressure, and metabolic stimuli, respectively. Mean pressure decrease is negligible in the conductive vessels and modest in prearterioles; the predominant drop in pressure occurs in the arterioles. Reproduced with permission from Camm AJ: *The ESC Textbook of Cardiovascular Medicine*, 2nd ed. Oxford University Press; 2009.[2]

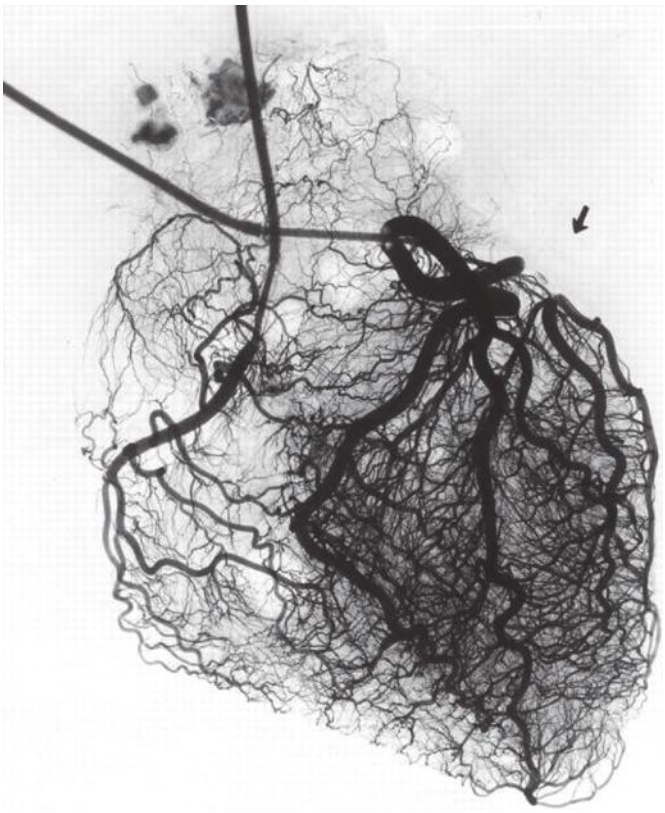


FIGURE 35–3. Coronary microcirculation. Extensive collateral circulation of 10 to 20 µm diameter vessels imaged in this ex vivo arteriogram of the heart. Reproduced with permission from Berry C, Balachandran KP, L'Allier PL, et al: Importance of collateral circulation in coronary heart disease. *Eur Heart J*. 2007 Feb;28(3): 278-291.[5]

Risk factors for developing CMD have some overlap with traditional cardiovascular risk factors. Diabetes mellitus, hyperlipidemia, and hypertension have been correlated with endothelial dysfunction (ED).[6-8] Although the causal relationships between these factors and CMD have not been well defined, systemic inflammation likely plays a role. Illnesses such as obesity and diabetes are recognized as inflammatory processes and are linked to CMD.[9,10] In addition, some systemic inflammatory processes, such as psoriasis and inflammatory bowel disease, are less typically considered to be related to heart disease but have been linked to CMD as well.[11,12] Strong correlations have been observed between CMD and collagen vascular diseases.[13]

Aside from inflammatory processes, primary hyperparathyroidism has been recently described as a cause of CMD. In a study of 100 hyperparathyroidism patients, coronary flow reserve (CFR) was lower than case-matched normal subjects, and 27 had CFR of less than or equal to 2.5. Among these 27 patients, all had restoration of normal CFR after parathyroidectomy.[14] Another cohort of 56 hyperparathyroidism patients were noted to have CMD as well as left ventricular hypertrophy and diastolic dysfunction; substantial improvements were noted after surgical resection of the parathyroid glands.[15] In multiple logistic regression analysis that included total serum calcium level, only parathyroid hormone level increased the probability of CFR less than or equal to 2.5. These findings directly implicate elevated parathyroid hormone levels as a completely reversible cause of CMD.

Other lines of evidence, however, suggest that there are as of yet unidentified factors contributing to clinical and laboratory measures of CMD.[16-18] Obstructive atherosclerosis is discussed elsewhere in this text; however, it should be noted that CMD and atherosclerosis frequently coexist. In some cases, both are overtly observed while in others a seemingly normal coronary angiogram underestimates large burden of atherosclerotic plaque.[19,20] Although multiple studies have linked atherosclerosis risk factors (eg, age, history of hypertension, systolic blood pressure, inflammatory markers) with CMD, these factors have only a small contribution to reduced CFR.[18] However, recent data suggest that in addition to age, hydraulic factors related conduit artery stiffness, such as aortic pulse wave velocity and central aortic blood pressure, provide a major contribution to reduced CFR.[16] Sometimes these myocardial scars are not localized to the distribution of a major coronary artery, perhaps suggesting an inflammatory cause for the area of infarction.[21] Myocardial infarction can also be observed in patients without obstructive atherosclerosis, although when examined with intravascular ultrasound (IVUS), ulcerated plaque is often noted.[22]

ENDOTHELIAL DYSFUNCTION

The endothelium plays a pivotal role in coronary autoregulation by release of compounds, including nitric oxide (NO), other reactive oxygen species, and arachidonic acid metabolites with a key mechanism being the production of NO from L-arginine.[23] The NO is produced in response to many stimuli, including shear stress, sympathetic tone, and muscarinic activation by acetylcholine. Endothelial release of NO elicits dilation and helps preserve normal parenchymal function by inhibiting inflammation, proliferation, and thrombotic processes.[1] NO also regulates expression of adhesion molecules, inhibits glycoprotein 2b/3a, and inactivates activated B lymphocytes, cells that may reside in or migrate into the vascular wall.

In addition to the effect of NO, the endothelium helps regulate vascular tone through the production of prostacyclin, natriuretic peptides, endothelin, thromboxanes, and prostaglandins. Dysfunction of the endothelium is closely related to a number of risk factors for developing atherosclerotic plaque and may exist on a continuum of atherosclerotic disease.[24] Oxidized low-density lipoprotein, for example, is key to both ED and plaque formation. Presence of oxidized lipids stimulates production of free radicals such as superoxide, which neutralizes biologically active NO.[25] Reduced biologically active NO can then alter any of the normal processes it regulates. Increases in platelet activation through the glycoprotein 2b/3a pathway may predispose patients to thrombus formation, leading to acute coronary syndromes (ACS) without obstructive CAD.

SMOOTH MUSCLE DYSFUNCTION

Coronary smooth muscle cells are regulated by both endothelium-dependent and endothelium-independent mechanisms. Specific pharmacological testing can be performed to make some distinctions between the two. Smooth muscle dysfunction can manifest in a variety of ways. An increase in the activational state of coronary vascular smooth muscle cells may result in spasm specifically in the microvasculature, sparing the macrovessels but resulting in the same clinical presentation.[26] Chronically elevated tone in the microvessel musculature may be an etiology of "slow flow" on coronary angiography,[27] which could also explain the observation of angina at rest sometimes reported in these patients.

NONOBSTRUCTIVE CORONARY ATHEROSCLEROSIS

Moving along the spectrum of coronary diseases, nonobstructive coronary atherosclerosis is the next step moving from isolated CMD toward obstructive or occlusive CAD. Historically, it was thought that conditions leading to myocardial ischemia, other than obstructive CAD, were uncommon or rare. This was despite evidence that a nontrivial

proportion of patients with angina symptoms and ischemia on stress testing that were noted to have normal coronary arteries on angiography.[28] This phenomenon has been explained away as "false-positive" stress testing. Meanwhile, contemporary data show us that 20% to 30% of angina patients continue to have symptoms despite technically successful revascularization of the coronary arteries. In large international registries of patients referred for coronary angiography, the prevalence of nonobstructive CAD in women with angina symptoms may be as high as 65%.[29] This is less common in men but not negligible at 14% to 32%.[29,30]

The condition of angina with so-called "normal angiography" or more accurately termed *nonobstructive CAD* (Fig. 35–4) is increasingly observed and is significantly more frequent among women than men.[31] In a study of 11,223 men and women undergoing invasive coronary angiography to evaluate anginal symptoms, one-third of men and two-thirds of women have nonobstructive CAD.[30] This observation is despite the fact that women generally present for evaluation of symptoms at a later age than men, with a higher prevalence of cardiac risk factors, including hypertension, diabetes, and dyslipidemia. As previously stated, angina with nonobstructive CAD has substantial overlap with CMD. In a study of 1439 patients with angina and nonobstructive CAD, comprehensive assessment for endothelium-dependent CMD with acetylcholine and endothelium-independent coronary flow velocity reserve with adenosine was performed. Evidence of CMD on one or both tests was found in 81% of patients.[32] More detailed analysis with IVUS and coronary computed tomography (CT) has demonstrated that most patients with "normal angiography" actually harbor atherosclerotic plaque that does not encroach on the lumen. In other cases, patients may have long segments of mild, uniform narrowing, resulting in significant decreases in perfusion by fractional flow reserve.

These patients were presumed to have trivial mortality risk, an assumption that has since been proven incorrect. Although the presence of obstructive CAD imparts a higher risk of cardiovascular events during follow-up, patients with nonobstructive CAD are still at elevated risk as compared to healthy cohorts. Data from the Women's Ischemia Syndrome Evaluation (WISE) showed that at 10 years follow-up, women with nonobstructive CAD fared worse than those with no detected CAD (ie, no stenosis > 20% luminal narrowing).[33] The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM) is a CT coronary angiography registry, which showed similar findings. In CONFIRM, among 24,775 patients undergoing CT coronary angiography, risk of death at 2.3 years was 60% higher for patients with nonobstructive CAD as compared to those with what appeared to be "normal" coronary arteries.[34] In nonobstructive CAD patients, the extent of coronary plaque is linked to future cardiovascular events. A cohort of 3242 patients undergoing CT coronary angiography for suspected CAD were divided into nonextensive nonobstructive, extensive nonobstructive, and obstructive CAD groups and compared to those with normal coronary arteries. The hazard ratios for death or myocardial infarction at 3.6 years were 3.1, 3.0, and 3.9 respectively, demonstrating the marked risk of nonobstructive CAD.[35] Bridging the gap between CMD and nonobstructive CAD, low CFR has been directly linked to adverse events.[36] In the cohort study by Jespersen, patients with angina and nonobstructive CAD (adjusted hazard ratio, 1.85) or normal coronary arteries (adjusted hazard ratio, 1.52) both had elevated risk for cardiac events versus a reference population (Fig. 35–5).[30]

In addition to the hazard associated with nonobstructive CAD, it is a very costly condition. Patients incur notable direct (office visits,

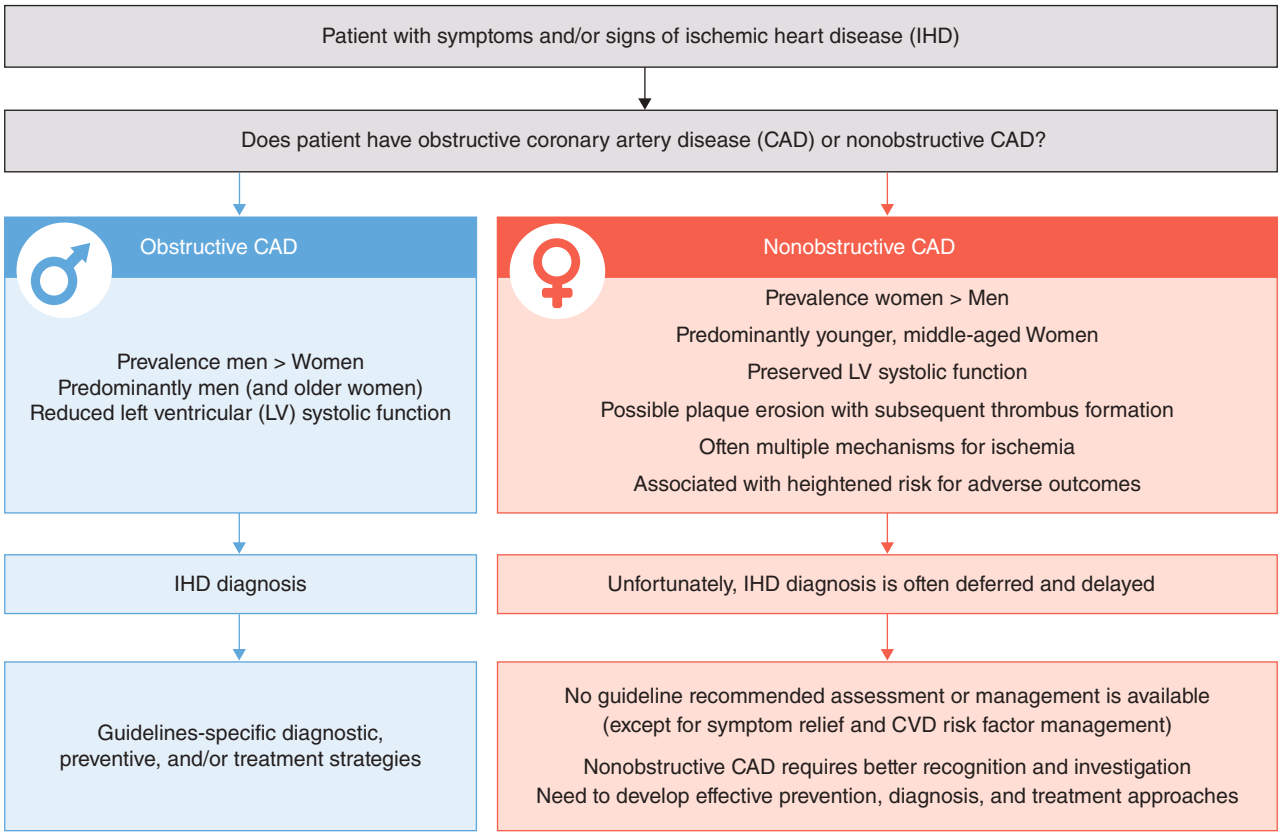
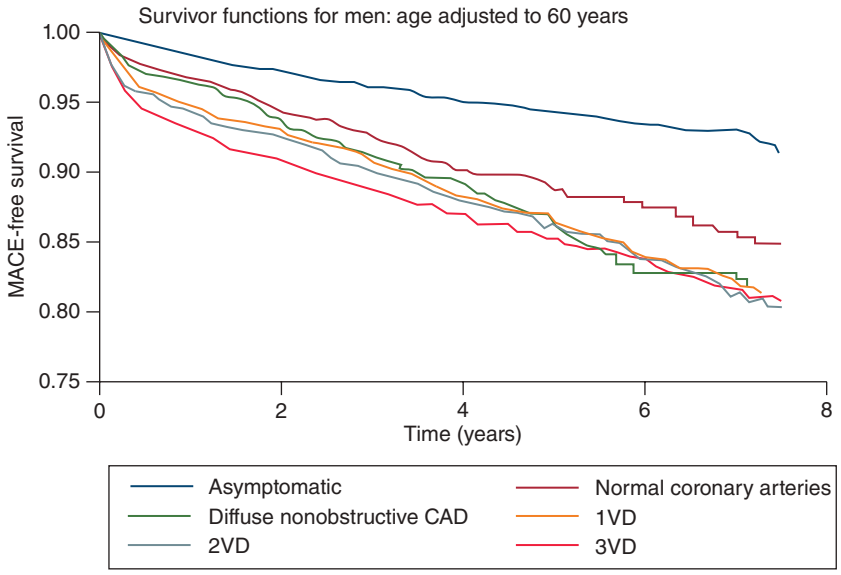
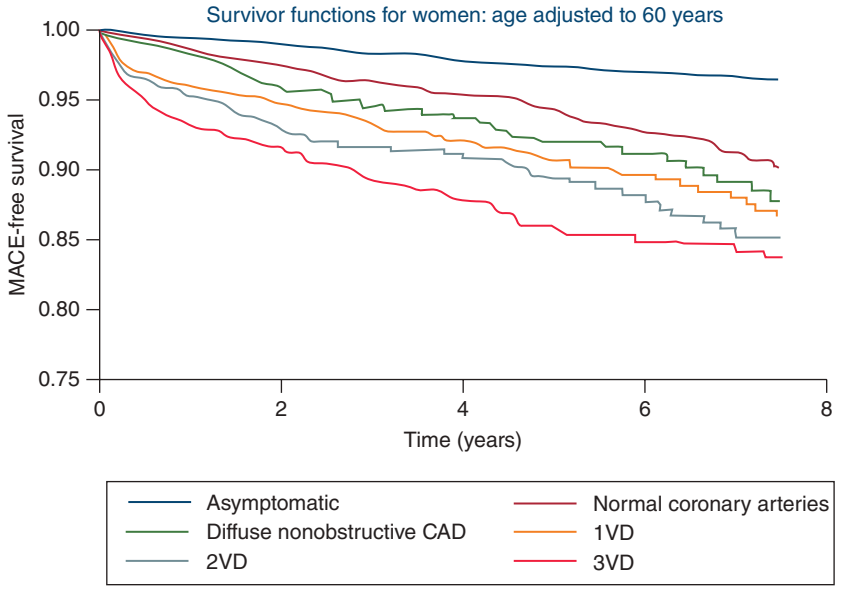


FIGURE 35–4. Classification of ischemic heart disease patients. CAD, coronary artery disease; CVD, cardiovascular disease; FFR, fractional flow reserve; IHD, ischemic heart disease; LV, left ventricular. Reproduced with permission from Pepine CJ, Ferdinand KC, Shaw LJ, et al: Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography. *J Am Coll Cardiol*. 2015 Oct 27;66(17):1918-1933.[4]



Numbers at risk	0	2	4	6
Asymptomatic	2359	2231	2101	1738
Normal CA	1214	854	597	367
Dif. nonobstr. CAD	869	557	362	174
1VD	1475	1072	783	474
2VD	1105	806	583	342
3VD	1783	1312	984	632



Numbers at risk	0	2	4	6
Asymptomatic	3346	3213	3044	2600
Normal CA	2237	1597	1155	721
Dif. nonobstr. CAD	809	527	336	187
1VD	777	567	411	252
2VD	377	274	209	143
3VD	471	333	256	161

FIGURE 35–5. Survival free of major adverse coronary events (MACE) stratified by severity of coronary disease. The top panel shows results for men and the bottom for women stratifying survival free of MACE over 7 years of follow-up. Patients with anginal symptoms and normal coronaries or nonobstructive coronary artery disease (CAD) have higher risk than those without symptoms. In this figure 1VD = one vessel disease, 2VD = two vessel disease, and 3VD = three vessel disease. Reproduced with permission from Jespersen L, Hvelplund A, Abildstrøm SZ, et al: Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events, *Eur Heart J*. 2012 Mar;33(6):734-744.[30]

hospitalizations, cardiovascular testing) and indirect costs (lost wages, travel). In a cohort of 883 women followed for 5 years in the WISE, the estimated lifetime cost associated with nonobstructive CAD was similar to that with one-vessel obstructive CAD (~ $767,288).[37]

Aside from the chronic risks associated with nonobstructive CAD in patients with chronic stable anginal symptoms, these patients also may develop ACS. A recent meta-analysis of randomized trials of ACS patients found that approximately 10% have no obstructive CAD at the time of angiography.[38] Although data on this condition are heterogeneous with wide ranges of angiography use and prevalence of nonobstructive CAD, they indicate that an ACS patient with nonobstructive CAD is more likely to be a woman without diabetes or prior CAD/myocardial infarction. Death or myocardial infarction rates at 30 days for these patients appear lower than for patients with obstructive CAD (odds ratio 0.15, 95% confidence interval 0.11-0.20). The Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) Registry documents a similar overall prevalence with nonobstructive CAD (~9.5%) in non-ST elevation ACS patients: ~15.1% of female patients, 6.8% of male patients.[39]

EVALUATION AND TREATMENT

To evaluate for the presence of CMD, a provocative agent and a measurement technique must be selected. Within the provocative agents, some are dependent on healthy, functional endothelium, whereas others act directly on vascular smooth muscle and are considered endothelium-independent.

The most commonly used pharmacological agent for endothelium-dependent testing is acetylcholine, which must be administered via the intracoronary route. In normal coronary arteries, acetylcholine releases NO from endothelium, overriding its direct effects at the vascular smooth muscle muscarinic receptor to induce vascular smooth muscle contraction, resulting in vasodilation. In arteries with diseased or dysfunctional endothelium, insufficient biologically active NO is released in response to acetylcholine. The drug's direct effect to activate vascular smooth muscle predominates and vasoconstriction occurs. Acetylcholine can be used effectively for distinguishing normal coronaries from those with epicardial spasm and/or microvascular spasm.[40,41]

Adenosine is the most commonly used so-called "endothelium-independent" pharmacological agent. It can be given by bolus intracoronary injection or intravenously, by constant infusion. Activation of adenosine A_{2A} receptors on vascular smooth muscle results in reproducible smooth muscle relaxation. Regadenoson is a selective A_{2A} adenosine receptor agonist also used in pharmacologic stress testing because of reduced side effects (eg, less bradycardia related to stimulation of adenosine A_1 and less bronchoconstriction related to stimulation of adenosine A_{2B} receptors, respectively). Regadenoson has a 2- to 3-minute biological half-life, compared with adenosine's 10-second half-life. As a result, regadenoson stress protocols use a single bolus, instead of a 4- to 6-minute continuous infusion, as with adenosine. Dipyridamole is sometimes used as an alternative agent.

Another important concept to understand is that adenosine receptors are present in endothelium. As much as 25% of the hyperemic response obtained with intravenous adenosine infusion (140 μg/kg/min dose) is the result of endothelial-dependent vasodilation because it can be blocked by infusion of NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthase.[42] A similar endothelial-related response is reasonable to expect if very high doses of intracoronary adenosine are used (ie, intracoronary doses that match the intravenous adenosine effect).

In addition to invasive testing strategies, CMD can be measured using noninvasive methods. Noninvasive testing of the coronaries with single-photon emission CT myocardial perfusion imaging may demonstrate ischemia in some patients with CMD. However, the test methods do not allow for reliable isolation of the microvasculature from obstructive atherosclerosis. Advances in positron emission tomography (PET) offer global and regional CFR in response to adenosine may allow for noninvasive evaluation of the microvasculature.

Perfusion imaging with PET is currently considered the reference standard for assessment of myocardial blood flow achieved by quantifying uptake of a specific radioisotope per gram of myocardium. Abnormal flow reserve to adenosine by this technique has been independently linked with adverse cardiovascular outcomes.[43] Multislice detector CT with iodinated contrast can provide an estimate of myocardial blood flow and CFR by measuring attenuation changes over time in basal and hyperemic conditions and plotting time-attenuation curves. The 320-row scanners permit acquisition of a full cardiac tomographic dataset within a single heartbeat, reducing iodine contrast volumes and radiation doses.

Pulsed-wave Doppler recording of left anterior descending artery coronary blood flow velocity by transthoracic echocardiography before and during adenosine infusion appears to be a reliable noninvasive method to assess CFR noninvasively. As such, it is now assigned the same class (IIb) recommendation as intracoronary adenosine testing during coronary angiography in the European guidelines. Others have proposed using myocardial contrast echocardiography to detect perfusion defects and estimate CFR.

Invasive measurement of coronary blood flow and CFR is predominantly performed using an intracoronary Doppler flow wire (Fig. 35–6).[44] The wire directly measures coronary blood flow velocity and can be combined with a pressure sensor. Volumetric blood flow can be calculated as the product of velocity and vessel lumen area measured by quantitative coronary angiography or IVUS. The technique is limited to laboratories with extensive expertise in the intracoronary use of these Doppler wires. Accurate measurement of the vessel lumen can be difficult, adequate administration of vasodilator agents requires optimal guide catheter placement, and common artifacts must be recognized and accounted for. Thermodilution and gas exchange techniques have been described but are not commonplace.[45]

Treatments for CMD and nonobstructive CAD have not been rigorously studied in large controlled trials. Guideline recommendations are sparse because the evidence base is lacking. The most recent US guidelines for stable ischemic heart disease do not provide substantial recommendations for patients with nonobstructive CAD despite that fact that many statin trials have documented reduced progression of atherosclerosis in vessels with nonobstructive disease. Patients with CMD and nonobstructive CAD are often dismissed from specialty care based on the belief that their symptoms are not related to coronary dysfunction. This neglect is compounded when symptoms are overlooked in the primary care setting. Among the few recommended treatments for CMD and nonobstructive CAD, most have been adopted from the treatments for angina pectoris related to obstructive coronary atherosclerosis. Angiotensin II inhibition (either by converting enzyme inhibition [angiotensin-converting enzyme–I] or angiotensin receptor blockade) and statins have shown promise by reducing symptoms and improving CFR in several randomized trials of small sample size.[46,47] Several pilot type trials using the late sodium channel inhibitor ranolazine in a population of predominantly women with angina and no obstructive CAD suggested favorable short-term effects, but the drug did not appear to reduce symptoms or improve myocardial perfusion reserve by cardiac magnetic resonance imaging (MRI) in a more definitive, randomized, placebo-controlled trial of 142 subjects.[48]

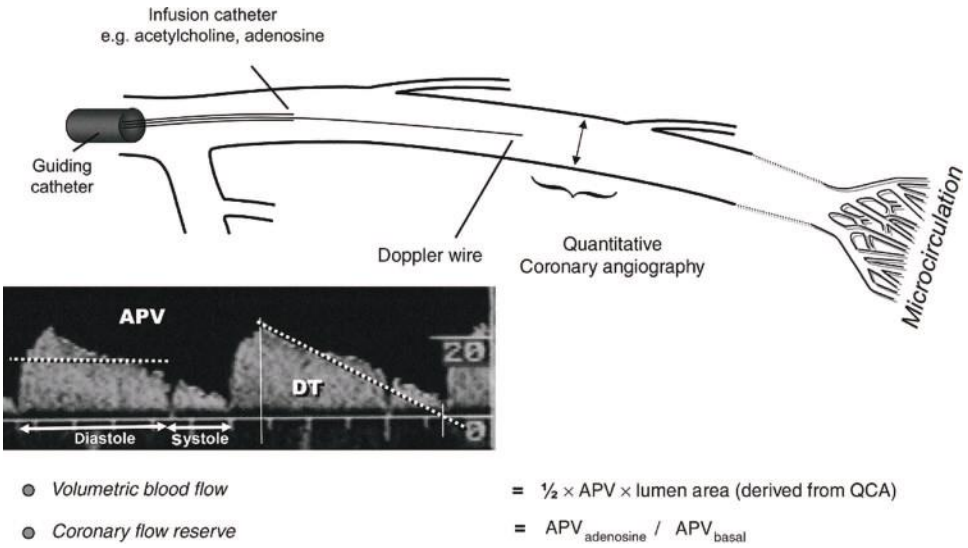


FIGURE 35–6. Invasive assessment of the microcirculation. Illustration of how the coronary arteries can be interrogated for coronary flow reserve using pressure transducing coronary wires and intracoronary infusions of medications. QCA, quantitative coronary angiography. Reproduced with permission from Schächinger V, Zeiher AM: Coronary microcirculation. Pathophysiology, clinical relevance, and importance for regenerative therapy after myocardial infarction. *Herz*. 2005 Nov;30(7):641-650.[44]

EPICARDIAL CORONARY SPASM

Spasm of the coronary arteries was suggested by Osler in 1910[49] and proposed based on observed clinical and electrocardiogram (ECG) findings by Prinzmetal and coworkers in 1959.[50] It was then documented angiographically by Gensini and colleagues in the early 1960s.[51] The syndrome included symptoms typical of angina pectoris, but occurring at rest and typically associated with transient elevation of the ST segments. Maseri and coworkers, in multiple reports from 1975 to 1995, provided experimental confirmation that coronary spasm was a central mechanism involved in a variety of ischemic syndromes and not limited to that described by Prinzmetal as variant angina. The contemporary term then became *vasospastic angina*. Because epicardial spasm has a much wider clinical spectrum of symptoms and ECG findings and may sometimes overlap with CMD, we prefer to use the simpler and clinically broader term, *coronary spasm*[52] (Fig. 35–7).[53]

The clinical findings (symptoms and ECG changes) associated with coronary spasm may occur without ST-segment elevation, and in fact they are often associated with ST-segment depression and/or T-wave changes and may be also at times result from small-vessel or regional coronary dysfunction. Depending on the severity and duration of spasm and the coexistence of obstructive CAD, myocardial necrosis, ventricular tachycardia/fibrillation, heart block, and/or sudden death can occur. The specific etiology of the spasm is not known but is thought to be related to both neurologic and pharmacologic stimuli that activate vascular smooth muscle to contract, severely reducing luminal diameter and hence limiting regional blood flow (Fig. 35–8).[54]

In addition to spontaneous occurrence, coronary spasm may occur in a variety of clinical situations, including general anesthesia; allergic reaction (histamine-induced, hypersensitivity angina); use of ergoline derivatives (eg, bromocriptine, methylergonovine, pergolide, lisuride); thyrotoxicosis; hypercholinergic crisis; use of triptans, dobutamine infusion during stress testing; use of capecitabine, dolasetron (5-hydroxytryptamine antagonist); and illicit substance use (eg, cocaine, butane, amphetamines, 3,4-methylenedioxy-methamphetamine [MDMA]). Coronary spasm can occur with mechanical stimulation related to catheter manipulation for diagnostic or interventional procedures (eg, angiography or catheter/balloon angioplasty); however, catheter-related spasm is a benign condition unrelated to the clinical syndrome described above. Recent reports[55] suggest a possible connection between inflammatory disease and vasospastic angina. Minor elevations of serum C-reactive protein suggest chronic low-grade inflammation may be involved in the pathogenesis of coronary spasm.[56,57] Elevated serum eosinophils,[58] monocytes,[59] and mast cells have been implicated in coronary spasm.

Coronary spasm is more common in younger patients and women than angina pectoris occurring because of obstructive atherosclerosis. However, some degree of atherosclerosis (as intimal thickening by IVUS or at autopsy) is likely present in all cases of coronary spasm. In patients dying with spasm, severe plaque was observed in a substantial proportion of sampled coronary segments (Fig. 35–9).[60] Atherosclerosis produces profound alteration of vascular responses that may lead to spasm in the coronary as well as the cerebrovascular bed. Leukocytes and platelets likely play an important role in the pathophysiology of spasm. Cigarette smoking and Asian ethnicity are risk factors for spasm, whereas other traditional cardiovascular risks are not strongly associated. Some patients have clustered angina episodes, experiencing two to four at a time before relief; episodes typically last for minutes at a time. Spasm is frequently observed in patients with ACS and must be considered as part of the diagnostic evaluation, particularly when the degree of atherosclerotic obstruction observed angiographically fails to explain the ischemic syndrome.[61]

A scoring system has been proposed to estimate risk of major adverse cardiac events (MACE) in patients with vasospasm (Table 35–1).[62] Using this system, patients can be stratified into low, moderate, and high risk of MACE. Early repolarization pattern on the resting ECG has been suggested as a predictor of cardiac events.[63]

Pharmacological agents, such as ergonovine, ergometrine, or acetylcholine, are used to test for the presence of coronary spasm during invasive angiography when spasm does not occur spontaneously during the procedure. Ergonovine activates multiple receptors (alpha-adrenergic, dopaminergic, and serotonin [5-HT]) directly activating vascular smooth muscle. The drug can be given intravenously in doses from 0.05 to 0.40 mg or by the intracoronary route with modest

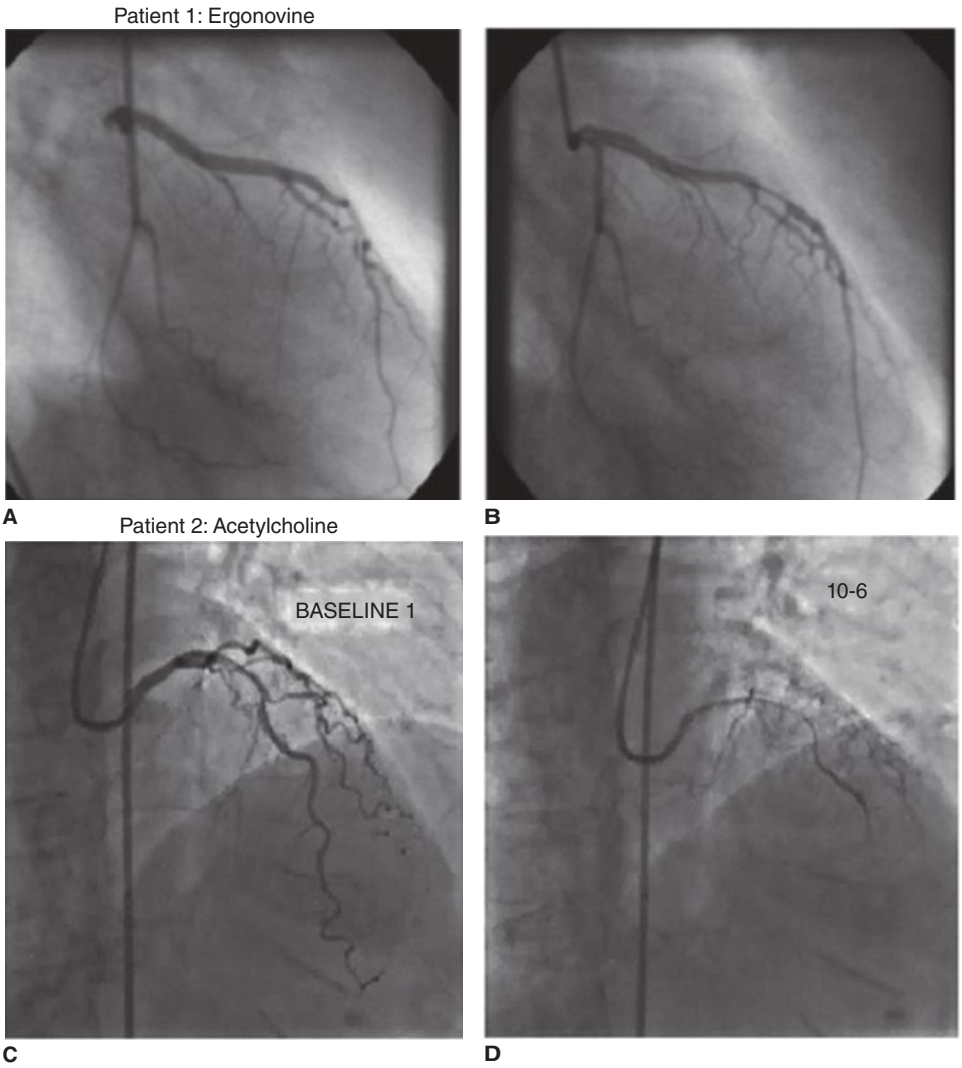


FIGURE 35–7. Coronary spasm in a 49-year-old woman with exertional angina. (**A, B**) Focal spasm of the left anterior descending (artery; LAD) before and after administration of ergonovine and (**C, D**) diffuse spasm of the LAD before and after administration of acetylcholine in a second patient. Reproduced with permission from Zaya M, Mehta PK, Merz CN: Provocative testing for coronary reactivity and spasm. *J Am Coll Cardiol*. 2014 Jan 21;63(2):103-109.

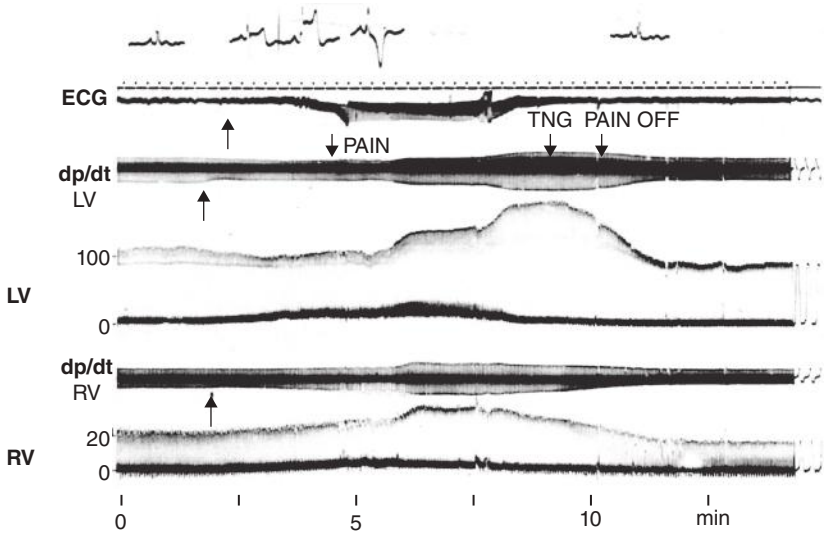


FIGURE 35–8. Hemodynamic and electrocardiogram (ECG) changes during coronary spasm. Continuous monitoring of patients with clinical vasospasm demonstrates that the initially detected event is a decrease in left and right ventricular dp/dt followed with ECG shifts. Pain and changes in chamber pressures do not occur until minutes after the onset of spasm. LV, left ventricle; RV, right ventricle. Reproduced with permission from Maseri A, Mimmo R, Chierchia S, et al: Coronary artery spasm as a cause of acute myocardial ischemia in man. *Chest*. 1975;Nov;68(5):625-633.[54]

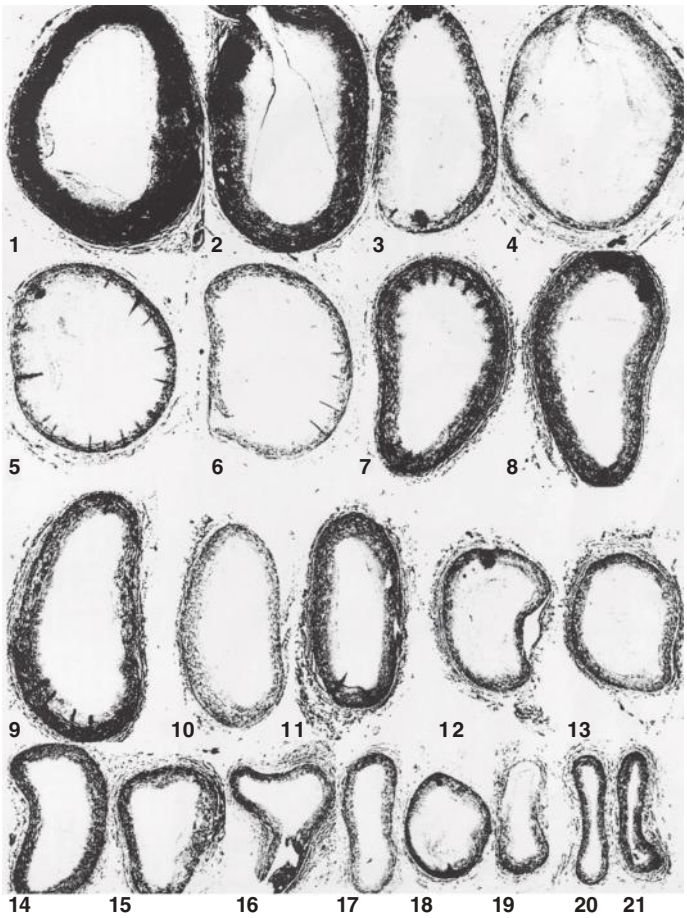


FIGURE 35–9. Cross-sectional segments of coronary artery in a patient with coronary spasm. Composite of coronary artery cross-sections of a patient with coronary spasm during life. Clinical spasm involved segments 3 to 7. Severe atherosclerotic plaque is seen in 8 of the 21 segments. Reproduced with permission from Roberts WC, Curry RC Jr, Isner JM, et al: Sudden death in Prinzmetal's angina with coronary spasm documented by angiography. Analysis of three necropsy patients. *Am J Cardiol*. 1982 Jul;50(1):203-210.[60]

TABLE 35–1. Risk Scoring System for Predicting MACE in Patients with Vasospasm

Factor	Score	
Out of hospital arrest	4	
Smoking	2	
Angina at rest alone	2	
Organic coronary stenosis	2	
Multivessel spasm	2	
ST elevation during angina	1	
Beta-blocker use	1	
Risk category	**Score**	**MACE**
Low	0 to 2	2.5%
Intermediate	3 to 5	7.0%
High	More than 5	13.0%

Abbreviations: MACE, major adverse coronary events.

Data from Takagi Y, Takahashi J, Yasuda S, et al. Prognostic stratification of patients with vasospastic angina: a comprehensive clinical risk score developed by the Japanese Coronary Spasm Association. *J Am Coll Cardiol*. 2013 Sep 24;62(13):1144-1153.[62]

accuracy for determining the presence of spasm. The drug can result in prolonged spasm and must therefore be given in a controlled clinical environment (ie, during angiography), where intracoronary nitroglycerin can be administered rapidly if needed. Unfortunately, it causes a generalized constriction of coronary arteries even when given to patients without spasm and an elevation of systemic blood pressure. This makes interpretation of anything except subtotal occlusion associated with symptoms and ECG changes difficult for the occasional user to interpret, particularly when the patient also has obstructive CAD.

Acetylcholine dilates arteries with functioning endothelium by stimulation of endothelial muscarinic receptors to release NO. When the endothelium is not functioning normally and/or vascular smooth muscle is activated, acetylcholine causes constriction. Acetylcholine is infused directly into the coronary artery usually over 1-minute intervals separated by 5 minutes, starting at 25 μg and increasing by 25-μg increments to a maximum of 100 to 200 μg. In general, patients with spasm will experience focal or sometimes generalized spasm with acetylcholine, although patients without vasospasm but with ED will experience a more diffuse, less severe constriction of the artery. Focal spasm may portend a worse prognosis versus more diffuse spasm, in response to acetylcholine infusion.[64]

Treatment of patients with coronary spasm includes elimination of risk factors, particularly smoking and exposure to noxious fumes such as those related to smoke and gasoline engine exhaust. Calcium antagonists are the cornerstone of treatment, sometimes with addition of nitrates. We have at times combined a dihydropyridine calcium antagonist with a nondihydropyridine (verapamil or diltiazem) for patients not adequately responsive to one agent. Nitrate therapy may not improve outcomes when added to calcium antagonist therapy.[65] However, nitrate tolerance is always a concern in these patients because nitrates are so effective in relieving and preventing symptoms related to coronary spasm. Cilostazol has recently been suggested to be effective for selected patients with coronary spasm not controlled by a calcium antagonist.[66] The benefit of alpha-adrenergic blockers and beta-blockers is limited, and use of these agents may limit dosing of more effective calcium antagonists due to hypotension.[67]

SYSTEMIC INFLAMMATORY ILLNESSES

The coronary arteries can be affected by systemic inflammatory illnesses, both general inflammatory diseases and those specific to vascular structures. Vasculitides are commonly organized by the size of the vessels affected: large (such as the aorta), medium (such as coronary vessels), and small (such as arterioles). Despite this nomenclature, vessel involvement is not limited to one vessel size and the disease processes commonly span multiple vessel size ranges. Cardiologists may encounter these diseases in the process of evaluating patients with nonspecific symptoms, such as fatigue. Recurrent fevers may prompt cardiology referrals requesting evaluation of the patient for endocarditis. A high index of suspicion must be kept to diagnose these diseases. A table of processes that may manifest with coronary arteritis is provided (Table 35–2). The effect of systemic vasculitides is variable, because some but not all contribute to accelerated atherosclerosis.[68]

Infectious agents may play a role in a number of vasculitides. Hepatitis B is linked to polyarteritis nodosa, and hepatitis C is a causative agent of cryoglobulin-related vasculitis. Bacteria associated with vasculitis include Rickettsiae, *Coxiella*, *Mycoplasma*, and *Toxoplasma*. Viral agents include herpes, Epstein-Barr, parvovirus, cytomegalovirus, and varicella.[69]

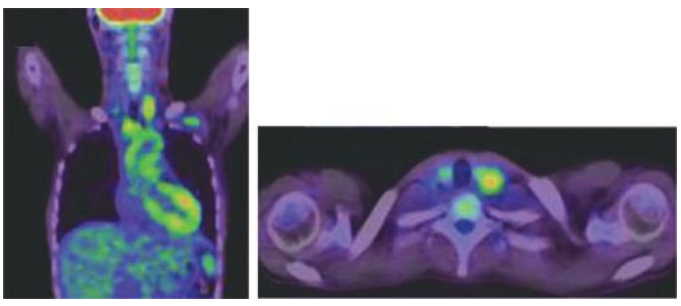
TABLE 35–2. Causes of Coronary Arteritis

Large-vessel vasculitis
Takayasu's arteritis
Giant cell arteritis
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small-vessel vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic polyangiitis (Churg-Strauss syndrome)
Antiglomerular basement membrane disease
Cryoglobulinemia
IgA vasculitis (Henoch-Schonlein purpura)
Thromboangiitis obliterans (Buerger disease)

LARGE-VESSEL VASCULITIS

Takayasu's Arteritis

The pathological cause of Takayasu's arteritis is not precisely known, but it is widely thought to result from an autoimmune process mediated by T cells and affect the vasa vasorum of large vessels with leukocyte infiltration. The disease is most prevalent in Asia and the Middle East with a female predominance and a peak incidence in the third decade of life.[70] Some familial cases have been reported, but the disease is generally considered sporadic. Early symptoms are nonspecific (fatigue, fever), whereas late manifestations include vision loss, renal impairment, and stroke. Although coronary involvement is thought to be uncommon, perfusion defect may be seen in a majority of patients, despite a lack of cardiac symptoms.[71] In a cardiology context, consideration should be given for this disease in young patients presenting with myocardial infarction and low risk of atherosclerosis. No specific serum test is available; markers of inflammation (C-reactive protein, sedimentation rate) are commonly used in facilitating diagnosis. Treatment is based on steroid suppression. CT and specifically PET/CT are useful for assessing arterial dilation and inflammatory activity in the vessels (Fig. 35–10).[70]



A B

FIGURE 35–10. Positron emission tomography (PET)/computed tomography (CT) imaging of Takayasu's arteritis. In **A** and **B**, hybrid imaging with PET and CT shows uptake of fluorodeoxyglucose in the large vessels: aortic arch, carotid, and brachiocephalic. Reproduced with permission from Isobe M: Takayasu arteritis revisited: current diagnosis and treatment. *Int J Cardiol*. 2013 Sep 20;168(1):3-10.[70]

Giant Cell Arteritis

Also known as temporal arteritis because of a predilection for the temporal arteries, giant cell arteritis (GCA) is a vasculitis predominantly of older (> 50 years) patients. Infiltration of the intima with giant cells can result in granuloma formation and thickening of the internal elastic lamina. Blindness and stroke are unfortunate presentations, whereas headache and fever are a more common combination. In rare cases, GCA may present initially with coronary manifestations.[72] A meta-analysis comparing GCA to non-GCA patients found that the subsequent risk of CAD was not different between the groups, although it is limited by high heterogeneity of the studies.[73] GCA is commonly diagnosed by biopsy of affected arteries, which is not feasible for the coronaries. Imaging studies may show pathological thickening of the large vessels (Fig. 35–11).[74] Treatment is with immunosuppression.

MEDIUM-VESSEL VASCULITIS

Polyarteritis Nodosa

Polyarteritis nodosa is a chronic systemic disease caused by necrotizing vasculitis most often affecting the skin and peripheral nerves. The disease is caused by an autoimmune response to an infectious agent, most commonly hepatitis B virus. As a result of vaccination in western populations, hepatitis B is decreasing infrequency, as is polyarteritis nodosa. Being linked to hepatitis B, the peak incidence is in the 40- to 50-year age range with a male predominance. Coronary artery involvement is present in a minority of cases (4%–30%).[75] The coronaries can become thrombosed, resulting in infarction or become aneurysmal and possibly rupture (Fig. 35–12).[76-78] No laboratory tests are specific for polyarteritis nodosa; antineutrophil cytoplasmic antibodies (ANCA) are typically negative. A five-factor score can be used to estimate risk of mortality, which is dependent on the organ systems involved.[79] Immune modulating drugs, including steroids, cyclophosphamide, azathioprine, and methotrexate, are used for treatment.

Kawasaki Disease

Kawasaki disease is a common childhood vasculitis that can manifest with coronary abnormalities. The disease is also known as mucocutaneous lymph node syndrome and is rare in adults. Typical presentation includes erythema of mucous membranes (conjunctivitis, mucositis, rash) and lymphadenopathy. An infectious agent is suspected, but no causative agent has been identified.[80] Widespread inflammation of medium-sized arteries results in coronary artery aneurysms, typically developing between 4 days and 4 weeks of symptom onset for about 25% to 30% of patients who are not treated early. Pathologically, necrotizing angiitis of the vaso vasorum damages the media and adventitia. Risk factors for aneurysm development are described in Table 35–3. Researchers encourage the use of standardized Z-scores of aneurysm size in order to optimize comparisons in the medical literature.[81] Widespread use of intravenous immunoglobulin has resulted in dramatic reductions in morbidity and mortality. Treatment with other immune modulating drugs is a current area of study.[82] Spontaneous regression of the aneurysm occurs in about half of vessels in 1 to 2 years after illness, predominantly determined by the size of the initial aneurysm. Aside from aneurysm development, other cardiac structures and function may be affected. Pericarditis, myocarditis, and arrhythmias have been reported. Noncoronary vascular symptoms include peripheral ischemia and, rarely, gangrene.

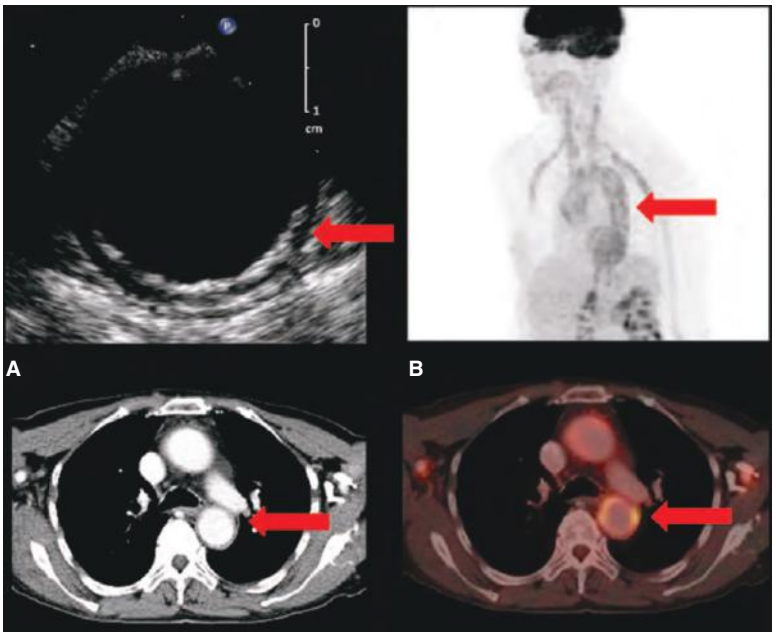


FIGURE 35–11. Imaging findings in giant cell arteritis. (**A**) Abnormal thickening of aorta on transesophageal echocardiography in febrile patient resulted in further evaluation for arteritis, (**B**) inflammation noted on fluorodeoxyglucose positron emission tomography (PET) imaging, (**C**) thickened aorta on computed tomography, and (**D**) inflammation on FDG-PET hybrid imaging. Reproduced with permission from Palmers PJ, Ameloot K, De Wever W, et al: An echocardiographic finding leading to the diagnosis of giant cell arteritis. *Eur Heart J Cardiovasc Imaging*. 2013 May;14(5):434.[74]

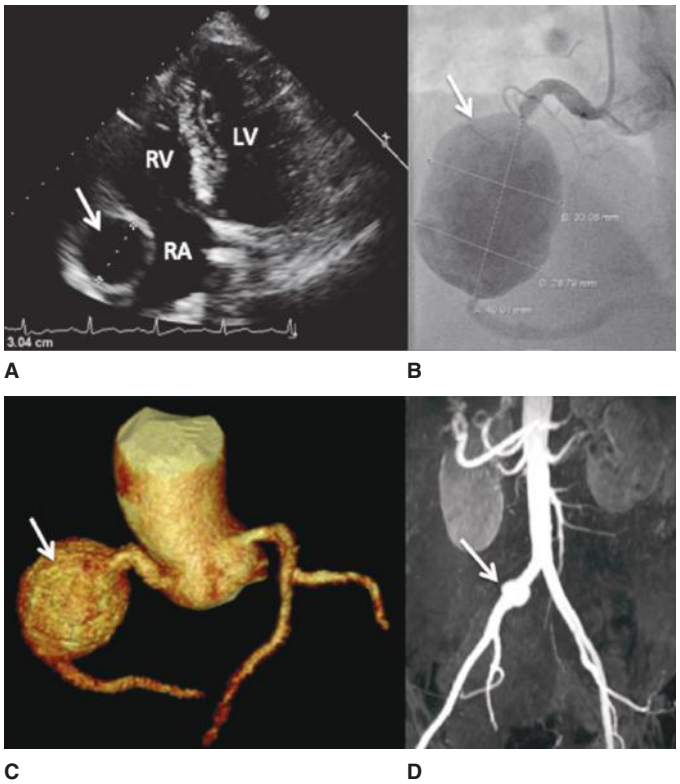


FIGURE 35–12. Massive coronary aneurysm in a patient with polyarteritis nodosa. (**A**) Echocardiogram demonstrating coronary aneurysm (*arrow*), (**B**) angiographic imaging, (**C**) three-dimensional reconstruction by computed tomography, and (**D**) magnetic resonance angiography of an additional inguinal artery aneurysm. LV, left ventricle; RA, right atrium; RV, right ventricle. Reproduced with permission from Ebersberger U, Rieber J, Wellmann P, et al: Polyarteritis nodosa causing a vast coronary artery aneurysm. *J Am Coll Cardiol*. 2015 Feb 10;65(5):e1-2.[77]

When Kawasaki disease goes undiagnosed in childhood, adults can suffer from late clinical manifestations (Fig. 35–13). In long-term (30 years) follow-up of Kawasaki patients, only 36% remained free of cardiovascular events.[83] A recent cohort of adult patients with coronary aneurysm noted during angiography found that 22% were believed to have "definite" Kawasaki disease as a child.[84] Echocardiographic evaluation of adults with history of Kawasaki disease suggests that persistent changes in the coronary intima may be a way to detect latent cardiovascular risk.[85] Late treatments of coronary artery aneurysm are similar to those for any other etiology. If ischemia or acute coronary syndrome develops, appropriate medical therapy is warranted and revascularization options span surgical and percutaneous methods. Retrospective data suggest that routine use of anticoagulation is associated with lower risk of occlusion, infarction, and death.[86]

TABLE 35–3. Risk Factors for Developing Coronary Artery Aneurysm for Kawasaki Disease

Delayed diagnosis and treatment
Poor response to treatment
Age < 1 or > 9 years
Male sex
Long fever duration
High CRP or ESR
Low albumin, sodium, or hemoglobin

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

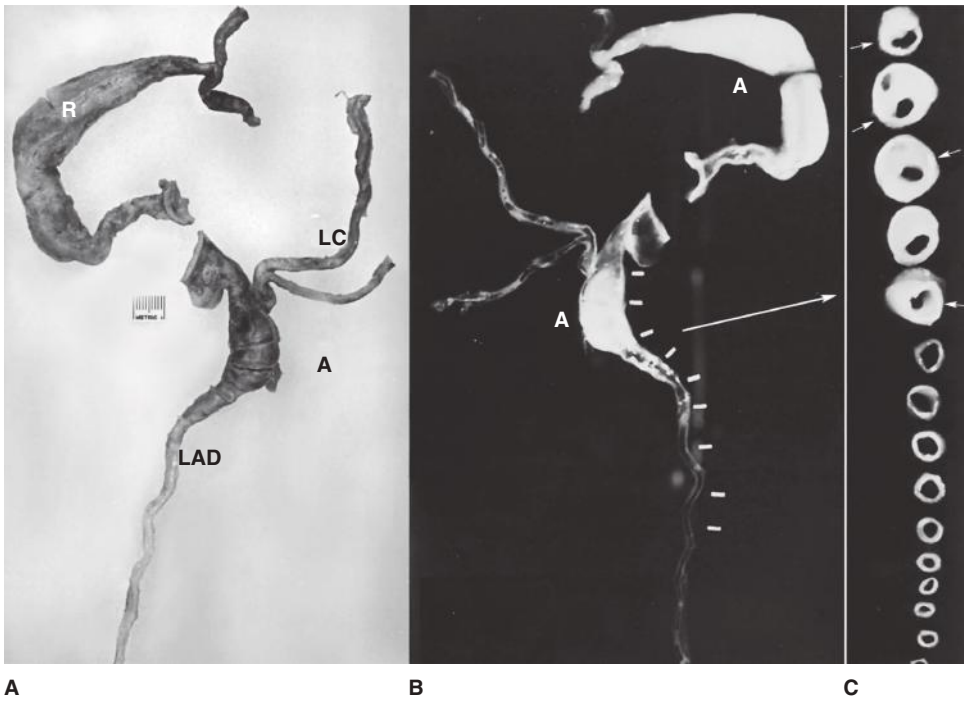


FIGURE 35–13. Gross specimen of the coronary arteries in an adult with probable Kawasaki disease as a child. (**A**) Significant aneurysmal dilatation of the right and left anterior arteries, (**B**) radiograph demonstrating calcification in the aneurysmal segments, and (**C**) cross-sectional images of the aneurysmal segment. A, aneurysm; LAD, left anterior descending coronary artery; LC, left circumflex coronary artery; R, right coronary artery.

SMALL-VESSEL VASCULITIS

ANCA-Associated Vasculitis

Within small-vessel vasculitides, two general groups emerge, those with antineutrophil cytoplasmic antibodies (ANCA) and those mediated by immune complexes. The ANCA-associated diseases include microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener's granulomatosis), and eosinophilic polyangiitis (formerly Churg-Strauss syndrome). These diseases are most commonly diagnosed in older adults and most commonly affect the kidneys, lungs, eyes, nerves, and skin. Presentations include glomerulonephritis, cough, pleuritic pain, conjunctivitis, optic neuropathy, peripheral neuropathy, and purpura. Serum tests and biopsies of affected organs are helpful in establishing the specific diagnosis. Cardiac involvement may not be considered part of the typical presentation. However, if an extensive evaluation is conducted, half of patients may have some cardiac abnormalities.[87] Cardiac MRI often demonstrates myocardial scarring.[88,89] Treatment options vary based on the specific processes observed and severity of disease. Immunomodulating drugs are the cornerstones of therapy.

Immune Complex–Mediated Small-Vessel Vasculitis

There are several small-vessel vasculitides without ANCA such as antiglomerular basement membrane disease (formerly Goodpasture's disease), cryoglobulinemia, and IgA vasculitis (formerly Henoch-Schonlein purpura). These diseases share the fact that immune complexes are deposited in vessel walls and damage the small vessels of the body. As with the ANCA-associated diseases, the lungs, kidneys, skin, and nerves are the most commonly affected organ systems. Little has been written about coronary involvement, but case reports linking these diseases to the heart have been published.[90,91] Depending on the severity of symptoms and the organs involved, supportive treatment or immunosuppressive therapy may be used.[92-94]

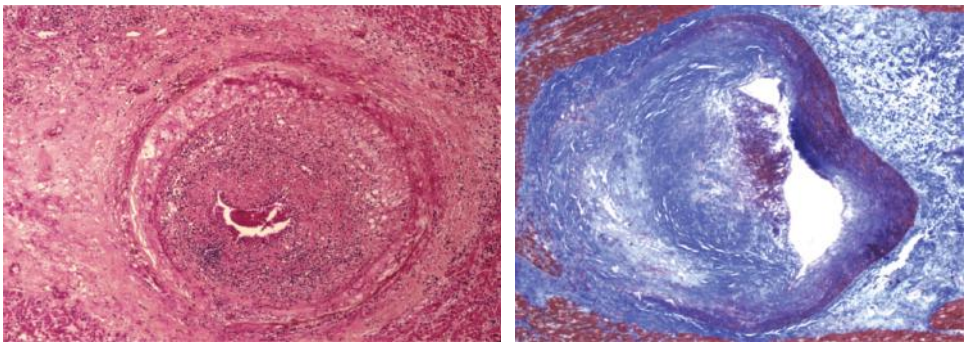
Thromboangiitis Obliterans (Buerger Disease)

Thromboangiitis obliterans is an uncommon, poorly understood non-necrotizing vasculitis strongly linked to smoking. It typically manifests as a peripheral vascular disease affecting the lower extremities. Claudication leading to ischemia, ulcer formation, and gangrene is a common sequence in the clinical presentation. Infectious, genetic, immunological and hypercoagulability causes have been proposed. Rarely, the coronaries may be involved.[95] Histopathologic review of biopsy specimens can distinguish this from other vasculitides. Tobacco cessation is thought key to management; no specific therapies alter the course of the disease and medical/surgical therapy is focused on relieving ischemic symptoms.

TRANSPLANT VASCULOPATHY

For some patients with advanced ischemic and nonischemic heart disease, orthotopic heart transplantation is a treatment option. More than 5000 heart transplants are performed worldwide annually—more than 2000 in the United States alone. After the initial surgical procedure, patients are required to maintain a strict regimen of immunosuppressive and anti-infective medications to prevent complications. These medication regimens have extended the average survival for heart transplant patients to over 10 years. With the additional longevity, diseases such as transplant vasculopathy (TV) have become more common with TV now the leading cause of late death after transplantation.[96]

TV is a process whereby the coronary arteries become diffusely and circumferentially narrowed with progressive luminal loss. The process differs from typical atherosclerotic processes. Findings often seen include: smooth muscle cell proliferation in the intima, fibrosis, and accumulation of T-lymphocytes (Fig. 35–14).[97] Separate from these events, atherosclerotic plaque may be present in the donor



A B

FIGURE 35–14. Histology of transplant vasculopathy and native atherosclerosis. (**A**) Concentric hyperplasia of the coronary intima seen in transplant vasculopathy resulting in near obliteration of the lumen and (**B**) native coronary atherosclerosis with predominance of fibrosis and eccentric luminal stenosis. Reproduced with permission from Pollack A, Nazif T, Mancini D, et al: Detection and imaging of cardiac allograft vasculopathy. *JACC Cardiovasc Imaging*. 2013 May;6(5):613-623.[97]

heart at the time of transplantation or develop subsequently. The process occurs in roughly one-fourth of patients after 5 years and one-half after 10 years. Greater donor age, younger recipient age, history of hypertension, and immune mismatches are risk factors for developing TV.

Clinically, patients may present with progressive anginal symptoms, graft dysfunction (ie, systolic dysfunction), or sudden death. Myocardial infarction can occur with or without symptoms because of variable innervation of the transplanted heart. A variety of techniques may be used to diagnose TV, including stress testing, coronary CT, and invasive coronary angiography with or without IVUS.[97] Most transplant centers screen their transplant patients with one or more of these techniques.

TV has few therapeutic options, with repeat transplantation being the only definitive treatment. Statins, calcium antagonists, and angiotensin-converting enzyme inhibitors have all demonstrated some effect at reducing TV.[98] Some immunomodulating drugs may be more effective than others.[99] Percutaneous coronary intervention is an option for focal stenoses but is not feasible for diffuse narrowing. Antiplatelet agents may be given to reduce risk of myocardial infarction, although the evidence supporting this is limited.[100]

CONGENITAL ABNORMALITIES

ANOMALOUS CORONARY ARTERIES

The normal origin and course of the coronary arteries is described above; variation from this pattern is observed in approximately 1% to 2% of people. Patterns of variation include anomalous origin (coronary atresia, separate ostia for circumflex and anterior descending arteries, coronary arising from the wrong aortic cusp, coronary arising from the pulmonary artery), anomalous course (interarterial, intraarterial, retroaortic), and anomalous branching (single coronary artery) (Fig. 35–15). Two of the most commonly observed patterns are right coronary arising from the left cusp coursing between the aorta/pulmonary artery and circumflex artery arising from the right sinus coursing retrograde around the aorta and not between the great arteries.[101] Origin of the entire coronary circulation from a single aortic ostium is termed *single coronary*. This anomaly is rare in the absence of other associated anomalies of the heart. Atresia of one of the two main coronary ostia may occur and may result in myocardial ischemia and infarction in infancy or childhood. The involved vessel becomes dependent on collateral coronary blood flow from the contralateral coronary artery.

Anomalous left coronary artery arising from the pulmonary artery (ALCAPA; also known as Bland-White-Garland syndrome) results in a different pathology than other anomalies involving the coronaries from the aorta. This condition is frequently fatal in the infant period of life. Those surviving into adulthood typically have developed a robust collateral flow system where the myocardium is supplied with oxygen from the right coronary alone and flow is reversed in the left system into the pulmonary artery (Fig. 35–16).[102] This causes a coronary steal phenomenon, left ventricular dysfunction, and sometimes ischemia and even sudden death.

Some of these patterns may be associated with myocardial ischemia and raise concern for adverse events, including sudden death.[103] The primary concern among these anomalies relates to arterial courses between the aorta and pulmonary artery. Normally, the coronary ostia are round to oval in shape, but in this anomaly, the coronary artery has an acute angle of origin that makes the ostium slitlike in shape. The mechanism of ischemia, infarction, and/or sudden death in this coronary anomaly may relate to the shape of the coronary ostium of the anomalous vessel. A multitude of causal mechanisms have been advanced, including hypoplasia of the artery, the acute angle of origin, a flaplike mechanism of the endothelium at the origin, and direct compression of the artery between the great arteries. Although the precise mechanism is unclear, what appears to occur is that with increased cardiac output, some combination of hemodynamic changes (eg, increase in systolic pressures, aortic dilation with stretching of the aortic wall) results in diminished flow down the coronary artery, leading to ischemia and all of its potential complications: angina, syncope, arrhythmia, infarction, and so on. Further investigation into the mechanisms of ischemia is underway.[104] Single coronary arteries do not commonly have the same acute takeoff/narrowing but may have elevated risk of adverse cardiac events caused by excessive blood flow in the single artery (Figs. 35–17, 35–18, and 35–19).[105,106]

When compared to patients with coronary arteries that do not travel between the great arteries, patients with an interarterial/intraarterial course are more likely to undergo surgical revascularization and may be at higher risk for myocardial infarction and/or sudden death.[101] Perhaps the most comprehensive understanding of risk associated with anomalous coronaries comes from Eckart, who reviewed sudden deaths in 6.3 million military recruits.[107] This selected population had gone through screening necessary for military service; 126 deaths were observed (64 caused by an identifiable

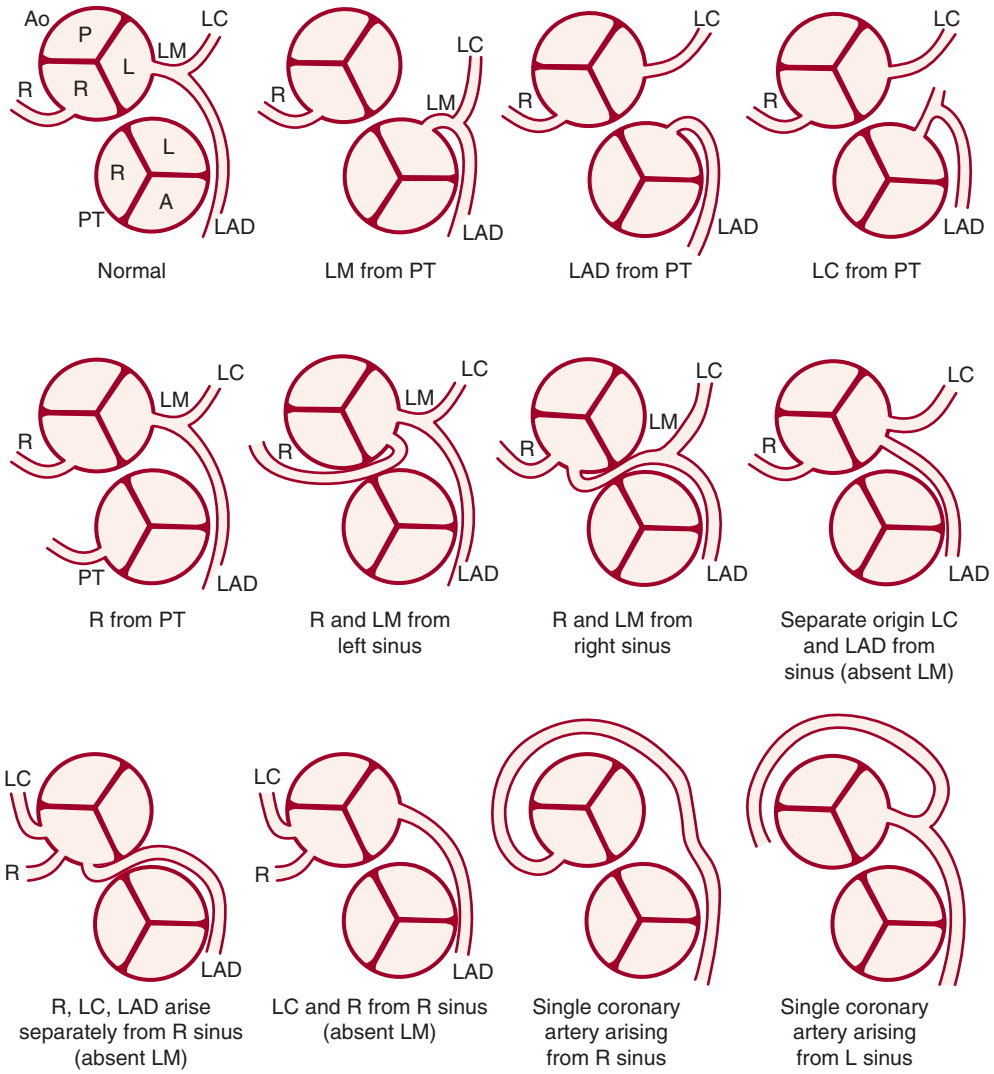


FIGURE 35–15. Diagram of coronary anomalies showing various congenital coronary artery anomalies that are associated with clinical symptomatic heart disease. A, anterior cusp; Ao, aorta; L, left cusp; LAD, left anterior descending (artery); LC, left circumflex (artery); LM, left main (artery); P, posterior cusp; PT, pulmonary trunk; R, right cusp or right coronary artery.

cardiac abnormality) at a rate of 13.0 per 100,000 recruit years. Among them, anomalous coronary arteries were considered responsible for one-third of deaths (21 of 64), all of which were left coronary arteries arising from the right sinus with a course between the aorta and pulmonary artery (Fig. 35–20).[108]

Less clear is the relationship between anomalous coronaries and clinical symptoms such as dyspnea, angina, and syncope, particularly among the elderly patients undergoing evaluation. For example, acute chest pain is a common reason to seek emergency medical care and cardiac CT is growing in popularity as an imaging methodology to evaluate acute chest pain patients. Given that 1% to 2% of people have anomalous coronary arteries, an increasing number may be detected that otherwise are actually incidental findings, unrelated to the clinical presentation.[109] When these anomalies are discovered in older patients, aggressive management becomes difficult to justify as these defects, present from birth, have not caused myocardial infarction or death in the patients up to the time of their discovery. Surgical revascularization can be performed; often surgeons request evidence of myocardial ischemia before embarking on a repair. Surgical approach is individualized to the anatomy of the patient and could take the form of reimplantation, pulmonary artery relocation, surgical repair of the coronary ostium, bypass grafting, or unroofing.[110] Surgical management of anomalous coronary from the pulmonary artery is typically achieved with coronary reimplantation.[111,112]

MYOCARDIAL BRIDGING

Coronary arteries typically course over the epicardial surface of the heart. Occasionally, segments of varying lengths may travel within the myocardium and reappear on the epicardium more distally in the arterial course. This is sometimes referred to as a *tunneled artery*, but the clinical phenomenon is most often referred to the description of the overlying muscle, a myocardial bridge. On pathological specimens, the coronary artery is surrounded, not by epicardial fat, but by myocardium. These can be observed during coronary angiography, where the lumen of the tunneled segment of the vessel decreases, particularly during systole. Autopsy studies suggest that myocardial bridges are much more common (> 15%) than observed on angiography (< 1%), likely because the degree of bridging and compression of the vessel lumen is variable, possibly relating to the varying depth of the tunneled segment within myocardium (Figs. 35–21, 35–22, and 35–23).[113-115]

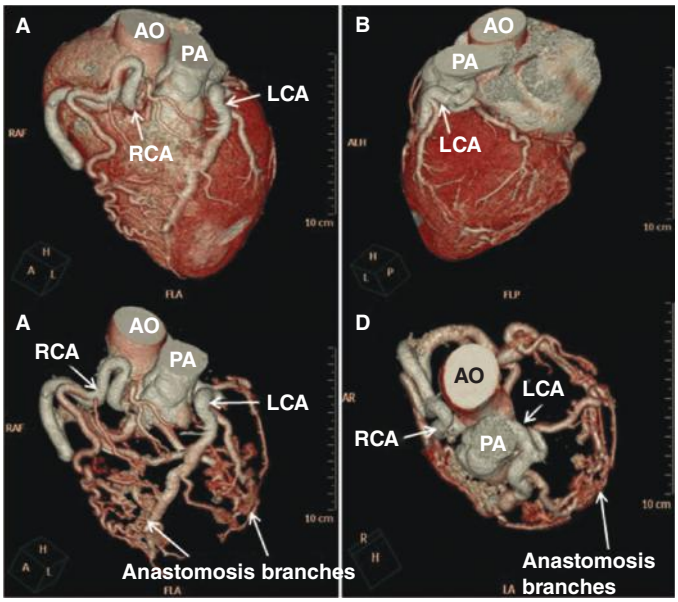


FIGURE 35–16. Computed tomography images of anomalous left coronary artery arising from the pulmonary artery (ALCAPA). **A** and **B** show the left coronary artery arising from the pulmonary artery instead of the aorta. **C** and **D** show robust dilation of coronary anastomoses, facilitating blood flow from the right coronary to the left and retrograde into the pulmonary artery (PA). AO, aorta; LCA, left circumflex artery; RCA, right coronary artery. Reproduced with permission from Wu WH, Sun JP, Ma L, et al: Anomalous origin of the left coronary artery from the pulmonary trunk. *Int J Cardiol*. 2015 Dec 15;201:165-167.[102]

Myocardial bridging appears to be more common than is clinically manifest; therefore, evaluating the hemodynamic significance of a bridge is an area without uniform agreement. Conceptually, compression of a tunneled artery should be limited mostly to myocardial systole because coronary blood flow occurs predominantly during diastole. However, many bridges also restrict expansion of the coronary artery in diastole. Additionally, augmentation of coronary blood flow required to meet increasing demands such as

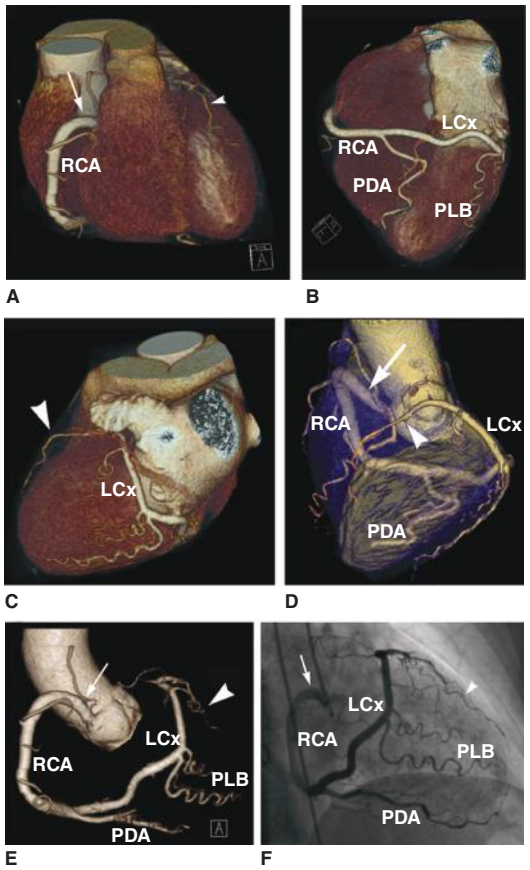


FIGURE 35–17. Computed tomography (CT) of single coronary artery. (**A–C**) Three-dimensional reconstruction of the single coronary artery arising from the right sinus of Valsalva coursing in the atrioventricular grooves and terminating in a small anterior descending artery, (**D**) semilucent reconstruction showing the course of the vessel, (**E**) CT angiogram simulation and invasive angiogram with vessel origin (*arrow*) and termination (*arrowhead*), and (**F**) Invasive angiography showing the same projection of the coronary as seen in (E). RCA, right coronary artery; LCx, left circumflex; PDA, posterior descending artery; PLB, posterior lateral branch. Reproduced with permission from Aldana-Sepulveda N, Restrepo CS, Kimura-Hayama E: Single coronary artery: spectrum of imaging findings with multidetector CT. *J Cardiovasc Comput Tomogr*. 2013 Nov-Dec;7(6):391-399.[105]

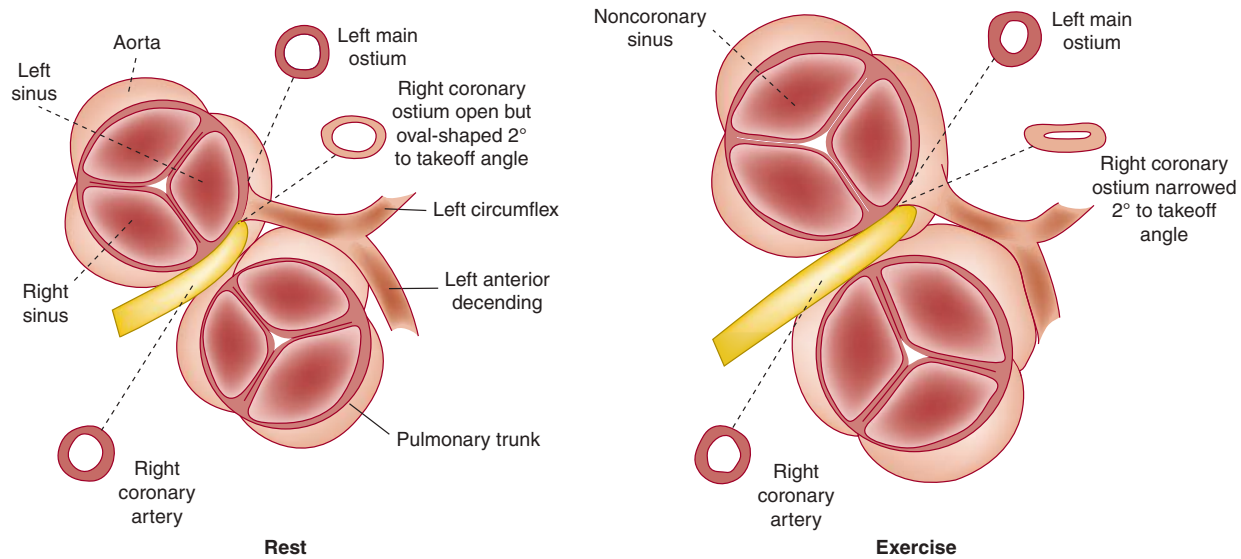


FIGURE 35–18. Anomalous right coronary arising from left sinus of Valsalva. Diagram showing the proposed mechanism of myocardial ischemia produced by anomalous origin of the right coronary artery from the left sinus of Valsalva. With exercise, the aorta and pulmonary trunk dilate, thereby reducing the already narrowed coronary ostium of the anomalous right coronary. Modified with permission from Roberts WC, Siegel RJ, Zipes DP. Origin of the right coronary artery from the left sinus of Valsalva and its functional consequences: analysis of 10 necropsy patients. *Am J Cardiol*. 1982;49(4):863-868.

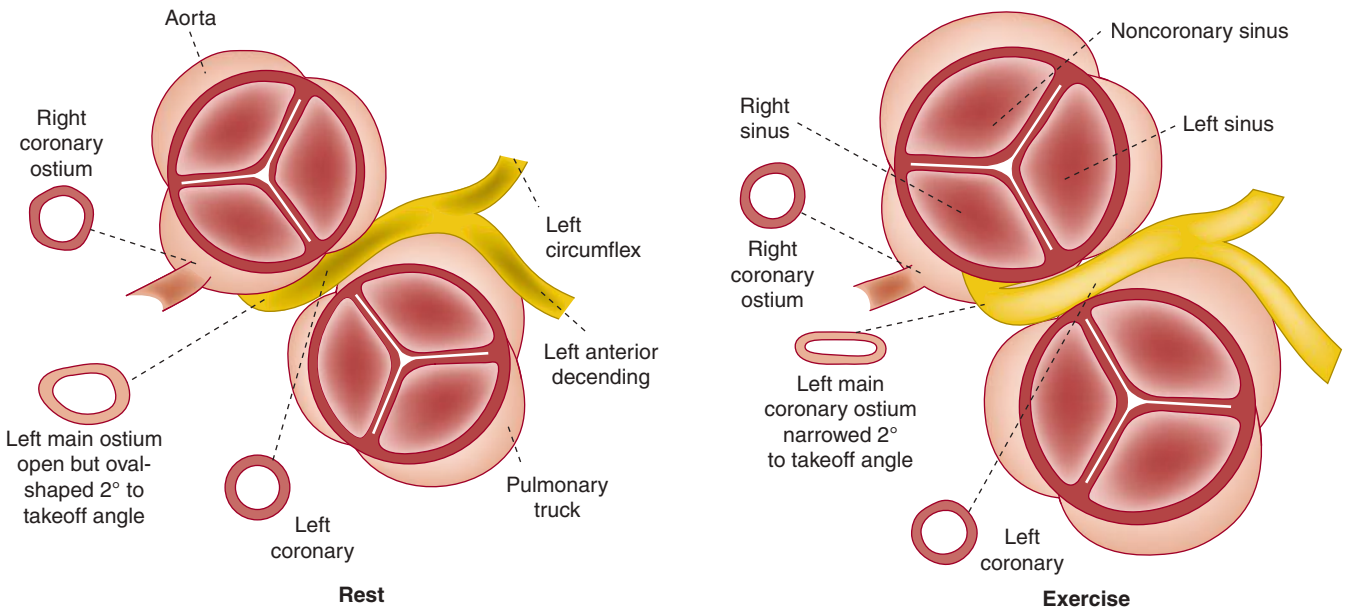


FIGURE 35–19. Anomalous left coronary arising from right sinus of Valsalva. Diagram showing the proposed mechanism of myocardial ischemia produced by anomalous origin of the left coronary artery from the right sinus of Valsalva. With exercise, the aorta and pulmonary trunk dilate, thereby reducing the already narrowed coronary ostium of the anomalous left coronary. From Roberts WC, Siegel RJ, Zipes DP.[106]

exercise is often accompanied by an increase in flow during systole because diastole is progressively limited by the increase in heart rate. Thus ischemia, myocardial infarction, arrhythmias, and sudden death have all been attributed to myocardial bridging.[116] A variety of techniques, including fractional flow reserve, nuclear myocardial perfusion imaging, IVUS, and intracoronary Doppler have been used to investigate the perfusion consequences related to bridging.[117,118] Bridges are frequently associated with other abnormalities such as ED, microvascular dysfunction, spasm, and other coronary pathologies.[31] Antianginal agents such as calcium antagonists and beta-blockers have been used as a conservative treatment, whereas surgery has been used for those with persistent symptoms and evidence of ischemia.[119]

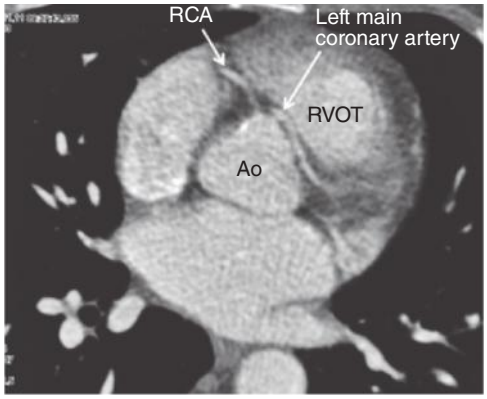


FIGURE 35–20. Computed tomography (CT) angiogram of left main coronary artery arising from right. In this CT angiogram, the left main coronary artery is seen arising from the right sinus of Valsalva and traveling between the aorta and pulmonary trunk in a fashion thought to impart risk of sudden death. This lesion is a common reason to undergo a surgical procedure to improve flow in the left coronary circulation. Ao, aorta; RVOT, right ventricular outflow tract. Reproduced with permission from Attili A, Hensley AK, Jones FD, et al: Echocardiography and coronary CT angiography imaging of variations in coronary anatomy and coronary abnormalities in athletic children: detection of coronary abnormalities that create a risk for sudden death. *Echocardiography*. 2013 Feb;30(2):225-233.[108]

CORONARY ARTERY FISTULAS

An abnormal communication between an epicardial coronary artery and a cardiac chamber, major vessel (vena cava, subpulmonary veins, pulmonary artery), or other vascular structure (mediastinal vessels, coronary sinus) is known as a coronary artery fistula. An example of a fistula between the left circulation and the pulmonary artery is illustrated in Fig. 35–24. These anomalies can be congenital or acquired; they can be present at birth or be observed later in life (Table 35–4). Congenital fistulas result from failure of fetal structures such as splanchnic veins or intramyocardial trabecular sinusoids to regress. The latter of these persist as Thebesian veins of normal anatomy.[120] Fistulas may be associated with other congenital abnormalities, including atrial/ventricular septal defects, patent ductus arteriosus, pulmonary atresia, and tetralogy of Fallot. Acquired fistulas can result from intracardiac operations, trauma, and transcatheter procedures as a result of abnormal healing between the damaged circulatory chambers and vessels.

Fistulas that connect the left circulation to left-sided chambers may not result in clinical disease and be incidentally found on angiography (Fig. 35–25).[121] However, some will raise diastolic pressure in the affected chamber causing dilation or hypertrophy. Fistulas between the left and right circulation result in shunt of blood flow, which may be clinically relevant, depending on the volume of flow. Fistulas predispose to endocarditis and may also present with continuous murmur, myocardial ischemia/angina, acute myocardial infarction, sudden death, coronary steal, congestive heart failure, arrhythmias, or coronary aneurysm formation.[120,122]

Historical data on prevalence from angiographic cohorts is typically about 0.1%; contemporary CT-based cohorts report a higher prevalence up to 0.9%.[123-125] Lim and colleagues found the most common fistula to be coronary artery to pulmonary artery; however in this CT-based cohort, the authors may have been less likely to detect

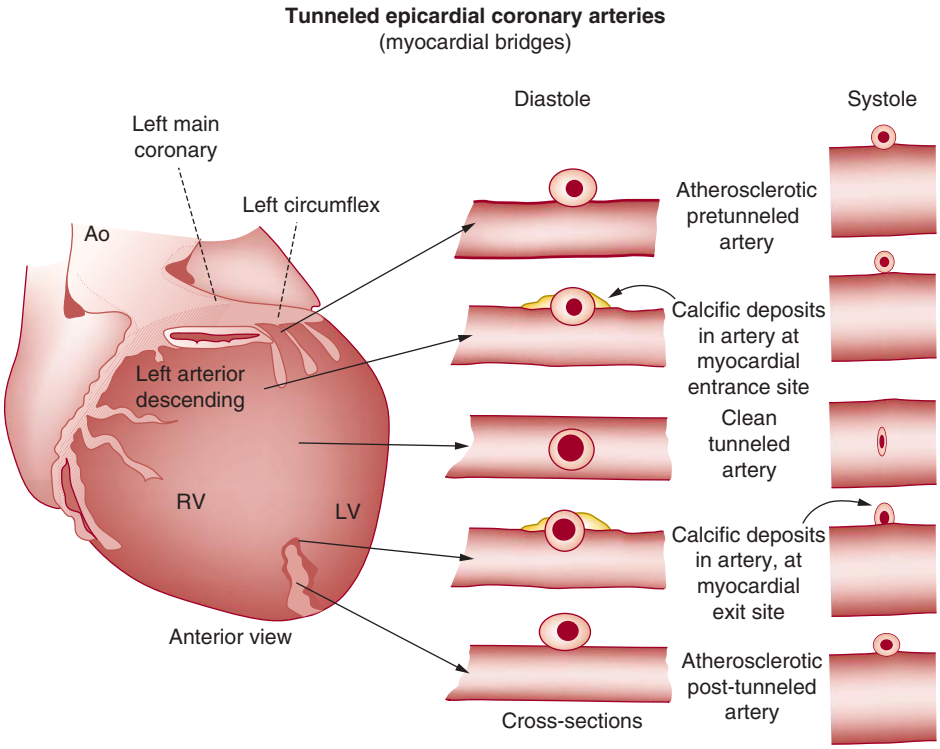


FIGURE 35–21. Diagram of myocardial bridging showing segments of tunneled and nontunneled epicardial coronary artery with changes during ventricular systole and diastole. Ao, aorta; LV, left ventricle; RV, right ventricle. Reproduced with permission from Wenger NK, ed. *Exercise and the Heart*, 2nd ed. Cardiovascular Clinics. Philadelphia: FA Davis; 1985.

direct connections from a coronary artery to a cardiac chamber. CT can readily detect surplus vessels but cannot readily detect a direct connection through the myocardium without the advantage of seeing active flow of contrasted blood from the coronary artery into the heart chambers.

If patients present with heart failure or ischemia symptoms, the traditional evaluation often includes coronary angiography, which is the most reliable method of detecting coronary fistulas. Patients with incidentally found, asymptomatic, left-to-left fistulas can be managed conservatively and will often remain stable and symptom-free for long periods of time. Interventional occlusion or surgical repair is indicated for patients with symptoms attributable to the fistula or heart failure/cardiac remodeling caused by shunting of blood. Successful repair can usually be achieved with low likelihood of residual shunting in long-term follow-up.[121] Percutaneous closure can also be performed.[126]

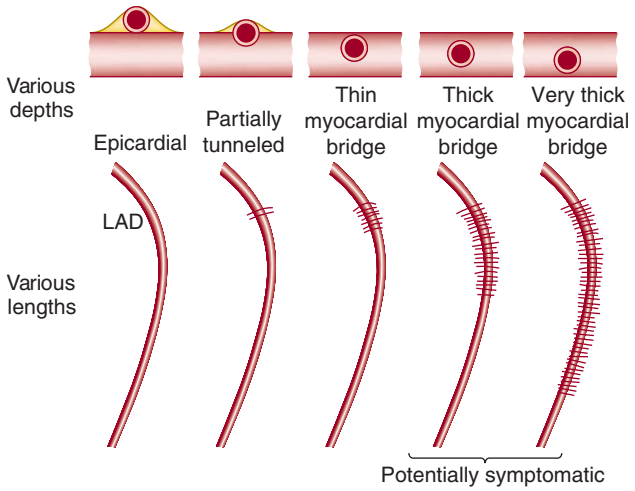


FIGURE 35–22. Diagram of myocardial bridging showing morphologic variations in tunneling (length of tunneled segment, depth of tunneled segment). LAD, left anterior descending. Reproduced with permission from Wenger NK, ed. *Exercise and the Heart*, 2nd ed. Cardiovascular Clinics. Philadelphia: FA Davis; 1985.

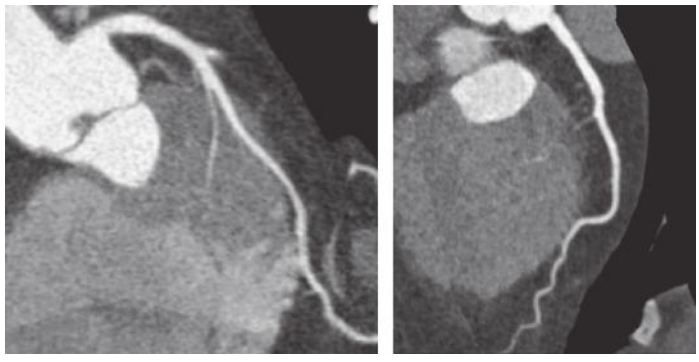


FIGURE 35–23. Computed tomography angiography of myocardial bridge. **A.** In this multiplanar reconstruction of the LAD, a substantial segment of the midvessel courses through the myocardium. **B.** Another example shown with a less extensive segment of bridging in the more distal portion of the vessel. Reproduced with permission from Brolin EB, Brismar TB, Collste O, et al: Prevalence of Myocardial Bridging in Patients With Myocardial Infarction and Nonobstructed Coronary Arteries. *Am J Cardiol*. 2015 Dec 15;116(12):1833-1839.[113]

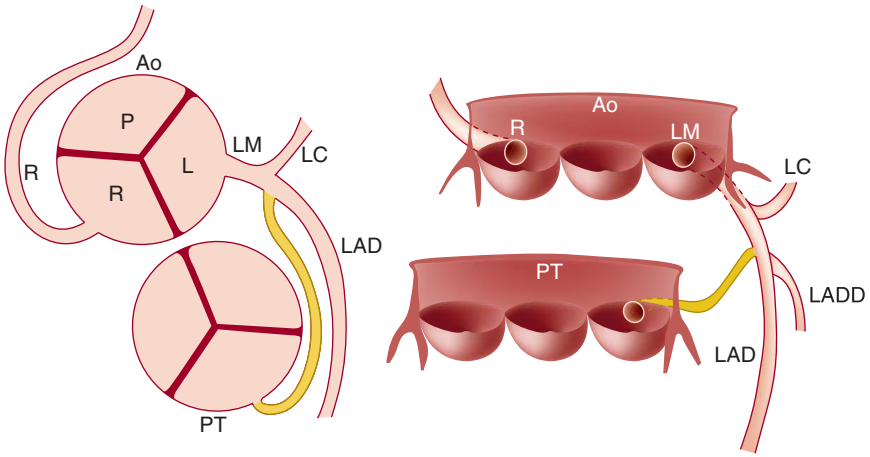


FIGURE 35–24. Diagram showing coronary artery fistula connecting pulmonary trunk and left anterior descending (LAD) artery. It originally was misdiagnosed as an anomalous coronary artery. Ao, aorta; L, left; LC, left circumflex; LADD, diagonal branch of LAD; LM, left main; PT, pulmonary trunk; R, right.

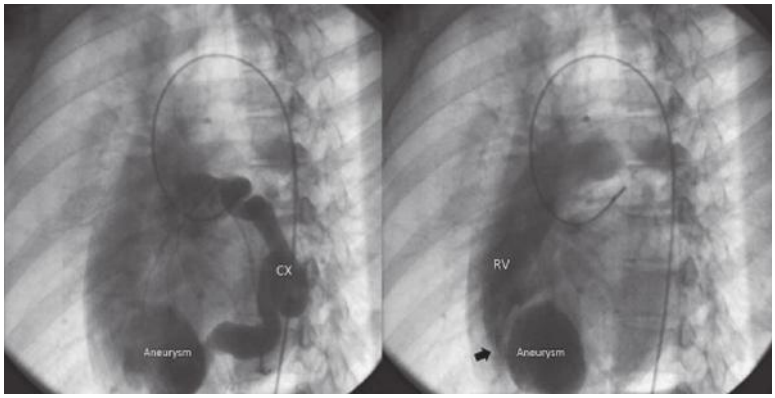
TABLE 35–4. Causes of Coronary Artery Fistula

Congenital
Embryonic
Multiple; systemic hemangioma
Acquired/Iatrogenic
Closed-chest ablation of accessory pathway
Percutaneous coronary intervention
Right/left ventricular septal myectomy
Penetrating and nonpenetrating trauma
Acute myocardial infarction
Dilated cardiomyopathy
Cardiac valve surgery
Tumor
Permanent pacemaker placement
Cardiac transplantation
Endomyocardial biopsy
Coronary artery bypass grafting

CORONARY ARTERY ANEURYSMS

An aneurysm of the coronary artery is a pathological dilation of the entire vessel wall: intima, media, and adventitia. Normal coronary artery diameter is 4.5 mm for the left main down to 1.9 mm in the distal portion of the left anterior descending; a typical coronary measures 2 to 3 mm.[127] Of note, women have smaller coronary arteries than men, even when corrected for body size. "Giant" aneurysms are often defined as those with diameters more than four times the normal diameter, but dilations of 20, 30, and 40 mm are not uncommon.[128] Aneurysms are present in about 1% of people at autopsy, the most common (up to 50% of cases) etiology is dilation secondary to vessel damage from atherosclerosis.[129] The malformation can be congenital or acquired secondary to atherosclerosis, trauma (external or iatrogenic), or inflammatory illnesses. Percutaneous coronary interventions with stenting or angioplasty, atherectomy, and laser-based procedures all can result in aneurysm formation. Kawasaki disease and Takayasu's arteritis are two of the inflammatory conditions most commonly associated with aneurysm formation (Table 35–5).

Aneurysms are typically asymptomatic and sometimes incidentally found on CT, angiography or, rarely, on echocardiography.[130] Ischemia and ACS can occur if thrombus formation results in luminal narrowing, embolization, or occlusion. Mass effects, such



A B

FIGURE 35–25. Angiographic appearance of coronary to ventricular fistula. (**A**) Selective angiography of the left circumflex demonstrates a dilated and tortuous aneurysmal vessel, which drains into the right ventricle (**B**). Reproduced with permission from Hou B, Ma WG, Zhang J, et al: Surgical management of left circumflex coronary artery fistula: a 25-year single-center experience in 29 patients. *Ann Thorac Surg*. 2014 Feb;97(2):530-536.[121]

TABLE 35–5. Causes of Coronary Arterial Aneurysms

Atherosclerosis (50%)
Congenital (20%–30%)
Inflammatory (10%–20%)
Kawasaki disease (mucocutaneous lymph node syndrome)
Arteritis (including syphilis, lupus erythematosus)
Takayasu's disease
Connective tissue (5–10%)
Ehlers-Danlos
Marfan
Fibromuscular dysplasia
Scleroderma
Iatrogenic (< 1%)
Angioplasty
Atherectomy
Trauma (< 1%)

as superior vena cava syndrome, have been reported in patients with giant aneurysms. Treatment of aneurysms should include medical management of any underlying conditions. For those with ischemic symptoms revascularization may be pursued. Surgical ligation or bypass was more common in the past; however, percutaneous techniques such as embolization and stenting are now more frequent. Stents covered with impervious graft material, such as polytetrafluoroethylene can create an exclusion of the aneurysmal segment and restore normal flow.[131,132] Patients who present with ACS can be especially challenging because layers of mural thrombus can form in large aneurysms where stasis of flow promotes clotting. Angiography does not readily demonstrate whether thrombus is newly formed or chronic. Because thrombosis in these vessels is a known complication, both antiplatelet and anticoagulation medications are commonly used, although the quality of the supporting evidence is low.

DISSECTION AND TRAUMA

Dissection refers to the separation of arterial wall layers and can occur spontaneously or as a secondary event. As a result, two lumens develop within the vessel a "true lumen" that represents the normal channel for blood to flow and a *false lumen*, which is a channel the blood flows into and does not have the characteristics wall layers of a normal coronary artery. Depending on the nature and severity of the dissection, the false lumen can compress or occlude the true lumen resulting in ischemia, infarction, or death (Fig. 35–26).[115]

Spontaneous or primary dissections are less common than secondary and are most commonly reported in young women, often associated with pregnancy.[133] The condition is rare, or at least rarely reported, with only 440 cases in the MEDLINE database between 1931 and 2008.[134] In a review of those cases, 70% (n = 308) were in women and 26.1% overall (n = 80) were pregnant; 83.8% of pregnancy-related

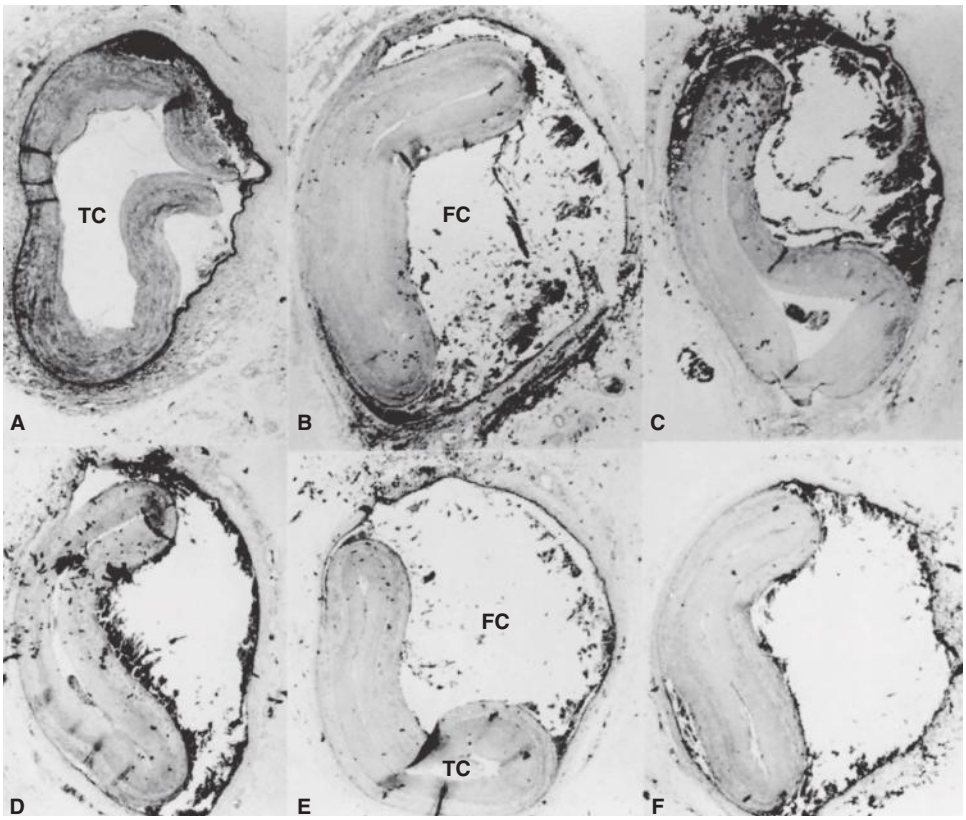


FIGURE 35–26. Pathologic specimens of coronary artery dissection—serial cross-sections (**A–F**) showing dissection of the left anterior descending coronary artery. The true channel (TC) is severely compromised by external compression from the false channel (FC) ("dissection channel"). Reproduced with permission from Wenger NK, ed. *Exercise and the Heart*, 2nd ed. Cardiovascular Clinics. Philadelphia: FA Davis; 1985.

dissections occurred in the postpartum period. Dissection can also be caused by cocaine use, connective tissue disorders, systemic inflammatory conditions, atherosclerosis, or iatrogenic causes. Heavy aerobic exercise and isometric physical activity have been reported as triggers of dissection. The heart is protected from chest trauma by the ribcage. However, blunt force trauma, crush injuries, and penetrating (stabbing and missile) injuries can still damage the heart: the pericardium, myocardium, valves, and the coronary arteries. Laceration of the coronaries occurring with stab and gunshot wounds is particularly problematic because the resulting bleeding can lead to tamponade (Figs. 35–27[135] and 35–28[136]).[135,136]

A dissection in the ascending thoracic aorta can propagate toward the heart and result in coronary dissection. Vessels can dissect in antegrade (toward the distal vessel) or retrograde (toward the vessel origin) patterns. If the intima is disrupted across the circumference of a vessel (which can occur during balloon angioplasty), a "spiral" dissection can occur where the vessel appears angiographically to dissect from side to side with a thin layer of endothelial tissue visible within the vessel lumen (Fig. 35–29).[115]

The signs and symptoms of dissection are similar to ACS resulting from atherosclerotic disease: chest pain, ischemic ECG changes, and elevated cardiac biomarkers.[135] With modern equipment, the rate of dissection during coronary intervention and interrogation is low (< 1%).[137] Percutaneous and surgical treatments are options; however, many dissections are managed conservatively without need for revascularization.[138] Antegrade dissections are often treated with stenting to prevent further propagation of the dissection and ischemic complications. Because of the direction of blood flow, retrograde dissections can often be treated conservatively (ie, without further intervention). Spiral dissections are technically challenging from a percutaneous perspective and often managed either conservatively or with surgical revascularization if ischemic symptoms develop.

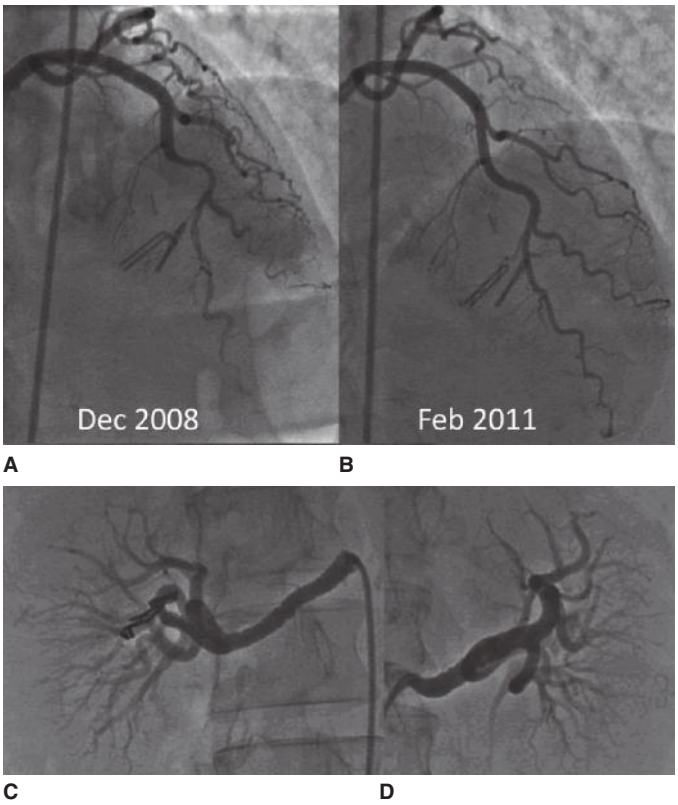


FIGURE 35–27. Dissection and follow-up imaging of left anterior descending artery dissection in a patient with fibromuscular dysplasia (FMD). (**A**) Dissection with poor antegrade flow in the LAD, (**B**) follow-up angiography with improved LAD flow, and (**C** and **D**) irregularity of renal vessels consistent with FMD. Reproduced with permission from Saw J1, Ricci D, Starovoytov A, et al: Spontaneous coronary artery dissection: prevalence of predisposing conditions including fibromuscular dysplasia in a tertiary center cohort. *JACC Cardiovasc Interv*. 2013 Jan;6(1):44-52.[135]

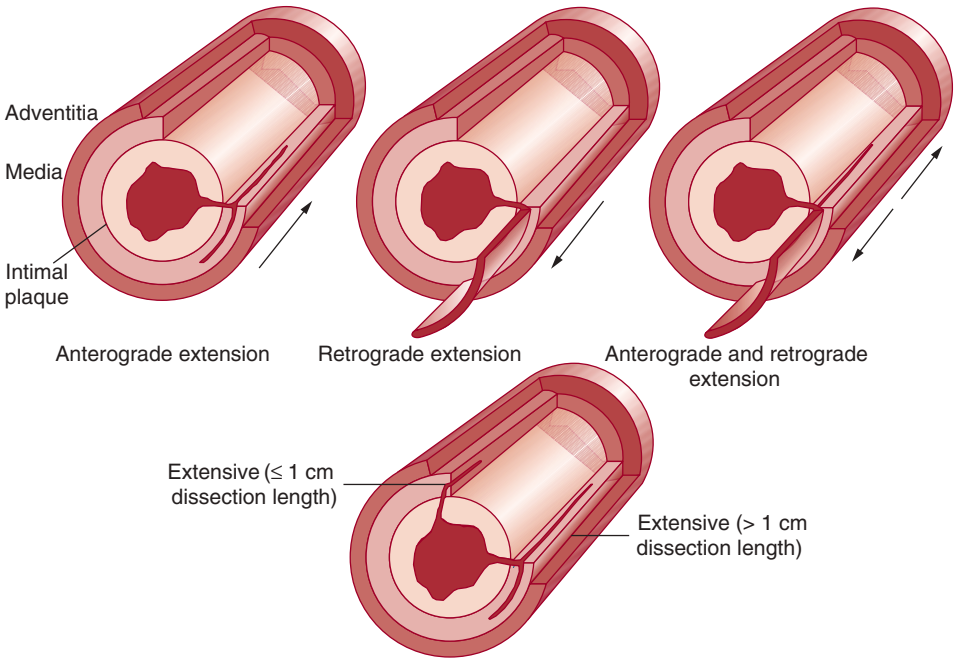


FIGURE 35–28. Dissection in percutaneous coronary intervention. Diagram showing morphologic definition of coronary artery dissections in balloon angioplasty (long-axis plane): localized (mechanism) (1 cm in total dissection length) and extensive (complications) (> 1 cm in total length). Reproduced with permission from Waller BF, Orr CM, Pinkerton CA, et al: Coronary balloon angioplasty dissections: "the good, the bad and the ugly". *J Am Coll Cardiol*. 1992 Sep;20(3):701-706.[115]

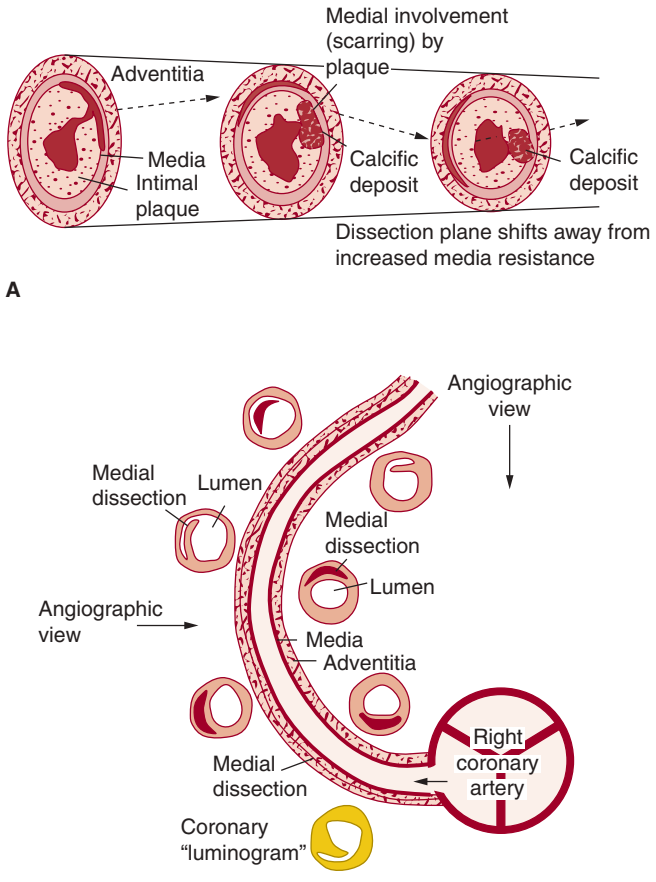


FIGURE 35–29. Spiral dissection of a coronary artery. Diagram showing pathologic change accounting for angiographic appearance of coronary artery "spiral" dissection. (**A**) Alteration in course of dissection and (**B**) angiographic appearance of unaltered course of dissection. Reproduced with permission from Waller BF, Orr CM, Pinkerton CA, et al: Coronary balloon angioplasty dissections: "the good, the bad and the ugly". *J Am Coll Cardiol*. 1992 Sep;20(3):701-706.[115]

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CHAPTER 36

DEFINITIONS OF ACUTE CORONARY SYNDROMES

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INTRODUCTION: EPIDEMIOLOGY AND PUBLIC HEALTH IMPACT

Coronary artery disease (CAD) accounts for 30% of all global deaths, representing the single most common cause of adult mortality and equivalent to the combined number of deaths caused by nutritional deficiencies, infectious diseases, and maternal/perinatal complications.[1,2] Recent growth in the global burden of cardiovascular disease (CVD) is primary attributable to the rising incidence across low- and middle-income countries.[3] Among European member states of the World Health Organization (WHO), for example, CVD death rates for men and women were highest in the Russian Federation and Uzbekistan, respectively, whereas risk was lowest in France and Israel.[4] Conversely, in the United States, over 15 million Americans, or 6.2% of the adult population, have coronary heart disease (CHD), with a myocardial infarction (MI) occurring once every 43 seconds.[5] Health care resource utilization as a result of CHD is significant, as over 1.1 million hospital discharges in 2010 listed MI or unstable angina (UA) as a primary or secondary diagnosis.[5] Health care expenditures are also substantial; costs for MI and CHD were approximately $11 billion and $10 billion, respectively, in 2011.[6] These diagnoses constitute two of the most expensive discharge diagnoses and are expected to increase by 100% by 2030.

Despite these sobering statistics, important strides in the diagnosis, prevention, and management of CHD have occurred over the past 50 years. In the United States, for example, several population-based studies have shown a reduction in both the incidence and case fatality rate associated with MI.[7,8] These favorable trends have been attributed to greater utilization of evidence-based therapies and improvements in control and burden of risk factors.[9] Concordant changes in the epidemiology of acute coronary syndromes have occurred over the past 10 years as a result of changing demographics and updated definitions of MI. In this chapter, we focus primarily on the definition and diagnostic criteria for acute coronary syndromes.

ACUTE CORONARY SYNDROMES

The term *acute coronary syndrome* (ACS) is a unifying construct representing a pathophysiologic and clinical spectrum culminating in acute myocardial ischemia. This is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis and is associated with an increased risk of myonecrosis and cardiac death.[10] ACS encompasses UA and ST-segment elevation MI (STEMI) or acute non–ST-segment elevation MI (NSTEMI). Distinguishing these presentations is predicated on the presence or absence of myocyte necrosis coupled with the electrocardiographic tracing at the time of symptoms. ACS without myocardial necrosis is defined as UA, whereas myocardial necrosis is a necessary, but not sufficient, component of either STEMI or NSTEMI, respectively. Recognizing a patient with ACS is important because the diagnosis triggers both triage and management. Those deemed to have an ACS in the emergency department should be triaged immediately to an area with continuous electrocardiographic monitoring and defibrillation capability. Patients with suspected ACS should be managed immediately with antiplatelet and anticoagulant therapies and considered for immediate mechanical or pharmacologic revascularization if new ST-segment elevation is noted.[11]

The diagnosis of ACS relies on integrating clinical information from the patient history with the initial ECG and laboratory results. In the initial hours after presentation, distinguishing between STEMI, NSTEMI, and UA may be difficult, because biomarkers of myonecrosis can initially be normal. However, as a result of the life-threatening nature of ACS, it is prudent to have a low threshold in suspecting this diagnosis, and therefore, diagnostic sensitivity is usually favored over specificity. Additional details surrounding the pathophysiology and diagnosis of ACS are provided in Chap. 37.

Initial triage of patients suspected of having acute coronary ischemia should identify patients as having (1) ACS; (2) a non-ACS cardiovascular condition such as myocarditis/myopericarditis, stress-related cardiomyopathy, aortic dissection, or pulmonary embolism; (3) a noncardiac cause of chest pain such as gastroesophageal reflux; or (4) a noncardiac condition that is yet undefined, such as sepsis.[12] ACS patients with new ST-segment elevation on the presenting electrocardiogram (ECG) are labeled as having STEMI and should be considered for immediate reperfusion therapy by thrombolytics or percutaneous coronary intervention (PCI); those without ST-segment elevation but with evidence of myonecrosis are deemed to have an NSTEMI; and those without any evidence of myonecrosis are diagnosed with UA (Fig. 36–1). Further details on the management of different types of ACS are provided in Chaps. 39-41.

UNSTABLE ANGINA

UA is usually secondary to abrupt reduction in myocardial perfusion as a result of nonocclusive coronary thrombosis. In this event, however, the nonocclusive thrombus that developed on a disrupted atherosclerotic plaque does not result in biochemical evidence of myocardial necrosis. Accordingly, UA and NSTEMI can be viewed as very closely related clinical conditions with similar presentations and pathogenesis but variable clinical severity. Nevertheless, given the increased reliance on highly sensitive biomarkers of myocyte necrosis, the incidence of troponin-negative ACS or UA is decreasing.[13] This shift in ACS epidemiology was illustrated in a report from the US Nationwide Inpatient Sample, which demonstrated an 87% decline in the prevalence of UA between 1998 and 2001 but an increase in NSTEMI.[14]

As a result of the lack of objective criteria used to define this condition, UA must be diagnosed from the clinical history and is thus the

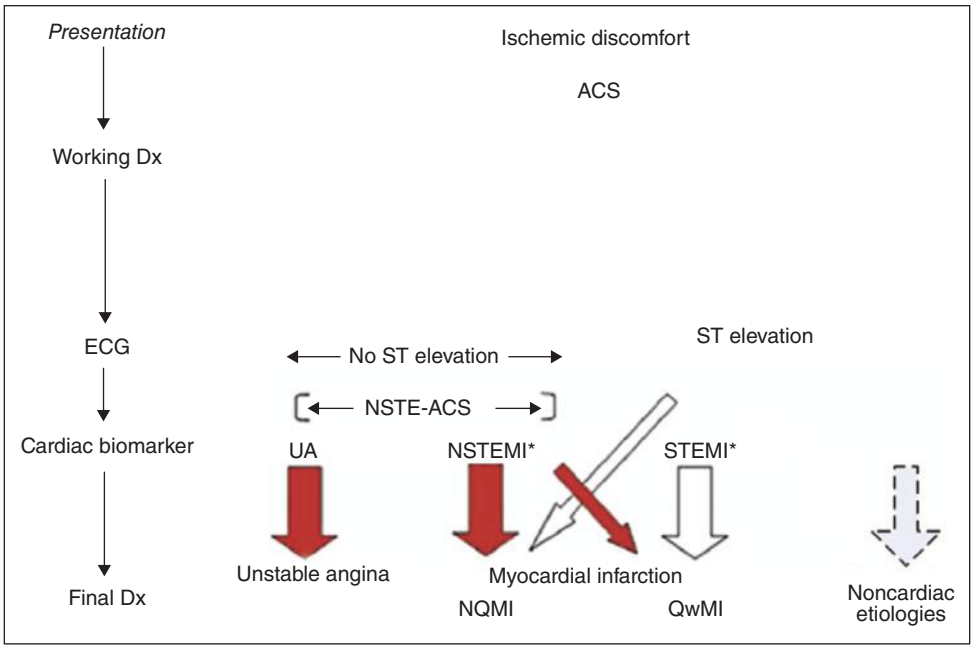

FIGURE 36–1. Clinical, pathologic, electrical, and biochemical correlates of acute coronary syndrome. ACS, acute coronary syndrome; Dx, diagnosis; ECG, electrocardiogram; NQMI, non–Q-wave myocardial infarction; NSTE, non–ST-segment elevation; NSTEMI, non–ST-segment elevation myocardial infarction; QwMI, Q-wave myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina. Reproduced with permission from Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014 Dec 23;64(24):e139-e228.

most subjective of the ACS diagnoses. There are three principal clinical presentations of UA: (1) rest angina or angina with minimal exertion usually lasting at least 20 minutes; (2) new-onset severe angina (Canadian Cardiovascular Society grade III or higher; Table 36–1); and (3) crescendo angina, defined as previously diagnosed angina that has become distinctly more frequent, precipitated by less severe degrees of exertion, or more severe.[15,16] Despite a clear and consistent definition for UA, the subjective nature of these criteria may compromise diagnostic accuracy, thereby leading to misclassification. In one report, for example, 20% of patients diagnosed with UA and referred for coronary angiography did not have any angiographically apparent obstructive epicardial CAD.[17]

NON–ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

For many years, the diagnosis of an acute MI was defined by the WHO based on two of the following three criteria: (1) typical ischemic chest pain; (2) typical ECG pattern including the development of Q waves; and (3) typical rise and fall in serum markers of myocardial injury, usually creatine kinase myocardial band (CK-MB).[18] If the patient did not have ST-segment elevation or Q waves and the CK-MB was elevated, the patient was diagnosed with an NSTEMI. Patients with acute ischemic chest pain without ST-segment elevation or Q waves and who had negative CK-MB levels were classified as having UA.

With the introduction of serum troponin levels, which were much more sensitive and specific for myonecrosis than CK-MB levels, a joint European Society of Cardiology and American College of Cardiology committee in 2000 proposed the following definition of an acute, evolving, or recent MI: typical rise and gradual fall of serum troponin levels or a more rapid rise and fall of serum CK-MB levels in addition to presenting with ischemic symptoms, development of pathologic Q waves on ECG, ST-segment changes indicative of ischemia, or coronary artery intervention (eg, PCI).[19] This has since been replaced with the currently accepted Universal Definition of MI, which relies on biomarker evidence of myocardial necrosis (preferably troponin), in the clinical context of myocardial ischemia.[20]

Although greater use of troponin measurements has led to a reduction in the diagnosis of UA, an opposite trend has been observed with respect to the epidemiology of NSTEMI. Data from the National Registry of Myocardial Infarction demonstrate an increase in the proportion of patients diagnosed with NSTEMI, from 14% to 59% between 1990 and 2006[7] (Fig. 36–2). This change occurred with a concordant increase in the proportion of patients in whom a troponin assay was performed, from 67% in 1998 to 96% in 2008.[7] Nevertheless, the increasing incidence of NSTEMI was apparent before widespread use of troponin assays, suggesting that changes in population demographics or increasing use of preventive medications may also be contributory.[21,22]

TABLE 36–1. Canadian Cardiovascular Society Grading of Angina

Class	Description of Stage
I	Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
II	Angina occurs on walking > 2 level blocks and climbing > 1 flight of ordinary stairs at normal pace and under normal conditions
III	Angina occurs on walking 1-2 level blocks and climbing 1 flight of ordinary stairs under normal conditions and at normal pace.
IV	Anginal symptoms may be present at rest.

Non–ST-Segment Elevation Acute Coronary Syndrome Risk Stratification

As articulated by Braunwald et al[23] and subsequently embedded within clinical practice guidelines, the initial steps in the evaluation of patients presenting with chest pain is to first determine the likelihood of CAD as the underlying etiology followed by an assessment of short-term risk.

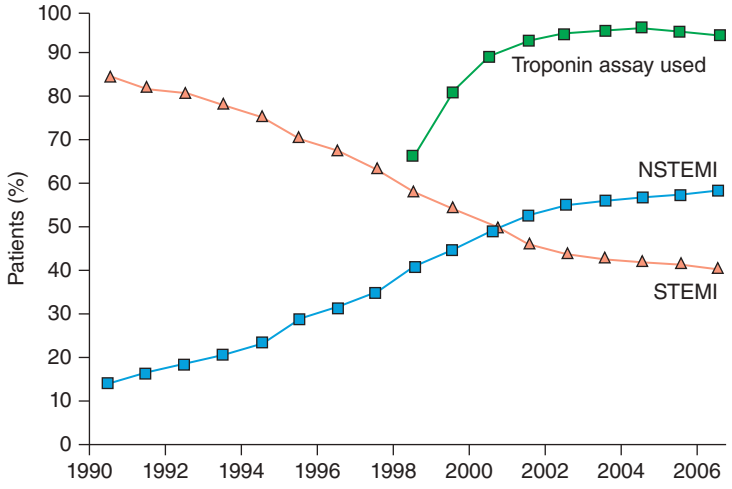

FIGURE 36–2. Prevalence of ST-segment elevation myocardial infarction (STEMI) and non–ST-segment myocardial infarction (NSTEMI) in the National Registry of Myocardial Infarction from 1990 to 2006 and proportion of patients in whom a troponin assay was used to diagnose myocardial infarction. Reproduced with permission from Rogers WJ, Frederick PD, Stoehr E, et al: Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J.* 2008 Dec;156(6):1026-1034.

With respect to the former, the following parameters (ranked in order of importance) are most strongly linked with CAD, representing the pathologic substrate for chest pain symptoms: nature of anginal symptoms, prior history of CAD, male sex, older age, and number of traditional risk factors (Table 36–2).[24,25] The need to accurately and rapidly triage chest pain patients into those with versus without symptomatic CAD is highlighted by the fact that although over 7 million patients present to the emergency department with chest pain annually, 20% to 25% are ultimately diagnosed with non–ST-segment elevation ACS (NSTE-ACS). Among those with noncardiac chest pain, the most common etiologies appear to be gastrointestinal, musculoskeletal, or psychiatric in nature.[26,27] As a result, the differential diagnosis for chest pain must incorporate noncardiac, vascular, and nonatherosclerotic coronary pathology. Focal coronary spasm or Prinzmetal angina, for example, is caused by exaggerated coronary vasomotor tone and/or endothelial dysfunction. In addition, patients with chronic stable CAD may present with chest pain as a result of noncoronary conditions that increase myocardial oxygen demand, such as fever or tachycardia, reduce coronary blood flow, or decreased myocardial oxygen content, such as hypoxemia or anemia. In such settings, the magnitude of ischemia might even result in myonecrosis, classified as type 2 MI according to the Universal Definition.

Once CAD has been established as the likely cause of chest pain, it is necessary to estimate, or stratify, risk for adverse events using qualitative or quantitative methods. As shown in Table 36–3, the tempo and severity of chest pain, extent of electrical abnormality, and magnitude of serum biomarker elevation all portend a higher risk for adverse events. Among these, biomarker evidence of myocyte necrosis is the strongest and most consistent correlate of risk. Quantitative risk scores provide an alternative and more precise approach to risk stratification. Perhaps the most widely used is the integer-based Thrombolysis in Myocardial Infarction (TIMI) risk score, which allots a single point for each of the following in patients with chest pain: age > 65 years; aspirin use within 7 days prior to presentation; ST deviation > 0.5 mm; severe angina; at least three risk factors for CAD; raised cardiac biomarker; and known coronary stenosis.[28] Short-term risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization within 14 days varied from 1.4% for patients with very low scores (0-1) to 40% for those with the highest scores. Other scores with a greater number of variables and computational complexity have been developed, some of which have online calculators to facilitate ease of use and point-of-care application, as shown in Table 36–4.[29] Not only do these scores provide important information on prognosis, but they also dictate clinical management. Patients at higher risk benefit more from aggressive interventions compared to those with lower scores. This allows for more rational and cost-effective allocation of health care resources. The importance of this principle is reflected in clinical practice guidelines, which provide a class I recommendation for the use of validated algorithms to stratify risk during the initial evaluation of patients presenting with chest pain.[11]

Biomarkers of Myonecrosis

Serum biomarkers indicating myocardial injury and/or necrosis are critical elements in the diagnostic evaluation of a patient with presumed cardiac chest pain and are essential to distinguish between UA and overt infarction. Ideally, such biomarkers would be specific to cardiac muscle, absent from nonmyocardial tissue, released quickly into the peripheral blood after onset of injury, and reflect the magnitude of necrosis. Moreover, the marker should be easy to use, quick and

TABLE 36–2. Likelihood That Signs and Symptoms Represent an Acute Coronary Syndrome Secondary to Coronary Artery Disease

Feature	High Likelihood: Any of the Following	Intermediate Likelihood: Absence of High-Likelihood Features and Presence of Any of the Following	Low Likelihood: Absence of High- or Intermediate-Likelihood Features But May Have the Following
History	Chest or left arm pain or discomfort as chief symptom reproducing documented angina; known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom; age > 70 years; male sex; diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate-likelihood characteristics; recent cocaine use
Examination	Transient MR, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥ 0.05 mV), or T-wave inversion (≥ 0.2 mV) with symptoms	Fixed Q waves; abnormal ST segments or T waves not documented to be new	T-wave flattening or inversion in leads with dominant R waves; normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK- MB	Normal	Normal

Abbreviations: CAD, coronary artery disease; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; TnI, troponin I; TnT, troponin T.

TABLE 36–3. Short-Term Risk of Death or Nonfatal MI in Patients With Unstable Angina/NSTEMI

Feature	High Risk: At Least 1 of the Following Features Must Be Present	Intermediate Risk: No High-Risk Feature But Must Have 1 of the Following	Low Risk: No High- or Intermediate-Risk Feature But May Have Any of the Following
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (> 20 min) rest pain	Prolonged (> 20 min) rest angina, now resolved, with moderate or high likelihood of CAD; rest angina (< 20 min) or relieved with rest or sublingual nitroglycerin	New-onset or progressive CCS class III or IV angina within the past 2 wk without prolonged (> 20 min) rest pain but with moderate or high likelihood of CAD =
Clinical findings	Pulmonary edema, most likely caused by ischemia; new or worsening MR murmur; S_3 or new/worsening rales; hypotension, bradycardia, tachycardia; age > 75 y	Age > 70 y	
ECG	Angina at rest with transient ST-segment changes > 0.05 mV; bundle branch block, new or presumed new; sustained ventricular tachycardia	T-wave inversions >0.2 mV; pathologic Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated (eg, TnT or TnI > 0.1 ng/mL)	Slightly elevated (eg, TnT > 0.01 but < 0.1 ng/mL)	Normal

Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; NSTEMI, non–ST-segment myocardial infarction; TnI, troponin I; TnT, troponin T.

inexpensive to measure, and stable in vitro. Historically, myoglobin, creatine kinase, and the cardiac-specific CK-MB isoform have served this purpose in the diagnosis of MI. The main limitation of these markers is the lack of cardiac specificity, as each may also be variably released from skeletal muscle and other tissues, such as the tongue, small intestine, uterus, and prostate. As a result, earlier definitions of MI did not require the presence of these cardiac biomarkers for diagnosis but rather considered their elevation along with clinical symptoms and electrical signs of myocardial ischemia.[18]

The introduction of monoclonal antibody–based immunoassays in the late 1980s and early 1990s capable of detecting cardiac-specific troponins (troponin I [TnI] and troponin T [TnT]) represented a major advance in the diagnostic armamentarium.[30,31] The troponin complex consists of three subunits that regulate contraction of cardiac muscle. TnI binds to actin and inhibits the actin-myosin interaction, whereas TnT binds to tropomyosin, which attaches the troponin complex to the thin filament. In the early phases of myocyte necrosis, troponin present in cytosolic pools is released rapidly into the bloodstream, whereas a more protracted release occurs over several days as actin is degraded.[32] Because TnI and TnT are found only in myocardial tissue, elevated levels of either marker reflect myocyte injury and, therefore, represent the sine qua non of MI as articulated in the Universal Definition.[20]

The approval and widespread availability of troponin assays in clinical practice has substantial implications for the classification, prognosis, and management of ACS patients. With respect to classification, several studies have shown that approximately 25% to 30% of patients

TABLE 36–4. Quantitative Risk Scores to Predict Outcomes in Patients with Acute Coronary Syndrome

Risk Score	Outcome	Time Point	Components	Website
GRACE	Death Death or MI	6 months to 3 years	Age; heart rate; systolic blood pressure; CHF or diuretic use; serum creatinine or renal failure; ST-segment deviation; cardiac arrest at admission; elevated troponin	http://gracescore.org/WebSite/WebVersion.aspx
TIMI	All-cause mortality, new or recurrent MI, severe ischemia requiring urgent revascularization	14 days	Age ≥ 65; ≥ 3 CAD risk factors; known CAD (stenosis ≥ 50%); aspirin use in past 7 days; severe angina in last 24 hours; ECG ST deviation ≥ 0.5 mm; positive cardiac marker	http://www.mdcalc.com/timi-risk-score-for-uanstemi/
PREDICT	Death	30 days; 2 years; 6 years	Age; shock; CHF; ECG severity; renal function; Charlson index; prior MI; hypertension; stroke; CABG; pre-MI angina	N/A
PURSUIT	Death Death or MI	30 days	Age; sex; CCS class in prior 2 weeks; CHF; ST-segment depression	N/A

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; N/A, not applicable; PREDICT, Predicting Risk of Death in Cardiac Disease Tool; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; TIMI, Thrombolysis in Myocardial Infarction.

diagnosed as having UA based on normal CK-MB levels manifest elevations in cardiac troponin (cTn), increasing the number of patients with NSTEMI at the expense of a diagnosis of UA.[33] Whether or not the diagnosis of UA will persist as a distinct clinical entity with the ongoing evolution of high-sensitivity cTn assays has been questioned[13] and remains controversial.

From a prognostic perspective, cTns demonstrate a graded, dose-dependent association with increasing cardiovascular risk. Antman et al[33] illustrated this relationship in a post hoc analysis of a randomized trial evaluating various pharmacologic approaches in patients with ACS, demonstrating that unadjusted mortality rates at 42 days increased from 1.0% to 7.5% among those with the lowest versus highest levels of cTn. In addition, changes in cTn confer an independent and stronger impact on subsequent risk than clinical symptoms, ECG signs, or other biomarkers.[34]

In terms of treatment, randomized trials have shown the beneficial impact of managing patients with elevated levels of cTn in an aggressive fashion using potent antiplatelet, anticoagulant, and invasive approaches. These findings form the foundation for current guideline recommendations that support the routine measurement of cTn in diagnostic and therapeutic algorithms for ACS patients. Similar findings were also reported in an observational study evaluating the impact of implementing a sensitive troponin assay on the classification and management of ACS patients in clinical practice.[35] In this study, lowering the diagnostic threshold for MI increased the frequency of diagnosis by 29%. In addition, patients diagnosed with MI under the more sensitive criteria were more likely to receive aggressive therapy, translating to a significant reduction in adverse events at 6 months. Given these benefits of assessing and formulating clinical decisions based on detecting cTn, the Universal Definition of MI considers this biomarker preferentially over CK-MB. In addition, American College of Cardiology/American Heart Association guidelines no longer consider the routine measurement of CK-MB as necessary for diagnosis of MI, providing a class III recommendation against routine use of this test.[12]

The advantages to cTn testing notwithstanding, as with any diagnostic test, gains in sensitivity occur at the expense of specificity. This paradigm also extends to measuring troponin and is particularly relevant given the iterative evolution of even more sensitive troponin assays. Several studies have shown that troponin elevations may occur in non-ACS clinical settings, such as heart failure, renal dysfunction, and pulmonary embolism. Troponin may even be detected in apparently healthy community-dwelling adults, as shown in the Dallas Heart Study.[36] In that report, investigators found the following clinical conditions independently associated with detectable levels of cardiac troponin: left ventricular hypertrophy, diabetes mellitus, chronic kidney disease, and heart failure. Newby et al[37] introduced a conceptual model to delineate the various possible scenarios in which elevated levels of serum troponin might be detected, as shown in Fig. 36–3. Embedded within this framework is the principle that not all elevated troponin represents an MI and that not all myonecrosis reflects an ACS event, even when ischemic in etiology. As a result, the diagnosis of type 1 MI requires not only the presence of elevated cardiac troponin, but also a clinical context supporting an ischemic etiology. The underlying pathophysiology of elevations in serum troponin outside the ACS context remains unclear. Postulated mechanisms surround normal cellular turnover, which might be accelerated by age, exercise, or other factors, and increases in myocyte cellular permeability as a result of transient episodes of ischemia.[38,39]

In summary, cardiac troponins have emerged as the biochemical marker of choice in the evaluation of myonecrosis and diagnosis of MI. Their greater sensitivity and specificity for cardiac muscle damage and proven prognostic value have established their current clinical position.

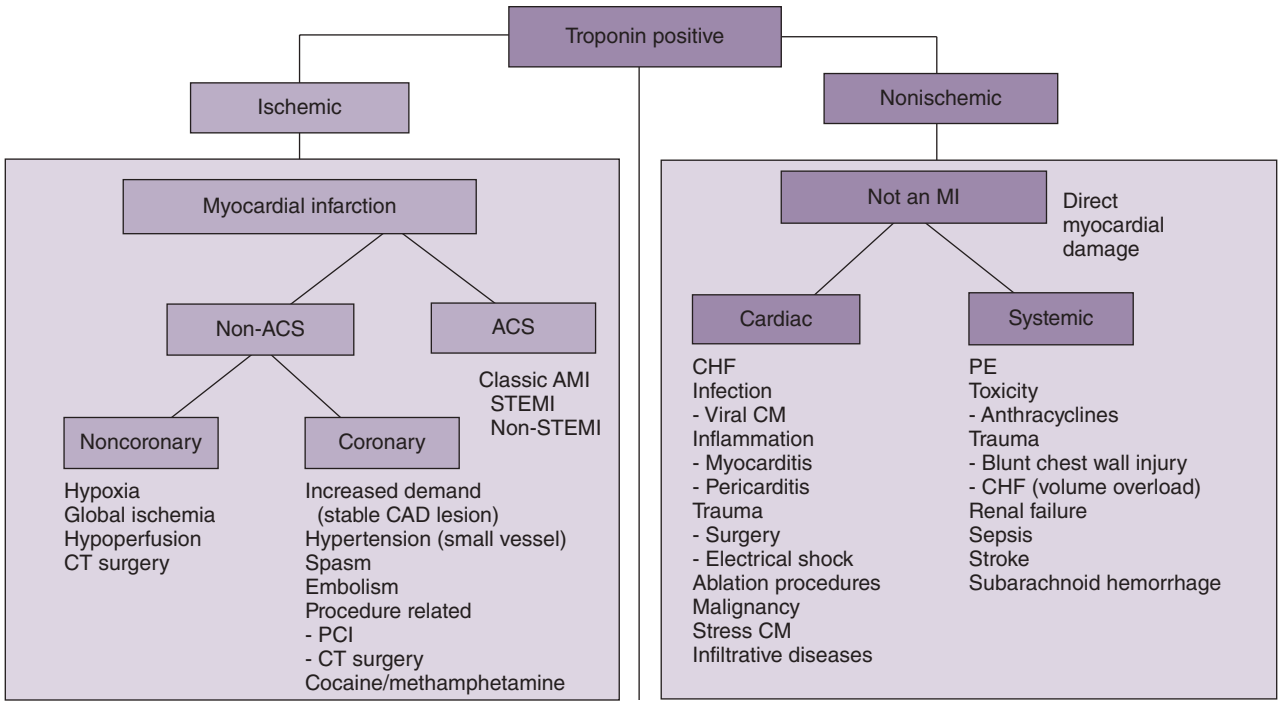

FIGURE 36–3. Conceptual model for clinical distribution of elevated troponin. ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure; CM, cardiomyopathy; CT, cardiothoracic; MI, myocardial infarction; PCI, percutaneous coronary intervention; PE, pulmonary embolism; STEMI, ST-segment elevation myocardial infarction. Reproduced with permission from Newby LK, Jesse RL, Babb JD, et al: ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2012 Dec 11;60(23):2427-2463.

Gains in troponin assay sensitivity may continue to decrease the incidence of troponin-negative ACS or UA, while increasing the number of patients diagnosed with NSTEMI.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

STEMI represents the most lethal form of ACS, in which a completely occlusive thrombus typically results in total cessation of coronary blood flow, manifested electrically as elevation of the ST segment on the ECG. Pathologic Q waves may evolve because of full- or nearly full-thickness necrosis of the ventricular wall segment supplied by the occluded artery. Accurate diagnosis of STEMI is of paramount importance because it mandates immediate consideration of reperfusion therapy, either by typically mechanical approaches or, less frequently, by infusion of one of several thrombolytic agents. In the absence of contraindications, thrombolytic therapy is favored for patients with very early presentations or substantial delays in accessing a facility capable of performing primary PCI (pPCI). In addition, thrombolytics remain the only therapeutic option for less developed medical systems without pPCI facilities. In contrast, patients presenting with shock, older age, or several hours after symptom onset should be referred for PCI if available.

Although widespread adoption of troponin measurements in the diagnostic evaluation of ACS has influenced the detection of UA and NSTEMI, the diagnosis of STEMI is less sensitive to changes in biomarkers of cardiac injury. Indeed, the incidence of STEMI has continued to decline, even after the introduction of sensitive troponin assays.[8] In addition, case fatality rates associated with STEMI have also improved.[7] Several factors may account for these trends. First, as the population ages, presentation with NSTEMI versus STEMI is the more common manifestation of MI.[21] Second, increased use of preventive therapies in the population at large, such as aspirin and statins, increases the probability of nonocclusive rather than occlusive thrombus at the site of plaque rupture culminating in NSTEMI rather than STEMI.[22] Third, reductions in the overall burden and improved control of risk factors may reduce the propensity to thrombotic complications of atherosclerosis.[9]

UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION

Criteria for diagnosis of MI have evolved substantially over the past 50 years. Classically, as articulated by the WHO in 1971, the diagnosis of MI required a consensus of at least two of the following three parameters: clinical presentation, ECG changes, and temporal changes in serum biomarkers.[18] The need for consensus in these historical definitions was a result of the variability in clinical presentation of patients with acute MI and reliance on nonspecific biomarkers that might indicate either cardiac or noncardiac injury, such as creatine kinase, lactate dehydrogenase, serum glutamic oxaloacetic transaminase (or aspartate aminotransferase), or myoglobin. The introduction of novel assays sensitive to very low levels of highly specific cardiac enzymes, however, allowed clinicians to identify patients sustaining myocyte necrosis with nearly 100% certainty. Nevertheless, elevations in cardiac-specific biomarkers do not provide insight into the underlying mechanism of injury, highlighting the need for a more refined definition incorporating both clinical context and pathobiology. Accordingly, in 2007, the World Heart Federation, in concert with major European and American cardiovascular societies, convened a global task force to introduce the Universal Definition of MI. The result was a clinicopathologic classification of MI that considers five different MI types, each representing a distinct clinical and pathologic entity culminating in myocyte necrosis. The Universal Definition has been updated twice, with the most recent iteration published in 2012.[20]

There are several important advantages to standardized diagnostic criteria for MI. First, the prevalence and incidence of coronary events can be estimated accurately, a necessary process to examine trends and overall burden of disease. Second, assessing the effects of therapeutic interventions, pharmacologic or device based, requires end points that are clearly defined, reproducible, and reflect the pathologic substrate that the intervention is intended to modify. Third, a lack of standardized definitions precludes comparative inferences across trials, populations, or time.

The new accepted universal criteria for diagnosing an acute MI state that one of the following criteria must be present in the proper clinical setting leading to evidence of myocardial necrosis:

- Detection of rise and/or fall of an acceptable cardiac biomarker (preferably troponin, but CK-MB mass method is an alternative) with at least one value above the 99th percentile of the upper reference limit (URL), in addition to evidence of myocardial ischemia by one of following:
  1. Symptoms of ischemia
  2. ECG changes indicative of new ischemia (new ST/T-wave changes or new left bundle branch block [LBBB])
  3. Development of new pathologic Q waves on ECG
  4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Sudden or unexpected cardiac death, involving cardiac arrest, often preceded by symptoms of coronary ischemia and accompanied by new ST-segment elevation or new LBBB with evidence of fresh intracoronary thrombus detected by angiography or autopsy when death occurred before blood was obtained or an expected rise in serum biomarkers could occur.
- For patients with normal baseline biomarker levels undergoing PCI, a periprocedural increase of cardiac biomarkers above the 99th percentile URL is deemed abnormal. An increase of a biomarker greater than five times the 99th percentile URL is defined as a PCI-related MI.
- For patients undergoing coronary artery bypass graft (CABG) with normal baseline biomarker levels, increases greater than five times the 99th percentile URL accompanied by either new pathologic Q waves or new LBBB, angiographically documented graft or native artery occlusion, or new imaging evidence of loss of viable myocardium is labeled as a CABG-related MI.
- Pathologic evidence of MI.

In addition to revising the criteria for MI diagnosis, the Global Task Force added a clinical classification of MI encompassing most of the common etiologies leading to myocardial necrosis.

Each etiology of MI differs with respect to short- and long-term mortality rates.

- Type 1 MI occurs as a result of a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.
- Type 2 MI occurs secondary to ischemia from either increased oxygen demand or decreased supply, for example, coronary artery spasm, embolism, anemia, arrhythmias, hypertension, or hypotension.
- Type 3 MI occurs in the setting of sudden cardiac death, including cardiac arrest, that may be preceded by ischemic symptoms, accompanied by new ST-segment elevation, new LBBB, or evidence of fresh thrombus by coronary arteriography or autopsy. Death could occur

before blood samples are obtained or before cardiac biomarkers appear in the blood.

- Type 4 MI is associated with PCI and is further classified as Type 4a or 4b.
  1. Type 4a MI is associated with PCI.
  2. Type 4b MI is associated with stent thrombosis as documented by angiography or at autopsy.
- Type 5 MI is associated with CABG.

THE ROLE OF IMAGING

The universal MI document stressed the role of imaging in the diagnosis of MI, both in the acute and chronic phases.[20] Because regional hypoperfusion and ischemia lead to myocardial dysfunction, cell death, healing, and fibrosis, imaging techniques that evaluate myocardial perfusion, myocyte viability, myocardial thickness, thickening and motion, and the effects of fibrosis are valuable tools aiding diagnosis of MI. Echocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, and magnetic resonance imaging (MRI) are commonly used modalities. Positron emission tomography and x-ray computed tomography (CT) are less common.

Echocardiography can help in diagnosis of both acute and prior MI.[40] Because of its wide availability and mobility, it has become a highly valuable tool in distinguishing true myocardial ischemia from common nonischemic causes of chest pain such as myopericarditis, valvular heart disease, cardiomyopathy, pulmonary embolism, or aortic dissection. It can help detect mechanical complications of acute infarction such as free wall rupture, acute ventricular septal defect, and mitral regurgitation. Furthermore, regional myocardial hypocontractility with thinned walls implies not an acute MI but subacute or remote MI.

Radionuclide tracers such as thallium-201, technetium-99m methoxyisobutyl isonitrile, tetrofosmin, and F2-fluorodeoxyglucose allow viable myocytes to be imaged directly, the only technique to do so.[41] Furthermore, the common single-photon–emitting tracers also detect myocardial perfusion in addition to infarction.

MRI is well validated for assessment of myocardial function and therefore similar to echocardiography in diagnosis of MI, except in the realms of availability and mobility. Paramagnetic contrast agents can assess myocardial perfusion and the increase in extracellular space associated with the fibrosis of chronic infarction.[42]

CT imaging can detect infarcted myocardium as a focal area of left ventricular enhancement, and later imaging shows hyperenhancement similar to late gadolinium imaging by MRI.[43,44] This is relevant to distinguish acute MI from pulmonary embolism or aortic dissection.

Several in vivo imaging modalities such as virtual histology intravascular ultrasound (VH-IVUS) and optical coherence tomography (OCT) complement coronary angiography and provide insight into the natural history, prognosis, and determinants of risk in ACS patients. In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, VH-IVUS defined thin cap fibroatheroma as an independent nonculprit lesion-based predictor of adverse events in patients presenting with NSTE-ACS undergoing PCI.[45] The relevance of these findings is highlighted by the fact that most of these lesions were angiographically mild, with a mean diameter stenosis of only 32%. Compared to other imaging modalities, the detailed resolution of OCT allows microstructural characterization of plaque morphology, such as cap thickness, thrombus, and calcific nodules. In a study of 126 ACS patients, the NSTE-ACS presentation was most common with underlying OCT erosion, whereas plaque rupture was most frequently observed in patients with STEMI, consistent with prior autopsy data.[46,47] Whether these findings can guide clinical decision making at the time of angiography requires further study.

PERIPROCEDURAL MYOCARDIAL INFARCTION

Myocardial injury culminating in necrosis may result from embolization of thrombotic or plaque debris during PCI or as a consequence of periprocedural events, such as coronary dissection, slow flow/no reflow, or side branch occlusion. Strategies to prevent injury using adjunctive filters have not yet been effective. Moreover, the optimal threshold and prognostic relevance of such infarction remain controversial.[48] In a post hoc analysis of randomized trials evaluating different pharmacologic strategies in NSTE-ACS patients, there was no significant association between postprocedural MI (PPMI) and 6-month mortality.[49] This notwithstanding, the third universal MI definition defines PPMI (type 4a) as cTn elevations greater than five times the 99th percentile URL occurring within 48 hours of the procedure with other manifestations of ischemia or angiographic evidence of a flow-limiting complication. For patients with a baseline elevation of cTn, an increase > 20% compared to baseline is required. The diagnosis of MI following CABG (type 5) requires cTn elevations > 10 times the 99th percentile URL during the first 48 hours after CABG with other manifestations of ischemia or angiographic evidence of a new occlusion within a bypass graft or native coronary artery.

In 2013, the Society for Cardiovascular Angiography and Interventions proposed an alternative set of criteria to define "clinically relevant" PPMI.[50] In contrast to the universal approach, the Society for Cardiovascular Angiography and Interventions document advocates the use of CK-MB over cTn and a common threshold for CK-MB elevation (≥ 10 times upper limit of normal) to diagnose MI following either PCI or CABG. In the setting of pathologic Q waves or persistent LBBB, a lower threshold of CK-MB elevation ≥ 5 times the upper limit of normal is allowed to diagnose PPMI. These varying taxonomies reflect inconsistencies across studies in linking periprocedural myonecrosis with cardiac risk[51] and the lack of clear and reproducible diagnostic thresholds above which either CK-MB or cTn may be considered harmful.[52,53] Longitudinal studies with long-term follow-up are required to examine the relative merits of either definition on prognosis following coronary revascularization.

CONCLUSION

The definitions of ACS have become more important as more effective therapies have been developed to treat patients with thrombotic manifestations of coronary atherosclerosis, with or without myocardial necrosis. Assessing a patient's symptoms, ECG pattern, and serum biomarker levels are critical components of the diagnostic evaluation and have remained remarkably constant for approximately 50 years. A false-negative diagnosis may deprive a patient of beneficial treatment, whereas false-positive results expose patients to unnecessary risk and cost. As a result, the current paradigm for the diagnosis of MI centers on measuring very sensitive and specific biomarkers of myocyte necrosis in a clinical scenario consistent with ischemia. Integration of increasingly sophisticated imaging modalities complements other parameters in distinguishing coronary from noncoronary etiologies of chest pain. Changes in the performance of diagnostic tests will continue to impact the number of patients classified as having ACS, with important implications for both prognosis and treatment.

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CHAPTER 37

PATHOLOGY OF MYOCARDIAL INFARCTION AND SUDDEN DEATH

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PATHOPHYSIOLOGY OF MYOCARDIAL ISCHEMIA/REPERFUSION

The major cause of acute myocardial infarction (MI) is coronary atherosclerosis with superimposed luminal thrombus, which accounts for more than 80% of all infarcts. MIs resulting from nonatherosclerotic diseases of the coronary arteries are rare. In past decades, there have been several trends regarding the epidemiology and outcome of patients hospitalized with acute MI. Over the time span from 1975 to 2009, patients became significantly older, were more likely to be women, and were more likely to receive effective cardiac medications. Despite a greater prevalence of comorbidities, hospital survival rates have globally improved over time.[1] However, mortality has remained unchanged for patients undergoing primary percutaneous coronary intervention for ST-segment elevation MI,[2] mostly because of secular trends as a result of changing population.[3] Reperfusion (blood flow restoration into the ischemic territory) is the only available treatment to stop the progression of ischemic damage during an MI but comes at a price, inducing additional harm to the myocardium.[4] Reperfusion injury, which accounts for up to 40% of total infarct size, is thus considered "a necessary evil."[5]

MECHANISMS OF MYOCARDIAL INJURY

The normal function of the heart muscle is supported by high rates of myocardial blood flow, oxygen consumption, and combustion of fat and carbohydrates (glucose and lactate). Under normal aerobic conditions, cardiac energy is derived from fatty acids, supplying 60% to 90% of the energy for adenosine triphosphate (ATP) synthesis (Fig. 37–1). The rest of the energy (10%-40%) comes from oxidation of pyruvate formed from glycolysis and lactate oxidation. Almost all of the ATP formed comes from oxidative phosphorylation in the mitochondria; only a small amount of ATP (< 2%) is synthesized by glycolysis. Approximately two-thirds of the ATP used by the heart goes to contractile shortening, and the remaining third is used by sarcoplasmic reticulum Ca^{2+} ATPase and other ion pumps.

Sudden occlusion of a major branch of a coronary artery shifts aerobic or mitochondrial metabolism to anaerobic glycolysis within seconds of reduced arterial flow. Myocardial ischemia primarily affects mitochondrial metabolism, resulting in a decrease in ATP formation by shutting off oxidative phosphorylation. The reduced aerobic ATP formation stimulates glycolysis and an increase in myocardial glucose uptake and glycogen breakdown (Fig. 37–2). Decreased ATP inhibits Na^+/K^+-ATPase, increasing intracellular Na^+ and Cl, leading to cell swelling. Derangements in transport systems in the sarcolemma and sarcoplasmic reticulum increase cytosolic Ca^{2+}, inducing activation of proteases and alterations in contractile proteins. Pyruvate is not readily oxidized in the mitochondria, leading to the production of lactate, a decrease in intracellular pH, and a reduction in contractile function. The decrease in pH also leads to greater ATP requirement to maintain Ca^{2+} homeostasis.[6,7]

Electron microscopic alterations result from reversible and irreversible myocardial ischemic injury and are similar across animal species, with some variation in time course. Reversibly injured myocytes are edematous and swollen from the osmotic overload. The cell size is increased with a decrease in the glycogen content.[8-10] The myocyte fibrils are relaxed and thinned; I-bands are prominent secondary to noncontracting ischemic myocytes.[7] The nuclei show mild condensation of chromatin at the nucleoplasm. The cell membrane (sarcolemma) is intact, and no breaks can be identified. The mitochondria are swollen, with loss of normal dense mitochondrial granules and incomplete clearing of the mitochondrial matrix but without amorphous or granular flocculent densities (Fig. 37–3). Irreversibly injured myocytes contain shrunken nuclei with marked chromatin margination. The two hallmarks of irreversible injury are cell membrane breaks and mitochondrial presence of small osmiophilic amorphous densities.[11] The densities are composed of lipid, denatured proteins, and calcium.[12] The cell membrane breaks are small and are associated with subsarcolemmal blebs of edema fluid (see Fig. 37–3B).

Irreversible ischemic injury is characterized by a variety of processes involving the sarcolemmal membrane eventuating in its disruption and cell death. Increased cytosolic Ca^{2+} and mitochondrial impairment cause phospholipase activation and release of lysophospholipids and

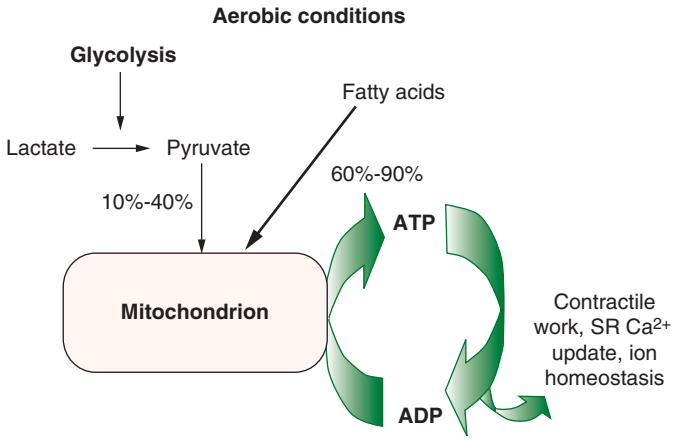

FIGURE 37–1. Cardiac energy metabolism under normal aerobic conditions. Fatty acids are the primary source of energy for the heart, supplying 60% to 90% of the energy for adenosine triphosphate (ATP) synthesis. The balance (10%-40%) comes from the oxidation of pyruvate formed from glycolysis and lactate oxidation. Almost all of the ATP formation comes from oxidative phosphorylation in the mitochondria; only a trivial amount of ATP (< 2% of the total) is synthesized by glycolysis. ADP, adenosine diphosphate; SR, sarcoplasmic reticulum. Reproduced with permission from Stanley WC. Changes in cardiac metabolism: a critical step from stable angina to ischemic cardiomyopathy. *Eur Heart J Suppl*. 2001;3(suppl O):O2-07.

free fatty acids, which are incorporated within the cell and are damaged by peroxidation from free radicals and toxic oxygen species. Cleavage of anchoring cytoskeletal proteins and progressive increases in cell membrane permeability result in physical disruption and cell death.[12]

DIFFERENT TYPES OF CARDIOMYOCYTE DEATH DURING MYOCARDIAL INFARCTION: NECROSIS, APOPTOSIS, AUTOPHAGY, AND NECROPTOSIS

MI has traditionally been viewed as a manifestation of necrotic cell death, but recently, different forms of cardiomyocyte death have been identified during reperfused MI.[4] Necrosis is morphologically characterized by myofibrillar contraction bands, swollen and ruptured

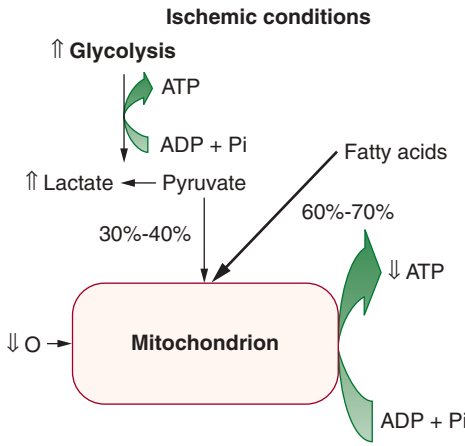

FIGURE 37–2. Cardiac energy metabolism during ischemia of moderate severity (~40% of normal blood flow). The *up* and *down arrows* indicate the changes compared with normal conditions. Relative to aerobic conditions, ischemia results in an increase in glycolysis without an increase in the rate of pyruvate oxidation, thus causing lactate to accumulate in the cell. Despite accelerated glycolysis and lactate production, the relatively high rate of residual oxygen consumption is fueled primarily by the oxidation of fatty acids. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, inorganic phosphate. Reproduced with permission from Stanley WC. Changes in cardiac metabolism: a critical step from stable angina to ischemic cardiomyopathy. *Eur Heart J Suppl*. 2001;3(suppl O):O2-07.

mitochondria, destruction of cardiomyocyte membranes, microvascular destruction, hemorrhage, and inflammation. Most of these morphologic features are aggravated and made more manifest by reperfusion.[13-17] Necrosis is thought to result from unregulated and uncoordinated pathophysiologic mechanisms. During ischemia, the developing acidosis from anaerobic glycolysis increases the influx of Na^+ through the Na^+/H^+ exchanger, and intracellular Na^+ accumulation is increased by the inhibition of Na^+/K^+-ATPase as a result of the lack of available ATP.[18,19] The subsequent exchange of Na^+ for Ca^{2+} by reverse mode operation of the sarcolemmal Na^+/Ca^{2+} exchanger induces intracellular Ca^{2+} overload. Upon reperfusion, the rapid normalization of pH and re-energization in the context of elevated cytosolic Ca^{2+} induces oscillatory release and re-uptake of Ca^{2+} into the sarcoplasmic reticulum, causing uncontrolled excess myofibrillar hypercontraction.[19-21] The normalization of the acidic pH also activates calpain, which digests the cytoskeleton and the sarcolemma.[22] The high cytosolic concentrations of Na^+ and Ca^{2+} result in intracellular edema when extracellular osmolarity is rapidly normalized by reperfusion. Finally, excess formation of reactive oxygen species contributes to sarcolemmal disruption.[23] Necrosis is typically followed by an inflammatory response.

Unlike necrosis, apoptosis, autophagy, and necroptosis are regulated processes with specific underlying signal transduction mechanisms.[24,25] Apoptosis is an energy-consuming form of cell death characterized by characteristic DNA strand breaks that are identified by DNA laddering and/or terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining.[26] Apoptosis can be initiated extrinsically by activation of sarcolemmal receptors, notably Fas and tumor necrosis factor-α receptors,[27] or intrinsically by mitochondrial release of cytochrome C, which initiates a cascade of caspase activation leading to intracellular proteolysis, typically without an inflammatory response.[25] A pivotal event in the initiation of apoptotic cell death is the opening of the mitochondrial permeability transition pore (MPTP).[28] The MPTP is a large-conductance megachannel that is closed under physiologic conditions but opens in response to increased concentrations of calcium, inorganic phosphate, or reactive oxygen species and to a decreased inner mitochondrial membrane potential, all of which are present in myocardial ischemia/reperfusion.[29,30] Formation and opening of the MPTP result in mitochondrial matrix swelling, ultimately leading to rupture of the outer membrane and release of cytochrome C to the cytosol, where it activates the caspase cascade. Pro- and antiapoptotic proteins of the Bcl family interact with the MPTP.[31] Recently, the traditional view of the MPTP has been questioned because all of its purported constituents are dispensable under some conditions, and it is possible that the MPTP originates from F-ATP synthase.[32] Autophagy is a regulated process of lysosomal degradation and re-cycling of proteins, including mitochondrial proteins (mitophagy).[33] Autophagy is characterized by the presence of double-membrane vesicles (autophagosomes) and increased expression of beclin-1, light chain 3, the autophagy-related gene 5-12 complex, p62, and parkin, with the last two being essential for mitophagy.[34] Somewhat paradoxically, cell death by autophagy is considered protective rather than detrimental.[35] For example, in pigs subjected to 45 minutes of coronary occlusion and reperfusion, the purported autophagy inducer chloramphenicol reduced infarct size.[36] However, the role of autophagy in myocardial ischemia/reperfusion injury in humans remains contentious.[37,38] Necroptosis shares features with necrosis and apoptosis but is distinctly regulated by activation of receptor-interacting protein kinases 1 and 3[39] and can be inhibited by substances such as necrostatin.[40]

It is currently unclear to what extent necrosis, apoptosis, autophagy, and necroptosis are mutually exclusive processes and to what extent each contributes to infarct size. Typical features of apoptosis (TUNEL

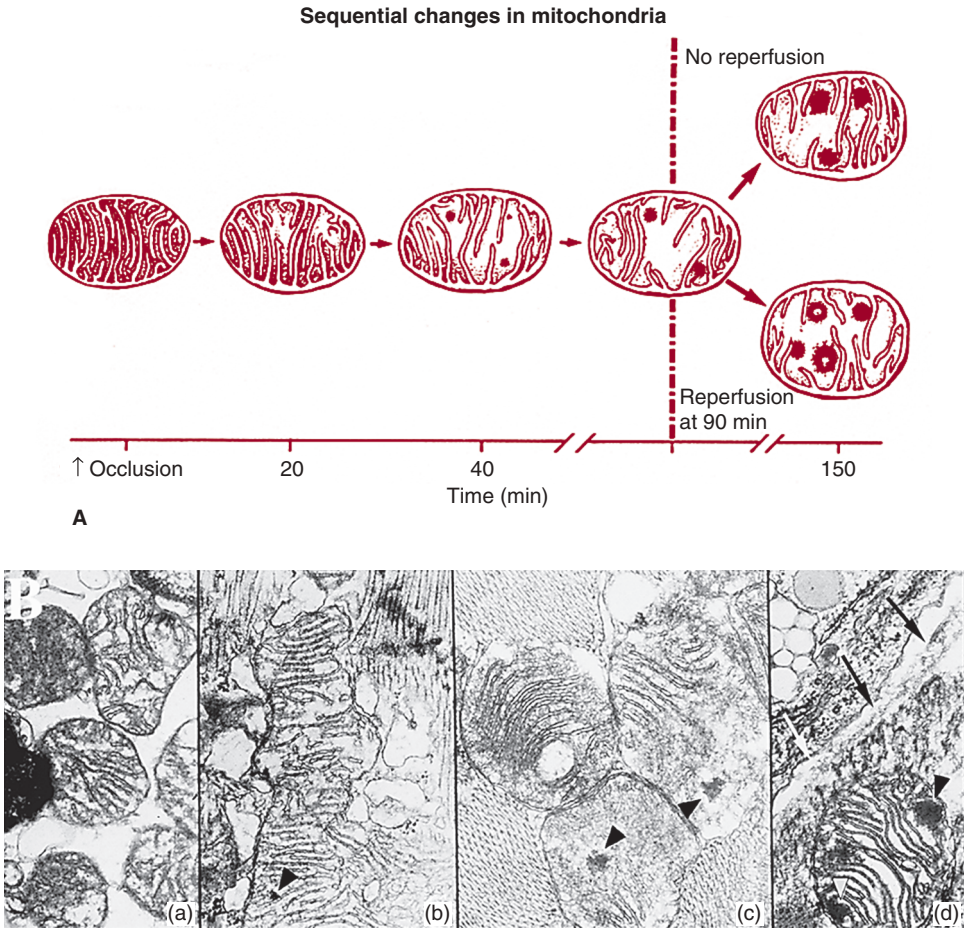

FIGURE 37–3. A. Sequential changes within mitochondria with varying time intervals of myocardial ischemia. At 20 minutes of ischemia, there is mild mitochondrial swelling. Matrix space between cristae show disorganization. At 40 minutes of ischemia, there is greater mitochondrial swelling, and prominent amorphous matrix densities are present, which indicate irreversible injury. With a longer duration of coronary occlusion, mitochondria show larger amorphous matrix densities, and they also become more numerous. On reperfusion, both amorphous and granular densities are seen. Granular densities, however, seem larger and more fully developed. Adapted with permission of American Heart Association from Jennings and Ganote.[11] **B.** Electron micrographs showing progressive changes in mitochondria as a result of ischemia in the canine model. *Panel a.* Mitochondria showing reversible changes of ischemia after 10 minutes of coronary occlusion and reperfusion: mitochondria are swollen, there is clearing of mitochondrial matrix, and some cristae show disorganization. *Panel b.* Similar changes as in *panel a* with only one of the mitochondria showing amorphous matrix densities (*arrowhead*) after 90 minutes of ischemia. *Panel c.* Note the presence of large amorphous matrix densities (*arrowheads*) in two of the three mitochondria in a dog with 120 minutes of coronary occlusion. *Panel d.* Ischemic myocyte with mitochondria containing multiple large amorphous matrix densities (*arrowheads*) after 3 days of permanent coronary occlusion. Note the break in the plasma lemma (*arrow*). Reproduced with permission from Virmani R, Forman MB, Kolodgie FD: Myocardial reperfusion injury. Histopathological effects of perfluorochemical. *Circulation*. 1990 Mar;81(3 Suppl):IV57-IV68.

staining) and autophagy (characteristic protein expression) are both found in the triphenyltetrazolium chloride staining–defined infarct zone, which has traditionally been considered necrotic. The opening of the MPTP appears to be decisive for necrosis, apoptosis, and necroptosis, and mitochondria are also decisive in mitophagy/autophagy. The importance of regulated forms of cardiomyocyte cell death in ischemia/reperfusion injury is probably related more to their specific signal transduction mechanisms. Recognition of the different modes of cardiomyocyte death during infarction suggests the possibility of identifying therapeutic targets that can modulate these processes. From the clinical perspective, cardiomyocyte death is equally relevant whatever the mechanism.

EVOLUTION OF MYOCARDIAL INFARCTION, DETERMINANTS OF INFARCT SIZE, AND VENTRICULAR REMODELING

Myocardial ischemia occurs when oxygen and nutrient supply does not meet myocardial demand, and necrosis or infarction occurs when ischemia is severe and prolonged. Although biochemical and functional abnormalities begin almost immediately at onset of ischemia, severe loss of myocardial contractility occurs within 60 seconds, and other changes take a more protracted course; for example, the loss of viability (irreversible injury) takes at least 20 to 40 minutes after total occlusion of blood flow.[41]

Two zones of myocardial damage occur: a central zone with no flow or very low flow, and a zone of collateral vessels in a surrounding marginal zone. The survival of the marginal zone depends on the level of ischemia and the duration of ischemia. In autopsy hearts, the size of the ischemic zone surrounding an acute MI is associated with increased apoptosis and degree of occlusion of the infarct-related artery.[42] The extent of coronary collateral flow is one of the principal determinants of infarct size. Indeed, at autopsy, it is common to see chronic total coronary occlusion and an absence of MI in the distribution of that artery. Absence of myocardial ischemia (revealed by electrocardiographic changes or angina during transient coronary balloon occlusion) is associated with presence of well-developed collateral vessels, suggesting that patients with well-developed collateral vessels have

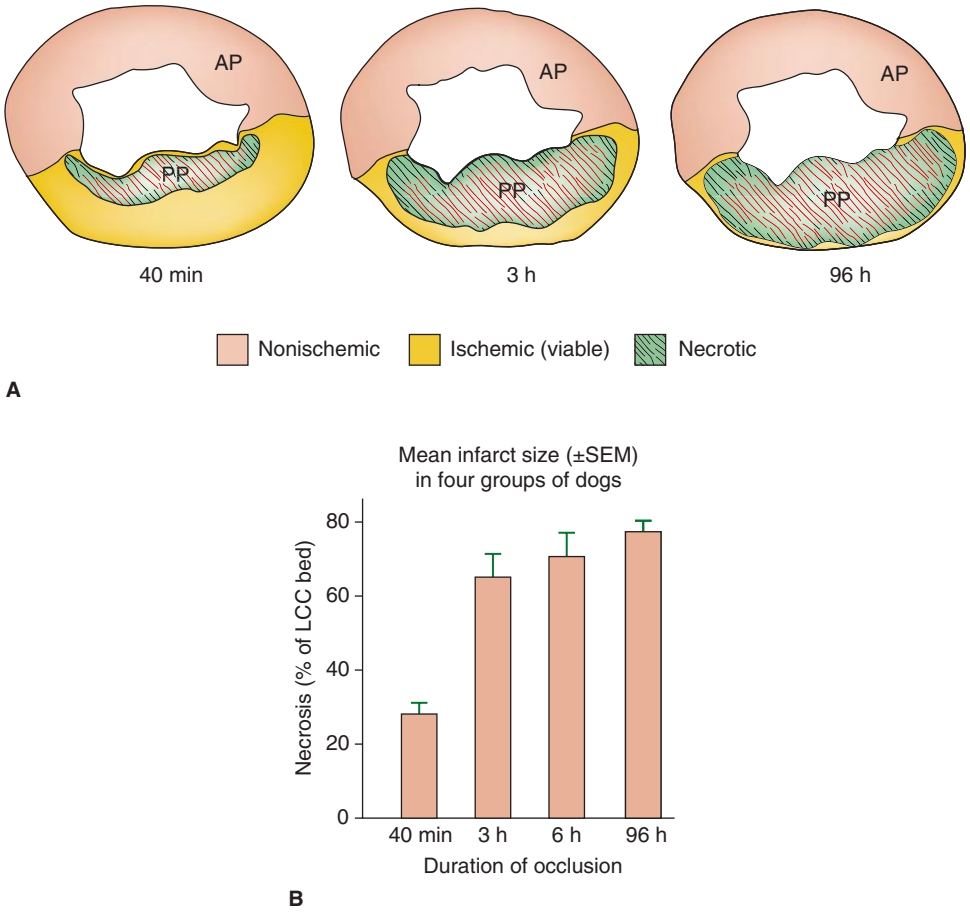

FIGURE 37–4. A. Progression of cell death versus time after experimental occlusion of the left circumflex coronary artery in the dog. Necrosis occurs first in the subendocardial region of the myocardium. With extension of the occlusion time, a wavefront of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. **B.** Infarct size variation with increasing duration of coronary occlusion. The infarct size dramatically increases from 40 minutes to 3 hours; however, there is very little increase between 3 and 6 hours and between 6 and 96 hours of coronary artery occlusion. AP, anterior; LCC, left circumflex coronary bed; PP, posterior. Reproduced with permission from Reimer KA, Jennings RB: The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest*. 1979 Jun;40(6):633-644.[13]

a low risk of developing acute MI upon abrupt closure of the culprit coronary artery.[43] Collaterals are better developed in patients with angina and in younger individuals than in older patients with acute infarcts.[44,45] Because infarct size is an important determinant of survival as well as development of congestive heart failure, efforts have been directed to limit infarct size by early reperfusion, reduction of myocardial oxygen demand, and prevention of reperfusion injury.

Reimer and Jennings, initially in 1979, showed that if a canine coronary artery was occluded for 15 minutes, for 40 minutes, for 3 hours, or permanently for 4 days, myocardial necrosis progressed as a "wave front phenomenon" (Fig. 37–4A).[13,46] The extent of myocardial necrosis therefore depended on the duration of coronary occlusion. After only 15 minutes of occlusion, no infarct occurred. At 40 minutes, the infarct was subendocardial, involving only the papillary muscle, resulting in 28% of the myocardium at risk. At 3 hours after coronary artery occlusion and reperfusion, the infarct was significantly smaller compared with nonreperfused permanently occluded infarct (62% of area at risk). The infarct size was the greatest in permanent occlusion, becoming transmural and involving 75% of the area at risk (Fig. 37–4B).[13] In the dog model, it is impossible to achieve 100% infarction of the area at risk because of species-related native collaterals. In humans, it has been shown that approximately 40% of patients with acute MI have well-developed collateral circulation.[44,45]

Other than the presence of collateral circulation, factors that influence infarct size include preconditioning, which may greatly reduce infarct size, and reperfusion.[41] However, there is a balance between benefits of reperfusion in reducing infarct size and reperfusion injury, which is dependent on the time of onset. In general, if ischemic myocardium is reperfused early, the degree of myocardial salvage greatly exceeds damage from free radicals and calcium loading caused by reperfusion. These positive functional consequences of reperfusion are most beneficial within the initial 12 hours after occlusion in humans.

It was documented in the late 1970s that transmural infarcts may increase in size for weeks after the initial event, and the degree of this expansion is associated with a decrease in survival rate.[47] The processes involved in postinfarction ventricular dilatation are known as *ventricular remodeling*. In general, transmural extent of necrosis is a major determinant of infarct expansion (remodeling) based on large infarct size and the persistence of the occlusion. The preservation of islands of viable myocardium in the subepicardial regions is associated with decreased remodeling or infarct expansion. Other factors that are implicated in reduced ventricular remodeling include microvascular integrity[48] and initial ventricular compliance.[49] The effect of reperfusion on ventricular remodeling is clear as far as early reperfusion is concerned because there are definite benefits in reducing infarct size and expansion. The benefits of late reperfusion beyond myocardial salvage are unclear. It has been demonstrated that remodeling is

affected by the presence of viable zones after successful late percutaneous coronary intervention (PCI).[50] In general, the mechanisms of ventricular remodeling are poorly understood because different techniques have been used to assess myocardial viability in human subjects, animal studies, and postmortem specimens. The immune system and the release of matrix metalloproteinases are now being linked to remodeling.[51-54]

THE NO-REFLOW PHENOMENON AND REPERFUSION INJURY

The no-reflow phenomenon (also termed *microvascular obstruction*) was originally described by Kloner et al[55] in 1974 in an experimental canine model of MI. They demonstrated homogenous distribution of thioflavin S dye after 40 minutes of ischemia and reperfusion. However, after 90 minutes of ischemia, areas of no-reflow were identified mainly in the subendocardial regions as zones not staining with thioflavin S. By electron microscopy, they showed swollen endothelial protrusions and membrane-bound intraluminal bodies, which obstructed the capillary lumen and resulted in plugging of the capillaries by red blood cells, neutrophils, platelets, and fibrin thrombi. The areas not stained by thioflavin S were characterized by low regional myocardial blood flow. It is now well-known that angiographic no-reflow is also a strong predictor of major cardiac events, similar to congestive heart failure, malignant arrhythmias, and cardiac death, after acute MI.[4]

The process of restoring blood flow to ischemic myocardium has shown utility in limiting cell death in the presence of severe ischemia. Reperfusion, however, has paradoxical effects on myocardium that can result in adverse reactions, thereby reducing its beneficial actions. During reperfusion, the myocardium is subject to abrupt biochemical and metabolic changes governed by several mediators that interact with each other in complex ways.[4,56] The term *reperfusion injury* was coined to describe reperfusion-related expansion or worsening of the ischemic cardiac injury as assessed by contractile performance, the arrhythmogenic threshold, conversion of reversible to irreversible myocyte injury, and microvessel dysfunction.

The coronary microcirculation, the interface between the epicardial vessel and the cardiomyocytes, plays a critical role in the complex phenomenon of no-reflow and reperfusion injury. No matter how efficiently and rapidly the blood flow is restored to the epicardial artery, if there is a microvascular obstruction, the myocardial tissue will remain without efficient perfusion.[4] Potential mediators of reperfusion injury include oxidative stress (oxygen paradox), sudden increases in intracellular Ca^{2+} (calcium paradox), rapid restoration of physiologic pH (pH paradox), and inflammation.[4,56] Neutrophils are activated early during myocardial ischemia and precede the appearance of histologic tissue injury. Reperfusion markedly enhances the infiltration of neutrophils into the ischemic region. The essential initiating step involves interaction of neutrophils with vascular endothelial cells (adhesion). This is followed by activation, diapedesis, and extravascular migration into surrounding myocytes. Production of additional chemoattractants by activated neutrophils amplifies the initial inflammatory response. Neutrophil activation causes a greatly enhanced oxygen uptake by the cell, resulting in the production of large quantities of reactive oxygen species that may lead to disruption of excitation-contraction coupling and inactivate antiproteases present in the plasma.[57]

At the time of myocardial reperfusion, there is an abrupt increase in intracellular Ca^{2+}, leading to a disturbance in the normal mechanisms that regulate Ca^{2+} within the cardiomyocyte, known as the *calcium paradox*.[56] This intracellular Ca^{2+} overload induces death by causing hypercontracture of myofibrils and mitochondrial permeability transition pore (PTP) opening.[4,56] Mitochondrial PTP is a nonselective channel located on the inner mitochondrial membrane and is a critical determinant of lethal reperfusion injury. Opening the channel, as occurs within the first few minutes after reperfusion, uncouples oxidative phosphorylation, resulting in ATP depletion and cell death.

In addition, experimental studies have shown that reperfusion of ischemic myocardium generates reactive oxygen species (oxygen paradox). This oxidative stress results in extension of the myocardial injury beyond that induced by ischemia alone. A key mechanism involves the reduction of the bioavailability of the nitric oxide, a cardioprotective signaling molecule. Nitric oxide inhibits neutrophil accumulation, inactivates superoxide radicals, and improves coronary blood flow.[56] Further contributing to reperfusion injury is the rapid restoration of physiologic pH that occurs after washout of lactic acid and the activation of the sodium-hydrogen exchanger and the sodium-bicarbonate symporter.[6]

The understanding of mechanisms leading to myocardial death during ischemia/reperfusion injury has led to several potential strategies to limit infarct size. These are beyond the scope of this chapter and are described in Chap. 38.

MICROEMBOLIZATION

Acute coronary thrombosis with or without percutaneous intervention results in the embolization of microparticles, including fragments of fibrin-platelet thrombus and necrotic core. Coronary microembolization is associated with arrhythmias, contractile dysfunction, microinfarcts, and reduced coronary reserve.[58] Early autopsy studies showed a 30% rate of microembolization in cardiac disease, often associated with focal myocyte necrosis; however, more recent studies show a significantly higher rate of distal embolization 54%.[59,60] The rate of coronary microembolization is highest in patients with documented epicardial coronary thrombosis, especially in those with acute MI. Few data are available that compare acute plaque rupture with acute plaque erosion and the rate of embolization, but it has been suggested that distal embolization is more frequent in erosions (70%) than ruptures (42%).[60] These emboli and microvessel obstructions have a prominent clinical role because myonecrosis is often associated with these findings.

Other potential sources of distal embolization include primary PCI, PCI of atherosclerotic plaque in native and saphenous vein grafts, and thrombolysis. Thus, angiographic evidence of distal embolization in patients presenting with acute MI undergoing primary PCI ranges from 15% to 70% (Fig. 37–5).[61-63] A detailed description of the mechanisms leading to microvascular obstruction during MI (ischemia/reperfusion) can be found in Chap. 38.

HIBERNATING MYOCARDIUM

Left ventricular systolic dysfunction caused by ischemia may arise in dead myocardium or from hypocontractile areas of viable myocardium. In the early 1980s, Rahimtoola et al[64] found significant improvement in left ventricular function after coronary revascularization in a subset of patients with depressed ventricular performance. They postulated that the mechanism of poor myocardial contractility was chronic ischemia, which could be improved by revascularization. The premise behind this rationale was dependent on the surviving myocardium being in a functional, albeit depressed, state, suggesting that the myocardium may adapt to chronic ischemia by decreasing its contractility but preserving viability.[65,66] Reversibly, dysfunctional tissue is commonly referred to as *hibernating myocardium*. Sheiban et al[67] demonstrated that 5 to 7 minutes of angioplasty balloon inflations in the coronary arteries of patients undergoing interventional procedures, followed by tracking of the resolution of the regional wall motion abnormalities over the next 5 days, showed persistence

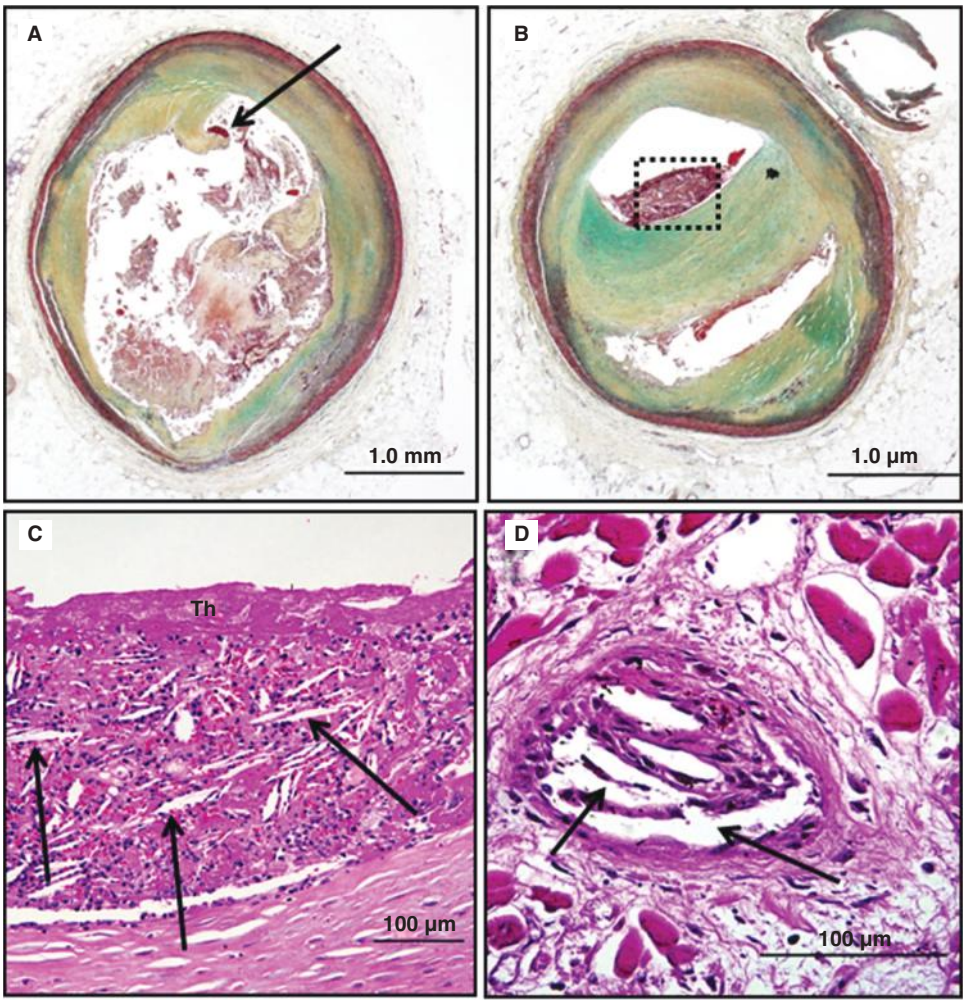

FIGURE 37–5. Representative micrographs of distal microembolization of plaque material from ruptured atheroma. **A.** Low-power (Movat pentachrome) view of rupture site (*arrow*) showing luminal fibrin and cholesterol clefts. **B.** Adjacent distal segment to rupture site demonstrates nonocclusive thrombus composed of necrotic core material. **C.** High-power image demonstrating cholesterol clefts (*arrows*) with superimposed thrombus (Th) (hematoxylin and eosin). **D.** High-power image of intramural coronary artery atheroembolus consisting of cholesterol clefts (*arrows*) and surrounded by healing myocardium in a patient who underwent percutaneous coronary intervention for acute myocardial infarction.

of regional wall motion abnormalities for up to 36 hours. Similarly, return of left ventricular function has been studied after acute MI. Delayed recovery of wall motion was observed in the infarct region, with a positive change in wall motion from 0.2 at 3 days to 1.0 at 6 months in patients with reperfusion but not in those without reperfusion, as measured by the centerline method.[68]

The concept of myocardial hibernation was initially based on clinical observation. Subsequently, there have been a number of experimental studies to support the concept that ischemia is not the result of simple inadequacy of blood flow for myocardial contraction but that there is a stepwise decrease in function based on incremental decrease in oxygen-supplying perfusion (so-called *perfusion-contraction matching*). Evidence suggests that repeated episodes of ischemia-reperfusion may result in a state of chronic hibernation, with alterations in the flow-function relationship and decreased oxygen demand. Chronically hibernating myocardium demonstrates alterations in adrenergic control and calcium responsiveness. Substances that are upregulated in chronic hibernating myocardium include heat shock protein, hypoxia-inducible factor, inducible nitric oxide synthase, cyclooxygenase-2, and monocyte chemotactic protein. Because some of these pathways are involved in preconditioning, a relationship between cardiac hibernation and preconditioning is postulated.

Morphologically, hibernating myocytes show loss of contractile elements, especially in the perinuclear region and occasionally throughout the cytoplasm. The space left by the dissolution of the myofibrils is occupied by glycogen, as evidenced by the strong positivity for the periodic acid–Schiff reagent. Ultrastructurally, there is depletion of sarcomeres, most pronounced in the perinuclear region, with increased glycogen. The nuclei are enlarged, with a tortuous nuclear membrane and evenly distributed heterochromatin. The mitochondria are elongated, shrunken, and osmiophilic.[69] The interstitium shows an increase in connective tissue. Increased numbers of apoptotic myocytes, using the technique of DNA nick-end labeling,[70] as well as an increase in autophagic and oncotic cell death, have been demonstrated.[71,72]

The composition and distribution of sarcomeric, cytoskeletal, and membrane-associated proteins is significantly altered in chronic myocardial hibernation.[73] There is a disorderly increase in cytoskeletal desmin, tubulin, and vinculin, with a decrease in contractile proteins myosin, titin, and actinin. More recently, decreased connexin 43, a membrane transport protein, has been associated with reduced gap junction size and a proposed propensity for arrhythmias in the hibernating state.[74]

Advances in noninvasive imaging techniques have helped in the characterization of the hibernated myocardium in patients. Clinical

functional techniques such as stress echocardiography and cardiac magnetic resonance are more specific but less sensitive than nuclear modalities, which assess perfusion and metabolic activity, in the detection of hibernating myocardium.[65] Radionuclide imaging with positron emission tomography (PET) seems to be especially suitable in assessing cardiac metabolism.[75] However, recent advances in magnetic resonance make this method a comprehensive modality that can accurately determine the amount of hibernating myocardium as well as the presence and degree of myocardial ischemia and the extent of the scar.[75,76]

PLAQUE MORPHOLOGY AND SITE OF THROMBUS IN ACUTE MYOCARDIAL INFARCTION

The vast majority of MIs occur in patients with coronary atherosclerosis, with more than 90% associated with superimposed luminal thrombi. Arbustini et al[77] found coronary thrombi in 98% of patients dying with clinically documented acute MI, and of those thrombi, 75% were caused by plaque rupture and 25% by plaque erosion. There are gender differences in the causation of coronary thrombi leading to acute MI: Arbustini et al[77] showed that 37% of thrombi in women were erosion compared with only 18% in men. The thrombus age also varies; the majority of acute thrombi (< 1 day) have been observed in plaque rupture, whereas the majority of thrombi in plaque erosion are organizing (> 1 day)[78] (Fig. 37–6). Kramer et al[79] have reported their findings in thrombi retrieved from patients presenting with ST-segment elevation MI during percutaneous coronary angioplasty intervention and demonstrate that more than 50% of thrombi show organization of more than 1 day in duration. Furthermore, the age of the thrombus, in addition to other risk factors, was an independent predictor of long-term mortality, especially within the first 2 weeks as well as at 4 years after PCI.

Although an individual severe stenosis is more likely to become occluded by a thrombus than a lesion with less severe stenosis, the less severely narrowed plaques give rise to more occlusions because there are many more sites that are mild to moderately narrowed.[80] We have observed that the mean percent stenosis underlying coronary plaque erosion is 70% versus 80% at the site of plaque rupture; however, 82% of fatal plaque erosions result in total occlusions compared with only 57% of plaque ruptures.[81] The majority of thin cap fibroatheromas, acute and healed ruptures, and lesions with fibroatheromas occur predominantly in the proximal portion of the three major coronary arteries, and about 50% arise in the midportion of these arteries. By far, the proximal portion of the left anterior descending (LAD) coronary artery is the most frequent location, with sites in the proximal right and left circumflex contrary arteries about half as common. The culprit coronary artery of infarction at autopsy is most frequently the LAD (~ 50%), followed by the right coronary artery (30%-45%) and then the left circumflex artery (15%-20%).[78] No thrombi are found in fewer than 5% of acute MIs.

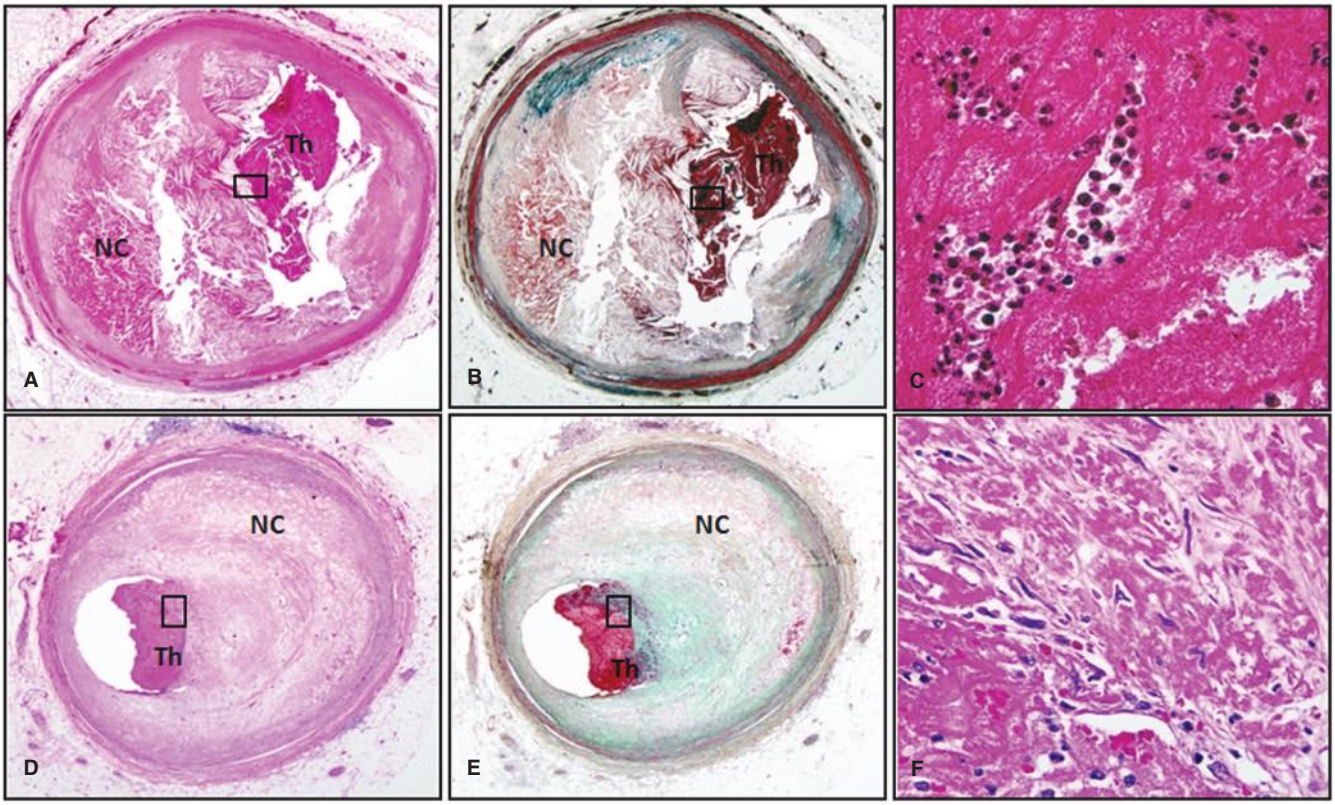

FIGURE 37–6. Morphology of coronary thrombi associated with plaque rupture and erosion. **A** and **B.** Low-power views of a human ruptured coronary lesion showing a relatively large necrotic core (NC) and superimposed thrombus (Th) (early, nonhealing, < 1 day in age). **C.** Higher magnification of thrombus area referenced by the *insert* in **A** showing platelets and fibrin and focal collections of neutrophils. **D** and **E.** Low-power views of a human ruptured coronary lesion showing a macrophage-rich early fibroatheroma with coronary plaque erosion with a superimposed healing thrombus (> 7 days of age). **F.** Higher magnification of healing thrombus composed of layers of smooth muscle cells and proteoglycan-collagen matrix. Parts A to D, ×20 magnification, hematoxylin and eosin (H&E) staining; parts B and E, ×20 magnification, Movat pentachrome staining; parts C and F, ×400 magnification, H&E staining.

PATHOLOGY OF ACUTE MYOCARDIAL INFARCTION

GROSS PATHOLOGIC FINDINGS

The earliest change that can be grossly discerned in the evolution of acute MI—pallor of the myocardium—occurs 12 hours or later after the onset of irreversible ischemia. The gross detection of infarction can be enhanced by the use of tetrazolium salt solutions, which form a colored precipitate on gross section of fresh heart tissue in the presence of dehydrogenase-mediated activity. The tetrazolium salts (nitroblue tetrazolium [NBT] and 2,3,5-triphenyltetrazolium chloride [TTC]) are dyes that are sensitive to the presence of tissue dehydrogenase enzyme activity, which is depleted in the infarcted myocardium. It has been shown that myocardial infarct can be detected by NBT as early as 2 to 3 hours in dogs and in a little less time in pigs because of poor collaterals.[82] Red color (TTC) or blue color (NBT) only forms in the normal noninfarcted myocardium, thus revealing the pale, nonstained, infarcted region (Fig. 37–7). In humans, the necrotic myocardium can be detected within 2 to 3 hours after infarct by immersion of the fresh heart slices in a solution of TTC or NBT. TTC staining has a diagnostic sensitivity of 77% and a specificity of 93% compared with routine histology, with predictive values of positive and negative test of 81% and 91%, respectively.[83]

At approximately 24 hours after the onset of irreversible ischemia, the pallor is enhanced (Fig. 37–8). However, in the present era, most patients receive primary PCI or thrombolytic therapy with percutaneous intervention as reperfusion strategy; therefore, most in-hospital patients will have received tissue plasminogen activator, streptokinase, or glycoprotein IIb/IIIa inhibitors with balloon angioplasty and stenting, which lyse the thrombus and restore blood flow into the area of infarction. Consequently, in a reperfused infarct, the infarcted region will appear red from trapping of the red blood cells and hemorrhage from the rupture of the necrotic capillaries (Fig. 37–9). However, if there has been no reperfusion, the area of the infarct is better defined at 2 to 3 days with a central area of yellow discoloration that is surrounded by a thin rim of highly vascularized hyperemia (see Fig. 37–8). At 5 to 7 days, the regions are much more distinct, with a central soft area and a depressed hyperemic border. At 1 to 2 weeks, the infarct begins to heal with infiltration by macrophages as well as early fibroblasts at the margins. At the same time, the infarct begins to be more depressed, especially at the margins where organization takes place, and there is a white hue to the borders (Table 37–1; see also Fig. 37–8). Healing may be complete as early as 4 to 6 weeks in small infarcts or may take as long as 2 to 3 months when the area of infarction is large. Healed infarcts are white from the scarring, and the ventricular wall may or may not be thinned (aneurysmal). In general, infarcts that are transmural and confluent are likely to result in thinning, but subendocardial and nonconfluent infarcts are not.

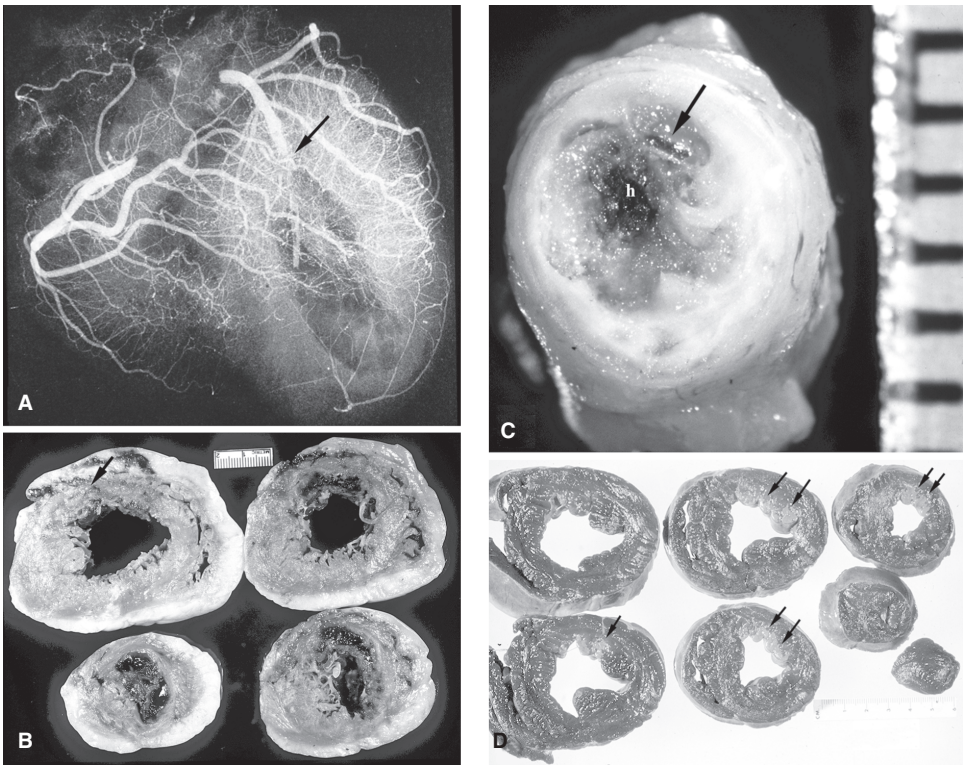

FIGURE 37–7. Regional distribution of vascular supply to the ventricles with right coronary artery dominance. **A.** Postmortem angiogram of the heart in a patient with acute myocardial infarction with total occlusion (*arrow*) of the proximal left anterior descending (LAD) coronary artery in a 65-year-old woman who presented with persistent chest pain of 6 hours in duration. **B.** At autopsy, she had a hemopericardium with rupture site (*arrow*) identified on the anterior wall of the left ventricle. Note extensive hemorrhagic (h) transmural infarction involving the anterior wall of the left ventricle near the base of the heart (*upper slices*) and extending into the septum in the mid and apical slices (*lower slices*). **C.** Gross photography of the LAD showing hemorrhage into the necrotic core and more than 90% luminal narrowing; barium is seen within the lumen (*arrow*). **D.** Dog heart slices after 15 minutes of incubation in 2% triphenyltetrazolium chloride (TTC) at 98.6°F (37°C). The animal had undergone 60 minutes of LAD occlusion distal to the first diagonal branch followed by reperfusion and was sacrificed at 24 hours. Injecting monastery dye after reocclusion of the LAD and just before sacrifice identified the myocardium at risk of infarction. The heart was sliced and then immersed in TTC. The viable myocardium at risk stains red, the area not at risk is blue-red, and the infarcted region is creamy white (*arrows*). Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

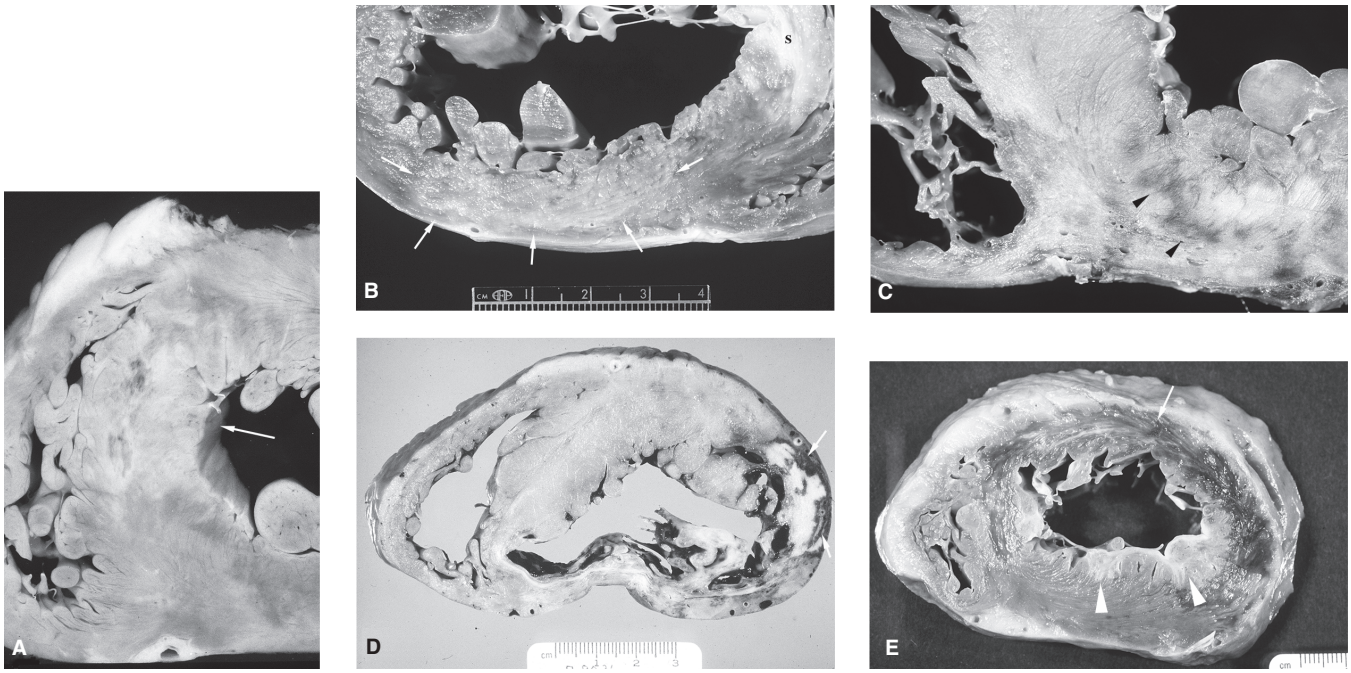

FIGURE 37–8. Gross photographs of hearts with varying ages of acute myocardial infarction. **A.** A 50-year-old hyperlipidemic and hypertensive man presented with unstable angina, underwent emergency percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending (LAD) coronary artery, and died 20 hours after onset of chest pain. At autopsy, he had a pale, ill-defined, slightly raised region in the anterior ventricular septum suggestive of an acute transmural infarct (*arrow*), which was confirmed by the presence of hypereosinophilic myocytes localized to the septum with sparing of the subendocardial myocytes. The LAD at the PTCA site was totally occluded by a luminal thrombus and an underlying 60% atherosclerotic lesion. **B.** Another high-power view of a different acute transmural myocardial infarct involving the posterior wall of the heart, showing a well-defined, pale, creamy tan, slightly raised infarct. Note the absence of hyperemia in the border region—the infarct is 24 to 36 hours old. An older infarct can be seen in the septum. **C.** An older infarct dated 36 to 72 hours showing hyperemic areas (*arrowheads*) surrounding the subendocardial infarct (age 3 days) with a paler area in the outer half of the posterior wall of the left ventricle (infarct extension). The more recent infarct involves the posterior portion of the ventricular septum and the posterior wall of the right ventricle (36-48 hours). **D.** Gross photograph of a heart slice close to the base of the heart shows a 1-week-old acute transmural myocardial infarct involving the posterolateral wall of the heart. Note the marked pale region in the inner two-thirds of the infarct, with surrounding prominent hyperemic zone (*arrows*). Also present is a healed transmural myocardial infarct involving the posterior wall and posteroseptal region of the heart. The patient died in severe congestive heart failure. **E.** Gross photograph of a transmural healing myocardial infarct involving the septum and anterior and lateral walls of the left ventricle in an apical slice of the heart. Note the depressed, gelatinous appearance (*arrow*) of the infarct, which is 3 weeks old. Focal areas of scarring can be seen (*arrowheads*). Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

LIGHT MICROSCOPIC FINDINGS IN NONREPERFUSED INFARCTION

The earliest morphologic characteristic of MI that can be discerned and observed between 12 and 24 hours after onset of chest pain is the hypereosinophilic myocyte (Fig. 37–10). Despite the hypereosinophilia of the cytoplasm, which is seen best on routine hematoxylin and eosin staining, the myocyte striations appear normal, and some chromatin condensation may be seen in the nucleus. The area of infarction may show interstitial edema; however, this change is difficult to appreciate in human autopsy hearts and better appreciated in animal experiments. It has been suggested in experimentally induced infarction that the appearance of "wavy fibers" may be the earliest change and is thought to be the result of stretching of the ischemic noncontractile fibers by the adjoining viable contracting myocytes. Wavy fiber change is, however, nonspecific and occurs in the absence of ischemia, especially in the right ventricle. Neutrophil infiltration is present by 24 hours at the border areas. As the infarct progresses between 24 and 48 hours, coagulation necrosis is established with various degrees of nuclear pyknosis, early karyorrhexis, and karyolysis. The myocyte striations are preserved, and the sarcomeres elongate. The border areas show prominent neutrophil infiltration by 48 hours (see Fig. 37–10).

At 3 to 5 days, the central portion of the infarct shows loss of myocyte nuclei and striations; in smaller infarcts, neutrophils invade within the infarct and fragment, resulting in more severe karyorrhexis (nuclear dust). Loss of myocyte striations is best appreciated by using the Mallory trichrome stain. Markers of ischemia include hypoxia-inducible factor-1 and cyclooxygenase-2, which can be demonstrated immunohistochemically.[42] The influx of inflammatory cells, including mast cells, induces a cascade of chemokines, which suppress further inflammation and result in scar tissue.[84,85] Macrophages and fibroblasts begin to appear in the border areas. By 1 week, neutrophils decline, and granulation tissue is established with neocapillary invasion and lymphocytic and plasma cell infiltration. Although lymphocytes may be seen as early as 2 to 3 days, they are not prominent in any stage of infarct evolution. Eosinophils may be seen within the inflammatory infiltrate but are only present in 24% of infarcts.[86] There is phagocytic removal of the necrotic myocytes by macrophages, and pigment is seen within macrophages.

By the second week, fibroblasts are prominent, but their appearance may be seen as early as day 4 at the periphery of the infarct. There is continued removal of the necrotic myocytes as the fibroblasts are actively producing collagen and angiogenesis occurs in the area of healing. The healing continues, and depending on the extent of necrosis, the healing may be complete as early as 4 weeks or may require 8 weeks or longer to complete (see Fig. 37–10). The central area of infarction may remain unhealed, showing mummified myocytes for extended periods even though the infarct borders are completely healed. For this reason, it is important to evaluate the age of the infarct by examining the border areas that adjoin the noninfarcted muscle.

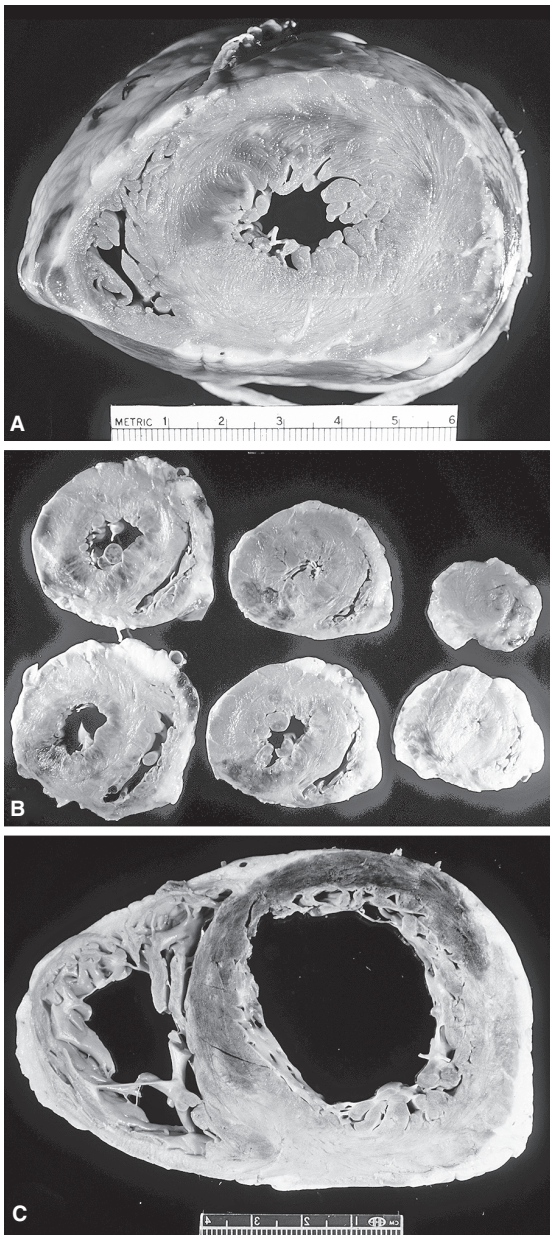

FIGURE 37–9. A. A 47-year-old man presented with unstable angina that evolved into a Q-wave infarct. On catheterization, he had a total occlusion of the left anterior descending coronary artery and severe stenosis of the right and left circumflex coronary arteries. The patient underwent emergency bypass graft to all three vessels. He died secondary to refractory arrhythmias on the third hospital day. Note subendocardial hyperemic region in the anteroseptal wall of the left ventricle. **B.** The patient presented with acute myocardial infarction of 6 hours in duration, received streptokinase in the emergency room, and died 2 days after successful reperfusion of a cerebral bleed. Note that a hemorrhagic transmural infarct involves the posteroseptal wall of the left ventricle, extending from the base to the apex of the heart with approximately 20% to 25% of the myocardium infarcted. **C.** A 60-year-old man admitted with onset of chest pain while mowing the lawn. He did not seek medical treatment until 8 hours after onset of chest pain. The patient received streptokinase, developed arrhythmias, was treated with lidocaine, went into cardiogenic shock, and died 3 days after infarction. Note the transmural confluent hemorrhagic infarct of the anteroseptal wall of the left ventricle involving at least 40% of the left ventricle. Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

The magnitude of repair and healing depends not only on the infarct size but also on local and systemic factors. If there is good collateral blood flow locally, healing will be relatively rapid, especially at the lateral borders where viable myocardium interdigitates with necrotic myocardium. There may be various levels of healing within an infarct, because of differences in blood flow in adjoining vascular beds caused by variable extent of coronary narrowing. The border areas may show hemorrhage and contraction band necrosis, depending on regional variations in blood flow. Systemic factors that influence repair of myocardium are the systemic blood pressure and cardiac output, which are severely decreased in the hearts of patients with multisystem failure.

LIGHT MICROSCOPIC APPEARANCE OF REPERFUSED ACUTE MYOCARDIAL INFARCTION

In dogs, the amount of myocardium that can be salvaged depends on the duration of total occlusion of the artery supplying the area of infarction. The maximal salvage is possible, both in dogs and humans, if the artery is opened within 6 hours. The myocardium in dogs after 90 minutes of occlusion followed by reperfusion and sacrifice at 24 hours shows a hemorrhagic infarct limited to the area of occlusion, which is subendocardial in extent. Hemorrhage occurs when the myocardial blood flow during the occlusion period is less than one-fifth of normal. The myocytes are thin, hypereosinophilic, and devoid of nuclei or showing karyorrhexis, with ill-defined borders and interspersed areas of interstitial hemorrhage. There is a diffuse but mild neutrophil infiltration. Within 2 to 3 days, macrophage infiltration is obvious, and there is phagocytosis of necrotic myocytes and early stages of granulation tissue. The infarct healing in dogs is more rapid than that in humans, most likely a result of nondiseased adjoining coronary arteries (collaterals) and a lack of underlying myocardial disease. In humans with acute MI, there is often chronic ischemia secondary to extensive atherosclerotic disease.

In man, if reperfusion occurs within 4 to 6 hours after onset of chest pain or electrocardiographic (ECG) changes, there is myocardial salvage, and the infarct is likely to be subendocardial without transmural extension. There will be a nearly confluent area of hemorrhage within the infarcted myocardium, with extensive contraction band necrosis. The extent of hemorrhage depends on the extent of reperfusion of the infarct, as well as the extent of capillary necrosis. The larger the infarct and the longer the duration of the infarct, the greater is the hemorrhage. The degree of hemorrhage may be variable and nonuniform because blood flow depends on the residual area of coronary narrowing and the amount of thrombolysis. Within a few hours of reperfusion, neutrophils are evident within the area of necrosis, but they are usually sparse (Fig. 37–11). In contrast to nonreperfused infarcts, neutrophils do not show concentration at the margins. However, reperfused infarcts often demonstrate areas of necrosis at the periphery with interdigitation with noninfarcted myocardium. Macrophages begin to appear by day 2 or 3, and stromal cells show enlarged nuclei and nucleoli by days 3 and 4 (see Fig. 37–11). Neutrophil debris, which may be concentrated at the border areas in cases of incomplete reperfusion, is seen by 3 to 5 days. Fibroblasts appear by days 3 to 5, with an accelerated rate of healing compared with nonreperfused infarcts. By 1 week, there is collagen deposition with disappearance of neutrophils and prominence of macrophages containing pigment derived from ingested myocytes (see Fig. 37–11). Angiogenesis is prominent, and lymphocytes are often seen. Infarcts at 5 to 10 days are more cellular, and there is prominent myocytolysis (loss of myofibrils). As early as 2 to 3 weeks, subendocardial infarcts may be fully healed (see Fig. 37–11). Five to 10 layers of subendocardial myocytes are spared without necrosis. However, myofibrillar loss, which is a result of ischemia not severe

TABLE 37–1. Gross and Microscopic Evolution of Reperfused and Nonreperfused Acute Myocardial Infarction

	Permanent Occlusion/No Reperfusion		Reperfusion After Occlusion	
Time of Occlusion	Gross	Histologic	Gross	Histologic
12 h	No change or pallor	Wavy fibers	Mottled, prominent hemorrhage	CBN
24-48 h	Pallor to yellow, soft	Hypereosinophilic fibers, PMNs at borders	Prominent hemorrhage	Hypereosinophilic fibers + CBN + PMNs + hemorrhage throughout
3-5 d	Yellow center, hyperemic borders	Large number of PMNs at border, coagulation necrosis, loss of nuclei	Prominent hemorrhage	Aggressive phagocytosis profuse fibroblast infiltration + collagen
6-10 d	Yellow, depressed central infarct, tan-red margins	Mummified fibers in center, macrophage phagocytosis + granulation tissue at borders	Depressed red-brown infarct with gray-white intermingled	Aggressive healing with greater collagen
10-14 d	Gray-red borders, infiltrating central tan-yellow infarct if large	Marked granulation tissue, collagen deposition, subendocardial myocyte sparing	Gray-white intermingled with brown	Aggressive healing with greater collagen
2-8 wk	Gelatinous to gray-white scar, greater healing at border zone	Collagen deposition with prominent large capillaries	White intermingled with groups of myocytes with red myocardium	Collagen intermingled with groups of myocytes

CBN, contraction band necrosis; PMN, polymorphonuclear cell.

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enough to cause cell death, is prominent in this subendocardial zone. Larger infarcts and those reperfused after 6 hours take longer to heal. Infarcts reperfused after 6 hours show larger areas of hemorrhage compared with occlusions of shorter duration and more immediate reperfusion (see Fig. 37–9). However, myocytes maintain their striations and become stretched and elongated, and because they do not respond to calcium influx, they do not show significant contraction band necrosis. Even though reperfusion should occur within 6 hours of occlusion for maximal myocyte salvage, there appears to be some benefit in opening an artery regardless of the duration of coronary occlusion.

IN VIVO PATHOLOGY OF MYOCARDIAL INFARCTION

Histologic evaluation has been classically considered the gold standard for the evaluation of myocardial tissue. However, it is poorly suited for serial measurements into the required follow-up clinical field. Conversely, several imaging modalities have been developed for the in vivo characterization of the heart, including PET, single-photon emission computed tomography (SPECT),[87] and computed tomography (CT).[88] However, the noninvasive technique of cardiac magnetic resonance (CMR) has captured most of the attention in preclinical and clinical arenas because it offers a combination of high spatial resolution and high soft tissue contrast with no ionizing radiation.[89] In fact, CMR is able to perform in vivo tissue characterization, which is considered a surrogate for histologic evaluation.

Testing the efficacy of cardioprotective therapies in clinical and preclinical trials benefits from measuring both infarct size and area at risk to calculate the amount of myocardial salvage. By subtracting infarct size from area at risk (the so-called *salvaged index*), it can better quantify the efficacy of a therapy (ie, proportion of potential myocardial loss = area at risk that finally is salvaged).[41,90] CMR has become the in vivo gold standard for quantifying salvage myocardium. Depiction and quantification of area at risk by CMR rely on the concept that the entire area at risk shows an edematous reaction, regardless of the outcome (death or salvage) of the tissue. Hyperintense areas on qualitative T2-weighted CMR imaging have been classically proposed as having a good correlation with post-MI edema and, thus, with area at risk.[91] However, it is still a matter of controversy whether these hyperintense areas can accurately track the real area at risk.[92,93] Newer quantitative CMR methods such as T1 and T2 mapping, which allow actual tissue characterization by measuring intrinsic tissue properties in the form of T1 and T2 relaxation times, respectively, may overcome some of the limitations of qualitative CMR imaging, providing accurate measures of tissue properties,[94] including post-MI edema (Fig. 37–12).[95,96] Indeed, infarct core T1 values have been inversely associated with adverse remodeling and outcomes after MI.[97]

It has been assumed for a long time that, in the context of MI, myocardial edema appears early after ischemia/reperfusion and persists in a stable form for at least 1 week.[98,99] This notion set the basis for the retrospective evaluation of area at risk during this time window. However, the accepted evolution of post-MI edema has been recently challenged using reference histologic and CMR imaging techniques in a human-like preclinical MI model suggesting that the postinfarction edematous reaction is not stable, but rather follows a bimodal pattern.[95,100] An initial wave of edema appears abruptly upon reperfusion and dissipates at 24 hours and is a result of reperfusion itself, whereas a deferred wave of edema appears several days after MI, increasing to a maximum on postreperfusion day 7. The latter second wave of postinfarction edematous reaction is a result of early healing processes (Fig. 37–13).[101] Nonreperfused hearts exhibit different dynamics of the bimodal edema phenomenon, with a delay in healing.[101] This novel finding has important biologic, diagnostic, prognostic, and therapeutic implications.

Macroscopic scar fibrosis after MI can be accurately detected and quantified by delayed enhancement sequences both in CMR and CT,[102] with its size and distribution being well correlated with

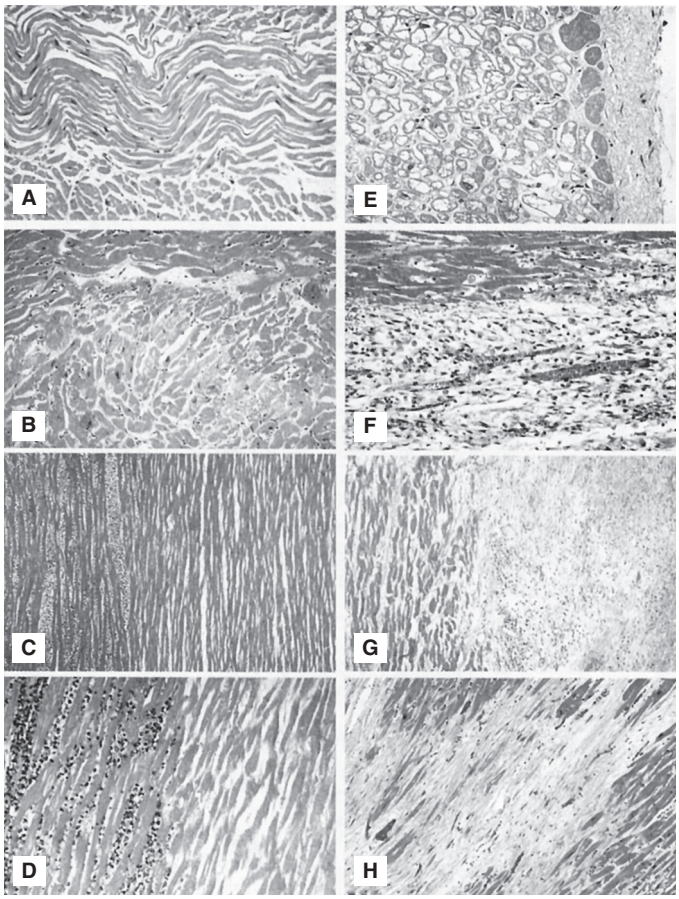

FIGURE 37–10. Histologic characteristics of myocardial infarction (MI) after total occlusion of a coronary artery. **A.** The earliest change seen is within 12 hours after the onset of chest pain and has been described as wavy fibers with elongation of myocytes and narrowing of the myocyte diameter. **B.** Hypereosinophilic myocyte fibers representing early features of coagulation necrosis can be seen between 12 and 24 hours after onset of chest pain, the nucleus is intact, and the cross-striations are well seen. **C.** By 48 to 72 hours, the neutrophils are now concentrated at the border of the infarcted and viable myocardium, and the extent of neutrophil infiltration depends on the collateral flow as well as the extent of coronary perfusion of the adjacent bed. The central zone of infarction now shows all the features of coagulation necrosis with karyolysis and loss of cross-striations. **D.** Photomicrograph showing a high-power view of the border zone of a 5-day-old infarct with marked neutrophil infiltration that has undergone karyopyknosis and karyorrhexis. The adjoining infarcted myocardium shows coagulation necrosis with loss of nuclei and cross-striations. **E.** A high-power view of the subendocardial region, which is usually ischemic but viable, showing myocyte vacuolization and loss of myofibrils. **F.** Almost complete removal of the necrotic myocardium. Note the presence of neovascular channels and surrounding macrophages and few lymphocytes (granulation tissue) at 7 to 10 days after acute MI. **G.** The infarct is heavily infiltrated with fibroblasts with early collagen deposition and interspersed neocapillaries and few lymphocytes (infarct age, 3-4 weeks). **H.** A fully healed infarct with dense collagen and few interspersed myocytes at the border region of the healed infarct. The infarct age may be 6 weeks or older. Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

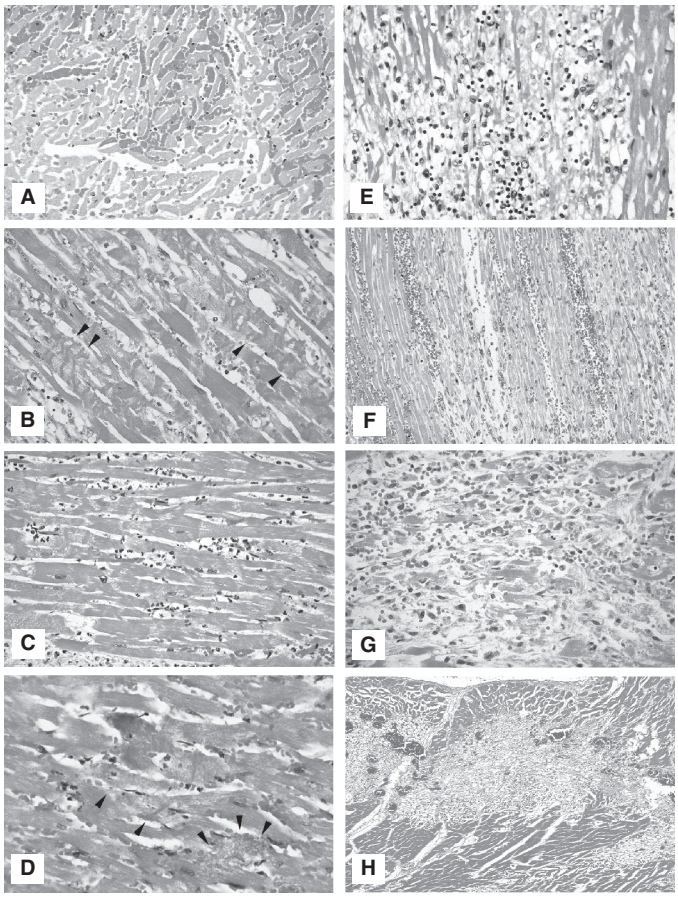

FIGURE 37–11. Histologic characteristics of a reperfused infarct after occlusion and reperfusion either with thrombolysis (tissue plasminogen activator [tPA], streptokinase, or glycoprotein IIb/IIIa) or balloon angioplasty with or without stenting or surgical revascularization. **A.** A cross-section of myocytes shows necrosis with interstitial hemorrhage. Note the pale myocyte nuclei and very early neutrophil infiltration. **B.** Myocytes cut longitudinally in a patient who was admitted with chest pain of 2 hours in duration followed by infusion of streptokinase. The patient died within 6 hours. Note the extensive contraction band necrosis (dark bands alternating with lighter bands, *arrowheads*), a hallmark of reperfusion injury. There are interstitial red cells and a few neutrophils, which were scattered throughout the infarct. **C.** Note that the number of neutrophils is greater than the previous example. There is mild red blood cell extravasation and contraction band necrosis. The duration of chest pain was 3 hours before reperfusion, and the patient died 24 hours later. **D.** It is common to see single or a few necrotic myocytes with calcification (*arrowheads*) in patients with reperfused infarcts. **E.** Note the presence of macrophages and lymphocytes with early dissolution of the necrotic myocytes. These areas of necrosis are interdigitating with viable noninfarcted myocardium (4- to 5-day-old reperfused infarct). **F.** Note the interstitial hemorrhage and infiltrating macrophages seen in the lower fifth and right third of the photomicrograph. **G.** High-power view of another infarct showing dissolution of the infarct and replacement with macrophages and early angiogenesis. Hemorrhage is still present, but no neutrophils are seen (5- to 7-day-old infarct). **H.** Low-power view of a healing infarct at 7 to 10 days; note angiogenesis and early replacement fibrosis. Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

remodeling and prognosis.[102-105] In addition, evaluation of delayed enhancement may facilitate the study of scarring-related ventricular arrhythmias after MI.[106] Conversely, conventional delayed gadolinium enhancement CMR sequences are less suitable for in vivo detection of microscopic fibrosis as a result of smaller collagen deposits, as occurs in the remote myocardium.[107,108] However, relying on quantification of the T1 relaxation times in remote myocardial areas before (native T1)[109] and after contrast enhancement equilibrium (myocardial extracellular volume fraction),[107] CMR can provide noninvasive prognostic information associated with left ventricular remodeling and cardiac events after MI.[109]

Finally, novel noninvasive imaging methods such as CMR, SPECT, or PET, using targeted imaging agents, allow imaging of the molecular processes underlying the post-MI immune cell response[110] and subsequent remodeling.[111] These probes can target apoptosis, necrosis, inflammatory cells, angiogenesis, and extracellular matrix and have

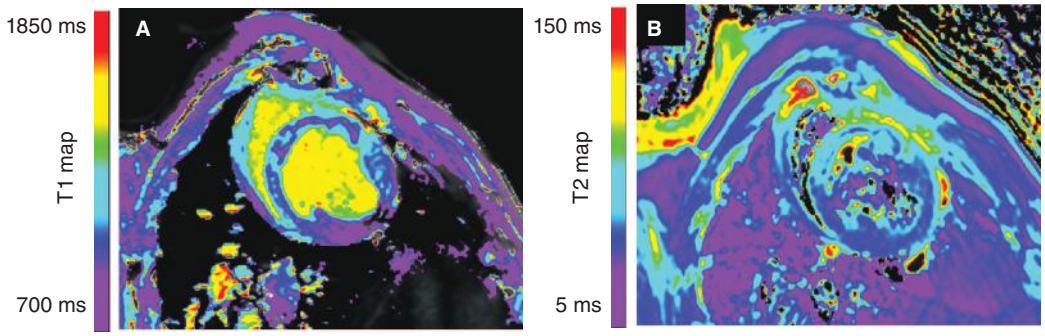

FIGURE 37–12. Measurement of intrinsic tissue properties by cardiac magnetic resonance in the form of T1 mapping (**A**) and T2 mapping (**B**) in a pig model of myocardial ischemia/reperfusion. Note abnormal T1 and T2 relaxation times over anterior ventricular wall 1 week after myocardial infarction. Reproduced with permission from Fernández-Jiménez R, Fernández-Friera L, Sánchez-González J, et al: Animal Models of Tissue Characterization of Area at Risk, Edema and Fibrosis. *Curr Cardiovasc Imaging Rep*. 2014;April;7:9259.

been assessed in preclinical models. However, translating this work to the patient in a cost-effective, clinically beneficial manner remains a significant challenge.[112]

MYOCARDIAL REMODELING AFTER MYOCARDIAL INFARCTION

Myocardial remodeling is defined as changes in size, shape, and function of the heart occurring secondary to molecular, cellular, and interstitial events after MI. Left ventricular remodeling begins within the first few hours after an infarct and continues to progress, and the infarcted myocardium undergoes rapid turnover during the first 1 to 2 weeks after MI. Myocardial remodeling is influenced by both the severity of the infarct and recurrent infarction.

MI generates a systemic inflammatory response, with activation of the complement cascade, transforming growth factor-β, and chemokines and free radical generation. In the first 24 hours of reperfusion,

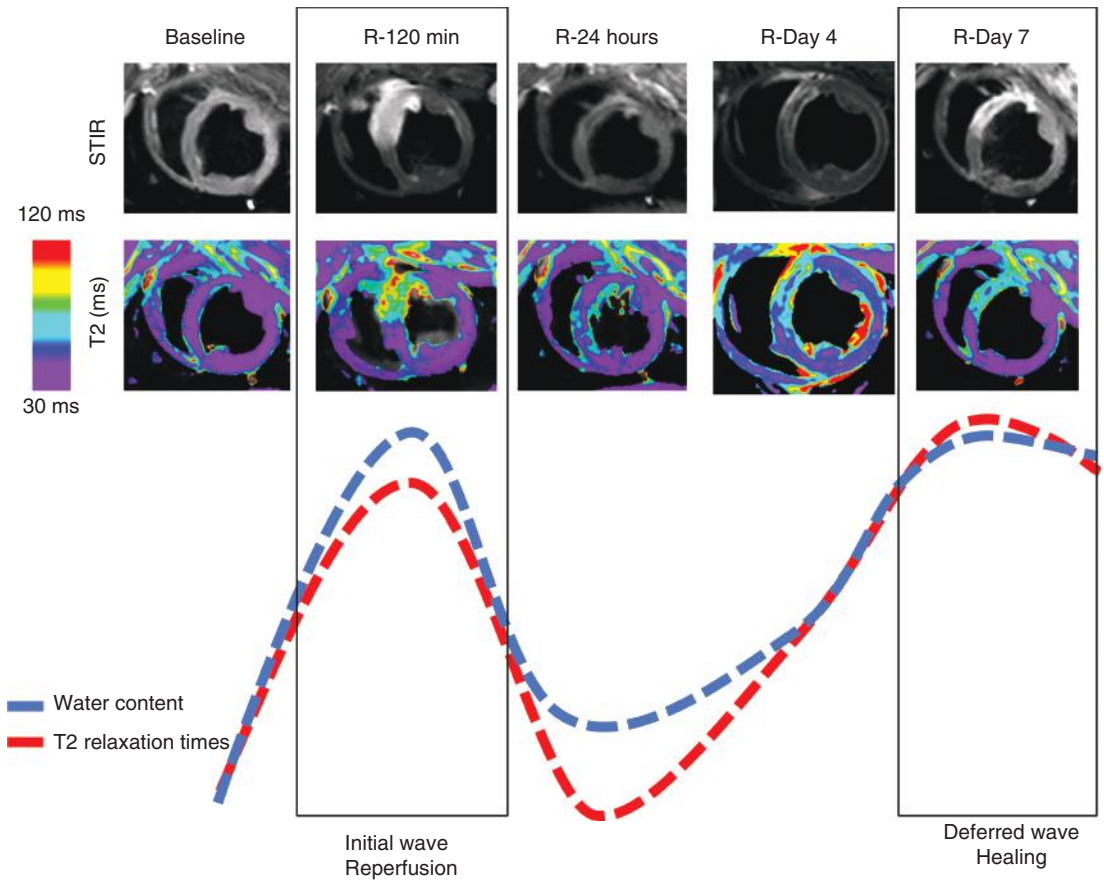

FIGURE 37–13. Parallel courses of cardiac magnetic resonance (CMR) fluctuations (*dashed red line*) and histologically determined edema (*dashed blue line*). *Dashed red line* represents post–myocardial infarction (MI) time course of absolute T2 relaxation time values (in milliseconds) in the ischemic myocardium during the first week in a preclinical model of ischemia/reperfusion. The top of the panel shows representative images from a pig that underwent 40-minute to 7-day ischemia/reperfusion with CMR T2-weighted short-tau inversion recovery (STIR) and T2-mapping examinations at all time points. Hyperintense areas in STIR imaging are suggestive of edema. All T2 maps were scaled between 30 and 120 milliseconds. Reproduced with permission from Fernández-Jiménez R, Sánchez-González J, Agüero J, et al: Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: imaging and histological tissue characterization. *J Am Coll Cardiol*. 2015 Feb 3;65(4):315-323.

neutrophils, monocytes, and lymphocytes infiltrate the myocardium, and resident mast cells release preformed mediators that initiates the cytokine cascade. Cytokine-stimulated myocytes in the ischemic border zone, expressing intercellular adhesion molecule-1, may be susceptible to neutrophil-mediated cytotoxic injury. During the healing phase, infiltrating monocytes differentiate into macrophages, which, along with mast cells accumulate in the healing scar, inducing fibroblast proliferation. Classically activated M1 macrophages are the first line of defense that influence the subsequent phase of the healing process by M2 macrophages. The prolonged presence of M1 macrophages extends the proinflammatory environment and causes expansion of the infarcted area. A delayed transition to M2 macrophages thus hampers the formation of scar tissue, predisposing to heart failure development as a result of expansion of the injured ventricular wall (negative remodeling). Improved healing may be attained by modulating macrophage polarization toward the M2 phenotype, thus promoting the resolution of inflammation and improved infarct healing.[113] The differentiation of M1 to M2 requires the presence of T regulatory cells and stimulator of cytokine signaling-1, whereas for M1, polarization occurs in the presence of interferon regulator factor-5, collapsing response mediators-2, and stimulator of cytokine signaling-3. Additionally, in studies where M2 polarization has been enhanced, resolution of inflammation has been observed, with early infarct healing resulting in the prevention of negative remodeling.[113] Monocytes are recruited from the spleen and further differentiate at the injury site, as has been shown in animal models. Patients with acute MI show a higher splenic metabolic activity, as determined by whole-body fluorine-18–fluorodeoxyglucose PET-CT,[114] similar to that described in mice.[115]

COMPLICATIONS OF MYOCARDIAL INFARCTION

The complications of MI may manifest immediately or may appear late and depend on the location and extent of infarction. The acute complications consist of arrhythmias and sudden death, cardiogenic shock, infarct extension, fibrinous pericarditis, cardiac rupture (including papillary muscle rupture), and mural thrombus and embolization.

ARRHYTHMIAS AND SUDDEN DEATH

Arrhythmias after MI are varied and include atrial arrhythmias, ventricular arrhythmias (the major source of sudden death), and conduction system disturbances. Almost 90% of patients develop a cardiac rhythm abnormality after acute infarction.

Atrial fibrillation occurs in approximately 5% to 10% of patients after infarction, especially in older patients with heart failure,[116] and is associated with increased risk of mortality in MI patients.[117] Adequate rate control is important to reduce myocardial oxygen demand and to improve cardiac performance and can be performed by administration of β-blockers, digoxin, or amiodarone. Urgent cardioversion may be considered in patients presenting with hemodynamic instability.[118,119]

Ventricular tachyarrhythmias that occur after reperfusion period may be a manifestation of a serious underlying condition, such as continuing myocardial ischemia, heart failure, altered autonomic tone, hypoxia, and electrolyte and acid-base disturbances. Ventricular fibrillation occurs in approximately 4.5% of patients, with the greatest incidence in the first hour.[120] Sudden death occurs in 25% of patients after MI, often before patients reach the hospital. The proportion of deaths from ischemic heart disease that are sudden is almost 60%.

The long-term prognostic significance of early (< 48 hours) ventricular fibrillation or sustained ventricular tachycardia in patients with acute MI is still controversial. Ventricular arrhythmias are important markers of electrical instability and are helpful in predicting patients who will die suddenly after MI.[121] Several types of tachyarrhythmias are associated with decreased survival, including subacute and late premature ventricular complexes, nonsustained ventricular tachycardia of late onset, and sustained monomorphic ventricular tachycardia in the acute post-MI phase. Early mortality is higher when ventricular fibrillation occurs in the acute phase after infarction, but if the patient survives, long-term prognosis is unaffected.[122] The early administration of β-blockers in the context of acute MI and no contraindications seem to reduce the burden of ventricular arrhythmias.[123-126]

The mechanism of postinfarct arrhythmias involves the adjoining ischemic but noninfarcted myocardium. In this acidotic arrhythmogenic zone, there is the release of metabolites such as potassium, calcium, and catecholamines, with low levels ATP and hypoxemia. Later in the course of MI, arrhythmias may occur as a result of scar tissue surrounding viable myocytes.[127] Experimental data suggest an association between sodium (Na^+) channel loss of function and sudden cardiac death. An effect of oxidative stress on Na^+ channel function has been postulated to play a role in postinfarct arrhythmias. Na^+ channel dysfunction may involve lipid peroxidation.[128]

Arrhythmias in the remodeled ischemic myocardium evolve from sites of slow conduction near the border zone, which is characterized by rate-dependent slowing and reentry. It is believed that blockade of the Na^+ channel is responsible for this slowing because cells of the epicardial border zone show postrepolarization refractoriness, a key requirement for the initiation of ischemia-related ventricular tachycardia.

Emerging clinical imaging techniques are being used to measure areas at risk for arrhythmias. Infarct surface area and mass, as measured by cardiac magnetic resonance imaging (MRI), are better identifiers of patients who have a substrate for inducible ventricular tachycardia than left ventricular ejection fraction.[129-131] The extent of the peri-infarct zone measured by MRI is correlated with the risk of arrhythmias.[129-131] The role of adrenergic imbalance in the generation of arrhythmias associated with acute coronary syndromes has been emphasized.[129]

After acute infarction, 25% of patients experience a cardiac conduction disturbance within 24 hours. Bradyarrhythmias during the first few hours of acute MI are triggered by inferior MI and are usually benign, with conduction disease beyond the first 24 hours requiring the most attention. Conduction disturbances (right bundle branch block and left anterior fascicular block) resulting from anterior MI are associated with higher mortality because of necrosis of the conduction system.

CARDIOGENIC SHOCK

Heart failure after MI ranges from pulmonary congestion to profound organ hypoperfusion or cardiogenic shock. Cardiogenic shock is caused by decreased systemic cardiac output in the presence of adequate intravascular volume. Cardiogenic shock after MI usually occurs if there is loss of at least 40% of the left ventricular mass, either acutely or in combination with scarred myocardium from old healed infarcts.[132,133] In approximately 10% of patients who develop cardiogenic shock, shock occurs before hospitalization immediately upon presentation. Much more commonly, shock develops while the patient is in the hospital, presumably from infarct extension (Fig. 37–14A). Cardiogenic shock accounts for almost half of the short-term deaths after MI. The remainder of deaths are the result of cardiac rupture and arrhythmias. Patients with extension of infarction (reinfarction) into subendocardial zones remote from the larger infarct may develop cardiogenic shock (Fig. 37–14B). In turn, cardiogenic shock renders

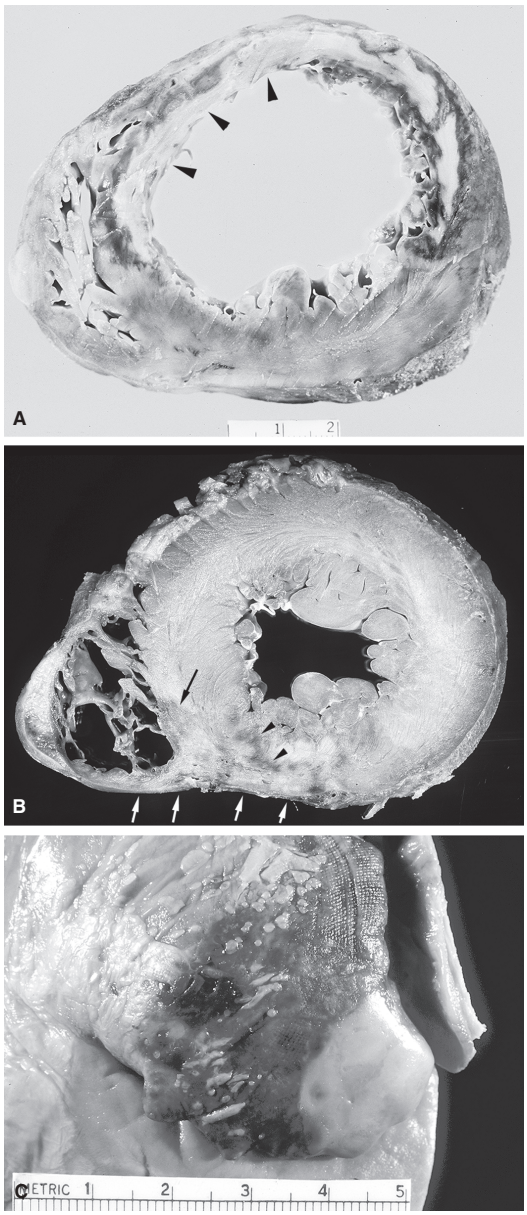

FIGURE 37–14. A. A 54-year-old man with history of acute myocardial infarction (MI) had an anteroseptal transmural MI. On day 3, the patient went into severe congestive heart failure and died on day 10. Note the markedly thinned transmural anteroseptal infarct (*arrowheads*) involving 60% of the basal slice of the heart. The anteroseptal region shows infarct expansion. **B.** A 47-year-old man presented with chest pain, elevated creatine kinase (CK) and creatine kinase myocardial band (CK-MB), and a non–Q-wave MI involving the posterior wall of the left ventricle on electrocardiogram (ECG). The patient had an uneventful hospital course with cardiac enzymes (CK-MB) falling close to baseline. On hospital day 3, he developed another episode of chest pain with an increase in cardiac enzymes and new ECG changes of ST-segment elevation in precordial leads. The patient was diagnosed with infarct extension and right ventricular infarction. The ventricular slice shows an older subendocardial infarct with hyperemic border (*arrowheads*) and a more recent infarction involving full thickness of the posterior wall and portion of the ventricular septum of the left ventricle with extension into the posterior wall of the right ventricle (*arrows*). **C.** A 51-year-old man presented with chest pain of longer than 24 hours in duration. A diagnosis of acute MI involving the inferior wall of the left ventricle and a right atrial infarction was made. Note the hemorrhagic right atrial border and that the tip is pale and dusky; the surface shows fibrin deposits on the pericardial surface. Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

the remaining viable myocardium prone to ischemic necrosis because of poor perfusion. In patients presenting with cardiogenic shock, transthoracic (and transesophageal if necessary) echocardiography is mandatory to exclude mechanical complications and to evaluate left ventricular ejection fraction and right ventricular function. Management of cardiogenic shock includes medical therapy with inotropic (dobutamine) and/or vasopressor agents (norepinephrine), mechanical circulatory support, and emergent revascularization.[118,119]

Two related but distinct complications of MI are infarct extension and infarct expansion, or remodeling (see the Evolution of Myocardial Infarction section). Infarct extension results from an incremental increase in absolute necrotic myocardium and may be the result of infarction remote from the original infarct in either the right or left ventricle (see Fig. 37–14). Infarct extension usually occurs between 2 and 10 days after infarction, at a time when ECG changes are evolving and the troponin I or T is still high. However, the rapidly decreasing serum creatine kinase myocardial band (CK-MB) after the first 24 hours may be useful for the detection of infarct extension along with new Q wave on ECG. The risk factors associated with infarct expansion are cardiogenic shock, subendocardial infarct, female gender, and previous infarcts.

CARDIAC RUPTURE

Left ventricular free wall rupture results in cardiac tamponade, and if there is prolonged survival, pseudoaneurysm formation. The incidence of rupture of the left ventricular free wall is between 10% and 20%; patients with first infarct have a rate of approximately 18%.[134] In contrast, rupture of the ventricular septum is only 2%.[134] Left ventricular wall rupture is much more common than right ventricle rupture. Although reperfusion therapy has reduced the incidence of cardiac rupture, late thrombolytic therapy may increase the risk of cardiac rupture (Fig. 37–15).

Factors associated with cardiac rupture include female gender, age older than 60 years, hypertension, and first MI. Additional risk factors include multivessel atherosclerotic disease, absence of ventricular hypertrophy, poor collateral flow, transmural infarct involving at least 20% of the wall, and location of the infarct in the mid anterior or lateral wall of the left ventricle.[134] Transthoracic echocardiography is a fast and sensitive test for the diagnosis; contrast echocardiography also has been suggested.[135]

Defective cardiac remodeling, involving matrix metalloproteinases and the extracellular matrix, may predispose the heart for rupture. In addition to surgery, management includes hemodynamic monitoring, β-blockers, and angiotensin-converting enzyme inhibitors in select cases.[136]

Cardiac rupture usually occurs within 1 to 4 days after the infarct, which is when coagulation necrosis and neutrophilic infiltration are at their peak and have weakened the left ventricular wall. However, at least 13% to 28% of ruptures occur within 24 hours of onset of infarction when inflammation and necrosis are not prominent.[134] Infarcts with rupture contain more extensive inflammation and are more likely to demonstrate eosinophils compared with nonruptured infarcts.[137] Rupture most frequently occurs at the border of the infarcted region with the viable myocardium. Ruptures usually are not seen beyond 10 days after healing occurs. However, ruptures in infarcts with healing generally occur in the center of the infarct, unlike earlier ruptures (see Fig. 37–15). Nearly half the deaths from cardiac rupture occur as out-of-hospital sudden deaths and therefore are never seen by a clinician. The mortality rate in the prethrombolytic era was extremely high, with 50% mortality in surgically treated patients and 90% mortality in medically treated patients. Surgical options include both open procedures and percutaneous seals.[138]

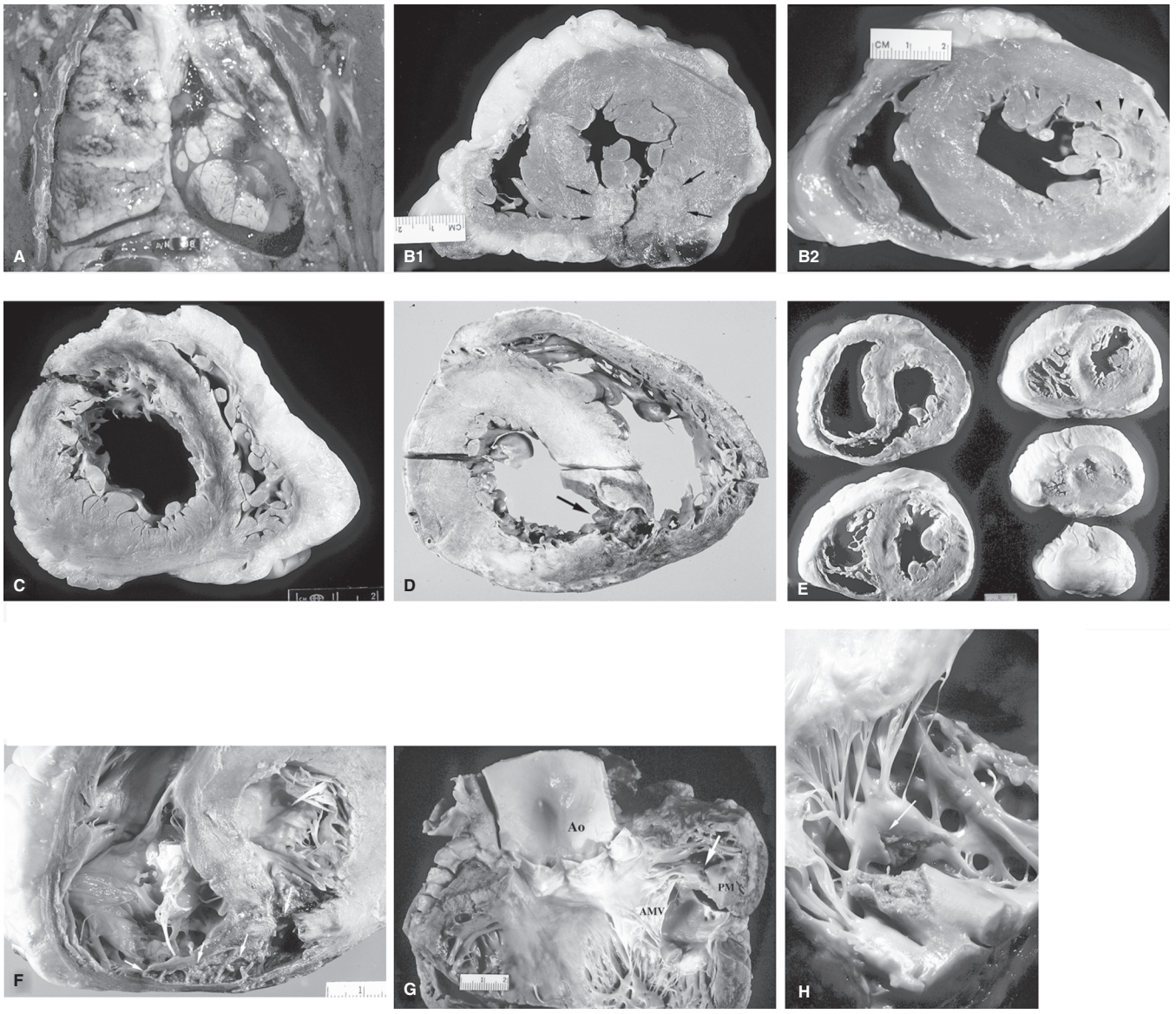

FIGURE 37–15. Ruptured acute myocardial infarction (MI). **A.** Hemopericardium in a 70-year-old man with history of chest pain and diagnosis of acute transmural infarction who died suddenly while walking to the bathroom 24 hours after admission. **B1.** The pericardium contained 300 mL of blood, and a rupture site was identified on the posterior wall of the left ventricle. Note the early transmural infarct (pale area on the posterior wall [*arrows*]) with the rupture site close to the viable myocardium but within the infarct zone. **B2.** A lateral wall rupture. Note that the rupture site is close to the viable and infarcted myocardium (*arrowheads*). **C.** A 50-year-old man presented with chest pain of 7 hours in duration. He received streptokinase and underwent balloon angioplasty of the proximal left anterior descending coronary artery. At autopsy, the patient had hemopericardium and a transmural hemorrhagic reperfused infarct that involved the anteroseptal wall of left ventricle. The rupture occurred close to the viable myocardium on the anterior wall. **D.** Rupture of the posterior ventricular septum (*arrow*) 2 weeks after an acute MI. The patient died with severe congestive heart failure, and the diagnosis of ventricular septal rupture was clinically missed. (A four-chamber cut had been made before short-axis slicing.) **E.** Ventricular septal rupture involving the inferobasal portion of the heart, which extends through the posterior septum and into the right ventricle, causing a dissection of the posterior wall of the right ventricle. **F.** A high-power view of the inferobasal portion of the heart showing the rupture through the septum extending into the right ventricle and piercing the right ventricular wall (*arrow* along the rupture tract). **G.** A patient with transmural MI of the posterior wall of the left ventricle with rupture of one of the two heads of posteromedial (PM) papillary muscle (*arrow*). The base of the heart has been opened along the left ventricular outflow tract. **H.** High-power view showing total severance of one of the papillary heads (*arrow*) of the posteromedial papillary muscle. Ao, aorta; AMV, anterior mitral leaflet. Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

Myocardial rupture, in addition to the free wall, may involve solely the papillary muscle or the ventricular septum. Ruptures of the ventricular septum are classified into simple or complex. Simple ruptures have a discrete defect and a direct through-and-through communication across the septum, are usually associated with anterior MI, and are located in the apex. Complex ruptures are characterized by extensive hemorrhage with irregular serpiginous borders of the necrotic muscle, usually occur in inferior infarcts, and involve the basal inferoposterior septum.[139] The diagnosis is confirmed by echocardiography. Intra-aortic balloon pump may stabilize patients in preparation for surgery. Mortality remains high in all patients, especially for those with inferobasal defects.[119] Percutaneous closure is a less invasive option that might allow for initial hemodynamic stabilization, but experience with this approach is limited.[118]

Rupture of papillary muscle is less common than septal or free wall rupture and may occur as a complication of small subendocardial or

larger transmural MIs. More than 80% of infarcts underlying papillary muscle rupture involve the posteromedial muscle, which has a single blood supply from the right coronary artery (see Fig. 37–15). Because the anterolateral papillary muscle has a dual blood supply from the LAD and the left circumflex coronary artery, it rarely undergoes isolated ischemic rupture. However, it may rarely rupture if there is a single supply via one diagonal branch. Patients with papillary muscle rupture present with sudden mitral regurgitation with variable severity. Pulmonary edema and cardiogenic shock may occur rapidly. Diagnosis is made by transthoracic and/or transesophageal echocardiography, including three-dimensional and transgastric imaging.[140] Treatment is based on afterload reduction if blood pressure allows, including intravenous diuretics, vasodilator/inotropic support, and intra-aortic balloon pump, which may stabilize patients in preparation for surgery. Operative mortality is high, but there is good long-term survival after operative repair.[141]

RIGHT-SIDED AND ATRIAL INFARCTION

Right ventricular infarction is a common complication of inferior transmural MI (see Fig. 37–14B). Its pathophysiology and clinical manifestations are distinctly different from those of left ventricular infarction. Necropsy studies demonstrate right ventricular infarction in 14% to 60% of patients who die with inferior left ventricular MI and is usually seen as a triad of findings consisting of inferior-posterior wall, posterior septum, and posterior right ventricular wall necrosis, which is contiguous, and, rarely, with anterolateral right ventricular wall extension.[142] It has been reported that 78% of right ventricular infarctions occurring in patients with inferior left ventricular infarcts had concomitant right ventricular hypertrophy.[143] Isolated right ventricular infarction may occur infrequently in the absence of coronary disease in patients with chronic lung disease and right ventricular hypertrophy.[144] Atrial infarction occurs in 10% of all left ventricular inferior wall infarcts and typically involves the right atrium.[145,146]

Right ventricular cardiogenic shock after acute infarction is associated with younger age, lower prevalence of previous infarctions, fewer anterior infarct locations, and less multivessel disease.[147] It frequently presents with the triad of hypotension, clear lung fields, and raised jugular venous pressure. ECG and echocardiography confirm diagnosis. Treatment is based on fluid loading, inotropic/vasopressor support, and emergency revascularization if not performed before. Mechanical circulatory support should be considered in suitable patients with refractory cardiogenic shock.

PERICARDIAL EFFUSION AND PERICARDITIS

Pericardial effusion is reported in 25% of patients with acute MI and is more common in patients with anterior MI, large infarcts, and congestive heart failure.[148,149] Pericardial effusion secondary to acute MI may occur as a transudative effusion or as an exudate in association with acute pericarditis. Importantly, the diagnosis of left ventricular rupture should be considered until proven otherwise in patients with moderate to severe pericardial effusion early after MI.[150,151]

MI-associated pericarditis is a common cause of chest pain after MI, with its frequency depending on how it is defined. The incidence of acute pericarditis after MI has decreased with reperfusion therapy.[152] Pericarditis occurs less often than pericardial effusion and is seen only in patients with transmural acute MI. Pericarditis, in contrast to postinfarction effusions, may be localized to the area of necrosis and is accompanied by chest pain. Pericardial involvement is related to the infarct size and is associated with poor prognosis. CMR has emerged as an accurate imaging modality to assess post-MI pericardial injury.[153,154] Pericarditis consists of fibrin deposition in addition to inflammation and may be present from day 1 after infarction to as late as 6 weeks after infarction. Pericardial effusion after MI usually takes several months to reabsorb. Anticoagulation should be discontinued in the presence of a significant (≥ 1 cm) or enlarging pericardial effusion.

Postinfarction syndrome (Dressler syndrome) consists of pleuropericardial chest pain, friction rub, fever, leukocytosis, and pulmonary infiltrates; occurs weeks to months after MI; and is often recurrent. Previously reported to occur in 3% to 4% of patients with MI, its incidence had been greatly reduced because of the extensive use of thrombolysis/primary percutaneous angioplasty and treatments that dramatically decrease the size of myocardial necrosis and modulate the immune system.[152,155]

CHRONIC CONGESTIVE HEART FAILURE

Patients with large acute MI and persistent ischemia are the most likely to develop heart failure. The occurrence of heart failure has long been recognized as a strong predictor of increased morbidity and mortality after MI. The therapeutic impact of renin-angiotensin system inhibition, early blockade, and aggressive reperfusion strategies has been investigated in a number of clinical trials.[156] Newer approaches, including inhibition of nitric oxide synthase and new mechanical support devices, may further decrease mortality rates, which nevertheless remain high.[157]

At autopsy, congestive heart failure is characterized by dilatation of both atria and the ventricles, which show either a large healed infarct (Fig. 37–16) or multiple smaller infarcts with or without a transmural scar.[158] Scarring of the inferior wall of the left ventricle often involves the posteromedial papillary muscle, which gives rise to mitral regurgitation, contributing to congestive heart failure (see Fig. 37–16).[158] Microscopically, the subendocardial regions of ischemia show myocytes with myofibrillar loss and that are rich in glycogen, suggesting a state of hibernation (see Hibernating Myocardium section).[159] It is sometimes difficult to differentiate ischemic cardiomyopathy from idiopathic dilated cardiomyopathy when infarcts are few and small and only one-vessel disease is present; in such situations, we tend to call this *idiopathic dilated cardiomyopathy with incidental coronary artery disease*.

TRUE AND FALSE ANEURYSMS

The overall incidence of left ventricular aneurysm is currently nearly 12%.[160] Angiographically, single-vessel disease, proximal LAD stenosis, total LAD occlusion, end-diastolic pressure, and left ventricular score are higher in patients who develop aneurysms after infarction, as compared to nonaneurysmal infarcts. By multivariate analysis, single-vessel disease, absence of previous angina, total LAD occlusion, and female gender are independent determinants of left ventricular aneurysm formation after anterior infarction.[161] Patients receiving reperfusion therapy and exhibiting a patent infarct-related artery have a lower incidence of aneurysm formation.[160]

A large acute transmural myocardial infarct that has undergone expansion is the most likely infarct that will result in a true aneurysm. The pulsatile force from the blood in the cavity stretches and thins the necrotic muscle, which heals, forming the wall of a true aneurysm. An aneurysm is defined clinically as a discrete, thinned segment of the left ventricle that protrudes during both systole and diastole and has a broad neck (Fig. 37–17). Morphologically, the wall of a true aneurysm develops after MI and consists of fibrous tissue with or without interspersed myocytes. In contrast, a false aneurysm has a small neck (from a prior rupture of the free wall of the left ventricle caused by infarct and is contained by the adherent pericardium), and

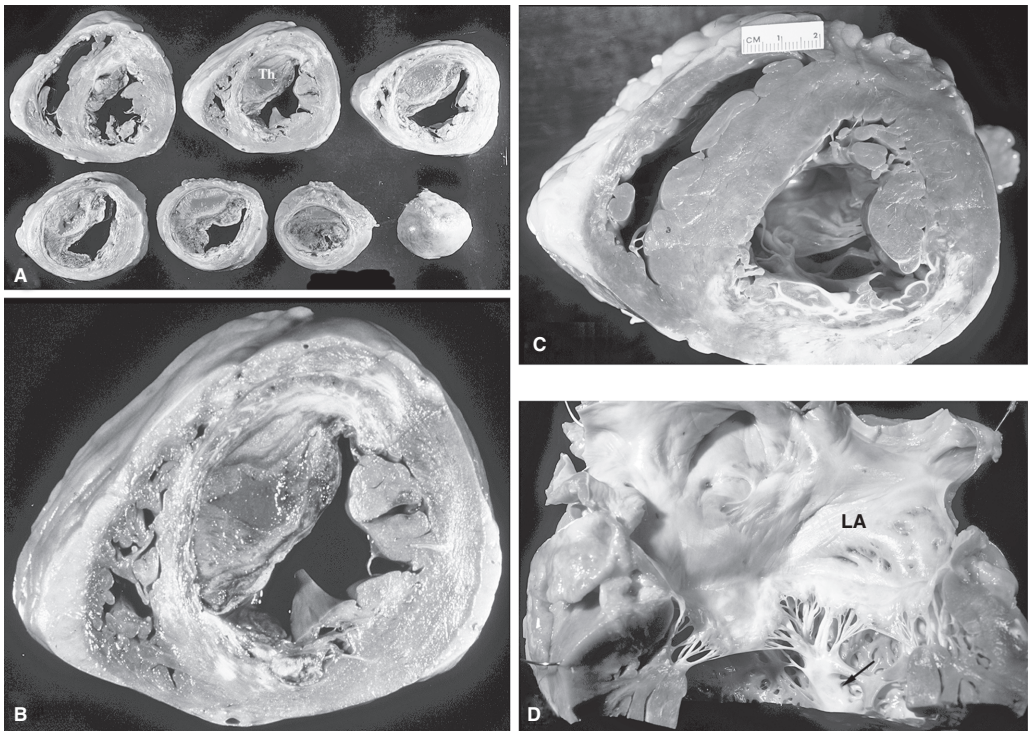

FIGURE 37–16. Thrombus of left ventricle with healed myocardial infarction (MI). **A.** Ventricular slices of a heart with healed MI involving the anteroseptal wall of the left ventricle with extension from the base to the apex. Note the dilatation of the left ventricular cavity and the presence of an organizing thrombus (Th). **B.** Close-up view of the basal ventricular slice (*middle slice from top row* in A). Note the large transmural healed infarct with overlying organizing infarct. At autopsy, the patient had multiple infarcts in the kidneys and one in the spleen. **C.** A 60-year-old man with congestive heart failure and mitral regurgitation who had a healed MI of the posterolateral wall of the left ventricle at autopsy. **D.** Note the scarred and thinned posteromedial papillary muscle (*arrow*); the anterolateral papillary muscle is hypertrophied. Note the dilated left atrium (LA). Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

a wall of the aneurysm is formed by fibrous pericardium (not from the left ventricular MI and healing). The aneurysm is usually filled by a thrombus that is organizing (see Fig. 37–17). False aneurysms often require urgent surgical repair because of their propensity to rupture; false aneurysms may also give rise to congestive heart failure. The cavity of the false aneurysm is usually filled with large blood clots, both old and new. The presence of hypertension and the use of steroids and nonsteroidal anti-inflammatory drugs may promote aneurysm formation.[162]

Aneurysms are usually associated with two-or-more-vessel coronary disease with poorly developed collaterals.[163] Four of five aneurysms involve the anteroapical wall of the left ventricle and are four times more frequent in this wall than in the inferior or posterior wall. The pericardium is usually adherent to the aneurysm and may calcify. True aneurysms rarely rupture; rupture is more common of a false aneurysm (see Fig. 37–17). The cavity of the aneurysm usually contains an organizing thrombus, and the patient may present with embolic complications. The mortality is significantly higher in patients with aneurysm than without.

Mills et al[164] suggested that aneurysmectomy should be performed in patients having true aneurysms because of poor prognosis. They reported a 27% 3-year survival in an autopsy series and a 70% survival in the Coronary Artery Surgery Study. Percutaneous closure has also been successfully reported.[138,165] The survival of patients with false aneurysm is also better after surgery. It has been said that more than half of false aneurysms are located in the posterior or inferior walls, but true aneurysms mostly involve the anterior wall. There is speculation regarding the reasons for these differences because large inferoposterior infarcts that could lead to aneurysms are more often fatal and posterior rupture is more often contained by the pericardium, allowing false aneurysms to develop.[166]

MURAL THROMBUS AND EMBOLIZATION

Early data from the pre-reperfusion and thrombolytic eras suggest that in the setting of acute MI, mural thrombus forming on the endocardial surface over the area of the acute infarction occurred in 20% of all patients, with an incidence of 40% for anterior infarcts and 60% for apical infarcts.[167] Currently, the reported incidence is lower.[168] Patients with left ventricular thrombi have poorer global left ventricular function and poorer prognosis than patients without thrombi.[168] The poor prognosis is secondary to complications of a large infarct and not from emboli.[167] It is reported that those that form thrombi have endocardial inflammation during the phase of acute infarction. The thrombi tend to organize, but the superficial portions may embolize in approximately 10% of cases (Fig. 37–18).[168] The usual sites of symptomatic embolization are the brain, eyes, kidney, spleen, bowel, legs, and coronary arteries. Symptomatic emboli are usually caused by larger fragments; small particles of thrombus that embolize generally do not cause symptoms. In the prethrombolytic era, embolic complications were reported in approximately 10% of cases, whereas now, they occur in 2% to 3% of patients. The risk of embolization is greatest in the first few weeks of acute MI.[168,169] Once diagnosed, mural thrombi require oral anticoagulant therapy with vitamin K antagonists for up to 6 months. However, in patients receiving dual platelet treatment, repeated imaging of the left ventricle after 3 months of therapy may allow discontinuation of anticoagulation earlier than 6 months if evidence of thrombus is no longer present, particularly if there is recovery of apical wall motion.[119]

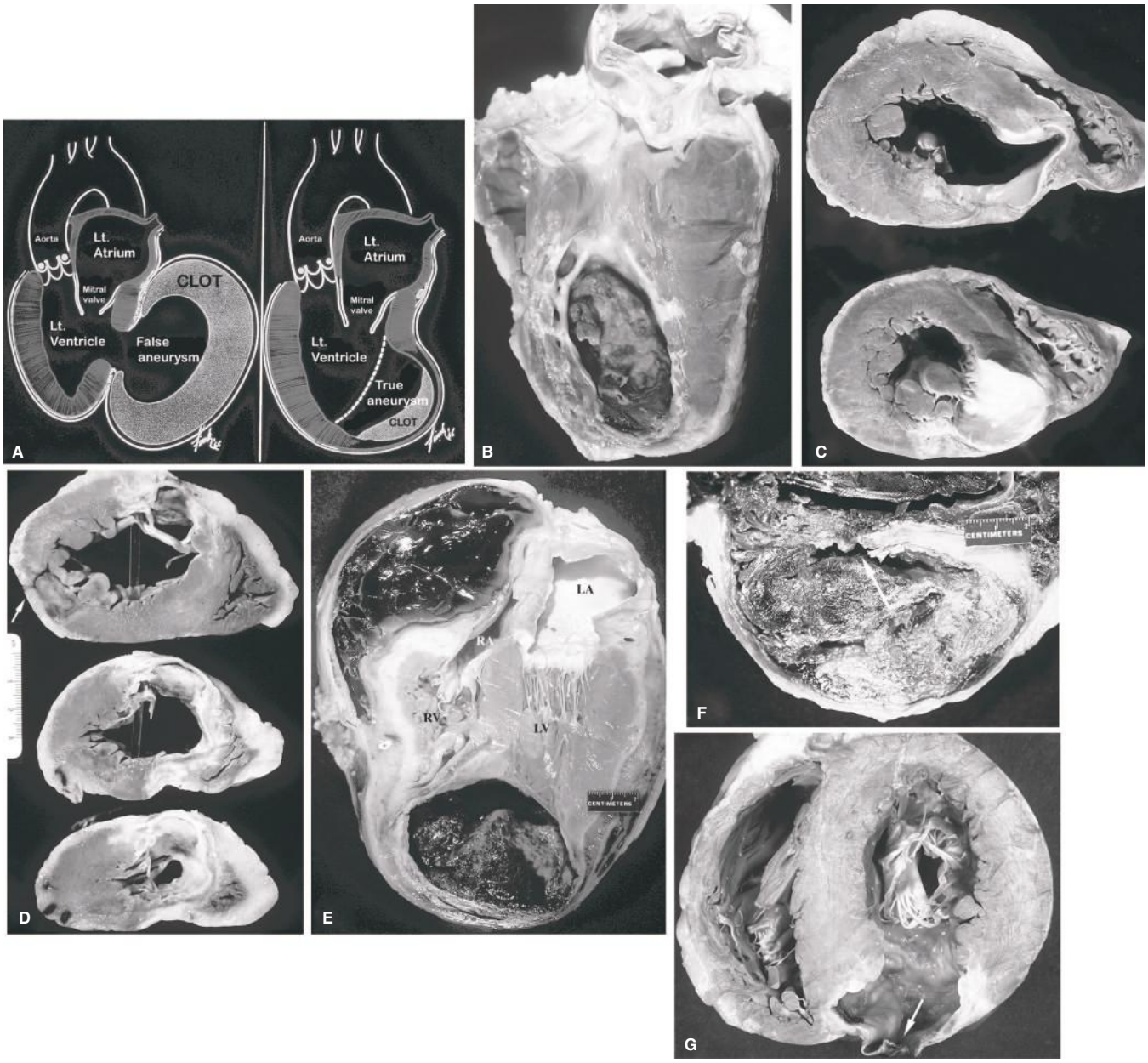

FIGURE 37–17. A. Diagram of a false (*left*) and a true (*right*) aneurysm. Note a rupture of the left ventricular (LV) wall with the blood contained by the pericardial wall. The LV does not form the wall of the aneurysm, and the neck of the aneurysm is narrow. The wall of the true aneurysm is formed by the wall of the infarcted myocardium, and the neck of the aneurysm is wide. **B.** A true aneurysm is seen at the apex of the heart involving the anteroseptal apical two-thirds of the LV. The aneurysm is filled with a thrombus, and there is endocardial thickening around the edges of the infarct. **C.** Healed transmural infarction of the posteroseptal wall of the LV. Note the thinned and bulging aneurysm of the posterior and septal wall with marked endocardial thickening. No thrombus was identified within the cavity of the aneurysm. **D.** A 54-year-old man died suddenly without any significant medical history. At autopsy, there was cardiac tamponade with ventricular rupture of the posterolateral wall (*arrow*) secondary to a transmural acute infarction. Ventricular slices of the heart showing the presence of a localized small anterior aneurysm from a healed myocardial infarction (MI) involving the anterior and septal wall of the LV. Note the organizing thrombus in the aneurysmal cavity. **E.** False aneurysm. A 47-year-old man presented with sudden-onset shortness of breath and died in the emergency department. At autopsy, there was a loculated hemopericardium and an LV anteroapical aneurysm secondary to a healed MI with overlying thrombus. A four-chamber cut of the heart showed extensive adhesions between the visceral and the parietal pericardium, and loculated fresh blood was present in the pericardial space above the right atrium (RA) and right ventricle (RV), as well as organizing hemorrhage around the heart. **F.** A deeper posterior cut revealed the rupture site in the aneurysmal wall (*arrow*). Note the narrow communicating neck of the true aneurysm with the false aneurysm. A diagnosis of rupture of a true aneurysm with a secondary false aneurysm was made. **G.** Rupture of a healed inferior wall aneurysm (*arrow*) in a 56-year-old man who developed chest pain and died while undergoing a stress test. At autopsy, there was hemopericardium (500 mL). Part A, used with permission from Dr. William C. Roberts. Parts D and G reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

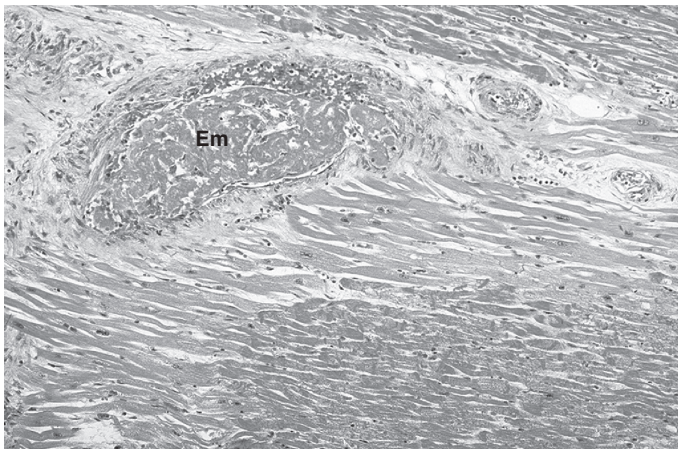

FIGURE 37–18. Intramyocardial thrombus with surrounding acute myocardial infarction (MI) in a patient with history of MI 6 months before the current presentation with chest pain. On echocardiography, he had a thrombus in the left ventricular (LV) cavity overlying the healed infarct. No acute thrombus was seen in any of the epicardial coronary arteries at autopsy. However, the anterolateral wall of the LV showed intramyocardial coronary emboli (Em) and surrounding infarction of less than 24 hours in duration. LA, left atrium. Reproduced with permission from Virmani R, Burke AP, Farb A, et al: *Cardiovascular Pathology*, 2nd ed. Philadelphia: WB Saunders; 2001.

PATHOLOGY OF SUDDEN CORONARY DEATH

INCIDENCE OF CORONARY THROMBOSIS

The frequency of coronary thrombosis in sudden coronary death varies from 20% to 70%.[170-172] The time interval between onset of symptoms and death, the presence of concurrent conditions that may cause arrhythmias (scars, ventricular hypertrophy), and the type of prodromal symptom (stable angina, unstable angina, no apparent symptoms) all affect the incidence of thrombi in coronary sudden cardiac death. Coronary thrombosis may occur over two major substrates: rupture of thin cap fibroatheroma and plaque erosion; however, calcified nodules have been reported but are uncommon. Plaque erosions occur in men and women younger than age 50 years and are less common. Plaque rupture is more common, occurs at all ages in adults, and is associated with hypercholesterolemia. We have shown in sudden coronary death that coronary thrombosis is most frequently the result of plaque rupture (65%), less frequently a result of plaque erosion (30%-35%), and uncommonly a result of calcified nodule (2%-5%).[60,173]

MYOCARDIAL FINDINGS

In our series of sudden coronary death with epicardial thrombosis, there is an approximate 10% incidence of acute MI and 40% incidence of healed MI; in 40%, no myocardial ischemia is identified.[173] In these cases, it is presumed that ischemia has not been manifest because of the short time interval between thrombosis and death. In sudden coronary death victims without epicardial thrombi, there is a low incidence of acute MI (4%), with a 60% rate of healed infarct and 35% without evidence of acute or healed infarct. Consequently, given that approximately 50% of cases of sudden coronary death occur in the absence of coronary thrombosis, 15% to 40% of hearts demonstrate stable coronary atherosclerotic plaque in the absence of acute or healed infarction in the ventricles. The role of cardiac hypertrophy and other arrhythmogenic factors in these deaths has not been studied in detail.

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CHAPTER 38

MOLECULAR AND CELLULAR MECHANISMS OF MYOCARDIAL ISCHEMIA/REPERFUSION INJURY

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INTRODUCTION AND GENERAL CONSIDERATIONS

Acute myocardial infarction is a leading cause of mortality and morbidity worldwide. It is the result of an acute occlusion of an epicardial coronary artery. The myocardium supplied by the occluded artery suffers severe ischemia. Prolonged ischemia, if there is no collateral circulation, results in irreversible damage to heart muscle, which is replaced by fibrotic noncontracting tissue (myocardial scar). Depending on the size of the territory distal to the occlusion site, the global ventricular function can be significantly impaired, resulting in postinfarction chronic heart failure.[1] Classical studies performed in large animal models demonstrated that blood flow restoration (reperfusion) was able to limit the progression of myocardial injury in a timely manner.[2,3] Reperfusion was shown not only to limit the progression of myocardial death but also to change the pattern of myocardial tissue healing. This concept was rapidly introduced into the clinics, and a long series of successful trials demonstrated that early reperfusion was able to reduce the extent of myocardial injury and, more importantly, to reduce mortality. Since then, timely reperfusion has become the standard treatment for patients suffering an acute myocardial infarction. Extensive preclinical and clinical studies have shown that reperfusion itself induces damage to the formerly ischemic myocardium (Fig. 38–1). Since reperfusion is the prerequisite for myocardial salvage, the damage inflicted on the myocardium during a myocardial infarction is known as *ischemia/reperfusion injury* (IRI; ie, the result of ischemia- and reperfusion-related damage). Myocardial IRI is a complex phenomenon involving many players, all contributing to the final damage inflicted on the myocardium.[1] Figure 38–2 summarizes the highly complex process of IRI and the multiple mechanisms involved in it. The first critical player is the epicardial artery (represented as 1 in Fig. 38–2). Atherosclerotic plaque rupture with superimposed thrombus results in an abrupt cessation of oxygen and nutrient supply distal to the occlusion site. The opening of the epicardial vessel by mechanical or pharmacologic means, as well as the reduction in thrombus burden by adjuvant antiplatelet/anticoagulant therapies, is only the first step toward the salvage of myocardium. During the reperfusion process (whether it is mechanical by primary angioplasty or pharmacologic by thrombolytics), thrombus material and other plaque debris can be distally embolized, contributing to microvascular obstruction (MVO). Circulating cells contribute to the damage inflicted to the myocardium: activated platelets and leukocytes in the bloodstream not only contribute to the thrombus generation, but also can form plugins that can embolize distally into the microcirculation through resting blood flow across the culprit lesion (a process independent from plaque debris microembolization). The microcirculation is a critical player in the fate of the myocardium during ischemia/reperfusion. Once the epicardial vessel flow is restored, efficient tissue perfusion is dictated mainly by the microcirculation. Plaque debris and platelet/neutrophil aggregates can induce a mechanical obstruction of the microcirculation precluding efficient tissue perfusion despite the opening of the epicardial artery (which is known as the no-reflow phenomenon). The generation of tissue edema following reperfusion can result in external compression of the microcirculation, reducing the perfusion capacity of the capillary network (arrowheads in Fig. 38–2). Finally, the microcirculation can be disintegrated as a result of previous damage, which allows circulating cells to leak into the interstitial space (dashed lines in the capillary of Fig. 38–2). Hemorrhage is especially harmful because of the release of iron, contributing to subsequent inflammatory reactions. Cardiomyocytes that have survived the ischemic phase suffer during the reperfusion period as a result of several intracellular pathways triggered at reperfusion. After the acute phase of the ischemia/reperfusion insult has passed, the significant infiltration of myocardial tissue by inflammatory cells can induce additional damage to the myocardium. In this chapter, we summarize the cellular and molecular mechanisms involved in IRI; however, it is important to keep in mind that it is the combination of these different mechanisms that leads to the progression of myocardial injury at reperfusion and, more importantly, that these mechanisms are interconnected.

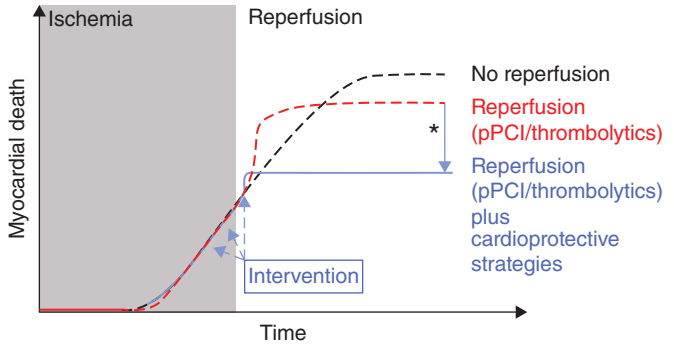

FIGURE 38–1. Impact of reperfusion injury on final infarct size. Myocardial death during coronary occlusion increases exponentially with time. Unrelieved ischemia (no reperfusion) results in death of the entire area at risk (*black dashed line*). Reperfusion, either mechanical by primary angioplasty (primary percutaneous coronary intervention [pPCI]) or pharmacologic by thrombolytic agents, results in myocardial salvage and reduction of infarct size compared to no reperfusion (*red dashed line*). Reperfusion injury adds to the injury developed during initial ischemia (note the progression of death [*stepped slope of red line*] immediately after reperfusion). If reperfusion-related damage is abrogated by cardioprotective strategies, infarct size does not progress after reperfusion (*blue line*). The difference between infarct size presented in the *red* and *blue lines* is the contribution of reperfusion injury to final infarct size (represented by *arrow*). The administration of a given therapy (*dashed arrows*) any time before reperfusion (including immediately before) can attenuate reperfusion injury. Adapted with permission from Garcia-Dorado D, Piper HM: Postconditioning: reperfusion of "reperfusion injury" after hibernation. Cardiovasc Res. 2006 Jan;69(1):1-3.

CLINICAL RELEVANCE OF MYOCARDIAL INFARCT SIZE

DETERMINANTS OF INFARCT SIZE

After the onset of a myocardial infarction (ie, coronary occlusion), the hypoperfused myocardial region, known as the area at risk (AAR), is at jeopardy of developing irreversible injury. Unrelieved ischemia, in the absence of significant collateral flow, results in death of the entire AAR. Given that today's mainstay treatment for myocardial infarction is reperfusion, part of the AAR remains free of necrosis: the so-called salvaged myocardium. The seminal studies by Ross and coworkers four decades ago[2,3] first demonstrated that early reestablishment of blood flow (reperfusion) salvages myocardium from infarction. These landmark studies demonstrated that there is a temporal progression of myocardial death during ongoing coronary occlusion: the sooner the reperfusion, the smaller is the proportion of AAR that becomes necrotic. These experimental studies primed the development of reperfusion strategies to limit the size of necrosis in patients suffering an acute myocardial infarction.[4] Despite being the prerequisite for myocardial salvage, reperfusion per se can cause some damage to the formerly ischemic myocardium, something known as reperfusion injury. Although the contribution of reperfusion injury to final infarct size has been disputed in the past, today it is well accepted that reperfusion can induce additional damage to the myocardium. This view is supported by strong evidence that interventions applied at the end of the ischemic period (ie, coinciding with reperfusion) can reduce infarct size. It was already recognized in the mid-1980s that gentle reperfusion at low pressure resulted in significantly less edema and a smaller infarct size than standard abrupt reperfusion at normal pressure.[5] This idea was later developed, and a reduction of infarct size by brief episodes of coronary reocclusion/reflow at the time of reperfusion, a strategy called *ischemic postconditioning*,[6,7] was demonstrated (discussed later in this chapter). Because these interventions are applied at the end of the ischemic period, they cannot reduce infarct size by reducing ischemic damage and thus must reduce reperfusion-related damage. From these observations, it is clear not only that reperfusion injury contributes to infarct size, but also that all conditioning strategies that protect the myocardium and reduce infarct size act only in conjunction with eventual reperfusion.[8,9]

Within a given AAR, both the duration and the severity of coronary blood flow reduction determine the nature and amount of injury.[1] A complete coronary occlusion of less than 20 minutes in duration results in only reversible injury (ie, contractile dysfunction with a slow, but complete recovery during reperfusion, a phenomenon called *myocardial stunning*). The underlying mechanisms of the prolonged contractile dysfunction relate to the enhanced formation of reactive oxygen species (ROS) during early reperfusion and impaired excitation-contraction coupling after oxidative modification of the sarcoplasmic reticulum and the contractile proteins.[10] Repeated coronary occlusions of short duration or prolonged moderate reduction in coronary blood flow results in hibernating myocardium, a phenomenon of reduced contractile function with retained viability and, thus, eventual recovery after reperfusion. Hibernating myocardium displays both signs of injury (loss of contractile proteins, small doughnut-like mitochondria, fibrosis) and signs of adaptation (short-term energetic recovery, altered expression of mitochondrial proteins and proteins related to cardioprotection).[11] When the reduction in coronary blood flow is severe and lasts longer than 20 to 40 minutes, infarction develops first in the inner subendocardial layers of the core of the AAR and then spreads in a "wavefront" to the outer subepicardial layers and the borders of the AAR over time. The wavefront of infarct development reflects the lateral and transmural distribution of coronary blood flow, which is less in the inner than the outer layers of the myocardium and less in the core than in the borders of the AAR.[12] The evolution of infarction varies with species and depends on the existence and extent of a collateral circulation. Dogs have a well-developed native collateral circulation, and infarction starts after 40 minutes of coronary occlusion and spreads to affect 70% of the AAR after 6 hours.[12] Therefore, in dogs, infarct size is best quantified as a fraction of the AAR and normalized to the residual blood flow.[13] Pigs have a negligible native collateral circulation, and infarction starts after 15 to 35 minutes of coronary occlusion and affects ≥ 80% of the AAR after 60 to 180 minutes.[14] Primates have few innate collaterals but are relatively resistant to myocardial ischemia; there is no infarction after 40 to 60 minutes of coronary occlusion, and even after 90 minutes of coronary occlusion, infarct size is smaller than in pigs.[15]

Fortunately, infarct development in humans is slower than in these large mammals. Even after 4 to 6 hours of coronary occlusion, 30% to 50% of the AAR remains viable and thus salvageable, as one can estimate from magnetic resonance imaging and from the amount of salvage by reperfusion.[16-18] Salvageable myocardium remains even after 12 hours from symptom onset.[19] To what extent the resistance of the diseased human heart is attributable to a developed collateral circulation at the time of infarction, as in the native dog heart, or reflects an inherently greater resistance to ischemic injury, such as in the primate heart, or is a result of preceding episodes of brief ischemia/reperfusion is unclear at present. In contrast to prior notions, the hemodynamic situation has little impact on the development of myocardial infarction, and the little impact it has is largely through its impact on coronary blood flow and its spatial distribution; heart rate determines infarct progression to some extent. Variations in coronary blood flow not only determine the nature and extent of myocardial injury, but paradoxically also determine protection from it. Repeated brief episodes of coronary occlusion preceding a prolonged coronary occlusion with reperfusion reduce infarct size (a phenomenon known as ischemic preconditioning, which is discussed later).[20] Likewise, repeated brief coronary occlusion during early reperfusion reduces infarct size, a phenomenon known as ischemic postconditioning[6] (discussed later).

Therefore, there are several determinants of myocardial infarct size (Table 38–1). The most widely supported by experimental and clinical

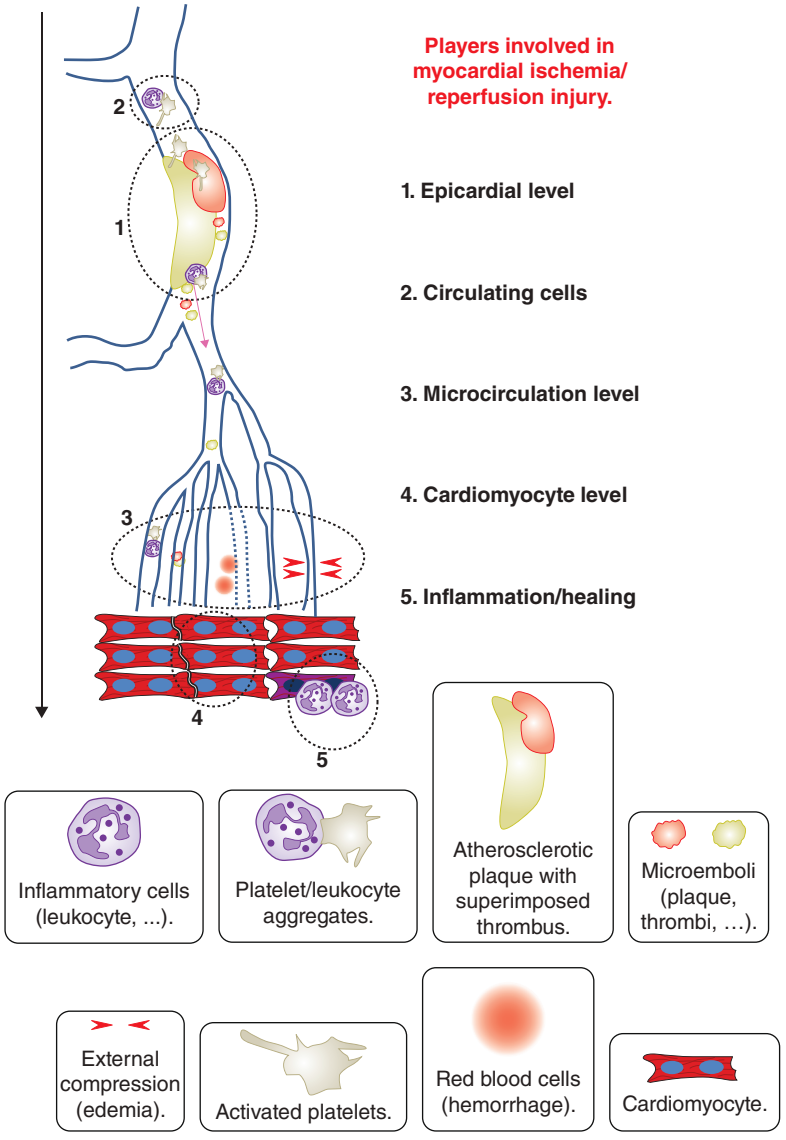

FIGURE 38–2. Gradient of events during ischemia/reperfusion injury (IRI). *Arrow* in the left side of the figure illustrates the sequence of events (see text for details). To attain cardioprotection and salvage the jeopardized myocardium, a hierarchical chain of events must occur. The *arrow* in the left of the figure represents the gradient of events contributing to final damage during IRI. If any of these events is not managed, the chain of protection is broken and damage will continue (eg, if the microcirculation is severely damaged, no matter how well the cardiomyocyte mitochondrial transition pore is preserved, that cardiomyocyte will not survive the event as a result of poor tissue perfusion). According to this scheme, it is intuitive to understand that protective interventions targeting only one of the layers are unlikely to significantly protect the heart from damage. Therapies targeting multiple layers of this chain of damage or multiple therapies applied simultaneously will have higher chances of resulting in protection.

studies are (1) the size of the AAR[21]; (2) the duration of myocardial ischemia[12,22]; (3) the amount of residual blood flow through collaterals[12,21]; (4) the temperature of the tissue during ischemia[23]; and (5) the degree of reperfusion injury.[1] In this chapter, we focus on the mechanisms leading to ischemia- and reperfusion-related damage.

INFARCT SIZE DETERMINES POSTINFARCTION MORTALITY AND MORBIDITY

The final extent of necrosis (infarct size) has been revealed as a major determinant of postinfarction mortality.[24,25] Large infarctions are associated with an irreversible impairment of the contractile function of the heart and concomitant chronic heart failure.[9] Beyond their impact on left ventricular systolic impairment (quantified as left ventricular ejection fraction [LVEF]), large infarctions are associated with increased risk of sudden death. The widespread implementation of reperfusion strategies has resulted in a significant reduction in the acute mortality associated with myocardial infarction. In fact, in-hospital mortality has decreased from approximately 20% in the late 1980s to approximately 5% today.[26,27] Paradoxically, this massive reduction of infarction-related acute mortality has resulted in an increase in the incidence of chronic heart failure. The obvious reason is that patients with severely depressed cardiac function would not have survived the acute phase of infarction in the past, but with the advent of reperfusion, they now survive the index episode and live with a significantly damaged heart.[26] In fact, myocardial infarction is a main contributor to chronic heart failure worldwide. Chronic heart failure treatment is one of the main contributors to healthcare expenditures, and thus, it is important to implement strategies to reduce its incidence. After acknowledging that infarct size is the main determinant of adverse postinfarction outcomes, including heart failure,[25] therapies able to reduce infarct size are urgently sought under the hypothesis that smaller infarctions will result in better long-term heart performance and that this will translate into fewer adverse clinical events.[28,29] The identification of therapies able to reduce infarct size, including amelioration of IRI, is a major challenge in the 21st century.

MECHANISMS OF CARDIOMYOCYTE DEATH DURING ISCHEMIA/REPERFUSION

ISCHEMIA/REPERFUSION-INDUCED CARDIOMYOCYTE DEATH

Cardiomyocyte death is the most important consequence of myocardial IRI and is the main cause of heart failure, arrhythmias, and death in patients with acute myocardial infarction.

TABLE 38–1. Determinants of Infarct Size

Determinant	Effect on Infarct Size	Reference
Area at risk (AAR) extent	The larger the AAR, the larger is the extent of infarction.	21
Duration of myocardial ischemia	The longer the duration of myocardial ischemia (coronary occlusion), the larger is the extent of infarction.	12,22
Collateral circulation	Poor collaterals are associated with larger infarctions.	12,21
Temperature of the tissue during ischemia	The lower the temperature during coronary occlusion, the larger is the extent of infarction.	23
Ischemia/reperfusion injury (IRI)	Damage driven by reperfusion increases the size of infarction.	1

Major determinants of infarct size and some references as guide. The table shows those determinants with stronger evidence from experimental studies. There are other determinants that have been associated with the extent of infarct size but are less widely validated.

Cardiomyocyte death secondary to reperfusion injury is mainly dependent on mechanisms taking place within cardiomyocytes themselves. In fact, the most important aspects of IRI in the intact heart can be recapitulated in isolated cardiomyocytes submitted to transient hypoxia/reoxygenation or to similar conditions.[30-32] However, as discussed later, other cells can contribute to cardiomyocyte cell death occurring upon myocardial reperfusion. The mechanism of these interactions is complex and incompletely understood and may take place independently of impairment of microvascular flow. For example, platelet activation and adhesion increase cardiomyocyte death independently of aggregation and of any effects on myocardial flow.[33,34]

It is widely admitted that a large fraction of cell death caused by lethal myocardial IRI occurs during the initial minutes of reperfusion, thus requiring early administration of cardioprotective interventions in order to prevent it.[31] Some studies have suggested the existence of additional delayed IRI during the first hours of reperfusion, but the importance of this phenomenon needs to be established.[35,36] In this context, it is important to notice that noncardiomyocyte cells have a better tolerance to ischemia than cardiomyocytes. This is particularly relevant in the case of endothelial cells, the metabolism of which is largely independent of mitochondrial respiration.[37]

Although there have been controversies about the contribution of apoptosis to IRI, it is clear now that IRI causes cardiomyocyte death mainly through necrosis.[38,39] It has been described that adult cardiomyocytes do not express executioner caspases 3 or 7 and that their selective genetic ablation does not modify infarct size or postinfarction remodeling in mice submitted to transient coronary occlusions. Recent studies have shown that necrosis may occur in different forms, ranging from sarcolemmal rupture resulting in massive calcium overload to programed forms of necrosis involving precise signal cascades, in particular necroptosis, a form of programmed necrotic cell death dependent on receptor-interacting protein kinase 3.[40] Reperfused infarcts are mainly composed of contraction band necrosis, a pathologic pattern reflecting sarcolemmal disruption and extreme cell shortening.

MECHANISMS OF CARDIOMYOCYTE NECROSIS DURING REPERFUSION

Studies using magnetic resonance spectroscopy, fluorescence/confocal microscopy, and electrophysiologic methods have allowed us to characterize the changes in ionic concentrations, pH, energy-storing molecules, and transmembrane potentials in cardiomyocytes during ischemia and reperfusion. Severe ischemia causes the immediate arrest of mitochondrial respiration and switch to anaerobic metabolism. This, in combination with very reduced catabolite washout, results in a rapid fall in intracellular pH, reaching 6.4 within a few minutes. Mitochondrial membrane potential progressively dissipates during ischemia, and adenosine triphosphate (ATP) concentration falls and reaches the very low levels, triggering rigor contracture (in approximately 20-40 minutes of severe normothermic ischemia in large animals).[41] Inversion of respiratory complex V (ATP synthase) activity from ATP synthesis to ATP degradation and proton pumping into the intermembrane space delay complete mitochondrial depolarization at the expense of accelerating complete ATP exhaustion.[42] Very low levels of ATP mark the onset of a progressive increase in cytosolic Ca^{2+}, mainly through reverse-mode Na^+/Ca^{2+} secondary to the Na^+ overload produced, mainly, by the inactivity of the Na^+/K^+-ATPase pump.[30]

ALTERED CA^{2+} HANDLING AND NORMALIZATION OF INTRACELLULAR PH

Reperfusion results in rapid changes in cardiomyocytes that can lead to their survival and progressive functional recovery or to cell death, depending mainly on the situation of the cardiomyocytes at the time of reperfusion. These changes include, prominently, rapid restoration of energy availability and intracellular pH, additional Ca^{2+} influx and uptake by the sarcoplasmic reticulum (SR), and a marked increase in ROS[43,44] (Fig. 38–3).

Although normalization of ATP concentration caused by reperfusion may take some time, normalization of the free energy of dissociation of ATP is rapid. Mitochondria of ATP-depleted cardiomyocytes may rapidly repolarize and start respiration and ATP synthesis within seconds of restoration of blood flow and oxygen availability.[42] Normalization of intracellular pH is completed within a few minutes after reperfusion and restoration of catabolite washout, thanks in part to the activation of the sarcolemmal Na^+/H^+ exchanger and the Na^+/CO_3H^- co-transporter.[45]

Altered Ca^{2+} handling is one of the most prominent and relevant aspects of cardiomyocyte reperfusion. Reperfusion causes further Ca^{2+} influx through the Na^+/Ca^{2+} exchanger in response to Na^+ overload. During the initial minutes of reperfusion, Na^+ influx associated with normalization of intracellular pH and passage of Na^+ from adjacent cells via gap junctions may lead to severe Na^+ overload in the presence of altered Na^+ pump function.[46] Ca^{2+} influx occurring during initial reperfusion adds up to Ca^{2+} overload occurring during ischemia and results in increased cytosolic Ca^{2+} concentration.[44] An important consequence of increased Ca^{2+} is activation of the Ca^{2+}-dependent proteases calpains. Calpains translocate to the sarcolemma during ischemia in response to Ca^{2+} overload but are activated only during reperfusion when intracellular pH is normalized, as calpains are inhibited by low pH.[47] Calpain-mediated hydrolysis of fodrin, the cytoskeleton protein responsible or the proper anchorage of the Na^+ pump to the sarcolemma, has been shown to worsen Na^+ overload and contribute to cardiomyocyte death, as its pharmacologic or genetic inhibition consistently reduces infarct size.

Restoration of ATP availability allows the sarcoplasmic Ca^{2+} pump (SERCA) to take large amounts of Ca^{2+} into the SR. When the Ca^{2+} capacity of the SR is exceeded, Ca^{2+} is released back into the cytosol through the ryanodine receptor channel (RyR2). This results in Ca^{2+} oscillations that propagate across the cell and may have several adverse consequences, favoring the generation of ventricular arrhythmias, excessive contractile activation, and mitochondrial Ca^{2+} overload and permeability transition.[48] Excessive contractile activation may cause hypercontracture, resulting in disruption of cardiomyocyte

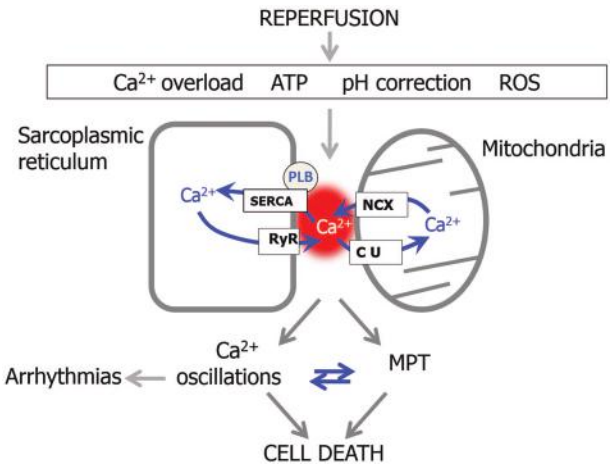

FIGURE 38–3. Central role of calcium handling in cardiomyocyte death during early phases of reperfusion. See text for detailed description. ATP, adenosine triphosphate; MPT, mitochondrial permeability transition; ROS, reactive oxygen species.

architecture that can cause sarcolemmal rupture and cell death, as demonstrated in studies showing that transient contractile inhibition during the initial minutes of reperfusion may prevent cell death and limit infarct size in different models ranging from isolated cardiomyocytes to intact large animals.[49]

THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE (MPTP)

There is solid evidence demonstrating that mitochondria play a key role in the events determining cardiomyocyte death or survival during reperfusion. Reperfusion results in immediate restoration of respiration, proton gradient across the inner mitochondrial membrane, and ATP synthesis. However, during reperfusion, respiration is associated with increased ROS generation, in part as a result of reoxidation of large amounts of succinate accumulated during ischemia by succinate dehydrogenase and reverse electron transport between complex II and complex I of the respiratory chain.[50,51] However, restoration of mitochondrial membrane potential favors mitochondrial Ca^{2+} uptake through the Ca^{2+} uniporter and Ca^{2+} overload.[44]

Mitochondrial Ca^{2+} overload and increased ROS production are important triggers of mitochondrial permeability transition, an abrupt increase in the permeability of the inner mitochondrial membrane resulting in mitochondrial depolarization and swelling, arrest of respiration, and release of molecules from the mitochondrial matrix into the cytosol.[52,53] Mitochondrial permeability transition is caused by the opening of the mitochondrial permeability transition pore (MPTP), a large conductance channel in the inner mitochondrial membrane allowing passage of large molecules up to 1.5 kDa. MPTP opening was first observed in isolated mitochondria exposed to high Ca^{2+} concentrations, can be triggered by ROS, and is favored by low ATP concentration but is completely inhibited by low pH.[54]

During ischemia, the MPTP does not open because of the inhibiting effect of intracellular acidosis. However, the MPTP may open during the first few minutes of reperfusion when intracellular pH returns to normal values,[55] and there is strong evidence of the involvement of MPTP opening in cardiomyocyte death secondary to IRI. MPTP has been documented in mitochondrial preparations exposed to Ca^{2+} overload and ROS by monitoring the release of fluorescent molecules previously loaded into mitochondria or mitochondrial swelling, and has been shown to occur in isolated cardiomyocytes submitted to simulated ischemia-reperfusion.[54] Inhibition of MPTP opening by genetic ablation of cyclophilin D, a molecule that modulates the sensitivity of MPTP to Ca^{2+}, has been shown to prevent MPTP opening in isolated mitochondria and cardiomyocytes during simulated reperfusion and to limit infarct size in mice submitted to transient coronary occlusion.[56] Pharmacologic inhibition of cyclophilin D with cyclosporine, a calcineurin inhibitor used as an immunosuppressant, has also been shown to inhibit MPTP opening in isolated mitochondria and cardiomyocytes and to limit infarct size in preclinical studies, although in a less consistent way.[57-59]

The understanding of the regulation and function of the MPTP is at present limited by the lack of a precise knowledge of its molecular structure. After different models involving ANT, VDAC, and other molecules were discarded, more recent studies suggest that the MPTP is formed by the ATP synthase (complex V of the respiratory change), the channel being formed by either the rotor unit or by a conformational change of the dimeric organization of the ATP synthase molecules.[60] This model, like all previous ones, accounts for the regulatory role of cyclophilin D.

INTERACTION BETWEEN MITOCHONDRIA AND SARCOPLASMIC RETICULUM

The mechanism by which MPTP opening may cause necrosis with sarcolemmal rupture within minutes of reperfusion is not well understood. A potential explanation is that it causes hypercontracture. It has been shown that opening of the MPTP in part of the mitochondria may cause hypercontracture in Ca^{2+}-overloaded cardiomyocytes by allowing the release of its Ca^{2+} contents while nonpermeabilized mitochondria ensure ATP availability.[61] However, SR-driven Ca^{2+} oscillations may induce MPTP opening.[48] This is favored by the tight physical connection between the SR and mitochondria mediated by specific anchoring proteins and resulting in the creation of Ca^{2+} micro-domains in which ryanodine receptor (RyR) channels and SERCA are in close proximity to the mitochondrial Ca^{2+} uniporter.[62] These micro-domains allow a preferential communication between SR and mitochondria and may translate SR Ca^{2+} oscillations into mitochondrial Ca^{2+} overload.[48] Thus, there is an important crosstalk between MPTP opening and Ca^{2+} oscillation-driven hypercontracture as causes of cell death in reperfused cardiomyocytes. The relative importance of these two mechanisms may depend on the conditions, in particular on the duration of the ischemia; the role of MPTP opening appears to be less important after brief periods of ischemia.[63]

During reperfusion, increased ROS generation inside and outside mitochondria may favor cardiomyocyte cell death by mechanisms other than by directly inducing MPTP opening.[64] ROS may oxidize tetrahydrobiopterin and cause endothelial nitric oxide synthase dissociation, favoring the generation of toxic peroxynitrite and further oxidative stress and reducing nitric oxide availability and cyclic guanosine monophosphate–protein kinase G signaling. In addition to directly modulating MPTP opening,[65,66] protein kinase G signaling is reduced in reperfused myocardium,[67] and this favors SR-driven Ca^{2+} oscillations via protein kinase A–mediated effects on phospholamban, a regulator of SERCA.[68] Figure 38–4 summarizes intracellular changes leading to cell damage/death during reperfusion.

THE CORONARY CIRCULATION IN MYOCARDIAL ISCHEMIA/REPERFUSION INJURY

Myocardial IRI injury affects not only the cardiomyocyte compartment, but also the coronary circulation.[69] Coronary occlusion after atherosclerotic plaque rupture with superimposed thrombosis is the cause and origin of myocardial ischemia, and reperfusion of the occluded coronary artery with restoration of coronary blood flow not only terminates myocardial ischemia but also inflicts additional injury. The spatial and temporal evolution of coronary occlusion and reperfusion determines both the size of the affected myocardial region and the nature of the outcome from ischemia/reperfusion (ie, reversible [stunning] or irreversible [infarction] injury and, vice versa, protection from injury [hibernation, conditioning]).

THE CORONARY CIRCULATION AS A DETERMINANT OF REPERFUSION AND REPERFUSION INJURY

Only 2 years after the demonstration by John Ross's group that reperfusion was the only way to rescue myocardium from impending infarction,[2,3] the dark side of coronary reperfusion became apparent, when Robert Kloner first reported the coronary no-reflow phenomenon.[70] And again, only a few years later, Keith Reimer and Robert Jennings reported in a series of detailed dog studies that signs of irreversible myocardial injury became particularly manifest during reperfusion[12]; at that time, it was not clear whether the irreversible injury was caused by reperfusion or only became more obvious during reperfusion. The long debate over the existence of lethal reperfusion injury was finally ended by the recognition of the ischemic postconditioning phenomenon when Jakob Vinten-Johansen reported that repeated coronary

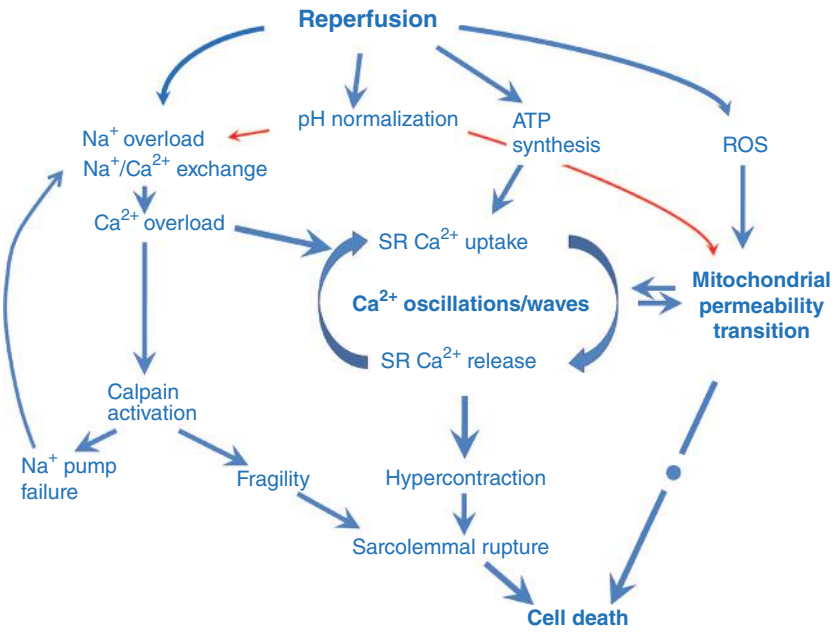

FIGURE 38–4. Summary of intracellular changes leading to cell damage/death during reperfusion. See text for more details. ATP, adenosine triphosphate; ROS, reactive oxygen species; SR, sarcoplasmic reticulum.

reocclusion during early reperfusion reduced infarct size in dogs.[6] The fact that a modified procedure of reperfusion could indeed attenuate irreversible injury once again revived earlier studies[7] on gentle reperfusion (ie, the reduction of functional and morphologic signs of injury by reperfusion at reduced perfusion pressure[71] or reduced coronary blood flow[72]). With the unequivocal notion that reperfusion is both mandatory for salvage from impending infarction and causes irreversible injury per se, a complex picture arises in that both ischemia and reperfusion contribute to the ultimate injury, but their individual contribution to ultimate injury depends on the duration and severity of coronary blood flow reduction.[73] Although ischemic injury increases with the severity and the duration of coronary blood flow reduction, there is a maximum of reperfusion injury in more moderate ischemic injury.

MANIFESTATIONS OF MYOCARDIAL ISCHEMIA/REPERFUSION INJURY IN THE CORONARY CIRCULATION

The manifestations of myocardial ischemia/ reperfusion in the coronary circulation range from mild and reversible functional impairment to severe and irreversible destruction.

Vascular Permeability and Edema

Edema develops within minutes of acute myocardial ischemia[74] and is both intracellular and interstitial. Intracellular edema develops in cardiomyocytes and endothelial cells largely as a consequence of the rapidly developing energetic deficit and the reduced function of energy- dependent ion pumps. Interstitial edema develops as a consequence of increased interstitial osmolarity from increased ion and catabolite concentrations and a dysfunction of the endothelial barrier function during myocardial ischemia (as depicted in Fig. 38–2). The endothelial barrier function is made up by endothelial cells, pericytes, and the glycocalyx. Endothelial cytoskeletal derangement and hypercontracture induce gap formation.[75-77] Degradation of the glycocalyx also contributes to reduced endothelial barrier function and edema formation[78] and promotes leukocyte[79] and platelet adherence.[80] Upon reperfusion, interstitial edema is greatly enhanced by reactive hyperemia and the rapid washout of osmotically active molecules from the intravascular space. Edema development during reperfusion follows a bimodal pattern,[81] where an initial maximum of water content after 120 minutes is associated with a beginning leukocyte infiltration and a secondary peak after 7 days is associated with enhanced collagen deposition[82] (Fig. 38–5). Edema during reperfusion has been proposed to reflect the AAR on cardiac magnetic resonance (CMR), but such bimodal pattern questions the use of T2-weighted edema measurement for AAR delineation.[83]

Vasomotion

The coronary microcirculation distal to a severe coronary stenosis or coronary occlusion has traditionally been considered as maximally dilated after exhaustion of autoregulatory reserve. However, even during myocardial ischemia that limits regional contractile function, a pharmacologically recruitable vasodilator reserve persists[84] or, conversely, the coronary microcirculation remains responsive to vasoconstrictor mediators, notably α-adrenergic coronary vasoconstriction.[85,86] The release of vasoconstrictor substances such as thromboxane, serotonin,[87] and endothelin[88] from the culprit lesion into the microcirculation, in conjunction with the impairment of endothelial function by ischemia/reperfusion per se[89] or by tumor necrosis factor-α (TNF-α),[87] can contribute to such enhanced vasoconstrictor responsiveness during myocardial ischemia/reperfusion. With more prolonged ischemia in hibernating myocardium, there is structural remodeling of the microvasculature with hypertrophy of smaller vessels and atrophy of larger vessels, reduced vascular distensibility, and increased vasoconstriction in response to endothelin.[9]

Microembolization

Plaque fissure or rupture occurs spontaneously and is induced traumatically/iatrogenically by percutaneous coronary interventions. Atherosclerotic debris with superimposed thrombotic material is then dislodged and embolized into the coronary microcirculation where

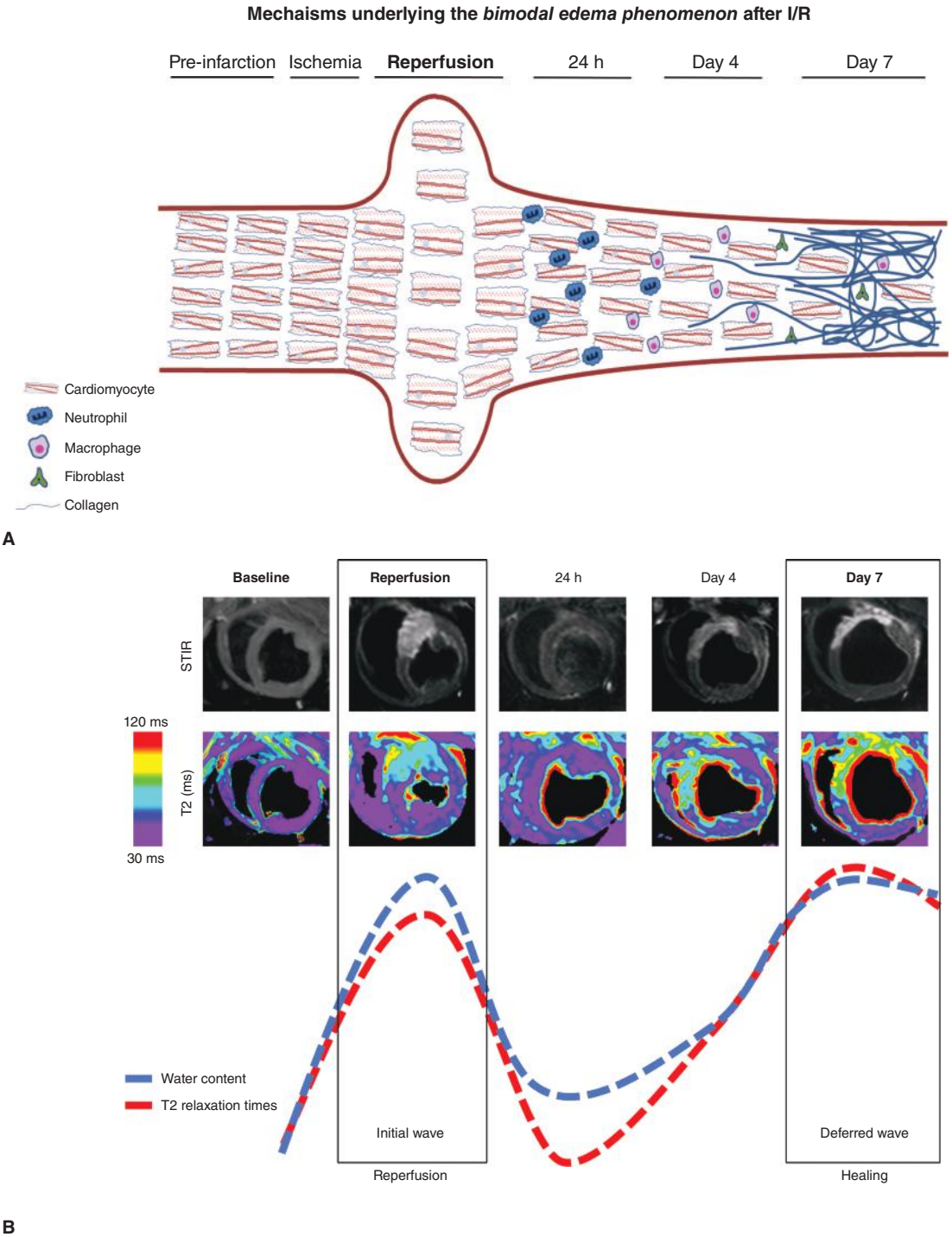

FIGURE 38–5. Edema formation after ischemia/reperfusion (I/R): mechanisms underlying the bimodal edema phenomenon. The two distinct waves of edema emerging within the first week after I/R are a result of different pathophysiologic processes. The initial wave of edema, appearing abruptly upon reperfusion, is a direct consequence of the reperfusion process itself. The deferred wave of edema, appearing progressively days after I/R and peaking around day 7, is mainly a result of the tissue healing processes. **A.** Dynamic histologic changes occurring in the myocardium during the first week after infarction. Reperfusion is associated with a significant abrupt edematous reaction that separates myocardial fibers from each other and that resolves by day 1. In the days following infarction, there is an initial neutrophil infiltration (peaking by day 1), followed by macrophage infiltration (peaking by day 4). From day 4 on, necrotic cardiomyocytes are progressively replaced by granulation tissue and collagen. **B.** Dynamic changes of myocardial edema following experimental I/R as evaluated by cardiac magnetic resonance (CMR) and histology. This bimodal edema reaction following myocardial I/R was documented both by state-of-the-art CMR imaging T2 mapping (*dashed red line*) and by histologic evaluation of edema (*dashed blue line*). Note the parallel course of the fluctuations in CMR and histologically determined edema (*dashed red lines*). STIR, short tau inversion recovery. Reproduced with permission from Fernández-Jiménez R, Sánchez-González J, Agüero J, et al: Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: imaging and histological tissue characterization. *J Am Coll Cardiol*. 2015 Feb 3;65(4):315-323

it induces patchy microinfarcts with an inflammatory reaction. Such microinfarcts add to the infarct size caused by sustained coronary occlusion with reperfusion.[90,91] Somewhat paradoxically, the increase in TNF-α expression secondary to coronary microembolization can also induce protection and reduce infarct size from subsequent coronary occlusion/reperfusion[92] such that the actual impact of coronary microembolization on infarct size depends critically on timing and is difficult to predict.

Stasis and Microvascular Obstruction

Myocardial ischemia and reperfusion increase the expression of adhesion molecules such as intercellular adhesion molecules (ICAM), vascular cell adhesion molecules, and selectins on endothelium and circulating cells and thereby promote the interaction of platelets, leukocytes, and endothelium and the adherence of platelet aggregates and platelet-leukocyte aggregates to the endothelium.[93] Such aggregates are either released from the epicardial atherosclerotic culprit lesion and dislodged into the microcirculation or are formed in the coronary microcirculation. These cellular aggregates contribute to the impairment of microvascular perfusion. In pronounced forms of no-reflow, typical erythrocyte aggregates are found that block the capillaries.[94]

Capillary Destruction and Hemorrhage

The most severe form of coronary microvascular injury from myocardial ischemia/reperfusion, as already detailed in the original report of coronary no-reflow by Kloner,[70] is the massive swelling of capillary endothelial cells with consequent rupture of the vascular wall and leakage of circulating cells into the interstitium (ie, hemorrhage). No-reflow and hemorrhage carry an adverse prognosis.[95,96]

CORONARY MICROVASCULAR INJURY: CAUSE OR CONSEQUENCE OF MYOCARDIAL ISCHEMIA/REPERFUSION?

The available studies indicate a close correlation between infarct size and no-reflow. Still, correlations cannot resolve questions of causality, and the lack of adequate techniques to make serial measurements of infarcted tissue and no-reflow with reasonable spatial resolution is largely responsible for the fact that causality between myocardial infarction and coronary microvascular no-reflow has not been established. With microembolization of atherosclerotic debris, plugging of platelet/leukocyte aggregates, and vasoconstriction in response to soluble mediators, the resulting coronary MVO could be a cause of myocardial infarction. With this rationale, thrombaspiration, protection devices and coronary vasodilators are used to reduce perinterventional reperfusion injury, but there is no conclusive evidence that these measures indeed reduce infarct size.[90] Also, recombinant angiopoietin-like protein-4 has been demonstrated to stabilize the endothelial barrier and subsequently reduce infarct size and no-reflow in mice, but it is unclear whether or not this molecule also has cardiomyocyte-protective properties.[77] Vice versa, there may be primary damage to cardiomyocytes that only subsequently progresses to coronary microvascular damage, as seen in animal models with mechanical occlusion/reperfusion of virgin coronary arteries without a culprit lesion.[97] Whether cardiomyocyte damage per se is causal for subsequent coronary microvascular damage or both are consequences of the same fundamental pathomechanism (eg, excessive ROS formation) remains unclear.[98]

Most experimental studies on myocardial ischemia/reperfusion are done in healthy and young animals that have a virgin coronary circulation. Such studies accordingly cannot account for the presence of atherosclerosis with impaired endothelial function, exhaustion of autoregulatory mechanisms, and coronary vascular remodeling distal to coronary stenosis,[9] the development of a significant collateral circulation, and pre-existing myocardial disease (patchy microinfarcts and fibrosis) or adaptation (hibernation). These limitations contribute to the difficulties in translating data from animal studies to the patient with acute myocardial infarction undergoing reperfusion therapy.[28]

ROLE OF CIRCULATING CELLS AND INFLAMMATION IN MYOCARDIAL ISCHEMIA/REPERFUSION INJURY

As depicted in Figure 38–2, circulating cells are critical players in IRI. During ischemia, there is a systemic proinflammatory milieu resulting in the activation of white blood cells (WBC) and platelets, among other cells. Within the WBC, neutrophils play a critical role in the acute phase of myocardial infarction. As described earlier in this chapter, circulating neutrophils and platelets aggregate and form plugins that upon reperfusion are distally embolized and can be physically stuck in the microcirculation, contributing to MVO.[99-102] The presence of MVO contributes to maintain tissue ischemia despite the opening of the epicardial vessel, something known as the no-reflow phenomenon (see above). Besides the role of neutrophil/platelet plugins in MVO, these cells infiltrate the postischemic myocardial tissue and contribute to the reperfusion-related damage. The presence of neutrophils infiltrating the reperfused myocardium has been traditionally believed to represent a pathophysiologic response to injury[103]; however, this response also contributes to the damage triggered by reperfusion. In fact, influx of neutrophils in the postischemic myocardium is detected long before there is any need for scavenging of any debris. Neutrophils are typically found in close connection with platelets, and the interaction between both cell types is known to occur in many acute stress conditions, not just in IRI. Prolonged ischemia not only affects cardiomyocytes, but endothelial cells are also affected, resulting in a dysfunctional endothelium. Upon reperfusion, activated neutrophils bind to the activated endothelium as a first step to infiltrate the myocardial tissue. The migration of neutrophils is initiated by tethering and rolling on inflamed vessels, a process mediated by endothelial selectins.[104] Activation of integrins then allows firm adhesion, after which leukocytes actively crawl on the endothelium before they extravasate into the reperfused myocardium.[105] A distinct feature of leukocytes recruited to inflamed vessels is the rapid shift from a symmetric morphology into a polarized form, in which intracellular proteins and receptors rapidly segregate.[106] The relevance of neutrophil/platelet interaction in the infiltration of the former into the postischemic tissue has been recently unraveled: neutrophils recruited to injured vessels extend a domain into the lumen and scan for the presence of activated platelets. Only when productive neutrophil-platelet interactions occur do neutrophils organize additional receptors needed for intravascular migration.[107] The contribution of neutrophil infiltration to reperfusion-related damage is established from preclinical studies. The depletion of neutrophils (even by employing leukocyte filters) has been shown to reduce infarct size and preserve coronary endothelial function in several models.[108-111] The use of antineutrophil serum, resulting in complete removal of neutrophils from the circulation without affecting other WBCs, has been demonstrated to reduce infarct size, clearly demonstrating the relevant role of neutrophils in the damage associated with IRI.[108] Once the role of neutrophils in damage associated with IRI was determined, more sophisticated approaches targeting different neutrophil adhesion receptors were tested. The use of antibodies against Mac-1,[112,113] CD18,[114] ICAM-1,[115,116] and P-selectin[117,118] resulted in significant reduction of infarct size in different, but not all,[119] preclinical studies. Unfortunately, this solid experimental evidence has not been translated into a clinical benefit. The administration of a monoclonal antibody

against CD18 in myocardial infarction patients undergoing thrombolytic therapy[120] or primary angioplasty[121] did not reduce infarct size in two independent, randomized, placebo-controlled clinical trials. Other indirect approaches targeting postinfarction inflammation, such as the use of the anti-C5 complement antibody pexelizumab, did not reduce infarct size or improve outcomes in randomized clinical trials.[122,123] These neutral effects in the clinical arena have reduced the interest in developing strategies to inhibit neutrophil infiltration into the postischemic myocardium as a therapy to reduce infarct size. However, the clear preclinical evidence[124] and the potential confounders affecting clinical results leave a door open for this strategy. It might be the case that the targets chosen for the translation into clinical studies (blocking neutrophil-endothelium adhesion) were not the ideal ones. In this regard, it has been recently proposed that the mechanism by which the β_1-selective adrenergic receptor antagonist metoprolol reduces infarct size[18,125] involves the interaction between neutrophils and platelets during IRI.[126]

STRATEGIES TO ATTENUATE MYOCARDIAL ISCHEMIA/REPERFUSION INJURY

More than 50 years ago, Jennings et al[127] first suggested that reperfusion may actually hasten the necrotic process of myocytes irreversibly injured during ischemia, with the concept that reperfusion could induce the death of reversibly injured cardiomyocytes.[8,9] Currently, despite inducing additional damage to the myocardium,[128] reperfusion is the mainstay treatment for patients with acute ST-segment elevation myocardial infarction (STEMI). Therefore, any therapy able to reduce the size of infarction must do so in conjunction with reperfusion (either mechanical [primary angioplasty] or pharmacologic [thrombolytics]). Despite significant data demonstrating that reperfusion-induced injury significantly contributes to final infarct size (reviewed earlier in this chapter), at present, there is still no effective therapy in routine clinical use for reducing lethal myocardial reperfusion injury in reperfused STEMI or cardiac surgery patients.[129] Therefore, reperfusion injury is still a neglected therapeutic target.[1,31] In the following sections, we review the strategies potentially available to attenuate IRI and for protecting the heart against acute myocardial infarction and myocardial reperfusion injury.

ISCHEMIC CONDITIONING

The possibility of "preparing" the myocardium for a subsequent ischemic insult is termed *conditioning* in the context of this chapter. The execution of brief episodes of ischemia and reperfusion is known as ischemic conditioning if these brief episodes of ischemia occur before the index episode (eg, brief coronary occlusion/reperfusion before prolonged coronary occlusion–myocardial infarction) or after the index episode (eg, brief episodes of coronary occlusion/reperfusion at the end of a prolonged coronary occlusion–myocardial infarction). This conditioning can be local (ie, the brief episodes of ischemia occur at the same organ) or remote (ie, the brief episodes of ischemia occur at a different distant organ) (Fig. 38–6).[130] The existence of "natural" local ischemic preconditioning has been known for several decades; for example, patients suffering preinfarction anginal episodes (representing brief episodes of spontaneous occlusion/reperfusion [eg, thrombosis- spontaneous lysis] of the coronary artery preceding STEMI) have smaller infarctions and better prognoses than patients without preinfarction angina (ie, straight coronary occlusion).[131] In the following sections, we describe different forms of ischemic conditioning as well as their clinical applications.

ISCHEMIC PRECONDITIONING

For patients suffering a STEMI or undergoing cardiac surgery (a paradigmatic "model" of planned myocardial IRI), the phenomenon known as ischemic conditioning provides an endogenous strategy that is capable of protecting the heart from the detrimental effects of acute IRI and that has the therapeutic potential to improve clinical outcomes in patients with ischemic heart disease.

This remarkable cardioprotective strategy is the term given to a number of related endogenous cardioprotective procedures, which are all based on rendering the heart tolerant to acute IRI by "conditioning" it with one or more brief cycles of ischemia and reperfusion. Discovered by Murry, Jennings, and Reimer in 1986,[20,132] it remains the most consistent and powerful form of cardioprotection at our disposal to date. What makes it so important is that it can be seen in all species examined, including man, and can be readily applied to other organs and tissues (reviewed in Yellon and Downey[133] and Bulluck and Hausenloy[134]). Other than direct reperfusion of a blocked coronary artery, ischemic preconditioning (IPC) remains the most powerful intervention for reducing myocardial infarction size in the ischemic heart.

IPC has been shown to induce two distinct windows of cardioprotection. The first, usually referred to as classic preconditioning, occurs immediately after the IPC stimulus and lasts 2 to 3 hours followed by a disappearing of the effect. This is followed by a second window of protection or delayed effect appearing 12 to 24 hours later and lasting 48 to 72 hours.[135,136] Despite intensive investigation, the actual mechanisms that mediate the cardioprotective effect induced by IPC are not fully

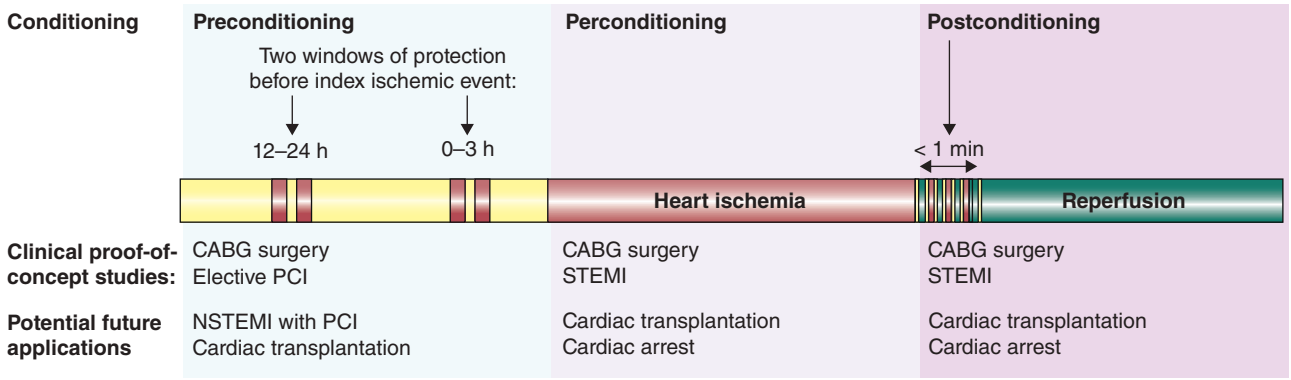

FIGURE 38–6. Different strategies to accomplish conditioning of the myocardium to ameliorate ischemia/reperfusion injury. Scheme of the different strategies of myocardial conditioning. CABG, coronary artery bypass graft; NSTEMI, non–ST-segment myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment myocardial infarction. Reproduced with permission from Hausenloy DJ, Yellon DM: The therapeutic potential of ischemic conditioning: an update. *Nat Rev Cardiol*. 2011 Jun 21;8(11):619-629.

understood. Importantly a large number of signaling pathways have been identified, which are briefly mentioned below (for more comprehensive review, see Yellon and Downey[133] and Heusch[137]). In brief, the sublethal cycles of short bursts of ischemia and reperfusion, which make up the IPC stimulus, produce a number of endogenous biological factors (ie, autacoids) from the myocyte including adenosine, bradykinin, endothelin, acetylcholine, and opioids, which can bind to their respective receptors on the plasma membrane. This will direct the appropriate cardioprotective communication pathway that will convey the protective signal to the mitochondria. It is believed that within the cell a signaling ROS is produced that activates protein kinases such as Akt, Erk1/2, tyrosine kinase, and protein kinase C that provide the "memory" for the cardioprotective effect such that the effect lasts up to 2 to 3 hours (for classical or acute IPC); the role of protein kinase C in such memory is somewhat controversial.[138] In the second window of protection or delayed conditioning, these protein kinases activate transcription factors (such as STAT1/3, NFκB, AP-1, Nrf2, and HIF-1α), which mediate the synthesis of distal mediators (such as inducible nitric oxide synthase, heat shock protein, and cyclooxygenase-2), which then induce the cardioprotective effect 12 to 24 hours following the IPC stimulus.[139] In terms of preventing myocardial IRI, IPC has been shown to recruit prosurvival signaling pathways at the onset of reperfusion including the reperfusion injury salvage kinase (RISK) pathway, first identified by Yellon's group in 2002 and comprising Akt and Erk1/2,[140,141] and the survivor activator factor enhancement (SAFE) pathway, comprising TNF-α and JAK-STAT3 and identified by Lecour's group in 2008.[141-143]

Although the end effectors of cardioprotection in classical and delayed IPC remain unclear, it has been suggested that preservation of mitochondrial function with less calcium overload, attenuated ROS production, and MPTP inhibition all contribute to the protective effect.[133,144,145] It is hoped that functional genomics of myocardial tissue may provide further insights into the potential mechanisms underlying IPC strategies.[146]

Clinical Application of Ischemic Preconditioning

The first clinical study to apply an IPC stimulus in patients was by Yellon's group in 1993 in the setting of coronary artery bypass grafting (CABG) surgery.[147] They found that intermittent clamping and declamping of the aorta of patients undergoing CABG surgery preserved myocardial ATP levels in a similar manner to that seen by Murry and colleagues in their seminal preconditioning paper. Since then, a number of small studies[148] have confirmed the cardioprotective effect of IPC, as measured by serum cardiac enzymes, in terms of reducing the extent of perimyocardial injury in patients undergoing CABG surgery; a recent meta-analysis of 22 trials of 933 patients found that IPC reduced ventricular arrhythmias, decreased inotrope requirements, and shortened the intensive care unit stay.[149] Despite these potential beneficial effects, the need to intervene on the heart directly and the inherent risk of thromboembolization arising from clamping an atherosclerotic aorta have prevented IPC from being adopted in this clinical setting.[150]

Interestingly it has been suggested that the phenomenon of IPC can be observed in a number of clinical scenarios in which the heart is able to protect itself with brief episodes of ischemia (eg, in the setting of "warm-up angina," which refers to the occurrence in which a patient with stable ischemic heart disease is able to increase his or her exercise tolerance following an episode of angina followed by a period of rest).[151] In addition, antecedent angina prior to an acute myocardial infarction, or preinfarct angina, has also been suggested to account for the cardioprotective effects of smaller myocardial infarction size and improved clinical outcomes.[131]

ISCHEMIC POSTCONDITIONING

The major disadvantage of IPC as a cardioprotective strategy is the requirement to intervene prior to the index ischemic event, which in the case of an acute myocardial infarction is not possible. However, in 2003, Zhao et al[6] made the exciting discovery that the heart could be protected against acute myocardial infarction by interrupting myocardial reperfusion with several short-lived episodes of myocardial ischemia; they termed this phenomenon *ischemic postconditioning* (IPost).[152] These authors found that applying three cycles of 30-second left anterior descending coronary artery reocclusion and reflow within 1 minute of myocardial reperfusion could reduce myocardial infarction size by 44% in the canine heart.[6] In addition, IPost was found to confer a myriad of protective effects with preserved endothelial function and reduced levels of myocardial edema, oxidative stress, and polymorphonuclear neutrophil accumulation, findings that were consistent with there being less myocardial reperfusion injury in postconditioned hearts.[6]

Interestingly, the concept of modifying reperfusion as a strategy to limit myocardial infarction size had already been introduced in the 1980s with the strategies of gentle[5] and gradual[153] reperfusion.[7] Indeed, in 1996, Na et al[154] had already coined the term *postconditioning* when they described the phenomenon by which intermittent reperfusion, induced by ventricular premature beats, prevented reperfusion-induced ventricular fibrillation in ischemic feline hearts. However, the concept of IPost has captured the imagination and restored efforts to target myocardial reperfusion injury as a therapeutic strategy for reducing myocardial infarction size. Importantly, this phenomenon has been shown to reduce myocardial infarction size in rodents, rabbits, pigs, and other species including man, although the cardioprotective effect of IPost does not appear to be as robust as IPC.[137,155]

IPost appears to share many of the same signaling mechanisms recruited at the time of reperfusion by IPC,[134,137] which include the activation of cell-surface receptors on the cardiomyocyte (such as adenosine, bradykinin, opioids) and the recruitment of prosurvival signaling pathways (such as the RISK, SAFE, and cyclic guanosine monophosphate pathways)[156] that converge on mitochondria and mediate cardioprotection by preserving mitochondrial function (less calcium overload, attenuated oxidative stress, and inhibited MPTP opening).

Ischemic Postconditioning in ST-Segment Elevation Myocardial Infarction

The ability to apply the therapeutic intervention at the onset of reperfusion in STEMI patients has greatly facilitated the translation of IPost into the clinical setting,[73,157] where it was shown that following direct stenting, IPost, performed within 1 minute of reflow by four episodes of 1-minute inflation and 1-minute deflation of an angioplasty balloon positioned upstream of the stent, reduced enzymatic myocardial infarction size (total creatine kinase) by 36% and improved myocardial perfusion (assessed by myocardial blush grade).[157] This study provided the first evidence that confirmed the existence of myocardial reperfusion injury in man,[158] as it clearly demonstrated that intervening at the onset of reperfusion was able to reduce myocardial infarction size.

A number of small studies have confirmed the myocardial infarction–limiting effects of IPost using serum troponin release,[159] myocardial single-photon emission computed tomography,[160,161] and cardiac magnetic resonance imaging,[162] with apparent long-term benefits on cardiac function.[161] However, a number of recent studies have also failed to show any beneficial effects with IPost,[163] and there are even some studies reporting possible detrimental effects with IPost.[164,165] Although recent meta-analyses have confirmed the myocardial infarction–limiting effects of IPost in STEMI patients,[166-168] the largest clinical study of more than 700 STEMI patients failed to find any benefits with

IPost in terms of ST-segment resolution, peak creatine kinase myocardial band levels, myocardial blush grade, or major adverse cardiovascular event at 30 days.[169] The reasons for these discrepancies are not fully understood but may have a variety of explanations.[28,170,171]

REMOTE ISCHEMIC CONDITIONING

The major disadvantage of IPC and IPost is that they both require an intervention to be applied to the heart directly; therefore, with the discovery of the phenomenon of remote preconditioning by Przyklenk and colleagues,[172] the idea that conditioning may indeed have a practical role to play in protecting the heart from IRI has been realized. Remote ischemic conditioning (RIC) is the phenomenon whereby the application of one or more brief cycles of nonlethal ischemia and reperfusion to an organ or tissue protects the heart against a lethal episode of acute IRI.

The actual mechanism through which an episode of brief ischemia and reperfusion in an organ or tissue away from the heart exerts protection against a subsequent sustained insult of acute myocardial IRI injury is currently unclear.[173-175] It has been suggested that the underlying mechanistic pathways and signaling cascades activated within the protected organ may be similar to those recruited in the setting of IPC and IPost (Fig. 38–7).[137,173] What remains uncertain is the mechanistic pathway responsible for conveying the cardioprotective signal from the remote preconditioned organ or tissue to the heart. The current paradigm suggests a neurohormonal pathway is central to the protective effect underlying RIC. In this regard, it has been shown that a substance or humoral factor generated by the preconditioning ischemia is transported to the heart to elicit protection. It has been shown that blood taken from a rabbit that has been preconditioned reduced MI size when transfused into a naïve rabbit,[176] suggesting the transfer of one or more humoral cardioprotective factors. Furthermore hexamethonium (a ganglion blocker),[177] resection of the neural innervation of the limb,[178,179] genetic inhibition of preganglionic vagal neurons in the brainstem,[180] and resection of the vagal nerve supply to the heart[181] have all been shown to abrogate the myocardial infarction–limiting effects of limb RIC, suggesting the requirement for an intact neural pathway for RIC cardioprotection. The exact details of the neural pathway have not been completely elucidated. The stimulation of the neural pathway in the RIC-treated organ or tissue appears to be a result of the local production of autacoids such as adenosine[182,183] and bradykinin.[184] Furthermore, proteomic analysis of plasma harvested from RIC-treated animals has failed to identify the cardioprotective factor(s), although the evidence suggests that the factor(s) is thermolabile and hydrophobic and is in the range of 3 to 8.5 kDa in size.[182-186] Recent studies have

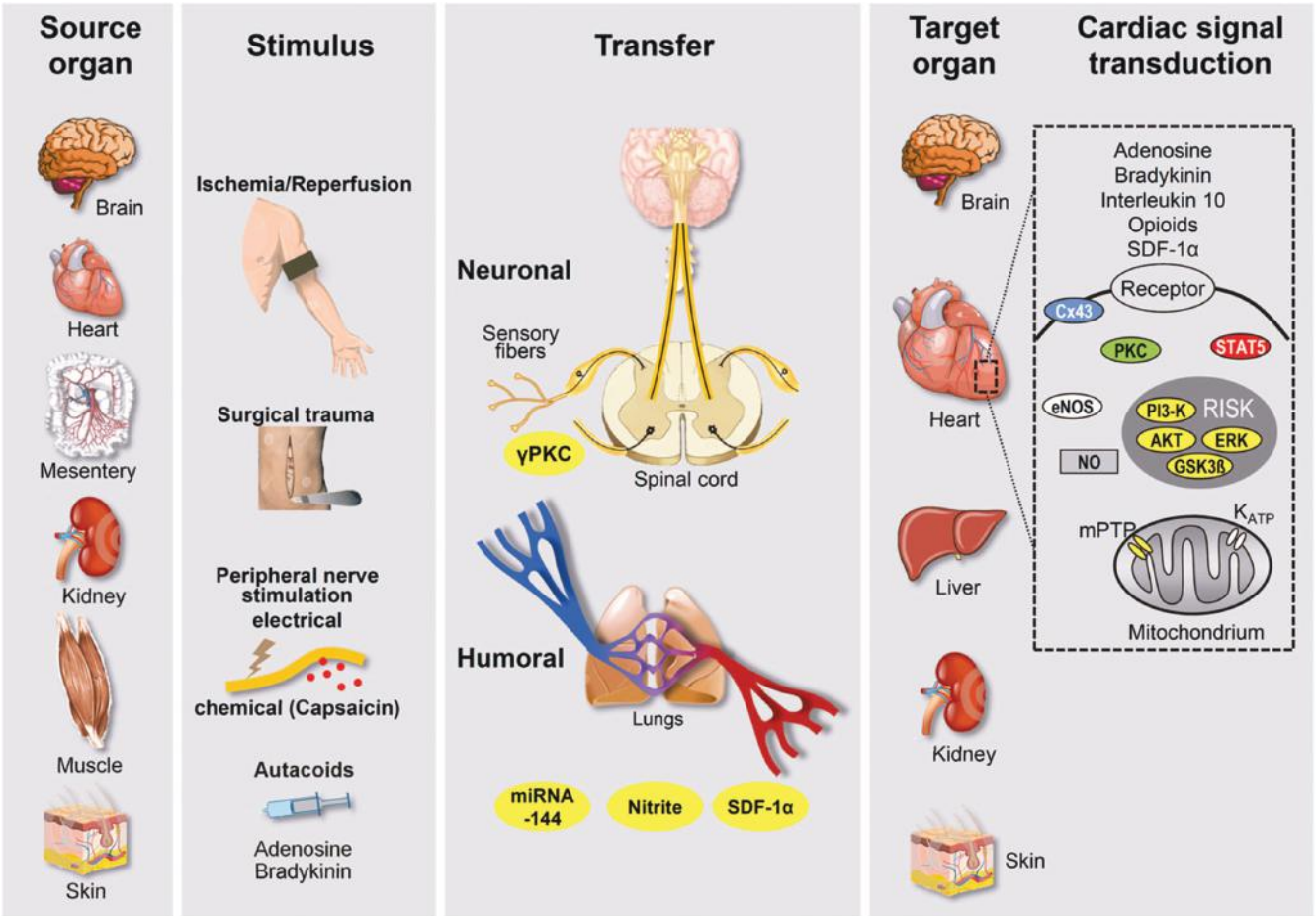

FIGURE 38–7. Schematic diagram of the signal transduction of remote ischemic conditioning from the source organ in response to several stimuli via neuronal and/or humoral transfer to the heart and other organs where a protective intracellular signal transduction cascade is activated. See text for details. Akt, protein kinase B; Cx 43, connexin 43; ERK, extracellular regulated kinase; eNOS, endothelial nitric oxide synthase; γPKC, protein kinase C γ; GSK3ß, glycogen synthase kinase 3ß; KATP, ATP-dependent potassium channel; mPTP, mitochondrial permeability transition pore; NO, nitric oxide; PI3-K, phosphoinositol-triphosphate kinase; RISK, reperfusion injury salvage kinase; SDF-1α, stromal derived factor 1α. Adapted with permission from Heusch G, Bøtker HE, Przyklenk K, et al: Remote ischemic conditioning. *J Am Coll Cardiol*. 2015 Jan 20;65(2):177-195

provided experimental evidence implicating calcitonin gene-related peptide,[187] stromal derived factor-1α,[188] nitrite,[189] and microRNA-144[190] as possible mediators of RIC cardioprotection, although conclusive evidence for their role as the bloodborne transferrable cardioprotective factors in RIC is lacking.

Furthermore, the generation of this cardioprotective factor has been shown to be dependent on an intact neural pathway to the RIC-treated limb,[191] with neural stimulation of the limb using direct nerve stimulation,[192] electroacupuncture,[193] topical capsaicin,[192] or transcutaneous electrode stimulation[194] generating a bloodborne transferrable cardioprotective factor and reducing myocardial infarction size in animal models. Finally, Jensen et al[195] have confirmed the need for an intact neural pathway to the limb by showing that the bloodborne transferrable cardioprotective factor was not produced by limb RIC in diabetic patients with a sensory neuropathy of the limb. In the myocardium, RIC activates both the RISK and the SAFE pathways, and their activation is species dependent[196]; in humans, RIC activates STAT5 in the myocardium.[197]

Studies are required to tease out the exact interplay between the neuronal and hormonal pathways underlying RIC and to identify the bloodborne cardioprotective factor(s) that mediate RIC cardioprotection.

Clinical Application of Remote Ischemic Conditioning

The discovery by Kharbanda et al[198] that cardioprotection could be achieved noninvasively by simply inflating and deflating a blood pressure cuff placed on the upper arm or thigh has facilitated a simple means of translating this phenomenon into the clinical setting. With the rush to clinical trial, the RIC stimulus to the limb itself has not been properly characterized and appears to be taken from experimental animal models most often using 5 to 15 minutes. However, the most effective limb RIC stimulus is still not known. Importantly, however, RIC can be delivered at different time points with respect to the ischemia/reperfusion insult, including 24 hours prior to the index ischemia (delayed remote IPC), immediately prior to the index ischemia (remote IPC), after the onset of index ischemia but prior to reperfusion (remote ischemic perconditioning),[199] at the onset of reperfusion (remote IPost),[200,201] and even 15 to 30 minutes into reperfusion (delayed remote IPost),[202] allowing its application in a wide variety of clinical settings of acute IRI.

Remote Ischemic Conditioning in Cardiac Surgery RIC using limb ischemia was first investigated by Guanydin et al in 2000[203] in a small eight-patient study, although perioperative myocardial injury was not assessed. In 2006, Cheung et al[204] were the first to demonstrate a cardioprotective effect with limb RIC in children undergoing cardiac surgery for congenital heart disease. They used four 5-minute cycles of lower limb ischemia and reperfusion induced by inflating and deflating a blood pressure cuff on the thigh and demonstrated reduced perioperative myocardial injury (less troponin I), reduced inotrope requirements, and decreased airway pressure. Yellon's group went on to report beneficial effects in terms of a 43% reduction in perioperative myocardial injury (72-hour area under the curve troponin T)[205] in adults undergoing CABG surgery.

Although recent meta-analyses appeared to confirm the cardioprotective effect of limb RIC in terms of reducing perioperative myocardial injury, the fundamental question was whether such a supposed benefit could be seen in terms of clinical outcome.[206-209] Most important in this regard are the recently reported large prospective multicenter randomized clinical trials (adequately powered to detect major adverse cardiovascular events) that confirm that limb RIC has no beneficial effects on major clinical outcomes in patients undergoing cardiac surgery.[210-212]

There have been many proposed reasons why RIC has not been observed in the setting of CABG, and this is the subject of much debate.[213-216]

Remote Ischemic Conditioning in Planned Percutaneous Coronary Intervention The setting of planned percutaneous coronary intervention (PCI) has also been used to examine the potential cardioprotective effects of RIC. It is known that injury occurs in about 30% of stable patients and up to 80% of unstable patients undergoing urgent PCI. The injury is measured by the release of serum cardiac enzymes. However, the etiology of this form of injury is not a result of acute IRI per se, but is mainly caused by acute ischemic injury (arising from distal branch occlusions and coronary embolization), which are complications that are more frequent following multivessel and complex PCI.[217] In 2006, Iliodromitis et al[218] were the first to investigate limb RIC in this clinical setting and found that in 41 patients RIC using bilateral upper arm cuff inflations/deflations actually exacerbated myocardial injury. In 2010, in a much larger study, Hoole et al[219] found that this intervention reduced the magnitude of PCI-related myocardial injury. The reasons for this discrepancy are not clear, but a recent meta-analyses found benefit in patients undergoing elective coronary intervention.[220]

Remote Ischemic Conditioning in ST-Segment Elevation Myocardial Infarction Compared to the above settings of CABG and PCI, the clinical setting of STEMI provides the most promising setting to investigate any cardioprotective therapy that targets myocardial IRI. To date, a number of proof-of-concept studies have reported cardioprotective effects with limb RIC in STEMI patients treated by primary angioplasty. This form of treatment is effective when given by paramedics in the ambulance,[221] as well as on arrival at the hospital prior to primary angioplasty[222,223] and at the onset of reperfusion at the time of primary angioplasty.[224] Importantly, as with the setting of CABG mentioned earlier, outcome studies will inform us as to whether RIC can indeed find a place in cardiovascular medicine, and this is now being jointly investigated in the CONDI2 and ERIC-PPCI trials (ClinicalTrials.gov Identifier: NCT01857414). The aim of these studies is to demonstrate whether RIC can reduce the rates of cardiac death and hospitalization for heart failure at 12 months.

PHARMACOLOGIC CARDIOPROTECTION

Finding appropriate pharmacologic therapy to protect against IRI has been ongoing for many years. It was with the improved understanding of the pathophysiology of ischemia-reperfusion, as well as the advent of the mechanisms associated with preconditioning, that the identification of a number of molecular targets amenable to pharmacologic manipulation became apparent.[132,133,136,139-141,218]

The history of pharmacologic cardioprotection has been hugely disappointing, with antioxidants, magnesium, calcium channel blockers, anti-inflammatory agents, erythropoietin, and atorvastatin all failing to reduce myocardial infarction size and/or improve clinical outcomes.[225] A number of pharmacologic cardioprotective strategies, such as adenosine[226] and glucose-insulin-potassium therapy,[227] have had mixed results, with cardioprotective efficacy depending on study design. A more targeted pharmacologic approach has also failed to limit myocardial infarction size or improve clinical outcomes in recent clinical studies that investigated the cardioprotective effects of therapeutic hypothermia,[228,229] mitochondria-targeted agents (eg, MTO-131),[230] cyclosporine A (CsA), and modulation of nitric oxide signaling using nitrite or inhaled nitric oxide.[231,232] Although cyclosporine A (CsA) was shown to reduce myocardial infarction size in an initial proof-of-concept clinical study,[233] it failed to improve clinical outcomes in a subsequent large multicenter clinical trial (the CIRCUS trial),[234] illustrating the challenge of translating cardioprotection into clinical benefit. The reason for the failure of CsA to reduce myocardial infarction size and improve clinical outcomes in STEMI patients is not completely understood. A number of factors to consider include the

inconclusive preclinical data, with some experimental studies failing to show a cardioprotective effect with CsA administered at reperfusion; the limited clinical data with only one positive clinical study with CsA in STEMI; the use of the CicloMulsion formulation of CsA; and the potential failure of CsA to reach its molecular target in time.[235,236]

Metoprolol

On a more optimistic note, there are a number of pharmacologic strategies that have shown promise. An interesting example of this is metoprolol. Early β-blocker therapy in reperfused STEMI patients is controversial and had largely been investigated in the pre-reperfusion era. However, recently, Ibanez and colleagues demonstrated that intravenous (IV) metoprolol administered prior to reperfusion in a porcine model reduced myocardial infarction size.[237] They followed this by undertaking a clinical trial (METOCARD-CNIC trial) demonstrating that IV metoprolol administered in the ambulance prior to primary angioplasty reduced myocardial infarction size and improved clinical outcomes (as a secondary end point) in anterior STEMI patients presenting early (< 6 hours from symptom onset).[18,125] More importantly, in the METOCARD-CNIC trial, not only did patients receiving pre-reperfusion IV metoprolol have CMR-evaluated smaller infarctions[18,238] and better long-term LVEF,[125] but also the incidence of left ventricular severe systolic dysfunction was significantly reduced.[125] Recently, the results of the EARLY BAMI trial have been reported. This trial recruited 600 STEMI patients (any location) presenting within 12 hours from symptom onset. Patients were randomized to IV metoprolol (10 mg) or placebo.[239] The primary end point was myocardial infarction size as assessed by CMR 1 month after infarction. The trial was neutral, and infarct size was not smaller in patients allocated to IV metoprolol. There were no signs of adverse effects in patients receiving IV metoprolol, and the incidence of ventricular fibrillation was significantly lower in metoprolol-treated patients. These data support the safety of this strategy in Killip I-II STEMI patients.

There are important differences between the METOCARD-CNIC and EARLY BAMI trials. Dose and timing of IV metoprolol administration were different between trials. In contrast to the METOCARD-CNIC trial, in the EARLY BAMI trial, patients received only one 5-mg dose at recruitment, and per protocol, the second dose was given in the catheter lab immediately before PCI. In fact, the first dose of metoprolol did not have any effect on blood pressure or heart rate, suggesting an underdosing effect. In this regard, a recent subanalysis from the METOCARD-CNIC trial demonstrated that the longer the "onboard" metoprolol time at the time of reperfusion, the higher was the infarct-reduction effect.[240] In fact, patients receiving IV metoprolol close to reperfusion had a mild protective effect, whereas those with a long time between the metoprolol 15-mg bolus and reperfusion had the largest reduction in infarct size and greatest improvement in long-term LVEF. These differences in dose and timing of metoprolol administration might explain the different conclusions from both trials. Given the clear safety profile and the low cost of this therapy (< $2.00), it is worth it to continue the clinical research and perform a definite large end point–powered trial. In the near future, the MOVE ON! trial (Ibanez and Fuster, principal investigators) will be initiated, and more than 1200 anterior STEMI patients will be recruited and randomized to IV metoprolol (15 mg immediately after diagnosis is made in the out-of-hospital setting) or placebo. The primary end point will be the composite of cardiovascular death, heart failure, implantable cardioverter-defibrillator insertion, or severe left ventricular dysfunction.

$P2Y_{12}$ Inhibition

As we know, optimal medical management of acute coronary syndromes at the time of initial presentation consists of many facets that include analgesia, supportive therapies where required (eg, inotropes, mechanical intra-aortic balloon pump), and dual antiplatelet therapy consisting of both the cyclooxygenase inhibitor aspirin and an adenosine diphosphate $P2Y_{12}$ receptor antagonist (clopidogrel, prasugrel, or ticagrelor). These latter antiplatelet interventions are orally loaded at the time of presentation in an attempt to reduce platelet aggregation and optimize postinterventional outcomes and coronary flow in the culprit vessel(s). Of great interest is the unanticipated significant mortality benefit of the $P2Y_{12}$ inhibitor ticagrelor in the PLATO study.[241] However, the benefits of this drug may not be fully explained by a pure antiplatelet effect. In this regard, ticagrelor has been shown to increase the levels of extracellular adenosine,[242] a mediator known to exert a wide range of benefits including vasodilation, inhibition of platelet aggregation, and leukocyte adherence to the vessel wall. In addition, it has recently been shown that cangrelor is significantly cardioprotective in mice,[243] rats,[244] rabbits,[170] and primates.[245] Interestingly, the protection conferred by cangrelor is dependent upon the presence of blood, with no evidence of protection ex vivo in crystalloid-perfused Langendorff heart.[170,244] Downey's group has shown that this protection is mediated through pathways typically recruited by ischemic conditioning, suggesting that $P2Y_{12}$ inhibition, via a blood component, leads to conditioning-like protection.[170,244] Therefore, IV $P2Y_{12}$ inhibition may thus have the dual advantage of optimizing both platelet inhibition and offering cardioprotection. Consequently, although the protective potential of these agents in the clinical arena has yet to be fully realized, given the strength of preclinical data and plausible mechanism, there is clear potential for harnessing and optimizing $P2Y_{12}$ inhibition at the time of reperfusion with the exciting prospect for further improving clinical outcomes.

Other Promising Agents

Another pharmacologic approach that has shown promise is that of exenatide, a synthetic version of exendin-4 (a peptide isolated from the saliva of the Gila lizard). Exenatide is an analogue of glucagon-like peptide-1 (GLP-1), a hormone that lowers blood glucose by stimulating insulin secretion.[246] Interestingly, GLP-1 and its analogues, such as exenatide, have been reported in experimental animal studies to reduce MI size through the activation of prosurvival intracellular signaling pathways when administered prior to reperfusion.[247,248] Clinical studies have found that administering exenatide prior to primary angioplasty increased salvage index in STEMI patients,[248-251] with most benefit observed in patients presenting with shorter ischemic times (< 132 minutes).[250] Whether this effect of exenatide translates to improved clinical outcomes in reperfused STEMI patients is not known and remains to be determined in a large randomized clinical trial.

Atrial natriuretic peptide given prior to myocardial reperfusion has also been shown to reduce myocardial infarction size in experimental animal studies. This is believed to occur via the activation of known prosurvival signaling pathways.[252] Kitakaze et al[253] translated this therapeutic approach in a large clinical study comprising 569 STEMI patients, in which administering carperitide (an atrial natriuretic peptide analogue) at the time of primary PCI was associated with a modest reduction in myocardial infarction size. Further studies are required to confirm these findings and investigate whether this therapeutic approach can improve clinical outcomes in reperfused STEMI patients.

COMBINATION REPERFUSION THERAPY: A NOVEL THERAPEUTIC STRATEGY

As detailed earlier, most attempts to reduce myocardial infarction size in STEMI patients have relied on using a single agent to target one single component of myocardial reperfusion injury. As detailed in Figure 38–2, myocardial IRI is the result of several mechanisms, and thus targeting

on individual phenomenon will unlikely reduce infarct size. The possibility of targeting several mechanisms simultaneously (either with one agent targeting different layers or by several agents administered simultaneously) is attractive, although not widely undertaken. The use of combination reperfusion therapy is still in its infancy, but because of the complex pathophysiology associated with IRI, this could be considered an important option. Interestingly, the RISK and SAFE signaling pathways have been shown to interact in remote limb perconditioning in combination with local IPost.[254] Alburquerque-Béjar et al[255] recently combined RIC with glucose-insulin-potassium and exenatide in a porcine acute myocardial infarction model and demonstrated an additive benefit in terms of myocardial infarction size reduction. The Combination Therapy in Myocardial Infarction (COMBAT-MI) study (ClinicalTrials.gov identifier: NCT02404376) is set to investigate the potential benefits of using RIC with exenatide on myocardial infarction size reduction in STEMI patients treated by primary PCI. Although an initial small clinical study failed to show an additive cardioprotective effect with RIC and IPost administered in combination in reperfused STEMI patients,[256] a recently published large study found increased myocardial salvage in patients given RIC and IPost in combination when compared with patients given IPost alone.[257]

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CHAPTER 39

EVALUATION AND MANAGEMENT OF NON–ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

David J. Moliterno and James L. Januzzi, Jr.

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As discussed in Chap. 36, *acute coronary syndromes* (ACS) refer to a pattern of clinical symptoms that are consistent with acute myocardial ischemia (Fig. 39–1)[1]; the pathophysiology, findings, and treatment of ACS range along a common spectrum. This chapter discusses two closely related forms of ACS, namely unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI).

The pathophysiology of ACS classically involves erosion or rupture of an atherosclerotic plaque with thrombus formation that obstructs the coronary artery lumen. Accordingly, patients with an ACS are frequently treated similarly with individual variations in management depending on the classification of patient risk.[1,2]

DEFINITION AND CLASSIFICATION

UA/NSTEMI is also termed *non–ST-segment elevation ACS (NSTE-ACS)*. Angiographic, intravascular ultrasound (IVUS), and angioscopic studies indicate that acute UA/NSTEMI usually results from the disruption of an atherosclerotic plaque with a subsequent platelet-rich thrombus that obstructs microvascular blood flow and may transiently or partially obstruct epicardial blood flow.

Initial diagnosis and management are based on information available at the time of presentation and are updated using new information accumulated over time.[1,2] Initial patient evaluation includes rapid efforts to distinguish noncardiac chest pain from myocardial ischemia. The clearest separation between UA and NSTEMI is the absence or presence, respectively, of abnormal concentrations of biomarkers indicative of myocardial necrosis, either the troponins (which are structural proteins) or creatine kinase-MB (which is a cardiac enzyme); the clearest separation between this end of the spectrum and ST-segment elevation myocardial infarction (STEMI) is made by the electrocardiogram (ECG).

A patient with symptoms consistent with ACS should have an ECG performed and interpreted within 10 minutes. The most important goal of the early ECG is to identify patients with STEMI who are candidates for immediate reperfusion therapy. Each patient should be given a provisional diagnosis of (1) definite ACS, which should be classified as STEMI, NSTEMI, or UA; (2) possible ACS; (3) a non-ACS cardiac condition (eg, chronic stable angina or heart failure); or (4) a noncardiac diagnosis, which should be as specific as possible. If a provisional diagnosis of ACS is assigned, risk assessment should be performed to determine the probability of major cardiac complications.[1,2] Such risk assessment is not just important among individuals with *definite* ACS; among patients with *possible* ACS, risk assessment should be used to determine the contingent probability of an adverse cardiac event *if the diagnosis of ACS is confirmed* because this information will guide appropriate triage, medical therapy, and timing of subsequent evaluation, including the use of invasive procedures.

Mismatch between myocardial oxygen supply and demand is the cause of myocardial ischemia. Most cases of UA/NSTEMI are attributable to acute reductions in myocardial oxygen supply, which are caused by a platelet-rich thrombus that develops after rupture or erosion of an atherothrombotic plaque (see Chaps. 33, 36, 37, and 38). The thrombus may be flow limiting but usually does not completely occlude the epicardial lumen; microembolization of platelet aggregates

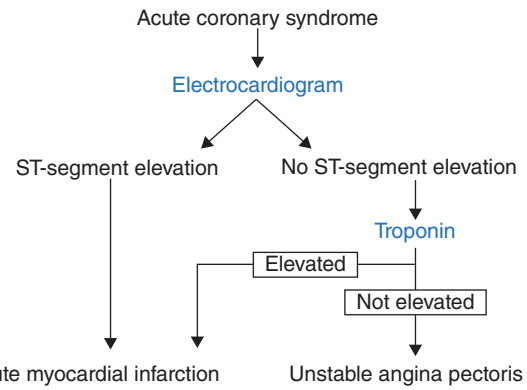

FIGURE 39–1. Framework for definition of the acute coronary syndromes. Syndromes presenting without ST-segment elevation on the 12-lead electrocardiogram are further subcategorized by the presence or absence of an elevated cardiac troponin concentration. Acute coronary syndromes without troponin elevation would be classified as unstable angina pectoris, whereas the presence of an elevated troponin concentration in the absence of ST-segment elevation defines patients with non–ST-segment elevation myocardial infarction.

and components of the disrupted plaque are key components of the acute ischemic syndromes and are likely responsible for the release of markers of myonecrosis.

Other less common causes of UA/NSTEMI include dynamic obstruction, which may be a result of intense focal spasm of a segment of an epicardial coronary artery (Prinzmetal or variant angina, as discussed specifically in the later section Variant Angina). UA/NSTEMI may also occur because of severe fixed narrowing of the epicardial coronary artery without spasm or thrombosis, which may occur because of progressive atherosclerosis or restenosis after percutaneous coronary intervention (PCI). In such cases, the presentation may be more gradual than among those with a de novo plaque rupture and may initially manifest consequent to increase in myocardial oxygen demand beyond what can be supplied by the diseased epicardial coronary arteries. Less commonly, UA/NSTEMI may be caused by coronary dissection or vasculitis; spontaneous dissection of the coronary artery (SCAD) is an increasingly recognized entity, particularly in younger, female patients.[3]

Secondary UA/NSTEMI occurs when the precipitating condition is extrinsic to the coronary arterial bed. Such patients usually have underlying fixed coronary atherosclerotic narrowing; however, secondary UA/NSTEMI may also be seen in the absence of severe obstructive disease with acute increases in myocardial oxygen demand (eg, fever, tachycardia, hypertensive emergency), reductions in coronary blood flow (eg, hypotension), or diminution in myocardial oxygen delivery (eg, severe anemia), or a combination of these (eg, pulmonary embolism, sepsis). Among individuals with severe left ventricular (LV) hypertrophy, secondary UA/NSTEMI may occur with a lesser degree of imbalance of oxygen supply and demand.

INITIAL PRESENTATION

UA may present as angina that is new onset; it may manifest as angina increasing in frequency, duration, or severity; or it may present immediately as rest angina. NSTEMI typically presents with rest symptoms that are more prolonged or intense. The different presentations of UA reflect differences in pathophysiology and short-term prognosis, which have implications for therapy. Whereas rest angina more commonly results from an unstable coronary plaque (as described earlier and in Chaps. 33, 37, and 38), new-onset or progressive exertional angina more commonly is caused by fixed atherosclerotic disease without plaque rupture. Other settings include UA/NSTEMI within 1 year after PCI, which may be caused by restenosis or from acute thrombosis of a drug-eluting stent; the latter scenario typically occurs in the context of suspension of dual antiplatelet therapy (DAPT).

Patients with ACS may present with "atypical" symptoms, which include acute dyspnea, indigestion, unusual locations of pain, agitation, altered mental status, profound weakness, and syncope. Such presentations are more common in women, advanced elderly individuals, and patients with long-standing diabetes mellitus and are associated with higher risk for death and major complications.[4] In addition, UA/NSTEMI may be present without evident clinical symptoms, particularly among patients in the perioperative state and those with comorbid medical conditions such as diabetes.

DIAGNOSIS

Patients with symptoms suggestive of ACS require a rapid evaluation and expedient decision making, with the intensity of monitoring and therapy determined both by the probability of ACS and the associated likelihood of a poor outcome if ACS is subsequently confirmed and/or managed without revascularization. Factors that modulate the development and outcomes of ACS are listed in Table 39–1. Approximately 15% of patients evaluated in US emergency departments with symptoms suggestive of ACS ultimately have an ACS diagnosis confirmed; conversely, patients with unrecognized ACS have a substantially higher mortality risk. Thus, an organized, efficient, and systematic strategy is needed to avoid exposing patients to risk associated with both the diagnostic procedures as well as the therapies used and unnecessary resource utilization, while simultaneously ensuring accuracy of diagnosis. Formal chest pain or ACS protocols or critical pathways are

TABLE 39–1. Factors That Modulate the Development and Complications of Acute Coronary Syndromes

Location of the culprit coronary lesion
Stenosis morphology and severity
Extent of plaque rupture or erosion
Inflammatory substrate
Endothelial function
Degree of coronary vasoconstriction
Microembolization and microvascular obstruction
Extent of collaterals
Platelet aggregability and reactivity
Resistance to antiplatelet agents
Leukocyte activation
Thrombotic factors and intrinsic clotting activity
Level of fibrinolytic activity
Blood viscosity
Heart rate and blood pressure
Catecholamine levels (smoking, cocaine, stress)
Blood lipid levels
Medical comorbidities (eg, thyroid, renal, pulmonary disease)
Compliance with lifestyle and pharmacologic therapies

recommended strategies to provide a systematic approach to the evaluation of possible ACS and to provide greater adherence to guideline recommendations.[1,2]

INITIAL EVALUATION

The initial evaluation of a patient with possible UA/NSTEMI is focused on addressing two interrelated questions[1,2]: (1) How likely are the presenting symptoms and signs to be attributable to an ACS event? (2) If ACS is confirmed, what is the risk to the patient? This early assessment of short-term risk determines the intensity of initial and often subsequent treatment. Determining whether the presentation is attributable to ACS may prove challenging in the absence of ECG changes or typical patterns of cardiac biomarker elevation. In a patient with known coronary artery disease (CAD), typical symptoms are more likely to be caused by myocardial ischemia, especially if the current symptoms are identical to previous episodes when CAD was objectively documented as the cause. However, because the accuracy of descriptive chest pain characteristics is only moderate, a systematic approach to patient evaluation is required.

HISTORY

Patients with ACS often experience discomfort typical of angina, but such episodes are more severe, prolonged, and with lower threshold; they often occur at rest or with very low levels of exertion. Also, chest discomfort because of UA/NSTEMI is less likely to be completely relieved by nitroglycerin (NTG) than pain from stable angina. Some patients may have no chest discomfort but present solely with jaw, neck, ear, arm, or epigastric discomfort or with dyspnea in the absence of pain. These can be "anginal equivalents."

Nausea, perspiring, and/or shortness of breath may accompany episodes of chest discomfort. In elderly or diabetic patients, these symptoms may be the only indication that myocardial ischemia is present. Women also present challenges with regard to diagnosis as they are more likely than men to have ACS with an "atypical" presentation[4] and diagnoses such as SCAD are much more common in women; because SCAD usually occurs in coronary arteries without substantial atherosclerosis, affected patients are often medically quite healthy (without conventional risk factors for CAD), making consideration for ACS less likely. When UA is suspected in a patient younger than age 50 years, it is particularly important to consider cocaine use. Cocaine can cause coronary vasoconstriction, vasospasm, and thrombosis in addition to its direct effect on altering myocardial oxygen demands through increases in heart rate and blood pressure.[5]

Evaluation of patients with suspected UA/NSTEMI should include the physician's opinion of the *probability* of the symptoms being caused by myocardial ischemia, categorizing the presentation into high-, intermediate-, or low-probability categories (Table 39–2).

TABLE 39–2. Likelihood That Chest Symptoms Are Caused by Myocardial Ischemia Attributable to Obstructive Coronary Artery Disease

High likelihood
Known coronary disease (particularly recent PCI)
Typical angina reproducing prior documented angina
Hemodynamic or ECG changes during pain
Dynamic ST-segment elevation or depression of ≥ 1 mm
Marked symmetric T-wave inversion in multiple precordial leads
Elevated cardiac enzymes in a rising and falling pattern
Intermediate likelihood
Absence of high-likelihood features and any of the following:
Typical angina in a patient without prior documented angina
Atypical anginal symptoms in diabetics or in nondiabetics with two or more other risk factors
Male gender
Age older than 70 y
Extracardiac vascular disease
ST depression 0.5-1.0 mm or T-wave inversion of ≥ 1 mm
Low-level troponin elevation that is "flat" and does not rise or fall
Low likelihood
Absence of high- or intermediate-likelihood features but may have:
Chest discomfort reproduced by palpation
T waves flat or inverted < 1 mm
Normal ECG

Abbreviations: ECG, electrocardiogram; PCI, percutaneous coronary intervention.

ELECTROCARDIOGRAPHY

The diagnostic yield of the 12-lead ECG is enhanced greatly if it can be recorded during an episode of chest discomfort; consideration for frequently obtaining repeat tracings may increase sensitivity. Although a completely normal ECG during chest pain does not rule out ACS, it reduces the probability significantly and is a favorable prognostic sign. Transient ST-segment depression of at least 0.5 mm (Fig. 39–2) that appears during chest discomfort and disappears after relief provides objective evidence of transient myocardial ischemia. When it is a constant finding with or without chest pain, it is less specific. A common but nonspecific ECG pattern in patients with UA/NSTEMI consists of persistent negative T waves over the involved area (Fig. 39–3). Deeply negative T waves across the precordial (anterior) leads suggest a proximal, severe, left anterior descending coronary artery stenosis as the culprit lesion and are considered a marker of high risk.

ECG abnormalities may appear or progress in the absence of new symptoms or signs in patients with ACS. Accordingly, it is appropriate and diagnostically useful to obtain serial ECGs during the initial observation period, before discharge, and during recurrent episodes of chest pain.

BIOCHEMICAL CARDIAC MARKERS

Biochemical cardiac markers are useful for both the diagnosis of myocardial necrosis and the estimation of prognosis. Cardiac troponins are the preferred biomarkers for the diagnosis of myocardial infarction (MI), whereas the MB band of creatine kinase (CK-MB) is a less preferred option and should only be used when troponin is not available.[6] Cardiac troponins T and I (cTnT and cTnI) are structural components of the cardiac contractile apparatus (they are not enzymes) and are found not only in the sarcomere of the cardiomyocyte, but also in small concentrations within the cytosol. Both cTnT and cTnI are thought to be nearly entirely cardiac in origin; this confers very high cardiac specificity. Numerous studies have demonstrated that even minor troponin elevations are independently associated with adverse events in populations with non–ST-segment elevation ACS.[7] Many of these

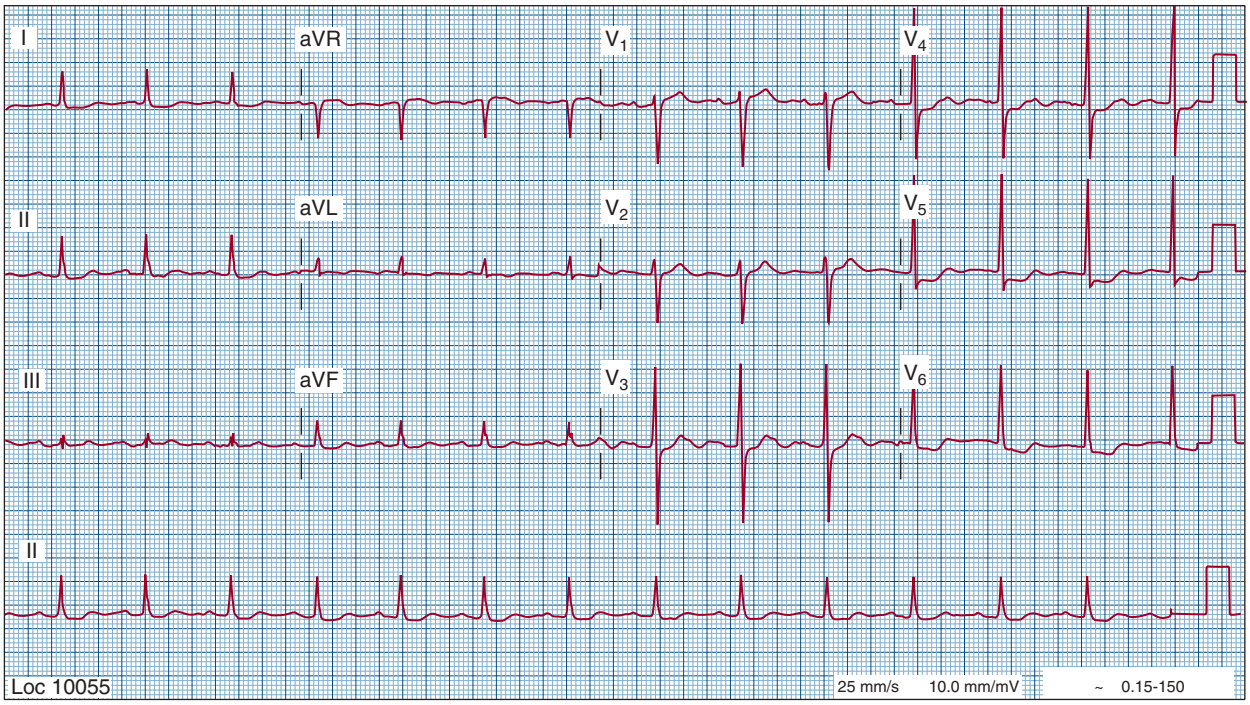

FIGURE 39–2. Electrocardiogram recorded during an episode of chest pain at rest in a patient with unstable angina. ST-segment depression above 1 mm is present in leads V_4 to V_6. This abnormality was not present on the baseline tracing. The chest pain and ST-segment depression disappeared promptly after the administration of sublingual nitroglycerin.

patients will have normal levels of CK-MB. Coronary angiographic trials have demonstrated that in patients with ACS, troponin elevation is associated with multivessel coronary disease, complex lesion morphology, and visible thrombus, as well as with impairment in microvascular function.[8] These findings explain the consistent association between troponin concentration, even at low levels, and recurrent ischemic events in patients with ACS.

As troponin assays become more sensitive, the proportion of individuals with elevation continues to increase; with current assays, more than 30% of individuals with a presentation of UA/NSTEMI have detectable levels of cTnI or cTnT, and with more sensitive assays that will soon be clinically available, the proportion is two- to three-fold higher. Such highly sensitive troponin (hsTn) assays are increasingly available in several countries. The main advantages of hsTn assays

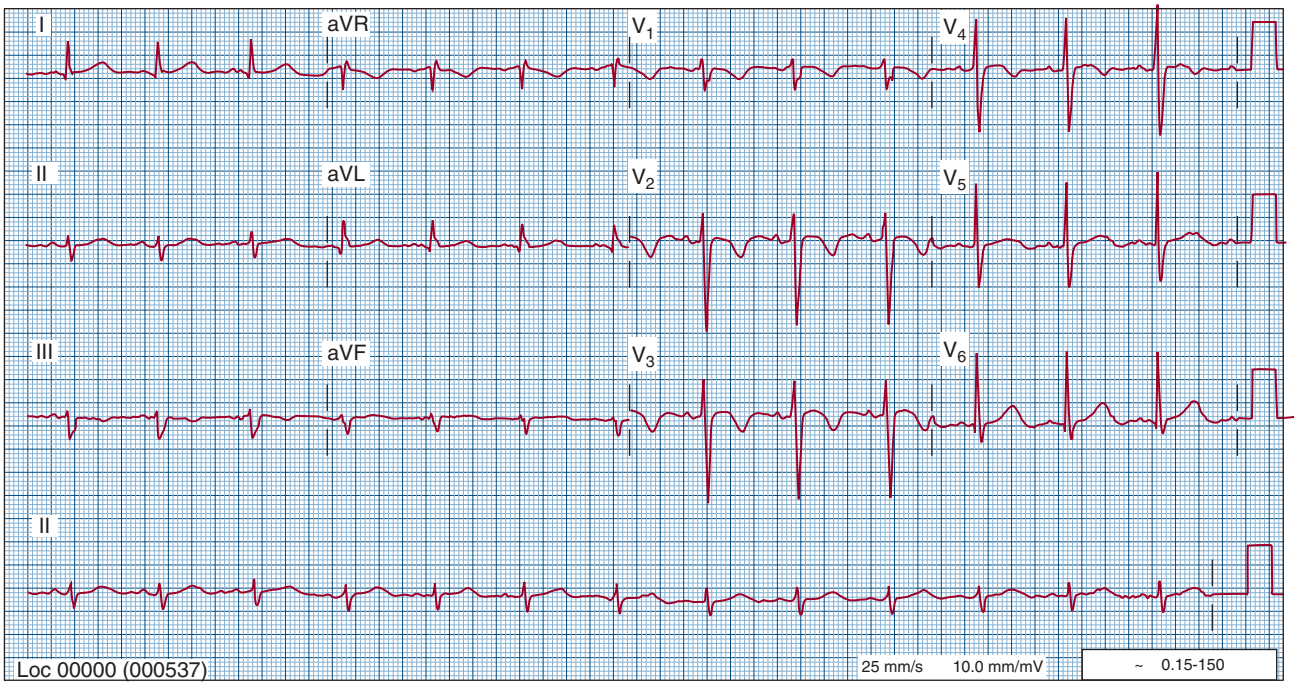

FIGURE 39–3. Electrocardiogram recorded during a pain-free interval from a patient hospitalized with unstable angina. The negative T waves in leads V_1 to V_4 had been upright on a previous tracing. The culprit lesion was located in the left anterior descending coronary artery.

over conventional methods are superior sensitivity to detect minute quantities in TnT or TnI concentrations and increased analytical precision at these very low concentrations. In this regard, compared to conventional troponin methods, hsTnT and hsTnI have both been shown to be more likely to be abnormal at first draw (Fig. 39–4), to provide incremental prognostic information, and (as noted) to reclassify the diagnosis from UA to NSTEMI in approximately 30% of patients.[9] The increased sensitivity of hsTn assays also allows for very rapid exclusion of myocardial injury, if extremely low concentrations are noted at presentation[10]; such patients could still have UA, however. Lastly, the increased analytical precision (which allows for resolution of small changes in hsTn over short periods of time) facilitates strategies of accelerated diagnostic pathways to exclude NSTEMI in as little as 1 hour.[11] With broader availability of hsTnT and hsTnI will come greater experience with these novel assays.

Present recommendations support serial measurement of troponins in patients with suspected NSTE-ACS, seeking a rise and/or fall in troponin concentration and reserving the diagnosis of NSTEMI for patients with clinical signs/symptoms, ECG changes, or loss of myocardial function on noninvasive assessment.[6] Short of these corroborating elements, caution is necessary. It is clear that patients who have isolated elevation in troponin levels should be classified as having an NSTEMI, *provided the clinical syndrome is consistent with ACS.* This caveat is critically important and is discussed further in the later sections. A reflex cardiac evaluation based solely on an elevated cardiac biomarker without considering whether the episode is indeed consistent with an ACS is inappropriate and may be harmful. In recent years, several different "rule-in" and "rule-out" protocols have been proposed. The most recent European Society of Cardiology (ESC) guidelines for the management of ACS provide excellent examples of both by using the highest sensitivity troponin assays.[2]

Although troponins are highly specific for myocardial injury, they are not specific for the *cause* of cardiac injury. Multiple noncardiac diagnoses may cause cardiac injury and lead to troponin elevation (Table 39–3). Particular consideration should be given to the diagnosis of acute pulmonary embolism, which may present with nonspecific chest symptoms, tachycardia, and ST- and T-wave changes along with low-level elevation in cardiac troponins. Moreover, among individuals with chronic cardiovascular (CV) conditions, such as heart failure or chronic CAD, as well as individuals from the general population with diabetes, chronic kidney disease, or asymptomatic LV hypertrophy or LV dysfunction, *chronic* troponin elevation may be seen, even in the absence of signs and symptoms of ischemia.[12-14] Therefore, it is crucial to interpret troponin values in the context of the clinical presentation and available clinical information; this will become all the more important as hsTnT and hsTnI become available.

In most non-ACS conditions associated with cardiac injury, patients with detectable troponin are at increased risk for adverse cardiac outcomes.[14,15] However, it should be recognized that in patients with atypical presentations, elevation in troponin may be caused by a process other than ACS. Interpreting troponins in patients with renal failure presents unique problems. Although persistent troponin elevation frequently occurs in patients on hemodialysis even in the absence of signs of ACS, detectable cTnT or cTnI is still associated with very high cardiac event rates.[16-18] Knowledge of prior troponin values may help to assess whether a current troponin elevation is new or changing (ie, potentially caused by ACS) or chronic. If ACS is suspected, troponin elevation should be interpreted similarly in patients with and without chronic kidney disease.

As troponin assays become increasingly sensitive, elevations from causes other than ACS are becoming more common and more frustrating for consultant cardiologists. Indeed, recent estimates suggest that as many as 50% of troponin elevations occurring in the hospital setting may be attributable to disease processes other than ACS, including heart failure.[19,20] Although hsTn assays improve early sensitivity for MI detection,[21] they will increase the proportion of elevated levels from causes other than ACS.

At present, few data are available to help clinicians distinguish ACS causes of troponin elevation from other causes. Elevations caused by ACS are usually of a greater magnitude and should demonstrate a dynamic pattern characterized by a transient increase or decrease in values. Demonstration of a transient increase or decrease may improve the specificity for ACS. When a cause other than ACS is suspected, treatment should focus on the underlying disease process. An echocardiogram should be considered, given the frequent association of chronic troponin elevation with cardiac structural abnormalities. Empiric treatment with aspirin (ASA) is recommended unless contraindicated, and in selected individuals, empiric treatment with β-blockers and an evaluation for ischemia may be considered after the acute illness has been stabilized.

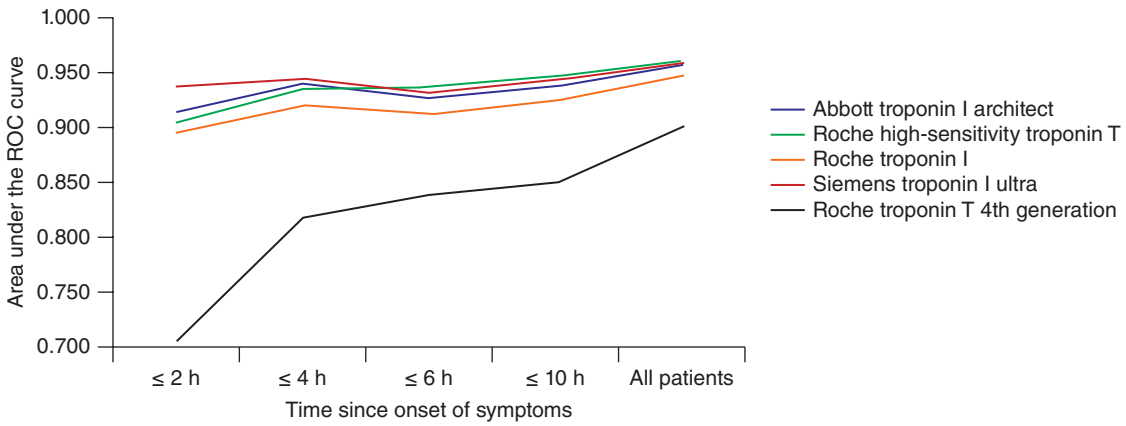

FIGURE 39–4. Comparison of the diagnostic sensitivity and specificity (expressed as area under the receiver operating characteristic [ROC] curve) for acute myocardial infarction as judged by conventional troponin T versus several highly sensitive troponin assays. Among patients with chest pain, the more sensitive troponin methods were more likely to be abnormal at presentation, compared to conventional troponin methods, whose accuracy was better at later time points. Data from Reichlin T, Hochholzer W, Bassetti S, et al: Early diagnosis of myocardial infarction with sensitive cardiac troponin assays, *Engl J Med.* 2009 Aug 27;361(9):858-67

TABLE 39–3. Causes of Troponin Elevation Other Than Acute Coronary Syndromes

Acute Disease

Cardiac and vascular

- Acute heart failure
- Acute aortic dissection
- Apical ballooning syndrome
- Endocarditis
- Myocarditis
- Pericarditis
- Cerebrovascular accident
  - Ischemic stroke
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- Kawasaki disease
- Critical illness
  - Hypotension
  - Gastrointestinal bleeding
  - Thrombotic thrombocytopenic purpura

Respiratory

- Acute pulmonary embolism
- Acute respiratory distress syndrome

Muscular damage

- Rhabdomyolysis

Infectious

- Sepsis
- Viral illness

Other acute causes of troponin elevation

- Toxic exposure
  - Carbon monoxide
  - Hydrogen sulfide
  - Colchicine

Chronic Disease

- Chronic heart failure
- Cardiac infiltrative disorders
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
  - Scleroderma
- Hypertension
- Diabetes
- Hypothyroidism
- End-stage renal disease

Myocardial Injury

- Cancer chemotherapy
- Envenomation
- Endurance athletics

CHEST PAIN UNITS

The evaluation of patients with chest pain who may have an ACS can be difficult and uncertain. Hospitalizing all such patients for an extensive workup is unwise and results in unnecessary tests with patient risk and expense. However, missing the diagnosis of MI is one of the leading causes of malpractice claims for emergency department physicians in the United States, and patients with missed MI have a higher mortality rates. The chest pain unit was developed as a strategy to provide systematic care, prevent missed MI diagnoses, and avoid unnecessary hospitalizations.

Most chest pain units are in or near the emergency department and are designed to monitor patients with either possible ACS or definite ACS but with low-risk features. Criteria usually include chest pain or related symptoms that may indicate myocardial ischemia but with a normal or nondiagnostic ECG and a normal initial set of cardiac enzymes. In most units, cTnT or cTnI is measured at serial intervals for 6 to 9 hours; as noted, hsTn assays increase first-draw sensitivity and provide utility to considerably shorter "rule-out" protocols.[21,22]

Patients promptly receive ASA, an intravenous (IV) line, ECG monitoring, and a 12-lead ECG at specific intervals. If cardiac biomarkers remain negative and no ischemia is detected, a symptom-limited stress test may be performed for diagnostic and prognostic purposes or the patient may be discharged and sent home.[1] In low-risk patients who present at night or on the weekend, it is reasonable to perform the stress test as an outpatient, provided it can be done within 72 hours.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

Coronary computed tomography angiography (CTA) is a potentially useful test among some patients undergoing an ACS/chest pain evaluation[23,24] (see Chap. 17), providing high-quality imaging of the coronary artery anatomy and high sensitivity for CAD (Fig. 39–5). The high sensitivity of CTA for coronary plaque has been found to impart a high negative predictive value for ACS among low- to intermediate-risk patients typically seen in chest pain observation units. Emerging techniques, such as identification of high-risk plaque, help to add to the evaluation of patients with coronary atherosclerosis detected on CTA.[25] Other advantages of CTA are that the procedure allows for visualization of other cardiac and pulmonary structures (potentially allowing for detection of unsuspected pathology, such as pericardial effusion) and delivers good sensitivity for detection of less common causes of ACS, including SCAD.

In contrast to the high sensitivity of CTA for plaque presence, specificity is a limitation with CTA because many lesions that appear obstructive by CTA are nonobstructive with coronary angiography; this is most often a result of "negative remodeling" of the coronary vessel, such that large plaque burden may not project into the lumen of the artery. Because of this, the positive predictive value is moderate for significant luminal obstruction.[26] Additional limitations of CTA include difficulty in plaque severity quantification in the context of heavy coronary calcification, the requirement for intravenous contrast administration, and exposure to ionizing radiation; newer algorithms for CTA performance now allow for substantial reduction in radiation exposure, however. Establishment of a CTA program requires institutional commitment along with specialized training for interpreting physicians.

Randomized comparative effectiveness studies suggest that appropriate use of CTA in patients at low to moderate risk for ACS may reduce need for hospital discharge and shorten time to disposition from the emergency department.[27] In such studies, CTA was highly sensitive to detect presence of coronary atherosclerosis and thus provided high sensitivity for ACS. Outcomes were largely the same in

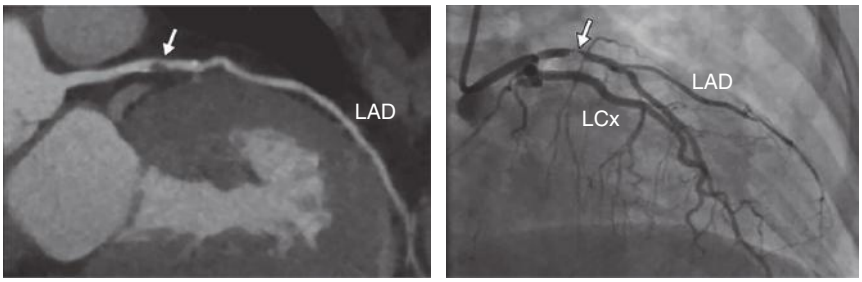

FIGURE 39–5. Side-by-side comparison of computed tomographic coronary angiography versus invasive angiography in a patient presenting with chest discomfort, ambiguous electrocardiography, and normal troponin concentrations. A severe stenosis of the left anterior descending (LAD) artery is identified using computed tomographic coronary angiography (left panel, *white arrow*) and confirmed at invasive angiography (right panel, *white arrow*). LCx, left circumflex artery.

those evaluated with CTA versus standard methods (such as myocardial perfusion imaging); downstream testing (such as invasive coronary angiography) may also be increased, presumably as a result of visualization of coronary anatomy.

In the balance, CTA represents a potentially useful test when the probability of severe CAD is low to moderate, study quality may be optimized (heart rate can be reduced to 70 bpm or lower with a β-blocker, and nitrates may be provided), dye exposure is not contraindicated, and anatomic rather than physiologic information is preferred. How the use of CTA will be affected by more widespread use of hsTnT and hsTnI is ambiguous, but the combination appears promising.[28]

RISK STRATIFICATION

Initial risk assessment of UA/NSTEMI dictates the appropriate intensity of initial therapy. At the low end of the risk scale, a patient may be discharged home with ASA and an early outpatient stress test. By contrast, high-risk patients may be hospitalized in a coronary care unit, treated with multiple drugs, and undergo coronary angiography urgently as a prelude to revascularization.

CLINICAL FEATURES

The American College of Cardiology (ACC)/American Heart Association (AHA) 2014 Guideline Update for the Management of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction[1] and the 2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation[2] recommend (Class I, Level of Evidence [LOE] B) using risk-stratification models, such as the Global Registry of Acute Coronary Events (GRACE) Risk Model Nomogram[29] or the Thrombolysis in Myocardial Infarction (TIMI) Risk Score[30] to assess prognosis. Web-based applications from GRACE (gracescore.org) and TIMI (timi.org) are available.

Features suggesting high risk include ongoing chest pain that lasts longer than 20 minutes, reversible ST-segment changes of at least 0.5 mm, elevated markers of myonecrosis, and signs of significant LV dysfunction. In addition to these features, the GRACE Risk Model Nomogram uses Killip class, vital signs, age, and creatinine in a stepwise scoring system and considers whether the patient had cardiac arrest at admission. Generally, lower risk patients are younger, have worsening angina without rest pain, have a normal or unchanged ECG without evidence of previous infarction, and have normal cardiac enzymes.

It is increasingly recognized that risk assessment should be both integrative and dynamic. Tools that account for multiple risk predictors provide clear enhancement over evaluation of single variables, as discussed later. Moreover, the risk assessment should be updated during hospitalization. For example, continuing angina with ST-segment changes despite medical therapy is an ominous sign that should prompt urgent coronary arteriography with probable revascularization. Episodes of silent ST-segment depression detected by ambulatory ECG recordings also predict an unfavorable course.

ELECTROCARDIOGRAPHY

The ECG is too often overlooked as a powerful risk stratification tool in patients with UA/NSTEMI. Even minor ST depression (> 0.5 mV) is associated with a markedly increased mortality rate. Among 9461 patients enrolled in the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) study, mortality at 30 days was 5.1% in patients with ST-segment depression versus 2.1% among those without ST-segment depression.[31] Also, patients with isolated T-wave inversion have a more favorable prognosis than do those with ST-segment depression.[32] It bears repeating that repeat ECG is recommended in those with an initially normal tracing, particularly during periods of repeat symptoms when an initially normal tracing was obtained at a time when chest discomfort was not present.

BIOCHEMICAL MARKERS

Troponin measurements should be used in the risk stratification of patients with UA/NSTEMI to supplement the assessment from clinical and ECG data; consensus documents suggest that CK-MB not be used when troponin is available.[6] The combination of troponin elevation and ST-segment depression identifies a group at particularly high risk.[33] The association of troponin elevation with high-risk coronary lesion morphology provides mechanistic insight into studies demonstrating that patients with even minor elevations in cTnT or cTnI derive substantial benefit from an aggressive approach with antithrombotic therapies and an early invasive management strategy.[33-35]

Plasma levels of B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP) may increase in response to cardiac ischemia in proportion to the size and severity of the ischemic insult.[36] In patients with UA/NSTEMI, higher levels of BNP or NT-proBNP measured at presentation or during hospitalization are associated with increased risk for subsequent death or heart failure. As such, measurement of BNP or NT-proBNP may add additive information to troponin values; such measurement receives a Class IIb indication in the 2014 guidelines. Because coronary ischemia in a patient with incident or prevalent heart failure is associated with substantially greater risk than in a patient without heart failure and because coronary ischemia may lead to decompensation of heart failure itself, use of natriuretic peptide testing may be helpful to round out the diagnostic picture in such patients.

Although many other biomarkers have been proposed for measurement at various time points after ACS, with the exception of troponin and BNP or NT-proBNP,[37] few have demonstrated the level of robust evidence necessary for consideration of measurement in routine practice. With increased use of hsTn, the bar will be even higher for newer biomarkers to show clinical utility.

NONINVASIVE TESTING FOR ISCHEMIA

Stress testing (Table 39–4) is commonly used for risk assessment in patients with UA/NSTEMI who are managed with an initial conservative

TABLE 39–4. American College of Cardiology/American Heart Association Noninvasive Risk Stratification

High risk (> 3% annual mortality rate)
1. Severe resting LV dysfunction (LVEF < 0.35)
2. High-risk treadmill (score ≤ 11)
3. Severe exercise LV dysfunction (exercise LVEF < 0.35)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilatation or increased lung uptake
7. Stress-induced moderate perfusion defect with LV dilatation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving > 2 segments) developing at a low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (≤ 120 bpm)
9. Stress echocardiographic evidence of extensive ischemia
Intermediate risk (1%-3% annual mortality rate)
1. Mild to moderate resting LV dysfunction (LVEF 0.35-0.49)
2. Intermediate-risk treadmill score (score −11 to +5)
3. Stress-induced moderate perfusion defect without LV dilatation or increased lung intake
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses or dobutamine involving ≤ 2 segments
Low risk (< 1% annual mortality rate)
1. Low-risk treadmill (score ≥ +5)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

Abbreviations: LV, left ventricular; LVEF, left ventricular ejection fraction.

strategy (also called an *ischemia-guided strategy*; see below). Low-risk and some intermediate-risk patients who stabilize with medical therapy are candidates for stress testing for risk stratification. Stress tests should be symptom limited rather than submaximal, and a stress ECG without adjunctive imaging is appropriate unless baseline ECG abnormalities would preclude adequate interpretation. Those with high-risk findings, such as ST-segment depression at low exercise levels, or large, reversible perfusion defects should undergo coronary arteriography; those with negative or low-risk results can be treated medically. Low-risk patients who complete a stay in a chest pain unit without objective evidence of myocardial ischemia can safely undergo stress testing for diagnosis and prognostic purposes either immediately or, when possible, within 48 hours as an outpatient.[1]

In patients who are unable to exercise, pharmacologic testing with dipyridamole, adenosine, regadenoson, or dobutamine can be used to provide the stress, and sestamibi imaging or echocardiography can be used as a method of assessment (see Chaps. 13, 15, and 18). Stress testing is not needed in patients whose clinical features already put them into a high-risk category; instead, they should undergo early coronary arteriography.

CORONARY ANGIOGRAPHY

The use of coronary CTA has been previously discussed (see also Chap. 17). Among patients with stable CAD, risk is proportional to the number of vessels with greater than 50% diameter stenosis and the presence and severity of LV dysfunction. However, the relative prognostic impact of the extent of CAD is probably less with ACS because the risk of short-term events is dominated by features of the *culprit lesion*, such as whether it induces ST-segment depression or troponin release.

Among patients with UA/NSTEMI who undergo arteriography, approximately 25% have one-vessel disease, 25% have two-vessel disease, and 25% have three-vessel disease. Ten percent have significant main stenosis, and the other 15% will have coronary luminal narrowing of less than 50% or normal-appearing vessels on arteriography[38] (see also Chap. 20). Patients with left main stenosis of at least 50% or three-vessel disease with LV dysfunction derive a survival benefit from coronary artery bypass graft (CABG) surgery compared with medical therapy. Importantly, patients with *no* significant lesions at angiography benefit from a reorientation of their management. Noncardiac causes of chest pain should be considered (including pulmonary embolism), as well as "syndrome X" and variant angina. If the coronary arteries are completely angiographically normal, antithrombotic and antiplatelet drugs can often be discontinued and the need for antianginal medication reassessed. Patients who are most likely to have no significant lesions at angiography tend to be women with no ECG changes. Nevertheless, the finding of no significant lesions at angiography is usually unanticipated. Importantly, symptomatic patients without significant obstructive CAD seen with angiography may have more severe atherosclerosis detected by IVUS caused by eccentric coronary artery remodeling, which preserves the lumen size. Therefore, in selected patients, more invasive testing at the time of coronary arteriography, including use of IVUS or measurement of coronary flow reserve using adenosine as a vasodilating agent, may be indicated to help better establish the cause of the acute chest pain.

RISK MODELS AND RISK SCORES

Risk models and scores predict a probability for adverse outcomes based on combinations of clinical, ECG, and laboratory data available at presentation. These tools integrate multiple predictors and thus provide a more comprehensive risk assessment than does focus on a single variable. Whereas the TIMI and PURSUIT scores were derived from clinical trial databases, the GRACE score was derived from a large international registry.[30,31,39] Although all three methods discriminate patients at high versus low risk for short- and intermediate-term adverse outcomes, the GRACE model provides better calibration between predicted and observed rates of death.[40,41] The TIMI score does not include any measurement of heart failure. The GRACE model was developed in a less-selected patient population and includes renal insufficiency as a variable, which are two potential advantages over the other methods. The major advantage of the TIMI score is that it is a simple integer sum that can be calculated at the bedside without a calculator (see Fig. 39–6); PURSUIT and GRACE use weighted averages of multiple risk factors and may require a computer to calculate. None of the models incorporates information from biomarkers such as troponin or BNP/NT-proBNP.

In summary, the short-term outcome of UA/NSTEMI can be predicted by a variety of methods, and the TIMI and GRACE risk scores are the most systematic and widely tested approaches. The most important elements of these scores are the patient's age, clinical presentation, and comorbidities; ECG findings; elevated troponin concentrations; and continuing episodes of pain despite medical therapy.

PROGNOSIS

Prognosis in patients with UA or NSTEMI depends on the combination of the morbidity or mortality expected from the extent of coronary stenosis and LV dysfunction and the short-term risk associated with the

culprit lesion and the unstable state of ACS. Risk is highest early after the onset of symptoms. Published reports concerning UA/NSTEMI are influenced by patient selection and treatment and can be misleading. The inclusion and exclusion criteria for clinical trials introduce bias by sometimes eliminating low- or high-risk patients. Comparisons of incidence and outcome of UA/NSTEMI since the adoption of routine troponin testing are problematic because the proportion of patients classified as having NSTEMI has increased, and the overall mortality risk of NSTEMI may have fallen as a consequence.[42] Data from the GRACE study show a 6-month mortality rate of 6.2% in patients with NSTEMI and 3.6% in those with UA. Rehospitalization rates over the 6-month period were approximately 20%, and revascularization rates were approximately 15%.[43]

INITIAL TREATMENT DECISIONS

TREATMENT OVERVIEW

Please see Table 39–5 for recommendations for acute treatments (ie, early hospital care) from the 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes. The aims of therapy for UA/NSTEMI patients are to relieve ischemia, control symptoms, and prevent complications; such complications may include recurrent episodes of myocardial ischemia or myonecrosis, heart failure, and death.

β-Blockers, nitrates, and (to a lesser extent) calcium channel blockers (CCBs) reduce the risk of recurrent ischemia. Revascularization eliminates ischemia in many patients. The risk of progression to MI, or recurrent MI, is diminished by antiplatelet and antithrombotic drugs and by invasive treatment of the culprit lesion. Aggressive statin therapy plays an increasingly important role after ACS.

Hospitalized patients with non–ST-segment elevation and ACS patients should be treated with DAPT (aspirin and a $P2Y_{12}$ inhibitor), antithrombin therapy, a β-blocker, and a statin. In selected high-risk individuals, a glycoprotein (GP) IIb/IIIa inhibitor may be indicated. Furthermore, critical decisions are required regarding the angiographic strategy. One option, commonly termed the *early invasive strategy*, incorporates an angiographic approach in which patients undergo coronary angiography within 24 to 48 hours and revascularization is performed if suitable coronary anatomy is identified. The alternative approach, the *early conservative strategy*, is guided by myocardial ischemia, with angiography reserved for patients with recurrent ischemia at rest or findings on a predischarge noninvasive evaluation for ischemia that do not support low-risk status. This strategy is better described as *selective invasive* because it requires aggressive medical intervention and risk stratification. Regardless of the angiographic strategy used, an assessment of LV function should be strongly considered because it carries prognostic information, and it is imperative to treat patients who have impaired LV systolic function with both angiotensin-converting enzyme (ACE) inhibitors and β-blockers unless contraindicated. It is also important to consider a more aggressive approach to revascularization, including CABG surgery in appropriate candidates.

USE OF ANTI-ISCHEMIC DRUGS

β-Adrenergic Blockers

β-Blockers reduce heart rate, contractility, and blood pressure, thereby reducing myocardial oxygen demand (MVO_2). Slowing of the heart rate with β-blockers also increases the duration of diastole, which improves coronary and collateral blood flow. These effects are mediated by competitive antagonism of β_1-receptors in cardiomyocytes. In contrast, antagonism of β_2-receptors in the peripheral circulation and the lungs may cause vasoconstriction and bronchoconstriction.

It is recommended that β-blockers be initiated orally within the first 24 hours after it has been determined that the patient is not in heart failure or at significant risk for cardiogenic shock and does not otherwise have contraindications such as significant sinus bradycardia (heart rate < 50 bpm), hypotension (systolic blood pressure < 90 mm Hg), or evidence of significant heart failure (rales > lung bases). If there are concerns about possible intolerance to β-blockers, initial selection should favor a short-acting β_1-specific drug such as metoprolol or esmolol if a very short-acting agent is needed. Mild wheezing or a history of asthma or chronic obstructive pulmonary disease does not preclude use of a β-blocker, but initiating therapy with a low dose of a short-acting cardioselective agent is prudent. IV β-blockers should be reserved for patients with a clear indication for parenteral therapy and an absence of risk factors for cardiogenic shock or other contraindications.

Nitrates

NTG dilates vascular smooth muscle cells in an endothelium-independent manner and has venous, peripheral, and coronary vascular effects. Nitrates improve oxygen supply by dilating coronary and collateral blood vessels and reduce oxygen demand (MVO_2) by dilating the venous bed and reducing preload.

Patients whose symptoms are not relieved with sublingual NTG may experience symptom relief from IV NTG, and such therapy is recommended in the absence of contraindications for patients with ongoing ischemia or heart failure. Nitrates are absolutely contraindicated with concomitant use of phosphodiesterase-5 inhibitors (eg, sildenafil, tadalafil, or vardenafil) because concomitant therapy may lead to severe hypotension.

Clinical trial evidence does not support benefit of nitrates on "hard" adverse outcomes among patients with suspected ACS beyond the first 48 hours of treatment.[44] Thus, nitrates should not be administered routinely or for extended periods in the absence of ongoing or recurrent chest pain or heart failure symptoms. However, nitrates represent excellent treatment options for patients with acute or chronic symptomatic ischemia as well as among patients in whom the ACS presentation is associated with hypertension or pulmonary congestion from heart failure.

Morphine

Morphine effectively relieves chest pain and symptoms of anxiety in patients with ACS. It has venodilating properties that may be particularly helpful in relieving symptoms related to pulmonary congestion when heart failure complicates ACS. Morphine may be reasonable for patients with persistent or recurrent symptoms after initiation NTG or other anti-ischemic agents, but reduction in discomfort after morphine administration should not be necessarily held as improvement in ischemia. Morphine should be administered in IV boluses of 1 to 5 mg, which are repeated as needed to relieve symptoms provided careful blood pressure monitoring is performed. Recent studies have suggested a delayed onset of action of $P2Y_{12}$ inhibitors when the loading dose is administered soon after IV morphine; this is presumably a result of a delay in drug absorption from the gut.

Calcium Channel Antagonists

These agents inhibit vascular smooth muscle cell function and have effects on sinus node and atrioventricular (AV) nodal function. All of these agents are coronary and peripheral vasodilators, but members of the drug class differ notably with regard to their effects on cardiac

TABLE 39–5. American College of Cardiology/American Heart Association Guideline Recommendations for Early Care of Patients With Suspected Acute Coronary Syndrome

Treatment		Recommendation	Level of Evidence
Oxygen	Administer supplemental oxygen only with oxygen saturation < 90%, respiratory distress, or other high-risk features for hypoxemia	I	C
Nitrates	Administer sublingual nitroglycerin every 5 minutes × 3 for continuing ischemic pain and then assess need for IV nitroglycerin	I	C
	Administer IV nitroglycerin for persistent ischemia, HF, or hypertension	I	B
	Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor	III: Harm	B
Analgesic therapy	IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications	IIb	B
	NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization	III: Harm	B
β-Adrenergic blockers	Initiate oral β-blockers within the first 24 hours in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to β-blockade	I	A
	Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for β-blocker therapy with concomitant NSTE-ACS, stabilized HF, and reduced systolic function	I	C
	Reevaluate to determine subsequent eligibility in patients with initial contraindications to β-blockers	I	C
	It is reasonable to continue β-blocker therapy in patients with normal LV function with NSTE-ACS	IIa	C
	IV β-blockers are potentially harmful when risk factors for shock are present	III: Harm	B
Calcium channel blockers	Administer initial therapy with nondihydropyridine calcium channel blockers with recurrent ischemia and contraindications to β-blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval > 0.24 seconds, or second- or third-degree atrioventricular block without a pacemaker	I	B
	Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of β-blocker and nitrates in the absence of contraindications	I	C
	Calcium channel blockers are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects	I	C
	Long-acting calcium channel blockers and nitrates are recommended for patients with coronary artery spasm	I	C
	Immediate-release nifedipine is contraindicated in the absence of a β-blocker	III: Harm	B
Cholesterol management	Initiate or continue high-intensity statin therapy in patients with no contraindications	I	A
	Obtain a fasting lipid profile, preferably within 24 hours	IIa	C

Abbreviations: HF, heart failure; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-segment elevation acute coronary syndrome.

Reproduced with permission from Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014 Dec 23;64(24):e139-e228.[1]

contractility and electrophysiologic effects. Verapamil and diltiazem have broad effects, slowing heart rate and AV nodal conduction, reducing contractility, and causing peripheral vasodilation. In contrast, the dihydropyridines (eg, amlodipine and nifedipine) have powerful vasodilatory effect but show minimal or no direct effects on sinus or AV nodal function.

Rate-limiting calcium antagonists should be considered second- or third-line agents to treat persistent or recurring ischemia in patients on full doses of β-blockers and nitrates or in whom these agents are contraindicated or poorly tolerated. Several randomized trials assessing the use of diltiazem or verapamil in patients with UA/NSTEMI suggest that these agents relieve or prevent symptoms and ischemia but should be avoided in patients with heart failure or known LV dysfunction because they have been shown to increase mortality in this setting.[1]

Dihydropyridine CCBs do not play a primary role in the management of ACS but may be useful agents for blood pressure control when persistent hypertension is present after initiation of β-blockers and ACE inhibitors or angiotensin receptor blockers (ARBs). Only long-acting dihydropyridines such as amlodipine should be used for this purpose; short-acting preparations of nifedipine *must be avoided* in ACS because they cause adverse outcomes.

Antagonists of the Renin-Angiotensin-Aldosterone System

Although not specifically anti-ischemic agents, ACE inhibitors antagonize adverse neurohormonal pathways that contribute to adverse ventricular remodeling and heart failure after ACS. In patients with acute MI, particularly when complicated by LV systolic dysfunction, ACE inhibitors show powerful long-term mortality benefits.[45] Although data focusing specifically on populations with UA/NSTEMI are sparse, ACE inhibitors have also demonstrated risk reduction among high-risk subsets with chronic CAD, including those with normal LV function.[46] Accordingly, ACE inhibitors should be used in patients with UA/NSTEMI complicated by heart failure or LV dysfunction, as well as in those with hypertension (see Chap. 25) or diabetes (see Chap. 28). ARBs are effective alternatives to ACE inhibitors in patients with LV dysfunction or heart failure after acute MI but should not routinely be used in combination with ACE inhibitors.[47] Because of the larger evidence base for ACE inhibitors, ARBs should predominantly be used in place of ACE inhibitors in patients with ACE inhibitor intolerance.

Aldosterone antagonists such as spironolactone or eplerenone should be considered for high-risk UA/NSTEMI patients with an LV ejection fraction ≤ 0.40 and either symptomatic heart failure or diabetes mellitus,

provided they are receiving adequate doses of ACE inhibitors and do not have significant renal dysfunction or hyperkalemia.[1]

EARLY INVASIVE VERSUS CONSERVATIVE STRATEGIES

An algorithm for clinical management from the 2014 Update of the AHA/ACC Guidelines for Management of UA/NSTEMI is shown in Fig. 39–6.[1] The decision between early invasive and ischemia-guided strategies has been moved to a very proximal time point in the management algorithm of NSTE-ACS.[1] Although initial treatments for these strategies are very similar, patients to undergo an early invasive approach are separated into immediate (< 2 hours), early (< 24 hours), and delayed (1-3 days) groups according to the urgency of coronary angiography. Patients needing immediate angiography are those with refractory angina, sustained ventricular tachyarrhythmias, worsening heart failure or shock, or new or worsening mitral regurgitation. Patients with a low-risk score can be initially managed with an ischemia-guided strategy covered below. Early, but not immediate, angiography is performed for patients at increased risk by the TIMI or GRACE risk score, whereas a delayed invasive approach can be considered for patients at intermediate risk.

In prior studies, two broad strategies were considered with regard to the early use of coronary angiography and revascularization after non–ST-segment elevation ACS. In the *early invasive* strategy, patients are referred for coronary angiography, typically within 24 to 48 hours of presentation, with coronary revascularization (either PCI or CABG) performed based on anatomic findings identified during angiography.

In the *early conservative* strategy, which is more appropriately termed a *selective invasive* strategy, or now called an *ischemia-guided* strategy, angiography is deferred and reserved for patients with spontaneous recurrent ischemia, development of heart failure, or evidence of significant ischemia or LV dysfunction detected on a predischarge noninvasive evaluation. As discussed later, both strategies should incorporate aggressive antiplatelet and antithrombotic strategies, although there are some differences in the preferred options depending on the strategy selected. Proponents of the early invasive strategy argue that it allows earlier and more definitive risk stratification. It identifies the 10% to 15% of patients without obstructive coronary stenoses and the approximately 20% of patients with three-vessel or left main CAD. Proponents of the early conservative strategy argue that the high- and low-risk patients can also be identified with appropriate noninvasive imaging.

Several, now older, large, randomized controlled trials compared a routine early invasive strategy with selective invasive strategies in patients with non–ST-segment elevation ACS and produced conflicting results.[48-53] Comparisons among the trials were difficult because the studies included heterogeneous patient populations, and the comparisons could not account for the rapid advances in PCI technology and medical therapies over time. Nonetheless, meta-analysis of these studies showed that applying a routine early invasive approach was associated with a trend toward an early hazard (more periprocedural ischemic and bleeding events) without a reduction in long-term mortality. In contrast, when considering patients at high risk for adverse events, an early invasive approach reduced episodes of refractory angina and MI during early and late follow-up.

As an example, in the TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)–TIMI 18 trial, the benefit of the early invasive approach was confined to patients at intermediate or high risk, as defined using troponin elevation, ECG changes, or the TIMI risk score.[51] In the meta-analysis by Hoenig et al,[54] five studies including nearly 8000 patients were assessed and revealed an approximately 25% reduction in early and late MIs and a halving of refractory angina events. Long-term mortality rates were similar between the strategies, although it is noted that a substantial proportion of patients initially assigned to a conservative approach ultimately undergo an invasive procedure.

Moreover, an early invasive strategy appears to be cost effective.[55] Thus, in high-risk patients, a routine invasive strategy is generally preferred if there are no contraindications to coronary angiography and if the patient is a good candidate for prolonged DAPT.[1] Among high-risk patients, the benefits of an invasive approach are well established; among low-risk patients, no benefit exists for a routine early invasive approach (see Fig. 39–7).

TIMING OF INVASIVE THERAPY

Beyond favoring an early invasive strategy for many intermediate- to high-risk ACS patients, there has been a steady move to have patients undergo coronary angiography earlier. The rationale for earlier intervention includes a desire to arrive at a definitive treatment plan and shorten hospital stays as much as possible, as well as the recognition that improvements in interventional technique largely driven by coronary stenting, radial artery access, and adjunctive antiplatelet and antithrombin therapy have increased the safety of catheter interventions.

However, in contrast to STEMI, acceleration of the timing of invasive therapy does not appear to markedly improve outcomes for most patients with UA/NSTEMI. In the Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial,[56] 3031 patients with UA/NSTEMI were randomized to routine angiography performed early (within 24 hours of randomization) or delayed (≥ 36 hours from randomization). The median times to angiography in the two groups were 14 and 50 hours, respectively. At 6 months, the primary outcome of death, MI, or stroke occurred in 9.6% of patients in the early intervention arm and 11.3% of patients in the delayed intervention arm (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.68-1.06; $P = .15$). No differences in bleeding or other safety end points were found between the two arms. Refractory ischemia was significantly reduced at 30 and 180 days in the early arm, but other individual secondary end points were not different between the groups. In a prespecified subgroup in the highest tertile of GRACE risk score (> 140), the primary end point was reduced by 35% in the early intervention arm ($P = .006$); in contrast, no difference was observed among patients at intermediate or low risk (see Fig. 39–7).[56]

These findings, considered together with other trials comparing timing of PCI after UA/NSTEMI,[57] suggest that for most low- and intermediate-risk patients with UA/NSTEMI in whom an invasive approach is planned, outcomes are similar when PCI is performed earlier versus later in the hospital stay; as such, there is no indication for urgent (ie, immediate) intervention, and it is appropriate to consider logistical issues when determining the timing of coronary angiography and PCI. On the other hand, because no hazard has been observed with earlier intervention, catheterization and PCI within 24 hours (or earlier) may prove efficient in many circumstances and would be generally preferred in the highest risk patients if logistically feasible in that health care system. A meta-analysis including four trials, over 4000 patients, and with extended follow-up yielded similar findings—a lower occurrence of recurrent ischemic events and shorter hospital stays among patients undergoing an earlier invasive approach.[58]

NONINVASIVE TEST SELECTION IN PATIENTS MANAGED CONSERVATIVELY

A detailed discussion of noninvasive stress testing in patients with CAD is presented in the ACC/AHA Guidelines for Exercise Testing,

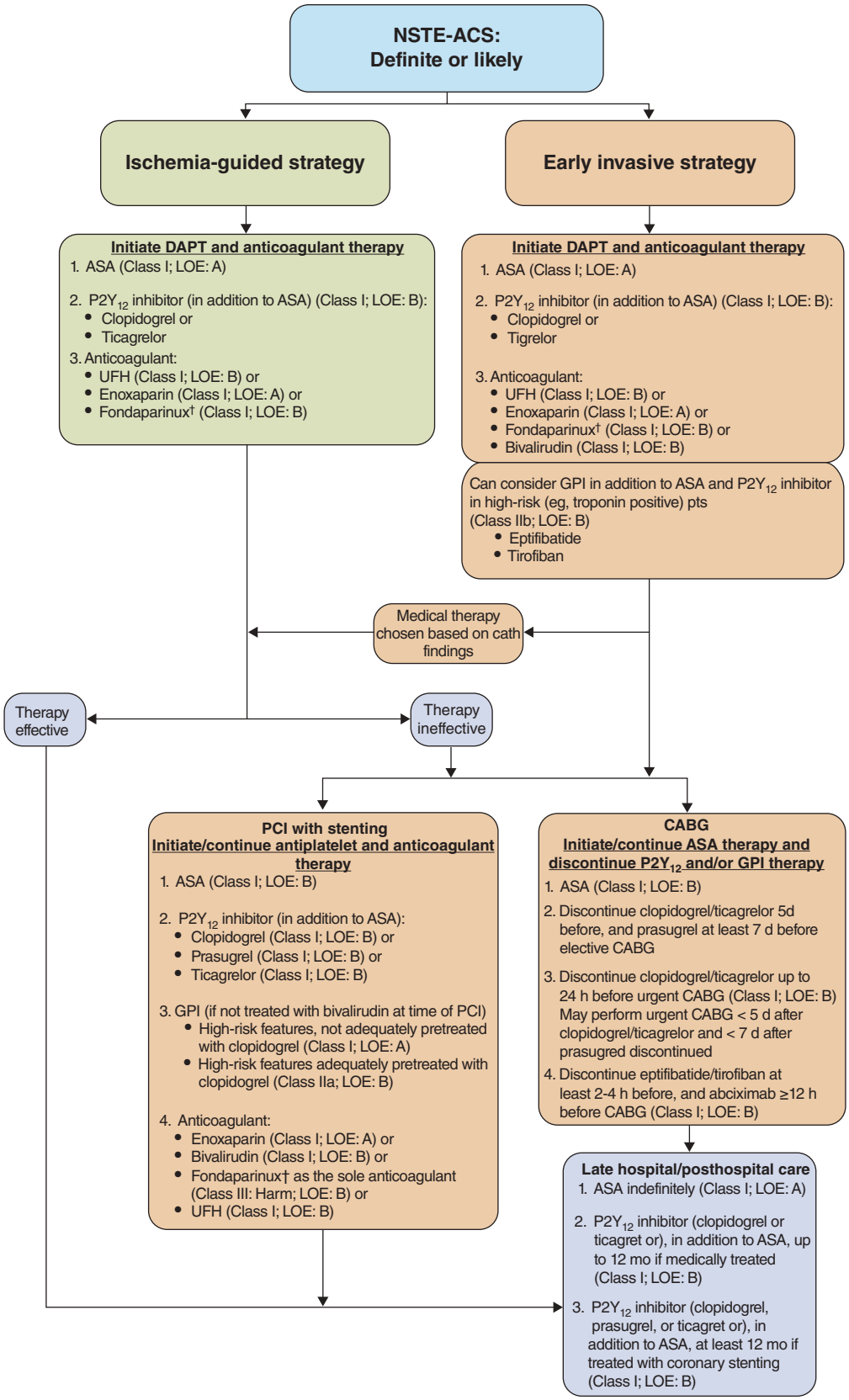

FIGURE 39–6. Algorithm for the management of patients with definite or likely non–ST-segment elevation acute coronary syndrome (NSTE-ACS) from the 2014 American Heart Association/American College of Cardiology non–ST-segment myocardial infarction guidelines. †In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing percutaneous coronary intervention (PCI), an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. ASA, aspirin; CABG, coronary artery bypass graft; cath, catheter; COR, Class of Recommendation; DAPT, dual antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; LOE, Level of Evidence; pts, patients; UFH, unfractionated heparin. Reproduced with permission from Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014 Dec 23;64(24):e139–e228

ACC/AHA Guidelines for the Clinical Use of Cardiac Radionuclide Imaging, and ACC/AHA Guidelines for the Clinical Application of Echocardiography. Likewise, Chaps. 13-19 cover all contemporary modalities for noninvasive cardiac testing. Coronary angiography is usually indicated in patients with UA/NSTEMI who either have recurrent symptoms of ischemia despite adequate medical therapy or who are at high risk as categorized by clinical signs (congestive heart failure, malignant ventricular arrhythmias) or noninvasive test findings (significant LV dysfunction: ejection fraction < 0.35, large anterior or multiple perfusion defects) (see Table 39–4 for low-, intermediate-, and high-risk predictors from noninvasive testing).

CORONARY REVASCULARIZATION

Coronary revascularization (PCI or CABG) is performed to improve prognosis, relieve symptoms, prevent ischemic complications, and improve functional capacity. The decision to proceed from diagnostic angiography to revascularization is influenced not only by the coronary anatomy but also by a number of additional factors, including anticipated life expectancy, LV function, comorbidity, functional capacity, severity of symptoms, quantity of viable myocardium at risk, and the individual patient's preferences. Careful clinical judgment is required when deciding which lesions identified at coronary angiography merit revascularization.

Data from both retrospective observations and randomized clinical trials indicate that PCI success rates are now very high in most patients with UA/NSTEMI. Procedural safety appears to be enhanced by the use of a radial approach to vascular access, particularly among high-risk ACS patients. Patients with multivessel CAD can now often undergo complete revascularization with the use of multiple drug-eluting stents (DESs). Although it is not clear that PCI of nonculprit stenoses at the time of culprit lesion intervention improves outcomes, increasing procedural safety and improving revascularization durability may be affording more single-setting complete revascularization procedures. Data to guide selection between PCI and CABG in patients with ACS and multivessel CAD continue to give some preference for surgical revascularization, especially among patients with more extensive disease and diabetes. In general, the indications for CABG in UA/NSTEMI are similar to those for stable angina.[1] High-risk patients with diabetes mellitus or LV dysfunction and multivessel CAD and those with two-vessel disease with severe proximal involvement of the left anterior descending artery or severe three-vessel or left main disease should be considered for CABG. However, some of these patients may be candidates for multivessel PCI.[59] Moreover, although the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) study (Chap. 42) did not focus specifically on patients with ACS, the demonstration of exaggerated benefits of CABG over multivessel PCI among individuals with more diffuse and complex CAD likely applies to the ACS population as well.[60] Thus, selection between PCI and CABG in patients with multivessel CAD without diabetes is based on patient preference, lesion morphology, and the likelihood of a complete revascularization result with PCI.[59]

ANTIPLATELET THERAPY

Antiplatelet and antithrombotic agents (see also Chap. 41) are cornerstone therapies to help passivate the active vascular disease process and prevent thrombotic complications, including death and recurrent myocardial ischemia. Currently, a combination of ASA, a $P2Y_{12}$ antagonist (clopidogrel, prasugrel, or ticagrelor), antithrombin therapy (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux, or bivalirudin), and in certain instances, a platelet GP IIb/IIIa receptor antagonist represents the leading effective options. The intensity and duration of treatment are tailored to individual risk though nearly all patients should receive DAPT and an antithrombin initially.[1]

ASPIRIN

ASA irreversibly acetylates and inhibits cyclooxygenase-1 within platelets, preventing the formation of thromboxane A_2, which is a potent platelet activator and vasoconstrictor. In patients with UA/NSTEMI, ASA reduces the probability of death or MI by 25% to 30%.[61]

ASA should be initiated in patients with UA/NSTEMI at a dose of 160 or 325 mg, with the first dose chewed to rapidly establish a high blood level.[1] Thereafter, daily doses of 75 to 325 mg are prescribed and continued indefinitely. Data generally support a lower dose of maintenance aspirin to minimize bleeding, especially when combined with a $P2Y_{12}$ inhibitor. Debate remains regarding the optimal ASA dose after coronary artery stenting; although many interventional cardiologists prefer a 325-mg dose for 1 month after stent implantation. One arm of the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes (CURRENT)/Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS) 7 trial compared high-dose (300-325 mg) versus low-dose (75-100 mg) ASA in approximately 25,000 patients with ACS (70% with UA/NSTEMI; 70% with PCI). No difference in early efficacy or safety was seen between ASA doses, including in the subgroup undergoing PCI.[62] In the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, post hoc analysis of aspirin dose on outcome was performed to understand the striking difference in efficacy of ticagrelor between countries outside North America versus inside North America. A strong association between ticagrelor superiority (over clopidogrel) was found when patients received low-dose aspirin. For this reason, the NSTEMI guidelines specifically recommend low-dose aspirin be used in combination with ticagrelor when DAPT is prescribed.[63] The 2015 ESC NSTEMI guidelines recommend low-dose aspirin for maintenance therapy regardless.

ORAL $P2Y_{12}$ INHIBITORS

Clopidogrel

Clopidogrel is a thienopyridine derivative that blocks binding of ADP to the $P2Y_{12}$ receptor on the platelet surface, inhibiting adenosine diphosphate (ADP)–mediated platelet activation and aggregation by approximately 50% to 60%. Because ASA and $P2Y_{12}$ antagonists inhibit platelet function via different pathways, combined use of the two drugs represents an attractive antiplatelet strategy. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial randomized 12,562 patients with UA/NSTEMI to ASA alone or to the combination of ASA and clopidogrel for 3 to 12 months (average, 9 months).[64] The composite end point of CV death, MI, or stroke occurred in 11.5% of patients assigned to placebo versus 9.3% assigned to clopidogrel (relative risk, 0.80; $P < .001$). Importantly, this benefit was similar whether patients were managed with medical therapy or with coronary revascularization.[65] Major bleeding was increased in the clopidogrel arm (3.7% vs 2.7%; $P = .003$). Bleeding was notably increased in patients who underwent CABG surgery within the first 5 days of stopping clopidogrel.[64]

In a subgroup analysis of CURE consisting of the 2658 patients who underwent PCI after UA/NSTEMI, CV death or MI was reduced by

31% in the clopidogrel plus ASA group versus the ASA alone group (P = .002).[66] In the Clopidogrel for the Reduction of Events During Observation (CREDO) trial,[67] 2116 patients scheduled to undergo PCI were randomized to clopidogrel or placebo in addition to ASA. A 27% reduction in the composite outcome of CV death, MI, or stroke was reported in patients treated with combination clopidogrel and ASA for 1 year versus those treated for 1 month (8.5% vs 11.5%; P = .02). As with CURE, there was an increased risk of major bleeding in the combination-therapy group (8.8% vs 6.7%; P = .07), but this excess was largely restricted to patients who underwent CABG. Thus, elective CABG (and other major surgery) should be delayed for at least 5 days after the last dose of clopidogrel. In some practices, therefore, physicians have preferred to withhold clopidogrel (as well as other thienopyridines) until the coronary anatomy is known to be certain CABG will not be delayed if needed.

It is important to recognize that the PCI-CURE and CREDO trials were performed before newer DESs were available. DESs inhibit vascular smooth muscle cell proliferation and prevent in-stent restenosis; however, they also delay regrowth of the protective vascular endothelium, which results in a longer time period during which patients are at risk for stent thrombosis.[68] Because stent thrombosis has been observed up to and even beyond 1 year following placement of a first-generation DES, current guideline recommend *at least 1 year of DAPT after placement of a DES.*[69] Patients who, for any reason, are poor candidates for long-term clopidogrel, including those who are planned for major surgery in the near future (in the next few months after the PCI procedure), should not receive a first-generation DES. Some data suggest lower rates of major adverse CV events in those treated with prolonged DAPT compared to treatment for 1 year.[70] Several meta-analyses have been performed comparing different durations of DAPT following DES. Most include approximately 30,000 patients and report lower bleeding rates and lower overall mortality with shorter-duration DAPT (6-12 months), but with lower rates of stent thrombosis and MI with prolonged DAPT (> 12 months).[71-74] The 2014 AHA/ACC NSTEMI guidelines recommend DAPT for up to 12 months irrespective of treatment strategy.

In addition to the ASA dose comparison described earlier, the CURRENT/OASIS 7 trial compared standard-dose (300-mg load; 75 mg/d) clopidogrel versus "double-dose" clopidogrel (600-mg load; 150 mg/d × 7 days; then 75 mg/d). In the overall study population, no difference was observed in the primary end point of CV death, MI, or stroke at 30 days; however, a significant interaction was observed with PCI, such that in the subgroup undergoing PCI, the higher dose strategy resulted in a 15% reduction in the primary end point and a 29% reduction in stent thrombosis. In contrast, among patients not undergoing PCI, there was a nonsignificant trend toward worse outcomes in the higher dose clopidogrel arm. Bleeding rates were increased significantly in the high-dose clopidogrel arm, both in the overall population as well as the PCI subgroup.[62] The OASIS 7 results are consistent with multiple studies evaluating platelet function outcomes in supporting use of a 600-mg clopidogrel dose before PCI among ACS patients.

Clopidogrel Resistance

All thienopyridines are prodrugs that require more than one step of metabolism before achieving their antiplatelet effects. Clopidogrel has complex pharmacokinetic and pharmacodynamic properties that result in widely variable levels of the circulating active metabolite. The in vitro response to clopidogrel, as assessed by inhibition of ADP-mediated platelet aggregation, is heterogeneous with a normal (bell-shaped) distribution of response among individuals. After absorption, clopidogrel requires a two-step oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite. Multiple CYP enzymes are involved (CYP3A4, CYP3A5, CYP2C9, CYP1A2, CYP2B6, and CYP2C19), several of which have important genetic variants and are affected by concomitant medications. The clinical relevance of these findings is likely muted by the multiple other factors affecting outcome and the benefit of concomitant medications such as proton pump inhibitors. For example, initial studies suggested an in vitro interference of antiplatelet effects of clopidogrel by omeprazole,[75] yet clinical trials have not generally detected a conclusive signal to suggest concomitant omeprazole use in clopidogrel-treated patients should be avoided, especially because a lower rate of gastrointestinal bleeding has been noted.[76] Use of other proton pump inhibitors without such in vitro interaction may be considered[77] if concerns remain.

Although response variability to clopidogrel has emerged as a potentially important issue in recent years, the clinical implications remain controversial for several reasons. First, many studies have defined "clopidogrel resistance" on the basis of a single measurement of platelet reactivity performed on clopidogrel; however, residual platelet aggregation to ADP is determined only in part by response to clopidogrel because patient-related factors such as diabetes, smoking, and proximity to the ACS event also contribute to platelet aggregation. Second, the limitations of currently available platelet function tests are noteworthy because the available tests correlate poorly with each other and capture neither the full functionality of the platelet nor the response to clopidogrel.

Prasugrel

Prasugrel is a thienopyridine that, similar to clopidogrel, requires conversion to an active metabolite to bind to the $P2Y_{12}$ receptor. Prasugrel requires only a one-step hepatic metabolism with CYP3A, CYP2B6, CYP2C9, and CYP2C19. This more favorable pharmacokinetic profile translates into better pharmacodynamics with faster onset of action, more potent and irreversible platelet inhibition, and lower interindividual variability as compared to even high doses of clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial,[78] which enrolled 13,608 patients with STEMI or high-risk UA/NSTEMI who were scheduled to undergo PCI, prasugrel (60-mg load; then 10 mg/d) was compared with clopidogrel (300-mg load; 75 mg/d). Both drugs were initiated at the time of PCI with no pretreatment administered in advance of PCI. The primary efficacy end point—the same as was used in the CURE trial—was a composite of CV death, MI, and stroke and was reduced from 12.1% in the clopidogrel arm to 9.9% in the prasugrel arm over a median duration of 14.5 months of follow-up (HR, 0.81; 95% CI, 0.73-0.90; P < .001) (Table 39–6). This benefit was mediated by a 24% reduction in nonfatal MI without a significant effect seen with mortality or stroke. Two-thirds of the MI events were procedural MIs detected based on serial cardiac enzyme measurement rather than clinical recognition of symptoms and signs.

Importantly, definite or probable stent thrombosis (per the Academic Research Consortium definition) was reduced from 2.4% with clopidogrel to 1.1% with prasugrel (P < .001).[78] Interestingly, most of the stent thromboses were observed within the first 30 days after randomization, regardless of whether DES or bare metal stents were used, a finding that highlights the relatively high frequency of early stent thrombosis after ACS, in distinction to much lower rates after elective PCI. Interpreting the magnitude of benefit on stent thrombosis and procedural MI is challenging, given that clopidogrel was not administered before catheterization and the dose used was only 300 mg.

TABLE 39–6. Comparison of Novel Oral Antiplatelet Therapies with Clopidogrel

	TRITON-TIMI 38 (n = 13,608)			PLATO (n = 18,624)		
End Point	Prasugrel	Clopidogrel	HR (95% CI)	Ticagrelor	Clopidogrel	HR (95% CI)
CV death, MI, stroke	9.9%	12.1%	0.81 (0.73-0.90)	9.8%	11.7%	0.84 (0.72-0.92)
Stent thrombosis	1.1%	2.4%	0.48 (0.36-0.64)	2.2%	2.9%	0.75 (0.59-0.95)
Non-CABG TIMI major bleeding[a]	2.4%	1.8%	1.32 (1.03-1.68)	4.5%	3.8%	1.19 (1.02-1.38)

[a]TIMI major bleeding (non-CABG) was the primary bleeding end point in TRITON-TIMI 38 and was an additional bleeding end point in PLATO.

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; PLATO, Study of Platelet Inhibition and Patient Outcomes; TIMI, Thrombolysis in Myocardial Infarction; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel.

Bleeding rates were significantly increased in the prasugrel arm of the trial, including an increase from 1.8% to 2.4% in TIMI major bleeding (HR, 1.32; 95% CI, 1.03-1.68; $P = .03$) as well as notable increases in life-threatening and fatal bleeding. Patients older than age 75 years or with body weight below 60 kg were at particular risk for bleeding, such that the increase in bleeding negated any efficacy advantage. Those with prior stroke or transient ischemic attack had a prohibitive increase in bleeding, and a net harm was identified; in such patients, prasugrel is contraindicated. Among individuals who underwent CABG after at least one dose of study drug, major bleeding rates were 13.4% in the prasugrel arm and 3.2% in the clopidogrel arm ($P < .0001$).[78] Thus, although some institutions have become comfortable performing CABG after clopidogrel administration, such a strategy would not be prudent after using prasugrel given the much higher rates of surgical bleeding anticipated.

Ticagrelor

Ticagrelor is a nonthienopyridine, direct-acting, and *reversible* oral antagonist of the $P2Y_{12}$ receptor. This agent does not require conversion to an active metabolite and provides more rapid onset of action and a more potent and predictable antiplatelet response than clopidogrel. Ticagrelor achieves rapid antiplatelet activity after oral loading, with therapeutic activity observed within 30 minutes and near full activity at 2 hours.[79]

In PLATO,[80] ticagrelor (180-mg loading dose; 90 mg twice daily) was compared with clopidogrel (300- to 600-mg loading dose; 75 mg/d) in 18,624 patients with STEMI or UA/NSTEMI, including patients managed with and without PCI. At the end of the 12-month follow-up period, the primary end point (CV death, MI, and stroke) was reduced from 11.7% in the clopidogrel arm to 9.8% in the ticagrelor arm (HR, 0.84; 95% CI, 0.77-0.92; $P < .001$) (see Table 39–6). In addition to significant reductions in MI alone, there was also a significant 21% relative risk reduction in vascular mortality and a 22% reduction in total mortality (5.9% vs 4.5%; $P < .001$). Similar to the CURRENT/OASIS 7 and TRITON-TIMI 38 trials, stent thrombosis was reduced significantly with the more potent oral antiplatelet regimen. Also consistent with prior studies, an increase in non-CABG major bleeding was observed in the ticagrelor arm (4.5% vs 3.8%; $P = .03$); however, bleeding rates after CABG were lower with ticagrelor, likely because of the shorter half-life and more rapid reversibility of the drug.[80]

In contrast to TRITON-TIMI 38, clopidogrel pretreatment was permitted in PLATO; however, only 27% of patients received 600 mg of clopidogrel within the first 24 hours after their ACS event, again raising questions of what the comparative benefit of this novel compound would be versus a more aggressive clopidogrel strategy.

Several unique side effects have been observed with ticagrelor, which may be adenosine mediated, and contribute to a slightly higher rate of discontinuation of ticagrelor than clopidogrel. These include dyspnea, which tends to occur early after starting the drug in 10% to 15% of treated patients but is not associated with evidence of heart failure and usually lasts less than a week. Ventricular pauses also occurred more commonly in the ticagrelor group early after treatment initiation, but these also tended to decrease in frequency over time, were rarely symptomatic, and were not associated with clinically significant bradycardia. It should be noted that although reversible, this drug still has residual antiplatelet effects for up to 5 days among individuals on chronic therapy.[79]

Clopidogrel, prasugrel, and ticagrelor each receive a Class I recommendation in the current AHA/ACC NSTEMI guidelines, with a preference for ticagrelor over clopidogrel for patients managed with an early invasive or ischemia-guided strategy (Class IIa).[1]

GLYCOPROTEIN IIB/IIIA INHIBITORS

When the platelet is activated, the GP IIb/IIIa receptors on the platelet surface increase in number and demonstrate improved binding affinity for fibrinogen. The binding of fibrinogen to receptors on different platelets results in aggregation. The platelet GP IIb/IIIa receptor antagonists act by occupying the receptors sites, thus opposing fibrinogen and von Willebrand factor binding. The occupancy of 80% or more of the receptor sites and inhibition of platelet aggregation to ADP by 80% or more results in potent antiplatelet effects. The various GP IIb/IIIa antagonists, however, possess significantly different pharmacokinetic and pharmacodynamic properties (see Chap. 41). The role of GP IIb/IIIa inhibitors in the contemporary treatment of patients with ACS continues to undergo a reappraisal, and overall usage has decreased significantly in recent years. The main reasons for the decreased utilization stems from lack of benefit evidenced from pretreatment versus in-lab provisional use and the introduction of rapidly acting, potent oral antiplatelet agents. For these reasons, the current AHA/ACC NSTEMI guidelines give GP IIb/IIIa inhibitors a Class IIb recommendation when used with DAPT in an early invasive approach.

Adjunctive Glycoprotein IIb/IIIa Use During Percutaneous Coronary Intervention

The efficacy of GP IIb/IIIa antagonists during PCI has been documented in numerous trials, with particular benefit seen for patients

with NSTEMI. In many of the earlier trials, however, high-dose clopidogrel loading had not occurred. Subsequently, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT)-2 study compared abciximab versus placebo immediately before PCI in 2022 patients with UA/NSTEMI who were treated with ASA and 600 mg of clopidogrel. Abciximab reduced the primary end point of death or MI by 25% ($P = .03$). This benefit was restricted to patients with elevated troponin values.[81]

Comparison of Upstream Versus Delayed Glycoprotein IIb/IIIa Use

Two recent trials have compared routine upstream versus delayed selective GP IIb/IIIa inhibitor use in high-risk patients with UA/NSTEMI. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Timing trial, 9207 patients assigned to receive a GP IIb/IIIa inhibitor in the primary ACUITY randomization were randomized subsequently in a 2 × 2 factorial design to routine upstream GP IIb/IIIa initiation or deferred selective therapy started in the catheterization laboratory.[82] In the upstream arm, 98.3% of patients received GP IIb/III inhibitors versus 55.7% in the delayed arm. At 30 days, the composite ischemia outcome was not significantly different between the two arms, but rates of major bleeding were significantly higher in the upstream GP IIb/IIIa inhibitor arm. A major limitation of this study was that in the early upstream arm, GP IIb/IIIa inhibitors were only started an average of 4 hours before PCI.[82]

The Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial also compared a strategy of early, routine GP IIb/IIIa inhibition (with eptifibatide) versus a strategy of delayed provisional use among 9492 patients with non–ST-segment elevation ACS who were planned for invasive therapy.[83] Early ACS required an infusion of 12 hours or more before PCI in the upstream eptifibatide arm, and patients received an average of 21 hours of therapy before PCI compared with 4 hours in ACUITY Timing. Provisional GP IIb/IIIa inhibitor use at the time of PCI was used in only 26% of patients. Compared with the delayed, provisional strategy, upstream eptifibatide did not result in a significant reduction in the primary end point of death, MI, urgent revascularization for ischemia, or a thrombotic complication during PCI at 4 days (9.3% vs 10.0%; odds ratio, 0.92; $P = .23$). Moreover, no significant difference was observed in the secondary end point of death or MI at 30 days. No benefit was observed in key subgroups, including those who were troponin positive and those not loaded with clopidogrel. In contrast, rates of TIMI major (2.6% vs 1.8%; $P = .015$) and minor (3.6% vs 1.7%, $P < .001$) bleeding were significantly increased in the early upstream eptifibatide arm.[83]

Taken together, these findings suggest that an appropriate strategy is to defer GP IIb/IIIa use until the decision to perform PCI has been made and to use them selectively among high-risk patients defined clinically or angiographically. Upstream use should be restricted to patients with ongoing clinical instability and perhaps those with dynamic ST-segment changes, particularly when oral ADP receptor antagonist loading is not performed. Upstream use is no longer recommended simply on the basis of troponin elevation.

ANTICOAGULANT THERAPY

Anticoagulants available for parenteral use include UFH, LMWH, a synthetic pentasaccharide, and direct thrombin inhibitors. All receive a Class I recommendation in the treatment guidelines (see also Chap. 41).

UFH is a heterogenous mixture of polysaccharides of various molecular weights, which accelerate the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, and factor Xa. UFH prevents thrombus generation but is not active against clot-bound thrombin. LMWHs are relatively more potent inhibitors of factor Xa than of thrombin. Relative to UFH, LMWH has more specific binding, a longer half-life, and more predictable anticoagulation, permitting once- or twice-daily subcutaneous administration. Use of LMWHs does not usually require laboratory monitoring except during pregnancy and with changing renal function. Direct thrombin inhibitors (DTIs) act by binding directly to the anion binding and catalytic sites of thrombin to produce potent, predictable anticoagulation. Unlike UFH and LMWH, DTIs are active against clot-bound thrombin (see Chap. 41).[84]

UNFRACTIONATED HEPARIN

Several trials have compared UFH with placebo and form the basis of the class I recommendation for use of UFH with ASA for patients with UA/NSTEMI.[1] In a meta-analysis of six trials with end point assessment varying from 2 to 12 weeks, death or MI was reduced by 33% in UFH-treated patients ($P = .06$).[85]

Pharmacokinetic limitations of UFH translate into poor bioavailability and marked variability in anticoagulant response. UFH requires monitoring with the activated partial thromboplastin time (aPTT). A weight-adjusted regimen is recommended, with an initial bolus of 60 U/kg (maximum, 5000 U) and an initial infusion of 12 $U \cdot kg^{1} \cdot 1\ h^{1}$ (maximum, 1000 U/h). Guideline committees recommend dosage adjustments of the nomograms to correspond to a therapeutic range equivalent to heparin levels of 0.3 to 0.7 U/mL by antifactor Xa determinations, which correlates with aPTT values between 50 and 75 seconds.

Serial platelet counts are necessary to monitor for heparin-induced thrombocytopenia for patients receiving more than 96 hours of therapy or being readministered heparin following a recent prolonged heparin course. Thrombocytopenia from heparin takes two forms. One form involves a mild decrease in platelet counts (rarely < 100,000/μL) that occurs early (1-4 days) after initiation of therapy, reverses quickly after discontinuation of heparin, and is of little clinical consequence because it is not antibody mediated. The more severe form of thrombocytopenia is an immune-mediated thrombocytopenia that typically occurs more than 4 days from therapy, although it may occur earlier in patients who have received heparin within the previous several months. Heparin immune thrombocytopenia is caused by a heparin-dependent, antiplatelet antibody that can activate normal platelets. This syndrome can be associated with thrombosis that can produce severe morbidity and mortality. It should be treated with a pentasaccharide or direct thrombin inhibitor initially, especially if thrombosis is present, and then with an oral anticoagulant after hospital discharge.

LOW-MOLECULAR-WEIGHT HEPARIN

Several large, randomized trials have directly compared LMWH with UFH (see Chap. 40). Important differences have emerged depending on the approach to revascularization used in the studies.

Among the earlier trials, those studying enoxaparin versus UFH for medical therapy showed a consistent reduction in ischemic events. The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE)[86] and TIMI 11B[87] trials found approximately a 15% to 20% reduction in death or MI at 4- to 6-week follow-up. Both trials reported a small excess in bleeding in the enoxaparin arms.

In contrast to a conservative-approach trial, the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial (n = 10,027) was an open-label superiority trial comparing enoxaparin with UFH among patients with a planned early-invasive strategy.[88] GP IIb/IIIa inhibitors were used in

more than 50% of patients. The primary end point of death or nonfatal MI occurred in 14.0% of patients randomized to enoxaparin versus in 14.5% of patients randomized to UFH (HR, 0.96; 95% CI, 0.86-1.06). Rates of TIMI major bleeding were increased among patients receiving enoxaparin (9.1% vs 7.6%).

FONDAPARINUX

Fondaparinux is a synthetic pentasaccharide that can bind antithrombin and inactivate factor Xa. It has no effect on thrombin and thus is a pure factor Xa inhibitor. It offers predictable pharmacokinetics and a half-life of 15 hours, allowing once-daily subcutaneous dosing without a need for routine laboratory monitoring. In the OASIS 5 trial,[89] which enrolled more than 20,000 patients with UA/NSTEMI, 2.5 mg/d of fondaparinux versus 1 mg/kg twice a day of enoxaparin yielded similar rates of the primary end point of death, MI, or refractory ischemia at 9 days (5.8% vs 5.7%). However, major bleeding events were reduced by 48% with fondaparinux, and mortality trended lower in the fondaparinux group at 30 days (2.9% vs 3.5%; $P = .02$) and at 180 days (5.8% vs 6.5%; $P = .05$); all but three of the 64 excess deaths with enoxaparin were associated with major or minor bleeding.[89]

Several caveats to the OASIS 5 trial merit mention. First, patients were allowed entry with a creatinine up to 3.0 mg/dL. Major bleeding risk was particularly high among patients treated with weight-adjusted enoxaparin who had a creatinine clearance below 30 mL/min (9.9% rate of major bleeding). Second, UFH was administered after randomization in a larger proportion of enoxaparin-treated patients, a practice that is thought to increase bleeding risks. Third, the long half-life of fondaparinux may create logistical problems in centers that perform early cardiac catheterization. Finally, among patients undergoing cardiac catheterization, an excess in catheter-related thrombotic complications was observed, a finding that has also been observed in other trials using fondaparinux.

Although fondaparinux receives a Class I recommendation in the latest AHA/ACC NSTEMI guideline, other anticoagulants represent better first-line options when an invasive approach is planned, given the long half-life of the agent, lack of reversibility, and the need to administer additional UFH at the time of PCI to prevent catheter-associated thrombus in patients who have received fondaparinux. In contrast, fondaparinux represents a more attractive alternative in conservatively managed patients and is a preferred agent among conservatively managed patients at increased risk for bleeding.

DIRECT THROMBIN INHIBITORS

Several DTIs are commercially available (argatroban, lepirudin, and bivalirudin), although bivalirudin has been the most studied and widely used. Bivalirudin is a semisynthetic direct-acting antithrombin with a 25-minute half-life. In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE) II trial,[90] bivalirudin alone was noninferior to the combination of UFH plus GP IIb/IIIa inhibitor with regard to death, MI, or urgent revascularization at 30 days (odds ratio, 1.09; 95% CI, 0.90-1.32). Major bleeding was significantly lower in the bivalirudin arm (2.4% vs 4.1%; $P < .001$).

The ACUITY trial was a complex trial performed in 13,819 patients with UA/NSTEMI, all of whom underwent cardiac catheterization within 72 hours.[91] Patients were randomized to one of three arms: UFH or enoxaparin plus routine GP IIb/IIIa inhibition, bivalirudin plus routine GP IIb/IIIa inhibition, or bivalirudin alone (with provisional GP IIb/IIIa use only). Results from this trial largely support the findings from REPLACE II, demonstrating significantly lower bleeding rates without a significant increase in the primary ischemic end point (death, MI, or unplanned revascularization for ischemia) in patients treated with bivalirudin alone compared with UFH (or enoxaparin) plus a GP IIb/IIIa inhibitor.[91] Importantly, however, in the GP IIb/IIIa arms, no safety or efficacy benefits of bivalirudin were noted over UFH or enoxaparin; thus, bivalirudin is not indicated when GP IIb/IIIa inhibitor use is planned. Because the median duration of pretreatment prior to PCI in ACUITY was only 4 hours, this study does not provide support for use of this agent outside the catheterization laboratory. Moreover, there was a treatment interaction based on whether patients are pretreated with clopidogrel before PCI. Among patients who were pretreated with a thienopyridine, ischemic outcomes were similar between the bivalirudin alone and heparin plus GP IIb/IIIa inhibitor arms. In contrast, among patients not pretreated with a thienopyridine, ischemic outcomes were worse in the bivalirudin arm. In aggregate, these studies support bivalirudin as a safe alternative to UFH or enoxaparin during PCI, provided patients have been pretreated with a $P2Y_{12}$ inhibitor or a postprocedure infusion of bivalirudin until the $P2Y_{12}$ effect is present. A meta-analysis including 13 trials with 24,605 ACS patients randomized to bivalirudin versus UFH with or without GP IIb/IIIa inhibitors confirmed a marked reduction in major bleeding with bivalirudin (odds ratio, 0.52; 95% CI, 0.45-0.60; $P < .001$) versus UFH with GP IIb/IIIa inhibitors. When GP IIb/IIIa inhibitors were provisionally used with UFH, the bleeding advantage of bivalirudin was attenuated (odds ratio, 0.66; 95% CI, 0.33-1.32). The rate of subacute (< 24 hours) stent thrombosis was several-fold higher with bivalirudin, although the rate of stent thrombosis at 30 days was not different between the bivalirudin and heparin groups.[92]

LONG-TERM ANTICOAGULATION

Several studies have evaluated the combination of warfarin and ASA after ACS. In initial trials, low fixed-dose warfarin was not superior to ASA monotherapy, and the combination was associated with excess bleeding risk. More recently, several studies have shown that the combination of ASA and warfarin may be effective in preventing ischemic events after ACS when the international normalized ratio is maintained at a higher level consistently and carefully monitored.[93,94] However, these findings are of questionable significance in light of the results of more recent antiplatelet trials, which demonstrated similar or greater benefit with a simpler regimens of ASA and ADP receptor antagonists. Warfarin should be prescribed for UA/NSTEMI patients who also have other well-proven indications for warfarin, such as atrial fibrillation and mechanical prosthetic heart valves. In such patients, combination with low-dose ASA is reasonable if the bleeding risk is not markedly increased.

One issue of particular concern is the extended-duration combination of ASA, clopidogrel, and warfarin. Evidence suggests that "triple therapy" is associated with substantially increased risks for bleeding. In one recent retrospective study of more than 40,000 patients discharged from Danish hospitals with ACS, admission for bleeding occurred in over 12% of patients in a 15-month period, a rate more than four-fold higher than among patients treated with ASA alone.[95] Bleeding rates were also markedly increased in patients treated with only clopidogrel and warfarin. It may be expected that risks will be even higher with combinations that include the newer and more potent antiplatelet agents such as prasugrel and ticagrelor. As such, it is recommended that attempts be made to minimize the duration of triple therapy. For patients who require triple therapy, the ASA dose should be reduced to 81 mg, the international normalized ratio should be maintained at the lower end of the therapeutic range, and gastrointestinal prophylaxis (eg, pantoprazole) should be considered. When the indication for warfarin is atrial fibrillation, a careful reevaluation of the risks of stroke (using

a tool such as the $CHADS_2$ score) and bleeding (HAS-BLED score) should be performed; in general, the threshold at which warfarin is initiated or continued should be higher among patients receiving ASA and clopidogrel. It should be noted that, although it is not as effective as warfarin for stroke prevention, ASA combined with clopidogrel is superior to ASA alone.[96] In patients with atrial fibrillation receiving bare metal stents, it may be reasonable to treat with ASA and clopidogrel for 1 month if the $CHADS_2$ score is low, at which time the clopidogrel or aspirin can be stopped and warfarin reinitiated.[97] Until data are available, prasugrel should be avoided with warfarin except in special circumstances, such as stent thrombosis with clopidogrel.

Several large trials with over 10,000 patients are ongoing assessing whether aspirin can be discontinued among patients with an indication for DAPT and anticoagulant therapy. In some trials, novel oral anticoagulants are replacing warfarin, whereas in others, more potent $P2Y_{12}$ inhibitors are replacing clopidogrel. These trials follow the intriguing results from the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) study.[98] In WOEST, 573 patients with a long-term indication for oral anticoagulant therapy (eg, chronic atrial fibrillation) and undergoing PCI with stent placement were randomized to triple therapy (DAPT plus warfarin) versus double therapy (clopidogrel with warfarin). At 1-year follow-up, bleeding events were substantially less frequent in the double therapy group (odds ratio, 0.36; 95% CI, 025-0.50; $P < .0001$). More impressive, perhaps, is that the 1-year occurrence of ischemic events was also lower in the group without aspirin.

TIMING AND INTENSITY OF LIPID LOWERING

A series of large randomized controlled trials has evaluated the role of statin therapy in patients with ACS. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, 3086 patients were randomized to treatment with 80 mg/d of atorvastatin or placebo 24 to 96 hours after an ACS.[99] After 16 weeks, the primary end point of death, MI, resuscitated cardiac arrest, or recurrent myocardial ischemia was reduced from 17.4% in the placebo group to 14.8% in the atorvastatin group ($P = .048$).

The Zocor (Z) phase of the A to Z trial compared an early intensive statin regimen (40 mg followed by 80 mg of simvastatin) with a delayed and less intensive regimen (placebo for 4 months followed by 20 mg of simvastatin) for up to 24 months in 4497 patients with ACS.[100] The primary end point of CV death, MI, readmission for ACS, or stroke occurred in 14.4% of patients in the early intensive statin arm versus in 16.7% of patients in the delayed, less intensive arm (HR, 0.89; 95% CI, 0.76-1.04). CV death was reduced by 25% in the early intensive statin arm ($P = .05$). During the first 4 months, no difference was evident between treatment groups, but from 4 to 24 months, the primary end point was reduced in the intensive statin group.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial, an intensive statin regimen of 80 mg of atorvastatin was compared with a standard statin regimen of 40 mg/d of pravastatin among 4162 patients with ACS.[101] The atorvastatin arm achieved an average low-density lipoprotein (LDL) cholesterol of 62 mg/dL versus an average of 95 mg/dL in the pravastatin arm. The primary end point of death, MI, UA, or revascularization after 30 days was reduced by 16% in the atorvastatin arm ($P < .0001$).

Thus, findings are generally consistent with a "lower is better" approach to LDL cholesterol management after ACS. Current clinical practice guidelines eschew targets for LDL concentrations, recommending immediate use of high-dose statin therapy (eg, atorvastatin 80 mg) for patients with ACS.[1,102]

POSTHOSPITAL DISCHARGE AND CARE

The risk of progression to MI or the development of recurrent MI or death is highest during the first few months after the index ACS event. At 1 to 3 months after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable CAD (see Chap. 45).

The broad goals during the hospital discharge phase are two-fold: (1) to prepare the patient for normal activities to the extent possible and (2) to use the acute event as an opportunity to implement long-term care, particularly lifestyle and risk factor modification.

Preparing patients for resumption of normal activities after discharge should include education regarding risk factors for coronary atherosclerosis, importance of medication therapy, and the importance of healthy behaviors including proper diet and exercise habits. Patients should be educated not only about their medications but also which medications should be avoided after discharge (eg, nonsteroidal anti-inflammatory drugs). Discussion regarding referral to CV rehabilitation program is appropriate at this time. Such programs provide an excellent means by which patients may achieve the goals discussed.

There is no better time to implement long-term improvements in care for CV disease than soon after hospital discharge following an ACS. Goals for continued medical therapy after discharge are to ensure that (1) all potential therapies that have been demonstrated to improve long-term outcomes are administered to eligible patients, including ASA (with or without DAPT), β-blockers, statins, and ACE inhibitors (especially for patients with LV ejection fraction < 40%); (2) ischemic symptoms are controlled, using as-needed nitrates, β-blockers, calcium antagonists, and occasionally ranolazine; and (3) major risk factors such as hypertension, smoking, hyperlipidemia, and diabetes mellitus (see Chaps. 25-29 and 45) are optimally managed. Monitoring for depression after hospital discharge is recommended and may be achieved in a cardiac rehabilitation environment.

SPECIAL PATIENT GROUPS

Several patient groups with UA/NSTEMI deserve special commentary.

THE ELDERLY

Older patients with NSTE-ACS should generally be managed similarly to younger patients, but patient-centered decision making is necessary in older patients, and it is important to individualize pharmacotherapy to older patients, given differences in renal function and more medical comorbidities.[103]

CARDIOGENIC SHOCK

Although cardiogenic shock is much less common in patients with NSTE-ACS compared to those with STEMI, should cardiogenic shock complicate UA/NSTEMI, management should be similar to those with STEMI, including revascularization, whenever possible.[104]

SPONTANEOUS CORONARY ARTERY DISSECTION

Spontaneous dissection of the coronary artery (SCAD) is an increasingly recognized cause of ACS, particularly in women age 30 to 50 years.[105] The pathophysiology of SCAD is unknown; many cases occur in situations such as uncontrolled hypertension, in the puerperium, in those with fibromuscular dysplasia, or as a complication of disorders of collagen integrity, such as Marfan syndrome. The diagnosis of SCAD should be entertained when younger (usually female) patients present with symptoms and signs of acute coronary ischemia in the absence of

FIGURE 39–7. Invasive coronary angiogram of a patient with spontaneous coronary artery dissection. Diffuse irregularity of the left anterior descending artery is noted, along with extension into side branches, including the diagonal artery.

other risk factors. Diagnostic studies for those with SCAD should be similar to those without the diagnosis; the presence of a coronary dissection plane may be challenging to recognize at the time of coronary angiography (Fig. 39–7), so a high level of suspicion for presence of the diagnosis should be maintained during such procedures.

Standard treatment for SCAD is not established. For many, conservative management may be quite effective, particularly if flow is present in the coronary artery at the time of diagnostic coronary angiography; spontaneous healing of the dissection may be seen at the time of follow-up angiography.[106] Should revascularization be indicated (ie, occlusion of a coronary vessel is present), both PCI and CABG have been reported as effective choices, although risk for further dissection is present in the context of a fragile vessel, so caution is advised. Given the high prevalence of unrecognized fibromuscular dysplasia in affected patients,[107] some recommend screening for presence of intracranial aneurysm in those affected by SCAD.

STRESS CARDIOMYOPATHY

Widely recognized as an ACS "mimic," stress cardiomyopathy (also known as "apical ballooning" syndrome or takotsubo cardiomyopathy as a result of resemblance of the dysfunctional LV to a Japanese octopus pot trap) was first reported in Japan in 1990. Following more widespread recognition of this entity, incidence and prevalence of stress cardiomyopathy have grown; stress cardiomyopathy is found in 1.7% to 2.2% of patients presenting with ACS, and the vast majority (> 90%) are women.[108]

Stress cardiomyopathy most often follows an acute emotional stress, such as the death of a loved one, and may appear indistinguishable from a high-risk ACS, with typical angina, rise and fall of troponin, and onset of heart failure symptoms. Characteristic ECG changes of stress cardiomyopathy include development of symmetric T-wave inversion in most leads; however, such changes are not specific enough to stress cardiomyopathy to avoid diagnostic coronary angiography. At angiography, nonobstructed coronary arteries are the rule, along with characteristic myocardial dysfunction of the LV apex, with compensatory basal hyperkinesis (Fig. 39–8).

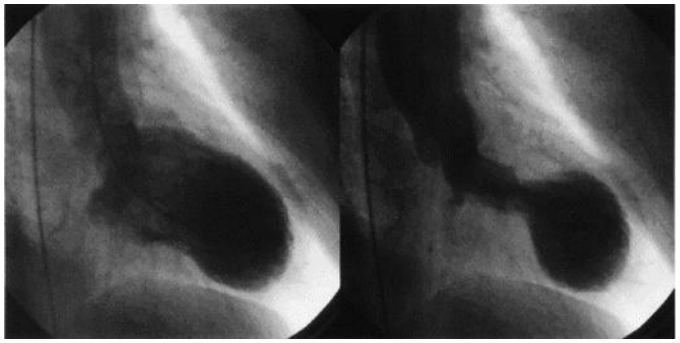

FIGURE 39–8. Characteristic left ventriculogram of a patient with stress cardiomyopathy. Also known as "apical ballooning" or takotsubo syndrome (the latter because of the similar appearance of the affected left ventricle to a Japanese octopus trap), this syndrome is a common mimic of acute coronary syndrome, often presenting with chest pain, abnormal electrocardiogram, and elevation in cardiac troponin. Reproduced with permission from Abe Y, Kondo M, Matsuoka R, et al: Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol*. 2003 Mar 5;41(5):737-742.

Management of patients with stress cardiomyopathy is typically supportive[109]; patients most often recover rapidly after presentation, though shock at presentation is not uncommon. Use of vasodilating inotropic agents or intra-aortic balloon counterpulsation in those with shock may actually worsen hemodynamics as such treatment may precipitate LV outflow tract obstruction in the context of basal hyperkinesis. β-Blockers and ACE inhibitors or ARBs are often used during convalescent periods, but their value in stress cardiomyopathy is unknown.

VARIANT ANGINA

In 1959, Prinzmetal described a syndrome characterized by angina at rest with transient marked ST-segment elevation.[110] The attacks were cyclic in nature, often occurring at rest and in the early morning hours. Ventricular arrhythmias and AV block sometimes occurred at the peak of an attack, and both MI and sudden death were reported as potential consequences. With the use of coronary angiography, it soon became evident that the syndrome was caused by coronary spasm, usually focal and often at the site of a coronary artery stenosis. Coronary spasm might occur in more than one artery in some patients, and the site of spasm may fluctuate from one coronary artery to another.

Variant angina is more common in heavy cigarette smokers, but their age, gender, and risk factor profiles are otherwise similar to those of other coronary patients. Of patients with variant angina, 25% have a history of migraine headaches, and approximately 25% have symptoms of Raynaud phenomenon. Syncope that occurs during rest angina, likely caused by ischemia-induced ventricular arrhythmia or AV block, is a clue to the diagnosis.

Pathophysiologically, it is thought that coronary spasm is a result of abnormalities in endothelial function and nitric oxide activity at sites of coronary spasm.[111] Severe spasm rapidly induces transmural ischemia, resulting in ST-segment elevation. The risks of serious ventricular arrhythmias and conduction abnormalities (including compete heart block) increase in proportion to the severity and extent of ischemia. Prolonged spasm may lead to MI.

Patients with variant angina can be diagnosed most easily by an ECG recorded during an episode of rest angina, particularly if ST-segment elevation that occurs during an attack disappears promptly after the administration of NTG. Ambulatory ECG monitoring or an event monitor can sometimes be useful to confirm the diagnosis. Exercise testing provokes angina with ST-segment elevation in approximately one-third of patients with variant angina during an active phase of

the disease. All patients with variant angina should undergo coronary angiography unless an absolute contraindication is present.

Patients with variant angina are often difficult to treat because attacks are unpredictable and often occur without an obvious precipitating factor. NTG relieves variant angina attacks within minutes and should be used promptly; long-acting nitrates are initially effective in preventing variant angina attacks. CCBs are very effective in preventing attacks of variant angina; higher CCB doses are frequently required. For example, long-acting nifedipine (90 mg/d), diltiazem (360 mg/d), verapamil (480 mg/d), and amlodipine (20 mg/d) are commonly used.[112] Statin therapy is also indicated, given the beneficial effects of statins on endothelial function and the common presence of atherosclerosis underlying focal spasm.

Although intuitively logical, the use of revascularization to manage spasm should be reserved for absolutely refractory cases, where documented spasm continues despite optimal medical therapy; results of revascularization procedures in such circumstances are mixed as a result of recurrence of spasm in other coronary territories.

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CHAPTER 40

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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EPIDEMIOLOGY

Ischemic heart disease is the leading cause of morbidity and mortality in Western society and is a worldwide epidemic. In 2008, it was estimated that, worldwide, ischemic heart disease was responsible for 12.7% of all deaths (7.25 million total) with low-income countries now accounting for 80% of all deaths with a falling mortality in high-income countries.[1] Approximately 1,100,000 Americans suffer from an acute coronary syndrome (ACS) per year, nearly one-third of which are caused by an acute ST-segment elevation myocardial infarction (STEMI).[2] The incidence of acute myocardial infarction (AMI) has declined over the past two decades from 244 per 100,000 population in 1975 to 162 per 100,000 population in 2006.[3] The in-hospital mortality rate also has declined from 18% in 1975 to 10% in 2006.[4] Despite these improvements, AMI continues to be a major public health problem, and it has been estimated that the number of years of life lost because of an AMI is 17.1 years, and the cost to American society (both direct and indirect) is $165.4 billion per year.[2]

The management of STEMI patients is complex, multidisciplinary, and involves the following four different stages of care: (1) prehospital care, (2) emergency department, (3) cardiac catheterization laboratory, and (4) coronary care unit. This chapter discusses the diagnosis and management of STEMI patients in each of these four settings. The pathophysiology of disease is discussed in Chap. 37, and the ACSs of unstable angina and non–ST-segment elevation myocardial infarction are discussed in Chap. 39.

DIAGNOSIS

SYMPTOMS

The classic symptom of acute myocardial ischemia is precordial or retrosternal discomfort, commonly described as a pressure, crushing, aching, or burning sensation. Radiation of the discomfort to the neck, back, or arms frequently occurs, and the pain is usually persistent rather than fleeting. The discomfort typically achieves maximum intensity over several minutes and can be associated with shortness of breath, nausea, diaphoresis, generalized weakness, and a fear of impending death. Some patients, particular the elderly, may also present with syncope, unexplained nausea and vomiting, acute confusion, agitation, or palpitations. Symptoms in the advanced elderly (> 75 years old) are more likely to be atypical (new or worsening dyspnea) than in younger patients and can lead to a missed diagnosis if a medical professional is not vigilant in the initial assessment.

Approximately 20% of AMI patients are asymptomatic or have atypical symptoms that are not initially recognized. Painless myocardial infarction occurs more frequently in the elderly, women, diabetics, and postoperative patients. These patients tend to present with dyspnea or frank congestive heart failure as their initial symptom.[5] Some patients with ST-segment elevation do not have occlusive thrombosis and have a unique regional cardiomyopathy called takotsubo syndrome, which is described at the end of the chapter.

PHYSICAL EXAMINATION

Patients often appear anxious and uncomfortable. Those with substantial left ventricular (LV) dysfunction at presentation may have tachypnea, tachycardia, pulmonary rales, and a third heart sound. The presence of a systolic murmur suggests ischemic dysfunction of the mitral valve apparatus or papillary muscle or ventricular septal rupture and needs to be distinguished from a pericardial friction rub secondary to pericarditis or possible partial rupture with adhesions.

In patients with right ventricular (RV) infarction, increased jugular venous pressure, Kussmaul sign (rise in jugular venous pressure with inspiration), and an RV third sound may be present. Such patients typically have inferior infarctions as a result of proximal right coronary artery occlusion, usually without evidence of left heart failure, and may have exquisite blood pressure sensitivity to nitrates or hypovolemia. In patients with extensive ongoing ischemia or LV dysfunction, shock is indicated by hypotension, diaphoresis, cool skin and extremities, pallor, oliguria, and possible altered mental status.

ELECTROCARDIOGRAM

The classic initial electrocardiographic (ECG) manifestations of STEMI are discussed in Chap. 12 and involve an increase in the amplitude of the T wave (peaking), followed within minutes by ST-segment elevation. Diagnostic ST elevation in the absence of LV hypertrophy or left bundle branch block (LBBB) is defined by the European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction as new ST elevation at the J point in at least two contiguous leads of 2 mm (0.2 mV) in men or 1.5 mm (0.15 mV) in women in leads V_2 to V_3 and/or of 1 mm (0.1mV) in other contiguous chest leads or the limb leads.[6]

The R wave may initially increase in height but soon decreases, and often Q waves develop. If the jeopardized myocardium is reperfused, the ST segment may promptly decrease, although T waves can remain inverted, and Q waves may or may not regress. Persistent ST-segment elevation after restoration of flow in the epicardial coronary artery is a marker of abnormal myocardial perfusion and associated with an adverse prognosis. In the absence of reperfusion, the ST segment gradually returns to baseline in several hours to days, and T waves become symmetrically inverted. Failure of the T wave to invert within 24 to 48 hours suggests regional pericarditis.

The specific leads with ST-segment elevation can help localize the infarct (see Chap. 12): ST-segment elevation in the inferior, anterior, or high lateral leads is seen with infarction of the corresponding areas of myocardium. ST-segment elevation in lead aVR is an ominous sign and is more frequent in patients with left main artery occlusion than in patients with left anterior descending coronary artery or right coronary artery occlusion.[7] In a study of STEMI patients, ST-segment elevation in lead aVR that was greater than or equal to the extent of ST-segment elevation in lead V_1 had 81% accuracy for diagnosing left main occlusion.[7] ST-segment elevation in lead V_1 in the setting of inferior myocardial infarction suggests RV involvement. Because no leads on the standard 12-lead ECG directly represent the posterior myocardium, isolated infarction of this area may be difficult to diagnose but is typically manifested by ST-segment depression in V_1 to V_3, a mirror image of anterior myocardial infarct.[8] Depending on the affected artery (right coronary vs circumflex), posterior myocardial infarction is frequently associated with either inferior or lateral injury, with ECG manifestations of STEMI corresponding to those areas of myocardium. Sensitivity of detecting posterior myocardial infarction may be enhanced by the use of additional ECG leads (V_7-V_9) designed to represent the posterolateral myocardium.[9,10] ST-segment elevation in these additional leads is suggestive of posterior involvement.

New-onset (or not known to be old) LBBB in the setting of chest pain is typically considered and treated as an STEMI.[11] The diagnosis of STEMI in the setting of old LBBB can be difficult. Findings suggesting STEMI include (1) a pathologic Q wave in leads I, aVL, V_5, or V_6 (two leads); (2) precordial R-wave regression; (3) late notching of the S wave in V_1 to V_4; and (4) deviation of the ST segment in the same direction as that of the major QRS deflection.[12] Similar findings may be expected in RV pacing with LBBB structure of the QRS. In one study, patients with paced rhythm had higher in-hospital and 1-year mortality, in part because of undertreatment, which illustrates the difficulty of AMI diagnosis in this setting.[13,14]

Analysis of ECG data from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I study identified three criteria for diagnosing myocardial infarction in the presence of the LBBB: (1) ST-segment elevation ≥ 1 mm concordant with the QRS complex; (2) ST-segment depression ≥ 1 mm in leads V_1, V_2, or V_3; and (3) ST-segment elevation ≥ 5 mm discordant with the QRS.[14]

The ECG, however, has several limitations: (1) Even though ST-segment elevation usually signifies acute coronary occlusion, acute coronary occlusion may not cause ST-segment elevation in certain circumstances, such as a circumflex artery occlusion; (2) in addition, not all ST-segment elevation is caused by AMI, including conditions such as electrolyte abnormalities, myocarditis, and prior LV aneurysm; and (3) finally, an old LBBB limits the usefulness of the ECG for AMI diagnosis in this subset of patients.

LABORATORY STUDIES

Damaged cardiomyocytes release several proteins in the circulation, including myoglobin, creatine kinase (CK) and its myocardial band isoenzyme (CK-MB), troponins (I and T), myoglobin, aspartate aminotransferase, and lactate dehydrogenase (see Chap. 38). Figure 40–1 shows the timing of release.[15] Cardiac troponins are currently the preferred biomarkers for myocardial damage because of their high sensitivity and specificity.[16] CK-MB is the best alternative, if cardiac troponin assays are not available. CK-MB, because of its more rapid appearance and disappearance from the blood, can be used (1) in patients presenting early after symptom onset; (2) to time the onset of injury if the troponin is increased; and (3) to detect reinfarction later in the hospital course. Determinations of total CK, aspartate aminotransferase, and lactate dehydrogenase are no longer recommended. Blood sampling for biomarker determination is recommended at hospital admission, at 6 to 9 hours, and at 12 to 24 hours if the earlier samples were negative and the clinical index of suspicion is high (see Chap. 38).[16]

Myoglobin

Myoglobin is a 17.8-kDa protein that is released from injured myocardial cells. As shown in Fig. 40–1, myoglobin release occurs within hours after the onset on infarction, reaches peak levels at 1 to 4 hours, and remains elevated for approximately 24 hours. Although the rapid

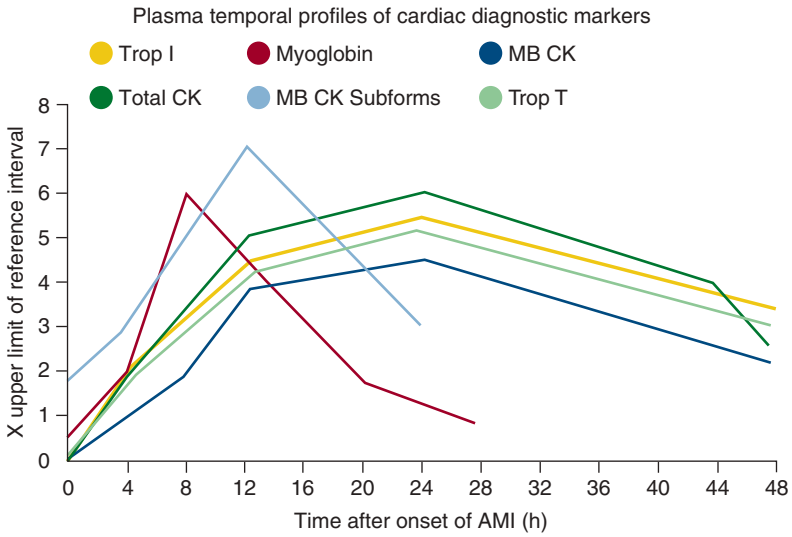

FIGURE 40–1. Shown here is the temporal profile of the diagnostic biomarkers used for detecting acute myocardial infarction (AMI). The plasma temporal profile for early detection is illustrated for myoglobin and myocardial band (MB) creatinine kinase (CK) subforms. The markers MB CK, total CK, and cardiac troponins (Trop) I and T are all released with a similar initial time profile. However, troponins I and T remain elevated for 10 to 14 days and thus are better markers for late diagnosis than MB CK.

rise allows for its use as an early marker for STEMI, myoglobin is not specific to myocardial cells and should not be used in isolation as a method for diagnosing myocardial infarction.

Creatine Kinase-MB

The MB isoenzyme of CK is present in largest concentration in myocardium, although small amounts (1%-2%) can be found in skeletal muscle, tongue, small intestine, and diaphragm. CK-MB appears in serum within approximately 3 hours after the onset of infarction, reaches peak levels at 12 to 24 hours, and has a mean duration of activity of 1 to 3 days.[15] Other cardiac, but non-AMI etiologies of increased CK-MB levels can occur after cardioversion, cardiac surgery, myopericarditis, and percutaneous coronary intervention (PCI), and occasionally after rapid tachycardia. Noncardiac causes of increased CK-MB levels may occur with hypothyroidism, extensive skeletal muscle trauma, rhabdomyolysis, the muscular dystrophies, and some other neuromuscular disorders.

Occasionally, the concentration of CK-MB isoenzyme may be increased in the presence of normal total levels of CK enzyme. This finding usually indicates a small amount of myocardial necrosis in a patient whose baseline total CK enzyme level is at the low-normal end of the range (see Chap. 38).

Troponins

The cardiac troponins regulate the interaction of actin and myosin and are more cardiac specific than CK-MB. There are two isoforms of cardiac troponin: T and I. Their levels start to rise 3 to 12 hours after the onset of ischemia, peak at 12 to 24 hours, and may remain elevated for 8 to 21 days (troponin T) or 7 to 14 days (troponin I). Several new high-sensitivity troponin assays can detect lower concentrations of circulating troponins compared with previous assays. These assays were recently evaluated by two large multicenter studies revealing corroborating results. The high-sensitivity assays proved more sensitive in the diagnosis of myocardial infarction than older assays (94%-96% vs 85%-90%) at the expense of a reduced specificity (90.2% vs 97.2%).[17,18] The high-sensitivity troponins are an integral part of diagnosis for myocardial infarction including STEMI. There are emerging data that ultra–high-sensitivity troponin assays with ranges of detection 0.2 pg/mL provide prognostic information in ACS patients with undetectable high-sensitivity troponin levels.[19] In summary, it is clear that elevated troponin levels correlate with pathologically proven myocardial necrosis and indicate poor prognosis in patients with suspected ACSs (see Chap. 36).[20-24]

PREHOSPITAL DIAGNOSIS AND REGIONAL SYSTEMS OF CARE

Rapid diagnosis is a pivotal component of the management of STEMI patients. Early diagnosis can be achieved with a prehospital ECG that is obtained in the field by emergency medical personnel and transmitted to an emergency department physician or cardiologist on-call. This allows for early administration of fibrinolytic therapy or activation of the cardiac catheterization team before arrival of the patient and has been demonstrated in several studies to reduce both the door-to-needle and door-to-balloon time.[25-27]

Specifically, analysis of data from the National Registry of Myocardial Infarction revealed that only 4.5% (1599 of 35,370) of patients receiving thrombolytic therapy and 8% (1696 of 21,277) of patients undergoing primary PCI had a prehospital ECG.[26] The analysis also showed that a prehospital ECG resulted in a significantly shorter door-to-needle time (24.6 vs 34.7 minutes; $P < .0001$) for those receiving fibrinolytic therapy and a shorter door-to-balloon time (94 vs 110 minutes; $P < .0001$) for primary PCI patients.[26]

The use of newer automated wireless technologies for the transmission of prehospital ECGs was studied in the ST-Segment Analysis Using Wireless Technology in Acute Myocardial Infarction (STAT-MI) trial.[28] In this study, the ECGs of 20 patients with STEMI were transmitted via cellular phones to a tertiary care center. Compared with data obtained in patients who did not receive prehospital ECGs, wireless transmission resulted in the improvement of the following times: door-to-intervention (80.1 vs 145.6 minutes; $P < .001$), door-to-cardiologist notification (14.6 vs 61.4 minutes; $P < .001$), door-to-arterial access (47.6 vs 108.1 minutes; $P < .001$), and time to first angiographic injection (52.8 vs 119.2 minutes; $P < .001$). These data further illustrate the importance of early evaluation and triage of patients with suspected STEMI to facilitate rapid and

appropriate treatment. The availability and cost of this technology, however, may preclude its widespread use.

Based on these data and data from regional systems in both the United States and Europe, the American College of Cardiology (ACC)/AHA[29] and the ESC[30] guidelines for STEMI emphasize the importance of systems of care for patients with suspected AMI/STEMI. The ACC/AHA have developed regional systems of STEMI care aimed at improving the coordination and likelihood of getting time to treatment goals achieved.

Specifically, the ACC/AHA Guidelines[29] recommend the following:

Class I

1. *All communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS [emergency medical system] and hospital-based activities. Performance can be facilitated by participating in programs such as Mission: Lifeline and the D2B Alliance. (Level of Evidence: B)*
2. *Performance of a 12-lead ECG by EMS personnel at the site of first medical contact (FMC) is recommended in patients with symptoms consistent with STEMI. (Level of Evidence: B)*

The goal of the regional systems of care is to maximize the opportunity for timely reperfusion for STEMI patients. In that regard, the ACC/AHA STEMI guideline provide prehospital transport recommendations and criteria.

Patients with possible ischemic symptoms are encouraged to use EMS and ambulances rather than private vehicles for transportation to hospital because (1) one out of 300 patients with chest pain transported by private vehicle will suffer a cardiac arrest in transportation,[31] and (2) as stated above, transportation with EMS is associated with earlier activation of reperfusion services and faster time to reperfusion.

Additionally, the guidelines specifically note that a prehospital ECG can activate the PCI team while in transport to the hospital, that the emergency department physician can also activate the PCI team, and that one call with feedback to the PCI team on time metrics should be the goal for reperfusion centers.

Figure 40–2 provides a schematic from the guidelines for considering transportation to regional hospitals for reperfusion as outlined in the AHA Mission Lifeline program.

The timely reperfusion goals include determining the closest primary PCI center for the preferred primary PCI (within 90 minutes of first medical contact), determining acceptable delays that allow transfer of patients to get primary PCI reperfusion within 120 minutes, and quickly treating patients who are outside of those windows with fibrinolytic therapy followed by possible transfer for invasive care as needed.

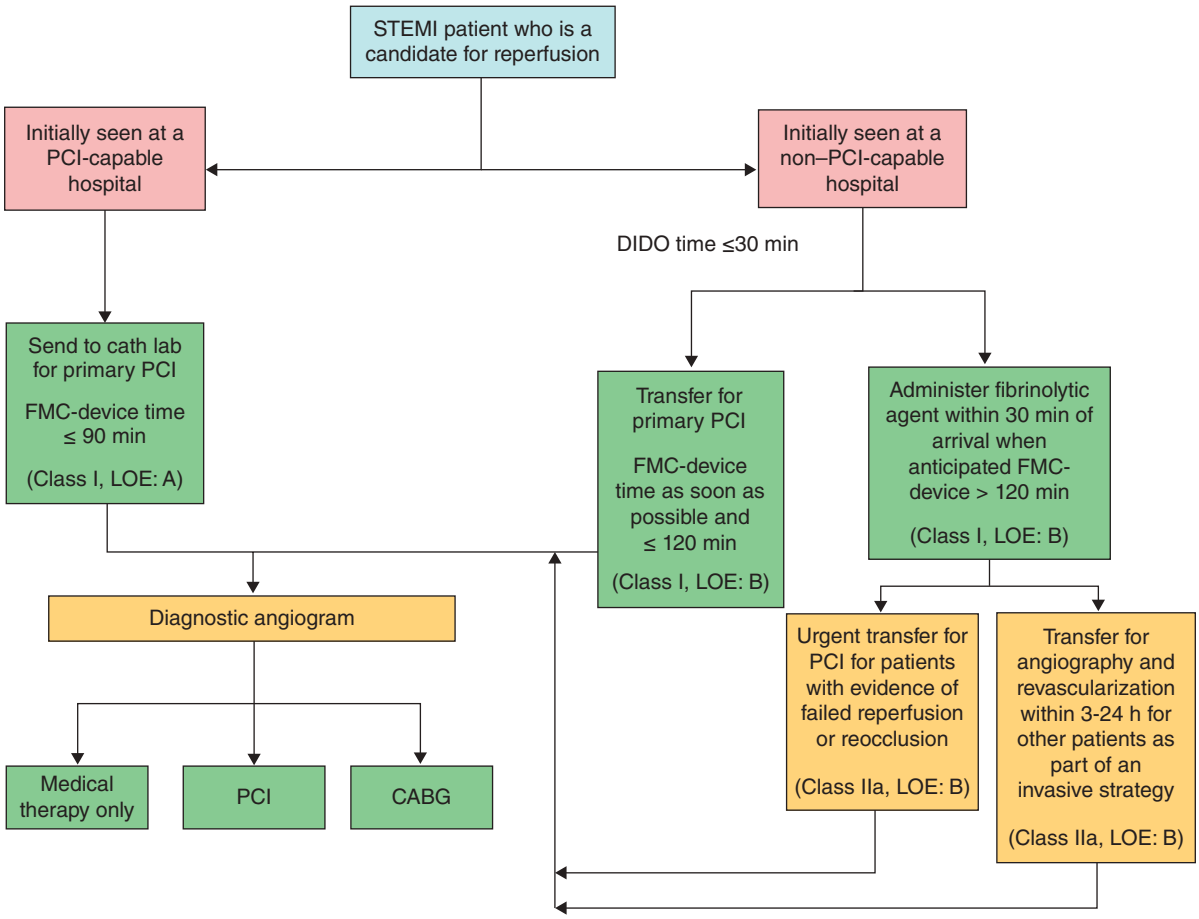

FIGURE 40–2. Schematic from the American College of Cardiology/American Heart Association (AHA) guidelines for considering transportation to regional hospitals for reperfusion as outlined in the AHA Mission Lifeline program. CABG, coronary artery bypass graft; DIDO, door in to door out time; FMC, first medical contact; LOE, level of evidence; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction. Reproduced with permission from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013 Jan 29;127(4):e362-e425.

These regional system goals are captured in the following recommendations[29]:

Class I

1. *Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the prior 12 hours. (Level of Evidence: A)*
2. *Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators. (Level of Evidence: A)*
3. *EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal FMC-to-device time system goal of 90 minutes or less. (Level of Evidence: B)*
4. *Immediate transfer to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI who initially arrive at or are transported to a non–PCI-capable hospital, with an FMC-to-device time system goal of 120 minutes or less. (Level of Evidence: B)*
5. *In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays. (Level of Evidence: B)*
6. *When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival. (Level of Evidence: B)*

Class IIa

1. *Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of ongoing ischemia. Primary PCI is the preferred strategy in this population. (Level of Evidence: B)*

PREHOSPITAL FIBRINOLYTIC THERAPY

Given the transport time to hospitals and centers for primary PCI, the time delay can be substantial, and many have investigated delivering prehospital fibrinolytic therapy as a reperfusion strategy for patients in areas without primary PCI capabilities.

Multiple randomized trials have shown that this strategy is feasible and would reduce treatment delays, and a meta-analysis of six higher quality randomized controlled trials has demonstrated that a 60-minute reduction in treatment delay is possible with a resultant 17% reduction in mortality.[32]

TRIAGE AND EVALUATION

The cornerstone of STEMI therapy is a rapid and accurate evaluation at first medical contact. All patients presenting with complaints of chest discomfort should be rapidly triaged and allowed to bypass the emergency department waiting room. An ECG should be obtained within the first 10 minutes of arrival at the emergency department, and a focused history and physical examination assessing the symptoms and signs described in the diagnosis section of this chapter should be quickly performed.

The physical examination also provides a method for the risk stratification of STEMI patients. As shown in Table 40–1, the Killip classification can be used as a method to stratify patients and predict clinical outcomes, and it is noteworthy that this classification has stood the test of time.[33] With modern therapy, the mortality of those in cardiogenic shock has improved from 83% to approximately 50%.[34]

TABLE 40–1. Killip Classification for Patients With ST-Segment Elevation Myocardial Infarction

Killip Class		Hospital Mortality (%)
I	No congestive heart failure	6
II	Mild congestive heart failure, rales, S_3, congestion on chest radiograph	17
III	Pulmonary edema	38
IV	Cardiogenic shock	81[a]

[a]Has improved to approximately 60% with current therapy.

In addition to the rapid evaluation of the ECG (within 10 minutes of arriving), guidelines have recommended a targeted physical exam in the emergency department focusing on the cardiovascular and neurologic systems, and repeated ECGs if the initial ECGs are not diagnositic.[35]

Class I

1. *The targeted history of STEMI patients taken in the emergency department should ascertain whether the patient has had prior episodes of myocardial ischemia, such as stable or unstable angina, myocardial infarction, coronary bypass surgery, or PCI. Evaluation of the patient's complaints should focus on chest discomfort, associated symptoms, sex- and age-related differences in presentation, hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding, and clinical cerebrovascular disease (amaurosis fugax, face/limb weakness or clumsiness, face/limb numbness or sensory loss, ataxia, or vertigo). (Level of Evidence: C)*
2. *A physical examination should be performed to aid in the diagnosis and assessment of the extent, location, and presence of complications of STEMI. (Level of Evidence: C)*
3. *A brief, focused, and limited neurologic examination to look for evidence of prior stroke or cognitive deficits should be performed on STEMI patients before administration of fibrinolytic therapy. (Level of Evidence: C)*
4. *A 12-lead ECG should be performed and shown to an experienced emergency physician within 10 minutes of emergency department arrival on all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of STEMI. (Level of Evidence: C)*
5. *If the initial ECG is not diagnostic of STEMI but the patient remains symptomatic and there is a high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous 12-lead ST-segment monitoring should be performed to detect the potential development of ST elevation. (Level of Evidence: C)*
6. *In patients with inferior STEMI, right-sided ECG leads should be obtained to screen for ST elevation suggestive of RV infarction. (Level of Evidence: B)*

INITIAL THERAPY IN THE EMERGENCY DEPARTMENT

The initial management of patients in the emergency department may be brief because the goal for STEMI is to reduce the time to reperfusion. In fact, over the last several years, the use of adjunctive therapies such as oxygen, β-blockers, and initiation of anticoagulation in the emergency department has decreased.

OXYGEN

Low-flow oxygen therapy delivered by nasal cannula was previously recommended to be routinely given during the first 24 to 48 hours and perhaps several days after AMI in most patients. Although routine use of supplemental oxygen is common practice, hard evidence supporting its use during the acute phase of a STEMI is lacking.[36] In fact, a Cochrane analysis that pooled the results of three trials found a threefold higher risk of death in patients getting oxygen with confirmed infarctions compared to patients on room air.[37] Supplementary oxygen may also increase coronary vascular resistance.[38] Therefore, oxygen is not routinely indicated but is used in patients with clinically significant hypoxemia and evidence of heart failure.

ASPIRIN

Aspirin decreases mortality in myocardial infarction and should be administered as early as possible and continued indefinitely in patients with ACSs. In cases of aspirin allergy or major intolerance, clopidogrel should be substituted. In the International Study of Infarct Survival 2 (ISIS-2), 77,187 STEMI patients were randomized to treatment with aspirin, streptokinase, or placebo. The 5-week incidence of vascular death decreased by 23% with aspirin and heparin, by 25% with streptokinase and heparin, and by 41% with the combination of all three agents.[39] Thus, the effect of aspirin was surprisingly nearly as great as that of streptokinase alone in that study, and the benefits of each were partially additive. Therefore, 160 to 325 mg of chewable aspirin should be given to patients at presentation, with a subsequent preferred dose of 81 mg daily. For those with a history of a documented significant adverse reaction to aspirin, 300 mg of clopidogrel can be used as an alternative.

The clinical practice guidelines recommend the following aspirin recommendations as part of STEMI care with reperfusion as a planned treatment[29]:

Class I

1. *Aspirin 162 to 325 mg should be given before primary PCI. (Level of Evidence: B)*
2. *Aspirin 162 to 325 mg should be given before fibrinolysis. (Level of Evidence: B)*
3. *Aspirin should be continued indefinitely. (Level of Evidence: A)*

Class IIa

1. *It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI. (Level of Evidence: B)*
2. *It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after fibrinolysis. (Level of Evidence: B)*

$P2Y_{12}$ INHIBITORS

Thienopyridines (clopidogrel and prasugrel) and now direct $P2Y_{12}$ inhibitors such as ticagrelor are oral antiplatelet agents that inhibit platelet activation through the adenosine diphosphate (ADP)-mediated pathway. Several factors contribute to the choice of antiplatelet agent (clopidogrel, prasugrel, or ticagrelor), as well as the initial dose. Unless contraindicated, these antiplatelet agents should be initiated upon presentation of STEMI. See the Adjuvant Antiplatelet Therapy section in this chapter for further discussion and the clinical practice guidelines regarding $P2Y_{12}$ inhibitors.

β-BLOCKERS

The results of clinical trials investigating the use of β-blockers in ACSs have documented a decrease in early and late mortality. In pooled data from 28 trials of β-blockers, the average mortality decrease was 28% at 1 week, with the majority of benefit occurring in the first 48 hours.[40] Specifically, reinfarction was reduced by 18% and cardiac arrest by 15%.[40] The long-term effects of β-blockade for the secondary prevention of death after myocardial infarction were established by large-scale randomized trials. In a recent meta-analysis of 82 randomized trials of β-blockers, there was a significant reduction in long-term, but not short-term, mortality.[41] The number of patients needed to treat with a β-blocker to prevent one death over 2 years was 42, compared with 24 for thrombolytics, 94 for standard-dose statins, and 153 for antiplatelet agents.

Traditionally, metoprolol has been the agent of choice and was initially administered intravenously followed by an oral dose. The Thrombolysis in Myocardial Infarction (TIMI) 2B study of early (immediate intravenous load followed by oral dosing) versus delayed (no intravenous load) therapy in STEMI patients who were undergoing reperfusion therapy with thrombolytic therapy showed no difference between the two groups in mortality or ejection fraction at the time of discharge.[42] Data from COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial), which involved 45,852 patients, demonstrated that β-blockade resulted in a 15% to 20% relative risk reduction in the rate of recurrent infarction, but in a 30% relative increase in the risk of cardiogenic shock.[43] Early metoprolol use has also been shown to be cardioprotective and reduce infarct size.[44,45] Therefore, the use of β-blockade in patients with evidence of hemodynamic instability or heart block should be delayed until the patients become stable. Also, the routine initial intravenous administration of β-blockers is no longer considered standard therapy due to the potential risk of worsening status in patients with severe heart failure or cardiogenic shock. Finally, the benefits of β-blockade in patients undergoing primary PCI remain unclear, and there have been no randomized prospective studies.

ANALGESIA

Morphine is frequently used for pain relief and is best administered intravenously in boluses of 1 to 2 mg, to a maximum of 10 to 15 mg for a normal adult. Respiratory depression can occur, and care must be taken not to oversedate patients. Morphine should be used with caution in patients with hemodynamic instability because of its effects on reducing cardiac preload. In patients with inferior myocardial infarction and possible RV involvement, preload reduction is poorly tolerated, particularly in patients already volume depleted due to poor intake, vomiting, diaphoresis, and older age, and drugs such as morphine and nitrates should be used with caution.

Several studies have demonstrated an increased risk of adverse cardiovascular events with the administration of nonsteroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase-2 inhibitors.[46,47] These agents should not be administered for analgesia at any time during presentation with or hospitalization for STEMI.

NITRATES

Nitrates cause non–endothelium-dependent coronary vasodilatation, systemic venodilatation, reduced cardiac preload, and enhanced perfusion of ischemic myocardial zones (see Chap. 43). Animal and human data demonstrate that nitrate use may result in a reduction of infarct size; however, there is no benefit of nitrates in reducing mortality.[48-50] For patients with *symptomatic* ischemia, however, intravenous nitroglycerin may be very effective, although nitroglycerin tolerance has been observed as early as 12 hours after institution of intravenous therapy. Often, hemodynamic intolerance to nitroglycerin may be a problem, especially in patients with inferior infarction, hemodynamically significant RV infarction, or concomitant aortic valve stenosis, or among the elderly, particularly in the setting of preexisting volume depletion. Often the hypotension is accompanied by a bradycardia as a manifestation of the von Bezold-Jarisch reflex, particularly in patients with RV infarction.

Intravenous nitroglycerin should be initiated at 5 to 10 μg/min and gradually increased with a goal of a 10% to 30% reduction in systolic blood pressure and symptomatic pain relief. In most patients, use of this agent will be tapered within 24 to 36 hours. Nitrates should not be administered to patients with recent sildenafil use. In addition, approximately 40% of patients with an inferior STEMI will have involvement of the right ventricle, and nitrates should be used with caution in these patients in order to avoid profound hypotension, which usually responds promptly to intravenous volume replacement.

The management of STEMI patients with adjunctive therapies is presented in Table 40–2 from the ACC/AHA guidelines.[29]

ANTICOAGULATION

Heparins

Anticoagulation with heparin is standard in the management of STEMI. Currently two forms of heparin are used: unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). The use and pharmacology of these agents is explained in detail in Chap. 41.

When bound to antithrombin III, UFH inactivates factor Xa and thrombin. Its use has been widely studied, and UFH is considered a Class I indication for patients with STEMI undergoing primary PCI or receiving fibrin-specific thrombolytic agents.[29] An initial bolus of 60 U/kg (4000 U maximum) followed by a 12 U/kg/h (1000 U/h maximum) infusion should be administered promptly. A goal-activated partial thromboplastin time of 1.5 to 2.0 times normal should be achieved. The anticoagulation effects of UFH, however, can be variable as a consequence of unpredictable protein binding.

The LMWHs are glycosaminoglycans consisting of chains of alternating residues of D-glucosamine and uronic acid. When compared with UFH, they have a more predictable anticoagulation effect as a result of a longer half-life, better bioavailability, and dose-independent clearance. Unlike UFH, the LMWHs have a greater activity against factor Xa than thrombin, and their anticoagulation effect cannot be measured with standard laboratory tests.[51]

The use of the LMWH enoxaparin in conjunction with fibrinolysis has been studied in the ASSENT 3 (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen) and TIMI-25 EXTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment) trials.[52,53] In the ASSENT 3 trial, patients treated with enoxaparin plus tenecteplase had a lower combined end point of 30-day mortality, in-hospital reinfarction, and in-hospital refractory ischemia than did those treated with UFH plus tenecteplase (11.4% vs 15.4%; $P = .0002$). The TIMI-25 EXTRACT trial randomized 20,506 patients receiving fibrinolytic therapy for STEMI to anticoagulation with enoxaparin through the entire index hospitalization or UFH for the initial 48 hours. The combined primary end point of death or recurrent myocardial infarction at 30 days occurred in 9.9% of patients in the enoxaparin group and in 12% of those in the heparin group ($P < .001$).

Because of the delay in the onset of action of subcutaneous administration, an initial intravenous loading dose of 30 mg of enoxaparin followed by the traditional 1 mg/kg subcutaneous dose every 12 hours was used in both trials for patients younger than 75 years of age. Use of enoxaparin, however, was associated with a higher risk of minor and major bleeding when compared with UFH in the TIMI-25 EXTRACT trial.[41] Switching from LMWH to UFH was also associated with an increase in bleeding in the SYNERGY trial.[54] In general, when this transition is needed, starting the UFH at the time of the next dose of LMWH may be sensible.

Direct Thrombin Inhibitors

Direct thrombin inhibitors bind directly to thrombin and have been used as an alternative to heparin in patients with heparin-induced thrombocytopenia. Several studies have compared direct thrombin inhibitors with heparin for the management of STEMI patients.[55,56] The Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial randomized 17,073 STEMI patients to the direct thrombin inhibitor bivalirudin or heparin. Thirty-day mortality was similar in both groups; the incidence of reinfarction was decreased at the cost of an increased risk of mild and moderate bleeding.[55] A meta-analysis of 11 randomized trials demonstrated that compared with heparin, direct thrombin inhibitors were associated with a lower risk of death or myocardial infarction both at the end of treatment (4.3% vs 5.1%; $P = .001$) and at 30 days (7.4% vs 8.2%; $P = .02$).[57] This difference was primarily a result of a reduction in the incidence of reinfarction (2.8% vs 3.5%; $P < .001$) with no difference in mortality (1.9% vs 2.0%; $P = .69$). There was no excess in intracranial hemorrhage with direct thrombin inhibitors compared with heparins.[57]

The use of direct thrombin inhibitors in STEMI patients undergoing primary PCI was studied in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial.[58] The trial randomized 3602 STEMI patients to bivalirudin alone or heparin plus a glycoprotein IIb/IIIa inhibitor before undergoing primary PCI. The combined primary end point of major bleeding as well as adverse clinical events (death, reinfarction, target vessel revascularization, or stroke) was lower in those treated with bivalirudin compared with those receiving heparin plus glycoprotein IIb/IIIa inhibitor (9.2% vs 12.1%; $P = .005$). The primary end point, however, was primarily driven by a reduction in major bleeding (4.9% vs 8.3%; $P < .001$). In addition, further subgroup analysis revealed that bivalirudin reduced the 30-day rate of cardiovascular death (1.8% vs 2.9%; $P = .03$) and all-cause death (2.1% vs 3.1%; $P = .047$). Use of bivalirudin, however, resulted in an increase in acute stent thrombosis within the first 24 hours compared with heparin plus glycoprotein IIb/IIIa (1.3% vs 0.3%; $P < .001$). The HEAT PPCI (Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention) trial evaluating bivalirudin versus UFH in a single-center all-comers STEMI trial did not show a mortality benefit for bivalirudin, but did show the consistent finding of stent thrombosis.[59] In fact, a meta-analysis of several randomized trials of bivalirudin versus UFH in patients with STEMI found that a bivalirudin-based regimen increases the risk of myocardial infarction and stent thrombosis but decreases the risk of bleeding, with the magnitude of the reduction depending on concomitant glycoprotein IIb/IIIa inhibitor use.[60]

The BRIGHT (Bivalirudin in Acute Myocardial Infarction Versus Glycoprotein IIb/IIIa and Heparin Undergoing Angioplasty) randomized

TABLE 40–2. Selected Routine Medical Therapies

Therapy	Indications	Dose/Administration	Avoid/Caution
Beta-Receptor Antagonists	• Oral: All patients without contraindication • IV: Patients with refractory hypertension or ongoing ischemia without contraindication	Individualize: • Metoprolol tartrate 25 to 50 mg every 6 to 12 h orally, then transition over next 2 to 3 d to twice-daily dosing of metoprolol tartrate or to daily metoprolol succinate; titrate to daily dose of 200 mg as tolerated • Carvedilol 6.25 mg twice daily, titrate to 25 mg twice daily as tolerated • Metoprolol tartrate IV 5 mg every 5 min as tolerated up to 3 doses; titrate to heart rate and BP	• Signs of HF • Low output state • Increased risk of cardiogenic shock • Prolonged first-degree or high-grade AV block • Reactive airways disease
ACE Inhibitors	• For patients with anterior infarction, post-MI LV systolic dysfunction (EF ≤ 0.40) or HF • May be given routinely to all patients without contraindication	Individualize: • Lisinopril 2.5 to 5 mg/d to start; titrate to 10 mg/d or higher as tolerated • Captopril 6.25 to 12.5 mg 3 times/d to start; titrate to 25 to 50 mg 3 times/d as tolerated • Ramipril 2.5 mg twice daily to start; titrate to 5 mg twice daily as tolerated • Trandolapril test dose 0.5 mg; titrate up to 4 mg daily as tolerated	• Hypotension • Renal failure • Hyperkalemia
ARB	• For patients intolerant of ACE inhibitors	• Valsartan 20 mg twice daily to start; titrate to 160 mg twice daily as tolerated	• Hypotension • Renal failure • Hyperkalemia
Statins	• All patients without contraindications	• High-dose atorvastatin 80 mg daily	• Caution with drugs metabolized via *CYP3A4*, fibrates • Monitor for myopathy, hepatic toxicity • Combine with diet and lifestyle therapies • Adjust dose as dictated by targets for LDL cholesterol and non-HDL cholesterol reduction
Nitroglycerin	• Ongoing chest pain • Hypertension and HF	• 0.4 mg sublingual every 5 min up to 3 doses as BP allows • IV dosing to begin at 10 mcg/min; titrate to desired BP effect	• Avoid in suspected RV infarction • Avoid with SBP < 90 mm Hg or if SBP > 30 mm Hg below baseline • Avoid if recent (24 to 48 h) use of 5′-phosphodiesterase inhibitors
Oxygen	• Clinically significant hypoxemia (oxygen saturation < 90%) • HF • Dyspnea	• 2 to 4 L/min via nasal cannula • Increase rate or change to face mask as needed	• Caution with chronic obstructive pulmonary disease and CO_2 retention
Morphine	• Pain • Anxiety • Pulmonary edema	• 4 to 8 mg IV initially, with lower doses in elderly • 2 to 8 mg IV every 5 to 15 min if needed	• Letharaic or moribund natiunt • Hypotension • Bradycardia • Known hypersensitivity

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CO_2, carbon dioxide; EF, ejection fraction; HDL, high-density lipoprotein; HF, heart failure; IV, intravenous; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; RV, right ventricular; and SBP, systolic blood pressure.

Reproduced from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-e425.

trial comparing generic bivalirudin versus heparin with or without tirofiban found a clinical benefit with bivalrudin.[61] The EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) study showed no benefit in prolonged bivalirudin infusion but did confirm the reduction in bleeding events in STEMI patients.[62]

Hence, the physicians caring for patients with STEMI will have to weigh the risks of bleeding versus thrombosis in their patients to make the decision regarding UFH and bivalirudin.

Factor Xa Inhibitors

The factor Xa inhibitor fondaparinux was investigated in the OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial. In this study, 12,092 STEMI patients were randomized to fondaparinux for 8 days or placebo with standard heparin therapy.[63] The primary end point of death or reinfarction at 30 days occurred in 9.7% of patients in the fondaparinux group and 11.2% of those in the placebo group ($P = .008$). Patients treated with fibrinolytic therapy had the most benefit, and there was no significant increase in the rate of bleeding.

In a subset of the OASIS-5 trial, fondaparinux was compared with enoxaparin in 20,078 patients with ACS, 6238 of whom underwent PCI.[64] Although similar rates of death, myocardial infarction, and stroke were seen between groups (6.2% vs 6.3% for fondaparinux and enoxaparin, respectively; $P = .79$), the use of fondaparinux reduced major bleeding by one-half compared with enoxaparin (2.4% vs 5.1%; $P < .00001$). The rates of catheter-related thrombosis, however, were higher in those receiving fondaparinux alone compared with those receiving enoxaparin alone (0.9% vs 0.4%, respectively; hazard ratio, 2.3), which was completely obviated in both groups by the addition of UFH at the time of PCI without any increased risk of bleeding. Therefore, the use of upstream fondaparinux in patients with ACS undergoing PCI appears reasonable, although adjunctive UFH is recommended at the time of cardiac catheterization to prevent catheter-related thrombosis.

The clinical practice guidelines recommend the following[29,35,65]:

Class I

1. *Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for a minimum of 48 hours (Level of Evidence: C) and preferably for the duration of the index hospitalization, up to 8 days (regimens other than UFH are recommended if anticoagulant therapy is given for more than 48 hours because of the risk of heparin-induced thrombocytopenia with prolonged UFH treatment). (Level of Evidence: A)*

   Anticoagulant regimens with established efficacy include:

   a. *UFH (initial intravenous bolus 60 U/kg [maximum 4000 U]) followed by an intravenous infusion of 12 U/kg/h (maximum 1000 U/h) initially, adjusted to maintain the activated partial thromboplastin time at 1.5 to 2.0 times control (approximately 50-70 seconds) (Level of Evidence: C). (Note: The available data do not suggest a benefit of prolonging the duration of the infusion of UFH beyond 48 hours in the absence of ongoing indications for anticoagulation; more prolonged infusions of UFH increase the risk of development of heparin-induced thrombocytopenia.)*
   b. *Enoxaparin (provided the serum creatinine is < 2.5 mg/dL in men and 2.0 mg/dL in women): for patients less than 75 years of age, an initial 30-mg intravenous bolus is given, followed 15 minutes later by subcutaneous injections of 1.0 mg/kg every 12 hours; for patients at least 75 years of age, the initial intravenous bolus is eliminated and the subcutaneous dose is reduced to 0.75 mg/kg every 12 hours. Regardless of age, if the creatinine clearance (using Cockcroft-Gault formula) during the course of treatment is estimated to be less than 30 mL/min, the subcutaneous regimen is 1.0 mg/kg every 24 hours. Maintenance dosing with enoxaparin should be continued for the duration of the index hospitalization, up to 8 days. (Level of Evidence: A)*
   c. *Fondaparinux (provided the serum creatinine is less than 3.0 mg/dL): initial dose 2.5 mg intravenously; subsequently subcutaneous injections of 2.5 mg once daily. Maintenance dosing with fondaparinux should be continued for the duration of the index hospitalization. (Level of Evidence: B)*

2. *For patients proceeding to primary PCI who have been treated with aspirin and a P2Y12 inhibitor, recommended supportive anticoagulant regimens include the following:*

   Class I

   1. *For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended:*
      a. *UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP [glycoprotein] IIb/IIIa receptor antagonist has been administered (Level of Evidence: C); or*
      b. *Bivalirudin with or without prior treatment with UFH. (Level of Evidence: B)*

   Class IIa

   1. *In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist. (Level of Evidence: B)*

   Class III: Harm

   1. *Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis. (Level of Evidence: B)*

REPERFUSION STRATEGIES

The main goal of STEMI management is rapid reperfusion to establish coronary blood flow to ischemic myocardium. Currently, there are three main reperfusion strategies: fibrinolytic therapy, primary PCI, and fibrinolytic-facilitated primary PCI.

FIBRINOLYTIC THERAPY

Fibrinolytic therapy for STEMI has been shown to be effective in numerous randomized trials involving more than 100,000 patients.[66] It is widely available, easily administered, and relatively inexpensive. However, only approximately 50% of STEMI patients are eligible for fibrinolytic therapy (Table 40–3), and only 50% to 60% of patients treated with fibrinolytics will achieve complete reperfusion (TIMI grade 3 flow). In addition, 10% to 20% of patients will experience reocclusion, and 1% will suffer from a stroke caused by intracranial hemorrhage. Fibrinolytic therapy is most effective when given within 3 hours from onset of chest pain.[67]

Although streptokinase is still widely used around the world, fibrin-specific agents are almost exclusively used in the United States. These therapies are summarized in Table 40–4 and are molecular modifications of the tissue plasminogen activator (tPA) molecule. The impetus

TABLE 40–3. Absolute and Relative Contraindications for Thrombolytic Therapy in Patients With ST-Segment Elevation Myocardial Infarction

Absolute contraindications
Any prior intracranial hemorrhage
Known structural cerebrovascular lesion
Known intracranial neoplasm
Ischemic stroke within the past 3 mo (except for acute stroke within 3 h)
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 mo
Relative contraindications
History of chronic, severe, poorly controlled hypertension
Systolic pressure > 180 mm Hg or diastolic > 110 mm Hg
History of prior ischemic stroke > 3 mo previously, dementia, or known intracranial pathology not covered in absolute contraindications
Recent (within 2-4 wk) internal bleeding
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Current use of anticoagulants: the higher the international normalized ratio, the higher the risk of bleeding
For streptokinase/anistreplase: prior exposure (> 5 d previously) or prior allergic reaction to these agents

for their development was the hope that increasing fibrin specificity (tenecteplase) or prolonging the plasma half-life (reteplase, tenecteplase, lanoteplase) would increase TIMI grade 3 flow rates in the infarct-related artery beyond the approximately 50% found at 90-minute angiography for tPA. Phase I and II trials of these agents have shown TIMI grade 3 flow rates in excess of 60%; however, there was no significant reduction in mortality or in the incidence of stroke.[68,69]

The clinical practice guidelines focus on getting primary PCI as the mode of reperfusion within 120 minutes, and recommend the following regarding fibrinolysis when the delay to reperfusion is anticipated to be greater than 120 minutes[29]:

Class I

1. *In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of FMC. (Level of Evidence: A)*

Class IIa

1. *In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability. (Level of Evidence: C)*

Class III

1. *Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI [myocardial infarction] is suspected or when associated with ST elevation in lead aVR. (Level of Evidence: B)*

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

See Chap. 42 for a more detailed discussion. Approximately 95% of patients who are treated with primary PCI obtain complete reperfusion versus 50% to 60% of patients who are treated with fibrinolytics. Primary PCI is also associated with a lower risk of stroke than treatment with fibrinolysis, and diagnostic angiography quickly defines coronary anatomy, LV function, and mechanical complications.

A meta-analysis by Keeley et al[70] of 23 trials that included 3872 patients treated with primary PCI and 3867 patients treated with fibrinolytics showed that PCI was superior to fibrinolytic therapy. Primary PCI was associated with a lower mortality rate (7% vs 9%; $P = .0002$), less reinfarction (3% vs 7%; $P = .0001$), and fewer strokes (1% vs 2%; $P = .0004$) at 30 days when compared with fibrinolysis. PCI capability, however, is available at fewer than 50% of hospitals in the United States, and each 30-minute delay from symptom onset to balloon inflation during primary PCI is associated with a 7.5% relative increase in mortality at 1 year.[71] In addition, a meta-analysis by Nallamothu

TABLE 40–4. Fibrin-Specific Thrombolytic Agents

Characteristic	Alteplase (tPA)	Reteplase (rPA)	Tenecteplase (tPA)	Lanoteplase (nPA)
Immunogenicity	No	No	No	?
Plasminogen activation	Direct	Direct	Direct	Direct
Fibrin specificity	++	+	+++	+
Plasma half-life	4-6 min	18 min	20 min	37 min
Dose	15-mg bolus plus 90-min infusion up to 85 mg	10 + 10 unit boluses 30 minutes apart	± 0.5 mg/kg single bolus	120 KU/kg single bolus
PAI-1 resistance	No	?	Yes	?
Genetic alteration to native tPA	No	Yes	Yes	Yes
	Recombinant version	Finger, EGF, and kringle-1 regions deleted	2 single amino acid substitutions in kringle-1 and substitution of 4 amino acids in catalytic domain	Finger, EGF regions deleted and glycosylation sites in kringle-1 domain modified

Abbreviations: EGF, epidermal growth factor; PAI, plasminogen activator inhibitor; nPA, lanoteplase; rPA, reteplase; tPA, tissue plasminogen activator.

and Bates[72] of data from 23 trials that included 7739 patients, which compared fibrinolytic therapy with primary PCI, demonstrated that the mortality advantage of primary PCI is lost if the door-to-balloon time is 60 minutes greater than the door-to-needle time for fibrinolytic therapy.

Three large-scale, randomized trials have compared fibrinolysis with transfer for primary PCI in STEMI patients (Table 40–5). The combined end point of death, reinfarction, and disabling stroke at 30 days was significantly lower in the patients treated with primary PCI. Although transfer for primary PCI appears to be the treatment of choice, two important points need to be made. First, the transport time in these trials was extremely short (median time in the DANAMI-2 [Danish Trial in Acute Myocardial Infarction-2] trial was 32 minutes), and these times may not be achievable outside of a clinical trial and in areas in which longer distances and weather may play a substantial role in hindering rapid transport. Second, fibrinolytic therapy still has a critically important role during the "golden hour" (Fig. 40–3) of myocardial infarction or when there is a delay in transfer.[67] The mortality rates and infarct size in patients treated with thrombolytic therapy within the first 60 to 90 minutes of symptoms are extremely low, suggesting that fibrinolytic therapy still plays a vital role in the management of patients presenting to hospitals without primary PCI capability. Also, the benefit of primary PCI appears to be mainly in high-risk patients, which were a minority of the patients in the trial (Fig. 40–4).[73]

TABLE 40–5. Trials Comparing In-Hospital Thrombolysis With Transfer for Percutaneous Coronary Intervention (PCI) in Patients Presenting < 12 Hours From the Onset of Chest Pain

Death, Reinfarction, Disabling Stroke at 30 Days

	No. of Patients	Thrombolysis (%)	Transfer for PCI (%)	*P*
PRAGUE-2[265]	850	15.2	8.4	< .003
AIR PAMI[266]	138	13.6	8.4	.33
DANAMI-2[267]	1572	13.7	8.0	< .001

Abbreviations: AIR PAMI, Air Primary Angioplasty in Myocardial Infarction; DANAMI-2, Danish Trial in Acute Myocardial Infarction-2; PRAGUE-2, Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized Percutaneous Transluminal Coronary Angioplasty Units With or Without Emergency Thrombolysis;

The clinical practice guidelines recommend the following[29,65]:

Class I

1. *Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration. (Level of Evidence: A)*
2. *Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from FMC. (Level of Evidence: B)*
3. *Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF [heart failure], irrespective of time delay from MI onset (Level of Evidence: B)*

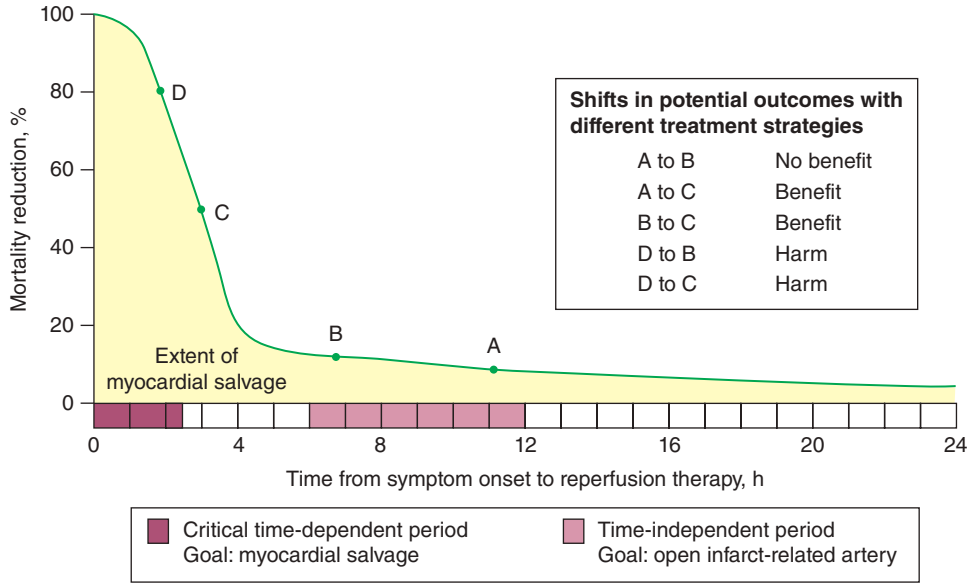

FIGURE 40–3. Hypothetical construct of the relationship among the duration of symptoms of acute myocardial infarction (MI) before reperfusion therapy, mortality reduction, and extent of myocardial salvage. Mortality reduction as a benefit of reperfusion therapy is greatest in the first 2 to 3 hours after the onset of symptoms of acute MI, most likely a consequence of myocardial salvage. The exact duration of this critical early period may be modified by several factors, including the presence of functioning collateral coronary arteries, ischemic preconditioning, myocardial oxygen demands, and duration of sustained ischemia. After this early period, the magnitude of the mortality benefit is much reduced, and as the mortality reduction curve flattens, time to reperfusion therapy is less critical. If a treatment strategy, such as facilitated percutaneous coronary intervention (PCI), is able to move patients back up the curve, a benefit would be expected. The magnitude of the benefit will depend on how far up the curve the patient can be shifted. The benefit of a shift from points A or B to point C would be substantial, but the benefit of a shift from point A to point B would be small. A treatment strategy that delays therapy during the early critical period, such as patient transfer for PCI, would be harmful (shift from point D to point C or point B). Between 6 and 12 hours after the onset of symptoms, opening the infarct-related artery is the primary goal of reperfusion therapy, and primary PCI is preferred over fibrinolytic therapy. The possible contribution to mortality reduction of opening the infarct-related artery, independent of myocardial salvage, is not shown. From *JAMA*. 2005;293(8):979-986,[67] which was modified from Gersh BJ, Anderson JL. Thrombolysis and myocardial salvage: results of clinical trials and the animal paradigm—paradoxic or predictable? *Circulation*. 1993;88:296-306.

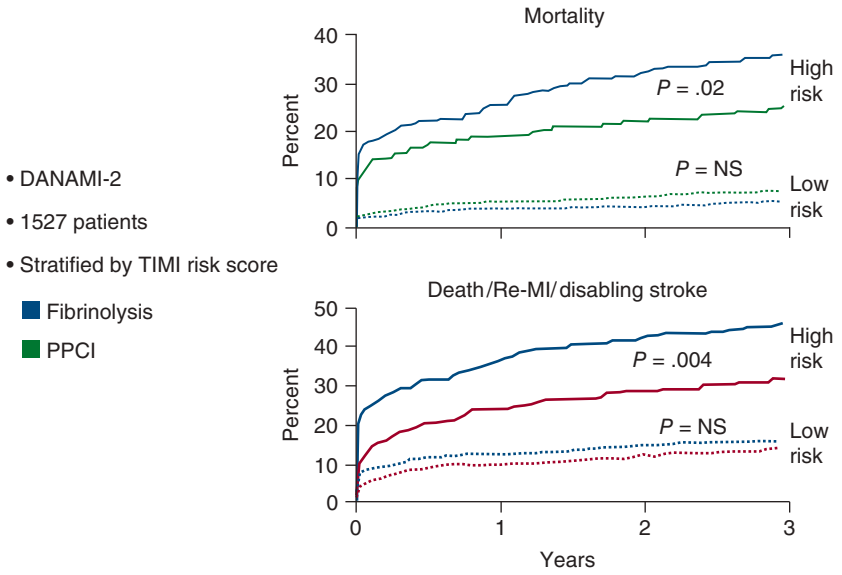

FIGURE 40–4. Risk stratification and the results of primary percutaneous coronary intervention (PPCI) in patients from the DANAMI-2 trial. MI, myocardial infarction; NS, not significant; TIMI, Thrombolysis in Myocardial Infarction. Reproduced with permission from Thune JJ, Hoefsten DE, Lindholm MG, et al: Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. *Circulation*. 2005 Sep 27;112(13):2017-20.

Class IIa

1. *Primary PCI is reasonable in patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia between 12 and 24 hours after symptom onset. (Level of Evidence: B)*

Despite prior observational studies demonstrating no benefit and potentially harm in patients getting non–infarct-related artery PCI, several small to moderate-sized randomized trials have demonstrated possible benefit with multivessel PCI either at the time of STEMI or in a staged fashion.[74-76] This is discussed in detail later in the chapter. This has led to a revision in the clinical practice guidelines:

Class IIb

PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure. (Level of Evidence: B)

FIBRINOLYTIC-FACILITATED PERCUTANEOUS CORONARY INTERVENTION

Facilitated PCI refers to the pretreatment with fibrinolytics in STEMI patients as a bridge to intended routine *immediate* PCI. This pretreatment was proposed as a method to initiate earlier reperfusion and reduce ischemic time and infarct size in patients who experience a delay before the onset of PCI. Fibrinolytic-facilitated therapy, however, can expose patients to a higher risk of bleeding, including intracranial bleeding. Two large trials of facilitated PCI, ASSENT-4 and FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events), have investigated the use of fibrinolytic-facilitated PCI in STEMI. The ASSENT-4 trial randomized 1666 STEMI patients undergoing immediate PCI to pretreatment with a fibrinolytic (tenecteplase) or placebo. The data safety monitoring board halted the trial before the enrollment of the 4000 anticipated patients because of an increased 30-day mortality rate in the facilitated PCI group (6.0% vs 3.8%; $P = .004$).[77] Patients in the fibrinolytic plus PCI group also had a greater incidence of stroke (1.81% vs 0%; $P < .001$), bleeding (31.3% vs 23.4%; $P < .001$), and reinfarction (4.1% vs 1.9%; $P = .01$).

In the FINESSE trial, 2452 STEMI patients undergoing immediate PCI were randomized to receive one of the following three strategies: half-dose fibrinolytic (reteplase) plus the glycoprotein IIb/IIIa inhibitor abciximab (combination-facilitated PCI), early administration of abciximab (abciximab-facilitated PCI), or late administration of abciximab (primary PCI).[78] A primary composite end point that included death from all causes and complication of myocardial infarction through day 90 showed no significant differences among all three groups (9.8%, 10.5%, and 10.7%, respectively; $P = .55$). Safety end points indicated a significant difference between the combination-facilitated PCI and primary PCI groups, showing increased nonintracranial TIMI major or minor bleeding (14.5% vs 6.9%; $P < .001$). Treatment with early abciximab was associated with a trend toward increased bleeding.

Therefore, based on the results of ASSENT-4 and FINESSE, the data do not support the use of facilitated PCI as a routine reperfusion strategy in STEMI.

PHARMACOINVASIVE STRATEGIES

Unlike facilitated PCI, in which PCI is performed *immediately* after fibrinolysis, pharmacoinvasive strategies refer to PCI that is routinely performed between 3 and 24 hours after fibrinolysis in hemodynamically stable patients as opposed to "rescue PCI." The TRANSFER-AMI (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) is the largest and most recent among five studies that have evaluated routine early PCI after fibrinolysis.[79] In this study, 1059 STEMI patients who received fibrinolytic therapy were randomized to either standard treatment (transfer for angiography no less than 24 hours after lysis) or PCI of the infarct-related artery within 6 hours of fibrinolysis ("early PCI"). The primary end point was a composite of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock. At 30 days, the primary end point occurred in 11% of the early PCI group versus 17.2% of the standard group ($P = .004$). The favorable results for the early PCI group were primarily driven by a decreased rate of reinfarction. Notably, groups did not differ in the incidence of major bleeding.

The results of the four smaller studies investigating early PCI after fibrinolysis (CAPITAL AMI [Combined Angioplasty and

Pharmacological Intervention Versus Thrombolytics Alone in Acute Myocardial Infarction],[80] CARESS-in-AMI [Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction],[81] SIAM III [Southwest German Interventional Study in Acute Myocardial Infarction],[82] and GRACIA [Grupo de Análisis de la Cardiopatía Isquémica Aguda] 1[83]) are consistent with the findings of TRANSFER-AMI. However, the optimal window to perform PCI after receiving fibrinolytic therapy is still uncertain. The interval between fibrinolysis and PCI in the aforementioned studies ranged from 2 to 17 hours, with each interval suggesting similar efficacy.[84] After fibrinolysis, the risk of reocclusion increases within 24 hours. The STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial demonstrated a trend toward improved outcomes at 30 days with a pharmacoinvasive approach with revascularization at 3 hours compared to primary PCI.[85,86] Additionally, studies have demonstrated reductions in heart failure, shock, and infarct size with early pharmacoinvasive strategies.[87] Therefore, until further data are available, striving for early PCI between 2 and 24 hours appears to be most reasonable.

In a meta-analysis[88] including seven randomized controlled trials of early transfer after fibrinolysis for catheterization, a strategy of routine early catheterization fibrinolysis was associated with a statistically significant reduction in the incidence of death or myocardial infarction at 30 days and 1 year.

For STEMI patients, when available, primary PCI is the preferred reperfusion strategy. However, when this therapy is not available, fibrinolysis followed by PCI within 2 to 24 hours appears to be a reasonable alternative.

The clinical practice guidelines recommend the following[35,65]:

Class I

1. *Immediate transfer to a PCI-capable hospital for coronary angiography is recommended for suitable patients with STEMI who develop cardiogenic shock or acute severe HF, irrespective of the time delay from MI onset. (Level of Evidence: B)*

Class IIa

1. *Urgent transfer to a PCI-capable hospital for coronary angiography is reasonable for patients with STEMI who demonstrate evidence of failed reperfusion or reocclusion after fibrinolytic therapy. (Level of Evidence: B)*
2. *Transfer to a PCI-capable hospital for coronary angiography is reasonable for patients with STEMI who have received fibrinolytic therapy even when hemodynamically stable and with clinical evidence of successful reperfusion. Angiography can be performed as soon as logistically feasible at the receiving hospital, and ideally within 24 hours, but should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. (Level of Evidence: B)*

DELAYED INVASIVE MANAGEMENT: RESCUE PERCUTANEOUS CORONARY INTERVENTION

Approximately 40% to 50% of patients who receive fibrinolytic therapy fail to achieve optimal reperfusion, and 20% suffer reinfarction within the first 12 hours. The optimal management of these patients was investigated in the REACT (Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis) trial, which randomized 427 patients who failed to achieve reperfusion with fibrinolysis to repeat fibrinolysis, conservative therapy, or rescue PCI.[89]

The combined primary end point of death, reinfarction, stroke, or severe heart failure within 6 months was lower in the rescue PCI group (15.3%) compared with those in the repeat fibrinolysis and conservative management groups (31% and 29.8%, respectively; $P < .001$). The primary end point was mainly driven by a decrease in recurrent myocardial infarction in the rescue PCI group compared with the repeat fibrinolysis and conservative management groups (2.1% vs 10.6% and 8.5%, respectively; $P < .01$). There was no difference in major bleeding among groups, although a significant increase in minor bleeding with rescue PCI was observed ($P < .001$), due mainly to sheath-related bleeding.

Recently, longer-term outcomes of the REACT trial were reported, with the results indicating that rescue PCI remains superior to more conservative, noninvasive strategies.[90] One-year clinical follow-up was available in 91% of the 427 randomized patients. At 1 year, event-free survival for patients was 81.5% for rescue PCI compared with 64.1% and 67.5% for repeat fibrinolysis and conservative therapy, respectively ($P = .004$). More importantly, a significant reduction in long-term mortality was seen in the rescue PCI group. At 4.4 years from randomization, there were 77 total deaths; 11.2% were from the rescue PCI group compared with 22.3% and 22.4% from the repeat fibrinolysis and conservative therapy groups, respectively ($P = .026$).

These and other data support the recommendation that rescue PCI should be considered for patients in whom fibrinolytic therapy fails to achieve reperfusion in STEMI.

The clinical practice guidelines state the following[29]:

Class I

1. *Cardiac catheterization and coronary angiography with intent to perform revascularization should be performed after STEMI in patients with any of the following:*
   a. *Cardiogenic shock or acute severe HF that develops after initial presentation (Level of Evidence: B);*
   b. *Intermediate- or high-risk findings on predischarge noninvasive ischemia testing (Level of Evidence: B); or*
   c. *Myocardial ischemia that is spontaneous or provoked by minimal exertion during hospitalization. (Level of Evidence: C)*

Class IIa

1. *Coronary angiography with intent to perform revascularization is reasonable for patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy. Angiography can be performed as soon as logistically feasible. (Level of Evidence: B)*
2. *Coronary angiography is reasonable before hospital discharge in stable patients with STEMI after successful fibrinolytic therapy. Angiography can be performed as soon as logistically feasible, and ideally within 24 hours, but should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. (Level of Evidence: B)*

SELECTION OF THE OPTIMAL REPERFUSION STRATEGY

Figure 40–2 outlines a systematic, evidence-based framework for selecting reperfusion strategies in STEMI patients.[91] STEMI patients presenting to PCI-capable hospitals should undergo primary PCI with a target door-to-balloon time of less than 90 minutes. If the hospital does not have PCI capability, the clinician must first determine whether the patient is eligible for fibrinolytic therapy (see Table 40–3). Patients ineligible for fibrinolytic therapy should be transferred for primary PCI. For those who are eligible for fibrinolytic therapy, the clinician must then consider two important factors: duration from onset of symptoms (*fixed* ischemia time) and transport time to the nearest PCI facility (*incurred* ischemia time). These two factors can be incorporated into a 2 × 3 table to select a reperfusion strategy (Fig. 40–5).

Transport time ("incurred ischemic time")	Duration from onset of symptoms ("fixed ischemic time")	
	0-3 h	> 3 h
0-30 min	PCI + GP IIb/IIIa	PCI + GP IIb/IIIa
30-60 min	Thrombolytic + Clopidogrel	PCI + GP IIb/IIIa
> 60 min	Thrombolytic + Clopidogrel	Thrombolytic + Clopidogrel or PCI + GP IIb/IIIa

FIGURE 40–5. Table organizing the treatment strategies for thrombolytic-eligible ST-segment elevation myocardial infarction patients who present to hospitals without facilities for percutaneous coronary intervention (PCI). GP IIb/IIIa, glycoprotein IIb/IIIa inhibitor; lytics, thrombolysis (patients should be immediately transferred to a PCI facility after thrombolysis); PCI, transfer for percutaneous coronary intervention.

Patients facing a transport time of less than 30 minutes should be transferred for primary PCI. Fibrinolytic-eligible patients who present less than 2 to 3 hours from onset of symptoms and have a transport time precluding primary PCI within 120 minutes of first medical contact should receive fibrinolytic therapy. Patients presenting more than 2 to 3 hours after the onset of chest pain and who have a transport time of 60 minutes or less should be promptly transported for primary PCI. If the anticipated transport time is more than 60 minutes and anticipated first medical contact to reperfusion is 120 minutes, then patients can be treated with either fibrinolytic therapy or primary PCI.

Duration of symptoms and time to treatment play a crucial role in the decision to administer fibrinolytics or to proceed with transfer for primary PCI. Specifically, data from the rapid reperfusion project in North Carolina have indicated that when patients were taken directly to PCI hospitals bypassing non-PCI hospitals they had shorter times to reperfusion.[92] For those eligible to receive fibrinolytics, prehospital administration (as opposed to in-hospital administration) of fibrinolytic therapy is a means to decrease time to reperfusion. The CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction) trial is the only study to compare prehospital fibrinolysis and primary PCI as a function of time from onset of symptoms. The trial randomized 840 STEMI patients to prehospital fibrinolysis or primary PCI. Outcomes were assessed according to time between symptom onset (< 2 hours or > 2 hours) and randomization to each group. Results indicated that regardless of time of symptom onset, there was no significant difference between prehospital fibrinolysis and primary PCI in the primary end point of combined death, reinfarction, or disabling stroke (7.4% vs 6.5% [P = .855] in those with < 2 hours from symptom onset and 9.1% vs 5.9% [P = .326] in those with > 2 hours from symptom onset). There was, however, a trend toward increased mortality in those randomized within 2 hours who received primary PCI versus fibrinolytic therapy (5.7% vs 2.2%; P = .058). This trend was almost completely reversed in those randomized after 2 hours (7% for PCI vs 11% for fibrinolysis; P = .470). Although patients randomized early who underwent primary PCI also experienced significantly more cardiogenic shock (5.3% vs 1.3%; P = .032), this secondary end point was driven primarily by transport time.

The results of CAPTIM are consistent with those of PRAGUE-2 (Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized Percutaneous Transluminal Coronary Angioplasty Units With or Without Emergency Thrombolysis), which showed similar mortality rates for fibrinolysis and primary PCI when patients presented within 3 hours of symptom onset, but a higher mortality with fibrinolysis when patients were randomized after 3 hours. Long-term mortality data of CAPTIM were recently published, indicating outcomes consistent with those of the initial study.[93]

These data suggest that duration of symptoms should be a strong consideration in the selection of prehospital fibrinolytic versus primary PCI therapy for STEMI. Barring exclusion criteria, in patients experiencing a symptom duration of less than 2 to 3 hours, prehospital fibrinolysis may be a viable option if there is an anticipated transfer time of greater than 60 minutes.

All patients receiving fibrinolytic therapy should be transferred to a PCI facility for potential failure to achieve reperfusion (ongoing chest pain or < 50% resolution of ST-segment elevation at 90 minutes) and rescue PCI. As mentioned earlier, the meta-analysis of randomized data suggests that all STEMI patients who are treated with fibrinolytic therapy benefit from routine coronary angiography during the index hospitalization.[94]

ADJUVANT ANTIPLATELET THERAPY

CLOPIDOGREL

Clopidogrel is an oral thienopyridine prodrug whose active metabolite inhibits the activation of platelets by ADP. Its antiplatelet effects are more potent than aspirin and less potent than the glycoprotein IIb/IIIa inhibitors.

Use With Fibrinolytic Therapy

Clopidogrel in combination with fibrinolytic therapy has been studied in the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28) trial.[95] In this trial, 3491 STEMI patients 75 years of age or younger who were treated with thrombolytics were randomized to therapy with aspirin plus placebo or aspirin plus clopidogrel. Clopidogrel was given as a 300-mg loading dose within minutes of thrombolysis and 75 mg daily thereafter. The composite primary end point of death, reinfarction before angiography, or occluded infarct-related artery at angiography occurred in 15% of patients in the clopidogrel group and 22% of patients in the placebo group (P < .001). The use of clopidogrel was not associated with a higher rate of major or minor bleeding.

Although a loading dose of 300 mg of clopidogrel was not associated with a greater risk of bleeding, patients older than 75 years of age were excluded from the study. Patients older than 75 years of age were included in the COMMIT trial[43] (a randomized, placebo-controlled trial of adding clopidogrel to aspirin in 46,000 AMI patients), which randomized 45,849 STEMI patients treated with fibrinolysis to therapy with aspirin plus placebo or aspirin plus clopidogrel. Unlike in the CLARITY trial, a 300-mg loading dose was not given. Instead, patients randomized to the clopidogrel arm received 75 mg of clopidogrel at the time of fibrinolysis and then 75 mg daily for the duration of

hospitalization. Patients in the clopidogrel arm had a lower rate of the composite end point of death, reinfarction, or stroke (9.3% vs 10.1%; $P = .002$) and no increase in major or minor bleeding.

The data from these two trials suggest that patients treated with fibrinolysis should receive clopidogrel. For patients older than 75 years of age, 75 mg of clopidogrel without a loading dose should be used. In patients 75 years of age or younger, the current data suggest that a 300-mg loading dose followed by 75 mg daily of clopidogrel is beneficial and safe.

Use With Primary Percutaneous Coronary Intervention

Data from the PCI-CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial (effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing PCI)[96] demonstrated that the early use of clopidogrel in non–ST-segment elevation ACS patients who eventually undergo PCI is of benefit (see Chap. 42). The effectiveness of clopidogrel in the setting of primary PCI for STEMI is unproven, but extrapolation of the data indicating that upstream clopidogrel dosing improves PCI outcomes in non–ST-segment elevation myocardial infarction and scheduled PCI has led to the recent reasonable recommendation for oral clopidogrel loading at STEMI presentation and long-term maintenance therapy, barring contraindications in those younger than age 75.[65]

PRASUGREL

The advent of prasugrel, a novel thienopyridine with potent $P2Y_{12}$ platelet receptor-blocking capability, generated several recent studies comparing the efficacy of this agent to clopidogrel in patients undergoing PCI in both acute and scheduled settings.

To date, the largest trial to study prasugrel use in PCI is the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction 38).[97] The study randomized 13,608 patients with ACSs (including 3534 patients with STEMI) undergoing PCI to loading followed by maintenance doses of prasugrel or clopidogrel for 6 to 15 months. The primary end point was cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Compared with clopidogrel, the prasugrel group had a significantly reduced primary end point (9.9% vs 12.1%; $P < .001$), as well as significantly reduced ischemic events (7.4% vs 9.7%; $P < .001$) and stent thromboses (1.1% vs 2.4%; $P < .001$). The benefits of prasugrel, however, were at the expense of increased non–coronary artery bypass graft–related major bleeding (2.4% vs 1.8%; $P = .03$), life-threatening bleeding (1.4% vs 0.9%; $P = .01$), and fatal bleeding (0.4% vs 0.1%; $P = .002$).

Due to the higher rates of bleeding with prasugrel, a post hoc analysis was performed to identify subgroups who were especially at risk for harm with prasugrel use. The analysis revealed a particular concern for those with a history of transient ischemic attack or stroke. Compared with clopidogrel, prasugrel use in these patients had a higher rate of intracranial hemorrhage (2.3% vs 0%; $P = .02$) and a strong trend toward a greater rate of TIMI major bleeding (5.0% vs 2.9%; $P = .06$). In addition, patients older than 75 years and those weighing less than 60 kg were also identified as being at risk for bleeding. Although not statistically significant, the absolute rate of TIMI major bleeding was increased in the latter two groups, and they received no net clinical benefit from prasugrel administration.[97]

A subset analysis of the 3534 STEMI patients in TRITON-TIMI 38 was also performed.[98] The analysis corroborated the results of the full cohort, revealing the effectiveness of prasugrel versus clopidogrel in reducing the primary end point (6.5% vs 9.5%; $P = .0017$). In addition, there were less cardiovascular events (8.8% vs 6.2%; $P < .0042$) and stent thromboses (2.4% vs 1.2%; $P < .008$). This effect was maintained at both 30 days and 15 months. Unlike the increased risk of bleeding seen in the full cohort, STEMI patients exhibited no differences in TIMI major bleeding (2.4% vs 2.1%; $P = .6451$) or life-threatening bleeding (1.3% vs 1.1%; $P = .7500$) when comparing prasugrel with clopidogrel. STEMI patients requiring urgent coronary artery bypass grafting, however, exhibited significantly increased TIMI major bleeding in the prasugrel arm compared with the clopidogrel arm (18.8% vs 2.7%; $P = .0033$).

Thus, the use of prasugrel in STEMI patients undergoing primary PCI appears reasonable and appropriate for select patient subgroups. The risk of increased bleeding, however, particularly in those with a history of cerebrovascular events, needs to be further investigated and may limit its use. The current US Food and Drug Administration label approves prasugrel use for the reduction of thrombotic cardiovascular events in patients with unstable angina or myocardial infarction who undergo PCI. However, a boxed warning regarding bleeding risk emphasizes that prasugrel is not recommended for patients with a history of transient ischemic attack or stroke, patients over age 75 years, or patients who are likely to undergo coronary artery bypass grafting within the ensuing 7 days.[99]

TICAGRELOR

Unlike clopidogrel and prasugrel, ticagrelor is a reversible, nonthienopyridine $P2Y_{12}$ receptor antagonist that does not require metabolic conversion to active drug. This allows a rapid onset of action that has been tested in ACS patients, including those with STEMI.

The PLATO (Platelet Inhibition and Patient Outcomes) study evaluated 18,264 patients with ACS comparing ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) with clopidogrel (300- or 600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events. It is notable that 35% of the patients in the study had STEMI.[100] Among the patients with STEMI who underwent primary PCI, findings were consistent with the overall trial results. Ticagrelor reduced stent thrombosis, and there were fewer numeric total deaths, although there were more strokes and episodes of intracerebral hemorrhage with ticagrelor.[101] It should be noted that a prespecified subgroup analysis in the PLATO trial showed a significant interaction between treatment effect and geographic region, with a smaller ticagrelor effect in North America than in other areas. Although this interaction could have been due to chance alone,[102] a contribution from higher aspirin doses, as more commonly used in the United States, could not be excluded. Therefore, the package insert from the US Food and Drug Administration, consistent with the practice guidelines, recommends aspirin at a dose less than 100 mg when using ticagrelor.

The clinical practice guidelines for thienopyridine use state the following[35,65]:

Class I

1. *A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include*
   a. *Clopidogrel 600 mg (Level of Evidence: B); or*
   b. *Prasugrel 60 mg (Level of Evidence: B); or*
   c. *Ticagrelor 180 mg (Level of Evidence: B)*
2. *$P2Y_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS [bare metal stent] or DES*

[drug-eluting stent]) during primary PCI using the following maintenance doses:

a. Clopidogrel 75 mg daily (Level of Evidence: B); or

b. Prasugrel 10 mg daily (Level of Evidence: B); or

c. Ticagrelor 90 mg

Class III: Harm

1. *Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack. (Level of Evidence: B)*

GLYCOPROTEIN IIB/IIIA INHIBITORS

Glycoprotein IIb/IIIa inhibitors are potent agents that inhibit the final common pathway for platelet aggregation. There are currently three intravenous agents available in the United States: abciximab, tirofiban, and eptifibatide.

Use With Fibrinolytic Therapy

Fibrinolysis has been shown to be a potent activator of platelets,[103] and the concomitant use of aspirin has been shown to be beneficial.[104] Two dose-finding studies[105,106] have shown that the glycoprotein IIb/IIIa inhibitor abciximab, when used in combination with half-dose thrombolytics, improves coronary artery blood flow in STEMI patients. Three subsequent randomized trials (Table 40–6) have investigated combination therapy with a glycoprotein IIb/IIIa inhibitor and half-dose fibrinolytic therapy.[52,107,108] The largest of the trials was the GUSTO-V trial, which included 16,588 patients with STEMI who presented within 6 hours from the onset of chest pain. The primary end point, 30-day mortality, occurred in 5.6% of patients treated with abciximab plus half-dose reteplase and in 5.9% of patients treated with full-dose reteplase ($P = .43$).[107] Patients treated with the combination therapy had a higher rate of major (1.1% vs 0.5%; $P < .0001$) and minor bleeding (20% vs 11.4%; $P < .0001$).[107] This increased risk of bleeding and lack of survival benefit with combination therapy was also seen in the ASSENT-3[52] and INTEGRITI (Integrilin and Tenecteplase in Acute Myocardial Infarction)[108] trials (see Table 40–6). Based on the results of these three trials, glycoprotein IIb/IIIa inhibitors should not be used in combination with fibrinolytic therapy.

Use With Primary Percutaneous Coronary Intervention

The early (before arrival in the catheterization laboratory) versus delayed (at the time of catheterization) use of glycoprotein IIb/IIIa inhibitors in STEMI patients was investigated in eight randomized trials (Table 40–7) involving abciximab,[109-111] tirofiban,[112-114] and eptifibatide.[115,116] A meta-analysis of six of these trials by Montalescot et al[117] showed that early administration of glycoprotein IIb/IIIa inhibitors in STEMI patients was associated with a greater prevalence of TIMI grade 2 or 3 flow (41.7% vs 29.8%; $P < .001$) in the infarct-related artery before PCI. Because prior studies have shown that better coronary artery flow after PCI is associated with less in-hospital and 1-year adverse outcomes,[118-120] early administration of glycoprotein IIb/IIIa inhibitors should probably be encouraged.

Although abciximab has historically been the glycoprotein IIb/IIIa inhibitor of choice during primary PCI due to the large number of studies utilizing this agent, there is growing evidence that eptifibatide and tirofiban may be acceptable alternatives in STEMI patients. A meta-analysis of six randomized trials comparing abciximab versus eptifibatide or tirofiban in STEMI patients undergoing primary PCI revealed no difference in outcomes among the three agents.[121] The analysis included 2197 patients randomized to either abciximab or one of the small-molecule agents (tirofiban or eptifibatide). TIMI grade 3 flow was similar between groups (89.8% vs 89.1%; $P = .72$), as was ST-segment resolution (67.8% vs 68.2%; $P = .66$). Thirty-day mortality (2.2% vs 2.0%; $P = .66$), reinfarction (1.2% each; $P = .88$), and major bleeding complications (1.3% vs 1.9%; $P = .27$) were also similar between the two classes of agents. These findings are encouraging, as the small-molecule glycoprotein IIb/IIIa inhibitors are less expensive and easier to use in the acute care setting than abciximab.

MANAGEMENT IN THE CARDIAC CATHETERIZATION LABORATORY

RAPID TRANSPORT PROTOCOL

For STEMI patients who present to hospitals without PCI capabilities, a well-developed plan for transfer to a PCI hospital is essential. This plan should be evidence based, easy to activate, and time efficient. It requires a multidisciplinary approach and coordination of personnel at the PCI facility, community hospital, and emergency transport service.

The Mayo Clinic developed a "Fast Track" protocol to facilitate the management and transport of STEMI patients from surrounding community hospitals. The protocol has 23 activated regional hospitals and

TABLE 40–6. Randomized Trials Comparing Combination Therapy With a Glycoprotein IIb/IIIa Inhibitor Plus Half-Dose Thrombolytic Therapy With Full-Dose Thrombolytics in Patients With ST-Segment Elevation Myocardial Infarction

				Mortality Rate (%)		Major Bleeding Rate (%)	
	No. of Patients	Glycoprotein IIB/IIIA Inhibitor	Thrombolytic Agent	Combination Therapy	Thrombolytic-Only Therapy	Combination Therapy	Thrombolytic-Only Therapy
GUSTO-V[107]	16,588	Abciximab	Reteplase	5.6	5.9	1.1	0.5
ASSENT-3[52]	6095	Abciximab	Tenecteplase	6.6	6.0	4.3	2.2
INTEGRITI[108]	438	Eptifibatide	Tenecteplase	3.0	5.0	7.6	2.5

Abbreviations: ASSENT, Assessment of the Safety and Efficacy of a New Thrombolytic; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; INTEGRITI, Integrilin and Tenecteplase in Acute Myocardial Infarction.

TABLE 40–7. Early Administration of Glycoprotein IIb/IIIa Inhibitors in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention

			Timi Flow Grade 2 or 3 (% of Patients)		
	No. of Patients	Agent	Early Administration	Late Administration	*P*
Zorman et al[109]	112	Abciximab	32	13	.04
REOMOBILE[110]	100	Abciximab	52	48	NS
ERAMI[111]	74	Abciximab	31	26	NS
On-TIME[114]	307	Tirofiban	43	34	.04
TIGER-PA[112]	100	Tirofiban	46	18	.007
Cultip et al[113]	58	Tirofiban	39	27	NS
Cultip et al[115]	60	Eptifibatide	57	13	< .01
INTAMI[116]	102	Eptifibatide	42	33	.01

Abbreviation: NS, not significant.

three helicopters covering a service area extending 100 nautical miles. This rapid transport protocol involves four key concepts:

1. The identification and elimination of inefficient practices involved in the management of STEMI patients from referring hospitals.
2. Developing an evidence-based protocol to standardize the care of STEMI patients.
3. Implicating a communication network to ensure easy activation of the rapid transport protocol system by community hospitals.
4. Reducing the time for activation of the cardiac catheterization laboratory team.

The implication of these processes has resulted in a significant reduction in the median door-to-balloon times from 202 to 107 minutes in all STEMI patients transferred to the Mayo Clinic.[122]

Primary PCI should be performed by operators who perform at least 75 PCIs per year, 36 of which are primary PCI for STEMI patients in a catheterization laboratory that performs at least 200 PCIs per year.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION WITHOUT ON-SITE SURGICAL BACKUP

Primary PCI at centers without surgical backup has been proposed as a possible method of increasing the availability of PCI to STEMI patients. Aversano et al[123] conducted the multicenter, prospective, randomized C-PORT (Atlantic Cardiovascular Patient Outcomes Research Team) trial to investigate the feasibility of off-site primary PCI. In this study, 11 centers with cardiac catheterization facilities, but no surgical backup, randomized 451 fibrinolytic therapy–eligible STEMI patients to fibrinolytic therapy or primary PCI at the community hospital. The composite primary end point of death, recurrent myocardial infarction, and stroke at 6 months occurred in 19.9% of those in the fibrinolytic group and 12.4% of those in the PCI group ($P = .03$).

The Mayo experience with off-site primary PCI has been positive. Of the 1007 PCIs performed at a Mayo Clinic affiliate hospital between 1999 and 2005, 285 were primary PCIs for STEMI patients.[124]

There was a 93% success rate without any major complications, and no patients required emergency bypass surgery. The survival of primary PCI patients treated at the off-site catheterization laboratory was identical to that of patients treated at the Mayo Clinic.

The ACC/AHA guidelines for PCI recommend the following[125]:

Class IIb

1. *Primary PCI for patients with STEMI might be considered in hospitals without onsite cardiac surgery, provided that appropriate planning for program development has been accomplished, including appropriately experienced physician-operators (more than 75 total PCIs and, ideally, at least 11 primary PCIs per year for STEMI), an experienced catheterization team on a 24 hours per day, 7 days per week call schedule, and a well-equipped catheterization laboratory with digital imaging equipment, a full array of interventional equipment, and intraaortic balloon pump capability, and provided that there is a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital with appropriate hemodynamic support capability for transfer. The procedure should be limited to patients with STEMI or myocardial infarction with new or presumably new LBBB on ECG and should be performed in a timely fashion (goal of balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (at least 75 PCIs per year) and at hospitals performing a minimum of 36 primary PCI procedures per year. (Level of Evidence: B)*

Class III

1. *Primary PCI should not be performed in hospitals without onsite cardiac surgery and without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate hemodynamic support capability for transfer. (Level of Evidence: C)*

DISTAL PROTECTION AND THROMBECTOMY DEVICES

Distal embolization of the intracoronary thrombus at the time of PCI and subsequent no reflow is a concern. To prevent embolization, distal protection devices have been used in STEMI patients. The EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris) trial investigated the use of the Guidewire Plus distal occlusion device (Boston Scientific, Marlborough, MA) in 501 STEMI patients. Participants were randomized to conventional primary PCI or PCI with the Guidewire Plus device. The primary end point of

ST-segment resolution measured 30 minutes after PCI by continuous Holter monitoring and infarct size measured by technetium (Tc)-99m sestamibi imaging between days 5 and 14 was similar between both groups.[126] Another distal protection device, the Filter Wire-EX (Boston Scientific), was investigated in the PROMISE (Protection Devices in PCI Treatment of Myocardial Infarction for Salvage of Endangered Myocardium) trial. Two hundred AMI patients undergoing PCI were randomized to conventional therapy or PCI with the Filter Wire-EX distal protection device.[127] The primary end point of maximal adenosine-induced Doppler flow velocity in the recanalized infarct artery was similar in both groups. The secondary end point of infarct size as determined by magnetic resonance imaging was also similar between the two groups.

Mechanical debulking of intracoronary thrombus has also been proposed as a method to reduce distal embolization. The AIMI (AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction) trial randomized 480 STEMI patients to conventional PCI or PCI plus rheolytic thrombectomy with the AngioJet thrombectomy device (Boston Scientific). Patients in the thrombectomy group had a larger infract size (12.5% vs 9.8%; $P = .03$) and a lower rate of postprocedure TIMI grade 3 flow (92% vs 96%; $P < .02$).

In addition to mechanical aspiration, manual aspiration of thrombus material may also be considered to reduce distal embolization and microvascular obstruction. In the Thrombus Aspiration During Primary Percutaneous Coronary Intervention (TAPAS) study, 1071 STEMI patients undergoing primary PCI were randomized to manual aspiration through a 6-Fr Export Catheter (Medtronic, Edgewater, MD) before angioplasty versus conventional therapy.[128] The primary end point, a TIMI myocardial blush grade of 0 or 1, occurred in 17.1% of the aspiration group and 26.3% of the conventional PCI patients ($P < .001$). In addition, several secondary end points favored the thrombus-aspiration group compared with the conventional therapy group, including complete ST-segment elevation resolution (56.6% vs 44.2%; $P < .001$), absence of persistent ST-segment deviation (53.1% vs 40.5%; $P < .001$), and absence of pathologic Q waves on ECG (24.5% vs 15.9%; $P = .001$).

The ATTEMPT (Pooled Analysis of Trials on Thrombectomy in Acute Myocardial Infarction Based on Individual Patient Data) study, a recently published pooled analysis of patient data comparing standard PCI with or without thrombectomy, includes results from the TAPAS trial.[129] In this analysis, data from 2686 STEMI patients enrolled in 11 prospective trials were randomized to standard PCI versus PCI with thrombectomy device. The primary end point was all-cause mortality at 1 year. Results indicated a significantly lower all-cause mortality for the thrombectomy group versus the standard PCI group ($P = .049$). Subgroup analyses indicated that these results were primarily driven by reduced mortality in those who underwent thrombectomy in the presence of glycoprotein IIb/IIIa inhibitors. More importantly, the survival benefit was seen only in patients treated with manual thrombectomy devices.

However, three multicenter randomized trials, two of which were large trials with routine manual thrombectomy in STEMI patients, have not shown a mortality benefit. The TASTE (Thrombus Aspiration During ST-Segment Elevation Myocardial Infarction) trial (n = 7244) and the TOTAL (Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI) trial randomized 10,732 patients with STEMI to either aspiration thrombectomy before primary PCI or primary PCI only. The TOTAL trial also found an increase in stroke in patients undergoing routine aspiration.

The clinical practice guidelines recommend the following[35]:

Class IIb
The usefulness of selective and bailout aspiration thrombectomy in patients undergoing primary PCI is not well established .(Level of Evidence: C)

Class III: No Benefit
Routine aspiration thrombectomy before primary PCI is not useful. (Level of Evidence: A)

DRUG-ELUTING STENTS

Several studies have demonstrated that drug-eluting stents (DESs) significantly reduce the occurrence of restenosis in patients undergoing elective PCI.[130-133] More recently, however, multiple studies have investigated the efficacy and safety of DES in STEMI patients undergoing primary PCI. In the TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty) trial, 712 STEMI patients who were to undergo primary PCI were randomized to receive either a Cypher DES (Cordis, Hialeah, FL) or a bare metal stent.[134] The combined primary end point of death, reinfarction, or target vessel revascularization at 1 year occurred in 7.3% of the patients in the Cypher group and in 14.3% of patients in the bare metal stent group ($P = .0036$). The end point, however, was mainly driven by a reduction in target vessel revascularization (3.7% vs 12.6%; $P < .0001$). Rates of stent thrombosis were similar in both groups (3.4% Cypher vs 3.6% bare metal).

The PASSION (Paclitaxel Eluting Stent Versus Conventional Stent in ST-Segment Elevation Myocardial Infarction) trial randomized 619 STEMI patients who were to undergo primary PCI to the Taxus DES (Boston Scientific) or to an Express bare metal stent (Boston Scientific).[135] Unlike the TYPHOON trial, use of the Taxus DES was not associated with a significant difference in the 1-year combined primary end point of death, reinfarction, or target vessel revascularization (8.7% Taxus vs 12.6% bare metal; $P = .12$). The rate of target vessel revascularization was 6.2% in the Taxus group and 7.4% in the bare metal stent group ($P = .23$).

To date, HORIZONS-AMI is the largest trial of DES in STEMI patients undergoing primary PCI.[136] In this study, after emergent angiography, 3006 STEMI patients were randomized in a 3:1 ratio to receive either paclitaxel-coated (Taxus) stents (2257 patients) or bare metal stents (749 patients). Two primary end points, one for efficacy and one for safety, were identified: 12-month target lesion revascularization due to ischemia and a composite safety outcome of death, reinfarction, stroke, or stent thrombosis. At 12 months, target lesion revascularization occurred in 4.5% of the paclitaxel group versus 7.5% of the bare metal stent group ($P = .002$). Importantly, safety outcomes between the groups were essentially equal, occurring in 8.1% and 8.0% of the DES and bare metal stent groups, respectively ($P = .92$).

A 2009 meta-analysis that included the PASSION, TYPHOON, and HORIZONS-AMI studies identified 13 randomized trials and 18 registries comparing the outcomes of bare metal stents with those of paclitaxel or sirolimus DES in STEMI.[137] Among the 13 trials, 7352 STEMI patients were randomized to receive bare metal stent or DES. Specific outcomes included mortality, myocardial infarction, target vessel revascularization, and stent thrombosis. Results showed a reduction in target vessel revascularization for those treated with DES compared with bare metal stents (5.3% vs 11.5%; $P < .001$). More importantly, there was no difference between DES and bare metal stent in mortality (3.7% vs 4.3%; $P = .36$), myocardial infarction

(3.4% vs 3.8%; $P = .12$), or stent thrombosis in the first year (2.7% vs 2.6%; $P = .81$).

The registry data, including 26,521 STEMI patients, were also consistent with those seen in randomized trials. Results indicated a significant reduction in target vessel revascularization in the DES-treated patients (relative risk [RR], 0.54; $P < .01$) without a difference between groups in myocardial infarction. In addition, the use of DES reduced mortality (RR, 0.68; $P < .01$) and stent thrombosis (RR, 0.52; $P = .01$) at 1 year. These effects, however, were not significant at 2 years.[137] These data imply the use of DES in STEMI to be efficacious and safe, although US Food and Drug Administration approval for their use in this setting is still pending.

For those patients who do receive a DES, the importance of dual antiplatelet therapy must be emphasized. A registry of AMI patients who received DES revealed that 13.6% of patients stop taking clopidogrel after the first month of therapy. These patients had a 1-year mortality rate of 7.5%, which was significantly greater than the death rate of 0.7% in those who were compliant with dual antiplatelet therapy.[138]

The clinical practice guidelines recommend the following[35]:

Class I

1. *Placement of a stent (bare-metal stent [BMS] or drug-eluting stent [DES]) is useful in primary PCI for patients with STEMI. (Level of Evidence: A)*
2. *BMS should be used in patients with high bleeding risk, inability to comply with 1 year of dual antiplatelet therapy (DAPT), or anticipated invasive or surgical procedures in the next year. (Level of Evidence: C)*

Class III: Harm

1. *DES should not be used in primary PCI for patients with STEMI who are unable to tolerate or comply with a prolonged course of DAPT because of the increased risk of stent thrombosis with premature discontinuation of one or both agents. (Level of Evidence: B)*

NON–INFARCT-RELATED ARTERY CORONARY INTERVENTION AT TIME OF ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION CARE

Prior versions of the STEMI guidelines had recommended against treatment of nonculprit stenoses during the initial STEMI revascularization procedure or during the same hospitalization in the absence of clinical instability or further testing documenting ischemia. The three new randomized studies have challenged this concept, leading to a focused update of the STEMI guideline and the new Class IIb assignment for treatment of nonculprit stenoses in the setting of primary PCI.[74-76] The PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) trial randomized patients with > 50% stenosis felt to be treatable by the operator during primary PCI.[74] The CvLPRIT (Complete Versus Lesion-Only Primary PCI Trial) trial required the nonculprit artery stenosis to be 70% in one view and > 50% in two views.[76] Although treatment during the primary PCI was encouraged, treatment during the initial hospitalization was possible. Finally, in DANAMI3-PRIMULTI, nonculprit stenosis were required to be > 50% with fractional flow reserve < 0.80 for treatment or > 90%.[76] These three studies demonstrated varied levels of clinical benefit, mostly as a result of worsening symptoms and need for urgent revascularization. This has led to the change to a Class IIB recommendation and ongoing studies.

MANAGEMENT IN THE CORONARY CARE UNIT

FIBRINOLYTIC-TREATED PATIENTS

It should be noted that most patients with STEMI at hospitals without PCI capabilities may receive fibrinolysis if primary PCI is not immediately possible (within 60 minutes). These patients in general should be referred for elective angiogram within 3 to 24 hours if logistically possible.

ADDITIONAL PHARMACOTHERAPY

Inhibition of the Renin-Angiotensin-Aldosterone System

Angiotensin-Converting Enzyme Inhibitors Nine trials, with cumulative enrollment of more than 100,000 patients, have documented the effects of angiotensin-converting enzyme (ACE) inhibitors on mortality in a prospective randomized fashion. These trials can be conveniently divided into those in which all patients were given the drug and those in which drug administration was limited to only patients who were at higher risk. The four nonselective trials include the Cooperative New Scandinavian Enalapril Survival Study-2 (CONSENSUS-2),[139] the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-3 (GISSI-3),[140] the Fourth International Study of Infarct Survival (ISIS-4),[50] and the Chinese Cardiac Study (CCS-1).[141] In CONSENSUS-2, intravenous enalaprilat was administered within 24 hours of presentation followed by oral enalapril.[139] In the remaining studies, patients did not receive an initial IV load, and in three of these four trials, the drug was initiated within 24 hours of presentation. In CONSENSUS-2, mortality was nonsignificantly increased in the treatment group, but in the remaining three trials, a statistically significant reduction in mortality was observed in the treatment group with approximately 5 lives saved per 1000 patients receiving ACE inhibitor therapy.

Five trials studied the selective use of ACE inhibitors after AMI. These included the Survival and Ventricular Enlargement (SAVE) study,[142] the Trandolapril Cardiac Evaluation (TRACE) study,[143] the Acute Infarction Ramipril Efficacy (AIRE) study,[144] the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study,[145] and the Captopril and Thrombolysis Study (CATS).[146] In SAVE and TRACE, patients were selected by laboratory evidence of an LV ejection fraction of less than 40% or wall motion abnormality. In AIRE, transient heart failure was the entrance criterion. Clinically and statistically significant mortality reduction of 40 to 70 lives saved per 1000 patients treated was documented in four of these five trials.

Given the results of these trials, it is reasonable to initiate therapy with ACE inhibitors within the first 24 hours as long as no contraindications exist and the patient is hemodynamically stable. Patients with an ejection fraction greater than 45% and no clinical evidence of heart failure, significant mitral regurgitation, or hypertension can have therapy discontinued after determination of risk status while still hospitalized. Because captopril has the shortest half-life, overdosing and inadvertent hypotension may be most easily correctable with the use of this agent. In addition, the short half-life allows for more rapid titration. Intravenous administration is unnecessary unless the patient is unable to take oral medication. Duration of treatment is uncertain; however, many patients will be treated indefinitely.

Angiotensin Receptor Blockers Additional blockade of the renin-angiotensin system with the angiotensin receptor blocker valsartan was investigated in VALIANT (Valsartan in Acute Myocardial Infarction Trial).[147] This was a prospective, randomized, double-blinded trial

involving 14,808 AMI patients complicated by impaired LV function (ejection fraction ≤ 0.35 on echocardiography or contrast angiography and ≤ 0.40 on radionuclide ventriculography) who were randomized to one of three groups: captopril only, valsartan only, or both captopril and valsartan. After a median follow-up of 25 months, the primary end point of cardiovascular death was 16.9% in the captopril group, 16.8% in the valsartan group, and 16.9% in the combination group (P = not significant). The combination group, however, experienced a statistically significant greater amount of hypotension and renal dysfunction. The results of VALIANT suggest that valsartan is as effective as captopril in the management of AMI patients with LV dysfunction, but the combination of an ACE inhibitor and an angiotensin receptor blocker should be avoided.

In OPTIMAAL (Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan), 5477 AMI patients were randomized to therapy with losartan or captopril.[148] The 3-year primary end point of all-cause mortality occurred in 18% of patients in the losartan group and in 16% of those in the captopril group (P = .07). These studies suggest that ACE inhibitors should be used as primary therapy and that angiotensin receptor blockers should be used in those who cannot tolerate ACE inhibitors.

Aldosterone Antagonists The use of an aldosterone antagonist in patients with AMI complicated by LV dysfunction was studied in the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial.[149] The 6642 patients with AMI and a resulting ejection fraction < 0.40 were randomized to the aldosterone antagonist eplerenone or placebo 3 to 14 days after admission. After a median follow-up of 16 months, the primary end point of death from any cause occurred in 14.4% of patients in the eplerenone group and 16.7% of patients in the placebo group (P = .008). As expected, eplerenone use was associated with a greater amount of hyperkalemia and less hypokalemia. Based on the results of the EPHESUS trial, it is reasonable to use an aldosterone antagonist in conjunction with β-blockade and ACE inhibition in patients with AMI and subsequent LV dysfunction (ejection fraction < 0.40). Diligent monitoring of the serum potassium must occur with patients who are treated with an aldosterone antagonist.

β-Blockade

Initiation of β-blockade therapy in the coronary care unit is essential in the management of STEMI patients. β-Blockers have both acute and long-term benefits in STEMI patients treated with either lysis or primary PCI. A meta-analysis of 24,000 AMI patients demonstrated a significant 14% reduction in acute mortality and a 23% reduction in long-term mortality. Short-acting β-blockade with metoprolol should be initiated as early as possible and rapidly titrated to the maximally tolerated dose. In patients who present with shock or heart failure, the initiation of β-blockers should be delayed until patients become hemodynamically stable.

The clinical practice guidelines recommend the following[29]:

Class I

1. *Patients receiving β-blockers within the first 24 hours of STEMI without adverse effects should continue to receive them during the early convalescent phase of STEMI. (Level of Evidence: A)*
2. *Patients without contraindications to β-blockers who did not receive them within the first 24 hours after STEMI should have them started in the early convalescent phase. (Level of Evidence: A)*
3. *Patients with early contraindications within the first 24 hours of STEMI should be reevaluated for candidacy for β-blocker therapy. (Level of Evidence: C)*

Statins

Numerous trials have demonstrated that statins should be used in the secondary prevention of patients with coronary artery disease.[150] In addition to lowering low-density lipoprotein (LDL) cholesterol, statins also improve endothelial function, have antiplatelet effects, and reduce inflammation.[151] The benefits of initiating statin therapy during the acute setting in STEMI patients was investigated in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) TIMI 22 trial.[152] In this study, 4162 ACS patients (33% with STEMI) were randomized to standard therapy with 40 mg of pravastatin or to intense lipid-lowering therapy with atorvastatin 80 mg daily within the first 10 days of hospitalization for ACS. The combined primary end point of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke occurred in 26.3% of the patients in the pravastatin group and 22.4% of patients in the atorvastatin group (P = .005). The final LDL was 95 mg/dL in the pravastatin group and 62 mg/dL in the atorvastatin group (P < .001).

It is therefore reasonable to initiate statin therapy during the acute setting of STEMI. Although the data are not clear regarding the benefits of early statin use, STEMI patients are more likely to be on statin therapy in the post–myocardial infarction period if treatment is initiated during the index hospitalization. An LDL goal of less than 70 mg/dL should be achieved.

Several studies have investigated the long-term benefits of statin therapy as secondary prevention in patients with coronary artery disease.

HEMODYNAMIC COMPLICATIONS

The most common major mechanical complications of acute STEMI include cardiogenic shock, RV infarction, acute mitral regurgitation, ventricular septum rupture, and free wall rupture.

Cardiogenic shock

Cardiogenic shock as a result of severe LV dysfunction occurs in approximately 7% of patients with myocardial infarction and has a historic mortality of approximately 80%.[153] A population-based study analyzed temporal trends in cardiogenic shock complicating AMI in 9076 patients between the years 1975 and 1997.[154] The frequency of cardiogenic shock remained relatively stable at 7.1%, and the mortality rate was approximately 72%. There was a trend toward increased in-hospital survival in the mid to late 1990s, which correlated with the increased application of reperfusion technologies.[155] The SHOCK II (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock II) trial showed that the cardiogenic shock mortality remains elevated at near 50%.[34]

The goals for treatment are two-fold: first, hemodynamic stabilization to ensure adequate oxygenation, acid-base balance, and tissue perfusion; and second, rapid investigation of any potentially reversible causes for the patient's condition. Hypovolemia, which is more common in older patients, those receiving chronic diuretic therapy, and those receiving narcotics or preload-reducing agents, must be corrected. Hemodynamic monitoring by using a balloon-tipped pulmonary artery catheter allows immediate access to valuable hemodynamic information. Forrester and others[156,157] described the treatment of patients on the basis of hemodynamic subsets related to pulmonary artery wedge pressure and cardiac output (Table 40–8). The basic goals of this approach include adjustment of the intravascular volume status to bring the pulmonary artery capillary wedge pressure to 18 to

TABLE 40–8. Forrester Classification of Myocardial Infarction

	Cardiac Index (L/min/m^2)	Wedge (mm Hg)
Class I	> 2.2	< 18
Class II	> 2.2	> 18
Class III	< 2.2	< 18
Class IV	< 2.2	> 18

20 mm Hg and optimization of cardiac output with inotropic and/or vasodilating agents. Severely hypotensive patients can be temporarily aided by intra-aortic balloon pumping or possibly by a ventricular assist device. However, the benefits from these mechanical treatments are often temporary, and there may be a significant risk of complications.

Many observational studies suggest that reperfusion therapy, especially with primary PCI, can reduce the incidence of cardiogenic shock. In one of the largest observational series, 1321 patients with shock in the GUSTO-1 trial were analyzed with respect to revascularization within 30 days versus no revascularization therapy. After multivariable logistic regression analysis, revascularization was independently associated with reduced 1-year mortality (odds ratio [OR], 0.6; 95% CI, 0.4-0.9; $P = .007$). In-hospital mortality, however, remained high at 56%.[158]

The SHOCK trial evaluated the effect of early revascularization in AMI complicated by cardiogenic shock.[159,160] The 302 patients with shock caused by LV dysfunction complicating myocardial infarction were randomly assigned to either emergency revascularization (n = 152) or initial medical stabilization (n = 150). Eighty-six percent of patients in both groups had intra-aortic balloon counterpulsation placement, and revascularization was accomplished by either coronary artery bypass grafting or angioplasty. The median time from symptom onset to revascularization was approximately 12 hours. The revascularization group had lower all-cause mortality at 30 days (46.7% vs 56%; $P = .11$), 6 months (50.3% vs 63.1%; $P = .027$), and 1 year (53.3% vs 64.4%; $P < .03$). There was an interaction between the effect of therapy and age in that only patients younger than age 75 years benefited from revascularization. Although the 20% relative mortality reduction was more modest than expected on the basis of observational studies, only eight patients would have to receive early revascularization to prevent one death at 6 months. This result compares very favorably with benefits achieved by fibrinolytic therapy or primary PCI in patients without shock.

Although vasoconstriction has traditionally been associated with cardiogenic shock, vasodilatation can also be present. The mechanism of vasodilatation occurs from an increase in inducible nitric oxide synthase and subsequent increased production of nitric oxide. Use of the nitric oxide synthase inhibitor N^G-monomethyl-L-arginine had been proposed as a potential therapy for these patients with vasodialtion,[161] but definitive randomized clinical trials demonstrated no benefit of this therapy over placebo.[162]

The SHOCK II trial randomized patients to planned intra-aortic balloon pump (IABP) with PCI versus PCI alone. The trial found that there was not a significant reduction in mortality with IABP use. This has led to a change in guideline recommendations for routine IABP use with shock to Class IIA.

The clinical practice guidelines recommend the following[29]:

Treatment of Cardiogenic Shock: Recommendations
Class I

1. *Emergency revascularization with either PCI or CABG [coronary artery bypass graft] is recommended in suitable patients with cardiogenic shock due to pump failure after STEMI irrespective of the time delay from MI onset. (Level of Evidence: B)*
2. *In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI and cardiogenic shock who are unsuitable candidates for either PCI or CABG. (Level of Evidence: B)*

Class IIa

1. *The use of intra-aortic balloon pump (IABP) counterpulsation can be useful for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy. (Level of Evidence: B)*

Class IIb

1. *Alternative LV assist devices for circulatory support may be considered in patients with refractory cardiogenic shock. (Level of Evidence: C)*

Cardiogenic Shock in Patients With ST-Segment Elevation Myocardial Infarction May Be Caused by Right Ventricular Infarction Involvement of the right ventricle is a common sequela of acute inferior myocardial infarction,[163] especially after proximal right coronary artery occlusion.[164] However, hemodynamically significant dominant RV dysfunction is much less common, particularly in the reperfusion era, occurring in relatively few patients with RV infarction (RVI).

The diagnosis of hemodynamically significant RVI rests on the clinical triad of hypotension, increased jugular venous pressure, and clear lung fields in a patient with acute inferior myocardial infarction. Additional diagnostic techniques that can document RV involvement include ST-segment elevation in right-sided chest leads (V_3R or V_4R), visualization of RV wall motion abnormalities, and RV dilatation on radionuclide angiography or echocardiography.

Hemodynamic measurements in patients with significant RVI demonstrate elevation of the right atrial pressure, usually more than 10 mm Hg, and often show a right atrial pressure/pulmonary artery wedge pressure ratio of 0.8 or more. However, in cases with significant LV dysfunction and increased wedge pressure, this ratio may be lower and does not exclude the presence of significant RV involvement. Rarely, substantial arterial desaturation may be observed because of opening of a patent foramen ovale as a result of increased right atrial pressure and right-to-left atrial shunting. The incidence of bradyarrhythmias is increased in patients with RVI and can be detrimental because an increased heart rate may be necessary to compensate for the decrease in RV (and as a result LV) stroke volume caused by the RVI. Similarly, high-grade atrioventricular block may lead to loss of the atrioventricular synchrony with RV underfilling and further decrease in the RV and LV stroke volume.[165]

Treatment of RVI initially involves volume loading with normal saline to achieve a pulmonary artery wedge pressure of 18 to 20 mm Hg. In some patients, this alone is sufficient to improve cardiac output and systemic pressure. However, some patients will not respond to fluid-loading alone. This may be a result of marked RV enlargement within a relatively noncompliant pericardium, which may result in functional LV compression because of ventricular interaction. In addition to volume loading, use of dobutamine improves cardiac index.[166] Patients requiring temporary pacing for heart block may also benefit from

arteriovenous sequential pacing rather than lone ventricular pacing. Reperfusion by thrombolysis,[167] and especially with primary PCI,[168] improves both RV function and clinical outcomes.

The natural history of dominant RVI may be favorable because the right ventricle is very resistant to ischemia and usually recovers.[163] Most patients, even those with substantial RV dysfunction, spontaneously improve in 48 to 72 hours after the acute event. Patients in shock may benefit from angioplasty of the occluded right coronary artery or from temporary use of an RV assist device; however, many of these patients have associated significant LV dysfunction, which complicates the picture.[169] The overall balance between the extent of RV and LV dysfunction is a major determinant of long-term outcome, and the majority of patients with RVI and significant hemodynamic compromise usually have evidence of extensive biventricular infarction and cardiogenic shock.

The clinical practice guidelines recommend the following[29]:

Class I

1. *Patients with inferior STEMI and hemodynamic compromise should be assessed with a right precordial V4RR lead to detect ST-segment elevation and an echocardiogram to screen for RV infarction. (See the ACC/AHA/ASE [American Society of Echocardiography] 2003 Guideline Update for the Clinical Application of Echocardiography.) (Level of Evidence: B)*
2. *The following principles apply to therapy for patients with STEMI and RV infarction and ischemic dysfunction:*
   a. *Early reperfusion should be achieved if possible. (Level of Evidence: C)*
   b. *Atrioventricular synchrony should be achieved, and bradycardia should be corrected. (Level of Evidence: C)*
   c. *RV preload should be optimized, which usually requires initial volume challenge in patients with hemodynamic instability provided the jugular venous pressure is normal or low. (Level of Evidence: C)*
   d. *RV afterload should be optimized, which usually requires therapy for concomitant LV dysfunction. (Level of Evidence: C)*
   e. *Inotropic support should be used for hemodynamic instability not responsive to volume challenge. (Level of Evidence: C)*

Class IIa

1. *After infarction that leads to clinically significant RV dysfunction, it is reasonable to delay coronary artery bypass graft surgery for 4 weeks to allow recovery of contractile performance. (Level of Evidence: C)*

Acute Mitral Regurgitation

Severe mitral regurgitation caused by papillary muscle rupture is responsible for approximately 5% of deaths in AMI patients. Rupture may be complete or partial, and it usually involves the posteromedial papillary muscle because its blood supply is derived only from the posterior descending artery, whereas the anterolateral papillary muscle has a dual blood supply from both the left anterior descending and the circumflex coronary arteries. Most patients have relatively small areas of infarction with poor collaterals, and up to half of the patients may have single-vessel disease.

The clinical presentation of papillary muscle rupture is the acute onset of pulmonary edema, usually within 2 to 7 days after inferior myocardial infarction. The characteristics of the murmur vary; as a result of a rapid increase of pressure in the left atrium, no murmur may be audible. Thus a high degree of suspicion, especially in patients with inferior wall infarction, is necessary for diagnosis. Two-dimensional echocardiographic examination demonstrates the partially or completely severed papillary muscle head and a flail segment of the mitral valve. LV function is hyperdynamic as a result of the severe regurgitation into the low-impedance left atrium; this finding alone, in a patient with severe congestive heart failure, should suggest the diagnosis.

The cornerstones of successful therapy are prompt diagnosis and emergency surgery. Emergent placement of an IABP and blood pressure control may be beneficial. The current approach of emergency surgery accrues an overall operative mortality of 0% to 21%, but this appears to be decreasing, and the late results of this approach can be excellent.[170,171]

The clinical practice guidelines recommend the following[29]:

Class I

1. *Patients with acute papillary muscle rupture should be considered for urgent cardiac surgical repair unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (Level of Evidence: B)*
2. *Coronary artery bypass graft surgery should be undertaken at the same time as mitral valve surgery. (Level of Evidence: B)*

Ventricular Septal Rupture

Before the reperfusion era, rupture of the ventricular septum occurred in 1% to 3% of acute infarctions and caused approximately 5% of peri-infarction deaths. Data from GUSTO-1, however, indicate that ventricular septal rupture (VSR) was confirmed in only 0.2% of more than 41,000 patients who received lytic therapy for ACS.[172] These data indicate that mechanical complications of myocardial infarction appear to be substantially reduced since the advent of reperfusion therapies. When VSR occurs, however, the substrate is quite similar to that of free wall rupture in terms of number of vessels diseased and infarct size. Typically, VSRs associated with anterior infarction are located in the apical septum, and those associated with inferior infarction are located in the basal inferior septum. The prevalence of anterior and inferior infarctions is approximately equal, unlike papillary muscle rupture.[173]

The diagnosis should be suspected clinically when a new pansystolic murmur is present. As with other cardiac ruptures, surgical management is advocated, although the outcome is not as gratifying as in acute mitral regurgitation, because the extent of myocardial necrosis is generally larger.[172,174] Percutaneous closure using occluding devices has been done in nonsurgical candidates with variable results: three of seven patients survived to hospital discharge in one report.[175]

The outcome of 91 patients seen in a single institution with VSR after AMI was reviewed by Lemery et al.[174] Advanced age, cardiogenic shock, and long delay between septal rupture and surgery correlated with adverse outcome. In patients with cardiogenic shock and ventricular septal defect, only those operated on within 48 hours survived; thus the proportion surviving in this group was only 38%. For patients not in shock, mortality was similar for surgery either within 2 to 14 days or after 14 days; however, the clinical course was unpredictable, with rapid deterioration and death in approximately 50% of these patients.

The incidence and outcome of peri-infarction ventricular septal defect in the fibrinolytic era were reported in a study from the GUSTO-1 database.[172] In 84 patients (0.2%), ventricular septal defect developed after fibrinolysis, and the median time from symptom onset to the diagnosis of ventricular septal defect was 1 day. Mortality at 30 days in this group was 73.8%, and in patients selected for surgical repair versus those managed medically, 30-day mortality was 47% versus 94%, respectively. All patients presenting in Killip class III or IV died regardless of therapy; however, 1-year survival was excellent in patients surviving the initial 30 days after infarction.

The clinical practice guidelines recommend the following[29]:

Class I

1. *Patients with STEMI complicated by the development of a VSR should be considered for urgent cardiac surgical repair unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (Level of Evidence: B)*
2. *Coronary artery bypass grafting should be undertaken at the same time as repair of the VSR. (Level of Evidence: B)*

Free Wall Rupture

Rupture of the free wall of the left ventricle occurs in 1% to 4.5% of AMI patients and accounts for 10% to 15% of early AMI deaths.[176-181] Rupture is more common in women, the elderly, and persons with delayed admission to hospital.[176,178,181] Although any wall may be involved, rupture of the lateral wall is probably most common. Rupture occurs within the first 5 days of infarction in 50% of cases and within 14 days in 87% of cases. The area of rupture always occurs within the area of infarction but usually is eccentrically located near the junction with normal myocardium. The incidence of rupture has decreased in the fibrinolytic era, but the timing is earlier (24-48 hours).[178] Further decrease in the rate of rupture can be achieved by primary PCI.[177,181] Survival to discharge in patients with cardiogenic shock included in the SHOCK trial[133] was 39.3%, similar to the survival of the other patients.[182]

The clinical presentation is usually sudden electromechanical dissociation. Most patients die even when rapid resuscitative measures, including pericardiocentesis, IABP insertion, and emergent cardiac surgery, are attempted.[183] Surgical correction of acute free wall rupture is the treatment of choice, even though surgical mortality can be high.[184] Surgical correction can be challenging because of the friability of the tissue that surrounds the rupture. A sutureless patch technique has shown encouraging initial results.[185] Early diagnosis is critical and can be achieved by a high degree of suspicion in any patient with sudden hemodynamic deterioration, particularly in the absence of evidence for recurrent ischemia or infarct extension.

Alternatively, rupture may be subacute, with periodic small amounts of blood leaking into the pericardial space.[183,186] ECG evidence of regional pericarditis may be a warning of impending rupture. Persistent and severe pericardial pain also may be a manifestation of this phenomenon, and the subsequent inflammatory process may serve to wall off the area of pericardial leakage from the remaining pericardial space, forming a false or pseudoaneurysm of the left ventricle. The entity is easily and reliably detected by two-dimensional echocardiography and, when acute, mandates early surgical intervention because of the risk of further expansion of the false aneurysm or rupture producing tamponade and death. It is critically important to have a heightened level of sensitivity for the possibility of subacute rupture in all patients with evidence of pericarditis and especially if a friction rub is present. Immediate performance of echocardiography is mandatory. Chronic LV false aneurysm has a relatively low risk of rupture. Survival is reduced from multiple causes. In one observational series of 21 patients followed for a mean of 3.6 years, mortality was 64%, although no patient died of rupture.[187]

The clinical practice guidelines recommend the following[29]:

Class I

1. *Patients with free-wall rupture should be considered for urgent cardiac surgical repair, unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (Level of Evidence: B)*
2. *Coronary artery bypass grafting should be undertaken at the same time as repair of free wall rupture. (Level of Evidence: C)*

ELECTRICAL COMPLICATIONS

Bradyarrhythmias

The bradyarrhythmias are reviewed, but in the modern reperfusion era, the incidence and permanent pacemaker use have declined significantly.[188]

Bradyarrhythmias usually result from ischemic injury to the sinus node/conduction system or abnormal reflexes that are vagally mediated or both. The blood supply to the sinus node arises from the proximal right coronary artery in 55% of patients and from the proximal left circumflex in the remainder. The blood supply to the atrioventricular node arises from the distal branches of the right coronary artery in 90% of patients and from the distal portions of the left circumflex artery in the remaining 10% of patients. The right bundle branch is supplied primarily by the septal perforator vessels originating from the left anterior descending artery, as is the distal portion of the anterior left bundle branch. The main left bundle branch has a dual supply from both distal branches of the right coronary and proximal circumflex vessels, and the posterior division of the left bundle branch is supplied from branches of the circumflex coronary artery.

In general, conduction disturbances associated with inferoposterior infarction are related to enhanced vagal activity, tend to be more transient, are often responsive to atropine, and imply a somewhat more benign outcome than those involved in anterior infarction. Conversely, major conduction disturbances associated with anterior infarction usually imply extensive septal necrosis and more significant reduction in LV function.

Sinus Bradycardia Sinus bradycardia and sinus pauses are usually benign. First-degree atrioventricular block occurs in 4% to 13% of myocardial infarctions. Observation and avoidance of any medications that might prolong atrioventricular conduction are required.

Second-Degree Atrioventricular Block This usually develops within the first 24 hours of myocardial infarction in 3% to 10% of individuals. With type I second-degree atrioventricular block, progressive prolongation of the PR interval is observed. This is usually seen in inferoposterior infarction and may often respond to atropine. A narrow QRS complex is usually present, and temporary pacing is not needed unless the ventricular rate decreases to less than 45 bpm or symptoms of impaired perfusion develop. Type II second-degree atrioventricular block is identified by intermittent dropped beats in the absence of progressive PR prolongation and implies extensive infranodal conduction system injury. Often the QRS complex is wide, indicating associated bundle branch block, and progression to complete heart block occurs in approximately one-third of these patients. Most patients with anterior infarction and type II second-degree atrioventricular block need temporary transvenous pacing because of the unpredictable risk of complete heart block.

Complete Heart Block This occurs in 3% to 12% of AMIs.[189,190] In general, patients with inferoposterior infarction progress to third-degree heart block after a period of second-degree heart block and again may demonstrate some responsiveness to atropine or aminophylline.[191] A stable junctional escape rhythm is often present, and recovery tends to occur within 3 to 7 days. The occurrence of complete heart block in a patient with inferior infarction confers a 1.5- to 4-fold increase in risk of in-hospital mortality.[189,190] Consequently, these patients should be carefully observed, often with standby temporary transcutaneous pacing patches in place. Complete heart block in the presence of anterior

infarction usually indicates an extensive area of myocardial necrosis and has a poor prognosis. Most patients require temporary transvenous pacing, and some physicians advocate permanent transvenous pacing. Late mortality in these patients is usually the result of contractile failure or ventricular fibrillation rather than persistent, high-grade atrioventricular block.

Bundle Branch Block The occurrence of any new bundle branch block with AMI also identifies patients with extensive infarction who are at higher risk for complications. Unifascicular block, especially left anterior hemiblock, occurs in approximately 5% of patients and has a relatively benign prognosis. Complete right or left bundle branch block occurs in 10% to 15% of patients and most commonly (two-thirds of cases) involves the right bundle branch. Both LBBB and right bundle branch block are associated with higher in-hospital and long-term mortality.[192] In the past, the new occurrence of left or right bundle branch block has been a generally accepted indication for temporary transvenous pacing.

Permanent transvenous pacing is indicated in patients with persistent complete or high-grade atrioventricular block or persistent type II second-degree atrioventricular block after myocardial infarction and in patients with a new bundle branch block and transient but resolved complete heart block during the acute course of infarction. Occasionally, patients may require an electrophysiologic study to determine the site of atrioventricular block and to aid in the decision about whether permanent pacing is indicated. Permanent pacing also may be indicated in the rare patient with profound sinus node dysfunction. However, this complication is rarely related to myocardial infarction.

The clinical practice guidelines recommend the following[29]:

Class I

1. *Permanent ventricular pacing is indicated for persistent second-degree atrioventricular block in the His-Purkinje system with bilateral bundle branch block or third-degree atrioventricular block within or below the His-Purkinje system after STEMI. (Level of Evidence: B)*
2. *Permanent ventricular pacing is indicated for transient advanced second- or third-degree infranodal atrioventricular block and associated bundle branch block. If the site of block is uncertain, an electrophysiology study may be necessary. (Level of Evidence: B)*
3. *Permanent ventricular pacing is indicated for persistent and symptomatic second- or third-degree atrioventricular block. (Level of Evidence: C)*

Class IIb

1. *Permanent ventricular pacing may be considered for persistent second- or third-degree atrioventricular block at the atrioventricular node level. (Level of Evidence: B)*

Class III

1. *Permanent ventricular pacing is not recommended for transient atrioventricular block in the absence of intraventricular conduction defects. (Level of Evidence: B)*
2. *Permanent ventricular pacing is not recommended for transient atrioventricular block in the presence of isolated left anterior fascicular block. (Level of Evidence: B)*
3. *Permanent ventricular pacing is not recommended for acquired left anterior fascicular block in the absence of atrioventricular block. (Level of Evidence: B)*
4. *Permanent ventricular pacing is not recommended for persistent first-degree atrioventricular block in the presence of bundle-branch block that is old or of indeterminate age. (Level of Evidence: B)*

Tachyarrhythmias

Multiple factors play a role in the genesis of tachyarrhythmias in patients with myocardial infarction. Decreased blood flow leads to anaerobic metabolism, and decreased venous outflow allows accumulation of by-products of this process, resulting in acidosis, increase in extracellular potassium concentration, and an increase in intracellular calcium concentration. In addition to these ionic changes, there may be alterations in sympathetic and vagal tone and increased concentrations of circulating catecholamines. The electrophysiologic correlates of these cellular abnormalities include slowing of conduction and prolongation of refractoriness, which, coupled with the inhomogeneous nature of the infarction process, produces an ideal situation for the occurrence of reentrant arrhythmias. The presence of injury currents may directly enhance phase IV depolarization of Purkinje cells, resulting in increased automaticity. Fiber stretch, resulting from increased atrial and ventricular end-diastolic pressures, is also arrhythmogenic. Finally, reperfusion, possibly caused by intracellular calcium overload or production of free oxygen radicals, may generate reperfusion arrhythmias that may be either automatic or reentrant.

Supraventricular Arrhythmias

Sinus tachycardia may occur in up to 25% of patients with acute infarction and often results from pain, anxiety, and sometimes hypovolemia. Persistent sinus tachycardia may be a marker of severe LV dysfunction and is a poor prognostic sign. After relief of pain and assessment for the presence of pulmonary congestion, it is desirable to decrease the heart rate to less than 70 bpm by intravenous administration of β-adrenergic receptor blockers. A short-acting β-adrenergic receptor blocker, such as esmolol, may be appropriate for patients in whom the extent of LV dysfunction is of particular concern.

Although its incidence in the era of reperfusion with lytics and PCI has declined, atrial fibrillation may occur in approximately 6% to 21% of patients with acute infarction.[193-195] Risk factors for the development of atrial fibrillation in AMI include advanced age, heart failure symptoms, LV dysfunction, and tachycardia on admission.[195] Its early presence signifies atrial ischemia; later, it may also represent atrial stretch caused by increased filling pressures, which is why it is associated with such an adverse prognosis. This adverse prognosis is not only limited to the primary hospitalization. Long-term mortality regardless of the treatment received for the presenting myocardial infarction is also affected. Immediate cardioversion is the best treatment for patients with symptomatic rapid atrial fibrillation or in whom the rapid ventricular response produces ischemia. If the ventricular response is only moderate and the patient is asymptomatic, diltiazem or esmolol (in patients with a normal ejection fraction) given intravenously is useful for control of heart rate, along with digoxin given orally; the latter may take 4 to 8 hours for full effect. Recurrent episodes of atrial fibrillation should be suppressed with an antiarrhythmic agent such as procainamide or intravenous amiodarone. The treatment of atrial flutter is similar to that of atrial fibrillation, except that drug treatment is less effective in controlling the ventricular response. Occasionally, atrial overdrive pacing may be used to terminate atrial flutter without resorting to cardioversion. Atrial fibrillation in the setting of AMI, especially if it occurs after admission, is associated with higher mortality and incidence of stroke.[193,194]

The clinical practice guidelines recommend the following[29]:

Class I

1. *Sustained atrial fibrillation and atrial flutter in patients with hemodynamic compromise should be treated with one or more of the following:*
   a. *Synchronized cardioversion with an initial monophasic shock of 200 J for atrial fibrillation and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. (Level of Evidence: C)*
   b. *For episodes of atrial fibrillation that do not respond to electrical cardioversion or recur after a brief period of sinus rhythm, the use of antiarrhythmic therapy aimed at slowing the ventricular response is indicated. One or more of these pharmacologic agents may be used:*
      i. *Intravenous amiodarone. (Level of Evidence: C)*
      ii. *Intravenous digoxin for rate control, principally for patients with severe LV dysfunction and heart failure. (Level of Evidence: C)*
2. *Sustained atrial fibrillation and atrial flutter in patients with ongoing ischemia but without hemodynamic compromise should be treated with one or more of the following:*
   a. *β-Adrenergic blockade is preferred, unless contraindicated. (Level of Evidence: C)*
   b. *Intravenous diltiazem or verapamil. (Level of Evidence: C)*
   c. *Synchronized cardioversion with an initial monophasic shock of 200 J for atrial fibrillation and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. (Level of Evidence: C)*
3. *For episodes of sustained atrial fibrillation or flutter without hemodynamic compromise or ischemia, rate control is indicated. In addition, patients with sustained atrial fibrillation or flutter should be given therapy with anticoagulants. Consideration should be given to conversion of sinus rhythm in patients without a history of atrial fibrillation or flutter before STEMI. (Level of Evidence: C)*
4. *Reentrant paroxysmal supraventricular tachycardia, because of its rapid rate, should be treated with the following in the sequence shown:*
   a. *Carotid sinus massage. (Level of Evidence: C)*
   b. *Intravenous adenosine (6 mg IV [intravenously] over 1-2 seconds); if no response, 12 mg IV after 1-2 minutes may be given; repeat 12 mg dose if needed. (Level of Evidence: C)*
   c. *Intravenous β-adrenergic blockade with metoprolol (2.5-5.0 mg every 2-5 minutes to a total of 15 mg over 10-15 minutes) or atenolol (2.5-5.0 mg over 2 minutes to a total of 10 mg in 10-15 minutes). (Level of Evidence: C)*
   d. *Intravenous diltiazem (20 mg [0.25 mg/kg]) over 2 minutes followed by an infusion of 10 mg/h. (Level of Evidence: C)*
   e. *Intravenous digoxin, recognizing that there may be a delay of at least 1 hour before pharmacologic effects appear (8-15 μg/kg [0.6-1.0 mg in a person weighing 70 kg]). (Level of Evidence: C)*

Class III

1. *Treatment of atrial premature beats is not indicated. (Level of Evidence: C)*

Ventricular Tachyarrhythmias

Accelerated idioventricular rhythm may occur in up to 40% of continuously monitored patients and may be a marker of reperfusion in some. This rhythm disturbance is generally considered benign and is usually untreated (see Chap. 85).

The *clinical practice guidelines* recommend the following[29]:

Class III

1. *Antiarrhythmic therapy is not indicated for accelerated idioventricular rhythm. (Level of Evidence: C)*
2. *Antiarrhythmic therapy is not indicated for accelerated junctional rhythm. (Level of Evidence: C)*

Ventricular tachycardia occurs in up to 15% of patients during AMI. The ventricular rate is usually between 140 and 200 bpm, and this rhythm disturbance may degenerate to ventricular fibrillation. The rhythm disturbance usually responds to lidocaine given intravenously. However, procainamide, bretylium, cardioversion, ventricular overdrive pacing, or amiodarone may all be required in the acute stages for resistant cases. The use of lidocaine prophylactically for prevention of ventricular tachycardia is not currently recommended. Pooled results of studies showed that the incidence of ventricular tachycardia was decreased, but fatal asystole was more common and no survival advantage was observed.

Ventricular fibrillation is seen in approximately 8% of patients surviving to hospitalization for acute infarction. It is more frequent in large ST-segment elevation infarcts and may occur with or without warning arrhythmias. The occurrence of ventricular fibrillation within the first 24 hours of hospitalization was previously thought not to confer any long-term risk to patients successfully resuscitated; however, some studies indicate a poorer outcome for patients with ventricular fibrillation at any time during their hospital course. Ventricular fibrillation or tachycardia occurring late in the hospital course may be the result of pump failure, severe electrolyte imbalance, effects of antiarrhythmic medications, or other metabolic derangements; it is usually associated with decreased LV systolic function and portends a poor prognosis. Sustained monomorphic ventricular tachycardia (VT), occurring early or late during the hospital course, is not common but implies a fixed arrhythmogenic substrate and a propensity for recurrence after dismissal. An invasive electrophysiologic study can be justified in these patients before discharge from the hospital.

The clinical practice guidelines recommend the following[29]:

Class I

1. *Sustained (> 30 seconds or causing hemodynamic collapse) polymorphic VT should be treated with an unsynchronized electric shock with an initial monophasic shock energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and, if necessary, a third shock of 360 J. (Level of Evidence: B)*
2. *Episodes of sustained monomorphic VT associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) should be treated with a synchronized electric shock of 100 J of initial monophasic shock energy. Increasing energies may be used if not initially successful. Brief anesthesia is desirable if hemodynamically tolerable. (Level of Evidence: B)*
3. *Sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure < 90 mm Hg) should be treated with:*
   a. *Amiodarone: 150 mg infused over 10 minutes (alternative dose 5 mg/kg); repeat 150 mg every 10 to 15 minutes as needed. Alternative infusion: 360 mg over 6 hours (1 mg/min), then 540 mg over the next 18 hours (0.5 mg/min). The total cumulative dose, including additional doses given during*

cardiac arrest, must not exceed 2.2 g over 24 hours. (Level of Evidence: B)

b. Synchronized electrical cardioversion starting at monophasic energies of 50 J (brief anesthesia is necessary). (Level of Evidence: B)

Class IIa

1. *It is reasonable to manage refractory polymorphic VT by:*
   a. Aggressive attempts to reduce myocardial ischemia and adrenergic stimulation, including therapies such as β-adrenoceptor blockade, intraaortic balloon pump use, and consideration of emergency PCI/coronary artery bypass graft surgery. (Level of Evidence: B)
   b. Aggressive normalization of serum potassium to greater than 4.0 mEq/L and of magnesium to greater than 2.0 mg/dL. (Level of Evidence: C)
   c. If the patient has bradycardia to a rate less than 60 beats/min or long QTc, temporary pacing at a higher rate may be instituted. (Level of Evidence: C)

Class IIb

1. *It may be useful to treat sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure <90 mm Hg) with a procainamide bolus and infusion. (Level of Evidence: C)*

Class III

1. *The routine use of prophylactic antiarrhythmic drugs (ie, lidocaine) is not indicated for suppression of isolated ventricular premature beats, couplets, runs of accelerated idioventricular rhythm, and nonsustained VT. (Level of Evidence: B)*
2. *The routine use of prophylactic antiarrhythmic therapy is not indicated when fibrinolytic agents are administered. (Level of Evidence: B)*
3. *Treatment of isolated ventricular premature beats, couplets, and nonsustained VT is not recommended unless they lead to hemodynamic compromise. (Level of Evidence: A)*

Implantable Cardiac Defibrillator Several trials have demonstrated a mortality benefit with the use of implantable cardiac defibrillators (ICDs) as primary prevention for sudden cardiac death in patients with chronic ischemic cardiomyopathy. The DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) investigated the used of ICD therapy early after AMI. In this study, 674 patients within 6 to 40 days after an AMI with subsequent LV dysfunction (ejection fraction < 35%) were randomized to ICD therapy or placebo. After a median follow-up period of 30 months, there was no significant difference in the mortality rate between the two groups. These results were somewhat surprising given that the highest incidence of sudden cardiac death in the VALIANT trial occurred during the first 3 months after myocardial infarction.[147]

AMI patients with LV dysfunction should not receive an ICD during the early period for prophylactic indications. ICD therapy is recommended in those who have recurrent sustained episodes of VT during the post–myocardial infarction period. A repeat assessment of LV dysfunction 30 to 40 days after the acute event should be performed, and those with an ejection fraction less than 35% should receive an ICD. Antiarrhythmic therapy has not been demonstrated to prevent sudden cardiac death in the post–myocardial infarction setting in patients without sustained ventricular arrhythmias.

STEMI patients with abnormal LV function who are not candidates for ICD implantation remain at risk for sudden cardiac death due to arrhythmia. The use of a home automated external defibrillator was studied in the Home Use of Automated External Defibrillators for Sudden Cardiac Arrest (HATS) trial.[196] The study randomized 7001 post-STEMI patients to one of two responses should cardiac arrest occur at home: conventional emergency medical service response with home cardiopulmonary resuscitation versus the use of an automated external defibrillator (AED) followed by the conventional response. Of the 450 patients who died after home cardiac arrest, there was no difference in survival between conventional resuscitation and home AED use (6.5% vs 6.4%; $P = .77$). At this time, data do not support the recommendation for routine AED access at home. Currently these patients may be considered for wearable defibrillators. However, more data are needed, and an ongoing trial is under way in patients with reduced LV ejection fraction and AMI (VEST) (ClinicalTrials.gov identifier: NCT01446965). A scientific statement also provides impetus for more data on use of wearable defibrillators.[197]

The clinical practice guidelines recommend the following[29]:

Implantable Cardioverter-Defibrillator Therapy Before Discharge
Class I

1. *Implantable cardioverter-defibrillator (ICD) therapy is indicated before discharge in patients who develop sustained VT/VF [ventricular fibrillation] more than 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities. (Level of Evidence: B)*

Assessment of Risk for SCD: Recommendation

Class I

1. *Patients with an initially reduced LVEF [LV ejection fraction] who are possible candidates for ICD therapy should undergo reevaluation of LVEF 40 or more days after discharge (Level of Evidence: B)*

CARDIAC REHABILITATION

Rehabilitation after myocardial infraction is an important aspect of secondary prevention and is described in Chap. 45.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION MIMIC: TAKOTSUBO SYNDROME

Takotsubo syndrome (stress-related or apical ballooning) is characterized by transient systolic and diastolic dysfunction that is often preceded by physical or emotional triggers. Takotsubo syndrome was first described in Japan in 1990[198] and is derived from a Japanese word that means "octopus pot," named for the fishing pot with a narrow neck and wide base that is used to trap octopus, to describe the characteristic ballooning of the LV apex. The regional dysfunction of the left ventricle is transient, extends beyond the territory perfused by a single coronary artery, and occurs in the absence of angiographically obstructive coronary artery disease or plaque rupture on imaging or histopathologic evaluation. The left ventricle in its most common typical form demonstrates hypokinesis or akinesis of mid and apical segments, while the basal walls remain hyperkinetic.

EPIDEMIOLOGY

There has been increasing recognition of this syndrome since its initial description. Across multiple series, stress cardiomyopathy occurs in 1% to 2% of patients presenting with STEMI or troponin-positive ACS. Of 2944 patients who underwent left heart catheterization and

presented with troponin-positive ACS, 1.2% (35 patients) presented with wall motion abnormalities typical of this syndrome.[199] In a systematic review of 14 studies (from 1996 to 2005), Gianni and colleagues[200] described apical ballooning in 2% of patients presenting with STEMI. There were 6837 (0.02%) patients diagnosed with takotsubo syndrome among 33,506,402 hospitalizations in a recent Nationwide Inpatient Sample (NIS).[201] The incidence of hospitalization with takotsubo syndrome increased more than 4- to 19-fold from 2006 to 2012 in the NIS.[202,203] Similarly, hospitalization rates for Medicare fee-for-service beneficiaries with principal and secondary diagnosis of takotsubo syndrome increased from 5.7 per 100,000 person-years in 2007 to 17.4 in 2012, but whether the increase represents greater recognition or a true epidemiologic trend is unclear.[204]

PATHOGENESIS

The underlying mechanisms of takotsubo syndrome remain unknown. The association of Takotsubo syndrome with physical and emotional stressors and its presence in conditions with catecholamine excess (pheochromocytoma, dobutamine stress echocardiography) point to a pathophysiologic role of catecholamine. Plasma catecholamine levels in 13 patients with stress-related cardiomyopathy were elevated when compared to 7 patients with Killip class III myocardial infarction[205]; however other studies do not report similar increase in the levels of adrenergic hormones.[206] In eight patients with takotsubo syndrome who underwent serial endomyocardial biopsies during the acute and recovery phases, Nef and colleagues[207] observed contraction bands and increases in cytoplasmic proteins and glycogen without evidence of cell death, suggesting catecholamine-mediated microcirculatory disturbance inducing ischemia and direct catecholamine myocardial toxicity. The mechanisms underlying the association of sympathetic overactivity and myocardial ischemia could be caused by resultant vasoconstriction; however, the results are conflicting. In a study of 30 patients with takotsubo syndrome from Japan, coronary angiography revealed spontaneous coronary artery spasm in 3 patients, and among 14 patients, ergonovine or acetylcholine induced single (n = 4) or multivessel (n = 6) spasms.[206] In a meta-analysis, spontaneous multivessel spasm was uncommon (3 of 212 patients; 1.4%), and results of spasm on provocation varied and ranged from 9% to 100%, indicating involvement of other underlying potential mechanisms.[200] Reversible myocardial dysfunction can result from multivessel coronary spasm; however, in its absence, diffuse coronary microvascular impairment has been put forward as an explanation for the dynamic nature and more extensive myocardial involvement. Elesber and colleagues[208] noted abnormal myocardial perfusion in 29 of 42 patients (69%) presenting with takotsubo syndrome, which correlated with the extent of myocardial injury. Measurement of coronary microcirculation assessed by coronary flow velocity reserve and deceleration time of diastolic velocity were abnormal in patients with takotsubo syndrome and recovered 3 weeks later during remeasurement, suggesting a role of abnormal coronary microcirculation in the pathogenesis of takotsubo syndrome.[208] In another study from the Mayo Clinic, 10 patients underwent coronary epicardial and microvascular response to intracoronary acetylcholine. Six patients demonstrated epicardial vasoconstriction, and seven (70%) had < 50% increase in coronary blood flow, indicating abnormal microvascular response.[209]

There is no proven pathophysiologic mechanism to explain the unique cardiac appearance in takotsubo syndrome. In a rat model, Paur and colleagues[210] demonstrated apical-basal gradients with higher apical β_2-adrenergic receptor density and sensitivity than basal cardiomyocytes, which can explain mid and apical myocardial predilection. Inability of norepinephrine at similar or higher doses to initiate stress-related cardiomyopathy excluded the possibility of coronary vasospasm or role of β_1-adrenergic–mediated signaling in its pathophysiology.[210]

PRESENTATION

Clinical

Takotsubo syndrome typically affects postmenopausal women. The International Takotsubo Registry reported 89.8% of women (mean age, 66.8 years) among 1750 patients with this diagnosis.[211] In the NIS sample, 90% of patients with Takotsubo syndrome were women, and 90% were older than 50 years.[201] In the Swedish Coronary Angiography and Angioplasty Register, between 2009 and 2013, among 505 patients diagnosed with Takotsubo syndrome, 87.5% of patients were women, with a mean age of 67 years.[212] In a cohort of 136 consecutive patients with takotsubo syndrome, about one-third were male, ≤ 50 years old, without a stressor, or with in-hospital death, nonfatal recurrence, embolic stroke, or delayed normalization of ejection fraction, underscoring the clinical and demographic diversity of takotsubo syndrome at presentation.[213]

Patients with takotsubo syndrome typically present with clinical and ECG features indistinguishable from more common ACS (angina, shortness of breath, palpitations, syncope, or cardiogenic shock) occurring as a consequence of plaque rupture; however, patients with takotsubo syndrome may describe a wave of pressures from the chest to the neck or head, consistent with the catecholamine surge frequently associated with diaphoresis and heightened anxiety.[214] In the largest takotsubo registry, chest pain (75.9%), dyspnea (46.9%), and syncope (7.7%) were the predominant symptoms.[211]

Electrocardiographic

ECG findings are insufficient to differentiate between AMI and takotsubo syndrome.[215] The ECG changes are transient and resolve within months in most cases. In the International Takotsubo Registry, 90% of patients with takotsubo syndrome had sinus rhythm, and patients with takotsubo syndrome had similar rates of STEMI (31.1%) and lower rates of ST-segment depression compared with patients with ACS.[211] In a study from the Mayo Clinic, anterior STEMI or new LBBB was absent in two-thirds of patients with takotsubo syndrome; these patients presented with deep T-wave inversion (30%; > 3 mm in three contiguous leads) or nonspecific ST-T–wave abnormalities.[216] Subsequent T-wave inversion and Q-wave formation also are frequently noted with this syndrome. Most series have reported anterior STEMI at the time of presentation in > 90% of patients, which rapidly evolved into deep symmetrical T-wave inversions within 24 to 48 hours associated with prolongation of the QT interval and transient anteroseptal Q waves.[217]

Triggers

Physical or emotional triggers such as unexpected death in the family, abuse, fierce argument, financial loss, and natural disasters (earthquakes), among others, typically precede the presentation of patients with takotsubo syndrome (Table 40–9).[214,218] The incidence of triggers varies among different series and ranges from 14% to 100%.[199,206,213,219-223]

In the International Takotsubo registry,[211] neurologic or psychiatric disorders were present in more than half of patients with takotsubo syndrome (55.8%), and these disorders were evident in only 25.7% of patients presenting with ACS ($P < .001$).

The distinction between primary or principal versus secondary diagnosis of takotsubo syndrome is important because outcomes for secondary diagnosis of takotsubo syndrome are likely driven by the primary reason for hospitalization.[7,17] Patients with takotsubo syndrome

Table 40–9. Stressors Reported to Trigger Apical Ballooning Syndrome

Emotional stress
Death or severe illness or injury of a family member, friend, or pet
Receiving bad news—diagnosis of a major illness, daughter's divorce, spouse leaving for war
Severe argument
Public speaking
Involvement with legal proceedings
Financial loss—business, gambling
Car accident
Surprise party
Move to a new residence
Physical stress
Noncardiac surgery or procedure—cholecystectomy, hysterectomy
Severe illness—asthma or chronic obstructive airway exacerbation, connective tissue disorders, acute cholecystitis, pseudomembranous colitis
Severe pain—fracture, renal colic, pneumothorax, pulmonary embolism
Recovering from general anesthesia
Cocaine use
Opiate withdrawal
Stress test—dobutamine stress echo, exercise sestamibi
Thyrotoxicosis

Reproduced from Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J*. 2008;155:408-417.

with principal diagnoses of ACS more likely represent primary coronary presentations, whereas hospitalizations with secondary diagnoses of takotsubo syndrome reflect underlying acute medical illness as the primary reason for admission, and in the latter situation, acute medical illness precipitates takotsubo syndrome. Patients with secondary diagnosis have worse short- and long-term prognosis.[224]

DIAGNOSIS

Approach

In a patient presenting with suspected ACS (particularly postmenopausal women), the diagnosis of takotsubo syndrome rests on the reversible nature of the LV dysfunction and its extension beyond single epicardial coronary distribution; absence of any evidence of culprit atherosclerotic coronary artery disease; significant increase in natriuretic peptide; and a positive but relatively small elevation of serum troponin levels (Table 40–10). The clinical manifestations and electrocardiographic abnormalities are generally out of proportion to the degree of elevation in cardiac biomarkers. An identifiable physical or emotional trigger is often, but not always, present.

The diagnosis of takotsubo syndrome generally requires coronary angiography, serial assessment of LV systolic function (initial assessment generally by ventriculography or echocardiography with subsequent assessment by echocardiography), an ECG, and cardiac troponin level. Several diagnostic criteria have been proposed, including those by the Mayo Clinic (modified in 2008), the Japanese Takotsubo Cardiomyopathy Group, the Gothenburg Group, and the Takotsubo Italian Network and, more recently, by the Heart Failure Association of the ESC (see Table 40–10).

Special Considerations

Coronary Artery Disease Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture is an important criterion; however, the diagnosis of takotsubo syndrome can still be made in the presence of coronary artery disease if the wall motion abnormalities are not in the distribution of the coronary disease. This exception is made because some patients with stress cardiomyopathy have concurrent coronary disease (15.3% in the International Takotsubo Registry, 9.6% in the Takotsubo Italian Network Registry).[225]

Pheochromocytoma Catecholamine surge triggers reversible LV dysfunction and is encountered in about 10% of cases of pheochromocytoma. Most diagnostic criteria for takotsubo syndrome exclude patients with pheochromocytoma, myocarditis, intracranial bleed, or significant coronary artery disease. The pathophysiology and clinical phenotype of pheochromocytoma are identical with takotsubo syndrome, and such patients were included in the recent Heart Failure Association criteria as cases of secondary takotsubo syndrome. Patients with pheochromocytoma presenting with takotsubo syndrome were younger (fourth to fifth decade), had fewer antecedent stressors, had a lower incidence of typical features of pheochromocytoma (headache, palpitations, diaphoresis, and hypertension), and had higher presentation with shock.[226]

Myocarditis Distinction of myocarditis from takotsubo syndrome is sometimes difficult, especially when myocardial edema and inflammation overlap in the anatomic distribution seen in patients with acute takotsubo syndrome.[227-229] A careful history of antecedent viral illness, rise in inflammatory markers, diffuse ventricular involvement on echocardiogram or LV angiogram, late gadolinium enhancement with nonischemic distribution, and inflammatory cells on myocardial biopsy help differentiate myocarditis from takotsubo syndrome.[214]

Biomarkers and Takotsubo Syndrome

Cardiac Biomarkers Serum cardiac troponin levels are elevated in most (> 90%) patients with takotsubo syndrome (eg, median initial troponin of 7.7 times the upper limit of normal with an interquartile range of 2.2 to 24 in the International Takotsubo Registry study); however, the rise in troponin or creatinine kinase is disproportionately low relative to the extent of regional wall abnormality or LV dysfunction.[230] In contrast, levels of brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) are elevated in most patients with stress cardiomyopathy. BNP levels were elevated in 82.9% of patients with takotsubo syndrome in the International Takotsubo Registry study, with a median level 6.12 times the upper limit of normal (interquartile range, 2.12-15.70), and exceeded those seen in a matched cohort of patients with ACS. Best differentiation of takotsubo syndrome and ACS is possible by determining a ratio between peak levels of NT-proBNP (ng/L) to troponin T (μg/L). A cut-off value of NT-proBNP (ng/L)/troponin T (μg/L) ratio of 2889 distinguished takotsubo syndrome from ST-elevation myocardial infarction (sensitivity: 91%; specificity: 95%), whereas an NT-proBNP (ng/L)/troponin T (μg/L) ratio of 5000 distinguished well between takotsubo syndrome and non–ST-segment elevation myocardial infarction (sensitivity: 83%; specificity: 95%).[231]

Radionuclide Myocardial Perfusion Imaging Radionuclide myocardial perfusion imaging is generally not indicated in patients presenting with suspected takotsubo syndrome because most have high-risk features for ACS (eg, elderly, elevated cardiac troponin levels) and will require coronary angiography. Patients with suspected non–ST-segment elevation ACS with low- or intermediate-risk features may undergo radionuclide myocardial perfusion imaging. Hypocontractile LV segments demonstrate normal perfusion but reduced uptake of ^{18}F-fluorodeoxyglucose

TABLE 40–10. Diagnostic Criteria of TC

Diagnostic Criteria	Initial Mayo Clinic[217]	Revised Mayo Clinic[218]	Japanese[268]	Gothenburg[269]	Hopkins[270]	Italian Network[271]	Madias[272]	European Society of Cardiology[214]
An acute identifiable trigger (either emotional or physical)	–	+	+	+	+	+ (optional)	+	+
Transient akinesis/dyskinesis of the left apical and midventricular segments with regional wall motion abnormalities extending beyond a single epicardial vascular distribution	+	+	+	+	Mandatory	+	+	+
Recovery of ventricular systolic function on cardiac imaging at follow-up (3-6 months)	–	–	+ (within 1 month)	–	+ Mandatory criteria recovery in days to weeks	+ (6 weeks)	–	+ (3-6 months)
Dynamic LV obstruction	–	–	+	–	–	–	–	–
RV involvement	–	–	+		–	–	+	–
Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture	+	+	+	–	Mandatory criteria (absence of coronary thrombosis or plaque rupture)	+	Ischemia, myocarditis, toxic damage, and tachycardia (among others) that may more credibly explain the regional dysfunction	+
Normal or near-normal left ventricular filling pressure	–	–	–	+	–	–		+
New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion)	+	+	+	–	+	+	+	+
Diffuse deep T-wave inversion (may be present on admission or may evolve during the first several hospital days)	+	+	+	–	+	+	+	+
QT interval prolongation (usually maximal by 24-48 h)	–	–	+	–	+	–	+	+
Absence of							Absence of ischemia, myocarditis, toxic damage, and tachycardia	
Recent significant head trauma	+			Conditions that can explain regional dysfunction				
Intracranial bleeding			+ (Cerebrovascular disease)					
Pheochromocytoma	+							
			+					
	+							
Obstructive epicardial coronary artery disease		+						
			+				+	
Myocarditis	+							
			+					
				+				
Hypertrophic cardiomyopathy	+							
		+				+		
	+							
No elevation or modest elevation in cardiac troponin (ie, disparity between the troponin level and the amount of dysfunctional myocardium)	–	+	+	+	–	CK–MB < 50 U/L	–	+
Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase	–	–	–	–	–	–	–	+

Abbreviations: BNP, B-type natriuretic peptide; CK-MB, creatine kinase myocardial band; LV, left ventricular; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RV, right ventricular.

and ^{123}I-metaiodobenzylguanidine (MIBG).[232-234] The extent of the metabolic defects and innervation abnormalities are overlapping, and with improvement in LV function, progressive improvement of both glucose metabolism and sympathetic innervation is noted. A recent study evaluated cardiac sympathetic activity by MIBG scan in 32 patients who presented with initial symptoms and signs closely mimicking those of takotsubo syndrome with suspicion of ST-segment elevation ACS. The major findings were that patients with takotsubo syndrome showed cardiac hypersympathetic activity (decreased heart-to-mediastinal ratio and increased washout rate on MIBG scan) in the subacute phase, compared with their recovery at 4 months.[235]

Cardiac Magnetic Resonance Imaging Cardiac magnetic resonance imaging is helpful in borderline cases, especially when the distinction needs to be made from myocarditis. In a prospective study of 256 cases of takotsubo syndrome, cardiovascular magnetic resonance imaging data (available for 239 patients [93%]) revealed four distinct patterns of regional ventricular ballooning: apical (n = 197 [82%]), biventricular (n = 81 [34%]), midventricular (n = 40 [17%]), and basal (n = 2 [1%]); and accurately identified all cases using specific criteria: a typical pattern of LV dysfunction, myocardial edema, absence of significant necrosis/fibrosis, and markers for myocardial inflammation.[236] Follow-up cardiovascular magnetic resonance imaging showed complete normalization of LV ejection fraction and inflammatory markers in the absence of significant fibrosis in all patients.

Traditionally, the absence of late gadolinium enhancement (LGE) is a common diagnostic criterion for takotsubo syndrome.[236] Subtle fibrosis presenting as LGE may be seen in patients with takotsubo syndrome; however, the myocardial scarring is patchy, and the signal intensity and extent of the late gadolinium enhancement are smaller.[237] Absence of significant late gadolinium enhancement combined with myocardial edema and marked ballooning of the left ventricle is a unique feature of takotsubo syndrome. The inverse flow metabolism mismatch noted with positron emission tomography in patients with takotsubo syndrome has not been well studied.[238]

Coronary and Left Ventricular Angiography and Echocardiography Coronary angiography is indicated in most patients because of their high-risk presentation with ECG abnormalities and elevation of cardiac biomarkers. Incidental coronary artery disease can be present in up to 10% of cases; however, characteristics of coronary angiography and intravascular ultrasound in patients with takotsubo syndrome include absence of plaque rupture, thrombus, and coronary dissection.[239-241] In addition, degree and type of LV dysfunction on LV angiography exceed the angiographic findings. LV angiography should be performed as soon as a diagnosis of takotsubo syndrome is suspected. If LV angiography cannot be performed, transthoracic echocardiography is the preferred noninvasive imaging technique. Advantages of echocardiography include confirmation of findings of LV angiography without the need of contrast administration, right ventricle involvement, and mechanical complication (rupture), and detection of mitral regurgitation and LV outflow obstruction.[242-244] In the Italian Takotsubo Network, echocardiographic features like low ejection fraction, elevated E/e′ ratio, reversible moderate-to-severe mitral regurgitation, and age ≥ 75 years were independent risk factors for acute heart failure, cardiogenic shock, and in-hospital death.[245] Echocardiogram can be safely repeated to demonstrate timeline and degree of improvement of LV function.

Ventricular Dysfunction and Variants Ubiquity and reversibility of LV dysfunction are the hallmarks of takotsubo syndrome. Reduced LV ejection fraction (mean 40.7% ± 11.2%) was noted in 86.5% of patients with takotsubo syndrome on admission but in only 54.2% of patients with an ACS in the International Takotsubo Registry. In a systematic review of 14 studies, the LV function ranged from 20% to 49%.[200] Lower ejection fraction is also a predictor for cardiogenic shock. This complication is noted in 2.8% to 12.4% of patients with takotsubo syndrome.[246-249] The focus of most studies of takotsubo syndrome is on LV dysfunction; however, there is evidence that about one-third of cases involve both right and left ventricles.[236] Based on LV angiography or transthoracic echocardiography, takotsubo syndrome is classified as one of the following five types (Fig. 40–6).[211]

Apical Type The left ventricle regional wall motion abnormality, as seen using the echocardiogram or LV angiography, is one of the characteristic features of takotsubo syndrome. Among the several patterns, the apical type is most common and is characterized by systolic apical ballooning of the left ventricle, reflecting depressed mid and apical segments with hyperkinesis of the basal walls. This type was present in 81.7% of patients in the International Takotsubo Registry study.

Midventricular Type In this type of takotsubo syndrome, the base and apical portions of the left ventricle are spared, with ventricular hypokinesis restricted to the mid-ventricle. This type was present in 14.6% of patients in the International Takotsubo Registry study.

Basal Type This type is also referred to as reverse or inverted takotsubo syndrome and is characterized by hypokinesis of the base with sparing of the mid-ventricle and apex. This type was present in 2.2% of patients in the International Takotsubo Registry study.

Focal Type This rare variant is characterized by isolated dysfunction of the left ventricle, commonly the anterolateral segment. This type was present in 1.5% of patients in the International Takotsubo Registry study.

Global Type Rarely, patients with takotsubo syndrome have global hypokinesis.

TREATMENT

Overview

The presentation of patients with takotsubo syndrome overlaps with that of patients presenting with ACS. Clinical suspicion of takotsubo syndrome should not delay the management because presentation in a significant majority of these patients is a result of plaque rupture that would benefit from early reperfusion. Patients with ST elevation on ECG should undergo urgent cardiac catheterization with the aim to perform primary PCI. The diagnosis of takotsubo syndrome should be suspected if coronary angiography fails to demonstrate critical coronary artery disease especially with features of plaque rupture. LV angiography showing apical ballooning or mid-wall hypokinesis confirms the diagnosis of takotsubo syndrome. In patients treated with fibrinolytic therapy, subsequent angiogram without significant coronary artery disease favors the diagnosis of takotsubo syndrome; however, recanalization of the infarct-related artery with recovery of LV function and ACS with intact fibrous cap blurs the distinction between takotsubo syndrome and ACS.[250] Patients without ST-segment elevation with high-risk features (eg, age, positive biomarkers, congestive heart failure) may merit early coronary angiography that would help the clinicians make the diagnosis of takotsubo syndrome.

Stable or Low-Risk Patients

The major objective of treatment in patients with takotsubo syndrome is to support the left ventricle and manage complications during the acute phase of presentation. Management of heart failure during acute presentation should follow the standard guidelines and should include β-blockers and ACE inhibitors. Recommendations for anticoagulation to prevent thromboembolism in patients with takotsubo syndrome are similar to those for patients with ventricular thrombus in the setting of ACS.

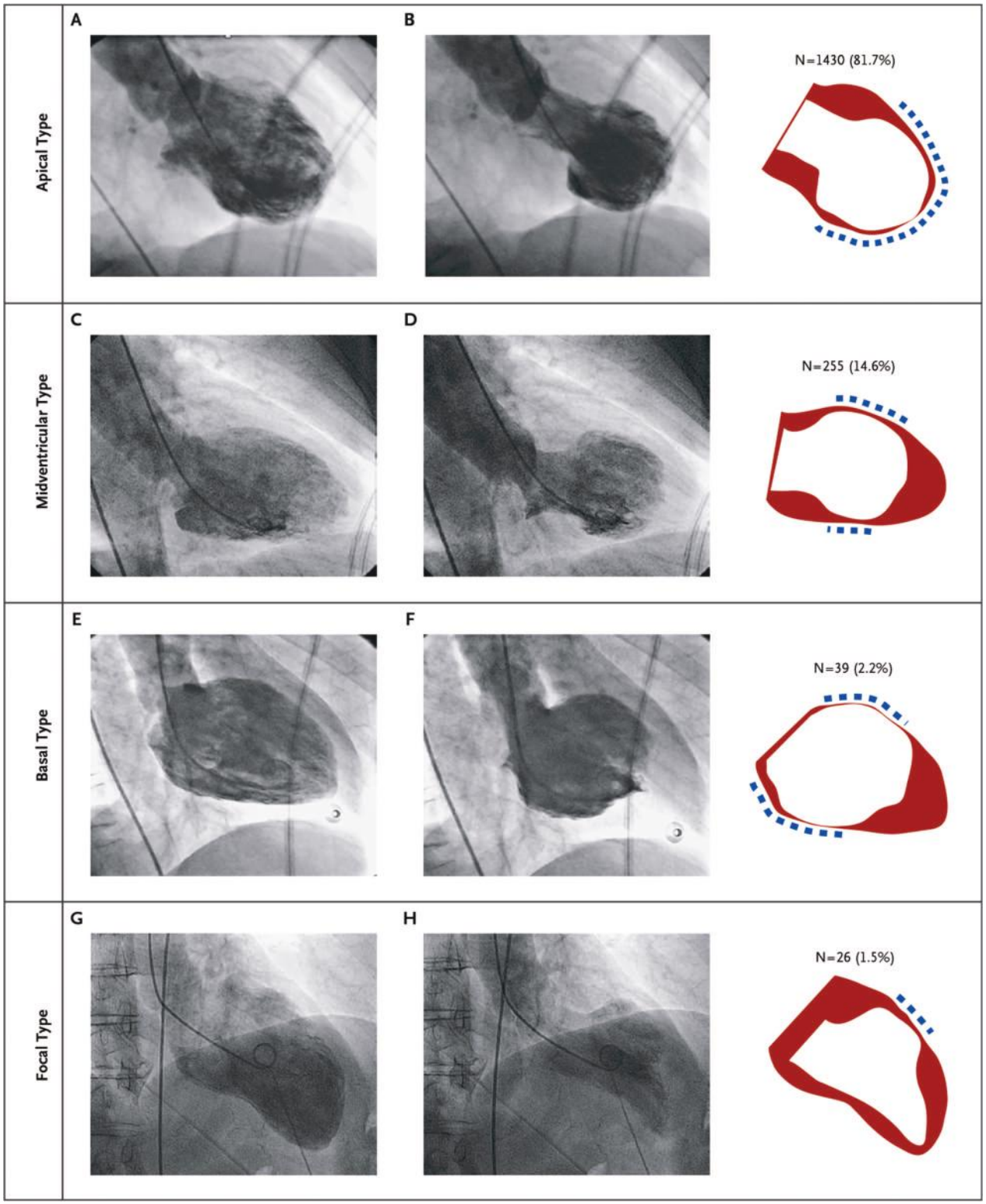

FIGURE 40–6. Four types of takotsubo syndrome. Among the 1750 study patients, the most common type of takotsubo syndrome was the apical type (in 81.7% of patients) (**A** and **B**), followed by the midventricular type (in 14.6% of patients) (**C** and **D**), the basal type (in 2.2% of patients) (**E** and **F**), and the focal type (in 1.5% of patients) (**G** and **H**). All left ventricular angiograms were obtained in the right anterior oblique view (30 degrees) during diastole (*left column*) and systole (*middle column*). In the *far right column*, the wall motion abnormality that was observed with each type of the disorder is shown, with *red* indicating diastole, *white* indicating systole, and the *dashed line* indicating the location of the wall motion abnormality.

High-Risk Patients

Heart Failure Heart failure should be managed in the critical care setting with continuous ECG monitoring. Systolic heart failure is the most common complication during the acute phase. Independent predictors of acute heart failure are advanced age, low ejection fraction at presentation, higher admission and peak troponin levels, and a physical stressor preceding the onset of symptoms.[214] Acute systolic failure, especially in the setting of cardiogenic shock, may require assessment of LV outflow tract. LV outflow obstruction with gradients ranging between 20 and 140 mm Hg has been observed in 10% to 25% of patients.[251] In addition, dynamic outflow tract obstruction caused by hyperkinesis of the basal LV segments and the resultant systolic anterior motion of the mitral valve may cause and/or worsen hypotension. Patients with takotsubo syndrome who have hypotension or are in shock should get urgent echocardiography to rule out LV outflow obstruction. Increase in preload with judicious use of intravenous fluids and reduction in myocardial contractility with short-acting β-blockers are helpful. Peripheral vasoconstrictors such as phenylephrine can be given if β-blockers or fluid administration are contraindicated or ineffective. Mitral regurgitation and outflow obstruction improve with improvement in the LV function.

Patients with hypotension and shock but without significant LV outflow obstruction should receive cautious fluid resuscitation and mechanical support with temporary left ventricle assist devices and extracorporeal membrane oxygenation.[252,253] The use of inotropes (dopamine, dobutamine, epinephrine, or norepinephrine) is generally contraindicated because these agents further activate the catecholamine receptors and worsen the clinical status and prognosis of these patients.[254] IABP may worsen the LV outflow obstruction and should be avoided.[214] The use of levosimendan, a noncatecholaminergic inodilator, has been studied in small series, and its role in the management of patients with takotsubo syndrome with acute systolic heart failure is ill defined.[255]

Arrhythmias Arrhythmias such as atrial fibrillation (seen in 5%-15%), VT, and ventricular fibrillation (seen in 5%-9%) are not uncommon in takotsubo syndrome.[248,256-258] In a systematic review, life-threatening arrhythmias such as third-degree atrioventricular block, VT, ventricular fibrillation, and cardiac arrest were seen in 37 of 353 patients (14.6%; 95% CI, 10.9%-18.3%).[230] In the International Takotsubo Registry, VT, thrombus, and cardiac rupture were seen in 3.0%, 1.3%, and 0.2% of patients, respectively.[211] Atrial arrhythmias can worsen the cardiac output and heart failure, whereas ventricular arrhythmias can cause cardiac arrest in 4% to 6% of patients, and the standard guidelines for treatment should be followed.

Left Ventricular Thrombus Significant LV dysfunction is a nidus for thrombus formation. It is seen in 2% to 8% of patients presenting with takotsubo syndrome and can result in peripheral arterial embolism.[248] Most thrombi develop within the first week; however, thrombus formation at 2 weeks after symptom onset has been described.[259,260] Once recognized, patients should be treated with oral anticoagulation for 3 months. Follow-up imaging is recommended to confirm recovery of apical contractile function.

RECOVERY OF LEFT VENTRICULAR FUNCTION

Complete recovery of LV systolic function is necessary to confirm the diagnosis of takotsubo syndrome. The recovery time varies and can be as short as several days or as long as several weeks. In the International Takotsubo Registry, mean LV ejection fraction increased from 41.1% at admission to 51.2% prior to discharge before reaching normal values (59.9%) at 60-day follow-up.[211] It is recommended to follow the same approach to treat LV systolic dysfunction as that for other causes of cardiomyopathy (with ACE inhibitors and β-blockers), at least until LV systolic function recovers.

RECURRENCE

Recurrence rates following an index episode are approximately 10%. Five-year recurrence rates of 5% to 22% have been noted.[217,218,257,261] The rate of recurrence in the International Takotsubo Registry was 1.8% per patient-year, with a span of 25 days up to 9.2 years following the index episode.[211] A study from the Mayo Clinic detected a recurrence rate of 11.4% in 100 patients at a mean follow-up of 4.4 ± 4.6 years. In that study, the mortality rate was 16%, which was similar to an age- and sex-matched local population.[247]

PROGNOSIS

Previously, the prognosis of takotsubo syndrome was considered benign,[262] and a meta-analysis showed that only 1.1% of reported patients died during the index hospitalization.[200] In a study from the Mayo Clinic, 4-year survival was not different from that of an age- and gender-matched population.[247] These observations could be a result of small sample size of previous studies, selection bias with inclusion of lower risk patients, and rapid recovery of LV function. However, worse short- and long-term prognosis has been recently reported. A Swedish registry study found a 30-day mortality of 4% in 302 patients with takotsubo syndrome, which was similar to patients presenting with non–ST-segment elevation myocardial infarction but lower to patients with STEMI.[263] The International Takotsubo Registry reported a 30-day mortality of 5.9%.[211] The rate of death during long-term follow-up was 5.6% per patient-year, and men had a higher incidence of short- and long-term mortality and morbidity as compared to women. Data from a large, multicenter registry suggested better outcomes for elderly patients with emotional triggers and a worse prognosis for younger patients with physical triggers and emotional or psychiatric diseases. Furthermore, a recent bicentric study in 286 prospectively identified patients with takotsubo syndrome revealed 28-day, 1-year, and long-term mortality rates of 5.5%, 12.5%, and 24.7%, respectively.[264] Long-term mortality was noted to be higher as compared to patients with STEMI (24.7% vs 15.1%; hazard ratio, 1.58; 95% CI, 1.07-2.33; $P = .02$). These findings challenge the initial notion of a favorable prognosis in patients presenting with takotsubo syndrome. Prognosis of patients presenting with secondary takotsubo syndrome is worse compared with patients presenting with ACS (primary or principal takotsubo syndrome). Murugiah et al[204] examined the US Medicare database and reported 30-day and 1-year mortality rates of 2.5% and 6.9% for patients with principal takotsubo that compared favorably to rates of 4.7% and 11.4% for patients with secondary takotsubo, respectively.[204] Excess mortality dominantly occurs in the first 4 years after diagnosis, is noncardiac, and is largely a result of illnesses such as malignancy.

FOLLOW-UP

The follow-up of patients with takotsubo syndrome is no longer considered favorable. The novel insights gleaned from recent studies confirm that patients are prone to severe complications during the acute and subacute phases of the disease, including heart failure, cardiogenic shock, life-threatening arrhythmias, or thromboembolic complications. Therefore, the latest position statement from the ESC suggests close monitoring in coronary care units, in a similar fashion as recommended for patients with ACS. The ESC recommends documentation of recovery of LV function, and ECG changes should be documented during regular follow-up visits.[214]

CONCLUSION

Despite the numerous improvements in the management of STEMI, it remains one of the leading causes of morbidity and mortality worldwide. The key steps in the management of STEMI patients include rapid diagnosis, prompt delivery of initial therapeutic agents, immediate reperfusion, and diligent in-hospital management, which includes the aggressive implementation of secondary prevention strategies. Future improvements in each of these categories, some of which are logistical, need to be made if any significant reductions in the morbidity and mortality are to be obtained. The persistently high mortality of myocardial infarction in the elderly provides a formidable but highly important challenge for the future.

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CHAPTER 41

ANTIPLATELET AND ANTICOAGULANT THERAPY IN ACUTE CORONARY SYNDROMES

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ANTICOAGULATION FOLLOWING THE ACUTE PHASE OF ACUTE CORONARY SYNDROME / 1095
- Oral Vitamin K–Dependent Anticoagulants / 1095
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Acute coronary syndromes (ACS), including non ST-elevation (NSTE) ACS (unstable angina [UA]/non–ST-segment elevation myocardial infarction [NSTEMI]), and ST-segment elevation myocardial infarction (STEMI), represent the clinical complications of atherosclerosis mediated by plaque rupture, fissure and superficial endothelial cell erosion that produce nonocclusive and occlusive thrombus formation.[1-3] NSTEMI accounts for more than 1.6 million annual admissions, representing up to 75% of all cases of myocardial infarction (MI) in US hospitals.[4] Appropriate care for patients with ACS is informed by a wealth of randomized controlled trials, the findings of which have been summarized into national clinical practice guidelines by the American College of Cardiology (ACC)/American Heart Association (AHA)[4-6] and the European Society of Cardiology (ESC).[7-9] This chapter will review the pharmacology of antiplatelet, anticoagulant, and fibrinolytic agents and also focus on evidence-based recommendations for the use of antithrombotic therapy in ACS. Given the evolving understanding of the prognostic implications, including mortality, associated with the most important adverse effect associated with antithrombotic agents (ie, bleeding), an assessment of the net clinical benefit of a particular antithrombotic agent—namely, balancing efficacy and safety—will be elaborated.[10-14] Bleeding complications are secondary to multiple factors including impaired oxygen delivery, adverse effects of transfusion (ie, proinflammatory, old vs new blood), and cessation of antithrombotic medications.[10-14] There are important sex- and age-related factors that promote bleeding as a result of excessive dosing.[15,16] Understanding the trade-off between reduction of ischemic events (ie, recurrent MI, stent thrombosis, stroke) and risk of bleeding complications associated with antithrombotic agents is essential for the practicing clinician. Recommendations from the most recent guideline updates will also be provided. Importantly, guideline adherence rate is significantly associated with in-hospital mortality. In an observational analysis of hospital care in 350 academic and nonacademic US centers of 64,775 patients enrolled in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) trial, every 10% increase in composite adherence at a hospital was associated with an analogous 10% decrease in its patients' likelihood of in-hospital mortality.[17] Thus, a thorough knowledge of pharmacologic therapy and guideline-recommended treatments is the foundation for optimizing outcomes for patients with ACS.

ANTITHROMBOTIC THERAPY: GENERALITIES

Arterial thrombosis following atherosclerotic plaque complications is the major determinant of ACS.[18] Plaque rupture, fissure, or erosion, with exposure of the subendothelium, leads to recruitment and activation of platelets, as well as generation of thrombin, which leads to the formation of a fibrin-rich thrombus. A nonocclusive or transiently occlusive thrombus most frequently characterizes patients with a NSTE-ACS, which include UA and NSTEMI.[18] More stable and occlusive thrombus prevails in STEMI.[18] Platelet-activated thrombosis follows three main steps: (1) platelet adhesion, (2) platelet activation and additional recruitment, and (3) platelet aggregation.[19,20] Platelet adhesion during the rolling phase is mediated by the interaction between von Willebrand factor (vWF) and the glycoprotein (GP) Ib/V/IX receptor complex located on the platelet surface, and between platelet collagen receptors (eg, GP VI and GP Ia) and collagen exposed at the site of vascular injury. After adhesion, intraplatelet signaling allows for enhancement of the interactions among adherent platelets and release of activation factors and promotes further recruitment and activation of circulating platelets. These activation factors include adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), serotonin, epinephrine, and thrombin. Activated platelets also lead to expression of proinflammatory molecules (eg, P-selectin and soluble CD40 ligand) and expression of platelet procoagulant activity. The final pathway for all agonists is the conversion of the platelet integrin GP IIb/IIIa ($\alpha IIb\beta 3$), the main receptor mediating platelet aggregation, into its active form. The activated GP IIb/IIIa receptors bind to the extracellular ligands fibrinogen and vWF, leading to platelet aggregation and thrombus formation mediated by platelet-platelet interactions.[19,20] In addition, vascular injury also exposes subendothelial tissue factor, which forms a complex with factor VIIa, activating the clotting cascade and leading to thrombin generation.[19-22] However, only a modest amount of thrombin is produced as a result of the coagulation cascade, and its main source

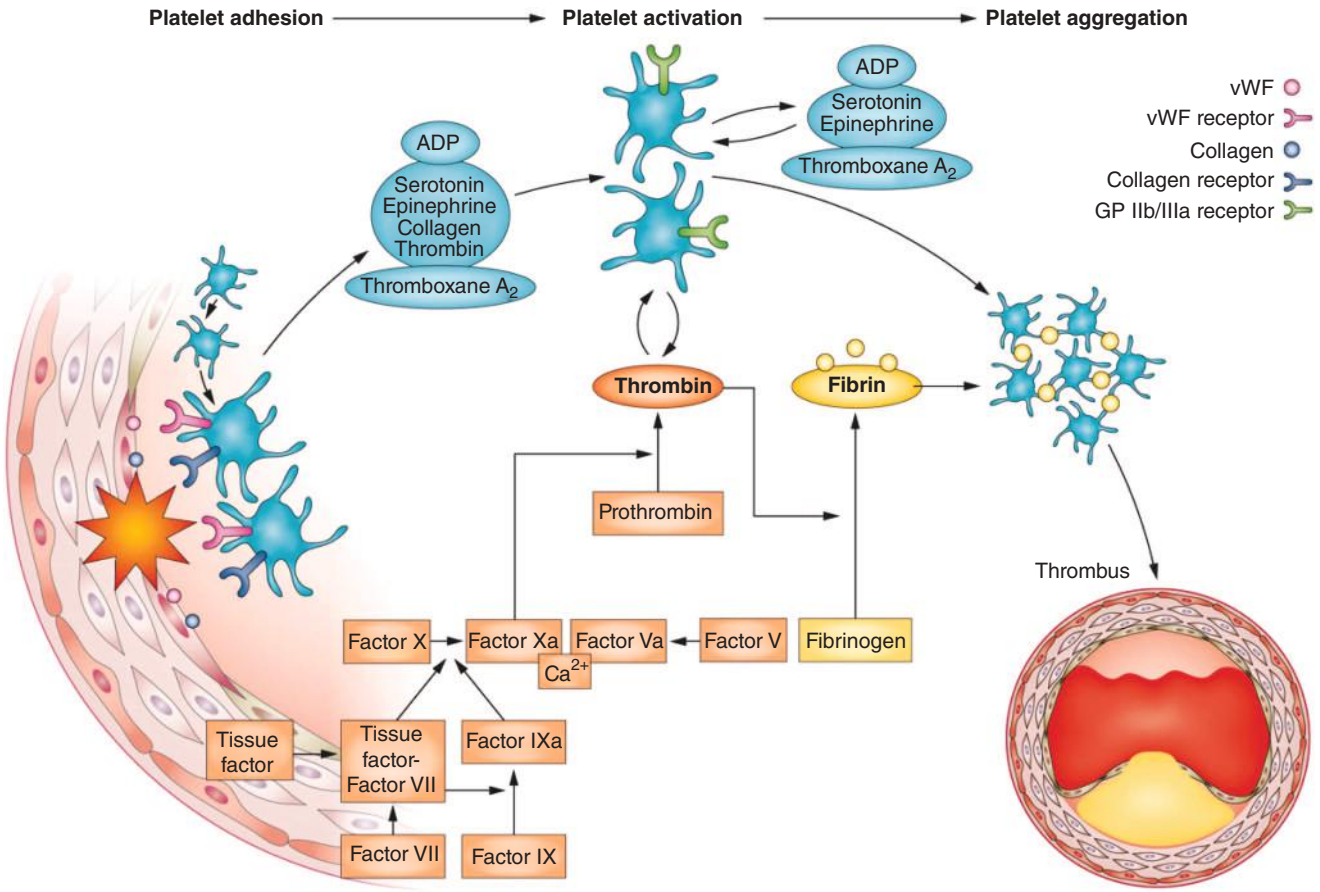


FIGURE 41–1. Mechanism of thrombus formation with platelet-thrombin-coagulation interaction. Plaque rupture exposes the subendothelium components. Platelet adhesion during the rolling phase is mediated by the interaction between the von Willebrand factor (vWF) and the glycoprotein (GP) Ib/V/IX receptor complex located on the platelet surface, and between platelets collagen receptors (GP VI and GP Ia) and collagen exposed at the site of vascular injury. Binding of collagen to the GP VI receptor triggers intracellular mechanisms that induce the release of activating factors (adenosine diphosphate [ADP], thromboxane A_2 [TXA_2], serotonin, epinephrine, and thrombin), which enhance the interactions among adherent platelets and promote further recruitment and activation of circulating platelets. Platelet activation by these factors and collagen leads to change in platelet shape, expression of proinflammatory molecules (eg, P-selectin and soluble CD40 ligand), expression of platelet procoagulant activity, and the conversion of the platelet integrin GP IIb/IIIa (αIIbβ3) into its active form. The activated GP IIb/IIIa receptors bind to the extracellular ligands fibrinogen and vWF, leading to platelet aggregation and thrombus formation mediated by platelet-platelet interactions. Vascular injury also exposes subendothelial tissue factor (TF), which forms a complex with factor VIIa. TF-VIIa complex activates factor IX and factor X. Factor V is slowly activated by factor Xa. Factor Xa then binds to factor Va and Ca^{2+} and forms the prothrombinase complex, which initiates conversion of prothrombin to thrombin (factor IIa). Only a modest amount of thrombin is produced as a result of the coagulation cascade, and its main source within a platelet plug is the surface of activated platelets. Thrombin converts fibrinogen to fibrin, generating a fibrin-rich clot, and further activates platelets, binding to the protease-activated receptor (PAR)-1 and PAR-4. Reproduced with permission from Franchi F, Angiolillo DJ: Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol*. 2015 Jan;12(1):30-47.

within a platelet plug is the surface of activated platelets. Thrombin converts fibrinogen to fibrin, generating a fibrin-rich clot, and further activates platelets, binding to protease-activated receptor (PAR)-1 and PAR-4.[19-22] Therefore, pathogenic thrombosis is a complex interplay between cellular (ie, platelets) and plasma (ie, coagulation factors) components, which interact in an autoamplified process (Fig. 41–1). These considerations underscore the need for antiplatelet and anticoagulant therapies for the treatment of patients with ACS.[19-22]

ANTIPLATELET THERAPY

Multiple receptors and signaling pathways are involved in the process leading to arterial thrombosis, which may be targeted by antiplatelet agents (Fig. 41–2).[19,20] Currently, there are four different classes of antiplatelet agents that are approved for the treatment and/or secondary prevention of recurrent events in patients with ACS: (1) cyclooxygenase-1 (COX-1) inhibitors (aspirin); (2) ADP $P2Y_{12}$ receptor antagonists (thienopyridines [ticlopidine, clopidogrel, and prasugrel] and nonthienopyridines [ticagrelor and cangrelor]); (3) GP IIb/IIIa inhibitors (tirofiban, eptifibatide, and abciximab); and (4) PAR-1 receptor antagonists (vorapaxar). Antiplatelet agents are orally administered, with the exception of cangrelor and the GP IIb/IIIa inhibitors, which are the only available for intravenous (IV) administration. These agents are mostly used in combination in patients presenting with an ACS, in particular those undergoing percutaneous coronary intervention (PCI).[19-24] Details of each of these classes of antiplatelet agents and their indications for use are provided in the following sections.

ASPIRIN

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile

Aspirin (acetylsalicylic acid) is one the most important medications used in cardiovascular medicine. In particular, aspirin irreversibly inactivates COX activity of prostaglandin H (PGH) synthase 1 and synthase 2, also referred to as COX-1 and COX-2, respectively.[25,26]

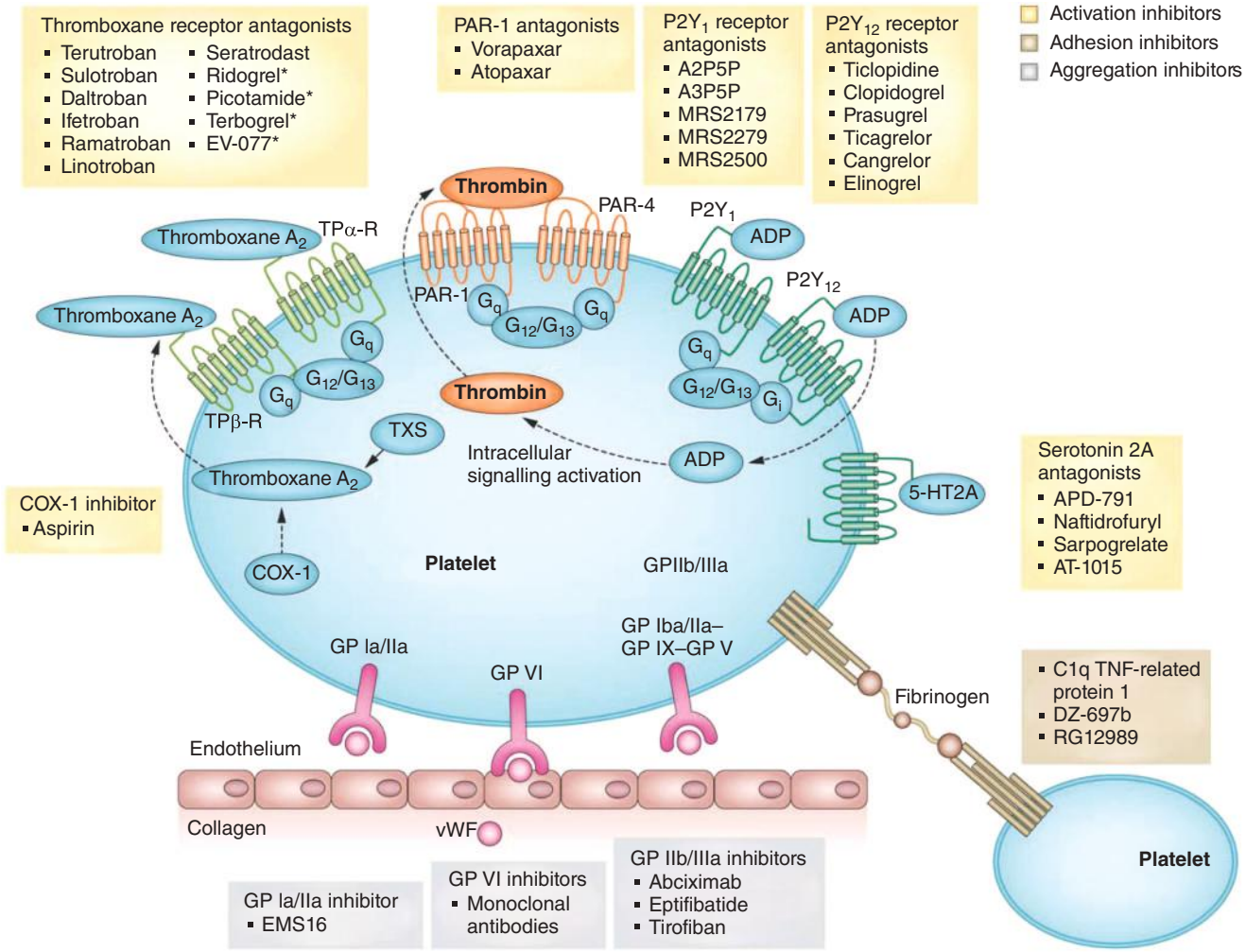


FIGURE 41–2. Platelet activation pathways and sites of action of current and emerging antiplatelet agents. Platelet adherence to the endothelium occurs at sites of vascular injury through the binding of glycoprotein (GP) receptors to exposed extracellular matrix proteins (collagen and von Willebrand factor [vWF]). Platelet activation occurs via complex intracellular signaling processes and causes the production and release of multiple agonists, including thromboxane A_2 (TXA_2) and adenosine diphosphate (ADP), and local production of thrombin. These factors bind to their respective G protein–coupled receptors, mediating paracrine and autocrine platelet activation. Further, they potentiate each other's actions ($P2Y_{12}$ signaling modulates thrombin generation). The major platelet integrin GP IIb/IIIa mediates the final common step of platelet activation by undergoing a conformational shape change and binding fibrinogen and vWF, leading to platelet aggregation. The net result of these interactions is thrombus formation mediated by platelet-platelet interactions with fibrin. Current and emerging therapies inhibiting platelet receptors, integrins, and proteins involved in platelet activation include the TXA_2 synthase inhibitors, thromboxane (TP) receptor inhibitors, the ADP receptor antagonists, the GP IIb/IIIa inhibitors, and the novel protease-activated receptor (PAR) antagonists and adhesion antagonists. 5-HT2A, 5-hydroxy tryptamine 2A receptor. Reproduced with permission from Franchi F, Angiolillo DJ: Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol*. 2015 Jan;12(1):30-47.

These isozymes catalyze the conversion of arachidonic acid to PGH2, an unstable intermediate that is the substrate for multiple downstream isomerases that lead to the generation of several prostanoids, including TXA_2 and prostacyclin (PGI_2) (Fig. 41–3A).[25,26] Aspirin diffuses through the cell membrane and enters the COX "channel," which is a narrow hydrophobic channel connecting the cell membrane to the catalytic pocket of the COX enzyme. Aspirin acetylates a serine residue (serine 529 in human COX-1 and serine 516 in human COX-2) located in the narrowest section of the channel, thus impeding arachidonic acid from gaining access to the catalytic site of the COX enzyme. Higher doses of aspirin are needed to inhibit COX-2 than to inhibit COX-1. These differences explain why very high doses of aspirin are needed to achieve anti-inflammatory and analgesic effects, whereas low doses of aspirin lead to antiplatelet effects. Vascular endothelial cells and newly formed platelets express both COX-1 and COX-2. However, only COX-1 is expressed in mature platelets. Importantly, TXA_2 (an amplifier of platelet activation and a vasoconstrictor) is derived largely from COX-1 (mostly from platelets), and its biosynthesis is highly sensitive to inhibition by aspirin, whereas vascular PGI_2 (a platelet inhibitor and a vasodilator) is derived predominantly from COX-2 and is less susceptible to inhibition by low doses of aspirin. Therefore, low-dose aspirin ultimately preferentially blocks platelet formation of TXA_2, diminishing platelet aggregation mediated by thromboxane (TP) receptor pathways. Aspirin may also inhibit thrombosis via acetylation of guanosine triphosphate binding proteins, thrombin receptors, and prothrombin.[27]

Aspirin is rapidly absorbed in the upper gastrointestinal tract and is associated with measurable platelet inhibition within 60 minutes.[25,26] The plasma half-life of aspirin is approximately 20 minutes, and peak plasma levels occur 30 to 40 minutes after ingestion. Enteric-coated aspirin delays absorption, with peak plasma levels at 3 to 4 hours.[28] Because the blockade of COX-1 induced by aspirin is irreversible, COX-mediated TXA_2 synthesis is prevented for the entire life span of the platelet (~7-10 days). Therefore, even low doses of aspirin can produce long-lasting platelet inhibition.

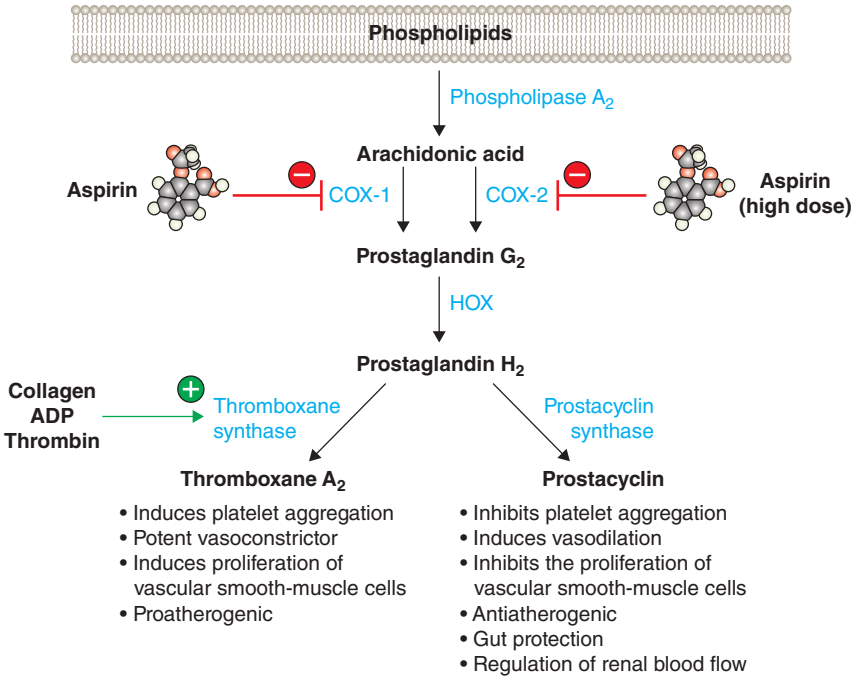


FIGURE 41–3. A. Mechanism of action of aspirin. Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is released from membrane phospholipids by several forms of phospholipase A_2, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin H synthases, which have both cyclooxygenase and hydroperoxidase (HOX) activity, to the unstable intermediates prostaglandin G_2 and prostaglandin H_2, respectively. The synthases are also termed cyclooxygenases and exist in two forms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Low-dose aspirin selectively inhibits COX-1, whereas high-dose aspirin inhibits both COX-1 and COX-2. Prostaglandin H_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell membrane receptors of the superfamily of G protein–coupled receptors, such as the thromboxane receptor, the prostaglandin D_2 receptors, the prostaglandin E_2 receptors, the prostaglandin $F_{2\alpha}$ receptors, and the prostacyclin receptor. **B.** Absolute effects of antiplatelet therapy with aspirin on the risk of vascular events. The benefit of aspirin therapy in reducing vascular events, including nonfatal myocardial infarction, nonfatal stroke, or death from vascular causes, in five groups of high-risk patients is shown. The figure is based on an analysis of data from the Antithrombotic Trialists' Collaboration. Reproduced with permission from Capodanno D, Angiolillo DJ: Aspirin for Primary Cardiovascular Risk Prevention and Beyond in Diabetes Mellitus.*Circulation*. 2016 Nov 15;134(20):1579-1594.

Dosing and Recommendations

The optimal dose of aspirin for prevention of cardiovascular events has been the subject of controversy. Pharmacodynamic studies show that aspirin may be effective in inhibiting the COX-1 enzyme at doses as low as 30 mg/d.[25,26] The Antiplatelet Trialists' Collaboration showed that a daily oral aspirin dose of 75 to 150 mg is as effective as higher doses for long-term treatments, whereas aspirin doses < 75 mg have been less widely assessed in clinical trials, and their use is generally not recommended.[29,30] Registry data show that higher doses of aspirin (> 150 mg) do not offer greater protection from recurrent ischemic events.[29,30] When given in combination with clopidogrel, the dose of aspirin should generally be lowered to 75 to 100 mg. This is based on a post hoc analysis of data from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study in which similar efficacy but less major bleeding was seen in the low-dose (< 100 mg) aspirin group.[31] It is important to note that some pharmacodynamic studies have suggested high-dose aspirin (eg, 325 mg) may be associated with enhanced antithrombotic effects as a result of COX-1–independent mechanisms.[32] However, these pharmacodynamic observations do not translate into improved clinical outcomes as tested in the first large-scale prospective randomized study to compare high- versus low-dose aspirin, the CURRENT/OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Organization to Assess Strategies in Ischemic Syndromes) trial.[33] This study included patients with ACS (n = 25,087) scheduled to undergo angiography. The study had a 2 × 2 factorial design, and patients were randomized in a double-blind fashion to high (600-mg loading dose followed by 150 mg daily for 7 days and then 75 mg daily thereafter) or standard (300-mg loading dose followed by 75 mg daily thereafter) doses of clopidogrel for a month and also included an open-label randomization to high-dose (300-325 mg daily) versus low-dose (75-100 mg daily) aspirin. The trial did not show significant differences in efficacy between high- and low-dose aspirin. Although there were no differences in major bleeds between the two aspirin doses, a trend toward a higher rate of gastrointestinal bleeds in the high-dose group (0.38% vs 0.24%; $P = .051$) was observed. It should be taken into consideration that this trial lasted only 1 month, whereas studies showing increased bleeding with high-dose aspirin were typically of longer duration.

The introduction into clinical practice of newer generation oral $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) characterized by greater potency than clopidogrel and that are used in combination with aspirin has also led to questions about the optimal dose of aspirin in these patients. Although aspirin dosing did not affect the safety and efficacy profile of patients treated with prasugrel in the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study, a higher dose of aspirin (≥ 300 mg) was associated with reduced efficacy, albeit no differences in bleeding, in patients treated with ticagrelor in the PLATO (Platelet Inhibition and Outcomes) trial.[34,35]

Overall, the lack of a dose-response relationship in clinical studies evaluating aspirin's antithrombotic effects and the dose dependence of its side effects support the preferential use of low-dose (< 100 mg) aspirin regimens in ACS patients.[4-9] This is particularly relevant when combining aspirin with a $P2Y_{12}$ receptor antagonist (eg, clopidogrel, prasugrel, or ticagrelor), also known as dual antiplatelet therapy (DAPT), which is the standard of care after ACS, irrespective of how

these patients are managed (ie, invasive or noninvasive). Similarly, low-dose (< 100 mg) aspirin should be considered in patients requiring concomitant treatment with an oral anticoagulant (eg, vitamin K antagonists, dabigatran, rivaroxaban, apixaban, edoxaban).[36,37] In aspirin-treated patients, the use of nonsteroidal anti-inflammatory drugs (eg, ibuprofen) should be avoided because of their competition for the COX-1 active site.[38]

Evidence for Use

Clinical trials and expert consensus statements evaluating the use of aspirin for primary prevention of cardiovascular events are controversial and beyond the scope of this chapter.[39-45] On the contrary, aspirin is still the antiplatelet drug of choice for secondary prevention of recurrent ischemic events in patients with various clinical manifestations of coronary artery disease (CAD), including stable CAD and ACS, and those undergoing coronary revascularization (percutaneous or surgical).[4-9] The benefit of aspirin therapy in reducing vascular events including nonfatal MI, nonfatal stroke, or death from vascular causes in five groups of high-risk patients is illustrated in Fig. 41–3B. In these patients, particularly those with ACS or undergoing PCI, aspirin should be given as promptly as possible, at an initial dose of 162 to 325 mg, followed by a daily dose of 75 to 162 mg.[4-9]

The benefit of aspirin therapy in the management of patients with ACS has been repeatedly demonstrated in earlier trials. There are four randomized trials demonstrating beneficial effects of aspirin in patients with UA/NSTEMI showing an approximately 50% reduction in the risk of death or MI.[46-49] The Swedish angina pectoris aspirin trial, in which patients (n = 2035) were allocated to receive 75 mg of aspirin daily or placebo,[50] showed that aspirin led to significant reductions in death and MI among patients with UA (46% reduction), those undergoing PCI (53% reduction), and those with stable angina (33% reduction). In the setting of STEMI, aspirin was found to decrease the rate of angiographic reocclusion by more than 50% in a meta-analysis of 32 angiographic trials.[51] In the Second International Study of Infarct Survival (ISIS-2) trial, STEMI patients (n = 17,187) presenting within 24 hours from the onset of symptoms were randomized to receive IV streptokinase, 162.5 mg of aspirin daily for 30 days, both, or neither.[52] In patients receiving aspirin therapy alone, there was a significant 23% reduction in vascular mortality and a nearly 50% reduction in the risk of nonfatal reinfarction and nonfatal stroke at the end of 5 weeks. This benefit occurred irrespective of heparin use.

The benefits of aspirin in reducing recurrent ischemic events, including cardiovascular death, MI, and stroke in patients with CAD,[29,30] have also led to the near-universal use of this medication for patients undergoing PCI, which currently represents the predominant management strategy in patients with ACS (60%-70% of ACS patients undergo PCI). The initial studies involving aspirin in PCI included combined antiplatelet regimens with dipyridamole or ticlopidine. The combination of aspirin plus dipyridamole was shown to reduce the incidence of periprocedural MI during PCI by 77% compared with patients receiving placebo when administered 24 hours before PCI and continued for 4 to 7 months.[53] Dipyridamole was shown to provide no additional benefit beyond that conveyed by aspirin alone during elective angioplasty.[54] Aspirin has been shown to be effective in reducing recurrent ischemic events in patients undergoing intracoronary stent placement, especially in combination with a thienopyridine.[55-58]

Aspirin is recommended for patients who undergo coronary artery bypass grafting (CABG). CABG with saphenous vein grafts is associated with a 5% to 15% graft occlusion rate during the first postoperative month.[59,60] In the immediate postoperative period, aspirin reduces the rate of early thrombotic graft occlusion by approximately 50%, and continued aspirin therapy for 1 year further decreases occlusive events.[59] Although there is no evidence of the additional benefit of aspirin on long-term graft patency after 1 year of therapy, prolonged aspirin therapy is required for secondary prevention of atherothrombotic events in this group of patients with proven, complex coronary artery disease.[61]

Adverse Effects

In the Antithrombotic Trialists' Collaboration meta-analysis,[29,30] the proportional increase in risk of a major extracranial bleed with antiplatelet therapy was approximately 60%. The proportional increase in fatal bleeds was not significantly different from that for nonfatal bleeds; however, only the excess of nonfatal bleeds was significant.[62] In one small study, aspirin (75-325 mg/d) was associated with a significant decrease in creatinine clearance and a decrease in uric acid excretion after 2 weeks of therapy in elderly patients.[63] Three types of aspirin sensitivity have been described: respiratory sensitivity (asthma and/or rhinitis), cutaneous sensitivity (urticaria and/or angioedema), and systemic sensitivity (anaphylactoid reaction).[29,30] The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10%, and for aspirin-induced urticaria, the prevalence varies from 0.07% to 0.2% in the general population.[64] In patients with CAD presenting with allergy or intolerance to aspirin, clopidogrel is the treatment of choice.[4-9] Desensitization using escalating doses of oral aspirin can also be performed and may be an option in patients requiring long-term DAPT with aspirin and a $P2Y_{12}$ receptor inhibitor.[65] This approach should be confined to patients for whom adherence to continued aspirin has a very high likelihood because of the risks associated with discontinuation followed by reintroduction of aspirin after desensitization.

$P2Y_{12}$ RECEPTOR INHIBITORS

Platelet ADP signaling pathways mediated by the $P2Y_1$ and $P2Y_{12}$ receptors play a central role in platelet activation and aggregation (Fig. 41–4).[65-68] Although both receptors are needed for aggregation, ADP-stimulated effects on platelets are mediated mainly by G_i-coupled $P2Y_{12}$ receptor activation, which leads to sustained platelet aggregation and stabilization of the platelet aggregate, whereas $P2Y_1$ is responsible for an initial weak and transient phase of platelet aggregation and change in platelet shape.[68,69] In particular, $P2Y_1$ is coupled to a G_q protein, which regulates activation of phospholipase C, resulting in diacylglycerol and inositol triphosphate production. Diacylglycerol activates protein kinase C, leading to phosphorylation of myosin light chain kinase and granule secretion; inositol triphosphate leads to mobilization of intracellular calcium. The $P2Y_1$ receptor is coupled to another G protein that leads to change in platelet shape. Activation of the $P2Y_{12}$ receptor, on the other hand, leads to a complex series of intracellular signaling events that culminate in activation of the platelet GP IIb/IIIa receptor, granule release, amplification of platelet aggregation, and stabilization of the platelet aggregate. The $P2Y_{12}$ receptor is coupled to a G_i protein, which regulates activation of phosphoinositide-3-kinase and inhibition of adenylyl cyclase. Phosphoinositide-3-kinase activation leads to GP IIb/IIIa activation through activation of intraplatelet kinases, whereas inhibition of adenylyl cyclase decreases cyclic adenosine monophosphate (cAMP) levels. Reduction of cAMP levels modulates the activity of cAMP-dependent protein kinases, which in turn reduces cAMP-mediated phosphorylation of vasodilator-stimulated phosphoproteins and eliminates its protective effect on GP IIb/IIIa receptor activation.[68,69]

Several families of $P2Y_{12}$ inhibitors have been developed. Currently, thienopyridines and nonthienopyridines are approved for clinical use and are described in detail in the following sections.

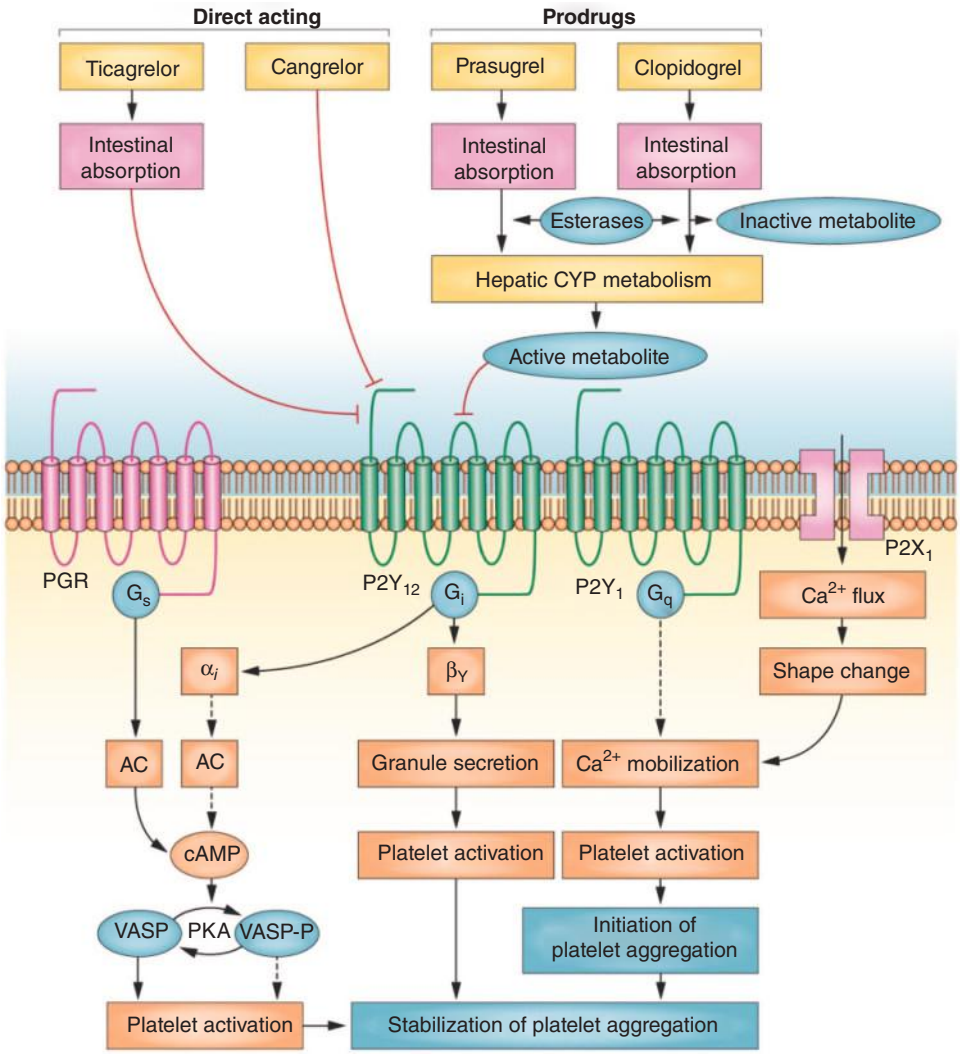


FIGURE 41–4. $P2Y_{12}$ inhibitor metabolism and mechanism of action. Clopidogrel is an oral prodrug, and after intestinal absorption, approximately 85% of clopidogrel is hydrolyzed by carboxylase to an inactive metabolite. The remaining approximately 15% is rapidly metabolized by hepatic cytochrome (CYP) P450 isoenzymes in a two-step oxidation process with the generation of a highly unstable active metabolite. Prasugrel is also an oral prodrug with a similar intestinal absorption process. However, in contrast to clopidogrel, esterases are part of prasugrel's activation pathway, and prasugrel is oxidized more efficiently to its active metabolite via a single CYP-dependent step. Direct-acting antiplatelet agents (cangrelor and ticagrelor) have reversible effects and do not require hepatic metabolism for achieving pharmacodynamic activity. Ticagrelor is orally administered and, after intestinal absorption, directly inhibits platelet activation by allosteric modulation of the $P2Y_{12}$ receptor, binding to a site on the receptor distinct from the adenosine diphosphate (ADP)–binding site. Cangrelor is intravenously administered and directly inhibits the $P2Y_{12}$ receptor, bypassing intestinal absorption. P2Y receptors are a family of purinergic G protein–coupled receptors activated by extracellular nucleotides, such as ADP. Platelets express at least two ADP receptors, $P2Y_1$ and $P2Y_{12}$, which couple to G_q and G_i, respectively. The activation of $P2Y_{12}$ inhibits adenylyl cyclase (AC), causing a decrease in the cyclic adenosine monophosphate (cAMP) level, and the activation of $P2Y_1$ causes an increase in the intracellular Ca^{2+} level, leading to platelet aggregation through the change in the ligand-binding properties of the glycoprotein IIb/IIIa receptor. Clopidogrel, prasugrel, ticagrelor, and cangrelor bind to the $P2Y_{12}$ receptor and ultimately inhibit platelet activation and the aggregation processes by modulating intraplatelet levels of cAMP and vasodilator-stimulated phosphoprotein (VASP) phosphorylation (VASP-P). *Solid black arrows* indicate activation. *Dotted black arrows* indicate inhibition. PDE, phosphodiesterase; PKA, protein kinases. Reproduced with permission from Franchi F, Angiolillo DJ: Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol*. 2015 Jan;12(1):30-47.

Thienopyridines

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile The thienopyridine derivatives (ticlopidine, clopidogrel, and prasugrel) are nondirect, orally administered antiplatelet agents that selectively and irreversibly inhibit the $P2Y_{12}$ ADP receptor (see Fig. 41–4; Table 41–1).[19,20,70] When given in combination with aspirin, thienopyridines have a synergistic effect and therefore achieve greater platelet inhibition than either agent alone.[71,72] The inhibition of platelet aggregation by thienopyridines is concentration-dependent. However, thienopyridines are prodrugs and are thus inactive in vitro and need to be metabolized by the hepatic cytochrome P450 (CYP) system in order to produce an active metabolite capable of selectively inhibiting the $P2Y_{12}$ receptor. Because blockade of $P2Y_{12}$ is irreversible, platelet inhibitory effects induced by thienopyridines last for the entire life span of the platelet.

Ticlopidine was the first thienopyridine to be developed and was approved for clinical use in 1991. Ticlopidine at the dose of 250 mg twice daily showed its superiority in combination with aspirin when compared with aspirin alone or anticoagulation in combination with aspirin in a number of trials for prevention of recurrent ischemic events in patients undergoing PCI.[54-58] However, because of safety concerns (mainly high rates of neutropenia) and twice-daily dosing, ticlopidine has been largely replaced by clopidogrel (a second-generation thienopyridine) because of its better safety profile.[73] Pooled data

TABLE 41–1. Pharmacologic Properties of $P2Y_{12}$ Receptor Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Pharmacologic class	Thienopyridine	Thienopyridine	CPTP	ATP analogue
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible
Administration route	Oral	Oral	Oral	IV
Frequency	Once daily	Once daily	Twice daily	Bolus plus infusion
Prodrug	Yes	Yes	No[a]	No
Onset of action	2-8 h	30 min-4 h[b]	30 min-4 h[b]	2 min
Offset of action	7-10 d	7-10 d	3-5 d	30-60 min
CYP drug interaction	CYP2C19	No	CYP3A	No
Approved settings	ACS and stable CAD PCI	ACS undergoing PCI	ACS (full spectrum)	$P2Y_{12}$ receptor inhibitor–naïve patients undergoing PCI

Abbreviations: ACS, acute coronary syndrome; ATP, adenosine triphosphate; CAD, coronary artery disease; CYP, cytochrome P450; CPTP, cyclopentyltriazolopyrimidine; IV, intravenous; PCI, percutaneous coronary intervention.

[a]Although most of ticagrelor-mediated antiplatelet effects are direct, approximately 30% to 40% are attributed to an active metabolite (AR-C124910XX).

[b]Depending on clinical setting.

from more than 10,000 patients undergoing PCI demonstrated that clopidogrel was associated with a significant reduction in the incidence of major adverse cardiac events, including mortality, compared with ticlopidine.[74]

Clopidogrel, a second-generation thienopyridine approved for clinical use in 1997, differs structurally from ticlopidine by the addition of a carboxymethyl group.[67-70] The inhibition of platelet aggregation by clopidogrel is also concentration-dependent. Clopidogrel is an inactive prodrug that requires oxidation by the CYP system to generate an active metabolite (see Fig. 41–4 and Table 41–1). However, approximately 85% of the prodrug is hydrolyzed by esterases to an inactive carboxylic acid derivative. Therefore, only 15% of the prodrug is metabolized by the CYP system into an active metabolite. In particular, the thiophene ring of clopidogrel is oxidized to form an intermediate metabolite (2-oxo-clopidogrel), which is further oxidized, resulting in the opening of the thiophene ring and the formation of a carboxyl and thiol group. CYP3A4, CYP3A5, CYP2C9, and CYP1A2 are involved in one oxidation step; CYP2B6 and CYP2C19 are involved in both steps. The reactive thiol group of the active metabolite of clopidogrel forms a disulfide bridge between one or more cysteine residues of the $P2Y_{12}$ receptor, resulting in its irreversible blockade. Although clopidogrel has a half-life of only 8 hours, it has an irreversible effect on platelets that lasts from 7 to 10 days.

Compared with ticlopidine, clopidogrel has the advantage of being able to be administered as a loading dose, allowing antiplatelet effects to be achieved within hours after administration. The approved loading and maintenance doses of clopidogrel are 300 mg and 75 mg, respectively. However, numerous pharmacodynamic studies have shown that higher doses can achieve greater platelet inhibition. In particular, most of these studies have been performed in patients undergoing PCI and evaluated high loading dose regimens. Most studies have consistently shown that high (≥ 600 mg) loading dose regimens are associated with faster and more potent platelet inhibitory effects as compared with 300 mg.[75-81] A high loading dose regimen has also been associated with a reduction in periprocedural MI in patients undergoing PCI.[79-81]

Prasugrel is a third-generation thienopyridine approved for clinical use in 2009. As all thienopyridines, prasugrel is a prodrug that, after oral administration, requires hepatic metabolism to give origin to its active metabolite (see Fig. 41–4 and Table 41–1).[19,20] Importantly, prasugrel activation involves fewer steps than clopidogrel, and it is rapidly converted to an active metabolite that binds specifically and irreversibly to the $P2Y_{12}$ receptor.[82-85] In fact, prasugrel is more effectively converted to its active metabolite than clopidogrel through a process involving hydrolysis by carboxyesterases mainly in the intestine, followed by only a single hepatic CYP-dependent step, involving CYP3A, CYP2B6, CYP2C9, and CYP2C19 isoforms. This more favorable pharmacokinetic profile translates into better pharmacodynamic effects than earlier generation thienopyridines. A 60-mg loading dose of prasugrel achieves 50% platelet inhibition in 30 minutes and 80% to 90% inhibition in 1 to 2 hours. In fact, pharmacodynamic studies have shown prasugrel to be characterized by more potent antiplatelet effects, lower interindividual variability in platelet response, and a faster onset of activity compared with clopidogrel, even when used at high loading and maintenance doses.[85]

Dosing and Recommendations Clopidogrel is approved for the treatment and prevention of secondary atherothrombotic events across the spectrum of patients with ACS, irrespective of the treatment strategy (invasive or noninvasive).[4-9] This recommendation is independent of whether patients are revascularized or not (ie, medical management) and irrespective of strategy for those undergoing PCI (ie, similar for bare metal stent [BMS], drug-eluting stent [DES], or balloon angioplasty). Clopidogrel is also the only oral $P2Y_{12}$ receptor inhibitor approved for patients with stable CAD undergoing PCI. The recommended loading dose of clopidogrel is 300 to 600 mg. However, in the setting of PCI, a 600-mg loading dose is most commonly used.[4-9] A 300-mg loading dose of clopidogrel, in addition to aspirin, should also be given in patients < 75 years old with STEMI treated with fibrinolytic therapy; patients ≥ 75 years old treated with fibrinolytic therapy should be treated with clopidogrel 75 mg (without a loading dose). After loading dose administration, a maintenance dose of 75 mg daily should be initiated. No dosage adjustment is necessary for patients with renal impairment, including patients with end-stage renal disease. These recommendations have come about in light of the results of several large-scale clinical trials that have shown a clear benefit of clopidogrel in addition to aspirin in terms of preventing recurrent ischemic events,

including stent thrombosis, when compared with aspirin alone.[86-91] In patients with ACS, clopidogrel 75 mg daily should be given for at least 12 months.[4-9] If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. Continuation of clopidogrel beyond 1 year may also be considered on an individualized basis. In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least 5 days in patients receiving clopidogrel.[4-9] However, because of the increased risk of bleeding complications of patients undergoing CABG < 5 days from clopidogrel administration, the optimal timing of clopidogrel administration has been debated. In turn, in clinical practice, it is not uncommon that, in patients undergoing an invasive strategy, coronary anatomy be defined prior to administering a $P2Y_{12}$ receptor inhibitor to rule out the need for CABG.

Clopidogrel is contraindicated in patients with active pathologic bleeding, such as peptic ulcer or intracranial hemorrhage, and in patients with hypersensitivity to clopidogrel or any component of the product. Given that genetic variants of the CYP2C19 enzyme, which is involved in both metabolic steps of biotransformation of clopidogrel into its active metabolite, have been associated with variations of the pharmacokinetic and pharmacodynamic profiles of clopidogrel, and have affected clinical outcomes, drug-regulating authorities recommend alternative treatments in patients identified as CYP2C19 poor metabolizers.[92] In patients taking clopidogrel, the use of drugs that are strong or moderate CYP2C19 inhibitors should be avoided; in particular, the concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and antiplatelet activity.[93] Pantoprazole and esomeprazole have less effect on the pharmacological activity of clopidogrel than omeprazole, whereas dexlansoprazole and lansoprazole have marginal effects on clopidogrel metabolism.[94]

Prasugrel is currently approved for patients with ACS undergoing PCI and should be administered only after coronary anatomy has been established, with the exception of STEMI patients undergoing primary PCI in whom treatment may be initiated even prior to defining coronary anatomy.[4-9] Treatment with prasugrel should be initiated with a single 60-mg oral loading dose and continued at 10 mg orally once daily. Prasugrel is not recommended in non–invasively managed ACS and in stable CAD patients undergoing PCI. Important safety information needs to be considered in order to minimize the risks associated with prasugrel and maximize its clinical benefits. It is contraindicated in patients at high risk of bleeding, with previous stroke/transient ischemic attack, and with hypersensitivity to the drug. Patients who experience a stroke or transient ischemic attack (TIA) while on prasugrel generally should have the therapy discontinued. In patients ≥ 75 years of age, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered. In the elderly, the European Medical Agency recommends a 5-mg dose, whereas the US Food and Drug Administration (FDA) recommends the standard 10-mg dosing. Both agencies recommend dose adjustment to 5 mg in low-body-weight patients (< 60 kg). The rationale for the 5-mg dosing is primarily derived from pharmacodynamic and pharmacokinetic studies showing that prasugrel 5 mg in elderly and low-weight patients achieves similar platelet inhibitory effects as 10 mg in nonelderly and non–low-weight patients.[95,96] Patients pretreated with clopidogrel can switch to prasugrel, leading to enhanced levels of platelet inhibition that are achieved more promptly when switching using a 60-mg loading dose rather than a 10-mg maintenance dose, and without any drug interactions.[97] As a result of its irreversible binding to the $P2Y_{12}$ receptor and its greater potency than clopidogrel, prasugrel administration should be stopped at least 7 days before surgery in order to reduce the risk of bleeding.[98]

Drug compatibility studies have shown that prasugrel can be administered with drugs that are inducers or inhibitors of CYP enzymes, including proton pump inhibitors (eg, omeprazole), which have not been shown to interfere with its pharmacodynamic properties.[99] Moreover, genetic polymorphisms of CYP2C19 do not interfere with prasugrel effects.[100] Prasugrel should be used with caution when coadministered with oral anticoagulants or nonsteroidal anti-inflammatory drugs used chronically because of the potential for increased risk of bleeding.[36,37] No dosage adjustment is necessary for patients with renal impairment, including patients with end-stage renal disease.

Evidence for Use. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial evaluated the efficacy of clopidogrel (75 mg daily) versus aspirin (325 mg daily) in reducing the risk of ischemic outcomes in patients (n = 19,185) with a history of recent MI, recent ischemic stroke, or established peripheral artery disease. The overall results showed a significantly lower annual rate of the composite end point (vascular death, MI, or ischemic stroke) with clopidogrel (5.32% vs 5.83%; $P = .043$).[101] Because aspirin and clopidogrel act through different mechanisms to inhibit platelet activity, the potential synergy of these two agents has been explored in several large-scale clinical trials, particularly in high-risk patients, showing greater efficacy of this strategy.[86-91]

The pivotal ACS and PCI trials comparing DAPT with aspirin and clopidogrel versus aspirin alone on ACS settings are summarized in Table 41–2. The CURE trial evaluated the short-term and long-term effects of clopidogrel in combination with aspirin compared with aspirin alone in the prevention of ischemic complications in patients (n = 12,562) with UA/NSTEMI.[86] Clopidogrel plus aspirin provided a 20% relative risk reduction in the primary composite outcome (cardiovascular death, nonfatal MI, or stroke) compared with aspirin alone. The long-term clinical benefit associated with DAPT with aspirin and clopidogrel was independent of coronary revascularization and present in both medically managed patients and those undergoing PCI or CABG. More patients in the clopidogrel plus aspirin group than in the aspirin alone group showed major bleeding (3.7% vs 2.7%; relative risk, 1.38; $P = .001$). Although all groups showed an advantage with clopidogrel plus aspirin, the benefit appeared greatest in the high-risk group.[102] A subgroup analysis of patients (n = 2658) from the CURE study who underwent PCI (PCI-CURE) showed that clopidogrel pretreatment significantly reduced post-PCI cardiovascular death or MI, with a 31% overall relative risk reduction ($P = .03$).[87] The Clopidogrel for the Reduction of Events During Observation (CREDO) trial evaluated the benefit of clopidogrel in patients undergoing elective PCI.[88] Patients who were given aspirin plus clopidogrel for 12 months experienced a 26.9% ($P = .02$) reduction in the relative risk of vascular events versus aspirin alone. A prespecified subgroup analysis of patients pretreated with a 300-mg clopidogrel loading dose at least 6 hours before PCI suggested a 38.6% ($P = .051$) reduction in periprocedural adverse events. The CURE, PCI-CURE, and CREDO trials all reported long-term benefit of DAPT (9-12 months) over single antiplatelet therapy in patients with ACS. The benefit of clopidogrel has also been demonstrated in patients with STEMI in the Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) and Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trials, when given in addition to aspirin or aspirin plus fibrinolytic therapy (see Table 41–2).[89-91]

In contrast to the positive results of the trials described earlier, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial showed that,

TABLE 41–2. Phase III Trials of Clopidogrel Therapy for ACS, PCI, and Secondary Prevention of Atherothrombotic Disease

Trial Name	No. of Patients	Patients	Treatment	Primary End Point	Results	*P*
CAPRIE	19,185	Previous stroke or MI or symptomatic PAD	Clopidogrel vs ASA	Ischemic stroke, MI, or vascular death at 1 year	5.3% vs 5.8% RRR: 8.7% [0.3-16.5]	.043
CURE	12,562	NSTE-ACS, unstable angina	Clopidogrel + ASA vs ASA	CV death, nonfatal MI, and stroke at 1 year	9.3% vs 11.4% HR: 0.80 [0.72-0.90]	< .001
CREDO	2116	ACS with PCI	Clopidogrel + ASA vs ASA	CV death, MI, or stroke at 1 year	8.5% vs 11.5% RRR: 26.9% [3.9%-44.4%]	.02
PCI-CURE	2658	NSTE-ACS with PCI	Clopidogrel + ASA vs ASA	CV death, MI, or revascularization within 30 days	4.5% vs 6.4% RR: 0.70 [0.50-0.97]	.03
CLARITY	3491	STEMI	Clopidogrel + ASA + FA vs ASA + FA	Occluded infarct-related artery, death, or recurrent MI before angiography	15.0% vs 21.7% OR: 0.64 [0.53-0.76]	< .001
COMMIT	45,852	STEMI	Clopidogrel + ASA vs ASA	CV death, reinfarction, or stroke at 28 days	9.2% vs 10.1% OR: 0.91 [0.86-0.97]	.002
CHARISMA	15,603	CVD or multiple risk factors	Clopidogrel + ASA vs ASA	MI, stroke, or CV death at 28 months	6.8% vs 7.3% RR: 0.93 [0.83-1.05]	.22
CURRENT-OASIS 7	25,087	ACS with planned early invasive management with intended PCI	Double-dose clopidogrel + ASA vs low-dose clopidogrel + ASA	CV death, MI, or stroke at 30 days	4.2% vs 4.4% HR: 0.94 [0.83-1.06] (overall cohort)	.37

Abbreviations: ACS, acute coronary syndromes; ASA, aspirin; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events trial; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy trial; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction trial; CREDO, Clopidogrel for the Reduction of Events During Observation trial; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events trial; CURRENT-OASIS 7, Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Intervention trial; CV, cardiovascular; CVD, cardiovascular disease; FA, fibrinolytic agent; HR, hazard ratio; MI, myocardial infarction; NSTE, non–ST-segment elevation; OR, odds ratio; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RR, relative risk; RRR, relative risk reduction; STEMI, ST-segment elevation myocardial infarction.

Note. Clopidogrel was given as a loading dose of 300 mg then 75 mg daily in CURE, CREDO, PCI-CURE, CLARITY, COMMIT, and CHARISMA. Clopidogrel 75 mg daily was administered in CAPRIE. In CURRENT-OASIS 7, double-dose clopidogrel was defined as a 600-mg loading dose and 150 mg once daily for 7 days, followed by 75 mg once daily. Standard-dose clopidogrel was defined as a 300-mg loading dose, followed by 75 mg once daily. Patients were also randomized to receive low-dose (75-100 mg/d) or high-dose (300-325 mg/d) aspirin.

after 28 months, addition of clopidogrel to aspirin was not better than aspirin alone in reducing the primary composite end point (cardiovascular death, MI, or stroke) in lower risk patients (n = 15,603) with established cardiovascular disease or multiple cardiovascular risk factors, in the absence of ACS or PCI.[103] Increased bleeding and higher mortality rates were reported when patients with multiple risk factors alone (n = 3284) were analyzed, providing evidence that DAPT should not be used in patients without a history of established vascular disease. In the subgroup of patients with clinically evident atherothrombosis (n = 12,153), there was a 12% relative risk reduction in event rates with clopidogrel ($P = .046$). A subsequent analysis of CHARISMA data from patients (n = 9478) with prior MI, stroke, or symptomatic peripheral arterial disease, also known as "CAPRIE-like," showed that a dual antiplatelet regimen offered significant benefit, reducing the relative rate for ischemic events by 17% ($P = .01$).[104] Taken together, the results of the clinical trial experience with clopidogrel suggest that DAPT is useful in high-risk settings, such as in patients with various clinical manifestations of ACS or undergoing PCI, and has not been proven beneficial in lower risk patients.

Most recently, the CURRENT/OASIS-7 trial evaluated the efficacy and safety of double-dose clopidogrel in patients (n = 25,087) with ACS.[33] In this trial, double-dose clopidogrel was defined as a 600-mg loading dose and 150 mg once daily for 7 days, followed by 75 mg once daily. Standard-dose clopidogrel was defined as a 300-mg loading dose, followed by 75 mg once daily. Patients were also randomized to receive low-dose (75-100 mg/d) or high-dose (300-325 mg/d) aspirin. In the overall study population, there was no significant difference in the primary end point (composite of cardiovascular death, MI, or stroke) at 30 days between patients receiving double-dose versus standard-dose clopidogrel (4.4% vs 4.2%; $P = .37$). However, two positive interactions were encountered, which included PCI and high-dose aspirin. In patients who underwent PCI (n = 17,232), double-dose clopidogrel was associated with a significant 15% relative reduction ($P = .036$) in the primary end point and a 42% relative reduction ($P = .001$) in definite stent thrombosis versus the standard-dose regimen. There was a modest excess in CURRENT-defined major bleeds, but no difference in Thrombolysis in Myocardial Infarction (TIMI) major bleeds, intracranial hemorrhage (ICH), fatal bleeds, or CABG-related bleeds between the two clopidogrel treatment arms. In addition, there was an interaction with aspirin dose, as patients receiving high-dose clopidogrel had better outcomes when treated with high-dose aspirin. The explanation to the latter finding remains unknown.

The TRITON trial showed that prasugrel (60-mg loading dose/10-mg maintenance dose) plus aspirin was significantly more effective than clopidogrel (300-mg loading dose/75-mg maintenance dose) plus aspirin in preventing ischemic events in moderate- to high-risk

ACS patients (n = 12,608) with and without STEMI undergoing PCI (Table 41–3).[105] The primary efficacy end point of cardiovascular death, nonfatal MI, or nonfatal stroke at a median follow-up of approximately 14.5 months occurred in 9.9% of patients receiving prasugrel compared with 12.1% of patients receiving clopidogrel (relative risk reduction, 19%; $P < .001$).[105] These events were mainly driven by a reduction in MI.[106] There was also a 52% relative reduction in definite/probable stent thrombosis (1.13% vs 2.35%; $P < .0001$).[105] A landmark analysis showed that the benefits associated with prasugrel were both early (< 3 days) and late (up to 15 months),[107] and this benefit was irrespective of GP IIb/IIIa inhibitor use.[108] However, prasugrel was also associated with significantly higher risks for TIMI major non-CABG bleeding, including life-threatening bleeding, compared with clopidogrel. A prespecified analysis of net clinical benefit (death from any cause, nonfatal MI, nonfatal stroke, and TIMI major hemorrhage) favored prasugrel over clopidogrel in the overall patient cohort (12.2% vs 13.9%, respectively; $P = .004$). The observed increase in bleeding events prompted several post hoc analyses to determine net clinical benefit or harm from prasugrel in various patient subgroups. Patients with stroke or TIA had net clinical harm from prasugrel (hazard ratio [HR] 1.54; $P = .04$), whereas patients age ≥ 75 years (HR 0.99; $P = .92$) and patients weighing < 60 kg (HR 1.03; $P = .89$) had no net benefit from prasugrel. In contrast, the net clinical benefit from prasugrel was greater in patients with diabetes (n = 3146; HR 0.74; $P = .001$) and in patients undergoing PCI for STEMI (n = 3534; HR 0.81; $P = .02$), without excess major bleeding.[109,110] Moreover, prasugrel was associated with a greater reduction in recurrent ischemic events compared with clopidogrel.[111] Based on TRITON-TIMI 38 data, prasugrel appears to be most appropriate for use in patients with ACS managed with PCI who (1) have no history of TIA/stroke; (2) are < 75 years of age; and (3) weigh ≥ 60 kg. In patients < 75 years old and > 60 kg with no prior TIA/stroke, the primary efficacy end point occurred in 8.3% of patients treated with prasugrel and in 11.0% of patients treated with clopidogrel, thus resulting in a significant 25% relative reduction with prasugrel (HR 0.75; 95%

TABLE 41–3. Major Completed Phase III Clinical Trials on Newer Generation Antiplatelet Agents in ACS

Trial	Patient (No.)	Setting	Treatment Arms	Primary End Point	Results
TRITON-TIMI 38	13,608	ACS patients undergoing PCI	Aspirin + prasugrel vs aspirin + clopidogrel	CV death, nonfatal MI, or nonfatal stroke at 14.5 months	9.9% vs 12.1% HR: 0.81 [0.73-0.90] $P < .001$
TRILOGY-ACS	9326	Medically managed NSTE-ACS	Aspirin + prasugrel vs aspirin + clopidogrel	CV death, MI, or stroke at 17 months in patients with age < 75 years	13.9% vs 16.0% HR: 0.91 [0.79-1.05] $P = .21$
ACCOAST	4033	NSTEMI scheduled for angiography	Pretreatment with prasugrel 30 mg vs placebo	CV death, MI, stroke, GPI bailout, or urgent revascularization at 7 days	10.0% vs 9.8% HR: 1.02 [0.84-1.25] $P = .81$
PLATO	18,624	ACS	Aspirin + ticagrelor vs aspirin + clopidogrel	Death from vascular causes, MI, or stroke at 12 months	9.8% vs 11.7% HR: 0.84 [0.77-0.92] $P < .001$
ATLANTIC	1862	STEMI transferred for primary PCI	Prehospital ticagrelor vs in-hospital ticagrelor	Patients without ≥ 70% resolution of ST-segment elevation before PCI[a]	86.8% vs 87.6% OR: 0.93 [0.69-1.25] $P = .63$
				Patients without TIMI flow grade 3 in the infarct-related artery at initial angiography[a]	82.6% vs 83.1% OR: 0.97 [0.75-1.25] $P = .82$
PEGASUS	21,162	Patients with prior MI 1-3 years earlier	Ticagrelor 90 mg BID vs ticagrelor 60 mg BID vs placebo[b]	CV death, MI, or stroke at 36 months	90 mg vs placebo: 7.85 vs 9.04; HR: 0.85 [0.75-0.96] $P = .008$ 60 mg vs placebo: 7.77 vs 9.04; HR: 0.84 [0.74-0.95] $P = .002$
CHAMPION-PHOENIX	11,145	Patients undergoing PCI	Aspirin + clopidogrel + cangrelor vs aspirin + clopidogrel	Death from any cause, MI, IDR, and stent thrombosis at 48 hours	4.7% vs 5.9% OR: 0.78 [0.66-0.93] $P = .005$
TRACER	12,944	NSTE-ACS	Standard APT + vorapaxar vs standard APT + placebo	CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization at 2 years	18.5% vs 19.9% HR: 0.92 [0.85-1.01] $P = .07$
TRA 2P-TIMI 50	26,449	Patients with history of MI, ischemic stroke, or PAD	Standard APT + vorapaxar vs standard APT + placebo	CV death, MI, or stroke at 36 months	9.3% vs 10.5% HR: 0.87 [0.80-0.94] $P < .001$

Abbreviations: ACS, acute coronary syndrome; APT, antiplatelet therapy; BID, twice a day; CV, cardiovascular; GPI, glycoprotein IIb/IIIa inhibitor; HR, hazard ratio; IDR, ischemia-driven revascularization; MI, myocardial infarction; NSTE, non–ST-segment elevation; OR, odds ratio; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Note. See text for trial acronyms.

[a]Coprimary end point.

[b]On a background of aspirin therapy.

confidence interval [CI], 0.66-0.84; $P < .001$). In this cohort, there was no significant increase in the risk of TIMI major non–CABG-related bleeding (2.0% vs 1.5%; HR 1.24; 95% CI, 0.91-1.68; $P = .17$).

The efficacy of prasugrel compared to clopidogrel in medically managed ACS was tested in the TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial[112] (see Table 41–3). Aspirin-treated patients (n = 9326) with NSTE-ACS in whom a medical management was chosen were randomized to receive either prasugrel (30-mg loading dose/10-mg maintenance dose) or clopidogrel (300-mg loading dose/75-mg maintenance dose). Of note, prasugrel maintenance dose was adjusted to 5 mg for patients with age ≥ 75 years or who weighed less than 60 kg. Clopidogrel pretreatment prior to randomization occurred in approximately 96% of patients. The primary end point was a composite of cardiac death, MI, or stroke among patients age < 75 years (n = 7243). After a median follow-up of 17 months, there were no differences between prasugrel and clopidogrel in the primary end point (13.9% vs 16%; HR 0.91; $P = .21$). The rates of severe and intracranial bleeding were low and similar between groups.[112] Moreover, in the secondary analysis on patients (n = 2083) age 75 years or older, prasugrel 5 mg was not associated with an ischemic benefit compared to standard clopidogrel, although there was no increase in bleeding.[113] Interestingly, in the prespecified substudy on patients < 75 years old who underwent angiography before randomization (n = 3085), prasugrel reduced the risks of the composite primary end point compared with clopidogrel, with a trend toward increased risk of major bleeding.[114] Furthermore, although the frequency of the primary end point was similar between groups through 12 months, a trend (P for interaction = .07) toward a reduced risk in the prasugrel group after 12 months was seen, and a prespecified secondary analysis on multiple recurrent events showed a lower risk among patients < 75 years old treated with prasugrel (HR 0.85; $P = .04$).[112]

Most recently, the impact of prasugrel pretreatment (before defining coronary anatomy) in patients with NSTE-ACS was tested in the ACCOAST (Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) trial[115] (see Table 41–3). In this trial, $P2Y_{12}$ receptor inhibitor–naïve patients with NSTEMI were randomly assigned to receive either pretreatment with a prasugrel 30-mg loading dose or matching placebo as soon as possible after diagnosis. After angiography (performed within 2-48 hours after loading dose, with median time of 4.3 hours), patients (n = 4033) undergoing PCI received an additional prasugrel 30-mg loading dose if in the pretreatment arm or a 60-mg loading dose if in the control arm. Prasugrel pretreatment failed to improve the primary end point (a composite of death from cardiovascular causes, MI, stroke, urgent revascularization, or GP IIb/IIIa inhibitor bailout) at 7 days compared to standard delayed administration (10.0% vs 9.8%; HR 1.02; $P = .81$) but was associated with a significant three-fold increase in non–CABG-related TIMI major bleeding and six-fold increase in life-threatening bleeding. Importantly, results were consistent across the cohort that underwent PCI (68.7% of the patients), the cohort that underwent CABG (6.2%), and the cohort that received medical treatment only (25.1%).[115] Therefore, the results of the ACCOAST trial do not support the use of prasugrel before angiography in patients with NSTE-ACS.[4-9]

Adverse Effects In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), major peripheral or bleeding complications were similar between clopidogrel (1.3%) and ticlopidine (1.2%).[73] In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0% and 2.7% in patients treated with clopidogrel and aspirin, respectively.[101] The incidence of ICH was 0.4% for clopidogrel compared with 0.5% for aspirin. In CURE, clopidogrel use with aspirin was associated with an increase in bleeding compared with placebo with aspirin (3.7% vs 2.7%; relative risk, 1.38; $P = .001$).[86] The risk of bleeding, however, was increased in patients using higher doses of aspirin. There was an excess in major bleeding, primarily gastrointestinal and at puncture sites, in patients receiving clopidogrel plus aspirin compared with placebo plus aspirin. The rates of ICH (0.1%) and fatal bleeding (0.2%) were the same in both groups. In CREDO, CLARITY, and COMMIT, there were no significant differences in major bleeding between patients receiving clopidogrel plus aspirin compared with placebo plus aspirin.[88-90]

Other adverse effects include diarrhea, nausea, and vomiting, which are common with ticlopidine and may occur in up to 30% to 50% of patients.[116] Skin rash occurs rarely.[117] Neutropenia is a serious side effect, and the incidence associated with ticlopidine is 1.3% to 2.1% as compared with 0.10% with clopidogrel.[118,119] Neutropenia can be severe (< 450 neutrophils/μL in 0.9% of patients treated with ticlopidine) and occasionally fatal.[120] In the CAPRIE trial, the neutrophil count fell below 450 neutrophils/μL for five (0.05%) and four (0.04%) patients in the clopidogrel and aspirin groups, respectively.[101] With ticlopidine, most cases develop within the first 3 months of therapy and initially may be clinically silent. Therefore, complete blood counts should be performed every 2 weeks during the first 3 months of therapy.[121] Bone marrow aplasia and thrombotic thrombocytopenia purpura have been reported with ticlopidine, with an estimated incidence of 1 per 1600 to 5000 patients treated; this incidence is lower with clopidogrel.[122,123] Ticlopidine had been reported to increase serum cholesterol by an average of 9%,[124] but no change was associated with clopidogrel in the CAPRIE trial. Although hematologic complications may occur with clopidogrel (hemolytic uremic syndrome and thrombotic thrombocytopenic purpura), they appear to be rare.[125] Overall, allergic or hematologic reactions occur in approximately 1% of patients taking clopidogrel, which is the thienopyridine of choice. Limited information on switching thienopyridine in patients with adverse reactions is available. In a recent study composed of 76 patients, 14 patients (27%) who had an allergic or hematologic adverse reactions to clopidogrel had a similar reaction (most commonly rash) to ticlopidine; none developed a life-threatening reaction.[126] Desensitization protocols using escalating doses of oral clopidogrel have been proposed in allergic patients.[127]

In the TRITON-TIMI 38 trial, the rate of study drug discontinuation as a result of adverse events was 7.2% for prasugrel and 6.3% for clopidogrel.[105] Bleeding was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5% and 1.4% for prasugrel and clopidogrel, respectively). Overall, in the trial, rates of non–CABG-related TIMI major or minor bleeding were significantly higher on prasugrel than on clopidogrel (4.5% vs 3.4%; $P = .002$).[105] In particular, the rate of major bleeding was 2.2% with prasugrel and 1.7% with clopidogrel ($P = .029$), and rates of life-threatening bleeding were 1.3% and 0.8% with prasugrel and clopidogrel, respectively. Although the incidence of symptomatic ICH was similar (0.3%), fatal bleedings were numerically higher with prasugrel than with clopidogrel (0.3% vs 0.1%). Of note, patients with history of stroke or TIA, age ≥ 75 years, or body weight < 60 kg had a more than two-fold higher risk of major bleeding compared with patients without these conditions. Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were as follows (prasugrel and clopidogrel, respectively): epistaxis (6.2%, 3.3%), gastrointestinal hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%), subcutaneous hematoma (0.5%, 0.2%), postprocedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), pericardial effusion/hemorrhage/tamponade (0.3%, 0.2%), and retinal hemorrhage (0.0%, 0.1%). CABG-related major or minor bleeding was also significantly higher on prasugrel than on clopidogrel. In particular, CABG-related TIMI major bleeding occurred in 11.3% of patients treated with prasugrel and 3.6%

of patients treated with clopidogrel ($P < .001$).[128] Of interest, there was a reduction in mortality despite the increased risk of bleeding among prasugrel-treated patients undergoing CABG.[128]

The rate of other adverse events not related to hemorrhage was similar in the prasugrel and clopidogrel groups.[105] Thrombotic thrombocytopenia purpura, a rare but serious condition that can be fatal, occurred in 0.06% of prasugrel-treated patients, as compared with 0.04% of patients treated with clopidogrel. Other common or relevant nonhemorrhagic adverse events were, for prasugrel and clopidogrel respectively, anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). Leukopenia was less frequent on prasugrel than on clopidogrel (2.8% vs 3.5%). During TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. Known gastrointestinal bleeding preceded the diagnosis of colonic neoplasms in nine patients (seven in the prasugrel group and two in the clopidogrel group).

In the ACCOAST trial, the rates of TIMI major bleeding and of TIMI major or minor bleeding at 7 days were significantly higher in the prasugrel pretreatment group than in the control group.[115] In particular, there was a three-fold increase in non–CABG-related major bleeding (1.3% vs 0.5%) and an almost six-fold increase in life-threatening bleeding not related to CABG (0.8% vs 0.2%). TIMI minor bleeding events were also increased with pretreatment as compared with no pretreatment. The higher bleeding rate with prasugrel pretreatment was persistent up to 30 days.

In the TRILOGY trial, the rate of non–CABG-related severe or life-threatening bleeding events (according to Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] criteria) and major bleeding (according to TIMI criteria) at 30 months were similar among patients under the age of 75 years treated with prasugrel and clopidogrel in the two study groups (GUSTO severe or life-threatening bleeding: 0.9% with prasugrel vs 0.6% with clopidogrel; TIMI major bleeding: 2.1% with prasugrel vs 1.5% with clopidogrel).[112]

Nonthienopyridines

Several nonthienopyridines have been developed to selectively inhibit the $P2Y_{12}$ receptor.[20] Of these, ticagrelor has been the most extensively studied and is being increasingly used in clinical practice. Cangrelor is another nonthienopyridine agent that was recently approved for clinical use. It is the only $P2Y_{12}$ receptor inhibitor available for IV administration. Elinogrel is a direct-acting, reversible $P2Y_{12}$ receptor antagonist that was being development in both an IV and oral formulation. However, the clinical development of this agent has been halted and thus will not be discussed.[129-131]

Ticagrelor

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile Ticagrelor is a nonthienopyridine forming part of a new class of $P2Y_{12}$ inhibitors called cyclopentyltriazolopyrimidines (CPTPs) approved for clinical use by the FDA in 2011.[20,132] Ticagrelor has a direct mechanism of action with very rapid onset (2 hours) and does not require metabolic transformation to inhibit the $P2Y_{12}$ receptor (see Fig. 41–4 and Table 41–1).[20,132] However, approximately 30% to 40% of ticagrelor-mediated antiplatelet effects are attributed to an active metabolite (AR-C124910XX) generated through the hepatic CYP3A system. It reversibly inhibits $P2Y_{12}$ signaling through allosteric modulation of the receptor.[20,132] Ticagrelor is rapidly absorbed and has a half-life of 7 to 12 hours, thus requiring twice-daily dosing. Compared with clopidogrel, ticagrelor exhibits a higher degree of platelet inhibition, a more rapid time to maximal inhibition of platelet aggregation, and more consistent inhibition of platelet aggregation.[133-137] Moreover, ticagrelor has a faster speed of offset than clopidogrel because of its reversible binding.[137]

Non–$P2Y_{12}$-mediated effects of ticagrelor related to increased adenosine plasma levels have also been described (Fig. 41–5).[138-140] Under normal conditions, adenosine has a very short half-life of a few seconds,

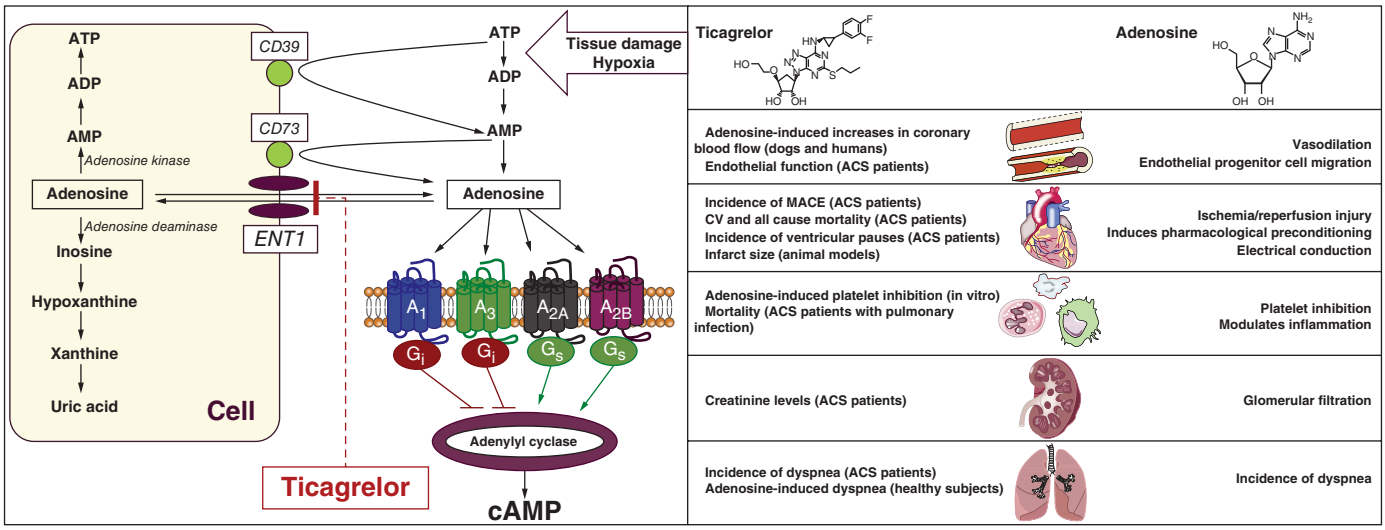


FIGURE 41–5. Major biologic effects mediated by ticagrelor and adenosine. Because adenosine degradation is primarily restricted to the intracellular space, inhibition of cellular uptake of adenosine via the cellular sodium-independent equilibrative nucleoside transporter type 1 (ENT1) results in prolonging the half-life of adenosine, thereby increasing its extracellular (plasma) concentration. Hence, ENT1 inhibition by ticagrelor results in enhanced responses to adenosine, mediated by interaction with the adenosine receptor subtypes A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R, which are coupled to G_s or G_i proteins. There are similarities between the biologic effects of adenosine and the pharmacologic effects of ticagrelor, which suggests that at least some of the non–$P2Y_{12}$-mediated effects of ticagrelor may be mediated by the drug-induced inhibition of ENT1. ACS, acute coronary syndrome; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; CV, cardiovascular; MACE, major adverse cardiovascular events. Reproduced with permission from Cattaneo M, Schulz R, Nylander S: Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol*. 2014 Jun 17;63(23):2503-259.

as it is rapidly taken up by red blood cells and metabolized. Ticagrelor has been shown to significantly inhibit cellular uptake of adenosine by blocking the sodium-dependent equilibrative nucleoside transporters (ENT-1) and thus increasing adenosine plasma concentrations.[138-140] Adenosine has multiple cardiac and extracardiac properties. It inhibits platelet aggregation mainly through the activation of A_{2A} G-coupled receptors, which are particularly upregulated following vascular injury and inflammation; it contributes to arterial vasodilation, reduces inflammatory response, has a negative chronotropic and dromotropic effect, stimulates pulmonary vagal C fibers mediating the sensation of dyspnea, and has a role in the regulation of kidney glomerular filtration.[138-140] Therefore, ticagrelor does not directly act on adenosine receptors, but enhances the biological effects of adenosine, which may contribute to the overall benefits of ticagrelor, including reduction in cardiovascular mortality.[138] These off-target effects may thus contribute to the nonbleeding side effects of ticagrelor, such as higher incidence of dyspnea and ventricular pauses and increased levels of creatinine and uric acid during treatment compared with clopidogrel.[138]

Dosing and Recommendations Ticagrelor is currently approved for the treatment and prevention of secondary atherothrombotic events across the spectrum of patients with ACS, irrespective of the treatment strategy (invasive or noninvasive) and can be administered before coronary anatomy is known as well as in patients pretreated with clopidogrel.[4-9] Treatment with ticagrelor should be initiated with a single 180-mg oral loading dose and continued at 90 mg orally twice daily. Ticagrelor has not been tested in patients with stable CAD and thus is not indicated for this condition. Ticagrelor is contraindicated in patients with high risk of bleeding, with prior hemorrhagic stroke or intracranial bleeding, with severe hepatic dysfunction, and with hypersensitivity. Ticagrelor should not be used in patients with sick sinus syndrome or high-degree atrioventricular block without pacemaker protection. No dose adjustment is required in elderly or low-body-weight patients. Despite the more rapid speed of offset of antiplatelet effects compared to thienopyridines, the high levels of platelet inhibition achieved with ticagrelor warrant a 5-day washout period for patients requiring surgery.[4-9] Because ticagrelor is also metabolized by CYP3A4/5 enzymes, which leads to the generation of an active metabolite (AR-C124910XX) responsible for 30% to 40% of its platelet inhibitory effects, patients taking ticagrelor should avoid the use of strong inhibitors (ie, ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin) or inducers (ie, rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital) of CYP3A; in addition, the use of simvastatin and lovastatin doses > 40 mg should be avoided, and monitoring digoxin levels is recommended with initiation of, or any change in, ticagrelor therapy. Genetic polymorphisms of CYP2C19 or proton pump inhibitors have not been shown to interfere with the effects of ticagrelor.[141,142] High doses of aspirin should be avoided in patients treated with ticagrelor; when aspirin is used in combination with ticagrelor, the dose of aspirin should be < 100 mg daily.[4-9]

Evidence for Use The efficacy and safety of 1-year treatment with ticagrelor plus aspirin versus clopidogrel plus aspirin in patients with ACS (n = 18,624) derive from the phase III PLATO trial (see Table 41–3).[143] Patients included in the trial were admitted either with STEMI intended for primary PCI (38%) or with UA/NSTEMI intended for an invasive or medical approach (62%). Patients were randomized to treatment with either a ticagrelor 180-mg loading dose followed by 90 mg twice daily or a clopidogrel 300-mg or 600-mg loading dose followed by 75 mg daily for prevention of cardiovascular events. At 12 months, the primary end point (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (relative risk reduction, 16%; $P < .001$). The benefits of ticagrelor were driven by a reduction in cardiovascular mortality and MI. Of note, the rate of all-cause death was 22% lower with ticagrelor versus clopidogrel ($P < .001$). Moreover, the benefits of ticagrelor over clopidogrel were irrespective of management (invasive or noninvasive), clinical presentation (NSTE-ACS or STEMI), or revascularization strategy (no revascularization, PCI, or CABG).[144-147] Consistent benefits were observed in key subgroups, such as patients with STEMI, diabetes mellitus, and chronic renal function.[148-150] In a landmark analysis, the difference in treatment effect was apparent within the first 30 days of therapy and persisted up to 12 months after excluding patients with any primary event during the first 30 days. Ticagrelor also reduced the risk of recurrent ischemic events.[151] Among patients who received stents (~ 60% of the study population), ticagrelor was associated with a 25% relative risk reduction in definite/probable stent thrombosis compared with clopidogrel (2.2% vs 2.9%; HR 0.75; $P = .02$). No significant difference in the rates of major bleeding using study definition criteria was found between the ticagrelor and clopidogrel groups, but ticagrelor was associated with a higher rate of major bleeding not related to CABG, including more instances of fatal intracranial bleeding.[152] There were no subgroups that were identified to be at higher risk of bleeding complications, including the elderly and patients with prior TIA/stroke.[153,154]

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) study evaluated the clinical efficacy of prolonged ticagrelor use in patients > 50 years old with a history of MI 1 to 3 years before enrollment plus at least one additional risk factor (≥ 65 years of age, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction) (see Table 41–3).[155] Patients were randomized to either one of two doses of ticagrelor (90 or 60 mg twice a day) or placebo in addition to aspirin. The primary efficacy end point (cardiovascular death, MI, or stroke) was significantly reduced to a similar extent in patients treated with either dose of ticagrelor at 3 years (7.85% in 90 mg twice a day vs 7.77% in 60 mg twice a day vs 9.04% in placebo; $P = .004$ for 90 mg vs placebo and $P = .008$ for 60 mg vs placebo). However, major bleeding was increased with ticagrelor. Major bleeding was numerically lower with the 60-mg dose compared with the 90-mg dose (2.60% in 90 mg vs 2.30% in 60 mg vs 1.06% in placebo; $P < .001$ both for 90 mg vs placebo and 60 mg vs placebo). Importantly, ticagrelor was not associated with an increase in fatal bleedings or ICH. A dose-dependent effect on dyspnea was observed, which also contributed to increased rates of treatment discontinuation. Overall, these findings are supportive of the use of ticagrelor 60 mg twice a day for secondary prevention of long-term ischemic events among patients who experienced a prior MI (> 1 year), although these occur at the expense of increased non–life-threatening major bleeding.[155]

The role of ticagrelor pretreatment in STEMI was tested in the ATLANTIC (Administration of Ticagrelor in the Cath Laboratory or in the Ambulance for New ST-Segment Elevation Myocardial Infarction to Open the Coronary Artery) trial, where patients (n = 1862) undergoing emergency angiography were randomly assigned to receive either prehospital (in the ambulance) or in-hospital (in the cardiac catheterization laboratory) treatment with a 180-mg loading dose of ticagrelor, in addition to aspirin (see Table 41–3).[156] The median time difference in the administration of the loading dose between the two strategies was only 31 minutes. Prehospital ticagrelor did not reduce the co-primary end points (the proportion of patients without a 70% or greater resolution of ST-segment elevation before PCI and the proportion of patients without TIMI flow grade 3 in the infarct-related artery at initial angiography). Although the trial was not powered for

clinical end points, rates of major bleeding were low and very similar between the two groups, suggesting the safety of prehospital ticagrelor administration. Given the extremely low number of events, the finding of a significant reduction in the rate of definite acute (≤ 24 hours) stent thrombosis (0% in the prehospital group vs 0.8% in the in-hospital group) should be considered as exploratory only.

Adverse Effects In the PLATO trial, non–CABG-related major or minor bleeding events (defined according to PLATO criteria) were higher in patients treated with ticagrelor compared with clopidogrel (7.7% vs 6.2%).[152] In particular, non–CABG-related major bleeding was significantly higher in patients treated with ticagrelor (4.5% vs 3.8%; $P = .03$). Also, with ticagrelor as compared with clopidogrel, there were more episodes of intracranial bleeding (0.3% vs 0.2%; $P = .06$), including fatal intracranial bleeding (0.1% vs 0.01%; $P = .02$). On the contrary, CABG-related major bleeding (7.4% vs 7.9%), non–CABG-related plus CABG-related major bleeding (11.6% vs 11.2%), life-threatening or fatal bleeding (5.8% vs 5.8%), and ICH (0.3% vs 0.2%) were similar in ticagrelor- and clopidogrel-treated patients.[152]

Interestingly, a predefined subgroup analysis of patients enrolled in the PLATO trial showed a borderline significant interaction with enrollment geographic area ($P = .05$), driven by a trend toward more efficacy of clopidogrel rather than ticagrelor among patients recruited in North America.[35] This interaction was attributed to the different dosing regimen of aspirin, whereas in North America there was a higher prevalence of high-dose (> 300 mg) aspirin use. The greatest benefit of ticagrelor was among patients using low-dose aspirin (< 100 mg). For this reason, when aspirin is used in combination with ticagrelor, only low-dose aspirin (< 100 mg) should be used.[4-9]

In the PEGASUS trial, patients treated with ticagrelor in addition to aspirin experienced significantly increased TIMI major bleeding compared with aspirin alone (1.7% vs 0.8%), as well as more TIMI major and minor bleeding (2.4% vs 1.0%). The rates of fatal bleeding (0.2% vs 0.2%) and ICH (0.4% vs 0.3%) were low and similar between patients receiving ticagrelor and those receiving placebo, respectively.[155]

In PLATO, rates of other adverse events were higher with ticagrelor versus clopidogrel: dyspnea (13.8% vs 7.8%; $P < .001$), syncope (1.1% vs 0.8%; $P = .08$), ventricular pauses ≥ 3 seconds during the first week of treatment (5.8% vs 3.6%; $P = .01$), and increase in serum uric acid and serum creatinine at 1 month and 1 year ($P < .001$ for each comparison).[143] Discontinuation of the study drug as a result of adverse events occurred more frequently with ticagrelor than with clopidogrel (7.4% of patients vs 6.0%; $P < .001$). Interestingly, a predefined subgroup analysis of patients enrolled in the PLATO trial showed a borderline significant interaction with enrollment geographic area ($P = .05$), driven by a trend toward more efficacy of clopidogrel than ticagrelor among patients recruited in North America.[35] In the PEGASUS trial, the rate of dyspnea in patients receiving ticagrelor was even higher compared with that reported in PLATO. Of note, the incidence of this adverse event was lower in patients receiving ticagrelor 60 mg (15.8%) than those receiving ticagrelor 90 mg (18.9%).[155]

In clinical trials, dyspnea was usually mild to moderate in intensity and often resolved during continued treatment but led to study drug discontinuation in 0.9% of ticagrelor-treated patients in PLATO and 4.5% of patients treated with ticagrelor 60 mg and 6.5% of patients treated with ticagrelor 90 mg in PEGASUS.[143,155] Importantly, in a substudy of PLATO, 199 subjects underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no signal of a negative effect of ticagrelor treatment on pulmonary function assessed after 1 month or after at least 6 months of chronic treatment.[157] If a patient develops new, prolonged, or worsened dyspnea that is determined to be related to ticagrelor, no specific treatment is required; ticagrelor should be continued without interruption if possible. In the case of intolerable dyspnea requiring discontinuation of ticagrelor, another antiplatelet agent should be prescribed.

Cangrelor

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile Cangrelor is an IV adenosine triphosphate (ATP) analog (see Fig. 41–5 and Table 41–1).[20,158] Compared with ADP, ATP has less affinity to the $P2Y_1$ and $P2Y_{12}$ receptors because it is rapidly metabolized by ectonucleotidases.[14,15] The final therapeutic compound of cangrelor [2-trifluoropropylthio, N-(2-(methylthio)ethyl)-β,γ-dichloromethylene ATP] was modified from ATP to confer higher affinity for the $P2Y_{12}$ receptor, longer half-life, and higher antagonistic properties with a potency increased by six times.[20,158] As a result, cangrelor has high affinity for the $P2Y_{12}$ receptor and a higher resistance to ectonucleotidases, does not require hepatic conversion, and is directly active. Although its binding site at the $P2Y_{12}$-receptor level is not clearly defined, cangrelor is associated with high levels of receptor occupancy, preventing ADP signalling.[20,158] Cangrelor reaches steady-state concentrations within few minutes, and its linear dose-dependent pharmacokinetic profile results in predictable plasma levels and more stable pharmacodynamic effects.[158-160] In the setting of ACS, more than 80% of patients showed complete inhibition of ADP-induced platelet aggregation with an infusion dose of 4 μg/kg/min.[158-160] Because cangrelor has a very short plasma half-life (3-6 minutes) and is promptly inactivated through dephosphorylation, recovery of platelet function is very rapid (30-60 minutes) after discontinuation of IV infusion.[158-160]

Dosing and Recommendations Cangrelor was approved by the FDA in 2015 as an adjunct to PCI for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet receptor inhibitor and are not being given a GP IIb/IIIa inhibitor (GPI). Cangrelor should be administered with a 30 μg/kg IV bolus prior to PCI followed immediately by a 4 μg/kg/min infusion for at least 2 hours or the duration of the procedure, whichever is longer. Cangrelor was also approved for clinical use by the European Medical Agency for patients undergoing PCI who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable.

Given the different pharmacologic properties of cangrelor and oral $P2Y_{12}$ receptor antagonists (see Table 41–1), concerns have emerged about the potential for drug interactions when these different agents are concomitantly administered, which could result in increased platelet reactivity and lack of protection from antithrombotic complications.[19,161] Investigations conducted in healthy volunteers showed that administration of clopidogrel during a cangrelor infusion leads to inadequate clopidogrel-induced antiplatelet effects, as clopidogrel cannot bind to the $P2Y_{12}$ receptor while this is occupied by cangrelor.[161] However, clopidogrel-induced antiplatelet effects are not affected when it is administered after cangrelor infusion, given the very rapid offset of action of cangrelor.[162] Similar findings were observed in blood incubated with cangrelor before the addition of the active metabolites of clopidogrel or prasugrel, in which the capacity of these thienopyridines to inhibit platelet aggregation was strongly reduced.[162] Conversely, addition of cangrelor to blood preincubated with the active metabolites of clopidogrel or prasugrel, as well as blood from patients treated with these agents, led to enhanced and sustained platelet inhibition.[162,163] Pharmacodynamic studies in patients with stable coronary artery disease have been conducted to define the optimal transition strategy from cangrelor to oral agents.[164-166] These studies showed no interaction when cangrelor was administered on top of prasugrel or ticagrelor.[164,165] No interaction was also demonstrated when transitioning from cangrelor to ticagrelor.[164] The transition from cangrelor to prasugrel

was instead associated with transient recovery of platelet aggregation within 1 hour after cangrelor discontinuation, which was attenuated when prasugrel was administered 30 minutes before stopping cangrelor infusion.[165] On the other hand, administration of clopidogrel 30 minutes or 1 hour before discontinuation of the cangrelor infusion did not prevent recovery of platelet reactivity more effectively than administration at the end of the infusion.[166] The presence of an interaction between thienopyridines and cangrelor, but not between ticagrelor and cangrelor, is probably the result of the different sites and types of binding of these drugs to the $P2Y_{12}$ receptor, as well as their different half-lives (see Table 41–1).[19,161]

Results of these pharmacodynamic studies have been endorsed by the FDA, which recommend that, when transitioning from cangrelor to an oral agent, the loading dose of ticagrelor can be administered at any time during cangrelor infusion or immediately after discontinuation, while the loading doses of prasugrel and clopidogrel should be administered immediately after infusion discontinuation. The European Medical Agency suggests to administer prasugrel immediately following discontinuation of the cangrelor infusion or up to 1 hour before, optimally at 30 minutes, to limit recovery of platelet reactivity.

Although cangrelor has been tested as a bridging strategy in patients undergoing CABG, it has yet to be tested as a bridging strategy in other surgeries and is not approved by drug-regulating authorities for this indication.[167]

Evidence for Use The role of cangrelor as adjunctive antiplatelet therapy in patients requiring PCI has been tested in three large-scale phase III clinical trials.[168-170] Although, the first two trials, namely the CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition)-PCI and the CHAMPION-PLATFORM trials were interrupted for futility and failed to document any ischemic benefit of cangrelor over DAPT with aspirin and clopidogrel, pitfalls in study end point definitions (eg, MI definition) may have contributed to these results.[168,169,171] In fact, a pooled analysis of the CHAMPION-PCI and CHAMPION-PLATFORM trials, which used the Universal Definition of MI to define MI events, showed a significant reduction in the primary end point with the use of cangrelor.[171] The hypothesis-generating data from this analysis led to the design of the CHAMPION-PHOENIX trial, which evaluated whether addition of cangrelor on top of DAPT with aspirin and clopidogrel in patients undergoing PCI could reduce the occurrence of acute ischemic complications (see Table 41–3).[170] The study included $P2Y_{12}$ receptor inhibitor–naïve patients across the spectrum of CAD manifestations (stable angina, NSTE-ACS, and STEMI). After angiography, patients (n = 11,145) were randomized to receive either cangrelor bolus (30 μg/kg) followed by infusion (4 μg/kg/min for 2-4 hours) or clopidogrel loading dose (300 or 600 mg before or immediately after the PCI, as per institutional standard). In the cangrelor arm, patients received 600 mg of clopidogrel at the end of infusion. The primary efficacy end point was a composite of death from any cause, MI, ischemia-drive revascularization, and stent thrombosis at 48 hours. Adjunctive cangrelor therapy significantly reduced the primary efficacy end point at 48 hours (4.7% vs 5.9%; adjusted odds ratio [OR] with cangrelor, 0.78; $P = .005$), primarily driven by a reduction in the hazard of MI (3.8% vs 4.7%; $P = .02$). The use of cangrelor led to a significant reduction in the rate of stent thrombosis at 48 hours (0.8% vs 1.4%; OR 0.62; $P = .01$). Intraprocedural stent thrombosis, which was shown to be associated with an increase in adverse outcomes at 48 hours and 30 days, was also significantly reduced.[172] The rate of severe bleeding at 48 hours was not significantly increased by cangrelor with GUSTO criteria, as well as with other definitions of bleeding. However, the rate of major bleeding according to the more sensitive Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) criteria was significantly higher in patients treated with cangrelor, primarily driven by a higher incidence of hematoma at the site of vascular access. Importantly, in a post hoc analysis, the primary efficacy end point and the primary safety end point were combined to provide a composite end point of the net rate of adverse clinical events, which was significantly reduced by the use of cangrelor (4.8% vs. 6.0%; OR 0.80; $P = .008$). The clinical benefit of adjunctive cangrelor therapy was consistent at 30 days and across multiple prespecified subgroups, such as different clinical presentation (stable angina, NSTE-ACS, or STEMI), dose and timing of clopidogrel loading, stent type, and duration of study drug infusion. These results were further confirmed by a pooled analysis on approximately 25,000 patients enrolled in the three CHAMPION trials.[173]

Cangrelor has also been tested as a bridging strategy in patients (n = 210) on thienopyridine treatment (including patients with a recent MI) and requiring CABG, showing high and stable levels of platelet inhibition after up to 7 days of infusion (0.75 μg/kg/min), with a rapid offset after discontinuation prior to surgery. This strategy was not associated with an increased risk of major bleeding or side effects before or during CABG, although these findings need to be interpreted with caution because the study was not powered for clinical outcomes.[167]

Adverse Effects In the CHAMPION-PHOENIX trial, the primary safety end point was severe non–CABG-related bleeding at 48 hours, according to the GUSTO criteria.[174] Addition of cangrelor to DAPT with aspirin and clopidogrel did not significantly increase the rate of GUSTO-defined severe bleeding (0.16% in the cangrelor group vs 0.11% in the clopidogrel group; OR 1.50; $P = .06$), as well as the rates TIMI major and type 3 Bleeding Academic Research Consortium (BARC) bleeding, at 48 hours. Accordingly, the use of cangrelor did not increase the occurrence of GUSTO severe or moderate bleeding, TIMI major or minor bleeding, or the need for blood transfusions. No significant difference in the rate of GUSTO severe or moderate bleeding was shown in any subgroup. However, the rate of major bleeding according to the more sensitive ACUITY criteria was significantly higher in patients receiving cangrelor (4.3% vs 2.5%; OR 1.72; $P < .001$). This was primarily driven by more hematomas in the site of vascular access.[31] Although after excluding hematomas ≥ 5 cm the difference between groups was no longer significant (0.8% vs 0.5%; $P = .05$), the effects on bleeding events were consistent irrespective of access site (femoral vs radial).[175] The analysis of pooled data on all the patients enrolled in the three CHAMPION trials showed that treatment with cangrelor did not increase the risk of severe bleeding events, as measured by GUSTO severe or life-threatening bleeding, GUSTO moderate bleeding rates, or TIMI major bleeding rates.[173] It also did not increase the rate of transfusions, though it did increase the rate of less severe bleeding events such as GUSTO mild, TIMI minor, or ACUITY bleeds. The safety profile of cangrelor in the pooled analysis of the CHAMPION trials was consistent regardless of the periprocedural use of GPIs (P for interaction = .493).[173] Overdosing with cangrelor was not associated with an increase in bleeding rates, and there was no overall correlation between bleeding and the magnitude of cangrelor overdose, which may be attributed to the rapid offset of effects.[176] Overall, cangrelor increases bleeding events compared with control, although this was only apparent considering fairly sensitive measures of bleeding, which correspond to less clinically severe events.

In the CHAMPION trials, patients treated with cangrelor experienced a higher incidence of transient dyspnea (1.1% vs 0.4%; $P < .001$).[173,174] However, dyspnea-related treatment discontinuations were rare, although more frequent in the cangrelor group (0.1% vs 0%). Accordingly, in the BRIDGE trial, prolonged infusion with cangrelor (up to 7 days; median duration, ~ 3 days) led to a low but numerically increased incidence of dyspnea (1.9% vs 1%).[167]

GLYCOPROTEIN IIB/IIIA INHIBITORS

The GP IIb/IIIa receptor is an integrin that mediates the final common pathway of platelet aggregation.[177] There are approximately 80,000 receptors on the platelet surface.[178] Integrins are heterodimers consisting of noncovalently associated α- and β-subunits.[179] The GP IIb/IIIa receptor consists of the α IIb and β 3 subunits. The α-subunit is a 136-kDa molecule with a light and heavy chain; the light chain contains a short cytoplasmic tail, a transmembrane region, and a short extracellular domain, whereas the heavy chain is entirely extracellular.[180] The β-subunit is a 84.5-kDa molecule with a short intracellular tail, a transmembrane region, and a large extracellular domain.[181] Platelet activation leads to a conformational change in the GP IIb/IIIa receptor, markedly increasing its affinity for its ligands through its binding sites.[182] There are two main binding sites on the GP IIb/IIIa receptor. One recognizes the amino acid sequence arginine-glycine-aspartic acid (Arg-Gly-Asp or RGD) that is found on multiple ligands (fibronectin, vWF, and vitronectin) but most importantly on fibrinogen, the major GP IIb/IIIa ligand, in which the RGD sequence occurs twice.[183] The other peptide sequence is the Lys-Gln-Ala-Gly-Asp-Val, which is only located at the carboxyl terminus of the γ chain of fibrinogen.[184] By competing with fibrinogen and vWF for GP IIb/IIIa binding, GP IIb/IIIa antagonists interfere with platelet aggregation.[185] Because the GP IIb/IIIa receptor represents the final common pathway leading to platelet aggregation, these agents are more effective than other antiplatelet agents, such as aspirin and clopidogrel, in inhibiting platelets. The pharmacology of parenteral glycoprotein IIb/IIIa inhibitors are summarized in Table 41–4.

Parenteral Glycoprotein IIb/IIIa Inhibitors

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile Currently, there are three parenteral GP IIb/IIIa antagonists in clinical use: abciximab, eptifibatide, and tirofiban. These agents are indicated only in patients with ACS undergoing PCI. Therefore, they are only administered within the hospital setting and are not used in the long-term care of patients with atherothrombotic vascular disease. Both preclinical and clinical pharmacodynamic studies have set the range of greater than 80% inhibition of platelet aggregation by light transmission aggregometry as the target for clinically effective antiplatelet activity.[186] The degree of platelet inhibition appears central to the efficacy of GPIs; achieving > 95% platelet inhibition 10 minutes after the bolus in patients undergoing PCI was associated with a 55% reduction in major adverse cardiac events compared with those patients with < 95% platelet inhibition.[187] Although GPIs have been shown to reduce major adverse cardiac events (death, MI, and urgent revascularization) by 35% to 50% in patients undergoing PCI, their broad use has been limited because they are associated with an increased risk of bleeding complications.[188] Moreover, their use has declined over the past few years because of treatment alternatives, such as bivalirudin, associated with a more favorable safety profile (ie, less bleeding) as well as the introduction of potent $P2Y_{12}$ receptor inhibitors.

Abciximab is a large chimeric monoclonal antibody with a high binding affinity that translates into a prolonged pharmacologic effect.[189,190] In particular, it is a monoclonal antibody that is a Fab (fragment-antigen binding) fragment of a chimeric human-mouse genetic reconstruction of 7E3. The Fc portion of the antibody was removed to decrease immunogenicity, and the Fab portion was attached to the constant regions of a human immunoglobulin. Abciximab has a high affinity for its receptor. Abciximab binding is specific for the β_3-subunit and explains its ability to bind other β_3-receptors. It has an almost equal potency for inhibition of the vitronectin ($\alpha V\beta_3$) receptor and a lower affinity for cross-reacting with Mac-1 receptor (CD11b/CD18, $\alpha M\beta_2$) found on leukocytes.[191] Unlike the small-molecule GPIs, abciximab interacts with the GP IIb/IIIa receptor at sites distinct from the ligand-binding RGD sequence site and exerts its inhibitory effect noncompetitively.[192] Its plasma half-life is biphasic, with an initial half-life of less than 10 minutes and a second-phase half-life of approximately 30 minutes.[193] However, because of its high affinity for the receptor, it has a biological half-life of 12 to 24 minutes, and because of its slow clearance from the body, it has a functional half-life up to 7 days.[194] Because of the high affinity of abciximab for GP IIb/IIIa, the number of abciximab molecules bound to platelets is considerably higher than the free plasma pool of the drug for the duration of treatment, and platelet-associated abciximab can be detected for more than 14 days after the infusion is stopped.[193] With an average period of platelet circulation of approximately 7 days, it appears that abciximab molecules can freely dissociate and reassociate with GP IIb/IIIa as the turnover of platelets in the circulation continues. The recommended dose for abciximab is 0.25 mg/kg bolus followed by an IV infusion of 0.125 μg/kg/min for 12 hours. No renal adjustments are required.[4-9]

Eptifibatide and tirofiban are also known as small-molecule agents. Contrary to abciximab, these agents do not induce immunologic reactions and have lower affinity for the GP IIb/IIIa receptor. The stoichiometry of both eptifibatide and tirofiban is > 100 molecules of drug per GP IIb/IIIa receptor needed to achieve full platelet inhibition. This compares with a stoichiometry of 1.5 molecules of abciximab for each receptor.[195,196] Eptifibatide is a small, reversible, and highly selective heptapeptide with a rapid onset

TABLE 41–4. Pharmacology of Glycoprotein IIb/IIIa Inhibitors

	Abciximab	Eptifibatide	Tirofiban
Molecule	Fragment antigen binding (Fab)[7E3]	Synthetic peptide	Nonpeptide mimetic
Molecular weight	~ 50,000	~ 800	~ 500
Stoichiometry (drug to GP IIb/IIIa)	~ 1.5:1	> 100:1	> 100:1
Binding	Noncompetitive	Competitive	Competitive
Half-life	Plasma: 10-15 h	Plasma: 2-2.5 h	Plasma: 2-2.5 h
	Biologic: 12-24 h	Biologic = plasma	Biologic = plasma
PCI dosing	Bolus: 0.25 mg/kg (10-60 min)	Bolus: 180 μg/kg[a] + 180 μg/kg (after 10 min)	Bolus: 25 μg/kg (30 min)
	Infusion: 0.125 μg/kg/min (12 h)	Infusion: 2 μg/kg/min (24-48 h)[b]	Infusion: 0.10 μg/kg/min (48 h)
Renal adjustment	No	Bolus: 180 μg/kg	Bolus: 12.5 μg/kg (30 min)
		Infusion: 1 μg/kg/min (24-48 h)	Infusion: 0.10 μg/kg/min (48 h)

Abbreviations: GP, glycoprotein; PCI, percutaneous coronary intervention.

[a]Started immediately before PCI.

[b]Started immediately after the first bolus.

and a short plasma half-life (2-2.5 hours).[195,196] Its molecular design is based on barbourin, a 73-amino acid peptide isolated from the venom of the Southeastern pygmy rattlesnake *Sistrurus miliarius barbouri*.[196] This is a unique member of the disintegrin family that contains a novel Lys-Gly-Asp (KGD) sequence, making it highly specific for the GP IIb/IIIa receptor. Plasma concentration of eptifibatide is proportional to the administered dose. Approximately 25% of eptifibatide molecules in the plasma are protein bound, leaving the remaining 75% to constitute the pool of pharmacologically active drug.[195] The recommended dose for eptifibatide depends on its indication for use.[4-9] The initial bolus treatment ranges from 135 μg/kg when administered for the treatment of an ACS to a double bolus of 180 μg/kg when administered for PCI. Accordingly, the recommended continuous infusion dosing regimen ranges from 0.5 μg/kg/min to 2.0 μg/kg/min for an ACS (for up to 72 hours) versus PCI (for a minimum of 12 hours), respectively. With the recommended bolus (180 μg/kg followed by second 180 μg/kg bolus) and infusion (2 μg/kg/min) regimen, peak plasma levels are established shortly after the bolus dose, and slightly lower concentration are subsequently maintained throughout the infusion period. Plasma concentration decreases rapidly after the infusion is discontinued. Because the majority of the drug is eliminated via the kidney, a lower infusion dose (1 μg/kg/min) of eptifibatide is recommended in patients with creatinine clearance less than 50 mL/min. Substantial recovery of platelet aggregation is apparent within 4 hours of completion of infusion, whereas bleeding times return to baseline within 1 hour.[195]

Tirofiban is a tyrosine-derived nonpeptide inhibitor that functions as a mimic of the RGD sequence and is highly specific for the GP IIb/IIIa receptor.[197] Tirofiban is associated with a rapid onset and short duration of action, with a plasma half-life of approximately 2 hours.[186] Like eptifibatide, substantial recovery of platelet aggregation is apparent within 4 hours of completion of infusion.[195] The recommended dosing regimen for an ACS is a bolus of 0.4 μg/kg/min for 30 minutes followed by infusion of 0.10 μg/kg/min. Because the majority of the drug is eliminated through renal mechanisms, doses need adjustments for patients with renal insufficiency starting at a creatinine clearance of 30 mL/min (bolus of 0.2 μg/kg/min for 30 minutes followed by infusion of 0.05 μg/kg/min). In patients undergoing PCI, the dose of 10 μg/kg bolus followed by infusion of 0.15 μg/kg/min for 18 to 24 hours was used for many years. However, studies have documented that this approved bolus and infusion regimen for tirofiban achieves suboptimal levels of platelet inhibition for up to 4 to 6 hours that likely accounted for inferior clinical results in the PCI setting.[198] Subsequent pharmacodynamic investigations have shown improved platelet inhibition with higher bolus regimens, with a loading bolus dose of 25 μg/kg leading to better early platelet inhibition.[199,200] The high-dose bolus regimen, consisting of 25 μg/kg bolus over 3 minutes followed by a 0.15 μg/kg/min infusion for up to 18 hours at the time of PCI was approved in Europe in 2010. It achieves greater than 90% inhibition of platelet aggregation within 10 minutes. In patients with renal insufficiency (creatinine clearance ≤ 60 mL/min), the dose is reduced to 25 μg/kg over 3 minutes followed by a 0.075 μg/kg/min infusion. The benefit of the high-dose bolus regimen was confirmed in a multitude of studies.[200] A high-dose bolus regimen of tirofiban was recently approved by the FDA in 2013, which indicates to administer the drug intravenously with a dose of 25 μg/kg within 5 minutes and then 0.15 μg/kg/min for up to 18 hours. In patients with creatinine clearance ≤ 60 mL/min, give 25 μg/kg within 5 minutes and then 0.075 μg/kg/min.

Dose-finding studies for both tirofiban and eptifibatide have identified the dose of these agents associated with similar pharmacodynamic effects of abciximab, which have also resulted in noninferiority of these drugs. These have led to changes in the level of evidence of the use of small-molecule GPIs in practice guidelines, which is now similar to that of abciximab.[4-9]

Evidence for Use Before the era of pretreatment with high loading doses of clopidogrel, the safety and efficacy of GP IIb/IIIa inhibition were tested in a large number of clinical studies that included patients with ACS as well as stable CAD. The landmark trial demonstrating efficacy of GP IIb/IIIa inhibition in the PCI setting was the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial.[201] In this study, high-risk patients undergoing balloon angioplasty were randomized to abciximab bolus and infusion versus abciximab bolus alone versus placebo. The group treated with abciximab bolus and infusion had a 35% lower rate of death, MI, or unplanned urgent revascularization at 30 days compared with the placebo group (8.3% vs 12.8%; $P = .008$). No significant benefit with abciximab bolus alone was observed, suggesting that shorter duration of platelet inhibition was insufficient to favorably affect clinical outcomes. A significant reduction in the primary end point with abciximab was also observed up to 3 years.[202] Major bleeding complications occurred in a high proportion of patients treated with abciximab compared with placebo (major bleeding 14% vs 7%, transfusion 15% vs 7%, respectively). A series of procedural modifications, including performing front-wall arterial access only, reducing arterial sheath size (from 8-Fr to 6-Fr), reducing heparin dosing (target activated clotting time [ACT] 200-250 seconds rather than > 300 seconds), removing sheaths as soon as possible (ACT < 180 seconds) rather than keeping them overnight, and abandoning the use of routine venous sheaths, markedly reduced major bleeding complications to less than 1% to 1.5% in future trials.

After the EPIC trial, the Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) trial was performed and also included patients undergoing balloon angioplasty but who were at a lower risk than patients in EPIC.[203] In EPILOG, abciximab was given with two different lower doses of weight-adjusted heparin than those administered in EPIC; a lower weight-adjusted infusion dose of abciximab was also implemented. This study was stopped prematurely as a result of efficacy with a significant reduction in the incidence of death and MI in patients treated with abciximab. Bleeding was lowest in patients who received the lower dose of heparin. Similar results were reported in the Evaluation of Platelet GP IIb/IIIa Inhibition in Stenting (EPISTENT) trial, which was the first randomized trial examining the use of GPIs among patients undergoing stent placement.[204] This trial randomized 2399 patients to stent plus placebo, stent plus abciximab, or balloon angioplasty plus abciximab. The primary 30-day end point, a combination of death, MI, or urgent revascularization, occurred in 10.8% of patients in the stent plus placebo group, 5.3% of those in the stent plus abciximab group (HR 0.48; $P < .001$), and 6.9% in the group undergoing balloon angioplasty plus abciximab (HR 0.63; $P = .007$). These benefits were maintained up to 1 year, with a significant reduction in 1-year mortality in patients treated with stent plus abciximab compared with stent without the IIb/IIIa inhibitor (2.4% vs 1.0%; $P = .037$).[205] No significant differences in bleeding complications were noted among the various groups.

The first major trial to investigate eptifibatide was the Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis-II (IMPACT-II) trial.[206] In this trial, a significant reduction of ischemic events was found 24 hours after PCI. However, by 30 days, the difference was no longer statistically significant. Retrospective pharmacodynamic analysis of platelet function determined that a suboptimal dose of eptifibatide had been selected.[207] Therefore, the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin (ESPRIT) trial used a higher dose of eptifibatide than was used in IMPACT-II.[208] The ESPRIT

trial randomized 2064 patients undergoing stenting to eptifibatide (180 μg/kg bolus followed by a 2.0 mg/kg/h infusion with a second bolus of 180 μg/kg given 10 minutes after the first bolus) or placebo. In this trial, patients were administered a loading dose of clopidogrel or ticlopidine on the day of the procedure. The trial was terminated early for efficacy. The primary end point (composite of death, MI, urgent revascularization, or thrombotic bailout at 48 hours) was reduced by 37% with eptifibatide (10.5% vs 6.6%; $P = .0017$). These benefits were maintained at 6 months[209] and up to 1 year.[210] Major bleeding was rare but occurred more frequently in patients receiving eptifibatide compared with placebo (1.3% vs 0.4%, respectively; $P = .027$).

On the basis of these trials, GPIs became a cornerstone in treatment of patients undergoing PCI because of their ability to improve short- and long-term outcome, mostly by reducing the occurrence of periprocedural MI. Subsequently, however, it was shown that the benefits of GP IIb/IIIa blockade were reduced if patients were pretreated with a thienopyridine.[211,212] In the first Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, low- to intermediate-risk patients (n = 2159) undergoing elective PCI, all of whom had been pretreated for at least 2 hours with a 600-mg loading dose of clopidogrel, were randomized to receive either abciximab therapy or placebo in a double-blind manner.[213] The composite end point (death, MI, and urgent target vessel revascularization at 30 days) was similar in the two treatment groups ($P = .82$). The benefit was sustained at 1 year.[214] Overall, these findings suggest that abciximab offers no further clinical benefit in low- to intermediate-risk patients scheduled for PCI if they have been pretreated with 600 mg of clopidogrel for at least 2 hours. The impact of adjunctive abciximab treatment in patients pretreated with a 600-mg loading dose of clopidogrel in an ACS setting was evaluated in the ISAR-REACT 2 trial.[215]

Diabetic patients with CAD who undergo PCI, particularly those requiring insulin, represent a special group of patients characterized by a worse outcome after PCI as a result of an increased risk of both thrombosis and restenosis.[216] A meta-analysis of six large trials evaluating the effect of GPIs in ACS patients observed a 22% reduction of mortality at 30 days in diabetes mellitus patients (n = 6458) associated with the use of GP IIb/IIIa blockers compared with those not receiving these agents (4.6% vs 6.2%; $P = .007$), whereas nondiabetic patients (n = 23,072) had no benefit in survival.[217] Of note, the benefit among diabetic patients was greater in patients (n = 1279) who underwent PCI during the index hospitalization (1.2% vs 4%; $P = .002$). However, few patients included in these trials were adequately pretreated with a thienopyridine.

The Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) trial was the first dedicated randomized trial evaluating GP IIb/IIIa blockade in diabetic patients scheduled for elective PCI.[218] The trial was designed similarly to ISAR-REACT, and patients were randomized to treatment with abciximab or placebo after having all been pretreated with a 600-mg loading dose of clopidogrel. However, in this trial, abciximab did not reduce incidence of the composite end point (death or MI) at 30 days or 1 year (abciximab 8.3% vs placebo 8.6%; $P = .91$). Interestingly, angiographic restenosis and target vessel revascularization was significantly lower in the group of diabetic patients who received abciximab ($P = .01$ and $P = .03$, respectively). The impact of abciximab on the reduction of restenosis was subsequently investigated in the Intracoronary Stenting or Angioplasty for Restenosis in Small Arteries (ISAR-SMART) 2 trial, in which abciximab failed to reduce the incidence of angiographic restenosis after PCI of small coronary arteries.[219] The inability of abciximab to reduce restenosis was also shown in other studies.[220-222]

Glycoprotein IIb/IIIa Inhibitors in Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction Patients The first trial to evaluate abciximab in patients with an ACS was the EPIC trial, in which only patients undergoing PCI were included and there was a 35% reduction in the combined end point for the group of patients treated with an abciximab bolus plus infusion.[201] In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, 1265 patients with refractory angina undergoing PCI were randomly assigned to receive abciximab 18 to 24 hours before PCI and for 1 hour after completion of the procedure or placebo.[223] The primary end point, composite of death, MI, or urgent revascularization, was reduced in the abciximab group compared with placebo (15.9% vs 11.3%; $P = .012$). There was a significant increase in major bleeding (1.9% vs 3.8%; $P = .043$) and the need for transfusion (3.4% vs 7.1%; $P = .005$) in the abciximab group compared with placebo. Importantly, in a retrospective subgroup analysis of patients with an elevated and normal troponin T, it was demonstrated that only patients with an elevated troponin derived benefit from abciximab.[224] The role of abciximab in ACS patients treated medically was investigated in the Global Use of Strategies to Open Occluded Arteries IV-Acute Coronary Syndrome Trial (GUSTO-IV ACS),[225] in which 7800 patients with UA/NSTEMI were randomized to receive placebo, abciximab for 24 hours, or abciximab for 48 hours. In this trial, PCI was prohibited by protocol for the first 60 hours after enrollment. This was the first study of abciximab that failed to show any benefit. In fact, not only was there no benefit, but there was a trend toward higher rates of MI and death with abciximab, which was greatest with the longer duration of treatment. Bleeding and thrombocytopenia were significantly increased by abciximab. Therefore, there is no evidence supporting the use of abciximab in ACS patients not undergoing PCI.

In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, 10,948 patients with UA/NSTEMI were randomized to eptifibatide or placebo.[226] A third arm with low-dose eptifibatide (1.3 μg/kg/min) was stopped prematurely by design after 3218 patients had been randomized, and the safety of the high-dose eptifibatide (2.0 μg/kg/min) arm was found to be acceptable. The primary end point of 30-day death or MI was reduced in patients receiving eptifibatide versus placebo (14.2% vs 15.7%; $P = .042$). This treatment benefit was more pronounced among patients undergoing PCI within 72 hours of presentation (11.6% vs 16.7%; $P = .01$). Moderate or severe hemorrhage was more common in the eptifibatide group (12.8% vs 9.9%; $P < .001$).

Tirofiban was studied in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, in which 1915 patients with high-risk UA/NSTEMI were assigned to tirofiban, tirofiban plus heparin, or heparin alone.[227] The combination of tirofiban and heparin led to a 32% risk reduction in the rate of death, MI, or recurrent refractory ischemia at 7 days compared with heparin alone (12.9% vs 17.9%; $P = .004$). The tirofiban treatment effect was also observed in patients (n = 475) undergoing PCI, with a 44% relative reduction in death or MI at 30 days.

Limited data are available on head-to-head comparisons of the different GPIs. Two GPIs, tirofiban and abciximab, were compared in the Do Tirofiban and ReoPro Give Similar Efficacy Outcomes (TARGET) trial, which randomized 5308 patients to tirofiban or abciximab before undergoing PCI with the intent to perform stenting.[222] The primary end point was a composite of death, nonfatal MI, or urgent target vessel revascularization at 30 days. The primary end point (6.0% vs 7.6%; $P = .038$) and the incidence of MI (5.4% vs 6.9%; $P = .04$) were significantly lower in the abciximab group compared with the tirofiban group. There was no significant difference in the rate of major bleeding between the two groups; however, the incidence of minor bleeding and

thrombocytopenia was significantly greater in the abciximab group. It was subsequently shown that the loading dose of tirofiban used in the trial was too small to inhibit platelet aggregation sufficiently in the crucial first 20 minutes after tirofiban had been given. In fact, the FDA approved dosing regimens for abciximab and eptifibatide that result in profound platelet inhibition (> 80%) within 10 minutes of the bolus. In contrast, the dosing regimens for tirofiban in the PRISM-PLUS (0.4 μg/kg/min load over 30 minutes followed by an infusion of 0.1 μg/kg/min for 12-24 hours thereafter) and TARGET trials (10 μg/kg bolus followed by an infusion of 0.15 μg/kg/min for 18-24 hours after PCI) led to inadequate platelet inhibition (60%-80%) up to 3 to 6 hours after the bolus, leading investigators to recommend that the bolus dose for tirofiban may need to be increased 2.5- to 3-fold.[199,200,228] Subsequent studies revealed that the loading dose had to be 2.5 times larger than was used in TARGET to provide the same degree of inhibition of aggregation as abciximab, with several small randomized clinical trials showing that tirofiban was as effective as abciximab.[200,228]

Timing of Administration of Glycoprotein IIb/IIIa Inhibitors in Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction Patients Two different timing strategies for the administration of GPIs have been used in the large randomized trials reviewed earlier: either early after the diagnosis of ACS before angiography (*upstream* treatment) or in the cardiac catheterization laboratory in patients about to undergo PCI. The optimal timing strategy of GP IIb/IIIa administration was assessed in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Timing trial, in which a total of 9207 ACS patients undergoing an invasive treatment strategy were randomly assigned to receive either routine upstream versus selective in-lab treatment with a GPI.[229] All three GPIs currently in clinical use (abciximab, tirofiban, and eptifibatide) could be used. The main result of the trial is that after 30 days, the routine upstream use of GPIs in ACS patients with an invasive strategy produced a nonstatistically significant 12% decrease in the combined end point of death, MI, or target vessel revascularization. The difference (7.9% for in-lab vs 7.1% for upstream) did not meet the criterion for noninferiority. Importantly, the duration of upstream treatment was somewhat limited (~4 hours). Most recently, the Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial evaluated early administration of eptifibatide versus matching placebo infusion with provision of eptifibatide after angiography (delayed eptifibatide) in 9492 patients with UA/NSTEMI undergoing invasive management.[230] The primary end point occurred in 9.3% of patients in the early-eptifibatide group and in 10.0% in the delayed-eptifibatide group ($P = .23$). At 30 days, the rate of death or MI was 11.2% in the early-eptifibatide group compared with 12.3% in the delayed-eptifibatide group ($P = .08$). Patients in the early-eptifibatide group had significantly higher rates of bleeding and red cell transfusion. Overall, the findings of the previously mentioned studies do not support the routine use of upstream compared with in-lab GP IIb/IIIa inhibition in ACS patients undergoing PCI.[4-9]

Ultimately, the trials that favored GP IIb/IIIa inhibition in ACS patients undergoing PCI, particularly patients who were troponin positive, were not designed to address the impact and value of GPIs in the era of routine treatment with a high loading dose of clopidogrel before PCI. This was assessed in the ISAR-REACT 2 trial.[215] The objective of ISAR-REACT 2 was to assess whether abciximab, administered in the catheterization laboratory, is associated with a clinical benefit in patients with an ACS undergoing PCI more than 2 hours after pretreatment with 600-mg loading dose of clopidogrel. In this double-blind randomized trial, 2022 patients were included and assigned to receive either abciximab or placebo in addition to treatment with IV heparin, aspirin, and the 600-mg loading dose of clopidogrel. The study revealed that the administration of abciximab significantly reduced the incidence of the primary end point of death, MI, or target vessel revascularization at 30 days (relative risk, 0.75; 95% CI, 0.58-0.97; $P = .03$). The benefit of abciximab treatment, however, was restricted only to those patients who presented with an elevated troponin. Troponin-negative patients demonstrated substantially lower and almost identical event rates with abciximab versus placebo. Overall, based on the results of ISAR-REACT 2 trial and retrospective analysis of other randomized trials, these findings suggest that in the modern era of interventional cardiology using high clopidogrel dosing regimens, GP IIb/IIIa inhibition should be reserved only for high-risk ACS patients with positive cardiac markers.

Duration of Infusion Indeed, it may be argued that the increased risk of bleeding associated with GPI use may be associated with their prolonged duration of infusion. This has advocated the potential that shorter duration of treatment may be a safer treatment option. The Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention (BRIEF-PCI) trial evaluated the possibility of shortening the eptifibatide infusion recommended (18 hours) in patients with ACS or recent STEMI (< 48 hours) who underwent successful and uncomplicated nonemergent PCI (n = 624).[231] The trial demonstrated noninferiority between standard 18-hour infusion (mean, 16.8 ± 3.4 hours) and early discontinuation of eptifibatide infusion (< 2 hours; mean, 1.4 ± 0.78 hours) without any compromise in ischemic benefit, measured as periprocedural myonecrosis, but with a lower incidence of major bleeding (1.0% vs 4.2%; $P = .02$). Indeed, larger studies are warranted to support the concept of short duration of GPI treatment. The ongoing Shortened Aggrastat Versus Integrilin in Percutaneous Coronary Intervention (SAVI-PCI) trial (NCT01522417) was designed to evaluate the possible association of a high-dose bolus of tirofiban plus a shortened infusion duration versus label-dosing eptifibatide in patients undergoing PCI, with a noninferior composite rate of death, PCI-related MI, urgent target vessel revascularization, or in-hospital major bleeding within 48 hours following PCI or hospital discharge.

Glycoprotein IIb/IIIa Inhibitors in Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction The first trial to investigate the impact of abciximab treatment in STEMI patients treated with PCI was the ReoPro and Primary Percutaneous Transluminal Coronary Angioplasty Organization and Randomized Trial (RAPPORT), in which 483 patients with STEMI within 12 hours of presentation were randomized to placebo or abciximab during balloon angioplasty.[232] The primary end point was a composite of death, reinfarction, or any target vessel revascularization at 6 months. The composite end point occurred in 28.1% of patients in the abciximab arm as compared with 28.2% in the placebo arm ($P = .97$). However, abciximab significantly reduced the incidence of death, reinfarction, or urgent target vessel revascularization at all time points assessed (9.9% vs 3.3%, $P = .003$, at 7 days; 11.2% vs 5.8%, $P = .03$, at 30 days; and 17.8% vs 11.6%, $P = .05$, at 6 months). Major bleeding occurred significantly more frequently in the abciximab group (16.6% vs 9.5%; $P = .02$), mostly at the arterial access site.

In the Abciximab Before Direct Angioplasty and Stenting in Myocardial Stenting Regarding Acute and Long-Term Follow-Up (ADMIRAL) trial, 300 patients with acute MI were randomized to abciximab plus stenting or stenting alone before they underwent coronary angiography.[233] At 30 days, the primary end point (composite of death, reinfarction, or urgent target vessel revascularization) had occurred less frequently in the abciximab group compared with the placebo group (6.0% vs 14.6%; $P = .01$). This beneficial effect was sustained at 6 months (7.4% vs 15.9%; $P = .02$). Similar results were observed in the Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) trial, in which 401 STEMI patients were randomized to receive either

abciximab and reduced-dose heparin or full-dose heparin alone for PCI.[234] Thirty days after PCI, the composite clinical end point of death, reinfarction, and target vessel revascularization was reached in 5.0% of the abciximab group versus 10.5% of the control group ($P = .038$). After 1 year of follow-up, the absolute reduction in the composite clinical end point with abciximab was still 5.7%, although the difference was no longer statistically significant.

The largest trial investigating the impact of GP IIb/IIIa inhibition in STEMI patients was the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complication (CADILLAC) trial, in which 2082 patients with acute MI were randomized in a 2 × 2 factorial design to balloon alone, balloon plus abciximab, stenting alone, or stenting plus abciximab.[235] The primary end point was a composite of death from any cause, reinfarction, repeated intervention or revascularization of the target vessel as a result of ischemia, or disabling stroke during the first 6 months after the index procedure. The composite end point occurred in 8.3% of patients in the balloon alone group, 4.8% in balloon plus abciximab, 5.7% in stenting alone, and 4.4% in stenting plus abciximab ($P = .02$).

The value of abciximab in STEMI patients was evaluated in a large meta-analysis of randomized trials indicating substantial benefits from abciximab in STEMI patients treated with PCI.[236] In this meta-analysis, a total of 11 trials in which 27,115 patients had been enrolled were analyzed. The meta-analysis demonstrated that the administration of abciximab to STEMI patients was associated with a significant reduction in 30-day (2.4% vs 3.4%; $P = .047$) and long-term (4.4% vs 6.2%; $P = .01$) mortality in patients treated with primary angioplasty. The frequency of reinfarction at 30 days was also significantly reduced by the administration of abciximab (2.1% vs 3.3%; $P < .001$).

All of the previously mentioned studies evaluating GPIs in STEMI were conducted in patients who had not been pretreated with clopidogrel. Whether there is added value from administering abciximab to patients suffering an STEMI and undergoing PCI after pretreatment with a high loading dose of clopidogrel was investigated in the third Bavarian Reperfusion Alternatives Evaluation (BRAVE-3) trial. A total of 800 patients with STEMI within 24 hours from symptom onset, all treated with 600 mg of clopidogrel, were randomly assigned in a double-blind fashion to receive either abciximab (n = 401) or placebo (n = 399) before being sent to the catheterization laboratory.[237] The primary end point, infarct size measured by single-photon emission computed tomography with technetium-99m sestamibi before hospital discharge, was 15.7% ± 17.2% (mean ± standard deviation) of the left ventricle in the abciximab group and 16.6% ± 18.6% of the left ventricle in the placebo group ($P = .47$). At 30 days, there were no differences in the composite of death, recurrent MI, stroke, or urgent revascularization of the infarct-related artery in the abciximab group (5.0%) and placebo group (3.8%) ($P = .40$). In conclusion, this study supports that upstream administration of abciximab is not associated with a reduction in infarct size in patients presenting with acute MI within 24 hours of symptom onset and receiving 600 mg of clopidogrel.

Costs have also been considered an issue when choosing GPIs, with abciximab being more expensive than small-molecule inhibitors. Therefore, replacing abciximab with tirofiban, administered as a single high-dose bolus regimen, could represent a promising cost-saving strategy. The Single High-Dose Bolus Tirofiban and Sirolimus Eluting Stent Versus Abciximab and Bare Metal Stent in Myocardial Infarction (STRATEGY) trial evaluated the clinical and angiographic impact of single high-dose bolus tirofiban plus sirolimus-eluting stenting versus abciximab plus BMS in patients (n = 175) with STEMI.[238] The cumulative incidence of death, reinfarction, stroke, or target vessel revascularization was significantly lower in the tirofiban plus sirolimus-eluting stent group (18%) versus the abciximab plus BMS group (32%; HR 0.53; $P = .04$), predominantly reflecting a reduction in the need for target vessel revascularization. The MULTI-STRATEGY trial was a 2 × 2 factorial design study that evaluated the effect of high-dose bolus tirofiban and of sirolimus-eluting stents as compared with abciximab infusion and uncoated-stent implantation in patients (n = 745) with STEMI undergoing PCI.[239] ST-segment resolution occurred in 302 (83.6%) of 361 patients who had received abciximab infusion and 308 (85.3%) of 361 patients who had received tirofiban infusion ($P < .001$ for noninferiority). Ischemic and hemorrhagic outcomes were similar in the tirofiban and abciximab groups. At 8 months, major adverse cardiac events occurred in 14.5% of patients with uncoated stents and 7.8% with sirolimus stents ($P = .004$), predominantly reflecting a reduction of revascularization rates. In conclusion, this study showed that in patients with STEMI undergoing primary PCI, compared with abciximab, tirofiban therapy was associated with noninferior resolution of ST-segment elevation at 90 minutes after coronary intervention, whereas sirolimus-eluting stent implantation was associated with a significantly lower risk of major adverse cardiac events than uncoated stents within 8 months after intervention.

Facilitated Percutaneous Coronary Intervention With Upstream Glycoprotein IIb/IIIa Inhibitor With or Without Half-Dose Fibrinolytic Therapy Effective and rapid reperfusion of the infarct-related coronary artery, irrespective of the manner with which it is achieved, is the critical goal in the treatment of acute MI. The optimal pharmacologic strategy for bridging between admission and performance of PCI in a patient with acute MI has not been fully defined. Primary PCI is more effective than thrombolytic therapy for the treatment of STEMI.[240] However, time to reperfusion is a critical determinant of outcome with both these strategies.[241] Facilitated PCI offers both theoretical and practical appeal to overcome time limitations. To date, trials that have compared primary PCI with facilitated PCI with full-dose fibrinolytics have failed to show a clinical benefit, although infarct artery patency rates before the PCI were significantly higher with facilitated PCI.[242] This has prompted the investigation of the potential benefits of other facilitated PCI strategies, which include the use of upstream GPIs alone or in combination with a reduced-dose fibrinolytic.[243]

In the ADMIRAL study, patients who received their randomly assigned treatment with abciximab early had a greater benefit with respect to the primary end point at both 30 days and 6 months than did those treated with abciximab in the intensive care unit or catheterization laboratory, thereby demonstrating the potential benefit of a facilitated strategy.[233] The investigators attributed the better outcome of abciximab to higher levels of TIMI grade 3 flow in the target vessel immediately before (16.8% vs 5.4%; $P = .01$) and immediately after (95.1% vs 86.7%; $P = .04$) the procedure.

The Integrilin in Acute Myocardial Infarction (INTAMI) trial evaluated adjunctive therapy with eptifibatide administered early in the emergency department (n = 53) compared with late, optional administration in the catheterization laboratory (n = 49).[244] TIMI grade 3 flow at the time of angiography was higher in the early eptifibatide group compared with the late/no eptifibatide group (34.0% vs 10.2%; $P = .01$). The presence of visible thrombus also trended lower in the early group (57.7% vs 70.8%; $P = .1$). However, there was no difference in post-PCI TIMI grade 3 flow, TIMI grade 3 myocardial perfusion, ST-segment resolution, and clinical events or bleeding by 30 days. The Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN–TIMI 34) trial compared a strategy of early initiation of eptifibatide in the emergency department (n = 174) with that of initiating eptifibatide in the cardiac catheterization laboratory (n = 142).[245] The primary end point of corrected TIMI frame count on diagnostic angiography was lower in the emergency department group (77.5 frames vs 84.3 frames; $P = .049$).

TIMI grade 3 myocardial perfusion was present more frequently in the emergency department group (24.3% vs 14.2%; $P = .026$).

Upstream administration of GPIs before PCI in patients presenting with acute MI has been studied in three trials. In the Tirofiban Given in the Emergency Room Before Primary Angioplasty (TIGER-PA) Pilot Trial, 100 patients with acute MI were randomized to either administration of tirofiban in the emergency department or later administration in the catheterization laboratory.[246] Angiographic analysis showed a statistically significant difference in initial TIMI grade 3 flow (32% vs 10%; $P = .007$), initial corrected TIMI frame counts (44 ± 20 vs 66 ± 23 frames; $P = .005$), and TIMI grade 3 myocardial perfusion grade (32% vs 6%; $P = .001$). There were no differences noted between the two groups with regard to bleeding complications. This pilot study suggests that early administration of tirofiban improves angiographic outcomes without increasing the risk of bleeding. Similarly, eptifibatide was shown to improve TIMI grade 2 or 3 flow when given upstream to patients presenting with STEMI undergoing primary PCI compared with a historical control group of 30 patients receiving eptifibatide at the time of the PCI.[247] The Ongoing Tirofiban in MI Evaluation (ON-TIME) study randomized 507 patients within 6 hours of symptom onset to tirofiban started before transportation to a PCI center or tirofiban started on arrival at the PCI center. The trial showed a significant improvement in the number of patients with TIMI grade 2 or 3 flow for those who received upstream tirofiban compared with those who received tirofiban at the PCI center (43% vs 34%; $P = .04$).[248] In the ON-TIME 2 study, 984 patients with STEMI who were candidates to undergo PCI were randomly assigned to either high-bolus dose tirofiban (n = 491) or placebo (n = 493) in addition to aspirin, heparin, and a 600-mg loading dose of clopidogrel. The primary end point was the extent of residual ST-segment deviation 1 hour after PCI, which was significantly lower in patients pretreated with high-bolus dose tirofiban ($P = .003$). The rate of major bleeding did not differ significantly between the two groups ($P = .36$).[249]

These small studies set the basis for larger studies to help clarify the safety and efficacy of different regimens of facilitated PCI using GPIs alone or in combination with a reduced-dose fibrinolytic. In the Immediate Angioplasty Versus Standard Therapy With Rescue Angioplasty After Thrombolysis in the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) trial, 600 patients were treated with half-dose reteplase, abciximab, heparin, and aspirin and randomly assigned to immediate transfer to the nearest interventional facility for PCI or to management in the local hospital, with transfer only in case of persistent ST-segment elevation or clinical deterioration.[250] Of the 299 patients assigned to immediate PCI, 289 (97.0%) underwent angiography, and 255 (85.6%) received PCI. Rescue PCI was done in 91 patients (30.3%) in the standard care/rescue PCI group. The primary outcome (composite of death, reinfarction, or refractory ischemia at 30 days) occurred in 4.4% of patients in the immediate PCI group compared with 10.7% in the standard care/rescue PCI group (HR 0.40; log-rank $P = .004$). There were no significant differences in major bleeding (3.4% vs 2.3%, respectively; $P = .47$). Overall, this trial demonstrates that immediate transfer for PCI improves outcome in high-risk patients with STEMI treated at a noninterventional center with half-dose reteplase and abciximab.

In the Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial, patients (n = 2452) with STEMI who presented ≤ 6 hours after the onset of symptoms were randomized to receive combination-facilitated PCI, abciximab-facilitated PCI, or primary PCI.[251] All patients received heparin (unfractionated heparin or enoxaparin) before PCI and a 12-hour infusion of abciximab after PCI. The primary end point (composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization) occurred in 9.8%, 10.5%, and 10.7% of the patients in the combination-facilitated PCI group, abciximab-facilitated PCI group, and primary-PCI group, respectively ($P = .55$); 90-day mortality rates were 5.2%, 5.5%, and 4.5%, respectively ($P = .49$). Overall, the FINESSE study shows that neither facilitation of PCI with reteplase plus abciximab nor facilitation with abciximab alone significantly improved the clinical outcomes as compared with abciximab given at the time of PCI in patients with STEMI.

Intracoronary Administration of Glycoprotein IIb/IIIa Inhibitors in ST-Segment Elevation Myocardial Infarction The finding that patients with STEMI undergoing primary PCI have an increased risk of very early thrombotic complications, despite advancements in the field of interventional pharmacotherapy, has led to the investigation of different modalities of use or combinations of GPIs in STEMI patients undergoing primary PCI. In particular, questions that have emerged include the benefits associated with GPIs if (1) given intracoronary (IC) instead of systemically, (2) used as a bolus only, or (3) used in conjunct with bivalirudin; in addition, its role in the era of more potent $P2Y_{12}$ receptor inhibitors has also been questioned. The pivotal clinical trials analyzing these aspects are outlined below.

Several small-scale studies and meta-analyses have suggested the potential benefits of IC over IV administration of abciximab.[252,253] Given the inherent limitations to small studies and meta-analyses, the larger scale Abciximab Intracoronary Versus Intravenously Drug Application in ST-Elevation Myocardial Infarction (AIDA STEMI) trial was specifically designed to evaluate the safety and efficacy of IC versus IV abciximab bolus (0.25 mg/kg bodyweight) during PCI with a subsequent 12-hour IV infusion of 0.125 μg/kg/min (maximum 10 μg/min).[254] The trial randomized 2065 patients with recent STEMI (< 24 hours) and failed to show statistical differences in the combined primary ischemic end point of all-cause mortality, recurrent MI, or new congestive heart failure at 90 days, although there was a reduction in rates of congestive heart failure. Accordingly, current guidelines provide a weak recommendation for IC GPI use.[4-9]

The role of the administration of only a bolus of GPI was evaluated in the Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction (INFUSE AMI) trial.[255] This trial randomized high-risk patients within 4 hours of STEMI undergoing primary PCI (n = 452) with bivalirudin anticoagulation in an open-label, 2 × 2 factorial design to bolus IC abciximab delivered locally at the infarct lesion site versus no abciximab and to manual aspiration thrombectomy versus no thrombectomy. The trial demonstrated that an IC bolus of abciximab delivered to the infarct lesion site significantly reduced infarct size at 30 days (assessed by cardiac magnetic resonance imaging) in patients with large anterior STEMI with bivalirudin anticoagulation compared with manual aspiration thrombectomy.[255]

Although the newer generation $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor are characterized by more prompt and potent response than clopidogrel, pharmacodynamic investigations have demonstrated that in STEMI patients undergoing primary PCI, the effects of these drugs may still be delayed by 2 to 4 hours.[256-259] This exposes these patients to an increased risk of thrombotic complications, underscoring a role for fast-acting and potent therapies such as GPIs. The role of GPIs in patients treated with prasugrel was evaluated in the Facilitation Through Aggrastat by Dropping or Shortening Infusion Line in Patients With ST-Segment Elevation Myocardial Infarction Compared to or on Top of Prasugrel Given at Loading Dose (FABOLUS PRO) trial.[260] This trial evaluated STEMI patients (n = 100) who randomly received prasugrel 60 mg versus tirofiban 25 μg/kg bolus with or

without a post-bolus 2-hour infusion of tirofiban, with or without concomitant prasugrel. The primary end point was the inhibition of platelet aggregation stimulated with 20 μmol/L ADP at 30 minutes. The study concluded that prasugrel alone provides a suboptimal platelet inhibition for at least 2 hours in STEMI patients and that prasugrel associated with a bolus only of tirofiban eludes the necessity of post-bolus infusion and practically eliminates residual variability of inhibition of platelet aggregation after treatment, reaching the higher and more consistent inhibition of platelet aggregation level after both agents.[260]

Glycoprotein IIb/IIIa and Thrombocytopenia

ACS trials tended to report higher incidence of thrombocytopenia compared with PCI trials, perhaps because of longer heparin infusions producing heparin-induced thrombocytopenia (HIT).[261] In a meta-analysis,[262] abciximab increased the incidence of mild thrombocytopenia (> 50,000 but < 90,000-100,000) compared with placebo (4.2% vs 2.0%; $P < .001$; OR 2.13). Patients receiving abciximab also had more than twice the incidence of severe thrombocytopenia (> 20,000 and < 50,000) than those receiving placebo (1.0% vs 0.4%; $P = .01$; OR 2.48). Eptifibatide or tirofiban did not increase mild or severe thrombocytopenia compared with placebo. Severe and profound (< 20,000) thrombocytopenia is more commonly associated with abciximab use and requires immediate cessation of therapy. An algorithm for evaluation of these patients has been proposed.[263] Pseudothrombocytopenia secondary to platelet clumping and HIT needs to be ruled out. The platelet count usually returns to normal within 48 to 72 hours in most cases. Regardless of its etiology, thrombocytopenia in patients undergoing PCI is associated with more ischemic events, bleeding complications, and transfusions.[263] The mechanism(s) of thrombocytopenia is unknown. The platelet count falls within hours of GP IIb/IIIa administration. Readministration of abciximab, but not the small-molecule inhibitors (eptifibatide and tirofiban), is associated with a slight increased risk of thrombocytopenia.[264]

Oral Glycoprotein IIb/IIIa Inhibitors

Investigations of oral GPIs, including sibrafiban, orbofiban, xemilofiban, and lotrafiban, have been halted as a result of negative results from several large trials in patients with ACS or undergoing PCI.[265-268] Meta-analysis of these trials further demonstrated an increased bleeding risk and increased mortality in patients treated with oral GPIs.[269,270] One of the possible explanations for the poor outcomes and increased mortality in these trials was the interindividual variability in the level of platelet inhibition over time.[271] Another potential mechanism is that partial-agonist properties of oral GPIs enhance platelet activation, especially at times when the serum drug levels are low, leaving more GP IIb/IIIa receptors available for binding fibrinogen. Proinflammatory effects have also been considered as an explanation for the adverse events with oral GPIs.[272] Currently, only parenteral GPIs are approved for clinical use.

PAR-1 RECEPTOR ANTAGONISTS

DAPT with a combination of aspirin and a $P2Y_{12}$ receptor inhibitor targets primarily pathways associated with TXA_2 and ADP-mediated platelet activation.[19,20] Thus, other pathways, such as thrombin-mediated platelet activation, remain unaffected and may in part account for the residual risk of ischemic events.[21] Because thrombin is a key mediator of platelet activation and levels of thrombin are known to be elevated after an ACS, targeting thrombin-mediated effects has represented an important area of clinical investigation.[21] Two different strategies can be pursued to block thrombin effects: indirect modulation by blockade of the platelet PAR receptor and direct inhibition of either thrombin or other upstream coagulation factors (ie, factor X).[19-24] In this latter scenario, several trials have recently tested the use of non–vitamin K antagonist oral anticoagulants (NOACs) in patients with ACS. A detailed description of their role is described in the anticoagulant section. We hereby describe the PAR-1 receptor antagonism.

The serine protease thrombin is one of the most potent platelet activators, and the surface of activated platelets is the main source of circulating thrombin.[21] PARs are a family of G-protein–coupled receptors. In humans, four types of PARs have been described; PAR-1 and PAR-4 are expressed on human platelets, but PAR-1 has the principal role of mediating platelet activation at low concentrations of thrombin, whereas PAR-4 reacts only at high concentrations (Fig. 41–6).[21] Several PAR–1 antagonists have been developed so far, of which only vorapaxar has completed phase III clinical investigations and has been approved for clinical use as of 2014.[21,273]

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile

Vorapaxar, a synthetic tricyclic 3-phenylpyridine, is a selective, competitive, oral, potent PAR-1 inhibitor. It is rapidly absorbed, with

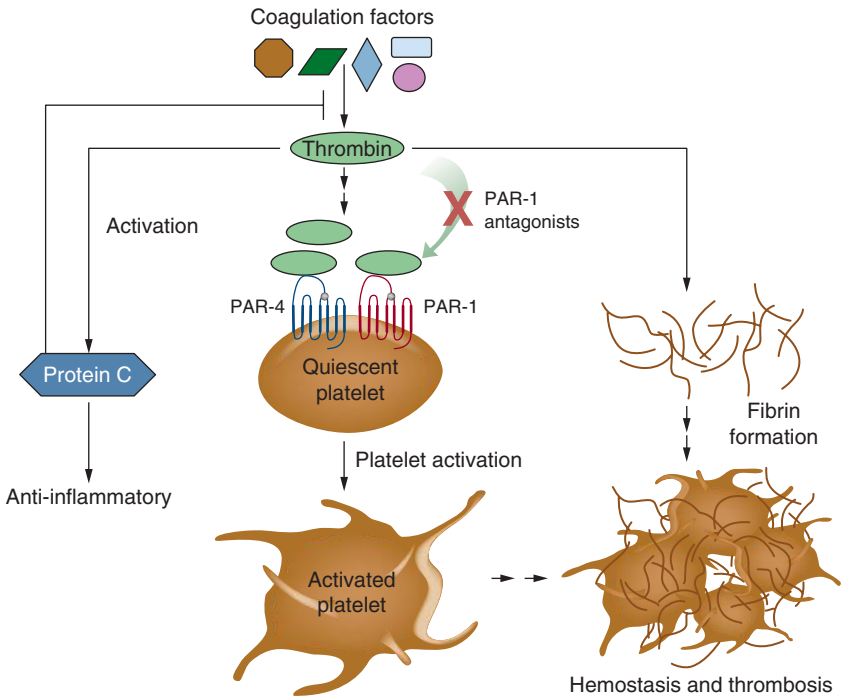


FIGURE 41–6. Role of thrombin-mediated protease-activated receptor (PAR)-1 signaling in hemostasis versus thrombosis. In addition to activating PARs on platelets, thrombin facilitates fibrin formation and protein C activation. Available data in mice and nonhuman primate models indicate that PAR antagonists have the potential to block platelet activation by thrombin while sparing the other functions of thrombin, including coagulation, that are absolutely necessary for hemostasis. Murine studies suggest that fibrin(ogen) is relatively more important than thrombin-induced platelet activation for hemostasis, and this is supported by the high bleeding risk associated with the use of anticoagulants in man. Thus, inhibition of thrombin-induced platelet activation with PAR-1 inhibitors might provide for a larger therapeutic index than can be achieved with coagulation inhibitors for the prevention or treatment of arterial thrombosis. Reproduced with permission from Angiolillo DJ, Capodanno D, Goto S: Platelet thrombin receptor antagonism and atherothrombosis. *Eur Heart J*. 2010 Jan;31(1):17-28.

high bioavailability (> 90%) after oral administration, with a dissociation half-life as long as 20 hours and a long terminal half-life (126-269 hours).[21,273] Vorapaxar is metabolized in the liver by CYP3A4 and provides a dose-dependent inhibition of TRAP-induced platelet aggregation.[21,273] A 40-mg loading dose achieves a ≥ 80% inhibition of platelet aggregation in almost all patients at 2 hours, and a 2.5-mg once-daily maintenance dose provides a consistent effect in the maintenance phase.[21,273] Vorapaxar was tested in two large-scale phase III clinical trials: TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) and TRA 2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50) trial (see Table 41–3).[274,275]

Dosing and Recommendations

Vorapaxar at a dose of 2.5 mg once daily is indicated for the reduction of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease and must be used in addition to antiplatelet therapy (aspirin and/or clopidogrel), as per standard of care, since there is no experience with monotherapy. Vorapaxar is contraindicated in patients with a history of stroke, TIA, or ICH and with active pathologic bleeding. Concomitant use of vorapaxar with strong CYP3A inhibitors or inducers should be avoided. No dose adjustment is required in patients with renal dysfunction and with mild and moderate hepatic impairment; it is not recommended in patients with severe hepatic impairment.

Evidence for Use

The TRACER trial aimed to investigate whether the use of vorapaxar in addition to standard antiplatelet therapy was superior to placebo in reducing recurrent ischemic cardiovascular events in patients with NSTE-ACS and to determine its safety profile.[274] Patients (n = 12,944) were randomly assigned to receive either vorapaxar (40-mg loading dose followed by a 2.5-mg daily maintenance dose) or placebo in addition to standard-of-care antiplatelet therapy, which included aspirin in 96% of patients and clopidogrel in 91.8% patients. After an unplanned safety review in January 2011, the data and safety monitoring board recommended that the trial be stopped early, although the protocol-defined target number of primary efficacy end points had been reached. Vorapaxar treatment was associated with a nonsignificant reduction in the primary efficacy end point at 2 years (a composite of death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization; 18.5% vs 19.9%; HR 0.92; $P = .07$) at the expense of a significant 35% increase in the rate of GUSTO moderate or severe bleeding (7.2% vs 5.2%; $P < .001$) and a threefold increase in ICH (see Table 41–3). Of note, vorapaxar significantly reduced by 11% the prespecified key secondary end point (a composite of cardiovascular death, MI, or stroke) compared with placebo (14.7% vs 16.4%; $P = .02$), mainly driven by a reduction in the hazard of MI, although these data should be considered as hypothesis generating.[274] The study results were consistent across multiple subgroups; interestingly, in the small cohort of patients (n = 1312) undergoing CABG during the index hospitalization, adjunctive vorapaxar treatment seemed to be associated with a clinical benefit, perhaps because of the enhanced thrombin generation that characterizes this setting.[275]

Another phase III trial, the TRA 2P-TIMI 50 study, investigated the efficacy and safety of vorapaxar in patients with chronic atherosclerotic cardiovascular disease, defined as a spontaneous MI or ischemic stroke within 2 weeks to 12 months or peripheral artery disease (PAD) associated with a history of intermittent claudication in conjunction with either ankle-brachial index of less than 0.85 or previous revascularization for limb ischemia.[276] The study limited the number of patients with a qualifying diagnosis of either stroke or PAD, not exceeding 15% of the total anticipated sample size. In January 2011, after enrollment was completed and at a median follow-up of 24 months, because of an excess in of ICH among patients with a history of stroke enrolled in the vorapaxar group of the trial (as well as in the companion TRACER trial), the safety review board recommended discontinuation of the study drug in patients with a history of stroke in the TRA 2P trial, including those with a new stroke during the study. Continuation of the trial in patients without a history of stroke was also recommended. Vorapaxar (2.5-mg daily maintenance dose) added on top of aspirin and/or a thienopyridine, mostly clopidogrel, being used as part of standard of care, significantly reduced the risk of cardiovascular death, MI, or stroke at the expense of a higher rate of moderate to severe bleeding and ICH events after a median follow-up of 30 months (see Table 41–3). The net clinical benefit from vorapaxar was higher in patients with a history of MI than those with prior stroke or PAD (P for interaction = .058).[276,277] Importantly, among patients with a prior MI, outcomes were consistent irrespective of the timing of the qualifying MI and use of a thienopyridine.[277,278] The risk of CV death, MI, or stroke was also significantly reduced with a 2.5-mg maintenance dose of vorapaxar compared with placebo in patients with MI or PAD who had no history of stroke or TIA, which constitutes the population intended for clinical use according to the instructions of drug-regulating agencies.[279] A marked benefit of vorapaxar was observed in patients with diabetes mellitus.[280] Meanwhile, vorapaxar increased rates of major bleeding and ICH without reducing ischemic outcomes in patients with a history of stroke.[281] Because elderly and low-body-weight patients are at increased risk of bleeding, vorapaxar should be used with caution in these patients.[279] The efficacy and safety of vorapaxar coadministered with prasugrel or ticagrelor are unknown.

Adverse Effects

In the TRA 2P-TIMI 50 trial, the bleeding end points in the post-MI or PAD patients without a history of stroke or TIA were defined as GUSTO severe bleeding (fatal, intracranial, or bleeding with hemodynamic compromise requiring intervention) and GUSTO moderate bleeding (bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise).[276] The rate of combined severe or moderate GUSTO bleeding was 3.7% in the vorapaxar group and 2.4% in the placebo group (HR 1.55; 95% CI, 1.30-1.86; $P < .001$). This difference was driven by an increase in GUSTO moderate bleeding (2.6% vs 1.4%; $P < .001$). The rate of GUSTO severe bleeding was 1.3% with vorapaxar versus 1.0% with placebo (HR 1.24; 95% CI, 0.92-1.66; $P = .16$). The rate of TIMI major bleeding was increased in the vorapaxar group compared with placebo (2.5% vs 1.9%; $P = .015$), as was TIMI minor bleeding (1.7% vs 0.8%; $P < .001$). ICH occurred in 0.6% of the vorapaxar group compared with 0.4% of the placebo group (HR 1.46; 95% CI, 0.92-2.31). The rate of fatal bleeding was 0.2% in both the vorapaxar and placebo groups.

In TRA 2P, 367 post-MI or PAD patients without a history of stroke or TIA underwent CABG surgery. Study investigators were encouraged not to discontinue treatment with study drug (ie, vorapaxar or placebo) prior to surgery. Approximately 12.3% of patients discontinued vorapaxar more than 30 days prior to CABG.[276] The relative risk for GUSTO moderate or severe bleeding was approximately 1.2 on vorapaxar versus placebo. Patients with a history of ischemic stroke in the TRA 2P study had a higher rate of ICH on vorapaxar therapy than on placebo.[281]

Adverse reactions other than bleeding in patients treated with vorapaxar that occurred at a rate of at least 2%, and also at a 10% greater

rate than in the placebo group, were anemia, depression, and rashes, eruptions, and exanthemas.[276]

In the TRACER trial, the rate of GUSTO moderate or severe bleeding was significantly higher in patients receiving vorapaxar compared with placebo (7.2% vs 5.2%; $P < .001$). Accordingly, the rates of clinically significant TIMI bleeding (20.2% vs 14.6%; $P < .001$) and GUSTO severe bleeding (2.9% vs 1.6%; $P < .001$) were increased among patients treated with vorapaxar.[274] The excess hazard of bleeding events continued to accrue during follow-up. The vorapaxar group also had threefold higher rates of ICH (1.1% vs 0.2%; $P < .001$), with an incremental risk over time. Rates of CABG-related bleeding during the index hospitalization, reoperation for bleeding, and fatal bleeding were similar between the two groups.

ANTIPLATELET THERAPY: SPECIFIC CONSIDERATIONS

The introduction into clinical practice of numerous antiplatelet therapies and the evolution of how ACS patients are approached have led to changes in practice patterns. Updates in practice guidelines, primarily from the ACC/AHA and the ESC, summarize the level of recommendations, based on the degree of evidence, to support a specific approach as well as to indicate strategies that should be avoided because of their potential harm. Guideline recommendations for both oral and IV antiplatelet therapies in both the NSTE-ACS and STEMI setting are summarized in Tables 41–5 and 41–6.[4-9] For some of the newer agents such as cangrelor and vorapaxar, there are no or limited recommendations provided because these agents were not approved for clinical use at the time of guideline development. This section summarizes aspects related to the use of antiplatelet therapy that are key to clinical practice.

Timing of Drug Administration

In patients presenting with an ACS, timely administration of antiplatelet therapy is critical. At time of presentation, all patients should be treated with a loading dose of aspirin. In the past, when time from clinical presentation to the catheterization laboratory was delayed and when the more potent oral $P2Y_{12}$-inhibiting therapies were still not available, upstream treatment with GPIs was commonly used. However, in modern-day practice patterns, with more rapid access to the catheterization laboratory (Fig. 41–7), the evidence for routine upstream treatment with GPIs in ACS patients, both NSTE-ACS and STEMI, is weak.[230] Therefore, when GPI use is considered, this should be reserved for patients undergoing an invasive evaluation, with intent to undergo PCI, after defining coronary anatomy.[4-9] However, in selected high-risk cases, upstream GPI use may still be considered.[4-9] There are no studies with upstream treatment with cangrelor, which is reserved for use in the catheterization laboratory in patients with defined coronary anatomy undergoing PCI. Timing of administration of the oral $P2Y_{12}$ receptor inhibitors has been a subject of controversy, and practice patterns may vary in different geographical regions.[282-284] In fact, although early administration of antiplatelet therapy may protect the patient from thrombotic events in the vulnerable period before and immediately after PCI, pretreatment may result in an increased risk of bleeding complications or prolong hospitalization in patients requiring CABG (~ 10%-15% of patients hospitalized for NSTE-ACS). Guideline recommendations have also varied over the years.[4-9]

In patients with NSTE-ACS, for years, ACC/AHA and ESC guidelines provided a Class I recommendation for preloading with $P2Y_{12}$ receptor inhibitors as soon as possible after admission. Although the level of evidence for pretreatment was high in these documents, the supporting references did not relate to any randomized trial of upstream versus downstream use of $P2Y_{12}$ inhibitors.[282] Notably, in the more recent guidelines, there is no longer a specific recommendation for early initiation of $P2Y_{12}$ inhibitors in this setting, and pretreatment with prasugrel is now not recommended (Class III).[4-9]

Most of the available data on pretreatment in NSTE-ACS derive from studies with clopidogrel. Results of the PCI-CURE study support the hypothesis that an effective antiplatelet regimen with clopidogrel

TABLE 41–5. Summary of ACC/AHA and ESC Guidelines for The Initial Management of Oral and Intravenous Antiplatelet Therapy in Patients With NSTEMI

Recommendations	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Oral therapy				
Non–enteric-coated oral aspirin (150-325 mg) promptly after presentation (or 80-150 mg intravenous); aspirin MD (preferably ≤ 100 mg/d) continued indefinitely	I	A	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to aspirin and maintained over 12 months unless there are contraindications such as excessive risk of bleeding:	I	B	I	A
- Prasugrel (60 mg LD, 10 mg/d MD) in patients in whom coronary anatomy is known and who are proceeding to PCI	IIa	B	I	B
- Ticagrelor (180 mg LD, 90 mg BID MD) regardless of initial treatment strategy including those pretreated with clopidogrel	IIa	B	I	B
- Clopidogrel (600 mg LD, 75 mg/d MD), only when prasugrel or ticagrelor are not available or are contraindicated	IIa	B	I	B
Pretreatment with prasugrel in patients in whom coronary anatomy not known is not recommended.			III	B
Intravenous therapy				
GPIs should be considered for bail-out situation or thrombotic complications.			IIa	C
Cangrelor may be considered in $P2Y_{12}$ inhibitor–naïve patients undergoing PCI.			IIb	A
GPIs added to aspirin should be considered prior to angiography in high-risk patients not preloaded with $P2Y_{12}$ inhibitors.	I	A	IIa	C
In high-risk patients, eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT.	IIa	B	IIb	C
In patients undergoing PCI, routine upstream use of GPIs is not recommended.			III	A

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BID, twice a day; COR, class of recommendation; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; GPI, glycoprotein IIb/IIIa inhibitor; LD, loading dose; LOE, level of evidence; MD, maintenance dose; NSTEMI, non–ST-segment myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 41–6. Summary of ACC/AHA and ESC Guidelines for the Initial Management of Oral and Intravenous Antiplatelet Therapy in Patients With STEMI

Recommendations	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Oral therapy				
Oral aspirin (150-325 mg) promptly after presentation (or 80-150 mg intravenous); aspirin MD (preferably ≤ 100 mg/d) continued indefinitely	I	A	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to aspirin early as possible or at time of primary PCI and maintained over 12 months unless there are contraindications:	I	B	I	A
- Prasugrel (60 mg LD, 10 mg/d MD) if no contraindications - Ticagrelor (180 mg LD, 90 mg BID MD) if no contraindications - Clopidogrel (600 mg LD, 75 mg/d MD), only when prasugrel and ticagrelor are not available or are contraindicated	I	B	I	B
In patients receiving fibrinolytic therapy, clopidogrel is indicated in addition to aspirin (300 mg LD for patients ≤ 75 years old, 75-mg dose for patients > 75 years old) followed by an MD of 75 mg/d.	I	A	I	A
Intravenous therapy				
GPIs should be considered for bail-out or evidence of no reflow or a thrombotic complication.			IIa	C
Upstream use of a GPIs may be considered in high-risk patients.	IIb	B	IIb	B

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BID, twice a day; COR, class of recommendation; ESC, European Society of Cardiology; GPI, glycoprotein IIb/IIIa inhibitor; LD, loading dose; LOE, level of evidence; MD, maintenance dose; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

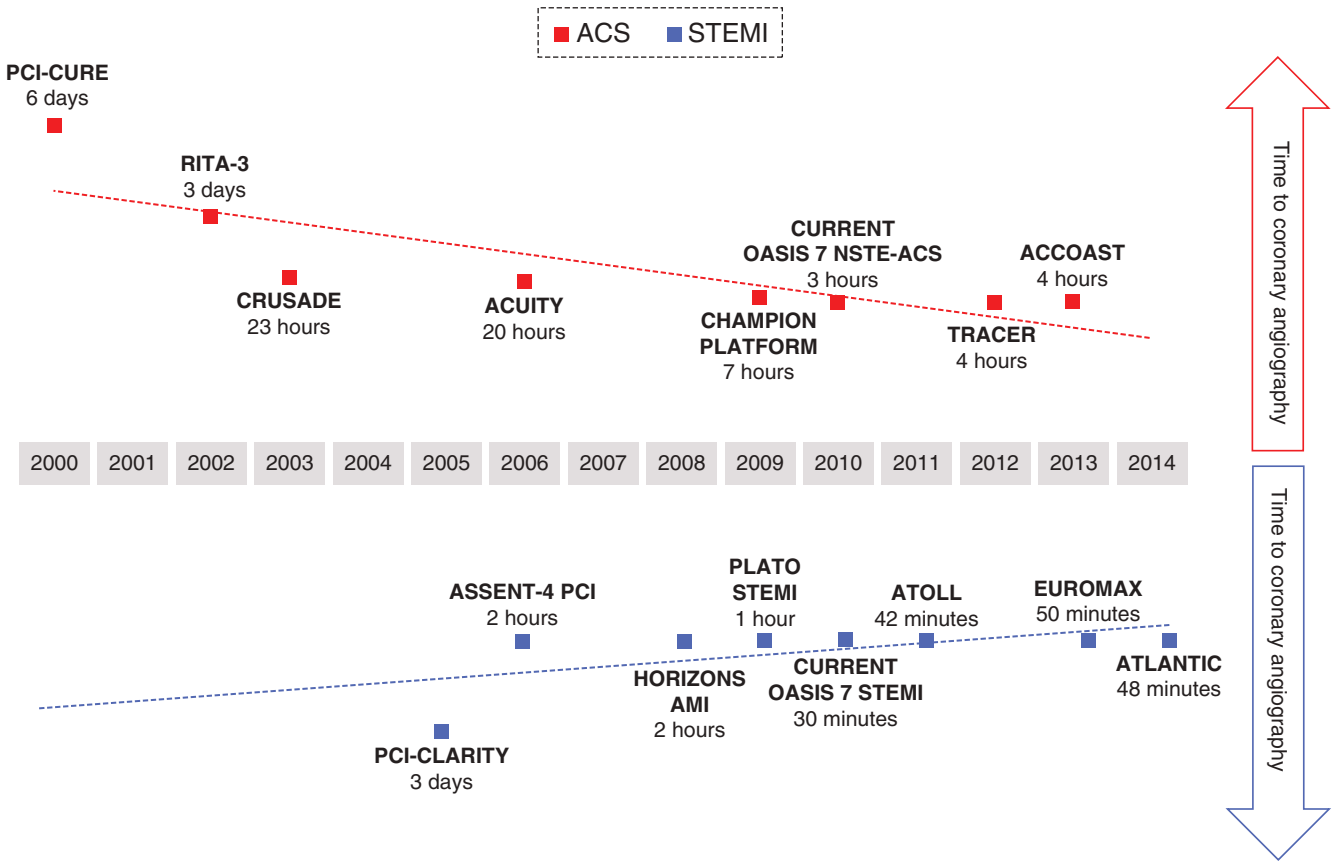


FIGURE 41–7. Time from hospital admission or first medical contact to coronary angiography in studies of non–ST-segment elevation (NSTE) acute coronary syndrome (ACS) and ST-segment elevation myocardial infarction (STEMI). See text for trial acronym definitions. Reproduced with permission from Capodanno D, Angiolillo DJ: Pretreatment with antiplatelet drugs in invasively managed patients with coronary artery disease in the contemporary era: review of the evidence and practice guidelines. *Circ Cardiovasc Interv*. 2015 Mar;8(3):e002301.[282]

started before PCI can reduce long-term adverse ischemic events.[87] However, this reflects a practice pattern that is now outdated as a result of the long pretreatment period (median of 10 days) in this setting and the use of a 300-mg loading dose. To achieve the pretreatment benefit of early clopidogrel, patients must be treated at least > 6 hours, and preferably > 12 hours, before PCI.[285] In a meta-analysis of the results of three randomized trials, clopidogrel pretreatment before PCI was associated with a reduction in ischemic events and was safe, regardless of whether a GPI was used at the time of PCI.[286] However, a meta-analysis in patients with NSTE-ACS from randomized clinical trials and from observational analyses of randomized clinical trials found no differences in mortality with clopidogrel pretreatment versus no pretreatment.[287] In the TRITON-TIMI 38 trial, administration of prasugrel before coronary angiography was not allowed in patients enrolled with NSTE-ACS.[105] Because of this gap, the impact of prasugrel pretreatment in patients with NSTE-ACS was tested in the ACCOAST trial, which showed no ischemic benefit and increased bleeding with pretreatment, which explains its Class III recommendation for upstream use.[4-9,115] Whether these data may apply also to pretreatment with ticagrelor is currently unknown as this has not yet been tested. In fact, the benefits of ticagrelor pretreatment have not been evaluated in any randomized clinical trial. It should be noted that all patients in the PLATO trial were pretreated.[143]

For patients with STEMI undergoing primary PCI, the 2014 ESC guidelines for myocardial revascularization recommend administration of a $P2Y_{12}$ inhibitor, including clopidogrel, prasugrel, and ticagrelor, at the time of first medical contact.[7] The ACC/AHA guidelines for STEMI give a Class I recommendation for the administration of a loading dose of a $P2Y_{12}$ receptor inhibitor as early as possible or at time of primary PCI.[5] Because pharmacodynamic studies have shown a delayed onset of antiplatelet effect of $P2Y_{12}$ inhibitors in patients with STEMI,[256-259] pretreatment seems an appealing strategy to provide a stronger platelet inhibition at the time of primary PCI, even if there are insufficient available supporting data. Although evidence supporting clopidogrel pretreatment in patients undergoing primary PCI is conflicting,[282] in the STEMI subgroup of a large meta-analysis on patients undergoing PCI, pretreatment with clopidogrel was associated with an approximately 50% reduction in mortality.[287] In TRITON-TIMI 38, only 32% of patients with STEMI undergoing primary PCI (≤ 12 hours after symptoms onset) and 20% of those undergoing secondary PCI (> 12 hours) received the loading dose before PCI; therefore, the value of pretreatment with prasugrel in STEMI has not been specifically demonstrated.[105,110] The role of ticagrelor pretreatment in STEMI was tested in the ATLANTIC trial, in which prehospital ticagrelor did not reduce the co-primary end points (the proportion of patients without a 70% or greater resolution of ST-segment elevation before PCI and the proportion of patients without TIMI grade 3 flow in the infarct-related artery at initial angiography). Although the trial was not powered for clinical end points, rates of major bleeding were low and similar between the two groups, suggesting the safety of prehospital ticagrelor administration.[156] Overall, available data suggest that if primary PCI is performed with a short medical contact-to-balloon time, residual platelet reactivity before PCI is considerably high in patients treated or pretreated with prasugrel or ticagrelor.[256-259] Use of IV agents, such as GPIs or cangrelor, in the catheterization laboratory has the potential to provide immediate platelet inhibition until the full antiplatelet effect of oral $P2Y_{12}$ inhibitors is achieved.[256]

Choice of Oral $P2Y_{12}$ Receptor Inhibitor

For over a decade, DAPT with aspirin and clopidogrel has been the cornerstone of antiplatelet treatment in ACS patients.[19-22] Despite the efficacy of this combination, trials of newer generation $P2Y_{12}$ receptor antagonists (prasugrel and ticagrelor), which have consistently shown more prompt, potent, and predictable platelet inhibition, lead to significantly better clinical outcomes, albeit at the expense of an increase in the rates of major bleeding.[19-22] Therefore, in the absence of contraindications, prasugrel and ticagrelor are preferred for the initial treatment of ACS patients, both with NSTE-ACS and STEMI.[4-9] Therefore, clopidogrel should be used only when both prasugrel and ticagrelor are contraindicated. Clopidogrel is still the treatment of choice in ACS or PCI patients who require oral anticoagulation, such as patients with atrial fibrillation, in whom the use of prasugrel and ticagrelor is not recommended because of the increased bleeding risk.[36,37] In the absence of head-to-head clinical comparisons between these two agents, the selection of one drug over the other should take into account the specific contraindications of each drug and the patient characteristics. The ongoing ISAR-REACT 5 trial (NCT01944800) will provide a head-to-head clinical comparison between prasugrel and ticagrelor in approximately 4000 patients with ACS with planned invasive strategy.[288]

Given its reversible binding to the $P2Y_{12}$ receptor and its plasma half-life of 8 to 12 hours, ticagrelor requires twice-daily administration.[132] Therefore, patients with poor compliance may not be optimal candidates for ticagrelor, and the use of an irreversible inhibitor, which requires only a once-daily administration, should be preferred. However, the reversible binding property of ticagrelor also translates into a faster offset of action, leading to a shorter wash-out period before surgery and potentially to reduced periprocedural-related bleeding.[132]

The type of management strategy should also be considered in the choice of the $P2Y_{12}$ receptor inhibitor. In ACS patients treated with PCI, all three agents—clopidogrel, prasugrel, and ticagrelor—can be used.[4-9] Although in patients with STEMI the probability of performing PCI is usually high, thus allowing to choose among all drugs, in patients with NSTEMI, either the choice to pretreat or uncertainties about the following management strategy can limit the choice between clopidogrel and ticagrelor.[4-9] In fact, only clopidogrel and ticagrelor, but not prasugrel, are approved for pretreatment, before defining coronary anatomy. Moreover, these agents, but not prasugrel, are also approved for treatment of ACS patients who are medically managed.[4-9] In this latter scenario, ticagrelor represents the first-line treatment as a result of the benefit showed over clopidogrel in the medically managed subgroup of the PLATO trial.[4-9]

Ultimately, it is important to note that although platelet function and genetic testing have been proposed to help identify patients who may benefit from treatment with the latest generation $P2Y_{12}$ receptor inhibitors, these agents should be used based on clinical grounds as described earlier. In fact, over the past few years, there has been a growing body of evidence on the variability of clopidogrel response profiles and the association between inadequate platelet inhibition induced by clopidogrel and higher risk of atherothrombotic events.[70,289-291] However, although some registry data have shown that the utilization of platelet function and genetic testing can allow one to optimize platelet inhibition in selected patients and in some studies improve clinical outcomes, all prospective randomized trials have failed to show any benefit.[292-295] In line with these observations, practice guidelines do not support the routine use of platelet function and genetic testing.[4-9] Some limitations in the designs of these studies may have contributed to these unfavorable outcomes.[296] Therefore, tailoring therapy according to platelet function and genetic testing still remains a field of ongoing investigation. The Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) trial (NCT01959451) will assess the value of platelet function testing in identifying patients who could safely be treated with a less potent antiplatelet therapy. The Tailored Antiplatelet Therapy

Following PCI (TAILOR-PCI; NCT01742117) trial will be testing a similar concept, but using a point-of-care genetic test. Algorithms on the choice of $P2Y_{12}$ receptor inhibitor are given in Fig. 41–8.[297]

Duration of Dual Antiplatelet Therapy

An intense area of investigation with DES has been whether the risk of late (30 days to 1 year) and very late (beyond 1 year) stent thrombosis may be diminished by the extended use of DAPT. Because of the important prognostic implications associated with stent thrombosis with fatality rates in up to 40% to 50% of patients,[298] as a precautionary measure and based on trials associating thienopyridine discontinuation within the first 6 months with risk of DES thrombosis, the guideline recommendation had advocated 12 months of DAPT after DES placement in patients without contraindications and bleeding risk. However, this recommendation was not based on any prospective randomized trial evidence associating extended duration of DAPT with a reduction in late stent thrombosis. Currently, there have been a large number of randomized trials that have now specifically addressed optimal duration of DAPT. Most trials have shown that prolonging therapy does not reduce the risk of thrombotic complications, and all studies have consistently shown an increase in bleeding complications.[299-302] Outcomes, however, may vary according to the risk profile of patients enrolled, with differences between patients with and without an ACS.[303] Details of these studies go beyond the scope of this chapter, which will focus on recommendations for DAPT duration in ACS patients.

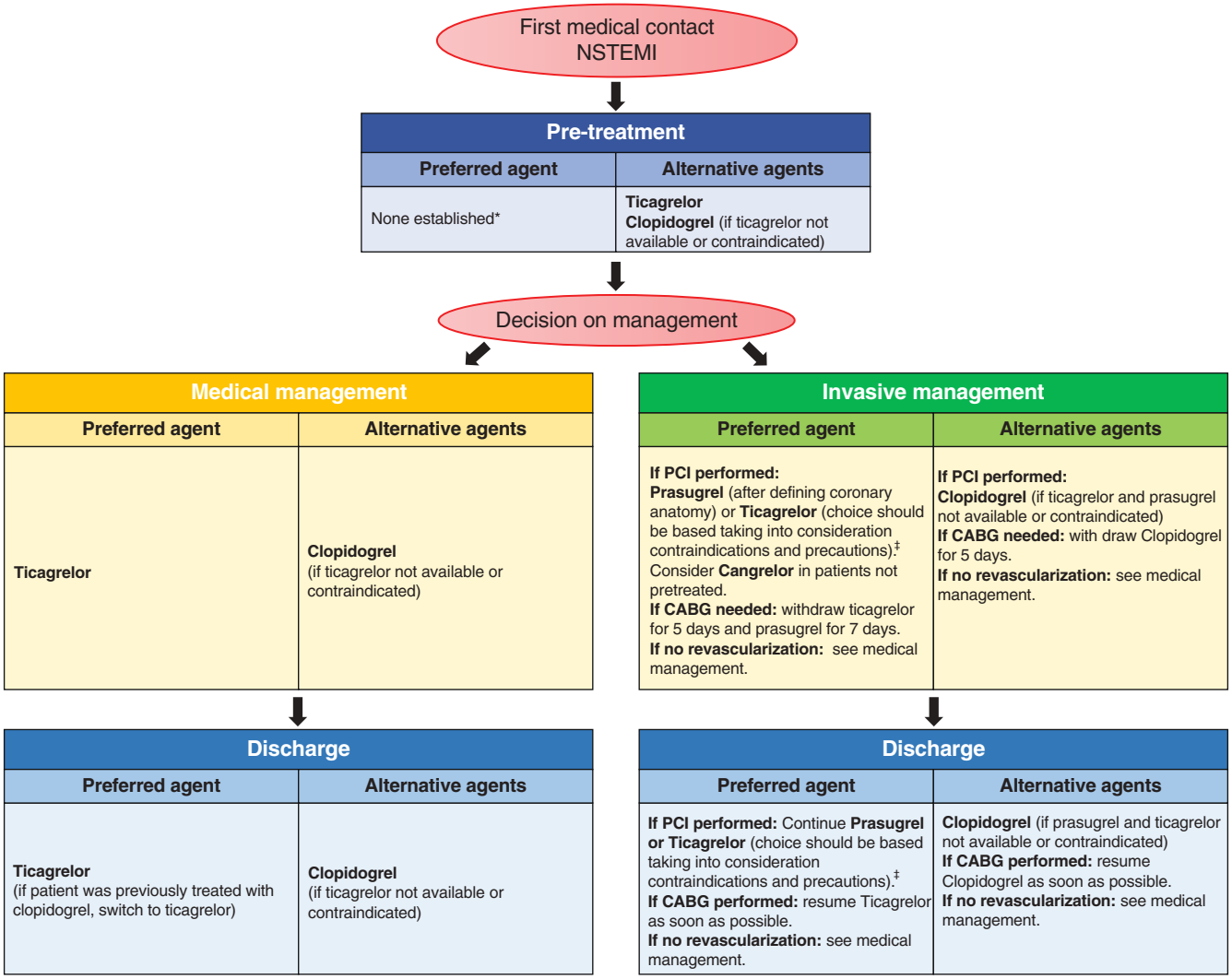


FIGURE 41–8. A. Algorithm for choice of $P2Y_{12}$ receptor antagonists in patients with non–ST-segment elevation myocardial infarction (NSTEMI). *The choice to pretreat with a $P2Y_{12}$ receptor antagonist should be based on the risk/benefit ratio of such an approach, taking into consideration the thrombotic and bleeding risk. Early administration of antiplatelet therapy may protect the patient from thrombotic events in the vulnerable period before and immediately after percutaneous coronary intervention (PCI). However, pretreatment may result in an unnecessary excess of platelet inhibition and related bleeding risk when patients do not undergo PCI, such as patients found not to have coronary artery disease or patients requiring coronary artery bypass graft (CABG). ‡If patient was previously treated with clopidogrel, switching to prasugrel or ticagrelor should be considered. Adapted with permission from *Myocardial Infarction: A Companion to Braunwald's Heart Disease*. New York, NY: Elsevier; 2016.[297] **B.** Algorithm for choice of $P2Y_{12}$ receptor antagonists in patients with ST-segment elevation myocardial infarction (STEMI). *Tested only in a few small nonrandomized studies of patients undergoing delayed PCI. ‡The choice to pretreat with a $P2Y_{12}$ receptor antagonist should be based on the risk/benefit ratio of such approach, taking into consideration the thrombotic and bleeding risk. Early administration of antiplatelet therapy may protect the patient from thrombotic events in the vulnerable period before and immediately after PCI. However, pretreatment may result in an unnecessary excess of platelet inhibition and related bleeding risk when patients do not undergo PCI, such as patients found not to have coronary artery disease or patients requiring CABG. ‡If patient was previously treated with clopidogrel, switching to prasugrel or ticagrelor should be considered. LD, loading dose. Adapted with permission from Morrow DA: *Myocardial Infarction: A Companion to Braunwald's Heart Disease*. St. Louis: Elsevier; 2016.

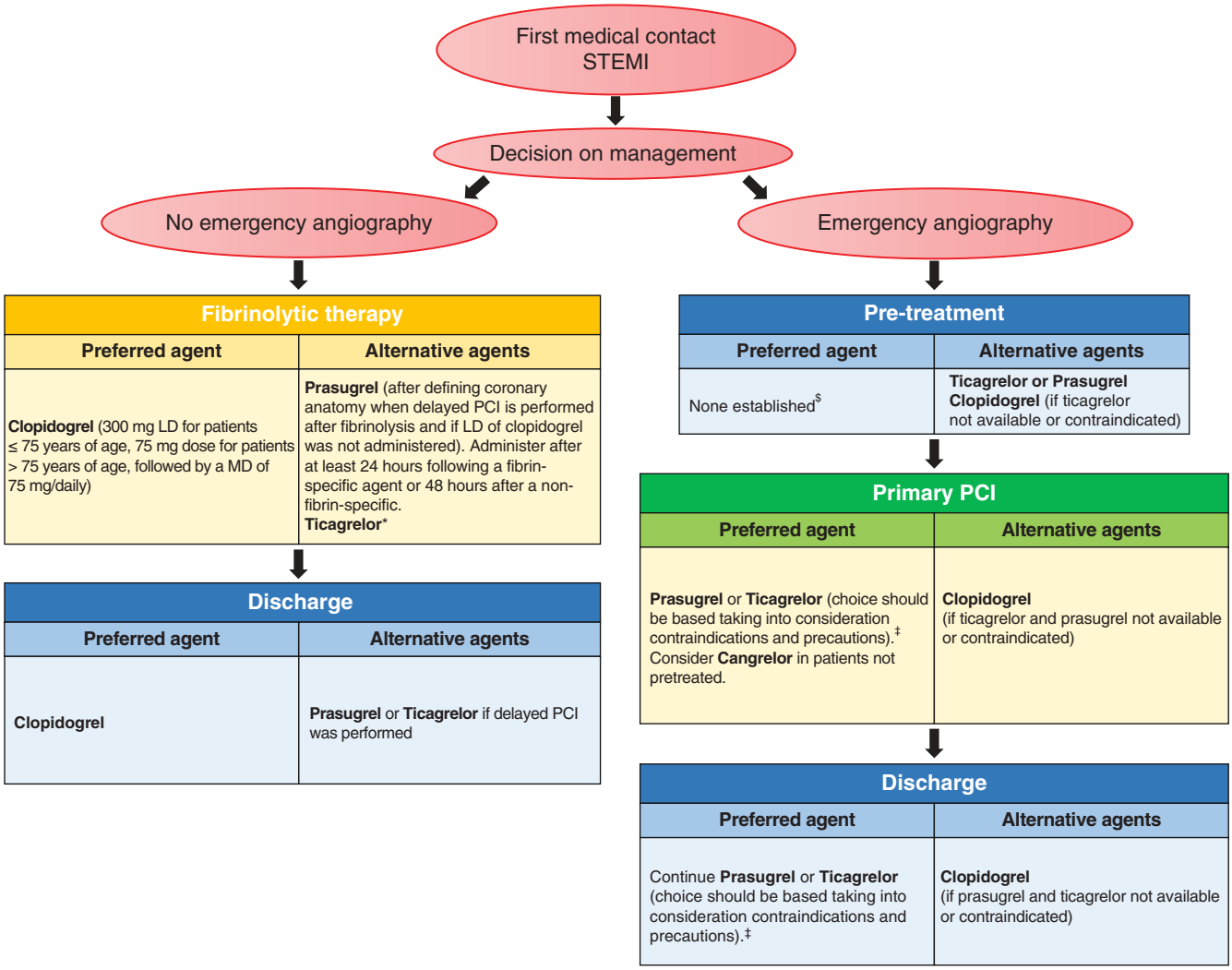


FIGURE 41–8. (*Continued*)

Current guidelines recommend that DAPT should be continued for up to 1 year in ACS patients, irrespective of management (invasive or noninvasive).[4-9] However, ACS patients continue to experience ischemic events even after 1 year, often unrelated to the target lesion responsible for their acute event. This raises questions about the optimal duration of more intensified antiplatelet therapy.[304] A post hoc analysis of the CHARISMA trial showed a benefit of prolonging DAPT with aspirin (75-162 mg daily maintenance dose) and clopidogrel (75-mg maintenance dose) up to 3 years among patients with a prior MI.[104] In line with this observation, the TRILOGY ACS trial showed an ischemic benefit beyond 12 months of therapy, particularly among patients with coronary artery disease confirmed by angiography.[114] Moreover, among patients with a prior MI enrolled in the TRA 2P-TIMI 50 study, there was an ischemic benefit associated with adjunctive vorapaxar therapy, irrespective of the timing of prior MI (0-3, 3-6, or 6-12 months), up to approximately 3 years of treatment.[277] Overall, these observations were indeed hypothesis generating for the development of specifically designed studies assessing the impact of prolonged treatment, such as the recently published DAPT (Dual Antiplatelet Therapy) and PEGASUS-TIMI 54 trials.[155,234]

In the DAPT study, including patients free from ischemic and bleeding events at 1 year after stenting, prolonging DAPT with a thienopyridine (75-mg daily maintenance dose of clopidogrel or 10-mg daily maintenance dose of prasugrel) and low-dose aspirin for an additional 18 months significantly reduced the incidence of the co-primary ischemic end points compared with aspirin therapy alone: stent thrombosis (0.4% vs 1.4%; HR 0.29; 95% CI, 0.17-0.48; $P < .001$) and major cardiovascular or cerebrovascular events (4.3% vs 5.9%; HR 0.71; 95% CI, 0.59-0.85; $P < .001$).[305] Importantly, about 55% of the ischemic benefit of prolonged DAPT was derived from the reduction of MI not related to stent thrombosis. The magnitude of risk reduction in major cardiovascular or cerebrovascular events (composite of death, MI, or stroke) was greater in patients with MI (3.9% vs 6.8%; HR 0.56; $P < .001$) than those without MI (4.4% vs 5.3%; HR 0.83; $P = .08$; P for interaction = .03).[306] However, prolonging thienopyridine use significantly increased moderate or severe bleeding events (2.5% vs 1.6%; HR 1.61; 95% CI, 1.21-2.16; $P = .001$).[234] Moreover, the rate of death from any cause was higher in the group that continued thienopyridine therapy than the placebo group (2.0% vs 1.5%; HR 1.36; 95% CI, 1.00-1.85; $P = .05$) as a result of an unexpected higher rate of noncardiovascular death, which was attributed to an imbalance in cancer-related deaths in the randomized populations. In a post hoc sensitivity analysis, which excluded nine individuals with cancer death related to malignancy present before enrolment, no significant difference was observed in all-cause mortality

between the treatment groups. Also, thienopyridine use was not associated with the development of new cancer; cancer-related deaths in prolonged thienopyridine users were not higher than in placebo users after excluding patients in whom the fatal cancer had been diagnosed before enrollment.[307] The PEGASUS-TIMI 54 study, described earlier, was the first study to specifically study patients with a prior MI, 1 to 3 years before enrollment, plus at least one additional risk factor (≥ 65 years of age, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction).[155] Patients were randomized to either one of two doses of ticagrelor (90 or 60 mg twice a day) or placebo in addition to aspirin. The study showed that prolonging ticagrelor therapy was associated with a reduction in the primary efficacy end point (cardiovascular death, MI, and stroke), although this occurred at the expense of increased bleeding. Because the reduction of ischemic events occurred to a similar extent in patients treated with either dose of ticagrelor (60 or 90 mg), but bleeding was numerically lower with the 60-mg dose, these findings are supportive of the use of ticagrelor 60 mg twice a day for secondary prevention of long-term ischemic events among patients who experienced a prior MI (> 1 year). A meta-analysis of randomized trials comparing more than a year of DAPT with aspirin alone in high-risk patients with a history of MI conducted in a total of 33,435 patients followed over a mean 31 months showed that extended DAPT decreased the risk of major adverse cardiovascular events compared with aspirin alone (6.4% vs 7.5%; risk ratio [RR] 0.78; P = .001) and reduced cardiovascular death (2.3% vs 2.6%; RR 0.85; P = .03), with no increase in noncardiovascular death (RR 1.03; P = .76). The resultant effect on all-cause mortality was an RR of 0.92 (P = .13). Extended DAPT also reduced MI (RR 0.70; P = .003), stroke (RR 0.81; P = .02), and stent thrombosis (RR 0.50; 95% CI, 0.28-0.89; P = .02). There was an increased risk of major bleeding (1.85% vs 1.09%; RR 1.73; P = .004) but not fatal bleeding (0.14% vs 0.17%; RR 0.91; 95% CI, 0.53-1.58; P = .75).[232]

Guidelines currently recommend the use of DAPT for 1 year in patients experiencing an ACS.[4-9] This is also supported in the most recent ACC/AHA guideline update on DAPT duration.[308] Although studies support that prolonging intensified antiplatelet therapy beyond 1 year is associated with a reduction in ischemic recurrences, including stent thrombosis, these occur at the expense of an increased risk of bleeding complications.[303] Clinicians should use best clinical judgment on the whether or not to prolong DAPT beyond 1 year in ACS patients as indicated in practice guidelines. In particular, patients treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable. Similarly, shorter DAPT duration may also be considered, such as in patients who develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (eg, major intracranial surgery), or develop significant overt bleeding, in whom discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable. Overall, decisions should be individualized taking into consideration both the ischemic and bleeding risk profile of each patient (Fig. 41–9). The DAPT score[309] was recently developed as a clinical decision tool to identify patients expected to derive benefit versus harm from continuing thienopyridine beyond 1 year after PCI.

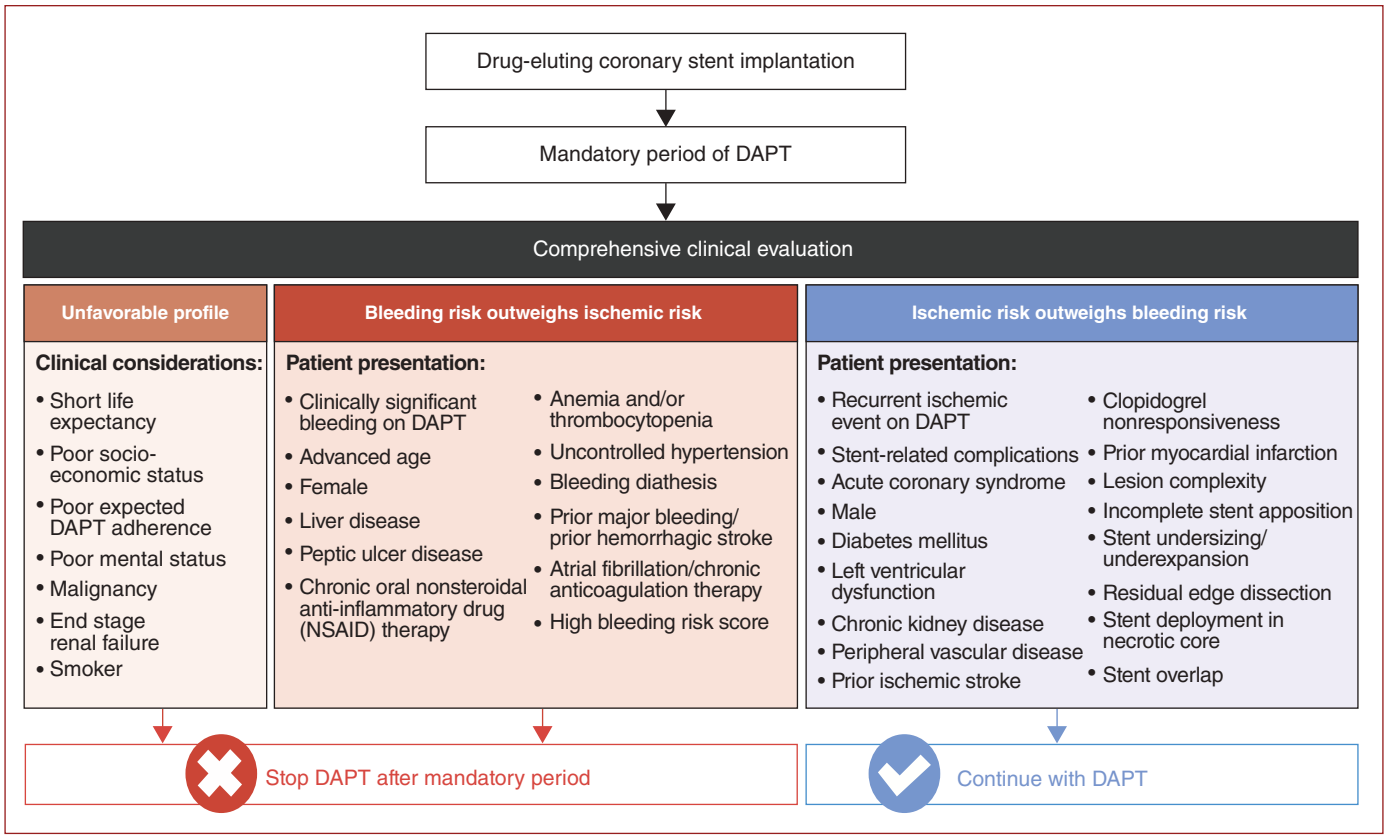


FIGURE 41–9. Decision making after the mandatory dual antiplatelet therapy (DAPT) period. When a mandatory period of DAPT is completed, a careful evaluation of the patient's ischemic risk and bleeding risk and of the overall clinical profile should be undertaken. NSAID, nonsteroidal anti-inflammatory drug. Reproduced with permission from Montalescot G, Brieger D, Dalby AJ, et al: Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Review of the Evidence. *J Am Coll Cardiol*. 2015 Aug 18;66(7):832-847.[299]

Switching $P2Y_{12}$ Receptor Antagonists

The availability of different oral $P2Y_{12}$ receptor inhibitors available for clinical use makes switching between $P2Y_{12}$ inhibiting therapies common in clinical practice.[310] Recommendations for switching between oral and IV $P2Y_{12}$ receptor inhibitors are summarized in Fig. 41–10. Switching from clopidogrel to a newer agent, prasugrel or ticagrelor, frequently occurs in ACS patients who are pretreated with clopidogrel.[310] Switching from clopidogrel to ticagrelor occurred in nearly half of the patients enrolled in the PLATO trial, which showed consistent safety and efficacy results irrespective of prior exposure to clopidogrel.[143] In the trial, patients randomized to ticagrelor therapy were treated with a 180-mg loading dose irrespective of timing of last dose of clopidogrel. Accordingly, a similar approach should be applied in clinical practice whenever switching from clopidogrel to ticagrelor. Although switching from clopidogrel to prasugrel was not explored in the TRITON trial, because patients pretreated with clopidogrel were excluded from the study, data from registries have not shown any major safety concerns (eg, bleeding) related to such switching.[310] Surrogate data from dedicated pharmacodynamic studies showed that patients pretreated with clopidogrel can switch to prasugrel, which leads to enhanced levels of platelet inhibition. These are achieved more promptly when switching using a 60-mg loading dose rather than a 10-mg maintenance dose, and without any drug interactions, irrespective of whether a patient was on 75 mg/d maintenance therapy or recently exposed to a 600-mg loading dose of clopidogrel.[97,311] Therefore, administering a 60-mg loading dose should be the strategy to use when switching from clopidogrel to prasugrel in the acute setting.

Switching from a later generation $P2Y_{12}$ receptor inhibitor to clopidogrel also commonly occurs in clinical practice but with limited data to support this approach.[310] Reduced costs associated with a generic formulation of clopidogrel as well as concerns about bleeding with prasugrel and ticagrelor remain key reasons for switching to clopidogrel. In the absence of clinical studies investigating the effects of such strategy, based on pharmacodynamic considerations, whenever switching from prasugrel or ticagrelor is required, clopidogrel should be administered with a 600-mg loading dose, given its unpredictable platelet inhibitory profile.[310]

Registry data indicate that switches between the latest generation $P2Y_{12}$ receptor inhibitors occur rarely.[310] In this setting, limited data are available. Switching from ticagrelor to prasugrel has shown to be associated with an acute (24-48 hours) increase in platelet reactivity, potentially as a result of a drug interaction, which is reduced with the administration of a 60-mg loading dose.[312] Conversely, small pharmacodynamic investigations showed that platelet inhibition is enhanced when switching from prasugrel to ticagrelor.[313] Based on the best

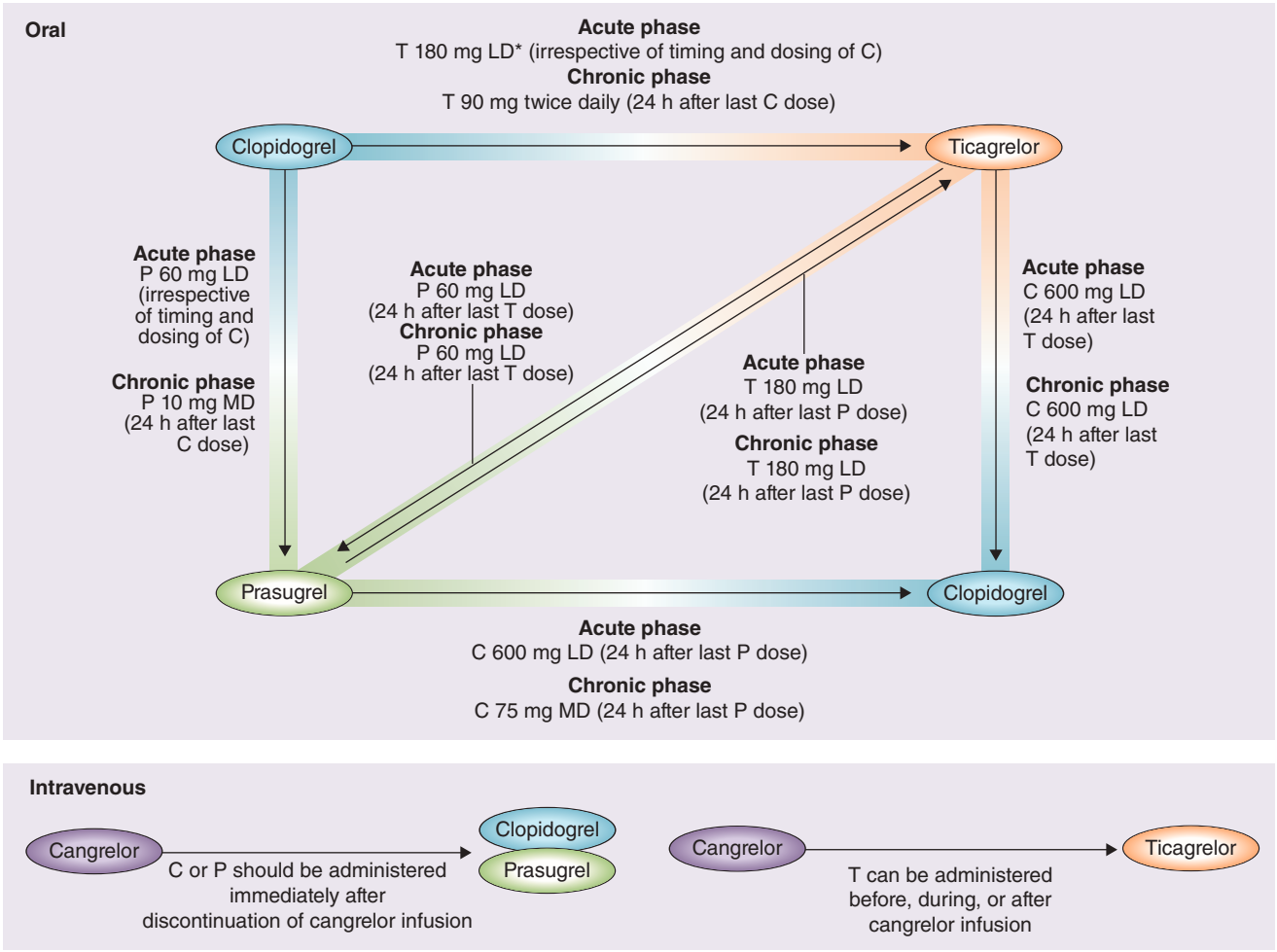


FIGURE 41–10. Practical recommendations for switching between oral and intravenous antiplatelet agents. Switching from an oral agent is shown in the *upper panel*, and switching from an intravenous agent is shown in the *lower panel*. *Followed by ticagrelor (T) 90 mg twice daily with first maintenance dose (MD) administered 12 hours after the loading dose (LD). C, clopidogrel; P, prasugrel. Reproduced with permission from Rollini F, Franchi F, Angiolillo DJ: Switching P2Y12-receptor inhibitors in patients with coronary artery disease. *Nat Rev Cardiol*. 2016 Jan;13(1):11-27.[310]

available evidence, the administration of a loading dose is preferred when switching between new $P2Y_{12}$ receptor inhibitors.[310]

Switching from IV cangrelor to clopidogrel has been tested in large-scale clinical trials, whereas data on switching to the new agents derive from small pharmacodynamic studies. Overall, available data suggest that clopidogrel and prasugrel should be administered immediately after discontinuation of cangrelor infusion to avoid a pharmacodynamic interaction given that these agents compete for $P2Y_{12}$ receptor binding.[161,165] In contrast, ticagrelor can be administered before, during, or after cangrelor infusion.[164] No drug interaction has been described when transitioning from any oral $P2Y_{12}$ receptor inhibitor to cangrelor, which can thus be started at any time.[310]

OTHER ANTIPLATELET AGENTS

Over the years, a large number of antiplatelet agents have been developed. Although some of these have been approved for clinical use, they may not have an indication for ACS patients but for patients with other atherosclerotic disease manifestations such as PAD or cerebrovascular disease. These include the phosphodiesterase inhibitors cilostazol, dipyridamole, and pentoxifylline, which exert their effects on platelets, and other cell lines, by increasing intracellular levels of cAMP. However, given the lack of indication for clinical use in ACS patients, these will not be discussed.[19] Although TXA_2 is the major agonist of TP receptor–mediated platelet activation, other eicosanoids, such as isoprostanes and endoperoxides, are important activators of the TP receptor through nonenzymatic pathway (see Fig. 41–2).[314] As ischemic events continue to occur despite the blockage of TXA_2 synthesis mediated by aspirin, it has been hypothesized that TP receptor antagonism may potentially offer advantages over COX-1 inhibition. Notably, many TP receptor antagonists also exert an inhibitory effect on TXA_2 synthase.[314] TP receptor antagonists include terutroban, sulotroban, daltroban, ifetroban, ramatroban, linotroban, and seratrodast, whereas combined TXA_2 synthase/TP receptor inhibitors include ridogrel, picotamide, terbogrel, and EV-077. Despite favorable early-phase investigations, the results from clinical studies evaluating TP antagonists have thus far been disappointing. Ridogrel, the only agent tested in the ACS setting, failed to show any benefit over aspirin as adjunct therapy to thrombolysis in patients with acute MI.[315] Terutroban and picotamide did not improve outcomes compared to aspirin in patients with a recent cerebrovascular accident and PAD, respectively.[316,317] EV-077 is a potent dual TP receptor antagonist/TXA_2 synthase inhibitor that has shown potent and additive platelet inhibitory effects on multiple pathways in healthy volunteers and in patients with DM.[314,318,319] EV-077 is in phase II development, and no clinical studies are currently ongoing.

Several other agents targeting different platelet signaling pathways are currently in early-phase clinical development (see Fig. 41–2). These include $P2Y_1$ receptor antagonists (MRS2179, MRS2500); oral GPIs (MNS, RUC-1); inhibitors of collagen-platelet interaction, such as glycoprotein VI antagonists (kistomin, revacept) or glycoprotein Ib antagonists (6B4-Fab monoclonal antibody); nitric oxide donors (LA846, LA419); prostaglandin E receptor 3 antagonists (DG-041); serotonin receptor inhibitors (APD791); and phosphatidylinositol-3-kinase inhibitors (TGX-221).[320]

ANTICOAGULANTS [Fig. 41–11]

UNFRACTIONATED HEPARIN

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile

Unfractionated heparin (UFH) is a heterogeneous mixture of variable molecular weight (2000-30,000 Da) polysaccharide molecules. There are two key structural components to UFH that determine its function: (1) a unique pentasaccharide sequence mainly responsible for factor Xa inhibition, and (2) saccharide chain lengths > 18 units long, which are necessary to achieve thrombin inhibition. The pentasaccharide sequence is required for binding of UFH to antithrombin (AT), thereby increasing the potency of AT by up to 1000-fold. This UFH:AT complex inactivates multiple proteases, including factors Xa, IXa, XIa, and XIIa and thrombin. Thrombin and factor Xa are the most sensitive to activated AT, but thrombin is 10 times more susceptible than factor Xa.[321] The pentasaccharide binding to AT causes a conformational change in AT, converting AT from a slow to a very rapid thrombin inhibitor.[322,323] However, to inhibit thrombin, the UFH chain lengths must be sufficiently long to bridge between AT and thrombin to form a ternary complex.[324] Once formed, this ternary complex inhibits thrombin to a greater degree than factor Xa. Through thrombin inactivation, UFH prevents fibrin formation and inhibits thrombin-induced activation of platelets, factor V, and factor VIII, thereby preventing thrombus propagation.[325] Shorter UFH chains of < 18 saccharide units are unable to form this ternary complex (UFH:AT:thrombin) and, therefore, primarily inhibit factor Xa via AT over thrombin (see later section on low-molecular-weight heparins).[326]

A secondary anticoagulant mechanism of UFH is mediated by its activation of heparin cofactor II (HCII). HCII-mediated thrombin inactivation is pentasaccharide-independent (and thus AT-independent) but requires at least 24 saccharide units and higher UFH concentrations.[327] A third anticoagulant mechanism of UFH is independent of AT and HCII and requires very high doses (well beyond doses used in clinical practice) of UFH to result in charge-mediated binding to factor IXa and inhibition of factor Xa activation.[328]

The UFH polysaccharide chain is degraded in gastric acid and therefore must be administered via IV or subcutaneously (SC). Heparin should not be given intramuscularly because of the danger of hematoma formation. UFH is partially metabolized in the liver by heparinase to uroheparin, which has only slight antithrombin activity.[329] Immediate anticoagulant effect can be achieved after IV bolus injection followed by continuous IV infusion, making IV administration the preferred route for ACS. In contrast, after a SC dose, the anticoagulant effect is delayed for approximately 1 hour with the peak plasma levels occurring at approximately 3 hours.[330] The bioavailability of UFH is approximately 10% lower with SC versus IV dosing.[331] Once it enters the bloodstream, UFH binds to a number of plasma proteins, endothelial cells, macrophages, and vWF, which reduces its anticoagulant activity, leads to heparin resistance, and inhibits vWF-dependent platelet function.[332-335] These varied binding properties of UFH contribute to its variable anticoagulant response, particularly among patients with thromboembolic disorders,[332] and further complicate its pharmacokinetics.[336]

Clearance of UFH occurs via two different processes. The primary elimination pathway is by a rapid but saturable depolymerization process that occurs when UFH binds to endothelial cells and macrophages.[337,338] The majority of UFH at therapeutic doses is cleared through this cellular mechanism, leading to a nonlinear anticoagulant response with respect to peak effect and duration of action.[336] The half-life of UFH ranges from 30 minutes after an IV bolus of 25 U/kg to 150 minutes with a bolus of 400 U/kg.[339-341] The slower, first-order mechanism of clearance occurs via nonsaturable renal clearance, although this applies mainly to supraclinical dose levels of UFH.[340] Given the relatively rapid clearance, the anticoagulant effect of UFH is lost within a few hours after its interruption, leading to a risk of reactivation of the coagulation process and thereby a transiently increased risk of thrombosis, despite simultaneous aspirin treatment.[47] This *heparin rebound* effect is supported by evidence of increased thrombin activity after cessation

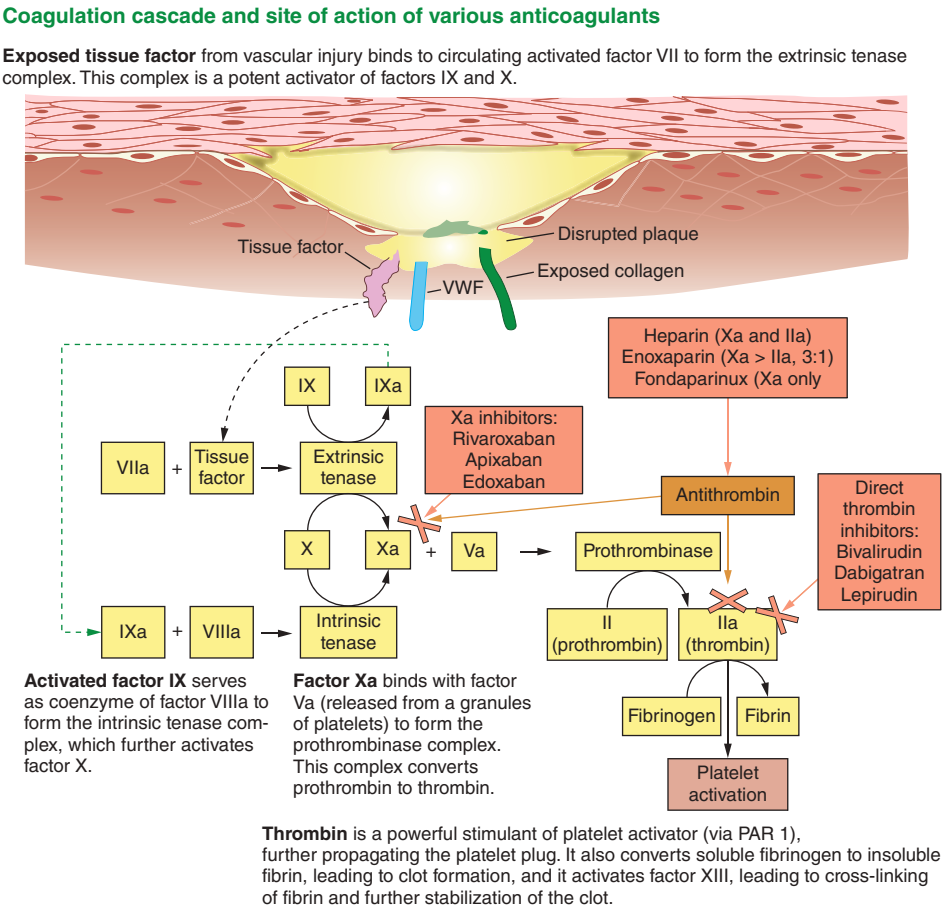


FIGURE 41–11. Coagulation cascade and site of action of various anticoagulants. Exposed tissue factor from vascular injury binds to circulating activated factor VII to form the extrinsic tenase complex. This complex is a potent activator of factors IX and X. Activated factor IX serves as coenzyme of factor VIIIa to form the intrinsic tenase complex, which further activates factor X. Factor Xa binds with factor Va (released from a granules of platelets) to form the prothrombinase complex. This complex converts prothrombin to thrombin. Thrombin is a powerful stimulant of platelet activator, further propagating the platelet plug. It also converts soluble fibrinogen to insoluble fibrin, leading to clot formation, and it activates factor XIII, leading to cross-linking of fibrin and further stabilization of the clot. Reproduced with permission from Singh D, Gupta K, Vacek JL: Anticoagulation and antiplatelet therapy in acute coronary syndromes. *Cleve Clin J Med*. 2014 Feb;81(2):103-114.

of UFH. This may be mitigated by transitioning from IV to SC dosing before cessation of UFH.[342,343]

UFH has anticoagulant activity as well as many other biologic effects, resulting from its heterogeneous binding properties to a variety of cells and proteins. In vitro studies on UFH have demonstrated that higher weight moieties lacking the high-affinity pentasaccharide recognition site for AT bind more efficiently to platelets than low-molecular-weight heparin (LMWH), leading to altered platelet function[344,345] and, for example, the prolongation of bleeding time.[346] UFH also increases vessel wall permeability[347] and suppresses smooth muscle cell proliferation[348] via actions largely independent of its anticoagulant activity.[349] A clinically relevant, nonanticoagulant effect of UFH is the inhibition of osteoblast formation and osteoclast activation, which promote bone loss, resulting in heparin-induced osteoporosis.[350,351]

The most clinically significant nonanticoagulant effect of UFH is its potential to induce immune-mediated platelet activation, known as *heparin-induced thrombocytopenia* (HIT). Simultaneous binding of heparin-dependent immunoglobulin G antibodies to a conformationally modified epitope on platelet factor-4 and to Fc receptors on the platelet results in platelet activation and a prothrombotic state coupled with increased removal of platelets from the circulation.[352,353] Thrombocytopenia, defined as a platelet count < 100,000/μL or a 50% reduction in baseline platelet count, occurs with higher frequency with UFH (incidence ~ 0.3%) compared with LMWH and may be accompanied by both venous and arterial clotting.

Heparin resistance describes the phenomenon of inadequate response to UFH, which necessitates higher than usual doses of UFH to achieve the desired anticoagulant effect. Several potential mechanisms may explain this resistance, including more rapid clearance,[354] increased heparin-binding proteins,[333] AT deficiency, and increased factor VIII levels.[355]

Pharmacogenetic data for UFH are limited to thrombotic complications and HIT. These include the PLA2 polymorphism of the glycoprotein IIIa gene, platelet FcyRIIA H131, and platelet factor-4 polymorphisms. These associations are weak, and the data are controversial.[356-361]

Dosing, Monitoring, and Reversal

Initial dosing of UFH in patients with ACS should begin with an IV weight-based bolus followed by continuous IV infusion according to evidence-based recommendations and available clinical trial data, which have been incorporated in the ACC/AHA[4] and ESC[9] guidelines. The goal of the weight-based dosing is to achieve "therapeutic" anti–factor Xa levels (0.3-0.7 U/mL), which correlate to an activated partial thromboplastin time (aPTT) of approximately 60 to 80 seconds.[4,9,336]

As a result of laboratory variation, nomograms should be established at each institution that are designed to achieve aPTT values in the target range (eg, for a control aPTT of 30, the target range of 1.5-2.5 times control would correspond to 45-75 seconds). For UA/NSTEMI, an initial IV bolus of 60 to 70 U/kg (maximum 4000 U) followed by continuous infusion of 12 to 15 U/kg/h (maximum 1000 U/h is recommended).[4] For STEMI patients receiving nonstreptokinase fibrinolytic therapy regimens, the dosing of UFH is at the lower end of this range with an initial IV bolus of 60 U/kg (maximum 4000 U) followed by continuous infusion of 12 U/kg/h (maximum 1000 U/h), adjusted to maintain the aPTT at 1.5 to 2.0 times control (~ 50-70 seconds). The duration of UFH infusion after fibrinolytic therapy should generally not exceed 48 hours.[362] In addition to low body weight, older age and female sex have been associated with higher aPTT responses to UFH and should be considered in dosing decisions. Smoking and diabetes have been associated with an attenuated response to UFH.[363,364]

Monitoring of aPTT should be performed 6 hours after any dosing change or if there is a significant change in the patient's condition. The hemorrhagic and nonhemorrhagic complications with UFH are increased with higher doses,[365,366] prolonged or repeated exposure,[367] and concomitant use of fibrinolytic agents[368-370] or GPIs.[201] Hemoglobin and platelet count should be assessed daily during UFH infusion. A mild, clinically insignificant drop in platelet count may occur in up to 20% of patients with the platelet counts remaining above 100,000/μL. However, if HIT is suspected based on drop in platelet count, immediate cessation of all UFH therapy (including IV flush) should be instituted, along with screening for anti–platelet factor-4 antibodies, followed by the more definitive serotonin release assay.[367,371,372]

Protamine, a small arginine-rich (ie, cationic) nuclear protein purified from fish sperm, binds to and neutralizes UFH, forming a stable salt. Reversal of the anticoagulant effect of UFH can be achieved rapidly with an IV bolus of protamine using 1 mg of protamine to neutralize 100 U of UFH. Allergic hypersensitivity reactions and anaphylaxis to protamine may occur in patients who use protamine-containing insulin, have a fish allergy, or who have had a vasectomy. Severe adverse reactions to protamine, such as hypotension and bradycardia, have been observed and can be minimized if administered slowly.[373,374]

Evidence for Use

Guideline recommendations for UFH use in ACS are based on meta-analyses of six relatively small randomized, placebo-controlled trials with UFH for treatment of UA/NSTEMI.[375-381] Treatment with aspirin plus UFH compared with aspirin alone resulted in a 54% reduction in the rate of death or nonfatal MI, but at the cost of an increase in the risk of bleeding. Adjunctive anticoagulation with UFH is recommended during PCI or in combination with fibrinolytic therapy for the treatment of STEMI.

European Society of Cardiology Guideline for Use of Unfractionated Heparin in the Management of patients with Non-ST-Segment Elevation Acute Coronary Syndromes

In patients with NSTE-ACS, parenteral anticoagulation, in addition to antiplatelet therapy, is recommended for all patients at the time of diagnosis according to both ischemic and bleeding risks.[9]

- *UFH 70-100 IU/kg IV (50-70 IU/kg if concomitant with GPIs) is recommended in patients undergoing PCI who did not receive any anticoagulant (Class IB).*
- *In patients on fondaparinux (2.5 mg SC daily) undergoing PCI, a single IV bolus of UFH (70-85 IU/kg, or 50-60 IU/kg in the case of concomitant use of GPIs) is recommended during the procedure (Class IB).*

American College of Cardiology/American Heart Association Guideline for Use of Unfractionated Heparin in the Management of ST-Segment Elevation Myocardial Infarction[5]

1. For patients with STEMI undergoing primary PCI, we recommend: UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered. (Class 1C)

- *If use of GP IIb/IIIa receptor antagonist is planned: heparin dose should be 50- to 70-U/kg IV bolus to achieve therapeutic ACT‡*
- *If use of GP IIb/IIIa receptor antagonist is not planned: heparin dose should be 70- to 100-U/kg bolus to achieve therapeutic ACT§*

‡The recommended ACT with planned GP IIb/IIIa receptor antagonist treatment is 200 to 250 s.

§The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 s (HemoTec device) or 300 to 350 s (Hemochron device).

2. For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with intravenous UFH, additional boluses of intravenous UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. (Grade 1C)

3. For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis we recommend weight-based IV bolus and infusion of UFH adjusted to obtain aPTT of 1.5 to 2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization. (Grade 1C)

LOW-MOLECULAR-WEIGHT HEPARIN

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile

LMWHs are produced through depolymerization of the polysaccharide chains of UFH, which results in fragments ranging from 2000 to 10,000 Da.[382] These shorter chain lengths contain the unique pentasaccharide sequence necessary to bind to AT but are too short (< 18 saccharides) to form the ternary complex crosslinking AT and thrombin. Therefore, the primary effect of LMWHs is limited to AT-dependent factor Xa inhibition. In comparison to UFH where the ratio of factor Xa-to-thrombin inhibition is 1:1, LMWHs result in a factor Xa-to-thrombin inhibition ratio ranging from 2:1 to 4:1.[336,383] LMWHs also have reduced binding to plasma proteins and cells compared with UFH, thereby providing a more favorable and predictable pharmacokinetic profile.[336,384]

Although many different LMWH preparations have been developed, enoxaparin is the most studied in clinical trials of UA/NSTEMI, STEMI, and PCI. The primary difference among the LMWHs is their molecular weight and therefore the relative anti-Xa–to–AT ratio. For example, enoxaparin has a mean molecular weight of 4200 Da with an anti-Xa–to–AT ratio of 3.8; dalteparin, with a mean molecular weight of 6000 Da, has an anti-Xa–to–AT ratio of 2.7.[385]

The theoretical pharmacologic advantages of LMWH over UFH arise from the preferential binding ratio to factor Xa over thrombin, less plasma protein binding, attenuated platelet activation, lower risk of HIT, and reduced binding to osteoblasts.[351,385-388] After subcutaneous injection, LMWHs have a more predictable anticoagulant response and greater than 90% bioavailability.[389] Anti-Xa levels peak 3 to 5 hours after an SC dose of LMWH.[385] The elimination half-life of LMWHs is largely dose independent and occurs 3 to 6 hours after an SC dose.[390] However, LMWHs are cleared by the kidney, leading to prolonged anti-Xa effect and linear accumulation of anti-Xa activity in patients with a creatinine clearance below 30 mL/min.[391,392]

The anticoagulant effect of LMWHs can be measured via anti–factor Xa levels, with a target peak anti-Xa level between 0.6 and 1.0 U/mL derived from studies of venous thromboembolism treatment.[393,394] However, given the predictable anticoagulant response to LMWHs, routine monitoring of anti–factor Xa levels in most clinical settings is unnecessary. Pharmacokinetic and pharmacodynamic properties of enoxaparin were determined from patients enrolled in the TIMI 11A study and included an enoxaparin clearance of 0.733 L/h, a distribution volume of 5.24 L, and an elimination half-life of 5.0 hours.[395] Hemorrhagic complications were modeled and predictable based on enoxaparin clearance, which was significantly related to patient weight and creatinine clearance. Creatinine clearance below 30 mL/min correlated with a 27% decrease in enoxaparin clearance, leading to a 3.8-fold increased risk of major hemorrhage.[396] In this setting of severe renal impairment with creatinine clearance below 30 mL/min, the dose of enoxaparin should be cut in half (eg, 1 mg/kg/d).[336] The risk of bleeding with LMWH is dose-related and increases with age, female sex, lower body weight, reduced renal function, and interventional procedures.[336]

Although LMWHs are equally reactive as UFH in activation assays of washed platelets using serum from HIT patients,[367,397] LMWHs are approximately three times less likely than UFH to cause anti–platelet factor-4 antibody formation[367,398] and less likely to produce HIT in patients who have formed anti–platelet factor-4 antibodies.[367,398] Nonetheless, use of LMWHs in the presence of HIT increases the risk of both thrombocytopenia and new thrombotic events and, therefore, LMWHs are contraindicated in this setting. Also, because of the lower affinity of LMWHs for bone cells, the osteopenic effect is reduced with LMWHs compared with UFH.[399]

If hemorrhagic complications occur as a result of LMWH, protamine sulfate may be administered to neutralize the AT effect of LMWH; however, the degree to which the anti-Xa activity of LMWH is neutralized by protamine is variable and uncertain.[400] For patients treated with enoxaparin within 8 hours, protamine should be administered as 1 mg of protamine per each 1 mg of enoxaparin. Smaller doses of protamine may be used if the time since the last dose of enoxaparin exceeded 8 hours.[336]

There are no clear data demonstrating a pharmacogenetic effect in LMWH treatment. However, polymorphisms of the interleukin-1 receptor antagonist may be a marker to identify patients who would benefit from LMWH as a result of attenuated release of vWF.[401]

Evidence for Use

The safety and efficacy of LMWHs have been established in patients with UA/NSTEMI and STEMI as well as patients undergoing PCI. Nine randomized trials directly compared LMWH with UFH[402-410] in UA/NSTEMI patients presenting with substantial heterogeneity between the trials. In two studies using dalteparin[402,403] and one with nadroparin,[404] no significant differences in death or MI were observed in patients treated with LMWH compared with UFH. However, in a meta-analysis of six trials evaluating 21,946 patients randomized to enoxaparin or UFH, a significant reduction in the combined end point of death or nonfatal MI at 30 days was observed favoring enoxaparin over UFH (10.1% vs 11.0%; OR 0.91; 95% CI, 0.83-0.99).[411] There were no significant differences in major bleeding or blood transfusion within the first week of therapy. The largest and most recent trial comparing enoxaparin with UFH randomized 10,027 high-risk patients with UA/NSTEMI intended for an early invasive strategy using guideline-recommended aspirin, clopidogrel, and GPIs.[405] At 30 days, the primary composite end point of death or MI was no different between enoxaparin and UFH (14% vs 14.5%; OR 0.96; 95% CI, 0.86-1.06). TIMI major bleeding was significantly higher with enoxaparin compared to UFH (9.1% vs 7.6%; $P = .008$). Increased bleeding with enoxaparin was attributed to time-guided rather than ACT-guided sheath removal in the enoxaparin arm as well as anticoagulant switching effects as a result of prerandomization anticoagulant use.

The use of enoxaparin compared to UFH in patients with STEMI treated with primary PCI has been evaluated in several nonrandomized trials with similar conclusions showing a reduction in ischemic end points without increased bleeding favoring the LMWH.[412-416] The randomized ATOLL trial[417] evaluated 910 patients with STEMI who were assigned to receive IV enoxaparin 0.5 mg/kg or UFH prior to PCI. GPIs were used in approximately 80% of patients in both arms. UFH was administered as a 50- to 70-U/kg bolus if GPIs were used or as a 70- to 100-U/kg bolus without GPI use. The primary outcome, represented by a composite of 30-day death, MI, procedure failure, or major bleeding, favored enoxaparin over UFH but did not quite reach statistical significance (28% vs 34%; RR 0.83; 95% CI, 0.8-1.01; $P = .06$). In a meta-analysis[418] of 10 studies including 16,286 patients treated with LMWH or UFH in the setting of primary PCI for STEMI, LMWH treatment was associated with a statistically significant reduction in mortality (RR 0.51; $P < .001$) and major bleeding (RR 0.68; $P = .02$) compared with UFH.

The safety and efficacy of enoxaparin versus UFH as adjunctive pharmacotherapy for STEMI patients receiving fibrinolytics have been evaluated in two trials. When compared with UFH, enoxaparin added to fibrinolytic therapy reduced the risk of in-hospital reinfarction or refractory ischemia[419] but increased the rate of ICH among patients over the age of 75 years.[420] With this in mind, the ExTRACT-TIMI 25 trial investigators randomized 20,506 STEMI patients receiving fibrinolytic therapy to enoxaparin or UFH for at least 48 hours.[362] Importantly, a lower dose of enoxaparin was given to patients older than 75 years (no bolus was given and the SC dose was reduced to 0.75 mg/kg twice daily) and to those with impaired renal function, defined as estimated creatinine clearance < 30 mL/min (1 mg/kg SC once daily). Enoxaparin treatment was associated with a significant reduction in the risk of death and reinfarction at 30 days when compared with UFH (9.9% vs 12%; $P = .001$). TIMI major bleeding was significantly increased in the enoxaparin group (2.1% vs 1.4% with UFH). The net clinical benefit (absence of death, nonfatal infarction, or ICH) favored enoxaparin and was observed regardless of the type of fibrinolytic agent and the age of the patient.[421,422]

European Society of Cardiology Guideline for Use of Low-Molecular-Weight Heparins in the Management of Patients With Non–ST-Segment Elevation Acute Coronary Syndrome[9]

1. Enoxaparin 1 mg/kg subcutaneously every 12 hours should be initiated at the time of presentation (Reduced dosing of 1 mg/kg subcutaneously once daily if eGFR [estimated glomerular filtration rate] < 30 mL/min/1.73 m^2. (Class 1B)

2. Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated with enoxaparin SC upstream. (Class IIa-B)

3. *We recommend against routine monitoring of the anticoagulant effect of LMWH.*

4. *If the last dose of enoxaparin was given < 8 h before PCI, we recommend no additional anticoagulant therapy. If the last dose of enoxaparin was given 8-12 h before PCI, we recommend a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI.*

5. *Crossover between UFH and LMWH is not recommended. (Class IIIB)*

American College of Cardiology Foundation/American Heart Association Guideline for Use of Low-Molecular-Weight Heparins in the Management of Patients With ST-Segment Elevation Acute Coronary Syndromes[5]

1. *Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive enoxaparin administered according to age, weight, and creatinine clearance, given as an intravenous bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to 8 days or until revascularization. (Class 1A)*

2. *Recommended dosing for enoxaparin for age < 75 years is 30-mg IV bolus followed by 1 mg/kg SC every 12 h (maximum of 100 mg for the first 2 SC doses) and for age > 75 years is no IV bolus, 0.7 mg/kg SC every 12 h (maximum of 7 mg for the first 2 SC doses). (Class 1A)*

3. *For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last dose of enoxaparin was given < 8 h before PCI, we recommend no additional anticoagulant therapy. If the last dose of enoxaparin was given 8-12 h before PCI, we recommend a 0.3mg/kg bolus of IV enoxaparin at the time of PCI. (Class 1B)*

FACTOR XA INHIBITORS

Fondaparinux

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile Fondaparinux (molecular weight 1728 Da) is a synthetic analog of the unique AT-binding pentasaccharide sequence found in UFH. Fondaparinux is a selective factor Xa inhibitor that binds reversibly to AT and produces an irreversible conformational change at the reactive site of AT that enhances its reactivity with factor Xa.[423] Once released from AT, fondaparinux is available to activate additional AT molecules, but because it is too short to bridge AT to thrombin, fondaparinux does not increase the rate of thrombin inhibition by AT. Although fondaparinux inhibits factor Xa–dependent thrombin generation, it does not have any inhibitory action against thrombin that is already formed.[336]

In healthy volunteer studies, fondaparinux was shown to have 100% bioavailability after SC injection with rapid absorption, achieving a steady state after three to four daily doses.[424,425] The elimination half-life is 17 hours with primary clearance via the kidney, and therefore, fondaparinux is contraindicated in patients with severe renal impairment.[4,336,426] Fondaparinux produces a predictable anticoagulant response and exhibits linear pharmacokinetics when given in SC doses of 2 to 8 mg or in IV doses ranging from 2 to 20 mg that result in anti-Xa activity that is roughly seven times that of LMWHs.[424,425]

The anticoagulant effect of fondaparinux can be measured in anti–factor Xa units, although monitoring is not required. Fondaparinux does not affect other parameters of anticoagulation, including aPTT, ACT, or prothrombin time.[426] The excellent bioavailability and predictable anticoagulant response are reflective of its minimal nonspecific binding to plasma proteins.[427] Fondaparinux does not induce the formation of UFH:platelet factor-4 complexes and does not cross-react with HIT antibodies, making HIT unlikely to occur.[428] Although not labeled for treatment of HIT, fondaparinux has been used successfully to treat HIT patients.[429,430] Fondaparinux has no effect on osteoblasts and is therefore unlikely to induce osteoporosis.[431] In addition, although it has not been adequately studied in pregnancy, fondaparinux does not appear to cross the placental barrier.[432]

Dosing, Monitoring, and Reversal Based on a dose-ranging study of fondaparinux versus enoxaparin in the setting of UA/NSTEMI involving 1147 patients, fondaparinux 2.5 mg daily was shown to have the best efficacy/safety profile when compared with 4-, 8-, and 12-mg doses of fondaparinux and with enoxaparin 1 mg/kg twice daily.[433] Coagulation monitoring is not recommended and has not been studied as part of the clinical development of this drug. Fondaparinux has not been effectively studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); in those with moderate renal impairment (30-50 mL/min), fondaparinux dose should be reduced by half.[336] Although anti-Xa levels can be measured to assess the anticoagulant effect of fondaparinux, the standard therapeutic level is unknown. Importantly, reversal of the anticoagulant effect of fondaparinux cannot be achieved with protamine. If life-threatening bleeding occurs as a result of fondaparinux, recombinant factor VIIa may be given to reverse the anticoagulant effect.[434]

Evidence for Use The efficacy and safety of fondaparinux (2.5 mg SC daily) compared with enoxaparin (1 mg/kg SC twice daily) in patients with UA/NSTEMI were evaluated in the OASIS-5 trial (n = 20,078).[435] The primary outcome of noninferiority of combined death, MI, or refractory ischemia at 9 days was achieved (5.8% fondaparinux vs 5.7% enoxaparin; $P = .007$). Major bleeding was significantly lower with fondaparinux (2.2% vs 4.1% with enoxaparin; $P < .001$), resulting in superior net clinical benefit (composite of death, MI refractory ischemia, or major bleeding) with fondaparinux compared with enoxaparin (7.3% vs 9.0%; $P < .001$). Importantly, mortality at 6 months was also reduced with fondaparinux compared with enoxaparin (5.8% vs 6.5%; $P = .05$). However, in the group of patients who underwent PCI, there was evidence for more catheter-related thrombus formation with fondaparinux (0.9% vs 0.4%; $P < .001$), indicating that anticoagulation with fondaparinux alone is insufficient for PCI.[435]

In patients with STEMI, fondaparinux was evaluated as an alternative to standard adjunctive anticoagulation in the OASIS-6 trial (n = 12,092).[436] Fondaparinux was administered at 2.5 mg SC daily for 8 days and compared with either no UFH (stratum I) or UFH infusion (stratum II) for 48 hours. Primary PCI was performed in approximately 25% of patients; fibrinolytic therapy was administered to approximately half the patients, of whom 73% received streptokinase. The primary outcome of 30-day death or MI was significantly reduced in patients who received fondaparinux (9.7% vs 11.2%; $P = .008$), although this was driven by patients in stratum I only. Patients who underwent primary PCI or who were in stratum II had no significant benefit with fondaparinux. Of concern, patients who underwent primary PCI with fondaparinux had more catheter-related thrombi (n = 22 vs n = 0; $P < .001$), more coronary complications (n = 270 vs 225; $P = .04$), and a trend toward higher death or MI compared with UFH (6.1% vs 5.1%; $P = .19$). It is important to note that despite guideline recommendations for the use of fondaparinux in ACS, fondaparinux is not currently approved for such use by the FDA in the United States.

European Society of Cardiology Guideline for Use of Fondaparinux in the Management of Patients with Non-ST-Segment Elevation Acute Coronary Syndromes[9]

1. *Parenteral anticoagulation is recommended at the time of diagnosis of UA/NSTEMI according to both ischemic and bleeding risks. (Class 1B)*

2. Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy–safety profile regardless of the management strategy. (Class 1B)

3. In patients on fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure. (Class 1B).

American College of Cardiology/American Heart Association Guideline for Use of Fondaparinux in the Management of Patients with ST-Segment Elevation Acute Coronary Syndromes[5]

1. Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis. (Class IIIB)

2. For patients with STEMI receiving fibrinolytic therapy, adjunctive fondaparinux 2.5 mg IV for the first dose and SC daily for up to 8 days or until revascularization is reasonable if the estimated creatinine clearance is greater than 30 mL/min. (Class 1B)

DIRECT THROMBIN INHIBITORS

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile

Direct thrombin inhibitors (DTIs) currently available and approved for use include lepirudin, argatroban, and bivalirudin. All DTIs exert their anticoagulant effects by binding to thrombin directly (see Fig. 41–12B), thereby inhibiting thrombin activity and the formation of fibrin from fibrinogen. Thrombin-mediated activation of other coagulation factors[437] and thrombin-induced platelet aggregation[438] are also inhibited by DTIs. In vitro data indicate that clot-bound thrombin and free thrombin are susceptible to inhibition by DTIs, thereby providing a potential rationale for clinical use in ACS.

Lepirudin (Recombinant Hirudin)

Lepirudin is the commercially available recombinant form of the 65-amino acid polypeptide hirudin (isolated from the salivary glands of the medicinal leech) that irreversibly inhibits thrombin.[439] The plasma half-life of hirudins is 60 minutes after IV injection.[440] Clearance occurs primarily through the kidneys, necessitating dose reduction in even mild renal impairment.[440] The current use of lepirudin is limited to treatment of patients with HIT, although it has been studied in patients with ACS, as described below. The drug is administered with a bolus and drip to achieve an aPTT of 1.5 to 2.5 times baseline (bolus 0.4 mg/kg followed by infusion of 0.15 mg/kg/h).[336] Lepirudin can induce antibody formation to hirudin in up to 40% of patients, who may then experience anaphylaxis if reexposed.[336]

Argatroban

Argatroban is a small-molecule competitive inhibitor of thrombin that binds to thrombin noncovalently, thereby forming a reversible complex.[441,442] Argatroban is metabolized via the cytochrome P450 3A4 pathway in the liver with a half-life of 45 minutes. There is no renal excretion of argatroban, so dose adjustment with renal impairment is unnecessary. It should be used with caution in patients with hepatic failure.[443] The primary indication for argatroban is HIT. Argatroban is given as a continuous IV infusion at a dose of 2 μg/kg/min with dose titration to achieve an aPTT 1.5 to 3 times normal.[336]

Bivalirudin

Bivalirudin is a 20-amino acid polypeptide and is a synthetic version of hirudin.[444] Its amino-terminal D-Phe-Pro-Arg-Pro domain, which interacts with active site of thrombin, is linked via four Gly residues to a dodecapeptide analogue of the carboxy-terminal of hirudin (thrombin exosite)[445] (see Fig. 41–12B). Bivalirudin forms a 1:1 stoichiometric complex with thrombin, but once bound, the amino terminal of bivalirudin is cleaved by thrombin, thereby restoring thrombin activity.[446]

Bivalirudin has a half-life of 25 minutes,[447] with proteolysis, hepatic metabolism, and renal excretion contributing to its clearance.[448] The half-life of bivalirudin is prolonged with severe renal impairment, and dose adjustment is required for dialysis.[449] In contrast to hirudin, bivalirudin is not immunogenic, although antibodies against hirudin can cross-react with bivalirudin with unknown clinical consequences.[336]

Bivalirudin is currently FDA approved for use during PCI as an alternative to UFH. The recommended dose in PCI is a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of PCI. There is robust clinical trial experience supporting the use of bivalirudin in patients with UA/NSTEMI upstream of the cardiac catheterization laboratory,[450] in patients with STEMI undergoing primary PCI as an alternative to UFH plus GPI,[451] in patients undergoing CABG,[452] and in HIT.[453]

Reversal of Anticoagulant Effects

Recombinant factor VIIa can reverse the anticoagulant effect of DTIs in healthy volunteers, although the short half-life of these agents typically precludes the need for active reversal.[454]

Evidence for Use: Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction

The OASIS-2 trial randomized 10,141 patients with UA/NSTEMI to a 72-hour infusion of either the DTI lepirudin (0.4 mg/kg bolus, 0.15 mg/kg/h infusion) or UFH.[455] This study demonstrated a nonsignificant difference between lepirudin and UFH in the primary outcome of cardiovascular death or MI at 7 days. However, lepirudin was associated with a significantly increased risk of major, but not life-threatening, bleeding. A pooled analysis of the OASIS, GUSTO-2B, and TIMI-9B trials showed superiority of hirudin compared with UFH for the prevention of death or MI at 30 to 35 days.[455]

In the Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2) study, patients (n = 6010) undergoing urgent or elective PCI were randomized to receive bivalirudin with provisional GP IIb/IIIa inhibition or UFH with planned GP IIb/IIIa inhibition.[456] The study demonstrated that bivalirudin was noninferior to UFH plus GP IIb/IIIa inhibition with regard to ischemic end points and was associated with significantly less major and minor bleeding. In the ACUITY study, patients with UA/NSTEMI (n = 13,189) were randomized to one of three antithrombotic regimens: UFH or enoxaparin plus GPI, bivalirudin plus GPI, or bivalirudin alone.[450] Bivalirudin alone was noninferior with respect to the combined ischemic end point and superior for bleeding (3.0% vs 5.7% for UFH/enoxaparin plus GPI; $P < .001$), leading to superior net clinical benefit with bivalirudin alone (10.1% vs 11.7%; $P = .02$). Importantly, prerandomization treatment with UFH or enoxaparin did not abrogate the net clinical benefit of bivalirudin.

Evidence for use: ST-Segment Elevation Myocardial Infarction

In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarctions (HORIZONS-AMI) trial,[451] STEMI patients (n = 3602) who presented within 12 hours after onset of symptoms were randomized to UFH plus GP IIb/IIIa inhibition or to treatment with bivalirudin alone for primary PCI. At 30 days, the bivalirudin-alone group demonstrated lower rates of death (2.1% vs 3.1%; $P = .047$) and major bleeding (4.9% vs 8.3%; $P < .001$) compared with the heparin plus GP IIb/IIIa inhibition group, leading to a

significantly lower rate of net adverse clinical events (9.2% vs 12.1%; P = .005). Acute stent thrombosis occurred more frequently in patients assigned to bivalirudin compared with heparin plus a GPI (1.4% vs 0.3%; P < .001), indicating the potential importance of $P2Y_{12}$ inhibitor preloading.[457] After 1 year, the rates of cardiac mortality (2.1% vs 3.8%; HR 0.57; 95% CI, 0.38-0.84; P = .005) and all-cause mortality (3.5% vs 4.8%; HR 0.71; 95% CI, 0.51-0.98; P = .037) were significantly lower in the bivalirudin-alone treatment group.[458] Similar benefits in cardiac mortality (2.9% vs 5.1%; P = .001) and all-cause mortality (5.9% vs 7.7%, P = .03) were sustained at 3 years with bivalirudin therapy compared with UFH plus GP IIb/IIIa inhibition,[459] although only a portion of the mortality benefit could be attributed to a reduction in bleeding with bivalirudin.[460]

The European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial[461] randomly assigned 2218 patients with STEMI being transported to a primary PCI facility to receive upstream bivalirudin or heparin (UFH or LMWH) with optional GPI. The primary outcome at 30 days was the composite of death and non-CABG major bleeding, which was significantly reduced in the bivalirudin group compared with the heparin group (5.1% vs 8.5%; P = .001). A significant increase in acute stent thrombosis in patients treated with bivalirudin versus heparin was observed (1.1% vs 0.2%; P = .007). This trial used a more contemporary approach to PCI compared with HORIZONS-AMI, with the goal of reducing bleeding in order to assess whether the benefit of bivalirudin over heparin would still exist. Despite the high rate (~ 50%) of more potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor), radial artery access (47%), and optional GPI use (11.5% with bivalirudin and 69% with heparin), the composite of death and major bleeding favored bivalirudin. However, the higher rate of acute stent thrombosis with bivalirudin was not mitigated even with prehospital initiation of anticoagulant, post-PCI extended infusion of bivalirudin, more frequent use of potent $P2Y_{12}$ inhibition, and optional use of GP IIb/IIIa inhibition.[461]

The Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention (HEAT-PPCI) study[462] was designed to minimize bleeding risk and thus allow a more balanced evaluation of the two antithrombotic agents (bivalirudin and heparin) during primary PCI for STEMI. In this trial, 1829 patients with STEMI were randomly assigned to bivalirudin or heparin. GPI use was limited to bailout purposes only, and thus a similar, yet low, association rate was observed (13% with bivalirudin and 15% with heparin). Other important variables included the high approximate 90% utilization of more potent $P2Y_{12}$ inhibitors, no post-PCI bivalirudin infusion, and roughly 80% use of the radial approach for PCI. The primary outcome at 28 days was the composite of death, cerebrovascular accident, reinfarction, or unplanned target vessel revascularization, and notably, this did not include bleeding. The primary outcome occurred more frequently in patients treated with bivalirudin versus heparin (8.7% vs 5.7%; P = .01). Major bleeding was not significantly different between the two groups. Acute stent thrombosis was significantly more frequent with bivalirudin treatment.

In the Bivalirudin in Acute Myocardial Infarction Versus Heparin and GPI Plus Heparin Trial (BRIGHT),[463] patients with STEMI undergoing PCI were randomly assigned to bivalirudin with a 3-hour post-PCI infusion, heparin alone, or heparin plus tirofiban. Given the conflicting results of the safety and effectiveness of bivalirudin in STEMI,[459,461,462] the goal of this study was to determine whether the increased rate of acute stent thrombosis seen in the previous trials with bivalirudin in STEMI could be mitigated by a prolonged, post-PCI infusion. The BRIGHT trial demonstrated a significant decrease in 30-day net adverse clinical events defined as death, MI, target vessel revascularization, stroke, or bleeding in patients randomized to bivalirudin as compared to heparin alone or heparin plus tirofiban (8.8% vs 13.2% vs 17%, respectively; P < .001). The benefit with bivalirudin was driven primarily by a reduction in bleeding. Acute stent thrombosis was not significantly different between the groups.

The conflicting evidence on the superiority of bivalirudin compared with heparin for ACS patients undergoing PCI was further evaluated in the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX (MATRIX) study.[464] This trial randomized 7213 patients (45% with NSTEMI, 55% with STEMI) to bivalirudin or heparin during PCI. A subsequent randomization in the bivalirudin group to a post-PCI infusion was also studied for its potential impact on acute stent thrombosis. No differences were observed between the groups with regard to the major adverse cardiovascular events (composite of death, MI or stroke) or net adverse events (death, MI, stroke, or major bleeding). Post-PCI bivalirudin infusion was not shown to alter the composite rate of net adverse events, definite stent thrombosis, or urgent target vessel revascularization. There was a lower rate of bleeding with bivalirudin, but this was not accounted for by the site of access for PCI. Definite stent thrombosis was higher in patients treated with bivalirudin than with heparin.

There are several differences in trials designs that may be cited to explain the conflicting evidence on this topic. Some of these differences include the alternative definitions used for adjudication of ischemic and bleeding end points, variability in blinding, different patient populations, and changes in clinical management over time. Three recent meta-analyses share the common conclusions in patients with STEMI undergoing primary PCI that bivalirudin increases the risk of acute stent thrombosis (Fig. 41–12) and does not convey a mortality benefit (Fig. 41–13) compared to heparin treatment.[465-467] Although a reduction in major bleeding has been shown with bivalirudin compared to heparin, the magnitude of this bleeding reduction varied greatly depending on the planned or provisional use of concomitant glycoprotein IIb/IIIa inhibitors[465-467] (Fig. 41–14).

European Society of Cardiology Guideline for Use of Bivalirudin in the Management of Patients With Non–ST-Segment Elevation Acute Coronary Syndromes[9]

1. Parenteral anticoagulation is recommended at the time of diagnosis of UA/NSTEMI according to both ischemic and bleeding risks. (Class 1B)

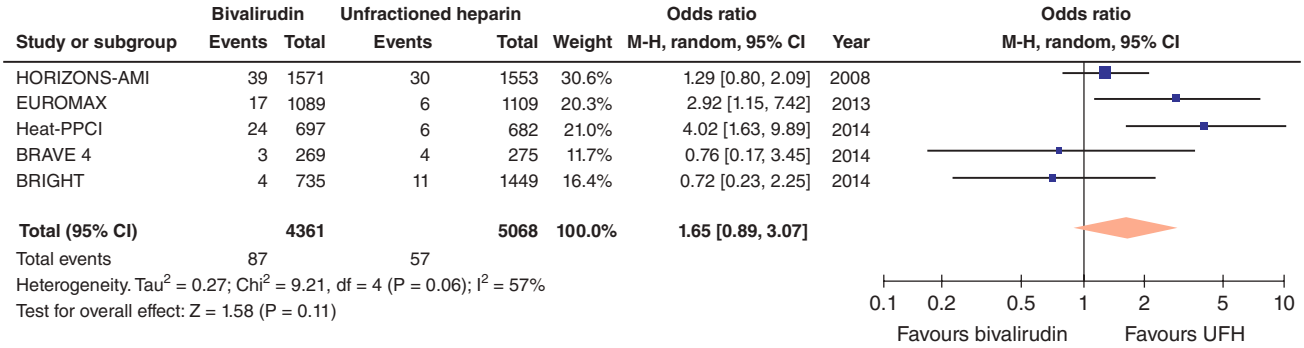
2. Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI. (Class 1A)

American College of Cardiology Foundation/American Heart Association Guideline for Use of Bivalirudin in the Management of ST-Segment Elevation Myocardial Infarction[5]

1. For patients with STEMI undergoing primary PCI, bivalirudin with or without prior treatment with UFH is recommended. (Class 1B)

2. In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist. (Class 2A-B)

3. Bivalirudin should be given as a 0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg can be given if needed. Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min. (Class 1B)



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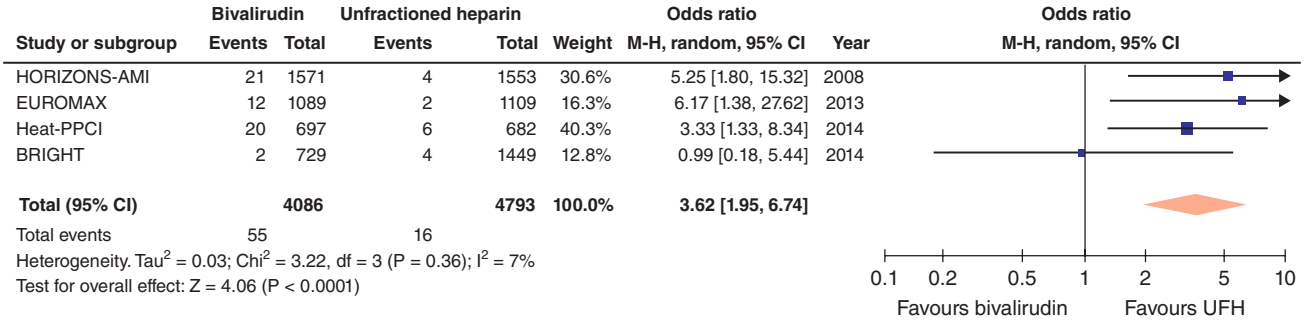

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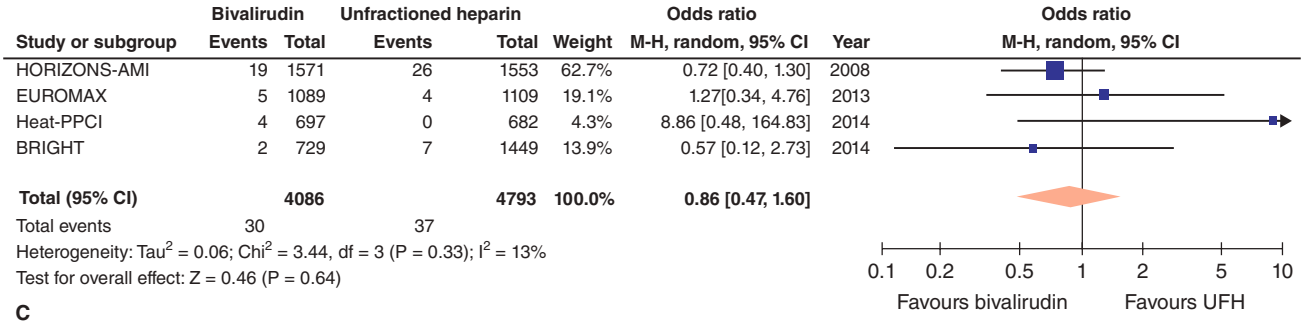

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FIGURE 41–12. Any, acute, and subacute stent thrombosis with bivalirudin versus unfractionated heparin (UFH) in predominantly ST-segment elevation myocardial infarction (STEMI) studies: (**A**) any stent thrombosis, (**B**) acute stent thrombosis (< 24 hours), and (**C**) subacute stent thrombosis (≥ 24 hours to 30 days). CI, confidence interval. Reproduced with permission from Farag M, Gorog DA, Prasad A, et al: Bivalirudin versus unfractionated heparin: a meta-analysis of patients receiving percutaneous coronary intervention for acute coronary syndromes. *Open Heart*. 2015 Oct 1;2(1):e000258.[466]

FIBRINOLYTIC AGENTS

Fibrinolytic therapy has been shown to successfully restore normal flow of the infarct-related coronary artery occlusion in patients with STEMI,[468] although up to 40% of treated patients do not achieve optimal tissue-level reperfusion[469,470] or develop early reocclusion after initial successful reperfusion.[469] Timely fibrinolytic treatment minimizes ventricular dysfunction, improves ventricular remodeling, and increases survival.[471-478]

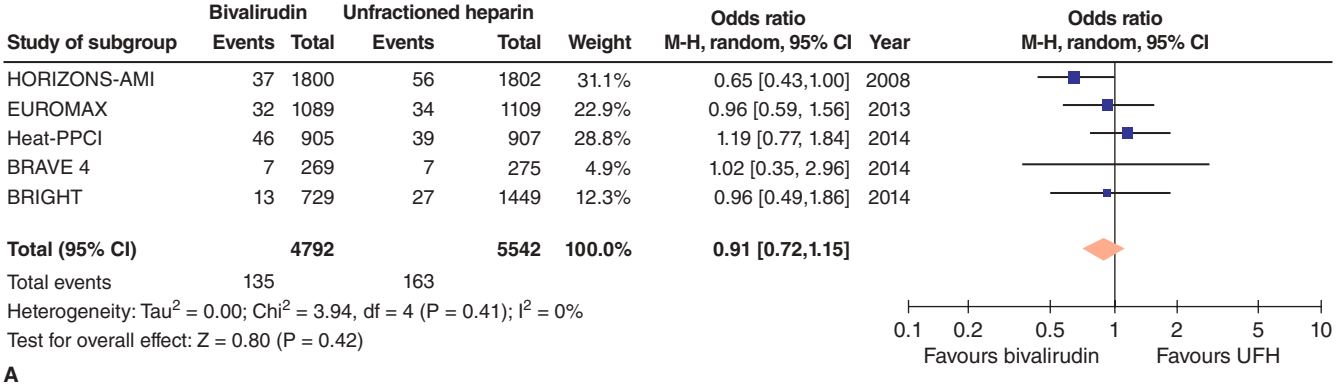
MECHANISM OF ACTION AND PHARMACOLOGY

All fibrinolytic agents convert plasminogen to the active enzyme plasmin, which in turn digests fibrin to soluble degradation products.[479] This section will review streptokinase, tissue-type plasminogen activator (tPA), and second-generation tPA derivatives (Table 41–7).

Streptokinase (SK) is a bacterial protein that consists of three plasminogen-binding domains, although none can activate plasminogen independently. Once bound to plasminogen, this activator complex of SK/plasminogen converts plasminogen to the active enzyme, plasmin, which cleaves fibrin. Plasmin generation by SK is not fibrin-specific, and treatment with SK leads to proteolysis of fibrinogen and factors V and III and depletion of clotting factors that may result in increased bleeding.[480] SK is highly immunogenic, and neutralizing antibody formation generally precludes readministration. With IV administration, peak plasma levels occur rapidly, with maximal fibrinolytic effect after 30 minutes. The plasma half-life is 30 to 40 minutes with hepatic-mediated clearance.[481,482] SK remains the most frequently administered fibrinolytic agent worldwide.

tPA is a 70-kDa serine protease that mediates endogenous fibrinolytic mechanisms after endothelial cell release. The structure of tPA includes five key domains (fibronectin finger, epidermal growth factor, kringle 1, kringle 2, and serine protease) that affect its pharmacokinetic profile.[483,484] Second-generation agents were designed for bolus administration, enhanced potency, and plasminogen activator inhibitor-1 resistance to enhance the efficiency of reperfusion.[479] The relative fibrin specificity of a fibrinolytic agent may play an important role in its efficacy and safety profile, although clinical data are controversial.

Reteplase (rPA) is the smallest (39 kDa) tPA derivative, engineered to lack the fibronectin finger, epidermal growth factor, and kringle-1



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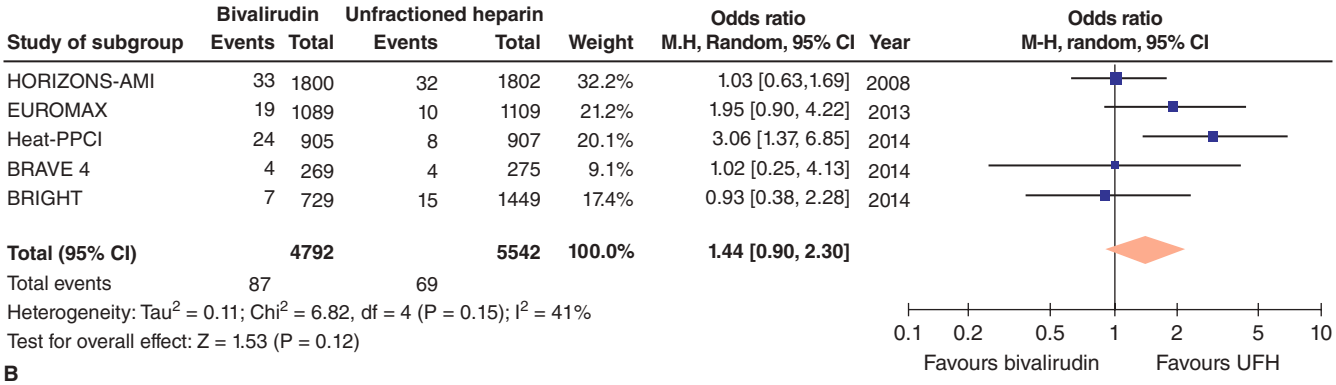

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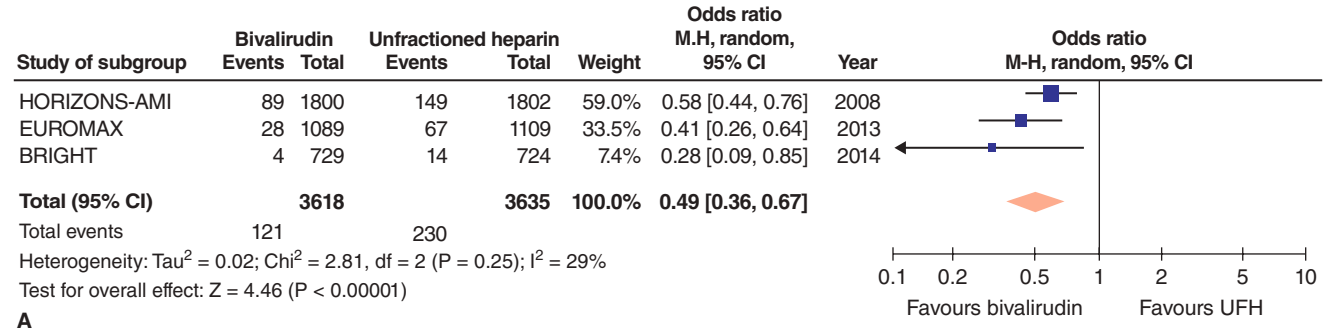
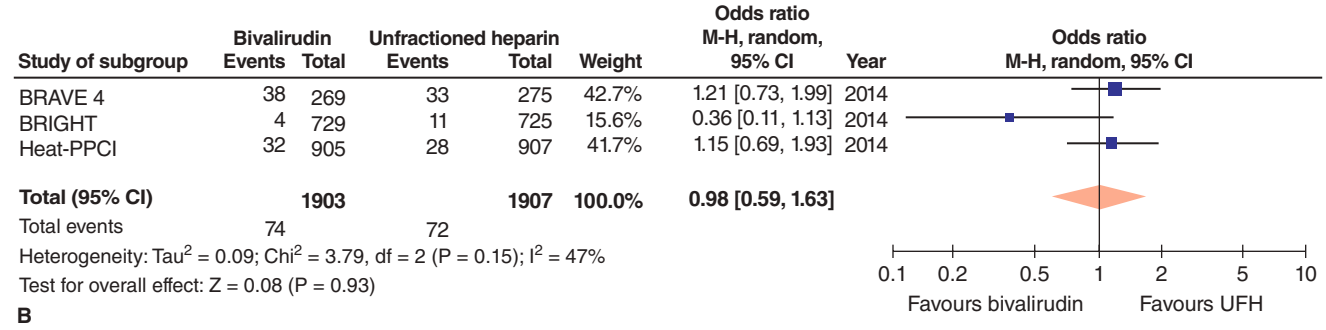
FIGURE 41–13. Death (**A**) and myocardial infarction (**B**) with bivalirudin versus unfractionated heparin (UFH) in predominantly ST-segment elevation myocardial infarction (STEMI) studies. CI, confidence interval. Reproduced with permission from Farag M, Gorog DA, Prasad A, et al: Bivalirudin versus unfractionated heparin: a meta-analysis of patients receiving percutaneous coronary intervention for acute coronary syndromes. *Open Heart*. 2015 Oct 1;2(1):e000258.[466]



A



B

FIGURE 41–14. Major bleeding with bivalirudin versus unfractionated heparin (UFH) in predominantly ST-segment elevation myocardial infarction (STEMI) studies: (**A**) glycoprotein IIb/IIIa inhibitors (GPI) predominantly provisional in the bivalirudin arm versus planned use in the heparin arm, and (**B**) provisional GPI use in both arms. CI, confidence interval. Reproduced with permission from Farag M, Gorog DA, Prasad A, et al: Bivalirudin versus unfractionated heparin: a meta-analysis of patients receiving percutaneous coronary intervention for acute coronary syndromes. *Open Heart*. 2015 Oct 1;2(1):e000258.[466]

TABLE 41–7. Characteristics of Thrombolytic Therapies

Characteristic	SK	tPA	rPA	nPA	TNK
Mode of administration	Infusion over 30-60 min	Bolus + infusion over 90 min	Double bolus 30 min apart	Single bolus	Single bolus
Dose	1.5×10^6 U	≤ 100 mg[a]	10 U + 10 U	120 ku/kg	30-50 mg/kg
Weight-adjusted dosing	No	Yes	No	Yes	Yes
Antigenicity	++	–	–	–	–
Plasma half-life, mean (SD), min	30 min	3.5 (1.4)	14 (6)	47 (13)	17 (7)
Plasma clearance, mean (SD), mL/min	–	572 (132)	283 (101)	57 (19)	151 (55)
Excretion	Hepatic	Hepatic	Renal/hepatic	Hepatic	Hepatic
Fibrin specificity[b]	–	++	+	+	++++
90-min patency	++	+++	++++	+++/++++	+++/++++
Mortality reduction	+	++	++	++	++
Hemorrhagic stroke	++	++	++	+++	++
Cost[c]	+	+++	+++	NA	+++

Abbreviations: NA, not applicable as nPA is not commercially available; nPA, lanoteplase; rPA, reteplase; SD, standard deviation; SK, streptokinase; TNK-tPA, tenecteplase; tPA, tissue-type plasminogen activator (alteplase).

[a]Bolus: 15 mg. Infusion: 0.75 mg/kg, not exceeding 50 mg over 30 minutes; 0.5 mg/kg, not exceeding 35 mg over the next hour.

[b]Semiquantitative scale based on depletion of fibrinogen and other measures of systemic anticoagulation.

[c]Based on average wholesale price listings in *Drug Topics Red Book 2000* and November Update (Tenecteplase [TNKase] for thrombolysis. *Med Lett Drugs Ther*. 2000;42:106).

Reproduced with permission from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004 Aug 4;44(3):E1-E211.

domains. The remaining single chain of amino acids includes only the kringle-2 and serine protease domains.[485] The loss of these three domains leads to reduced plasma clearance, increased plasma half-life, and reduced fibrin-specific binding.[479] rPA is administered as a fixed-dose double bolus 30 minutes apart. Excretion of rPA is achieved by both renal and hepatic elimination.

Lanoteplase (nPA) is a fibrinolytic agent engineered from tPA by deleting its fibronectin finger and epidermal growth factor domains.[486-489] Elimination of a glycosylation site was designed to improve the fibrin-specific binding of nPA.[490] nPA is administered as a single, weight-adjusted bolus, which is eliminated entirely via the liver.[479]

Tenecteplase (TNK) is a designer tPA analogue with several modifications to decrease plasma clearance (kringle-1 glycosylation site mutation), increase fibrin specificity, and endow resistance to PAI-1 (tetra-alanine substitution into the protease domain). All five domains present in the parent tPA molecule remain, so that TNK has a comparable molecular weight of 75 kDa.[491,492] TNK is administered as a weight-adjusted, single-dose bolus and is cleared via the liver. The resultant reduction in systemic fibrinogen and plasminogen levels 1 hour after administration of TNK is only 3% and 13%, respectively, which is markedly less than all other available thrombolytic agents.[493]

Several known genetic polymorphisms may influence the effect of fibrinolytic agents; however, the available data and clinical significance are limited. The C1562T polymorphism of the matrix metalloproteinase-9 gene,[494] the glycoprotein IIIa PlA2 polymorphism,[495,496] and the PAI-1 4G/5G polymorphism[497] do not appear to influence the efficacy or safety of fibrinolytic therapy. The factor XIII Val34Leu polymorphism affects the stability and structure of the fibrin clot and may lead to variable responsiveness to fibrinolysis.[498] Factor XIII strengthens the bond between fibrin monomers, thereby decreasing the ability of plasmin to degrade fibrin.[499,500] In clinical studies, this factor XIII polymorphism was associated with reduced efficacy of fibrinolysis and worse outcomes.[498,501,502] Polymorphism of the methylenetetrahydrofolate reductase gene was independently associated with persistent coronary occlusion of the infarct-related artery after thrombolysis for the treatment of STEMI.[503]

REVERSAL

Aminocaproic acid and tranexamic acid are lysine analogues that bind to the kringle domain of plasminogen, thus attenuating fibrin binding and plasmin activation.[504] Tranexamic acid is 10 times more potent than aminocaproic acid and binds plasminogen more strongly. Tranexamic acid injection is indicated in patients with hemophilia for short-term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and after tooth extraction. Although not currently approved for use to reverse fibrinolytic agents, its pharmacology suggests it may be useful. IV dosing for the approved indication is 10 mg/kg three to four times daily for up to 8 days. Because this drug is primarily excreted through the kidneys, significant dose adjustment is necessary in patients with impaired renal function.[505]

EVIDENCE FOR USE

The superiority of SK over placebo treatment for patients with STEMI is supported by two large randomized trials,[52,473] demonstrating a 25% early mortality reduction (with initial SK and aspirin compared with placebo) that is sustained after 10 years of follow-up with 23 fewer deaths per 1000 patients treated.[506] Despite this significant mortality advantage for SK therapy, it was recognized that < 50% of patients treated with SK achieved complete angiographic reperfusion.[476] Evaluation of an accelerated tPA regimen compared with SK was evaluated in the GUSTO mega-trial (n = 41,021) of patients

presenting within 6 hours of STEMI symptom onset.[476] Treatment with tPA was associated with a 1% absolute (14% relative) reduction in 30-day mortality. Despite an excess of hemorrhagic stroke for patients treated with tPA (0.7% vs 0.5% for SK), the net clinical benefit at 1 year favored tPA, saving 10 lives per 1000 patients treated with t-PA compared with SK.[507]

The development of engineered tPA analogues was based on the clinical imperative of enhancing the speed and extent of reperfusion with easy-to-administer bolus regimens. Enhancing fibrin specificity was favored to decrease overall bleeding risk. Additionally, modifying adjunctive anticoagulant regimens (ie, lower aPTT, weight-based dosing algorithms corrected for age and renal insufficiency) became an important focus to reduce hemorrhagic risk, particularly ICH.[508,509] Two mortality end point trials, GUSTO-III (Global Use of Strategies to Open Occluded Coronary Arteries)[510] and ASSENT (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen)-2,[511] showed no significant mortality difference between rPA and TNK, respectively, when compared with accelerated tPA. TNK resulted in fewer noncerebral bleeding complications (26.43% vs 28.95%; $P = .001$) and blood transfusions (4.25% vs 5.49%; $P = .002$).[511] Although increased fibrin specificity of TNK compared with tPA appeared to reduce noncerebral bleeding, TNK did not impact the rate of ICH.

Recent clinical trials of fibrinolytic agents have focused on adjunctive pharmacotherapy with antiplatelet[90,512] and anticoagulant[362,436] agents to improve efficacy and safety. The Extract TIMI-25 trial (n = 20,506) randomized STEMI patients treated with fibrinolysis (20% SK) to receive enoxaparin throughout the index hospitalization or weight-based UFH for at least 48 hours.[362] Major bleeding occurred more frequently with enoxaparin in the first 30 days (2.1% vs 1.4%; $P < .001$), but the rate of ICH was similar despite the longer duration of enoxaparin therapy. Net clinical benefit (the composite of death, nonfatal reinfarction, or nonfatal ICH) favored enoxaparin over UFH (10.1% vs 12.2%; $P < .001$). Based on this study, using adjunctive enoxaparin compared with UFH would result in 15 fewer nonfatal reinfarctions, seven fewer episodes of urgent revascularization, and six fewer deaths at the cost of four additional episodes of nonfatal major bleeding (with no increase in the number of nonfatal ICHs) per 1000 patients treated.[362]

Clopidogrel therapy (75 mg daily) with[90] or without[512] a 300-mg loading dose was shown to improve infarct-related artery patency when added to thrombolytic therapy in STEMI patients. Importantly, the 36% relative reduction in the combined end point of TIMI 0/1 flow, death, or recurrent MI before angiography was seen regardless of the type of thrombolytic agent used.[90]

AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/AMERICAN HEART ASSOCIATION GUIDELINES FOR USE OF THROMBOLYTICS IN THE MANAGEMENT OF ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION[5]

1. In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC [first medical contact]-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays. (Class 1B)

2. When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival. (Class 1B)

3. In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability. (Class IIa)

4. Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR. (Class IIIB)

5. Fibrin-specific fibrinolytic agents (tenecteplase, reteplase, alteplase) are preferred over streptokinase if available.

INDICATIONS AND CONTRAINDICATIONS TO FIBRINOLYTIC THERAPY

Indications for fibrinolysis include symptoms of myocardial ischemia and ST-segment elevation greater than 0.1 mV in two contiguous leads or new (or presumably new) left bundle branch block. Successful reperfusion of the infarct-related artery diminishes with the passage of time. The greatest benefit occurs when therapy is given within the first hour and up to 12 hours from the onset of symptoms. The mortality benefit is greater in the setting of anterior STEMI. In general, thrombolysis shows detrimental effects in patients presenting with only ST-segment depression. Contraindications and cautions for fibrinolytic therapy in STEMI are listed in Table 41–8.

ANTICOAGULATION FOLLOWING THE ACUTE PHASE OF ACUTE CORONARY SYNDROME

ORAL VITAMIN K–DEPENDENT ANTICOAGULANTS

Mechanism of Action and Pharmacokinetic/Pharmacodynamic Profile

The class of vitamin K–dependent anticoagulants (VKAs) refers to coumarin and its derivatives. The primary agent currently used is warfarin. Vitamin K is required by factors II, VII, IX, and X and protein C and S to achieve normal biologic activity and their normal procoagulant properties. VKAs block the cyclic interconversion of vitamin K and its epoxide, which are the cofactors required for the carboxylation of the aforementioned coagulation factors. This inhibition of vitamin K carboxylation results in the hepatic synthesis of reduced-activity clotting factors and, thereby, an anticoagulated state.[513-515]

Warfarin is composed of an R and S isomer as a racemic mixture. Absorption of warfarin after oral ingestion is rapid, and maximal blood concentrations are reached by 90 minutes in healthy individuals. Warfarin is highly protein bound and is metabolized in the liver via the cytochrome P450 2C9 system. Anticoagulation onset occurs within 24 to 72 hours. The half-life elimination is 20 to 60 hours.[514,516-518] Warfarin response may be affected by a multitude of drug interactions, genetic polymorphisms of CYP 2C9, dietary vitamin K consumption, and malabsorption.[514,519,520]

Dosing, Monitoring, and Reversal

Initial dosing of warfarin should begin at roughly 5 mg/d with daily monitoring of the prothrombin time (PT) with a goal international normalized ratio (INR) > 2.0. Once the goal INR is achieved for 2 consecutive days, the frequency of INR testing can be reduced and individualized based on patient response. The therapeutic window for warfarin is relatively small and includes an INR range from 2.0 to 3.0 depending on the indication and the guideline document cited.[514,521] Bleeding is the most common complication associated with warfarin therapy and is linked exponentially to higher INR values. The goal in managing a high INR is to reduce the INR back to a therapeutic, safe level. The manner in which this is achieved is dependent on the clinical

TABLE 41–8. Contraindications and Cautions for Fibrinolytic Therapy in ST-Segment Elevation Myocardial Infarction

Major Contraindications[a]
Structural intracranial disease
Previous intracranial hemorrhage
Ischemic stroke within 3 mo
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
Relative contraindications[b]
Systolic BP > 180
Diastolic BP > 110
Recent bleeding (nonintracranial)
Recent surgery
Recent invasive procedure
Ischemic stroke more than 3 mo previously
Anticoagulated (eg, VKA therapy)
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age > 75 y
Low body weight (eg, < 60 kg)
Female
Black race

[a]The presence of major contraindications usually precludes use of thrombolytic therapy; consequently, these factors have not been well studied as risk factors for bleeding associated with thrombolytic therapy. Patients with 1 or more major contraindication are usually considered to be "high risk for bleeding with thrombolytic therapy." The factors listed in this table are consistent with other recommendations for the use of thrombolytic therapy in patients with PE.

[b]The increase in bleeding associated with a risk factor will varywith: (1) severity of the risk factor (eg, extent of trauma or recent surgery) and (2) temporal relationships (eg, interval from surgery or a previous bleeding episode; believed to decrease markedly after approximately 2wk). Risk factors for bleeding at critical sites (eg, intracranial, intraocular) or noncompressible sites are stronger contraindications for thrombolytic therapy. Depending on the nature, severity, temporality, and number of relative contraindications, patientsmay be considered "high risk of bleeding with thrombolytic therapy" or "non-high risk for thrombolytic therapy." Patients with no risk factors, 1-2 minor risk factors (eg, female and black race) are usually considered "low risk of bleeding with thrombolytic therapy." Among 32,000 Medicare patients (≥ 65 y) with myocardial infraction who were treated with thrombolytic therapy, the following factors were independently associated with intracranial haemorrhage: age ≥ 75 y (OR, 1.6); black (OR, 1.6); female (OR, 1.4); previous stroke (OR, 1.5); systolic BP ≥ 160 mm Hg (OR, 1.8); women ≤ 65 kg or men ≤ 80 kg (OR, 1.5); INR > 4 (OR, 2.2). The rate of intracranial hemorrhage increased from 0.7% with 0 or 1 of these risk factors, to 4.1% with ≥ 5 risk factors. Among 32,000 patients with myocardial infraction who were treated with thrombolytic therapy in 5 clinical trials, the following factors were independently associated with moderate or severe bleeding: older age (OR, 1.04 per year); black (OR, 1.4); female (OR, 1.5); hypertension (OR, 1.2); lower weight (OR, 0.99 per kg). We estimate that systemic thrombolytic therapy is associated with relative risk of major bleeding of 3.5 within 35 d (RR, approximately 7 for intracranial bleeding); about three-quarters of the excess of major bleeds with thrombolytic therapy occur in the first 24 h.

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acuity of the patient. In the absence of bleeding, INR lowering is best done expectantly by simply holding warfarin doses, which will take 3 to 4 days to normalize. If significant bleeding is present or the INR is markedly elevated, reversal of the anticoagulant effect of warfarin can be achieved more quickly by administering vitamin K. Oral vitamin K doses between 1 and 2.5 mg may be used for INR values up to 10, which will typically lower the INR to < 5 within 24 hours. INR values > 10 typically require higher doses of oral vitamin K (5-10 mg). SC administration of vitamin K has an unpredictable response. IV vitamin K has a rapid reversal effect but may be associated with life-threatening anaphylaxis and should be approached with extreme caution.[514,522,523]

Evidence for Use

Following the acute phase of ACS, persistent activation of the coagulation cascade exists and results in persistent thrombin generation.[524] This finding prompted a large amount of research investigating the optimal choice of antithrombotic therapy following ACS over the past 30 years. These studies have looked at various combinations and doses of aspirin and warfarin alone or in combination. Improvements in cardiovascular ischemic outcomes have been demonstrated with the combination of warfarin and aspirin compared with aspirin alone.[525-530] However, other trials showed conflicting results in similar post-MI patients treated with aspirin and warfarin combinations compared with aspirin alone.[531,532] Several of these trials identified increased major bleeding with warfarin plus aspirin, raising the question of net clinical benefit.[528,531,532]

Two large meta-analyses[533,534] supported the use of warfarin plus aspirin following ACS to lower the risk of major adverse cardiovascular events. Similarly, both studies identified an increased risk for major bleeding with the combination of aspirin and warfarin. It should be noted that the studies included in both meta-analyses largely predated the stent era and did not include PCI patients. One of the most important changes to the standard of care for ACS was the routine use of intracoronary stenting, which became mainstream in the late 1990s. As discussed previously, the CURE trial[86] set the standard of care for dual antiplatelet therapy with aspirin and clopidogrel for up to 12 months following ACS. The routine use of PCI in the management of ACS combined with the anticipated increased prevalence of atrial fibrillation[535,536] in our aging population has brought about a treatment conundrum wherein the need for long-term oral anticoagulation meets the need for dual antiplatelet therapy. Given the well-documented increased bleeding risk with triple therapy[537,538] (aspirin, warfarin, and clopidogrel), the optimal antithrombotic regimen for patients who require long-term oral anticoagulation and subsequently have a PCI is of the utmost importance. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting?) study[539] enrolled 573 patients who required chronic warfarin therapy to treatment with clopidogrel alone or in combination with aspirin following PCI. The primary outcome of bleeding at 1 year was significantly lower in the double-therapy group compared with the triple-therapy group (19.4% vs 44.4%; HR 0.36; $P < .0001$). Despite the lack of aspirin in the double-therapy group, there was no significant increased risk for thrombotic or thromboembolic events observed.

American College of Cardiology Foundation/American Heart Association Guidelines for Use of Warfarin in the Management of ST-Segment Elevation Myocardial Infarction[5]

Class I

1. Anticoagulant therapy with a vitamin K antagonist should be provided to patients with STEMI and AF [atrial fibrillation] with $CHADS_2$ score value greater than or equal to 2, mechanical heart valves, venous thromboembolism, or hypercoagulable disorder. (Level of Evidence: C)

2. The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding. (Level of Evidence: C)

Class IIa

1. *Anticoagulant therapy with a vitamin K antagonist is reasonable for patients with STEMI and asymptomatic LV mural thrombi. (Level of Evidence: C)*

Class IIb

1. *Anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis. (Level of Evidence: C)*
2. *Targeting vitamin K antagonist therapy to a lower international normalized ratio (eg, 2.0 to 2.5) might be considered in patients with STEMI who are receiving DAPT. (Level of Evidence: C)*

ORAL FACTOR XA INHIBITORS

Oral factor Xa (FXa) inhibitors have been considered as an addition to DAPT for treatment of patients with ACS based on the same grounds as warfarin was studied.[524] Three FXa inhibitors (apixaban, rivaroxaban, and darexaban) have been evaluated in phase II dose-finding ACS studies.[540-542] The phase II evaluations of darexaban[541] and apixaban[542] demonstrated an increased risk of major bleeding and intracranial bleeding with FXa inhibition, and therefore, these agents did not progress to phase III study.

Rivaroxaban is a highly selective, reversible inhibitor of both free FXa and FXa bound in the prothrombinase complex. Rivaroxaban is primarily metabolized by the CYP3A4 system and is thus contraindicated with concomitant potent CYP3A4 inducers/inhibitors. The half-life is 7 to 12 hours, and excretion occurs via urine, feces, and biliary mechanisms. Caution is recommended if used in patients with severe renal impairment (creatinine clearance 15-30 mL/min). Rivaroxaban is contraindicated in patients with creatinine clearance < 15 mL/min or with severe hepatic impairment.[543-545]

Rivaroxaban (2.5 mg twice a day and 5 mg twice a day) was studied in a large, randomized, placebo-controlled trial of 15,526 patients with ACS stratified by planned dual antiplatelet utilization.[546] Patients who received rivaroxaban had a significant reduction in the composite of cardiovascular death, MI, or stroke compared to those who received placebo (8.9% vs 10.7%; $P = .008$). Rivaroxaban treatment compared to placebo increased the rate of non-CABG major bleeding (2.1% vs 0.6%; $P < .001$) and intracranial hemorrhage (0.6% vs 0.2%). The lower dose of rivaroxaban 2.5 mg twice a day conveyed a lower cardiovascular death rate compared to placebo (2.7% vs 4.1%; $P = .002$) and was associated with less fatal bleeding compared to the higher dose of 5 mg twice a day (0.1% vs 0.4%; $P = .04$). Based on this study, the lower dose of rivaroxaban 2.5 mg twice a day was approved for use in Europe for patients with ACS but has not been approved in the United States for this indication.

Reversal

Andexanet alfa is an intravenously administered recombinant modified human FXa decoy protein that binds to the active site of FXa inhibitors with high affinity. The half-life of the drug is 1 hour. In 101 healthy volunteers treated with either apixaban or rivaroxaban, andexanet reversed the anticoagulant effect of the FXa inhibitors within 2 to 5 minutes of receiving the bolus, and this inhibition continued up to 1 hour after stopping the infusion. No safety concerns or thrombotic events were seen.[547] A phase IIIB/IV study, ANNEXA-4, is currently evaluating the safety and efficacy of andexanet in patients with FXa inhibitor–associated major bleeding (ClinicalTrials.gov: NCT02329327).

European Society of Cardiology Guideline for Use of Rivaroxaban in the Management of Patients With Non–ST-Segment Elevation Acute Coronary Syndromes[9]

1. *In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation. (Class IIB)*

ORAL DIRECT THROMBIN INHIBITORS

The safety and indicators of efficacy with dabigatran added to DAPT following ACS were evaluated in the Randomized Dabigatran Etexilate Dose-Finding Study in Patients With Acute Coronary Syndromes (RE-DEEM) trial.[548] This phase II dose-escalation study demonstrated a dose-dependent increase in major and clinically relevant minor bleeding events for patients randomized to dabigatran compared to patients receiving placebo. Ischemic end points were low overall and not appreciably different between the dabigatran and placebo groups, although the study was not powered to detect meaningful differences.

Reversal

IV administration of idarucizumab, a monoclonal antibody fragment that binds free and thrombin-bound dabigatran with high affinity, has been shown to completely reverse the anticoagulant effect of dabigatran.[549] The safety, tolerability, and efficacy of IV idarucizumab was demonstrated in three small studies of healthy volunteers, elderly patients, and renally impaired patients.[550,551] A larger, ongoing, prospective cohort study (Reversal Effects of Idarucizumab on Active Dabigatran [RE-VERSE AD])[552] of patients anticoagulated with dabigatran who develop serious bleeding or are in need of emergent surgery is currently enrolling patients to examine the efficacy and safety of idarucizumab administered as two infusions of 2.5 g in 50-mL bolus less than 15 minutes apart. The interim analysis of the first 90 patients treated in this cohort demonstrated complete reversal of the anticoagulant effect of dabigatran as measured by the dilute thrombin time or ecarin clotting time within 4 hours after administration of idarucizumab. Five patients experienced thrombotic events including deep venous thrombosis, left atrial thrombus, and NSTEMI.[553] Based on these data, the US FDA has granted accelerated approval of idarucizumab for use in patients treated with dabigatran who require emergent surgery or have a life-threatening bleed.

INVESTIGATIONAL ANTITHROMBOTIC AGENTS

Anticoagulant strategies directed at the initiation of coagulation targeting tissue factor or factor VII are also of interest. Recombinant nematode anticoagulant protein c2 (rNAPc2) binds initially to factor X and then the tissue factor:factor VIIa complex, resulting in inhibition of the extrinsic pathway of coagulation.[554] In a phase II study of patients with UA/NSTEMI undergoing an early invasive approach, the addition of rNAPc2 to UFH at doses that suppress thrombin formation (7.5-10 µg/kg) reduced ischemia, as evidenced by continuous ECG monitoring; however, rNAPc2 without UFH is associated with procedural thrombotic complications.[555]

Factor IXa is a novel therapeutic target for anticoagulation because of its central and potent prothrombotic role in activating factor X. Inhibition of factor IXa has been shown to balance bleeding risk with antithrombotic efficacy in animal models. Four drug classes of factor IXa inhibition have undergone evaluation including active site-blocked inhibitors, oral inhibitors, monoclonal antibodies, and RNA

aptamers.[556] The latter have advanced through phase I trials to phase II clinical studies given the advantage of the aptamer approach to initiate prompt anticoagulation that can be reversed immediately with the complimentary RNA strand. The REG1 aptamer system includes a single-stranded RNA factor IXa inhibitor (pegnivacogin) and its reversal agent (anivamersen). Small phase I trials led to the phase II randomized RADAR trial,[557] which demonstrated the safety of a strategy based on the REG1 system in patients with NSTE-ACS treated with early cardiac catheterization. The REGULATE-PCI study was a randomized, open-label, active-controlled, superiority, phase III trial to test the hypothesis that near-complete factor IXa inhibition with pegnivacogin during PCI would provide a greater reduction in ischemic events than bivalirudin without increased bleeding as a result of anticoagulant reversal with anivamersen after PCI. The trial enrolled 3232 patients out of a planned 13,200 because the data safety monitoring board recommended permanent termination of the trial based on findings of excess rates of allergic reactions with REG1 without evidence of offsetting benefit. Future investigations are planned to identify the mechanism of allergic reactions associated with REG1 anticoagulation system.[558]

Inhibition of factor XIa has undergone initial evaluation as an anticoagulant that offers a tantalizing hope to balance the risk between therapeutic anticoagulation and risk of bleeding. The prospect of an approach that inhibits thrombosis while preserving hemostasis is the appeal potentially offered by inhibiting the intrinsic coagulation cascade without affecting the extrinsic pathway via factor XIa inhibition.[559] This is currently in the preclinical study phase. A factor XIa inhibitor (fasxiator) was isolated from the venom of the banded krait snake and was shown to prolong the activated partial thromboplastin time with effects on prothrombin time.[560]

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CHAPTER 42

PERCUTANEOUS CORONARY INTERVENTIONS IN ACUTE MYOCARDIAL INFARCTION AND ACUTE CORONARY SYNDROMES

William O'Neill, Cindy Grines, and George Dangas

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INTRODUCTION

At its inception,[1] coronary angioplasty was envisioned as a procedure for patients with stable, single-vessel coronary artery disease (CAD). Original angioplasty balloon catheters were too large, bulky, and difficult to navigate through vessels other than the proximal portions of major epicardial vessels. Coronary lesions were required to be concentric and noncalcified. Even in these simple lesions, the initial success rate was 64%.[2] Over the past 40 years, improvements in catheter design, development of atraumatic steerable guidewires, development of flexible, highly deliverable stents, and development of highly effective antithrombotic and antiplatelet therapy have made percutaneous coronary intervention (PCI) a dominant revascularization strategy. Furthermore, use of PCI has revolutionized the care of patients with acute myocardial infarction (AMI) and acute coronary syndrome (ACS).

Although PCI was originally used in stable patients, recent data from the National Cardiovascular Data Registry[3] demonstrate that the use of PCI has now shifted to use in AMI and ACS (Fig. 42–1); from 2010 to 2014, use of PCI has remained constant in AMI/ACS, whereas there has been a 50% reduction in use for stable CAD patients. Currently, in US practice, PCI is used in 80% of AMI/ACS patients and only 20% of stable CAD patients.

This chapter will provide a historical perspective and review of the seminal trials that led to establishment of PCI as the backbone of therapy for AMI/ACS. ST-segment elevation myocardial infarction (STEMI) can be easily diagnosed with an inexpensive, widely available tool (12-lead electrocardiogram [ECG]); similarly, ACS can be easily diagnosed with biomarker (troponin) and ECG changes. These illnesses present dramatically, can be lethal, and have been a scourge of Western civilization for the past 50 years. Fortunately, the enormous mortality risk has prompted AMI/ACS to be prospectively studied in hundreds of thousands patients. As a result, an enormously robust data set of clinical trials has tested all aspects of care from ambulance arrival to hospital discharge. We will review the evidence base using a patient-centered approach. We will discuss evidence-based decisions from admission to discharge. We will conclude with review of the evidence that widespread adoption of PCI for AMI/ACS has contributed to decline in overall adjusted cardiovascular mortality in the West.

HISTORICAL OVERVIEW OF MECHANICAL REPERFUSION IN ACUTE MYOCARDIAL INFARCTION

Reperfusion therapy for AMI had its inception with the initial treatise by Fletcher et al[4] describing the use of intravenous (IV) thrombolytic therapy in patients with thromboembolic disorders, including myocardial infarction (MI).[4] Shortly after this, Boucek and Murphy[5] published their observations of using catheters to deliver fibrinolytic therapy to the aortic root of patients presenting with AMI, and Favaloro et al[6] applied saphenous vein aortocoronary bypass surgery to patients presenting with acute infarction. Two groups, one in Spokane, Washington,[7] and one in Göttingen, Germany,[8] performed emergency catheterization before surgical revascularization for AMI, and for the first time, knowledge of the coronary anatomy during AMI became available. DeWood et al[9,10] described the high prevalence of total coronary occlusion in the early hours after acute transmural MI and defined the role of the ECG injury current in identifying a population of patients most likely to have acute total occlusion of the infarct artery and thus most likely to benefit from emergency revascularization.

In 1978, Rentrop et al[11-13] performed emergency guidewire recanalization of an acute thrombotic coronary occlusion and subsequently reported on the first 13 patients with AMI treated with mechanical

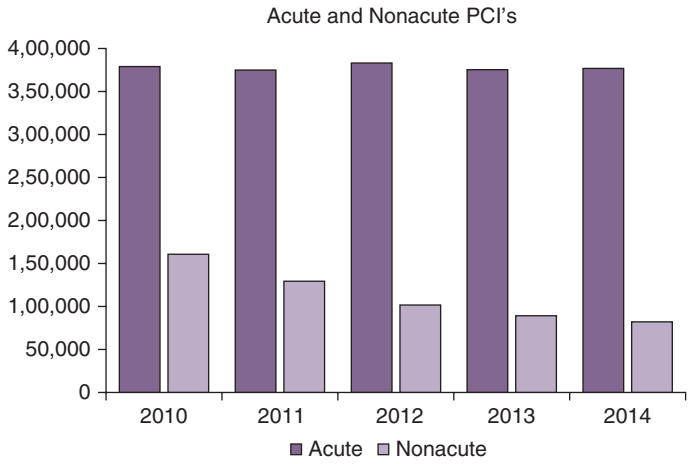

FIGURE 42–1. Between 2010 and 2014, the number of percutaneous coronary interventions (PCIs) for myocardial infarction/acute coronary syndrome remained stable in the United States. The number of interventions performed for stable coronary artery disease dropped from 160,000 in 2010 to 80,000 in 2014.

reperfusion. These investigators reported their selective catheter infusion of intracoronary streptokinase results at the American Heart Association (AHA) meetings in 1979, and the modern era of reperfusion therapy was born.[14] When the works of DeWood and Rentrop were disseminated, enormous research interest in reperfusion therapy was generated in both Europe and the United States, and a number of randomized trials quickly followed. Khaja et al[15] first demonstrated the efficacy of intracoronary streptokinase administration in establishing coronary reperfusion, and the Western Washington investigators documented improved survival in patients with AMI treated with intracoronary streptokinase therapy.[16] Because of the necessity of selective coronary angiography for this treatment, it quickly became apparent that a severe residual stenosis persisted in most patients after successful fibrinolysis. O'Neill et al[17] demonstrated that balloon angioplasty could effectively treat the residual stenosis and that this resulted in less recurrent ischemia and better preservation of ventricular function. This report was the first to suggest an advantage of balloon angioplasty over fibrinolytic therapy. Logistic constraints and the limited number of trained operators and catheterization facilities hindered the development of both intracoronary streptokinase and primary angioplasty as reperfusion strategies in the mid-1980s.

The large Gruppo Italiano per lo Studio del la Sopravvivenza nell'Infarto Miocardico (GISSI)[18] and International Study of Infarct Survival (ISIS)-2[19] trials, published in 1986 and 1988, respectively, definitively established the efficacy of IV streptokinase in improving survival in patients with AMI. IV streptokinase with aspirin gained widespread use and became the standard of care as reperfusion therapy for patients with AMI. Research interest soon focused on the development of new fibrin-specific fibrinolytic drugs that could be administered IV. However, many investigators were still concerned about the severe underlying residual stenosis remaining after medical reperfusion therapy. Three major randomized trials, the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial, Thrombolysis in Myocardial Infarction (TIMI) II-A trial, and a European Cooperative trial,[20-22] were designed to determine the value of routine percutaneous transluminal coronary angioplasty (PTCA) after thrombolytic therapy. These studies gave surprising and disappointing results. Not only was routine PTCA unnecessary, but it actually appeared harmful, and balloon angioplasty was mostly abandoned as an immediate adjunct to reperfusion with fibrinolytic therapy in the 1990s.

Interest still persisted in the use of PTCA without antecedent fibrinolytic therapy (primary PTCA). Large credit should be given to the pioneering work of Hartzler et al[23] in Kansas City, Kansas, who demonstrated the feasibility of primary PTCA. At the same time, Brodie et al[24] in Greensboro, North Carolina, as well as O'Neill et al[25] and Grines et al[26] in Royal Oak, Michigan, concluded that primary PTCA had been inadequately tested as a reperfusion modality. These three groups joined forces and organized the original Primary Angioplasty in Myocardial Infarction (PAMI) study group. This group, as well as investigators from the Zwolle group[27] and the Mayo Clinic,[28] published the results of the first large randomized trials comparing primary PTCA with fibrinolytic therapy in 1993. These trials demonstrated superior outcomes with primary PTCA compared with fibrinolytic therapy and established primary PTCA as the preferred reperfusion strategy for patients with AMI.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION VERSUS FIBRINOLYTIC THERAPY OUTCOME COMPARISONS

CLINICAL OUTCOMES

Keeley et al[29] performed a meta-analysis of 23 randomized trials incorporating 7739 patients comparing primary PCI with fibrinolytic therapy for STEMI. Primary PCI is superior to fibrinolytic therapy in reducing short-term mortality (5.3% vs 7.4%; $P = .0003$); nonfatal reinfarction (2.5% vs 6.8%; $P < .0001$); stroke (1.0% vs 2.0%; $P = .0004$); and the composite end point of death, nonfatal reinfarction, and stroke (8.2% vs 14.3%; $P = .0001$) (Fig. 42–2). These results were maintained at long-term follow-up and were independent of the type of thrombolytic agent used (streptokinase vs fibrin-specific thrombolytics) and whether patients were directly admitted or transferred emergently for primary PCI. The incidence of intracranial hemorrhage was significantly less with primary PCI (0.05% vs 1.1%; $P < .0001$), but the overall risk of major bleeding (mostly related to access site bleeding) was higher with primary PCI (6.8% vs 5.3%; $P = .03$).

The survival benefit of primary PCI compared with fibrinolytic therapy reported in this meta-analysis was substantial (21 lives saved per 1000 patients treated) and is of similar magnitude to the survival benefit of fibrinolytic therapy compared with placebo reported by the Fibrinolytic Therapy Trialists Collaborative Group[30] (19 lives saved per 1000 patients treated). The relative reduction in death and nonfatal reinfarction is similar across all subgroups of patients treated, including elderly patients, women, diabetics, patients with anterior versus nonanterior infarct location, and patients with prior infarction, and all patient risk groups. Of note, the greatest absolute benefit occurs in patients who are at highest risk, especially if they are younger than 75 years of age. The SHOCK (Should We Revascularize Occluded Coronaries for Cardiogenic Shock?) trial,[31] which randomized 302 patients with cardiogenic shock to emergency revascularization versus medical stabilization, found a lower 6-month mortality with emergency revascularization (50% vs 63%; $P = .03$). The survival benefit was especially pronounced in patients who were treated within 6 hours of symptom onset and in patients younger than age 75 years.

The initial early clinical benefit of primary PCI over fibrinolytic therapy in reducing death and reinfarction appears to be maintained at late follow-up. The PAMI investigators found that death or reinfarction was lower at 2 years with primary PCI than with fibrinolytic therapy[32] (14.9% vs 23.0%; $P = .03$). Similarly, the Zwolle Netherlands investigators found lower mortality (13.4% vs 23.9%; $P = .01$) and less reinfarction (6.2% vs 21.9%; $P < .0001$) with primary PCI than with

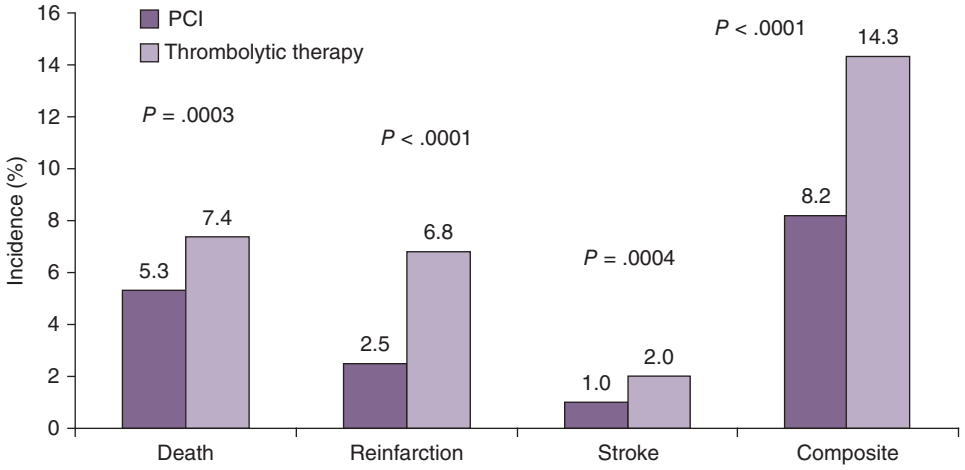

FIGURE 42–2. Meta-analysis of 23 randomized trials comparing short-term outcomes with primary percutaneous coronary intervention (PCI) versus thrombolytic therapy for acute myocardial infarction. Data from Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003 Jan 4;361(9351):13-20.

streptokinase at 5 years.[33] Both studies found a lower frequency of hospital readmissions with primary PCI. The meta-analysis by Keeley et al[34] also showed that the initial benefit with primary PCI was maintained at late follow-up at 6 to 18 months.

ANGIOGRAPHIC OUTCOMES AND MYOCARDIAL SALVAGE

Since 2005, there has been consensus that timely reperfusion can improve survival through achievement of coronary patency and salvage of ischemic myocardium. Primary PCI can achieve TIMI grade 3 flow in the infarct artery in more than 90% of patients[35-40] versus 54% with fibrinolytic therapy.[35,36] Achieving TIMI grade 3 flow has a major impact on short- and long-term mortality,[35] and the advantage of primary PCI in achieving high rates of TIMI grade 3 flow is likely responsible for much of the observed mortality advantage. Indeed, there appears to be a tight inverse relationship between the ability to achieve TIMI grade 3 flow and short-term mortality with either reperfusion strategy (Fig. 42–3). Newer fibrinolytic strategies using combination therapy with low-dose fibrinolytics and platelet glycoprotein (GP) IIb/IIIa inhibitors have shown improved TIMI grade 3 flow rates in small pilot trials,[41-43] but these rates are well below the TIMI grade 3 flow rates achieved with primary PCI, and they have not shown any mortality advantage in the large GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) V[44] and ASSENT (Assessment of the Safety and Efficacy of a New Treatment Strategy)-3 trials.[45]

Late angiographic outcomes with primary PCI have been substantially improved with the use of stents.[46,47] With stenting, reocclusion occurs in 5% to 6% of patients,[48] restenosis in 20% to 22% of patients, and target vessel revascularization in 7% to 8% of patients. After fibrinolytic therapy, late reocclusion of the infarct artery occurs in 20% to 28% of patients when adjunctive PCI is not used.[49,50]

There is a broad scientific consensus that when facilities and resources are available, primary PCI is the superior reperfusion modality.[51] With that debate settled, attention has turned to limitation of infarction size. The last decade has seen numerous pharmacologic and mechanical strategies to limit infarct size. They are summarized in Table 42–1. To conduct comparative trials, new laboratory methods of quantifying infarct size were required. Extensive work has been done with technetium-99m scintigraphy.[52-54] Stone et al[55] pooled scintigraphy data from four reperfusion trials to determine predictors of final infarct size. First, it is apparent that large heterogeneity of final infarct size exists after PCI. Infarct (< 10% of left ventricular mass) occurred when the infarct artery had baseline TIMI grade 3 flow or when the right coronary artery was the culprit. Symptom onset to balloon time was critically important up to 3 hours of symptom duration. After 3 hours, MI size did not appear to vary with prolonged times to reperfusion. More recently, cardiac magnetic resonance imaging (CMRI) has emerged as a powerful tool to accurately measure region at risk and final infarct size.[56] The CRISP (Counterpulsation Reduces Infarct Size Pre-PCI) AMI investigators have analyzed 333 patients with anterior MI undergoing primary PCI (PPCI) with or without balloon counterpulsation. While no reduction with balloon pump was found, extensive data on predictors of MI size were found.[57] MI size was moderate at 1 to 4 hours and large after 4 hours. Baseline TIMI grade 3 flow predicts a small MI. Importantly, large heterogeneity of infarct sizes occurred. Factors such as extent of collateral flow, extent of repetitive

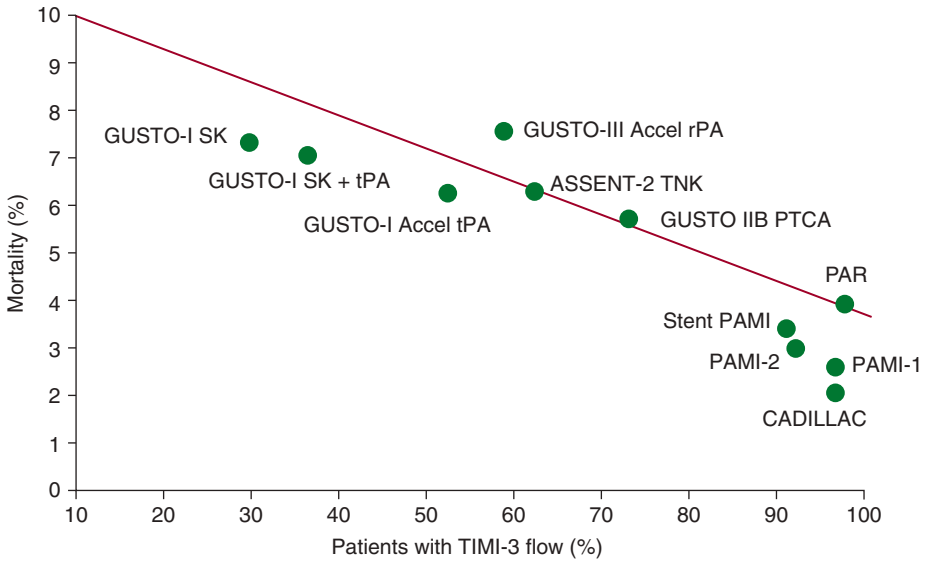

FIGURE 42–3. Relationship between short-term mortality and the frequency of achieving Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow measured acutely in the infarct artery in trials with thrombolytic therapy and primary percutaneous coronary intervention (PCI). The thrombolytic trials include GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries), GUSTO-III, and ASSENT-2 (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen). The primary PCI trials include CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications), PAMI-1 and -2 (Primary Angioplasty in Myocardial Infarction), Stent PAMI, PAR (Primary Angioplasty Registry), and GUSTO-IIB. PTCA, percutaneous transluminal coronary angioplasty; rPA, reteplase; SK, streptokinase; TNK, tenecteplase; tPA, tissue plasminogen activator.

TABLE 42–1. Infarct Size Reduction

Proven
1. Baseline TIMI grade 3 flow
2. Total ischemia time <3 hours
3. Nonanterior MI location
4. Remote ischemic conditioning
Potentially useful in anterior STEMI
1. IV metoprolol
2. SSA O_2
3. IV adenosine (high dose, early treatment)
4. Hypothermia
Ongoing trials
1. LV unloading
2. Steroids
3. Colchicine

Note. Methods or factors associated with small final infarction size are tabulated. Remote ischemic conditioning is the only therapy to appear to decrease MI size and provide lasting clinical benefit.

Abbreviations: IV, intravenous; LV, left ventricular; MI, myocardial infarction; SSA O_2, hyperoxemic oxygen therapy; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

occlusion-reperfusion, left ventricular wall stress, and other determinants of local oxygen demand cannot be measured. For this reason, although statements about broad populations can be made, risk of large infarction can only be crudely predicted on an individual basis. Opportunities to decrease infarct size based on decreasing time to reperfusion exist, but are narrowly confined to anterior MI location when reperfusion can occur within 3 to 4 hours of symptom onset. These two basic observations help explain the results of most recent trials attempting to limit infarct size after PPCI.

SYSTEMS OF CARE AND TIME TO REPERFUSION

An international consensus has developed over that past 10 years regarding mechanical reperfusion therapy. The Keeley et al[29] meta-analysis of 23 trials comparing angioplasty to fibrinolytic therapy first coalesced the scientific opinion regarding use of PCI when catheterization laboratories and operators were immediately available. Subsequently, Danish investigators demonstrated that PCI provided better outcomes not only when patients presented to a PCI-capable facility, but also when transport to a PCI facility was required.[58]

For these reasons, scientific debate has turned from acceptance of the superiority of PCI to attempts to more widely apply this therapy to entire populations. Wharton et al[59] have promulgated initiation of PCI programs in nonsurgical centers. Aversano et al[60] have proven that excellent PCI results can be obtained in the C-Port (Atlantic Cardiovascular Patients Outcomes Research Team) investigation. The C-Port trial evaluated PPCI at hospitals with catheterization laboratories but without cardiac surgery or elective PCI. Using skilled operators who perform PCI at nearby tertiary centers, the C-PORT investigators documented lower 6-month composite event rates of death, reinfarction, or stroke with PPCI versus lytic therapy (12.4% vs 19.9%; $P = .03$).[58]

The American College of Cardiology (ACC)/AHA guidelines recommend PPCI as the preferred reperfusion strategy for patients with STEMI if it can be performed promptly (within 90 minutes of recognition) by experienced operators.[51] Based on these guidelines, there has been a nationwide effort through the ACC, the AHA, and others to reduce door-to-balloon times to less than 90 minutes.[61,62] Hospitals with coronary interventional services, dedicated physicians, nursing and administrative leadership, and established detailed protocols are best able to meet these guidelines.

An alternate approach to expanding PCI sites is to centralize care and to create regional PCI centers. Henry et al[63] and Ting et al[64] have demonstrated excellent clinical results with organized referral networks throughout Minnesota. Similarly, the RACE (Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments) investigators demonstrated improved care processes and improved reperfusion times throughout North Carolina.[65] A nationwide initiative, based on the success of the RACE program in North Carolina, was recently implemented to create networks in nearly 20 areas around the United States,[66] with the goal of increasing the number of patients treated within guideline goals for first medical contact to device times. Preliminary results showed a modest but significant increase in the proportion of patients who achieved reperfusion in a timely manner across the United States.[67]

The management of patients with STEMI presenting to hospitals without interventional services is more challenging. The results from randomized trials (predominantly from Europe) indicate that outcomes are better when patients with STEMI who present to non-PPCI hospitals are transferred promptly to an interventional facility for PPCI compared with being given fibrinolytic therapy at the local hospital.[68-72] The additional treatment delays of PPCI compared with fibrinolytic therapy (door-to-balloon time minus door-to-needle time) in these trials have ranged from 55 to 103 minutes. Unfortunately, in the United States, transfer delays are much longer than this. Data from the National Registry of Myocardial Infarction found median delays of 180 minutes from arrival at the noninterventional hospital to balloon inflation at the PPCI hospital, with only 4.2% of transferred patients achieving door-to-balloon times of less than 90 minutes.[73] Consequently, many patients presenting to non-PPCI hospitals in the United States may not be eligible for PPCI because of the long potential treatment delays. There are currently nationwide and statewide efforts to reduce time to PPCI. It has been shown that with well-defined goals, commitment from administrative and clinical leaders, standardized protocols, integrated systems of transfer, and data feedback to monitor progress, door-to-balloon times for patients presenting to noninterventional hospitals can be dramatically reduced and can approach and meet guidelines for timely treatment with PPCI.[74,75] In addition, regionalization of STEMI care to interventional centers using coordinated emergency medical technician transport and in-the-field teletransmitted ECGs can markedly reduce transfer delays.

Currently, the ACC/AHA guidelines recommend that patients with cardiogenic shock and patients who are ineligible for fibrinolytic therapy should be transferred for PPCI. Decisions regarding triage of remaining STEMI patients should depend on an assessment of time and risk—time to presentation, time delay to PCI, risk of bleeding from fibrinolytic therapy, and risk of the STEMI. High-risk patients presenting early with long delays to PPCI should preferentially be treated with fibrinolytic therapy, but patients presenting later should preferentially be transferred for PPCI, even with longer delays to PCI.

In metropolitan areas, a new approach has been tried. Major hospitals are designated as STEMI centers. Ambulances are equipped to perform 12-lead ECGs, and when a STEMI is identified, these patients are selectively taken to STEMI centers even if other non-STEMI hospitals are closer.[76,77] In Ottawa, Canada, Le May et al[78] demonstrated that this system saves at least 1 hour of ischemic time. Even when patients

delay in calling an ambulance for up to 80 minutes, reperfusion was achieved within a mean of 158 minutes of symptom onset.[77] It has long been demonstrated that field ECGs can save at least 1 hour of ischemic time. Now linking this program to triage to STEMI centers appears to dramatically lower total ischemic time.

Unfortunately, the United States lags in implementation of this approach. A 2013 survey by Bagai et al[79] found that bypass in emergency department (ED) markedly shortened reperfusion times but was only implemented in 119 of US hospitals. Since the greatest delay occurs with patient arrival to the ED, it is not surprising that national efforts to shorten door-to-balloon time (DBT) have not resulted in substantial reductions in hospital mortality. Menees et al[80] reported that 515 hospitals in the Cath PCI Registry improved DBT from 83 to 67 minutes between July 2008 and July 2009 ($P < .001$). Mortality was nearly identical (4.8% vs 4.7% $P = .43$). Similarly, Nallamathu et al[81] reported that 423 hospitals in the Cath PCI Registry found DBT decreased from 83 to 63 minutes ($P < .001$) between 2006 and 2011. A disturbing increase in risk-adjusted hospital mortality (4.7% vs 5.3%, $P = .06$) and an increase in 6-month mortality (12.9% vs 14.4%, $P = .001$) occurred. These sobering observations suggest that unless American systems of care change to the more uniform European models with more ambulance admission and triage to PCI facilities, it is unlikely that further improvement of in-hospital processes of care will result in any further reduction of mortality.

Gersh et al,[75] Stone et al,[55] and Brodie et al[24] have shown the critical time dependence of myocardial salvage. In the setting of anterior MI, salvage is likely to occur only if total ischemic duration (pain-to-balloon time) is less than 3 hours. Figure 42–4 depicts the time intervals for current MI care delivery models and the impact that delays have on final MI size.

Patients arrive in EDs by ambulance or car, can present to catheterization or noncatheterization facilities, and can present in metropolitan or remote locations. For the sake of argument, let us assume some standard time delay intervals. Let us assume that, whatever care setting exists, the patient has 30 minutes of pain before initiating action. The patient calls an ambulance or is driven to an ED. An ambulance arrives and hopefully is equipped to perform field ECGs. The most rapid reperfusion occurs when ambulances drive to a PPCI center where a STEMI alert has been called. Even more time can be saved when the emergency medical technician bypasses the hospital ED and transports the patient directly to the catheterization lab.[82] Total ischemic durations of 60 to 90 minutes are realistic and would allow a substantial number of patients to have an MI aborted. Incremental delays occur if a patient is driven to an ED. Arrival, the initial encounter, undressing, and performing the ECG add at least 30 minutes. In total, even when a DBT of 90 minutes is achieved, patients will not be reperfused within 3 hours of total symptom duration. If the emergency medical technician bypasses a PPCI center, add 30 minutes of ambulance time,

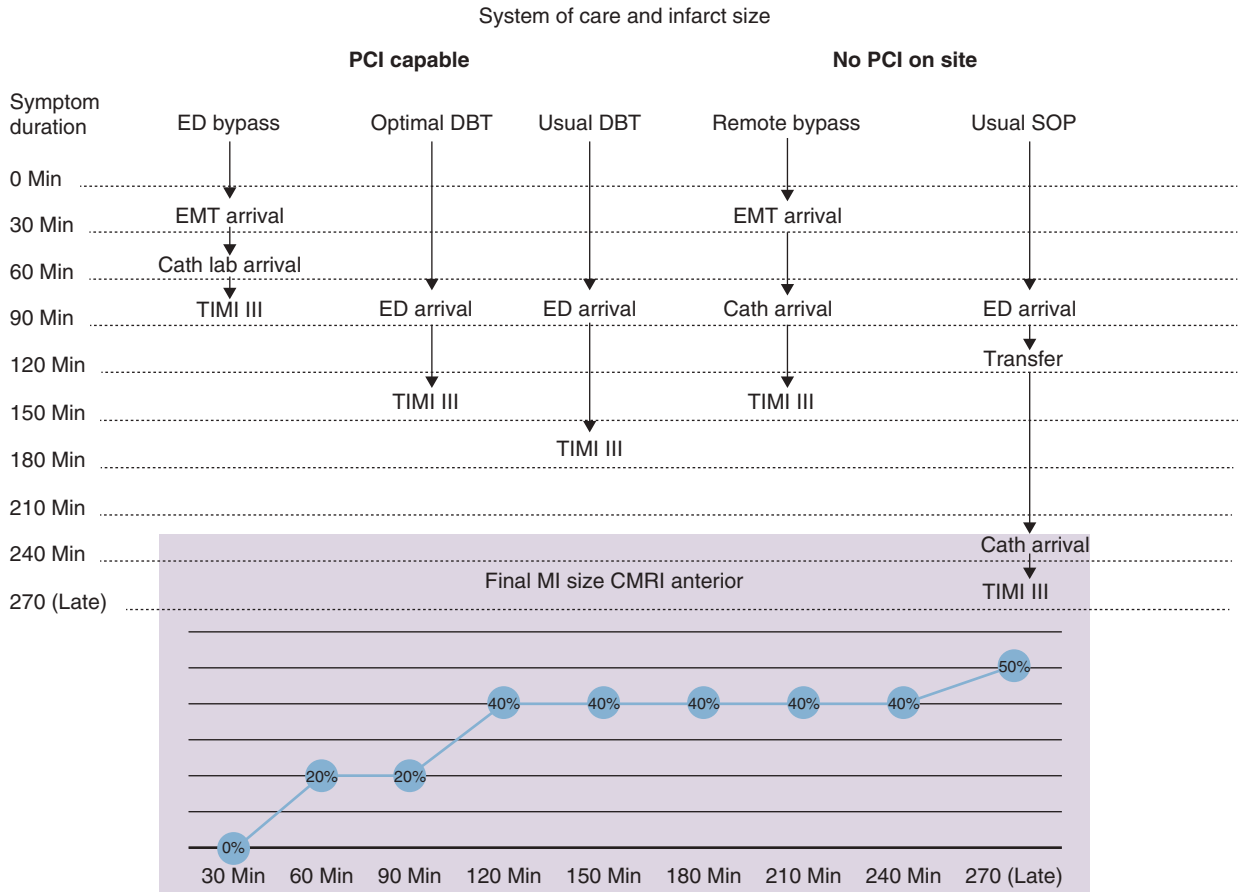

FIGURE 42–4. Time of symptom onset to reperfusion can vary widely based on how a patient arrives to hospital and whether the hospital is equipped to perform primary percutaneous coronary intervention (PCI). The most rapid care occurs when emergency medical transport (EMT) performs and transmits remote electrocardiograms and bypasses the emergency department (ED). The most prolonged time occurs when a patient is driven to an ED in a remote location. In the lower panel, final anterior myocardial infarction (MI) size from the CRISP AMI (Counterpulsation Reduces Infarct Size Pre-PCI for Acute Myocardial Infarction) trial is depicted. CMRI, cardiac magnetic resonance imaging; DBT, door-to-balloon time; SOP, standard operating procedure; TIMI, Thrombolysis in Myocardial Infarction.

and reperfusion still occurs under 3 hours. Patients driven by car to non-STEMI centers in metropolitan areas have further increments of time: time to ECG, time to decision to transfer, time to transfer, and time to catheterization laboratory. In the best of settings, reperfusion is unlikely to occur within 3 hours. Finally, for remote centers, if field ECGs are done, the time to transfer of 2 hours still permits reperfusion in 3 hours. It is unlikely that patients driven by car to remote EDs will be reperfused within 3 hours. This exercise demonstrates the central role of the 12-lead ECG and suggests that national attention be placed on educating patients to request ambulance transport and mandate that all ambulances picking up chest pain patients have the capability to perform and transmit 12-lead ECGs. It is realistic to believe that a national program, such as the DANAMI (Danish Trial in Acute Myocardial Infarction) effort, may result in timely reperfusion for the majority of patients.

PREVENTING REPERFUSION INJURY AND DECREASING INFARCT SIZE

As previously discussed, without dramatic changes in systems of care, it is unlikely that most US patients will be reperfused before 2 to 3 hours of total symptom duration. For this reason, other measures to decrease infarct size have been actively explored (see Table 42–1). One method may be to decrease reperfusion injury.[83] Reperfusion injury refers to damage to the myocardial tissue caused when blood supply returns to the tissues after a period of ischemia. In this situation, restoration of flow results in inflammation and oxidative stress damage. Furthermore, reperfusion injury may be related to a complement-dependent inflammatory response, the formation of oxygen-free radicals, or another mechanism and manifested as no-reflow phenomenon. Studies evaluating agents to reduce reperfusion injury have generally been disappointing. Adenosine can potentially reduce reperfusion injury by suppressing free radical formation and by preventing neutrophil activation. AMISTAD I[84] (Acute Myocardial Infarction Study of Adenosine) evaluated adenosine in STEMI patients who were treated with PPCI or lytic therapy. They found a 33% reduction in infarct size in patients with anterior wall infarction who were treated with adenosine but no benefit in inferior infarction. AMISTAD II,[85] which evaluated only patients with anterior wall infarction, found no benefit with adenosine in the primary end point of death or congestive heart failure at 6 months but did find a trend toward smaller infarct size with adenosine (17% vs 27%; $P = .07$) and a significantly smaller infarct size in the high-dose adenosine group (11% vs 27%; $P = .02$). In a post hoc analysis of AMISTAD II, Kloner et al[86] reported that when patients were treated within 3 hours of symptom duration mortality was lower at 1 month (5% vs 9%; $P = .014$) and 6 months (7% vs 11%; $P = .033$). In addition, combined death and congestive heart failure were lower at 6 months in the adenosine group (12% vs 17%; $P = .022$). Thus, there appears to be a signal for clinical benefit for anterior MI patients who are treated within 3 hours with high-dose IV adenosine.

Intracoronary administration of supersaturated oxygen with an arterial oxygen partial pressure of 760 to 1000 mm Hg has been tested in two clinical trials— Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT) I[87] and AMIHOT II.[88] The outcome in the anterior MI groups treated within 6 hours were pooled and reported by Stone et al.[88] The authors reported on 301 patients with anterior MI who were treated with less than 6 hours of symptom duration with control (n = 79) or a 90-minute selective intracoronary infusion of supersaturated oxygen after PCI. They found a reduction in infarct size by technetium-99m sestamibi of 25% versus 18% ($P = .02$). No difference in 30-day major adverse cardiovascular and cerebrovascular events occurred. The investigators plan a confirmatory 60-minute infusion trial in the same population.

Numerous studies in experimental animal models of AMI have documented the effectiveness of systemic hypothermia, initiated before reperfusion, in reducing infarct size. New technology has now made systemic hypothermia feasible in patients with STEMI. Current endovascular systems used for achieving systemic hypothermia deploy catheters with coils that are placed in the inferior vena cava via the femoral vein through which cold saline is circulated. These systems can provide rapid cooling and have been evaluated in patients with STEMI in the COOL MI (Hypothermia as an Adjunctive Therapy to PCI in Patients With Acute Myocardial Infarction)[89] and ICE-IT (Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention) trials.[90] Because of logistical problems resulting in delays in initiating cooling in both of these trials, many patients were not cooled to target temperatures before reperfusion, and neither of these trials met its primary end point, which was reduction in infarct size. More recently, two small trials—RAPPID ICE[91] and CHILL-MI[92]—have pooled results and demonstrated a reduction of infarct size and decrease in heart failure for anterior MI. The pooled results of these trials suggested that hypothermia reduced infarct size in patients with anterior infarction when cooling to target temperature was achieved before reperfusion.

Nichol et al[93] have studied use of ice-saline peritoneal lavage as a method to rapidly cool patients. They found no reduction in infarct size and a evidence of increased stent thrombosis for patients who were cooled. Overall, these small trials suggest a benefit for reduction in infarct size primarily in anterior MI patients, but there are no definitive conclusions and the suggestion of increased acute stent thrombosis must be addressed.

A simple, noninvasive method of limiting postreperfusion infarct size has been tested in three trials. Experimental models suggest that transient, intermittent limb ischemia[94] decreases myocardial infarct size in an ischemia-reperfusion model. This phenomenon is likely caused by production of platelet-derived microvesicles, which are produced in the ischemic limb and decrease reperfusion injury.[95] Botker et al[96] randomized 251 consecutive patients to four cycles of 5 minutes of upper limb ischemia caused by a blood pressure cuff inflated 20 mm Hg above systolic pressure. Cycles involved 5 minutes of ischemia and 5 minutes of release for four cycles. Overall, a trend toward lower MI size occurred for the treatment group, and salvage index was higher in the remote ischemic conditioning group (0.69 vs 0.57; $P = .03$). Importantly, Sloth et al[97] subsequently reported that long-term outcome was improved with remote ischemic conditioning. The major adverse cardiovascular and cerebrovascular events rate was lower (13.5% vs 25.6%; $P = .018$) at 3.8 years, and mortality was also lower (4% vs 12%; $P = .027$). Subsequently Crimi et al[98] reported on 100 patients with anterior MI treated < 6 hours after symptom onset who were randomized to repetitive lower limb ischemia or sham. Creatine kinase myocardial band (CK-MB) area under the curve was reduced by 20% ($P = .043$) and 50% ECG ST resolution was improved (66% vs 37%; $P = .015$). White et al[99] randomized 197 patients with TIMI grade 0 flow to remote ischemic conditioning or control and measured infarct size by CMRI. They found that remote ischemic conditioning reduced MI size by 27% (18% ± 10% vs 24% ± 12%; $P = .009$). Peak troponin T was also lower in the remote ischemic conditioning group (2296 ± 263 ng/L vs 2736 ± 325 ng/L; $P = .037$). These three trials provide strong but not definitive evidence that infarct size is decreased and long-term outcomes are improved for patients with large MI treated before reperfusion. In addition, Yellon et al[100] even suggest this technique may be of benefit in less developed countries that only have IV thrombolysis capability.[100]

Another simple, inexpensive drug to limit MI size (IV metoprolol) has been tested in a moderate-size randomized trial. Ibanez et al[101] and Pizarro et al[102] have reported the outcomes on 270 patients with Killip class I to II anterior MI presenting < 6 hours after symptom onset. Patients were randomized to treatment with up to three IV bolus infusions of metoprolol 5 mg or placebo. CMRI infarct size was smaller with metoprolol treatment (25 ± 15 g vs 32 ± 22 g; $P = .012$). In addition, 6-month CMRI ejection fraction was higher (48.7% ± 9.9% vs 45% ± 11.7%; $P = .025$). The prespecified combined end point of death, congestive heart failure admission, reinfarction, and malignant arrhythmia was lower with metoprolol (10.8% vs 18.3%; $P = .065$). Unfortunately, these promising initial results did not translate into clinical benefit in the Early BAMI (Beta Blocker Acute Myocardial Infarction) trial recently reported at the 2016 ACC Scientific Sessions. In summary, these clinical trials suggest some room for optimism concerning infarct size reduction.

ELECTROCARDIOGRAM TRIAGE

Pardee[103] first linked the acute injury current on the ECG to the diagnosis of AMI in 1918. It was not until 1979, however, that DeWood linked ST elevation to acute coronary occlusion. The demonstration of a high prevalence of thrombotic occlusion in the early hours of STEMI was the catalyst for reperfusion therapy either with thrombolytic or mechanical reperfusion. Shortly thereafter the Western Washington Group[104] demonstrated the marked prognostic difference between anterior and nonanterior myocardial infarction. The pooled analysis of technetium-99 single-photon emission computed tomography infarct size by Stone et al[55] has furthered linked the prognostic difference in MI location to the demonstration that left anterior descending artery infarcts are larger than left circumflex or right coronary artery infarcts. In addition, they demonstrated that a steep gradient of time dependence for myocardial salvage exists for anterior MI up to 3 hours of symptom duration. Thereafter, myocardial infarct size has little time dependence. Conversely, nonanterior MIs are generally smaller and have little time dependence for myocardial salvage. Thus, infarct reduction strategies must be focused on anterior MI patients in whom reperfusion is likely within 3 hours.

Figure 42–5 outlines the ECG triage for infarct size reduction. In particular, patients presenting early with large anterior MI must be rapidly reperfused, and the entire team should treat these patients as though a knife has entered the heart. The therapeutic agents aimed at decreasing infarct size previously discussed are most likely to benefit these patients.

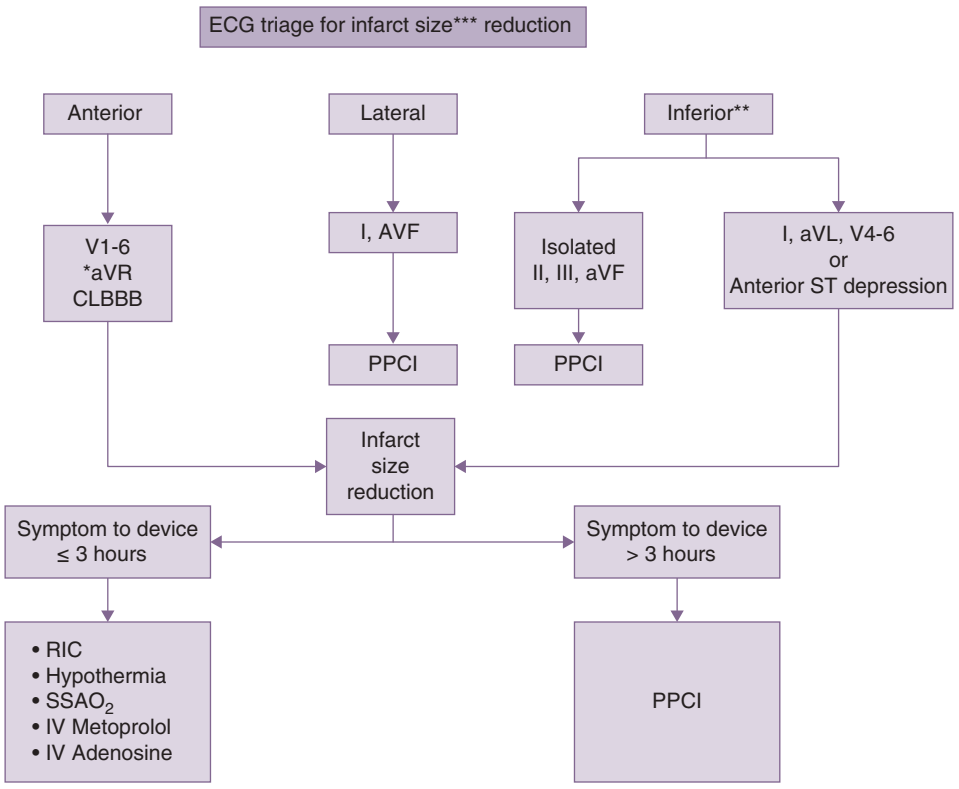

FIGURE 42–5. Electrocardiogram triage for infarct size reduction. *ST elevation in aVR might signify left main coronary occlusion.[196] **Inferior ST-segment elevation myocardial infarction (STEMI) requires ST elevation in at least two leads (II, III, or aVF). ***To date, no therapies have been shown to limit myocardial infarction size when symptom duration greater than 4 hours exists. CLBBB, complete left bundle branch block; PPCI, primary percutaneous coronary intervention; RIC, remote ischemic conditioning; $SSAO_2$, super saturated aqueous oxygen.

ADJUNCTIVE THERAPIES WITH PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Mechanical reperfusion therapy has improved greatly since its introduction in the early 1980s as a result of increased operator experience, better equipment, and the introduction of new adjunctive therapies. The most important and widely studied of these adjunctive therapies have been platelet inhibitors, antithrombotics, stents, distal protection, thrombectomy, and multivessel PCI.

ANTITHROMBOTIC THERAPY AND ARTERIAL ACCESS

The initial inciting event during STEMI is a plaque rupture with thrombotic occlusion mediated by platelet activation, thrombin-mediated cleavage of fibrinogen to fibrin and platelet-fibrin crosslinks to form the initial hemostatic plug. Some component of mechanical obstruction from the disrupted plaque also occurs. Enormous scientific effort has been undertaken to treat each arm of this acute occlusion (Fig. 42–6). It is not possible to predict how important each factor is in individual patients. The reason mechanical reperfusion will always be superior to thrombolytic therapy is because a mechanical obstruction to flow exists in up to 50% of cases,[105] and this can never be overcome by pharmacologic means alone.

When primary angioplasty was started in the 1980s, an IV heparin bolus of 5000 to 10,000 U was the only anticoagulant available. Oral aspirin was also administered in the ED based on data from the thrombolytic trials. Great strides have been made in optimizing dosage of heparin based on rapidly available activated clotting time (ACT) measurements.[106] Most scientific effort in the late 1980s revolved around understanding whether immediate PTCA could be performed after thrombolytic therapy. While thrombolytics dissolved coronary clots, they also activated platelets

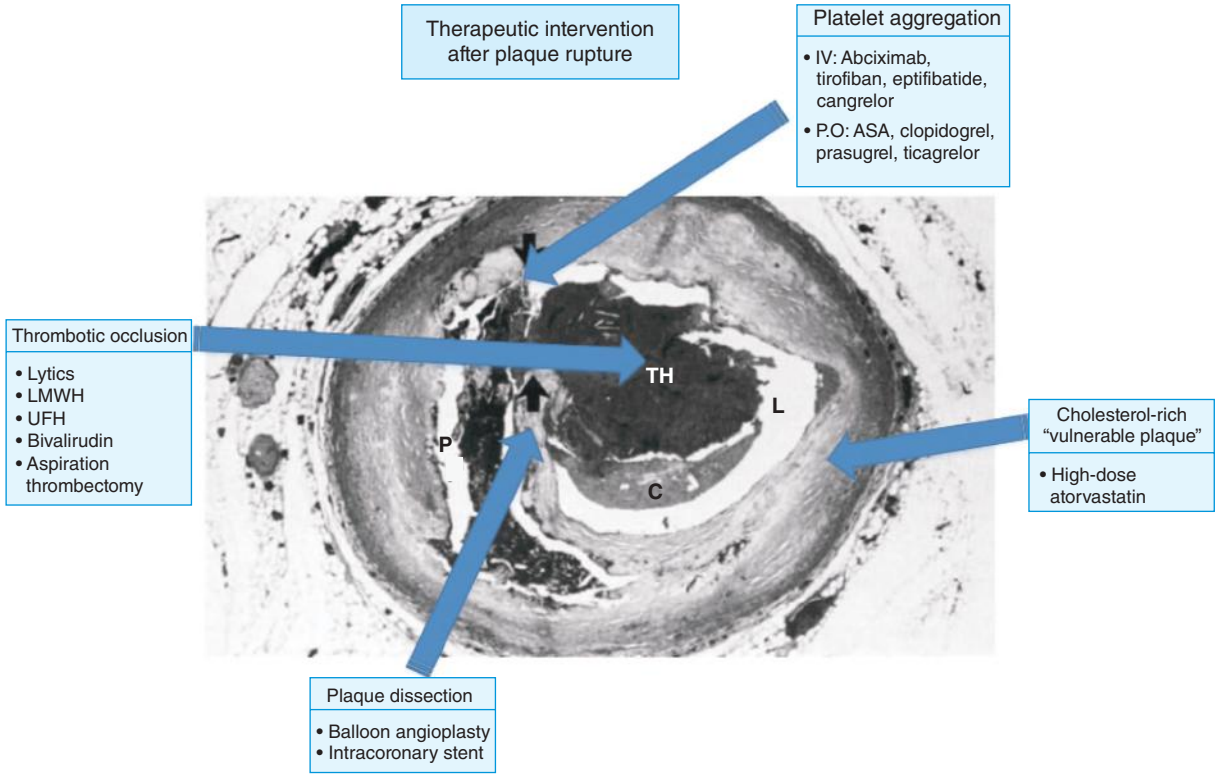

FIGURE 42–6. A plaque rupture precipitating acute myocardial infarction or acute coronary syndrome is depicted from Davies et al. Therapeutic interventions dealing with plaque, platelet and thrombus are depicted. IV, intravenous; LMWH, low-molecular-weight heparin; PO, oral; UFH, unfractionated heparin. Adapted with permission from Davies MJ, Thomas AC, Knapman PA, et al: Intramyocardial platelet aggregation in patients with unstable angina suffering sudden ischemic cardiac death. *Circulation*. 1986 Mar;73(3):418-427.

though a thrombin-mediated pathway and caused intramural plaque hematoma.[107] Both of these outcomes led to recurrent occlusion after PTCA; thus, overall outcomes were harmful.

In the early 1990s, it became apparent that platelet activation was crucial to arterial thrombosis. At this time, the first the IV antiplatelet agent abciximab became available.[108] Five large, randomized trials have evaluated abciximab as adjunctive therapy with PPCI and have shown a reduction in the composite end point of death, reinfarction, or urgent target vessel revascularization (TVR) at 30 days. These trials have been summarized in a meta-analysis.[109] The greatest benefit was seen in the ADMIRAL (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up) trial,[110] in which abciximab was often given early at the time of randomization before PPCI. In addition to better clinical outcomes, the ADMIRAL trial found improved infarct artery patency before PCI and improved left ventricular ejection fraction at 6 months with abciximab. In contrast, the CADILLAC[47] (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial showed improvement in 30-day outcomes with abciximab, but most of the benefit of abciximab was seen in patients treated with PTCA alone (4.8 % vs 8.4 %; P = .02) and no benefit was seen in stented patients (4.5% vs 5.7%; P = not significant). There was no improvement in left ventricular ejection fraction at 7 months. Abciximab did reduce acute thrombosis in stented patients (0% vs 1.0%; P = .03) and decreased arterial reocclusion in all patients (0.4% vs 1.4%; P = .01).

The route of abciximab administration has been tested. Stone et al[111] found that intracoronary administration of abciximab decreased infarct size in anterior MI patients. Subsequently, eight other randomized trials have been performed, and pooled data[112] found that compared with IV administration, intracoronary abciximab decreased major adverse cardiovascular events (MACE) and reinfarction but did not reduce overall mortality. Abciximab is still an important adjunct during PPCI. IV administration allows reliable, profound, immediate platelet blockade. Dosing is not affected by renal function and can provide an excellent bridge until oral antiplatelet agents become effective. Finally, the agent is immediately reversible with platelet transfusions. All of these factors makes it an attractive agent for IV antiplatelet therapy during PPCI.

Currently, abciximab has a Class IIa indication in the ACC/AHA guidelines for use with PPCI for STEMI, and eptifibatide has a Class IIb recommendation.[113] Recently, the novel IV direct-acting $P2Y_{12}$ inhibitor cangrelor has been tested in PCI patients. Steg et al[114] summarize the patient-level data on 24,910 patients, 12% of whom had PPCI. Overall, acute stent thrombosis was decreased by 41% (P = .008), whereas mild bleeding was increased (P > .0001) when cangrelor was tested against placebo or clopidogrel. Subgroup analysis of the STEMI patients were not reported. Administration of cangrelor with switch to an oral $P2Y_{12}$ inhibitor may provide optimal initial and long-term antiplatelet therapy. The immediate onset of action and IV route of administration make this agent an attractive option during PPCI.

Around the same time that abciximab was developed, new direct thrombin inhibitors were being tested during elective PTCA.[115] It became apparent that bleeding complications were significantly decreased with weight-adjusted, double bolus administration of bivalirudin.

The HORIZONS[116] (Harmonizing Outcomes With Revascularization and Stents)-AMI trial compared bivalirudin with unfractionated heparin (UFH) plus GP IIb/IIIa inhibition in STEMI patients undergoing PPCI in an effort to determine the optimum anticoagulant therapy. This trial randomized 3602 patients with STEMI and symptom onset of 12 hours or less. At 30 days, patients who were assigned to receive bivalirudin alone had a significantly reduced rate of net adverse clinical events compared with the control group (9.2% vs 12.1%; relative risk [RR], 0.76; 95% confidence interval [CI], 0.63-0.92; $P = .005$) because of a lower rate of major bleeding (4.9% vs 8.3%; RR, 0.60; 95% CI, 0.46-0.77; $P < .001$), with similar rates of major cardiovascular events. The clinical benefit of bivalirudin over heparin plus GP IIb/IIIa that was driven by reduced bleeding was preserved at 3 years of follow-up. This study was done in nonshock patients with 94% use of femoral access.

Subsequent to the HORIZONS-AMI trial, three other major trials (Euromax,[117] HEAT PPCI [How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention],[118] and BRIGHT [Bivalirudin in Acute Myocardial Infarction Versus Glycoprotein IIb/IIIa and Heparin Undergoing Angioplasty][119]) performed direct comparisons of safety with UFH versus bivalirudin. Table 42–2 summarizes these results. It is apparent that a gradient of benefit exists for bivalirudin when femoral access is used more frequently. UFH appears to be as equally as safe as bivalirudin when radial access is used.

Now that consensus exists about use of PPCI as the optimal reperfusion therapy and now that processes of care (ie, DBT) have been optimized, attention has turned to optimize the safety and durability of PPCI. Major technical advances have changed the performance of PCI in general and PPCI in particular. Stent technology has vastly improved, and bare metal and drug-eluting stents can both be delivered routinely through 6-Fr catheters. This in turn has allowed radial artery access to be routinely used in men and women. European, Canadian, and Asian operators have more rapidly adopted this technique compared to US operators. Once operators became proficient in radial access, this technique became increasingly used for STEMI intervention. Karrowni et al[120] performed a meta-analysis of 12 studies (n = 5055) comparing outcomes of radial versus femoral intervention. The mortality was decreased for radial intervention (2.7% vs 4.7%; $P < .001$), and site bleeding was also decreased (2.1% vs 5.6%; $P < .001$). Stroke risk was not increased, and DBT was not prolonged. For these reasons, Hinohara and Rao[121] have urged adoption of radial access as the optimal approach during STEMI intervention. Hess et al[122] describe a learning curve that stabilizes after operators perform 30 to 50 radial interventions. Unfortunately, in the HORIZONS-AMI trial, which was predominantly based in the United States, only 6% of interventions were performed via radial access. Recently, Kadakia et al[123] have demonstrated that radial intervention is particularly effective for rescue PCI, showing less bleeding complications in this high-risk population.

STENT AND ANTIPLATELET THERAPY

When stents were first tested in the 1990s during elective PCI, a substantial risk of stent thrombosis was noticed.[124] Colombo et al[125] at made a major contribution to the field by proving that high-pressure balloon inflation decreased thrombotic risk. Leon et al[126] further demonstrated that ticlopidine therapy also decreased risk of stent thrombosis. Since AMI angioplasty was being performed in a thrombotic milieu, stents were not tested in these setting until Grines et al[46] conducted the Stent PAMI [Primary Angioplasty in Myocardial Infarction] trial. The Stent PAMI trial first documented a clear benefit of stenting by comparing the heparin-coated Palmaz-Schatz stent with balloon angioplasty. Placement of stents reduced restenosis, reocclusion, and the need for TVR after PPCI for STEMI. However, stented patients had lower TIMI grade 3 flow rates after PCI and a disturbing trend toward higher mortality at 1 year. The CADILLAC trial[47] evaluated the role of stenting and platelet GP IIb/IIIa inhibition with abciximab in 2082 patients with STEMI who were treated with PPCI. Stented patients had a clear benefit over balloon angioplasty alone in reducing 6-month restenosis (22% vs 41%; $P < .01$), reocclusion (5.7% vs 11.3%; $P = .01$), ischemic TVR (6.8% vs 14.7%; $P < .001$), and MACE (10.9% vs 18.3%; $P < .001$). In contrast to Stent PAMI, the CADILLAC trial, using the newer generation MultiLink stent (Guidant Corporation, Indianapolis, IN), showed no degradation of TIMI flow after stenting and no difference in 6-month mortality. Based on these data, stenting is recommended for routine use in eligible patients with STEMI who are treated with mechanical intervention.

Drug-eluting stents (DES) have proven very effective in reducing restenosis and TVR compared with bare metal stents (BMS) after elective and urgent PCI. There is concern that the incidence of stent thrombosis with DES may be higher in the setting of STEMI and that the benefits of DES may not be as great as with elective and urgent PCI. Two randomized trials found conflicting results with DES versus BMS in STEMI. The TYPHOON[127] (A Multicenter Randomized Trial Comparing Sirolimus-Eluting Stents to Bare Metal Stents in Primary Angioplasty for Acute Myocardial Infarction) trial (n = 705) found less TVR with sirolimus-eluting stents versus BMS (5.6% vs 13.4%; $P < .001$), whereas the PASSION[128] (Randomized Comparison of

TABLE 42–2. Major Bleeding

Trial	No.	Bivalirudin (%)	Heparin (%)	Rate Femoral Access (%)
HORIZONS[a]	3602	3.1	5.0	94
Euromax[a]	2198	1.3	2.1	52
HEAT[a]	1917	3.5	3.1	18
BRIGHT[b]	1464	1.5	3.8	21

Note. Major trials of primary percutaneous coronary intervention that compared heparin to bivalirudin are tabulated. The advantage of bivalirudin in decreasing bleeding risk appears to interact with radial versus femoral access. The risk of bleeding appears particularly decreased when femoral access is used.

[a]TIMI (Thrombolysis in Myocardial Infarction) major bleed.

[b]Bare 3-5 bleed.

Paclitaxel-Eluting Stent Versus Conventional Stent in ST-Elevation Myocardial Infarction) trial (n = 617) found no difference in target lesion revascularization between paclitaxel-eluting stents and BMS (6.2% vs 7.4%; $P = .23$).

In the pooled data from several clinical trials with follow-up ranging from 8 months to 1 year, DES resulted in a marked reduction in target lesion revascularization with similar rates of death, reinfarction, and stent thrombosis. Recently, Sabaté et al[129] have provided definitive proof of long-term superiority of DES over BMS in the EXAMINATION (Clinical Evaluation of the Xience-V Stent in Acute Myocardial Infarction) trial. Patients undergoing PPCI (n = 1498) were randomized 1:1 to everolimus-eluting stents or BMSs and followed for 5 years. All-cause mortality was reduced with everolimus-eluting stents (9% vs 12%; $P = .047$). Thus, when resources are available and compliance with long-term $P2Y_{12}$ inhibitor therapy is expected, DES is preferred over BMS for PPCI.

Biodegradable stents may further enhance arterial patency. They have now been tested in PPCI. The Prague group[130] found excellent 1-year patency in 67 patients with STEMI intervention. A large interventional trial is being planned that will test the efficacy of these new platforms in PPCI.

ORAL ANTIPLATELET THERAPY

In CLARITY-TIMI-28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28),[131] 3491 patients receiving fibrinolytic therapy for STEMI were randomized to a 300-mg oral loading dose of clopidogrel and 75 mg daily thereafter versus placebo. The primary composite efficacy end point of an occluded infarct-related artery at angiography, death, and recurrent MI before angiography (between 48 and 192 hours after the start of study medication) occurred in 21% of the placebo group and 15% of the clopidogrel group (odds ratio [OR], 0.64; 95% CI, 0.53-0.76) without significant increase in the rate of bleeding. Dangas et al[132] further demonstrated that pretreatment with 600 mg is superior to 300 mg without an increase in bleeding during PPCI.

The TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel)-TIMI 38[133] investigators tested the new $P2Y_{12}$ receptor antagonist prasugrel in 3534 patients undergoing PPCI. Seventy-one percent of patients received UFH, and femoral access was used in 91% of patients. The primary end point of cardiovascular death, nonfatal MI, or nonfatal stroke was lower in the prasugrel group (6.5% vs 9.5%; $P = .0017$). Zeymer et al[134] studied the pharmacokinetics of clopidogrel 300 mg versus prasugrel 60 mg. They demonstrated a higher level of platelet inhibition at 2 and 4 hours after therapy for prasugrel patients. Even then, 53% of prasugrel patients had inadequate platelet inhibition after 2 hours. The delayed length of onset for platelet inhibition with these oral agents explains a 2% to 4% incidence in acute thrombosis that occurs in some of the bivalirudin trials. It is possible that rapid termination of bivalirudin leaves patients unprotected because oral $P2Y_{12}$ agents have not yet achieved therapeutic levels. Thus, in patients who would have catastrophic consequence to stent occlusion, IV abciximab or cangrelor should be considered.

Oral ticagrelor has also been compared to clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial.[135] Ticagrelor is a rapid oral $P2Y_{12}$ inhibitor. A total of 18,624 patients with AMI and ACS PCI where randomized to clopidogrel 300 mg or ticagrelor 90 mg loading dose and subsequent therapy of 90 mg twice a day. A total of 7008 patients (37%) were undergoing STEMI intervention. The ticagrelor group had a lower event rate (9.8% vs 11.7%; $P < .0001$). Stent thrombosis was decreased from 3.8% to 2.9% ($P = .01$). An even more rapid onset of platelet inhibition can be achieved by crushing the ticagrelor tablet for oral administration. Time to maximal plasma concentration decreased from 4 to 2 hours, and substantial platelet inhibition occurred within 1 hour of oral administration.[136] Thus, when drug availability permits, prasugrel or oral crushed ticagrelor are the preferred $P2Y_{12}$ inhibitors. If any doubt about efficacy exists, abciximab or cangrelor should be administered.[137]

TREATMENT OF MULTIVESSEL DISEASE

In the initial trials of primary PCTA, plaque dissection and intraluminal thrombosis were difficult to treat with balloon angioplasty and heparin alone. Reocclusion of the infarct-related artery occurred in 5% to 15% of cases and worsened survival. In this context, treating other vessels that were stenosed but had normal blood flow was considered harmful. Thus, the practice of primary angioplasty evolved with treatment of the infarct artery only. As antithrombotic, antiplatelet, and stent therapy became established, the issue of complete revascularization was again raised. Three recently performed well-done randomized trials provide enormous information on this issue. Wald et al[138] first reported the PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) trial. In this trial, 2420 patients with STEMI undergoing PPCI were screened, and 465 patients with multivessel disease were randomized to immediate multivessel PCI of PCI of the infarct artery only. Two-vessel disease occurred in 61% and three-vessel disease in 39% of patients. The primary end point of death, recurrent MI, or refractory angina was lower in the multivessel PCI group (21 of 234 vs 53 of 231 patients; $P < .001$). Cardiac mortality was also lower (11 of 234 vs 22 of 231 patients; $P = .004$).

In a similar trial, Gershlick et al[139] randomized 297 patients to multivessel (n = 146) versus culprit-only (n = 150) PPCI. MACE was lower in patients assigned to multivessel PCI (10% vs 21.2%; $P = .009$), whereas mortality trended but was not significantly lower (1.3% vs 4.1%; $P = .14$). Engstrøm et al[140] took a different approach in the PRIMULTI trial. These investigators used physiologic lesion assessment with fractional flow reserve to treat infarct-only vessels versus treatment of all hemodynamically significant lesions. They screened 3854 patients who required STEMI intervention and randomized 313 patients to infarct vessel–only PCI or multivessel PCI guided by fractional flow reserve. The primary end point of death, reinfarction, or ischemia-driven revascularization occurred in 22% of culprit-only versus 13% of multivessel PCI patients ($P = .004$). In aggregate, these trials suggest that in a background of high usage of $P2Y_{12}$ inhibitors, multivessel PCI is safe and associated with improved clinical outcomes compared with culprit-only revascularization. Whether PCI of nonculprit vessels can be deferred for 1 or more days remains to be established.

DISTAL PROTECTION AND THROMBECTOMY

PPCI is effective in restoring normal *epicardial* coronary flow (TIMI grade 3 flow) in more than 90% of patients with STEMI, but more than half of these patients will have suboptimal flow at the tissue level, as evidenced by poor angiographic blush scores or lack of complete ECG ST-segment resolution.[141] Although achieving TIMI grade 3 flow in the *epicardial* coronary artery is important, optimal outcomes with reperfusion therapy also require optimal *myocardial* reperfusion. Patients with suboptimal myocardial reperfusion, as evidenced by abnormal myocardial blush or lack of ST-segment resolution, have worse outcomes.[142]

The causes of abnormal myocardial reperfusion after PPCI are not clear. One potential cause is distal embolization of thrombus and fragments of atherosclerotic plaque at the time of PCI, resulting in obstruction of the distal microcirculation. Several distal protection devices, including the PercuSurge System (Medtronic, Sunnyvale, CA) and the Filter Wire (Boston Scientific, Natick, MA), have been tested in clinical trials with the hope that distal protection will prevent distal embolization and will result in improved myocardial reperfusion and better outcomes. The EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberalized Debris) trial[143] showed no benefit with the GuardWire (PercuSurge System) in reducing infarct size or improving ST-segment resolution or myocardial blush despite retrieving visible thrombus or atheroma in more than 70% of patients.

RHEOLYTIC THROMBECTOMY

The largest randomized trial using the AngioJet (Boston Scientific), the AIMI (AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction) trial,[144] showed no benefit compared with PPCI alone. There was no difference in ST-segment resolution and myocardial blush, and surprisingly, infarct size was slightly larger with the AngioJet. There was also an increased mortality in the AngioJet group, raising safety concerns. However, recent experience from several registries has documented the safety of the device. The AIMI study investigators concluded that there is no indication for the routine use of rheolytic thrombectomy with PPCI for STEMI.

Based on the results of the EMERALD[143] and AIMI[144] studies, there is general agreement that distal protection and rheolytic thrombectomy are not indicated for routine use with PPCI for STEMI. However, patients with large thrombus burden (Fig. 42–7) frequently have distal macroembolization, and studies have shown that macroembolization is harmful and leads to impaired myocardial reperfusion and worse clinical outcomes. Therefore, it seems reasonable to perform adjunctive thrombectomy in patients with angiographically large thrombus burden before PPCI.

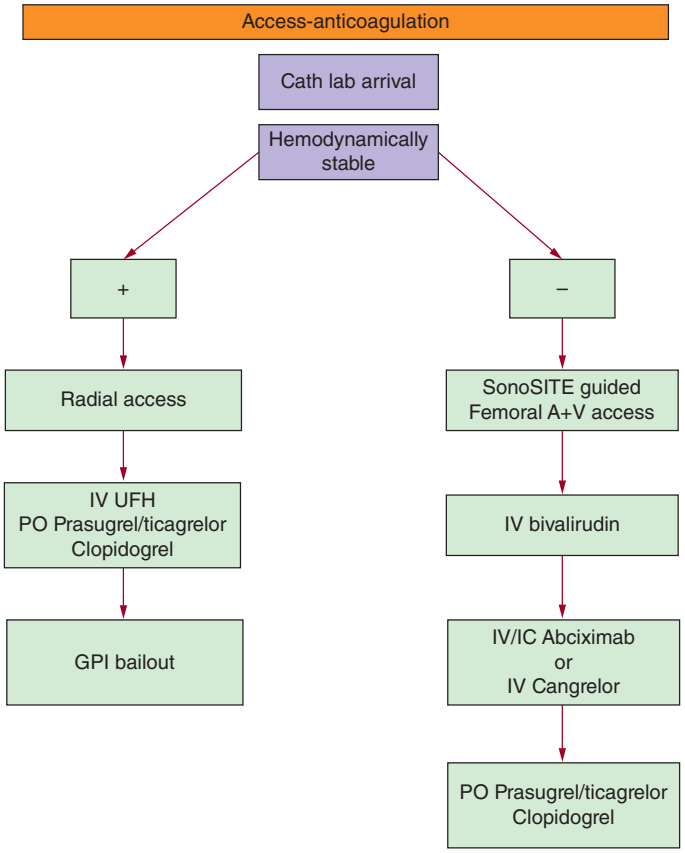

FIGURE 42–7. Adjunctive pharmacotherapy to optimize safety of primary percutaneous coronary intervention is dependent on hemodynamic stability and route of access. Patients who are unstable require femoral access and possibly circulatory support. To minimize bleeding risk in these patients, bivalirudin is preferred, and to decrease risk of early stent thrombosis, intravenous (IV) abciximab or IV cangrelor should be considered. Stable patients can be treated via radial access and with heparin anticoagulation. GPI, glycoprotein IIb/IIIa inhibitor; IC, intracoronary; PO, oral; UFH, unfractionated heparin.

ASPIRATION THROMBECTOMY

Vlaar et al[145] reported the 1-year results of the single-center TAPAS (Thrombus Aspiration Compared to Balloon Angioplasty) trial, which randomized 1071 patients (before angiography) with STEMI and symptom onset within 12 hours to a simple aspiration catheter before PCI or to PPCI alone. Adjunctive aspiration resulted in enhanced rates of normal angiographic myocardial perfusion (blush) and ST-segment resolution. At 1 year, mortality was significantly lower in patients treated with thrombectomy (5.6% vs 9.9%; hazard ratio [HR], 1.81; CI, 1.16-2.84; $P = .009$). The EXPIRA (Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Intervention) trial[146] demonstrated a reduction in infarct size by cardiac magnetic resonance and a reduction in microvascular obstruction at 3 months in patients treated with thrombectomy during PPCI.

The initial enthusiasm for routine use of aspiration thrombectomy has been dramatically tempered by two large nationwide randomized trials. The first large nationwide study was performed through a nationwide Swedish coronary angiography and angioplasty registry.[147] A total of 7244 patients undergoing PPCI were randomized to manual aspiration or control while undergoing PPCI. All-cause mortality rate at 30 days was 2.8% in thrombectomy patients versus 3.0% in control patients. The TOTAL trial[148] was an unblinded randomized trial of 10,372 patients undergoing PPCI from August 2010 to July 2014. The primary end point of cardiovascular death, recurrent MI, cardiogenic shock, or New York Heart Association class IV heart failure occurred in 6.9% of thrombectomy patients versus 7.0% of PPCI patients ($P = .86$). At 6 months, stroke risk was higher in the thrombectomy group. These findings were maintained at 1 year.[149] Ghatak et al[150] performed a meta-analysis of 20 published trials of aspiration thrombectomy. A total of 21,281 patients were treated in these trials. Rates of mortality, TVR, recurrent MI, and stent thrombosis were the same. Only stroke was different and higher in the thrombectomy patients. Thus, routine thrombectomy does not enhance outcomes and should be reserved for large thrombus burden before or after stent implantation.

TECHNICAL ASPECTS OF PRIMARY PERCUTANEOUS CORONARY INTERVENTION

TREAT IN THE EMERGENCY DEPARTMENT

Strong evidence suggests that mechanical reperfusion is most effective in promoting myocardial salvage when it can be accomplished less than 3 hours after symptom onset. This is especially true for patients presenting with anterior MI. For this reason,

systems should be in place to facilitate admission to the catheterization laboratory. Bradley et al[151] have shown that local "service champions" are required to establish an institutional philosophy for rapid reperfusion. In the ED, a brief, focused history and physical examination and a 12-lead ECG should be all that is required to initiate a "STEMI ALERT."

Most established programs have well-designed paging systems and can quickly activate catheterization laboratory staff and interventional attending staff. Patients should be given an IV heparin bolus and a loading dose of an adenosine diphosphate (ADP) blocker at first medical contact; they can be switched to bivalirudin in the catheterization laboratory if bleeding risk is increased or femoral access is required. Nitrates should be avoided, especially in patients with inferior MI with right ventricular involvement. Use of nitroglycerin in this setting may lead to hypotension. Rapid transfer to the catheterization laboratory is critical, and any other test, consult, or imaging that delays transport should be avoided unless absolutely necessary (eg, suspected intracranial hemorrhage or acute stroke).

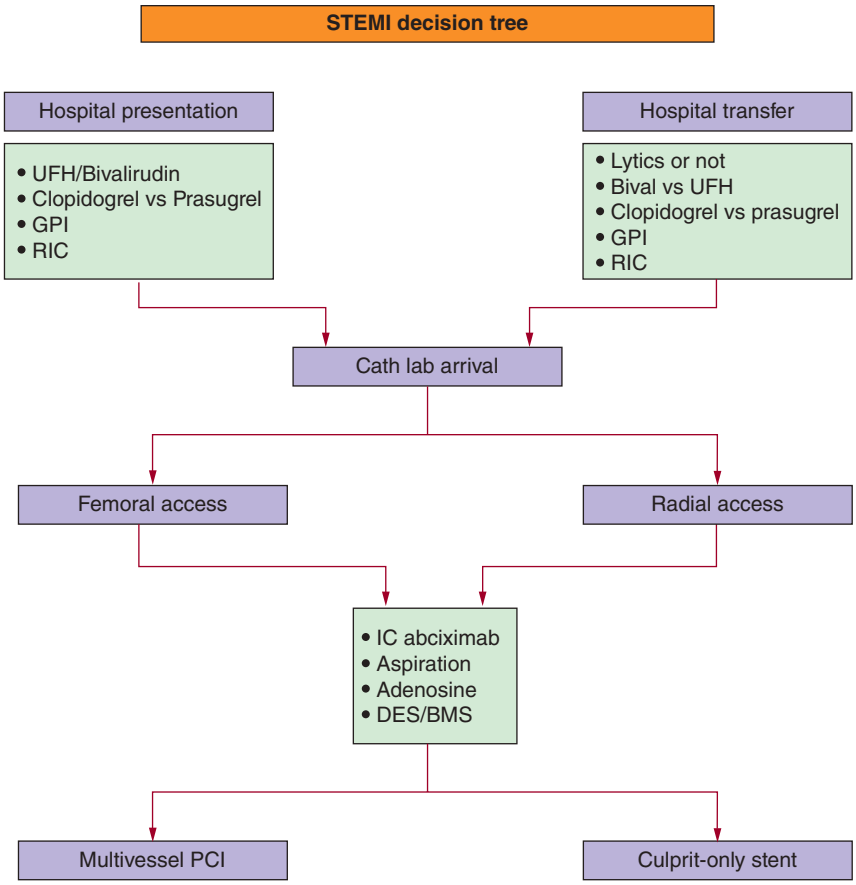

FIGURE 42–8. A variety of decisions must be made in process of care for primary percutaneous coronary intervention (PCI). The treatments received prior to catheterization lab arrival and the route of access chosen will impact the antithrombotic and antiplatelet therapy administered. Findings at catheterization will impact procedural therapies and also determine whether nonculprit intervention is required. Patient adherence to prolonged dual antiplatelet therapy will help determine whether drug-eluting stents (DES) or bare metal stents (BMS) are used. Bival, bivalirudin; GPI, glycoprotein IIb/IIIa inhibitor; IC, intracoronary; RIC, remote ischemic conditioning; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Arterial access should be performed by the route that the cardiologist is most experienced with. Ideally, radial intervention is preferred (Fig. 42–8). In patients who are unstable and in whom right heart catheterization, temporary pacing, or circulatory support may be required, ultrasound-guided femoral access should be performed. Access route will impact further management, as depicted in Fig. 42–7. If radial access is chosen, continued UFH therapy should occur. For patients who require femoral approach, switching to bivalirudin may decrease bleeding risk. An ACT is measured, and additional UFH or bivalirudin is given to prolong the ACT to greater than 300 seconds or 200 to 250 seconds if platelet GP IIb/IIIa inhibitors are used. Left ventriculography is valuable before intervention, even in patients who are hemodynamically unstable, to assess the severity of ventricular and valvular dysfunction, to help identify the infarct artery (if this is uncertain), and to aid in making decisions regarding the necessity for adjunctive therapy, such as mechanical circulatory support and pulmonary artery catheter insertion. Occasionally, papillary muscle rupture, ventricular septal defect, or, rarely, even frank free wall rupture will be demonstrated when not previously suspected, prompting urgent surgery. Alternatively, demonstration of normal left ventricular function may raise early concerns of nonischemic diagnoses such as aortic dissection or pericarditis. A femoral venous sheath may be helpful in patients with occlusion of the right coronary artery to allow access for temporary transvenous pacing if necessary, although most operators do not routinely obtain venous access. In patients with hypotension or in patients who are hemodynamically unstable, placement of a pulmonary artery catheter is useful to define and monitor hemodynamics. The use of a pulse oximeter to monitor oxygen saturation may be helpful. After diagnostic coronary and left ventricular angiography, patients are triaged to the most appropriate therapy. Approximately 10% of patients who are undergoing emergency coronary angiography do not undergo primary angioplasty and are triaged to bypass surgery or medical therapy.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION PROCEDURE

If stenting is planned and an ADP blocker had not been previously given, one is given before initiation of PCI. Crushed ticagrelor or prasugrel may provide faster-onset antiplatelet blockade. If any concern remains regarding platelet inhibition, abciximab or cangrelor should be administered. PPCI is generally performed with 6- or 7-Fr standard guiding catheters and soft- or floppy-tipped 0.014-inch steerable guidewires. The soft tip can almost always cross the soft, fresh thrombus (in contrast to a chronic total occlusion) and is less traumatic than stiffer wires. The guidewire is advanced well down the infarct artery to ensure that it is in the true lumen and not in a small side branch or under an intimal dissection because navigation distal to the occlusion is usually done blindly. If the infarct-related artery is totally occluded, reperfusion will often be established after the occlusion is crossed with the guidewire. If not, it may be preferable to cross the occlusion with a balloon and then withdraw the balloon without inflating it (*dottering* the lesion) to establish reperfusion. The more gradual reperfusion provided with

the wire or dottering technique may result in fewer reperfusion arrhythmias than immediate balloon inflation and allows assessment of the thrombus burden and the size of the distal vessel. Balloon angioplasty or stenting of the infarct lesion is performed with techniques similar to conventional PCI. No flow (TIMI grade 0-1 flow) or slow flow (TIMI grade 2 flow) may occur after successful opening of the epicardial infarct artery obstruction. This is generally caused by microvascular dysfunction from spasm, distal emboli, or endothelial injury and may be treated with intracoronary adenosine, nicardipine, or nitroprusside, which often helps to improve flow. Intracoronary abciximab may also help with no reflow, although this approach is mainly supported by small clinical studies. Performance of culprit-only versus multivessel PCI depends on the patient's clinical stability, total contrast usage, and complexity of nonculprit lesions. Simple, short lesions may be approached, whereas complex, calcified, or bifurcation lesions might be better treated later after the patient has stabilized and therapeutic antiplatelet effect is present. Exceptions to this rule are made in patients with severe multivessel disease and refractory cardiogenic shock. Proper stent sizing is crucial, especially if a DES is used. DES undersizing can lead to stent malapposition, which is associated with stent thrombosis. To properly size the vessel, angiography assessment after intracoronary nitroglycerin injection should be performed. Operators should have a low threshold for use of intravascular ultrasonography when the vessel diameter is in doubt.

AFTER CARE FOR PERCUTANEOUS INTERVENTION

Postprocedure care has been standardized in a number of recent randomized trials. After the procedure, anticoagulation is discontinued unless there are other reasons to resume it, such as the need for mechanical circulatory support, severe left ventricular dysfunction with concern about left ventricular thrombus, or atrial fibrillation. If a femoral artery closure device is not used, the sheath is generally removed at 2 to 3 hours when the ACT is below 170 seconds. If bivalirudin is used, the sheath is generally removed at 2 hours. Patients who are not at high risk can be transferred from the catheterization laboratory directly to the subacute unit (rather than the coronary care unit) and can be targeted for discharge on day 2 (day 0 = day of admission). All patients without contraindications should be treated with aspirin indefinitely, an ADP blocker for 1 year, β-blockers, and a statin. Angiotensin-converting enzyme (ACE) inhibitors should be used in patients with congestive heart failure, hypertension, or low ejection fraction (< 40%). Patients who develop symptoms or ECG changes of recurrent ischemia or reinfarction should undergo emergency repeat catheterization and intervention if indicated.

DECISION MAKING IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION INTERVENTION

From the time of presentation, the clinical team treating a patient with STEMI is faced with complex decisions that interact and may counteract other decisions. For this reason, bottom line conclusions drawn from randomized trials or guidelines can never dictate a treatment path for each individual patient. Decisions faced in STEMI intervention are depicted in Fig. 42–8. Regardless of mode of presentation, rapid performance and competent analysis of the 12-lead ECG are the first steps. Skilled reading either on site or by transmission is essential so that "false activations" can be limited. Once a firm diagnosis of STEMI is made, activation of the STEMI team and transport to the catheterization lab are essential. A heparin bolus and a $P2Y_{12}$ inhibitor should be rapidly administered. If logistically feasible, strong consideration should be given to remote ischemic conditioning while en route to the catheterization lab. If a patient was treated with thrombolytics, heparin and abciximab have been most studied and are likely to provide the safest antithrombotic and antiplatelet therapy.

Upon arrival to the catheterization lab, a rapid assessment of hemodynamic stability is made. If stable and if the operator is experienced with the radial approach, heparin should be continued with ACT titrated to 250 to 300 seconds. Choice of antiplatelet therapy should take into account age, history of stroke, and likelihood of oral tolerance. Chewable ticagrelor may have the earliest onset of platelet blockade and bridges the gap until oral agents become therapeutic.

If patients are unstable, early initiation of hemodynamic support makes the procedure safer. In addition, encouraging data suggest that unloading the left ventricle with true mechanical support may decrease infarct size.[152] Use of intra-aortic balloon counterpulsation has proven ineffective in this setting. Recently the Impella 2.5 (Abiomed, Danvers, MA) axial flow left ventricular support device was approved by the US Food and Drug Administration (FDA) and currently is the only FDA-approved device for hemodynamic support in AMI cardiogenic shock. Radial access for coronary angiography and angioplasty with angiographically guided femoral puncture (from a catheter inserted to the distal aorta) for the mechanical support device placement may be an ideal approach when circulatory support is required.

Once the infarct artery is identified, intracoronary abciximab may be considered if not already administered. Routine thrombectomy is not useful, but if extensive clot burden exists (Fig. 42–9), it will prevent extensive macroembolization. Routine use of DESs should occur. Proper sizing and proper stent opposition are essential to prevent stent thrombosis, and intravascular ultrasound–guided implantation should be strongly considered. Finally, whether to treat other severely stenotic vessels immediately or not depends on clinical stability, underlying renal function, and total contrast dose administered. Fractional flow reserve–guided revascularization of the nonculprit lesions is extremely helpful.

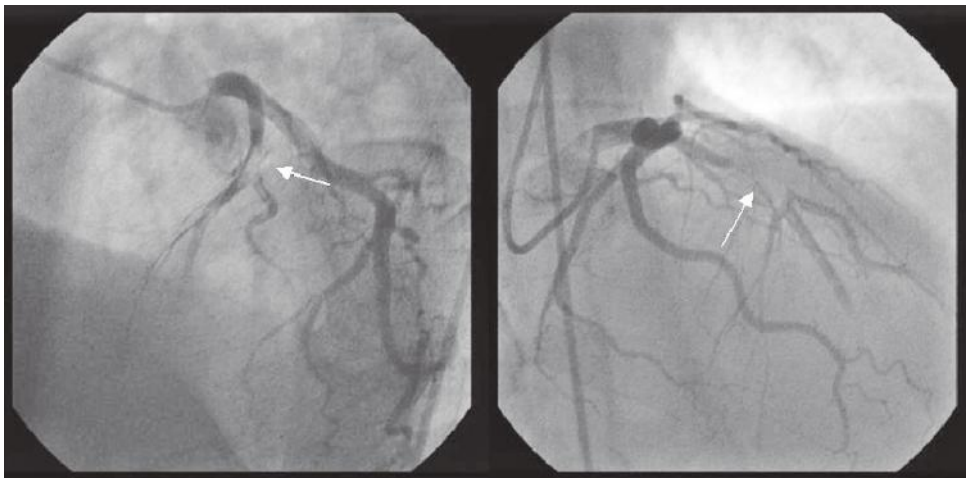

FIGURE 42–9. Coronary angiogram of a patient with an anterior wall myocardial infarction showing a large thrombus burden (*arrows*) in the proximal left anterior descending artery.

If other severe lesions cannot be treated at the initial procedure, patients should return to the catheterization lab in 2 to 5 days but definitely prior to discharge so that complete revascularization can be accomplished. Patients who are hemodynamically unstable or in frank shock should have complete revascularization at the initial procedure, with circulatory support in place.

NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

INVASIVE VERSUS CONSERVATIVE APPROACHES

Most patients with non–ST-segment elevation (NSTE)-ACS in the United States undergo cardiac catheterization. The evidence for invasive management is based on several randomized trials that showed improvement in MACE, improved symptoms, improved quality of life, and reduction in readmission. Moreover, early definition of coronary anatomy has been shown to be associated with earlier discharge.

A 2006 meta-analysis of seven trials that randomized 8375 patients[153] found that the invasive approach improved mortality (4.9% vs 6.5%; RR, 0.75; 95% CI, 0.63-0.90), nonfatal MI (7.6% vs 9.1%; RR, 0.83; 95% CI, 0.72-0.96), and readmission for unstable angina (RR, 0.69; 95% CI, 0.72-0.96) (Fig. 42–10). Similarly, in a propensity score–matched retrospective study of 19,704 patients, an invasive approach in patients with ACS was associated with reduction in cardiac mortality, all-cause mortality, and readmission.[154] The benefits were greater in patients with higher risk (ie, elevated biomarker, ST-segment changes, higher TIMI or GRACE [Global Registry of Acute Coronary Events] risk scores). An updated meta-analysis of 10,150 patients[155] found that both men and women with positive biomarkers or ST deviation benefit from an invasive strategy. Interestingly, men with negative biomarkers or ST deviation also had benefit, with reduction in the risk of death, MI, or rehospitalization. On the basis of these randomized trial findings, US guidelines recommend early catheterization, particularly in intermediate- and high-risk NSTE-ACS patients[156] (Table 42–3).

Timing of catheterization has been evaluated in randomized and observational trials. Initially, it was thought that it may be beneficial to "cool off" an ulcerated thrombotic lesion with antiplatelet and anticoagulant agents for a few days. However studies found that earlier intervention is better, particularly in higher risk patients. The TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial randomized 3031 patients with NSTE-ACS to early (< 24 hours) versus delayed (> 36 hours) coronary angiography.[157] Early catheterization was performed at a median of 14 hours after randomization and was associated with reduced refractory ischemia (1.3% vs 3.3%; $P < .0001$), but early catheterization did not improve the primary end point of death or MI (9.6% vs 11.3%). However, 25% of the delayed group crossed over to early catheterization. Also, in high-risk ACS patients, there was a significant reduction in the risk of death, MI, or stroke (14.1% vs 21.6%; $P = .008$). The ISAR-COOL [Intracoronary Stenting With Antithrombotic Regimen Cooling Off] trial randomized 410 intermediate- to high-risk ACS patients to very early (median time, 2.4 hours) versus delayed (median, 86 hours) catheterization.[158] Early catheterization was associated with a reduction in death or large MI at 30 days (5.9% vs 11.6%; $P = .04$). The ABOARD (Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes) trial randomized 352 high-risk ACS patients to immediate (median, 70 minutes) versus next working day (median, 21 hours) catheterization.[159] There were no differences in peak troponin levels or clinical events.

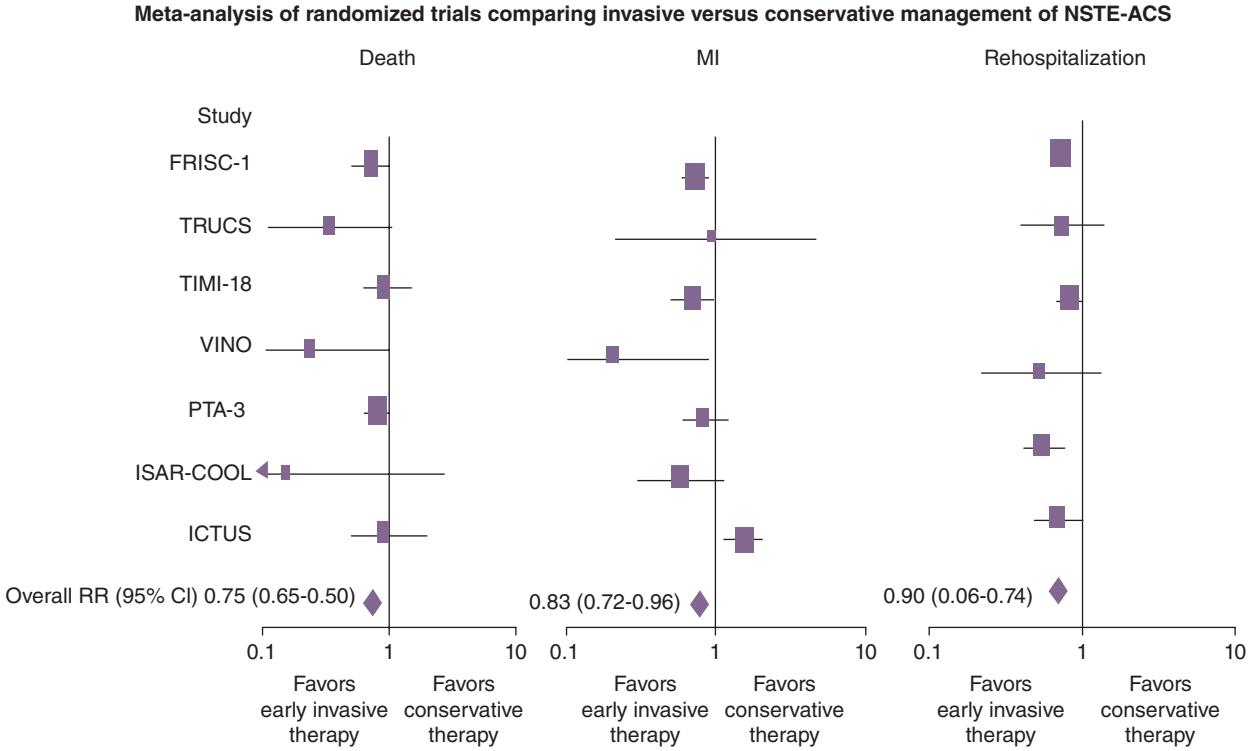

FIGURE 42–10. Meta-analysis of randomized trials comparing invasive versus conservative management of non–ST-segment elevation acute coronary syndrome (NSTE-ACS). CI, confidence interval; MI, myocardial infarction; RR, relative risk. Adapted with permission from Bavry AA, Kumbhani DJ, Rassi AN, et al: Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol.* 2006 Oct 3;48(7):1319-1325.

TABLE 42–3. Acute Coronary Syndrome (ACS) Guidelines

ACS Guidelines
CLASS I
• An urgent/immediate invasive strategy is indicated for (Level of Evidence A)
• refractory angina or hemodynamic or electrical instabillity
• An early invasive strategy is indicated in patients with elevated risk (Level of Evidence B)
CLASS IIa
• It is reasonable to choose an early invasive strategy in patients
• initially stabilized high-risk patients with NSTE-ACS
• for those not at high/intermediate risk (Level of Evidence B)
CLASS IIB
• In initially stabilized patients, an ischemia-guided strategy may be considered (Level of Evidence B)
CLASS III: No Benefit
• An early invasive strategy, is not recommended in patients with:
• extensive comorbidities, likely to outweigh the benefits of revascularization (Level of Evidence C)
• acute chest pain and a low likelihood of ACS (Level of Evidence C)
• who are troponin-negative, especially women (Level of Evidence: B)

Abbreviation: NSTE, non–ST-segment elevation.

Conversely, the RIDDLE-NSTEMI (Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients) trial[160] randomized 323 non–ST-segment elevation MI (NSTEMI) patients to immediate (median, 1.4 hours) versus delayed (61 hours) intervention. The immediate strategy was associated with a lower composite of death or new MI at 30 days (4.3% vs 13%; $P = .008$) and at 1 year (6.8% vs 18.8%; $P = .002$). Although the LIPSiA-NSTEMI (Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention) trial[161] reported no differences in outcomes in immediate versus early versus selective invasive strategies, 85% of patients in the "selective" arm underwent catheterization. Thus, one would not expect any difference in clinical outcome. In a post hoc analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, which randomized NSTE-ACS patients to different pharmacologic strategies, PCI was performed in 7749 patients.[162] Approximately one-third of patients were treated within 8 hours of presentation, one-third between 8 and 24 hours, and the remainder after 24 hours. The two groups in which PCI was done early (< 24 hours) did equally well; however, patients who had PCI after > 24 hours had a significant increase in the individual components of death, MI, and ischemia. These differences were observed in both intermediate- and high-risk patients (Fig. 42–11).

Thus, in intermediate- to high-risk or unstable NSTE-ACS patients, it appears that earlier catheterization is better, whereas in low-risk, stable patients, catheterization may be delayed. Immediate angiography is recommended for hemodynamic instability, congestive heart failure, ongoing or recurrent ischemia, dynamic ECG changes, ventricular arrhythmias, or mechanical complications such as mitral regurgitation or ventricular septal defect (Table 42–4). In other ACS patients, catheterization is often performed the next working day.

FINDINGS OF CATHETERIZATION IN THE PATIENT WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME AND HOW IT INFLUENCES TREATMENT

Unlike STEMI, the cause of NSTE-ACS is often a "nonocclusive" ruptured plaque. When the plaque is further analyzed, it may contain

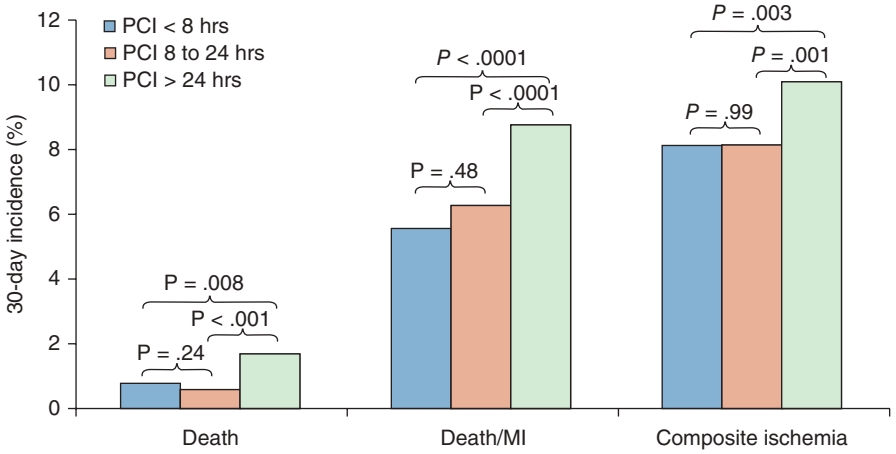

FIGURE 42–11. Timing of percutaneous coronary intervention (PCI) after clinical presentation and 30-day outcome: composite of death, myocardial infarction (MI), and revascularization. Reproduced with permission from Sorajja P, Gersh BJ, Cox DA, et al: Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial. *J Am Coll Cardiol*. 2010 Apr 6;55(14):1416-1424.

TABLE 42–4. Factors Associated With Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

Immediate invasive (within 2 h)	Refractory angina
	Signs or symptoms of HF or new or worsening mitral regurgitation
	Hemodynamic instabillity
	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Sustained VT or VF
Early Invasive (within 24 h)	None of the above, but GRACE risk score > 140
	Temporal change in Tn (Section 3.4)
	New or presumably new ST depression
Delayed invasive (within 25-72 h)	None of the above but diabetes mellitus
	Renal insufficiency (GRF <60 mL/min/1.73 m^2)
	Reduced LV systollic function (EF <0.40)
	Early postinfarction angina
	PCI within 6 mo
	Prior CABG
	GRACE risk score 109-140; TIMI score ≥2
Ischemia-guided strategy	Low-risk score (eg, TIMI (0 or 1), GRACE (< 109)
	Low-risk Tn-negative female patients
	Patients or clinician preference in the absence of high-risk features

Abbreviations: CABG, coronary artery bypass graft; EF, ejection fraction; GRACE, Global Registry of Acute Coronary Events; GRF, glomerular filtration rate; HF, heart failure; LV, left ventricular; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Reproduced with permission from Amsterdam, E.A. et al. 2014 AHA/ACC Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014 Dec 23;130(25):2354-2394.

platelet thrombi, not fibrin-laden clots. Thus, thrombolytic therapy is not beneficial and, in fact, may be harmful and is not recommended. In our clinical and trial experience, single-vessel disease is found in the majority of STEMI patients, and PPCI is performed in approximately 90%. Conversely, in the NSTE-ACS patient,[163] single-vessel disease is present in only 30% of cases; multivessel disease is present in 40% to 50%, left main disease in 4% to 10%, and nonsignificant disease in 10% to 20%. Thus, catheterization (or coronary computed tomography angiography in low-risk patients) is essential to determine the most appropriate treatment strategy. Even In the 10% to 20% of patients with nonsignificant disease, defining the coronary anatomy has been shown to reduce readmissions.

To date, only one trial randomized patients with unstable angina to PCI versus coronary artery bypass grafting (CABG).[164] In this trial of 454 high-risk patients, there was no difference in mortality at 36 months but more angina and revascularization in the PCI group. Other trials of both stable and unstable angina comparing PCI and CABG in patients with multivessel disease had similar findings. Thus, the choice of PCI or CABG often depends on the presence of factors that influence survival (diabetes, SYNTAX [Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery] score) but not on the presence of NSTE-ACS. The use of CABG varies widely based on patient risk and hospital center; publications from early randomized trials reported CABG rates of 16% to 50% in NSTE-ACS patients. A more recent publication reported that CABG was performed in 10% of NSTE-ACS patients.[165]

THROMBECTOMY FOR NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Although angiographic evidence of thrombus may be present in up to 40% of ACS cases, it is usually not flow occlusive. A single study randomized 440 patients with ACS to adjunctive thrombectomy versus PCI alone.[166] There was no difference in microvascular obstruction as assessed by cardiac magnetic resonance imaging. Thus, routine thrombectomy is not recommended for patients with NSTE-ACS undergoing PCI.

RADIAL ACCESS FOR NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

One of the most common complications of the invasive strategy for NSTE-ACS is a vascular access complication, including bleeding. Although bleeding avoidance strategies include cautious dosing of antithrombotics, radial access has emerged as a valuable approach. Several trials and registries have reported reduction in bleeding using radial compared to femoral access. Valgimigli et al[167] randomized 8404 patients with ACS to radial versus femoral approach and found reductions in MACE and major bleeding as well as improved survival (1.6% vs 2.2%; RR, 0.72; 95% CI, 0.53-0.99; P = .045) in the radial group. The improvement in survival occurred predominantly in the NSTE-ACS group. A meta-analysis of nine studies with 220,126 NSTE-ACS patients[168] found reduction in major bleeding (OR, 0.52; 95% CI, 0.36-0.73; P = .0002), transfusions (OR, 0.61; 95% CI, 0.41-0.91; P = .02), and 1-year mortality (OR, 0.72; 95% CI, 0.55-0.95; P = .02). These data suggest that radial access should be the preferred approach for NSTE-ACS patients undergoing an invasive strategy.

PHARMACOTHERAPY FOR PATIENTS PRESENTING FOR PERCUTANEOUS CORONARY INTERVENTION DURING NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

The primary goal of pharmacotherapy for NSTE-ACS is to alleviate ischemia using antiplatelets, antithrombotics, and adjunctive therapies to reduce myocardial oxygen demand. Pharmacotherapy in NSTE-ACS is crucial for management, because a substantial portion of patients will not immediately undergo coronary angiography and/or revascularization. Here, we summarize these therapies and translate their use into clinical practice.

Oral Antiplatelet Agents

Aspirin Evidence-based guidelines universally advocate that patients with NSTE-ACS should routinely and indefinitely receive low-dose (75-100 mg) non–enteric-coated aspirin, after an initial loading dose of 300 to 325 mg. Aspirin is routinely given to all patients with CAD, and is assumed to equally benefit those undergoing and not undergoing an invasive management strategy.[169,170] Early evidence regarding the benefits of aspirin in the specific context of coronary revascularization arose from ISIS-2 [Second International Study of Infarct Survival], a double-blind, randomized, two-by-two factorial, placebo-controlled trial that evaluated the effect of aspirin as an

adjunct to thrombolysis (streptokinase) in the management of AMI. This large study demonstrated that 1 month of aspirin given alone or in combination with revascularization therapy significantly improved outcomes.[171] It has subsequently been shown that high-dose and low-dose aspirin have equivalent cardiovascular outcomes; thus, low-dose (<150 mg daily) aspirin would seem most prudent in the absence of a direct comparison.[172]

Clopidogrel The addition of ticlopidine to aspirin substantially benefited patients with NSTE-ACS and established dual antiplatelet therapy (DAPT) as the standard of care. Clopidogrel was subsequently developed to circumvent the adverse side effect profile of ticlopidine. The efficacy of clopidogrel was initially studied in the CURE [Clopidogrel in Unstable Angina to Prevent Recurrent Events] trial, which randomized patients in double-blind fashion to receive clopidogrel or placebo.[173,174] Clopidogrel reduced the composite end point of cardiovascular death, MI, and TVR within 30 days of PCI, and the reduction in MACE was maintained to 9 months of follow-up without differences in major bleeding. Studies also demonstrated that pretreatment with clopidogrel improves outcomes for invasively managed NSTE-ACS, with only a modest increase in minor bleeding. Several subsequent trials and meta-analyses have clarified the current preferred loading and maintenance doses of clopidogrel (600 mg followed by 75 mg daily).[175,176] If PCI is not planned for the same day, a 300-mg loading dose may be used.

Prasugrel Prasugrel has a more rapid onset of action and reduced response variability compared with clopidogrel. TRITON-TIMI 38 randomized clopidogrel-naïve patients with moderate- to high-risk ACS undergoing PCI to receive either prasugrel or clopidogrel (both in combination with aspirin). Randomization occurred following ascertainment of coronary anatomy, with the exception of patients with STEMI. At 15 months of follow-up, the primary end point (composite of cardiovascular death, nonfatal MI, or stroke) was lower with prasugrel, driven by nonfatal MI and stent thrombosis. These benefits were somewhat offset by a significant risk of major and fatal bleeding in the prasugrel-treated versuss clopidogrel-treated group. Prasugrel increased mortality in patients with a prior stroke, and as such should not be given to patients with a history of transient ischemic attack or stroke.[177] Additionally, caution should be used in patients with low body weight (< 60 kg) or those > 75 years of age. It should also be noted that the TRILOGY [Prasugrel Versus Clopidogrel for Acute Coronary Syndromes without Revascularization] trial showed that there was no benefit of prasugrel compared with clopidogrel in ACS patients without ST elevation not undergoing PCI, and as such, it is not recommended in guidelines for NSTE-ACS without PCI.

Ticagrelor Ticagrelor was developed as the first reversible nonthienopyridine in an effort to avoid the variable pharmacokinetics of clopidogrel and the adverse safety profile of prasugrel. The PLATO trial randomized ACS patients to receive ticagrelor or clopidogrel. Patients with moderate- to high-risk ACS received an additional, blinded loading dose of clopidogrel or its placebo. At 12 months, ticagrelor significantly reduced the primary end point (cardiovascular death, nonfatal MI, or stroke), driven by reductions in cardiovascular mortality, nonfatal MI, and stent thrombosis without any difference in overall bleeding. An adenosine-mediated mechanism has been suggested for the survival benefit, and improved endothelial function has been found in separate studies with this agent. Major bleeding was higher in ticagrelor-treated patients, including fatal intracranial hemorrhage, but not all-cause fatal bleeding. Several adverse effects with ticagrelor were observed and were associated with discontinuation of therapy, including acute episodic dyspnea, bradycardia (rarely), and elevated serum creatinine and uric acid.[178] Because adverse events may be mediated by adenosine, taking the medication with coffee has been suggested. Lastly, patients taking > 100 mg of aspirin daily had increased bleeding rates with ticagrelor, and as such, aspirin doses < 100 mg are recommended.

Pretreatment With Oral Antiplatelet Agents Administration of clopidogrel prior to PCI is known to improve outcomes. The PCI-CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study revealed that patients who received pre-PCI treatment with clopidogrel had reduced cardiovascular death, MI, and stent thrombosis when compared with placebo.[174] This can be explained by clopidogrel's slow onset, which is circumvented by early administration. In the ACCOAST [A Comparison of Prasugrel at PCI or Time of Diagnosis in Patients With Non-ST Elevation Myocardial Infarction] trial, pretreatment with prasugrel did not decrease ischemic complications when compared with administration at the time of PCI and was associated with higher risk for major bleeding.[179] Prasugrel has a very fast onset, thereby rendering pretreatment unnecessary. Pretreatment with ticagrelor has only been studied in the STEMI PCI patient population, and given its rapid onset of action, pretreatment also did not result in any significant net clinical benefit compared to "on the table" administration.

Duration and Interruption of Oral Dual Antiplatelet Therapy Based on guidelines and available data, we recommend at least 1 year of continuous DAPT in patients with NSTE-ACS and continuation as needed for patients with a low risk of bleeding. For patients with high bleeding risk, lower doses of prasugrel (5 mg daily) and ticagrelor (60 mg twice daily) are available if clinical judgement points to long-term use of a lower dose. Despite these recommendations, "real-world" practice often necessitates DAPT interruption within a year of PCI.[180] The context and process of making this decision are important to review; if DAPT is interrupted based on a specific physician-driven decision based on a new clinical development, outcomes were not unfavorable; however, if the DAPT course was disrupted without cardiologist input, then major complications occurred within a week. If DAPT interruption is warranted (eg, for an urgent noncardiac surgery), then clopidogrel is stopped for 5 days, prasugrel for 5 to 7 days, and ticagrelor for 5 days (despite its pharmacokinetic "reversibility"). Individual patient responses may vary, and platelet reactivity testing has been suggested to guide the timing of surgery but without a clinically proven algorithm.

Intravenous Antiplatelet Agents

Cangrelor Cangrelor is an IV rapid-onset and rapidly reversible $P2Y_{12}$ inhibitor, making it a special agent for acutely ill patients who are unable to take or absorb oral medications. It achieves almost complete and immediate inhibition of ADP-induced platelet aggregation when administered as a bolus of 30 μg/kg, and continuous infusion sustains the high degree of inhibition. The plasma half-life is approximately 3 to 5 minutes, normal platelet function is restored within 1 hour after cessation of the infusion, and it has been studied in high-risk patients awaiting CABG.[181] The rapid cessation is also beneficial if patients suffer a life-threatening complication. After initial trials showed favorable bleeding profiles, the CHAMPION-PHOENIX (Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Patients Who Require PCI) study, a randomized, double-blind, double-dummy trial, was designed to evaluate the efficacy of cangrelor against clopidogrel loading during PCI in patients who had not previously received a $P2Y_{12}$

antagonist (including patients with stable angina and ACS). A composite end point of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours was lower in the cangrelor group compared with the clopidogrel group, driven by the reduction of acute periprocedural MI and particularly intraprocedure stent thrombosis; there were no differences in adverse events.[182] Future studies are needed to determine the optimal way to transition ACS PCI patients from cangrelor to oral $P2Y_{12}$ inhibitors.

Glycoprotein IIb/IIIa Inhibitors A large number of trials before the era of DAPT showed that patients undergoing angioplasty (greatest benefit) or stent experienced lower ischemic events, mainly driven by reduction in MI, when receiving adequately dosed GP IIb/IIIa inhibitors (GPIs) combined with UFH instead of UFH alone. In a head-to-head trial, abciximab was found to be superior to tirofiban during PCI.[183] Currently, GPIs (particularly eptifibatide and tirofiban) are indicated at the time of PCI in high-risk patients, whether or not they have been pretreated with a $P2Y_{12}$ inhibitor. GPI use has been limited as a result of high bleeding with GPIs because of the long post-PCI infusion and their delayed reversibility in case of an acute bleed (only by platelet transfusions with abciximab and with a 4- to 6-hour half-life for tirofiban and eptifibatide). GPIs are infrequently used as pretreatment in NSTE-ACS patients who receive DAPT and have intermediate- or high-risk features, as both the EARLY-ACS [Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome] and ACUITY-Timing [Acute Catheterization and Urgent Intervention Triage Strategy Timing] studies showed no benefit to upstream GPI use in all ACS patients versus "on the table" administration only in those patients undergoing PCI.[184,185] If a patient has high-risk features, ongoing ischemia, and a long time to PCI (eg, patient awaiting transfer to a PCI-capable center), it is reasonable to initiate GPI therapy while awaiting PCI. Renal dose adjustment is important for eptifibatide and tirofiban safety because these and other agents are often incorrectly dosed in patients with renal dysfunction.[186]

Antithrombotic Agents

Anticoagulation is recommended for all NSTE-ACS patients undergoing PCI at the time of diagnosis (class I practice guideline).[170] This is typically administered in the ED or in the cardiology unit as an IV infusion of UFH or a subcutaneous injection of low-molecular-weight heparin; the former requires dose adjustment to target an activated partial thromboplastin time of 50 to 70 seconds but may be more flexible (faster elimination) if an interruption is necessary. The latter does not require monitoring, but a dose reduction according to the renal function is pertinent, and the elimination half-life is many hours.

Parenteral anticoagulants used in patients with NSTE-ACS undergoing PCI include UFH (most commonly, 50 U/kg bolus followed by an infusion for partial thromboplastin time of 50-70 seconds), low-molecular-weight heparin (usually enoxaparin 0.3 mg/kg IV bolus or 1 mg/kg every 12 hours in the absence of renal failure), bivalirudin (with PCI, 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion; with dose reduction in renal failure), and fondaparinux (typically used without PCI). Heparin and bivalirudin are the agents of choice in the United States for patients undergoing an invasive approach because of their rather short half-lives in comparison to the longer elimination time of other agents, which may complicate arterial sheath removal timing after PCI.[187] In a recent meta-analysis of available trials comparing bivalirudin and heparin, the use of bivalirudin was associated with increased risk of stent thrombosis (mostly in STEMI patients, within a few hours of PPCI) but was associated with significantly less bleeding than heparin; however, the risk of bleeding was attenuated with transradial access rather than femoral access and when potent oral $P2Y_{12}$ inhibitors rather than GPIs were used.[188]

A recent large trial in ACS patients treated with a mostly radial approach for PCI (which has been shown to lower access site–related bleeding) has shown similar composite cardiovascular outcomes between heparin and bivalirudin during PCI, lower bleeding, and lower total mortality. A post-PCI bivalirudin infusion appeared to limit acute stent thrombosis with this agent in STEMI.[189]

Other Adjunctive Therapies

In addition to antiplatelets and antithrombotics, adjunctive therapy with oxygen is empirically administered in all patients, and especially for patients with oxygen saturation < 90%. If patients are experiencing ischemic chest discomfort, sublingual or IV nitroglycerin can be used. β-Blockade should be initiated within 24 hours to reduce heart rate, contractility, and blood pressure, as long as patients are not experiencing heart failure or low output, are at increased risk of cardiogenic shock, or have other contraindications to β-blockade.[190] Nondihydropyridine calcium channel blockers can be administered to reduce myocardial oxygen demand if β-blockers are contraindicated (eg, as a result of bradycardia or wheezing). Lastly, high-intensity statin therapy with either atorvastatin 80 mg or rosuvastatin 40 mg should be administered as soon as possible in patients presenting with NSTE-ACS. The PROVE-IT TIMI 22 [Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22] trial revealed that patients who are treated with a high-intensity statin have reduced rates of recurrent MI, coronary heart disease mortality, need for revascularization, and stroke than patients treated with a moderate- or low-intensity statin.[191]

CONCLUSIONS

In the 20th century, an explosive increase in deaths as a result of heart disease occurred in the United States (Fig. 42–12). The deaths were overwhelmingly related to ischemic heart disease and AMI. This epidemic became rampant after World War II and spawned a massive effort to understand and develop new therapies. Once acute thrombotic occlusion was recognized as the inciting event, therapies including coronary bypass, PCI, and thrombolytic therapy were developed in the last quarter of the 20th century. These therapies, control of risk factors, and treatment of elevated lipids have resulted in substantial reduction in cardiac deaths. The trend started in 2000 and has continued.

Shah et al[192] have found that PPCI use increased from 53% to 80% of STEMI interventions in a sample of all nonfederal hospitals in the United States from 2003 to 2011. This has been associated with a 25% reduction in hospital death rates. This decrease in risk of death occurred despite the fact that a significant increase in myocardial infarction occurred for patients older than 85 years.[193] Krumholz et al[194] have demonstrated that from 1999 to 2013, as cardiac deaths have decreased, overall Medicare expenditure has dropped.

The most conclusive proof of national benefit to widespread use of PPCI comes from the comparison of the contemporary Swedish and British experience. National comprehensive databases allow detailed analysis of volumes and mortality. Chung et al[195] report that Sweden adopted PPI more rapidly than Britain. Between 2004 and 2010, an excess of 10,000 deaths occurred in Britain. The largest difference in mortality occurred in 2004 when PPCI was more widely adopted in Sweden. By 2010, 50% of STEMI patients in both countries were treated with PPCI, and mortality rates were equivalent.

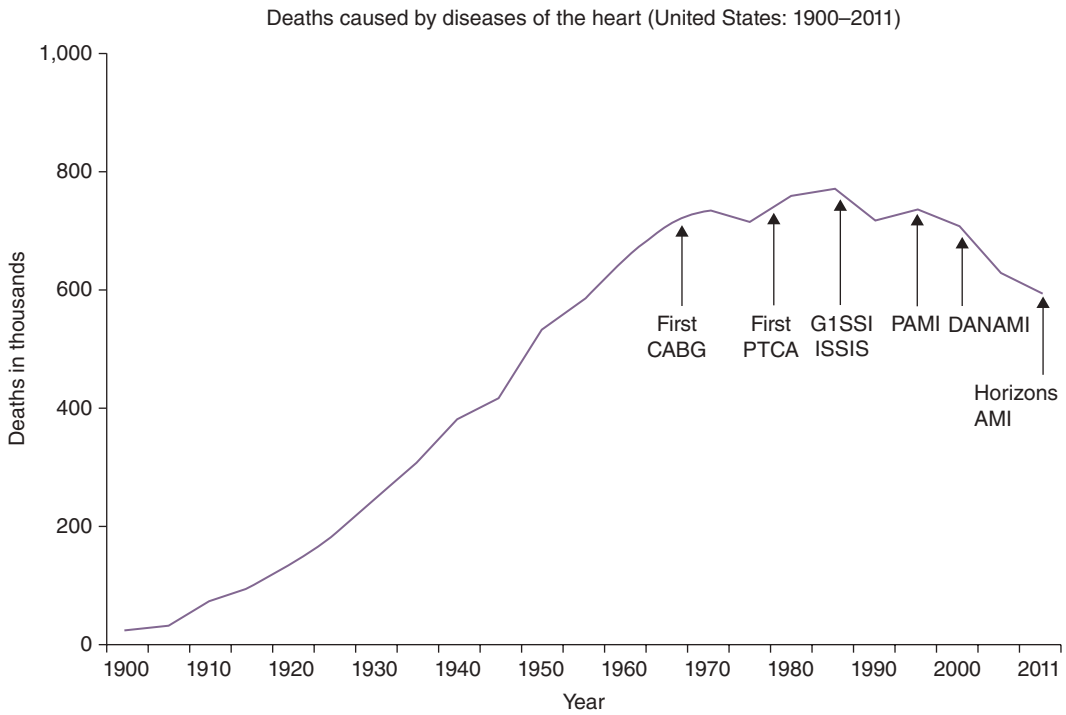

FIGURE 42–12. Heart disease deaths by year are depicted. Deaths have decreased in part as a result of increased usage of reperfusion therapy of ST-segment elevation myocardial infarction. In particular, increased use of primary percutaneous coronary intervention has been associated with lower mortality. CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.

Overall, these observations strongly suggest that the decline in cardiac death that started in 2000 in the United States has been strongly related to widespread adoption of timely reperfusion therapy.

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CHAPTER 43

THE EVALUATION AND MANAGEMENT OF STABLE ISCHEMIC HEART DISEASE

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Stable ischemic heart disease (SIHD) is a major public health concern in most developed nations and has become a leading cause of death and disability in high- as well as low- and middle-resource countries.[1] Thrombosis complicating an atherosclerotic plaque is the proximate cause of acute myocardial infarction (MI) in patients with coronary artery disease (CAD) and represents the leading cause of death for men and women worldwide.[2] Globally, CAD accounts for 7.4 million deaths annually, and in the United States, it is responsible for one in seven deaths per year, which in 2013 totaled approximately 370,200 fatalities.[3] Despite advancements in the identification of atherosclerotic risk factors and effective therapies for primary and secondary prevention, it is estimated that annually 660,000 Americans are hospitalized or die from an initial MI, 305,000 suffer from recurrent MI, and an additional 160,000 individuals develop a clinically silent MI.[3] In these patients, the transition from a clinically stable coronary atherosclerotic substrate to an acute life-threatening event remains a focus of intense investigation spanning genetic, basic, translational, and epidemiologic avenues of scientific exploration.[4] In addition, there is an imprecise temporal and biological boundary on the other end of the clinical spectrum from acute coronary syndrome to SIHD. This chapter reviews methods for diagnosing CAD, the clinical profile of patients affected by SIHD, and predictive models for assessing risk to inform treatment. Findings from contemporary landmark clinical trials that have influenced the use of specific medical, percutaneous, surgical, and hybrid treatments will also be discussed.

OVERVIEW OF STABLE ISCHEMIC HEART DISEASE

ETIOLOGY AND CLASSIFICATION

Myocardial ischemia is mediated by an imbalance between oxygen supply and demand at the cardiomyocyte cellular level (see Chap. 34). Coronary atherosclerosis impairs coronary blood flow (CBF) via a variety of mechanisms and is the dominant cause of angina under conditions of elevated myocardial oxygen demand, such as exercise or emotional stress. However, CBF is impaired even in the absence of epicardial CAD in several other disease states, including severe aortic valve disease with left ventricular hypertrophy (LVH), systemic hypertension, idiopathic dilated cardiomyopathy, and hypertrophic cardiomyopathy. In patients with LVH, ischemia may result from a combination of inadequate capillary density, pathologic changes within small intramyocardial arteries and arterioles, reduced coronary flow reserve, systolic compressive forces, and markedly elevated diastolic pressures within the vulnerable subendocardium. Nonobstructive epicardial CAD may nevertheless result in endothelial dysfunction and impaired coronary flow reserve, which is a major mechanism underlying the expression of microvascular angina. A primary reduction in myocardial oxygen supply following intraluminal thrombus formation and/or epicardial constriction underlies the development of acute coronary syndromes (Table 43–1). There are other, nonatherosclerotic causes of abrupt reductions in CBF, including spontaneous dissection and embolization. Chronic reductions in oxygen supply may also occur with severe, diffuse, and extensive CAD, resulting in myocardial hibernation. Oxygen supply can also be reduced in the setting of severe anemia or hemoglobinopathies, and under these circumstances, the threshold for developing ischemia or myocardial injury can be lowered. The major determinants of myocardial oxygen demand are heart rate, wall stress, and contractility. These factors may act singularly or in combination to trigger an ischemic cascade in a vulnerable patient.

TABLE 43–1. Conditions Provoking or Exacerbating Ischemia

Increased Oxygen Demand	Decreased Oxygen Supply
Noncardiac	*Noncardiac*
Thyroid dysfunction	Anemia
Sympathomimetic toxicity (cocaine)	Hypoxemia: pneumonia, asthma, COPD, pulmonary hypertension, IPF, OSA
Hypertension	Sickle cell anemia
Anxiety	Hyperviscosity
Arteriovenous fistulae	Polycythemia
Cardiac	*Cardiac*
Hypertrophic cardiomyopathy	Aortic stenosis
Aortic stenosis	Hypertrophic cardiomyopathy
Dilated cardiomyopathy	High-grade coronary artery obstruction
Tachycardia	Microvascular circulatory disease

Abbreviations: COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; OSA, obstructive sleep apnea.

Adapted with permission from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/ PCNA/SCAI/ STS Guidelines for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society of Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.

CLINICAL FEATURES

For over two centuries, it has been recognized that cardiac angina can be diagnosed effectively by a careful patient interview. William Herberden is credited with the initial description of angina in 1772 in his chapter entitled, "Pectoris Dolor," in *Commentaries on the History and Cure of Diseases*.[5] Remarkably, several elements from this original characterization of cardiac angina remain pertinent to the management of CAD today. Herberden correctly identified that certain descriptive features of angina, such as the occurrence of chest pain at rest, portend a particularly grave prognosis.

The Canadian Cardiovascular Society (CCS) classification, now four decades old, remains the most commonly used system for grading angina severity (Table 43–2).[6] Increasing CCS class positively correlates with the number of diseased epicardial coronary arteries discovered at angiography, the presence of impaired left ventricular (LV) function, and need for revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery.[7] The CCS classification system can also be used to predict outcome in patients with chronic CAD: compared with CCS class I status, CCS class IV status is associated a significant increase in all-cause mortality and nonfatal MI 30 months following revascularization.[7] However, CCS class alone does not necessarily inform clinical decision making in patients with SIHD. Although it has major impact upon quality of life, other factors in addition to symptom severity determine survival and may dictate the therapeutic approach.[8] In fact, data suggest that qualitative descriptions of symptoms alone may be inaccurate in diagnosing CAD.[8,9] This is particularly the case for patients with who do not report chest pain, but in whom the sole symptom at presentation is jaw, neck, ear, arm, or epigastric discomfort. Among this constellation of cardiac angina equivalent symptoms, exertional dyspnea should be considered a potentially high-risk finding as a result of the association between this symptom and adverse outcome in patients with CAD.[9] These observations have prompted the consideration of alternative diagnostic strategies that link angina classification with CAD burden directly. For example, a modification of the Diamond-Forrester approach, which considers the likelihood of CAD based on various clinical risk factors, was demonstrated to predict angiographically proven obstructive CAD effectively if age and sex were added to angina type (eg, typical or atypical).[10] This approach may be particularly important given differences in clinical presentation between men and women. Compared to men, women are less likely to present with typical angina symptoms, but more likely to present with throat, jaw, or neck pain, shortness of breath, fatigue, and nonchest discomfort.[11] In complimentary work, analyzing levels of high-density lipoprotein, aspartate aminotransferase, and high-sensitivity C-reactive protein (HS-CRP) increased the accuracy of the use of age, sex, and angina type for predicting functionally significant CAD.[12]

ASYMPTOMATIC ISCHEMIA

Myocardial ischemia is characterized as asymptomatic, or *silent*, when it occurs in the absence of angina or an anginal equivalent.[13] When present, asymptomatic ischemia is correlated positively with

TABLE 43–2. The Canadian Cardiovascular Society Angina Scale

I	II	III	IV
Ordinary physical activity does not cause angina including: Walking and climbing stairs	Slight limitation of ordinary activity including: Walking stairs rapidly; Walking uphill; Stair climbing after meals	Marked limitation of ordinary physical activity.	Inability to perform any physical activity without discomfort.
Angina occurs: Only with strenuous, rapid, or prolonged exertion at work or recreation	*Angina occurs:* A few hours after awakening; Walking > 2 city blocks (level ground); Walking 1 flight of ordinary stairs at a normal pace	*Angina occurs:* Walking ≤ 1 city block (level ground); Climbing one flight of stairs under normal conditions and at a normal pace	*Angina occurs:* With minimal activity; May be present at rest

Adapted with permission from Naghavi M1, Libby P, Falk E, et al: From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003 Oct 7;108(14):1664-1672.

incident ischemic heart disease and confers an unfavorable prognosis.[14] The pathophysiology of asymptomatic ischemia remains controversial. Leading contemporary theories emphasize the presence of defective sensory afferent nerve function, which impairs normal sensory conduction from the atria and ventricles to the thoracic sympathetic ganglia and dorsal roots of the spinal cord. Asymptomatic ischemia is frequently observed among patients with diabetes, presumably due to the associated neuropathy. Other patient populations at risk for asymptomatic ischemia include those with a previous MI.[15] Cohn and colleagues[13] estimate that 50,000 patients per year experience an asymptomatic MI within 30 days of an initial event. Asymptomatic ischemia occurring during the hospital phase of MI is predictive of future cardiovascular events over the next 5 years.[13] Early repolarization pattern on electrocardiography has also been linked to CAD in asymptomatic populations.[16] In selected patients with SIHD, the prognostic value of asymptomatic ischemia on treadmill exercise stress testing is similar to that associated with symptomatic ischemia, particularly when present at low workloads.[17,18] Ischemia is detected in nearly twice as many asymptomatic patients with diabetes compared to age- and gender-matched patients without diabetes when myocardial perfusion imaging is added to conventional exercise electrocardiogram (ECG) testing,[19] clarifying further the scope of asymptomatic ischemia in at-risk patients.

Although abnormalities in ankle-brachial index, carotid intimal thickness, HS-CRP level, and coronary artery calcification burden may have important implications for the identification of vascular disease, which is strongly associated with myocardial ischemia in asymptomatic patients, the utility of analyzing these factors in asymptomatic populations for the purpose of revascularization remains unresolved.[20] This dilemma is reinforced by findings from a small retrospective subgroup analysis of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial in which the addition of PCI to optimal medical therapy (OMT) was not associated with a definitive decrease in nonfatal cardiac events or death compared to OMT alone in patients with *silent* myocardial ischemia[21] (see later section on COURAGE trial). Therefore, implementation of clinical management strategies beyond conventional primary and secondary prevention are not recommended currently across the spectrum of asymptomatic patients, although advanced diagnostic and therapeutic measures may be appropriate in selected individuals at intermediate risk (ie, global risk estimate for hard clinical events of ~10%-20% over 10 years).

HEART FAILURE, ARRHYTHMIAS, AND EMBOLIC DISEASE

Impaired LV systolic function is the primary cardiovascular form of end-organ damage in patients with SIHD. Systolic heart failure (HF), or heart failure with reduced ejection fraction (HFrEF), is most likely to occur under conditions in which ≥ 20% of myocardium is injured from chronic ischemia or prior MI(s). Longitudinal remodeling of cardiomyocytes following ischemic injury promotes adverse changes to LV geometry, including elongation and dilation, which together with replacement fibrosis, impair LV systolic function. Diminished contractile performance, stroke volume, and cardiac output result in overactivation of the renin-angiotensin-aldosterone axis and neurohumoral signaling, which, collectively, cause detrimental effects on cardiac and systemic vascular function.[22] The aggregate consequences of these changes include an unfavorable hemodynamic profile that promotes increased myocardial oxygen demand and LV afterload, which, in turn, propagate further ischemic injury and clinical HF. The role of medical therapy to attenuate ischemia as a trigger of HF is discussed below. See Chap. 68 for a review of the pathophysiology of HF and Chap. 70 for the broader use of β-adrenergic receptor antagonists, renin-angiotensin-aldosterone inhibitors, nitrates/hydralazine, and diuretics for management of HF with reduced LV systolic function.

Ischemic Mitral Regurgitation

Mitral regurgitation (MR) from ischemia-mediated LV remodeling occurs as a consequence of papillary muscle displacement, leaflet tethering, and/or annular dilatation and is strongly associated with HF and poor long-term outcomes in a graded fashion. The optimal treatment of ischemic MR remains controversial, particularly since this is not primarily a valvular disorder but develops as a consequence of LV dysfunction and adverse remodeling. Restrictive annuloplasty with a downsized rigid ring constitutes the standard surgical approach. Smith and colleagues[23] examined the role of mitral valve repair at the time of CABG surgery. Among 301 patients with *moderate* ischemic MR (as assessed by an integrative echocardiographic method), the addition of mitral valve repair to CABG surgery did not improve indexed LV end-systolic volume, 1-year mortality, or major adverse cardiac and cerebrovascular events (MACCE) compared to CABG surgery alone, but was associated with a significant increase in cardiopulmonary bypass time, longer postoperative hospital length of stay, and significantly more early neurologic events and supraventricular arrhythmias.[23] Significantly fewer patients who underwent CABG with repair had recurrent moderate or severe MR at 1 year (11%), compared with patients who had CABG alone (30%), yet fully 70% of the latter group had none, trace, or mild MR at 1 year. Two-year outcomes were similar between groups.[24] Accurate predictors of the response to CABG alone are needed. For patients with *severe* ischemic MR, no differences in LV end-systolic volumes or MACCE were reported at 1- and 2-year follow-up among 251 patients randomized to mitral valve replacement or repair.[25,26] Of note, in patients with severe ischemic MR, mitral valve repair resulted in a significantly increased risk of recurrent moderate or severe MR, more HF events and cardiovascular readmissions, and a trend to reduced quality of life. These findings have prompted reevaluation of surgical treatment for ischemic MR late after MI. Device therapy for ischemic MR is under active investigation in the United States.

Ischemic Cardiomyopathy

The role of surgical revascularization in patients with ischemic cardiomyopathy has also been addressed. The Surgical Treatment for Ischemic Heart Failure (STICH) trial evaluated the role of CABG surgery in patients with decreased LV systolic function (LV ejection fraction [LVEF] ≤ 35%) and CAD.[27] In this study, 127 clinical sites from 26 countries contributed a total of 1212 patients (median LVEF = 28%) who were largely CCS class II/III and New York Heart Association (NYHA) functional class II/III. Compared to OMT, the primary end point of death from any cause at a median follow-up of 56 months was not significantly different in patients randomized to CABG surgery plus OMT (41% vs 36%; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.72-1.04; $P = .12$), although the combined end point of death from any cause or hospitalization for cardiovascular causes occurred significantly less often in the CABG group (HR, 0.74; 95% CI, 0.64-0.85; $P < .001$). At a median follow-up of 9.8 years, however, the rates of death from any cause, death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes were significantly lower among patients who underwent CABG.[28] In a nonrandomized substudy of the STICH trial, the role of preoperative viability testing assessed by single-photon emission computed tomography (SPECT) or dobutamine stress echocardiography was assessed. The presence of viability as defined in this study did not identify a

group of patients who had a differential response to CABG.[29] Identifying specific subgroups of ischemic cardiomyopathy patients for whom surgical revascularization may be beneficial remains an important topic for future clinical trial investigations.

Ischemic heart Failure, Pulmonary Hypertension, and Thromboembolism

Pulmonary hypertension (PH), defined currently[30] as a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg, is an independent risk factor for mortality in patients with HF as a result of ischemic heart disease. In this scenario, left atrial hypertension due to impaired LV systolic function induces pulmonary vascular congestion and is linked to right HF.[31] Atrial fibrillation is the most common arrhythmia among patients with ischemic HF; ventricular tachycardia is of greatest clinical concern. Sustained monomorphic ventricular tachycardia may arise in or near an area of myocardial scar formation, whereas polymorphic ventricular tachycardia or ventricular fibrillation may occur as a consequence of acute ischemia, electrolyte imbalance, or drug effect. Indeed, unstable ventricular arrhythmias may occur in SIHD patients even in the absence of significant changes in clinical status. Patients with atrial fibrillation (see Chap. 83) or those with specific, acquired forms of structural heart disease (eg, LV aneurysm or LV apical akinesis) are at increased risk for systemic thromboembolism. Anticoagulant therapy is indicated for stroke prevention according to the patient's individualized risk profile and in alignment with published clinical management guidelines.

FACTORS THAT PROMOTE THE PROGRESSION OF CHRONIC CORONARY ARTERY DISEASE

Coronary atherosclerotic plaque formation occurs as a consequence of aberrant molecular signaling pathways that increase vascular inflammation, induce injury to blood vessel wall cellular components, and promote adverse vascular remodeling.[32] An understanding of the cellular mechanisms that contribute to atherogenesis has helped focus efforts on imaging modalities for detection and characterization of CAD. Cardiac computed tomography (CT) is very sensitive for the detection of coronary artery calcifications, the imaging signature of chronic atherosclerosis.[33] Molecular imaging techniques for quantitative evaluation of plaque inflammation may help identify at-risk lesions in vulnerable patients, but are not used in routine practice. Progress in catheter-based infrared fluorescence, plaque thermography, contrast-enhanced magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography (PET) suggests that clinical applicability of these modalities for real-time diagnosis and enhanced characterization of CAD may be realized.[34,35] For example, ^{18}F-sodium fluoride PET, which localizes to osteogenic (ie, calcific) activity, has been used to delineate culprit from nonculprit coronary lesions in small clinical studies.[36] Coupling intravascular ultrasound with high-resolution optical coherence tomography in a single device has also been used in vivo and paves the way for simultaneous near-field assessment of vascular wall contour and plaque penetration depth.[37]

THE VULNERABLE PLAQUE/VULNERABLE PATIENT

Predicting future cardiovascular events in patients with CAD remains a difficult task. The identification of specific patients who are at elevated risk for acute MI as a result of the presence of certain atherosclerotic lesion characteristics and/or clinical factors is a central focus of evaluation and management strategies in clinical practice. Ongoing research is focused on discriminating at-risk atherosclerotic lesions based on propensity for rupture, rapid progression in size, or the expression of other features that suggest a high likelihood for future thrombotic complications.[34] Collectively, these characteristics describe a *vulnerable plaque*, a lesion the attributes of which predict a higher likelihood of thrombosis, MI, and/or ventricular arrhythmias (see Chap. 37 for detailed discussion of myocardial ischemia and MI). Active inflammation, large lipid core and thin fibrous cap, and luminal stenosis of > 90% are some of the key criteria used to identify the vulnerable plaque (Table 43–3). Although plaque risk stratification remains within the preclinical domain, there is accumulating evidence to suggest that cutting-edge diagnostic methods may be able to discern plaque stability in patients in the future. In one study of 203 patients undergoing coronary angiography, an increased lipid plaque burden index detected by near-infrared spectroscopy was independently associated with future major adverse cardiac events.[38] Similar findings are reported for cardiac CT coronary angiography, in which the relationship between certain plaque features (eg, luminal stenosis, positive remodeling, low-attenuation plaques) and adverse clinical events has been demonstrated in studies involving over 21,000 CAD patients.[39]

In the current era, widespread use of statin therapy has attenuated the inflammatory burden of atherosclerotic lesions, which has led some to emphasize other mechanisms, particularly factors promoting superficial erosion leading to fibrous remodeling, for defining the vulnerable plaque. This proposed shift may provide a pathobiological correlate to trends suggesting a recent decrease in the prevalence of ST-segment elevation MI (STEMI) (ie, plaque rupture) with a corresponding relative increase in the prevalence of non–ST-segment elevation MI (NSTEMI) in which culprit lesions tend to be fibrous (see Chap. 37 for pathobiology of MI).[32] In addition, the vulnerable plaque concept has been expanded in recent years to include *vulnerable patients* at risk for an acute coronary syndrome (ACS) or sudden cardiac death (SCD) based on their metabolic, atherogenic, hematologic, and/or myocardial substrate. Examples include patients with metabolic syndrome, CAD, and hypercoagulable disorders, and patients with certain forms of cardiomyopathy that predispose to electrical-mechanical instability and unstable arrhythmias.[32,34]

CONVENTIONAL RISK FACTORS

There is a great deal of overlap between conventional risk factors associated with the de novo development of atherosclerosis and those that promote progression of existing disease. Identifying treatable risk factors in

TABLE 43–3. Criteria for Defining Vulnerable Plaque

Major criteria
Active inflammation (eg, monocyte, macrophage, ± T-cell infiltration)
Thin cap with large lipid core
Endothelial denudation with superficial platelet aggregation
Fissured plaque
Luminal stenosis > 90%
Minor criteria
Superficial calcified nodule
Glistening yellow appearance (pathologic diagnosis)
Intraplaque hemorrhage
Outward remodeling
Endothelial dysfunction

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patients with chronic CAD should be accomplished as recommended by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for secondary prevention and cardiac rehabilitation.[40] These guidelines call for a nine-point strategy focused on specific biochemical, psychosocial, and exercise training–associated goals to decrease the progression of chronic CAD and its manifestations (Table 43–4). Interventions that decrease the incidence of ischemic events include those that lead to reductions in cigarette smoking, low-density lipoprotein (LDL) cholesterol, systemic hypertension, LVH, and factors that promote thrombosis.

HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

Numerous observational studies have demonstrated a positive, continuous, and graded relationship between systemic blood pressure and cardiovascular disease risk.[41,42] In SIHD patients, hypertension is a risk factor for recurrent MI, an observation that is likely a consequence of the associated endothelial dysfunction and the adverse effects of persistently elevated afterload on myocardial function and oxygen demand. In patients with diabetes, uncontrolled hypertension is a strong predictor of premature death, cardiovascular morbidity, and progressive nephropathy. The Systolic Blood Pressure Intervention Trial (SPRINT) tested whether the conventional systolic blood pressure (SBP) goal of 140 mm Hg is sufficient to reduce cardiovascular events in nondiabetic, nonstroke patients at increased cardiovascular risk. Compared to a standard treatment goal SBP < 140 mm Hg, patients randomized to intensive therapy (SBP < 120 mm Hg) had lower risk for the composite end point of MI, other ACSs, stroke, HF, or death from cardiovascular causes at 1 year (HR, 0.75; 95% CI, 0.64-0.89; $P < .001$). Directionally similar findings were observed for all-cause mortality, although the beneficial effects of intensive therapy were associated with an attendant increase in the number of medications prescribed, systemic hypotension, syncope, electrolyte abnormalities, and acute kidney injury.[43]

The presence of LVH or increased LV mass confers an increased risk for incident MI, HF, and SCD in patients with SIHD, as well as in community-based populations of adults free of known CAD.[44,45] It has been proposed that the risk imposed by LVH may be reversible. For example, ECG evidence of LVH *regression* in treated hypertensive patients is associated with a significant reduction in cardiovascular disease event rates.[46]

SOCIOECONOMIC, ENVIRONMENTAL, AND IATROGENIC FACTORS

Early Life Programming and Ischemic Heart Disease

In addition to the conventional risk factors associated with coronary heart disease events discussed earlier, novel associations between environmental risk factors and the progression of ischemic heart disease have been identified. Barker and Osmond[47] first proposed that perinatal factors such as low birth weight or intrauterine growth restriction increased the risk for chronic cardiovascular disease in adulthood. These findings are supported further by recent data suggesting, more specifically, that birth weight < 2500 g or > 3500 g forecasts subclinical atherosclerosis in adulthood, as assessed by abnormal carotid intima medial thickness.[48]

Socioeconomic Factors, Geography, Environmental Exposures, and Ischemic Heart Disease

An inverse association between income status or education level and revascularization has been reported in the United States,[49] whereas Gerber and colleagues[50] demonstrated that low socioeconomic status and limited access to health care confer a significantly elevated risk for adverse long-term (~10 years) outcome in post-MI patients.[51] Chronic exposure

TABLE 43–4. Summary of the Core Components of Cardiac Rehabilitation/Secondary Prevention Programs

Core Component	Objective
Patient assessment	**Medical history**: Review cardiovascular, medical, and surgical diagnoses, comorbidities, symptoms of cardiovascular disease, and medications.
	Physical examination: Assess cardiopulmonary systems, postcardiovascular procedure wound sites, orthopedic and neuromuscular status, and cognitive function.
	Testing: ECG testing should occur when appropriate.
Nutritional counseling	**Evaluation:** Assess daily caloric intake, dietary content of saturated fat, trans fat, cholesterol, sodium, and nutrients. Evaluate dining habits.
	Weight management: For patients with body mass index > 25 kg/m^2 and/or waist > 100 cm in men and 88 cm in women, establish short- and long-term weight reduction goals (eg, 1-2 lb/wk over 6 mo to achieve ≥ 5% reduction in body weight).
Blood pressure management	**Evaluation:** Measure seated resting blood pressure at ≥ 2 visits and in both arms.
	Intervention: For blood pressure 120-139/80-89 mm Hg, recommend key lifestyle modifications (eg, weight loss, alcohol consumption reduction).
	For blood pressure ≥ 130/≥ 80 mm Hg, pharmacotherapy may be appropriate in addition to lifestyle modification in the setting of comorbid chronic kidney disease, heart failure, or diabetes.
	For blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic, recommend lifestyle modification and pharmacotherapy.
Lipid management	**Evaluation:** Obtain fasting measures of total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. Evaluate lipid-lowering medication compliance.
	Intervention: Initiate or intensify lipid-lowering therapy in patients with a measured low-density lipoprotein level > 100 mg/dL, or > 70 mg/dL if enhanced therapy can be safely provided. Initiate interventions directed toward management of triglycerides to attain non–high-density lipoprotein cholesterol < 130 mg/dL.
Diabetes management	**Evaluation:** Confirm presence or absence of diabetes. For patients with diabetes, educate patients regarding signs and symptoms suggestive of hyperglycemia or hypoglycemia.
	Intervention: Lifestyle modification and diabetes treatment should occur in accordance with recommendations outlined by the American Diabetes Association.[a]
Tobacco cessation	**Evaluation:** Assess smoking status and use of other tobacco products. Determine readiness to change tobacco use habits.
	Intervention: If readiness to change tobacco habits is not expressed, provide motivational message. If readiness to change is expressed, individual or group counseling, pharmacologic, or supplemental strategies (eg, hypnosis) may be appropriate.

(*continued*)

TABLE 43–4. Summary of the Core Components of Cardiac Rehabilitation/Secondary Prevention Programs (*Continued*)

Core Component	Objective
Psychosocial management	**Evaluation:** Identify the presence of psychological distress (eg, depression) or the use of psychotropic medications. **Intervention:** Offer individual or group education and counseling on the adjustment to heart disease. Refer patients with clinically significant psychosocial distress to appropriate mental health specialists for further evaluation.
Physical activity	**Evaluation:** Assess current physical activity level and readiness to change physical activity behaviors. **Intervention:** Encourage patients to perform 30-60 min/d of moderate-intensity physical activity on ≥ 5 d/wk. Caution patients to avoid performing unaccustomed vigorous physical activity.
Exercise training	**Evaluation:** A symptom-limited exercise test should be performed prior to participation in an exercise-based cardiac rehabilitation program. **Intervention:** Develop an individualized exercise prescription for aerobic and resistance training that is based on evaluation findings, risk stratification, and comorbidities.

[a]American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care*. 2003;26:S33-S50.

Abbreviation: ECG, electrocardiogram.

Data from Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update. A scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology, the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism, and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2007;115:2675-2682.

to air pollution (ie, fine particulate pollution) is also associated with an increased risk of coronary heart disease mortality that is believed to occur as a consequence of increased vascular inflammation or dysregulation of cardiovascular autonomic function. Conversely, SIHD patients in rural geographic locations appear to demonstrate lower rates of cholesterol assessment and statin use and register fewer ambulatory physician visits as compared to urban patients,[52] although it is not known whether this accounts for differential trends in CAD prevalence across these settings.

The role of substance abuse in the development and progression of CAD is increasingly recognized. The adverse effects of tobacco use, including exposure to second-hand smoke, on the cardiovascular system are well established.[53] It is estimated that tobacco use alone is responsible for approximately 467,000, or 20%, of all deaths in the United States annually.[54] Perhaps equally important is the prevalence of recreational cocaine use and its contribution to coronary heart disease. Nearly 34 million people in the United States have reported a history of cocaine use, of whom approximately 1% report use within the last month.[55] Cocaine can accelerate coronary atherosclerosis, enhance platelet aggregation, induce coronary vasospasm, and increase myocardial oxygen demand via its effects on heart rate and blood pressure.[56]

Risk factors for CAD unique to low- and middle-resource countries include psychosocial stress associated with migration, massive pollution, inadequate sanitation, persistently elevated rates of tobacco use and second-hand tobacco exposure, and limited opportunities to exercise. In addition, other factors, such as body weight, should be considered when considering CHD risk in patients from low- and middle-resource countries.[57]

Malignancy, Human Immunodeficiency Virus, and Ischemic Heart Disease

Treatment of several noncardiac medical conditions, such as various malignancies, may also predispose to coronary heart disease events in vulnerable populations. Mantle radiation for the treatment of Hodgkin lymphoma is associated with a significantly increased incidence of proximal CAD, higher coronary artery calcification scores (see Coronary Artery Calcification Score in Ischemic Heart Disease section), and an elevated likelihood of the need for revascularization therapy.[58] Several chemotherapeutic agents, particularly 5-fluorouracil, capecitabine, nilotinib, ponatinib, temsirolimus, thalidomide, and lenalidomide, are linked to the development of angina from epicardial or microvascular abnormalities.[59] Although patients with orthotropic heart transplantations may develop epicardial CAD, graft failure long term is most commonly a result of a diffuse, small-vessel arteriopathy that is immune mediated.[60] Patients infected with the human immunodeficiency virus (HIV) appear to be at increased risk for a wide range of inflammatory vascular diseases, including CAD. This may occur as a manifestation of HIV itself; low $CD4^+$ T-cell count has been associated with the presence of coronary artery stenotic lesions > 50% of luminal diameter.[61] Alternatively, CAD in HIV-infected individuals could occur as a consequence of highly active antiretroviral therapy (HAART) use.[62] Compared to HIV-negative patients, the prevalence of noncalcified coronary plaques is approximately three-fold higher in HIV-positive patients on HAART therapy (odds ratio [OR], 3.26; 95% CI, 1.30-8.18),[63] which may account for parallel findings in similar patients suggesting that the risk of incident MI is increased approximately four-fold.[64] The mechanistic link between HAART and CAD remains speculative but may involve cross-reactivity between protease inhibitors and lipid metabolism–regulating proteins that results in dyslipidemia, insulin resistance, central adiposity, and lipodystrophy.[62,65] In selected HIV patients at elevated risk for cardiovascular disease, protease inhibitors may be inappropriate; under these circumstances, consultation with an infectious disease specialist to determine optimal HIV therapy is advised, as is the early institution of aggressive risk factor control (eg, statin therapy).

DIAGNOSTIC TESTING IN CHRONIC CORONARY ARTERY DISEASE

Technologic advances in the past two decades have expanded the noninvasive options available for diagnosis and risk stratification of patients with chronic CAD. Although guidelines and appropriate use criteria have been published, practice patterns vary widely in the application of testing to the individual patient. Noninvasive testing, with or without imaging as dictated by specific patient attributes, is appropriate for the vast majority of patients. There are high-risk clinical features, however, that would substantiate the use of invasive coronary angiography as the first step (Fig. 43–1).

EXERCISE ELECTROCARDIOGRAM STRESS TESTING

Numerous studies involving thousands of patients have validated the prognostic utility of ECG treadmill testing. Data from patients with medically managed SIHD enrolled in the Coronary Artery Surgery Study (CASS) demonstrated that failure to complete stage 1 of a standard Bruce protocol was associated with a markedly elevated mortality risk 4 years after testing.[17] Others have shown that the presence of exercise-induced ST-segment depression, an abnormal blood pressure response to exercise, and poor functional capacity on stress testing are associated with early mortality from cardiovascular disease.[66]

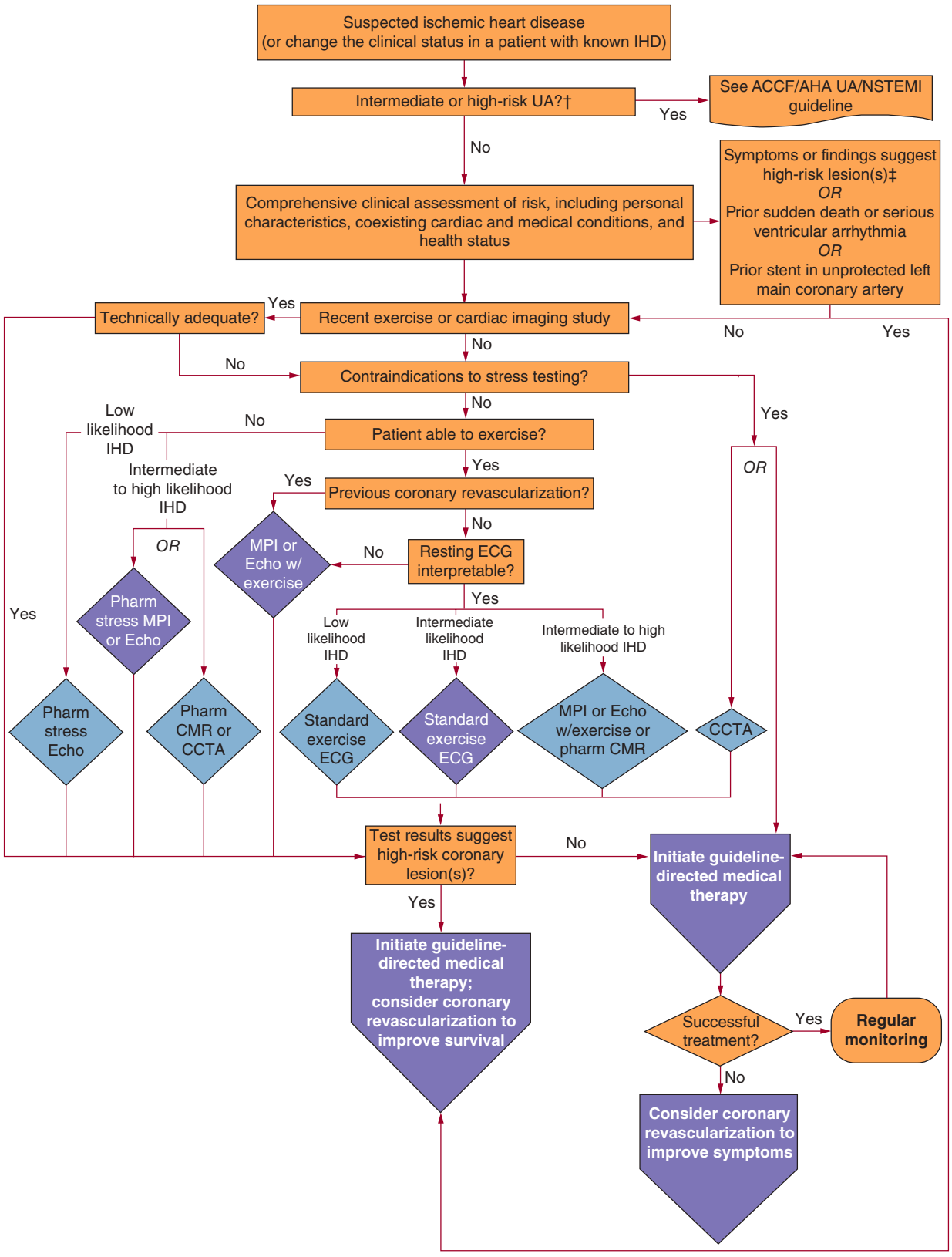


FIGURE 43–1. Diagnosis of patients with suspected ischemic heart disease. *Colors correspond to the class of recommendations in the ACCF/AHA Table 1. ‡CCTA is reasonable only for patients with intermediate probability of IHD. CCTA, computed coronary tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiogram; Echo, echocardiography; IHD, ischemic heart disease; MI, myocardial infarction; MPI, myocardial perfusion imaging; Pharm, pharmacological; UA, unstable angina; UA/NSTEMI, unstable angina/non–ST-segment elevation myocardial infarction. Reproduced with permission from Fihn SD, Gardin JM, Abrams J, et al: 2012 ACCF/AHA/ACP/AATS /PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.[121]

The Duke Treadmill Score (DTS) is commonly used in clinical practice for predicting the probability of a future MI or cardiovascular death in patients with CAD and is widely available at point of care including via the use of the DTS smartphone mobile application. In this model, a numeric score is generated that reflects patient exercise time, extent of ST-segment depression, and presence of anginal symptoms. The DTS correlates with future cardiovascular mortality; is valid in the era of diuretics, renin-angiotensin-aldosterone axis inhibitors, and β-adrenergic receptor antagonists; and is predictive in both men and women.[67] The DTS and other similar models that use functional capacity and ECG findings as the chief performance measures may be confounded by baseline ECG abnormalities and limitations to exercise from noncardiovascular causes. These scoring systems do not include information regarding the anatomic distribution, extent, and severity of ischemia, nor do they involve an assessment of LV function during exercise stress. Access to these data often enhances the prognostic valve of stress testing and provides the clinician with a more informed understanding of ischemic burden from which to guide treatment decisions in specific patients.[68] Importantly, cardiopulmonary exercise testing, which is being used increasingly to evaluate patients with unexplained dyspnea, does not use a standardized protocol for provoking ischemia. Instead, this method identifies ischemia as a cause of symptoms occurring during exercise, and clinicians intending to assess inducible ischemia should rely on standardized exercise protocols (eg, Bruce protocol) validated for this purpose.

REST AND STRESS ECHOCARDIOGRAPHY

Resting transthoracic echocardiography is useful to characterize LV systolic and diastolic function in patients with SIHD, especially in those with prior MI and HF. Reduced LVEF is strongly associated with an increased risk for incident ventricular tachycardia and SCD. In select patients following MI, low ejection fraction (EF) alone (≤ 0.30) is sufficient to warrant certain forms of device therapy such as an implantable cardioverter-defibrillator (ICD). In ischemic cardiomyopathy patients (EF ≤ 0.35) with HF symptoms, ICD therapy for primary prevention of SCD is also indicated. Stress echocardiography is more sensitive and specific than ECG stress for the detection of CAD. In patients with chronic CAD, the presence of LVH, diminution in systolic wall thickening in one or more segments during stress, or compensatory hyperkinesis in nonischemic segments portends increased risk for future cardiovascular events.[69,70]

MYOCARDIAL PERFUSION IMAGING

Myocardial perfusion imaging (MPI) typically involves SPECT with visual and quantitative analysis. There is increasing experience with positron emission tomography (PET). Attenuation correction algorithms improve SPECT test performance. ECG gating is used for analysis of global and regional LV performance. Table 43–5 summarizes the comparative advantages of stress SPECT MPI and stress echocardiography for CAD diagnosis. A normal stress MPI study in a patient with an ischemic ECG response to exercise defines a favorable prognosis for which an invasive treatment strategy is usually not justified, especially if an adequate workload was achieved during the study.[71]

Abnormal stress MPI in patients with established CAD is predictive of cardiac death and nonfatal MI.[72] Transient, stress-induced LV dilation and a decrease in EF of > 5% are independent predictors of cardiac death and are useful in risk stratification of patients with chronic CAD.[73] Stress cardiac MRI is sensitive, predicts territorial ischemia accurately, and is not subject to breast or gastrointestinal signal attenuation that may confound the interpretation of SPECT imaging results in women.[74] Provocable ischemia on stress MRI enhances the discriminatory value of conventional risk stratification methods by up to seven-fold and, in one study, resulted in reclassification of 91% of patients at moderate risk (65.7% to low risk; 25.8% to high risk).[75] Abnormal coronary flow reserve (CFR) on MPI can be a prognostic marker in patients without overt CAD. In a cohort of 761 patients undergoing evaluation for CAD in whom a prior positive cardiac biomarker was known, decreased CFR was associated with major cardiovascular events over a 2.8-year period compared to patients with normal CFR (HR, 2.25; 95% CI, 1.31-3.86; P = .003).[76] Converging data suggest that CFR may be useful in place of diagnostic angiography for quantifying ischemic burden in patients without significant epicardial coronary stenoses for whom small-vessel CAD is believed to be responsible for cardiovascular events.[77]

TABLE 43–5. Comparative Advantages of Stress Echocardiography and Stress Myocardial Perfusion Imaging in Diagnosis of Coronary Artery Disease

Advantages of stress echocardiography
1. Higher specificity
2. Versatility; more extensive evaluation of cardiac anatomy and function
3. Greater convenience/efficacy/availability
4. Lower cost
Advantages of stress perfusion imaging
1. Higher technical success rate
2. Higher sensitivity, especially for single-vessel coronary disease involving the left circumflex artery
3. Better accuracy for evaluating possible ischemia when multiple resting left ventricular wall motion abnormalities are present
4. More extensive published database, especially in evaluation of prognosis

Reproduced with permission from Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol*, 1999 Jun;33(7):2092-2197.

THE CLINICAL IMPLICATION OF HIGH ISCHEMIC BURDEN ON MYOCARDIAL PERFUSION IMAGING TESTING

MPI data are useful for identifying high-risk chronic stable CAD patients for whom revascularization therapy may be appropriate.[78] Table 43–6 summarizes criteria for high, intermediate, and low risk based on noninvasive diagnostic testing. Referral for angiography to search for CAD extensive enough to warrant surgical revascularization is reasonable for patients with high-risk features. A subset analysis of 314 patients from the COURAGE trial suggested that adding PCI to OMT may be more efficacious than OMT alone for the treatment of SIHD patients when a quantitative ischemic burden exceeding 10% of the myocardium is established.[78-80] Furthermore, a decrease in ischemic burden by ≥ 5% with either PCI plus OMT or OMT alone resulted in a significant increase in event-free survival over 5 years (Fig. 43–2). These data suggest that a large myocardial ischemic burden on MPI testing may be a useful metric for the consideration of PCI as an initial treatment strategy. These subgroup analyses should be considered hypothesis generating and await prospective validation in larger numbers of patients with multivessel CAD (see later section on ISCHEMIA Trial).

TABLE 43–6. Noninvasive Risk Stratification of Coronary Artery Disease

High risk (> 3% annual death or MI)

1. Severe resting LV dysfunction (LVEF < 35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities ≥ 10% of the myocardium in patients without prior history or evidence of MI
3. Stress ECG findings including ≥ 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF < 45% or drop in LVEF with stress ≥ 10%)
5. Stress-induced perfusion abnormalities encumbering ≥ 10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving > 2 segments or 2 coronary beds)
8. Wall motion abnormality developing at low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 120 beats/min)
9. CAC score > 400 Agatston units
10. Multivessel obstructive CAD (≥ 70% stenosis) or left main stenosis (≥ 50% stenosis) on CCTA

Intermediate risk (1% to 3% annual death or MI)

1. Mild/moderate resting LV dysfunction (LVEF 35% to 49%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities in 5% to 9.9% of the myocardium in patients without a history or prior evidence of MI
3. ≥ 1 mm of ST-segment depression occurring with exertional symptoms
4. Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating 1 vascular territory with abnormalities but without LV dilation
5. Small wall motion abnormality involving 1 to 2 segments and only 1 coronary bed
6. CAC score 100 to 399 Agatston units
7. One vessel CAD with ≥ 70% stenosis or moderate CAD stenosis (50% to 69% stenosis) in ≥ 2 arteries on CCTA

Low risk (< 1% annual death or MI)

1. Low-risk treadmill score (score ≥ 5) or no new ST segment changes or exercise-induced chest pain symptoms; when achieving maximal levels of exercise
2. Normal or small myocardial perfusion defect at rest or with stress encumbering < 5% of the myocardium*
3. Normal stress or no change of limited resting wall motion abnormalities during stress
4. CAC score < 100 Agaston units
5. No coronary stenosis > 50% on CCTA

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Reproduced with permission from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/ PCNA/SCAI/STS Guidelines for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society of Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.

CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Coronary CT angiography (CCTA) provides an anatomic assessment of the epicardial coronary arteries. Because of its high spatial resolution and negative predictive value, CCTA is especially helpful to exclude important CAD in patients with a low pretest likelihood of disease. CCTA is also well suited to visualize suspected congenital coronary artery anomalies and great vessel anatomy. Appropriate use criteria for advanced testing, including CCTA and stress imaging, are provided in Table 43–7. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) study evaluated CCTA as an initial diagnostic strategy for symptomatic patients with CAD (n = 10,003). Compared to exercise stress testing, CCTA did not result in a reduction in the composite end point of death, MI, hospitalization for unstable angina, or major procedural complications at 25 months (3.3% vs 3.0%; adjusted HR, 1.04; 95% CI, 0.83-1.29; $P = .75$), although patients in the CCTA arm underwent fewer diagnostic coronary angiograms indicating no obstructive CAD (3.4% vs 4.3%; $P = .02$).[81] Overall, routine use of this technology in those with SIHD is not recommended.[82]

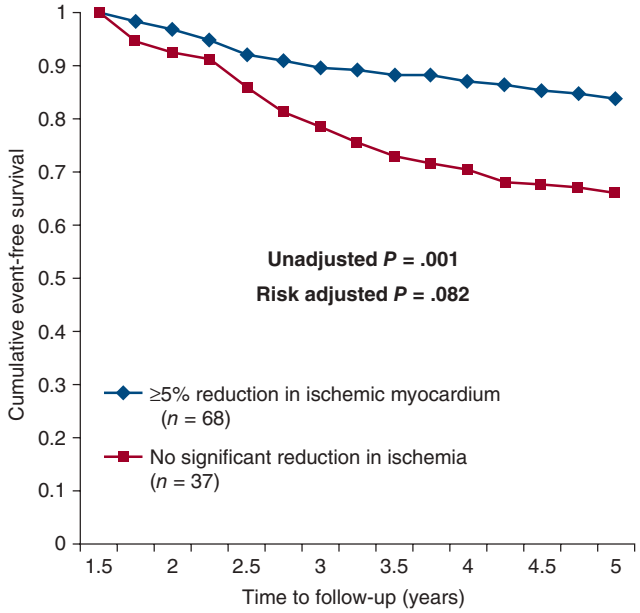


FIGURE 43–2. The effect on event-free survival of decreasing ischemic myocardial burden ≥ 5% assessed by myocardial perfusion imaging in stable coronary artery disease patients enrolled in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. Patients were treated for 6 to 18 months with either optimal medical therapy (OMT) or OMT plus percutaneous coronary intervention. Reproduced with permission from Shaw LJ, et al. COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. Mar 2008 11;117(10):1283-1291.[78]

CORONARY ARTERY CALCIFICATION SCORE IN ISCHEMIC HEART DISEASE

Coronary artery calcification observed on cardiac CT strongly correlates with the presence of established atherosclerosis.[83] The coronary artery calcification score is a quantitative measure of *overall* vascular calcium burden. The presence of calcium in the vessel wall does not correlate with the degree of luminal obstruction, although the overall burden may predict future coronary heart disease events.[84] Serial coronary artery calcification scoring to assess the rate of disease progression is not recommended.[85]

INVASIVE CORONARY ANGIOGRAPHY

Referral for invasive coronary angiography in patients with SIHD is most often indicated for refractory symptoms or high-risk features on noninvasive testing and serves as a prelude to revascularization. In individuals with symptoms suggestive but not diagnostic of CAD,

TABLE 43–7. Appropriate Use Criteria for Advanced Imaging and Stress Testing in Patients Suspected of Chronic Stable Ischemic Heart Disease

	Exercise Status		ECG Interpretable		Pretest Probability of IHD				
Test	Able	Unable	Yes	No	Low	Intermediate	High	COR	LOE
Patients able to exercise									
Exercise ECG	X		X			X		I	A
Exercise with nuclear MPI or Echo	X			X		X	X	I	B
Exercise ECG	X		X		X			IIa	C
Exercise with nuclear MPI or Echo	X		X			X	X	IIa	B
Pharmacological stress CMR	X			X		X	X	IIa	B
CCTA	X		Any			X		IIb	B
Exercise Echo	X		X			X		IIb	C
Pharmacological stress with nuclear MPI, Echo, or CMR	X		X			Any		III No Benefit	C
Exercise stress with nuclear MPI	X		X		X			III No Benefit	C
Patients unable to exercise									
Pharmacological stress with nuclear MPI or Echo		X	Any			X	X	I	B
Pharmacological stress Echo		X	Any		X			IIa	C
CCTA		X	Any		X	X		IIa	B
Pharmacological stress CMR		X	Any			X	X	IIa	B
Exercise ECG		X		X		Any		III No Benefit	C
Other									
CCTA	Any		Any			X		IIa	C
If patient has any of the following: a) Continued symptoms with prior normal test, or b) Inconclusive exercise or pharmacological stress, or c) Unable to undergo stress with MPI or Echo									
CAC score	Any		Any		X			IIb	C

Abbreviations: CAC, coronary artery calcium; CCTA, cardiac computed tomographic imaging; CMR, cardiac magnetic resonance imaging; COR, class of recommendations; ECG, electrocardiogram; Echo, echocardiography; IHD, ischemic heart disease; LOE, level of evidence; MPI, myocardial perfusion imaging; N/A, not available.

Adapted with permission from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/ PCNA/SCAI/STS Guidelines for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society of Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.

invasive angiography may be appropriate if their occupations constitute a risk to themselves or others (eg, airline pilots, firefighters, others).[86] In certain patients for whom the diagnosis of CAD on clinical grounds may be elusive as a result of atypical chest pain characteristics or asymptomatic ischemia (eg, patients with diabetes), a lower threshold for coronary angiography may be appropriate. As a result of atypical symptomatology and relatively lower diagnostic accuracy rates on conventional stress testing, women are more frequently considered for invasive angiography in the setting of an ambiguous presentation and/or inconsistent noninvasive data, but consideration of this approach should be weighed against the low but finite risks of the procedure. Moreover, findings from population studies suggest that in the United States, coronary angiography may be overused as an initial diagnostic test for CAD.[87] In fact, invasive angiography should not be considered as the first diagnostic strategy in women patients presenting with atypical chest pain or who are at low risk for CAD. Additional indications for invasive angiography include the evaluation of CAD in patients with reduced EF (< 0.40), patients surviving SCD, or patients with ventricular arrhythmias and a high or intermediate likelihood of CAD.[86]

TREATMENT OF STABLE ISCHEMIC HEART DISEASE

Goal-directed therapy in the management of SIHD is focused on (1) prevention of death and MI and (2) reducing symptoms and signs of myocardial ischemia. The intensity of treatment is dictated by the magnitude of risk and the severity of the ischemic burden. The decision to initiate medical, percutaneous, surgical, or hybrid treatment is

developed in the context of a patient's specific clinical, coronary angiographic, and LV functional profiles. Patient values and preferences should also be taken into account.

ANTIPLATELET THERAPY

Aspirin exerts an antithrombotic effect by irreversibly inhibiting cyclooxygenase-1 and the downstream synthesis of platelet thromboxane A_2. In the Physicians' Health Study, aspirin given on alternative days to asymptomatic men was associated with a decreased incidence of MI.[88] In the Swedish Angina Pectoris Aspirin Trial, SIHD patients receiving 75 mg of aspirin demonstrated an approximately 33% reduction in MI, sudden death, and vascular events compared with placebo.[89] In 2009, the Antithrombotic Trialists' Collaboration Group published a meta-analysis of 16 randomized placebo-controlled trials evaluating the effect of aspirin on future vascular events (eg, MI, stroke, or vascular death) in approximately 17,000 patients with established CAD.[90] Treatment with aspirin significantly decreased the rate of major vascular events, particularly MI (4.3% vs 5.3% per year; rate ratio [RR], 0.69; 95% CI, 0.60-0.80) and stroke (2.08% vs 2.54% per year; RR, 0.81; 95% CI, 0.71-0.92), without inducing a significant increase in the risk of hemorrhagic stroke. Daily use of aspirin (75-162 mg/d) for secondary prevention of MI in both men and women with SIHD is an AHA/ACC Class I recommendation.[86] Low-dose aspirin (75 or 81 mg) is recommended for maintenance therapy in combination with $P2Y_{12}$ inhibitors for patients who undergo PCI.

Clopidogrel is used in combination with aspirin as part of a strategy of dual antiplatelet therapy (DAPT) following PCI in patients with SIHD or ACS (including unstable angina, NSTEMI, and STEMI). The recommended minimal duration of DAPT after PCI with non–first-generation drug-eluting stents is 6 months for patients with SIHD and 12 months for patients with ACS, but this remains a "moving target" with the introduction of newer generation stents. Minimal DAPT duration differs for patients treated with bare metal stents (30 days). Based on the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study, clopidogrel is also provided for up to 1 year in patients with non–ST-segment elevation ACS managed medically.[91] Clopidogrel is a Class I recommendation for STEMI patients treated with fibrinolysis or not receiving reperfusion therapy, with an intended 1-year course of treatment.[92] Because of their superior efficacy, prasugrel and ticagrelor, two other $P2Y_{12}$ inhibitors, are preferred over clopidogrel for maintenance therapy (in combination with low-dose aspirin) after PCI for ACS, provided there are no contraindications to their use. Neither prasugrel nor ticagrelor has been studied in the setting of PCI for SIHD, and thus, only clopidogrel is approved for this indication. Prasugrel should not be used in patients with prior stroke or TIA and is generally avoided in patients over 75 years or of low body weight (< 60 kg) because of a lack of net clinical benefit.

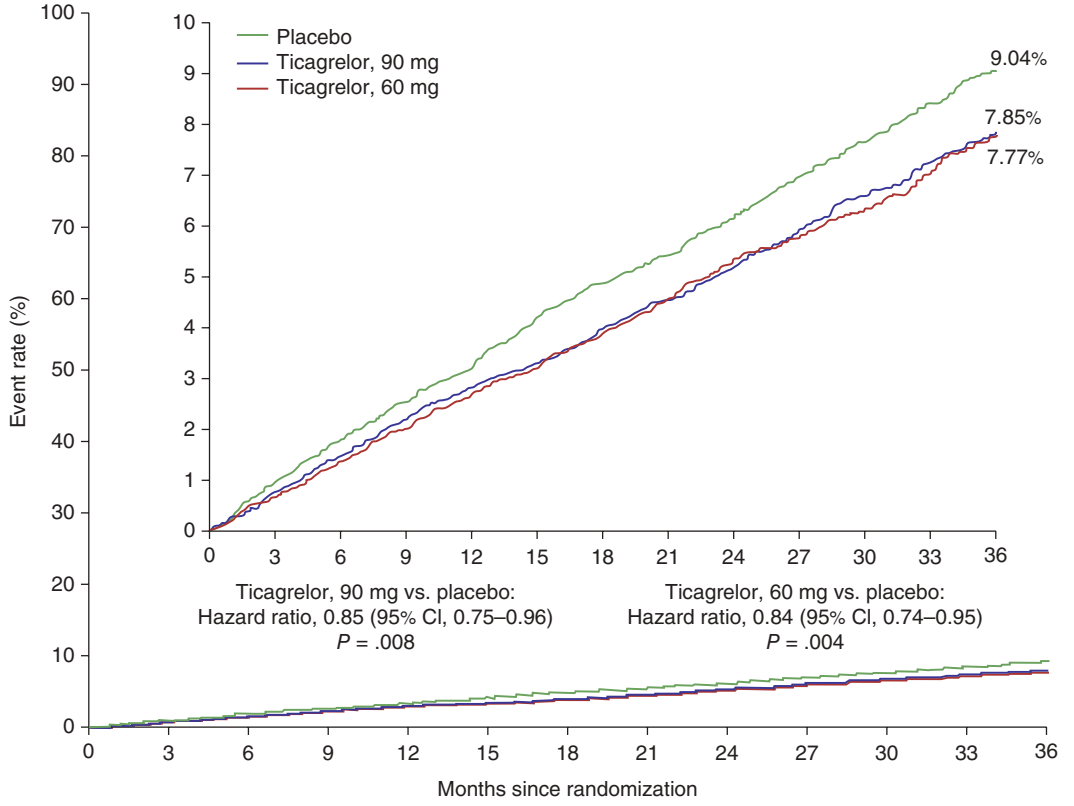
Interest in extended-duration DAPT stems in part from a subgroup analysis of post-MI patients enrolled in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial in which nearly a 25% reduction in a composite end point of cardiovascular death, MI, and stroke with clopidogrel plus aspirin compared with aspirin alone was observed.[93] Several underpowered trials have examined the utility of long-term DAPT in patients after PCI across a spectrum of clinical indications (reviewed in Wang et al[94] and Keach et al[95]). The drug-eluting stent (DES) arm of the Dual Antiplatelet Therapy (DAPT)[96] study randomized 9961 patients who were clinically stable and without bleeding complications 12 months after PCI (38% for stable angina) to an additional 18 months of aspirin plus a thienopyridine (clopidogrel or prasugrel) or aspirin alone. Prolonged DAPT was associated with a significant reduction in stent thrombosis and major adverse cardiac and cerebrovascular events, at the expense of an increased risk of bleeding. The treatment benefit was driven by a reduction in MI related to both stent thrombosis and de novo events in other locations. There was an increased rate of ischemic events over the 3 months after cessation of thienopyridine therapy at completion of the trial. The small absolute increase (0.5%) in total mortality for patients treated with DAPT in this study has not been observed in other studies of DAPT for both cardiac and neurologic indications. The US Food and Drug Administration performed a separate meta-analysis and concluded that there is not an incremental mortality risk with DAPT.

The Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial assessed the effects of DAPT on cardiovascular death, MI, and stroke in patients 1 to 3 years after MI.[97] A total of 21,612 post-MI patients were randomized to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, in addition to aspirin. At a median follow-up of 33 months, there were small but significant reductions in the composite primary end point in both ticagrelor arms (HR, 0.85 for ticagrelor 90 mg; 95% CI, 0.75-0.96; $P = .008$; HR, 0.84 for ticagrelor 60 mg; 95% CI, 0.74-0.95; $P = .004$) compared to placebo (Fig. 43–3). For every 10,000 patients treated with ticagrelor 90 mg twice daily, 40 primary end points would be prevented at the expense of 41 Thrombolysis in Myocardial Infarction (TIMI) major bleeds; for every 10,000 patients treated with ticagrelor 60 mg twice daily, 42 primary end points would be averted at the expense of 31 TIMI major bleeds. The US Food and Drug Administration has approved the 60-mg ticagrelor dose in combination with aspirin (81 mg) for secondary prevention. Follow-up analyses of the PEGASUS-TIMI 54 trial suggested that the benefit of adding ticagrelor to aspirin for long-term secondary prevention is more marked for post-MI patients continuing on or restarting $P2Y_{12}$ inhibition after only a brief interruption, especially when compared with patients who have declared themselves stable for 2 or more years after MI and off $P2Y_{12}$ inhibitor therapy for more than 1 year.[98] Data assessing the role of prasugrel under similar clinical circumstances are lacking.

Protease-activated receptor (PAR)-1 antagonism with vorapaxar inhibits thrombin-induced activation of platelets. Morrow and colleagues[99] tested the effect of vorapaxar on outcomes in a 26,449 patients with SIHD, defined in this study as prior history of MI, ischemic stroke, or peripheral artery disease. At 2 years of follow-up, patients randomized to treatment with vorapaxar 2.5 mg daily had a significant decrease in the risk of cardiovascular death, MI, stroke, or ischemia requiring revascularization compared to placebo (HR, 0.88; 95% CI, 0.82-0.95; $P = .001$). However, the risk for moderate or severe bleeding was also increased significantly in the treatment arm (HR, 1.66; 95% CI, 1.43-1.93; $P < .001$), and the study was discontinued early for patients with a history of intracranial hemorrhage. When considering bleeding risk as part of the overall study outcome, there was no difference between groups for the prespecified composite end point of cardiovascular death, MI, stroke, or moderate/severe bleeding (HR, 0.97; 95% CI, 0.90-1.04; $P = .40$). Decisions regarding long-term DAPT with $P2Y_{12}$ inhibitors or use of vorapaxar must be individualized, taking into account ischemic risk versus bleeding hazard.

ANTICOAGULANT THERAPY

Oral anticoagulant therapy with a vitamin K antagonist such as warfarin is an effective strategy to prevent recurrent MI when the dose is titrated to a target international normalized ratio (INR) of 2.0 to 3.0.[100] Hurlen and colleagues[101] randomized 3630 post-MI patients to



No. at risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

FIGURE 43–3. Effect of long-term ticagrelor in patients with prior myocardial infarction. Kaplan-Meier rates of cardiovascular death, myocardial infarction, and stroke through 3 years, according to study group. Study drugs were administered twice daily. The inset shows the same data on an enlarged y axis. Reproduced with permission from Bonaca MP, Bhatt DL, Cohen M: Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015 May 7;372(19):1791-1800.[97]

warfarin, aspirin, or combination warfarin plus aspirin for 4 years. Compared with aspirin alone, warfarin or combination warfarin plus aspirin conferred an approximate 19% relative risk reduction for the primary composite end point of death, nonfatal recurrent MI, or stroke. However, warfarin was associated with an elevated rate of major (nonfatal) bleeding complications. Under most circumstances, long-term treatment with aspirin is favored over vitamin K antagonist therapy for the secondary prevention of MI in patients with SIHD, unless an independent indication for warfarin use is present (such as atrial fibrillation).[102]

Direct oral anticoagulants are used for stroke prevention in patients with atrial fibrillation and elevated CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category) scores and for the management of venous thromboembolism. Early studies with dabigatran showed an increased risk with this agent for MI compared with warfarin.[103] Low-dose rivaroxaban has been used in combination with DAPT in patients with ACS and is associated with decreased rates of hard clinical end points but with increased bleeding risk.[104] Management of patients who require long-term anticoagulation (eg, mechanical valve, atrial fibrillation with CHA_2DS_2-VASc score > 2) and DAPT after ACS must be individualized to strike the appropriate balance between the risks of stent thrombosis and bleeding. Consideration of bare metal stent use to shorten the duration of DAPT and use of warfarin targeted to a lower therapeutic INR range (2.0-2.5) have been recommended.[105] There is limited experience with both direct oral anticoagulants and $P2Y_{12}$ inhibitors other than clopidogrel in this context. The What Is the Optimal Antiplatelet and Anticoagulation Therapy in Patients With Oral Anticoagulation Trial (WOEST) was an open-label, multicenter, clinical study in Belgium and the Netherlands testing the effect on outcome of clopidogrel alone or combination therapy with clopidogrel plus aspirin in PCI patients on standing anticoagulant therapy with warfarin (n = 573). There was significantly less bleeding in patients assigned to double therapy (warfarin plus clopidogrel) compared to patients assigned to aspirin, clopidogrel, and warfarin (HR, 0.36; 95% CI, 0.26-0.50; $P < .0001$) without an attendant increase in MI, cardiac death, stroke, or stent thrombosis at 1 year of follow-up.[106] Additional studies are in progress.

LIPID-LOWERING THERAPY

Previous secondary prevention recommendations emphasized aggressive lipid management to a target LDL cholesterol < 100 mg/dL for all ischemic heart disease patients or < 70 mg/dL if it can be safely achieved in high-risk patients.[40] Current guideline recommendations emphasize use of moderate- or high-intensity statin therapy for four patient groups, including those with SIHD. Specifically, in patients age ≤ 75 years with a history of a prior cardiovascular event, high-intensity statin therapy (eg, rosuvastatin 20-40 mg daily or atorvastatin 40-80 mg daily) is recommended; moderate-intensity statin therapy (eg, rosuvastatin 10-20 mg daily or atorvastatin 20-40 mg daily) is recommended for SIHD patients > 75 years of age. Contraindications to drug therapy,

including drug-drug interactions or drug intolerance, should be used to influence dose selection. The Scandinavian Simvastatin Survival Study (4S) demonstrated that treatment with simvastatin in patients with SIHD and a baseline total cholesterol > 210 mg/dL was associated with an approximate 35% reduction in mortality and major coronary event rates.[107] In the Cholesterol and Recurrent Events (CARE) study, men and women with previous MI, total cholesterol levels < 240 mg/dL, and LDL cholesterol levels of 115 to 174 mg/dL treated with pravastatin demonstrated a 24% reduction in the risk of future MI compared with placebo.[108] LaRosa and colleagues[109] tested the hypothesis that high-dose statin therapy is superior to low-dose statin therapy for the secondary prevention of cardiovascular events in patients with SIHD. In the randomized, prospective Treating to New Targets (TNT) trial, 10,001 such patients (enrollment LDL < 130 mg/dL) were randomized to receive 80 or 10 mg of atorvastatin daily over 6 years. Patients treated with 80 mg of atorvastatin achieved a mean LDL cholesterol level of 77 mg/dL versus 101 mg/dL for those allocated to 10 mg of atorvastatin. High-dose atorvastatin therapy was associated with a 22% relative risk reduction for the combined primary end point of death from ischemic heart disease, nonfatal MI, or stroke.[109] The lowest optimal level of LDL cholesterol for primary or secondary prevention has not been established.

Stitziel and colleagues in collaboration with the Myocardial Infarction Genetics Consortium Investigators sequenced exons of the NPC1L1 protein in a large cohort of patients with coronary heart disease and in normal controls and reported that carriers of inactivating mutations had LDL cholesterol levels that were 12 mg/dL lower than in noncarriers ($P = .04$). Carrier status was associated with a relative reduction in risk for coronary heart disease events of 53% (OR, 0.47; 95% CI, 0.25-0.87; $P = .008$).[110] These findings coincided with clinical trial data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) suggesting that simvastatin (40 mg daily) in combination with ezetimibe (10 mg daily), which targets the *NPC1L1* gene, was more effective than simvastatin alone for decreasing LDL levels and cardiovascular events at 6 years after ACS.[111] Alirocumab and evolocumab are monoclonal antibodies that inhibit proprotein convertase subtilisin kexin type 9 (PCSK9), which degrades hepatic LDL receptors. These therapies have been approved for the treatment of patients who are heterozygous for familial hypercholesterolemia and in patients with clinical atherosclerotic disease who require additional LDL cholesterol lowering or are unable to tolerate guideline-recommended doses of statins plus ezetimibe.

β-ADRENERGIC RECEPTOR ANTAGONISTS

β-Adrenergic receptor antagonists (when administered orally) are associated with increased short- and long-term survival rates in post-MI patients.[112-114] The use of these agents in the acute phase of MI has been influenced by the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) results.[115] Numerous long-term trials of β-adrenergic receptor antagonists attest to their efficacy for secondary prevention of recurrent MI and cardiac death, but to date, no trial has tested whether β-blockers reduce mortality in patients with SIHD, years after or without antecedent MI. In general, their effectiveness is relatively greater among higher risk patients, particularly among those with reduced EF, HF, or ventricular arrhythmias. In lower risk patients, however, β-adrenergic receptor antagonists are recommended only for up to 3 years after uncomplicated MI without other relative indications (eg, atrial fibrillation, reduced EF). In patients with SIHD and HF, treatment should be restricted to the use of carvedilol, long-acting metoprolol, or bisoprolol, agents shown to reduce adverse outcomes in this population.[116-118] On a physiologic level, β-adrenergic receptor antagonists favorably influence myocardial oxygen supply-demand balance by reducing heart rate, myocardial contractility, systemic arterial pressure, and LV wall stress. The reduction in heart rate may also allow for enhanced CBF as a result of longer diastolic filling times, and anginal frequency and nitroglycerin use are decreased.[119]

The therapeutic benefit of β-adrenergic receptor antagonists appears to be a class effect with the exception of agents that express intrinsic sympathomimetic activity. In patients with severe angina (ie, CCS class III/IV), full drug efficacy depends largely on dose titration to achieve a heart rate ≤ 60 bpm at rest or ≤ 75 bpm with exertion (or ≤ 75% of the heart rate at which angina occurs). Ambulatory monitoring may be necessary to ensure that severe bradycardia (ie, ≤ 40 bpm) or advanced atrioventricular (AV) block does not occur.

Recent registry data affirm earlier findings that the benefit of β-adrenergic receptor antagonists is observed principally in the post-MI period. Observational data from the Reduction of Atherothrombosis for Continued Health (REACH) registry, for example, demonstrated that among a total cohort of 44,708 patients, rates for the composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke did not differ relative to β-adrenergic receptor antagonist use in patients with CAD without prior MI, with remote history of MI, or with only risk factors for CAD.[120] The initiation of β-adrenergic receptor antagonists following MI and continuing for 3 years is a Class I indication in patients with normal LV function. Use of β-adrenergic receptor antagonists is also a Class I indication in patients with LV systolic dysfunction and HF or prior MI, unless contraindicated.[121]

Fatigue, lethargy, insomnia, nightmares, worsening claudication, and impotence are potential adverse effects and may adversely affect medication adherence. Absolute contraindications to the use of β-adrenergic receptor antagonists include severe bradycardia (heart rate < 60 bpm at rest), preexisting AV block (PR interval > 0.24 seconds, second- or third-degree AV block), sick sinus syndrome, or acutely decompensated HF. Asthma, severe depression, brittle diabetes, and peripheral vascular disease are relative contraindications that require cautious use, but β-adrenergic receptor antagonists may be an important part of medical management strategies in patients with these disorders and as a rule tend to be underused in patients with chronic obstructive pulmonary disease in particular.

β-Adrenergic receptor antagonists are frequently used in combination with other antianginal medications for maximum benefit and symptom control. Adding a β-adrenergic receptor antagonist to nitrates, for example, appears more effective in controlling anginal symptoms than monotherapy with either agent alone.[122] Similar observations have been made with combination calcium channel blockers; long-acting dihydropyridine derivatives are preferred to avoid excessive bradycardia in this setting.[86,122]

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) decrease vascular smooth muscle cell and cardiac myocyte transmembrane calcium flux. They induce vasodilatation of epicardial coronary arteries to improve CBF and attenuate vasospastic and exertional angina. CCBs also improve angina by lowering systemic vascular resistance and mean arterial blood pressure to decrease LV afterload, thereby decreasing myocardial oxygen demand. The negative inotropic effects of these agents also favorably influences myocardial oxygen supply-demand balance, but may affect cardiac function adversely in patients with significantly impaired LV function. In patients with normal LV systolic function, CCBs may result in increased myocardial contractility as a compensatory response to lowered systemic vascular resistance.

Antianginal efficacy with CCBs is comparable to that obtained with β-adrenergic receptor antagonists.[42] However, the efficacy of CCB monotherapy for reducing MI or cardiac death in patients with SIHD has not been demonstrated convincingly. The primary indications for CCB therapy include blood pressure or heart rate control and alleviation of anginal symptoms after optimization of β-adrenergic receptor, nitrate, and angiotensin-converting enzyme inhibitor therapy.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS

Several randomized controlled trials in support of long-term angiotensin-converting enzyme (ACE) inhibition for the reduction of cardiovascular death, recurrent MI, and stroke in intermediate- and high-risk patients with SIHD have been reported. The Heart Outcomes Prevention Evaluation (HOPE) study tested the efficacy of ramipril (10 mg/d) on cardiovascular outcomes in a large cohort of patients with CAD, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor.[123] Patients with comorbid HF were excluded, and participants were not known to a have a decreased LVEF. Compared with placebo, ramipril therapy resulted in a significant reduction in the rate of death from cardiovascular causes, MI, stroke, or any cause over 5 years (14.0% vs 17.8%; RR, 0.78; 95% CI, 0.70-0.86). ACE inhibitor therapy also reduced incident diabetes. In the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA), a trial that enrolled patients with chronic CAD and relatively lower risk profiles, perindopril therapy was associated with a directionally similar reduction in cardiovascular disease outcomes.[124] The consequences of adding perindopril to standing β-adrenergic receptor antagonist therapy were analyzed in a retrospective analysis of the EUROPA trial. This subgroup study showed that combination therapy reduced the relative risk of the primary end point of cardiovascular death, nonfatal MI, or resuscitated cardiac arrest by 24% compared with placebo plus β-adrenergic receptor antagonist therapy (HR, 0.76; 95% CI, 0.64-0.91; $P = .02$).[125] The salutary effects of ACE inhibitors were not as firmly established among lower risk patients enrolled in the Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy (PEACE) trial, especially among patients with normal LV function, optimal lipid profiles, and prior revascularization.[126] ACE inhibitors are a Class I recommendation for all SIHD patients with LV dysfunction (EF < 0.40), hypertension, diabetes, or chronic kidney disease and a Class IIa recommendation for patients with both SIHD and other vascular disease.[126] Angiotensin receptor blockers (ARBs) are an appropriate alternative for patients who cannot tolerate ACE inhibitors.[121,127] They should not be used in combination with ACE inhibitors. The mineralocorticoid receptor antagonists spironolactone and eplerenone have been demonstrated to be beneficial for patients with both advanced (NYHA Class III/IV and EF < 0.35) and lesser degrees of HF.[128-130] Initiation of eplerenone, in addition to the use of β-adrenergic receptor antagonist and ACE inhibitor therapy, is a class I recommendation for treatment of patients after MI with reduced EF (< 0.40), HF, or diabetes.[131] Use of these agents must be considered in the context of renal function and potassium homeostasis. Indications for the use of combination sacubitril/valsartan, in preference to an ACE inhibitor or ARB, are reviewed in Chap. 70.

ORGANIC NITRATES

Organic nitrates (eg, nitroglycerin, isosorbide dinitrate) are nitric oxide donors that activate soluble guanylyl cyclase in vascular smooth muscle cells to increase intracellular cyclic guanosine monophosphate and induce blood vessel relaxation. These medications treat ischemia by (1) inducing venodilation of capacitance vessels to decrease preload, thus decreasing LV wall stress and myocardial oxygen demand; (2) dilating epicardial coronary arteries to improve CBF; and (3) recruiting coronary collaterals. In patients with CAD, use of nitrates is associated with lower angina frequency and increased time to ischemic ECG findings on treadmill testing.[86] Nitroglycerin also expresses antithrombotic properties, predominately via attenuation of platelet aggregation. Monotherapy with nitrates does not influence survival or decrease cardiovascular death rates in SIHD patients.

Tachyphylaxis to organic nitrate use is common in clinical practice, although the precise mechanisms remain unclear. Pentaerithrityl tetranitrate (PETN) has been shown in preclinical studies to exert properties that delay nitrate tolerance. However, a randomized, controlled study of 655 patients demonstrated that PETN did not affect exercise duration significantly compared to placebo in patients with SIHD. There was a signal of possible benefit in a prespecified subgroup of patients with low exercise tolerance at baseline.[132] Nevertheless, in the absence of available nitrate derivatives for which drug tolerance is not a concern, integrating a nitrate-free interval (8-12 hours) or longer drug holidays has been suggested (ie, intermittent drug cessation for 2- to 3-day periods). Co-administration of nitrates with sildenafil greatly increases the risk of potentially life-threatening hypotension because both agents increase cyclic guanosine monophosphate bioactivity to potentiate vasodilatation.[133]

RANOLAZINE

Ranolazine is a selective inhibitor of late sodium influx into myocytes, which in turn leads to decreased myocardial contractility.[134] Early clinical trials established that ranolazine monotherapy is effective in improving exercise tolerance in patients with SIHD.[135] In the prospective, randomized, placebo-controlled Combination Assessment of Ranolazine in Stable Angina (CARISA) trial, ranolazine (750-1000 mg twice daily) in combination with standard doses of atenolol, amlodipine, or diltiazem, significantly increased time to onset of angina and exercise performance compared with placebo.[136] Additionally, ranolazine significantly reduced the frequency of angina and nitroglycerin requirements during the 12-week period following randomization. Findings from a meta-analysis of seven randomized controlled trials (including CARISA) comparing ranolazine with placebo or usual care support a benefit with ranolazine on exercise tolerance and angina frequency.[137] Adverse effects include dizziness and constipation; discontinuation rates in large trials have been approximately 1%.[138] Although rare, QT interval prolongation has been seen with ranolazine therapy but not yet linked to clinically important arrhythmias. Drug interactions may be important, however, and the use of ranolazine is not recommended in patients receiving nondihydropyridine CCBs, quinolones, or azole antifungal medications, among others. Ranolazine is best reserved for patients with persistent symptoms despite maximal medical therapy or for patients unable to tolerate other antianginal therapies because of adverse effects.

CORONARY ARTERY REVASCULARIZATION

BACKGROUND, MAJOR TRIALS, AND OBSERVATIONAL STUDIES

Intensive lifestyle modification and evidence-based drug therapy remain the cornerstones of treatment for patients with SIHD.[139] Patients with refractory symptoms despite OMT and/or elevated clinical or angiographic risk profiles and suitable coronary anatomy can benefit from revascularization with PCI or CABG surgery. Considerations regarding revascularization in the SIHD patient are distinctly different from those in the ACS patient. Quality-of-life and

cost-effectiveness analyses support the concept of a staged approach in most instances, although it remains to be determined whether the medication and lifestyle adherence rates achieved in clinical trials can be realistically duplicated in routine contemporary clinical practice.

Indications for coronary artery revascularization in patients with SIHD can be considered in terms of those that prolong life and those that are targeted to symptom relief and/or ischemia reduction (Table 43–8). The choice of revascularization strategy (ie, PCI vs CABG) relates to coronary artery anatomy, LV systolic function, systemic factors (eg, diabetes), and patient values and preferences. The benefits of surgical revascularization are generally greater for patients with extensive and complex CAD, as well as when LV systolic dysfunction or diabetes is present. A heart team approach to patient-centered shared decision making is recommended with left main or multivessel CAD, especially with reduced EF. The ACC/AHA appropriate use criteria for coronary revascularization include 155 specific clinical scenarios for which PCI or CABG surgery may be considered.[79]

PERCUTANEOUS CORONARY INTERVENTION VERSUS OPTIMAL MEDICAL THERAPY

COURAGE Trial

Boden and colleagues[80] conducted a prospective, randomized controlled trial involving 2287 SIHD patients recruited between 1999 and 2004. Participants with symptomatic but stabilized angina (CCS class < IV), at least one ≥ 70% flow obstructing lesion in at least one proximal epicardial coronary artery, and objective evidence of myocardial ischemia were included in the trial. Exclusion criteria were nonstabilized CCS class IV angina, a markedly positive (high-risk) stress test result, refractory HF, and prior revascularization ≤ 6 months before study.[80] Patients were randomized to receive OMT alone or in combination with PCI. For PCI, a strategy of target lesion revascularization was used, whereas OMT included aspirin or clopidogrel, long-acting metoprolol, amlodipine, and isosorbide dinitrate, alone or in combination with an ACE inhibitor or ARB, and a lipid-lowering agent. These medications were provided to study participants free of charge, and patients were assigned a nurse manager to track their individual progress and adherence to assigned treatments. All patients were instructed in smoking cessation, diet, and expectations for physical activity. Median follow-up was 4.6 years. There were no statistically significant baseline clinical differences between treatment groups, other than an excess of proximal left anterior descending artery (LAD) disease among patients allocated to OMT. PCI relieved anginal symptoms more effectively than OMT alone over the first 36 months of the trial, after which freedom from angina rates were comparable. There was no significant difference in overall survival, survival free of MI, and survival free of ACS. Extended survival data on a subgroup of 1211 COURAGE trial patients demonstrated no significant mortality difference between PCI and OMT groups at a mean of 6.2 years (25% vs 24%; HR, 1.03; 95% CI, 0.83-1.21; $P = .76$; Fig. 43–4).[140] These observations were directionally similar to those reported in a meta-analysis of > 50,000 patients.[141] In the COURAGE trial, 238 patients (21%) crossed over from OMT to the PCI group over the course of the study, a fact that illustrates the dynamic nature of the disease substrate and the importance of individualized care.

Cost-effectiveness and quality-of-life measures in patients undergoing an initial OMT or PCI strategy for the treatment of SIHD were also evaluated in the COURAGE trial. Both treatment groups demonstrated significant improvement in standardized measures to assess angina-specific health status (using the Seattle Angina Questionnaire) and overall physical and mental well-being (using the RAND 36-item health study). Although the OMT plus PCI group was more likely to

TABLE 43–8. Evidence for Revascularization Strategy by Clinical Scenario

Anatomic Setting	COR	LOE
UPLM or complex CAD		
CAEG and PCI	I—Heart Team approach recommended	C
CABG and PCI	IIa—Calculation of STS and SYNTAX scores	B
UPLM		
CABG	I	B
PCI	IIa—For SIHD when both of the following are present: • Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score of ≤ 22, ostial or trunk left main CAD) • Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality ≤ 5%)	B
	IIa—For UA/NSTEMI if not a CABG candidate	B
	IIa—For STEMI when distal coronary flow is TIMI flow grade < 3 and PCI can be performed more rapidly and safely than CABG	C
	IIb—For SIHD when *both* of the following are present: • Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (eg, low-intermediate SYNTAX score of < 33, bifurcation left main CAD) • Clinical characteristics that predict an increased risk of adverse surgical outcomes (eg, moderate—severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted operative mortality > 2%)	B
	III: Harm—For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B
3-vessel disease with or without proximal LAD artery disease*		
CABG	I	B
	IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (eg, SYNTAX score > 22) who are good candidates for CABG.	B
PCI	IIb—Of uncertain benefit	B
2-vossal disease without proximal LAD artery disease*		
CABG	I	B
PCI	IIb—Of uncertain benefit	B
2-vessel disease without proximal LAD artery disease*		
CABG	IIa—With extensive ischemia	B
	IIb—Of uncertain benefit without extensive ischemia	C
PCI	IIb—Of uncertain benefit	B
1-vessel proximal LAD artery disease		
CABG	IIa—With LIMA for long-term benefit	B
PCI	IIb—Of uncertain benefit	B

(*continued*)

TABLE 43–8. Evidence for Revascularization Strategy by Clinical Scenario (*Continued*)

1-vessel disease without proximal LAD artery involvement		
CABG	II: Harm	B
PCI	II: Harm	B
LV dysfunction		
CABG	IIa—EF 35% to 50%	B
CABG	IIb—EF 35% without significant left main CAD	B
PCI	Insufficient data	
Survivors of sudden cardiac death with presumed ischemia-mediated VT		
CABG	I	B
PCI	I	B
No anatomic or physiological criteria for revascularization		
CABG	II: Harm	B
PCI	II: Harm	B

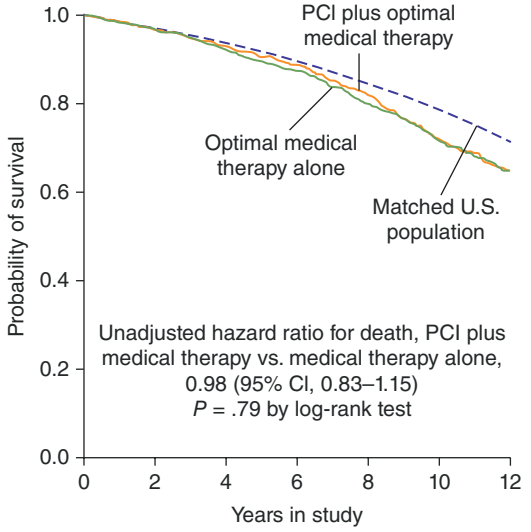
Abbreviations: CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; COR, class of recommendation; EF, ejection fraction; LAD, left anterior descending; LIMA, left internal mammary artery; LOE, level of evidence; LV, left ventricular; N/A, not available; PCI, percutaneous coronary intervention; SIHD, stable chronic ischemic heart disease; STEMI, ST-elevation myocardial infarction; STS, Society of Thoracic Surgeons; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIMI, thrombolysis in Myocardial Infarction; UA/NSTEMI, unstable angina/non-ST elevation myocardial infarction; UPLM, unprotected left main disease; VT, ventricular tachycardia.

Adapted with permission from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/ PCNA/SCAI/STS Guidelines for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society of Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.

report freedom from angina and improved quality of life early after randomization, there were no significant differences between groups 24 months following treatment assignment.[142] Furthermore, the additional financial cost of PCI was not offset by gains in life-years or quality-adjusted life-years.

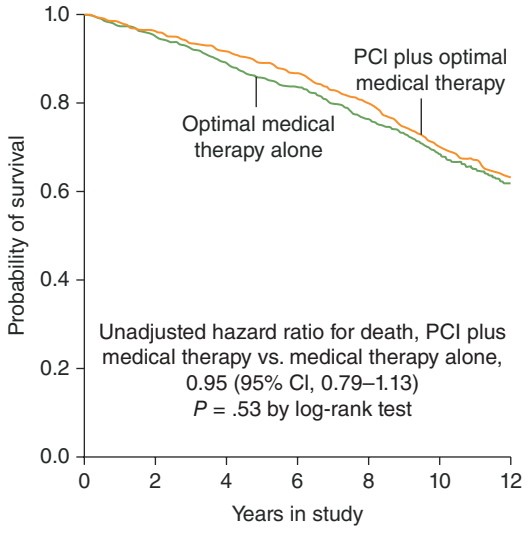
ISCHEMIA Trial

Subgroup data from the COURAGE trial suggest that PCI plus OMT may be preferred over OMT alone in patients with SIHD and high residual ischemic burden on MPI (see earlier section on MPI). However, the question of whether moderate or severe ischemia is a sufficient determinant of treatment strategy in this population has not been subjected to sufficiently powered prospective clinical studies.[143] In clinical practice, proponents in favor of OMT are matched by those in favor of revascularization for patients with this clinical profile. There is strong agreement, therefore, that additional trials are needed to address this clinical equipoise and guide management of this sizeable and potentially vulnerable patient population.[144] The International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial aims to address this issue by studying patients with SIHD, defined by ≥ 10% ischemic myocardium by MPI, ≥ 3 of 16 segments with stress-induced severe hypokinesis or akinesis by echocardiography, ≥ 12% ischemic myocardium by stress cardiac MRI, or ST depression > 2.0 mm observed at a low exercise workload in patients with typical angina during an exercise treadmill testing (NCT01471522 at ClinicalTrials.gov). Investigators anticipate involving approximately 300 participating sites from 30 countries. Subjects with normal renal function undergo CCTA upon enrollment to exclude anatomic left main disease or the absence of obstructive



No. at risk							
Optimal medical therapy	1138	1072	869	590	455	403	280
PCI plus optimal medical therapy	1149	1088	894	620	486	416	302

A Whole study cohort



No. at risk							
Optimal medical therapy	598	569	533	500	455	403	280
PCI plus optimal medical therapy	613	589	561	529	486	416	302

B Extended follow-up study cohort

FIGURE 43–4. Effect of percutaneous coronary intervention (PCI) on long-term survival in patients with stable ischemic heart disease. Kaplan-Meier estimates of survival in the two treatment groups. **A.** Number of patients at risk in the whole study cohort. It also shows the expected survival (without censoring of data) of 2287 persons who were matched by age and sex to the COURAGE population according to data from the US vital statistics report for 2009. **B.** Number of patients at risk in the cohort of patients with extended follow-up. The curves in both panels have been truncated at 12 years, which is the approximate median duration of follow-up in the extended follow-up cohort. Reproduced with permission from Sedlis SP, Hartigan PM, Teo KK: Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease. *N Engl J Med*. 2015 Nov 12;373(20):1937-1946.[140]

epicardial CAD. Patients are then randomized to an invasive strategy (OMT plus revascularization) or a conservative strategy (OMT alone). Over an average follow-up time of 3 years, differences between groups for the composite primary end point of cardiovascular death and nonfatal MI will be assessed, as well as various secondary end points.[145]

FAME Trials

Assessing fractional flow reserve (FFR) involves measuring the pressure gradient across a fixed coronary stenosis at the time of maximal coronary vasodilation, usually after adenosine infusion. Findings from the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial demonstrated that stenting atherosclerotic lesions defined by FFR < 0.75 was associated with a decrease in cardiovascular end points.[146] These data shifted the approach to lesion selection for PCI from an anatomic basis to one determined by physiology. By assessing the functional relevance of atherosclerotic lesions, particularly 50% to 70% occlusions, FFR analysis provides a point-of-care diagnostic opportunity to determine the functional significance of lesions that may appear otherwise equivocal on two-dimensional angiography. To determine whether FFR could be used in a manner akin to high ischemic burden on MPI for guiding appropriateness of PCI in SIHD, the FAME-2 trial[147] measured outcomes in this patient population when referred for angiography and randomized to FFR-guided PCI plus OMT or OMT alone. Findings from the study suggested a benefit in the FFR-guided PCI plus OMT group, in which the composite end point of death, MI, or urgent revascularization was significantly reduced compared to OMT alone (4.3% vs 12.7%; HR, 0.32; 95% CI, 0.19-.053; $P < .0001$; Fig. 43–5). The composite end point reduction was driven by a decrease in the need for urgent revascularization; the individual end points of death and MI did not differ between groups. Directionally similar findings have been reported in other large clinical trials.[148,149] Although findings from FAME-2 are encouraging and provide an additional framework for the application of FFR in clinical practice, additional data to substantiate these findings will be forthcoming.

BARI 2D Trial

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial established that an *initial* revascularization strategy with either PCI or CABG surgery offered no significant survival advantage over OMT alone in patients with type 2 diabetes and SIHD.[150,151] In this trial, 2368 type 2 diabetic patients with SIHD were selected for revascularization with either PCI or CABG surgery at the discretion of the managing physician. Approximately 13% of those enrolled had proximal LAD disease, whereas nearly one-third had three-vessel CAD. Patients were randomized to receive either prompt revascularization (within 4 weeks) or OMT, unless their angina progressed and required more urgent revascularization. Patients were subsequently randomized in a 2×2 factorial design to receive either insulin provision or insulin-sensitization therapy. Among patients undergoing PCI, 34.7% received a DES, 56.0% received a bare metal stent, and 9.3% did not receive a stent.[150] At 5 years, rates of survival and freedom from major adverse cardiovascular events did not differ between the medical and revascularization arms or between those allocated to insulin provision versus insulin sensitization (Fig. 43–6). Patients for whom CABG was the intended method of revascularization (CABG stratus) and who were assigned to revascularization had significantly fewer major cardiovascular events than did patients in the CABG stratum who were assigned to the medical therapy group. Forty-two percent of patients assigned to medical therapy crossed over to revascularization over the course of the study. It should be emphasized that BARI 2D was not a study of PCI versus CABG among patients with diabetes and chronic CAD.

Data from a recent multicenter, longitudinal, cross-sectional analysis of 2.7 million PCI procedures between 2009 and 2014 revealed important trends in nonacute PCI use that may reflect practice changes in response to data reported in the COURAGE and BARI-2D trials. From this study, nonacute PCI volume was observed to decrease from 89,704 in 2010 to 59,375 in 2014. Furthermore, patients undergoing nonacute PCI had higher angina severity levels, had greater use of antianginal medication, and were more likely to have high-risk findings on MPI in 2014 as compared to 2010.[152] Additional factors other than clinical trial data that may have influenced these trends include Appropriate Use Criteria for Coronary Revascularization[153] or other factors not yet studied. Among these may be the integration of certain clinical variables that assist in identifying patients who are likely to benefit from early CABG surgery. In one substudy of the BARI-2D trail, increase in myocardial jeopardy index (is, the ratio of myocardial territories supplied by diseased coronary arteries or their branches) and total number of coronary lesions, as well as prior coronary revascularization and decreased LVEF, identified a group of patients treated with CABG for whom the 5-year rate of death, MI, or stroke was substantially decreased compared to OMT. An increase in the magnitude of this effect was observed when considering patients with worrisome angiographic findings and increased Framingham risk score.[154]

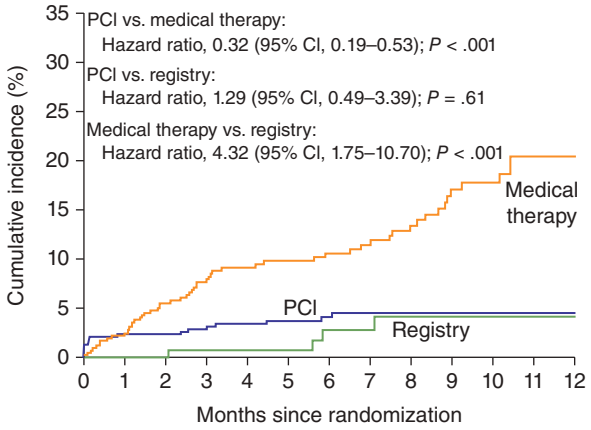
PERCUTANEOUS CORONARY INTERVENTION VERSUS CORONARY ARTERY BYPASS GRAFT SURGERY

The conventional approach to patients with high-risk multivessel CAD has favored surgical revascularization. This strategy is an outgrowth of results from older randomized trials, including the CASS study, which demonstrated a long-term survival benefit for patients undergoing initial therapy with CABG surgery in whom isolated left main CAD, left main equivalent CAD, or three-vessel CAD with LV systolic dysfunction was known.[155] Importantly, the efficacy of surgery in these studies was greatest in patients with impaired LV systolic function and/or severe symptoms.

Numerous comparisons between PCI and CABG surgery for patients with multivessel CAD have been conducted. Evolving technologic advances in stent design, antiplatelet therapies, techniques for chronic total occlusion, and lipid-lowering drugs; improvement in myocardial preservation techniques; and use of arterial conduits at surgery have confounded the application of these older data to contemporary practice.

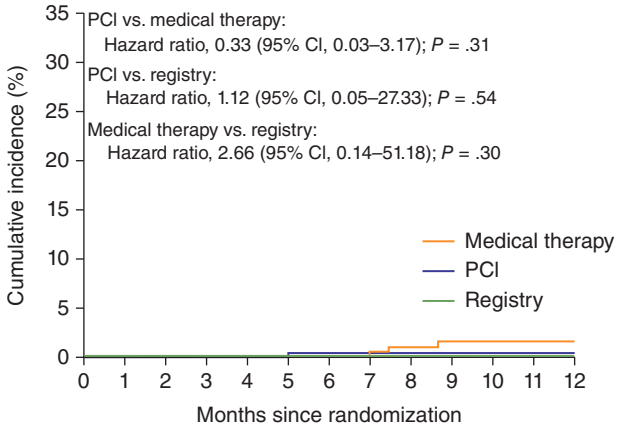
As a result of increased utilization of angioplasty as an initial revascularization strategy for patients with symptomatic CAD in the early 1990s, the Bypass Angioplasty Revascularization Investigation 1 (BARI-1) trial was conducted to test the hypothesis that balloon angioplasty and CABG surgery are equally effective strategies for patients with multivessel CAD and angina.[156] In BARI-1, 1829 multivessel CAD patients were randomly assigned to undergo percutaneous transluminal coronary angioplasty (PTCA) or CABG surgery and were followed for > 5 years. No long-term survival advantage was seen for CABG surgery versus PTCA, although a subset of patients with treated diabetes demonstrated improved survival with surgery when the left internal thoracic artery was used for LAD bypass. Importantly, patients with anatomically significant left main CAD (> 50% stenosis) or a history of unsuccessful PTCA or stent placement were excluded from trial entry. Only 43 subjects had disease of the proximal LAD, and the mean EF was 56%. Many experts have argued that the BARI-1 patients were not representative of those thought to benefit most from surgical revascularization. The BARI-1 trial was conducted prior to the DES era.

To investigate the influence of DES use on PCI versus CABG outcomes in patients with chronic CAD, Hannan and colleagues[157] performed an observational study using 2003 to 2004 data from the Cardiac Surgery Reporting System (CSRS) and the Percutaneous



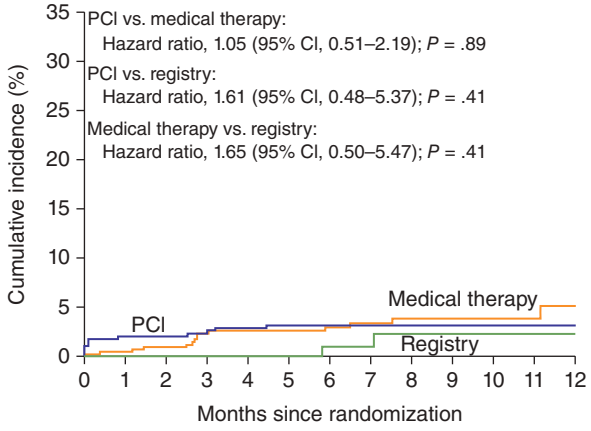
No. at risk													
Medical therapy	441	414	370	322	283	253	220	192	162	127	100	70	37
PCI	447	414	388	351	308	277	243	212	175	155	117	92	53
Registry	166	156	145	133	117	106	93	74	64	52	41	25	13

A Primary end point



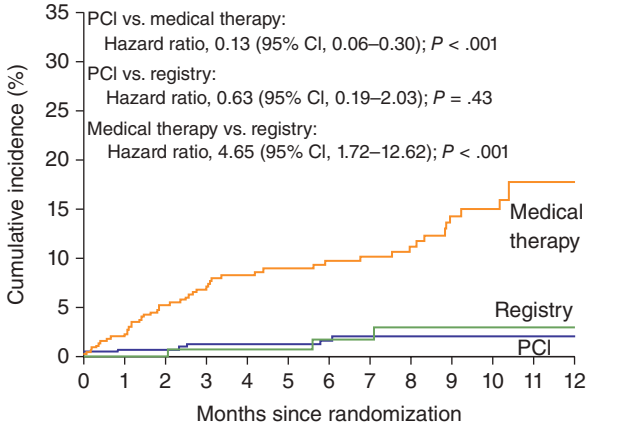
No. at risk													
Medical therapy	441	423	390	350	312	281	247	219	188	154	122	90	54
PCI	447	423	396	359	318	288	250	220	183	163	122	95	54
Registry	166	156	145	134	118	107	96	76	67	55	43	27	13

B Death from any case



No. at risk													
Medical therapy	441	421	386	341	304	273	239	212	182	148	117	85	48
PCI	447	414	388	352	309	278	244	214	177	157	119	94	54
Registry	166	156	145	134	118	107	95	75	65	53	42	26	13

C Myocardial infarction



No. at risk													
Medical therapy	441	414	371	325	286	256	223	195	164	129	101	71	38
PCI	447	421	395	356	315	285	248	217	180	160	119	93	53
Registry	166	156	145	133	117	106	94	75	65	53	42	26	13

D Urgent revascularization

FIGURE 43–5. Fractional flow reserve–guided percutaneous coronary intervention (PCI) and outcome in patients with stable ischemic heart disease. Kaplan-Meier curves are shown for the cumulative incidence of the primary end point of death, myocardial infarction, or urgent revascularization (**A**) and the individual components of the primary end point (**B**, **C**, and **D**) in the group that was randomly assigned to PCI and the best available medical therapy (PCI), the group that was randomly assigned to the best available medical therapy alone (medical therapy), and the group that did not undergo randomization and was enrolled in a registry (registry). After 12 months, a total of two primary end point events occurred in the PCI group, none in the medical therapy group, and one in the registry cohort. No deaths occurred after 12 months in any of the groups. Two patients in the PCI group, none in the medical therapy group, and one in the registry cohort had a myocardial infarction after 12 months. One patient in the registry cohort and none in the other two groups had an urgent revascularization performed after 12 months. Reproduced with permission from De Bruyne B, Pijls NH, Kalesan B, et al: Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012 Sep 13;367(11):991-1001.[147]

Coronary Intervention Reporting System (PCIRS) of the New York State Department of Health. Patients with a history of revascularization, left main CAD, or MI < 24 hours after treatment were excluded. Surgical revascularization for three- or two-vessel CAD was associated with lower rates of death and death or MI compared with PCI with DES over 18 months of follow-up. The survival rates of patients with diabetes were significantly higher in the surgical revascularization group; a subset analysis showed lower rates of death and MI in patients with EF ≤ 0.40 treated with surgery. The results from this study were akin to previous observations in the pre-DES era, as consolidated in a meta-analysis, suggesting that CABG surgery for the treatment of multivessel CAD is associated with lower long-term mortality rates than PCI in a real-world setting.[158] Directionally similar findings were reported in the ASCERT 1 observational study, which retrospectively analyzed outcome data from 189,793 patients with two- or three-vessel CAD without acute MI undergoing CABG surgery (n = 86,244) or PCI (n = 103,549). Although at 1 year of follow-up there was no significant difference between groups for outcome, the adjusted mortality rate at 4 years was lower for CABG patients compared to PCI patients (RR, 0.79; 95% CI, 0.76-0.82).[159-162]

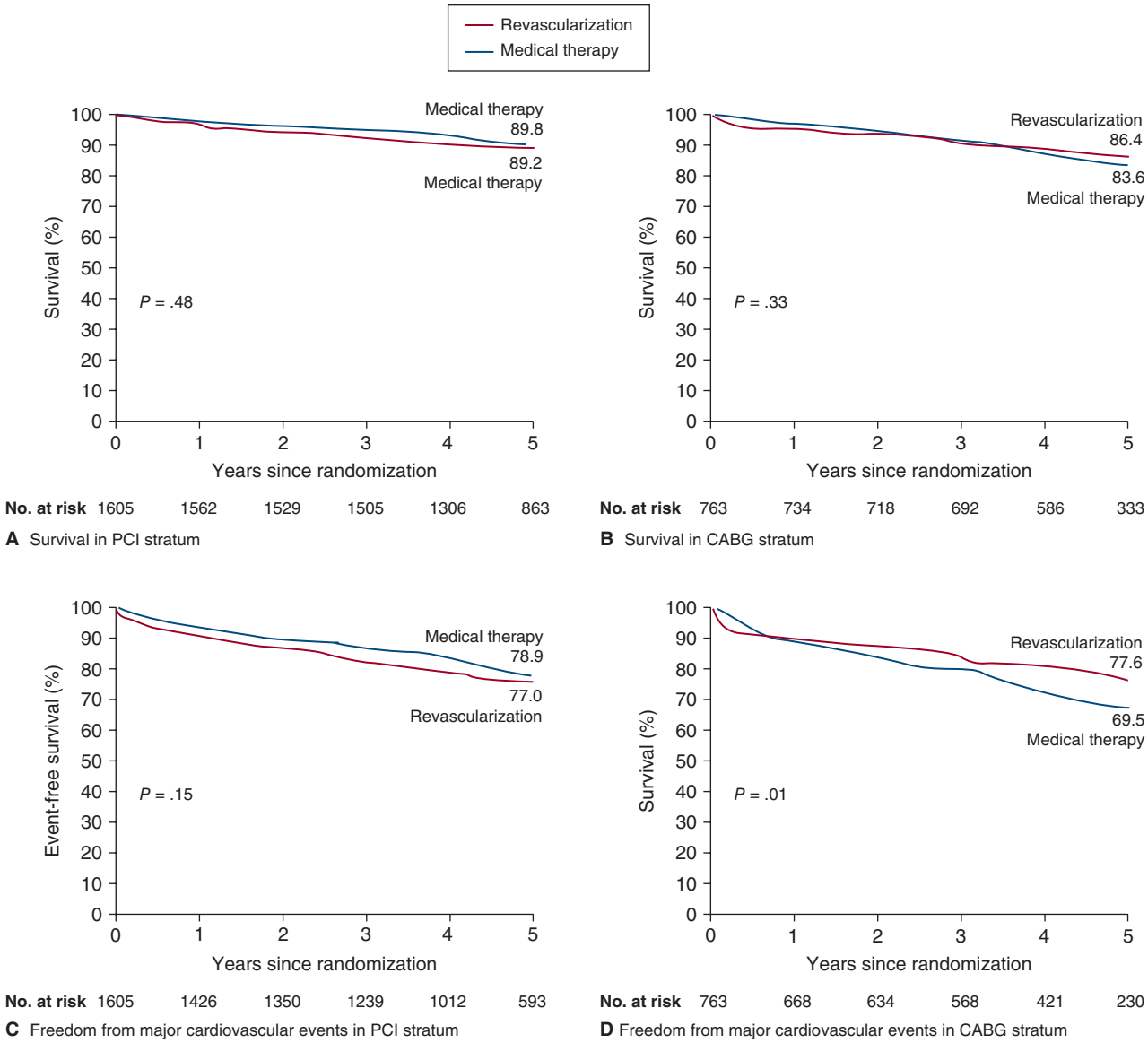


FIGURE 43–6. The effect of percutaneous (**A**, **C**) or surgical (**B**, **D**) revascularization compared with medical therapy alone on survival and freedom from major cardiovascular events (death, myocardial infarction, or stroke) in type 2 diabetic patients with chronic coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Reproduced with permission from The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Eng J Med*. 2009 June 11;360(24):2503-2515.[150]

SYNTAX TRIAL

The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial was designed to demonstrate noninferiority between multivessel PCI (with a first-generation paclitaxel-eluting stent) and CABG surgery for patients with multivessel CAD for the primary composite end point of death from any cause, stroke, MI, or repeat revascularization during the 12 months following treatment.[163] The SYNTAX trial differed from previous studies by virtue of DES use, inclusion of patients with significant left main CAD in both treatment arms, and joint involvement of interventional cardiologists and cardiac surgeons in the assessment of CAD severity and treatment allocation. The results suggested that surgical revascularization resulted in a significantly lower rate of the combined primary end point. This effect was largely driven by the reduced need for revascularization after surgery versus PCI. Surgery resulted in an increased likelihood of periprocedural stroke, although there was no difference between treatment groups for the combined end point of death from any cause, stroke, or MI.

Among the strengths of the SYNTAX trial was the use of a numerical score for the objective evaluation of coronary disease severity and likelihood of revascularization success. The SYNTAX score is generated by summarizing various qualitative plaque features and stenosis locations and serves as an objective measure of coronary disease severity that can be used to stratify anticipated patient outcomes (Table 43–9; also see syntaxscore.com).[163] Patients with high (≥ 33) and intermediate (23-32) SYNTAX scores had lower rates of MACCEs with surgery compared with PCI out to 5 years (high SYNTAX score: 26.8% surgery vs 44.0% PCI; $P < .0001$; intermediate SYNTAX score: 25.8% surgery vs 36.0% PCI). Event rates were similar for patients with low SYNTAX scores (≤ 22). The trial also established that PCI is noninferior to bypass surgery for treatment of left main CAD (31.0% MACCE rate in the CABG surgery group vs 36.9% in the PCI group; $P = .12$).[164]

TABLE 43–9. Key Angiographic Characteristics That Influence the SYNTAX Score

Right, left, or codominant coronary circulation
Number of atherosclerotic lesions
Number of artery segments involved per atherosclerotic lesion
Total occlusion:
Number of segments involved
Age of total occlusion
Presence of a blunt stump
Presence of bridging collateral
Antegrade vs retrograde filling of the first segment beyond the occlusion
Side branch involvement
Trifurcation lesion: number of vessel segments diseased
Bifurcation lesion: angulation between the distal main vessel and the side branch < 70°
Presence of an aorto-ostial atherosclerotic lesion
Presence of severe vessel tortuosity at lesion site
Atherosclerotic lesion length > 20 mm
Presence of heavily calcified plaque
Presence of thrombus
Presence of diffuse or small-vessel disease

Abbreviation: SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.[163]

SYNTAX SCORE II

One limitation to the original SYNTAX score was that patient-specific clinical variables were not used to inform decision-making with respect to the choice between CABG or PCI (Fig. 43–7). The SYNTAX II score was developed to account for baseline clinical/demographic features. The SYNTAX II score, which predicted a difference in outcome according to CABG or PCI therapy, is composed of the following eight variables: anatomic SYNTAX score, age, creatinine clearance, LVEF, presence of unprotected left main CAD, peripheral vascular disease, female sex, and chronic obstructive pulmonary disease. Results from this analysis suggested that patients who are older with unprotected left main CAD and chronic obstructive pulmonary disease require a higher SYNTAX score (more complex coronary artery anatomy) to favor treatment with CABG (Fig. 43–8). Overall, this study provides evidence in support of individual-specific algorithms for determining risk and optimal treatment strategy for complex CAD patients.[165]

REVASCULARIZATION AND CLINICAL DECISION MAKING IN STABLE ISCHEMIC HEART DISEASE

Progress in Coronary Stent Technology

Sufficient long-term follow-up data have been accrued for patients undergoing PCI with conventional bare metal stent, cobalt-chromium everolimus-eluting stent (EES), paclitaxel-eluting stent (PES), and sirolimus-eluting stent (SES), as well as bioabsorbable polymer-based biolimus-eluting stent (BES).[166] Based on data from 51 randomized clinical trials (n = 52,158 patients), Palmerini and colleagues[167] reported that EES therapy was superior to other stents at a median follow-up of 3.8 years for decreasing mortality, stent thrombosis, and MI. They further distinguish zotarolimus-eluting stents as having lower rates of stent thrombosis than SES and lower rates of MI than bare metal stent or PES. These findings are in concert with clinical trial data suggesting incremental benefit in outcome according to technologic iteration of stents. For example, the Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System (SPIRIT IV) trial randomized 3687 patients with inducible angina or ischemia undergoing PCI and found that patients receiving EES had improved outcome compared to patients receiving PES based on lower rates of the primary end point of target lesion failure (4.2 vs 6.8%; RR, 0.62; 95% CI, 0.46-0.82; $P = .001$), as well as the secondary end points of MI and stent thrombosis.[168] Other factors that influence PCI efficacy include optimal stent placement (apposition), concomitant use of intravascular ultrasound or optical coherence tomography, and measurement of FFR.

Progress in Off-Pump Coronary Artery Bypass Graft Surgery

Traditional CABG surgical strategy is associated with stroke or cognitive impairment (ie, postperfusion syndrome) as a result of microemboli formation in the cardiopulmonary bypass filter, instrumentation of the aorta, and adverse changes in arteriolar tone/permeability of the central nervous system circulation.[169] By contrast, off-pump CABG surgery, in which graft anastomosis is performed on the beating heart to avoid cardiopulmonary bypass, has been proposed as an alternative strategy to conventional CABG surgery that is safer. Indeed, a number of meta-analyses suggest a decrease in risk for mortality, stroke, renal failure, blood transfusion requirement, inotropic support, or hemodynamic support among patients undergoing off-pump versus conventional CABG surgery.[170,171] However, head-to-head trials comparing these approaches are limited, although availability of these data would seem to be important given the technical difficulty of performing vascular grafting on the beating heart. In the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) study, patients > 75 years of age referred for first-time CABG surgery (n = 2539) were randomized to the off-pump or conventional surgical approach. There was no difference between groups for the composite end point of death, stroke, MI, or repeat revascularization at 30 days or 1 year, calling into question the advantage of the off-pump approach even in a patient cohort at increased risk based on age at enrollment.[172]

Hybrid Revascularization

CABG surgery remains the favored revascularization strategy for patients with multivessel CAD and high SYNTAX scores, particularly in the presence of LV systolic dysfunction or diabetes. However, the principal driver of clinical benefit in this patient group appears to be based on the efficacy of internal mammary artery anastomosis to the LAD coronary artery.[173] By contrast, vein graft occlusion may occur in up to 30% of patients within 1 post-operative year, whereas DES patency rates in non-LAD coronary arteries are on par or better than that reported for vein grafts.[174] This raises the possibility that a hybrid approach involving left internal mammary artery–LAD graft placement surgery and PCI using DES to atherosclerotic non-LAD lesions, or hybrid coronary revascularization (HCR), may be an optimal revascularization approach in patients with multivessel CAD. Although definitive outcome data for HCR remain lacking, this approach appears safe and technically feasible but at present is markedly underused.[174] In one study of 147 patients with multivessel CAD treated with HCR and case matched to a cohort of patients undergoing off-pump CABG surgery with sternotomy, no difference between groups was observed for 5-year survival (86.6% vs 84.3%; $P = .61$), although the need for repeat revascularization or blood transfusion was higher and lower, respectively, in the HCR group.[175] A number of prospective clinical trials examining the role of HCR in multivessel

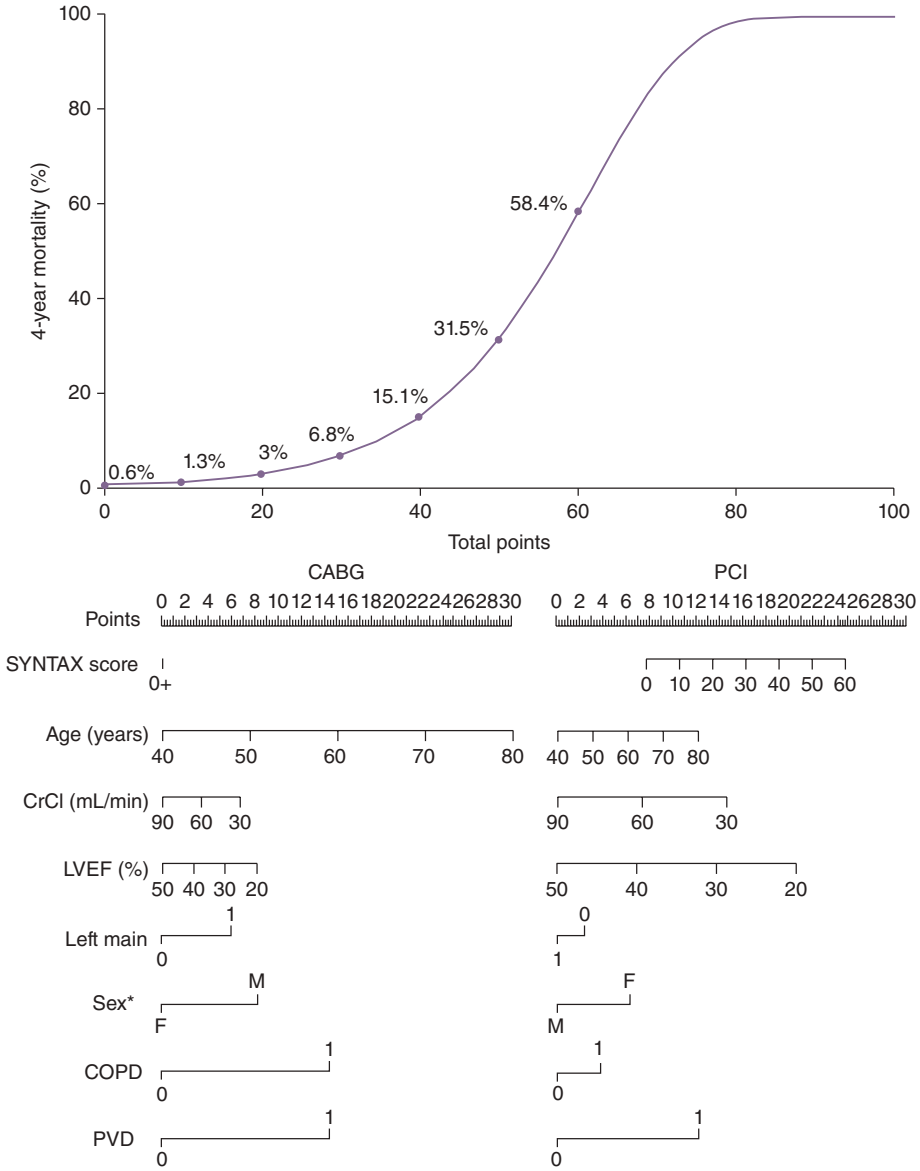


FIGURE 43–7. The SYNTAX II nomogram. The total number of points for eight factors can be used to accurately predict 4-year morality for the individual patient proposing to undergo for coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). For example, a 60-year-old man with an anatomic SYNTAX score of 30, unprotected left main coronary artery disease, creatinine clearance of 60 mL/min, left ventricular ejection fraction (LVEF of 50%), and chronic obstructive pulmonary disease (COPD) would have 41 points (predicted 4-year mortality, 16.3%) to undergo CABG and 33 points (predicted 4-year mortality, 8.7%) to undergo PCI. The same example without COPD included would lead to identical points (29 points) and 4-year mortality predictions (6.3%) for CABG and PCI. CrCL, creatinine clearance; Left main, unprotected left main coronary artery disease; PVD, peripheral vascular disease; 3-VD, three-vessel disease. Reproduced with permission from Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013 Feb 23;381(9867):639-650.[165]

CAD patients and accounting for high-risk subphenotypes, such as diabetes, are ongoing (eg, NCT02504762, NCT02293928 at ClinicalTrials.gov).

LESS TRADITIONAL THERAPIES IN PATIENTS WITH REFRACTORY ANGINA

For patients with angina refractory to conventional medical or revascularization therapies, palliative treatment with spinal cord stimulation, enhanced external counterpulsation (EECP), or surgical transmyocardial laser revascularization (TMLR) may be considered.[86]

SPINAL CORD STIMULATION

The efficacy of spinal cord stimulation depends on the accurate placement of the stimulating electrode in the dorsal epidural space, usually at the C7 to T1 level. Data in favor of spinal cord stimulation as a useful treatment for refractory angina are mainly limited to case series and small clinical trials. The Electrical Stimulation Versus Coronary Artery Bypass Surgery in Severe Angina Pectoris (ESBY) study randomized 104 patients with end-stage ischemic heart disease to spinal cord stimulation or CABG surgery.[176] Participants in the ESBY trial were at elevated surgical risk and had preoperative clinical profiles that did not predict a clear prognostic benefit from surgery. Compared with surgery, spinal cord stimulation resulted in lower 6-month mortality with similar improvement in angina frequency and severity.[176] Subsequent trials have been underpowered or have not shown a compelling benefit with respect to angina, quality of life score, or improvement in exercise tolerance with spinal cord stimulation in patients with severe, refractory angina.[177] Nonetheless, spinal cord stimulation appears safe, and speculation remains that this intervention favorably influences sympathetically and parasympathetically mediated neurovascular tone, improves CBF, and exerts anti-ischemic effects in some patients.[178]

ENHANCED EXTERNAL COUNTERPULSATION

EECP uses cuff inflation for the application of compressed air-induced pressure to the lower extremities that is synchronized with the cardiac cycle. Specifically, in early diastole, positive pressure is applied sequentially from the lower legs to the lower and upper thighs for the facilitation of increased retrograde aortic blood flow and increased coronary diastolic perfusion pressure. In patients with refractory angina, EECP (~35 hours of treatment time) is associated with a reduction in angina frequency and nitrate use, increased exercise tolerance, and improved quality of life.[179,180] Patients with severely limiting angina and without a smoking history are most likely to benefit.[181] Certain forms of valvular heart disease (eg, aortic regurgitation), recent revascularization, and severe hypertension are contraindications to this form of therapy. Nevertheless, the favorable response to EECP observed in select patients with refractory angina has raised speculation that it should be implemented earlier in the treatment course. Sufficiently powered randomized clinical trials of EECP versus OMT are lacking.

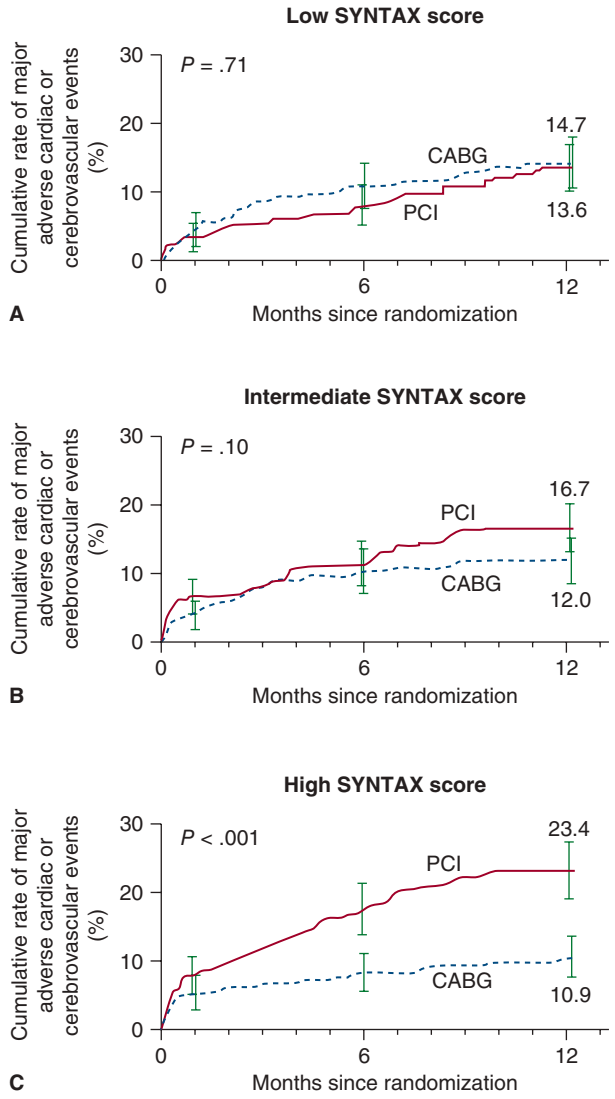


FIGURE 43–8. The role of atherosclerotic lesion severity as assessed by the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score in determining efficacy of percutaneous coronary intervention (PCI) or surgical revascularization in patients with three-vessel or left main coronary artery disease enrolled in the SYNTAX trial. The rates of major adverse cardiac or cerebrovascular events 12 months following therapy are reported for patients with low (**A**), intermediate (**B**), or high (**C**) SYNTAX score. The I bars indicate 1.5 standard errors. Note the improved outcomes among patients with high SYNTAX scores who underwent revascularization. CABG, coronary artery bypass graft. Reproduced with permission from Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009 Mar 5;360(10):961-972.[162]

TRANSMYOCARDIAL LASER REVASCULARIZATION

TMLR has been performed in the operating room (using a carbon dioxide or holmium:YAG laser) or catheterization laboratory by percutaneous approach with a specialized (holmium:YAG laser) catheter. Early uncontrolled studies suggested that percutaneous TMLR may provide symptomatic relief in patients with angina refractory to maximal medical therapy.[182] However, subsequent randomized, placebo-controlled trials were unable to substantiate these findings and demonstrated no benefit for percutaneous TMLR beyond that of a sham procedure when patients were blinded to treatment status.[183] Findings from prospective randomized controlled trials support surgical TMLR beyond medical therapy alone for symptom relief and decreased hospitalization frequency. Furthermore, in a multicenter randomized trial comparing surgical TMLR with medical therapy in 192 patients with angina refractory to maximal medical therapy, Frazier and colleagues correlated improvements in CCS class from surgical TMLR with a decrease in the number of fixed or reversible perfusion defects evaluated by MPI.[185] These findings have not been widely replicated. The mechanism by which TMLR reduces angina is also not resolved. As a result of discrepancies among reports on efficacy and concern for increased rates of iatrogenic morbidity following surgical or percutaneous TMLR, including ventricular perforation, cardiac tamponade, stroke, and MI, the use of this strategy is controversial.[121]

CHELATION THERAPY

Sodium ethylenediamine tetra acetic acid (EDTA) has long been recognized for its capacity to bind di- or trivalent cations, including some implicated in the pathobiology of atherosclerotic CAD, such as calcium (Ca^{2+}). On the heels of promising data from small, uncontrolled trials suggesting a potential benefit with chelation therapy in patients with CAD, the Trial to Assess Chelation Therapy (TACT) was completed and serves as the first sufficiently powered trial studying EDTA therapy in CAD. In this double-blind placebo-controlled 2 × 2 factorial multicenter randomized trial, 1708 patients (> 50 years old, > 6 weeks post-MI, serum creatinine < 2.0 mg/dL) were randomized to receive 40 infusions of 500 mL of chelation solution fortified with B vitamins versus placebo and to an oral vitamin regimen or placebo. A favorable effect on the primary end point of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for recurrent angina was observed in patients randomized to chelation compared to placebo (HR, 0.82; 95% CI, 0.69-0.99; $P = .035$), which did not appear to hinge on randomization to the oral vitamin therapy stratum.[186] The effect of chelation was most pronounced in patients with diabetes or prior anterior MI, setting the framework for the forthcoming TACT-2 trial that aims to assess the benefit of combination chelation plus oral vitamin and mineral therapy in diabetic CAD patients specifically.[187] A pathophysiologic mechanism accounting for the benefits of chelation therapy in the original TACT study remains unclear, however, and additional data are necessary to clarify indications, timing, and duration of the chelation therapy.

FOLLOW-UP OF PATIENTS WITH STABLE ISCHEMIC HEART DISEASE

Following initiation and titration of OMT, reevaluation every 4 to 6 months is recommended. A general assessment of functional capacity, response to treatment, changes in quality of life, and any adverse medication effects is advised. Patients should be screened for depression, social isolation, chronic kidney disease, peripheral vascular disease, sexual dysfunction, and obstructive sleep apnea.[188-190]

An assessment of LVEF and segmental wall motion by echocardiography or MPI is recommended in patients with a change in symptoms or evidence of MI by history or ECG,[191] but not routinely in the absence of these clinical indications. Laboratory assessment of fasting lipids and glucose should be performed in accordance with current guideline recommendations.[192] In the stable patient without weight change or dietary modification, lipids can be assessed every 6 to 12 months.

Guidelines are imprecise regarding the frequency with which routine noninvasive testing should be repeated in patients with SIHD. Echocardiography, SPECT MPI, CCTA, or cardiac MRI is not recommended in SIHD patients when performed more frequently than at 5-year intervals after CABG or 2-year intervals after PCI.[191] Patients at relatively low risk for future cardiovascular events (eg, those with stable

TABLE 43–10. American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine Recommendations for Cardiovascular Testing During Patient Follow-Up

	Exercise-Status		ECG Interpretable			
Test	Able	Unable	Yes	No	COR	LOE
Patients able to exercise*						
Exercise ECG	X		X		I	B
Exercise with nuclear MPI or Echo	X			X	I	B
Exercise with nuclear MPI or Echo	X		Any		IIa	B
Pharmacological stress nuclear MPI/Echo/CMR	X		X		III No Benefit	c
Patients unable to exercise						
Pharmacological stress nuclear MPI or Echo		X	Any		I	B
Pharmacological stress CMR		X	Any		IIa	B
Exercise ECG		X		X	III No Benefit	C
Irrespective of ability to exercise						
CCTA	Any		Any		IIb	B
CCTA	Any		Any		IIb	B
CCTA	Any		Any		III No Benefit	B

*Patients are candidates for exercise testing if they are capable of performing at least moderate physical exercise and have no disabling comorbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.

Abbreviations: CABG, coronary artery bypass graft surgery; CCTA, cardiac computed tomographic angiography; CMR, cardiac magnetic resonance imaging; COR, class of recommendation; ECG, electrocardiogram; Echo, echocardiography, LOE, level of evidence; MPI, myocardial perfusion imaging; N/A, not available; SIHD, stable ischemic heart disease; UA, unstable angina.

Adapted with permission from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/ PCNA/SCAI/STS Guidelines for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society of Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.

CCS class, preserved LV function, unchanged functional capacity) do not require annual stress testing.[86] Routine follow-up stress testing at 3- to 5-year intervals may be useful in selected patients, including those with diabetes or known incomplete revascularization. Table 43–10 provides the ACC/AHA indications for performing echocardiography, exercise treadmill testing, stress MPI, and coronary angiography in the follow-up setting.

CHEST PAIN WITHOUT SIGNIFICANT EPICARDIAL CORONARY DISEASE

MICROVASCULAR CIRCULATORY DISEASE

Angina with normal-appearing epicardial coronary arteries may reflect microvascular circulatory dysfunction and impaired intramyocardial perfusion. Formerly termed *cardiac syndrome X*, recent investigations have defined more clearly the pathophysiology of microvascular circulatory dysfunction (Table 43–11).[193,194] The original epidemiologic observations that reported a clustering of patient characteristics associated with this clinical phenomenon (eg, female predominance, hypertension, obesity) have been redefined to emphasize the histologic and pathophysiologic processes that increase the probability of disease expression (Table 43–12). Abnormal coronary vascular reactivity from impaired endothelial-dependent and -independent signaling likely explains decreased coronary flow reserve associated with most forms of this condition.[195]

Microvascular ischemia is often difficult to diagnose. Comparison of myocardial blood flow under basal conditions and after intracoronary infusion of adenosine with a Doppler flow wire can be performed once obstructive epicardial CAD has been excluded at angiography.[193] Assessment of CFR or myocardial perfusion reserve using PET or cardiac MRI is the most common and reliable noninvasive method for diagnosing microvascular circulatory dysfunction. Many investigators and clinicians use a cutoff of < 3.0 mL/min/g myocardial tissue (quantified at peak hyperemia relative to rest) to diagnose microvascular circulatory disease provided the patient has cardiac angina and that no epicardial coronary stenosis > 50% is present.[196]

Data from the Women's Ischemia Syndrome Evaluation (WISE) study demonstrated a positive association between impaired coronary microvascular reactivity and abnormal functional capacity.[197] In this analysis, 190 women (18% with epicardial coronary luminal stenosis > 50%) underwent invasive assessment of coronary flow velocity in response to intracoronary adenosine injection. Women with a decreased coronary flow velocity response were significantly more

TABLE 43–11. Clinical Causes of Coronary Microvascular Circulatory Disease

Coronary microvascular dysfunction in the absence of obstructive CAD and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states). It can be identified by noninvasive assessment of coronary flow reserve. This type is at least partly reversible, and coronary flow reserve can also be used as a surrogate end point to assess efficacy of treatments aimed at reducing the burden of risk factors.
Coronary microvascular dysfunction in the presence of myocardial diseases	This type is sustained in most instances by adverse remodeling of intramural coronary arterioles. It can be identified by invasive or noninvasive assessment of coronary flow reserve and may be severe enough to cause myocardial ischemia. It has independent prognostic value. It remains unclear whether medical treatment may reverse some cases. It is found with primary (genetic) cardiomyopathies (eg, dilated and hypertrophic) and secondary cardiomyopathies (eg, hypertensive and valvular).
Coronary microvascular dysfunction in the presence of obstructive CAD	This type may occur in the context of either stable CAD or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors. It is more difficult to identify than the first two types and may be identified through the use of an integrated approach that takes into account the clinical context with the use of a combination of invasive and noninvasive techniques. There is some early evidence that specific interventions might prevent it or limit the resultant ischemia.
Iatrogenic coronary microvascular dysfunction	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization. It can be identified with the use of either invasive or noninvasive means on the basis of a reduced coronary flow reserve, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore coronary flow reserve, and it may also change the clinical outcome. The likelihood of distal embolization can be reduced by the use of appropriate devices during high-risk procedures.

Abbreviation: CAD, coronary artery disease.

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likely to have reduced exercise tolerance compared with women with normal vascular reactivity. Treatment of patients with microvascular disease should focus on pathophysiologic mechanisms that contribute to endothelial dysfunction, with emphasis on smoking cessation, lipid and glycemic management, and blood pressure control. Conventional anti-ischemic therapy may control symptoms in some patients, but

TABLE 43–12. Pathogenic Mechanisms of Coronary Microvascular Circulatory Disease

Alterations	Causes
Structural	
Luminal obstruction	Microembolization in acute coronary syndromes or after recanalization
Vascular-wall infiltration	Infiltrative heart disease (eg, Anderson-Fabry cardiomyopathy)
Vascular remodeling	Hypertrophic cardiomyopathy, arterial hypertension
Vascular rarefaction	Aortic stenosis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
Dysfunction of smooth muscle cell	Hypertrophic cardiomyopathy, arterial hypertension
Autonomic dysfunction	Coronary recanalization
Extravascular	
Extramural compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension
Reduction in diastolic perfusion time	Aortic stenosis

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overall results are usually mixed.[198] Microvascular disease was not previously thought to confer an elevated risk of future adverse cardiovascular events or early mortality.[199,200] Up to 30% of women diagnosed with microvascular circulatory disease will develop clinically evident CAD within 10 years, and women with this condition experience 5-year cardiovascular disease event rates of approximately 8%.[201] In women with non–flow-limiting epicardial CAD who experience ACS, 30-day mortality rates of 2% have been reported.[202] As a result of persistent variability in treatment responsiveness to β-adrenergic receptor antagonists, CCB, ACE inhibitors, and nitrate therapy in this patient population, comprehensive longitudinal studies of novel therapies designed to characterize patient outcome are needed.

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CHAPTER 44

CORONARY ARTERY BYPASS GRAFTING AND PERCUTANEOUS INTERVENTIONS IN STABLE ISCHEMIC HEART DISEASE

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Great advances have been made in the consideration of coronary revascularization for patients with stable ischemic heart disease (SIHD). Perhaps the greatest advance over the past decade has been the establishment of the heart team approach. This is when clinical cardiologists, interventional cardiologists, and cardiovascular surgeons, along with nursing staff, consider together the revascularization options for our patients with SIHD. The heart team approach facilitates better engagement of the patient in the informed consent and decision-making processes.

DEFINITION OF STABLE ISCHEMIC HEART DISEASE

The diagnosis of SIHD is based on symptomatology and primarily obtained through the history of the patient (see Chap. 43). The traditional risk factors for the development of obstructive coronary artery disease (CAD) are ascertained to estimate its likelihood. Stable angina often presents with retrosternal heaviness and aching, which may or may not radiate to the jaw(s) or shoulder(s) and is provoked by exertion or emotional stress and relieved within 5 minutes of rest or nitroglycerine use. Patients with diabetes and other chronic conditions may present with atypical symptoms including the feeling of general malaise after exertion. In combination with the physical examination and 12-lead electrocardiogram (ECG), the important risk markers of hemoglobin A1C, lipid profile, renal and liver function tests, thyroid function tests, and hemoglobin should all be part of the initial evaluation.

ASSESSMENT OF ISCHEMIA ON THE BASIS OF NONINVASIVE TESTING

The identification of ischemic heart disease has largely relied on the documentation of ischemia by noninvasive testing (see Chap. 43). Noninvasive testing largely pertains to patients who are at intermediate risk for establishment of SIHD. Because the workup of noninvasive testing will be the topic of another chapter, it is important to emphasize that noninvasive testing is reserved for men over 40 and women over 60 with a strong history of the presence of angina. With the advancement of noninvasive technology spanning into computed tomography (CT), stress methoxyisobutylisonitrile (MIBI), and echocardiography, the most reliable noninvasive test should be accessible and of high expertise. The choice of noninvasive testing is based on whether or not the ECG is normal or whether or not a left bundle branch block or ventricular paced rhythm is present.

OPTIMAL MEDICAL EXPERTISE

All patients with a history of SIHD should be treated with optimal medical therapy (OMT; see Chap. 43), and it is important to follow evidence-based guidelines for OMT for all patients considered for coronary revascularization.[1] Routinely, patients would receive aspirin daily with or without additional $P2Y_{12}$ inhibitor antiplatelet therapy depending on the history of ischemic acute coronary syndrome. All patients with SIHD should be on a potent statin therapy and at high doses. All patients should be considered for an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, in particular patients with low ejection fraction, chronic kidney disease, diabetes, and hypertension. β-Blocker therapy should be considered in patients with SIHD and especially those with an ejection fraction < 40%. The β-blocker dose should be titrated to a heart rate between 50 and 60 bpm.

REVASCULARIZATION THERAPY

It is important to establish the reason for consideration of coronary revascularization in SIHD. Coronary revascularization is indicated for the improvement of angina symptoms and quality of life. The evidence for reduction of major adverse coronary and cerebrovascular events and reduction in mortality is largely limited to surgical coronary revascularization (coronary artery bypass grafting [CABG]). When approaching a discussion with the patient, there are a number of factors that need to be considered from the outset.

DEFINING THE EXTENT OF CORONARY ARTERY DISEASE

Coronary angiography is largely reserved for two major groups of patients, namely those who have inadequate symptom relief or persistent reduction in quality of life despite OMT and those with noninvasive testing indicating risk for ischemic events. Currently, the National Heart, Lung, and Blood Institute is sponsoring the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial to evaluate the benefit of coronary angiography in patients with high-risk features on noninvasive testing compared to OMT alone.[2] This pivotal trial carried out in 10 countries and in more than 200 centers will help us to better define which patients will be referred for consideration of coronary revascularization.

In the meantime, the criteria listed in Table 44–1 will be used to define patients who should be referred for coronary angiography,[3] including specific findings on noninvasive testing.

TABLE 44–1. Criteria for Referring Patients to Coronary Angiography

Exercise Treadmill
Exercise treadmill, > 2 mm of ST depression;
Exercise-induced ST-segment elevation;
Exercise-induced ventricular tachycardia/ventricular fibrillation; and
Failure to increase systolic pressure to > 120 mm Hg or a sustained decrease of > 10 mm Hg during exercise
Myocardial Perfusion Imaging
Severe left ventricular dysfunction, not readily explained;
Resting perfusion abnormalities > 10% of the myocardium;
Severe stress-induced left ventricular dysfunction;
Stress-induced perfusion abnormalities involving > 10% of the myocardium or stress and mental scores indicating multiple territories at risk;
Stress-induced left ventricular dilatation; and Increased lung uptake.
Stress Echocardiography
Inducible wall motion abnormalities involving > 2 segments or 2 coronary beds
Coronary Computed Tomography
Multivessel obstructive coronary disease or left main stenosis

Modified with permission from Mancini GB, Gosselin G, Chow B, et al. Canadian Cardiovascular Society. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease. *Can J Cardiol*. 2014 Aug;30(8):837-849.

MODE OF CORONARY REVASCULARIZATION

The mode of coronary revascularization is an individualized decision-making process for each patient. Beyond the heart team deliberation, the patient's own wishes and the balance of risk and benefits for each patients with regard to quality of life, duration of life, and potential adverse events should be considered. The consideration of technical issues, such as the potential for the completeness of revascularization, should also play a role.

The following review is largely based on recommendations of the 2014 American College of Cardiology (ACC)/American Heart Association (AHA)/American Association for Thoracic Surgery (AATS)/Preventive Cardiovascular Nurses Association (PCNA)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Thoracic Surgeons (STS) focused update on the guidelines for the diagnosis and management of patients with SIHD.[4] For the sake of discussion, we will be focusing on contemporary coronary artery bypass surgery using at least one arterial conduit and contemporary percutaneous coronary intervention largely involving drug-eluting stents.

ASSESSMENT OF DISEASE COMPLEXITY: ROLE OF THE SYNTAX SCORE

The extent and complexity of CAD are important parameters informing triage to percutaneous coronary intervention (PCI) versus CABG in patients with stable multivessel CAD. The SYNTAX Score (SS), developed for use in the multicenter Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial provides a semiquantitative angiographic measure of disease complexity that is useful for this purpose.[5] For a given patient, the SS represents a sum of scores for every lesion with > 50% diameter stenosis in vessels with a diameter > 1.5 mm. As outlined in Table 44–2, scores for individual

TABLE 44–2. The SYNTAX Score Algorithm

1. Dominance
2. Number of lesions
3. Segments involved per lesion, with lesion characteristics
4. Total occlusions with subtotal occlusions: a. Number of segments b. Age of total occlusions c. Blunt stumps d. Bridging collaterals e. First segment beyond occlusion visible by antegrade or retrograde filling f. Side branch involvement
5. Trifurcation, number of segments diseased
6. Bifurcation type and angulation
7. Aorto-ostial lesion
8. Severe tortuosity
9. Lesion length
10. Heavy calcification
11. Thrombus
12. Diffuse disease, with number of segments

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lesions reflect both the anatomic "importance" of the stenosis (derived from population-based estimates of the proportion of myocardium subtended by a given vascular segment) and the presence of features influencing the technical complexity of PCI (chronic total occlusion, bifurcation features, ostial location, lesion length, calcification, tortuosity, and presence of thrombus).[2,6] Accordingly, although the SS does provide a rough index of disease *burden* in a given patient, it is more accurately interpreted as a metric of the expected complexity of PCI.

The SYNTAX trial demonstrated that such complexity is an important determinant of the comparative effectiveness of PCI versus CABG. Among 1800 patients with previously untreated three-vessel CAD, left main CAD, or both randomized to PCI with a first-generation paclitaxel-eluting stent or CABG, patients with the least complex disease (SS ≤ 22) experienced similar rates of a composite of death, stroke, myocardial infarction, and repeat revascularization with PCI and CABG.[6] In contrast, patients with more complex disease (SS of 23-32 or ≥ 33) experienced a significantly higher rate of major adverse cardiovascular events with PCI as compared with CABG, driven by excesses of both repeat revascularization and myocardial infarction.

OVERALL POPULATION

The use of PCI with stenting in the drug-eluting stent (DES) era has increased in absolute numbers, but the degree of angiographically documented disease has brought into question whether a threshold exists beyond which CABG is preferred. For each operator and center, this threshold will differ.

LEFT MAIN CORONARY ARTERY DISEASE

With recent advances in PCI platforms, the consideration of optimal revascularization of left main CAD has been the topic of a number of clinical trials. Left main CAD is found in approximately 4% of patients undergoing coronary interventions.

There are a number of features that have made the consideration of a percutaneous approach for left main CAD more attractive. Most important has been the early risk of coronary bypass surgery in this population combined with the significant improvement in stent platform and technology.

Until recently, the main limitation of early trials of PCI versus CABG for unprotected left main artery disease has been the lack of long-term follow up. Recently, the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angiogram Trial) study using DESs in patients with left main CAD was published in the *Journal of the American College of Cardiology*.[7] This trial followed over 600 patients who had at least a 50% lesion of the left main coronary artery who were randomized to PCI with DESs versus CABG with a left internal mammary artery graft. The 5-year results show that there was a nonsignificant trend toward a benefit in the bypass surgery group in the primary end point of all-cause mortality, myocardial infarction, stroke, and ischemia-driven target vessel revascularization. The PCI group had an event rate of 17.5% versus 14.3% in the CABG group, leading to a hazard ratio of 1.27 (95% confidence interval [CI], 0.84-1.90; P = .26). The primary driver of the difference between the two groups was ischemia-driven revascularization. Target vessel revascularization was almost double in the PCI group (11.4% vs 5.5%; hazard ratio, 2.11; P = .012). In a landmark analysis after the first year of entry into PRECOMBAT, there continues to be a trend for more repeat revascularization procedures in the PCI group. Importantly, the PRECOMBAT trial enrolled not only patients with isolated unprotected left main CAD, but also patients with multivessel CAD. In the patients with left main CAD and triple-vessel disease, the results significantly favored bypass surgery. Overall, it appears in the PRECOMBAT era that patients with unprotected main CAD have similar major adverse cardiac event rates with PCI-DES and CABG. This is with the caveat that a repeat revascularization procedure may be needed at a rate of about 2% per year and that patients with more extensive disease, particularly those with diabetes, should undergo CABG as their front-line therapy. The preponderance of data calls for an individualized approach to the problem. We await the results of the landmark randomized Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial to definitively inform the use of PCI in patients with left main disease (Fig. 44–1).[8]

DIABETES

The presence of diabetes at the time of coronary revascularization is one of the strongest predictors of outcome and is a major determinant of the optimal mode of revascularization.[9] Over the last 20 years, a great deal of emphasis has been placed on the diabetic subgroup, and this has been further delineated in recent years by randomized trials, primarily conducted in the diabetic subpopulation.

The presence of diabetes is a marker of a greater extent of CAD; greater likelihood of important comorbidities such as renal dysfunction, thrombosis, and left ventricular dysfunction; and greater likelihood of heart failure. In addition, rates of in-stent restenosis and target vessel revascularization are higher in diabetic than nondiabetic patients.[10] In the era of DESs, there have been four major clinical trials. These are summarized in Table 44–3. They include the CARDia trial, VA CARDS trial, the diabetic subgroup of the SYNTAX trial, and the FREEDOM trial.[10-13] Across the board, diabetic patients with multivessel CAD involving at least two major coronary artery beds have reduced major adverse cardiovascular and cerebrovascular events (MACCEs) after CABG compared to multivessel PCI.

When evaluating the components of the MACCE outcome, it is important to emphasize that although each of the individual components may be considered separately, within a single trial, these are typically post hoc analyses that are underpowered and must be considered hypothesis generating only. For the purposes of powering a randomized controlled trial, a composite primary end point has typically been required due to feasibility of enrolling large sample sizes. By combining data between multiple trials, meta-analysis may provide a better assessment of the individual components of MACCE.

ALL-CAUSE MORTALITY

A number of meta-analyses have been conducted with these four clinical trials. The most comprehensive is the meta-analysis by Verma and colleagues,[14] which demonstrated that CABG was associated with a 33% reduction in mortality at 5 years compared to PCI (relative risk, 0.67; 95% CI, 0.52-0.86; P = .002; Fig. 44–2).[14] This was also matched by reductions in myocardial infarction and repeat revascularization.

The FREEDOM trial was designed to address the optimal coronary revascularization strategy in patients with diabetes and multivessel CAD in the absence of left main disease, prior CABG, prior stenting within 6 months, and current ST-segment elevation myocardial infarction. In FREEDOM, the overall 5-year Kaplan-Meyer estimates of the primary composite end point of death, nonfatal myocardial infarction, and nonfatal stroke indicated a 26.6% event rate in the first-generation DES group compared to 18.7% in the CABG group (P < .005; Fig. 44–3). Indeed, in FREEDOM, CABG was associated with a significantly reduced

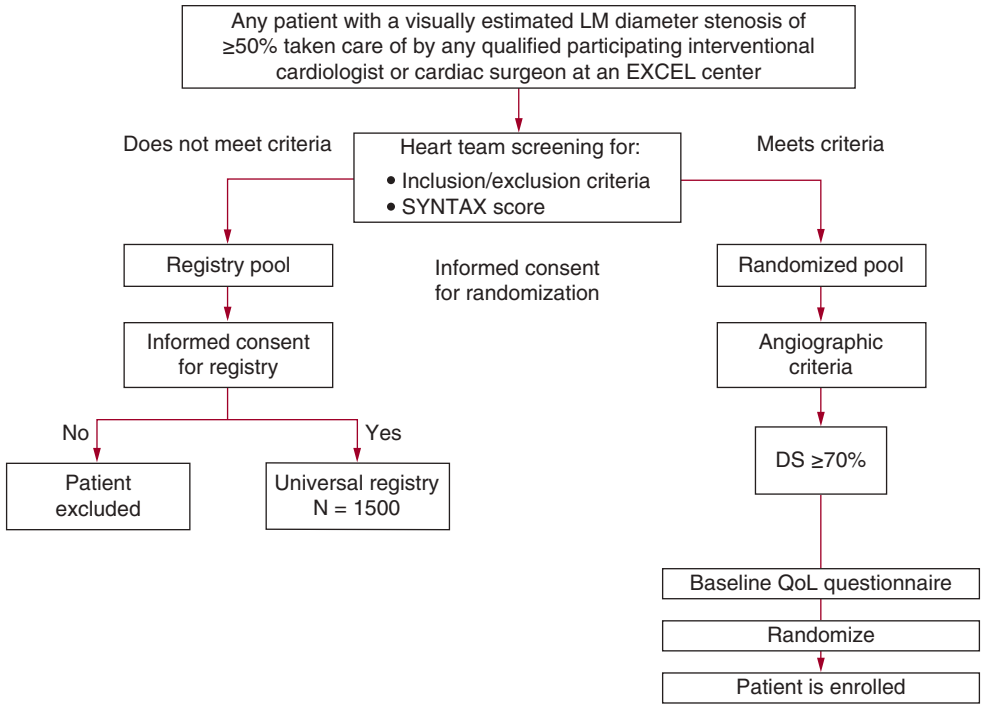


FIGURE 44–1. EXCEL trial design. DS, diameter stenosis; LM, left main; QoL, quality of life; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

TABLE 44–3. Trials of PCI With Stents Versus CABG in Diabetic Patients

	BMS				DES			
	ERACI II n = 78/450	ARTS n = 208/1205	SoS n = 142/988	MASS II n = 115/407	CARDia n = 510	SYNTAX n = 452/1800	FREEDOM n = 1900	VA CARDS n = 207
Trial characteristics								
Funding	Industry	Industry	Industry	Public	Public/industry	Industry	Public/industry	Public
Number of centers	7	67	53	1	24	85	140	22
Enrolment period	Oct 1996-Sept 1998	Apr 1997-Jun 1998	Nov 1996-Dec 1999	May 1995-May 2000	Jan 2002-Jul 2007	Mar 2005-Apr 2007	Apr 2005-Apr 2010	Aug 2006-Mar 2010
Mean follow-up duration (years)	5	5	6 (median)	4.6 (median) 5.0 (median)	5.1 (median)	5	3.8 (median)	2
Characteristics of patients								
Male (%)	79	76	79	61	74	71	71	99
Previous MI (%)	28	43	46	41	NR	32	26	41
Triple-vessel disease (%)	56	32	43	61	62	83	83	NR
Intervention PCI								
% DES	0	0	0	0	69	100	100	100

Abbreviations: BMS, bare metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; MI, myocardial infarction; n, number of patients with diabetes/total number of patients; NR, not reported; PCI, percutaneous coronary intervention.

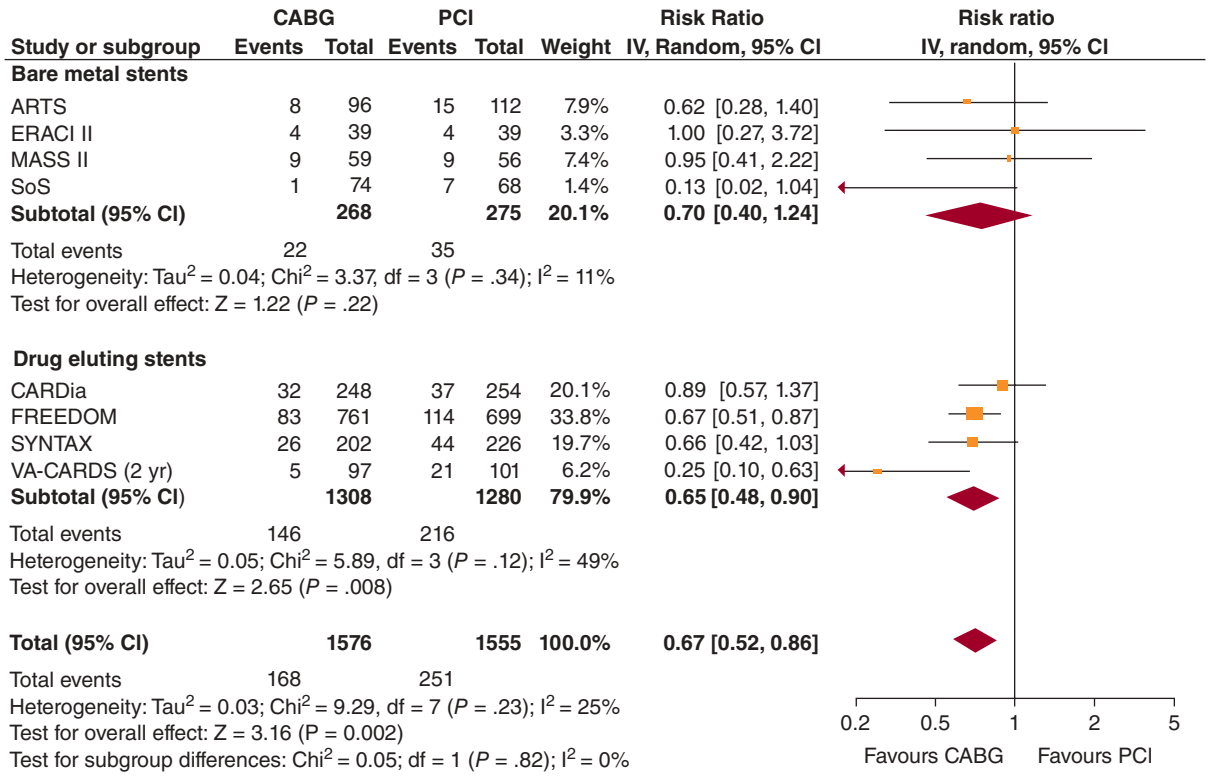


FIGURE 44–2. Forest plots for individual studies and pooled risk ratios for all-cause mortality in randomized controlled trials comparing patients with diabetes and multivessel coronary artery disease who underwent coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) after 5 years or the longest follow-up. CI, confidence interval. Reproduced with permission from Verma S, Farkouh ME, Yanagawa B, et al: Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2013 Dec;1(4):317-328.[14]

all-cause mortality risk compared to PCI at 5 years, and the mortality curves continued to diverge in favor of CABG throughout follow-up. Eight-year follow-up of the FREEDOM trial is pending but is likely to demonstrate a striking survival benefit for CABG compared to multivessel PCI in diabetic patients. The results of FREEDOM and the subsequent meta-analysis lead to a Class I recommendation in the 2014 ACC/AHA guidelines stating that CABG was associated with improved survival in diabetics with multivessel CAD.[4] This was upgraded from a Class II recommendation in 2012. CABG remains the revascularization treatment of choice for diabetic patients with multivessel disease. This is particularly true if a left internal mammary artery (LIMA) graft to the left anterior descending artery was performed.

STROKE

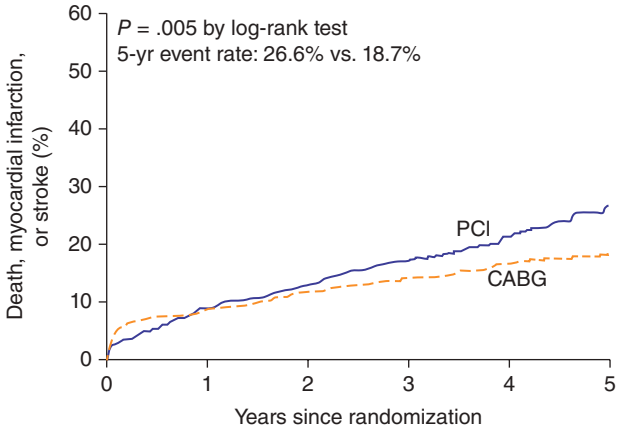
For patients with diabetes undergoing CABG in the FREEDOM trial, there was an excess of early stroke compared to PCI. The difference accrued mostly over the first 30 days after follow-up. In a recent analysis from the FREEDOM CABG cohort, Domanski et al[15] described the predictors of early stroke. These include a history of stroke, the use of warfarin, and whether CABG was performed outside North America. In long-term follow-up, the strongest predictor of stroke was the presence of chronic renal insufficiency. Over 5 years of follow-up, CABG was still associated with a significantly higher stroke rate compared to PCI (5.2% vs 2.4%; *P* = .03).

RENAL DISEASE

Perhaps the most complicated subpopulation is patients with chronic renal insufficiency. These patients have increased risk for mortality and MACCE events. In addition, patients who are not yet dialysis dependent are also at risk for exacerbating renal insufficiency. Both CABG and PCI are associated with worsening renal insufficiency. Direct randomized comparisons of CABG versus PCI are limited because of small numbers of renal failure patients enrolled in the pivotal clinical trials. Consideration of the optimal revascularization strategies in patients with chronic kidney disease is made more complicated because there are essentially two subgroups of patients: those who have end-stage renal disease or who are on hemodialysis or peritoneal dialysis and those with chronic kidney disease not yet on dialysis. This distinction is quite important as we evaluate the evidence. In addition, the rates of utilization of cardiac catheterization and medical therapy are traditionally reduced in patients with chronic kidney disease, and this has been repeatedly recognized in multiple international registries.[16,17]

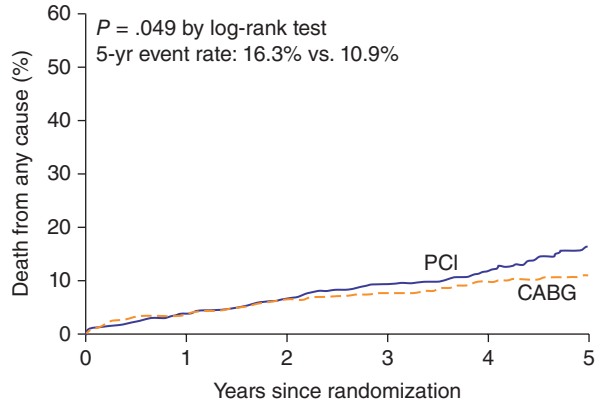
For patients with end-stage renal disease, the ACC/AHA guidelines recommend that CABG should be carried out in patients with multivessel CAD.[4] For patients with moderate to severe chronic kidney disease with multivessel CAD, the 2014 European Society of Cardiology guidelines also recommend the use of bypass surgery over PCI.[18]

The use of newer generation stents, however, has brought these recommendations into question. Recently, Bangalore and colleagues[19] from the New York State Registry retrospectively studied over 5000 patients who were propensity-matched and reported that long-term mortality rates for PCI and CABG were equal (hazard ratio, 1.07; 95% CI, 0.92-1.24), as shown in Figure 44–4. PCI was associated with a higher risk of myocardial infarction and risk of repeat revascularization, but a lower risk of stroke (hazard ratio, 0.56; 95% CI, 0.41-0.76). In the same analysis, 243 matched pairs of patients with end-stage renal disease on hemodialysis were studied; PCI was associated with a higher risk of mortality (hazard ratio, 2.0; 95% CI, 1.40-2.93). Although there



No. at risk						
PCI	953	848	788	625	416	219
CABG	947	814	758	613	422	221

A Primary outcome



No. at risk						
PCI	953	897	845	685	466	243
CABG	947	855	806	655	449	238

B Death

FIGURE 44–3. Kaplan-Meier analyses of **(A)** primary outcome (composite of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) and **(B)** mortality in the FREEDOM trial. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. Reproduced with permission from Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012 Dec 20;367(25):2375-2384.[13]

continues to be an ongoing debate as to the use of optimal PCI versus contemporary CABG in patients with chronic kidney disease, CABG remains the treatment of choice for renal failure patients with multivessel CAD. This will be the topic of ongoing discussions in the decade to come, and multiple groups are proposing a definitive cardiovascular randomized trial in patients with moderate to severe chronic kidney disease with renal outcomes as an important co-primary end point.

LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AND HISTORY OF HEART FAILURE

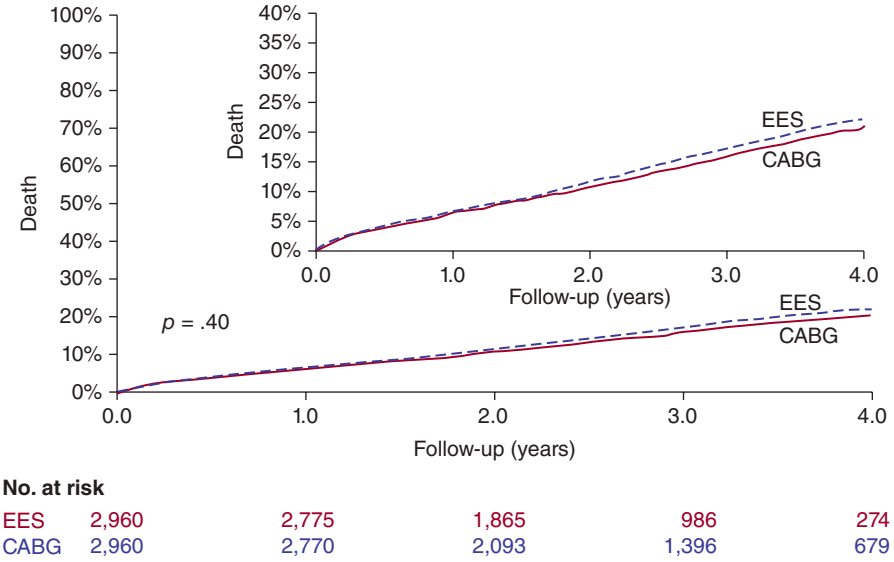
For the important subgroup of patients with left ventricular systolic dysfunction, there are few data from randomized trials suggesting the optimal revascularization strategy. This group has largely been dependent on the heart team approach due to multiple variables ranging from myocardial variability to clinical judgement to patient preference. A meta-analysis in *The Lancet* in 2009 suggests that CABG is the preferred mode of revascularization in patients with left ventricular dysfunction[20]; however, this analysis was largely limited to patients in the bare metal stent era. A recent analysis from the APPROACH investigators in Alberta, Canada, identified 2925 patients with CAD with left ventricular dysfunction undergoing CABG (n = 1326) or PCI (n = 1599) between 1995 and 2008.[21] In a Cox proportional hazards analysis of the propensity-matched subgroups, CABG was associated with lower rates of mortality and repeat revascularization when compared to PCI with up to 15 years of follow-up. These rather robust data appear to confirm recommendations for most of the major societies. Overall, because of the small numbers in randomized trials, a definitive trial of CABG versus PCI in patients with left ventricular systolic dysfunction may be difficult to perform. In a recent analysis from the Surgical Treatment for Ischemic Heart Failure (STICH) study, patients with ischemic cardiomyopathy and an ejection fraction of 35% or less were randomly assigned to CABG versus OMT alone and followed for 9.8 years. There were more cardiovascular deaths in the OMT group (297 deaths, 49.3%) compared to the CABG group (247 deaths, 40.5%; hazard ratio, 0.79; 95% CI, 0.66-0.93; $P = .006$).[22]

PRIOR CORONARY ARTERY BYPASS GRAFTING

The increasing use of PCI in patients with prior bypass surgery is largely due to patient preference to avoid redo CABG and the attendant risk of perioperative mortality and morbidity.[23] Indeed, the number of redo CABG procedures continues to fall in the United States.[24] There are no prospective randomized data to guide decision making; however, adjusted comparisons in the subpopulation of prior bypass surgery patients appear to be slightly better for PCI when compared to redo CABG and medical therapy alone in the APPROACH registry.[25] This will require further evaluation in the years to come.

SPECIAL CONSIDERATIONS FOR DECISION MAKING: PERCUTANEOUS CORONARY INTERVENTION AND CORONARY ARTERY BYPASS GRAFTING

1. The importance of co-intervention: The importance of OMT has been stressed on all fronts. One of the important weaknesses of many clinical trials is that patients are not being treated equally in the PCI and CABG arm with regard to OMT. For example, in the SYNTAX trial, only 75% of patients in the bypass arm were discharged with statin therapy compared to over 85% in the PCI arm.[6] It is possible that more balanced administration of OMT might have led to even greater improvement in outcomes in the CABG group compared to the PCI group. The effective co-intervention is an important variable when evaluating results of clinical trials because many patients do not reach guideline-directed targets for major medical risk factors.[26]
2. The importance of newer generation stenting: With the advent of newer generation stents and reductions in stent thrombosis, there has been consideration for the need of yet another PCI versus CABG trial with a newer platform of stents. The authors caution against this reasoning. Comparing the hazard ratio for mortality from the original BARI trial published in 1995 versus those after the advent of bare metal stents in the publications of the ARTS and SOS trials and the Hlatky meta-analysis versus those in the publications of the FREEDOM and SYNTAX trials and subsequent



No. at risk

EES	2,960	2,775	1,865	986	274
CABG	2,960	2,770	2,093	1,396	679

FIGURE 44–4. Everolimus-eluting stent (EES) versus coronary artery bypass grafting (CABG): longer-term risk of death in the propensity score–matched cohort of patients who underwent either percutaneous coronary intervention with EES or CABG. There was no statistically significant difference in death between the two cohorts. Reproduced with permission from Bangalore S1, Guo Y, Samadashvili Z, et al: Revascularization in Patients With Multivessel Coronary Artery Disease and Chronic Kidney Disease: Everolimus-Eluting Stents Versus Coronary Artery Bypass Graft Surgery. *J Am Coll Cardiol*. 2015 Sep 15;66(11):1209-1220.[19]

Verma meta-analysis, the hazard ratio for mortality has stayed relatively constant, in the range of approximately 0.70 for CABG versus PCI. With long-term follow-up, it is unlikely that PCI in any form would make up this difference without a significant impact on non–culprit lesion progression.

The introduction of newer generation DESs has improved the safety profile for PCI, particularly by reducing rates of stent thrombosis. The recent TUXEDO trial from India demonstrates the superiority of the everolimus-eluting stent strategy over the paclitaxel stented group for reducing target vessel failure ($P = .005$), spontaneous myocardial infarction (1.2% vs 3.2%; $P = .004$), stent thrombosis (0.4% vs 2.1%; $P = .002$), and target vessel revascularization (1.2% vs 3.4%; $P = .002$) at 1 year in a diabetic population.[27]

The question of whether newer generation stenting will improve MACCE outcomes and reduce the difference in MACCE outcomes between PCI and CABG in advanced CAD remains unknown. It is highly unlikely that trials such as SYNTAX and FREEDOM will be performed with the newer stent platforms since even significant reductions in stent thrombosis are not going to make up the majority of the differences in cardiovascular outcomes. This again remains a topic for future investigation.

3. The importance of multiple arterial grafting in bypass surgery versus a single LIMA to left anterior descending artery (LAD): Models for the determination of the single pivotal variable that favors a mortality benefit of CABG over PCI indicate that implantation of the LIMA to the LAD graft appears to confer the most benefit.[28]

   Data from the Mayo Clinic involving 8622 patients with isolated CABG from multivessel CAD from 1993 to 2009 evaluated the use of LIMA plus saphenous vein grafts versus multiple arterial grafting.[29] The operative mortality was not significantly different between the two groups. When evaluating late survival at 15 years, multiple arterial grafting revealed a significant survival advantage. Multi-arterial grafting remained a strong predictor of survival (hazard ratio, 0.79; 95% CI, 0.66-0.94). We await the 10-year results of the randomized trial of bilateral versus single internal mammary coronary artery grafting (the ART trial) in the years to come. The 1-year findings of ART suggest that there are similar clinical outcomes for single internal mammary versus bilateral internal mammary grafting, with a 1.3% increase in the need for sternal wound reconstruction with bilateral internal mammary surgery.[30] In a meta-analysis by Weiss et al[31] of bilateral internal mammary artery (BIMA) versus LIMA grafting alone, there appears to be a long-term survival benefit associated with BIMA versus LIMA alone. This was based entirely on observational data. The long-term survival advantage was associated with a hazard ratio of 0.78 (95% CI, 0.72-0.84; $P < .00001$). This survival benefit was noted among both diabetic and nondiabetic patients in another large retrospective series, in which BIMA conferred a 35% reduction (95% CI, 12%-52%; $P = .006$) in the long-term hazard of death equally for nondiabetic and diabetic patients.[32] Cardiologists and surgeons alike should advocate for the safe adoption of more multiarterial grafting in patients referred for surgical coronary revascularization.

4. Completeness of revascularization: The importance of completeness of revascularization cannot be overstated as a critical determinant of which revascularization strategy is selected in an individual patient. Patients with a very low likelihood of complete revascularization by PCI may be appropriately steered to CABG. The importance of the completeness of revascularization was emphasized in a report from the New York State Registry.[33] This showed that incomplete revascularization with stenting was associated with adverse impact on long-term outcome (hazard ratio, 1.15; 95% CI, 1.01-1.30) when compared with complete revascularization. Those at highest risk were patients with incomplete revascularization with residual total occlusion and/or a total of two or more vessels with incomplete revascularization.

   A subsequent analysis by Wu and colleagues[34] evaluated the association of complete revascularization and long-term mortality in 6511 pairs of propensity-matched patients and showed that 5-year survival was lower for patients after incomplete revascularization by PCI compared to those with complete revascularization (79.3% vs 81.4%; $P < .0004$). This underscores the importance of this variable in considering the optimal approach to our patients.

5. The importance of on-pump coronary artery bypass surgery compared to off-pump coronary artery bypass (OPCAB) surgery: The recent United Kingdom national adult cardiac audit registry demonstrates

no difference in the 5-year survival in patients undergoing on-pump versus off-pump surgery.[35] This confirms the 1-year findings of the large international CORONARY trial in which there was no difference in the rate of death, myocardial infarction, stroke, or new renal failure, as well as no differences in quality of life and neurocognitive function between the off-pump and on-pump groups.[36] Overall, there was an influence of operator on outcomes, with a recommendation that OPCAB be performed by surgeons who were more experienced and who perform at least 10% of their surgeries as OPCAB.[37] Moreover, OPCAB has shown greater benefit in patients at higher preoperative risk, including women.[38] These findings have been confirmed in large retrospective analyses of the STS National Cardiac Database.[39] Regional differences for outcomes in surgery need to be further evaluated not only for off-pump surgery but also for stroke risk.

6. The risk of stroke associated with CABG: With the emergence of CABG as the preferred mode of revascularization for patients with diabetes, left ventricular dysfunction, renal failure, and greater comorbidities, it is important to evaluate ways to reduce stroke, particularly in the first 30 days after bypass. Strokes may be caused by multiple etiologies, including coincident cerebral vascular disease and, importantly, manipulation of the aorta at the time of surgery. In a large multicenter registry, off-pump bypass surgery did not result in a lower risk of stroke when stratified by the Northern New England Cardiovascular Disease Study Group (NNECDSG) strata for perioperative stroke, nor did it result in any significant improvement in long-term cognitive function when compared to on-pump grafting.[40] However, in a larger sample of the STS Database, OPCAB was strongly associated with a reduced risk of 30-day stroke (adjusted odds ratio, 0.66; 95% CI, 0.62-0.71; $P < .0001$; n = 876,081 patients).[41] With regard to concomitant cerebrovascular disease, staging of procedures so that the most unstable territory is intervened upon first is the approach that has been most widely adopted. For example, patients having unstable carotid disease and SIHD may proceed to carotid intervention first. Other approaches, including concomitant procedures, have also been undertaken. A study from the Cleveland Clinic shows that in long-term follow-up with adjustment after the first year, staged carotid artery stenting–open heart surgery (OHS) was associated with a significantly lower composite end point of death, myocardial infarction, and stroke compared with both staged carotid endarterectomy (CEA)-OHS (hazard ratio, 0.33; 95% CI, 0.15-0.77; $P = .01$) and combined CEA-OHS (hazard ratio, 0.35; 95% CI, 0.18-0.70; $P = .003$).[42]

   In the effort to reduce operative and perioperative risk of stroke with CABG, there are multiple important issues that need to be considered, including the following: (1) the preoperative screening for cerebrovascular disease; (2) the operative screening of the ascending aorta to individualize surgical techniques to avoid distal atherothrombotic emboli; (3) the influence of post-operative atrial fibrillation and appropriate anticoagulation; and (4) the importance of dual antiplatelet therapy in selected patients (particularly patients after acute coronary syndrome) and the disruption of dual antiplatelet therapy in the postoperative period. These issues and others will remain the subject of ongoing research undertaken to understand ways to reduce the risk of stroke after bypass.

7. Sternal wound infections: The serious complication of deep sternal wound infections can occur in 0.5% to 2% of patients and is commonly associated with diabetes and obesity.[43] In diabetic patients, the use of BIMA is linked to both significantly improved long-term survival and increased rates of perioperative deep sternal wound infection.[44] In particular, obese, female patients with poorly controlled diabetes are at elevated risk of deep sternal wound infections, and BIMA grafting should be avoided in this group.[45] Continuous intravenous insulin infusion should be implemented during surgery and early postoperatively in cardiac surgery patients whenever glucose levels are elevated in order to minimize risk of deep sternal wound infections.[46]

RECENT DEVELOPMENTS

OPTIMAL ANTIPLATELET THERAPY: INTENSITY, DURATION, AND BLEEDING BALANCE

Antiplatelet therapy is the cornerstone of drug therapy to prevent recurrent ischemic events after coronary revascularization. Dual antiplatelet therapy (DAPT), consisting of aspirin plus an inhibitor of the platelet $P2Y_{12}$ receptor, is considered standard of care after PCI. Once uniform after DES implantation, decision making about DAPT has grown increasingly complex as stent technologies have improved,[47,48] newer more potent $P2Y_{12}$ inhibitors have come to market,[49,50] and a growing body of evidence has tested durations of therapy longer or shorter than the classic 12-month period.[51-53] Central to this complexity is the judgment of an individual patient's dynamic balance of ischemic and bleeding risks.

Substantial overlap exists between risk factors for ischemic and bleeding events after PCI. Of note, acuity is an important determinant. Individuals undergoing PCI for unstable angina and acute myocardial infarction are, in general, at higher risk for both events. For the purposes of this review, we will restrict our discussion to patients with SIHD. The most important predictor of stent thrombosis, a sentinel ischemic event after PCI, is premature disruption of DAPT. Additional predictors of stent thrombosis include renal failure, diabetes mellitus, bifurcation lesions, calcified lesions, reduced left ventricular ejection fraction, small stent diameter and longer stent length, malignancy, prior stroke, dissection, and presence of intermediate coronary disease proximal and distal to a culprit lesion.[54-57] Additional predictors of bleeding include age, female sex, heart failure, renal failure, and peripheral vascular disease.[58] Predictors of post-discharge bleeding, in particular, include older age, lower baseline hemoglobin, lower platelet reactivity on clopidogrel, and use of chronic oral anticoagulant therapy.[59]

Seminal trials establishing the anti-ischemic efficacy and supporting US Food and Drug Administration approval of the newer oral platelet $P2Y_{12}$ inhibitors prasugrel and ticagrelor were conducted in patients with acute coronary syndromes. The utility of these more potent agents in patients with SIHD is less certain. Promising data from the PEGASUS-TIMI 54 trial indicate that DAPT with aspirin and ticagrelor, initiated greater than 1 year after myocardial infarction, is associated with a 15% reduction in the primary composite end point of death, myocardial infarction, and stroke ($P < .01$).[60]

The role of DAPT after CABG is less well established. It is uncertain whether DAPT improves graft patency. In a single-center study of 249 consecutive patients randomized to aspirin 100 mg or aspirin 100 mg plus clopidogrel 75 mg daily after elective CABG, DAPT was associated with improved venous graft patency at 3 months.[37,61] In a second randomized study of aspirin 162 mg versus aspirin 162 mg plus clopidogrel 75 mg daily after CABG, there was no difference in the primary end point of intravascular ultrasound–determined saphenous vein graft intimal hyperplasia and no difference in freedom from major adverse cardiovascular events.[38,62]

A separate potential benefit of DAPT may be added reduction in incidence of stroke after coronary revascularization.[39,63] Larger trials are required to assess efficacy and safety of DAPT after CABG with particular attention to stroke outcomes.

BIORESORBABLE VASCULAR SCAFFOLDS: SUCCESSORS TO STENTS?

Ongoing investigation and intense interest are presently focused on bioresorbable vascular scaffolds (BVS) as a prospective successor to stents. Although risks of ischemic complications, and in particular stent thrombosis, have progressively declined with evolution of DES technology, the best available DESs continue to pose several putative disadvantages. Permanent metallic stents, with or without drug elution, can impede future coronary instrumentation and contribute to chronic inflammation,[40,64] endothelial dysfunction,[41,65] and adverse remodeling.[42,66] In theory, a BVS might ameliorate these problems while providing a temporary period of radial support after PCI.

There is now experience with use of one first-generation BVS, the everolimus-eluting Absorb BVS (Abbott Vascular, Redwood City, CA), in over 100,000 patients worldwide. In ABSORB III, a large, multicenter randomized comparison of the Absorb BVS versus the everolimus-eluting Xience (Abbott Vascular) stent,[43,67] rates of target lesion failure (cardiac death, target vessel myocardial infarction, and ischemia-driven target lesion revascularization) were higher at 1 year in patients randomized to receive a BVS (7.8% vs 6.1%). Subjects randomized to receive a BVS also experienced a nonsignificantly higher rate of device thrombosis (1.5% vs 0.7%). The studied BVS platform satisfied prespecified criteria for noninferiority. Observed excesses in ischemic events may stem from a learning curve in optimal deployment of BVS, which appears to rely on meticulous lesion preparation. Validation of the proposed long-term benefits of a BVS for angina and late ischemic events awaits results of the ongoing ABSORB IV trial.[68]

HYBRID REVASCULARIZATION

The use of a hybrid approach to coronary revascularization is gaining popularity and may be an appropriate alternative for a carefully selected subset of patients with limited CAD involving the proximal or mid LAD and at least one other non-LAD coronary artery. In hybrid coronary revascularization (HCR), a minimally invasive surgical approach is used to bypass the LAD with a LIMA graft in combination with stenting of non-LAD targets. This is believed to leverage the advantages of surgical arterial revascularization of the LAD and substitution of advanced stent technology for saphenous vein grafts for the other targets. In a recent analysis from the STS Adult Cardiac Surgery Database, HCR is offered in about one-third of hospitals but represents less than 1% of CABG procedures in the United States.[69] The current body of evidence is limited to observational studies and a small pilot randomized trial (Fig. 44–5). Overall, pooling of the studies shows a trend for fewer MACCE events (odds ratio, 0.69; 95% CI, 0.41-0.92; $P = .18$) in favor of HCR over conventional CABG. Although stroke was reduced by 80% ($P = .039$) in the HCR group, there was an excess of repeat revascularization (odds ratio, 4.05; $P < .001$).

The current ACC/AHA guidelines on coronary revascularization consider HCR only when PCI of the LAD is considered suboptimal, and therefore, it is given a Class IIa recommendation.[4] A large prospective randomized trial may be necessary to define the benefit of this new alternative technique.

HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION

Advances in technique and technology have dramatically improved the safety of elective PCI. For a subset of patients, however, elective

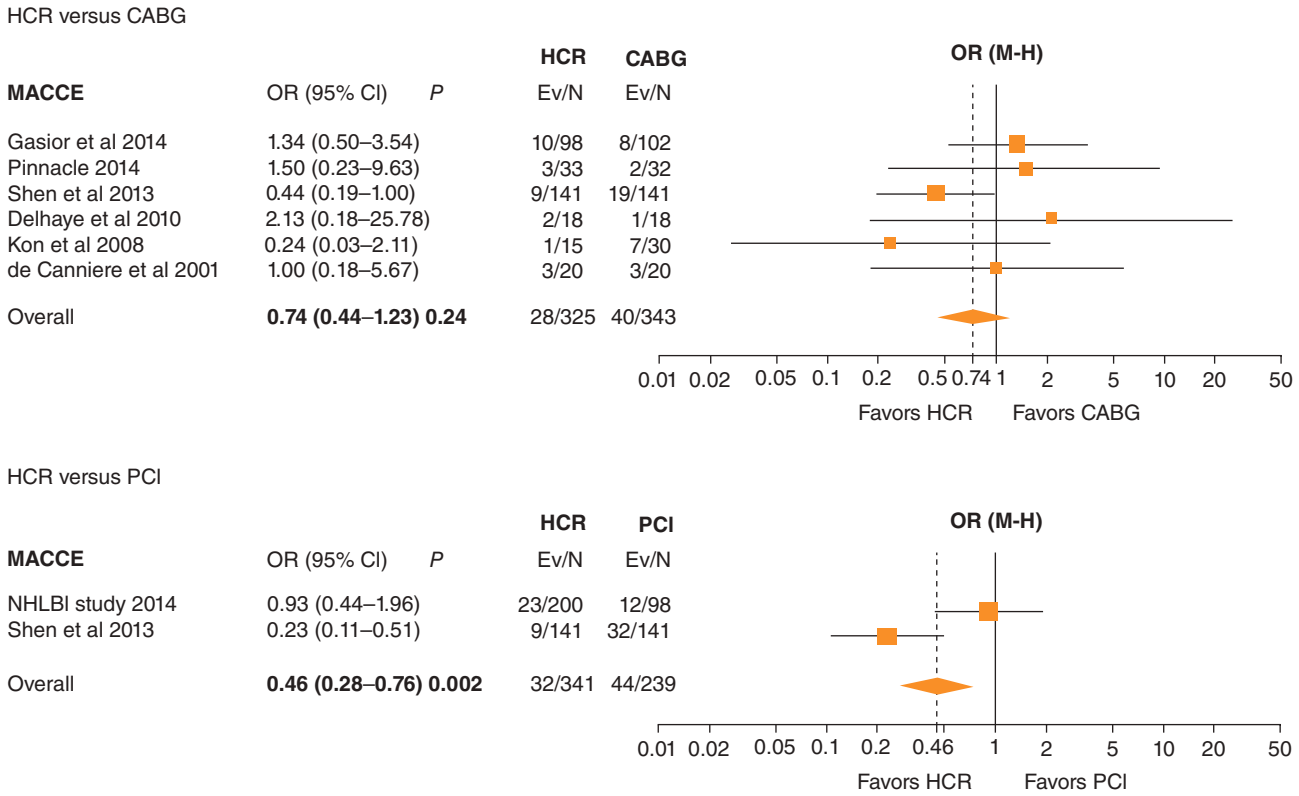


FIGURE 44–5. Hybrid procedures and outcomes versus conventional coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). HCR, hybrid coronary revascularization; MACCE, major adverse cardiovascular and cerebrovascular events; NHLBI, National Heart, Lung, and Blood Institute; OR, odds ratio. Reproduced with permission from Harskamp RE: Current state and future direction of hybrid coronary revascularization. *Curr Opin Cardiol*. 2015 Nov;30(6):643-649.

PCI continues to pose substantial risk of morbidity and mortality. Candidates for so-called "high-risk PCI" are typified by advanced age, multiple comorbidities, severe left ventricular dysfunction, unsuitability for surgery, and little room for error in the catheterization laboratory. Lesions are frequently complex and may be characterized by multivessel disease, unprotected left main disease, or involvement of a last remaining coronary vessel.

Assessment of a proposed PCI as high risk is a clinical judgment made by an experienced heart team. Risk models developed from analysis of large registries can help in predicting likelihood of in-hospital mortality after elective PCI. One such model is the Mayo Clinic Risk Score (MCRS), derived from a cohort of 7640 patients undergoing PCI between 2000 and 2005,[3,70] and subsequently validated in a data set of over 300,000 patients as a predictor of in-hospital mortality after PCI.[71] The MCRS (Fig. 44–6) incorporates seven variables: age, serum creatinine, left ventricular ejection fraction, preprocedural shock, myocardial infarction within 24 hours, heart failure on presentation, and peripheral vascular disease. Patients at high risk for elective PCI are often also at high risk for surgery, and indeed, the MCRS correlates strongly with the STS score for risk of mortality after CABG.[72]

Selected cases of high-risk PCI may benefit from adjunctive use of mechanical circulatory support. An expanding armamentarium of percutaneous devices for this purpose today includes intra-aortic balloon pump (IABP), centrifugal flow (TandemHeart; CardiacAssist, Pittsburgh, PA) and axial flow (Impella; Abiomed, Danvers, MA) ventricular assist devices, and extracorporeal membrane oxygenation (CardioHelp; Maquet, Wayne, NJ). Recent studies of device support have helped to define current concepts of high-risk elective PCI.

The Balloon Pump-Assisted Coronary Intervention Study (BCIS-1) randomized 301 patients with multivessel CAD and left ventricular ejection fraction ≤ 30% to PCI with or without IABP support. Major adverse cardiac and cerebrovascular events were equally common in the hospital (15.2% vs 16.0%; $P = .85$).[73] Mortality in this cohort was high at 5-year follow-up (33%) and, surprisingly, significantly lower in IABP-treated patients (hazard ratio, 0.66; 95% CI, 0.44-0.98; $P = .039$).[74]

The PROTECT II trial, which was underpowered due to early termination, randomized 452 symptomatic patients with complex three-vessel CAD or unprotected left main CAD and left ventricular ejection fraction ≤ 30% to PCI with IABP or Impella support.[75] Both IABP and Impella-supported patients experienced significant improvements in functional status and left ventricular ejection fraction after PCI. At 30 days, there was no difference in a broad primary composite end point of major adverse events (40.1% vs 35.1%; $P = .23$). After discharge, however, there was a lower rate of death, stroke, myocardial infarction, and repeat revascularization in patients randomized to Impella.

In considering these data, a few salient points emerge. First, patients with ischemic cardiomyopathy and severe left ventricular dysfunction are indeed at high risk, with substantial short-term jeopardy of morbidity and mortality. Second, these patients benefit from revascularization, with improvement in symptoms and left ventricular function. Third, and perhaps most interestingly, the benefits of adjunctive mechanical circulatory support may not appear in the hospital but rather accrue with passage of time. The explanation for this final observation remains uncertain but may relate to differences in completeness or quality of PCI under conditions of mechanical circulatory support.

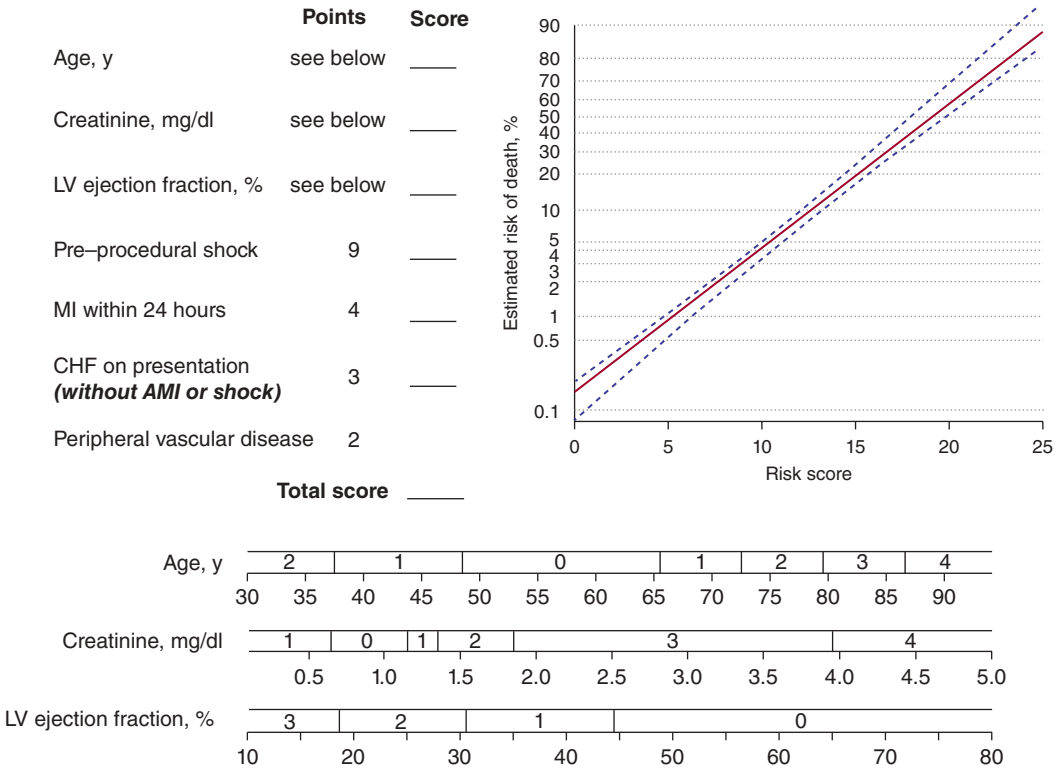


FIGURE 44–6. New Mayo Clinic risk model for prediction of in-hospital death. Coefficients for age, left ventricular (LV) ejection fraction, and serum creatinine can be determined from the nomograms at the bottom. Note that congestive heart failure (CHF) needs to be entered only for patients not presenting with myocardial infarction (MI) or shock. The equation for log-odds of death is as follows: LogOdds = −6.082 + 0.2883 × score. For missing values, if creatinine is unavailable, do the following: add 1 point if patient is male, and 1 point if patient has CHF. If ejection fraction is unavailable, do the following: add 1 point if patient has CHF. For other variables, if a risk factor is unknown, no points are added. AMI, acute myocardial infarction. Reproduced with permission from Singh M, Gersh BJ, Li S, et al: Mayo Clinic Risk Score for percutaneous coronary intervention predicts in-hospital mortality in patients undergoing coronary artery bypass graft surgery. *Circulation*. 2008 Jan 22;117(3):356-362.[72]

THE IMPACT OF FRACTIONAL FLOW RESERVE

Major trials[10-13] informing current management of multivessel CAD have relied predominantly on angiographic criteria for study inclusion and lesion selection. Yet recent studies of physiologic lesion assessment using fractional flow reserve (FFR) have underscored the limitations of anatomy-guided PCI.

FFR is a lesion-specific index of stenosis severity defined as the ratio of maximum *flow* in the presence of stenosis to normal maximum *flow*.[76] In practice, FFR is estimated as the ratio of coronary artery *pressure* distal to a lesion of interest to aortic *pressure*, averaged over the entire cardiac cycle, with variation in microvascular resistance minimized by pharmacologic induction of maximal hyperemia. Dedicated fiberoptic pressure wire systems have helped make FFR measurement simple, safe, and widely available in clinical practice.

FFR is useful to reclassify the functional severity of angiographically indeterminate coronary lesions[77] and to define the utility of PCI. When a lesion is functionally insignificant, as defined in the DEFER trial by an FFR ≥ 0.75, PCI may be safely deferred without excess risk of cardiac death or myocardial infarction.[78] Use of FFR guidance improves both efficacy and appropriateness of PCI. In the FAME study, which randomized 1005 patients with multivessel CAD to PCI guided by angiography alone or angiography plus FFR, a strategy of FFR guidance was associated with a reduced rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year (13.2% vs 18.3%; $P = .02$) as well as a reduced usage of stents per patient (1.9 ± 1.3 vs 2.7 ± 1.2; $P < .001$).[79] Indeed, when a lesion is functionally significant, as defined by an FFR ≤ 0.80, revascularization is beneficial. In the FAME 2 trial, which randomized 888 patients with at least one functionally significant stenosis to PCI plus medical therapy or medical therapy alone, PCI conferred a significant reduction in death, nonfatal myocardial infarction, and urgent revascularization at 2 years.[80]

Whether the advantages of FFR guidance for PCI may be extrapolated to CABG remains uncertain. Physiologic differences in the mechanism of CABG invoke separate considerations, including risk of conduit failure and potential for lesion progression. Furthermore, the standard of care for CABG has been founded on a principle of complete anatomic revascularization, rendering the notion of omitting bypass of FFR-negative intermediate stenosis as exploratory. In a retrospective study of 627 patients undergoing CABG, of whom 198 underwent grafting or deferral of grafting of at least one intermediate stenosis based on an FFR cut point of 0.80, the use of FFR guidance was associated with a lower number of graft anastomoses, a lower rate of angina, and no excess of death, myocardial infarction, or target vessel revascularization at 36 months.[81] Results are awaited from randomized clinical trials currently under way to evaluate the role of FFR guidance for CABG planning.

Based on presently available data, the authors advocate a central role for FFR guidance in determining appropriateness for PCI (Fig. 44–7).

FUTURE DIRECTIONS

Presently, PCI is the most common treatment for limited CAD with SSs less than 22. More complex disease (SS > 32) is more effectively managed with CABG. Intermediate disease may be technically amenable to either strategy, but results in patients with intermediate disease are better with CABG in higher risk groups. Diabetic patients with multivessel disease and patients with low ejection fraction or renal failure have better intermediate and late outcomes with CABG, and CABG remains the treatment of choice in those subgroups. New techniques for minimizing aortic manipulation during CABG and increasing the use of multiple arterial conduits are available and should be routinely

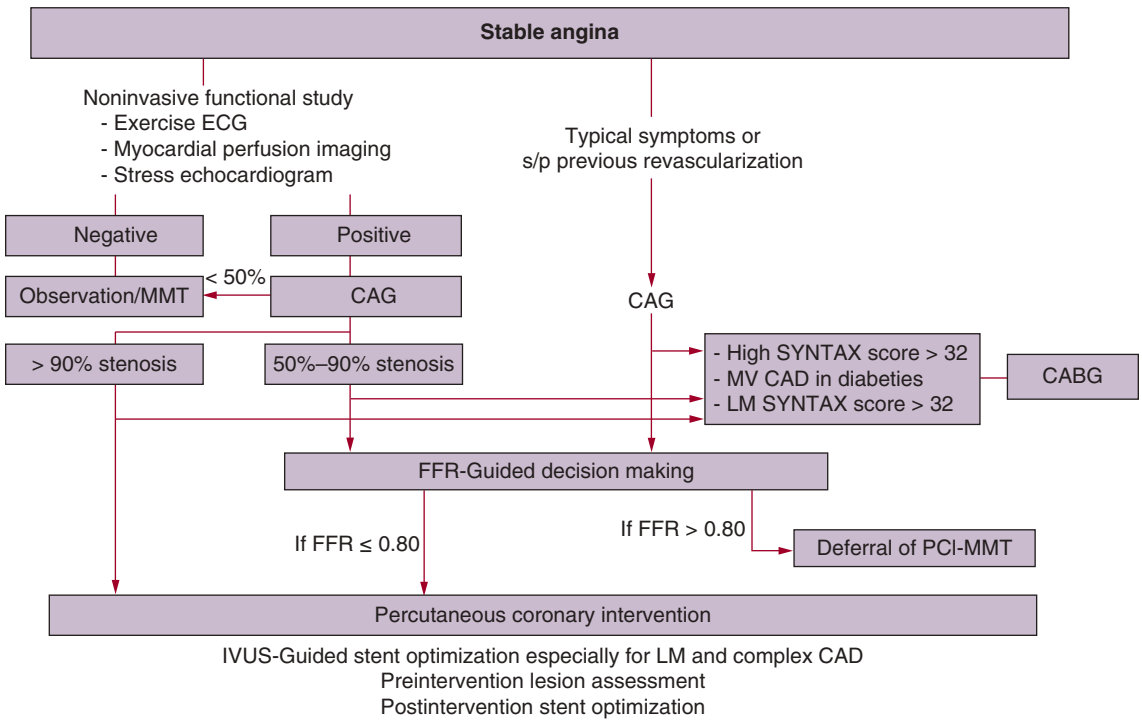


FIGURE 44–7. Proposed algorithm for assignment to revascularization in stable ischemic heart disease. CABG, coronary artery bypass grafting; ECG, electrocardiogram; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LM, left main; MMT, XXXX; MV CAD, multivessel coronary artery disease; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

applied to improve clinical outcomes after CABG. Similarly, technical improvements in PCI devices and an evolving understanding of the role of FFR in selecting vessels and patients will contribute to improve outcomes with PCI in the future. Reducing stroke after bypass surgery and optimizing medical co-intervention with the newer low-density lipoprotein–lowering drugs in all patients will potentially change the coronary revascularization landscape as well. Together, the heart team approach can ensure that each patient with coronary disease enjoys the best possible outcomes.

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CHAPTER 45

REHABILITATION OF THE PATIENT WITH CORONARY HEART DISEASE

Mary Ann McLaughlin

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INTRODUCTION

Cardiac rehabilitation (CR) represents an important component of cardiovascular (CV) risk reduction and promotion of CV health. A key component of integrated care, CR provides implementation of exercise training, CV risk reduction, specifically in relation to nutrition and weight, diabetes management, lipid management, hypertension control, and stress reduction. The goal of CR services is to stabilize or reverse progression of atherosclerosis, reduce the risk of myocardial infarction and sudden death, control cardiac symptoms, and enhance the patient's psychosocial and vocational status.

The beneficial effects of exercise have been investigated for centuries. In 1768, Herbeden observed that a patient with angina improved after chopping wood for 30 minutes a day. This finding is one of the first publications noting the CV benefit of exercise in patients with coronary disease.[1] William Stokes advocated walking for patients with heart disease in the mid-1800s, but this was in contradiction to the popular opinion stressing the importance of bed rest for weeks after a CV event. In the 1950s, Samuel Levine and Bernard Lown noted both physical and psychological benefits of early mobilization following acute coronary symptoms.[2] Concurrent with gradual changes from sedentary convalescence to early mobilization after acute coronary events, the importance of risk factors and lifestyles in the genesis of coronary disease was realized, and the concept of CR was born. The first structured rehabilitation program was pioneered in Israel in 1955.[3]

Furthermore, the differentiation between primary and secondary prevention of CHD was challenged. Pathologic studies confirmed that atherosclerosis may develop insidiously over decades and may be advanced at time of presentation with symptoms or an acute event. Newer diagnostic tests for acute coronary syndromes have shown that myocardial infarction represents a continuum of damage. The presentation of a person with angina, an acute coronary syndrome, or coincidental asymptomatic disease should now trigger the initiation of a lifelong program of risk factor modification including physical exercise.

In parallel with this philosophy, CR has evolved and is considered a class I indication in most clinical practice guidelines for patients with stable angina, acute myocardial infarction within the last 12 months, percutaneous coronary intervention (PCI) with or without stenting, or coronary artery bypass graft (CABG) surgery. In addition, CR is recommended for patients with peripheral arterial disease,[4] valvular disease,[5] congestive heart failure,[6] and heart transplant. Additional candidates for CR include those with pulmonary hypertension and congenital heart disease.[7]

CR has developed worldwide but differs widely among countries, from highly structured inpatient programs to informal home-based programs. Although there may be no ideal rehabilitation program, the majority consist of regular outpatient exercise and educational programs. Comprehensive rehabilitation involves a multidisciplinary team comprising a physician, program manager, CV nurse, exercise physiologist or physical therapist, and access to a registered dietician and clinical psychologist.

This chapter, in addition to defining the essential components of CR programs, will provide an update on recently published studies that will impact the future of CR and health promotion programs. Specific studies address survival benefit, utilization of services, and alternative delivery strategies.

GUIDELINES: HISTORICAL PERSPECTIVE

CR and secondary prevention programs are now accepted as an integral component of the comprehensive care of patients with CV disease. Typically, CR comprises exercise and educational programs with the aim to promote the uptake and maintenance of appropriate physical activity and healthier lifestyle changes, so as to positively influence the individual's recovery and as a means of secondary prevention. Since the 1980s, a variety of working groups and committees have published guidelines and recommendations for CR.[8-13]

In 1995, the US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research issued guidelines[8] that are still widely used, describing CR as a comprehensive long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling, designed to limit the physiologic and psychological effect of cardiac illness, reduce the risk of sudden death or reinfarction, control cardiac symptoms, and enhance the psychological and vocational status of the individual patient.

Early in the 21st century, the European Society of Cardiology[10] published guidelines regarding evaluation and intervention in all aspects of CR. These initiatives were aimed at assisting CR staff with the development of CR programs in Europe. Physical activity is also strongly emphasized in the current European guidelines on CV disease prevention.[14]

The most recent advisory from the American Heart Association (AHA) makes a compelling argument for the importance of CR and secondary prevention (SP) programs: "Given the significant benefits that CR/SP programs bring CV disease prevention, every recent major evidence-based guideline from the AHA and the American College of Cardiology (ACC) about the management and prevention of CHD provides a Class 1 level recommendation for referral for those patients with acute coronary syndrome (ACS) or MI [myocardial infarction], chronic stable angina, heart failure or after coronary artery bypass surgery or PCI; CR is also indicated for those patients after valve surgery or cardiac transplantation."[15] The Centers for Medicare and Medicaid Services (CMS) have mandated that CR services be individualized to provide optimal efficient care. In this era of patient-centered medical homes and accountable care organizations, CR/SP programs should be positioned to improve CV disease outcomes by providing important services to high-risk populations.

RATIONALE: THE EVIDENCE

MORTALITY AND CARDIOVASCULAR OUTCOMES

During the past 20 years, clinical trials and meta-analyses have reported the following CV benefits for patients enrolled in exercise training programs: reduced mortality at up to 5 years, decrease in CV events, improvement in modifiable CV risk factors, improvement in adherence to preventive medications, improvement in exercise capacity, and improvement in quality of life.[16-18] Evidence for the benefit of CR spans many subsets of patients with coronary heart disease (CHD). Studies of patients with stable CHD or those who have undergone vascularization with PCI provide evidence for reduction in all-cause mortality compared to control groups receiving usual care.[19]

The most recent and comprehensive meta-analysis of 63 trials of patients after either myocardial infarction (MI) or revascularization was published in 2016 and confirmed that exercise-based CR reduces CV mortality and hospital admissions and improves quality of life consistently across patient types. This evaluation included 14,486 participants after MI or revascularization followed for 12 months.[17] Results included the following:

- A lower risk of CV mortality (relative risk [RR], 0.74; 95% confidence interval [CI], 0.64-0.86)
- A lower risk of hospital admission (RR, 0.82; 95% CI, 0.70-0.96).
- No significant effect on rates of all-cause death, MI, or revascularization

Patients who have undergone CABG were evaluated in a community-based analysis of 846 patients. Those who participated in a CR program (compared to those who did not) had reduced incidence of all-cause mortality at 10 years (23.0% vs 35.7%; adjusted hazard ratio [HR], 0.54; 95% CI, 0.40-0.74).[20]

DOSE RESPONSE

The relationship between the number of CR sessions completed in older patients found a dose-dependent reduction in mortality and recurrent MI. Of 30,161 Medicare patients, those who attended 36 sessions had a 14% lower risk of death (HR, 0.86; 95% CI, 0.77-0.97) than those who attended 24 sessions over a period of 5 years.[21] Improvements in functional capacity and quality of life may translate to increased probability of returning to work or to maintenance of independent living in older patients. The relationship between completion of CR and mortality was also noted in a prospective cohort study of 5886 patients (70% with an acute coronary syndrome) referred for CR. Those who attended 36 sessions had a reduced rate of hospitalizations and a 22% lower risk of death than those who completed 12 sessions (HR, 0.78; 95% CI, 0.71-0.87).[22]

Taken collectively, these studies suggest that reported mortality reductions associated with exercise-based rehabilitation may apply to both patients with acute coronary syndromes and those who have undergone revascularization. Psychological benefits, improved coronary blood flow and functional capacity, and reductions in risk factors and inducible ischemia have also been reported.[2,9,17]

PHYSIOLOGIC BENEFITS

Exercise has been shown to improve CV risk factors, including blood pressure, lipid profile, weight, smoking, and prevention and treatment of diabetes mellitus.[16,23] Following MI, exercise training results in lower blood pressure and heart rate for a given level of exertion and may improve aerobic capacity. Resistance training in combination with aerobic training has been shown to improve both endurance and skeletal muscle strength.

Exercise is associated with positive atherogenic and anti-inflammatory effects. In addition, studies have shown improved endothelial function and a more favorable fibrinolytic balance.[24] Specific biologic mechanisms for the benefit of exercise are summarized in Table 45–1.

Heart Rate Recovery

Heart rate recovery is an indicator of CV health, and impaired heart rate recovery predicts mortality. In a study of 544 patients with abnormal heart rate recovery prior to starting CR, the exercise program resulted in a 41% improvement in heart rate recovery. Importantly, those who had evidence of poor heart rate recovery at the completion of CR had a higher likelihood of all-cause mortality.[25]

Left Ventricular Remodeling

Following MI, exercise training has proven benefits on left ventricular (LV) function and remodeling. The most recent evaluation of this topic is a 2011 systemic review. In clinically stable patients after MI, exercise training had a positive effect on LV remodeling.[26] The effects were greatest when exercise training started 1 week after MI and lasted longer than 12 weeks.[26]

Psychological Benefit

Depression is associated with fatigue, reduced exercise capacity, and reduced quality of life. The association between depression and CHD

TABLE 45–1. Biologic Mechanisms for Benefit of Exercise

- Antiatherogenic effects
  - Reduction of elevated plasma triglycerides
  - Increase in high-density lipoprotein cholesterol levels
- Anti-inflammatory effects
- Effects on endothelial function
- Autonomic functional changes
- Anti-ischemic effects
- Antiarrhythmic effects
- Reduction in age-related disability

is well known, with an estimated 20% to 45% of patients demonstrating significant depression after MI.[27] In addition, anxiety is associated with a worse prognosis in patients with CHD.[28] CR programs assess psychological stress and depression at intake and provide access to group and individual counseling sessions. In a 40-month study of 500 consecutive CHD patients, improved fitness was associated with decreased depressive symptoms and decreased mortality. Patients with depression demonstrated a fourfold increase in mortality compared with nondepressed patients (22% vs 5%).[29]

PRINCIPLES OF CARDIAC REHABILITATION

The indications and contraindications for CR are summarized in Table 45–2. To establish a safe and effective program of comprehensive CV disease risk reduction and rehabilitation, each patient should undergo a careful medical evaluation and exercise test before participating in an outpatient CR/SP program. The specific components of the medical evaluation should include a medical history, physical examination, and resting electrocardiogram (ECG). The exercise test should be repeated any time that symptoms or clinical changes warrant, as well as in the follow-up assessment of the exercise training outcome[30] (Table 45–3).

TABLE 45–2. Clinical Indications and Contraindications for Inpatient and Outpatient Cardiac Rehabilitation[2]

Indications

- Medically stable after myocardial infarction
- Stable angina
- Coronary artery bypass graft surgery
- Percutaneous transluminal coronary angioplasty or other transcatheter procedure
- Compensated congestive heart failure
- Cardiomyopathy
- Heart or other organ transplantation
- Other cardiac surgery including valvular and pacemaker insertion (including implantable-cardioverter defibrillator)
- Peripheral arterial-vascular disease
- High-risk cardiovascular disease ineligible for surgical intervention
- Sudden cardiac death syndrome
- End-stage renal disease
- At risk for coronary artery disease, with diagnosis of diabetes mellitus, hyperlipidemia, hypertension, etc.
- Other patients who may benefit from structured exercise and/or patient education (based on physician referral and consensus of the rehabilitation team)

Contraindications

- Unstable angina
- Resting systolic blood pressure > 200 mm Hg or diastolic > 110 mm Hg
- Orthostatic blood pressure decrease of > 20 mm Hg with symptoms
- Critical aortic stenosis (peak systolic pressure gradient of > 50 mm Hg with an aortic valve orifice area of < 0.75 cm^2 in an average-size adult)
- Acute systemic illness or fever
- Uncontrolled atrial or ventricular arrhythmias
- Uncontrolled sinus tachycardia (> 120 bpm)
- Uncompensated congestive heart failure
- Third-degree heart block (without pacemaker)
- Active pericarditis or myocarditis
- Recent embolism
- Thrombophlebitis
- Resting ST-segment displacement (> 2 mm)
- Uncontrolled diabetes (resting blood glucose > 300 mg/dL [17 mmol/L] or > 250 mg/dL [14 mmol/L]) with ketones present
- Orthopedic problems prohibiting exercise
- Other metabolic conditions such as acute thyroiditis, hypokalemia or hyperkalemia, hypovolemia, etc.

TABLE 45–3. Absolute and Relative Contraindications to Exercise Training[30]

Absolute

- Recent change in the resting electrocardiogram (ECG) suggesting significant ischemia, recent MI, or other acute cardiac event
- Unstable angina
- Uncontrolled cardiac arrhythmias
- Symptomatic severe aortic stenosis or other valvular disease
- Decompensated symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute noncardiac disorder that may affect exercise performance or may be aggravated by exercise (eg, infection, thyrotoxicosis)
- Acute myocarditis or pericarditis
- Acute thrombophlebitis
- Physical disability that would preclude safe and adequate exercise performance

Relative[a]

- Electrolyte abnormalities
- Tachyarrhythmias or bradyarrhythmias
- High-degree atrioventricular block
- Atrial fibrillation with uncontrolled ventricular rate
- Hypertrophic obstructive cardiomyopathy with peak resting left ventricular outflow gradient of > 25 mm Hg
- Known aortic dissection
- Severe resting arterial hypertension (systolic blood pressure [BP] > 200 mm Hg and diastolic BP > 110 mm Hg)
- Mental impairment leading to inability to cooperate with testing

[a]Contraindications can be superseded if benefits outweigh risks of exercise.

Data from American Association of Cardiovascular and Pulmonary Rehabilitation. AACVPR Cardiac Rehabilitation Resource Manual. Champaign: Human Kinetics; 2013.

PHASES

Worldwide, CR is structured in different ways. The term *phase* is used to describe the varying time frames following a cardiac event. There are four phases of CR in both Europe and the United States (Table 45–4), but variations in the structure of these phases exist.

Phase I

Inpatient Phase I traditionally begins in the hospital. The patient is reviewed by the nutritionist, social worker, and physical therapist. Individual risk factors are discussed, and the patient is first introduced to the concept of lifelong lifestyle changes. Simple breathing and leg exercises are commenced with a program of gradual mobilization. The emphasis at this stage is to counteract the negative effects of deconditioning after a cardiac event. A patient is considered appropriate for daily ambulation/mobilization if (1) there has been no new or recurrent chest pain during the previous 8 hours; (2) neither troponin nor creatine phosphokinase (CPK) is increasing; (3) there are no signs of decompensated heart failure; and (4) there is no significant change in ECG or rhythm in previous 8 hours.[31] A discharge plan is formulated taking into account individual needs (eg, return to work, medications, exercise program).

TABLE 45–4. Traditional Terminology for the Phases of Cardiac Rehabilitation[2]

Phase I
Inpatient rehabilitation, usually lasting for the duration of hospitalization. This phase emphasizes a gradual, progressive approach to exercise and an education program that helps the patient understand the disease process, the rehabilitation process, and initial preventive efforts to slow the progression of disease.

Phase II
Multifaceted safe physical activity to improve conditioning with continued behavior modification aimed at smoking cessation, weight loss, healthy eating, and other factors to reduce disease risk. Initiate an exercise prescription.

Phase III
Supervised rehabilitation lasting 6 to 12 months. Establishes a prescription for safe exercise that can be performed at home or in a community service facility, such as a senior center or YMCA, and continues to emphasize risk factor reduction.

Phase IV
Maintenance; indefinite.

Adapted with permission from Braunwald E, Zipes D, Libby P, et al: Braunwald's Heart Disease, *A Textbook of Cardiovascular Medicine*, 7th ed. New York: Elsevier Saunders; 2005.

TABLE 45–5. Absolute and Relative Contraindications to Exercise Testing[24]

Absolute contraindications
- Acute myocardial infarction (MI), within 2 days
- Ongoing unstable angina
- Uncontrolled cardiac arrhythmia with hemodynamic compromise
- Active endocarditis
- Symptomatic severe aortic stenosis
- Decompensated heart failure
- Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis
- Acute myocarditis or pericarditis
- Acute aortic dissection
- Physical disability that precludes safe and adequate testing

Relative contraindications
- Known obstructive left main coronary artery stenosis
- Moderate to severe aortic stenosis with uncertain relation to symptoms
- Tachyarrhythmias with uncontrolled ventricular rates
- Acquired advanced or complete heart block
- Hypertrophic obstructive cardiomyopathy with severe resting gradient
- Recent stroke or transient ischemic attack
- Mental impairment with limited ability to cooperate
- Resting hypertension with systolic or diastolic blood pressures > 200/110 mm Hg

After Discharge The length of time between discharge and commencement of the phase II program varies between countries and facilities. The usual mode of exercise prescribed initially is walking on level ground. The intensity should be maintained between 2 and 4 METS or a score of 11 to 12 on the Rating of Perceived Exertion (RPE) Scale in the early stages.[30] Patients should be told to increase their walking distance progressively to 3 to 5 km daily after 4 to 6 weeks.

Phase II (Outpatient Exercise Program)

The aim of this phase of the CR program is to enable the patient to exercise safely in a structured environment and to understand the benefits of exercise. Prior to commencing an exercise program, it is usual for a patient to undergo a symptom-limited exercise stress test. Exercise testing can be used as either a diagnostic or prognostic tool or as a test of functional capacity. It is mainly for the latter reason that exercise testing is recommended in CR. This information aids assessment for exercise prescription and return to work evaluation and helps in an estimation of prognosis. The absence of a test may lead to an inappropriate exercise prescription.[30] Absolute and relative contraindications to exercise testing are shown in Table 45–5.

Recommended intensities for the structured exercise in phase II (outpatient phase) vary depending on the technique used to prescribe exercise intensity. Cardiac patients should exercise in the low to moderate range of exercise intensity, corresponding to 60% to 75% of maximum heart rate (HR_{max})[13] or 60% to 70% of maximum heart rate reserve,[30] corresponding to a score of 12 to 14 on the RPE Scale.[13] Although most accurately measured using a cardiac stress test, the most common way of calculating the HR_{max} is to subtract the patient's age from 220. The heart rate reserve is calculated by subtracting the resting heart rate from the HR_{max}.

The types of exercises used during the exercise program should promote total physical conditioning, including treadmills, cycle and arm ergometers, stair climbers, and rowing machines.[31] These exercises are mainly aerobic in nature, but resistance training can be used in lower to moderate risk cardiac patients. However, it is recommended that patients spend some time on aerobic-type exercises first before progressing to resistance exercise. The type and quantity of equipment available will depend on the resources available, the available space, and the number of patients in the group. It is usual for 8 to 10 patients of similar functional capacities to exercise together, but this number will vary depending on the patients' functional limitations and the availability of staff. A warm-up period of approximately 15 minutes is followed by the exercise session, which lasts for 30 to 35 minutes; the exercise session is followed by a cool-down period of 10 minutes.

Phase III

During phase III, the patient may continue to exercise in the same CR facility, without telemetry monitoring, but with the supervision of an exercise physiologist or physical therapist. Most phase III programs are available 2 to 3 days a week, while promoting independent exercise and lifelong lifestyle modifications.

Phase IV

Phase IV is a maintenance program often in the form of a gym or health club facility membership, ideally with occasional sessions to help sustain lifestyle change.

TARGET POPULATION

Traditionally, for patients with CHD, CR is offered to patients after uncomplicated MI or after successful revascularization with coronary artery bypass surgery or PCI.[32] In addition, higher risk subjects, such as elderly patients with comorbidities, patients with automatic internal cardiac defibrillators, and patients before and after cardiac transplantation, often participate in tailored CR programs.

The exercise goals of a CR program are developed based on the individual's baseline ability and limitations. An exercise prescription is developed and is composed of the mode, frequency, duration, and intensity of exercise.[24] Risk stratification is performed with each

patient prior to initiation of exercise program. The guidelines published by the AHA use the following four categories according to clinical characteristics. Most patients who are referred to CR programs are class B or C, where supervised exercise is associated with a small risk of adverse events.[24]

1. Class A individuals are apparently health without increased CV risk with exercise.
2. Class B individuals have clinical stable CHD and are at low risk of CV complications with vigorous exercise (Table 45–6).
3. Class C individuals are at moderate or high risk of cardiac complications during exercise due to one of the following: history of multiple MIs or cardiac arrest; New York Heart Association class III or IV angina, exercise capacity of less than 6 METs, and significant ischemia on exercise stress test (Table 45–7).
4. Class D individuals are those with unstable disease who require restriction of activity and for whom exercise is contraindicated.

TABLE 45–6. Risk Classification for Exercise Training: Class B: Presence of Known, Stable Cardiovascular Disease With Low Risk for Complications With Vigorous Exercise, but Slightly Greater Than for Apparently Healthy Individuals[24]

This classification includes individuals with any of the following diagnoses:

1. Coronary artery disease (myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris, abnormal exercise test, and abnormal coronary angiograms); includes patients whose condition is stable and who have the clinical characteristics outlined below
2. Valvular heart disease, excluding severe valvular stenosis or regurgitation, with the clinical characteristics as outlined below
3. Congenital heart disease; risk stratification for patients with congenital heart disease should be guided by the 27th Bethesda Conference recommendations
4. Cardiomyopathy: ejection fraction ≤ 30%; includes stable patients with heart failure with clinical characteristics as outlined below, but not hypertrophic cardiomyopathy or recent myocarditis
5. Exercise test abnormalities that do not meet any of the high-risk criteria outlined in Class C (see Table 45–5)

Clinical characteristics (must include all of the following):

1. New York Heart Association class I or II
2. Exercise capacity > 6 METs
3. No evidence of heart failure
4. No evidence of myocardial ischemia or angina at rest or on the exercise test at or below 6 METs
5. Appropriate rise in systolic blood pressure during exercise
6. Absence of sustained or nonsustained ventricular tachycardia at rest or with exercise
7. Ability to satisfactorily self-monitor intensity of activity

Activity guidelines: Activity should be individualized, with exercise prescription provided by qualified individuals and approved by primary health care provider

Supervision required: Medical supervision during initial prescription session is beneficial.

Supervision by appropriate trained nonmedical personnel for other exercise sessions should occur until the individual understands how to monitor his or her activity. Medical personnel should be trained and certified in advanced cardiac life support. Nonmedical personnel should be trained and certified in basic life support (which includes cardiopulmonary resuscitation).

Electrocardiographic and blood pressure monitoring: Useful during the early prescription phase of training

TABLE 45–7. Risk Classification for Exercise Training: Class C[a]: Those at Moderate to High Risk for Cardiac Complications During Exercise or Unable to Self-Regulate Activity or to Understand Recommended Activity Level[24]

This classification includes individuals with any of the following diagnoses:

1. CAD with the clinical characteristics outlined below
2. Valvular heart disease, excluding severe valvular stenosis or regurgitation, with the clinical characteristics as outlined below
3. Congenital heart disease; risk stratification for patients with congenital heart disease should be guided by the 27th Bethesda Conference recommendations
4. Cardiomyopathy: ejection fraction ≤ 30%; includes stable patients with heart failure with clinical characteristics as outlined below but not HCM or recent myocarditis
5. Complex ventricular arrhythmias not well controlled

Clinical characteristics (any of the following)

1. New York Heart Association class III or IV
2. Exercise test results
   - Exercise capacity < 6 METs
   - Angina or ischemic ST depression at a workload < 6 METs
   - Fall in systolic blood pressure below resting levels during exercise
   - Nonsustained VT with exercise
3. Previous episode of primary cardiac arrest (ie, cardiac arrest that did not occur in the presence of an acute myocardial infarction or during a cardiac procedure)
4. A medical problem that the physician believes could be life-threatening

Activity guidelines: Activity should be individualized, with exercise prescription provided by qualified individuals and approved by primary health care provider

Supervision: Medical supervision during all exercise sessions until safety is established

Electrocardiographic and blood pressure monitoring: Continuous during exercise sessions until safety is established

Abbreviations: CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; MET, metabolic equivalent; VT, ventricular tachycardia.

[a]Class C patients who have successfully completed a series of supervised exercise sessions may be reclassified as Class B, provided that the safety of exercise at the prescribed intensity is satisfactorily established by appropriate medical personnel and that the patient has demonstrated the ability to self-monitor.

COMPONENTS OF CARDIAC REHABILITATION

The way in which CR is delivered may differ nationally and internationally, but certain standard core components, including baseline patient assessment, psychosocial interventions, nutritional counseling, risk factor management (lipids, blood pressure, weight, diabetes mellitus, and smoking), physical activity counseling, and exercise training, have been adopted by Europe and the United States.[12]

EXERCISE TRAINING

Exercise Stress Testing

The exercise stress test, using a standard graded increase in demand, assesses exercise capacity while monitoring symptomatic and hemodynamic responses. The World Health Organization expert committee on CR states that the primary purpose of an exercise test is to determine the responses of the individual to efforts at given levels and, from this information, to estimate probable performance in specific life and occupational situations.[31] Indications for exercise stress testing include diagnostic, prognostic, and therapeutic applications. In CR, the exercise test is used to determine the target heart rate for exercise prescription.[33] Exercise stress testing in CR is performed to measure

the ischemic threshold, assess for arrhythmias, assess exercise tolerance, evaluate hemodynamic response (blood pressure, heart rate), and observe for signs and symptoms of ischemia. Table 45–5 outlines the contraindications to stress testing.

Various protocols are available for exercise testing, and the choice should depend on the outcome and the clinical characteristics of the patient. The Bruce protocol is perhaps one of the most common protocols that is used, although the increments between each stage are quite large; thus for older or deconditioned patients, protocols such as the Naughton protocol may be more appropriate.[31] The test is traditionally carried out using a treadmill or a cycle ergometer (for those with orthopedic issues) with monitoring of ECG, heart rate, and blood pressure. The RPE Scale and the individual's description of his or her levels of angina and dyspnea are also assessed. The exercise test usually lasts for 8 to 12 minutes and is terminated when the patient develops symptoms or when he or she achieves a physiologic end point, such as 85% of maximal predicted heart rate. Other absolute and relative indications for terminating the test are given in Table 45–8.

The subject's general appearance during the exercise test is also of value and should be carefully observed during the exercise test. Signs of poor perfusion, such as cyanosis or pallor, and increasing nervous system symptoms, such as ataxia, dizziness, and vertigo, serve as absolute test termination criteria. Although the diagnostic value has not been confirmed, cardiac auscultation immediately after exercise has been proposed to assess cardiac function. The development of a mitral regurgitant murmur, fourth heart sound, or a palpable precordial bulge after exercise could suggest LV dysfunction resulting from exercise.[24]

TABLE 45–8. Indications for Terminating Exercise Testing[30]

Absolute indications

- ST-segment elevation (> 1.0 mm) in leads without preexisting Q waves because of prior myocardial infarction (other than aVR, aVL, and V_1)
- Drop in systolic blood pressure > 10 mm Hg, despite an increase in workload, when accompanied by any other evidence of ischemia
- Moderate-to-severe angina
- Central nervous system symptoms (eg, ataxia, dizziness, near syncope)
- Signs of poor perfusion (cyanosis or pallor)
- Sustained ventricular tachycardia (VT) or other arrhythmia, including second- or third-degree atrioventricular (AV) block, that interferes with normal maintenance of cardiac output during exercise
- Technical difficulties in monitoring the electrocardiogram or systolic blood pressure
- The subject's request to stop

Relative indications

- Marked ST displacement (horizontal or down sloping of > 2 mm, measured 60 to 80 ms after the J point [the end of the QRS complex]) in a patient with suspected ischemia
- Drop in systolic blood pressure > 10 mm Hg (persistently below baseline) despite an increase in workload, in the absence of other evidence of ischemia
- Increasing chest pain
- Fatigue, shortness of breath, wheezing, leg cramps, or claudication
- Arrhythmias other than sustained VT, including multifocal ectopy, ventricular triplets, supraventricular tachycardia, and bradyarrhythmias that have the potential to become more complex or to interfere with hemodynamic stability
- Exaggerated hypertensive response (systolic blood pressure > 250 mm Hg or diastolic blood pressure > 115 mm Hg)
- Development of bundle branch block that cannot immediately be distinguished from VT

Exercise Capacity

Aerobic exercise capacity is one of the best predictors of risk for future adverse events in apparently healthy individuals, those at increased risk for CV disease, and virtually all patient populations, independent of other traditional risk factors. One MET is defined as 3.5 mL O_2 uptake/kg/min, or the resting oxygen uptake in a sitting position. A meta-analysis including 33 studies reported that a 1-MET increase in aerobic capacity resulted in a 13% and 15% decrease in rates of all-cause death and CV events, respectively.[34] In estimating exercise capacity, the amount of work performed in METs (or exercise stage achieved) is preferred to the number of minutes of exercise due to variations in protocols. Aerobic capacity should be reported as both the actual value achieved and a percent-predicted value.[24]

EXERCISE PROGRAM

Entry into a CR program begins 1 to 3 weeks after discharge from the hospital after MI or PCI, depending on the clinical status of the patient. Patients who have undergone cardiac surgery should delay upper extremity training for 4 to 6 weeks. Sessions are scheduled for either 2 or 3 days per week and last for 9 to 36 weeks (average, 12 weeks) depending on patient's achievement in significant improvement in functional status. Each session includes warm-up and flexibility exercises, which gradually increase heart rate into target range. Aerobic activity using a treadmill, stationary bike, or stepper is recommended for 20 to 30 minutes, followed by a cool down for 5 to 10 minutes involving low-intensity exercise to allow gradual recovery. ECG monitoring continues 6 to 8 minutes after exercise or if blood pressure, heart rate, and ST segments have not returned to normal.[24]

INTENSITY

The intensity for exercise training can be calculated from the exercise test, and for cardiac patients, the heart rate is the most common method used. There are three methods of using the heart rate, and these include the direct method, the percentage of HR_{max}, and the heart rate reserve.[24] In the direct method, the heart rate is plotted against oxygen consumption, and the appropriate exercise intensity is extrapolated (Fig. 45–1). The percentage of HR_{max} method uses 65% to 75% of the heart rate achieved during the exercise test, which approximates to 40%

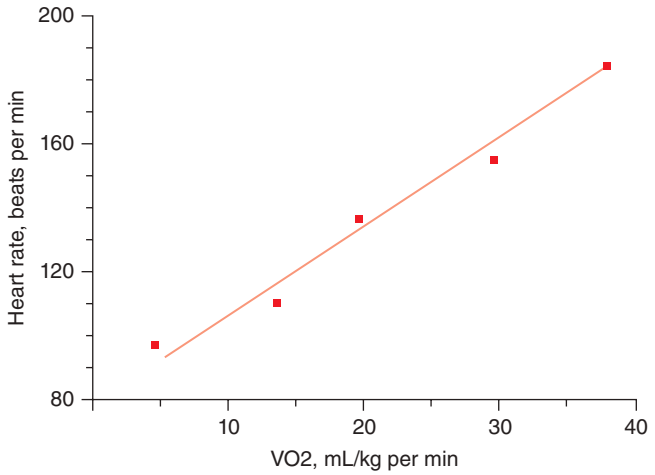

FIGURE 45–1. Relation between heart rate and oxygen uptake (VO_2) during exercise. One metabolic equivalent (MET) is defined as 3.5 mL O_2 uptake/kg/min. Mean values of approximately 10 METs (VO_2 35 mL/kg/min) can be achieved by nonathletic, healthy, middle-aged men; this should occur at a heart rate of approximately 175 bpm. Data from Reddy HK, Weber KT, Janicki JS, et al: Hemodynamic, ventilatory and metabolic effects of light isometric exercise in patients with chronic heart failure. *J Am Coll Cardiol*. 1988 Aug;12(2):353-358.

TABLE 45–9. Borg Scale for Rating Perceived Exertion[76]

6 7 8	Very, very light
9 10	Very light
11 12	Fairly light
13 14	Somewhat hard
15 16	Hard
17 18	Very hard
19 20	Very, very hard

to 60% of an individual's maximal oxygen consumption (VO_2 max). In the heart rate reserve method, the resting heart rate is subtracted from the maximal heart rate (estimated as 220 minus the age in years) to give the heart rate reserve. If an exercise prescription of 60% to 80% of maximal oxygen consumption is required, then 60% and 80% values of the heart rate reserve are calculated, and the resting heart rate is added to each value to give the training heart rate values.[24]

Patients are taught to measure intensity of exertion by heart rate and RPE Scale (or Borg scale; Table 45–9). Using this scale, an RPE of 12 to 13 (somewhat hard) corresponds to 60% VO_2 max, and an RPE of 16 (hard to very hard) corresponds to 85% VO_2 max. Low-risk patients (class B) may use low-level resistance training to increase muscle strength and endurance.[24]

SAFETY OF CARDIAC REHABILITATION

The risk of a cardiac event in patients diagnosed with CHD is increased when there is extensive damage to the myocardium, residual ischemia, and ventricular arrhythmias.[30] The AHA Scientific Statement on exercise and acute CV events noted that the risk of any major CV complication is one event in 60,000 to 80,000 hours of supervised exercise.[33] The observation that the incidence of cardiac arrest is six-fold higher than the death rate indicates the value of successful resuscitation during supervised CR but also suggests that the death rate likely would be higher during unsupervised exercise. Staff supervising such exercise programs must be appropriately trained in advanced cardiac life support with ECG monitoring available for patients deemed high risk.[31]

MULTIDISCIPLINARY COMPONENTS: REDUCING TOTAL CARDIOVASCULAR RISK

Recommendations on prevention and rehabilitation acknowledge that patient management should be based on an assessment of total risk. The various components addressed by CR programs will generally include attention to the following aspects:

- Behavior change
- Smoking
- Weight management
- Nutrition

TABLE 45–10. Guiding Principles to Effect Behavioral Change

1. Provide a tailored and individualized approach.
2. Recognize that knowledge is necessary but not sufficient for behavior change.
3. Promote a positive sense of self and the personal relevance of risk reduction.
4. Promote self-efficacy and the power of control.
5. Promote readiness to change.
6. Set goals to promote a Specific, Measurable, Achievable, Realistic/Relevant, and Time-framed (SMART) plan of action.
7. Promote independence through consciousness raising and self-monitoring skills.
8. Provide routine feedback and rewards to celebrate success.
9. Help patients create positive environmental cues to action.
10. Promote helping relationships and engage role models.

- Lipids
- Blood pressure
- Psychosocial factors
- Cardiopulmonary resuscitation training

BEHAVIOR CHANGE

A primary principle of patient education is to facilitate necessary behavior change known to improve health outcomes. Changing health behavior requires assessment of a patients' knowledge, attitudes, and beliefs as well as psychological health (especially anxiety and depression). The American Association of Cardiovascular and Pulmonary Rehabilitation acknowledges several guiding principles in effecting necessary change, as listed in Table 45–10. Support from the physician, program staff, and family contributes to the effective behavioral change. CR programs offer the opportunity for comprehensive, evidence-based, lifestyle modification.[30]

SMOKING

Cigarette smoking, a major risk factor for the development of CHD, remains a leading cause of preventable death worldwide.[35] It is expected that the number of smokers worldwide will increase to > 1.6 billion by 2025.[36] The causal relationship between smoking and CV disease is well established. The effects of smoking on the CV system include stimulation of smooth muscle proliferation and cell migration to intima, increase in platelet adhesion to the endothelium, and an increase in fibrinogen levels (increased clotting).[2] Smoking cessation will reduce the subsequent risk of mortality by up to 9% in absolute terms.[36] Observational studies in post-MI patients suggest that this may be reflected as a halving of long-term mortality.[37]

CR programs are the ideal setting in which to promote smoking cessation. Educating patients about the association between smoking and heart disease at this vulnerable period may be the trigger to motivate smoking cessation. Numerous nonpharmacologic and pharmacologic agents are available to aid the patient and health professional with this campaign. Both group therapy and individual counseling to instigate behavioral change are useful in helping the patient to quit smoking. Nicotine replacement therapy in the form of transdermal patches, chewing gum, nasal spray, oral inhalers, and sublingual tablets may augment the process of smoking cessation.[2]

WEIGHT MANAGEMENT

Obesity is a major public health problem throughout the developed world. Overweight, obesity, and excess abdominal fat are related to

important CHD risk factors including high levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, blood pressure, fibrinogen, and insulin and low levels of high-density lipoprotein cholesterol.[38]

For overweight and obese patients with CHD, the combination of a reduced-energy diet and increased physical activity is recommended. An energy deficit is most readily achievable through choice of foods low in total fat content, with a reduction in saturated fat being more preferable. Further reductions in total energy intake can be achieved by reducing refined carbohydrate intake.[2]

NUTRITION AND LIPIDS

Nutrition plays a pivotal role in the etiology and development of CV disease. A range of dietary measures can make a favorable contribution to the secondary prevention of coronary artery disease.[30] Changes in the quantity and quality of dietary fat improve the lipid profile. Blood pressure is lowered by reducing sodium intake and by adhering to the Dietary Approaches to Stop Hypertension (DASH) diet, a diet rich in vegetables, fruits, and low-fat dairy products and low in saturated and total fat. Consumption of a diet relatively low in fat, *trans*-fatty acids, saturated fatty acids, cholesterol, and sodium or relatively high in fruit, vegetables, polyunsaturated fatty acids, monounsaturated fatty acids, fish, fiber, and potassium is likely to reduce the risk of CV disease.[39-41] Dietary therapy is additive to drug therapy and further reduces CV risk. Failure to adopt a cardioprotective diet may result in the need to use higher doses or combinations of medications.[42,43] A cardioprotective diet pattern has been developed for easy incorporation into CR programs. The cumulative advantage accruing from all food and nutrients in an integrated dietary pattern offers the prospect of a substantial reduction in risk of CV disease for individuals and populations.[44]

This dietary pattern (which is based on the Mediterranean diet) may be summarized as follows:

- Low in saturated fatty acids
- Low in *trans*-fatty acids
- Replace saturated fats with monounsaturated and polyunsaturated fats
- Omega-3 fatty acids (eg, oily fish)
- Replace some fat intake with soluble fiber
- Reduce salt
- Five or more portions of fruit and vegetables daily

There is insufficient evidence to recommend nutrition supplements of antioxidant vitamins, minerals, or trace elements for the treatment of CV disease. There is evidence to support the effectiveness of nutritional education in generating positive and long-lasting changes in the dietary habits of patients involved in CR.[45] Therefore, nutritional evaluation, counseling, and monitoring must occur as part of a comprehensive CR program.

CR nutrition education is conducted over four phases to facilitate patient learning. Some patients may require more information/nutrition counseling than they can obtain in the context of a group program, such as patients with additional health needs (eg, diabetes mellitus, obesity, chronic heart failure) and patients from culturally and linguistically diverse backgrounds.[2] A structure for nutritional education sessions is available in Appendix 45–1.

HYPERTENSION

Evidence exists regarding the importance of hypertension as a risk factor for CV disease and the importance of lifestyle measures and appropriate medication to treat and control hypertension.[14] (See Chap. 25 for medical therapy of hypertension.)

Management of Hypertension

It is well recognized that hypertensive vascular disease is a continuum. Genetic, environmental, and coexisting risk factors influence the rapidity and progression of vascular changes within the blood vessel walls. Ambulatory blood pressure monitoring is recommended to confirm diagnosis.[46] Change in lifestyle behaviors may have important effects on BP control. Excessive alcohol consumption is associated with hypertension, and reduction or cessation of consumption of alcohol has been shown to improve blood pressure and reduce need for medication.[46] A majority of people with hypertension are salt-sensitive, and reductions in dietary salt are effective. There is a direct link between increasing body weight and blood pressure levels, particularly if fat distribution is central.[38] Obesity contributes to hypertension through its effect on the sympathetic and renin-angiotensin-aldosterone systems. Stress has a major effect on blood pressure, and recognition and elimination of this factor may have important effects. A weight loss of 5 kg has been shown to correspond to a blood pressure reduction of 10/5 mm Hg. Secondary causes of hypertension may be diagnosed if one of the following is noted: blood pressure of ≥ 180/110 mm Hg, uncontrolled hypertension despite three medications, or nondipping of blood pressure during 24-hour ambulatory blood pressure monitoring.

Lifestyle changes and patient education are paramount in the management of hypertension. Such lifestyle measures include smoking cessation, regular exercise, weight reduction, and dietary changes. These measures will also enhance the effects of antihypertensive medication and demonstrate favorable influence on overall CV risk. The recommended DASH diet (low in salt and saturated fat and high in fiber, fruit, and vegetables) can lower blood pressure as effectively as nondietary measures using maximum monotherapy.[47] Effective implementation of nonpharmacologic measures requires knowledge, time, and resources best undertaken by well-trained health professionals. CR provides an ideal setting to improve CV risk factors.

PSYCHOSOCIAL FACTORS

Psychosocial factors may impact on the occurrence and recurrence of CHD and may affect rehabilitation. Psychosocial factors are numerous and include anxiety and/or depression, personality issues (eg, hostility, cynicism, mistrust), social isolation, anger and hostility, type D (or distressed) personality, lack of social support, chronic or subacute life stress (eg, stress at work, high demands, limited decision making, low rewards), or accumulation of painful and difficult situations during a relatively short period of time.[2] Psychological stress can be as dangerous to the heart as physical stress for people with coronary artery disease. The link between depression, social isolation, and lack of quality social support and heart disease is strong and consistent. Depression, social isolation, and lack of quality social support are as risky to heart health as abnormal levels of blood fats, smoking, and high blood pressure. Prospective cohort studies provide strong evidence that psychosocial factors, particularly depression and social support, are independent etiologic and prognostic factors for CHD.[2]

Pathophysiologic mechanisms with acute stress and intense emotion lead to sympathetic nervous system stimulation with an increase in heart rate and blood pressure, vasoconstriction, proarrhythmic potential, reduced endothelial dysfunction, endothelial injury, platelet activation, and/or hemostatic changes, all of which can result in the clinical consequences of myocardial ischemia, arrhythmias, and the potential for thrombosis. Positive psychological effects of CR have been demonstrated, although the variety of instruments used to assess health-related quality of life makes quantitative analysis difficult.[48]

Anxiety and depression are prevalent in both cardiac patients and their families and are associated with increased morbidity and mortality. Although they may be normal responses after a cardiac event and a natural part of recovery after any life-threatening or stressful event, in excess, they may seriously impede rehabilitation. Anxiety can affect both short- and long-term recovery after a cardiac event. It may relate more to how an individual responds to his or her condition than to its severity. Anxiety may trigger a variety of physiologic responses such as increased levels of circulating lipids, platelet and macrophage cell activation, and increased heart rate, blood pressure, and myocardial oxygen demand, all of which have the potential to contribute to atherosclerosis and acute coronary syndromes. These responses have implications for the development of atherosclerosis, ischemia, MI, and sudden death.[2]

CR programs provide a valuable chance to assess cardiac patients for anxiety and depression and provide interventions for those who need specialized care. Many instruments are available to CR professionals to assess anxiety and depression. The most practical method is the use of a self-report scale. Within psychology, psychometric robustness (which includes reliability and validity), sensitivity to change over time, brevity (which minimizes demands on patients), and a track record of having been used in past well-designed studies are some of the important hallmarks of good self-report measures for use in assessment, intervention, and evaluation studies with patients with chronic illness.[49] A commentary on these instruments is included in Appendix 45–2. There is evidence that the use of active coping, rather than avoidant coping strategies, may lead to positive psychological adjustment and improved quality of life. The principles of self-management programs are outlined in Appendix 45–3.

CARDIOPULMONARY RESUSCITATION TRAINING FOR RELATIVES OF CARDIAC PATIENTS

Sudden cardiac death is defined as follows: "An unexpected death due to cardiac causes that occurs within one hour of symptom onset. Cardiac arrest, usually due to cardiac arrhythmias, is the term used to describe the sudden collapse, loss of consciousness and loss of effective circulation that precedes biologic death."[50]

Recognition and treatment of potentially lethal arrhythmias in the coronary care unit has reduced mortality; however, up to 75% of fatalities occur out of hospital. Of these out-of-hospital cardiac arrests, it is estimated that a majority occur in the home with the spouse or family member being a witness.[51]

An important need identified by spouses of recovering cardiac patients is the need to learn what to do if their spouse has a cardiac arrest at home.[52] Various professional associations have made recommendations regarding cardiopulmonary resuscitation (CPR) training for the relatives of cardiac patients. The AHA endorsed CPR training of the lay public in 1971, and from 1992, the AHA guidelines recommend targeting courses to relatives and close friends of persons at risk. The AHA International Guidelines starting in 2000 strongly recommend targeting family members of high-risk adult and pediatric patients, stating that: "Healthcare professionals should recommend CPR training for family members as part of the discharge teaching plan for high-risk patients. Persons caring for high-risk populations must be educated to recognize airway or CV emergencies and must be taught how to intervene appropriately and to contact the emergency medical system."[53]

BARRIERS TO UTILIZATION OF TRADITIONAL CARDIAC REHABILITATION PROGRAMS AND THE FUTURE

The most common barrier to CR is lack of physician referral. Despite national guidelines in the United States designating CR as a Class IA recommendation, Menezes et al[54] report that up to 80% are not referred. In particular, women, those of lower socioeconomic status, and patients over age 65 have lower rates of referral.[11,55,56] Additionally, patients who have limitations due to geographic location or insurance coverage issues are less likely to be referred and to participate.[15] Of those who are referred, patient factors for nonparticipation include financial burden, transportation difficulties, and competing priorities.[15,54,57] Importantly, once referred to CR, reasons for nonattendance were more likely due to personal factors, such as perceptions of heart disease and family influence, versus physical issues.[58] In Europe, the EuroAspire survey analyzed records and interviews of 9000 patients in 22 countries in Europe and reported that only one-third of patients with CHD received any form of CR.[59] Even among those referred to CR, the dropout rate is high among post-MI patients (29% dropout at 1 month).[60] Patient-related factors include affordability, including insurance coverage, transportation difficulties, and competing priorities. From a systems perspective, lack of personnel and resources have been cited as having a significant impact on utilization.

Global Issues

CR is a Class 1 recommendation from the AHA, the ACC, and the European Society of Cardiology.[61,62] In European CR programs, patients who are referred are more likely to enroll and complete CR due to both national health insurance coverage and employer support.[63] Although most of the literature regarding CR originates from higher income countries, CR has been evaluated in low- and middle-income countries (LMICs) and has demonstrated improved clinical results, but lower enrollment rates.[64] Worldwide, only 39% of countries offer CR, with a breakdown of 68% of high-income countries versus 23% of LMICs.[65] Although fewer randomized trials of SP programs have been undertaken in LMICs, improvement in clinical outcomes should be expected with CR programs, given the particularly poor rates of control of CV disease risk factors. Due to both financial constraints and geographic challenges, the use of home- or community-based programs warrants investigation in LMICs. Strategies to improve CR availability are necessary and include supportive public health policies as well as novel models of delivery.[65]

Delivery Systems

In light of the known barriers to care, innovative strategies to bring CR to more patients necessitates newer delivery models. In addition to telemedicine models, Internet-based, home-based, and community-based programs may complement the current facility-based programs.[66] A systematic review and meta-analysis of home-based versus facility-based CR concluded that for low-risk patients after MI and revascularization, home-based CR improved health-related quality of life and clinical outcomes including death, revascularization, or hospital admission equally as well as center-based CR.[67] The out-of-facility delivery models should augment the various needs of individuals based on their individual CV risk, age, and social support. Recently, investigators from Toronto, Canada, compared health behaviors and outcomes of women randomly assigned to women-only CR programs with women assigned to participation in traditional programs and found both physical activity and quality of life improved in both groups.[68] Other alternatives for providing comprehensive CV risk reduction include electronic media programs.[69] Mobile health technologies such as the Circle of Health app provide education, motivation, and instruction for all individuals interested in maintaining CV health.[70] Mobile technologies may be used in connection with at-home or facility-based programs with the potential to improve outcomes.

CONCLUSION

CR programs provide comprehensive risk factor assessment and treatment and reduce morbidity and mortality in patients with chronic CV disease. Despite powerful evidence of clinical benefit, quality of life improvement, and cost-effectiveness, reimbursement for most services remains low. Although mortality from CV diseases is on the decline, there has been a dramatic increase in clinical conditions, such as obesity, diabetes mellitus, and the metabolic syndrome, that will lead to increases in CV morbidity. In addition, as the world's population ages, CR will need to be provided to a growing number of elderly patients, many of whom will have a variety of comorbidities.

Although traditional CR focuses on secondary prevention, the future scope of CR should encompass aspects of primary prevention and promotion of wellness by providing intensive lifestyle management for physical, medical, and psychological support and education. Preventing these chronic conditions from developing into acute and chronic CV disease is vital. The nature of current CR is changing. Lower risk patients may be able to benefit from CR in community settings, and increasing numbers of higher risk patients with increasing complex medical conditions will require supervised, monitored CR. Both low- and high-risk patients, as well as at-risk patients, may benefit from mobile health technologies and novel hybrid delivery systems of care. As medical interventions and medications continue to lead to successful physical outcomes for cardiac patients, it will be necessary to continue to evaluate the efficacy of CR in terms of behavior change and health-related quality of life.

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APPENDIX 45–1. Structure of Nutrition Education Sessions[2]

Phase I: Coronary care unit/wards

1. Each patient is seen individually as an inpatient or outpatient by the clinical nutritionist/dietitian. Diet history is taken, and an individual dietary prescription is completed for the patient.
2. Full risk factor profile is recorded.
3. Anthropometric measurements including weight/height are taken.

Phase II: Immediate postdischarge follow-up (4-6 weeks) to further assess risk factors and adherence to lifestyle change recommendations

4. Patients are seen in outpatient department for anthropometry and motivational talk (cognitive-behavioral therapy approach).
5. Food diaries are given to patients to complete at home for 5 days.

Phase III: Structured cardiac rehabilitation program

6. Patients attend two 1-hour nutrition talks.
7. Food diaries are collected and analyzed. Food diaries are returned, and urgent areas for improvement are highlighted.

Phase IV: Post–cardiac rehabilitation program to facilitate long-term maintenance of lifestyle changes

8. Patients attend outpatient department for review, including anthropometry.

APPENDIX 45–2. A Sample of Assessment Protocols Used in the Psychological Evaluation of Patients Undergoing Cardiac Rehabilitation[2]

Psychological adjustment/mood disturbance

The 18-item version of the Brief Symptom Inventory (BSI-18)[71]The BSI-18[71] and the short form of the Profile of Mood States (POMS-SF) are particularly good measures of psychological adjustment. The BSI-18 has good criterion validity and is a highly reliable way of screening patients with clinically significant psychological adjustment problems. The POMS-SF is useful for detecting changes in mood states over time because of its high sensitivity to such changes.

Health-related quality of life

The self-report version of the Psychosocial Adjustment to Illness Scale (PAIS-SR)[71]

The Seattle Angina Questionnaire (SAQ)[72]

The SAQ[72] appears to be reliable and valid from the testing to date. It also appears to be able to detect changes over time. The SAQ is a specific measure of functional status for patients with coronary artery disease. It covers clinically important dimensions including physical limitation, anginal stability, patient satisfaction with treatment, and perception of heart disease.

Physical disability associated with having a chronic illness coupled with psychological mood disturbance problems reduces the overall health-related quality of life of patients with chronic disease.[49] The self-report version of the PAIS-SR[71] is a well-established measure of health-related quality of life in patients with chronic illness. It has good construct validity and covers the full range of areas relevant to overall quality of life, specifically health care orientation, vocational environment, domestic environment, sexual relationships, extended family relationships, social environment, and psychological distress.

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APPENDIX 45–3. Interventions to Promote Psychological Health[2]

This appendix outlines the principles of cognitive-behavioral therapy, individual psychotherapeutic interventions, relaxation and stress management, mindfulness meditation, and social support in the context of cardiac rehabilitation.

Cognitive-behavioral therapy

It has been shown that patients with mild levels of anxiety and depression can benefit from psychosocial interventions provided alongside exercise in cardiac rehabilitation. Cognitive-behavioral therapy is practiced and taught within many cardiac rehabilitation programs to enable patients to regain control over adverse emotional events arising from or exacerbated by the cardiac event. Solution-focused brief therapy is an intervention suited to patients who need to reanimate their latent strengths and talents that may have been challenged by acquiring the label of cardiac patient. Cognitive-behavioral therapy offers a range of clinical techniques for enhancing active coping strategies, some of which have been incorporated into patient-focused psychoeducational programs for newly diagnosed cancer patients. Effective programs include some or all of the following components: health education, stress management training, coping skills and problem-solving skills training, assertiveness and anger management skills training, and group support.[2] Long-term maintenance for relapse of depression and reduction in mortality rates remains a problem for clinicians treating patients with both depression and coronary heart disease.

Individual psychotherapeutic interventions

Clinical psychologists, counseling psychologists, and psychotherapists attached to cardiac rehabilitation teams often assess patients for individual interventions. Therapy is tailored to meet individual patient responsiveness needs and requires specialist therapist input. Length of sessions is usually about 1 h/wk, and treatment can be brief and symptom focused (8-12 sessions). For patients with depression, treatment may require longer intervention (12-40 sessions) to prevent symptom relapse. Research has shown that duration of psychological therapy does impact on outcomes. A consistent finding across studies indicates that therapy involving <8 sessions is unlikely to be effective and that 75% of clients show improvement by 26 sessions of therapy. Maintenance of change may require up to 40 sessions.[2]

Mindfulness meditation

Ma and Teasdale[73] and, later, Williams and colleagues suggested that the skills learned from cognitive therapy training for individuals with depression may not necessarily be practiced and maintained by patients when they are in a recovery phase of depression. These patients depend on the presence of depression or negative automatic thought. Mindfulness (attentional) training, in contrast, can be practiced on a variety of thoughts including those related to depression. It is also an intrinsically positive experience, which is more likely to reinforce continued practice. Finally, it appears to be associated with a reduction in ruminative thinking, which is associated with more hopeless cognition.[74] Mindfulness training is about teaching individuals to be in full awareness of their thoughts and feelings from moment to moment. This training turns patients toward thoughts and feelings, both positive and negative, rather than away, which may impact on ability to recognize and identify early signs of depressive feelings, thus facilitating the seeking of preventative actions.

Social support

Cardiac patients who live alone or lack a source of emotional support face a significantly higher risk of recurrent myocardial infarction, sudden death, and all-cause mortality than those with adequate sources of support.

Social support can take many forms, from a close friend to older child; however, it is usually the female spouse who is associated with social support. Wives have a pivotal influence on lifestyle change and in promotion of heart healthy behaviors. A frequent reason given for nonattendance at cardiac rehabilitation programs has been reported as a lack of support from the spouse. A spouse's ability to deal with the cardiac illness impacts on the patient's adaptation to illness.

The need for information seems to be the main requirement of spouses both during the acute event and throughout the recovery period in cardiac rehabilitation, especially because fear of reoccurrence and death are prevalent. For many spouses, worries about the future are important. O'Farrell et al[75] found that of 213 female spouses of patients undergoing cardiac rehabilitation, 66% were significantly distressed, and concerns about treatment, recovery, and prognosis were the most prevalent stressors. Therefore, it is vital to invite and include the cardiac patient's significant family members or friends to participate in the rehabilitation process, from inpatient to long-term maintenance. Frequently, the time schedules of cardiac rehabilitation programs (ie, during working hours) prohibit family participation; evening sessions, family-only groups, and other options must be considered to ensure their inclusion.

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Valvular Heart Disease

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CHAPTER 46

ACUTE RHEUMATIC FEVER

Liesl Zühlke, Jagat Narula, and Jonathan R. Carapetis

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INTRODUCTION

Acute rheumatic fever (ARF) is a multisystem autoimmune response to untreated or partially treated group A *Streptococcus* (GAS) pharyngitis. A single severe episode of ARF or recurrent episodes of ARF can result in permanent heart valve damage known as rheumatic heart disease (RHD). Despite a marked decline in ARF and RHD in the developed world, ARF and RHD persist as major public health problems in developing regions of the world, indicative of inadequate access to health care, poorly functioning health systems, and social inequality.

EPIDEMIOLOGY OF ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

The incidence of ARF began to decline in developed countries toward the end of the 19th century, and by the second half of the 20th century, ARF had become rare in most affluent populations. This decline is attributed to more hygienic and less crowded living conditions, better nutrition, improved access to medical care, and, to a lesser extent, the advent of antibiotics in the 1950s. The decline in prevalence of RHD in wealthy countries has followed a similar pattern, albeit with a delay compared to ARF incidence, which is explained by the chronic nature of RHD. However, these diseases continue largely unabated in resource-poor countries and in some populations living in relative poverty in industrialized countries.[1]

It was previously estimated that approximately 470,000 individuals acquire ARF each year, of whom 97% are in developing countries, where the incidence of ARF exceeds 50 per 100,000 children per year.[2] The most recent estimates from the Global Burden of Disease study puts the RHD burden at 33 million prevalent cases, causing 275,000 deaths and more than 9 million disability-adjusted life-years lost each year.[3,4] The major burden of ARF and RHD is in sub-Saharan Africa, South Asia, and the Pacific region (Fig. 46–1).

The peak incidence of ARF occurs in those age 5 to 15 years, with a decline thereafter such that cases are rare in adults older than age 35 years.[1] First attacks are rare in the very young; only 5% of first episodes arise in children younger than age 5 years, and the disease is almost unheard of in those younger than age 2 years. Recurrent attacks are most frequent in adolescence and young adulthood and are diagnosed infrequently after age 45 years. By contrast, RHD, which usually represents the accumulated damage from multiple ARF episodes in childhood, is most highly prevalent in the young adult years.[5]

ARF is equally common in males and females, but RHD is more common in females in almost all populations.[5,6] Whether this trend is a result of innate susceptibility, increased exposure to GAS because of greater involvement of women in child rearing, or reduced access to preventive medical care for females is unclear.[1] No association with ethnic origin has been found. There is some evidence that between 3% and 6% of any population is susceptible to ARF.[7]

PATHOGENESIS

Epidemiologic and immunologic evidence clearly implicates GAS in the initiation of ARF in a susceptible host.[6,7] Most patients with ARF have elevated titers of antistreptococcal antibodies. Outbreaks of ARF usually follow epidemics of streptococcal pharyngitis. Adequate treatment of streptococcal pharyngitis reduces the incidence of subsequent ARF, and appropriate antimicrobial prophylaxis prevents recurrences after initial attacks. It has generally been considered that certain strains of GAS are more prone to result in ARF, and this "rheumatogenicity" was thought to be a feature of strains belonging to certain M serotypes. More recent studies suggest that rheumatogenicity may not be serotype specific. The long-held opinion that only streptococcal pharyngitis, and not streptococcal skin infections such as impetigo, may be followed by ARF has also been challenged.[8] Studies in populations where ARF is common find no definite association between GAS sequence type and site of infection or ability to cause disease.[9,10] Thus, the distinction between rheumatogenic and nonrheumatogenic strains, and between those trophic for the skin or throat, is considered by some to become blurred in areas where ARF is common and multiple different GAS strains circulate within small populations.[1]

The streptococcal M protein shares an α-helical coiled structure with cardiomyocyte contractile proteins such as myosin, and since antibodies isolated from ARF patients cross-react both with M protein and heart tissue, molecular mimicry and autoimmunity was proposed to be the primary pathogenetic basis of ARF and carditis.[8] The pathogenesis of RHD is now strongly considered to be an intricate interplay between multiple streptococcal antigens, various cross-reactive antibodies, and multiprong immune targets.

The antibodies that contribute to rheumatic valvulitis target the *N*-acetyl-β-D-glucosamine–dominant epitope of the GAS carbohydrate,[9] but also recognize sequences in α-helical proteins (eg, myosin and tropomyosin).[10] These antibodies are elevated in patients with valvular involvement in ARF, significantly reduce after surgical removal of inflamed valves, and correlate with poor prognosis.[11] Cross-reactive M-protein antibodies might recognize the intracellular biomarker antigen cardiac myosin but target the valve surface endothelial antigen laminin, or similar extracellular or basement membrane proteins.[12] The

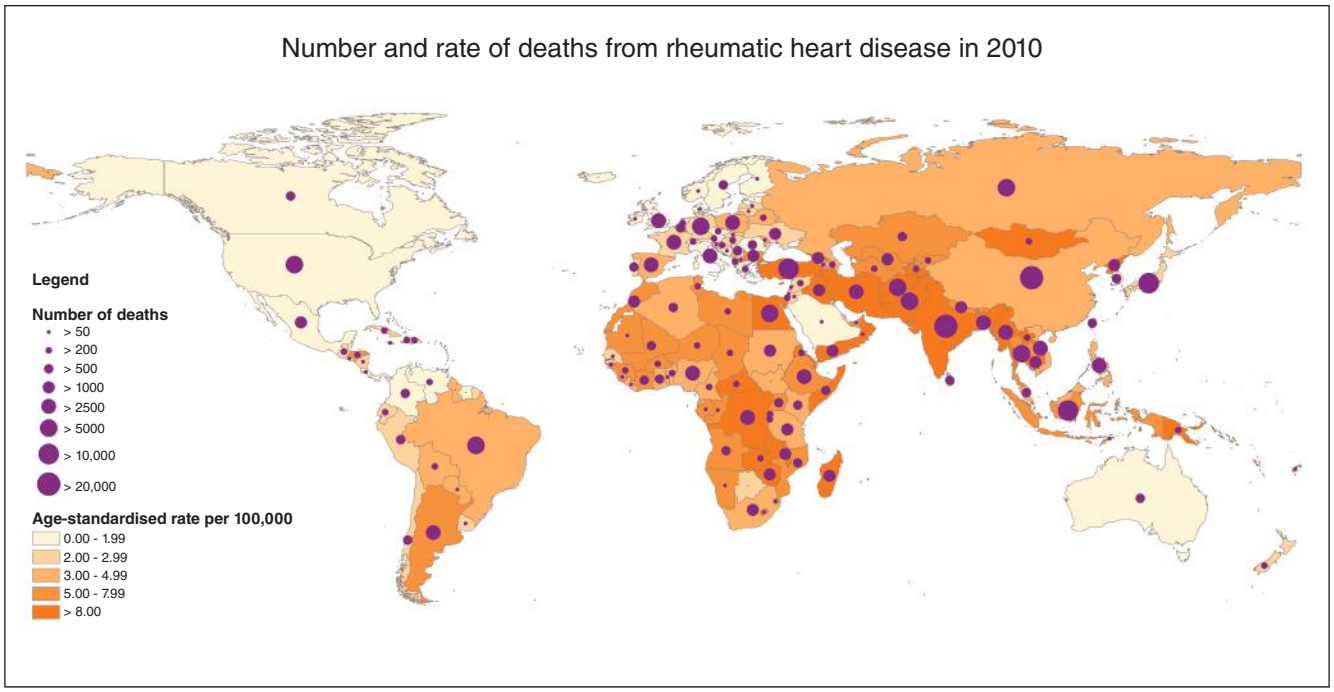

FIGURE 46–1. Number and rates of deaths from rheumatic heart disease in 2010.

initial antibody-mediated damage to the endocardium leads to expression of vascular cell adhesion protein 1 on the valvular surface, which in turn facilitates the infiltration of T cells into the valve substance, resulting in scarring and neovascularization.[13] The concept of the target that resides on the cell surface and initiates the disease process in response to or in association with an intracellular biomarker antigen is also demonstrated in the manifestation of ARF Sydenham chorea, wherein the biomarker antigen in the brain is tubulin and the antigen target on the cell surface leads to calcium/calmodulin-dependent kinase II activation and dopamine release.[11]

Host factors have been considered to be important ever since familial clustering was reported last century. Associations between disease and human leukocyte antigen (HLA) class II alleles have been identified, but the alleles associated with susceptibility or protection differ depending on the population investigated.[14] High concentrations of circulating mannose-binding lectin and polymorphisms of transforming growth factor-β_1 and immunoglobulin genes also are associated with ARF.[15-17]

Certain B-cell alloantigens are expressed to a greater level in patients with ARF or RHD than controls, with family members having intermediate expression, suggesting that these antigens are markers of inherited susceptibility. The best characterized is D8/17, which is associated with ARF and RHD in several populations worldwide.[18] Further investigation is needed before B-cell alloantigen markers can be used to identify individuals with, or at risk for, ARF or RHD. There is, as yet, no specific investigation that reliably identifies individuals who are at risk of ARF or who will develop chronic rheumatic valvular heart disease.

The histopathologic manifestations of ARF are characterized by connective tissue alterations and are essentially similar in various organs. Collagen is a recognized target for autoantibodies in various autoimmune diseases, and on the basis of histopathologic characteristics, systemic involvement, and complete healing in most tissues, it has been proposed that collagen could be the primary site for inflammation in ARF.[19] It has been demonstrated that streptococcal M proteins form a complex with human collagen type IV in subendothelial basement membranes and might initiate an autoantibody response to the collagen.[20-22] This appears somewhat similar to pathogenesis of Goodpasture syndrome and Alport syndrome wherein the autoantibodies are directed at the basement membrane collagen type IV. The autoantigen is the mutated collagen IV (COL4 A3/A4/A5/A6) in Alport syndrome and the altered quaternary structure of the NC1 subunits of the α3 and α5 chains of collagen type IV of the lung and kidney in Goodpasture syndrome.[22,23] In ARF, M protein binds to the collagen IV through an octapeptide motif (Fig. 46–2); mice immunized with the collagen-binding octapeptide produced anticollagen antibodies[20,21,24] that did not cross-react with inducing M proteins, excluding the likelihood of molecular mimicry. Sera from ARF patients demonstrates collagen antibodies as well as increased titers for M proteins.[25] In the Northern Australian Territory with endemic rheumatic fever, where prevalence of GAS is infrequent and pharyngeal isolation of group G infections is common, the M-like fibrinogen-binding protein of group G streptococci (FOG) interacts with the collagen family, similar to M protein.[25,26]

The long-term clinical consequence of ARF is related to permanent cardiac damage. Although rheumatic carditis involves the pericardium, myocardium, and endocardium, fibrinous pericarditis and interstitial myocardial involvement resolve without residual damage, whereas verrucous valvulitis is associated with permanent damage. Notably, the pathologic changes also indicate that, unlike in the more common lymphocytic form of myocarditis, heart muscle cells are spared in rheumatic carditis (Fig. 46–3).[19]

Despite the widespread endothelial activation and the diffuse collagen alterations in ARF, the endothelium has an immense capacity to heal, and the subendothelial damage is limited to a shallow depth, resulting in healing in the other manifestations of ARF. The endothelial cells demonstrate substantial structural and functional variability and may be responsible for the differential response in the valves.

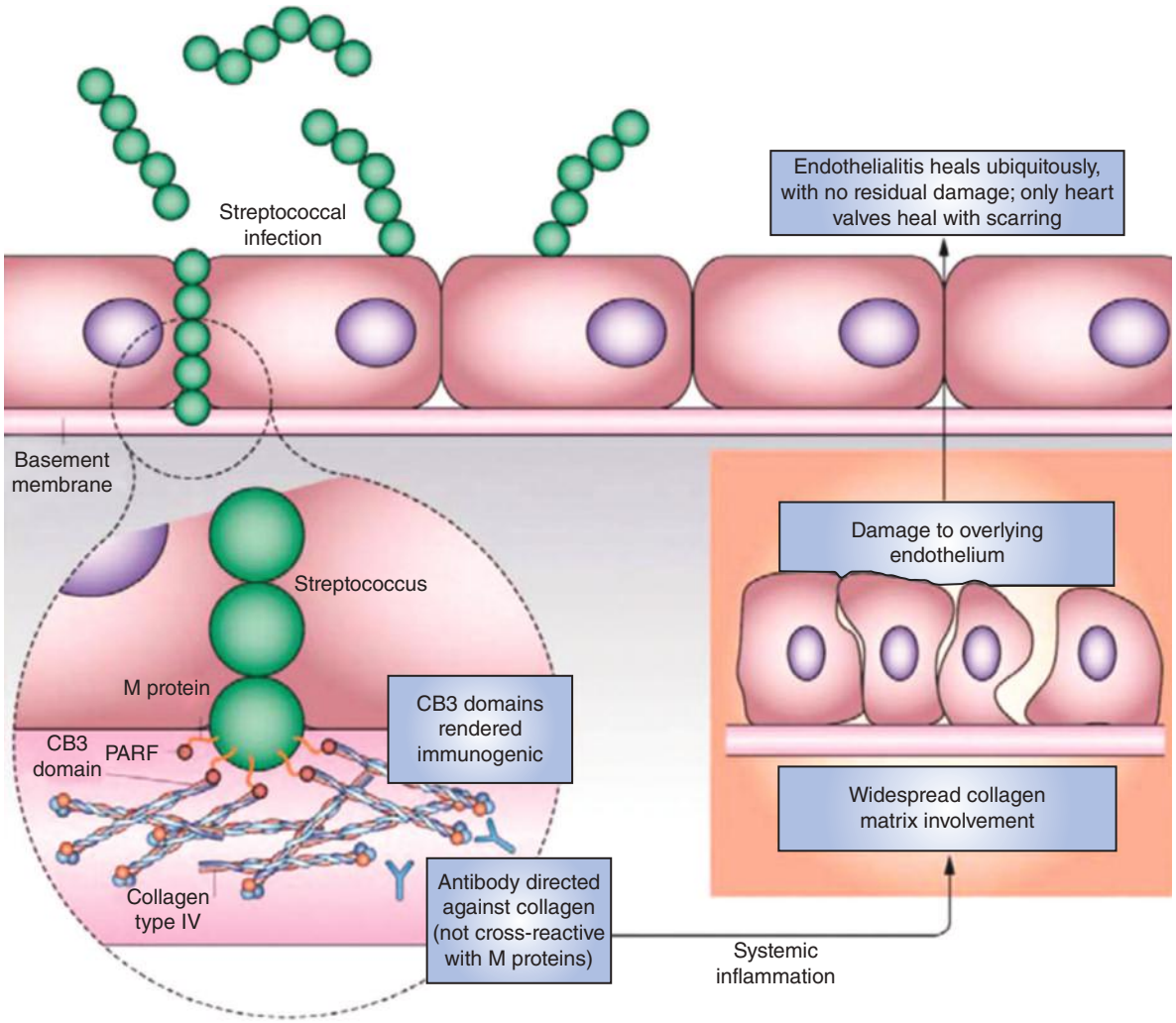

FIGURE 46–2. Proposed pathogenesis of rheumatic fever. Reproduced with permission from Tandon R, Sharma M, Chandrashekhar Y, et al: Revisiting the pathogenesis of rheumatic fever and carditis. *Nat Rev Cardiol.* 2013 Mar;10(3):171-177.[19]

Endothelial-cell heterogeneity is best exemplified in the valvular endothelial cells; endothelial cells on the aortic side of the aortic valve have different expression profiles on microarrays from those on the ventricular side. With valvulitis, neoangiogenesis develops within the substance of the valve tissue, which introduces more vascular endothelium and more collagen inflammation, leading to a vicious cycle of valvular damage, healing, and progressive scarring.[27]

CLINICAL PRESENTATION

The protean manifestations of this condition were well described in the early part of the last century with a set of diagnostic criteria proposed by Duckett Jones in 1944[28] and subsequently modified and updated in 1992 and 2002.[29-33] These revisions increased specificity but decreased sensitivity, particularly in endemic populations with potential missed diagnoses and failure to provide secondary prophylaxis to deserving patients.[34] Local guidelines have been adapted to the Jones criteria to reflect the pattern of disease in high-prevalence regions, local evidence, and current best practice, particularly relating to contemporary echocardiographic techniques.[35,36] The Jones criteria recently underwent an extensive revision.[37] This revision has aligned itself with international guidelines by defining high-risk populations, recognizing the variability in disease burden and presentation, categorizing recommendations according to the favored Classification of Recommendations and Level of Evidence categories, and reflecting the era of Doppler echocardiography[38] (Table 46–1).

The disease usually has an acute febrile onset and presents with variable combinations of major and minor manifestations. The diagnosis of ARF is made when the patient develops two major manifestations, or one major manifestation and at least two minor manifestations; in addition, evidence of preceding infection with GAS must be demonstrated using streptococcal serology. The exceptions are patients who present with chorea or indolent carditis because these manifestations may only become apparent months after the inciting streptococcal infection so that additional manifestations may not be present and streptococcal serology testing may be normal.[39]

CARDITIS

Carditis is the single most important component of the disease in determining prognosis. The carditis of ARF occurs in > 50% of patients and is characterised predominantly by valvulitis of the mitral valve (mitral regurgitation) and, less frequently, the aortic valve (aortic

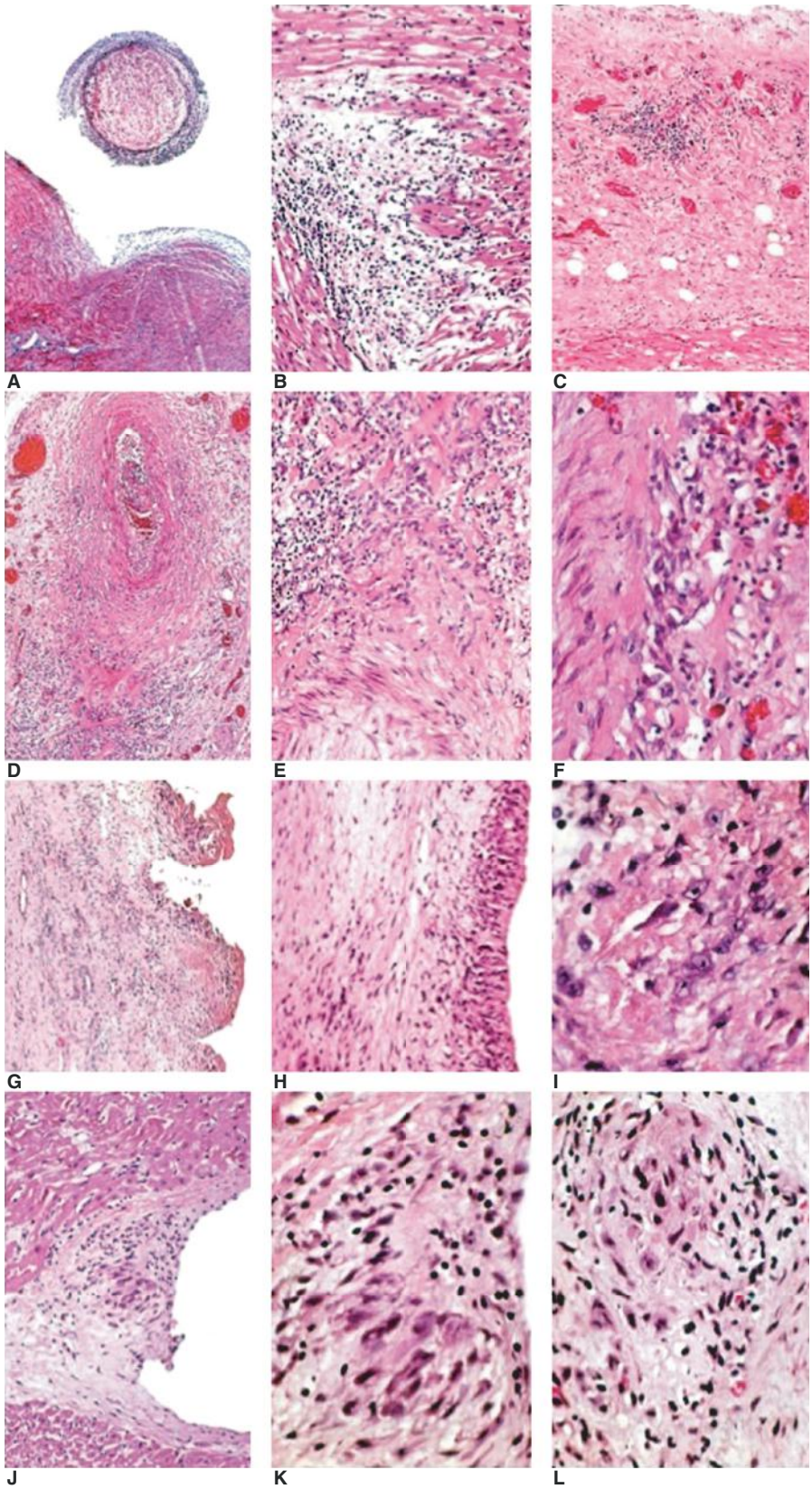

FIGURE 46–3. Hematoxylin and eosin staining of the heart and vasculature suggests connective tissue involvement in rheumatic fever. Modified with permission from Narula J, Virmani, R, Reddy KS, et al: *Amer. Reg. Path*. AFIP, Washington DC, 1999.

TABLE 46–1. The Revised Jones Critieria[29] for the Diagnosis of Acute Rheumatic Fever

Primary episode of rheumatic fever	Two major or one major and two minor manifestations **plus** evidence of a preceding group A streptococcal infection[a]	
Recurrent attack of rheumatic fever	Two major or one major and two minor manifestations or 3 minor **plus** evidence of a preceding group A streptococcal infection[a]	
Risk stratification	**Low-risk population**	**Moderate-/high-risk population**
	ARF incidence < 2 per 100,000 school-aged children (usually 5-15 years) per year or an all-age prevalence of RHD of ≤ 1 per 1000 population per year	Not clearly from a low-risk population depending on their reference population
Major criteria		
Carditis	Clinical and/or subclinical	Clinical and/or subclinical
Arthritis	Polyarthritis only	Monoarthritis or polyarthritis
		Polyarthralgia
	Chorea	Chorea
	Erythema marginatum	Erythema marginatum
	Subcutaneous nodules	Subcutaneous nodules
Minor criteria		
Arthralgia	Polyarthralgia	Monoarthralgia
Fever	≥ 38.5°C	≥ 38°C
ESR	ESR ≥ 60 mm in the first hour	ESR ≥ 30 mm/h
	CRP ≥ 3.0 mg/dL	CRP ≥ 3.0 mg/dL
	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

[a]Supporting evidence of a preceding streptococcal infection within the last 45 days: elevated or rising antistreptolysin-O or other streptococcal antibody, or a positive throat culture, rapid antigen test for group A streptococci, or recent scarlet fever.

Abbreviations: ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RHD, rheumatic heart disease.

regurgitation).[40-42] Pathologically, ARF produces a pancarditis, with involvement of the pericardium, myocardium, and endocardium. Clinical manifestations may vary widely and range from subclinical to life-threatening heart failure. Pericarditis may manifest with typical pericardial pain and a friction rub. Auscultation may reveal new murmurs or changing murmurs. Stenotic lesions are uncommon in the early stages of the disease, but a transient apical mid-diastolic murmur (Carey-Coombs) may occur in association with the murmur of mitral regurgitation. This murmur occurs in patients with mitral valvulitis due to ARF. It is a short, mid-diastolic rumble best heard at the apex, which disappears as the valvulitis improves. It can be distinguished from the diastolic murmur of mitral stenosis by the absence of an opening snap before the murmur. The murmur is caused by increased blood flow across a thickened mitral valve.[43]

Atrioventricular conduction delay, resulting in a prolonged PR interval, is an important and helpful diagnostic clue. Recent data strongly substantiates the importance of subclinical carditis based on Doppler echocardiography.[42,44-47] Hence, echocardiographic evaluation for all patients with suspicion of ARF is recommended in the 2015 Jones criteria, and both clinical and subclinical carditis fulfil a major criterion, even in the absence of classical auscultatory findings.[48] Subclinical carditis of the mitral or aortic valves requires all four criteria to be met in order to fulfil the major criterion. Additional morphologic features may also be present.

ARTHRITIS AND ARTHRALGIA

The conventional description is of a polyarthritis affecting large joints, with the lower limb joints involved first, and involvement of each joint overlapping giving the impression that the process "flits." The arthritis of ARF responds promptly to anti-inflammatories, and thus, the classical presentation may be uncommon where medication with nonsteroidal anti-inflammatory drugs before the diagnosis is considered or confirmed.

The differential diagnosis of polyarticular arthritis in children and adolescents is wide (Table 46–2).[49] Monoarticular arthritis is increasingly recognized to be important in populations where ARF is common. The arthritis of ARF presents a difficult diagnostic challenge, especially in the patient presenting with an initial monoarthritis.[50] The arthritis of ARF is highly responsive to anti-inflammatory drugs (both aspirin and nonsteroidal anti-inflammatory drugs), and if the patient does not respond within 48 to 72 hours, alternate diagnoses should be considered. Poststreptococcal reactive arthritis is diagnosed in patients who have an arthritis that is not typical of ARF but who recently had streptococcal infection. This condition is said to occur after a shorter latent period than ARF, responds less well to anti-inflammatories, and may be associated with renal manifestations, and evidence of carditis is usually not seen. The distinction between post-streptococcal reactive arthritis and ARF is unclear, and many would recommend that a diagnosis of post-streptococcal reactive arthritis not be made in populations in which ARF is common.[49] Even if the diagnosis is considered, it is appropriate to offer a period of secondary penicillin prophylaxis, as for episodes of ARF in such populations.

TABLE 46–2. Differential Diagnosis[a] of Carditis and Polyarthritis in Children and Adolescents

Carditis	Polyarthritis
Physiologic mitral regurgitation	Connective tissue and other autoimmune diseases such as juvenile idiopathic arthritis
Mitral valve prolapse	Reactive arthropathy
Myomatous mitral valve	Septic arthritis
Fibroelastoma	Poststreptococcal reactive arthritis
Congenital mitral valve disease	Infective endocarditis
Congenital aortic valve disease	Lyme disease
Infective endocarditis	Lymphoma/leukemia
Cardiomyopathy	Viral arthropathy
Myocarditis, viral or idiopathic	Sickle cell disease
Kawasaki disease	Gout and pseudogout
	Henoch-Schönlein purpura

[a]Excludes presentations with chorea.

Data from Gewitz MH, Baltimore RS, Tani LY, et al: Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015 May 19;131(20):1806-1818.

CHOREA

Sydenham chorea may be associated with other manifestations of ARF but may also be the sole expression of the disease. It is a neurologic disorder characterized by involuntary, purposeless, rapid, and abrupt movements associated with muscular weakness and emotional lability. Chorea occurs in up to 30% of cases of ARF. The abnormal movements disappear during sleep.

Mild chorea may best be demonstrated by asking the patient to squeeze the examiner's hand. This results in repetitive irregular squeezes labeled as *the milking sign.* Emotional lability manifests in personality changes, with inappropriate behavior, restlessness, and outbursts of anger or crying.[51]

ERYTHEMA MARGINATUM

Erythema marginatum is a nonitchy, evanescent rash that is pink or slightly red and that affects the trunk predominantly. The rash extends centrifugally, and the skin in the center returns toward normal. The rash may be fleeting and disappear within hours. It may be brought out by a warm bath or shower. It is reported to be found in only 4% to 15% of cases and may be difficult to detect in dark-skinned patients.

SUBCUTANEOUS NODULES

These nodules generally appear later in the course of the disease after several weeks of illness and are seen most commonly in patients with carditis. They are firm and painless; the overlying skin is not inflamed and may vary in size from a few millimeters to several centimeters. They are most commonly located over bony surfaces or tendons such as elbows, wrists, knees, occiput, and spinous processes of the vertebrae. These occur in less than 10% of cases of ARF.

DIAGNOSIS AND INVESTIGATIONS

There is no definitive laboratory test for ARF, with the diagnosis based on a combination of clinical manifestations and laboratory evidence of previous streptococcal infection. Evidence of preceding streptococcal infection may be demonstrated by increased or rising antistreptolysin O titer, other streptococcal antibodies, a positive throat swab culture, or rapid antigen test for group A β-hemolytic streptococci. The revised Jones critieria[37] present two distinct decision paths depending on the risk category (high and moderate risk vs low risk) of the population (see Table 46–1). The changes to the major and minor criteria represent a significant attempt at weighing sensitivity versus specificity in its diagnostic acumen in both low- and moderate-/high-risk populations.

The three key changes are the risk stratification, adaptation of both major (carditis and arthritis/arthralgia) and minor (arthralgia, fever, and erythrocyte sedimentation rate [ESR] cutoffs) criteria, and the definition of recurrent ARF episodes.

RISK STRATIFICATION

Recent data have emphasized the disproportionate burden, pattern, and presentation of ARF and RHD.[52-54] The 2015 iteration of the Jones criteria defines low risk as coming from a population with an ARF incidence of < 2 per 100,000 per year for school-aged children or an all-age RHD prevalence of < 1 per 1000 population per year, with those not clearly coming from a low-risk population considered to be a moderate to high risk with the modified major and minor criteria applying (Class IIa, Level of Evidence C). This has important practical implications for clinicians working in countries with mixed risk populations.[55,56]

CHANGES IN MAJOR AND MINOR CRITERIA

Carditis

Subclinical carditis or clinically silent but echocardiographically evident valvulitis has long been recognized as a manifestation of ARF with a weighted pooled prevalence of 16.8%.[57-60] As a result, the comprehensive evaluation of all cases of confirmed and suspected ARF includes echocardiography with Doppler, regardless of the findings on auscultation (Class I, Level of Evidence B).

Arthritis

In moderate-/high-risk populations, monoarthritis in addition to the more classic polyarthritis has been demonstrated to be an important clinical manifestation of ARF.[61,62] Previously reflected in the Australian and New Zealand guidelines,[63,64] the consideration of monoarthritis as part of the ARF spectrum is now included, although limited to moderate- to high-risk populations (Class I, Level of Evidence C). Monoarthralgia is now also included as a minor criterion in moderate-/high-risk populations, although this will only apply when arthritis (monoarthritis/polyarthritis and/or polyarthralgia) has not been used as a major criterion.

Fever and Erythrocyte Sedimentation Rate

Finally, revised cutoffs have been introduced for three of the minor criteria in order to improve sensitivity in the higher risk populations. The cutoff for fever has been lowered to 38.0°C (compared to 38.5°C in low-risk patients), and the ESR has been lowered to > 30 mm/h (compared to 60 mm/h in moderate-/high-risk patients).

DEFINITION OF RHEUMATIC FEVER RECURRENCES

Prior to the 2015 iteration, there were no specific diagnostic criteria for ARF recurrences. The new criteria now state that with a reliable past history of ARF or RHD and in the face of documented GAS infection, two major, or one major and two minor, or three minor manifestations may be sufficient for a presumptive diagnosis of an ARF recurrence (Class IIb, Level of Evidence C).

The current guidelines seek to increase sensitivity in populations that have a high incidence of ARF and maintain high specificity in low-risk populations. They rely on considerable diagnostic and echocardiographic acumen complemented by laboratory testing to confirm and monitor disease activity. Table 46–2 presents the differential diagnoses for polyarthritis and carditis in children and adolescents. The Doppler findings in rheumatic valvulitis are presented in Table 46–3. Laboratory investigations, other than those to confirm GAS exposure and ESR and C-reactive protein, are otherwise nonspecific. Modest normochromic normocytic anemia of chronic inflammation is frequent.

The electrocardiogram may be unhelpful apart from reflecting sinus tachycardia. Prolongation of the PR interval serves as a useful minor criterion and may be particularly helpful in recurrences where previous electrocardiograms are available.

TREATMENT

MANAGEMENT OF THE ACUTE EPISODE

The aims of treatment of ARF are to suppress the inflammatory response so as to minimize cardiac damage, to provide symptomatic relief, and to eradicate pharyngeal streptococcal infection.[51] Patients are usually hospitalized, and the long-standing recommendation of bedrest or chair rest is appropriate if heart failure is present. Ambulation is usually started once fever has subsided and joint pain and heart failure are controlled.

TABLE 46–3. Findings on Echocardiogram in Rheumatic Valvulitis

Doppler Findings in Rheumatic Valvulitis of Either the Mitral or the Aortic Valve
(All four Doppler echocardiographic criteria must be met in each category)

Pathologic Mitral Regurgitation	Pathologic Aortic Regurgitation
Seen in two views	Seen in two views
In at least one view, jet length ≥ 1 cm	In at least one view, jet length ≥ 2 cm
Velocity ≥ 3 m/s for one complete envelope	Velocity ≥ 3 m/s in early diastole
Pansystolic jet in at least one envelope	Pandiastolic jet in at least one envelope

Morphologic Findings on Echocardiogram in Rheumatic Valvulitis Morphological Features of RHD

Acute Mitral Valve Changes	Chronic Mitral Valve Changes (Not Seen in Acute Carditis)	Aortic Valve Changes (Acute or Chronic)
Annular dilatation	Leaflet thickening	Irregular or focal thickening
Chordal elongation	Chordal thickening and fusion	Coaptation defect
Chordal rupture resulting in flail leaflet	Restricted leaflet motion	Restricted leaflet motion
Anterior (or less commonly posterior) leaflet tip prolapse	Calcification	Leaflet prolapse
Beading/nodularity of leaflet tips		

Adapted with permission from Gewitz MH, Baltimore RS, Tani LY, et al: Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015 May 19;131(20):1806-1818.

Although evidence of active infection is unusual during the acute phase, it is recommended that patients receive a single dose of benzathine penicillin or a 10-day course of penicillin V (or erythromycin if penicillin allergic) to curtail exposure to streptococcal antigens. After completion of the course, secondary prophylaxis should be commenced. This recommendation is based on observational and longitudinal data.[5]

Anti-inflammatory agents, including salicylates and corticosteroids in appropriate dose, provide dramatic improvement in symptoms such as arthritis and fever soon after starting treatment. Doses of aspirin of 80 to 100 mg/kg/d in children and 4 to 8 g/d in adults may be needed initially. The usual dose of prednisone or prednisolone is 1 to 2 mg/kg/d. There is no good evidence that steroids are superior to aspirin in terms of altering the natural history of the disease. Some believe that they do result in more rapid resolution of carditis and can be lifesaving, but this is unproven.[49,65]

Patients with severe heart failure require usual antifailure treatment. When carditis complicated by marked valvular regurgitation causes severe hemodynamic compromise, valve surgery is life-saving and should not be delayed by trials of anti-inflammatory medication. Valve repair rather than replacement is the preferred option for RHD surgery, considering the concerns regarding adherence to anticoagulation.[66] However, repair should be performed by a surgeon experienced in rheumatic valvular surgery.[67,68]

PREVENTION

Primary prevention refers to antibiotic treatment of GAS pharyngitis to prevent subsequent attacks of ARF. A single intramuscular injection of 600,000 or 1.2 million units of benzathine penicillin (depending on weight) or 10-day course of penicillin V is advised (Table 46–4). Efforts

TABLE 46–4. Prevention of Acute Rheumatic Fever

Agent	Dose	Route	Duration
Primary prevention (treatment of group A streptococcal pharyngitis)			
Benzathine penicillin G	≥ 27 kg: 1.2 million units < 27 kg: 600,000 units	Intramuscular (IM) injection	Once
Penicillin V	Children 250 mg × 2-3/d Adults 500 mg × 2-3/d	Oral	10 d
If penicillin allergy, options include narrow-spectrum cephalosporin, clindamycin, azithromycin, and clarithromycin. Consult local guidelines or see American Heart Association guideline.[9]			
Secondary prevention (prevention of recurrent attacks)[a]			
Benzathine penicillin G	≥ 20 kg: 1.2 million units (< 20 kg: 600,000 units) every 4 wk[b]	IM injection	
Penicillin V	250 mg × 2/d	Oral	
Erythromycin	250 mg × 2/d	Oral	

[a]Duration of secondary prophylaxis depends on history of carditis and if valvular involvement persists. In most cases, minimum duration is 10 years since last acute rheumatic fever (ARF) episode or until age 21 years, whichever is longer, with prolongation until age 35 to 40 years in individuals with significant valvular disease.

[b]Although injections every 4 weeks are effective, if good adherence can be assured, benzathine penicillin G may be given more frequently (every 3 or every 2 weeks) if there is a desire to further increase the efficacy in preventing recurrent ARF.

Data from Rutstein DD. Report of the committee on standards and criteria for programs of care of the council of rheumatic fever and congenital heart disease of the American Heart Association: Jones criteria (modified) for guidance in the diagnosis of rheumatic fever. *Circulation*. 1956;13:617-620; and Vijayalakshmi IB, Mithravinda J and Deva AN. The role of echocardiography in diagnosing carditis in the setting of acute rheumatic fever. *Cardiol Young*. 2005;15:583-8.

at primary prevention are confounded by the fact that many patients who develop ARF are not aware of preceding sore throat, there are no simple specific clinical signs diagnostic of streptococcal pharyngitis, and throat swabs and cultures are expensive. In an individual patient, antibiotic treatment for streptococcal sore throat is effective in reducing the occurrence of subsequent attacks of ARF by 70% to 80%.[69] While it is important in populations with a high incidence of ARF to promote presentation to primary health care with sore throat and proper diagnosis and management by the health system,[70] there is no definitive proof that this approach is effective in reducing overall ARF incidence in the population.[71,72]

Secondary prevention, the long-term administration of antibiotics to prevent recurrences, is of proven benefit and is cost-effective.[73] Benzathine penicillin 600,000 or 1.2 million units intramuscularly every 4 weeks is the standard recommendation.[50,74] An injection once every 2 or 3 weeks is more effective but may be more difficult to implement.[73] Oral penicillin V 250 mg orally twice daily is preferred by some practitioners, particularly in very thin patients who are on warfarin anticoagulation after valve replacement surgery when deep intramuscular injections may be undesirable.[75] However, no studies have compared oral penicillin V with intramuscular benzathine penicillin in the prevention of rheumatic fever.

Prophylaxis is usually advised until age 21 years or for at least 10 years after the last attack of ARF, whichever is longer, with longer durations for individuals who have persistent and significant valvular damage. Duration of secondary prophylaxis should be individualized, taking into account factors influencing risk of recurrence. Prophylaxis until age 35 to 40 years, or sometimes for life, is recommended for patients with severe valve disease or after valve replacement surgery.

PROGNOSIS

Cardiac involvement remains the most serious manifestation of ARF with severe life-threatening heart failure in the acute stages due to the acute valvulitis.[76,77] Inadequate coverage with antibiotic prophylaxis to prevent future attacks of ARF puts patients at risk for repeated episodes of ARF, scarring of the heart valves, chronic valvular heart disease, heart failure, and death, usually before middle age. The revised Jones criteria provide an important opportunity to improve the diagnostic accuracy of ARF, particular in moderate-/high-risk populations. These, together with increased awareness and global advocacy, will improve case detection, foster research, and accurately determine the global burden of ARF and RHD.

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CHAPTER 47

AORTIC VALVE DISEASE

Blase A. Carabello and Rebecca T. Hahn

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AORTIC STENOSIS

ETIOLOGY

In developed countries, the etiology of aortic stenosis (AS) is a process akin to atherosclerosis (Fig. 47–1), wherein the initial lesion is plaque-like with a central core of lipids and macrophages.[1] Over time the plaque becomes calcified and in 15 % of cases actually contains lamellar bone. The process holds in common many of the risk factors for atherosclerotic coronary disease including hyperlipidemia, hypertension, and the metabolic syndrome. Approximately 1% to 2% of the population is born with a bicuspid instead of a tricuspid aortic valve. About one-third of such valves become stenotic, with significant stenosis occurring about one to two decades sooner in bicuspid than in tricuspid valves. Why there is earlier progression in bicuspid valves is uncertain but may be in part genetic in origin and in part as a result of the flow characteristics of bicuspid valves. Because of the resemblance of the AS lesion to that of coronary atherosclerosis, it was postulated that statins, so effective in treating coronary disease, might retard the progression of AS. Unfortunately, three randomized trials failed to show any benefit of statin use in AS when applied to patients with a range of disease severity.[2-4] On one hand it could be argued that even earlier application of statins would be required to show benefit, or on the other hand, statin failure could be because of the tendency for statins to promote plaque calcification.[5] This tendency helps stabilize the coronary plaque, avoiding rupture and subsequent coronary events; conversely this tendency in the aortic plaque might cause decreased leaflet mobility, worsening rather than retarding progression.[6] Although statins failed to alter the progression of AS, it is clear that AS is an active disease in which inflammation is involved. As such, many potential therapeutic targets exist. One promising target is lipoprotein(a) (LP(a)), which seems more tightly associated with AS than is LDL and which can be dramatically reduced by PCSK9 inhibitors. These agents reduce both lipid moieties but are not known to be pro-calcific.[7]

In the developing world, rheumatic heart disease is still the most common cause of AS. Other causes include congenital AS and unicuspid and quadricuspid aortic valve.

PATHOPHYSIOLOGY AND ITS RELATIONSHIP TO SYMPTOMS

As shown in Fig. 47-2A, depicting the natural history of AS in 1968 and modified by changes in that history over time (Fig. 47-2B), the presence or absence of the classic symptoms of AS—angina, syncope and heart failure (primarily dyspnea)—demarcate a dramatic change in disease outcome.[8,9] In the absence of symptoms, mortality is low (about 1% /y), not much higher than that seen in a normal population. Once symptoms develop, the mortality rate increases precipitously to about 25% per year. Thus evaluation of patient symptoms takes a central role in disease management. In the initial assessment of outcome (Fig. 47–2A), the average age of patients was about 48 years and many had congenital or rheumatic AS. By the 21st century, etiology had changed to the atherosclerotic-type disease noted above and the age of affected patients increased by about 20 years. Concomitantly the advent of Doppler echocardiography allowed for accurate and longitudinal noninvasive assessment, making detection possible at earlier stages of the disease.[10] Thus the 75-year-old patient might disregard symptoms, ascribing dyspnea, for instance, to aging while his or her physician might underestimate the impact of milder although still severe disease.

As the aortic valve orifice narrows, the left ventricle (LV) must generate progressively more pressure to drive blood past the obstruction, creating a pressure gradient between the LV and the aorta (Fig. 47–3). Gradient = flow^2/AVA^2, where AVA = aortic valve area. Reduction in AVA from its normal 3.0 cm^2 aperture to half that size produces little increase in LV pressure, about 10 mm Hg. However, further reduction in AVA produces a geometric increase in pressure gradient such that a valve area of 1.0 cm^2 produces a 25-mm Hg gradient, an AVA of 0.75 cm^2 generates a of 50-mm Hg gradient, and a valve area of 0.5 cm^2 causes a 100-mm Hg systolic difference between LV and aortic pressure.

In response, the LV remodels by increasing wall thickness. Usually the process is associated with increased muscle mass (concentric hypertrophy), but in some cases wall thickness increases while LV volume decreases so that LV mass is static (concentric remodeling). These changes in LV geometry are both adaptive and pathologic. Left ventricular ejection varies inversely with afterload, the force opposing ejection. Afterload is often quantified as systolic wall stress (σ), where $\sigma = P \times r / 2\ th$, and P= LV pressure, r = LV radius, and th = LV thickness. As the pressure overload increases, the numerator of this Laplace equation can be offset by increased thickness in the denominator, maintaining normal wall stress and ejection fraction. Unfortunately left ventricular hypertrophy (LVH) has pathologic consequences and is responsible for many of the symptoms and symptom-related mortality of AS.

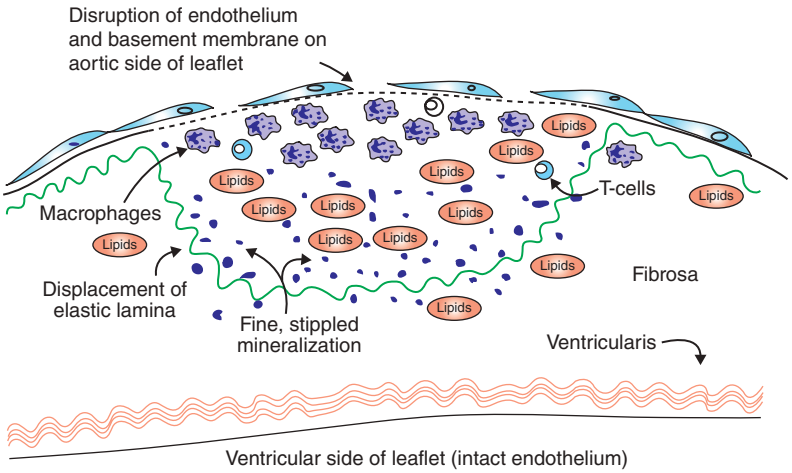
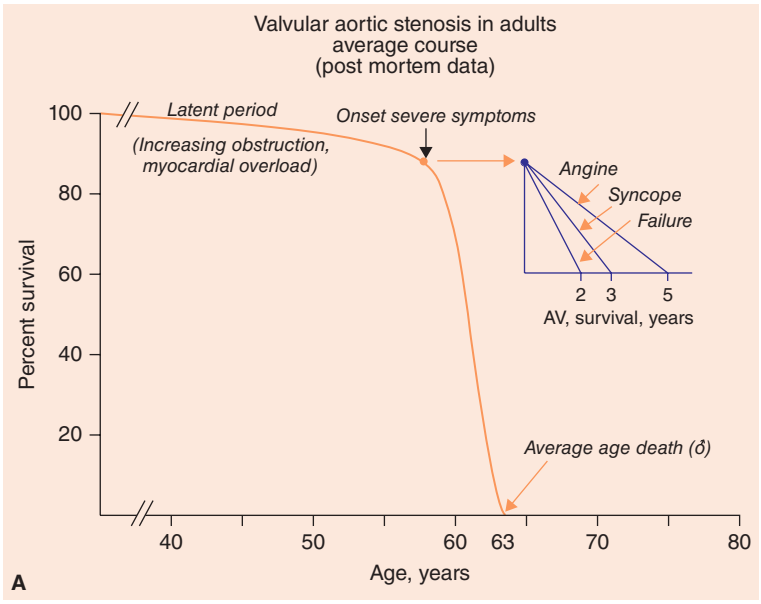


FIGURE 47–1. The early plaque of aortic stenosis demonstrating similarities to an atherosclerotic plaque. Reproduced with permission from Otto CM, Kuusisto J, Reichenbach DD, et al: Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation*. 1994 Aug;90(2):844-853.



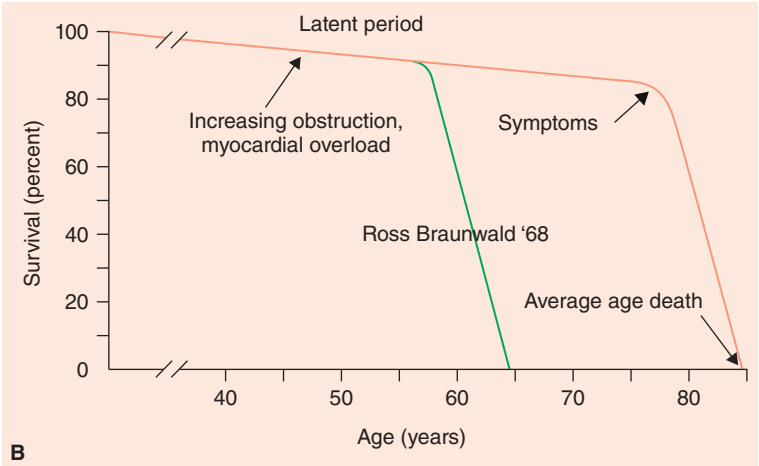


FIGURE 47–2. A. The natural history of aortic stenosis demonstrating a dramatic decline in survival when symptoms develop. **B.** The natural history of aortic stenosis today (pink line) showing onset of symptoms at a much later age in life than in the 20th century (white line). **A,** reproduced with permission from Ross J Jr, Braunwald E: Aortic stenosis, *Circulation*. 1968 Jul;38(1 Suppl):61-67. **B,** used with permission from Dr. Robert Bonow.

Angina

Angina is the presenting symptom in about 35% of AS patients and occurs even with normal epicardial coronary anatomy. In general, angina occurs when coronary oxygen demand exceeds oxygen supply. In normal subjects coronary blood flow can increase six- to eightfold to accommodate increased oxygen demand but LVH severely limits this reserve to two- to threefold and thus is at least in part responsible for the angina of AS patients.[11] Reduced coronary reserve in patients with LVH may be caused by failure of capillary ingrowth to match increased muscle mass.[12] Alternatively, increased LV filling pressure caused by decreased LV compliance (see below) may reduce the diastolic gradient for endocardial blood flow, in turn leading to angina.[13]

Heart Failure

Increased LV wall thickness reduces LV chamber compliance, requiring increased pressure to fill the LV to a given volume (Fig. 47–4).[14] Compliance is further reduced when hypertrophy becomes imbued with increased collagen fibers causing a still greater increase in LV filling pressure.[15] Reduced compliance leads to decreased stroke volume and increased filling pressure leading to heart failure with preserved ejection fraction. Long-standing and severe pressure overload often leads to excess afterload when LVH is inadequate to normalize wall stress, reducing ejection fraction (EF) and cardiac output.[16]

Pressure overload can also induce myocardial changes that reduce innate contractility. These changes include impaired calcium handling, apoptosis, the effects of intermittent ischemia, and cytoskeletal changes that act as an internal stent inhibiting contraction.[13,17-20] It is likely that there is an inherent genetic predisposition to these events because similar pressure overload yields widely dissimilar LV geometry.[21,22]

Syncope

Syncope occurs when cerebral blood flow is inadequate to maintain consciousness. The mechanism by which AS leads to syncope remains controversial, but when syncope does occur in AS patients it is almost always during exercise. A standard explanation is that the narrowed aortic orifice prevents the usual exercise-induced increase in cardiac output while exercise-induced peripheral vasodilation occurs normally or is even exaggerated by a vasodepressor response. Because blood pressure = cardiac output × peripheral resistance, blood pressure falls during exercise in AS patients, leading to syncope. The small hypertrophied LV of AS also limits the ability of stroke volume to increase during exercise.[23]

DIAGNOSIS

Physical Exam

The diagnosis of AS is often first considered when the health care provider hears the typical AS systolic ejection murmur during physical examination. The term "ejection" indicates a space between S1 and the onset of the murmur representing the time it takes for the LV to generate enough pressure to

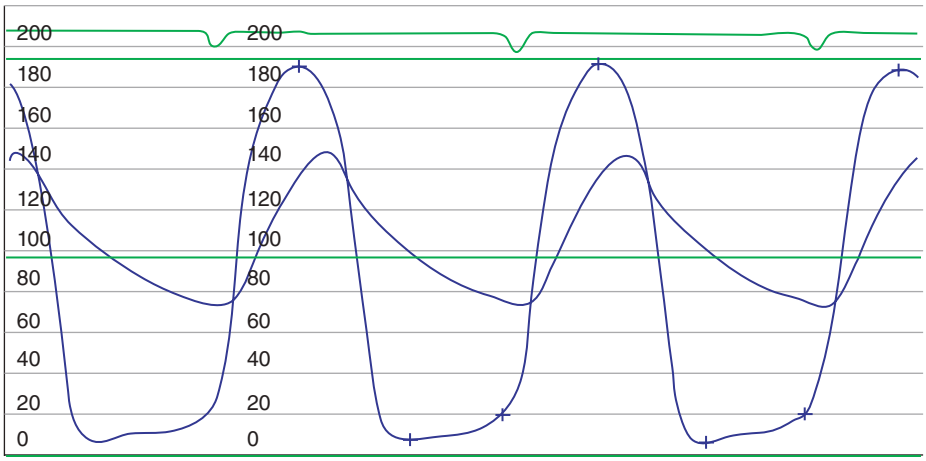


FIGURE 47–3. A typical pressure gradient from a patient with severe aortic stenosis. Reproduced with permission from Crawford MH: *Current Diagnosis and Treatment in Cardiology*. Norwalk: Appleton & Lange; 1995.

open the aortic valve causing ejection to begin. The murmur radiates to the neck and peaks in mid-systole in mild to moderate disease, giving it a crescendo-decrescendo quality. However, as disease severity worsens, peak intensity becomes progressively later in systole so that in very severe disease the murmur peaks at end systole. In some cases the murmur is heard loudly over the aortic area, diminishes over the sternum, and then reappears over the LV apex, (Gallavardin's phenomenon), misleading the examiner into believing that a second murmur of mitral regurgitation is also present. Palpation of the carotid arteries finds the pulse low in volume and delayed in upstroke (parvus et tardus) (Fig. 47–5),[24] as obstruction to flow absorbs energy.

The simultaneous palpation of weakened carotid pulses and a forceful apical beat is an important clue that an obstruction lies between the heart and the aorta. The second heart sound may be soft and single as the aortic component is lost because valve motion is restricted, although this quality seems less today than decades ago when the disease was typically more severe.

Imaging: Assessment of Valve Anatomy and Stenosis Severity

Transthoracic echocardiography is the mainstay in diagnosing AS and is indicated when there is an unexplained systolic murmur, a single second heart sound, a history of a bicuspid aortic valve, or symptoms that might be a result of AS.[25,26] In the current AHA/ACC valvular heart disease guideline,[25] the stages of valvular AS are defined by symptoms, valve hemodynamics, and the effect of valve obstruction on ventricular and vascular structure and function.

Echocardiography assesses valve morphology (Fig. 47–6), severity of stenosis, LV remodeling and function, mitral valve regurgitation, and pulmonary hypertension. The echocardiographic parameters used to assess the severity of AS are shown in Fig. 47–7 and are divided into two general categories (Table 47–1): flow-dependent measurements and flow-independent measurements. Flow-dependent measurements are obtained from continuous-wave Doppler across the stenotic aortic valve and include jet velocity and peak and mean gradients. Gradient is related to the velocity of flow, and is derived from the modified Bernoulli equation: $\Delta P = 4v^2$, where ΔP = LV pressure gradient and v = jet velocity. Mean gradient is measured by averaging the instantaneous gradient over the systolic ejection period.

The flow-independent measurements of stenosis severity include the aortic valve area calculated from the continuity equation and the Doppler index. The continuity equation uses the theory of conservation of mass such that AVA = $(V_{LVOT} \times CSA_{LVOT})/V_{AS\text{-}jet}$ where CSA_{LVOT} is the cross-sectional area of the LV outflow tract (LVOT): $\pi(D/2)^2$. Doppler echocardiography measures the vena contracta of the transaortic jet stream, which typically is smaller than the anatomic valve area as the Gorlin formula predicts. The PARTNER trial[27] defined severe AS as a valve area of < 0.8 cm^2, which is supported by data from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) trial.[3] Nonetheless, a continuity equation valve area of < 1.0 cm^2 predicts outcomes and thus remains a reliable tool for diagnosis and management of these patients as suggested in the most recent ACC/AHA guidelines.[25,28,29]

Because the greatest error in the AVA calculation is the squared LVOT diameter measurement, using the ratio of $V_{lvot}/V_{AS\text{-}jet}$ (Doppler velocity index, DVI), which eliminates LVOT diameter, is a useful indicator of AS severity where a DVI of < 0.25 indicates severe stenosis.[30]

Concordance and Discordance of the Data All four of these variables (valve area, DVI, jet velocity, and mean transvalvular gradient) used to assess AS severity are correlated with outcomes[28-30,32]; unfortunately they often do not correlate well with each other,[31] leaving the practitioner in a dilemma as to which parameter to choose. Most importantly, no single defining variable stands by itself. Each must be integrated into a diagnostic framework that contains all the information available including history, physical examination, imaging, and invasive hemodynamics (if needed) woven together by clinical judgment.

Current AHA/ACC guidelines subdivide the severe, symptomatic AS group of patients into three separate categories: high-gradient AS (D1);

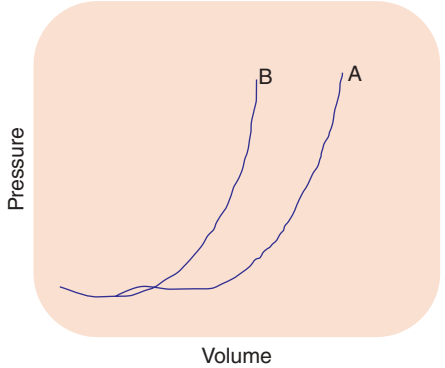


FIGURE 47–4. Diastolic pressure volume data from two patients. A. Normal subject. B. An aortic stenosis patient demonstrating increased pressure for any given filling volume (reduced LV compliance).

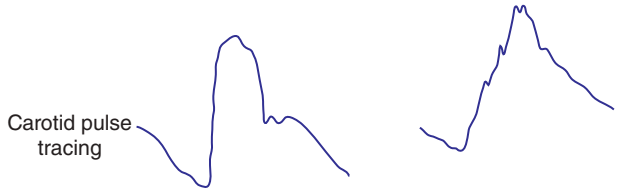


FIGURE 47–5. A normal carotid pulse (*left*) compared with the delayed pulse of a patient with aortic stenosis (*right*). Reproduced with permission from Crawford MH: *Current Diagnosis and Treatment in Cardiology*. Norwalk: Appleton & Lange; 1995.

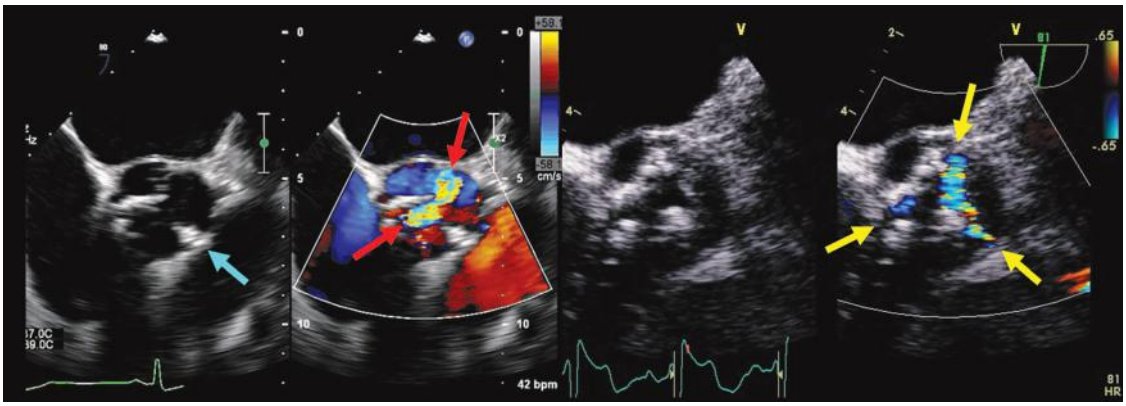


FIGURE 47–6. Aortic valve morphology. The diagnosis of a bicuspid aortic valve relies on short-axis imaging of only two leaflets opening in systole. In these transesophageal images, a severely calcified raphe (*panel A, blue arrow*) may not be easily distinguished from calcium in a commissure. Color Doppler in systole may be helpful in distinguishing a single opening between two leaflets (*panel A, red arrows*) from immobile trileaflet aortic valves without commissural fusion (*panel B, yellow arrows*).

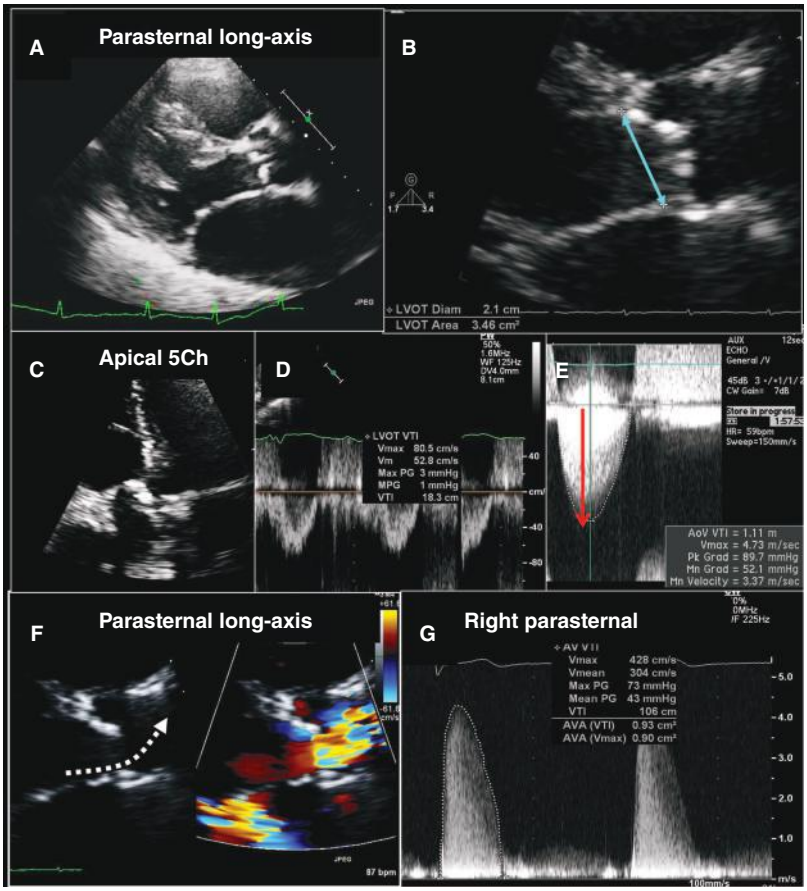


FIGURE 47–7. Hemodynamic assessment of the aortic valve. A comprehensive hemodynamic assessment of the aortic valve includes measurement of the peak velocity, peak and mean gradients, and calculation of the aortic valve area by the continuity equation. Panels **A** and **B** are from the parasternal long-axis window with appropriate measurement of the left ventricular outflow tract (LVOT) diameter (*panel B, blue arrow*) for calculation of the LVOT area. Panels **C**-**E** are acquired from apical imaging windows. The apical five-chamber view aligns the flow across the aortic valve parallel to the insonation beam and thus allows a measurement of the LVOT flow by pulsed-wave Doppler (panel **D**) as well as transaortic flow by continuous-wave Doppler (panel **E**). If the transaortic jet is anteriorly directed as seen in the parasternal long-axis view in panel **F**, then the highest transaortic velocity may require imaging from nonapical views (panel **G**, right parasternal window).

low-flow/low-gradient AS with reduced ejection fraction (D2), and low-gradient AS with normal ejection fraction (D3). These subcategories highlight the importance of the interaction between hemodynamic measures of stenosis and other factors that affect pressure and flow: ventricular systolic and diastolic function, arterial compliance, preload, and afterload. An increase or decrease in flow, mediated in part by changes in load, may significantly affect gradients and velocities. Because velocity and gradient are flow dependent, the AS severity criteria outlined above are most appropriate in patients with normal flow rates and blood pressure. High gradients, however, may occur in moderate AS if flow rate across the valve is increased (eg, significant aortic regurgitation or thyrotoxicosis). Conversely, low gradients may occur in severe AS if flow rate across the valve is reduced (ie, significant mitral regurgitation or reduced LV function). In these instances, flow-independent measurements are necessary to determine the severity of stenosis.

Logically the cardiac output required by an individual is dependent on body size; thus indexing the AVA to BSA is also used as a measure of severity and indexing valve area is particularly important in smaller patients with height < 135 cm (65 inches), BSA < 1.5 m^2 or BMI < 22.[30] Although the ACC guidelines used an indexed AVA of < 0.6 cm^2/m^2 to define severe AS, the PARTNER trial echocardiographic inclusion criteria used < 0.5 cm^2/m^2.

Noninvasive estimates of severity are often compared to invasively derived measures, but it is important to note that discrepancies in gradient measurements may occur between catheterization and echocardiographic derived data. Echocardiographically measured peak velocities correspond to the peak instantaneous pressure gradient.[33,34] Conversely, LV-to-peak aortic pressure gradients often "eyeballed" at catheterization are not instantaneous and do not accurately reflect instantaneous Doppler gradients. Differences in catheterization and echocardiographic measured gradients can also arise because of downstream pressure recovery.[35,36] As blood crosses a narrow orifice, the jet stream continues to narrow just beyond the orifice and is referred to as the vena contracta. The highest jet velocities

TABLE 47–1. Echocardiographic Parameters Used to Assess the Severity of AS

	Mild	Moderate	Severe
Valve Anatomy			
	• Mild to moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion, or • Rheumatic valve changes with commissural fusion		• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening
Quantitative Parameters (Flow-Dependent)			
Peak velocity	2.0–2.9 m/s	3–3.9 m/s	≥ 4 m/s
Mean gradient	< 20 mm Hg	20–39 mm Hg	≥ 40 mm Hg
Quantitative Parameters (Flow-Independent)			
Doppler index	> 0.5	0.26–0.5	≤ 0.25
AVA	> 1.5 cm^2	1.1–1.5 cm^2	≤ 1.0 cm^2
AVA index*	> 0.85 cm^2/m^2	0.61–0.85 cm^2/m^2	≤ 0.6 cm^2/m^2

* Indexing the valve area is particularly important in smaller patients with height < 135 cm (65 inches), BSA < 1.5 m^2, or BMI < 22.

Abbreviations: AVA, aortic valve area; BSA, body surface area; BMI = body mass index.

occur at the vena contracta and are measured by Doppler echocardiography. Because energy tends to be conserved, the kinetic energy of the jet stream beyond the vena contracta is converted to potential energy or pressure. This downstream pressure recovery within the aorta may be measured at catheterization, resulting in a lower pressure gradient compared to that measured by Doppler.

Other Measures of AS Severity Other measures of stenosis severity may have significant prognostic information in subgroups of patients with severe AS where standard measures are fraught. This is true especially in low-flow, low-gradient AS patients, because although we stated earlier that valve area is flow independent, valve area can become flow dependent in very–low-flow conditions perhaps because low flow fails to open the valve to its full extent.[37] Two approaches to the flow-dependence of valve area have been utilized: determination of valve resistance and determination of global afterload or impedance. Aortic valve resistance is the pressure gradient/flow rate ratio expressed in units of dyne.s.cm^{-5}. By echocardiography, it is simply calculated as 1.333 × 4 $Vmax^2$/ (area LVOT × velocity LVOT). As such, valve resistance is a functional index of hemodynamic impairment and may be less flow dependent than valve area.[38] The curvilinear and inverse relationship between valve area and valve resistance has previously been described; the slope becomes steeper with increasing severity of AS.[39] Thus in patients with severe AS, small reductions in valve area result in large increases in valve resistance. However, this relationship also limits the utility of valve resistance to monitor patients with mild or moderate disease, because large changes in valve area may not be easily detected.

Energy loss index (ELI) attempts to account for the total fluid mechanical energy loss related to both valve area and ascending aorta area.[40] The ELI is calculated as ELI = [EOA × A_A/A_A–EOA]/BSA, where EOA = effective orifice area, A_A = ascending aortic area, and BSA = body surface area. Although similar to valve area, it is less flow dependent than gradient or peak velocity, takes into account pressure recovery, and is roughly equivalent to EOA calculated invasively.[41] Using ELI, a substudy of the SEAS trial reclassified 47.5% of patients from severe to nonsevere AS.[41] The energy loss is most significant in small aortas (< 30 mm). An ELI of ≤ 0.5-0.6 cm^2/m^2 is consistent with severe AS.[40-42]

Finally, an index of global LV hemodynamic load has recently been extensively studied as a marker for poor outcomes. It takes into account increased systemic vascular resistance that may be a compensatory mechanism in the setting of reduced transvalvular flow. Concomitant arterial hypertension is present in a large proportion (35%-51%) of patients with AS[43,44] and accounts for a substantial part of total LV load. Thus the global ventricular load should account for both the load of AS and vascular resistance and is referred to as valvuloarterial impedance. Valvuloarterial impedance (Zva), is calculated as Z_{va} = SBP+ΔP_{Mean}/SVI, where SBP = systolic blood pressure and SVI = stroke volume index. Several investigators have shown that the risk of mortality was increased with an increase in Zva.[43,45] Hachicha and associates found an increase in mortality of 2.76-fold in patients with Zva ≥ 4.5 mm Hg·mL^{-1}·m^2 and by 2.30-fold in those with a Zva between 3.5 and 4.5 mm Hg·mL^{-1}·m^2 after adjusting for other risk factors.[43] Considering the uncertainties involved in defining severe AS, it is hoped that additional research will demonstrate that these or other novel indexes will improve prediction of outcome in AS patients.

Advanced Imaging for Assessment of AS Severity: Comparison With Standard Echocardiography

Three-Dimensional Echocardiography Although two-dimensional (2D) echocardiography remains the imaging gold standard, real-time three-dimensional (RT3D) imaging is rapidly emerging as a useful tool. Aortic valve morphology and aortic root measurements are more accurate and reproducible using RT3D imaging compared to 2D imaging.[46] Larger left ventricular outflow tract areas and calculated AV dimensions and areas are obtained by RT3D TEE[47] compared to 2D imaging. Planimetry of the aortic valve area by RT3D is accurate and reproducible.[48] Planimetry of the AV and LV outflow tract area using 3D echocardiography is more reproducible than 2D imaging and may influence surgical decision-making in the setting of moderate to severe AS.[49] Although a single diameter measurement of the LVOT is used to calculate EOA, 3D methods may be more accurate than 2D estimations using multiple measurements.[51]

MultiSlice Computed Tomography Compared to multislice computed tomography (MSCT), 2D echo underestimates the true LVOT area and thus valve area.[50,51] On the other hand, CT overestimates LVOT area compared to magnetic resonance imaging or 3D echo.[52] Furthermore, a recent study concluded that thresholds for excess mortality

differed between imaging modalities: EOA ≤ 1.0 cm^2 for echocardiographic methods versus ≤ 1.2 cm^2 for CT methods.[53] However, because of strong outcome data using traditional 2D methods of measuring LVOT and calculating EOA, the long-axis diameter of the LV outflow tract should continue to be used to guide management of this disease.

The prognostic importance of valve calcium has long been recognized,[28,54] and MSCT measurement of calcium burden (in arbitrary units or AU) correlates well with outcome.[55-57] In addition, MSCT can aid in the determination of severity of disease by planimetry[57] and calcium quantification.[58] In patients with low-flow AS, the severity of calcification may help distinguish those patients with true AS from those patients with pseudosevere AS a condition where a small AVA is calculated because of low flow that underestimates true valve area when higher flow opens the valve appropriately.[58-60] Although in all patients a receiver-operating curve cut-off of 1651 AU differentiated patients with severe AS from nonsevere AS based on an AVA of 1 cm,[2,60] sex-specific criteria have now been established with cutoffs of AV calcium ≥ 1275 AU in women and 2065 AU in men, AV calcium indexed to body size ≥ 637 AU/m^2 in women and 1067 AU/m^2 in men, and AV calcium density (calcium indexed to annular area) ≥ 292 AU/cm^2 in women and 476 AU/cm^2 in men.[58]

Strain Imaging Although not yet routinely used in management decisions, myocardial strain promises to become an important tool in assessing LV function in AS. Strain (deformation of the myocardium) can be assessed using both tissue Doppler imaging and speckle tracking.[61] Strain is the fractional change in the length of a myocardial segment (expressed as percent of the baseline length). The deformation of the myocardium is directional: lengthening is represented by positive strain, and shortening by negative strain. Systolic strain can be measured along the anatomic coordinates of the cardiac chambers: longitudinal (negative strain), radial (positive strain), and circumferential (negative strain). The strengths and weaknesses of strain measurement have been well described[61]; however, the recent standardization of strain Digital Imaging and Communications in Medicine (DICOM) format will reduce inter-vendor variability, which, along with improved software analysis and automation packages, will likely increase the clinical use of this powerful technique.[62]

Strain imaging has been used widely for assessing left ventricular function in aortic valve disease. Even in the presence of normal EF, increasing severity of AS is associated with reduced global longitudinal strain (GLS)[63-65] and is a predictor of all-cause mortality.[66,67] GLS was a superior predictor of outcomes in patients referred for surgery compared to standard predictors such as risk score, presence of ischemic heart disease, and EF.[67] In patients with low-flow, low-gradient, and preserved EF, GLS was independently associated with survival after aortic valve replacement.[68] In patients with low-flow, low-gradient, and reduced EF, stress GLS measured during dobutamine stress echocardiography may provide incremental prognostic value beyond GLS measured at rest.[69] Finally, 3D GLS may be a better predictor of outcome compared to 2D strain. [70]

Regional strain abnormalities in patients with severe AS may add precision in diagnosis. In patients with cardiac amyloid, relative apical sparing (with preserved apical longitudinal strain) was sensitive (93%) and specific (82%) in differentiating amyloid from controls, some of whom had severe AS. In patients with moderate or severe AS and concomitant coronary disease, on the other hand, worse apical and mid-longitudinal strain parameters were predictive of significant coronary stenosis.[71,72]

Because mortality is significantly associated with symptom development,[9] but symptom status is subjective, strain has been postulated as a possible early marker of ventricular dysfunction in asymptomatic patients with severe AS and thus may be a useful tool in determining the timing of intervention in this population. Carasso and coworkers[72] showed that longitudinal strain was low in asymptomatic patients with severe AS with supernormal apical circumferential strain and rotation. In symptomatic patients, however, longitudinal strain was significantly lower with no compensatory circumferential myocardial mechanics. Other investigators suggest that after adjusting for AS severity and ejection fraction, only basal longitudinal strain (and not GLS) was an independent predictor of symptomatic status.[73-75]

Biomarkers

Currently management of AS is primarily based upon symptomatic status and LV function. It is hoped that newer objective biologic measures might make that assessment more accurate. Investigation into some of these biologic markers is discussed below.

The association with bleeding and AS is in part attributed to acquired von Willebrand syndrome, which improves following AV replacement.[76-80] There is a strong graded relationship between von Willebrand factor (VWF) or VWF-related indices and AS gradient. And VWF indices also predicted mortality or the need for aortic valve replacement.[80]

Natriuretic proteins have long been associated with outcomes in a variety of cardiovascular diseases, including valvular heart disease. B-type natriuretic peptide (BNP) exists as a pro-hormone that is cleaved into inactive *N*-terminal fragment (*N*-terminal proBNP) and the biologically active hormone before release into the circulation. BNP and pro-BNP have correlated well with AS severity, LV mass, symptoms, and outcomes.[81-88]

Henri and associates[89] showed that asymptomatic patients with higher annualized BNP changes (> 20 pg/mL/y) had a significantly higher risk of cardiac events (hazard ratio 2.73, 95% confidence interval: 1.27-5.86; $P = 0.010$) after adjustment for age, dyslipidemia, and echocardiographic parameters. In asymptomatic patients with AS, Capoulade and coworkers[90] showed that an increase in BNP during exercise predicted mortality or aortic valve replacement dictated by class I indications. Outcomes were incrementally worse for patients with a BNP of 43 to 92 pg/mL (HR = 2.9; $P = 0.002$) and BNP 92 to 956 pg/mL (HR = 5.3; $P < 0.0001$). The resting echocardiographic variables that predicted peak exercise BNP were mean gradient, indexed LA area, and Zva. Both resting and exercise BNP levels may be useful to predict outcomes in individual patients with asymptomatic AS who might benefit from early intervention.

Other Markers of Outcomes

Despite its simplicity, ejection fraction (EF) is still a useful marker of outcome in AS.[91] In fact, a recent meta-analysis of 26 studies and nearly 6900 patients showed that patients with baseline low EF and severe AS have higher mortality following TAVR compared to normal EF patients, despite a significant and sustained improvement in EF.[92]

The effect of left ventricular diastolic function on outcome in AS is controversial, predicting outcome in some studies[93,94] but not others.[95]

Stress Testing in Aortic Stenosis

Stress testing for valvular heart disease is used for at least three purposes: determination of the etiology of symptoms in the setting of borderline severity, confirmation of asymptomatic status in the setting of severe disease, and evaluation of patients with concomitant valve disease and myocardial dysfunction.[96-100] Stress testing in severe AS is safe in patients without apparent symptoms but should not be performed in clearly symptomatic patients where risk is high. A number of parameters have been used to indicate a positive exercise treadmill test in the setting of AS. Amato and coworkers[97] used the development of symptoms, complex ventricular arrhythmias, blood pressure failing to increase by 20 mm Hg, or the development of horizontal or down-sloping ST depression (1 mm or more in men, 2 mm or more in women) as criteria for a positive test. Maréchaux and associates[98] considered symptoms (limiting breathlessness, chest pain/tightness,

dizziness, syncope), a fall in blood pressure ≥ 10 mm Hg, ST segment depression ≥ 5 mm measured 80 ms after the J point, and more than three consecutive ventricular premature beats to indicate a positive test. Lancellotti and colleagues noted worse outcomes in patients with a baseline AVA < 0.75 cm^2 and abnormal exercise results (symptoms, ST-segment depression, or < 20 mm Hg increase in blood pressure).[99]

Despite variation in definition of a positive test, the presence of exercise-limiting symptoms has a positive predictive accuracy for the need for aortic valve replacement (AVR) of 57% in the whole population and 79% for patients aged < 70, whereas blood pressure response and ST depressions were less predictive. The negative predictive accuracy of stress testing is high. In summary, in patients without overt symptoms, symptom onset (within 1-2 y) can be predicted by those who demonstrate (1) a decrease in systolic BP below baseline or a failure of BP to increase by at least 20 mm Hg or (2) a significant decrease in exercise tolerance compared with age and sex normal standards. Patients who previously were thought to be asymptomatic but who clearly demonstrate symptoms during exercise testing should be recategorized as being symptomatic.

CARDIAC CATHETERIZATION

Most AS patients are older than 40 years of age where coronary artery disease may also be present requiring assessment either by coronary angiography or CT angiography prior to AVR. Invasive hemodynamic measurement is reserved for situations when there is discordance in clinical presentation and noninvasive data regarding AS severity. In such cases direct measurement of aortic valve gradient (*g*) and cardiac output (CO) is indicated. These data are entered into the Gorlin equation: $AVA=CO/ 44.3\sqrt{g}$, where cardiac output is expressed as flow per systole. Because by definition invasive data are being obtained because the diagnosis is unclear, careful attention must be paid to proper pressure and cardiac output measurement.[37]

SEX DIFFERENCES IN RESPONSE TO AORTIC STENOSIS

Valve pathology, disease progression, and natural history in patients with AS vary with gender.[101-104] For similar valve area indices, women have higher peak and mean gradients, higher relative wall thickness, smaller ventricular volumes, and higher indices of systolic function including fractional shortening, ejection fraction, maximum positive dP/dt, and cardiac index. Women also have lower aortic valve calcium scores on multislice computed tomography scans for the same severity of AS,[58,104] and women have more concentric remodeling compared to men[103,105] and accordingly lower end-systolic wall stress.[101]

In addition to these differences in ventricular and hemodynamic responses to AS, there are sex differences in presentation and progression of disease. The SEAS study prospectively followed initially asymptomatic, mild to moderate AS patients. Women with asymptomatic AS were older; had a lower prevalence of comorbidities such as hypertension, renal dysfunction, and coronary artery disease compared to men; and had a smaller aortic valve area at initial presentation; but the four-year rate of progression of AS did not differ by sex.[3] Women had a 50% lower rate of both stroke and coronary artery disease requiring concomitant bypass grafting at the time of aortic valve replacement, and a 31% lower all-cause mortality rate, independent of covariates including differences in age, prevalence of hypertension, AS severity, LV geometry, and LV systolic function.

MEDICAL THERAPY

AS is a mechanical obstruction to LV outflow that only has a mechanical solution, AVR. Thus there is no proven medical therapy for AS. Although there likely will be phamacologic targets to retard or prevent progression of the disease in the future, none have been employed as yet. However, many patients with AS also have hypertension that requires therapy. No specific class of antihypertensive agents is indicated for treatment of AS patients. Although there is concern that vasodilators might be more likely to cause hypotension in AS because of impaired cardiac output, these agents have been used cautiously in some circumstances. In general the treatment of hypertension in AS patients should obey the rule "start low and go slow."

TIMING OF SURGERY

The Symptomatic Patient With Severe Aortic Stenosis

As noted earlier, the onset of the symptoms of AS—angina, syncope, and dyspnea (or other symptoms of heart failure)—mark a dramatic change in the natural history of the disease, while AVR increases longevity substantially (Fig. 47–8).[106] Thus when there is severe AS, as defined by a transvalvular jet velocity ≥ 4 m/sec, or a mean gradient ≥ 40 mm Hg, or an AVA ≤ 1.0 cm^2 and the patient develops these classic symptoms, AVR is indicated unless other factors such as severe comorbidities preclude valve replacement.

The Asymptomatic Patient With Severe Aortic Stenosis

In the truly asymptomatic AS patient the risk of sudden death is small, probably less than 1% per year.[29,107] However, AVR is recommended for very rare asymptomatic patients who have developed LV dysfunction and for the patient with severe AS undergoing another cardiac operation where it would be unwise to fail to correct severe AS during surgery.[25,26] Pivotal in this management strategy is the symptomatic status of the patient. Unfortunately many patients may not recognize their symptoms or may adjust their lifestyle to avoid them or even deny them. As noted, exercise testing is often very helpful in revealing exercise intolerance, hemodynamic instability, or undeclared symptoms, situations that militate for AVR. Furthermore, the natural history of AS is one of constant although highly variable progression. If the disease is already very

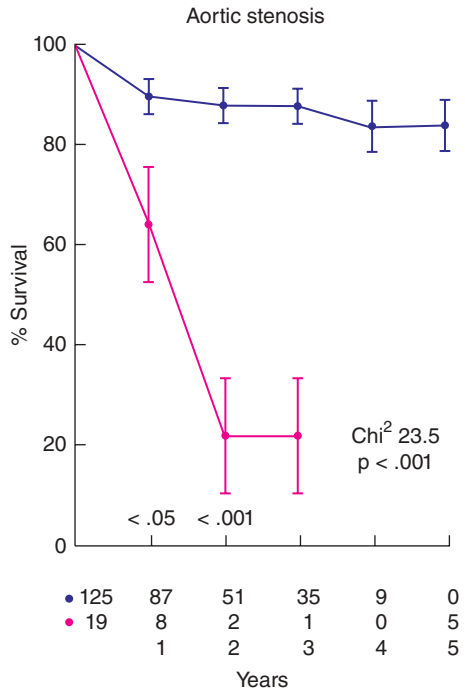


FIGURE 47–8. Survival of symptomatic patients with AS who underwent AVR (*black circles*) is compared to that of patients who refused surgery. Reproduced with permission from Schwarz F, Baumann P, Manthey J, et al: The effect of aortic valve replacement on survival. *Circulation*. 1982 Nov;66(5):1105-1110.

severe (jet velocity > 5.0 m/sec or AVA < 0.6 cm^2),[29] symptom onset is likely within the next year, making early intervention appealing. Aortic valve replacement is also usually advisable for patients with moderate AS (AVA 1.0-1.5 cm^2) who are undergoing coronary revascularization because of the likelihood that the AS will progress to severe symptomatic disease within the next 5 years (ACC/AHA guideline class 2a).

AORTIC VALVE REPLACEMENT OPTIONS

Overview

Until very recently, AVR was performed using standard surgical techniques during cardiopulmonary bypass utilizing extracorporeal circulation. However, transcatheter AVR (TAVR), introduced in 2003, is evolving and will assume a progressively greater share of total AVRs as the devices become lower in physical profile and easier and safer to deploy. Because these techniques are less invasive and do not require cardiopulmonary bypass, they were initiated in inoperable patients or those at very high risk for surgery.[27] However, it is likely that by the time this text is in print, TAVR will be approved for use in moderate-risk patients.[108]

Surgical Aortic Valve Replacement

Four surgical options are available for surgical aortic valve replacement (SAVR): implantation of mechanical prostheses, heterograft bioprostheses, homograft bioprostheses, and pulmonary autografts. Mechanical valves are generally more durable than tissue valves but all require vitamin K antagonist (VKA) anticoagulation. There is currently no evidence that easier-to-take non-VKA anticoagulants are safe and effective for use with mechanical heart valves. Unfortunately the risk of thromboembolic events despite VKA anticoagulants and or the risk of serious hemorrhage approaches 1% to 2% per year.[109] Thus although the durability mechanical valves makes them more attractive for avoiding reoperation in younger patients, the complications of VKA anticoagulants are more likely to occur because mechanical valves will have been implanted for a longer period of time. Bioprostheses avoid the need for anticoagulation but are less durable than mechanical valves, and structural deterioration is accelerated at younger ages of implantation. Although it was hoped the homograft prostheses would be more durable than heterografts, it is not clear that this is the case, and when coupled with the difficulty in procuring homografts they have become less popular than in the past. In general, mechanical valves are employed in patients younger than 55 years of age or in whom a second condition such as atrial fibrillation also requires anticoagulation.[25,26] However, because the risk of reoperation has diminished over the past two decades, many younger patients prefer a bioprostheses to avoid VKA anticoagulation in favor of a possible reoperation later in life.

Employment of the pulmonary autograft or Ross operation entails transplanting the patient's own pulmonary valve into the aortic position and replacing the pulmonary valve with a homograft, assuming that it will be more durable in the low-pressure pulmonary circuit than in the aortic position. This operation is much harder to perform and should only be performed in young patients by surgeons expert in the procedure. In experienced hands, the operation is superior to homograft implantation.[110]

Transcatheter Aortic Valve Replacement

TAVR has emerged as a reasonable alternative to SAVR in many patients.[27,111-113] The Placement of Aortic Transcatheter Valves (PARTNER) trial was the first randomized trial comparing TAVR using a balloon-expandable valve to so-called medical therapy in inoperable patients and to SAVR in high-risk patients therapies in a rigorous fashion.[27,111] TAVR was superior to medical therapy[27,111] in inoperable patients and equivalent[111] to SAVR in high-risk patients; these benefits were sustained over time.[114,115] The CoreValve Pivotal Trials showed similar procedural success with the self-expanding device, with possible superiority to surgery in high-risk patients.[113] Early studies suggested that residual aortic regurgitation (AR) was an important predictor of mortality[114]; however, rapidly developing design modifications have already reduced the incidence of this complication and the current self-expanding iteration, the Evolut R, allows for repositioning to also reduce the incidence of paravalvular regurgitation.[116]

Since commercial approval of the Sapien and CoreValve valves, the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC) developed the STS/ACC Transcatheter Valve Therapy (TVT) Registry in concert with multiple stakeholders, including regulatory agencies and industry.[117] The registry was generated to help capture commercial TAVR patient characteristics, procedural variables, and outcomes including quality of life, in a real-life setting, and currently serves as the primary platform for FDA-approved postmarket surveillance studies for new generations of current and future devices. An annual report has been generated from this registry showing a number of interesting trends.[117-120] When comparing patients implanted in 2012 to 2013 to those implanted in 2014, the STS risk score over the latter recorded period is lower (8.16% vs 8.34%). There was also greater use of the technology to salvage failed bioprosthetic valves. The most common intraprocedural cardiac complication was the need for a new pacemaker, which occurred in approximately 10% of patients overall, but has increased over time most likely as a result of the self-expanding CoreValve, which has been associated with a higher incidence of conduction system abnormalities. There was a significant downward trend in vascular complications, because of the reduction in access sheath size. Stroke rates remained low over the follow-up time period (2.1%-2.2%) as did in-hospital mortality (4.4% for 2014). There was a significant reduction in the incidence of moderate or severe paravalvular AR, but this figure may be affected by potential differences between on site-reported incidence of AR versus core lab evaluation from earlier trials (5.3% and 4.8% for the two time points).

As the safety profile of transcatheter devices improves, this procedure may become a viable option for lower-risk groups. In fact, early reports for the SAPIEN 3 intermediate risk (average STS = 5.3) registry (n = 1059) revealed a 30-day all-cause and mortality rate of 1.1% and a cardiovascular mortality rate of 0.9%.[121] Data from the CoreValve ADVANCE study (996 patients) showed that patients with STS ≤ 7% (versus > 7%) had lower rates of all-cause (28.6 vs 45.9, $P < 0.01$) and cardiovascular (19.0 vs 30.2, $P < 0.01$) mortality at 3 years after transcatheter aortic valve implantation.[121] The low-risk Nordic Aortic Valve Intervention Trial (NOTION) (average STS scores, 2.9-3.1) reported comparable outcomes (mortality/stroke) at 2 years in the TAVR and SAVR arms.[122] Even in this low-risk population, demonstrable benefits of TAVR are shown by lower bleeding risk, reduced atrial fibrillation, and less acute kidney injury compared with SAVR, but at the risk of higher rates of permanent pacemaker and more aortic regurgitation.

Despite these early successes, it remains to be seen whether these excellent outcomes can be maintained. A recent retrospective study comparing traditional surgical replacement, sutureless aortic valve replacement, and TAVR, suggests that the intermediate risk group may still benefit from the surgical approach, with improved overall survival in the two surgical groups.[123]

In the case of a failed surgically implanted bioprosthesis it may be possible to replace the failing valve by placing a TAVR inside the prosthesis (valve-in-valve). This procedure is only possible if the initial valve is large enough (preferably 23 mm or greater) to allow normal function of the TAVR.

TAVR is currently in its infancy and will evolve rapidly over the next decade at a very rapid pace, requiring constant attention to the available data and recommendations for use.

SPECIAL CASES

Low-Flow AS With Reduced Ejection Fraction

Current AHA/ACC guidelines have subdivided the severe, symptomatic AS group of patients into three separate categories: high-gradient (HG) AS (D1); low-flow/low-gradient (LF/LG) AS with reduced EF (D2), and LG AS with normal EF (D3). LF has been arbitrarily defined as an indexed LV stroke volume ≤ 35 mL/m^2 and LG as a mean transaortic pressure gradient < 40 mm Hg.[25] The D2 and D3 categories are class IIa indications for intervention, but also highlight the discrepancies between gradient and valve area calculation that frequently occur. Low-flow, low-gradient, low-EF patients have severe LV contractile dysfunction and a poor prognosis compared to high-gradient normal EF patients[16,124-127] However, some patients with this syndrome improve following AVR, and dobutamine stress testing can help improve risk assessment in this group.

Valve area at rest is difficult to assess in low LVEF patients,[127-131] and dobutamine stress echocardiography (DSE) can help clarify the issue by allowing reassessment of the AVA at a higher flow. With normalized flow, a patient with true severe AS increases the mean transaortic gradient in tandem with valve flow so that AVA remains nearly constant. If the patient has pseudo-severe AS, a condition where low flow causes an overestimation of AS severity, higher flow will be achieved with little increase in gradient, resulting in increased AVA. Because of a high rate of side effects (serious cardiac arrhythmia or symptomatic hypotension) with full-dose DSE, a low-dose protocol (ie, up to 20 µg/kg/min) should be used in these patients with consideration of using longer stages (5 to 8 min instead of 3 to 5 min) to confirm that the maximum hemodynamic effect is attained with a more gradual increase in heart rate, prior to proceeding to the next stage. In the setting of a reduced ejection fraction of < 50% the goal of DSE is to determine if valve area will increases with an increase (> 20%) transvalvular flow rates. Dobutamine testing also is important in surgical risk assessment. Surgical mortality is about 10% in patients who increase stroke volume ≥ 20% (inotropic reserve), compared to a 30% operative mortality in patients without inotropic reserve (Fig. 47–9).[126]

However, subsequent studies have shown that although patients with no contractile reserve on DSE have high perioperative mortality, some survivors still benefit from AV replacement with improved EF and significantly lower 5-year mortality compared to medical management.[132] Other independent predictors of operative mortality included concomitant bypass surgery and baseline mean transaortic pressure gradient ≤ 20 mm Hg.[133]

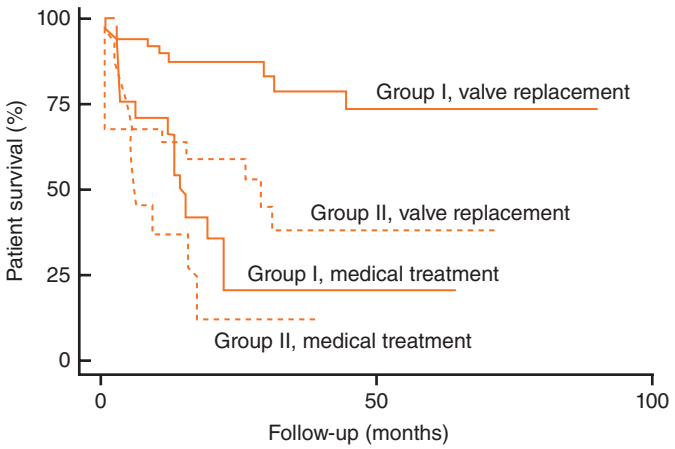


FIGURE 47–9. Survival with "medical" versus surgical therapy for AS patients who did (group I) or did not demonstrate inotropic reserve (group II) during dobutamine infusion. Data from Schwarz F, Baumann P, Manthey J, et al: The effect of aortic valve replacement on survival. *Circulation*. 1982 Nov;66(5):1105-1110.

The myocardial response to DSE, however, is not always consistent, and suboptimal increases in flow rate may prevent the accurate interpretation of this test. To overcome this limitation, the investigators of the TOPAS (Truly or Pseudo Severe Aortic Stenosis) multicenter study[134] proposed a new echocardiographic parameter: the projected (proj) AVA at a standardized normal flow rate. This parameter "normalizes" for differences in flow rate by plotting the AVA against the mean flow rate at each stage of the DSE. Once the slope of the regression line is determined, then the "projected" valve area at a standardized flow rate of 250 mL/s (AVAproj) can be determined as AVAproj = AVArest + slope x (250 – Qrest). A simplified formula for calculating the slope was later validated as the change in AVA from baseline to the peak stage of DSE divided by the change in Q from baseline to peak.[135] Subsequent studies from this group have identified significant predictors of mortality to include Duke Activity Status Index ≤ 20, 6-minute walk test distance ≤ 320 m, AVAproj ≤ 1.2 cm^2, and peak DSE LVEF ≤ 35%.[130,134] In addition, the AVAproj correlated well with explanted valve weight whereas traditional DSE parameters did not, suggesting this parameter is a better measure of severity of disease.

Low-Flow, Low-Gradient AS With Normal Ejection Fraction

The D3 category of LG/severe AS with normal EF is also known as "paradoxical AS" because there is low flow despite a preserved EF. In fact, there are likely four different hemodynamic categories of AS patients based on flow and gradient: NF/high gradient (HG), NF/LG, LF/HG. and LF/LG. Patients with NF/HG and LF/HG have similarly good outcomes. They may have more severe or longer duration of AS, higher BNP, and lower strain despite normal ejection fraction[135] but still have relatively normal contractility because reduced flow is primarily caused by afterload excess.[16] Patients with severe AS but NF/LG are particularly vexing but probably do not have truly severe AS. Rather, the discordance in parameters may be related to inherent inconsistencies in the accepted grading scheme mentioned earlier, where a maximum velocity of 4 m/s may be associated with mean gradients of 30 to 35 mm Hg[31]; or more likely, to measurement errors that result in underestimation of stroke volume and thus underestimate AVA and/or underestimation of gradient; or failure to account for the importance of body size.[136] Controversy has surrounded patients with LF/LG AS and normal EF since initial studies suggested that these patients have more advanced disease, significantly higher Zva, and worse outcomes compared to patients with normal flow (NF).[137,138] Other studies suggested patients with LF/LG AS with normal EF had outcomes similar to patients with moderate AS.[139] A recent meta-analysis of 18 studies,[140] however, showed that patients with LF-LG AS have higher risk of overall mortality compared with those with moderate AS, NF/LG AS, and HG AS. Unfortunately, compared with patients with HG AS, those with LF/LG AS were significantly less likely to be referred for surgery.

Multiple explanations for low forward flow in the setting of normal EF have been proposed.[140-142] It is generally held that this group has small LV volumes (concentric remodeling), so that a normal EF of a small end-diastolic volume produces a small stroke volume and hence a low gradient. However, it should be noted that strain imaging shows reduced LV function despite normal EF in this group.[142,143] Other etiologies of LF have also been identified in this patient population. Hypertension has been shown to reduce the transaortic gradients in experimental models and patients, primarily because of changes in transvalvular flow rates and not directly as a result of to changes

in arterial compliance.[140,141] And right ventricular dysfunction, atrial fibrillation, and mitral regurgitation are independently associated with low-flow low-gradient AS.[142] In summary, when all evidence (not just AVA alone) points to severe symptomatic With AS in a patient with low-flow and normal EF, AVR is indicated.

HEART TEAM

Because so many devices for treating AS are available, the decision about which one is best for the patient should not be made by a single practitioner. Rather a team composed of cardiac imagers, interventionalists, cardiac surgeons, and the patient should be engaged in a thorough discussion about the best course of action for that patient. In this way the most informed decision can be made without personal prejudice for or against one approach or the other.

AORTIC REGURGITATION

ETIOLOGY

Aortic regurgitation (AR) occurs when disease of the valve leaflets, the aortic root, or both causes backward flow across the aortic valve (Table 47–2).[144] Common leaflet pathologies causing AR include bicuspid aortic valve, infective endocarditis, collagen vascular disease (especially lupus erythematosus), and leaflet prolapse. Common root pathologies leading to AR include Marfan syndrome, aortic dissection, annulo-aortic ectasia as a result of hypertension, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, syphilis, and ankylosing spondylitis.

BICUSPID AORTIC VALVE AND AORTOPATHY

The presence of a bicuspid aortic valve is sometimes but not always associated with aortic root and ascending aortic aneurysmal dilatation, which may cause AR or be of concern for the potential of aortic rupture even if coincident AR is absent or mild. Two major theories are invoked to explain these findings: (1) that there is an inherent genetic aortopathy associated with bicuspid aortic valve that leads to aneurysmal dilatation; or (2) that the valve abnormality alters the flow of blood as it exits the aorta, focusing flow on different aortic segments, increasing shear stress that activates matrix metalloproteinases, resulting in weakening of the aortic wall at those sites.[145-150] Both theories may be in part correct. Importantly, when the aortic diameter approaches 5.5 cm, the risk of rupture increases such that surgical or endovascular repair is indicated.[25] If aortic root dilatation is related to a syndrome known to lead to aortic dissection, eg, Marfan syndrome, prophylactic surgery is indicated when root diameter approaches 4.5 cm.

TABLE 47–2. Etiologic Classification of Aortic Regurgitation

Mechanism	Specific Etiology
Congenital/leaflet abnormalities	Bicuspid, unicuspid, or quadricuspid aortic valve
	Ventricular septal defect
Acquired leaflet abnormalities	Senile calcification
	Infective endocarditis
	Rheumatic disease
	Radiation induced valvulopathy
	Toxin induced valvulopathy: fenfluramine, carcinoid
Congenital/genetic aortic root abnormalities	Annuloaortic ectasia
	Connective tissue disease: Loeys Deitz, Ehlers-Danlos, Marfan syndrome, osteogenesis imperfecta
Acquired aortic root abnormalities	Idiopathic aortic root dilatation
	Systemic hypertension (?)
	Autoimmune disease: systemic lupus errthematosis, ankylosing spondylitis, Reiter syndrome
	Aortitis: Syphilitic, Takayasu's arteritis
	Aortic dissection
	Trauma

PATHOPHYSIOLOGY AND ITS RELATIONSHIP TO SYMPTOMS

Aortic regurgitation places both a volume and a pressure overload on the LV. The blood flow regurgitated into the LV during diastole is compensated by increasing the total LV stroke volume, a process requiring LV dilatation, and thus AR creates an LV volume overload. The extra volume is pumped into the aortic during systole, where it widens pulse pressure (PP), that is, PP~ SV/*e*, where SV = stroke volume and *e* = aortic elastance and increases in systolic blood pressure. Recalling the formula for stress given earlier, $\sigma = P \times r/2\ th$, the increase in both the radius and pressure terms increase stress (afterload), which can be as high in AR as it is in AS, the typical pressure overload lesion.[151,152] Not surprisingly the LV in AR remodels to accommodate both types of overload, with increased chamber volume as well as increased wall thickness.[153] Over time, increased wall thickness reduces LV compliance, so that the high diastolic volume of AR must also increase diastolic pressure, leading to pulmonary congestion and the symptoms of heart failure, primarily dyspnea on exertion. Diastolic aortic run-off into the LV lowers diastolic systemic pressure, in turn lowering the pressure head driving both coronary and cerebral blood flow. Although not as prevalent in AR as in AS, both angina and syncope may occur through this mechanism. Although AR may be tolerated for many years,[154,155] eventually prolonged hemodynamic overload leads to systolic dysfunction. Reduced LV performance stems both from uncompensated afterload excess and also reduced intrinsic contractility.[152] The latter is due in part to interstitial fibrosis of the myocardium with replacement with of contractile elements.[156]

DIAGNOSIS

Physical Exam

The physical of the patient with severe AR is one of the most dynamic in cardiology and occasionally the diagnosis can be made from the patient's doorway. The enlarged LV displaces the apical beat downward and to the left and is often easily visible and palpable on physical examination. The murmur of AR is a diastolic blowing sound best heard along the left sternal border with the patient sitting up and leaning forward. It may be short in duration in mild AR but becomes more holodiastolic as AR severity worsens. The backward regurgitant jet often strikes the mitral valve, partially closing it and causing it to vibrate. This action might be responsible for a murmur (Austin Flint) that is indistinguishable from that of mitral stenosis.

The large total stroke volume and widened pulse pressure produce a myriad of physical signs. The carotid upstrokes are sharp followed by a rapid decline (Corrigan pulse) and may have a bifid quality. The impact on the carotids may cause the head to bob (de Musset's sign), a quality that may be bothersome to the patient, sometimes associated with carotid pain or a "whooshing" sound that the patient may also report. Traction on the thumbnail may cause the nail bed to be plethoric in systole and blanch in diastole (Quinke's pulse). Placement of

the stethoscope over the femoral pulse may find a pistol shot sound, while pressure placed on the artery with the stethoscope bell can cause a to-and-fro bruit (Duroziez's sign). The normal augmentation of systolic pressure in the leg compared to the arm is often augmented and exceeds 40 mm Hg (Hill's sign).

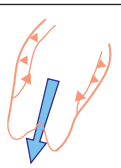
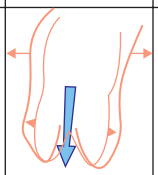
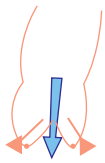
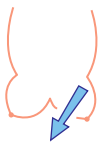
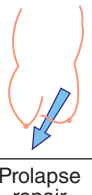
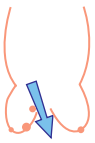
AI class	Type I Normal cusp motion with FAA dilatation or cusp perforation				Type II Cusp prolapse	Type III Cusp restriction
	Ia	Ib	Ic	Id		
Mechanism						
Repair techniques (primary)	STJ remodeling *Ascending aortic graft*	Aortic value sparing: *Reimplantation or Remodeling with SCA*	SCA	Patch repair *Autologous or bovine pericardium*	Prolapse repair *Plication* *Triangular resection* *Free margin Resuspention* *Patch*	Leaflet repair *Shaving* *Decalcification* *Patch*
(Secondary)	SCA		STJ annuloplasty	SCA	SCA	SCA

FIGURE 47–10. Repair-oriented functional classification of aortic insufficiency (AI) with description of disease mechanisms and repair techniques used. FAA, Functional aortic annulus; STJ, sinotubular junction; SCA, subcommissural annuloplasty. Reproduced with permission from Boodhwani M, de Kerchove L, Glineur D, et al: Repair-oriented classification of aortic insufficiency: impact on surgical techniques and clinical outcomes. *J Thorac Cardiovasc Surg*. 2009 Feb;137(2):286-294.

Imaging Native Valve Anatomy

Congenitally abnormal valves can easily be diagnosed by imaging the number of the leaflets and the morphology of the valve opening in the short-axis view of the aortic valve. The most common congenital abnormality is the bicuspid aortic valve, occurring in 1% to 2% of the population[157] with a male: female prevalence ratio of 3.7:1. A number of classification systems have been proposed for congenitally bicuspid valves and are based on the fusion of cusps and orientation or number of the raphe.[158-160] Some of these classification systems then identified patients with no raphe as "pure" BAV or type 0.[160] A recent classification system identifies just two BAV phenotypes: fusion of the right and left coronary cusps (BAV-AP) and fusion of the right or left coronary cusp and noncoronary cusp (BAV-RL).[161] Morphology may provide valuable data regarding risk stratification of BAV patients.[161-163] Kang et al showed in a population of 167 patients, that moderate to severe AS is more prevalent in patients with BAV-RL (66.2% vs 46.2% in BAV-AP; $P = 0.01$), while moderate to severe AR is more prevalent in BAV-AP (32.3% vs 6.8% in BAV-RL; $P < 0.0001$).[161] In addition, the association with BAV and dilatation of the ascending aorta has been well established.[164-166] In patients with good-quality transthoracic images who do not have dense BAV calcification, diagnostic sensitivity and specificity for identifying valve phenotypes are > 70% and > 90%, respectively. However, diagnostic uncertainty may remain in 10% to 15% of patients after echocardiogram,[167] and diagnostic and phenotyping accuracy can be significantly improved with the use of higher-resolution imaging techniques such as transesophageal echocardiography (TEE) and three-dimensional (3D) imaging.[168-172]

In trileaflet aortic valves, an understanding of the mechanism responsible for AR is essential in determining the reparability of the valve. Several functional classifications have been used. Adaptation of the Carpentier classification originally designed for the mitral valve[173] has been described for AR[174] and can be used to guide the repair technique and to predict recurrence of AR.[175] Similar to the mitral valve, this scheme classifies dysfunction based on the leaflet morphology (Fig. 47–10). Type 1 morphology is associated with normal leaflet motion and can be subcategorized based on the exact pathology of either the aortic root or valve. Type Ia AR (Fig. 47–11A) occurs in the setting of sinotubular junction (STJ) enlargement and dilatation of the ascending aorta. Type Ib is a result of dilatation of the sinuses of Valsalva and the STJ, type Ic is a result of dilatation of the ventriculoarterial junction (ie, the annulus), and type Id results from cusp perforation or fenestration without a primary functional aortic annular lesion. Type II is associated with excessive leaflet motion from leaflet prolapse as a result of either excessive leaflet tissue or commissural disruption (Fig. 47–11B). Type III is associated with restricted leaflet motion seen with congenitally abnormal valves, degenerative calcification, or any other cause of thickening/fibrosis or calcification of the valve leaflets (Fig. 47–11C)

Because two-dimensional echocardiography may not be sufficient to completely characterize or quantify the mechanism of AR, transesophageal echocardiography (TEE) may improve diagnostic accuracy. Understanding leaflet as well as aortic root morphology is essential in the preprocedural planning for surgical repair and likely more important in the planning of transcatheter repair or replacement devices when they are approved for treating AR. Intraoperative TEE accurately identifies AR etiology, and this functional anatomy is strongly and independently predictive of valve reparability and postoperative outcome.[176]

Imaging Native Valvular Hemodynamics

Cineangiographic Assessment Cineangiographic assessment of AR relies on the relative density of contrast media in the LV versus the aorta[177] and is highly subjective and dependent on observer's experience as well as the numerous technical factors—including the intensity of fluoroscopy, the use of single or biplane imaging, the volume of the contrast medium injected, and type and position of the catheter tip—which result in significant variability in grading.[178]

Sellers and associates interpreted the cineangiogram using a single projection and injecting 35 to 40 mL of 75% Hypaque. Although biplane techniques may increase the accuracy of angiographic grading, this technique remains highly subjective but has the advantage of directly imaging flow instead of flow velocity used in color-flow Doppler examination.

Echocardiographic Assessment

Color-Flow Doppler Diastolic flow from the aorta into the LV imaged by color-flow Doppler is the sonographic hallmark of AR.[179,180] Although the apical approach is the most sensitive for detection, color-Doppler jets from this view are frequently eccentrically directed, constrained by

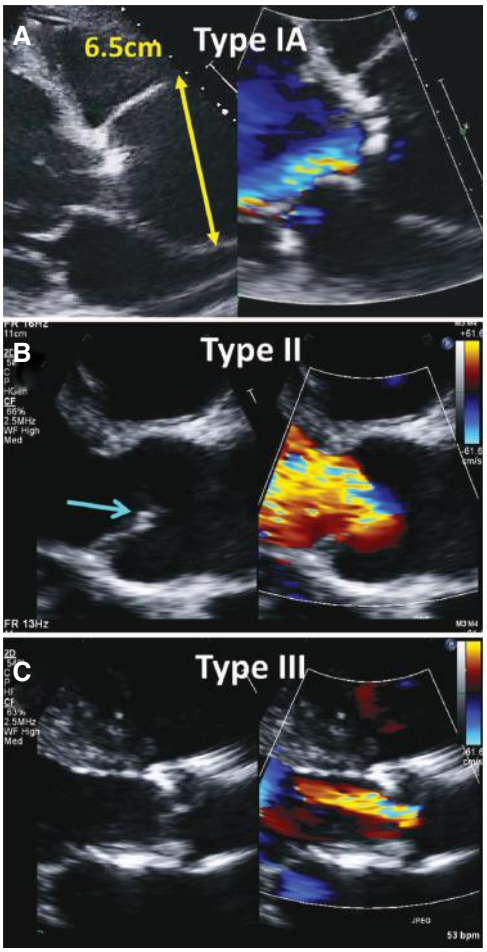


FIGURE 47–11. Echocardiographic examples of aortic regurgitation morphology. **A.** Type IA regurgitation results from marked dilatation of the sinuses of Valsalva and proximal ascending aorta (*yellow arrow*) with relative sparing of the annulus. **B.** Type II is associated with excessive leaflet motion from leaflet prolapse (*blue arrow*) as a result of either excessive leaflet tissue or commissural disruption. **C.** Type III is associated with restricted leaflet motion seen with degenerative calcification.

the LVOT, or entrained within the LVOT, leading to rapid jet broadening. Jet length is dependent on the diastolic aortic pressure but also on ventricular diastolic function. Thus unlike mitral regurgitation, jet length or area from the apical windows is not used for assessing severity of aortic regurgitation. The parasternal long and short axis views are essential in evaluating the origin of the jet and its semi-quantitative characteristics. It is important to visualize the three components of the color jet (flow convergence, vena contracta, and jet area) for a better assessment of the origin and direction of the jet and its overall severity (Fig. 47–12).

The width of the AR jet (JW) compared to the LVOT diameter in centrally directed jets can be used to assess the severity of regurgitation semi-quantitatively. This ratio is obtained in the parasternal long-axis view, within 1 cm of the aortic valve (and just beyond the vena contracta). A ratio < 25% generally indicates mild, 25% to 64% moderate, and ≥ 65% severe AR. Similarly, a ratio of the area of the jet in cross-section (short-axis view) to LVOT area is a measure of AR severity (Table 47–3). In the setting of eccentric or multiple jets, these measurements are not valid.

The vena contracta (VC) is the narrowest portion of the color Doppler jet at or just distal to the anatomic regurgitant orifice. If well-imaged, the VC of both eccentric and central jets can be measured. A VC < 0.3 cm indicates mild, 0.3 to 0.6 cm moderate, and > 0.6 cm

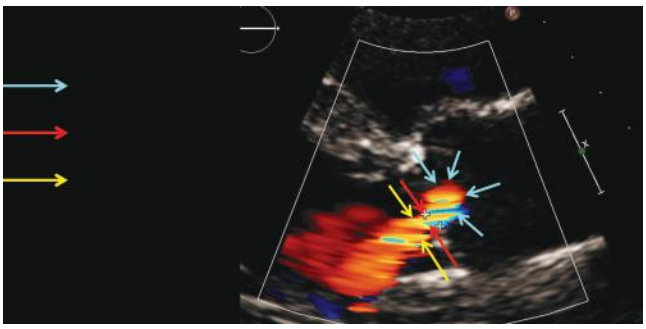


FIGURE 47–12. Three components of the aortic regurgitant jet. Optimizing imaging of the three components of the aortic regurgitant jet is necessary for accurate assessment of regurgitant severity. The presence of a proximal flow convergence (*blue arrows*) usually indicates at least mild disease. The vena contract (*red arrows*) represents the narrowest portion of the regurgitant jet. The jet height within 1 cm of the vena contracta and within the left ventricular outflow tract (*yellow arrows*) can also be measured; however, the jet area within the left ventricle is not an accurate measure of severity (see text).

severe AR and can be assessed by either TTE or TEE.[181] Of the semi-quantitative methods of assessing AR, a vena contracta > 0.6 cm has a sensitivity, specificity, and positive and negative predictive values of 81%, 83%, 78%, and 85%, respectively.[182]

Proximal flow convergence can be used both qualitatively and quantitatively for evaluation of AR severity. Zoomed views of the LVOT in either the parasternal or apical long axis are the best windows to record the proximal flow convergence, with a baseline shift of the Nyquist limit in the direction of the jet to measure the flow convergence radius. Using this radius in the calculation of the proximal isovelocity surface area (PISA) that assumes a hemisphere shape, flow (mL/s) is calculated as the product of the PISA and the aliasing velocity. Measurement of the AR peak velocity and velocity time integral by CW Doppler allows calculation of the regurgitant orifice area and regurgitant volume with EROA ≥ 0.30 cm^2 and regurgitant volume > 60 mL (Table 47–3) consistent with severe disease.[26]

Pulsed-Wave Doppler Diastolic reversal of flow in the aorta in the setting of a normal aorta valve is typically early and brief. Holodiastolic reversal of flow within the descending aorta detected by pulsed-wave Doppler is an abnormal finding typically consistent with at least moderate (present in the proximal descending aorta) or severe (present in the abdominal aorta) AR. However, in the absence of AR, holodiastolic retrograde aortic flow can also be seen most commonly in hypertensive patients with reduced aortic compliance[183] but also in other conditions such as a left-to-right shunt across a patent ductus arteriosus, upper extremity arterio-venous fistula, a ruptured sinus of Valsalva, or aortic dissection with diastolic flow into the false lumen. It is thus important to assess diastolic flow reversal in the context of these possible confounders.

Quantitation of flow with pulsed-wave Doppler for the assessment of AR is based on comparison of measurements of aortic stroke volume at the LVOT with mitral or pulmonic stroke volume. Unlike the PISA method, which first calculates the EROA and then derives the regurgitant volume, the quantitative method first calculates regurgitant volume (Fig. 47–13) and then derives the EROA by dividing the regurgitant volume by the AR velocity time integral. The difference between these two methods is significant. PISA-based quantitation relies on a single measurement of radius in early diastole (at the same time as the measurement of peak AR velocity); thus noncircular, dynamic, or multiple jets may not be accurately assessed.[184] Quantitative Doppler measures the total systolic stroke volume of the LVOT and subtracts the forward stroke volume at either the pulmonic or mitral valve

TABLE 47–3. Classification of AR Severity

Parameter	Mild	Moderate		Severe
Valve Anatomy				
	Mild to Moderate • Calcification of a tri-leaflet valve • Bicuspid aortic valve (or other congenital valve anomaly) • Dilated aortic sinuses • Rheumatic valve changes • Previous IE			• Calcific aortic valve disease • Bicuspid valve (or other congenital abnormality) • Dilated aortic sinuses or ascending aorta • Rheumatic valve changes • IE with abnormal leaflet closure or perforation
Qualitative				
Jet density (CW Doppler)	Incomplete/faint	Dense		Dense
Jet deceleration (PHT by CW))	Slow > 500	Medium 500–200		Steep < 200
Reversal of PW flow (Desc Ao)	Brief, early diastolic reversal	Intermediate		Prominent holodiastolic rev (> 20 cm/s)
Semi-quantitative				
Vena contracta	< 0.3	0.3–0.60		> 0.60
Jet width/LVOT width (%)	< 25	25–45	46–64	≥ 65
Jet area/LVOT CSA (%)	< 5	5–20	21–59	≥ 60
Quantitative				
Regurgitant volume (mL/beat)	< 30	30–44	45–59	≥ 60
Regurgitant fraction (%)	< 30	30–39	40–49	≥ 50
EROA (cm^2)	< 0.10	0.10–0.19	0.20–0.29	≥ 0.30

(assuming no mitral or pulmonic regurgitation). This method is valid in the setting of noncircular, dynamic, or multiple jets; however, the errors inherent in the measurement of diameters (particularly of the right ventricular outflow tract and mitral annulus) and the assumptions of a circular area used for each stroke volume calculation may also reduce the accuracy of this method. The use of 3D echocardiography may improve the quantitation of AR.[184]

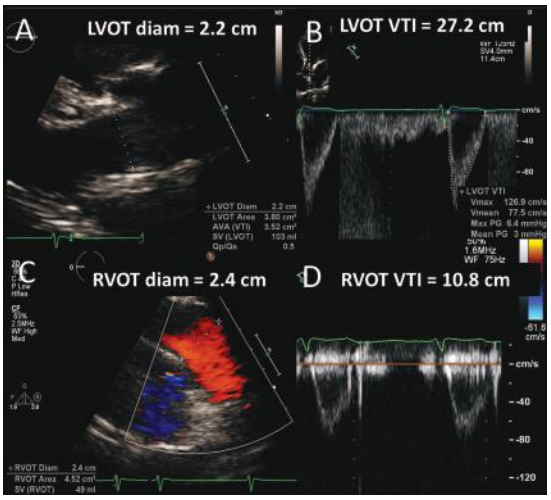


FIGURE 47–13. Quantitative Doppler measurements. To quantify the regurgitant volume, the total systolic stroke volume of the LVOT is calculated by measuring the LVOT diameter and calculating the area using a circular formula (**A**), then multiplying this area by the LVOT velocity time integral (VTI) (**B**). The LVOT stroke volume in this case is 103 mL, and represents the sum of the forward stroke volume and the regurgitant volume. The RVOT stroke volume is then calculated using the RVOT diameter (**C**) and RVOT VTI (**D**), resulting is a forward stroke volume of 49 mL. Subtracting the forward stroke volume from the total stroke volume results in a regurgitant volume of 54 mL.

Continuous-Wave Doppler Accurate assessment of AR severity using continuous-wave Doppler relies on aligning the regurgitant jet parallel to the insonation beam. Thus any window that can accomplish this throughout diastole will result in a measurable spectral profile. Unfortunately, most AR jets are curvilinear, either caused by the eccentricity of the jet at the leaflet level or because of the shape of the left ventricular outflow tract. Thus use of continuous-wave Doppler has significant limitations.

The density of the CW Doppler signal reflects the volume of regurgitation, particularly when compared to the density of the forward flow. A faint or incomplete jet indicates mild or trace regurgitation, while a dense jet may be compatible with more significant regurgitation but cannot differentiate between moderate and severe AR.

Measuring the pressure half-time of the AR spectral Doppler slope can be an indicator of severity. A steep slope indicates a more rapid equalization of pressures between the aorta and LV during diastole. A pressure half-time > 500 ms suggests mild AR, and < 200 ms severe AR. However, because this parameter is affected by the compliance of the LV, patients with severe chronic regurgitation with well-compensated ventricular function may have a pressure half-time in the "moderate" range. In contrast, mild AR in patients with severe diastolic dysfunction may have short pressure half-time.

Cardiac Magnetic Resonance Imaging CMR imaging provides accurate measures of regurgitant volume and regurgitant fraction in patients with AR, as well as assessment of aortic morphology, LV volume, and LV systolic function. In addition to its value in patients with suboptimal echocardiographic data, CMR is useful for evaluating patients in whom there is discordance between clinical assessment and severity of AR by echocardiography.

Exercise Testing Exercise stress testing is helpful in confirming the presence or absence of symptoms and in assessing objective exercise capacity and symptom status in patients with equivocal symptoms.

Although adding stress imaging is of uncertain value, if exercise imaging is performed, attention should be focused on LV ejection fraction at exercise. Failure to reduce end-systolic volume or increase the ejection fraction at exercise was specific for predicting LV dysfunction at follow-up.[185] The absence of contractile reserve evidenced by a decrease in LV ejection fraction by 5% at exercise may identify the presence of latent LV dysfunction earlier than conventional echocardiographic parameters obtained at rest. Park and colleagues[186] reported a significant discordance between the presence of contractile reserve and the guidelines-recommended LV dimension criteria for aortic valve replacement. In their study, one-third of patients with larger dimensions were contractile reserve (+), whereas one-third of patients with smaller LV dimensions not qualifying for surgery did not have contractile reserve, suggesting that exercise testing may be able to further stratify the current guidelines for aortic valve replacement. However, the extreme changes in loading that occur in AR during exercise make changes in these load-dependent variables difficult to use in assessing contractility. Thus the utility of imaging of LV function during exercise remains controversial.

Strain Imaging Cardiac mechanics can now be partially assessed with the use of both tissue Doppler and speckle tracking for the measurement of myocardial displacement.[187] The strengths and weaknesses of strain measurement have been well described, and results must be interpreted in the context of loading; prospective studies of adult patients have shown that strain parameters by speckle tracking could detect early myocardial systolic and diastolic dysfunction. Lower strain values were associated with disease progression in medically managed patients, or impaired outcomes in surgically treated patients,[188] and a systolic radial strain rate < 1.82/s was a good predictor of postoperative left ventricular dysfunction.[189] In a prospective study, 60 patients with chronic aortic regurgitation were followed for 64 months and global longitudinal strain (four-chamber view only) was an independent predictor of mortality (hazards ratio 1.313, 95% CI 1.010-1.706, $P = 0.042$).[190] Adding to these findings, Kusonose et al prospectively followed 159 consecutive patients with asymptomatic aortic regurgitation with no guidelines -recommended indications for intervention.[191] In the 30 ± 21 months of follow-up, 31% of patients underwent aortic valve replacement. In multivariate analysis, resting LV strain, resting RV strain, and exercise tricuspid annular plane systolic excursion (TAPSE) were independently associated with the need for earlier aortic surgery.

CARDIAC CATHETERIZATION

Noninvasive imaging is almost always adequate to resolve management issues regarding AR. However, invasive pressure measurement may be useful to confirm that elevated filling pressure and reduced cardiac output are the cause of the patient's symptoms. Further clarification may be achieved by hemodynamic observation during exercise and by performing aortography when done by an experienced operator using at least 60 mL of radiographic contrast.

MEDICAL THERAPY

As with AS, AR is a mechanical problem that requires a mechanical solution. Because afterload is often excessive in AR, there have been attempts to lower afterload using ACE inhibitors, direct vasodilators, or dihyropyridine calcium channel blockers in hope of forestalling the need for AVR. These efforts have met with confusing and contradictory results, such that no clear recommendation can be made about their usage.[192-194] However, hypertension, if present, must be treated as is indicated. If heart failure has already ensued, it should be treated with guideline-driven therapy. Although there is concern about the use of beta-blockers that might lengthen diastole, thereby increasing AR, it appears that such therapy is safe.[195]

TIMING OF SURGERY

As with all valve disease, the onset of symptoms represents a negative demarcation in the natural history of the disease and symptom onset is a clear indication of surgical intervention.[196] However, some patients develop LV dysfunction without having or noticing symptom onset. To avoid persistent postoperative LV dysfunction, AVR should occur before EF declines to 50% to 55% or before LV end-diastolic dimension increases to 50 to 55 mm.[197,198] Surveillance for LV dysfunction using these parameters requires periodic echocardiography, every 1 to 2 years depending on disease severity and the initial amount of LV dilatation.

SURGICAL OPTIONS

When aortic root pathology is the cause of AR or when there is excess tissue leading to leaflet prolapse, it may be possible to preserve or repair the native aortic valve, sparing the patient risks inherent in valve prostheses.[199] However, in most cases AVR is standard therapy. Because TAVR relies on native valve calcification to hold the TAVR in place, TAVR is not widely used in treating AR, although newer valve designs may overcome this problem.

ACUTE AORTIC REGURGITATION

Acute severe AR presents with much more subtle cardiac findings than does chronic severe AR, yet its consequences are much more deadly, so it is treated here as a separate entity form chronic AR.

ETIOLOGY

The most common etiologies of acute aortic regurgitation (AR) are bacterial endocarditis, aortic dissection, or blunt chest trauma.[200] Other less common causes of acute AR include nonbacterial endocarditis,[201,202] spontaneous aortic tears,[204] spontaneous rupture of leaflet fenestrations,[205] and complications of invasive procedures such as aortic valvuloplasty[206] and percutaneous balloon dilatation of aortic coarctation.[207] Fortunately, acute AR, which has a poor prognosis, is rare.

PATHOPHYSIOLOGY AND RELATIONSHIP WITH SYMPTOMS

Unlike chronic AR, in which the left ventricle adapts to the volume load and remodels to increase forward stroke volume, acute aortic regurgitation results in an acute increase in preload, resulting in the left ventricle operating on the less compliant portion of the pressure-volume curve, resulting in rapid development of symptoms. End-diastolic pressure rises, effective stroke volume falls, heart rate increases to maintain cardiac output, and peripheral vascular resistance increases to maintain systemic arterial pressure. High left ventricular end-diastolic pressures may exceed left atrial pressure in late diastole, causing premature closing of the mitral valve. In addition, opening of the mitral valve may be delayed because of prolonged systolic ejection in the setting of greater ventricular volume. Although reduced mitral valve opening results in elevated left atrial pressures, the high LV diastolic pressure is not transmitted to the left atrium if the mitral valve is competent.

Patients with acute severe AR present with symptoms of congestive heart failure, which can often be timed to the onset of the AR. The history may help with the diagnosis: fevers and chills or an infectious process

point to acute infectious endocarditis, whereas acute chest pain radiating to the back suggests an acute aortic dissection. However, rapidly developing pulmonary edema may dominate the clinical picture and the physical exam and echocardiogram may be the only clues to the diagnosis.

PHYSICAL EXAM

Patients with acute severe AR appear acutely ill with evidence for low cardiac output and systemic vasoconstriction: pale, cool distal extremities, peripheral cyanosis, and tachycardia with a reduced peripheral pulse. A wide pulse pressure is not seen, as a result of a combination of high LV filling pressure and significant vasoconstriction, limiting peripheral runoff. Although a number of eponyms have been attributed to severe aortic regurgitation, most occur in chronic disease, because they are predicated upon a large total stroke volume and widened pulse pressure, which are usually absent in acute AR.

The jugular venous pulse responds to the rise in right ventricular filling pressure in the presence of biventricular failure. The mean pressure (superficial jugular vein) and the crests of the A- and V-waves (deep jugular) increase. In contrast to chronic severe aortic regurgitation, the dominant pulsations in the neck are venous, not arterial. Precordial movement and palpation reveal a relatively unsustained left ventricular impulse that is neither hyperdynamic nor significantly displaced to the left, because the velocity of left ventricular contraction is not rapid and left ventricular end-diastolic dimensions are not conspicuously increased. Thus, cardiac contraction does not impart a rocking motion to the chest.

Auscultation

The murmur of acute AR is short and soft, because a rapid rise in LV diastolic pressure attenuates the gradient between aorta and LV that drives the murmur. Particular attention should be paid to S1. A soft S1 may indicate mitral preclosure or first-degree AV block—the first a sign of life-threatening severe AR and the second a possible sign of a ring abscess affecting the conducting system.

DIAGNOSIS

Echocardiographic findings of acute AR include premature mitral valve closure and fluttering of the mitral valve leaflets, most effectively demonstrated using M-mode echocardiography. The duration of the regurgitant jet in acute AR may be short, making the diagnosis difficult with color Doppler. Continuous-wave Doppler of the regurgitant jet usually demonstrates a markedly shortened pressure half-time. Depending on the etiology of the AR, aortic root abnormalities may also be present, including aortic dissection or aneurysm.

TIMING OF SURGERY

In acute AR, immediate surgical intervention is necessary because the acute volume overload results in life-threatening hypotension and pulmonary edema.[207] Vasodilator therapy with sodium nitroprusside may stabilize the patient during transport to the operating department. Aortic balloon counterpulsation is contraindicated because it worsens AR. Beta-blockers should be avoided in acute AR because they prolong diastole and may worsen AR. Atrial pacing to increase heart rate might be of theoretical benefit[208]; however, this does not have an established role in clinical practice. Several studies have demonstrated that emergency aortic valve replacement can be performed with low operative mortality and good long-term results in acute AR. In the setting of active infective endocarditis, however, the outcomes are not as good, with an operative mortality or in-house mortality of 15% to 24% if surgery was performed in the active phase.[209,210]

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CHAPTER 48

DEGENERATIVE MITRAL VALVE DISEASE

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The normal mitral valve permits one-way blood flow from the left atrium to the left ventricle in an efficient, nearly frictionless fashion.[1] Although even a normal competent valve may allow a trivial amount of reversed flow, more than a trace of mitral regurgitation is considered pathologic.[2] Mild to moderate mitral regurgitation is tolerated indefinitely as long as it does not worsen. However, severe mitral regurgitation causes left ventricular remodeling reduced forward cardiac output, neurohumoral activation, left ventricular damage, heart failure, and ultimately death.[3] The natural history of mitral regurgitation depends intimately on its etiology, the severity of left ventricular volume overload as well as its contractile performance, and the appearance of overlapping clinical conditions secondary to reversal flow such as atrial fibrillation and pulmonary hypertension.[4] In this setting, myxomatous degeneration of the mitral valve, a very common pathologic substrate of mitral valve billowing (normal valve coaptation) and prolapse (deficient valve coaptation), is the most prevalent cause of isolated severe mitral regurgitation requiring surgical intervention in the United States.[5] The following is a review of the normal mitral valve anatomy as well as a summary of causes, consequences, and treatment of degenerative mitral valve regurgitation.

MITRAL VALVE ANATOMY

The mitral valve is located in the left atrioventricular groove, and allows unidirectional flow of oxygenated blood from the left atrium into the relaxed left ventricle during diastole. The mitral valve apparatus is a very complex three-dimensional assembly of separate anatomical components including the annulus, the leaflets and commissures, the chordae, the papillary muscles, and the ventricle.[6] During systole, a coordinated interaction of these anatomical components closes the valve against ventricular pressure. Therefore, its anatomy should be scrutinized systematically to identify the lesions (the abnormalities in valve structure) that lead to the valve's dysfunction (the alteration in closure that results in mitral regurgitation).[7]

MITRAL ANNULUS

The mitral annulus is a fibromuscular ring located in the left atrioventricular groove, which serves as an attachment and hinge point for the mitral valve leaflets. The mitral annulus is subjectively divided into anterior and posterior segments based on the attachments of the anterior and posterior mitral leaflets, but can also be segmented by location into septal and lateral components. The anterior portion of the mitral annulus is in continuity with the fibrous skeleton of the heart, defined by the right and left fibrous trigones and the aortic mitral curtain. This portion of the mitral annulus is thus fibrous in nature, and is much less prone to dilation in comparison to the posterior portion of the annulus (Fig. 48–1). Because the fibrous skeleton is discontinuous along the posterior portion of the mitral annulus, this portion dilates or increases its circumference in the setting of chronic mitral valve regurgitation with associated atrial and ventricular dilatation.[8] The resultant increase in mitral annular dimension tends make the annulus more circular in shape, compared to its normal "kidney-bean shape," which in turn compromises the coaptation of the mitral leaflets as a result of the increase in septal-lateral or anterior-posterior dimension. The hinge point of the posterior portion of the mitral annulus may become "atrialized" in long-standing posterior leaflet prolapse, and may also be affected by diffuse pathologic calcification. The normal mitral annulus also has a three-dimensional saddle shape, and the anterior portion of the annulus tends to bulge during systole to accommodate the aortic root. The overall circumference of the annulus may decrease by as much as 20% during systole, promoting central leaflet coaptation.[9]

MITRAL LEAFLETS AND COMMISSURES

The mitral valve has an anterior and posterior leaflet with similar surface areas but markedly different shapes.[10] The anterior leaflet is

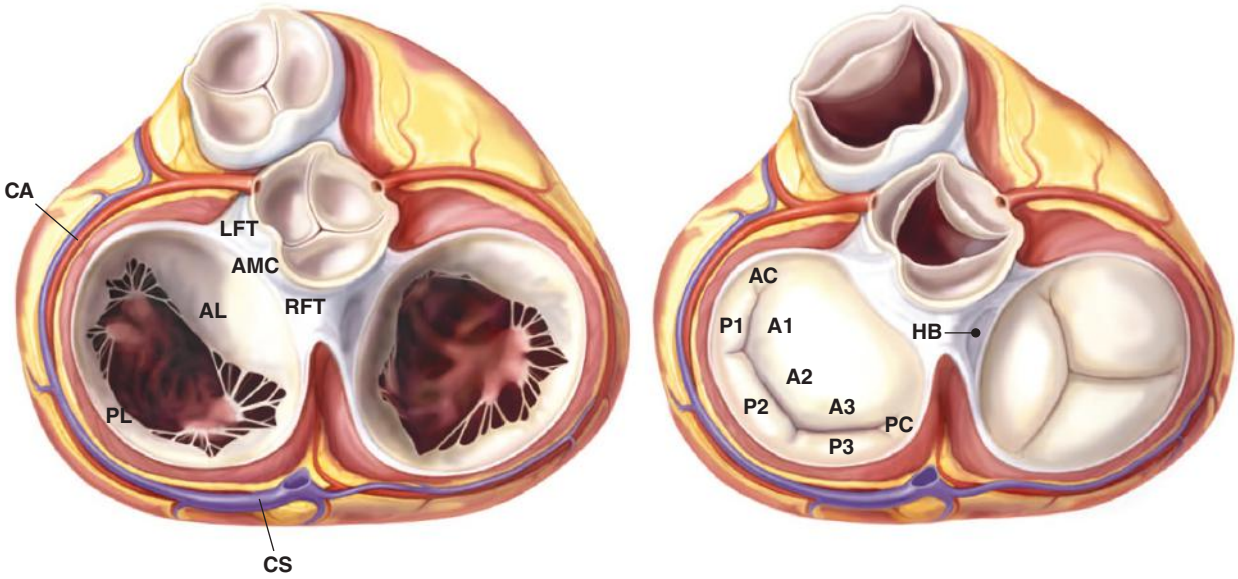

FIGURE 48–1. Anatomic view of the cardiac valves in diastole (*left*) and systole (*right*) with the left and right atrium cropped away and the great vessels transected. The illustration highlights the anatomical relations of the mitral valve, particularly its continuation with the aortic valve through the aorto-mitral curtain. AC, anterior commissure; AL, anterior leaflet; AMC, aorto-mitral curtain; CA, circumflex artery; CS, coronary sinus; HB, Hiss bundle; LFT, left fibrous trigone (anterolateral trigone); PC, posterior commissure; PL, posterior leaflet; RFT, right fibrous trigone (posteromedial). Modified with permission from Carpentier AC, Adams DH, Filsoufi F: *Carpentier's Reconstructive Valve Surgery*. St. Louis: Saunders/Elsevier; 2010.

taller than the posterior leaflet but with a shorter base, attaching to one-third of the annular circumference between the right and left fibrous trigones. During systole the anterior leaflet forms a portion of the left ventricular outflow tract through its continuity with the aorto-mitral curtain. The posterior leaflet is broader based, extending along the remaining two-thirds of the annulus, and has a shorter height. Despite their different shapes, the overall surface areas of the two leaflets are similar. The different orientations of the two leaflets ensures during systole the closure line of the mitral valve will be located in the posterior one-third of the valve orifice, which prevents systolic anterior motion of the tip of the anterior leaflet in into the outflow track. Both leaflets present two zones from its base to the free margin: *the body zone* (smooth and translucent) and the *coaptation zone* (thicker and rough as a result of the attachment of numerous chordae). During systole the coaptation zones of the respective leaflets join together to form a seal anywhere from a few millimeters to a centimeter, ensuring mitral valve competence (Fig. 48–2). The leaflets of the mitral valve can be "segmented" by location of the clefts or indentations in the posterior leaflet that subdivide it into individual "scallops." The middle scallop of the posterior leaflet is designated as P2 and adjacent lateral and medial scallops are designated as P1 or P3 (See Fig. 48–1). The anterior leaflet does not typically have natural indentations, but the corresponding areas of this leaflet are designated by opposition to the segments in the posterior leaflet as A1, A2, and A3.

In addition to anterior and posterior leaflet segments, the mitral valve has posterior medial and anterior lateral commissures, which represent small segments of leaflet tissue presenting at the insertional junction of the anterior and posterior leaflets. These distinct areas of leaflet tissue are supported by chordal fans, and are critical to insure a good surface of coaptation at the junctions of the two leaflets. The height of commissural leaflet tissue can vary from a few millimeters to over 1 cm.

CHORDAE TENDINAE

The chordae tendinae attach the mitral leaflets to the papillary muscles and left ventricle, creating a suspension system that allows full opening

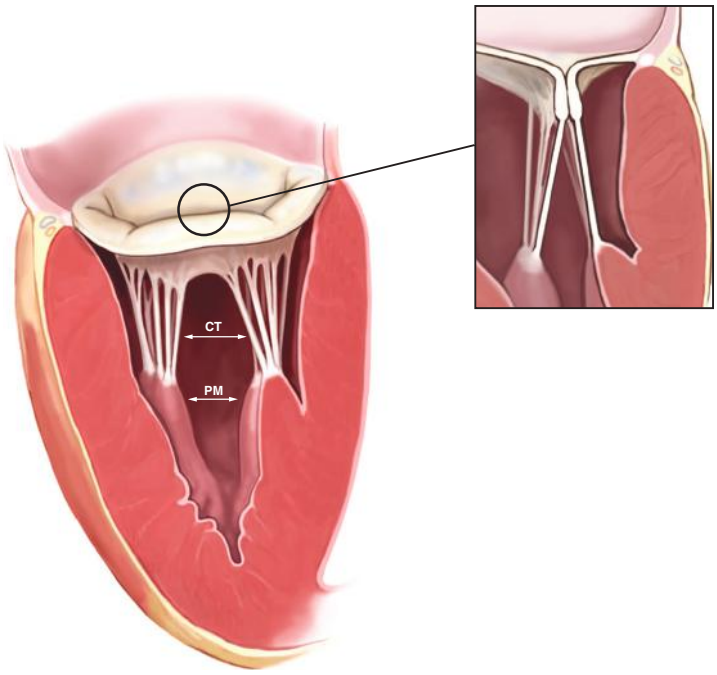

FIGURE 48–2. The mitral valve apparatus consists of the mitral leaflets, mitral annulus, chordae tendinae, papillary muscles, and left ventricle. Normal function of the mitral apparatus brings both leaflets together in systole and creates the coaptation zone. CT, chordae tendinae; PM, papillary muscles. Modified with permission from Carpentier AC, Adams DH, Filsoufi F: *Carpentier's Reconstructive Valve Surgery*. St. Louis: Saunders/Elsevier; 2010.

of the leaflets during diastole and prevents displacement of the leaflets above the annular plane during systole. Chordae tendinae are classified according to their attachment between the free margin and the base of the leaflets.[11] Primary or marginal chordae attach along the margin of the leaflets and are critical to prevent leaflet prolapse and to align the rough zones of the anterior and posterior leaflets during systole. Typically primary chordae insert every 3 to 5 mm along the margin of both leaflets. Secondary or body chordae, attach to the ventricular side of the body of the leaflets, provide ventricular annular continuity and balance of leaflet tension during systole. Tertiary or basal chordae, attached to the base of the leaflet hinge, providing additional linkage to the ventricle.[12]

PAPILLARY MUSCLES AND THE LEFT VENTRICLE

The mitral valve leaflets are attached by the chordae tendinae to the papillary muscles, which are a part of the left ventricle. The papillary muscles vary in the number of heads and exact position in the ventricle, but generally there are two main groups comprising the anterior and posterior papillary muscles. Each papillary muscle is identified according to the relationship to the valve commissures, and each provides a fan chord to its corresponding commissure as well as to both anterior and posterior leaflets. The anterior papillary muscle's blood supply can originate from both the left anterior descending artery as well as the circumflex artery, whereas the posterior papillary muscle is dependent primarily on the posterior descending artery. This explains the relative vulnerability of the posterior papillary muscle to ischemia, and subsequent involvement in localized remodeling in the setting of ischemic mitral valve regurgitation. The left ventricle supports the entire mitral apparatus by way of the papillary muscles, and thus ventricular dimensional changes in the setting of volume overload and remodeling can lead to leaflet tethering and mitral valve regurgitation irrespective of etiology.[13] This important relationship of volume overload and remodeling to mitral valve dysfunction has led to the common observation that "mitral regurgitation begets mitral regurgitation."

DEGENERATIVE MITRAL VALVE REGURGITATION

DYSFUNCTION

It is important to clarify the etiology and lesions that lead to clinically significant mitral valve regurgitation, as treatment options and long-term outcomes vary in different clinical scenarios. It is also useful to identify the valve dysfunction that results from the lesions of the mitral valve apparatus. The main dysfunctions, lesions, and etiologies that can result in mitral valve regurgitation are listed in Fig. 48–3. Carpentier described this pathophysiologic triad, and it is a useful tool in everyday practice when assessing patients with mitral valve regurgitation.[7]

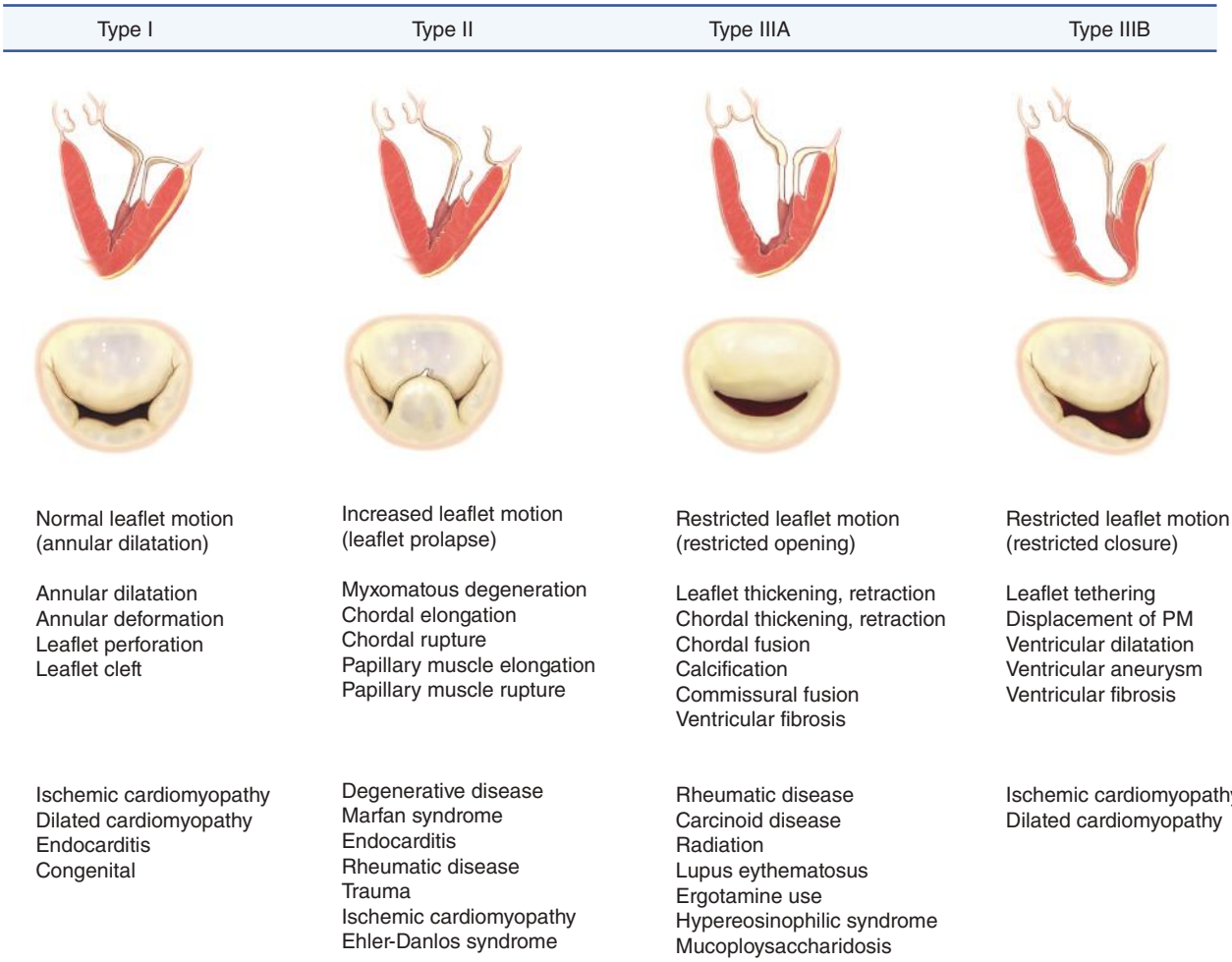

FIGURE 48–3. Pathophysiologic triad of mitral valve regurgitation composed of (top to bottom of each column): ventricular view, atrial view, leaflet dysfunction, valve lesions, and etiology.

Dysfunctions are classified on the basis of the position of the leaflet margins in relationship to the plane of the mitral annulus. Type I dysfunction implies normal leaflet motion, is the most common cause of significant mitral valve regurgitation, and often results from isolated annular dilatation or leaflet perforation; the former is common in the setting of primary atrial fibrillation. Type II dysfunction implies excess leaflet motion, and is most commonly associated with chordal elongation or rupture in the setting of degenerative mitral valve disease. Type IIIA dysfunction designates restricted opening and closing leaflet motion, and results typically from rheumatic valve disease or other inflammatory diseases that lead to chordal and leaflet scarring and calcification. Type IIIB dysfunction is associated with restricted leaflet motion in systole, and is most commonly associated with papillary muscle displacement and associated leaflet tethering in the setting of ischemic or nonischemic dilated cardiomyopathy. Some others have chosen to designate conditions associated with type I, II, and IIIA dysfunction as primary or organic mitral regurgitation, because the valve components (annulus, leaflets, and chords) are diseased, whereas type IIIB dysfunction is classified as secondary or functional mitral regurgitation, because it is caused by perturbations in ventricular geometry.[14]

ETIOLOGY AND LESIONS

Although rheumatic heart disease is still the most common cause of mitral regurgitation worldwide, it is no longer a common cause of mitral regurgitation in developed countries.[15] Ischemic mitral regurgitation resulting from myocardial infarction accounts for 10% to 20% of mitral regurgitation in developed countries, but earlier intervention in acute coronary syndromes may be limiting the number of such cases in the future.[16] In developed countries, degenerative mitral valve disease is now the leading cause of mitral valve disease and regurgitation.[17] Degenerative mitral valve diseases is defined by a spectrum of lesions, varying from simple chordal rupture involving prolapse of an isolated segment (particularly P2 or the middle scallop of the posterior leaflet) in an otherwise normal valve, to multisegment prolapse involving one or both leaflets in a valve with significant excess tissue and a large annular size (Fig. 48–4). This spectrum of degenerative disease is evident in clinical practice and carries important surgical and clinical implications. Furthermore, based on this spectrum of lesions, degenerative disease may be further divided into two main entities, fibroelastic deficiency and Barlow disease.[18-20] Other terms used to describe degenerative mitral valve disease include floppy valve syndrome, mitral valve prolapse, click-murmur syndrome, and parachute valve—a morass of terms causing much confusion. For instance, mitral valve prolapse can cause a click and murmur on physical examination, but the terms fail to clarify etiology.[21]

Fibroelastic deficiency usually occurs in patients over the age of 60 years[22] who have a relatively short history of valve disease, and their mitral regurgitation is usually holosystolic and severe. Fibroelastic deficiency describes a condition associated with fibrillin deficiency, which often leads to a rupture of one or more thinned and elongated chordae usually involving the middle scallop of the posterior leaflet. Chordal rupture is the most common lesion causing mitral regurgitation in fibroelastic deficiency. Leaflets are usually thin and translucent, although the prolapsing segment may show myxomatous degeneration with leaflet segment thickening and distension in long-standing regurgitation. The key characteristic of fibroelastic deficiency within the spectrum of degenerative disease is that the adjacent segments to

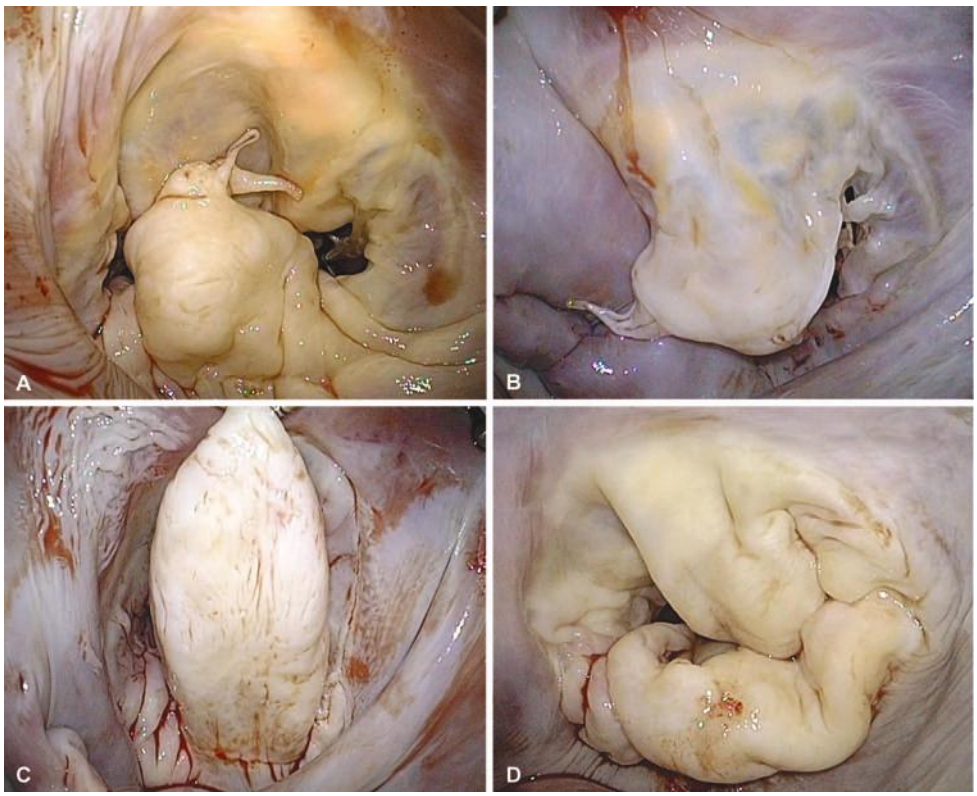

FIGURE 48–4. Valve lesions in degenerative mitral valve disease. **A.** Fibroelastic deficiency; isolated P2 prolapse secondary to chordal rupture and mild segmental thickening. **B.** Fibroelastic deficiency; anterior leaflet prolapse as a result of multiple ruptured chordae. **C.** Barlow disease; very tall and thickened P2 segment with otherwise normal P1 and P3 segments. **D.** Barlow disease; large valve with redundant, thick, bulky leaflets. Note the blurring of the junction between atrium and leaflet with fissures.

the prolapsing segment are generally normal in size, height, and character.[19,20,23] The valve annular size, as defined by anterior leaflet surface area, is generally ≤ 32 mm. In contrast, patients with Barlow disease are generally younger (< 60 years of age) at the time of surgical referral, an often present with long history of follow-up for a murmur. Barlow valve disease causes a more diffuse and complex redundancy of the valve, producing prolapse and myxomatous degeneration of multiple segments in one or both leaflets. The most common lesions are excess leaflet tissue, leaflet thickening, and distention, with diffuse chordal elongation, thickening, and/or rupture. Severe annular dilatation with giant valve size is evident (> 36 mm).[24] Additionally, varying degrees of annular calcification are often observed, as well as subvalvular fibrosis and calcification of the papillary muscles, in particular the anterior papillary muscle.[25] These extremes of the spectrum of lesions bracket a continuum of a more myxomatous form of fibroelastic deficiency and forme fruste disease, a term given to certain valves with some but not all pathologic features of Barlow disease (Fig. 48–5).

No specific cause of these lesions associated with abnormalities in the extracellular matrix, matrix metalloproteases, and subnormal leaflet and chordal strength has been identified (Fig. 48–6).[26] Some genetic abnormalities[27] have been described but no one genetic variation still fully explains the variation of pathology seen. It is likely that genetic abnormalities render the valve susceptible to the degenerative process and after mitral regurgitation develops it places progressively more hemodynamic stress on the valve perpetually worsening the disease. At present no useful strategies have emerged for preventing or slowing the progression of degenerative mitral regurgitation.

PATHOPHYSIOLOGY

Mitral regurgitation imparts a volume overload on the left ventricle because it must compensate for the volume lost to regurgitation. Mild to moderate mitral regurgitation is well tolerated, possibly for long periods of time, as long as the severity of mitral regurgitation does not increase. The grades of severity as suggested by the *AHA/ACC Guidelines for the Management of Valvular Heart Disease*[28] are listed in (Table 48–1). Although these are only guidelines, they stem in part from the fact that when regurgitant fraction has been calculated for patients requiring mitral valve surgery, the regurgitant fraction almost always exceeds 50%.

Severe mitral regurgitation can be subdivided into three stages: acute, chronic compensated, and chronic decompensated (Fig. 48–7). In acute mitral regurgitation as might occur from rupture of a marginal chordae tendinae, a small unprepared left ventricle is suddenly confronted with a large volume overload from blood returning from the pulmonary veins summed with the regurgitant volume from the left ventricle. The volume overload causes existing sarcomeres to stretch maximally, increasing end-diastolic volume and also stroke work through the Frank-Starling mechanism. The extra pathway for ejection into the left atrium unloads the left ventricle, reducing end-systolic volume. Increased

	Fibroelastic deficiency	Fibroelastic deficiency +	Forme fruste	Barlow's disease
Age at diagnosis	> 60 years old	Likely > 60 years old	Likely < 60 years old	< 60 years old
History of MR	< 5 years	Likely < 5 years	Likely > 10 years	> 10 years
Annular dilatation	≤ 26 mm	Likely ≤ 32 mm	Likely 32 mm - 36 mm	≥ 36 mm
Leaflet tissue	Thin, translucent ○ ○ ○	Translucent, mild thickening ● ○ ○	Moderate excess ● ● ○	Diffuse excess ● ● ●
Segmental distribution	Single segment (P2)	Single segment (P2)	Posterior segments	Multisegmental
Chordae tendinae	Thin, ruptured	Thin, ruptured	Elongated, ruptured	Irregular, elongated
Degree of calcification	○ ○ ○	○ ○ ○	● ○ ○	● ● ●
Repair phylosophy	Respect tissue	Likely respect tissue	Small resection	Resection
Difficulty of repair	● ● ○	○ ○ ○	● ○ ○	● ● ●
Repair techniques	Chordal transfer PTFE neochordoplasty Loop techniques	Leaflet displacement Free edge plication Loop techniques Triangular resection	Leaflet displacement Triangular resection Limited quadrangular Annular plication Limited sliding plasty Posterior leaflet flip	Leaflet displacement Targeted resections Cleft closure Quadrangular resection Sliding plasty Commissuroplasty Posterior leaflet flip

FIGURE 48–5. Characteristic clinical and surgical differences between fibroelastic deficiency and Barlow disease.

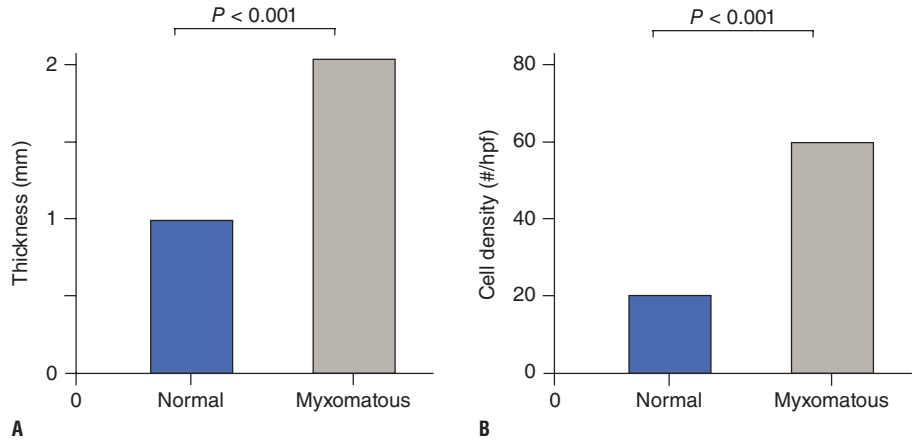

FIGURE 48–6. Quantitative analysis of mitral posterior leaflet tissue demonstrating significant thickening and increased cellularity of myxomatous valves. Data from Grande-Allen KJ, Griffin BP, Ratliff NB, et al. Glycosaminoglycan profiles of myxomatous mitral leaflets and chordae parallel the severity of mechanical alterations. *J Am Coll Cardiol*. 2003 Jul 16;42(2):271-277.

preload, decreased afterload and a reflexive sympathetically mediated increase in contractility act in concert to increase total stroke volume and ejection fraction. However, because 50% or more of the total stroke volume is regurgitated into the left atrium, forward stroke volume and cardiac output are reduced. Additionally, the left atrium, of normal size and compliance, receives its very high total volume at high filling pressure, in turn leading to pulmonary congestion. Thus although left ventricular function is normal or even supernormal, the patient suffers the low output and pulmonary congestion typical of left ventricular failure. Many patients will require immediate corrective surgery at the time acute severe mitral regurgitation develops. In others there may be a more gradual progression to severe mitral regurgitation so that it is better tolerated. Such patients may enter a chronic compensated phase. In this phase eccentric hypertrophy develops, increasing left ventricular volume. Because the radius term in the Laplace equation for wall stress has increased (stress $\sigma = p \times r / 2th$, where p = LV pressure, r = radius, and th = thickness), afterload returns from subnormal to normal. However, increased preload and normal contractility permit a higher than normal ejection fraction of a large end-diastolic volume so that total stroke volume is greatly increased.[29] This permits forward stroke volume to return to normal. Left atrial size

TABLE 48–1. Stages of Primary Mitral Regurgitation

Grade	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MR	• Mild mitral valve prolapse with normal coaptation • Mild valve thickening and leaflet restriction	• No MR jet or small central jet area < 20% LA on Doppler • Small vena contracta < 0.3 cm	• None	• None
B	Progressive MR	• Severe mitral valve prolapse with normal coaptation • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE	• Central jet MR 20%-40% LA or late systolic eccentric jet MR • Vena contracta < 0.7 cm • Regurgitant volume < 60 mL • Regurgitant fraction < 50% • ERO < 0.40 cm^2 • Angiographic grade 1-2+	• Mild LA enlargement • No LV enlargement • Normal pulmonary pressure	• None
C	Asymptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR > 40% LA or holosystolic eccentric jet MR • Vena contracta ≥ 0.7 cm • Regurgitant volume ≥ 60 mL • Regurgitant fraction ≥ 50% • ERO ≥ 0.40 cm^2 • Angiographic grade 3-4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension may be present at rest or with exercise • C1: LVEF > 60% and LVESD < 40 mm • C2: LVEF ≤ 60% and LVESD ≥ 40 mm	• None
D	Symptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR > 40% LA or holosystolic eccentric jet MR • Vena contracta ≥ 0.7 cm • Regurgitant volume ≥ 60 mL • Regurgitant fraction ≥ 50% • ERO ≥ 0.40 cm^2 • Angiographic grade 3-4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension present	• Decreased exercise tolerance • Exertional dyspnea

Abbreviations: ERO, effective regurgitant orifice; IE, infective endocarditis; LA, left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD; left ventricular end-systolic dimension; MR, mitral regurgitation.

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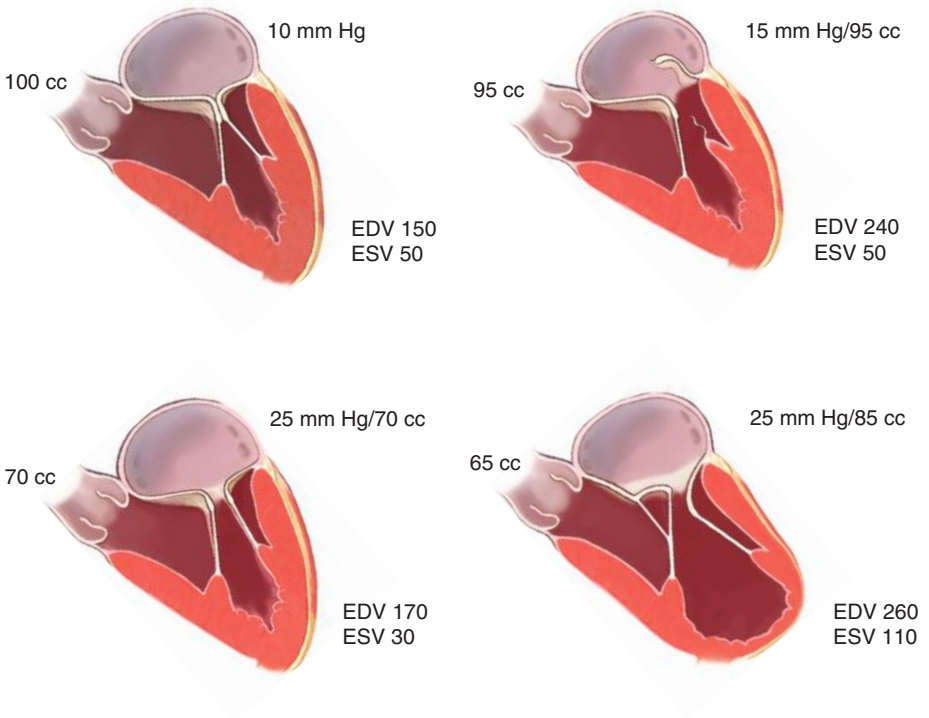

	Preload (SL)	Afterload (ESS)	Contractile function	Ejection fraction	Regurgitant fraction	Stroke volume (cc)
Control	2.07	90	N	0.67	0.0	100
Acute MR	2.25	60	N	0.82	0.5	70
Compensated MR	2.19	90	N	0.79	0.5	95
Decompensated MR	2.19	100		0.58	0.7	65

FIGURE 48–7. Normal physiology (control) is compared to that of acute mitral regurgitation (chordal rupture), compensated mitral regurgitation, and decompensated chronic mitral regurgitation. The sudden opening of a new pathway for regurgitant flow into the left atrium increases left atrial pressure and preload (sarcomere length), in turn mildly increasing end-diastolic volume because resting sarcomere length is still 90% of maximum length. Afterload (end-systolic stress) is decreased, allowing more complete left ventricular ejection fraction, reducing end-systolic volume. These changes in loading increase ejection fraction and total stroke volume, but because 50% of the total stroke volume is lost to regurgitation (regurgitant fraction), forward stroke volume is decreased. Therefore, despite normal contractile fraction and increased ejection fraction, the patient presents with the hemodynamics of congestive heart failure. In the presence of decompensated chronic mitral regurgitation, muscle damaged caused by prolonged severe volume overload reduces the effectiveness of ventricular ejection and end-systolic volume increases. There is a further increase in diastolic volume, which is not compensatory, resulting in a decrease in total and forward stroke volumes. EDV, end diastolic volume; ESS, end-systolic stress; ESV, end-systolic volume; MR, mitral regurgitation; SL, sarcomere length. Modified with permission from O'Gara P, Sugeng L, Lang R, et al: The role of imaging in chronic degenerative mitral regurgitation. *JACC Cardiovasc Imaging*. 2008 Mar;1(2):221-237.

is now enlarged, permitting it to accept the large regurgitant volume at nearly normal pressure. Thus the patient now has a near normal cardiac output and filling pressure and is likely to be asymptomatic even during exercise. Although the patient may enjoy a period of compensation for years, eventually contractile dysfunction sustained from prolonged hemodynamic overload ensues and decompensation becomes manifest.[30] Impaired contractility causes increased end-systolic volume and reduced stroke volume and cardiac output. Filling pressure is re-elevated and the patient may develop heart failure symptoms. Although mitral regurgitation is usually thought to be a phenomenon that unloads the left ventricle, in decompensated mitral regurgitation, the increased radius term in the Laplace equation causes systolic wall stress to increase and afterload is greater than normal, contributing to left ventricular dysfunction.[31] In mitral regurgitation, increased left ventricular radius is not offset by increased thickness, leading to the increase in wall stress. Thus the relatively thin wall of the mitral regurgitant ventricle is beneficial to diastolic function and left ventricular filling but is detrimental to left ventricular systolic function because maladaptive left ventricular remodeling causes increased afterload.[32,33] It is important to note that ejection fraction may be held in the normal range by enhanced preload despite contractile dysfunction and afterload excess.

The left ventricular dysfunction caused by severe mitral regurgitation stems from multiple pathologic processes. At the cellular level there is loss of contractile elements in the endocardium in experimental models of mitral regurgitation and in the papillary muscles of humans.[34,35] This abnormality can be reversed by valve repair/replacement in the experimental animal and in man and also by administration of beta-blockers in the experimental animal.[36-38] These data suggest that sympathetic overdrive, present in both human and experimental mitral regurgitation, contributes to the cellular pathology of the disease.[39,40] In addition, the force-frequency relation of the mitral regurgitant ventricle is depressed but can be normalized by the administration of forskolin, suggesting that abnormalities in calcium handling contributes to left ventricular dysfunction.[41]

The left ventricular remodeling of mitral regurgitation is unique and probably dictated by the loading conditions present. Mitral regurgitation stands out as a pure volume overload.[42] In most other volume overloads such as anemia, heart block, and aortic regurgitation, the extra volume generated by the left ventricle is ejected into the aorta, where the high stroke volume generates a widened pulse pressure and an element of systolic hypertension. Thus most volume overloads are in fact a combination of volume and pressure overload and the left ventricle remodels accordingly. In aortic regurgitation, for instance, not only is left ventricular volume increased to compensate for the regurgitated volume but left ventricular thickness is also greater than normal.[43] Conversely, in mitral regurgitation the extra volume is ejected into the left atrium and systolic pressure is often low normal. In turn, left ventricular thickness is low normal, producing a thin-walled large left ventricle as noted earlier.

Several decades ago Grossman and coworkers proposed a paradigm for left ventricular remodeling wherein the increased systolic wall stress of pressure overload was transduced to generate new sarcomeres laid down in parallel such that myocyte thickness and left ventricular wall thickness increased.[44] Increased wall thickness in the denominator of the Laplace equation offset increased pressure term in the numerator,

keeping wall stress (afterload) normal, facilitating left ventricular ejection. On the other hand, the increased diastolic stress from the sarcomere stretch of volume overload led to new sarcomeres laid down in series, increasing myocyte length and ventricular volume, allowing the ventricle to increase stroke volume. In experimental acute pressure overload, a 35% increase in contractile protein synthesis occurs within 6 hours of the onset of the pressure overload.[45] Conversely, following the acute volume overload of mitral regurgitation and during chronic mitral regurgitation, no increase in protein synthesis was detected.[46] Because increased muscle mass can only accrue from either increased protein synthesis or decreased protein degradation, and because synthesis is not increased, it suggests that the hypertrophy of mitral regurgitation develops from a process opposite of that of pressure overload, that is, decreased protein degradation instead of increased protein synthesis. It might be that older contractile proteins are less robust, a factor in part responsible for the left ventricular dysfunction that ultimately develops.

As noted earlier, if mitral regurgitation is corrected before left ventricular dysfunction is long standing, ventricular function can recover dramatically both in the experimental animal and in humans. Recovery is marked by restoration of myocyte contractile elements and a reduction in adrenergic drive.

In summary, the pure volume overload of mitral regurgitation is compensated by eccentric left ventricular hypertrophy, which enables rapid left ventricular diastolic filling and an increase in stroke volume. However, this remodeling eventually encumbers systolic emptying. This maladaptive geometry together with the adrenergic over activation results in contractile protein loss, abnormal calcium handling, and a decrease in contractility. If mitral regurgitation is corrected in a timely fashion this pathophysiology can be reversed.

CLINICAL PRESENTATION

The typical symptoms of mitral regurgitation are those of left ventricular failure and include dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. If pulmonary hypertension has developed, ascites and edema may also occur. Debate continues as to whether or not there is a mitral valve prolapse syndrome, that is, a group of symptoms associated with degenerative mitral valve disease. These symptoms are thought to include palpitation, fatigue, and chest pain, atypical of classic angina and syncope or pre-syncope.[47,48] These symptoms are very common in the general population, and whether they occur more frequently in patients with mitral valve prolapse continues to be a subject of controversy.

On physical examination the reduced forward stroke volume tends to reduce systolic blood pressure and pulse pressure, but this finding is quite variable and some patients are actually hypertensive. The apical beat is displaced downward and to the left in chronic severe disease owing to left ventricular dilatation. The typical murmur is holosystolic if the lesion is chordal rupture, and is heard best at the apex and radiates to the axilla. There is a weak positive correlation between mitral regurgitation severity and murmur intensity.[49] Severe mitral regurgitation is often accompanied by an S_3 produced by the emptying of the large left atrial volume under higher than normal pressure into the left ventricle. The presence of an S_3 is often evidence that the mitral regurgitation is severe rather than indicating that the patient is in heart failure.

Mitral valve prolapse in Barlow disease is sometimes referred to as click-murmur syndrome, indicative of the typical findings on physical examination of a mid-systolic click followed by a late systolic murmur. The click is generated as the elongated chordae are stretched taut. The valve leaflets then move past their coaptation point and the murmur ensues. Physical maneuvers that decrease left ventricular volume, such as standing or the Valsalva maneuver, cause the click and murmur to come earlier in systole and consequently to increase in intensity. This occurs because a decrease in left ventricular volume reduces tension on the mitral valve, in effect lengthening the valve apparatus. Maneuvers that increase left ventricular volume such as squatting or lying down may cause the opposite effect or may cause the click and murmur to disappear altogether. In some patients only the click or murmur is present, or mitral valve prolapse may occur without any physical findings. As the severity of mitral regurgitation worsens, the murmur becomes progressively more holosystolic and the click may disappear.

LABORATORY FINDINGS

The electrocardiogram and chest x-ray often demonstrate nonspecific abnormalities. The ECG may show evidence of left atrial enlargement and left ventricular hypertrophy, and T-wave abnormalities have been reported in the inferior leads in patients with prolapse. Because atrial fibrillation is common in patients with mitral regurgitation, a baseline ECG is important to have on file in case this arrhythmia occurs later. The chest x-ray may show cardiac enlargement and pulmonary congestion if heart failure has intervened.

Although the above studies are very modestly useful in diagnosing mitral regurgitation, the echocardiogram is indispensable.[50,51] Transthoracic images can demonstrate the pathoanatomy or lesions responsible for mitral regurgitation, the degree of severity of mitral regurgitation, and the effect of mitral regurgitation on left ventricular remodeling and function, and help clarify the likelihood of eventual valve repair.[52-54] Because the esophagus virtually abuts the left atrium, transesophageal echocardiograms usually produce clear images of the mitral valve and of the left atrium and ventricle.[55]

ECHOCARDIOGRAPHIC PATHOANATOMY

The typical echocardiography features of fibroelastic deficiency and Barlow disease are demonstrated in Fig. 48–8. In patients with fibroelastic deficiency, echocardiographic findings typically include an isolated segmental prolapse, with flail leaflet segment caused by chordal rupture leading to holosystolic mitral regurgitation. Conversely, echocardiographic findings in patients with Barlow disease include mid-systolic and frequently diffuse regurgitation with multiple jets consistent with chordal elongation effecting grossly thickened myxomatous leaflets. The posterior leaflet is often displaced towards the left atrium away from the ventricular hinge, resulting in a cul-de-sac along the posterior portion of the annulus, which potentially becomes a precipitating factor for the development of annular fissures and calcification.[56]

Real-time three-dimensional echocardiography replicates the "surgical view," the view of the mitral valve the surgeon will see upon opening the left atrium. Quantitative analysis using proprietary software also allows precise determination of prolapsing or restricted segments within the plane of the annulus.[57] As such this imaging technique is very useful in identifying the leaflet segments involved with disease and planning the surgical approach to repair the mitral valve.

ECHOCARDIOGRAPHIC SEVERITY ASSESSMENT

Transthoracic echocardiography provides most of the diagnostic data needed for baseline evaluation of patients with mitral regurgitation (MR). The role of imaging is twofold: (1) to determine the severity of MR and (2) to determine the etiology of the disease. The severity of MR is based on the integration of several quantitative parameters, including measurement of vena contracta width, regurgitant volume, regurgitant fraction, and effective regurgitant orifice area (Table 48–1, Fig. 48–9).[28,58,59] This helps minimize the effects of technical or measurement errors inherent to each method. In addition, TTE provides useful information about LV size and function, RV function, left atrial size, and pulmonary artery pressure.

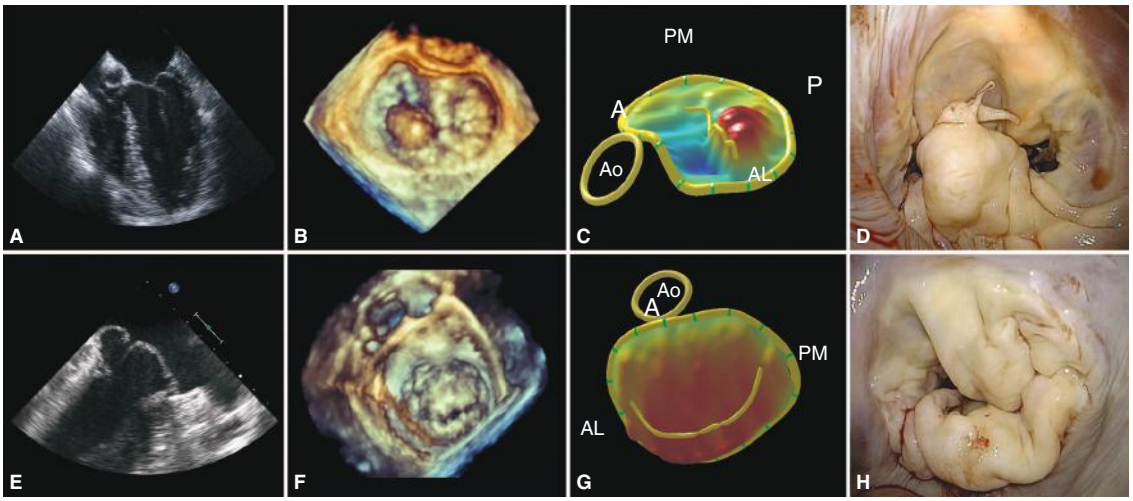

FIGURE 48–8. Transesophageal echocardiographic correlation of 2D and 3D in the differentiation of degenerative mitral disease. **A.** Fibroelastic deficiency with a ruptured chord to P2 (posterior middle scallop). **B.** 3D volume rendering of the same valve. **C.** 3D rendering using quantitative analysis (*red area* corresponds to prolapsing area). **D.** Surgical view. **E.** Barlow disease with multi-segment prolapse and excess leaflet tissue. **F.** 3D volume rendering of the same valve. **G.** 3D rendering using quantitative analysis (*red areas* correspond to prolapsing areas). **H.** Surgical view.

Etiologic differentiation of primary MR is crucial for guiding treatment and management decisions. Primary MR is characterized by abnormalities of the mitral valve itself and the majority of the structural abnormalities can be identified on transthoracic echocardiogram (TTE). Although transesophageal echocardiogram (TEE) is more accurate than TTE in locating the site and severity of structural abnormalities and quantifying the severity of MR, TEE during an initial diagnostic evaluation is only indicated in patients with inconclusive or technically difficult TTE

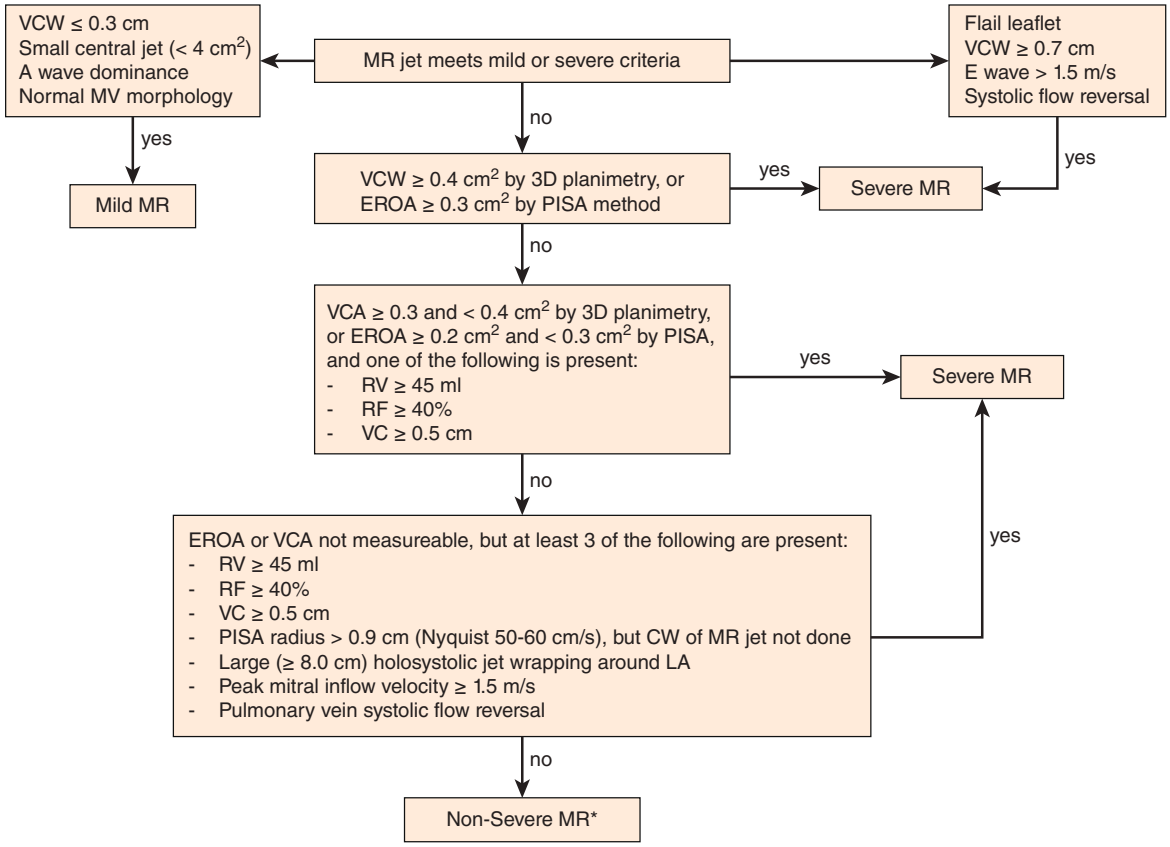

FIGURE 48–9. Algorithm for distinguishing severe from nonsevere mitral regurgitation (MR) in patients with clinically MR jets on color Doppler imaging. Severe MR corresponds to angiographic grades 3+ and 4+ per American College of Cardiology/American Heart Association guidelines. The first step is to determine whether MR severity is obviously mild or severe by American Society of Echocardiography/European Association for Echocardiography criteria (see text). If not, quantitative parameters are applied in a systemic, integrated fashion to determine whether MR is severe. Unless the MR is unequivocally mild in step 1, no attempt is made to distinguish mild from moderate MR (nonsevere), because studies comparing quantitative echocardiographic measures to an independent reference standard show substantial overlap. VCW, vena contracta width; MV, mitral valve; VCA, vena contracta area; 3D, 3-dimensional; EROA, effective regurgitant orifice area; PISA, proximal isovelocity surface area; RV, regurgitant volume; RF, regurgitant fraction; VC, vena contracta; CW, continuous-wave Doppler; and LA, left atrium. Reproduced with permission from Grayburn PA, Weissman NJ, Zamorano JL. Quantitation of mitral regurgitation. *Circulation*. 2012 Oct 16;126(16):2005-2017.

examinations. On the other hand, following a surgical consultation, TEE is routinely used in the perioperative period for confirming the mechanism of MR and guiding surgical planning. Recent advances in real-time 3D TEE technique allow accurate quantification of vena contracta area, regurgitant orifice area, and regurgitant volume. However, these techniques are relatively new, and their test-retest characteristics, prognostic value, threshold for severity classifications, and multicenter studies of accuracy and reproducibility require further standardization.[60]

Assessment of myocardial function is challenging for patients with MR. Left ventricular ejection fraction may remain in the normal or supernormal range for long periods of time, even if alterations in contractility develop. Moreover, a marked drop in LV ejection fraction can occur after surgery, even when the preoperative LV ejection fraction is normal. Therefore, earlier detection of LV contractile dysfunction is of pivotal importance so that surgical correction of chronic MR can be performed in a timely manner. There has been growing interest in using newer dedicated software that can track natural myocardial markers, or speckles in echocardiography images, for characterizing myocardial functional abnormalities beyond ejection fraction.[61] Several studies have suggested that assessment functional abnormalities of the LV in the longitudinal direction may provide windows for characterizing subclinical LV dysfunction in patients with severe MR.[62]

STRESS ECHOCARDIOGRAPHY

Exercise Doppler echocardiography can be used in asymptomatic patients with moderate to severe primary MR with preserved LV ejection fraction for immediate risk stratification and to guide the timing of mitral valve surgery, especially for those in whom the risk-to-benefit ratio of surgical intervention is uncertain or borderline.[63] Worsening of valvular regurgitation severity, exercise-induced pulmonary hypertension, impaired LV contractile reserve, inducible ischemia, and altered exercise capacity, together with the development of symptoms during exercise echocardiography, provide the clinician with information for a more accurate definition of the optimal timing of intervention in patients with valvular regurgitation. Exercise Doppler echocardiography can also be useful in patients with secondary MR in the following situations: (1) patients with exertional dyspnea out of proportion with the severity of resting LV dysfunction or MR; (2) patients with moderate MR in whom acute pulmonary edema occurs without an obvious contributing factor; (3) those with moderate MR before surgical revascularization; (4) those in whom individual risk stratification is requested; and (5) those operated on for mitral valve problems but with persistent post-operative pulmonary hypertension.[64]

COMPUTED TOMOGRAPHY AND CARDIAC MAGNETIC RESONANCE

Computed tomography and cardiac magnetic resonance techniques have been compared to echocardiography for MR assessment, but are not routinely recommended unless there are critical considerations regarding chamber remodeling, the presence of cardiac neoplasm, or coronary artery disease using viability assessments.[65,66] With the developments in transcatheter techniques for treating MR, there has been growing interest in using CT techniques for assessing the geometry and sizing of the mitral valve apparatus.[67] MRI of the valve apparatus may be useful in evaluating the amount of regurgitant flow with velocity encoding using model-independent measurements of stroke volumes of RV and LV with higher precision and accuracy than echocardiographic techniques.[68]

CARDIAC CATHETERIZATION

Once the mainstay of evaluation, invasive hemodynamic evaluation is now reserved for cases in which the diagnosis of the severity and impact of mitral regurgitation is uncertain. Although the exact mechanisms of dyspnea are not entirely understood, in cardiac disease, dyspnea correlates best with elevated left atrial pressure. Thus elevated left atrial or wedge pressure at rest or during dynamic or handgrip exercise during heart catheterization can demonstrate the hemodynamic underpinnings of a patient's symptoms. The presence of a large v-wave (twice the mean left atrial pressure) in the pulmonary capillary wedge or left atrial tracing may further indicate severe mitral regurgitation. Remembering that left ventriculography visualizes actual flow of blood from left ventricle to left atrium whereas color-flow Doppler only visualizes flow velocity, a well-performed ventriculogram can help clarify mitral regurgitation severity in some cases, provided a sufficient dye load is used.

MEDICAL THERAPY

INFECTIVE ENDOCARDITIS PROPHYLAXIS AND PREOPERATIVE DENTAL CLEARANCE

The risk of infective endocarditis is significantly increased in patients with mitral valve prolapse, especially in patients with thickened redundant valves.[69] Because of this risk, antibiotic prophylaxis was recommended prior to undergoing procedures that are known to cause bacteremia such as teeth cleaning, scaling, and colonoscopy. This recommendation was based upon the theory (with little proof) that prophylaxis was actually effective. Recently amid controversy, the AHA/ACC guidelines were changed and no longer make such prophylaxis mandatory.[28] The change was based in part upon the lack of proof of prophylaxis effectiveness and in part because bacteremia is a daily occurrence with eating and dental flossing yet antibiotic prophylaxis for these activities would be impossible. In the same context, the need of preoperative dental work, or in other words the need of preoperative dental clearance, also remains unclear.[70] Although general dental work is indeed not associated with an increased risk of endocarditis or preoperative mortality, tooth extraction or root treatment still is.[71] The indication for any dental work before mitral surgery should be clearly defined, and this is particularly true for dental extractions. Although poor dental hygiene might or might not need special attention, a periodontal infection (requiring extraction) and the presence of an apical abscess (requiring extraction and potential debridement) do. Therefore, individualization is mandatory upon decision making, focusing on stability of the patient (ie, flash pulmonary edema) and complexity of the potential procedure (concomitant coronary artery bypass grafting, valve or Maze procedure). Dental infections should not be neglected in the setting of valve disease, but complex dental interventions (especially extractions) should be performed by an oral surgeon and a cardiac anesthesiologist with familiarity with hemodynamic monitoring, anticoagulation or antiplatelet therapy, and intensive care.

VASODILATOR THERAPY

In acute severe mitral regurgitation, agents that reduce afterload such as vasodilators or even the intra-aortic balloon pump are effective in relieving heart failure.[72] Such therapy works by causing preferential flow away from the left atrium and into the aorta as resistance to flow into the aorta is reduced. Success of afterload reduction in acute mitral regurgitation led to trials of vasodilators in patients with long-standing mitral regurgitation. Although no large randomized trials have been conducted afterwards, the small trials that have been performed have been confusing but largely negative.[73] Although vasodilators and other agents should be used to treat hypertension in patients with mitral regurgitation there is no evidence that they will slow the need for eventual valve surgery.

β-ADRENERGIC BLOCKADE

Adrenergic overstimulation appears to be a significant detriment in the pathophysiology of mitral regurgitation and there is evidence of benefit to the use of beta-blockers in experimental mitral regurgitation.[74] There is also some observational data that patients with mitral regurgitation already receiving beta-blockers may have a better outcome than those not taking the drugs.[75] However, no trials exist to indicate that beta-blockers are effective therapy in mitral regurgitation other than as therapy for hypertension. Thus the use of beta-blockers to treat mitral regurgitation in normotensive subjects should be viewed as experimental only.

TIMING OF SURGERY

The 2014 guidelines introduced a new classification of the severity of valve lesions based on multiple criteria, including findings on the physical examination and their subsequent correlation with data from a comprehensive TTE.[28,76] Intervention in patients with degenerative mitral valve disease is dependent on (1) severity of mitral regurgitation; (2) presence or absence of symptoms (mainly shortness of breath or unusual limitations in exercise capacity); (3) ventricular response to chronic volume overload[77,78]; (4) impact of volume overload on pulmonary or systemic circulation[79]; and (5) new arrhythmias (likely atrial fibrillation from atrial enlargement).[80,81] The stages of degenerative mitral valve disease (primary mitral regurgitation) are (A) patients at risk of disease or with risk factors for development of the disease (mild prolapse or leaflet thickening with normal coaptation); (B) patients with progressive disease (moderate to severe prolapse with still normal coaptation); (C1) severe prolapse with loss of coaptation in an otherwise preserved ventricle; (C2) severe prolapse in a patient with left ventricular dysfunction; and (D) severe prolapse in a symptomatic patient (Fig. 48–10).[28]

STAGES A AND B: LESS THAN SEVERE MITRAL REGURGITATION

Currently there is no indication to intervene in less than severe mitral regurgitation, except in symptomatic patients where there is a high suspicion that MR grade may be underestimated. In such patients, exercise testing as described above is useful to clarify the decision making.[82]

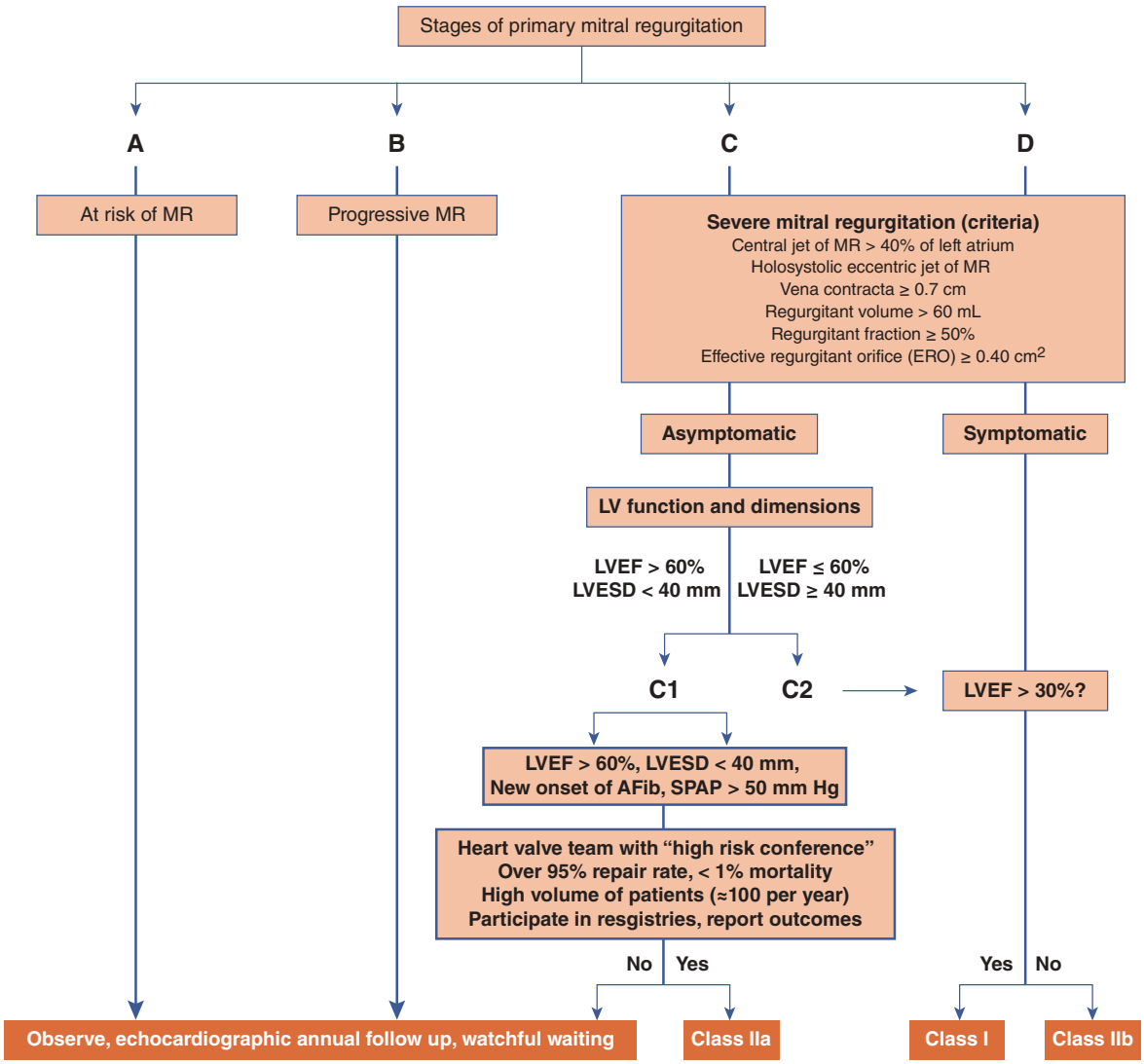

FIGURE 48–10. Proposed algorithm for the management of patients with degenerative mitral valve disease. AFib, atrial fibrillation; EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure.

STAGE C1: ASYMPTOMATIC SEVERE MITRAL REGURGITATION WITH PRESERVED LEFT VENTRICULAR FUNCTION

Over the past decade, the management of mitral valve regurgitation has changed dramatically and there has been a shift towards a more aggressive approach in terms of surgical timing and of course interpretation of the natural history of the disease.[83,84] Nowadays, prompt correction of asymptomatic mitral regurgitation with preserved left ventricular function (class IIa), in other words before development of guideline triggers (class I), is based on several axioms: (1) severe MR is not a benign condition,[85] and if left uncorrected carries a significant excess mortality associated with increased rates of heart failure and atrial fibrillation[86]; (2) surgical correction in patients with severe MR is unavoidable; (3) patients with severe MR or/and ventricular dysfunction may or may not develop symptoms; and (4) mitral valve prolapse is a 100% repairable disease in reference centers with excellent operative outcomes (mortality and stroke rates < 1%) and durability (Fig. 48–11).[87-89] However, in the setting of preserved left ventricular function (LVEF > 60% and LVESD < 40 mm), early surgery still remains solely based upon a major tenet.[90,91] This is that mitral valve repair will almost certainly be performed under at least a 95% probability of repair (based upon preoperative echocardiographic evaluation of the valve anatomy) with a mortality rate of < 1%. Such outcomes mandate patient referral to a "reference center," which by definition should have a high volume of patients (≈ 100 per year), a heart valve team with "high-risk conference," and involvement in data registries with subsequent report of outcomes (data quality control) (see Fig. 48–10). If a mitral valve replacement with its higher operative risk and more morbid postoperative outcome were performed the unwarranted risk of early surgery would absolutely not be justified.[92] In the same context, stage C1 of degenerative mitral valve disease, the presence of pulmonary hypertension or the new onset of atrial fibrillation[93] are also considered class IIa triggers for mitral surgery in asymptomatic patients with preserved left ventricular function.[94] Pulmonary hypertension and exercise-induced pulmonary hypertension are frequent in asymptomatic patients with degenerative mitral valve disease.[95] Pulmonary hypertension and its severity have been demonstrated to be a strong independent predictor of exercise-induce pulmonary hypertension and in turn a predictor of survival.[96,97]

STAGE C2: ASYMPTOMATIC SEVERE MITRAL REGURGITATION WITH LEFT VENTRICULAR DYSFUNCTION

The standard class I indications for mitral valve surgery are the onset of symptoms and/or of left ventricular dysfunction (Figs. 48–12 and 48–13).[28,98] As LV dysfunction develops in MR, many patients become symptomatic but some do not.[84,99] However, if MR is not corrected at that time, LV function will worsen and dysfunction may become permanent, leading to a poor surgical outcome and eventually to death.[30] In those patients lacking symptoms some other objective measure of LV

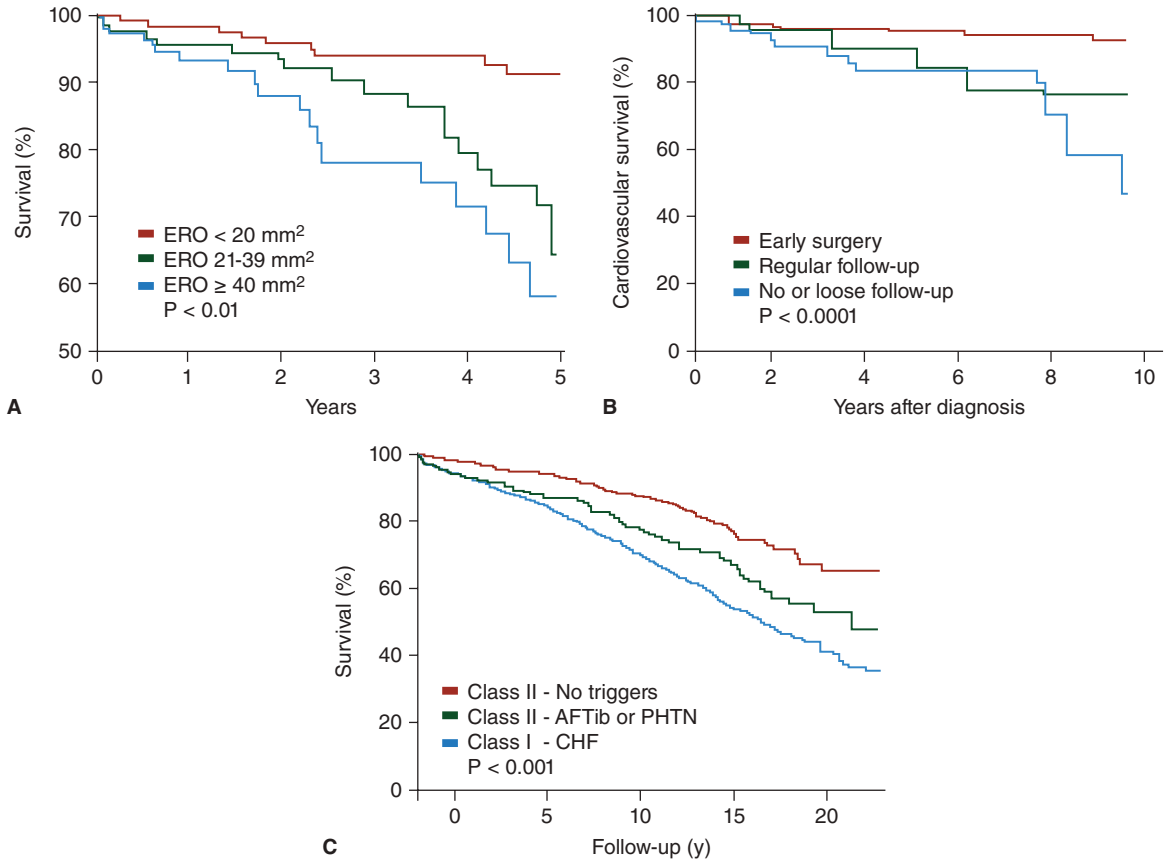

FIGURE 48–11. A. Rates of overall survival among patients with asymptomatic mitral regurgitation under medical management according to the effective regurgitant orifice (ERO); reproduced with permission from Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al: Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005 Mar 3;352(9):875-883. **B.** Cardiovascular survival compared with patients having early surgery, those treated conservatively and followed regularly, or those treated conservatively and with irregular follow-up. Reproduced with permission from Montant P, Chenot F, Robert A, et al. Long-term survival in asymptomatic patients with severe degenerative mitral regurgitation: A propensity score-based comparison between an early surgical strategy and a conservative treatment approach. *J Thorac Cardiovasc Surg*. 2009 Dec;138(6):1339-1348. **C.** Reproduced with permission from Enriquez-Sarano M, Suri RM, Clavel MA, et al. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation, *J Thorac Cardiovasc Surg*. 2015 Jul;150(1):50-58.

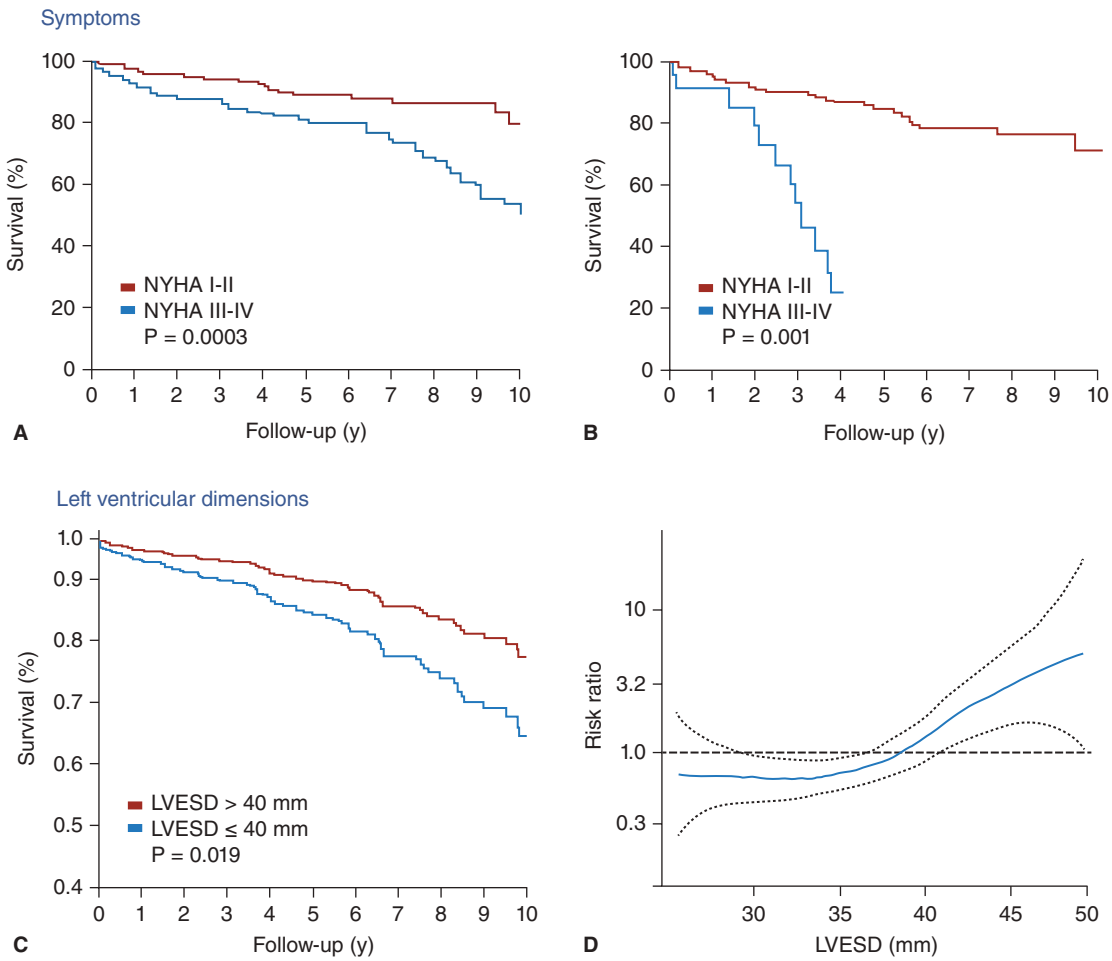

FIGURE 48–12. **A.** Overall postoperative survival compared for patients in New York Heart Association (NYHA) class I/II and those in class III/IV who had a preoperative left ventricular ejection fraction ≥60%; reproduced with permission from Tribouilloy CM, Enriquez-Sarano M, Schaff HV, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation*. 1999 Jan 26;99(3):400-405. **B.** Long-term survival with medical treatment, according to New York Heart Association class; reproduced with permission from Ling LH, Enriquez-Sarano M, Seward JB, et al: Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med*. 1996 Nov 7;335(19):1417-1423. **C, D.** Overall survival according to left ventricular end-systolic diameter (LVESD) in patients with organic mitral regurgitation; reproduced with permission from Tribouilloy C, Grigioni F, Avierinos JF, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. *J Am Coll Cardiol*. 2009 Nov 17;54(21):1961-1968.

function must be used to determine the need for mitral valve surgery.[100] Two accepted benchmarks indicating the onset of LV dysfunction are an ejection fraction ≤ 60% or a left ventricular end-systolic dimension ≥ 40mm.[101,102] When these indicators become evident on echocardiography mitral surgery should be undertaken.[63,103] Recent studies from the Mayo Clinic have suggested superior survival if the end-systolic dimension is < 40 mm[102] and superior recovery of left ventricular function if the EF is ≥ 65% at the time of mitral surgery,[100] emphasizing the importance of timely identification of changes in left ventricular function in asymptomatic patients. Once a patient has been identified as having severe MR, follow-up with history, physical exam, and serial echocardiograms (or other imaging studies) should be conducted every 6 to 12 months to ensure that the best time for intervention is not overlooked.[104] The above measures of LV function though useful are imprecise and reflect changes in the LV after the negative impact of MR has already been realized. It is likely that more sophisticated measures of LV function (novel echocardiographic parameters) and the use of new markers indicating an adverse myocardial response to MR will help to better determine the optimum timing of surgery in a very near future. In this context, new potential triggers for surgical intervention in asymptomatic patients might include high brain natriuretic peptide (BNP) levels,[105] lower percent of age/sex-predicted metabolic equivalents or lower heart rate recovery after exercise,[82] the left ventricular ejection index,[106,107] and left atrial dimensions (Fig. 48–14).[108,109]

STAGE D: SYMPTOMATIC SEVERE MITRAL REGURGITATION

The occurrence of severe NYHA class III or IV preoperative symptoms confers a poor prognosis for patients postoperatively even if left ventricular function is preserved (see Fig. 48–12).[110-112] Thus it is important to correct mitral regurgitation at the onset of even mild symptoms because waiting for symptoms to progress appears dangerous. In fact the onset of symptoms represents a change in cardiac physiology as the mitral regurgitation has begun to affect cardiac output and left atrial filling. In addition there may be a small risk of sudden death in patients who have developed symptoms.[113,114] Thus symptom onset is a clear indication for mitral valve surgery. Although guidelines currently contemplate mitral valve replacement as an acceptable option, mitral valve repair should be the only option in patients with mitral valve prolapse.

ADHERENCE TO GUIDELINES IN REAL WORLD PRACTICE

Several studies have suggested discordance with timely referral of patients with chronic mitral valve regurgitation for surgical intervention despite the presence of one or more accepted guideline indications

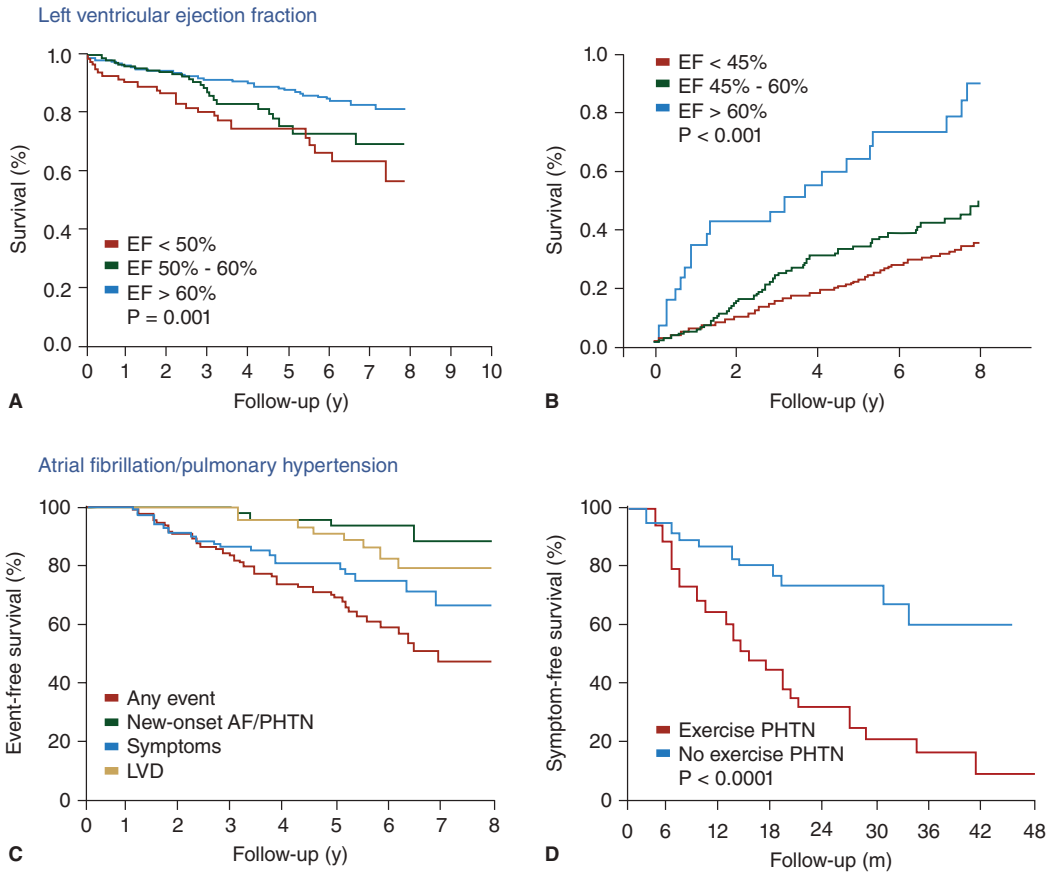

FIGURE 48–13. A. Late survival according to preoperative ejection fraction; reproduced with permission from Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation*. 1994 Aug;90(2):830-837. **B.** All-cause mortality according to ejection fraction (EF) in patients with organic mitral regurgitation under conservative management; reproduced with permission from Tribouilloy C, Rusinaru D, Grigioni F, et al. Long-term mortality associated with left ventricular dysfunction in mitral regurgitation due to flail leaflets: A multicenter analysis. *Circ Cardiovasc Imaging*. 2014 Mar;7(2):363-370. **C.** Survival free of symptoms, survival free of asymptomatic LV dysfunction, and survival free of asymptomatic pulmonary hypertension or recurrent atrial fibrillation in patients under watchful waiting; reproduced with permission from Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006 May 9;113(18):2238-2244. **D.** Symptom free survival in patients with severe asymptomatic mitral regurgitation according to the development of exercise pulmonary hypertension; reproduced with permission from Magne J, Lancellotti P, Pierard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. *Circulation*. 2010 Jul 6;122(1):33-41.

for surgery. A substudy of the *Euro Heart Survey* showed that 49% of patients with symptomatic severe mitral regurgitation of various etiologies were not referred for surgery, and that clinicians were placing too much emphasis on age and ejection fraction in their decision to not offer patients surgery.[115] Another study involving a large number of Canadian cardiologists in either university-based or community-based practice suggested that nearly half were unfamiliar with even class I indications for surgical intervention in patients with severe mitral regurgitation.[116] A separate recent study at the University of Michigan similarly found that over one-third of patients with degenerative disease and a guideline indication for surgical intervention were not referred for surgical evaluation, despite the fact that no high-risk patients were turned down for surgery during the study period, and surgical results in this subgroup were excellent.[117] Thus it appears that "perceived risks" of surgical intervention in real world practice are often overestimated, suggesting the need for continued education of practicing clinicians regarding current guidelines and best practice outcomes.[118]

MITRAL VALVE REPAIR FOR DEGENERATIVE DISEASE: A SUBSPECIALTY

Severe mitral valve regurgitation in the setting of degenerative mitral valve disease is a mechanical problem with an only definitive mechanical solution; at this time the only definitive treatment is mitral valve repair.[119] As mentioned before, all prolapsing valves are repairable and mitral valve replacement should not be an option if appropriate referral patterns are followed.[120] Degenerative mitral valve disease along with annular dilatation is the most repairable form of surgical mitral valve disease, and repair should be recommended. Mitral valve repair is favored over replacement for several reasons, including a lower perioperative risk, improved preservation of left ventricular function, improved event-free survival in the majority of operated patients, and greater freedoms from prosthetic valve-related complications such as thromboembolism, anticoagulant-related hemorrhage, and endocarditis (Fig. 48–15).[121-123] Although no randomized trials comparing outcomes of mitral valve repair versus replacement exist (and it seems very unlikely that such trials would be conducted, particularly in the setting of degenerative mitral valve disease), the vast majority of available retrospective data strongly support the long-term advantage of mitral valve repair.

MITRAL VALVE REPAIR IN THE ELDERLY

The risk-adjusted advantage of mitral valve repair versus mitral valve replacement is also patent in the elderly (Fig. 48–16).[124,125] The prevalence of mitral valve disease increases with age and around 10% of patients above 75 years who require hospitalization have significant mitral regurgitation, predominantly caused by fibroelastic deficiency.[16]

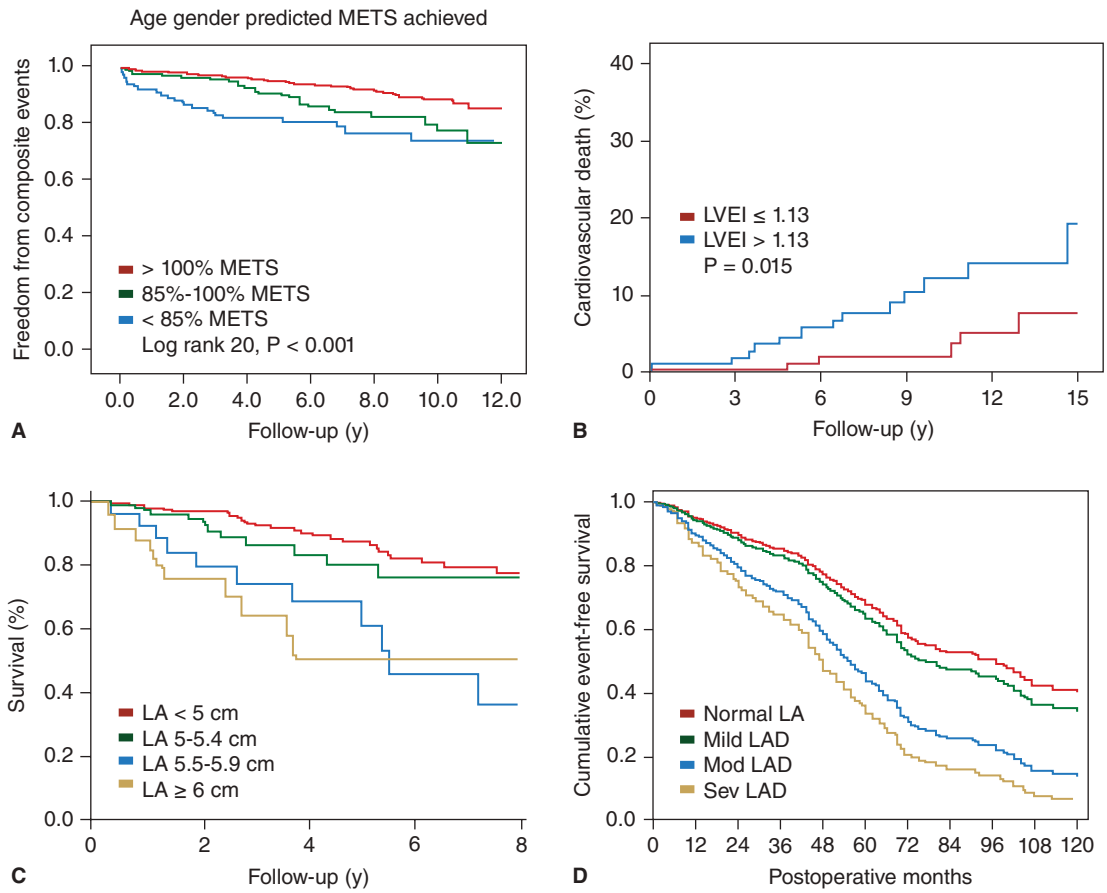

FIGURE 48–14. A. Freedom from composite events (death, myocardial infarction, stroke, and progression to congestive heart failure) according to METS; reproduced with permission from Naji P, Griffin BP, Asfahan F, et al. Predictors of long-term outcomes in patients with significant myxomatous mitral regurgitation undergoing exercise echocardiography. *Circulation*. 2014 Mar 25;129(12):1310-1319. **B.** Cardiovascular death according to left ventricular ejection index; reproduced with permission from Magne J, Szymanski C, Fournier A, et al. Clinical and prognostic impact of a new left ventricular ejection index in primary mitral regurgitation because of mitral valve prolapse. *Circ Cardiovasc Imaging*. 2015 Sep;8(9):e003036. **C, D.** Survival and event-free survival according to leaft atrial dimensions or degree of dilatation; reproduced with permission from Rusinaru D, Tribouilloy C, Grigioni F, et al. Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: Results from a large international multicenter study. *Circ Cardiovasc Imaging*. 2011 Sep;4(5):473-481; Athanasopoulos LV, McGurk S, Khalpey Z, et al. Usefulness of preoperative cardiac dimensions to predict success of reverse cardiac remodeling in patients undergoing repair for mitral valve prolapse. *Am J Cardiol*. 2014 Mar 15;113(6):1006-1010.

However, surgery is often contraindicated in elderly patients with multiple comorbidities such as coronary artery disease, renal failure,[126] or neurological impairments.[124] In a recent series, Chikwe and associates analyzed a consecutive series of 322 octogenarian patients with degenerative mitral valve disease (most of them with fibroelastic deficiency) and showed that 30-day mortality was 2.5-fold higher in those patients who underwent mitral valve replacement. Later on, Badhwar and associates conducted a retrospective study that involved over 14,000 patients over 65 years of age from the STS National Cardiac Registry and US Medicaid. The authors reported an overall 2.6% mortality with a 68% 5-year survival.[127] Finally, Dodson and coworkers interrogated the National Medicare database to elucidate outcomes of isolated mitral valve surgery among patients above 65 years. This study, the largest to date, demonstrated that the proportion of patients undergoing mitral valve repair significantly increased from 24.7% to 46.9% (versus bioprosthetic valve replacement 23.8% to 33.0%). Although the latest data clearly suggest that elderly patients with degenerative mitral valve disease benefit from the better success rates and numerous advantages of mitral valve repair, the reality is that surgeons, especially those at low-volume centers, are often reluctant to attempt repair because of the potential need for longer bypass times or a more likely conversion to standard sternotomy.[128] In addition, the integration of quality of life and functional scoring systems seems to be important in order to assess surgical benefit versus futility.[129] In this context, novel transapical techniques may become an alternative therapeutic option only for patients who are not eligible for any surgical approach until transcatheter techniques[130] show proof of better efficacy.[131,132] This is an important point in patients with degenerative mitral valve disease, because residual moderate mitral regurgitation has been demonstrated to be associated with poorer outcomes in survival and symptom relief, and with greater recurrence.[129]

HOSPITAL AND SURGEON PROCEDURAL VOLUME AS A QUALITY METRIC

Surgical management of degenerative mitral valve disease has evolved considerably and so have the quality metrics to assess outcomes. Now that there is quorum among surgical leaders about the superiority of mitral valve repair over replacement and the need for repair in every single patient with mitral prolapse, attention has been shifted to non-patient factors that influence feasibility of repair and operative mortality such as hospital teaching status, surgeon procedural volume, and hospital procedural volume.[133]

Although mitral valve repair rates have risen throughout the last decade, and currently approach 70% in the Society of Thoracic Surgery Database,[134] its application remains quite variable with some surgeons

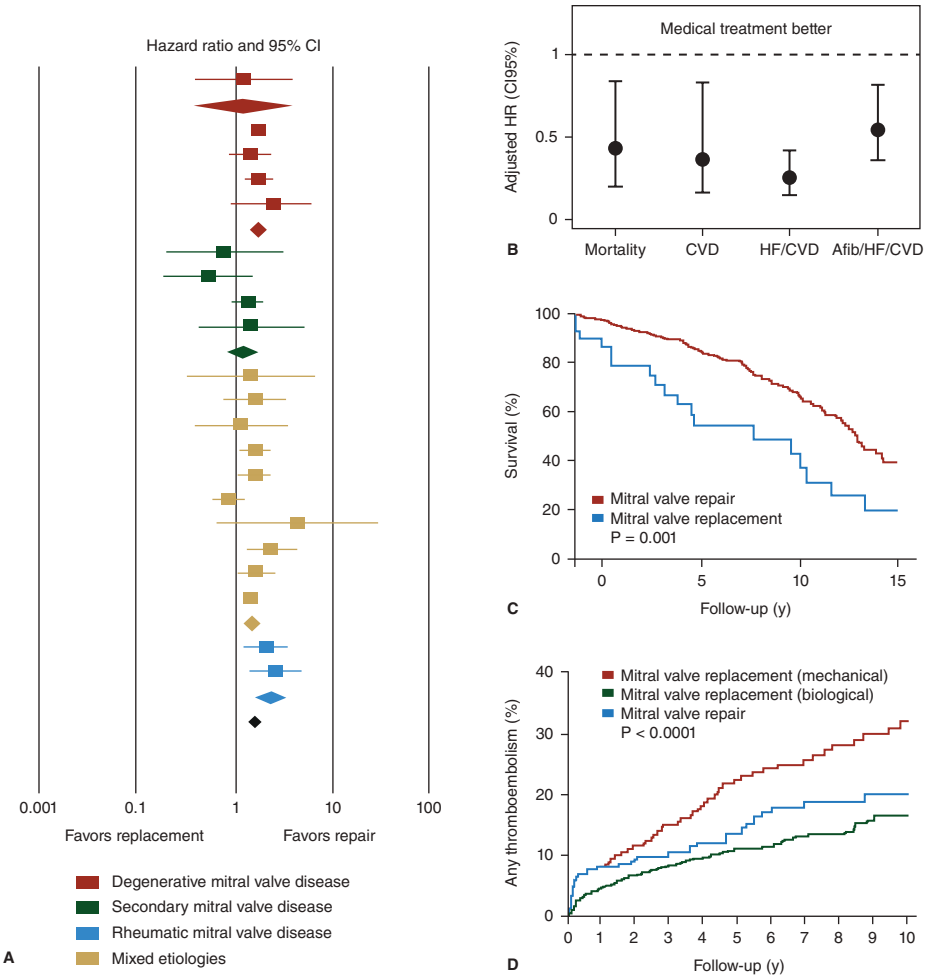

FIGURE 48–15. Superiority of mitral valve repair over valve replacement in patients with degenerative mitral valve disease. **A.** Reproduced with permission from Shuhaiber J, Anderson RJ. Meta-analysis of clinical outcomes following surgical mitral valve repair or replacement. *Eur J Cardiothorac Surg*. 2007 Feb;31(2):267-275. **B.** Reproduced with permission from Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets a multicenter european study. *JACC Cardiovasc Imaging*. 2008 Mar;1(2):133-141. **C.** Reproduced with permission from Suri RM, Schaff HV, Dearani JA, et al. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. *Ann Thorac Surg*. 2006 Sep;82(3):819-826. **D.** Reproduced with permission from Russo A, Grigioni F, Avierinos JF, et al. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. *J Am Coll Cardiol*. 2008 Mar 25;51(12):1203-1211.

performing five or fewer mitral operations per year with repair rates of less than 30%, particularly for more complex scenarios such as anterior or bileaflet prolapse (Fig. 48–17).[135] In Europe, an analysis of over 5000 mitral valve operations from the United Kingdom mandatory adult cardiac surgical database suggests a significant impact of surgeon volume on mitral valve repair rates.[136] Even in high-volume centers, the repair rates can be low; in patients with degenerative mitral regurgitation, repair rates at high-volume centers were as low as 36%, and only three high-volume centers had repair rates above 85%.[136] One of the first institutional reports to demonstrate the implications of surgeon volume in mitral valve repair rates was published in 2008.[137] Gillinov and coworkers observed that some surgeons were independent predictors of mitral valve replacement in patients with degenerative mitral valve disease. Since then, several authors have emphasized the exponential correlation between surgeon volume and mitral valve repair rates, repair quality, and shortened cross-clamp times (Fig. 48–18).[138-140] The most recent analysis of the Nationwide Inpatient Sample (NIS) including over 50,000 patients showed that although hospital volume accounted for 11% of the surgeon volume effect on increased mortality for low-volume surgeons, surgeon volume accounted for 74% of the hospital volume effect on increased mortality in low-volume hospitals.[141] Furthermore, significant trends were observed in regard to repair rates, with increasing surgeon volume demonstrating stronger correlation with the odds of repair than hospital volume, thus highlighting the importance of learning curves in mitral valve repair.[142]

FEASIBILITY AND DURABILITY OF MITRAL VALVE REPAIR

Carpentier's repair philosophy and techniques are the foundation of contemporary mitral valve repair strategies.[7] A "lesion-specific approach" addresses leaflet, chordal, and annular pathology according to the wide spectrum of lesions encountered in patients with degenerative mitral valve disease. After systematic analysis, mitral valve repair should be performed following a sequential approach such as (1) annuloplasty sutures, (2) repair of the posterior leaflet, (3) annuloplasty, (4) leaflet resuspension when required, and (5) repair any prolapse of the anterior leaflet or commissures after inspection of the line of closure during a saline test (Fig. 48–19). An optimal mitral valve repair should meet the following criteria: (1) the valve is competent on saline testing, (2) there is good surface of coaptation, (3) the closure line is symmetric and located where the anterior leaflet occupies at least 80% of the valve area, (4) there is no residual leaflet billowing, and (5) there is no tendency to systolic anterior motion.[143,144]

The most frequent lesion encountered in degenerative mitral valve disease is posterior leaflet prolapse, which accounts for about 70% of patients. In this scenario, triangular resection and leaflet resuspension (if the adjacent native chords do not look totally healthy or in light of further disease progression) remain the most popular techniques.[145] Most centers would report repair rates above 90% in patients with isolated posterior leaflet prolapse. However, repair rates fall drastically in the presence of more complex lesions such as severe annular dilatation, involvement of three or more segments, anterior leaflet prolapse, various degrees of calcification, scarcity of leaflet tissue, and opposite dysfunction. Regardless of the leaflet and chordal approach, essentially all mitral valve repairs should include an annuloplasty,[146] which reshapes the annulus and addresses posterior annular dilatation that is always present in long-standing severe mitral valve regurgitation (Fig. 48–20).[147-149]

As a fast-growing number of asymptomatic patients with degenerative mitral valve disease are expected to be referred for surgery, it seems mandatory to ensure mitral valve repair rates above 95% with minimal perioperative risk and optimal long-term outcomes. This goal has been proved to be feasible at reference centers with specialized valve teams that include cardiologists, anesthesiologists, intensivists, and surgeons. From a surgical point of view, the use of a systematic surgical strategy that embraces a broad armamentarium of techniques (as opposed to subscribing to a single technique or philosophy) should lead to achieve

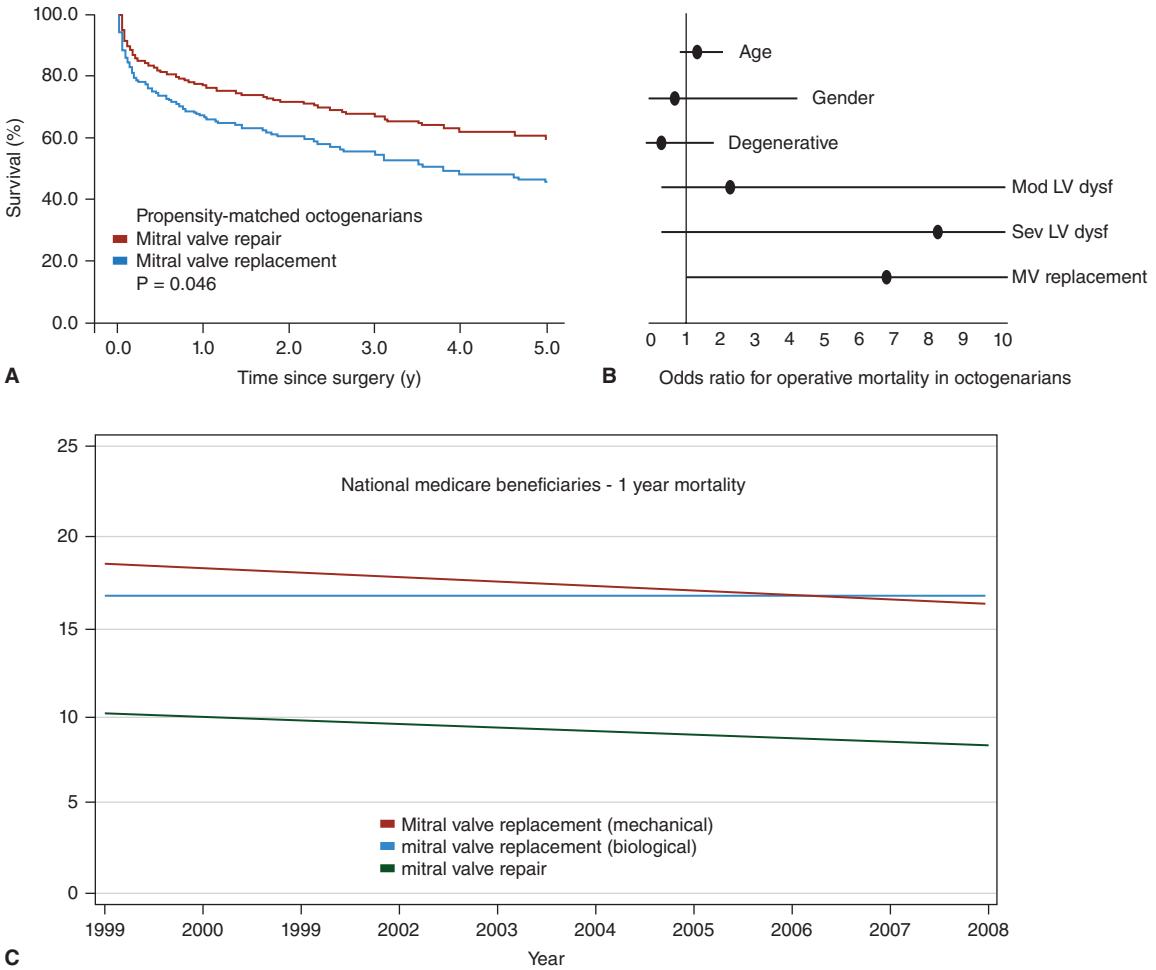

FIGURE 48–16. Superiority of mitral valve repair over valve replacement in elderly patients with degenerative mitral valve disease. **A.** Reproduced with permission from Chikwe J, Goldstone AB, Passage J, et al. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valve repair versus replacement in octogenarians. *Eur Heart J*. 2011 Mar;32(5):618-626. **B.** Reproduced with permission from Nloga J, Henaine R, Vergnat M, et al. Mitral valve surgery in octogenarians: Should we fight for repair? A survival and quality-of-life assessment. *Eur J Cardiothorac Surg*. 2011 Jun;39(6):875-880. **C.** Reproduced with permission from Dodson JA, Wang Y, Desai MM, et al. Outcomes for mitral valve surgery among medicare fee-for-service beneficiaries, 1999 to 2008. *Circ Cardiovasc Qual Outcomes*. 2012 May;5(3):298-307.

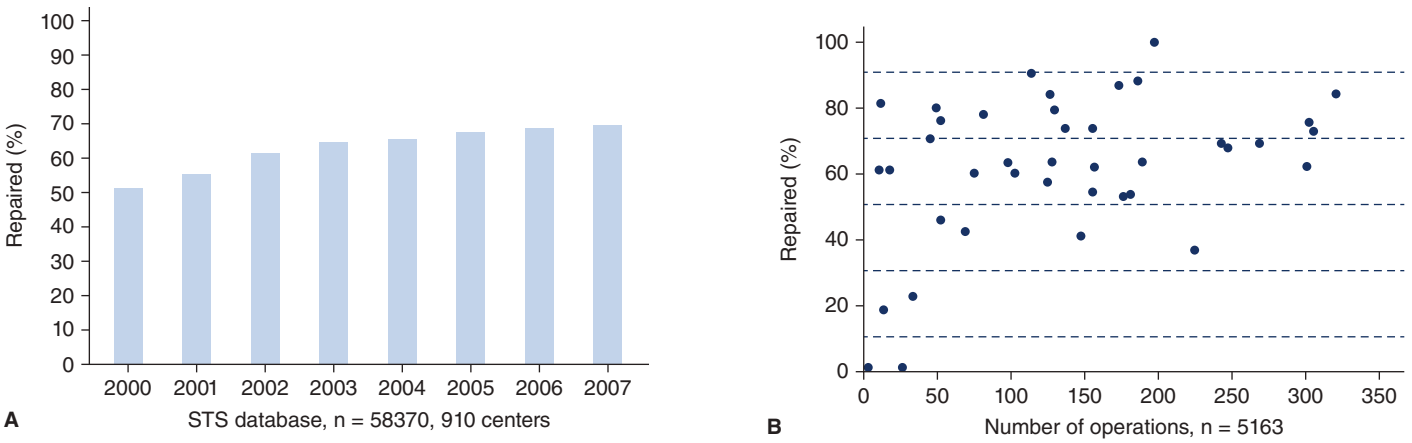

FIGURE 48–17. Mitral valve repair rates in the United States (Society of Thoracic Surgery) and United Kingdom (mandatory adult cardiac surgical database). **A.** Reproduced with permission from Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the united states: Results from the society of thoracic surgeons adult cardiac surgery database. *Ann Thorac Surg*. 2009 May;87(5):1431-1437. **B.** Reproduced with permission from Anyanwu AC, Bridgewater B, Adams DH. The lottery of mitral valve repair surgery. *Heart*. 2010 Dec;96(24):1964-1967.

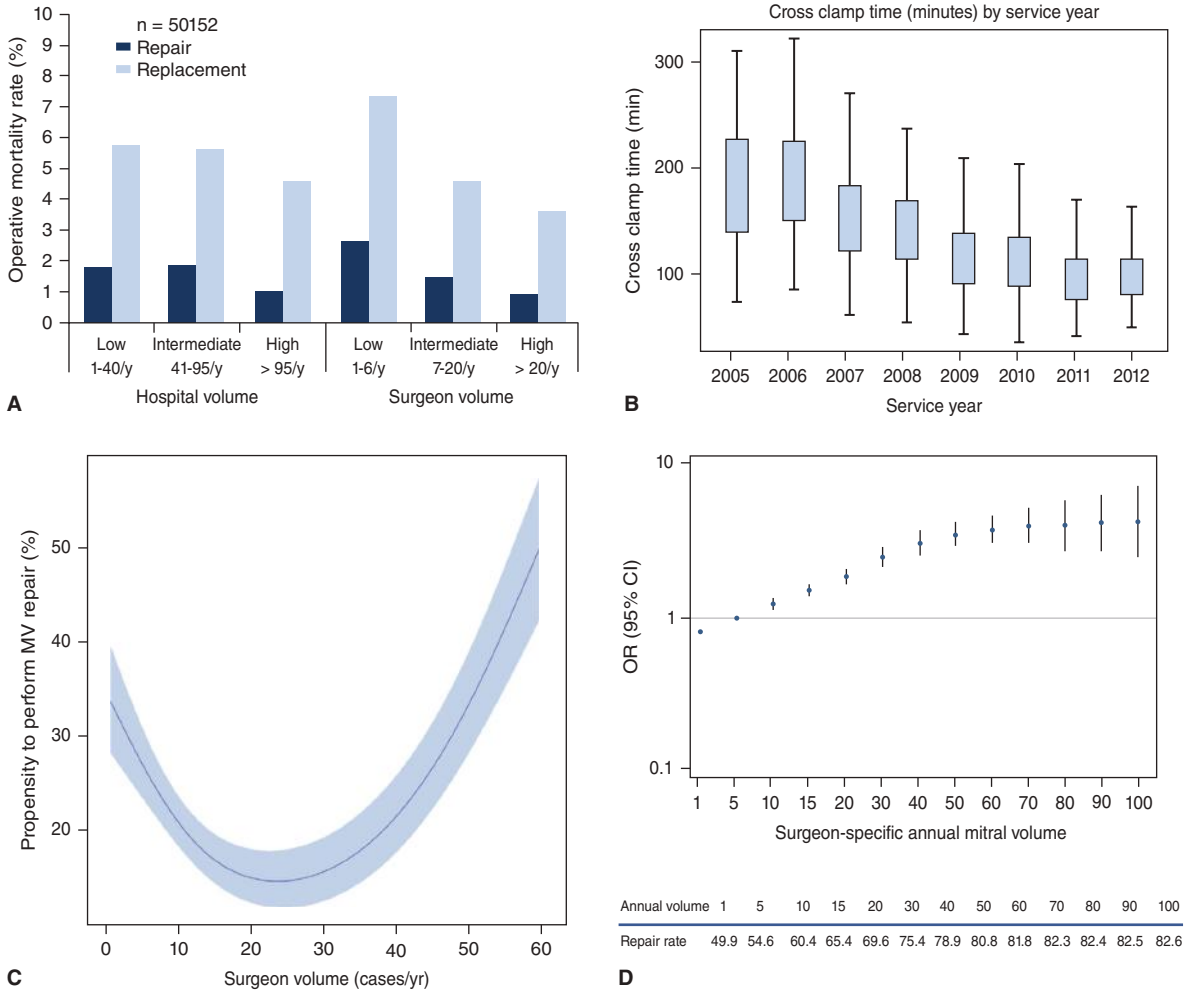

FIGURE 48–18. Impact of hospital volume and surgeon volume on the feasibility of mitral valve repair. **A.** Reproduced with permission from Operative outcomes in mitral valve surgery: Combined effect of surgeon and hospital volume in a population-based analysis. *J Thorac Cardiovasc Surg*. 2013 Sep;146(3):638-646. **B.** Reproduced with permission from Weiner MM, Hofer I, Lin HM, et al. Relationship among surgical volume, repair quality, and perioperative outcomes for repair of mitral insufficiency in a mitral valve reference center. *J Thorac Cardiovasc Surg*. 2014 Nov;148(5):2021-2026. **C.** Reproduced with permission from LaPar DJ, Ailawadi G, Isbell JM, et al. Mitral valve repair rates correlate with surgeon and institutional experience. *J Thorac Cardiovasc Surg*. 2014 Sep;148(3):995-1003. **D.** Reproduced with permission from Bolling SF, Li S, O'Brien SM, et al. Predictors of mitral valve repair: Clinical and surgeon factors. *Ann Thorac Surg*. 2010 Dec;90(6):1904-1911.

very high repair rates in experienced hands. On the other hand, the role of a multidisciplinary heart team approach is crucial to achieve contemporary benchmarks. In this context, the presence of advanced myxomatous degeneration, long-standing regurgitation with ventricular dysfunction, calcification, or previous failed repairs might require longer cross-clamp times to perfect the repair, which in turn might make postoperative management and recovery more difficult.

Mortality after mitral valve repair in patients with degenerative disease correlates with age, with an average risk of 1% for patients below 65 years (estimated risk for all comers in high-reference centers regardless of age), 2% for those aged 65 to 80 years, and 4% for octogenarians.[150] Some of the identified independent predictors of postoperative survival include severe symptoms (NYHA class III or IV), LV dysfunction (EF < 60% or LVESD > 40 mm), a regurgitant orifice area ≥ 40 mm^2, left atrial dimensions (left atrial index ≥ 60mL/m^2 or LA > 55 mm), or the presence of pulmonary hypertension or long-standing atrial fibrillation. It is important to highlight that those patients referred to surgery with severe symptoms will have greater postoperative risk despite symptom relief as a result of the absence of ventricular remodeling, particularly if the EF is < 50%. Repair durability, strictly defined as echocardiographic freedom from moderate or greater mitral regurgitation (as opposed to freedom from symptoms or reoperation), has been reported to be around 90% at 10 years in reference centers such as the Mayo Clinic, the Cleveland Clinic, Toronto General Hospital, and Mount Sinai Hospital, with a recurrent rate of 1% per year up to 20 years after the procedure (Fig. 48–21).[151-154] When durability rates are stratified according to leaflet involvement,[155] patients with bileaflet or isolated anterior leaflet prolapse have slightly lower repair durability, ranging from 75% to 85% at 5 years.[120,156] Additional factors that impact durability of repair include failure to use an annuloplasty device or the use of chordal shortening techniques (which are now abandoned).[157] Although technical failures account for residual and some early repair failures,[158] progression of disease with new pathology is the most common cause of long-term failure.[159]

SURGICAL ACCESS

Mitral valve surgery has progressively evolved over the past decade, particularly in patients with degenerative mitral valve disease. Without doubt, surgical indications, repair techniques. and approaches represent the most important[160] aspects of an already established best practice revolution in mitral valve repair. Regarding the latter aspect,

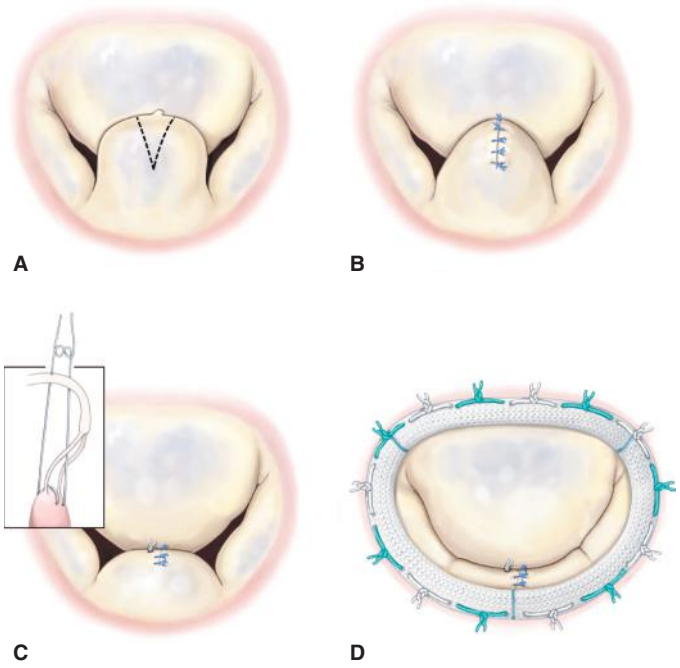

FIGURE 48–19. The current most applied techniques in mitral valve repair are triangular resection and leaflet resuspension with a polytetrafluoroethylene neochord.

the current gold standard and still most popular approach is median sternotomy, which allows central cannulation and assures good myocardial protection (direct cardioplegia), and most importantly, permits direct access if a complication occurs. The trend towards more cosmetic incisions has triggered the adoption of very limited median incisions as small as 7 to 9 cm in selected patients.[161] However, the term "minimally invasive" in today's cardiac surgery is understood as a video-assisted approach including right thoracotomy and robotic surgery.[162] In this context, cardiopulmonary bypass is accomplished through peripheral cannulation (most commonly via femoral artery and vein-retrograde arterial perfusion). Although traditionalists have claimed that minimally invasive mitral valve surgery is technically more complex (thus potentially affecting mitral valve repair rates) and implies a learning curve that not every surgeon overcomes,[142] even in high-volume centers, the reality is that extraordinary outcomes from a few experienced high-volume centers have challenged their opinions.[156,163,164] This is also true[165] even in complex scenarios such as Barlow disease or anterior leaflet prolapse.[166,167]

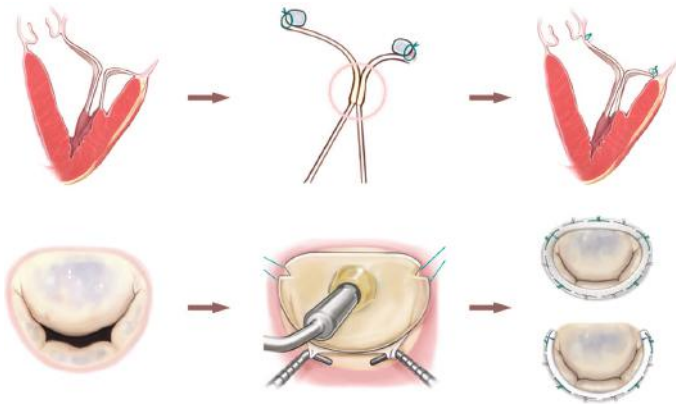

FIGURE 48–20. Annuloplasty with a complete ring or a posterior band.

The most important goal for patients with degenerative mitral valve disease and the physicians involved in their care (referring cardiologist and surgeons) is to achieve not only a competent repair of the mitral valve but a durable one, as emphasized by the new guidelines. In ideal conditions, these axioms should be met in all prolapsing valves regardless of the surgical approach and the final cosmetic outcome. We are convinced that as technology advances, minimally invasive techniques will expand. However, at this time, the average repair rates dictate that the use of these techniques should be restricted to selected, high-volume, specialized centers.

CONCOMITANT TRICUSPID VALVE REPAIR IN PATIENTS WITH DEGENERATIVE MITRAL VALVE DISEASE

Tricuspid valve disease affects around 1% of the general population, and most patients remain asymptomatic despite having moderate to severe degrees of tricuspid regurgitation. However, increasing attention has been given to the tricuspid valve in parallel to a better understanding of the negative impact of right-sided heart failure on the clinical outcome of patients regardless the presence or severity of left-sided valve disease.[168] Although primary tricuspid regurgitation is rare (often seen in patients with pacemakers, chest trauma, or endocarditis), secondary (functional) tricuspid regurgitation as a result of pulmonary hypertension and right ventricular dilation as a result of left-sided valve disease is common. However, although the number of tricuspid procedures has double over the last decade,[169] the management of secondary tricuspid regurgitation remains as one of the most heated debates, particularly in regard to the best surgical option in patients with severe tricuspid regurgitation and whether concomitant "prophylactic" tricuspid procedures are necessary in patients with mild to moderate tricuspid regurgitation.[170,171]

At the present time, there are two opposing schools of thoughts regarding the need for concomitant tricuspid valve repair at the time of mitral repair in patients with degenerative valve disease, both of them supported by leading experts in mitral valve repair. The main explanation for these contrary opinions is the difficulty in accurately assessing the degree of tricuspid regurgitation as a result of the significant dependence of the right ventricle on preload conditions. In order to avoid this bias, many authors have suggested an annular dilatation of 40 mm or 21 mm/m^2 as an independent criterion for tricuspid intervention. Recently, our group demonstrated that this strategy, applied in two-thirds of patients undergoing mitral valve repair, does not lead to a difference in mortality, morbidity, or requirement of a permanent pacemaker.[172] An even more recent paper from De Bonis and colleagues confirmed these findings and also noted that half of the untreated patients presented with either severe tricuspid regurgitation or a progression of at least two grades of tricuspid regurgitation 7 years after the procedure.[173] On the other hand, only around 10% of patients receive concomitant tricuspid annuloplasty at Toronto General Hospital or the Mayo Clinic. Objectively, we can assert that preoperative functional class (as a surrogate of ventricular dysfunction) should play a major role in decision making. Those patients in NYHA class III or IV, who have not developed at least moderate TR at the time of surgical intervention, will most likely not develop TR after mitral valve repair. Likewise, patients with preserved left ventricles and none or mild degrees of tricuspid regurgitation are also unlikely to develop tricuspid regurgitation. It may be that earlier the mitral valve repair will lead to fewer patients requiring tricuspid intervention.

Overall, secondary or functional tricuspid regurgitation is the most common etiology of TV disease, and thorough interrogation is mandatory in patients undergoing mitral valve repair. Concomitant tricuspid valve repair does not carry a significant additional surgical burden and might lead to improved perioperative outcomes, functional class, and

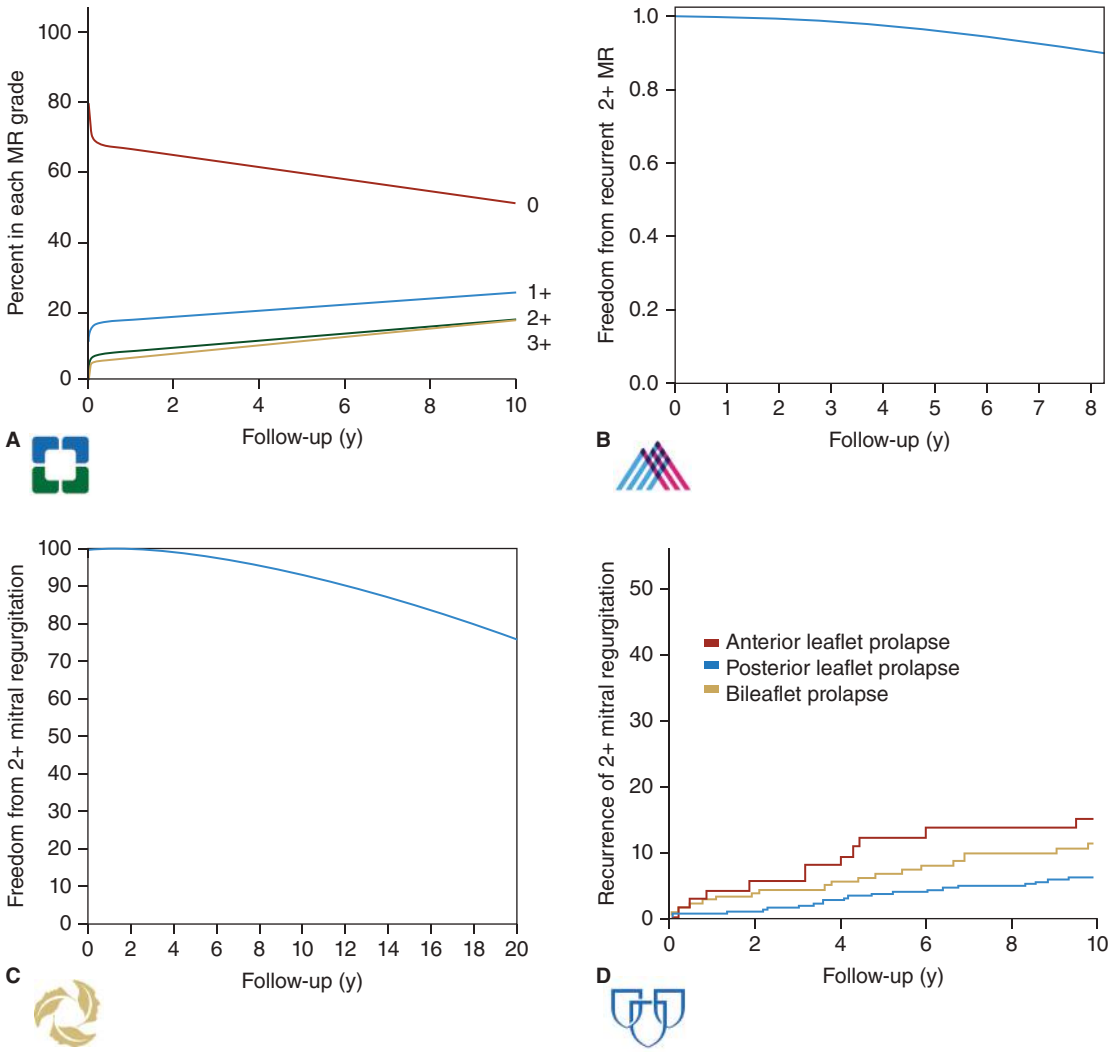

FIGURE 48–21. Freedom from moderate MR in reference centers. **A.** Reproduced with permission from Gillinov AM, Mihaljevic T, Blackstone EH, et al. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? *Ann Thorac Surg*. 2010 Aug;90(2):481-8. **B.** Reproduced with permission from Castillo JG, Anyanwu AC, Fuster V, et al. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: Implications for future guidelines. *J Thorac Cardiovasc Surg*. 2012 Aug;144(2):308-312. **D.** Reproduced with permission from Suri RM, Clavel MA, Schaff HV et al. Effect of recurrent mitral regurgitation following degenerative mitral valve repair: Long-term analysis of competing outcomes. *J Am Coll Cardiol*. 2016 Feb 9;67(5):488-498.

survival. Tricuspid regurgitation does not always regress after correction of left-sided valve disease[174] and reoperations for residual or recurrent tricuspid regurgitation are associated with a higher mortality risk in experienced centers (up to 15%).[175] The final decision should be guided not only by the degree of regurgitation (≥ moderate) but also by annular dimensions (diameter ≥ 7 cm from anteroseptal to anteroposterior commissures, or 40 mm when measured by echocardiography); leaflet coaptation or mismatch between leaflet and annulus on direct inspection; and presence of atrial fibrillation, pulmonary hypertension, right ventricular dysfunction, and/or left ventricular dysfunction. As for the type of repair, the authors favor the use of a disease-specific open ring with a rigid component located in the region corresponding to the right ventricular free wall aspect of the annulus (remodeling) with flexible open ends for wider accommodation of the conduction system to reduce iatrogenic injury.[176]

PERCUTANEOUS APPROACHES TO MITRAL VALVE REPAIR AND REPLACEMENT

At present there are over 20 investigational devices for repair or replacement of the mitral valve. Some make use of the proximity of the coronary sinus to the mitral annulus, wherein devices cinch the coronary sinus, thereby reducing annular dimension and reducing MR. Percutaneous valve replacement is in its infancy with a large number of valve designs being tested.[130,177]

Currently the MitraClip is the only device approved in the United States and is employed for treatment of inoperable patients with primary MR. The device is inserted transeptally and clips the two mitral leaflets together in their mid-portions, substantially reducing MR, usually from severe to moderate degrees of regurgitation. Five-year follow-up is now available and demonstrates both persistent reductions in MR as well as persistent symptomatic improvement.[178]

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CHAPTER 49

ISCHEMIC MITRAL REGURGITATION

John D. Groarke, Blasé A. Carabello, and Patrick T. O'Gara

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INTRODUCTION

Mitral regurgitation (MR) can be classified into two major etiologic categories: primary (degenerative) and secondary (functional). Primary MR is a consequence of disease affecting the leaflets or chordae tendineae, such as mitral valve prolapse, myxomatous degeneration, infective endocarditis, or rheumatic disease. These disease processes are discussed in Chap. 48. In secondary MR, leaflet structure is normal and the valve is more of an "innocent bystander." Regurgitation results from a distortion of the normal spatial and functional relationships of the left ventricle (LV) and valve apparatus, usually as a consequence of adverse LV remodeling. The trigger for LV remodeling can be ischemic (following myocardial infarction [MI]) or nonischemic (as with dilated cardiomyopathy) (Fig. 49–1). This chapter will focus on chronic ischemic MR (IMR) and will not discuss acute severe MR caused by papillary muscle rupture in the acute/subacute phase of MI.

INCIDENCE

The reported incidence of IMR following MI has ranged from 19% to 50%.[1-4] Estimates vary in relation to the nature of the screening techniques utilized. Of 1209 patients with coronary artery disease (CAD) amenable to coronary artery bypass grafting (CABG) and LV ejection fraction (LVEF) ≤ 35% enrolled in the Surgical Treatment for Ischemic Heart Failure (STICH) trial, mild, moderate, and severe MR were present in 46%, 15%, and 3% of patients, respectively.[5] It is estimated that IMR affects 1.6 million to 2.8 million patients in the United States.[6]

STAGES

Analogous to but somewhat different than other types of valvular heart disease, the natural history of IMR can be considered across four overlapping stages:

- Stage A: "At-risk" stage (eg, early following MI).
- Stage B: Symptomatic progressive stage (eg, during the phase of active LV remodeling).
- Stage C: Asymptomatic severe stage (prior to onset of heart failure symptoms).
- Stage D: Symptomatic severe stage (following onset of HF symptoms).

Descriptions of valve anatomy, valve hemodynamics, associated cardiac findings, and symptoms for each stage are presented in Table 49–1. Boundaries between these stages are not rigid and patients with moderate IMR may also develop heart failure (HF) symptoms (see below and Table 49–1 and Table 49–2 for definitions of moderate and severe ischemic MR). Angina may also be a feature of the disease process.

MECHANISMS

Normal MV function is dependent on a complex interplay between the LV and the individual components of the MV apparatus, including the papillary muscles and subjacent myocardium, chordae tendineae, MV leaflets, and mitral annulus (Fig. 49–2A). Distortion or dysfunction of any of these components can result in MR. IMR results from a combination of apical and lateral displacement of the papillary muscles, systolic tethering of the mitral leaflets, annular dilation, and an imbalance of valve closing and tethering forces.[6,7] Annular enlargement is typically less pronounced in patients with IMR than in those who have secondary MR as a result of dilated cardiomyopathy. Adverse LV remodeling can occur as a consequence of MI because of myocardial thinning and dilation. Regional LV remodeling (eg, following a postero-basal infarct) with displacement of the posteromedial papillary muscle can result in asymmetric tethering of the posterior leaflet, producing an eccentric and posteriorly directed MR jet (Fig. 49–2B). The anterolateral papillary muscle has a dual blood supply from the left anterior descending and left circumflex arteries, whereas the posteromedial muscle has a singular blood supply from the right or dominant left circumflex coronary artery. Thus IMR is more common following inferior-posterior rather than an anterior MI.[8] Alternatively, global LV remodeling after a large anterior MI causing apical and lateral displacement of both papillary muscles with symmetric tethering of both MV leaflets typically results in a central regurgitant jet (Fig. 49–2C). Leaflet coaptation is displaced apically away from the annular plane compromising complete leaflet closure. In addition, mitral annular dilation

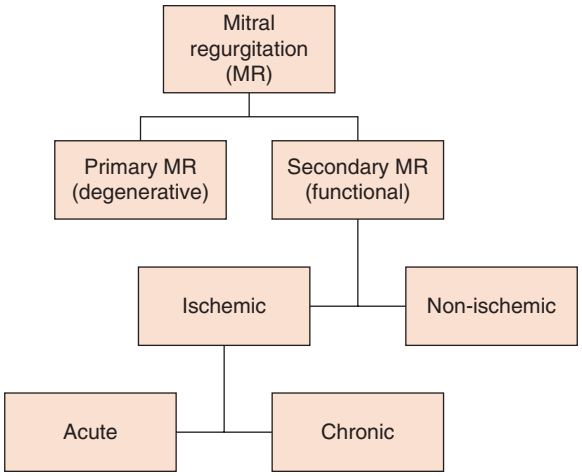

FIGURE 49–1. Classification of mitral regurgitation.

can further stretch the MV leaflets and contribute to incomplete valve closure. The nonplanar saddle-shape of the MV annulus is important for MV competence, and loss of this saddle shape during remodeling has also been implicated in the genesis of IMR.[9]

PROGNOSIS

IMR is an independent predictor of cardiovascular mortality and HF following MI.[1,2] The magnitude of risk is proportional to the severity of MR.[3,10] Although even mild MR is associated with increased mortality, prognosis is particularly poor for patients with severe IMR, with 1-year mortality estimates ranging from 15% to 40%.[11] In a multivariate analysis of 303 patients in the chronic post-MI phase, IMR was associated with an adjusted relative risk of cardiovascular mortality of 1.83 (95% confidence interval [CI], 1.13-2.96), and this risk increased as a function of MR severity.[12] Similarly, IMR was associated with an adjusted relative risk of HF and cardiac death of 3.65 (95% CI, 1.86-7.75) and 2.96 (95% CI, 1.77-5.16), respectively, in a study of 173 asymptomatic patients following MI who were followed for a mean of 7.6 ± 7.4 years; a graded relationship between MR severity and risk of each outcome was again observed.[13]

As a result of consistent evidence of the prognostic utility of post-MI MR in predicting HF and cardiovascular death, assessment of MR is an accepted component of post-MI risk stratification. Adverse outcomes are associated with a smaller calculated effective regurgitant orifice (ERO) in IMR compared to primary MR, prompting a threshold ERO of ≥ 0.2 cm^2 for defining severe regurgitation in IMR compared to a corresponding threshold of ≥ 0.4 cm^2

TABLE 49–1. Stages of Secondary Mitral Regurgitation With Associated Valve Anatomy, Valve Hemodynamics, Cardiac Findings, and Symptoms

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	• Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	• No MR jet or small central jet area < 20% LA on Doppler • Small vena contracta < 0.30 cm	• Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities • Primary myocardial disease with LV dilation and systolic dysfunction	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	• Regional wall motion abnormalities with mild tethering of mitral leaflet • Annular dilation with mild loss of central coaptation of the mitral leaflets	• ERO < 0.20 $cm^{2\dagger}$ • Regurgitant volume < 30 mL • Regurgitant fraction < 50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥ 0.20 $cm^{2\dagger}$ • Regurgitant volume ≥ 30 mL • Regurgitant fraction ≥ 50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥ 0.20 $cm^{2\dagger}$ • Regurigitant volume ≥ 30 mL • Regurgitant fraction ≥ 50%	• Regional wall motion abnormalities with reduced LV systolic function. • LV dilation and systolic dysfunction due to primary myocardial disease	• HF symptoms due to MR persist even after revascularization and optimization of medical therapy • Decreased exercise tolerance • Exertional dyspnea

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO due to the crescentic shape of the proximal convergence.

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TABLE 49–2. Supportive Echocardiographic Criteria for Diagnosis of Severe Ischemic Mitral Regurgitation

Effective regurgitant orifice area (EROA) ≥ 0.2 cm^2
Regurgitant volume (RV) ≥ 30 mL
Vena contracta width ≥ 0.7 cm
Color-flow regurgitant jet area/left atrial area ≥ 40%
Peak mitral valve E-wave velocity > 1.2 m/s
Dense, triangular continuous-wave Doppler profile
Systolic flow reversal in the pulmonary veins
Enlarged LV size
Enlarged LA size
Large, wall-impinging or swirling jet pattern
± LV systolic impairment

Note differences in EROA and RV between secondary and primary MR for definition of "severe."

in secondary MR (Tables 49–1 and 49–2).[14] Unlike in primary MR where an ERO ≥ 0.4 cm^2 indicates severe MR that eventually causes LV damage, definition of severe secondary MR is fraught with some uncertainty because the LV is *already* damaged when secondary MR develops. Although some investigators have recommended that an ERO of 0.2 cm^2 is consistent with severe secondary MR on the basis of natural history studies, recent large clinical trials have defined severe secondary MR as ≥ 0.4 cm^2.[6] Thus, the definition of what constitutes severe secondary MR should not rely on a single variable but should take all indicators of severity into account in an integrative manner (see the next section).

ASSESSMENT

PHYSICAL EXAMINATION

Findings on physical examination depend on duration and severity of IMR as well as the degree of clinical compensation. The pulse may be unremarkable, irregular because of coexistent atrial fibrillation (AF), or rapid because of sympathetic overdrive in the context of HF. Systolic blood pressure and pulse pressure may be reduced as a result of reduced forward stroke volume, but this finding is nonspecific and variable. The venous pressure may be elevated. The apex beat is displaced downward and to the left in chronic severe IMR as a result of LV dilatation. The typical murmur is holosystolic, loudest at the apex, and radiates to the axilla. The murmur may be more easily heard with the patient lying in the left lateral position in forced expiration and can be made louder with maneuvers that increase LV afterload. Although there is a correlation between murmur intensity and severity of MR, this correlation is weaker for patients with IMR than primary MR.[15] Severe mitral regurgitation may be accompanied by a third heart sound (S_3) produced by rapid emptying of a large left atrial volume under higher than normal pressure into the LV; in this setting, an S_3 may be an indicator of MR severity rather than HF severity.

TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) is recommended to confirm the etiology of MR, assess LV size and systolic function, quantitate the severity of MR, screen for the presence of other valve or structural abnormalities, and provide an estimate of pulmonary artery pressures.[14] TTE also allows for an assessment of the MV apparatus including leaflet morphology, displacement of the papillary muscles, systolic tethering of mitral leaflets, and annular dilation (Videos 49–1 to 49–4).

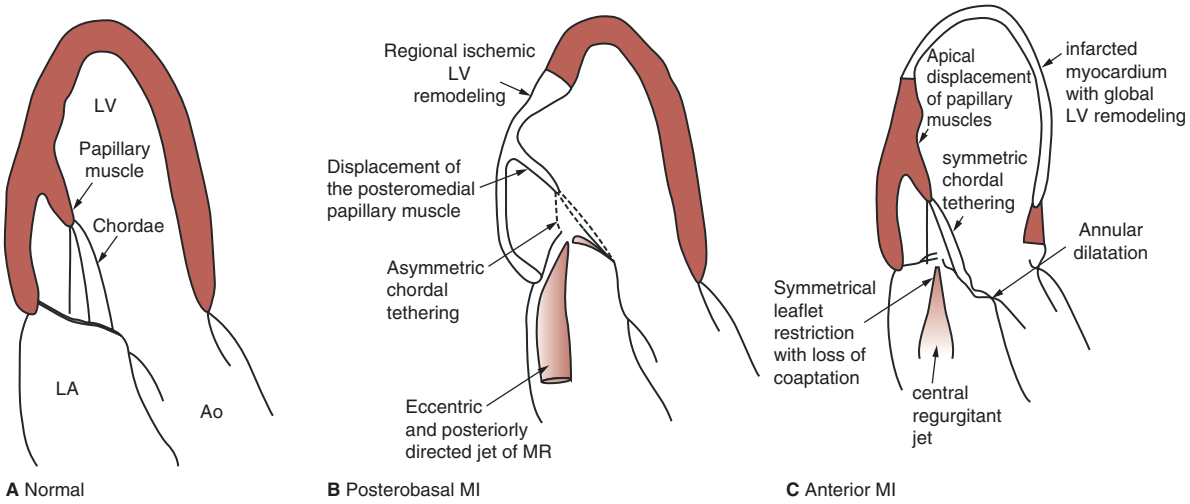

FIGURE 49–2. Mechanisms of ischemic mitral regurgitation. Panel **A** demonstrates normal mitral valve and left ventricle anatomy. Panel **B** demonstrates mechanisms of ischemic mitral regurgitation following posterobasal myocardial infarction where regional LV remodeling results in displacement of the posteromedial papillary muscle with asymmetric tethering of the posterior mitral leaflet and eccentric MR. Panel **C** illustrates mechanism of MR following an anterior myocardial infarction where global LV remodeling causes apical and lateral displacement of both papillary muscles; subsequent symmetric tethering of both mitral leaflets and annular dilatation generate central MR. Ao, Aortic root; LA, left atrium; LV, left ventricle.

Color-Flow Doppler Assessment of IMR Severity

Color-flow regurgitant jet area is obtained by calculating the average of the MR jet area traced in the apical two- and four-chamber views. The MR regurgitant jet area/left atrial area ratio is then calculated, and MR is graded as follows:

- < 20%: Mild MR
- 20% to 39%: Moderate MR
- ≥ 40%: Severe MR

The often eccentric nature of the regurgitant jet in IMR renders this semiquantitative method less helpful in assessment of MR severity in cases of IMR compared to primary MR. In addition, jet area is influenced by physiological loading conditions (eg, blood pressure, volume status).

Vena contracta width is a simple, semiquantitative method of grading MR severity that measures the width of the narrowest portion of the MR jet that occurs at or just downstream from the regurgitant orifice (Fig. 49–3). MR is graded as follows:

- < 0.3 cm: Mild MR
- 0.3-0.69 cm: Moderate MR
- ≥ 0.7 cm: Severe MR

This method is less influenced by loading conditions than regurgitant jet area.

Effective regurgitant orifice area (EROA) and MR regurgitant volume can be measured using the proximal isovelocity surface area (PISA) method. This method is based on the principle that mitral regurgitant flow converges uniformly and radially towards the MV orifice, creating concentric hemispherical shells with gradually decreasing surface area and increasing velocity on the LV side of the MV leaflets. As flow accelerates toward the MV orifice on color-flow Doppler imaging, the aliasing velocity (Nyquist limit) is exceeded and the color reverses, producing a colored hemisphere (Fig. 49–4). The velocity at the surface of the hemisphere equals the Nyquist limit. Applying the conservation of mass principle, flow at the surface of the hemisphere is the same as flow through the regurgitant orifice. Therefore, EROA can be calculated from the radius of the PISA hemisphere at the first aliasing boundary, the aliasing velocity, and the peak MR velocity on continuous-wave Doppler, using the following equation:

$$\text{EROA} = 2 \times \pi \,(\text{radius})^2 \times \text{aliasing velocity/peak MR velocity}.$$

Regurgitant volume can then be calculated using the EROA and the velocity time integral (VTI) obtained from tracing the continuous-wave Doppler profile of the regurgitant jet, using the following equation:

$$\text{Regurgitant volume} = \text{EROA} \times \text{VTI of the MR jet}$$

The PISA method assumes that the proximal flow convergence is hemispheric, which is rarely the case with eccentric IMR jets. This can result in an underestimate of EROA in IMR cases. This may partly explain why lower thresholds of EROA are associated with worse prognosis in IMR and why valvular heart disease guidelines propose lower threshold values of EROA (≥ 0.2 cm^2 rather than 0.4 cm^2) and regurgitant volume (≥ 30 mL rather than 60 mL) for defining severe IMR compared to those used for primary MR (Table 49–2). IMR is more a disease of the LV than the MV and natural history studies have shown these lower thresholds to be prognostically important. In the context of established LV dysfunction, smaller regurgitant volumes are associated with worse survival, but no study has convincingly demonstrated that correction of secondary MR improves survival. Using Koch's postulates, this argues against a cause-and-effect relationship between smaller MR volumes and reduced longevity in this setting. Other limitations of the PISA method include lack of validation for multiple jets and poor reproducibility.

Other indicators of severe MR include a peak mitral valve E-wave velocity > 1.2 m/s, a dense triangular continuous-wave Doppler profile, and systolic flow reversal in the pulmonary veins.[16] Grading of IMR should not rely on any single parameter, but rather defining severe MR requires careful integration of multiple echocardiographic parameters,

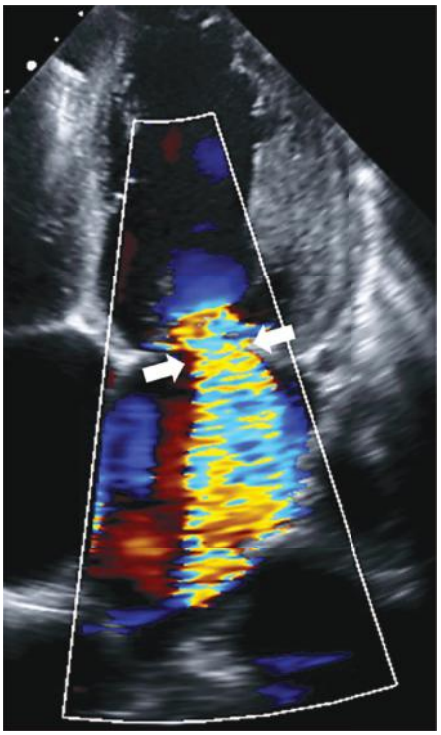

FIGURE 49–3. Vena contracta of ischemic mitral regurgitation jet. *White arrows* indicate the narrowest portion of the regurgitant jet.

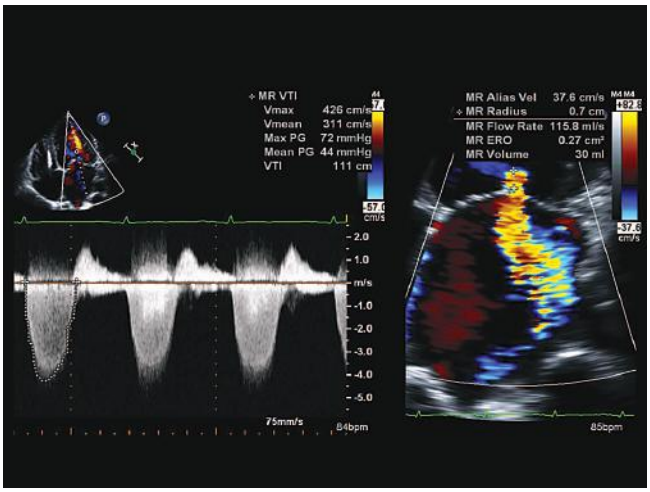

FIGURE 49–4. Peak mitral regurgitation velocity and velocity time integral (VTI) obtained from tracing the continuous-wave Doppler profile of mitral regurgitant jet (left) and proximal flow convergence region of color-flow Doppler assessment (right) in a patient with ischemic mitral regurgitation. The effective regurgitant orifice area (EROA) can be calculated from the radius of the hemisphere at the first aliasing boundary, the aliasing velocity, and the peak MR velocity on continuous-wave Doppler, using the following equation: EROA = 2 × π (radius)² × aliasing velocity/peak MR velocity. Regurgitant volume can then be calculated from the product of EROA and VTI of the regurgitant jet.

clinical data, and assessment of LV size and function, with discounting of poor-quality data.[17]

TRANSESOPHAGEAL AND THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) can be complementary to TTE, and often offers superior visualization of the valve apparatus. In particular, the anatomy of individual segments (scallops) of the MV leaflets is better assessed with TEE. In addition, TEE is useful for confirming the necessary anatomic characteristics for sufficient leaflet tissue for mechanical coaptation using the MitraClip system: a leaflet coaptation length of at least 2 mm and a coaptation depth of no more than 11 mm (Fig. 49–5).[18] Given that MR is sensitive to loading conditions, MR grade as assessed at time of TEE in the sedated/anesthetized patient is often lower than in the setting of baseline ambulatory loading conditions. Because intraoperative loading conditions alter assessment of MR severity, surgical planning is based on preoperative assessment of MR severity in the awake patient.

Three-dimensional echocardiography can provide superior imaging of leaflet morphology and allows for direct visualization and measurement of the EROA, offering a more precise alternative to the two-dimensional PISA method of EROA assessment.[19]

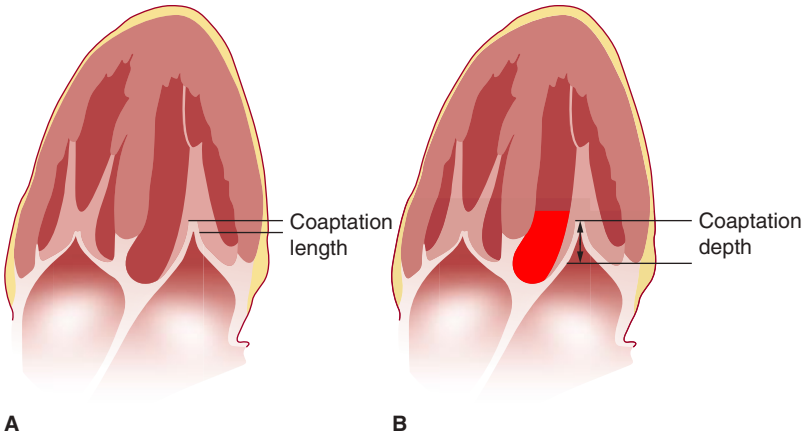

FIGURE 49–5. Coaptation length (**A**) and coaptation depth (**B**): key anatomic considerations in assessing eligibility for the MitraClip device.

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging is used increasingly to assess LV volumes and function in patients with MR. In addition, valve leaflet morphology, regional LV function, LA size, and myocardial viability on delayed enhancement imaging, can all be assessed with this single test[20] (Video 49–5, Fig. 49–6). Indeed, the extent of basal scarring on delayed enhancement imaging in patients undergoing surgical therapy for IMR correlates with LV functional recovery and postoperative adverse outcomes.[21]

EXERCISE TESTING

IMR is a dynamic lesion, and MR severity can vary over time and during exercise.[22] Thus, the severity of IMR at rest does not necessarily reflect the severity of MR during exercise. Exercise-induced increase in IMR provides additional prognostic information over resting evaluation and identifies patients at higher risk of adverse clinical outcomes.[23] For example, an increase in EROA of ≥ 13 mm^2 during exercise is associated with increased mortality and HF hospitalizations.[24] Exercise echocardiography has been proposed to evaluate patients with exertional dyspnea out of proportion to the degree of resting IMR and LV dysfunction, patients with IMR and unexplained acute pulmonary edema, and patients with moderate IMR at rest who are due to undergo surgical revascularization with CABG.[23,25] Exercise echocardiography is preferred over dobutamine stress echocardiography because of dobutamine-mediated decreases in afterload and therefore MR severity.[22]

Furthermore, given the central importance of symptoms in the management algorithm for IMR, it is paramount that patients' subjective reports of exertional symptoms are corroborated with objective data. An objective assessment of functional capacity and exercise limitation can be obtained from exercise treadmill testing, 6-minute walk distance, and cardiopulmonary exercise testing (CPET). Such assessments may unmask unrecognized exertional symptoms/limitation.

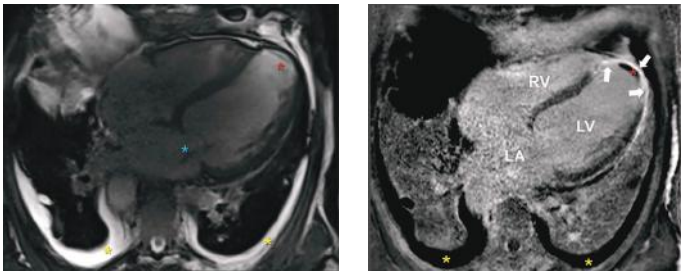

FIGURE 49–6. A. Still frame from a four-chamber steady-state free precession (SSFP) cine cardiac magnetic resonance image (Video 48–5) demonstrating a dilated left ventricle (LV) with severely impaired systolic function and regional wall-motion abnormalities including akinesis of the LV apex and apical segments caused by prior myocardial infarction. A jet of ischemic mitral regurgitation (*blue asterisk*), LV apical thrombus (*red asterisk*), and bilateral pleural effusions (*yellow asterisks*) are evident. **B.** Four-chamber view from delayed enhanced cardiac magnetic resonance imaging from same patient as in panel A (Video 48–5). There is transmural late gadolinium enhancement (*white arrows*) involving the apex, apical septum, and apical lateral segments of the left ventricle (LV) consistent with myocardial infarction. In addition, LV apical thrombus (*red asterisk*) and bilateral pleural effusions (*yellow asterisks*) are again noted. LA, left atrium; LV, left ventricle; RV, right ventricle.

CORONARY ANGIOGRAPHY AND NONINVASIVE STRESS IMAGING/VIABILITY ASSESSMENT

In cases of IMR and LV systolic impairment, it is important to evaluate for myocardial ischemia and/or hibernating viable myocardium given the potential for improvement in LV function with revascularization. Noninvasive evaluation for myocardial ischemia can be performed with either exercise or pharmacological stress nuclear myocardial perfusion imaging (single-photon emission computed tomography [SPECT] or positron emission tomography [PET]), CMR, or echocardiography. Viability assessment can also be performed with SPECT, PET, dobutamine stress echocardiography, or CMR. Identification of ischemic or hibernating viable myocardium should prompt consideration of invasive coronary angiography to define coronary anatomy, with subsequent revascularization as appropriate.

TREATMENT

Treatment of IMR depends on symptoms, the severity of regurgitation, the degree of LV systolic dysfunction, and its potential improvement with medical and surgical interventions. Therapy consists of an appropriate

combination of lifestyle, medical, device, percutaneous, and/or surgical interventions. The pathophysiological differences between primary MR and secondary IMR dictate distinct and separate treatment recommendations for these disease processes. Management decisions for more complex patients with IMR should involve a multidisciplinary "heart" team that includes but is not restricted to interventional cardiologists, cardiac surgeons, anesthetists, imaging specialists, and heart failure specialists.[26] Established surgical risk scores (eg, Society for Thoracic Surgeons [STS] score, EuroSCORE) should be used as adjuncts to clinical assessment for better risk stratification of patients and to inform management decisions.[27]

MEDICAL THERAPY

Patients with IMR and HF with reduced LVEF should receive standard guideline directed medical therapy for HF, including angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibition (ARNI) as indicated, beta-blockers, aldosterone antagonists, and diuretics.[14] Patients with IMR and HF with preserved ejection fraction may enjoy symptom relief from a trial of loop diuretic therapy. All patients should be educated regarding lifestyle modifications including sodium restriction, fluid restriction, smoking cessation, and regular aerobic exercise as for any patient with HF. Appropriate secondary prevention with moderate or high-intensity statins and antithrombotic therapy should be emphasized. Anticoagulation is indicated for patients who develop AF.

DEVICE THERAPY

Left ventricular dyssynchrony resulting from left bundle branch block (LBBB) or right ventricular (RV) pacing can contribute to the development of secondary MR.[28,29] Cardiac resynchronization therapy (CRT) significantly reduced severity of secondary MR in a small study of 24 patients with HF and LBBB.[30] In another study of 98 patients with moderate to severe secondary MR who underwent CRT, 49% demonstrated an improvement of ≥ 1 grade in MR at 6 months post-device implantation compared to baseline, and this improvement was associated with improved survival.[31] Similarly, Di Biase et al. demonstrated an improvement of ≥ 1 grade in MR after 12 months of CRT in 46% of 275 patients with moderate to severe or severe secondary MR at baseline.[32] This study also demonstrated that MR improvement after 3 months of CRT predicts subsequent MR improvement at 12 months, and so 3 months has been proposed as a waiting period beyond which MR reduction in response to CRT is unlikely and other treatment options should be considered.[33] CRT-mediated improvement in IMR is associated with LV reverse remodeling[34] while associated changes in LV contraction and MV apparatus geometry can reduce mitral leaflet tethering.[7] Thus CRT is recommended for symptomatic patients with chronic severe IMR with guideline indications for device therapy, including HF with QRS duration > 150 msec.[14] In addition, many patients with IMR will often have a coexisting or independent indication for implantable cardioverter defibrillator (ICD) therapy given the associated LV systolic impairment and history of MI.

SURGERY

Significant improvements in surgical techniques and outcomes over recent decades, as reported by high volume-major referral centers of excellence, have lowered the threshold for operative intervention in patients with valvular heart disease. Surgical outcomes depend on the experience of the center and surgeon, and these factors should be considered in decision making. There is general agreement that IMR that is less than moderate in severity does not require surgical intervention. Surgical decisions require consideration of operative morbidity and mortality, type of operation (repair vs replacement), durability of MR reduction, and downstream clinical end points, including functional capacity, HF hospitalizations, and survival. To date, studies have failed to show a survival benefit with surgery for IMR, and thus conservative recommendations have been adopted. Surgical intervention for moderate or severe IMR is discussed below.

Surgery for Moderate IMR

Although moderate IMR is common among patients referred for surgical coronary revascularization, the role of MV repair during CABG in these patients remains uncertain. Revascularization alone may result in sufficient LV reverse remodeling to reduce IMR and improve functional capacity. However, improvement in IMR following CABG alone is variable, difficult to predict and likely a complex function of regional myocardial viability, papillary muscle synchrony, and LV size. Because untreated and persistent, moderate IMR may limit the extent of reverse remodeling that can occur with CABG alone, surgeons have traditionally chosen to perform down-sized annuloplasty repair at the time of CABG, though evidence favoring this approach has been largely observational.

The first single-center randomized trial of patients with moderate IMR assigned 102 patients to CABG plus MV repair (n = 48) or CABG alone (n = 54) and demonstrated significant decreases in LV end-systolic and end-diastolic dimensions, pulmonary artery systolic pressure, mean MR grade (by qualitative assessment), and New York Heart association (NYHA) functional class with CABG plus MV repair versus CABG alone.[8] There was no between group difference in survival at 5 years. HF outcomes were not reported. Nearly 40% of patients randomized to CABG alone had only trivial or mild MR at 5 year follow-up. Aortic cross-clamp and cardiopulmonary bypass times were significantly longer in the CABG plus MV repair group. The multicenter, single blinded Randomized Ischemic Mitral Evaluation (RIME) trial randomized 73 patients referred for CABG with moderate IMR to CABG alone (n = 39) or CABG with MV repair using a downsized annuloplasty ring (n = 34). Functional capacity as assessed by peak oxygen consumption at one year (primary end point) was reported for only 59 patients, but significantly improved in the CABG plus MV repair cohort compared to the CABG alone cohort by a difference of 2.2 mL/kg/min (95% CI 0.7-3.6, $P = .004$). Similarly, greater LV reverse remodeling and reduction in MR volume and plasma B-type natriuretic peptides (BNP) were observed at one year in the CABG plus MV repair cohort. However, the addition of MV repair to CABG was associated with increased operation duration, blood transfusions, intubation duration, and length of hospital stay.[35] In contrast, a larger randomized trial that assigned 301 patients with moderate IMR to CABG alone (n = 151) versus CABG plus MV repair (n = 150) failed to demonstrate a clinically meaningful advantage of adding MV repair at 1 year. The degree of LV reverse remodeling (the primary end point of this trial) at 1 year was similar in both groups, despite a reduced prevalence of moderate or severe MR in the CABG plus MV repair group compared to the CABG alone group (11.2% vs 31%, respectively; $P < .001$). It is interesting to note that the severity of IMR in 69% of patients in the CABG alone group had improved to none or mild MR at 1 year. This trial redemonstrated longer bypass times and longer lengths of hospital stay with combined CABG and MV repair, as well as an increased rate of serious neurologic events (stroke, transient ischemic attack, and metabolic encephalopathy) and supraventricular arrhythmias, but no mortality difference between treatment groups.[36] Two-year results from this study did not identify any significant differences in LV reverse

remodeling, overall hospital readmissions, mortality or a composite end point of death, stroke, subsequent mitral-valve surgery, hospitalization for HF, or worsening functional class between treatment groups. The frequency of moderate to severe MR remained lower in the combined CABG-MV repair group (11.2% vs 32.3% for CABG alone, $P < .001$). Neurologic events and supraventricular arrhythmias remained more frequent in the combined CABG-MV repair group.[37]

In summary, the addition of MV repair to CABG in patients with moderate IMR does not appear to increase perioperative mortality risk but may increase perioperative morbidity as performed in some centers.[38] Studies to date have not been powered to detect differences in survival or functional outcomes between CABG alone and CABG combined with MV repair. Although surgical revascularization alone can decrease MR severity in patients with preoperative moderate IMR, the addition of MV repair is associated with reduced prevalence of moderate or severe MR in follow-up, but whether this translates into clinically meaningful improvements in hard end points remains uncertain. The AHA/ACC Guidelines for Management of Patients With Valvular Heart Disease provide a class IIb recommendation (level of evidence: C) that MV repair may be considered for patients with chronic moderate, secondary MR who are undergoing other cardiac surgery (Table 49–3).[14]

TABLE 49–3. Summary of 2014 AHA/ACC and 2012 ESC Recommendations for Surgical and Percutaneous Interventions for Chronic Moderate or Severe IMR

2014 AHA/ACC Recommendations	2012 ESC Recommendations
Surgery: Chronic Moderate Secondary MR	
MV repair may be considered for patients with chronic moderate secondary MR undergoing other cardiac surgery (COR IIb; LOE C)	Surgery should be considered in patients with moderate MR undergoing CABG (COR IIa; LOE C)
Surgery: Chronic Severe Secondary MR	
MV surgery is reasonable for patients with chronic severe secondary MR undergoing CABG or AVR (COR IIa, LOE C)	Surgery is indicated in patients with severe MR undergoing CABG and LVEF > 30% (COR I; LOE C)
MV surgery may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe secondary MR (COR IIb, LOE B)	Surgery should be considered in symptomatic patients with severe MR, LVEF < 30%, option for revascularization, and evidence of viability (COR IIa, LOE C)
—	Surgery may be considered in patients with severe MR, LVEF > 30%, who remain symptomatic despite guideline directed medical management (including CRT if indicated) and have low comorbidity, when revascularization is not indicated (COR IIb, LOE C)
Percutaneous Edge-to-Edge Repair	
—	Percutaneous MitraClip system may be considered in patients with symptomatic severe secondary MR despite guideline directed medical management (including CRT if indicated), who fulfill echocardiographic criteria for eligibility, have a life expectancy of > 1 year, and are judged inoperable or at high surgical risk by a multidisciplinary heart team (COR IIb, LOE C)

Surgery for Severe IMR

Observational data from the STICH trial suggest that adding MV repair to CABG in patients with LVEF ≤ 35% and moderate to severe MR may improve survival compared to CABG alone (adjusted hazard ratio (HR) for mortality 0.41 (95% CI, 0.22-0.77); $P = .006$), though the number of events in this trial was small.[5] Current AHA/ACC recommendations state that MV surgery is reasonable for patients with chronic severe IMR (stages C and D) who are undergoing CABG or aortic valve replacement (class of recommendation: IIa; level of evidence: C). Surgery may also be considered for patients with chronic severe IMR (stage D) who remain severely symptomatic (NYHA class III to IV) despite optimal guideline-directed medical therapy for HF (class of recommendation: IIb; level of evidence: B).[14] A summary of AHA/ACC and ESC recommendations for surgical management of chronic severe MR is presented in Table 49–3.

In the setting of severe IMR, debate has focused on the role of MV repair versus MV replacement (MVR). Repair has been felt safer with lower perioperative mortality and morbidity, though generally associated with a higher rate of recurrent MR compared with replacement. A randomized multicenter trial assigned 251 patients with severe IMR to undergo either MV repair (n = 126) or chordal-sparing MVR (n = 125) and did not demonstrate any significant difference in LV end-systolic volume indexed to body surface area at 1 and 2 years (primary end point). No differences in survival or the incidence of major adverse cardiac and cerebrovascular events were found. The rate of recurrence of moderate or severe MR was significantly higher in the repair compared to the replacement group (32.6% vs 2.3% at 1 year, $P < .001$; and 58.8% versus 3.8% at 2 years, $P < .001$), resulting in more adverse events related to HF and cardiovascular readmissions. [6,11] Numerous observational studies have identified echocardiographic predictors of recurrent MR following MV annuloplasty, including an LV end-diastolic diameter > 65 mm, coaptation depth > 1 cm, and systolic sphericity index > 0.7.[26] In the randomized trial of repair versus replacement, only basal aneurysms and dyskinesis were significantly associated with recurrent moderate or severe MR in patients following repair for severe IMR.[39] It is important to note that none of the prediction models for recurrent MR have been externally validated. Durability of repair is also influenced by the natural history of underlying ventricular dilation over time; progressive dilation will undermine the integrity of MV repair.

PERCUTANEOUS INTERVENTIONS

Although a variety of percutaneous therapies for MR have been developed, the MitraClip system (Abbott Vascular, CA, USA) has emerged clinically as the most tolerated and effective approach to date. The MitraClip is a transcatheter mitral device for use in high-risk or inoperable patients with severe MR and suitable anatomic criteria. Favorable and unfavorable anatomic criteria are presented in Table 49–4. By means of venous access, the device is advanced into the left atrium using a transseptal approach and grasps the mitral valve leaflets, achieving edge-to-edge approximation, and thereby creating a double mitral valve orifice (Fig. 49–7). It is currently approved by the US Food and Drug Administration for use in symptomatic patients with primary (degenerative) MR who are at prohibitive risk for surgery; it is not approved for treatment of IMR in the United States, but is under investigation for this indication through the Clinical Outcomes Assessment of MitraClip Percutaneous Therapy for Extremely High-Surgical-Risk Patients (COAPT) trial.[16] In contrast, the MitraClip system has already received a class IIb recommendation by the European Society of Cardiology for secondary MR (Table 49–3). Worldwide, it is estimated that approximately two-thirds of the MitraClip procedures have been performed in patients with secondary MR.

TABLE 49–4. Favorable and Unfavorable Anatomic Criteria for Percutaneous Edge-to-Edge Repair of MR

Anatomical MV and LV Characteristics for Percutaneous Edge-to-Edge Repair of MR	
Desirable Criteria	**Undesirable Criteria**
• Moderate to severe MR (≥ grade 3)	• Commissural lesion
• Pathology in the A2-P2 zone	• Short posterior leaflet
• Coaptation length ≥ 2 mm	• Severe asymmetric tethering
• Flail gap < 10 mm	• Calcification in the grasping area
• Flail width < 15 mm	• Severe annular calcification
• MV orifice area > 4 cm^2	• MV cleft
• MV leaflet length > 1 cm	• Severe annular dilation
	• Severe LV remodeling
	• Large (> 50%) inter-commissural extension of regurgitant jet
	• Severe myxomatous degeneration with multi-scallop prolapse

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Only 27% of patients in the original EVEREST (Endovascular Valve Edge-to-Edge Repair) II study, which was designed to assess the safety and effectiveness of the MitraClip device, had secondary MR.[40] In contrast, 77% of 567 patients enrolled in the European prospective, muticenter, nonrandomized postapproval ACCESS-EU study of MitraClip therapy had secondary MR. Of patients with secondary MR in this real-world postapproval experience, 41% were over 75 years of age (mean age = 73 y) and 48% had a logistic EuroSCORE ≥ 20%. Mortality at 1 year for these patients was 17%. Most patients (91.7%) achieved reduction in MR to ≤ 2+ at discharge, but 21.5% manifested > 2+ MR at 12 months. Improvements were observed in NYHA functional class, six-minute walk distance, and Minnesota Living with HF Questionnaire score.[41] Fifty-nine percent of the 78 patients with severe symptomatic MR and an estimated surgical mortality rate of ≥ 12% who underwent the MitraClip procedure as part of the EVEREST II high-risk study had secondary MR. In this study, the MitraClip device reduced MR in the majority of patients, resulting in LV reverse remodeling, improvement in NYHA functional class, and improvements in quality of life over 12 months. Furthermore, the 12-month survival rate for this high-risk cohort treated with MitraClip was 76% compared to 55% in a group of patients screened concurrently but not enrolled in the study who received standard of care.[42] Direct, nonrandomized comparisons between MitraClip therapy and surgery are difficult because of significant differences in patients referred for either strategy.

It will be necessary to continuously reappraise safety and efficacy of MitraClip therapy as experience grows in high-volume centers treating higher surgical risk patients with secondary MR with advanced LV dysfunction/remodeling and greater burden of comorbidities. In summary, percutaneous edge-to-edge repair using the MitraClip system is an alternative that can reduce symptoms and induce LV reverse remodeling but is often associated with residual and recurrent MR. As such, it can be considered as an adjunct to guideline directed medical therapy (with or without CRT) in stage D IMR who fulfill anatomical criteria and are judged high-risk or inoperable by a multidisciplinary heart team in Europe,[26] but it is not currently approved for IMR in the United States outside of clinical

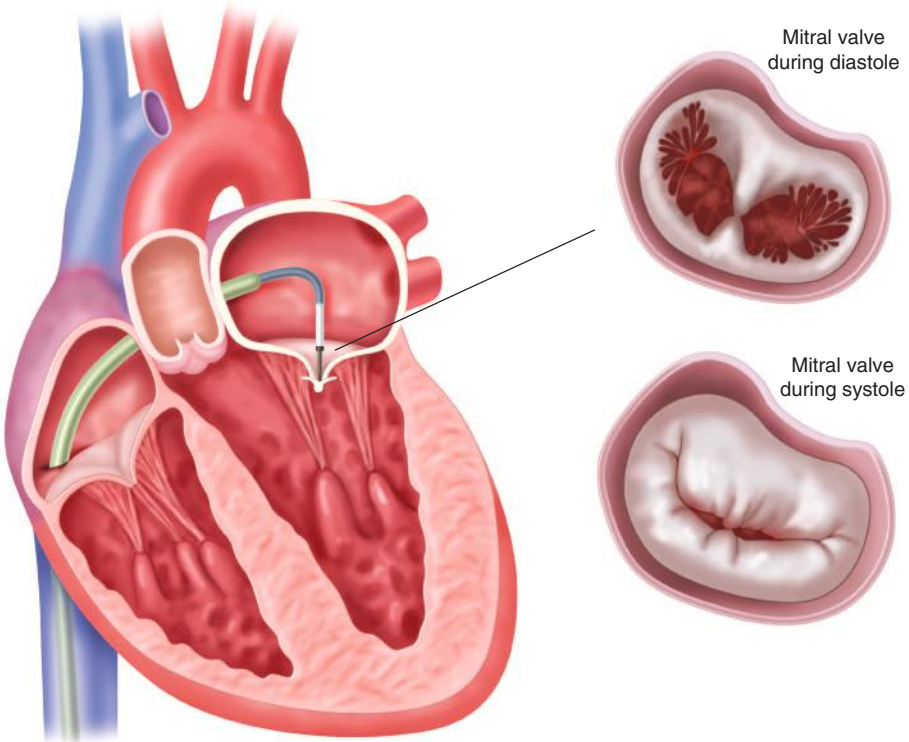

FIGURE 49–7. Percutaneous edge-to-edge repair of the mitral valve. The MitraClip is advanced through a catheter placed in the femoral vein across the interatrial septum into the left atrium. The open clip is advanced through the mitral valve into the left ventricle. The device is then pulled back to grasp the mitral leaflets and the clip is closed to establish an edge-to-edge approximation of the mitral valve leaflets, creating a double mitral valve orifice.

trials. Intense investigational efforts are underway in the application of other transcatheter therapies in the management of MR.[43]

MANAGEMENT OF CAD

Given the causal association of CAD and IMR, guideline-directed management of CAD is important in patients with IMR.[44] Prompt reperfusion in the setting of acute ST-elevation myocardial infarction to minimize adverse LV remodeling and injury to papillary muscles is paramount to prevent/reduce subsequent IMR. Evidence of myocardial ischemia and/or myocardial viability on cardiac imaging in patients with IMR should prompt consideration of percutaneous or surgical revascularization, in the hope of promoting LV reverse remodeling.

MANAGEMENT OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is commonly associated with MR, and is present in up to 50% of patients undergoing MV surgery.[45] LA chamber enlargement as a consequence of increased pressure and volume load to the LA from MR is implicated in genesis of AF.[46] AF may be a marker of disease progression and worse prognosis in IMR. Management of AF in terms of rate control, rhythm control, and anticoagulation should be according to international practice guidelines.[47] Surgical approaches for atrial fibrillation with/without left atrial appendage ligation can be considered in patients undergoing MV surgery. Risk factors for return of AF after the Cox maze procedure include duration of preoperative AF, left atrial size, and reduced LV function.[48]

ADVANCED HEART FAILURE THERAPIES

Select patients with advanced stage D heart failure and IMR, who are refractory to guideline-directed medical therapy, should be referred to an advanced heart failure service for consideration of cardiac transplantation and/or durable mechanical circulatory support (eg, left ventricular assist device) either as destination therapy or bridge to transplantation. Advanced age and significant burden of comorbidities render many patients with IMR ineligible for these therapies.

PALLIATIVE CARE

The morbidity and mortality associated with IMR increase with severity of disease, and the trajectory of the disease is unpredictable. Therefore, it is important to consider referral to palliative care services at a timely point in this chronic life-limiting illness. Involving palliative care specialists can facilitate conversations around advanced care planning.[49]

CONCLUSIONS

IMR frequently complicates ischemic heart disease and is associated with functional and prognostic limitations. The mechanism of IMR is related to distortion of the normal spatial and functional relationships of the LV and MV apparatus, usually as a consequence of LV adverse remodeling following myocardial ischemia/infarction. Noninvasive imaging, which usually employs echocardiography at rest and stress, is useful to establish etiology and severity of IMR, and to assess for myocardial ischemia and/or viability. Accurate grading of IMR severity is challenging and requires careful integration of multiple imaging parameters at rest and/or during exercise, and clinical data, in addition to a careful assessment of LV size and function. Given that IMR is primarily a disease of the myocardium, guideline-directed medical therapies of associated CAD and HF, including appropriate use of CRT, that may promote LV reverse remodeling are paramount in IMR. The role of MV surgery in IMR remains controversial, especially in patients who do not require concomitant CABG or other valve surgery. Percutaneous mitral valve repair offers an invasive alternative to surgery in select patients and its role in management of IMR is the subject of a large randomized clinical trial (COAPT). IMR appropriately remains the focus of much clinical research because of the need for better therapies to improve outcomes for this common, progressive, and morbid disease.

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CHAPTER 50

MITRAL STENOSIS

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ETIOLOGY

Worldwide, most cases of mitral stenosis (MS) are caused by rheumatic heart disease (RHD) (Fig. 50–1).[1] However, rheumatic fever (RF) has become quite rare in developed nations and so too has MS. Indeed, most MS in the United States occurs in patients who have emigrated here from countries where rheumatic fever is still commonplace. Why rheumatic fever has waned in developed nations is unclear. Although antibiotic use almost certainly plays a role,[2] the decline in disease incidence began before antibiotics were widely available, suggesting that socioeconomic factors also play a key role in the disease process. In addition, the organism responsible (group A *Streptococcus*) itself may have mutated to a less rheumatologic agent. Degenerative calcific MS may be confused with rheumatic MS. Although the incidence of degenerative calcific MS increases in the very elderly, the MS is most often mild to moderate, and does not require intervention.

RHD remains prevalent in developing countries. Using echocardiographic screening, the prevalence of RHD ranged from 20 to 30 per 1000 school children.[3,4] This leads to a large pool of rheumatic MS. Forty percent of patients with RHD have isolated MS but only 60% of these patients report a past history of rheumatic fever.[4,5]

Rheumatic MS is a progressive disease. The time interval between rheumatic fever and the clinical appearance of MS varies considerably among various countries. In developed countries, the disease appears to take two to four decades before symptoms appear.[5-8] Thus presentation in the west is in the fifth to sixth decades of life.[5-11] In developing countries, the disease may progress much more rapidly, leading to symptoms by the age of 20 (juvenile MS), often within five years of the initial attack of RF.[12] This is likely to be as a result of recurrences of RF (either clinical or subclinical). The mean age of symptom onset in developing countries is between the third and fourth decades.[11,13] Progression from mild to severe disability takes a decade.[6,8] Once symptoms develop, the prognosis becomes poor if left untreated. Among 271 symptomatic patients,[7] the 10-year survival of patients in functional class II, III, and IV was 69%, 33%, and 0%, respectively. Only half of the patients in functional class II remained alive at 20 years with none among class III patients. Overall, the mortality was 70% over an average period of 11 years.[7]

There is a progressive reduction in the valve area by an average of 0.09 cm^2 per year.[14,15] There is considerable inter-individual variability, with 27% of the patients having no change and one-third of the patients having a more rapid decrease (> 0.1cm^2/y).[14] Those with a larger initial valve area had a greater rate of decrease in valve area.[14] Another study noted that those with a Wilkin's echocardiographic score greater than 8 were more likely to have a progressive course.[15] Eighty percent of those with a score ≥ 8 had a progressive course as compared to only 5% with a score < 8.[15] Although it is clear that rheumatic fever causes the disease, the exact mechanisms are still controversial. It is generally agreed that rheumatic fever occurs after infection with group A *Streptococcus*.[16-18] The bodily defense against the organism attacks "M" protein antigens shared by the bacterium and the heart in some patients.[17] Thus, there is an inflammatory response that leads to cardiac damage, potentially of all three cardiac layers, the pericardium, myocardium, and endocardium. However, it is the endocardium, from which the cardiac valves are derived, that is most severely affected. Although all four valves may become damaged, the mitral valve is virtually always affected, but the reasons for this propensity are unclear. Perhaps greater mechanical stress on the mitral valve causes the inflammatory process to be manifested more severely there than on other valves.

The initial attack causes inflammation, thickening, and retraction of the mitral leaflets, usually causing mild mitral regurgitation, which may disappear as the attack subsides. Why MS develops later is not entirely clear, but at least three factors contribute to the process: gender, the severity of carditis in the first attack, and the number of subsequent attacks. Mitral stenosis is primarily a disease of women, with a 3:1 female preponderance. If after the initial attack there is little evidence of valvulopathy and no subsequent attacks occur, the chance that the patient will develop severe MS later in life is probably less than 5%.[19] Subsequent attacks can be prevented by faithful adherence to antibiotic prophylaxis. However, what pathologic processes occur between the initial attack of acute rheumatic fever and eventual development of MS (when it does occur) are uncertain. At the time of surgery for MS there are active Aschoff nodules (the pathognomonic lesion of rheumatic fever) in the left atrial appendages of many patients, suggesting that a smoldering rheumatic process persists years after the last acute attack.[20] Alternatively, it may be that after the initial lesion is created by rheumatic fever, hemodynamic stress on the valve may lead to continued inflammation and scarring. In fact, C-reactive protein is elevated in many MS patients, indicative of ongoing inflammation from either or both processes.[21,22]

Occasionally MS develops from nonrheumatic causes. Extensive annular calcification in the elderly may limit valve area.[23] Approximately 50% of such patients progress to more severe disease over time.

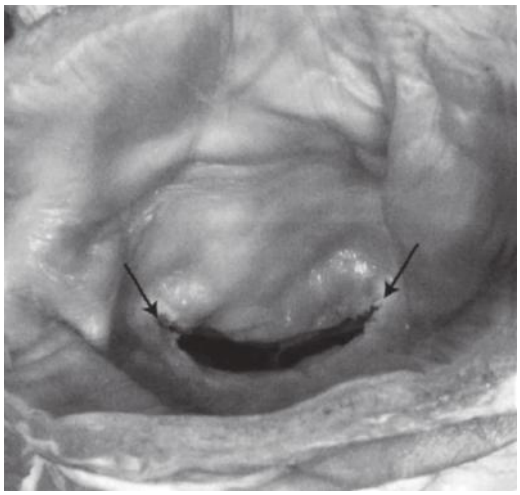

FIGURE 50–1. The typical *fish mouth* appearance of rheumatic mitral stenosis is shown. Reproduced with permission from Otto CM, ed. *Valvular Heart Disease*. Philadelphia: WB Saunders; 1999.

Radiation and restrictive mitral valve repair for mitral regurgitation are additional rare causes.[24,25] At the other end of the age spectrum, congenital malformation is another cause of MS.

PATHOPHYSIOLOGY

The main pathology in rheumatic MS is commissural fusion, leaflet thickening, and choral fusion and shortening leading to a typical "fish-mouth" appearance. In normal subjects, mitral valve area (MVA) is 4.0 to 5.0 cm^2, such that in diastole there is hemodynamically a common chamber of the left atrium (LA) and left ventricle (LV). Thus, as shown in Fig. 50–2A, there is an initial small gradient across the mitral valve that rapidly dissipates so that throughout most of diastole, pressures in the LA and LV are equal. However, in MS, as the mitral valve becomes progressively narrowed, a gradient develops across the valve (Fig. 50–2B) so that LA pressure exceeds LV pressure.[26] As MS worsens, LA pressure becomes progressively higher, in turn creating progressively more pulmonary congestion The force needed to overcome the increased LA pressure and to drive blood past the stenotic mitral valve is generated by the right ventricle (RV), such that right ventricular pressure and pulmonary pressure become elevated. As MS becomes severe, secondary vasoconstriction in the pulmonary bed causes a further increase in pulmonary artery pressure, and pulmonary hypertension may become extreme. The exact cause of pulmonary vasoconstriction in MS is unknown. It is known that pulmonary hypertension is almost always reversed by relief of MS[27] and also can be reversed by administration of phosphodiesterase inhibitors such as sildenafil[28] or by nitric oxide inhalation.[29] These data suggest that the nitric oxide pathway is in some way involved in the mechanism of pulmonary vasoconstriction and pulmonary hypertension in MS. Occasional patients have structural changes in the pulmonary bed leading to a disproportionate pulmonary hypertension that is not completely resolved with relief of MS.

The 2014 ACC/AHA guidelines[30] for the management of valvular heart disease have provided a new staging system for rheumatic MS along with a revision of the grades of severity (Table 50–1). The definition of "severe" MS has been based on the severity at which symptoms occur and at a level when interventional treatment improves symptoms. Severe MS has now been defined as ≤ 1.5 cm^2, unlike previous guidelines[31] where it was ≤ 1.0 cm^2 (Table 50–2).This will make comparisons with historical cohorts problematic. Further, a large number of patients remain asymptomatic even with valve areas of 1.3 to 1.4 cm^2 and the guidelines make it clear that intervention is not indicated in such patients.

HEART FAILURE AND LEFT VENTRICULAR FUNCTION

It is generally held that MS "protects" the LV from damage. That is, unlike other left-sided valve lesions, MS creates no overload on the LV and in fact may decrease preload by impairing LV filling. It is of interest then that approximately one-third of patients with MS have reduced indexes of LV ejection performance.[32-34] The mechanism of reduced LV ejection has been the subject of controversy for many years, and some have invoked a "myocardial factor" (myocardial damage from rheumatic fever) as the cause. Although rheumatic fever may cause LV damage in developing countries where the rheumatic process may be very aggressive,[35] in developed countries, LV contractility in MS appears to be normal. Instead, reduced LV performance is caused by abnormal loading conditions. Unexpectedly, afterload may be abnormally high in some patients with MS.[34] Increased afterload accrues in part from arterial vasoconstriction caused by sympathetic reflexes to decreased cardiac output. In addition, the LV in some MS patients remodels in such a way that the LV is thinner than normal, increasing wall stress (afterload).[34,35] In most other cardiac diseases, increased afterload is offset by increased preload to maintain stroke volume. However, MS limits LV filling, preventing full utilization or preload reserve, and thus ejection fraction is reduced. Proof of this concept follows from the changes seen immediately after balloon mitral valvotomy, where acute relief of LV inflow obstruction results in rapid correction of LV ejection indexes, indicating that loading abnormalities rather than a myocardial factor must have been involved.[36]

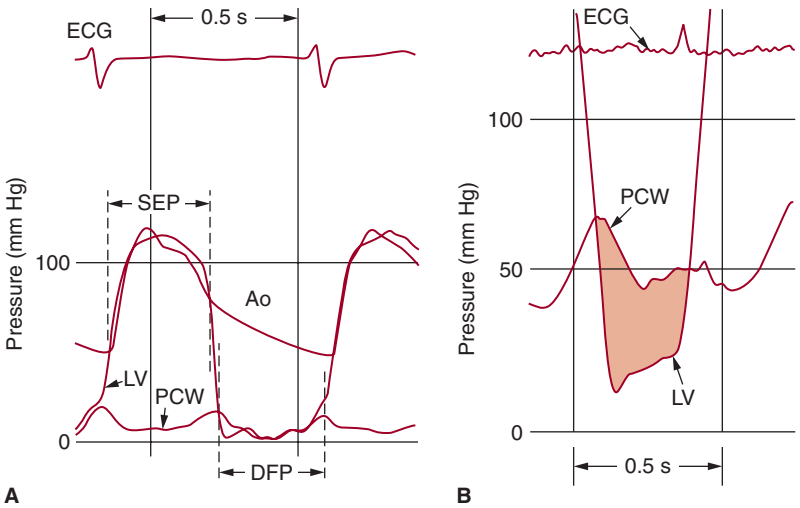

FIGURE 50–2. A. Normal left ventricular (LV), left atrial (LA), and aortic (Ao) pressure tracings are shown. DFP, diastolic filling period; ECG, electrocardiogram; SEP, systolic ejection period. **B.** The pressure gradient between pulmonary capillary wedge pressure (PCW) and left ventricle (LV) is shown for a patient with MS. In this figure, the LV end-diastolic pressure is atypically elevated, consistent with coincident mitral regurgitation. Reproduced with permission from Baim DS, Grossman W: *Grossman's Cardiac Catheterization, Angiography, and Intervention*, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.

TABLE 50–1. Stages and Severity of Mitral Stenosis

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MS	Mild diastolic valve doming	Normal transmitral flow velocity	None	None
B	Progressive MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimetered MVA > 1.5 cm^2	1. Increased transmitral flow velocities 2. MVA > 1.5 cm^2 3. Diastolic pressure half-time < 150 ms	1. Mild-to-moderate LA enlargement 2. Normal pulmonary pressure at rest	None
C	Asymptomatic severe MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimetered MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS)	1. MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS) 2. Diastolic pressure half-time ≥ 150 ms (diastolic pressure half-time ≥ 220 ms with very severe MS)	1. Severe LA enlargement 2. Elevated PASP > 30 mm Hg	None
D	Symptomatic severe MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimetered MVA ≤ 1.5 cm^2	1. MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS) 2. Diastolic pressure half-time ≥ 150 ms (diastolic pressure half-time ≥ 220 ms with very severe MS)	1. Severe LA enlargement 2. Elevated PASP > 30 mm Hg	1. Reduced exercise tolerance 2. Exertional dyspnea

MVA, Mitral valve area

Data from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014 Jun 10;63(22):2438-2488.

TABLE 50–2. Mitral Stenosis Severity as per ACC/AHA 2006 Guidelines

Mild MS	MVA > 1.5 cm^2, Mean gradient < 5 mm Hg[a], PASP < 30 mm Hg
Moderate MS	MVA 1-1.5 cm^2, Mean gradient 5-10 mm Hg[a], PASP 30-50 mm Hg
Severe MS	MVA < 1.0 cm^2, Mean gradient > 10 mm Hg[a], PASP > 50 mm Hg

[a]Valve gradients are dependent upon transvalvular flow. The gradients suggested in this table assume a normal cardiac output and may not pertain to patients with abnormally high or low transvalvular flows. MVA, mitral valve area.

Data from American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists. Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006 Aug 1;114(5):e84-e231.

Diastolic function in MS may also be abnormal. Reverse LV remodeling to smaller than normal volume and regional tethering caused by distortion of the subvalvular apparatus lead to abnormal LV compliance. Like the systolic abnormalities noted earlier, these are also reversed rapidly after balloon valvotomy.[37]

RIGHT VENTRICULAR FUNCTION

The pulmonary hypertension that develops in MS causes right ventricular pressure overload and eventual RV failure. Although the irregular shape of the RV makes assessment of contractility difficult, most studies have concluded that RV failure, like LV failure, in MS is mostly caused by afterload excess rather than contractile dysfunction.[38,39] This is in contradistinction to experimental RV pressure overload, where contractile dysfunction has been well documented. Thus MS causes reduced cardiac output and pulmonary congestion typical of LV failure, yet these abnormalities are more the consequence of abnormal loading and LV remodeling rather than of myocardial dysfunction. Likewise, RV failure also seems to be a consequence of increased afterload rather than of myocardial dysfunction.

CLINICAL PRESENTATION

HISTORY

Most patients with mild MS are asymptomatic. Indeed, many women are unaware that they have the disease until the increased cardiac demands of pregnancy cause symptoms to appear. Conditions that increase cardiac output and/or heart rate such as infection, hyperthyroidism, anemia, or atrial fibrillation (AF) may precipitate symptoms. As MS worsens, symptoms typical of left-sided heart failure occur. Thus dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea are common. Pulmonary edema may be precipitated. If pulmonary hypertension develops, ascites and edema may follow. The development of pulmonary hypertension may paradoxically reduce dyspnea by creating a proximal obstruction. A symptom seen in MS but rare in other causes of heart failure is hemoptysis, usually during activity. As predicted by the Gorlin formula,[40] if exercise causes cardiac output to double, the transmitral gradient will quadruple, causing a sudden increase in LA pressure. This increase is thought to cause rupture of small pulmonary vein anastomoses, leading to frank hemoptysis to be distinguished from the pink frothy sputum seen in pulmonary edema. In cases where the LA becomes so large that it impinges on the left recurrent laryngeal nerve, hoarseness appears (Ortner syndrome).

PHYSICAL EXAMINATION

Physical examination of the patient with MS may reveal a plethora of signs, many of which are subtle, so that the exam should take place in a quiet, undisturbed setting. If the patient is experiencing rapid atrial fibrillation, many signs may be inaudible, obscuring the diagnosis. The sensitivity, specificity and predictive value of these cardiac findings, either singly or in combination, has never been examined, most of which were described in the era preceding that of evidence-based medicine. Cardiac examination may find the irregularly irregular pulse of atrial fibrillation, common in older patients with MS. The pulse

pressure may be reduced, indicating a low stroke volume. This may lead to the typical "mitral" faces with plethoric cheeks with bluish patches. The jugular venous pulse may show a prominent a wave in the presence of pulmonary hypertension. With atrial fibrillation, the "a" wave and "x" descent are absent. The apex beat is usually in its normal position of a tapping nature, but palpation may reveal a diastolic thrill when the patient is examined in the left lateral decubitus position. Palpation of the sternum may find an RV lift in the presence of pulmonary hypertension. A loud P_2 may be palpable in the second intercostal space. S_1 is typically quite loud because the transmitral gradient holds the valve open throughout diastole rather than allowing the valve to drift closed just before systole, as it normally does. Thus systole closes the valve from its fully open (albeit stenotic) position, creating a loud S_1. However, in far advanced disease, the valve may have little motion and S_1 becomes soft. S_2 may be normal, or its P_2 may be loud if pulmonary hypertension has developed. S_2 is then followed by an opening snap (OS), and the S_2-OS interval gives a good clue to the severity of the MS. As severity worsens, the LA pressure increases so that LA pressure exceeds LV pressure (the force that opens the valve) relatively soon after S_2, and the S_2-OS interval is short, approximately 60 ms, just a bit longer than the normal splitting interval of A_2 and P_2 during inspiration. Conversely, in mild disease, the S_2-OS interval is long, approaching 120 ms, similar in cadence to an S_3. It should be noted that S_3 and S_4, sounds produced by rapid LV filling, are typically absent in this disease that impairs the transfer of blood from LA to LV. After the OS, the typical low-pitched rumble of MS is heard best at the LV apex with the bell of the stethoscope in the left lateral position with the breath held in expiration. If the patient is in sinus rhythm, there may be presystolic accentuation of the murmur. The murmur may be very soft in obese patients, those with emphysema, and those with a low cardiac output and fast ventricular rate. The duration of the murmur correlates with severity of MS. In mild MS, the murmur is short, while in severe MS it heard throughout diastole. With the onset of AF, the intensity of S_1 becomes variable with louder S_1 in short cycles. The A2-OS interval varies directly with the previous cycle length in MS with AF. In AF, following short diastoles, the presystolic accentuation may persist.[41] This is seen in pliable valves only. Persistence of the mid-diastolic murmur up to S_1 during long RR cycles indicates significant MS. Examination of the lungs may detect rales, although it is remarkable that some patients with very high LA pressure have clear lung fields upon auscultation. It is thought that lymphatic hyperfunction clears the alveoli of transudated fluid that would be expected to form from high LA pressure.[42]

If pulmonary hypertension has ensued, the high-pitched murmur of pulmonary insufficiency (Graham-Steell) may be heard in the pulmonic area. However, the concomitant presence of aortic insufficiency is often mistaken for this murmur.[43] Neck vein distension, ascites, hepatomegaly, and edema reflect RV failure.

COMPLICATIONS

Atrial fibrillation is the most common complication developing in approximately 40% patients.[44] It is initially paroxysmal (often subclinical) and subsequently becomes permanent. Development of AF has a profound effect on the course of MS, leading to hemodynamic deterioration (discussed later) and placing the patient at risk of thrombus formation and systemic embolism. Age and the severity of MS are the most important determinants for development of AF.[45] AF is related to LA enlargement, the latter often a result rather than the cause of AF.[46]

Systemic embolism occurs in up to 20%[31,47-49] of patients, with 60% to 75% occurring to the brain. Increasing age and presence of atrial fibrillation are main predictors. Previous thromboembolism is positively associated with risk of embolism. When embolization occurs in the presence of sinus rhythm (as seen in up to 20% cases[47,50]), transient AF and infective endocarditis should be considered.[49] Transient subclinical AF[51] has been shown to be a major predictor for systemic embolic events. The risk of infective endocarditis in isolated mitral stenosis is low. Other complications include hemoptysis (sometimes massive), pulmonary embolism, and respiratory infections.[52]

In the presurgical era, 62% of the deaths were caused by heart failure, 22% from thromboembolic complications and 8% from infections.[7]

DIAGNOSTIC STUDIES

The electrocardiogram and the chest X-ray provide valuable insights into the anatomic changes affecting the various chambers of the heart and the lungs in MS. They should be carefully assessed but they are by no means diagnostic. The echocardiogram is the imaging modality of choice to diagnose MS.

ELECTROCARDIOGRAM

If the patient is in sinus rhythm, large p-waves may be present, indicating LA enlargement (p mitrale). Tall "R" waves in the right precordial leads may be a clue to RV hypertrophy. These ECG findings have high specificity but low sensitivity. Atrial fibrillation is often present.

CHEST X-RAY

Before the easy applicability of echocardiography, the chest x-ray was often the key diagnostic study. Important features include a double density along the right heart border reflecting the shadow of the enlarged LA outside the image of the right atrium. The pulmonary artery segment is enlarged, a consequence of pulmonary hypertension. Straightening of the left heart border (as a result of prominent left atrial appendage, dilated pulmonary artery, and an underfilled aortic knuckle), widening of the carinal angle, and posterior displacement of the esophagus (on lateral view) may be seen. Redistribution of blood flow to the lung apices (cephalization of blood flow) and Kerley B lines in the lung fields reflect chronic pulmonary venous hypertension and hypertrophy of lung septae. Loss of the retrosternal air space in the lateral view indicates RV enlargement.

ECHOCARDIOGRAPHY

The echocardiogram is the modality of choice in the assessment of MS. It establishes the diagnosis, determines the etiology, quantifies the severity, detects concomitant valve involvement, assesses suitability for balloon mitral valvotomy (BMV) and enables serial follow-up.[53,54] Valve images show the typical "hockey-stick" appearance of the mitral valve, immobility of the posterior leaflet, and "fish-mouth" narrowing of the valve orifice (Fig. 50–3).[51] Valve area can be estimated by direct planimetry (either 2D or 3D), by the continuity equation, by the pressure half-time technique (dividing an empirical constant of 220 by the mitral inflow pressure half-time), and the proximal isovelocity surface area (PISA) method. In some cases these measures are concordant, but in others, all measures must be taken into account and clinical judgment used to decide on MS severity. Planimetry by three-dimensional echocardiography has better reproducibility and intraobserver variability than two-dimensional echocardiography and has the closest agreement with invasive Gorlin-derived MVA.[55] It provides better evaluation of commissural anatomy in patients undergoing BMV (Fig. 50–4). The mean pressure gradient across the MV can be determined using the continuous-wave Doppler signal. Although this parameter is affected by flow and heart rate, it correlates well with invasive measurement. In the

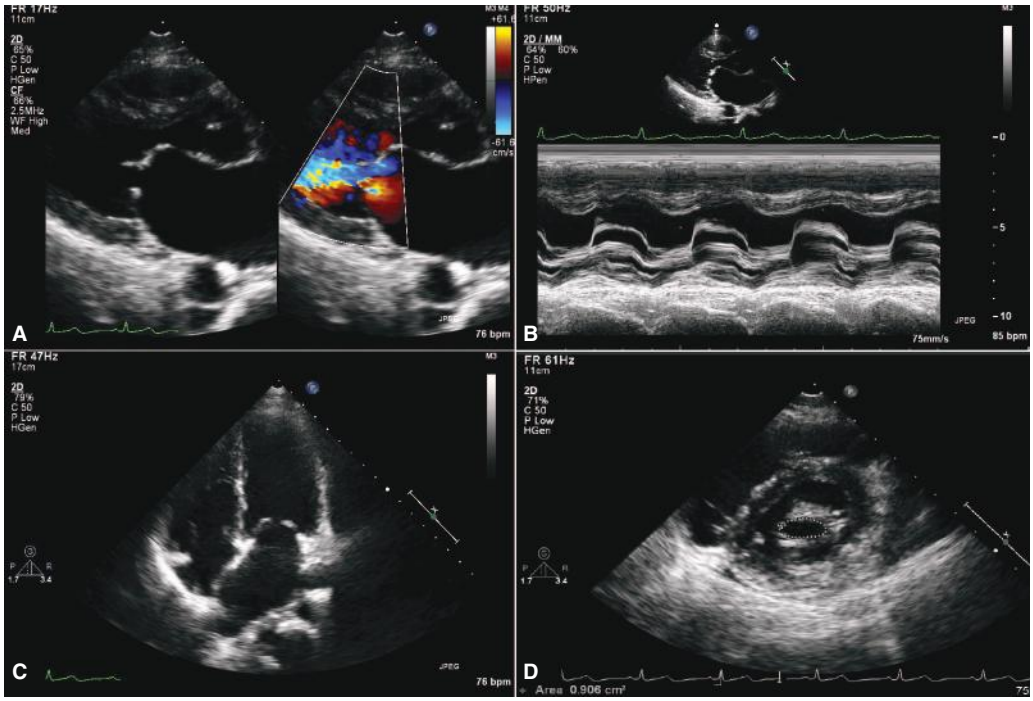

FIGURE 50–3. **A.** Transthoracic two dimensional echocardiogramparasternal long-axis view demonstrating "hockey-stick" appearance of anterior mitral leaflet. **B.** M-mode echocardiogram across tips of mitral valve leaflets showing reduced E-F slope and paradoxical anterior motion of posterior leaflet. **C.** Four-chamber view showing thickening of both leaflets and immobility of posterior mitral leaflet. **D.** Planimetry of mitral valve in short axis with valve area of 0.9 cm^2.

presence of atrial fibrillation, an average of 5 beats with least variation should be taken. LA dimension and volume also give clues to the impact of the disease on that chamber. If tricuspid insufficiency is present, the jet velocity across the tricuspid valve can be used to estimate peak pulmonary artery (PA) pressure. Assuming a right atrial pressure of 10 mm Hg, PA pressure is estimated as $4v^2$ +10, where v = the tricuspid jet velocity. Recalculation of MV gradient and PA pressure during exercise may be helpful in explaining exercise-induced symptoms when right-sided pressures are normal or nearly normal at rest. Although no longer considered an indication for intervention in the AHA/ACC guidelines because it may occur in normal subjects, an exercise-induced Pulmonary artery systolic pressure (PASP) > 60 mm Hg should warrant further investigation as to its cause.

Echocardiography is also important in evaluating patients for balloon mitral valvotomy (BMV), the therapy of choice for suitable valves, as well as for guiding BMV (see below).[56] Valve leaflet thickness, leaflet mobility, valve calcification, and subvalvular apparatus deformity are scored from 1 to 4, where 1 indicates mild abnormality and 4 indicates severe pathology. Valves scored 8 or less generally respond well to BMV, although this rule is not invariable, and some patients with higher scores still achieve a good result with BMV.[57] Other echocardiographic scores have been developed but none has proven to be superior to another.[53] All have a limited value in predicting the success (or complications) of BMV. Rather, scoring systems should be considered complementary to one another. Because the mechanism of BMV is splitting of commissures, assessment of commissural calcium is vital. Bicommissural calcification is a contraindication for BMV. The presence and severity of concomitant mitral regurgitation (MR) is also assessed because BMV may worsen existing MR. More than mild (1+) MR is usually considered a relative contraindication to BMV. BMV may be safely performed in patients with grade 2 MR, especially if the MR is central. Grade 3–4 MR is usually considered an absolute contraindication.[10] If after transthoracic echocardiography, BMV is contemplated, transesophageal echocardiography is then performed to

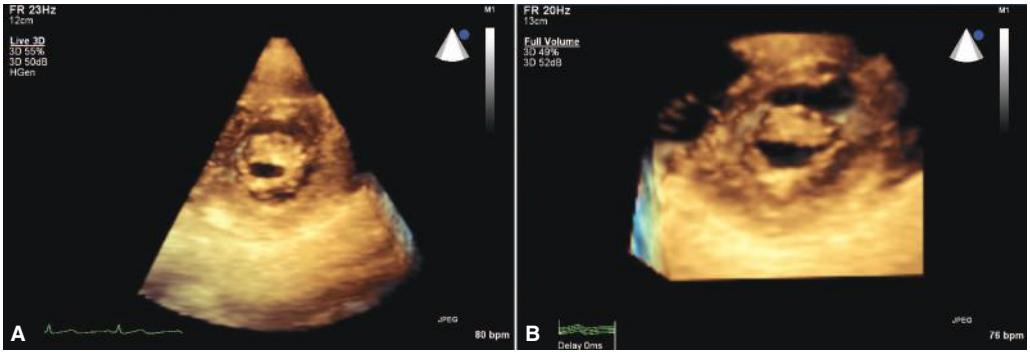

FIGURE 50–4. **A.** Three-dimensional echocardiogram showing typical "fish-mouth" appearance of mitral stenosis **B.** Three-dimensional echocardiogram after balloon mitral valvotomy demonstrating a completely split lateral commissure and partially split medial commissure indicative of successful BMV.

TABLE 50–3. LA/LAA Clot Classification

Type Ia:	LA appendage clot confined to appendage
Type Ib:	LA appendage clot protruding into LA cavity
Type IIa:	LA roof clot limited to a plane above the plane of fossa ovalis
Type IIb:.	LA roof clot extending below the plane of fossa ovalis
Type III:	Layered clot over the interatrial septum (IAS)
Type IV:	Mobile clot which is attached to LA free wall or roof or IAS
Type V:	Ball valve thrombus (free floating)

LA, left atrium; LAA, left atrial appendage; IAS, interatrial septum.

Data from Manjunath CN, Srinivasa KH, Ravindranath KS, et al: Balloon mitral valvotomy in patients with mitral stenosis and left atrial thrombus. *Catheter Cardiovasc Interv*. 2009 Oct 1;74(4):653-661.[58]

examine for thrombus in the LA and its appendage (LAA). Presence of LA/LAA thrombus has traditionally been a contraindication to BMV.[30] If thrombus is detected, warfarin anticoagulation is initiated and the patient is reimaged in 3 months.[30] Theoretically, this may entail placing the patient at an increased risk of systemic embolism during the 3-month period (as opposed to performing a mitral valve replacement/open mitral valvotomy immediately). This needs to be weighed against the potential long-term complications associated with a prosthetic valve. If the thrombus has resolved, BMV may then be performed. Persistence of thrombus after anticoagulation has been an indication for open mitral valve surgery. Of late, some studies have shown that it is feasible to perform BMV in selected patients with LA/LAA appendage thrombus after 8 to 12 weeks of anticoagulation.[58] The LA/LAA thrombus was classified into five types based on the location (Table 50–3). 108 patients with LA/LAA thrombus type Ia, Ib, and IIa underwent BMV using a modified over the wire technique that virtually excluded the LA from the track of the septal dilator and balloon catheter exchanges.[58,59] BMV was successfully performed in 98% of cases. Only one patient had a transient ischemic attack 6 hours after the procedure, and recovered completely. It is to be noted that BMV was performed by experienced operators (> 500 procedures) in this study.

Post BMV, echocardiography enables assessment of commissural splitting, the degree and mechanism of MR, MV gradients, MVA by planimetry, and any complications (pericardial effusion). Follow-up echocardiography is recommended among asymptomatic individuals at intervals of 3 to 5 years in those with MVA > 1.5 cm^2, every 1 to 2 years with MVA ≤ 1.5 cm^2, and yearly in those with MVA < 1 cm^2.[30]

CARDIAC CATHETERIZATION

In most cases, MS evaluation can be completely assessed noninvasively. However, if after echocardiography the issue of MS severity is still in doubt, the diagnosis may be resolved during cardiac catheterization. Data from invasive hemodynamics are used in the Gorlin formula (MVA = CO/$dfp \times hr/38.5\sqrt{h_2 - h_1}$), where MVA = mitral valve area (cm^2), CO = cardiac output (mL/min), dfp = diastolic filling period (seconds), hr = heart rate, and $h_1 - h_2$ = the mean transmitral gradient.[25] Simultaneous measurement of the LV and LA pressures by means of transseptal puncture are needed (Fig. 50–5). A carefully obtained pulmonary capillary wedge pressure (time adjusted) may be substituted for LA pressure in measuring the transvalvular gradient.[60] If resting hemodynamics are unrevealing, dynamic or handgrip exercise may show significant elevation in pulmonary capillary wedge pressure and PA pressure, demonstrating the cause of the patient's symptoms.

Because most patients with MS in whom cardiac surgery is contemplated are of an age to be at risk for coronary artery disease, coronary angiography or multislice CT examination is usually performed before operation to preoperatively evaluate coronary anatomy.

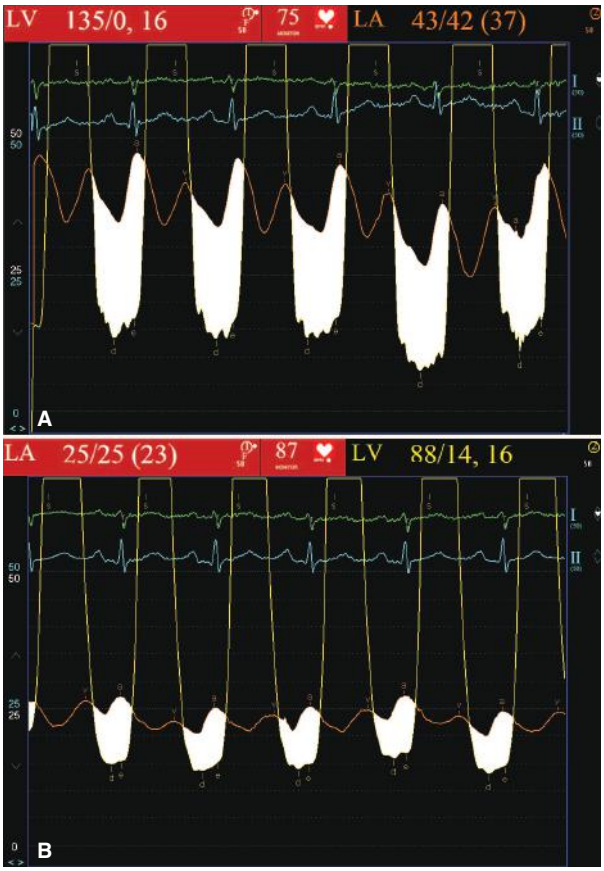

FIGURE 50–5. A. Simultaneous left atrial (LA) and left ventricular (LV) pressure tracings in a patient with severe MS (mean transmitral gradient 20.4 mm Hg) **B.** Simultaneous LA and LV pressure tracings in the same patient after successful balloon mitral valvotomy (mean transmitral gradient reduced to 6.6 mm Hg, reduction in mean LA pressure and "v" wave height).

MEDICAL THERAPY

RATE CONTROL IN ATRIAL FIBRILLATION

The onset of atrial fibrillation (AF) with a rapid ventricular response may have markedly severe clinical consequences. Transit of blood flow from LA to LV is obviously impaired in MS patients, even in sinus rhythm. As heart rate accelerates, diastolic filling period is shortened, further impairing LA emptying. Hemodynamically, shortened diastolic filling time and loss of atrial systole result in further increases in LA pressure and a decrease in cardiac output. Thus the patient may experience acute pulmonary edema and shock. The speed at which rate control must be achieved is dictated by clinical circumstances. In very ill patients, immediate DC cardioversion is indicated to restore sinus rhythm. If the consequences of rapid AF are less severe, rate control may be accomplished by intravenous administration of a β-blocker such as metoprolol or esmolol, a calcium channel blocker such as diltiazem, or digoxin. The latter agent gains rate control less rapidly but may be preferable if blood pressure is tenuous. Intravenous amiodarone can be used to control the heart rate in patients where beta-blockers or heart-rate–regulating calcium channel blockers (CCBs) cannot be used or have not been effective.[30]

When elective cardioversion is planned for AF lasting > 24 hours, anticoagulation should be given for 3 weeks prior or a TEE should be performed immediately to rule out an atrial thrombus. The decision for cardioversion should take into consideration the duration of AF, the hemodynamic response to AF, the LA size, the past history of AF, and the limitation to exercise capacity. As MS progresses, it becomes more difficult to maintain sinus rhythm.

In chronic AF, adequate rate control is also a cornerstone of good therapy. Control should be evaluated both at rest and during modest activity, such as walking down the clinic corridor. Too often the patient is only assessed on the examining table and found to have a satisfactory heart rate, yet during activity heart rate may be quite rapid, potentially leading to rate-related cardiomyopathy.[61] Beta-blockers and heart-rate–regulating CCBs are the mainstay, while digoxin may be added if optimal heart rate control is not achieved.[30] A resting heart < 80 beats per minute and an exercise (moderate) heart rate < 100 beats per minute is recommended for symptomatic patients.[62,63]

At the time of MV surgery (replacement or repair), the performance of a biatrial maze or pulmonary vein isolation enabled more than 60% patients to remain in sinus rhythm at one year.[64] Successful BMV enables patients in sinus rhythm to persist in sinus rhythm.[65] However, BMV does not promote reversion to sinus rhythm in patients with chronic AF.[66] In a subgroup of patients (LA size < 45 mm, duration of AF < 1 year), successful BMV was associated with increased probability of cardioversion (chemical with/or without electrical).[67]

ANTICOAGULATION

The MS patient with AF has a very high risk of stroke, approaching 15% per year unless adequately anticoagulated.[68] Faster heart rates in AF contribute to an increased clotting tendency.[69] Because of the high stroke risk, only dire contraindications such as active bleeding should prevent anticoagulation in such patients. Anticoagulation with vitamin K antagonist (VKA) is recommended for MS patients with AF (paroxysmal, persistent, or permanent), those with a prior embolic event, and those with a left atrial/left atrial appendage thrombus to maintain an INR of 2.5 (range 2-3) for an indefinite duration.[30] The use of anticoagulation in patients in sinus rhythm with large LA (diameter > 55 mm)[70] or those with spontaneous echo contrast may be beneficial but this has not been adequately studied. Low-dose aspirin (81 mg/d) may be added to the regimen safely to further lower the risk of stroke. Newer oral anticoagulants such dabigatran, apixaban, and rivoraxaban have been approved for prevention of systemic embolism in nonvalvular AF. They are currently not approved for patients with MS with indications for anticoagulation.[30] The RE-ALIGN study that compared dabigatran with warfarin in patients with mechanical heart valves was terminated early because of excess thromboembolic and bleeding events in the dabigatran arm.[71]

INFECTIVE ENDOCARDITIS PROPHYLAXIS

Among valve lesions, patients with MS are at relatively low risk for developing infective endocarditis (IE).The ACC/AHA[10] and the National Institute for Health and Clinical Excellence (NICE)[72] guidelines currently do not recommend preprocedural antibiotic therapy for the prevention of IE in patients with mitral stenosis unless the patient has had a previous episode of IE. The new guidelines are based on the lack of evidence that prophylaxis is effective and the fact that bacteremia occurs routinely with eating, yet prophylaxis for that activity would be impossible. Not all international societies are in agreement with this recommendation. The Brazilian[73] and the Australasian guidelines (indigenous Australians)[74] continue to recommend antibiotic prophylaxis for RHD given that this condition is still rampant and many of these patients would have poor oral hygiene. Two recent studies from the United States[75] and UK[76] have shown a disturbing increase in the incidence of IE following the change in guidelines. As such individual judgement should be used in advising prophylaxis.

Secondary prevention of rheumatic fever (preferably long-acting benzathine penicllin G) should be continued. The risk of for recurrence of RF declines with increasing age and the number of years from the last attack.

HEART FAILURE

Although, the ultimate therapy for symptomatic MS is mechanical relief of the obstruction to LV inflow, loop diuretics and dietary salt restriction are usually effective in treating congestive symptoms. Digoxin may be useful in patients with left and/or right ventricle dysfunction. Whether β-blockers are useful in treating heart failure symptoms remains controversial.[77] Slowing of the heart rate reduces mean transvalvular gradient by allowing more time for LA emptying. However, β-blockers also tend to increase LV diastolic pressure so that mean LA pressure changes little at rest. However, for patients prone to a robust sinus tachycardia with exercise, β-blockade may be effective in controlling exercise-induced symptoms. Ivabradine, a negative chronotropic agent, may have an advantage over beta-blockers in patients with sinus rhythm, as it has no effect on myocardial contractility. Studies have demonstrated that ivabradine is better or at least as effective beta-blockers in improving exercise tolerance in patients with mild to moderate MS in sinus rhythm.[78,79] Anemia, fever, infections, and hyperthyroidism should be corrected.

TIMING OF MECHANICAL THERAPY

Three procedures are routinely practiced for the relief of MS: BMV, open commissurotomy (OMV), and mitral valve replacement (MVR). In some areas, closed commissurotomy (CMV) is still practiced quite effectively and does not entail the cost of the catheters and balloons needed for BMV. Because BMV is less morbid and carries a lower mortality than does surgery, the timing for BMV is more liberal than for the surgical procedures at both ends of the clinical spectrum. It may be applied for mild symptoms caused by severe MS or in late-stage disease in patients at high risk for surgery from various comorbidities. Advanced symptoms worsen prognosis (Fig. 50–6), and thus BMV or surgery should

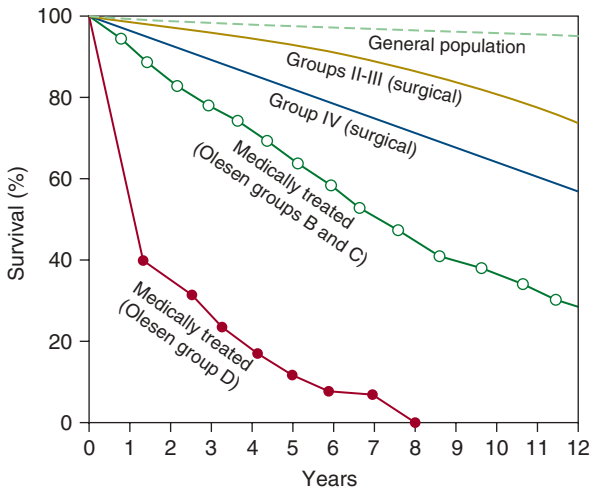

FIGURE 50–6. Survival according to therapy and symptomatic status for patients with mitral stenosis is shown. NYHA classes II, III, and IV are roughly equivalent to Olesen groups B, C, and D, respectively. Reproduced with permission from Roy SB, Gopinath N: Mitral Stenosis. *Circulation*. 1968 July;38(1 Suppl):68-76.[80]

be performed before the patients reaches New York Heart Association class III.[80] Additionally, pulmonary hypertension defined as a peak systolic pressure > 50 mm Hg at rest also worsens prognosis and increases surgical risk.[81] Thus mechanical relief of obstruction should ideally take place before this degree of severity has developed.

BALLOON MITRAL VALVOTOMY

BMV was first performed by Inoue in 1984,[82] followed by Lock in 1985.[83] BMV is the procedure of choice for relieving MS,[30] with surgery being reserved only for patients who are not candidates for BMV. It is recommended for the following groups of patients[30]: (1) symptomatic patients (class II-IV) with severe MS (MVA ≤ 1.5 cm^2) (class 1 indication) or asymptomatic patients with very severe MS (MVA ≤ 1.0 cm^2) (class 2a indication) with a favorable valve morphology in the absence of left atrial thrombus and moderate to severe MR; (2) asymptomatic patients with severe MS (MVA ≤ 1.5 cm^2) with new-onset AF and suitable valve anatomy (class 2b indication); (3) symptomatic patients with MVA > 1.5 cm^2 and hemodynamically significant MS during exercise (mean MV gradient > 15, PCWP > 25 mm Hg, class 2b indication; and (4) severely symptomatic patients (NYHA class III-IV) with severe MS (MVA ≤ 1.5 cm^2) with suboptimal valve anatomy and high risk for surgery (class 2b indication).

The steps for BMV are demonstrated in Fig. 50–7. First, a transseptal puncture is performed (Fig. 50–7A), and the inter-atrial septum is dilated with a dilator (Fig. 50–7B). A balloon is then advanced across the septum, into the LA across the mitral valve. Stepwise inflation causes commissures separation (Fig. 50–7C, D; Fig. 50–5B), permitting a dramatic increase in leaflet motion and valve area. BMV can be performed using a hourglass-shaped balloon (triple lumen Inoue balloon[82] or double lumen Accura balloon[84,85]), a single[83] or double peripheral angioplasty balloon,[86] or a reusable valvulotome.[87] Although the three techniques produce a similar outcome,[86,88] currently the hourglass-shaped balloons are preferred. The procedure should be performed by experienced, skilled operators. The mortality rate is approximately 1% in experienced centers. Other complications include severe MR requiring surgery (2%), embolic events (1%), and cardiac perforation (1%).[10] Retrograde BMV without transseptal puncture using a steerable guidewire is an alternative to conventional BMV.[89,90]

Randomized trials have shown BMV to be superior to closed commissurotomy with a larger postprocedure valve area when the two procedures were compared in patients with valves suitable for BMV,[91-94] and similar results have been shown for BMV and open commissurotomy.[95] Although successful BMV is usually defined as a postprocedure valve area > 1.5 cm^2 (without > grade 2 MR), valve area often exceeds 1.8 cm^2 and is durable for a decade or more. There is an immediate reduction in transmitral gradient, LA mean pressure, and pulmonary artery pressure. Even patients with systemic or suprasystemic PAP have an immediate significant drop in PAP after successful BMV.[96] Reduction in PAP is associated with improvement in tricuspid regurgitation in some but not all patients. Successful BMV has been shown to reduce systemic embolism[49] but does not appear to revert AF.[66] Long-term studies with follow-up for up to 20 years are available.[97,98] Among 912 patients with a median age of 48 years,[97] cardiovascular survival without reintervention and cardiovascular survival without surgery was 38% and 46% at 20 years. For patients < 50 years, the figures were 45% and 57%, respectively.[97] The overall survival and cardiovascular survival at 20 years was 75% and 85%, respectively.[97] In another study of 547 patients with a mean age of 31 years,[98] freedom from restenosis at 10 and 19 years was 78% and 26%, respectively.

The BMV technique and hardware has remained essentially unchanged over the past three decades, but the indications of BMV have expanded encompassing patients with calcified valves, severe submitral disease, LA/LAA clot, moderate MR (grade 2), MV restenosis (post BMV/CMV/OMV/mitral valve repair), pregnancy, children, and those with difficult anatomy (anomalous inferior vena cava connections, dextrocardia, kyphoscoliosis).

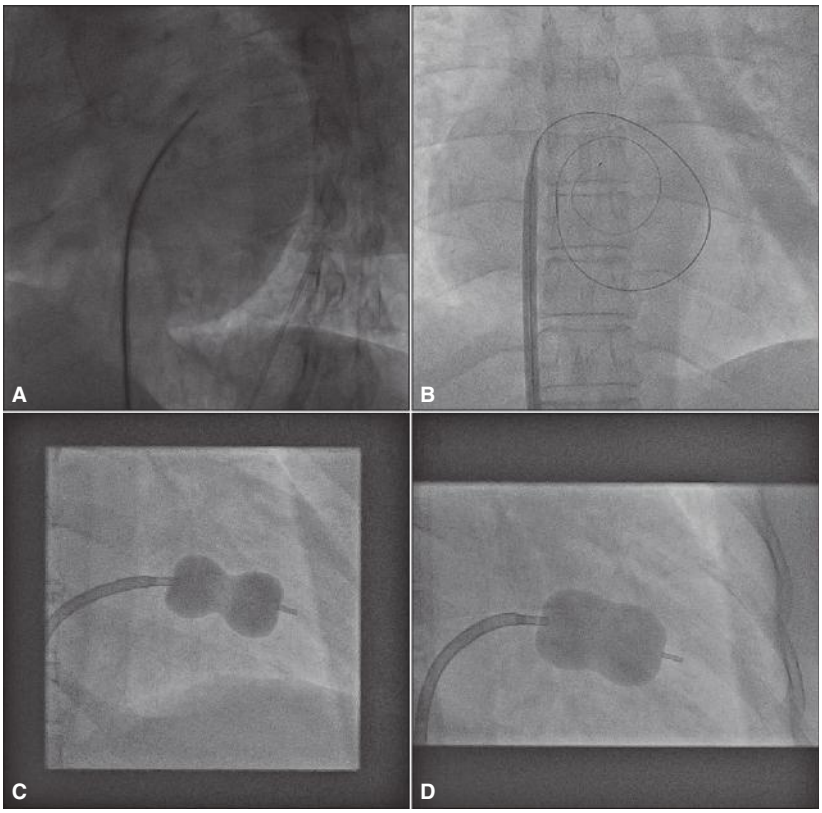

FIGURE 50–7. The steps for balloon mitral valvotomy are shown. **A.** Transeptal puncture. **B.** Dilatation of interatrial septum with dilator. **C.** Balloon inflation creating a waist at the site of the stenosis. **D.** Full balloon inflation with giving of waist.

CARDIAC SURGERY

Relief of MS by surgery may be done either by closed mitral valvotomy (CMV), open mitral valvotomy (OMV), or mitral valve replacement (MVR). CMV, via transatrial or transventricular route, is still practiced successfully in many developing countries. However, the results of BMV are superior to CMV with lower morbidity. As such, CMV is indicated only if BMV is not available. OMV is done under cardiopulmonary bypass and enables direct visual inspection of MV, enabling direct splitting of commissures, splitting of fused chordae tendinae and papillary muscles, and debridement of calcific deposits. LA thrombi may be removed and the LA appendage amputated to reduce future thromboembolic events. Further, moderate to severe TR can be repaired. The results are dependent on the surgical skills, and the main advantage of OMV is that it avoids a prosthetic valve. When extensive calcification and severe subvalvular disease make BMV/OMV unfeasible, MVR is the surgical treatment of choice. The indication for MVR are as follows[30]: (1) severely symptomatic patients (NYHA class III/IV) with severe MS (MVA < 1.5 cm^2) who are not high risk for surgery and who are not candidates for, or have failed, previous BMV (class 1

indication); (2) severe MS (MVA < 1.5 cm^2) undergoing other cardiac surgery (eg, aortic valve surgery, CABG) (class 2a indication); and (3) mitral valve surgery and LAA excision may be considered for patients with severe MS (MVA ≤ 1.5 cm^2, stages C and D) with recurrent embolic events despite adequate anticoagulation (class 2b indication). Further, patients with moderate to severe TR do better after surgery that includes a tricuspid valve repair.[99] Given the morbidity and mortality associated with MVR and the potential long-term complications associated with a prosthetic valve (prosthetic valve thrombosis, infective endocarditis, prosthesis mismatch, bleeding complications with anticoagulation), the threshold for MVR is higher than for BMV and is limited to NYHA class III and IV patients. The operative mortality rate is 3% to 8%, but it may reach as high as 10% to 20% with NYHA class IV patients.[100] Therefore the patient should not be allowed to reach NYHA class IV during postponement of surgery. Even if the patient does present in NYHA class IV, surgery should not be denied, as the outlook without surgery is very poor. BMV can be an alternative in such cases after careful discussion.[30] The type of valve inserted will depend on the patient's age and the risk of anticoagulation, but is increasingly more dictated by patient choice. However, if the patient has long-standing AF and must be anticoagulated anyway, a mechanical valve may be inserted. On the other hand, a young patient in sinus rhythm may opt for a bioprosthetic valve to avoid the hazards of anticoagulation, with an understanding of the need for future redo surgery for valve deterioration. If AF is less chronic, a maze procedure may be used at the time of MVR,[64] although its success in a purely rheumatic population is less certain than in a nonrheumatic population. Although it is often hoped that relief of MS will result in restoration of sinus rhythm, AF in MS is due not only to increased LA size but also to rheumatic scarring and histologic changes in the LA.[101] Thus relief of mitral obstruction may[65] or may not prevent AF[102] or allow for return to sinus rhythm.

SPECIAL CIRCUMSTANCES

PREGNANCY

As noted earlier, MS is primarily a disease of women and may become manifest during pregnancy when the cardiac output demands on the heart increase by 70%. As predicted by the Gorlin formula, an increase in cardiac output of 1.7-fold would increase the transvalvular gradient by 1.7^2 or 2.89-fold. Thus a small pregravid transmitral gradient of 4 mm Hg might become 11 mm Hg during the second trimester and cause symptoms to appear. Typically, symptomatic status follows the *rule of one class*. That is, the patient's symptoms will increase by one New York Heart Association class during pregnancy. Thus the asymptomatic patient may develop class II symptoms, whereas a class II patient may become class III. Effects on the fetus include intrauterine growth retardation, low birthweight, preterm delivery, and fetal loss.[103] Ideally, asymptomatic patients with severe MS (MVA ≤ 1.5 cm^2) with suitable valve should undergo BMV before conception.[30] Diuretics can usually be used safely to control mild symptoms. Overaggressive use of diuretics can lead to placental hypoperfusion. Therapy is targeted to reduce heart rate and prolong diastolic filling period. This includes restriction of physical activity and use of beta-blockers (those with selective beta-1 activity are preferred). Metoprolol is preferred over atenolol as it has a lower incidence of intrauterine growth retardation.[30] In patients with atrial fibrillation, digoxin can be safely used. Pregnant patients with severe MS (MVA ≤ 1.5 cm^2) who continue to remain symptomatic (NYHA class III-IV) despite medical therapy should undergo BMV if the valve is suitable.[30] A combined analysis of 515 patients who underwent BMV during pregnancy found a success rate of 98% (94%-100% in large-volume centers).[104] Maternal mortality was 1%. In the largest of these studies, the average fluoroscopic time was 3.6 ± 3.2 minutes.[105] The radiation to fetus is estimated to be less than 0.2 rad. Long-term follow-up of these children up to seven years revealed no fetal anomalies.[106] The procedure should be performed by experienced operators. It is best performed after 20 weeks in the second trimester if the patient's symptoms permit. Technical aspects include use of minimal fluroscopy with avoidance of right heart study and LV angiogram, utilization of echo guidance, stepwise dilation technique, and use of pelvic and abdominal shield.

For symptomatic patients with valve anatomy unsuitable for BMV, mitral valve surgery is indicated if there are refractory NYHA class IV HF symptoms.[107] However, valve operation in pregnancy has a high risk, with 30% to 40% fetal loss and maternal mortality rate of up to 9%.[108]

Pregnant patients with MS who have or develop AF will need anticoagulation. The use of warfarin during the first trimester (6-12 weeks) is associated with a high risk of embryopathy.[109] However, pregnancy is a prothrombotic state, and the risk of stroke in a pregnant woman with both AF and MS is presumably quite high. The risk of warfarin-associated embryopathy appears to be dose-related. The incidence is < 3% with a daily dose ≤ 5 mg, but increases to > 8% with a warfarin dose > 5 mg/d.[110] DC cardioversion after transesophageal echocardiography that reveals no atrial thrombus is preferable. If thrombus is present or cardioversion fails, then clear-cut options are limited. Options include (as for mechanical heart valves) continuing warfarin (if dose < 5 mg/d) or the use of unfractionated heparin (IV infusion or subcutaneous injections twice daily) or low molecular weight heparin (monitored with factor Xa levels) in the first 6 to 12 weeks followed by a switch to warfarin.[30,111] The decision regarding the choice of the regimen should be made after a thorough discussion with the patient.[111]

JUVENILE MS

Rheumatic mitral stenosis presenting below 20 years is termed juvenile MS.[12] This condition is uncommon in developed countries but may constitute up to a quarter of cases of all rheumatic MS in developing countries.[12] Unlike in adults, boys are more commonly affected.[12] Heart failure/pulmonary edema is a frequent finding, while atrial fibrillation is uncommon. Severe PAH with gross pulmonary vascular obstruction is common. Although MV calcification and LA thrombi are absent, the valve morphology is associated with severe subvalvular disease and thickened leaflets. BMV has been successfully preformed with acute success rates of 94% to 100%[112-114] (comparable to adult series). Event-free survival at intermediate to long-term follow-up ranged from 75% to 79% at 5 to 10 years follow-up.[115,116] Restenosis rates were 14% to 16%.[116] Important procedural aspects include the use of stepwise graded dilatation, the use of a balloon size 2 to 4 mm less than the calculated size, and indexing the MVA to BSA to define procedural success (MVA > 1.0 cm^2 /m^2 BSA).[112,115] There was significant drop in the PA pressure immediately after the procedure[115] followed by further substantial regression over long-term follow-up.[116]

CONCOMITANT VALVE DISEASE

As noted, rheumatic fever may affect all four heart valves. Perhaps the most common lesion is mixed mitral stenosis and regurgitation (MR). The lesions are almost never balanced, with one more prominent than the other. From the standpoint of management, LV remodeling gives the best clue regarding which lesion is dominant and therefore which to treat. If the LV is dilated, MR is the dominant lesion, and strategies for MR therapy should be followed, whereas if the LV remains

normal in volume, MS predominates, and the patient should be treated accordingly.

Aortic insufficiency (AI) is the next most common accompanier of MS, and its evaluation may be misleading. The aortic valve can only regurgitate what it receives from the mitral valve. Mitral stenosis reduces cardiac output and LV volume. Thus many of the clinical clues to AI severity may be missing in the MS patient, both upon clinical and echocardiographic examination.[117]

Perhaps the most important concomitant lesion is tricuspid regurgitation (TR). Although rheumatic deformity of the tricuspid valve does occur, most TR is functional, resulting from RV dilatation secondary to pulmonary hypertension. It is often believed that once the MS is corrected and pulmonary hypertension disappears, the TR will also improve. Although this does occur in some cases,[118] it fails to materialize in others, and the need to address TR surgically as a second operation after successful mitral surgery carries a high operative risk.[119] Therefore, it is preferable to perform ring tricuspid annuloplasty at the time of mitral surgery if even mild TR is present, because TR may paradoxically worsen if left unattended. On the other hand, it is probably acceptable to gauge TR before BMV and follow the patient for regression of TR. If TR does not improve, tricuspid repair as a first cardiac surgery seems reasonable.

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CHAPTER 51

TRICUSPID AND PULMONARY VALVE DISEASE

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Mild tricuspid valve disease is common, and usually clinically silent.[1] Moderate and severe tricuspid regurgitation, however, are increasingly recognized as an important marker of morbidity and mortality.[2] By far the commonest etiology is secondary or functional tricuspid regurgitation, where the valve leaflets are structurally normal, and regurgitation is primarily a result of annular dilatation in the setting of right or left heart dysfunction or dilatation, or pulmonary hypertension.[3] Secondary tricuspid regurgitation is a very dynamic lesion, commonly seen in patients with left-sided valvular disease, ischemic heart disease, and atrial fibrillation. Primary tricuspid disease is most commonly a result of endocarditis, carcinoid heart disease, and rheumatic valve disease, with lead- and catheter-related pathology from cardiac devices as an increasingly recognized cause. Apart from congenital lesions involving the pulmonary valve or the right ventricular infundibulum and carcinoid heart disease, pulmonary valve disease as an acquired condition in adults is extremely rare. The pulmonary valve is the least commonly involved in infectious processes such as rheumatic fever and bacterial endocarditis.

THE TRICUSPID VALVE

Tricuspid valve disease is present in 15% of the population.[4] The tricuspid valve has recently become a more prevalent focus of interest, but used to be described as "the forgotten valve," reflecting a clinical and research predilection for the left-sided heart valves.[5] The most common valve lesion is secondary tricuspid regurgitation,[6] also known as functional regurgitation.[4] It is characterized by valvular insufficiency in an otherwise structurally normal valve, resulting from annular dilatation caused by right heart dysfunction or dilatation,[7] pulmonary hypertension,[8] or left heart dysfunction.

ANATOMY

The tricuspid valve is the most apically (or caudally) placed valve with largest orifice among the four valves.[9] The tricuspid apparatus includes leaflets or cusps, chordae and papillary muscles, and tricuspid annulus in addition to the right atrium and right ventricle (Fig. 51–1).

Annulus

The tricuspid annulus is oval in shape and becomes more circular when dilated. The annulus has a complex nonplanar shape with the posteroseptal portion being the lowest and the anteroseptal being the highest.[9] It tends to become more planar with moderate or severe "functional" tricuspid regurgitation. The annular orifice area is approximately 20% larger than the mitral annulus area, with a major diameter of 3.0 to 3.5 cm in adults. The larger orifice provides for the inflow to occur at lower velocities and lower pressure decreases. Both early and late diastolic velocities are lower than the mitral inflow. The annulus expands in diastole and constricts in mid-systole, with a nearly 30% reduction in annular area. Structures that are in close proximity to the tricuspid annulus, and that may be compromised by disease processes or tricuspid valve surgery, include the atrioventricular conduction tissue that lies at the apex of the triangle of Koch (formed by the coronary sinus, septal annulus, and tendon of Todaro) (Fig. 51–2), the mid-portion of the right coronary artery, and the noncoronary cusp of the aortic valve (see Fig. 51–1).

Leaflets

The normal tricuspid valve has three distinct leaflets: septal, anterior, and posterior (see Fig. 51–1). The septal and the anterior leaflets are larger. The septal leaflet is in immediate proximity to the membranous ventricular septum (see Fig. 51–2), and its extension provides a basis for spontaneous closure of the perimembranous ventricular septal defect. The larger anterior leaflet is attached to the anterolateral margin of the annulus and is often voluminous and might appear sail-like in abnormal scenarios such as in Ebstein anomaly.

Papillary Muscles and Chordae Tendinae

There are three sets of smaller papillary muscles (when compared to left ventricular papillary muscles); each set is composed of up to three muscles. The chordae tendineae arising from each set are inserted into two adjacent leaflets. Thus the anterior set chordae insert into half of the septal and half of the anterior leaflets. The medial and posterior sets are similarly related to adjacent valve leaflets.[10]

TRICUSPID VALVE DISEASE

Diastolic valve opening with expansion of the annular orifice provides for unimpeded inflow. Although systolic narrowing of the orifice is intended to result in effective valve closure, some degree of valvular regurgitation with color Doppler imaging is quite common.[11] Nearly 50% to 60% of young adults have trace tricuspid regurgitation. A smaller proportion of normal adults, up to 15%, have mild tricuspid regurgitation.[4]

Tricuspid valve disease or dysfunction may be classified as primary (also known as organic or intrinsic), where pathology (most commonly rheumatic valve disease, endocarditis, carcinoid heart disease, and trauma) results in structural leaflet damage; as opposed to secondary or functional tricuspid regurgitation, where the leaflets appear macroscopically normal.[12]

Primary Tricuspid Valve Disease

Primary tricuspid valve disease is relatively uncommon. The most common congenital abnormalities include Ebstein anomaly, tricuspid

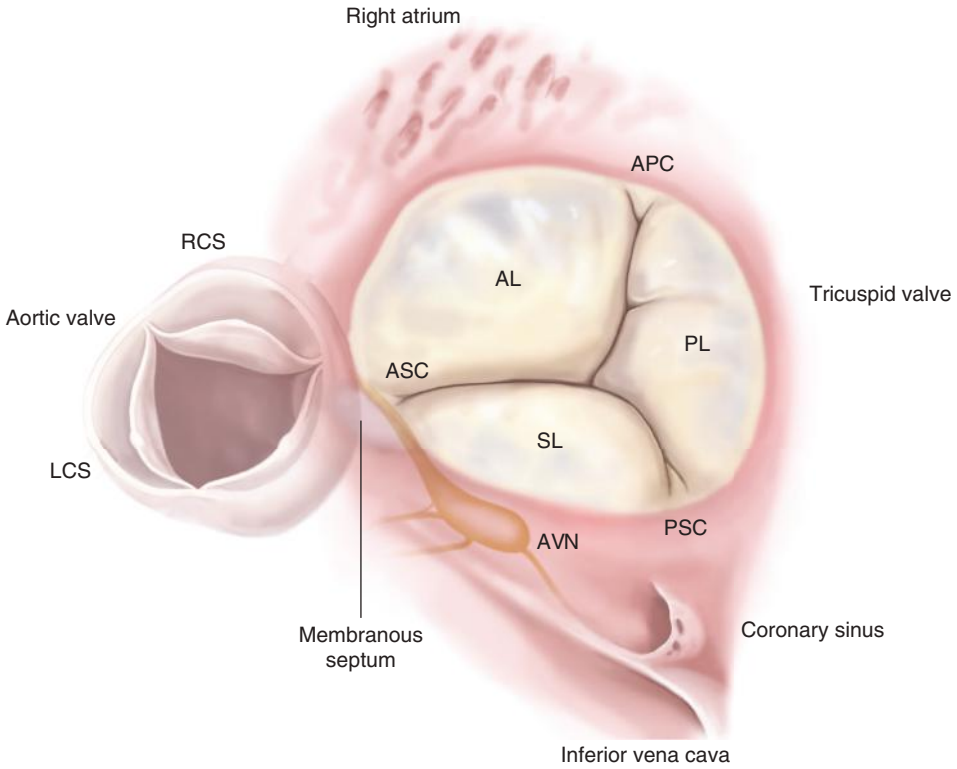

FIGURE 51–1. Relationship of the tricuspid valve to the aortic valve, conduction tissue and other surrounding anatomical structures. AL, anterior leaflet; APC, anteroposterior commissure; ASC, anteroseptal commissure; AVN, atrioventricular node; LCS, left coronary sinus; PL, posterior leaflet; PSC, posteroseptal commissure; RCS, right coronary sinus; SL, septal leaflet.

valve atresia/dysplasia/hypoplasia, cleft valve in conjunction with atrioventricular canal defects and tricuspid valve stenosis, or double-orifice tricuspid valve. Acquired diseases of the tricuspid valve are endocarditis, rheumatic disease, carcinoid heart disease, tricuspid valve prolapse, radiation lesions, trauma, iatrogenic (right ventricular myocardial biopsy), and the presence of indwelling cardiac catheters or cardiac leads (PPM, ICD). The latter is increasingly recognized as a cause of significant tricuspid valve regurgitation.[13]

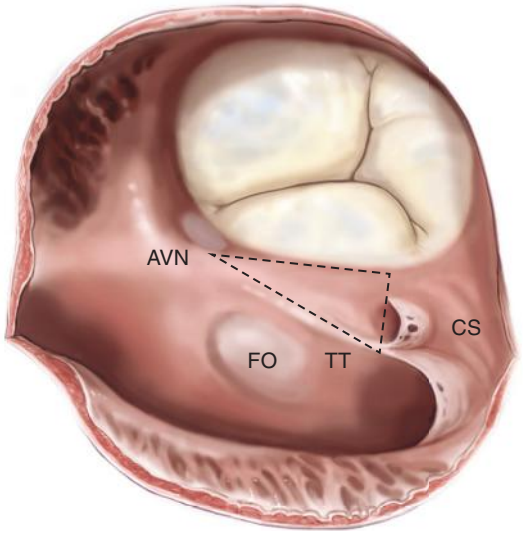

FIGURE 51–2. Atrial view of the tricuspid valve showing the key anatomical landmarks to avoid injuries of the conduction system. AVN, atrioventricular node; CS, coronary sinus; FO, foramen ovale; TT, tendon of Todaro. Dashed lines represent the triangle of Koch with base denoted by the Coronary sinus, upper border parallel to the septal annulus, lower border parallel to the tendon of Todaro, and apex indicating location of the atrioventricular nodal tissue and the membranous septum.

Rheumatic Tricuspid Valve Disease Rheumatic involvement of the tricuspid valve is far less common than with the mitral and the aortic valves.[14] Isolated rheumatic tricuspid valve disease is rare. However, clinically significant tricuspid valve disease, in association with mitral or aortic valve disease, is reported in between 10% and 20% of patients.[15] In addition, other inflammatory disorders like rheumatoid arthritis, systemic lupus erythematosus, and anti-phospholipid syndrome are also associated with primary tricuspid leaflet lesions that may result in significant dysfunction.[16] Rheumatic tricuspid valve disease is often predominantly functional, but is occasionally characterized by leaflet involvement with thickened, fibrosed, and shortened leaflets, and commissural fusion. The resulting clinical syndrome is one of mixed stenosis and regurgitation. The murmur of tricuspid stenosis is heard along the lower left sternal border and is louder with inspiration. The opening snap is not often heard. A systolic murmur of tricuspid regurgitation is often soft, medium pitched, and increases with inspiration. Inspiratory increase in jugular venous pressure is common and simulates the Kussmaul sign in constrictive pericarditis. However, the jugular venous pulse with rheumatic tricuspid valve stenosis and regurgitation fails to show rapid "y" descent. The echocardiographic appearance of a thickened distorted valve establishes a correct diagnosis.

Treatment of rheumatic tricuspid valve disease consists of valve repair with annuloplasty when the valve dysfunction is not severe. However, in the presence of severe disease, valve replacement with a low-profile prosthetic valve is indicated. In terms of prosthetic preference, because of the higher risk of complications such as

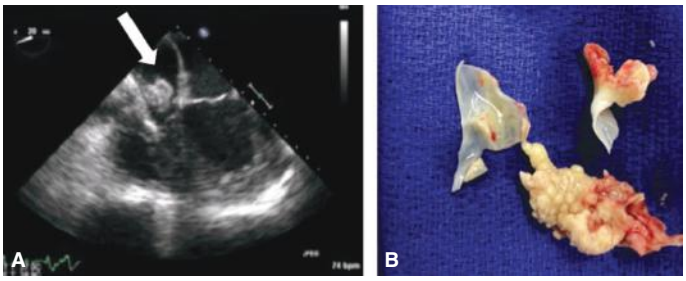

FIGURE 51–3. Tricuspid valve endocarditis in a patient with fungemia and a 20-year history of implanted cardiac defibrillator and coronary bypass surgery. **A.** Large mass attached to the anterior leaflet (*white arrow*), prolapsing into the right ventricle. **B.** Resected anterior leaflet of the tricuspid valve with vegetation attached.

thrombosis and infection with mechanical valves, bioprostheses are preferred despite a risk of structural failure in younger subjects.[17] Tricuspid valve balloon valvuloplasty has been advocated for predominant stenosis with mixed results. A common consequence is an aggravation of tricuspid regurgitation.

Infective Endocarditis Tricuspid valve endocarditis is not uncommon among intravenous drug users or patients with long-term intravenous lines associated with dialysis and chemotherapy (Fig. 51–3; see Chap. 67). Multiple vegetations attached to the foreign materials further extending over the atrial and ventricular surfaces of an already abnormally thickened leaflet are often seen. In this context, leaflet perforations or annular abscesses are less frequent.[18]

The clinical presentation is one of general systemic symptoms such as fever, weight loss, anemia, and fatigue, or of pulmonary embolism or right heart failure with hepatic congestion, peripheral edema, and ascites. The diagnostic confirmation is made by echocardiographic lesions suggestive of vegetations and positive blood cultures (Fig. 51–4).

Treatment of drug addicts with infective endocarditis is especially challenging. A prosthetic valve is at a great risk of recurrent infection as the intravenous drug use is resumed. Surgical excision of the infected tricuspid valve has been attempted with some initial success, but poor long-term outcome. Surgical repair is usually possible, and this condition among intravenous drug users continues to be a difficult management problem.

Carcinoid Heart Disease Carcinoid tumors are rare slow-growing neuroendocrine malignancies most commonly originating from enterochromaffin cells located in the gastrointestinal tract.[19] As a result of these inherent neuroendocrine properties, they have the capacity of synthetizing, storing, and secreting large amounts of vasoactive substances including 5-hydroxytryptamine (serotonin), histamine, tachykinins, prostaglandins, and possibly other growth factors.[20] In healthy subjects, serotonin is usually recaptured by a cellular transporter, mostly inactivated by the hepatic monoamine oxidase, and then metabolized to urinary 5-hydroxyindolacetic acid (5-HIAA) for renal clearance.[21] In the presence of hepatic metastases, metastatic active foci of enterochromaffin cells secrete copious amounts of serotonin that will exceed and bypass the degradation capacity of the liver.[22] As a result, a significant concentration of these substances is integrally released into the systemic circulation, leading to a constellation of clinical symptoms known as carcinoid syndrome.[23] The most frequent symptoms that characterize carcinoid syndrome are cutaneous flushing, gastrointestinal hypermobility, and cardiac involvement.[24] Cardiac manifestations, also known as carcinoid heart disease, are secondary to a plaque-like endocardial deposition of fibrous tissue that most frequently extends to the right-sided valves (tricuspid > pulmonary) and very often involves the subvalvular apparatus leading to different patterns of valve dysfunction.[25] Exceptions to this pathophysiologic pathway are ovarian carcinoids, which drain directly into the systemic circulation, or very rare (< 1%) cases of extensive retroperitoneal lymph node metastases with drainage to the thoracic duct.[26,27] The development of left-sided lesions implies a persistent cardiac shunt or a very severe or poorly controlled tumor activity that may overcome the pulmonary potential to inactivate serotonin.[28] Left-sided CHD only occurs in approximately 10% to 15% of the patients with carcinoid syndrome (Fig. 51–5).[29]

Carcinoid heart disease is typically characterized by an evident endocardial deposition of a pearly white fibrotic conglomerate of smooth muscle cells, myofibroblasts, and collagen[30], also known as carcinoid "plaque" (Fig. 51–6).[31] Plaque formation causes annular constriction leading to relative degrees of valvular stenosis, as well as leaflet thickening and retraction, and subvalvular fusion and shortening[32]. In the early stages, there is mild thickening of the right-sided valves with changes of the normal concave leaflet curvature and altered motion during diastole. As the disease progresses, thickening of the leaflets extends to the subvalvular apparatus, resulting in a greater restricted motion.[33] Chordae are usually fused, and different patterns (from thick and focal to thin and diffuse) of "plaque" deposition might be observed.[34] In very advanced stages, the marked degeneration of leaflet architecture leads to a very severe leaflet retraction and non-coaptation of the valve, which remains fixed in a severely regurgitant semiopen position.[35]

The clinical features are those of the carcinoid tumor and right-heart failure. The echocardiographic appearance of the thickened restricted valve leaflets is quite characteristic. Color-flow Doppler reveals wide-open tricuspid regurgitation often with laminar regurgitant flow into a large right atrium. Spectral Doppler tracing with continuous-wave

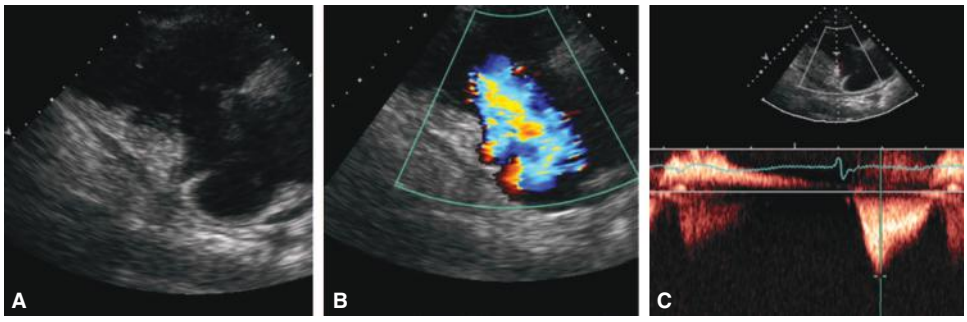

FIGURE 51–4. Severe secondary tricuspid regurgitation caused by extreme tethering of the tricuspid valve without intrinsic leaflet pathology. **A.** The right ventricular inflow view from a parasternal transducer position shows a markedly tethered valve in late systole. **B.** Color Doppler shows flow acceleration and a jet of severe tricuspid regurgitation without turbulence. **C.** Continuous-wave Doppler shows an early peaking systolic profile associated with high right atrial pressure, which was estimated to be 25 mm Hg. The peak tricuspid regurgitation velocity is measured at 9 mm Hg and thus indicates the right ventricular systolic pressure to be 34 mm Hg (9 + 25).

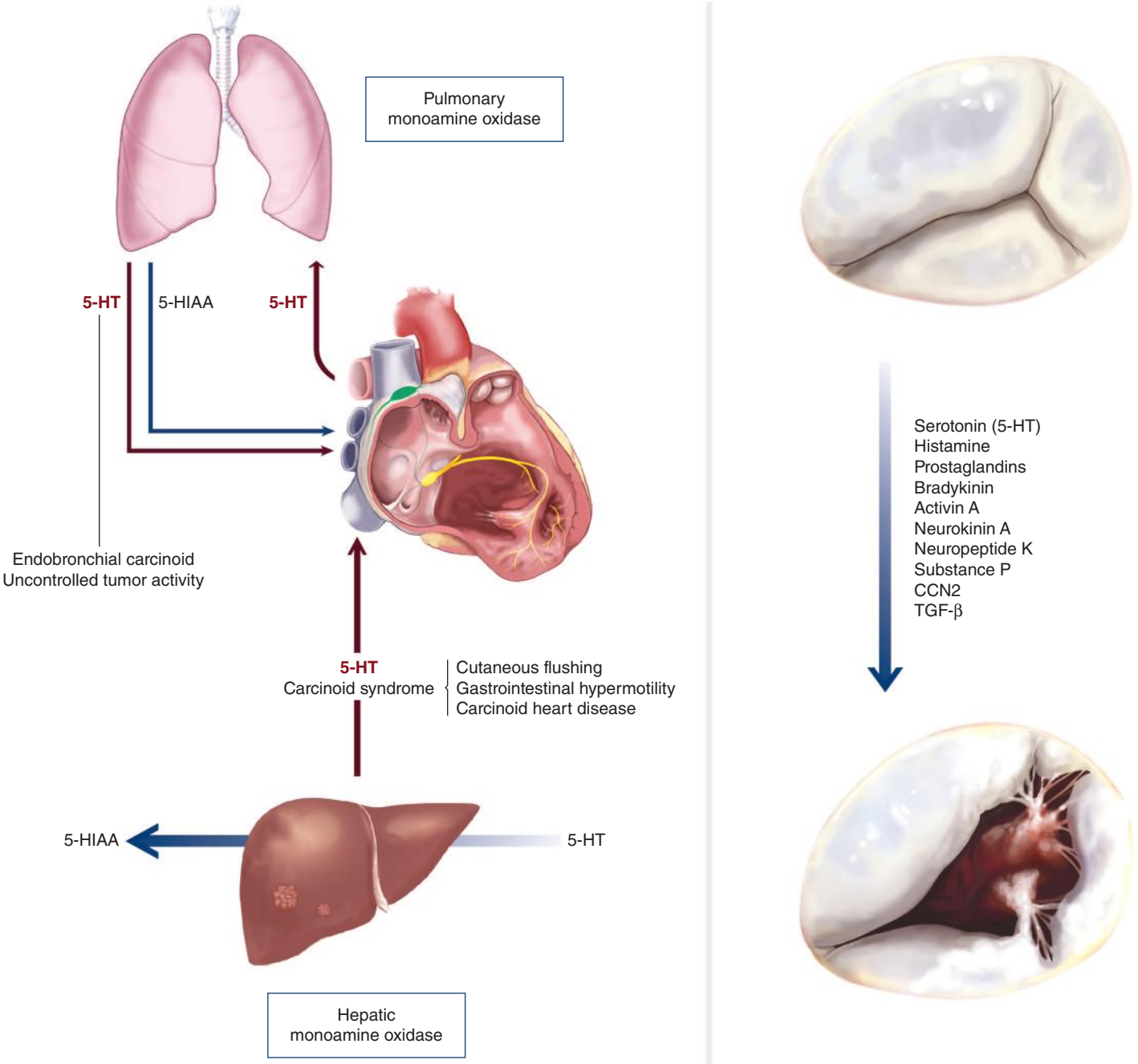

FIGURE 51–5. Pathophysiology of carcinoid syndrome and carcinoid heart disease. The blue line depicts the normal metabolic pathway of serotonin. 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin.

Doppler shows a characteristic pattern of early peaking profile suggestive of marked elevation of right atrium pressure (Fig. 51–7).

Echocardiography is the primary imaging modality used for diagnosis and assessment of the extent and severity of carcinoid heart disease.[36] Tricuspid (TV) and pulmonary (PV) valves are typically thickened and retracted (type IIIA valve dysfunction). Unpublished data from our institutional ongoing research has revealed a potential role of speckle-tracking echocardiography and strain techniques in surgical referral. Classically, the evaluation of patients with CHD has been exclusively focused on estimations of functional valve disease. However, strain techniques have been recently proposed for the assessment of RV function as an indirect measure of endocardial fibrosis. Recent series have shown a significant reduction in RV function (assess by strain) in those patients with CHD when compared to healthy controls.[37] In addition to echocardiography, cardiac magnetic resonance imaging is an alternative imaging modality for the evaluation of CHD that can affect decision making and management because it

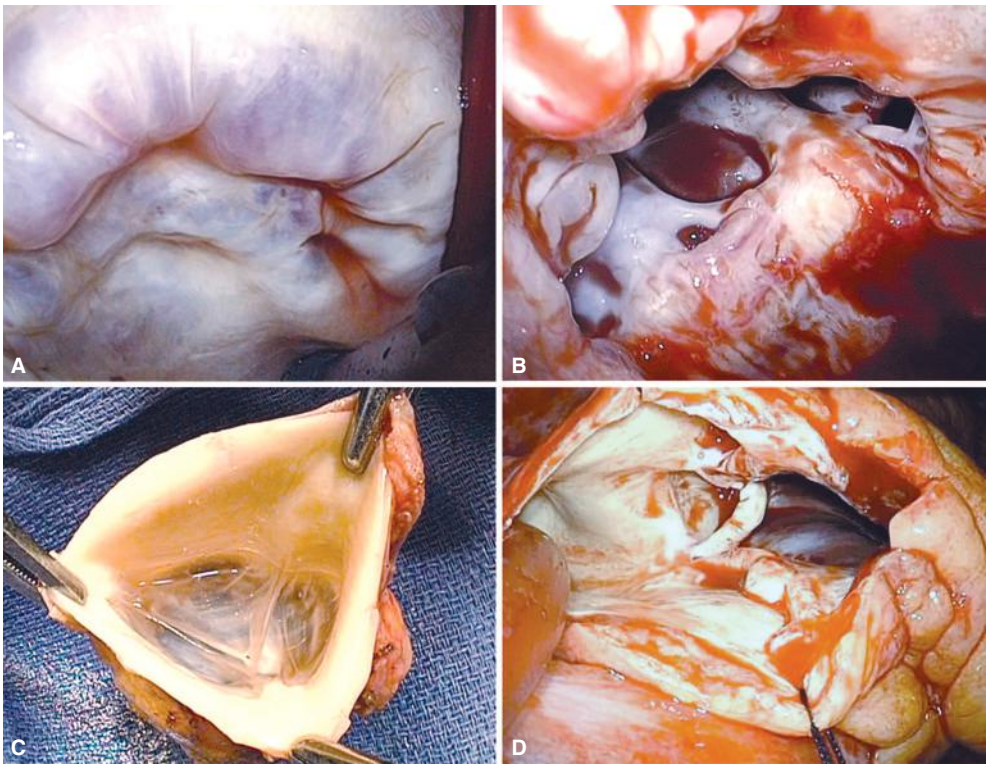

FIGURE 51–6. Upper panels demonstrate an intraoperative atrial view of a normal tricuspid valve (**A**) and a pathologic tricuspid valve with carcinoid heart disease (**B**). Lower panels show a normal pulmonary valve as an autograft during a Ross procedure (courtesy of Paul Stelzer, MD) (**C**) and an outflow view of a pathologic pulmonary valve in a patient with carcinoid heart disease (**D**).

provides accurate assessment of the volume and function of the right heart and enables quantification of the size of possible myocardial metastases and offers information regarding extension into surrounding structures (Fig. 51–8).[38]

The gold standard treatment for carcinoid heart disease is usually tricuspid valve replacement and pulmonary valve replacement with patch enlargement of the right ventricular outflow tract.[39] Although TV replacement has been traditionally accepted by most authors, the need for PV replacement (versus isolated valvectomy) has been debatable. It is certainly true that some patients may tolerate pulmonary regurgitation; however, long-standing pulmonary regurgitation after valvectomy may have a negative impact on RV remodeling. Additionally,

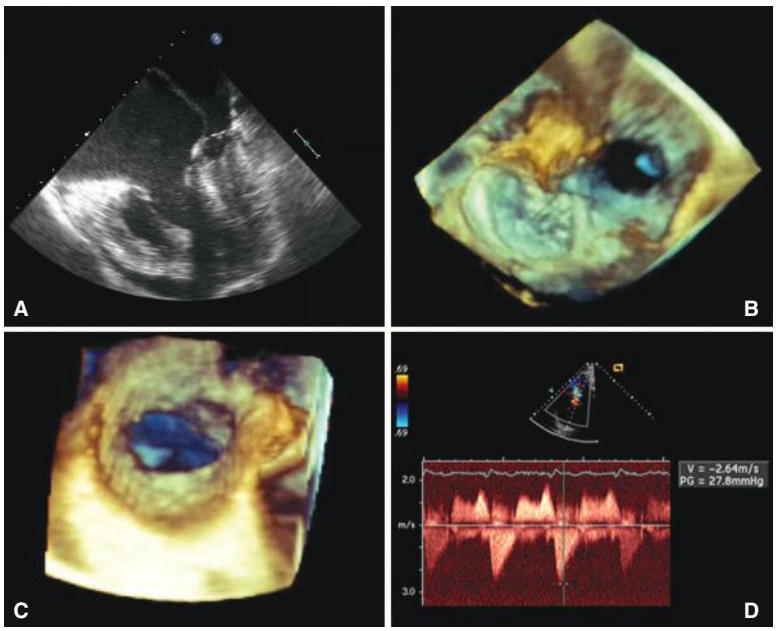

FIGURE 51–7. **A.** Transesophageal echocardiography shows severe retraction, tethering, and fibrosis of the tricuspid valve leaflets. **B.** 3D echocardiography demonstrates opening of the tricuspid valve in late systole; note the complete cooptation of the mitral valve. **C.** Ventricular view of the tricuspid valve leaflets in late diastole. **D.** The continuous-wave Doppler shows systolic velocity of early peak and a rapid deceleration indicating high right atrial pressure. The diastolic velocity with slow early deceleration and a prominent presystolic flow is consistent with some degree of tricuspid stenosis.

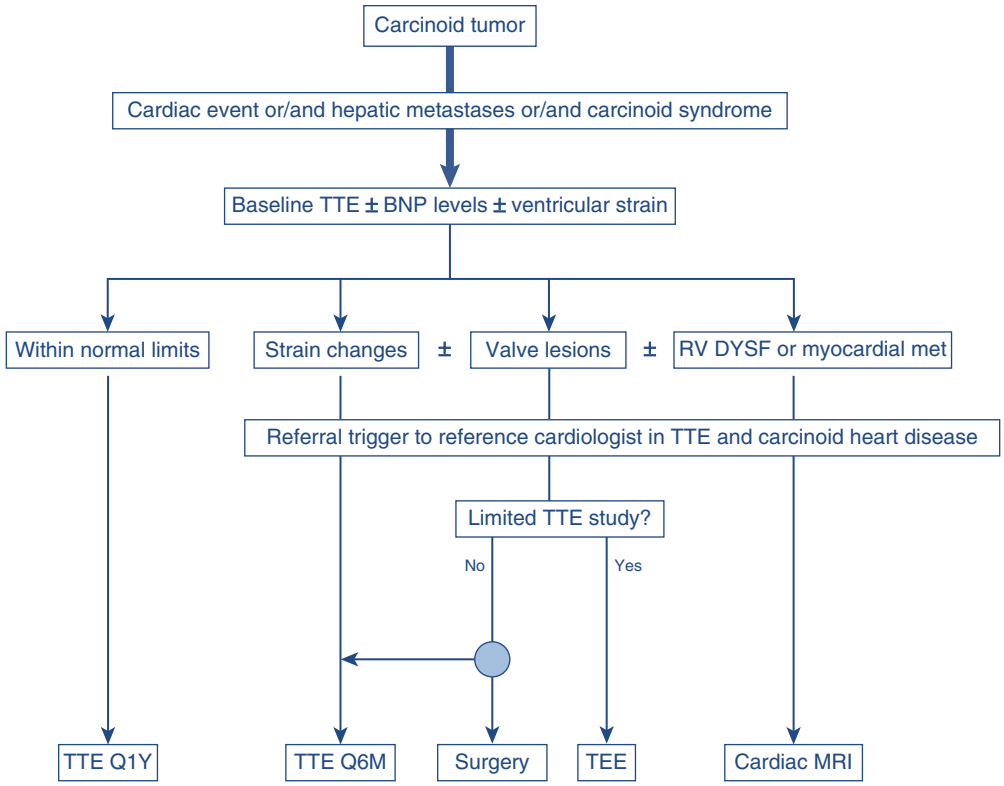

FIGURE 51–8. Management algorithm for patients with carcinoid syndrome and/or carcinoid heart disease. BNP, brain natriuretic peptide; Dysf, dysfunction; MRI, magnetic resonance imaging; Q, each; RV, right ventricle; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram; Y, year.

a more uneventful postoperative recovery has been described among those patients undergoing PV replacement and additional patch enlargement of the RVOT.[40]

Traumatic Tricuspid Regurgitation The traumatic injury might be external, such as blunt chest wall injury with disruption of chordal structures (Fig. 51–9); or internal, generally iatrogenic, resulting from damage from pacemaker leads, a stiff guidewire, or radiofrequency ablation for the treatment of arrhythmias.[41] Tricuspid regurgitation resulting from a pacemaker lead either may be from perforation of a leaflet or its restriction as a result of chronic fibrotic changes of the leaflet and subvalvular apparatus (Fig. 51–10). It is often unrecognized because the functional consequences are slow to develop, and the regurgitation is often progressive.

Treatment is based on recognition of the cause of regurgitation. Transthoracic and transesophageal echocardiography provide important clues. Although the valve pathology is often repairable, the timing of surgery will be determined by clinical evidence of severe regurgitation before deterioration of RV function or elevations in liver enzymes.

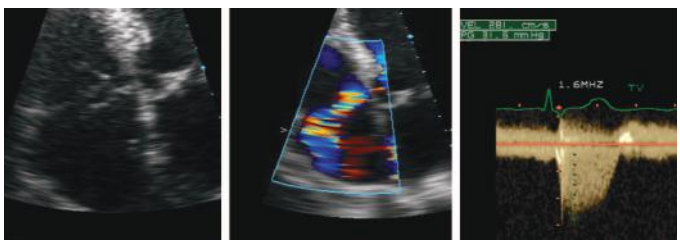

FIGURE 51–9. A 56-year-old patient with mitral valve prolapse exhibiting spontaneous rupture of the tricuspid valve. **A.** The flail septal leaflet of the tricuspid valve is shown in systole. **B.** The resulting eccentric tricuspid regurgitation jet directed laterally because of flail leaflets. **C.** The continuous-wave Doppler recording of the regurgitant jet with a peak systolic gradient between the right ventricle and the right atrium of 32 mm Hg. The inferior vena cava was measured at 2.5 cm and showed no discernible collapse, indicating estimated right atrial pressure of 20 mm Hg. Thus, the right ventricular systolic pressure is estimated as 52 mm Hg.

Ebstein Anomaly This congenital lesion may first be detected at an adult age, in individuals with milder cases living up to the sixth decade of life (see Chap. 56). The characteristic features are apical displacement of the septal leaflet of the tricuspid valve and a large, sail-like anterior leaflet that results in atrialization of the right ventricular inflow. Functionally, a variable degree of tricuspid regurgitation is observed.[42] The right heart chambers are markedly dilated. A right-to-left shunt at the atrial level may be present if atrial septal defect coexists. The clinical presentation is marked by cardiomegaly involving right heart chambers, quiet precordium with a soft systolic murmur, and abnormal electrocardiogram results with a wide QRS complex and a short PR internal. Symptomatic supraventricular arrhythmias are common. The electrocardiogram exhibits a diagnostic apical displacement of the septal and anterior tricuspid leaflets with a large, sail-like anterior leaflet. Moderate low-velocity tricuspid regurgitation may be observed.[43] Treatment ranges from medical management in milder forms of the disease to valve repair or valve replacement in more advanced symptomatic patients.[44,45]

Tricuspid Valve Prolapse Degenerative mitral prolapse is associated with tricuspid prolapse (Fig. 51–11).[46] In most cases, there are no distinctive physical signs (see Chap. 48). Echocardiography reveals billowing of the septal and anterior leaflets. The associated tricuspid regurgitation is generally mild. Rarely, spontaneous chordae rupture may result in

FIGURE 51–10. Intraoperative views of pacing lead-related injuries of the tricuspid valve, characterized by a severe fibrotic reaction around the lead with leaflet thickening and retraction.

severe regurgitation. When moderate or severe tricuspid regurgitation with dilatation of the annulus accompanies severe mitral regurgitation with degenerative mitral valve disease, the management consists of tricuspid annuloplasty in addition to mitral valve repair (Table 51–1).

Secondary Tricuspid Valve Disease

Secondary tricuspid regurgitation might be a consequence of right ventricular and tricuspid annular dilatation (left-sided valve disease, myocardial disease, intrinsic pulmonary hypertension, or ventricular remodeling),[47] chronic right ventricular pacing (dyssynchrony), and chronic atrial fibrillation. Mechanisms frequently coexist, and contribute to decreased leaflet coaptation. The progression of functional tricuspid regurgitation has been described as occurring in three phases:

1. An initial phase in which right ventricular and annular dilatation are present, either with or without tricuspid regurgitation.
2. An intermediate phase in which significant tricuspid regurgitation is caused by progressive annular and right ventricular dilatation.
3. An advanced phase where papillary muscle displacement as a result of right and/or left ventricular dysfunction causes leaflet tethering and more severe tricuspid regurgitation.[48]

Annular dilatation is an early consequence of right ventricular dilatation or dysfunction, because of the lack of an anatomic fibrous annulus.[49] The annular circumference may increase from approximately 100 to 170 mm. Annular dilatation does not occur symmetrically; the posterior and anterior annulus are relatively unsupported and tend to dilate more than the septal annulus.[50]

Pathophysiology The primary mechanism causing regurgitation is transmission of pressure overload from pulmonary hypertension to the tricuspid valve as a raised right ventricular systolic pressure. In the absence of pulmonary hypertension, the main mechanisms underlying tricuspid regurgitation are annular dilatation and leaflet tethering.

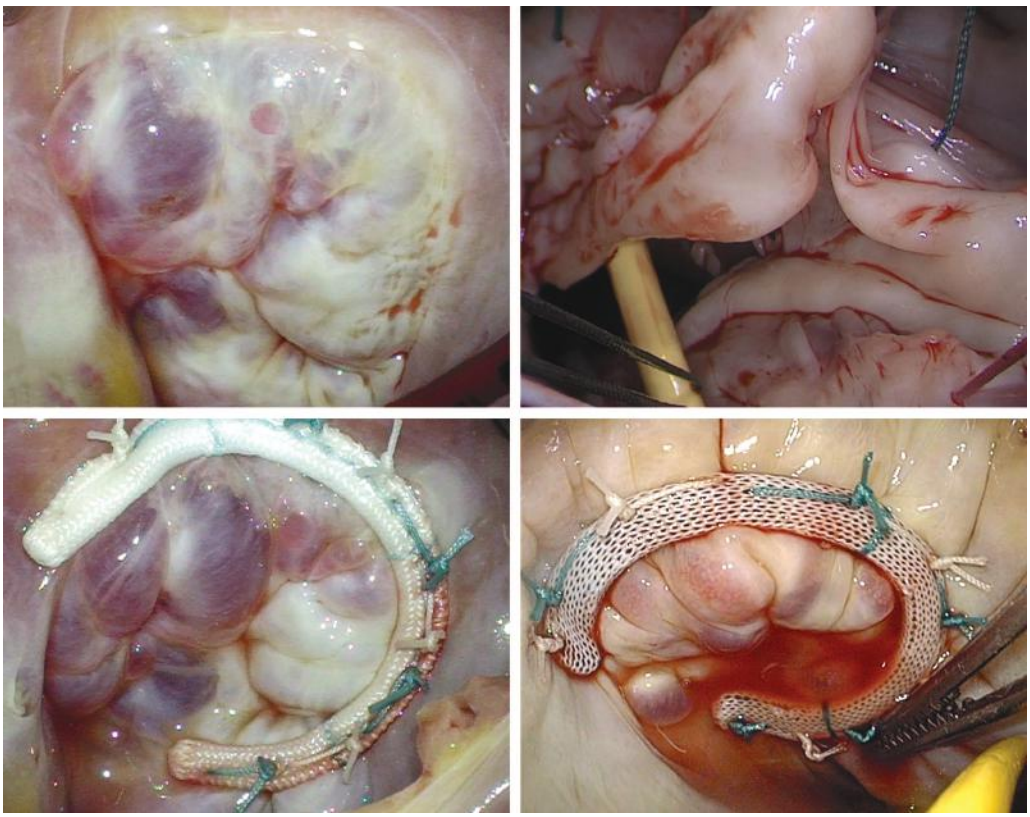

FIGURE 51–11. Intraoperative views of redundant prolapsing tricuspid valve leaflets (top panels). Tricuspid annuloplasty with a semirigid incomplete ring (left) and a rigid ring (right).

TABLE 51–1. Comparison of Management Guidelines for Tricuspid Regurgitation from the American Heart Association/American College of Cardiology[1] and the European Society of Cardiology[76]

AHA/ACC Recommendations	AHA/ACC	ESC	ESC Recommendation
Diagnosis			
Transthoracic echocardiography is indicated to evaluate severity of tricuspid regurgitation or stenosis, determine etiology, measure right-sided chambers and inferior vena cava, assess RV systolic function, estimate pulmonary pressure, and characterize left-sided heart disease.	I C		
Invasive measurement of pulmonary artery pressures and pulmonary vascular resistance can be useful in patients with tricuspid regurgitation or stenosis when clinical and noninvasive data regarding their values are discordant.	IIa C		
Cardiac magnetic resonance of real-time 3D echocardiography may be considered fo assessment of right ventricular systolic function and diastolic volumes in patients with severe tricuspid regurgitation and suboptimal 2D echocardiograms.	IIb C		
Exercise testing may be considered for the assessment of exercise capacity in patients with severe tricuspid regurgitation with no or minimal symptoms.	IIb C		
Medical Therapy			
Diuretics can be used for patients with severe tricuspid regurgitation and signs of right-sided heart failure.	IIa C		
Medical therapies to reduce elevated pulmonary artery pressures and/or pulmonary vascular resistance might be considered in patients with severe functional tricuspid regurgitation.	IIb C		
Intervention			
Tricuspid valve surgery is recommended in patients with severe tricuspid regurgitation undergoing left-sided valve surgery.	I C	I C	Surgery is indicated in patients with severe primary or secondary tricuspid regurgitation undergoing left-sided valve surgery.
Tricuspid valve surgery can be beneficial for patients with symptoms caused by severe primary tricuspid regurgitation that are unresponsive to medical therapy.	IIa B	I C	Surgery is indicated in patients with severe isolated primary tricuspid regurgitation without severe right ventricular dysfunction.
Tricuspid valve surgery is recommended for patients with isolated, symptomatic severe tricuspid stenosis.	I C	I C	Surgery is indicated in patients with severe tricuspid stenosis.
Tricuspid valve surgery is recommended in patients with severe tricuspid stenosis undergoing left-sided valve surgery.	I C	I C	Surgery is indicated in symptomatic patients with severe tricuspid stenosis undergoing left-sided valve surgery.
Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional tricuspid regurgitation at the time of left-sided valve surgery, with either (1) tricuspid annular dilatation or (2) prior evidence of heart failure.	IIa B	IIa C	Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation with dilated annulus (> 40 mm or 21 mm/m^2) undergoing left-sided valve surgery.
Tricuspid valve repair may be considered for patients with moderate functional tricuspid regurgitation and pulmonary artery hypertension at the time of left-sided valve surgery.	IIb C	IIa C	Surgery should be considered in patients with moderate primary tricuspid regurgitation undergoing left-sided valve surgery.
Tricuspid valve surgery may be considered in asymptomatic or mildly symptomatic patients with severe primary tricuspid regurgitation and progressive degrees of moderate or greater right ventricular dilatation and/or systolic dysfunction.	IIb C	IIa C	Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary tricuspid regurgitation and progressive right ventricular dilatation or deterioration of right ventricular function.
Reoperation for isolated tricuspid repair or replacement may be considered for persistent symptoms caused by severe tricuspid regurgitation in patients who have undergone previous left-sided valve surgery.	IIb C	IIa C	After left-sided valve surgery, surgery should be considered in patients with severe tricuspid regurgitation who are symptomatic or have progressive right ventricular dysfunction in the absence of left-sided valve dysfunction, severe right or left ventricular dysfunction, and severe pulmonary vascular disease.
Percutaneous balloon tricuspid commissurotomy might be considered in patients with isolated symptomatic severe tricuspid stenosis without regurgitation.	IIb C		

Pulmonary Hypertension Severe left-sided cardiomyopathy and valvular heart disease are commonly associated with elevated left atrial filling pressures directly transmitted to the pulmonary vasculature. Pulmonary hypertension is caused by the resultant increased afterload as well as compensatory pulmonary vasoconstriction, which results in chronic vascular remodeling.[51] This causes right ventricular pressure overload, which may directly result in tricuspid regurgitation. Pulmonary hypertension partially determines the degree of secondary tricuspid regurgitation, but the relationship is not a direct one, and functional tricuspid regurgitation may also develop in the absence of demonstrable pulmonary hypertension, suggesting additional underlying mechanisms.

Annular Dilation Annular dilation results in loss of leaflet coaptation. Annular dilatation is a strong independent predictor of secondary

tricuspid regurgitation. In addition to dilating, valves with functional tricuspid regurgitation lose their normal saddle-shaped annular geometry, becoming flattened and circular with asymmetrical loss of annular contraction.[52]

Leaflet Tethering Leaflet tethering occurs as a result of shortening or displacement of the subvalvular apparatus (for example shortening of the papillary muscles and chordae in rheumatic valve disease, or papillary muscle displacement in right ventricular dilatation). Secondary tricuspid regurgitation resulting from septal leaflet tethering may be observed in the context of normal right ventricular function, dimensions, and pulmonary pressure. This suggests that left ventricular pathology can contribute to functional tricuspid regurgitation, possibly caused by a dysfunctional or displaced interventricular septum causing tethering of the septal tricuspid leaflet. In one analysis of 75 patients with dilated right ventricles, *eccentricity* of the right ventricle and tricuspid valve tethering area were most strongly predictive of the severity of functional tricuspid regurgitation, whereas right ventricular function, dimension, and pulmonary artery pressures were not significant determinants.[53]

Clinical Presentation

Clinical presentation depends on whether the valve dysfunction is predominantly stenotic, regurgitant, or a mixture; on the grade and chronicity of tricuspid valve dysfunction; and on the severity and nature of the causative etiology, including left-sided heart disease.

Symptoms Moderate tricuspid regurgitation is well tolerated, and most patients with isolated functional tricuspid regurgitation are asymptomatic. Symptoms of left heart disease predominate in patients with functional tricuspid regurgitation.[54] Any history of intracardiac wires, catheters, biopsies, or intravenous injections should be elicited. Functional tricuspid regurgitation may occur late after correction of left-sided pathology, including mitral and aortic valve intervention. The symptoms specific to advanced tricuspid valve disease are related to decreased cardiac output (eg, fatigue) and right-sided hypertension (eg, liver congestion resulting in right upper quadrant discomfort, gut congestion with symptoms of dyspepsia and indigestion, and fluid retention with leg edema and ascites). Importantly, significant tricuspid disease may be asymptomatic until a late stage of the disease where symptoms are a result of the sequelae of severe right ventricular dysfunction.[53]

Physical Examination Characteristic physical signs may result from etiology causing tricuspid valve disease, including atrial fibrillation, congestive heart failure, pulmonary hypertension, or endocarditis. Clinical examination should include assessment of the chest, neck, arms, and abdomen for sites of previous or current venous access, indwelling catheters, wires, and cardiac devices, and cardiac surgery. Clinical signs of chronic venous congestion include dependent pitting edema, venous stasis, and ascites.

Tricuspid stenosis results in characteristic changes in the jugular venous pulse in the form of a slow V to Y descent and prominent "a" waves. The liver is enlarged with a firm edge and is pulsatile in pre-systole. Auscultation reveals a low- to medium-pitched diastolic rumble with inspiratory accentuation. This is usually localized to the lower sternal border (see Chap. 11).[55]

Tricuspid regurgitation results in the jugular venous pulse exhibiting a prominent C-V wave or systolic wave. There is often a parasternal lift from right ventricular enlargement. The liver shows systolic pulsation, is enlarged, and is often tender. The cardiac auscultation reveals a soft early or holosystolic murmur, which is augmented with inspiratory effort (Carvallo sign). A systolic honk may be present with tricuspid prolapse.[56] Substantial tricuspid regurgitation may exist without the classic auscultatory findings.

Diagnosis

Electrocardiography There are no specific markers of tricuspid valve disease, although the following clues may be present: (1) right ventricular hypertrophy and "strain" with right axis duration and (2) right atrial enlargement with prominent P-waves.

Chest Radiography Cardiomegaly associated with prominent right heart borders may be noted. There are no specific radiographic findings to suggest a diagnosis of tricuspid valve disease.

Echocardiography Two-dimensional echocardiography with spectral and color-flow Doppler evaluation provides the most accurate and comprehensive laboratory test in the evaluation of tricuspid valve disease (Fig. 51–12).[57-59] Valve morphology helps differentiate primary from secondary tricuspid regurgitation. The right heart chamber enlargement is best visualized in apical four-chamber and subcostal views, although accurate quantitation of chamber size and ejection fraction are problematic. An indirect measure of right ventricular ejection fraction is based on systolic displacement of the tricuspid annulus using M-mode recording. Tissue Doppler imaging of the annulus provides similar correlation between annular systolic velocity and right ventricular function. Real-time three-dimensional echocardiography provides additional information on morphology and function of the tricuspid valve.[60]

Tricuspid valve morphology is best assessed using the parasternal tricuspid inflow view, apical and subcostal four-chamber views, and parasternal short-axis view. Abnormal structure and function of the valve provide insights into the likely underlying cause. The functional tricuspid regurgitation is characterized by annular dilatation, the extent of which may determine its severity.

Quantitation of valve lesion is obtained using spectral and color-flow Doppler approaches. Tricuspid stenosis is detected by presence of flow acceleration on the atrial side of the valve and turbulence downstream with the right ventricular inflow. The severity of tricuspid stenosis is based on mean and end-diastolic gradients measured using continuous-wave Doppler recordings. The normal mean gradient is less than 2 mm Hg, and the end-diastolic gradient is nearly zero. Significant stenosis of the tricuspid valve may be present with a mean gradient of 3 to 5 mm Hg and an end-diastolic gradient of 1 to 3 mm Hg. The use of pressure half-time to estimate tricuspid valve area and of two-dimensional echo-based planimetry of the tricuspid orifice has not been documented, and these are rarely, if ever, used.[58] Tricuspid regurgitation is detected using color Doppler imaging. Its severity may be semi quantitated based on the extent of the regurgitation jet penetration into the right atrium and inferior vena cava. Whereas the jet of the mild tricuspid regurgitation occupies up to 2 cm into the right atrium, the jet of moderate regurgitation extends deeper (3-5 cm) into the atrium but does not exhibit systolic reversal in hepatic or caval flow. However, with severe tricuspid regurgitation, there is consistent systolic flow reversal in the hepatic vein using the pulsed Doppler approach.[61] A more quantitative assessment of tricuspid regurgitation may be obtained by using flow acceleration, proximal isovelocity surface area methods, and width of the vena contracta (see Chap. 15). A simpler approach is based on measuring the proximal isovelocity surface area radius. For the simpler method, the aliasing scale is adjusted at approximately one-twelfth of the peak regurgitation velocity (normally < 3.0 m/s by shifting the color scale baseline to approximately 25-30 cm/s). The proximal isovelocity surface area radius at this adjusted aliasing scale of 1 to 4 mm indicates mild regurgitation, 5 to 8 mm indicates moderate regurgitation, and greater than 9 mm indicates severe regurgitation. The width of vena contracta greater than 7.0 mm is an additional indicator of severe regurgitation.

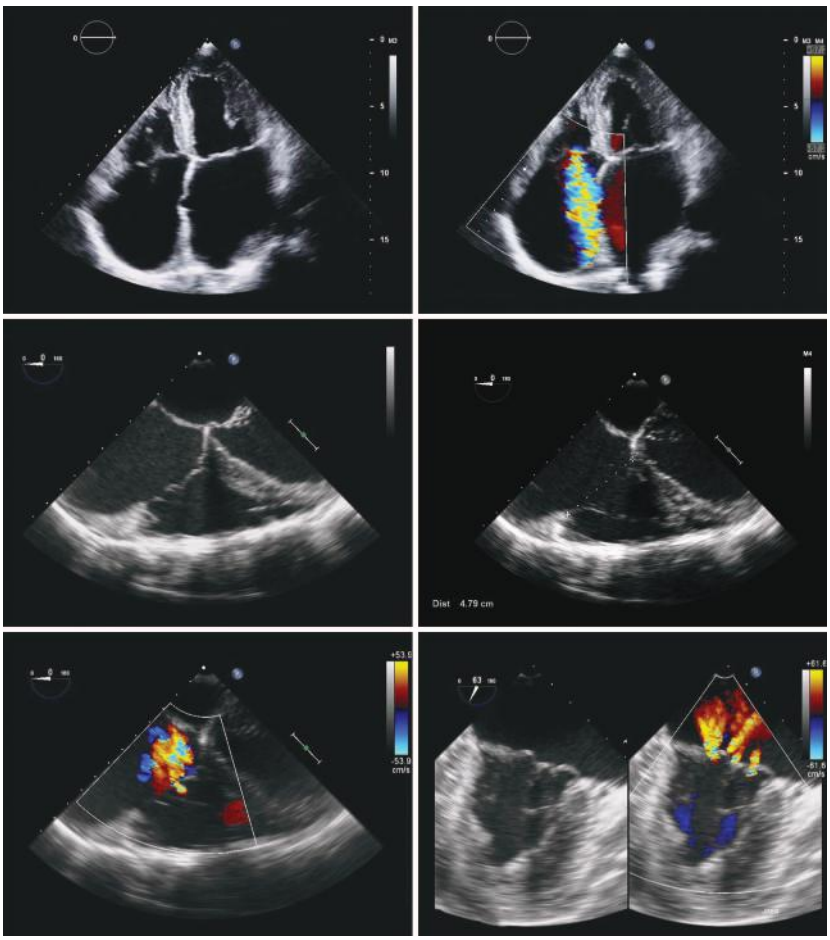

FIGURE 51–12. Transthoracic echocardiography shows severe dilatation of the tricuspid annulus with a severe regurgitant jet (top panels). Transesophageal echocardiography corroborates severe annular dilatation up to 4.8 cm (middle panels). Intraoperative echocardiography shows a central regurgitant jet in a patient who was referred for mitral valve surgery resulting from type I dysfunction and severe annular dilatation. Note the characteristic multiple jets seen in patients with type I dysfunction of the mitral valve.

A spectral display of tricuspid regurgitation velocity is obtained using the continuous-wave Doppler approach generally from right ventricular inflow view, short-axis view, or four-chamber view. The peak velocity used to estimate right ventricular systolic pressure is calculated as follows: right ventricular systolic pressure = 4 × peak tricuspid regurgitation velocity + right atrial pressure (see Chap. 15). The right atrial pressure is assumed to be 7 to 10 mm Hg, but may also be estimated based on the inferior vena cava size and its change with a sniff test.

The estimated right ventricular systolic pressure correlates well with that measured at cardiac catheterization. However, the upper limit of measured peak systolic pressure using the Doppler approach is 40 mm Hg rather than the 30 mm Hg measured directly. This discrepancy is partly a result of respiratory variations and assumed right atrial pressure, which may vary by 3 to 5 mm Hg from the measured mean atrial pressure. It must be emphasized that the magnitude of the velocity does not indicate the severity of regurgitation but rather the height of right ventricular systolic pressure.[62]

Thus a peak velocity between 3.0 and 3.9 m/s indicates moderate and in excess of 4.0 m/s severe pulmonary hypertension even if the tricuspid regurgitation severity is mild and vice versa. The shape of the velocity profile gives considerable hemodynamic information. An early peak with rapid deceleration indicates equalization of right ventricular and right atrial pressures in late systole, generally from a large CV wave. A broadly rounded tricuspid regurgitation velocity profile that occupies 50% more of the R-R interval is indicative of impaired right ventricular function.

Transthoracic echocardiography is often of diagnostic quality because the tricuspid valve and the right ventricle are closer to the anterior chest wall and several parasternal, apical, and subcostal views are used to image these structures. However, transesophageal echocardiography is indicated for better anatomic definitions of the valve lesions or precise measurement of the tricuspid annulus (Fig. 51–12). The assessment of severity of tricuspid stenosis or regurgitation is generally more accurate with transthoracic echocardiography. This is especially true in the intraoperative setting, where severity of tricuspid regurgitation may be underestimated as a result of lowered pulmonary vascular resistance and reduced preload from the anesthetic agents and the fasted state.

In the intraoperative setting, transesophageal echocardiography is especially used for measuring the tricuspid annulus diameter. This is done in the mid-esophageal four-chamber view and a plane perpendicular (90°) to it.

Cardiac Catheterization Invasive measurement of pulmonary artery and right atrial and ventricular pressures and pulmonary vascular resistance is helpful to guide clinical decision making in patients where physical examination and echocardiographic findings conflict; or when tricuspid jet velocity is inadequate to estimate pulmonary artery pressure.

A Fick cardiac output should be measured for calculation of pulmonary vascular resistance, as thermodilution cardiac output is inaccurate in the setting of severe tricuspid regurgitation.

Treatment of Tricuspid Valve Disease

Several large studies have reported on the adverse effects of long-standing tricuspid regurgitation.[2,54,63] If treated medically, moderate to severe tricuspid regurgitation carries a mortality of 26% at 5 years. In addition, TR has been associated with reduced survival in patients with left ventricular systolic dysfunction.

The management of tricuspid valve disease is guided by the underlying cause and pathology of tricuspid disease. Consensus guidelines for management of tricuspid valve disease are summarized in Table 51–1. The mainstay of medical management of severe secondary tricuspid regurgitation includes loop diuretics and aldosterone antagonists to decrease volume overload in patients with peripheral edema and ascites.[1] Specific pulmonary vasodilators may be helpful to reduce right ventricular afterload in patients with reversible pulmonary hypertension evaluated with cardiac catheterization. Left-sided pathology including left ventricular failure and systemic hypertension should be optimized.

Surgical correction of tricuspid valve disease is most commonly performed at the time of mitral valve surgery.[12] It is less commonly performed in conjunction with aortic valve surgery, coronary artery bypass grafting, atrial fibrillation surgery, or as an isolated procedure. The goals of operative management of tricuspid regurgitation are to address abnormal anatomy and pathophysiology. This includes annular reduction and correction of significant left-sided pathology with the aim of improving of pulmonary hypertension and ventricular remodeling.[64]

Isolated Tricuspid Surgery Patients undergoing isolated tricuspid valve surgery present a unique set of challenges: right-sided valve lesions are tolerated relatively well until very late in the disease process, when severe right ventricular dysfunction and severe pulmonary hypertension become common. Severe tricuspid regurgitation makes accurate assessment of right ventricular dysfunction and pulmonary hypertension very difficult. In this context, preoperative right heart catheterization to quantify pulmonary hypertension, pulmonary vascular resistance, and right ventricular stroke work; and cardiac magnetic resonance imaging to identify the etiology of the cardiomyopathy and quantify valvular and ventricular dysfunction; are particularly helpful. Careful attention should also be paid to assessment of liver function: although moderate degrees of dysfunction caused by to hepatic congestion often improve after surgery, advanced cirrhosis (which is often present despite relatively mild derangements of liver enzymes and bilirubin) is commonly characterized postoperatively by refractory coagulopathy, vasoplegia, and hepato-renal syndrome.[65] Current series report perioperative mortality rates between 4% and 17% in patients undergoing isolated tricuspid surgery, with repair rates around 70%.[66,67] Independent predictors of mortality include age, right ventricular failure, and pulmonary hypertension.

Years after left-sided surgery, patients might present with isolated severe tricuspid regurgitation. The problems inherent in mediastinal reentry[68] in the setting of advanced cardiomyopathy and pulmonary and hepatic dysfunction are reflected in the high rate of postoperative vasoplegia, cardiogenic shock, and respiratory failure in these patients in whom multiorgan dysfunction and sepsis are among the commonest modes of death.[69]

In particular cases such as carcinoid heart disease, one of the goals of surgery is to facilitate subsequent hepatic resection of metastases, which may be extensive.[70] Management of these patients is complicated by carcinoid syndrome associated with hepatic metastases, and which requires infusion of octreotide and avoidance of exogenous catecholamines to reduce the incidence of carcinoid crises, residual effects of prior chemotherapy, and hepatic dysfunction.[71]

Surgical Treatment of Secondary Tricuspid Regurgitation Annular dilatation and abnormal geometry is effectively addressed by tricuspid annuloplasty,[72] the most widely used repair technique. The many annuloplasty options can be divided into either suture or ring annuloplasty; rings may be flexible, semiflexible, or rigid, and most are incomplete. Tricuspid valve replacement is not indicated for repair of moderate functional regurgitation, as it introduces the additional risks of thromboembolic and hemorrhagic complications inherent with mechanical prostheses, or the risk of structural valve degeneration requiring reoperation associated with bioprostheses.[73]

Tricuspid Valve Repair The aim of tricuspid annuloplasty is to restore the dilated annulus to its physiological size, either by suturing a rigid or semi-rigid ring to the annulus or using a continuous suture to "purse-string" the annulus, relying on continued integrity of the suture and annular contraction and fibrosis to maintain the new annular dimensions.[74] Both methods stabilize the anterior and posterior annulus, which is most at risk of dilatation. Depending on the choice of annuloplasty ring, the septal annulus is kept relatively free of sutures, particularly in the anteroseptal commissural area where the conduction tissue is at risk (Fig. 51–13). Methods of plicating the posterior annulus, or sewing the leaflet edges together, have fallen out of favor as long-term results have shown relatively poor freedom from residual and recurrent regurgitation. A remodeling ring may offer the best long-term durability, and observational studies suggest that the ring repairs are more durable than the suture repairs.[75] Data from the surgical literature suggest that over 85% of patients having a ring annuloplasty for functional tricuspid regurgitation will be free from moderate or severe tricuspid regurgitation 5 to 10 years after surgery.[65]

Although the presence of moderate or greater tricuspid regurgitation in patients undergoing mitral valve repair is an indication for concomitant tricuspid valve annuloplasty,[1,76] the management of secondary tricuspid regurgitation in patients with mild to moderate tricuspid regurgitation[77,78] remains debatable, particularly in regard to the best surgical option and whether concomitant "prophylactic" tricuspid annuloplasty is necessary. As tricuspid regurgitation is a dynamic lesion, which is downgraded by general anesthesia, the absence of tricuspid regurgitation in intraoperative transesophageal echocardiography is an unreliable indicator of severity under normal loading conditions, and the presence of tricuspid regurgitation on preoperative echocardiography becomes a more reliable indicator. Tricuspid dilatation > 4.0 cm in the four-chamber view is a measurement that is relatively independent of loading conditions, and predictive of functional tricuspid regurgitation; this may be an indication for concomitant tricuspid annuloplasty at the time of mitral valve repair, in the absence of significant tricuspid regurgitation on echocardiography (Fig. 51–14). In this context, the final decision should be guided not only by the degree of regurgitation (≥ moderate) but also by annular dimensions (diameter ≥ 7 cm from anteroseptal to anteroposterior commissures, or 40 mm when measured by echo), leaflet coaptation or mismatch between leaflet and annulus on direct inspection, presence of atrial fibrillation, pulmonary hypertension, right ventricular dysfunction, and/or left ventricular dysfunction. As for the type of repair, most authors favor the use of a disease-specific open ring with a rigid component located in the region corresponding to the right ventricular free wall aspect of the annulus (remodeling), with flexible open ends for wider accommodation of the conduction system to reduce iatrogenic injury.[79] Finally, direct intraoperative inspection may be used to

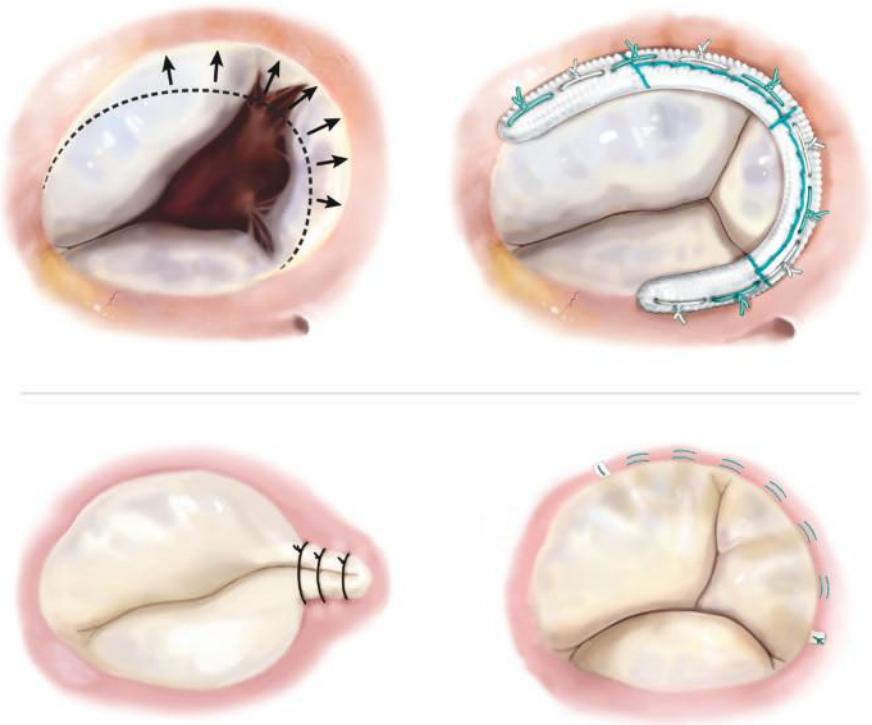

FIGURE 51–13. Common surgical techniques in tricuspid valve repair. Tricuspid valve annuloplasty with a semirigid incomplete ring (top figure). Other common surgical techniques include annular plication or Kay technique (mostly abandoned nowadays; bottom left) or annular cinching techniques such as the modified or posterior De Vega annuloplasty (bottom right).

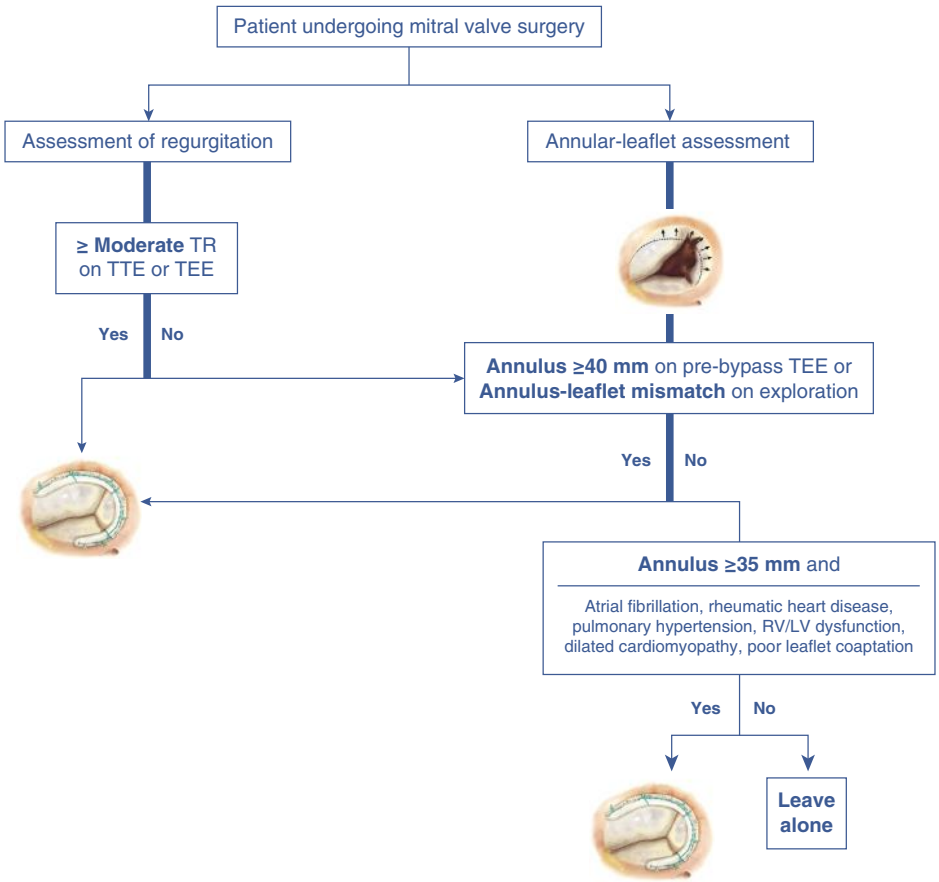

FIGURE 51–14. Management algorithm for patients undergoing mitral valve disease and concomitant tricuspid valve regurgitation. LV, left ventricle; RV, right ventricle; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram; TR, tricuspid regurgitation.

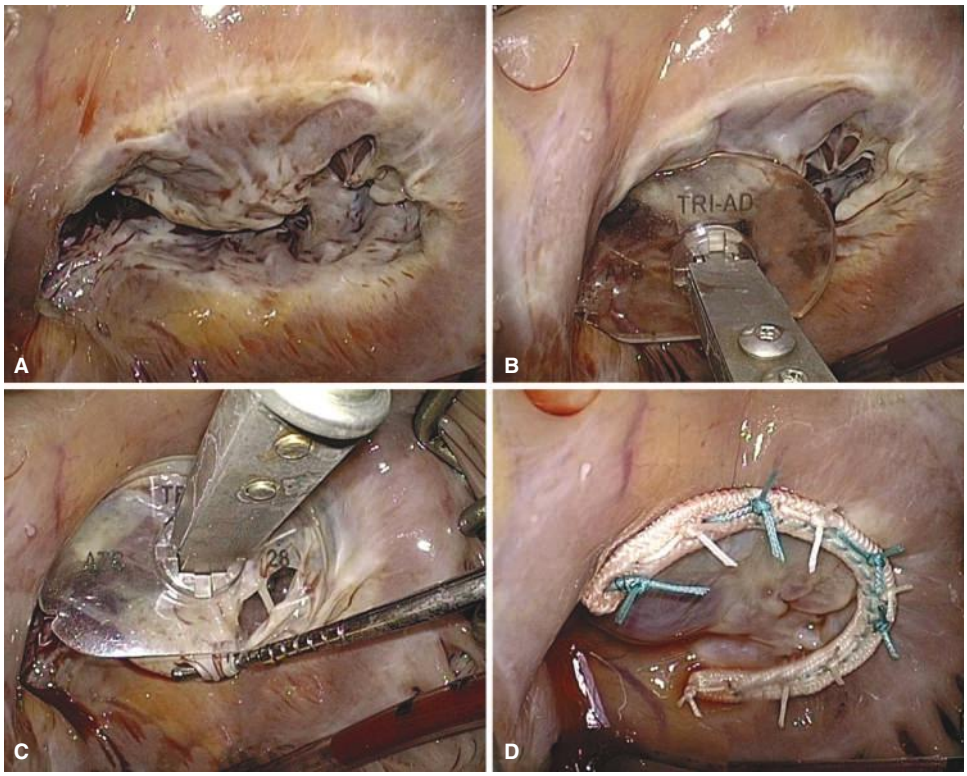

FIGURE 51–15. **A.** Tricuspid valve with annular dilatation. **B.** 28-mm ring sizer. Note the degree of annular dilation in the region of the anteroposterior commissure corresponding to the right ventricular free wall. **C.** Sizing the annulus to the surface area of the anterior and posterior leaflets. **D.** Final view demonstrating the competent tricuspid valve after ring implantation.

compare the size of the annulus to the leaflet surface area, to determine the need for tricuspid annuloplasty (Fig. 51–15).

In tricuspid endocarditis the tricuspid valve may be repaired after careful debridement of vegetations, repairing small leaflet perforations primarily and larger ones with autologous pericardium, and stabilizing the annulus with a ring. Tricuspid regurgitation caused by long-term pacing wires usually requires resection of the fibrotic mass from the leaflets, which may then require patch repair. Flail leaflets can be resuspended using neochordae or chordal translocation.

Tricuspid Valve Replacement Tricuspid valve replacement is required for severe tricuspid disease unsuitable for repair. This may be a result of organic tricuspid valve disease or advanced functional tricuspid regurgitation caused by to severe right ventricular dilatation and dysfunction, where isolated correction of annular dilatation will be insufficient to achieve a durable repair. Unlike left-sided valve prostheses, the main issue in prosthesis selection is usually the inability of most patients requiring replacement to comply with anticoagulation. In the case of patients with carcinoid valve disease requiring liver resection, with significant baseline hepatic dysfunction, the difficulties inherent in anticoagulation must be weighed against the levels of tumoral activity, which are inversely related to the longevity of bioprostheses in that position—high serotonin or 5HIAA levels may be associated with severe structural valve degeneration in as little as 2 years.[80] In patients undergoing tricuspid valve replacement, permanent epicardial pacing wires are often placed, in view of the increased risk of postoperative complete heart block and the contraindication to transvalvular pacing wires.

Percutaneous Techniques Because of the inherent risk of tricuspid valve surgery, especially in the setting of reoperative sternotomy, there is an exponential interest in the development of transcatheter techniques.[81] However, according to the experts, several anatomical inconveniences must be overcome before achieving success including: a large nonplanar annulus, absence of minor degrees of calcification or fibrosis to provide anchoring support, the presence of more trabeculations or muscle bands, and the close proximity of crucial structures such as the coronary sinus, vena cavae, or the conduction system.[82] All these caveats have precluded valve replacement up to date; however, alternative techniques have recently emerged such as heterotopic caval valve implantation, transcatheter annuloplasty devices, coaptation devices, or the application of the Mitraclip.

Outcomes of Tricuspid Surgery

Isolated Tricuspid Surgery Isolated tricuspid valve surgery has an associated mortality of 10% to 15% in national registries[83,84]—much higher than that for isolated surgery of other valves, likely because of the much higher prevalence of advanced right heart failure and end-organ dysfunction in these patients before surgery. A decrease in operative mortality compared to historical series has resulted from incremental changes in patient selection and perioperative management including more liberal use of inhaled pulmonary inodilators such as nitric oxide and epoporostenol; management of right ventricular dysfunction using inotropes and mechanical support; and prevention and more effective treatment of end-organ dysfunction, coagulopathy, and sepsis in the postoperative period. The challenges of renal and hepatic dysfunction, right heart failure, and carcinoid crises mean that valve replacement for carcinoid disease is associated with a mortality of 10% to 20%. Long-term data on event-free survival are limited. In one recent series, the 10-year survival of patients undergoing isolated tricuspid repair was 69%, compared to 50% for those undergoing tricuspid valve replacement; and freedom from reoperation in patients with bioprostheses at 10 years has been reported to be 95%, compared to 80% at 10 years for mechanical valves.[85,86]

Concomitant Tricuspid Repair In contrast to outcomes of tricuspid regurgitation late after left-sided valve surgery, the incremental mortality risk posed by concomitant tricuspid annuloplasty at the time of mitral valve surgery in contemporary practice appears to be minimal. The incidence of heart block requiring pacemaker insertion is potentially greater with concomitant tricuspid surgery, although this has not been shown to be the case in experienced centers, and it is highly dependent on the choice of annuloplasty technique described above. Similarly, the theoretical incremental risk of postoperative bleeding incurred by the addition of a right atriotomy suture line has not been confirmed by studies available to date. Midterm freedom from significant tricuspid regurgitation appears significantly greater in patients with tricuspid annular dilatation or moderate functional tricuspid regurgitation undergoing concomitant tricuspid annuloplasty compared to those undergoing isolated mitral surgery, with evidence of associated improvement in right ventricular remodeling.

THE PULMONARY VALVE

ANATOMY

The pulmonary valve is a complex, delicate anatomical structure. The most proximal part of the valve is a continuation of the distal sleeve of the free-standing right ventricular infundibulum. This is muscular over its entire circumference, forming an independent cylindrical sleeve that can be removed from the right ventricle without any contact with the left ventricle. The sleeve of infundibular muscle gives rise to the fibroelastic wall of the pulmonary trunk at the junction between the right ventricle and the pulmonary artery (Fig. 51–16). Like this, the pulmonary valve leaflets are not directly supported by the muscular ventricular septum and lay attached in a semilunar fashion. This line of attachment crosses the anatomic ventriculoarterial junction at six different points. The semilunar line of attachment forms the border of the sinuses, with the sinus wall made up distally by arterial tissue and proximally by right ventricular muscle. Between every base of the sinuses are the fibrous interleaflet triangles. Their borderlines are the line of attachment of the leaflets laterally and the right ventricular infundibulum basally. Distally the sinuses are confined by the sinutubular junction. Although the pulmonary leaflets are thickened along their semilunar locus of attachment between the sinutubular ridge and the muscular nadirs of the sinuses, as seen in the aortic valve, this anchor zone is considered more delicate and less amenable to manipulation than in the aortic root.

PULMONARY VALVE DISEASE

Apart from congenital lesions involving the pulmonary valve or the right ventricular infundibulum, pulmonary valve disease as an acquired condition in adults is extremely rare (Table 51–2). The pulmonary valve is the least commonly involved in an infectious process such as rheumatic fever and bacterial endocarditis. It may be pathologically affected in carcinoid heart disease with resulting stenosis and regurgitation (Fig. 51–6).

Clinical Presentation

Bedside examination may provide important clues. Pulmonary valve stenosis is associated with characteristic auscultatory findings depending on the severity.[87,88] Mild stenosis is characterized by a systolic ejection click and a short early systolic murmur. With progressive severity, the murmur gets louder, longer, and peaks later in systole. The ejection click is often more prominent in expiration. This seemingly paradoxical behavior of the pulmonary ejection click is explained by an inspiratory increase in right ventricular end-diastolic pressure, which opens the valve in late diastole and hence the absence of systolic ejection clicks during the inspiratory phase. Thus the ejection click may be absent

TABLE 51–2. Causes of Pulmonary Valve Disease

Etiology	Pulmonary Stenosis	Pulmonary Regurgitation
Congenital	Idiopathic stenosis Bicuspid valve Infundibular stenosis Tetralogy of Fallot Noonan syndrome Pulmonary atresia	Absent pulmonary valve syndrome
Carcinoid heart disease	X	X
Rheumatic valve disease	X	X
Idiopathic aneurysm	X	–
Infective endocarditis	X	X
Iatrogenic	eg, Ross	eg, tetralogy of Fallot, PBV
Annular/RV dilatation	–	X
Pulmonary hypertension	X	X
Hemodialysis	–	X

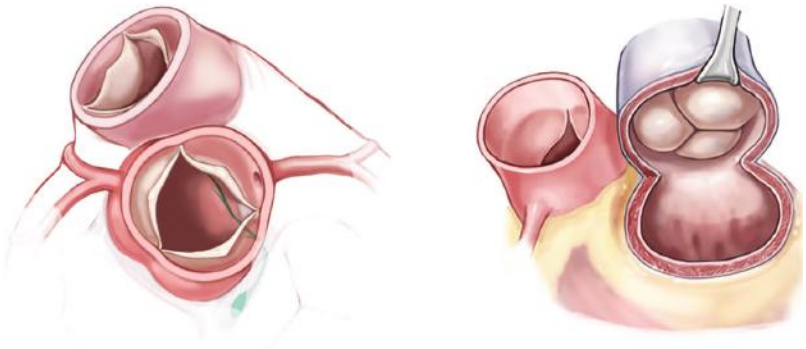

FIGURE 51–16. Views of the pulmonary valve and adjacent structures.

in the most severe stenosis in which right ventricular end-diastolic pressure is consistently above the pulmonary arterial pressures. The behavior of the second heart sound is also of diagnostic importance. In milder cases, the pulmonary component of the second heart sound (P_2) is delayed but retains further widening with inspiration (see Chap. 11). As stenosis increases in severity, the pulmonary component becomes softer, the murmur in very severe cases spills past the aortic component, and the pulmonary component is inaudible. Clinical assessment of infundibular pulmonary stenosis reveals a systolic murmur peaking in late systole and well-preserved but delayed P_2.

Clinical assessment of pulmonary regurgitation is often more challenging. A high-pitched diastolic murmur after a prominent P_2 may be evident in patients with pulmonary regurgitation secondary to pulmonary hypertension. This murmur is often described as the Graham-Steell murmur and may be erroneously interpreted to indicate aortic regurgitation, because both may be heard best along the left sternal border. Mild or even moderate pulmonary regurgitation may be present without an audible murmur.

Diagnostic Tests

Evidence of right heart chamber enlargement is shown by 12-lead ECG and chest radiography. The echocardiogram provides diagnostic and quantitative assessment of pulmonary valve stenosis, infundibular pulmonary stenosis, and pulmonary regurgitation (see Chap. 15). The pulmonary valve morphology shows doming and incomplete opening in presence of pulmonary valve stenosis. Although the valve cusps are normal in infundibular stenosis, a characteristic midsystolic closure and prominent presystolic a-wave are often diagnostic clues. The pulmonary artery and branches are dilated in pulmonary hypertension, idiopathic pulmonary artery dilatation, and severe pulmonary regurgitation. In rare cases of pulmonary valve endocarditis, a mobile vegetation may be observed (see Chap. 67). Hypertrophied and dynamic right ventricular infundibulum is characteristic of infundibular stenosis, whether it is congenital or associated with hypertrophic cardiomyopathy. Spectral Doppler and color-flow Doppler reveal high-velocity turbulent flow in the main pulmonary artery in patients with pulmonary valve stenosis, and a late-peaking, high-velocity flow with turbulence in the right ventricular outflow tract are noted in infundibular pulmonary stenosis. Trivial and mild pulmonary regurgitation are normal findings in most children as well as adults. However, moderate and severe regurgitation are associated with right ventricular volume overload and subsequent dilatation and dysfunction. The pulmonary regurgitation velocity waveform provides a unique insight into pressure difference between the pulmonary artery and RV during diastole. Because right ventricular diastole pressure equilibrates with right atrial pressure in the absence of tricuspid stenosis, an estimation of pulmonary arterial diastolic pressure is obtained using the end-diastolic velocity of pulmonary regurgitation and size of the inferior vena cava, which is used to estimate right atrial pressure.

Cardiac Catheterization and Selective Angiography

Diagnostic right heart catheterization is useful to measure pulmonary artery pressures and pulmonary wedge pressure and to calculate pulmonary vascular resistance. These are useful to differentiate and quantify precapillary and postcapillary pulmonary arterial hypertension. Although quantification of pulmonary valve stenosis is generally made using echo Doppler methods, catheter-based measurements before and after pulmonary balloon valvotomy are used to evaluate successful dilatation of the stenotic pulmonary valve. Selective angiography is less useful for diagnostic and therapeutic interventions.

Treatment

Mild and even moderate pulmonary valve stenosis and regurgitation do not result in right ventricular overload and may require no specific treatment other than prophylaxis for bacterial endocarditis (Table 51–3). Moderately severe and severe pulmonary valve stenosis is currently treated by percutaneous balloon valvotomy. Surgical valvotomy is rarely needed. Similarly, severe pulmonary regurgitation in the absence of pulmonary hypertension may require valve replacement to prevent irreversible right ventricular damage from long-standing volume overload and dilatation. A bioprosthetic valve is generally used. Recent advances in percutaneous valve replacement to treat patients with severe pulmonary regurgitation are noteworthy. The long-term efficacy of this approach remains to be proven.

TABLE 51–3. 2006 American College of Cardiology/American Heart Association Guidelines for the Management of Patients With Valvular Heart Disease

Evaluation of Pulmonic Stenosis in Adolescents and Young Adults

Class I

1. An ECG is recommended for the initial evaluation of pulmonic stenosis in adolescent and young adult patients and serially every 5 to 10 y for follow-up examinations. (*Level of Evidence: C*)
2. Transthoracic Doppler echocardiography is recommended for the initial evaluation of pulmonic stenosis in adolescent and young adult patients and serially every 5 to 10 y for follow-up examinations. (*Level of Evidence: C*)
3. Cardiac catheterization is recommended in adolescent and young adult patients with pulmonic stenosis for evaluation of the valvular gradient if the Doppler peak jet velocity is greater than 3 m/s (estimated peak gradient >36 mm Hg); balloon dilatation can be performed if indicated. (*Level of Evidence: C*)

Class III

Diagnostic cardiac catheterization is not recommended for the initial diagnostic evaluation of pulmonic stenosis in adolescent and young adult patients. (*Level of Evidence: C*)

Indications for Balloon Valvotomy in Pulmonic Stenosis

Class I

1. Balloon valvotomy is recommended in adolescent and young adult patients with pulmonic stenosis who have exertional dyspnea, angina, syncope, or presyncope and a RV-to-pulmonary artery peak-to-peak gradient greater than 30 mm Hg at catheterization. (*Level of Evidence: C*)
2. Balloon valvotomy is recommended in asymptomatic adolescent and young adult patients with pulmonic stenosis and RV-to-pulmonary artery peak-to-peak gradient greater than 40 mm Hg at catheterization. (*Level of Evidence: C*)

Class IIb

Balloon valvotomy may be reasonable in asymptomatic adolescent and young adult patients with pulmonic stenosis and an RV-to-pulmonary artery peak-to-peak gradient 30 to 39 mm Hg at catheterization. (*Level of Evidence: C*)

Class III

Balloon valvotomy is not recommended in asymptomatic adolescent and young adult patients with pulmonic stenosis and RV-to-pulmonary artery peak-to-peak gradient less than 30 mm Hg at catheterization. (*Level of Evidence: C*)

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CHAPTER 52

PROSTHETIC HEART VALVES

Joanna Chikwe and Javier G. Castillo

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INTRODUCTION

The burden of valvular heart disease leads to over 300,000 heart valve replacements each year worldwide.[1] This number will probably triple by 2050, and valvular heart disease will likely be considered as the future next cardiac epidemic.[2] Despite tireless efforts and perseverance from engineers and cardiovascular specialists, a growing niche like valve replacement still lacks an ideal therapy. In the 1950s Dwight Harken coined the "Ten Commandments" for the perfect prosthetic heart valve.[3] The optimal heart valve prosthesis would have endless durability, absence of thrombogenicity to avoid anticoagulation, and no inherent postoperative gradient. However, almost 70 years later, there is still no perfect valve substitute[4]: those patients who undergo heart valve replacement exchange valvular heart disease for prosthetic heart valve disease.[5] The most influential factors affecting prosthesis selection include the individual surgical risk, the estimated life expectancy, barriers to lifelong anticoagulation, and the patient's personal preference. The latter must be based on an informed understanding of the trade-offs between the incremental risk of thromboembolic and hemorrhagic complications associated with mechanical valve replacement and lifelong anticoagulation, versus the risk of reoperation for structural valve degeneration associated with bioprosthetic valve replacement.[5,6] Management of patients with prosthetic heart valves consists of surveillance and prophylaxis, both focused on prevention and diagnosis of the major complications associated with prosthetic heart valves. Patient outcomes continue to improve after valve replacement thanks to clinical and technical developments: in the field of surgical valve replacement these developments have been characterized in recent years by steady incremental progress, contrasting sharply with the rapid technological evolution[7] and uptake of transcatheter valve replacement, a difference that will likely define this field.[8,9]

TYPES OF PROSTHETIC VALVES

There are two main categories of prosthetic valve: mechanical and biological (bioprostheses) (Fig. 52–1). The profusion of models in each of these categories in contemporary use is largely the result of failure to produce any single prosthesis with an optimal risk profile, despite seven decades of effort. The proportion of bioprosthetic valves implanted in all age groups has increased steadily over the last decade,[10] most markedly in patients between 55 and 64 years, and today mechanical valves are generally implanted in a minority of patients.[9] In addition, high volume (> 250 cases per year) and academic centers are more likely to use biological valves (Fig. 52–2).

MECHANICAL VALVES

The first prosthetic heart valves were mechanical prostheses. In 1954, Charles Hufnagel implanted a mechanical prosthesis consisting of a glass tube[11] with sewing rings at either end and containing a plastic ball occluder, in the descending aorta of a patient with severe aortic insufficiency.[12] The first subcoronary valve replacement was performed in the aortic position by Dwight Harken in 1960 using a similar design. In the mitral position, Nina Braunwald implanted a ball-and-cage prosthesis designed in her laboratory. Later on, in collaboration with Lowell Edwards (Edwards Lifesciences Irvine, CA), a retired hydraulics engineer, Albert Starr, cardiothoracic surgeon, developed a ball-valve to industrial quality standards, and by 1968 more than 2000 Starr-Edwards ball-and-cage valves had been implanted. Subsequently, monoleaflet prostheses, followed by bileaflet prostheses (tilting discs made of pyrolytic carbon), almost completely superseded ball-and-cage valves in the 1980s, thanks to their superior hemodynamics and lower profile (Fig. 52–3). Three types of mechanical prostheses may be encountered in clinical practice: ball and cage valves (highly unlikely even in reoperations), monoleaflet valves (not implanted in current practice but still encountered in reoperations), and bileaflet mechanical valves (by far the most commonly implanted mechanical valve nowadays).[13]

Ball-and-Cage Valves

Although ball-and-cage valves are no longer commercially available, patients with these prostheses might still be encountered in clinical practice.[14] The advantages of the ball-and-cage design stem from the fact that the silastic occluder travels completely out of the valve orifice in systole, reducing the risk of pannus or thrombus spreading from the sewing ring and interfering with the valve mechanism. Additionally, it has been suggested that the continuously changing points of contact reduce wear.[15] The main drawbacks of these first-generation mechanical prostheses remain (1) the high thrombogenic risk, attributed in part to the lack of central blood flow; and (2) the bulky profile of the prosthesis, which can result in left ventricular outflow tract obstruction when implanted in the mitral position (see Fig. 52–3).

Monoleaflet Valves

Monoleaflet valves, in which a single circular disc tilts to occlude or open the valve orifice, were introduced 1969. The Bjork-Shiley (Shiley Laboratories) valve was the first such valve approved for clinical use, and was implanted in over 250,000 patients. The Medtronic-Hall valve (Medtronic Irvine, CA), which consists of a pyrolytic carbon-coated

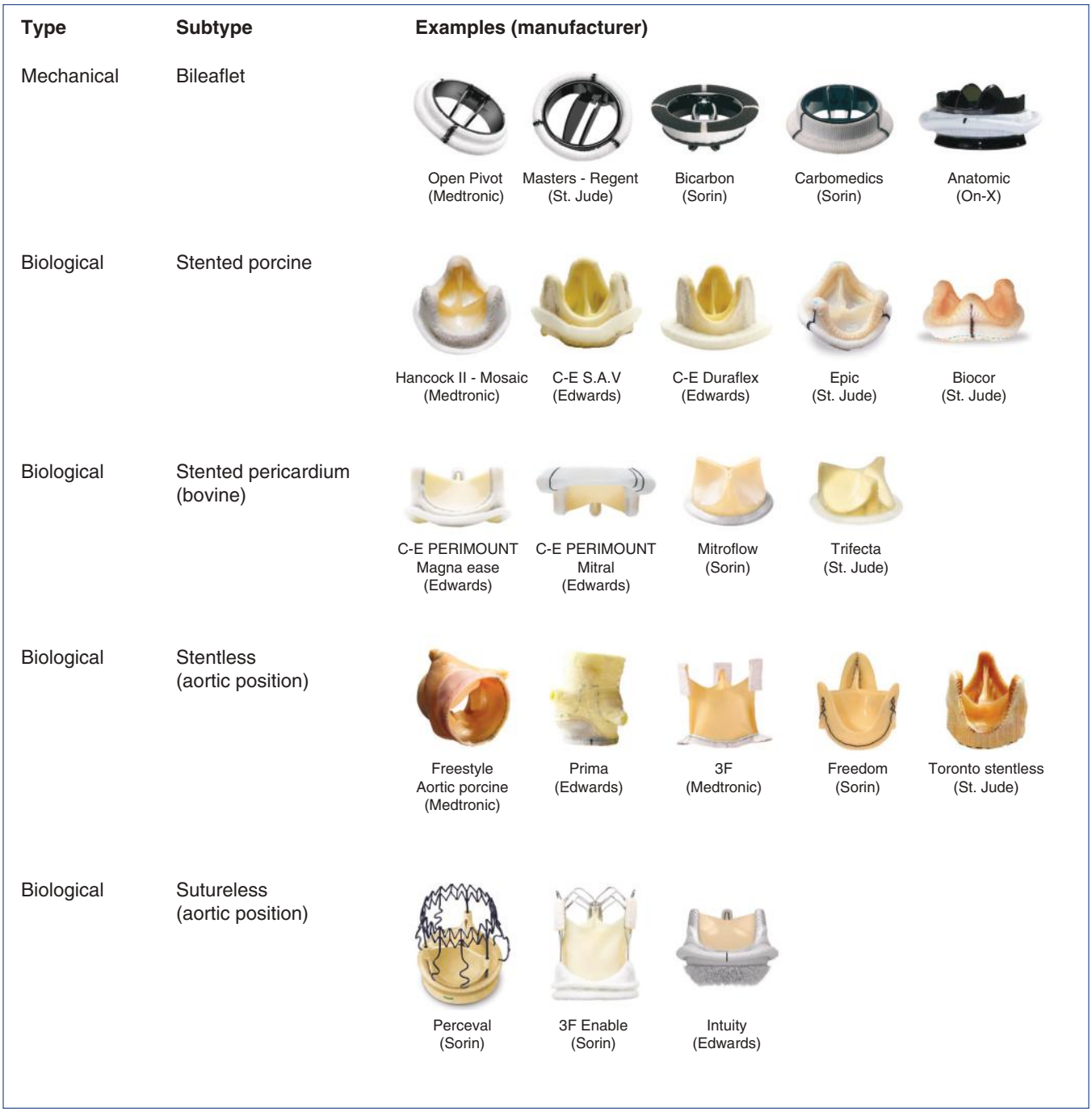

FIGURE 52–1. Currently available surgical prosthetic heart valves from the major manufacturers. Courtesy of Medtronic, Inc., Minneapolis, MN; St. Jude Medical, Inc., Minneapolis, MN; Sorin Group, Inc., Milan, Italy; On-X Life Technologies, Inc., Austin, TX; Edwards Lifesciences, Ltd., Irvine, CA.

disc in titanium housing, has only recently been discontinued.[16] The main advantages of monoleaflet over ball-and-cage valves were the lower profile with less risk of impingement or outflow obstruction; central blood flow; and lower thrombogenicity. However, stasis and turbulent flow, in conjunction with the location of the occluder fixation points within the orifice, mean that these prostheses were prone to thrombus and pannus interfering with the motion of the disc (see Fig. 52–3). Additionally, the asymmetrical design requires careful orientation during implantation to avoid outflow obstruction. Finally, the 60-degree Convexoconcave Bjork-Shiley valve manufactured by Shiley Laboratories was significantly more prone to mechanical failure, caused by fracture of the outlet strut allowing the occluder to embolize from its housing—an often fatal complication reported in 600 patients by 1998, of the 86,000 patients who received the valve prior to its discontinuance.[17]

Bileaflet Valves

Bileaflet valves, such as the Regent valve (the most recent evolution of the bileaflet design by St. Jude Medical, Minneapolis, MN), are the most widely used mechanical valve prostheses today (see Fig. 52–1). First implanted in 1977, bileaflet prostheses rapidly superseded monoleaflet

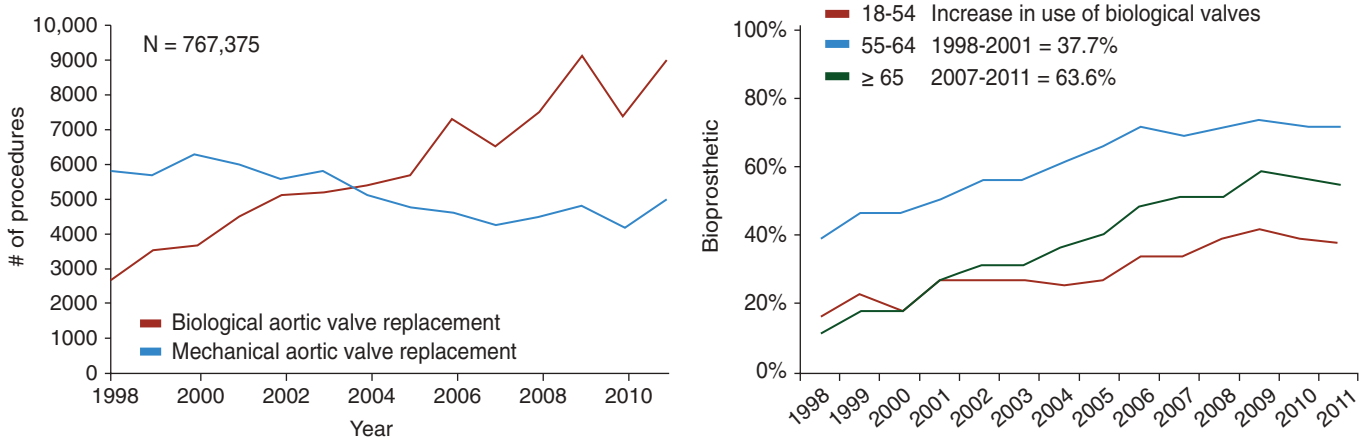

FIGURE 52–2. Estimated national volume of bioprosthetic and mechanical aortic valve replacement procedures, by year, from 1998 to 2011(left). Percentage of aortic valve replacements in which bioprosthetic valves were implanted, over time, by patient age (right). Reproduced with permission from Isaacs AJ, Shuhaiber J, Salemi A, et al: National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. *J Thorac Cardiovasc Surg*. 2015 May;149(5):1262-1269.

valves thanks to the greater effective orifice area for a given valve size, lower transvalvular gradients, reduced valvular insufficiency, lower rates of thromboembolism, and easier insertion. Over 2 million bileaflet prostheses have been implanted. The prostheses comprise two flat pyrolytic carbon-coated leaflets in a solid carbon housing reinforced with a radiopaque titanium ring, with the hinge socket placed either on the leaflet housing or the leaflets themselves (Fig. 52–4).

BIOPROSTHETIC VALVES

Bioprosthetic valves were developed in an effort to find a nonthrombogenic alternative to mechanical prostheses[18] with the inherent avoidance of life-long anticoagulation. Early structural failure[19] of the first porcine valves implanted led to the use of alternative tissue, including fascia lata, dura mater, and pericardium, with minimal improvement in prosthesis longevity until Alain Carpentier's breakthrough discovery in the mid-1960s, that glutaraldehyde fixation could produce a durable bioprosthesis.[20] Glutaraldehyde fixation extends tissue longevity by cross-linking collagen fibers and reducing cell viability, enzymatic degradation, and tissue antigenicity.[21]

Modern bioprosthetic valves are constructed from animal tissue, predominantly bovine pericardium or porcine aortic valves, both fixed in glutaraldehyde (see Fig. 52–4). Pericardial valves are thought to have the potential for greater durability due primarily to the greater amount of collagen in pericardium compared to porcine valve tissue; and secondly because of improved hemodynamics associated with more symmetrical function of the leaflets; but there are few data confirming superior long-term durability. First-generation bioprosthetic valves underwent glutaraldehyde fixation at normal closing pressures (60-80 mm Hg): this was subsequently discovered to lead to loss of normal tissue architecture, with calcification observed in up to one-third of patients within 10 years.[22] Zero or low-pressure fixation was employed in second-generation valves with the aim of reducing the rate of calcification: depending on the patient's age at implantation, calcification in second-generation valves occurs between 10 and 15 years after implantation. Third-generation prostheses were introduced in the early 1990s with the addition of calcium-mitigating agents including surfactant and heat to reduce the rate of calcification.[23]

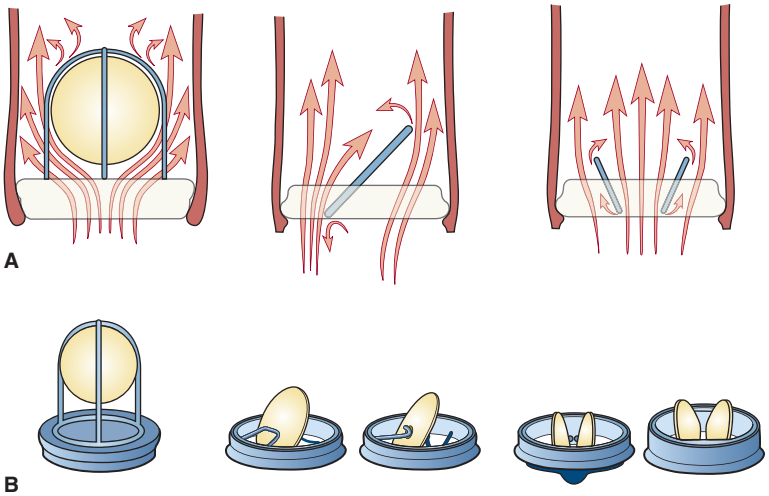

FIGURE 52–3. Profile and hemodynamics of each main valve type. **A.** Whereas ball and cage valves are associated with a lack of central blood ejection fraction, tilting disc valves are associated with turbulent blood flow at the lesser orifice. **B.** Bileaflet valves have the lowest profile compared with ball and cage valves and tilting disc valves.

Stented Bioprosthetic Valves

To facilitate implantation, surgical bioprostheses are mounted either on a metal frame (stented), or a polyethylene terephthalate cloth (stentless) (see Fig. 52–1). The bioprosthetic models used most widely in contemporary surgical practice are stented valves, and include second-generation prostheses such as the Hancock II (Medtronic) or the Carpentier-Edwards Standard (Edwards), and third-generation prostheses such as the Carpentier-Edwards Perimount Magna Ease (Edwards), the Mosaic porcine valve (Medtronic), and the Mitroflow pericardial valve (Sorin Milan, Italy).

Initially the pericardial valve leaflets were stitched onto the stent, a structural weakness that was addressed by mounting the pericardial tissue onto a stent that did not require stitching in the Carpentier-Edwards Perimount valve and its subsequent iteration the Carpentier-Edwards Perimount Magna valve which was constructed with a narrower sewing cuff for suprannular implantation. In an effort to increase the effective orifice area for a given valve size, the stent was placed outside rather than inside the pericardial leaflets in the Mitroflow valve (Sorin). Given the asymmetry of porcine valves, the right coronary cusp was replaced with a leaflet from another porcine valve to produce the Hancock Modified Orifice valve in an attempt to improve the hemodynamic profile of the new generation of porcine valves.

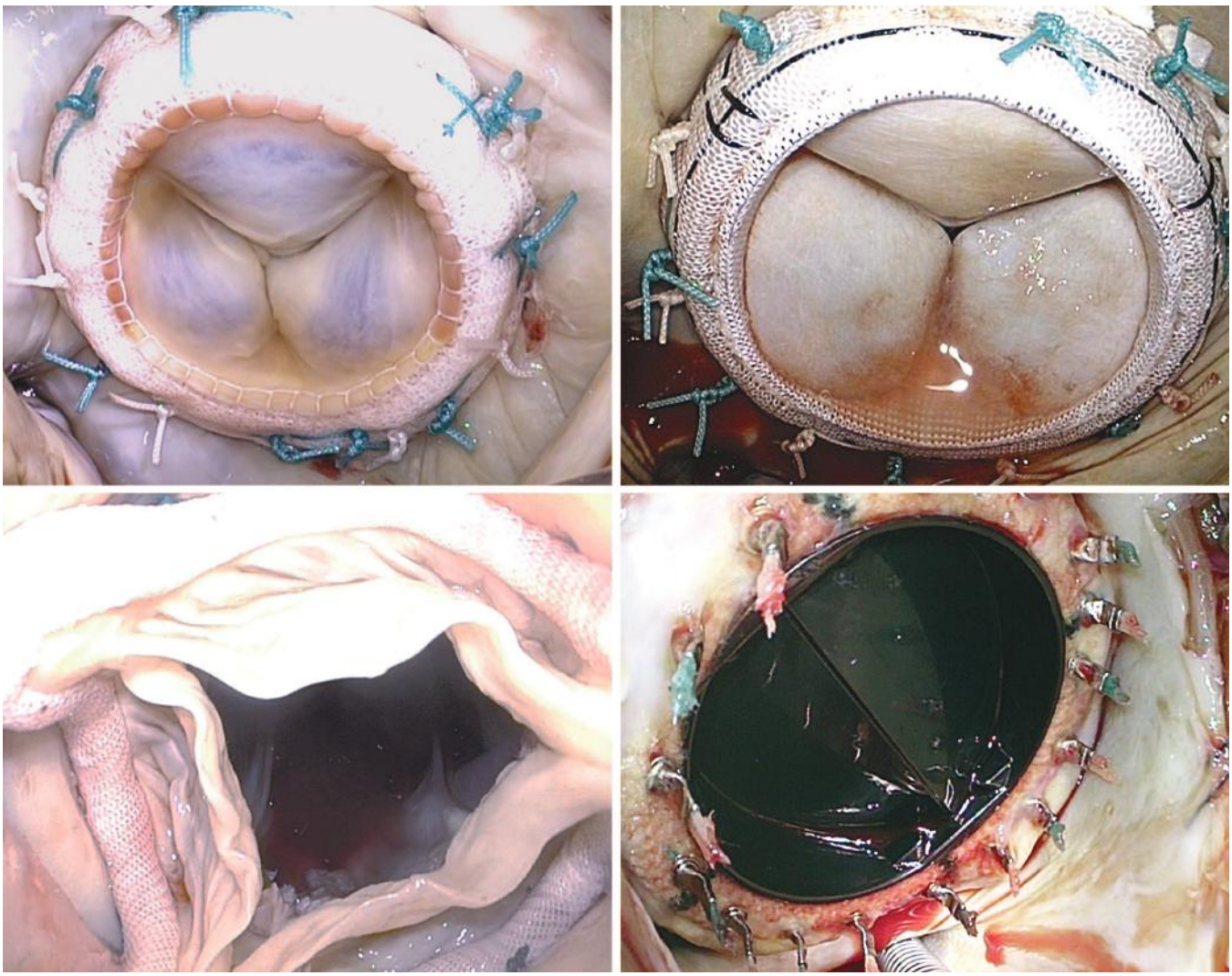

FIGURE 52–4. Valve replacement with a biological porcine valve (top left and bottom left), a biological bovine pericardial valve (top right), and a double disc mechanical valve (bottom right). Used with permission from David H. Adams, MD.

Stentless Bioprostheses

The first aortic xenograft was implanted in 1986. The lack of rigidity (no metal stent) leads to minimal gradients across the aortic valve, but these valves are not designed for use in the mitral position, and their implantation is technically less straightforward and reproducible than stented valves because reattachment of the coronary buttons is necessary (Fig. 52–5). Examples include the Medtronic Freestyle in which an entire porcine aortic root is mounted on a cloth sewing ring.[24]

Sutureless Bioprostheses

Although it seems beyond paradoxical, sutureless prosthetic heart valves were initially developed in the 1960s. However, their use was abandoned as a result of high rates of complications such as paravalvular leaks and thromboembolic events. Nowadays, the "relative" tolerance to paravalvular leaks or mild degrees of aortic insufficiency in patients undergoing transcatheter procedures has triggered the resurrection of sutureless valves.[25]

Transcatheter Valves

Transcatheter prostheses consist of glutaraldehyde-fixed pericardium, mounted on expandable and compressible metal stents that can be reexpanded when in position. The valve may be introduced via the femoral, subclavian, or axillary artery, ascending aorta, or left ventricular apex through catheters that range from 30F down to 14F in more recent models. Transcatheter valve therapies are discussed in Chaps. 47 to 51.

CHOICE OF PROSTHETIC VALVE

Randomized and observational data suggests that, for most patients undergoing valve replacement, there is no significant survival benefit with one prosthesis type over another.[26-31] The most important determinants of survival after valve replacement are patient related rather than prosthesis related: optimal valve selection hinges on the trade-off between the increased risk of thromboembolic and hemorrhagic complications associated with mechanical valve replacement and lifelong anticoagulation, versus the risk of reoperation for structural valve degeneration associated with bioprosthetic valve replacement.[5,6] Consequently, the most influential factors to consider when deciding between mechanical and bioprosthetic valve replacement include the recipient's estimated life-expectancy, barriers to lifelong anticoagulation, and patient preference (Figs. 52–6 and 52–7).

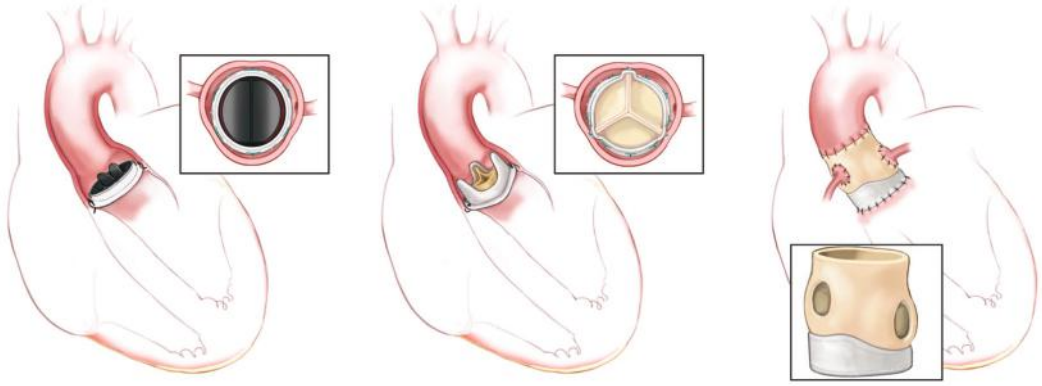

FIGURE 52–5. Aortic valve replacement with a mechanical prosthesis (left), a bioprosthesis (center), and a stentless valve (right). Note the need for coronary reanastomosis in the latter.

SURVIVAL

The majority of classic literature comparing outcomes of mechanical valves and bioprostheses is observational and presents significant baseline differences in patient demographics, comorbidities, and operative techniques. Unfortunately, the latter makes surgical randomization and comparison extremely difficult. In this context, a total of three randomized trials have been conducted to date: two comparing older valve models in elderly patients (the Edinburgh Heart Valve Trial and the Veterans Affairs Cooperative Study on Valvular Heart Disease) and a more recent one that randomized more modern valves in a middle-aged population.[28,30,31]

The Society of Thoracic Surgeons (STS) database has recently published the 2015 (period from 2006 to 2015) executive summary, which included over 250,000 isolated aortic valve replacements[32] performed over a decade. The in-hospital mortality for patients undergoing isolated valve replacement ranged from 2.5% to 3.2%, from 4% to 5.5% in those patients receiving concomitant coronary artery bypass, and from 8.5% to 11.4% in those patients receiving concomitant mitral valve replacement. The mortality in patients undergoing isolated mitral valve replacement ranged from 5% to 6.2% and from 8.8% to 10.8% in patients receiving additional coronary artery bypass grafting. Data from the National Inpatient Sample (n=767,375) have also shown an in-hospital mortality of 4.4% in patients undergoing isolated aortic valve replacement and 4.9% in patients undergoing isolated mitral valve replacement.[10] In contrast, in a very recent multicenter study from high-volume institutions and surgeons, Thourani et al reported the "real world" outcomes of surgical aortic valve replacement with an operative mortality of 2.7% in 2002 to 2006 and 2.5% in 2007 to 2010.[9]

The lack of a clear survival benefit for most patients with either mechanical or bioprosthetic valve replacement means that valve selection becomes more focused, balancing the relative risks of major morbidity—primarily stroke, reoperation, and bleeding—and on lifestyle considerations primarily related to lifelong anticoagulation.[33] However, currently there is a clear trend towards utilizing bioprostheses, particularly in high-volume centers.[34,35] In older patients, and patients with a life-expectancy estimated to be less than 10 years, event-free survival is better with a bioprostheses: these valves pose a very low lifetime risk of reoperation for structural degeneration, and they avoid most of the major thrombotic and hemorrhagic complications associated with mechanical prostheses and lifelong anticoagulation.[36] Current consensus guidelines therefore recommend bioprosthetic valves in patients over the age of 70 years, in whom they now represent over 80% of prostheses implanted. In patients aged between 50 and 70 years, survival appears to be equivalent with either a bioprosthetic or mechanical prosthesis, and both are reasonable choices. These class IIa recommendations are based on the results of three randomized controlled trials,[28,30,31] two of which were historical series. Analysis of large, contemporary multicenter patient cohorts supports the view that either prosthesis is a reasonable choice in patients aged 50 to 69 years, and in contemporary practice the majority of these patients receive bioprosthetic valves.[37] In younger patients, observational data suggest that survival is similar with bioprosthetic and mechanical valve replacement in adults aged less than 50 years of age (Fig. 52–8).[38]

MANAGEMENT OF PATIENTS WITH PROSTHETIC HEART VALVES

Patients who undergo heart valve replacement exchange valvular heart disease for prosthetic heart valve disease. Therefore, the medical management consists of surveillance and prophylaxis, both focused on prevention and diagnosis of the major complications associated with prosthetic heart valves. Patients with mechanical valves should be discharged from hospital after surgery with a therapeutic international normalized ratio (INR) (Table 52–1), and are usually maintained in a euvolemic state with low-dose diuretic therapy, on β-blockade as tolerated, and on an optimal heart failure regimen if indicated. Patients with bioprosthetic valves require similar management, but the role of early (for 3 months after surgery) anticoagulation still remains debatable, and only 58% of these patients are treated with anticoagulation.[39]

ASSESSMENT AND FOLLOW-UP

At 6 to 12 weeks after surgery, a complete evaluation including clinical history and examination, 12-lead EKG, and transthoracic echocardiography should be performed to assess functional status, blood pressure and rhythm, ventricular function, prosthetic valve function, gradients, and any paravalvular regurgitation; as well as a review of anticoagulation adherence.[40,41] Consensus guidelines recommend annual and symptom-triggered follow-up by a cardiologist for life, with the aim of detecting prosthesis dysfunction and progression of other valvular heart disease. Specifically, transthoracic echocardiography should be performed annually after the fifth year postoperatively in patients with bioprosthetic valves; earlier in young patients who are at higher risk of accelerated valve dysfunction; and in any patient with a prosthetic valve if any new symptoms occur or there is clinical suspicion of complications based on clinical examination. Transprosthetic gradients should be

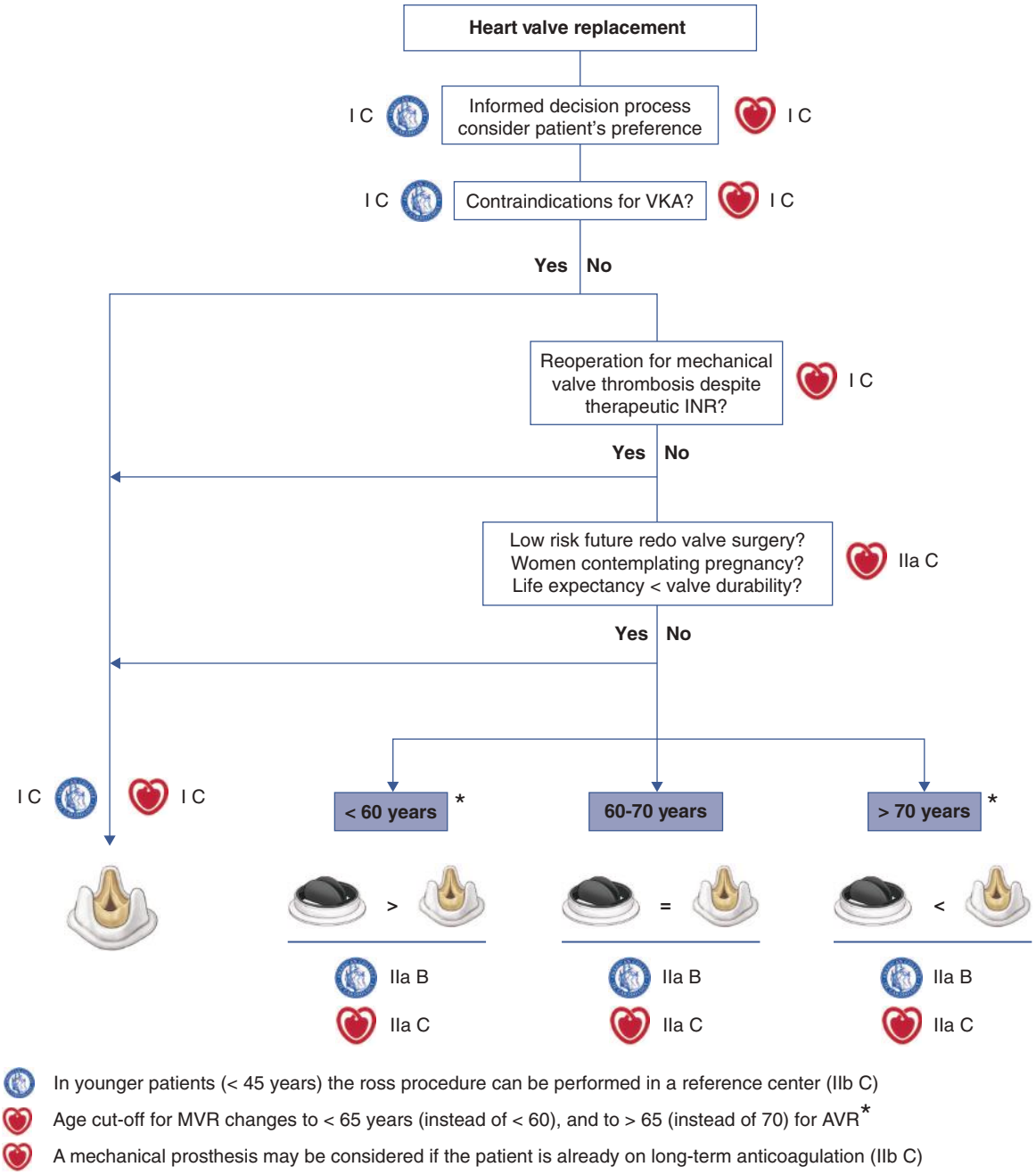

FIGURE 52–6. Proposed algorithm for prosthesis choice. AVR, aortic valve replacement; MVR, mitral valve replacement; INR, international normalized ratio; VKA, vitamin K antagonists. Logos represent the European Association of Cardiology (*red*) and the American College of Cardiology (*blue*). Data from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;63:2438-2488; and Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardiothoracic Surgery, Vahanian A, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451-2496.

compared to baseline values obtained in the first few months postoperatively, and transesophageal echocardiography is recommended if the transthoracic echocardiography provides inadequate images, and for all cases of suspected prosthetic valve dysfunction or endocarditis. Additional evaluation of pannus or valve thrombosis can be obtained using fluoroscopy or multislice CT.

ANTITHROMBOTIC THERAPY

Recommendations for anticoagulation and antiplatelet therapy are summarized in Table 52–1. The role of routine early anticoagulation in patients with bioprostheses is subject to debate: historically these patients were anticoagulated for 3 months, but this practice has been superseded by antiplatelet therapy because of the incidence of hemorrhagic complications with warfarin. In this context, although recipients of bioprosthetic valves should be appropriately managed with long-term aspirin, recent insights from study protocol MRI imaging of bioprosthetic valves in transcatheter and surgical cohorts[42] suggests that early valve thrombosis may be under-recognized and under-treated.[43]

In patients with mechanical valves and no active bleeding or coagulopathy, anticoagulation is usually commenced on postoperative day 2 or 3, with a loading dose of warfarin and unfractionated heparin started

A 60 year-old patient with a 20-year life expectancy who needs an **aortic valve replacement** comes for consultation and would like to have an expert opinion "Okay doctor, so which one do you think I should choose?"

Inherent characteristics	Reduced life expectancy Valve "clicks" may interfere your routine, sleep... Lifetime anticoagulation (INR goal 2-5-3.5) Possible easy bruising/bleeding from anticoagulation Frequent INR tests to achieve stabilization Interaction of anticoagulation with food, medication... New anticoagulants are not effective	Reduced life expectancy Need for multiple reinterventions or surgeries Transcatheter valve-in-valve not established yet
Operative mortality	2-4% in most registries and large series Lower mortality in high volume centers Slightly lower due to patient selection (younger)	2-4% in most registries and large series Lower mortality in high volume centers Slightly higher due to patient selection (older)
Survival	70-85% at 10 years - slightly lower in mitral patients No difference in survival including reoperations	70-85% at 10 years - 55% in mitral patients No difference in survival including reoperations
MAPE	40% risk at 5 years Mid-term difference at 5 years (more in MVR) 30-50% risk at 10 year 50% lifetime risk	20% risk at 5 years Mid-term difference at 5 years (more in MVR) 30-50% risk at 10 years 50% lifetime risk
Structural valve deterioration	Not an issue Malfunction due to pannus/thrombosis not excluded	25-40% at 15 years Less durable in younger patients
Thromboembolism	0.50%/pt-year (linearized), 20% at 10 years, Valve thrombosis is often sudden Valve thrombosis carries a 50% mortality at 10 years Therpaeutic INR does not assure freedom from CVA Mortality after stroke is 19%	0.25%/pt-year (linearized), 10% at 10 years Valve thrombosis is more insidious Mortality after stroke is 19%
Major hemorrhagic events	1.5%/pt-year (linearized),10-20% at 10 years Up to 40% at 10 years including minor events Readmission for bleeding carries a 13% mortality	0.7%/pt-year (linearized), 5-10% at 10 years Up to 20% at 10 years including minor events Readmission for bleeding carries a 13% mortality
Reoperation	2-5% lifetime reoperation risk Higher risk in the mitral position,10% at 10 years Higher risk of paravalvular leak in the mitral position Higher risk of dehiscence in the mitral position	25-40% lifetime reoperation risk Higher risk of paravalvular leak in mitral position Higher risk of dehiscence in mitral position

FIGURE 52–7. Model of informed decision process for a 60-year-old patient who requires an aortic valve replacement. CVA, cerebrovascular accident; MAPE, major adverse prosthesis-related event; MVR, mitral valve replacement; INR, international normalized ratio; Pt, patient.

if the patient has a subtherapeutic INR by postoperative day 4 or 5. Anticoagulation in the first month after mechanical valve replacement should be monitored much more frequently than usual, because it is subject to increased variability, the early postoperative period is one of maximum thrombogenicity, and these patients may be unfamiliar with an anticoagulation protocol. Low molecular weight heparin is not recommended for transitioning patients with mechanical valves in this setting for several reasons, primarily because it is an off-label use, it cannot be easily reversed, and effective therapy in patients with renal failure or morbid obesity is challenging. The use of direct oral inhibitors of factor IIa or Xa, such as dabigatran, rather than warfarin, is not recommended in patients with mechanical prostheses based on the results of clinical trials that showed increased incidence of hemorrhagic and bleeding events.[44]

Interruption of anticoagulant therapy in patients with mechanical valves may be needed electively, for surgical and interventional procedures or pregnancy; or emergently in the setting of potentially life-threatening hemorrhage. The risk of thromboembolism and valve thrombosis is less than 1% per day in a patient with a mechanical valve and a subtherapeutic INR, but the risk of these potentially catastrophic complications generally outweighs the benefits of anticoagulation cessation for relatively minor procedures such as dental extraction, diagnostic cardiac catheterization, and cataract removal. For more major elective surgery requiring an INR < 2.0, patients should be bridged to operation once warfarin is stopped with unfractionated heparin. The use of low molecular weight heparin is not approved for this purpose in patients with mechanical valves.[5,6] For those patients with a single subtherapeutic INR in the outpatient setting, low molecular weight

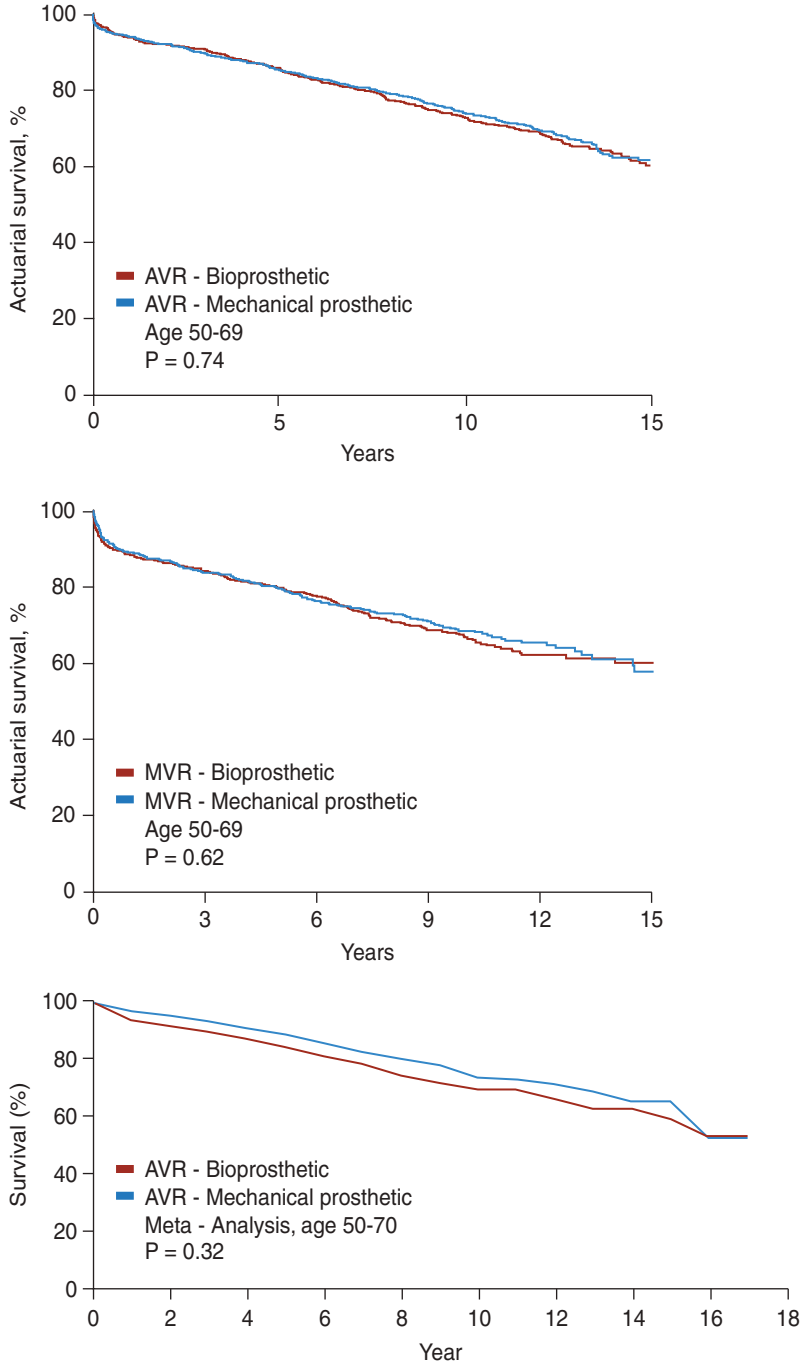

FIGURE 52–8. Survival after aortic (*top* and *bottom*) and mitral valve replacement (*middle*) in middle-aged patients. AVR, aortic valve replacement; MVR, mitral valve replacement. Adapted with permission from Zhao DF, Seco M1, Wu JJ, et al: Mechanical Versus Bioprosthetic Aortic Valve Replacement in Middle-Aged Adults: A Systematic Review and Meta-Analysis. *Ann Thorac Surg*. 2016 Jul;102(1):315-327.

heparin or unfractionated heparin are reasonable agents to supplement warfarin until the patient is therapeutic.

The risk of major bleeding increases exponentially with an INR > 6.0, which therefore usually requires rapid reversal.[45] In the absence of active hemorrhage or major risk factors for bleeding, it is reasonable to stop warfarin and allow the INR to fall gradually. In a patient with other risk factors for bleeding, oral vitamin K in increments of 1 mg will reverse the INR more quickly, with 5 mg of vitamin K indicated to reverse INR > 10. Vitamin K can be given intravenously, although the risk of anaphylaxis is higher than giving it orally. In the setting of active major bleeding including intracranial hemorrhage, bleeding resulting in organ dysfunction, hemodynamic instability, or need for transfusion, intravenous prothrombin and oral vitamin K combined are recommended over transfusion of fresh frozen plasma. The risk of thromboembolism in patients with mechanical valves is low in comparison to the immediate risk posed by major bleeding if the INR is subtherapeutic for a short period. Every effort should be made, however, to identify and control the source of any bleeding that occurs when the

TABLE 52–1. Comparison of Guidelines for Antithrombotic Therapy After Valvular Surgery from the American Heart Association/American College of Cardiology and the European Society of Cardiology

AHA Recommendations	AHA	ESC	ESC Recommendation
Mechanical mitral or mechanical aortic valve with risk factors: VKA INR goal 3.0 ASA 75-100 mg long-term.	I	I B	Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.
Mechanical aortic valve without risk factors.	I		
VKA INR goal 2.5 ASA 75-100 mg long-term.			
		I C	Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.
		IIa C	The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerosis disease.
		IIa C	The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.
Bioprosthetic mitral valve: VKA INR goal 2.5 first 3 months.	IIa	IIa C	Oral anticoagulation should be considered for the first three months after implantation of a mitral or tricuspid bioprosthesis.
Bioprosthetic mitral valve: VKA INR goal 2.5 first 3 months.	IIb	IIa C	Low-dose aspirin should be considered for the first three months after implantation of an aortic bioprosthesis.
		IIb C	Oral anticoagulation may be considered for the first three months after implantation of an aortic bioprosthesis.
Bioprosthetic aortic or mitral valve prosthesis: ASA 75-100 mg long-term.	IIa		
Transcatheter aortic valve replacement: Clopidogrel 75 mg ASA, 75-100 mg first 6 months.	IIb		

INR is in the therapeutic range, to minimize the length of time patients with mechanical valves spend with a subtherapeutic INR.[46]

Patients with mechanical valves may have concomitant indications for antiplatelet therapy. The addition of antiplatelet mediation to anticoagulation increases the likelihood of bleeding, and consequently a careful analysis of the risk-benefit ratio of additional antiplatelet medication should be a continuous part of these patients' follow-up. Addition of antiplatelet therapy should occur at the low dose, and only after the patient is stabilized on warfarin. Recommendations for antiplatelet therapy in patients with mechanical valves are listed in Table 52–1. It has been suggested that recipients of mechanical valves undergoing percutaneous coronary intervention should receive bare metal rather than drug-eluting stents to minimize the required duration of antiplatelet therapy.[47]

ENDOCARDITIS PROPHYLAXIS

The risk of infectious endocarditis is significantly higher in patients with prosthetic heart valves, but there is insufficient evidence available (1) to define the threshold for and type of prophylaxis required to minimize this risk and (2) to define the incremental risk posed to by adverse outcomes related to antibiotic use including anaphylaxis and antibiotic resistance.[5,48] Current consensus guidelines recommend antibiotic prophylaxis prior to dental procedures that involve manipulation of gingiva or apical tissue, or breach of the oral mucosa (Table 52–2). Routine antibiotic prophylaxis is not recommended for patients with prosthetic valves undergoing gastrointestinal or genitourinary procedures, unless the patient has known sepsis or is immunocompromised.[5,48]

PREGNANCY

Maternal mortality in women with mechanical valves has been estimated to be 1% to 4%.[49] The increased hemodynamic requirements of pregnancy can contribute to heart failure in the setting of patient-prosthesis mismatch or prosthetic valve dysfunction. Additionally, the hypercoagulable state during pregnancy can predispose to valve thrombosis: prepregnancy counseling with a cardiologist with specialist interest in pregnancy in the setting of valvular heart disease is recommended for a tailored approach to antithrombotic management.[50] Patients with mechanical valves are ideally monitored by a dedicated heart valve team including anesthesiologists and obstetricians with expertise in the management of high-risk patients (Table 52–3).

Baseline transthoracic echocardiography is recommended to determine valve function and hemodynamics, and to identify valve dysfunction that requires intervention prior to pregnancy; and repeat

TABLE 52–2. Comparison of Guidelines for Endocarditis Prophylaxis and Treatment After Valvular Surgery from the American Heart Association/American College of Cardiology and the European Society of Cardiology

AHA Recommendations	AHA	ESC	ESC Recommendation
Prophylaxis			
		IIa C	Antibiotic prophylaxis should be considered for patients with any prosthetic valve.
Prophylaxis against infective endocarditis is reasonable for patients with prosthetic cardiac valves who undergo dental procedures that involve manipulation of gingival or periapical tissue or perforation of oral mucosa.	IIa B		Dental procedures: antibiotic prophylaxis should only be considered for dental procedures requiring manipulation of gingiva or periapical region of teeth, or perforation of oral mucosa.
		III C	Antibiotic prophylaxis is not recommended for local anesthetic injections in noninfected tissues, treatment of superficial caries, removal of sutures, orthodontic appliances, or trauma to lips and oral mucosa.
Antibiotic therapy is not recommended for nondental procedures, eg, transesophagela echocardiography, esophagogastroduodenoscopy, or colonoscopy in the absence of active infection.	III B	III C	Antibiotic therapy is not recommended for respiratory tract procedures, eg, bronchoscopy and laryngoscopy, transnasal or endotracheal intubation, gastroscopy, colonoscopy, cystoscopy, vaginal or caesarian delivery, transesophageal echocardiography, skin or soft-tissue procedures.
Diagnosis			
At least two sets of blood cultures should be obtained, in patients with prosthetic heart valves who have unexplained fever for more than 48 hours or newly diagnosed left-sided valve regurgitation.	I C		
Patients with infective endocarditis should be evaluated and managed with a multispecialty Heart Valve Team including an infectious disease specialist, cardiologist, and cardiac surgeon, with a cardiac anesthesiologist in surgically managed patients.	I B	IIa B	Patients with complicated infectious endocarditis should be evaluated and managed at an early stage in a reference center with immediate surgical facilities and the presence of a multidisciplinary Endocarditis Team including an infectious diseases specialist, a microbiologist, a cardiologist, imaging specialist. and a cardiac surgeon.
Transesophageal echocardiography is reasonable to diagnose prosthetic valve endocarditis in the presence of a persistent fever without bacteremia or new murmur.	IIa B	I B	Transesophageal echocardiography is recommended in patients with clinical suspicion of infectious endocarditis when a prosthetic heart valve is present.
Cardiac CT is reasonable to evaluate morphology / anatomy in the setting of suspected paravalvular infections when anatomy cannot be delineated by echocardiography.	IIa B		
Management of Prosthetic Valve Endocarditis			
Surgery is recommended for prosthetic valve endocarditis and relapsing infection (defined as recurrence of bacteremia after complete course antibiotics and subsequent negative blood cultures) without other identifiable source of infection.	I C		
Early surgery (during initial hospitalization before full course antibiotics) is indicated in patients with persistent infection manifested by persistent bacteremia or fevers lasting longer than 5 days after onset appropriate antibiotic therapy.	I B		
Early surgery (during initial hospitalization before full course antibiotics) is indicated in patients with infectious endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions.	I B	I B	Aortic or mitral prosthetic valve endocarditis with acute severe regurgitation, obstruction, or fistula causing refractory pulmonary edema or cardiogenic shock must be treated by emergency surgery.

(*continued*)

TABLE 52–2. Comparison of Guidelines for Endocarditis Prophylaxis and Treatment After Valvular Surgery from the American Heart Association/American College of Cardiology and the European Society of Cardiology (*Continued*)

Early surgery (during initial hospitalization before full course antibiotics) is indicated in patients with infectious endocarditis who present with valve dysfunction resulting in heart failure	I B	I B	Aortic or mitral prosthetic valve endocarditis with severe regurgitation or obstruction causing heart failure or echocardiographic signs of poor hemodynamic tolerance must be treated by urgent surgery.
Early surgery (during initial hospitalization before full course antibiotics) is indicated in patients with left-sided infectious endocarditis caused by *S. aureus*, fungal or other highly resistant organisms.	I B	IIa C	Prosthetic valve endocarditis caused by staphylococci or non-HACEK gram-negative bacteria is an indication for urgent surgery.
Early surgery (during initial hospitalization before full course antibiotics) is indicated in patients with persistent vegetations and recurrent emboli despite appropriate antibiotics.	IIa	I B	Aortic or mitral prosthetic valve endocarditis with persistent vegetations > 10 mm after one or more embolic episode despite appropriate antibiotics must be treated by urgent surgery.
		IIa B	Aortic or mitral prosthetic valve endocarditis with isolated very large vegetations should be treated by urgent surgery.
		IIb C	Aortic or mitral prosthetic valve endocarditis with isolated large (> 1 5 mm) vegetations and no other indication may be treated by urgent surgery.

transthoracic echocardiography should be performed in pregnant patients with changing symptomatology. Increased cardiac output results in increasing mean transvalvular gradients during the first and second trimesters.

The risk of miscarriage, fetal abnormalities, and fetal mortality is increased with any anticoagulant regime. Warfarin crosses the placenta but heparin does not. Warfarin can be teratogenic during the first trimester; however the use of warfarin throughout pregnancy is associated with less risk to mother and fetus than the use of unfractionated heparin.[51] This is because unfractionated heparin has the highest risk of thromboembolic events and maternal death in patients with mechanical valves, and is also associated with maternal thrombocytopenia, osteoporosis, and increased risk of infection from long-term intravenous administration. During the second and third trimester, when warfarin has little teratogenic effect, warfarin or heparin may be used. The risk of embryopathy is dose related, and in patients with mechanical valves who require > 5 mg warfarin daily to achieve a therapeutic INR, dose-adjusted low molecular weight heparin at least twice daily with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL between 4 to 6 hours postdose during the first trimester is thought to represent the safest balance between maternal thromboembolism and fetal teratogenesis. Antiplatelet therapy is recommended in the second and third trimester (see Table 52–3).

Because warfarin crosses the placenta and anticoagulates the fetus, there is an increased risk of fetal intracranial hemorrhage during vaginal delivery if the mother has a therapeutic INR; it is therefore recommended that warfarin be discontinued and an unfractionated heparin infusion started with a target APTT > 2 times control, stopping just prior to delivery.[5,6]

COMPLICATIONS OF PROSTHETIC HEART VALVES

As mentioned before, effective and meaningful comparison or randomization of cardiac surgical patients is one of the most significant challenges of the cardiovascular literature. In an attempt to facilitate analysis and reporting (the approach or technical gap between surgeons seems unavoidable) of clinical results of various therapeutic approaches to heart valve disease, various professional societies joined forces in 1988 to release the first "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations."[52] Nowadays, these guidelines have evolved in parallel to cardiac surgery to include an enhanced understanding of patient- and disease-related factors affecting outcomes, new prostheses, novel repair methods, and the rapid progress of percutaneous interventional techniques.[53] The guidelines apply uniformly, irrespective of whether the therapy was carried out as a conventional open operation, as a minimally invasive surgical procedure, or with percutaneous interventional catheter techniques. In regard to reporting outcomes in patients receiving a prosthetic heart valve, the guidelines distinguished between in-hospital mortality and 30-day mortality, and establish precise definitions of structural valve deterioration, nonstructural dysfunction, embolism, bleeding event, endocarditis, and valve-related morbimortality (Table 52–4).

HEART BLOCK AND ARRHYTHMIAS

Varying degrees of heart block, junctional rhythm, and new-onset atrial fibrillation are common after valve surgery, and usually transient resolving by the time of discharge. Pacemakers were implanted in 6.9% patients undergoing valve surgery in the United States between 2002 and 2010.[54] The risk of permanent pacemaker implantation increased with concomitant ablation procedures[55] (OR: 1.31; 95% CI: 1.27-1.41) mitral valve compared to aortic valve surgery (OR: 1.37; 95% CI: 1.2-1.67) and concomitant tricuspid surgery (OR: 1.79; 95% CI: 1.69-2.77), and concomitant multivalve surgery.[56] The incidence of heart block and pacemaker requirement after transcatheter aortic valve replacement is dependent on the device used: rates of permanent pacemaker requirement up to 28% have been reported with self-expanding devices, compared to 6% with balloon expanding devices.[57]

PROSTHETIC VALVE STENOSIS

Causes of prosthetic valve stenosis include bioprosthetic valve dysfunction, valve thrombosis, endocarditis with large burden of vegetation, and ingrowth of fibrous tissue (pannus).[58] Prosthetic valves, particularly stented bioprostheses, have a much less efficient hemodynamic profile

TABLE 52–3. Comparison of Guidelines for Management of Pregnant Patients With Prosthetic Valves from the American Heart Association/American College of Cardiology and the European Society of Cardiology

AHA Recommendations	AHA	ESC	ESC Recommendation
Monitoring			
All patients with a prosthetic valve should undergo a clinical evaluation and baseline transthoracic echocardiogram before pregnancy.	I C	I C	Pre-pregnancy risk assessment and counseling is indicated in all women with acquired cardiovascular disease.
All patients with a prosthetic valve should have pre-pregnancy counseling by a cardiologist with specific expertise before pregnancy.	I C	I C	Risk assessment should be performed in all women with cardiac disease of childbearing age and after conception.
All pregnant patients with a prosthetic valve should undergo transthoracic echocardiogram if not done before pregnancy.	I C		
All pregnant patients with a prosthetic valve should undergo repeat transthoracic echocardiogram if they develop symptoms.	I C	I C	Echocardiography should be performed in any pregnant patient with mechanical valve and unexplained or new cardiovascular signs or symptoms.
All pregnant patients with a prosthetic valve should undergo transesophageal echocardiogram if they experience an embolic event or prosthetic valve obstruction.	I C	I C	Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnea or an embolic event.
All pregnant patients with a mechanical valve should be monitored in a tertiary care center with a dedicated Heart Valve team of cardiologists, surgeons, anesthesiologists, and obstetricians.	I C	I C	High-risk patients should be treated in a specialized center by a multidisciplinary team.
Anticoagulation			
Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical valve.	I B	I C	Change of anticoagulation regime should be implemented in hospital.
Warfarin is recommended in pregnant patients with a mechanical valve to achieve a therapeutic INR in the second and third trimesters.	I B	I C	Oral anticoagulants are recommended in pregnant patients with mechanical valves during the second and third trimesters until the 36th week.
		I C	If delivery starts while on oral anticoagulants for mechanical valve, Cesarean delivery is indicated.
		IIa	Continuation of oral anticoagulants should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is < 5 mg/day after patient information and consent.
Dose-adjusted low molecular weight heparin at least twice a day (target anti-Xa level 0.8 U/mL-1.2 U/mL, 4-6 hours postdose) during the first trimester is reasonable in pregnant patients with a mechanical valve if the dose of warfarin > 5 mg to achieve therapeutic INR.	IIa B	IIa C	Discontinuation of oral anticoagulant between weeks 6 – 12 and replacement by dose-adjusted continuous intravenous unfractionated heparin (target aPTT > 2× control) or low molecular weight heparin at least twice a day (target anti-Xa level 0.8 U/mL-1.2 U/mL, 4-6 hours postdose) should be considered in pregnant patients with a mechanical valve if the dose of warfarin > 5mg to achieve therapeutic INR.
Dose-adjusted continuous intravenous unfractionated heparin (target aPTT > 2× control) during the first trimester is reasonable in pregnant patients with a mechanical valve if the dose of warfarin > 5 mg to achieve therapeutic INR,	IIa B		

(*continued*)

TABLE 52–3. Comparison of Guidelines for Management of Pregnant Patients With Prosthetic Valves from the American Heart Association/American College of Cardiology and the European Society of Cardiology (*Continued*)

Dose-adjusted low molecular weight heparin at least twice a day (target anti-Xa level 0.8 U/mL-1.2 U/mL, 4-6 hours postdose) during the first trimester may be reasonable in pregnant patients with a mechanical valve if the dose of warfarin < 5 mg to achieve therapeutic INR.	IIb B	IIa C	Discontinuation of oral anticoagulant between weeks 6-12 and replacement by dose adjusted continuous intravenous unfractionated heparin (target aPTT > 2× control) or low molecular weight heparin at least twice a day (target anti-Xa level 0.8 U/mL-1.2 U/mL, 4-6 hours postdose) may be considered in pregnant patients with a mechanical valve if the dose of warfarin < 5mg to achieve therapeutic INR.
Dose-adjusted continuous intravenous unfractionated heparin (target aPTT > 2× control) during the first trimester may be reasonable in pregnant patients with a mechanical valve if the dose of warfarin < 5 mg to achieve therapeutic INR.	IIb B		
Low molecular weight heparin should not be administered to pregnant patients with mechanical prostheses unless anti-Xa levels are monitored 4-6 hours after administration.	III	III	Low molecular weight heparin be avoided unless anti-Xa levels are monitored.

than the normal native aortic valve; consequently mild to moderate transvalvular aortic gradients are very common after bioprosthetic valve replacement,[59] particularly in smaller sizes (≤ 21mm).[60,61] Patient-prosthesis mismatch refers to the imbalance between the orifice area of a small but normally functioning prosthetic aortic valve and the patient's body size. It is measured by echocardiographic assessment of the indexed effective orifice area. In a normal adult, the effective orifice area of the aortic valve indexed to body surface area is 2.0 ± 0.3 cm^2/m^2. Moderate patient-prosthesis mismatch is defined as occurring when the indexed effective orifice area is < 0.85 cm^2/m^2. Severe patient-prosthesis mismatch is defined as an indexed effective orifice area < 0.65 cm^2/m^2.

Severe patient-prosthesis mismatch has been reported in 2% to 11% of patients after aortic valve replacement.[62-67] Patient-prosthesis mismatch appears to be associated with higher transvalvular gradients and less regression of left ventricular hypertrophy, but there are conflicting data on the clinical consequences of this. In a retrospective analysis of 13,258 aortic valve replacements (including almost 9000 stented bioprostheses and over 5000 mechanical valves) with 69,780 patient-years of follow-up, there was no significant difference in long term survival seen according to indexed internal orifice areas down to 1.1 cm^2/m^2. However, instead of using echocardiographically measured effective orifice area this study relied on manufacturer measurements of internal orifice area, a less reliable assessment of valve function (Fig. 52–9).[63]

Patient-prosthesis mismatch has been associated with decreased cardiac index, reduced functional improvement, less left ventricular mass regression, worse survival, and more adverse events in long-term follow-up. However, there are several confounding variables associated with smaller indexed effective orifice area and with worse postoperative outcomes, including advanced age, female gender, and obesity; and it is unclear to what extent these confounding variables contribute to the worse outcomes observed in patients with patient-prosthesis mismatch.[67]

Consensus guidelines recommend using manufacturer tables to assess risk of patient-prosthesis mismatch, so that surgery can be tailored to avoid this. For example, a 21-mm Carpentier-Edwards Perimount valve has an internal orifice area of 1.2 cm^2, and would likely provide an indexed effective orifice area of < 0.8 cm^2/m^2 if inserted into a patient with a body surface area greater than 1.6 m^2, whereas a 23-mm Carpentier-Edwards Perimount valve has an internal orifice area of 1.5 cm^2, and could be implanted into a patient with a body surface area of up to 2.0 m^2 without meeting the threshold for moderate patient-prosthesis mismatch. In small valve sizes, superior hemodynamics are generally provided by newer-generation valves compared to older ones, stentless valves compared to stented valves, mechanical valves compared to any bioprosthetic valve, and transcatheter valves to surgical bioprostheses.[58] Suprannular bioprostheses permit a larger valve to be placed for a given annular diameter than intrannular devices. No incremental clinical benefit was observed at 3 years from the reduced transvalvular gradients seen with stentless compared to stented bioprostheses in a meta-analysis of 17 randomized and 14 nonrandomized studies involving 3802 patients. Most surgeons aim to insert the largest size valve that the aortic root will accommodate, particularly in the setting of low gradient, low ejection fraction aortic stenosis, where there appears to be most benefit in minimizing postoperative transvalvular gradient.[65,66] Root enlargement or root replacement may be reasonable options in the very small aortic root, but there appears to be an associated incremental risk: overall operative mortality has been reported to be as high as 5% for root enlargement in a large single-center series, and 4.2% reported for root replacement nationally, increasing to 15% in patients over 80 years old, compared to < 2% for isolated aortic valve replacement.[25,34,68] The indications for reoperation for prosthetic valve stenosis are similar to those for first-time surgery (see Reoperation Risk later in the chapter).

PARAVALVULAR LEAKS AND HEMOLYSIS

The incidence of paravalvular leaks is reported at 0% to 1.5% per patient year.[69] A paravalvular leak present in the immediate postoperative period suggests difficult suture placement, most commonly because of calcified or friable tissue (Figs. 52–10 and 52–11). Paravalvular leaks that occur late in follow-up are more suggestive of prosthetic valve endocarditis.

TABLE 52–4. American College of Cardiology/American Heart Association Guidelines for Reporting Morbidity and Mortality After Cardiac Valve Intervention

Term	Definition
Mortality or operative mortality	Death within 30 days of operation regardless of the patient's geographic location. Follow-up for 30-day mortality must be complete. *Hospital mortality* is death within any time interval after operation if the patient is not discharged from the hospital. Hospital-to-hospital transfer is not considered discharge; transfer to a nursing home or rehabilitation unit is considered hospital discharge unless the patient subsequently dies of complications of the operation.
Structural valvular deterioration (SVD)	Any change in function (a decrease of one NYHA functional class or more) of an operated valve including: • Operated valve dysfunction or deterioration *exclusive of infection or thrombosis* as determined by reoperation, autopsy, or clinical investigation. • Wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components (eg, leaflets, chordae) of an operated valve.
Nonstructural dysfunction	Any abnormality, exclusive of *thrombosis and infection*, resulting in stenosis or regurgitation at the operated valve that is not intrinsic to the valve itself (eg, pannus, tissue, or suture; paravalvular leak; inappropriate sizing or positioning; residual leak or obstruction from valve implantation or repair; clinically important hemolytic anemia).
Valve thrombosis	Any thrombus, in the *absence of infection*, attached to or near an operated valve that occludes the path of blood flow or impedes the operation of the valve.
Embolism	Any embolic event that occurs in the *absence of infection* after the immediate perioperative period. A *neurologic event* includes any new, temporary, or permanent focal or global neurologic deficit. Patients who do not awaken or who awaken after an operation with a new stroke are *excluded* in tabulations of valve-related morbidity. A *peripheral embolic* event is an operative, autopsy, or clinically documented embolus that produces symptoms from complete or partial obstruction of a peripheral (noncerebral) artery. Emboli proven to consist of nonthrombotic material (eg, atherosclerosis, myxoma) are excluded.
Bleeding event (formerly anticoagulant-related hemorrhage)	Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (eg, vision loss) or necessitates transfusion. The complication *bleeding event* applies to all patients whether or not they are taking anticoagulants or antiplatelet drugs because bleeding events can occur in patients who are not receiving anticoagulants. Embolic stroke complicated by bleeding is classified as a neurologic event under embolism and is not included as a separate bleeding event.
Operated valvular endocarditis	Any infection *involving* an operated valve.
Reoperation	Any operation that repairs, alters, or replaces a previously operated valve.
Valve-related mortality	Death caused by structural valvular deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or death related to reoperation of an operated valve. Sudden, unexplained, unexpected deaths of patients with an operated valve are included as valve-related mortality. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not included.
Sudden, unexpected, unexplained death	The cause of these deaths is unknown, and the relationship to an operated valve is also unknown. Therefore, these deaths should be reported as a separate category of valve-related mortality if the cause cannot be determined by clinical data or autopsy.
Cardiac death	All deaths resulting from cardiac causes. This category includes valve-related deaths (including sudden unexplained deaths) and non–valve-related cardiac deaths (eg, congestive heart failure, acute myocardial infarction, documented fatal arrhythmias).
Permanent valve-related impairment	Any permanent neurologic or other functional deficit caused by structural valvular deterioration, nonstructural dysfunction, valve thrombosis, thrombotic embolism, bleeding event, operated valvular endocarditis, or reoperation.

(*continued*)

TABLE 52–4. American College of Cardiology/American Heart Association Guidelines for Reporting Morbidity and Mortality After Cardiac Valve Intervention (*Continued*)

NYHA, New York Heart Association.

Data from Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *Eur J Cardiothorac Surg*. 2008 Apr;33(4):523-528.

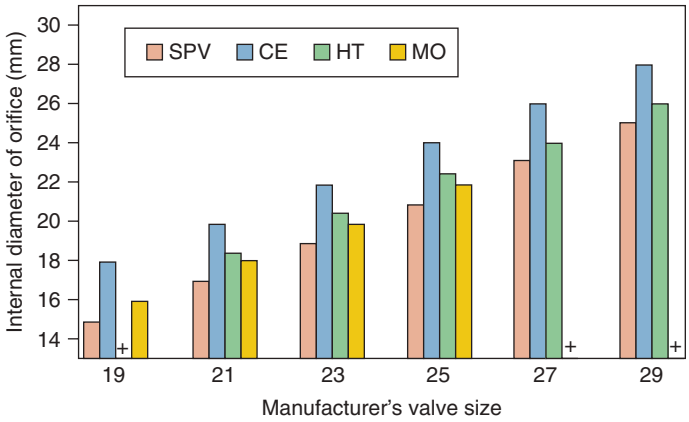

FIGURE 52–9. The measured internal orifice area differs from the manufacturer's size: Dimensions for the Toronto stentless porcine valve (SPV), Carpentier-Edwards porcine valve (CE), Hancock II valve (HT), and Hancock Modified Orifice valve (MO). Reproduced with permission from Christakis GT, Buth KJ, Goldman BS, et al: Inaccurate and misleading valve sizing: a proposed standard for valve size nomenclature. *Ann Thorac Surg*. 1998 Oct;66(4):1198-1203.

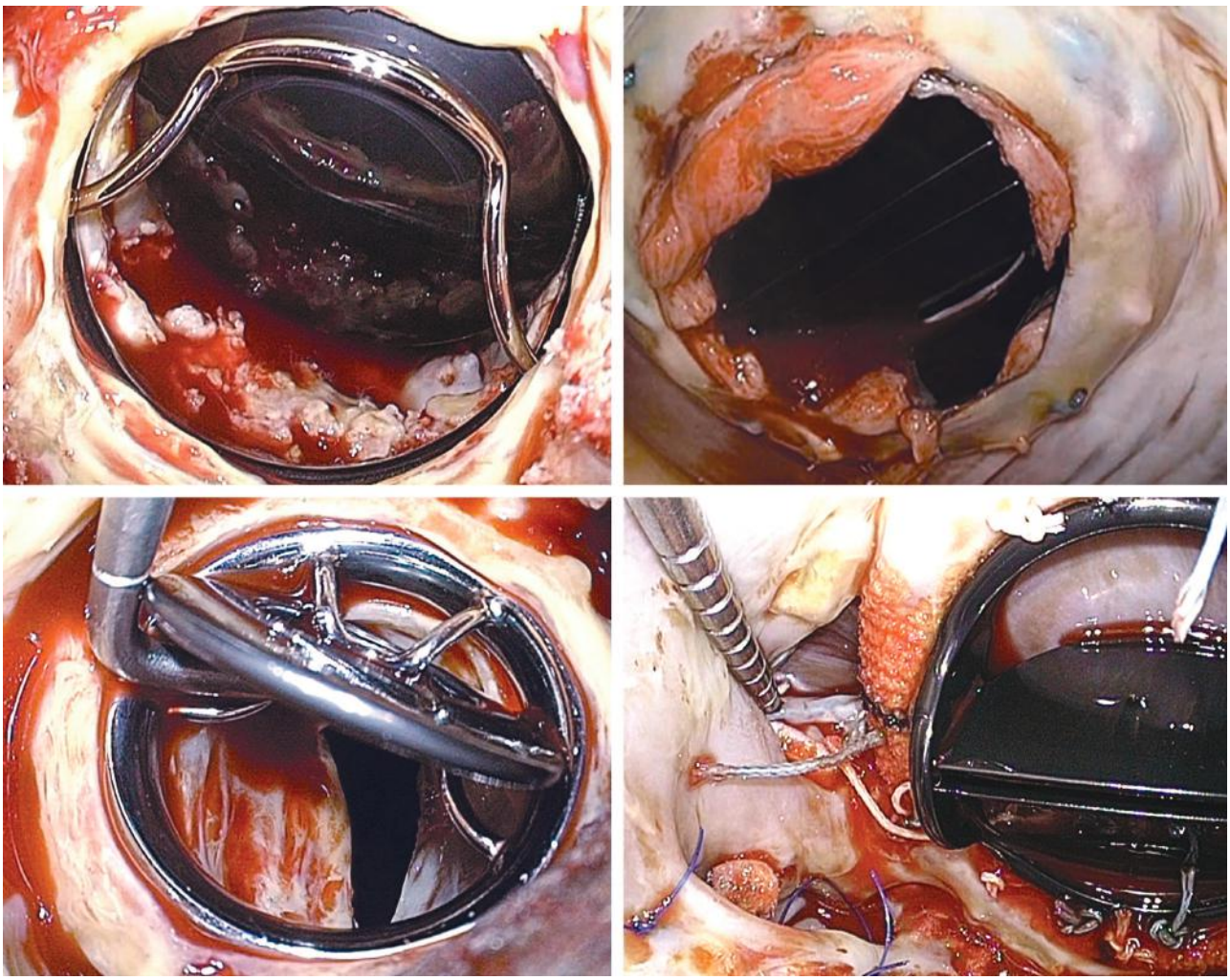

FIGURE 52–10. Operative views of failed mitral valve replacements with mechanical prostheses. Subvalvular calcification and pannus formation in a patient with a monoleaflet mechanical prosthesis (top left). Pannus ingrowth and severe thrombosis in a patient with a bileaflet mechanical prosthesis (top right). Growth of a subvalvular membrane causing inflow obstruction and valve dysfunction in a patient with a monoleaflet mechanical prosthesis (bottom left). Paravalvular leak (bottom right). Used with permission from David H. Adams, MD.

Choice of valve prosthesis does not appear to affect the incidence of paravalvular leaks except for the St Jude Silzone valve, where a silver-impregnated sewing ring designed for antimicrobial properties, prevented endothelialization, and higher rates of paravalvular leak were reported.[70] Paravalvular leaks commonly cause hemolysis, whereas a normally functioning valve prosthesis is unlikely to cause hemolysis. Although mild cases of hemolysis may be managed with supplemental iron and folate, severe, symptomatic hemolysis warranting frequent transfusion is an indication for reoperation or percutaneous device closure.[71]

COMPLICATIONS OF ANTICOAGULATION NONCOMPLIANCE

Patients unable to take anticoagulation reliably make up a large group.[72] The main reasons for this include comorbid contraindications to anticoagulation, patient preference, socioeconomic barriers, and childbearing. In older patients, comorbid conditions that may pose an obstacle to anticoagulation and are consequently relative contraindication to mechanical valve replacement include dialysis-dependent renal failure,[73] a history of bleeding diatheses including gastrointestinal and intracranial bleeds, liver dysfunction, and thrombocytopenia.

In younger patients these comorbid conditions are less common, and other barriers to anticoagulation assume greater importance.[74] In an analysis of Medicaid patients, age less than 55 years was one of the strongest independent predictors of nonadherence to an anticoagulation regimen.[75] This study also identified inadequate housing and care support, mental illness, and substance abuse as significant barriers to patient adherence with anticoagulation. Pregnancy is an additional consideration in women of childbearing age undergoing valve replacement, for whom the balance of risks favors bioprosthetic valve replacement. This is because maternal mortality in recipients of mechanical valves has been reported to be as high as 5%.[49] This is because (1) there is significant risk of thromboembolic events irrespective of the anticoagulation regime employed during pregnancy, (2) because of the risk of hemorrhage during the postpartum period, and (3) because of the low operative mortality associated with elective reoperative valve replacement in this age group.

In developing countries where rheumatic valve disease is especially prevalent in younger patients and long-term access to healthcare most challenging, these challenges affect a large number of patients.[76] In a multinational registry of patients with rheumatic heart disease in predominantly low- and middle-income countries, almost 10% of patients with mechanical valves were not taking oral anticoagulants, 12% of patients on oral anticoagulants had no access to INR monitoring, and 34% had undergone three or fewer INR checks in the 6 months prior to

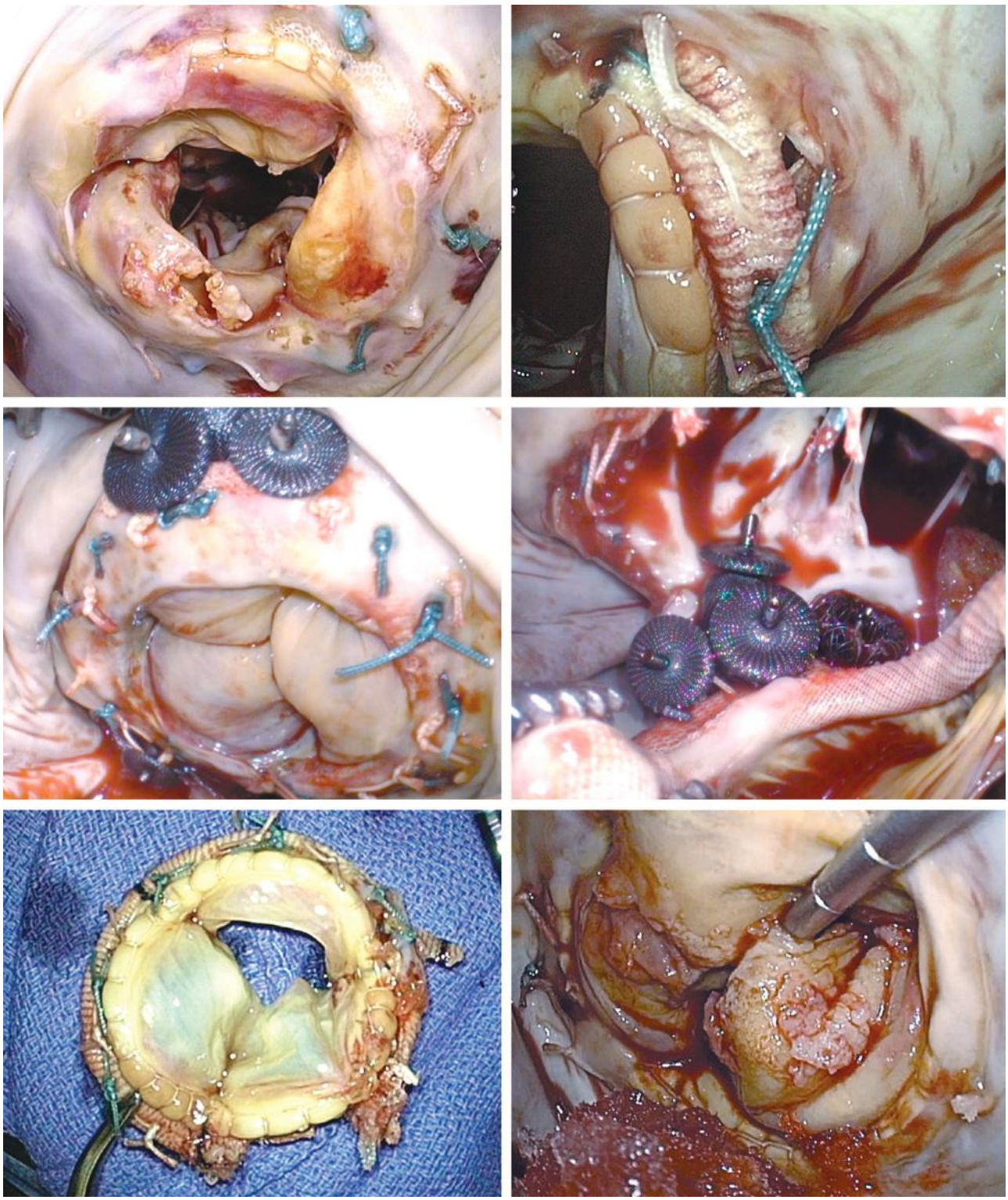

FIGURE 52–11. Operative views of failed mitral valve replacements with bioprostheses. Leaflet tear, calcification, and perforation in a patient with acute endocarditis (top left). Paravalvular leak (top right). Amplatzer vascular plug occluders in a patient with a paravalvular leak (middle left). Subvalvular view showing up to seven devices to attempt percutaneous repair of the paravalvular leak (middle right). Calcification and leaflet stiffness over time (bottom left) Thrombus and pannus formation (bottom right). Used with permission from David H. Adams, MD.

registry enrollment. For those patients taking warfarin, their INR was within the therapeutic range in only 23%. Among women with rheumatic valve disease younger than 51 years of age, fewer than 5% were taking contraception, 4% were pregnant, and more than 20% of pregnant women were taking warfarin. In this context the immediate safety profile of bioprosthetic valves may offset the long-term risks of structural valve degeneration and need for reoperation as well as the reduced survival associated with bioprosthetic mitral valve replacement.[76]

Finally, patient preference is a class I indication for bioprosthetic valve implantation. For a significant minority of patients, concerns about the noise associated with mechanical valves is an under-reported but important, occasionally overwhelming, source of dissatisfaction postoperatively.[72] Much more prevalent, however, is a desire to avoid life-long anticoagulation and the associated lifestyle restrictions. A multicenter quality-of-life survey in recipients of prosthetic valves aged between 18 and 50 years found that patients with mechanical valves are significantly more likely to report dissatisfaction with their prosthesis choice, disruption of their career and income, and continued disability after surgery.[77]

THROMBOEMBOLISM

Embolism is defined as any embolic event that occurs in the absence of infection after the immediate perioperative period. The annual risk of thromboembolism is highest in the immediate postoperative period, and linear thereafter at < 1% for bioprosthetic valves, compared to 1% to 2% for mechanical valves with appropriate anticoagulation.[26-31] Thromboembolic events are related to the INR, but are observed even in patients who are in the therapeutic range of anticoagulation at interval testing (Fig. 52–12).[78] Additionally, most patients complying with anticoagulation regimes will have an INR outside of the therapeutic range up to 40% of the time.[79]

Long-term stroke risk after aortic valve replacement does not appear to be affected by prosthesis choice, whereas after mitral valve surgery long-term stroke risk may be higher after mechanical versus bioprosthetic valve replacement (see Figs. 52–10 and 52–11).[26-31] Transthoracic echocardiography is recommended as the first line of investigation in patients with suspected valve-related thromboembolism.[5,6] Transesophageal echocardiography should be performed to evaluate the mitral valve, left atrium, and left atrial appendage. In patients with mechanical valves the adequacy of anticoagulation should be assessed. If subtherapeutic INRs have been documented, then warfarin dose should be increased appropriately, and the patient bridged with heparin if there are no contraindications. In patients with a therapeutic INR, the target INR may be increased by 0.5. Low-dose aspirin should be added to anticoagulation regimes for mechanical valve recipients, and in patients with bioprostheses and thromboembolic events who are taking aspirin consideration should be given to starting formal anticoagulation. The available evidence suggests that patients managed by pharmacy-directed anticoagulation protocols have the lowest rates of hemorrhagic and thromboembolic complications.[74] Reoperation to replace a mechanical prosthesis with a bioprosthetic valve may be considered for patients with recurrent major thromboembolic episodes, or major difficulties achieving a therapeutic anticoagulation range.[6] The risk posed by elective valve reoperation in a patient without significant comorbidities is 2% to 5%, and a careful discussion of the risks and benefits is crucial.[80]

VALVE THROMBOSIS

Valve thrombosis is any thrombus in the absence of infection attached to or near an operated valve that occludes part of the blood flow path or that interferes with the function of the valve (see Figs. 52–10 and 52–11). Mechanical valve thrombosis generally occurs in the setting of

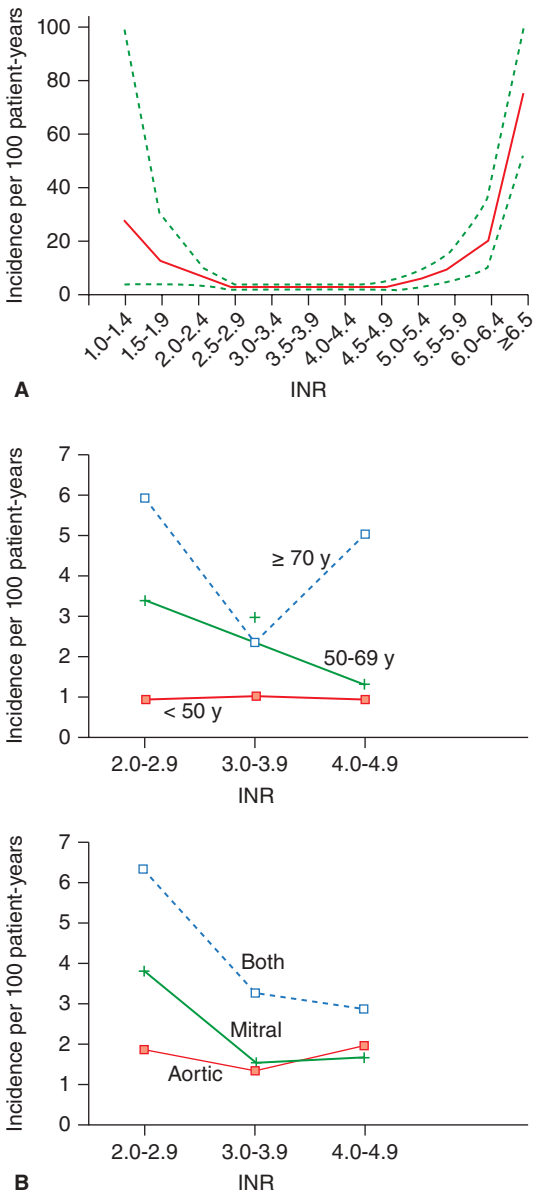

FIGURE 52–12. A. International normalized ratio (INR)–specific incidence of all adverse events in patients with mechanical valves (all episodes of thromboembolism, all major bleeding episodes, and unclassified stroke) according to INR. The dotted lines represent the 95% confidence interval and according to INR, age, and position of valve. **B.** Incidence of thromboembolic events according to INR and patient age (upper graph) or prosthesis position (lower graph). Modified with permission from Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med*. 1995; July 6;333(1):11-17.

subtherapeutic anticoagulation, or with a background of obstruction of the valve mechanism from chronic pannus ingrowth.[66] The annual incidence in mechanical valves is 0.5% to 1%.[5,6,69,79] Mortality in patients presenting with acute mechanical valve thrombosis has been reported to be over 30%. Acute mechanical valve thrombosis requires emergency intervention in patients who may be hemodynamically extremely compromised by acute severe valvular stenosis and insufficiency.

Valve thrombosis may have a subacute presentation resembling that of pannus formation (see Figs. 52–10 and 52–11). Differentiating between these two entities relies on establishing a history of subtherapeutic anticoagulation, and usually an acute onset of symptoms and valve dysfunction—which both suggest valve thrombosis rather than

pannus.[81,82] Clinical examination may be notable for a diminution or change in the quality of valve sounds, as well as signs of acute congestive heart failure. Echocardiography, cardiac CT, and fluoroscopy can image the valve leaflets and document lack of mobility. Echocardiography is required for hemodynamic evaluation, specifically the transvalvular gradient and grade of valvular insufficiency; and allows assessment of left and right ventricular and atrial size and function and pulmonary artery pressures. Transesophageal echocardiography additionally provides better images of thrombus on the left-sided heart valves, which may be obscured by shadowing artifact on transthoracic echocardiography. This may allow differentiation between thrombus and pannus: thrombus tends to be bulkier, less dense, and more mobile than pannus.[83]

Medical management with several days of intravenous unfractionated heparin infusion is recommended for mild symptoms resulting from low thrombus burden. Fibrinolysis with a 10-mg intravenous bolus of recombinant tissue plasminogen activator, and then 90 mg infused intravenously over 2 hours, is recommended for small thrombi that persist despite heparinization, and for larger left- and right-sided thrombi. If fibrinolysis is successful, heparin infusion is continued for several days. Mobile thrombi and those > 1.0 cm in diameter are associated with significantly higher rates of major adverse events after fibrinolysis.[84] Additional factors that increase the risk of adverse outcomes with thrombolysis include active bleeding; a history of intracranial bleeding, trauma, or neoplasm; hemorrhagic retinopathy; blood pressure > 200 mm Hg, and congestive heart failure.[85] Fibrinolytic therapy restored normal valve function in 64% of cases in one randomized trial, with 5% incidence of mortality and 10% incidence of a composite end point of death, stroke, or major embolic complications.[86]

Surgery for valve thrombosis carries an operative mortality of 5% to 10%, is more successful at restoring normal valve function than fibrinolysis, and appears to be associated with lower rates of recurrent thromboembolism, major bleeding, and recurrent thrombosis. Consensus guidelines therefore recommend surgical intervention for left-sided prosthetic valve thrombosis, unless the patient has minimal symptoms and the thrombus is small.[5,6]

BLEEDING

Guideline statements on valve-related complications define bleeding events as any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury.[5,6] These events are major complications, with 30-day mortality after a major bleed reported to be > 10% in two multicenter studies.[26,27] Additionally, the impact on patients of lesser bleeding episodes, and curtailed lifestyle as a result of risk of bleeding, can be substantial.[77] It is difficult to separate out the relative effect of variation in anticoagulation regimes from differences caused by prosthesis type, both of which contribute to the different bleeding rates reported between mechanical and bioprosthetic valves in the aortic and mitral position. However, the incidence of bleeding in long-term follow-up is significantly higher in recipients of mechanical valves compared to bioprosthetic valves in most randomized and observational studies.[26,28-30] Younger patients are at lower risk of bleeding complications than older patients, which may be one reason why the difference in bleeding rates between mechanical and bioprosthetic valves in younger cohorts is less significant: for example, in a randomized trial of mechanical bileaflet valves versus second-generation bioprosthetic valves in 310 patients between the ages of 55 and 75 years, no difference in bleeding rates between the groups was identified.[31] This may also result from this small study being underpowered to detect a difference, from a more aggressive anticoagulation strategy in patients with bioprosthetic valves, or from a lower-intensity anticoagulation regime (INR: 2.0-2.5) adopted in patients with mechanical valves. Mechanical prostheses are associated with more major bleeding events, experienced by 6.6% of patients with a bioprosthesis compared to 13.0% of patients with mechanical valves by 15 years after surgery in one multicenter analysis.[26] Importantly, the 30-day mortality after a major bleeding event in this study was 13.2%. Studies comparing low-intensity, self-monitored anticoagulation regimes with standard anticoagulation in patients with mechanical valves have not shown a significant reduction in major bleeding or thromboembolic events.

PROSTHETIC VALVE ENDOCARDITIS

Prosthetic valve endocarditis is an infection involving an operated valve (see Fig. 52–11). Early prosthetic valve endocarditis, defined with an arbitrary cut-off as occurring within 1 year of implantation, has an incidence of approximately 1%, and likely results from periprocedural contamination of the valve—either directly at the time of implantation, or from bacteremia associated with catheters, cannula, and wound infections.[87] The common causative organisms in early prosthetic valve endocarditis are *Staphylococcus aureus*, *Staphylococcus* epidermidis, and gram-negative bacteria.[88] The annual incidence of late prosthetic endocarditis is around 0.2% to 0.4%, with no significant difference between mechanical and bioprosthetic valves. The etiology of late prosthetic valve endocarditis is primarily noncardiac sepsis with similar organisms grown to those found in native valve endocarditis (*Streptococcus*, *Staphylococcus*), although some cases are associated with less virulent organisms such as *S epidermidis* that may have been introduced in the early postoperative period.[89]

At least two sets of blood cultures at separate times from different sites should be obtained, using strict aseptic technique, in patients with suspected endocarditis before initiation of antibiotic therapy. If the patient is stable, three sets of blood cultures should be drawn more than 6 hours apart to maximize the chance of diagnosing the specific organism. Clinical stigmata of endocarditis are not often present during the early disease stage, and a high index of clinical suspicion is warranted as delay in diagnosis and effective treatment can result in irreversible damage to heart and end-organs, including stroke, renal failure, and peripheral and visceral ischemia. Once a valve prosthesis is colonized it is virtually impossible to eradicate endocarditis without surgical valve replacement.

Echocardiography is indicated to detect and quantify valve dysfunction, vegetations, and abscess formation. Transesophageal echocardiography is superior to transthoracic echocardiography in the visualization of abscesses, small vegetations, and pericardial effusions, and should be performed in patients with prosthetic valves and persistent fever even without a bacteremia or clinical signs such as a new murmur.[5,6] This is because prosthetic valve endocarditis is frequently caused by organisms that can cause extensive tissue damage before serological detection. It may be reasonable to stop or reduce anticoagulation in patients with suspected prosthetic valve endocarditis to reduce the risk of hemorrhagic complications, particularly hemorrhagic stroke in the acute phase of endocarditis.

A prolonged course of appropriate intravenous antibiotic therapy may be sufficient to treat early prosthetic valve endocarditis caused by sensitive organisms without recourse to operative reintervention. Reoperation is frequently required, with around 50% of cases undergoing operation in single-institution observational series, and a fifth of patients denied surgery because of major complications or morbidity.[90] In a subgroup analysis of a series of 1025 patients, the patients with new left-sided regurgitation, paravalvular abscess, or fistula, prosthetic valve dehiscence had better one-year survival if they underwent early surgery (83% compared to medical therapy (50%, $P < .010$).[90] Early surgery is performed during the initial hospitalization before completion of a full therapeutic

course of antibiotics (see Table 52–2).[91,92] For patients with relapsing prosthetic valve endocarditis, surgery should be considered, with attention to eradicating possible extracardiac sources of residual infection.

STRUCTURAL VALVE DEGENERATION: VALVE DURABILITY

Prosthetic valve regurgitation in mechanical valves is most commonly the result of paravalvular leak, which may be present immediately after surgery because of the difficulty securing or placing sutures in calcified or friable annular tissue; or which may appear in later follow-up when tissue erosion from endocarditis is a possible cause formation (see Figs. 52–10 and 52–11). Partial obstruction of a mechanical valve leaflet in an open position by tissue entrapment at the time of implantation, or by thrombus or pannus in later follow-up, can cause significant regurgitation formation (see Fig. 52–10). Structural degeneration of mechanical valves is extremely unusual, with the notable exception of the Bjork-Shiley Convexoconcave valve, which had approximately 700 fractures out of 86,000 implants,[17] and the Duromedics valve, which had 49 known fractures in 20,000 valves implanted between 1982 and 1988; both were withdrawn from clinical use.[93]

Early bioprosthetic valve regurgitation may be caused at the time of surgery by suture entrapment of a leaflet, or occasionally in the early postoperative period by prosthetic valve endocarditis or thrombosis. By far the commonest mechanism of regurgitation in bioprosthetic valves, however, is leaflet calcification and fracture resulting in structural valve degeneration.[42] Bioprosthetic structural valve degeneration is defined as any change in function (a decrease in one New York Heart Association functional class or more) of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation. Structural valve degeneration is the commonest valve-related complication in bioprosthetic valves.[69] It occurs more rapidly in younger patients compared to older patients, and earlier in the mitral position, compared to the aortic position (Fig. 52–13). The hazard of structural valve degeneration is nonlinear: after an initial low hazard interval, rates increase sharply at 8 to 12 years postoperatively. Approximately 10% to 15% of patients aged > 70 years of age at the time of aortic valve implantation have evidence of structural valve degeneration at 15 years after surgery. Table 52–5 summarizes the freedom from structural valve degeneration of commonly used first-, second-, and third-generation bioprostheses. Key patient characteristics, valve type, and position differ between these series, preventing direct comparison of outcomes between studies. Bioprosthetic durability has improved steadily over the decades with successive models.[58] Among the bioprostheses in current use, however, there is no clear evidence that porcine valves offer superior durability to pericardial valves, or stentless bioprosthesis have superior durability compared to stented bioprosthetic valves in randomized trials.

Echocardiography is the mainstay of surveillance and diagnosis, with transesophageal echocardiography offering optimal views of left-sided valves and the left atrium, which is shadowed by the valve in transthoracic windows. There is no definitive medical treatment. Intervention is recommended to treat prosthetic valve regurgitation in patients with intractable hemolysis, heart failure, or severe symptoms. Asymptomatic patients with severe regurgitation resulting from bioprosthetic structural degeneration should be considered for elective surgery, because of the risk posed by sudden decompensation caused by the valve leaflet tearing. Percutaneous approaches include closure of paravalvular leaks by catheter-based delivery of occluder devices, and transcatheter valve-in-valve replacement. Procedural success is over 80% in selected patients, with a 5% to 10% incidence of major complications including mortality rate of around 2%, vascular or cardiac injury, stroke, and major bleeding. The residual regurgitation rate for percutaneous device closure of paravalvular leaks is approximately 14%.[94]

Reoperation is the definitive management for selected patients with low predicted operative mortality. The need for reoperation is higher after bioprosthetic compared to mechanical valve replacement in patients < 70 years of age (Fig. 52–14). By 15 years after surgery, 12.1% of patients aged 50 to 69 years with bioprostheses had undergone aortic valve reoperation, compared to 6.9% with mechanical prostheses. Only one randomized study was designed to detect differences in long-term mortality and major morbidity in this age group,[31] and larger retrospective analyses are limited to single-center studies with follow-up dependent on patients returning to the same institution. In patients aged 18 to 49 years, our most recent analysis of outcomes in New York State showed an almost 50% reduction in reoperation at 15 years from 22.6% to 9.8% with mechanical aortic valve replacement compared to bioprosthetic valve replacement (manuscript in press). This difference in reoperation did not appear to affect long-term survival: one reason for this may be that the 30-day mortality associated with reoperation on bioprosthetic valves was very low in this cohort, at only 2.7%.

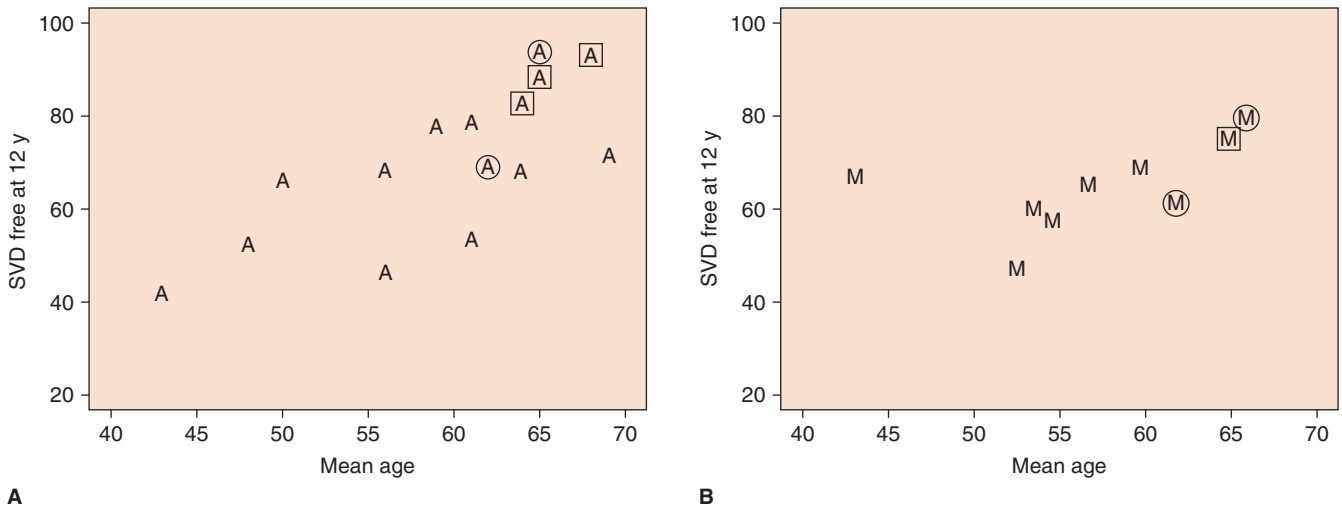

FIGURE 52–13. Relationship between freedom from structural valve degeneration (SVD) at 12 years and mean patient age at implantation for aortic (**A**) and mitral (**B**) bioprostheses. Each symbol represents one series; pericardial valves are represented by *squares*, "second-generation" valves are represented by *circles*, and first-generation porcine valves are represented by *unenclosed letters*. Reproduced with permission from Grunkemeier GL, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. *Curr Probl Cardiol*. 2000 Feb;25(2), 73-154.

TABLE 52–5. Freedom From Structural Valve Deterioration of Commonly Used First-, Second-, and Third-Generation Bioprostheses in Large Studies

		Number				% Freedom from SVD		
Author, Year	Mean Follow-Up (y)	AVR	MVR	Time of SVD Estimate	Age (y)	AVR	MVR	Comments
Jamieson et al.,[66] 1988	5.6	572	509	10	30–59	81 ± 4	78 ± 5	Carpentier-Edwards standard porcine
					> 60	91 ± 3	71 ± 9	
Cohn et al.,[67] 1989	6.0	971	708	15	< 40	68 ± 9	68 ± 10	Hancock porcine
					41–69	86 ± 2	68 ± 10	
					> 70	94 ± 3	84 ± 10	
Jones et al.,[68] 1990	8.3	610	528	10	< 40	46 ± 7	47 ± 8	Hancock (or Carpentier-Edwards porcine)
					40–49	60	48 ± 8	
					50–59	79	61	
					60–69	92 ± 2	80 ± 6	
Burdon et al.,[69] 1992	7.3	857	793	15	16–39	33 ± 7	37 ± 6	Hancock I and Hancock modified orifice
					40–49	54 ± 10	38 ± 12	
					50–59	57 ± 6	38 ± 15	
					60–69	73 ± 6	61 ± 15	
					> 70	93 ± 3	62 ± 6	
Burr et al.,[70] 1992	—	574	500	7	< 65	94 ± 1	88 ± 2	Carpentier-Edwards standard porcine
					65–69	98 ± 1	90 ± 4	Carpentier-Edwards standard, improved
					70–79	100	95 ± 3	annulus, supraannular porcine
					80	100	100	
				13–15	< 65	62 ± 8	37 ± 7	
					65–69	98 ± 3	63 ± 8	
					70–79	95 ± 5	74 ± 19	
					80	100	—	
Pelletier et al.,[71] 1992	7.0	451	547	10	< 45	70	55	Carpentier-Edwards standard, improved annulus, supraannular porcine
					45–54	84	64	
					55–64	84	69	
					> 65	93	95	
Jamieson et al.,[72] 2001	6.2	836	332	12	51–60	92 ± 3	90 ± 3	
					61–70	96 ± 2		
					> 70	98 ± 1	97 ± 3	

(*continued*)

TABLE 52–5. Freedom From Structural Valve Deterioration of Commonly Used First-, Second-, and Third-Generation Bioprostheses in Large Studies (*Continued*)

Rizzoli et al.,[73] 2006	12	809	484	10	< 60	93 ± 4	89 ± 4	Hancock II
					60–65	99 ± 1	98 ± 1	
					> 65	99 ± 1	97 ± 2	
				15	< 60	70 ± 8	78 ± 5	
					60–65	97 ± 1	88 ± 3	
					> 65	97 ± 1	90 ± 4	

AVR, aortic valve replacement; MVR, mitral valve replacement; SVD, structural valve degeneration.

Data from American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease); Society of Cardiovascular Anesthesiologists, Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2006;48:e1-e148.

Transcatheter valve-in-valve replacement has been utilized as an alternative to surgical reoperation in older patients where the procedural mortality has been reported to be 7.6%.[95] The low mortality of reoperative valve surgery in young patients, however, suggests that the utility of transcatheter valve-in-valve as an alternative to reoperation in this context may be limited to second or subsequent reoperative procedures where the risk of operative mortality increases. Approximately 30% of patients undergoing transcatheter valve-in-valve replacement will have significant transvalvular gradient or regurgitation.[96,97]

REOPERATION RISK

A patient with a mechanical valve has a linear risk of approximately 5% to 10% over 15 years of undergoing reoperation to replace the prosthetic valve, most commonly because of paravalvular leak, endocarditis, or pannus formation. The risk of reoperation to replace a bioprosthetic valve is initially similar, but with a hinge point that is related to the age of the patient at time of implantation, the hazard increases steeply at 8 to12 years postoperatively as a result of increasing incidence of structural valve dysfunction—which is the commonest indication for reoperation on bioprostheses.[26-31,69]

The operative mortality associated with reoperation in contemporary series is 2% to 5%.[69] Mechanical valve dysfunction resulting from pannus or thrombosis commonly presents as an emergency: the associated mortality of mechanical valve thrombosis is over 30%.[87] Bioprosthetic valve failure is usually a chronic process, and elective reoperation is usually relatively low in risk.[26,27] Transcatheter valve-in-valve replacement has been performed in patients with bioprosthetic

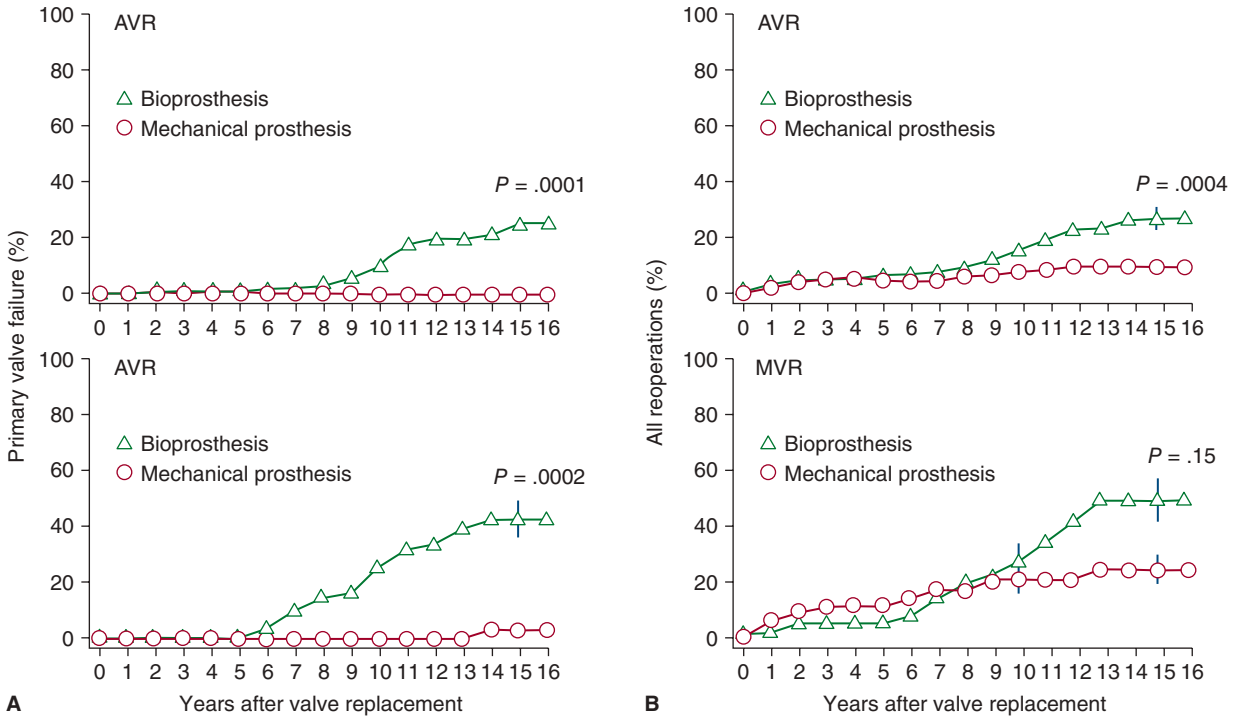

FIGURE 52–14. Rates of structural valve deterioration (left figures) and reoperation (right figures) for mechanical versus bioprosthetic valves in the 15-year follow-up of the Veterans Affairs randomized valve study. Reproduced with permission from Hammermeister K, Sethi GK, Henderson WG, et al: Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000 Oct;36(4):1152-1158.

valve dysfunction, who are adjudicated to be at high risk of operative mortality. A multicenter series of 202 transcatheter aortic valve-in-valve replacements reported 30-day procedural mortality of 7.6%.[95] In this observational cohort, 28% of patients had postprocedural mean transvalvular gradients ≥ 20 mm Hg, and this approach is currently ideally limited to patients with a surgical valves sized 21 and greater in the aortic position. Mitral transcatheter valve-in-valve replacement has been successfully performed in a smaller number of patients.[98]

Patients undergoing reoperative valve surgery are generally older, with more significant comorbidity than patients undergoing valve surgery for the first time.[99] Investigation of the patient requiring reoperative valve replacement should include transesophageal echocardiography to assess native and prosthetic valve function, evaluate presence and extent of endocarditis, thrombus, and pannus, and determine cardiac function including presence of pulmonary hypertension and right ventricular dysfunction.[99,100] Cardiac catheterization should be performed to document native coronary artery anatomy, the presence and patency of coronary bypass grafts, and hemodynamics including pulmonary artery pressures, cardiac output, and transvalvular gradients. Noncontrast chest CT is helpful to plan sternal reentry, which may be complicated by inadvertent division of structures adherent to the sternum including the right ventricle, pulmonary artery, aorta, innominate vein, and patent bypass grafts. Prior operative reports are useful to confirm the size and type of previous prosthesis, location of bypass grafts, and technical challenges encountered at first surgery, which may affect the conduct of reoperation.

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CHAPTER 53

ANTITHROMBOTIC THERAPY FOR VALVULAR HEART DISEASE

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The worldwide burden of valvular heart disease (VHD) continues to grow as a result of increases in life expectancy combined with the high incidence of rheumatic heart disease in developing nations.[1] Patients with VHD and certain comorbid conditions or prosthetic heart valves (PHVs) are at high risk for thromboembolic complications and often require antithrombotic therapy (Table 53–1). Although bleeding is a risk with all antithrombotic agents, the frequency and consequences of a stroke make drug therapy appropriate in many patients with VHD.[2]

NATIVE VALVE DISEASE

Antithrombotic therapy among individuals with native valve disease (defined as VHD in absence of PHV or mitral stenosis) is based on the presence of concomitant risk factors (Fig. 53–1). The most common risk factors for thromboembolism include atrial fibrillation (AF) and left ventricular systolic dysfunction.

ATRIAL FIBRILLATION

Nonvalvular AF has been defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.[3] Multiple randomized controlled trials have demonstrated the clinical benefits of antithrombotic therapy with either warfarin or aspirin compared with placebo or no treatment in reducing ischemic events among individuals with "nonvalvular" atrial fibrillation. Based on a meta-analysis of over 28,000 patients comprising 29 trials, adjusted-dose warfarin therapy was associated with a 60% and 40% reduction in ischemic stroke compared with placebo and antiplatelet therapy, respectively.[4] Antiplatelet therapy alone reduced the risk by 20%.[4] The addition of clopidogrel to aspirin further reduced ischemic events, including stroke, among patients with atrial fibrillation who were unsuitable for vitamin K antagonist therapy,[5] but was inferior to warfarin in warfarin-eligible patients.[6] Data from contemporary trials have shown that there has been a significant reduction in stroke event rate over the past two decades as a result of greater time spent in therapeutic anticoagulation (stroke or systemic embolism rate of 1.66% per year).[7] The benefits of anticoagulation are graded, increasing as the risk for ischemic stroke increases. Multiple risk stratification schemes exist for guiding clinicians in assessing stroke risk among individuals with nonvalvular atrial fibrillation, but currently the CHA 2DS2-VASc is preferred as it has a broader range and includes a larger number of risk factors.[3] In summary, warfarin is recommended in any atrial fibrillation patient who has had a stroke/transient ischemic attack/systemic embolus. It is also recommended in those with a CHA 2DS2-VASc score ≥ 2. For patients with a CHA 2DS2-VASc of 0, no antithrombotic therapy is needed; for those with a score of 1, either aspirin or an oral anticoagulant may be considered.[3] The newer oral anticoagulants (dabigatran, apixaban, rivaroxaban) are not indicated for atrial fibrillation associated with rheumatic MS, mechanical or bioprosthetic heart valve, or after mitral valve repair.[2,3] Post-hoc analysis of the ARISTOTLE trial found that one-fourth of the study population had at least moderate valvular disease (excluding more than mild mitral stenosis)[8] whereas 14% of the patients in the ROCKET-AF trial had significant valvular disease (without hemodynamically significant MS).[9] In both of these analyses, the efficacy of apixaban and rivaroxaban was similar to that of warfarin in reducing stroke and systemic embolism among patients with valvular heart disease. As such, the newer oral anticoagulants may be considered as an alternative to warfarin in patients with valvular heart disease (mild to moderate severity) with atrial fibrillation without MS/PHV/MV repair with consideration given to the cost, tolerability, and patient preference and the fact that definitive trials in this subset are awaited.[10]

Patients with MS (of any severity) with AF increase the risk of stroke 17-fold (as compared to nonvalvular AF, which increases the risk fivefold).[10] Anticoagulation with warfarin is indicated in patients with MS with AF irrespective of the severity.[2]

LEFT VENTRICULAR DYSFUNCTION

Among clinically stable individuals with left ventricular dysfunction, the rate of thromboembolism ranges from 1% to 3% per year.[11] This risk may be partially attributable to blood stasis and hypercoagulability. The WARCEF trial found no significant overall difference between warfarin and aspirin among patients with LV dysfunction in sinus rhythm.[13] Although ischemic stroke was reduced with warfarin therapy, this was offset by increased risk of major hemorrhage. Given the sufficiently low rates of thromboembolism, there is no compelling indication for the use of warfarin or aspirin in patients with LV dysfunction without a specific indication (eg, atrial fibrillation, thromboembolism, or CHADS2 score ≥ 2).[12]

TABLE 53–1. Valve Disease and Antithrombotic Therapy

Prevention of thromboemboli should be addressed each time a patient with valve disease is seen.
Lifelong antithrombotic therapy is required in patients with atrial fibrillation (paroxysmal, persistent, or permanent).
Warfarin therapy is required in all patients with a mechanical prosthesis.
Antithrombotic therapy should be started early after valve surgery.
The choice of the anticoagulation regimen during pregnancy should be made after a thorough discussion with the patient.
Antithrombotic therapy should be individualized during noncardiac surgery and cardiovascular procedures.

PREVIOUS THROMBOEMBOLI

A thromboembolic event defines patients who are at high risk for having a recurrent event in clinical situations unrelated to valve disease (eg, in patients with atrial fibrillation, MS, or a PHV). It is unclear whether this is true in patients with native valve disease, but lifelong warfarin therapy should be considered if there are no contraindications to its use.

HYPERCOAGULABLE CONDITIONS

Hypercoagulable states clearly increase the risk of venous thrombosis. The most common are the factor V Leiden and prothrombin gene mutations, defects in protein C, protein S, or antithrombin, and many malignancies. Less is known about their effect on the incidence of thromboemboli related to valve disease, but their presence is a reason to more strongly consider anticoagulation.

OTHER POTENTIAL THROMBOEMBOLIC RISK FACTORS

Beyond an assessment of left ventricular systolic dysfunction, the use of transthoracic and transesophageal echocardiography to determine which patients are at risk of thromboemboli is not yet well defined. Left atrial enlargement or thrombi, a patent foramen ovale, an atrial septal aneurysm, or spontaneous echocardiographic contrast are occasional findings of concern. The value of treatment based on these findings remains unproven.

Both mitral and aortic valve calcifications are associated with an increased risk of stroke, coronary events, and cardiovascular mortality.[14-18] Further, mitral annular calcification is associated with increased risk for the development of conduction system disease, atrial fibrillation, and mitral valve disease.[18] To date, however, there have been no formal trials to assess the efficacy of antithrombotic therapy in reducing stroke risk among patients with calcified valvular lesions in the absence of other known indications for oral anticoagulation. Based on the increased embolic risk among such individuals, however, low-dose aspirin (75-100 mg/d) or clopidogrel (75 mg/d) is reasonable in the presence of calcific mitral or aortic valve disease that is complicated by systemic embolism, stroke, or transient ischemic attack.[19, 20]

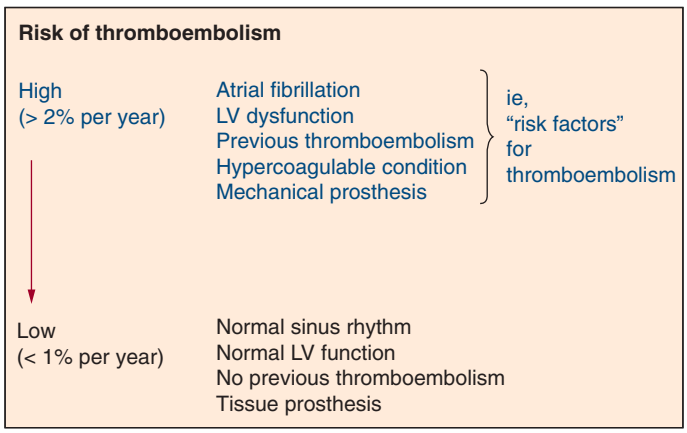

FIGURE 53–1. Risk of thromboembolism. Clinical variables define valve disease patients as being at high or low risk of thromboembolic events. LV, left ventricle.

PROSTHETIC HEART VALVES

Thromboembolic risk and antithrombotic therapy for PHV vary based on type of valve (bioprosthetic or mechanical), valve position (aortic or mitral), time from surgery, and other stroke risk factors. In general, embolic risk is greater for mitral compared with aortic PHVs[2,19,21] and is also higher in the first few days and months after surgery prior to full endothelialization of the sewing ring.

MECHANICAL VALVES

Observational data from patients with mechanical PHV in the aortic or mitral position or both suggest that the incidence of valve thrombosis, major embolism, and total embolism in the absence of anticoagulation approaches 1.4, 4.0, and 8.6 per 100 patient-years, respectively, with an approximate doubling of embolic risk associated with mitral versus aortic prosthetic valves.[22] With warfarin, this risk is reduced to 0.2 (OR: 0.11; 95% CI: 0.07 to 0.2), 1.0, and 1.8 (OR: 0.21; 95% CI: 0.16 to 0.27) per 100 patient-years respectively With aspirin alone, these figures are 1, 1.4, and 7.5 events per 100 patient-years, respectively, indicating inadequate protection. Thrombogenicity of mechanical valves is greatest for caged-ball valves, followed by tilting-disk valves and bileaflet valves.[21] To date, no randomized trials have compared initial bridging with unfractionated heparin (UFH) versus low molecular weight heparin (LMWH) after surgery for mechanical PHV replacement.[19] The use of LMWH is off-label in patients with mechanical prosthetic valves. Based on nonrandomized and observational data, LMWH may be a efficacious alternative to bridging with unfractionated heparin in the immediate postoperative period,[23] but a meta-analysis of 23 studies including 9534 patients noted higher bleeding rates with early bridging therapy with LMWH.[24] A reasonable approach is to initiate bridging therapy with unfractionated heparin after surgery, once hemostasis is secure (usually within 24-48 hours). The activated partial thromboplastin time (aPTT) should be maintained at a "therapeutic effect" level (Table 53–2) until warfarin therapy has achieved the recommended INR level.[2]

Anticoagulation with VKA with INR monitoring is recommended for all patients with a mechanical heart valve.[2] For patients with mechanical aortic valve replacement (AVR) (bileaflet or current-generation single tilting disc) and no risk factors for thromboembolism, the recommended target INR is 2.5 (range 2-3).[2] A target INR of 3 (range 2.5-3.5) is recommended for patients with mechanical mitral valve replacement (MVR), combined AVR and MVR, older-generation mechanical AVR (ball-in-cage), and those with mechanical AVR with additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions).[2]

TABLE 53–2. Therapeutic Effect of Heparin

Unfractionated heparin	An aPTT at 8 h after a dose that has been calibrated[a] to reflect a heparin level of 0.35 to 0.7 anti-factor Xa units
LMW heparin	An aPTT at 8 h after a dose that has been calibrated[a] to reflect a heparin level of 0.7 to 1.1 anti-factor Xa units

[a]Calibration of aPTT to heparin levels is performed in each clinical laboratory; thus, the time (number of seconds) of the aPTT reflecting the therapeutic effect levels will vary.

During pregnancy, aPTT levels do not accurately reflect heparin levels. Anti-factor Xa levels should be 0.4 to 0.7 at 8 hours after a dose of unfractionated heparin and 0.8 to 1.2 U/mL 4 to 6 hours after LMW heparin. .

aPTT, activated partial thromboplastin time; LMW, low molecular weight.

A systematic review found that adjunctive therapy with aspirin in addition to oral anticoagulation was associated with a reduction in overall mortality and thromboembolic events among patients with mechanical PHV at the cost of increased bleeding.[25] This increased risk of bleeding was not seen among low-dose aspirin trials (aspirin 100 mg/d) (OR: 0.96, 95% CI: 0.60 to 1.55, $P = 0.87$). On the other hand, the effectiveness of low-dose aspirin (100 mg/d) was similar to that of higher-dose aspirin. Accordingly, the addition of low-dose aspirin (< 100 mg) is recommended by the American College of Cardiology and American Heart Association for all patients with mechanical valves.[2] The ESC 2012[26] guidelines are more selective and recommend the addition of low-dose aspirin in mechanical valve patients with concomitant atherosclerotic disease or after thromboembolism despite adequate INR. The ACCP guidelines[19] recommend low-dose aspirin only if the risk of bleeding is low. Clopidogrel may be considered if aspirin cannot be taken.

The importance of anticoagulation variability on long-term outcomes was demonstrated by Butchart and colleagues[27] in a prospective study involving more than 1400 patients who underwent single-valve replacement with a tilting disk (Medtronic Hall, Minneapolis, MN) prosthesis. Anticoagulation variability emerged as the strongest independent predictor of survival; patients whose INR levels were therapeutic < 70% of the time experienced a 32% reduction in survival compared with those whose levels were therapeutic at least 80% of the time. One method to improve the quality of oral anticoagulation control is INR self-monitoring and adjustment.[28] Meta-analysis have shown a significant reduction in the rate of thromboembolic complications but not in major bleeding or overall mortality.[29,30] Advantages of this strategy over conventional laboratory-based methods include improved patient compliance, convenience, and greater frequency of monitoring. However, as compared to the routine laboratory-based monitoring, self-testing was associated with only a modest increase in the time in therapeutic range.[30] There was a significant improvement in patient satisfaction and quality of life.[31] Despite the clear benefits of INR self-management, barriers to widespread implementation of such programs include increased cost and patient training and education. More than one half of the patients in various RCTs had to be to excluded from self-management because of physical limitations, lack of competence with the device, or patient refusal.[28]

The use of newer anticoagulants that are direct inhibitors of factor II or factor X (dabigatran, rivaroxaban, apixaban) is contraindicated in patients with mechanical prosthetic valve.[2,26] The RE-ALIGN trial[32] evaluated three doses of dabigatran (150, 220, or 300 mg twice daily based on kidney function) versus warfarin (INR 2-3 or 2.5-3.5 as per thromboembolic risk) among 252 patients who had undergone mechanical AVR or MVR. The trial was terminated prematurely because of excess thromboembolic (9% vs 5%) and bleeding events (27% vs 12%) among patients in the dabigatran group.

BIOPROSTHETIC VALVES

Thromboembolic risk associated with bioprosthetic valves appears to be greatest in the first 3 months after implantation.[33] The risk is greater after mitral valve surgery. Based on this risk, antithrombotic therapy with a vitamin K antagonist is recommended for first 3 months after bioprosthetic MVR or mitral valve repair to achieve an INR of 2.5 (range 2.0 to 3.0).[2,26] After 3 months, the tissue valve and the repaired valve can be treated as native valve and anticoagulation discontinued. Anticoagulation needs to be continued in those with associated risk factors for thromboembolism: AF, previous thromboembolism, hypercoagulable condition, or severe LV dys function (EF < 0.3). For bioprosthetic AVR, the need for anticoagulation for the first 3 months has been challenged because of the low risk of thromboembolism in these patients (albeit greater than in the normal population). Most centers use low-dose aspirin 75-100 mg/day (class IIA).[26] However, one large observational registry of 4075 patients undergoing isolated bioprosthetic AVR demonstrated significant reduction in the risk of stroke and cardiovascular death without a significant increase in the risk of bleeding among patients treated with VKA versus those without.[34] Anticoagulation with VKA (to achieve an INR of 2.5) may still be reasonable for the first 3 months after bioprosthetic AVR[2] (class IIb). After the first 3 months, low-dose aspirin (75-100 mg/d), should be continued indefinitely for bioprosthetic AVR or MVR and mitral valve repair patients[2] because this is associated with a reduction in thromboembolic events compared with no antithrombotic treatment.[35]

For patients undergoing transcatheter aortic valve replacement, clopidogrel 75 mg daily is recommended for the first 6 months after the procedure along with lifelong low-dose aspirin (75-100 mg daily).[2] For patients with atrial fibrillation, the use of VKA with a single antiplatelet agent (low-dose aspirin) is recommended.[36] Development of transcatheter valve thrombosis (clinical or subclinical) should lead to initiation of anticoagulation therapy.[37,38]

SPECIAL CLINICAL SITUATIONS

ALTERED NATIVE VALVES

Valve disease is treated increasingly by interventional catheter techniques or surgical valve repair. The recommendations given for treatment of native valve disease would seem most applicable in such patients; that is, antithrombotic treatment depends on associated stroke risk factors. Data on thrombotic complications after the Ross procedure are limited, but the risk seems low, and the recommendations for a biologic valve seem reasonable.[39]

Following percutaneous edge-to-edge repair for mitral regurgitation using the Mitra-Clip device, aspirin (325 mg/d) is recommended for 6 months along with clopidogrel (75 mg/d) for 30 days after the procedure.[40] After percutaneous balloon mitral/aortic valvuloplasty, no specific antithrombotic therapy is recommended unless it is needed for another indication (eg, left atrial thrombus, atrial fibrillation).

NONCARDIAC SURGERY

The risk of bleeding during surgery for a patient while on antithrombotic therapy has to be weighed against the thromboembolic risk caused by stopping the therapy. This should take into account the

type of surgical procedure; risk factors for thromboembolism; and the type, location, and number of mechanical valves.[2] In a worst-case scenario (mechanical valve with previous thromboembolism), the risk of embolus is 0.08-0.16% if VKA therapy is stopped for 3 days,[41] Although antithrombotic therapy must be individualized, some generalizations apply. For procedures where bleeding is unlikely or would be inconsequential if it occurred, antithrombotic therapy should not be stopped. This can apply to surgery on the skin, dental prophylaxis, or simple treatment for dental caries.[2] Eye surgery, in particular surgery for cataracts or glaucoma, is usually associated with very little bleeding; many ophthalmologists do not alter antithrombotic therapy.

For patients with bileaflet aortic valve and no risk factors for thromboembolism, the risk of stopping VKA for a few days is small and these patients do not need bridging therapy. VKA is stopped 2-4 days before surgery, to allow the INR to fall < 1.5 when surgery can be safely performed. Once bleeding risk allows (usually 12-24 hours after surgery) VKA is restarted.[2]

For patients with mechanical MVR, older-generation AVR (ball-in-cage valve, eg Starr Edwards valve), and mechanical AVR with other risk factors for thromboembolism (AF, previous thromboembolism, hypercoagulable condition, LV systolic dysfunction (LVEF < 30%), or > 1 mechanical valve), bridging anticoagulation with intravenous UFH or subcutaneous LMWH is recommended to reduce the risk of adverse effects.[2] VKA is stopped 2-4 days before surgery. When the INR falls to < 2.0, intravenous heparin infusion or weight-adjusted LMWH (twice daily) is initiated. This is stopped 4-6 hours (for IV UFH) or 12 hours (for LMWH) before surgery. Once bleeding risk allows (usually 12-24 hours after surgery), a VKA is restarted. Bridging heparin after surgery needs to be individualized depending on the bleeding risk and risk of thrombosis. The use of LMWH allows outpatient bridging but has the disadvantage of partial anticoagulation reversal with protamine, a long half-life, and is contraindicated in those with severe renal failure.

If a patient is taking aspirin, it should be discontinued 7 days before the procedure and restarted as soon as it is considered safe by the surgeon. Clopidogrel and ticagrelor should be stopped 5 days before the procedure whereas prasugrel should be stopped 7 days in advance.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Urgent cardiac catheterization procedures can be performed in patients taking warfarin. For nonurgent cases, warfarin should be stopped 72 hours before cardiac catheterization so that the INR is < 1.8 (for femoral access) or < 2.2 (for radial access) at the time of the procedure,[42] and restarted the same day after the procedure for patients who are at low risk for thromboembolism. For patients at high thromboembolic risk, heparin should be started 48 hours before the procedure and continued until warfarin is resumed and the desired INR is achieved. Of note, the European guidelines advocate avoidance of interruption of VKAs (but not NOACs) in elective PCI (with radial access as the preferred option) in order to avoid the bleeding or ischemic complications associated with bridging therapy.[43] A post hoc analysis of the WOEST trial[44] found that uninterrupted oral anticoagulation (periprocedural INR 2.5) was not associated with excess bleeding complications and tended to have reduced major adverse cardiac events as compared to bridging therapy. In patients who are scheduled to undergo transseptal puncture, all antithrombotic therapy should be discontinued, and the INR should be < 1.2 prior to the procedure.[41]

CORONARY ARTERY STENTS IN PATIENTS WITH VALVE DISEASE

Dual antiplatelet therapy (DAPT) with aspirin and a thienopyridine (eg, clopidogrel, prasugrel) is superior to oral anticoagulation for preventing stent thrombosis in patients following percutaneous coronary intervention (PCI) with stent implantation.[45] On the other hand, oral anticoagulation is superior to DAPT for the prevention of thromboembolic events in patients with atrial fibrillation and mechanical valves.[46,47] Hence patients with a compelling indication for anticoagulation (eg, mechanical valves, MS with AF, CHA2DS2-VASc score ≥ 2), undergoing PCI require triple therapy with aspirin, clopidogrel, and an oral anticoagulant (VKA in case of mechanical valve and MS with AF).[43,48] Triple antithrombotic therapy with aspirin, clopidogrel, and warfarin increases the bleeding risk with increasing duration.[49] In order to balance the ischemic and bleeding complications, certain recommendations with general consensus have been made[43,48]: (1) the duration of triple therapy must be kept as short as possible; (2) low-dose aspirin (< 100 mg) should be used; (3) the use of prasugrel or ticagrelor as part of triple therapy should be avoided; (4) prophylactic proton pump inhibitor use is recommended to reduce GI bleeding; (5) a lower target INR of 2-2.5 is recommended; and (6) for patients with a low risk of bleeding (HAS BLED score ≤ 2), the newer generation drug-eluting stents (DES) are recommended in preference to bare metal stent (BMS), given that the former are associated a lower risk of restenosis and stent thrombosis. For patients with a high risk of bleeding (HAS BLED score > 2), the choice of stent between a BMS and DES should be individualized. A BMS is preferred if the risk of bleeding is very high and the risk of restenosis low.

The optimal duration of triple therapy depends on the clinical setting (stable CAD or ACS), the risk of stent thrombosis, and the risk of bleeding.[38,43] For stable coronary artery disease (CAD), patients undergoing PCI with a high bleeding risk (HAS BLED score > 2), triple therapy (oral anticoagulants, aspirin 75-100 mg daily, and clopidogrel 75 mg daily) is recommended for 4 weeks followed by dual therapy with an oral anticoagulant and clopidogrel 75 mg/d (or alternatively, aspirin 75-100 mg/d) up to 12 months.[50] For patients at low bleeding risk (HAS BLED score ≤ 2), the minimum duration of triple therapy is 4 weeks (not to exceed 6 months depending on risk of stent thrombosis with 6 months recommended for ACS)[51] followed by dual therapy with oral anticoagulant and clopidogrel 75 mg/d (or alternatively, aspirin 75-100 mg/d) up to 12 months. The WOEST trial[50] compared dual therapy (VKA plus clopidogrel alone) to triple therapy (VKA plus aspirin and clopidogrel) in 573 patients taking long-term OAC who received a coronary stent. The primary outcome of any bleeding was significantly reduced in the dual therapy arm without any increase in the rate of thrombotic events (stent thrombosis). Further, there was a significant reduction in the all-cause mortality (secondary end point) at 12 months in the dual therapy arm. On the other hand, the ISAR TRIPLE trial,[51] which randomized 614 patients with an indication for oral anticoagulation to either 6 weeks or 6 months of triple therapy with aspirin, clopidogrel, and warfarin, followed by double therapy with aspirin and warfarin thereafter, found no difference in the primary end points of death, myocardial infarction, definite stent thrombosis, stroke, or thrombolysis in myocardial infarction (TIMI) major bleeding at 9 months. There was no difference in the individual end points either. However, Bleeding Academic Research Consortium (BARC) type ≥ 2 bleeding was reduced in the dual therapy arm.[51]

After 12 months, stable CAD patients may be managed with oral anticoagulants alone. But in the case of mechanical valves, the addition of low-dose aspirin to anticoagulant therapy has been shown to be beneficial in the long term and is recommended. In select cases such as left main stenting, proximal bifurcation stenting, or proximal LAD stenting, clopidogrel 75 mg/d may be preferred over low-dose aspirin for the long term treatment.

PREGNANCY

Pregnancy with a mechanical heart valve constitutes the WHO risk class III (significantly increased risk of maternal mortality or severe morbidity).[52] Pregnancy is associated with alterations in hemostasis and coagulability that increase the risk of thromboembolic events among women with mechanical PHVs.[53] Estimates of maternal mortality range from 1%[53] in developed countries to 3% in emerging countries,[54] with most deaths attributable to thrombotic complications. The possibility of fetal toxicity and changes in dose requirements of antithrombotic agents during pregnancy further complicate management decisions in this high-risk population. The primary objective should be to prevent the occurrence of valve thrombosis and its lethal consequences for both the mother and the fetus.[52] There is no ideal anticoagulation regimen. Anticoagulation options are (1) use of VKA (warfarin) throughout pregnancy with switch to UFH at 36 weeks; (2) use of UFH/LMWH restricted to the first 6-12 weeks, followed by warfarin up to 36 weeks with a switch to heparin; and (3) use of UFH/LMWH throughout pregnancy.[2,52,55,56] The last regimen is usually not favored, as continuous use of UFH/LMWH throughout pregnancy markedly increases the risk of prosthetic heart valve thrombosis (PHVT).

Warfarin crosses the placenta and is associated with teratogenicity, increased incidence of spontaneous abortion, prematurity, stillbirth, and fetal bleeding (including cerebral hemorrhage).[57] Embryopathy resulting from in utero exposure to warfarin appears to be greatest during the first trimester, particularly between weeks 6 and 12 of gestation. The risk of warfarin-associated embryopathy appears to be dose-related. The incidence is < 3% with a daily dose of ≤ 5 mg but increases to > 8% with a warfarin dose of > 5 mg/d.[58,59] Some centers have used acenocoumarol (a coumarin derivative) with a very low incidence of warfarin-related embryopathy.[60] With respect to valve thrombosis and thromboembolism, warfarin given throughout pregnancy is the safest option.[61] UFH does not cross the placenta and is considered a safer alternative to warfarin in terms of fetal adverse effects (no teratogenicity or fetal bleeding), but it may be less efficacious in reducing maternal thromboembolic risk compared with warfarin.[61] Heparin is preferably given as an intravenous infusion rather than subcutaneous injections. Prolonged exposure to heparin is associated with thrombocytopenia and osteoporosis. Given the short half-life of heparin and the change in its volume of distribution during pregnancy, frequent dose adjustments and higher doses may be needed. There is also the added risk of intravenous line infection, which may rarely lead to prosthetic valve infective endocarditis.

In the absence of controlled clinical trials, current recommendations are based on limited, observational data. In a systematic review comprising 24 studies of over 900 pregnant women with mechanical PHVs, Chan and colleagues[61] evaluated maternal and fetal outcomes according to the type of antithrombotic regimen used during pregnancy: oral anticoagulants alone, oral anticoagulants substituted with heparin during the first trimester, heparin throughout pregnancy, or antiplatelet agents alone. Results from this analysis (Table 53–3) suggested that warfarin is more efficacious than unfractionated heparin for thromboprophylaxis of pregnant women with mechanical PHVs but is associated with an increased risk of embryopathy. Warfarin therapy throughout pregnancy is recommended for patients with a daily dose requirement of < 5 mg/d and for those who at are at very high risk of thromboembolism (older generation mitral valve prosthesis or those with previous history of thromboembolism).[2]

LMWHs offer several advantages over unfractionated heparin with longer half-life, greater bioavailability, and more predictable anticoagulant response. During pregnancy, LWMHs do not cross the placenta and have a lower incidence of osteopenia and thrombocytopenia compared with unfractionated heparin.[62] Previously, several authors had reported fatal valve thrombosis in pregnant women receiving weight-adjusted LMWH alone.[63,64] Of late, there have been a number of reports of successful pregnancies using dose-adjusted LMWH (twice daily) according to anti-Xa levels (see Table 53–3).[65,66] Using this approach, the rates of valve thrombosis and spontaneous abortions are lower than UFH.[2] The dosage requirement of LMWH may increase by as much as 50% over the course of pregnancy. Hence frequent dose adjustments are needed. There remain some unresolved questions—the Optimal anti-Xa levels, the importance of peak vs trough levels, the best time interval for monitoring anti-Xa level, and the optimal timing of dosage (twice a day or three times a day). In the absence of monitoring of anti-Xa levels, LMWH should not be used.[2,62]

TABLE 53–3. Frequency of Fetal and Maternal Complications by Anticoagulation Regimen During Pregnancy

Anticoagulation Regimen	Congenital Fetal Anomalies	Thromboembolic Complications
Regimen 1 (oral anticoagulants alone)[a]	35/549 (6.4%)	31/788 (3.9%)
Regimen 2 (heparin during first trimester/ oral anticoagulants)[a]	6/174 (3.4%)	21/229 (9.2%)
Regimen 3 (heparin alone)[a]	0/17 (0.0%)	7/21 (33.3%)
Regimen 4 (no anticoagulation)[a]	3/92 (3.3%)	26/107 (24.3%)
LMWH throughout pregnancy[66]	0/92	9/92 (9.8%)

[a]Regimen 1, oral anticoagulants throughout pregnancy; regimen 2, heparin during the first trimester followed by oral anticoagulants throughout pregnancy with or without heparin prior to delivery; regimen 3, heparin throughout pregnancy; and regimen 4, no anticoagulants during pregnancy, which includes use of antiplatelet agents alone.

Data from Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: A systematic review of the literature. Arch Intern Med. 2000;160:191-196 and McLintock C. Thromboembolism in pregnancy: Challenges and controversies in the prevention of pregnancy-associated venous thromboembolism and management of anticoagulation in women with mechanical prosthetic heart valves. *Best Pract Res Clin Obstet Gynaecol*. 2014;28:519-536.

The decisions on the choice of anticoagulation should be made by both the physicians and patient, who needs to be fully informed of the potential risks and benefits associated with the various therapeutic options.[52]

Current guidelines recommend frequent monitoring of anticoagulation therapy during pregnancy irrespective of the antithrombotic regimen chosen.[2,52,56] INR should be measured weekly. For mechanical MVR, older-generation AVR, and those with risk factors for thromboembolism the target INR should be 3 (range 2.5-3.5). For patients with a bileaflet aortic valve and no risk factors for thromboembolism, the recommended target INR is 2.5 (range 2-3). Low-dose aspirin (75-100) is recommended for pregnant patients with either mechanical or bioprosthetic valves in the second and third trimester. The dose of unfractionated heparin should prolong the 6-hour postinjection aPTT to at least twice the control. Recommendations on LMWH suggest twice-daily administration to achieve an anti-factor Xa level of 0.8 to 1.2 U/mL 4 to 6 hours[2] after injection performed every 1-2 weeks.[52,62]

Delivery should be planned so that the mother does not enter labor in a fully anticoagulated state, which would increase the risk of severe maternal hemorrhage and place the neonate at risk of intracranial hemorrhage (in case of VKA).[52] A switch from VKA to UFH/LMWH is done at 36 weeks. LMWH is switched to UFH 36 hours before planned delivery. UFH is discontinued 4-6 hours before planned delivery and restarted 4-6 hours after delivery if there are no bleeding complications. Vaginal delivery is preferred. Catheter placement for epidural

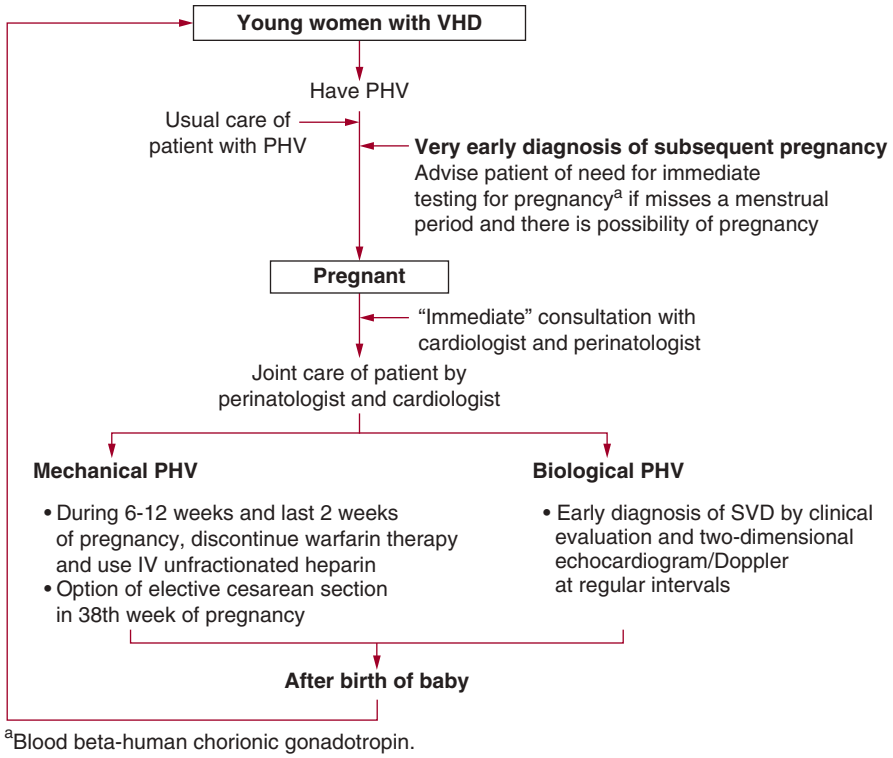

FIGURE 53–2. Management of a woman with a prosthetic heart valve (PHV) at time of pregnancy. IV, intravenous; SVD structural valve deterioration; VHD, valvular heart disease.

anesthesia is not advisable within 12 hours of the last LMWH dose because of the risk of spinal or epidural hematoma. VKA can be restarted on same day of an uneventful vaginal delivery and after 1-2 days in those with caesarean section. A complete switchover to VKA should be done in-hospital. VKA is safe during breast feeding, as warfarin is highly protein bound and not readily detectable in breast milk.

In case of an emergency delivery with the patient on UFH/LMWH, protamine is used to reverse the effect of heparin although it only partially reverses the anticoagulant effect of LMWH (60%-80%). If emergency delivery occurs with the patient on VKA, the neonate is at risk of intracranial hemorrhage during vaginal delivery. Hence caesarean section is recommended.[52] Prothrombin complex concentrates or fresh frozen plasm is administered to achieve an INR < 2. A management algorithm for pregnant women with PHV is outlined in Fig. 53–2.[67]

THERAPY AT THE TIME OF A THROMBOEMBOLIC EVENT

ACUTE MANAGEMENT

For eligible patients with ischemic stroke (cardioembolic stroke), presenting within 3 hours of stroke onset, administration of intravenous recombinant tissue plasminogen activator (tPA, 0.9 mg/kg) is recommended.[68] This therapy is not recommended if the INR > 1.7 or PT > 15 seconds for patients on anticoagulation or for those with current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests.[68] The therapeutic window has been extended to up to 4.5 hours but with additional exclusion criteria: patients > 80 years old, those taking oral anticoagulants regardless of INR, those with a baseline National Institutes of Health Stroke Scale (NIHSS) score > 25, those with imaging evidence of ischemic injury involving more than one-third of the middle cerebral artery (MCA) territory, or those with a history of both stroke and diabetes mellitus are excluded.[68] Intra-arterial fibrinolysis can be administered up to 6 hours after stroke onset, and can be used for those with contraindications for IV thrombolysis (eg, oral anticoagulation).[68] Urokinase has been well studied for this indication. Recently, a number of trials have shown the superiority of mechanical thrombectomy (using stent retrievers) over intravenous thrombolytic therapy.[69-71] Mechanical thrombectomy (with stent retrievers) is recommended up to 6 hours after stroke onset.[72] They have the added advantage that they may be used in those with contraindications for fibrinolytic therapy (eg, oral anticoagulants, newer oral anticoagulants). They had better recanalization rates of up to 58% to 88%[69-71] as compared to 30%[73] with intravenous tPA (for MCA territory).

There is much debate regarding the optimal timing for initiating or continuing anticoagulants in patients in whom an embolus is the presumed cause of a stroke. The risk of early stroke recurrence has to be balanced against the risk of hemorrhagic transformation following the initiation of anticoagulation. Other potential benefits of early anticoagulation include prevention of deep vein thrombosis and coronary events. The risk of cardioembolic stroke recurrence within 2 weeks is in the range of 0.3-0.5% per day.[68] The risk of symptomatic hemorrhagic transformation (HTr) ranges from 3% to 5%[74,75] (asymptomatic HTr is more common[75]). This risk is greater with larger infarcts. A meta-analysis of seven randomized controlled trials[74] (4624 patients) of anticoagulation in acute cardioembolic stroke did not find any reduction in risk of recurrent stroke or mortality but was associated with excess intracranial bleeds. Current guidelines do not recommend urgent anticoagulation for the prevention of early stroke recurrence or halting neurological worsening (class III recommendation) in view of the risk of HTr.[68] This was evident in a large prospective study of 1029 consecutive cardioembolic stroke patients, which found that the best time to initiate anticoagulation is 4 to 14 days after stroke onset.[75] On balance, it seems preferable to withhold therapy for at least 72 hours.

If a computed tomography (CT) scan at that time reveals little or no hemorrhage, heparin should be administered to maintain an aPTT at the lower end of the therapeutic level until warfarin, started at the same time, results in the desired INR. If the CT scan demonstrates significant hemorrhage, antithrombotic therapy should be withheld until the bleed is treated or has stabilized.

The optimal timing for the resumption of anticoagulation after intracranial hemorrhage (ICH) is also uncertain.[76] Previous guidelines indicated that anticoagulation could be restarted after 7-14 days.[77] A large retrospective study of 234[78] patients with warfarin related ICH found that the risk of rebleeding with early resumption of anticoagulation exceeded the risk of thromboembolism from withholding it, whereas with later resumption, the opposite was true. The authors suggested a delay of at least one month after ICH, and found that the combined risk of ischemic plus hemorrhagic stroke was minimized when anticoagulation was reinitiated after ≈10 weeks.[78]

LONG-TERM MANAGEMENT

If the embolic event occurs when a patient is off antithrombotic therapy, long-term warfarin therapy is required. If the embolic event occurs while the patient is on adequate antithrombotic therapy with the following parameters, the therapy should be altered as follows[41]:

- If on warfarin with INR of 2.0 to 3.0: increase dose to achieve an INR of 2.5 to 3.5.
- If on warfarin with INR of 2.5 to 3.5: increase dose to achieve an INR of 3.5 to 4.
- Not taking aspirin: initiate aspirin at 75-100 mg/d.
- If on warfarin with INR of 2.5 to 3.5, plus aspirin 75 to 100 mg/d: aspirin dose may also be increased to 325 mg/d.
- If on aspirin alone: aspirin dose may be increased to 325 mg/d and/or clopidogrel 75 mg/d may be added. Patients with a bioprosthetic valve with embolic events on aspirin (75-100 mg/d) may need consideration for anticoagulation with VKA.

Embolism occurring after this medical approach should lead to consideration of possible valve surgery if the valve is the likely source of the thrombus.

EXCESSIVE ANTICOAGULATION

Most patients with an INR above the therapeutic range can be managed by withholding warfarin and following the level of anticoagulation with serial INR determinations. Excessive anticoagulation (INR > 5.0) greatly increases the risk of hemorrhage. However, rapid decrease in INR can lead to the INR falling below the therapeutic level and increase the risk of thromboembolism. For patients with an INR between 5 and 10 who are not bleeding, most patients can be managed by withholding VKA and serial INR monitoring (without administration of vitamin K).[2,28] For patients with an INR > 10 without bleeding, in addition to holding VKA, oral vitamin K (2.5 mg) is recommended.[2,28] Once the INR returns to therapeutic range, warfarin therapy can then be restarted and dose-adjusted appropriately.

For patients who present with serious/life-threatening bleeding (eg, intracranial hemorrhage), irrespective of INR elevation, immediate reversal of anticoagulation using prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) to achieve an INR < 1.5 after 30 minutes is recommended.[2,28,79] In addition, slow infusion of IV vitamin K (5-10 mg) is given to sustain the effects of these products because of their relatively short half-lives. IV vitamin K may, very rarely, cause anaphylaxis. Four-factor PCC (II, VII, IX, and X) (25-50 U/kg) is preferred over FFP (15-30 mL/kg).[79] Four-factor PCC can completely reverse the coagulopathy within 10 minutes but is expensive. FFP is inexpensive and widely available, but has the disadvantage of transfusion reactions, risk of transmitting infections, preparation times, and the need to administer large volumes. The data for use of recombinant factor VIIa in VKA-associated bleeding are limited and this is currently not recommended.[2,28,79]

When bleeding occurs, especially with the INR in the therapeutic range, the presence of an underlying occult lesion needs to be ruled out (GI tract, urinary tract).[26]

THROMBOSIS OF PROSTHETIC HEART VALVE

Prosthetic heart valve thrombosis (PHVT) is a potentially life-threatening complication occurring in inadequately anticoagulated mechanical valve patients. This is rare in developed countries (0.3%-1.3% per patient-year) but frequent in developing countries (6.1% per patient-year).[2,80] Patients may be asymptomatic or may present with worsening dyspnea, cardiogenic shock, or thromboembolic events. Clinical examination may reveal muffling of the valve click and appearance of a new regurgitant/obstructive murmur. Differentiation of thrombus versus pannus is required, as thrombolytic therapy is ineffective in the latter. Diagnostic workup for patients with suspected PHV thrombosis begins with a transthoracic echocardiogram.[2,26] Most will also benefit from transesophageal echocardiography (TEE), which allows superior visualization of valve and valve motion along with a more precise measurement of thrombus size and differentiation between thrombus and pannus (Fig. 53–3A). Cinefluroscopy is a readily available, noninvasive imaging modality to visualize mechanical valve motion (Fig. 53–3B). It does not enable differentiation between a thrombus and pannus. CT scan is another promising modality for the three-dimensional visualization of mechanical valve and also enables differentiation between a thrombus and pannus.[2]

If a patient has a thrombotic obstruction of a right-sided PHV, fibrinolytics are the first choice of therapy because they are successful in 80% to 100% of treated patients.[2,19,26]

The optimal therapy for left-sided PHVT includes surgery (thrombectomy or valve replacement), fibrinolytic therapy, or heparin. There are no randomized trials comparing these modalities and all modalities are associated with a high risk. A meta-analysis[80] of seven observational studies comparing surgery with thrombolytic therapy that included 690 episodes of left-sided PHVT (73% in NYHA III/IV) found no difference in mortality (13.5% vs 9%), but surgery was associated with greater restoration of normal valve function (90% vs 70%), lower rates of thromboembolism (1.4% vs 16%), lesser major bleeding (1.4% vs 5%), and recurrent prosthetic valve thrombosis (7% vs 25%) compared to thrombolytic therapy.

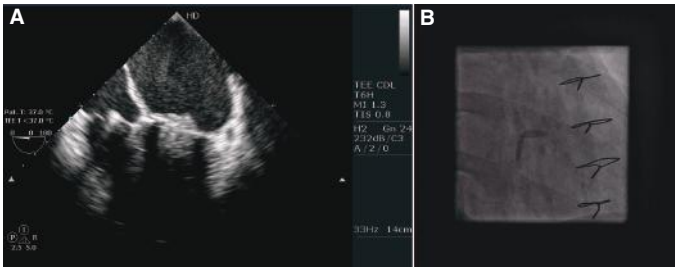

FIGURE 53–3. A. Transesophageal echocardiography showing a large thrombus on mitral valve. **B.** Cinefluoroscopy showing one stuck leaflet (lower).

Another meta-analysis[81] of 44 studies with 2302 patients found greater mortality with surgery as compared to fibrinolytic therapy (18% vs 6.6%). This meta-analysis included single-arm (fibrinolytic therapy or surgery alone) as well as comparative studies unlike the previous meta-analysis that included only comparative studies. The stroke rate, success rate, and bleeding rates were similar with both therapies whereas embolic events were greater in the fibrinolytic arm. The lack of randomized trial data has contributed to disagreement among the guidelines issued by various international bodies.[2,19,26,82] The ACC/AHA 2014[2] valvular heart disease guidelines recommend emergency surgery (class 1 recommendation) for left-sided PHVT with moderate to severe (NYHA 3-4) symptoms. Emergency surgery is also preferred in patients with a mobile or large thrombus (> 0.8 cm^2).[36] For patients with mild symptoms (NYHA 1-2) of recent onset (< 14 d) and small thrombus burden (< 0.8 cm^2), an initial trial with intravenous infusion of unfractionated heparin may be given.[2] If this is unsuccessful, fibrinolytic therapy is recommended. Various regimens using tissue plasminogen activator (tPA), streptokinase, and urokinase have been used.[2,83,84] TPA appears to be superior although cost remains a concern in developing countries. During thrombolysis, heparin is withheld. TPA is given in a loading dose of 10 mg followed by 90 mg over 2 hours. A lower dose of 20-mg IV bolus followed by 10 mg/hour for 3 hours may be given in those at increased risk of bleeding. Streptokinase is given in a loading dose of 250,000 units over 30 minutes followed by an infusion of 100,000 units/hour up to 48-72 hours.[83] Another protocol used a loading dose of 500,000 units over 20 minutes with an infusion of 1.5 million units over 10 hours. In case of hemodynamic instability, shorter protocols are recommended (eg, 1.5 million units over 60 minutes).[84] In the event of a successful outcome, fibrinolytic therapy is followed by intravenous unfractionated heparin with vitamin k antagonist to achieve an INR of 3-4 for AVR and 3.5-4.5 for MVR. Low-dose aspirin is also recommended. If thrombolysis is unsuccessful, surgery is recommended. One prospective study noted delayed spontaneous normalization of valve motion in almost half the patients with failed thrombolysis over a mean period of 3 months with intensive anticoagulation.[85] This may be of relevance in low-resource settings in NYHA class 1-2 patients.

The ACCP 2012[19] guidelines recommend early surgery for large thrombus area (≥ 0.8 cm^2) and fibrinolytic therapy for small thrombus area (< 0.8 cm^2).

The ESC 2012[26] guidelines recommend urgent or emergency surgery for obstructive PHVT in critically ill patients who are not at high risk for surgery. Surgery is also recommended for large nonobstructive thrombi > 10 mm complicated by embolism or which persist despite optimal anticoagulation. Fibrinolysis is recommended by the ESC for critically ill patients with serious comorbidities or with severely impaired heart function or if surgery is not immediately available. The Society of Heart Valve Disease[82] takes a contrarian approach and recommends fibrinolytic therapy for all patients with surgery recommended only if lytic therapy has failed or is contraindicated. Finally, it appears that local expertise and resource availability appears to drive the choice of therapy in PHVT.

The risk of thrombosis with bioprosthetic valves after 3 months of implantation is very low. Symptomatic thrombosis after transcatheter aortic valve replacement is also rare (<1%). This has been treated successfully with anticoagulation with heparin followed by VKA.[48,49]

THERAPY AT THE TIME OF A BLEED

With significant bleeding, antithrombotic therapy should be stopped, and if the patient is at risk of further bleeding, drug effects should be reversed.[2] If possible, the cause of bleeding should be corrected, and antithrombotic therapy should be restarted as soon as possible. If this is not possible, treatment decisions are difficult. In patients with a mechanical prosthesis or multiple risk factors for thromboemboli, acceptance of intermittent bleeding with acute management for the bleeds may be necessary. In valve patients who are at lower risk of emboli or in whom the role of antithrombotic treatments is less clear (eg, those with LV dysfunction), it may be optimal to withhold chronic therapy or, if a patient is on warfarin, to switch to aspirin. With mechanical PHVs, consideration should be given to replacing the mechanical valve with a biologic valve in patients who have had multiple, large, life-threatening or organ-threatening bleeds.

ANTITHROMBOTIC THERAPY IN THE PATIENT WITH ENDOCARDITIS

Patients with infective endocarditis (IE) are at a high risk of embolic events (up to 40%) with the brain being the most common site.[86] The routine use of antithrombotic therapy for prevention of thromboembolism is not recommended in patients with IE,[2,19] and may in fact be harmful (with more bleeding).[87] Anticoagulation is recommended for patients with IE who have other indications for anticoagulant therapy[2,19] (eg, mechanical valve, mitral stenosis with AF, AF with a CHADS2 score ≥ 2). At the time of presentation, vitamin K antagonists are replaced with unfractionated heparin or LMWH until it is clear that there is no central nervous system involvement and that invasive procedures will not be required. Once the patient has stabilized without central nervous system involvement, anticoagulation with vitamin K antagonist therapy can be restarted.[19] In the event that a patient with IE does develop signs of CNS involvement (embolism or stroke), anticoagulation is temporarily discontinued irrespective of other indications of anticoagulation for fear of risk of hemorrhagic transformation of infarct.[2]

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CHAPTER 54

MANAGEMENT OF MIXED VALVULAR HEART DISEASE

Blasé A. Carabello

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INTRODUCTION

The 2006 ACC/AHA guidelines for the treatment of valvular heart disease (VHD) were notable for the paucity (0.3%) of the recommendations supported by a level of evidence A—that is, evidence supported by two or more randomized controlled trials (RCTs).[1] Although several RCTs have been published since then and the evidence level supporting the 2014 guidelines improved markedly,[2] there are no RCTs and indeed only limited data-driving management decisions in mixed VHD. In a 230-page document the current guideline devotes scarcely two pages to the topic. The following chapter will summarize some of the modest data that are available.

TRICUSPID REGURGITATION AND LEFT-SIDED VALVE DISEASE

Most tricuspid regurgitation (TR) is secondary to overload caused by left-sided heart disease or by lung disease. Causes of primary TR include blunt trauma such as might occur in a motor vehicle accident, direct trauma from errant myocardial biopsies, carcinoid syndrome (or use of drugs with serotonin similarities), rheumatic heart disease, infective endocarditis, and interference from transvalvular pacing electrodes.

The general rule for treating secondary TR is to optimize therapy for the primary cause. Thus if left-sided heart failure has resulted in pulmonary hypertension with adverse effects on the right ventricle, treatment of heart failure will reduce pulmonary pressure and improve secondary TR. Or if lung disease has created cor pulmonale, therapy to improve pulmonary function is apt. However, this rule may be inappropriate when secondary TR is caused by left-sided valve lesions. Although it has long been hoped that correction of the hemodynamic overload produced by mitral or aortic valve disease would improve secondary TR, the results are unpredictable, with TR sometimes improving, sometimes worsening, and sometimes even arising de novo following left-sided valve surgery.[3-8] Although there is general agreement that severe TR, irrespective of its cause, should be addressed during surgery for left-sided disease, the approach to less than severe secondary TR is the subject of intense controversy. If leaving moderate TR uncorrected results in worsening rather than improvement in TR following successful left-sided surgery, the patient is then consigned either to the consequences of right-sided heart failure despite the correction of the primary valve lesion or to a second operation to address the residual TR, which has had an unusually variable and sometimes high mortality rate in reports of small series.[3,9,10] The variable response of TR to correction of left-sided valve disease is in part related to the causes and effects of the left-sided disease and its correction. As noted in other chapters, if the left-sided disease is secondary mitral regurgitation, LV dysfunction is almost surely present and is not addressed by mitral surgery, serving as a cause for persistently elevated left- and right-sided chamber pressures, perpetuating TR. Even if pulmonary pressure is reduced by left-sided surgery, left sided cardiac output may be improved in turn increasing right ventricular (RV) volume load.

As shown in Fig. 54–1, the severity of TR (90% of which was secondary) impacted survival. This was true even in the absence of pulmonary hypertension and even when left ventricular (LV) ejection fraction was normal.[11] Thus it would seem logical that preventing TR following left-sided surgery would improve mortality; however, this contention is unproven.

OUTCOMES OF TR CORRECTION DURING LEFT-SIDED SURGERY

It seems clear that tricuspid intervention during left-sided surgery reduces postoperative TR and RV dilatation. However, it has been difficult to show that TR surgery reduces mortality (Table 54–1).[7,12-19] However, lack of mortality benefit might be predicated on surgery that was performed for secondary MR that inherently has a poor prognosis, or from retrospective series that were not designed to detect a mortality difference.

Although tricuspid repair reduces postoperative heart failure and TR, it has increased the risk of postoperative conduction abnormalities, requiring permanent pacemaker implantation in some but not all reports.[16,20]

In summary, *severe* primary and secondary TR is usually corrected during left-sided valve surgery. Most,[7,12-17] but not all,[18] data support addressing *less than severe* TR during left-sided valve surgery. Tricuspid regurgitation is corrected because of unpredictable changes in TR after successful correction of mitral and aortic lesions and for the fear of residual postoperative right-sided heart failure. It is most probably this concern driving an increased rate of tricuspid surgery in the United States today.[21]

TRICUSPID REPAIR VERSUS REPLACEMENT

Although no randomized trial exists, tricuspid valve repair is generally favored over replacement. However, in cases of tricuspid disease where repair is impossible, a prosthetic valve is inserted instead. In a large meta-analysis, 10-year survival (about 60%) was nearly identical for bioprostheses versus mechanical prostheses.[22] As usual,

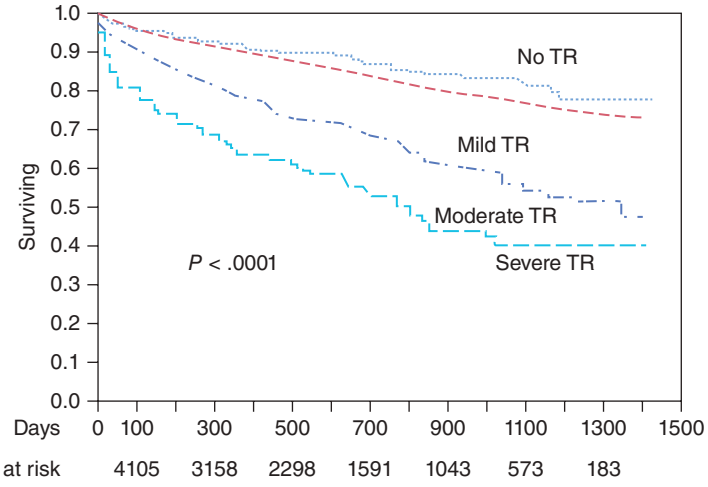

FIGURE 54–1. Survival according to the severity of tricuspid regurgitation is shown. Reproduced with permission from Nath J, Foster E, Heidenreich PA: Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol*. 2004 Feb 4;43(3):405-409.

bioprostheses inserted at an early age were more likely to suffer structural valve deterioration, and patients receiving mechanical valves were more likely to encounter thromboembolic or hemorrhagic complications from over- or under-anticoagulation with vitamin K antagonists.

AORTIC STENOSIS AND MITRAL REGURGITATION

In developed countries, aortic stenosis (AS) is usually the result of an atherosclerotic-like process that does not affect the mitral valve (see Chap. 47) and the pressure overload of AS is usually accompanied by concentric chamber remodeling. When mitral regurgitation (MR) coexists with aortic stenosis (AS), MR is usually secondary to left ventricular (LV) remodeling in which there is also an element of ventricular dilatation or eccentric remodeling that accompanies concentric remodeling. The pressure (P) overload of AS is approximately equal to the transaortic gradient (LVP-AoP). The transmitral gradient is obviously affected by LVP and equals left ventricular minus left atrial pressure. Correction of AS that decreases the transaortic pressure gradient and decreases LVP also decreases the transmitral gradient, reducing the driving pressure propelling blood backward across the mitral valve. Thus it is hoped that correction of AS will concomitantly reduce coexisting MR. Unfortunately this is not always the case, especially when the mitral valve is structurally abnormal, as might occur in rheumatic disease or coincidentally from the presence of independent myxomatous mitral disease. However, although secondary MR often regresses after aortic valve replacement, sometimes MR fails to improve or even worsens after surgical aortic valve replacement (SAVR). There is general agreement that *primary* severe and even *primary* moderate MR should be addressed with either concomitant mitral repair or replacement at the time of surgical AVR. However, the

TABLE 54–1. Comparison of Surgery vs No Surgery for 2° TR

Author	Study Type	Left Op	Indication for TR Op	No. TR Op	No. TR Op	Results
Dreyfus[7]	R, NR	MV Repair	Annular size >70 mm	148	163	Identical survival TR annuloplasty group lower NYHA 1.59 to 1.11. TR increased by 2 grades in 48% of No TR Op group vs 2% in the Op group.
Chan[12]	R, NR R, NR	MVR 1° MR	≥ +2 TR	125	106	Similar survival: Less HF in the repair group. 8% of pts with repair had worsened TR vs 17% who had no repair.
Calafiore[13]	R NR	2° MR	≥ +2 TR	51	59	Adjusted 5-year survival 75% in the treated group vs 45% in the untreated group, although crude survival similar. Progression of TR 5% in the treated group vs 40% in the untreated group.
Navia[14]	R, PM	Multiple	+2 TR	91	91	7% 3-4 + TR in repair group vs 15% in the untreated group.
Kim[15]	R, NR	236	≤ +2	123	113	No diff in mortality or HF/AT 5 years; freedom of severe TR 93% repair vs 61% no repair.
Chikwe[16]	R, NR	645 primary MR	Annular enlargement vs no indication	413	232	No diff in mortality or pacemaker, less late moderate TR in the treatment group and faster return to normal RV function.
Benedetto[17]	RCT	44 mitral surgery	≤ +2 TR	22	22	Moderate to severe TR 28% in untreated vs 0% treated group at 1 year! Greater improvement in 6-minute walk in treated group.
Yilmaz[18]	R, NR	699 10 MR	None	0	699	TR progression post-op very rare and only 1 patient required re-op but 1/3 had at least moderate post-op TR.
Kusajima[19]	R, NR	96	+2 TR MV surgery	47	96	TR decreased early but increased late in patients without TRS. At 10 years no patients with TVS had ≥ +3 TR vs 53.3% without TVS.

HF, heart failure; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; NR, nonrandomized; PM, propensity matched; R, retrospective; RCT, randomized controlled trial; TR, tricuspid regurgitation; TVS, tricuspid valve surgery.

management of less than severe *secondary* MR remains controversial. Absil and associates[23] and Wan and coworkers[24] matched patients with mild versus moderate MR who underwent isolated AVR and found no difference in midterm mortality, and Takeda and colleagues reported similar findings in a study of unmatched patients.[25] Conversely, Countinho and associates found that failure of MR to improve following AVR did impact late survival.[26] Because of the unpredictable behavior of moderate secondary MR following AVR, many surgeons prefer to address secondary MR with at least an annuloplasty at the time of AVR.

The advent of transcatheter aortic valve replacement (TAVR) offers further insights and challenges regarding coexistent MR. In high-risk but operable AS patients, the presence of MR must be considered in the decision of SAVR versus TAVR, because the MR is not addressed directly at the time of TAVR but can be repaired during SAVR. Thus it would be important to be able to predict the fate of MR following TAVR in making AVR decisions. Nombela-Franco and colleagues reviewed the fate of MR in thousands of patients undergoing TAVR[27] (well summarized in Fig. 54–2).[28-40] The most common response was for MR to remain the same following TAVR, whereas MR in some patients improved but worsened in others. Although Toggweiler and coworkers[35] found that MR was more likely to improve when it was secondary, when there was an aortic gradient >40 mm Hg, and when atrial fibrillation was absent, the outcome of MR following TAVR still remains difficult to predict. When surgery is feasible, *severe* MR should be addressed during the operation. Decisions about the management of *moderate* MR are more difficult. If SAVR is performed, *primary moderate* MR is usually corrected during surgery. For *secondary moderate MR*, the course of action is less clear and predicated upon the risk factors noted above and the overall operative risk. It must be recognized that many patients with AS also have systemic hypertension. Failure to treat hypertension following AVR may do little to relieve LV afterload, in turn lessening the probability that MR will improve despite successful surgery.[41]

MIXED AORTIC VALVE DISEASE

Irrespective of etiology, it is unusual for mixed aortic valve disease to have equal components of aortic stenosis (AS) and regurgitation (AR). In rare cases AR is dominant, and thus physical exam should favor AR, producing accentuated carotid upstrokes, a displaced apical beat, and a long diastolic murmur. Imaging should demonstrate ventricular dilatation and the patient should be followed using guideline-directed management for AR (see Chap. 47).

However, in cases of moderate combined AS/AR, the LV behaves much more as it would in pure AS rather than AR, and outcomes resemble those of AS.[42] Aortic regurgitation causes increased systolic flow through the moderately stenotic valve, thereby increasing jet

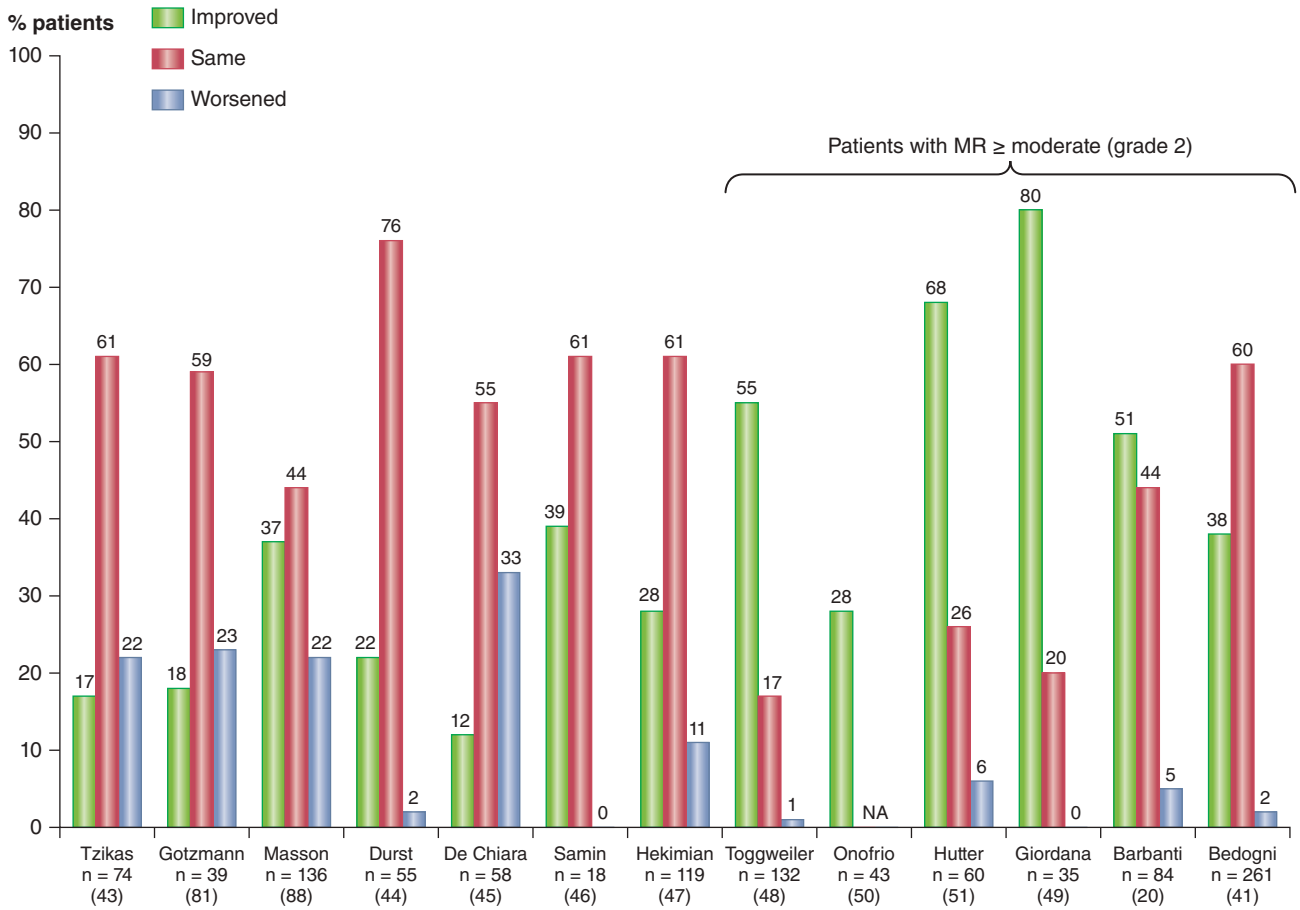

FIGURE 54–2. Fate of mitral regurgitation following TAVR. Reproduced with permission from Nombela-Franco L1, Ribeiro HB2, Urena M, et al: Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. *J Am Coll Cardiol*. 2014 Jun 24;63(24):2643-2658.

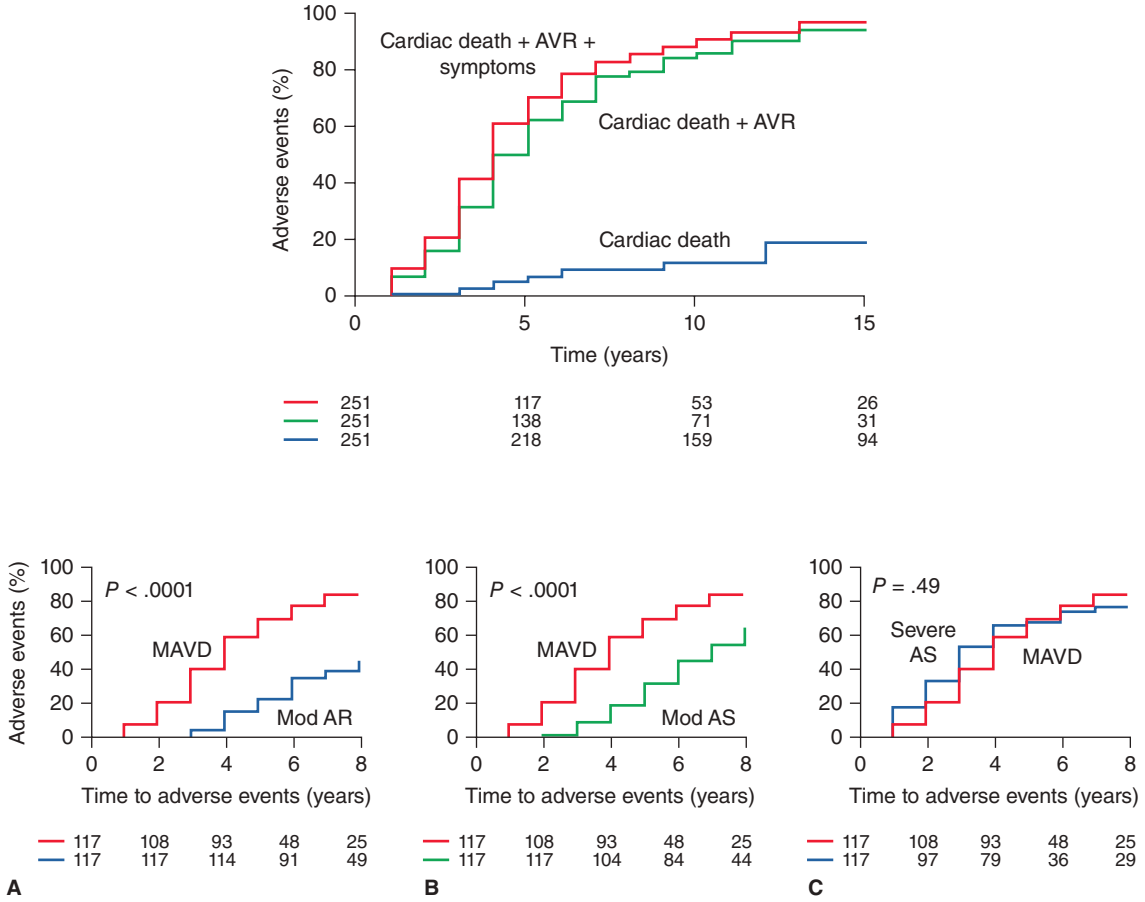

FIGURE 54–3. Outcome over time is demonstrated for patients with mixed aortic valve disease and is plotted in the upper panel. Outcome for mixed aortic valve disease (MAVD) is compared to that of moderate aortic regurgitation (**A**), moderate aortic stenosis (**B**), and severe aortic stenosis (**C**). Outcome for MAVD most closely resembles that of severe aortic stenosis. Reproduced with permission from Egbe AC, Luis SA1, Padang R, et al: Outcomes in Moderate Mixed Aortic Valve Disease: Is it Time for a Paradigm Shift? *J Am Coll Cardiol*. 2016 May 24;67(20):2321-2329.

velocity, pressure gradient, and in tandem, pressure overload on the LV. In turn, the patient and his or her LV respond primarily to the pressure overload. Figure 54–3 demonstrates that outcome for mixed disease compares best with that of severe AS, and substantially worse than moderate AS or moderate AR.[43] Thus management of mixed AS/AR should follow the guideline strategy for managing patients with pure AS. Aortic valve replacement should be performed at symptom onset and might be considered for patients with jet velocity exceeding 5 m/sec or patients with abnormal exercise tolerance tests (see Chap. 47).

MIXED MITRAL DISEASE

Mixed mitral stenosis (MS) and mitral regurgitation (MR) usually occur in the context of rheumatic heart disease. The management dilemma often presented to clinicians is whether the presence of symptoms in a patient with moderate MS and moderate MR is the result of the valve disease, because neither lesion by itself would probably cause symptoms. Further, if the valve is causing symptoms, current guidelines are unclear with respect to management. Thus although symptom onset in VHD is almost always cause for mechanical intervention, moderate disease is not. In such cases, invasive hemodynamics performed at rest or during exercise often clarifies the issue. If exercise generates filling pressures that are high enough to cause the patient's symptoms, it is highly likely that MS/MR is the cause of both the clinical and hemodynamic consequences. Because mitral balloon valvotomy (MBV) is usually contraindicated because it may worsen MR, mitral valve replacement (MVR) is indicated (in the absence of contraindications) for relief of symptoms. Unfortunately no series of such patients is large enough to assess whether MVR would increase longevity.

MITRAL STENOSIS AND AORTIC REGURGITATION

Seen almost always in the setting of rheumatic heart disease, the combination of MS and AR may be confusing, especially by understating the severity of AR.[44] Because MS limits LV in-flow, total LV volumes and the manifestations of volume overload for any degree of AR are lessened, potentially causing underestimation of AR severity both during physical examination and during imaging. If AR appears less than severe and the mitral valve anatomy is amenable to MBV, this procedure can be performed first, followed by standard reevaluation of the patient's AR. Severe AR may become manifest at that time, in turn leading to AVR. If MBV is not feasible and surgery is contemplated, a full qualitative and quantitative assessment of AR severity should be performed and double valve replacement considered if the degree of AR is greater than mild.

MITRAL AND AORTIC STENOSIS

The combination of AS and MS is caused by rheumatic disease in the developing world and by mitral annular calcification and calcific AS in the developed world. In the former, MBV and AVR is the preferred strategy when the mitral valve is suited for MBV. The latter combination is much more problematic. The calcified mitral annulus cannot be balloon-dilated. Therefore double valve replacement with its attendant higher operative risk must be employed, weighing the obvious risks and benefits.[45]

SUMMARY

Treatment of the patient with mixed VHD is fraught by lack of randomized trials to give us guidance. When secondary TR complicates left-sided VHD, there is clearly a trend toward tricuspid annuloplasty at the time of surgery. The risk of performing the procedure in experienced hands is small and seems outweighed by the risk of postoperative TR causing persistent symptoms of heart failure. Likewise, although secondary MR should improve after surgical transcatheter AVR, it often does not, a fact that must be considered in management strategy when both SAVR and TAVR are feasible. Combined moderate AS/AR usually behaves like isolated AS and should be treated accordingly. However little data we have to guide us for treating those lesions, we have even less regarding other types of combined VHD. For those lesions, common sense and clinical judgment tempered by available hemodynamic data should determine therapy.

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SECTION 9

Congenital Heart Disease

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CHAPTER 55

MENDELIAN BASIS OF CONGENITAL AND OTHER CARDIOVASCULAR DISEASES

Ali J. Marian, Ramon Brugada, and Robert Roberts

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ESSENTIALS OF GENETIC DISORDERS

Genetic factors play a significant role in almost all cardiovascular disorders. Genetic defects are responsible for malformations of the heart and blood vessels, which account for the largest number of human birth defects. The estimated incidence of congenital heart disease is approximately 1% of all live births.[1] The prevalence is estimated to be 10-fold higher among stillbirths.[2] Genetic defects are responsible for familial cardiovascular disorders, such as cardiomyopathies, the long QT (LQT) syndromes, as well as sporadic forms of such disorders. Over 3600 genes have been identified to date for single-gene disorders with Mendelian patterns of inheritance. Likewise, genetic factors predispose to common complex phenotypes, such as atherosclerosis and hypertension. Over 4000 loci have been mapped for complex phenotypes. Molecular genetic studies provide the opportunity to decipher the genetic basis and pathogenesis of many disorders, especially cardiovascular diseases. Genetic discoveries have the potential to lead to identification of new targets for the prevention and treatment of human diseases. This is best illustrated in the case of *PCSK9* gene, which was genetically mapped in 2003 as a cause of autosomal dominant hypercholesterolemia.[3] Recently, the discovery led to subsequent development of PCSK9 inhibitors (evolocumab and alirocumab), which are highly effective for treatment of certain forms of hypercholerolemia.[4,5] Partial deciphering of the genetic basis of cardiovascular disease has also ushered in routine genetic testing for various diseases, leading to an accurate genetic-based diagnosis and intervention. Given the rapid pace of genetic discoveries, it is expected that genetic diagnosis and genetic-based interventions will become incorporated into standard practice of medicine in the future. Thus, this chapter provides an overview of the genetic principles, and discusses the genetic basis for

cardiovascular disorders as well as the medical and ethical implications of genetic findings.

THE HUMAN GENOME

A genome is the complete set of the genetic material of each cell or individual: the nuclear and the mitochondrial genomes. The nuclear genome is composed of 3.2 billion base pairs. There are four types of nucleotides in each genome, two of which are purine (adenine, guanine) and two are pyrimidine (cytosine, thymine). The nuclear genome is distributed among 22 pairs of double-stranded autosomal chromosomes and two sex chromosomes (XX in females and XY in males). The sizes of chromosomes vary, with chromosome 1 being the largest at ~250 million base pairs and chromosome 21 the smallest at 48 million base pairs. The nuclear genome contains approximately 20,000 protein-coding genes.[6] A gene has a 5′ transcriptional regulatory region, exons (which contain the protein coding sequence), introns (which are the intervening regions between exons), and the 3′ untranslated region (Fig. 55–1). The nuclear genome also contains several thousands of non–protein-coding genes that get transcribed into noncoding ribonucleic acids (RNAs) including microRNAs and long-noncoding RNAs. About 1% of the genome, which is approximately 300 million base pairs, code for the proteins. More than 50% of the human nuclear genome is composed of repetitive deoxyribonucleic acid (DNA) elements. The functions of the repetitive elements and noncoding regions of the nuclear genome are largely unknown.

Transcription of the nuclear genome is pervasive, as the vast majority of the nuclear genome is transcribed into RNA.[7] The primary transcripts of genes are spliced to exclude introns and produce the messenger RNAs (mRNAs). Splicing of each primary transcript is not uniform and often multiple splice variants are generated with one being the predominant isoform. Each unit of three bases, referred to as a *codon*, encodes a specific amino acid. There are 61 amino acid codons and 3 stop codons in the nuclear genome. Thus, each amino acid has multiple codons.

The second genome in each cell is the mitochondrial DNA (MtDNA). Mitochondrial DNA is a circular DNA, composed of 16,700 nucleotides. It contains 37 mitochondrial genes, which code for 13 protein-coding genes, two ribosomal RNAs, and 22 transfer RNAs.

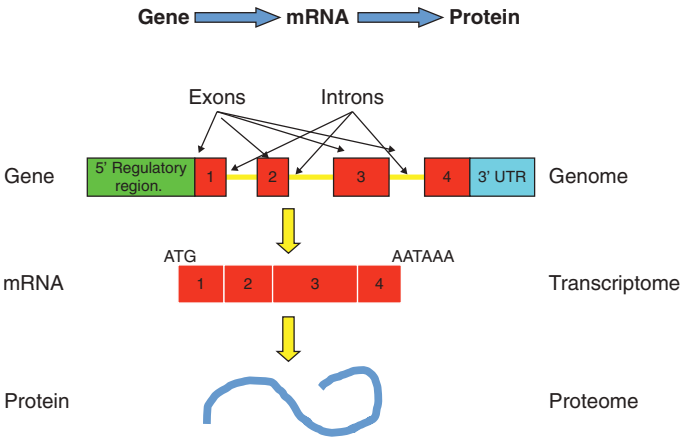

FIGURE 55–1. The cartoon illustrates the flow of information from genes to mRNA to protein. Each gene has a 5′ regulatory region, where transcription factors bind and initiate expression of mRNA. A gene also contains coding segments referred to exons and the intervening sequences referred to as introns. Finally, the 3′ regulatory region in each gene serves as an additional regulatory mechanism. The primary transcript through the process of alternative splicing generates one major and several minor isoforms of each mRNA. Translation machinery synthesizes proteins using the mRNA codons.

Each cell typically contains a large number of mitochondria and each mitochondrion might contain several copies of its genome. The codons are slightly different between nuclear and mitochondrial genomes, as there are 60 codons for amino acid and four stop codons in mtDNA. Likewise, transcription of mtDNA is a contiguous as opposed to discontinuous transcription of the nuclear genome.

BASIS FOR GENETIC TRANSMISSION

All hereditary information is transmitted through nuclear DNA. The gene is the basic hereditary unit. Each individual has two copies of each gene, called *alleles*. The genes are localized in a linear sequence along 23 pairs of chromosomes, comprised of 22 pairs of autosomes (chromosomes 1 to 22) and two sex chromosomes, X and Y. Females have two X chromosomes, whereas males carry one X and one Y chromosome. Each parent contributes one of each chromosome pair (the members of the pair are referred to as *homologous chromosomes*) and thus one copy of each gene. The site at which a gene is located on a particular chromosome is referred to as the *genetic locus*. A given gene always resides at the same genetic locus on a particular chromosome. Therefore, the loci on homologous chromosomes are identical. However, alleles residing at these loci may be identical or different, leading to *homozygous* (identical alleles) and *heterozygous* (two different alleles present at the locus) states.

The genetic information is encoded by the linear sequence of the four bases of the DNA. Translation of this genetic information into a protein is through a "translational code" passed on through mRNA. The transcribed mRNA serves as the template that determines sequence of the amino acids in the resulting polypeptide. Both autosomal chromosomes are usually transcribed into mRNA and translated into protein. However, expression of a gene can be restricted to specific cells and organs. The gene is regulated during the developmental stage because of regulation by cell- and tissue-specific transcription factors and epigenetic factors. In cells that carry two X chromosomes, only one X is active and the other X is silent after early embryogenesis.

CLASSIFICATION OF GENETIC DISORDERS

In general, DNA nucleotide sequences remain stable during transmission to offspring. Nonetheless, because of the rare error rate of DNA replication machinery, occasional base sequence changes do occur. These are referred to as sequence variants or polymorphisms or mutations. Mutations represent stable, heritable alterations in DNA. Mutations may occur in somatic and the germ cells. Somatic mutations, however, are not inheritable. A number of mutagenic factors—such as environmental agents (radiation and chemicals)—can induce mutations. Mutations can involve a visible alteration at the level of the chromosome (chromosomal abnormalities). This can result in the deletion or translocation of a portion of the chromosome, whereby several genes are often eliminated or altered. In contrast, mutations can be restricted to minor alterations in the DNA sequence, which vary from the substitution of a single nucleotide to that of the deletion or addition of multiple nucleotides. Thus, hereditary and congenital diseases are conventionally classified into three broad categories: (1) chromosomal abnormalities, (2) single-gene or monogenic disorders, and (3) polygenic disorders or complex traits.

Chromosomal Abnormalities

Each human cell has two copies of each chromosome (*diploids*). Chromosomes are double stranded and have two arms, referred to as the long, or "q," and the short, or "p," arms. The arms of the chromosomes meet at a primary constriction, referred to as the *centromere*. Mutations

typically occur during DNA replication and meiosis when chromosomes separate. Mutations can involve large deletions, duplications, translocations, and rearrangements. This can result in aneuploidy: too few or too many chromosomes. Chromosomal abnormalities are relatively common during embryonic life and lead to spontaneous abortion, often during the first trimester of pregnancy. However, a significant number of fetuses with chromosomal abnormalities survive. Chromosomal aberrations, numerical or structural, occur in approximately 1 in 150 liveborn infants.[8] Most diseases caused by chromosomal abnormalities are detected in the neonates or infants because of involvement of many genes causing distinctive phenotypes that are easily diagnosed on physical examination. Chromosomal abnormalities often lead to structural heart defects and are found in 5% to 13% of live born children with congenital heart disease.[1,2]

The usual cause for gain of a chromosome is nondisjunction, resulting from failure of a homologous pair of chromosomes to separate during meiosis. When an additional copy of the chromosome is added during fertilization, three copies of the same chromosome (or only one copy) are found in the new zygote instead of the chromosome pair. Two of the most common chromosomal disorders causing heart disease in the adult, namely Down syndrome (trisomy 21) and Turner syndrome (XO), are both commonly caused by nondisjunction. Chromosomal rearrangements occur when a chromosome breaks and rejoins within itself incorrectly, which can result in an inversion of the genetic material. Inversion occurs when a chromosome breaks at two points and the intermediate segment reunites in inverted orientation. Typically, there is no apparent phenotype in persons carrying an inversion, unless it disrupts a gene or its regulatory regions. Isochromosomes are formed when one of the chromosome arms is lost and two long or short arms are joined to form a single chromosome. Chromosome duplications or gains of chromosomal material may also be associated with phenotypic abnormality, but most commonly, they cause no obvious aberration.

Chromosome deletions are large deletions (equal to or greater than 10^6 base pairs) that commonly lead to loss of a large amount of DNA and loss or disruption of multiple genes. Consequently, a series of phenotypes in a single individual may be present as a result of interruptions in a series of genes within the loci of a single chromosome.

Alterations in chromosome structure could lead to structural variations (SVs), which are defined as changes such as inversion, duplication, deletion, and rearrangements. Each human genome also contains several thousand structural variations.[9,10] The size of the structural variations could vary from 2 base pairs, but typically larger than 1 kbp, to several million base pairs. Insertion or deletion structural variations that change the copy number of the genes are commonly referred to as copy number variants (CNVs). Structural variants or CNV are relatively common in the population, but do not necessarily cause a gross phenotype, as typically observed in chromosomal abnormalities. However, structural variations including CNVs play significant roles in susceptibility to complex phenotypes, such as developmental abnormalities associated with congenital heart defects and neurological disorders.

Single-Gene Disorders

A single-gene disorder is an inherited disease caused by a mutation in a single gene (monogenic). Only a small fraction of cardiovascular disorders is monogenic. Single-gene disorders that occur in families are characterized by Mendelian patterns of inheritance (Fig. 55–2). They are classified as autosomal dominant, autosomal recessive, or X-linked (dominant or recessive). The majority of monogenic diseases exhibit an autosomal dominant mode of inheritance. In an autosomal dominant disease, approximately half of the members of the family carry the causal mutation and are affected. Monogenic disorders

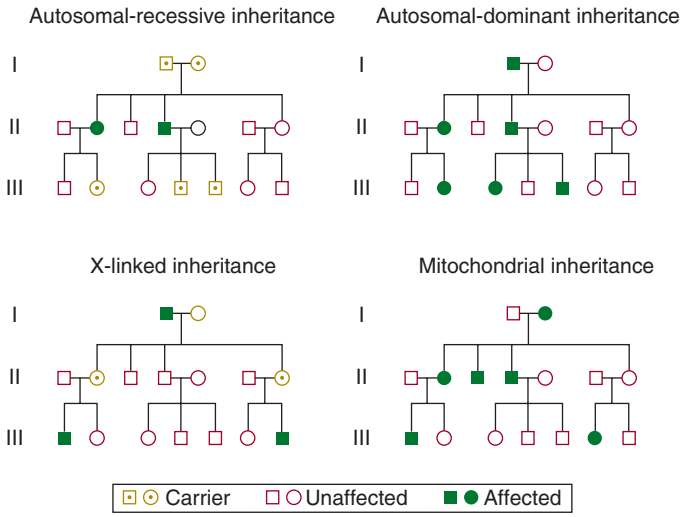

FIGURE 55–2. This typical set of pedigrees outlines the usual inheritance patterns for autosomal dominant and recessive traits, X-linked inheritance, and mitochondrial inheritance. *Squares* signify males; *circles* signify females. Filled-in circles and squares are affected females and males, respectively.

with an autosomal recessive inheritance are caused by mutations in both copies of the gene. Therefore, in a given family only 25% of the offspring exhibit the phenotype, 50% carry the mutation, and 25% are normal. In X-linked inheritance, males exhibit the disease and females are usually free of the phenotype but carry the mutation. However, if the mutation involves a major protein, the effect of the mutation may be dominant and females can exhibit the clinical phenotype. There is also no father to son transmission in X-linked inheritance. In diseases caused by mitochondrial DNA mutations, inheritance is from the mother (no male-to-male transmission), because mitochondrial DNA is predominantly inherited from the ovum.

The DNA mutation could give rise to a change in the corresponding amino acids of the encoded protein and exerts its deleterious effects via functional alterations. A change in even one amino acid located in a critical domain of the protein can enhance the function (gain-of-function mutation) or impair the function (loss-of-function mutation), with a concomitant change in the clinical phenotype. On average, a mutation occurs every 1.2×10^8 nucleotides during meiosis, resulting in about 30 to 50 de novo variants in each offspring.[11,12] Only mutations occurring in the gametes (male or female germ cells) are transmitted.

In single-gene disorders, a mutation in a single gene typically causes the disease. However, various factors including genetic variants other than the causal variant affect phenotypic expression of the disease. Genetic factors that influence phenotypic expression of the disease are called the modifier genetic variants. Modifier genes and the environmental factors are major determinants of phenotypic expression of a single-gene disorder. Typically, penetrance (proportion of the mutation carriers showing the phenotype) is less than complete and given the age-dependent penetrance of single gene disorders, young mutation carriers might not express the disease. Occasionally, diseases that are conventionally known as single-gene disorders are digenic or oligogenic in origin as two or more mutations in the given gene or in multiple genes cause the phenotype.

Common Polygenic Disorders

Polygenic disorders such as coronary artery disease (CAD) and systemic arterial hypertension are caused by the stochastic and nonlinear interactions of the genetic and environmental factors. In this setting,

the presence of a single variant is neither sufficient to cause a disease nor its absence prevents development of the disease. Essentially, all of the common disorders have a genetic predisposition, which is imparted by the genetic variants. Polygenic disorders account for the majority of the cardiovascular diseases, including atherosclerosis, hypertension, obesity, diabetes mellitus, and peripheral arterial disease. In polygenic diseases, multiple genes predispose to the condition, each contributing modestly. The genetic variants associated with complex diseases are typically single nucleotide variants (SNVs), which are also called single nucleotide polymorphisms (SNPs). SNVs are distributed throughout the human genome with a frequency of about 1 per 800 base pairs (bps).[13-15] Thus each genome contains about 4 million SNVs. The vast majority of these variants have negligible biological effects and are clinically insignificant.[16,17] A fraction of SNVs are functional variants and contribute to the pathogenesis of common complex diseases. The effects of SNPs could confer protection against or susceptibility towards a complex phenotype. Technological advances since 2005 have provided the opportunity to perform genome-wide association studies (GWAS), which has led to the mapping of thousands of loci predisposing to polygenic diseases, including coronary artery disease (discussed later in this chapter).

CLASSIFICATION OF MUTATIONS

Most human diseases exhibit *genetic heterogeneity*, defined as being caused by different genes and mutations causing the same phenotype. The heterogeneity may arise from multiple mutations in one gene (*allele heterogeneity*) or in two or more genes (*locus heterogeneity*). Within any one family, however, typically there is one causal gene and mutation in all affected members; uncommonly there are two different causal mutations or genes transmitted for the same disease in a given family. A good example is familial hypertrophic cardiomyopathy (HCM), which involves more than a dozen different genes (locus heterogeneity) with multiple mutations in each (allelic heterogeneity). In less than 10% of the cases, HCM is caused by double or triple mutations.[18,19]

Mutations can involve a microscopically visible alteration, such as deletion or translocation of a portion of the chromosome (chromosomal abnormalities), or a minute change in the DNA sequence, such a change from adenine (A) to guanine (G), resulting in a change in the amino acid sequence. Mutations involving only a single nucleotide are known as *point mutations* and are responsible for 70% or more of all adult single-gene disorders (http://www.hgmd.cf.ac.uk/). A point mutation may be a substitution of one nucleotide for another, changing the amino acid sequence (*missense mutation*); or it may change from encoding an amino acid to become a stop codon, which will truncate the protein (*truncated* or *nonsense mutation*); or it may eliminate a stop codon so the protein is elongated (*elongated mutant*). Finally, it may change the codon without changing the amino acid sequence (*synonymous mutation*). All genes during transcription (synthesis of a RNA from a DNA template) and translation (synthesis of a protein from a messenger RNA template) are read from 5′ to 3′ orientation (see Fig. 55–1), with each triplet of bases (*codon*) coding for a specific amino acid. If a nucleotide is deleted (*deletion*) or an additional one is inserted (*insertion*), it will shift the reading frame. The resulting protein would be entirely different (*frameshift mutation*) and usually nonfunctional. If a purine nucleotide is substituted for a pyrimidine or vice versa, the mutation is referred to as a *transversion*. If purine or pyrimidine substitutes for another purine or pyrimidine, respectively, it is called a *transition*. Other mutations may result from the deletion or addition of several nucleotides. In one form of myotonic dystrophy, for example, a triplet repeat of several thousand nucleotides in length is inserted into the 3′ end of the gene. Another type of mutation is known as a *gene conversion*, where two genes interact and part of the nucleotide sequence of one gene becomes incorporated into that of the other. Mutations in genes exert their deleterious effects via a structural alteration of the protein that has functional consequences, as noted.

GENETIC PENETRANCE AND EXPRESSIVITY

Penetrance is defined as the percentage of individuals within a family who have inherited the causal mutation and have one or more features of the disease. Penetrance is an all-or-none phenomenon. Any manifestation, however minute, indicates that the gene has penetrance in that individual. *Nonpenetrance* refers to lack of any observable phenotype. This feature is distinct from *expressivity*, which refers to the variable nature of the clinical phenotype, such as the severity. Thus, by definition, to have expressivity, the trait must be penetrant. Numerous genetic and environmental factors can affect expression of a gene, making it nearly impossible to determine which factor is most important in a specific individual or disease. Table 55–1 shows these factors.

PATTERNS OF INHERITANCE

Inherited disorders caused by a single abnormal gene are transmitted to offspring in a predictable fashion termed *Mendelian transmission*. As previously noted, each individual has two copies of each gene, referred to as alleles, one transmitted from each parent. Per Mendel's first law, each of the two alleles, located on separate chromosomes, segregates independently and is transmitted unchanged to offspring. Thus, the chance of inheriting the mother's allele versus the father's is 50%. Mendel's second law states that genes on the same chromosome also assert themselves independently through the process of crossover between segments of chromosomes (discussed below). The greater the distance between two loci, the more likely they are to be separated during genetic transmission. Mutant genes located on any of the 22 autosomal pairs or the 2 sex chromosomes may produce phenotypes inherited by simple patterns classified as autosomal (dominant or recessive) or X-linked, respectively. The terms *dominant inheritance* and *recessive inheritance* refer to characteristics of the phenotype. Dominant inheritance implies that a person with one copy of a mutant allele and one copy of the normal allele develops the phenotype associated with the mutant allele. Recessive traits, on the other hand, require both alleles to be mutant in order to produce a phenotype.

TABLE 55–1. Factors Affecting the Phenotype in Genetic Disorders

1. Causal genes and mutations including multiple mutations
2. Modifier genes (genetic background)
3. Age
4. Gender
5. Exogenous or environmental factors such as exercise or diet
6. Maternal and paternal factors
7. Epigenetic alterations (such as DNA methylation)
8. Posttranscriptional and posttranslation modifications of proteins (such as phosphorylation, acetylation, and ubiquitinylation)
9. Gene–gene (epistasis) and gene–environmental interactions
10. Noncoding RNAs including microRNAs and long noncoding RNAs

Autosomal Dominant Inheritance

Dominant disorders are those exhibiting a phenotype in heterozygous individuals, as noted. Males and females are equally affected, and offspring of an affected heterozygote have a 50% chance of inheriting the mutant allele (see Fig 55–2). In a sporadic case, the mutation occurs *de novo* and in one of the germ lines of parents (typically sperm). By definition, it is absent in the somatic cells (cells other than the germ cells) of parents. Autosomal dominant inheritance can be misdiagnosed as sporadic if there is low expressivity in the phenotypically normal parent carrying the mutant allele or if extramarital paternity has occurred. Table 55–2 lists the features characteristic of autosomal dominant inheritance.

Autosomal Recessive Inheritance

Autosomal recessive phenotypes are clinically apparent when the patient carries two mutant alleles (ie, is homozygous) at the locus responsible for the disease (see Fig. 55–2). The disease-causing gene is found on one of the 22 autosomes. Thus, both males and females are equally affected. Clinical uniformity is typical and disease onset generally occurs early in life. Recessive disorders are more commonly diagnosed in childhood than are dominant diseases. On average, only 1 in 4 children (25%) will be affected (see Table 55–2).

X-Linked Inheritance

X-linked inherited disorders are caused by defects in genes located on the X chromosome. Because females have two X chromosomes, they may carry either one mutant allele (heterozygote) or two mutant alleles (homozygote). The trait may therefore display dominant or recessive expression. Males have a single X chromosome (and one Y chromosome). Consequently, a male is expected to display the full syndrome whenever he inherits the abnormal gene from his mother. Hence, the terms *X-linked dominant* and *X-linked recessive* apply only to the expression of the gene in females. Because a male must pass on his Y chromosome to all male offspring, no male-to-male transmission in X-linked disorders can occur. On the other hand, a male must contribute his one X chromosome to all daughters (see Fig. 55–2). All females receiving a mutant X chromosome are known as *carriers*, and

TABLE 55–2. Characteristic Features of Patterns of Inheritance

A. Autosomal dominant transmission
   1. Each affected individual has an affected parent unless the disease occurred because of a new mutation or the heterozygous parent has low expressivity.
   2. Equal proportions (ie, 50–50) of normal and affected offspring are likely to be born to an affected individual.
   3. Normal children of an affected individual bear only normal offspring.
   4. Equal proportions of males and females are affected.
   5. Both sexes are equally likely to transmit the abnormal allele to male and female offspring, and male-to-male transmission occurs.
   6. Vertical transmission through successive generations occurs.
   7. Delayed age of onset.
   8. Variable clinical expression.

B. Autosomal recessive transmission
   1. Parents are clinically normal (in alternate generations) but genetically are heterozygotes.
   2. Alternate generations are affected, with no vertical transmission.
   3. Both sexes are affected with equal frequency.
   4. Each offspring of heterozygous carriers has a 25% chance of being affected, a 50% chance of being an unaffected carrier, and a 25% chance of inheriting only normal alleles.

C. X-linked transmission
   1. No male-to-male transmission.
   2. All daughters of affected males are carriers.
   3. Sons of carrier females have a 50% risk of being affected and daughters have a 50% chance of being carriers.
   4. Affected homozygous females occur only when an affected male and carrier female have children.
   5. The pedigree pattern in X-linked recessive traits tends to be oblique because of the occurrence of the trait in the sons of normal carriers but not in the sisters of affected males (ie, uncles and nephews affected).

D. Mitochondrial transmission
   1. Equal frequency and severity of disease for each sex.
   2. Transmission through females only, with offspring of affected males being unaffected.
   3. All offspring of affected females may be affected.
   4. Extreme variability of expression of disease within a family (may include apparent nonpenetrance).
   5. Phenotype may be age-dependent.
   6. Organ mosaicism is common.

those who become affected clinically with the disease are known as *manifesting female carriers*. Table 55–2 lists the characteristic features of X-linked inheritance. Examples of X-linked disorders of the heart include X-linked cardiomyopathy, Barth syndrome, and Duchenne, Becker, and Emery-Dreifuss muscular dystrophies.

Mitochondrial Inheritance

Spermatocytes contribute few or no mitochondria to the zygote. The entire mitochondrial DNA in an embryo is derived from the mitochondria already present in the cytoplasm of the oocyte. Thus, phenotypes caused by mitochondrial DNA mutations demonstrate only maternal inheritance (see Fig. 55–2). Table 55–2 lists the characteristic features of mitochondrial inheritance.

CHROMOSOMAL MAPPING IN SINGLE-GENE DISORDERS

To locate a particular gene, one must first map the chromosomal locus, which requires knowledge of certain chromosomal landmarks, referred to as *DNA markers*. A DNA marker is a polymorphic sequence of DNA with a known chromosomal position, which can be detected by analyzing an individual's DNA. Initial genetic linkage studies were performed using short tandem repeat (STR) DNA markers. In recent years, SNPs have been used for genetic linkage. The typical SNP linkage panel contains several thousands SNPs that are positioned throughout the genome with an average distance of approximately 0.5 Mbp. Genetic distance is measured in terms of centimorgans (cMs), named after the geneticist T.H. Morgan. One cM approximates 1 million bp (Mbp). DNA markers like genes have two alleles in a given individual and are transmitted to offspring according to Mendel's law, with the individual being heterozygous or homozygous for that marker. If a marker is homozygous, it is not informative for genetic linkage, as one cannot track cosegregation of the maternal or paternal copy of the marker with the disease. When all of the markers are placed together on each chromosome and the genetic distance between them is estimated, a *genetic map* is produced.

Identification of a particular locus is made possible by showing that the causal gene of interest is in close proximity to a DNA marker on the same chromosome, a method referred to as *genetic linkage analysis*. A fundamental requirement for linkage analysis is a family in which the disease of interest is transmitted to offspring over at least two and preferably three generations. At least six affected individuals are required for analyzing cosegregation of DNA markers with inheritance of the disease, although a larger number of affected individuals would be preferable.[20]

Family History and Evaluation

The most important part of an evaluation for genetic disease is the family history. It may give clues to the diagnosis of a particular phenotype and inheritance patterns within an individual family. For instance, an individual's ethnic background may suggest the need for specific types of genetic screening, such as for hemoglobinopathies in individuals of African or Mediterranean ancestry or for Tay-Sachs disease in individuals of eastern European (Ashkenazi) Jewish ancestry. The individual with the medical problem who brought the family to the attention of the physician is referred to as the *proband* or *propositus* (*proposita* for females) or index case. Information should generally be collected on all individuals who are first-, second-, or third-degree relatives of the proband. A pedigree chart is then generated. This information should include medical problems and pregnancies. If relatives are deceased, the age at death and the cause of death should be recorded. With a pedigree chart and specific family information, general questions are asked, including whether other family members have the same or similar problems. Information is sought about various types of birth defects, early infant deaths, miscarriages, stillbirths, or other diseases or handicaps in the family. With some disorders, there may be a variability of a particular condition (ie, clinical heterogeneity), even within a family. A pregnancy history may provide information to support a possible teratogenic exposure. Pregnancy and family histories can then be used in conjunction with the findings on physical examination to derive a potential etiologic diagnosis and to plan for further diagnostic studies. The term *etiologic diagnosis* should suggest whether a specific cardiac defect is familial (by family history), genetic but not familial (sporadic), teratogenic (by pregnancy history), or multifactorial. Prognosis and recurrence risk are linked strongly to an accurate diagnosis and its probable etiology. In sum, accurate phenotypic characterization is essential for all genetic studies.

Concept of Genetic Linkage Analysis

Despite the independent assortment of chromosomes and genes during meiosis, genes (alleles) on two or more loci in close proximity to each other are often coinherited. Two loci that coinherited more than 50% of the time are considered genetically linked. To map the chromosomal locus responsible for a causal gene, DNA markers that are evenly distributed across the chromosomes are selected. DNA is collected from all members of a family (normal and affected) and genotyped for the selected markers. If a DNA marker is coinherited with the phenotype in the affected individuals, the chromosomal locus where the DNA marker resides is in close physical proximity to the locus of the causal gene. This is referred to as *genetic linkage* between the disease (causal gene) and the DNA marker. Figure 55–3 illustrates the concept of linkage analysis. The odds for and against linkage are calculated using computational algorithms. Linkage exists if the odds in favor of linkage are at least 1000:1. Commonly, the logarithm of the odds, referred to as the *LOD score* (log of the odds), is used and a LOD score of 3 or greater indicates linkage. A LOD score of –2 (ie, 10^2 or 100:1 odds against linkage) excludes the linkage. The likelihood of two genes being separated by recombination increases in proportion

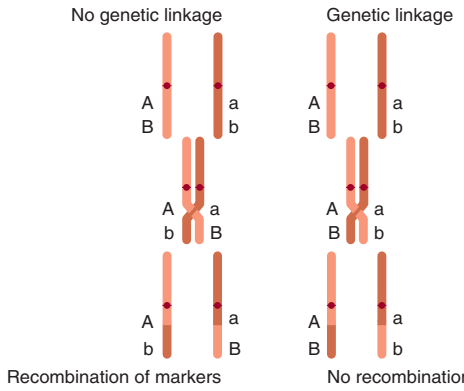

FIGURE 55–3. Linkage analysis. Shown in the left panel is an illustration of genetic linkage between a locus for a DNA marker and that of a disease that is inherited in a Mendelian dominant fashion. The locus, designated with an "A," carries the allele responsible for the disease. The corresponding locus, "a," on the homologous chromosome, has the allele that codes for the same protein but has not undergone a mutation and is thus the normal allele. The loci designated "B" and "b" represents alleles of a DNA marker of known location that has nothing to do with the disease. In the right panel, the disease and the marker loci are so close that they tend to be coinherited within the family. In contrast, in the left panel, the "A" and "b" loci are so far apart that recombination and crossover occurs between the two markers; thus they segregate independently.

to the distance between them. The distance between a marker and a disease-causing gene when genetically linked is quite variable and may be anywhere from 1 to 50 Mbp but is usually within 1 to 10 Mbp. Thus, the inherent resolution of genetic linkage analysis is not better than 1 million base pairs Mbp.

It is possible on the basis of linkage analysis alone to construct a chromosomal map of all of the DNA markers, with the distance between the various markers estimated in centimorgans. This is a complex calculation derived from the number of recombinations between the DNA markers during meiosis. The recombination frequency between two markers, two genes, or a gene and a marker is the ratio of the number of crossover events to the total number of meioses. The lower the recombination frequency between the locus of a DNA marker and that of a disease-causing gene, the closer those two are in physical distance on the chromosome. However, despite the close physical proximity of the loci of the DNA marker and the disease-causing gene, recombination still may occur. The extent to which recombination does occur reflects roughly the physical distance between the two loci. The recombination fraction (or *theta*) is used to develop a means of estimating the genetic distance (in centimorgans) between genetically linked loci. A recombination frequency or crossover of 1% between two loci, whether occupied by two genes or one gene and a DNA marker, reflects a physical distance of approximately 1 cM between them. For a marker and a gene separated by 1 cM, this means the chance of a crossover between them during meiosis is only 1%; thus, the chance of their being coinherited is 99%. This is a statistically derived genetic map, however, and the distances are only approximate.

Identification of the Gene and Causal Mutation

Once the chromosomal location of a gene has been mapped, the first technique in attempting to identify the gene is referred to as the positional *candidate gene approach*. There are about 20,000 genes in the genome. Known genes in the mapped chromosomal region are sequenced as candidate genes that contain the causative mutation. If none of the candidate genes in the region is shown to have a mutation that cosegregates with the disease, it may be necessary to clone the region. This approach is referred to as *positional cloning*, so named because a region is cloned knowing only its position relative to the genetically linked DNA markers. Positional cloning is usually unnecessary as most genes in the human genome have been mapped and identified. However, if attempted, it is necessary to reduce the region (containing the gene) to 1 cM or less. It is often necessary to expand the family with the hope of finding crossovers such that DNA markers common to all affected would span only a short distance (< 1 cM). The cloned genes or PCR-amplified DNA is then analyzed, commonly by direct sequencing, for the presence of the mutation. With the advent of massively parallel sequencing, often referred to as Next Generation Sequencing, typically the entire exome and even the genome is sequenced in all family members and the sequence variants are used in the linkage analysis.[21] To strengthen the causality, the mutation must be shown to co-segregate with the disease and not with the unaffected members in the family. In addition, it is crucial to show that the variant is absent in large number of normal individuals with the same ethnic background and hence, it is not a polymorphism. Finally, to support the causality, *in vivo* and *in vitro* functional studies are necessary. Table 55–3 summarizes the approach to chromosomal mapping of hereditary diseases by linkage analysis and subsequent isolation of the gene.

TABLE 55–3. Chromosomal Mapping and Gene Identification in Single-Gene Disorders

1. Identification of a family with a familial disease.
2. Collection of clinical data from the family.
3. Clinical assessment to provide an accurate diagnosis of the disease using a consistent and objective criterion to separate normal individuals from those affected and from those who are indeterminate or unknown.
4. Collection of blood samples for immediate DNA analysis from several family members of at least three generations.
5. Development of lymphoblastoid cell lines for a renewable source of DNA.
6. Development of a family pedigree.
7. DNA analysis for markers of known chromosomal loci that span the human genome in an attempt to find a marker locus linked to the disease.
8. Identification of the gene.
9. Identification of mutation(s) causing the disease.
10. Demonstration of a causal relationship between the mutant gene and the disease.
11. Development of a convenient test to screen for the mutation.

GENETIC COUNSELING PRINCIPLES

Genetic counseling should provide information about the diagnosis, possible etiology, and prognosis of a disease, as well as genetic-based interventions. In addition, psychosocial issues, reproductive options, and the availability of prenatal diagnosis should be discussed. Genetic counseling should be nondirective, providing information in a nonjudgmental, unbiased manner. The family should then be able to make decisions based on medical information in the context of their religious, moral, cultural, and social backgrounds and their financial situation. Although a genetic counselor may occasionally feel frustrated with a specific couple's decision, an effective counselor does not let personal biases interfere with the counseling role. Conflicts leading to major ethical issues and disputes may arise, however, and may be particularly apparent regarding issues of nonpaternity, sex selection, pregnancy termination, and selective nontreatment of malformed infants. Couples have many potential reproductive options, but not all may be acceptable religiously or culturally. Nevertheless, potential options should be mentioned in a sensitive manner. A common misunderstanding among families in genetic counseling is the issue of prenatal diagnosis and its relationship to abortion. Prenatal diagnosis does not imply that a parent should or would terminate the pregnancy. In many circumstances the information from prenatal diagnosis may help to reassure a couple that their risk of having another handicapped child is, in fact, much lower than expected. Conversely, if defects are found, the subspecialist may use more diagnostic approaches to make rational decisions about medical management of the infant prior to or immediately after delivery.

The accelerated pace of progress in gene discovery, molecular medicine, and molecular diagnostics has begun to allow for improved genetic counseling and portends the possibility of genetic-based therapies.[22] As knowledge about the genetic basis of disease grows, however, so does the potential for discriminatory health insurance policies to exclude individuals who are at risk for an illness or to charge prohibitively high rates on the basis of predetermined illness. For this reason, planners of the Human Genome Project recognized the need to protect individuals who volunteer for genetic study as well as those diagnosed by molecular methods in the future. Also for this reason, the National Institutes of Health–Department of Energy Working Group on Ethical, Legal, and Social Implications of the Human Genome Project was developed. After years of debate in Congress, the Genetic Information

Non-discrimination Act (GINA) was enacted May 21, 2008. The bill is designed to protect Americans against discrimination based on genetic information for hiring or insurance.[23]

CARDIOVASCULAR ABNORMALITIES CAUSED BY CHROMOSOMAL DEFECTS

Table 55–4 lists chromosomal defects that cause cardiovascular abnormalities. The most common chromosomal defects are described briefly below.

DOWN SYNDROME

Down syndrome, or trisomy 21, is a major cause of congenital heart disease, with a characteristic set of facial and physical features. The incidence of Down syndrome is approximately 1 in 700 livebirths, affecting more than 350,000 individuals in the United States alone.[24-26] The risk of having a liveborn with Down syndrome increases with maternal age. It is estimated at 1 in 1000 at age 30 years and 10-fold higher at age 45 years.[27] The recurrence rate in the offspring is approximately 1%. Clinical manifestations include congenital anomalies of the heart and gastrointestinal tract, epicanthal folds, flattened facial profile, small and rounded ears, upslanted palpebral fissures, excess nuchal skin, and brachycephaly.[24] An increased risk of leukemia, immune system defects, and an Alzheimer-like dementia are associated with Down syndrome. Cardiac abnormalities are present in approximately half of the cases.[26,28-31] The most common cardiac abnormalities are atrioventricular canal defect and isolated VSD, which occur in 45% and 35% of cases, respectively. The incidence of atrioventricular septal defect is about 1000-fold higher in patients with Down syndrome as compared to the general population.[29,30] Isolated secundum atrial septal defect (ASD) is present in 8% and tetralogy of Fallot in 5% of cases.[26,28-31]

Down syndrome is caused by trisomy 21. It is full trisomy in 95%, chromosomal translocation in 2%, and mosaic in 3%. The vast majority of errors in meiosis leading to trisomy 21 are of maternal origin and occur during the first meiosis in two-thirds and during second meiosis in one-fifth of the cases. The exact causal genes responsible for the cardiovascular defects are unknown. The prevailing hypothesis implicates dosage-sensitive genes on chromosome 21 as the main mechanism. Likewise, multiple genes might act in concert to affect specific biological pathways and lead to cardiac phenotypes. However, the exact causal genes for cardiovascular anomalies in Down syndrome are unknown. Several Down syndrome critical regions (DSCRs) have been mapped but not conclusively shown to be responsible for cardiac defects. Among the candidate genes are *DSCAM*, encoding the Down syndrome cell adhesion molecule, which is the only gene in one of the mapped critical regions that is expressed in the heart.[32] Likewise, *COL6A1*, which is highly expressed at the atrioventricular cushions in the heart; *CREDL1*, which encodes a cell adhesion molecule; and *RCAN1*, a regulator of protein phosphatase calcineurin 1, are implicated in cardiac anomalies in Down syndrome.[33,34]

TABLE 55–4. Partial List of Chromosomal Abnormalities Associated with Heart Disease

Chromosome Defects	Syndromes	Carciac Phenotype
45X	Turner syndrome	Bicuspid aortic valve, coarctation of the aorta, ASD, aortic aneurysm and dissection
Trisomy 5		Interrupted aortic arch
Trisomy 13	Patau syndrome	CHD, VSD
Trisomy 18	Edwards syndrome	CHD, VSD
Partial trisomy 20q		Dextrocardia
Trisomy 21	Down syndrome	CHD, ASD, VSD, PDA
Trisomy 22		VSD
Partial tetrasomy 22	Schmid-Fraccaro syndrome	CHD Anomalous pulmonary venous return
Deletion 4p	Wolf-Hirschhorn syndrome	CHD
Deletion 7q11.23	Williams syndrome	CHD, supravalvular aortic stenosis, hypertension, MVP
Deletion paternal 15q11	Prader-Willi syndrome	CHD
Deletion 17p	Miller Dieker syndrome	CHD, ASD
Deletion 22q11	CATCH-22, DiGeorge, and velocardiofacial syndromes	CHD
Rearrangement 5p15.1–3	Cri du chat	CHD
Recombination chromosome 8	San Luis Valley syndrome	Tetralogy of Fallot

ASD, atrial septal defect; CHD, congenital heart disease; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

TURNER SYNDROME

Turner syndrome is characterized by a constellation of findings that result from partial or complete monosomy of the X chromosome.[24,35] It is the most common chromosomal abnormality in females, with an incidence of 50 per 100,000 liveborn girls, which corresponds to approximately 2 million cases worldwide.[36] It is characterized by cardiovascular anomalies, short stature, low-set ears, excess nuchal skin, broad chest with widely spaced nipples, peripheral lymphedema, and ovarian dysgenesis.[24] Turner syndrome is associated with increased risk of diabetes mellitus, hypothyroidism, osteoporosis, aortic dissection, and hypertension. Cardiac abnormalities are common, with a prevalence estimated to be between 20% and 40%.[36] The most common cardiovascular abnormalities are bicuspid aortic valve, which is present in 20% to 30%, coarctation of aorta, present in 10% to 15% of the adult cases, and aortic dilatation and aneurysm, present in 10% to 40% of the cases.[36] The prevalence of these abnormalities is higher in children. Less common cardiovascular anomalies include aortic stenosis, systemic hypertension, mitral valve prolapse, conduction defects, partial anomalous venous drainage, and ventricular septal defect (VSD). Women with Turner syndrome are more susceptible to aortic aneurysms and ischemic heart disease. Patients with Turner syndrome should undergo periodic cardiovascular evaluation, including 12-lead ECG and echocardiography.

Turner syndrome is caused by complete or partial absence of an X chromosome. The most common karyotype is monosomy X (45,X).[35,36] The classic 45X karyotype account for about half of the Turner cases. Approximately 5% to 10% of the cases have duplication of the long arm of one X (46,X,i[Xq]) and the rest have mosaicism. The pathogenesis of Turner syndrome is not fully understood. It likely entails haploinsufficiency of genes (located on the X chromosome) that, under normal conditions, escape inactivation. Inactivation of one copy of the X chromosome during early embryogenesis is partial and several genes escape inactivation. Specific genes that account for the cardiovascular phenotype in Turner syndrome are unknown. *SHOX* (short stature

homeobox-containing gene) or *PHOG* (pseudoautosomal homeobox-containing osteogenic gene), which encode two isoforms of a homeodomain protein, are considered responsible for the short stature in Turner syndrome.[37,38] Hormone replacement therapy including administration of low-dose estrogen and growth hormone might be beneficial in attenuating metabolic abnormalities, ovarian failure, and growth retardation in children with Turner syndrome.[39]

EDWARDS SYNDROME

Edwards syndrome, or trisomy 18, is the second most common trisomy, with a prevalence of approximately 1 in 6000 to 8000 livebirths.[40] Its prevalence increases with increasing maternal age. The majority of the infants die within a couple of weeks and approximately 5% to 10% survive more than a year.[40] The major causes of death include central apnea, cardiac failure, and respiratory failure. The syndrome is characterized by anomalies of the heart and microcephaly with a prominent occiput, a narrow forehead, low-set and malformed ears, micrognathia, clefting of the lip and palate, clenched hand with overlapping digits, rocker-bottom feet, and various hernias.[40] Cardiovascular anomalies are present in approximately 90% of the cases.[41] They include VSD, ASD, patent ductus arteriosus (PDA), pulmonary stenosis, tetralogy of Fallot, transposition of the great arteries, bicuspid aortic valve, dysplastic valves, and coarctation of the aorta.[41,42] Complex cardiac malformations occur in approximately 10% of the cases. Full trisomy occurs in about 90%, chromosomal translocation in 3%, and mosaicism in 5% of cases. The causal gene(s) for the cardiovascular anomalies remain unknown.

PATAU SYNDROME

Patau syndrome, or trisomy 13, is a rare disorder with an incidence of 1 per 5000 to 1 in 20,000 livebirths and a high early mortality.[43,44] Approximately 50% of the affected infants die within the first month and 85% within first year of life.[44] Patau syndrome is characterized by cardiac, urogenital, craniofacial, and central nervous system anomalies. Specific anomalies include microcephaly with sloping forehead, microphthalmia, cleft lip and palate, overlapping fingers with postaxial polydactyly, renal abnormalities including polycystic kidney disease, and cutis aplasia. Cardiac abnormalities are present in approximately 80% of the cases. They include VSD, ASD, PDA, pulmonary stenosis, coarctation of the aorta, dextrocardia, and truncus arteriosus.[44]

Patau syndrome is caused by nondisjunction of chromosome 13 during meiosis in the vast majority of cases and rarely by translocation. Five percent of the cases are mosaic. The causal genes for cardiovascular anomalies in trisomy 13 are unknown.

22Q11.2 DELETION, DIGEORGE (CATCH-22) AND VELOCARDIOFACIAL SYNDROME

22q11.2 deletion syndrome, formerly known as DiGeorge and velocardiofacial syndromes, is an autosomal dominant congenital syndrome caused by hemizygous microdeletion of a large segment of the long arm of chromosome 22 (22q11). The deletion leads to anomalies of multiple organs including the heart and facial bones. The prevalence is approximately 1 in 4000, accounting for approximately 15% of all congenital heart defects.[45] The term *CATCH-22* denotes *c*ardiac, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, *h*ypocalcemia (as a result of parathyroid hypoplasia), and the *22*nd chromosome. Cardiac anomalies are present in approximately two-thirds of the cases. A diverse array of congenital heart defects, specifically those involving the aortic arch, include tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, and PDA. The 22q11.2 deletion syndrome accounts for approximately 15% of Tetralogy of Fallot cases.[46] Patients with velocardiofacial syndromes exhibit craniofacial anomalies, cleft palate, and a variety of cardiac abnormalities, such as aortic arch anomalies, tetralogy of Fallot, and VSD. Cardiac valves and the myocardium are usually spared.

DiGeorge syndrome is caused by microdeletion of approximately 3 Mbp of DNA encompassing approximately 30 genes. Genetic analysis in mouse and mutation analysis of the candidate genes in the region have led to identification of mutations in *TBX1*, which encodes a T-box transcription factor.[47] TBX1 is critical for embryogenesis of the second heart field and the aortic and pulmonary outflow tracts. Loss-of-function mutations in *TBX1* result in haploinsufficiency. The downstream target genes of TBX1 and the pathways involved in the pathogenesis of cardiac phenotype are mostly unknown. Likewise, a common copy number variant involving SLC2A3 seems to be a genetic modifier of 22q11.2 deletion syndrome.[48]

A recent whole exome sequencing of 184 individuals with 22q11.2 syndrome, including 89 cases with severe congenital heart defects, implicated genes involved in epigenetic regulation of gene expression through histone modifications in the pathogenesis of this syndrome.[49] Rare deleterious variants were enriched in *JMJD1C*, *PREB1*, *MINA*, and *KDM7A*, which encode proteins involved in demethylations of H3K9 and H3K27.[49] These findings are in accord with the recent large-scale sequencing projects implicating epigenetics in the pathogenesis of a garden-variety form of congenital heart disease, particularly congenital heart disease in conjunction with neurological abnormalities.[50,51]

Another candidate gene is *UFD1L*, which encodes a protein involved in degradation of ubiquitinated proteins. However, its role in 22q11.2 deletion syndrome has not been established.

GENETIC BASIS OF SPECIFIC CONGENITAL HEART DISEASES

Congenital heart diseases often occur in isolation and are not part of complex phenotypes, as observed in chromosomal abnormalities. Recently, the causal genes for several congenital heart diseases have been identified. Preliminary studies depict a common theme in the pathogenesis of isolated congenital heart defects, which implicate deficiency of several transcriptional and epigenetic factors that regulate cardiac gene expression during embryogenesis. However, there is considerable phenotypic, locus, and allelic heterogeneity.

SUPRAVALVULAR AORTIC STENOSIS

Supravalvular aortic stenosis is an autosomal dominant disease characterized by discrete narrowing of the ascending aorta above the level of the sinus of Valsalva. It commonly occurs as a phenotype of Williams syndrome (or Williams-Beuren syndrome) in conjunction with significant development delay in some, and exceptional talents in others, hypercalcemia, characteristic facial appearance, and stenosis of other major arteries.[52] The prevalence of supravalvular aortic stenosis is estimated to be 1 in 25,000 livebirths.

The gene responsible for supravalvular aortic stenosis was initially mapped to chromosome 7q11.23 and subsequently identified as *ELN*, encoding elastin.[53,54] Point and deletion mutations in *ELN* gene are the main causes of isolated supravalvular aortic stenosis. Mutations result in elastin deficiency, which in the vascular system leads to inelasticity of the vessel wall and subsequent fibrosis as a result of an altered stress–strain relation (elastin arteriopathy). Thus haploinsufficiency underlies the pathogenesis of supravalvular aortic stenosis.

Patients with Williams syndrome may exhibit additional cardiovascular phenotypes, including but less commonly pulmonary arterial

stenosis, aortic and mitral valve abnormalities, and tetralogy of Fallot.[54] In 98% of cases of Williams syndrome the deletion mutation includes 1.5 Mbp of DNA comprising *ELN* and another 20 contiguous genes. Contribution of these genes to pathogenesis of specific phenotypes in Williams syndrome remains unknown.

FAMILIAL ATRIAL SEPTAL DEFECT

ASD is among the most common congenital heart diseases, with an estimated incidence of 1 in 1000 livebirths.[1] ASD is usually sporadic. However, familial ASD with an autosomal dominant mode of inheritance also occurs. Individuals with ASD are commonly asymptomatic until the third or fourth decades, when they may present with signs and symptoms of right heart failure, pulmonary hypertension, and decreased exercise tolerance. Common symptoms are palpitations, commonly caused by supraventricular arrhythmias, and symptoms associated with pulmonary hypertension and right-sided volume overload resulting in left-to-right shunt. Uncorrected ASD can lead to heart failure, Eisenmenger syndrome, and premature death in the fourth or fifth decade of life.

The first gene identified for familial ASD is *NKX2–5*, which is the human homologue of *Nkx2.5* in mouse and *tinman* in *Drosophila melanogaster*.[55] The gene is located on 5q35 and encodes NKX2-5, a predominantly cardiac-specific transcription factor that regulates expression of several cardiac genes and heart development in various organisms.[56,57] A multiplicity of mutations has been described in patients with secundum ASD and conduction defects. Mutations often result in haploinsufficiency and those located in the DNA-binding domain reduce the binding affinity of NKX2-5 for the promoter region of its target genes and hence, reduced gene expression.[58] The spectrum of clinical phenotypes caused by mutations in NKX2.5 extends beyond secundum ASD and comprises VSDs, tetralogy of Fallot, subvalvular aortic stenosis, pulmonary atresia, and others.[59]

The second causal gene for familial ASD with an autosomal dominant mode of inheritance is *GATA4* on chromosome 8p22–23.[60] The mutations diminish DNA-binding affinity and transcriptional activity of GATA4 transcription factor, and block its physical interaction with TBX5, another transcription factor involved in the pathogenesis of congenital heart disease.[60]

The third causal gene for familial ASD is *MYH6*, which is located in chromosome 14q12 and encodes myosin heavy chain 6.[61] Missense mutations in *MYH6* are rare causes of isolated ASD of ASD occurring in conjunction with atrial fibrillation. The MYH6 protein is expressed at high levels in atrial tissues and is a major component of the sarcomere.

HOLT-ORAM SYNDROME

Holt-Oram syndrome is a rare autosomal dominant inherited disorder characterized by anomalies of the heart and upper extremities, hence the name *hand–heart syndrome*.[62,63] The most common congenital heart defects are ASD and VSD followed by conduction system abnormalities and atrial fibrillation. Less common cardiac abnormalities include truncus arteriosus, mitral valve defect, PDA, and tetralogy of Fallot. Anomalies of the upper limb vary from mild malformation of the carpal bones to phocomelia, but upper limb preaxial radial abnormalities are commonly present.

Mutations in *TBX5* on chromosome 12q24, which codes for transcription factor TBX5, are responsible for the cardiac and skeletal abnormalities in Holt-Oram syndrome (Fig. 55–4).[64] A number of mutations have been described and most are nonsense, frameshift, or splice-junction abnormalities. The proposed molecular mechanism is haploinsufficiency, resulting in reduced expression level of TBX5. Haploinsufficiency because of truncation or frameshift mutations results in severe birth defects in the heart and hands, whereas point mutations predominantly affect either hand or heart development.[65] Mutations in the 5′ end of the gene exhibit a preponderance of cardiac abnormalities with mild skeletal abnormalities, and those in the 3′ end lead to severe skeletal and mild cardiac abnormalities.

ELLIS-VAN CREVELD SYNDROME

Ellis-van Creveld syndrome is an autosomal recessive skeletal dysplasia, which is associated with congenital heart disease in the majority of cases.[66] Skeletal anomalies include short limbs, short ribs, postaxial polydactyly, and dysplastic nails and teeth.[66] ASD and common atrium are the typical cardiac anomalies present in two-thirds of the cases.[66] Several splice donor, truncation, and missense mutations in *EVC1* and

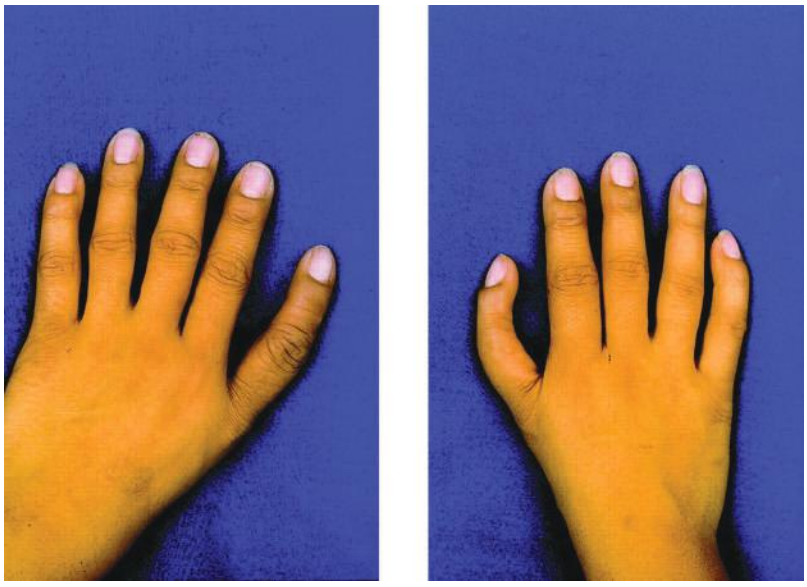

FIGURE 55–4. Photograph of the hands of a patient with Holt-Oran syndrome. Reproduced with permission from Böhm M: Holt-Oram syndrome. *Circulation*. 1998 Dec 8;98(23):2636-237.

EVC2 (LBN) genes, located on chromosome 4p16, have been identified as causes of Ellis-van Creveld syndrome.[67] The genes are coexpressed in atrial septum primum.[68] However, the pathogenesis of Ellis-van Creveld syndrome remains unknown.

FAMILIAL PATENT DUCTUS ARTERIOSUS (CHAR SYNDROME)

Patent ductus arteriosus (PDA) can occur as a sole cardiac anomaly or in conjunction with other congenital heart disease. Familial PDA with an autosomal dominant inheritance has been described in patients with Char syndrome. Char syndrome is a congenital disease that was first described by Florence Char in 1978. It is characterized by a constellation of facial dysmorphism, fifth-finger middle phalangeal hypoplasia, and PDA. Variation of this syndrome is associated with bicuspid aortic valve, distinctive facial appearance, polydactyly, and fifth-finger clinodactyly. The predominant clinical features are those of PDA, which include symptoms and signs of left-heart failure and pulmonary hypertension.

The gene responsible for Char syndrome in two families was recently mapped to chromosome 6p12–21.[69] Subsequently mutations in the *TFAP2B*, which encodes a neural crest-related helix-span-helix transcription factor, were identified.[70] TFAP2B regulates cell growth, differentiation, and apoptosis.[71]

NOONAN AND LEOPARD SYNDROMES

Noonan syndrome is an uncommon autosomal dominant disorder (estimated prevalence 1:1000 to 1:2000 newborns) characterized by dysmorphic facial features, including hypertelorism and low-set ears, hypertrophic cardiomyopathy, pulmonic stenosis, mental retardation, and bleeding disorders (Fig. 55–5).[72,73] Leopard syndrome (*l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonic stenosis, *a*bnormal genitalia, *r*etardation of growth, and *d*eafness) is an allelic variant of the Noonan syndrome. Pulmonic stenosis and HCM are the primary cardiac phenotypes. Others include atrioventricular septal defects, aortic coarctation, ASD, mitral valve defects, PDA, and fibroelastosis. Noonan syndrome is also seen in conjunction with cardiofaciocutaneous syndrome and other congenital abnormalities, such as neurofibromatosis. Noonan syndrome has phenotypic resembles to Turner syndrome and hence it is often referred to as male Turner syndrome. However, Turner is a distinct genetic eitity caused by 45X chromosomal disorder.

TABLE 55–5. Causal Genes for Noonan Syndrome Exhibiting HCM-like Phenotype

Gene	Protein Name	Protein Function
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11	Phosphatase
SOS1	SOS Ras/Rac guanine nucleotide exchange factor 1	Regulates RAS proteins
RAF1	Raf-1 proto-oncogene, serine/threonine kinase	A member of MAPK pathway
KRAS	Kirsten rat sarcoma viral oncogene homolog	A member of the small GTPase superfamily
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog	A protein with GTAPase activity
SHOC2	SHOC2 leucine-rich repeat scaffold protein	A component of the RAS/ERK MAP kinase pathway
CBL	Cbl proto-oncogene, E3 ubiquitin protein ligase	A RING finger E3 ubiquitin ligase

Noonan syndrome is sporadic in half of the cases and an autosomal dominant disease in the other half. Several genes for Noonan syndrome have been identified and all are the components of the RAS /MAPK pathway (Table 55–5). *PTPN11*, encoding protein tyrosine phosphatase, nonreceptor type 11, is the most common gene responsible for autosomal dominant Noonan and Leopard syndromes.[74,75] Overall, mutations in *PTPN11* are found in approximately one-half to two-thirds of the cases of Noonan syndrome. Mutations are typically gain-of-function mutations leading to increased signaling through RAS/MAPK pathway.

FIGURE 55–5. Phenotypic expression of Noonan syndrome. Reproduced with permission from Roberts AE, Allanson JE, Tartaglia M, et al: Noonan syndrome. *Lancet*. 2013 Jan 26;381(9863):333-342.

Mutations in SOS1, *KRAS*, *SOS1*, *RAF1*, *NRAS*, and *SHOC2* are also responsible for Noonan syndrome.[73] *SOS1* is probably the second most common causal gene for Noonan syndrome, accounting got about 15% of the cases. *SOS1* mutations are also gain-of-function mutations, leading to increased activity of the MAPK pathway.[73] Mutations in the other genes collectively account for about 10% of all Noonan syndrome cases.

FAMILIAL MYXOMA SYNDROME (CARNEY COMPLEX)

Myxomas are the most common cardiac tumors. Myxomas are generally sporadic but familial forms with an autosomal dominant mode of inheritance also occur in approximately 10% of cases, as a part of Carney complex.[76-78] Carney complex is characterized by the constellation of cardiac myxoma, endocrine disorders, and skin pigmentation.[77,78] LAMB (*l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma, *b*lue nevi) and NAME (*n*evi, *a*trial myxoma, *m*yxoid neurofibromata, *e*phelides) syndromes are considered variants of Carney complex. Atrial, ventricular, and skin myxomas, endocrine tumors and disorders, such as Cushing syndrome, and skin lesions, such as lentiginosis, are part of the phenotypic expression of Carney complex. These myxomas are commonly found in the right atrial-ventricular groove. Clinical features of atrial myxoma may include fever, arthralgia, dyspnea, diastolic rumble, tumor plop, and systemic embolisms (Fig. 55–6).[78]

Carney complex exhibits locus heterogeneity, and at least two loci on chromosome 17q24 and 2p16 have been mapped.[78-80] The majority of familial cardiac myxomas (Carney complex) are caused by mutations in the *PRKRA1A* gene on chromosome 17q24.[81] This gene encodes the α-regulatory subunit of cyclic adenosine monophosphate (cAMP)-dependent protein kinase. Frameshift mutations in *PRKRA1A* result in haploinsufficiency, which suggests that the *PRKRA1A* functions as a tumor-suppressor gene.[78] Recently, a missense mutation in the perinatal myosin heavy-chain gene (*MYH8*) was identified in members of a family with Carney complex and trismus-pseudocamptodactyly syndrome.[82] In addition, *PRKACA* and *PRKACB* genes are also implicated in Carney Complex. However, their pathogenic role remains uncertain.

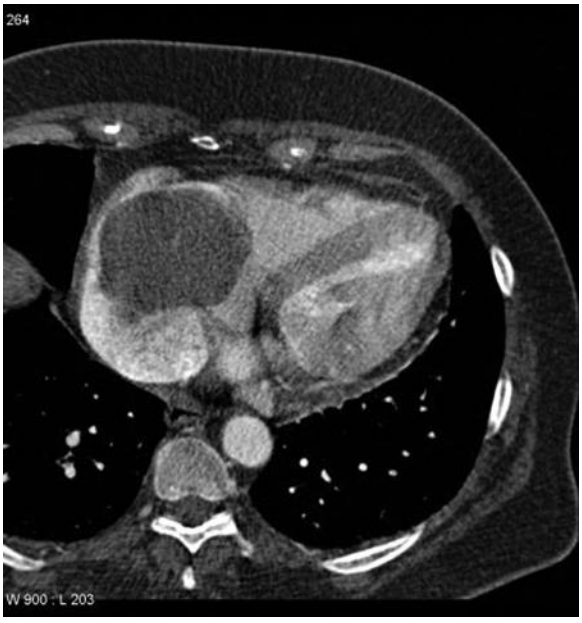

FIGURE 55–6. Right atrial myxoma detected by cardiac MR imaging. Case courtesy of Dr. Donna D'Souza, Radiopaedia.org. http://radiopaedia.org/articles/cardiac-myxoma.

SITUS INVERSUS

Situs inversus is a disorder of laterality leading to reversal of the asymmetric anatomic position of visceral organs. In situs inversus totalis, all visceral organs are reversed in a mirror-image manner (involving the chest and abdomen). It is part of primary ciliary dyskinesia (PCD), previously known as immotile cilia syndrome. Situs inversus might occur in conjunction with sinusitis and bronchiectasis, which is known as Kartagener syndrome. Most cases of situs inversus are sporadic. Autosomal recessive, autosomal dominant, and X-linked forms have been reported.[83]

Situs inversus, as a component of PCD, such as that in Kartagener syndrome, is caused by defect in NODAL signaling. It typically exhibits an autosomal recessive inheritance and is caused by mutations in *DNAH5*, *DNAH11*, and *DNAL1*, encoding dyanein proteins.[83-85] Dyneins are large proteins with adenosine triphosphatase (ATPase) activity that interact with intermediary filaments to produce energy and motion. Mutations in dynein axonemal intermediate chain 1 (*DNAI1*) on chromosome 9p13-p21, dynein axonemal heavy chain 5 (*DNAH5*) on chromosome 5p, and dynein axonemal heavy chain type 11 (*DNAH11*) on chromosome 7p21 have been found in patients with primary ciliary dyskinesia (and situs inversus).[83]

Mutations in several other genes including *ZIC3*, encoding a zinc-finger protein of the cerebellum, are associated with laterality defects and situs inversus.[83]

ALAGILLE SYNDROME (ARTERIOHEPATIC DYSPLASIA)

Alagille syndrome is an autosomal dominant disorder characterized by anomalies of the right side of the heart and developmental abnormalities of eyes, skeleton, and kidney. Cardiac abnormalities are present in approximately 70% of cases; the most common is diffuse pulmonary artery stenosis. Others include hypoplastic pulmonary circulation, pulmonary atresia, tetralogy of Fallot, coarctation of aorta, secundum ASD, PDA, and VSD.[86] The most common causal gene is the Jagged-1 gene (*JAG1*), located on chromosome 20p12.[87,88] Deletion or point mutations in *JAG1* are found in approximately 90% of the patients with Alagille syndrome.[86-88] JAG1 is a cell-surface protein that is a ligand for the Notch receptor. The Notch intercellular signaling pathway mediates cell fate decisions during development. The proposed molecular mechanism is haploinsufficiency leading to defective cell adhesions. Recently, mutations in *NOTCH2* were found in those who did not have JAG1 mutations.[86,89] Collectively, the findings indicate that Alagille syndrome is a disease of the Notch signaling pathway.

GENETIC DISEASES OF CARDIAC MUSCLE

The term *cardiomyopathy* denotes an exclusive group of disorders in which the primary defect is in the myocardium, affecting cardiac myocyte structure and/or function. The primary defect, however, does not need to be exclusive to the heart. It can also involve other tissues and organs, as in cardiomyopathies arising from metabolic disorders and mitochondrial myopathies. Myocardial dysfunction can also occur because of systemic, infiltrative, restrictive, toxic, and endocrine disorders, coronary atherosclerosis, and valvular pathologies. In such conditions, the primary defect is not in the myocardium. Thus myocardial involvement is considered secondary. In a sense cardiac involvement in such disorders does not meet the pure definition of cardiomyopathy.

Cardiomyopathies are classified according to their phenotypic characteristics. The four common groups are hypertrophic, dilated, arrhythmogenic, and restrictive cardiomyopathy. Phenotypic classification, although clinically convenient and useful, does not necessarily reflect the molecular and genetic basis of cardiomyopathies.

GENETIC BASIS OF HYPERTROPHIC CARDIOMYOPATHY

HCM is a relatively common autosomal dominant disease diagnosed clinically by the presence of unexplained cardiac hypertrophy.[90,91] Commonly, a left ventricular wall thickness of 13 mm or greater, in the absence of hypertension or valvular heart disease, is used to define HCM.[90] The prevalence of HCM is approximately 1 in 500 in young adults.[92] It is likely higher in the elderly population because of age-dependent penetrance.

Cardiac hypertrophy, the clinical hallmark of HCM, is asymmetric in approximately two-thirds of the cases with predominant involvement of the interventricular septum (Fig. 55–7). Hence the term *asymmetric septal hypertrophy* is used to describe this condition. Occasionally, hypertrophy is restricted to apex of the heart (apical HCM). Morphologically, the left ventricular cavity is small and the left ventricular ejection fraction, a measure of global systolic function, is increased. However, more sensitive indices of myocardial function show impaired contraction and relaxation secondary to "myocyte disarray."[93,94] Diastolic function is commonly impaired, leading to an increased left ventricular end-diastolic pressure and thus frequently to symptoms of heart failure.

Patients with HCM exhibit protean clinical manifestations ranging from minimal or no symptoms to severe heart failure. The clinical manifestations often do not develop until the third or fourth decades of life, but the onset is variable. The majority of patients are asymptomatic or mildly symptomatic. Predominant symptoms include dyspnea, chest pain, palpitations, and/or syncope. Severe systolic heart failure is uncommon. It occurs in a small fraction of patients in whom the disease evolves into a dilated cardiomyopathy (DCM) phenotype. In contrast, cardiac diastolic function is usually impaired and left ventricular end-diastolic pressure is elevated. A dynamic left ventricular outflow is present in approximately 25% of the patients. It could contribute to mitral regurgitations and symptoms of heart failure. Left ventricular outflow tract obstruction is an important determinant of heart failure in patients with HCM.[95] Cardiac arrhythmias, in particular atrial fibrillation and nonsustained ventricular tachycardia, are relatively common and are associated with adverse clinical outcome.[96] Wolff-Parkinson-White (WPW) syndrome is present in about 5% of patients with HCM.[97] Its presence suggests the possibility of a phenocopy, typically a glycogen storage disease (discussed later in this chapter).[98]

Unexplained syncope is a serious symptom.[99-101] It is often a result of serious cardiac arrhythmias and associated with an increased risk of sudden cardiac death (SCD).[99,101,102] HCM, although uncommon, is the most common cause of SCD in young, competitive athletes.[103] It accounts for almost half of all cases of SCD in athletes younger than 35 years of age in the United States.[103] SCD is often the first and tragic manifestation of HCM in young apparently healthy individuals. Table 55–6 lists the factors associated with an increased risk of SCD. Overall, in the assessment of the risk of SCD, the combination of all known risk factors should be considered. In the absence of major risk factors for SCD, HCM has a relatively benign course with an estimated annual mortality of about 1% in the adult population and even less in those who have undergone a defibrillator implantation.[91,104] Apical HCM is characterized by giant T-wave inversion in the precordial leads on the electrocardiogram. The overall prognosis of patients with apical HCM is similar to those with the garden-variety form of HCM.[91,105]

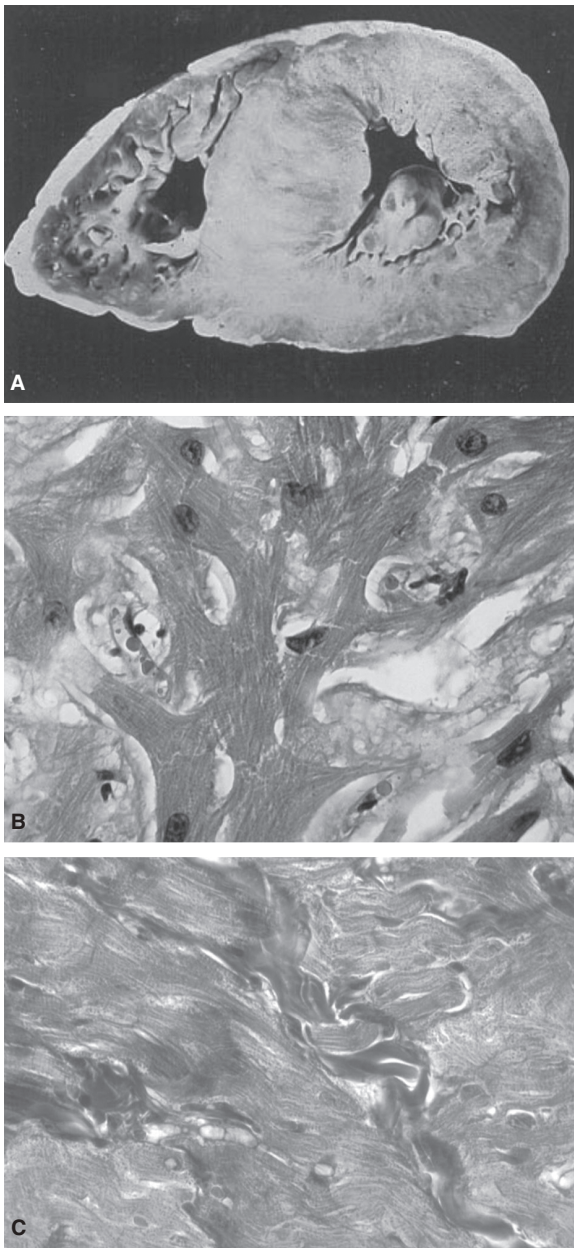

FIGURE 55–7. Main pathologic features of hypertrophic cardiomyopathy. **A.** Gross cardiac hypertrophy with predominant involvement of the interventricular septum and a small left ventricular cavity. **B.** Myocyte disarray and hypertrophy. **C.** Interstitial fibrosis.

TABLE 55–6. Potential Risk Factors for SCD in Patients with HCM

Aborted SCD (sudden cardiac arrest)
Family history of SCD (more than 1 victim of SCD)
Causal mutations, including double mutations
Genetic background (modifier genes, which might be obtained by family history)
History of unexplained syncope
Severe cardiac hypertrophy
Sustained and repetitive nonsustained ventricular tachycardia
Left ventricular outflow tract gradient
Histologic phenotypes (interstitial fibrosis and myocyte disarray)
Abnormal blood pressure response to exercise

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.

The pathologic hallmark of HCM is cardiac myocyte disarray.[106] It is defined as maligned, distorted, and often short and hypertrophic myocytes oriented in different directions (Fig. 55–7). Myocyte disarray often comprises more than 20% of the ventricle, as opposed to < 5% of the myocardium in normal hearts.[107,108] It is more prominent in the interventricular septum, but commonly is found throughout the myocardium. Other pathologic features of HCM include myocyte hypertrophy, interstitial fibrosis, thickening of media of intramural coronary arteries, and on occasion malpositioned mitral valve with elongated leaflets. In addition to cardiac hypertrophy and myocyte disarray, interstitial fibrosis is also associated with the risk of SCD, mortality, and morbidity in patients with HCM.[109,110] Late gadolinium enhancement is used as a surrogate marker for interstitial fibrosis and is a predictor of the risk of SCD in patients with HCM.[109,110] Other pathologic features of HCM include thickening of the media of intramural coronary arteries, abnormal positioning of the mitral valve apparatus, and elongated mitral valve leaflets.

Molecular Genetics of Hypertrophic Cardiomyopathy

HCM is a genetically heterogeneous disease with an autosomal dominant mode of inheritance. Approximately two-thirds of patients have a family history of HCM. In the remainder, the disease is sporadic. Familial and sporadic cases both are caused primarily by mutations in contractile sarcomere proteins.[90,91] In sporadic cases, mutations are de novo and could be transmitted to the offspring of the index cases.[111] Because hypertrophy is a common response of the heart to all forms of injury or stimuli, a phenotype of hypertrophy in the absence of an increased external load could also occur because of mutations in genes encoding proteins other than sarcomere proteins. As such, unexplained cardiac hypertrophy, which clinically denotes HCM, could also occur in storage disorders, metabolic disorders, mitochondrial diseases, and triplet repeat syndromes, as well as congenital heart diseases.[90,112] Although the gross phenotype is similar, the pathogenesis of HCM caused by different classes of mutant proteins, at least in part, could differ. Therefore such conditions are considered phenocopy (diseases mimicking HCM).

Causal Genes and Mutations The pioneering works of Christine and Jonathan Seidman have led to elucidation of the molecular genetic basis of HCM. In 1990, an arginine-to-glutamine substitution at codon 403 (R403Q) in the β-myosin heavy chain (MHC) was identified as the first causal mutation.[113] Since then, several hundred different mutations in more than a dozen genes encoding sarcomere proteins have been identified (Table 55–7). Consequently, HCM (excluding phenocopy conditions) is considered a disease of contractile sarcomere proteins (Fig. 55–8). Systematic screening of sarcomere genes suggests that mutations in *MYHC* and *MYBPC3*, which encode β-MHC and myosin-binding protein C (MYBPC3), respectively, are the most common causes of human HCM, together accounting for approximately

TABLE 55–7. Causal Genes for Hypertrophic Cardiomyopathy

Gene	Symbol	Frequency	Predominant Mutations
Genes Coding for Thick-Filament Proteins			
β-Myosin heavy chain	*MYH7*	~25%	Missenses
Myosin binding protein-C	*MYBPC3*	~25%	Splice-junction and insertion/ deletion
α-Myosin heavy chain	*MYH6*	Rare	Missense and rearrangement mutations (association)
Essential myosin light chain	*MYL3*	< 3%	Missenses
Regulatory myosin light chain	*MYL2*	< 3%	Missense and 1 truncation
Muscle ring protein 1 (MuRF1)	*TRIM63*	< 1%	Missense and stop codon
Genes Coding for Thin-Filament Proteins			
Cardiac α-actin	*ACTC*	< 3%	Missense mutations
Cardiac troponin T	*TNNT2*	~3-5%	Missenses
Cardiac troponin I	*TNNI3*	~3-5%	Missense and deletion
Cardiac troponin C	*TNNC1*	Rare	Missense mutations (association)
α-Tropomyosin	*TPM1*	< 3%	Missenses
Pan-Sarcomere			
Titin	*TTN*	< 3%	Missense mutations
Z Disk Proteins			
Telethonin (Tcap)	*TCAP*	Rare	Missense mutations
Myozenin 2	*MYOZ2*	1:250	Point mutations
α-Actinin	*ACTN2*	Rare	Point mutations
Others			
Caveolin 3	*CAV3*	Rare	Point mutations
Phospholamban	*PLN*	Rare	Point mutations
Calsequestrin	*CASQ2*	Rare	Point mutations
Junctophilin 2	*JPH2*	Rare	Point mutations

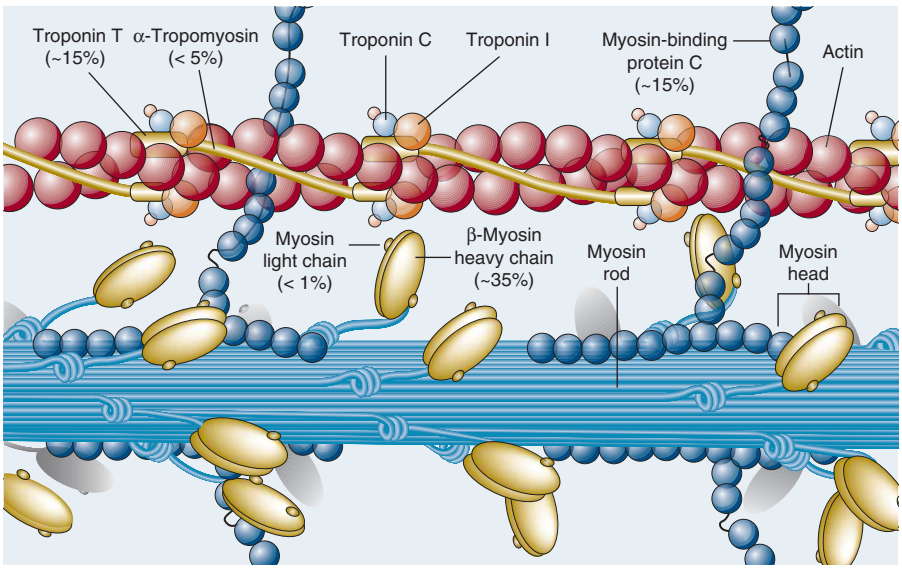

FIGURE 55–8. Schematic representation of sarcomere proteins involved in cardiomyopathies.

half of all cases.[114-117] Mutations in *TNNT2* and *TNNI3*, encoding cardiac troponin T and I, respectively, are relatively uncommon, each accounting for approximately 3% to 5% of HCM cases.[117] Thus, mutations in *MYH7*, *MYBPC3, TNNT2*, and *TNNI3* collectively account for approximately 60% of all HCM cases. A small fraction of HCM cases are caused by mutations in genes encoding αtropomyosin (*TPM1*), titin (*TTN*), cardiac α-actin (*ACTC*), telethonin *(TCAP)*, and essential and regulatory light chains (*MYL3* and *MYL2*, respectively).[90] Rare mutations in several other genes coding for thick and think filament of the sarcomeres as well as the Z-disk proteins have been reported.[118,119] Likewise, rare mutations in non-sarcomere proteins including calcium regulatory proteins are associated with HCM.[118,119] Overall, the causal genes and mutations for approximately two-thirds of HCM cases have been identified. The remainder remain to be identified and/or might be caused by phenocopy conditions.

Molecular Genetics of HCM Phenocopy

A phenotypic feature of several diseases, particularly storage diseases, is cardiac hypertrophy mimicking HCM, and hence such conditions are referred to as *HCM phenocopy*. Despite phenotypic similarities, however, the distinction between true HCM and HCM phenocopy is important, as the pathogenesis of the two conditions differs. Table 55–8 provides a partial list of HCM phenocopy conditions. The prevalence of HCM phenocopy is not precisely known but might comprise approximately 5% to 10% of the clinically diagnosed adult cases with HCM and even more in children.[120-122] A prototypic example of HCM phenocopy is Fabry disease, an X-linked lysosomal storage disease.[121,122] Fabry disease is present in approximately 1% to 5% of cases with the clinical diagnosis of HCM in the adult population.[122,123] The causal gene is *GLA* on chromosome Xq22, which codes for lysosomal hydrolase α-Gal A protein.[124] The phenotype results from deficiency of α-galactosidase A (α-Gal A), also known as ceramide trihexosidase. Deficiency of the enzyme results in deposits of glycosphingolipids in multiple organs, including the heart. The phenotype is characterized by angiokeratoma, renal insufficiency, proteinuria, neuropathy, transient ischemic attack, stroke, anemia, corneal deposits, and cardiac hypertrophy. Cardiac hypertrophy, which is often indistinguishable from the true HCM, is associated with high QRS voltage, conduction defects, cardiac arrhythmias, and SCD. Other cardiac phenotypes include valvular regurgitation, coronary artery disease, myocardial infarction, and aortic annular dilatation.[121-123] The disease predominantly affects males. Female carriers could exhibit a milder form. The diagnosis is established by measuring α-Gal A levels and activity in leukocytes. However, in many cases the diagnosis is difficult to establish both at the genetic level as well as after measurement of α-Gal A enzymatic activity. Enzyme replacement therapy using human α-Gal A (agalsidase α) or recombinant human α-Gal A (agalsidase β) has been advocated with some evidence of improvement in progression and reversal of the disease.[125-128]

Glycogen storage disease caused by mutations in the *PRKAG2* gene is another HCM phenocopy.[98,129-132] Cardiac hypertrophy results predominantly from storage of glycogen in myocytes but probably also from cardiac myocyte proliferation.[133] The gene encodes the γ_2 regulatory subunit of adenosine monophosphate (AMP)-activated protein

TABLE 55–8. Genes Known to Cause Hypertrophic Cardiomyopathy Phenocopy

Gene Symbol	Protein	Frequency
GLA	α-Galactosidase A	3%
PRKAG2	AMP activated protein kinase, γ subunit	1–2%
LAMP2	Lysosome-associated membrane protein 2	1–2%
MOY6	Unconventional myosin 6	Rare
FRDA	Frataxin (Friedreich ataxia)	Rare
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11	Uncommon, higher in children
DMPK, DMWD	Myotonin protein kinase (Myotonic dystrophy)	Uncommon
TTR	Transthyretin	Rare
FHL1	Four and a half LIM domain 1	Rare
MTTG, MTTI	Mitochondrial genes	Rare

kinase (AMPK), which is considered the energy biosensor of the cell. Mutations in *PRKAG2* lead to cardiac hypertrophy, conduction defects, and WPW.[98,129,132]

HCM phenocopy also occurs in trinucleotide repeat syndromes, a group of genetic disorders caused by expansion of naturally occurring trinucleotide repeats. HCM phenocopy occurs in Friedreich ataxia, an autosomal recessive neurodegenerative disease caused by expansion of GAA repeat sequences in the intron of *FRDA*.[134]

HCM phenocopy also occurs in patients with Noonan syndrome. The phenotype is characterized by dysmorphic facial features, pulmonic stenosis, mental retardation, bleeding disorders, and cardiac hypertrophy, as discussed earlier.[73]

Metabolic diseases also cause HCM phenocopy. Refsum disease, Pompe disease (glycogen storage disease type II), Danon disease, Niemann-Pick disease, Gaucher disease, hereditary hemochromatosis, and CD36 deficiency are examples of metabolic disorders that cause HCM phenocopy.[112,135] Defective mitochondrial oxidative phosphorylation pathways also cause HCM phenocopy. Kearns-Sayre syndrome is a mitochondrial disease characterized by a triad of progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects, and less frequently HCM phenocopy.[112,135,136]

Genotype-Phenotype Correlation

A remarkable feature of HCM is the presence of considerable variability in its phenotypic expression, whether it is the degree of cardiac hypertrophy or the risk of SCD.[137,138] The molecular basis of such variability is not fully known. It is probably partly because of the diversity of the causal genes and mutations, which impart a spectrum of functional and structural defects. In addition, the presence of multiple mutations simultaneously present, detected in a small fraction of patients, is associated with a severe phenotype.[19,139] Environmental factors, such as competitive sports and exercise could potentially contribute to the phenotypic expression of HCM. However, there is insufficient data to support their contributions to the phenotype.

Causal genes and mutations are the primary determinant of expressivity of cardiac phenotype, including the severity of hypertrophy and the risk of SCD. Initial genotype-phenotype correlation studies implied gene- and mutation-dependent phenotypic expression of HCM. For example, p.R403Q mutation was considered a high-risk mutation associated with increased risk of SCD (Fig. 55–9). Likewise, patients with mutations in *MYH7* were shown to have more severe hypertrophy than patients with mutations in *MYBPC3* or *TNNT2*.[140-144] Likewise, the overall impression is that *TNNT2* mutations, despite exhibiting a milder hypertrophic phenotype, were associated with a higher risk of SCD.[140,145-147] Such generalizations, however, are not broadly applicable as the results of genotype–phenotype correlation studies in HCM are subject to a large number of confounding factors, including the small size of the families, small number of families with identical mutations, low frequency of each mutation, phenotypic variability, homozygosity for the causal mutations or compound mutations, and the influence of modifier genes and environmental factors. Collectively, the existing data indicate that mutations exhibit highly variable clinical, ECG, echocardiographic, and cardiac MRI manifestations, and no particular phenotype is mutation specific.

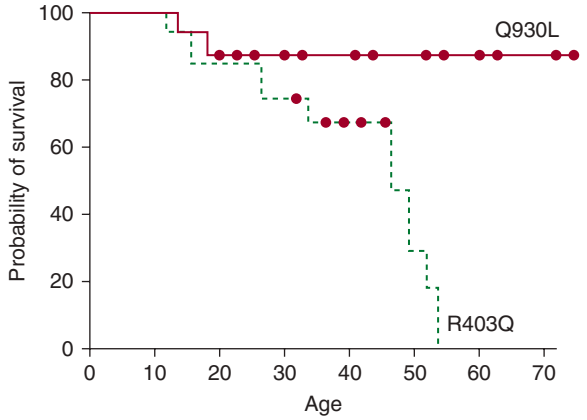

FIGURE 55–9. Kaplan-Meier survival curves in patients with hypertrophic cardiomyopathy. Shown are survival curves in two families with two different mutations, namely arginine-to-glutamine substitution at amino acid 403 (R403Q) and glutamine-to-lysine change at amino acid 930 (Q930L) in the *MYH7*.

Modifier Genetic Factors The presence of considerable phenotypic variability among affected members of different families with identical causal mutations emphasizes the significance of the genetic background to phenotypic expression of HCM. Genes other than the causal genes that affect the phenotype are referred to as the "modifier" genes. Unlike the causal genes, modifier genes are neither necessary nor sufficient to cause HCM.[148] However, they influence the severity of cardiac hypertrophy, risk of SCD, and expression of other cardiac phenotypes in HCM. DNA polymorphisms, including SNPs located in the coding or regulatory regions or splice junctions in genes involved in cardiac hypertrophy, are the prime candidates to modify phenotypic expression of HCM. The specific modifier genes in HCM are largely unknown. Five modifier loci have been mapped through genome-wide linkage studies and several genes have been implicated.[149-153] The effect sizes of the modifier loci are considerable as the loci in homozygous form could influence expression of cardiac hypertrophy markedly. Functional variants of genes coding for the components of the renin-angiotensin-aldosterone system are the most extensively studied candidates. *ACE*, encoding angiotensin-I converting enzyme 1 (ACE-1), was the first gene implicated as a modifier of cardiac phenotype including severity of cardiac hypertrophy and the risk of SCD in human HCM.[152,153] Observational data show cardiac hypertrophy accelerates during puberty and adolescence in patients with HCM.[154] The findings are in accord with the role of growth factors in contributing to expression of cardiac hypertrophy.[155] Differential expression of four-and-a-half domains protein 1 (FHL1) in human HCM has been shown, and alternative 5′ start usage is considered a modifier of cardiac phenotype including sex-dependent differences in a mouse model of HCM.[156,157] Overall, the final phenotype in HCM is determined not only by the causal mutations but also by the effects of modifier genes, environmental factors, epigenetic and epistatic factors, and posttranscriptional and posttranslational modifications of the proteins.

Pathogenesis of Hypertrophic Cardiomyopathy

As the diversity of the causal mutations would suggest, there is no single initial defect that is common to all mutations (Table 55–9). The diversity of the clinical phenotypes, such as hypertrophic, dilated, or restrictive cardiomyopathy arising from mutations in the same gene further adds to the complexity of the pathogenesis. Topography of the causal mutation is likely to be important, as the initial defect is likely to be triggered by protein domain. Given that each sarcomere protein has multiple functions, mutations in different domains of the same protein could impart several initial defects.

The causal mutation initiates a series of molecular events, which begins with alteration of the molecular structure and function of the protein (see Table 55–9). Because the majority of mutant sarcomere proteins differ from the wild type only by a single amino acid (missense mutations), the mutant proteins typically incorporate into the sarcomere, albeit sometimes inefficiently. Following incorporation,

TABLE 55–9. Initial Defects Caused by Mutations in Sarcomere Proteins

1. Mechanical defect
   - Altered actomyosin interaction
   - Altered cardiac myocyte and myofibril contractile performance
2. Biochemical defects
   - Altered protein-protein binding
   - Altered Ca^{2+} affinity of myofibrillar force generation
3. Bioenergetics
   - Altered myofibrillar adenosine triphosphatase activity
4. Structural defects
   - Altered sarcomere assembly
   - Altered subcellular localization of sarcomere proteins
   - Altered stoichiometry

mutant sarcomere proteins exert diverse functional defects, such as alterations in myofibrillar Ca^{2+} sensitivity and ATPase activity. Altered calcium sensitivity of the myofibrils seems to be a common biological effect of the sarcomere protein mutations.[158] Functional phenotypes lead to activation of secondary molecules, which are largely unknown but expected to include activating of many intracellular signaling pathways. The secondary molecular phenotype mediates induction of the morphologic and histologic phenotypes. Accordingly, hypertrophy and fibrosis are considered secondary phenotypes because of activation of intermediary molecular phenotypes (see Fig. 55–10).

Many HCM mutations involve deletions or truncations that are considered null alleles because of the possible expression of unstable mRNA and proteins.[114,116,117,158] Although there might be a partial allelic compensation (the wild type allele partly compensating the deficiency of the encoded protein), a truncation or a null mutation might lead to haploinsufficiency and alter stoichiometry of the sarcomere proteins, resulting in HCM. Regardless of the initial primary defect, cardiac hypertrophy, the clinical hallmark of HCM, is considered a compensatory phenotype resulting from upregulation and activation of various trophic and mitotic factors. The predominant involvement of the left ventricle and its frequent absence in the low-pressure right ventricle, despite equal expression of mutant sarcomere protein in both, suggest contribution of the environment, such as the loading conditions, to the development of hypertrophy. Furthermore, variation in hypertrophic response because of the genetic background, its absence early on in life, and its attenuation through pharmacologic interventions, at least

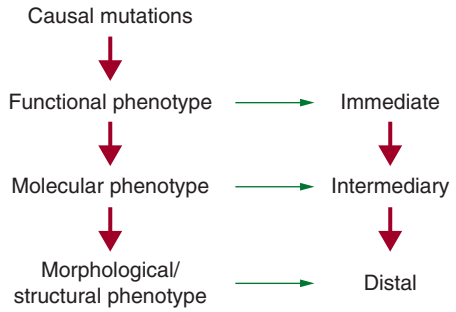

FIGURE 55–10. Sequence of phenotype characterization in the pathogenesis of cardiomyopathies.

in animal models, supports the secondary nature of hypertrophy. The primary impetus for hypertrophy is not well defined. It is likely to involve altered Ca^{2+} sensitivity of the myofilaments and activation of various calcium-dependent and independent signaling pathways in response to increased cell mechanical stress.

In keeping with the diversity of cardiac phenotypes in HCM, expression levels of a variety of genes, in response to the mutant protein, are altered. Expression of genes encoding contractile sarcomere proteins, cytoskeletal proteins, ion channels, intracellular signaling transducers, proteins maintaining the reduction–oxidation state, and those involved in transcriptional and translation machinery are changed.[156,159] Likewise, expression of a number of microRNAs (miRs) is disregulated and circulating levels of a number of miRs are increased in patients with HCM.[160-162] Plasma levels of miR-29a are associated with cardiac hypertrophy and fibrosis in patients with HCM.[160,163]

Potential New Therapeutic Interventions

Current pharmacologic interventions in HCM are empiric without a firm evidence of efficacy in regression of hypertrophy, fibrosis, and disarray. Pharmacological therapy is restricted primarily to the use of beta-blockers and on occasion calcium channel blockers and antiarrhythmic drugs, as indicated. Nonpharmacological interventions include surgical septal myectomy (Morrow procedure) and catheter-based septal ablation, typically upon infusion of alcohol to the main septal branch of the left anterior decending coronary artery, and are very effective in reducing the left ventricular outflow tract obstruction, improving symptoms, and even possibly survival. However, septal myectomy, whether surgical or catheter-based, does not address the underlying pathology as hypertrophy, fibrosis, and disarray typically persist. Currently, there is no suitable method to correct the underlying genetic defect in humans. Therefore, the emphasis has been on prevention, reversal, and attenuation of the phenotype through pharmacologic interventions aimed at blockade of intermediary molecular phenotypes of genetic interventions in animal models. Recent studies have shown potential clinical usefulness of angiotensin II receptor blockers, beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and antioxidants in prevention, attenuation, and reversal of cardiac phenotypes in animal models of HCM.[164-169] However, preliminary data in human patients with HCM have not shown significant benefits of statins.[170,171] Likewise, blockade of the renin-angiotensin-aldosterone system has shown only a modest if any beneficial effect.[172-176] Preliminary studies suggest potential beneficial effects of pretreatment with diltiazem, an L-type Ca^{2+} channel blocker, on echocardiographic indices of cardiac size and function in HCM mutation carriers.[177] Randomized clinical trials in human patients with HCM using N-acetylcysteine (HALT-HCM), eleclazine (LIBERTY-HCM), and several others are ongoing (https://clinicaltrials.gov).

GENETIC BASIS OF PRIMARY DILATED CARDIOMYOPATHY

Primary DCM is a disease of the myocardium that manifests by dilatation of the left ventricular along with a gradual decline in contractility. The diagnosis is based on a left ventricular ejection fraction of less than 0.45 and a left ventricular end-diastolic diameter of > 2.7 cm/m^2. Primary DCM has a prevalence of 40 cases per 100,000 individuals and an incidence of 5 to 8 cases per 100,000 persons.[178] Patients with DCM are often asymptomatic in the early stages but gradually develop symptoms and signs of heart failure, syncope, cardiac arrhythmias, and SCD. A significant number of affected relatives of patients with DCM are asymptomatic and are diagnosed for the first time on additional testing (such as an echocardiogram or ECG).[179] A normal history and physical examination in a subject at risk, particularly in the early decades of life,

does not exclude DCM. A family history of DCM is present in approximately half of all index cases with idiopathic DCM. In the remainder, DCM is considered sporadic. Familial DCM is commonly inherited as an autosomal dominant disease, which clinically manifests during the third and fourth decades of life.[179]

An X-linked DCM is suspected when only male members of a family exhibit symptoms and signs of DCM and there is no male-to-male transmission. Three common forms of X-linked DCM have been identified, include Duchenne/Becker muscular dystrophies, Emery-Dreifuss syndrome, and Barth syndrome. DCM also occurs in multiorgan disorders, such as mitochondrial DNA mutations, triplet repeat syndromes, and metabolic disorders.

Molecular Genetics of Dilated Cardiomyopathy

DCM is an extremely heterogeneous disease, as indicated by the heterogeneity of the mapped loci and genes for familial DCM (Table 55–10). The predominant mode of inheritance is autosomal dominant; however, autosomal recessive and X-linked DCM also occur. The most common causal gene for primary DCM is *TTN*, which encodes the giant sarcomere protein titin.[180] Several causal genes for autosomal dominant DCM have been identified. Several causal genes encode sarcomere proteins, which are also known to cause HCM. Thus, despite the contrasting phenotypes of HCM and DCM, mutations in sarcomere genes can cause either of the very different phenotypes. Because many of the known causal genes for DCM involve the myocyte cytoskeleton, DCM is mostly but not exclusively a disease of cytoskeletal proteins.

Causal Genes and Mutations The gene encoding cardiac α-actin (*ACTC*) was the first causal gene identified for autosomal dominant DCM.[181] Subsequently, mutations in genes encoding additional components of the sarcomere, namely *MYH7*, *TNNT2, TTN*, and *TCAP*, were found in patients with DCM. Using next-generation sequencing of a large DCM cohort, truncating mutations in *TTN* were found to be responsible for 25% of the cases of DCM.[180] Because mutations in *ACTC*, *MYH7*, and *TNNT2* are also known to cause HCM, these findings point to the commonality of the genetic basis of DCM and HCM. The diversity of the phenotype may reflect the topography of the causal mutations on the protein as well as the genetic background of the individuals. The molecular basis of such extreme phenotypic diversity remains largely unknown.

Mutations in several cytoskeletal proteins, such as delta sarcoglycan, beta sarcoglycan, metavinculin, and dystrophin are important causes of DCM.[182] Mutations in alpha sarcoglycan (adhalin) cause an autosomal recessive form of DCM that occurs in conjunction with limb-girdle muscular dystrophy. Mutations in cysteine and glycine-rich protein 4 (*CSRP3*) and LIM domain-binding protein 3 (LDB3), members of muscle LIM proteins, also cause DCM.

Another intriguing category of genes causing DCM is genes encoding for ion channels, suggesting the presence of overlap syndromes between arrhythmias and heart failure. Mutations in *ABCC9*, which encodes the regulatory SUR2A subunit of the cardiac K(ATP) channel as well as mutations *SCN5A*, which codes for a sodium channel and is a causal gene for Brugada syndrome, cause DCM.[183,184] A mutation in KCNQ1, encoding a potassium channel, is also associated with cardiac arrhythmias and DCM.[185] Cardiac arrhythmias are often the main presentation of this category of DCM and typically disproportionate to cardiac dysfunction. The term arrhythmogenic cardiomyopathy encompasses this group of DCM.

Mutations in the gene encoding lamin A/C (LMNA), which is a nuclear envelope protein, are important causes of DCM, typically in conjunction with conduction defect. *LMNA* interacts with large segments of chromatin. Consequently, *LMNA* mutations cause a diverse array of phenotypes including DCM, progressive conduction disease, atrial arrhythmias, SCD, muscular dystrophy, lipodystrophy, insulin resistance, and progeria.[186]

A subgroup of DCM is caused by protein aggregation in the myocardium (proteotoxicity).[187,188] Mutations in the intermediary filament protein desmin and its associated protein alpha/B-crystallin cause DCM in part through protein aggregation in the myocardium.[188] Often such mutations lead to a phenotype of cardiac and skeletal myopathy that is referred to as *desmin-related myopathy*.

Finally, mutations in RNA-binding motif protein 20 (RBM20), which regulates RNA spicing, cause DCM by influencing splicing of cardiac genes.[189,190] Collectively, these findings indicate the diversity of the causal genes responsible for DCM and render DCM genetically among the most heterogeneous diseases, with mutations affecting the integrity of the sarcomere and cytoskeleton being the main causes.

Genotype-Phenotype Correlation in Dilated Cardiomyopathy

Given the extreme genetic heterogeneity of DCM, the focus of genotype-phenotype correlation is on the presence of concomitant phenotype, cardiac or otherwise, that might offer clues to the underlying pathogenesis of the disease. Typically, mutations in genes encoding cardiac sarcomere proteins, such as MYH7, TNNT2, and TPM1 cause isolated forms of DCM without accompanying phenotypes, such as conduction defects, deafness, or skeletal myopathy. In contrast, mutations in the *LMNA* gene typically cause DCM in conjunction with progressive conduction defects, atrial arrhythmias, and SCD.[186] In addition, *LMNA* mutations also cause an autosomal-dominant form of Emery-Dreifuss syndrome.[191] Mutations in desmin and alphaB-crystallin genes are commonly associated with skeletal myopathy as well as DCM with unique pathologic features, a phenotype referred to as the *desmin-related myopathy*.[187] Mutations in the dystrophin gene commonly lead to skeletal and cardiac myopathy. The severity of the myopathic phenotype is partly determined by the type of mutation. Those that are frame-shift mutations—for example, insertion or deletion of a single base—cause a severe form, whereas missense mutations often lead to a mild form of DCM and muscular dystrophy. Mutations in the 5′ region of the dystrophin gene are associated with DCM without skeletal involvement.[192]

Cardiac involvement is quite common in triplet repeat syndromes and includes DCM, conduction disorders, and arrhythmia. Prevalence of cardiac involvement increases with advancing age, and approximately three-quarters of adult patients exhibit conduction defects, such as first-degree atrioventricular block and intraventricular conduction defects.[193] There is also a correlation between the severity of the disease and the severity of cardiac involvement and the number of CTG repeats.[193]

Pathogenesis of Dilated Cardiomyopathy

A diverse array of mechanisms is likely to be involved in the pathogenesis of hereditary DCM. Among notable mechanisms are impaired sarcomere structure and function, cytoskeletal integrity and mechanical force transmission, and impaired ATPase activity.[182,194] Identification of mutations in *MLP*, *LDB3*, and *TCAP* emphasize the significance of the Z disk in maintaining normal cardiac function. Similarly, identification of mutations in the dystrophin-associated protein complex as causes of DCM signifies the role of sarcolemma in the pathogenesis of DCM. Mutations in the dystrophin gene lead to decreased expression levels of dystrophin, a major cytoskeletal protein in skeletal and cardiac muscles. Decreased levels of dystrophin are expected to impair mechanical coupling and myocyte shortening. Interestingly, using the CRISPR-Cas9 system to target the mutant dystrophin leads to increase dystrophin levels and improvement of muscle and cardiac phenotype.[195-198]

TABLE 55–10. Causal Genes for Dilated Cardiomyopathy (DCM)

Gene	Symbol	Prevalence/Phenotype
Sarcomere Filaments		
Titin	*TTN*	The most common gene, ~25% of DCM cases, Also causes HCM
β-Myosin heavy chain	*MYH7*	~ 5%, Also causes HCM
Cardiac α-actin	*ACTC*	Also causes HCM
Cardiac troponin T	*TNNT2*	Also causes HCM
Cardiac troponin I	*TNNI3*	Also causes HCM
Cardiac troponin C	*TNNC1*	Also causes HCM
α-Tropomyosin	*TPM1*	Also causes HCM
Cytoskeletal		
α-Sarcoglycan	*SGCA*	Limb–girdle muscular dystrophy
β-Sarcoglycan	*SGCB*	
δ-Sarcoglycan	*SGCD*	
Dystrophin	*DMD*	Muscular dystrophy
Cysteine and glycine rich protein 3	*CSRP3*	
Ankyrin repeat domain 1	*ANKRD1*	~ 1%
Intermediary Filaments		
Desmin	*DES*	Also causes RCM
αB-crystallin	*CRYAB*	Desminopathy
Z Disk		
LIM domain binding 3 (Z-band alternative Spliced PDZ motif)	*LDB3*	
Telethonin (T-cap)	*TCAP*	
Alpha actinin 2	*ACTN2*	
Nuclear Membrane		
Lamin A/C	*LMNA*	DCM, laminopathies, progeria
Emerin	*EMD*	
Vinculin	*VCL*	Metavincluin isoform
Desmosomes		
Desmoplakin	*DSP*	Also causes ARVC
Others		
Taffazin (G4.5)	*TAZ*	Ventricular noncompaction
RNA-binding motif protein 20	*RBM20*	Spliceosome protein
Bcl2-associated athanogene 3	*BAG3*	Co-chaperone
Sodium channel	*SCN5A*	Sodium channel
Phospholamban	*PLN*	Inhibitor of SERCA2
ATP binding cassette subfamily C member 9	*ABCC9*	SUR2 protein subunit of K channels
Potassium channel, voltage gated KQT-like subfamily Q, member 1	*KCNQ1*	Potassium channel.
Troponin I interacting kinase	*TNNI3K*	DCM, conduction defect, atrial fibrillation

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

Pathogenesis of DCM resulting from mutations in desmin and alphaB-crystallin involves deposition of desmin and alphaB-crystallin aggregates in the myocardium.[187] The molecular pathogenesis of DCM caused by mutations in lamin A/C or emerin remains largely unknown, but is likely to involve perturbed epigenetic regulation of gene expression as well as disruption of integrity of the cytoskeleton.[186] The pathogenesis of cardiomyopathies in patients with the triplet repeat syndromes is not fully known but pertains to altered splicing of cardiac genes (multiple species of transcripts resulting from inclusion or exclusion of one or several coding exons).[186] It is evident that there is no unique mechanism but multiple mechanisms are involved in the pathogenesis of DCM caused by various genes and mutations.

GENETIC BASIS OF ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic cardiomyopathy (AC), also known as arrhythmogenic right ventricular cardiomyopathy (ARVC), is an uncommon cardiomyopathy with characteristic clinical and pathologic features.[199-201] It is

best defined as primary cardiomyopathy whose cardinal manifestation is cardiac arrhythmias, typically ventricular tachycardia, and it occurs disproportionate to cardiac dysfunction. This is contrast to ventricular tachycardia in DCM, which typically occurs in the presence of severely depressed cardiac function. The disease often has a "concealed" stage, which is characterized by minor ventricular arrhythmias and subtle pathologic findings. It is followed by symptomatic ventricular arrhythmias and gradual progression to right-heart failure and, finally, global cardiac failure. The prototypic form of AC is ARVC, which predominantly involves the right ventricle until in advanced stages, when the left ventricle is also involved.[201,202] The clinical phenotype comprises ventricular arrhythmias, primarily originating from the right ventricle, SCD, and heart failure. Involvement of the left ventricle typically portends an advanced stage and a poor prognosis.[202] In addition, left dominant AC is also described. The pathologic phenotype is characterized by the gradual replacement of the cardiac myocytes by adipocytes and fibrosis (Fig. 55–11).

Electrocardiographic features include the characteristics and yet uncommon epsilon wave, depolarization and repolarization abnormalities in the right precordial leads, and ventricular arrhythmias originating from the right ventricle.[203,204]

AC is an important cause of SCD in young and apparently healthy individuals.[201,205,206] In the US population, it accounts for 3% to 5% of SCD associated with physical activity in the young athletes.[103] In some reports, AC was found in up to 25% of the cases of nontraumatic SCD.[207-209] Collectively, the data suggest ARVC is an important cause of SCD in young, competitive athletes.

Significant fatty infiltration of the myocardium could be present in normal individuals, particularly in the elderly. Cor adiposum (fatty infiltration of the myocardium) is distinguished from true ARVC by the absence of right ventricular myocardial thinning, myocyte atrophy and apoptosis, patchy fibroadipocytic replacement of myocytes, predominantly in the right ventricle, and lymphocytic myocarditis.[210] Right ventricular dilatation, fibrosis, myocyte atrophy, and excess adipocytes have been observed in patients with Becker muscular dystrophy, Emery-Dreifuss muscular dystrophy, and myotonic dystrophy. The distinction between muscular dystrophies and ARVC is usually not problematic because of the skeletal involvement in muscular dystrophies. Given the difficulty in the accurate diagnosis of ARVC, the Task Force committee recommends requirement of two major criteria, or one major and two minor criteria, or four minor criterial for the diagnosis of ARVC.[211]

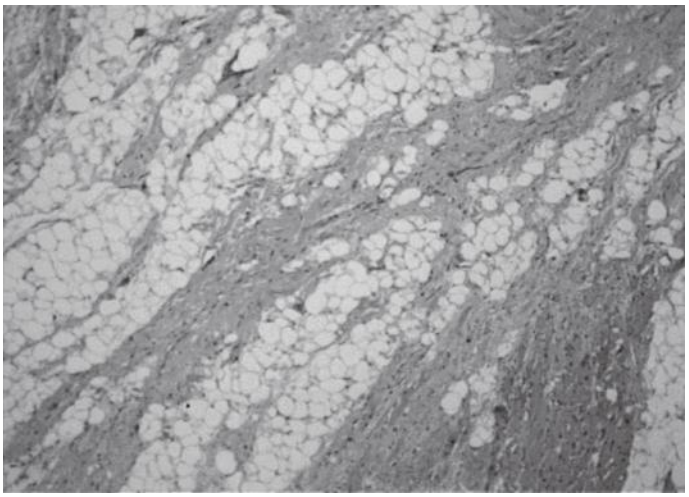

FIGURE 55–11. Histologic features of arrhythmogenic right ventricular dysplasia (ARVC). Fibrofatty infiltrate in the right ventricle is shown.

Molecular Genetics of Arrhythmogenic Cardiomyopathy

Classic ARVC, which is a subtype of AC, is a primarily genetic disorder of intercalated disk proteins (Table 55–11). Mutations in several genes encoding protein constituents of intercalated disks, which include desmosomes, are established causes of ARVC. Mutations in *DSP*, *JUP*, *PKP2*, *DSC2*, and *DSG2*, encoding desmosomal proteins desmoplakin (DP), plakoglobin (PG), plakophilin 2 (PKP2), desmocollin 2, and desmoglein 2 (DSG2), are among the most common causes of ARVC (see Table 55–11). Mutations in *PKP2* appear to be the most common causes of ARVC, accounting for approximately 25% of the cases. A significant number of *PKP2* mutations cause a frameshift and hence are expected to lead to premature termination of the proteins. *DSG2* and *DSP* genes each account for approximately 10% of the ARVC cases.

A subgroup of arrhythmogenic cardiomyopathy, because of expression of desmosome proteins in the skin and the heart, exhibits cardiocutaneous manifestations including keratoderma and woolly hair. The classic cardiocutaneous syndrome is Naxos disease (described first in a family from the island of Naxos in Greece), which is caused by a recessive truncating mutation in *JUP*, encoding junction protein plakoglobin.[212,213] Carvajal syndrome is another form of a cardiocutaneous syndrome wherein the left ventricle is the predominant site of involvement as opposed to the right ventricle in Naxos disease.[199,212] Carvajal syndrome is caused by mutations in the *DSP* gene.[212]

Mutations in *TMEM43* encoding transmembrane protein 43 are considered rare causes of classic ARVC.[214,215] The initially discovered mutation was considered fully penetrant and was associated with a high risk of lethal cardiac arrhythmias.[215] Not much is known about the structure and function of TMEM43 and the mechanisms by which it leads to AC, except that it appears to be a nuclear membrane protein with yet-to-be determined function.

TABLE 55–11. Causal Genes for Arrhythmogenic Cardiomyopathy

	Gene Symbol	Protein	Prevalence
Classic intercalated disk proteins	*PKP2*	Plakophilin 2	~25%
	DSP	Desmoplakin	~10%
	DSG2	Desmoglein 2	~10%
	DSC2	Desmocollin 2	~10%
	JUP	Plakoglobin	< 5%
	CTNNA3?	αT-Catenin	< 5%
Nuclear membrane	*TMEM43*	Transmembrane protein 43	< 5%
	LMNA	Lamin A/C	< 5%
Sarcomere/ Intermediate filament	*DES*	Desmin	< 5%
	TTN	Titin	< 5%
Calcium homeostasis	*PLN*	Phospholamban	< 5%
	RYR2?	Ryanodine receptor 2	< 5%
Ion channel	*KCNQ1?*	Iks channels	< 5%
Mitotic factor	*TGFB3 ?*	Transforming growth factor β3	< 5%

Phenocopy. *RYR2* mutations cause catecholaminergic polymorphic ventricular tachycardia and not true arrhythmogenic right ventricular cardiomyopathy.

ARVC also added to the diversity of phenotypic expression of the *LMNA* gene, which causes over a dozen distinct phenotypes.[216] Likewise, the gene encoding phospholamban (PLN) and Titin (TTN) are considered causal genes for AC, presenting as DCM and ventricular arrhythmias.[217,218]

Point mutations in the 5′ untranslated region of the *TGFB3* gene have been associated with ARVC.[219] However, the causal role of these variants in ARVC remains unsettled.

Idiopathic right ventricular outflow tract tachycardia and stress-induced (catecholaminergic) polymorphic ventricular tachycardia, caused by mutations in cardiac ryanodine receptor (RYR2), often present with arrhythmias resembling those in ARVC.[220,221] The absence of structural or histologic cardiac abnormalities suggests phenocopy and not true ARVC.

Pathogenesis of Arrhythmogenic Cardiomyopathy

The molecular pathogenesis of AC is largely unknown. The prevailing hypothesis implicates impaired mechanical integrity of myocyte-myocyte attachment as the instigator of activation of the mechanosensitive signaling pathways.[222,223] Among the pathways activated by impaired mechano-transduction is the Hippo pathway, which is activated in AC.[224] Activation of the upstream molecules of Hippo pathways through cascade phosphorylation of the downstream molecules leads to phosphorylation and inactivation of the YAP molecules, which results in reduced gene expression through TEAD transcription factor.[224] YAP also interacts with beta-catenin, the effector of the canonical Wnt signaling pathway, leading to cytoplasmic sequestration of beta-catenin and reduced gene expression through TCF7L2 transcription factor.[223,224] Additional mechanisms, such as partial translocation of membrane JUP to the nucleus, also further suppress gene expression through the canonical Wnt signaling.[223,225] Suppression of the canonical Wnt signaling in a subset of cardiac cells leads to their differentiation to adipocytes.

The heart is a cellular heterogeneous organ. The molecular events described above also occur in cells other than mature and terminally differentiated myocytes. The latter cells are not expected to transdifferentiate. Prevailing data suggest that a subset of cardiac mesenchymal cells, in addition to cardiac myocytes, express desmosome proteins and differentiate to adipocytes in AC.[225,226] The origin of fibrosis in AC and its molecular mechanisms are unknown.

GENETIC BASIS OF RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is a heart-muscle disease characterized by severely enlarged atria as a result of elevated right and left ventricular filling pressures, normal or reduced ventricular volumes, and usually preserved global systolic function.[227] The clinical manifestations are those of heart failure, often with predominance of right-sided signs and symptoms. The age of onset of the disease is variable, and the prognosis is relatively poor. RCM can occur because of systemic infiltrative disorders, such as amyloidosis and sarcoidosis, and storage diseases such as Fabry disease.[227,228] Such disorders are also genetic in etiology but their hemodynamic phenotype exhibits a restrictive physiology, and hence they phenocopy true RCM. Imaging, systemic tests, and pathology are needed to sometimes decipher these different forms of RCM.

Molecular Genetics of Restrictive Cardiomyopathy

RCM partly shares a genetic etiology with DCM and HCM, as mutations in the sarcomere gene could lead to either of the phenotypes.[229-233] In addition, a subset of patients with HCM or DCM exhibits a predominantly restrictive hemodynamic physiology. Accordingly, mutations in *MYH7*, *TNNT2*, *TNNI3*, *TTN*, and *MYPN* cause RCM.[229,232–234] Mutations in *DES*, encoding intermediary filament desmin, are also causes of familial RCM, occurring in conjunction with skeletal myopathy and atrioventricular conduction defects with an autosomal dominant pattern of inheritance.[235] As discussed, the phenotype of restrictive hemodynamic physiology resembling RCM also occurs in various other conditions including Noonan syndrome, caused by mutations in the protein tyrosine phosphatase, nonreceptor type II.[233]

GENETIC BASIS OF CARDIOMYOPATHIES IN TRIPLET REPEAT SYNDROMES

Cardiac involvement is common in neuromuscular disorders. A subset of neuromuscular disorders involves expansion of the naturally occurring GC-rich triplet repeats in genes and is referred to as triplet repeat syndromes.[236-239] The group comprises more than 10 different diseases, including myotonic muscular dystrophy and Huntington disease. Cardiac involvement is common in several forms of triplet repeat syndromes and is a major determinant of morbidity and mortality.[238,239] The phenotype commonly includes DCM, HCM, conduction disorders, and arrhythmias. Average life expectancy of the affected individuals is about 30 to 40 years.

Genetic Basis of Cardiomyopathies in Myotonic Dystrophy

Myotonic dystrophy (DM) is an autosomal dominant disorder with highly variable penetrance.[238-240] The estimated prevalence of DM is approximately 1 in 8000 in the North American population.[238-240] It is the second most common muscular dystrophy after Duchenne muscular dystrophy. DM commonly manifests itself as progressive degeneration of muscles and myotonia, cardiomyopathy, conduction defects, male-pattern baldness, infertility, premature cataracts, and endocrine abnormalities.[238-240] Cardiomyopathy is a common phenotypic manifestation of myotonic DM.[238,239] Cardiac conduction defects, such as first-degree atrioventricular block and intraventricular conduction defects, are present in approximately three-quarters of adult patients.

Expansion of CTG (CUG in mRNA) repeats in the 3′ untranslated region of the *DMPK* gene, encoding dystrophica myotonica protein kinase, and is the underlying pathogenic mutation in myotonic dystrophy.[241] The number of CTG repeats in normal individuals varies between 5 and 37. It expands from 50 to more than several thousand in patients with DM.[241] The length of the CTG repeats often correlates with the severity of clinical phenotypes, including conduction defects and cardiomyopathy. Expansion of the repeats leads to folding of the RNA into hairpin-like structures and a number of biological events including transcriptional, translational, and posttranslational changes. Among notable changes is sequestration of muscle blind-like protein-1 (MBNL1) and increased expression of ETR3-like factor-1 (CELF1), which are involved in regulating splicing of various genes including genes encoding cardiac sarcomere proteins.[242-244]

The second gene responsible for DM is zinc finger protein 9 (*ZNF9*), located on 3q21.[245] Expansion of a CCTG tetranucleotide repeats in the first intron of *ZNF9* leads to expression of abnormal RNA. The underlying mechanisms responsible for various phenotypic effects of the triplet repeat expansion in *ZNF9* are less well understood.[244]

Genetic Basis of Cardiomyopathies in Friedreich Ataxia

Friedreich ataxia (FRDA) is an autosomal recessive neurodegenerative disease. It primarily involves the central and peripheral nervous system and less frequently manifests as cardiomyopathy and occasionally as

diabetes mellitus.[246] FRDA is caused by the expansion of the GAA trinucleotide repeats in intron 1 of *FRDA*.[247] The encoded protein is frataxin, which is a soluble mitochondrial protein with 210 amino acids. Cardiac involvement can manifest as either DCM or HCM. The severity of clinical manifestations of FRDA also correlates with the size of the repeats. The pathogenesis of cardiomyopathies in FRDA is likely to involve impaired iron homeostasis, leading to iron accumulation in the mitochondria, and increased oxidative stress.[246]

GENETIC BASIS OF CARDIOMYOPATHIES IN NEUROMUSCULAR DISORDERS

Duchenne and Becker Muscular Dystrophies

The phenotype is characterized by progressive degeneration of skeletal and cardiac muscle function with an incidence of 1 in 3500 newborn males.[248] It commonly manifests itself during the first or second decades of life in male patients as mild but progressive skeletal myopathy, early contractures, and cardiomyopathy. Female family members are commonly spared. However, they may exhibit a mild phenotype, typically late in life. Duchenne muscular dystrophy is a severe form and Becker muscular dystrophy a milder form of the disease. Patients with Becker muscular dystrophy typically show onset of muscular symptoms in the second or third decades of life. This is in contrast to patients with Duchenne muscular dustrophy, who typically exhibit neuromuscular symptoms within the first decade of life. Cardiac involvement includes progressive atrioventricular block, arrhythmia, loss of P-wave amplitude on the ECG, atrial standstill, DCM, akinesis/dyskinesis of the left ventricular walls, particularly the posterobasal wall, and SCD.[249] Often DCM is the primary feature of Duchenne and Becker muscular dystrophies. Approximately 90% of patients will eventually develop DCM. Death often occurs by the third decade of life.

The gene responsible for Duchenne and Becker muscular dystrophies is dystrophin, located on Xp21, which encodes a large cytoskeletal protein. Mutations, which are typically frame-shift variants, result in the absence of dystrophin.[250] DCM can also occur in the absence of skeletal myopathy. Mutations leading to a frameshift induce a severe form, while missense mutations often lead to a mild form of the disease. Mutations in the 5′ region of the dystrophin gene can cause DCM without skeletal involvement.

The molecular mechanisms are diverse and include altered mechanotransduction and stretch-activated channels, calcium sensitivity, NO signaling, mitochondrial dysfunction, and oxidative stress, among others.[249] A number of experimental approaches are used to induce expression of dystrophin; stop-codon read-through therapies, upregulation of utrophin, CRISPR-Cas9-mediated gene editing, and recombinant viruses have been used to increase expression of dystrophin and alleviate muscle pathology.[249]

Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy is an X-linked degenerative disorder characterized by mild but progressive skeletal and cardiac myopathy.[251] Clinical features include muscle weakness and atrophy, flexion deformities of the elbows, and mild pectus excavatum. Cardiac phenotypes include cardiomyopathy, arrhythmia, SCD, conduction defects, loss of P-wave amplitude on the ECG, and atrial standstill.

The first causal gene identified for Emery-Dreifuss muscular dystrophy is *EMD*, which encodes nuclear membrane protein emerin.[252] Likewise, mutations in *LMNA*, encoding nuclear membrane protein lamin A/C, also cause Emery-Dreifuss muscular dystrophy.[253] Finally, mutations in *FHL1*, *TMEM43*, *SYNE1*, and *SYNE2* have been associated with phenotypic variants of Emery-Dreifuss muscular dystrophy.[251,254]

Barth Syndrome

DCM is a major phenotypic component of the Barth syndrome, an X-linked disorder characterized by skeletal and cardiac myopathy, neutropenia, and abnormal mitochondria. Barth syndrome is caused by mutations in *TAZ* encoding tafazzin (formerly known as G4.5), which is involved in fatty acid metabolism.[255] The majority of the mutations are missense mutations, but frame-shift and splice junction mutations have also been described. Mutations affect levels of unsaturated cardiolipin leading to mitochondrial dysfunction and oxidative stress, leading to muscle weakness and DCM.[256]

GENETIC BASIS OF CARDIOMYOPATHIES IN STORAGE DISORDERS

Cardiomyopathies observed in storage diseases encompass a group of disorders in which there is the primary metabolic abnormality in the heart (Table 55–12). This metabolic abnormality also may involve other organs; however, cardiac involvement is direct and not a consequence of secondary changes in other organs. Secondary involvement of the myocardium in systemic metabolic disorders is not included in this section. The phenotype typically resembles that of HCM or DCM caused by mutation in sarcomere proteins (phenocopy).

A prototype of storage cardiomyopathies is glycogen storage disease type II (glycogenosis type II or Pompe disease).[257] Pompe disease is an autosomal recessive disorder caused by mutations in *GAA* gene, which encodes acid alpha-galactosidase. Mutations lead to deficiency of α-1,4-glucosidase (acid maltase), which degrades α-1,4 and α-1,6 linkages in glycogen, maltose, and isomaltose. Deficiency of the enzyme leads to storage of glycogen in lysosomal membranes. Phenotypic expression of Pompe disease includes HCM, DCM, conduction defects, and muscular hypotonia. A high-protein diet and recombinant acid α-glucosidase have been used effectively to treat this disorder. Enzyme replacement therapy with algucosidase alpha early in the course of the diseases has beneficial clinical effects.[257]

Fabry disease, which is a relatively common HCM phenocopy, was discussed under HCM. In brief, it is an X-linked lysosomal storage disease caused by mutations in *GLA*, which encodes α-galactosidase.[121-124] Mutations lead to deficiency of α-galactosidase A and deposits of glycosphingolipids in multiple organs, including the heart. Enzyme replacement therapy with human agalsidase α or recombinant agalsidase β imparts beneficial effects.[125-128]

Mutations in the gene encoding the AMP-activated γ2 noncatalytic subunit of protein kinase A (*PRKAG2*) cause a glycogen storage disease with phenotypic expression as HCM and WPW syndrome.[98,129-132] AMP-activated kinase is a biosensor of the cellular energy state. Cardiac involvement varies from a predominant phenotype of preexcitation and conduction abnormalities to a predominant phenotype of cardiac hypertrophy.

TABLE 55–12. Selected Metabolic Cardiomyopathies

Protein	Symbol	Mutations/Phenotype
AMP-activated protein kinase, γ2 regulatory subunit	*PRKAG2*	Point and insertion mutations, HCM, WPW, and conduction defect
Acid maltase gene	*GAA*	Pompe disease, DCM, HCM, conduction defects
Phytanoyl-CoA hydroxylase	*PAHX or PHYH*	DCM, HCM, and conduction defects

AMP, adenosine monophosphate; CoA, coenzyme A; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; WPW, Wolff-Parkinson-White syndrome.

TABLE 55–13. Causal Genes for Mucopolysaccharidosis

Disease	Gene	Protein	Phenotype
MPS1	*IDUA*	α-L-iduronidase	Hurler syndrome, Cardiomyopathy, valvular heart disease
MPSII	*IDS*	Iduronate-2-sulfatase	Valvular heart disease, heart failure, obstructive coronary artery disease
MPSIIIA	*SGSH*	Heparan-N-sulfatase	Cardiac hypertrophy
MPSIIIB	*NAGLU*	α-N-acetylglucosaminidase	Charcot-Marie-Tooth disease type 2V, Sanfilippo syndrome
MPSIIIC	*HGSNAT*	Acetyl-CoA:α-glucosaminide acetyltransferase	Cardiac hypertrophy
MPSIIID	*GNS*	N-acetylglucosamine 6-sulfatase	Cardiac hypertrophy
MPSIVA	*GALNS*	N-acetylgalactosamine-6-sulfate sufatase	Valvular heart disease
MPSIVB	*GLB1*	β-Galactosidase 1	
MPSVI	*ARSB*	N-acetylgalactosamine-4-sulfatase (Arylsulfatase B)	Valvular heart disease, cardiomyopathy
MPSVII	*GUSB*	β-D-Glucuronidase	

Refsum disease is an autosomal recessive disorder characterized clinically by a tetrad of retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and elevated protein levels in the cerebrospinal fluid.[258] Cardiac involvement includes ECG abnormalities, which are common. Cardiac hypertrophy and heart failure are uncommon. Mutations in the gene encoding phytanoyl-coenzyme A (CoA) hydroxylase (*PAHX* or *PHYH*) are responsible for Refsum disease.[259,260] Mutations reduce the enzymatic activity and lead to accumulation of phytanic acid, an unusual branched-chain fatty acid in tissues and body fluids.[258]

The heart is also involved in patients with mucopolysaccharidosis, Niemann-Pick disease, and Gaucher disease. Cardiac phenotype entails cardiomyopathies, valvular disease, and obstructive coronary artery disease.[261] Table 55–13 lists various forms of mucopolysaccharidosis and the associated cardiovascular phenotypes.

Hereditary hemochromatosis is an autosomal recessive disease commonly caused by mutations in *HFE* gene on chromosome 6p12.3.[262] The encoded protein regulates iron absorption and leads to iron storage in various organs including liver and heart.[262] Cardiac involvement includes cardiac hypertrophy, heart failure, atrial fibrillation, and conduction defects.

GENETIC BASIS OF CARDIOMYOPATHIES IN MITOCHONDRIAL DISORDERS

Cardiomyopathies are common in patients with mitochondrial disorders. Mitochondrial cardiomyopathy exhibits a matrilineal transmission. Mitochondrial DNA (MtDNA) is a circular double-stranded genome of approximately 16.5 kb, encoding 13 polypeptides of the respiratory chain complexes I, III, IV, and V subunits; 2 ribosomal RNAs; and 22 tRNAs (transfer ribonucleic acids). Each mitochondrion has multiple copies of mtDNA DNA and each cell contains thousands of mitochondria. Nuclear genes encode for the vast majority of mitochondrial proteins that primarily regulate mitochondrial function. Thus mutations in nuclear genes are the primary causes of mitochondrial myopathies. Examples include mutations in *SCO2*, *FRDA*, and *ATP12* leading to HCM seen in patients with Leigh syndrome and Friedreich ataxia.[263] Mutations in genes encoding mitochondrial oxidative phosphorylation pathways often result in a complex phenotype involving multiple organs, including the heart. Cardiac involvement can lead to hypertrophy as well as dilatation. Mitochondrial DNA mutations typically result in a significant degree of heteroplasmy, because of the presence of a very large number of mitochondria in each cell, and multiple copies of mtDNA in each mitochondria. Heteroplasmy increases over time as the mitochondria multiply. In general, the majority of the mtDNA must mutate in order to affect mitochondrial function and lead to a clinical phenotype.

Kearns-Sayre syndrome is a mitochondrial disease caused by sporadically occurring mutations in mtDNA. Kearns-Sayre syndrome is characterized by a triad of progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects.[264] The classic cardiac abnormality in Kearns-Sayre syndrome is conduction defects; however, DCM and HCM are also rarely observed.[264]

L-Carnitine deficiency is a cause of mitochondrial myopathy resulting from mutations in nuclear DNA.[265] The phenotype is characterized by skeletal myopathy, congestive heart failure, abnormalities of the central nervous system and liver, and rarely, HCM. Carnitine is an important component of fatty acid metabolism and is necessary for the entry of long-chain fatty acids into mitochondria. Mutations in the chromosomal gene encoding solute carrier family 22, member 5 (*SLC22A5*), also known as *OCTN2* transporter, impair transport of carnitine to mitochondria and cause systemic carnitine deficiency.[266] Similarly, mutations in genes encoding enzymes involved in the transfer and metabolism of carnitine can cause carnitine deficiency. The list includes carnitine mitochondrial carnitine palmitoyltransferase I (CATI or CPT-1), located in the outer mitochondrial membrane; carnitine-acylcarnitine translocase (*SLC25A20*), located in the inner membrane; and carnitine palmitoyl transferase 2 (CPTII).[267] Mutations in genes coding for enzymes involved in carnitine biosynthesis, such as *TMLHE* and *BBOX1*, are also involved in carnitine deficiency.[265]

Mitochondria regulate fatty-acid oxidation as a major energy source in the heart. Mutations in proteins regulating fatty-acid beta-oxidation, such as *CPTIII*, *MTP*, and *VLCAD*, lead to lipid accumulation in cardiac muscle and heart failure, typically in conjunction with hypotonia, hypoglycemia, encephalopathy, hepatic dysfunction, skeletal myopathy, and SCD.[267] Likewise, mutations in *ABHD5* and *PNPLA2*, encoding alpha/beta-hydrolase domain-containing protein 5 and patatin-like phospholipase domain containing 2, respectively, lead to neutral lipid storage disease that occasionally involves the heart.[267]

GENETIC DISEASES OF CARDIAC RHYTHM AND CONDUCTION

Cardiac rhythm and conduction abnormalities could occur as the primary phenotypes of genetic disorders or secondary phenotypes resulting from genetic diseases that primarily affect structure of the heart. In general, cardiac arrhythmias and conduction defects result from abnormalities in three main families of proteins: contractile sarcomeric proteins, such as that in HCM; the cytoskeletal proteins, which are responsible for DCM; and the ion channels and their regulators, which are responsible for familial arrhythmias and conduction defects. As discussed earlier, there is significant phenotypic overlap as mutations in the same gene could cause a variety of cardiac rhythm and conduction disorders. This is best exemplified by mutations in sodium channel SCN5A, which could cause long QT syndrome, Brugada syndrome, and familial conduction disease.[268] Therefore, a simplistic classification of genetic disorders is considered preliminary and some of the key genetic findings used to risk-stratify for SCD or arrhythmias are based on studies in only few families. Table 55–14 summarizes the list of genetic disorders in which the primary phenotype is cardiac arrhythmias and conduction defects.

TABLE 55–14. Genetic Disorders Causing Cardiac Arrhythmias in the Absence of Structural Heart Disease (Primary Rhythm Disorders)

	Rhythm	Inheritance	Locus	Gene
Supraventricular				
Atrial fibrillation	AF	AD	10q22	—
		AD	6q14–16	—
		AD	10p11-q21	—
		AD	12p12	—
		AD	5p15	—
		AD	11p15	*KCNQ1*
		AD	21q22	KCNE2
		AD	21q22	KCNE1
		AD	11q13	KCNE3
		AD	17q23	KCNJ2
		AD	12p13	KCNA5
		AD	1p13	KCND3
		AD	1q21	*GJA5*
		AR	5p13	*NUP155*
		AD	3p21	*SCN5A*
		AD	19q13	*SCN1B*
		AD	11q23	*SCN2B*
		AD	11q24	*SCN3B*
		AD	8p23	*GATA 4*
		AD	20q13	*GATA 5*
		AD	18q11	*GATA 6*
		AD	1p36-35	*NPPA*
Atrial standstill	SND, AF	AD	3p21	*SCN5A*
Sick sinus syndrome	SND	AD	15q24	*HCN4*
		AR	3p21	*SCN5A*
		AD	14q11	*MYH6*
Absent sinus rhythm	SND, AF	AD	—	—
WPW	AVRT	AD	—	—
		AD	14q11	*MYH6*
Familial PJRT	AVRT	AD	—	—
Conduction Disorders				
PCCD	AVB	AD	19q13	TRPM4
			3p21	*SCN5A*
Ventricular				
LQT syndrome (RW)	TdP	AD		
			11p15	*KCNQ1*
			7q35	*KCNH2*
			3p21	*SCN5A*
			4q25	*ANK2*
			21q22	*KCNE1*
			21q22	*KCNE2*
			17q23	*KCNJ2*
			12p13	*CACNA1C*
			3p25	*Cav3*
			11q23	*SCN4B*
			7q21-q22	*AKAP9*
			20q11.2	*SNTA1*
			11q24	*KCNJ5*
			1q42	*RYR2*
			19q13	*SCN1B*
			14q32	*CALM1*
			2p21	*CALM2*
LQT syndrome (JLN)	TdP	AR	11p15	*KCNQ1*
			21q22	*KCNE1*
			6q22	*TRDN*
SQT syndrome	VF	AD		
			7q35	*HERG*
			11p15	*KCNQ1*
			17q23	*KCNJ2*
			12p13	*CACNA1C*
			10p12	*CACNB2*
			7q21	*CACNA2D1*
Catecholaminergic PVT	VT	AD	1q42	*RYR2*
			14q32	*CALM1*
			2p21	*CALM2*
		AR	1p13-p11	*CASQ2*
			6q22	*TRDN*
Brugada syndrome	VT/VF	AD	3p21	*SCN5A*
		AD	3p22	*GPD-1L*
		AD	12p13	*CACNA1c*
		AD	10p12	*CACNB2b*
		AD	11q13	*KCNE3*
			19q13	*SCN1B*
			11q23	*SCN2B*
			11q24	*SCN3B*
			3p22	*SCN10A*
			17p13	*RANGRF*
			3p14	*SLMAP*
			12p11	*PKP2*
			12p12	*ABCC9*
			12p12	*KCNJ8*
			15q24	*HCN4*
			1p13	*KCND3*
			7q21	*CACNA2D1*
			19q13	*TRPM4*
			Xq22	*KCNE5*

AD, autosomal dominant; AF, atrial fibrillation; AR, autosomal recessive; AVB, atrioventricular block; AVRT, atrioventricular reentrant tachycardia; JLN, Jervell and Lange-Nielsen; LQT, long QT; PCCD, progressive cardiac conduction defect; PJRT, paroxysmal junctional reentrant tachycardia; RW, Romano-Ward; SND, sinus node dysfunction; TdP, torsades de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

ION CHANNELOPATHIES AS THE BASIS FOR CARDIAC ARRHYTHMIAS AND CONDUCTION DEFECTS

Ion channels, crucial units in cardiac excitability, are glycoproteins embedded in the membrane of the cardiac myocytes, which allow flux of ions in and out of the cell to modulate the electrical gradient. Many different ion channels and chaperone proteins, which maintain protein homeostasis, are activated in an orderly manner to give rise to the electrical current that will ultimately be responsible for the development of the myocyte excitability. This is a complex process and requires a very well controlled ionic balance to prevent arrhythmogenesis. Genetic defects in these proteins will be responsible for channelopathies, inherited diseases that may be associated with arrhythmias and/or sudden cardiac death.[269]

BRUGADA SYNDROME AND ITS VARIANTS

Brugada syndrome is identified by a characteristic ECG pattern consisting of right bundle branch block and ST-segment elevation in V_1 to V_3 (Fig. 55–12) and sudden death at a young age. It was described originally in 1992 based on electrocardiographic pattern and occurrence of syncope or sudden death episodes in patients with a structurally normal heart.[270] The episodes of syncope and sudden death are caused by fast polymorphic ventricular tachycardia.

Brugada syndrome usually manifests in subjects in the third or fourth decades of life, but may cause symptoms at any age, and even cause sudden infant death syndrome (SIDS).[271] In 1997, it was shown that Brugada syndrome was underlying some of the cases of SUDS (sudden unexpected death syndrome), which is prevalent in Southeast Asia.[272] SUDS is estimated to affect up to 1% of the population and it is the most common cause of death in young males in Thailand. Death often occurs at night and more commonly in male subjects (male-to-female ratio is 10:1). Electrocardiographically, the disease is identical to Brugada syndrome.[273] As in Brugada syndrome, mutations in *SCN5A* have been found responsible for SUDS and biophysical data indicate a nonworking *SCN5A* or accelerated inactivation.

Genetics of the Brugada Syndrome

The α subunit of the cardiac sodium channel gene, *SCN5A*, was identified as the first causal gene for Brugada syndrome in 1998. *SCN5A*, which is responsible for phase 0 of the cardiac action potential, has been studied extensively during the past years. *SCN5A* was first cloned and characterized in 1995 and localized to 3p21. The gene is comprised of 28 exons that code for a 2016 amino-acid protein. It contains four homologous domains (DI to DIV), each of which contains six membrane-spanning segments (S1 to S6). In 1995, Wang and associates linked mutations in *SCN5A* to long QT syndrome, a disease characterized by prolongation of the QT interval and sudden death at a young age.[274] Subsequently, mutations in *SCN5A* were linked to idiopathic ventricular fibrillation, the Brugada syndrome, progressive conduction defect, SIDS, and SUDS. Important overlap exists between phenotypes, as it is not uncommon to observe several electrocardiographic features in a same family.[268] These data suggest mutations in *SCN5A* cause variable phenotypic manifestations that span Brugada syndrome, LQT3, and progressive conduction defects (see Fig. 55–12). Figure 55–13 shows the phenotypes arising from mutations in *SCN5A*.

In Brugada syndrome, *SCN5A* is responsible for 25% to 30% of familial cases. As in many other genetic disorders, Brugada syndrome also exhibits locus heterogeneity. Currently, more than 300 pathogenic variants have been identified in 19 genes (*ABCC9, CACNA1C, CACNA2D1, CACNB2b, GPD1-L, HCN4, KCND3, KCNE3, KCNE5, KCNJ8, PKP2, RANGRF, SCN10A, SCN1B, SCN2B, SCN3B, SCN5A, SLMAP*, and *TRPM4*) (Table 55–14), which affect sodium, potassium, and calcium currents.[275] *PKP2* mutations are also associated with Brugada syndrome, a finding that suggests structural proteins by decreasing I_{Na} and reducing the number of channels at the intercalated disc could be responsible for Brugada syndrome.[276]

Pathogenesis of Brugada Syndrome

Biophysical characterization of mutations in *SCN5A* suggests that mutations decrease the Na^{1+} current availability by two main mechanisms: decreased expression of the mutant channel or acceleration of inactivation of the channel. In addition, the alteration in the ionic currents that worsen at higher temperatures has been implicated for certain mutations, such as the T1620M.[277] The clinical relevance of this mechanism is corroborated by the observation of several cases of ventricular fibrillation during febrile illnesses in patients with Brugada syndrome.[278] Compared to LQT3, the pathogenesis of Brugada syndrome could be considered a mirror image. Biophysical data indicate that LQT3 mutations cause a delayed inactivation of the channel,

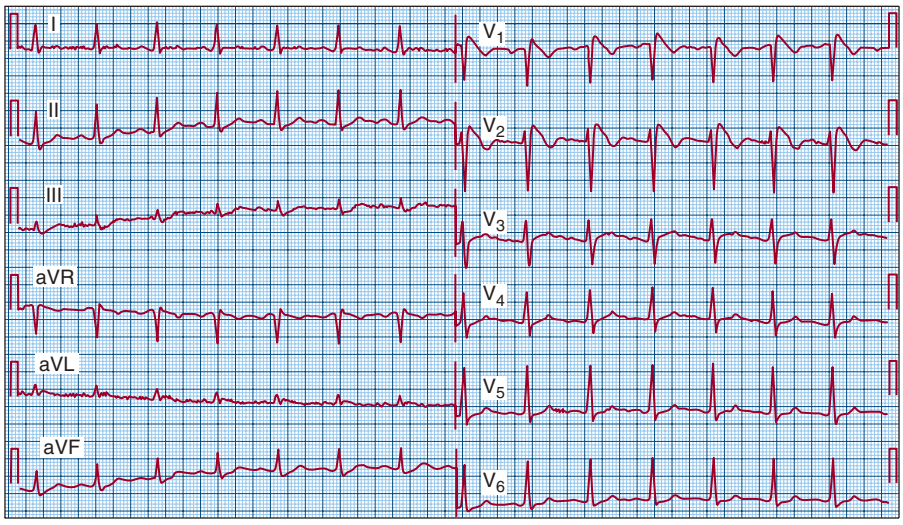

FIGURE 55–12. Typical electrocardiogram of Brugada syndrome. Note the pattern resembling a right bundle branch block and the ST elevation in leads V_1 to V_2.

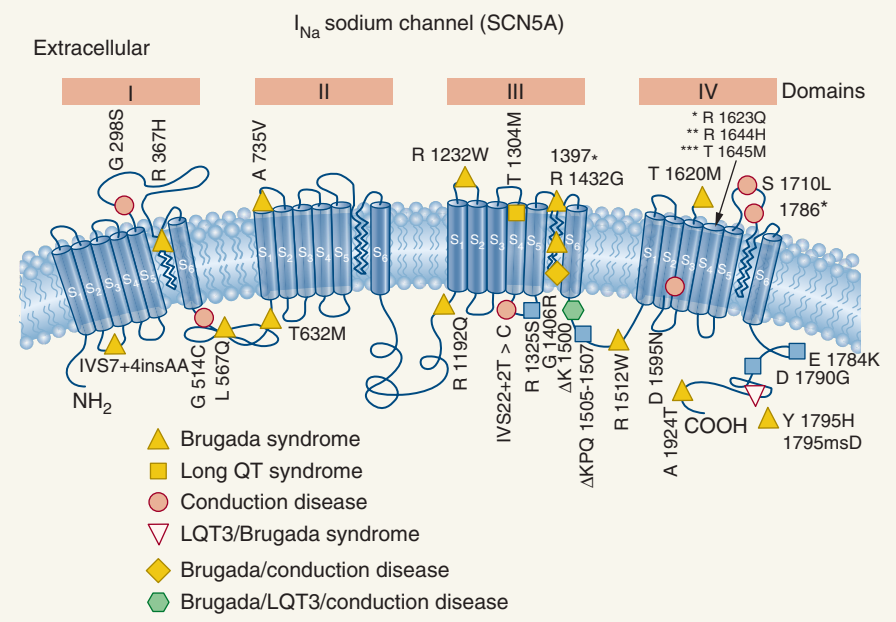

FIGURE 55–13. Schematic structure of I_{Na} sodium channel (SCN5A) and phenotypes arising from mutations in *SCN5A*.

which is exactly the opposite as in Brugada syndrome, where there is an accelerated inactivation.[268]

How Na^{1+} current alteration causes elevation of the ST segment in the right precordial leads is still a matter of controversy. Two main hypotheses are considered in the pathogenesis of Brugada syndrome: the repolarization versus depolarization hypotheses.[279]

In the repolarization hypothesis it is claimed that mutations in *SCN5A* in patients with Brugada syndrome will have decreased availability of sodium ions, which could shift the ionic balance in favor of transient outward potassium current (I_{to}) during phase 1 of the action potential. This disequilibrium will generate a shortening of the subepicardial action potential, with elevation of the ST segment in the right precordial leads, and cause a susceptibility to phase 2 reentry. This current alteration can be better seen in the RVOT, as it seems that this is the area where the equilibrium is more critical.

On the other hand, the depolarization hypothesis suggests that the substrate for arrhythmogenicity is right ventricular (RV) conduction delay, caused by the genetic defects in *SCN5A*.[280] Evidence towards the depolarization hypothesis has been accumulating in these last years with the detection of abnormal late potentials in the free wall of the RVOT epicardium, with the interstitial fibrosis without transmural repolarization differences, in an explanted heart from a patient with BrS, or with the increased fibrosis, more severe in aging males, affecting all cardiac regions, but especially the RV in the *SCN5A* knock-out animal model.[281,282] Strong evidence favoring depolarization hypothesis has been made available in recent years with a new form of treatment: epicardial ablation of the RVOT epicardium, which has resulted in disappearance of the ECG pattern, inducibility during electrophysiological studies, as well as decrease in event recurrence. This technique, only performed at present in patients with an implanted defibrillator, has the potential to significantly alter the current therapeutic approach in Brugada syndrome.[283,284]

Genotype–Phenotype Correlation in Brugada Syndrome

Interestingly, limited data are available regarding the correlation between genotypes and phenotype in patients with Brugada syndrome. This may partly reflect very recent identification of the first causal gene, phenotypic variability of *SCN5A*, and allelic and locus heterogeneity of Brugada syndrome. It has been suggested that electrocardiographic parameters, such as longer conduction intervals (PQ and HV) on baseline ECG, could distinguish the carriers of sodium channel mutations from the noncarriers.[285]

In the last years, polymorphisms have been acquiring greater importance to explain certain phenotypes of genetic diseases. In the *SCN5A* locus, the common H558R polymorphism has been shown to restore (at least partially) the sodium current impaired by other simultaneous mutations causing either cardiac conduction disturbances or Brugada syndrome. Thus, this polymorphism seems to alter clinical phenotype by modulating the effect of nearby mutations.[286-289] Genome-wide association studies have shown that cardiac conduction may be modulated by genetic polymorphisms in *SNC5A* and *SCN10A* and influence risk of cardiac arrhythmia.[290] However the role of *SCN10A* as a causative gene in Brugada syndrome appears to be minimal.[291]

LONG QT SYNDROME

LQT syndrome (LQTS) is a disease of ventricular repolarization identified by the prolongation of the QT interval on ECG. The diagnosis of the disease is based on the presence of a QTc > 480 msec, a LQTS score > 3 (a scoring system ranking from 1 to 9, based on ECG findings, clinical history, and family history), or the presence of a confirmed pathogenic LQTS mutation, irrespective of QT duration.[292]

LQTS has a prevalence of 1/2500 to 1/5000 and it is characterized by syncopal episodes, malignant ventricular arrhythmias, and ventricular fibrillation. The majority of patients with the LQT syndrome are asymptomatic. However, approximately one-third present with syncope or aborted malignant ventricular arrhythmias including torsades de pointes, which is the most typical ventricular arrhythmia in LQT syndrome. SCD is relatively common. Prognosis of the symptomatic cases, if untreated is poor. The annual rate of SCD in untreated patients is estimated at approximately 0.9%.[293] In syncope patients the rate rises to 5%.[294]

The LQT syndrome is either acquired, which is iatrogenic and commonly induced by drugs, or congenital. A common cause of the acquired disease is the use of medications such as antiarrhythmics, antidepressants, and phenothiazines (Table 55–15). In addition, electrolyte imbalance, such as hypokalemia, hypomagnesemia, and hypocalcemia, especially in the presence of predisposing medications, could cause LQT syndrome.

Two patterns of inheritance have been described in the congenital LQT syndrome: (1) autosomal recessive disease, described by Jervell and Lange Nielsen in 1957, which is associated with deafness; and (2) autosomal dominant disease, described by Romano and Ward, which is not associated with deafness and is more common than the recessive form.[295]

Long QT syndrome is caused by mutations in several genes, which are responsible for Na^{1+}, K^{1+}, and Ca^{2+} currents. The most common forms, however, are defects that cause K^{1+} and Na^{1+} current alterations. The pathogenesis of LQT syndrome could be summarized as mutations in K^{1+} channel resulting in inadequate opening and decreased potassium outward currents, while mutations in Na^{1+} channels lead to inadequate closure of the channels and excessive sodium inward currents. The ensuing result is inadequate maintenance of electrical gradient (loss of function) during an action potential and prolongation of the QT interval. Pathogenesis of LQT syndrome caused by CACNA1C mutations (Timothy syndrome) involves delayed channel closing, prolonged inward current through L-type calcium channels, and QT prolongation.

TABLE 55–15. Selected Medications Associated with Prolonged QT Interval

Antiarrhythmic drugs
Quinidine (Class Ia)
Procainamide hydrochloride (Class Ia)
Disopyramide phosphate (Class Ia)
Propafenone (Class Ic)
Sotalol hydrochloride (Class III)
Amiodarone (Class III)
Ibutilide fumarate (Class III)
Dofetilide (Class III)
Anesthetics/antiasthmatics
Droperidol
Adrenaline
Antibiotics
Clarithromycin
Erythromycin
Pentamidine
Trimethoprim-sulfamethoxazole
Ketoconazole
Fluconazole
Antihistamines
Terfenadine
Diphenhydramine
Antihyperlipidemic
Probucol
Central nervous system active drugs
Droperidol
Haloperidol
Pimozide
Risperidone
Gastrointestinal stimulants
Cisapride

Autosomal Dominant LQT Syndrome (Romano-Ward Syndrome)

In the last 25 years, at least 18 genes have been identified as being responsible for the long QT syndrome (see Table 55–14). The known genes are responsible for 80% to 85% of cases. All encode proteins that are responsible for automaticity of the electrical activity in the cardiac cells. Mutations in these genes disrupt electric currents, alter cardiac action potential, and create a voltage gradient especially at the ventricular level, leading to reentrant arrhythmias. Three genes are responsible for the most part (60%-70%) of long QT syndrome. These will be described in the next sections.

LQT Syndrome 1 The causal gene for LQT1 is *KVLQT1* (or *KCNQ1*), which encodes a voltage-gated potassium channel α subunit and is strongly expressed in the heart. It consists of 16 exons spanning 400 kb, which form 6 transmembrane segments. It coassembles with the β subunit min K (KCNE1) to form the slow-activating potassium current I_{Ks}. Mutations in this gene disrupt the normal function of the protein, causing a decrease in the potassium current. Several mutations have been described in *KCNQ1* to date.

LQT Syndrome 2 The LQT2 gene is *KCNH2* (or *HERG*, "human ether-a-go-go related" gene), which was isolated in 1994 from hippocampus and named human ether-a-go-go related gene because of its homology to the *Drosophila* "ether-a-go-go" gene. The gene is localized on chromosome 7q35-q36. It contains 16 exons spanning approximately 55 Kb of genomic sequence. It encodes a protein that forms six transmembrane segments. The protein is responsible for the rapidly activating delayed rectifier potassium current I_{Kr} after coassembly with MIRP1 (KCNE2). As in the case of LQT1, mutations in *HERG* cause an abnormal protein with a resulting loss of potassium current.

LQT Syndrome 3 The causal gene is *SCN5A*, located on chromosome 3, which encodes for the cardiac sodium channel. Mutations in *SCN5A* also cause Brugada syndrome and progressive conduction system disease, as discussed earlier. Electrophysiologic studies following expression of the mutant proteins in xenopus oocytes indicate a gain of function mutations evidenced by delayed inactivation and persistent sodium influx after phase 0 of the action potential.[269]

Other genes have been described, affecting sodium, potassium or calcium currents, but they are responsible for a low percentage of cases. In addition, some of these long QT cases will present with extracardiac features The other genes are described in the next two sections.

LQT Syndrome 7 Andersen syndrome is characterized by the constellation of periodic paralysis, cardiac arrhythmias, long QT, and dysmorphic features such as short stature, scoliosis, clinodactylism, hypertelorism, lowset or slanted ears, micrognathia, and broad forehead. The causal gene is *KCNJ2*, located on chromosome 17q23. It encodes the inward rectifier potassium channel Kir2.1, expressed in skeletal and cardiac muscles. Kir2.1 is a strong inward rectified channel that prevents passage of any current at potential greater than 40 mV. Electrophysiologic studies indicate the mutant protein exerts a dominant negative effect on Kir2.1 function with an ultimate decrease in potassium current.

LQT Syndrome 8 LQT8, also known as Timothy syndrome, is characterized by the presence of facial dysmorphic features, syndactyly, small

teeth, mental retardation, and severe QT prolongation. Mutations in *CACNA1C*, encoding for the α subunit of the L-type calcium channel, have been identified as responsible for the syndrome. The mutations cause a gain of function defect, increasing the inward current and prolonging the action potential.[296]

Other genes have been described affecting sodium, potassium, or calcium currents.

Autosomal Recessive LQT Syndrome (Jervell and Lange-Nielsen Syndrome) The autosomal recessive forms of the LQT syndrome have been linked to mutations in the genes encoding I_{Ks} current, namely *KCNQ1, KCNE1*, and *TRDN*.[297]

For the LQT recessive phenotype, which in *KCNQ1* and *KCNE1* is also associated with sensorineuronal deafness, the patients must inherit a mutation from both parents. Consequently, it is less common than the Romano-Ward syndrome but is associated with a more malignant course and a longer QT interval. The phenotype could also arise in recessive forms when different mutations in the same gene are inherited from the parents (compound heterozygote).[298]

Management in Long QT Syndrome

There are several recommendations in patients with LQTS. Given the role of external factors in affecting the QT interval, patients with LQTS are advised to avoid QT-prolonging drugs, electrolyte abnormalities, and genotype-specific triggers for arrhythmias. On the other hand, all LQTS patients, irrespective of genotype and symptoms, are advised to be treated with beta-blockers. Silent genetic carriers have a risk of cardiac events estimated at 10% until age 40; thus beta-blockers are also indicated in this population. ICD implantation should be considered in patients with previous cardiac arrest, in patients with syncopal episodes despite beta-blocker therapy, and in asymptomatic patients with a QTC > 500 msec. Left cardiac sympathetic denervation can be considered in patients who remain symptomatic. Finally, sodium channel blockers can be considered in patients with LQT3.

Genotype–Phenotype Correlation in LQT Syndrome

Given the availability of a large number of families with the LQT syndrome, several genotype–phenotype correlation studies have been performed to identify the genetic determinants of triggering events, electrocardiographic phenotype, and response to therapy. The studies predominantly, encompass the three most common forms of LQT syndrome—LQT1, LQT2, and LQT3—and have significant limitations inherent to genotype–phenotype correlation studies described earlier. Despite their limitations, characteristic features have emerged that could guide the analysis of the patients toward a specific genetic defect (Table 55–16).

Triggering Events Characteristic features have emerged that help in part guide the analysis of patients towards a specific genetic defect. In general, individuals with LQT1 exhibit symptoms during physical activity, especially in swimming activities. Individuals with LQT3 are symptomatic during sleep.[299]

Electrocardiographic Phenotypes LQT1 patients have a T wave that usually begins just after the QRS, becoming long and broad based. LQT2 patients have a small or notched T wave and LQT3 patients show a very late T wave with a prolonged ST segment.[300]

Clinical Phenotypes According to Genotype Mutations also carry prognostic significance, and in all three groups (LQT1, 2, and 3) there is a correlation between cardiac events and the QT interval. In general, patients with LQT1 and LQT2 have a higher risk of cardiac events than patients with LQT3. The latter, despite having fewer events, have a relatively higher mortality, which indicates higher lethality of the events.[301]

Biophysical Phenotypes There have been few studies that have assessed the biophysical effect and location of the mutation and correlated it with the severity of the phenotype. Pore mutations in KCNH2 and transmembrane KCNQ1 mutations are associated with a higher incidence of events.[302,303]

Response to Therapy In addition, response to drug therapy seems to correlate with the genotype (class IIa). Beta-blockers are considered the first line of therapy in LQTS, despite previous work that indicated that LQT3 did not benefit as much from this medication. Preliminary data suggest LQT3 patients might benefit from Na^{1+} channel blockers, such as mexiletine (class IIb).

TABLE 55–16. Genotype–Phenotype Correlation in Long-QT Syndromes

Phenotype	Gene	T Wave	Trigger
LQT1	*KCNQ1*	Early onset, broad-base T	Emotion, swimming
LQT2	*HERG*	Low amplitude	Auditory
LQT3	*SCN5A*	Late T, normal amplitude	Sleep

Induced or Acquired Long QT Syndrome

Induced or acquired long QT is iatrogenic, caused by a long list of medications (see Table 55–15) and electrolyte abnormalities. A large number of factors determine the risk of developing long QT syndrome in an individual in response to drug therapy. They include bioavailability of the drug, the interaction with other medications that affect the same repolarizing current, and the presence of SNPs. SNPs play a major role in determining pharmacodynamics and pharmacokinetics of drugs and thus the risk of LQT syndrome. The final effect on the repolarization will depend on the so-called *repolarizing reserve*, or the degree of alteration that the ionic currents can sustain before repolarization is compromised. Any combination of genetic and environmental factors (drug, electrolyte abnormalities) that decrease this "repolarization reserve" below a safe threshold will place the individual at risk of arrhythmia.[304]

SHORT QT SYNDROME

The short QT syndrome is a disease characterized by the presence of shortening of the QT interval on ECG and clinically by episodes of syncope, paroxysmal atrial fibrillation, and/or life-threatening cardiac arrhythmias. Short QT syndrome usually affects young and healthy individuals with no structural heart disease. It may be present in sporadic cases, as well as in families. It was originally described in 2000.[305] In 2003, a link was provided between the short QT syndrome and familial sudden death with the first clinical report of two families with short QT syndrome and a high incidence of SCD.[306]

Clinical Manifestations

Most patients with short QT syndrome have a history of familial sudden death and/or atrial fibrillation, short refractory periods, and inducible ventricular fibrillation at electrophysiologic study. The age at onset of clinical manifestations could be extremely young. Malignant forms of short QT syndrome responsible for neonatal SCD have been attributed to SIDS. The severity of the clinical manifestations of short

QTs is highly variable, ranging from asymptomatic to atrial fibrillation, and recurrent syncope to sudden death.[307]

The characteristic sign for the disease is the presence of a very short QT interval on ECG. The T wave remains upright and the interval between the peak and end of the T wave is not prolonged. The appearance of a well-separated U wave has also been reported in several cases. It is difficult to define the normal QT interval, as the correcting equations have several limitations. Nevertheless, at a heart rate of 60 beats/min, the uncorrected QT interval is usually higher than 360 milliseconds. Clinical guidelines recommend making the diagnosis of SQTS with a QTc of < 340. In addition, SQTS is diagnosed in patients with a QTC < 360 msec and a confirmed pathogenic mutation, a family history of SQTSm, and a family history of sudden death at age < 40 years or after survival of VT/VF episode in the absence of structural heart disease.

Molecular Genetics and Electrophysiology

Genetics and biophysical analysis have provided important information regarding the pathophysiologic mechanisms that cause the short QT syndrome. Short QT syndrome, as are the majority of primary familial electrical diseases, is caused by mutations in genes encoding cardiac ion channels. Three genes have so far been discovered thereby proving that the disease is genetically heterogeneous. These genes will be described in the next sections.

Short QT Syndrome 1 *KCNH2* expresses a protein that makes up the channel responsible for the rapidly activating outward K^+ current involved in phase 3 repolarization. The protein is often referred to as HERG. The first genetic basis for the disease was obtained with the identification of two different missense mutations in the same residue in *KCNH2* in three unrelated families. Both mutations resulted in the substitution of asparagine for lysine at codon 588 (N588K), an area at the outer mouth of the channel pore.[308]

Analysis of the current generated after transferring the mutated channels into human mammalian cells showed that the mutation abolished the inactivation of the channels, thus resulting in an increased developing current. The biophysical analysis therefore showed that the mutation induced a "gain of function" in I_{Kr} current, thus causing a shortening of the action potential.

The presence of paroxysmal atrial fibrillation in some affected individuals and especially in one of the families as the only clinical manifestation suggested that the increased heterogeneity would also be present at the atrial level and could be responsible for the arrhythmia.[309]

Short QT Syndrome 2 The *KCNQ1* gene encodes a subunit of the proteins responsible for the slowly activating delayed outward K^+ current. A missense mutation in this gene causing short QT syndrome was first identified by Bellocq and colleagues in a 70-year-old individual who suffered ventricular fibrillation and had a QT interval of 290 milliseconds after resuscitation. He was not inducible at electrophysiologic study and had no cardiac structural abnormalities.[310] A second mutation in *KCNQ1* has been identified in several cases of fetal bradycardia, atrial fibrillation, and short QT syndrome.[311]

Biophysical analysis showed that both mutations were leading to a gain of function in the outward current that explains the short QT syndrome phenotype.

Short QT Syndrome 3 The third form of short QT syndrome has been linked to mutations in the *KCNJ2* gene, which codes for the channel protein responsible for the inward rectifier current (a current that moves inside the cells to stabilize the resting membrane potential). The proband and her father with the mutation both displayed short QT intervals of 315 and 320 milliseconds, respectively. ECG recordings showed asymmetrical T waves with an abnormally rapid terminal phase. When expressed in Chinese hamster ovary cells, the mutated channels generated electrical currents that did not rectify (decreased) as much as the normal channels in their functional positive range of potentials (80 to 30 mV). Such a range of voltages corresponds to the very end of phase 3 repolarization and to phase 4. Simulation of the effects of the mutated channels on the morphology of the ventricular action potential showed a selective speeding of late repolarization, thus shortening significantly the action potential duration at 90% repolarization.[312]

Finally, pathogenic variants in *CACNA1C* and *CACNB2* have been associated with overlapping of BrS and a shortened QT interval.[313]

Phenotype–Genotype Correlation

Robust phenotype–genotype correlation data are not yet available for short QT syndrome. The disease is clinically highly heterogeneous, as indicated by the fact that in the three families with the same mutation there is a tremendous variation in symptoms and presentation.

Treatment Strategy of Short QT Syndrome

Preliminary data show that there may be effective pharmacologic therapy for this disease (class IIb). However, the high incidence of SCD warrants the implantation of an intracardiac cardioverter/defibrillator, especially in individuals with aborted sudden death.

Because QT shortening is likely caused by an increase in the outward current, it was suggested that blocking the current with class III antiarrhythmic drugs (known to increase the QT interval) could be a potential therapeutic approach for the treatment of short QT syndrome (class IIb). Gaita and coworkers showed that treatment with quinidine prolonged the QT interval, decreased inducibility, and therefore had the potential to be an effective therapy for these patients (class IIb).[314] Clinical follow-up in one family with paroxysmal atrial fibrillation indicates that the episodes respond well to treatment with the class Ic agent propafenone (class IIb).

PROGRESSIVE FAMILIAL HEART BLOCK

Familial heart block is autosomal dominant progressive disease of cardiac conduction system characterized by initial development of bundle branch block and gradual progression to complete heart block. Two forms have been recognized. In type I, the onset is early and the disease is rapidly progressive. In type II, the onset is later in life and commonly the QRS complex is narrow and AV nodal block predominates. Clinical features of the disease include syncope, SCD, and Stokes-Adams attacks (sudden syncope related to paraoxysmal or chronic AV block, SA block, or paroxysmal tachycardia or fibrillation). A locus was identified in a large family of Portuguese descent on chromosome 19q13. The gene *TRPM4* was identified in 2010 in three different families.[315] Immunohistochemistry showed that *TRPM4* channel signal level was highest in Purkinje fibers, with mutations resulting in a gain of function. As discussed earlier, mutations in *SCN5A* have also been shown in some families with familial heart block. In addition, AV block in conjunction with congenital heart disease, such as ASD (*NKX2.5* mutations), and DCM (lamin A/C mutations) have been described; these were discussed earlier.[316,317]

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Ryanodine receptors are responsible for release of calcium from the sarcoplasmic reticulum and are activated by the incoming calcium; therefore they are Ca^{2+}-activated Ca^{2+} channels.

Familial polymorphic ventricular tachycardia is an autosomal-dominant inherited disease with a mortality rate of approximately 30% by the age of 30 years. Phenotypically, it is characterized by runs of bidirectional and polymorphic ventricular tachycardia in response to vigorous exercise in the absence of evidence of structural myocardial disease. The prevalence of the disease is estimated at 1/10,000. An added difficulty in the diagnosis is the fact that the basal electrocardiogram is usually normal, and patients have to be diagnosed with an electrocardiogram during exercise. The value of this test is very dependent on the families, as in some cases it does not reach a diagnosis of 50% of genetic carriers.[318]

Currently, six genes have been associated with the disease, following an autosomal dominant (*CALM1, CALM2, KCNJ2*, and *RyR2*), and autosomal recessive (*CASQ2* and *TRDN*) pattern of inheritance (see Table 55–1). A comprehensive genetic study identifies pathogenic variants in nearly 60% of all clinically diagnosed cases. The main gene responsible for CPVT is *RyR2* (CPVT type 1). It is responsible for nearly 50% of all cases. Thus all other genes together are responsible for nearly 10% of CPVT cases.[319]

Therapy in CPVT is based on lifestyle modifications (avoiding competitive sports, strenous exercise, and stressful environments), beta-blocker and flecainide therapy, and ICD implantation and left cardiac sympathetic denervation in those who remain symptomatic despite medical therapy.

SICK SINUS SYNDROME

Sick sinus syndrome is characterized by the occurrence of sinus bradycardia, sinus arrest, and chronotropic incompetence. Sinus node dysfunction has been linked to loss of function mutations in *HCN4*, and in recessive form to *SCN5A*.[320] *HCN4* contributes to native f-channels in the sinoatrial node, the natural cardiac pacemaker region. In 2006, a loss of function defect in *HCN4* was also linked to familial sinus bradycardia.[321]

FAMILIAL ATRIAL FIBRILLATION

Atrial fibrillation is the most common sustained rhythm disorder or arrhythmia encountered in clinical practice, with a prevalence of 1% in the general population, which increases with age to about 6% in people over the age of 65. It is responsible for over one-third of all cardioembolic episodes.

AF was not generally appreciated to be a familial inherited disorder. AF was first reported as a familial form in 1943. In later years, published studies have shown several lines of evidence supporting the genetically determined heritable basis to AF. A study by Darbar and associates indicated that the familial form of the disease may have a higher prevalence than previously suspected and emphasized the importance of expanding genetics studies. Familial AF may be a monogenic disorder and is often identified as AF being present in many members of the same family. The first locus for familial atrial fibrillation was identified in 1997, in 10q22.[322] Several other loci and genes have been identified since then.

Atrial Fibrillation Associated with Genetic Alterations in Potassium Currents

Most of the single-gene mutations that have been discovered in families with AF cause cardiac K^+-channel defects. The first gene responsible for familial AF, *KCNQ1*, was identified in 2003, linking the disease to an ion channelopathy.[323] *KCNQ1* encodes the pore-forming α-subunit of the cardiac slow delayed-rectifier (I_{Ks}) channel and its loss of function had been previously associated with long QT syndrome. The analysis of *KCNQ1* identified a missense mutation resulting in the amino acid change S140G. Electrophysiological studies revealed a gain of function in Iks current when the mutated channel was expressed with the β-subunits *KCNE1* and *KCNE2*. This gain of function explained well the shortening of the action potential duration and effective refractory period, which are thought to be the culprits of the disease. In an interesting new finding, a gain of function mutation in codon 141, next to the one described in the above-mentioned family, was found responsible for a severe form of AF *in utero* and short QT syndrome.[324]

Identification of mutations in *KCNE2, KCNJ2, KCNE5*, and *KCNA5* further confirmed the role of genetic defects in potassium channels in the etiology of familial atrial fibrillation.[325-328]

Atrial Fibrillation Associated with Genetic Alterations in Sodium Current

The α-subunit of the cardiac sodium channel gene, *SCN5A*, responsible for phase 0 of the cardiac action potential, has been studied extensively. Because of its key role in phase 0 of the cardiac action potential, *SCN5A* is involved in several primary arrhythmia syndromes. Gain of function mutations, mainly caused by the inability to inactivate, have been associated with long QT syndrome type 3, and loss of function has been associated with Brugada syndrome, sudden infant death syndrome, Lev-Lenègre syndrome, SUDS, and dilated cardiomyopathy. Variants in *SCN5A* have been linked with lone and familial AF, and also associated with long QT syndrome.[403] In recent years, loss of function mutations in beta subunits, *SCN1B, SCN2B, SCN3B* have been identified in patients with AF. These findings further support the hypothesis that decreased sodium current enhances AF susceptibility.[329,330]

Atrial Fibrillation Associated with Genetic Mutations in Genes Other Than Ion Channel Genes

Atrial natriuretic peptide precursor (*NPPA*) encodes atrial natriuretic peptide (ANP). ANP modulates ionic currents in cardiac myocytes and can play a role in shortening of the atrial conduction time, which could be a potential substrate for atrial reentrant arrhythmias. In 2008, Hodgson-Zingman and coworkers identified a frame-shift mutation in *NPPA* in a large family with AF.[331]

Zhang and associates identified a new gene associated with a clinical phenotype characterized by a neonatal onset, with autosomal recessive inheritance.[332] They identified a mutation in *NUP155*, which encode a member of the nucleoporins. Although still unknown, the mechanism by which *NUP155* may be associated with AF could be related to modulation of calcium-handling proteins and ion channel and expression of its possible target genes, like *HSP70*. The mutation was associated with inhibition of both export of HSP70 mRNA and nuclear import of Hsp70 protein, indicating that loss of function of *NUP155* caused the disease by altering mRNA and protein transport. This gene is located in 5p13 and had been also associated with sudden death in the family.

Somatic Mutations in Atrial Fibrillation

In 2006 three missense mutations in *GJA5* were identified in atrial tissue specimens from patients with idiopathic AF.[333] *GJA5* encodes the gap junction protein connexin 40, which is involved in electrical coupling and its disruption may cause atrial arrhythmias. In addition, atrial tissue genetic mosaicism was detected in a patient with a loss-of-function Cx43 mutation associated with atrial fibrillation.[334]

FAMILIAL WOLFF-PARKINSON-WHITE SYNDROME

Familial WPW syndrome is a rare syndrome with autosomal dominant mode of inheritance. It occurs in isolation or in conjunction with other disorders, such as HCM and Pompe disease. It is characterized by evidence of preexcitation on electrocardiogram, palpitation, and syncope

as a result of supraventricular arrhythmias. The phenotype of WPW in conjunction with HCM and conduction defect was found in patients with mutations in *PRKAG2*, as discussed earlier. WPW has also been reported in patients with Pompe disease caused by mutations in α-1,4-glucosidase, in patients with HCM caused by mutations in *TNNI3* and *MYBPC3*, and in Leber hereditary optic neuropathy, which is caused by mutations in mitochondrial DNA.[335]

GENETIC BASIS OF CORONARY ARTERY DISEASE

The results of modifying lifestyle and drug intervention have documented the importance and the effect of both primary and secondary prevention in common polygenic disorders such as coronary artery disease (CAD) and related traits. Drug therapy alone has been shown repeatedly in multiple clinical trials to decrease the incidence of clinical events from CAD by at least 30% to 40%.[336-338] Despite the reduction, cardiovascular disease remains the number one cause of death for both men and women in the United States.[339] Continued health care burden of CAD mandates new approaches to diagnosis and treatment of patient with CAD, including addressing the genetic basis of this complex phenotype. It is estimated that at least 50% of susceptibility for CAD is the result of a genetic component.[340] Furthermore, most of risk factors such as hypertension, hypercholesterolemia, and obesity have an inherent significant genetic component. Identification of the genes that predispose to CAD and related traits may be necessary for comprehensive prevention of these traits and CAD. Secondly, elucidation of the molecular pathways through which these genes mediate their effects should provide targets for development of new therapies. This is best exemplified by the case of *PCSK9*, which was discovered through genetic linkage analysis in a family with autosomal dominant hypercholesterolemia.[3] The discovery led within a period of ~10 years to development of monoclonocal antibodies that target the PCSK9 protein and lower plasma LDL-C levels markedly.[4,5]

HERITABILITY OF CORONARY ARTERY DISEASE

CAD is a heritable trait influenced by a number of environmental factors. Heritability is defined as the proportion of inter-population variation in susceptibility to a disease that is caused by genetic factors. Twin studies clearly illustrate the marked influence of genetic factors in susceptibility to CAD and death from coronary heart disease.[341] Likewise, family studies show that those with a family history of heart disease in first-degree relatives are at a two- to threefold higher risk of premature CAD.[342-344] Early-onset CAD has a greater genetic component with a heritability estimate attributed to nonlipid risk factors of greater than 50%.[345] There is also a clustering of susceptibility to CAD in families that have risk factors associated with abnormalities such as lipid metabolism, hypertension, diabetes, and obesity, indicating a genetic basis for these conditions and risk factors.[346,347]

APPROACH TO GENETIC STUDIES OF COMPLEX DISEASES INCLUDING CAD

Common polygenic disorders, such as CAD, are in part caused by interactions of a large number of genetic variants and the environmental factors, each contributing modestly to the risk of CAD. The most commonly used approach to identify the susceptibility variants is referred to as a Genome Wide Association Study (GWAS). A GWAS commonly has a case-control study design comprised of several thousand individuals mapped for several hundred-thousand to millions of SNVs spanning the genome.[17,348] Population allele frequencies are calculated in each group and compared between cases and controls to identify variants associated with the phenotype. Because a very large number of SNVs are analyzed at a much higher significance threshold, typically a *P* value of 5×10^{-8} is set to reduce the high incidence of false-positive associations. A very large sample size of the GWAS not only reduces the chance of spurious association resulting from inadequate population stratification but also enables detecting modest effect sizes of the variants.

GWAS by design analyzes known variants and typically those that are common, defined as a population frequency of 1% or greater. In addition, GWAS typically identifies variants that are in linkage disequilibrium with the true risk allele. Moreover, the effect sizes of the common variants are rather modest, typically accounting for a very small fraction of the risk.[17,348] To complement these shortcomings, deep sequencing approaches are used to identify the rare variants, true risk variants, and those that might potentially impart larger effect sizes.

GWAS has led to identification of over 100 susceptibility loci for CAD, the majority of which has been validated (http://www.ebi.ac.uk/gwas/home). However, collectively, loci identified through GWAS explain less than 10% of heritability of CAD, indicating a large number of yet-to-be-identified loci and genetic factors.[340] The so-called missing heritability might be in part inherent to the design of GWAS, which analyzes only the common variants and the small effect of the risk variants. Sequencing-based approaches would enable identification and analysis of rare susceptibility variants, which typically exert larger effect sizes, and may be in part responsible for susceptibility for CAD.[349] The "missing heritability," however, might have several other components, including overestimation of the heritable etiology of coronary atherosclerosis and the presence of stochastic and typically nonlinear interactions among multiple etiological determinants including genetics, genomics, and environmental factors.[349] It is important to note that the modest effect size of the risk alleles mapped for CAD through GWAS do not detract from the power of the discoveries in providing new insights into the pathogenesis of CAD and hence identifying new preventive and therapeutic targets. For example, variants in *HMGCR*, which encodes HMGCoR, the main target of statins, shift plasma LDL-C levels only modestly and yet statins are the cornerstone of treatment of high plasma LDL-C levels.

Not surprisingly, GWAS have identified SNVs in several genes involved in cholesterol biosynthesis and metabolism as susceptibility variants for CAD.[177,350] GWAS studies of CAD have also led to identification of a large number of genes previously not implicated in the pathogenesis of CAD (Table 55–17). The discoveries have the potential to lead to identification of novel molecular mechanisms involved in the pathogenesis of CAD, and hence offer the opportunity to develop novel therapies. However, the task of identifying the true risk allele is quite tedious because of the complexity of the genomic structure, which also includes long-distance interactions among the variants.

Among the notable discoveries are the 9p21 and 1p13 loci, which are among the intensely studies GWAS loci for CAD.[351-355] The 9p21 locus expresses the long noncoding RNA *ANRIL*, which targets cell cycle regulator CDKN2B and hence is referred to as *CDKN2B-AS1*. The variant allele at the 9p21 locus affects increased expression of *CDKN2B-AS1*, which in turn targets cell cycle regulators and leads to enhanced proliferation and reduced senescence of smooth muscle cells.[356] Likewise, SNVs at the 9p21 locus disrupt a STAT1 enhancer and impair response to interferon gamma.[357]

The 1p13 locus contains several genes including *CELSR2*, *PSRC1*, *MYBPHL*, and *SORT1*.[354,355] The latter, which encodes Sortilin 1, has emerged as the prime susceptibility gene for coronary atherosclerosis. The underlying mechanism remains inadequately understood but likely relates to the influence of Sortilin 1 on hepatic ADPOB secretion, LDL-C catabolism in the liver, and possibly expression of the inflammatory markers.[358,359] The risk variant generates a binding site for the

TABLE 55–17. Partial List of Loci and Genes Identified in GWAS of CAD

Locus	Functional Class	Candidate Gene(s)	Locus	Functional Class	Candidate Gene(s)
1p13.3	3′ region	*CELSR2, PSRC1, SORT1*	5q11.2	Intron	*C5orf67*
1p31.3	Intron	*DOCK7, ANGPTL3*	5q13.3	3′ region	*HMGCR*
1p32.2	Intron	*PPAP2B*	5q14.2	Intron	*XRCC4, XRCC4*
1p32.3		*PCSK9, BSND*	5q21.1	Intron	*CTD-2151A2.1*
1p34.1	Intron	*MMACHC, PRDX1*	5q22.2		*YTHDC2 - KCNN2*
1p36.2	Missense, Intron	*MTHFR, C1orf167, PARK7, ERRFI1*	5q31.3		*SPRY4 - RPS12P10*
1q21.1	Intron	*HFE2, TRH-GTG1-1, TRK-CTT2-1*	5q33.2	Intron	*GRIA1*
1q21.3	UTR-3	*ILR6*	5q35.3		*F12, GRK6, RGS14, PRR7, DBN1, UIMC1, SLC34A1, NSD1, PRELID1, MXD3, LMAN2*
1q24.2	Synon	*SELP, F5*			
1q24.3		*FMO1*	6p12.3	Intergenic	*EEF1A1P42, MUT, FTH1P5, RPS15AP20*
1q32.1	Intron	*PPP1R12B*	6p21.1		*MIR4642, SUPT3H, VEGFA, LINC01512*
1q41	Intron	*MIA3*	6p21.3	Intron	*ANKS1A, COL11A2, C6orf10, B3GALT4, HLA-DQB1, MTCO3P1, BTNL2, HCG27, HLA-C*
1q42.1	Intron	*GALNT2*			
1q43	Intron, intergenic	*FMN2, MTR*	6p22.2	Intron	*SLC17A3*
2p12	Intergenic	*MTND5P27, RPL37P10*	6p22.3		*MRPL42P2, GMPR*
2p16.2	Intron	*ACYP2*	6p24.1	Intron	*PHACTR1*
2p21	Intron	*ABCG8*	6q13		*LINC00472, KRT19P1, C6orf155*
2p23.3	Intron	*GCKR*	6q14.1	Intergenic, Intron	*FAM46A, IBTK, MYO6*
2p24.1		*APOB, TDRD15, LDAH, TTC32, WDR35. OSR1, CISD1P1*	6q16.1		*FHL5,- RPS7P8*
			6q23.2	UTR-3	*TCF21, TARID*
2p25.1		*E2F6*	6q25.1	Intron	*ESR1, MTHFD1L*
2q21.2	Intron	*GPR39*	6q25.3	Intron, missense	*SLC22A3, LPA, LPAL2, FNDC1*
2q21.3	Intron	*TMEM163*	6q26/6q25.3	Intron	*LPA*
2q24.1	Intergenic	*GALNT13, ACVR1, UPP2*	7p12.3	Intergenic	*TTC4P1, HMGN1P19*
2q24.2	Intron, intergenic	*TANC1*	7p21.1	Intron	*TWIST1, HDAC9*
2q31.2	Intron	*ZNF385B*	7p21.3	Intergenic	*ARL4A, RBMX2P4*
2q32.1	Missense, intergenic	*TFPI, IMPDH1P, CALCRL*	7q11.2	3′ region, intron	*TBL2, MLXIPL, BAZ1B, BCL7B*
2q32.3	Intron	*TMEFF2*	7q21.1	Intron	*GTPBP10*
2q33.2	Intron	*WDR12*	7q21.3	5′ region	*OCM2*
2q34	Missense	*CPS1*	7q22.3	Intron	*BCAP29*
2q35	Intron	*FN1*	7q31.2	5′ region	*ASZ1*
2q36.3		*NYAP2, MIR5702*	7q32.2	Missense	*ZC3HC1*
2q37.1	Intron	*INPP5D*	7q36.1	Intergenic	*WDR86-AS1, CRYGN*
3p25.1	Intron	*BTD*	8p21.3	Intron	*LPL, RPL30P9*
3p26.3	Intron	*CHL1*	8p23.1	Intron	*LOC157273, PPP1R3B*
3q22.3	3′ region, intron	*MRAS*	8q11.2		*EFCAB1, SNAI2*
3q23	Intron	*CLSTN2, SPSB4*	8q13.1	Intron	*DNAJC5B, TRIM55, CRH*
3q26.1	Intergenic	*OTOL1, TOMM22P6*	8q21.1		*PXMP3, HIGD1AP18, PKIA*
3q27.3	Missense	*AHSG, FETUB, HRG, RFC4, ADIPOQ, KNG1*	8q22.3		*LRP12, RPL23P9*
4p16.2	Intron	*STK32B*	8q24.1		*MIR548AZ, NOV, TRIB1, LINC00861*
4q22.1	Intron	*AFF1*	8q24.2	Intron	*ZFAT*
4q25	Intergenic	*PITX2, MIR297*	9p21.3	Intergenic, Intron	*CDKN2B-AS1, ANRIL, UBA52P6, DMRTA1,*
4q26	Intergenic	*MIR1973, TRMT112P1*	9p22.3	Intron, intergenic	*TTC39B, HEMGN, ANP32B*
4q31.2	Intergenic, 5′	*TTC29, MIR548G, PRMT5P1, EDNRA*	9q31.1	Intron	*ABCA1*
4q32.1		*MTND1P22 - GUCY1A3*	9q34.2		*ABO, SURF6*
4q35.2	Intron, ncRNA	*F11, F11-AS1*	10p11.2	Missense	*KIAA1462*
5p13.2		*RANBP3L, RNA5SP181*	10p12.3	Intron	*ARL5B*

(*continued*)

Table 55-17. Partial List of Loci and Genes Identified in GWAS of CAD (*Continued*)

Locus	Functional Class	Candidate Gene(s)	Locus	Functional Class	Candidate Gene(s)
10p13	Missense, intron	*TRDMT1, CUBN*	15q22.3	Intron	*SMAD3*
10q11.2		*LINC00841, CXCL12*	15q24.1		*CYP1A1, CYP1A2*
10q23.3	Intron	*LIPA, PLCE1,*	15q24.2	Intron	*SIN3A*
10q24.3	Intron	*NT5C2, CNNM2, YP17A1*	15q25.1	Intron, missense	*RPL18P11, DNM1P37, ADAMTS7, MORF4L1, CHRNB4*
11p14.3	Intergenic	*CCDC179, MIR8054*			
11q12.2	Intron	*FADS1*	15q25.2	Intron	*UBE2Q2P1, AGBL1*
11q14.3	Intron	*NOX4*	15q26.2		*MCTP2, RPL26P5, LINC01197*
11q21	Intron, Intergenic	*MAML2*	16p13.2		*RNA5SP404, GRIN2A*
11q22.3		*MTND1P36, MIR4693, PDGFD, ALKBH8, SMARCWP1*	16q13		*HERPUD1, CETP*
			16q22.1	Intron, ncRNA	*DPEP2, LCAT, GFOD2*
11q23.3	Intron	*ZPR1, ZNF259, APOA1, APOA5, APOA4, APOC3*	16q23.3	Intron	*CDH13*
			16q24.3		*DPEP1, CHMP1A, FANCA*
11q24.2	Intron	*ST3GAL4*	17p11.2		*EEF1A1P43, RASD1, PEMT, RAI1*
12q12		*ANO6,, LINC00938*	17p12	Intron	*SHISA6*
12q13.1	Synon	*ATF1*	17p13.3	Intron	*SMG6, RAP1GAP2, SMG6, SRR*
12q21.2		*RPL10P13,- PHLDA1*	17q12	Intron	*ASIC2*
12q21.3	Intron	*ATP2B1, DCN, C12or79*	17q21.3	Intron	*UBE2Z, SNF8, GIP, ATP5G1*
12q22		*CLLU1, C12orf74, PLEKHG7*	17q23.2	3′ region, intergenic	*MARCH10*
12q23.1	Intergenic	*RMST, TTC41P*	17q23.3	Intron, intergenic	*PECAM1*
12q24.1	Intron	*CUX2, KCTD10, MYL2, MVK, MMAB, UBE3B, MYO1H*	17q24.3	Intergenic	*CALM2P1, CASC17*
			18p11.3	Intergenic	*SCML2P1, LAMA1*
12q24.1	Missense, intron	*ATXN2, BRAP, SH2B3, ALDH2, RPL6, PTPN11, ACAD10, C12orf51, HECTD4, C12orf51, NAA25*	18q11.2	Intron	*KCTD1*
			18q21.1		*SMUG1P1, LIPG, ACAA2*
			19p13.1		*CILP2, PBX4, SUGP1 ZNF101*
12q24.3	Intergenic	*RPL12P33, HNF1A-AS1, HSPE1P20, FLJ37505*	19p13.2	Intron	*LDLR, SMARCA4*
			19q13.3	Intron, 3′ and 5′ regions, Synon	*RSHL1, RSPH6A, APOC2, APOE, APOC4, APOC1 FUT2*
13q12.1	Intron	*PARP4*			
13q12.3	Intron	*FLT1*	20p12.1	Intron	*MACROD2*
13q22.1		*KLF12, RNY1P5*	20q11.2	Intron	*MYH7B, EDEM2, TRPC4AP, PROCR*
13q31.1	Intergenic	*LINC00333, RNF219, RPL21P111*	20q13.3	Intron	*CDH4*
13q34	5′ region, intron	*COL4A1, COL4A2, F7*	21q22.1		*LINC00310, KCNE2, MRPS6*
14q11.2	ncRNA, intron	*AP1G2, LOC102724814*	21q22.3	Intron	*CBS*
14q24.3	Intron	*TTLL5, ZDHHC22*	22q12.1	intergenic, intron	*RPL15P22, MN1, SEZ6L*
14q31.3	Intergenic	*FLRT2, GALC*	22q13.1	Intergenic	*PDGFB, RPL3*
14q32.2	Missense	*DEGS2, HHIPL1*	Xq23	Intron	*CHRDL1*
15q21.3	Intron	*LOC102724766*			

CEBPA adipogenic transcription factor on the 5′ regulatory region of *SORT1* gene, enhancing its expression.[358,360] The discovery of *SORT1* as a new susceptibility gene for atherosclerosis has rendered it as a potential target for hypercholesterolemia and therefore modification and treatment.

GENETIC BASIS OF LIPID DISORDERS

Plasma levels of lipids are complex traits determined by interactions of a large number of SNVs and the environmental factors, including diet. Over 50 GWAS have been reported along with identification of several hundred loci associated with plasma levels of LDL-C, HDL-C, TG, and various apolipoproteins.[177,361-364] A complete searchable list of the GWAS related to lipid disorders is found in the GWAS catalog web page (http://www.ebi.ac.uk/gwas/home).

As is common to GWAS of complex traits, SNVs identified through GWAS influence plasma levels of cholesterol, triglycerides, and lipoproteins only modestly. For example, SNVs associated with plasma HDL-C level shift the level by 1 mg/dL or less, and those associated with plasma LDL-C typically by less than 5 mg/dL.[177,361-364] The modest effect sizes of the GWAS findings, however, do not mitigate the clinical impact of discovering the genetic basis of lipid disorders through GWAS. The clinical significance of the GWAS discoveries relates to

their potentials in leading to identification of novel preventive and therapeutic targets. The point is illustrated for the effect sizes of the common variants in *HMGCR*, encoding HMG coenzyme A reductase, the target of statins, which shift plasma LDL-C by less than 5 mg/dL and yet inhibition of this enzyme with statins is the mainstay of treatment of dyslipidemias. *SORT1* is an example of discovery of a novel gene for LDL-C through GWAS, which was discussed earlier.[354,355]

Monogenic forms of dyslipidemias are described briefly next.

FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia (FH) is an autosomal dominant disorder with a prevalence of 1 in 500 in the mild form and in 1 in 100,000 people in its severe form.[365,366] FH is characterized by severely elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) (type IIa hyperlipidemia) and premature atherosclerosis.[366] Plasma levels of total cholesterol are in the range of 300 to 400 mg/dL in affected heterozygous individuals, and greater than 500 mg/dL in homozygous subjects. The affected individuals develop severe atherosclerosis involving multiple vascular territories, tendon xanthomata, and corneal arcus. Subjects homozygous for the causal mutations exhibit clinical atherosclerosis in the first or second decades of life and heterozygous subjects in the fourth or fifth decades. These patients often suffer from ischemic symptoms and/or cardiac events requiring revascularization procedures very early in life.[366]

A common causal gene is *LDLR*, which is located on chromosome 19p13.[367-369] It encodes LDL-C receptors. More than 1000 point, deletion, and splice mutations in *LDLR* have been identified in patients with FH. Approximately 60% of the mutations are missense mutations, 20% are minor rearrangements, 13% are major rearrangements, and 7% are splice-junction mutations. Mutations cause FH by perturbing the function of LDL-C receptors.[367-369] Mutations could affect synthesis and targeting to the cell membrane, binding of the receptor to LDL-C, internalization of the receptor following binding to LDL-C, and recycling of the receptors. The ensuing biologic effect is impaired removal of apolipoprotein B (apoB) and apoE from the circulation. Mutations affect LDL-C receptor function to variable degrees, leading to variable clinical manifestations. In general, there is an inverse correlation between plasma levels of LDL-C and the level of residual LDLR activity. Mutations that completely inactivate the receptors lead to severe premature atherosclerosis in childhood. Frameshift mutations by markedly altering the structure of the LDL-C receptors cause severe phenotype. In contrast, mutations that partially inactivate the receptors cause mild to moderate hypercholesterolemia. Thus the development and severity of coronary atherosclerosis in part vary according to causal mutations, that is, residual LDL-C receptor activity. Genetic background, diet, environmental factors, and epigenetic factors are also likely to contribute to the phenotype.

The second causal gene for FH is the *APOB* gene, located on chromosome 2q24. Mutations in APOB gene lead to familial defective apolipoprotein B (FDB). The causal mutation involves amino acid 3500 in > 99% of the cases, with the predominant mutation being R3500Q and, rarely, R3500W. Mutations decrease the affinity of LDL receptors for apolipoprotein B, which results in accumulation of VLDL-C and LDL-C in the plasma and blood vessels. Phenotypically it is similar to heterozygous FH and includes premature coronary artery disease and tendon xanthoma, in addition to elevated plasma levels of LDL-C. However, the LDL receptor activity is normal in these individuals. FDB is a relatively common disorder, with an estimated frequency of 1 in 1000 people, but the prevalence varies worldwide. The frequency of the mutation varies in different regions of the world.

The third causal gene for autosomal dominant hypercholesterolemia was mapped in 2003 and identified as *PCSK9*, which encodes proprotein convertase subtilisin/kexin type 9, also known as neural apoptosis-regulated convertase (NARC1).[3] Pathogenesis of the phenotype involves enhanced degradation of the LDL receptors by *PCSK9*.[370] Population genetic studies have extended the clinical spectrum of SNVs in *PCSK9* including identification of gain- and loss-of-function mutations in *PCSK9* influencing plasma levels of LDL-C and the clinical effects.[370-374] Since the discovery of *PCSK9* and partial elucidation of the responsible mechanisms, monoclonocal antibodies that target this molecule have been developed and have been shown to be extremely effective in lowering not only plasma LDL-C levels but also cardiovascular outcomes.[4,5,375]

More recently, *STAP1I*, located on 4p13 and encoding signal transducing adaptor family member 1, has been identified as a plausible fourth gene for FH. The phenotype seems to be a milder form of FH.[376,377]

AUTOSOMAL RECESSIVE HYPERCHOLESTEROLEMIA

Autosomal recessive hypercholesterolemia is a rare disease with a phenotype similar to FH. The causal gene is *LDLRAP1* (also known as *ARH*), which encodes an adaptor protein that binds to LDL receptors and hence is called LDL receptor adaptor protein 1 (LDLRAP1).[378,379] The protein contains a phosphotyrosine-binding domain that interacts with the cytoplasmic tail of LDL receptors. The pathogenesis of the phenotype involves impaired clearance of plasma LDL-C, despite normal activity of LDL receptors.[379]

HYPOBETALIPOPROTEINEMIA

Hypobetalipoproteinemia, or abetalipoproteinemia, is a rare disease characterized by extremely low plasma levels of apolipoprotein B, total cholesterol, and LDL-C; high-density lipoprotein cholesterol (HDL-C) levels are high and atherosclerosis is very uncommon.[380] The phenotype often presents in childhood with failure to thrive, fat malabsorption, celiac disease, vitamin A and E deficiency, ataxia, demyelination of the central nervous system, and low plasma LDL-C levels, underscoring the importance of the need of cholesterol for cell function and growth. Sporadic and familial cases with an autosomal dominant mode of inheritance have been reported. A causal gene is *MTTP* on chromosome 4q22–24, which encodes the microsomal triglyceride transfer protein.[381,382] *MTTP* is a heterodimer of a unique large subunit and the protein disulfide isomerase, which catalyzes the transport of triglyceride, cholesteryl ester, and phospholipid from phospholipid surfaces. Mutations encode truncated nonfunctional protein, thus leading to very low levels of apolipoprotein B, LDL-C, and total cholesterol.[380]

Familial hypobetalipoproteinemia is also caused by loss-of-function heterozygous mutations in *PCSK9*, which was discussed earlier. It also can arise because of truncation mutations in *APOB*. It is also a rare disorder characterized by very low plasma levels of LDL-C and total cholesterol.[383] Another form of familial hypobetalipoproteinemia is the chylomicron retention disease, which is an autosomal dominant disease characterized by the selective absence of apoB-48.[380,383] Chylomicrons are absent in plasma of the affected individuals after a fat-containing meal. The phenotype is characterized by steatorrhea, growth retardation, malnutrition, and acanthocytosis. The causal gene is *SAR1B (SARA2)* located on chromosome 5q31. The encoded protein is involved in intracellular trafficking of proteins in COP-coated vesicles. Finally, recessive mutations in *ANGPTL3*, encoding for angiopoietein-like 3, cause familial combined hyperlipidemia, characterized by reduced levels of plasma LDL-C, HDL-C, and triglycerides.[384]

FISH-EYE DISEASE

Fish-eye disease is a rare autosomal dominant condition caused by deficiency of lecithin:cholesterol acyltransferase (LCAT).[385] The *LCAT* gene is located on chromosome 16q22.1 and codes for a protein involved in the synthesis from prealphalipoprotein A1 and conversion of HDL_3 to HDL_2 cholesterol. Deficiency of LCAT leads to premature coronary atherosclerosis, proteinuria, anemia, renal failure, and corneal opacification.[385,386]

TANGIER DISEASE

Tangier disease is an autosomal codominant disease characterized by the virtual absence of HDL-C and very low plasma levels of apolipoprotein A1.[387] Deposition of cholesteryl esters results in characteristic hypertrophic orange-colored tonsils, hepatosplenomegaly, premature myocardial infarction, and stroke. Other clinical features might include thrombocytopenia, anemia, gastrointestinal disorders, and corneal opacities.[387] Mutations in the ATP-binding cassette transporter (*ABCA1*) gene cause Tangier disease and familial hypoalphalipoproteinemia, its allelic variant.[388,389] The *ABCA1* gene is located on chromosome 9q31 and codes for a protein of 2261 amino acids. ABCA1 is a transmembrane protein with 12 transmembrane domains. It acts as a flippase (transmembrane lipid transporter protein) at the plasma membrane, stimulating cholesterol and phospholipid efflux to apolipoprotein AI and HDL-C.[390] Normally, ABCA1 transports free cholesterol to the extracellular space, where it binds to apolipoprotein AI synthesized by the liver and forms nascent HDL particles from VLDL. In the absence of ABCA1, free cholesterol is not transported extracellularly and lipid-poor apolipoprotein AI rapidly degrades. Common polymorphisms in the *ABCA1* gene have been associated with coronary atherosclerosis in the general population.[391,392]

GENETIC BASIS OF SYSTEMIC ARTERIAL HYPERTENSION

The predominant form of systemic arterial hypertension is essential hypertension, which accounts for 95% of all cases. Hypertension is a complex phenotype caused by the interactions of multiple genes and environmental factors. GWAS have led to identification of over 100 genes for essential systolic and diastolic hypertension (http://www.ebi.ac.uk/gwas/). Among the genes identified by GWAS as regulators of systemic arterial blood pressure are *UMOD*, which encodes uromodulin, and *NPR3*, coding for natriuretic peptide receptor-3 and targeting natriuretic peptides for cleavage.[393-395] Each variant, as is the case for most if not all complex traits, exerts a very modest effect on the blood pressure, typically within the error of measurement. Nevertheless, as discussed earlier, the impact is on identification of novel mechanisms and novel preventive and therapeutic targets. In this chapter, we will discuss monogenic forms of hypertension. Systemic arterial hypertension will be elaborated in another chapter.[396]

GLUCOCORTICOID-REMEDIABLE ALDOSTERONISM

Glucocorticoid-remediable aldosteronism is a rare autosomal dominant disorder and the first described familial form of hyperaldosteronism.[396] It is caused by a chimeric mutation that joins the promoter region of the 11β-hydroxylase (*CYP11B1*) gene to the coding region of the aldosterone synthase (*CYP11B2*) gene.[397] The new chimeric gene, located on chromosome 8q24, lacks the negative feedback regulation imparted by angiotensin II. The promoter of the fusion gene, which is made up of the 5′ fragment of the *CYP11B1* gene, is responsive to adrenocorticotropic hormone. Thus expression of aldosterone remains unchecked, and excess aldosterone synthesis leads to the retention of sodium and salt and fluid and subsequent hypertension. Glucocorticoid-remediable aldosteronism responds to treatment with glucocorticoids, which suppress the production of adrenocorticotropic hormone. Alternatively, treatment with mineralocorticoid receptor blockers also controls the hypertension.

APPARENT MINERALOCORTICOID EXCESS

Apparent mineralocorticoid excess is a rare autosomal recessive disease of peripheral metabolism of cortisol.[396] Clinical manifestations of apparent mineralocorticoid excess, in addition to hypertension, include hypokalemia, low plasma renin activity, and responsiveness to spironolactone. There are two types of apparent mineralocorticoid excess, defined on the basis of severity of the biochemical phenotype. Both clinical variants are caused by mutations in the *HSD11B2* gene on chromosome 16q22, which encodes 11β-hydroxysteroid dehydrogenase II.[398] The enzyme is responsible for the peripheral conversion of biologically active cortisol to inactive cortisone. Point mutations in *HSD11B2* reduce or abolish the activity of 11β-hydroxysteroid dehydrogenase in the conversion of cortisol to cortisone. Thus cortisol accumulates, leading to retention of salt and fluid through activation of mineralocorticoid receptors and hypertension. Accordingly, patients with apparent mineralocorticoid excess respond to blockade of mineralocorticoid receptors.

LIDDLE SYNDROME

Liddle syndrome is a rare autosomal dominant disease characterized by hypertension, hypokalemic metabolic alkalosis, low plasma renin activity, and suppressed aldosterone secretion. The phenotype usually develops early in life and hypertension is frequently severe. The first gene identified was the *SCNN1B*, located on locus 16p12, which encodes the β subunit of the amiloride-sensitive Na^{1+} channel.[399] The renal epithelial Na^{1+} channel has three subunits: α, β, and γ. Subsequently mutations in the γ subunit of epithelial sodium channels were also identified (*SCNN1G*).[400] The mutations activate the channel (gain-of-function mutations) and lead to sodium retention and hypertension.

PSEUDOHYPOALDOSTERONISM TYPE II

Pseudohypoaldosteronism type II, also known as the Gordon hyperkalemia–hypertension syndrome, is a rare autosomal dominant disorder characterized by hypertension and hyperkalemia early in life, mild hyperchloremia, metabolic acidosis, and suppressed plasma renin activity. Two causal genes for pseudohypoaldosteronism type II—*WNK4* on chromosome 17q21 and *WNK1* on chromosome 12p—have been identified. *WNK4* and *WNK1* encode serine threonine kinases expressed in the distal nephron.[401] Missense and deletion mutations exert a gain-of-function effect, increasing the expression levels of the proteins in the kidney and leading to increased renal salt reabsorption and reduced renal K^+ excretion. Recently *KLHL3*, coding for Kelch-like 3, and *CUL3*, encoding Cullin 3 (*CUL3*) also have been identified as causal genes for hypertension and electrolyte abnormalities.[402]

GENETIC DISORDERS OF THE PULMONARY CIRCULATION

FAMILIAL PRIMARY PULMONARY HYPERTENSION

Primary pulmonary hypertension (PPH) is diagnosed when mean resting pulmonary artery blood pressure is greater than 25 mm Hg in the absence of known secondary causes such as lung disease or pulmonary

venous congestion secondary to heart failure.[403] Dyspnea is the most common symptom. It is the first symptom in 60% of the cases. Other clinical manifestations include exercise intolerance, fatigue, cyanosis, syncope, and SCD.[403] Clinical manifestations often start in the third and fourth decades of life and are about twice as common in females. Median survival in those with established PAH is about 3 years. Prevalence is 1 to 2 per 1,000,000 individuals.[403]

PPH is a familial disease with an autosomal dominant mode of inheritance in 5% to 10% of the cases. PPH is a genetically heterogenous disease. Mutations in bone morphogenic protein receptor type II (*BMPR2*), mapped to chromosome 2q31–33, are responsible for approximately 50% of the familial PPH and 10% to 15% of the sporadic cases.[404,405] The spectrum of mutations includes nonsense and frameshift mutations expected to produce dysfunctional protein.[406-408] Bone morphogenic protein (BMP) receptor is a cell-surface receptor that belongs to the transforming growth factor β (TGFβ) family. Binding of ligands to *BMPR2* activates signaling through Smad molecules.

Mutations in *ACVRL1*, which codes for a type I receptor of the TGF-β family, cause an autosomal-dominant vascular disorder characterized by pulmonary hypertension, hereditary hemorrhagic telangiectasia (HHT), and visceral arteriovenous malformations.[409] Likewise, mutations in *SMAD9*, *ENG* encoding endoglin, *CAV1* encoding caveolin 1, *KCNA5* and *KCNK3*, both encoding potassium channels, and *EIF2AK4*, coding for eukaryotic translation initiation factor 2 alpha kinase 4, are causes of PPH.[406-409]

The pathogenesis of pulmonary hypertension caused by mutations in the *TGFβ1* pathway includes haploinsufficiency, wherein defective TGFβ signaling via SMAD molecules results in proliferation of smooth muscle cells and reduced apoptosis. Other mechanisms include altered resting membrane potential in pulmonary vascular cells (*KCNA5* and *KCNK3* mutations) and angiogenesis in response to cellular stress (*EIF2AK4* mutations).[406,407]

GENETIC BASIS OF CARDIAC DISEASE IN CONNECTIVE TISSUE DISORDERS

MARFAN SYNDROME

Marfan syndrome is a primary disorder of connective tissue characterized by cardiovascular, ocular, and skeletal abnormalities.[410,411] There is significant variability in the clinical manifestations of Marfan syndrome, but the predominant features are progressive dilatation of the aortic root, aortic aneurysm, dissection, and aortic and mitral valve regurgitation. The estimated incidence of Marfan syndrome is 1 per 5000 population. The age of onset of clinical manifestations of Marfan syndrome is variable, but cardiac phenotypes commonly occur in the third or fourth decades of life. Aortic dissection is the leading cause of premature death in patients with Marfan syndrome. In addition to cardiovascular abnormalities, marfanoid habitus (increased height, disproportionately long limbs and digits), lens dislocation or subluxation, arachnodactyly, thoracic abnormalities, and increased joint laxity are common clinical features.

Marfan syndrome is an autosomal dominant disease that exhibits locus and allelic heterozygosity. The first causal gene to be identified is *FBN1*, which is located on 15q15.23 and encodes fibrillin.[411-413] Fibrillin is a cysteine-rich protein with a molecular mass of 350 kDa; it is the major component of extracellular microfibrils in both elastic and non-elastic connective tissues. Several hundred nonrecurring unique mutations in *FBN1* have been described that encompass missense, nonsense, and deletion mutations, as well as abnormal splicing or exon skipping.[411] Mutations are spread throughout most of the gene, and the frequency of each particular mutation is relatively low, which makes screening for mutations tedious.

The Loeys-Dietz syndrome is an autosomal dominant aortic-aneurysm syndrome characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.[414] Loeys-Dietz syndrome is caused by mutations in the *TGFβR1* and *TGFβR2*.[410,413]

There is a significant variability in the phenotypic expression of Marfan syndrome. The phenotypic variability may be partly caused by locus and allelic heterogeneity and partly by the effect of modifier genes and perhaps environmental factors. The clinical spectrum varies from ectopia lentis in the absence of any other phenotype to neonatal Marfan syndrome and premature death, often within the first 2 years of life. Mutations inducing premature termination of the protein result in approximately a 50% reduction in the level of fibrillin and more frequent ocular manifestations.

Contractural arachnodactyly is characterized by Marfan-like appearance, severe kyphoscoliosis, generalized osteopenia, flexion contractures of the fingers, abnormally shaped ears, and less frequently, mitral regurgitation and congenital heart disease. Point mutations in the *FBN2* gene have been described as causes of contractual arachnodactyly.[415] *FBN2* mutations clustered in limited regions alter amino acids in the calcium-binding consensus sequence in the EGF-like domains. Mutations affect either the conserved cysteine residues or residues of the calcium-binding consensus sequence of the cbEGF motifs, and often result in premature termination of the protein, which therefore results in the phenotype just described.

The pathogenesis of Marfan syndrome entails decreased expression levels of the fibrillin protein, and reduced deposition of fibrillin in vascular adventitia, which results in weakening of the adventitia and aortic aneurysm formation as well as impaired mechano-transduction.

EHLERS-DANLOS SYNDROME

Ehlers-Danlos syndrome (EDS), a relatively uncommon disorder, encompasses a group of conditions characterized by increased elasticity of the skin and connective tissue diseases.[416] The classic form of EDS is characterized by joint hypermotility and fragile, bruisable skin that heals with peculiar "cigarette-paper" scars. Other clinical features include translucent elasticity of the skin, mitral valve prolapse, spontaneous rupture and aneurysm of large arteries, particularly the aorta and its branches, kyphoscoliosis, atrophic scars, and hematomas in the joint areas, especially in the knees and elbows. In the severe form, spontaneous aneurysmal rupture of large arteries and even rupture of the large and small intestines is common. In the benign form, the only manifestations may be hyperextensibility of joints and easy bruisability. The age of onset of clinical manifestations is variable and ranges from childhood to late adulthood.

EDS has several different forms that are inherited in three different patterns of transmission—autosomal dominant, autosomal recessive, and X-linked recessive.[416] Cardiovascular abnormalities are more common in forms I and IV and include congenital malformations, such as tetralogy of Fallot, atrial septal defects, and valvular abnormalities such as mitral and tricuspid valve prolapse.

EDS is genetically an exceedingly heterogenous disease.[417] Ehlers-Danlos type IV, caused by mutations in *COL3A1*, is considered the most malignant form because of susceptibility to spontaneous rupture of the bowel and large arteries as well as a high incidence of pregnancy-related complications.[418] Cardiac manifestations include aortic and coronary artery aneurysms with a high incidence of rupture. Mutations in various collagen genes such as *COL5A1/COL5A2, COL1A1, COL1A2, COL3A1, COL1A1, COL1A1/COL1A2*, and *COL1A1/COL1A2* are

described in patients with EDS.[417] Likewise, mutations in genes encoding for the components of the extracellular matrix proteins or that target such proteins, such as *ADAMTS2, TNXB*, PLOD1, *CHST14, SLC39A13, ZNF469*, and *PRDM5*, have been reported.[417]

CUTIS LAXA

Cutis laxa comprises a heterogeneous group of acquired and genetic disorders characterized by redundant, wrinkled, loose, sagging skin that slowly returns to normal after stretching. Cardiac manifestations include pulmonic stenosis, aortic aneurysms, and right-sided heart failure. Vessels are very tortuous, resembling corkscrews on the angiogram.

Autosomal dominant, autosomal recessive, and X-linked forms have been described, and mutations in the elastin gene (*ELN*) have been identified in the autosomal dominant form.[419] A homozygous missense mutation in the fibulin-5 (*FBLN5*) gene has been identified as responsible for the recessive form.[420]

PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum is a genetic disorder characterized by dermatologic, ocular, and cardiovascular abnormalities resulting from degeneration of the elastic fibers.[421] Manifestations include pseudoxanthoma, especially in areas of the neck and axillae, angioid streaks in the optic fundus, and gastrointestinal hemorrhagic and occlusive disease. Cardiovascular abnormalities include calcification of the peripheral arteries, with resulting intermittent claudication, coronary artery disease, mitral valve prolapse, and hypertension.[421]

Recently, mutations in the ATP-binding cassette (ABC) transporter gene (*ABCC6*) on chromosome 16p13 were identified as the cause of pseudoxanthoma elasticum.[422] The exact biologic function of ABCC6 protein and the mechanism(s) by which mutations in ABCC6 cause pseudoxanthoma elasticum are unknown.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta comprises a heterogeneous class of connective tissue disorders characterized by bone fragility. Bone fragility results from defective collagen synthesis, which leads to decreased bone mass, disturbed organization of bone tissue, and altered bone geometry (size and shape). Cardiovascular abnormalities include valvular lesions, such as mitral and aortic regurgitation, and an increased fragility of the blood vessels.[421]

Mutations in one of the two genes encoding type I collagen, namely *COL1A1* and *COL1A2*, have been identified as the cause. Over 1000 mutations in collagen genes have been described.[421] In addition, mutations in over a dozen genes have been reported in patients with various types of osteogenesis imperfecta.[421]

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CHAPTER 56

CONGENITAL HEART DISEASE IN ADOLESCENTS AND ADULTS

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The incidence of moderate and severe forms of congenital heart disease (CHD) is 6 per 1000 live births. If bicuspid aortic valves (BAVs) are included, the incidence increases to 19 per 1000 live births.[1] Without early medical or surgical treatment, the majority of patients with complex CHD would not survive to adulthood.[2] Surgical and medical advances over the past 60 years have dramatically altered the once bleak prognosis of patients with CHD. In the current era, more than 85% of patients with CHD survive to reach adulthood, and most live productive and functional lives.[3,4] Many patients have undergone surgical interventions that were once thought to be curative. However, with the exception of early surgical ligation of a patent ductus arteriosus (PDA), a surgical "cure" for complex CHD without operative sequelae or need for reoperation does not exist.[5]

Adults with operated and unoperated CHD require long-term follow-up. This long-term care should include cardiologists with experience in or who specialize in adult CHD (ACHD). Standardized diagnostic and treatment guidelines have emerged from the American College of Cardiology (ACC) and American Heart Association (AHA).[6] Cardiologists trained and experienced in patients with complex CHD can minimize diagnostic and treatment errors with a strong knowledge base in pathophysiology, cardiovascular hemodynamics, and prognosis of congenital lesions.

These patients may also face a variety of psychosocial issues, including self-image problems; difficulties in acquiring and maintaining health and life insurance; exercise and activity limitations; and issues of sexuality, contraception, and reproduction. Patient referral to a regional team of experts in a recognized ACHD center is encouraged to facilitate specialized counseling and management.

Specialized ACHD centers have developed in North America and Europe, but there remains a need for more specialized centers even in these regions.[7] Requirements for comprehensive ACHD care centers include dedicated ACHD clinics, ACHD cardiologists, congenital cardiac surgeons, nurse specialists, and consultants. Training and research are of pivotal importance. The development of management, research, and training guidelines over the past two decades is a major step forward for the field of ACHD.[6,8-11] Another encouraging development is the establishment of the Adult Congenital Heart Association (ACHA) in the United States. This nonprofit patient-initiated association seeks to improve the quality of life and extend the lives of adults with CHD by leading legislative efforts, sponsoring patient and physician conferences, and identifying and certifying comprehensive ACHD centers in the United States. Multicenter and prospective clinical research in ACHD has increased in frequency and variety.[12] A dedicated multicenter research network, the Association for Adult Research in Congenital Cardiology, was established in 2007 in North America to foster and implement multicenter research.[13] A recent collaboration between the ACHA and the National Heart, Lung, and Blood Institute also strives to identify and promote key areas of research in ACHD.

MEDICAL CONSIDERATIONS

Many adults with CHD have not had, or may never require, surgical intervention. The most common defects incidentally encountered in adulthood are small ventricular septal defect (VSD) or atrial septal defect (ASD), mild pulmonary stenosis, BAVs, and mitral valve prolapse. Less common but more complex conditions include nonrestrictive central shunts with right-to-left shunt reversal resulting in the cyanotic Eisenmenger syndrome and pulmonary hypertension. Most patients require long-term follow-up to monitor for disease progression, appropriately treat possible sequelae or complications, and reinforce the need for a healthy lifestyle and diligent dental care.[6] Women of childbearing age and men wishing to father children should be informed of the risks of pregnancy and the increased risk of CHD in their biological children.[14]

An increasing number of patients who underwent childhood palliative procedures, such as Glenn or Fontan cavopulmonary shunts, or corrective operations, such as intracardiac repair of tetralogy of Fallot, are reaching adulthood. Many patients are under the false impression that they are "cured" and are lost to follow-up until symptoms bring them back to medical attention. Uncorrected, corrected, and palliated patients often require repeat operations, interventional catheterizations, and electrophysiologic therapies in adulthood. All adults with CHD should have a consultation with an ACHD center at least once to determine optimal frequency and center for follow-up. Performance of advanced diagnostic studies and interventions at experienced centers

is highly recommended given the potential complexity and rarity of some conditions.[6]

HEMODYNAMICS

Progressive myocardial dysfunction with resultant heart failure is a leading cause of morbidity and mortality in patients with CHD. Patients may present with left, right, biventricular, and, at times, univentricular failure. The etiology of systolic or diastolic heart failure is often multifactorial and may include pressure or volume overload, chronic hypoxia, and/or pulmonary vascular disease. Intrinsic myocardial abnormalities may result in restrictive diastolic properties, leading to a chronic low cardiac output state, volume overload, congestive hepatopathy or nephropathy, ascites, and protein-losing enteropathy. Complications of restrictive cardiomyopathy are often progressive and difficult to manage; cardiac transplantation is the ultimate therapeutic option.

Physical examination includes a thorough assessment of volume status with specific attention to the jugular venous filling pressure and waveform. Pulmonary hypertension or ventricular filling abnormalities are often accompanied by an amplified A wave in the jugular venous pulse. Right-sided atrioventricular (AV) valve regurgitation may result in an amplified jugular venous V wave proportional to the severity of regurgitation. Percussion and palpation of the liver to evaluate for pulsatility and degree of hepatomegaly are recommended. Doppler echocardiography is indispensable for noninvasive evaluation of hemodynamics and shunt fractions.[15,16] Exercise testing is helpful to evaluate for exertional symptoms and, when combined with echocardiography, is also useful for correlating symptoms with exercise-induced gradients in obstructive lesions. Invasive cardiac catheterization is important for patients with inadequate acoustic windows that limit the utility of transthoracic echocardiography or in those in whom pulmonary vascular resistance, shunt fractions, or chamber pressures cannot be gleaned from noninvasive methods and must be measured directly. Cardiac magnetic resonance imaging (MRI) is an important adjunct modality for quantification of biventricular function, calculation of systemic and pulmonary flow, and quantification of valvular regurgitation.[17]

Operations to palliate or repair congenital cardiovascular lesions were originally devised to address physiologic issues, specifically to increase or diminish the supply of blood to the pulmonary circulation. The early era of congenital cardiac surgery was marked by giant leaps forward in the physiologic treatment of lesions. In the 1940s, the development of aortopulmonary shunts, such as the famed Blalock-Taussig shunt, allowed palliation of patients with pulmonary atresia or a functional single ventricle[18] (Fig. 56–1). Another major

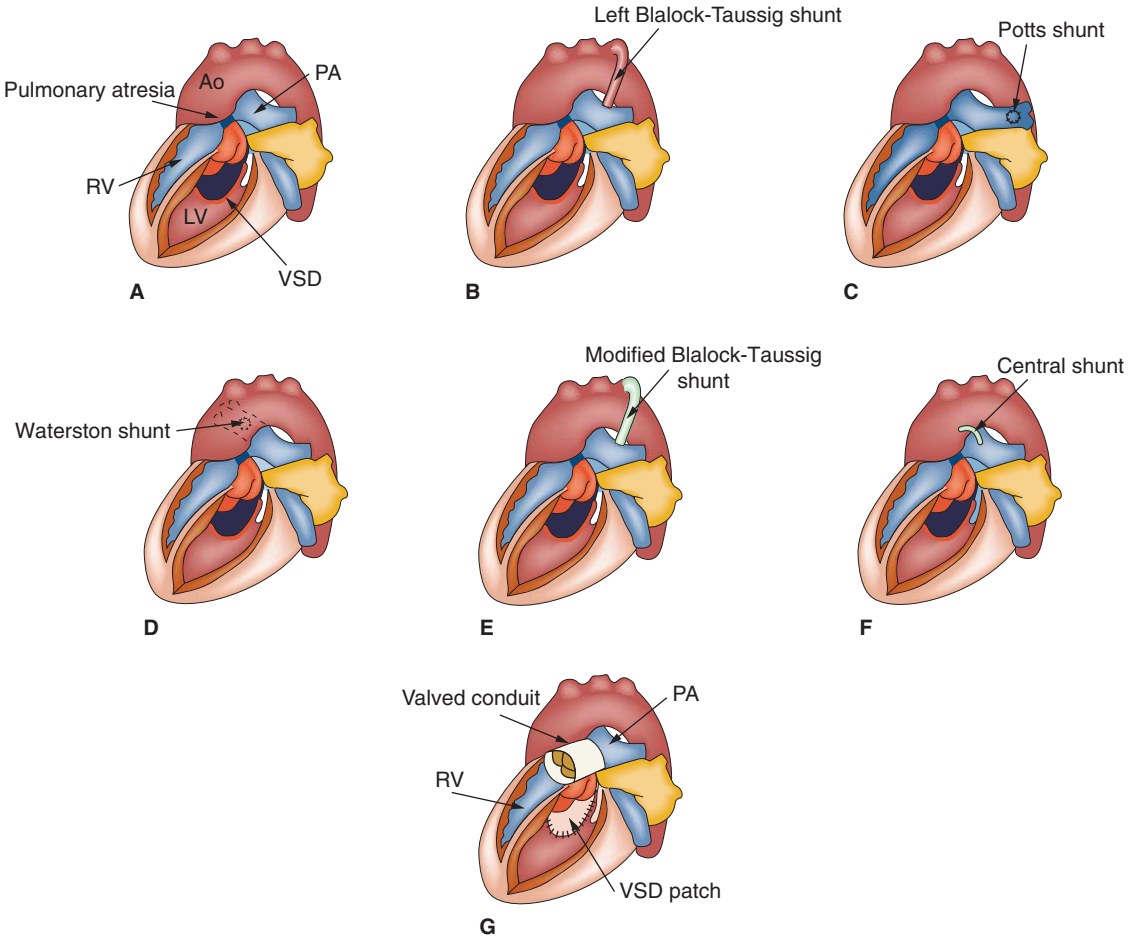


FIGURE 56–1. **A.** Unrepaired tetralogy of Fallot (TOF) with pulmonary atresia. There is no anterograde flow from the right ventricle (RV) to the pulmonary artery (PA). A large nonrestrictive ventricular septal defect (VSD) allows communication between the left ventricle (LV) and the RV. There is an overriding aorta (Ao). **B.** Classic left Blalock-Taussig shunt consisting of direct connection of the divided left subclavian artery to the left pulmonary artery. **C.** Potts shunt consisting of a direct connection between the anterior wall of the descending Ao and left PA. **D.** Waterston shunt consisting of a direct connection of the posterior wall of the ascending Ao and the right PA. **E.** Modified Blalock-Taussig shunt consisting of a synthetic (Gore-Tex) tube connection the left subclavian artery to the PA. **F.** Central shunt consisting of a synthetic tubular connection from the ascending Ao to the PA. **G.** Intracardiac repair consisting of VSD patch closure and placement of a valved conduit from the RV to the PA.

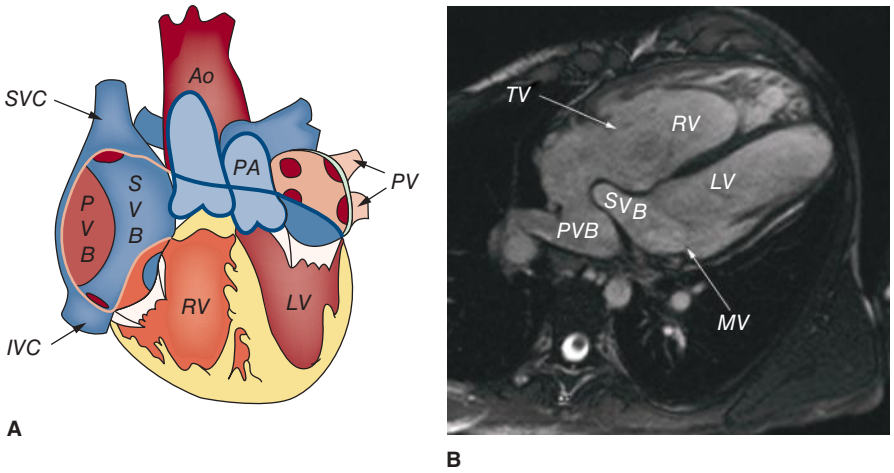


FIGURE 56–2. A. Valentine diagram of the cardiac anatomy in a patient with dextro-transposition of the great arteries who has undergone the Mustard or Senning atrial switch operation. Deoxygenated blood (*blue*) returning from the superior and inferior vena cava (SVC and IVC, respectively) is redirected via a systemic venous baffle (SVB) to the left ventricle (LV) and thereafter into the transposed pulmonary artery (PA). Oxygenated blood (*red*) returning from the lungs via the pulmonary veins (PVs) is redirected via a pulmonary venous baffle (PVB) to the systemic right ventricle (RV) and then to an anterior and rightward aorta (Ao). **B.** Cine-cardiac magnetic resonance imaging scan (axial plane) demonstrating the SVB directing deoxygenated blood via the mitral valve (MV) to the subpulmonic LV and PVB directing oxygenated blood via the tricuspid valve (TV) to the systemic RV.

surgical development was the atrial switch operation, also known as the Mustard or Senning procedure, for correction of complete or dextro-transposition of the great arteries (TGA; Fig. 56–2), in which deoxygenated blood is redirected by the atrial baffle from the cavae to the left ventricle (LV) and thereafter to the pulmonary arterial circulation. The oxygenated pulmonary venous blood returns to the systemic right ventricle (RV). These operations are successful in diverting blood flow to improve or correct physiology but do not normalize anatomy or optimize hemodynamics. Patients with systemic RVs or those with functional single ventricles are especially susceptible to deteriorating ventricular function. The heterogeneous morphology and loading conditions for these ventricles suggest that standard indices of ventricular function, namely echo or other imaging-derived ejection fraction, may not be as useful in identifying the highest risk subsets. Use of echocardiographic strain is helpful in diagnosing early myocardial dysfunction and carries important prognostic value in hypertrophic cardiomyopathy or acquired cardiomyopathy and is being studied in the ACHD population.[19,20] Cardiac MRI has been studied and demonstrated to be superior to echocardiography for quantification of RV volumes and ejection fraction in patients with transposition.[21] Elevations of serum brain natriuretic peptide (BNP) may help identify patients with increased ventricular wall tension often accompanied by ventricular enlargement and dysfunction.[22] Atrial and ventricular arrhythmias increase in frequency and severity as ventricular function deteriorates and themselves lead to further decreases in cardiac output. Medical and surgical interventions are aimed at preservation of function and prevention of arrhythmias.

Postoperative residual defects may be a major cause of progressive deterioration decades after surgery. Severe chronic pulmonary regurgitation may be well tolerated for decades after surgery.[23] Eventually, progressive RV dilatation and elevated filling pressures, particularly if ventriculotomy scars coexist, may create the substrate for ventricular arrhythmias. Medical therapy for heart failure in patients with CHD is adapted from the guidelines for patients with ischemic and nonischemic cardiomyopathies.[24] There is a paucity of prospective randomized data evaluating heart failure therapies in patients with CHD. The renin-angiotensin system may not play as deleterious a role in certain subsets of patients with CHD compared with those with ischemic and nonischemic cardiomyopathies. For example, patients with systemic RVs with depressed systolic function do not demonstrate increased angiotensin levels and therefore do not appear to derive demonstrable intermediate-term benefit from the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).[25,26] Selective β-blockers may delay the progression of ventricular dysfunction and decrease the likelihood of arrhythmias.[27] Diuretics have not been rigorously evaluated in patients with CHD but are frequently used to regulate volume status in patients with chronic volume-loaded conditions, such as Fontan patients.

CYANOSIS

Adults with CHD may be cyanotic because of decreased pulmonary blood flow or mixture of desaturated systemic venous blood with pulmonary venous blood. Decreased pulmonary blood flow may occur in the presence or absence of pulmonary vascular disease. The latter is exemplified by unrepaired tetralogy of Fallot (TOF) with pulmonary atresia, in which pulmonary vasculature is supplied by aortopulmonary collaterals. Cyanosis in the presence of pulmonary vascular disease may be secondary to unrepaired central shunts (Eisenmenger syndrome) or the coincidence of idiopathic pulmonary hypertension in the presence of an ASD.[28]

In 1897, Victor Eisenmenger described the autopsy findings of a 32-year-old man who had been cyanotic from infancy; findings included a large VSD, pulmonary arteriosclerosis, and pulmonary artery thrombosis. The cause of death was pulmonary hemorrhage. The *Eisenmenger complex*, coined by Maude Abbott, specifically refers to a reversed shunt (right to left) in the presence of a nonrestrictive VSD[29] (Fig. 56–3). The term *Eisenmenger syndrome* also refers to a reversed central shunt but is used more broadly to encompass a heterogeneous series of congenital lesions in which the pulmonary vasculature is exposed to elevated or even systemic pressures, eventually leading to this physiology. During the first few years of life, the small muscular pulmonary artery branches are capable of relaxing, and the defect can be closed with a subsequent gradual decrease in pulmonary vascular resistance. After 2 to 3 years, reactive intimal fibrosis begins to obliterate the lumen of the muscular arteries, and they no longer respond to

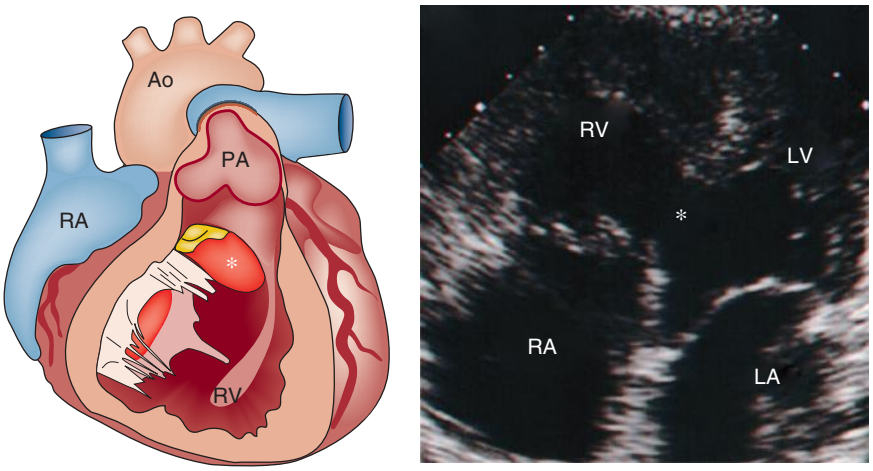


FIGURE 56–3. **A.** Rendering of a heart with Eisenmenger complex, characterized by a nonrestrictive ventricular septal defect (VSD) (*asterisk*). The right ventricle (RV) is hypertrophied, and the main pulmonary artery (PA) is dilated and has evidence of atheroma formation. Also labeled are the right atrium (RA) and the aorta (Ao). **B.** Transthoracic echocardiographic image of apical four-chamber view of a heart with Eisenmenger complex. There is a large nonrestrictive VSD (*asterisk*). The RV is enlarged and hypertrophied. The left ventricle (LV) and left atrium (LA) are labeled.

vasodilating agents such as acetylcholine, adenosine, or nitric oxide.[30] This obliterative process represents a fixed obstruction to flow; the shunt reverses, and surgical correction is contraindicated. Patients with trisomy 21 (Down syndrome) are especially susceptible to developing pulmonary vascular disease.[31] Patients with cyanosis secondary to pulmonary vascular disease and shunt reversal experience significantly decreased maximal and submaximal exercise capacity compared with other patients with complex CHD (Fig. 56–4).[32,33]

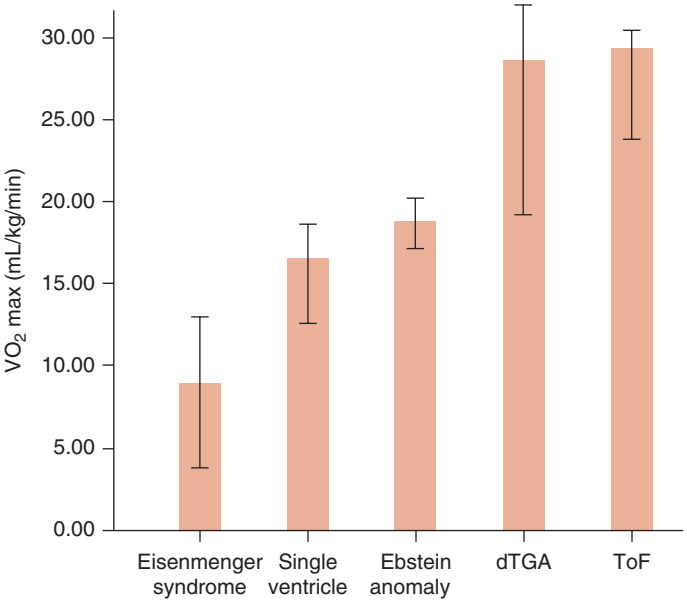


FIGURE 56–4. Distribution of maximum oxygen consumption (VO_2 max) in 78 adults with various types of congenital heart disease followed at the Ahmanson/University of California, Los Angeles, Adult Congenital Heart Disease Center. Surgically repaired patient with tetralogy of Fallot (ToF) and patients with dextro-transposition of the great arteries (dTGA) who have undergone an atrial switch operation performed significantly better than other subgroups. Patients with Eisenmenger syndrome had a mean VO_{2max} of less than 10 mL/kg/min, which was significantly lower than all other subgroups.

Survival in patients with Eisenmenger syndrome is reduced by approximately 20 years compared with healthy control subjects; nearly 50% of patients survive to the sixth decade of life.[34,35] Decreased functional capacity, heart failure, renal dysfunction, and arrhythmias are predictors of decreased survival. Patients with unrepaired truncus arteriosus and those with single-ventricle morphology have a poorer prognosis than patients with nonrestrictive VSD (Eisenmenger complex).[36] With single-ventricle morphology, especially RV morphology, progressive ventricular dysfunction is a concern. Causes of death include pulmonary hemorrhage, pulmonary arterial thrombosis, pulmonary artery dissection, ventricular arrhythmias, and ventricular failure.[36]

Interestingly, patients with cyanotic CHD demonstrate an antiatherogenic substrate and are less susceptible to atherosclerotic heart disease than noncyanotic control subjects.[37-39] The coronary arterial circulation in cyanotic patients is characterized by markedly dilated and tortuous extramural coronary arteries and a well-developed microcirculation within the myocardium.[38,39] Serum lipid levels are low in cyanotic patients and remain low years after correction of cyanosis, suggesting the modulation of as-yet unidentified operator genes by cyanosis. The antiatherogenic state of these patients is further characterized by elevated bilirubin levels; increased nitrous oxide production by vascular endothelial cells because of increased shear stress from hyperviscosity; and low platelet levels, incurring less thrombotic risk.[37,40] Patients with chronic cyanosis also develop defective hemostasis from abnormalities in platelet function and in the coagulation and fibrinolytic systems.[41,42] Interestingly, the pulmonary arterial circulation is not spared from atherosclerosis and thrombosis. As a matter of fact, these patients often demonstrate an aggressive atherosclerotic process within the pulmonary arterial tree that correlates with the duration of pulmonary hypertension.[43] Cardiac computed tomography (CT) may be used to quantify calcium deposition within the pulmonary arterial tree, as calcium is a surrogate marker for atherosclerosis (Fig. 56–5). Histologic

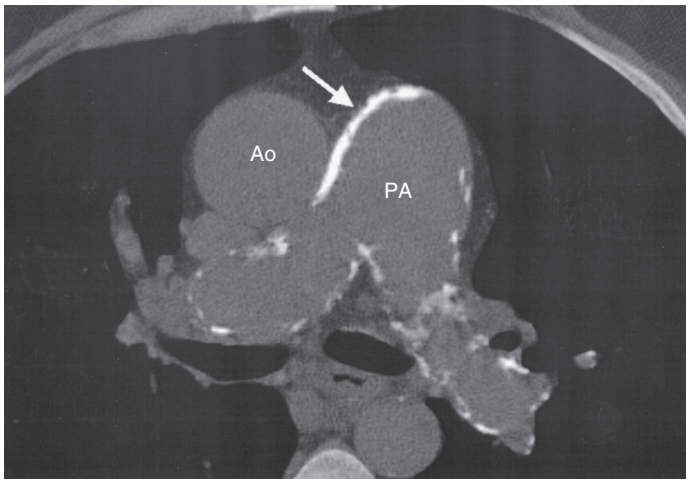


FIGURE 56–5. Noncontrast computed tomography scan of a 60-year-old man with Eisenmenger complex demonstrating extensive white calcium deposits (*arrow*) within the walls of the pulmonary artery (PA) and branch pulmonary arteries. The ascending aorta (Ao) is labeled. Note the relative paucity of calcium in the walls of the Ao compared with the PA.

examination of necropsy or autopsy pulmonary artery specimens demonstrates a mix of typical calcified lipid-rich atherosclerotic plaques and dystrophic intimal calcification. Pulmonary arterial thrombosis is common, especially in older patients, those with biventricular dysfunction, and those with decreased pulmonary blood flow velocity.[44,45] Unlike pulmonary emboli, in situ pulmonary arterial thrombosis is challenging to treat and may not respond to anticoagulation. Chronic anticoagulation increases the risk of life-threatening pulmonary hemorrhage, particularly in patients with thrombocytopenia, and is of unclear mortality benefit. As such, it should be avoided unless the patient has other definitive indications (eg, atrial fibrillation or deep venous thrombosis).[36]

Chronic cyanosis leads to secondary erythrocytosis and, if uncompensated, may result in hyperviscosity. The risk of symptomatic hyperviscosity is low in patients with a hemoglobin level below 20 g/dL who are not dehydrated. Symptoms of hyperviscosity include headache, dizziness, fatigue, and blurry vision. Judicious phlebotomy may improve these symptoms but should be reserved for patients who do not respond to aggressive hydration.[46] Regular phlebotomies should be strictly avoided regardless of the hemoglobin level because the resultant iron deficiency leads to microcytic and less deformable red blood cells that do not pass through the microcirculation as readily as more deformable iron-replete cells.[41] As a result, the paradoxical anemia of erythrocytotic patients with iron deficiency may increase the risk of stroke.[42,47] Iron repletion in these patients should be instituted with care because of the tendency for excessive erythrocytosis. Hyperuricemia is common because of increased red blood cell turnover and decreased renal excretion of uric acid; however, urate crystal nephropathy is rare despite the elevated serum uric acid levels. Patients with elevated uric acid levels rarely develop tophaceous deposits within the soft tissue of the elbows or digits; these can be painful and tender (Fig. 56–6). Arthralgia is well recognized, and frank gouty arthritis is rare.[48]

FIGURE 56–6. The hand of a 59-year-old woman with pulmonary hypertension, a large atrial septal defect, cyanosis, and hyperuricemia. Note the cyanosis and clubbing of the digits. A tophaceous urate deposit (T) is noted on the middle phalanx of the second digit.

Cyanotic patients with right-to-left shunts are at risk for "paradoxical" emboli from the venous to the systemic arterial circulation, leading to cerebrovascular accidents, renal impairment, or myocardial infarction. Air filters should be used with all intravenous (IV) lines, and chronic indwelling venous catheters should be avoided. Anticoagulation may be considered in patients who must have chronic indwelling lines (eg, patients with infective endocarditis who require prolonged IV antibiotic therapy). All cyanotic patients are at a heightened risk for infective endocarditis, and antibiotic prophylaxis for bacterial endocarditis is mandatory prior to bacteremic procedures, including dental work. Septic emboli may cause cerebral abscesses and must always be considered in cyanotic patients with fever and neurologic symptoms.

Promising advances have occurred over the past decade in the treatment of patients with pulmonary hypertension. The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) is the first prospective and randomized clinical trial performed solely in patients with Eisenmenger syndrome randomized to either a nonselective endothelin inhibitor (bosentan) or placebo.[49] Patients receiving bosentan had a significant decrease in pulmonary vascular resistance and systemic vascular resistance, resulting in increased pulmonary and systemic blood flow, respectively. They also had a significant increase in 6-minute walk distance (51 m). Patients were followed for 16 weeks. Long-term follow-up of patients placed on endothelin blockers suggests an attenuation of the benefits over time.[50] Phosphodiesterase-5 inhibitors are also effective in the treatment of patients with Eisenmenger syndrome and result in a similar improvement in functional capacity and lowering of pulmonary vascular resistance as endothelin blockade.[51] IV prostacyclin use is generally avoided because of the requirement for chronic indwelling venous catheters, which increases the risk of thrombosis and paradoxical embolism across the right-to-left shunt. Moreover, the presence of a central right-to-left shunt results in much of the IV-administered drug bypassing the pulmonary bed and resulting in systemic hypotension. Inhaled prostacyclin may be more efficacious in this patient population; however, at this time, there is a paucity of data on the use of this agent in patients with Eisenmenger syndrome. Serum BNP is a diagnostically and prognostically important marker in various forms of systolic and diastolic heart failure as well as primary and secondary forms of pulmonary hypertension. Serum BNP is elevated in most patients with Eisenmenger syndrome; however, an outpatient level 250 pg/mL or above in clinically euvolemic patients predicts impending heart failure admission or death.[52]

INFECTIVE ENDOCARDITIS

Patients with CHD (corrected or uncorrected) are at risk for developing infective endocarditis.[53] Certain subgroups are considered at higher risk for infective endocarditis. Guidelines from the European Society of Cardiology and the AHA/ACC on prevention of infective endocarditis place patients with prosthetic valves, cyanosis, and systemic or pulmonary artery conduits, as well as patients with previous endocarditis, into a high-risk subgroup.[53-55] Most other congenital cardiac conditions are in a moderate-risk category, except for patients who have undergone surgical or transcatheter repair of ASD, VSD, or PDA (without residua beyond 6 months) who are considered low risk provided there are no sequelae (eg, aortic valve prolapse, aortic regurgitation). In patients at high risk, the ESC and AHA/ACC recommend antibiotic prophylaxis for dental procedures associated with significant bleeding from hard or soft tissues, periodontal surgery, scaling, and professional teeth cleaning. Other procedures requiring prophylaxis include respiratory, genitourinary, and gastrointestinal procedures. Poor dental hygiene may produce bacteremia even in the absence of dental procedures. Individuals who are at risk for developing bacterial

endocarditis should establish and maintain the best possible oral health to reduce potential sources of bacterial seeding. Optimal oral health is maintained through regular professional care and diligent brushing and flossing on the part of the patient. High-risk patients are advised to use a minimally abrasive soft bristle toothbrush to minimize bleeding. In 2008, the National Institute for Health and Clinical Excellence of the United Kingdom recommended complete cessation of antibiotics for endocarditis prophylaxis, resulting in a 90% decrease in antibiotic prescriptions. A study of endocarditis cases from 2000 to 2013 in the United Kingdom observed a significant increase in endocarditis cases after the 2008 recommendations.[56] Despite this increase, the National Institute for Health and Clinical Excellence has not recommended any changes to the 2008 recommendations, pending further study. A structured questionnaire mailed to 515 dentists and 85 cardiologists in Ireland revealed that most cardiologists are familiar with the cardiac conditions that pose a risk for dental patients but did not educate their patients on the importance of dental health. On the other hand, dentists were good at identifying dental procedures that place patients at risk but less informed about which cardiac conditions warranted prophylaxis, choice of prophylaxis, and appropriate treatment intervals.[57] A survey questionnaire of 102 adults with CHD found that patients' knowledge of their underlying condition, endocarditis risk, and prevention measures was sorely lacking.[58]

There is an under-recognized risk of bacteremic infective endocarditis in patients who acquire tattoos or body piercings.[59] Patient education is of paramount importance, and patients should carry an information card with them that clearly identifies their endocarditis risk category.

The symptoms of infective endocarditis are often subtle and nonspecific, including low-grade fever, malaise, fatigue, and headache. The diagnosis of endocarditis should be entertained in any patient with unexplained fever or malaise and should prompt blood cultures and echocardiographic imaging. Echocardiography is an integral tool in the diagnosis and follow-up of patients with infective endocarditis.[60] The use of transesophageal echocardiography (TEE) is recommended in cases with high clinical suspicion and equivocal or negative findings on transthoracic echocardiography or when a prosthetic valve or conduit is involved[61] (Fig. 56–7). Injudicious use of antibiotics without prior blood cultures often makes the culprit organism more difficult to identify by culture, making appropriate treatment more difficult.

ELECTROPHYSIOLOGIC PROBLEMS

Arrhythmias and conduction defects are common in operated and unoperated patients with CHD and have a major impact on survival and quality of life. Although the principles for diagnosis and treatment of arrhythmias are similar to those used in patients with anatomically normal hearts, there are some notable exceptions. Atrial rhythm disturbances that may be well tolerated with a rate control strategy in a structurally normal heart may be poorly tolerated in complex CHD. Patients with functional single-ventricle or tricuspid atresia who have undergone total cavopulmonary (Fontan) connection exemplify this

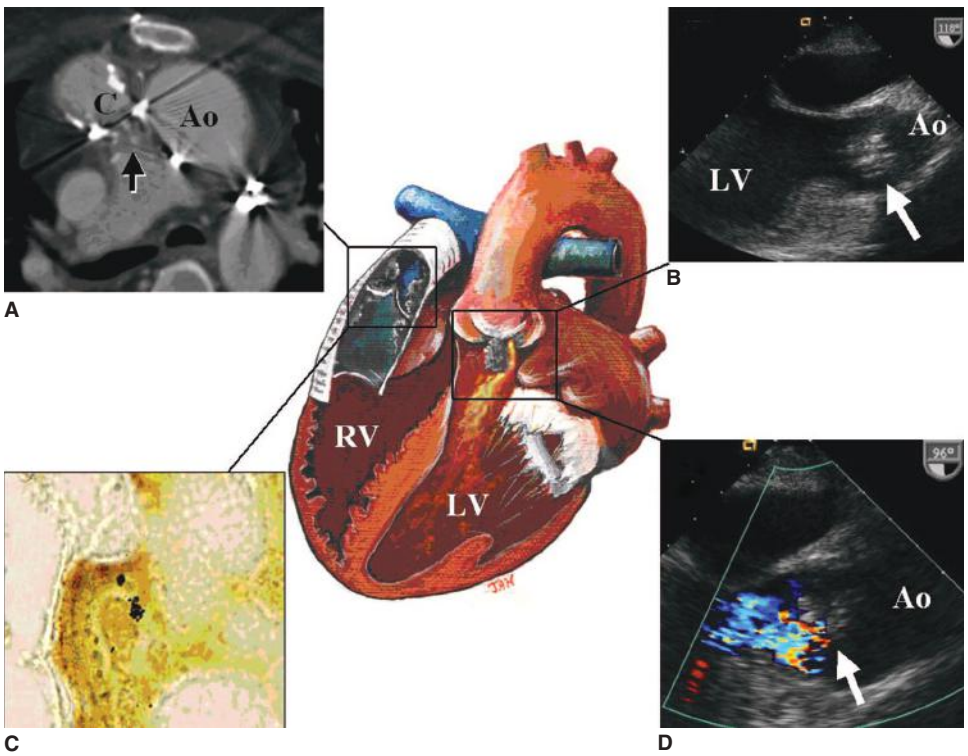


FIGURE 56–7. Illustration of a 36-year-old woman with dextrocardia, a ventricular septal defect (VSD), double-outlet right ventricle, and pulmonary atresia. At 13 years of age, she underwent corrective surgery using the Rastelli procedure with baffling of the left ventricular (LV) blood via the VSD to the aorta and placement of a 22-mm valved Dacron conduit from the right ventricle to the main pulmonary artery. The right ventricle (RV) is connected to the pulmonary artery via a valved Dacron conduit. Note the grayish vegetation within this structure. The LV is the systemic ventricle. A baffle directs LV outflow to the aortic valve. The aortic valve has grayish vegetation on it that prolapses into the LV outflow tract and causes aortic regurgitation. **A.** Computed tomography angiogram at the level of the distal RV to pulmonary artery conduit (C). The *arrow* points to the grayish vegetation within the conduit. The ascending aorta is labeled (Ao). **B.** Transesophageal echocardiogram demonstrating the vegetation (*arrow*) prolapsing in diastole from the Ao to the LV. **C.** Warthin-Starry stain of the grayish vegetation demonstrates a cluster of *Bartonella henselae* that appear as black specks. **D.** Transesophageal echocardiogram with color-flow Doppler demonstrating aortic regurgitation around the area of vegetation. The *arrow* points to the vegetation.

in that atrial tachyarrhythmias frequently result in deleterious hemodynamics, a decrease in cardiac output, and functional deterioration despite adequate rate control.[62] Atrial arrhythmias occur in 15% of adults with CHD. The lifetime incidence increases exponentially with advancing age, and atrial arrhythmias affect more than 50% of adults with complex CHD.[63,64] Bradyarrhythmias are common in certain subsets of patients, such as those with TGA. Special consideration must be given to the use of therapies that have negative chronotropic and inotropic properties. The clinical significance of arrhythmias depends greatly on the hemodynamic context in which they occur.

The 2014 ACC/AHA guidelines on the management of atrial fibrillation recommends use of the CHA_2DS_2-VASc scoring system to risk stratify patients with nonvalvular atrial fibrillation for stroke.[65] This risk stratification scheme assigns a score based on the presence of congestive heart failure or systemic LV systolic dysfunction, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled), vascular disease, younger age (65-74 years), and sex (female). Considering these scores and the recommendation to consider anticoagulation in patients with a risk score ≥ 1, anticoagulation is thus recommended for most patients with atrial fibrillation or flutter. However, such risk scoring systems do not consider the presence of CHD. Patients with CHD may be more predisposed to thrombus formation as a result of chamber dilation with slow flow, presence of prosthetic material including valves, intracardiac shunts, and associated hypercoagulable states. Patients with a Fontan circulation are at particularly high risk for thrombotic complications. Long-term anticoagulation is therefore recommended in patients with CHD of severe complexity and is reasonable in those with moderate forms of CHD.[66] In patients requiring anticoagulation, oral vitamin K antagonists are widely used. However, use of the non–vitamin K, novel oral anticoagulants is increasing quickly based on clinical trials in patients with atrial fibrillation demonstrating noninferiority in stroke prevention, as well as decreased incidence of intracranial bleeds.[67-70] Further study of safety of novel oral anticoagulants in the CHD population is ongoing.

Abnormalities of sinus node function are common in adults with CHD, especially in patients who have undergone atrial surgery. Patients with surgically corrected ASD, specifically those with superior sinus venosus defects, are at a heightened risk of developing postoperative sinus node dysfunction (SND) because of the proximity of the defect to the sinus node.[71] Patients with uncorrected atrial shunts causing chronic right atrial volume overload and right atrial stretch undergo a process of electrical remodeling with increases in effective refractory period, conduction delay at the crista terminalis, and SND. Conduction delay at the crista terminalis persists beyond ASD closure and may contribute to the long-term atrial arrhythmia substrate in this condition.[72] Patients who have undergone surgeries that involve extensive atrial reconstruction are particularly prone to SND. A retrospective follow-up study of 137 patients who had undergone the Mustard or Senning operation for complete TGA (see Fig. 56–2) demonstrated that nearly 50% of patients had SND; however, the presence of SND did not influence mortality.[73] Frequency of SND is also increased after surgery for correction of TOF, placement of cavopulmonary shunt (Glenn or Fontan), and numerous other congenital heart operations. High-grade AV node block is a well-recognized problem in patients with unoperated congenitally corrected TGA; many patients are initially diagnosed in adulthood when they present with signs and symptoms of bradycardia from high-grade heart block. Injury to the AV node and ventricular conduction tissue may result from surgery for lesions such as VSD, TOF, and mitral or tricuspid valve repair or replacement. Transient complete AV block in the postoperative period has been shown to have prognostic significance, especially if the induced block is below the bundle of His.[74] Postoperative right bundle branch block is frequent after right ventriculotomy and is likely secondary to transection of distal Purkinje fibers and postsurgical scarring, creating an area of slowed conduction and a substrate for reentrant ventricular arrhythmias.[75,76] Although bradycardia has been postulated as the cause of death in some conditions, evidence indicates that tachyarrhythmia is the more likely culprit. However, the presence of underlying bradycardia as a substrate for initiation of tachycardia is well recognized.[77] Indications for pacemaker implantation in asymptomatic patients with SND or conduction system disease are controversial because the arrhythmia is benign in the majority of cases. Patients who are asymptomatic at rest or with low levels of activity may become more fatigued and dyspneic with greater levels of exertion. Electrocardiographic (ECG) stress testing identifies patients with chronotropic incompetence leading to decreased exercise capacity.

Pacemaker implantation may be challenging in patients with complex underlying or postoperative anatomy.[78] The choice of pacemaker depends on the specific indication. In patients who have isolated SND, a single atrial lead should suffice. Patients who require chronic ventricular pacing often develop progressive cardiomyopathy and ventricular dyssynchrony if a single ventricular pacing is performed, which is a problem that may be ameliorated by multisite ventricular pacing.[79] Cardiac resynchronization therapy (CRT) is indicated in CHD patients with a systemic LV ejection fraction ≤ 35%, sinus rhythm, left bundle branch block with a QRS duration ≥ 150 milliseconds, and New York Heart Association (NYHA) class II to ambulatory IV heart failure. The available data suggest a potential role for CRT in patients with systemic RV anatomy, but studies of CRT in patients with systemic RV have largely been small retrospective studies with limited follow-up.[66]

Tachyarrhythmias occur in patients with operated and unoperated forms of CHD. Atrial tachyarrhythmias are common in patients who have undergone atrial surgery (eg, Senning or Mustard operations) and those in whom AV valve disease or shunts lead to atrial volume or pressure overload. Scar-mediated reentrant atrial flutter is a common theme in the majority of patients who have undergone some form of atrial reconstruction. The various modifications of the Fontan operation were developed to decrease the very high incidence of poorly tolerated atrial tachyarrhythmias seen with the right atrial–to–pulmonary artery Fontan repair that was initially performed in 1971[62,80] (Fig. 56–8). Medical or electrical cardioversion should be carried out promptly to restore sinus rhythm; antiarrhythmic medications may be necessary to help maintain it. Surgical cryoablation and transvenous catheter ablation aided by three-dimensional electroanatomic mapping can be used as a therapeutic intervention in atrial tachyarrhythmias.[81-83] Electroanatomic mapping and radiofrequency ablations in patients with CHD represent some of the most challenging electrophysiologic procedures because of the complex pre- and post-surgical anatomy, chamber dilatation, variable anatomy of the conduction system, and presence of intracardiac scars leading to multiple reentrant circuits. An experienced congenital electrophysiology team, including operators and technicians familiar with the complexity of the anatomy, arrhythmias, and substrates, is key in the management of patients with CHD.

Ventricular arrhythmias may occur in a variety of settings, particularly after repair of TOF.[84] First-generation intracardiac repairs were performed via a large anterior ventriculotomy and frequently included incision of the pulmonary valve annulus and placement of a transannular patch made of pericardium or synthetic material (eg, Gore-Tex or Dacron). This technique successfully relieved the outflow tract obstruction but inevitably resulted in pulmonary valvar incompetence and pulmonary regurgitation (Fig. 56–9). Pulmonary regurgitation was thought to have minimal adverse clinical consequences, an assertion that held generally true for the first two decades after transannular patch repair. However, with time, the adverse hemodynamic effects

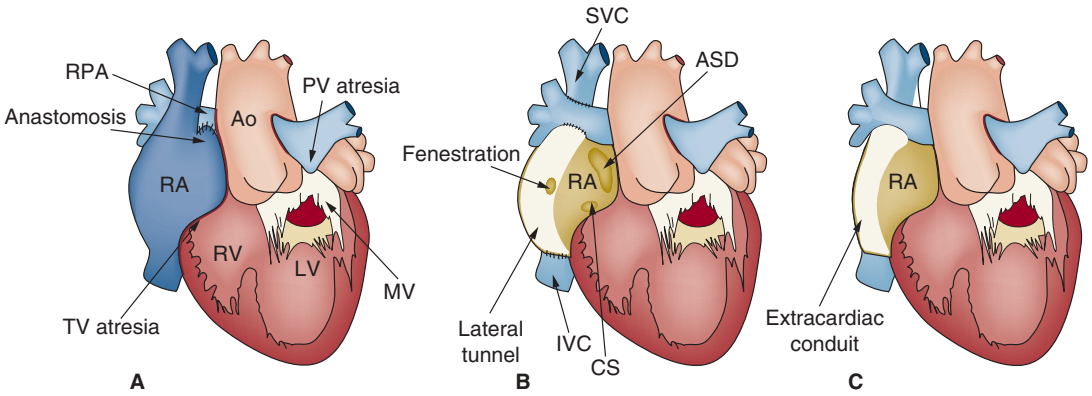


FIGURE 56–8. Most commonly used modifications of the Fontan operation. **A.** Right atrial (RA) to pulmonary artery (PA) Fontan connection with the right atrial appendage directly sutured to the right pulmonary artery (RPA) in a patient with tricuspid and pulmonary atresia. The right ventricle (RV), left ventricle (LV), mitral valve (MV), RPA, and aorta (Ao) are labeled. **B.** In the fenestrated lateral tunnel Fontan, a synthetic material (eg, Gore-Tex) is used to extend a tunnel along the inside lateral wall of right atrium to the RPA, and the superior vena cava (SVC) is sutured directly to the RPA. The fenestration in the wall of the synthetic conduit allows right-to-left shunting and depressurization of the lateral tunnel at the expense of systemic desaturation. **C.** Extracardiac Fontan operation is the current standard. The entire RA is bypassed by a synthetic conduit from the inferior vena cava directly to the RPA. The SVC is sutured directly to the RPA.

of severe low-pressure pulmonary regurgitation become evident. The RV gradually dilates and becomes hypokinetic, and wall stress invariably increases. Ventricular tachycardia is likely to occur under such conditions and often arises from the region of the transannular patch or ventriculotomy suture lines. Programmed ventricular stimulation resulting in monomorphic or polymorphic ventricular tachycardia is of prognostic importance in these patients.[85] In a cohort of 793 patients with repaired TOF followed for a mean 21.1 years, ventricular tachycardia occurred in 4.2% and sudden cardiac death occurred in 2% of patients.[19] Transventricular and transannular repairs were associated with ventricular tachycardia and sudden cardiac death. QRS width on the surface ECG has additive prognostic value.[86] Gatzoulis and colleagues[23] reported that 88% of such patients with ventricular tachycardia and 63% of patients with sudden death had a QRS duration of ≥ 180 milliseconds (see Fig. 56–15A). Patients invariably have a right bundle branch block that results from early injury because of surgical VSD closure and ventriculotomy followed by subsequent QRS lengthening secondary to RV dilatation. The presence of ventricular

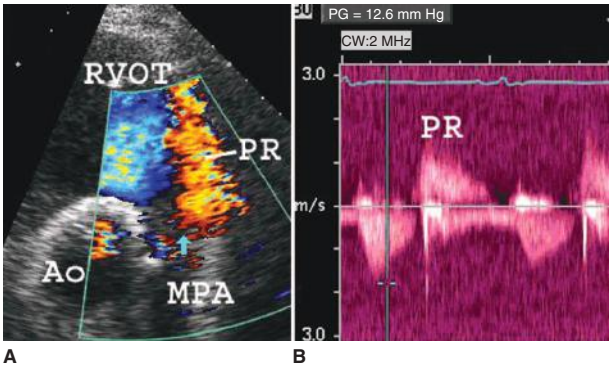


FIGURE 56–9. A 28-year-old patient with tetralogy of Fallot repaired during childhood with transannular patch placement. **A.** Transthoracic two-dimensional and color-flow Doppler in the parasternal short-axis projection demonstrating severe pulmonary regurgitation (PR) from the main pulmonary artery (MPA) to the right ventricular outflow tract (RVOT). The aortic valve is labeled (Ao). The *blue vertical arrow* points to a flail portion of the remaining pulmonary valve. **B.** Continuous-wave Doppler interrogation of the RVOT and MPA in the parasternal short-axis projection demonstrates a low-velocity (< 2 m/s) jet of pulmonary regurgitation (PR) that ends before the onset of systole, consistent with elevated right ventricular diastolic pressure and restrictive right ventricular physiology. There is mild residual pulmonary stenosis.

tachycardia (spontaneous or induced; monomorphic or polymorphic) in a patient with moderate or severe pulmonary regurgitation is an indication for surgical pulmonary valve replacement and ventricular scar excision. Transvenous radiofrequency ablation may be deferred in favor of surgical cryoablation in patients requiring surgical valve replacement. Transvenous radiofrequency ablation is feasible in patients with repaired TOF who have ventricular tachycardia originating from ventriculotomy or transannular patch scar sites and should be attempted in patients who do not require surgical valve or conduit replacement.[87-89] Defibrillator placement may be considered in patients who continue to have inducible ventricular arrhythmias or spontaneous symptomatic ventricular arrhythmias despite radiofrequency ablation or surgical repair. Subcutaneous defibrillator systems allow ICD placement in patients whose anatomy is not conducible to a transvenous system, such as patients with single-ventricle anatomy.[90] There is a disparity between the high frequency of ventricular arrhythmia and the much lower incidence of sudden death in this population.[91] Prophylactic antiarrhythmic therapy has not demonstrated efficacy in asymptomatic patients, and there is insufficient evidence to advocate prophylactic antiarrhythmic therapy in these patients. Identification of asymptomatic individuals who are at risk for ventricular tachycardia or sudden cardiac death remains a challenge. A very wide QRS (> 180 milliseconds) on the surface ECG is a marker for increased risk but has low predictive accuracy in individual cases.[92] LV diastolic dysfunction and elevated LV filling pressure are predictors of ventricular arrhythmias and appropriate defibrillation in adults with repaired TOF.[93,94] Further refinements in risk stratification are necessary and may involve electrophysiologic testing, exercise testing, evaluation of ventricular late potentials using signal averaged ECG, heart rate variability, and presence of repolarization abnormalities.[95-97]

PREGNANCY

An increasing number of women with complex CHD are surviving to reproductive age because of the surgical advances of the past five decades. Pregnancy counseling is mandatory for all patients, whether operated or unoperated. Counseling should begin when the patient reaches menarche and continue well into adulthood. The maternal and fetal risks of pregnancy and transmitted risk of CHD should be discussed in women with CHD who are of childbearing age, preferably before pregnancy. Evaluation should include a detailed medical

and social history with specific attention paid to functional capacity, which is an important prognostic determinant of maternal and fetal outcomes.[98-100] Among risk factors for adverse outcomes, advanced NYHA functional class and history of heart failure are well recognized. The detrimental effects of smoking include arrhythmias and increases in systemic vascular resistance, systemic blood pressure, pulmonary artery pressure and vascular resistance, atrial pressures, and heart rate.[101,102] Transthoracic echocardiography determines ventricular and valvar function as well as pulmonary artery pressure. Impaired subpulmonary or subaortic ventricular function is associated with adverse maternal and fetal outcomes.[98,100] Exercise echocardiography further assesses functional capacity, ventricular function, and valvar function.

The maternal cardiovascular system undergoes a myriad of changes during pregnancy that include a doubling of intravascular volume and cardiac output accompanied by a decrease in systemic vascular resistance. Obstructive lesions are less well tolerated than regurgitant lesions or left-to-right shunts. Severe aortic valve stenosis may be well tolerated if LV function is not impaired.[100] When LV systolic function deteriorates, pregnancy becomes hazardous for the mother and the fetus. The maternal mortality rate for patients with a depressed ejection fraction and severe aortic stenosis is 5.9%.[100] In general, women with valvular regurgitation and left-to-right shunts tolerate pregnancy well. However, patients with severe pulmonary regurgitation who have depressed subpulmonary ventricular function are at increased risk for adverse outcomes during pregnancy and at delivery.[98] Heart failure followed by arrhythmia is the main complication of pregnancy in patients with various CHDs.

Patients with univentricular hearts or tricuspid atresia who have undergone the Fontan operation with normal systolic function tolerate pregnancy well but have an increased risk of miscarriage.[103] The outcomes may also be affected by single-ventricle morphology, specifically the decreased capacity of a morphologic RV to adapt to the volume and pressure changes that face the heart during pregnancy and the peripartum period. Thus, Fontan patients with an RV are at higher risk of developing congestive heart failure than those with an LV. Patients with repaired TOF, specifically those with depressed RV function and severe pulmonary regurgitation as a result of surgical valvotomy or transannular patch repair, are at an increased risk of adverse events.[104] Thirteen percent of patients had cardiac complications in a study by Veldtman and colleagues.[104] Decreased LV systolic function and pulmonary hypertension were similarly correlated with poor maternal and fetal outcomes. Six percent of infants in this study had CHD.

Patients with cyanosis face the most problems in carrying fetuses to term, and pregnancy is strongly advised against (Table 56–1).[105] There is a high incidence of early spontaneous abortion inversely related to the degree of cyanosis. In a study by Presbitero et al,[105] only 12% of pregnancies in women with an oxygen saturation lower than 85% resulted in live births. The maternal complication rate has improved with close monitoring and meticulous care during pregnancy and delivery but is still considerable (32%). There are scant data on management strategies for patients seen late in pregnancy when safe termination is not feasible. Vaginal delivery is generally preferable because it results in less blood loss than cesarean section. Many maternal deaths occur after successful delivery when maternal intravascular volume and systemic vascular resistance increase, exceeding the capacity of the patient's cardiovascular system to adapt. It is the practice of established adult CHD centers to counsel and advise our cyanotic patients against becoming pregnant and to advise pregnancy termination if it is acceptable to the patient.

Maternal mortality in patients with Eisenmenger syndrome has been reported to be as high as 50%.[106] Despite advances in medical therapy, pregnancy outcomes in patients with pulmonary hypertension remain

TABLE 56–1. Fetal Outcome in Cyanotic Congenital Heart Disease and Its Relation with Maternal Cyanosis

Hemoglobin[a] (g/dL)	Pregnancy (No.)	Live Births (No.)	Live Born (%)
≤ 16	28	20	71
17-19	40	18	45
≥ 20	26	2	8
Arterial Oxygen[b] Saturation (%)	**Pregnancy (No.)**	**Live Births (No.)**	**Live Born (%)**
≤ 85	17	2	12
85-89	22	10	45
≥ 90	13	12	92

[a]Hemoglobin level unknown in two pregnancies.

[b]Arterial oxygen saturation unknown in 44 pregnancies.

Adapted with permission from Presbitero P, Somerville J, Stone S, et al: Pregnancy in cyanotic congenital heart disease: Outcome of mother and fetus. *Circulation*. 1994;Jun; 89(6):2673–2676.[105]

patients with severe RV impairment and/or significant symptoms of heart failure. Oral phosphodiesterase inhibitors may be considered in pregnant patients with normal RV function who are minimally symptomatic. Endothelin receptor blockers and soluble guanylate cyclase stimulators are pregnancy category X and should be avoided. At the time of delivery, close monitoring with a central venous catheter and arterial line are recommended.[107]

Patients with connective tissue abnormalities of the aorta, particularly Marfan syndrome, are at increased risk of aortic dissection or rupture if the ascending aorta is dilated (> 40 mm).[108,109] Patients with BAVs, independent of the degree of valvular stenosis, demonstrate a medial abnormality of the ascending aorta that places them at increased risk as well. Therapy with β-blockers in the peripartum period may decrease the risk of aortic dissection and rupture and is usually well tolerated. Severe valvular aortic stenosis places both the mother and fetus at risk because the decrease in systemic vascular resistance and large volume shifts during pregnancy and the postpartum period result in exaggerated valve gradients and increased filling pressure.[110,111] Minimization of vascular volume and resistance alterations can be accomplished by avoidance of large IV volume infusions, avoidance of anesthetics known to decrease systemic vascular resistance, and use of adequate pain control to blunt increases in systemic blood pressure. Patients with severe aortic stenosis and congestive heart failure may require balloon valvuloplasty. The literature on aortic valvuloplasty in pregnancy consists of case reports and small case series. Balloon dilatation of a calcified aortic valve can tear the valve leaflets and cause severe poorly tolerated aortic regurgitation. Pregnant patients with heavily calcified valves and significant aortic regurgitation who are in congestive heart failure or are hemodynamically unstable may require surgical valve placement and cesarean delivery of the fetus.[112]

The management of pregnant women with mechanical valve prostheses is challenging for a number of reasons. Pregnant women are inherently hypercoagulable, and their risk of valve thrombosis is increased, thus necessitating appropriate anticoagulation.[113,114] Oral warfarin accomplishes this task well and is associated with a lower maternal risk, but it is teratogenic to fetuses, especially in the first trimester; the risk of teratogenicity is low after the eighth week of gestation.[115] Therefore, warfarin is recommended by the ACC/AHA guidelines in the second and third trimesters of pregnancy. Given the low risk of teratogenicity

with warfarin doses < 5 mg, warfarin may be used in the first trimester if the baseline dose is < 5 mg. If the baseline warfarin dose is > 5 mg, then heparin may be used in the first trimester. Unfractionated heparin can be given subcutaneously twice a day or as a continuous IV infusion; even with meticulous control, there is still an increased risk of valve thrombosis.[113,116] Subcutaneous low-molecular-weight heparin is more effective but requires frequent anti–factor Xa level monitoring.[113] Because warfarin crosses the placental barriers and results in anticoagulation of the fetus and the mother, warfarin should be discontinued and IV heparin initiated prior to planned vaginal delivery. Cesarean section may be considered as an alternative to vaginal delivery in order to minimize interruption in therapeutic anticoagulation.[113]

The hemodynamic deteriorations during and after labor can be minimized by avoidance of rapid volume and pressure shifts. Planned induction 1 to 2 weeks before the expected term minimizes the risk of spontaneous labor and delivery. Invasive hemodynamic monitoring has not been shown to favorably affect outcomes and is often reserved for the highest risk subsets of patients (eg, those with critical valvular stenosis, severely depressed ventricular function with heart failure, or severe pulmonary hypertension). Vaginal delivery is recommended unless there are obstetric indications for cesarean section, such as a fetus in the breach position. The use of antibiotics for endocarditis prophylaxis after rupture of the membranes is controversial given the absence of randomized controlled trials addressing this topic. The 2014 ACC/AHA valvular heart disease guidelines do not recommend antibiotics for genitourinary procedures in the absence of infection, whereas the 2008 ACC/AHA ACHD guidelines and the American College of Obstetrics and Gynecology favor use of antibiotics for endocarditis prophylaxis in the highest risk patients undergoing vaginal delivery.[6,113,117] In this situation, each patient must be individualized, and the proper medical management should be addressed by the ACHD team.

GENETICS AND GENETIC COUNSELING

CHD is the leading cause of birth defects and noninfectious mortality in the first year of life.[1] The cause of CHD is multifactorial. Genetic and environmental factors each play an important role in the development of CHD. Environmental insults such as chemical teratogens (eg, retinoic acid, lithium) and viral infections (eg, rubella) are known to increase the risk of CHD. Genetic factors also play a role in the development of CHD as demonstrated by the increased incidence of CHD in patients with chromosomal abnormalities such as microdeletions of chromosome 22q11 and trisomy 21. Most defects are not part of a syndrome, and patients have no family history of CHD. Even in seemingly sporadic cases of CHD, epidemiologic evidence demonstrates an increased likelihood of recurrence of CHD in subsequent pregnancies, supporting the existence of a genetic predisposition to CHD. It has been estimated that approximately 8% of CHD cases are caused by inherited genetic abnormalities.[118] In an analysis of 6640 pregnancies in patients with a first-degree family history of CHD, the observed incidence of CHD in pregnancies referred because of sibling CHD and paternal CHD was 2% to 3%.[119] There was a similar incidence of CHD for pregnancies referred because of maternal CHD (2.9%) or paternal CHD (2.2%). A study of a 1094 patients with CHD demonstrated an increased risk of CHD in the offspring of mothers with CHD (5.7%) versus fathers with CHD (2.2%).[120] This study did challenge the polygenic basis for all forms of CHD by demonstrating that AV septal defect is a single-gene defect and TOF is a polygenic disorder with a small number of interacting genes. Isolated TGA is likely a sporadic defect. The risk of recurrence of CHD increases with the number of affected siblings or relatives, and genetic counseling should be provided for potential parents.[121]

The molecular mechanisms leading to CHD are complex, and the causes of the cardiac malformations observed in humans are still unclear. Furthermore, most patients do not have family history of CHD; thus, the mutations are likely spontaneous. The combining of expertise in cardiac anatomy, pathology, and molecular genetics is essential to adequately comprehend CHD. CONgenital CORvitia (CONCOR), a national DNA bank and registry of patients with CHD, will help facilitate research on the genetic contribution to CHD and allow investigation into the molecular basis of CHD.[122]

DIAGNOSTIC CATHETERIZATION AND IMAGING

Cardiac catheterization with angiocardiography has long been the gold standard for making and confirming hemodynamic and anatomic findings in patients with CHD. This position of preeminence is being challenged in the current era by an array of noninvasive imaging techniques, each with certain strengths and weaknesses, yet together capable of almost complete noninvasive anatomic and functional cardiovascular assessment. Transthoracic echocardiography with Doppler is the most widely used and cost-effective tool for diagnostic imaging in patients with CHD. Two-dimensional and, more recently, three-dimensional echocardiography provides a plethora of anatomic and functional data in a matter of minutes at low cost and without any radiation or contrast exposure (Fig. 56–10). Continuous-wave, pulsed-wave, and color-flow Doppler have added incremental value and are the most widely used techniques for quantifying valvar pathology and estimating intracardiac pressure. Tissue Doppler, a form of pulsed-wave Doppler, allows quantification of myocardial velocities and determination of ventricular electromechanical synchrony. The various Doppler-based methods may be used together to estimate atrial pressures, pulmonary artery pressure, and ventricular diastolic function.[123] For example, the ratio of the early diastolic ventricular filling velocity (E) to the early diastolic annular velocity (E′) provides an accurate estimate of atrial pressure.[124] Tissue Doppler and speckle tracking for determination of ventricular strain and torsion provide a plethora of information regarding ventricular systolic and diastolic function.[125]

The Achilles heel of transthoracic echocardiography is the difficulty of image acquisition in patients with poor acoustic windows. Obesity, chest wall deformities, lung disease, or breast implants may adversely impact image quality. Moreover, posterior cardiac structures, such as pulmonary veins and atrial appendages, are often inadequately visualized. TEE traverses many of the previously mentioned hurdles of transthoracic echocardiography and is ideal for the visualization of pulmonary venous anatomy, atrial anatomy, AV valve morphology, ventricular outflow tract lesions, and vegetations or thrombi. Intraoperative TEE is particularly helpful during repair of congenital defects.

In parallel with the decreasing need for diagnostic catheterization, there has been a dramatic increase in the number of transcatheter

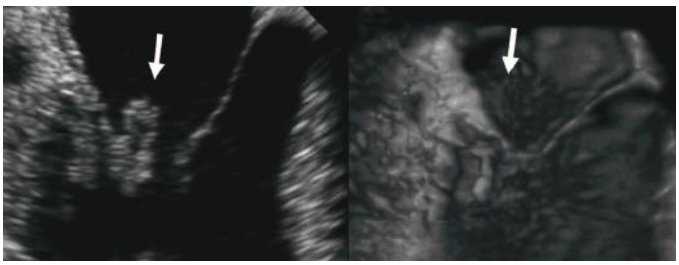


FIGURE 56–10. A. Transesophageal two-dimensional echocardiographic image of a mitral valve vegetation (*arrow*). **B.** Live three-dimensional acquisition of the same vegetation (*arrow*).

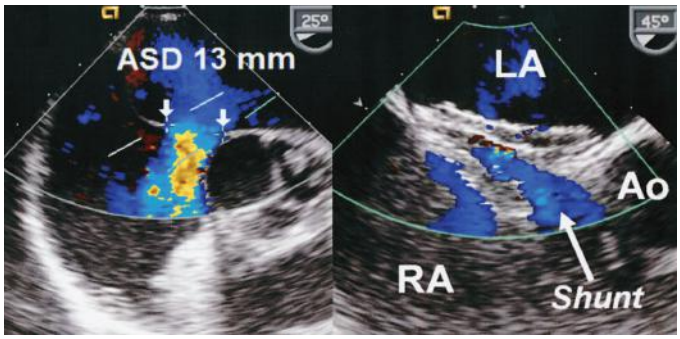


FIGURE 56–11. A. Transesophageal two-dimensional echo with color-flow Doppler demonstrating a 13-mm secundum atrial septal defect (ASD) with a thin posterior rim and an absent anterior (retro-aortic) rim. Note the left-to-right shunt (blue color-flow Doppler signal) across the ASD. **B.** The same patient after closure of the ASD with an Amplatzer septal occluder. A small central left-to-right shunt (*arrow*) from the left atrium (LA) to the right atrium (RA) is a common finding after device closure. The shunt usually resolves within a few weeks as the device endothelializes.

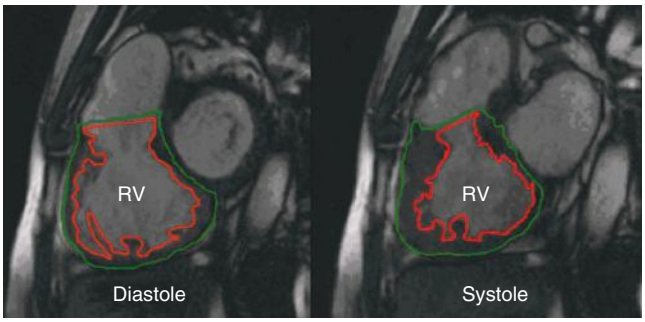


FIGURE 56–12. A stack of contiguous sagittal (short-axis) tomographic slices is acquired using cine-magnetic resonance imaging from the base to the apex of the heart. **A.** Short-axis image at the level of the mid right ventricle (RV) at end diastole. The endocardial (*red*) and epicardial (*green*) borders are traced. **B.** The RV at end systole with the endocardial and epicardial borders defined. These borders are defined in a stack of images from the base to the apex of the RV. According to Simpson's rule, the ventricular volume is equal to the sum of the endocardial areas multiplied by the distance between the centers of each slice. The systolic and diastolic volumes obtained by this method are independent of geometric assumptions and dimensionally accurate. Reproduced with permission from Strugnell WE, Slaughter I R, Riley RA, et al: Modified RV short axis series--a new method for cardiac MRI measurement of right ventricular volumes. *J Cardiovasc Magn Reson*. 2005;7(5):769-774.[130]

cardiac interventions in patients with CHD.[126] The majority of secundum ASDs can now be closed via transcatheter delivery of a closure device (Fig. 56–11). The success of percutaneous transcatheter closure of ASDs is contingent upon proper patient selection.[127] TEE is widely used to assess the size, shape, and rim adequacy of ASDs and to exclude the presence of atrial thrombi or an anomalous pulmonary venous connection. Intracardiac echocardiography can also be used to guide ASD closure.[128]

Cardiovascular MRI provides important incremental anatomic and functional data in patients with CHD. Ultrasound waves are not propagated through air; therefore, echocardiography (transthoracic or transesophageal) is of limited utility for imaging the extracardiac pulmonary vasculature, the site of frequent pathology in certain subsets of CHD. Magnetic resonance angiography (MRA) is invaluable in identifying the size, course, and degree of obstruction of medium to large vascular structures. Velocity mapping and flow quantification provide hemodynamic data such as the volume of pulmonary valve regurgitation per cardiac cycle.[129] Gradient-echo cine-MRI provides incremental information regarding ventricular systolic and diastolic wall motion, segmental strain, and ventricular volumes (Fig. 56–12).[130,131] Four-dimensional phase-contrast MRI is in clinical use and has been demonstrated to have improved sensitivity for and depiction of hemodynamically significant shunts and valvular regurgitation.[132] Myocardial fibrosis detected by late gadolinium enhancement MRI is common in patients with repaired TOF.[133] The degree of late gadolinium enhancement is related to adverse clinical markers, including ventricular dysfunction, exercise intolerance, neurohormonal activation, and arrhythmia. MRA of the coronary arteries is feasible, but imaging beyond the proximal coronary tree is suboptimal. Metallic structures, such as stents and valves, alter the local magnetic field and result in artifacts, thus limiting the utility of cardiac MRI in a significant subset of patients. The presence of a permanent pacemaker or defibrillator is considered a relative contraindication for cardiac MRI. The issues surrounding pacemakers are complex. Various generations of pulse generators and leads make generalizations regarding suitability for MRI problematic. Therefore, patients with pacemakers should not be scanned unless special circumstances arise and then only in centers with special cardiac MRI experience.

Cardiac CT has developed into a widely used noninvasive method for defining anatomy. ECG-gated multidetector CT provides tomographic two-dimensional data that can be sculpted into three-dimensional images, thus clarifying complex anatomy and enhancing the understanding of structure and form (Fig. 56–13).[134] MRI tomographic images can

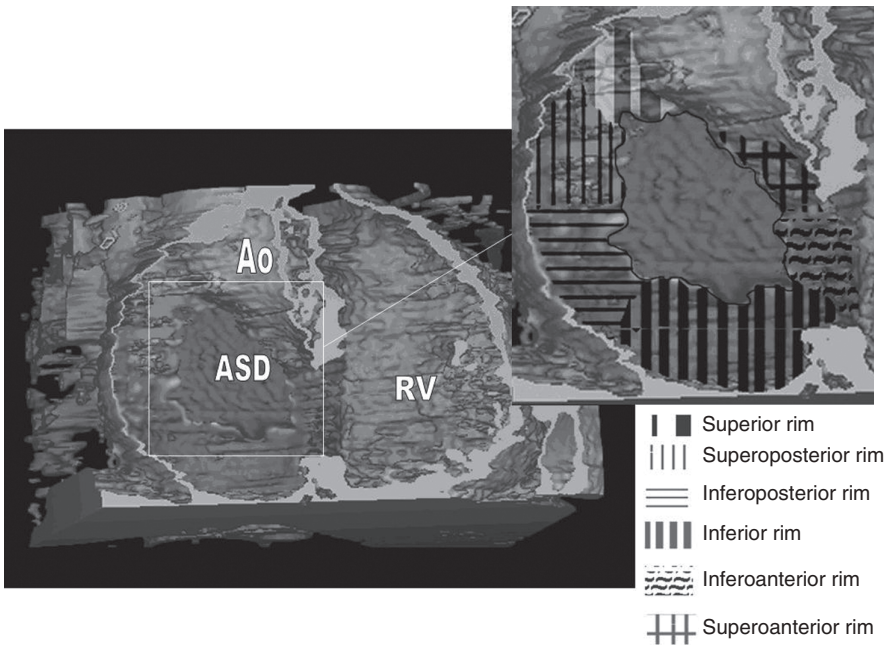


FIGURE 56–13. Computed tomography angiogram with three-dimensional surface rendering of a patient with a large secundum atrial septal defect (ASD) as viewed from a shallow right anterior oblique and slightly caudal perspective. Three-dimensional rendering software has been used to remove the anterior wall of the right atrium and right ventricle (RV). The inset demonstrates an outline of the ASD with division of the atrial septal rim into six quadrants. Assessment of three-dimensional ASD size and rim adequacy facilitates appropriate patient selection for percutaneous versus surgical defect closure. Ao, aorta. Reproduced with permission from AboulHosn J, French WJ, Buljubasic N, et al: Electron beam angiography for the evaluation of percutaneous atrial septal defect closure. *Catheter Cardiovasc Interv*. 2005 Aug;65(4):565-568.[186]

similarly be reconstructed into three-dimensional structures. CT angiography (CTA) allows visualization of the coronary arterial tree, with a high sensitivity, specificity, and negative predictive value for identifying obstructive coronary disease.[135] CT has outperformed MRA in this respect as a result of superior spatial resolution and faster acquisition time. CTA has another advantage in that it does not require as much specialized training and technical knowledge as MRI.[136,137] For these reasons, CTA is set to become the method of choice for noninvasive cardiovascular angiography in community practice, while cardiac MRI remains confined to specialized regional centers despite certain advantages of MRI over CT (eg, the lack of radiation exposure and superiority in the provision of functional information). Moreover, cardiac CT can be performed in the presence of metallic structures or pacemakers, a relative contraindication for MRI.[138]

Cardiac catheterization with angiocardiography remains the gold standard method for identifying anatomy, quantifying shunts, and measuring hemodynamics. Although the less invasive methods described earlier often obviate the need for invasive evaluation, numerous circumstances necessitate invasive evaluation. These include cases in which the noninvasive techniques give inconsistent or conflicting data or cases in which exact pressures and resistances must be measured. For example, patients with single-ventricle physiology may be candidates for the Fontan operation if certain hemodynamic and functional criteria are met (Table 56–2). Direct invasive measurement of pulmonary artery pressure and calculation of resistance must be performed to make the decision to proceed or not proceed with the Fontan operation.

STRESS TESTING

Exercise and pharmacologic stress testing provide important prognostic information regarding exercise capacity, cardiopulmonary reserve, and chronotropic response.[32,33] Exercise capacity is generally decreased in adults with CHD, and drastically so in patients with Eisenmenger syndrome (see Fig. 56–4). The decreased exercise capacity in patients with CHD is comparable to patients with ischemic and nonischemic cardiomyopathy. Chronotropic incompetence is common in certain subsets of patients, specifically those with previous operations or taking β-blockers. Lack of a heart rate response to exercise, pulmonary arterial hypertension, and impaired ventilatory function are correlates of maximum exercise capacity. A blunted heart rate response to exercise identifies patients at increased risk of dying.[139] Cardiopulmonary exercise testing adds incremental diagnostic and prognostic information in patients with CHD. Maximum oxygen consumption is decreased in patients with CHD (see Fig. 56–4). Poor exercise capacity identifies ACHD patients at risk for hospitalization or death. Cyanotic patients with right-to-left shunts (eg, Eisenmenger syndrome) fail to demonstrate a normal increase in pulmonary blood flow with exercise. The systemic arterial resistance decreases with no appreciable change in pulmonary arterial resistance; therefore, more deoxygenated blood is shunted away from the pulmonary arterial bed, and patients desaturate with exercise. The carotid chemoreceptors located at the bifurcation of the internal and external carotid arteries detect this hypoxia, and via a complex feedback mechanism involving the respiratory control centers of the brain stem, increase the minute ventilation, resulting in hyperventilation during exercise (Table 56–3). Ventilatory response to exercise is abnormal across the spectrum of CHD but is most markedly abnormal in cyanotic patients irrespective of pulmonary arterial hypertension. An increased ratio of minute ventilation to CO_2 production (VE/VCO_2 slope) is a strong exercise predictor of death in noncyanotic CHD patients.[26] Oxygen uptake (VO_2) slowly increases in the later stages of exercise yet remains markedly reduced in patients with cyanotic heart disease (see Fig. 56–4). Submaximal exercise capacity as measured by 6-minute walk distance is used widely and is of prognostic importance in patients with pulmonary arterial hypertension and correlates closely with peak VO_2.[140]

TABLE 56–2. Criteria for Performance of the Fontan Operation at the Ahmanson–University of California, Los Angeles, Adult Congenital Heart Disease Center

Morphologic criteria
Tricuspid atresia with pulmonary stenosis or atresia
Single ventricle with pulmonary stenosis or atresia
Hypoplastic ventricle that precludes biventricular repair
Hemodynamic criteria
Pulmonary arterial mean pressure < 15 mm Hg
Pulmonary arterial mean pressure ≤ 22 mm Hg if the Qp:Qs ratio ≥ 2:1 or aortic saturation reaches 85%, provided the pulmonary vascular resistance is < 4-5 Wood units × m^2
Normal or mildly decreased ventricular systolic function (LV ejection fraction ≥ 50%; RV ejection fraction ≥ 40%)
No more than mild valve regurgitation
Ventricular end-diastolic pressure ≤ 12 mm Hg

Abbreviations: LV, left ventricle; RV, right ventricle.

TABLE 56–3. Discriminating Gas Exchange Measurements During Exercise in Patients with Cyanotic Congenital Heart Disease

Low peak VO_2
Low AT
Reduced phase I VO_2
Increased ventilatory response to exercise (VE/VCO_2)
Immediate worsening of hypoxemia at start of exercise

Abbreviations: AT, anaerobic threshold; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption.

SURGICAL AND INTERVENTIONAL CONSIDERATIONS

REOPERATIONS

Reoperations in adults with CHD are common and provide particular challenges.[141] The risks of reoperation are often greater than for the primary procedures, often requiring careful entry into the chest with extensive dissection of scar tissue and longer cardiopulmonary bypass times and greater use of blood products.[142] Careful preoperative planning should include an in-depth understanding of the underlying cardiovascular anatomy and the alterations caused by previous surgical intervention. CT or MRA may be used to determine the anatomic relationships and quantify the proximity of the heart to the sternum. Sternal entry is particularly risky when a high-pressure ventricle, great artery, or conduit lies immediately posterior to the sternum. Moreover, these imaging modalities help identify arterial and venous collateral vessels that may need to be ligated during the course of reoperation. The need for reoperation may come as a surprise to patients and their families, who frequently have a misconception that the previously performed operation was curative.

Inevitable Reoperation

Childhood repair of CHDs that involved insertion of prosthetic valves or conduits often requires reoperation. The prostheses used in infants and children are often too small for adult patients or have undergone degeneration, resulting in stenosis or regurgitation. Development of conduit obstruction is influenced by the type and size of the conduit as well as the timing of the original operation.[143] In the minority of patients with TOF and pulmonary atresia, transannular patch placement is usually not possible; instead, a valved conduit is placed from the RV to the distal pulmonary trunk or confluence of the right and left pulmonary arteries. The early conduits consisted of Dacron into which a bioprosthetic valve was sewn. However, these conduits tend to develop obstruction or regurgitation, requiring replacement in the majority of patients older than 10 to 15 years and have generally been abandoned in favor of allograft (pulmonary or aortic) conduits.[144] For all conduits, calcification and obstruction remain significant complications. The signs of severe obstruction may be subtle, and patients should be evaluated with this in mind. Transthoracic echocardiography with Doppler is an invaluable tool for monitoring ventricular size and function as well as flow velocity through the conduit with estimation of a peak instantaneous and mean pressure gradient.

Right-sided and anterior conduits are often not well visualized by transthoracic echocardiography and may require further imaging with CT or MRA. Diagnostic cardiac catheterization and angiography may be needed if the degree of stenosis is unclear or there are conflicting data from the noninvasive studies. The consequences of chronic pressure overload, specifically on the RV, are chamber dilatation, decreased systolic function, and diastolic dysfunction. These changes increase the risk of surgery and may not be fully reversible. Careful monitoring of ventricular size and function by transthoracic echocardiography is paramount in identifying these processes early in their course to avoid irreversible damage. Serial stress echocardiography is especially useful in estimating exercise-induced gradients, determining ventricular function with exercise, and quantifying functional capacity. Reoperation is usually indicated if the RV pressure is 75% of the systemic pressure or if there is evidence of deteriorating ventricular function or declining functional capacity.

RESIDUAL AND RECURRENT DEFECTS

Residual or recurrent defects can affect long-term prognosis in patients with CHD, so attention should be paid to their presence after operative repair. Patients with TOF who have undergone early intracardiac repair with placement of a transannular patch inevitably develop chronic low-pressure pulmonary regurgitation. This represents the most common indication for reoperation in adults.[145] Chronic pulmonary regurgitation was thought to have minimal adverse clinical consequences, an assertion that held true for the first two decades after transannular patch repair. However, with time, the adverse hemodynamic effects of severe low-pressure pulmonary regurgitation became evident. The RV gradually dilates and becomes hypokinetic, and wall stress invariably increases. The RV outflow tract in the region of the transannular patch becomes dyskinetic, thus causing turbulence and energy loss. The tricuspid annulus frequently dilates, and tricuspid regurgitation often occurs. Therefore, the RV suffers under an additive source of volume overload in the presence of tricuspid regurgitation. Ventricular arrhythmias are more likely to occur under such conditions and often arise from the region of the transannular patch or ventriculotomy suture lines. In a cohort of 793 patients with repaired TOF followed for a mean 21.1 years, ventricular tachycardia occurred in 4.2%, and sudden cardiac death occurred in 2% of patients.[23] Transventricular and transannular repairs with subsequent severe pulmonary regurgitation were associated with ventricular tachycardia and sudden cardiac death. Indications for pulmonary valve replacement include progressive RV dilatation, decreasing systolic function, the presence of arrhythmias, and decreasing exercise tolerance.[146,147]

STAGED REPAIR

In patients with complex CHD, specifically those with cyanotic lesions, definitive "correction" may not be possible until the anatomy and physiology have been optimized by one or more "palliative" procedures. This course is often necessary in patients with extreme forms of TOF with pulmonary atresia, hypoplastic or discontinuous pulmonary arteries, and multiple aortopulmonary collaterals. These patients frequently require complex "unifocalization" of aortopulmonary collaterals, consisting of incorporation of these collaterals into a pericardial tube that receives arterial blood via a surgically created arterial shunt.[148] Unifocalization alone has failed to show a mortality benefit; however, it is used as the first step in a staged repair that subsequently leads to surgical pulmonary artery connection and insertion of a conduit from the RV to the pulmonary artery with concomitant VSD closure.[149,150] A one-stage repair including unifocalization and total intracardiac repair has been described and may become a preferable option as various centers accrue more experience with this procedure.[151]

Other situations in which definitive repair is delayed while palliative procedures are performed include patients with single-ventricle physiology (LV or RV morphology) who often undergo early placement of palliative arteriopulmonary shunts and pulmonary artery banding. Thereafter, these patients often undergo partial (Glenn) or total (Fontan) cavopulmonary connection if they fulfill the stringent criteria for this operation (see Table 56–2).

HEART AND HEART-LUNG TRANSPLANTATION

Heart and heart-lung (block) transplantation are ultimate therapeutic options in patients who continue to deteriorate with optimal medical therapy and have no other good reparative surgical options. Despite the often complex anatomy, multiple previous thoracotomies, adhesions, and often coexistent pulmonary vascular disease, orthotopic heart transplantation has been associated with good outcomes.[152,153] Patients with Eisenmenger syndrome may be offered lung transplantation with repair of the cardiac defect or heart-lung transplantation. The success of either approach in these patients has been limited.[47,154] Given the advancements in the management of patients with pulmonary hypertension and the limited success of these operations, mainly the sickest patients who fail to stabilize or improve on pulmonary arterial vasodilator therapy are referred for transplantation.

NONCARDIAC SURGERY

An awareness of the significance of various repaired or unrepaired congenital lesions in adults is imperative to the safe management of patients during and after noncardiac surgery. All of the anesthetic and bleeding risks encountered for cardiovascular operations also apply to noncardiac surgery. Many patients with CHD are at increased risk for arrhythmias that may be exacerbated by sympathomimetic agents and elevated catecholamine levels. Moreover, anesthetic agents that depress ventricular function must be used with care. Patients with poor cardiac function and those with Fontan connections often have a prolonged circulation time and may not respond as quickly to IV agents as other patients. This should be taken into account when monitoring the effect of anesthetics and titrating medication doses. The surgeon must also be aware of the potential presence of a pacemaker or defibrillator and pacing leads that may affect the safety of electric cautery. In patients with

pulmonary vascular disease, general anesthesia may result in a sudden decrease in systemic vascular resistance and hypotension.[155] Avoidance of vasodilating anesthetic agents is recommended. Cyanotic patients often have impaired hemostasis, and bleeding may be increased. Use of particle filters on all IV lines in patients with intracardiac shunts is imperative in preventing systemic embolization. The safety of noncardiac surgery is greatly increased when the procedures are performed by physicians and staff who are familiar with these issues with concomitant consultation by an ACHD specialist.

TRANSCATHETER INTERVENTIONS

Major advances in percutaneous transcatheter interventions have been made over the past 25 years in the field of CHD.[156] In 1976, Mills and King[157] published the first report of transcatheter closure of an ASD using a double umbrella device. Since then, improvements in device, imaging, and catheterization technologies and procedural techniques have brought interventional cardiology to the forefront as a therapeutic intervention that may delay or obviate surgery. The advances in noninvasive cardiovascular imaging, specifically echocardiography, MRI, and CTA, have made diagnostic cardiac catheterization and angiocardiography necessary in a shrinking pool of patients. These include patients who have undergone the Fontan operation and those in whom noninvasive evaluation has resulted in ambiguous or conflicting results. Adult congenital cardiac catheterizations today are often performed solely for reparative or palliative transcatheter interventions. Interventional catheterization has largely replaced surgery as the treatment of choice for a number of congenital cardiovascular conditions, including secundum ASD, coarctation of the aorta, PDA, and pulmonary artery or valve stenosis.[156,158] Technologies for percutaneous valve replacement are under intense clinical evaluation, and results are encouraging.[159-162] Careful patient selection and imaging are imperative to the safety and success of transcatheter procedures. Noninvasive imaging helps clarify anatomy before intervention and can be used as a means of monitoring for sequelae or complications. MRA and CTA are excellent tools for defining two- and three-dimensional vascular anatomy and are ideal for imaging of the aorta after transcatheter stent deployment (Fig. 56–14). The preprocedural images are key to defining lesion anatomy and precisely identifying neighboring structures that may be affected by the intervention.[134] MRI or CT images may be used to develop three-dimensional models unique to individual patients, allowing for testing of devices ex vivo.

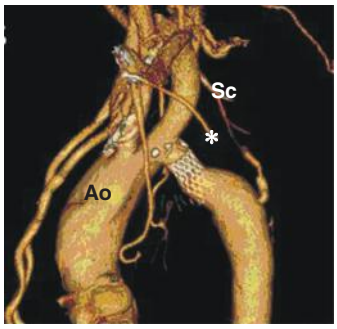


FIGURE 56–14. Electrocardiography-gated cardiovascular computed tomography angiogram with three-dimensional reconstruction viewed from the left anterior oblique projection in a 46-year-old patient with a native coarctation of the aorta (Ao) after transcatheter stent implantation (*asterisk*). The stent appears widely patent and does not intrude upon the ostium of the left subclavian artery (Sc).

ELECTROPHYSIOLOGIC AND DEVICE-BASED THERAPIES

The past two decades have seen the explosive growth of electrophysiology as a major diagnostic and interventional field in cardiology. Adults with CHD are often plagued by a plethora of electrophysiologic problems, namely, supraventricular tachyarrhythmias, ventricular tachycardia, and various forms of bradycardia. Therefore, the technical advancements in invasive electrophysiologic diagnostics and interventions have been of enormous benefit to patients with operated and unoperated CHD. Diagnostic electrophysiologic testing is recommended in symptomatic patients and in those in whom arrhythmias can be detected by ECG monitoring.[66] Transcatheter radiofrequency ablation is successful in the treatment of many supraventricular tachycardias but may be deferred in favor of surgical cryoablation in patients requiring surgical intervention for other reasons (eg, pulmonary valve replacement in a patient with TOF). Transcatheter radiofrequency ablation is less successful in the treatment of ventricular tachycardia originating from ventriculotomy or transannular patch scar sites but should be attempted in patients who do not require surgical valve or conduit replacement.[88,89] Transvenous defibrillator placement should be considered in patients who continue to have inducible ventricular arrhythmias or spontaneous symptomatic ventricular arrhythmias despite radiofrequency ablation or surgical repair (Fig. 56–15).[66]

Electrical resynchronization via multisite ventricular pacing has demonstrated efficacy in patients with various forms of cardiomyopathy

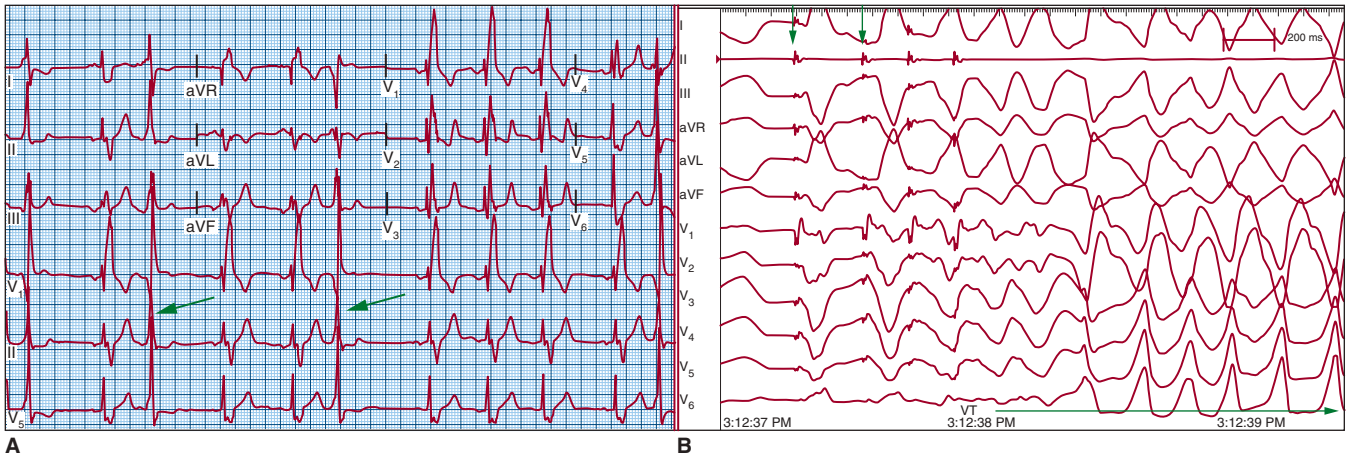


FIGURE 56–15. A. A 12-lead surface electrocardiogram of a patient with tetralogy of Fallot 23 years after intracardiac repair with transannular patch placement who presented with syncope. The patient is in a low atrial rhythm and has a right bundle branch block measuring 185 milliseconds in duration. The *black arrows* indicate frequent premature ventricular complexes. **B.** Intracardiac electrogram recorded during right ventricular programmed stimulation (*small vertical black arrows*). This pacing train initiates rapid and poorly hemodynamically tolerated ventricular tachycardia (VT).

and dyssynchronous ventricular contraction. Approximately 4% to 9% of patients with complete or congenitally corrected TGA are eligible for resynchronization therapy based on degree of heart failure symptoms, ventricular systolic function, and QRS duration.[163] Initial clinical results have been favorable, but the small number of studies and the heterogeneous patient populations make definitive conclusions difficult; however, resynchronization therapy in appropriate candidates appears to improve ventricular function and clinical status.[164-166]

SPECIFIC LESIONS

ATRIAL SEPTAL DEFECT

ASDs are commonly encountered and occur in one-third of adults with CHD (Fig. 56–16; see also Figs. 56–11 and 56–13). Various types exist, but secundum ASD present in the area of the fossa ovalis is the most common, accounting for 75% of defects.[167] Ostium primum defects associated with endocardial cushion defects and inlet-type VSDs occur in 20% of cases. Sinus venosus defects (usually superiorly located) occur in 5% of patients. The rarest type is unroofed coronary sinus. Associated lesions may occur and include pulmonary stenosis, VSD, mitral valve abnormalities (regurgitation or stenosis), and syndromic problems such as Down syndrome and Holt-Oram syndrome. Most cases of ASD are sporadic, but familial cases of ASD have been reported, especially in patients with coexistent prolongation of the PR interval.[168]

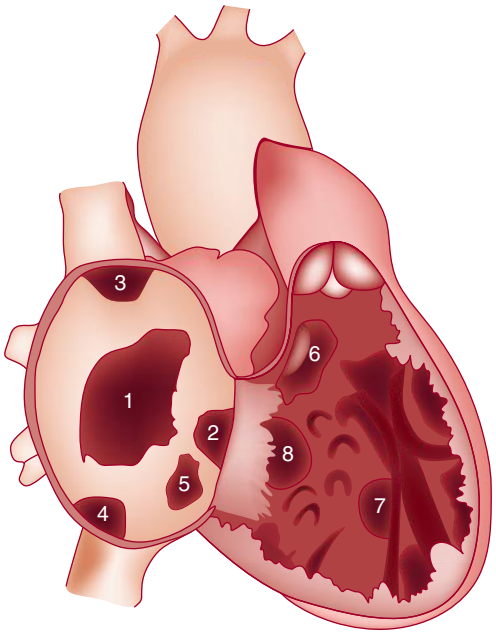


FIGURE 56–16. Various types of atrial and ventricular septal defects (ASD and VSD, respectively). The heart is viewed from a right anterior oblique projection, and the right ventricular and right atrial free walls have been removed. **1.** Secundum-type ASD. **2.** Primum-type ASD. **3.** Superior sinus venosus ASD. **4.** Inferior sinus venosus ASD. **5.** Coronary sinus ASD. **6.** Perimembranous VSD. **7.** Muscular VSD. **8.** Inlet VSD.

Natural History

ASDs often go unrecognized for the first two decades because of the indolent clinical course and benign findings on physical examination. Careful inspection of the ECG usually demonstrates a characteristic RSR′ complex in the anterior precordial leads with a rightward QRS axis in patients with secundum-type defects and left-axis deviation in those with primum-type ASD (Fig. 56–17). Initial diagnosis in adulthood is common, and survival into adulthood is the rule. However, life expectancy is not normal in unrepaired patients, with mortality increasing by 6% per year after age 40 years.[169,170] Progressive symptoms of dyspnea on exertion and palpitations frequently occur in adulthood and are caused by increasing right-sided chamber enlargement, pulmonary hypertension, RV failure, tricuspid regurgitation, and atrial arrhythmias. Patients with large ASDs causing left-to-right shunts develop RV volume overload, which is relatively well tolerated for the first two decades but thereafter results in right heart failure and arrhythmias. The subsequent increase in serum BNP levels and decrease in exercise capacity are correlated with the magnitude of left-to-right shunting.[171] The degree of left-to-right shunt may increase with age as LV compliance decreases and systemic arterial resistance increases after the fourth decade of life. Paradoxical embolism may occur but is a rare complication. The risk of infective endocarditis is low unless the patient has coexistent valvular disease (eg, cleft mitral valve).

Management and Results

Surgical repair via direct suture of small defects and patch closure of larger defects has been performed for more than 40 years and has been efficacious and safe provided the pulmonary arterial resistance is not

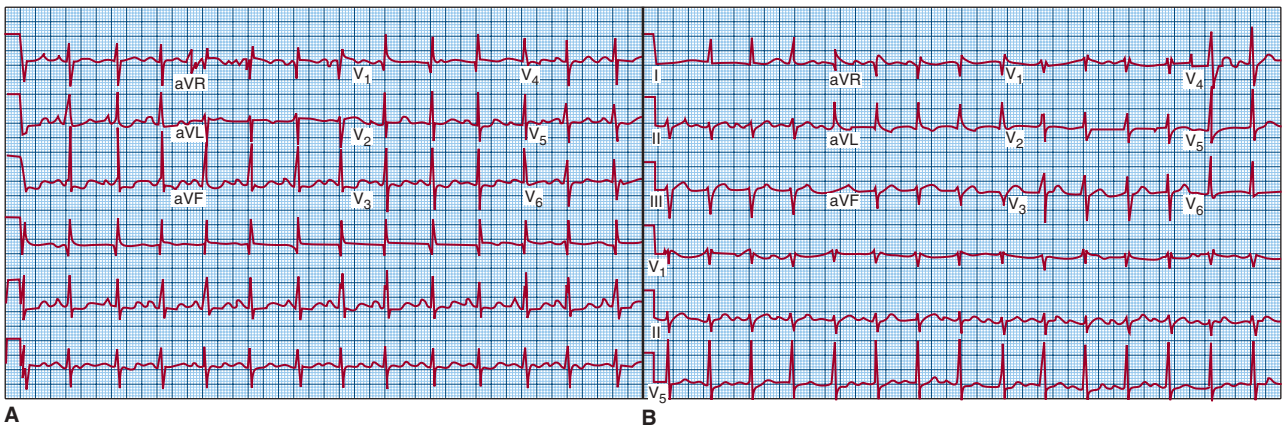


FIGURE 56–17. A. A 12-lead electrocardiogram (ECG) of a 30-year-old woman with a large secundum-type atrial septal defect (ASD; 42 mm in diameter by transesophageal echocardiography) and moderate pulmonary artery hypertension (PAP = mm Hg). Note the right-axis deviation and tall precordial R waves consistent with right ventricular enlargement or hypertrophy. There is evidence of right atrial abnormality. **B.** An ECG of 33-year-old man with a primum-type ASD surgically repaired at 3 years of age. Note the continued presence of a characteristic RSR complex in lead V_1 and QRS left-axis deviation.

severely elevated.[167,172] Closure of small defects (< 1 cm) in asymptomatic patients diagnosed after 25 years of age is controversial, with no significant difference in clinical outcomes between medically and surgically treated patients followed for over 20 years.[173] A retrospective study by Konstantinides et al[174] of 179 patients diagnosed after the age of 40 years with a Qp:Qs ratio of 1.5:1 or greater demonstrated a relative risk of 0.31 for patients who underwent surgical closure, as compared with patients treated medically ($P = .02$). Estimated probability of survival was 95% at 10 years for surgically treated patients and 84% for patients treated medically. Predictors of increased mortality in the surgical group included older age at operation, advanced heart failure (NYHA class III or IV), Qp:Qs ratio of 2.5:1, pulmonary artery systolic pressure above 40 mm Hg, and pulmonary vascular resistance above 1.6 Wood units. Nonfatal clinical outcomes such as supraventricular arrhythmias occurred with similar frequency between the two groups. However, the operations carried out in this study did not include atrial arrhythmia surgery (maze or Cox-maze procedures), which is known to decrease arrhythmia recurrence in patients undergoing surgical ASD closure.[175] A prospective, randomized study by Attie et al[176] of surgical versus medical management of ASD in 241 patients older than age 40 years did not demonstrate similar survival advantages over 7 years of median follow-up. However, a significantly lower percentage of patients in the surgical group reached the composite end point of heart failure, recurrent pneumonia, peripheral or pulmonary embolism, or death ($P = .0046$), leading the authors to conclude that surgical closure should be performed in all patients with an ASD and pulmonary artery systolic pressure below 70 mm Hg and Qp:Qs ratio above 1.6:1.

Pulmonary artery vasodilator therapy with prostaglandins, endothelin blockers, and phosphodiesterase-5 inhibitors may reduce pulmonary arterial pressure and resistance to a level that allows consideration of shunt closure in these patients, but this should only be considered at centers experience in the management of such patients.[177] Current ACC/AHA guidelines recommend consideration of closure if pulmonary artery pressure is less than two-thirds of systemic level, pulmonary vascular resistance is less than two-thirds systemic vascular resistance, or there is a positive response to either pulmonary vasodilator therapy or test occlusion of the defect.[6] Pulmonary vasoreactivity testing and a trial of pulmonary vasodilators for several months may help risk stratify patients with borderline pulmonary pressures for closure. In a study by Balint et al,[178] many patients with ASDs and pulmonary arterial hypertension continued to have elevated pulmonary artery pressures after closure, and 15% had persistent severe pulmonary hypertension. Closure is contraindicated in patients with severe irreversible pulmonary arterial hypertension and no evidence of left-to-right shunt.[6] Severe pulmonary hypertension in patients with ASD usually represents the coincidence of idiopathic pulmonary hypertension or pulmonary hypertension secondary to another process (eg, scleroderma) and ASD.[28] Unlike patients with large, unoperated, nonrestrictive central shunts (eg, VSD) who experience pulmonary hypertension from birth and develop pulmonary vascular disease within the first few years, patients with large ASDs of similar shunt magnitude do not necessarily develop severe pulmonary hypertension, and right-to-left shunting or the onset of pulmonary hypertension is delayed into late adulthood.[179] However, a large ASD may well contribute to the development of pulmonary hypertension but may not be the sole cause of the underlying pulmonary vascular disease in a cyanotic patient. Patients with trisomy 21 (Down syndrome) may develop accelerated pulmonary vascular disease in the presence of ASD (primum or secundum).

Transcatheter device closure of secundum-type ASD was first performed in 1976 by Mills and King.[157] Advancements in device design and catheterization technology have led to the availability of a variety of occlusion devices (see Fig. 56–11).[180-182] Transcatheter device closure compares favorably with surgical closure in terms of efficacy and is associated with shorter hospital stays and fewer postprocedural complications.[181,183] Appropriate patient selection is imperative and may be accomplished via a variety of noninvasive and invasive imaging methods.[184-187] Transcatheter device closure techniques have supplanted surgery at many institutions as the method of choice for ASD closure in properly selected patients; complications are rare. Short-term complications have included device embolization, aortic root or atrial wall perforation, and cardiac tamponade.[188] Mid- and long-term complications include thrombus formation, device erosion into the aortic root, atrial dysrhythmias, and infective endocarditis. The use of platelet inhibitors for at least 6 months after device closure is recommended to decrease the risk of device thrombosis.[189] The long-term outcomes of device closure using the Amplatzer septal occluder are excellent, as evidenced by no deaths and minimal complications in 151 patients followed for 6.5 years after ASD closure.[190]

VENTRICULAR SEPTAL DEFECT

Isolated VSD is the most commonly encountered form of CHD in the pediatric population (see Fig. 56–16). This is not the case in the adult population for a number of reasons.[191,192]

1. Most children with hemodynamically significant defects are diagnosed and undergo repair in childhood because they develop signs and symptoms of LV enlargement and failure. Children growing up in developing countries often go undiagnosed and unrepaired well into adulthood because of absent or intermittent medical attention.
2. Small unrepaired perimembranous or muscular VSDs often spontaneously decrease in size or close with age. However, small VSDs initially encountered in adulthood (in patients older than 20 years of age) are unlikely to close spontaneously.
3. Large nonrestrictive defects that are not surgically corrected within the first 2 years of life result in incompletely reversible pulmonary vascular disease and are associated with increased mortality in childhood (see Fig. 56–3).

Therefore, the spectrum of isolated residual VSD encountered in the adult patient usually consists of:

1. Small restrictive defects or defects that have closed partially with time. The pulmonary vascular resistance is not significantly elevated, and the left-to-right shunt magnitude is mild (Qp:Qs ratio ≤ 1.5:1). The intensity of the precordial holosystolic murmur is inversely related to the size of the defect; therefore, a disturbingly loud and harsh precordial holosystolic murmur in a patient with VSD should be viewed as a reassuring sign, not a cause for alarm.
2. Large nonrestrictive defects in cyanotic patients who have developed the Eisenmenger complex, with systemic pulmonary vascular resistance and shunt reversal (right to left).
3. Patients with moderately restrictive defects (Qp:Qs ratio ≥ 1.6:1 and ≤ 2:1) who have not undergone closure for some reason. These patients often have mild to moderate pulmonary hypertension.
4. Patients who have had their defects closed in childhood. These patients may have small but generally inconsequential VSD patch leaks that may be identified by careful color and two-dimensional Doppler scanning of the entire interventricular septum during echocardiographic examination.

Natural History

Small restrictive defects of the muscular or membranous septum may be watched conservatively without the need for operative intervention. Patients are at increased risk for endocarditis as a result of the

turbulent, high-velocity jet impinging on the septal leaflet of the tricuspid valve that partially closes many perimembranous defects. Six percent of patients with small perimembranous defects may develop aortic valve prolapse and resultant aortic regurgitation that may be progressive.[193] The prolapsing aortic valve cusp (usually the right coronary cusp) may partially or completely close the VSD. Aortic valve repair or replacement may be necessary in patients with aortic regurgitation who develop exertional symptoms or progressive LV dilatation.[113,194] In a long-term follow-up registry, the overall survival rate was 87% for all patients with unoperated VSD.[179] For patients with small defects (Qp:Qs ratio < 1.5 and low pulmonary artery pressure), the survival rate was 96% at 25 years. Patients with moderate and large defects fare worse, with 25-year survival rates of 86% and 61%, respectively. Those with cyanosis (Eisenmenger complex) had a much lower 25-year survival rate of 41.7%.

In patients with large nonrestrictive VSD, pulmonary vascular disease begins at or soon after birth with abnormal vascular remodeling; if the VSD is not surgically repaired, patients eventually develop obliterative pulmonary vascular disease.[192] Systemic pulmonary vascular resistance results in a balanced bidirectional shunt or shunt reversal and cyanosis, a condition first described by Eisenmenger in 1897 and coined "the Eisenmenger complex" by Maude Abbott in 1927.[195] Survival is generally decreased in these patients, although with proper medical care and protection against certain risks (eg, dehydration, endocarditis), survivors have been reported into the seventh decade of life.[47,196] Patients develop compensatory erythrocytosis, which is an appropriate response to the decreased systemic oxygen saturation from right-to-left shunting of deoxygenated blood. Phlebotomy is not warranted unless patients develop symptoms of hyperviscosity (headache, visual changes) that are refractory to hydration. As a matter of fact, routine phlebotomy does not reduce cerebral complications and leads to iron deficiency anemia. Microcytic iron-deficient red blood cells carry less oxygen and are less deformable in the microcirculation than iron-replete red blood cells, thus resulting in worsening cyanosis and increased cerebral complications, which are properly treated by judicious iron repletion.[47]

Management and Results

Patients with small restrictive defects (Qp:Qs ratio ≤ 1.5:1 and low pulmonary artery pressure) are generally asymptomatic and should be managed conservatively and followed up regularly.[179] Although antibiotics for endocarditis prophylaxis are no longer recommended by the ACC/AHA guidelines, patients are at increased risk for endocarditis.[113] Patients should be instructed in dental and skin care. Small defects with aortic valve prolapse and aortic regurgitation may be repaired to avoid progressive aortic regurgitation.[197] Larger defects may be repaired in the absence of severe pulmonary hypertension and severely elevated pulmonary vascular resistance (> 10 Wood units × m^2), which incurs a high perioperative risk.[198,199] Postoperative life expectancy is not normal but has improved over the past 50 years with improved surgical techniques and experience. Postoperative conduction defects are common, but complete heart block is rare in the current era. The postoperative risk of infective endocarditis is low. Transcatheter device occlusion of muscular and perimembranous VSD is feasible, and trials demonstrate a good safety and efficacy profile.[200-203] Complete heart block has been noted to occur in up to 6% of children and 1% of adults.[200,202]

ATRIOVENTRICULAR SEPTAL DEFECTS

Atrioventricular septal defect is an umbrella term used to describe endocardial cushion defects representing a spectrum of lesions involving the atrial and ventricular septum, AV valves, and LV outflow tract (LVOT).

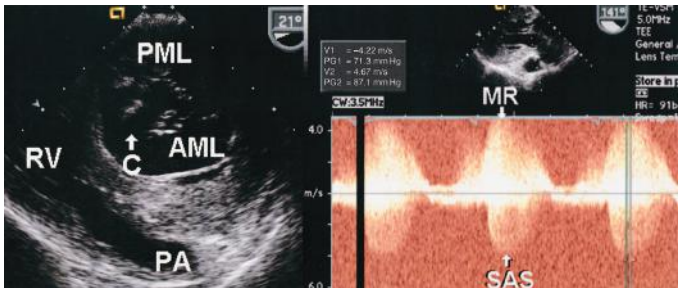


FIGURE 56–18. A. Transesophageal two-dimensional echocardiographic image as viewed from the transgastric view, demonstrating a cleft (C) in the anterior mitral leaflet (AML). Also labeled are the posterior mitral leaflet (PML), right ventricle (RV), and main pulmonary artery (PA). **B.** Continuous-wave Doppler across the mitral valve and left ventricular outflow tract (LVOT) performed form the transgastric position, demonstrating mitral regurgitation (MR) through the cleft AML and severe subaortic stenosis (SAS) with a maximum velocity of 4.67 m/s, caused by chordal attachments from the AML to the LVOT.

The defects are classified into "partial" or "complete" forms. In the partial form, patients have a primum ASD but no VSD (see Fig. 56–16). The complete form includes both a primum ASD and an inlet VSD (see Fig. 56–16). The deficiency of the inlet ventricular septum along with abnormalities of the AV valves (overriding, straddling, or cleft) produces an elongated LVOT that has characteristically been described as having a "goose neck" appearance on left ventriculography. Subaortic stenosis (SAS) is a common association often caused by chordal attachments of the cleft anterior mitral valve to the LV outflow septum (Fig. 56–18). SAS may also occur de novo after surgical repair because of a discrete fibrous membrane.[204]

Natural History

Approximately 5% of infants with CHD have AV septal defect, with two-thirds of patients having the complete form.[205] Trisomy 21 and other chromosomal abnormalities are frequently associated, and these patients usually have the complete form. The natural history of partial AV septal defect patients depends on the size of the defect, and in many ways, these primum ASDs behave in a similar manner to secundum ASD (see earlier). Patients with Down syndrome may have accelerated pulmonary vasculopathy, resulting in pulmonary hypertension at an earlier age. Mitral valve regurgitation, secondary to the presence of a common AV valve and "cleft" (see Fig. 56–18), if present, leads to greater left-to-right shunt magnitude and earlier signs of pulmonary hypertension and heart failure. Patients with complete defects that are unrepaired in infancy or childhood frequently develop severe pulmonary hypertension and eventual shunt reversal, characteristic of Eisenmenger syndrome (see earlier).

Management and Outcomes

Surgical repair involves patch closure of the primum ASD and VSD closure in patients with the complete form of AVSD. "Cleft" mitral valve repair should be attempted to restore valvar competence, the assessment of which can be made using intraoperative TEE.[206,207] Percutaneous ASD closure of a primum defect is contraindicated given the close proximity of the defect to the tricuspid and mitral valves as well as the ostium of the coronary sinus. Surgical mortality is 15% within the first 30 days after surgery.[208] Adverse predictors of mortality include the complete type of AV septal defect, the presence of pulmonary hypertension, and the absence of cleft mitral valve repair. Survival late after operation in a study of 121 patients demonstrated that survival was 80% at 1 year, 78% at 10 years, and 65% at 20 years. Freedom from

reoperation was 91% at 1 year, 79% at 10 years, and 76% at 20 years. Mitral valve regurgitation necessitating valve repair or replacement was the most frequent indication for reoperation.

TETRALOGY OF FALLOT

TOF is the most common cyanotic congenital heart malformation and one of the first complex lesions to be successfully repaired. TOF occurs in 7% to 10% of children with CHD. The four characteristic findings in TOF are (1) a malaligned VSD, (2) RV outflow or pulmonary valve or artery stenosis or atresia, (3) a dextraposed over-riding aorta, and (4) RV hypertrophy (see Fig. 56–1A). In the modern era, early surgical repair consisting of VSD closure and alleviation of RV outflow obstruction has gained favor over early palliation with an aortopulmonary shunt followed by intracardiac repair. Surgical outcomes are excellent and dramatically improve prognosis. However, these patients are not "cured" and are at significant risk of developing subsequent electrical and hemodynamic problems. Operated patients with TOF should be evaluated at regular intervals by a cardiologist trained in CHD; any symptoms suggestive of hemodynamic or electrical compromise should spur further investigation. Advances in imaging, medical therapy, electrophysiology, device and resynchronization therapy, and percutaneous intervention provide clinicians with a number of therapeutic options.

Natural History

The natural history of unoperated patients is in large part determined by the severity of obstruction to RV outflow. A total of 66% of unoperated patients live to age 1 year, 49% live to age 3 years, 24% live to age 10 years, and only 3% of patients reach 40 years of age.[209] The chance of survival is greatly diminished when complete pulmonary atresia, instead of a variable degree of pulmonary stenosis, is present. Complications of right-to-left shunting across a nonrestrictive VSD include cyanosis, erythrocytosis, thrombocytopenia, and an increased risk of paradoxical emboli and cerebral abscess formation. Patients are at high risk for developing infective endocarditis. Malignant ventricular arrhythmias and congestive heart failure are major causes of death.

Management and Results

Since Blalock and Taussig performed a successful clinical palliative shunt in 1945, the survival and quality of life for patients with TOF has improved dramatically, truly one of the great accomplishments for cardiovascular medicine in the 20th century (see Fig. 56–1). Surgical palliation consists of systemic arterial–to–pulmonary arterial shunts designed to increase blood flow to the pulmonary arteries. Palliative surgery was followed subsequently by intracardiac repair that included VSD closure and relief of the RV outflow obstruction (see Fig. 56–1). Surgical techniques have changed significantly since the early intracardiac repairs of the 1960s and 1970s. The deleterious hemodynamic and electrical effects of pulmonary regurgitation and ventriculotomy scars have spurred efforts to ensure pulmonary valvar competence and minimize the extent of ventricular incisions. Advancements in surgical repair now confer an 85% survival into adulthood in the United States.[210] The technique used for repair depends on the level and extent of outflow obstruction. Simple pulmonary valvar stenosis with a nondysplastic well-developed pulmonary valve requires the least extensive surgery, which consists of VSD and pulmonary valvotomy. More extensive or more severe outflow tract stenoses necessitate a more extensive reconstruction of the RV outflow tract or complete bypass of the RV outflow tract by placement of a valved conduit. The first generation of intracardiac repairs was performed via a large anterior ventriculotomy and frequently included incision of the pulmonary valve annulus and placement of a transannular patch made of pericardium or synthetic material. This technique successfully relieved the outflow tract obstruction but resulted in pulmonary valvar incompetence and severe pulmonary regurgitation (see Fig. 56–9). Pulmonary regurgitation was thought to have minimal adverse clinical consequences, which may be true for the first two decades after transannular patch repair. However, with time, the adverse hemodynamic effects of severe low-pressure pulmonary regurgitation results in RV dilation and increased wall stress. The RV outflow tract in the region of the transannular patch becomes dyskinetic, causing turbulence and energy loss. The tricuspid annulus frequently dilates, and tricuspid regurgitation often occurs. Therefore, the RV suffers under an additive source of volume overload in the presence of tricuspid regurgitation. Additionally, the RV develops "restrictive" diastolic properties that further compromise energy-efficient hemodynamics[211] (see Fig. 56–9). Ventricular arrhythmias are more likely to occur under such conditions and often arise from the region of the transannular patch or ventriculotomy suture lines.[212] Programmed ventricular stimulation resulting in monomorphic or polymorphic ventricular tachycardia is of prognostic importance in these patients.[85] In a cohort of 793 patients with repaired TOF followed for a mean of 21 years, ventricular tachycardia occurred in 4.2%, and sudden cardiac death occurred in 2% of patients.[23] Transventricular and transannular repair were associated with ventricular tachycardia and sudden cardiac death. QRS width on the surface ECG has additive prognostic value; 88% of patients with ventricular tachycardia and 63% of patients with sudden death had a QRS duration of ≥ 180 milliseconds.[23] Patients invariably have a right bundle branch block that results from early injury caused by surgical VSD closure and ventriculotomy followed by subsequent QRS lengthening secondary to RV dilatation. Therefore, severe pulmonary regurgitation leads to RV dilatation, which in turn leads to systolic and diastolic functional deterioration and increasing QRS duration, creating a vicious cycle; all of these factors combine to increase the risk of malignant ventricular arrhythmias. LV systolic and diastolic dysfunction are additional high-risk markers.[93,213,214]

Patients with an RV–to–pulmonary artery valved conduit may develop progressive conduit stenosis but do not usually develop significant pulmonary regurgitation. Atrial arrhythmias are a cause of morbidity and confer a worse prognosis in patients with repaired TOF, especially in patients with tricuspid valve regurgitation and right atrial enlargement.[23,215] AV block may occur after initial repair and VSD closure and is usually the result of damage to the conduction system at or below the bundle of His incurred during VSD closure. These patients require implantation of a permanent pacemaker (usually dual chamber) and are often pacemaker dependent. Chronic RV pacing is known to lead to deterioration of biventricular function and dyssynchronous ventricular contraction.[216] Biventricular resynchronization may improve dyssynchrony and increase cardiac output.[217,218] LV systolic and diastolic dysfunction may occur in the presence of severe pulmonary regurgitation. The interventricular septum bows leftward during diastole, resulting in impaired LV diastolic filling and asynchronous septal contraction. A decrease in LV ejection fraction is ominous.[219] Abnormal strain patterns by cardiac MRI are associated with adverse clinical outcomes.[20,220] Approximately one in 10 patients will require subsequent reoperation for RV outflow repair, conduit replacement, or pulmonary valve replacement.[221] Additional tricuspid valve annuloplasty and right atrial maze cryoablation are often performed in patients with severe tricuspid regurgitation and atrial arrhythmias. In patients with mild or moderate tricuspid regurgitation and dilated tricuspid annular size, tricuspid regurgitation improves after pulmonary valve replacement, regardless of whether tricuspid annuloplasty was performed.[222,223] Every effort should be made by the surgeon to excise

the ventriculotomy scar tissue that serves as the source of reentrant ventricular arrhythmias. Reoperation carries a low perioperative risk of mortality.[145]

Transcatheter pulmonary valve (TCPV) replacement can alleviate RV outflow tract (RVOT) conduit dysfunction whether caused by stenosis, regurgitation, or both, thereby delaying the need for open heart surgery and essentially decreasing the number of operations with their associated morbidities.[224] The Melody (Medtronic, Dublin, Ireland) TCPV was the first valve to receive US Food and Drug Administration (FDA) approval, initially under humanitarian device exemption in 2010 and thereafter for clinical use in 2014. The Melody valve is widely used for the treatment of dysfunctional RV–to–pulmonary artery conduits and bioprosthetic valves, and more recently has been used to treat dysfunctional native RVOT lesions. The various Sapien transcatheter bovine pericardial stent valves (Edwards, Irvine, CA; Sapien, Sapien XT, and Sapien 3) are FDA approved for use in the aortic position and are being used by multiple centers for off-label implantation in the pulmonary position. The larger diameter Sapien valves (26 and 29 mm) allow for implantation in large dysfunctional native RVOTs. Short-term follow-up after Melody valve implantation has been promising, with hemodynamic and clinical improvement and acceptable durability of the valve.[225] Greater improvement in exercise capacity is seen in patients with both RVOT stenosis and regurgitation, compared with those with only RVOT regurgitation.[226] Favorable longer term outcomes were seen after a median follow-up of 4.5 years in 148 patients in the US Melody valve investigational device exemption trial, with a 5-year freedom from reintervention of 76% and a 5-year freedom from explant of 92%.[227] Stent fracture and endocarditis have been the primary causes for reintervention.[228-232]

Stent fracture often occurs in patients with conduits or native RVOT dysfunction and is likely caused by repetitive stress on the platinum iridium frame (Fig. 56–19). Prestenting before Melody valve placement has significantly reduced the incidence of stent fracture. Also, valve-in-valve implantation is a successful treatment option for Melody valve stent fracture. As for endocarditis, adherence with subacute bacterial endocarditis prophylaxis is imperative; however, data suggest there is an increased risk of infective endocarditis with implanted Melody valves.[230,231,233] Other complications, such as conduit or pulmonary artery dissection or rupture, are life threatening but rare and can be treated with covered stent placement. There is a 5% risk of coronary artery compression, but this risk can be reduced by performing simultaneous balloon inflation in the RVOT with coronary or aortic root angiography to test for coronary artery compression. TCPV replacement has also been successfully performed within failed bioprosthetic valves, not as part of RV–to–pulmonary artery conduits, with excellent outcomes. In the subset of CHD patients with native RVOT or RVOT patch repairs, there is a growing body of literature on the utility of commercially available valves used off label.

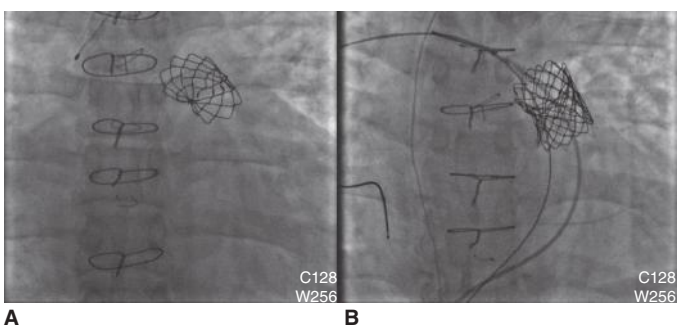


FIGURE 56–19. A. Stent fracture of a Melody transcatheter pulmonary valve. **B.** After stenting of the fractured stent and placement of a new Melody transcatheter pulmonary valve.

The timing of pulmonary valve replacement in asymptomatic patients remains controversial, especially in the repaired TOF patient. Severe RV dilation or dysfunction and the development of atrial arrhythmias are the most common indications for pulmonary valve replacement in the otherwise asymptomatic patient, although the RV volume threshold for pulmonary valve replacement varies by ACHD center. Therrien et al[147] demonstrated that patients with TOF and severe pulmonic regurgitation had normalization of RV end-diastolic volumes after pulmonic valve replacement if the preoperative indexed RV end-diastolic volume was ≤ 170 mL/m^2. An indexed RV end-diastolic volume of ≥ 160 mL/m^2 or an indexed RV end-systolic volume ≥ 65 mL/m^2 has therefore been suggested as an indication for pulmonary valve replacement.[146] However, the advent of transcatheter valve therapies may be lowering the threshold for pulmonary valve replacement. Some experts argue that all patients with severe pulmonary regurgitation should undergo pulmonary valve replacement prior to the development of RV dilation or dysfunction.[234] This aggressive early intervention approach must be weighed against the procedural risks, the potential for infective endocarditis, and the potential decrease in the internal orifice diameter of surgically placed conduits or bioprosthetic valves with multiple transcatheter pulmonary valve implants over a patient's lifetime.[235]

PULMONARY STENOSIS

Isolated pulmonary valve stenosis is commonly seen in adults with CHD. The valvar stenosis is typically characterized by a trileaflet valve with fused commissures as opposed to the more rare dysplastic valve without commissural fusion. The exception is Noonan syndrome, in which a dysplastic and stenotic pulmonary valve is commonly present. RV hypertrophy, including excessive hypertrophy of the infundibulum, occurs in response to RV pressure overload from the stenotic valve. Isolated infundibular stenosis is rare, as is isolated supravalvar stenosis.

Natural History

Survival into adulthood is usual. Severe pulmonary stenosis that is uncorrected may result in progressive RV hypertrophy, dilatation, and symptoms of right heart failure. Moderate or mild pulmonary stenosis generally does not progress and is well tolerated.

Management and Outcomes

Mild and moderate degrees of pulmonary stenosis (peak gradient ≤ 50 mm Hg) are well tolerated and generally do not require surgical or percutaneous intervention.[93] Infective endocarditis of the pulmonary valve is rare; endocarditis prophylaxis during bacteremic procedures is not recommended.[6] Asymptomatic patients with severe pulmonary stenosis and a peak gradient ≥ 60 mm Hg or a mean gradient ≥ 40 should undergo intervention to reduce the severity of the stenosis. Symptomatic patients with a peak gradient ≥ 50 mm Hg or a mean gradient ≥ 30 mm Hg should undergo intervention.[6]

Surgical valvotomy for isolated pulmonary stenosis has been successfully and safely performed for 50 years. Perioperative and late results are excellent, especially if surgery is performed in the first two decades of life.[236] Various degrees of pulmonary regurgitation occur and are well tolerated in the short and medium term. Severe pulmonary regurgitation is more common when pulmonary valvectomy or transannular patching is performed, usually for dysplastic valves or narrowed annulus. Severe chronic regurgitation results in progressive RV dilatation and dysfunction with an increased rate of coexistent ventricular and supraventricular arrhythmias (see earlier section Tetralogy of Fallot).

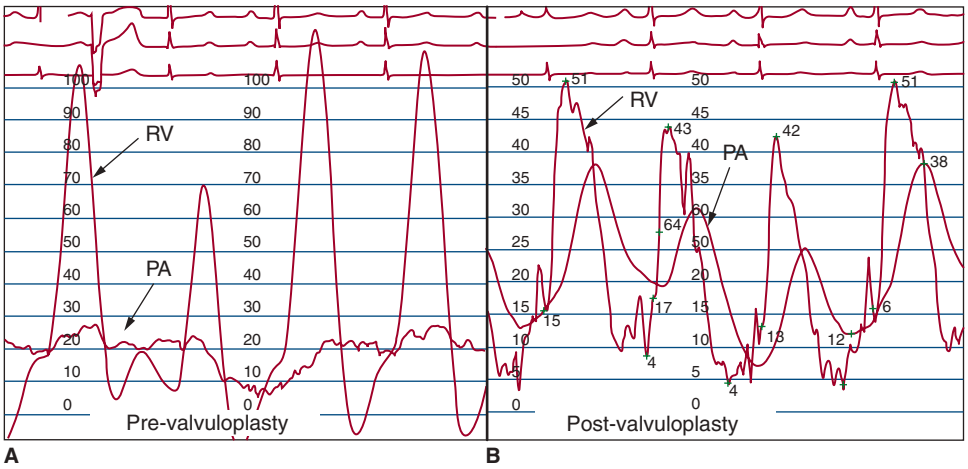


FIGURE 56–20. A. Simultaneous transcatheter pressure recordings in the right ventricle (RV) and pulmonary artery (PA) in a 47-year-old woman with unoperated isolated severe pulmonary valve stenosis before balloon valvuloplasty. Note that the right ventricular systolic pressure exceeds 100 mm Hg except on the beat after an interpolated premature ventricular complex. Also note the absence of systolic deflections on the PA pressure waveform indicative of severe valvar pulmonary stenosis. The maximum pressure gradient between the RV and PA at times exceeds 100 mm Hg. **B.** Simultaneous RV and PA pressure tracings after transcatheter balloon valvuloplasty, demonstrating a lower RV systolic pressure (40-50 mm Hg) and an increase in PA pressure with clear systolic deflections indicating resolution of severe stenosis. The patient has a residual gradient of 15 to 20 mm Hg consistent with mild stenosis.

The advent and widespread use of transcatheter balloon valvuloplasty in the past three decades have made surgical valvotomy unnecessary in most cases of isolated valvar stenosis (Fig. 56–20).[156,237,238] The immediate and midterm results of balloon valvuloplasty in mobile nondysplastic pulmonary valvar stenosis are favorable.[239] Subvalvar infundibular hypertrophy often results in a dynamic subvalvar gradient across the infundibulum that often increases after valvuloplasty because of the relief of downstream obstruction. β-Blocker therapy before and after valvuloplasty helps decrease this dynamic gradient and avoid the rare but catastrophic severe infundibular stenosis characterizing the "suicide ventricle."[240]

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

LVOT obstruction (LVOTO) may occur at the subvalvar, valvar, or supravalvar levels.[241] These obstructions to forward flow may present alone or in association with other levels of obstruction, as in the frequent association of a BAV with coarctation of the aorta. LVOTO imposes increased afterload on the LV and, if severe and untreated, results in hypertrophy and eventual dilatation and failure of the LV and life-threatening arrhythmias.

LVOTO is congenital in the majority of patients younger than age 50 years in the United States; some variants of subaortic obstruction are the exception (eg, subaortic membranes). Patients with LVOTO are at risk for developing infective endocarditis. Fixed SAS may be caused by a discrete fibrous membrane, a muscular narrowing, or a combination of the two. The obstruction may be focal or more diffuse, resulting in a tunnel leading out of the LV. The discrete form of fibromuscular SAS is most frequently encountered (90%), but the tunnel-type lesions are associated with a greater degree of stenosis.[242] In some patients with AV septal defects and cleft mitral valve, abnormal accessory mitral valve tissue or chords may cause SAS (see Fig. 56–20B). SAS may be a congenital isolated lesion but may also be acquired. A BAV is present in 23% of patients.[242] SAS may also present as part of a complex of obstructive lesions, as in the Shone complex, which frequently includes parachute mitral valve, mitral stenosis, BAV, and coarctation of the aorta. A total of 37% of patients with SAS may also have concomitant VSDs of the perimembranous type.[242]

BAV is one of the most common congenital cardiovascular malformations with an estimated incidence of 1% to 2%.[243] BAV is sometimes inherited, and family clusters have been studied. Inheritance patterns are autosomal dominant with variable penetrance.[244] Variants of BAV range from a nearly trileaflet bicommissural valve with mild cuspal inequality to a unicuspid unicommissural valve. The aortic root tissue structure is abnormal. The histology of the ascending aortic wall demonstrates medial abnormalities that are similar but less advanced than those of the Marfan syndrome.[245] Although aortic dilatation above a stenotic BAV has previously been attributed to "poststenotic" turbulence, several studies have clearly demonstrated that dilatation and histologic abnormalities of the ascending aorta in BAV occur irrespective of the degree of valvar stenosis or regurgitation.[246]

Supravalvar aortic stenosis (SVAS) is the rarest type of LVOTO and is defined by a focal or diffuse narrowing starting at the sinotubular junction and often involving the entire ascending aorta.[247] SVAS is frequently associated with Williams-Beuren syndrome, a multisystem disorder with an autosomal dominant inheritance pattern that occurs in 1 in 20,000 births.[248]

Natural History

In the absence of LV hypertrophy, dilatation, or failure, intervention in patients with SAS may be safely deferred; however, there should be careful lifelong follow-up for symptoms and stenosis progression. Aortic regurgitation may result from damage to the valve by the turbulent flow caused by SAS. The clinical course of SAS is usually progressive with increasing obstruction and progression of aortic regurgitation in the majority of untreated patients.[249,250] The primary hemodynamic effect on the LV is one of increased afterload, resulting in increased intracavitary pressure and wall stress. Patients may present with one of the triad of symptoms associated with severe valvar aortic stenosis (ie, angina, heart failure, or syncope). Patients with SAS are at increased risk for developing infective endocarditis, which frequently involves the aortic valve and often leads to aortic regurgitation.[251] Even in the absence of endocarditis, when the Doppler-derived LVOT peak instantaneous gradient reaches 50 mm Hg or above, there is an increased risk of moderate to severe aortic regurgitation.[252]

BAV disease is gradually progressive in the majority of cases. Abnormal folding and creasing of the valve leaflets throughout the cardiac cycle, extended areas of valve contact, turbulent flow, and restricted motion of the leaflets lead to valve damage, scarring, calcification with resultant stenosis, and regurgitation.[253] Turbulent flow into the ascending aorta added to the medial abnormalities discussed above may lead to progressive dilatation and an increased likelihood of rupture or dissection.[253,254] Atherosclerotic changes have been identified in BAV and are similar to those seen with calcific degenerative stenosis of trileaflet aortic valves. The presence of dyslipidemia may be associated with accelerated progression of BAV stenosis.[255,256] Aortic stenosis is the most common complication of BAV. Patients with a mobile BAV have a systolic ejection sound after the first heart sound best heard at the LV apex. This ejection sound is present until valve calcification restricts mobility. Concomitant aortic regurgitation results in an early diastolic decrescendo murmur; when well heard at the right mid sternal border, it suggests the presence of a dilated ascending aorta. Evidence of echocardiographic sclerosis can be seen as early as the second decade of life. Thickening and calcification often occur in the fourth decade of life, and only 15% of patients with BAV have a normally functioning valve in the fifth decade.[257] Moreover, a BAV predisposes patients to the development of aortic regurgitation. Progression of aortic regurgitation may occur via several mechanisms and, in most cases, is directly correlated with the degree of aortic root and annular dilatation.[258] Other mechanisms include leaflet prolapse, degeneration, and retraction. Infective endocarditis of the BAV may cause leaflet destruction and perforation along with intimal dissection leading to a sudden worsening of aortic regurgitation that is poorly tolerated hemodynamically and is a surgical emergency. Aortic dissection is an infrequent but deadly complication. Asymptomatic patients with a peak transvalvar systolic velocity of 4 m/s or above are likely to develop symptoms related to stenosis (dyspnea, chest pain, syncope) within 5 years.[113,259] The ascending aorta in patients with BAV gradually dilates at a mean of 0.9 mm/year.[260,261] The risk of dissection in patients with BAV is estimated to be five to nine times that of the general population and is highest in patients with concomitant coarctation.[262,263] Patients with a BAV and ≥ 55-mm aortic root diameter should be referred for surgical aortic root wrapping or replacement.[113]

Fifty percent of patients with SVAS may have concomitant aortic valve abnormalities, most commonly a BAV.[264] Fatigue stress and shear forces are increased on the aortic valve leaflets in the setting of a poorly distensible sinotubular junction and may result in leaflet thickening and damage with resultant regurgitation, stenosis, or both.[265] SAS occurs in 16% of patients and may contribute to aortic valve damage.[266] Impaired coronary perfusion may occur because of varying degrees of aortic valve leaflet adhesion to the narrowed sinotubular junction, restricting diastolic filling of the coronary arteries.[267] Furthermore, the coronary arteries are subjected to elevated systolic pressures in SVAS, which leads to dilatation, tortuosity, and accelerated atherosclerosis.[268]

Management and Results

Surgical resection is the intervention of choice for treatment of SAS and is usually done via a transaortic approach. Surgical mortality is low, and complications are generally minimal.[269] Surgical management consists of discrete membrane excision or blunt dissection (or both) in focal SAS with focal septal myotomyectomy. Tunnel-type SAS is more surgically challenging and often necessitates application of the Konno-Rastan procedure to reconstruct the LVOTO.[270] Concomitant repair of the aortic valve is performed if the severity of the aortic regurgitation is more than mild. SAS recurs in up to 37% of cases after surgical resection.[242] In this series, tunnel-type SAS recurred in 71% of patients versus a 14.7% recurrence rate for discrete SAS over 6 years of follow-up. The presence of an immediate postoperative gradient above 10 mm Hg led to progressive recurrent SAS in 75% of patients; therefore, attention must be paid to the excision of all abnormal tissue and removal of the membrane from the anterior mitral leaflet. Progressive aortic regurgitation may develop despite relief of SAS. Percutaneous balloon dilatation of a fixed focal stenosis causes short-term improvement in the gradient and may be considered for palliation of SAS.[271] In one case series, 25-year freedom from reintervention was 77%.[272]

There are currently no proven medical therapies that alter the course of aortic stenosis or regurgitation in patients with BAV. β-Blockers may delay the progression of ascending aortic dilatation.[113] Patients with hypertension and aortic regurgitation may benefit from afterload reduction with ACE inhibitors, hydralazine, or calcium channel blockers. However, a randomized, prospective trial of enalapril or nifedipine versus placebo in patients with severe aortic regurgitation revealed no differences in regurgitant volume, LV size, or ejection fraction over 7 years of follow-up.[273] Aortic valve replacement should be performed in patients with severe symptomatic aortic valve stenosis. Aortic valve replacement is also recommended in asymptomatic patients with severe aortic stenosis if the LV ejection fraction is < 50% or if the patient is undergoing other cardiac surgery. Surgery may be considered in asymptomatic patients with very severe stenosis with a peak velocity ≥ 5 m/s if patients are assessed to be low surgical risk.[113] Because stenosis is secondary to bicuspid commissural fusion, balloon valvuloplasty may safely decrease the gradient and improve symptoms in those without a calcified valve.[274,275] Surgical repair or replacement is indicated for patients with severe stenosis (peak instantaneous Doppler velocity of ≥ 4 m/s) who are symptomatic.[113] Surgery should also be considered in those with less severe stenosis who have concomitant moderate or severe aortic valve regurgitation or a dilated ascending aorta. Asymptomatic patients with severe BAV stenosis who desire to become pregnant or to exercise more vigorously should also be considered for surgery. Severe aortic regurgitation, if associated with symptoms, severe aortic root enlargement, or LV dilatation and decreased ejection fraction, should be surgically corrected.[113] Numerous surgical techniques have been used to repair or replace the aortic valve. Valve repair has shown promising results and should be considered if the valve is not calcified.[113,276] If valve replacement is needed, bioprosthetic valves are generally preferred in patients older than 65 years, women of childbearing age wishing to avoid warfarin, and patients refusing to take or who are allergic to warfarin. These bioprosthetic valves generally deteriorate over 10 to 20 years and require replacement. Mechanical prostheses have superior durability in patients who can tolerate warfarin. The Ross procedure has been used successfully in patients with BAV and is favored in the pediatric population. However, after the Ross procedure, patients are at risk for developing neoaortic dilatation, progressive aortic regurgitation, neopulmonary homograft regurgitation, and myocardial ischemia.[277]

Patients with SVAS may undergo surgical enlargement of the narrowed sinotubular region and adjacent ascending aorta if they have symptoms of angina, dyspnea, syncope, or heart failure, or a mean pressure gradient of 50 mm Hg or above. Surgical relief of obstruction consists of excision of a focal stenosis with end-to-end anastomosis of the ascending aorta, patch enlargement of the sinotubular junction, or more complex aortoplasty involving patch placement into two or more sinuses of Valsalva. The Ross procedure has also been used to replace the aortic root in patients with concomitant aortic valve disease. Balloon angioplasty of SVAS does not result in relief of obstruction and risks aortic dissection or rupture.

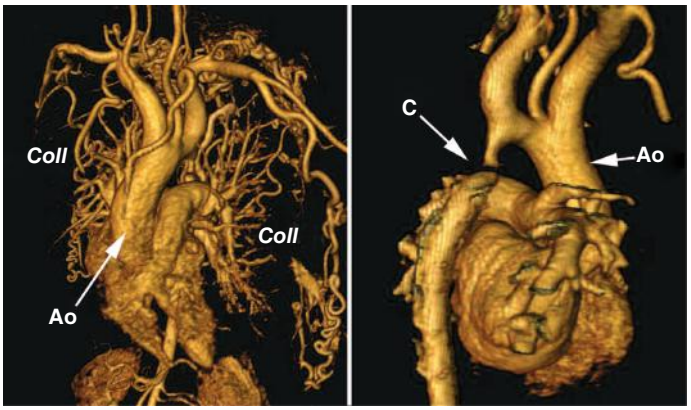


FIGURE 56–21. A. Three-dimensional surface rendered reconstruction of cardiac magnetic resonance angiogram as viewed from a right anterior oblique and cranial projection in a 54-year-old woman with near-interruption of the aorta (Ao). The ascending Ao is moderately dilated, as are the arch vessels. A plethora of bypassing collaterals (coll) are present. Adult unoperated patients present with systemic arterial hypertension in the upper extremities. A normal patient should have a 5- to 10-mm Hg increase in systolic blood pressure in the lower extremities compared with the upper extremities. Absence of this increase or presence of a decrease in the lower extremities should arouse suspicion of coarctation. **B.** Right lateral projection with collaterals removed during the editing and three-dimensional rendering process. Complete interruption (C) of the aorta is evident.

COARCTATION OF THE AORTA

Coarctation of the aorta in adults is usually a discrete narrowing in the region of the ligamentum arteriosum (Fig. 56–21). More diffuse forms of the disease may involve the arch or isthmus. Coarctation of the aorta occurs in 7% of patients with CHD, and there is a small male predominance of 1.5:1. Coarctation is a diffuse arteriopathy characterized by cystic changes in the aortic media.[278] The descending aorta immediately distal to the segment of coarctation is often aneurysmal. A BAV is present in about half of cases. Intracranial aneurysms, often in the circle of Willis, have been detected in up to 10% of patients.[279] Adult unoperated patients present with systemic arterial hypertension in the upper extremities. A normal patient should have a 5- to 10-mm Hg increase in systolic blood pressure in the lower extremities compared with the upper extremities. Absence of this increase or presence of a decrease in the lower extremities should arouse suspicion of coarctation.

Natural History

Unoperated survival is poor, and median survival is only 35 years.[280] Patients die of congestive heart failure, aortic dissection or rupture, complications of infective endocarditis, and intracranial hemorrhage from ruptured aneurysms in the circle of Willis.

Management and Results

Excision of the narrowed segment and end-to-end anastomosis of the para-coarctation aorta is the preferred method for initial repair (Fig. 56–22). Subsequent modifications in surgical technique include the use of prosthetic overlay grafts, subclavian patch aortoplasty, and prosthetic tube grafts from the ascending to the descending aorta in patients with complete interruption (see Fig. 56–22). Percutaneous balloon angioplasty with stenting for primary coarctation has gained popularity and has displayed encouraging results. Stent implantation is preferable to angioplasty alone and has excellent long-term outcomes (see Fig. 56–14).[281,282]

Patients with successfully treated coarctation often continue to have systemic arterial hypertension despite the absence of significant residual coarctation.[283,284] Patients who undergo repair in childhood demonstrate very good long-term survival up to 60 years.[285] Late repair (> 14 years of age) is associated with higher rates of hypertension and decreased survival.[286] Patients with hypertension after late repair are at an increased risk of developing heart failure, atherosclerosis, stroke, and progressive aortic disease.

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

Complete TGA refers to a ventriculoarterial discordance characterized by medial transposition of the aorta, which arises anteriorly and rightward from a morphologic RV, and the pulmonary artery arises posteriorly and leftward from a morphologic LV. Simply, the aorta is anteriorly dextraposed and emerges from a normally located RV, and the pulmonary artery is posteriorly levoposed to emerge from the LV (see Fig. 56–2). As a result, the systemic and pulmonary arterial circulations run in parallel, not in series. Therefore, poorly oxygenated blood enters the aorta, and survival depends on the delivery of oxygenated blood to the systemic circulation via a left-to-right shunt. Atrial balloon septostomy (Rashkind procedure) may need to be urgently performed within the first few hours of life to create an intracardiac shunt. Other anomalies often coexist, including VSD (30%), LVOTO (10%), and more rarely, PDA and coarctation of the aorta.[205]

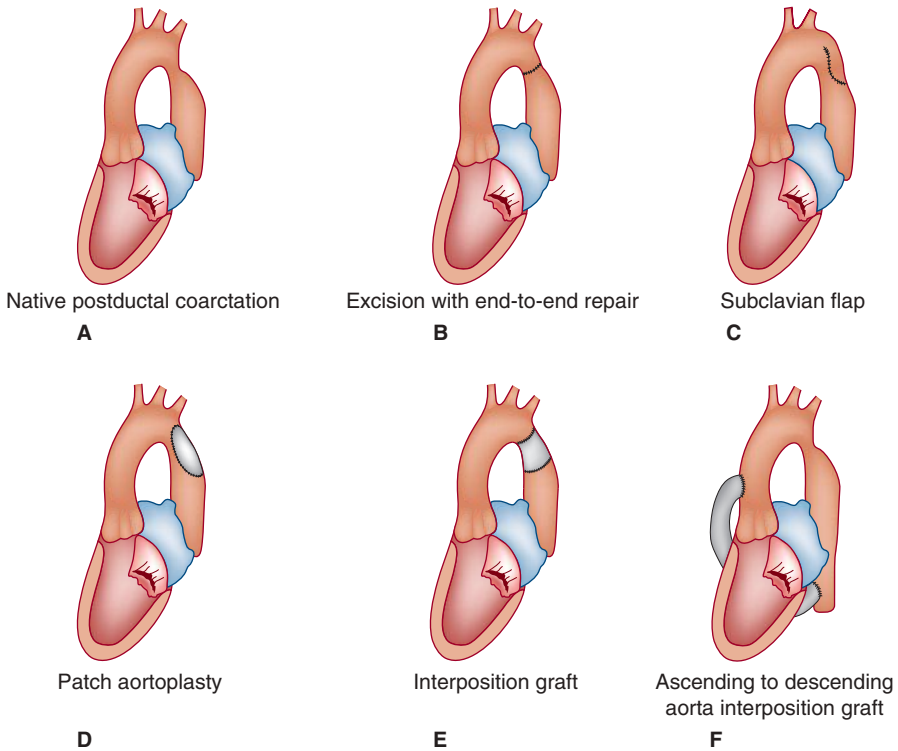


FIGURE 56–22. Surgical techniques for repair of coarctation of the aorta. **A.** Unrepaired coarctation of the aorta. **B.** Excision of the narrowed segment with end-to-end anastomosis. **C.** Subclavian flap repair. **D.** Prosthetic patch aortoplasty. **E.** Excision of the narrowed segment and placement of a prosthetic conduit. **F.** Prosthetic conduit placement from the ascending to the descending aorta.

Natural History

Surgical intervention in infancy is imperative for survival, and almost all adult patients with this condition have undergone prior correction. However, patients with large nonrestrictive shunts at the atrial, ventricular, or pulmonary arterial levels who may survive into adulthood often develop congestive heart failure in childhood and pulmonary vascular disease thereafter.

Management and Results

The use of balloon atrial septostomy in the infant with TGA, initially described by Rashkind and Miller[287] in 1966, allows enough left-to-right shunting of oxygenated blood to palliate the patient. The Senning operation, a description of which was initially published in 1959, followed by the Mustard operation in 1964, involved redirection of atrial blood via baffles to deliver oxygenated pulmonary venous blood to the systemic RV and deoxygenated systemic venous blood to the pulmonary LV (see Fig. 56–2).[288,289] The major difference between these two operations is that whereas the earlier Senning operation uses atrial and septal tissue to create the baffles described earlier, the Mustard operation uses extrinsic materials (ie, pericardium) for this purpose. These surgeries were performed in the majority of operated infants and children (usually between 1 and 12 months of age) until the late 1970s and early 1980s. Long-term follow-up demonstrates an 80% 28-year survival rate, with the majority of survivors in NYHA class I.[290] Atrial tachyarrhythmias and bradyarrhythmias occur over time, with SND and incisional reentrant atrial arrhythmias being frequent long-term complications. Loss of sinus rhythm is progressive but usually asymptomatic at rest. Patients often demonstrate evidence of chronotropic incompetence with exercise and may benefit from pacemaker insertion. Reentrant atrial tachyarrhythmias are a worrisome development and are notoriously difficult to treat and may require life-long anticoagulation. These arrhythmias often result in deleterious and poorly tolerated hemodynamic consequences and increase the risk of sudden cardiac death, especially in the presence of RV dysfunction.[291] Sudden death is a well-documented occurrence in up to 15% of patients and usually occurs during exercise.[290,292] Patients at increased risk for sudden cardiac death are older, have worse systemic RV function, and have a widened QRS complex (> 140 milliseconds).[293] Obstruction of the pulmonary or systemic venous baffles (usually the superior vena cava baffle) occurs in a minority of patients and can usually be treated with transcatheter angioplasty and stenting. Baffle leaks are more common than obstruction, and the majority are not hemodynamically significant; only 1% to 2% require intervention because of cyanosis or volume overload. Progressive systemic RV failure does not usually occur in the short and intermediate term but may be a problem beginning in early adult life. ACE or angiotensin receptor inhibition does not improve exercise performance or decrease serum BNP levels.[25,26,294] This may be explained by a lack of activation of the renin-angiotensin system and the presence of another yet unidentified mechanism for progressive systemic RV dysfunction and impaired exercise capacity. β-Blocker therapy, on the other hand, may be beneficial in halting adverse ventricular remodeling, decreasing the risk of life-threatening arrhythmias, and improving exercise capacity.[291,295]

The late complications sited earlier for atrial switch operations led to the increasing acceptance of the arterial switch (Jatene operation) as the operation of choice.[296] This procedure consists of anatomic correction by transection of the aorta and pulmonary artery at a level above the valve sinuses with detachment of the coronary arteries from the aorta. Thereafter, the positions of the transected great arteries are reversed so that the "neo-aorta" emerges from the LV and the "neopulmonary" artery emerges from the RV. The coronary arteries are sutured into place in the neo-aorta. This is a technically challenging surgery but has certain advantages over the atrial switch operations, namely, the LV is the systemic ventricle and the incidence of arrhythmias is lower.[297] Some authors have advocated performing the arterial switch operation after "conditioning" the LV with pulmonary artery banding in patients with a previous Mustard or Senning repair. The existing literature indicates a significant surgical mortality and inconsistent LV response to "conditioning" if the arterial switch is performed after childhood.[298,299] The long-term outcomes of the arterial switch operation are now becoming available, and the results are encouraging. The 10-year survival rate is 88% in patients without associated lesions such as VSD, in whom the operative mortality is higher and the 10-year survival is decreased to 80%.[300] Neo-aortic valve regurgitation occurs in approximately 15% of patients; however, only a minority of patients require reoperation for this problem.[301] Neopulmonary artery stenosis or branch pulmonary artery stenosis occurs in a minority of patients and may require transcatheter or operative intervention. Myocardial ischemia related to reimplantation, surgical manipulation, and distortion has been reported, and late deaths because of coronary events may occur in a minority of patients.[300]

CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

Congenitally corrected TGA is characterized by AV and ventriculoarterial discordance. From a circulatory oxygenation standpoint, these patients are "congenitally corrected," essentially "two wrongs make a right," and the pulmonary and systemic circulations run in series, not in parallel, as with dextro-TGA. There is ventricular inversion, and the respective AV valves follow the ventricles. Therefore, the systemic RV is transposed to the left, and the tricuspid valve goes with it. The left atrium empties into the RV, which then pumps to the leftward and usually anterior aorta (Fig. 56–23). The LV and mitral valve are dextraposed, and the pulmonary artery emerges posteriorly from the LV. Fewer than 10% of patients are free of associated abnormalities, which include VSD (membranous or muscular) in up to 80%, pulmonic stenosis (valvar or subvalvar) in up to 70%, and tricuspid valve abnormalities (usually Ebstein anomaly) in 33%.[302]

Natural History

In the minority of patients without associated defects, unoperated survival into adulthood is common, and survival into the eighth and ninth decades of life has been reported.[302] Most patients remain undiagnosed until early adulthood. However, these patients have an increased incidence of AV conduction problems and complete heart block with age.[303]

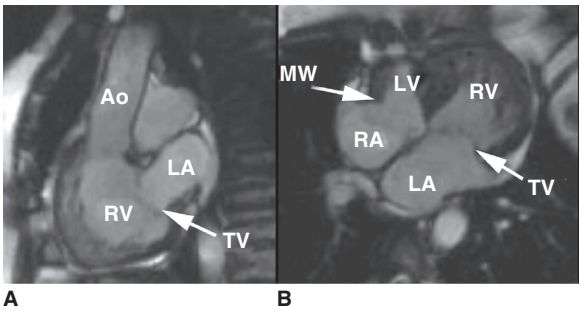


FIGURE 56–23. A. Cine-magnetic resonance imaging scan of a 62-year-old woman with congenitally corrected transposition of the great arteries as viewed from a sagittal projection. Note that the left atrium (LA) is connected to the transposed right ventricle (RV) via a tricuspid valve (TV). The aorta (Ao) emerges anteriorly from the RV. **B.** Axial cut (four-chamber view). Note that the morphologic smooth-walled left ventricle (LV) is dextraposed, thin walled, and not dilated. The right atrium (RA) empties into the LV via the mitral valve (MV). The morphologic RV is transposed to the left along with the TV.

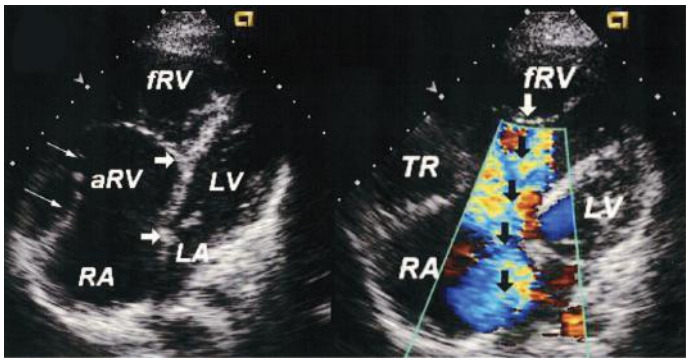
Complete heart block may be present from birth (in ~10%) and has been reported to develop in 2% of patients per year.[304] Systemic morphologic RV dysfunction and congestive heart failure occur in more than 50% of patients with associated lesions by the time they are 45 years of age.[303] Ebstein anomaly of the systemic AV valve is common, and regurgitation occurs in over 80% of adults with congenitally corrected TGA. Pulmonary morphologic LV dysfunction occurs less often but may be present in up to 20% of patients. Aortic regurgitation of some degree is present in 25% of adults but seldom requires surgical intervention.

Management and Results

Systemic AV (tricuspid) valve regurgitation is a common and progressive problem in these patients that can lead to morphologic RV dilatation and dysfunction if the valve is not replaced.[288,305] Early surgical intervention in patients with more than mild tricuspid regurgitation, to prevent systemic ventricular dysfunction, is warranted and is associated with improved intermediate- and long-term outcomes. Patients with a combination of pulmonic stenosis and VSD may be cyanotic because of the right-to-left shunt at the ventricular level. Surgical repair in these patients consists of VSD closure and pulmonary valvotomy or replacement, frequently accompanied by subinfundibular muscle bundle resection. Alternative surgical strategies involving the "double-switch" operation have been described. This surgery involves a Mustard- or Senning-type atrial redirection along with a Jatene-style great arterial switch, thus leaving the patient with a systemic LV after this complex surgery.[306] Patients with pulmonic stenosis or atresia and a VSD may undergo a modification of the double-switch operation by baffling of morphologic LV outflow through the VSD to the leftward and anterior aorta and placement of a conduit from the morphologic RV to the pulmonary artery.[307] Long-term follow-up after these surgical interventions is limited. Pacemaker placement is indicated for patients with Mobitz type II or complete heart block.

EBSTEIN ANOMALY OF THE TRICUSPID VALVE

Ebstein anomaly is characterized by apical displacement of the septal (and often the posterior) leaflet of the tricuspid valve into the RV cavity (Fig. 56–24). The RV is therefore divided into a proximal "atrialized" portion and a distal "functional" portion. The effective volume of the functional RV is often small.[308] The anterior leaflet is usually excessively long and may have attachments to the RV free wall. The "atrialized" portion of the RV is usually thin because of a congenital absence of myocardium. The effective right atrium (including the atrialized portion of the RV) is invariably large and becomes more so in the presence of tricuspid regurgitation, which is a very common occurrence. An ASD or patent foramen ovale is present in more than one-third of cases. Other associated lesions are far less common and may include pulmonary stenosis, VSD, and PDA. Ebstein anomaly is commonly found in patients with congenitally corrected TGA (see earlier discussion).



A B

FIGURE 56–24. A. Ebstein anomaly of the tricuspid valve in the apical four-chamber view by transthoracic two-dimensional echocardiography. Note the marked apical displacement of the septal leaflet of the tricuspid valve from the level of the true annulus (*large horizontal white arrows*). The anterior leaflet of the tricuspid valve (*small white arrows*) is long and redundant and has attachments to the free wall. The functional right ventricle (fRV) is small because much of the right ventricular inflow is "atrialized" (aRV). **B.** Color-flow Doppler through the tricuspid valve in systole demonstrating severe regurgitation (TR) starting at the apically displaced septal leaflet and directed medially (*black arrows*). The right atrium (RA), left ventricle (LV), and left atrium (LA) are also labeled.

Natural History

The clinical spectrum is variable and is heavily dependent on the severity of the deformity and the presence of associated defects. Patients presenting in infancy represent the worst end of the spectrum with severe tricuspid regurgitation and a high incidence of associated abnormalities such as pulmonary stenosis or atresia.[309,310] Patients surviving into adulthood without surgical valve repair or replacement may develop a variety of signs and symptoms, including cyanosis (because of right-to-left shunting across an ASD or patent foramen ovale), dyspnea and fatigue (as a result of decreased preload and cardiac output), or palpitations. In adolescents and adults, palpitations secondary to atrial arrhythmia are the most common clinical presentation. Ebstein anomaly is often associated with ventricular pre-excitation, which may involve more than one accessory pathway that may be endocardial or epicardial in location and often is challenging to map and ablate from an intravascular approach. Up to 20% of unoperated patients may die from heart failure, and approximately 5% may die suddenly, presumably from atrial or ventricular arrhythmias.[311] Heart failure results from RV dysfunction and tricuspid regurgitation and may be exacerbated by LV fibrosis and dysfunction.

Management and Results

There are numerous variations on the surgical management of Ebstein anomaly.[312] Most surgical approaches consist of some form of repair (or replacement if repair is not feasible) of the tricuspid valve, often accompanied by atrial or atrialized ventricle plication, and closure of an interatrial communication.[313,314] Eventual reoperation for recurrent tricuspid regurgitation after tricuspid valve repair is expected, and a tricuspid valve replacement is typically undertaken after failure of a repaired valve. With recent advancements in transcatheter valve replacement, valve repair with an annular ring or valve replacement is an increasingly attractive option in adults.[315,316] Valve repair may not be feasible in the most severe forms of Ebstein anomaly in which the long anterior leaflet of the tricuspid valve is adherent to the RV endocardium and there is almost complete atrialization of the RV; valve replacement is a good option in this subset of patients. The results of surgery in patients with poor RV function can be improved considerably if the RV is unloaded by a concomitant cavopulmonary (Glenn) shunt, also known as the one-and-a-half ventricle repair.[312,317] Furthermore, in the most severe cases with near complete absence of a functioning RV, a univentricular repair leading to a Fontan palliation may be necessary.[318,319] Intraoperative radiofrequency ablation or cryoablation (modified maze) and division of accessory pathways that are usually located in the posteroseptal or RV free wall are recommended at the time of valve repair or replacement.[320] Overall surgical mortality was 13% in a multicenter analysis, with young age at the time of operation as the only multivariate risk factor.[312] The long-term survival and functional capacity of operated patients are very good.[321]

PSYCHOSOCIAL ASPECTS

As patients with CHD make the transition from adolescence to adulthood, it is imperative that they come to understand the nature and implications of their heart problem and what interventions must and may need to be performed. Appropriate advice and guidance should be available regarding employment, insurance, socialization, contraception, and exercise.

EMPLOYMENT

The majority of operated and unoperated patients can be and are gainfully employed. Patients with simple forms of CHD, such as isolated VSD, pulmonary stenosis, or aortic valve stenosis, often achieve higher levels of education then the national standards.[322] A cross-sectional study from Holland in which CHD patients were asked to complete a questionnaire focusing on employment issues demonstrated that adults with complex CHD have reduced job participation compared with patients with mild CHD (59% vs 76% employed).[323] Many receive disability benefits or experience career problems or job handicaps. Career counseling focusing on physical abilities and level of education may help increase appropriate employment in this population. Adults with CHD are at a disadvantage when applying for employment because of the tendency of some employers to consider the potential for future deterioration of an applicant with a "known heart problem." In the United States, the National Rehabilitation Act of 1973 obliges employers to consider only the present capacity of a prospective employee to perform a given job.

Restrictions for employment do exist for certain jobs in which the safety of others is the direct responsibility of the patient with CHD. The clearest example of this is commercial airline pilots. It is the task of CHD specialists to estimate the risk of acute disability or sudden cardiac death in such patients. Low-risk rates are defined in only a small subset of patients with CHD.[324]

INSURANCE

Adults with CHD are significantly more likely to have difficulty obtaining life insurance.[325] Refusal rates appear to be independent of the type or severity of CHD, suggesting that the label of CHD has a negative impact by itself. This problem is compounded by the limited long-term survival data for specific CHD subtypes. An article by Vonder Muhll et al[326] discusses the scope of this problem and provides a summary of mortality data and predictors of adverse outcomes in various subsets of CHD along with practical tips for patients and physicians to assist with the insurance application process.[326] In general, insurance policies are restrictive, and patients with CHD are frequently insured at higher rates or not insured at all.[327] As a result, the patient must seek to obtain a new policy, which often excludes benefits for medical or surgical treatment of the congenital cardiovascular condition. In 2010, a health care bill was passed by the Congress of the United States that included extension of parental coverage until 26 years of age, expanded the government insurance programs for low-income individuals, and prohibited insurers from refusing to insure patients as a result of preexisting conditions.

Despite a call for near universal health care coverage, it remains unclear how such an initiative will be funded at the federal and state level. In a pilot study by Moons et al[328] and in a subsequent study by Mackie et al,[329] patients with CHD, particularly severe CHD, incurred considerably higher expenses than age- and gender-matched control subjects, Further data are clearly needed to predict the potential health care expenditure in various subsets of patients with CHD.

PSYCHOSOCIAL DEVELOPMENT

Most adults with CHD appear well adjusted. Utens et al[330] assessed the occurrence of a wide range of behavioral and emotional problems in 166 young adults long term after surgical correction compared with age-matched control subjects using the Young Adult Self-Report.[330] On most Young Adult Self-Report scales, no differences were found between the mean problem scores of the CHD patients and control subjects except for small differences in two scales (Somatic Complaints and Strange). No significant relationship was found between cardiac diagnosis and problem behaviors in CHD adults. Moreover, no relationship was found between IQ scores and problem behaviors. Psychosocial problems can occur in patients with CHD, manifesting in excessive psychologic stress that is unrelated to the clinical severity of the original cardiac defect.[331] In a study by Ternestedt et al,[332] two cohorts of patients operated on before the age of 15 years, one for TOF and the other for ASD, were queried 20 and 30 years after surgical repair regarding quality of life. There was no connection between quality of life and functional capacity. Interestingly, fewer patients in the TOF than in the ASD group considered that their lives were affected by their heart disease. Therefore, multiple questionnaire-based studies have demonstrated that the severity of the heart disease is not necessarily congruent with estimated quality of life, suggesting that patients develop coping strategies during childhood and adolescence.

Although most patients with CHD appear well adjusted, many have the feeling that they are different from their peers and experience isolation and low self-esteem, feelings that are compounded by exercise limitations, surgical scars, and parental overprotection. These factors, when added to the challenges of adolescence and young adulthood, can adversely affect psychosocial development. A number of large longitudinal series of patients with repaired TOF have demonstrated that suicide is a common cause of late death, ranging in frequency from 4.8% to 10%.[333-335] Psychosocial anxiety and neurotic behavior may be avoided by early repair in childhood.[336] Anxieties about sexuality, relationships, and reproduction are common and often prove difficult to adequately discuss with the physician in a busy clinic setting; such issues are more thoroughly dealt with by a multispecialty team that may include a psychologist, social worker, and nurse practitioner. Psychological support should be considered as one of the most important aspects in the long-term care of patients with CHD.

The impact of CHD on intellectual development appears more dependent on lesion type and severity than are psychosocial issues. Studies of intellectual development and capacity mostly exclude patients with genetic syndromes or overt neurologic defects. Cyanosis is associated with mild intellectual impairment; however, it is unclear that early repair of cyanotic lesions such as TOF results in improved intellectual function.[337,338] Neurodevelopmental outcomes in patients with single-ventricle physiology who have undergone the Fontan operation are in the normal range, but performance on examinations of IQ are lower than the general population.[339]

CONTRACEPTION

Advice regarding contraception should be available to adolescent and adult patients with CHD.[340] Unfortunately, contraceptive advice to patients with CHD is often inadequate or incorrect.[340,341] Cardiologists are often reluctant to discuss issues of contraception, partly because this is an area that is often outside their realm of expertise. When giving family planning advice to patients with CHD, it is important to review the risk of pregnancy for women, risk of CHD in the fetus, and risks and benefits of different modes of contraception for the individual patient. Therefore, understanding the normal physiology of pregnancy and its impact on various CHD subtypes is essential (refer

to the section on pregnancy). Contraceptive advice should be tailored to the individual patient in terms of his or her medical, social, and educational conditions. Surgical tubal ligation and hysteroscopic tubal coil occlusion are highly effective and permanent forms of contraception that are reserved for women who are at very high risk of adverse events with pregnancy, such as those with Eisenmenger syndrome. Traditional laparoscopic sterilization requires general anesthesia, placing cyanotic patients at significant risk for operative mortality.[47] However, hysteroscopic coil occlusion of the fallopian tubes may be performed under local anesthesia in the office setting or under moderate sedation, avoiding the anesthesia risks associated with laparoscopic procedures.

For women in long-term monogamous relationships, vasectomy for the male partner is also effective in preventing pregnancy. Hormonal contraception with low-dose estrogen is generally safe and effective[342]; however, in a minority of patients, exacerbation of systemic hypertension may occur with such formulations.[343] Combined estrogen and progesterone formulations have a lower contraceptive efficacy and carry a well-documented risk of thromboembolic complications and are best avoided in patients with previous thromboembolic events, those at high risk of thromboembolic events (eg, patients with Fontan connection and sluggish venous flow), and those who would tolerate thromboembolism poorly.[344,345] They are also inappropriate for patients with congestive heart failure because of the tendency for fluid retention. Barrier methods, such as diaphragms or condoms, are generally safe and effective but can only be relied upon in the most motivated patients; even then, there is a risk of contraceptive failure. Intrauterine contraceptive devices are effective, but they are associated with an increased risk of pelvic inflammatory disease. This is worrisome in patients with CHD because of the potential risk of infective endocarditis, although the actual occurrence of endocarditis in this setting is exceedingly rare.[346,347]

EXERCISE AND SPORTS

The physical and mental benefits of exercise are well established.[348,349] Participation in sports is also important for the normal socialization of children and adolescents. However, unoperated and operated patients with CHD often have diminished exercise capacity (see Fig. 56–4).[32] Reduced exercise capacity may reflect both the limitations set upon the individual by the underlying cardiovascular condition and the deconditioning that occurs from adopting a sedentary lifestyle. Inappropriate avoidance of exercise is often reinforced by protective parents or recommended by physicians who are unsure of the cardiovascular risk associated with a specific condition and choose to err on the side of short-term caution.[350] The long-term cost of this approach is that many patients with CHD do not reap the immense benefits of exercise.

The 36th Bethesda Conference focused on issues concerning exercise in patients with cardiovascular disease and provided exercise recommendations for this population.[351] In some patients with simple repaired CHD (eg, ligated PDA), exercise capacity is normal, and the risk of exercise is minimal. On the other extreme are patients with pulmonary vascular disease and cyanosis in whom exercise capacity is severely limited. Exercise results in almost immediate worsening of hypoxemia because of the decrease in systemic arterial resistance and increased shunting of deoxygenated blood away from the pulmonary alveolar bed. These patients should be advised to avoid isometric exercise and confine themselves to mild isotonic exercise.[351] Between these extremes, the recommendations should take into account the individual patient's underlying operated or unoperated cardiovascular defect, functional capacity, hemodynamic status, and form of exercise contemplated. Formal exercise testing can help delineate functional capacity. Walking protocols of 6 or 12 minutes can be used to determine the safety of submaximal exercise. Treadmill or bicycle protocols can determine the maximal exercise capacity, coronary artery ischemia, blood pressure response, and importantly, chronotropic response to exercise. Cardiopulmonary exercise testing adds incremental diagnostic and prognostic value and is highly recommended in patients with CHD.[32] Combining the exercise protocol with echocardiographic imaging is useful in determining ventricular function and valvar function and estimating pressure changes with exercise.

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CHAPTER 57

CLASSIFICATION OF CARDIOMYOPATHIES

Jagat Narula, Barry J. Maron, Navneet Narula, and Eloisa Arbustini

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As any classification is necessarily incomplete and acts as a bridge between complete ignorance and total understanding in any biological system, … further modification and changes are likely to occur.

— John Goodwin, London, 1982

INTRODUCTION

Clinical taxonomy aids understanding and facilitates appropriate categorization of diseases through the use of logical groups and hierarchies on the basis of predefined characteristics that are useful for the diagnosis and management of human ailments. The classification results in standardization of disease nomenclature. In the premolecular era, this process was predominantly driven by sorting clinical phenotypes (eg, heart failure, cardiomyopathies, arrhythmias) and pathology (eg, cancer). For clinically and etiologically complex diseases such as cardiomyopathies, the principles of classifications have been historically based on morphofunctional phenotypes shared by similar disorders with potentially overlapping treatments. Traditionally, the cardiomyopathies have been considered *idiopathic* diseases. In the past two decades, clinical and molecular genetics and advanced imaging have helped elucidate the etiopathogenetic basis of cardiomyopathy, and it is more than likely that the term *idiopathic* will gradually become obsolete. Most cardiomyopathies have a genetic basis, and for many of those that are not heritable, the mechanisms are now known. More than 100 disease genes have now been confirmed as candidate genes, and the number is continually increasing. Advances in biotechnology have allowed for rapid identification of underlying causes.

CLASSIFICATION OF CARDIOMYOPATHIES: A HISTORICAL PERSPECTIVE

Heart muscle disorders are relatively young diseases. In a famous editorial published in *Heart* in 1982, John F. Goodwin reviewed the 30-year history of cardiomyopathies,[1] starting from early 1950 when Brigden published the St. Cyres lecture on "Uncommon Myocardial Diseases: The Non-coronary Cardiomyopathies."[2] Then the evolution from description to definition and clustering of similar cardiomyopathies led to the first classification of cardiomyopathies in 1972, when Goodwin and Oakley defined cardiomyopathies as the heart muscle diseases of unknown cause and described them as dilated (DCM), hypertrophic (HCM), and restrictive (or obliterative) (RCM) types.[3] In 1980, the World Health Organization (WHO) adopted the classification of cardiomyopathies as "heart muscle diseases of unknown cause" (Fig. 57–1) to distinguish cardiomyopathy from cardiac dysfunction as a result of known cardiovascular entities such as hypertension, ischemic heart disease, or valvular disease.[4] In 1995, the WHO/International Society and Federation of Cardiology (ISFC) Task Force on the Definition and Classification of the Cardiomyopathies expanded the classification to include all diseases affecting heart muscle and to take into consideration etiology as well as the dominant pathophysiology.[5] The WHO/ISFC task force added two more classes: arrhythmogenic cardiomyopathy (ACM; ie, arrhythmogenic right ventricular cardiomyopathy [ARVC]) and unclassified cardiomyopathy.[5] In 1998, the ISFC evolved to become the World Heart Federation (WHF), and until recently, did not indulge in developing scientific statements, and the recommendations for both diagnosis and management of cardiomyopathies were not updated. The morphofunctional phenotype has continued to be the unique basis for classification of cardiomyopathy.

During this period, a substantial increase in the knowledge of the genetic etiology of cardiomyopathy led the American Heart Association (AHA) to propose revisions to the classification of cardiomyopathy. In a valiant departure from the original definition, Maron et al[6] classified cardiomyopathy primarily on its genetic basis and secondarily on its phenotypic description. The European Society of Cardiology (ESC)[7] retained the description in original morphofunctional categories but added subclassification into familial and nonfamilial varieties. Both AHA and ESC classifications preferred to exclude specific heart muscle diseases from consideration as cardiomyopathic disorders. In 2013, the WHF established its commitment to developing scientific statements and proposed a novel methodology for the classification of cardiomyopathies.[8,9] This update combined the best of both AHA and ESC classifications. The proposed nomenclature, inspired from the tumor-nodal (metastasis)-distant metastasis (TNM) staging of malignant tumors,[10] was descriptive, flexibly modifiable, and expandable.

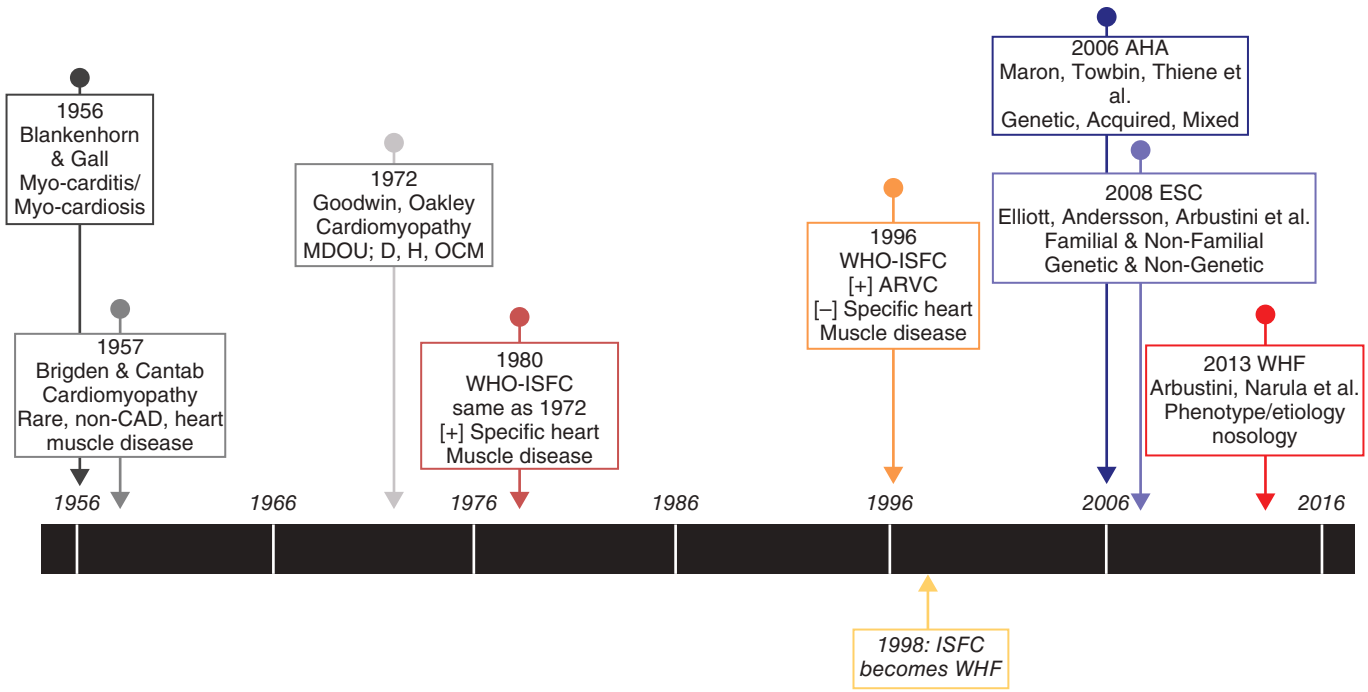

FIGURE 57–1. Classification of cardiomyopathies: a historical perspective. Cardiomyopathies were described only about 55 years ago. Their classification has gone through many contentious iterations. The classification has traditionally been provided by the World Health Organization (WHO) and International Society and Federation of Cardiology (ISFC; which latter evolved into the World Heart Federation [WHF]) in 1998, American Heart Association (AHA) in 2006, European Society of Cardiology (ESC) in 2008, and the comprehensive phenotype-to-genotype classification of WHF in 2013. ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; D, H, OCM, dilated, hypertrophic, other cardiomyopathy.

THE CURRENT INTERNATIONAL CLASSIFICATION OF DISEASES CODES FOR CARDIOMYOPATHIES

The International Classification of Diseases (ICD) of the WHO is the standard diagnostic tool for epidemiology, health management, and delivery of care. It is ubiquitous and easily able to monitor the incidence and prevalence of diseases and statistics related to morbidity and mortality. It underscores the importance of appropriate classification and reporting of diseases. It continues to classify cardiomyopathies based on the original WHO-ISFC recommendations.

In routine practice, physicians are expected to use ICD codes after completion of their diagnostic workup in patients with cardiomyopathy. Codes from the ICD-10 are available at the ICD website (http://www.icd10data.com/ICD10CM/Codes/I00-I99/I30-I52/I42-/).

The ICD code for cardiomyopathies is I42; cardiomyopathies complicating pregnancy and puerperium are excluded, as is ischemic cardiomyopathy. The I42 code recognizes DCM (or congestive cardiomyopathy) without specifications. The HCM codes distinguish obstructive and nonobstructive forms (I42.1 and I42.2). The endomyocardial disease code distinguishes endomyocardial fibrosis, a well-defined clinical and pathologic disease of the endocardium (I42.3); the code I42.3 also includes Loeffler endocarditis, which is now better classified as hypereosinophilic syndrome. Endocardial fibroelastosis is now recognized as a "reactive feature" associated with several different diseases, in particular, congenital heart diseases such as left ventricular (LV) hypoplastic heart syndrome, and is a common pathologic finding in overloaded hearts from any etiology. Restrictive cardiomyopathy also includes *constrictive cardiomyopathy*, which is an obsolete term no longer used in clinical practice. Other codes cover all unaccounted cardiomyopathies. Therefore, the statistics based on ICD codes are unlikely to be useful for any practical purposes. The WHO is working toward a revised classification system that is better aligned with current scientific knowledge and that is compatible with contemporary information systems and will submit the 11th revision of the ICD to the World Health Assembly in 2018.[11] The ICD system could become uniquely useful for the future global epidemiology of cardiomyopathies if the information is presented more systematically.

THE AMERICAN HEART ASSOCIATION (2006) CLASSIFICATION

THE BASIS

The diverse cardiomyopathy classifications presented through the years have been designed either for clinicians or biomedical scientists and have been based on etiology, anatomy, physiology, primary treatment, method of diagnosis (including histopathology), and patient symptoms. The AHA classification[6] was developed in response to the following drawbacks of the traditional WHO-ISFC classification:

1. *The traditional previously mentioned WHO-ISFC classification admixes morphologic with functional traits.* The AHA authors pointed out that the clinical classification *HCM-DCM-RCM* was fraught with major limitations. The classification combines anatomic and functional traits, wherein the same disease could legitimately cross over to two or even three of the phenotypes. In HCM, the key descriptor is morphologic (ie, thickened LV walls are present, and diastolic dysfunction is common). Similarly, in DCM, the key descriptor is morphologic (ie, LV dilation). However, systolic dysfunction is an obligatory part of the definition of the disease

and functionally more relevant than simple ventricular dilatation. On the other hand, the key property in RCM is mechanical (ie, diastolic dysfunction, generally with preserved systolic function). However, the disease has a precise morphologic phenotype characterized by dilated atria in the absence of LV hypertrophy or dilatation. Although in ARVC the original key descriptor was primarily right-sided morphologic involvement with a prominent arrhythmogenic profile, biventricular and predominantly left-sided variants are increasingly recognized. LV involvement complicates the clinical diagnosis, and it may be challenging to distinguish between ARVC with LV involvement from DCM with right ventricular involvement.

2. *The overlapping phenotypes render traditional classification difficult.* The HCM-DCM-RCM classification also failed to consider the heterogeneous clinical expression and natural history of these diseases. For example, HCM, infiltrative and storage cardiomyopathies are characterized by substantial LV hypertrophy with increased wall thickness in the absence of ventricular dilatation. These conditions are also frequently associated with restriction to diastolic filling, whereas purely restrictive forms of cardiomyopathy (without LV hypertrophy) are exceedingly rare. Investigation into the genetic basis of HCM and other cardiomyopathies has led to the identification of individuals with a disease-causing mutation who do not develop LV hypertrophy. Dilated forms of cardiomyopathy show a considerably increased cardiac mass with myocyte enlargement indicative of cardiac hypertrophy, although absolute LV wall thicknesses might remain normal. The end-stage phase of HCM could demonstrate hypertrophic, dilated, and restrictive components. Furthermore, some patients may evolve from one category to another as a consequence of remodeling during their natural clinical course. For example, HCM, amyloid, and other infiltrative myocardial diseases may progress from a nondilated (often hyperdynamic) state with ventricular stiffness to a dilated form with systolic dysfunction and heart failure. Finally, because quantitative assessments of ventricular size represent a continuum and patients can vary widely in the degree of chamber enlargement (and dimensional cutoff values are arbitrary), it is often difficult to discriminate dilated from nondilated forms of cardiomyopathy. This ambiguity may also apply to some rare, or newly identified, cardiac diseases in young patients for which little quantitative cardiac dimensional data are currently available.
3. *Etiologically/genetically diverse cardiomyopathies present with similar phenotypes.* Etiologic classification of cardiomyopathies also appears problematic, given that diseases with the same (or similar) phenotypes can harbor diverse etiologic mechanisms. For example, DCM may have genetic, infectious, autoimmune, and toxic causes (and in some cases still be designated as *idiopathic*); all may lead to the final common pathway of ventricular dilatation with systolic dysfunction. Alternatively, functional classifications with potential relevance to treatment considerations and theoretically most useful to clinicians are also flawed and of limited value because management strategies for these diseases constantly evolve.

THE DEFINITION

A heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, which usually exhibit inappropriate ventricular hypertrophy or dilatation, and are due to a variety of etiologies that frequently are genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.[6]

Within this broad definition, cardiomyopathies are usually associated with failure of myocardial performance, which may be mechanical (eg, diastolic or systolic dysfunction) or a primary electrical dysfunction that increases susceptibility to life-threatening arrhythmias. The ion channelopathies (long and short QT syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, among others) are primary electrical diseases without gross or histopathologic abnormalities in which the functional and structural myocardial abnormalities responsible for arrhythmogenesis are at the molecular level in the cardiomyocyte or sarcoplasmic membranes themselves. The basic pathologic abnormality in these diseases is not identifiable by either conventional noninvasive imaging or myocardial biopsy during life, or even by electron microscopic or autopsy examination of tissue. The ion channelopathies are included in this classification of cardiomyopathies based on the scientifically reasonable assertion that ion channel mutations are responsible for altering biophysical properties and protein structure of the cardiomyocyte, thereby creating structurally abnormal ion channel interfaces and architecture with electrical dysfunction, which are changes that could trigger primary life-threatening ventricular tachyarrhythmias.

THE CLASSIFICATION

Cardiomyopathies were divided into two major groups based on predominant organ involvement. The *primary* cardiomyopathies were those solely or predominantly confined to heart muscle (Fig. 57–2A).[6] The primary cardiomyopathies were further categorized into genetic, acquired, and mixed varieties and represented the novelty of the AHA classification. The *secondary* cardiomyopathies showed pathologic myocardial involvement as part of systemic (multiorgan) disorders. In prior classifications, the primary cardiomyopathies represented idiopathic processes. The systemic diseases associated with secondary forms of cardiomyopathies were previously referred to as *specific cardiomyopathies*[4] or *specific heart muscle diseases*[5] in prior classifications. Such vague nomenclature was abandoned in the AHA classification.

THE MAJOR ATTRIBUTES OF THE AMERICAN HEART ASSOCIATION CLASSIFICATION

The AHA classification introduced the concept of classification of primary cardiomyopathy based on *genetic* origin. A large body of evidence had become available in 2006 that supported the genetic basis of cardiomyopathies, and the writing group asserted that it was time that cardiomyopathies be appropriately termed on the basis of their cause (ie, genetic, acquired, or mixed). The phenotype hierarchically was subordinate to the genotype in the AHA classification, presaging the gigantic evolution of knowledge pertaining to the genetic etiology of cardiomyopathies and the need for integrating the diagnostic description with genotype first and phenotype subsequently. The AHA classification was a welcome change and was the result of expertise, knowledge, and deep research on the mechanism of disease. However, it has been somewhat difficult to translate the classification recommendation into clinical reality.

THE EUROPEAN SOCIETY OF CARDIOLOGY (2008) CLASSIFICATION

THE BASIS

The 2008 position paper of the ESC proposed the classification of cardiomyopathies that aimed at providing an algorithm for daily clinical practice.[7] The following were key tenets of the proposal, specifically

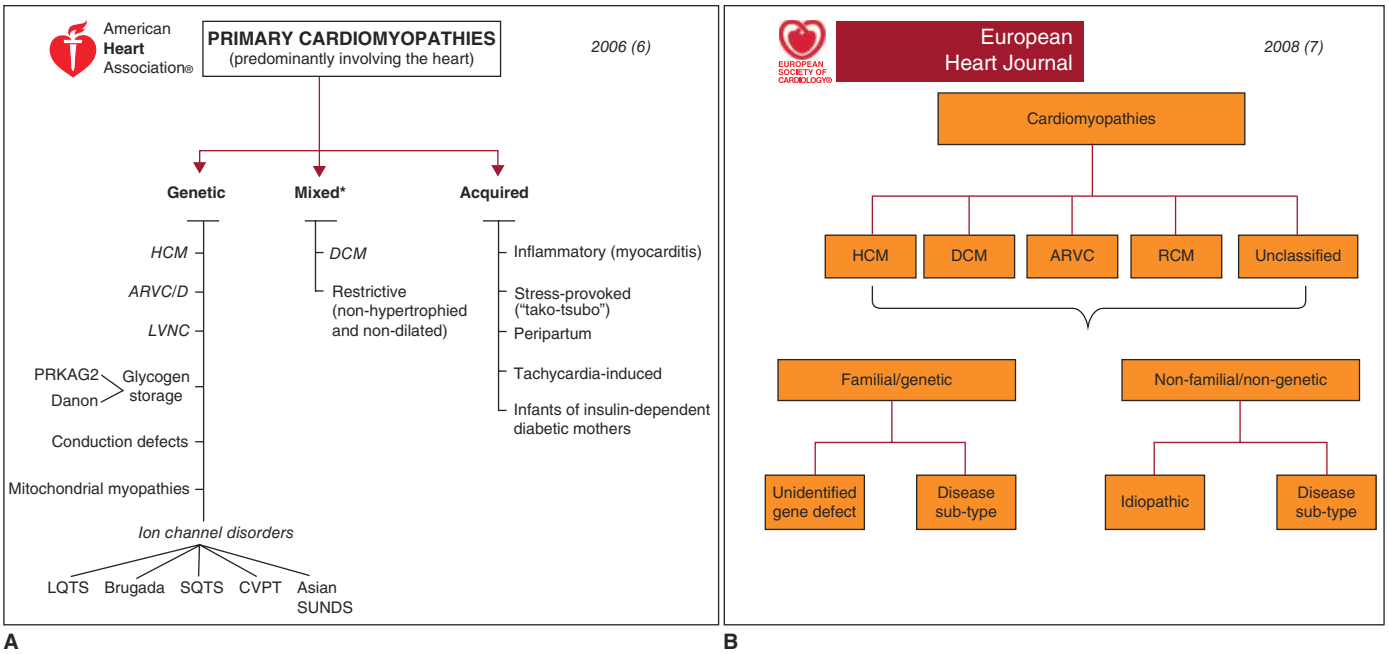

FIGURE 57–2. A. Graphical presentation of the American Heart Association (AHA) classification (2006). Primary cardiomyopathies in which the clinically relevant disease processes solely or predominantly involve the myocardium. The conditions have been segregated according to their genetic or nongenetic etiologies. *Predominantly nongenetic; familial disease with a genetic origin has been reported in a minority of cases. From Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006 Apr 11;113(14):1807–1816. **B.** Graphical presentation of the European Society of Cardiology (ESC) classification (2008). ARVC/D, arrhythmogenic right ventricular cardiomyopathy/ dysplasia; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; SQTS, short QT syndrome; SUNDS, sudden unexpected nocturnal death syndrome; DCM, Dilated cardiomyopathy; HCM, Hypertrophic cardiomyopathy; RCM, Restrictive cardiomyopathy. Reproduced with permission from Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2008 Jan;29(2):270–276.

in response to the original WHO-ISFC classification and 2006 AHA classification:

1. *Phenotypic characterization should precede genetic characterization*. Although the ESC endorsed the necessity for identifying the causative genetic defect as proposed by the AHA, the ESC scheme retained the morphofunctional phenotype as the basis of the classification and management of cardiomyopathy. Cardiomyopathy was grouped into morphofunctional phenotypes including DCM, HCM, RCM, ACM, and unclassified varieties. Each of these types was further divided into familial (genetic) and nonfamilial (nongenetic) forms. The insistence on the morphofunctional classification was based on the fact that the pathway from diagnosis to treatment in clinical practice rarely begins with the identification of the causative genetic mutation; instead, patients present with symptoms, clinical signs, or abnormal screening test results. Even if the genetic defect is identified in offspring or siblings, the clinically relevant disease necessitates demonstration of a morphologic phenotype.
2. *The broad classification between primary and secondary cardiomyopathy should not be necessary*. The original WHO-ISFC classification system had distinctly defined the cardiomyopathies as primary myocardial disorders (when the cause of the myocardial involvement was unknown) and secondary or specific-heart muscle diseases (when the etiology was known). However, in the AHA classification, the term *primary cardiomyopathy* was applied when the heart was the sole (or predominantly) involved organ, and the term *secondary cardiomyopathy* described heart muscle disease as an integral part of a systemic disorder.[6] It was further contended that the application of the terms *primary* and *secondary cardiomyopathy* per AHA recommendation would be difficult when primary cardiomyopathy was associated with major extracardiac manifestations, or secondary cardiomyopathy predominantly (or exclusively) involved the heart. Therefore, ESC panelists abandoned the distinction between primary and secondary cardiomyopathies.
3. *Ion channelopathy should not be considered cardiomyopathy*. Ion channelopathies, a genetic subtype included in the AHA classification of primary cardiomyopathy, was not accepted as cardiomyopathy in the ESC classification because genes encoding for ion channels might not be associated with overt myocardial dysfunction.[12] The ESC expert panel contested that the genes encoding ion channels implicated in patients with DCM, conduction disorders, and arrhythmia did not yet provide sufficient evidence for the redesignation of channelopathy as cardiomyopathy.
4. *The diagnosis of cardiomyopathy should be sought and not be considered a diagnosis of exclusion*. Traditionally, the diagnosis of cardiomyopathy has been established after exclusion of other cardiovascular disorders. However, it is increasingly recognized that patients with cardiomyopathy have uncommon, but well-described myocardial trait(s). Therefore, ESC panelists recommended a diagnostic workup toward a positive, logical search of cardiomyopathy instead of one that was exclusion based. The aim has been to promote a greater appreciation of the broad spectrum of diseases that can result in cardiomyopathy and to abandon the differentiation between cardiomyopathies and specific heart muscle diseases (noncoronary, valvular, hypertensive, or congenital).

THE DEFINITION

The 2008 ESC classification defined cardiomyopathy as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, which, in the absence of coronary artery, hypertensive,

valvular, and congenital disease, is sufficient to cause the observed myocardial abnormality.

THE CLASSIFICATION

In the 2008 ESC classification, cardiomyopathies are grouped into specific morphologic and functional phenotypes; each phenotype is then subclassified into familial and nonfamilial forms (Fig. 57–2B).[7] In this context, familial refers to the occurrence, in more than one family member, of either the same disorder or a phenotype that is (or could be) caused by the same genetic mutation and not a result of acquired cardiac or systemic diseases in which the clinical phenotype is influenced by a genetic polymorphism. Most familial cardiomyopathies are monogenic disorders wherein the gene defect is sufficient by itself to cause the trait. A monogenic cardiomyopathy can be sporadic when the causative mutation is *de novo* (ie, has occurred in an individual for the first time within the family). In this classification system, patients with identified *de novo* mutations are assigned to the familial category because their disorder can be subsequently transmitted to their offspring. Nonfamilial cardiomyopathies are clinically defined by the presence of a cardiomyopathy in the index patient and the absence of disease in other family members (based on pedigree analysis and clinical evaluation). They are subdivided into idiopathic (no identifiable cause) and acquired cardiomyopathies in which ventricular dysfunction is a complication of the disorder rather than an intrinsic feature of the disease. In a departure from the 1995 WHO-ISFC classification, but similar to the AHA categorization, this taxonomy also excludes LV dysfunction secondary to coronary artery disease, hypertension, valve disease, and congenital heart disease because the diagnosis and treatment of these disorders generally involve clinical management that may vary in some ways from management of cardiomyopathy. Different familial and nonfamilial genetic diseases may induce similar phenotype.

THE MAJOR ATTRIBUTES OF THE EUROPEAN SOCIETY OF CARDIOLOGY CLASSIFICATION

The ESC classification introduced the concept of "familial cardiomyopathies" and encouraged excavation for the genetic cause of the phenotype. Although it is implicit that a familial disease has a genetic origin, the definition of familial cardiomyopathy was directed at motivating physicians to elicit a detailed family history and execute thorough phenotyping assessment of probands and relatives to establish the diagnosis within the clinical encounter, independent of genetic testing that might not be universally available. In clinical practice, cardiologists still use the morphofunctional classification of cardiomyopathies (HCM, RCM, DCM, ARVC, and unclassified varieties) followed by further characterization into genetic or nongenetic subtypes. The subsequent documents of the ESC Working Group reinforced the recommendations for screening of relatives as the most powerful clinical tool for the recognition of familial cardiomyopathies[13] and clinical monitoring of families in a phenotype-driven mindset to formulate a pretest hypothesis of specific gene defects.[14]

THE WORLD HEART FEDERATION CLASSIFICATION (2013)

THE BASIS

The previously described classifications by the AHA and ESC have advanced the field substantially. The writing group of the AHA classification must be complemented for challenging an obsolete tradition and promulgating the importance of the genetic basis of cardiomyopathy. The ESC writing group, while recognizing the importance of the heritability of the cardiomyopathies, preferred to retain the practicality of their taxonomy for routine clinical use. Separately, both allow latitude for improvisation, and the WHF classification represents a stepwise union of the two and characteristics of phenotype and genotype into a cogent classification system.[8,9] The WHF writing group maintains that whereas a diagnosis based on phenotype is clinically useful, identification of genetic mutations provides comprehensive information about prognosis in cardiomyopathies. A substantially large number of disease genes have been either confirmed or suspected as candidate genes; genetic heterogeneity has been established, and the wider use of next-generation sequencing is likely to increase our understanding of the phenotypic expression of the disease process. The WHF classification is an attempt to combine the message of both preceding classifications and is based on the following principles:

1. *Most cardiomyopathies are familial diseases*. The epidemiology of cardiomyopathies is derived from studies executed in the pregenetic era, and as discussed earlier, in the AHA classification, the traditionally accepted prevalence of cardiomyopathy based on the diagnosis of overt phenotypes may be a gross underestimation of the actual prevalence of cardiomyopathic disorders. Familial cardiomyopathies are predominantly inherited as autosomal dominant traits and, less frequently, as autosomal recessive, X-linked recessive or dominant, and matrilineal disorders. Familial cardiomyopathy should be diagnosed when two or more family members are affected. The age dependence of the phenotype may require long-term follow-up for a comprehensive evaluation of the family. The diagnosis of familial cardiomyopathy is easily established in families where more members are contemporaneously affected. However, the diagnostic assumption of nonfamilial cardiomyopathy should rely either on the evidence of a nongenetic cause or should remain labeled as unknown wherein systematic screening is limited by family size, adoption, or deceased relatives. After comprehensive assessment of pedigree, cascade family screening is undertaken to allow for identification of all affected family members, including healthy carriers.
2. *Familial cardiomyopathies have a genetic origin and display clinical and genetic heterogeneity*. The list of candidate genes as the cause of cardiomyopathies is growing. Such genes are identified through linkage analyses, genome-wide association studies, and whole exome sequencing. With more than 100 genes identified, the list still remains incomplete, but the most common genes associated with the different types of cardiomyopathies have been recognized, and genetic testing is being translated into clinical reality.

Although all cardiomyopathic disorders are broadly classified as five major morphofunctional phenotypes, a careful clinical evaluation demonstrates high phenotypic variability.[9] Various cardiomyopathy subsets show variations in gender predisposition, age of onset, rate of progression, complications, and risk of developing end-stage heart failure or life-threatening ventricular arrhythmias. For example, DCM patients with *LMNA* mutations may develop life-threatening ventricular arrhythmias even in the presence of only mild LV enlargement and dysfunction, whereas those with dystrophin mutations may carry only low arrhythmogenic risk even with extreme LV dilatation or dysfunction. Similarly, there are HCM patients with severe LV hypertrophy (> 30 mm) but low arrhythmogenic risk and those with mild or moderate hypertrophy but high arrhythmogenic risk. In addition, gene-specific traits and diagnostic markers (red flags) may be reproducibly associated with subgroups of cardiomyopathy patients; such red flags include atrioventricular block (AVB),

pre-excitation syndrome (eg, Wolff-Parkinson-White [WPW] pattern or syndrome), repolarization abnormalities, or attenuated QRS voltage.[9] Furthermore, noninvasive imaging may reveal variable severity, distribution, and extent of myocardial hypertrophy; valve pathology; LV noncompaction; varying extents of ventricular dilatation and dysfunction; and variations in extent and distribution of myocardial fibrosis, or intramyocytic storage, and fatty infiltration within the myocardium. An integrated multidisciplinary workup including ascertainment of inheritance pattern, determination of major clinical phenotype (eg, DCM or HCM), identification of cardiac markers (eg, AVB, short PR interval, WPW), characterization of extracardiac organ involvement (eg, ocular, muscle, skeletal, or neurologic traits), or measurement of biomarkers (eg, increased serum creatinine phosphokinase or lactic acidemia) provides a preliminary filter for selecting genes for testing. For instance, cardiolaminopathies are associated with AVB in up to 80% of cases; dystrophinopathies are inherited in male patients in the absence of male-to-male transmission of the disease and are associated with increased serum creatinine phosphokinase (80%); and myocardial storage diseases typically demonstrate concentric LV hypertrophy with short PR interval and/or WPW pattern or syndrome. The presence of clinical red flags in probands and/or relatives guides genetic testing and provides for a sustainable strategy for clinical translation. After the conclusion of methodical clinical workup, genetic testing is offered to patients and their families.

The genetic heterogeneity complicates the diagnostic workup of familial cardiomyopathies: several genes influencing the same or different pathway(s) may be associated with similar phenotypes, and identical gene mutations may result in altogether different phenotypes. For instance, the sarcomeric gene defects may be associated with HCM and DCM; desmosome genes, which are typically associated with the classical ARVC, may cause DCM; genes encoding intermediate filaments such as nuclear lamins may also be associated with ARVC; and nonsarcomeric genes are also known to be associated with HCM. An increasing number of cardiomyopathies are recognized to be associated with complex genetics. Studies interrogating panels of genes in single patients have demonstrated a higher than expected rate of patients who are carriers of more than one and up to several mutations in the same or in different genes, which might imply that the incomplete genetic penetrance or variable expressivity of gene mutations represents incomplete genotyping or that the presumptive disease-causing role has erroneously been assigned to a wrong gene and mutation. Although *in vitro* functional studies can contribute to elucidating the role of protein mutations in a given cardiomyopathy, the detection of mutations will continue to be faster than developing animal models or performing *in vitro* studies for confirmation of their functional roles. An approach to genetic testing could be clinically guided or more broad based (eg, large panels of disease-associated/candidate genes). It is becoming evident that interpreting the results, rather than performing the tests, is the greater challenge in the modern era of next-generation sequencing.

3. *The knowledge of genetic background would allow an improved management strategy*. The major clinical decisions (eg, implantable cardioverter-defibrillator implantation) are still based on mechanical (eg, LV ejection fraction in DCM) or morphologic (eg, maximal LV wall thickness in HCM) characteristics, regardless of the intrinsic disease risk related to the underlying genotype.[14,15] However, such risk stratification based on anatomic and/or mechanical features has limitations. For example, patients with laminopathies may not always demonstrate substantial LV dysfunction and dilatation when their arrhythmogenic risk first manifests,[15,16] and those with dystrophinopathies may be significantly less susceptible to the risk of malignant arrhythmias even when the LV is dramatically enlarged and dysfunctional. Similarly, patients with troponinopathies may not manifest severe LV wall thickness but may live with a high arrhythmogenic potential.[16,17]
4. *Ever-increasing knowledge of genetic background may result in random nomenclature*. Based on the underlying gene mutations,[8] numerous new terms (eg, *desmosomalopathies*, *cytoskeletalopathies*, *sarcomyopathies*, *channelopathies*, *cardiodystrophinopathies*, *cardiolaminopathies*, *zaspopathies*, *myotilinopathies*, *dystrophinopathies*, *αB-crystallinopathies*, *desminopathies*, or *caveolinopathies*) are being proposed. These are likely to cloud the description of cardiomyopathy, and it has become important that a uniform nomenclature be developed.
5. *The taxonomy should be a flexible, user-friendly system that can be used at the bedside.* As was the case for the universal TNM staging for malignant tumors, an improved taxonomy for classification of cardiomyopathy should be comprehensive and user-friendly, allowing for easier communication among physicians and facilitating the development of multicenter/multinational registries to promote research in diagnosis and management of cardiomyopathies. We have received several suggestions from various investigators, and modifications have been proposed for ACM,[18] endomyocardial fibrosis,[19] and HCM.[20]

THE DEFINITION

The cardiomyopathies in the WHF classification are described as disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype.[8] In this classification, although the conventional phenotypic subtype of the cardiomyopathy continues to provide the basis for the classification, a genotype-based assessment dictates the diagnostic workup and treatment decisions in probands and relatives, as well as the follow-up plan. Once the genetic cause of the cardiomyopathy has been defined, the cascade family screening can help identify healthy mutation carriers who may eventually develop the phenotype over the ensuing years.[12] Avoidance of competitive sport activity and tailored monitoring with early medical treatment may favorably influence the natural history of the disease and the development of the manifest phenotype, as well as the risk of life-threatening arrhythmias. Identification of genetic diseases may also help subjects and alert physicians to refrain from the use of injurious agents. For instance, agents triggering malignant hyperthermia (succinylcholine) or volatile anesthetics (halothane and isoflurane) are to be avoided in emerinopathies and laminopathies causing muscular dystrophy.[21] Statins should be administered with caution in patients with genetic cardiomyopathies with possible involvement of the skeletal muscle, even when markers of myopathy are negative.[22] Patients with disorders of the respiratory chain may need surgeries in the long term, but anesthetics may interfere with metabolism and may trigger unexpected complications.[23] Patients with mitochondrial cardiomyopathy and epilepsy should not receive valproate because it could cause pseudoatrophy of the brain.[24] Common indications for heart transplantation in patients with end-stage cardiomyopathy should take into account the specific diagnosis; conditions such as Danon disease or other comorbidities, such as mental retardation, are a matter of debate regarding indication for heart transplantation.[25] Finally, genotype-based diagnoses can be pooled in large international databases for future clinical trials and validation of novel management strategies.

THE CLASSIFICATION

The most effective nosology system should encompass clinical presentation, organ involvement, genetic inheritance, and precise etiologic information. This could be optionally supplemented by the functional class/stage/status and should employ universally adopted terms. The WHF's MOGE(S) classification system is the first attempt to integrate morphofunctional phenotype-based description, information on the involvement of extracardiac organs/tissues, clinical genetics in familial diseases (pattern of inheritance), and molecular genetics (disease gene and mutation). MOGE(S) can also describe "sporadic" nongenetic cardiomyopathies and specify their etiology if known. In the case of phenotypically sporadic cardiomyopathies, a genetic origin of the disease cannot be excluded unless a nongenetic cause is proven and clinical family screening has ruled out a familial disease. When not certain, each cardiomyopathy should be considered as a potentially genetic disease, allowing families to receive the same screening options offered to families with known familial cardiomyopathy.

MOGE(S) classification is inspired by the TNM staging system; it is a descriptive nosology algorithm that includes five essential descriptors of cardiomyopathies (Fig. 57–3), inherited and noninherited.[8] These five attributes are morphofunctional phenotype (M), organ involvement (O), genetic or familial inheritance pattern (G), etiologic (E) description of genetic defect or nongenetic cause, and functional status (S), using the American College of Cardiology (ACC)/AHA stage (stage A-D) and New York Heart Association class (class I-IV). The "S" notation becomes especially useful when mutation carriers are healthy (phenotypically unaffected) or if they demonstrate preclinical imaging-verified early abnormalities suggestive of the cardiomyopathy.[9] The use of MOGE(S) is supported by the app for Android downloadable from Google Play (Fig. 57–4) or by the user-friendly web app at http://moges.biomeris.com/moges.html (Fig. 57–5). The cardiac phenotype description precedes genetic information. The approach to the evaluation of cardiomyopathies should involve a comprehensive family history and identification of other accompanying disease characteristics (red flags) that may predict candidate gene involvement. Even if genetic information is not available, consideration of heritability allows conceptualizing of the disease as a familial process.

Morphofunctional Phenotype, or M

The morphofunctional presentation is described as a subscript to the notation M; for example, M_D (DCM), M_H (HCM), M_A (ACM), M_R (RCM), and M_{NC} (LV noncompaction). ACM is categorized in three major subtypes, including classical right ventricular ACM (ARVC or RV-ACM), biventricular ACM (BV-ACM), and predominantly left ventricular ACM (LV-ACM). Unlike previous classifications, the mixed or overlapping phenotypes can be easily presented, such as HCM that evolves into dilated congestive phenotype (M_{H+D}) or HCM presenting with predominant restrictive pattern (M_{H+R}). Other combinations are possible such as M_{D+NC}, M_{A+NC}, M_{H+NC}, M_{H+R+D}. The M notation can add key clinical red flags such as short PR interval (↓PR), WPW pattern or syndrome, and AVB (displayed as $M_{H[\downarrow PR]}$, $M_{H[WPW]}$, and $M_{D[AVB]}$, respectively), or nonspecific or noncoded traits

NOTATION	M MORPHO-FUNCTIONAL PHENOTYPE	O ORGAN/SYSTEM INVOLVEMENT	G GENETIC INHERITANCE PATTERN	E ETIOLOGY	S STAGE
SUBSCRIPT	D Dilated H Hypertrophic R Restrictive R EMF Endomyocardial fibrosis *LV=left ventricle* *RV=right ventricle* *RLV=biventricular* A ARVC *M=major* *m=minor* *c=category* *LV= left ventricle* *RV=right ventricle* *RLV=biventricular* NC LVNC E Early, with type in parentheses NS Nonspecific phenotype NA Information non available 0 Unaffected*	H Heart *LV=left ventricle* *RV=right ventricle* *RLV=biventricular* M Muscle (skeletal) N Nervous C Cutaneous E Eye, Ocular A Auditory K Kidney G Gastrointestinal Li Liver Lu Lung S Skeletal 0 Absence of organ/system involvement*, e.g. in family members who are healthy mutation carriers; the mutation is specified in E and inheritance in G	N Family history negative U Family history unknown AD Autosomal dominant AR Autosomal recessive XLD X-linked dominant XLR X-linked recessive XL X-linked M Matrilineal 0 Family history not investigated* Undet Inheritance still undetermined S Phenotypically Sporadic (apparent or real)	G Genetic cause OC Obligate carrier ONC Obligate non-carrier DN *De novo* Neg Genetic test negative for the known familial mutation N Genetic defect not identified 0 No genetic test, any reason* G-A-TTR Genetic amyloidosis G-HFE Hemochromatosis *Non-genetic etiologies:* M Myocarditis V Viral infection (add the virus identified in affected heart) AI Autoimmune/immune-mediate; suspected (AI-S), proven (AI-P) A Amyloidosis (add type: A-K, A-L, A-SAA) I Infectious, non viral (add the infectious agent) T Toxicity (add cause/drug) Eo Hypereosinophilic heart disease O Other	ACC-AHA stage represented as letter **A, B, C, D** **NA** not applicable **NU** not used *followed by* NYHA class represented as Roman numeral **I, II, III, IV**

FIGURE 57–3. MOGE(S) classification of cardiomyopathies. MOGE(S) classification is inspired by the tumor-node-metastasis (TNM) staging system; it is a descriptive nosology algorithm that includes five descriptors of cardiomyopathies, inherited and noninherited. These five attributes are morphofunctional phenotype (M), organ involvement (O), genetic or familial inheritance pattern (G), etiologic (E) description of genetic defect or nongenetic cause, and the functional status (S) using the American College of Cardiology (ACC)/American Heart Association (AHA) stage (stage A-D) and New York Heart Association (NYHA) class (class I-IV). Reproduced with permission from Arbustini E, Narula N, Tavazzi L, et al. The MOGE(S) classification of cardiomyopathy for clinicians. *J Am Coll Cardiol.* 2014 Jul 22;64(3):304-301.[9]

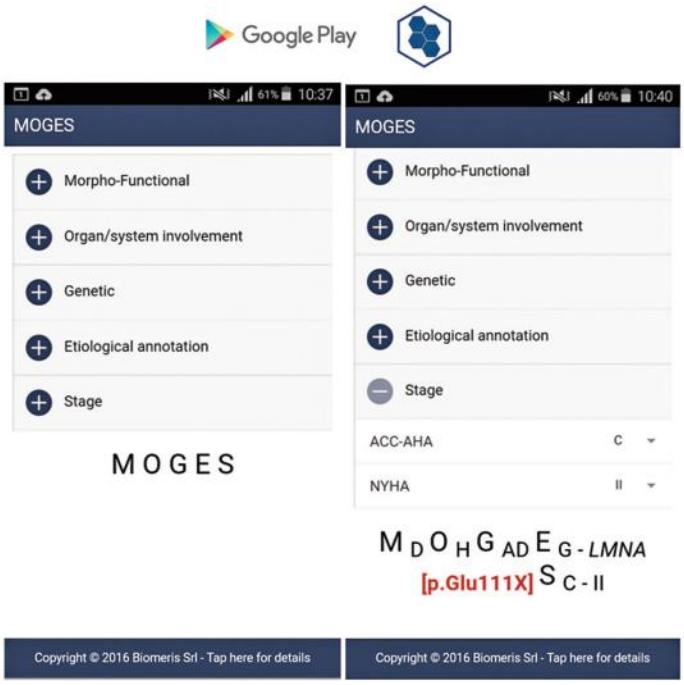

FIGURE 57–4. MOGE(S) is supported by a web app (desktop version is available at http://moges.biomeris.com/moges.html; Android version is downloadable from Google Play). ACC, American College of Cardiology; AHA, American Heart Association; NYHA, New York Heart Association.

(such as hypertrabeculation when criteria for LV noncompaction are not fulfilled or any other trait specifically associated with the disease) can be added (Fig. 57–6). Most importantly, M allows the description of *early* phenotypes (M_E), such as when the diagnostic criteria for the suspected clinical phenotype (such as DCM or HCM) are not fulfilled and imaging data indicate an increased LV diameter and a borderline LV function ($M_{E[D]}$) or possible LV hypertrophy ($M_{E[H]}$).[26] Clinically healthy mutation carriers are described as $M_{0[H]}$ or $M_{0[D]}$ (0 is for zero). When the information about the cardiac phenotype is not available, such as with the deceased relatives, the description is M_{NA}. Overall, the M notation is flexible and suitable for any clinical combination of disease phenotypes and clinical traits.

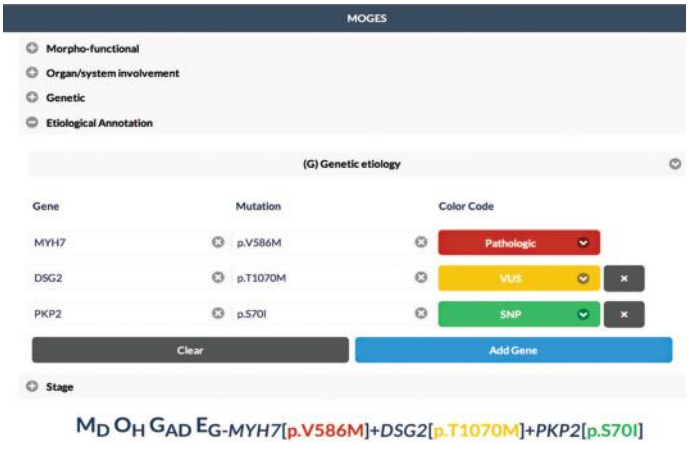

FIGURE 57–5. Drop-down menu for the easy adaptation of MOGE(S) classification (http://moges.biomeris.com/moges.html). This expanded view for the characterization of underlying genetic etiology highlights the pathologic mutations (*red*), variants of unknown significance (VUS; *yellow*), and single-nucleotide polymorphisms (SNP; *green*).

Organ Involvement, or O

The notation O describes organ involvement in the subscript. The comprehensive presentation of the organs involved helps identify syndromes. Primary cardiomyopathy (as described in the AHA classification), that is, only cardiac involvement, is represented as O_H. The involvement of other organs is added on the cardiac involvement, such as skeletal muscle involvement in dystrophin defect (O_{H+M}); involvement of kidney, gastrointestinal system, skin/cutaneous, and eye in Anderson-Fabry disease ($O_{H+K+G+C+E}$; Fig. 57–7); or involvement of auditory system, nervous system, liver, lungs, and mental retardation in mitochondrial DNA–related diseases (O_{H+A}, O_{H+N}, O_{H+L}, O_{H+Lu}, and O_{H+MR}, respectively). The involvement of uncommon organs can be adopted based on anatomic terms in the Systematized Nomenclature of Medicine topography (eg, thyroid [O_{H+T}] and adrenal glands [O_{H+AD}]). Healthy mutation carriers are described as (O_0) because the heart is still clinically unaffected (M_0). "O" is similarly represented in nongenetic disorders (eg, the liver involvement and hypereosinophilia [$O_{H+L+\uparrow Eo}$] in endomyocardial fibrosis).

Genetic Inheritance, or G

The notation G describes the genetic or familial inheritance as clinically identified from the family screening, with inheritance including autosomal dominant (G_{AD}), autosomal recessive (G_{AR}), X-linked (G_{XL}), X-linked recessive (G_{XLR}) or dominant (G_{XLD}), and matrilineal (G_M). A solitary involvement is described as sporadic (G_S) cardiomyopathy after the family screening and review of medical records of deceased relatives of the proband. The patient with unknown (G_U) or negative (G_N) family history should also be described.

Underlying Etiology, or E

The fourth notation of MOGE(S), E, is represented in two steps. The first step is presented as a coupled subscript for the genetic (E_G), or nongenetic nature (E_{NG}) of the disease. For the genetic background (E_G), if the genetic defect is identified and characterized, then the second step provides complete information on the gene mutation, such as in the case of HCM ($E_{G\text{-}MYH7[p.Arg403Glu]}$), familial amyloidosis ($E_{G\text{-}ATTR[p.Val122Ile]}$), or hemochromatosis ($E_{G\text{-}HFE[p.Cys282Tyr\ Homozygous]}$). When the mutation is identified or when more than one mutation/genetic variant is identified, it is described by the standard colors used for characterizing pathologic mutations in human mutations databases. The color code describes possible and probable pathologic mutations in red; genetic variants of unknown significance in yellow; and single-nucleotide polymorphisms with possible functional significance in green (the apps conveniently guide filing this annotation; see Figs. 57–4 and 57–5). If the genetic characterization is not available but the clinical and genetic family screening provides the necessary information, the (E_G) notation is to be specified as obligate carrier ($E_{G\text{-}OC}$), obligate noncarrier ($E_{G\text{-}ONC}$), or the sporadic/de novo occurrence of mutation ($E_{G\text{-}DN}$). These are important notations because they complement the data on inheritance in the G descriptor. A genetic test negative for the known family mutation is described as ($E_{G\text{-}NEG}$); a negative genetic test is described as ($E_{G\text{-}N}$). When the genetic test could not be done for any reason, the descriptor is ($E_{G\text{-}0}$). Reporting on healthy family members who test negative for the *culprit* mutation(s) is essential for segregation study in the family. When all members of a single family are described, the MOGE(S) nomenclature system highlights mutations that do not fully segregate with the phenotype. The international nomenclature of genetic variants provides the principles for their description (http://varnomen.hgvs.org/). The *in silico* evaluation supports the

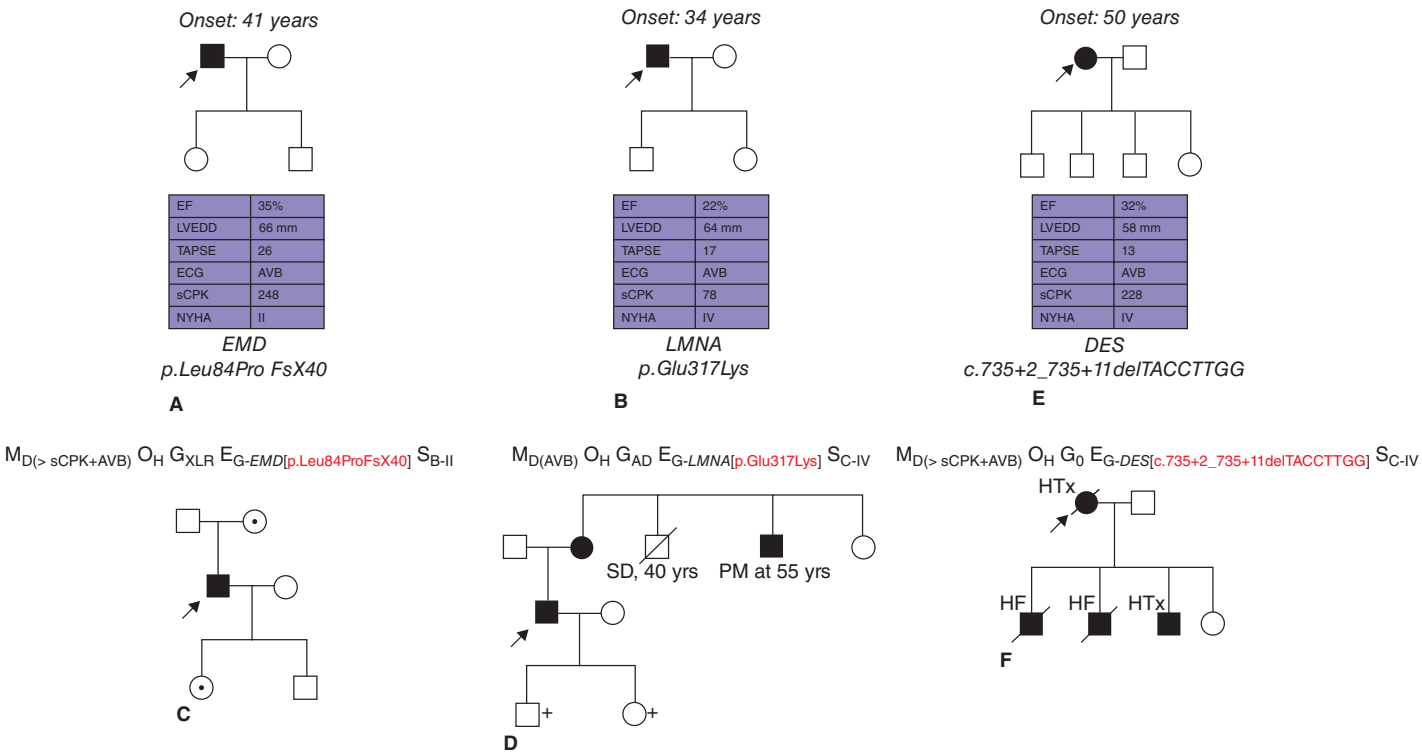

FIGURE 57–6. Morphologic descriptor and genotypic interaction. Three pedigrees with probands (*arrows*) demonstrating similar dilated cardiomyopathy (DCM) phenotypes (A-D) in the first two and restrictive cardiomyopathy (RCM; E-F) in the third patient. The identification of the causative genes and mutations underscores the importance of the genetic diagnosis on the management of the three families. The identification of a mutation in the *Emerin* (*EMD*) gene provides information about the genetic status of the offspring. The son of the proband is obligate negative because a male cannot transmit an X-linked defect to his son. However, the daughters of affected males in X-linked diseases are obligate carriers of the paternal mutations. The identification of a mutation in the lamin AC (*LMNA*) gene (*middle panel*) or desmin (*DES*) gene (*right panel*) provides evidence that offspring can inherit the mutation with 50% probability for each pregnancy. All patients had advanced atrioventricular block and increases in serum creatinine phosphokinase (sCPK) levels. Pedigree symbols are as follows: *circles* represent females, *squares* represent males, *diagonal lines* represent deceased, and *solid-filled symbols* denote the presence of the phenotype. ECG, electrocardiogram; EF, ejection fraction; HF, heart failure; HTx, heart transplantation; LVEDD, left ventricular end diastolic diameter; NYHA, New York Heart Association; PM, pace maker; SD, sudden death; TAPSE, tricuspid annular plane systolic excursion.

interpretation of the significance of each variant (http://genetics.bwh.harvard.edu/pph2/, http://sift.jcvi.org/, http://evs.gs.washington.edu/EVS/, http://www.1000genomes.org/, http://www.umd.be/HSF/). The family studies provide the segregation data, and the pathologic or *in vitro* studies may contribute to document the abnormal expression of the mutated protein.

Similar to the genetic diseases (E_G), the cause of the underlying disease in the nongenetic cardiomyopathies (E_{NG}) is specified as below in two steps, with first notation being couplet. The first notation (E_{NG}) is coupled as predominantly toxic/degenerative, inflammatory, infiltrative, or hypersensitivity disease or others, as presented in Fig. 57-3. The second step should detail the exact cause if known. Some specific examples are as below. A viral myocarditis caused by Coxsackie B3 virus, human cytomegalovirus, or Epstein-Barr virus using the taxonomy system as coded by the International Committee on Taxonomy of Viruses (http://www.ictvonline.org/index.asp) may be presented as $E_{NG\text{-}M[HCMV]}$, $E_{NG\text{-}M[CB3]}$, or $E_{NG\text{-}M[EBV]}$, respectively. Other types of myocarditides may include sarcoidosis ($E_{NG\text{-}M[Sarcoid]}$) or giant cell myocarditis ($E_{NG\text{-}M[Giant\ cell]}$). Other examples of nongenetic inflammatory variety include autoimmune etiology ($E_{NG\text{-}AI[TYPE]}$), hypersensitivity ($E_{NG\text{-}Hs[TYPE]}$), or eosinophilic disease as from a parasitic process ($E_{NG\text{-}Eo[Type\ of\ Parasitic\ Disease]}$). Eosinophilic Loeffler endomyocarditis may be described, according to the cause, as either being idiopathic or part of a myeloproliferative disorder associated with the somatic chromosomal rearrangement of the *PDGFRα* or *PDGFRβ* genes that generate a fusion gene encoding constitutively active PDGFR tyrosine kinases. Nonheritable amyloidosis with kappa ($E_{NG\text{-}A[K]}$), lambda ($E_{NG\text{-}A[L]}$), or serum amyloid A protein ($E_{NG\text{-}A[SAA]}$) characterization can be easily presented and distinguished from the genetic varieties ($E_{G\text{-}A[TTR]}$). Similarly, the toxic cardiomyopathies, such as pheochromocytoma-related ($E_{NG\text{-}T[Pheo]}$) or drug-induced ($E_{NG\text{-}T[Chloroquine]}$) cardiomyopathy, are classifiable; when the former is in the context of a syndrome (eg, von Hippel-Lindau, multiple endocrine neoplasia type 2A/2B, or neurofibromatosis type 1), the name of the syndrome could be added ($E_{NG\text{-}T[Pheo\text{-}VHL]}$).

Functional Status, or S

The notation S describes the heart failure ACC/AHA stage A to D and NYHA functional class I to IV, combined such as $S_{A\text{-}I}$ or $S_{C\text{-}III}$.[27] Although there has been some resistance to the universal application of ACC/AHA and NYHA staging, we believe that this allows the most practical solution to the description of early cardiomyopathies and mutation-carrying healthy family members. The ACC/AHA guidelines include patients with a family history of cardiomyopathy in stage A heart failure, and there has never been a way to include them in a cardiomyopathy classification. Although criteria for early diagnosis of cardiomyopathy are not systematically documented, the increasing family screening and monitoring have revealed that cardiomyopathies such as laminopathies reveal a long preclinical or subclinical incubation before the onset of manifest clinical disease.

The MOGE(S) nosology combines morphofunctional trait and organ (system) involvement with familial inheritance pattern, while characterizing heritable and nonheritable mechanisms of disease. ACC/AHA staging with NYHA class description offers special value for the inclusion of genetically mutated but yet unaffected individuals in the

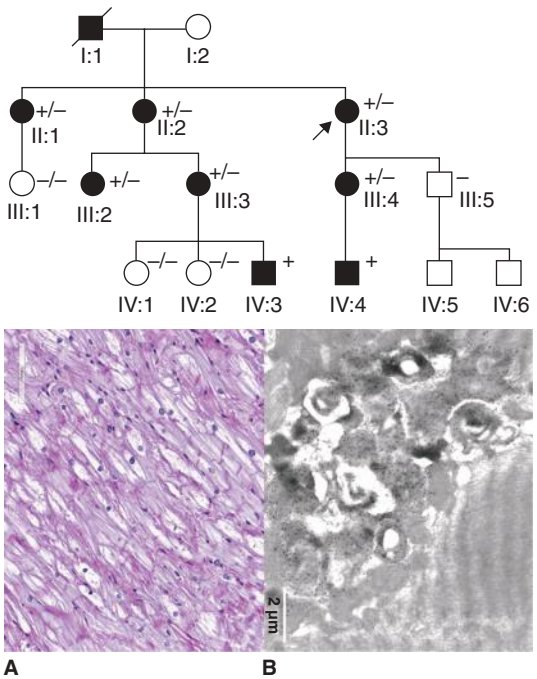

FIGURE 57–7. The pedigree shows a typical family with the X-linked Anderson-Fabry disease (AFD), cardiac variant, caused by p.(Asn215Ser) in the α-galactosidase. In the bottom half of the figure, the pathologic features of AFD in endomyocardial biopsy are shown. **A.** The hematoxylin and eosin stain shows a large number of vacuolated myocytes (glycosphingolipids are extracted in formalin-fixed, paraffin-embedded tissues). **B.** Immunogold electron microscopy view shows typical lamellar and dense osmiophilic bodies specifically immune-labeled by anti-GB3 antibodies. Pedigree symbols are as follows: *circles* represent females, *squares* represent males, *diagonal lines* represent deceased, and *solid-filled symbols* denote the presence of the phenotype.

classification. Just as was the case for the universal TNM staging for malignant tumors, it is expected that this description will be improved, revised, modified, and made more comprehensive and user-friendly in years to come. It will allow for a better understanding of the disease process and easier communication among providers and help develop multicenter and multinational registries to promote research in diagnosis and management of cardiomyopathies.

THE MAJOR ATTRIBUTES OF THE WORLD HEART FEDERATION CLASSIFICATION

MOGE(S) is an example of a coding system that has a sound basis and retains the phenotypic classification of cardiomyopathies (as in the ESC classification) but also incorporates the innovative soul of the AHA classification. Furthermore, because of its flexibility, MOGE(S) can be conveniently modified, adapted, and implemented.

The MOGE(S) system of classification of cardiomyopathies not only allows the possibility of retaining a phenotype-based description, but also allows inclusion of information about extracardiac organ involvement, the heritability of the disease, and data on both genetic and nongenetic mechanisms. Addition of information pertaining to functional status and disease state also allows description of mutation carriers who are clinically healthy or show subclinical or early disease. One of the main barriers encountered today in drawing reliable epidemiologic and clinical information from large, international databases lies in the difference in adopted definitions of the same object in various settings.[28] Descriptive definitions such as MOGE(S) might help to overcome such obstacles. If universally adopted, the cardiology community would have enough data to group cardiomyopathies based on their causes to herald an open era for the development of disease-specific drugs and clinical trials.

CLASSIFICATION OF THE CARDIOMYOPATHIES IN THE ERA OF PRECISION AND PERSONALIZED MEDICINE

> *This is the time of the precision medicine. Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier.*
> —President Barack Obama, addressing the United States on January 20, 2015, in a State of the Union Address

Although the major emphasis was placed on cancer and diabetes[29] in the 2015 State of the Union Presidential Address, the concept of *precision* applies to the entire field of medicine. We are in progressive transition from pathology-based descriptive medicine to specific etiology–driven medicine. *Precision medicine* and *personalized medicine* are often used interchangeably, but they represent two sides of the same coin wherein the precision is directed at the specific diagnosis and the personalized management is directed at an individually tailored approach.[30] Precision cardiology aims at detecting the primary causes of heart diseases and developing targeted, personalized therapies.[31,32] The impact of such an approach is expected to be almost immediate for the diseases caused by a unique factor, noxa, or genetic defect. Cardiomyopathies are paradigmatic examples of feasible and sustainable precision diagnostic workup. Their genetic origin and convenient genetic testing offer an ideal platform for providing patients and families with clinical and etiologic diagnosis. In most cardiomyopathy families, the most common autosomal dominant transmission lends itself to a precise diagnosis and plays a major role in family health for preimplantation, prenatal, preclinical, and presymptomatic assessment. Personalized medical therapy guided by pharmacogenetics and inducible pluripotent stem cells are also becoming an attractive emerging application for the clinical practice.[33] Precision data would remain underused if they are not incorporated in classifications, nosology, and coding systems that can make meaningful contributions in novel etiology-based epidemiology of diseases.

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CHAPTER 58

DILATED CARDIOMYOPATHY

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DILATED CARDIOMYOPATHY: DEFINITION

Dilated cardiomyopathy (DCM) is a chronic heart muscle disease characterized by "the presence of dilatation and systolic impairment of the left or both ventricles unexplained by abnormal loading conditions or coronary artery disease sufficient to cause the observed myocardial dilation and dysfunction."[1] According to the American Heart Association (AHA) classification, "dilated forms of cardiomyopathy are characterized by ventricular chamber enlargement and systolic dysfunction with normal LV wall thickness."[2]

In this chapter, DCM is intended as a primary disease of heart muscle. More than 60% of DCMs are proven to be familial diseases with identifiable genetic defects.[3,4] Acquired disorders manifesting with the DCM phenotype, or DCM phenocopies (defined as environmentally induced phenotypes mimicking one usually produced by a specific genotype), are sporadic and are categorized as nongenetic DCM. This distinction is essential to separate genetic DCM from acquired, nongenetic, and potentially reversible phenotypes arising from protean causes. The therapeutic options for acquired DCM often differ from those for familial DCM. Ischemic heart disease may manifest as or evolve into a DCM-like phenotype; it is discussed further in Chap. 43.

In its descriptive definition, DCM represents the *end phenotype* of heart muscle damage induced by different causes; the disease mechanisms are increasingly being identified by the implementation of molecular and genetic assays for patients and families, high-resolution and functional imaging, and novel biomarkers. In this end stage, most DCMs look phenotypically alike (Fig. 58–1). *Intermediate phenotypes* are manifest by borderline, persistent left ventricular (LV) dilation and/or dysfunction and may present with arrhythmias and/or conduction disease, now recognized as "early DCM."[5] In genotyped families, the *preclinical phase* of the disease can be diagnosed in phenotypically healthy but genetically affected relatives of probands with DCM. Therefore, DCM can be grouped mechanistically as genetic and nongenetic.

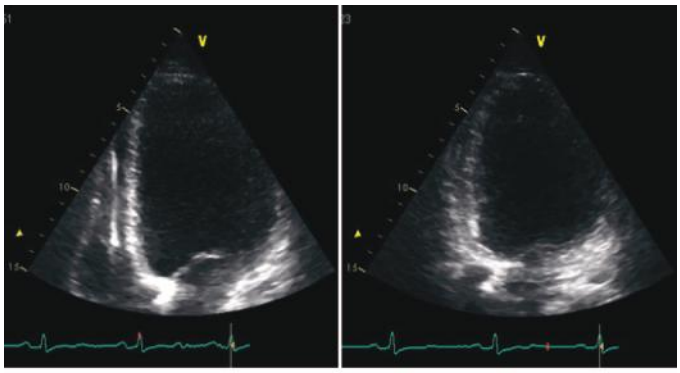
THE BURDEN OF DILATED CARDIOMYOPATHY

Current estimates of incidence are derived from phenotype-based studies. Phenotype-based incidence is estimated as 6.0 per 100,000 person-years and prevalence is 36.5 per 100,000 person-years (about 1:2500).[6] These epidemiology data are based on clinical diagnoses and have been obtained in the pregenetic era. New estimates are expected in the short term,[7] based on data obtained with early diagnoses, systematic family screening and monitoring, genetic testing, and advanced diagnostics for nongenetic DCM.[8-16] As long-term follow-up of familial DCM increases, the overall prevalence of disease is anticipated to increase.

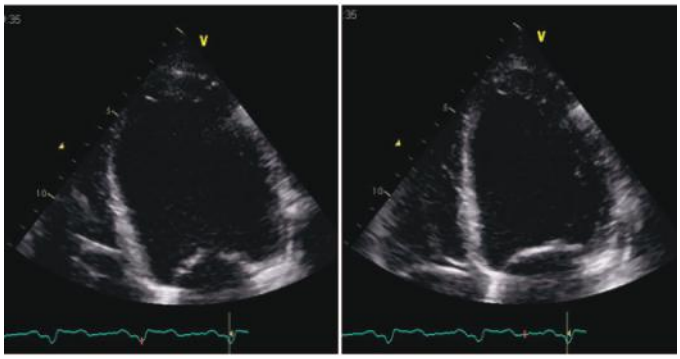
When DCM is defined by etiology, the prevalence data of each specific disease manifestation with a DCM phenotype is far less common, placing most DCM subtypes in the context of rare diseases (< 1:2000). Therefore, the burden of DCM in general, and of familial DCM (FDCM) in particular, is a dynamic issue that should be regarded as evolving and deserving of further efforts to generate a precise epidemiology of DCM.

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP IN INDEX PATIENTS

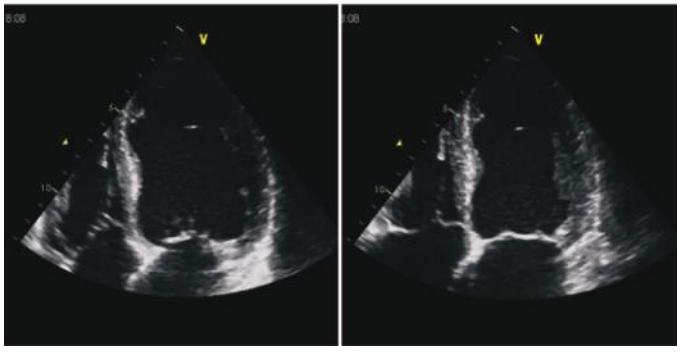
DCM typically manifests with systolic heart failure. The spectrum of symptoms is wide and nonspecific; it includes fatigue, breathlessness, palpitations, and signs of congestion/fluid retention in the presence of structural cardiac abnormalities corresponding to the diagnostic definition.[1,17] The clinical diagnosis is made in the presence of LV



♂, 41 years $M_{D(>\ sCPK)}\ O_{H+M}\ G_{XLR}\ E_{G\text{-}DMD[Delexons\ 45\text{-}47\ hemi]}\ S_{C\text{-}II}$



♂, 30 years $M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}BAG3[p.Gln251ArgfsX56]\ +\ MYH6[p.Ala1443Asp]\ +\ DSG2[p.Val920Gly]\ +\ PSEN2[p.Arg71W]}\ S_{C\text{-}II}$



♂, 60 years $M_{D(AVB)}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA[p.Arg72Cys]}\ S_{C\text{-}II}$

FIGURE 58–1. Phenotypically similar dilated cardiomyopathy (DCM) caused by defects in different genes: precise description by MOGE(S) nosology system. The figure shows three different examples of DCM; although the clinical diagnosis is the same, the diseases are different. In the MOGE(S) notation, **M** describes the morphofunctional phenotype (hypertrophic cardiomyopathy, DCM, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) as defined in current guidelines,[1] eventually adding key markers such as atrioventricular block; **O** describes the organs affected in the given patient (eg, Heart, Skeletal muscle, Auditory, ocular systems); **G** defines whether a cardiomyopathy is genetic or not and includes information on the pattern of inheritance (autosomal dominant, autosomal recessive, X-linked, matrilineal)[3]; **E** is the precision diagnostic descriptor and specifies the cause and, in case of genetic diseases, the disease gene(s) and the mutation(s); and **S** includes New York Heart Association functional class and American Heart Association stage. The practical use is supported by a free app at http://moges.biomeris.com/moges.html (see Chap. 57).

systolic dysfunction (impaired LV ejection fraction measured using two-dimensional echocardiography) and LV dilatation (as defined by Z-score > 2 standard deviations) for LV end-diastolic volumes or diameters (according to nomograms corrected for body surface area, height, and age). Coronary angiography is routinely used to exclude coronary atherosclerosis.[1,2,17] Coronary computed tomography (CT) angiography may be considered as an alternative anatomic assessment for the evaluation of obstructive coronary artery disease. The presence of flow-limiting luminal stenosis in one or more epicardial coronary arteries is considered sufficient to assign the cause of DCM to coronary artery disease. However, coronary and/or systemic atherosclerosis and DCM can exist concurrently and be demonstrated in genetic DCM.[18] Individualized decision making and testing are often necessary to clarify the extent of the contribution made by coronary artery disease in the pathogenesis of DCM. Functional testing, as with myocardial perfusion imaging, may determine presence and/or extent of ischemia and may be useful in this regard.

In the past decade, the clinical use of cardiac magnetic resonance (CMR) has entered routine evaluation, both helping to confirm the diagnosis and adding information on the type and extent of myocardial fibrosis.[19-21] CMR may further reveal hypertrabeculation or LV noncompaction (LVNC) patterns that can be associated with DCM (see Chap. 60). Three-dimensional echocardiography may add information on valvular anatomy and remodeling morphology, particularly in patients with limited views on two-dimensional echocardiography.[22] Contrast echocardiography enhances endocardial border definition, increases accuracy to two-dimensional and three-dimensional volume assessment, and highlights trabecular anatomy; it is not needed in routine evaluation but may help in cases of suboptimal image quality.[23] Myocardial deformation imaging techniques[24] and myocardial tagging by CMR are promising contributors to the diagnosis of "early" phenotypes.[5,25]

DIAGNOSIS OF FAMILIAL DILATED CARDIOMYOPATHY: THE ROLE OF FAMILY SCREENING

In more than 60% of cases of DCM, the disease is familial, as proven by clinical family screening demonstrating that more than one member is affected or showing traits that predict the development of the disease.[5,26] The diagnosis of FDCM is formulated when at least two members of the same family are affected. The clinical workup is a three-step investigation:

1. In the proband, deep phenotyping should include a general medical evaluation of anthropometric features and the integument, hair, vision, and musculoskeletal, auditory, and nervous systems.[27] General phenotype examination can add information about clinical traits potentially associated with the DCM and provides robust clinical data for geno-phenotype correlations and segregation studies in families.
2. The next step is genetic counseling with pedigree construction and information provided to patients about why family studies are necessary when a genetic disease is suspected. The collection of the clinical history of relatives and tracing of clinical reports of deceased relatives are uniquely useful for correct interpretation of fatal events in families.[26,27]
3. The third step is family screening, which is independent of genetic testing. Clinical family screening is based on physical examination, electrocardiography (ECG), transthoracic echocardiography, and biochemical testing, followed by regular monitoring of relatives. Once completed, information gleaned from the clinical family screening may modify the original pedigree. Determination of the type of inheritance of the DCM results from integration of pedigree and family data and is essential for guiding and interpreting data generated by genetic testing.[28-30]

Data achieved in family screening studies of consecutive patients demonstrate that relatives of patients with DCM can:

- Be affected, and therefore present the criteria for diagnosis, but be asymptomatic and unaware of their disease

- Manifest early, persistent (confirmed on more than one clinical occasion) signs of LV remodeling and/or borderline dysfunction[5]
- Demonstrate electrocardiographic abnormalities such as conduction disease, short PR interval/Wolff-Parkinson-White pattern, prolonged QT interval, T-wave abnormalities, early repolarization, or abnormal high or low voltages of the QRS[5,27]
- Demonstrate abnormal biochemical markers such as increased serum creatinine phosphokinase or lactic acid
- Exhibit extracardiac traits that may also occur in probands, such as hearing loss, diabetes mellitus, cutaneous lesions, skeletal abnormalities, abnormal faces, or ocular defects[27].

Family screening may by itself offer added value for family health.[3,5,27,28,30] Monitoring of family members helps generate reliable data on the natural history of the disease (Fig. 58–2). DCM is often characterized by subtle onset and slow progression; it shows a typical age dependency of the phenotype. Overall, clinical family screening is integral and indispensable for the diagnosis of FDCM.

GENETIC DILATED CARDIOMYOPATHY

INHERITANCE AND PHENOTYPE VARIABILITY

The increasing identification of genetic defects segregating with a particular phenotype in families confirms the genetic origin of the majority of FDCMs[26] (Table 58–1). Mendelian laws and rules of matrilinear inheritance govern the transmission of cardiomyopathies (see Chap. 57). Most FDCMs are autosomal dominant diseases; a minority shows autosomal recessive, X-linked recessive, and matrilineal inheritance. X-linked dominant forms are exceptional.[28,30] In autosomal dominant FDCM, each patient has a 50% probability of transmitting the mutation to offspring; in autosomal recessive FDCM, each parent is a healthy carrier of the mutation: the risk of transmission of the mutated allele from both parents is 25%. In X-linked recessive FDCM, the risk is 50% when the carrier is the mother; when the proband is the father, all daughters are obligate carriers, whereas all sons are noncarriers. In families with matrilineal cardiomyopathies, females transmit the mutation to both male and female offspring; accordingly, both genders can be affected. Vice versa, male carriers do not transmit the mutation. Mitochondrial DNA-related cardiomyopathies can demonstrate both dilated and hypertrophic phenotypes, with the latter frequently evolving through dilation and systolic dysfunction, mimicking typical DCM in later stages.[29]

Clinical traits, both cardiac and extracardiac, may help formulate pretest hypotheses.[27] ECG or imaging markers, skeletal muscle disease, auditory defects, ocular abnormalities, gastrointestinal disturbances, renal disease, cutaneous lesions, cognitive impairment, and cryptogenic stroke can be associated with DCM caused by different disease genes. Cardiomyopathies caused by mutations in mitochondrial DNA genes are commonly observed in the clinical context of syndromes with involvement of skeletal muscle (myopathies), brain (cryptogenic stroke), ear (sensorineural hearing loss), and kidney (renal failure); in mitochondrial diseases, diabetes is common and should be considered a phenotypic trait contributing to characterization of the phenotype in the family[26-28] (Table 58–2).

GENETIC HETEROGENEITY

Genetic DCM is the paradigmatic example of how "similar phenotypes" may be caused by "different genes and mutations." More than 100 genes are now included in the list of disease and candidate genes (see Table 58–1). Attempts to group disease genes according to the pathways or structures in which their products are involved may outline macro-groups of disease genes[31-39]:

- Sarcomere genes (*TTN, MYH7, MYBPC3, TNNT2, TNNI3, MYL2, MYL3*) in 25% to 30% of DCM patients.[31] Although truncation predicting mutations in *TTN* have been reported in 25% of DCM patients,[32] confirmatory data are necessary, because 1 in 500 individuals carried truncation-predicting variants in control series[33]
- Nuclear envelop genes (*LMNA, EMD, SYNE1, TMPO*) in about 7% to 10% of cases, with *LMNA* mutations accounting for the majority of DCM in this subgroup[34-37]
- Z-disc genes (*ACTN2, ANKRD1, BAG3, CRYAB, CSRP3, FHL2, LDB3, MYPN, MURC, NEXN, PGM1, VCL*), all together accounting for less than 10% of DCM[38,39]
- Genes coding intermediate filaments connecting sarcolemma with sarcomeres (*DES*) in about 1% of cases[40]
- Mitochondrial genes, both nuclear (eg, *G4.5, CTF1, SDHA, DNAJC19*) and mitochondrial DNA genes, in less than 5% of cases[41]
- Dystrophin defects in 6% to 7% of DCM in consecutive male series and dystrophin-associated glycoprotein complex (ie, *SGCA, SGCB, SGCD*) in less than 1% of DCM cases[42-44]
- Ion channels (*SCN5A*)[45,46] or genes such as *ABCC9* or *CHRM2*, in less than 1% of cases[47,48]
- Genes whose products are active in Golgi apparatus machinery (eg, *FKTN*) or in the sarcoplasmic reticulum (*PLN*) in less than 1% of cases.[49] The prevalence of *PLN*-related DCM varies in different geographic areas. Founder mutations such as *PLN* R14del in the Netherlands accounts for more than 10% of all DCM among the Dutch population.[50]

MECHANISMS OF MYOCARDIAL DAMAGE

The mechanisms through which mutations in different genes cause functional and structural myocyte damage depend on the gene and the role of its product(s) in the myocyte, type of mutation and its effects on the protein expression, epistasis (the action of one gene upon another), and epigenetic factors. The genetic heterogeneity of DCM indicates that different types of molecular insults may end in similar phenotypes.[51] Mechanisms such as haploinsufficiency (a single functional copy of a gene is insufficient to maintain normal function) have been demonstrated in dilated cardiolaminopathies and dilated cardiodystrophinopathies.[52-54] Two genes (*LMNA* and *DMD*) typically cause DCM, with or without arrhythmias, but do not cause hypertrophic cardiomyopathy (HCM). However, most DCM genes also cause other types of cardiomyopathy (HCM, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy). The paradigmatic example is DCM caused by mutations in sarcomeric genes such as *MYH7*; the understanding of the mechanisms that cause either HCM or DCM in carriers of *MYH7* mutations is still far from being elucidated. It has been proposed that mutant myosins with enhanced contractility lead to HCM, whereas those displaying decreased contractility lead to DCM. Gain or loss of function could be the primary consequence of a specific mutation.[55]

GENETIC TESTING

Genetic testing is now routinely performed using massive parallel sequencing of multigene panels (next-generation sequencing, NGS) for both nuclear genes[3,4] and mitochondrial DNA.[56] The time needed for testing is short, and the costs are lower than with Sanger-based technologies. The mismatch between fast rate of detection and the time needed for developing functional studies that assess the effects of mutations explains the multiple pipelines generated in the last decade to contribute to the interpretation of novel genetic variants including those with uncertain significance (see Chap. 9).

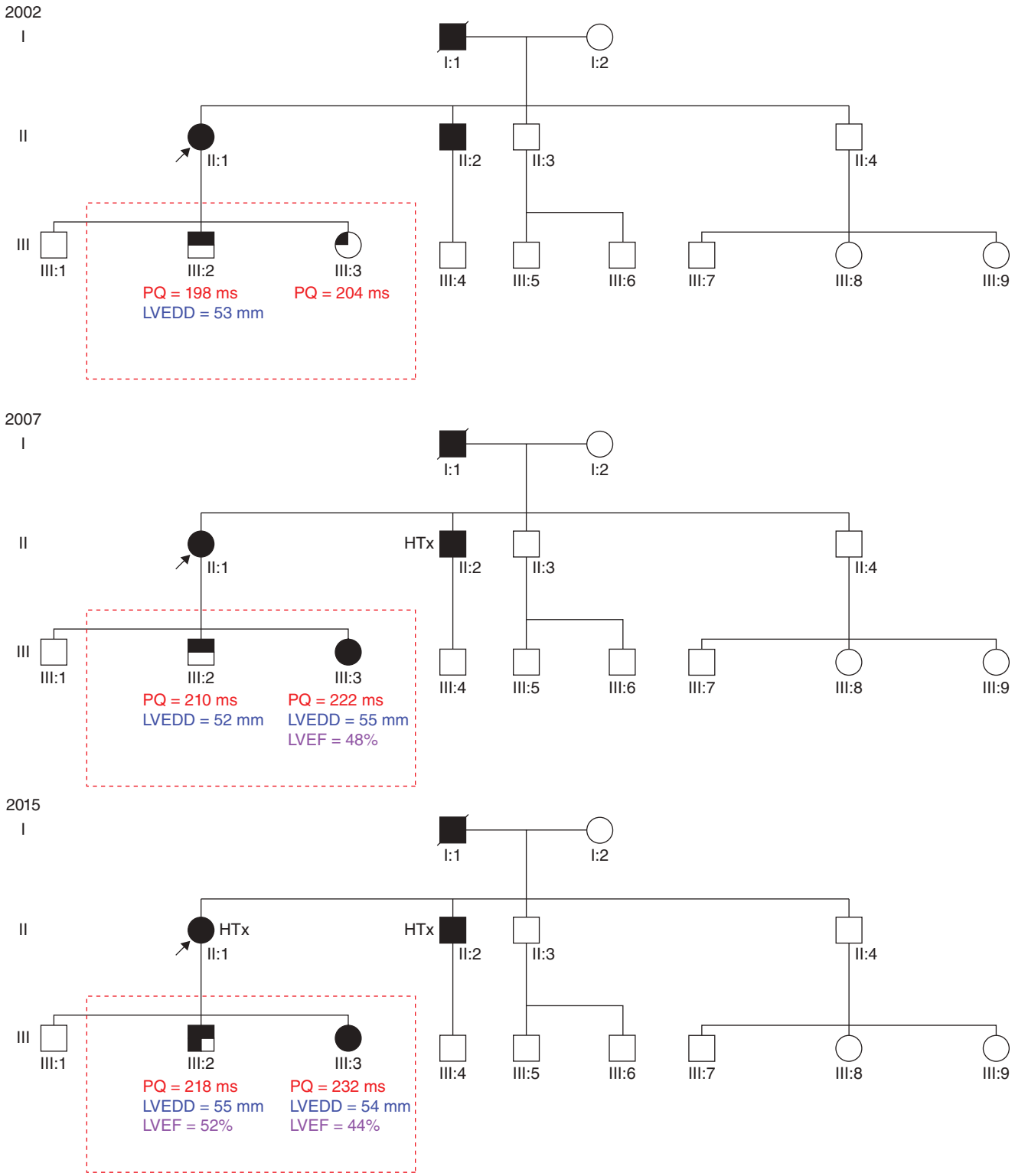


FIGURE 58–2. Dilated cardiolaminopathy. The figure shows the pedigree of a family in which the proband (II:1; *arrow*) was diagnosed with dilated cardiomyopathy (DCM) and conduction disease after the younger brother (II:2). Both siblings underwent pacemaker (PM) implantation. The father died of DCM that manifested 9 years after PM implantation; he died at age of 61 years from congestive heart failure. Clinical family screening included mother (I:2), who was hypertensive and diabetic, and the two siblings (II:3 and II:4) of the proband who showed normal left ventricular (LV) function and dimensions and normal PQ interval. The three children of the proband were screened; one (III:1) showed normal electrocardiographic (ECG) and echocardiographic features; one demonstrated borderline PQ interval and slightly increased LV end-diastolic diameter (LVEDD) diameter (III:2), and one showed atrioventricular block (AVB; III:3). Both were asymptomatic. The son of II:2 showed normal ECG and echocardiographic features. The five nephews (III:5, III:6, III:7, III:8, and III:9) of the proband showed normal ECG and echocardiographic features. *LMNA* genetic testing identified the *LMNA* p.(Arg89Leu) mutation in II:1. Cascade genetic screening in the family identified the same mutation in her brother (II:2) and in two of her offspring (III:2 and III:3). II:3, II:4, III:1, III:4 tested negative. During the course of 13 years, the daughter of the proband developed DCM, and the mutated son developed AVB, mild LV dilation, and borderline LV dysfunction. LVEF, LV ejection fraction.

TABLE 58–1. Genes Associated With DCM

Nuclear Genes	MIM[a] Gene	Protein	Other Cardiomyopathy	Phenotypes, Diseases, and Traits	Inheritance
ABCC9	601439	ATP-binding cassette, subfamily C, member 9, sulphanylurea receptor2		Cantu syndrome, hypertrichosis, familial atrial fibrillation	AD
ABLIM1	602330	Limatin (actin-binding LIM domain protein)	NC	LVNC	AD
ACTC1	102540	Cardiac actin alpha	H/R/NC	Nemaline myopathy	AD
ACTN2	102573	Alpha-actinin 2	H/NC		AD
ALMS1	606844	ALMS1-C		Alstrom syndrome (70%: DCM)	AR
ANO5	608662	Anoctamin 5		Limb girdle muscular dystrophy, gnathodiaphyseal dysplasia, Miyoshi muscular dystrophy 3; dysphagia	AR
ANKRD1	609599	Ankyrin repeat domain-containing protein 1	H		AD
BAG3	603883	BCL2-associated athanogene	H	BAG3-related myofibrillar myopathy, CRYAB-related myofibrillar myopathy, fatal infantile hypertrophy	AD
CALR3	611414	Calreticulin 3	H		AD
CASQ2	114251	Calsequestrin 2	NC		AD
CAV3	601253	Caveolin 3	H	sCPK elevated; long QT syndrome-9; muscular dystrophy, Limb-Girdle myopathy, distal, Tateyama type; Rippling muscle disease	AD
CHKB	612395	Choline kinase, beta		Muscular dystrophy, congenital, megaconial type	AR
CHRM2	118493	Cholinergic receptor, muscarinic 2		Anti-CHRM2 autoantibodies; atrial and ventricular arrhythmias	AD
CRYAB	123590	Alpha B crystallin	H/R	Posterior polar cataract	AD
CSRP3	600824	Cysteine- and glycine-rich protein 3	H		AD
CTF1	600435	Cardiotrophin 1			AD
CTNNA3	607667	Alpha 3-catenin	A	Susceptibility to Alzheimer disease	AD
DAG1	128639	Dystrophin-associated glycoprotein 1		Muscular dystrophy-dystroglycanopathy	AR
DES	125660	Desmin	H/R/A	DES-related myofibrillar myopathy, neurogenic scapuloperoneal syndrome, Kaeser type; AVB, sCPK	AD
DMD	300377	Dystrophin		Duchenne muscle dystrophy, Becker muscle dystrophy; sCPK/myopathy	XLR
DMPK	605377	Dystrophia myotonica protein kinase gene		Dystrophia myotonica type 1 or Steinert disease; AVB	AD
DOLK	610746	Dolichol kinase		Congenital disorder of glycosylation, type Im; myopathy, possible ichthyosiform dermatitis	AR
DSC2	125645	Desmocollin 2	A	With and without mild palmoplantar keratoderma and woolly hair	AD
DSG2	125671	Desmoglein 2	A		AD
DSP	125647	Desmoplakin	A	Lethal acantholytic epidermolysis bullosa, keratosis palmoplantaris striata II, skin fragility-woolly hair syndrome	AD
DTNA	601239	Dystrobrevin, alpha	NC	With or without congenital heart defects	AD
EMD	300384	Emerin		EDMD1, X-linked; AVB, myopathy, sCPK	XLR
EYA4	603550	Eyes absent 4		Deafness, autosomal dominant	AD
FHL1	300163	Four and a half LIM domains 1	H	EMDM6, X-linked myopathy, reducing body, childhood-onset, and severe early-onset myopathy with postural muscle atrophy, scapuloperoneal myopathy, XLD	XLR,XLD
FHL2	602633	Four and a half LIM domains 2			AD
FKTN	607440	Fukutin		Muscular dystrophy-dystroglycanopathy (with brain and eye anomalies), type A,4; (without mental retardation), type B,4; (Limb-Girdle), type C,4	AR
FHOD3	609691	FH1/FH2 domain-containing protein 2			AD
FOXD4	611080	Forkhead box D4-like 3		DCM with obsessive-compulsive disorder and suicidality	AD
GATA4	600576	GATA-binding protein 4		Congenital heart disease	AD
GATA5	611496	GATA-binding protein 5			AD
GATA6	601656	GATA-binding protein 6		Congenital heart disease	AD,AR

(*continued*)

TABLE 58–1. Genes Associated With DCM (*Continued*)

Nuclear Genes	MIM[a] Gene	Protein	Other Cardiomyopathy	Phenotypes, Diseases, and Traits	Inheritance
GATAD1	614518	GATA zinc finger domain containing protein 1			AR
HRC	142705	Histidine-rich calcium binding protein		Arrhythmogenic DCM	AD
ILK	602366	Integrin-linked kinase			AD
JUP (DP3)	173325	Plakoglobin, desmoplakin III	A	Naxos traits	AD, AR
LMNA	150330	Lamin AC	A/NC	DCM with conduction disease plus 11 additional phenotypes; AVB; possible sCPK	AD
LAMA2	156225	Laminin alpha, 2		Congenital merosin-deficient muscular dystrophy type 1A	AR
LAMA4	600133	Laminin alpha, 4			AD
LDB3	605906	LIM domain-binding 3	H/NC	ZASP-related myofibrillar myopathy; LVNC, possible > sCPK; Hypertrabeculation	AD
LIMS1	607908	LIM and senescent cell antigen like domains 1			AD
LIMS2	602567	LIM and senescent cell antigen like domains 2			AD
MIB1	608677	Midbomb, homolog of, *Drosophila*	NC	LVNC	AD
MURC	602633	Muscle-related coiled-coil protein, Z-line protein			AD
MYBPC3	600958	Myosin-binding protein C	H/NC		AD
MYH6	160710	Alpha-myosin heavy chain 6	H	Atrial septal defect, sick sinus syndrome	AD
MYH7	160760	Beta-myosin heavy chain 7	H/R/NC	Laing distal myopathy; myosin storage myopathy; scapuloperoneal syndrome, myopathic type; possible sCPK	AD
MYH7B	609928	Myosin heavy chain 7B	H/NC	Congenital myopathy?	AD, AR
MYL2	160781	Myosin light chain 2	H		AD
MYL3	160790	Myosin light chain 3	H/R		AD, AR
MYOZ1	605603	Myozenin 1,	H		AD
MYOZ2	605602	Myozenin 2	H		AD
MYPN	608517	Myopalladin	H/R		AD
NEBL	605491	Nebulette			AD
NEXN	613121	Nexilin	H		AD
NKX2-5	600584	NK2 homeobox 5; cardiac specific homeobox 1		Possible conduction system disease; congenital heart diseases; hypothyroidism; congenital nongoitrous	AD
OBSCN	608616	Obscurin	NC		AD, AR
PDLIM3	605889	PDZ and LIM domain protein 3			AD
PLN	172405	Phospholamban	A		AR
PLEKHM2	609613	Pleckstrin homology domain containing protein, family M, member	NC		AR
PKP2	602861	Plakophilin 2	A		AD
PRDM16	605557	PR domain containing 16	NC	LVNC	AD
PSEN1	104311	Presenilin 1		Familial acne inversa, 3; Alzheimer disease, 3; frontotemporal dementia; Pick disease	AD
PSEN2	600759	Presenilin 2		Alzheimer disease, type 4	AD
RBM20	613171	RNA-binding motif protein 20			AD
RYR2	180902	Ryanodine receptor 2	A/NC	Ventricular tachycardia, catecholaminergic polymorphic, 1	AD
SCN5A	600163	Sodium channel, voltage gated, type V, alpha subunit		LQT3, Brugada, atrial fibrillation, sick sinus syndrome, familial VF	AD
SDHA	600857	Succinate dehydrogenase subunit A		Leigh syndrome, MT respiratory chain complex II deficiency, paragangliomas, 5	AD, AR
SGCA	600119	α-Sarcoglycan		Limb-girdle muscular dystrophy, 2D	AR
SGCD	601411	Delta-sarcoglycan		Limb-girdle muscular dystrophy	AD
SYNE1	608441	Nesprin 1, synaptic nuclear envelop protein 1		EMD4, AD; spinocerebellar ataxia, autosomal recessive	AD, AR
SYNE2	608442	Nesprin 2, synaptic nuclear envelope protein 2		EMD5, AD	AD

(*continued*)

TABLE 58–1. Genes Associated With DCM (*Continued*)

Nuclear Genes	MIM[a] Gene	Protein	Other Cardiomyopathy	Phenotypes, Diseases, and Traits	Inheritance
TBX5	601620	T-box 5		Holt-Oram syndrome; CHD	AD
TBX20	606061	T-box 20		Atrial septal defect; CHD	AD
TCAP	604488	Titin-cap; telethonin	H	Muscular dystrophy, Limb-Girdle, type 2G; sCPK	AD
TCF21	603306	Transcription factor 21, epicardin		Hearing loss	AD
TGFB3	190230	Transforming growth factor beta 3	A	Rienhoff syndrome	AD
TMEM43	612048	Transmembrane protein 43	A	Emery-Dreifuss muscular dystrophy, AD	AD
TMPO	188380	Thymopoietin			AD
TNNC1	191040	Cardiac troponin C	H/R		AD
TNNI3	191044	Cardiac troponin I3	H/R/NC		AD
TNNI3K	613932	TNNI3-interacting kinase	R		AD
TNNT2	191045	Cardiac troponin T2	H/R/NC		AD
TPM1	191010	Tropomyosin 1	H/R/NC	Limb-girdle muscular dystrophy, early-onset myopathy with fatal CMP, proximal myopathy with early respiratory muscle involvement, tardive tibial muscular dystrophy	AD
TTN	188840	Titin	H/A		AD
VCL	193065	Vinculin	H		AD
AGK	610345	Acylglycerol kinase	H/NC	Cataract, myopathy, Senger syndrome	AR
ANT1 (PEOA2)	103220	Adenin nucleotide translocator 1	H	Mitochondrial DNA depletion syndrome 12 (cardiomyopathic type), AD-PEO with multiple mtDNA deletions	AD, AR
COX10	602125	Cytochrome C oxidase assembly protein, 10	H	Leigh syndrome due to mitochondrial COX4 deficiency	AR
COX15	603646	Cytochrome C oxidase assembly protein, 15		Cardioencephalomyopathy, fatal infantile as a result of COX deficiency 2	AR
DNAJC19	608977	DNAJ/HSP40 homolog, subfamily C, member 19	H	3-Methylglutaconic aciduria type V	AR
FXN	606829	Frataxin	NC	Friedreich ataxia, Friedreich ataxia with retained reflexes	AR
G4.5	300394	Tafazzin	H	Barth syndrome	XLR
NDUFB11	300403	NADH dehydrogenase 1b, subcomplex 11		Linear skin defects with multiple congenital anomalies	XLR
NDUFS2	602985	NAD-ubiquinone oxidoreductase Fe-S protein 2	H	Encephalopathy, MT complex I deficiency	AR
NDUFV2	600532	NAD-ubiquinone oxidoreductase flavoprotein 2	H	Hypotonia, encephalopathy, MT complex I deficiency	AR
POLG (PEOA1)	174763	DNA polymerase	H	Alpers-type syndrome, MNGIE type, AD-PEO and AR-PEO, SANDO syndrome, SCAE	AD, AR
SCO2	604272	Homolog of *Saccharomyces cerevisiae*, 2	H	Fatal infantile cardioencephalomyopathy as a result of COX1 deficiency	AR
SDHA	600857	Succinate dehydrogenase complex subunit A	H	Leigh syndrome, mitochondrial respiratory chain complex II deficiency, paragangliomas	AR
TMEM70	612418	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2		Neonatal mitochondrial encephalocardiomyopathy with ATP synthase deficiency	AR
PTPN11	176876	Protein tyrosin phosphatase, nonreceptor type 11	H	Noonan syndrome type 1; LEOPARD type 1	AD
KRAS	190070	V-KI-RAS2 Kirsten Rat sarcoma viral oncogene homolog	H	Noonan syndrome type 3; cardiofaciocutaneous syndrome type 2	AD
RAF1	164760	V-RAF-1 murine leukemia viral oncogene homolog 1	H	Noonan syndrome type 5, LEOPARD syndrome type 2	AD
NRAS	164790	Neuroblastoma RAS viral oncogene homolog	H	Noonan syndrome type 6	AD
RIT1	609591	Ric-like protein without CAAL motif 1	H	Noonan syndrome type 8	AD

Note. The table lists all genes reported to date to be associated with DCM; some of them are confirmed and replicated in several series. Other genes have been reported in small series of single families. The "Other Cardiomyopathy" column shows other cardiomyopathy phenotypes that have been reported as associated with mutations in the same genes.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; ATP, adenosine triphosphate; AVB, atrioventricular block; CHD, congestive heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MNGIE, mitochondrial neurogastrointestinal encephalopathy; MT, mitochondrial; NC, left ventricular noncompaction; PEO, progressive external ophthalmoplegia; RCM, restrictive cardiomyopathy; SANDO, sensory ataxia neuropathy dysarthria and ophthalmoplegia; SCAE, spinocerebellar ataxia with epilepsy; sCPK, serum creatine phosphokinase; VF, ventricular fibrillation; XLD, X-linked dominant; XLR, X-linked recessive.

TABLE 58–2. Clinical and Instrumental Markers to Be Annotated and Potentially Useful for Formulating Pretest Clinical Hypotheses of Specific Genetic DCMs or Syndromes

	Proband	Feature/Marker/Trait	Gene/s	Inheritance
ECG	M or F	AVB	*LMNA*	AD
	M		*EMD*	XLR
	M or F		*DES* (usually RCM)	AD, AR
	M or F	Short PR with or without WPW	*MtDNA*	Matrilineal
	M or F	Low QRS voltage	*PLN*[a]	AR
	M or F	High QRS voltage	Sarcomere genes	AD
	M or F	Increase or decrease QT interval	Ion channel genes	AD
	M	Atrial standstill/giant atria	*EMD*	XLR
	M or F		*NPPA*	AR
	M or F	SSS/atrial disease with/without DCM	*SCN5A*	AR
	M	Posterolateral Q waves	*DMD*	XLR
TTE and CMR	M	Left ventricular noncompaction Left ventricular hypertrabeculation	*G4.5*	XLR
	M or F		*LDB3*	AD
	M or F		*MIB1*	AD
	M or F		*DTNA*	AD
	M or F		*MtDNA*	Matrilineal
	M or F		*PRDM16*	AD
	M or F		*ACTN2*	AD
	M or F		*TNNT2, MYH7, MYBPC3, ACTC1, TPM1, DES*	AD
Biochemistry	M	> sCPK[b]	*DMD*	XLR
	M or F		*LMNA*	AD, AR
	M or F		*FKTN*	AR
	M or F		*LDB3*	AD
	M; M or F		DAG-related genes	AD, AR, XLR
	M		*EMD*	XLR
	F	> sCPK	Healthy carriers of *DMD* defects	XLR
	M	> sCPK[b]	Muscle dystrophies/myopathies	XLR
	M	> Lactacidemia	Mitochondrial diseases	AD, AR, matrilineal
	M	Hypocholesterolemia	*G4.5*	XLR
	M	Methylglutaconic aciduria/organic aciduria	*G4.5*	XLR
	M or F		*DNAJC19*	AR
	M	Leukocytopenia	*G4.5*	XLR
	M or F	Hypomagnesemia	*MtDNA*	Matrilineal
	M or F	Myoglobinuria	*MtDNA*	Matrilineal
Extracardiac Traits	M or F	Sensorineural hearing loss	*MtDNA*	Matrilineal
	M or F		Nuclear genes coding Mt proteins	AD, AR
	M or F		*Epicardin*	AD
	M or F		*EYA4*	AD
	M or F	Cryptogenic stroke	*MtDNA*	Matrilineal
	M or F	Fahr syndrome	*MtDNA*	Matrilineal
	M or F	Palpebral ptosis	*POLG1* and other nuclear genes coding mitochondrial proteins	AD
	M or F		*ANT1*	AD
	M or F		*MtDNA* genes	Matrilineal
	M; M or F	Myopathy/dystrophy[b]	Multiple genes	AD, AR, XLR

(*continued*)

TABLE 58–2. Clinical and Instrumental Markers to Be Annotated and Potentially Useful for Formulating Pretest Clinical Hypotheses of Specific Genetic DCMs or Syndromes (*Continued*)

	Proband	Feature/Marker/Trait	Gene/s	Inheritance
	M or F	Cataract	*CRYAB*	AD
	M or F		*AGK*	AR
	M or F	Palpebral ptosis	*POLG*	AD
	M or F	Diabetes[c]	*MtDNA*	Matrilineal
	M or F	Renal failure	*ALMS1*	AR
	M or F	Finger abnormalities	*TBX5*	AD
	M or F	Brachydactyly, mild hand; severe foot involvement	*LMNA*	AD
	M or F	Learning disability[d]	*MtDNA*	Matrilineal
	M		*LAMP2*	XLR
	M or F	Ataxia with and without retained reflexes	*FXN*	AR
	M or F	Woolly hair and keratoderma	*DSP*	AR
	M or F	Woolly hair, keratoderma, and tooth agenesis	*DSP*	AD
	M or F	Cutaneous collagenoma of the occipital scalp	*LMNA*	AD
	M or F	Hypergonadotropic hypogonadism (Malouf syndrome)	*LMNA*	AD
	M or F	Valproate-induced brain pseudoatrophy	*MTATP8*	Matrilineal
	F	Corpus callosum agenesis	*NDUFB11*	XLD
	M or F	Ataxia, 3-methylglutaconic aciduria	*DNAJC19*	AR
	M or F	Lipodystrophy	*LMNA*	AD
	M or F	Progeria and other premature aging syndromes	*LMNA*	AD
	M or F	Tautness of the skin, restrictive dermopathy	*LMNA*	AR
	M or R	Hypoplastic mandible with severe dental anomalies	*LMNA*	AR
Endomyocardial Biopsy	M or F	Histiocytoid cardiomyopathy	*MTCYB*	Matrilineal
	F		*NDUFB11*	XLD
	M or F		*AARS2*	AR
	M or F	Loss of endothelial cell loss[e]	*LAMA4*	AD
	M or F	Loss/irregular expression of nuclear Lamin[ac]	*LMNA*	AD
	M	Loss of expression of dystrophin, sarcolemma	*DMD*	XLR
	M	Loss of expression of emerin, nuclear membrane	*EMD*	XLR
	M or F	Severely reduced activity of complex II	*SDHA*	AR
	M or F	Decreased desmosomes, intercalate disc "paleness"[e]	*DSG2*	AD
	M or F	Desmin positive granulophilamentous material[e]	*DES*	AD, AR
	M	Loss of expression of LAMP2	*LAMP2*	XL
	M or F	Mitochondrial proliferation and abnormalities	*MtDNA* genes	Matrilineal
	M		*G4.5*	XLR
	M or F		Nuclear "mitochondrial" genes	AR, AD
	M or F	Myocyte iron storage	*FXTN*	AR

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AVB, atrioventricular block; CMR, cardiac magnetic resonance; DAG, dystrophin-associated glycoproteins; DCM, dilated cardiomyopathy; ECG, electrocardiogram; F, female; M, male; RCM, restrictive cardiomyopathy; sCPK, serum creatine phosphokinase; SSS, sick sinus syndrome; TTE, transthoracic echocardiography; WPW, Wolff-Parkinson-White; XLD, X-linked dominant; XLR, X-linked recessive.

[a]Up to 15% DCM and arrhythmogenic right ventricular cardiomyopathy in the Netherlands.

[b]The list includes several genes known to cause muscle dystrophies/myopathies.

[c]Common in families with mitochondrial DNA–related cardiomyopathies.

[d]More common in patients with hypertrophic cardiomyopathy.

[e]To be confirmed. Never observed to date in DCM phenotypes.

For several disease genes, a proven cause-and-effect relationship between gene mutations and disease is now robust enough to assign a diagnostic role to genetic testing; the causal link of the mutation with the disease is still provisional for several other candidate genes, especially those reported in one or a few families and still unconfirmed in larger series. Interpretation of genetic testing is the challenge of the next decade, considering that when multiple genes are tested and the gene panels include giant genes such as *titin* (*TTN*) or large and complex genes such as *Duchenne muscle dystrophy* (*DMD*) and *obscurin*, the probability of finding more than one mutation/individual increases.[3] Further developments are needed to generate efficient tools for exploring the functional effects and pathologic role of mutations, especially when considering that most heritable DCMs are Mendelian diseases transmitted through an autosomal dominant mode, a rule that does not change even in families in which more than one mutation is identified. This implies that one major (or leading) mutation or two mutations inherited from the same affected parent, play a causative role, with other variants potentially acting as phenotype modifiers. Misinterpretation of the role of the mutation in the pathogenesis of the DCM may have severe implications for the patient and family, especially when procreative plans include prenatal diagnosis.

The proportion of DCM causally linked with known genes can be posted as definite (ie, *LMNA, DYS*, and sarcomere genes) or considered provisional, especially among genes that have been reported in unique families/cases. Ethnic variations and founder mutations may explain different prevalence of mutations in disease genes; for example, *PLN* p.(Arg14Del) is rare in the general population but causes more than 10% of all FDCMs in the Netherlands.[50] Most studies available at the end of 2015 have been performed either testing a single gene or a few genes in different clinical series. In the future, the genetic epidemiology of DCM could change based on the results achieved with NGS testing panels of genes in large clinical series. At present, genetic defects are identified in about 60% of FDCM; this implies that additional disease genes will be added to this list.

The interpretation of the role of a putative mutation in a given family is a multistep process that is:

1. Predicted by the results and analysis of NGS tests: Pipelines starting from raw data that include thousands of genetic variants/patients and ending with one or a few probable or possible disease mutation(s).
2. Based on consolidated evidence of pathogenicity for known mutations: automated collection of information on mutations that have been previously reported and proven as pathogenic requires disease specific expertise and regular monitoring of disease databases. Identification of a mutation, while integral to the assignment of pathogenicity, cannot by itself, at least in some instances, be sufficient to establish pathogenesis. For example, although truncation-predicting mutations are likely to be pathologic, a few of them occur in nonaffected individuals and should be considered either nonpathologic or variants of uncertain significance.
3. Confirmed by in vivo or in vitro functional and pathologic studies (Fig. 58–3): either endomyocardial biopsy with immunohistochemical study of the protein coded by the mutated gene or in vitro studies on fibroblasts or induced pluripotent stem cell–derived myocytes obtained from circulating cells or fibroblasts from patients who carry the putative mutation.
4. Integrated into a clinical context, based on segregation studies in families (Fig. 58–4): mutated family members are affected and nonmutated members are not affected. Healthy mutation carriers are usually younger than affected mutated family members.

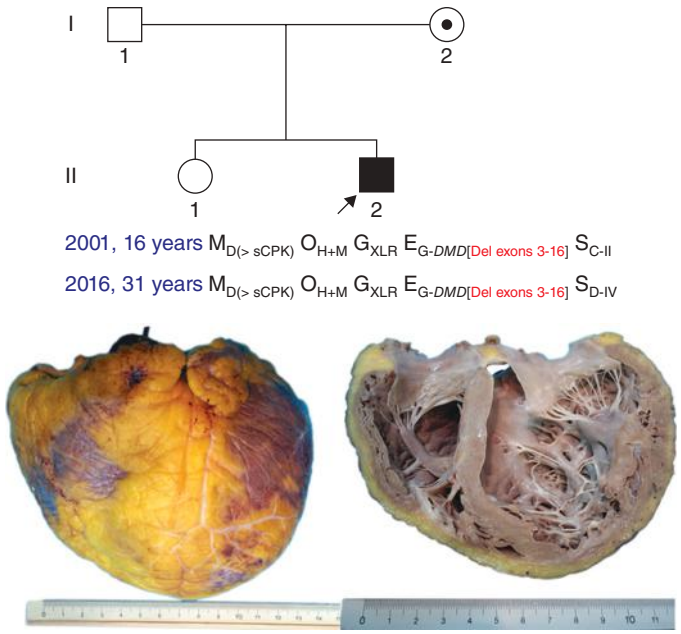


FIGURE 58–3. Dilated cardiodystrophinopathy. The figure shows the pedigree and the macroscopic view of a heart with dilated cardiomyopathy (DCM) from a young male patient who developed DCM at the age of 16 years; the disease showed slow progression to end-stage heart failure, and the patient underwent heart transplantation 15 years later. The dystrophin defect is not associated with severe muscle dystrophy.

The overall evidence gained by the combination of the above criteria should establish whether a mutation is pathologic and, therefore, should be posted as a disease-causing mutation.

GROUPING GENETIC DILATED CARDIOMYOPATHY BY DISEASE GENE

Although to date more than 100 disease and candidate genes have been associated with DCM, only a few of them have been confirmed and replicated in more clinical series and families. In addition, clinical markers typically recurring in DCM caused by mutations in these genes are now consolidated contributors in the pretest clinical orientation about the possible disease gene to be tested in the probands.[27] The following examples have been selected based on different criteria: cardiolaminopathies because of their high arrhythmogenic risk (they represent the first genetic DCM formally recognized based on the disease gene and types of mutations in guidelines for primary prevention of sudden death with implantable cardioverter-defibrillator [ICD] implantation); cardioemerinopathies because, although very rare, their phenotype may look similar to cardiolaminopathies (DCM with conduction disease and myopathy) but with different pattern of inheritance (X-linked recessive vs autosomal dominant); cardiodystrophinopathies because they may represent the major or unique phenotype in male patients with DCM and are associated with increased serum creatine phosphokinase in > 80% of cases; cardiozaspopathies because of the frequent association with prominent trabecular anatomy of the LV; cardiomyosinopathies because defects of the structural and regulatory myosin complex of the sarcomere may cause typical HCM but also DCM and HCM-DCM (ie, a phenotype that in the end-stage phases is similar to DCM but frequently maintains ECG features suggestive of LV hypertrophy); dilated cardioMITOmyopathies because of their high malignancy and the syndromic context in which the cardiomyopathy is observed; cardiotitinopathies because of their high

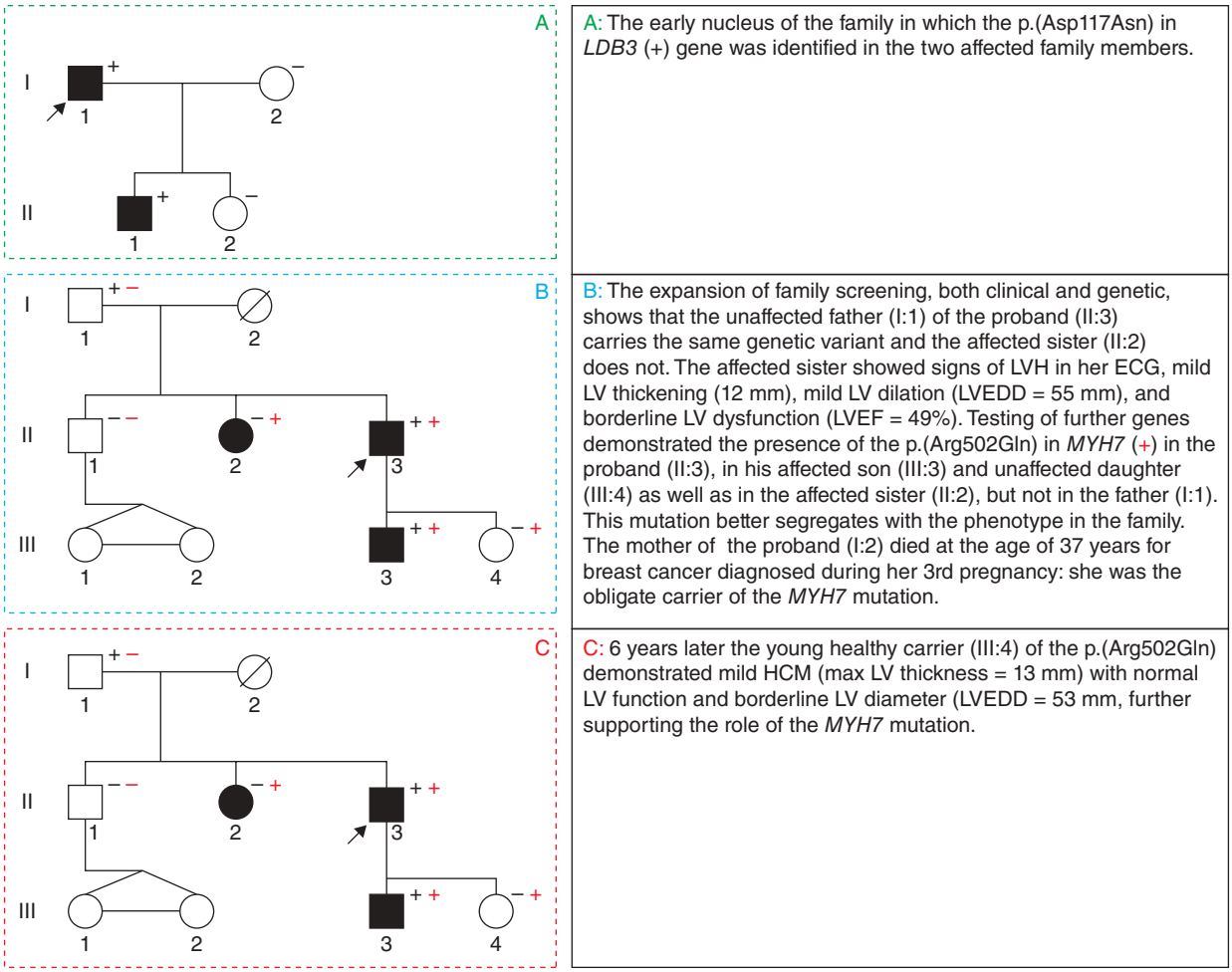


FIGURE 58–4. Segregation study in families. The figure shows the pedigree of a family in which the first genetic testing in the proband identified a genetic variant in the *LDB3* gene originally considered as the potential cause of the disease (**A**). Clinical and genetic family screening demonstrated that the variant did not segregate with the phenotype (**A** and **B**). Further genetic testing in the proband identified a second mutation in the *MYH7* gene (**B** and **C**). Long-term follow-up of the family supported the segregation of this latter mutation in the family (**C**). ECG, electrocardigram; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVH, left ventricular hypertrophy.

prevalence in DCM series; and phospholambanopathies because of the high arrhythmogenic risk and peculiar ECG markers.

Dilated Cardiolaminopathies

This subgroup of DCM can be described as dilated cardiolaminopathies, or DCM-LMNA; an individual description can be provided by the simple use of the MOGE(S) system (morphofunctional phenotype, organ involvement, genetic inheritance pattern, etiologic annotation including genetic defect or underlying disease/substrate, and functional status of the disease) supported by on online tool at http://moges.biomeris.com/moges.html (see Chap. 57). DCM-LMNA is phenotypically characterized by the association of the DCM with conduction system disease, which occurs in up to 80% of patients with cardiolaminopathies.[57] In the past 15 years, the association between *LMNA* gene mutations and DCM with conduction system disease has been replicated and confirmed.[58-60] Dilated cardiolaminopathies constitute 6% to 7% of all DCMs in consecutive series.[39] The development of conduction system disease usually precedes the appearance of the DCM[7,16]; the natural history is characterized by a long asymptomatic phase in which regular monitoring demonstrates a progressive prolongation of the PR interval and slowly progressive LV dilation and/or dysfunction. Cardiolaminopathies display high arrhythmogenic potential for both atrial and ventricular arrhythmias. The high risk of life-threatening ventricular arrhythmias is one of the characteristics of cardiolaminopathies, and such arrhythmias may manifest even in mildly dilated and dysfunctioning hearts.[59-62] Recent guidelines on the primary prevention of sudden cardiac death (SCD) recommend ICD implantation in patients with DCM and a confirmed disease-causing *LMNA* mutation and such clinical risk factors (Class IIa, Level B)[63] as nonsustained ventricular tachycardia during ambulatory ECG monitoring, LV ejection fraction (LVEF) < 45% on initial evaluation, male gender, and nonmissense mutations (insertion, deletion, truncation, or mutations affecting splicing). These factors correspond to those previously identified in a large European cohort of patients with dilated cardiolaminopathy.[60]

Dilated Cardioemerinopathies

Dilated cardioemerinopathies, or DCM-EMD, constitute a small subgroup of DCM but also provide a paradigmatic example of rare DCM that may phenotypically mimic cardiolaminopathies.[30,35] They are, in fact, typically associated with conduction disease; different

from cardiolaminopathies, they are inherited as X-linked recessive diseases and associated with muscle dystrophy. This latter feature is also possible in DCM-LMNA but less common. Emerin is a ubiquitous protein, major component of the nuclear envelope, and member of the nuclear lamina-associated protein family. Defects in emerin (EMD) cause X-linked recessive Emery-Dreifuss muscular dystrophy. Cardiac involvement is common and manifests with palpitations, presyncope and syncope, poor exercise tolerance, and heart failure. The clinical management includes treatments for cardiac arrhythmias, atrioventricular conduction disorders, and congestive heart failure, including antiarrhythmic drugs, cardiac pacemaker, ICD, and heart transplantation for end-stage heart failure.[35,64] Conduction disease is therefore the marker of the disease in patients with X-linked inheritance and DCM; the immediate clinical differential diagnosis with autosomal dominant laminopathies is the inheritance pattern.

Dilated Cardiodystrophinopathies

Dilated cardiodystrophinopathies, or DCM-DYS, typically manifest in male patients who carry large *DMD* gene rearrangements, both in-frame and out-of-frame deletions (> 80%)[42,43]; in a minority of cases, mutations are either nonsense or missense or splice. Mutations are associated with loss of protein expression at the level of the cardiomyocyte sarcolemma.[43] *DMD* gene (MIM#300377) mutations cause the following three phenotypes: Duchenne muscular dystrophy (MIM#310200), Becker muscular dystrophy (MIM#300376) and X-linked DCM (MIM#302045). Most data on cardio-phenotypes have been generated in series of patients with Duchenne muscular dystrophy and Becker muscular dystrophy; single case reports and a few series explored patients presenting with DCM phenotype at onset.[42,43] Milasin et al[65] first described a family with X-linked DCM associated with a splice donor site mutation in the *DMD* gene. Antidystrophin immunostain showed reduced but normally distributed protein in the skeletal muscle and no detectable protein in the myocardium suggesting that selective heart involvement in DCM-DMD is related to the absence in the heart of a compensatory expression of dystrophin from alternative promoters.[65] This case generated a cardio-specific interest; further reports of single cases demonstrated that mutations in the *DMD* gene may exclusively or predominantly affect the heart, with normal or early involved skeletal muscle.[66,67] The precise diagnosis can be missed and eventually determined after heart transplant, when muscle dystrophy may manifest and be attributed to statin treatments.[68]

Although rare, the above past studies facilitated the feasibility of heart transplantation in either patients with X-linked DCM or Becker muscular dystrophy with DCM as a major and initial presentation of dystrophinopathy (see Fig. 58–3). The diagnosis of X-linked DCM-DYS is feasible by endomyocardial biopsy, which demonstrates loss of protein expression; genetic testing confirms the diagnosis.[42,43] X-linked DCM-DYS carries a low arrhythmogenic risk even when patients show severely dilated and dysfunctioning hearts, requiring ICD for primary prevention of SCD according to current guidelines. No ICD shock was observed during a median follow-up of 14 months (interquartile range, 5-25 months) in 34 patients with DCM caused by defects of dystrophin.[43] DCM-DMD may show LVNC, which occurs in about 30% of cases and is now proposed as a prognostic marker.[69,70] The recent introduction of ventricular assist device implantation in children affected by DMD opens novel avenues for treatment of the most severe forms of DCM-DMD.[71,72]

Dilated Cardiozaspopathies

This small subgroup of DCM is caused by mutations in the *LDB3* gene that codes the Z-disc Cypher-ZASP protein. *LDB3* mutations were originally reported in adult-onset, isolated, dilated LVNC cardiomyopathy[73] (OMIM*605906.0007) (see Chap. 60). Therefore, LVNC and LV hypertrabeculation are the clinical markers that characterize DCM hearts of patients who are carriers of mutations in *LDB3*.[74-77] Mutations in the *LDB3* gene seem to also be associated with HCM[78] and myofibrillar myopathy type 4.[79] The more common "variant" in this gene is p.(D117N), which has been recently reported to represent a polymorphism in a Bedouin population in which it occurs in 5.2% of nonaffected individuals.[80] The possibility exists that mutations in *LDB3* may influence trabecular anatomy, leading to either increased trabeculation or LVNC, which by itself only describes an anatomic feature and not necessarily a functional phenotype. Although available data are not sufficient to post *LDB3* as a disease gene specifically associated with both DCM and LVNC, this latter marker should be a matter of further investigation in *LDB3* hearts to definitely assess its role in the trabecular anatomy of DCM hearts.

Dilated Cardiomyosinopathies

Recent studies have focused on the question of why mutations in the *MYH7* gene that typically cause HCM may also be associated with the development of DCM[55] rather than the most common HCM. In murine models investigating the S532P and F764L mutations in the *MYH7* gene and associated with the DCM phenotype, the molecular mechanism leading to DCM may be the depressed molecular function in cardiac myosin, which may initiate heart remodeling and pathologic dilation. Accordingly, mutations that lead to DCM may be those that are associated with loss of function; those that are associated with gain of function may be associated with HCM.[55,81] The reconstitution of the entire contractile system (actin and myosin[82,83] and tropomyosin 1, troponin C, troponin I, and troponin T[84,85]) seems to be necessary to fully understand the effects of *MYH7* mutations in HCM and DCM.[86] Alternative explanations include the possibility of compound mutations in mitochondrial DNA genes and in the *MYH7* gene; patients who carry the sole *MYH7* mutation demonstrate HCM, whereas those carrying both *MYH7* and mitochondrial DNA mutations develop hypertrophic dilated cardiomyopathy with an end phenotype resembling DCM.[87] Yet another explanation is the presence of more than one mutation in the same patient; depending on the mutation, the DCM phenotype should be explained by a complex genetic make-up when more than one mutation is present and contributing to the final phenotype.[28,30] Overall, the role of *MYH7* in DCM remains a matter of research and deserves specific investigation for any novel mutation identified in patients with DCM.

Dilated CardioMITOmyopathies

In this subgroup of patients, the DCM is usually observed in the context of multiorgan syndromes with a peculiar risk of complications such as cryptogenic strokes and intolerance to several drugs.[28-30,41,56] Mitochondrial cardiomyopathies can be caused by mutations both in mitochondrial DNA genes (maternal inheritance) and in nuclear genes (Mendelian inheritance: no male passes down the disease to children) coding mitochondrial proteins. They are characterized by either hypertrophic phenotype evolving through dilated and dysfunctioning hearts or DCM (Fig. 58–5). The clinical manifestations associated with mutations in mitochondrial DNA genes depend on the grade of heteroplasmy in affected organs. They are commonly observed in families in which mutation carriers also express noncardiac traits such as hearing loss, palpebral ptosis, myopathy, renal failure, cryptogenic stroke, diabetes, optic neuritis, and/or retinitis pigmentosa. Sequencing of mitochondrial DNA, either by Sanger-based techniques or NGS tools, identifies the causative mutation. Nuclear "mitochondrial"

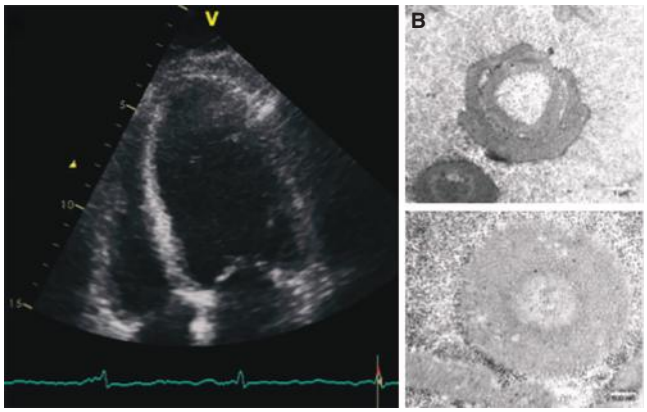


FIGURE 58–5. Mitochondrial cardiomyopathy. This figure shows the echocardiographic view (A) of the dilated cardiomyopathy (DCM) in a 53-year-old woman affected by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome. Her endomyocardial biopsy (B and C) showed typically abnormal mitochondria. The DCM phenotype was associated with hearing loss and mild myopathy.

cardiomyopathies are inherited according to Mendelian rules: they can be autosomal dominant or recessive. Typical cardiac phenotypes are primarily DCM, such as in the autosomal recessive DCM caused by *ANT1* mutations[88] or in autosomal dominant DCM and progressive external ophthalmoplegia caused by *POLG1* mutations.[89]

Dilated Cardiotitinopathies

The *titin* (*TTN*) gene encodes the largest human protein and the third most abundant striated muscle protein.[90] Of the different titin isoforms, the N2B and N2BA isoforms are predominantly expressed at the cardiac level[91]; the cardiac isoform Novex-3 titin (5600 amino acids) is less represented in cardiac tissue than full-length titin.[92] Truncation-predicting mutations have been identified in 25% of FDCMs and in 18% of sporadic DCMs.[32] The penetrance of *TTN* truncating mutations was more than 95% for patients who were older than 40 years of age. Clinical manifestations, morbidity, and mortality were similar to those observed in DCM patients who were noncarriers of *TTN* mutations. DCM was not accompanied by conduction system or skeletal muscle disease.[32] A further study in women with peripartum cardiomyopathy showed a distribution of truncating variants remarkably similar to that found in patients with DCM.[93] Missense variants have been further investigated in DCM distinguishing "bioinformatically severe" *TTN* versus nonsevere variants; carriers of "severe *TTN* variants" showed a clinical course similar to that of noncarriers.[94] *TTN* mutations have been involved in HCM (MIM#613765); muscular dystrophy of the Limb-Girdle, type 2J (MIM#608807); autosomal recessive early-onset myopathy with fatal cardiomyopathy (MIM#611705); tardive tibial muscular dystrophy (MIM#600334); and proximal myopathy, with early respiratory muscle involvement (MIM#603689).[95-98] Because 1 in 500 individuals in the general population carries a truncation variant in the *TTN* A-band, the interpretation of such mutations in DCM should be cautious.[33] The relevance of defining the precise role of *TTN* in DCM is now supported by the possibility that antisense-mediated exon skipping can be explored as a therapeutic strategy.[99]

Dilated Phopsholambanopathies

Dilated phopsholambanopathies are a distinct group of DCM caused by mutations in the *Phospholamban* (PLN) gene that encodes a protein expressed in the sarcoplasmic reticulum membrane. Phospholamban inhibits cardiac muscle sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) in the unphosphorylated state. Mutations in *PLN* impair sarcoplasmic reticulum calcium homeostasis and cause DCM.[50,100,101] Less commonly, mutations in *PLN* cause HCM.[102] p.(Arg14del) is the most frequently identified mutation in Dutch cardiomyopathy patients (10%-15%), both DCM and arrhythmogenic phenotypes.[50] Patients with p.(Arg14del) diagnosed with DCM demonstrate high arrhythmogenic risk and SCD as first disease presentation.[103] A common ECG pattern in *PLN* mutation carriers is a low-voltage QRS complex and inverted T waves in leads V_4 to V_6.[104] In non-Dutch patients, *PLN* mutations are less common but equally malignant.[105,106] Therefore, although rare, PLN mutations can be clinically suspected in patients with DCM, high arrhythmogenic risk, and low voltage on ECG.

Future Developments in Genetic Dilated Cardiomyopathy

As the number of patients and families diagnosed with DCM caused by different disease genes increases, the possibility of generating large groups of patients with shared genotypes and phenotypes will provide data for both novel and precise genetic epidemiology and for large disease-specific databases. Ideally, precisely diagnosed genetic DCM should be grouped per disease genes and mutations causing similar effects. Genetic epidemiology will help highlight proportions of different genetic DCM, guiding assignment of clinical priorities and engaging all stakeholders in research and development programs for disease-specific treatments aimed at managing the basic genetic defects and not just the phenotype.

NONGENETIC DILATED CARDIOMYOPATHY

Nongenetic DCM includes etiologically heterogeneous diseases whose onset and progression may largely differ from those of genetic DCM. Theoretically, DCM phenotypes associated with acquired diseases/conditions and/or toxic exposures are potentially reversible with recognition, control, and/or removal of the offending cause. The major subgroups of acquired DCM include the following:

- Autoimmune/immune-mediated DCM may manifest in patients with systemic autoimmune disease such as systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and polymyositis/dermatomyositis (see Chap. 100). The Churg-Strauss syndrome (historically included in this group of diseases) has been renamed as eosinophilic granulomatosis with polyangiitis and is reviewed in the chapter on myocarditis (see Chap. 63).
- Toxic DCM, both exogenous and endogenous, with the former being mostly caused by drug toxicity leading to structural and persistent myocardial damage and dysfunction and the latter being represented by the presence of noxae that affect the heart. The proof of causality is essential to label the disease as toxic DCM.
- Inflammatory cardiomyopathies that are clinically defined by the presence of diagnostic criteria of DCM and pathologic evidence of myocardial inflammation (see Chap. 63).
- Peripartum DCM that manifests during the last month of pregnancy or in the 5 months postpartum (see Chap. 103).

The current nosology of the above entities to nongenetic DCM is subject to future modifications; in fact, new genetic diseases are being described in the setting of autoinflammatory Mendelian disorders and in peripartum cardiomyopathy. Rare "autoimmune diseases" are now recognized as genetic diseases. Accordingly, the collection of family data and genetic counseling should be incorporated in the clinical workup of all patients with DCM to generate precise data for future research and progression of knowledge to better characterize the mechanism(s) underlying a particular DCM.

AUTOIMMUNE/IMMUNE-MEDIATED DILATED CARDIOMYOPATHY (SEE ALSO CHAP. 100)

INTRODUCTION

The clinical manifestations of autoimmune/immune-mediated cardiac involvement are heterogeneous and include ischemic heart disease when epicardial or intramural coronary arteries are involved, valve disease with possible dysfunction, conduction defects, arrhythmias, pericarditis, and myocardial damage, either showing chronic low-grade inflammation and fibrosis or isolated fibrosis. Pulmonary hypertension (see Chap. 74) can complicate autoimmune diseases.

Cardiac involvement can either follow a proven diagnosis of autoimmune diseases or be the first manifestation in undiagnosed patients. In this latter case, the cardiology workup should extensively investigate the entire spectrum of possible traits associated with each of the suspected diseases: ocular (ie, uveitis), cutaneous (ie, both diffuse cutaneous and limited cutaneous systemic sclerosis), respiratory (ie, pulmonary hypertension and fibrosis), thyroid (common in many autoimmune diseases), renal (either renal failure or acute crises in certain diseases), gastrointestinal (ie, esophagus in systemic sclerosis), and nervous and skeletal systems. Routine cardiologic evaluation includes history and physical examination, ECG, and transthoracic echocardiogram; further imaging investigations are planned according to the diagnosis and individual needs.

Familial clustering may manifest with the presence of different autoimmune diseases in more than one family member (Fig. 58–6). The emerging autoinflammatory genetic diseases constitute a novel clinical need for differential diagnoses; accordingly, collection of family data may also be clinically and scientifically useful for sporadic diseases.

Autoimmune diseases that commonly involve the heart and include DCM-like phenotype/heart failure in the spectrum of their possible cardiac manifestations are systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), polymyositis/dermatomyositis, and Sjögren syndrome, as well as overlapping syndromes (Table 58–3). Iatrogenic "cardiomyopathy" can result from common medications used for autoimmune diseases; the cardiac phenotypes are restrictive/dilated in case of hydroxychloroquine toxicity[107] and dilated in case of tumor necrosis factor (TNF)-α inhibitors (eg, etanercept, infliximab, adalimumab; see Chap. 61). Iatrogenic cardiomyopathy should be distinguished from the intrinsic risk of heart failure directly related to the different autoimmune diseases.

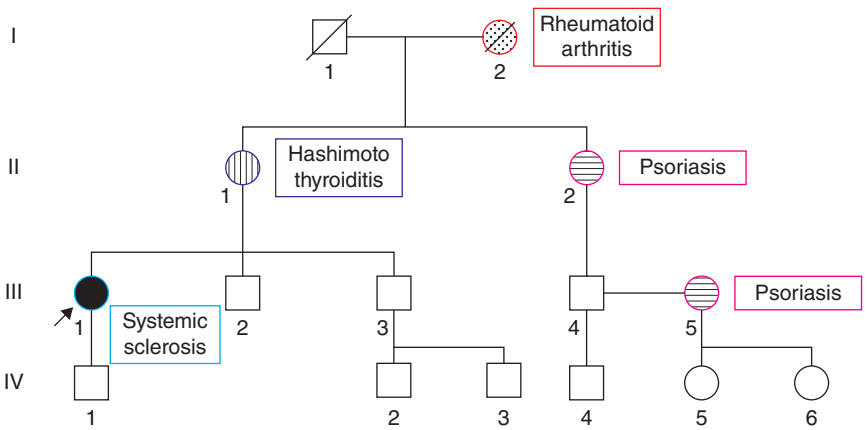


FIGURE 58–6. Familial clustering of autoimmune diseases. The figure shows the pedigree of a female patient (*arrow*) diagnosed with systemic sclerosis 5 years before developing mild dilated cardiomyopathy. In her family, different autoimmune diseases occurred in multiple members.

TABLE 58–3. The Spectrum of Cardiac Phenotypes in Autoimmune Diseases

Disease	Heart Involvement May Include
Systemic sclerosis[a]	HF/DCM, MVR, CD, pericarditis
Rheumatoid arthritis (RA)[a]	HF/DCM, MVR, CD, pericarditis
Systemic lupus erythematosus (SLE)[a]	Accelerated atherosclerosis, DCM/myocardial fibrosis/HF
Rhupus: overlapping features of both SLE and RA	HF and pericarditis
Mixed connective tissue disease	Pericarditis, MVR, CD, accelerated atherosclerosis
Undifferentiated connective tissue disease	Cardiomyopathy
Sjögren syndrome	Accelerated atherosclerosis
Vasculites	
Polyarteritis nodosa	Hypertension
Granulomatosis with polyangiitis (Wegener)	Uncommon
Microscopic polyangiitis	Uncommon
Other autoimmune diseases	
Behçet syndrome	Pericarditis, endocarditis, intracardiac thrombosis, MI, endomyocardial fibrosis
Dermatomyositis and polymyositis	Subclinical cardiac involvement; CAD
Adult Still disease	Rare myocarditis
Fibromyalgia[b]	Heart rate variability

Abbreviations: CAD, coronary artery disease; CD, conduction disease; DCM, dilated cardiomyopathy; HF, heart failure; MI, myocardial infarction; MVR, mitral valve regurgitation.

[a]Most common autoimmune diseases.

[b]Pregabalin-related risk for edema or congestive heart failure.

SYSTEMIC SCLEROSIS (SCLERODERMA)

Introduction

Systemic sclerosis (SS) is a clinically heterogeneous disorder of the connective tissue characterized by fibrosis of the skin and internal organs, vascular abnormalities, and presence of autoantibodies against various cellular antigens.[108] In limited cutaneous scleroderma, fibrosis mainly affects the face, arms, and hands; patients may demonstrate Raynaud phenomenon years before the skin manifestation and may develop pulmonary hypertension (see Chap. 74). In diffuse cutaneous scleroderma, fibrosis involves large cutaneous areas and internal organs, including the heart. Cardiologists contribute to the clinical workup, differential diagnosis, characterization of cardiac involvement, treatment of the heterogeneous clinical phenotypes, risk stratification, and decision making in emergency (eg, cardiac tamponade) or in chronic management of the disease. In the past decade, better awareness of the disease and early diagnoses have contributed to improved care.[109]

Epidemiology

Currently available data indicate a prevalence of SS ranging from 50 to 300 cases per 1 million persons and an incidence ranging from 2.3 to 22.8 cases per

1 million persons per year.[110] This wide range of prevalence variability reflects the diagnostic complexity of multifactorial syndromes with overlapping traits and manifestations and the different diagnostic criteria currently used to establish a precise diagnosis.[111] Classification and diagnostic criteria are a matter of continuous revision by scientific societies and experts.[112] Overlap syndromes, as well as silent, asymptomatic, early phases of the disease, impact the prevalence data. Female-to-male ratio ranges from 3:1 to 14:1; susceptibility to scleroderma demonstrates ethnic variations.[113]

Causes and Major Pathology Features

SS is a sporadic multifactorial disease in the majority of cases. Environmental factors and occupational risk factors have been reported in patients with scleroderma-like phenotypes.[108,114] Less commonly, SS clusters in families where members may show different autoimmune diseases.[115] These data suggest the contribution of genetic factors that could contribute with a small dose effect of multiple genes whose products are involved in innate and adaptive immunity, autoinflammation, cell signaling, extracellular matrix architecture, DNA or RNA degradation, and apoptosis or autophagy diseases.[116,117] Replication of genome-wide association studies independently confirmed the candidacy of many susceptibility genetic variants, including selected human leukocyte antigen (HLA) class II molecules.[118] The maternal-fetal microchimerism hypothesis may help explain the higher prevalence of SS in females: according to this hypothesis, fetal and maternal lymphocytes can cross the placenta during pregnancy and trigger a graft-versus-host-like microreaction that may culminate in scleroderma.[119] This hypothesis is further supported by the presence of allogeneic cells in peripheral blood and in skin biopsy samples obtained from patients with scleroderma[120] and by the short interval between pregnancy and onset of the disease, in particular in the first year after delivery.[121]

Interstitial fibrosis is the main pathologic feature observed in hearts affected by scleroderma (Fig. 58–7). Early features are microvascular damage and mononuclear cell infiltrates. In later stages, the main pathology features are dense fibrosis of the dermis, loss of interstitial cells and vasculature, and tissue atrophy.[122] Table 58–4 summarizes pathologic tissue and cellular changes as well as the expression of possible markers in affected tissue and autoantibodies.

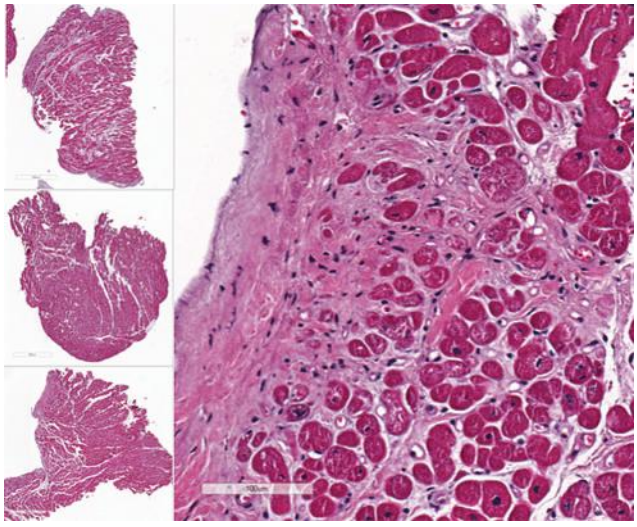


FIGURE 58–7. Endomyocardial biopsy in systemic sclerosis. The figure shows the endomyocardial biopsy of a 59-year-old woman diagnosed with dilated cardiomyopathy and systemic sclerosis in the same clinical occasion. The endomyocardial biopsy shows interstitial fibrosis and sparse inflammatory cells in the context of the fibrosis. There is no evidence of vasculitis or active myocarditis.

Cardiac Involvement

The heterogeneous clinical manifestations include myocarditis, pericarditis, and pericardial effusion; conduction disturbances; LV systolic and diastolic dysfunction; valve dysfunction; myocardial ischemia and coronary artery disease; and pulmonary hypertension.[123] Cardiac involvement (all manifestations) occurs in about 15% to 30% of patients with diffuse scleroderma.[124] A *dilated cardiac phenotype* (any cause) has been reported in up to 40% of patients with diffuse scleroderma.[125] However, because several potential causes may cause heart failure (HF), the proportion of HF attributable to heart muscle involvement rather than to an alternative mechanism (eg, ischemic heart disease, valvular heart disease, or hypertension caused by scleroderma renal crises) is difficult to establish.[126] *Myocardial fibrosis* is common[127] and differs from that observed in ischemic heart disease; in fact, it does not occur in tributary areas of affected arteries, and hemosiderin deposits that are typically seen in post-ischemic myocardium are characteristically absent.[128] *Low-grade inflammation* can involve either small vessels or the myocardial interstitium. In patients with newly developed cardiac manifestations, myocardial inflammation can occur[129] but with very low inflammatory burden. *Involvement of cardiac vessels* (capillaries, arteriolar and epicardial coronary arteries) can now be well assessed using CMR imaging and coronary angiotomography.[130] *Pericardial involvement* includes fibrinous or fibrous pericardial thickening, and focal adhesions and effusion are common; these abnormalities are often clinically silent and benign[128] (see. Chap. 66). In the majority of cases, small pericardial effusions do not cause clinical symptoms or impact prognosis.[131] Hemodynamically significant pericardial effusions can be associated with HF; a small amount of rapidly accumulating pericardial fluid in the rigid, fibrosclerotic pericardium may occasionally cause tamponade.[131,132] The pericardial fluid is generally noninflammatory and does not contain autoantibodies, immune complexes, or evidence of complement depletion. Histologically, the pericardium shows fibrous thickening and nonspecific inflammation. Valve disease and pulmonary artery hypertension can be part of the complex cardiac involvement in scleroderma.[123,126,128,132]

Conclusion

The increasing availability of disease- and organ-specific treatments targeting unique biologic networks and signaling pathways makes a precise diagnosis imperative: DCM-like end-phenotypes may benefit from common treatments for HF. Biologic therapies can target molecules involved in the mechanisms of the immune system, such as cytokines (TNF-α, interleukin [IL]-6), immune cells (B cells), or co-stimulation molecules (cytotoxic T-lymphocyte–associated antigen 4 [CTLA4]), and are currently used in several autoimmune diseases. These drugs provide an alternative to the existing treatment methods of disease-modifying antirheumatic drugs and other immunosuppressive medications.[133] Therefore, confounding scleroderma DCM with genetic DCM or other DCM phenotypes prevents or limits the identification of disease-specific causes.

RHEUMATOID ARTHRITIS

In patients diagnosed with rheumatoid arthritis (RA), DCM accounts for about 20% of mortality.[134] Compared to the general population, patients with RA still demonstrate higher mortality. In autopsy series, heart involvement was demonstrated in up to 60% of patients with RA.[134] As with other autoimmune diseases, RA hearts may show a variety of cardiovascular manifestations: DCM; pericarditis in up to 50% of cases[135] (but hemodynamically significant pericardial effusions is uncommon, 0.5% of patients); pericardial calcifications[136]; nodular thickening and calcifications of cardiac valves[137]; and coronary atherosclerosis.[134]

TABLE 58–4. Scleroderma: Myocardial and Cellular Changes, Expression of Possible Markers in Affected Tissue and Autoantibodies

Phase	Vascular Changes: Small Arteriolar Vessels	Fibrosis: Dermal and Interstitial Spaces	Cells Showing Abnormalities	Immunohistochemistry	Autoantibodies Against:
Early phase	• Loss of continuity of the endothelial layer with gaps between endothelial cells, cytoplasmic vacuolization of endothelial cells • Replication of basement lamina • Perivascular mononuclear infiltrates with rare lymphocytes • Hyperplastic small vessel disease	• Early fibrosis of the lower dermis and upper subcutaneous layer in parallel with progressive loss of small vessels • Different collagen types, proteoglycans, and elastic fibers including fibrillins	• ET cells • Pericytes • SMC • Fibroblasts	• Overexpression TGF-β • PDGF, which is linked to wound healing and fibrosis • Endothelin-1	• Topoisomerase I (Scl-70) • Centromere-associated proteins • Nucleolar antigens • Cell-surface antigens
Late phase	• Rarefaction of capillaries • Paucity of small blood vessels	Dense fibrosis with prevalence of type I collagen	Cell density decreases		

Abbreviations: ET, endothelial; PDGF, platelet-derived growth factor; SMC, smooth muscle cell; TGF, transforming growth factor.

Dilated Cardiomyopathy and Heart Failure

Congestive HF is a major cause of morbidity and mortality in RA patients.[138] The risk of HF remains high after adjustment for underlying coronary artery disease; in long-term follow-up studies, the burden of HF was significantly higher in RA patients than in a control population. Markers such as rheumatoid factor positivity and erythrocyte sedimentation rate, clinical traits such as extra-articular involvement, and treatments such as steroids are associated with risk of congestive HF after adjusting for coronary artery disease and risk factors, suggesting that RA is an independent risk factor for HF.[138] Diastolic dysfunction adds to systolic dysfunction in RA hearts.[139,140] The modification of cardiac mass in RA hearts is debated, with transthoracic echocardiography supporting this hypothesis versus CMR studies that did not confirm an increase in cardiac mass but rather showed lower LV volumes compared with age-matched controls.[141] The cause of diastolic dysfunction may be ascribed to the effects of inflammatory cytokines such as TNF-α, IL-1, and IL-6, all of which mediate inflammation and fibrosis; cytokine profiles seem to distinguish patients with moderate to severe diastolic dysfunction from those with normal heart function[142]; higher myocardial levels of citrullinated proteins compared with controls may partly account for myocardial involvement in RA.[143]

Iatrogenic Myocardial Damage Caused by Rheumatoid Arthritis Treatment

Disease-modifying drugs used to treat RA (and other connective tissue diseases) may lead to iatrogenic myocardial damage. Toxicity may result from long-term use of TNF inhibitors (TNF-I) and antimalarial agents such as hydroxychloroquine.[107,144,145] Hydroxychloroquine toxicity manifests with either hypertrophic-restrictive cardiomyopathy or DCM and is diagnosed with endomyocardial biopsy demonstrating myelin figures and curvilinear bodies (Fig. 58–8) (see Chaps. 61 and 100). The role of TNF-I in causing HF is debated. Etanercept and infliximab trials concordantly showed unfavorable outcomes.[146,147] However, other studies/registries reported that the prevalence of congestive HF is lower or comparable in treated patients versus nontreated patients; a meta-analysis of data from these registries concluded that

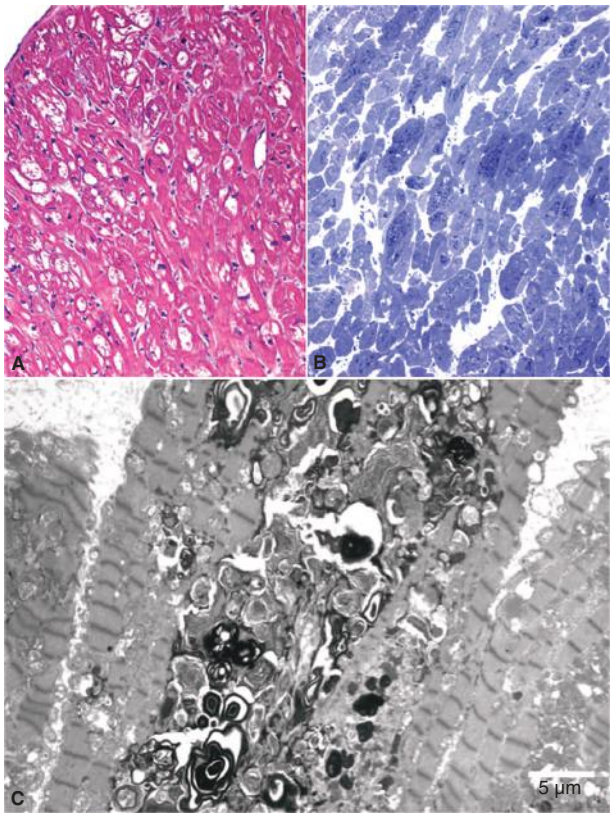


FIGURE 58–8. Chloroquine cardiotoxicity. The figure shows the endomyocardial biopsy of a female patient diagnosed with systemic sclerosis who developed hydroxychloroquine-related cardiotoxicity. **A.** The hematoxylin and eosin stain of the endomyocardial biopsy with optically empty myocytes. **B.** The toluidine blue semi-thin section shows the intramyocyte accumulation of sphingolipid bodies. **C.** The electron micrograph shows the typical lamellar and curvilinear bodies that characterize iatrogenic intracellular accumulation of osmiophilic material. The pathologic differential diagnosis in undiagnosed patients includes Anderson-Fabry disease in which the osmiophilic bodies show a typical lamellar pattern and specifically immune react with anti-GB3 antibodies.

the incidence of congestive HF is lower in treated than in nontreated patients.[148] In the last guidelines (2015) for treatment of RA, the Voting Panel of the American College of Rheumatology reported that recommendations are conditional because the evidence is of very low quality and noted that "there are no reports of exacerbation of HF using non-TNF biologics and the US Food and Drug Administration (FDA) warns against using TNF-I in this population based on worsening of congestive HF with TNF-I in the Adverse Event Reporting System database. A TNF-inhibitors should only be used if there are no other reasonable options, and then, perhaps, only in compensated heart failure"[149] (see Chap. 100).

Reactive Amyloidosis

Reactive amyloid A deposition occurs in RA as a result of long-term, uncontrolled inflammation. The rate of pathologic detection is 21% to 30% of patients with RA, with cardiac involvement in 28%.[150] Cardiac amyloidosis causes a restrictive phenotype with myocardial wall thickening and biventricular enlargement and atrial dilation. The diagnosis is suspected by imaging and by demonstration of involvement of other organs (renal or gastrointestinal tract, heart, spleen, liver, adrenal glands, and, less frequently, lungs, pancreas, thyroid, aorta, muscle, synovial membranes, lymph nodes, peripheral nerves, bones, and skin). The incidence of amyloidosis is likely related to the severity and duration of inflammation. Biologic therapy with anti-TNF agents may reverse amyloid deposition.[151]

Accelerated Atherosclerosis

Vascular heart disease may contribute to HF. Accelerated atherosclerosis is a major cause of morbidity and mortality in RA. A meta-analysis in 41,490 patients with RA from 14 studies showed a 48% increased risk of cardiovascular events compared with the general population.[152] Both classic risk factors (diabetes, dyslipidemia, obesity, hypertension, and smoking) and disease-related factors, such as RA disease duration, RA positivity, and disease activity, contribute to increase the risk of cardiovascular diseases.[152,153] Paradoxically, decreased lipid levels may precede the diagnosis of RA[154] but evolve during and after treatments when cholesterol increases in particular in treated and responder patients.[155] TNF-I increase total cholesterol and high-density lipoprotein levels without an equivalent effect on low-density lipoprotein levels[156]; statins may be required in treated patients with high low-density lipoprotein levels,[157] and discontinuation of statins in RA can increase the risk of myocardial infarction.[158]

Rheumatoid Arthritis Heart Can Display a Pan-Cardiac Involvement

Cardiac involvement in RA can clinically manifest with cardiomyopathy, pericarditis, and valve disease, and can further be complicated by the development of reactive amyloidosis. Iatrogenic myocardial damage is proven for hydroxyl-chloroquine but not confirmed for biologic drugs such as TNF-I, in particular regarding the development of HF. Several disease-specific risk factors and effects of medications add to traditional risk factors in the pathogenesis of the accelerated coronary atherosclerosis. Cardiovascular risk seems to decrease when combined methotrexate and TNF-I achieve a good control of the disease.[159]

SYSTEMIC LUPUS ERYTHEMATOSUS

Dilated Cardiomyopathy in Systemic Lupus Erythematosus

SLE is a multiorgan autoimmune disease demonstrating higher prevalence in African Americans than in whites and typically affects women of childbearing age.[160,161] The clinical course is characterized by cyclic evolution, with periods of quiescence alternating with periods of disease activity. The heart is commonly involved: DCM is one of the most serious forms of organ involvement in SLE,[160,161] and LV systolic dysfunction is associated with poor outcome.[162] In 2012, a consensus group of experts on SLE (the Systemic Lupus International Collaborating Clinics) revised the prior American College of Rheumatology criteria[163] for SLE and established the diagnostic criteria (Table 58–5).[164,165] Myocardial involvement is not included in diagnostic criteria; pericarditis is listed in the context of serositis and occurs in 10% to 30% of patients.[160,166] Although myocardial involvement does not provide a diagnostic contribution, it is common in early and late phases of the disease; diastolic dysfunction is

TABLE 58–5. Clinical and Immunologic Criteria Used in the SLICC Classification Criteria[164]

CLINICAL CRITERIA	1. Acute cutaneous lupus 2. Chronic cutaneous lupus 3. Oral ulcers 4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) 5. Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and 30 minutes or more of morning stiffness 6. Renal 7. Neurologic 8. Serositis 9. Hemolytic anemia 10. Leukopenia (levels may vary) 11. Thrombocytopenia (levels may vary)	CLINICAL CRITERIA	1. ANA above laboratory reference range 2. Anti-dsDNA above laboratory reference range, except ELISA: twice above labortaory reference range 3. Anti-Sm 4. Antiphospholipid antibodies: lupus coagulant; false-positive RPR; medium or high titer anticardiolipin (IgA, IgG, IgM); anti-β_2 glycoprotein I (IgA, IgG, IgM) 5. Low complement: • Low C3 • C4 • CH50 6. Direct Coombs test in the *absence of hemolytic anemia* → **Serositis includes typical pericardial pain** (pain with recumbency improved by sitting forward) for more than 1 day, or pericardial effusion, or pericardial rub, or pericarditis by ECG, *in the absence of other causes, such as infection, uremia, and Dressler pericarditis*

Note. The diagnosis of systemic lupus erythematosus (SLE) requires either 4 of 17 criteria (including at least 1 of the 11 clinical criteria and 1 of the 6 immunologic criteria), or the presence of biopsy-proven SLE nephritis and antinuclear antibodies (ANA) or anti–double-stranded DNA (dsDNA) antibodies. Only pericardial involvement is included in the diagnostic criteria.

Abbreviations: ECG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; RPR, rapid plasma reagin; SLICC, Systemic Lupus International Collaborating Clinics.

detected in 45% of patients without evidence of cardiac disease[167]; it also accounts for the majority of deaths.[168,169]

Epidemiology

Most SLE manifests between the ages of 16 and 50 years; estimated incidence rates in North America, South America, and Europe range from 1 to 23 per 100,000 per year.[169-172] Pediatric-onset SLE represents 10% to 20% of all SLE cases and is associated with greater disease severity than adult-onset SLE; the majority of pediatric-onset SLE patients will have developed irreversible disease manifestations within 5 to 10 years of disease onset, most commonly involving the musculoskeletal, ocular, renal, and neuropsychiatric systems.[170]

Pathogenesis

The current pathogenic hypothesis integrates the effects of both environmental factors and genetic predisposition; risk factors are both SLE specific and traditional. Women are more commonly affected; the role of estrogens (17β-estradiol) and related receptors has been investigated. Estrogens are involved in the regulation of cellular subsets of the immune system through estrogen receptor–dependent and –independent mechanisms[173]; estrogen receptors regulate innate immune cells and signaling pathways,[174] including all subsets of T cells and related cytokines,[175] and B cells, influencing B-cell differentiation, activity, function, and survival.[176]

Epigenetic factors, specifically hypomethylation of CpG sites within genes involved in different pathways, seem to be associated with increased production of autoantibodies (anti-dsDNA, anti-SSA, anti-Sm, and anti-RNP antibodies)[177] and also influence endothelial-inflammatory cell interactions and inflammatory responses. Among susceptibility alleles identified with genome-wide association studies, NCF2, encoding a core component of the multiprotein NADPH oxidase, confers susceptibility to SLE in individuals of European ancestry[178]; HLA-DRB1*15-DQB1*06 haplotype has recently been proposed as the greatest risk factor for development of disease in certain ethnic groups.[179] In a recent meta-analysis, the HLA-G 14-base pair I/D polymorphism was associated with susceptibility to a subgroup of autoimmune diseases such as SLE, but not RA.[180] Additional genes/loci have been assigned to SLE: *PTPN22*, *FCGR2A*, *FCGR2B*, *CTLA4*, *TEX1*, and *DNAS1* are all included in the Mendelian Inheritance in Man (MIM) catalogue as associated with increased susceptibility to SLE. However, at present, there is no evidence supporting a Mendelian inheritance of SLE, which thus remains a potential multifactorial autoimmune disorder.

Myocardial Involvement

Heart and vessels are commonly involved in SLE. The major pathology features include accelerated atherosclerosis, myocardial fibrosis, and HF.

Accelerated atherosclerosis[181] is not explained by traditional risk factors but likely promoted by systemic inflammation.[182] Traditional risk factors (eg, diabetes, hypertension, hyperlipidemia) are common in young SLE patients, often as a side effect of immunosuppressant therapy.[183] SLE-related risk factors include the presence of autoantibodies, such as antiphospholipid antibodies, anticardiolipin antibodies, and lupus anticoagulant,[183] which are produced in 30% to 40% of SLE patients. These antibodies do not fully explain the increased thrombotic risk in SLE; in fact, published data show that only 10% of "positive" patients experience a thrombotic event, and 40% of SLE thrombosis cases are in patients without such antibodies.[184] Treatment-related risk includes the effects of both corticosteroids and immunosuppressant drugs.[185] Risk stratification and modification for cardiovascular events should therefore be tailored on individual risk profile, based on modifiable risk factors and SLE-specific risk factors. Atherosclerosis is associated with increased risk of cardiac, cerebral, or peripheral arterial ischemic events and mortality; in a systematic review and meta-analysis including 17,187 patients from 32 studies, the incidence of cardiovascular events was almost 25%, and 4.5% of the patients had an acute myocardial infarction.[183] Although early subclinical atherosclerosis can manifest as intima-media thickening of carotid arteries, recent studies demonstrated that atherosclerotic plaque lesions can be found frequently in the absence of intima-media thickening in both SLE and SS patients; sonography of carotid and femoral arteries may identify additional atherosclerotic lesions and detect patients at a high risk for cardiovascular events.[186] Coronary contrast enhancement by CMR may detect subclinical disease in the coronary vessel wall, thus providing a novel direct marker of vessel wall disease.[187] Considering that traditional Framingham cardiovascular risk factors do not fully explain the excess of the risk of coronary artery disease in SLE,[181] it is likely that inflammatory and autoimmune mechanisms interact with genetic, environmental, and treatment-related factors.

Myocardial fibrosis represents a significant independent predictor of adverse cardiac outcomes in both ischemic and nonischemic cardiomyopathies.[188,189] Recent CMR studies confirmed that mid-wall myocardial fibrosis is frequent in SLE and is associated with age but not with disease duration or severity; in addition, late gadolinium enhancement comprising > 15% of LV mass may be associated with diastolic dysfunction and impaired exercise capacity.[190]

DCM/HF is common in patients with SLE; although the causes can be related to the systemic (cytokine burden) and local inflammation, the role of accelerated atherosclerosis is not easy to dissect from local damage potentially induced by chronic inflammation. However, SLE patients with cardiomyopathy have a prognosis similar to those with idiopathic DCM.[191]

The European League Against Rheumatism recommends baseline cardiovascular evaluation and regular, yearly cardiovascular follow-up to assess smoking, vascular events (cerebral/cardiovascular), physical activity, oral contraceptives, hormonal therapies, and family history of cardiovascular disease; to perform blood tests, including blood cholesterol and glucose; and to measure blood pressure and body mass index (and/or waist circumference).[192]

PERIPARTUM CARDIOMYOPATHY (SEE ALSO CHAP. 103)

DEFINITION

Precise diagnostic criteria of peripartum cardiomyopathy (PPCM) are essential to distinguish potentially reversible LV dilation and dysfunction from DCM with different causes, both genetic and nongenetic; pregnancy may in fact unmask an underlying genetic DCM. In the workshop held by the National Heart, Lung, and Blood Institute and the Office of Rare Diseases (2000), PPCM was defined as a "rare life-threatening cardiomyopathy of unknown cause that occurs in the peripartum period in previously healthy women: diagnosis is confined to a narrow period and requires echocardiographic evidence of LV systolic dysfunction,"[193] According to the European Society of Cardiology (ESC), "PPCM is an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. It is a diagnosis of exclusion."[194] The LV may not be dilated, but the ejection fraction (EF) is nearly always reduced below 45%.[194] Both definitions share the following concepts: (1) idiopathic condition (no detectable cause of HF); (2) temporal appearance (the last month of pregnancy or during the first 5 months postpartum in the former and toward the end of pregnancy or in the months following delivery in the

latter); (3) the absence of preexisting known heart disease; and (4) the presence of LV dysfunction. Therefore, the precise clinical diagnosis of PPCM should be based on these criteria. A further condition that could confirm the diagnosis is the regression of PPCM within 12 months after delivery.[194]

INCIDENCE

PPCM is estimated to occur in 0.1% of all pregnancies. The prevalence of PPCM ranges between 1:4000 and 1:1000 live births in the Western world.[195,196] Approximately 75% of cases are diagnosed within the first month after delivery, and 45% occur in the first week. Regional variation is wide: 1 case per 20,000 live births in Japan[197]; 1 case per 1000 live births in South Africa[198]; 1 case per 40,322 in China[199]; and 1 case per 300 live births in Haiti.[200] A high prevalence in Nigeria is likely caused by the tradition of ingesting kunun kanwa (dried lake salt) while lying on heated mud beds twice a day for 40 days postpartum to stimulate breast milk production.[201] This variable prevalence suggests that regional and cultural factors influence the risk of PPCM.

RISK FACTORS

Risk factors for PPCM include age (> 30 years), multiparity, African American race, obesity, substance use, pre-eclampsia, and chronic hypertension.[202,203] It is unclear whether race is an independent risk factor or whether the increased risk of PPCM results from the interaction of race with hypertension. Factors such as poor nutrition and lack of prenatal care are included in the list of risk factors but are unconfirmed. Climate may also contribute: PPCM seems to be more common in tropical regions with increased heat and humidity.[204]

ETIOLOGIC HYPOTHESES

Etiologic hypotheses include familial/genetic predisposition, maladaptive response to hemodynamic stresses of pregnancy, viral myocarditis, stress-activated cytokines, malnutrition and selenium deficiency, fetal micro-chimerism, prolactin, and prolonged tocolysis[205] (Fig. 58–9).

Genetic Hypothesis

In a recent study including 172 women (one-third of African descent) with PPCM versus 332 patients with DCM, sequencing of 43 DCM genes identified 26 heterozygous truncating variants in eight genes (17 mutations were identified in the *TTN* gene). The prevalence of truncation-predicting variants in PPCM (15%) was similar to that in DCM (17%) and significantly higher than in the reference population (4.7%); 65% of the truncating variants were in the *TTN* gene.[206] This study may have relevant implications for both PPCM and genetic DCM; in fact, *TTN* mutations have been reported in 25% of FDCM and in 18% of nonfamilial, sporadic DCM.[32] Persistence of the DCM phenotype in one-fifth of patients suggests the pathogenic role of the *TTN* mutation and implies that one-fifth of cases of PPCM are actually genetic DCM unmasked by pregnancy.[32] Conversely, if the phenotype regresses after pregnancy among women with mutated PPCM, the role of *TTN* variants could be questioned not only in PPCM but also in DCM associated with the same variants. At present, it appears prudent then to consider a genetic predisposition to PPCM rather than a genetic cause.

Abnormal Hemodynamic Response

During pregnancy, in particular in the last trimester, blood volume and cardiac output increase and afterload decreases because of relaxation of vascular smooth muscle cells; LV mass and arterial compliance also

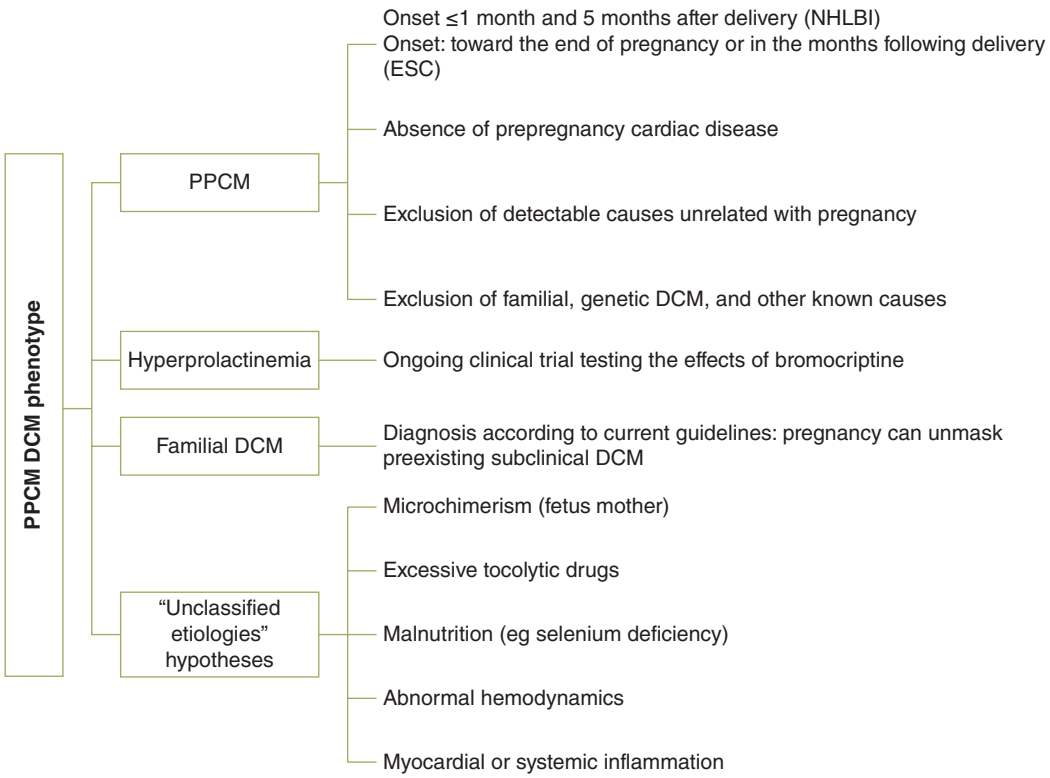


FIGURE 58–9. Pathogenesis of peripartum cardiomyopathy (PPCM). The figure summarizes key diagnostic criteria and pathogenetic hypothesis in PPCM. DCM, dilated cardiomyopathy; ESC, European Society of Cardiology; NHLBI, National Heart, Lung, and Blood Institute;

increase, whereas total vascular resistance decreases.[207] The consequent functional and transient LV "hypertrophy" aims at meeting fetal and maternal demands. In normal pregnancies, this transient LV functional and structural remodeling regresses shortly after birth.[207] Although PPCM might, in part, be a result of an exaggerated decrease in LV function when these hemodynamic changes of pregnancy occur, this hypothesis is unlikely to explain, by itself, PPCM.

Viral Myocarditis and Systemic Inflammation

Past studies proposed viral myocarditis as the main mechanism for PPCM.[208] This hypothesis remains unconfirmed. Clinical outcomes do not seem to differ in women with and without clinically diagnosed myocarditis. Increased levels of plasma inflammatory, apoptosis mediators and cytokines measured in women with PPCM do not correlate with LV function or outcomes. LVEF at the time of initial diagnosis remains the strongest predictor of outcome.[209]

Malnutrition and Selenium Deficiency

Deficiencies in selenium and other nutrients have also been advocated as causes of PPCM.[210] Selenium deficiency (serum selenium concentration < 70 μg/L) is a well-known cause of DCM and of increased susceptibility to viral infections, hypertension, and hypocalcemia.[211] Selenium deficiency is a risk factor for PPCM in Kano, Nigeria, and seems to be related to rural residency.[211]

Fetal Micro-Chimerism

During pregnancy, the trafficking of circulating cells generates bidirectional micro-chimerism (ie, fetus to mother and vice versa). Cell trafficking from fetus to the mother starts very early; the numbers of fetal cells increase in the maternal circulation in pregnancies affected by pre-eclampsia and before the onset of pre-eclampsia symptoms.[212] Adult women may bear chimeric blood cells from multiple sources.[213] For instance, microchimerism is one of the factors advocated in the pathogenesis of autoimmune diseases, which are more common in females than in males. The small shared epitopic-mimetic compound QKRAA has been proposed as contributor to the pathogenesis of RA by acting as a ligand that activates pro-arthritogenic signal transduction events.[214] Women who lack RA susceptibility HLA alleles encoding the small QKRAA epitope can acquire RA susceptibility alleles from microchimerism, thus increasing their risk of RA.[215]

Prolactin

Prolactin is one of the key candidates in the pathophysiology of PPCM. Increased levels of prolactin in pregnancy are associated with increased blood volume and levels of circulating erythropoietin and hematocrit and decreased blood pressure, angiotensin responsiveness, and levels of water, sodium, and potassium. In the last trimester of pregnancy, oxidative stress is enhanced; under defective antioxidative mechanisms, prolactin is increasingly cleaved into a 16-kDa fragment (16-kDa prolactin). This fragment may induce microvascular damage, leading to cardiac injury and dysfunction. The dopamine D_2 receptor agonist bromocriptine inhibits prolactin release and may represent a therapeutic option. This hypothesis was tested in a murine model that develops a PPCM-like phenotype; in this mouse model, the administration of bromocriptine prevented the development of the phenotype.[216,217] After successful testing in pilot series and single cases, a large clinical trial was planned and is ongoing, aimed at investigating the safety of the dopamine D_2 receptor agonist bromocriptine and its effects on LV function in women with PPCM.[218]

Prolonged Tocolysis

Prolonged use of tocolytic therapies has been associated with development of pulmonary edema in pregnant women[219]; based on this observation, chronic use of β-sympathomimetic medications was linked with PPCM. Prolonged tocolysis refers to the use of β-sympathomimetic drugs for more than 4 weeks. Although these agents are used for the management of various other conditions, the association between tocolytic therapies and HF appears to be unique to pregnancy.

DIAGNOSTIC WORKUP AND MANAGEMENT

Echocardiography is the first-line imaging test. Ideally, baseline data should be available and demonstrate normal baseline LV size and function. Such baseline data, however, are rarely available because echocardiography is not indicated routinely in pregnancy and the later development of PPCM is unpredictable. However, early diagnosis is possible, and when treated in the early phases, LV systolic function may normalize in a high percentage of cases.[194]

The increasing awareness of PPCM is contributing to earlier diagnosis and better management and outcomes. A major limitation is the absence of baseline echocardiographic evaluation in women who develop PPCM. However, the combined treatment with β-blockers plus angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers is now recommended (Class I) by the AHA and ESC Guidelines[17,220] for treatment of HF with reduced LVEF after delivery. ACE inhibitors and angiotensin receptor blockers are highly teratogenic and should be avoided during pregnancy.[221] After delivery, PPCM should be treated in accordance with the current ESC guidelines for HF. During pregnancy, treatment options include hydralazine, long-acting nitrates, and β_1-selective β-blockers; diuretics (furosemide and hydrochlorothiazide) should be used sparingly because they can cause decreased placental blood flow[194] (see Chap. 103).

RECOVERY OF LEFT VENTRICULAR FUNCTION IN PERIPARTUM CARDIOMYOPATHY

Although data reporting prognosis and outcome in PPCM differ (Table 58–6), most recent data concordantly demonstrate that LV function recovers in a significant percentage of cases (23% to

TABLE 58–6. Criteria for Diagnosing PPCM and Implication of a Precise Diagnosis of Pregnancy-Related Transient DCM Versus Persistent DCM

Diagnostic Criteria of PPCM	Evolution	Implications
1. Women without preexisting heart disease 2. Onset: 1 month before delivery or during the first 5 months postpartum 3. Exclusion of known causes and of familial, genetic DCM 4. LV dysfunction	1. Regression ≤ 12 months after delivery, with restoration of LVEF ≥ 50% 2. Persistence, progression/worsening of the phenotype after pregnancy 3. Timely treatment PPCM with diuretics and β-blockers	1. Advise women who would have new pregnancies 2. Establish pregnancy-specific monitoring and care programs 3. Warning: better assessed risk of recurrence, including all available tools for risk assessment

Abbreviations: DCM, dilated cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; PPCM, peripartum cardiomyopathy.

78%).[205,222-224] In a recent prospective study in 100 patients from 30 US and Canadian centers (Investigations of Pregnancy-Associated Cardiomyopathy [IPAC]), full recovery (LVEF ≥ 50% at 12 months postpartum) occurred in 72% of patients. Outcomes were unsatisfactory for 13% of women, who had major events or evolved through severe chronic cardiomyopathy (LVEF < 35%) during the 1-year observation time after delivery. Women of African heritage had more frequent hypertension (preeclampsia, gestational, and chronic) and a later PPCM diagnosis.[225] The most impressive data are from the German PPCM registry, with improvement in 85% of patients; the highest percentage of recovery (96%) was observed in patients treated with bromocriptine, β-blockers, and ACE inhibitors/angiotensin receptor blockers, albeit full recovery with an EF > 55% was present in only 47% of patients.[226] Event-free survival was significantly worse for women with a baseline LVEF < 30% compared with those with LVEF > 30% (1-year event-free survival rate, 82% vs 99%; $P < .004$) (Fig. 58–10).[226] Results recorded in the IPAC registry in women who did not receive bromocriptine were comparable with those reported by German investigators in PPCM patients who received bromocriptine in addition to standard evidence-based treatment.[226]

ALCOHOLIC HEART DISEASE

INTRODUCTION

Light to moderate alcohol intake is beneficial for cardiovascular health,[227] whereas habitual heavy alcohol consumption is associated with increased risk of LV dilatation and dysfunction (alcoholic cardiomyopathy [A-CMP]),[228] arrhythmias,[228,229] systemic hypertension,[230] ischemic heart disease,[231] stroke,[232] and skeletal muscle abnormalities.[233] Heavy alcohol consumption corresponds to daily ingestion of at least three standard-size drinks or alcohol consumption over 80 g; light-moderate alcohol intake corresponds to less than three standard-sized drinks or < 80 g/d. Because standard-sized portions of wine, liquor, or beer contain approximately the same amount of alcohol, the daily amount of ethanol is usually measured per number of standard drinks.[228,229]

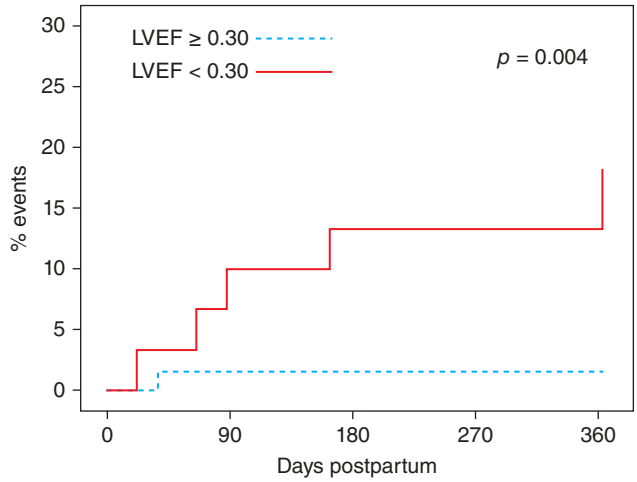


FIGURE 58–10. Severe impaired left ventricular function influences prognosis in peripartum cardiomyopathy (PPCM). Event-free survival is significantly worse in women with PPCM with a baseline left ventricular ejection fraction (LVEF) < 30% compared with those with an LVEF > 30%. Reproduced with permission from McNamara DM, Elkayam U, Alharethi R, et al. Clinical outcomes for peripartum cardiomyopathy in North America: results of the Investigations of Pregnancy Associated Cardiomyopathy (IPAC) study. *J Am Coll Cardiol*. 2015 Aug 25;66(8):905-914.[225]

ALCOHOLIC CARDIOMYOPATHY

A-CMP clinically manifests with DCM phenotype; it is considered a specific disease by both the ESC and AHA.[8,9] In the ESC consensus document on the classification of cardiomyopathies, A-CMP is included among the acquired forms of DCM.[9] Thiamine deficiency (beriberi) is no longer confused with A-CMP; the former fully responds to thiamine administration, whereas the latter does not.[228]

Among alcoholics, the prevalence of DCM is 0.43% in women and 0.25% in men.[234] An excessive ethanol intake is reported in 3% to 40% of patients with DCM.[235] The three criteria for diagnosing A-CMP include DCM phenotype, absence of other known and detectable causes of DCM, and a long history of heavy alcohol intake. The toxic effect is expected for daily alcohol consumption over 80 g (three or more standard-sized drinks per day) lasting 5 years or more before the onset or diagnosis.[234-236] The symptoms correspond to those of DCM, with patients presenting with HF as a result of reduced cardiac output and atrial and/or ventricular arrhythmias. The LV function ameliorates with either abstinence or reduction of the daily intake of alcohol.[228,234-236] There are no specific guidelines for the treatment of A-CMP; current management should include complete alcohol abstinence and therapies recommended to treat HF as a result of other causes (see Chap. 70).

MECHANISMS

The toxic damage of ethanol is attributed to a nonoxidative metabolic pathway for alcohol related to fatty acid metabolism in the heart, skeletal muscle, pancreas, and brain.[228,229] Factors that have been involved in the pathogenic mechanisms of A-CMP include apoptosis, abnormal excitation-contraction coupling, functional and structural mitochondrial damage, loss of contractile filaments, deregulation of protein synthesis, ATPase, L-type calcium channels, and activation of the renin-angiotensin and sympathetic nervous systems.[228,229] None of these factors and mechanisms has been confirmed, and they may all contribute. However, alcohol-induced mitochondria toxicity ends in mitochondrial dysfunction, loss of mitochondrial membrane potential and increase in mitochondrial oxidative stress, eventually culminating in cell death.[237] Nonselective mitochondrial damage could link oxidative stress, apoptosis, and mitochondrial loss and explain the multiorgan damage in those with alcohol use disorders.[237] Recent experimental studies showed that chronic plus binge ethanol feeding in mice causes alcohol-induced cardiomyopathies characterized by increased myocardial oxidative/nitrative stress, impaired mitochondrial function and biogenesis, and enhanced cardiac steatosis.[238]

PROGNOSIS

Current knowledge regarding A-CMP is mostly based on historical studies; data on prognosis using contemporary HF pharmacologic agents are not available. Alcohol withdrawal is associated with A-CMP regression in a 40% to 50% of cases but not in all of them, suggesting that factors other than alcohol abuse may contribute to the natural history of the disease.[228] A-CMP seems to have a better prognosis than idiopathic dilated cardiomyopathy; during a median follow-up of 59 months (interquartile range, 25-107 months), 94 consecutive patients with A-CMP demonstrated higher transplantation-free survival than 188 patients with nonalcoholic DCM. During follow-up, 63% of patients reported remaining abstinent, 32% continued alcohol consumption but had reduced intake to < 80 g/d, and only 5% were persistent or heavy alcohol drinkers (> 80 g/d). Atrial fibrillation, QRS width > 120 milliseconds, and the absence of β-blocker therapy identify patients with a poor outcome. ACM patients who reduced their alcohol intake to moderate levels exhibited similar survival ($P = .22$) and cardiac function recovery ($P = .8$) as abstainers.[239]

CIRRHOTIC CARDIOMYOPATHY

DEFINITION AND IMPACT OF THE DIAGNOSIS

Patients with cirrhosis frequently demonstrate hyperdynamic circulation and increased cardiac output, decreased systemic vascular resistance, and increased compliance of the arterial vessels. This combination of hemodynamic conditions corresponds to latent left HF where any stressor may clinically unmask the LV dysfunction.[240,241] According to the 2005 World Congress of Gastroenterology, cirrhotic cardiomyopathy is defined by "chronic cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease."[241] The impaired diastolic relaxation is more common in early phases, whereas systolic dysfunction and LV dilation are manifest in advanced phases; electrophysiologic abnormalities include prolongation of QT interval in more than 50% of cases, electromechanical dyssynchrony, and chronotropic and/or inotropic incompetence[240,242] (Table 58–7). Cardiac evaluation is increasingly relevant for patients who are candidates for liver transplantation and/or transjugular intrahepatic portosystemic shunt (TIPS) implantation. These may exacerbate the hyperkinetic circulation and compromise cardiac function. TIPS decompression of the portal hypertension increases the preload to the heart, pulmonary artery pressure, and systemic vascular resistances, thus lowering afterload. In the complex pathophysiology of cirrhosis-related cardiac and hemodynamic changes, diastolic dysfunction seems to predict death after TIPS implantation.[243]

In addition, pretransplant diastolic dysfunction predisposes patients with hepatic cirrhosis to post-transplant adverse cardiac events.[244] Of 107 patients who received liver transplantation, 24% developed HF in association with diastolic dysfunction prior to liver transplantation, and diastolic dysfunction was a predictor of a poor prognosis.[245] Cardiac causes of immediate death after liver transplantation include postreperfusion syndrome, pulmonary hypertension, and cardiomyopathy.[246] Therefore, cirrhotic cardiomyopathy may influence the evolution of post-TIPS and orthotopic liver transplantation; however, it does constitutes a contraindication to both procedures, in particular to liver transplantation.[247]

TABLE 58–7. Morphofunctional Imaging-Based, Electrophysiologic, Electromechanical, and Biochemical Criteria for Cirrhotic Cardiomyopathy

Cardiac Morphofunctional Criteria: Imaging		Other Criteria
Echocardiographic criteria		*Electrophysiologic criteria*
Systolic	Systolic dysfunction unmasked during pharmacologic or physiologic stress	QT interval prolongation
	Rest EF < 55%	Abnormal chronotropic response
Diastolic	E/A ratio < 1.0 (corrected by age)	*Electromechanical criteria*
	Prolonged deceleration time (> 200 ms)	Ventricular dyssynchrony
	Prolonged isovolumetric relaxation time (> 80 ms)	*Biomarkers*
Others	Tricuspid valve regurgitation	Increased natriuretic peptides (pro-BNP, pro-ANP)
	LA dilation	Increased high-sensitivity troponin T
	Increased cardiac mass	Soluble urokinase-type plasminogen activator receptor
MR myocardial stress testing		High-sensitive C-reactive protein

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; EF, ejection fraction; MR, magnetic resonance.

PATHOGENESIS

Hepatic failure and portal hypertension have been considered as possible factors for the development of cardiac changes in patients with cirrhosis. In the early phase of cirrhotic disease, the hemodynamic changes are compensated by the development of a hyperdynamic circulation. In later phases as splanchnic arterial vasodilation progresses, effective arterial blood volume declines, and there is subsequent activation of the renin-angiotensin-aldosterone system and development of LV dilation and dysfunction. Factors involved in the development of cardiac impairment include inflammation mediated by intestinal bacterial translocation,[248] cytokines that can influence both LV remodeling and function, and the negative inotropic effects of nitric oxide, carbon monoxide, and endogenous cannabinoids.[249]

DIAGNOSIS AND IMAGING

Cardiac evaluation of patients with cirrhosis requires special attention to clinically latent signs of HF, as it may influence candidacy for TIPS or liver transplantation. The presence of diastolic dysfunction should be recognized before liver transplant because it may be associated with intraoperative complications and may complicate the early postoperative course.[250] Latent cardiac dysfunction, defined by abnormal stroke volume response to unclamping of portal vein, is common in liver transplant recipients.[251] Preoperative low systemic vascular resistance and left atrial dilation are independent predictors of inadequate responses.[251] All cardiac imaging modalities contributing to better characterize diastolic dysfunction should be integrated to provide best assessment of diastolic dysfunction; echocardiography with tissue Doppler is the most common method to detect and monitor diastolic dysfunction. A few studies have applied CMR and contrast-enhanced CMR as well as cardiac CT with coronary artery calcification scoring. More studies are needed to establish the clinical contribution of both CMR and CT in patients with cirrhotic cardiomyopathy.[252] Tests with either physiologically or pharmacologically induced circulatory stress are useful to assess systolic dysfunction; echocardiography with tissue Doppler is the most common method to detect diastolic dysfunction (E/A and E/E′ ratio). Strain techniques can offer incremental information. The impaired cardiac pharmacologic response to stress can be additionally investigated with magnetic resonance myocardial stress testing; deformation parameters may be more sensitive in identifying abnormalities in inotropic response to stress than are conventional methods.[253] Cirrhotic cardiomyopathy (CCR) is therefore assuming an increasing relevance considering the negative impact that an unrecognized CCR may have during and after liver transplantation. An early diagnosis of cirrhotic cardiomyopathy with pretransplant treatment of HF may prevent an acute onset or worsening of cardiac failure after liver transplantation.[254] Pretransplant treatment of HF may improve quality of life before transplantation and reduce perioperative complications after liver transplantation.

TRANSIENT AND REVERSIBLE DILATED CARDIOMYOPATHY

Different types of DCM that have been variably included in past classifications of cardiomyopathies are potentially reversible. In future nosologies of cardiomyopathies, these entities should probably be separated from cardiomyopathies and be part of a disease-specific classification. Apart from PPCM and alcoholic and cirrhotic cardiomyopathies, other DCMs that potentially reverse when the cause is controlled and treated are tachycardia-induced cardiomyopathy, premature ventricular contraction–induced cardiomyopathy, takotsubo cardiomyopathy, metabolic cardiomyopathies (both endocrine and nutritional), cardiomyopathies complicating end-stage chronic diseases such as renal failure (uremic cardiomyopathy), and inflammatory and infectious cardiomyopathy. These latter are reviewed in Chap. 63. The existence of an independent "obesity cardiomyopathy" characterized by systolic dysfunction fulfilling criterion for the diagnosis of DCM is debated; recent studies highlight the role of obesity as an independent risk factor for the development of HF, but obesity-related HF is thought to be multifactorial.[255]

TACHYCARDIA-INDUCED CARDIOMYOPATHY

Tachycardia-induced cardiomyopathy is caused by persistent tachycardia that induces increased ventricular filling pressures, severe biventricular systolic dysfunction, reduced cardiac output, and increased systemic vascular resistance. Arrhythmias include atrial fibrillation, atrial flutter, atrial tachycardia, reentrant supraventricular tachycardia, accessory pathway tachycardia, frequent ectopic beats, and ventricular tachycardia; sustained rates above 115 or 120 bpm may be an important prognostic factor.[256] Sinus tachycardia has also been reported as a cause of cardiomyopathy.[257] The diagnosis is based on the absence of other causes of nonischemic cardiomyopathy (eg, hypertension, alcohol or drug use, stress) and on the absence of LV hypertrophy and relatively normal LV diameter (LV end-diastolic dimension < 5.5 cm). The recovery of LV function after control of tachycardia (by rate control, cardioversion, or radiofrequency ablation) within 1 to 6 months confirms the diagnosis.[258,259]

PREMATURE VENTRICULAR CONTRACTION–INDUCED CARDIOMYOPATHY

Premature ventricular contraction (PVC)–induced cardiomyopathy is characterized by LV dilation and/or dysfunction, diastolic dysfunction, and ventricular strain by speckle tracking imaging.[260] A dose-response relation has been demonstrated in serial evaluations of LV function among 239 consecutive patients with frequent PVCs and no obvious cardiac disease; > 20,000 PVCs per 24 hours were associated with subclinical deterioration in LVEF, whereas > 10,000 PVCs per 24 hours showed LV dilation without a change in LVEF.[261] An increasing PVC burden was associated with adverse outcomes in 1139 healthy participants of the Cardiovascular Health study (≥ 65 years) with an initial normal LVEF and no history of congestive HF who underwent 24-hour Holter monitoring. Over a median follow-up of > 13 years, a PVC burden in the upper quartile was associated with a threefold greater odds of a decrease in LVEF, a 48% increased risk of incident congestive HF, and a 31% increased risk of death, compared with the lower quartile.[262] PVC-induced cardiomyopathy appears reversible with reduction in ectopy burden. Rapid normalization of LV parameters follows successful radiofrequency ablation of the PVC focus.[263,264] After successful ablation, the rates of improvement in LVEF have varied between 47.1% and 100%.[263,264] Randomized trials are ongoing, aimed at assessing whether therapy for frequent PVCs in patients with idiopathic LV dysfunction modifies clinical outcomes. The Early Elimination of Premature Ventricular Contractions in Heart Failure study (ClinicalTrials.gov identifier: NCT01757067) is testing the effects of ablation versus medical therapy; the Reversal of Cardiomyopathy by Suppression of Frequent Premature Ventricular Complexes study (NCT01566344) is testing conventional HF therapy and PVC suppression therapy (ablation or amiodarone if unsuccessful ablation) versus HF therapy alone. In children, the proportion of PVC-induced cardiomyopathy seems higher than previously expected especially because ectopy tends to persist throughout follow-up. The possibility of radiofrequency ablation of the ectopic ventricular focus could be considered in children who manifest LV ventricular dilation or dysfunction.[265] The pathophysiology of PVC-induced cardiomyopathy remains unknown, and the optimal management of these patients is not yet established.

THE LEFT APICAL BALLOONING SYNDROME

The left apical ballooning syndrome, or takotsubo cardiomyopathy, is a transient hypocontractility of the mid and apical segments of the LV associated with hyperkinesis of the basal walls. This mismatched contractility causes a balloon-like appearance of the distal ventricular walls in systole. The phenomenon may mimic acute coronary syndrome in the absence of coronary artery disease or spasm (see Chap. 36). The transient dysfunction is most prevalent in older women exposed to emotional or physical stressors. The disease can manifest with atypical phenotypes such as reversed and right ventricular takotsubo and global hypokinesis.[266,267] Biomarkers include increased levels of circulating catecholamines, especially epinephrine. Takotsubo cardiomyopathy may not follow obvious physical or emotional stress; in addition, it may carry significant early and late serious complication risks. It can occur concomitantly in the presence of subcritical coronary artery disease; patients often demonstrate cardiovascular risk factors and associated comorbidities.[267] Primary takotsubo cardiomyopathy is frequently related to emotional stress, is largely reversible, and carries a benign prognosis; in contrast, secondary forms are associated with acute potentially severe conditions and may result in a higher event rate.[268] Although included in the cardiomyopathy classification, they do not share the chronic morphologic LV abnormalities and remodeling that characterize DCM.

METABOLIC CARDIOMYOPATHIES

Metabolic cardiomyopathies are secondary to effects of primary noncardiac defects of energy production leading to impaired cardiac function. They may be caused by several different endocrine diseases and nutritional deprivations. Endocrine cardiomyopathies include growth hormone (GH) excess and GH deficiency and thyroid hypo- and hyperfunction.[269-274]

Excess or Deficiency in Growth Hormone and/or Insulin-Like Growth Factor 1

Excess or deficiency in GH and/or insulin-like growth factor-1 (IGF-1) is deleterious for the cardiovascular system. Acromegaly is an endocrine disease with specific somatic changes caused by an excess of GH; in the majority of cases, the cause is a pituitary tumor producing GH. Chronic GH and IGF-1 excess causes a cardiomyopathy that is characterized by early concentric cardiac hypertrophy associated with diastolic dysfunction and by later evolution to systolic dysfunction.[269] The control of GH/IGF-1 excess is accompanied by a decrease in cardiac mass and improvement of cardiac function.[270] In patients with hypopituitarism, either childhood onset or adulthood onset, GH deficiency is characterized by decrease of cardiac mass and impairment

of systolic function; other effects include increased cardiovascular risk with changes in body composition, unfavorable lipid profile, insulin resistance, endothelial dysfunction, and atherosclerosis. In patients with GH deficiency, the administration of recombinant GH is followed by increase in cardiac mass, improvement in cardiac performance, and improvement of the cardiovascular risk factor profile.[270,271] Therefore, in acromegaly and GH deficiency, the control of GH/IGF-1 secretion reverses cardiomyopathy and risk factors and restores normal life expectancy.[271]

Thyroid Cardiomyopathy

Thyroid dysfunction may be associated with either high cardiac output cardiomyopathy in hyperthyroidism or low cardiac output cardiomyopathy in hypothyroidism. Thyroid hormone effects are exerted on β-adrenergic receptors, contractile apparatus, ion-ATPase pump, and the sarcoplasmic reticulum.[272] Clinically, thyroid function is usually investigated in patients that manifest high-output HF. Hyperthyroidism is characterized by resting tachycardia and increased blood volume, stroke volume, myocardial contractility, and EF. High-output HF may be a result of a tachycardia-mediated cardiomyopathy mechanism.[273] In hypothyroidism, thyroid hormone deficiency is associated with by bradycardia, decreased myocardial contractility and relaxation, and prolonged systolic and early diastolic times. Cardiac preload is decreased as a result of impaired diastolic function, cardiac afterload is increased, and chronotropic and inotropic functions are reduced. Subclinical hypothyroidism is associated with increasing risk of cardiovascular events but not of total mortality.[274] Medical or surgical treatment of either hyper- or hypothyroidism restores cardiac function.[274] Accordingly, thyroid cardiomyopathy is potentially reversible. Recurrent pericarditis and pericardial effusion are well-known complications of hypothyroidism (see Chap. 66); less commonly, pericarditis is observed in thyrotoxic crisis in Graves disease.[275] Two medical emergencies, myxedema coma and thyroid storm, are unrelated to thyroid cardiomyopathy but may involve cardiologists for the diagnosis and management. Myxedema coma is characterized by somnolence, lethargy, and hypothermia. It is precipitated by triggers such as cold exposure, infection, drugs trauma, stroke, HF, and gastrointestinal bleeding and is more common in old women presenting with altered consciousness and history of hypothyroidism, neck surgery, or radioactive iodine treatment (www.thyroidmanager.org). Thyroid storm presenting with palpitation, atrial arrhythmias, and hypertension is managed according to a multidisciplinary approach aimed at lowering thyroid hormone synthesis and secretion and circulating thyroid hormones and controlling the peripheral effects of thyroid hormone up to the resolution of systemic manifestations.[273]

Uremic Cardiomyopathy

Uremic cardiomyopathy is a common complication in chronic renal diseases and is considered a risk factor for morbidity and mortality among patients with chronic kidney disease (CKD) or end-stage renal disease.[276] Along with coronary artery disease, LV hypertrophy and congestive HF account for approximately 50% of deaths in patients with CKD. Nontraditional risk factors (eg, uremic toxins, renin-angiotensin-aldosterone system activation, sympathetic nervous system activation, anemia, calcium phosphate imbalance, inflammation) are emerging as factors involved in the pathogenesis of cardiac disease in CKD. Their specific role in uremic cardiomyopathy is not clarified.[277,278] A recent Kidney Disease Improving Global Outcomes report emphasized the need for unraveling the origin and mechanism of cardiac dysfunction and diagnosing asymptomatic LV dysfunction in patients with CKD.[279] Compared with conventional hemodialysis (3 days per week), frequent hemodialysis (nocturnal home hemodialysis, short daily hemodialysis, and peritoneal dialysis) optimizes the ultrafiltration rate with minimal reductions in intravascular volume and cooling the dialysate; this reduces dialysis-induced myocardial stunning and intradialysis hypotension. Kidney transplantation may improve or reverse uremic cardiomyopathy and confers a significant survival advantage over hemodialysis.[280] Early diagnosis of uremic cardiomyopathy contributes to risk stratification and decisions about proper type of dialysis therapy.[281]

CARDIOVASCULAR ONCOTOXICITY (ALSO SEE CHAP. 101)

INTRODUCTION

Cardiovascular toxicity during and after chemotherapy and radiotherapy for cancer has been and remains a potential limitation to leveraging the full benefits of most advanced treatments of malignancies in childhood and adulthood.[282] Progression in cancer treatments has significantly increased the number of long-term survivors but has also increased the possibility of toxicity manifesting to the cardiovascular system over time.[283,284] Cardiovascular toxicity includes a range of complications, including involvement of the myocardium (eg, DCM, myocarditis), pericardium (eg, pericarditis, pericardial effusion), and vascular system (eg, coronary atherosclerosis, peripheral arterial disease, acute aortic syndromes, coagulopathy, hypertension, and hypotension)[285,286] (Table 58–8). Although these possible complications are known, the individual risk of

TABLE 58–8. Examples of Patients Diagnosed With Genetically Proven DCM Who Developed Cancer Before or After the Diagnosis of Cardiomyopathy

Sex	DCM Age	Cancer Age	MOGE(S) Baseline	MOGE(S) Last	Event/Age (years)
M	53	71	$M_{D(AVB)}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA[p.\ Glu317Lys]}\ S_{C\text{-}II}$	$M_{D(AVB)}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA[p.\ Glu317Lys]\ +\ Lung\ Cancer\ +\ RX\ therapy}\ S_{C\text{-}IV}$	Death HF 76
F	40	51	$M_{D(AVB)}\ O_{H}\ G_{AD}\ E_{G\text{-}DMPK[E2,500\text{-}1000\ CTG]}\ S_{C\text{-}II}$	$M_{D(AVB)}\ O_{H}\ G_{AD}\ E_{G\text{-}DMPK[E2,500\text{-}1000\ CTG]\ +\ T\ Doxo\ in\ Breast\ Ca}\ S_{C\text{-}IIb}$	Alive 56
M	50	55	$M_{D(E)}\ O_{H}\ G_{AD}\ E_{G\text{-}MYBPC3[p.Q969X]}\ S_{B\text{-}I}$	$M_{D(E)}\ O_{H}\ G_{AD}\ E_{G\text{-}MYBPC3[p.Q969X]\ +\ T\ Doxo\ in\ Colon\ Ca}\ S_{C\text{-}IV}$	Death HF 58
F	66	49	$M_{D(AVB)}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA[p.\ Arg335Gln]}\ S_{C\text{-}IIb}$	$M_{D(AVB)}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA[p.\ Arg335Gln]\ +\ T\ Doxo\ in\ Breast\ Ca}\ S_{C\text{-}III}$	Alive 69
F	61	55	$M_{D(AVB)(>sCPK)}\ O_{H+M}\ G_{AD}\ E_{G\text{-}LMNA[p.\ Lys171Lys]}\ S_{C\text{-}II}$	$M_{D(AVB)(>sCPK)}\ O_{H+M}\ G_{AD}\ E_{G\text{-}LMNA[p.\ Lys171Lys]\ +\ T\ Doxo\ in\ Breast\ Ca}\ S_{C\text{-}IV}$	Death HF 67

Note. The genotypes and phenotypes are coded according to the World Heart Federation 2013 MOGE(S) classification (see Chapter 57).

Abbreviations: Ca, cancer; DCM, dilated cardiomyopathy; F, female; HF, heart failure; M, male; MOGE(S), morphofunctional phenotype, organ(s) involvement, genetic inheritance pattern, etiologic annotation including genetic defect or underlying disease/substrate, and functional status of the disease.

occurrence remains largely unpredictable. Whereas greater risk would be expected in older patients and those with a preponderance of traditional risk factors, clinical evidence across a range of ages indicates that underlying risk does not necessarily correlate with expression of phenotype. Pretreatment risk stratification requires meticulous consideration to prevent or limit the effects of potentially harmful treatments in patients at high risk while not excluding patients from receiving effective treatments.[287] New cardiovascular imaging tools (ie, strain imaging) and biomarkers (eg, troponin, B-type natriuretic peptide) are now contributing to early detection, better risk stratification, and monitoring of the cardiovascular toxic effects of chemotherapy.[288,289] None of these markers has been specifically generated for detection or monitoring of cardiovascular toxicity per se; rather, their use represents the extension of standards in cardiovascular diagnosis generally to chemotherapy-induced cardiovascular abnormalities specifically.

The relevance of oncocardiotoxicity and DCM is related to the paradigmatic and well-known anthracycline-induced DCM and to the possibility that patients with genetic DCM may develop cancer. A detailed discussion of cardiovascular toxicity induced by chemotherapy is provided in Chap. 101.

MYOCARDIAL TOXICITY

Patients who develop cancer may have either healthy cardiovascular systems or preexisting cardiovascular conditions, including DCM (see Table 58–8). The former is obviously the most common, favorable, and expected condition. The latter requires involvement of a cardiologist, multidisciplinary evaluation, and specific monitoring.[284,286,287,290-292] Heart muscle toxicity is generally characterized as *nonreversible injury* (type 1) as a result of the presence of structural damage (prototyped by the anthracycline or high-dose cyclophosphamide DCM in acute and chronic forms) and potentially reversible (on cessation of therapy) dysfunction (type 2) in the absence of structural abnormalities, as with targeted therapies (ie, trastuzumab, sunitinib, lapatinib).[291-297] In patients first treated with drugs causing type 1 injury and then with drugs causing type 2 injury, the damage may be cumulative. Myocardial toxicity occurs with many agents used in the treatment of cancer; examples are summarized in Table 58–9.[298-334]

Cancer Therapy-Related Cardiac Dysfunction

The concept of myocardial toxicity does not coincide with that of cardiomyopathy.[1] The substantial difference between the diagnostic criteria in toxic myocardial dysfunction related to cancer therapy (American College of Cardiology Foundation/AHA 5.4.3) versus nontoxic dysfunction (eg, inherited DCM) is the dynamic concept of the diagnosis. The cardio-oncotoxicity is a double-step diagnosis that implies normal baseline cardiovascular function and evidence of decline of function during or after treatment. Therefore, the definition of cancer therapy–related cardiac dysfunction (CTRCD) or chemotherapy-related cardiac dysfunction (CRCD) seems to better describe both type 1 and type 2 myocardial damage. Anthracyclines (see Table 58–9) are the best-known drugs increasing the risk of CTRCD caused by type 1 injury; the incidence rate is as high as 2.1% in randomized controlled trials and 26% in observational studies.[282] Targeted drugs such as trastuzumab, a monoclonal antibody targeting the human epidermal growth factor receptor-2 in breast or gastroesophageal malignancies, are associated with CTRCD caused by type 2 injury with 3-year cumulative incidence of 6.6% when trastuzumab is used with anthracyclines and 5.1% when used without anthracyclines. Higher risk in mid- and long-term follow-up is reported with trastuzumab after anthracycline treatment.[282,284,285] The possibility of CTRCD occurring in FDCM may confound the interpretation of the cause of the myocardial disease (Fig. 58–11).

In 2002, the Review and Evaluation Committee of Trastuzumab-Associated Cardiomyopathy supervising trastuzumab trials defined CRCD as follows: "(1) characterized by a decrease in cardiac left ventricular ejection fraction (LVEF), either global or more severe in the septum; (2) symptoms of heart failure (HF); (3) associated signs of HF, including but not limited to S3 gallop, tachycardia, or both; and (4) decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of HF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms. The presence of any one of the four criteria is sufficient to confirm a diagnosis of CRCD."[317] From 2002 to the present, the above criteria have been repeatedly discussed and applied in clinical trials, but their systematic application is still debated and guidelines for their application are still lacking.[282]

The type 1 or 2 classification of myocardial injury is not immediately evident, and the diagnosis of type 2 injury can only be made after cardiac abnormalities have resolved following cessation of chemotherapy. The definition of type 1 or 2 injury cannot be made a priori. Reversibility or nonreversibility of the CRCD requires evidence of regression or persistence of myocardial damage (as with imaging, pathology, biomarkers, or clinical evaluation).

Myocarditis

Myocarditis is a rare complication described in patients treated for cancer (ie, cyclophosphamide and hemorrhagic myocarditis). It may present as fulminant myocarditis.[335,336]

Pericardial Involvement

Pericardial effusion and pericarditis (excluding carcinomatous pericarditis) may occur commonly in patients treated with different classes of chemotherapeutic drugs. They may be reliable markers of cardiotoxicity, especially when it can be demonstrated that the pericardial abnormality was not present prior to the administration of chemotherapy (see Chaps. 66 and 101).

Rhythm Disturbances

Variations of cardiac rhythm and ECG intervals are common. Prolongation of the QT interval is a consequence of many classes of anticancer drugs[286] and, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, is graded from 1 to 4 (the grade 5 corresponds to death) based on the length of the corrected QT interval (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). The risk of malignant arrhythmias in patients who develop a prolonged QT interval is not necessarily the same as in patients with congenital prolonged QT syndromes. There are no studies comparing populations of patients with long QT syndromes and toxic prolongation of the QT interval. Nonetheless, drugs that prolong the QT interval should be discontinued when the QT interval approximates warning values indicated by the guidelines. Arrhythmias, both supraventricular and ventricular, can be subtle and may escape detection because they can be clinically silent, transient, and unperceived by patients. Once life-threatening arrhythmias are demonstrated in patients treated for cancer, exclusion of noncardiotoxic causes is essential to prevent an incorrect assignment of the event to the chemotherapeutics, to decide about premature termination of chemotherapy, and to appropriately manage the arrhythmias.

Arterial Blood Pressure

Chemotherapeutics may either increase or decrease blood pressure (see Table 58–9). Hypertension is common in adult patients; it should be

TABLE 58–9. Major Cardiovascular Toxicity Effects and Phenotypes in Cancer Patients Treated With Different Chemotherapeutic Agents

			Myo/peri/endocardial				Rhythm and Conduction Effects and Events						Vascular Toxicity				
Class	Drugs and Dose-Dependent Effects	Cardiovascular toxicity (ranges, %)	LV Dysfunction-DCM	(Endo)myocardial Fibrosis	Myocarditis	Pericarditis/Pericardial Effusion	Arrhythmias	Conduction Defects (not-otherwise described)	QT Interval Prolongation	Bradycardia and AV Block	Sudden Death/cardiac arrest	Ventricular Tachycardia/Fibrillation	Vasospasm/Arterial Constriction	Acute Coronary Syndromes	Arterial Thrombosis	Venous Thromboembolism	Aortic Dissection	Blood Pressure
Anthracycline	Doxorubicin[1,298,299]	3-48	●		●	●	●	●	●	●		●						
	Idarubicin[300]	5-18	●					●										
	Epirubicin[301,302]	< 1-3	●				●	●		●					●			
	Mitoxantrone[a,303]	< 1-30	●				●	●		●				●				↑
Alkylating Agents	Cyclophoshamide[304]	7-28	●		●	●	●					●						
	Ifosfamide[305]	17	●				●	●	●			●		●				
	Busulfan[306]			●		●	●				●			●				↑or↓
	Mitomycin[307]	10							●									
Antimetabolites	Clofarabine[308]	27	●			●			●									↑or↓
	5-Fluorouracil[309,310]	1-78					●			●	●		●	●				↓
	Capecitabine[311]	2-9					●		●	●		●	●	●	●			
	Cytarabine[312]					●								●				
Mab-Based Tyrosine Kinase I	Bevacizumab[313-315]	4-35	●						●					●	●		●	↑↑
	Trastuzumab[316-318]	2-28	●												●			↑or↓
	Pertuzumab[319]	3-7																
	Alemtuzumab[320]		●				●											↑or↓
	Rituximab[b]						●											↓
Small molecule tyrosine Kinase I	Dasatinib	2-4	●			●	●		●			●						↑
	Imatinib mesylate[321,322]	0.5-2	●			●	●						●					↑
	Lapatinib[323]	1.5-16	●				●		●				●	●	●			↑
	Sunitinib[324,325]	2.7-11	●				●		●					●	●	●	●	↓
	Sorafenib[326]	4-28							●					●	●		●	↑
	Pazopanib[327]	7-13							●					●	●			↑

(*continued*)

TABLE 58–9. Major Cardiovascular Toxicity Effects and Phenotypes in Cancer Patients Treated With Different Chemotherapeutic Agents (*Continued*)

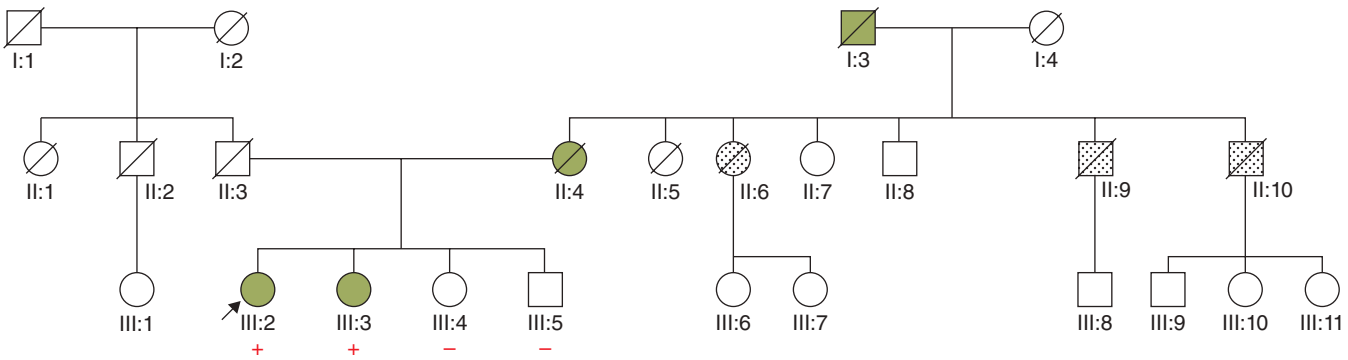
			Myo/peri/endocardial				Rhythm and Conduction Effects and Events							Vascular Toxicity				
Class	Drugs and Dose-Dependent Effects	Cardiovascular toxicity (ranges, %)	LV Dysfunction-DCM	(Endo)myocardial Fibrosis	Myocarditis	Pericarditis/Pericardial Effusion	Arrhythmias	Conduction Defects (not-otherwise described)	QT Interval Prolongation	Bradycardia and AV Block	Sudden Death/cardiac arrest	Ventricular Tachycardia/Fibrillation	Vasospasm/Arterial Constriction	Acute Coronary Syndromes	Arterial Thrombosis	Venous Thromboembolism	Aortic Dissection	Blood Pressure
Proteasome Inhibitors	Bortezomib[328]	2-5	●				●		●	●				●				
	Carfilzomib[329]		●															
Antimicrotubule	Paclitaxel[330,331]	< 1-31					●			●				●				
	Docetaxel[331]	< 2-8	●						●					●				
Angiogenesis Inhibitors	Lenalidomide[332]	3-75														●		↑
	Thalidomide[333]	1-58					●			●						●		↑
Platinum Agents	Cisplatin[334]	8.5					●			●		●	●	●		●	●	↑or↓
Antimicrotubule Agents	Vincristine[305]	25					●							●				↑or↓
Miscellaneous[329]	Interferon-α2b	25	●							●	●			●				↓
	Aflibercept	1-7												●	●			↓
	Pentostatin	3-10					●							●	●			
	All-trans-retinoic acid	6				●			●									↓
	Arsenic Trioxide	26-93							●									

Note. The prevalence ranges include data from both isolated and combined protocols.

Abbreviations: AV, atrioventricular; LV, left ventricular.

[a]Mitoxantrone being an anthracycline derivative, with immunosuppression effects, used in the past for multiple sclerosis is reported as potentially associated with the risk of acute leukemia.

[b]Angioedema: rare.



Pedigree	Clinical data	Age
I:3	Heart failure	Age: 43 years
II:3	IHD; colon polyposis	Age: 80 years
II:4	DCM, atrial fibrillation	Age: onset 55 years; death 68 years
II:6	HF in rheumatoid arthritis	Age: 55 years
II:9	IHD	Age: 77 years
II:10	IHD	Age: 80 years
III:2	Breast cancer; DCM	Cancer 52, DCM 53 years
III:3	DCM, ICD	Onset: 56 years
III:4	Negative clinical screening	Colon polyposis
III:5	Negative clinical screening	Hypertension

FIGURE 58–11. Cancer therapy–related cardiac dysfunction (CTRCD). The figure shows the pedigree of a family in which the proband (III:2) developed breast cancer that was treated with a trastuzumab-based protocol, and 1 year later, she developed dilated cardiomyopathy (DCM). One sister (III:3) is affected by DCM, whereas another sister (III:4) and the brother (III:5) are not affected. Genetic testing demonstrated the presence (+) in both sisters with DCM of the variant p.(Arg634Trp) in the *RBM20* gene; this variant was absent (–) in both nonaffected siblings (III:4 and III:5). The mother (II:4) was affected by DCM, whereas the father died of ischemic heart disease (IHD); none of them could be tested. In the same position of *RBM20*, p.(Arg634Gln) has been described in two families as a disease-causing mutation (Brauch et al. *J Am Coll Cardiol*. 229;54:930-941; Li et al. *Clin Transl Sci*. 2010;3:90-97). At present, we did not post the variant identified in our two sisters as a disease-causing mutation; although it seems to segregate with the DCM phenotype in the family, both unaffected siblings are younger, and we do not have functional data demonstrating the effect of this possible mutation. However, the family demonstrates that in patients with cancer and familial DCM, the interpretation of the causative role of CTRCD should be done cautiously. HF, heart failure; ICD, implantable cardioverter-defibrillator.

either excluded or recognized with certainty before assigning the hypertensive complication to chemotherapy.[314] The CTCAE version 4.03 grading of hypertension includes four grades (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf); grade 1, or prehypertension (systolic blood pressure of 120-139 mm Hg or diastolic blood pressure of 80-90 mm Hg), is very common in the general adult population (see Chaps. 23 and 24). In nonhypertensive patients, chemotherapy-induced endothelial dysfunction is associated with loss of vasorelaxant effects and suppression of anti-inflammatory and vascular repair functions. These effects may initiate and further maintain the development of hypertension, thrombosis, and atherogenesis. Hypertension is the most common cardiovascular complication associated with vascular endothelial growth factor inhibitors.[337] Effective antihypertensive treatment is mandatory before starting chemotherapy. In addition, drugs such as ACE inhibitors may exert a nonspecific protection to cardiotoxicity (see Chap. 25).[283,286,289]

Vascular Toxicity

Atherosclerosis-related events such as ischemic heart disease (both acute and chronic) and coagulation imbalances and related events (both thrombosis and hemorrhage) can be difficult to manage if a patient's vascular profile was unknown prior to initiation of treatment. Current protocols do not include definition of coronary anatomy or evaluation for coronary artery disease before prescribing chemotherapy in asymptomatic patients. A pretreatment risk assessment with either noninvasive evaluation of coronary tree (eg, angiographic CT coronary evaluation) in high-risk patients or evaluation of surrogate markers of atherosclerosis (combining risk factors with ultrasound evaluation of carotid arteries) could help cardiologists identify patients with different classes of risk, avoiding excess of vascular monitoring while selecting high-risk patients for more strict follow-up. Dynamic vascular reactions such as coronary spasm or Raynaud phenomenon are also described as an expression of vascular toxicity of several chemotherapeutics. Finally, rare cases of aortic dissection have been reported in patients treated with sunitinib,[338,339] gemcitabine,[340] sorafenib,[341] and bevacizumab.[342]

Overall, cancer therapy related cardiovascular toxicity may affect myocardium function and electrical properties of the heart, pericardium, aorta, and peripheral vessels and may also include coagulation imbalances. The role of cardiologists is increasingly complex as new classes of drugs enter clinical cancer programs and complications expand from CTRCD to electrical complications with variable risk of life-threatening arrhythmias. Cardio-oncology units should regularly operate in all cancer centers and units. (The list of drugs and current protocols is available and regularly updated at http://www.cancer.gov/about-cancer/treatment/drugs/.)

PROGNOSIS IN DILATED CARDIOMYOPATHY

The prognosis of DCM has been largely investigated in nongenotyped series of nonischemic DCM index patients. Prognostic stratification largely coincides with that of systolic HF (see Chap. 70). Currently available data are based on the phenotype and do not systematically

include the etiology. Exceptions include small series of genetic dilated cardiolaminopathies and dilated cardiodystrophinopathies, potentially reversible DCM, PPCM, and DCM in autoimmune diseases.

In the overall population of DCM patients, the prognosis has progressively and significantly improved over the past three decades.[343-345] The optimized use of ACE inhibitors, angiotensin receptor blockers, β-blockers, antialdosterone therapy, and resynchronization therapy[17,291] has substantially modified the natural history of DCM (see Chaps. 68 and 70). Annual incidence of major cardiac events (death and cardiac transplantation) declined, and transplant-free survival improved. HF-related deaths have decreased by 40% in the past 20 years.[346] Reasons for better survival and low event rate include early diagnosis, earlier medical treatment, resynchronization therapy, and primary prevention of sudden death with ICD implantation[347,348] (see Chaps. 72 and 73).

Recent studies demonstrate that patients enrolled in recent decades had a shorter history of HF, were less symptomatic for HF, and had fewer previous hospital admissions for HF and less severe heart disease; this modification has partly been attributed to the beneficial impact of systematic familial screening.[347] The enrollment in clinical series of family members (identified as affected in family screening studies) added a proportion of patients who were diagnosed in the early phases of the disease. In a single-center series, the incidence of major events declined to < 2 per 100 patients per year, with an 87% survival free from heart transplantation at 8 years in the last decade.[347] Earlier diagnoses imply earlier medical treatments, which are consequent further contributors to improved clinical outcome.

The pharmacologic and device-based actions modifying LV remodeling contribute to improvement of LVEF. Key drugs such as ACE inhibitors and β-blockers[17,291] and the use of aldosterone antagonists, improving LV remodeling and systolic function, positively impact prognosis[349-351]; up to 50% of patients receiving cardiac resynchronization therapy demonstrate significant reverse remodeling during the course of 24 months in nonischemic DCM with more evident benefits when follow-up is longer and patients demonstrate mild HF.[352] In patients in New York Heart Association class I/II, cardiac resynchronization therapy decreased all-cause mortality, reduced HF hospitalizations, and improved LVEF.[353]

Early reverse remodeling, achieved with both medical and device-based therapy, positively influences decisions on primary prevention, preventing unnecessary ICD implantation in patients with idiopathic DCM presenting with SCD in Heart Failure Trial criteria.[354] Reverse remodeling further influences mitral valve dysfunction, which is a further relevant negative prognostic contributor.[355] MitraClip can improve symptoms and promote reverse remodeling in nonresponders to cardiac resynchronization therapy.[356] The proportion of super-responders to cardiac resynchronization therapy in DCM series is difficult to establish; however, the predictors of responsiveness to cardiac resynchronization therapy can be usefully applied to DCM, especially because they include the lack of prior myocardial infarction.[357]

Overall, current prognostic markers and optimized medical and interventional treatments provide evidence that the natural history of DCM substantially improved in the last decades and can be further ameliorated. The open problem remains the arrhythmogenic risk stratification. Even super-responders to cardiac resynchronization therapy remain at risk for ventricular arrhythmias.[358] Imaging can contribute to predict arrhythmogenic risk; the association of myocardial fibrosis with mortality and SCD in patients with DCM is known.[359,360] However, beyond fibrosis, prognostic predictors such as low LVEF have limited sensibility and specificity. Selecting patients according to the current guidelines shows that most DCM patients do not actually benefit from ICD implantation, while suffering collateral effects. In addition, it is now evident that patients exhibiting mildly depressed LVEF can be at risk of sudden death. In the complex substrates underlying SCD, multiple risk factors can probably contribute to predict the risk of SCD.[62] Genetics can significantly contribute to stratify arrhythmogenic risk, as demonstrated in *LMNA* mutation carriers[59,60] and by the first introduction of genetics in the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and prevention of SCD.[63] Overall, we expect that in time the increased proportion of genotyped patients with DCM will generate data useful for progressing from the phenotype-based prognostic stratification to cause-specific risk stratification, either genetic or nongenetic.

CONCLUSION

The current descriptive diagnosis of DCM is based on a common end-phenotype that is functionally characterized by systolic dysfunction and LV remodeling with either mild or severe LV dilation. During the course of the past five decades, several different disorders, of myriad origins and causes, have been categorized as DCM simply based on shared phenotype. This "nosology strategy" was mainly based on the paucity of information about specific causes and pathophysiologic mechanisms of the different types of diseases that could culminate in a DCM phenotype and on the available, overlapping guideline-based treatments that influence the phenotype independent of the underlying mechanism. However, knowledge gleaned with novel DNA sequencing technologies, biomarkers, and advanced imaging is demonstrating that different causes of DCM call for different diagnostic and treatment strategies. The majority of DCMs have heterogeneous genetic origins, with more than 100 disease genes discovered to date. Other diseases with end-DCM phenotype are phenocopies of genetic DCM; each subtype is opening novel avenues of disease-specific research and paving the way for novel, targeted treatments. Typical examples are uremic and cirrhotic cardiomyopathies. DCM secondary to metabolic diseases or other potentially treatable causes such as persistent tachycardia may reverse with the control or treatment of the primary cause. It is time to separate DCM by cause, generating novel nosology and descriptors useful to improve disease-specific and individually tailored monitoring and treatments. Confounding different etiologies in the broad group of phenotypes is an obstacle to the development and delivery of personalized treatment. Cardiomyopathies in general and DCM in particular can generate precise disease models exportable to other cardiovascular diseases.

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CHAPTER 59

HYPERTROPHIC CARDIOMYOPATHIES

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DEFINITION AND EPIDEMIOLOGY

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy in the absence of abnormal loading conditions, such as severe hypertension or valve disease, sufficient to provoke the observed phenotype.[1] It occurs in approximately 1 in every 500 adults,[2-7] with a slightly higher prevalence in males but with no significant differences across ethnicities or geographical locations. Ventricular hypertrophy frequently develops during periods of rapid somatic growth, but can appear de novo at any time from infancy to old age.

The term "hypertrophic cardiomyopathy" embraces a range of disorders that can be grouped into familial/genetic and nonfamilial/nongenetic subtypes[1,8] (Fig. 59–1). The prevalence of individual disorders (phenocopies) varies with age. In 50% to 60% of adolescents and adults, HCM is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes. A further 5% of patients have metabolic or storage disorders, neuromuscular disease, chromosome abnormalities, and genetic syndromes such as cardio-facial-cutaneous disorders or phakomatoses. When all these disorders are excluded, 25% to 30% of cases remain unexplained.

HISTORICAL PERSPECTIVE

Patients with unexplained ventricular hypertrophy have been described for more than 100 years,[9] but it was not until the publication of Sir Russell Brock's paper on "functional obstruction of the left ventricle" in 1957[10] and Donald Teare's[11] description of asymmetrical myocardial hypertrophy in 1958 that HCM was established as a distinct disease. From the 1960s onward, diagnostic criteria for the disease evolved with the prevailing technologies used to interrogate the heart. An initial focus on clinical signs and symptoms and cardiac catheterization meant that dynamic left ventricular outflow tract obstruction was central to the diagnosis of the disease.[12-20] In the 1970s, the asymmetrical distribution of hypertrophy was emphasized by the use of M-mode echocardiography,[21-25] but with the advent of two-dimensional echocardiographic imaging and, later, cardiac magnetic resonance imaging, the complex spectrum of ventricular involvement is now better appreciated.[26,27]

Early clinical reports suggested that HCM is inherited in 30% to 50% of patients.[28] This was confirmed in prospective clinical genetic studies using two-dimensional echocardiography that suggested 50% to 60% of cases are inherited as an autosomal dominant trait.[29,30] In 1989, the first genetic mutation for HCM was mapped to chromosome 14[31,32] and then to the β-myosin heavy chain protein, a major component of the cardiac sarcomere.[33,34] Subsequently, hundreds of mutations have been identified, mostly involving the myofilaments of the cardiac sarcomere.[35,36]

GENETICS

HCM is the most common genetic cardiovascular disease. In approximately half of adolescents and adults with the disease, it is inherited as an autosomal dominant trait, characterized by a high locus and allelic diversity. More than 1500 mutations have been identified,[33,37-43] the majority of which (75%-80%) involve cardiac myosin heavy chain (*MYH7*) and cardiac myosin binding protein C (*MYBPC3*) (Fig. 59–2). Mutations in cardiac troponin T (*TNNT2*), troponin I (*TNNI3*), α- tropomyosin (*TPM1*), myosin light chains (*MYL2*, *MYL3*), and cardiac actin (*ACTC1*) account for 15% to 20% of mutation-positive individuals. Mutations in other sarcomere or related genes, including Z-disc protein genes like muscle LIM protein (*CSRP3*) or calcium-handling genes such as phospholamban (*PLN*), account for less than 1% of cases each. A further 5% to 10% of cases are caused by metabolic or storage disorders (eg, Anderson-Fabry disease, mitochondrial disorders, glycogen storage diseases), neuromuscular disorders, chromosome

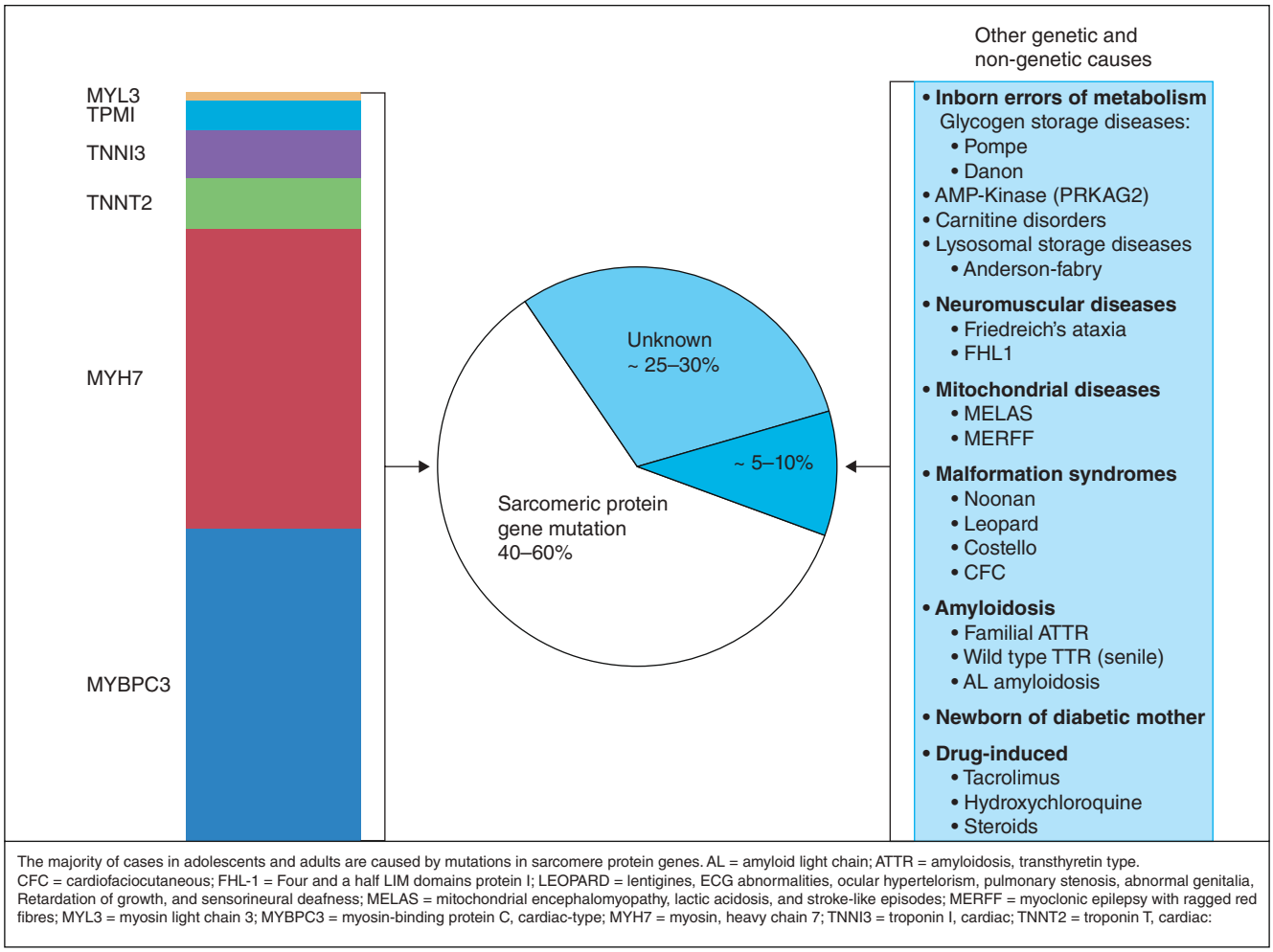


FIGURE 59–1. Causes of hypertrophic cardiomyopathy. Adapted with permission from Authors/Task Force, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J.* 2014 Oct 14;35(39):2733-2779.[1]

abnormalities, and genetic syndromes such as cardio-facial-cutaneous syndromes, including Noonan and LEOPARD syndromes.[44] The three most common metabolic causes of HCM, all with a prevalence of approximately 1%, are Anderson-Fabry disease, glycogen storage disease caused by *PRKAG2* mutations, and Danon disease.

Two pathogenic mechanisms are thought to account for disease associated with mutations in cardiac sarcomere proteins.[43] Missense single nucleotide variants (a nucleotide change that results in an amino acid being substituted by another amino acid in the protein) predominantly lead to a *dominant negative effect* (described as a "poison peptide" mechanism) in which the mutated protein is not destroyed but rather integrates into the sarcomere, leading to the disease phenotype; this is thought to be characteristic of *MYH7* variants.[41,45-47] Alternatively, nonsense single nucleotide variants or small frameshift insertion-deletions can introduce a premature stop codon and cause *haploinsufficiency* as a result of nonsense mRNA-mediated decay or proteolysis of a truncated (just partially translated) protein.[48] This mechanism is believed to be typical of the majority of *MYBPC3* disease-causing mutations.[49]

HCM is characterized by variable intra- and interfamilial expression and incomplete and age-dependent clinical penetrance.[42] This genotype-phenotype plasticity is largely unexplained.[50] Patients are routinely offered genetic testing in order to provide them with information about the likely impact of disease on their lives and to facilitate lifestyle and medical interventions that improve prognosis.[51] However, for this strategy to succeed, there must be a predictable relation between specific genotypes and disease expression. Meta-analysis of pooled data[52] shows that a small number of clinical variables are consistently associated with a positive sarcomeric protein genotype, specifically, younger age at presentation, greater hypertrophy, and a positive family history for HCM or sudden cardiac death. For each of these parameters, the pooled association is significant for the comparison between sarcomere mutation-positive and -negative patients, but not when comparing the two most frequently affected genes, *MYBPC3* and *MYH7*. Although data are limited, patients with more than one sarcomere mutation also seem to present earlier and/or with a more severe phenotype[35,53,54] and a higher likelihood of an evolution to a dilated phenotype.[55]

PATHOLOGY

Gross examination of the heart demonstrates asymmetric septal hypertrophy with a small left ventricular cavity (Fig. 59–3).[56-58] The mural endocardium may be thickened by fibrous tissue, and if left ventricular outflow tract obstruction is present, there is often a plaque located on the upper septal area where the mitral valve repeatedly has come in contact with the septum. The mitral valve itself may be abnormal, with elongation of the mitral chordae and anterior displacement of hypertrophied papillary muscles. Abnormal attachments of the mitral valve chordae into the septum, insertion of the papillary muscle head directly into the mitral leaflets, myocardial clefts, and increased ventricular

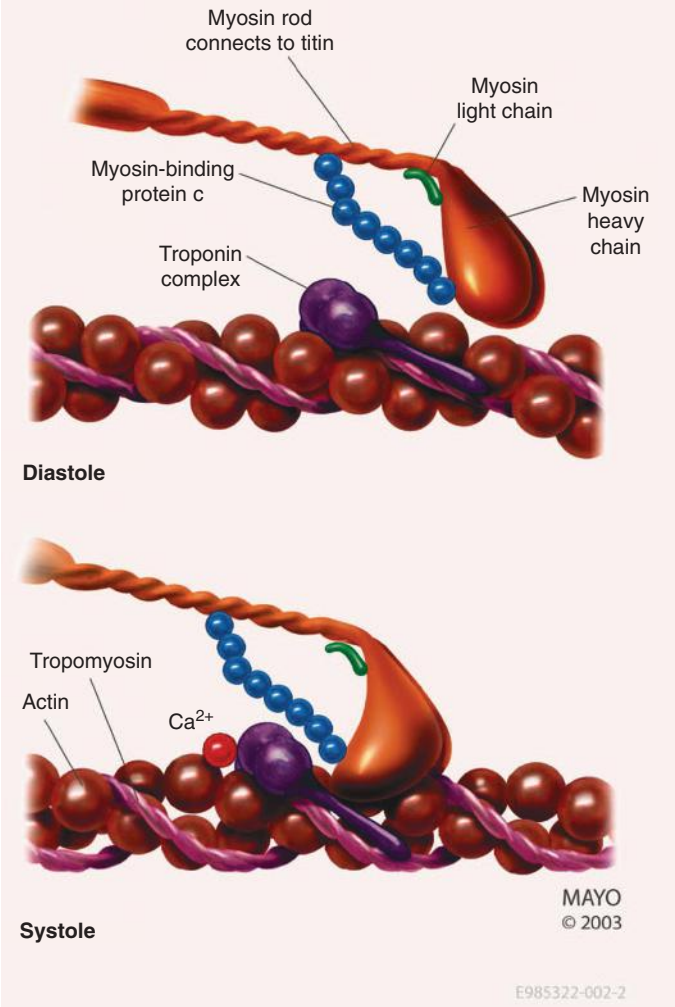


FIGURE 59–2. Schematic diagram of the sarcomere. In the majority of patients, hypertrophic cardiomyopathy is caused by mutations in genes encoding the thick and thin filaments of the sarcomere. The two most commonly affected are β-myosin heavy chain and cardiac myosin binding protein C.

trabeculation are also common.[59-61] The left (and sometimes the right) atrium is usually dilated in advanced disease as a result of mitral regurgitation and diastolic dysfunction. Although the epicardial coronary arteries are usually normal, they can follow an intramural course and be compressed during ventricular systole.[62]

The classical histopathologic appearance of HCM consists of cardiomyocyte hypertrophy and disarray, interstitial and replacement fibrosis, and dysplastic arterioles[62,63] (Fig. 59–4). In patients with some of the rarer phenocopies, other features such as myocyte vacuolation or infiltration may be observed.

CLINICAL PATHOPHYSIOLOGY

The pathophysiology of HCM is complex and consists of multiple interrelated abnormalities, including diastolic dysfunction, left ventricular outflow tract obstruction, and mitral regurgitation.

LEFT VENTRICULAR DYSFUNCTION

In most patients with HCM, a lifelong process of cardiac remodeling is present, characterized by myocardial fibrosis and wall thinning. In the early stages of this process, patients are often asymptomatic, and

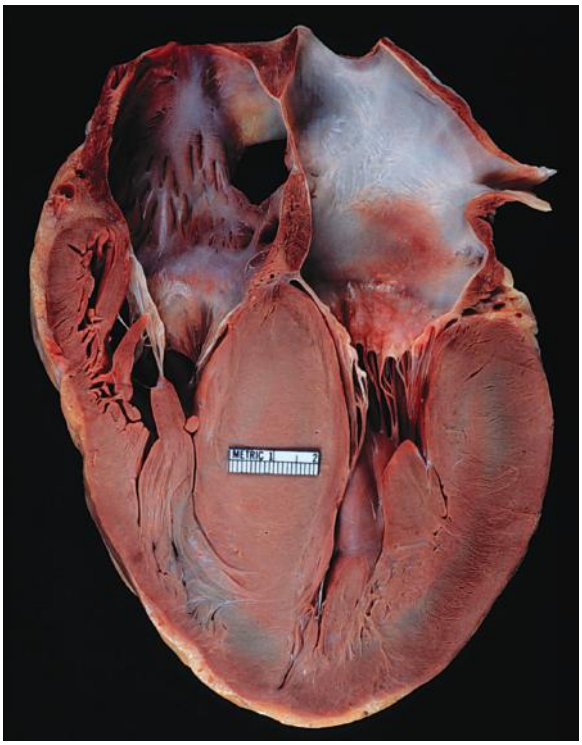


FIGURE 59–3. Pathologic specimen of a patient who died suddenly with hypertrophic cardiomyopathy. There is severe hypertrophy of the myocardium and a small left ventricular cavity. The left atrium is enlarged. Used with permission from Dr. W. D. Edwards, Mayo Clinic, Rochester, MN.

conventional noninvasive indices of left ventricular (LV) function are within the normal range. As the disease progresses, LV diastolic and systolic function progressively decline, causing either mild-to-moderate LV dilation, decreased LV wall thickness, and a reduction in LV ejection fraction (the so-called "burned-out" or hypokinetic dilated phase) or severe LV diastolic dysfunction characterized by marked atrial dilation with little or no LV dilation (the so-called "restrictive" phenotype). In some patients, moderate-to-severe pulmonary hypertension develops in these advanced stages.[64]

Diastolic dysfunction arises from multiple factors that affect both ventricular relaxation and chamber stiffness (Fig. 59–5).[65-68] Impairment of ventricular relaxation can result from the high systolic contraction

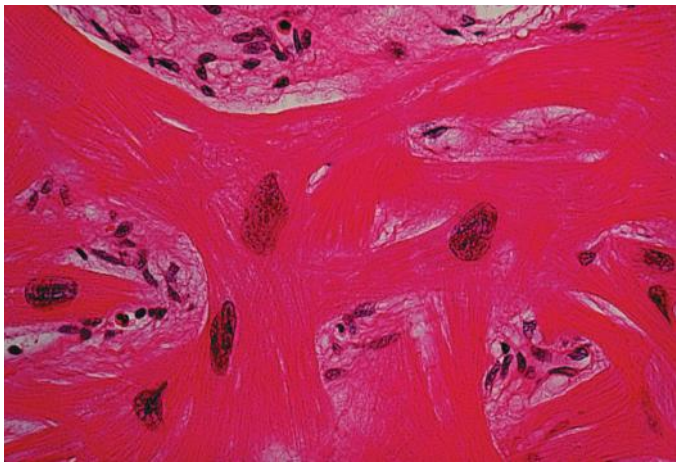


FIGURE 59–4. Microscopic section of the myocardium from a patient with hypertrophic cardiomyopathy showing myofiber disarray.

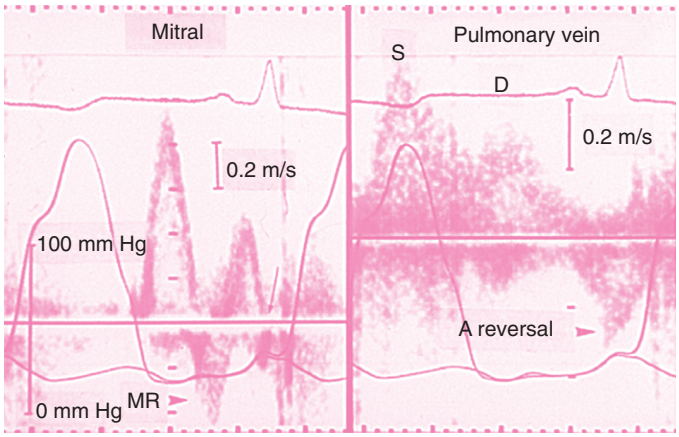


FIGURE 59–5. Evidence of severe diastolic dysfunction in a patient with hypertrophic cardiomyopathy. The left ventricular and left atrial pressures are shown in both the left and right panels. The mean left atrial pressure is severely elevated to 30 mm Hg. *Left*: The mitral flow velocity curve is shown, demonstrating a high E:A ratio and a short deceleration time. Diastolic mitral regurgitation (MR) is present. There is abrupt cessation of the "a" duration (*arrow*). *Right*: The pulmonary vein velocity curve is shown, with a high velocity at atrial reversal of long duration. The systolic forward flow (S) and diastolic forward flow (D) are shown.

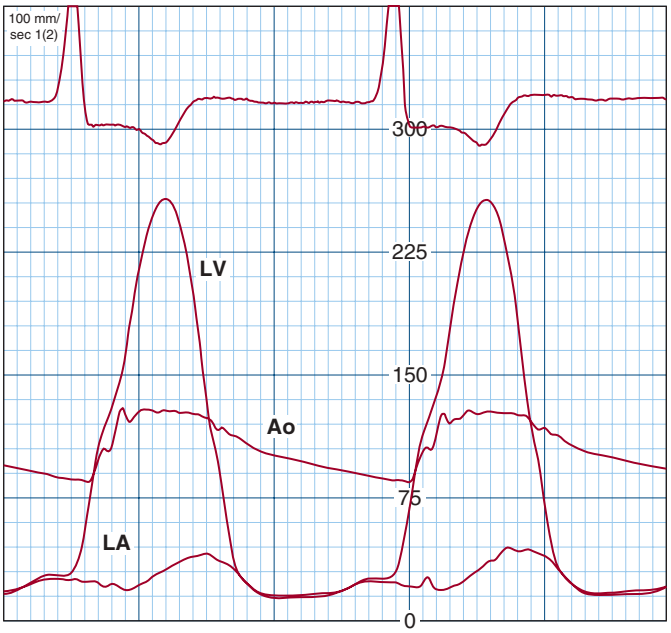


FIGURE 59–6. Cardiac catheterization pressure curves showing a severe left ventricular outflow tract obstruction. The gradient between the left ventricle (LV) and aorta (Ao) is nearly 100 mm Hg. The left atrial (LA) pressure is also elevated. There is a spike-and-dome pattern on the aortic pressure curve.

load caused by LV outflow tract obstruction, nonuniformity of ventricular contraction and relaxation, and delayed myosin-actin inactivation caused by abnormal intracellular calcium reuptake.[66-68] Diffuse myocardial ischemia caused by supply-demand mismatch also contributes to diastolic dysfunction.[69-72] Patients with HCM have increased oxygen demand as a result of ventricular hypertrophy and abnormal loading conditions but also have compromised coronary blood flow to the LV myocardium because of abnormally small and partially obliterated intramural coronary arteries.[69,70,73-75] In addition, myocardial energy metabolism is compromised as a result of inefficient cardiomyocyte contraction and is an early feature of the disease in carriers of sarcomeric protein mutation.[76] With exercise, diastolic function is further compromised by a decrease in the diastolic filling period and prolongation of the time to peak filling, which increase pulmonary venous pressure and cause dyspnea.[68]

Severe LV systolic dysfunction has a prevalence of 2% to 5% and an incidence of 0.5 to 1 case per 100 patient-years. It is associated with a poor prognosis as a result of high rates of refractory heart failure and sudden arrhythmic death.[64] Small observational series suggest that patients with some of the rarer HCM phenocopies are more likely to develop systolic impairment than those with disease caused by sarcomeric protein gene mutations.[77]

During exercise, approximately 25% of HCM patients have an abnormal blood pressure response defined by either a failure of systolic blood pressure to increase > 20 mm Hg or a decrease in systolic blood pressure.[78,79] The response is associated with a poorer prognosis in young adults.[79,80] The mechanism is complex and involves inappropriate systemic vasodilatation during exercise and a reduction in cardiac output reserve caused by small LV stroke volume.[81]

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Dynamic LV outflow obstruction caused by contact between the mitral valve leaflets during ventricular systole is present in one-third of patients at rest and a further one-third during exercise or physical maneuvers that reduce ventricular volume or increase contractility.[82] The mechanism of obstruction was initially thought to be narrowing of the LV outflow tract caused by systolic contraction of the hypertrophied basal ventricular septum and a resultant suction (Venturi) force that pulls the mitral valve leaflets anteriorly.[82,83] The modern concept is that flow against the abnormally positioned mitral valve apparatus in systole causes a drag force on a portion of the mitral valve leaflets that pushes the leaflets into the LV outflow tract.[84-88] Obstruction to the LV outflow typically varies with loading conditions and contractility of the ventricle (Figs. 59–6, 59–7, and 59–8).[89,82] Obstruction can also be present in the midcavity as a result of hypertrophied papillary muscles abutting against the septum.[90]

MITRAL REGURGITATION

Mitral regurgitation is common in patients with LV outflow tract obstruction and is an important cause of dyspnea.[1,2,91] Mitral regurgitation is usually caused by the distortion of the mitral valve apparatus from systolic anterior motion secondary to LV outflow tract obstruction. The jet of mitral regurgitation is directed laterally and posteriorly, predominates during mid and late systole (Fig. 59–9), and is proportional to the severity of LV outflow tract obstruction. Changes in ventricular load and contractility that affect the severity of outflow tract obstruction will similarly affect the degree of mitral regurgitation (see Fig. 59–8). It is important to identify patients who have additional intrinsic disease of the mitral valve apparatus (eg, prolapse or flail leaflets) because this finding influences subsequent treatment options.[1,92]

CLINICAL PRESENTATION

The majority of patients with HCM are asymptomatic, with the disease being diagnosed based on an abnormal electrocardiogram, heart murmur, or screening echocardiogram. When symptoms are present, they often vary from day to day and may be exacerbated during hot humid weather, presumably as a result of fluid loss and vasodilation that cause decreases in both preload and afterload. Similarly, symptoms may be more prominent after eating a large meal or after drinking alcohol. Other concomitant problems, such as anemia or fever, may also exacerbate symptoms.

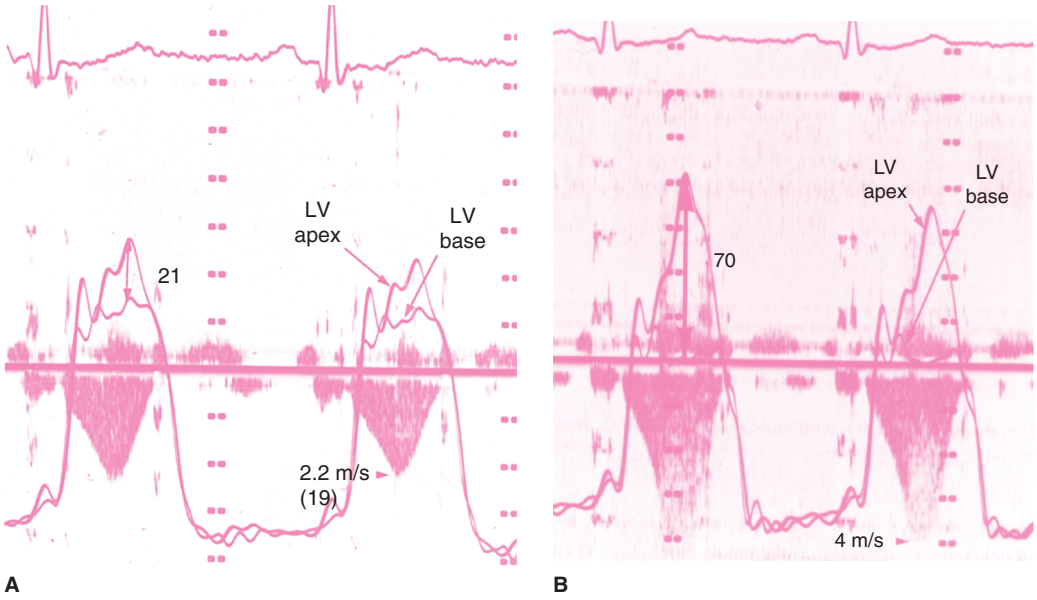


FIGURE 59–7. The dynamic nature of the left ventricular outflow tract obstruction is shown by simultaneous Doppler echocardiography and cardiac catheterization. The cardiac catheterization is performed with a pressure measurement of the left ventricular apex and left ventricular base. The gradient occurs during systole between the left ventricular apex and left ventricular base. The continuous wave Doppler velocities through the left ventricular outflow tract are shown. The calculated gradient from the Doppler echocardiogram is shown in parentheses. **A.** The gradient in the baseline state is 21 mm Hg as assessed by both cardiac catheterization and Doppler echocardiography. **B.** During inhalation of amyl nitrite, the gradient increases to 70 mm Hg.

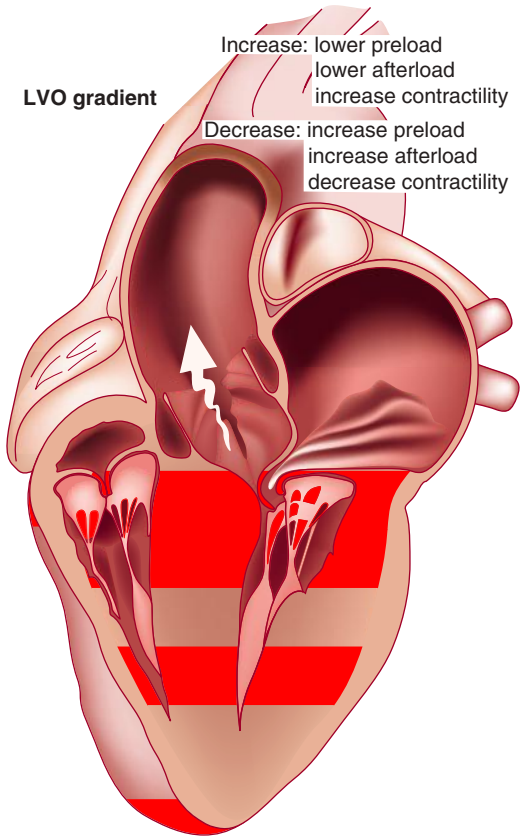


FIGURE 59–8. Schematic diagram of the left ventricle in hypertrophic cardiomyopathy during systole. There is projection of the basal septum into the outflow tract with systolic anterior motion of the mitral valve, which results in left ventricular outflow (LVO) tract obstruction. The obstruction is dynamic, dependent on the preload, afterload, and contractility of the heart.

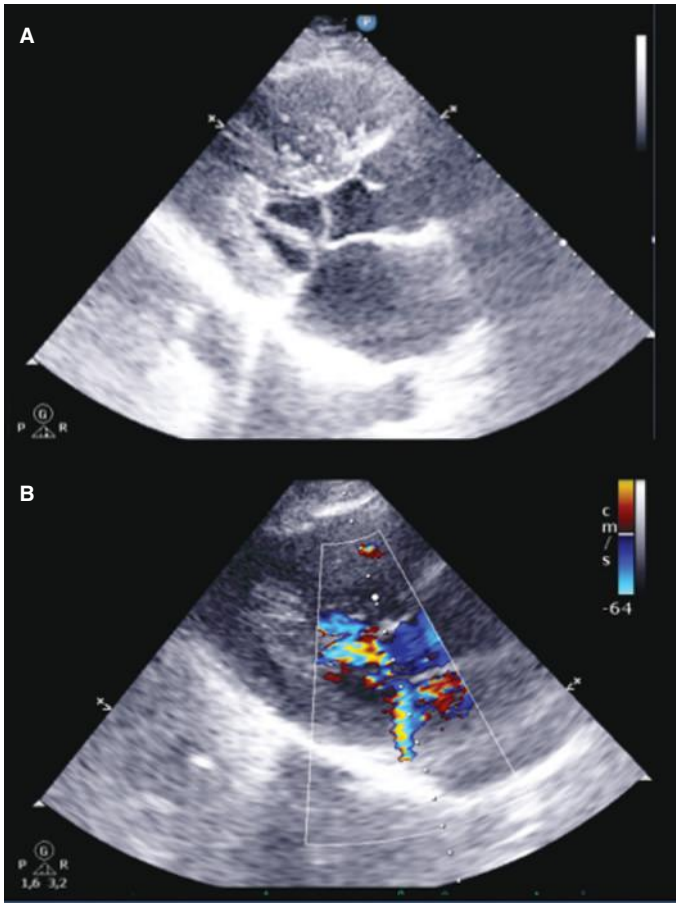


FIGURE 59–9. Two-dimensional and color flow Doppler imaging of a patient with hypertrophic cardiomyopathy, severe systolic anterior motion of the mitral valve, and secondary mitral regurgitation. **A.** A still-frame two-dimensional echocardiogram from the parasternal view showing complete systolic anterior motion of the mitral valve. **B.** Color flow imaging demonstrating a mosaic jet of mitral regurgitation directed posteriorly.

Dyspnea is usually caused by a combination of LV outflow tract obstruction, mitral regurgitation, and LV diastolic dysfunction. Angina, usually in the absence of epicardial coronary disease, is caused by a number of mechanisms, including small-artery narrowing, intramural compression of small arteries from myocardial hypertrophy, abnormal diastolic filling, oxygen supply-demand mismatch, and abnormal coronary flow reserve.[74,93] Transient loss of consciousness occurs in approximately 20% of HCM patients. In most cases, it is a result of syncope caused by LV outflow tract obstruction, activation of LV baroreceptors resulting in reflex vasodilatation, and atrial and ventricular arrhythmia.

The phenotype in many older patients varies from that in younger individuals in that many have a history of hypertension and a sigmoid septal configuration.[94-99] Atrial fibrillation is common in older patients (25%-30%) and may herald systemic embolism and further clinical deterioration.[94,100] Older patients may also have manifestations of other concomitant cardiac disease, such as coronary artery disease, degenerative valvular aortic stenosis, and mitral annular calcification. Amyloidosis (both light chain and transthyretin types) is an important differential diagnosis in elderly patients with HCM.[77]

PHYSICAL EXAMINATION

A systematic clinical approach should be used in all patients to identify specific disorders and guide the selection of further diagnostic tests, including molecular genetic analysis.[1,77,101] Table 59–1 presents some of the most important diagnostic "red flags."

CARDIAC EXAMINATION

The classical physical findings of HCM are present in patients who have an LV outflow tract gradient. Patients who do not have LV outflow tract obstruction may have findings of LV hypertrophy on physical examination.

ARTERIAL PULSE

The classic carotid pulsation is brisk with a spike-and-dome pattern, characterized by a rapid rise (percussion wave) followed by a mid-systolic drop that is, in turn, followed by a secondary wave (tidal wave). The mid-systolic fall in amplitude of the carotid pulse contour is caused by premature closure of the aortic valve and coincides with systolic anterior motion of the mitral valve. The late peak results from reduction of the outflow tract gradient as the mitral valve leaflet returns to its original position. In the presence of pronounced obstruction, there is a longer ejection time. The carotid pulsation with dynamic LV outflow tract obstruction differs from that of a fixed obstruction such as valvular or discrete subvalvular aortic stenosis, which is characterized by a decrease in both the rate of rise and the amplitude of the pulsation.

JUGULAR VENOUS PULSE

The jugular venous pressure is normal in most patients, but the *a* wave can be prominent, indicating a decrease in ventricular compliance caused by right ventricular hypertrophy, pulmonary hypertension from left-sided diastolic pressure elevation, or right ventricular outflow obstruction.

APICAL IMPULSE

The apical impulse is almost always abnormal in patients with HCM. Typically, it is a sustained systolic thrust that continues throughout most of systole and can be bifid as a result of a forceful atrial systole. There may be a triple impulse, with a third component occurring near the end of systole if outflow tract obstruction is present. A systolic thrill may be palpable at apex from severe mitral regurgitation or at the lower left sternal border from outflow tract obstruction.

CARDIAC AUSCULTATION

Auscultation usually reveals a normal or loud first heart sound. The second heart sound is usually split physiologically, although some patients have a paradoxical split as a result of either a concomitant left bundle branch block or severe LV outflow tract obstruction. A fourth heart sound is usually present, especially if there is severe hypertrophy. In young patients, an early diastolic filling sound is frequently heard, indicating rapid early filling. In the presence of severe mitral regurgitation, the excess flow across the mitral valve may result in a diastolic flow rumble.

The classic murmur from LV outflow tract obstruction is a crescendo-decrescendo murmur located primarily at the left sternal border. The murmur usually ends before the second heart sound. The murmur can radiate to the base of the heart as well as to the apex, but in contrast to valvular aortic stenosis, there is seldom radiation to the carotid arteries. Mitral regurgitation may be a separate murmur audible at the apex and is more holosystolic in nature. The presence of an aortic diastolic decrescendo murmur should suggest another disease, such as aortic valve disease or a discrete subvalvular stenosis.

Dynamic auscultation should be performed to differentiate the murmur of HCM from that of valvular aortic stenosis and mitral regurgitation. Maneuvers that decrease preload will increase the dynamic gradient and increase the intensity of the murmur (see Fig. 59–8). Although the change in murmur intensity during the strain phase of the Valsalva maneuver has been proposed as a method to diagnose the dynamic murmur of HCM, this classic response may not occur in all patients. A more reliable method for diagnosing a dynamic LV outflow tract obstruction is the response of the murmur to the stand-squat-stand position. From the standing position to a prompt squat, the murmur will markedly decrease in intensity, as a result of increases in afterload and preload. From the squatting to standing position, there will be an increase in intensity of the murmur immediately as afterload is reduced. A progressive increase in intensity of the murmur will continue for the next four to five beats as preload to the left side of the heart is reduced. Simple exercise, such as walking or climbing stairs, can also be used to provoke the murmur. Other maneuvers that are used to change the intensity of the murmur include leg-raising to increase preload (and thereby decrease the intensity of the murmur) and the inhalation of amyl nitrite to decrease afterload, increase heart rate, and increase the intensity of the murmur. There is also an increase in intensity of the systolic murmur after a premature ventricular beat.

DIAGNOSTIC TESTING

ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) is abnormal in the majority (~95%) of HCM patients.[1,94] The most frequent ECG alterations are repolarization abnormalities (eg, ST-segment depression and/or T-wave inversion).[102,103] A left-axis deviation is present in up to 30% of patients. Abnormal Q waves, simulating myocardial infarction, are seen in 25% to 30% of patients[102,103] (Fig. 59–10). Varying prevalences of 35% to 70% are reported for increased QRS voltage.[102-105] The ECG in patients with predominantly apical LV hypertrophy may show a distinctive pattern of diffuse symmetric and deep T-wave inversions across the precordium or the inferolateral leads (Fig. 59–11).[1,102] Some ECG

TABLE 59–1. Summary of the Main Clinical Features That Can Help Identify Specific Causes of Hypertrophic Cardiomyopathy

Cardiomyopathy	Inheritance	Age at Presentation	Extracardiac Manifestations	ECG	Laboratory Testing	Echocardiogram	CMR
Sarcomeric HCM	AD	Adolescent/young adult	No	Giant negative T-wave inversion in the precordial and/or inferolateral leads suggests involvement of the LV apex	For general assessment: hemoglobin, renal function; NT-brain natriuretic peptide		Midwall LGE LGE at the insertion zones of the RV in the septum
AFD	X-linked	Age > 30 years (male), > 40 years (female)	Acroparesthesias, hypohidrosis, sensorineural deafness, angiokeratomata, cataracts, lymphedema, others	Short PR AV block	Impaired GFR and proteinuria Low values or undetectable plasma and leukocyte α-galactosidase A present in male patients	Increased AV valve thickness RV hypertrophy Concentric LVH Papillary muscle enlargement	Posterolateral LGE
Cardiac amyloidosis	AD if inherited TTR Sporadic if senile or AL form	> 60 years for senile TTR, male predominance	Bilateral carpal tunnel syndrome (TTR), peripheral sensory neuropathy	AV block Low QRS voltages (50% of AL and 20% of TTR)	Impaired GFR and proteinuria Serum immunoglobulin free light chain assay, serum and urine electrophoresis if AL amyloidosis is suspected	Increased interatrial septum thickness Increased AV valve thickness RV hypertrophy Pericardial effusion "Ground glass" appearance of the myocardium Concentric LVH Global hypokinesia	Diffuse subendocardial LGE Changed gadolinium kinetics
Glycogen storage disease (GSD)	AR	Neonates/infants	Muscle weakness, neurologic involvement	Short PR Pre-excitation Extreme LVH (voltage)	Abnormal liver tests Raised creatine phosphokinase	Extreme concentric LVH	
Danon (GSD IIB)	X-linked	Neonates/infants	Mental retardation, deafness, muscle weakness	Short PR Pre-excitation AV block Extreme LVH (voltage)	Abnormal liver tests Raised creatine phosphokinase	Extreme concentric LVH Global hypokinesia	
PRKAG2	AD	Adolescent/young adult	Muscle weakness	Short PR Pre-excitation AV block		Concentric LVH Global hypokinesia	
RASopathies	AD	Infants	Mental retardation, dysmorphic features, lentigines, café-au-lait spots, woolly hair	Northwest QRS axis deviation		RV hypertrophy Congenital heart disease (eg, pulmonary stenosis) RV outflow tract obstruction	
Mitochondrial cardiomyopathy	Matrilinear (mitochondrial DNA) AD/AR/X-linked (nuclear DNA)	Neonates/infants	Wide range (eg, deafness, encephalopathy, diabetes, muscle weakness)	Short PR AV block	Impaired GFR and proteinuria Abnormal liver tests Raised creatine phosphokinase Elevated lactate	Global hypokinesia	
Desminopathies	AD or AR	Young adult (wide range)	Muscle weakness	AV block			

Abbreviations: AD, autosomal dominant; AFD, Anderson-Fabry disease; AR, autosomal recessive; AV, atrioventricular; CMR, cardiac magnetic resonance; ECG, electrocardiogram; GFR, glomerular filtration rate; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; LVH, left ventricular hypertrophy; NT, N-terminal; RV, right ventricle; TTR, transthyretin.

Data from Lopes LR, Elliott PM. New approaches to the clinical diagnosis of inherited heart muscle disease. *Heart*. Oct 2013;99(19):1451-1461; and Authors/Task Force, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. Oct 14 2014;35(39):2733-2779.[101]

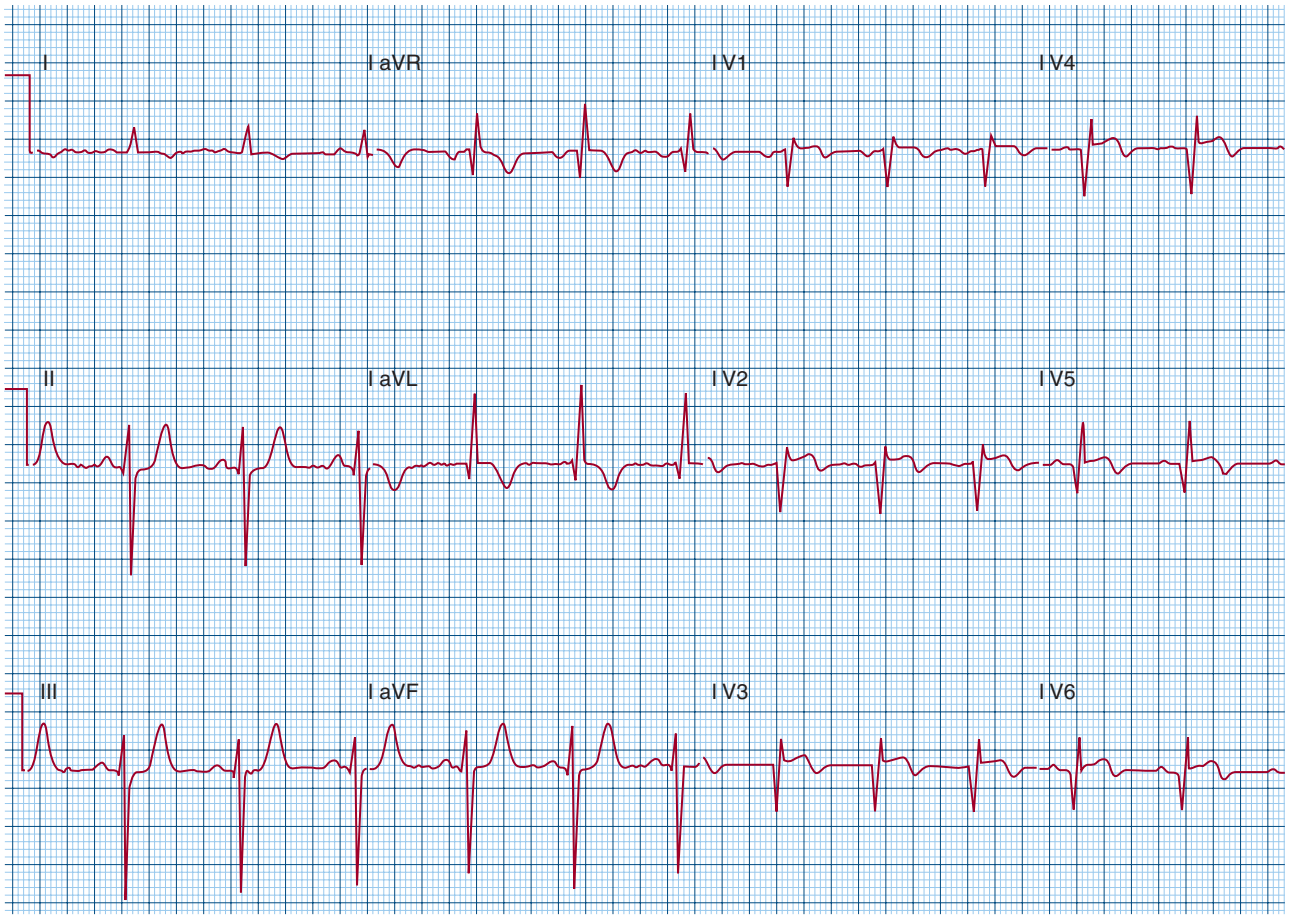


FIGURE 59–10. Twelve-lead electrocardiogram from a patient with hypertrophic cardiomyopathy. There is left-axis deviation and pathologic Q waves throughout the precordial leads, with ST elevation. Cardiac magnetic resonance (not shown) demonstrated extensive fibrosis.

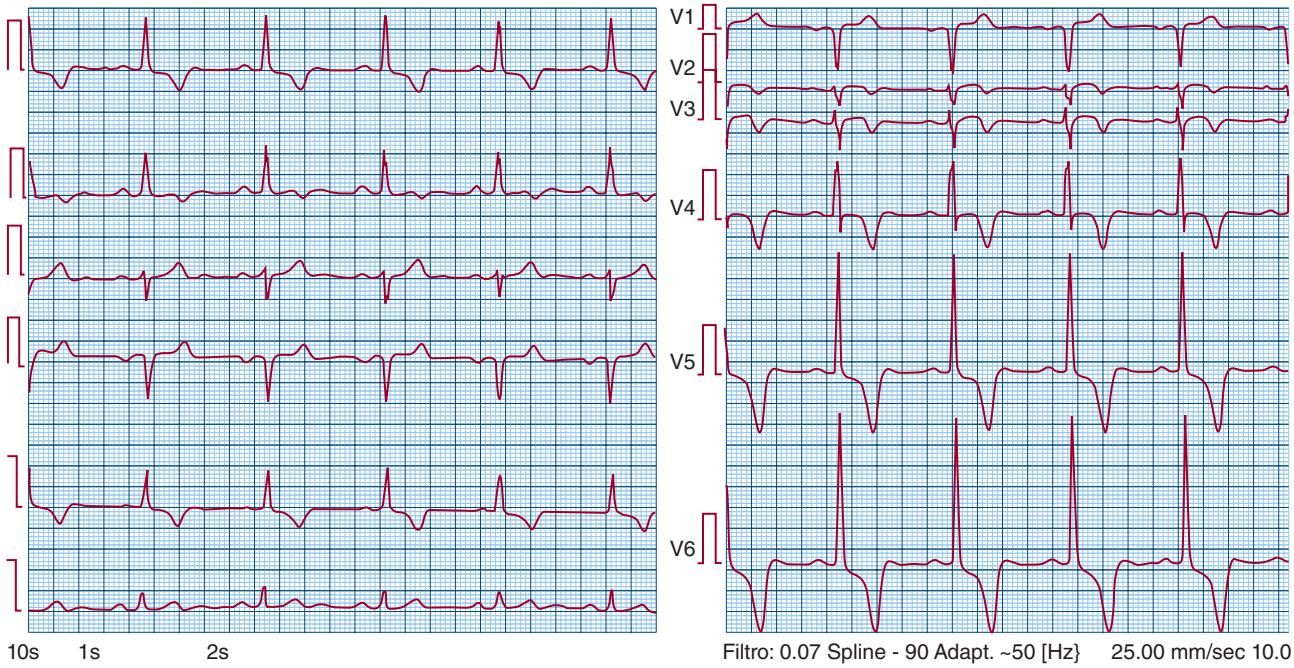


FIGURE 59–11. Twelve-lead electrocardiogram from a patient with the apical variant of hypertrophic cardiomyopathy. There are diffuse T-wave inversions across the precordium as well as left ventricular hypertrophy by voltage.

abnormalities, including pre-excitation and atrioventricular (AV) block, may suggest specific etiologies,[77] as summarized in Table 59–1.

Abnormalities in the ECG, in particular repolarization changes, can be the only abnormal diagnostic test present in relatives and carriers of mutations in the absence of hypertrophy on cardiac imaging. These patterns have been proposed as part of the diagnostic criteria for relatives and/or part of a "prehypertrophic" phenotype.[94,106]

Most patients are in normal sinus rhythm at initial diagnosis, but supraventricular tachycardia (up to 38%-46%), premature ventricular contractions (43%), and nonsustained ventricular tachycardia (25%) are frequent during ambulatory monitoring in adults.[1,107-109] Atrial fibrillation occurs in 25% to 30% of the older population.[100]

CHEST X-RAY

The chest x-ray usually shows mild-to-moderate enlargement of the cardiac silhouette. The LV contour is rounded, consistent with LV hypertrophy. There is usually enlargement of the left atrium, and the right-sided chambers are usually normal.

ECHOCARDIOGRAPHY

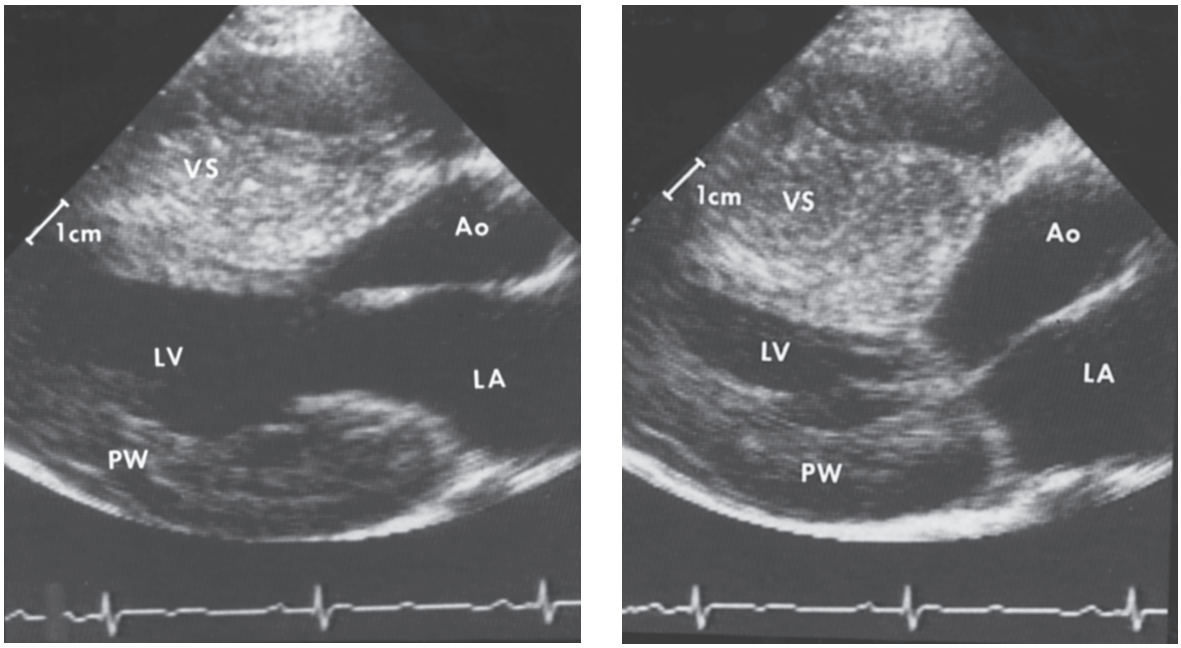
Increased LV wall thickness measured by any imaging technique is the basis for the diagnosis of HCM (Fig. 59–12). In an adult, a wall thickness ≥ 15 mm at end-diastole in one or more myocardial segments and, in children, a wall thickness more than two standard deviations greater than the predicted mean are sufficient to make the diagnosis. In first-degree relatives of patients with unequivocal disease, the diagnosis is based on the presence of an otherwise unexplained LV wall thickness ≥ 13 mm in one or more LV myocardial segments.

Hypertrophy can be distributed throughout the myocardium, including the right ventricle, but most commonly involves the interventricular septum (Fig. 59–13).[1,26,110-112] Because any segment of the LV can be involved, echocardiographic studies should systematically examine all the segments of the ventricular walls from base to apex. Measurements from the short-axis images are considered more accurate, but it is important not to include right ventricular structures (eg, moderator band or crista supraventricularis) in measurements of wall thickness. When image quality is poor (sometimes an issue with the lateral LV wall or the LV apex), intravenous contrast agents can help to visualize the endocardium.[1,110] The average maximal LV wall thickness in a population of HCM patients is usually 20 to 22 mm; however, 5% to 10% of patients will have maximal wall thickness in excess of 30 mm.

Patterns of hypertrophy may vary with age at presentation.[95] In the young population, hypertrophy usually involves the entire septum, creating a convex septal contour. In the older population, a "sigmoid" septum, in which the hypertrophy is localized to the basal and mid-septum and associated with increased angulation between the septum and the long axis of the aorta, is more frequent.

The differential diagnosis of LV hypertrophy is considerable. Increased afterload on the left ventricle from either hypertension or valvular aortic stenosis may cause an increase in the LV wall thickness. Infiltrative, metabolic, and neuromuscular diseases such as cardiac amyloidosis, Fabry disease, and Friedreich ataxia are also recognized phenocopies.[1,77,113-115] Echocardiographic characteristics that suggest the presence of particular causes of HCM are listed in Table 59–1. Echocardiographic modalities that assess myocardial deformation can be useful to distinguish between different causes of ventricular hypertrophy.[101,110]

It is important to correlate the findings of increased LV wall thickness on echocardiography with the ECG. For example, a relatively small QRS voltage on the 12-lead ECG in the presence of increased wall thickness should raise suspicion of an infiltrative disorder[1,77] (Fig. 59–14). The reverse can occur in glycogen storage disease (eg, Pompe disease) when ECG voltages are dramatically increased, sometimes in association with ventricular pre-excitation.[1,77]



A B

FIGURE 59–12. Two-dimensional echocardiogram from a patient with severe hypertrophic cardiomyopathy. There is a severe increase in left ventricular wall thickness, with a much greater increase in thickness of the ventricular septum (VS). The ratio of ventricular septal thickness to posterior wall (PW) thickness is 2.5:1. **A.** Parasternal long-axis view during diastole. **B.** Parasternal long-axis view during systole. There is systolic anterior motion of the mitral valve causing left ventricular outflow tract obstruction. Ao, aorta; LA, left atrium; LV, left ventricle.

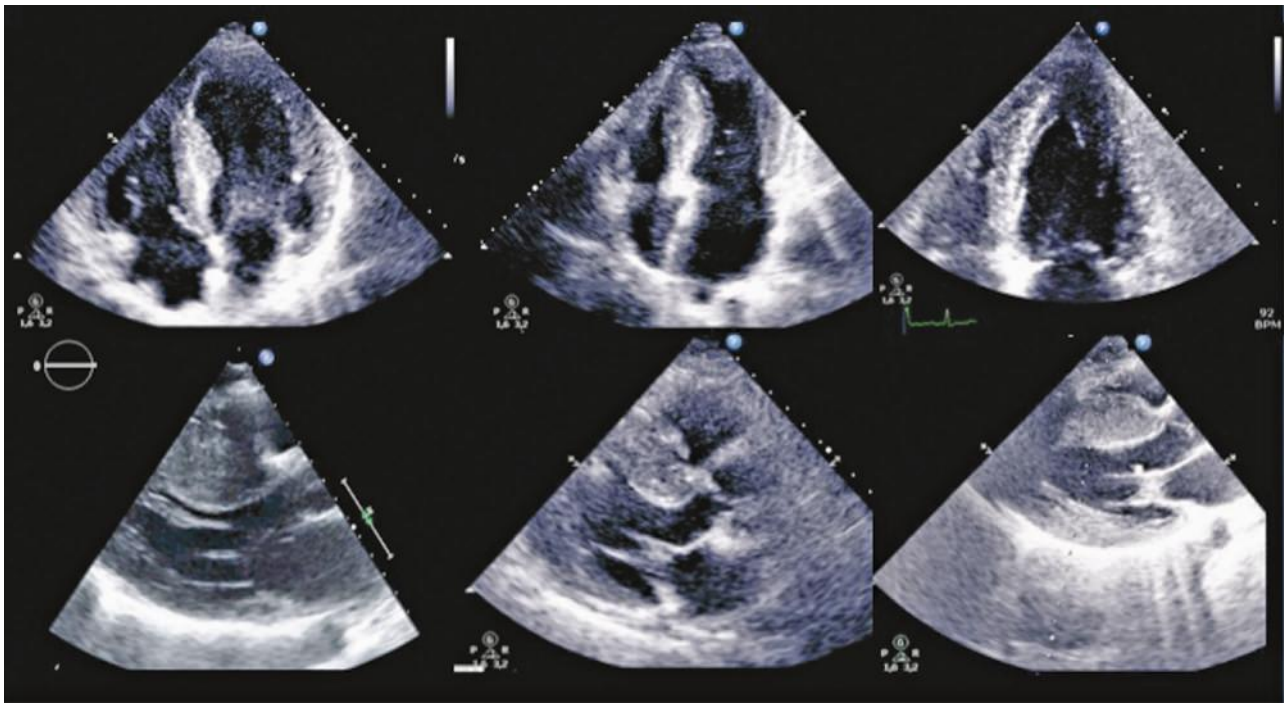


FIGURE 59–13. Different variants of hypertrophic cardiomyopathy visualized with echocardiography (six different patients). Upper row shows four-chamber views, and lower row shows parasternal long-axis views.

In athletes, physiologic adaptation to intense training can rarely cause an increase in LV wall thickness that is difficult to differentiate from HCM.[116,117] Elite athletes who have a dilated ventricular cavity with septal thickness < 14 to 15 mm most likely have "athlete's heart," but the combination of these findings may not always be present. A reduction in wall thickness after cessation of training is useful to identify the athletic heart but may not be practical in all patients.[116,117] Investigations with Doppler tissue imaging, myocardial strain, and cardiac magnetic resonance imaging may assist in differential diagnosis.[118-120]

Left Ventricular Outflow Tract Obstruction

Two-dimensional echocardiography is the primary tool for defining the presence and severity of LV outflow tract obstruction (LVOTO).[110,121] It is also essential for ruling out other causes of LVOTO such as a subaortic membrane[1,110,122] and to identify mitral valve structural abnormalities.

Dynamic LVOTO is characterized by systolic anterior motion (SAM) of the mitral valve apparatus and an open ventricular chamber. Most patients have SAM of the anterior leaflet, but it also occurs with the posterior leaflet.[110,123] Frequently, additional abnormalities of the mitral valve and supporting structures exist.[60,124] These include papillary muscle abnormalities (eg, hypertrophy, anterior and internal displacement, direct insertion into the anterior mitral valve leaflet) and mitral leaflet abnormalities such as elongation or accessory tissue.[1,110] The exact site of the obstruction is determined by visualizing the region of the SAM-septal contact.[110,125] In the classical form of obstructive HCM, obstruction occurs at the most basal portion of the septum as it projects into the LV outflow tract. In some patients, obstruction extends into the left ventricle from SAM of the chordal apparatus or mid-ventricular obstruction caused by hypertrophied papillary muscles.[90,110]

Dynamic LVOTO is characterized by a high-velocity, "dagger-shaped" signal on continuous wave Doppler (Fig. 59–15).[110,126] LVOTO is defined as an instantaneous peak Doppler LV outflow tract pressure gradient ≥ 30 mm Hg at rest or during physiologic provocation such as Valsalva maneuver, standing, or exercise. A gradient of ≥ 50 mm Hg is usually considered to be the threshold at which LVOTO becomes hemodynamically important.[1,110] Latent LVOTO (ie, present only during physiologic provocation) is present in approximately one-third of patients. In patients with outflow tract gradients < 50 mm Hg, provocation with the Valsalva maneuver (including on standing if no gradient is provoked at the lateral decubitus or sitting position) is recommended as part of the routine echocardiographic examination. In symptomatic patients without LVOTO, exercise stress echocardiography should be performed.[1]

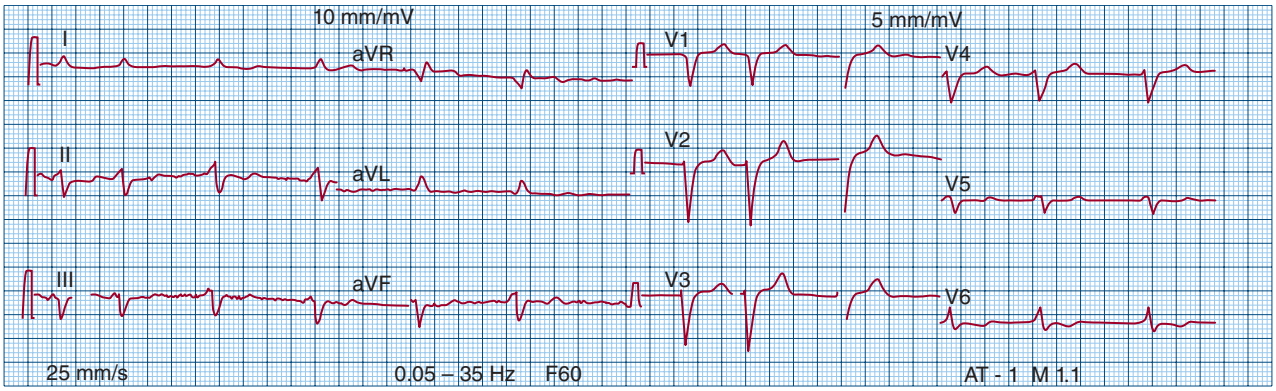
Doppler color flow imaging can be used to determine the presence and severity of mitral regurgitation (see Fig. 59–9).[110,127] If the mitral regurgitation is secondary to distortion of the mitral valve apparatus from the SAM, the color jet will be directed laterally and posteriorly. In addition, the regurgitation will predominate in mid to late systole. If there is a holosystolic signal of mitral regurgitation that is directed centrally or anteriorly, then a primary abnormality of the mitral valve apparatus should be suspected.[1,110] The mitral regurgitation signal by continuous wave Doppler may contaminate the outflow tract velocity signal, and care must be taken to differentiate the true outflow tract velocity from the mitral regurgitation jet (Fig. 59–16).[110]

Diastolic Dysfunction

Left atrial dimensions, pulmonary vein flows, pulmonary artery systolic pressure estimation, and Doppler tissue imaging together with the transmitral flow velocity curves provide estimates of LV filling pressures.[1,110] The left atrial size (measured as anteroposterior diameter, area, or volume) is also an important prognostic marker.[110]

Systolic Dysfunction

LV ejection fraction and fractional shortening can overestimate LV systolic function because radial contractile function is typically preserved



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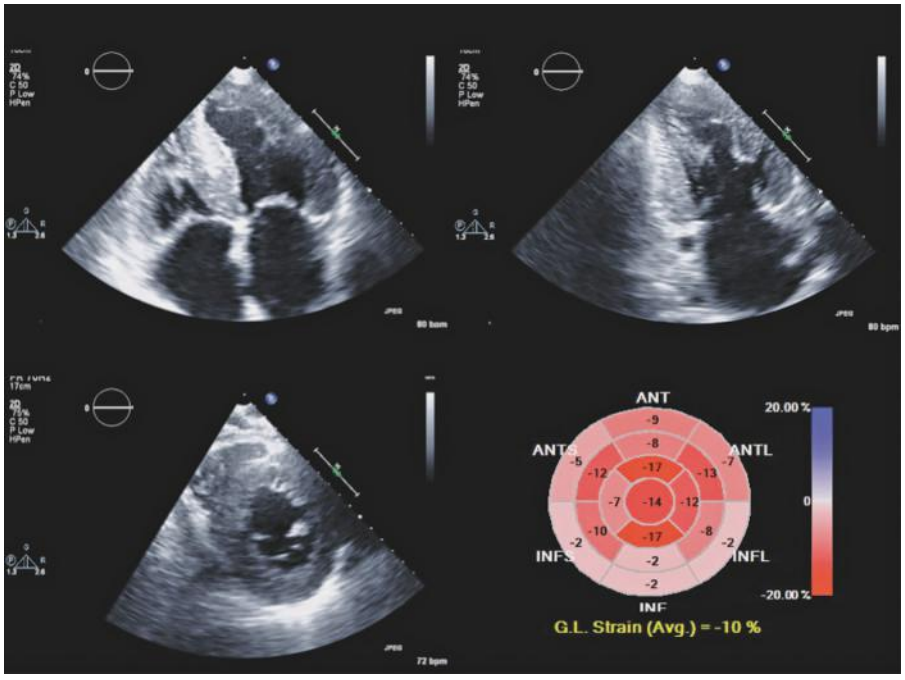

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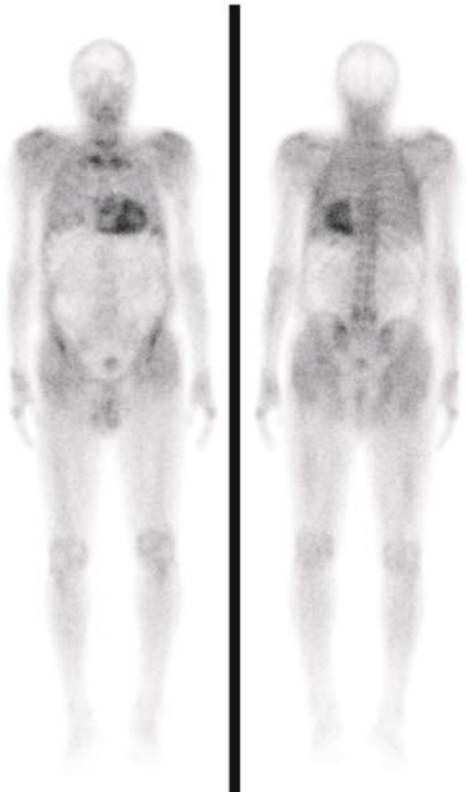


C

FIGURE 59–14. Cardiac investigations from a patient with wild-type transthyretin (TTR) amyloid heart disease. **A.** Twelve-lead electrocardiogram shows low voltage and pseudo-infarct pattern, consistent with infiltrative disease as responsible for the increased left ventricular wall thickness. **B.** Two-dimensional echocardiogram shows concentric hypertrophy; in the bull's eye (*lower right image*), note the relative apical sparing for the markedly diminished global longitudinal strain. **C.** Technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) scan showing strong myocardial uptake.

or increased in HCM.[110] Doppler tissue imaging of mitral annular motion is useful to evaluate longitudinal contraction of the ventricle and is usually abnormal in patients with HCM, despite normal or supranormal ejection fraction. Abnormally low annular velocities are useful in detecting subclinical disease (ie, patients who carry an HCM-associated genetic abnormality but have not yet developed increased LV wall thickness).[110,128-130] Tissue Doppler imaging may also be useful in distinguishing HCM from the physiologic increase in wall thickness observed in some athletes, who generally have preserved or increased annular velocities.[120]

Two-dimensional speckle tracking strain imaging often shows a decreased global longitudinal strain when LV ejection fraction is in the normal range.[110] Circumferential strain is either increased or decreased depending on the stage of the disease. Impaired regional or global longitudinal function has been suggested as a marker of mutation carriage in the absence of hypertrophy.[110]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

In most patients, anatomic and hemodynamic information can be obtained by transthoracic echocardiography alone, but transesophageal echocardiography may be useful in patients in whom discrete subvalvular stenosis or a primary abnormality of the mitral valve is suspected.[110] It is also mandatory for the peri- and intraoperative

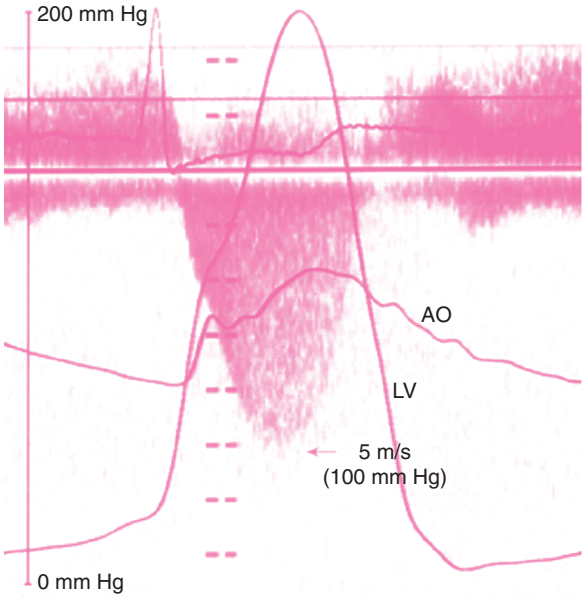


FIGURE 59–15. Simultaneous Doppler echocardiogram and cardiac catheterization demonstrating the presence of severe left ventricular outflow tract obstruction. The gradient between the left ventricle (LV) and aorta (Ao) at catheterization is 100 mm Hg. A continuous wave Doppler across the left ventricular outflow tract reveals a peak velocity of 5 m/s, which is consistent with a calculated left ventricular outflow tract gradient of 100 mm Hg.

monitoring of septal myectomy to confirm of the mechanism of LVOTO, guide the surgical strategy, and detect postsurgical complications such as ventricular septal defects and residual LVOTO.[1,110]

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging (CMRI) provides high-resolution images of the myocardium and accurately determines the site and extent of hypertrophy.[110,131] These properties are particularly important in patients with equivocal hypertrophy and/or difficult echocardiographic images.[131] CMRI is particularly useful in patients with hypertrophy affecting the LV apex and anterolateral wall.[27,131] Apical aneurysms are often only recognized with CMRI, and right ventricular hypertrophy is more easily appreciated with CMRI compared to echocardiography[131] (Fig. 59–17).

SAM of the mitral valve, elongation of the leaflets, papillary muscle abnormalities, accessory bundles, crypts, LV outflow tract flow turbulence, mitral regurgitation, perfusion abnormalities, and intramyocardial fibrosis or scarring can be visualized with CMRI.[131,132] Some of these features may occur in the absence of LV hypertrophy, as a part of a constellation of symptoms described as a "prehypertrophic" phenotype, in sarcomere gene mutation carriers.[110,131,133]

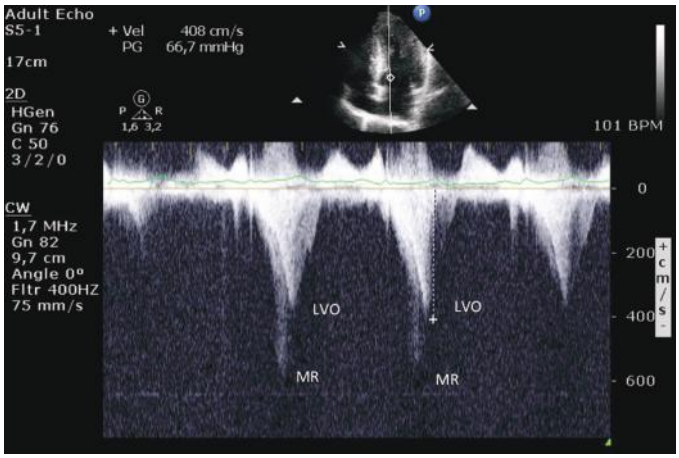


FIGURE 59–16. Continuous wave Doppler flow from a patient with both left ventricular outflow tract obstruction and mitral regurgitation, obtained during the immediate recovery phase of an exercise stress echocardiogram. The continuous wave Doppler jet has a different contour and maximal velocity for the left ventricular outflow (LVO) tract velocity, which is measured in the image, and the mitral regurgitation (MR) jet. The mitral regurgitation signal is of higher velocity, and the signal is holosystolic.

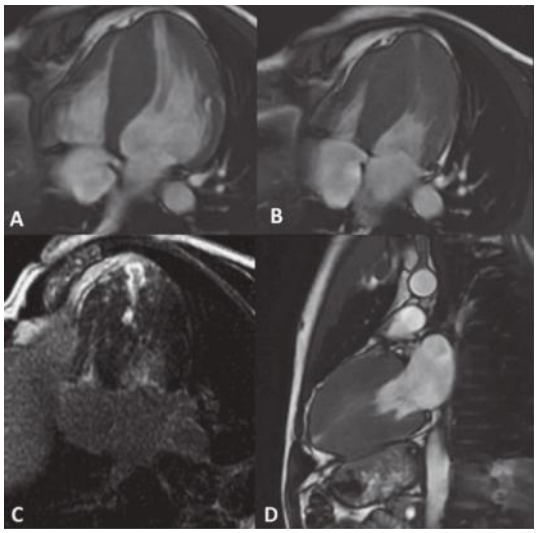


FIGURE 59–17. Cardiac magnetic resonance images of a patient with reverse curvature pattern of hypertrophy, showing a small apical aneurysm. **A.** Cine four-chamber view, end-diastole. **B.** Cine four-chamber view, end-systole. **C.** Late gadolinium enhancement, four-chamber view, showing enhancement at the intraventricular septum and apex. **D.** Cine two-chamber view, end-systole.

NUCLEAR IMAGING

Single-photon emission computed tomography myocardial perfusion imaging frequently shows reversible and fixed defects in HCM in the absence of epicardial coronary artery disease.[110] Positron emission tomography allows quantification of myocardial blood flow, which typically shows a blunted response to vasodilators.[71,110] In the most recent guidelines, no specific recommendation has been made for the use of nuclear imaging for ischemia assessment.[1] However, technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy is useful in detecting cardiac amyloidosis of the transthyretin (TTR) type (either inherited or wild-type/senile) (see Fig. 59–14C).[1,110]

CARDIAC CATHETERIZATION

Cardiac catheterization to assess LV function and dynamic LVOTO is not required in most HCM patients unless there is a discrepancy between the echocardiogram and the clinical presentation.[1] LVOTO can be assessed by placing an end-hole catheter at the LV apex and pulling it back to the base of the heart and then into the aorta. However, because the small LV cavity can cause catheter "entrapment," resulting in a falsely increased LV systolic pressure, the gradient is ideally assessed by a simultaneous LV inflow and LV outflow (or aortic) pressure,[65,134] but this requires a trans-septal approach.

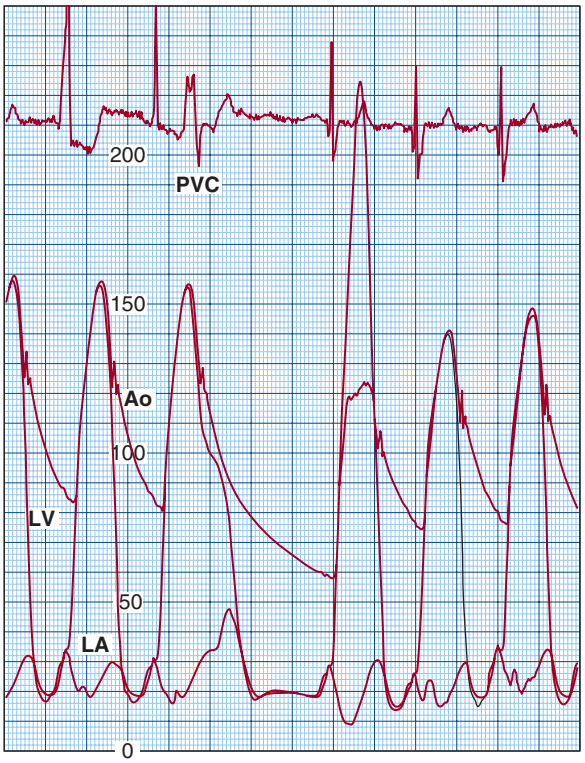


FIGURE 59–18. Cardiac catheterization from a patient with no resting left ventricular outflow tract obstruction. However, after a premature ventricular contraction (PVC), the left ventricular outflow tract gradient is close to 100 mm Hg. The pulse pressure of the ascending aorta (Ao) is decreased on the beat following the premature ventricular contraction. This phenomenon is termed the Brockenbrough phenomenon. LA, left atrium; LV, left ventricle.

When there is little resting obstruction, provocation using the Valsalva maneuver or infusion of isoproterenol can be performed in the catheterization laboratory. The Brockenbrough phenomenon—the hallmark of latent obstruction—refers to the phenomenon after a premature contraction, in which an increase in the contractility of the ventricle results in a marked increase in the degree of dynamic obstruction (Fig. 59–18) This is seen as an increase in the outflow gradient and a decrease in the aortic pulse pressure after the pause. This is in contradistinction to a fixed obstruction in which there is an increase in gradient from the increase in stroke volume but also an increase in aortic pulse pressure.

Left ventriculography usually reveals a small LV cavity size with hypertrophied papillary muscles further impinging into the cavity. Hyperdynamic radial systolic function causes complete obliteration of the mid and apical cavity in systole (Fig. 59–19). In the apical variant of HCM, there is obliteration of the apex by the hypertrophied muscle, causing a "spade-like" configuration. There may be an apical akinetic or dyskinetic pouch with "aneurysm" formation with mid-ventricular obstruction.

Coronary angiography is indicated when patients complain of angina out of proportion to the degree of obstruction.[1] Myocardial bridging is frequent (prevalence up to 15%-25%), particularly in younger patients with severe hypertrophy; however, the impact of bridging on outcomes is unclear.[62,135,136]

Endomyocardial biopsy is only recommended when the noninvasive workup suggests inflammatory, infiltrative, or metabolic disease that cannot be confirmed by other means (eg, biopsy of another tissue/organ).[1]

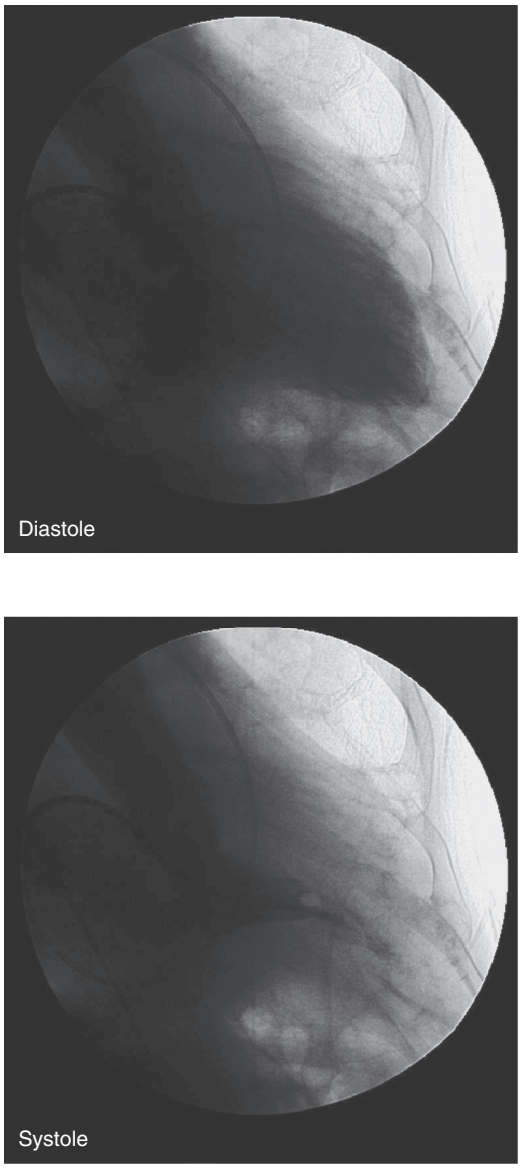


FIGURE 59–19. Left ventriculography from a patient with hypertrophic cardiomyopathy. There is near-complete systolic obliteration of the left ventricular cavity.

CARDIAC COMPUTED TOMOGRAPHY

Aside from the visualization and diagnosis of epicardial coronary disease, cardiac computed tomography can also be used in HCM for morphologic and even functional evaluation of the cardiac chamber dimensions, wall thickness, and systolic function in cases of poor echocardiographic acoustic window and contraindications or intolerance to CMRI.[1]

STRESS TESTING

Exercise stress testing is of limited value for the diagnosis of epicardial coronary disease in patients with HCM but is helpful in assessing prognosis and the mechanism of symptoms.[78,137,138] Cardiopulmonary exercise testing provides an objective measurement of exercise tolerance, and parameters such as ventilatory efficiency, anaerobic threshold, and peak oxygen consumption are predictors of death from heart failure.[139]

LABORATORY TESTING

General laboratory tests are useful in the assessment of comorbidities and symptoms and in the diagnosis of phenocopies (see Table 59–1 for some examples). N-terminal pro–B-type natriuretic peptide is a strong predictor of all-cause mortality and cardiac transplantation in HCM.[140] Measurement of plasma and leukocyte α-galactosidase A is used to screen for Fabry disease in male patients, and serum and urine immunofixation and measurement of free light chains should be measured when amyloid disease is suspected.[1,77] A raised creatine kinase is seen in younger patients with inborn errors of metabolism and muscular dystrophies.

GENETIC TESTING AND FAMILY SCREENING

Over the past few years, massively parallel sequencing platforms have replaced conventional Sanger sequencing in diagnostic genetic testing, allowing for a larger panel of genes (or even the entire exome/genome) to be evaluated.[141] However, the yield of definite pathogenic mutations in HCM is probably similar to that reported with conventional sequencing.[142,143]

Genetic evaluation of probands should be complemented by careful genetic counseling in all probands.[1,51] This includes the construction of a family pedigree, which can be valuable in assessing patterns of inheritance and in detecting etiologic clues.[1,77] When genetic testing is performed and a clear pathogenic mutation is identified in an affected patient, then their first-degree relatives may be screened using targeted DNA analysis for the same mutation. Relatives who carry a pathogenic mutation are kept under regular follow-up, and those who do not carry the mutation can be discharged because their risk of developing the disease is considered similar to that of the general population.[1,51] When no mutation or a DNA variant of unknown significance is detected, family screening will need to be performed using clinical assessment alone.[1,52] Economic modeling studies have suggested that genetic screening strategies are more effective than clinical screening alone.[1,144] Clinical screening of first-degree relatives should be performed every 12 to 18 months in adolescents and every 2 to 5 years in adults.[1,51]

NATURAL HISTORY

The natural history of individual patients with HCM is highly variable.[2,64,94] The early literature described a poor prognosis with high incidence of sudden death (4%-6% per year), but this was influenced by significant referral biases toward small cohorts of selected younger patients who had been referred because they were judged to be at high risk or had severe symptoms requiring specialized care.[2,94,145-149] Contemporary studies report much lower overall sudden death rates (0.5%-1% per year) as a result of the inclusion of patients with milder disease[2,94,148,149] and also because of the effect of modern treatment.[148,149] Nonetheless, there are clearly patient subgroups that are at high risk for death.[2,94]

SUDDEN CARDIAC DEATH

Sudden and unexpected death may be the first manifestation of HCM (incidence 0.8% per year).[1,2,4,5,94,150] Sudden cardiac death (SCD) is most frequent in young adults less than 30 years of age[1,2,4,5,94,150,151] but is rare in infants and very young children.

Pathophysiologic mechanisms involved in SCD include re-entry ventricular arrhythmia promoted by myocyte disarray, hypertrophy, and fibrosis. Abnormalities in intracellular calcium dynamics cause delayed afterdepolarizations and triggered ventricular arrhythmia.[152] Other mechanisms for SCD including asystole, rapid supraventricular arrhythmias, pulseless electrical activity, and AV block.[152]

TABLE 59–2. Major Risk Factors for Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Risk Factor	Comments
Age	• Two studies have shown a significant increased risk in younger patients • Some risk factors are more important in younger patients
Nonsustained ventricular tachycardia	• ≥ 3 consecutive beats at ≥ 120 bpm < 30 seconds • Independent predictor • HR 2.89; 95% CI, 2.21-3.58
Maximum left ventricular wall thickness	• Greatest risk of SCD in patients with a maximum wall thickness of ≥ 30 mm: HR 3.1; 95% CI, 1.81-4.40 • Severity and extent of LVH are associated with the risk
Family history of SCD	• ≥ 1 first-degree relative < 40 years old or any age if relative with an established diagnosis of HCM • HR 1.27; 95% CI, 1.16-1.38
Syncope	• Multiple causes in HCM • Within 6 months of evaluation may be more predictive • HR 2.68; 95% CI, 0.97-4.38
Left atrial diameter	• Two studies have reported an association of SCD with larger atria
Left ventricular outflow tract obstruction	• Association reported in a number of studies
Abnormal blood pressure response to exercise	• Failure to increase systolic pressure by at least 20 mm Hg from rest to peak exercise or a fall of > 20 mm Hg from peak pressure • Associated with a higher risk of SCD in patients age ≤ 40 years • HR 1.30; 95% CI, 0.64-1.96

Note: The hazard ratio (HR) and 95% confidence interval (CI) data are reported in a systematic review by Christiaans et al.[239]

Abbreviations: HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; SCD, sudden cardiac death.

Data from Authors/Task Force, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. Oct 14 2014;35(39):2733-2779; and O'Mahony C, Elliott PM. Prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Heart*. Apr 10 2013.

Several clinical features are associated with a high risk for SCD in patients with HCM (Table 59–2).[1,4,94,152-156] Patients who have had a prior cardiac arrest or spontaneous sustained ventricular tachycardia are at highest risk. A family history of premature SCD in a first-degree relative with HCM portends a high risk, particularly if there are multiple occurrences. Other risk markers include recent unexplained syncope, nonsustained ventricular tachycardia, abnormal blood pressure response to exercise, and extreme LV hypertrophy (> 30 mm). The presence of replacement scar in the myocardium on contrast-enhanced cardiovascular magnetic resonance may identify higher risk patients, although most data suggest that it is a better predictor of heart failure mortality than sudden death.[1,4,94,157,158] It has been proposed that genotype analysis might be used as a stratifying marker for prognosis because specific mutations have been shown to convey either favorable or adverse prognosis.[159] However, these studies are based on a relatively small number of genotyped families, and further work is required to establish the role of genetic testing in risk stratification.[1,159]

ATRIAL FIBRILLATION AND STROKE

The overall prevalence of paroxysmal and permanent atrial fibrillation (AF) is 22%, and the annual incidence is 3%.[100] This corresponds to a fourfold increase in prevalence in comparison with the general population. AF usually indicates advanced disease and is often associated with clinical deterioration. The onset of AF can result in hemodynamic deterioration.[1] Systemic embolism occurs in 6% of patients and is usually associated with AF.[100] Left atrial size and volume are associated with the development of AF and thromboembolism. Other risk factors for AF include severe wall thickness, vascular disease, higher New York Heart Association class, and older age.[160]

HEART FAILURE

Approximately 5% of patients progress to an end-stage phase (also called burned-out phase),[161-164] defined by an LV ejection fraction < 50%. This is associated with progressive congestive heart failure symptoms, exercise intolerance, and atrial arrhythmias.[64,150] The LV cavity enlarges, and the dynamic outflow tract gradient (if present at diagnosis) usually disappears. Eventually, the morphologic appearance of the ventricle resembles a dilated cardiomyopathy (hypokinetic-dilated subtype) or restrictive cardiomyopathy (hypokinetic-restrictive subtype).[64] These patients have a poor outlook with a high risk of death resulting from heart failure or SCD.[64,150,163]

INFECTIVE ENDOCARDITIS

Infective endocarditis occurs in 4% to 5% of patients with HCM.[164] The lesions are usually located on the interventricular septum, the ventricular surface of the mitral valve, or, less often, the aortic valve.

TREATMENT

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Medical Therapy

Patients with LVOTO should maintain hydration at all times, avoid excessive alcohol consumption, and maintain a healthy weight. Arterial and venous vasodilators should be avoided. Rapid AF is often poorly tolerated in patients with LVOTO and should be promptly managed with cardioversion. Digoxin is contraindicated because of the positive inotropic effects.[1]

Medical therapy should be considered the first-line therapy for the relief of symptoms in patients with obstructive HCM. β-Adrenergic blocking agents are usually the drugs of choice.[1,4,94,165-170] Theoretic actions of β-blockers include decreased heart rate response to exercise, relief of angina by a decrease in myocardial oxygen demand, and improvement in diastolic filling time. Acute hemodynamic studies have shown that β-blocking agents blunt the increase in gradient that occurs with exercise (or isoproterenol) but have little effect on the resting gradient. Clinical studies suggest an improvement in angina, exercise tolerance, and syncope in 60% to 80% of patients. However, only approximately 40% of patients continue to have sustained symptomatic improvement.[165,166,171] The dosage of β-blocker should be titrated to symptom relief or to obtain a resting heart rate of < 60 bpm.

Nondihydropyrine calcium channel blockers—specifically, verapamil and diltiazem—are also of value in the treatment of HCM,[66,172-176] particularly if β-blockers are contraindicated or ineffective.[1] By preventing calcium influx, they not only decrease inotropy and chronotropy, but also improve abnormal diastolic relaxation.[66,175-177] Verapamil is used most frequently because of its minimal effect on afterload. Clinical studies have shown a decrease in both basal and provoked gradients during acute drug intervention with verapamil. Verapamil has been shown to improve exercise tolerance by 20% to 30% in short-term follow-up. Calcium channel blockers may improve angina to a greater degree than β-blockers, but sustained symptomatic improvement is seen in < 50% of patients. The dose of verapamil should be titrated up to 480 mg/d to obtain a resting heart rate of 60 bpm.

A small subset of patients can deteriorate hemodynamically with verapamil, presumably because of a lowering of afterload.[178] This deterioration occurs particularly in the presence of severe outflow tract gradients (≥ 100 mm Hg), high diastolic filling pressures, and elevated pulmonary artery systolic pressures.[1] Diltiazem has greater vasodilating properties and should be considered when there is intolerance or contraindications for β-blockers or verapamil.[1] Dihydropyridine calcium channel blockers should be avoided in patients with LVOTO because these pure vasodilators can increase the severity of the outflow tract by reducing afterload.

Disopyramide is used to treat patients with obstructive HCM[1,4,168-170,179,180] by reason of its negative inotropic effect. Concomitant β-blockade may be important to prevent rapid AV node conduction, particularly during exercise or with coexistent AF.[1,179] It can also be used together with verapamil. The dose of disopyramide required to produce symptomatic benefit is between 300 to 600 mg/d. The corrected QT interval needs to be monitored at the initiation of disopyramide and dose reduced if > 480 milliseconds.[1] The anticholinergic adverse effects of the drug can limit its usefulness in older patients. Contraindications to its use include glaucoma, prostatism, and concomitant medication with QT-prolonging drugs.[1]

Septal Reduction Therapy

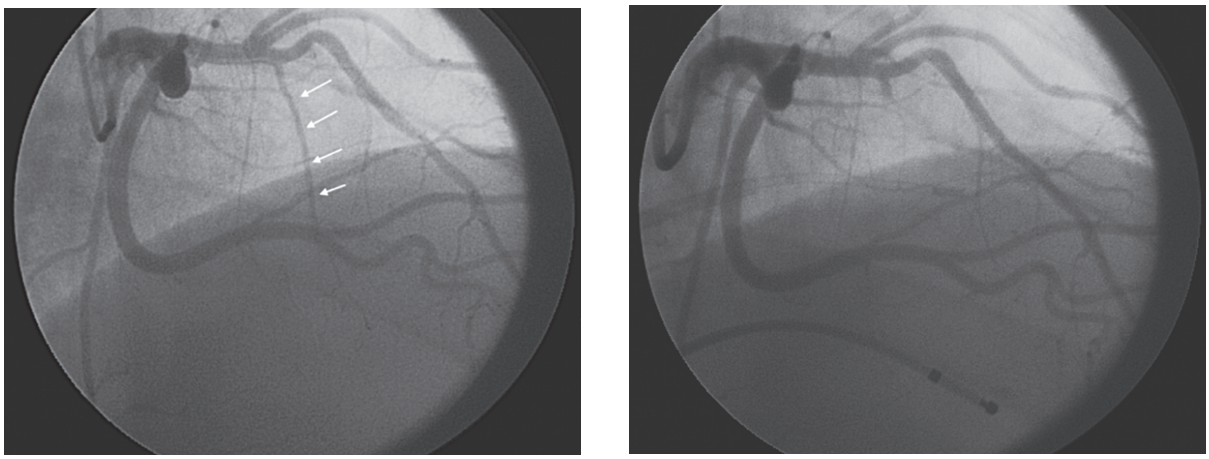
For patients who have an LVOTO gradient ≥ 50 mm Hg, moderate-to-severe symptoms (New York Heart Association functional class III-IV), or recurrent exertional syncope despite maximally tolerated drug therapy, other treatment options such as septal myectomy, septal ablation, or dual-chamber pacing should be considered.[1,4]

Surgical septal myectomy is the gold standard therapy for patients with obstruction and severe drug-refractory symptoms when performed in experienced surgical centers.[1,4,181-188] The procedure consists of a transaortic resection of a small amount of muscle from the proximal to mid-septal region (Morrow procedure). This enlarges the LV outflow tract and significantly decreases or totally abolishes LVOTO in 90% of patients. In patients with concomitant mitral regurgitation secondary to SAM of the mitral valve, mitral regurgitation usually diminishes as a result of the myectomy.[1,4,189,190]

A more extensive myectomy procedure is sometimes performed[191,192] when there is mid-cavity obstruction. However, follow-up data are more scarce for this more extensive procedure.[1] In patients with abnormalities of the papillary muscle, dissection and reduction of the anomalous papillary muscle apparatus may also be performed, as well as mobilization or realignment.[193,194]

Mitral valvuloplasty or plication in combination with myectomy is used in some patients with elongated mitral valve leaflets.[195-197] Mitral valve replacement is generally performed only when there is severe and unrepairable disease of the mitral valve.[1] Simultaneous mitral valve surgery is necessary in 11% to 20% of patients.[1] Another proposed surgical technique consists of cutting the thickened secondary mitral valve chordae combined with a shallow septal muscular resection.[198]

In large-volume centers, the operative mortality for septal myectomy is < 1%,[199,200] but the risk is higher (3%-4%) in elderly patients who require other procedures, such as aortic valve replacement, mitral valve repair, or coronary artery bypass grafting. Complications (AV nodal block, ventricular septal defect, and aortic regurgitation) of surgery are uncommon.[1,110,201-203]

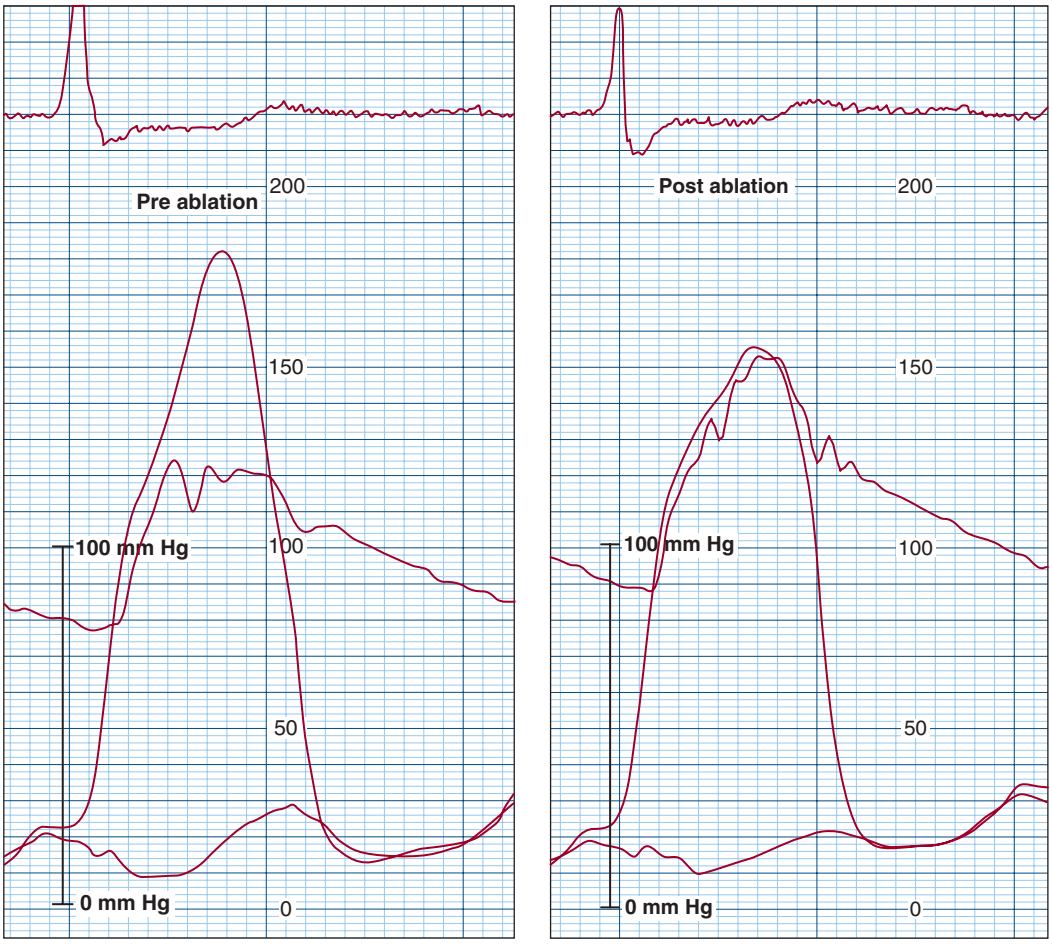


A B

FIGURE 59–20. Coronary angiogram of a patient undergoing septal ablation. A large first septal perforator artery is shown by the *white arrows*. In the *right panel*, following the septal ablation, there has been complete cessation of flow in the first septal perforator artery.

Alcohol septal ablation (ASA) is a procedure in which alcohol is infused in the septal perforator arteries in order to cause necrosis and scarring of the proximal interventricular septum.[1,4,204-206] The subsequent wall thinning and remodeling of the basal septum results in reduction of the outflow tract obstruction (Figs. 59–20 and 59–21).

Several centers have reported successful short-term outcomes following septal ablation.[205,207-222] The major complication of ASA is complete heart block, which, with small doses of alcohol and guidance with myocardial contrast echocardiography, occurs in 7% to 20% of patients.[1,4,221-224] Patients are more likely to experience complete heart



A B

FIGURE 59–21. A. Cardiac catheterization before ablation, demonstrating left ventricular outflow tract obstruction of 60 mm Hg. **B.** Following the septal ablation, there has been complete obliteration of the gradient across the left ventricular outflow tract.

block if left bundle branch block is present prior to the ablation procedure.[1,4,221,222,225,226] Other complications of septal ablation include coronary artery dissection, excessive myocardial infarction from leakage of the alcohol into other coronary arteries, ventricular septal defects, and myocardial perforation. A maximum LV wall thickness < 16 mm at the point of leaflet-septal contact is a risk factor for ventriculoseptal defects in both ASA or myectomy.[1] The periprocedural mortality is comparable to myectomy.[1,221,222]

Current guidelines[1,4] recommend a thorough anatomic and functional evaluation of the septum, mitral valve leaflets, and subvalvular apparatus to guide the choice of invasive septal reduction therapy. ASA may be less effective if extensive septal fibrosis is demonstrated on CMRI and in cases of massive septal hypertrophy. Septal myectomy is preferred in the presence of other abnormalities requiring surgical intervention.

Dual-Chamber Pacing for Left Ventricular Outflow Obstruction

Dual-chamber pacing from the right ventricular apex can decrease the outflow tract gradient as a result of alteration of ventricular contraction and a decrease in systolic projection of the basal septum into the LV outflow tract. It may also induce a chronic remodeling effect during continuous pacing with enlargement of the LV cavity and a further decrease in outflow tract obstruction.[1,2,4,94,227]

Several randomized trials have shown a decrease in outflow tract gradient of 25% to 40% of baseline values, but this was not associated with any improvement in quality of life scores or exercise capacity.[228] Nevertheless, dual-chamber pacing may be useful in selected patients with resting or provocable LVOTO ≥ 50 mm Hg, sinus rhythm, and drug-refractory symptoms who have contraindications for ASA or septal myectomy or are at high risk of developing heart block following ASA or septal myectomy.[1] Candidates for dual-chamber pacing also include patients who have significant bradycardia so as to facilitate an increased dosage of medication and patients who need an automatic defibrillator as a primary treatment.[1]

There are some technical considerations when using pacemaker therapy for treatment of patients with HCM.[229,230] Pacing or sensing the atrium, in addition to pacing the ventricle, is necessary to maintain the hemodynamic contribution of atrial contraction. There is an optimal AV delay for maximizing hemodynamic performance (Fig. 59–22).[231,232] If the paced AV interval is too short, it may increase left atrial pressure and reduce preload, whereas an overly long AV delay can result in incomplete pre-excitation of the right ventricle with suboptimal reduction in gradient. It is necessary to have the pacemaker tip placed in the apex of the right ventricle to achieve the maximum reduction in gradient, and pacing parameters need to be optimized to achieve maximum pre-excitation of the right ventricular apex with minimal compromise of LV filling.

TREATMENT OF NONOBSTRUCTIVE CARDIOMYOPATHY

β-Blockers and calcium channel blockers can been used to improve diastolic filling in symptomatic patients with normal LV ejection fraction and no resting or provoked outflow tract obstruction.[1,4,94] Diuretics can decrease elevated filling pressures.

For patients with reduced ejection fraction (< 50%), general guidelines for chronic heart failure apply, including the use of renin-angiotensin-aldosterone system inhibitors and diuretics.[1,4] Cardiac transplantation is the only therapy for patients who have severe symptoms and are unresponsive to conventional treatments. Post-transplantation survival is similar or better than for other disease (75% at 5 years; 60% at 10 years).[94]

Both β-blockers and calcium channel antagonists are the recommended pharmacologic options for angina, after excluding LVOTO or obstructive epicardial coronary artery disease.[1,4]

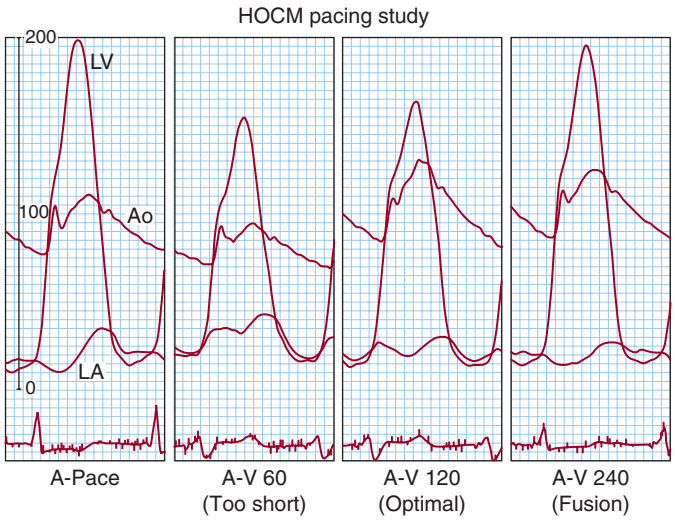


FIGURE 59–22. Cardiac catheterization study during atrioventricular sequential pacing in a patient with hypertrophic obstructive cardiomyopathy (HOCM), demonstrating the effect of the differing atrioventricular (A-V) intervals. The left ventricular (LV) pressure, aortic (Ao) pressure, and left atrial (LA) pressures are shown. In the baseline state (A pace), the patient is undergoing atrial pacing with native antegrade atrioventricular conduction. There is a left ventricular outflow tract obstruction of 100 mm Hg. *Left center panel*: The patient is undergoing atrioventricular pacing with an atrioventricular interval of 60 milliseconds. This interval is too short because atrial contraction is now occurring on top of a closed mitral valve, causing an elevation of left atrial pressure. Although the gradient is decreased, there is also a decrease in aortic pressure caused by the decreased preload in the left ventricle. *Right center panel*: This is the optimal atrioventricular interval of 120 milliseconds. The gradient has been decreased to 35 mm Hg. *Right panel*: The atrioventricular delay is 240 milliseconds. There is fusion between the antegrade conduction and the paced QRS complex with incomplete pre-excitation. The gradient across the left ventricular outflow tract is 60 mm Hg.

PREVENTION OF SUDDEN CARDIAC DEATH

Individuals with HCM are advised against participation in competitive sports and intense physical activity to reduce their risk of sudden ventricular arrhythmia.[1,233-236] Low-to-moderate levels of aerobic exercise are permitted as part of a healthy lifestyle after careful risk assessment.

Amiodarone has been shown in retrospective nonrandomized trials to be associated with improved survival in young HCM patients with nonsustained ventricular tachycardia, but there are no randomized trial data to suggest that antiarrhythmic agents in general improve survival in patients with HCM.[1,4,152,155,237,238] For this reason, implantation of an implantable cardioverter-defibrillator (ICD) is the most effective and reliable treatment option for protecting patients against SCD.

Estimation of SCD risk should be a routine part of clinical management. In adolescents and adults, the risk assessment should comprise clinical and family history, 48-hour ambulatory ECG, transthoracic echocardiogram (or CMRI in the case of poor echo windows), and a symptom-limited exercise test. The decision to recommend an ICD to patients is complex and requires individualized discussion of the long-term risks and benefits of the device.[1,4]

ICDs are generally indicated in patients with prior cardiac arrest or sustained spontaneous ventricular tachycardia.[1,4] Implantation of ICDs for primary prophylaxis is guided by the presence of a small number of clinical characteristics (see Table 59–2).[152] One approach is to consider an ICD in patients with more than one risk factor or when an individual risk factor is deemed sufficient by itself to warrant therapy (eg, multiple sudden deaths in a family or frequent unexplained syncope).[4,155] Contemporary evidence suggests that this approach is modestly successful in identifying high-risk patients,[239] but it also has some limitations; specifically, it estimates relative and not absolute risk; it does not account for the different effect size of individual risk

factors; and some risk factors such as LV wall thickness are treated as binary variables when they are associated with a continuous increase in risk.[152,154] One proposed solution is to consider other clinical features, such as myocardial fibrosis (determined by contrast-enhanced CMRI), LV apical aneurysms, and the inheritance of multiple sarcomere protein gene mutations, as arbiters that can be used to guide ICD therapy in individuals who are at an intermediate risk.[4,155] An alternative is to estimate risk using a multivariate prediction tool analogous to that used in other scenarios such as coronary artery disease prevention.[1,153] In all cases, decisions on ICDs must balance the likely benefit against the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status, and psychological health.[1]

STROKE PREVENTION

Anticoagulation is recommended for patients with AF and HCM.[1,4] Despite the absence of randomized controlled trials, a recent exploratory retrospective analysis showed a reduction in thromboembolic events with vitamin K antagonists.[160] The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or thromboembolism, vascular disease, age 65-74 years, sex category [ie, female sex]) does not correlate well with clinical outcome in patients with HCM and is not recommended to assess thromboembolic risk.[1,160] A recent systematic review and meta-analysis showed the feasibility of AF ablation in HCM, but more repeat procedures and antiarrhythmic drugs were needed to prevent recurrence.[240]

NEW DRUG TARGETS AND DISEASE-MODIFYING DRUGS

The growing number of preclinical carriers identified through genetic testing and family screening has led to increased interest in the development of new therapeutics that can inhibit or attenuate the development of the HCM phenotype.[241,242] Potential strategies that are under evaluation include small molecules that interfere with cross-bridge kinetics, manipulation of myofilament calcium sensitivity, modification of calcium cycling/homeostasis (eg, through late-sodium current inhibition), inhibition of fibrosis-promoting pathways and mediators, modification of cardiomyocyte energy metabolism, and genetic therapies such as exon skipping and RNA interference to reduce expression of mutant missense transcripts.[43,241,243]

PREGNANCY

All HCM patients who wish to become pregnant should be given prenatal counseling about the risk of transmission of disease to their offspring (autosomal dominant inheritance pattern with 50% risk for transmission to each child) and the risks associated with pregnancy.[1] Patients with HCM usually tolerate pregnancy well if they are not severely symptomatic prior to conception but should be managed by expert teams throughout.[1] Echocardiography is recommended each trimester or in the presence of new symptoms.

If patients have been on treatment with β-blockers or calcium blockers, these drugs should be continued throughout the pregnancy. β-Blockers are also indicated in the presence of new symptoms related to LVOTO,[1] with close monitoring of fetal growth. Verapamil, diltiazem, and disopyramide can be used when benefits are judged to outweigh potential risks.[1] Low-dose diuretics may be required if pulmonary congestion occurs. Birth should be planned and take place in a high-risk center. Epidural and spinal anesthesia should be used cautiously given the risks of vasodilation and hypotension in the presence of significant LVOTO but are not contraindicated in current guidelines.[1] Cesarean section should be considered in cases of severe LVOTO, preterm labor in patients receiving oral anticoagulant drugs, and severe heart failure symptoms.[1]

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CHAPTER 60

LEFT VENTRICULAR NONCOMPACTION

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DEFINITION

Cardiac trabecular anatomy is characterized by extreme individual and population variability that corresponds to a sort of individual *cardioprinting*. In normal hearts, trabeculae undergo continuous and quantifiable geometric changes during the cardiac cycle; they actively provide mechanical leverage during early systolic ejection through contraction, and relaxation occurs during late diastole at larger ventricular volumes.[1] In the left ventricle, trabeculae can be minimally represented or may be so numerous and prominent that they confer a "spongy" appearance to the endocardial surface of the ventricles. The latter corresponds to the term *left ventricular noncompaction* (LVNC).

LVNC describes a ventricular wall anatomy characterized by the presence of disproportionate, prominent left ventricular (LV) trabeculae, a thin compacted layer, and deep intertrabecular recesses that are in continuity with the LV cavity and separated from the epicardial coronary arteries.[2] By definition, noncompaction pertains to the LV but may also involve the right ventricle, as either a biventricular[3] or an isolated right ventricular variant.[4] The American Heart Association (AHA) classification defines LVNC as a genetic/congenital cardiomyopathy,[5] whereas the European Society of Cardiology (ESC) classification defines LVNC as a nonclassified entity.[6] The recent MOGE(S) nosology (*M*orphofunctional phenotype, *O*rgan(s) involvement, *G*enetic inheritance pattern, *E*tiologic annotation including genetic defect or underlying disease/substrate, and functional *S*tatus of the disease) proposes a simple description of the trait in individuals with either normal LV size and wall thickness and preserved systolic and diastolic function or in combination with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC).[7] This latter descriptive approach is the expression of the clinical uncertainties regarding the unique interpretation of LVNC as a cardiomyopathy.[8]

In the official guidelines of scientific societies, the requirements for the definition of a cardiomyopathy include "diseases of the myocardium associated with mechanical and/or electrical dysfunction" (AHA)[5] and "myocardial diseases characterized by structurally and functionally abnormal heart muscle and absence of other diseases sufficient to cause the observed myocardial abnormality" (ESC).[6] When isolated and benign, LVNC is not associated with mechanical and/or electrical dysfunction (AHA) and is characterized by some structural abnormality (trabeculation) with potentially normal function.[8] By itself, the diagnosis of LVNC is based on one of the attributes that define cardiomyopathies, namely the abnormal LV morphology, but this does not obligatorily imply LV dysfunction. The increasing number of reports that describe LVNC in the normal population questions the definition of LVNC as cardiomyopathy. This chapter illustrates the current criteria for diagnosing LVNC, available data in normal populations, the association of LVNC with cardiomyopathies and disease genes, congenital heart diseases, rare syndromes affecting or not affecting cardiac function, acquired and possibly reversible LVNC, and diagnostic workup.

CURRENT DIAGNOSTIC CRITERIA FOR LEFT VENTRICULAR NONCOMPACTION

Diagnostic criteria have been established for echocardiography, cardiac magnetic resonance (CMR), and multidetector computed tomography (MDCT). The list of different criteria is by itself evidence that common, standardized, and uniform rules do not exist. This is likely because isolated LVNC represents a spectrum of LV trabecular morphology rather than an independent heart muscle disease. Table 60–1[9-22] summarizes current diagnostic criteria that are based on ratios between thickness, mass, or volume or percentages of noncompacted (NC) and compacted LV. The number of NC segments provides information on the extent of LVNC. Alternative methods integrate the count or evaluation of the global trabeculation index. Figures 60–1 and 60–2 illustrate echocardiographic and CMR features of LVNC, respectively.

MDCT is useful when CMR is contraindicated or when echocardiography and CMR provide discordant data[22,23] and further adds the advantage of noninvasive investigation of the coronary tree. A computed tomography (CT) study that used the AHA 17-segment model and an end-diastolic NC-to-compacted (NC/C) ratio > 2.3 distinguished pathologic LVNC with 88% sensitivity and 97% specificity, with positive and negative predictive values of 78% and 99%, respectively.[23]

The independent diagnostic contribution of the maximum thickness of the compacted layer is limited. In the context of using ratios or proportions, the same ratio can result from different absolute values of the two components. In most diagnostic indices, the ratios between compacted and noncompacted thickness, volume, or mass drive the diagnosis. However, reduced thickness of the compacted layer has been proposed as a novel echocardiographic criterion for noncompaction cardiomyopathy; a maximal systolic thickness < 8 mm of the compacted layer seems to be specific for LVNC and to differentiate LVNC from normal hearts as well as hearts with myocardial thickening caused by aortic valve stenosis. The addition of this criterion may eventually contribute preventing the overdiagnosis of LVNC.[24]

Although the diagnostic gold standard is considered to be CMR, an ideal gold standard does not exist, and in fact, different CMR methods and software exist without concordance on diagnostic criteria.

LEFT VENTRICULAR NONCOMPACTION IN HEALTHY SUBJECTS

LVNC diagnosed according to current criteria may occur in functionally normal hearts. In 2012, the publication of data in 1000 participants (551 women; age, 68.1 ± 8.9 years) of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort suggested the need of re-evaluation of CMR criteria for LVNC. The thickness of trabeculated and compact myocardium was measured in eight LV regions on long-axis CMR steady-state free precession cine images. The study demonstrated (1) that 43% of subjects without cardiac disease or hypertension had an NC/C ratio > 2.3 in at least one myocardial segment; (2) NC/C ratio was not associated with age, sex, race/ethnicity, height, or weight; (3) the maximum thickness of trabeculation was positively associated with race/ethnicity (Chinese and black) and male sex; (4) there was a negative association of LV ejection fraction and a positive association of LV end-diastolic volume and LV end-systolic volume with the maximum NC/C ratio, versus a positive association of LV end-diastolic volume and LV end-systolic volume with maximum trabeculation thickness; and (5) there was a technique–related variability in measurement of thickness of trabeculation and compact myocardium as well as NC/C ratio. The study concluded that an NC/C ratio > 2.3 is common in a large population-based cohort.[25]

In 2014, long-term follow-up data in 2742 participants in the MESA cohort (mean age, 68.7 years; 52.3% women; 56.4% with hypertension; 16.8% with diabetes) demonstrated that even in subjects with excessive trabeculation, there were no clinically relevant differences in LV volumes and systolic function changes among the quintiles of trabeculation extent. The authors found that 25% of participants exhibited at least one cardiac segment with NC/C ratio > 2.3 and that 8% of participants displayed two or more affected segments. Although LV volumes increased and LV ejection fraction decreased in the 9.5 years between the first and last examinations, there were no differences across the maximal NC/C ratio quintiles, and patients with greater trabeculation showed even smaller LV end-diastolic volume changes. There were no racial variations in the maximal NC/C ratio. Finally, adverse clinical events were scarce, despite the apparently high proportion of participants with a potential unmasked cardiomyopathy.[26]

CMR studies in normal adult volunteers demonstrated the following sex- and age-related differences: (1) the compacted but not the trabeculated layer is thicker in men than in women; (2) the compacted layer thickens whereas the trabeculated layer thins with systole; (3) trabeculated LV segments show increased systolic thinning of trabeculated layers and greater thickening of the compact segments ($P < .05$) with age; (4) total wall thickening is neither sex nor age dependent; (5) there were no sex-specific differences in the trabeculated/compacted ratio at end systole or end diastole; and (6) in end systole, the trabeculated/compacted ratio was lower in older (50-79 years) compared to younger (20-49 years) subjects ($P < .05$).[16] Overall, the application of current diagnostic criteria demonstrates that LVNC may occur in a relevant proportion of healthy individuals.

EPIDEMIOLOGY

Epidemiology data reflect the context, methods, and clinical characteristics of the series in which LVNC has been observed. The precise proportion of LVNC remains elusive. Prevalence data demonstrate impressive discrepancies, with LVNC being paradoxically higher in imaging series obtained in normal individuals and in screening studies of volunteers[14,23,24] than in selected clinical series of children and adults.

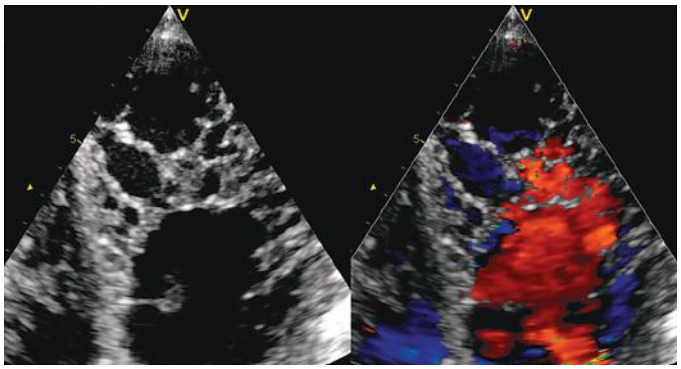
Data on annual incidence of LVNC in children report values less than 0.1 per 100,000.[27] Isolated LVNC accounted for 9.2% of all cases in a population-based retrospective cohort study of primary cardiomyopathies in Australian children[28] (with LVNC identified as the third most frequent cardiomyopathy after DCM and HCM). This prevalence was close to that recorded in the Texas Children's Hospital echocardiography database (9.5%).[29] In recent data from the Pediatric Cardiomyopathy Registry (1990-2008), 155 (4.8%) of 3219 children had LVNC. This was associated with DCM, HCM, RCM, or indeterminate cardiomyopathies in 120 children and isolated in 35 children. In the latter group, heart failure was not present in any individuals at time of diagnosis. The majority of children with isolated LVNC were referred for reasons such as heart murmurs, chest pain, or family history of cardiomyopathy. Few isolated patients with LVNC developed an associated cardiomyopathy phenotype during the 3.3-year follow-up.[30] In adult clinical series, the echocardiographic prevalence ranges from 0.014% to 0.26%.[31-35]

As for sex, LVNC is reported to be more common in men (56%-82%) than women.[31,36-38] Ethnic or racial differences have been suggested in studies, with higher prevalence in blacks than whites.[25,39,40] In three groups of volunteers including patients diagnosed with LVNC according to criteria by Jenni et al,[2] healthy whites, and healthy blacks, the

TABLE 60–1. Imaging Criteria for the Diagnosis of Left Ventricular Noncompaction (LVNC)

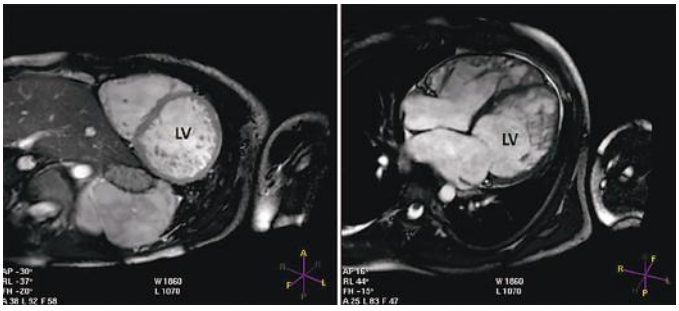
	Echocardiography	Cardiac Phase	Imaging Plan(s)	LVNC		Reference
Echocardiography	X = distance from the epicardial surface to the trough of the trabecular recess; Y = distance from the epicardial surface to peak of trabeculation	End diastole	• Parasternal short axis • Apical 4-chamber • Subcostal	X/Y ≤ 0.5		9
	Noncompacted/compacted (NC/C) > 2	End systole	• Parasternal short axis • Apical 4-chamber	NC/C > 2		10
	• > 3 trabeculations • Synchronous motion of trabeculae with compacted myocardium • Connection between ventricular cavity and intertrabecular recesses	End diastole	Parasternal short axis			11
	2-Layered wall	End systole	Modified apical 2-chamber			
	Maximal NC/C planimetric area Ratio of the maximum linear length of noncompacted to compacted myocardium (NC/C) Planimetered area of LVNC on apical 4-chamber view	End systole	Apical 4-chamber	**Linear NC/C (ratio)**	**Planimeter**	12
				0	0	
				Mild > 0 and < 1	≥ 0 cm^2 and < 2.5 cm^2	
				Moderate ≥ 1 and < 2	≥2.5 cm^2 and < 5.0 cm^2	
				Severe 2+	≥ 5.0 cm^2	
	CMR	**Cardiac Phase**	**Imaging Plan(s)**	**LVNC Cutoff**	**Normal**	
CMR; balanced steady-state free precession	NC/C ratio per segment using horizontal long axis (HLA) and vertical long axis (VLA); apex excluded	End diastole	• Horizontal long axis • Vertical long axis • Left ventricular outflow tract view	NC/C 2.3	1.1 ± 0.1	13
	A. Compacted LV mass subtracted from global LV mass after semiautomated contouring and indexing to BSA	End diastole	Short-axis stack	Mean TLVM 43 ± 19 g/m^2	9.0 ± 4.0 g/m^2	14
	B. Ratio of trabeculated LV mass (TLVM) to global LV mass expressed as percentage			TLVM > 20%	TLVM 12.5 ± 5.0%	
	17-Segment model excluding apex, evaluated for NC and C wall thickness in ED and ES, taking the peak value for NC per segment	Diastole and systole	Short-axis stack	—	NC/C ranges: End diastole: 0-0.9 End- systole: 0-0.5	15
	A. Software for contouring NC and C; epicardial border manually traced in ES and ED in HLA and registration marks applied	End diastole	• Horizontal long axis • Vertical long axis • Short axis stack	LV-MMI noncompacted, noncompacted LV myocardial mass index > 15 g/m^2 % LV-MMI noncompacted index > 25%	Ai 5.3 ± 2.4g/m^2 Aii 9.9 ± 4.5g/m^2	16
	B. Maximal NC/C from measurements in ED on SAX in 16 of 17 segments		Short axis stack	NC/C ≥ 3.1	—	
	Apical SAX 16 to 24 mm from the true apical slice for measurements; papillary muscles excluded; ES NC/C wall thickness ratio	End systole	Short axis stack	ES NC/C ≥ 2	—	17
	Java-based box-counting fractal analysis to extract the maximal apical fractal dimension (FD) after analyzing all SAX cines (excluding apex)	End diastole	Short axis stack	FD max apical ≥ 1.30	1.203 ± 0.06	18
	A. Segmental trabeculation index (STI) = NC/C ratio per segment 1-15 in SAX; apical values for segment 16 from HLA and VLA	End diastole	• Horizontal long axis • Vertical long axis • Short axis stack	STI range in DCM, 0.1-2.2 (apex included) or 0.1-1.5 (apex excluded)	—	19
	B. Global trabeculation index (GTI) = ratio of the sum of total NC to the sum of total C			Mean GTI in DCM, 0.68 0.32	—	
	Epicardial and endocardial contours, paps and trabecular-free LV/RV volumes manually outlined	End diastole	Short axis stack	LV trabecular volume/BSA not defined in LVNC	Males 4.31 ± 8.7 mL/m^2 Females 38.1 ± 5.9 mL/m^2	20
	MDCT					
CT	NC/C ratio > 2.2 in at least two segments can be considered diagnostic of LVNC	End diastole	Short axes (basal, midventricular, apical), and long axes (2-, 3-, and 4-chamber views), using the AHA cardiac segmentation model True apex (segment 17) excluded	≥ 2.2 in the NC/C ratio in ≥ 2 myocardial segments	—	21

Abbreviations: BSA, body surface area; CMR, cardiac magnetic resonance; CT, computed tomography; DCM, dilated cardiomyopathy; ED, end diastole; ES, end systole; LV, left ventricle; MDCT, multidetector computed tomography; MMI, myocardial mass index; RV, right ventricle; SAX, short axis.



A B

FIGURE 60–1. Echocardiographic and color Doppler images from a patient with left ventricular noncompaction (LVNC). **A.** In the echocardiographic image, an atypical four-chamber view was used to better illustrate the noncompaction in the left ventricular (LV) apex. **B.** The same view with color Doppler imaging. This view highlights perfusion of intertrabecular recesses from the LV cavity. Reproduced from *J Am Coll Cardiol*. 2014;64:1840-1850.[8]



A B

FIGURE 60–2. Cardiac magnetic resonance image from a patient with left ventricular (LV) noncompaction. **A.** Short-axis view showing the hypertrabeculation in all mid-LV segments apart from the interventricular septum. **B.** Long-axis view showing the hypertrabeculation mainly in the apical and mid-LV segments. Reproduced with permission from Arbustini E, Weidemann F, Hall JL. Left ventricular noncompaction: a distinct cardiomyopathy or a trait shared by different cardiac diseases? *J Am Coll Cardiol*. 2014 Oct 28;64(17):1840-1850.[8]

fractal dimension (FD) of the endocardial border was measured as a quantitative parameter distinguishing normal from abnormal trabecular patterns. Among healthy volunteers, blacks had a higher FD than whites in the apical third of the LV. Maximal apical FD was higher in individuals with LVNC compared to healthy volunteers.[19] In 38 healthy elite male football (or soccer in the United States) players (mean age, 23.0; range, 19-34 years; European, n = 28; African, n = 10) who underwent CMR and electrocardiography (ECG), hypertrabeculation was assessed using the NC/C ratio on long-axis and short-axis segments; a greater degree of LV hypertrabeculation was seen in healthy African athletes, combined with biventricular ejection fraction reduction at rest.[40] Overall, ethnical differences should be taken into consideration when evaluating individuals of different races, including athletes.

PATHOGENETIC HYPOTHESES

The most cited pathogenetic hypothesis is embryogenic arrest of the normal process of trabecular maturation during early intrauterine life[7] when the heart undergoes cardiac chamber maturation. Chamber maturation occurs through the formation of myocardial trabeculae, conduction system, and growth of compact myocardium. Cardiac trabeculation begins after the cardiac looping stage with the emergence of a network of myocardial cells covered by endothelial cells and projection in the left ventricular cavity. Projections propagate radially and vertically. The majority of myocytes are more differentiated in the luminal than mural side.[41] Trabeculae then undergo compaction. The epicardial layers enter the myocardial wall and generate the coronary network, which is strictly accompanied by the formation of the compact layer.

Several molecular pathways are active in cardiac chamber maturation. These include the (1) Notch signaling pathway that is involved in the maturation of endocardium and cardiac chambers, with downregulation in the compacted myocardial layer[42]; (2) bone morphogenic protein-10 signaling that modulates cardiomyocyte differentiation through activation of transcription factors[43]; (3) fibroblast growth factor family and related receptors that contribute to the proliferation of the compact myocardium[44]; (4) transmembrane paracrine ligand neuregulin, ERBB family receptors and ephrin signaling that regulate normal endothelial cell function and modulate directional migration of cardiomyocytes[45] (ephrin-B2 [EFNB2] and one of its receptors, EPHB4, are expressed in the endothelial cells lining trabeculae)[46]; (5) semaphorin signaling pathway that modulates gene transcription and cardiac patterning[47]; and (6) endothelin-1–endothelin-converting enzyme-1 and the G-protein–coupled endothelin receptor type A that modulate cardiomyocytes to differentiate into Purkinje cells.[48] Although all genes involved in pathways active in chamber maturation may potentially influence LV trabecular anatomy, none of the genes active in the above pathways to date has been identified as an LVNC-causing gene. The only exception is the *MIB1* gene encoding an ubiquitin ligase that regulates endocytosis of Notch ligands. Endocytosis of Notch ligands in the signal-sending cells is needed for Notch activation.[49] To date, mutations in this gene have been reported in individuals with LVNC in two Spanish families.[50] Finally, extracellular matrix (ECM) interacts with cell compartments. ECM contains collagen, versican, and nephronectin[51,52]; it separates endocardial, myocardial, and epicardial layers. ECM–cell interactions are mediated by integrins that modulate cell growth, migration, survival, and differentiation. During cardiac morphogenesis, matrix metalloproteases facilitate cell migration. ECM composition is regulated in part by the matrix metalloprotease ADAMTS1, which is necessary for trabeculation.[53]

According to the embryogenetic hypothesis, the occurrence and extent of LVNC would be conditioned by the stage at which the arrest of the normal embryonic myocardial maturation takes place, considering that during the 5th and 8th, weeks the myocardium becomes compacted from the basal segments to the apex and from epicardium to endocardium.[54] Causes of interruption of myocardial compaction are unknown.

Aside from the congenital embryonic hypothesis, serial echocardiographic evaluations demonstrate that there are forms of LVNC that are acquired and reversible[27] in training athletes,[55] pregnancy,[56] hematologic disorders,[57] myopathies,[58] chronic renal failure,[59] and bicuspid aortic valve.[60] In addition, patients with cardiomyopathies may develop LVNC during the course of the disease[61,62] (Fig. 60–3). Therefore, a unique pathogenetic hypothesis is unlikely to explain the possible acquired origin of the trait, the heterogeneity of disorders (cardiac and noncardiac) in which LVNC is observed, and its possible regression. At present, it appears prudent to describe the finding, whenever present, without assigning the definition of cardiomyopathy.[8]

LVNC can be regarded as an isolated entity or as one of the traits that may recur in other cardiac and noncardiac diseases. As a marker, it may suggest specific diagnoses (eg, tafazzinopathies [caused by mutations in the *TAZ* (*Tafazzin*, or *G4.5*) gene] in male infants with a dilated phenotype, or dystrobrevinopathy in adults).[63,64] As a structural trait with potential functional effects, it may cause or contribute to LV dysfunction in coexisting morphofunctional disorders such as

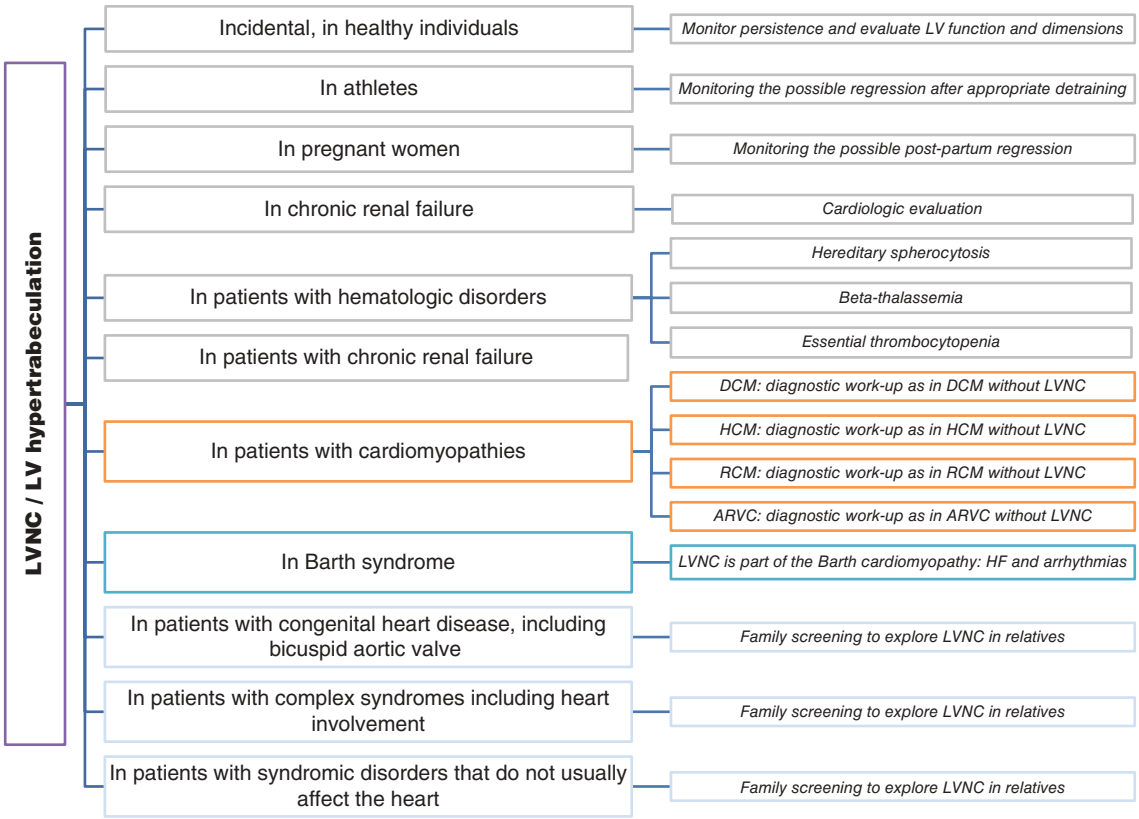


FIGURE 60–3. A summary of all known conditions and diseases in which left ventricular noncompaction (LVNC) has been reported. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricular; RCM, restrictive cardiomyopathy.

cardiomyopathies or congenital heart diseases (CHDs). When the dysmorphology of the LV wall is prominent in the LV with an otherwise normal size and function, long-term follow-up may provide information regarding its potential role as either a predisposing factor or marker of risk for future progression through cardiomyopathy.

BARTH SYNDROME

Barth syndrome is mentioned as a separate entity because it represents the paradigmatic example of LVNC cardiomyopathy. It should be suspected in all male infants with heart failure, DCM, and LVNC, especially when associated with other markers of disease. Barth syndrome is a rare X-linked recessive disorder characterized by cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, and distinctive facial characteristics. The disease is caused by mutations in the *G4.5* gene (*TAZ*).[64-66] The protein localizes to the mitochondrial membrane and plays a role in mitochondrial structure and function. LVNC and low mitochondrial membrane potential are reported as specific for Barth syndrome.[66] LVNC is commonly associated with LV dilation and dysfunction at onset.[64] Less commonly, Barth cardiomyopathy may present with a hypertrophic or hypertrophic-dilated phenotype. Heart involvement occurs in almost all children before the age of 5 years. Thereafter, the cardiomyopathy may demonstrate an intermittent course during which the heart can undergo remodeling. Improvement can be observed after infancy, with possible stabilization after the toddler years.[63] Heart failure is a major cause of morbidity and mortality. Overall, however, cardiac function varies and tends to decline over time. Arrhythmias, both supraventricular and ventricular, are more commonly reported in adolescents and young adults than in infants.[63,64]

LEFT VENTRICULAR NONCOMPACTION IN CARDIOMYOPATHIES

LVNC can occur in hearts fulfilling the diagnostic criteria for DCM, HCM, RCM, or ARVC. In these cases, cardiomyopathies and LVNC are both present. Family studies may contribute to unraveling whether the two traits (cardiomyopathy and LVNC) can exist as independent entities or are part of the same phenotype in all or some affected family members.

GENES AND LEFT VENTRICULAR NONCOMPACTION IN CARDIOMYOPATHIES

In the current Online Mendelian Inheritance in Man (OMIM) catalogue, 10 genes, one locus with unidentified gene, and one syndrome are formally associated with a Mendelian Inheritance in Man (MIM) phenotype number (Table 60–2). The candidacy of the *DTNA* gene for isolated LVNC is provisionally supported by absence of mutations in cardiomyopathies without LVNC. Alpha-dystrobrevinopathies are caused by mutations in *DTNA*, which is part of the cytoplasmic complex of the dystrophin-associated proteins.[67] Rare dilated and dysfunctional hearts and LVNC have been associated with mutations in *MIB1* that encode Dapk-interacting protein 1 acting in the Notch pathway.[50] LVNC can be observed in cardiomyopathies with overlapping phenotypes, typically dilated HCM such as in mitochondrial DNA-related cardiomyopathies[68] (Table 60–3). The lists of cardiomyopathy genes associated with LVNC demonstrate wide heterogeneity (Tables 60–2 and 60–4) and remain incomplete (Fig. 60–4). All genes associated

TABLE 60–2. Genes and Loci Formally Included in the OMIM Catalogue as Associated With LVNC

Locus	Phenotype	MIM Phenotype No.	*Gene*	MIM*	Disorders Allelic at the Same Locus	Inheritance
18q12.1	LVNC1	604169	*DTNA*	601239	With or without congenital heart defects	AD
11p15	LVNC2	609470	None	—	—	—
10q23.2	LVNC3	601493	*LDB3*	605906	DCM with or without LVNC, HCM, myofibrillar myopathy	AD
15q14	LVNC4	613424	*ACTC1*	102540	DCM, HCM, atrial septal defects	AD
14q11.2	LVNC5	613426	*MYH7*	160760	DCM, HCM, Liang distal myopathy, myopathy, myosin storage AD and AR, scapuloperoneal syndrome, myopathic type	AD
1q32.1	LVNC6	611494	*TNNT2*	191045	DCM, RCM, HCM	AD
18q11.2	LVNC7	615092	*MIB1*	608677	DCM	AD
1p36.32	LVNC8	615373	*PRDM16*	605557	DCM	AD
15q22.2	LVNC9	611878	*TPM1*	191010	DCM, HCM	AD
11p11.2	LVNC10	615396	*MYBPC3*	600958	DCM, HCM	AD

Note: The LVNC phenotypes are numbered from 1 to 10; 9 disease genes are known, while 1 is still unknown (LVNC2). This latter has been mapped at 11p15 locus; No disease-causing mutation identified to date.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MIM, Mendelian Inheritance in Man; OMIM, Online Mendelian Inheritance in Man; RCM, restrictive cardiomyopathy; XL, X-linked.

*Indicates the gene.

TABLE 60–3. Mitochondrial DNA Mutations Reported at Least Once as Associated With Cardiac Phenotypes Including LVNC

Mitochondrial DNA Genes			Allele	Phenotype
MTTL1	Transfer RNA leucine (UUR)	$tRNA^{Leu(UUR)}$	A3243G	MELAS, DCM, HCM
MTTQ	Transfer RNA glutamine	$tRNA^{Glu}$	T4373C	DCM, HCM, possibly LVNC-associated
MTRNR1	12S ribosomal RNA	12S rRNA	T721C	Possibly LVNC-associated
MTRNR1	12S ribosomal RNA	12S rRNA	T850C	DCM, possibly LVNC-associated
MTRNR1	12S ribosomal RNA	12S rRNA	T921C	DCM, possibly LVNC-associated
MTRNR1	12S ribosomal RNA	12S rRNA	T961C	DEAF; DCM, possibly LVNC-associated
MTRNR2	16S ribosomal RNA	16S rRNA	T2352C	DCM, possibly LVNC-associated
MTRNR2	16S ribosomal RNA	16S rRNA	G2361A	DCM, possibly LVNC-associated
MTRNR2	16S ribosomal RNA	16S rRNA	A2755G	DCM, HCM, possibly LVNC-associated
MTND1	NADH dehydrogenase subunit 1	ND1	T3308C (M-T)	Possibly LVNC-associated; MELAS, DEAF enhancer; PM[a]
MTND1	NADH dehydrogenase subunit 1	ND1	A3397G (M-V)	ADPD /possibly LVNC cardiomyopathy–associated
MTND1	NADH dehydrogenase subunit 1	ND1	T3398C (M-T)	DMDF+HCM /GDM/possibly LVNC cardiomyopathy–associated
MTND1	NADH dehydrogenase subunit 1	ND1	T4216C (Y-H)	LHON, possibly LVNC-associated
MTATP8	ATP synthase subunit 8	ATP8	A8381G (T-A)	MIDD/LVNC cardiomyopathy–associated
MTATP8/6	ATP synthase subunit 8	ATP8	C8558T (P-S)	Possibly LVNC cardiomyopathy–associated
MTATP6	ATP synthase subunit 6	ATP6	A9058G (T-A)	Possibly LVNC cardiomyopathy–associated
MTCYB	Cytochrome b	CytB	T15693C (M-T)	DCM, HCM, possibly LVNC–associated

Note: Confirmed pathogenic status is in bold. Other mutations are reported; "reported" status indicates that one or more publications have considered the mutation as possibly pathologic. This is not an assignment of pathogenicity by MITOMAP (http://www.mitomap.org/foswiki/bin/view/MITOMAP/) but is a report of the literature.

Abbreviations: ADPD, Alzheimer disease and Parkinson disease; DCM, dilated cardiomyopathy; DEAF, maternally inherited deafness or aminoglycoside-induced deafness; DMDF, diabetes mellitus and deafness; GDM, gestational diabetes mellitus; HCM, hypertrophic cardiomyopathy; LHON, Leber hereditary optic neuropathy; LVNC, left ventricular noncompaction; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MIDD, maternally inherited diabetes and deafness; PM, point mutation/polymorphism;

[a]Status indicates that some published reports have determined the mutation to be a nonpathogenic polymorphism.

TABLE 60–4. Genes That Have Been Associated With LVNC in at Least One Case/Family But Are Not Listed in the OMIM Catalogue as LVNC Genes

Gene	MIM*	Protein	MIM#	Inheritance	Phenotypes
ABCC9	601439	ATB-binding cassette, subfamily C members	608569	AD	DCM
			614050		Atrial fibrillation
			614050		Cantu syndrome
			—		1 reported variant in LVNC
ACTN2	102573	Alpha-actinin 2	612158	AD	HCM with/without LVNC
			612158		DCM with/without LVNC
CASQ2	114251	Calsequestrin 2	611938	AD	Catecholaminergic polymorphic ventricular tachycardia 2
HCN4	605206	Hyperpolarization-activated cyclic nucleotide-gated K channel 4	613123	AD	Brugada syndrome 8
			163800		Sick sinus syndrome 2
			—		LVNC and bradycardia: 1 report
LMNA	150330	Lamin AC	115200	AD	DCM, ARVC, no isolated LVNC
NNT	607878	Nicotinamide nucleotide transhydrogenase	614736	AR	Glucocorticoid deficiency 4
PLEKHM2	609613	Pleckstrin homology domain containing protein, family M, member 2	—	AD	DCM, LVNC in 1 report
RYR2	180902	Ryanodine receptor 2	604772	AD	Catecholaminergic polymorphic ventricular tachycardia 1
			600996		ARVC (LVNC associated with exon 3 deletion)
SCN5A	600163	Sodium channel, voltage gated, type V, alpha subunit	601144	AD	Brugada syndrome 1
			603830		Long QT syndrome 3
			614022		Familial atrial fibrillation
			608567		Sick sinus syndrome 1
			601154		DCM
			113900		Heart block nonprogressive
			113900		Heart block progressive, type IA
			603829		Familial Ventricular fibrillation,1
			272120		Susceptibility to sudden infant death syndrome
TNNI3	191044	Cardiac troponin I 3	611880	AR	DCM
			613286	AD	DCM
			613690	AD	HCM
			115210	AD	RCM

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MIM, Mendelian Inheritance in Man; RCM, restrictive cardiomyopathy.

*Indicates the gene.

#Indicates the phenotype.

with LVNC also cause cardiomyopathies. They include genes encoding sarcomere proteins, nuclear envelope components, Z-band proteins, and ion channels.

SARCOMERE GENES

Mutations in *ACTC1* (cardiac actin alpha) were first reported in LVNC by Klaassen et al[69] in 2008, with identification of the p.(Glu101Lys) mutation described previously in apical HCM.[70] LVNC associated with mutations in *ACTC1* gene is labeled in the OMIM catalogue as LVNC4. Mutations in the same gene also cause DCM, RCM, and HCM, as well as CHD.[71] Several mutations in the *MYH7* gene were reported in both children and adults with LVNC.[72-74] Nine diseases are allelic at the same locus (LVNC5, HCM, DCM, RCM, familial autosomal dominant Ebstein anomaly with LVNC, autosomal dominant and recessive myosin storage myopathy, Liang distal myopathy, and scapuloperoneal syndrome, myopathic type). Similar, but less complex, is the list of cardiomyopathies allelic at the *MYBPC3* locus (HCM, DCM, and LVNC).[75,76] A relevant clinical observation is the potentially lethal phenotype of cardiomyopathy with LVNC in infants who carry compound heterozygous, double

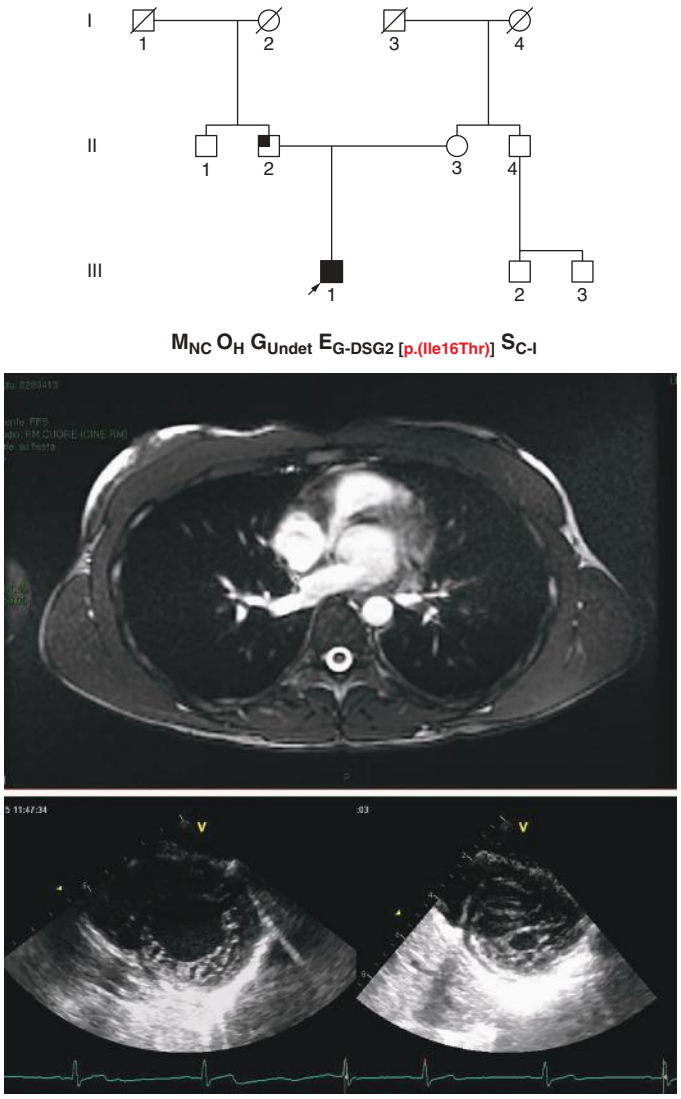


FIGURE 60–4. The figure shows the pedigree of a family in which the young proband (arrow, 23 years) had the first diagnosis of suspected left ventricular noncompaction (LVNC)/hypertrabeculation at the age of 13 years; he had played soccer for about 8 years. The boy suffered growth retardation and was treated with growth hormone (from the age of 5 to 16 years). Over the course of 10 years, he underwent several cardiology evaluations, including three cardiac magnetic resonance (CMR) scans and yearly echocardiographic evaluations, treadmill tests, and 24-holter monitoring, without a conclusive diagnosis. At present, his echocardiographic evaluation showed prominent apical trabeculation with a noncompacted-to-compacted (NC/C) ratio of 2.15. Left ventricular dimensions and functions are within normal ranges. Last CMR confirmed the hypertrabeculation, but measurements have been considered as not fulfilling criteria for the diagnosis of LVNC. The right ventricle did not show abnormalities. Clinical family screening was performed before deciding about genetic testing. Multigene panel analysis by next-generation sequencing demonstrated a novel variant in the *DSG2* gene, inherited from the father who does not show LVNC or hypertrabeculation but suffers lone atrial fibrillation. The patient is being monitored. This is a paradigmatic case of difficult diagnostic conclusion; similar cases are increasingly addressed using genetic evaluation to gather information for a possible definite diagnosis.

heterozygous, or homozygous truncating mutations.[77] Mutations in *TPM1* (LVNC6)[78] and *TNNT2* (LVNC9)[79] are less commonly associated with LVNC. The mechanisms by which mutations in sarcomere genes cause LVNC remain to be elucidated. Incomplete genotype is possible. Given the overlapping phenotypes associated with mutations of sarcomeric genes and the number of diseases allelic at the same loci, members of a family with the mutation may show different cardiac profiles, with or without the presence of LVNC (Fig. 60–5).

MUTATIONS IN GENES ENCODING NUCLEAR ENVELOPE PROTEINS

Mutations in genes encoding nuclear envelope proteins (ie, *LMNA*, which typically causes DCM and conduction disease) seem to be less common than those on sarcomere genes. To date, three *LMNA* mutations [p.(Arg644Cys), p.(Arg190W), and p.(Val455Glu)] have been described in patients with DCM and LVNC.[80-82] Given the high arrhythmogenic risk associated with *LMNA* mutations, these patients and families deserve the same monitoring and management strategies currently adopted for cardiolaminopathies without LVNC. Recent guidelines on the prevention of sudden death recommend that an implantable cardioverter-defibrillator (ICD) should be considered in patients with DCM, a confirmed disease-causing *LMNA* mutation, and clinical risk factors (Class IIa, Level B).[83] Risk factors include nonsustained ventricular tachycardia during ambulatory ECG monitoring, LV ejection fraction < 45% at first evaluation, male sex, and nonmissense mutations (insertion, deletion, truncation, or mutations affecting splicing). These factors correspond to those previously identified in a large European cohort of patients with dilated cardiolaminopathy.[84] LVNC can represent an early marker of cardiolaminopathy and may or may not segregate with DCM in the families (Fig. 60–6).

GENES CODING Z-LINE COMPONENTS

Genes coding Z-line components in both skeletal and cardiac muscle include the *CYPHER-ZASP* (*LDB3*) gene, which is a major candidate for LVNC.[85] In fact, carriers of mutations in *LDB3* may demonstrate DCM or LVNC (MIM# LVNC4) and, less commonly, HCM and ARVC.[86,87] Mutations in the same gene also cause myofibrillar myopathy; experimental ablation of Cypher, the PDZ-LIM domain Z-line protein, causes a severe form of congenital myopathy and DCM with premature death.[88] The p.(Asp117Asn) variant in the LIM domain-binding protein 3–encoding Z-band alternatively spliced PDZ motif gene (*ZASP*) has been described in a patient with LVNC and conduction disturbances.[89] Patients with DCM and LVNC/hypertrabeculation carriers of p.(Asp117Asn) commonly carry a second mutation in a cardiomyopathy gene.

CARDIOMYOPATHIES OFTEN COEXIST WITH MUSCLE DYSTROPHIES AND MYOPATHIES

Hypertrabeculation or noncompaction of the LV has been described in several neuromuscular disorders, including Duchenne muscular dystrophy (DMD) and mitochondrial myopathies.[12,62,63,68] In a large CMR study including 96 patients with DMD, 27 patients (28%) fulfilled criteria for the diagnosis of LVNC.[62] LVNC was defined as a diastolic NC/C ratio > 2.3 and was measured according to the AHA 16-segment model. In patients with ejection fraction < 55%, the median NC/C ratio was 2.46 versus 3.69 for isolated LVNC patients and 1.54 for normal controls. The relevant contribution of this study goes beyond the prevalence of LVNC in DMD. Serial CMR in 78 boys with DMD demonstrated a mean rate of change in NC/C ratio per year of +0.36 that resulted from the progressive decrease of the compacted layer and relative increase of the NC layer.[62] This information adds a "dynamic view" of NC anatomy in cardiomyopathies and potential prognostic information. LVNC was in fact associated with worsening LV systolic function. The progressive thinning of the

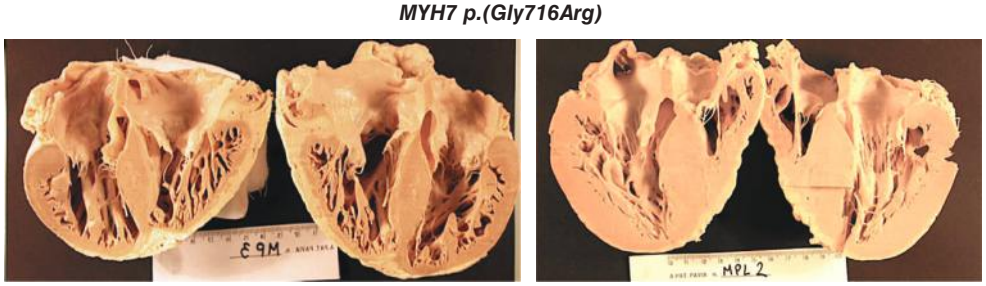
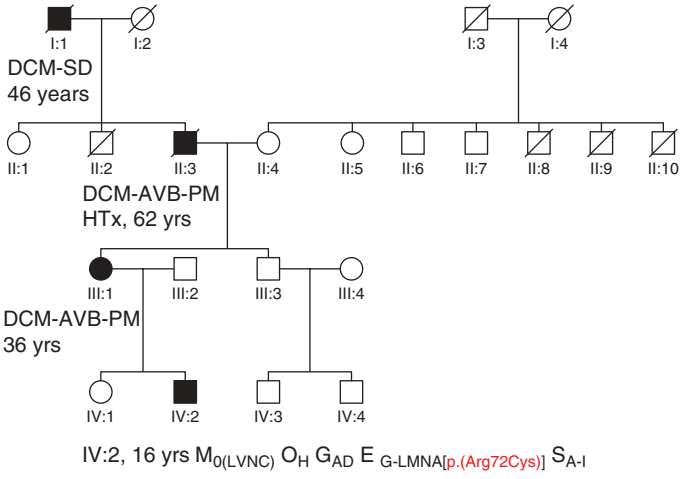


FIGURE 60–5. Phenotype heterogeneity in affected members of the same family and lack of segregation of the left ventricular noncompaction (LVNC) with the disease mutation. The figure shows the pedigree and the macroscopic view of the hearts excised at transplantation from I:1 and his son (II:2). The father was first diagnosed at the age of 36 years and underwent heart transplantation 10 years later; the son was first diagnosed with hypertrophic cardiomyopathy (HCM) at the age of 20 years and underwent heart transplantation 4 years later. Although father and son carry the same mutation in the *MYH7* gene, the cardiac remodeling in the two hearts differs. In I:1, the heart shows prominent trabeculae in both right and left ventricle; in II:2, the macroscopic phenotype is that of a typical HCM. I:1, MOGE(S) descriptor: the morphofunctional (M) phenotype indicates the hypertrophic cardiomyopathy (H), with dilated evolution (D) and associated noncompaction (NC); O (organ) specifies that the only involved organ was the heart (H); G (genetic) indicates that the disease had genetic basis and the inheritance was autosomal dominant (AD); E (etiology) specification indicates that the disease gene is *MYH7* and the mutation was p.(Gly716Arg); the pathologic mutation is in red.



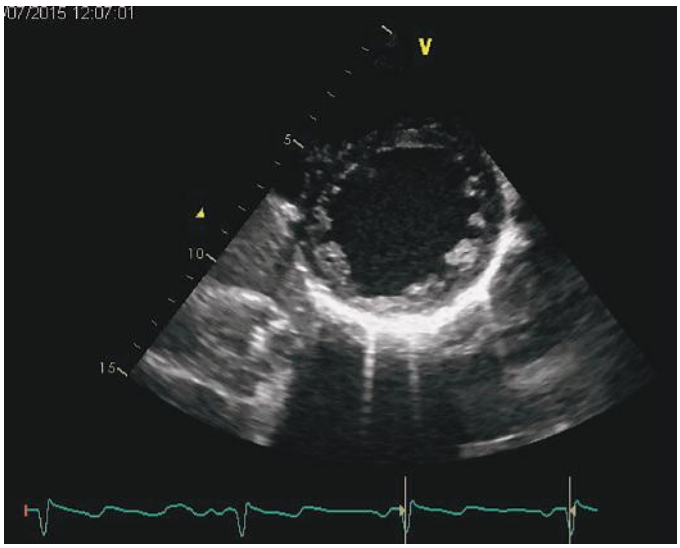


FIGURE 60–6. Autosomal dominant dilated cardiolaminopathy with conduction disease. Patient I:1 died suddenly at the age of 46 years; he was known to be affected by dilated cardiomyopathy (DCM) and had received pacemaker (PM) implantation a few years before death. Both patients II:3 and III:1 showed typical DCM phenotype with atrioventricular block (AVB). The young son (14 years, IV:2) of patient III:1 demonstrated prominent trabeculae and slightly increased left ventricular diameter (55 mm) with normal function. SD, sudden death.

compacted layer may result in a relative increased ratio of the two layers. This helps to explain the data reported by Kimura et al,[90] who found that LVNC is an independent negative prognostic factor in carriers of *DMD* defects.

ION CHANNEL GENES

Ion channel genes such as the sodium channel, type V, subunit alpha (*SCN5A*), genes encoding calcium-release channels such as the ryanodine receptor 2 (*RYR2*), and genes encoding calcium ion reservoir such as calsequestrin 2 (*CASQ2*, which is part of a protein complex that contains RYR2), typically cause diseases affecting the QT interval and catecholaminergic polymorphic ventricular tachycardia (CPVT; types 1 and 2). However, mutations in *SCN5A* have been reported in Japanese patients with LVNC.[91] Mutations in *RYR2* and *CASQ2* cause LVNC.[92,93] More than 80% of carriers of exon 3 deletion in the *RYR2* gene demonstrated LVNC and malignant arrhythmogenic phenotypes with syncope and CPVT.[92,93] A relevant contribution from *RYR2*-related LVNC is the demonstration that NC can develop during the evolution of the genetic disease. Specifically, a young patient with *RYR2* deletion of exon 3 showed normal LV function and structure at the age of 14 years when he presented with two episodes of exertion syncope and demonstrated LVNC with normal function 2 years later when he presented with a third episode of syncope.[92]

DESCRIPTORS OF CARDIOMYOPATHIES WITH LEFT VENTRICULAR NONCOMPACTION

The nosology description of clinical, imaging, and genetic data does not meet LVNC-specific rules and criteria. Diagnoses such as "dilated LVNC" versus "DCM with LVNC" or "hypertrophic LVNC" versus "HCM with LVNC" are equally used to describe the phenotypes. When LV dilation and dysfunction are present, the diagnosis of LVNC cardiomyopathy is supported more by the DCM phenotype than by the trabecular morphology. When LVNC is observed in hearts with HCM, the diagnosis of LVNC cardiomyopathy is supported more by the HCM criteria than those of LVNC. Nonetheless, both descriptors (either leading or subordinating the LVNC to the cardiomyopathy diagnosis) give an immediate perception of the phenotype. In comparison, the diagnosis of "LVNC cardiomyopathy" may limit clinical information and, in parallel, automatically assigns a driving role to LVNC in the diagnosis.

LEFT VENTRICULAR NONCOMPACTION IN CONGENITAL HEART DISEASES

LVNC can occur in hearts with CHD such as uni- or bicuspid aortic valves, aortic coarctation, diffuse aortic hypoplasia and subaortic stenosis, atrial/ventricular septal defects, Ebstein anomaly,[94-96] tetralogy of Fallot, double outlet right ventricle, and hypoplastic left heart syndrome.[97] These disorders can be sporadic or familial, with CHD recurring in more than one member of the family[94-97] (see Chap. 56).

SYNDROMIC LEFT VENTRICULAR NONCOMPACTION

Syndromes with LVNC (or syndromic LVNC) are either sporadic or familial. The NC morphology is one of the traits associated with both monogenic defects and chromosomal anomalies. Monogenic syndromes mostly include rare diseases. Some of them, such as Anderson-Fabry disease and Danon disease, are well known by cardiologists[98-100] because the HCM phenotype is often the first recognized manifestation. Other monogenic syndromes are less commonly observed in the cardiology setting (Table 60–5). Chromosomal anomalies are usually observed in complex syndromes that display several multiorgan defects. Chromosomal abnormalities include deletions, translocations, and trisomy or tetrasomy [1p36 deletion syndrome; interstitial 1q43-q43del; del(1)(q) syndrome; del5q35; 7p14.3p14.1 deletion; 8p23.1 del syndrome; 18p subtelomeric deletion; 22q11.2 deletion syndrome; 22q11.2 distal deletion syndrome; trisomy 13 and 18; tetrasomy 5q35.2–5q35; robertsonian translocation 13;14; mosaics such as 45,X/46XX and 45,X/46,X,i(Y)(p11)]. Most chromosomal abnormalities represent isolated cases.[94-96] Reasons for scientific and clinical interest include the possible identification of new disease or modifier genes when abnormal chromosomal regions involve novel candidate genes in patients with the typical syndrome and LVNC. Isolated LVNC has been reported in the Pierre-Robin sequence or syndrome (OMIM #261800), which is characterized by micrognathia, posterior displacement/retraction of the tongue (glossoptosis), upper airway obstruction, and congenital heart defects in 20% of cases.[101]

RIGHT VENTRICULAR NONCOMPACTION

Right ventricular noncompaction (RVNC) can occur as an isolated entity,[4,102,103] in association with LVNC,[5] with predominant right ventricular involvement,[104] or in patients with CHD.[105] In rare cases, it may cause right ventricular outflow tract obstruction as a result of hypertrophied spongy muscle at the infundibular region.[106] Given the complex trabecular anatomy of the right ventricle, the diagnosis is difficult but feasible with routine imaging tools and, when necessary, right ventriculography.[106] RVNC may be an occasional finding in family screening studies (Fig. 60–7).

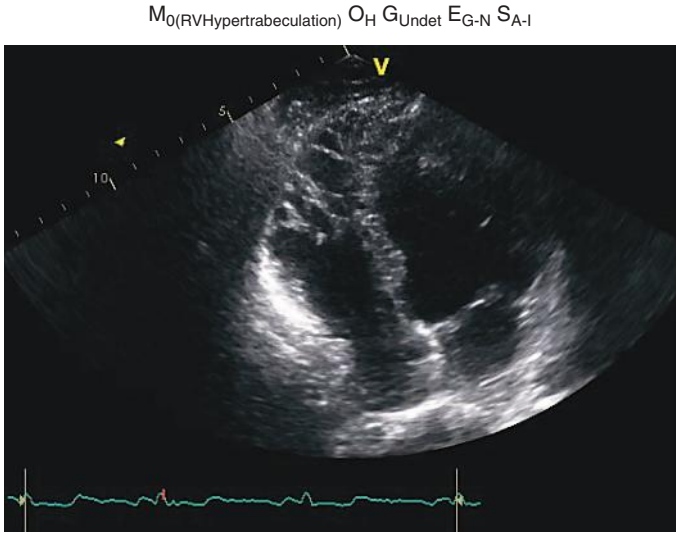


FIGURE 60–7. Prominent right ventricular trabeculations in a young man (36 years) who was addressed to genetic counseling after the sudden death of his first son (first day of life). The echocardiographic study showed normal left ventricular (LV) dimension and morphology; although trabeculae were prominent in the left ventricular apex, criteria for LV noncompaction (LVNC) were not fulfilled. The patient is undergoing regular clinical monitoring.

TABLE 60–5. Monogenic Syndromes With Cardiac Involvement Including LVNC

Gene	MIM*	Protein	MIM#	Inheritance	Phenotypes
G4.5	300394	Tafazzin	302060	XL	Barth syndrome with DCM-LVNC; rare HCM
ARFGEF2	605371	ADP-ribosylation factor guanine nucleotide-exchange factor 2	608097	AR	Periventricular heterotopia with microcephaly
DNAJC19	608977	DNAJ/HSP40 homolog, subfamily C, member 19	610198	AR	DCM with ataxia (DCMA)
LAMP2	309060	Lysosome-associated membrane protein 2	300257	XL	Danon disease
NNT	607878	Nicotinamide nucleotide transhidrogenase	614736	AR	Glucocorticoid deficiency 4 (GCCD4)
RSK2	300075	Ribosomal S6 kinase 2	303600	XL	Coffin-Lowry syndrome (faciodigital mental retardation syndrome)
			300844		Mental retardation
YWHAE (14-3-3ε)	605066	Monooxygenase activation protein, epsilon isoform	—	AD	LVNC and hypoplasia of the corpus callosum

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MIM, Mendelian Inheritance in Man.

*Indicates the gene.

#Indicates the phenotype.

ACQUIRED ISOLATED LEFT VENTRICULAR NONCOMPACTION

The acquired and reversible forms of LVNC question the unique and a priori interpretation of the NC morphology as a genetic disease and cardiomyopathy.[55-59,107,108] Acquired isolated LVNC has been reported in athletes[47,99,100] and pregnant women,[56] as well as in hematologic disorders,[57,109] chronic renal failure,[59] myopathies,[58] and bicuspid aortic valve.[60] These observations expand the spectrum of pathogenetic hypotheses from arrested embryogenesis maturation of LV trabeculae to acquired pathogenetic mechanisms, including hemodynamics, phenotype-driven trabecular gene expression, or epigenetic factors, as in CHD.[110]

ATHLETES

The identification of LVNC in preparticipation screening studies had demonstrated that intense physical training may induce increased trabeculation that may fulfill current diagnostic criteria for the diagnosis of LVNC. In a large series including more than 1000 asymptomatic athletes, 18% had increased LV trabeculation and 76 (8%) fulfilled echocardiographic criteria for LVNC.[55] The issue of athletes demonstrating LVNC is emerging from different sources[111,112] and in real life (Fig. 60–8). Distinguishing between pathologic LVNC and physiologic hypertrabeculation is a diagnostic challenge, and detection is becoming increasingly common with enhanced echocardiography and magnetic resonance imaging modalities.[111] The proportion of athletes who develop LVNC under intensive exercise is relevant (about 10%), but the proportion of those who do not develop LVNC under the same exercise levels is 90%. The impact of LVNC on otherwise normal hearts requires long-term follow-up studies to establish with certainty whether LVNC can be an early marker of myocardial disease or the phenotype of maladaptation of different individuals to strenuous physical effort. Therefore, "healthy" athletes diagnosed with LVNC should undergo deep phenotype examination, advanced imaging, and clinical monitoring as suggested by experts.[107]

PREGNANCY

A form of reversible LVNC has been described in pregnancy. In a prospective longitudinal echocardiographic study of 102 primigravida pregnant normotensive women (66 white women and 36 black women) without family history of cardiomyopathy or premature sudden cardiac death, 25% developed increased LV trabeculations during pregnancy. The finding was more common in black women than in white women. Furthermore, 10 women (9.8%) fulfilled the Jenni et al[2] criteria, 19 (18.6%) fulfilled the Chin et al[9]criteria, and 8 (7.8%) fulfilled both criteria for LVNC. There was no significant association between increased LV trabeculations and age, body mass index, systolic blood pressure, LV cavity dimension, stroke volume, or LV mass. Ethnicity was the only independent predictor for the presence of increased (three or more) trabeculations during pregnancy, with black women being almost three times more likely to develop increased LV trabeculations than white women during pregnancy after adjustment for the aforementioned factors. After delivery, 18 women (69.2%) showed complete resolution of LV trabeculations over a mean duration of 8.1 ± 4.2 months, whereas 7 women (27%) continued to display LV trabeculations, without predilection for ethnicity.[56] Further series are necessary to confirm this transient trabecular remodeling and the low risk.[113] However, the study[56] adds evidence to the possibility that LVNC can not only be acquired, but also transient and, therefore, does not necessarily represent a primary myocardial disorder.[114]

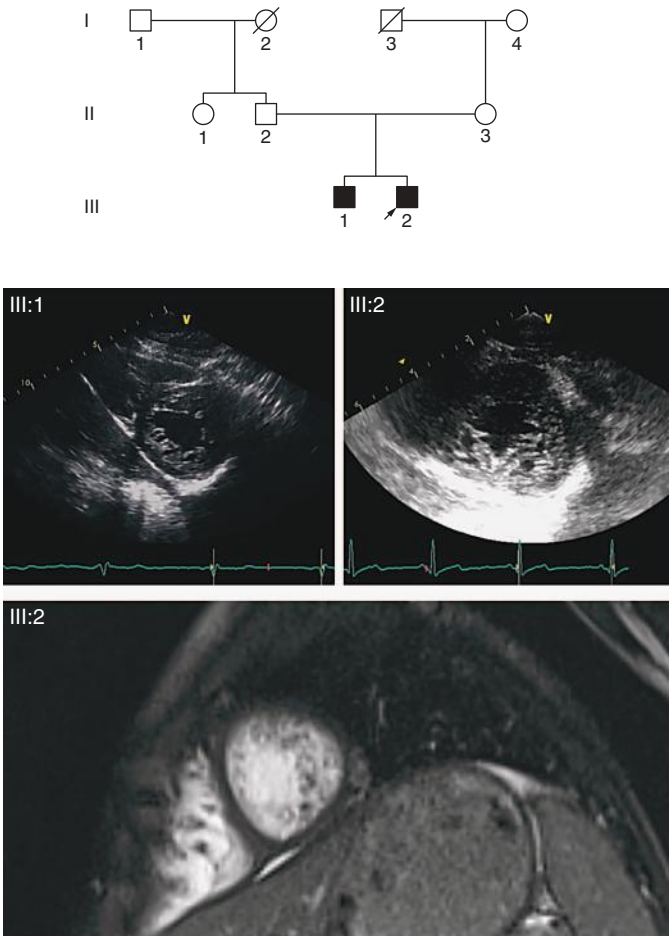


FIGURE 60–8. The figure shows the pedigree of a small family in which the proband (III:2) is a 12-year-old healthy boy, who plays soccer. He has been incidentally diagnosed with left ventricular noncompaction (LVNC) after identification of nonspecific electrocardiogram abnormalities in preparticipation screening (diphasic T waves in V_2-V_3, D_2, aVF). Left ventricular (LV) function and dimensions were within normal ranges (LV ejection fraction, 55%; LV end-diastolic diameter, 52 mm; according to Henry, 104.8; Z-score, 0.50). The echocardiographic evaluation of the brother (III:1; soccer player) showed prominent trabeculation confirmed by cardiac magnetic resonance (CMR), not fulfilling criteria for the diagnosis of LVNC. Both parents are not athletes and had normal echocardiographic evaluation. Extensive genetic testing analysis did not identify pathologic mutations. Both siblings are carriers of a genetic variant of unknown significance (p.Lys393Asn) in the *KCNQ1* gene. The two echocardiographic panels show the trabecular pattern in the two siblings; the CMR panel shows prominent trabeculae in III:2. The variant is inherited from the healthy father.

HEMATOLOGIC DISEASES

LVNC has been described in patients affected by different hematologic disorders such as hereditary spherocytosis,[115] essential thrombocytopenia,[116] and β-thalassemia[57,117] with and without myocardial overload. In patients with β-thalassemia, isolated LVNC was identified in 13.3% of patients.[57] The mechanisms by which chronic anemia, hemolysis, or ineffective erythropoiesis may influence the remodeling of the trabecular compartments are not known. In patients with myocardial iron overload and siderosis, a preferential distribution of intramyocyte iron in the compacted or NC layers has not been observed.[118] Myocardial T2*-weighted CMR values should be able to provide more information about intramyocyte iron storage. However, cardiac abnormalities could be triggered by toxic iron species such as non–transferrin-bound iron.[118] Whether LVNC represents a physiologic adaptation to the chronic nonprimary cardiac disorders or a disease-related pathologic effect is not clear.[109]

CHRONIC RENAL FAILURE

LVNC has been reported in two patients with chronic renal failure. In both cases, echocardiography demonstrated a dilated LV with thickened walls and a thin, compacted myocardium on the epicardial side and a thicker noncompacted endocardial layer. Ratio between the noncompacted myocardium and the compaction myocardial layer fulfilled diagnostic criteria in both cases. Clinically relevant is the fact that oral anticoagulation therapy was initiated in both patients after the diagnosis of LVNC. Family screening with echocardiography in first-degree relatives of one of the patients did not show additional affected members. Regular echocardiographic monitoring of patients with chronic renal failure is suggested to diagnose cardiovascular diseases including this rare association.[59]

BICUSPID AORTIC VALVE

A high prevalence of LVNC is reported in patients fulfilling the echocardiographic criteria for bicuspid aortic valve (BAV). Specifically, in one study, 12 (11.0%) of 109 patients with BAV fulfilled the criteria for LVNC, with nine of the 12 patients being men. Although the pathophysiologic basis of LVNC in patients with BAV is unclear, special attention should be given to the evaluation of LV trabecular anatomy.[60]

MYOPATHIES

LV hypertrabeculation may occur in patients affected by different neuromuscular diseases such as dystrophinopathies, metabolic myopathies, myotonic dystrophy, Leber hereditary optic neuropathy, and Barth syndrome. Several pathogenetic hypotheses have been advocated to explain the occurrence of LV hypertrabeculation, including "an inborn error to hypertrophy, which either starts during embryogenesis, early childhood, or in adulthood."[12] Alternative hypotheses include persisting sinusoids penetrating into the LV cavity or malfunctions of gap junctions.[12]

CONSIDERATIONS ON ACQUIRED LEFT VENTRICULAR NONCOMPACTION

All the above acquired conditions of LVNC demonstrate that a unique pathogenetic hypothesis of embryogenic defect is unlikely to explain acquired, late-onset, transient LVNC. Most studies on acquired LVNC are recent and constitute a stimulus to further explore this trait in cardiac and noncardiac diseases.

LEFT VENTRICULAR NONCOMPACTION: DIAGNOSTIC WORKUP

In patients with LVNC associated with cardiomyopathies, CHDs, or complex syndromes, clinical workup is guided by the primary disease rather than by the LVNC itself. Vice versa, in individuals demonstrating isolated LVNC with normal cardiac function and dimensions, the diagnostic workup should be tailored based on individual characteristics and findings emerging from cardiologic investigations, family history (and eventually screening), advanced imaging, and monitoring (Fig. 60–9). Over the past 20 years, LVNC has been repeatedly described as *LVNC cardiomyopathy*. Efforts by several groups of researchers to establish precise diagnostic criteria (Table 60–1) for

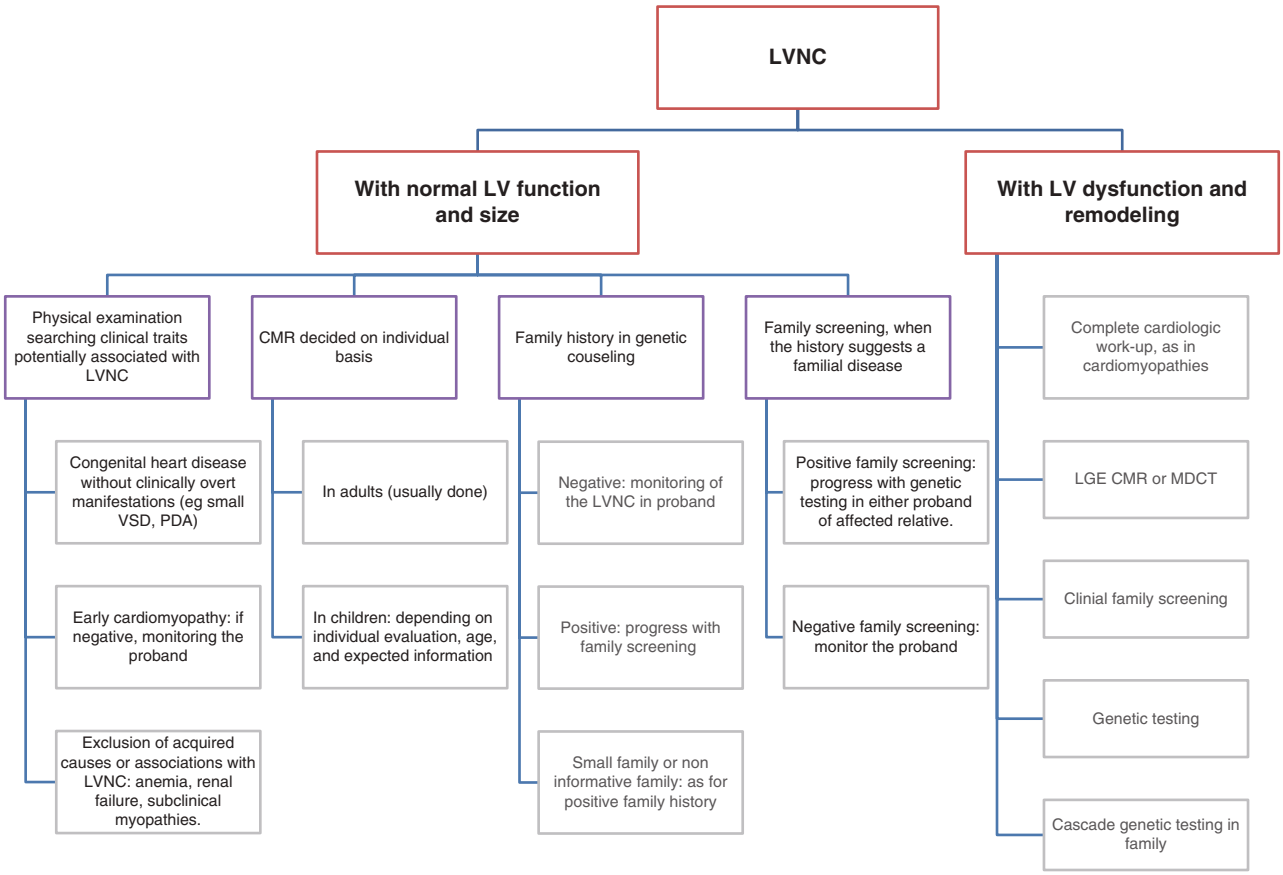


FIGURE 60–9. Flow chart showing possible workup in patients diagnosed with left ventricular noncompaction (LVNC) and normal left ventricular (LV) function and dimensions versus patients demonstrating LV dysfunction or other associated cardiac abnormalities. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; MDCT, multidetector computed tomography; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

diagnosing LVNC reflect the lack of gold standards for the diagnosis. The potentially dynamic evolution of LVNC, either progression or regression, and the possibility of controlling abnormal trabecular remodeling with current treatments are matters of investigation. A recent study reported LV mass reduction among patients with LVNC during β-blocker therapy.[119]

PHYSICAL EXAMINATION

In patients with heart disease and LVNC, physical examination can contribute to the diagnosis. Extracardiac traits recurring in patients with LVNC (and vice versa) can eventually help to generate a diagnostic hypothesis, particularly in genetic cardiomyopathies, syndromes, and congenital heart defects.[120] Deep cardiomiopathy phenotyping can help to generate a clinical hypothesis, especially in patients with LVNC.[120]

GENETICS AND FAMILY SCREENING

Genetic evaluation, both counseling and testing, is recommended for patients with cardiomyopathy and LVNC, patients diagnosed with one of the syndromes in which LVNC may recur, and individuals in whom LVNC is incidentally identified during medical screening.[121,122] A key question is whether the trait is familial or sporadic, and the answer may come from clinical family screening. In fact, isolated LVNC in individuals with normal LV size and function and nonthickened LV walls is asymptomatic and only detectable using imaging.

The medical genetic examination explores anthropometric profiles, facies, skin, eyes, hair, and skeletal and nervous systems.[120] Deep phenotyping may identify extracardiac traits that recur in syndromes with LVNC and that can be present in some family members. Data from probands and relatives contribute to generating family pedigrees, which give a "graphic" view of the mode of inheritance of the disease. In the post–genetic test phase, the pedigree shows the segregation of the mutation(s) with the phenotype, thus highlighting the correct interpretation of the genetic results.

Genetic testing should be performed in probands with LVNC and cardiomyopathy, in patients with familial CHD with LVNC, and in patients with syndromes including LVNC.[121] The indication to perform genetic testing in individuals with normal LV function and an incidental diagnosis of LVNC is not regulated by guidelines. Genetic counseling and extensive clinical information are essential.[120,121] Probands should be aware that activation of genetic testing, in particular multigene panels, can demonstrate the presence of genetic variants of unknown significance whose role in the determination of the trait may remain uncertain, and therefore, results can be inconclusive. Athletes are especially exposed to the risk of labeling a potentially reversible trait with the diagnosis of a possible genetic disease, with obvious implications regarding suitability for sport activity and lifestyles.

In families with LVNC and cardiomyopathy, affected members may demonstrate different or combined cardiac phenotypes, with isolated LVNC in some relatives and cardiomyopathy with or without LVNC in others. Therefore, the segregation of LVNC may not coincide with the segregation of a coexisting cardiomyopathy. This explains why segregation studies are major contributors in unraveling the role of mutations, especially in families with complex genetics, when more than one pathologic mutation is identified.[123] Information gathered from large families can be usefully transferred to small families or single patients, especially when evaluating the role of debated genetic variants such as *LDB3* p.(Asp117Asn), which was originally described as causing DCM and LVNC[85] and is now reported as a possible single nucleotide polymorphism.[124]

ELECTROCARDIOGRAPHY

ECG data do not provide LVNC-specific diagnostic information.[125] From available observations, it appears that although a normal ECG finding is rare in LVNC and observed in a minority of patients (from 6% to 13%), there are no changes specific to LVNC.[125-128] However, certain ECG changes, such as negative T waves > 1 mm in depth in two or more leads (particularly V_4-V_6, II and aVF, or I and aVL), ST-segment depression ≥ 0.5 mm in depth in any lead, or pathologic Q waves (> 3 mm in depth or > 40 milliseconds in duration) in two or more leads (except III and aVR), are more compatible with a cardiomyopathy. A significant number of black athletes (almost 13%) show negative T waves in the anterior precordial leads that are not associated with structural disease.[129]

IMAGING

ECHOCARDIOGRAPHY

Echocardiography is the first-choice imaging tool for suspecting or diagnosing LVNC. It is noninvasive and easy to both perform and repeat. Serial echocardiographic investigations are sustainable and can be offered in both screening studies and the diagnostic setting. The different diagnostic criteria proposed to date are summarized in Table 60–1. The role of the thickness of the compacted myocardial layer in the diagnosis should be emphasized.[24]

However, echocardiography has limitations. Visualization of the apex, which is commonly affected in LVNC, can be difficult. The profile of a dual-layered myocardium or trabeculations may not be sharp. Indistinct trabeculae may also result in diagnostic difficulty. Interpretation of echocardiographic findings may vary among experts. In a recent study, echocardiographic records from 100 patients with and without LV hypertrabeculation matched for age and systolic function were reviewed by experts according to the following predefined criteria: (1) greater than three prominent trabeculae at end diastole; (2) a noncompacted part of a two-layered myocardial structure formed by these trabeculations; (3) a ratio of > 2:1 of noncompacted to compacted layer at end systole; and (4) perfusion of the intertrabecular spaces from the ventricular cavity. The observers disagreed about presence or absence of LV hypertrabeculation in 35 cases, and even after mutual review, 11% cases remained questionable.[130] A possible limitation occurs when the short axis is not perpendicular to the LV long axis, which can give the morphologic appearance of prominent trabeculations mimicking LVNC.[13] The above limitations are those currently listed in most review articles and scientific communications. However, modern echocardiographic instruments are providing high imaging quality. In addition, contrast-enhanced echocardiography can better profile endocardial borders and show trabeculations alternating with the intertrabecular recesses.[131] Finally, three-dimensional echocardiography can further contribute to evaluate the extent of noncompacted myocardium. In 26 Olympic rowing athletes and 49 healthy volunteers, the trabeculated LV volume and its value normalized by LV end-diastolic volume were significantly higher in patients with LVNC as compared to controls and athletes. Given the high spatial resolution and accuracy in volumetric quantification, three-dimensional echocardiography can provide an accurate measurement of the extent of the noncompacted myocardium and identification of patients with LVNC.[132]

CARDIAC MAGNETIC RESONANCE

CMR is performed in patients with echocardiographic evidence or suspicion of LVNC. The use of balanced steady-state free precession (SSFP) cine imaging instead of simple gradient-echo imaging improves image quality and increases sensitivity for myocardial trabeculae, which are better seen at end diastole[14-20] (Table 60–1). In clinical practice, an NC/C ratio > 2.3 is considered diagnostic for LVNC (Petersen criteria). Measures are taken in short axis at the midcavity and basal segments. A four-chamber view may be preferred in hearts with prominent apical LVNC. As a result of the complex right ventricular trabecular anatomy, right ventricular involvement in LVNC or isolated RVNC can be better evaluated with CMR than with echocardiography.[133-135] Criteria for the diagnosis of RVNC are not established. From observations in autopsy series, transmural thickness of the noncompacted right ventricle > 75% should correspond to a diagnosis of RVNC.[136] Dilatation of the right ventricle may be a supportive feature for the diagnosis.[137] The three-dimensional view shows the entire volume of the heart independently of the thoracic conformation of patients.[138] CMR further provides information on possible associated CHD, endocardial thrombi, or incidental extracardiac pathologies. In general, CMR performance is superior to echocardiography for characterization of the ventricular trabecular anatomy.[17] Although myocardial fibrosis is not a criterion for the diagnosis of LVNC, late gadolinium enhancement is an adjunct value, useful in the general evaluation of the disease context in which LVNC is observed. CMR may have limitations in children because of lack of patient cooperation and small cardiac size.[17] In any case, CMR is superior to two-dimensional echocardiography in assessing the extent of noncompaction and provides supplemental morphologic information beyond that obtained with conventional echocardiography.[139] However, CMR also has limitations. It is contraindicated in patients with old intracavitary device implantation and in those suffering claustrophobia. CMR is more expensive than echocardiography and may be more time consuming. In addition, serial CMR studies can be performed but at reasonably longer intervals than serial echocardiography.

MULTIDETECTOR COMPUTED TOMOGRAPHY

MDCT offers advantages to both patients and operators. Duration of the test is short, making it especially advantageous for those who suffer from claustrophobia. Newer scanners and dose modulation techniques have decreased the effective radiation exposure. In addition, CT can be used for patients with defibrillators or resynchronizing devices. A major advantage of MDCT is the information obtained regarding coronary arteries that excludes coronary artery disease as a cause of LVNC and detects coronary anomalies.[23,140-142] With the increase in the number of thoracic and coronary MDCT angiographic studies, LVNC may be incidentally detected during examinations performed for other reasons. Major limitations include the administration of ionizing radiation and lower capability of characterizing myocardial tissue and identifying fibrosis compared with CMR. Cost-related limitations are similar to those of CMR, and serial studies are not routinely feasible.

BIOMARKERS AND PATHOLOGY

There are no specific biomarkers for LVNC. Potentially useful markers are either those that provide information on myocardial injury or heart failure, namely troponins and natriuretic peptides. In genetic cardiomyopathies with LVNC, relevant biomarkers may be those that characterize the genetic disease and are equally increased in cardiomyopathy patients independent of LVNC (eg, in dystrophin cardiomyopathy).[62,90]

Macroscopic pathology is highly informative. Both autopsy and hearts excised at transplantation may demonstrate typical features of LVNC.[8,136,143] However, microscopic features are nonspecific. Endomyocardial biopsy may show interstitial fibrosis, fibrous endocardial thickening, and nonspecific myocyte changes similar to those seen in cardiomyopathies. In rare cases of cardiac amyloidosis with imaging features of apical hypertrabeculations suggestive of LVNC, endomyocardial biopsy can play a diagnostic role for amyloid heart disease.[144]

LEFT VENTRICULAR NONCOMPACTION MANAGEMENT

In general, the management of patients with LVNC consists of evidence-based treatments for systolic heart failure and arrhythmias as well as oral anticoagulation to prevent mural thrombosis. Indications for ICD placement are similar to those in other patients with DCM.[145]

LVNC specific treatment does not exist. At present, the possible distinct clinical problem is the thrombogenic risk, which is present only in dysfunctional hearts. Therefore, decisions about anticoagulation can eventually be anticipated in patients with LV dilation and impaired systolic function.[146,147] Stroke and embolism are rare in patients with LV hypertrabeculation or LVNC, especially when rhythm and systolic function are normal. When present, atherosclerosis-related causes should be assessed.[146] The $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke) score may be useful for clinical decision making regarding oral anticoagulation for prevention of stroke and embolism in patients with increased LV trabeculations.[147]

Patients diagnosed with Barth syndrome with heart failure should receive standard medications as per guidelines. Aspirin can eventually be added to decrease the risk of stroke in patients with severe LV dysfunction. The monitoring of arrhythmias and related prevention strategies should be maintained over the course of the patient's life. Disease-specific treatments can include the administration of granulocyte colony-stimulating factor either routinely or in high-risk clinical situations (eg, infections, surgery) along with prophylactic antibiotics. Diets should include administration of uncooked cornstarch to prevent muscle protein loss overnight. Succinylcholine, a nondepolarizing neuromuscular blocker that could have a prolonged effect, should be avoided.[63] As a general rule, patients with Barth syndrome should be cared for by specialized pediatricians in the context of a multidisciplinary setting that guarantees continuity of care from the pediatric setting to adulthood.

In other conditions, such as HCM with LVNC or RCM with LVNC, anticoagulation treatment is driven more by complications of the native disease, such as left atrial dilation with and without arrhythmias.

Pregnant women can be incidentally diagnosed with LVNC or develop peripartum cardiomyopathy (PPCM; dilated, congestive phenotype) with features of LVNC.[148] The management of LVNC associated with PPCM and of LVNC in pregnant women with normal LV function and dimensions may differ. The former may require management of the PPCM with possible adjunct of anticoagulation (see Chap. 58), whereas the latter may potentially only require clinical monitoring.

The administration of medications such as β-blockers seems to decrease LV mass among patients with LVNC. It is not clear whether the effect is a result of the decrease of the trabeculae or the compacted LV myocardial mass or both. Effects of β-blocker treatment in LVNC require validation in prospective controlled studies.[119]

PROGNOSTIC STRATIFICATION

Prognosis in LVNC depends on the clinical presentation. Asymptomatic patients or individuals with LVNC and normal LV function have a good prognosis. This is demonstrated by the large group of asymptomatic (26%) first- and second-degree family members of patients with LVNC.[149] Alternatively, patients presenting with heart failure (New York Heart Association class III or IV), sustained ventricular arrhythmias, or left atrial dilation have an unfavorable prognosis.[149,150] Adverse outcomes of isolated LVNC occur in patients with advanced heart failure, dilated left heart with systolic dysfunction, reduced systolic blood pressure, pulmonary hypertension, and right bundle branch block.[149] Survival tracks closely with the presence of symptoms at presentation (69% when present v 100% when absent).[131] In subgroups of patients (eg, DMD, Becker muscular dystrophy), the presence of LVNC is significantly associated with rapid deterioration in LV function and higher mortality.[62,90] Therefore, prognosis depends on the severity of the underlying cardiac disease rather than the trabecular anatomy of the LV.

CONCLUSION

LVNC is a morphology-based diagnosis that does not have, by itself, corresponding LV dysfunction. Based on current diagnostic criteria, LVNC can be identified in healthy individuals, or it can be acquired and reversible in pregnant women, athletes, and patients with hematologic disorders, myopathies, chronic renal failure, and bicuspid aortic valve. The observation of reversible LVNC in athletes suggests that it may represent a phenotypic variant of athlete's heart.[151]

When associated with cardiomyopathies, CHDs, or syndromes, LVNC commonly has a genetic cause, which coincides with the cause of the underlying heart disease. The proportion of echocardiographic diagnoses is increasing, and this implies cascades of further clinical evaluation, including CMR, family studies, monitoring, and lifestyle modifications and/or restrictions.[152]

Genetics often contribute to the overall interpretation of the finding of LVNC even in healthy individuals with normally functioning hearts. The specific role or impact of LVNC remains difficult to separate from that of the underlying heart disease. Although anticoagulation plans can be eventually anticipated in dilated and dysfunctional hearts, specific treatments do not exist. Therefore, isolated LVNC should require a precise definition (trabecular anatomy variant, adaptation, or heart muscle disease) and be a matter of consensus diagnostic criteria by scientific bodies.

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CHAPTER 61

RESTRICTIVE HEART DISEASES

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INTRODUCTION

Restrictive physiology describes a pattern of ventricular filling in which increased myocardial stiffness causes a precipitous elevation of ventricular pressure matched by a limited increase in volume; the resultant diastolic dysfunction is characterized by a pattern of mitral inflow Doppler velocities with an increased ratio of early diastolic filling to atrial filling (≥ 2), decreased E-deceleration time (< 160 milliseconds), and decreased isovolumetric relaxation time.

Diastolic dysfunction occurs in several cardiac diseases with a range of etiologies.[1] Restrictive physiology can be observed in diseases affecting endocardium, myocardium, and epipericardial layers/structures (Table 61–1). The recent development of advanced technologies for DNA sequencing, refined imaging techniques, and identification of novel biomarkers have contributed to unraveling the primary causes of many of these different diseases, facilitating more targeted treatments. These dynamic technologies will continue to develop and will transform the past pathology-based nosology of heart diseases into a precise, etiology-based classification of restrictive cardiac diseases (see Chap. 57). This chapter illustrates the etiology, phenotypes, and management of these different diseases. In this context, cardiac amyloidosis is described as a separate entity; it represents a pan-heart disease affecting all cardiac structures and a unique disease model of extracellular infiltration by amyloid fibrils.

RESTRICTIVE CARDIOMYOPATHY

DEFINITION

According to the definition of the European Society of Cardiology (ESC), "Restrictive cardiomyopathies are defined as restrictive ventricular physiology in the presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes, and normal ventricular wall thickness."[2] According to the definition of the American Heart Association (AHA), "Primary restrictive non-hypertrophied cardiomyopathy is a rare form of heart muscle disease and a cause of heart failure that is characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal LV wall thickness and AV valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function."[3] Both definitions emphasize restrictive ventricular physiology, normal or reduced volume of one or both ventricles, and normal wall thickness. AHA further stipulates the presence of atrial dilation, normal atrioventricular (AV) valves, and normal systolic function.[3] End-stage hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) may manifest restrictive physiology, but these forms are not assigned to distinct subgroups of cardiomyopathies.[2] Precise epidemiology data are not available, but restrictive cardiomyopathy (RCM) is a less common form of cardiomyopathy. A nationwide epidemiologic survey in Japanese hospitals estimated a prevalence of 0.2 per 100,000 inhabitants.[4]

RCM can be primary/idiopathic or acquired[5]; recent advances in DNA sequencing demonstrated that the former are genetic diseases in both adults and children,[6,7] whereas the latter are phenocopies of genetic RCM. The criterion common to primary/idiopathic or acquired RCM is the restrictive ventricular physiology, but etiology is heterogeneous. The differentiation between primary/idiopathic RCM and other diseases manifesting restrictive ventricular physiology is essential because the precise diagnosis may determine monitoring, treatment, and prognosis.

PRIMARY AND IDIOPATHIC RESTRICTIVE CARDIOMYOPATHIES ARE GENETIC DISEASES

RCM is *morphologically* characterized by normal or reduced ventricular size, bi-atrial dilation, and absence of left ventricular (LV) hypertrophy with LV wall thickness ≤ 13 mm, and *functionally* defined by diastolic dysfunction with restrictive physiology and preserved systolic function.[1,2,8,9] The early clinical manifestations can be subtle, and morphofunctional modifications can be latent. Most RCMs demonstrate familial clustering and genetic origin; the genetic bases are heterogeneous. More than 15 genes have been reported to date in patients and families with RCM. The clinical course is characterized by the development of heart failure with preserved ejection fraction, with evolution to end-stage biventricular heart failure where heart transplantation is the most effective treatment option.[8]

Diagnosis in Probands

Probands (or index patients) are usually diagnosed because of signs and symptoms of heart failure with preserved ejection fraction.[8,9,10] The clinical workup includes physical examination, electrocardiogram (ECG), and two-dimensional echocardiography. Physical examination reflects the elevated systemic and pulmonary venous pressures, with prominent jugular venous pulse and X and Y descents. In the advanced course of the disease, the pulse volume is low, the stroke volume declines, and the heart rate increases. A systolic murmur and filling sound reflect AV

TABLE 61–1. Restrictive Heart Diseases: Myocardial, Pericardial, and Endocardial Diseases

Level	Diseases Demonstrating Restrictive Pathophysiology
Myocardial	Restrictive cardiomyopathy (RCM)
	Primary RCM
	Multiorgan genetic diseases with heart involvement and possible restrictive physiology
	• Systemic monogenic diseases
	• Pseudoxanthoma elasticum
	• Cystinosis
	• Hemochromatosis
	Phenocopies, acquired
	• POEMS
	• Diabetes mellitus–related cardiomyopathy
	• Chloroquine toxicity (the phenotype may overlap with dilated cardiomyopathy)
Endocardial/endomyocardial	Endocardial fibroelastosis
	Endomyocardial fibrosis
	Obliterative endocardial disease
	Carcinoid heart disease with fibrous valvular and endocardial fibrosis, focal (endocardial plaques) or diffuse (valves and endocardium)
	Iatrogenic diseases (serotonin, methysergide, ergotamine, mercurial agents, busulfan)
Epipericardial	Pericarditis
	Steatonecrotic, fibrous epicarditis of transplanted hearts
	Pericardial malignancies
	Post-pericardiectomy

Abbreviation: POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

valve regurgitation and fast early diastolic filling; a fourth heart sound (S_4) can be present. Hepatomegaly, ascites, and peripheral edema are common in decompensated patients. Echocardiographic criteria for diagnosing and grading diastolic dysfunction[11] are listed in Table 61–2.

In infants, RCM may present with failure to thrive, fatigue, and syncope.[7] Clinical examination usually does not show traits suggesting a specific etiology. ECG may demonstrate increased voltages and signs of atrial enlargement. Two-dimensional echocardiography is the key tool for the diagnosis.[11] In children, the most significant abnormalities are increased left atrial size, increased septal E′/E0, and lack of A wave and presence of mid-diastolic L0 wave; LV compliance may be decreased even with preserved early relaxation properties of the myocardium.[7,11] Interpretation of diastolic dysfunction[12] in children is complicated by the possible absence of key markers such as features of delayed relaxation and scarce contribution of mitral and pulmonary venous Doppler wave patterns.[11,12]

Cardiac magnetic resonance imaging (CMR) provides data for the characterization of different diseases manifesting with the RCM phenotype, for distinguishing RCM from constrictive pericarditis, and for evaluation of the extent of myocardial fibrosis.[13-15] Certain CMR features characterize RCM with different etiologies (eg, distinguishing metabolic diseases from inflammatory diseases).[16-18]

Endomyocardial biopsy (EMB) is uniquely useful for the diagnosis of desminopathies,[19] iron myocardial overload in both hemochromatosis[20] and Friedreich ataxia with cardiomyopathy,[21] cystinosis,[22,23] pseudoxanthoma elasticum,[24] lysosomal storage diseases,[25,26] and cardiac amyloidosis.[27] EMB may show endocardial fibrous thickening,[28] endocardial thrombosis, eosinophilic infiltration,[29] and granulomatous myocardial diseases.[30] EMB may further help distinguish RCM from constrictive pericarditis (specific pathology features can immediately provide a precise diagnosis; eg, restrictive cardiodesminopathy) and exclude diseases with contraindication to heart transplantation (eg, AL cardiac amyloidosis).

Deep phenotyping in probands involves the investigation of cardiac and extracardiac traits that typically occur in RCM with different causes to generate a clinical hypothesis on precise etiologies[31] by joining information on the clinical phenotype; inheritance pattern; ECG markers (conduction disease, Wolff-Parkinson-White pattern/short PR interval, QT prolongation, low or high voltages of QRS complex); echocardiographic markers such as LV noncompaction or hypertrabeculation; CMR information such as T2* for iron overload, as discussed later[17]; preferential distribution and pattern of late gadolinium enhancement on CMR[18] in amyloidosis[16]; and values of biomarkers such as increased creatinine phosphokinase, lactic acid, and N-terminal pro-brain natriuretic peptide (NT-proBNP).[31]

Differential Diagnosis Between Restrictive Cardiomyopathy and Constrictive Pericarditis (Table 61–3)

It is crucial to distinguish between RCM and constrictive pericarditis (CP) because RCM typically responds only to medical management and carries a poor prognosis, whereas CP may be curable by pericardiectomy and represents a potentially reversible cause of heart failure.[32] The clinical presentation of CP can mimic that of RCM, severe tricuspid regurgitation, and noncardiac conditions, like chronic obstructive airway diseases[33] (see Chap. 66).

Two-dimensional echocardiography, M-mode, and Doppler blood-flow evaluation including respiratory-related ventricular septal shift, preserved or increased medial mitral annular e′ velocity, and prominent hepatic vein expiratory diastolic flow reversal are independently associated with the diagnosis of CP.[34-36] The assessment of early diastolic annulus velocity and annulus reversus (reversal of the relationship between lateral and medial e′ velocities) by tissue Doppler imaging (TDI) improves the differentiation of constriction from restrictive myocardial disease and can be further facilitated by speckle tracking imaging as a complementary tool. Three-dimensional echocardiography precisely evaluates pericardial effusion or pericardial masses as it describes anatomic structures with higher accuracy than does two-dimensional echocardiography.[36]

Computed tomography (CT) and CMR detect global or loculated effusions and measure pericardial thickness, which, in normal conditions, is less than 4 mm and usually around 1 to 2 mm. Cardiac CT demonstrates pericardial thickening and effusions. Delayed gadolinium enhancement CMR detects pericardial and myopericardial inflammation. A multiparametric CMR approach distinguishes among active inflammation, chronic pericarditis with constriction, and effusion without inflammation.[37]

Cardiac catheterization is usually planned on an individual basis (eg, in patients with noncalcified or thickened pericardium especially before surgery); CP shows a more pronounced a wave and decline of rapid *y* descent suggesting LV filling abnormalities. However,

TABLE 61–2. Criteria in the American Society of Echocardiography Guidelines Used to Grade Diastolic Function (2013)

Parameter	Normal	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Mitral E/A ratio	> 0.8	≤ 0.8	0.8-2.0	> 2.0
Deceleration time (ms)	140-200	> 200	160-200	< 160
e′ septal (cm/s)	≥ 8	< 8	< 8	< 8
e′ lateral (cm/s)	≥ 10	< 10	< 10	< 10
Average E/e′ (cm/s)		< 8	9-12	≥ 13
Left Atrial Size (mL/m^2)	< 34	≥ 34	≥ 34	≥ 34
Pulmonary vein systolic inflow–diastolic inflow ratio (S/D ratio)		> 1	< 1	< 1
Ar-A (ms)		< 0	> 30	> 30
Change in E/A ratio with Valsalva		Decrease < 50%	Decrease ≥ 50%	Decrease ≥ 50%

catheterization may miss up to one-fourth of the cases of CP. Surgical exploration definitely gives an answer in unsolved cases. Finally, NT-proBNP levels are significantly higher in RCM than in CP.[38]

Family Studies

Genetic counseling, family history, and evaluation of clinical reports of family members are part of the clinical genetic workup for patients diagnosed with RCM.[39] Clinical family screening includes physical examination, ECG, and two-dimensional echocardiographic evaluations of family members. Further testing such as ambulatory Holter monitoring, treadmill testing, and CMR are performed on an individualized basis. Familial RCM demonstrates autosomal dominant inheritance in the majority of cases; clinically sporadic cases may mask autosomal recessive inheritance or *de novo* genetic diseases. Accordingly, all patients with RCM should receive genetic counseling and testing; relatives should be offered clinical screening.[31,39]

The clinical phenotype in affected members of the same family may vary: HCM or HCM with restrictive physiology or RCM that has progressed through dilation and dysfunction may occur in different family members.[40-44] This phenomenon is confirmed in several families and reflects phenotype heterogeneity: the genetic bases apparently coincide, but the end-phenotype may differ. The reasons are still unknown; hypotheses include complex genotypes, modifier genes, lifestyle factors (eg, athletes), or epigenetic factors (Fig. 61–1).

Family screening studies identify clinically and genetically affected members who may demonstrate borderline LV hypertrophy. RCM should be distinguished from HCM with a restrictive pattern[44,45]; on echocardiography, a maximum LV thickness less than 13 mm, the absence of LV outflow tract obstruction, and the absence of systolic anterior motion of the mitral valve leaflet favor the diagnosis of RCM. However, long-term follow-up may show progression from RCM to HCM-RCM (Fig. 61–2). Cascade genetic testing in families is indicated after identification of the disease-causing mutation in probands.[31,39,46-48]

RESTRICTIVE CARDIOMYOPATHY: GENETIC BASES

Genes associated with RCM encode sarcomeric structural and regulatory proteins, Z-disc proteins, and intermediate filaments. The *TNNI3* gene that encodes the thin filament troponin I is the most common disease gene responsible for RCM[49]; several reports confirm the major role of mutations in *TNNI3* in RCM.[40,42,50-52] Mutations in the troponin T2 gene (*TNNT2*) are less common in RCM and may also cause HCM and DCM.[53] Other sarcomeric genes involved in RCM include *ACTC1, MYL3, MYH7, TTN, TPM1, MYL3,* and *MYL2*.[44-47,54] Recent reports have described mutations in Z-disc protein-encoding genes, including *MYPN*, *FLNC*, and *BAG3*, in patients with RCM[55-58] (Table 61–4).

Restrictive Troponinopathies

The troponin complex is constituted of three subunits: cardiac troponin I, troponin C, and troponin T. It functions as sensor of the intracellular Ca^{2+} concentration and controls the interaction between the thick and thin filaments during cardiac contraction and relaxation. The inhibitory effect of cardiac troponin I is reversed by troponin C binding to Ca^{2+}, resulting in conformational changes of the troponin complex and leading to muscle contraction. Mutations in any one of the components of the troponin complex may modify $Ca2^{+}$ affinity and protein-protein interactions, thus potentially leading to the development of cardiomyopathy.

Founder mutations have been identified in the Netherlands in cardiac troponin I (*TNNI3*)[43] in families presenting with both RCM and HCM phenotypes in different affected members. Similar data were confirmed in other large families in which different affected members showed different phenotypes: RCM, HCM, and HCM with a restrictive pattern.[42] Intrafamily phenotype variability is not influenced by ethnicity as it is reported in families from different continents.[50] The majority of mutations in *TNNI3* are missense[49]; rare frameshift or splice mutations have also been reported to date.[51] The *TNNI3*-associated phenotype may manifest in children[52] (Fig. 61–3). RCM hearts in patients with troponin I mutations do not show significant loss of protein expression; however, myofibrillar disarray is present even in the absence of significant LV hypertrophy (Fig. 61–4). Although *TNNI3* should be considered the major candidate gene for RCM, *TNNT2* mutations are less commonly responsible.[53] Although the number of published cases and families is low and restrictive troponinopathies are rare, data from single cases and small series suggest that the clinical evolution is characterized by a poor prognosis.[42,43,50-52]

Nonsarcomeric Genetic Restrictive Cardiomyopathy

Recently, mutations in myopalladin (*MYPN*) and filamin-C (*FLNC*) have been reported, thus expanding the spectrum of genes potentially

TABLE 61–3. Major Criteria and Markers for Differential Diagnosis Between Restrictive Cardiomyopathy and Constrictive Pericarditis

Items	RCM	Endomyocardial Diseases	Constrictive Pericarditis	Amyloid Heart Disease
Ethnic data	None	Epidemics EMF, EFE	None	None; exceptions genetic ATTR
Clinical history	Nonspecific symptoms	Infections, fatigue	Possible: pericarditis, cardiac surgery, autoimmune diseases, malignancy	Nonspecific symptoms, fatigue, dyspnea
Family history	Frequently positive	Negative	Negative	Possibly positive
Physical examination				
Jugular veins	Large (a) or (v) waves with steep *y* descent		Short and steep y descent	Similar to RCM
Paradoxus pulse	Absent	Absent	Possible, 25%	Absent
Murmurs/tones (systole)	Common	Possible	No; friction sound	Common
Murmurs/tones (diastole)	Low-pitched S_3: 0.12-0.18 s after S_2, or an S_4	Possible	High-pitched pericardial knock: 0.06-0.12 s after S_2	Possible
Electrocardiogram				
P wave	High	High	Low	High
QRS voltage	High		Possible, 25%	Low, possible ~50%
Q wave	Common	Common	No	Possible
LVH	Possible		No	No
Atrioventricular block	Possible, according to the cause		No	Possible, 50%
Arrhythmias, atrial	Possible	Possible	No	Possible, common in advanced phases
Chest x-ray				
Cardiomegaly	Present (atrial dilation)	Possible	No	Possible
Pericardial calcification	No	No	25%	No
Pulmonary vascular congestion	Possible	Possible	No	Possible
Two-dimensional echocardiography				
Atrial dilation	Present	Present	Possible, mild	Present
Ventricular septal shift	Absent	Absent	Present	Absent
Respiratory variation/valves	Absent	Absent	Present	Absent
TDI é velocity	< 8 cm/s		> 8 cm/s	< 8 cm/s
Doppler, color M-mode	Slope > 100 cm/s		Slope < 100 cm/s	Slope > 100 cm/s
CT scan				
Pericardial calcification	Absent	Absent	Possible	Absent
Pericardial thickening	Absent	Absent	Present	Absent
CMR				
Pericardial thickening	Absent	Absent	Present	Absent
Respiratory variation/septal	Absent	Absent	Present	Absent
Ventricular morphology, tubular	Absent	Absent	Present	Absent
Tagging: perimyocardium	Systolic breakage		Absent	Systolic breakage
LGE: pericardium	Absent	Absent	Present	Absent
LGE: myocardium	Present	Present	Absent	Present
LGE: endocardium	Present	Present	Absent	Present
Catheterization				
Dip and plateau	Absent	Absent	Present	Absent
Diastolic pressure equalization	Absent	Absent	Present	Absent
Respiratory changes of RV and LV systolic pressures	Concordant	Concordant	Discordant	Concordant
RV/LV area, expiration vs inspiration	< 1.1	< 1.1	> 1.1	< 1.1
Biomarkers				
Inflammatory	Normal	Increased	Absent	Normal
BNP	Increased	Increased	< Normal values	Increased
Pathology: EMB				
Features	Can contribute to the diagnosis		Do not contribute to the diagnosis	Diagnostic

Abbreviations: BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; CT, computed tomography; EFE, endocardial fibroelastosis; EMB, endomyocardial biopsy; EMF, endomyocardial fibrosis; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; RCM, restricted cardiomyopathy; RV, right ventricular; TDI, tissue Doppler imaging.

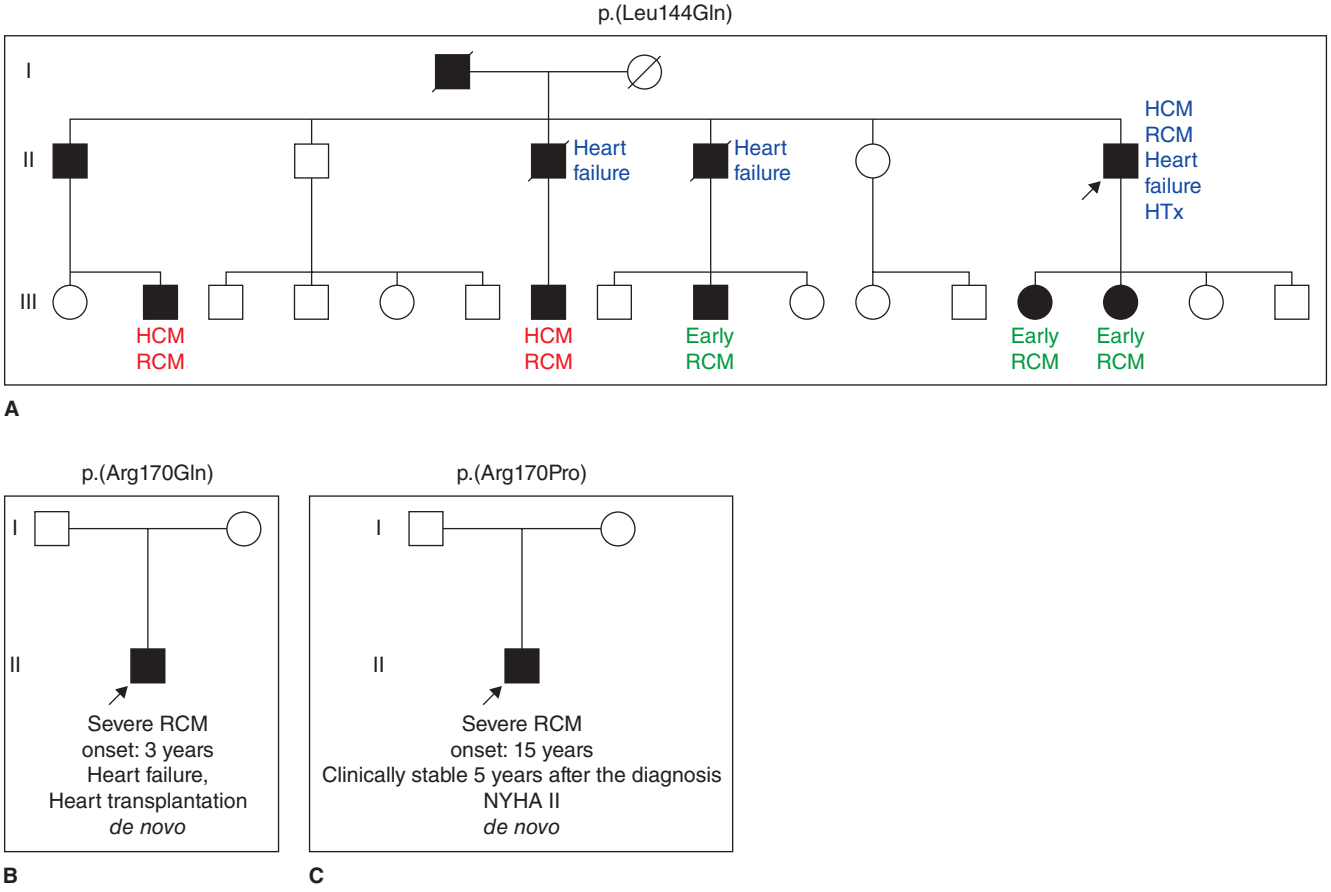


FIGURE 61–1. The figure shows the pedigrees of two families in which the probands were diagnosed with restrictive cardiomyopathy (RCM) caused by mutations in *TNNI3* gene. **A.** Autosomal dominant RCM in a family in which different affected family members showed hypertrophic cardiomyopathy (HCM; *red bordered symbols*), HCM with restrictive patterns (*blue bordered symbols*), and early RCM with no hypertrophy, mildly dilated left atrium, and New York Heart Association (NYHA) class I. **B.** *de novo* RCM in a boy who developed early RCM characterized by severe atrial dilation, absence of left ventricular (LV) hypertrophy, and fast progression to advanced disease. Both parents were clinically and genetically healthy. **C.** *de novo* RCM in a boy who developed RCM characterized by severe atrial dilation, absence of LV hypertrophy, and clinical stability. Both parents were clinically and genetically healthy.

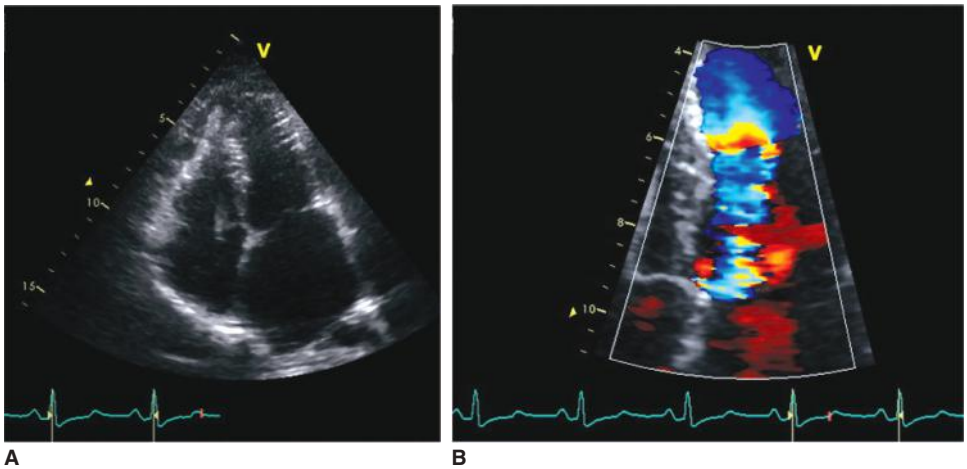


FIGURE 61–2. Two-dimensional and color Doppler echocardiography in a 14-year-old boy, who was a member of a family in which mutation in *TNNI3* was associated with restrictive cardiomyopathy (RCM), hypertrophic cardiomyopathy (HCM), and overlapping HCM-RCM. **A.** Apical four-chamber view with biatrial enlargement and a small hyperkinetic left ventricle; an implantable cardioverter-defibrillator (ICD) electrode is seen extending into the right ventricle. **B.** Midventricular obstruction on color Doppler imaging, with evident flow acceleration and turbulent flow, in the same young patient. The young patient was first diagnosed with HCM (mild left ventricular [LV] hypertrophy) at the age of 10 years; the diastolic dysfunction was apparent since the early detection of the disease. In his family, there were three sudden deaths (SDs), one aborted SD, and three heart transplantations. The boy received an ICD at the age of 13 years. Age 9: maximal LV thickness = 8 mm; age 10: maximal LV thickness = 11 mm; age 12: maximal LV thickness = 12 mm; atrial dilation; age 13: ICD; age 14: maximal LV thickness = 14 mm; atrial dilation; age 17: maximal LV thickness = 15 mm; atrial dilation, rest gradient = 22.3 mm Hg; after Valsalva: 40 mm Hg.

TABLE 61–4. Genes Associated With Restrictive Cardiomyopathy

MIM Gene	Nuclear Genes	Protein	Cardiomyopathy	Phenotypes/Diseases Allelic at the Same Locus	Inheritance
102540	*ACTC1*	Cardiac actin alpha	D/H/NC	Nemaline myopathy	AD
603883	*BAG3*	BCL2-associated athanogene	H/R	*BAG3*-related myofibrillar myopathy; myofibrillar myopathy	AD
123590	*CRYAB*	Alpha B crystalline	D/H	Cataract, multiple types; myofibrillar myopathy	AD
125660	*DES*	Desmin	D/H/A	Des-related myofibrillar myopathy; neurogenic scapuloperoneal syndrome, Kaeser type; AVB; > sCPK	AD, AD
102565	*FLNC*	Filamin C		Distal myopathy, myofibrillar myopathy.	AD
600958	*MYBPC3*	Myosin-binding protein C, cardiac	D/H/NC		AD
160760	*MYH7*	Beta-myosin heavy chain 7	D/H/NC	Laing distal myopathy; myosin storage myopathy; scapuloperoneal syndrome, myopathic type; possible > sCPK	AD, AR
160781	*MYL2*	Myosin, light chain 2, regulatory, cardiac, slow	H		AD
160790	*MYL3*	Myosin light chain 3	D/H		AD, AR
608517	*MYPN*	Myopalladin	D/H		AD
191040	*TNNC1*	Cardiac troponin C	D/H		AD
191044	*TNNI3*	Cardiac troponin I3	D/H/NC		AD, AR
191045	*TNNT2*	Cardiac troponin T2	D/H/NC		AD
191010	*TPM1*	Tropomyosin 1	D/H/NC		AD
188840	*TTN*	Titin	D/H/NC	Limb-Girdle muscular dystrophy; early-onset myopathy with fatal CMP; proximal myopathy with early respiratory muscle involvement; tardive tibial muscular dystrophy	AD

Note. The table lists genes, proteins, and phenotypes, inheritance, and nonrestrictive cardiomyopathies that have been reported to be allelic at the same loci of restrictive cardiomyopathy.

Abbreviations: A, arrhythmogenic cardiomyopathy; AD, autosomal dominant; AR, autosomal recessive; AVB, atrioventricular block; CMP, cardiomyopathy; D, dilated cardiomyopathy; H, hypertrophic cardiomyopathy; MIM, Mendelian Inheritance in Man; NC, left ventricular noncompaction; sCPK, serum creatine phosphokinase.

causing RCM.[55,57,58] In a large screening study of *MYPN*, different types of mutations were associated with different cardiac phenotypes: The Q529X-*MYPN* variant was found in familial RCM, whereas the Y20C-*MYPN* variant was associated with HCM or DCM. The mechanism proposed for the development of RCM is disturbed myofibrillogenesis, whereas the mechanism proposed for DCM or HCM of the Y20C-*MYPN* variant is perturbation of the *MYPN* nuclear shuttling and abnormal assembly of terminal Z-disc within the cardiac transitional junction and intercalated disc.[55] Mutations in *FLNC* segregated in two families with autosomal dominant RCM.[58] *FLNC* is an actin cross-linking protein expressed in heart and skeletal muscle. The cardiac myocytes showed cytoplasmic inclusions suggesting protein aggregates, which were *FLNC* specific for p.(Ser1624Leu) by immunohistochemistry. Cytoplasmic aggregates were also observed in transfected myoblast cell lines expressing this mutant *FLNC*, providing further evidence for its pathogenicity.[58] As a result of the small number of published cases and the recent association of mutations in these genes and RCM, prognostic data are still unavailable.

Restrictive Desminopathies

The desmin intermediate filament network is involved in striated muscle development and maintenance by coordinating cellular components necessary for intracellular mechanochemical signaling and trafficking processes.[59] Direct or indirect deregulation of this network causes myopathies and cardiomyopathies.[60-65]

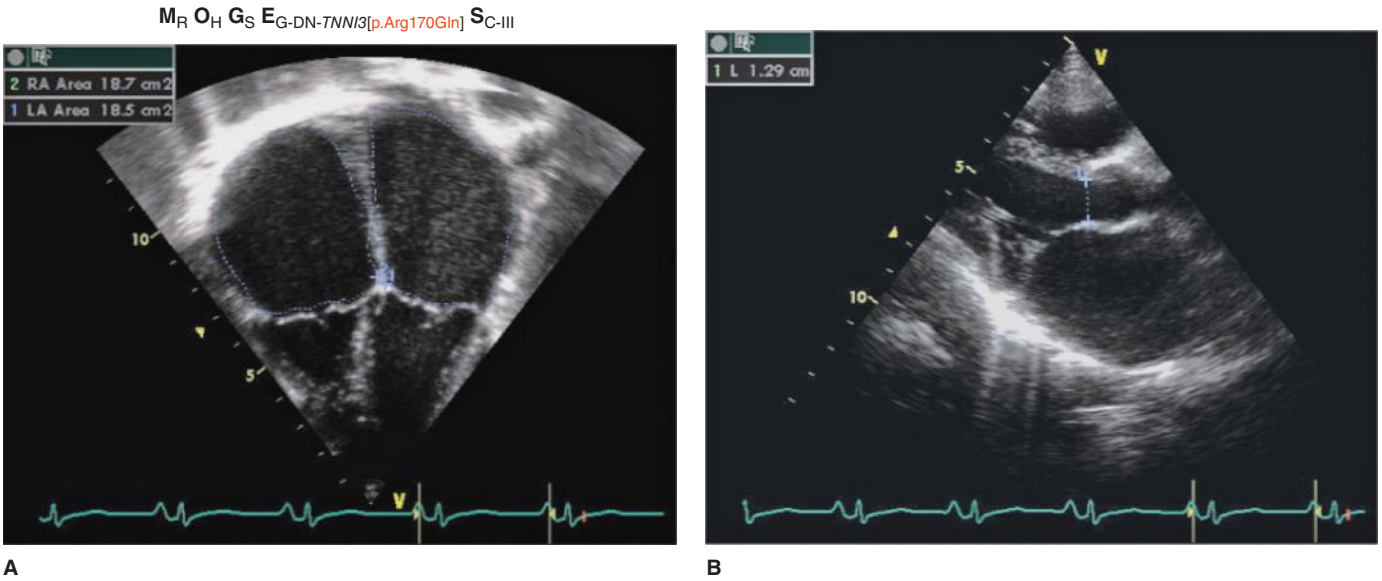


FIGURE 61–3. This figure shows the two-dimensional echocardiographic views in a boy with restrictive cardiomyopathy (RCM) associated with a *de novo* mutation in *TNNI3*. The phenotype and the genetic cause are summarized by the MOGES nosology $M_R O_H G_S E_{G\text{-}DN\text{-}TNNI3[p.Arg170Gln]} S_{C\text{-}III}$ in which M describes the morphofunctional phenotype (RCM, abbreviated as R); O describes the organs affected in the given patient (in this case, the heart was the only involved organ); G defines whether the cardiomyopathy is genetic or not and includes information on the pattern of inheritance or whether it appeared as sporadic in the family representing a possible *de novo* disease, which is confirmed after genetic testing; E is the precision diagnostic descriptor and specifies the cause, the disease gene(s), and the mutation(s) (in this patient, the mutation in *TNNI3* was proven *de novo*); and S is optional and includes New York Heart Association functional class (I-IV) and American Heart Association stage (A-D). The practical use is supported by a free app at http://moges.biomeris.com/moges.html.

Restrictive desminopathies are autosomal dominant diseases in the majority of cases and recessive and *de novo* in a minority of cases. They are clinically characterized by restrictive physiology, mild or absent LV hypertrophy, absence of LV outflow tract obstruction, atrial dilation, and conduction system disease that may precede the clinical manifestation of RCM[61,62] (Fig. 61–5). Subclinical or overt myopathy may occur in these patients.[61] Conduction disease is a typical marker of the disease: It is confirmed in animal models of desminopathy.[63] The course of the disease is characterized by progressive worsening of the cardiac dysfunction to end-stage heart failure. Heart transplantation is the only therapeutic option.[64] The typical RCM desminopathy is easily diagnosed by EMB demonstrating desmin immunoreactive granulofilamentous material accumulated within myocytes[61,62,65] (Fig. 61–6). Similar findings are observed in skeletal muscle biopsy independent of the presence of clinically overt myopathy. Fine-needle biopsy of the skeletal muscle provides diagnostic information when EMB cannot be performed.[61]

MULTIORGAN GENETIC DISEASES WITH HEART INVOLVEMENT AND POSSIBLE RESTRICTIVE PHYSIOLOGY

Lysosome storage diseases, cardiac amyloidosis, myocardial iron overload disorders, and collagen diseases may clinically manifest restrictive physiology. The cardiac phenotype is characterized by LV thickening with possible associated diastolic dysfunction and is therefore similar to HCM. These diseases should be separated from pure RCM to prevent confusion in the nosology of RCM. They are distinct genetic diseases, systemic in the majority of the cases, with disease-specific diagnostic workup and targeted treatments. Table 61–5 lists diseases with increased LV thickening and in which restrictive physiology is systematic (eg, amyloidosis) or recurrently present in early phases of the disease (iron storage diseases) or occasionally reported in single cases (lysosomal storage diseases such as glycogenoses, Anderson-Fabry disease, Danon disease, and Hurler disease).[66-82]

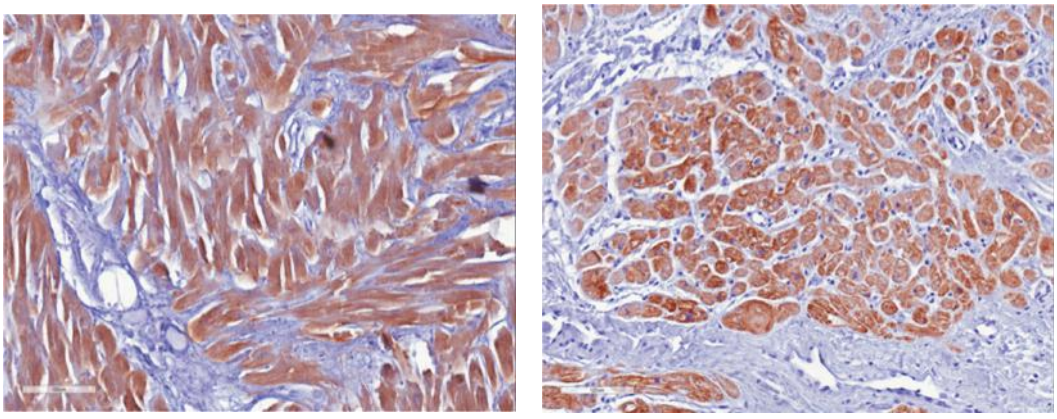


FIGURE 61–4. Anti–troponin I immunostain in myocardial samples from the heart of a patient with restrictive cardiomyopathy associated with the *TNNI3* p.(Leu144Gln) mutation. **A.** Disarray that typically recurs in cardiomyopathies caused by defects encoding sarcomere proteins. **B.** Prominent interstitial fibrosis.

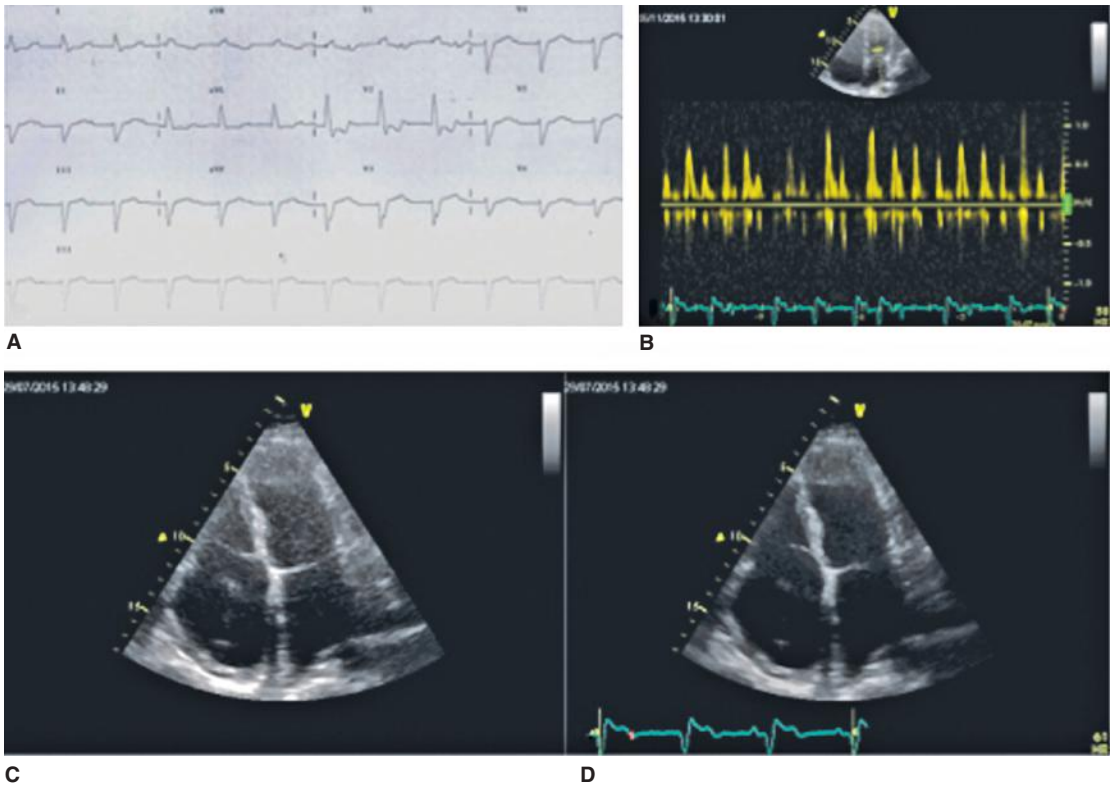


FIGURE 61–5. Restrictive cardiodesminopathy in a 43-year-old male patient. **A.** Electrocardiogram before pacemaker implantation with advanced atrioventricular block (PR interval 300 milliseconds). **B.** Doppler echocardiography with restrictive pattern (E/A wave ratio > 3 and shortened deceleration time) at the transmitral flow during an episode of atrial tachycardia. **C** and **D.** Left apical four-chamber view that demonstrates the biatrial enlargement. This patient also had moderate left ventricular systolic dysfunction.

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive systemic disease of the connective tissue that affects the extracellular matrix of multiple organs[83] with a prevalence that varies from 1 in 70,000 to 1 in 160,000. PXE involves the cutaneous, ocular, and cardiovascular systems.[83,84] The cutaneous lesions typically occur in flexural areas (Figure 61–7B), and the fundi may show angioid streaks radiating out from the optic discs, subretinal neovascularization, and/or hemorrhage.

The cardiovascular manifestations are characterized by the development of arterial calcifications,[85] premature coronary artery disease, peripheral vascular disease, and RCM.[66,86-89] Sudden death has been occasionally reported.[88,89]

The histopathologic marker of the disease is the mineralization and fragmentation of elastic fibers (Fig. 61–7A). PXE is caused by homozygous or compound heterozygous mutations in the *ABCC6* (ATP-binding cassette subfamily C member 6) gene that encodes a transmembrane adenosine triphosphate (ATP)-driven organic anion transporter. Carriers of heterozygous mutations may demonstrate mild

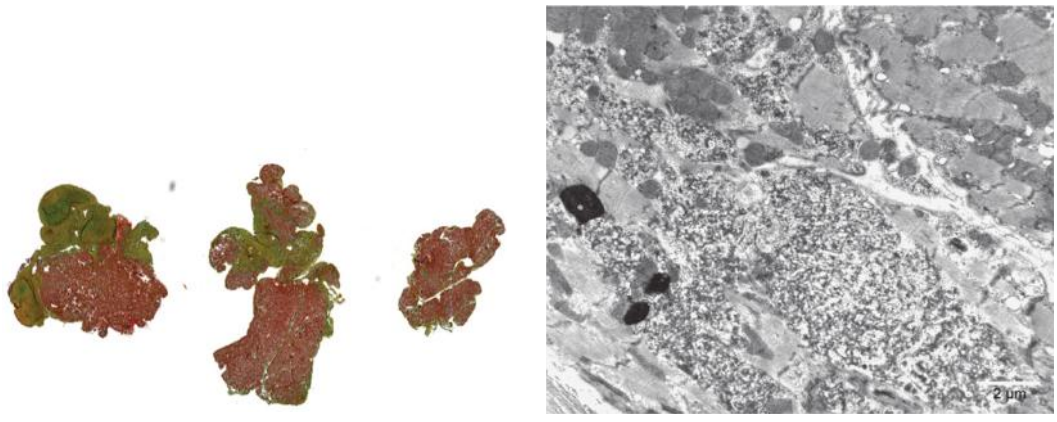


FIGURE 61–6. Endomyocardial biopsy (EMB), restrictive cardiodesminopathy. **A.** Low-magnification view of the EMB samples, with prominent endocardial and interstitial fibrosis. **B.** Electron micrograph demonstrates the typical intramyocyte accumulation of granulofilamentous material that corresponds to the abnormal desmin.

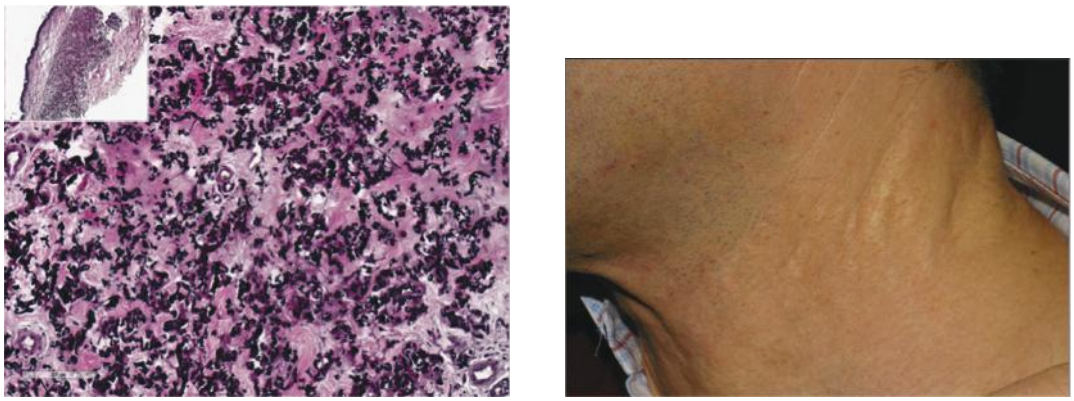
TABLE 61–5. Genes Causing Multiorgan/Systemic Diseases With Cardiac Involvement and Possible Restrictive Physiology

Diseases Potentially Associated With Secondary Cardiac Restriction					
MIM Gene	Nuclear Genes	Protein	Reference	Phenotypes/Diseases Allelic at the Same Locus	Inheritance
LV wall thickening (HCM phenotype) and diastolic dysfunction (restrictive pattern): frequently reported as restrictive cardiomyopathies[a]					
603234	*ABCC6*	Atp-binding cassette, sub-family C, member 6	66	Pseudoxanthoma elasticum	AR
107680	*APOA1*	Apolipoprotein of high-density lipoprotein	68	Amyloidosis, hereditary	AD
107670	*APOA2*	Apolipoprotein A-II	69	Amyloidosis, hereditary	AD
134820	*FGA*	Fibrinogen, A alpha polypeptide	70	Amyloidosis, hereditary, familial visceral	AD
137350	*GSN*	Gelsolin	75	Amyloidosis, Finnish type	AD
606464	*HAMP*	Hepcidin antimicrobial peptide	76	Hemochromatosis, type 2B	AR/AD
613609	*HFE*	HFE gene	77	Hemochromatosis	AD
608374	*HFE2*	Hemojuvelin	77	Hemochromatosis	AR/AD
604720	*TFR2*	Transferrin receptor 2	77	Hemochromatosis, type 3	AR/AD
604653	*SLC40A1*	Solute carrier family 40 (iron-regulated transporter), member 1	77	Hemochromatosis, type 4	AR/AD
LV wall thickening (HCM phenotype): rarely described as "restrictive" cardiomyopathies[b]					
610860	*AGL*	Amylo-1,6-glucosidase, 4-alpha-glucanotransferase	67	Glycogen storage disease IIIa, glycogen storage disease IIIb	AR
606800	*GAA*	Glucosidase, alpha, acid	71	Glycogen storage disease II	AR
606463	*GBA*	Glucosidase, beta, acid	72	Gaucher disease, perinatal lethal, types I, II, III, IIIC	AR
607839	*GBE*	Glycogen branching enzyme	73	Glycogen storage disease IV	AR
610681	*PFKM*	Phosphofructokinase, muscle type	80	Glycogen storage disease VII	AR
172471	*PHKG2*	Phosphorylase kinase, testis/liver, gamma-2	82	Glycogen storage disease IXc	AR
613741	*PYGL*	Glycogen phosphorylase, liver	82	Glycogen storage disease VI	AR
602671	*SLC37A4*	Solute carrier family 37 (glucose-6-phosphate transporter), member 4	83	Glycogen storage disease Ib, Ic	AR
602743	*PRKAG2*	Protein kinase, Amp-activated, noncatalytic, gamma-2	82	Cardiomyopathy, hypertrophic 6, glycogen storage disease of heart, lethal congenital, Wolff-Parkinson-White syndrome	AD
300644	*GLA*	Galactosidase, alpha	74	Fabry disease	XL
309060	*LAMP2*	Lysosome-associated membrane protein 2	79	Danon disease	XLD
252800	*IDUA*	Alpha-L-iduronidase	78	Hurler disease	AR

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MIM, Mendelian Inheritance in Man; XLD, X-linked dominant.

[a]This list includes the rare pseudoxanthoma elasticum, heritable amyloidosis, and heritable hemochromatosis; all of these diseases are frequently described as restrictive cardiomyopathies.

[b]These diseases are usually reported as hypertrophic cardiomyopathies and only rare, unique cases are described as restrictive cardiomyopathies.



A B

FIGURE 61–7. Pseudoxanthoma elasticum. **A.** Skin biopsy with the typical calcifications that characterize the disease; the inset shows the skin biopsy sample. **B.** Neck of patient with the typical cutaneous lesions in flexural areas; the patient is carrier of the homozygous p.(Arg1141X) mutation in the *ABCC6* gene.

and partial traits of the disorder.[90,91] Drugs potentially able to modify the protein conformation, such as sodium 4-phenylbutyrate, a drug approved by the US Food and Drug Administration for clinical use in urea cycle disorders, seem to be able to restore the plasma membrane localization of mutant *ABCC6*, thus opening the way to target treatment.[92,93] Chronic deficiency of *ABCC6* is also involved in generalized arterial calcification of infancy and PXE phenocopies in thalassemias; it is a susceptibility factor and/or a modifier for myocardial infarction, stroke, cardiac fibrosis, peripheral artery disease, age-related macular degeneration, chronic kidney disease, nephrocalcinosis, and dyslipidemia. A randomized controlled trial tested the oral phosphate binder sevelamer hydrochloride and demonstrated a reduction in both calcification levels and clinical scores.[94]

Cystinosis

Nephropathic cystinosis is a rare autosomal recessive disease resulting from intracellular accumulation of cystine, leading to multiple organ failure. The incidence is estimated around 0.5 to 1.0 per 100,000 live births. The disease is caused by mutations in the lysosomal cystine/proton symporter termed cystinosin (encoded by *CTNS* gene) and represents the most common cause of inherited renal Fanconi syndrome in the first year of life, which results in end-stage renal disease by the age of 10 years.[95] The pathology of affected tissues is characterized by the tissue deposition of cystine. Early administration of cysteamine reduces intracellular levels of cysteine and can delay progression of renal damage.[96] In cases that are diagnosed late, treatment options may be limited to renal transplantation.[97] In the European population, mutations of *CTNS* include a 65-kb deletion-involving marker D17S829 and 11 other small mutations.[98] Other *CTNS* mutations have been confirmed in African American patients with cystinosis.[99] Heart involvement is rare; the pathologic hallmark is the presence of cystine rectangular colorless crystals.[100]

Iron Overload Heart Diseases

Iron overload cardiomyopathy can result from a primary genetic disease caused by defects in genes coding proteins active in iron metabolism, typically hereditary hemochromatosis, or from secondary causes of iron overload such as acquired hematologic diseases.

Hereditary Hemochromatosis

Prevalence Hereditary hemochromatosis (HH) is a heritable disorder of iron metabolism that is characterized by tissue iron overload.[76,101] Heart failure causes approximately one-third of deaths of those with HH. Historically, the average survival was less than 1 year in untreated patients with severe cardiac impairment.[102,103] In classic HH, about 10% to 15% of affected adults present with cardiac symptoms at diagnosis. Heart failure may develop suddenly in patients with juvenile forms of hemochromatosis. The HH phenotype is clinically heterogeneous and is influenced by gender and complex interactions between genotype and environmental factors (eg, alcohol, other causes of hepatitis). The cardiac phenotype is characterized by early LV diastolic dysfunction with evolution through LV systolic dysfunction and dilation, which is influenced by endocrine dysfunction, neurohormonal activation, and inflammatory cytokines.[103]

Genetic Heterogeneity HH is characterized by genetic heterogeneity (Table 61–6).[104-110] The most common HH is HFE1 (or classical HH), which is associated with recurrent mutations [p.(Cys282Tyr) homozygotes or p.(Cys282Tyr)/p.(His63Asp) compound heterozygotes] in the *HFE* gene (Fig. 61–8). The most frequent causes of death are complications from cirrhosis, cardiomyopathy, and diabetes, but patients who undergo successful iron depletion before development of cirrhosis or diabetes have normal survival. The diagnosis of HH is established by genetic testing in patients with elevated serum ferritin (> 300 ng/mL) and transferrin saturation values (> 55%). Timely diagnosis and treatment prevent iron overload; however, early treatment is limited by the clinically silent or minimally symptomatic manifestations of the disease. Although population screening for HH is controversial, the low cost of genetic tests and the selection of high-risk populations are cost effective.[111] The current global prevalence of the different genetic causes of HH can be easily estimated using multigene panels by next-generation sequencing; this analysis also provides data on genetic epidemiology of the disease.[112]

Cardiac Involvement

Prevalence Symptomatic hemochromatosis is estimated to occur in 1 in 500 individuals.[113] Common presenting symptoms such as fatigue, malaise, and arthralgia are nonspecific.[103]

Physical Examination In the past, the clinical diagnosis was typically late and supported by the classic triad of cirrhosis, bronze skin, and diabetes. Today, the diagnosis is established in early phases of the disease when the clinical manifestations are attenuated but cardiac imaging may detect features suggestive of myocardial iron overload.

The Electrocardiogram The ECG is nonspecific and does not significantly contribute to the diagnosis of HH cardiomyopathy; low QRS complex voltage and nonspecific repolarization abnormalities are uncommon

TABLE 61–6. Genetic Diseases Causing Iron Overload Potentially Affecting the Heart

MIM* Gene	Nuclear Genes	Protein	*HFE*	Inheritance	Heart Involvement	Age of Onset and Disease Traits
613609	*HFE*	*HFE*-related HH	Hemochromatosis, type1	AR	X	Adult onset; arthropathy, skin pigmentation, liver damage, diabetes, endocrine dysfunction, hypogonadism
608374	*HJV*	Hemojuvelin	Hemochromatosis, type 2A	AR	XX	Earlier onset, < 30 years old, hypogonadotropic hypogonadism, liver damage and endocrine dysfunction
606464	*HAMP*	Hepcidin antimicrobial peptide	Hemochromatosis, type 2B	AR	X	
604720	*TFR2*	Transferrin receptor 2	Hemochromatosis, type 3	AR	X	Adult onset; arthropathy, skin pigmentation, liver damage, diabetes, endocrine dysfunction, hypogonadism
604653	*SLC40A1 (SLC11A3)*	Solute carrier family 40 (Iron-Regulated Transporter) Member 1	Hemochromatosis, type 4	AD	X	Adult onset; lower tolerance to phlebotomies, possible anemia
134770	*FTH1*	Ferritin Heavy Chain 1	Hemochromatosis, type 5	AR	X	Adult onset; heart involvement by magnetic resonance

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; HH, hereditary hemochromatosis; MIM, Mendelian Inheritance in Man.

in early phases; conduction disease may be present. Atrial fibrillation is the most common arrhythmia, whereas ventricular arrhythmias may occur when the LV dysfunction has manifested.[103]

Echocardiography With Tissue Doppler Imaging, Strain Imaging, and Speckle Tracking Two-dimensional echocardiographic evaluation shows early diastolic dysfunction[113] and later evolution through LV dilation and dysfunction. Restrictive physiology may persist in late disease[114]; in patients with asymptomatic cardiac involvement, it maintains stable after conventional phlebotomy treatment, regardless of their treatment history.[115] Echocardiography contributes to early diagnosis of cardiac involvement and provides information on the extent of iron storage and severity of systolic and diastolic dysfunction. In a multivariable analysis, spectral tissue Doppler lower early (E′) diastolic velocity was independently associated with hemochromatosis.[116] Mid-septal systolic and early diastolic velocities on TDI correlate with myocardial iron content predicted by magnetic resonance imaging.[117] Longer

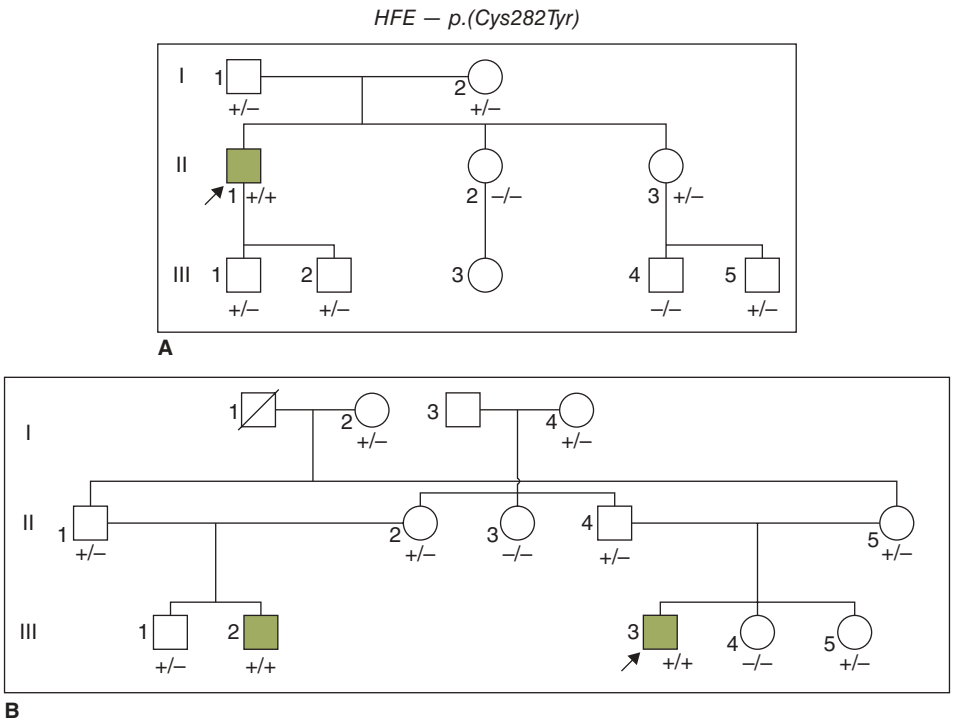


FIGURE 61–8. Family pedigrees of two patients with autosomal recessive hereditary hemochromatosis caused by homozygous mutation in the *HFE* gene. **A.** In this family the disease was apparently sporadic. After the diagnosis in the proband, family screening demonstrated that both parents of the proband are healthy carriers of heterozygous mutations p.(Cys282Tyr) in the *HFE* gene; both sons of the proband are obligate carriers. **B.** A family in which the genetic diagnosis in the proband led to family screening and identification of a second affected family member.

isovolumetric relaxation time and lower E′ velocity indicate mildly impaired diastolic function; with aging, filling pressures increase as demonstrated by elevated transmitral early (E) filling velocity, pulmonary venous systolic peak velocity, and higher E/E′ ratio.[118] Real-time three-dimensional echocardiography may contribute to earlier detection of left atrial dysfunction (eg, left atrial active emptying fraction) in asymptomatic patients with cardiac iron overload[119]; exercise stress TDI echocardiography may demonstrates subtle systolic abnormalities that would not have been detected by conventional echocardiography.[120]

Cardiac Magnetic Resonance Imaging The T2* method is highly sensitive and specific and is especially useful for detecting, grading, and monitoring iron deposition.[121-123] Patients demonstrating a T2* higher than 20 milliseconds are at low risk for development of heart failure (HF); T2* between 10 and 20 milliseconds indicates the presence of cardiac iron deposition and an intermediate risk of HF; and a T2* less than 10 milliseconds indicates high risk of HF and need for immediate chelation therapy.[124] The T2* index informs on the risk of HF and arrhythmias.[125] CMR further provides a comprehensive evaluation of myocardial viability, LV ejection fraction, and cardiac volume and mass.[126] The decline in LV ejection fraction correlates with the myocardial iron content measured with T2*.[127] EMB shows typical intramyocyte accumulation of iron (Fig. 61–9). However, when the diagnosis is established with clinical, imaging, and genetic data, EMB is no longer indicated.

Treatment and Monitoring Phlebotomy and iron chelators (parenteral deferoxamine or the oral iron chelators deferiprone and deferasirox) remain the standard therapy. Adequately treated patients (ie, target ferritin of 50-100 μg/L achieved) demonstrate better prognosis.[128] Chelation improves ventricular function, prevents ventricular arrhythmias, and reduces mortality in patients with secondary iron overload. In patients with thalassemia major and mild to moderate cardiac iron loading, combination treatment with additional deferiprone reduces myocardial iron and improves ejection fraction and endothelial function.[114] In patients with HF, management is based on the same basic principles as patients with DCM and systolic HF (see Chap. 70). Combined heart and liver transplantation should only be considered in severe cases refractory to standard therapies.[114,129] Iron overload–induced cardiomyopathy is reversible when therapy is started before the onset of overt HF.

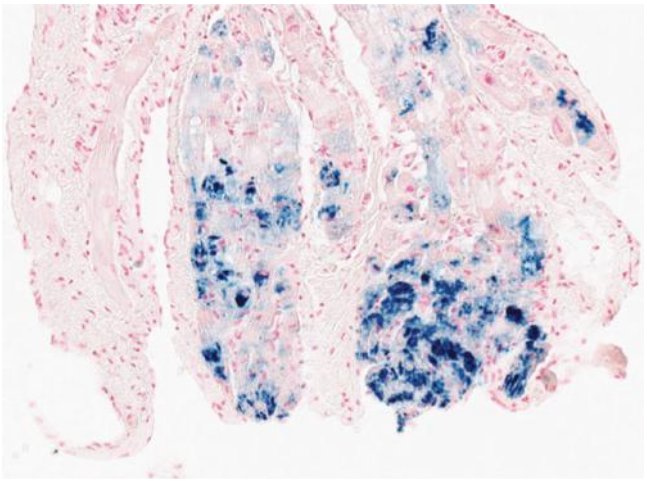


FIGURE 61–9. Endomyocardial biopsy obtained from a patient presenting with restrictive cardiomyopathy phenotype; the endomyocardial biopsy shows the intramyocyte accumulation of iron (*blue*; Perl's stain). In this patient, genetic testing identified the homozygous p.(Cys282Tyr) mutation in the *HFE* gene.

Family Studies HH is a genetically heterogeneous disease; common forms of HH are inherited as autosomal recessive diseases; in these families, heterozygous mutation carriers are phenotypically healthy and the illness may appear as sporadic (see Fig. 61–8). The diagnosis of HH in a proband should activate family screening including both clinical evaluation and genetic testing. However, at least one of the genetic HHs is autosomal dominant; in these families, genetic testing provides preclinical evidence of the disease. Therefore, family screening may contribute to early diagnosis and should be routinely recommended.

Non–Hereditary Hemochromatosis Iron Overload Iron overload potentially involving the heart occurs in hemoglobinopathies (β-thalassemia major, sickle cell disease),[130] sideroblastic anemia,[131,132] myelodysplastic syndromes,[133] aplastic anemia,[134] patients with chronic kidney disease and treated with intravenous iron supplementation,[135] and patients with iron toxicosis (iron poisoning).[136]

Iron overload may occur in β-thalassemia major, which is an inherited autosomal recessive hemoglobin disorder causing chronic hemolytic anemia that requires lifelong transfusion therapy.[137] β-Thalassemia is a global health issue; the original geographic prevalence in the Mediterranean area, Southeast Asia, Middle East, and North India has been modified by population migration to northern Europe and North America.[137] Cardiac involvement is caused by myocardial iron overload; it constitutes the primary cause of mortality and a major cause of morbidity for HF. The cardiac phenotypes include restrictive β-thalassemia cardiomyopathy and DCM[103] that is usually preceded by diastolic dysfunction (about 80% of cases)[138]; in 20% of cases, right ventricular dilation and dysfunction are associated with tricuspid regurgitation, increased pulmonary artery pressure, and restrictive LV filling.[130,139,140] Practice guidelines delineate recommendations for clinical monitoring and treatment (chelation therapy and cardiovascular medications).[141] The precise quantification of myocardial and hepatic iron load by CMR T2* imaging provides useful information on clinical response to iron chelation therapy.[124]

Sideroblastic anemias (SAs) can be either acquired or inherited and are characterized by impaired utilization of iron in the erythroblast, ineffective erythropoiesis, and variable systemic iron overload.[131,142] Heritable SAs are genetically heterogeneous diseases; heart involvement is occasionally reported. They include the X-linked recessive SA with ataxia caused by mutations in the *ABCB7* gene; the X-linked SA caused by mutations in the *ALAS2* gene; the autosomal recessive SA with myopathy and lactic acidosis caused by mutations in the *PUS1* and *YARS2* genes[132]; the autosomal recessive SA with B-cell immunodeficiency, periodic fevers, and developmental delay caused by mutations in the *TRNT1* gene; and the pyridoxine-refractory autosomal recessive SA caused by mutations in the *SLC25A38* and *GLRX5* genes. Mutations in *TRNT1* cause the autosomal recessive congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay. In patients diagnosed with SA with myopathy and lactic acidosis, HF with preserved ejection fraction and pericardial effusion has been reported.[132]

Mitochondrial Iron Overload: Friedreich Ataxia Friedreich ataxia is caused by homozygous GAA trinucleotide repeat expansion that induces a transcriptional defect of the Frataxin gene (*FXN*).[143] Frataxin is a small mitochondrial protein whose defects are associated with mitochondrial iron overload and are responsible for all phenotypic manifestations of Friedreich ataxia. The disease affects central and peripheral nervous, cardiovascular, skeletal, and endocrine (particularly pancreatic function) systems. The cardiac involvement in Friedreich ataxia is characterized by the HCM phenotype (see Chap. 59), evolving to LV dysfunction. A restrictive filling pattern is observed in end-stage

Friedreich cardiomyopathy.[144] Although early studies suggested that global diastolic function was preserved when examined by TDI,[145] recent studies demonstrate diastolic abnormalities in more than 25% of patients.[146]

PHENOCOPIES OF RESTRICTIVE CARDIOMYOPATHY

Acquired multiorgan systemic diseases or cardiotoxicity may cause RCM phenotype. This group of diseases includes POEMS, chloroquine toxicity (which may clinically overlap with HCM-DCM), and sarcoidosis. The latter is discussed in Chap. 63.

POEMS SYNDROME

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) is a paraneoplastic syndrome caused by a plasma cell neoplasm. Diagnoses can be delayed because the clinical manifestations of the syndrome may overlap with other more common neurologic disorders (eg, chronic inflammatory demyelinating polyradiculoneuropathy).[147] Cardiovascular involvement is rare and clinically heterogeneous; it may include heart block,[148] pulmonary hypertension,[149] HF,[150] myocardial infarction,[151] cardiomegaly and cardiomyopathy,[152] and aortic valve fibroma.[153] Although repeatedly mentioned in review articles, RCM is a rare complication.[152]

DIABETES MELLITUS–RELATED CARDIOMYOPATHY

Diabetes mellitus–related cardiomyopathy (DM-CMP) is a clinical condition diagnosed when ventricular dysfunction occurs in the absence of coronary atherosclerosis and hypertension.[154] DM-CMP was originally described as a DCM with eccentric LV remodeling and systolic LV dysfunction. Recent clinical studies outline the prominent restrictive phenotype as one of the major characteristics of the disease. The cardiomyopathy is characterized by both morphologic abnormalities (concentric LV hypertrophy) and functional abnormalities (diastolic LV dysfunction).[154-156] In DM-CMP, the restrictive phenotypes can progress from HF with preserved LV ejection fraction to HF with reduced LV ejection fraction[157,158] (see Chap. 70). According to a recent hypothesis, "the myocardial remodeling in HF with preserved LV ejection fraction is caused by coronary microvascular endothelial inflammation with cardiomyocytes only exposed to altered paracrine endothelial signaling, while HF with reduced LV ejection fraction is caused by cardiomyocyte cell death due to ischemia, viral infection, or toxic agents."[159] Therapeutic strategies differ between the two phenotypes with angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists clearly indicated for diabetics with HF with reduced ejection fraction, and diuretics and lifestyle modifications with a proven survival benefit in those with HF with preserved ejection fraction.[158]

Microvascular deposition of advanced glycation end-products in small myocardial vessels of patients with diabetic cardiomyopathy seems to be the pathologic hallmark of the disease.[160] Several factors have been proposed to play a role in the pathophysiology of the cardiomyopathy: the exposure of cardiac myocytes to hyperglycemia[161]; lipotoxicity and myocardial steatosis[162]; the microvascular deposition of end-products of glycation[163]; microvascular dysfunction and rarefaction[164]; autoimmune myocyte damage with release of troponins[165]; and insulin resistance/hyperinsulinemia that could explain myocyte hypertrophy.[160] The combination of the effects of these factors could induce either "restrictive" or "hypertrophic" cardiac phenotypes in patients with diabetes. The diagnostic criteria of the two different phenotypes are reported in the ESC guidelines on diabetes, prediabetes and cardiovascular diseases[166] (see Chap. 28).

OTHER CONDITIONS VARIABLY REPORTED AS RESTRICTIVE HEART DISEASES

Cardiotoxic manifestations induced by a variety of drugs or substances (eg, serotonin, methysergide, ergotamine, mercurial agents, busulfan, or heavy metals) have been variably reported. Such substances may cause cardiac toxicity with diastolic dysfunction. However, the maintenance of confounding classifications and nosology delay progression of research, especially when clinical phenotypes are nonspecific and causes are not proven. Diseases such as cardiac sarcoidosis or hypereosinophilic diseases are more appropriately grouped in the chapter on inflammatory heart diseases (see Chap. 63). Chloroquine cardiotoxicity, which may manifest with LV hypertrophy, dilation, and restriction, is reviewed in Chap. 58.

RESTRICTIVE ENDOMYOCARDIAL DISEASES

INTRODUCTION

Diseases affecting both endocardium and endomyocardial layers manifest with restrictive physiology and are functional phenocopies of genetic RCM. The three disorders that can be included in this subgroup of RCM are endocardial fibroelastosis, endomyocardial fibrosis, and "obliterative cardiomyopathy." From early to current classifications of cardiomyopathies, endocardial diseases have been placed in the group of unclassified cardiomyopathies.[2,3] Confusing terms (endocardial fibroelastosis, endomyocardial fibroelastosis, endomyocardial fibrosis, or obliterative cardiomyopathy) and phenotypes reflected the difficult nosology assignment of "pathology-based" diagnoses. The term *endocardial fibroelastosis* describes a pathologic feature rather than a precise disease. It represents an endocardial reactive process that may occur in a variety of cardiac diseases (cardiomyopathies and congenital heart diseases, decompensated hearts of different etiology) and is more an endocardial effect of hemodynamic stressors rather than a primary endocardial disease or endocardium-specific insult[167] (Fig. 61–10). In addition, the majority of cases of endocardial fibroelastosis have been described in pregenetic era. Vice versa, *endomyocardial fibrosis* (EMF), prevalently involving the right ventricle, is now recognized as a clinically and pathologically well-defined entity that affects primarily children and adolescents, often in resource-limited regions of sub-Saharan Africa, Latin America, and Asia[168]; it is the most common form of restrictive heart disease worldwide. Although the etiology remains elusive, the clinical profile and disease course are well established. *Obliterative cardiomyopathy*[169] is a term that confusingly includes cardiomyopathies with either fibrous obliteration of the ventricular apex or the fibrous organization of apical thrombi, typically occurring in hypereosinophilic syndromes or in other heart diseases where apical thrombi can eventually undergo organization and fibrosis. Hypereosinophilic syndromes are precisely classified and discussed in the chapter on inflammatory heart diseases (see Chap. 63).

ENDOCARDIAL FIBROELASTOSIS

The term *endocardial fibroelastosis* describes a thickening of the endocardium by layers of collagen and elastic fibers. These microscopic features are commonly observed in congenital heart diseases and cardiomyopathies and following cardiac surgery. The macroscopic appearance shows variable extension of endocardial thickening and

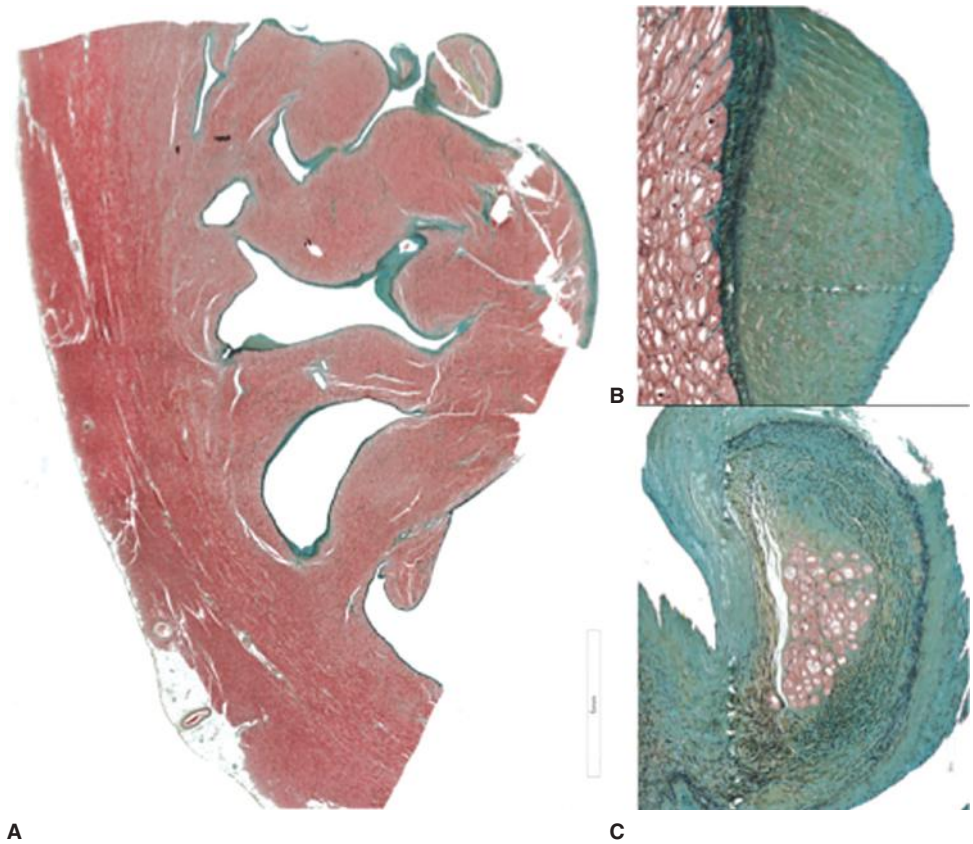


FIGURE 61–10. A-C. Pathologic characteristics of fibroelastotic endocardial thickening vs. fibrous endocardial thickening. The high-magnification views in **B** and **C** show the presence of elastic fibers; the low magnification in **A** gives the proportion of the features. Both findings are common and demonstrate variable extension in decompensated, end-stage hearts.

is characterized by "white" translucent endocardial ventricular areas versus the normal endocardial aspect.[167] By itself, it does not have a corresponding functional phenotype. Several attempts to identify and confirm a precise etiology have included a viral hypothesis, but mumps and Coxsackie B virus–related mechanisms have proven negative.[167] The possible involvement of lymphatic vessels of the heart has been proposed for both endocardial fibroelastosis and endocardial fibrosis and remains unconfirmed.[170] The term *endomyocardial fibroelastosis* is also used to describe the same entity.[171] Endocardial fibroelastosis (fibroelastotic thickening of the endocardium) has been repeatedly described in children with hypoplastic heart syndrome, but it does not, by itself, demonstrate a causative role; in hypoplastic heart syndrome, the endocardial fibroelastosis is now described as "endocardial fibroelastosis reaction."[172] Its detection in fetal life is a relevant marker for a condition that can now be considered for prenatal interventions aimed at treatment of diastolic dysfunction[173] (see Section 9).

In a critical review article published in 2009, Paul R. Lurie states: "The contemporary author of a report on the endocardial fibroelastosis is confronted by a perplexing literature; most of which was composed when much more was seen, but much less was understood. Confused outdated concepts need to be corrected."[167] We believe that the arguments discussed in this editorial are substantiated by evidence and that this term can be maintained in pathology to describe thickened fibroelastotic endocardium, which, however, does not have, by itself, a functional phenotype that justifies its placement in the list of cardiomyopathies. Past "fibroelastosis" cases, especially those that were observed in children with either cardiomyopathy or congenital heart diseases, may represent unrecognized genetic disorders.[174-177]

ENDOMYOCARDIAL FIBROSIS

EMF is a restrictive endocardiomyopathy that preferentially affects children and adolescents.[178] The variation in geographic distribution supports the hypothesis that common factors in these areas (infectious, nutritional, lifestyles, or climate) play a role in the pathogenesis of the disease.[178-180] Its occurrence in a range of African, Latin American, and Asian populations does not support the hypothesis that ethnicity factors are associated with the disease.[178-180] The etiology is unknown; research on nutritional deficiencies (cerium, magnesium deficiency, cassava, and malnutrition, in general), infections (parasitic and viral diseases), autoimmunity, and allergic etiology remains unproven. The right ventricular endocardium is most commonly affected; occasionally the disease may involve the LV.[178] Patients with right-sided EMF can be relatively asymptomatic, despite severe structural and functional abnormalities.[180]

Clinical Presentation and Diagnosis

The diagnosis is based on clinical manifestations and imaging and hemodynamic evaluations. Physical examination may demonstrate hyperpigmentation of the lips and gums, abdominal distension, exophthalmos, jaundice, parotid swelling, asthma-like episodes, finger clubbing, right-sided HF with ascites without lower limb edema even with voluminous ascites, and cyanosis.[181]

Chest x-ray shows cardiomegaly as a result of severe right atrial enlargement and/or pericardial effusion and a possible bulge over the left heart border related to infundibulum dilatation; lung fields are usually hypoperfused.

ECG abnormalities include low-voltage QRS complexes, nonspecific ST-T–wave changes, and conduction disturbances; in advanced

right-sided EMF, the right atrial wave can be prominent, and a QR pattern in V_3 and V_1 can be manifest. Atrial fibrillation is common, and ventricular arrhythmias may also occur.[181,182]

Two-dimensional echocardiography demonstrates the thickened ventricular endocardium and provides information on ventricular size and function; obliteration of the right ventricular trabecular portion; anatomy of AV valves and subvalvular apparatus, annulus dilatation, and valvular regurgitation; right atrial thrombi; pericardial effusion; and dilation of hepatic veins.[182-186] In advanced disease, the right side of the heart may physiologically act as a single functional chamber.[186]

CMR is the ideal tool for both diagnosis of EMF and monitoring after surgery.[187,188] It provides information on hemodynamics and fibrosis with precise topographic data and characterization of the extent of myocardial fibrosis.[188]

In advanced right EMF, there is equalization of pressures in the right atrium, right ventricle, and pulmonary artery. In cardiac catheterization, the right ventricular angiogram shows loss of trabeculated pattern, a flattened apex, reduction of ventricular volume, a dilated hypercontractile infundibulum, and free tricuspid reflux to severely dilated right atrium and cava veins.[189]

Pathology

EMF typically involves only the heart and spares other organs and tissues. The heart appears enlarged mostly as a result of atrial dilatation. The endocardium is thickened from fibrosis that is prominent in the right ventricle at the apical level. EMF embeds the right ventricular trabeculae, obliterates the apex of the right ventricle, and fixes the tricuspid valve apparatus.[190] The pulmonary valve leaflets and arteries are not involved. The coronary arteries and small intramural vessels are also usually spared. Histologic study shows endocardial fibrous thickening, with myocyte damage with loss of myofibrillar components in the inner portion of the myocardium.[185,191,192] Inflammation is rare, eosinophils are uncommon, and there is no evidence that pathogens such as *Plasmodium falciparum* are causally linked to the disease.[193]

Natural History

The disease seems to evolve through three pathologic stages: endocardial necrosis, thrombosis, and fibrosis. The rate of progression of the three stages is difficult to establish; in fact, the disease is commonly diagnosed in advanced phases when HF progresses rapidly and causes death within 2 years from onset of clinical manifestations.[178] In some patients, the disease course seems milder, showing periods of clinical stability; other patients may experience clinical remission. EMF patients usually die from complications of progressive chronic HF leading to protein-losing enteropathy and hepatic failure. Sudden death can be caused by massive pulmonary embolism, systemic embolic events, or arrhythmia.[194] The thrombogenic and pulmonary embolic risks are high; advanced EMF is associated with chronic pulmonary thromboembolic disease.[190,195,196]

Management

Although there is no specific and effective treatment for EMF, HF therapy is used to control symptoms and reduce the progression of the disease (see Chap. 70). Surgery, which resects the EMF layer and can include mitral and tricuspid valvoplasty, constitutes a major advancement in the treatment strategy of EMF and is indicated for symptomatic patients.[197] However, late presentation and/or lack of expertise and infrastructure for the surgical treatment are reported as a limitation for the expansion of surgical treatments. Surgery is complicated by high mortality rate, especially when the disease requires extensive endocardial resection or tricuspid valve replacement (15% and 30%). However, early surgery can prevent the development of pulmonary embolism and hypertension.[198]

The disease carries a poor prognosis; the morbidity and mortality related to refractory HF are high. Thromboembolism and arrhythmia further increase the risk of mortality.[199] When possible, heart transplantation can be considered.[200] Innovative surgical approaches to right-sided EMF preventing complete AV block, preserving the native AV valves, releasing the myocardium, and making use of viable myocardium in the obliterated area can improve postoperative mortality and quality of life.[201]

Additional Considerations

EMF remains one of the most neglected cardiovascular diseases with "limited attention from the scientific community."[178,179] Research should concentrate on early diagnosis, treatment, and monitoring; modern imaging could help better elucidate the natural history of the disease, and novel biotechnology tools could explore the evolving phenotypes and the cause(s) at the molecular level. Indirect evidence that the amelioration of living standards (nutrition, control of infectious diseases) may contribute to control the disease come from India, where the incidence of the disease declined during the past decades in areas where the disease was previously endemic.[196] However, EMF remains endemic in many African countries such as Uganda and Mozambique, where it represents a public health problem.

CARCINOID HEART DISEASE

Introduction

Carcinoid heart disease (Hedinger syndrome) is a rare condition that affects the right side of the heart in up to 60% of patients with neuroendocrine tumors (NETs) and systemic carcinoid syndrome (CS).[202] NETs are rare (2.5-5.0 cases per 100,000 of the population per year), slowly progressing, low-grade malignancies with metastatic potential to the liver and possible release of vasoactive amines into the systemic circulation. NETs more commonly associate with carcinoid heart disease originating in the small bowel (72%) followed by those originating in the lung, appendix, large bowel, pancreas, and ovary; the primary site of the tumor remains undetermined in up to 20% of cases.[203] Carcinoid heart disease should be specifically investigated in patients diagnosed with NETs and CS; it carries a poor prognosis and is the major cause of mortality and morbidity[203,204]; early data reported a mean survival of 1.6 years in patients with NET and cardiac involvement compared with 4.6 years in those with NET without CS.[205]

CS is caused by vasoactive substances secreted by NET cells; 5-hydroxytryptamine (serotonin) is the predominant peptide, followed by prostaglandins, histamine, bradykinin, tachykinins, and transforming growth factor-β (TGF-β). Both the tachykinins and TGF-β display profibrogenic properties inducing fibromyxoid plaques that affect the right ventricular endocardium, the ventricular side of the tricuspid valve apparatus (leaflets, chordae, and papillary muscles), the ventricular site of the pulmonary valve, and less commonly, the pulmonary artery. Fibromyxoid plaques covered by endothelial cells are composed of fibroblasts, myofibroblasts, smooth muscle cells, collagen, and myxoid material.[203] When the liver is spared by the neoplasm, vasoactive peptides are usually inactivated; however, when hepatic metabolic function is impaired by metastatic dissemination, the vasoactive peptides remain active, thus causing the classical CS.[206] The presence of liver metastases is nonobligate for the development of CS; ovarian NETs may drain into the systemic circulation,[207] and patients with retroperitoneal lymphatic metastases may develop CS.

Phenotype and Cardiac Involvement

The clinical phenotype of typical or classical CS is characterized by cutaneous flushing, gut hypermobility with diarrhea, and bronchospasm with wheezing and shortness of breath[203]; a lung variant is known and is characterized by episodes of flushing, headache, and shortness of breath.[208] Depending of the severity of endocardial and tricuspid involvement, the functional effects can be either valve regurgitation or stenosis. The left heart is usually spared but can be involved in patients with patent foramen ovale. Signs and symptoms can be subtle even in patients with cardiac involvement; when present, symptoms include exertional dyspnea and fatigue. As the disease progresses, dyspnea worsens, and right-sided HF may manifest.[209]

The clinical diagnosis is facilitated by the precise oncologic characterization of the neoplasm; the physical examination may demonstrate elevated jugular venous pressure and a palpable right ventricular impulse; murmurs caused by right-sided valvular regurgitation are frequent, whereas pulmonary and tricuspid stenosis murmurs are rare.[209]

Two-dimensional echocardiography demonstrates tricuspid regurgitation, thickened and hypomobile pulmonary leaflets, and right-sided chamber dilation and hypokinesia. In a large series of 252 patients with CS, 52 had carcinoid heart disease. In the most severe cases two-dimensional transthoracic echocardiography showed thickened, retracted, and noncoapting leaflets; the chordae and papillary muscles were thickened, fused, and shortened. Three-dimensional transesophageal echocardiography showed that all three leaflets were fixed in a semiopen position, thus confirming the noncoaptation. Transesophageal echocardiography demonstrated thickened right ventricular endocardium with probable deposition of carcinoid plaque.[210] Imaging-based monitoring is recommended by the Guidelines from the Consensus European Neuroendocrine Tumor Society: Annual echocardiography should be part of the routine surveillance of patients with carcinoid heart disease.[211,212] CMR and CT scans can be variably used to refine, confirm, or implement diagnostic data.[210]

Biomarkers contribute to both diagnosis and monitoring: Serum serotonin, platelet serotonin, and urinary 5-hydroxyindoleacetic acid levels are elevated[213]; chromogranin A has also been suggested as a sensitive marker for patients with NETs and carcinoid heart disease.[214] High levels of NT-proBNP are usually measured in patients with remodeled right ventricular chambers[215]; levels of connective tissue growth factor and TGF-β have been reported as independent predictors of right ventricular dysfunction.[216] Activin A levels can be increased independently of right ventricular dilation[217]; together with impaired myocardial function, levels of activin A seem to predict mortality in patients with carcinoid intestinal disease.[218]

Management

Once CS is diagnosed, the cardiac involvement should be systematically investigated, monitored, and treated; somatostatin analogues are well-established and well-tolerated antisecretory drugs that have been used as first-line treatment for symptomatic control in hormonally active NETs for three decades. They include depot formulations, long-acting repeatable octreotide, and lanreotide autogel. Treatment has been proven to be associated with significant prolongation of progression-free survival.[219] For patients with symptomatic carcinoid heart disease, tricuspid valve surgery is the only effective treatment option. Without operation, only 10% of patients survive 2 years after the onset of New York Heart Association (NYHA) functional class III or IV symptoms. A recent study investigated the short-term and long-term outcomes in 195 consecutive patients (70% in NYHA class III and IV) with carcinoid heart disease who underwent tricuspid valve replacement (and further pulmonary valve surgery, n = 157) during a 27-year period (1985 and 2012) at one institution. Perioperative death was 10% and declined after 2000 (6%). Survival rates (95% confidence intervals) at 1, 5, and 10 years were 69%, 35%, and 24% (18% to 32%), respectively. Older age, cytotoxic chemotherapy, and tobacco use were independent predictors of death.[220] The surgical risk also depends on the severity of the right ventricular dysfunction, the involvement of the LV chambers, and the possible occurrence of carcinoid crises during surgery.[221,222]

AMYLOID HEART DISEASE

The gigantic scientific achievements in the biomolecular bases of amyloidogenic processes and the development of novel drugs specifically targeting the different types of amyloidosis are rapidly contributing to change the fate of an ominous disease that, in the recent past, was hopeless and is now a prototype of a successful model of precision and personalized medicine with major clinical achievements. This section briefly reviews cardiac amyloidosis, focusing on cardiologic workup and role of cardiologists in its modern management. Extensive, recent reviews are cited in the text. This topic is included in the chapter on restrictive heart diseases because of the typical diastolic dysfunction that characterizes the clinical cardiac phenotype.

DEFINITION AND CLASSIFICATION

Amyloidosis is defined by the extracellular infiltration of amyloid fibrils originating from different precursor proteins that self-assemble with highly ordered, but abnormal cross-β-sheet conformation.[223] In 2016, the Nomenclature Committee of the International Society of Amyloidosis formulated recommendations for nomenclature of amyloid fibril proteins and clinical classification of the amyloidosis. This novel classification includes 36 known human extracellular fibril proteins and a large number of intracellular protein inclusions that display some of the properties of amyloid fibrils[224]; cardiac involvement occurs in most common forms of systemic amyloidosis and in localized atrial amyloidosis (Table 61–7).

Amyloidogenic proteins can be *abnormal* (eg, in acquired systemic immunoglobulin light chain [AL] amyloidosis or in genetic amyloidoses), *normal* (eg, reactive AA systemic amyloidosis, wild-type transthyretin amyloidosis [or senile amyloidosis], and atrial natriuretic peptide amyloidosis), or *normal but abundantly produced for prolonged periods of time* (eg, β_2-microglobulin dialysis-related amyloidosis).[225] Immunoglobulin light chain and transthyretin (TTR)-related amyloidoses are the most common types of systemic forms of amyloidosis with cardiac involvement; rare heritable forms are associated with mutations in genes such as *APOA1* and cause slowly progressive and severe cardiac wall thickening[226] (Fig. 61–11).

DIAGNOSTIC WORKUP IN CARDIAC AMYLOIDOSIS

The first diagnostic consideration is "thinking of the possibility of cardiac amyloidosis."[227] The diagnostic workup should start with a focused clinical suspicion in patients with variable combinations of signs and symptoms such as fatigue, weight loss, HF, nephrotic syndrome, nondiabetic peripheral neuropathy, autonomic neuropathy, hepatomegaly, macroglossia, purpura, carpal tunnel syndrome, and claudication of the jaw. Age, gender, and family history can contribute to formulate a clinical diagnostic hypothesis that constitutes the basis for a focused diagnostic workup.

TABLE 61–7. Classification of Amyloid Fibril Proteins and Their Precursors in Humans

Fibril Protein	Precursor Protein	Systemic (S)/Localized (L)	Acquired (A)/Heritable (H)	Target Organs	Heart
AL	Immunoglobulin light chain	S, L	A, H	All, except CNS	Frequent
AH	Immunoglobulin heavy chain	S, L	A	All, except CNS	Possible
AA	(Apo) serum amyloid A	S	A	All, except CNS	Rare, uncommon
ATTR	Transthyretin, wild-type	S	A	Heart (90% males); tenosynovium	Always
ATTR	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomeninges	Genotype dependent
Aβ2M	β_2-Microglobulin, wild-type β_2-Microglobulin, variant	L	A	Musculoskeletal system	Rare, uncommon
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C-terminal variants), skin (C-terminal variants)	Possible and severe
AANF	Atrial natriuretic factor	L	A	Cardiac atria	By definition (atria)
AMed	Lactadherin	L	A	Senile aortic, media	No

Abbreviations: ANS, autonomic nervous system; CNS, central nervous system; PNS, peripheral nervous system.

Age

Patients with signs or symptoms suggestive of amyloidosis are typically 60 to 80 years old. Light chain amyloidosis with cardiac involvement most commonly occurs after the fifth decade of life. The prevalence of ATTR wild-type (formerly known as senile) amyloidosis increases with age, and approximately 20% of males aged 80 or older suffer from this disease. However, occurrence in younger adults is possible in patients with heritable autoinflammatory diseases such as familial Mediterranean fever,[228,229] tumor necrosis factor receptor–associated autoinflammatory syndrome),[230] and cryopyrin-associated periodic syndromes.[231,232]

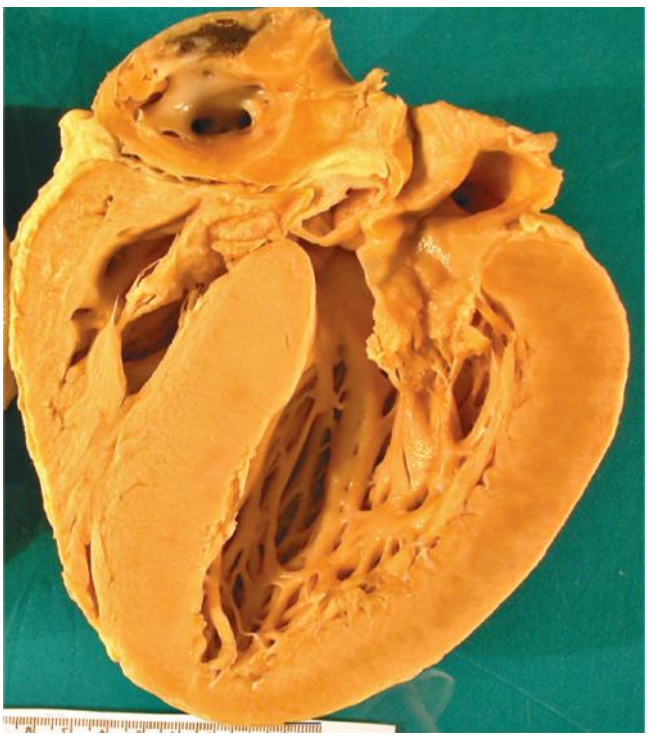


FIGURE 61–11. This figure shows the heart excised at transplantation from a patient with familial *APOA1* mutation. Both left and right ventricular walls are severely thickened; the mitral valve shows thickened leaflets. The *black bar* in the lateral wall corresponds to 1 cm.

Gender

Amyloidosis affects both genders. However, ATTR senile cardiac amyloidosis preferentially affects males older than 60 years.[227,233]

Family History

Family history may contribute to suspicion of heritable amyloidosis; the heart is one of the possible involved organs. The phenotype manifestations in affected members of the same family may differ in terms of severity and the organs that are involved (eg, heart, liver, kidney). By itself, a positive family history indicates the need to look for a precise genetic cause and to perform cascade family screening,[223,225] but sporadic cases are not uncommon.

Cardiology Evaluation

The cardiologic workup includes physical examination, ECG, echocardiography, biochemical testing, CMR, scintigraphy, CT imaging, and tissue biopsy.

Patients with cardiac amyloidosis usually report nonspecific symptoms such as fatigue, nonspecific neuropathic pain, and weight loss. Clinical onset may coincide with paroxysms of atrial fibrillation[234] (Fig. 61–12). Noncardiac traits are often associated in AL amyloidosis (skin dyschromia, macroglossia and purpura of the eyelids, jaw claudication, gastroparesis and intestinal pseudo-obstruction, polyarthralgia, muscle pseudohypertrophy, xerostomia, and alopecia). Peripheral neuropathy can occur both in AL and in ATTR-mutated amyloidosis. Carpal tunnel syndrome can be the earliest manifestation of ATTR amyloidosis.[235]

Biochemical tests are usually performed as part of the routine evaluation in patients with unexplained LV hypertrophy. Recommended

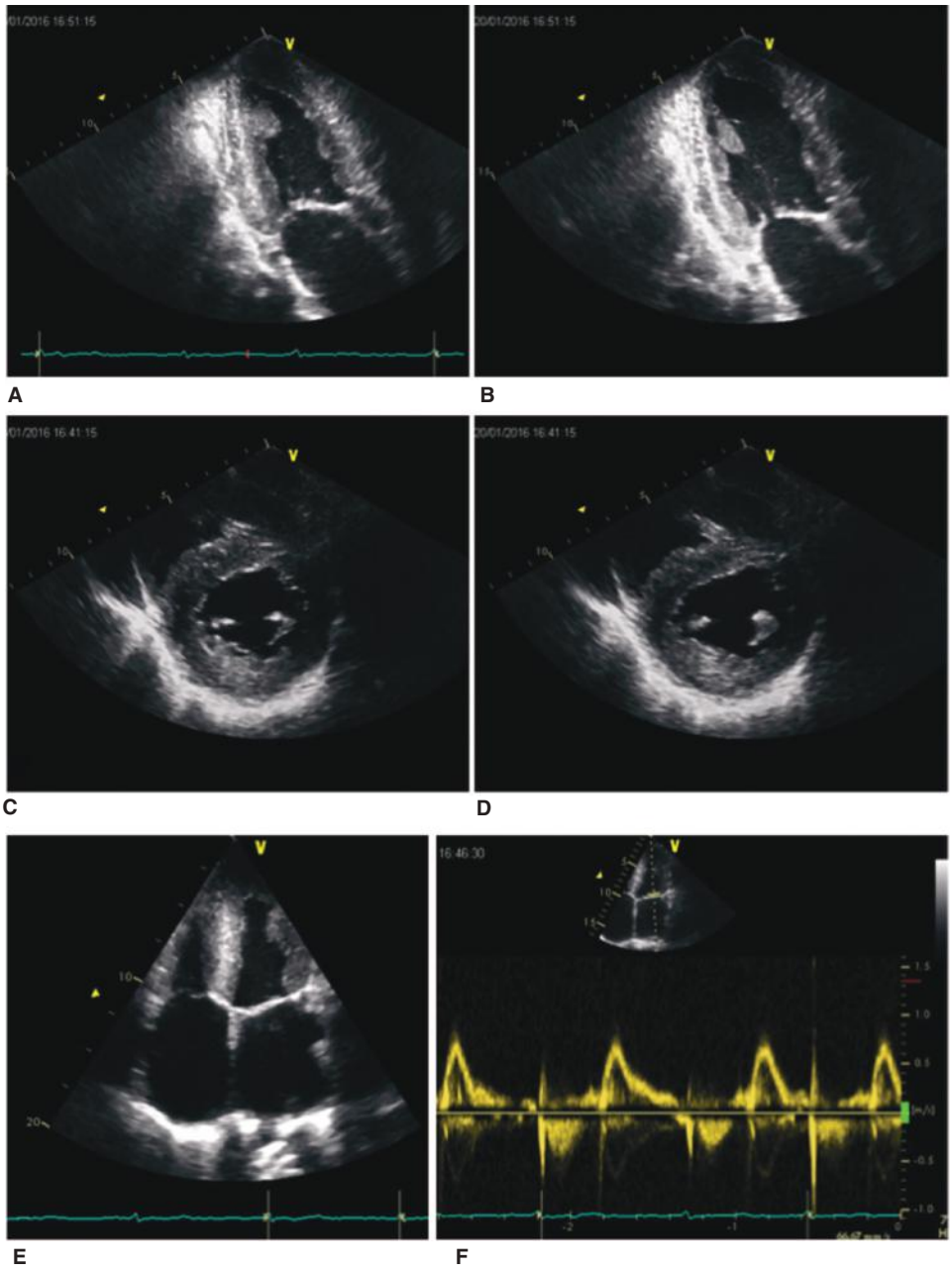


FIGURE 61–12. ATTR wild-type senile amyloidosis. The patient is a 75-year-old man who presented with paroxysmal atrial fibrillation (AF) in 2005; he underwent ablation, but AF recurred. He further underwent two additional ablation procedures that were followed by recurrence of AF that finally evolved into persistent AF. Ten years after the first AF episode, he was diagnosed with cardiac ATTR wild-type senile amyloidosis (by endomyocardial biopsy). The panels show the echocardiographic features. **A** and **B.** Two-chamber view shows normal systolic function. **C** and **D.** The parasternal short-axis view show concentric hypertrophy. **E.** Apical four-chamber view shows biatrial enlargement. **F.** The continuous wave Doppler highlights the restrictive pattern with absence of A wave in atrial fibrillation.

tests may differ, depending on the clinical suspicion for HCM, RCM, or amyloidosis. In the patient with unexplained LV hypertrophy and clinical suspicion for amyloidosis, biochemical testing should include evaluation for monoclonal protein production, serum immunofixation and electrophoresis, and serum free light chain assay.[223,225,227,236] When such data indicate the presence of a monoclonal protein, further tests provide conclusive results in the majority of cases. Negative tests for monoclonal protein exclude AL amyloidosis in up to 98% of cases but do not exclude ATTR amyloidosis that does not have corresponding biochemical markers.[223,225,236] NT-proBNP and BNP may be highly informative when the diagnosis is established.[237] However, they are typically increased in HCM or RCM decompensated hearts as well.[238] The highly sensitive troponin test does not discriminate between HCM, HF, and amyloidosis.[239,240] The clinical workup in patients presenting with HCM phenotype does not include screening tests for monoclonal protein production; biochemical tests exploring markers such as serum creatinine phosphokinase or levels of lactic acid or electrolytes, which are commonly performed in patients diagnosed with HCM, do not contribute to the diagnosis of cardiac amyloidosis.[31] This is one of the reasons why the diagnosis of cardiac amyloidosis is pursued based on the grounds of clinical suspicion. In cardiac amyloidosis, testing for proteinuria, serum creatinine, and alkaline phosphatase can reveal concomitant involvement of the kidney and liver.

The ECG may show decreased QRS voltages in more than 50% of cardiac amyloidosis; when present in older adult patients with RCM, granular sparking texture, LV thickening, and atrial dilation, this marker contributes to increase the diagnostic suspicion.[241] Notably, low voltages can be absent in ATTR wild-type amyloidosis. The PR interval can be short in thickened hearts of patients with lysosomal storage diseases such as Anderson-Fabry disease or glycogenosis but not in amyloid hearts. A Wolff-Parkinson-White pattern may occur in Danon disease, which is also associated with other traits such as myopathy and cognitive impairment not seen in amyloidosis. Conduction disease, particularly AV block, can occur in both HCM and cardiac amyloidosis.[31]

The two-dimensional echocardiographic evaluation distinguishes between sarcomeric HCM and nonamyloid phenocopies of HCM. Amyloidosis hearts usually show symmetric LV hypertrophy, biventricular wall thickening, atrial septum thickening, slightly depressed LV systolic function, pericardial effusion, AV valve thickening, and a typical granular sparking echo-reflectance (see Fig. 61–12).[242,243] Current diagnostic imaging criteria for cardiac involvement includes a mean LV wall thickness (septum plus posterior wall thickness divided by 2) greater than 12 mm in the absence of alternative explanations.[223,225,233] Diastolic dysfunction is often pronounced but may also occur in HCM.[242]

Patients with unexplained LV hypertrophy may now routinely undergo CMR, which plays a key role in diagnosing cardiac amyloidosis and in differentiating between primary AL and ATTR amyloidosis. Several recent reviews accurately describe major achievements of advanced imaging for cardiac amyloidosis. Because different tissues

have different T1 and T2 relaxation times, by mapping the T1 relaxation times of the myocardium, AL cardiac amyloidosis can be diagnosed with high diagnostic accuracy. The diagnosis of cardiac amyloidosis can be suspected with the use of CMR because the infiltrated myocardium has different gadolinium kinetics from that of normal myocardium.[244]

Cardiac CT can contribute to diagnosis and quantification of cardiac amyloidosis by allowing measurement of the myocardial extracellular volume. Dynamic equilibrium CT, a 5-minute contrast-enhanced gated cardiac CT, has potential for noninvasive diagnosis and quantification of cardiac amyloidosis.[245]

Technetium-99m [(^{99m}Tc)-3,3-diphosphono-1,2-propanodicarboxylic acid or ^{99m}Tc-pyrophosphate scintigraphy] is a highly sensitive technique for cardiac amyloid imaging in ATTR amyloidosis with potential for diagnosis in asymptomatic carriers of *ATTR* mutations or in elderly patients with HF of unknown etiology. In a recent study including 857 patients with histologically proven amyloid (374 with EMB), myocardial radiotracer uptake on bone scintigraphy was > 99% sensitive and 86% specific for cardiac ATTR amyloid, with false-positive results almost exclusively from uptake in patients with cardiac AL amyloidosis. The combined findings of grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy and absence of a monoclonal protein in serum or urine had a specificity and positive predictive value for cardiac ATTR amyloidosis of 100% (95% confidence interval, 98.0%-100%).[246]

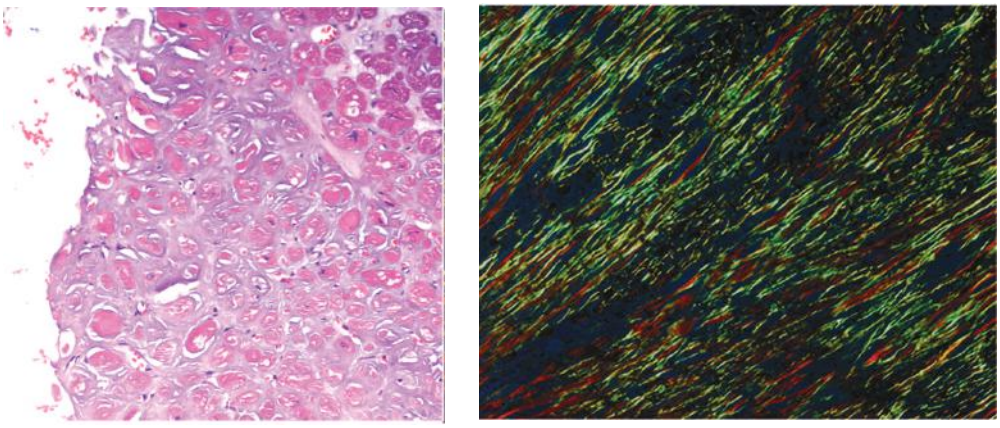
EMB has the dual advantage of being able to demonstrate amyloid deposition and allowing for immune characterization of amyloidogenic protein. In the majority of cases of systemic amyloidosis, fine-needle subcutaneous fat aspiration (SFA) provides informative tissue samples. EMB should be performed in patients with suspect cardiac amyloidosis (and negative abdominal fat aspirate) with a scintigraphic score < 3 or in the presence of monoclonal proteins[247-249]; in experienced centers, the procedure carries a minimal risk.[249] When the SFA study provides uncertain results in patients with suspected systemic amyloidosis, biopsy of a labial salivary gland is a minimally invasive procedure that can spare more than half of SFA-negative patients from the need to undergo a biopsy of an affected organ such as heart or kidney.[223,225,233] Amyloid is clearly visible on hematoxylin and eosin stain (Fig. 61–13A); the diagnosis is confirmed with Congo red stain (Fig. 61–13B) and electron microscopy. Immunoelectron microscopy demonstrates the immunostaining of amyloid fibrils with specific antibodies that recognize different amyloidogenic protein (Fig. 61–14). The rare possibility of a double type of amyloid fibrils is the reason why immunoelectron microscopy stains are systematically performed (anti-κ, λ, SAA, TTR, β_2-microglobulin) in parallel with positive controls. Immunoelectron microscopy data should be cross-validated with clinical and biochemical data. However, combining clinical, biochemical, and immunotyping data, especially in cases with a double type of amyloid deposits, should resolve possible discrepancies. Recently, mass spectrometry–based proteomics have been introduced as a valuable tool for amyloid typing, with the advantage of not being antibody dependent. This can be performed on whole tissues[250] or after laser capture microdissection of Congo red–positive areas.[251]

Genetic testing is indicated in all patients with non-AL amyloidosis to confirm results of tissue typing and to discriminate between hereditary and wild-type ATTR amyloidosis. The most common disease gene in heritable amyloidosis is *TTR*, a small gene mapping at 18q12.1; its screening is simple and affordable using conventional Sanger-based technology. Early detection of TTR familial amyloid polyneuropathy (FAP) is essential to improve the prognosis of TTR-FAP. The European Network for TTR-FAP recommends genetic counseling and routine monitoring for asymptomatic carriers of TTR-FAP.[252] *TTR* mutations are grouped according to their proven amyloidogenic potential (http://www.ibmc.up.pt/mjsaraiva/ttrmut.html). In probands with negative TTR testing and positive family history, additional genes known to be associated with less common forms of familial amyloidosis can be screened. In familial amyloidosis, the genetic workup includes pretest genetic counseling with construction of the family pedigree. Post-test counseling follows genetic tests.[31]

Family screening is indicated in heritable amyloidosis. Mutations in *TTR* gene are well known; their proven pathogenic role makes screening simple. Cascade genetic testing in families is the first step. Family members who test negative do not need to progress with further clinical evaluations. This simple screening is a major difference with sarcomeric HCM, which displays genetic heterogeneity and where all mutations should be confirmed with geno-phenotype segregation studies in families.

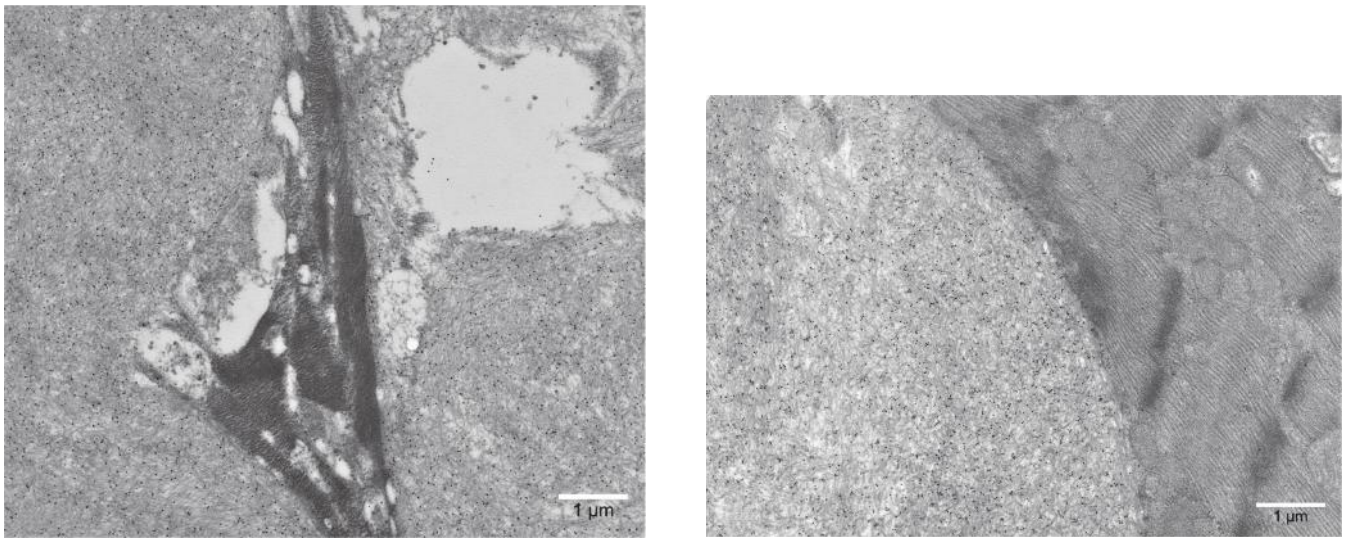
CARDIAC AMYLOIDOSIS: A PAN-HEART DISEASE

Cardiac amyloidosis is a pan-heart disease affecting the myocardium, valves, and vessels; the endocardium and pericardium can be focally involved without significant functional consequences.[253-255] The damage exerted by amyloid deposition in cardiac structures is a result of infiltration of amyloid deposits that surround single myocytes or expand in the interstitium at the endocardial and pericardial levels and in cardiac valves.



A B

FIGURE 61–13. Hematoxylin and eosin (**A**) and Congo red stain (**B**). **A.** Cardiac amyloid infiltration is clearly visible with hematoxylin and eosin stain. **B.** Congo red stain shows the typical apple-green birefringence under polarized light.



A B

FIGURE 61–14. **A.** Immunoelectron microscopy. A λ immunostain. **B.** Anti-k immunostain. (**A** and **B**) Gold particles decorate the amyloid fibril in cardiac AL λ and k cardiac amyloidosis.

Amyloid deposition affects cardiac vessel walls; severely affected vessels can demonstrate loss of patency of the lumen (Fig. 61–15). In AL amyloidosis, amyloid proteins further exert a direct cardiotoxic effect.[225] In advanced stages of disease, the amount of amyloid can be so prominent that few residual myocytes remain (Fig. 61–16). Heart valves are commonly infiltrated; their involvement is visible on echocardiography. When small intramural myocardial vessels are preferentially involved, clinical manifestations and pathologic damage are more similar to ischemic heart disease than to a cardiomyopathy.[248]

AL CARDIAC AMYLOIDOSIS

The incidence of AL amyloidosis is 3 to 5 cases per million population[256]; in the United Kingdom, the prevalence is 1 per 100,000 population[257]; in Sweden, the reported incidence of AL amyloidosis is 3.2 per million person-years.[258] Fibrils are constituted of immunoglobulin light chains produced by a clonal population of plasma cells with average bone marrow plasma cell content of 5% to 7%; less than 10% of cases demonstrate clinically overt multiple myeloma.[225,236] The primary care is usually performed by hematologists; cardiologists actively participate in the multidisciplinary workup for the management of cardiac amyloid disease (diagnosis, treatment of arrhythmias or HF, and monitoring). However, in patients with unrecognized AL amyloidosis, cardiac symptoms, atrial fibrillation, or HF can be the presenting phenotype. Therefore, the diagnostic workup can start from the cardiology setting, and then progress to a multidisciplinary workup.

Cardiac dysfunction in AL amyloidosis results from both amyloid infiltration with disruption of the myocardial architecture and from direct cytotoxic effect of the amyloidogenic light chains[259,260]; internalization into lysosomal compartments of amyloidogenic light chains has been proposed as a possible myocyte toxic mechanism in animal models.[36] The cardiotoxicity of amyloidogenic light chains could explain the clinical improvement of successfully treated patients before a reduction in the amyloid deposits at the affected organ(s) can occur; persistence of amyloid deposits after successful treatment and organ recovery also supports light chain toxicity as contributory factor of organ dysfunction.[236] Therefore, the burden of cardiac amyloidosis evaluated by cardioimaging may not inform on the responsiveness to treatments.

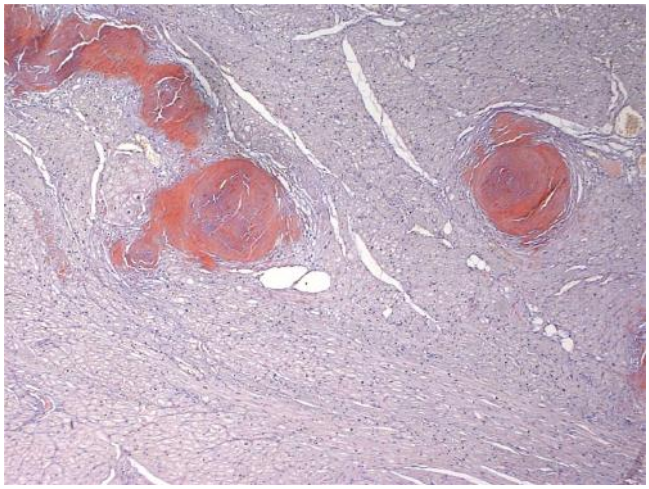


FIGURE 61–15. This figure shows the prevalent involvement of small intramural vessels by AL λ amyloidosis. The sample is from the left ventricular (LV) apex of a 66-year-old male patient with undiagnosed AL amyloidosis, who underwent urgent LV assist device implantation for severe and quickly worsening heart failure, after months of medical treatment for heart failure clinically attributed to myocarditis.

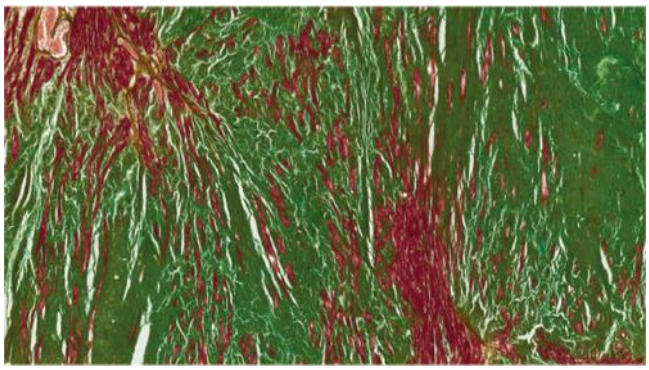


FIGURE 61–16. This figure shows the severe amyloid infiltration in an ATTR wild-type senile amyloidosis heart excised at transplantation. A few residual myocytes (*red*) are embedded in the dense amyloid ground (*green*). Movat pentachrome stain.

Diagnosis

Late diagnosis of cardiac AL amyloidosis is a major factor in the 30% mortality rate in the first year after diagnosis.[261] A recent survey showed that almost 40% of patients with this disease are diagnosed more than 1 year after the onset of symptoms.[262] The cardiologic diagnostic workup in patients diagnosed with AL amyloidosis aims at assessing the cardiac involvement and its severity. Cardiac biomarkers (troponin, NT-proBNP, or BNP) should be tested in all patients given their role as markers for cardiac involvement, prognostic contributors, and indicators of cardiac response to therapy. High concentration of NT-proBNP allows the detection of AL amyloidosis at presymptomatic stages with a diagnostic sensitivity of 100%. Thus, screening with NT-proBNP has been advocated in patients at risk of developing AL amyloidosis (ie, patients followed by hematologists for monoclonal gammopathy of undetermined significance and altered circulating free light chain ratio).[263] Cardiac imaging includes echocardiography; the typical granular sparkling feature in thickened myocardial walls suggests cardiac involvement. Cardiac dysfunction is primarily diastolic, with HF symptoms developing in patients with preserved (or only mildly impaired) systolic function. However, systolic dysfunction is also a relevant feature of cardiac AL amyloidosis and has prognostic relevance.[261] Doppler-based strain echocardiography can contribute to early diagnosis by assessing the ability of the myocardium to shorten upon contraction in a longitudinal plane.[263] CMR is an excellent tool for the diagnosis of cardiac amyloidosis; late gadolinium enhancement is the hallmark feature and correlates with histologic, laboratory, and clinical parameters.[244] Late gadolinium enhancement has prognostic value; transmural extension is associated with advanced cardiac involvement and poorer survival.[264]

Prognosis

In untreated patients, AL amyloidosis carries a poor prognosis. The historical median survival of untreated patients with AL amyloidosis was 8 months[256] compared with 24 to 66 months in patients with TTR cardiac amyloidosis.[265] The most commonly used prognostic scoring system is the standard Mayo staging system; it assigns 1 point to each of the following variables: cardiac troponin T ≥ 0.035 ng/mL (or cardiac troponin I > 0.1 ng/mL) and NT-proBNP ≥ 332 ng/L. Stage III patients, with both markers above the cutoff, have a median survival ranging from 3 to 6 months.[266,267] Low systolic blood pressure (< 100 mm Hg) and very high concentration of NT-proBNP (> 8500 ng/L) identify stage III patients with an even worse outcome (stage IIIb).[268] Additional systemic factors and biomarkers can contribute to prognostic stratification[225,238,239,266-273] (Table 61–8). Evaluation of cardiac response to treatments is based on decrease of markers such as NT-proBNP by > 30% and 300 pg/mL (when baseline NT-proBNP > 650 pg/mL) or improvement of NYHA functional class.[274]

Treatment

Treatment is aimed at improving survival, decreasing the burden of amyloidogenic light chains, and improving the function of the affected organs. Reduction of circulating free light chain is mirrored by NT-proBNP decrease and rapidly translates into clinical improvement, whereas the amount of amyloid deposited in the heart remains unaltered, pointing to a direct toxic effect of the circulating precursor as the main effector of cardiac dysfunction in AL amyloidosis.[275] Criteria for evaluating both hematologic response (decreased amyloidogenic light chains) and organ response (improvement of organ function) are well established and graded. Treatment options depend on eligibility for autologous stem cell transplantation as well as on individual criteria evaluating the tolerability of chemotherapeutic agents, including novel agent–based treatments with proteasome inhibitors, such as bortezomib, or immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide.[276] Elevated cardiac biomarkers (NT-proBNP > 5000 ng/L, cardiac troponin T > 0.06 ng/mL) are considered exclusion criteria for stem cell transplantation.[275] Standard chemotherapy requires dose reductions in stage IIIb patients. Nonchemotherapy approaches to the treatment of AL amyloidosis are now rapidly expanding. The antibiotic doxycycline is capable of counteracting the toxicity of amyloidogenic light chains in a *Caenorhabditis elegans* model.[277] The use of polyphenols as inhibitors of fibrillogenesis is also being considered with interest.[278] Amyloid resorption can be promoted by depleting serum amyloid P component (SAP), with a palindromic compound, CPHPC, a competitive inhibitor of SAP binding to amyloid fibrils, combined with an anti-SAP antibody.[279] Immunotherapy of systemic amyloidosis using antibodies specific for amyloid-related epitopes produced promising results and is being explored in phase III trials.[280]

Cardiologists are involved in supportive cardiac care for patients with amyloidosis with cardiac involvement to manage HF and prevent sudden death.[257] Loop diuretics and aldosterone antagonists are the mainstay of treatment. The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is limited by their contribution to hypotension. Because heart rate is a major contributor to maintain cardiac output in patients with fixed stroke volume, β-blockers should be either avoided or used with caution and at low dosages;

TABLE 61–8. Prognostic Markers in AL Amyloidosis

Markers Included in the Revised Mayo Score System			Factors Not Included in the Mayo Score System		New Possible Markers		
Mayo staging system for AL amyloidosis	Cardiac troponin T: ≥ 0.025 ng/mL	Myocyte injury	Additional	Multiorgan involvement (heart, liver, kidney); performance status (ECOG > 2); loss of weight (> 10% in 6 months); systolic BP < 100 mm Hg	Novel	Osteopontin (secreted phosphoglycoprotein)	Myocyte injury and biomechanical strain
	NT-proBNP: ≥ 1800 pg/mL	Heart failure		≥ 10% BMPCs; cytogenetic abnormalities [t(11;14) and trisomies]		sST2 (or IL-1RL1)	Cardiac remodeling, fibrosis
	dFLC: ≥ 18 mg/dL	Disease burden				Human placental growth factor	Endothelial dysfunction
				Serum uric acid (> 8 mg/dL)			

Abbreviations: BMPCs, bone marrow plasma cells; BP, blood pressure; dFLC, difference between involved and uninvolved free light chains; ECOG, Eastern Cooperative Oncology Group performance status; IL-1RL1, member of toll-like interleukin-1 cytokine receptor superfamily; NT-proBNP, N-terminal pro–B-type natriuretic peptide; sST2, Soluble suppression of tumorigenicity 2.

nondihydropyridine calcium channel blockers exerting a negative inotropic effect can worsen HF. The autonomic-driven hypotension can be supported with a selective α_1-adrenegic agonist and fluorohydrocortisone.[281] However, the use of fludrocortisone is limited by the effect it may have on fluid balance. Primary prevention of sudden death with an implantable cardioverter-defibrillator (ICD) in patients with HF and low ejection fraction is a complex decision based on expectancy of life, NYHA functional class, history of non–posturally mediated syncope, and/or demonstration of nonsustained ventricular tachycardia and ventricular tachycardia. A recent proposal is to integrate the Stanford Amyloid Center's ICD implantation criteria to select candidates who concurrently meet American College of Cardiology/AHA/Heart Rhythm Society guidelines.[282] Staged heart transplantation followed by autologous stem cell transplant therapy appears to provide good long-term outcome for AL amyloid in young patients with isolated advanced cardiac involvement.[283] An LV assist device is a further feasible option but probably better suited for senile ATTR amyloidosis.[284-286]

ATTR AMYLOIDOSIS

Mutated ATTR is caused by mutations in the *TTR* gene; inheritance is autosomal dominant. The most common *TTR* mutation is p.(Val122Ile), which is present almost exclusively in African Americans (allele frequency ranging from 3% to 3.9%).[287] In different European geographic areas and in Japan, the p.(Val30Met) allele is endemic.[288] Genotype-phenotype correlation studies demonstrate: (1) predominant cardiac involvement in patients who carry p.(Val122Ile) and p.(Leu111Met) mutations; (2) peripheral nervous system involvement in carriers of p.(Val30Met) (peripheral neuropathy, also known as FAP); and (3) mixed phenotype in carriers of p.(Glu89Gln) and p.(Thr60Ala) mutations. Genotype-phenotype correlations reflect age of onset (early onset manifesting with peripheral neuropathy, FAP), endemic factors (different prevalence of neurologic phenotype), and gender [female gender is protective in carriers of the p.(Val30Met) mutation].[289,290] Death occurs approximately 10 to 15 years after clinical disease onset.[233,289]

Cardiac Phenotype and Prognosis

The cardiac phenotype is characterized by LV thickening, left atrial enlargement, and marked diastolic dysfunction. The diagnostic workup is evolving; nonbiopsy diagnosis of cardiac ATTR is now feasible. Bone scintigraphy enables the diagnosis of cardiac ATTR amyloidosis to be made reliably without need for histology in patients who do not have a monoclonal gammopathy. The combined findings of grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy and absence of a monoclonal protein in serum or urine result in a specificity and positive predictive value for cardiac ATTR amyloidosis of 100%.[246]

In the large, prospective, longitudinal Transthyretin Amyloid Cardiac Study, the highest morbidity and mortality were observed in wild-type ATTR and in carriers of the ATTR p.(Val122Ile).[291] Median survival from diagnosis ranges from 25 to 36 months in mutated ATTR and from 24 to 66 months in wild-type ATTR. Atrial fibrillation and thromboembolic complications are common; atrial fibrillation was observed in 64% of ATTR patients with higher frequency in wild-type ATTR than in mutated ATTR[234]; intracardiac thrombosis leading to thromboembolism contributes significantly to mortality. Echocardiography demonstrates a statistically greater wall thickness and lower mortality in ATTR than in AL amyloidosis,[292] despite similar degrees of left systolic impairment. This paradox suggests an additional mechanism for LV dysfunction as light chain toxicity in AL amyloidosis, described previously.

Treatment

Medical Treatment and Devices Supportive cardiology management is similar to that for AL amyloidosis. Diuretics relieve congestion in patients with HF but should be administered with caution and then closely monitored because of the risk of hypotension and renal failure. The drugs typically used in patients with HF cannot be equally employed in cardiac amyloidosis; digoxin, which may cause abrupt cardiac rhythm disturbances or sudden death, must be avoided. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers are poorly tolerated. When needed, they can be cautiously used at the lowest tolerated dose. Implantable devices, both permanent pacemakers[293] and ICDs,[282] should be considered when indicated according to guidelines and specific clinical indications.

Transplantation Liver transplantation can be considered because 95% of TTR protein is produced by the liver. Long-term survival, especially for early-onset TTR Val30Met patients, is excellent, with 20-year survival of 55.3%.[294] The risk of delaying liver transplantation by testing alternative treatments such as TTR stabilizers, especially in early-onset TTR Val30Met patients, requires individual consideration.[294] Combined heart and liver transplantation is occasionally indicated for advanced disease.[283] Heart transplantation can be offered to patients with senile ATTR amyloidosis.

Transthyretin Stabilizers Diflunisal, a nonsteroidal anti-inflammatory drug, binds and stabilizes common familial TTR variants against acid-mediated fibril formation in vitro and has been tested in animal safety studies and human clinical trials. Tafamidis is a novel compound that binds to the thyroxine-binding sites of the TTR tetramer, inhibiting its dissociation into monomers and blocking the rate-limiting step in the TTR amyloidogenesis cascade. Silencers—small interfering RNA (ALN-TTR01, ALN-TTR02, and ALN-TTRSc)—are emerging as an endogenous cellular mechanism for controlling gene expression in which small interfering RNAs bound to the RNA-induced silencing complex mediate the cleavage of target messenger RNA and oligonucleotides.[295]

Degraders: Doxycycline/Tauroursodeoxycholic Acid and Anti-SAP Antibodies The combination of doxycycline and tauroursodeoxycholic acid has been reported to stabilize the disease for at least 1 year with an acceptable toxicity profile in the majority of patients with TTR amyloidosis.[296]

CONCLUSION

Myocardial and endocardial diseases with diastolic dysfunction include different disorders that have restrictive physiology in common. The list of diseases to be maintained in future classifications should be established on criteria useful for selecting limited subgroups of diseases that will have a clinical advantage from a united taxonomy. The typical example is primary or idiopathic RCM: this cardiomyopathy is a rare genetic disease, affecting children and young adults. *TNNI3* is the most common disease gene. The clinical phenotype is characterized by exclusive involvement of the heart and severe clinical evolution through end-stage HF requiring heart transplantation. The subgroup of restrictive desminopathies is easy to diagnose; the phenotype is unique and characterized by absence of significant LV hypertrophy, presence of conduction disease, and demonstration of intramyocyte accumulation of desmin-immunoreactive material. The involvement of skeletal muscle is well known but can be subclinical in patients with cardiomyopathy as major clinical phenotype. The involvement of smooth muscle is largely unexplored and should be a matter of future research to contribute to the best management of patients. Systemic or multiorgan storage and infiltrative genetic diseases with restrictive

phenotype must be differentiated because their precise diagnosis corresponds to a refined evaluation, monitoring, and treatment; the paradigmatic example is represented by diseases that cause iron overload.

For endocardial diseases, old diagnostic terms based on pathologic descriptions should be abandoned in favor of precise phenotype-based nosology such as infantile and juvenile right ventricular EMF. Although the causes of EMF remain elusive, the burden of disease in select resource-limited settings in Africa, Asia, and South America is a call to action for major efforts from the international clinical and scientific communities both for implementation of care and for research into mechanisms. Conditions such as the rare right ventricular carcinoid heart disease demonstrate pathologic similarity with EMF.

Finally, amyloid heart disease should be separated from other restrictive heart diseases and no longer confused into the group of storage diseases; amyloidosis is the sole infiltrative disease and the unique human model of noninflammatory extracellular infiltration. The recent progression of research is dramatically modifying the diagnosis, treatment, and prognosis of amyloidosis. Precise diagnoses provide the basis for the development of targeted treatments, and as for any discovery in medicine, the availability of specific treatments for the different types of amyloidosis is increasing the awareness of the disease and its diagnosis.

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CHAPTER 62

ARRHYTHMOGENIC CARDIOMYOPATHY

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INTRODUCTION AND DEFINITION

Arrhythmogenic cardiomyopathy is a rare primary myocardial disease that is clinically characterized by life-threatening ventricular arrhythmias secondary to fibrofatty replacement of ventricular myocytes.[1-3]

In the first systematic description of 24 adult cases in 1982, Marcus et al[4] outlined the profile of right ventricular (RV) dysplasia as a pathologic condition primarily affecting the right ventricle and characterized by partial or total absence of RV musculature due to substitution by fatty and fibrous tissue. The authors distinguished conditions in which the RV myocardium was almost completely absent from those in which the fatty and fibrous tissue was limited to portions of the right ventricle. The former showed cardiomegaly and clinically manifested with congestive heart failure. The latter showed mild RV remodeling and minimally impaired cardiac dysfunction. When ventricular tachycardia was the principal manifestation, the condition was termed *arrhythmogenic RV dysplasia* (ARVD).[4] The authors additionally described 34 adult cases and provided the clinical profile of the disease:

- Clinical presentation is characterized by ventricular tachycardia, supraventricular arrhythmias, right heart failure, or asymptomatic cardiomegaly.
- Electrocardiogram (ECG) shows T wave inversion in the right precordial leads.
- Increased right ventricular diastolic dimensions.
- Onset is in young adult age.
- Prevalence is higher in males than in females.

In 1988, Thiene et al[5] described the morphologic features of RV cardiomyopathy in 12 young people who died suddenly. Findings included:

- Normal or moderately increased heart weights
- Lipomatous transformation (6 of 12 patients) or a fibrolipomatous (6 of 12 patients) transformation of the RV free wall
- Substantially spared left ventricle
- Occasional myocardial degeneration and necrosis, with or without inflammatory infiltrates

In 1994, an International Task Force grouped criteria for the clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).[6] These criteria were aimed at facilitating recognition and interpretation of the clinical and pathologic features of ARVC/D and were grouped according to:

- Structural and histologic features
- ECG and arrhythmic features
- Familial features

These features were incorporated into criteria that were subdivided into major and minor categories according to the specificity of their association with ARVC/D. These criteria revealed high specificity but low sensitivity for early and familial disease.[6]

In 2010, task force criteria were modified to improve the diagnosis and management of ARVC/D. The modified criteria incorporated new knowledge on the genetic basis of the disease, improving diagnostic sensitivity and maintaining diagnostic specificity (Table 62–1). The structural, histologic, ECG, arrhythmic, and genetic features were structured in major and minor criteria. The task force document formally introduced the biventricular variant and the left dominant variant.[7] These latter criteria support the broader new term of *arrhythmogenic cardiomyopathy*. Therefore, the disease is currently called arrhythmogenic cardiomyopathy, ARVC/D, ARVC, or ARVD. In this chapter, the disease is named according to the task force criteria—arrhythmogenic cardiomyopathy (ACM).

The involvement of the left ventricle in ACM had been originally described by Marcus et al[4] and confirmed in several additional studies. Importantly, task force criteria are easy to apply to classical and manifested forms in adults but not in children. Recent studies report that many pediatric patients do not meet the current ACM diagnostic criteria, resulting in delays in diagnosis and treatment. According to pediatric cardiologists, the current criteria need further revision to encompass pediatric manifestations of the disease, suggesting that modified pediatric criteria would facilitate prompt diagnosis and management of ACM and structured research with the goal of improving outcomes.[8]

TABLE 62–1. Arrhythmogenic Cardiomyopathy: Task Force Criteria

Definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor criteria from different categories
Borderline diagnosis: 1 major and 1 minor or 3 minor criteria from different categories
Possible diagnosis: 1 major or 2 minor criteria from different categories

Type I Criteria	Type II Criteria	Type III Criteria	Type IV Criteria	Type V Criteria	Type VI Criteria
Global or Regional Dysfunction and Structural Alterations	Tissue Characterization of Wall	Repolarization Abnormalities	Depolarization/Conduction Abnormalities	Arrhythmias	Family History
Major					

By 2D echo:
• Regional RV akinesia, dyskinesia, or aneurysm
• and 1 of the following (end diastole):
  • PLAX RVOT ≥ 32 mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2)
  • PSAX RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥ 21 mm/m^2)
  • Fractional area change ≤ 33%
By MRI:
• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
• and 1 of the following:
  • Ratio of RV end-diastolic volume to BSA ≥ 110 mL/m^2 (male) or 100 mL/m^2 (female)
  • RV ejection fraction ≤ 40%
By RV angiography:
Regional RV akinesia, dyskinesia, or aneurysm
	• Residual myocytes < 60% by morphometric analysis (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals > 14 years of age (in the absence of complete right bundle branch block QRS ≥ 120 ms)	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	• Nonsustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• ACM confirmed in a first-degree relative who meets current Task Force criteria
					• ACM confirmed pathologically at autopsy or surgery in a first-degree relative
					• Identification of a pathogenic mutation[a] categorized as associated or probably associated with ACM in the patient under evaluation

Minor					

By 2D echo:
• Regional RV akinesia or dyskinesia
• and 1 of the following (end diastole):
  • PLAX RVOT ≥ 29 to < 32 mm (corrected for body size [PLAX/BSA] ≥ 16 to < 19 mm/m^2)
  • PSAX RVOT ≥ 32 to < 36 mm (corrected for body size [PSAX/BSA] ≥ 18 to < 21 mm/m^2)
  • Fractional area change > 33% to ≤ 40%
By MRI:
• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
• and 1 of the following:
  • Ratio of RV end-diastolic volume to BSA ≥ 100 to < 110 mL/m^2 (male) or ≥ 90 to < 100 mL/m^2 (female)
  • RV ejection fraction > 40% to ≤ 45%
	• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Inverted T waves in leads V_1 and V_2 in individuals > 14 years of age (in the absence of complete right bundle branch block) or in V_4, V_5, or V_6
		• Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals > 14 years of age in the presence of complete right bundle branch block
			• Late potentials by SAECG in ≥ 1 of 3 parameters in the absence of a QRS duration of ≥ 110 ms on the standard ECG
			• Filtered QRS duration (fQRS) ≥ 114 ms
			• Duration of terminal QRS < 40 μV (low-amplitude signal duration) ≥ 38 ms
			• Root-mean-square voltage of terminal 40 ms ≤ 20 μV
			• Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle branch block
				• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL), or unknown axis
				• > 500 ventricular extrasystoles per 24 hours (Holter)
					• History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
					• Premature sudden death (< 35 years of age) as a result of suspected ACM in a first-degree relative
					• ACM confirmed pathologically or by current Task Force criteria in second-degree relative

Abbreviations: 2D echo, two-dimensional echocardiography; ACM, arrhythmogenic cardiomyopathy; aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; BSA, body surface area; ECG, electrocardiogram; MRI, magnetic resonance imaging; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RV, right ventricle; RVOT, right ventricular outflow tract; SAECG, signal-averaged electrocardiogram.

[a]A pathogenic mutation is a DNA alteration associated with ACM that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ACM control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

EPIDEMIOLOGY

The prevalence of ACM is estimated to range from 1 in 1000 to 1 in 5000 in the general population.[1-3,9] A small proportion of patients progress to left ventricular (LV) dysfunction with ventricular arrhythmias remaining the clinical hallmark.[10] The prevalence of clinical manifestations is higher in males than in females (3:1) and typically manifests in young adults.[11-12] Of 439 index patients described by Groeneweg et al,[11] only 4 presented before the age of 13 years and none before the age of 10 years. The reasons for delayed manifestation may be related to the time required for completion of intercalated disk maturation or the need for prolonged exposure to exercise.[11]

PATHOBIOLOGY

ACM is an inherited cardiomyopathy, with autosomal dominant inheritance in the majority of cases and recessive inheritance in a minority.[13] Classical right-sided ACM is a genetic disease of the intercalated disks, which are the sites of contact between adjacent myocytes.

Intercalated Disks

Intercalated disks are highly specialized cell-cell junctions; they are the units of electromechanical continuity between cardiac myocytes[14] and are comprised of gap junctions, adherens junctions, and desmosomes (Fig. 62–1).

- *Gap junctions* (nexus, communicating junctions) are located in the lateral parts of the intercalated disks. Gap junctions mediate ionic traffic between adjacent cells and provide the basis for functional cell coupling. Key structural proteins are connexins; the connexins predominantly expressed by cardiac myocytes are Cx43, Cx40, and Cx45.
- *Adherens junctions* (fasciae adhaerentes) are located in the transverse parts of the intercalated disks where the actin filaments of the sarcomeres are anchored and connected with the plasma membrane. This anchorage provides the intercellular "mechanical continuity" between the myocytes supporting the transmission of force between cells and synchronous contraction and relaxation. Key structural proteins are nondesmosomal cadherins that are calcium-dependent transmembrane glycoproteins.
- *Desmosomes* (maculae adhaerentes) are located in both the transverse and lateral parts of the intercalated disks: they reinforce the adherens junctions and fix adjacent cells. Desmosomes bind desmin on the intracellular side, spans the cell membrane, and bind adjacent desmosomes on the extracellular side. Desmosome-forming proteins include plakophilin-2 (PKP2), desmoglein 2 (DSG2), desmocollin 2 (DSC2), plakoglobin (JUP), and desmoplakin (DSP).

Since the first detailed clinical description of ACM,[4] significant advances in imaging, epidemiology, animal models, and protein biochemistry have accelerated our understanding of disease pathogenesis and progression. However, much of our current understanding of ACM pathobiology is derived from genetic findings of rare, yet severe, autosomal recessive forms of cardiocutaneous diseases including Naxos disease and Carvajal disease. For example, Naxos disease, characterized by fully penetrant ACM, wooly hair, and palmoplantar keratoderma,[15] was the first direct evidence for dysfunction in the desmosomal gene product plakoglobin (*JUP*) in ACM (truncation of final 56 residues of protein).[16] Subsequently, desmoplakin (*DSP*) loss-of-function variants that inhibit the ability of desmoplakin to associate with desmin (see below) were implicated in Carvajal syndrome, a cardiocutaneous disease associated with left-dominant cardiac phenotype.[17] Since these original discoveries, advances in gene sequencing have revealed a host of protein pathways now linked with ACM pathogenesis. With rare exceptions, these findings illustrate a crucial role of a key cardiac membrane domain—the desmosome—in ACM pathobiology.

The Cardiac Desmosome

The cardiac desmosome is a central feature of the myocyte intercalated disk, a multifunctional membrane domain essential for both myocyte electrical and structural coupling. The desmosome is primarily composed of three families of proteins including cadherins, plakins, and armadillo proteins. Desmosomal cardiac cadherins are type 1 transmembrane proteins that include desmocollin (encoded by *DSC2*) and desmoglein (encoded by *DSG2*). These proteins span the extracellular space to physically link adjacent cardiomyocytes. The intracellular domains of desmocollin and desmoglein directly associate with plakins and armadillo linker proteins to integrate the membrane with the underlying intermediate filament network. In the heart, these linker proteins are primarily desmoplakin (encoded by *DSP*), plakophilin 2 (encoded by *PKP2*), and plakoglobin (encoded by *JUP*), whereas desmin (encoded by *DES*) is the central component of the intercalated disk intermediate filament network that extends across the length of the myocyte. DSP homodimers connect plakofillin 2 at the amino-terminal domain and desmin at the carboxy-terminal domain. Together, this multiprotein complex has fundamental roles in regulating mechanical force within myocytes and also between adjacent myocytes and myocyte networks.

Notably, the role of the desmosome for normal cardiac function is clearly illustrated by human gene mutations in *PKP2*, *JUP*, *DSP*, *DSG2*, and *DSC2* associated with autosomal dominant ACM.[18] For example, in the United States alone, approximately 50% to 60% of ACM patients harbor a loss-of-function gene variant in at least one of five desmosomal genes.[18] *PKP2* remains the most common ACM gene (45%), with *DSG2* loss-of-function variants present in nearly 10% of human ACM cases.[19] As discussed later in this chapter, approximately 86% of ACM patients harbor a single heterozygous gene variant, 7% show compound heterozygosity, and 7% show digenic heterozygosity (> 1400 variants identified to date; see www.arvcdatabase.info).[18,19] Desmosome and nondesmosome genes reported to date as being associated with ACM are routinely tested and contribute as major criteria to the diagnosis (Table 62–2).

Based on the central role of the cardiac desmosome in regulating inter- and intracellular mechanical forces, ACM pathophysiology has historically been attributed to dysfunction in desmosomal proteins, resulting in structural instability of this critical membrane domain. Thus, in the "degeneration" or "inflammation" models for ACM pathobiology, structurally compromised desmosomes are more sensitive to mechanical strain/forces, resulting in damaged cell-cell junctions, myocyte uncoupling, and ultimately inflammation, fibrosis, necrosis, and potentially adipogenesis.[20-22] These models are supported by multiple lines of evidence, including the following: (1) aberrant myocyte intercalated disk coupling in human ACM samples as observed by electron microscopy[23]; (2) abnormal myocyte intercalated disk widening in mice harboring human ACM variants as observed by electron microscopy[24]; (3) prevalence of ACM phenotypes in conditions of myocardial strain[19]; (4) accelerated ACM phenotypes and increased risk for sudden cardiac death in athletes[25]; (5) impact of disease on right ventricle (thin, distensible wall) versus left ventricle[19]; (6) reduced adhesive strength of cells expressing small interfering RNAs that silence selective desmosomal proteins[26]; and (7) accelerated ACM phenotypes in animal models harboring mutant desmosome genes following mechanical stress.[27,28] However, not all data necessarily support loss of cell adhesion in disease pathogenesis. For example, Hariharan et al[29] indicated that although neonatal rat ventricular myocytes deficient in plakoglobin or plakophilin showed reduced cell-cell adhesion, these same cultures expressing human ACM plakoglobin or plakophilin

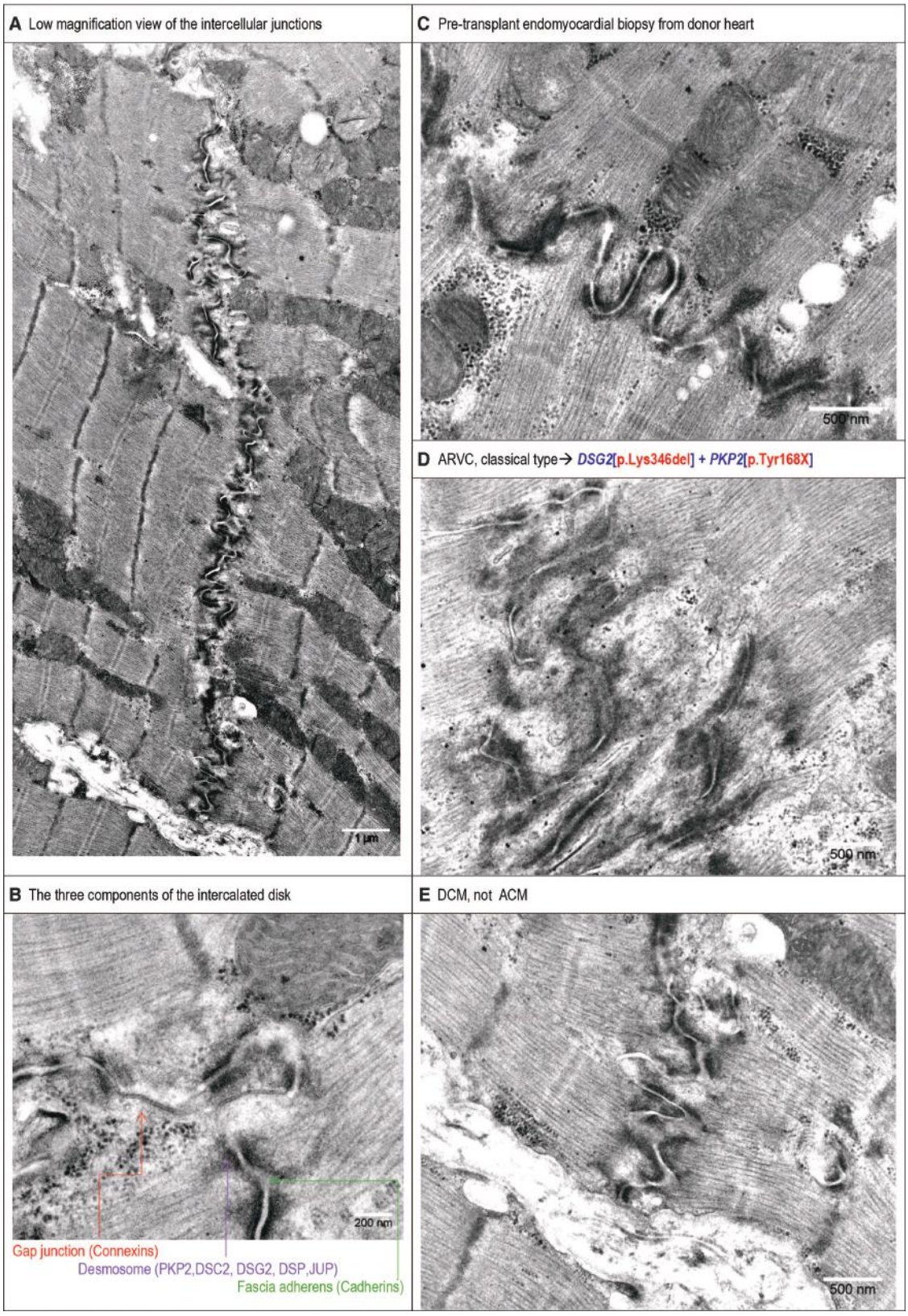


FIGURE 62–1. Electron micrographs showing myocyte intercalated disks. **A.** Low magnification view of two intercellular junctions (bar scale = 1 µm). **B.** The three components of the intercalated disk: the gap junction (*red arrow and text*); the desmosome (*violet arrow and text*); and the fascia adherens (*green arrow and text*) (bar scale = 200 nm). **C.** Normal heart: pretransplantation endomyocardial biopsy from donor heart (bar scale = 500 nm). **D.** Classic arrhythmogenic right ventricular cardiomyopathy (ARVC): abnormal intercalated disk. The disease is associated with double mutation in *DSG2* (p.Lys346del) and *PKP2* (p.Tyr168X) (bar scale = 500 nm). **E.** Dilated cardiomyopathy (DCM): intercalated disk (bar scale = 500 nm).

TABLE 62–2. Nuclear Genes Associated (in at least one published family) With ACM, Including Those That May Also Cause HCM, RCM, and LVNC

A	F	B	C	D	E	F
Genes	MIM[a] Gene	Protein	Disorder	Phenotypes/Diseases Allelic at the Same Locus	Inheritance	MIM[a] Gene
ADAM17	603639	Tumor necrosis factor alpha converting enzyme	ACM	Inflammatory skin and bowel disease, neonatal, 1	AR	603639
CTNNA3	607667	Alpha 3-catenin	ACM, DCM		AD	607667
DES	125660	Desmin	ACM, DCM, HCM, RCM	Des-related myofibrillar myopathy, neurogenic scapuloperoneal syndrome, Kaeser type; AVB, ↑ sCPK	AD, AD	125660
DSC2	125645	Desmocollin 2	ACM, DCM	With and without mild palmoplantar keratoderma and wooly hair	AD	125645
DSG2	125671	Desmoglein 2	ACM, DCM		AD	125671
DSP	125647	Desmoplakin	ACM, DCM	DCM with with wooly hair, keratoderma, and tooth agenesis; DCM with wooly hair and keratoderma; lethal acantholytic epidermolysis bullosa; keratosis palmoplantaris striata II; skin fragility–wooly hair syndrome	AD, AR	125647
JUP (*DP3*)	173325	Plakoglobin, desmoplakin III	ACM, DCM	Naxos traits	AD, AR	173325
LMNA	150330	Lamin A/C	ACM, DCM, LVNC	DCM with conduction disease plus 11 additional phenotypes; AVB; possible ↑ sCPK; 12 phenotypes allelic at the same locus	AD, AR	150330
PLN	172405	Phospholamban	ACM, DCM, HCM		AR	172405
PKP2	602861	Plakophilin 2	ACM, DCM		AD	602861
RYR2	180902	Ryanodine receptor 2	ACM, DCM, LVNC	Ventricular tachycardia, catecholaminergic polymorphic 1	AD	180902
TGFB3	190230	Transforming growth factor beta 3	ACM, DCM	Rienhoff syndrome or Loeys-Dietz syndrome 5	AD	190230
TMEM43	612048	Transmembrane protein 43	ACM, DCM	Emery-Dreifuss muscular dystrophy	AD	612048
TTN	188840	Titin	ACM, DCM, HCM	Limb-girdle muscular dystrophy; early-onset myopathy with fatal cardiomyopathy; proximal myopathy with early respiratory muscle involvement; tardive tibial muscular dystrophy	AD, AR	188840

Note. Columns A and C show genetic heterogeneity. Cardiologists should be aware that genes that cause ACM may also cause other diseases/syndromes (column D). The fact that genes causing ACM may also cause other types of cardiomyopathy does not give the proportion of genes associated with the different cardiomyopathies. Genetic epidemiology of cardiomyopathies is not complete.

[a]OMIM (http://www.omim.org/); last accessed July 2, 2016.

Abbreviations: ACM, arrhythmogenic cardiomyopathy; AD, autosomal dominant; AR, autosomal recessive; AVB, atrioventricular block; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MIM, Mendelian Inheritance in Man; RCM, restrictive cardiomyopathy; sCPK, serum creatine phosphokinase.

loss-of-function mutations displayed no significant differences in cell-cell adhesion. However, these same mutant myocytes displayed sheer stress phenotypes that were reversed by inhibition of glycogen synthase kinase 3β (GSK3β).[29] Further, Asimaki et al[30] have consistently identified decreased plakoglobin junctional expression in ACM samples, supporting the complexity of the disease, the variability in phenotypic penetrance/expressivity,[19] and the likelihood of secondary contributing pathogenic signaling mechanisms, as described below.

More recently, a second, yet non–mutually exclusive model for ACM pathobiology has emerged that frames the desmosome as a multifunctional signaling node for the myocyte. Specifically, the second model converges on nonjunctional transcriptional pathways mediated by the Wnt (wingless-related integration site) axis. In this model, in the nondiseased heart, baseline Wnt signaling is critical for normal cardiogenic transcriptional signaling.[18] This signaling is mediated by regulation of T-cell factor/lymphoid enhancer factor (Tcf/Lef) transcription factors by nuclear β-catenin (β-catenin is also found at cell junctions at baseline).[18] Also central to this model is the localization of junctional plakoglobin. In nondiseased heart, plakoglobin is concentrated at the intercalated disk membrane.[18] In fact, nonmembrane (cytosolic) populations of plakoglobin are maintained at low concentrations by ubiquitination and proteasomal degradation.[18] Although the precise mechanisms are still being elucidated, it is now thought that in ACM, compromised junctional infrastructure increases the cytosolic pool of plakoglobin. Ultimately, diffusion of this pool into the nucleus is proposed to suppress β-catenin/Wnt signaling to transition procardiogenic transcriptional signaling to transcriptional programming favoring inflammation, apoptosis, and adipogenesis.[31] Notably, expression, activity, and translocation of β-catenin are central to this pathway. Outstanding questions related to this model are the relative levels of junctional/cytosolic/nuclear plakoglobin and β-catenin at baseline and in disease, the impact of the local signaling environment (eg, activity of GSK3β on plakoglobin/β-catenin), the relative half-lives of plakoglobin/β-catenin in disease, and the specific roles/downstream targets of Tcf/Lef transcriptional signaling based on nuclear plakoglobin/β-catenin concentrations.

The impact of altered Wnt signaling in ACM pathogenesis was first described by Lombardi et al.[32] Mice lacking *Dsp* expression display suppression of the β-catenin/Wnt pathway favoring apoptosis, fibrosis, and adipogenesis.[32] In further support of this model, altered desmoplakin expression in a human-derived cardiomyocyte cell line alters plakoglobin nuclear translocation, ultimately altering β-catenin/Tcf/Lef

transcriptional signaling and adipogenesis.[31] Moreover, Wnt signaling is reduced in mice expressing a mutant form of plakoglobin lacking the C-terminus, resulting in nuclear plakoglobin translocation and adipogenesis.[32] Finally, in seminal work from the Marion Laboratory, fate-mapping techniques identified a select population of cardiac progenitor cells as the primary source of adipocytes in the heart.[33] These foundational data have sparked a wealth of studies that have elucidated new and unanticipated signaling pathways in the heart likely related to ACM pathogenesis.[34] Further, this work has suggested that ACM is a disease of multiple cardiac cell types, an observation that may further explain the variability in clinical presentation and disease progression.

Nondesmosomal Proteins

Although ACM pathogenesis has largely been attributed to dysfunction of the desmosome, new protein pathways associated with ACM continue to add to our understanding of disease pathophysiology. Mutations in junctional nondesmosomal proteins, intermediate filaments, nonjunctional proteins, sarcomeric proteins, membrane-anchored proteins, and adipogenic factors have been reported in patients with ACM phenotypes (often described as overlapping syndromes).

αT-catenin3 (CTTNA3) is a cell adhesion molecule. In cardiac intercalated disks, CTNNA3 is a component of the adherens junction, or area composita. Mice with deletion of the *Ctnna3* gene (αT-catenin–null mice) develop progressive cardiomyopathy. The loss of αT-catenin does not seem to affect adherens junction and desmosomal proteins; the exception is the desmosomal protein PKP2. In fact, immunogold labeling at the intercalated disk demonstrates preferential reduction of PKP2 at the area composita compared with the desmosome.[35] The p.Val281Asp (c.281T > A) and c.2293_2295delTTG (p.del765Leu) mutations have been identified in two probands with ACM[36]; yeast two-hybrid and cell transfection experiments suggested a causal relationship between *CTNNA3* mutations and ACM.

The desmin (*DES*) gene encodes a muscle-specific class III intermediate filament. Homopolymers of this protein form an intracytoplasmic filamentous network connecting myofibrils to each other and to the plasma membrane. *DES* mutations are associated with restrictive cardiomyopathy, desmin-related myopathy, a familial cardiac and skeletal myopathy, and distal myopathies. Searching for the genetic cause of autosomal dominant myofibrillar myopathy with ACM in a Swedish family, Hedberg et al[37] identified the p.(Pro419Ser) Ser mutation in the *DES* gene. In a series of 91 ACM index cases (including 53 negative and 38 positive for mutations in desmosomal genes), mutations in the *DES* gene were found in two cases: (1) the p.(Lys241Glu) substitution was detected in one patient who also carried the p.(Thr816ArgfsX10) mutation in the *PKP2* gene; and (2) p.(Ala213Val) was found in a second patient and was not associated with mutations in the desmosomal genes.[38] The *LMNA* gene encodes lamin A/C, which is a major structural component of the nuclear lamina. *LMNA* mutations are associated with different phenotypes (see Chap. 58). *LMNA* mutations were identified in 4 of 108 patients with ACM phenotype (borderline in 27 and definite in 81); three patients had severe RV involvement.[39] During follow-up, there were two sudden deaths and one death from congestive heart failure. These three patients had conduction abnormalities on resting 12-lead ECG. Myocardial tissue from two patients showed myocyte loss and fibrofatty replacement, and one patient had reduced/absent PKP2 staining of the intercalated disks in the myocardium.[39] Dilated cardiomyopathy (DCM)/ACM overlapping phenotype may be observed in patients who carry *LMNA* mutations[40] and in patients with ACM and Charcot-Marie-Tooth phenotype.[41]

The transmembrane protein 43 (*TMEM43*) gene encodes an inner nuclear membrane protein termed LUMA that interacts with lamin A/C and emerin. The missense mutation c.1073C>T (p.(Ser358Leu)) in *TMEM43* causes ACM and was identified in a founder population from Newfoundland. The p.(Ser358Leu)-associated phenotype is highly malignant and is characterized by poor R-wave progression, early ventricular ectopy, LV dilatation, heart failure, and early death.[42,43] *TMEM43* mutations, including p.(Ser358Leu), have been identified in individuals not from Newfoundland.[44] Further studies confirmed that *TMEM43* ACM subtype is a sex-influenced lethal ACM, with a unique ECG finding, LV dilatation, heart failure, and early death. The genetic presymptomatic diagnosis has the greatest clinical utility.[45] *TMEM43* sequencing is now incorporated into clinical genetic testing for ACM patients.[46,47] *TMEM43* protein is active in an adipogenic pathway regulated by PPARγ (an adipogenic transcription factor); this may explain the fibrofatty replacement of the myocardium. The pathogenetic mechanisms of this mutation are poorly understood. Mutant *TMEM43* exhibits normal cellular localization and does not disrupt integrity and localization of other nuclear envelope and desmosomal proteins.[47]

The phospholamban (*PLN*) gene encodes a protein that is a major substrate for the cAMP-dependent protein kinase in cardiac muscle and inhibits cardiac muscle sarcoplasmic reticulum Ca^{2+}-ATPase in the unphosphorylated state; inhibition is relieved by phosphorylation of the protein. Mutations in this gene cause ACM, DCM with refractory congestive heart failure, and familial hypertrophic cardiomyopathy.[48,49]

The ryanodine receptor-2 (*RYR2*) gene encodes a receptor located in cardiac muscle sarcoplasmic reticulum. The protein is a component of a calcium channel that is constituted of a tetramer of the ryanodine receptor proteins and a tetramer of FK506-binding protein 1B proteins, which supplies calcium to cardiac muscle. Mutations in this gene are more commonly associated with stress-induced polymorphic ventricular tachycardia and less commonly with ARVD (9% of ACM probands).[50,51]

The titin (*TTN*) gene encodes a large abundant protein of striated muscle. The protein is divided into two regions, an N-terminal I-band and a C-terminal A-band. Mutations in this gene are associated with DCM; familial hypertrophic cardiomyopathy; limb-girdle, type 2 muscular dystrophy; early-onset myopathy with fatal cardiomyopathy; proximal myopathy with early respiratory muscle involvement; and tardive tibial muscular dystrophy. In a screening study including 39 ACM families, 13% (5 of 39 families) carried *TTN* rare variants (11 affected subjects).[52] *TTN* variants were further investigated and were identified in seven families; the prominent Thr2896Ile mutation showed complete segregation with the ACM phenotype in one large family. This mutation affects a highly conserved immunoglobulin-like fold located in the spring region of titin and reduces the structural stability and increases the propensity for degradation of the immunoglobulin-like domain. Carriers of *TTN* mutations demonstrated history of sudden death (5 of 7 families), progressive myocardial dysfunction ending in death or heart transplantation (8 of 14 cases), frequent conduction disease (11 of 14 cases), and incomplete penetrance (86%).[53]

The transforming growth factor-β3 (*TGFB3*) gene encodes a secreted member of the TGF-β family that is involved in embryogenesis and cell differentiation.[54] Typically, *TGFB3* mutations cause Loeys-Dietz syndrome type 5. However, mutation screening of the promoter and untranslated regions (UTRs) of the *TGFB3* gene identified a nucleotide substitution (c.–36G>A) in the 5′ UTR of the gene invariably associated with the classical, right-sided ACM phenotype and an additional mutation (c.1723C>T) in the 3′ UTR of one proband. Both nucleotide changes were absent in control subjects. In vitro expression assays with constructs containing the mutations showed that mutated UTRs were two-fold more active than wild-types.

ADAM17 (a disintegrin and metalloproteinase 17 or tumor necrosis factor-α converting enzyme) sheds a number of ligands by cleavage of substrates (eg, ligands for the epidermal growth factor receptor and

tumor necrosis factor-α) in the juxtamembrane region, plays a role in ligand-independent Notch signaling, and sheds cell adhesion molecules including DSG2.[55] A homozygous loss-of-function *ADAM17* mutation causes the autosomal recessive neonatal inflammatory skin and bowel disease type 1, which is characterized by severe skin inflammation, increased susceptibility to infection, bowel inflammation, and cardiomyopathy. The cardiomyopathy and other phenotypes in this syndrome may be related, in part, to impaired *ADAM17*-mediated DSG2 processing.[56]

CLINICAL PRESENTATION

ACM is an underrecognized clinical entity that is associated with sudden cardiac death (SCD) in young people, particularly athletes.[57,58] In those aged ≤ 35 years, ACM accounts for 11% of cases of SCD overall and 22% of cases in young athletes.[57] The annual mortality in patients with ACM is reported to be as high as 2.3%.[59] Several studies have suggested a male predominance[60,61]; however, more recent studies have demonstrated no sex differences in terms of prevalence or clinical presentation.[11,62-64]

Those with ACM typically present between the second and fifth decades of life.[58] Symptoms are heterogeneous but most commonly reflect the presence of ventricular arrhythmias, which can range from isolated premature ventricular contractions (PVCs) to sustained ventricular tachycardia (VT). Supraventricular arrhythmias also occur in 14% of ACM patients, with atrial fibrillation being the most frequently reported.[65] In a study of 129 probands, symptoms on presentation included palpitations in 56%, dizziness in 29%, syncope in 26%, chest pain in 19%, and cardiac arrest in 22%.[64] Symptoms related to right heart failure are present in 6%.[59] These findings are consistent with other studies.[3,58,66,67]

ACM has the following three phases of pathophysiologic progression (Fig. 62–2).[66]

1. *Concealed stage*: Individuals are asymptomatic but potentially exposed to the risk of life-threatening arrhythmias during exertion. Diagnostic studies, including ECG, ambulatory monitoring, and imaging, may be normal.
2. *Electrical stage*: Electrical myocardial changes occur leading to minor ECG changes and increased risk of ventricular arrhythmias, which may manifest as symptomatic PVCs or VT on ambulatory monitoring. Hence, individuals have an increased risk of SCD. Subtle myocardial changes may also be present; however, RV dysfunction is not apparent.
3. *Structural stage*: There is progressive fibrofatty infiltration with loss of normal ventricular myocardium, which increases the risk of ventricular arrhythmias and SCD. Structural changes are apparent with RV dilatation and aneurysm formation. RV, LV, or biventricular dysfunction may occur depending on the extent of structural abnormalities[67] (Figs. 62–3 and 62–4).

Alternatively, the natural history of classical right-sided ACM can be divided into four stages in which the concealed and electrical stages are similarly defined but the structural stage distinguishes the overt RV failure with overall preserved LV function from the final phase, which is marked by overt LV involvement and biventricular heart failure.[10] The left-dominant ACM is characterized by primary (but not necessarily exclusive) LV involvement, and biventricular ACM is defined by early and parallel involvement of both ventricles.

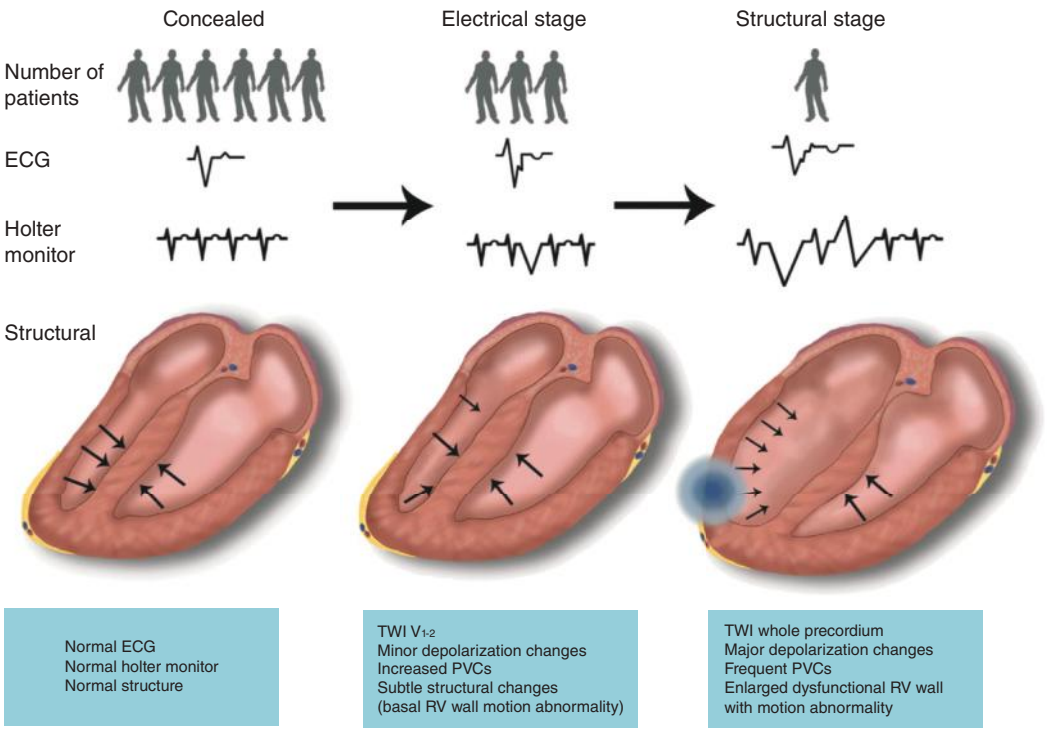


FIGURE 62–2. Three phases of arrhythmogenic right ventricular cardiomyopathy/dysplasia disease progression. ECG, electrocardiogram; PVC, premature ventricular contraction; RV, right ventricle; TWI, T-wave inversion. Reproduced with permission from te Riele AS, James CA, Rastegar N, et al. Yield of serial evaluation in at-risk family members of patients with ARVD/C. *J Am Coll Cardiol*. 2014 Jul 22;64(3):293-301.[66]

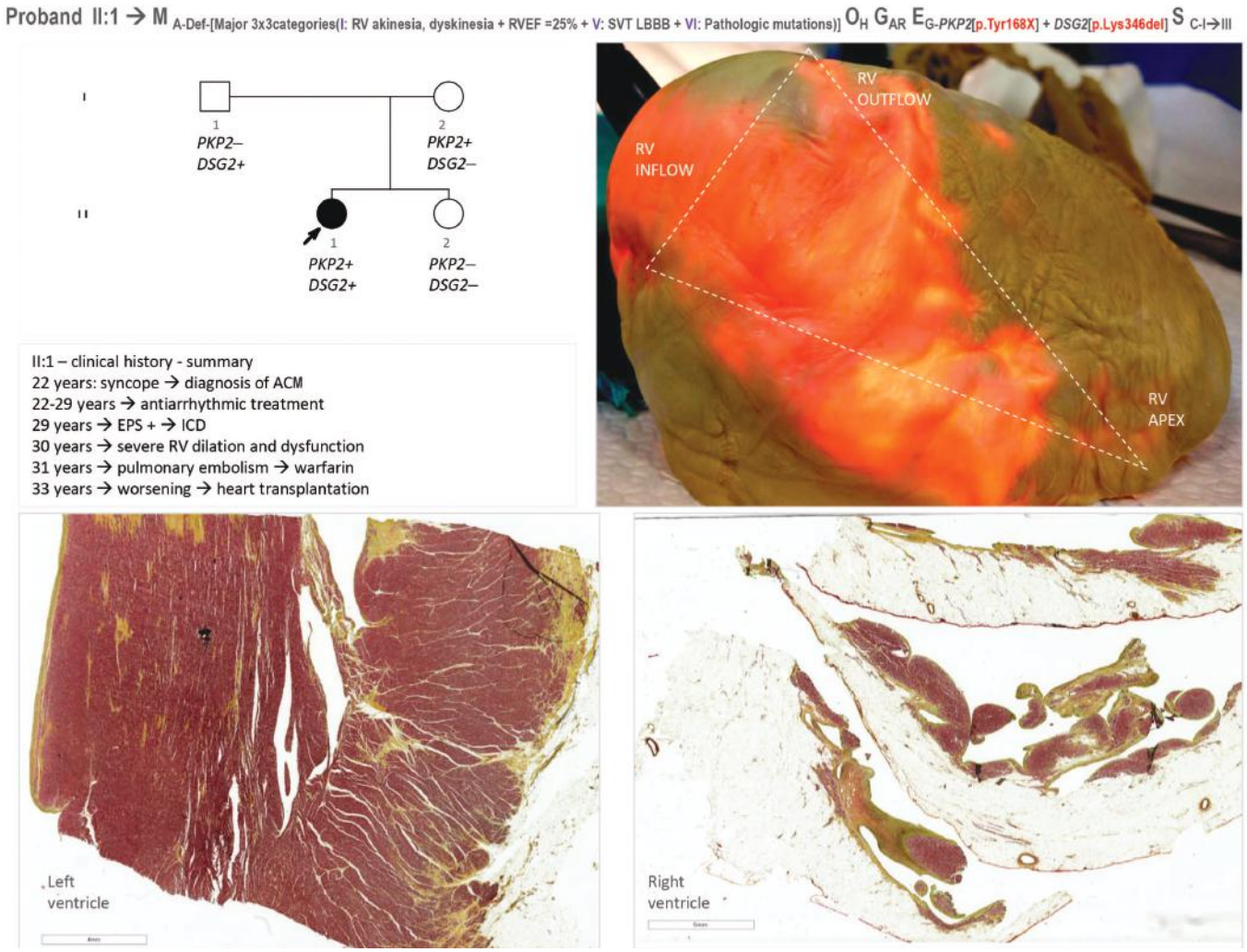


FIGURE 62–3. The figure shows the pedigree, the short summary of the clinical history of the proband, the macroscopic view of the right ventricle (the triangle of dysplasia is outlined with the *dashed white line*), and the low-magnification view of the left and right ventricle (Movat pentachrome).

Naxos disease and Carvajal syndrome are distinctive forms of ACM that are inherited in an autosomal recessive manner in association with extracardiac manifestations including wooly hair and plantopalmar keratoderma.[68] Carvajal syndrome is a variant of Naxos disease with predominant LV involvement.

EVALUATION AND DIAGNOSIS

As a result of variable phenotypic expression, diagnosis is obtained from multiple diagnostic modalities that are used to satisfy major and minor criteria established by the International Task Force.[7] The diagnostic modalities and criteria used for the diagnosis of ACM as part of the 2010 revised Task Force Criteria are reviewed below. The diagnosis requires fulfillment of certain major and minor criteria, as shown in Table 62–1.

- A definite diagnosis of ACM is established when two major, or one major and two minor, or four minor criteria from different categories are fulfilled.
- Borderline cases are defined as meeting one major and one minor or three minor criteria from different categories.
- Possible ACM is established when one major or two minor criteria from different categories are met.

12-Lead Electrocardiogram

Repolarization abnormalities consisting of T-wave inversion (TWI) in leads V_1 through V_3 or beyond occur in 87% of patients with ACM but in only < 3% of young healthy adults.[69,70] The sensitivity and specificity of TWI in V_1 through V_3 for ACM, in the absence of a right bundle branch block (RBBB), are 71% and 96%, respectively.[71] The sensitivity and specificity of TWI in V_1 through V_3 in the presence of an RBBB are suboptimal. In this situation, TWI in V_1 through V_4 improves the sensitivity and specificity for ACM. A similar pattern of TWI inversion in the precordial leads may be seen in asymptomatic athletes.[72] This finding lacks specificity in this population, and other criteria need to be carefully evaluated prior to establishing a diagnosis of ACM.

As a result of structural remodeling, electrical conduction through the RV is abnormal and delayed. This results in characteristic ECG abnormalities including delayed terminal activation of the S-wave upstroke in the right precordial leads. A prolonged S-wave upstroke ≥ 55 milliseconds (measured from the nadir of the S wave to end of QRS)

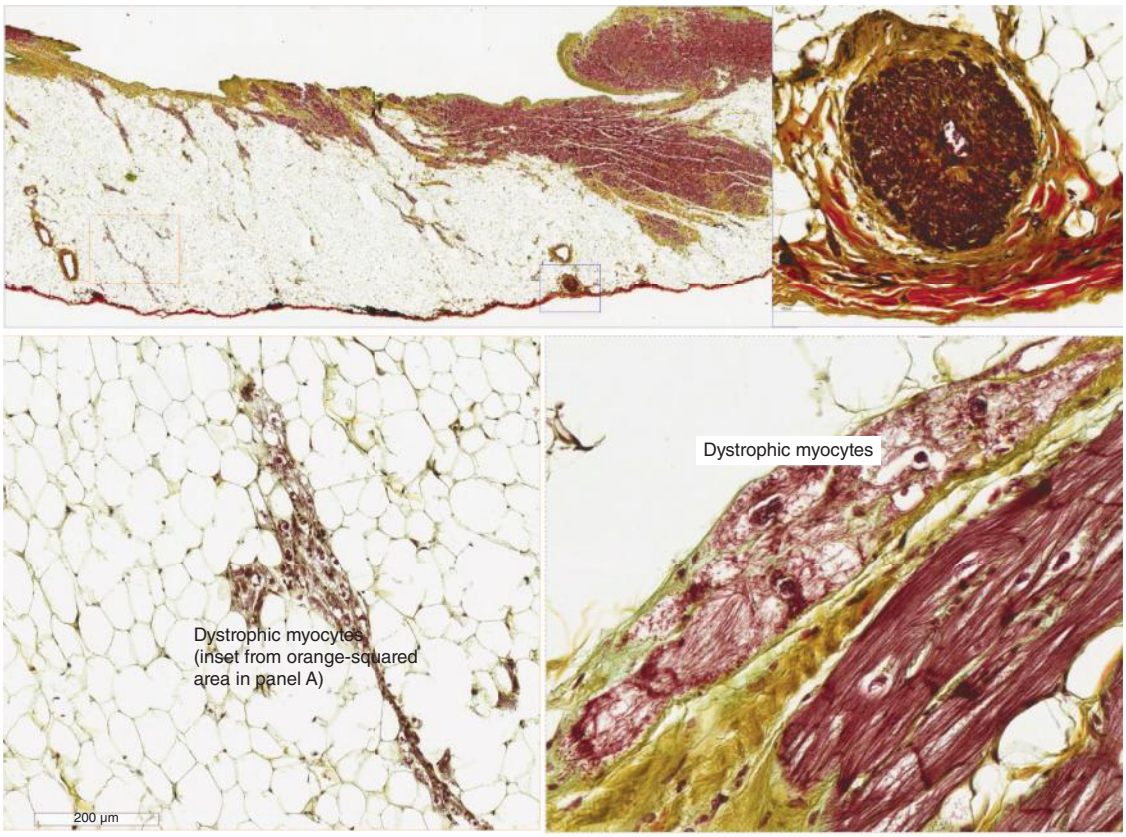


FIGURE 62–4. The figure shows the right ventricular wall of the heart excised at transplantation from the patient who is a carrier of the *DSG2* (p.Lys346del) and *PKP2* (p.Tyr168X) mutations. The blue-bordered panel shows a small epicardial arteriolar vessel with severe intimal hyperplasia and luminal subocclusion; this panel corresponds to the blue-bordered inset in the prior figure. The orange-bordered panel shows a few residual dystrophic myocytes (corresponding to the orange-bordered inset of the first panel), which are shown in the right lower panel at higher magnification. ACM, Arrhythmogenic Cardiomyopathy; EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; RV, right ventricular.

in leads V_1 through V_3 is present in 95% of patients with ACM and only about 2% of normal individuals.[69] The presence of delayed terminal activation cannot be interpreted on ECG when an RBBB is present. Epsilon waves, which are low-amplitude signals that represent late potentials, may be seen in between the QRS and T waves in the right precordial leads[69,71] and represent a major criterion for the diagnosis of ACM (Fig. 62–5).

ECG may also demonstrate ventricular arrhythmias, particularly PVCs and rarely nonsustained VT. These typically have a left bundle branch block (LBBB) morphology and may have an inferior axis (similar to patients with idiopathic right ventricular outflow tract [RVOT] VT) or superior axis in the inferior leads. Ventricular arrhythmias with an LBBB morphology and a superior axis in a young adult should raise suspicion for ACM.

Signal-Averaged Electrocardiogram

Signal-averaged ECG (SAECG) averages multiple QRS complexes to improve the signal-to-noise ratio and improve detection of late potentials. Although now infrequently used, detection of late potentials by SAECG is a minor criterion in current revision of the Task Force criteria.[7] Late potentials are considered to be present if one or more of the following three abnormal findings are present[7,73]: filtered QRS duration ≥ 114 milliseconds, duration of terminal QRS < 40 µV is ≥ 38 milliseconds, or root-mean-square voltage of terminal 40 milliseconds is ≤ 20 µV. Late potentials may also be present in other disease processes that cause myocardial scar, and normally, SAECG is considered positive if two of three of the above criteria are present. However, in ACM, the sensitivity and specificity are similar whether one or more of the abnormalities are present.[7] Therefore, the current Task Force criteria require that only one of the three abnormalities in the SAECG be present.

Ventricular Arrhythmias

Ventricular arrhythmias are an important manifestation of ACM, with 48% of individuals presenting with fatal or near-fatal events.[3] Frequent PVCs and VT occur in 67% and 77% of patients, respectively. Following an established diagnosis, up to 41% of patients will experience sustained monomorphic VT or polymorphic VT/ventricular fibrillation (VF) over 3 years of follow-up.[74] As previously stated, the morphology of VT is typically LBBB and may have an inferior or superior axis. Holter monitoring is beneficial in establishing the etiology of symptoms and to assess PVC burden; however, it is less useful in determining the morphology of the ventricular ectopy as a result of a limited number of leads. A burden of > 500 PVCs per 24 hours is a minor criterion for ACM.

Cardiac Imaging

RV angiography, transthoracic echocardiography, and cardiac magnetic resonance imaging (CMRI) can be used to evaluate for structural

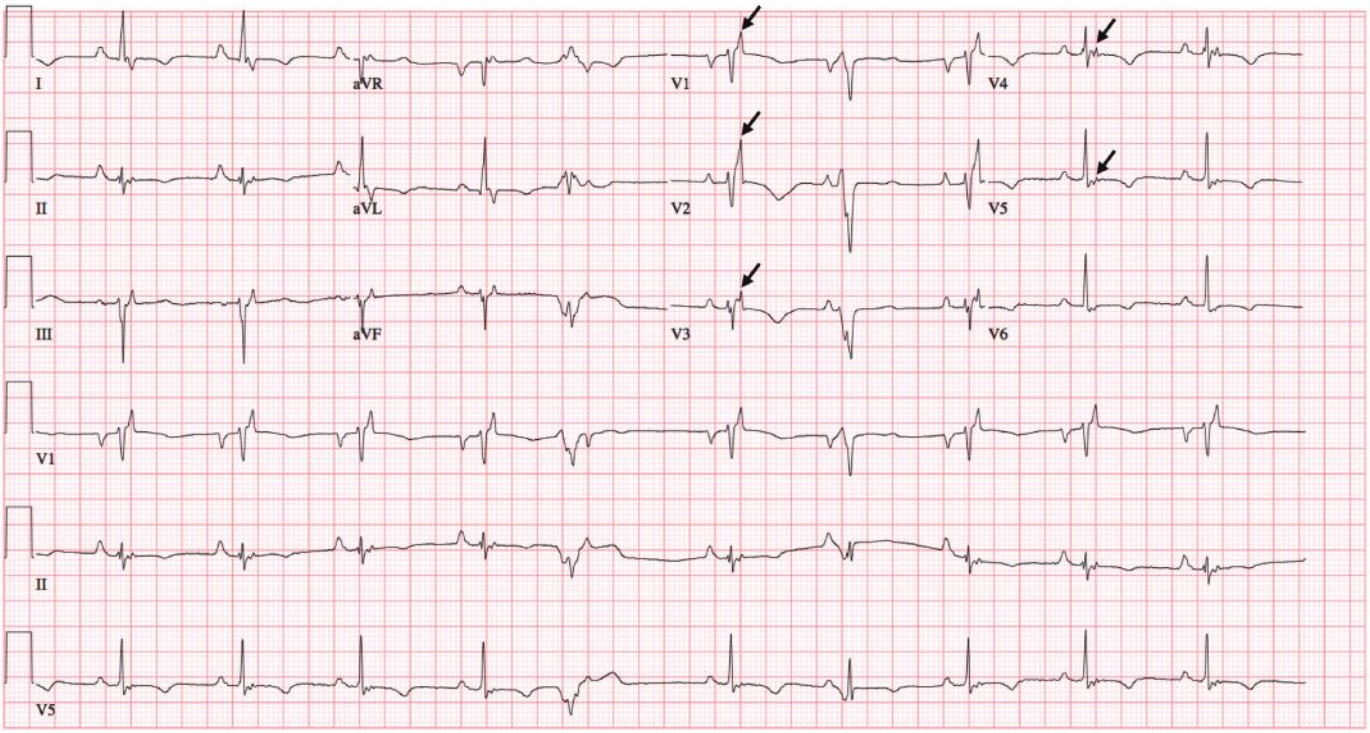


FIGURE 62–5. Baseline 12-lead electrocardiogram in a patient with arrhythmogenic cardiomyopathy (ACM) and sustained ventricular tachycardia. T-wave inversion can be seen in all precordial leads (V_1 to V_6). There are large epsilon waves seen in precordial leads V_1 to V_3 (arrows). These are large in amplitude in V_1 to V_3 and give the appearance of an R′ and right bundle branch block in these leads. These correspond with the lower amplitude signals in V_3 and V_4 (*arrows*). The fifth QRS complex is a premature ventricular contraction with left bundle branch block morphology and superior axis, which are commonly seen in ACM. The seventh complex is a fusion beat.

and functional abnormalities of the RV. RV angiography, although rarely performed, may demonstrate regional RV wall abnormalities including dyskinesia, akinesia, or aneurysm formation. Transthoracic echocardiography is more commonly used, and in addition to providing information on regional wall abnormalities, it can provide information regarding RV dimensions and function. In a study of ACM probands, Yoerger et al[75] demonstrated that RV dimensions were significantly larger and RV function, as measured by fractional area change, was significantly decreased in probands compared to controls. The RVOT was the most commonly enlarged area, and RV morphologic changes were present in many probands, with excessive trabeculations seen in 54%, hyperreflective moderator band seen in 34%, and sacculations seen in 17% of ACM probands but not controls (Fig. 62–6). Quantitative measures of RVOT enlargement and RV function were instituted in the current revision of the Task Force criteria (Table 62–1). Major criteria values were selected to yield a specificity of > 95%, and minor criteria values were selected to yield a sensitivity equal to specificity.[7]

Echocardiography provides a relatively limited assessment of RV structure and function as a result of the inherent limitation in assessing a complex three-dimensional chamber with limited two-dimensional views. These limitations are overcome with CMRI, which can provide a superior assessment of regional and global function as well as provide information on tissue

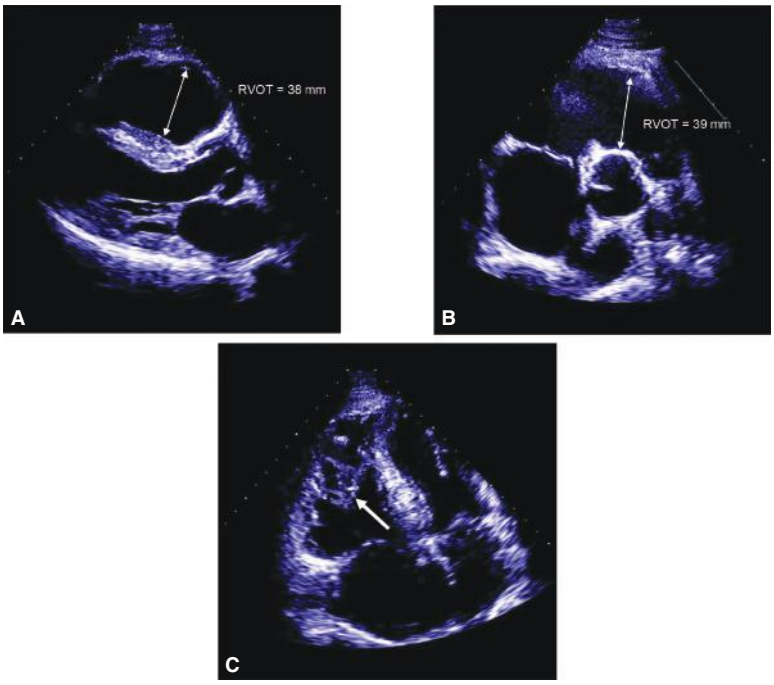


FIGURE 62–6. Transthoracic echocardiogram of a patient with Task Force criteria for definite arrhythmogenic cardiomyopathy (ACM). (**A**) The parasternal long axis view demonstrates that the right ventricular outflow tract (RVOT) measures 38 mm, and (**B**) the parasternal short axis view demonstrates a measurement of 39 mm for the RVOT. These measurements demonstrate an enlarged RVOT and, together with a dyskinetic segment of the RV, fulfill a major Task Force criterion. (**C**) The apical four-chamber view demonstrates a markedly enlarged RV with excessive trabeculation (*arrow*), which is characteristic of ACM.

characteristics (ie, fibrosis and intramyocardial fat).[76,77] A recent study comparing CMRI versus echocardiography demonstrated that only 50% of patients with imaging-positive CMRI had echocardiographic criteria for ACM.[78] Tissue characterization by CMRI and longer follow-up confirm three patterns of disease expression[67]:

1. *Classic*: Predominant RV involvement with little or no LV involvement
2. *Left dominant*: Mostly LV involvement with little RV involvement
3. *Biventricular*: Both RV and LV are equally affected

CMRI has also shown that the RV apex, which together with the RV inflow tract and outflow tract has been historically described as the *triangle of dysplasia*,[4] is only involved in advanced stages of the disease.[79] The triangle of dysplasia involves the epicardial subtricuspid region, RV basal anterior wall, and posterolateral LV, with the RV apex being mostly spared.[79]

Although CMRI has emerged as the preferred imaging modality for ACM, it is also one of the most common reasons for misdiagnosis. Common pitfalls include misinterpretation of variants of normal RV wall motion and inaccurate interpretation of intramyocardial fat infiltration.[80] It is important to note that in pediatric ACM patients, intramyocardial fat infiltration and myocardial fibrosis are uncommon findings by CMRI.[81]

Endomyocardial Biopsy

Endomyocardial biopsy is rarely performed but may be helpful in establishing a diagnosis of ACM when the etiology of cardiomyopathy or structural changes are unclear. The American College of Cardiology/American Heart Association consensus guidelines give a Class IIa (Level of Evidence C) indication for endomyocardial biopsy in patients with heart failure when a specific diagnosis is suspected that would influence therapy.[82] The demonstration of fibrofatty infiltration with loss of normal RV myocardium supports the diagnosis (Table 62–1).[7,83] There is a high rate of false negatives and low sensitivity as a result of the patchy nature of disease and predilection for specific areas of the RV.[83] Thus, conventional RV septal wall or LV biopsies are not helpful because these areas are commonly spared. Diagnostic yield may be improved by using electroanatomic voltage mapping to guide biopsy.[84] However, there is increased risk of cardiac perforation and tamponade with RV free wall biopsy.

FAMILY HISTORY AND GENETIC TESTING

The genetic bases of ACM are reviewed in the pathobiology section of this chapter. The predominant inheritance pattern is autosomal dominant with variable penetrance and expressivity, although an autosomal recessive inheritance pattern has been described with the cardiocutaneous syndromes of Naxos disease and Carvajal syndrome.[68] Approximately 60% of probands will have an identifiable pathogenic mutation.[11] Identification of a pathogenic mutation on genetic testing is a major criterion for the diagnosis of ACM (Table 62–1).[7] Currently, one of the major roles of genetic testing in ACM is for mutation-specific screening of family members following the identification of a pathogenic mutation in the proband. The Heart Rhythm Society and European Heart Rhythm Association expert consensus guidelines give this indication a Class I recommendation.[85] Although genetic testing may be useful for confirmed cases (Class IIa) or considered for borderline cases (Class IIb), it is not recommended (Class III) for those fulfilling only a single minor Task Force criterion.[85] The clinical genetic and molecular workup in the proband and his or her family should be performed as in other familial cardiomyopathies and include clinical and genetic screening of first-degree relatives (see Chap. 9). The major difference between ACM and other cardiomyopathies is that in the Task Force criteria, a "first-degree relative who meets current Task Force criteria" is defined as possibly affected. The same diagnosis, possible ACM, is formulated when "a pathogenic mutation categorized as associated or probably associated with ACM is found in the patient under evaluation."[7] In non-ACM cardiomyopathies, relatives of affected members are usually not considered as possibly affected, and clinically healthy carriers of pathologic mutations are usually defined as "healthy carriers" and not possibly affected. The difference may appear semantic; however, the impact of pathologic mutations in ACM is higher than in other genetic cardiomyopathies.

A positive family history of ACM is a risk factor for disease, with over a third of family members of affected individuals developing disease.[11,86,87] The cumulative 5-year and 10-year probabilities of developing ACM in first-degree family members are 7% and 21%, respectively, with siblings of probands having a three-fold higher risk compared to parents or children.[86] Pathogenic mutations are identified in 36% to 72% of selected family members, and up to 40% of these individuals will fulfill Task Force criteria for ACM.[11,88] Disease will still occur in 18% of those who are mutation negative.[11] Additionally, the presence of symptoms or the occurrence more than one genetic variant in family members increases the likelihood of Task Force criteria–confirmed disease.[11,86,88] The constellation of findings highlights the complexity of the genetics of ACM and firmly support the screening of family members of affected individuals (Figs. 62–7 and 62–8).

OTHER DIAGNOSTIC MODALITIES

Although not part of the Task Force criteria for diagnosis of ACM, isoproterenol and exercise testing have recently demonstrated potential benefit in the workup of selected individuals.[89,90] The diagnostic value of isoproterenol was evaluated in a recent study of 412 consecutive patients referred to a tertiary center for PVCs or suspected ACM.[89] Isoproterenol infusion of 45 μg/min was administered for 3 minutes, and the test was considered positive if there were polymorphic PVCs with one or more couplet or sustained/nonsustained VT with LBBB excluding outflow tract morphology. The test was positive in 91% of patients with ACM versus 11% in others ($P < .0001$). During a mean follow-up of 5.6 years, six patients who did not initially have ACM were subsequently diagnosed with disease. Interestingly, all six patients had positive isoproterenol tests. The sensitivity, specificity, positive predictive value, and negative predictive value were 91.4%, 88.9%, 43.2%, and 99.1%, respectively. These promising results need confirmation by other investigators prior to widely recommending this test.

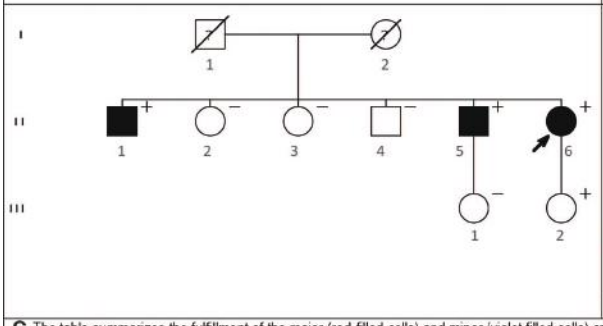
When comparing asymptomatic gene carriers versus healthy controls, exercise treadmill testing was found to more frequently induce depolarization abnormalities on ECG including appearance of epsilon waves, PVCs, and new QRS terminal activation duration ≥ 55 milliseconds.[90] Similar findings were seen in patients with ACM and history of ventricular arrhythmias or cardiac arrest, suggesting that exercise treadmill testing may have a role in identifying a developing substrate so that medical surveillance can be targeted at these individuals.

MANAGEMENT

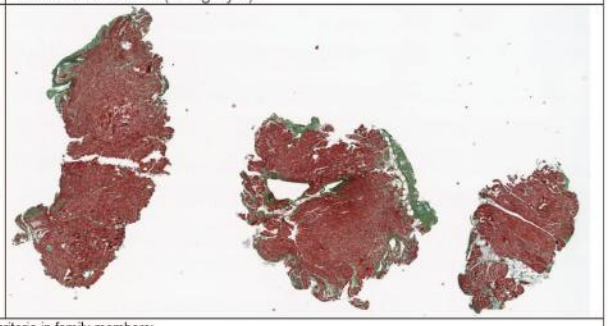
RISK STRATIFICATION AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR IMPLANTATION

There are no prospective, randomized clinical trials to elucidate which individuals are at highest risk for SCD and would benefit from implantable cardioverter-defibrillator (ICD) implantation. However, based on observational studies in ACM patients, a history of prior cardiac arrest,

A Pedigree of the family demonstrating 3 affected and mutated members. Genetic defect → *PKP2*[p.Arg413X]



B Endomyocardial biopsy (II:5) showing endocardial and interstitial fibrosis; microfoci of adipous tissue in two samples. The pathology features do not fulfill the TF criteria (category II).



C The table summarizes the fulfillment of the major (red-filled cells) and minor (violet filled cells) criteria in family members;

Family member/ Age: Onset → last follow-up (years)	Criteria Major (M) and minor (m)	Category I – RV Dysfunction and structural alterations	Category II – Tissue characteri-zation	Category III – Repola-rization abnormalities	Category IV – Depolarization/ conduction abnormalities	Category V – Arrhythmias	Category VI - Family history (FH)/ Mutated gene	Diagnosis: Definite Borderline Possible	Left ventricle (last evaluation)	AF	ICD	NYHA
Proband II:6	M		EMB Not				*FH + PKP2 +*	Definite	EF = 62%	-	+	I
37→54 years	m		done						LVEDD = 42mm		PP	
II:1	M		EMB Not				*FH + PKP2 +*	Definite	EF = 51%	-	+	II
42→69 years	m		done						LVEDD = 53mm		PP	
II:2	M		/				*FH + PKP2 –*	Possible	LVEF = 65%	-	/	I
55 →67 years	m								LVEDD = 45mm			
II:3	M		/				*FH + PKP2 –*	Possible	LVEF = 58%	-	/	I
58 → 65 years	m								LVEDD = 58mm			
II:4	M		/				*FH + PKP2 –*	Possible	LVEF = 55%	-	/	I
54 → 63 years	m								LVEDD = 46mm			
II:5	M		EMB: yes				*FH + PKP2 +*	Definite	EF = 43%	+ *	+	IIIb
32 → 68 years	m		(Panel B)						LVEDD = 47mm		PP	
III:1	M		/				*FH + PKP2 –*	Possible°	LVEF = 70%	-	/	I
26 → 31 years	m								LVEDD = 42mm			
III:2	M	2D-TTE and	/				*FH + PKP2 +*	Possible	EF = 66%	-	-	I
28 → 32 years	m	CMR: negative							LVEDD = 43mm			

*CHA2DS1VASC =1 / age; ° the diagnosis is possible just on the basis of the positive family history (affected father) but the genetic test is negative. PP = primary prevention

D II:5 → 2D-TTE and M-Mode views of the dilated RV

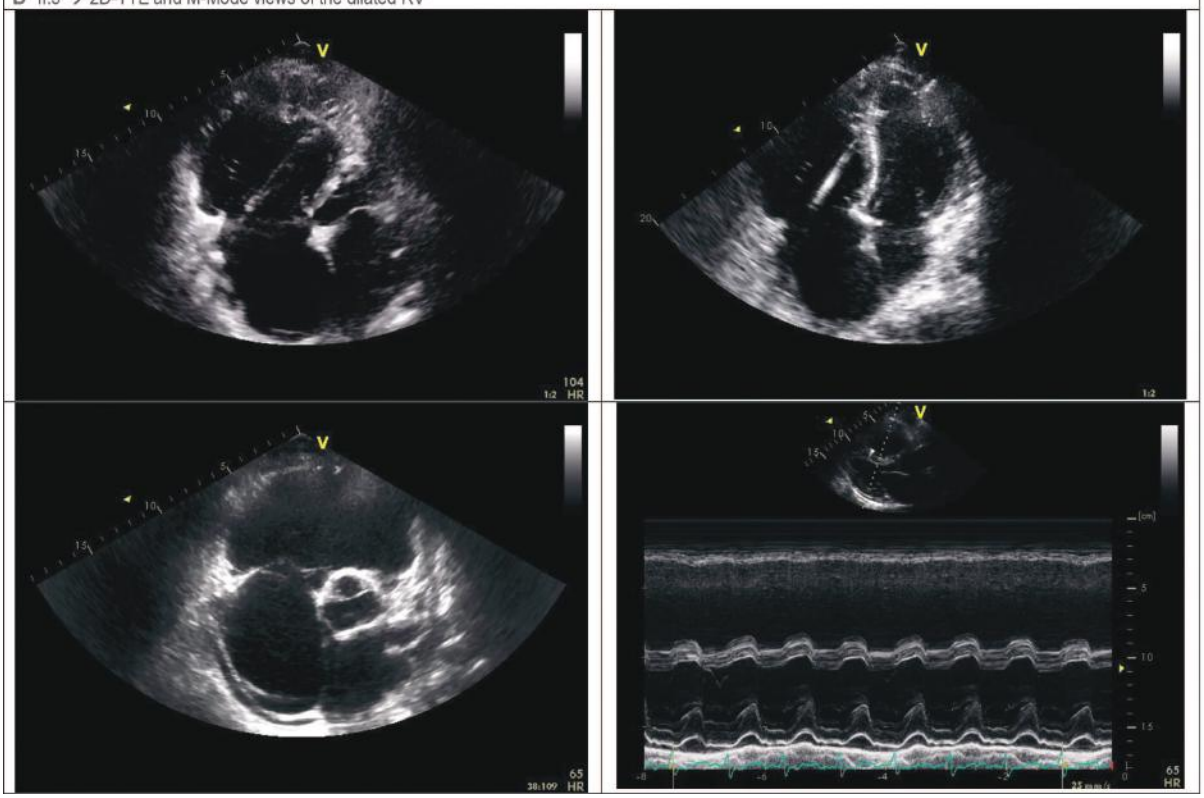


FIGURE 62–7. The panel collection of the figure summarizes the clinical workup in arrhythmogenic cardiomyopathy. **A.** The pedigree shows the segregation of the mutation (+) with the phenotype (*black-filled symbols*); the only mutated and unaffected family member is a young, asymptomatic girl whose electrocardiogram and imaging studies did not demonstrate signs of disease. **B.** The endomyocardial biopsy shows small foci of fat and interstitial fibrosis; the observed features do not fulfill Task Force criteria. **C.** The table shows the duration of follow-up in family members and the combination of major (M) (*red-filled cells*) and minor (m) criteria (*violet-filled cells*) in family members who underwent clinical screening; the diagnoses (*blue text*) are definite in three siblings (II:1, II:5, and II:6). According to the Task Force criteria Category 6, relatives of the three affected siblings are possibly affected because the disease is proven in II:1, II:5, and II:6. However, the risk of developing the disease is obviously higher in the young daughter (III:2) of the affected member II:6 because she is a carrier of the maternal mutation. **D.** Echocardiographic views of the heart of the proband (II:6). AF, atrial fibrillation; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic dysfunction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TF, Task Force; TTE, transthoracic echocardiography.

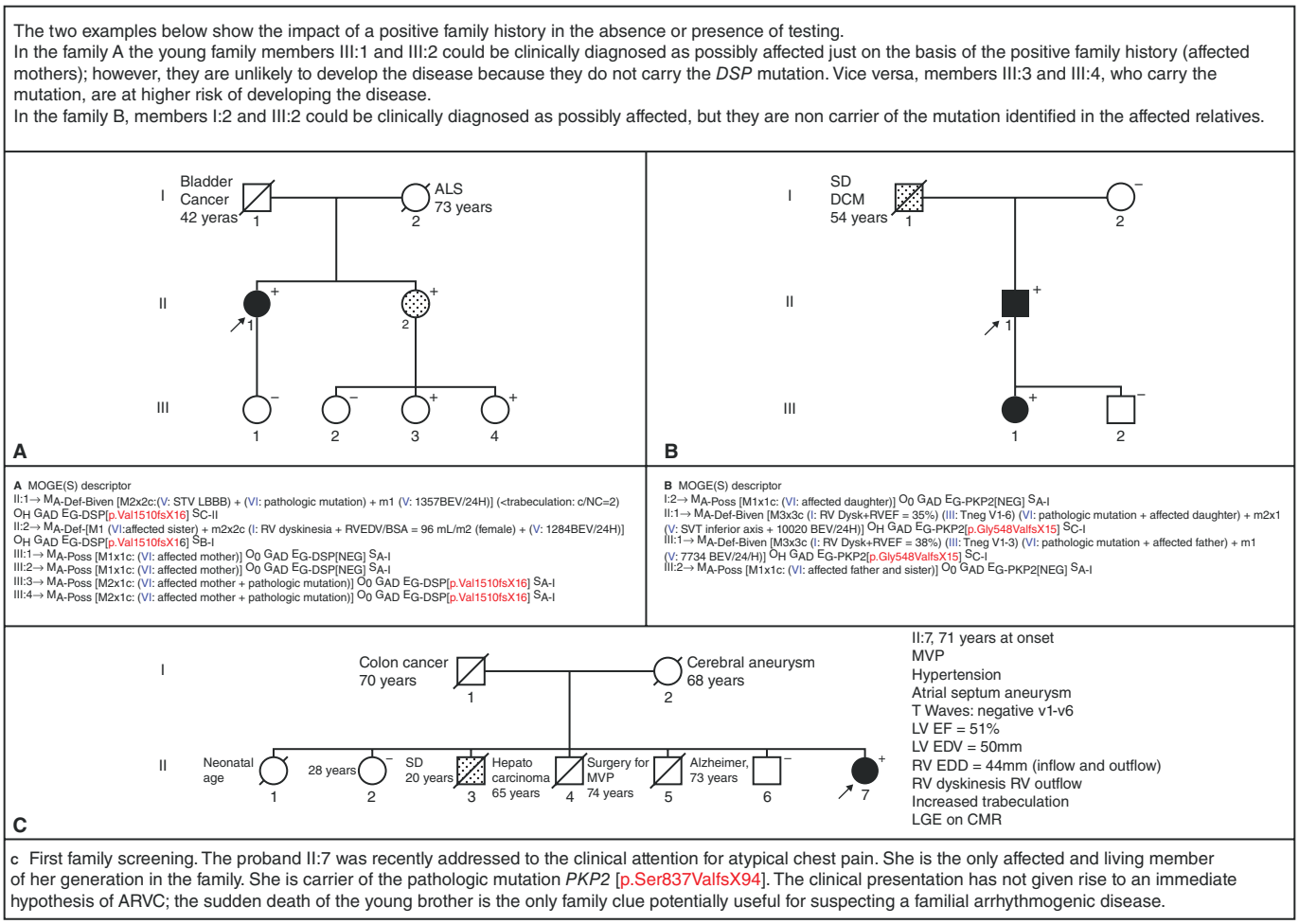


FIGURE 62–8. The figure contains three pedigrees of patients diagnosed with classical arrhythmogenic cardiomyopathy (ACM). **A** and **B**. Two pedigrees of small families in which both probands (A, II:1; B, II:1) satisfied the Task Force (TF) criteria for the diagnosis. The criteria included in Category 6 (family history and genetic mutation) of the TF criteria should be reconsidered because all first-degree relatives of proven affected family members should be considered as possibly affected; however, in families in which the mutation is identified, the genetic result should lead the assignment of criterion 6. Obviously, nonmutated relatives should not carry the risk of developing the disease. Below pedigrees A and B, the corresponding MOGE(S)-based description summarizes the morphofunctional (M) phenotype (A = arrhythmogenic cardiomyopathy), organ (O) involvement (H = heart only), genetic (G) information on inheritance pattern (AD = autosomal dominant), and the cause/etiology (E), which in this case is genetic and a result of a frameshift mutation in desmoplakin (*DSP*) in family A and plakofillin 2 (*PKP2*) in family B; (S) indicates the American Heart Association (AHA) stage and New York Heart Association (NYHA) functional class. **C**. The pedigree shows the case of an old female patient presenting with a nontypical clinical history; in this case, the family is noninformative. However, the mutation identified in the proband, *PKP2* p.(Ser837ValfsX94), has been repeatedly reported and confirmed as associated with ACM. The cardiomyopathy seems to be biventricular, and the arrhythmogenic profile is low. The identification of the pathologic mutation, however, gives the opportunity of supporting the future screening of the family members of the third generation (not shown).

sustained ventricular arrhythmias, unexplained syncope, younger age, extensive RV dysfunction, LV dysfunction, and the presence of heart failure are independently associated with subsequent ventricular arrhythmias.[59,74,91-97] In a study of patients receiving ICD for definite or probable ACM, 48% received an appropriate ICD therapy during a mean follow-up of 5 years.[98] The only independent predictors of ICD therapy were the presence of nonsustained VT and inducibility at electrophysiology study. The role of electrophysiology study for risk stratification is unclear because studies provide conflicting evidence.[91,93,98,99] Based on available data, the International Task Force provided consensus statements regarding high-, intermediate-, and low-risk factors (Table 62–3) and when ICD implantation is recommended (Fig. 62–9).[100] The only Class I recommendation is for patients at high risk based on a history of aborted SCD, sustained VT, or severe dysfunction of the RV, LV, or both. The estimated risks for major arrhythmic events for the high-, intermediate-, and low-risk groups are > 10%, 1% to 10%, and < 1% per year, respectively.[100]

PHARMACOLOGIC THERAPY

Similar to heart failure that occurs in other settings, patients with ACM and heart failure should undergo treatment with β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics. Additionally, because ventricular arrhythmias may be driven by exercise or increased sympathetic tone,[35,101] β-blocker therapy should be instituted in these patients. They also have a role in treating inappropriate ICD therapies as a result of supraventricular arrhythmias. However, for patients with scar-related reentrant VT, β-blockers are less effective, and amiodarone or sotalol should be used to decrease the risk of recurrent ventricular arrhythmias.[102-104] Antiarrhythmic

TABLE 62–3. Risk Factors for Major Arrhythmic Events[a] in ACM

I. High Risk
- Cardiac arrest, unstable sustained VT, sustained VT or VF
- Severe RV dysfunction (RV fractional change ≤ 17% or RVEF ≤ 35%)
- LV dysfunction (LVEF ≤ 35%)

II. Intermediate Risk

Major:
- Syncope
- Nonsustained VT
- Moderate RV dysfunction (RV fractional change between 24% and 17% or RVEF between 40% and 36%)
- Moderate LV dysfunction (LVEF between 45% and 36%)

Minor:
- Clinical signs of heart failure
- RA or RV dilatation
- Young age
- Male sex
- Complex genotype (compound or digenic heterozygosity)
- Proband status
- Inducible VT/VF
- Extent of electroanatomic scar on RV endocardial voltage mapping
- Fragmented electrograms on RV endocardial voltage mapping
- T-wave inversion in the inferior ECG leads
- Extent of T-wave inversions (≥ 3 precordial ECG leads)
- QRS fragmentation
- Precordial QRS amplitude ratio (sum of QRS voltages in V_1-V_3/sum of QRS voltages in V_4-V_6 < 0.48)

III. Low Risk
- Probands and relatives without risk factors
- Healthy gene carriers

[a]Major arrhythmic events are considered to be sudden cardiac death, appropriate ICD intervention, or ICD therapy on fast VT/VF.

Abbreviations: ACM, arrhythmogenic cardiomyopathy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular; RVEF, right ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Data from Corrado D, Wichter T, Link MS, et al. Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An International Task Force Consensus Statement. *Circulation*. 2015 Aug 4;132(5):441-53.

drugs do not reduce mortality and should not be used in place of ICDs. They are best used to reduce recurrent VT/VF episodes in those with an ICD in place.

CATHETER ABLATION

Catheter ablation is an option for the treatment of VT in ACM (Fig. 62–10). Its primary role is for the control of VT in patients with ICDs despite antiarrhythmic drug therapy or as an alternative to antiarrhythmic drugs. Similar to antiarrhythmic drugs, ablation does not reduce mortality and should not be used in place of ICDs. Initial results with endocardial ablation alone were disappointing.[105-107] These suboptimal results are not entirely surprising because ACM is a diffuse and extensive process that typically involves the RV epicardium.[108] Combined epicardial and endocardial catheter ablation has provided better results.[108-113] In a recent report of 62 ACM patients who underwent endocardial ablation with adjuvant epicardial ablation for VT, the VT-free survival during a mean follow-up of > 4 years was 71%.[113] Prior to ablation, 87% of patients had failed antiarrhythmic drugs, and following ablation, the majority were on β-blockers only or required no therapy.

CARDIAC TRANSPLANTATION

Approximately 2% to 4% of ACM patients undergo cardiac transplantation.[11,58] In a report from the John Hopkins ARVD Program Registry of 18 patients who underwent cardiac transplantation, 1-year survival was 94%, and 88% were alive at a mean follow-up of 6 years.[114] ACM patients who have severe drug refractory heart failure or ventricular arrhythmias that are recurrent despite ICD therapy, antiarrhythmic drugs, and catheter ablation may require heart transplantation.

EXERCISE RESTRICTION

Individuals with ACM are prone to ventricular arrhythmias and SCD during exercise and competitive sports.[2,5,7] In a murine model, endurance training was shown to accelerate the development of RV dysfunction and arrhythmias in ACM desmosome mutation carriers.[115] These findings were confirmed in human studies of desmosome mutation and nondesmosome mutation carriers with the demonstration that frequent exercise or endurance exercise was associated with increased risk of VT/VF, heart failure, structural abnormalities, and earlier onset of disease.[25,116] These findings confirm that exercise is a disease modifier in ACM. Based on these findings, recent guidelines from the American Heart Association and American College of Cardiology recommend that individuals with definite, borderline, or possible ACM refrain from competitive sports with the possible exception of low-intensity class 1A sports.[117] Exercise restriction to prevent disease progression and decrease risk of ventricular arrhythmias should be a treatment strategy in all ACM patients.

DIFFERENTIAL DIAGNOSES

The differential diagnosis of ACM includes idiopathic RV outflow tract VT (RVOT-VT), sarcoidosis, myocarditis, dilated cardiomyopathy, Brugada syndrome, athlete's heart, RV infarction, Chagas disease in endemic areas, pulmonary hypertension and congenital heart disease.

RIGHT VENTRICULAR OUTFLOW TRACT VENTRICULAR TACHYCARDIA

Idiopathic RVOT-VT should be differentiated from early ACM, when gross structural abnormalities are absent. Diagnosis is based on clinical data (Task Force criteria), pathology (endomyocardial biopsy), and imaging such as echocardiography and CMRI or positron emission tomography demonstrating or excluding scar and inflammation.[118,119] In general, in RVOT-VT:

- Twelve-lead surface ECG and SAECG are normal during sinus rhythm.
- A single VT morphology with LBBB pattern and an inferior axis is commonly recorded.[120]
- The application of an ECG-based scoring system can clarify the diagnosis. The scoring system provides 3 points for sinus rhythm

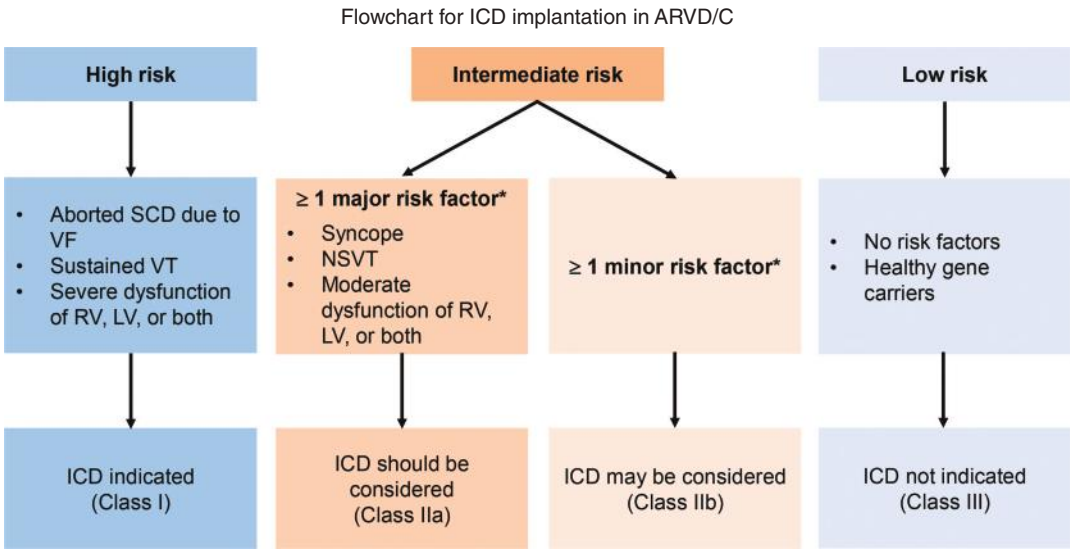


FIGURE 62–9. Flowchart for implantable cardioverter-defibrillator (ICD) implantation in arrhythmogenic cardiomyopathy (ACM). Major and minor risk factors are listed in Table 62–3. LV, left ventricle; NSVT, non-sustained ventricular tachycardia; RV, right ventricle; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia. Reproduced with permission from Corrado D, Wichter T, Link MS, et al. Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An International Task Force Consensus Statement. *Circulation*. 2015 Aug 4;132(5):441-453.[100]

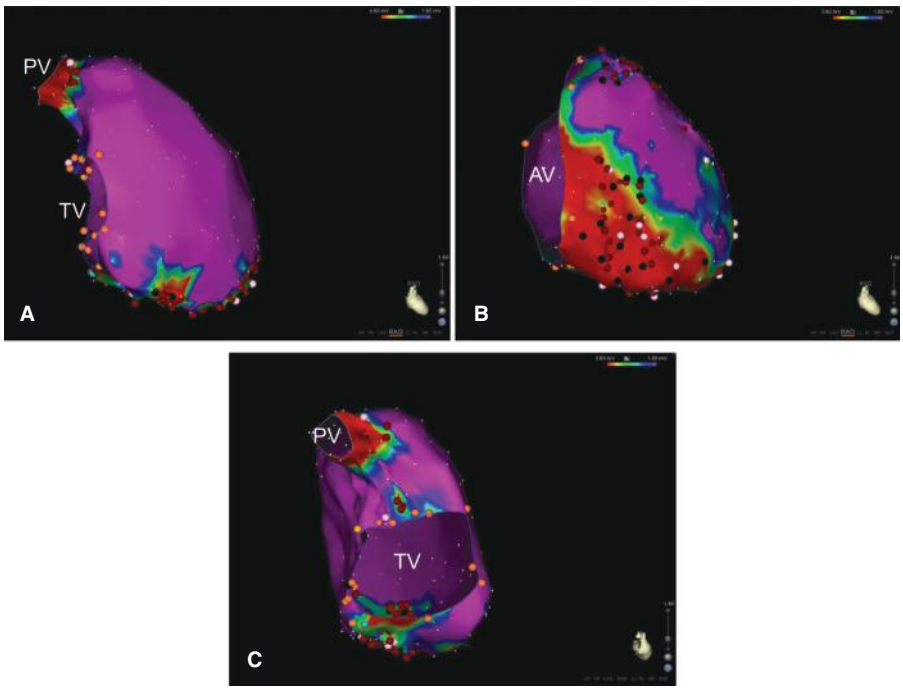


FIGURE 62–10. Bipolar voltage maps of the epicardial ventricular surface and right ventricular (RV) endocardium of the same patient in Fig. 62–3. This patient had ventricular tachycardia (VT) and underwent VT ablation. **A.** The RV endocardial map is shown in anteroposterior projection. The color range in bipolar voltage is 0.5 to 1.5 mV; *purple* represents normal tissue, and *red* represents severely diseased tissue. The free wall is normal with areas of diseased issue being around the pulmonary valve (PV) and inferior RV wall, which is not optimally seen in this view. Late potentials are represented by *black points* and fractionated potentials by *pink points*, which are targets for ablation (*red points*). **B.** The epicardial surface of the RV demonstrates a much larger area of diseased tissue and scar along the free wall. The area of scar extends to the epicardial and endocardial inferior wall of the RV, which is not seen here. **C.** A posteroanterior view of the RV endocardium. Areas of scar can be seen around the PV and inferior endocardial wall. During ablation, areas with late and fractionated potentials were targeted on the epicardial and endocardial surface. After the procedure conclusion, VT was noninducible. AV, atrioventricular groove; TV tricuspid valve.

anterior T-wave inversions in leads V_1 to V_3 and during ventricular arrhythmia, 2 points for QRS duration in lead I ≥ 120 milliseconds, 2 points for QRS notching, and 1 point for precordial transition at lead V_5 or later. A score ≥ 5 correctly distinguishes ACM from RVOT-VT in more than 90% of cases (sensitivity 84%; specificity 100%; positive predictive value 100%; negative predictive value 91%).[121]

- QRS duration during VT is longer (≥ 120 milliseconds in lead I).[122]
- Notched QRS complexes and precordial transition in lead V_6 occur in ACM but not in RVOT-VT.[123]
- RVOT-VT is difficult to induce by programmed ventricular stimulation.[119]

CARDIAC SARCOIDOSIS

Cardiac sarcoidosis can mimic ACM. Task Force criteria do not reliably distinguish between the two conditions. In a study of patients with suspected ACM and investigated with endomyocardial biopsy, cardiac sarcoidosis was identified in 15% of cases.[124] In a series of 18 patients with proven cardiac sarcoidosis or ACM, cardiac sarcoidosis was characterized by reduced LV ejection fraction, a significantly wider QRS, right-sided apical VT, and more inducible forms of monomorphic VT.[125] Additional signs in favor of sarcoidosis include respiratory and systemic symptoms, high-grade atrioventricular conduction block, septal involvement, and proven absence of familial disease. The diagnosis is confirmed by endomyocardial pathology and imaging studies (see. Chap. 63).

MYOCARDITIS

Cardiac phenotypes mimicking ACM include RV myocarditis. In a series of 30 consecutive patients with a noninvasive diagnosis of ACM, 29 had an abnormal voltage map. Three-dimensional electroanatomic mapping–guided endomyocardial biopsy confirmed the diagnosis of ACM in 15 patients and myocarditis in the remaining 15. Clinical features, structural and functional RV abnormalities, and three-dimensional electroanatomic mapping findings did not distinguish ACM from myocarditis.[126] ACM phenotype can also mimic acute myocarditis, as demonstrated in a 21-year-old woman who presented with fulminant lymphocytic myocarditis and subsequently developed isolated RV dysfunction with imaging and ECG criteria for ACM.[127]

DILATED CARDIOMYOPATHY

DCM is particularly difficult to distinguish from nonclassic ACM. Phenotype overlapping can be complicated by genetic overlapping as the same disease genes can cause either DCM or ACM. Early arrhythmic manifestations typically occur in ACM; however, they can also occur in DCM, particularly in patients who carry mutations in genes associated with high arrhythmogenic risk such as *LMNA*.[39] Overlapping of ACM and DCM phenotypes may occur in patients with titin mutations[52,53] and *PLN* mutations.[48,49]

BRUGADA SYNDROME

Brugada syndrome can mimic ACM. Both conditions may demonstrate RV conduction delay, and mutations typically occurring in Brugada syndrome were found in ACM patients and vice versa.[128,129] ECG markers that reflect ventricular conduction delay in ACM have been observed in patients with spontaneous or drug-induced type 1 ECG pattern of Brugada syndrome.[130] However, the presence of structural abnormalities supports the diagnosis of ACM.

CHAGAS DISEASE

Patients diagnosed with Chagas disease may demonstrate early and frequent RV involvement.[131] In a recent case-control and prevalence study including 31 controls and 61 patients with indeterminate form of Chagas disease, RV systolic dysfunction was present in 26%.[132] Chagasic cardiomyopathy is associated with decreased expression of the gap junction protein Cx43.[133] In endemic areas, Chagas disease should be included in the list of differential diagnoses with ACM.

ATHLETE'S HEART

ACM can be mimicked by RV changes that may develop in endurance athletes.[134] The differential diagnosis of athlete's heart and ACM is a difficult clinical problem. In a recent series of 1009 Olympic athletes (mean age, 24 ± 6 years; 64% males) participating in skill, power, mixed, and endurance sport, RV enlargement compatible with major and minor Task Force diagnostic criteria for ACM was observed in 41 (4%) and 319 (32%) athletes, respectively. Therefore, experts recommend referring to the 95th percentiles as reference values, or alternatively, only major diagnostic Task Force criteria for ACM may be appropriate.[135]

CONCLUSIONS

ACM is a genetic cardiomyopathy characterized clinically by life-threatening ventricular arrhythmias and structurally by fibrofatty substitution of the RV wall in its classic right-sided form and of both the LV and RV walls in biventricular and left dominant variants. The diagnostic workup is guided and supported by the modified Task Force criteria (2010), which are based on combined clinical, instrumental, and genetic major and minor criteria. Family screening is recommended for relatives of probands diagnosed with ACM as it allows preclinical and early diagnosis. In patients who are diagnosed early, clinical monitoring and primary prevention of SCD improves mortality. Genetic criteria, both clinical and molecular, are major diagnostic contributors and genetic testing is now recommended by official guidelines. Exercise is a key environmental trigger that may promote the development of the disease in susceptible individuals and influence the evolution; therefore, restriction of exercise is recommended in patients diagnosed with ACM.

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CHAPTER 63

MYOCARDITIS

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INTRODUCTION

The term *myocarditis* describes the presence of inflammatory cells in the myocardium and implies that the presenting clinical phenotype is attributable to myocardial inflammation. Therefore, myocarditis is diagnosed when myocardial inflammation is proven and there are clinical manifestations that can be causally linked to the inflammatory substrate. The descriptive diagnosis of myocarditis encompasses a wide spectrum of etiologically different diseases that share, as unique criterion, the presence of myocardial inflammation.

In the 1980s, the World Health Organization and the International Society and Federation of Cardiology defined myocarditis as an inflammatory disease of the myocardium wherein the diagnosis is established by histologic, immunologic, and immunohistochemical criteria. Idiopathic, autoimmune, and infectious forms of inflammatory cardiomyopathy were recognized.[1] Whereas the Dallas criteria[2] insisted on the demonstration of mononuclear cellular infiltration accompanying a demonstrable and ongoing myocyte damage, the definition of myocarditis recently updated by the European Society of Cardiology (ESC) working group on myocardial and pericardial diseases requires the presence of ≥ 14 lymphocytes/mm^2 including CD3-positive T lymphocytes ≥ 7 cells/mm^2 but no more than 4 monocytes/mm^2.[3] These descriptive definitions did not include etiologic basis of myocardial involvement and clinical information.

Myocarditis can be infectious or noninfectious in origin, and the latter includes autoimmune/immune-mediated, hypersensitivity, or toxic causes. Infective myocarditis is induced by myocardiotrophic viruses such as Coxsackie B virus or endotheliotropic parvovirus B19 followed by interstitial inflammatory cell infiltration and myocardial tissue damage manifesting clinically with symptoms, circulating biomarker abnormalities, and imaging-verified myocardial alterations. The clinical presentation is "fulminant," acute or chronic illness.[3] The diagnosis is either pathologically proven or considered suspect; only pathology-based evidence is accepted as a definitive diagnosis of myocarditis,[4] and surrogate terms such as *clinically suspected myocarditis* cannot be equated with the diagnostic certainty of histologically verified disease. Development of molecular imaging strategies targeting the presence of myocardial inflammation is not beyond the realm of possibility.[5]

At present, endomyocardial biopsy (EMB) remains the unique tool for the diagnosis in vivo; surgical samples can be equally informative, such as the left ventricular (LV) apex resected during ventricular assist device implantation. Reasons for not performing EMB are numerous. EMB is an invasive procedure and is associated with not negligible complications such as ventricular wall perforation, pericardial effusion, and tamponade. Although this reason is repeatedly cited as the major limitation, EMBs are routinely and frequently performed to monitor allogeneic reaction and opportunistic infections in transplanted patients and have been reported safe both in adults[4] and children.[6] The major reasons that clinical utilization of EMB is discouraged include (1) the lack of evidence-based effective treatment for myocarditis; (2) the nonuniform and non–universally agreed upon diagnostic criteria; and (3) the interobserver variability among pathologists interpreting the same biopsy samples. The reports of limitations of Dallas criteria–based interpretation[7] and the results of the National Institutes of Health Myocarditis Trial[8] have effectively changed the diagnostic workup for myocarditis as a disease entity.

EPIDEMIOLOGY

Precise epidemiologic estimates are difficult because of the different diagnostic criteria and clinically heterogeneous manifestations of the disease ranging from nonspecific signs and symptoms to life-threatening arrhythmias and cardiogenic shock. Autopsy reports have provided variable data. In a large autopsy report of 377,841 deceased persons, the prevalence of nonspecific myocarditis and giant cell myocarditis was 0.11% and 0.007%, respectively.[9] In another retrospective review of 17,162 postmortem records, myocarditis was histologically confirmed in 91 cases (0.53%; 95% confidence interval [CI], 0.4%-0.7%). However, in a prospectively planned standardized myocardial sampling in 605 autopsies, the prevalence was 5.1%,[10] which is substantially higher than the 2% rate of incidental myocardial infiltrates associated with myocyte necrosis in consecutive noncardiac deaths.[11]

Clinical reports have promulgated myocarditis based on varied phenotypes. A search algorithm based on sentinel reports (using International Classification of Diseases, Ninth Revision, codes 420.90,

420.99, 422.90, 422.91, and 429.0) identified 59 cases of suspected myopericarditis among 492,671 US military service personnel who received smallpox vaccine between 2002 and 2003.[12] In a well-characterized series of competitive athletes, myocarditis was reported as the third leading cause of sudden cardiac death.[13] However, of 672 young Finnish men presenting with myocardial infarction from 1977 to 1996, clinical diagnosis of myocarditis was suggested in 98 (0.17% [95% CI, 0.14%-0.21%]/1000 person-years); Coxsackie virus etiology was confirmed in 4% of the cases.[14] In 3055 patients who underwent EMB, myocardial inflammation was found in 17.2% (n = 525); only 182 of these 525 patients demonstrated decreased ejection fraction (< 45%), and viral genome was identified in 11.8%.[15] In a review of 1,698,397 patients age ≥ 16 years over 9.5 years from 29 Finnish hospitals, 3198 were discharged as having myocarditis (0.0019%); researchers reported a higher prevalence in affected young men and postmenopausal women.[16] Acute myocarditis has been reported to be more common in hospitalized patients age 18 to 29 years than acute myocardial infarction.[17]

A nationwide survey aimed at determining the clinicoepidemiologic features of myocarditis in Japanese children and adolescents demonstrated an incidence of 43.5 cases per year, or 0.24 cases per 100,000 population; pathogens were identified in 37 of 169 subjects, with Coxsackie virus accounting for 60%.[18] Of 62 children with clinical profiles of acute myocarditis and dilated cardiomyopathy (DCM) before diagnosis, 24 (39%) had a final diagnosis of myocarditis.[19] Of the 11 children (median age, 1 year; range 0-9 years) presenting with fulminant myocarditis between 1998 and 2003 in a single center, 5 were confirmed with viral etiology; 10 survivors were asymptomatic with normalized LV ejection fraction (LVEF) at a median follow-up of 58.7 months (range, 33.8-83.1 months).[20] Overall, currently available epidemiology data do not allow precise estimates on prevalence, type, and outcomes of myocarditis.

INFLAMMATORY CELLS IN NORMAL MYOCARDIUM

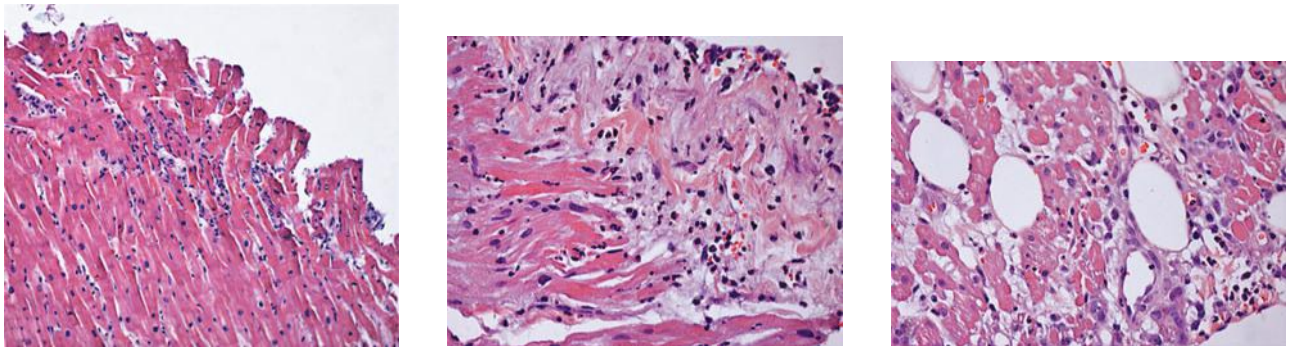
Myocardial inflammatory cells have been observed in autopsy reports of noncardiac death, wherein the inflammation was a presumptive but not proven contributor to the final outcome. In 384 consecutive hearts seen in consultation from a single medical examiner's office, infiltrates were most frequent in natural noncardiac deaths (31%) and least frequent in traumatic deaths (12%); eosinophilic infiltrates were especially common in patients on antibiotics (18%). Incidental inflammation with myocyte necrosis in 2% of noncardiac deaths happened to be less common.[11] Inflammatory infiltrates have been commonly observed in donor hearts before implantation.[21] Although normal myocardium is expected to be free from inflammatory infiltrates, incidental detection in noncardiac death suggests that, by itself, inflammatory cell may not have clinical significance (Fig. 63–1).

INFECTIOUS MYOCARDITIS

The list of infectious agents that have been associated with myocarditis include DNA and RNA viruses, bacteria, fungi, protozoa, and helminthes.[22-24] Viral infections are the most common causes of myocarditis in both children and adults (Table 63–1).[22] Nonviral cardiotropic infections, such as *Trypanosoma cruzi* in Chagas disease[25] and *Borrelia burgdorferi* in Lyme disease,[26] in immunocompetent individuals constitute special subgroups of myocarditis. In immunocompromised patients (eg, immunosuppressed, immunodepressed, malignancy, postsurgical, human immunodeficiency virus [HIV] infected), the myocarditis is associated with different infectious agents such as the human cytomegalovirus (HCMV) or *Toxoplasma gondii*. In pregnancy, HCMV infection could cause fetal malformations wherein the maternal infection remains clinically subtle partly because of delayed lymphoproliferative response in primary infection[27] and lower viral load.[28] Myocardial infection is diagnosed when the infectious agent is detected in myocardial tissue by pathologic and genomic studies.[29]

VIRAL MYOCARDITIS

The diagnostic workup of myocardial infection should begin with timely sampling of informative tissue and paired samples of peripheral blood. The diagnostic processes include cell culture, antibody detection, antigen detection, hemagglutination assay, nucleic acid detection, and gene sequencing. Specific antibodies are always produced when adaptive immune system encounters a virus. As general rule, immunoglobulin (Ig) Ms are highly effective at neutralizing viruses, are produced only for the initial few weeks, and are indicative of acute infections. IgGs are produced indefinitely and are tested to demonstrate prior infection. Antigens are detected by enzyme-linked immunosorbent assay (ELISA) in biologic fluids with immunofluorescence and immunoperoxidase as the alternative methods. Quantitative assays for measuring the viral genome copy number and nucleic acid sequencing establish the viral presence and the viral load. In the appropriate diagnostic workup, the serology is systematically performed, routine inflammatory markers are tested, and markers of myocardial damage



A B C

FIGURE 63–1. The figure shows three different examples of endomyocardial biopsies taken from donor hearts before implantation in the recipients. Inflammatory infiltrates are common and do not condition post-transplant early and late outcome; the three examples correspond to three long-term post-transplant survivors (A, B, and C: 14, 12, and 11 years, respectively).

TABLE 63–1. Different Causes of Myocarditis, Including the Most Common and Rare Causes

Acquired Myocarditis								
Infectious				Noninfectious		Autoimmune/Immune-Mediated		
RNA Viruses	DNA Viruses	Bacteria	Protozoa/Helminths/ Fungi	Medicaments	Toxic Agents/Poisons/ Physical Agents/Drugs	Autoimmune Diseases	Giant Cell, Granulomatous, Inflammatory Diseases	Heritable Myocarditis
• **Coxsackieviruses A and B** • Echoviruses • Polioviruses • Influenza A and B viruses • Respiratory syncytial virus • Mumps virus • Measles virus • Hepatitis C virus • Dengue virus • Yellow fever virus • Chikungunya virus • Junin virus • Lassa fever virus • Rabies virus • Rubella virus • Human immunodeficiency virus-1 • Coronavirus[a] • Cardiovirus B (Saffold virus)	• **Adenoviruses** • **Parvovirus B19** • Human cytomegalovirus • Human herpes virus-6 • Epstein-Barr virus • Varicella-zoster virus • Herpes simplex virus • Variola virus • Vaccinia virus • Polyoma virus • Trichodysplasia spinulosa-associated polyomavirus[b]	• ***Staphylococcus*** • ***Streptococcus*** • *Pneumococcus* • *Meningococcus* • *Gonococcus* • *Salmonella* • ***Corynebacterium diphtheriae*** • *Haemophilus influenzae* • *Leptospira (Weil disease)* • ***Borrelia burgdorferi* (Lyme disease)** • *Neisseria* • *Mycobacterium (tuberculosis)* • *Mycoplasma pneumoniae* • *Brucella* • *Tropheryma whipplei*	• ***Trypanosoma cruzi* (Chagas disease)** • ***Toxoplasma gondii*** • *Entamoeba histolytica* • *Leishmania* • *Echinococcus* • *Trichinella* • *Taenia solium* • *Fungal* • *Aspergillus,* • *Actinomyces* • *Blastomyces* • *Candida* • *Coccidioides* • *Cryptococcus* • *Histoplasma* • Mucormycosis • *Nocardia* • *Sporothrix*	• Penicillin, • Phenylbutazone • Methyldopa • Thiazide diuretics • Amitriptyline • Cefaclor • Colchicine • Furosemide • Isoniazid • Lidocaine • Tetracycline • Phenytoin • Sulfonamides • Phenylbutazone • Methyldopa • Thiazide diuretics • Dobutamine • Clozapine • Amitriptyline • Interleukin-2	• Lithium • Arsenic • Lead • Copper • Iron • Phosphorus • Carbon monoxide • Ethanol • Poisons by insect stings and bites • Electric shock • Heat • Radiation/ radiotherapy • Cocaine • Heroin	• Systemic lupus erythematosus • Rheumatoid arthritis • Churg-Strauss • syndrome • Kawasaki disease • Inflammatory bowel disease • Scleroderma • Polymyositis • Myasthenia gravis • Insulin-dependent diabetes mellitus • Thyrotoxicosis • Sarcoidosis • Wegener granulomatosis	• Sarcoidosis • Giant cell myocarditis • Tuberculous myocarditis • Myocardial involvement in systemic diseases with giant cells • Rheumatic heart disease with Aschoff nodules • Farber disease (lipogranulomatosis) • Foreign body reactions	• Heritable autoinflammatory diseases • Early-onset sarcoidosis • Familial hypereosinophilia

Note. The most common causes are in bold.

[a]Causing the novel Middle East respiratory syndrome.

[b]Human polyomavirus identified in 2010.

are monitored. Neutralizing antibodies in serum can be tested by the neutralization test based on the enzyme-linked immunospot assay.[30]

EMB is the gold standard for the confirmation of viral infection.[4,31] Inflammatory cells are detected with routine pathology stains such as hematoxylin and eosin. The immunophenotyping of inflammatory cells for prevalent subtypes of T lymphocytes including $CD4^+$ and $CD8^+$, B lymphocytes, natural killer cells, or macrophages may add information on the presence of effector and regulatory pathogenetic pathways. Immunohistochemical detection of the infective pathogen and molecular transcription signature from the affected myocardium can contribute to the diagnosis of inflammatory heart diseases.[32]

Enteroviruses

Enteroviruses belong to the family of Picornaviridae and are grouped into 12 species: enteroviruses A to H and J and rhinoviruses A to C. The disease in humans is caused by poliovirus, coxsackievirus, rhinovirus, enterovirus, and echovirus serotypes. The clinical presentation may be relatively mild (eg, fever, herpangina, conjunctivitis, hand-foot-mouth disease, tonsillitis, pharyngitis, lower respiratory tract infection, acute gastroenteritis) or, uncommonly, also severe (eg, pneumonia, meningitis, encephalitis, myocarditis, pericarditis, hepatic necrosis, coagulopathy).[33] The cardiotropic coxsackievirus B3 (CV-B3) is one of the most common causes of myocarditis.[33] The myocardial infection is initiated by the transmembrane coxsackievirus-adenovirus receptor (CAR); the ablation of CAR blocks viral affliction of myocardial cells and inflammation in the myocardium in experimental models.[34] Similarly, increased cardiac expression of CAR may partially explain increased susceptibility to myocarditis.[35] In CV-B3–infected myocytes, the cell damage is induced by direct cytotoxicity and mediated by viral proteinases.[36] CV-B3 replicates on the surface of autophagosomes[37,38] and enhances replication by employing microRNA (miRNA)[39,40]; CV-B3–induced differential expression of miRNA modulates expression of both host and viral genes.

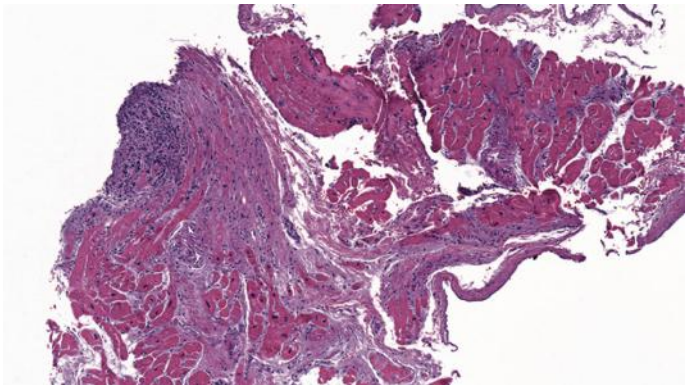
Patients with defects of dystrophin and dysferlin demonstrate increased susceptibility to myocardial CV-B3 infection by enhancing viral propagation to adjacent cardiomyocytes and disrupting membrane repair function.[41-43] The history of a recent flu episode in patients with X-linked DCM caused by defects of dystrophin could mislead the clinical diagnosis, but the possibility that a viral flu triggered the onset of a pre-existing asymptomatic disease cannot be excluded. Although myocarditis and viral genome may not be found in the EMB from patients with X-linked DCM,[44] the myocardium with dystrophin defects could sustain greater damage from coxsackievirus proteases known to affect host cell proteins such as dystrophin.[45]

In viral infections, the early innate immune response provides the first defense mechanism and is mediated by cytokines. The virus is recognized by specific receptors (toll-like, retinoic acid inducible gene-I–like, nucleotide-binding oligomerization domain-like, and C-type lectin receptors) through pathogen-specific molecules.[46,47] This interaction induces the production of proinflammatory cytokines (eg, tumor necrosis factor-α and interleukin-1) to recruit T cells (including regulatory T cells and interleukin-17–producing cells) and modulate immune response.[48] The late adaptive immune response contributes to the myocardial lymphocyte infiltration that must clear virus-infected cardiac myocytes in CV-B3 myocarditis and endothelial cells in parvovirus B19 myocarditis. Although this mechanism clears the virus, it also results in myocyte injury. Depletion or ablation of T lymphocytes, both $CD4^+$ and $CD8^+$, decreases the mortality rate and reduces cardiac inflammation and injury after CV-B3 infection.[49] In addition, a molecular mimicry between viral and host antigens has been proposed as a mechanism subsequently responsible for the postinfectious autoimmune-mediated damage of the myocardium.[50]

Acute infections are characterized by febrile illness that commonly evolves without complications; when complicated by myocarditis, the febrile illness is commonly reported as having preceded the cardiac symptoms. The cardiac manifestations range from mild, nonspecific symptoms to life-threatening complications such as cardiogenic chock and sudden cardiac death. The pathologic features of CV-B3 myocarditis are T-lymphocyte inflammatory infiltrate and myocyte damage/necrosis (Fig. 63–2). Markers of myocardial damage and systemic inflammation can be increased. IgMs are usually missed unless the diagnosis of myocarditis is done close to the onset of the systemic illness. In the acute phase, viral particles can be recognized in infected myocytes.[51,52] Polymerase chain reaction (PCR)–based demonstration of the viral genome in the affected myocardium concludes the diagnostic workup; molecular assays are paired in blood and myocardial samples.

Human Parvovirus B19

Human parvovirus B19 (B19V) belongs to the genus *Erythroparvovirus* of the Parvoviridae family, which is composed of a group of small DNA viruses with a linear single-stranded DNA genome.[53] B19V usually infects human erythroid progenitor cells to cause mild to severe hematologic disorders[54] but may also infect nonerythroid lineage cells such as myocardial endothelial cells.[55] Therefore, B19V infection typically presents clinically with erythema infectiosum, arthralgia, fetal death, transient aplastic crisis, and persistent infection in immunocompromised hosts; less common clinical manifestations include atypical skin rashes, neurologic syndromes, cardiac manifestations, and



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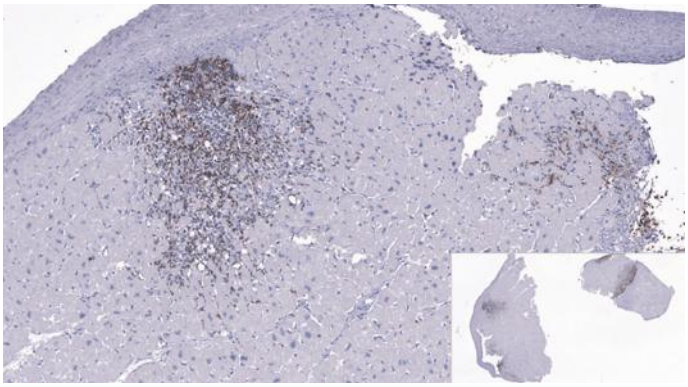


B

FIGURE 63–2. (A) Active myocarditis, with plurifocal inflammatory infiltrates demonstrating ($CD3^+$) immunoreactivity (B); the inset shows the very low magnification view of two endomyocardial biopsy (EMB) samples (coxsackievirus B3 positive; onset: 18 days before EMB).

cytopenias.[53,55] The cardiac manifestations of B19V range from mild and nonspecific symptoms (eg, fatigue, arrhythmias) to cardiogenic shock requiring mechanical support.

Mechanistically, the B19V-antibody complex enters the cells through an endocytosis process mediated by the direct interaction of antibody-bound complement factor C1q with its receptor CD93 on the cell surface.[56] B19V enters myocardial endothelial cells but does not replicate intracellularly.[57] B19V genome has been identified in the myocardial tissue of patients with myocarditis, patients with DCM, and control cases.[58,59] In 72 EMBs from 35 patients with DCM, 17 patients with active myocarditis, and 20 surgical myocardial samples from patients undergoing surgery for valve disease or coronary artery disease, real-time PCR failed to identify enteroviruses, Epstein-Barr virus, or herpes simplex viruses type 1 or 2; only one DCM patient tested positive for adenovirus. On the other hand, 20 of 52 patients (38%) with cardiomyopathy and 8 of 20 controls (40%) tested positive for B19V, disproving the hypothesis that persistent myocardial viral infection might be a frequent cause of DCM or myocarditis.[58] A possible hypothesis that could explain the role of B19V in myocarditis and cardiomyopathy is the potential role of trigger of the viral genome for innate immunity, inducing proinflammatory cytokine secretion[57] and myocardial inflammation.

EMB typically shows T-lymphocyte inflammatory infiltrates and prominent endothelial cells; myocytes may not show damage or necrosis (Fig. 63–3). B19V infection has also been associated with adult and pediatric autoimmune diseases, including systemic diseases that involve the heart, either directly or indirectly.[60-62] Documented mechanisms in B19-associated autoimmunity include molecular mimicry (IgG antibodies to B19 proteins cross-react with human autoantigens), virus-induced apoptosis with presentation of self-antigens to T lymphocytes, and the phospholipase activity of the B19 unique VP1 protein.

Human Herpesviruses

The human herpesviruses (HHV) are currently assigned to three subfamilies: α-, β-, and γ-herpesvirinae. Herpesvirus infections are characterized by their ability to establish lifelong infections with periods of latency followed by reactivation. The diagnosis of HHV myocarditis is based on the demonstration of HHV actively replicating in cardiac cells. In infected cells, HHV typically causes a morphologically manifest cytopathic effect, and commercially available antibodies can detect viral antigens expressed in the immediate/early and late phases of viral replication. PCR can selectively detect genes expressed by replicating viruses, and quantitative PCR measures the number of copies of viral genomes in the affected tissues compared to the peripheral blood. HHV6, adenovirus, and Epstein-Barr virus of the herpesvirinae family are associated with myocarditis, which may occur both in immunocompetent and immunocompromised hosts, as well as in children and adults.[63-69] In immunocompromised patients, the HHV6 myocarditis can be fatal.[66,67] The myocarditis is pathologically characterized by T-lymphocyte infiltration and myocyte injury.

Myocardial infection with HCMV is more commonly observed in immunocompromised hosts. The myocardial pathology is characterized by T-cell inflammatory infiltrate and by the presence of typical intranuclear amphophilic inclusion bodies that specifically immunestain with anti-HCMV antibodies. The virus infects both myocytes and endothelial cells. Seroepidemiologic studies suggest HCMV infection to be widespread and influenced by age, geography, and cultural and socioeconomic status. Children become infected early in life in developing countries, whereas up to 80% of the adult population is infected in developed nations. The course of primary infection is usually mild or asymptomatic in immunocompetent hosts as HCMV establishes a latent but persistent infection reflecting the inability of the immune system to clear the infection; immune evasion mechanisms allow infected cells to escape both innate and adaptive effector immunity.[70] In immunosuppressed patients (eg, solid organ or bone marrow transplantation recipients), the infection can be reactivated to result in systemic and organ infection; heart is a possible target for tissue infection, especially in heart transplant recipients. The diagnosis and treatment of viral infections in transplanted patients are managed by pre-emptive or prophylactic therapy, and antiviral treatment is based on established protocols.[71] Antiviral treatments can be administered when the viral diagnosis is established. For herpes simplex virus types 1 and 2 and for varicella-zoster virus, acyclovir (or its prodrug valacyclovir) and famciclovir have greatly reduced the burden of disease and have demonstrated a remarkable safety record. Drug resistance, in the otherwise healthy population, has remained below 0.5% after more than 20 years of antiviral use. Resistance is more common in immunocompromised patients, and alternative drugs with good safety profiles are needed. Ganciclovir and valganciclovir remain the drugs of choice for HCMV infection in immunocompromised hosts.[72,73]

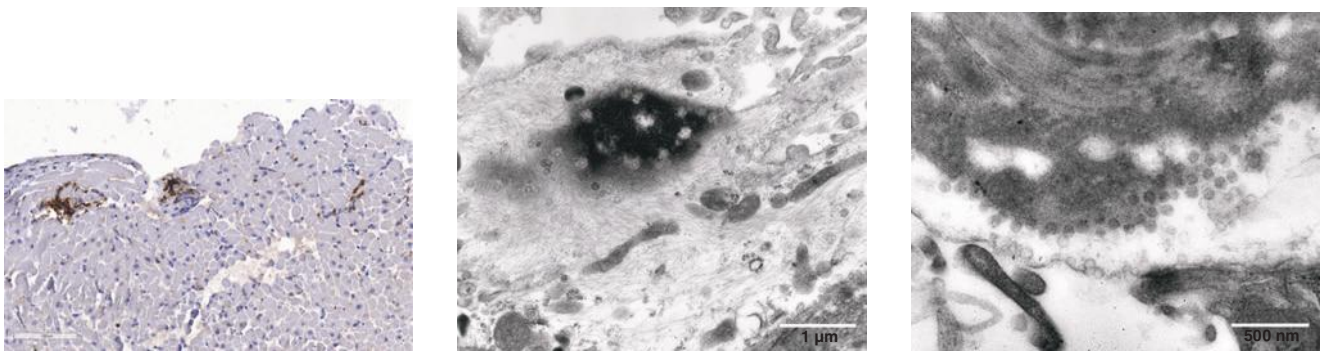


FIGURE 63–3. Parvovirus B19 (B19V) myocardial infection: cardiogenic shock, female age 37 years, ejection fraction = 10%. The patients was admitted to the hospital after 7 days of fever and one episode of syncope the night before; both children had suffered febrile flu in the course of the month before the onset of her symptoms. The patient was immediately supported with medical treatment and extracorporeal membrane oxygenation. The endomyocardial biopsy showed mild focal inflammatory infiltrates without significant myocyte damage. Molecular tests gave negative results for enteroviruses (coxsackievirus B3) and Ebstein-Barr virus. B19V was present as 402 copies/10^6 cells in blood and 109,496 copies/10^6 cells in myocardium. **A.** Anti-CD3 immunostain showing focal inflammatory infiltrates. **B** and **C.** Electron micrographs showing virus-like particles in endothelial cells. The patient experienced full recovery of left ventricular (LV) function during the next 10 days and was discharged 24 days later with LV ejection fraction of 54%.

Postacute Phase of Viral Myocarditis

Evolution of Myocarditis Myocarditis can have a fulminant course (rare), can heal spontaneously (common), or in a minority of cases, can evolve into a chronic, low-grade inflammatory myocardial disease (Fig. 63–4). The diagnosis of chronic myocarditis is ideally established by biopsy-proven evidence of the acute phase and demonstration of the persistent myocardial inflammation. Different terms are currently found in the literature describing the latter pathologic substrate, including chronic myocarditis, subacute myocarditis, inflammatory cardiomyopathy, and myocarditis-induced DCM. Each term incorporates the demonstration of myocardial inflammation. The term *inflammatory cardiomyopathy* was introduced in 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies and was defined as myocarditis associated with cardiac dysfunction.[1] The term and the definition were adopted by the ESC Working Group for Myocardial and Pericardial Diseases.[3] The term *inflammatory cardiomyopathy* does not describe the phenotype (dilated or arrhythmogenic) and does not specify the cause. Most available clinical series have rarely included both baseline and follow-up biopsies[74-76] and have only reported the initial EMB performed at onset of the symptoms. The non-EMB series inferred the diagnosis of chronic myocarditis based on clinical presentation suggestive of a recent-onset, flu-like syndrome shortly preceding the onset of cardiac symptoms, elevated inflammatory markers, and imaging characterization in patients with angiographically proven normal coronary arteries.[77] Past studies estimated that 30% of DCM evolved from myocarditis.[75,76,78,79] In a recent study, 82 patients with biopsy-proven active myocarditis were consecutively enrolled and followed-up for 147 ± 107 months. At 6 months, improvement or normalization of LVEF was observed in 53% of patients.[78] In another study including 174 patients with either active or borderline myocarditis, 124 patients were alive without being transplanted, 26 were dead or transplanted, and 24 (14%) were lost at a median follow-up of 23.5 months (interquartile range, 10-54 months).[79] A subsequent study included 181 consecutive patients with clinically suspected viral myocarditis; 69 patients fulfilled Dallas criteria for the diagnosis of myocarditis, 91 showed immunohistologic markers of inflammation, and 79 had a positive PCR-based genome search in the EMB. Twenty-two percent of the patients (n = 40) either died or underwent heart transplantation at a mean of 59 ± 42 months.[80]

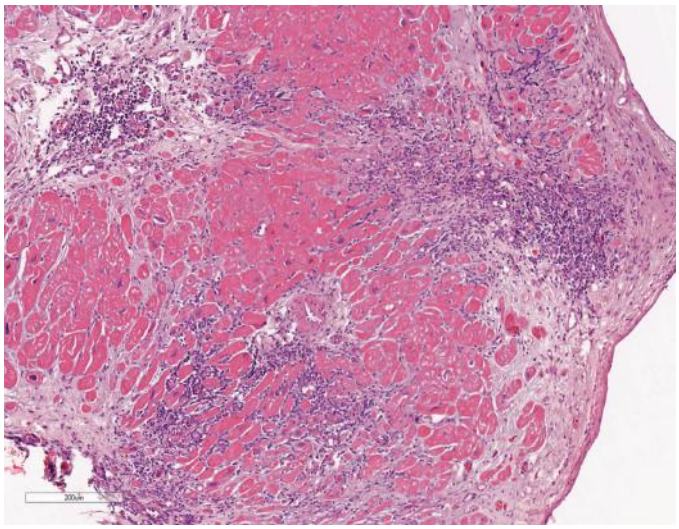


FIGURE 63–4. The figure shows ongoing active inflammation and early granulation tissue in coxsackievirus B3–positive myocarditis.

In another series of 222 consecutive patients with biopsy-proven viral myocarditis, mortality was 19.2% at a median follow-up of 4.7 years.[81] Overall, about one-fourth of patients with biopsy-proven myocarditis evolve through worsening of cardiac function and either undergo heart transplantation or die.

Predictors of Outcome Predictors of outcome vary in different myocardial biopsy studies. Persistence of New York Heart Association (NYHA) classes III to IV, left atrium enlargement, and improvement in LVEF at 6 months emerged as independent predictors of long-term outcome in one study.[78] Biventricular dysfunction at diagnosis was the main predictor of death/transplantation in another study.[79] Advanced NYHA functional class, immunohistologic signs of inflammation, and lack of β-blocker therapy (but not histologic characteristics [positive Dallas criteria] or detectability of viral genome) were found to relate to poor outcome[80]; high rates of cardiomyocyte apoptosis were associated with functional recovery at 1 year.[82] The presence of late gadolinium enhancement (LGE) emerged as the best independent predictor of all-cause and cardiac mortality, whereas the initial presentation with heart failure was a predictor of incomplete long-term recovery.[81] Similarly, a high LV end-diastolic dimension Z-score on admission in children also was a predictor of worse outcomes with higher mortality and incomplete recovery.[83] In 203 consecutive patients with an initial cardiac magnetic resonance (CMR)–based diagnosis of acute myocarditis (typical LGE) and a mean follow-up of 18.9 ± 8.2 months, an initial alteration of LVEF was the only independent CMR predictor of adverse clinical outcome.[84]

Therefore, the most consistent predictors of worse outcome included NYHA functional class and presence of heart failure or LV dilation and dysfunction and suggest little added value to myocarditis or postmyocarditis substrate.

Evolution of Acute Myocarditis to a Dilated Cardiomyopathy–Like Phenotype

Three pathogenetic hypotheses support the evolution from acute to chronic myocarditis or chronic inflammatory heart disease.

Immunopathogenetic Hypothesis It has been proposed that immunopathogenic or inflammatory reactions could lead to tissue damage uncoupled from the original viral injury.[33] The original myocyte damage induced by the acute inflammation might trigger an abnormal immune response that could subsequently smolder into a subacute and chronic phase of myocardial inflammation and myocyte damage. Few studies have reported the presence of anticardiac autoantibodies and immunoglobulins in blood samples.[85] This hypothesis supports the potential benefit of immunosuppression. However, it has also been suggested that the infectious agent, or virus in particular, could persist and induce chronic inflammation and myocyte damage.[33] Based on this hypothesis, antiviral agents could help cleanse the infected myocardium from the persistent viral infection. However, the pertinent issues include how to detect viral persistence, demonstrate its virulence, and implicate it as the basis of myocardial dysfunction. Several studies have questioned the validity of PCR-based detection of viral genome in myocardial tissue as cause of the underlying myocardial disease, because many nonmyocarditis and noncardiomyopathy controls also test positively for the viral genome load.[86-89] It is reasonable to propose that both mechanisms, including viral persistence and the autoimmune reaction, might contribute to the progression of myocardial damage, chronic myocardial remodeling, and dysfunction. Both mechanisms, although biologically plausible, have been variably demonstrated and lend importance to the antiviral and immunosuppressive interventions. However, the major missing link in patients with poor clinical outcome is the systematic evaluation of the family to exclude underlying genetic causes that can either cause or contribute to the eventual phenotype.[90]

Treatment of Viral Myocarditis

Treatment of myocarditis consists of supportive care with heart failure guideline–directed medical therapy and diuretics to relieve congestion.[91] The use of positive inotropic agents is reserved for patients with reduced cardiac output and impaired organ perfusion. Temporary or implantable mechanical support devices are frequently employed in patients with refractory cardiogenic shock.[92]

Immunosuppressive Therapy Current clinical guidelines do not support the use of immunosuppressive therapy in the routine management of acute myocarditis.[3] A study of 102 patients with acute-onset DCM classified as either reactive or nonreactive (based on the biopsy or other evidence of inflammation) failed to resolve LVEF after 9 months of prednisone treatment even after an early transient improvement in reactive patients.[93] The multicenter Myocarditis Treatment Trial randomized 111 patients with biopsy-proven myocarditis of unknown etiology and an LVEF less than 45% to conventional therapy versus immunosuppressive therapy consisting of prednisone together with azathioprine or cyclosporine. Both groups experienced an average LVEF increase of 9% over 28 weeks, but immunosuppressive therapy failed to attenuate clinical disease or improve survival.[8] Reserving immunosuppressive therapy for only those patients with ongoing inflammation has met with mixed success. A randomized study of 84 patients with unexplained DCM and increased human leukocyte antigen expression in biopsy specimens compared guideline-directed medical therapy of heart failure alone or in combination with prednisone and azathioprine.[94] The addition of immunosuppressive therapy was associated with an increase in LVEF and NYHA functional class at 3 and 24 months, but failed to reduce a primary composite end point of death, transplantation, or hospitalization. The favorable response to immunosuppressive therapy has been reported predominantly in virus-negative, autoimmune forms of myocarditis. In a study of 41 patients with active myocarditis and chronic heart failure treated with prednisone and azathioprine,[95] 21 patients were considered responders, experiencing an increase in LVEF from an average of 25.7% at baseline to 47.4% following treatment. Cardiac autoantibodies were present in 91% of these patients and in none of the nonresponders. Interestingly, viral genomes were detectable in 85% of the nonresponders and only 14% of responders. The Tailored Immunosuppression in Inflammatory Cardiomyopathy study was a randomized, placebo-controlled trial of prednisone and azathioprine in virus-negative myocarditis[96]; immunosuppressive therapy of 85 patients was associated with an increase in LVEF, reduction in LV volumes, and improved NYHA functional class.

Immunomodulatory Therapies High-dose intravenous immunoglobulin (IVIG) has both immunomodulatory and antiviral effects. Clinical trial results of its use in myocarditis have been mixed. In an open-label study, 9 of 10 adult patients with new-onset heart failure treated with IVIG had a significant improvement in LV function.[97] The Intervention in Myocarditis and Acute Cardiomyopathy trial was a randomized, placebo-controlled trial of IVIG that enrolled 62 patients with recent-onset DCM and LVEF < 40%.[98] Of these, 15% of patients had biopsy-proven myocarditis. No benefit of immunomodulation was demonstrated in terms of ejection fraction or survival at 6 and 12 months. Direct removal of circulating cardiac autoantibodies through the use of immunoadsorption has also been reported in a small, single-center study of patients with recent-onset cardiomyopathy.[99] In the absence of positive results from randomized controlled trials, it is not possible to make a recommendation for the use of IVIG or immunoadsorption.[3]

Antiviral Therapies In patients with enterovirus myocarditis and viral persistence, treatment with interferon-β (IFN-β) has been reported to produce hemodynamic and clinical improvement.[76,100] Twenty-two patients with adenoviral or enteroviral genomes from EMBs and heart failure refractory to guideline-directed medical therapy were treated for 6 months with IFN-β. Treatment produced structural and functional LV improvement, and a majority of patients showed an improvement in NYHA functional class; viral genome was successfully eliminated in all patients, and myocardial inflammation was substantially reduced. Long-term follow-up of this cohort and others who spontaneously cleared enterovirus infection showed improved survival as compared to those with viral persistence.[76] Elevated levels of IFN-β, either through spontaneous production or exogenous administration over 6 months, were associated with effective enterovirus clearance and improved outcome. Conversely, the lack of spontaneous IFN-β production was associated with enterovirus persistence and reduced long-term survival. In a recent phase II study, 143 patients with symptoms of heart failure and biopsy-based confirmation of the enterovirus, adenovirus, and/or B19V genomes in their myocardial tissue were randomly assigned to double-blind treatment with either placebo (n = 48) or 4×10^6 IU (n = 49) or 8×10^6 IU (n = 46) of IFN-β-1b for 24 weeks, in addition to standard heart failure treatment. Compared to placebo, virus elimination and/or virus load reduction was higher in the IFN-β-1b groups (odds ratio 2.33, $P = .048$; similarly in both IFN groups). IFN-β-1b treatment was associated with favorable effects on NYHA functional class and improvement in quality of life and patient global assessments. The frequency of adverse cardiac events was similar in the IFN-β-1b groups compared to the placebo group.[74] Results of major clinical trials are listed in Table 63–2.

NONVIRAL INFECTIOUS MYOCARDITIS

Bacterial Myocarditis

Although the list (see Table 63–1) of the causes of infective myocarditis may include several different bacteria, the proportion of bacterial myocarditis in immunocompetent hosts is low. Recent reports suggest a changing epidemiologic scenario of myocarditis-causing bacterial infections (eg, *Corynebacterium diphtheriae* infection is increasing worldwide, particularly in the developing countries).[101-104] Uncommon pathogens with atypical clinical presentation such as *Listeria monocytogenes* and *Leptospira* are rare causes of myocarditis, and *Legionella* typically associated with pneumonia may occasionally present with fulminant myocarditis.[105-107] Warning messages come from single case reports or small clinical series demonstrating myocarditis in both immunocompetent and immunodeficient patients with multidrug-resistant infectious agents.[108] Typhoid infection from H58 lineage is one of the numerous reports on the re-emergence of typhoid in southern and eastern Africa, particularly from in Blantyre since 2011, highlighting the need for identifying the reservoirs and transmission of disease.[108] Recently, nontyphoid *Salmonella*, most commonly *Salmonella enteritidis*, was reported to inflict an overall mortality of 24%, wherein 42% of patients required intensive care and myocarditis was associated with poor prognosis and affected young adults.[109] In immunocompromised hosts, myocarditis can complicate meningococcal infection with an extremely poor prognosis and high mortality.[110-112]

Bacterial coinfections with prevalent *Staphylococcus aureus* and *Streptococcus pneumoniae* in patients with influenza can cause myocarditis.[113] Children with pre-existing neurologic conditions and immunocompromise are at increased risk of pH1N1-associated death after intensive care unit admission. Secondary complications of pH1N1, including myocarditis, encephalitis, and clinical diagnosis of early presumed methicillin-resistant *S aureus* coinfection of the lung, have been reported as fatal risk factors.[114] Tubercular myocarditis is still known

TABLE 63–2. Clinical Trials in Myocarditis and Inflammatory Cardiomyopathies

Design and Diagnosis	No. of Patients	Treatments	Primary End Point	Results	Rerefence
• Randomized controlled trial • DCM	102	Prednisone vs placebo	> LVEF at 3 months or < LV end-diastolic dimensions	Mean LVEF > 4.3% ± 1.5% in the prednisone vs 2.1% ± 0.8% in the control group ($P = .054$)	93
• Randomized controlled trial • Biopsy-proven myocarditis (unknown etiology)	111	Prednisone + cyclosporine or azathioprine vs conventional therapy	LVEF at 28 weeks	No difference in LVEF or survival in the two groups ($P = .96$)	8
• Randomized controlled trial • Inflammatory DCM (unknown etiology, increased HLA expression on EMB)	84	Prednisone plus azathioprine vs placebo	Composite: death, heart transplantation, and hospital readmission over 2 years	No difference in primary end point (22.8% immunosuppression group vs 20.5% placebo group)	94
• Randomized controlled trial • Recent-onset unexplained DCM (≤ 6 months)	62	IVIG vs placebo	LVEF at 6 and 12 months	Similar improvement in LVEF at 6 and 12 months	98
• Randomized controlled trial • Inflammatory, virus-negative DCM	85	Prednisone plus azathioprine vs placebo	LVEF at 6 months	Significantly improved LVEF and decreased LV dimensions in immunosuppressive group	96
• Randomized controlled trial • Symptoms of HF and biopsy-based confirmation of EV, ADV, PVB19 genomes in myocardial tissue	143	4×10^6 (n = 49) and 8×10^6 IU (n = 46) interferon-β-1b vs placebo (n = 48)	Virus elimination and/or virus load reduction at 24 months	Virus elimination/load reduction: higher in the interferon-β-1b groups (odds ratio, 2.33; $P = .048$), similar in both interferon groups and strata	74

Abbreviations: ADV, adenovirus; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; EV, enterovirus; HF, heart failure; HLA, human leukocyte antigen; IVIG, intravenous immunoglobulin; LV, left ventricular; LVEF, left ventricular ejection fraction; PVB19, parvovirus B19.

to occur and cause sudden death.[115,116] Finally, myocarditis can follow medical treatments for rare infections such as ehrlichiosis.[117,118]

Fungal Myocarditis

In immunocompetent hosts, fungal myocarditis is rare; *Candida* and *Aspergillus* may occasionally cause myocarditis and can represent hospital-acquired infections.[119-121] Fungal infections are more commonly associated with endocarditis (see Chap. 67), in particular in postsurgical patients and in patients receiving implantable devices.

Myocarditis Associated With Parasitic Infections

Protozoal Infections In immunocompetent hosts, *T cruzi* is the most common parasitic infection known to be associated with myocarditis[22,24,25] (described later). Between 5 and 18 million people are currently infected, and the infection is estimated to cause more than 10,000 deaths annually.[22,24] *T gondii* causes a disease known as toxoplasmosis.[122] While the parasite is found throughout the world, the prevalence of human *Toxoplasma* infection varies in different parts of the world and has been reported with rates up to 75%.[123,124] Few infected individuals have symptoms. However, in pregnant women and individuals who have compromised immune systems, *Toxoplasma* infection can cause severe consequences. The implementation of prophylaxis with trimethoprim-sulfamethoxazole in transplanted patients has significantly contributed to prevent post-transplantation myocarditis.[124]

A rare infection is sarcocystosis, which typically affects muscle but rarely involves the heart[125]; it can be suspected in travelers returning ill from high-risk areas complaining of myalgia with or without fever. Acute muscular sarcocystosis shows an apparent biphasic course with fever and acute myalgia followed subsequently by elevated creatine phosphokinase, eosinophilia, and possible relapses.[126]

Helminthic Infections Helminthic infections rarely affect the heart. They can be suspected in endemic areas with trichinosis and echinococcal infections. Cases of cardiac involvement in leishmaniasis[127] or toxocariasis[128] are exceptional.

Trichinellosis or Trichinosis Eosinophilic myocarditis is a possible complication in patients with trichinosis, a zoonosis caused by nematodes of the genus *Trichinella*. The most common species affecting humans is *Trichinella spiralis*, which has a global distribution and is most commonly found worldwide in carnivorous and omnivorous animals.[129,130] The burden of annual infection worldwide is estimated around 10,000 cases. *Trichinella* is endemic in the areas with unregulated slaughter of pigs and particularly in areas where these are in contact with wild animals.[131,132] A systematic analysis of six international databases with 494 studies and 65,818 cases reported 42 deaths in 41 countries from 1986 through 2009. The World Health Organization European Region accounted for 87% of cases; 50% of those occurred in Romania during 1990 to 1999. With a prevalence of 1.1 to 8.5 infected cases per 100,000 population,[133] cardiac involvement continues to be a major complication in Romania.[134] The myocardial involvement occurs in the second phase of the infection cycles, and humans are affected when consuming raw or undercooked meat infected with the *Trichinella* parasite; high temperatures (> 77°C) and freezing (–25°C) are known to kill the larvae of the parasite. After exposure to gastric acid, the larvae are released from the cysts (after 1 week of the infection) and invade the small bowel mucosa where they develop into adult worms. Then the larvae migrate through peripheral blood and may reach striated muscles where the encystment is completed in 4 to 5 weeks, and the encysted

larvae may remain viable for several years. When informative, muscle biopsy shows inflammatory infiltrates, collagen capsule of the "nurse cell," and intersected muscle larva.[132-135]

The clinical presentation depends on the stage of infection, number of invading larvae, infected tissues, and general physical condition of the patient. The course of the infection can remain asymptomatic. Symptoms of trichinosis occur in two stages. Intestinal infection is the first stage and develops 1 to 2 days after consuming contaminated meat. The most common symptoms are nausea, diarrhea, abdominal cramps, and fever. The second stage corresponds to larval invasion of muscles and starts after about 7 to 15 days. The most common symptoms are muscle pain and tenderness, weakness, fever, headache, and swelling of the face, particularly periorbital swelling. The pain is pronounced in the respiratory, masticatory, retropharyngeal, and orbicular muscles and tongue. It may be accompanied by skin rash and ocular involvement.[132-135] Eosinophilic myocarditis may occur in the second stage of the disease; it can be life-threatening and may manifest with heart failure and arrhythmias; right ventricular outflow tract obstruction is rarely reported.[132,135] The diagnosis of trichinellosis should be based on clinical findings; pathology findings of muscle and/or EMB detecting larvae; laboratory findings of specific antibody response by indirect immunofluorescence, ELISA, or Western blot; hypereosinophilia (1000 eosinophils/mL) and/or increased total IgE levels; increased levels of muscle enzymes; and investigation of the possible source and origin of infection[129-132] (Table 63–3). When the diagnosis is proven, the treatment is based on antihelminthic drugs, such as albendazole or mebendazole, and supportive therapy in patients with heart failure.[132]

Echinococcosis Echinococcosis is endemic in several geographic areas such as North Africa, South America (Argentina), New Zealand, Greece, and Iceland. In infected patients, cardiac involvement is uncommon (< 2%), and even in patients with cardiac involvement, signs and symptoms are rare (< 10%). The host of *Echinococcus granulosus* is the dog; humans could serve as the intermediate host if they accidentally ingest ova from contaminated dog feces. Hydatid cysts more commonly affect liver and lungs and are usually solitary. Combined liver and extraliver cysts are observed in 25% of cases; cardiac cysts comprise 0.5% to 2% of all cases. Within the heart, hydatid cysts are usually located in the left ventricle (up to 60%) or right ventricle (up to 20%) and rarely found in the pericardium (10%-15%).[136] Pericardial cysts usually do not cause symptoms and remain silent until they grow large and result in cardiac compression, atrial fibrillation, and even sudden death. Myocardial cysts localized in the interventricular septum or LV wall remain segregated and undergo calcification or generate daughter cysts and undergo rupture.[137,138]

Depending on the localization, the effects of the ruptured hydatid cysts vary. It could result in pericarditis and may evolve to chronic constrictive pericarditis when ruptured in the pericardium; cardiac tamponade is uncommon.[139,140] When the cyst ruptures in right cardiac chambers, possible complications include pulmonary embolism and pulmonary hypertension.[141-143] Syncope can occasionally be the first manifestation of the disease.[144] The rupture of the hydatid cysts with release of the fluid may cause severe anaphylactic reaction. Symptoms may occur in patients with pericardial involvement or with mass-induced right-sided obstruction. Echocardiography and CMR may localize the myocardial cysts.[145] When present, eosinophilia may contribute to the diagnostic suspicion. Serologic tests such as the Casoni test demonstrate false-positive and false-negative results in up to 30% of cases; ELISA test has a sensitivity of 91% and specificity of 82%.[146]

Medical treatment is based on albendazole and mebendazole; surgical resection is the treatment of choice for the prevention of rupture of cysts. Novel application of the cardiac stabilizer (Octopus IV) was reported to safely lift the heart up and excise a hydatid cyst that was firmly adherent to the posterior surface of the heart.[147]

TABLE 63–3. European Center for Disease Control: Case Definition for Human Trichinellosis

Case classification:

1. Probable: nonapplicable
2. Possible: any person meeting the clinical criteria and with an epidemiologic link
3. Confirmed: any person meeting the laboratory criteria and with clinical criteria within the past 2 months
4. To be reported: confirmed cases should be reported to European Union level

Criteria Groups	Criteria
Clinical criteria	At least three of the following six: 1. Fever 2. Muscle soreness and pain 3. Gastrointestinal symptoms 4. Facial edema 5. Eosinophilia 6. Subconjunctival, subungual, and retinal hemorrhages
Laboratory criteria	At least one of the following two laboratory tests: 1. Demonstration of *Trichinella* larvae in tissue obtained by muscle biopsy 2. Demonstration of *Trichinella*-specific antibody response by indirect immunofluorescence, ELISA, or Western blot (ie, seroconversion)
Epidemiology criteria	At least one of the following three: 1. Consumption of laboratory-confirmed parasitized meat, 2. Consumption of potentially parasitized products from a laboratory-confirmed infected animal, 3. Epidemiologic link to a laboratory-confirmed human case by exposure to the same common source

Abbreviation: ELISA, enzyme-linked immunosorbent assay.

Toxocariasis Toxocariasis occurs worldwide. The highest prevalence is reported from tropical and subtropical countries.[130] Myocarditis is the most frequent clinical presentation (58%), followed by pericarditis (25%) with or without tamponade. Cardiac involvement in *Toxocara* infection is a potentially life-threatening complication. The cardiac workup is based on electrocardiography (ECG), chest x-ray, echocardiography, and laboratory tests. ECG may show nonspecific abnormalities including peripheral and thoracic low-voltage and nonspecific ST-T alterations. The chest x-ray shows cardiomegaly and signs of pulmonary congestion. Echocardiography shows wall thickening, hypokinesia, and a reduced LVEF with possible pericardial effusion or endomyocardial fibrosis and restrictive cardiomyopathy. Thrombotic complications may occur. The therapeutic regimens vary widely especially with regard to the duration of therapy, and the combination of an anthelmintic drug and corticosteroids appears to be a valuable option. Clinical manifestation of the tissue infection by parasites should be considered in cases of nonspecific organ manifestations (ie, heart, lungs, liver) accompanied by fever and eosinophilia, with or without allergic skin rash.[148,149]

MYOCARDIAL TRANSMISSION OF INFECTIONS IN HEART TRANSPLANTATION

Organ transplant recipients can develop infections as a result of transmission through the graft, reactivation of silent infection, reinfection in a healthy graft, or de novo infection. Infections can manifest in the post-transplant period as a consequence of immunosuppression.

In 2004, the United Network for Organ Sharing introduced the label of "high-risk donor" to identify donors who meet the Centers for Disease Control and Prevention criteria for high-risk behavior for infection.[150] In a recent single-center series including 55 recipients of heart transplants from high-risk donors, survival was excellent (short-term survival [1 year] 94%; long-term survival [3 years] 80%), and there was no increased incidence of perioperative or postoperative complications; the risk of transmission of infection from donors in this subgroup seemed to be minimal; only 1 of 55 patients (1.9%) had hepatitis C seroconversion at 105 days after receiving the transplant. After antiviral treatment, the patient had undetectable viral loads. All other patients (n = 54) had undetectable plasma viral loads of HIV, hepatitis C, and hepatitis B.[151] These data encourage revision of criteria for declining grafts from high-risk donors.

Some infectious diseases such as Chagas disease, endemic fungal infections, tuberculosis (which could be drug resistant), leishmaniasis, and other viral and parasitic diseases should be considered in the differential diagnosis of post-transplant infections in foreign-born recipients.[152]

MYOCARDITIS IN AUTOIMMUNE DISEASES

Several autoimmune diseases may involve myocardium, endocardium, pericardium, valves, and both small intramural vessels and epicardial coronary arteries. The diagnosis of myocardial involvement in autoimmune disease should be based on the recommendations of scientific societies.[3]

The diagnosis of isolated autoimmune myocarditis in patients who do not demonstrate systemic or extracardiac autoimmune disease is difficult and requires demonstration of both myocarditis and autoantibodies mediating myocyte damage or inducing inflammatory autoimmune reaction. This complex diagnostic workup is based on the demonstration of circulating autoantibodies. The significance and role of autoantibodies vary in the different diseases wherein they represent markers of disease, disease-inducing autoantibodies, or both. A paradigmatic example of autoimmune myocarditis is neonatal lupus or autoimmune congenital heart block (atrioventricular block) that is caused by the placental transfer of maternal Ro/La autoantibodies (SSA/Ro and anti-SSB/La antibodies) damaging the conduction tissues during fetal development.[153] Infants may demonstrate transient skin and systemic lesions and permanent atrioventricular block, associated with significant morbidity and mortality; pacemakers are implanted in two-thirds of cases. Acute myocarditis may appear in early phases of the disease and is characterized by lymphocytic infiltrates.[154,155]

Serum cardiac autoantibodies may be found in autoimmune myocarditis, DCM, and normal controls[3] and include anti-sarcolemmal (ASA), anti-fibrillary (AFA), organ-specific and partially organ-specific anti-heart (AHA), anti-intercalated disk (AIDA), anti-adenine nucleotide translocator (anti-ANT), anti-myolemmal (AMLA), anti-adrenergic receptor (anti-AR), anti-interfibrillary (anti-IFA), branched chain α-ketoacid dehydrogenase dihydrolipoyl transacylase (anti-BCKD), anti-heat shock protein (HSP), anti-myosin heavy chain (MHC), anti-myosin light chain 1 ventricular (MLC1v), anti-actin, anti-tropomyosin, and anti-laminin antibodies. The significance of these antibodies is still a matter of research.[3] Recommendation 9 of the recent position statement of the ESC Working Group on Myocardial and Pericardial Diseases suggests testing for cardiac autoantibodies based on the availability of tests and center expertise; unfortunately, no commercially available and standardized cardiac autoantibody tests have been validated.[3]

Autoantibodies in postviral cardiomyopathy can be secondary to the effects of primary myocyte damage induced by the viral infection; picornavirus infections (type 1 diabetes, myocarditis, or paralysis) demonstrate a strong association with autoimmunity, with particular evidence in type 1 diabetes and myocarditis.[156,157] The recent demonstration of T cells expressing dual T-cell receptors on a single cell induced as a natural consequence of Theiler virus infection, which may occasionally cause human myocarditis, could explain the pathogenicity resulting from induction of autoimmunity to organ-specific antigens.[158]

TOXIC MYOCARDITIS

Toxic substances can cause myocardial injury and inflammation (see Table 63–1). The myocardial insult can be transient and reversible or chronic and persistent.

DIRECT TOXIC SUBSTANCES

Well-known examples are myocarditis forms caused by lithium and arsenic. Historically, arsenic was used in agriculture to control parasites and pests, and exposure in industry is possible during processing of minerals and coloring of glass. Elimination from the body is easier for organic than for pentavalent or trivalent inorganic arsenic. Trivalent derivatives are 100 times more toxic than pentavalent forms. Injection of arsenic may cause myocarditis characterized by myocyte necrosis, infiltration of leukocytes and lymphocytes, and neutrophilic perivasculitis.[159] Lithium is used in psychiatry as an antimaniac and mood stabilizer. It can cause various adverse effects including myocarditis and arrhythmias[160]; sinus node dysfunction can occur with serum lithium levels in the therapeutic range.[161] Zinc phosphide has been used as a rodenticide and is toxic by ingestion; its conversion to phosphine gas that is absorbed into the bloodstream causes metabolic and nonmetabolic toxic effects, including myocarditis, pericarditis, acute pulmonary edema, and congestive heart failure.[162] Several other substances may cause toxic myocarditis (see Table 63–1). Their precise diagnosis is based on the identification of the toxic agent.

DRUG-INDUCED MYOCARDITIS

Different drugs may induce similar cardiac toxicity. The clinical manifestations include the entire spectrum of cardiac phenotypes, including cardiomyopathy, conduction disturbances, arrhythmias, hypertension, and coronary artery disease. Each of them is discussed in their corresponding chapter in this text. Myocarditis is one of the possible complications; it can either regress if the drug is discontinued or persist and evolve through a cardiomyopathy phenotype.

In the acute drug hypersensitivity syndrome, the clinical manifestations occur after a few weeks from initiation of a new drug; less commonly, the syndrome may manifest at any time after drug consumption. Drugs known to potentially cause hypersensitivity syndrome include antibiotics, antiepileptics, allopurinol, and sulfonamide-containing drugs (see Table 63–1). In addition, drugs used for hemodynamic support in patients with cardiogenic shock or acute heart failure such as dobutamine may trigger hypereosinophilia and hypersensitivity myocarditis. When present, traits such as cutaneous rash associated

TABLE 63–4. Acute Myocarditis[a]

Life-threatening events in the absence of CAD and known causes of HF
• Cardiogenic shock
• Aborted sudden death
New-onset HF
• Symptoms include dyspnea and fatigue or arrhythmias
• Signs of heart failure on physical examination
• ECG signs such as nonspecific ST/T changes, conduction disturbances, and arrhythmias
• Imaging data demonstrating impaired systolic LV and/or RV function, with mildly dilated LV and/or RV
Syndromes simulating ACS with acute chest pain and possible but not obligate, either single or combined
• ECG changes: ST/T-wave changes and T-wave inversions (when available, a prior ECG is useful for comparative evaluation)
• Imaging demonstrating global or regional LV and/or RV impairment
• Increased markers of myocyte injury (increased TnT/TnI) evolving as in AMI or persisting over several weeks or months
• Increased inflammatory markers
Arrhythmias
• Atrial arrhthmias
• Ventricular arrhythmias
• Isolated
• Associated with HF, ACS-like syndrome

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; LV, left ventricle; RV, right ventricle; TnI, troponin I; TnT, troponin T

[a]Clinical scenarios in patients with proven absence of acute IHD/CAD, negative family history, and absence of known cardiac and systemic illness potentially cause of the observed clinical manifestations.

with fever, eosinophilia, and multiorgan dysfunction (liver, kidney, and heart) may be indicative of drug toxicity. The cardiac involvement may be extensive and associated with LV dysfunction, hypotension, and thromboembolic risk.

Clozapine is an effective antipsychotic drug[163] that is selectively and cautiously used in patients with treatment-resistant schizophrenia because of its hematologic and cardiovascular adverse effects.[164] A recent review describes 250 cases of clozapine-induced myocarditis and highlights the possibility that myocarditis is underdiagnosed in patients receiving clozapine.[165] Warning data potentially useful for suspecting myocarditis in patients treated with clozapine include recent onset of treatment (mean 14 days), the occurrence of fever close to the initial administration of the drug, old age, concomitant treatment with sodium valproate, rapid drug titration, respiratory illness, or pneumonia. The incidence of myocarditis was approximately 3%, and the need of implementing monitoring procedures cannot be overemphasized. More precise data on the prevalence of myocarditis would lead to formal indications for cardiac monitoring. The higher prevalence of clozapine myocarditis reported in Australia likely results from awareness of the complications, as well as from the systematic data collection of the treated patients.[165] Clozapine myocarditis can be fatal and only diagnosed at autopsy.[166] Timely early diagnosis is feasible, and drug removal may reverse signs and symptoms.[167,168]

DIAGNOSTIC WORKUP IN MYOCARDITIS

MEDICAL HISTORY AND PHYSICAL EXAMINATION

Myocarditis is an unexpected, often sudden, and rapidly evolving condition. Patients presenting with acute myocarditis frequently describe episodes of recent febrile illness. The clinical manifestations range from severe and life-threatening, to recent onset of heart failure, to mild signs and symptoms such as fatigue and arrhythmias. Table 63–4 summarizes various scenarios of clinical manifestations. Fulminant myocarditis may present with life-threatening events (in the absence of coronary artery disease and known causes of heart failure), such as cardiogenic shock or aborted sudden death, associated with underlying giant cell myocarditis or acute viral myocarditis. However, patients presenting with aborted sudden death with a history of sudden death in the family should invoke investigation for genetic cardiomyopathy (Fig. 63–5).

Myocarditis may present as a new onset of heart failure with symptoms such as dyspnea and fatigue or arrhythmias and signs of heart failure on physical examination. With ECG nonspecific ST-T wave changes, conduction disturbances, and arrhythmias, these patients may demonstrate echocardiographic evidence of impaired systolic LV and/or right ventricular function, with mildly dilated ventricular chambers. The clinical distinction between such presentation of myocarditis and recent-onset DCM is complex and is dependent on pathologic demonstration of myocarditis as the cause of the phenotype. Family history is

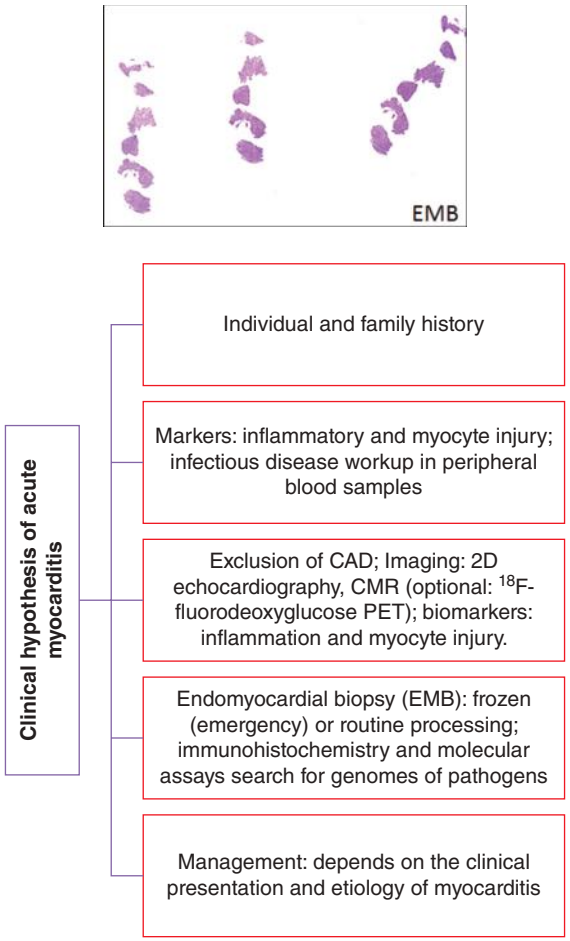


FIGURE 63–5. Clinical hypothesis of acute myocarditis. 2D, two-dimensional; CAD, coronary artery disease; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; PET, positron emission tomography.

usually negative. Chronic forms of myocarditis could also be associated with specific myocardial diseases such as sarcoidosis, autoimmune diseases, Chagas disease, or Lyme disease. The differential diagnosis between chronic myocarditis, inflammatory cardiomyopathy, and DCM is essential to prevent misdiagnosis. In clinical practice, a report concluding with the diagnosis of chronic myocarditis is uncommon, and most patients are diagnosed with DCM. Lack of investigation for genetic cause of the disease in recent-onset DCM may impact not only the management of patients but also the families.

Uncommonly, acute myocarditis masquerades as an acute coronary event with ST-T wave changes, global or regional LV hypokinesia, and elevated markers of myocyte injury.[169] The ECG alterations and wall motion abnormalities usually extend beyond a single coronary artery territory as expected in a coronary event, and the ECG and biochemical alterations are longer lasting and do not follow the usual pattern of evolution associated with acute coronary events. These abnormalities are likely to be diffuse or unrelated in myocarditis. Infrequently, myocarditis may also present with unexplained ventricular arrhythmias in a setting of DCM. A recent study evaluated fasting positron emission tomography (PET) scan findings in more than 100 consecutive patients referred with unexplained cardiomyopathy and ventricular arrhythmia for possible ablative therapy.[170] Almost 50% of patients exhibited focal fluorodeoxyglucose (FDG) uptake. The EMB revealed granulomatous inflammation representing sarcoidosis in a small subset of patients and also nongranulomatous inflammation suggestive of myocarditis in another. Correlation between low-voltage regions on electroanatomic mapping and FDG uptake was observed in 75%, and magnetic resonance imaging (MRI) findings matched abnormal PET regions in only 40%. These data suggested that significant proportion of patients considered idiopathic could have harbored occult inflammatory myocardial disease. Of the patients with FDG-based evidence of inflammation, 90% received immunosuppressive therapy and 60% underwent ablation; however, because of a lack of a control group, this study cannot be considered prescriptive and remains hypothesis generating.

Variability is immense in different series of reported patients who underwent EMB investigated with the support of molecular and immunohistochemistry; the final interpretation of pathology findings has been fraught with issues involving interobserver variability, tissue quality, stage of presentation, causes, and disease severity. Overall, clinical evaluation of the phenotype, family history, and investigation of autoimmune disease potentially associated with chronic myocardial inflammation are essential to formulate a clinical decision. Imaging strategies and biomarkers are being investigated for the supportive diagnosis, which needs to be validated against EMB.

IMAGING

The concept of imaging is progressively evolving from single-modality investigation to multimodality imaging strategies in which each test adds information that increases the specificity of the diagnostic markers for different types of myocarditis.

Echocardiography

Echocardiography is the initial investigation in patients with suspected myocarditis. Echocardiographic findings are nonspecific and include LV global or regional dysfunction with decreased ejection fraction, LV dilation, right ventricular involvement, and pericardial effusion.[171] Strain and strain rate imaging using speckle tracking may add information on early regional contractility and dysfunction[172]; in patients with biopsy-proven myocarditis, LV fractional shortening, longitudinal strain, and strain rate are reduced and correlate with the burden of myocardial inflammation.[173] In patients with suspected, but non-EMB proven, acute myocarditis, longitudinal strain and circumferential strain have specificities of 93% and 94%, respectively; the degree of strain correlates with the risk of future clinical events.[174] Irrespective of the specific contribution to myocarditis, echocardiography remains the first line of investigation.

Cardiac Magnetic Resonance

CMR provides detailed morphofunctional description of ventricular involvement[175] and offers important prognostic information. There is a substantially lower risk of events in patients with suspected myocarditis but normal CMR findings.[176] In addition, CMR also provides information on the presence and extent of pericardial effusion, which is commonly associated with myocarditis.[177] According to the Lake Louise CMR criteria, acute myocarditis is associated with (1) increased regional or global myocardial signal intensity in T2-weighted images (indicating myocardial edema); (2) increased global myocardial early gadolinium enhancement (EGE) ratio between myocardium and skeletal muscle in T1-weighted images (supporting hyperemia/capillary leakage); and (3) at least one focal lesion with nonischemic distribution in LGE T1-weighted images (suggestive of cell injury/necrosis).[175] The diagnostic accuracy does not increase with the addition of pericardial effusion.[178]

T2 Mapping for Myocardial Edema T2-weighted short tau inversion recovery (STIR) imaging can detect and localize epicardial, transmural, or global myocardial edema; T2-STIR high signal intensity identifies areas of tissue edema.[177] When evaluated as an independent measure, T2-STIR has demonstrated variable sensitivity (58%-74%) and specificity (57%-93%).[175] An alternative method for evaluation of myocardial edema is the low b-value diffusion-weighted echo-planar imaging sequence that has offered higher sensitivity (92% vs 54%) and diagnostic accuracy (95% vs 70%) compared with standard STIR-T2 images but similar specificity in acute myocarditis.[179,180] T2 mapping is able to quantitatively define the area of edematous myocardium[181] through a 16-LV segment T2-mapping protocol, which provides more robust imaging of myocardial edema than standard T2-weighted imaging.[182] Protocols based on gradient spin echo imaging techniques further improve accuracy and reduce acquisition time for T2 mapping.[181]

Early Gadolinium Enhancement EGE represents an increased distribution into the interstitial space early in the washout phase[5] as a result of hyperemia and capillary leakage.[183] EGE displays a sensitivity of 63% to 85% and specificity of 68% to 100% for the diagnosis of myocarditis in the given clinical context.[175] However, EGE does not describe relative regional distribution of gadolinium uptake and is a time-consuming process. An alternative method, the contrast-enhanced steady-state free precession technique, allows better visualization of hyperintense myocardial regions of gadolinium uptake. In a recent study of 19 patients with myocarditis, hyperemia was observed in 77% of patients and was associated with increased inflammatory markers and greater LGE.[183] CMR with contrast-enhanced steady-state free precession potentially represents a more efficient method for detecting hyperemia, but it should always be compared directly with traditional EGE.

T1 Mapping T1 prolongation also indicates myocardial edema and hyperemia.[184] A T1 value more than 990 milliseconds indicates myocardial injury and is used to create topographic maps representative of the degree of myocardial involvement.[185] In patients with clinically suspected myocarditis,[186] T1 mapping seems to be more sensitive and offers similar diagnostic accuracy as that of dark-blood T2 imaging, bright-blood T2 imaging, and LGE. The performance of T1 mapping has been reported to be similar to LGE and better than the T2-weighted imaging methods. Additional modified protocols showed that longer relaxation times were associated with high diagnostic accuracy.[187] Combined native T1 relaxation time combined with T2-weighted

imaging criteria increase sensitivity (92%), specificity (97%), and diagnostic accuracy (95%). T1 mapping improves the diagnostic confidence in cases in which traditional methods have failed to recognize any disease; incrementally elevated T1 thresholds were associated with enhancement on LGE images, suggesting a role for the absolute T1 value in determining size of myocardial injury.[188]

Late Gadolinium Enhancement T1-weighted LGE detects irreversible cell injury, myocyte necrosis, and myocardial fibrosis.[175,189] LGE detects the patchy distribution of the disease but can also demonstrate transmural patterns.[190] In acute myocarditis, automated calculation of LGE[190,191] correlates with LGE quantified by visual assessment.

Limitations and Perspectives CMR may not be specific for the process of myocardial inflammation and needs to be weaved into the clinical context; it also does not differentiate among the diverse causes of myocarditis.[153,187,188] In biopsy-proven myocarditis, tissue edema, EGE, and LGE were more common in infarct-like patterns; sensitivities in the infarct-like, cardiomyopathy, and arrhythmic patterns of presentations were 80%, 60%, and 40%, respectively. Promising evolution comes from the targeted experimental studies on in vivo uptake of perfluorocarbons in monocytes, macrophages, and granulocytes visualized by CMR imaging.[192,193] ^{19}F-labeled tracers, which may be incorporated into specific cell types, have been employed for targeted CMR.[4,5,159,193,194] A recent experimental study demonstrated the clinical feasibility of ^{19}F-MRI with perfluorooctyl bromide at 3.0 T for targeting myocardial inflammation.[195]

^{18}F-Fluorodeoxyglucose–Positron Emission Tomography

^{18}F-FDG-PET has played a diagnostic role in myocarditis[196] and in clinically suspected myocarditis, demonstrating a sensitivity of 46% and a specificity of 81%.[197] Although current evidence is not sufficient to support its routine use for the diagnosis of myocarditis, it may add functional information to the currently employed structural imaging. FDG accumulates in inflammatory cells. Sarcoidosis provides an informative example of combined approach of perfusion (eg, ^{13}N-NH_3) and inflammation (eg, ^{18}F-FDG) PET imaging in assessing myocardial inflammation, wherein normal perfusion and intense ^{18}F-FDG uptake indicate active cardiac sarcoidosis, hypoperfusion and high glucose metabolism indicate advanced sarcoidosis, and decreased or absent perfusion and negative FDG uptake indicate end-stage cardiac sarcoidosis. Parallel MRI allows localization of myocardial scars by LGE and determination of the extent of disease by T2 edema imaging.[198]

BIOMARKERS

Biomarkers may contribute to the diagnosis of acute myocarditis and its evolution to the chronic state. Beyond serology, antigenemia, viremia, and DNA-emia in infectious myocarditis, biomarkers may inform about inflammatory and myocyte injury processes.

Markers of Myocyte Injury or Damage

Diagnosis Myocarditis can be associated with increased levels of markers of myocyte injury such as cardiac troponin (cTn; troponins I and T)[164-167,198-201]; elevated cTn has been reported predominantly in the myocarditis with either fulminant or acute clinical presentation.[201] Past studies indicated that sensitivity of cTn for the diagnosis of myocarditis is low. Whereas only 34% of patients enrolled in the Myocarditis Treatment Trial had cardiac troponin I elevation,[202] recent studies have demonstrated superior predictive values of high-sensitivity troponin T for acute myocarditis when other causes of increased myocardial necrosis markers such as myocardial infarction have been systematically excluded.[203] Cardiac troponin T is routinely used in the clinical workup for both children[204] and adult patients.[205] In a screening report of the 38,197 veterans, 4469 tested positive for influenza virus. Of these, 600 had further cardiac biomarker testing, and 143 (24%) demonstrated an increase in one or more cardiac biomarkers, which was associated with acute congestive heart failure (6%), myocarditis (4%), atrial fibrillation (3%), noncardiac explanations (8%), or no documented explanation (31%).[206]

Although cTn levels have been reported as a prognostic marker in patients with giant cell myocarditis,[207] these data have not been confirmed in other studies, wherein cTn levels predict neither the diagnosis nor severity of disease.[208] cTn may be elevated in myocardial toxicity of known and novel drugs, such that in patients included in phase I trials of novel targeted therapies for a metastatic solid tumor, cTn is one of the most useful markers for measuring cardiac toxicity. In a series of 90 patients, 2 experienced chest pain and troponin I elevation and 8 revealed asymptomatic elevation of troponin I during follow-up.[209] Markers of myocyte injury can either contribute to the diagnosis or provide information for correlation with other clinical parameters in all forms of myocarditis with myocyte injury.

Overload N-terminal pro-B type (brain) natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP) levels increase in myocarditis associated with LV dysfunction, but normal values do not exclude myocarditis[210]; levels rapidly decline with recovery of the LV function.[211] In a pediatric series including 58 children with myocarditis and reduced ejection fraction < 30%, peak BNP > 10,000 ng/L and cardiac MRI late enhancement were identified as predictors of poor outcomes.[212] In a series of 70 patients with clinically suspected myocarditis and 42 patients with EMB-confirmed myocarditis, NT-proBNP in the highest quartile (> 4225 ng/mL) was predictive for cardiac death or heart transplantation at 7.5 months from the diagnosis.[212] However, newer biomarkers, such as copeptin or midregional pro-adrenomedullin, have not offered additional diagnostic or prognostic information.[212,213]

Serum cardiac autoantibodies (eg, anti-fibrillary, organ-specific and partially organ-specific anti-heart, anti-intercalated disks, anti-interfibrillary) in high levels have been described to be useful in the absence of viral genome in EMB, suggesting an immune-mediated myocarditis or inflammatory cardiomyopathy.[2,3]

The role of miRNA profiling is being investigated in acute, chronic, and fulminant myocarditis. miR-208b and miR-499 are upregulated after myocardial damage and can be measured in the plasma of patients with myocarditis.[27] Their simultaneous upregulation seems to characterize fulminant viral myocarditis.[214] Their role as possible positive regulators of toll-like receptor 4 in blood monocyte-derived dendritic cells and macrophages suggests that they can be future diagnostic contributors in patients with suspected myocarditis.[215] At present, no miRNA is demonstrated to be specific for patients with chronic myocarditis.

Markers of Inflammation

High-sensitivity C-reactive protein and erythrocyte sedimentation rate are routinely measured in patients with suspected myocarditis[216] but with limited contribution to the diagnosis. As correlation factors, C-reactive protein at admission does not seem to correlate with LGE on CMR in adult patients with myocarditis.[213] Conversely, increased levels of C-reactive protein can be critical early signs of drug toxicity myocarditis (eg, warranting close monitoring and serious consideration for cessation of drugs such as clozapine).[216,217] Experts recommend that C-reactive protein and troponin I levels should be measured at baseline, two times per week for 1 month, then once per week for another 1 month, and then once per month for the remainder of the first year.[218]

Viral serology can provide information in the acute phases of infectious myocarditis. These phases can be missed unless the clinical onset is cardiogenic shock or acute heart failure and patients are

tested shortly after onset of the illness. In chronic myocarditis and in inflammatory cardiomyopathy, the clinical contribution of viral serology is limited; IgG antibodies for cardiotropic virus can be found in the bloodstream of the general population without accompanying cardiac involvement.[219] Serology is routinely performed in parallel with molecular tests seeking genomes of the suspected pathogens. A positive virus PCR in peripheral blood does not prove viral myocarditis. However, when viral genome is present in the EMB, blood viral PCR can exclude or confirm systemic infection.[3] It may also differentiate an acute viral infection from endogenous viral reactivation in which there is higher virus replication.

ENDOMYOCARDIAL BIOPSY

EMB is the current gold standard for the diagnosis of myocarditis.[3,31] EMB samples are processed with conventional methods. The frozen samples are processed in case of clinical emergency such as nonischemic cardiogenic shock or resuscitated cardiac arrest, when EMB is performed during implantation of the circulatory support devices. EMB offers immediate information about the basis of cardiogenic shock allowing differentiation between fulminant myocarditis and nonmyocarditic causes. Although frozen sections for histomorphologic studies are not optimal, at least the diagnosis of myocarditis is feasible. In patients presenting with clinically stable heart failure, even of recent onset, EMB samples are routinely processed. The interpretation of pathologic features is based on light microscopic examination of routine stains and immunohistochemistry, and electron microscopy is undertaken when possible and indicated. One or more samples are used for viral investigation, both pathogen isolation and search of replicating pathogen.

Inflammation

The extent of myocardial inflammation and the type of inflammatory cells are major pathologic contributors to the diagnosis; acute myocarditis is characterized by conspicuous focal or diffuse inflammatory infiltrates. Inflammatory cells are routinely recognized on cytomorphology, but immunophenotyping of inflammatory infiltrates allows precise characterization of T-cell $CD4^+$ and $CD8^+$ subsets and identification of the extent of infiltration by the cells of monocyte-macrophage lineage. Neutrophilic and eosinophilic infiltrates, mast cells, and plasma cells are easily detectable using routine stains. Serial sectioning of routine EMB sampling (about 2-3 mm size/sample) usually provides sufficient material for multiple staining and immunohistochemical staining. Immunohistochemical characterization of the inflammatory infiltrate also provides for diagnosis of rare primary lymphomas of the heart or unusual cardiac involvement in diseases such as Erdheim-Chester disease. The presence of a few scattered inflammatory cells in the myocardium, even when highlighted by immunohistochemical stains, should not be labeled as myocarditis because some inflammatory cells can be present in the normal myocardium[8] and hearts affected by genetic cardiomyopathy.[220]

Eosinophilic inflammatory infiltrates are present in a variety of myocarditides of different origin. Eosinophilic granulocytes may infiltrate in both myocardium and endocardium. EMB can contribute to differentiate neoplastic, reactive, and secondary eosinophilic syndromes and eosinophilic syndromes of unknown significance.

Giant cells are found in giant cells myocarditis, sarcoid granulomas, tubercular myocarditis, rheumatic heart disease, and brucellosis. In giant cell myocarditis, inflammatory cells heavily infiltrate the myocardial tissue. In small EMB samples, giant cells may be missed.

Small intramural vessels occasionally demonstrate vasculitis, with inflammatory infiltrates involving small arteriolar walls. Small thrombi may occur in intramural vessels (Fig. 63–6). When both interstitial inflammatory infiltrates and vasculitis are present, patterns of myocarditis and ischemic myocyte damage may coexist.

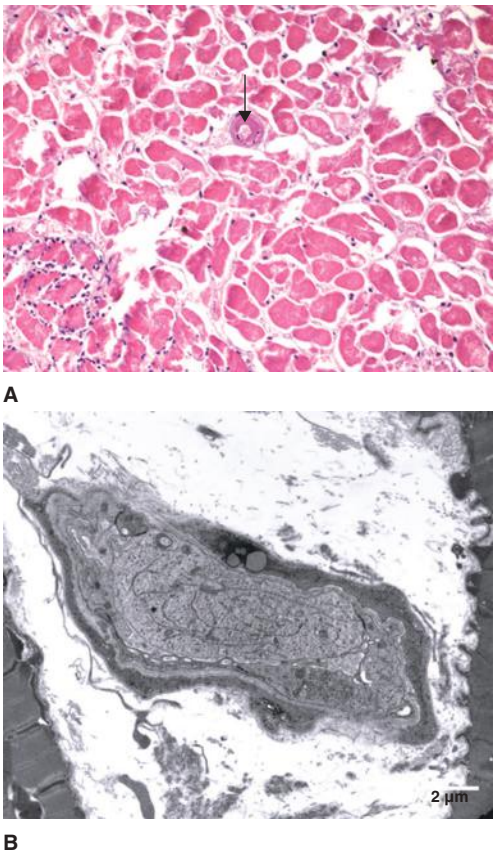


FIGURE 63–6. Small intramural vessels may show thrombi, either fibrin (**A**, *arrow*) or platelets (**B**; degranulated platelets occluding a small vessel).

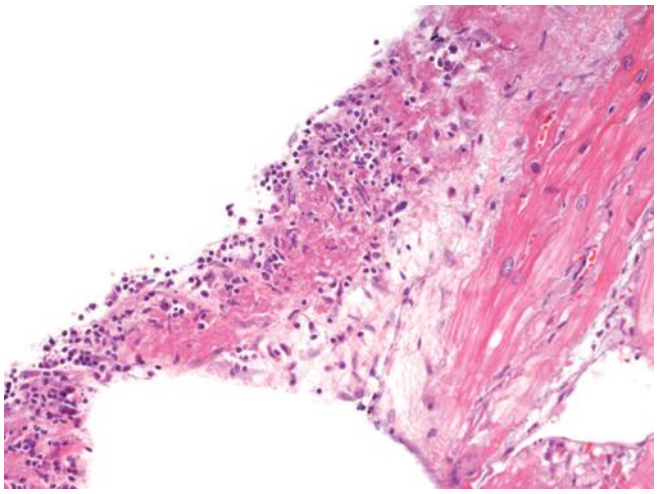
Endocardium may also show inflammatory cell infiltration, which should always be reported. In addition, the endocardium may occasionally show thrombotic stratification with or without inflammation. The finding may provide the rationale for antiaggregation or anticoagulation treatments (Fig. 63–7).

Myocardial Damage

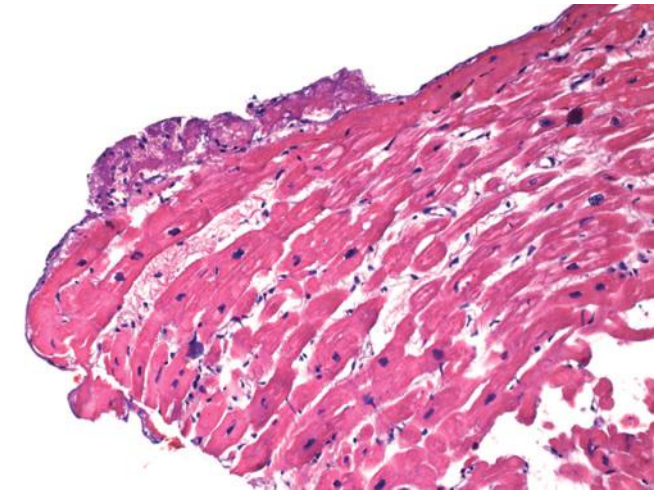
The myocyte injury is typically noncoagulative. It is easy to distinguish it from the coagulative necrosis in small EMB specimens on hematoxylin and eosin stain (Fig. 63–8); acid fuchsin orange G stain may further help differentiation. Myocyte injury in myocarditis reflects the cytotoxic effect exerted by T lymphocytes and related cytokines and is characterized by discontinuity/rupture of sarcolemma, myocyte edema, and loss of intracellular organelles in the interstitium. Nuclei may be prominent and show evident nucleoli. Unless microthrombi occur in small vessels, coagulative necrosis is absent. The inflammation-induced myocyte injury also differs from contraction band necrosis that may occur in cardiogenic shock in patients with pheochromocytoma.[221]

Pathologic Evidence of Myocardial Infection

There are pathogens that can be easily seen with routine hematoxylin and eosin stains; parasites, bacteria, and viral infections causing cytopathic effect are unlikely to be missed by routine pathology study. Morphologic evidence of infection is common in transplanted hearts, and HCMV shows a marked endotheliotropic effect usually coincident with increased viremia and DNA-emia and *T gondii*. Patients with acute CV-B3 infection



A



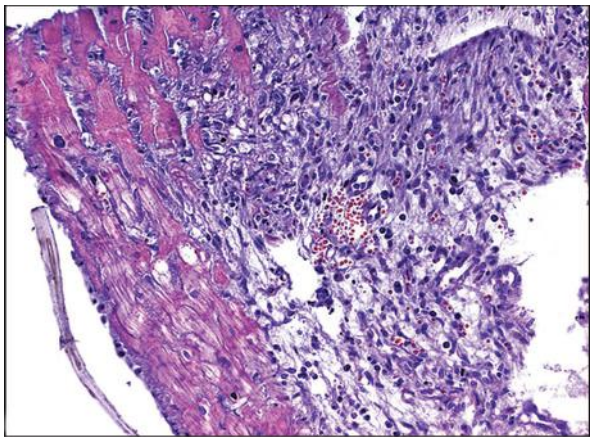
B

FIGURE 63–7. **A.** Endocardial thrombus with prominent inflammatory infiltrates. **B.** Endocardial thrombus with scattered inflammatory cells and early re-endothelialization.

with replicating virus in the myocardium may show ultrastructural evidence of viral infection; the confirmation is obtained by molecular analysis with reverse transcriptase PCR, which should be the standard for the etiologic diagnosis. There are viruses or phases of viral infection (and viral replication) that cannot be easily recognized using conventional pathology studies. In these cases, immunohistochemistry for detection of viral antigens is consistent with active viral replication.

MYOCARDITIS WITH GIANT CELLS

Giant cells are the morphologic marker of giant cell myocarditis (GCM) and sarcoidosis. Touton-like giant cells are also found in diseases such as Erdheim-Chester disease, a rare form of non–Langerhans cell histiocytosis, associated in more than 50% of *BRAF*^{V600E} mutations in early multipotent myelomonocytic precursors or in tissue-resident histiocytes. Heart and coronary "pseudo-tumor" infiltration and pleural and pericardial involvement have been reported in 11% and 9% of patients, respectively. The myocardial involvement seems to occur exclusively in old patients.[222] Tuberculosis is a less common cause of myocarditis. Three distinct forms of myocardial involvement are recognized: nodular tuberculosis of the myocardium characterized by



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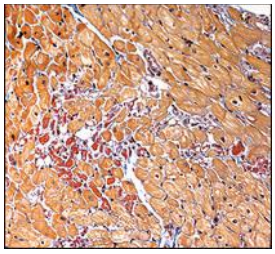

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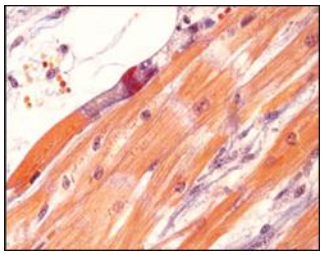
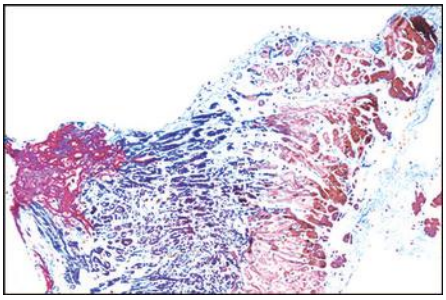


C



D

FIGURE 63–8. **A.** Typical myocyte damage in myocarditis. **B-D.** Coagulative necrosis in the absence of inflammatory infiltrates.

granulomatous disease with central caseation; miliary tuberculosis of the myocardium; and an uncommon diffuse giant cell and lymphocyte infiltrative type associated with tuberculous pericarditis.[223] The myocardium is involved by hematogenous spread, retrograde lymphatic spread from mediastinal lymph nodes, or direct invasion from the pericardium. The confirmatory diagnosis can be made by biopsy of the myocardium or of lymph nodes if clinical suspicion is strong and imaging findings are suggestive.[224-226]

GIANT CELL MYOCARDITIS

GCM is a rare disease characterized by myocardial inflammation with giant cells and myocyte necrosis.[227,228] Although the true statistics are unknown, data from autopsy series indicate relatively low prevalence rates of 0.007% to 0.051%.[229-231]

Etiology and Pathogenesis

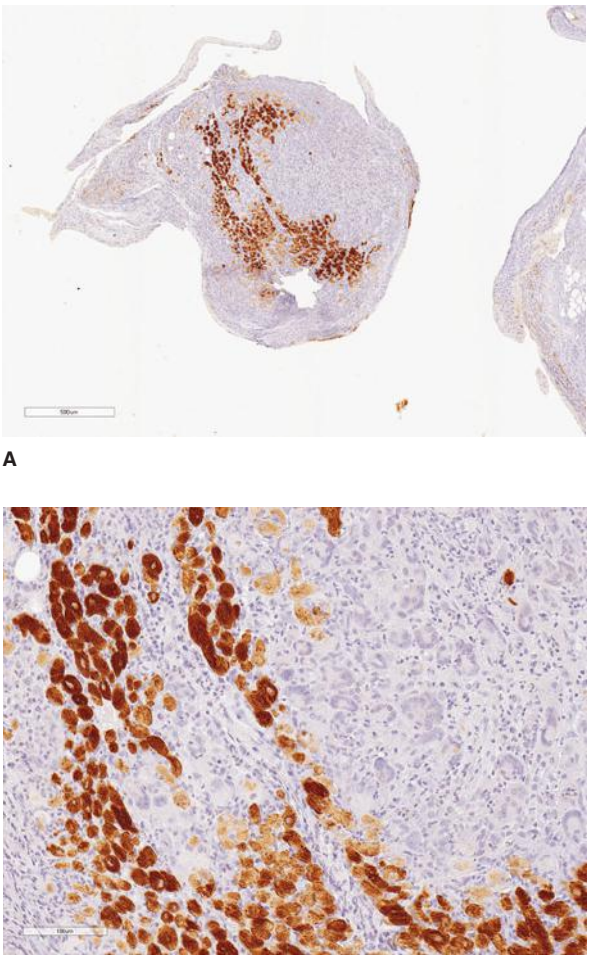
GCM is considered a multifactorial disease. Etiologic hypotheses include infectious causes, autoimmune diseases or autoimmune reactions, and genetic predisposition.[227,228,232] Infections reported in GCM include coxsackie B2 virus,[233] B19V,[234] and *Mycobacterium* tuberculosis.[235] In about one-fifth of cases, GCM seems to be associated with autoimmune diseases such as inflammatory bowel disease, cryofibrinogenemia, optic neuritis, fibromyalgia, hyper- or hypothyroidism[227,228] and Hashimoto thyroiditis,[236] rheumatoid arthritis,[227] thymoma,[237] myasthenia gravis,[238] Takayasu arteritis, alopecia totalis, vitiligo, orbital myositis, discoid lupus erythematosus,[236] autoimmune hepatitis,[236] Guillain-Barré syndrome,[239] systemic lupus erythematosus,[236] and Sjögren syndrome.[239] GCM is being reported among novel syndromes such as immune reconstitution inflammatory syndrome that may occur in patients receiving highly active antiretroviral therapy against HIV-1.[240]

The autoimmune or immune-mediated hypothesis is supported by partial remission of GCM in patients treated with immunosuppression,[227,228] as well as by a nonaggressive occurrence (10%-50%) of the disease during immunosuppression treatment in transplanted patients.[241] A recent hypothesis highlights the possibility that GCM is characterized by a chemokine profile related to toll-like receptors and dendritic cells.[242] Distinct differential gene expression profiles seem to discriminate tissues harboring giant cells (GCM and cardiac sarcoidosis) from those with active myocarditis or inflammation-free controls. The expression levels of genes coding for cytokines or chemokines, cellular receptors, and proteins involved in the mitochondrial energy metabolism are deregulated 2- to 300-fold in GCM.[243] Decreased expression of interleukin (IL)-17– and tumor necrosis factor-α–mediated plakoglobin is observed in GCM, cardiac sarcoidosis, and arrhythmogenic right ventricular cardiomyopathy but not in lymphocytic myocarditis.[244] These data need confirmation.

Clinical Manifestations and Diagnostic Workup

Clinical manifestations of GCM are variable. Most patients commonly present with cardiogenic shock requiring mechanical circulatory support, conduction disease such as atrioventricular nodal or infranodal heart block, and atrial or ventricular arrhythmias, which can be the first manifestation of the disease. Occasionally, GCM may mimic an acute myocardial infarction.[231,235] Less common is presentation as an atrial variant with atrial fibrillation, severe atrial dilation, but preserved ventricular function.[245,246]

A precise diagnosis of GCM is established only when typical pathologic features are demonstrated on EMB or surgical samples (Fig. 63–9). The inflammatory infiltrate is comprised of $CD8^+$ lymphocytes, eosinophils, and multinucleated giant cells (Fig. 63–10); myocytes show damage and necrosis. Sensitivity of right ventricular EMB is 68% to 80%.[228,247] CMR can help guide EMB sampling.[248] Differential diagnosis between GCM and cardiac sarcoidosis relies on pathologic features (noncaseating epithelioid granulomas in sarcoidosis) and is supported by the different T-cell subsets ($CD4^+$ in sarcoidosis and $CD8^+$ in GCM). Gene expression profiles vary between the two disorders and can contribute to differential diagnosis.[242-244] EMB is recommended by the Heart Failure Society of America in patients presenting with malignant arrhythmias out of proportion to LV dysfunction or in rapidly progressive clinical heart failure or ventricular dysfunction.[249]



A

B

FIGURE 63–9. A and B. Antidesmin antibody immunostain demonstrating a few residual layers of myocytes embedded in the context of severe giant cell myocarditis; the giant cells are clearly visible in the higher magnification panel (**B**).

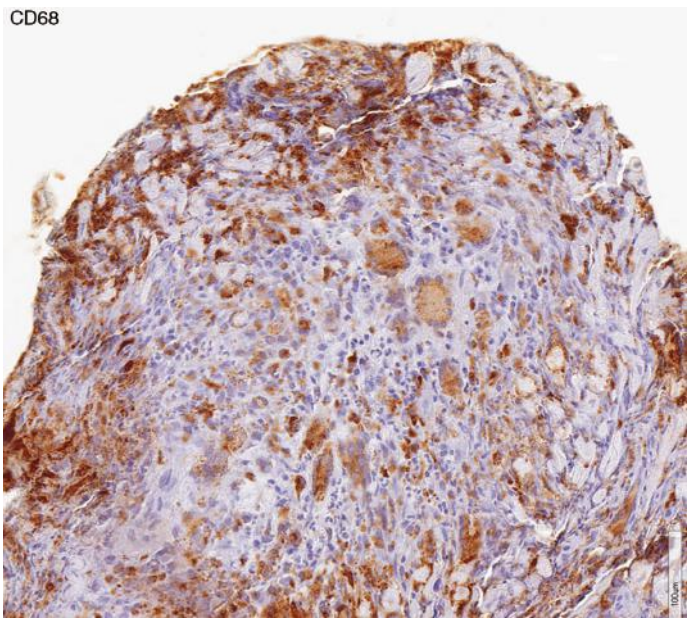


FIGURE 63–10. Giant multinucleated cells immunostained with anti-CD68 antibodies in giant cell myocarditis; fulminant onset.

Evolution

GCM carries a poor prognosis, with a median survival of 5.5 months from the onset of symptoms; in one report, 89% of patients either died or required cardiac transplantation,[227] and another report showed 1-year survival of 30% to 69%.[228] These data may underestimate the risk of death because some patients many die with undiagnosed disease.[250]

Treatment of Giant Cell Myocarditis

Heart failure treatment includes standard regimen with β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists as per guidelines.[251,252] The management of GCM has also included the use of muromonab-CD3, pulse steroids, and varying combinations of azathioprine, cyclosporine, and prednisone monitored with surveillance EMB (Table 63–5). Cytolytic therapy with other monoclonal or polyclonal antibodies is debated.[227,253] Mechanical circulatory support for bridge to recovery is rare, whereas it is more commonly used as bridge to transplant[254,255]; biventricular support has been frequently required. Patients most commonly end up needing cardiac transplantation despite immunosuppression.[227,228,255,256] Post-transplant survival is similar to that of patients who underwent heart transplantation for other diseases[227,228]; however, GCM may recur in 10% to 50% of transplanted hearts,[227,257] with variable response to immunosuppression,[257,258] and may require novel immune-modifiers such as the CD52-binding monoclonal antibody CAMPATH-1 or alemtuzumab.[241,259]

SARCOIDOSIS

Sarcoidosis is a chronic multisystem inflammatory disease of unknown etiology that carries the pathologic hallmark of noncaseating epithelioid granulomas in the affected tissues.[260] The incidence varies between 3 to 4 and 35 to 80 per 100,000, reflecting ethnicity, geographic preponderance, and gender bias.[261,262] The prevalence is 10 to 40 per 100,000 persons in the United States and Europe and is higher in Scandinavians and lower in Turkish[263,264]; the ratio between African Americans and Caucasians is 10:1 to 17:1.[265] Women between the age of 20 and 40 years are preferentially affected.[266] Cardiac involvement is influenced by ethnicity but not by gender; cardiac involvement is reported in 58% of Japanese patients, which happens to be the cause of death in up to 85%.[266] Sarcoidosis typically occurs in adults and is rare in children. It may manifest with the typical involvement of lungs, lymph nodes, and eyes, or with very early onset ("early-onset sarcoidosis") in skin, joints, and eyes evolving aggressively to cause blindness, joint destruction, and visceral involvement. The latter aggressive form of sarcoidosis is associated with heterozygous mutations in the *CARD15* gene that cause constitutive nuclear factor-κB activation.[267]

The prevalence of cardiac involvement ranges from 2% to 7% in patients diagnosed with systemic sarcoidosis; autopsy studies have demonstrated cardiac involvement in up to 25% of cases.[260,261,264] Greater cardiac involvement is reported in Japanese patients.[268] In imaging series, cardiac involvement ranges from 3.7% to 54.9%, depending on the techniques used and the population studied.[269] Sarcoid granulomas can be clinically silent.[270] Therefore, the real proportion of cardiac sarcoidosis is likely higher than clinically apparent.

TABLE 63–5. Treatment of Giant Cell Myocarditis

Drug Class	Drug
Calcineurin inhibitor	Cyclosporine
	Tacrolimus
Corticosteroids	Methylprednisolone
	Prednisone
Antimetabolite	Imuran
	Mycophenolate mofetil
Cytolytic therapy	ATGAM (antithymocyte globulin)
	Thymoglobulin
Combined treatments	Corticosteroids with cyclosporine
	Corticosteroids with azathioprine
	Corticosteroids, cyclosporine, and azathioprine
	Corticosteroids, cyclosporine, and OKT3
	Corticosteroids, azathioprine, and OKT3

Abbreviation: OKT3, muromonab-CD3.

Pathogenesis and Etiology

The current pathogenetic paradigm suggests a cell-mediated delayed hypersensitivity reaction in individuals with immune dysfunction. Antigen and effector $CD4^+$ helper T-cell interaction leads to secretion of IL-2 and IFN-γ, which stimulate a T-helper-1 (Th1) immune response, dysfunctional regulatory T-cell response, dysregulated toll-like receptor signaling, and oligoclonal expansion of $CD4^+$ T cells consistent with chronic antigenic stimulation.[271] Hyperimmune Th1 response to pathogenic microbial and tissue antigens could be associated with the aberrant aggregation of serum amyloid A within granulomas, which in turn promotes progressive chronic granulomatous inflammation in the absence of ongoing infection.[271] Mycobacterial ESAT-6 and *Propionibacterium acnes* proteins have been identified by matrix-assisted laser desorption ionization imaging/mass spectrometry in sarcoidosis granulomas, and immune responses to both microbes have been identified in bronchoalveolar lavage of patients with sarcoidosis,[272] which supports the role of infectious agents in the pathogenesis of sarcoidosis. Genetic factors are being investigated studying families of probands with sarcoidosis (Table 63–6); the co-twin of an affected twin carries a much greater risk of developing sarcoidosis compared to the general population.[273] In one study (A Case-Control Etiologic Sarcoidosis Study), the relative risk for the first- or second-degree relative of a sarcoidosis patient was 4.7 times that of controls.[274] Genetics studies have identified several candidate genes and susceptibility loci[275] for both sarcoidosis and autoimmune diseases; these studies are opening novel avenues in the research of the etiology and pathogenesis of the disease.

Clinical Presentation and Diagnostic Workup

The cardiac manifestations are caused by epithelioid granulomas that preferentially affect the myocardial layer, followed by endocardium, pericardium, and valves. They are most commonly located in the septum, free wall, papillary muscles, and right ventricular free wall in the areas that are not commonly involved by ischemic heart disease. The granulomas heal by fibrosis and evolve to form scars that can be transmural in advanced stages mimicking ischemic disease (Fig. 63–11). Clinical manifestations include arrhythmias, conduction disturbances, LV dilation, and systolic or diastolic dysfunction.[260,265] In patients with advanced sarcoidosis, pulmonary hypertension is highly prevalent, may result from both cardiac and pulmonary involvement, and serves as a predictor of poor prognosis.[276] Ventricular aneurysms occur in

TABLE 63–6. Genetic Predisposition to Systemic Sarcoidosis

Series	Relatives	Risk Compared With the General Population
Family Studies		
210 twin pairs	Twins, monozygotic	80-fold
	Twins, dizygotic	7-fold
ACCESS (A Case-Control Etiologic Study in Sarcoidosis)	First- or second-degree relative of a patient with sarcoidosis	4- and 7-fold
Genetic Studies		
Genetic association	Chromosome 6, MHC genes	• Acute sarcoidosis: HLA-DRB1*0301 • Remitting disease: HLA-DQB1*0201-DRB1*0301 • Chronic active disease: DQB1*0602-DRB1*150101 • Extrapulmonary manifestations: HLA-DRB1*11
Candidate genes	Case-control studies and family-based studies	• Variation of TNF production: *TNFA1/TNFA2*; rs1800629 • Chronic sarcoidosis: *IL23R*; rs11209026 (Arg381Gln) • Sarcoidosis and uveitis: *IL23R*; rs11209026 (Arg381Gln)
Genome-wide association studies	Susceptibility loci and candidate genes	• Butyrophilin-like 2 (*BTNL2*) gene: *BTNL2* rs2076530 A • Annexin A11 (*ANXA11*) gene: rs1049550 • Ras-related protein Rab-23 (*RAB23*): rs1040461 • Osteosarcoma amplified 9 (*OS9*): rs1050045 • Coiled-coil domain containing 88B (*CCDC88B*) • Peroxiredoxin 5 (*PRDX5*) gene • Neurogenic locus notch homolog protein 4 (*NOTCH4*) gene region: SNP rs715299
Gene-environment interactions	1101 patients with extrapulmonary sarcoidosis and exposed to insecticides, molds, and musty odors	*HLADRB1*

FIGURE 63–11. End-stage cardiac sarcoidosis. **A.** A low-magnification view of a left ventricular sample from a heart with end-stage sarcoidosis; note the large transmural scarred area alternated with preserved myocardial tissue and focal thinning of the compacted layer of the left ventricle. **B.** A scar area with residual giant cells.

up to 40% of patients and are also associated with poor prognosis.[277] Involvement of the pericardium and cardiac valves is uncommon.[260,265]

The diagnostic workup of cardiac involvement is relatively straight forward in patients with established systemic sarcoidosis. However, it happens to be more challenging when cardiac disease presents in isolation or represents the phenotype of onset because of the wide spectrum of clinical manifestations and the possibility that sudden death could be the first clinical manifestation of the disease.[278-280] The diagnosis of sarcoidosis is based on EMB or on pathologic evidence of the disease in lung or lymph nodes and is established based on major and minor criteria recommended by the consensus documents of National Institutes of Health, World Association of Sarcoidosis and Other Granulomatous Disorders, and Heart Rhythm Society (Table 63–7).[281-284] The clinical workup should include a thorough discussion of individual and family medical history, physical examination, ECG, 24-hour Holter monitoring, echocardiography, and advanced imaging, as appropriate.

ECG may show conduction disturbances, arrhythmia, or nonspecific ST- and T-wave changes. Signal-averaged ECG has a modest diagnostic sensitivity (52%) and reasonable specificity (82%).[285] Holter monitoring is often used as a screening tool for cardiac involvement in patients with systemic sarcoidosis; it predicts cardiac involvement with a sensitivity ranging from 50% to 67% and a specificity of 80% to 97% compared to CMR or PET as a reference standard.[286] Echocardiography remains the most commonly used imaging investigation in suspected sarcoidosis but detects late stages of the disease (in up to 80% of advanced cases) with regional wall motion abnormalities, LV dilation, LV aneurysms, thinning of the basal septum, and impaired left or right

TABLE 63–7. Diagnostic Criteria for Cardiac Sarcoidosis (CS)

1999 (revised 2006)[239,240]	2013[241]	2014[242,243]
Histologic diagnosis group CS is confirmed when endomyocardial biopsy specimens demonstrate noncaseating epithelioid granulomas with histologic or clinical diagnosis of extracardiac sarcoidosis	**Histologic diagnosis of cardiac sarcoidosis** Endomyocardial biopsy specimens with noncaseating epithelioid granulomas and no alternative cause identified	1. **Histologic diagnosis from myocardial tissue** CS is diagnosed in the presence of noncaseating granuloma on histologic examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).
Clinical diagnosis group Although endomyocardial biopsy specimens do not demonstrate noncaseating epithelioid granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than 1 of 6 basic diagnostic criteria: I. 2 or more of the 4 major criteria are satisfied II. 1 of 4 of the major criteria and 2 or more of the 5 minor criteria are satisfied	**Clinical diagnosis of probable cardiac sarcoidosis** Histologic diagnosis of extracardiac sarcoidosis and 1 or more of the following are present while reasonable alternative cardiac causes other than CS have been excluded: Corticosteroid or immunosuppressive therapy responsive cardiomyopathy or heart block Unexplained reduced LVEF (< 40%) Mobitz type II second-degree heart block or third-degree heart block Depressed LVEF < 50% Patchy uptake on cardiac FDG-PET in a pattern consistent with CS Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging in a pattern consistent with CS Positive gallium uptake in a pattern consistent with CS	2. **Clinical diagnosis from invasive and noninvasive studies** It is probable[a] that there is CS if: A. There is a histologic diagnosis of extracardiac sarcoidosis AND B. One or more of following is present 1. Steroid ± immunosuppressant responsive cardiomyopathy or heart block 2. Unexplained reduced LVEF (< 40%) 3. Unexplained sustained (spontaneous or induced) VT 4. Mobitz type II second-degree heart block or third-degree heart block 5. Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS) 6. LGE on CMR (in a pattern consistent with CS) 7. Positive gallium uptake (in a pattern consistent with CS) AND C. Other causes for the cardiac manifestation(s) have been reasonably excluded
Major criteria Advanced AV block Basal thinning of the interventricular septum Positive gallium-67 uptake in the heart Depressed left ventricular ejection fraction (LVEF) < 50%		
Minor criteria Abnormal ECG findings: ventricular arrhythmias (VT or multifocal or frequent PVCs), complete RBBB, axis deviation, or abnormal Q waves Abnormal echocardiography: wall motion abnormality or morphologic abnormality (aneurysm or wall thickening or ventricular dilation) Perfusion defects on nuclear imaging: thallium-201, technetium-99m SPECT Delayed gadolinium enhancement on CMR Interstitial fibrosis or monocyte infiltration on cardiac biopsy		

Abbreviations: AV, atrioventricular; CMR, cardiac magnetic resonance; FDG, fluorodeoxyglucose; PET, positron emission tomography; PVC, premature ventricular contraction; RBBB, right bundle branch block; SPECT, single-photon emission computed tomography; VT, ventricular tachycardia.

[a]In general, probable involvement is considered adequate to establish a clinical diagnosis of CS.

ventricular systolic function. Diastolic dysfunction may occur early. The right heart pressures are elevated in patients with lung disease. In early cardiac involvement, when LV function and size are normal, strain and strain rate imaging using speckle tracking are potentially useful for identifying subclinical myocardial involvement.[287,288]

CMR offers a high sensitivity and specificity for the assessment of cardiac involvement. Whereas T2 hyperenhancement identifies early edema, the LGE in a nonvascular distribution supports myocardial scarring. LGE correlates with cardiac biopsy findings of granulomatous inflammation[289,290]; extensive LGE reliably predicts adverse cardiac outcomes[291] and major cardiac events in survivors of sudden cardiac death.[292] The LGE features vary during acute inflammation and with scars. CMR-verified cardiac involvement correlates with decreased LVEF, increased diastolic interventricular septal thickness, and diastolic dysfunction.[293] In patients with preserved LVEF and extracardiac sarcoidosis, major adverse cardiac events including death and ventricular tachycardia are associated with a greater LGE and right ventricular involvement; preserved LVEF does not exclude the risk for adverse events.[293] Right ventricular involvement and dysfunction are common and are associated with LV involvement, lung disease, or pulmonary hypertension or may even be isolated.[294] However, cardiac PET using ^{18}F-FDG identifies regional inflammatory activity, defines the cause of arrhythmia, and guides treatment.[295] Quantitative imaging assessment can monitor changes in FDG uptake on serial studies. Reduced inflammatory activity with improvement of LVEF and decrease in size and/or intensity of resting perfusion defects (such as by ^{13}N-ammonia imaging) may indicate a favorable response to treatment but may also indicate progression of scarring processes. Novel indices of FDG uptake allow calculation of the burden of inflammation (cardiac metabolic volume) and the volume-intensity product (cardiac metabolic activity);

increased cardiac metabolic activity is associated with adverse clinical events in patients with cardiac sarcoidosis.[296] Using ^{18}F-FDG to assess inflammation after a high-fat/low-carbohydrate diet to suppress normal myocardial glucose uptake, 71 (60%) of 118 consecutive patients with suspected cardiac sarcoidosis demonstrated abnormal cardiac PET findings.[297] The presence of focal perfusion defects (rubidium-82 imaging in this report) and FDG uptake identified higher risk of death or ventricular tachycardia.[298] Overall, PET studies have proved to be clinically useful for diagnostic and prognostic information, especially for the risk of ventricular arrhythmias in patients with cardiac sarcoidosis. The potential translational impact of the serial PET scans could inform about evolution or regression of cardiac granulomas and about active myocardial inflammation or the process of healing. Although gallium-67 scintigraphy has also been employed for the detection of myocardial inflammation in systemic sarcoidosis and relates with response to treatment,[299,300] ^{18}F-FDG PET imaging is preferred both for diagnosis and prognostication because of superior sensitivity and reduced radiation exposure. FDG-PET is now included as a diagnostic criterion in the expert consensus statement on the diagnosis of cardiac sarcoidosis[284] (see Table 63–7).

Biomarkers are not included in the diagnostic criteria for cardiac sarcoidosis. There are no disease-specific markers for cardiac sarcoidosis.[301] The circulating level of serum angiotensin-converting enzyme is reported as increased in 60% of patients with systemic sarcoidosis[288] and 21.8% of patients with cardiac sarcoidosis.[302,303] Other biomarkers, including serum soluble IL-2 receptor,[304] IgG,[50] high-sensitivity troponin T, [301,305] and atrial and brain natriuretic peptides,[306] are neither sufficiently sensitive nor specific, and there are no data pertaining to their role in management of cardiac sarcoidosis.[307]

Cardiac sarcoidosis is diagnosed with certainty by EMB demonstrating noncaseating epithelioid granulomas[5,308] (Fig. 63–12). Although EMB has low sensitivity (19%-32%) as a result of the inherent sampling limitation for focal epithelioid granulomas, it offers high specificity for the diagnosis.[309] Biopsies are commonly performed in the right ventricle but LV EMB can be performed if necessary.[310] Besides epithelioid granulomas, EMB commonly reveals nonspecific findings including myocardial interstitial fibrosis, myofibrillar disarrangement and fragmentation, and inflammatory mononuclear cell infiltrates.

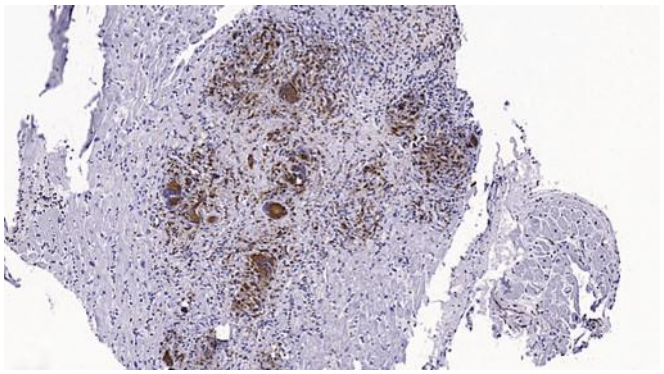
Treatment

Treatment options largely depend on the symptoms and the phase of the disease evolution and are summarized in Table 63–8 based on recommendations of the American College of Cardiology, American Heart Association,[310] and the Heart Rhythm Society.[283]

ENDEMIC MYOCARDITES

CHAGAS DISEASE

Chagas disease (CD) is caused by the protozoan parasite *T cruzi*,[311] which is transmitted through the feces of an infected triatomine, direct oral contact, contaminated blood transfusion, or bone marrow transplantation; it can also be congenital and transmitted vertically from mother to infant. Triatomines are found in the southern United States, Mexico, Central America, and South America, where CD is endemic.[312] Contamination of food and drink has been reported in northern South America, where transmission cycles may involve wild vector populations and mammalian reservoir hosts.[313] In the acute phase, the disease can manifest with myocarditis, conduction system abnormalities, and pericarditis. In untreated patients, the disease progresses to the chronic phase.[314-316]



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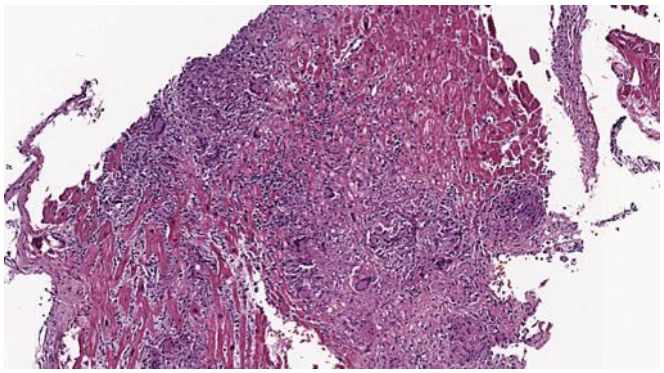


B

FIGURE 63–12. Active sarcoidosis. The figure shows the endomyocardial biopsy (EMB) sample of a 46-year-old male patient who presented with dyspnea. He showed conduction disease, left ventricular ejection fraction of 50%; left ventricular end-diastolic diameter of 56 mm; and maximum left ventricular thickness of 13 mm. Family history was negative. **A.** Anti-CD68 immunostain; note positive macrophages and giant cells. **B.** Hematoxylin and eosin view of the same EMB sample.

Etiology and Pathogenesis

The first description dates back to 1909, when Carlos Chagas isolated *T cruzi* from the blood of a Brazilian patient.[316] Global population epidemiology considers both the local resident population of Latin America and the population of Latin Americans migrating to other countries, particularly the United States. In endemic regions, infected vectors are prevalent in rural houses where people are exposed to the risk of infection for years. The incidence of new infection and transmission though the feces of an infected vector is relatively low and estimated at 1% per year, with a peak of 4% in Bolivian population.[317,318] The incidence of infected populations and CD cardiomyopathy increases with age. The large-scale migration from rural to urban areas and from Latin America to the United States, Spain, and other countries has been associated with endemic transfer of infected immigrants.[319-321] By systematic serologic screening and screening of congenital disease, the National Health Services in Latin America have significantly contained the infection, with the estimated global prevalence of *T cruzi* infection declining from 18 million in 1991 (when the first regional control initiative began) to 5.7 million in 2010.[319]

Clinical Manifestations and Diagnostic Workup

CD evolves in three phases: acute, intermediate, and chronic (Table 63–9). After the infected vector transmission, the incubation period is 1 to 2 weeks, and the acute disease lasts 2 to 3 months, comprising the period of parasitemia. In the acute phase, patients present with mild and nonspecific

TABLE 63–8. Summary of Treatments for Cardiac Sarcoidosis Based on Recommendations of the American College of Cardiology, American Heart Association, and the Heart Rhythm Society

Treatment	Medical Therapy, Device, or Transplantation	Level of Evidence	Mechanism	Potential Benefit/Class Recommendation
Medical therapy				
Immunosupressive therapy	Prednisone	C	Anti-inflammatory	^{18}F-FDG PET may guide steroid therapy (LVEF of 3.8% per reduction in SUV volume of 100 cm^3 above a threshold value, $P = .022$)
	Methotrexate	C	Antimetabolite and immunomodulator	Steroid-sparing. In a 3-year open-label study steroid + methotrexate had improved LVEF (44.5% ± 13.8% vs 60.7% ± 14.3%, $P = .04$)
	Steroid-sparing immunomodulators	C	Variable, depending on the medication	Case reports only have included: infliximab, azathioprine, cyclosporine, antimalarials, pentoxifylline, thalidomide
Heart failure	ACE-I/ARB	A	Improves cardiac remodeling	Class I; reduce mortality and morbidity of HFrEF; class IIa for structural heart disease without impaired LVEF or symptoms
	β-Blockers	C	Negative inotrope; delays AV conduction	Class I; reduce mortality and morbidity for HFrEF
	Diuretics and sodium-restricted diet	C	Fluid and sodium excretion	Class I for HFrEF and symptoms
Device				
Device therapy	ICD, secondary prevention	C	Defibrillation of potential recurrent VT/VF	Class I; reduce mortality in patients with structural heart disease and syncope, VT/VF, or sustained VT/VF inducible by EP study; class III if life expectancy < 1 year
	ICD, primary prevention	C	Defibrillation of potential VT/VF	• Class I; reduce mortality in patients with structural heart disease and EF < 30%-35% despite medical therapy. • Class IIa for patients needing pacemaker, unexplained syncope, or sustained VT/VF inducible by EP study; LGE on CMR may be used to consider EP study. • Class IIb for LVEF 36%-49% or RVEF < 40% despite medical therapy. • Class III when life expectancy < 1 year
	Pacemaker	C	Prevention of fatal arrhythmia	Class I; reduce mortality and symptoms from complete heart block and bradyarrhythmia
Surgery				
Surgical treatment	Heart and lung transplantation	C	Organ replacement therapy	In patients with end-stage organ dysfunction that may include refractory cardiogenic shock, intravenous inotrope dependence, peak oxygen consumption < 10 mL/kg/min with achievement of anaerobic metabolism, refractory VT/VF

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; EF, ejection fraction; EP, electrophysiologic; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardiac-defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; SUV, standardized uptake value; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 63–9. Chagas Disease: Three Phases

Acute Phase (duration: weeks)	Indeterminate Phase (duration: decades)	Chronic Phase (duration: decades)
• Fever • Malaise • Lymphadenopathy • Chagoma—inflammatory nodule at site of inoculation • Romana's sign—periorbital swelling • ECG abnormalities: sinus tachycardia, first-degree AV block • Myocarditis (rare)	• Asymptomatic (most) • Conduction abnormalities, regional LV wall motion abnormalities, or sudden cardiac death (rare)	• Asymptomatic • Cardiac: LV dilatation, congestive heart failure, conduction abnormalities, ventricular arrhythmias, thromboembolic disease, sudden cardiac death

Abbreviations: AV, atrioventricular; ECG, electrocardiogram; LV, left ventricular.

symptoms such as fever, malaise, hepatosplenomegaly, and atypical lymphocytosis. Chagoma (an inflammatory nodule at the site of inoculation) or unilateral painless periorbital swelling (Romana sign) is rarely observed. The majority of infections in the acute phase are not detected. Occasionally, acute CD imposes life-threatening consequences, such as meningoencephalitis and myocarditis.[322] About 30% of infected subjects develop cardiac complications[316] with arrhythmias and transient ECG abnormalities.[323] Subsequently, 30% of infected patients[324] develop systolic and diastolic dysfunction and end-stage DCM. This phase is characterized by positive serologic and parasitologic tests.[325] The cardiac manifestations include ECG abnormalities (prolongation of QRS complex and QT interval, right bundle branch block, and/or left anterior fascicular block) and ventricular segmental wall motion abnormalities; CMR detects cardiac fibrosis and diastolic dysfunction.[325,326] In this phase, illness is severe, with LV dilation and dysfunction, aneurysm, congestive heart failure, thromboembolism, ventricular arrhythmias, and sudden cardiac death, which is the leading cause of death in patients with Chagas heart disease.[327] Chagas cardiomyopathy can be complicated by stroke caused by embolization of intracardiac mural thrombi resulting from depressed LV function and/or aneurysm formation.[327]

Although a direct association between parasite burden and CD phase is not clear, parasite persistence remains central to the disease. A serologic test for IgG antibodies to *T cruzi* is the most effective diagnostic tool.[328,329] The mature form of the parasite (trypomastigote) can be detected by microscopy in blood samples during the acute phase, wherein quantitative PCR is the gold standard for quantitation. After the first 90 days, as the *T cruzi* burden is decreasing, the antiparasite serum antibodies show rising titers by serologic tests including indirect hemagglutination, indirect immunofluorescence, and enzyme-linked immunosorbent assays.

Management

Management of cardiac CD must importantly consider the high likelihood of ventricular arrhythmias and sudden death in patients with chronic CD.[330] Ambulatory ECG monitoring has been suggested for patients with an abnormal resting ECG or echocardiographic ventricular wall motion abnormalities. Patients with nonsustained ventricular tachycardia are usually candidates for electrophysiologic studies. Echocardiographic monitoring demonstrates both structural and functional changes in the early stages of cardiac involvement including regional wall motion abnormalities and diastolic dysfunction; the cardiac phenotype shows LV dilation and severe dysfunction in advance phases.[331]

Two antiparasitic drugs are available for the treatment of CD: benznidazole and nifurtimox.[332,333] These drugs commonly produce dermatologic side effects that are well controlled by antihistaminic drugs. An ongoing prospective international trial testing antitrypanocidal treatment is evaluating the efficacy of benznidazole in patients with chronic Chagas cardiomyopathy.[334] Heart failure is treated according to current guidelines. Because patients with CD may demonstrate lower blood pressure and higher incidence of bradyarrhythmias than non-CD patients, doses of angiotensin-converting enzyme inhibitors and β-blockers are tailored on individual needs. Cardiac resynchronization therapy in patients with severe systolic dysfunction (LVEF < 35%) and prolonged QRS duration[335] has been shown to improve NYHA functional class, increase LVEF, and enhance survival. Patients with end-stage heart failure refractory to medical treatment may receive an LV assist device and undergo cardiac transplantation.[336,337] Implantable cardioverter-defibrillator (ICD) is effective in both primary and secondary prevention of sudden cardiac death. The combination of ICD and amiodarone seems to be superior for secondary prevention, resulting in a 72% reduction in all-cause mortality and a 95% decrease in sudden cardiac death in the ICD group compared to those receiving amiodarone alone.[338] Permanent cardiac pacing is indicated in patients with high-degree atrioventricular block or with symptomatic bradycardia.[339]

LYME DISEASE

Lyme disease is a tick-borne disease caused by *B burgdorferi*; 60% to 80% of cases demonstrate a characteristic rash (erythema migrans) typically accompanied by fever, headache, and fatigue. Untreated Lyme disease can evolve to chronic arthritis and neurologic and cardiac manifestations.[340] Lyme disease is common in Europe and North America and may afflict 1 in 1000 persons in some US states and 1 in 300 people in southern Europe. Cardiac involvement occurs in a minority of patients and predominantly manifests with conduction abnormality, followed by arrhythmias, myocarditis, pericarditis, and DCM; the cardiac involvement is known as *Lyme carditis*. The rates of cardiac involvement in Lyme disease have declined measurably.[341,342] The main vertebrate reservoirs for Lyme *Borrelia* are small mammals, such as mice and voles, and some species of birds. In most tick habitats, deer are essential for the maintenance of tick populations because they are one of the few wild hosts that can feed sufficient numbers of adult ticks, but they are not competent reservoirs for spirochetes.[343] The reservoir hosts and patients can be coinfected with multiple *Borrelia* species or other tick-borne pathogens. Most human infections occur during spring, summer, and early fall months.[342]

Annual incidence of Lyme disease seems to increase from northern to southern parts of central Europe,[343] and ranges from 69 cases per 100,000 population in Sweden to 111 cases per 100,000 in Germany[344] and 155 cases per 100,000 in Slovenia; the lowest incidence in Europe is in the United Kingdom (0.7 per 100,000) and Ireland (0.6 per 100,000).[345] The incidence declines from south to north in Scandinavia and north to south in Italy, Spain, and Greece. In France, the yearly Lyme disease incidence rate averages 42 cases per 100,000 inhabitants.[346] In the United States and Canada, Lyme disease is the major vector-born zoonosis, with approximately 30,000 reported cases and an estimated 300,000 human cases occurring annually in the United States.[347,348] Men are more commonly infected than women. Although the distribution per age is bimodal (children 5-9 years old and adults 45-59 years old), patients of all ages are exposed to the risk of infection.

Pathogenesis and Etiology

The vector deposits Lyme *Borrelia* into the skin of a host that disseminates through blood or soft tissue to other locations. Several days or weeks elapse from the infection to the appearance of erythema migrans, which occurs in 60% to 80% of patients.[349] In the majority of patients, early infection is asymptomatic or presents with influenza-like symptoms, fever, fatigue, muscle or joint pain, and headache.[350] The second phase of involvement of organ systems, such as the cardiac or neurologic systems, may come to attention among untreated patients as part of early disseminated disease (Table 63–10).[351]

Clinical Manifestations and Diagnostic Workup

Lyme carditis is rare and typically manifests 2 to 5 weeks after the erythema migrans. Patients who develop Lyme disease may first manifest atrioventricular block at 14 days (range, 2-24 days) after the onset; only one-third of patients recall the erythema migrans.[352,353] Myopericarditis can present with chest pain, dyspnea, or syncope,[353] and the signs and symptoms of Lyme myopericarditis can mimic acute coronary syndrome, with ECG ST-segment alterations and elevated peripheral blood cardiac biomarkers. In such cases, echocardiography

TABLE 63–10. Clinical Manifestations of Lyme Disease

Organ/System	Signs and Symptoms
Skin	Erythema migrans
Neuromuscular system	Recurrent, brief attacks (weeks or months) of joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints
Nervous system	Lymphocytic meningitis; cranial neuritis, particularly facial palsy (may be bilateral); radiculoneuropathy; or, rarely, encephalomyelitis. Encephalomyelitis must be confirmed by demonstration of antibody production against *Borrelia burgdorferi* in the cerebrospinal fluid (CSF), evidenced by a higher titer of antibody in CSF than in serum
Cardiovascular system	Acute onset of high-grade (second-degree or third-degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis

demonstrates diffuse ventricular hypokinesis rather than the focal wall motion abnormalities expected with an acute coronary syndrome.[352] The mechanism of the development of cardiomyopathy in Lyme disease is debated, and myocardial persistence of *Borrelia* may contribute to the pathophysiology in individuals living in endemic areas[354]; this observation[355] seems to be supported by the finding of 20% of unexplained DCM patients who test positive for *Borrelia*. Diffuse erythema migrans throughout the body indicates dissemination. Subsequently, Lyme disease may present as inflammatory arthritis several months after the initial infection and has been reported to occur in approximately 11% of patients with untreated erythema migrans.

The history of tick bite combined with erythema migrans (see Table 63–10) should be carefully investigated in patients with suspected Lyme carditis. However, patients may not always recall a tick bite, and 20% to 40% of patients do not develop erythema migrans. The diagnosis is based on *Borrelia* isolation or on a two-step test including a sensitive ELISA screening test for IgM and IgG antibody and then confirmation through Western blot assay for positive or borderline results.[354] In the early stage of the disease, results may be false negative as a result of the delayed immune response. Methods such as immune PCR assay have been validated for detection of antibodies to the *Borrelia* C6 peptide.[356] Immune PCR exploits the amplification property of PCR to increase the sensitivity of standard ELISAs by 100- to 10,000-fold.[356] Methods based on metabolomics are being tested[357]; they are based on the use of liquid chromatography/mass spectrometry and statistical modeling to define a metabolic profile of biosignatures present in patients with early-stage Lyme disease.[355,357]

Treatment

Lyme disease is treated with a 10- to 21-day course of doxycycline or amoxicillin orally. Intravenous ceftriaxone (2 g every 24 hours for 2-3 weeks) may be indicated when the infection is not detected in the early stages or is refractory to initial treatments.[347,352] Treated patients who do not recover after *Borrelia* infection may experience chronic peripheral and central nervous system manifestations, including depression, fatigue, sleep disorders, and memory loss, for months to years after the initial infection. In pregnant women, doxycycline should be avoided because of the potential adverse effects to both fetus and mother.

HYPEREOSINOPHILIC SYNDROMES

Eosinophils are the descendants of the granulocytic lineage that differentiate in the bone marrow under the influence of IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor.[358] They produce and store enzymes, basic proteins, cytokines, chemokines, membrane-derived factors, and antifibrinolytic mediators.[358,359] Although their function is not fully clarified, they are involved in host immune response to infection, cancer surveillance, and maintenance of other immune cells.[358,359] In peripheral blood, the normal range of eosinophils is 3% to 5%, which corresponds to an absolute count of 350 to 500/μL.[359,360] Eosinophilia refers to an increased absolute eosinophilic count (AEC) in peripheral blood and is graded as mild (AEC from upper normal limit to 1500/μL), moderate (AEC 1500-5000/μL), or severe (AEC > 5000/μL).[360] The complex groups of eosinophilias encompasses a broad range of disorders including hematologic eosinophilias (clonal, neoplastic, primary), nonhematologic (secondary or reactive), eosinophilic diseases of unknown significance, and familial diseases with either known or unknown genetic causes; organ damage may occur in several of these forms (Table 63–11).[361] The heart is either potentially involved in the context of systemic diseases or is the major or unique clinically involved organ. During the course of the past 30 years, the progress of knowledge on both causes and markers of hypereosinophilic syndromes (HES) has led to development of diagnostic criteria[362] that were modified in 2006, when the definition of HES was expanded to include other previously distinct disease entities associated with eosinophilia such as eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome), chronic eosinophilic pneumonia, and eosinophilic gastrointestinal disorders.[363] In 2010, the time limit of a 6-month diagnostic period was substituted with the suggestion of an elevation of the AEC to > 1500/μL on at least two occasions.[364] Because tissue eosinophilic infiltration and related end-organ damage may occur in patients with peripheral AEC < 1500/μL, it was recommended that the diagnosis can be formulated in patients with "tissue eosinophilia and marked peripheral eosinophilia"; the AEC value is no longer a requirement for the diagnosis. The definition of HES was also expanded to include molecular evidence of end-organ damage.[364]

The age-adjusted prevalence is approximately 0.036 per 100,000 wherein the estimates are based on the International Classification of Diseases for Oncology (Version 3), coding 9964/3 (HES including chronic eosinophilic leukemia) and the Surveillance, Epidemiology, and End Results database from 2001 to 2005. In this estimate, eosinophilias with somatic genetic abnormalities (*PDGFRA/B*, *FGFR1*) account for a minority of cases (median, 23%; range, 3%-56%).[365] In developing countries, the *FIP1L1-PDGFRA* fusion occurs in approximately 10% to 20% of patients with idiopathic hypereosinophilia.[366,367] Idiopathic hypereosinophilia is usually diagnosed between the ages of 20 and 50, but also occurs in children and elderly.[368-372] In 131 incident cases observed between 2001 and 2005, the male-to-female ratio was 1.5, and rates increased with age (peak between 65-74 years).[365] Most patients with *FIP1L1-PDGFRA* or myeloproliferative variants are male,[367,373,374] whereas other eosinophilia subtypes do not show differences between the two genders.

ETIOLOGY AND PATHOGENESIS

The causes include malignancies, hypersensitivity myocarditis, autoimmune reactions in the heart (typically related to a drug reaction), parasitic infections, and EGPA (Churg-Strauss disease).[359,360,363,364] Patients who develop eosinophilic myocarditis often demonstrate fever, rash, ECG abnormalities, and peripheral eosinophilia. The pathologic substrate is myocardial eosinophilic inflammation associated with limited myocyte damage and necrosis. Endomyocardial fibrosis that typically affects the right ventricle is a distinct disease of the endocardium and may not be associated with hypereosinophilia. Eosinophilic myocarditis in its end-fibrotic endocardial stage is also distinct from carcinoid heart disease (see Chap. 61).

CLINICAL MANIFESTATIONS AND DIAGNOSTIC WORKUP

The clinical presentation is heterogeneous and demonstrates nonspecific signs and symptoms including weakness, fatigue, dyspnea, myalgias, angioedema, rash, fever, rhinitis, and diarrhea.[374] Patients demonstrate leukocytosis (eg, 20,000-30,000/μ or higher) with peripheral eosinophilia in the range of 30% to 70%, neutrophilia, basophilia, myeloid immaturity, and both mature and immature eosinophils with varying degrees of dysplasia.[374,375] Anemia occurs in more than 50% of patients; thrombocytopenia, bone marrow eosinophilia with Charcot-Leyden crystals, and possible increased blasts and marrow fibrosis can also recur.[360,361]

The most common organ/tissue manifestations occur in skin (about 70% of patients), followed by lung and gastrointestinal manifestations in 40% and 30% of cases, respectively. Cardiac involvement occurs in 20% of patients, the majority during the course of the disease,[376,377] and affects myocardial layers, endocardium, and valves. Eosinophilic infiltration of the myocardium with release of toxic mediators is associated

TABLE 63–11. 2008 World Health Organization Classification of Eosinophilic Disorders

Primary Eosinophilia

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*

- MPN with eosinophilia associated with *FIP1L1-PDGFRA* fusion gene
- MPN associated with *ETV6-PDGFRB* fusion gene or other rearrangement of *PDGFRB*
- Diagnostic criteria of MPN or acute leukemia associated with *FGFR1* rearrangement,

Chronic eosinophilic leukemia, not otherwise specified (NOS)

1. Eosinophil count $> 1.5 \times 10^9$/L
2. No Ph chromosome or *BCR-ABL* fusion gene or other MPNs or MDS/MPN
3. No t(5;12)(q31~q35;p13) or other rearrangement of *PDGFRB*
4. No *FIP1L1-PDGFRA* fusion gene or other rearrangement of *PDGFRA*
5. No rearrangement of *FGFR1*
6. The blast cell count in the peripheral blood and bone marrow $< 20\%$ and no inv(16)(p13q22) or t(16;16)(p13;q22) or other feature diagnostic of AML
7. Clonal cytogenetic or molecular genetic abnormality, or blast cells are $> 2\%$ in peripheral blood or $> 5\%$ in bone marrow

Idiopathic hypereosinophilic syndrome (HES)

Exclusion of the following:

1. Reactive eosinophilia
2. Lymphocyte-variant hypereosinophilia (cytokine-producing, immunophenotypically aberrant T-cell population)
3. Chronic eosinophilic leukemia, NOS
4. WHO-defined myeloid malignancies associated eosinophilia (eg, MDS, MPNs, MDS/MPNs, or AML)
5. Eosinophilia-associated MPNs or AML/ALL with rearrangements of *PDGFRA*, *PDGFRB*, or *FGR1*

Secondary Eosinophilia

Infections

Parasitic: helminths; *Strongyloides stercoralis*; *Isospora belli*; *Sarcocystis hominis*; viral: HIV and human T-cell leukemia virus (HTLV); fungal: coccidiomycosis, *Aspergillus*

Allergy/atopy

Allergic rhinitis, asthma, atopic dermatitis, allergic bronchopulmonary aspergillosis (ABPA), allergic gastroenteritis (with associated peripheral eosinophilia)

Drug reactions

Medications causing DIHS

- Anticonvulsants: carbamazepine, phenytoin, phenobarbital, lamotrigine, zonisamide
- Antimicrobials: metronidazole, piperacillin/tazobactam, ceftriaxone, nitrofurantoin, minocycline
- Antiretrovirals: abacavir, nevirapine
- Sulfonamides/sulfones: trimethoprim/sulfamethoxazole, dapsone, sulfasalazine
- Nonsteroidal anti-inflammatories: diclofenac, ibuprofen, naproxen
- Other: allopurinol, amitriptyline, fluoxetine

Medications causing organ-specific eosinophilic dysfunction

- Lung → Pulmonary infiltrates: sulfasalazine, nitrofurantoin, nonsteroidal anti-inflammatories
- Kidney → Acute interstitial nephritis: semisynthetic penicillins, cephalosporins, sulfonamides, phenytoin, cimetidine, nonsteroidal anti-inflammatories, allopurinol
- Gastrointestinal trait → Enterocolitis: nonsteroidal anti-inflammatories
- Hepatitis → Tetracyclines, penicillins
- Vasculitis → Allopurinol
- Asymptomatic eosinophilia → Penicillins, cephalosporins, quinine, fluoroquinolones

Systemic diseases

Churg-Strauss syndrome; granulomatosis with polyangiitis (Wegener); systemic lupus erythematosus; Crohn disease; polyarteritis nodosa; rheumatoid arthritis

Pulmonary eosinophilic diseases

Idiopathic acute or chronic eosinophilia pneumonia, tropical pulmonary eosinophilia; allergic bronchopulmonary aspergillosis, etc

Metabolic conditions such as adrenal insufficiency

Familial Eosinophilia (HE_F)

Hyper IgE syndrome

MIM	Gene	Inheritance
102582	*STAT3*	AD
611432	*DOCK8*	AR

Omenn Syndrome

MIM	Gene	Inheritance
605988	*DCLRE1C*	AR
179615	*RAG1*	AR
179616	*RAG2*	AR

Eosinophilic granulomatosis with polyangiitis (EGPA) (possible familial)

Eosinophilia, Unknown Significance (HE_{US})

Eosinophilia-myalgia syndrome

- With giant cell myocarditis
- Associated with tryptophan ingestion,
- Toxic oil syndrome

Eosinophilic gastrointestinal disease (EGID)

- Eosinophilic esophagitis (EoE) when the eosinophilia is limited to the esophagus
- Eosinophilic gastritis (EG) if it is limited to the gastric tract
- Eosinophilic colitis (EC) if it is limited to the colon
- Eosinophilic gastroenteritis (EGE) if the eosinophilia involves one or more parts of the gastrointestinal tract

Cytokine-associated angioedema syndromes (Gleich syndrome)

- Episodic angioedema with eosinophilia; increased IgM, IgE
- Nonepisodic angioedema with eosinophilia
- NERDS (nodules, eosinophilia, rheumatism, dermatitis, and swelling) syndrome; increased IgE

Abbreviations: AD, autosomal dominant; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AR, autosomal recessive; DIHS, drug-induced hypersensitivity syndrome; Ig, immunoglobulin; MDS, myelodysplastic syndrome; MIM, Mendelian Inheritance in Man; MPN, myeloproliferative neoplasm; WHO, World Health Organization.

with heart failure. Endocardial infiltration causes mural thrombi with increased embolic risk. Late phases are characterized by endocardial fibrosis manifesting with restrictive physiology. Valve regurgitation is prominently observed when mural endocardial thrombosis and fibrosis involve leaflets of the mitral or tricuspid valves.[376,377]

EOSINOPHILIC HEART DISEASE

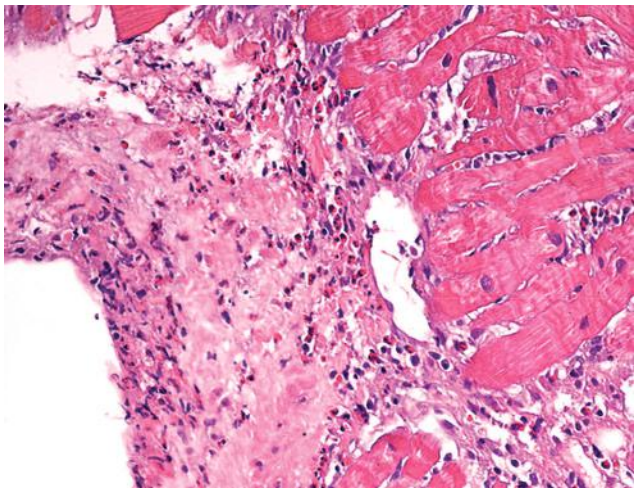
Cardiac involvement is a major cause of morbidity and mortality in HES.[378] The cardiac pathology is divided into three stages: (1) an acute necrotic stage, (2) a thrombotic stage, and (3) a fibrotic stage (Table 63–12).

The early, acute necrotic stage is characterized by eosinophilic and lymphocyte infiltration; in the myocardial interstitium, eosinophils undergo degranulation with release of biologically active factors that cause myocyte injury (Fig. 63–13). Clinical presentation may comprise nonspecific manifestations. Patients may infrequently present with acute heart failure or cardiogenic shock at onset.[379] ECG may show tachycardia, nonspecific ST-segment changes, or conduction delays. cTn levels may be increased, mimicking acute myocardial infarction.[380,381] Echocardiography may show increased LV wall thickness caused by interstitial edema, LV systolic dysfunction, and wall motion abnormalities. CMR shows endocardial delayed enhancement, and T2 mapping may demonstrate subendocardial edema.[382] EMB differentiates eosinophilic infiltration of the endocardium and subendocardial spaces. Corticosteroids inhibit the degranulation of eosinophils and are the first-line treatment for eosinophilic myocarditis.[383,384] In case of fulminant heart failure, mechanical support may become necessary.[385]

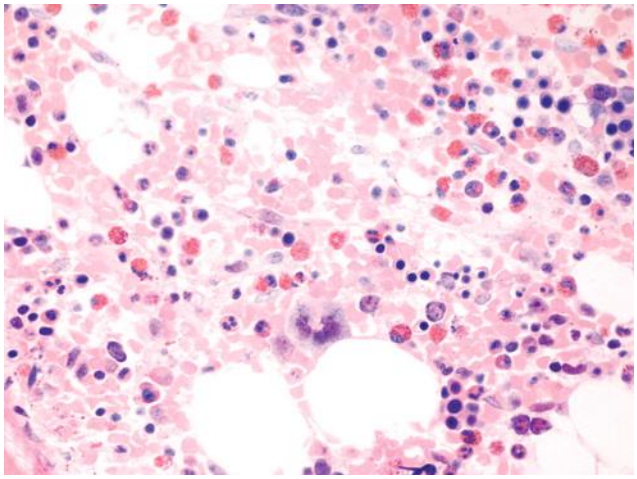
In the thrombotic stage, mural thrombi develop on the endocardium. Mechanisms potentially explaining the endocardial thrombophilia include the release of antifibrinolytic mediators such as PAI-2 and thrombomodulin-eosinophilic proteins that impair the anticoagulant property of the endocardial cells.[374] Thrombi most commonly involve the ventricular apex and further extend to subvalvular regions and, occasionally, to atria. Both echocardiography and CMR detect mural thrombi.[374,378] Thromboembolic complications occur in up to 30% of patients; oral anticoagulation is appropriate to prevent major embolic events. Antiplatelet therapy has also been proposed to prevent the formation of thrombi at the stage of eosinophilic myocarditis.

In the scarring, fibrotic stage both ventricles and subvalvular structures of the AV valves are involved. The functional phenotype is typically restrictive as in endomyocardial fibrosis. Echocardiography demonstrates regurgitation of the atrioventricular valves; spectral Doppler flow shows restrictive pattern. The severity of the endomyocardial fibrosis can be graded according to the combination of major and minor echocardiographic criteria.[378] CMR provides better profile of the endocardial diseases and confirms the diastolic dysfunction. The fibrotic state corresponds to an irreversible endomyocardial fibrosis.

Although surgery can be considered for releasing endocardium and subvalvular apparatus from fibrosis (as done in endomyocardial fibrosis), indications should be evaluated on individually tailored programs that consider cause, comorbidity, and complications. Heart transplantation has alternatively been proposed.[386,387]



A



B

FIGURE 63–13. The figure shows an endomyocardial biopsy (EMB) sample (A) with interstitial and endocardial inflammatory infiltrates largely constituted of eosinophils. The patient had heart failure at onset and demonstrated hypereosinophilia; the patient was diagnosed with clonal, neoplastic, primary hypereosinophilia (HE_N) (*PDGFRA/B* rearrangement). B. Bone marrow biopsy demonstrating a high number of eosinophilic granulocytes.

TABLE 63–12. Pathologic Features and Frequency of Symptoms in the Three Stages of Hypereosinophilic Syndrome

Acute Necrotic Stage	Thrombotic Stage	Fibrotic Stage
Myocarditis with eosinophilic and lymphocytic infiltration	Thrombus along damaged endocardium	Thrombi undergo organization, reabsorption and fibrosis, ending in endocardial scarring
Myocyte necrosis and apoptosis	Thrombi localize in the ventricular apex	Endocardial fibrosis involves the base of the heart
Possible rare microembolic phenomena	Thrombi can extend to the base of the heart and subvalvular regions	Fibrosis can involve valve structures with regurgitation
Symptoms: rare	Symptoms: possible embolic complications	Symptoms: the functional phenotype is diastolic dysfunction with restrictive pattern

CHURG-STRAUSS SYNDROME OR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Churg-Strauss syndrome has recently been renamed as EGPA,[358] which is a systemic necrotizing vasculitis that affects small to

medium-sized vessels. The recommendations for the management of small and medium-sized vessel vasculitides that apply to EGPA have recently been published.[388] Much progress has been made over the past 30 years in understanding, redefining, and treating systemic necrotizing vasculitis. EGPA belongs to the group of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) and is characterized by blood and tissue eosinophilia and asthma, thus differing from granulomatosis with polyangiitis (Wegener) and microscopic polyangiitis. ANCA positivity ranges from 30% to 70% of EGPA patients but is usually less frequently observed than in other AAV. Diagnostic and management algorithms for EGPA are summarized in Table 63–13.[388]

CONCLUSION

The term myocarditis remains fundamental to describe myocardial inflammation but does not specifically describe phenotype and etiologies. The recent advancements in the identification of the different causes of myocarditis, the novel emerging infectious diseases, and drug-resistant infections; the reclassification of syndromes such as eosinophilic diseases; and the recent discovery of "monogenic" myocarditis and autoinflammatory diseases challenge cardiologists in their diagnostic workup, when deciding about performing EMB, progressing from echocardiography to advanced imaging, or establishing appropriate treatments. A systematic approach to precise diagnosis should seek

TABLE 63–13. Churg-Strauss Syndrome or Eosinophilic Granulomatosis With Polyangiitis (EGPA)

The EGPA Consensus Task Force Recommendations	Level of Evidence
1. EGPA should be managed in collaboration with, or in, centers with established expertise in the management of small and medium-sized vessel vasculitides.	NA
2. Recommended: Serologic testing for toxocariasis and HIV, specific IgE and IgG dosages for *Aspergillus* spp, search for *Aspergillus* spp on a sputum and/or bronchoalveolar lavage fluid, tryptase and vitamin B_{12} dosages, peripheral blood smear (looking for dysplastic eosinophils or blasts), and chest CT scan are the minimal initial differential diagnosis workup; additional investigations should be guided by patient-specific clinical findings, and extensive search for causes of hypereosinophilia should be considered.	NA
3. Obtaining biopsies from patients with suspected EGPA is encouraged.	NA
4. ANCA testing (with indirect immunofluorescence and ELISA) should be done for patients with suspected EGPA.	NA
5. There is currently no reliable biomarker to measure EGPA activity.	NA
6. Once EGPA is diagnosed, evaluating possible lung, kidney, heart, GI, and/or peripheral nerve involvement is recommended.	NA
7. Definition of EGPA remission: The absence of a clinical systemic manifestation (excluding asthma and/or ENT).	NA
8. Definition of EGPA relapse: The new appearance or recurrence or worsening of clinical EGPA manifestation(s) (excluding asthma and/or ENT) requiring the addition, change, or dose increase of glucocorticoids and/or other immunosuppressants.	NA
9. Use of glucocorticoids is appropriate to achieve EGPA remission; the dose prescribed should be ~1 mg/kg/d of prednisone for patients with organ- or life-threatening manifestations.	A
10. Patients with life- and/or organ-threatening disease manifestations (ie, heart, GI, central nervous system, severe peripheral neuropathy, severe ocular disease, alveolar hemorrhage, and/or glomerulonephritis) should be treated with a remission-induction regimen combining glucocorticoids and an additional immunosuppressant (eg, cyclophosphamide).	B
11. Maintenance therapy (with azathioprine or methotrexate) is recommended for patients with life- and/or organ-threatening disease manifestations on a remission-induction therapeutic regimen.	C
12. Glucocorticoids alone may be suitable for patients without life- and/or organ-threatening disease manifestations; additional immunosuppression can be considered for selected patients for whom the prednisone dose cannot be tapered to 7.5 mg/d after 3-4 months of therapy or patients with recurrent disease.	C
13. Plasma exchanges are generally not effective in EGPA but can be considered for selected patients with ANCA and rapidly progressive glomerulonephritis or pulmonary-renal syndrome.	D
14. Rituximab can be considered for selected ANCA-positive patients with renal involvement or refractory disease.	C
15. IVIG can be considered a second-line therapy for patients on glucocorticoids (and/or other immunosuppressants) with EGPA flares refractory to other treatments or during pregnancy; in the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections, Ig replacement may be considered.	C
16. Interferon-α may be reserved as a second- or third-line drug for selected patients.	C
17. LRA can be prescribed, if needed, for EGPA patients.	B
18. Vaccinations with inactivated vaccines and against influenza and pneumococci should be encouraged; live-attenuated vaccines are contraindicated in patients taking immunosuppressants and/or ≥ 20 mg/d of prednisone.	D
19. Implementation of patient educational programs is encouraged.	D
20. Patients with peripheral nerve involvement and motor deficit(s) should routinely be referred to a physiotherapist.	D
21. Patients should be advised to avoid tobacco smoke and irritants.	D
22. Venous thromboembolic events and pulmonary embolism should be treated according to general guidelines for the management of thromboembolic disease; it is unknown whether anticoagulation should be prolonged in selected patients with persistent or recurring disease activity.	D

Abbreviations: ANCAs, antineutrophil cytoplasm antibodies; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss); ELISA, enzyme-linked immunosorbent assays; ENT, ear, nose, and throat; GI, gastrointestinal; HIV, human immunodeficiency virus; Ig, immunoglobulin; IVIG, intravenous immunoglobulins; LRA, leukotriene receptor antagonists; NA, not applicable.

the fundamental diagnostic information about myocardial inflammation. The individual history, family history, imaging, biomarkers, and molecular tests flanking the conventional infectious workup to identify the genome of the pathogens are now necessary for a complete diagnostic workup in infectious myocarditis. Different forms of noninfectious myocarditis and autoimmune or toxic diseases with myocarditis need to be supported by specific diagnostic algorithms. The clear distinction of the different forms of myocarditis would help generate reliable epidemiology data and bases for precise nosology and classification.

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CHAPTER 64

THE ATHLETE AND THE CARDIOVASCULAR SYSTEM

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INTRODUCTION

Evaluation and management of the athlete with cardiovascular disease and arrhythmias represents a unique challenge. Although athletes are symbols of the healthiest segment of our society, they are occasionally affected by cardiovascular conditions that come to the attention of the clinician. The physician can be faced with clinical judgments related to evaluation of symptoms, such as chest discomfort, or signs, such as a murmur, that can be either benign or a manifestation of an underlying cardiac condition. Clinical judgment commonly serves as the basis for recommendations for therapy and athletic participation. In this setting, there is the real risk of failing to detect a cardiac condition that may result in serious or even life-threatening consequences. There is also considerable risk of unnecessarily treating and restricting sports activity in an athlete misdiagnosed as having an underlying cardiac condition. The consequences of missing an important cardiac diagnosis can be life-threatening. The cardiovascular conditions that predispose to life-threatening complications with athletic activity are now known from pathologic studies[1,2] (Table 64–1). Recommendations for clinical evaluation, management, and athletic participation are also available to guide clinicians.[3] This chapter will review cardiovascular disease in the athlete from multiple perspectives. These include distinguishing physiologic cardiovascular adaptations to exercise from true cardiac disease, clinical evaluation of the athlete with suspected cardiovascular disease, arrhythmias in athletes, commotio cordis, guidelines for athletic restriction, and performance-enhancing substances.

THE ATHLETE'S HEART

The athlete's heart refers to the clinical syndrome of cardiac chamber enlargement, hypertrophy, and normal or augmented ventricular systolic function commonly accompanied by sinus arrhythmia, sinus bradycardia, and a systolic flow murmur.[4,5] The notion that the cardiovascular system differentiates physiologically, structurally, and functionally in response to athletic training was initially advanced more than a century ago.[5] Using cardiac auscultation and percussion, Henschen described enlargement of the heart caused by athletic activity in cross-country skiers.[5] He reported that right and left heart physiologic dilation and hypertrophy resulted from cross-country skiing and that these athletic hearts could perform more work than the heart of a nonathlete.[5]

Debate ensued about whether these adaptations to exercise are physiologic and benign or pathologic and the potential harbinger of disease and disability. The heart of the trained athlete was considered by some to be enlarged and weakened because of the strain of endurance training with potential deterioration of cardiac function and a clinical syndrome of heart failure.[4] However, it is now recognized that the athlete's heart represents a benign increase in cardiac mass, with specific circulatory and cardiac morphologic alterations, representing a physiologic adaptation to systematic training.[4] These cardiac changes represent physiologic cardiovascular adaptations to dynamic exercise, also known as isotonic or aerobic training. Thus, the clinical components of the athlete's heart are most commonly found in athletes participating in endurance or aerobic exercise.

The acute response to training for such athletic activities as cross-country skiing, long-distance running, swimming, or bicycling includes substantial increases in maximum oxygen consumption, cardiac output, stroke volume, and systolic blood pressure, associated with decreased peripheral vascular resistance.[4] With several weeks of endurance training, the chronic adaptations to training include increased maximal oxygen uptake from augmented stroke volume and cardiac output and increased arteriovenous oxygen difference. The response to endurance exercise predominantly produces a volume load on the left ventricle.

The morphologic adaptations to endurance training have been quantitatively characterized by multiple studies, largely relying on echocardiography.[4] The cardiac changes of athletes in response to systematic conditioning are variable, with cardiac remodeling in approximately one-half of trained athletes. These changes include alterations in ventricular chamber dimensions, including increased left and right ventricular and left atrial cavity size (and volume), associated with normal systolic and diastolic function.[4] Enlargement of the left ventricular (LV) chamber (≥ 60 mm) occurs in approximately 15% of highly trained athletes.[4,6] Occasionally enlargement of the LV is accompanied by a mild increase in absolute LV wall thickness exceeding upper normal limits (range, 13-15 mm).[4] Remodeling of LV mass is dynamic and develops after the initiation of vigorous conditioning. Because these changes are reversible with cessation of training, restriction from exercise and reassessment of LV size and wall thickness can be used to distinguish physiologic changes from those associated with hypertrophic cardiomyopathy (HCM).[4]

Differentiating the physiologic changes resulting from habitual exercise in the athletic heart syndrome with HCM or dilated cardiomyopathy represents a challenge to the clinician (Fig. 64–1). Physiologic cardiac adaptation from regular exercise leads to an increase in LV wall thickness. This can be difficult to distinguish from pathologic changes of HCM. Criteria favoring HCM include a high degree of LV hypertrophy (wall thickness, ≥ 16 mm) with an unusual distribution

TABLE 64–1. Cardiovascular Conditions Associated With Sudden Death in the Athlete

Structural heart diseases
Hypertrophic cardiomyopathy
Coronary artery anomalies
Left ventricular hypertrophy of indeterminate causation
Myocarditis
Ruptured aortic aneurysm (Marfan syndrome)
Arrhythmogenic right ventricular cardiomyopathy
Tunneled (bridged) coronary artery
Aortic valve stenosis
Atherosclerotic coronary artery disease
Dilated cardiomyopathy
Myxomatous mitral valve degeneration
Asthma (or other pulmonary condition)
Heat stroke
Channelopathies
Long QT syndrome
Short QT Syndrome
Catecholaminergic polymorphic ventricular tachycardia
Brugada syndrome
Idiopathic ventricular fibrillation

TABLE 64–2. Common Electrocardiographic Findings in Athletes

Sinus bradycardia (> 30 bpm)
Sinus arrhythmia
Ectopic atrial rhythm
First-degree AV block (PR > 200 ms)
Mobitz type I Wenckebach second-degree AV block
Incomplete right bundle branch block
Notched P waves
Isolated QRS voltage criteria for LVH; except: QRS voltage criteria for LVH occurring with any nonvoltage criteria for LVH such as left atrial enlargement, left-axis deviation, ST-segment depression, T-wave inversion, or pathologic Q waves
Early repolarization
Repolarization abnormalities, including ST-segment elevation or depression (ST elevation, J-point elevation, J waves or terminal QRS slurring)
Convex ("domed") ST-segment elevation
Combined with T-wave inversion in leads V_1-V_4 in black/African athletes; these common training-related electrocardiographic alterations are physiologic adaptations to regular exercise, considered normal variants in athletes, and do not require further evaluation

Abbreviations: AV, atrioventricular; LVH, left ventricular hypertrophy; RBBB, right bundle branch block.

(heterogeneous, asymmetric, or sparing the anterior septum), a small LV cavity (< 45 mm), the presence of striking electrocardiogram (ECG) abnormalities, and the persistence of hypertrophy after physical deconditioning. Although many athletes have increased intracavitary dimensions, LV end-diastolic diameter > 70 mm is distinctly unusual as a manifestation of the athlete's heart. Additionally, LV wall thickness > 12 mm is unusual even in highly trained athletes but not uncommon in elite rowers and cyclists. LV wall thickness ≥ 16 mm raises the possibility of HCM. Hypertrophy (> 12 mm) above the normal range is distinctly uncommon in female athletes. Athletes with LV wall hypertrophy may have increased cavity dimensions, which are rarely present in diseases with pathologic wall thickening.[4]

A spectrum of abnormal 12-lead ECG patterns is present in up to one-half of trained athletes, more commonly in men and in endurance athletes (Table 64–2).[7-12] The most commonly observed alterations include early repolarization patterns, increased QRS voltages, diffuse T-wave inversion, and deep Q waves. ECGs in endurance athletes can

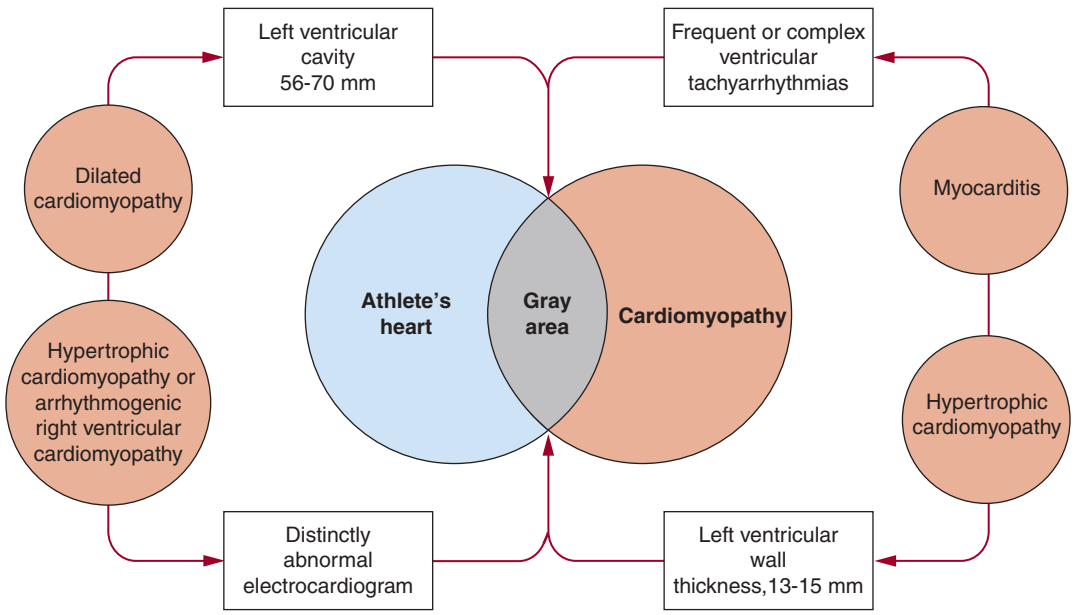


FIGURE 64–1. Gray area of overlap between athlete's heart and cardiomyopathies, including myocarditis, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. The important diagnostic features compatible with both physiologically based adaptations to athletic training (athlete's heart) and the pathologic conditions are shown. Reproduced with permission from Maron BJ. Sudden death in young athletes. *N Engl J Med*. 2003 Sep 11;349(11):1064-1075.[1]

show mildly increased P-wave amplitude, suggesting atrial enlargement, incomplete right bundle branch block, and increased voltages consistent with right ventricular and LV hypertrophy.[7-12] Among endurance athletes, voltage criteria for right ventricular hypertrophy are present in a substantial proportion. Abnormal and bizarre ECG patterns suggestive of cardiac disease are noted in a minority of elite athletes.[7-12] Most such ECGs represent only extreme manifestations of physiologic athlete's heart. A significant minority of asymptomatic elite athletes show distinctly abnormal ECG patterns usually associated with precordial T-wave inversions but without evidence of cardiac disease.[13] Many uncommon ECG findings in athletes are not considered normal variants and require further evaluation (Table 64–3). Arrhythmias commonly noted in athletes include sinus arrhythmia, sinus bradycardia, and junctional rhythm. They are frequently accompanied by other manifestations of enhanced parasympathetic tone. Atrioventricular (AV) conduction delays with first-degree and Wenckebach or Mobitz type I second-degree AV block are common in endurance athletes and attributable to enhanced vagal tone and withdrawal of sympathetic tone at rest.[13] Ambulatory monitoring of athletes has demonstrated ventricular arrhythmias including frequent premature beats, couplets, and nonsustained ventricular tachycardia. These arrhythmias can be within the spectrum of physiologic athlete's heart.[13] Such arrhythmias are generally not associated with symptoms or an increased risk of sudden cardiac death and are generally reduced with exercise or deconditioning.[14]

TABLE 64–3. Abnormal Electrocardiogram Findings in Athletes

T-wave inversion
1 mm in depth in two or more leads V_2-V_6, II, and aVF, or I and aVL (excludes III, aVR, and V_1)
ST-segment depression
≥ 0.5 mm in depth in two or more leads
Pathologic Q waves
> 3 mm in depth or > 40 ms in duration in two or more leads (except for III and aVR)
Complete left bundle branch block
QRS ≥ 120 ms, predominantly negative QRS complex in lead V_1 (QS or rS), and upright monophasic R wave in leads I and V_6
Intraventricular conduction delay
Any QRS duration ≥ 140 ms
Left-axis deviation
−30° to −90°
Left atrial enlargement
Prolonged P-wave duration of > 120 ms in leads I or II with negative portion of the P wave ≥ 1 mm in depth and ≥ 40 ms in duration in lead V_1
Right ventricular hypertrophy pattern
$R - V_1 + S - V_5 > 10.5$ mm AND right-axis deviation > 120°
Ventricular pre-excitation
PR interval < 120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS (> 120 ms)
Long QT interval
QTc ≥ 470 ms (male)
QTc ≥ 480 ms (female)
QTc ≥ 500 ms (marked QT prolongation)
Short QT interval
QTc ≤ 320 ms
Brugada-like ECG pattern
High take-off and downsloping ST-segment elevation followed by a negative T wave in ≥ 2 leads in V_1-V_3
Profound sinus bradycardia
< 30 bpm or sinus pauses ≥ 3 s
Atrial tachyarrhythmias
Supraventricular tachycardia, atrial fibrillation, atrial flutter
Ventricular arrhythmias
Couplets, triplets, and nonsustained ventricular tachycardia

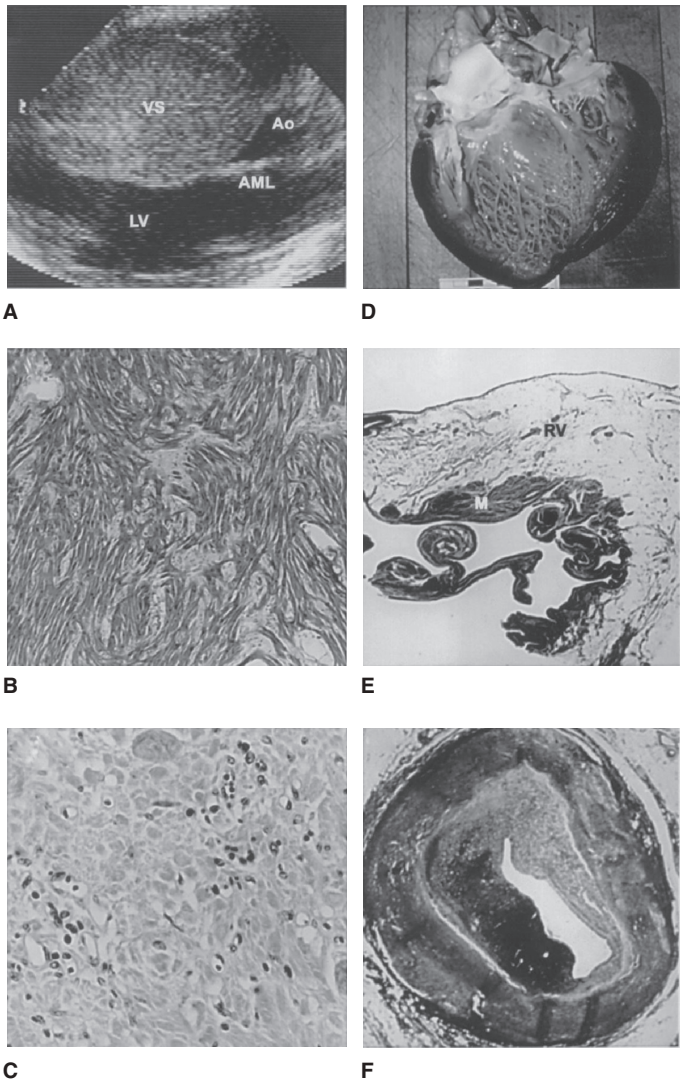
SUDDEN CARDIAC DEATH IN THE ATHLETE

The underlying cardiovascular conditions that predispose to the rare and tragic sudden deaths in young athletes are known.[1-3,15-18] Available population-based data show that these events occur with an incidence of 1 to 2 per 100,000 athletes (12-35 years of age) per year with the frequency eightfold lower in female athletes.[1-3,15-18] In athletes younger than age 35 years, inherited diseases such as HCM, arrhythmogenic right ventricular cardiomyopathy, and congenital coronary artery abnormalities of wrong sinus origin are the most common causes of sudden death. In athletes older than age 35 years, atherosclerotic coronary artery disease is the most common cause of death.[1-3,15-18]

HCM is the single most common cause of sudden cardiac arrest in athletes in the United States in which a definitive cardiac diagnosis can be made postmortem. HCM accounts for about one-third of sport-related sudden fatalities (Fig. 64–2).[1-3,15-18] HCM is a genetically transmitted disease characterized by genotypic and phenotypic heterogeneity. Usually, the characteristic hypertrophied, nondilated LV with increased wall thickness manifests during adolescence.[1] LV hypertrophy is characteristically asymmetric with a variety of patterns of wall thickening.[19]

The characteristic histopathologic marker of HCM is myocardial disarray with disorganized patterns of myocytes associated with increased interstitial fibrosis and often replacement scarring, with fibrosis considered an acquired phenomenon related to microvascular-based myocardial ischemia. The small-vessel disease in HCM involves the intramural coronary arteries, which commonly show dysplasia of the media, and luminal obstruction. Sudden cardiac arrest in athletes with HCM is attributable to ventricular tachyarrhythmias. Myocardial scarring observed in athletes dying suddenly supports the notion that acute episodes of silent myocardial ischemia can trigger the life-threatening cardiac arrhythmias.[1-3,15-18]

Arrhythmogenic right ventricular cardiomyopathy is an inherited heart muscle disorder characterized pathologically by fibrofatty replacement of right ventricular myocardium.[20-24] It represents the leading cause of sudden death on the athletic field in the Veneto region of Italy, accounting for approximately 25% of cardiovascular sudden death in young competitive athletes, but is distinctly uncommon in the United States (5% of athlete deaths).[20-24] Clinical manifestations include ECG depolarization and repolarization abnormalities commonly localized to right precordial leads. These include inverted T waves in V_1-V_3 in most patients with arrhythmogenic right ventricular cardiomyopathy. Less commonly, distinctive depolarization waves known as epsilon waves are seen after the QRS complex in the ST segment on the ECG. Cardiac imaging techniques demonstrate right ventricular global or regional morphologic and functional abnormalities.[20-24] Commonly, premature ventricular contractions or sustained monomorphic ventricular tachycardia with left bundle morphology originate from the right ventricle and are associated with exercise.[19-24] Myocardial



A D B E C F

FIGURE 64–2. Cardiac causes of sudden death in athletes: hypertrophic cardiomyopathy (A and B), myocarditis (C), dilated cardiomyopathy (D), arrhythmogenic right ventricular cardiomyopathy (E), and premature coronary artery disease (F). A. A two-dimensional echocardiogram in the parasternal long-axis view shows extreme asymmetric thickening of the ventricular septum (53 mm), diagnostic of hypertrophic cardiomyopathy. B. Histopathologic analysis shows a substrate of disorganized cardiac muscle cells and a chaotic architectural pattern (hematoxylin and eosin, ×40). C. An area of left ventricular myocardium with clusters of inflammatory mononuclear cells, diagnostic of myocarditis (hematoxylin and eosin, ×400). D. A greatly enlarged left ventricular cavity in a patient with dilated cardiomyopathy. E. Arrhythmogenic right ventricular cardiomyopathy with extensive fatty replacement of the wall of the right ventricle adjacent to a small area of residual myocytes (hematoxylin and eosin, ×8). F. A portion of the right coronary artery shows atherosclerotic narrowing and ruptured plaque in a patient with premature coronary artery disease. AML, anterior mitral leaflet; Ao, aorta; LV, left ventricle; M, myocytes; RV, right ventricle; VS, ventricular septum. Reproduced with permission from Maron BJ. Sudden death in young athletes. *N Engl J Med*. 2003 Sep 11;349(11):1064-1075.[1]

aneurysms are localized to the posterobasal, apical, and outflow tract regions, resulting in the clinical characterization of these regions as the triangle of dysplasia. Sudden death during physical exercise is likely related to hemodynamic factors, increased right ventricular volume and wall stress, and enhanced sympathetic tone that culminate in ventricular tachycardia.[20-25] Physical exercise can acutely increase right ventricular afterload and cavity enlargement, which in turn can trigger ventricular arrhythmias by stretching the diseased right ventricular musculature.[20-25]

Anomalies of coronary artery origin can precipitate sudden and unexpected cardiac arrest in athletes probably related to acute ischemia.[1-3,26] Most commonly, the anatomic finding at autopsy is the left main coronary artery arising from the right coronary sinus. The acute angle relative to the aorta taken by the anomalous artery leaves a narrowed and compromised lumen, frequently characterized as "slit-like," which limits coronary blood flow and myocardial perfusion with exercise.[1-3,26] Evidence of myocardial ischemia caused by anomalous origin of the coronary artery generally is not evident on 12-lead resting ECG and is rarely elicited with stress testing. Therefore, false-negative exercise stress tests are common in athletes who have subsequently died suddenly from coronary anomalies.[26] The diagnosis of anomalous origin of the coronary artery requires a high index of suspicion in young people presenting with exertional chest pain and/or syncope.[26]

Myocarditis, either acute or healed, is also associated with sudden death in the athlete presumptively by resulting in an inflammatory or fibrotic pathologic substrate predisposing to ventricular tachyarrhythmias.[1-3] Life-threatening ventricular arrhythmias in athletes can be associated with focal myocarditis that is "silent" and not reliably detected clinically or by endomyocardial biopsy.[1-3,26]

Approximately 10% of young athletes who die suddenly with exercise have no evidence of structural heart diseases. In many such patients, the cause of sudden death is likely a primary electrical heart disease. These include primary electrical abnormalities such as ventricular pre-excitation (Wolff-Parkinson-White syndrome) and inherited cardiac ion channelopathies including long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia.[27] These primary electrical abnormalities and other conditions predisposing to athletic sudden death have ECG changes (Table 64–4).[1-3,7-12]

COMMOTIO CORDIS

In the absence of underlying cardiovascular disease, blunt nonpenetrating chest blows[28-35] during athletic or recreational activities that cause sudden cardiac death are known as commotio cordis. Although first noted a century ago, it is only in the last 15 to 20 years that commotio cordis has been recognized as a not uncommon occurrence in youth sports and is now regarded as the second leading cause of sudden cardiac death in young athletes, with global recognition.[28-35] The most common sports associated with commotio cordis deaths in the United States are those in which projectiles are integral to the game (eg, baseball, softball, ice hockey, football, lacrosse).

Ages of victims range from 1 to 50 years, although the mean age of individuals experiencing commotio cordis is 14 years, with 30% of individuals older than 18 years. Collapse is usually instantaneous, although occasionally delayed 10 to 20 seconds after the chest blow. Cardiac arrhythmias documented soon after collapse are generally ventricular fibrillations (VF); however, as the time to first documented arrhythmia increases, asystole is more frequently evident. Early reports of resuscitated commotio cordis showed poor survival, although more recently, survival from these events has increased markedly to more than 50% as a result of more rapid response times and access to external defibrillation as well as greater public awareness of this condition.[28-35]

The mechanism by which commotio cordis occurs is complex and largely unresolved, and a porcine model was developed for study of this syndrome, which demonstrated that the immediate cause of collapse was VF (Fig. 64–3).[28-35] Use of this model has allowed definition of

TABLE 64–4. Electrocardiographic (ECG) Abnormalities Found in Various Disease States

Diagnosis of Heart Disease	ECG Abnormalities
Arrhythmogenic right ventricular dysplasia	T-wave inversions anteriorly
	Epsilon wave
	RBBB (complete or incomplete)
	Rarely normal
Hypertrophic cardiomyopathy (HCM)	Left ventricular hypertrophy
	Pseudoinfarct with Q waves
	T-wave inversion
	Rarely normal
Idiopathic dilated cardiomyopathy	LBBB
	Prolonged QT
	Can be normal
Long QT syndrome	Prolonged QT
	Abnormal appearance of ST segment
Brugada syndrome	RBBB (complete or incomplete)
	ST elevation anteriorly
	Changes can vary with time
Anomalous coronary artery	Typically no abnormalities
Coronary artery disease	Typically no abnormalities
	Q
	ST
Wolff-Parkinson-White syndrome	Short PR interval
	Delta waves
	Pseudoinfarct patterns

Abbreviations: LBBB, left bundle branch block; RBBB, right bundle branch block.

several important determinants of VF following a chest blow, including, most importantly, impact delivered directly over the heart and timing within the vulnerable phase of repolarization (a narrow 10- to 30-millisecond window just prior to the T-wave peak, equivalent to only 1%-2% of the cardiac cycle) associated with peak LV pressure caused by the blow, although a wide range of individual vulnerability to VF is evident in the model.[28-35] Furthermore, impact velocity appears to have a Gaussian distribution with a velocity of 40 mph most likely to trigger VF. In addition, hardness and reduced diameter of the impact object have been correlated directly with the risk of VF.[28-35]

Sudden cardiac death in commotio cordis appears to be a primary electrical event. The cellular determinants of VF induced by chest wall blows likely include ion channel activation caused by increased LV pressure.[28-32] The potassium–adenosine triphosphate ion channel mediates the initiation of VF in the swine model and has also been shown to be activated by atrial stretch.[28-32] It is possible that more stretch-activated ion channels are also involved.

Efforts to minimize the risk of SCD from commotio cordis have centered on the impact object, chest protectors, and changes in the rules of the sport.[28-35] Balls softer than standard baseballs have been demonstrated to reduce (but not abolish) the risk of commotio cordis.[28-35] Chest wall protectors intuitively should reduce the risk of commotio cordis. However, in the US Commotion Cords Registry, approximately one-third of the victims experiencing commotio cordis in organized sports were wearing chest protectors, and in the laboratory model, chest protectors did not reduce the risk of VF.[28-35] Ongoing efforts to develop more effective chest protectors can decrease the risk of sudden cardiac death in vulnerable athletes. American Heart Association (AHA)/American College of Cardiology recommendations promote the use of age-appropriate softballs to reduce the risk of commotio cordis, as well as the timely availability of automated external defibrillators.[36]

CLINICAL EVALUATION OF THE ATHLETE WITH SYMPTOMS

Commonly, athletes are referred to clinicians with symptoms potentially attributable to an arrhythmia. Arrhythmias can be nonsustained or sustained and hemodynamically significant or not significant. Thus, arrhythmia-related symptoms range from brief palpitations to syncope and resuscitated sudden death. The severity of the symptoms, the presence or absence of structural heart disease, and the family medical history determine the extent of the workup. As a general rule, the severity of the symptoms is related to the risk of subsequent sudden death. Thus, palpitations are frequently benign. Presyncope and certainly syncope are more concerning, and resuscitated sudden death is a major concern.

Palpitations can be caused by atrial or ventricular premature depolarizations, nonsustained arrhythmias such as atrial tachycardia or nonsustained ventricular tachycardia, or, even on occasion, sustained arrhythmias such as supraventricular or ventricular tachycardias that do not cause hemodynamic collapse. The critical element in the workup is to record the cardiac rhythm during symptoms. A 24-hour ambulatory Holter monitor or event loop recorder can be used in the athlete with daily or frequent symptoms. Subsequent cardiac workup and treatment depend on the specific arrhythmia found.

Syncope is a common symptom in young people and athletes. Syncope without prodromal symptoms or occurring at peak exercise is more concerning and likely represents underlying cardiac disease (Table 64–5). Injury secondary to syncope is more often seen in arrhythmic disorders and rarely seen in neurocardiogenic syncope. Athletes with syncope should at a minimum be tested with a resting 12-lead ECG and an echocardiogram. In athletes older than 35 years of age and those with syncope during exertion, an exercise tolerance test should be performed to evaluate for cardiac ischemia and exercise-induced arrhythmias.

Unfortunately, complete clinical and pathologic information is available in only a small fraction of athletes with sudden cardiac death because there is no mandatory reporting.[36-38] In those surviving an episode of cardiac arrest, a complete cardiovascular assessment is necessary. Thus, ECGs, long-term telemetry monitoring, echocardiography, and stress tests are generally warranted. These tests will identify most individuals with HCM, exercise-induced polymorphic ventricular tachycardia, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and possibly arrhythmogenic right ventricular cardiomyopathy. Cardiac catheterization, cardiac magnetic resonance imaging, and computed tomography should be selectively used if underlying heart disease is not found with this initial workup. Specific electrophysiologic tests for primary electrical diseases (eg, long QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome) are often warranted if the diagnosis is not clear.

Because many of the cardiac diseases that predispose to sudden death in athletes are inherited, the family medical history is important. Therefore, the presence of early sudden death or hereditary cardiac abnormality in the family of an athlete should prompt a thorough cardiac workup regardless of the presenting symptoms.[26]

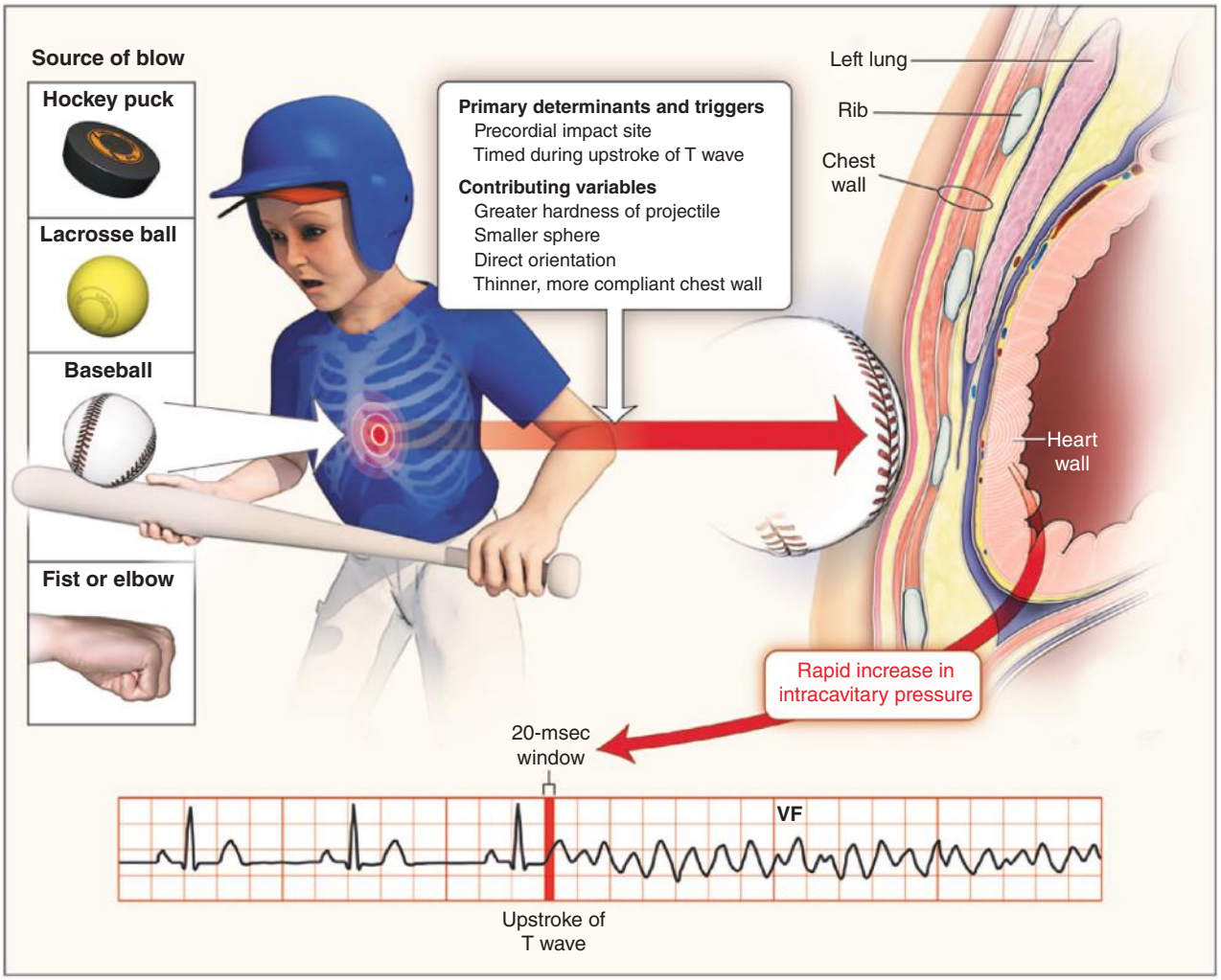


FIGURE 64–3. Pathophysiology of commotio cordis. In recreational and competitive sports, chest blows may involve balls or pucks or may be inflicted through bodily contact. The location of the blow on the chest and its timing relative to the cardiac cycle are the primary determinants of commotio cordis. Other factors that may contribute to the risk of an event include the density, size, and orientation of the projectile and the shape of the thorax; younger people are the most vulnerable because of their thinner, less developed rib cage and musculature. VF, ventricular fibrillation.

TABLE 64–5. Clinical Characteristics Helpful in Differentiating Arrhythmic From Nonarrhythmic Syncope

	Neurocardiogenic or Nonarrhythmic	Arrhythmic
Prodrome	Lightheadedness, warmth, nausea	None or brief lightheadedness
Number of episodes	Multiple	Few or 1
Situational factors	Fear, fright, upright posture	Exertional
		Unrelated to posture
Postsyncopal symptoms	Frequently fatigue	Usually none
Injury	Unusual	Common
Underlying heart disease	Unusual	Common

ELIGIBILITY GUIDELINES

The competitive athlete is defined as one who participates in an organized team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic and frequently intense training.[3,39,40] Although not subjected to a randomized trial design, there is nevertheless circumstantial evidence that SCD risk can be increased by vigorous training.[1-3,39] Furthermore, because of the considerable pressures of competitive sports, athletes are commonly unable to use judgment and control over their level of exertion or reliably discern or respond appropriately to cardiovascular symptoms, thereby increasing their risk.

Consensus recommendations regarding the eligibility of athletes with cardiovascular disease for competition in organized sports are available to guide clinicians both from the United States and Europe.[38-43] These recommendations have been based on the best available data and the consensus of expert panels considering a variety of genetic and/or congenital cardiovascular diseases that may place athletes at increased risk

for sudden and unexpected death or disease progression.[42,43] Eligibility and disqualification recommendations are presented according to specific cardiovascular diseases and with respect to a variety of athletic activities.[38-41]

Although the available consensus guidelines are largely focused on the competitive athlete, other recommendations are available for evaluating recreational athletes.[3,39-41] The disqualification and eligibility guidelines for competitive athletes with cardiovascular disease from the United States and Europe are similar in many respects, although the European version is restrictive in disqualifying those with long QT syndrome, HCM, and Marfan syndrome, particularly when diagnostic cardiac findings are borderline or when disease-causing mutations are not accompanied by phenotypic expression.[3,39-41] Although restricting competitive athletes with certain cardiovascular diseases (eg, HCM) from sports is clinically justified, it should be underscored that these recommendations are not evidence based and are formulated largely based on expert opinion.[39-41]

PREPARTICIPATION SCREENING

The central purpose of preparticipation screening of trained competitive athletes is to identify or raise suspicion of those cardiovascular abnormalities and diseases that are potentially responsible for sudden unexpected death on the athletic field.[40-49] When such athletes are recognized, they are exposed to eligibility and disqualification decisions that become the responsibility of the practicing physician and are a subject of this document.[39-49] There is general (although not universal) agreement with the principle that screening to detect important diseases and potentially prevent sudden death is justified and potentially beneficial.[13,38-48]

GENERAL CONSIDERATIONS

Currently, broad-based cardiovascular screening is practiced systematically in athletes at all levels of performance (not confined to the elite) in only three countries: in the United States with personal or family history and physical examination (but without ECGs) and in both Italy and Israel with 12-lead ECGs in addition to history and physical examination.[38-48] In many European countries, screening of athletes is limited to those performing at the elite level (eg, in international, Olympic, or professional sports), and there is little information on nonathlete students.[39-42] The potential benefit of such initiatives is identification of a small number of individuals with potentially lethal genetic and/or congenital cardiovascular diseases (eg, HCM) so that (1) they may be withdrawn from competitive sports to decrease their personal risk and generally make the athletic field a safer environment; and (2) in the process, some high-risk individuals will be identified who may be candidates for disease-modifying medical or surgical intervention or for prevention of sudden death with implantable defibrillators.

DEBATE AND CONTROVERSY

Italian investigators have intensely promoted screening with routine 12-lead ECGs (as well as history and physical) based on a unique > 30-year program mandated by Italian law and supported by sports medicine physicians dedicated full time to the program.[40-49] Since 1997, Israel has maintained a similar mandatory ECG-based initiative and national sports law.[50] For > 50 years, it has been customary practice in the United States to routinely screen high school– and college-aged athletes with history and physical examination (but without noninvasive testing).[39,44-46,51-57] In contrast, Denmark has pointedly rejected systematic screening for cardiovascular disease in both athletes and any other segment of the population as unjustified in consideration of the low event rate.[52] Other than Japan, no country has systematically attempted broad-based cardiovascular screening in general healthy populations (not limited to athletes), with or without ECGs.[58,59]

Universal Screening: Electrocardiogram Versus History and Physical Examination

Preparticipation screening for cardiovascular disease with personal or family history and physical examination has been the customary practice for all high school– and college-aged competitive athletes in the United States for decades independent of their performance level. This process is guided by the 14-point history and physical examination elements proposed by the AHA.[39,44-46] The AHA recommendations acknowledge that athletes and others with underlying (but undiagnosed) cardiovascular abnormalities may well manifest clinical warning signs (eg, chest pain, excessive exertional dyspnea, syncope) identifiable by careful and systematic history. Because most diseases responsible for sudden death in the young are genetic or familial, a thorough family history is likely to raise suspicion of the disorder. An organic heart murmur can alert the examining physician to valvular or other abnormalities, including LV outflow tract obstruction.

A controversy persists as to whether an ECG (in addition to history and physical examination) is superior to history and physical examination alone for detecting potentially lethal cardiovascular disease, particularly when taking into account the important issues of false-negative and false-positive results, as well as cost and resource availability.[53] Indeed, studies comparing these two strategies have failed to demonstrate a mortality benefit for ECG screening.[49]

The debate between those strongly promoting routine ECGs and those opposed to ECGs as a routine screening tool is not fully resolved as yet, although a substantial literature consisting largely of editorials and viewpoint commentaries is accumulating rapidly. Nevertheless, several points are indisputable. First, the 12-lead ECG, while a mainstay of hospital-based cardiovascular practice for decades, is an unproven diagnostic tool for reliable detection of cardiovascular disease in generally healthy populations.[59-61] Second, outcome data on athlete screening and mortality have been primarily driven by only one database, that of the Veneto region of Italy (9% of the national population) as part of their long-term screening program.[49,51] This ambitious Italian initiative has been shown to be successful in identifying some at-risk athletes with potentially lethal cardiovascular disease (primarily right ventricular cardiomyopathy, which appears to be endemic in this area of Italy), resulting in mandatory withdrawal from sports.[42] A sharp decrease in mortality rate over a 30-year period was demonstrated, which these investigators attributed to incorporation of the 12-lead ECG into the screening program in the early 1980s.[43,44]

Third, the Italian data showing that ECG screening reduces mortality in athletes have yet to be replicated elsewhere, and evidence from the United States and Israel appears to dispute and/or diminish the value of the ECG in reducing athlete mortality.[50,53] For example, contemporary mortality rates in US athletes from Minnesota, where screening is limited to history and physical examination, do not differ from those in the Veneto region of Italy where the ECG is routinely employed, and athlete mortality rates from Israel did not differ before and after legislation for mandatory ECGs.[50,53] The fact that it has been difficult to consistently show a reduction in athlete mortality directly attributable to routine ECGs is an observation that may be in part driven by the generally low event rates in competitive athletes with cardiovascular disease.[50,53]

Relevance of Sudden Death Incidence to Screening

Indeed, the low frequency with which sudden deaths occur in the competitive athlete population negatively impacts the justification for broad-based screening in large populations of young people, as well as the weight that can be afforded to this issue as a public health problem. In this regard, there is now overwhelming evidence that these events are relatively uncommon, albeit exceedingly tragic in each case. Most data place these cardiovascular sudden deaths in the range of about 1 per 80,000 to 1 per 200,000 participants per year, much less common in relative terms than motor vehicle accidents (5000-fold), suicide, drugs, homicide, or cancer in the same age group, and similar in frequency to that of fatal lightning strikes.[44,62,63] In a college (National Collegiate Athletic Association [NCAA]) athlete population, drugs and suicide combined accounted for a similar number of deaths as did confirmed cardiac disease, although a non–forensic-based analysis reported a higher incidence for sudden death.[64]

Furthermore, the absolute number of sudden deaths as a result of documented cardiovascular disease in competitive athletes is small in populations for which forensic data are reported. For example, the 33-year US Sudden Death in Athletes Registry has reported a maximum of 75 such deaths in any given year nationally, and the Veneto database has reported 55 sudden deaths in 26 years, or only about two deaths per year.[44] In other populations, the average number of confirmed cardiovascular deaths annually is much less (ie, less than one death in Minnesota high school athletes or about four deaths in college [NCAA] athletes).[36,46] Notably, false-negative screening results are a major concern in which the system fails to identify cardiac disease that is in fact established. Indeed, a substantial proportion of athletes (about 30%-40%) may die suddenly of cardiovascular abnormalities that would not necessarily be reliably detected by screening, even with ECGs.[64]

Universal Electrocardiogram Screening

On multiple occasions, AHA consensus expert panels have evaluated and decided not to support mandatory national athlete screening in the United States with routine use of ECGs.[43-46] Indeed, sudden cardiovascular deaths in athletes are rare (albeit tragic) events insufficient in number to be judged as a major public health problem or justify a change in national health care policy. The most frequently cited obstacles to mandatory national screening of trained athletes are as follows: (1) the large number of athletes to be screened nationally on an annual basis (ie, about 10-12 million); (2) low incidence of events; (3) substantial number of expected false-negative and false-positive results in the wide range of 5% to 20% depending on the specific ECG criteria used; (4) cost-effectiveness considerations (ie, extensive resources and expenses required vs few events in absolute numbers); (5) liability issues unavoidably impacting physicians (ie, charged with both enforcement and the sole responsibility to disqualify athletes from competition); (6) lack of resources or physicians dedicated to performing examinations and interpreting ECGs, in contrast to the long-standing sports medicine program in Italy; (7) influence of observer variability, technical considerations, and the impact of ethnicity/race on the interpretation of ECGs, particularly important for multicultural athlete populations such as in the United States; (8) need for repetitive (ie, annual) ECG screening during adolescence, given the possibility of developing phenotypic evidence of cardiomyopathies during this time period or later; (9) logistical challenges and cost related to second-tier confirmatory screening with imaging and other testing, should primary evaluations raise the suspicion of cardiac disease; and (10) recognition that even with testing, screening cannot be expected to identify all athletes with important cardiovascular abnormalities and that a significant false-negative rate can be expected.[39-49,65-69]

Nonuniversal Screening for Athletes

Screening programs on a smaller regional and non-national basis have been implemented in some high schools, colleges, and local communities using ECGs (or echocardiograms) with varying expertise, quality control, and results for identifying important cardiac disease. Consistently, the AHA has not opposed ECG-based screening initiatives (often performed by volunteers) in smaller venues. However, for such screening initiatives, the AHA has prudently advised adequate quality control with due consideration for the prominent limitations of the process (including false-negative and false-positive test results) so that the risks as well as benefits can be understood and are acceptable to all participants, communities, and organizations.[44-46] Sudden deaths caused by genetic or congenital heart disease are more common in nonathletes than athletes. This brings to the forefront an ethical issue regarding systematic screening of athletes exclusively.

There are certain known and anticipated limitations in using ECGs in population screening, including (but not limited to) false-positive and false-negative test results, technical and interpretation issues, "gray zone" ambiguous diagnoses, and cost and logistics involved in arranging second-tier diagnostic testing, all of which promote anxiety, uncertainty, and legal considerations.[44-45]

PERFORMANCE-ENHANCING SUBSTANCES

The use of performance-enhancing drugs and substances remains one of the most important and challenging issues in contemporary athletics. By definition, sports-related doping occurs when a prohibited substance or its metabolite is proven by testing or when an unapproved method is used to increase athletic performance.[70] Doping substances include stimulants, anabolic steroids, and peptide hormones.[71] Generally, the scientific evidence is insufficient to assess any desired performance-enhancing effect or toxicity. These substances have undergone formal evaluation for therapeutic use. Clinical observations indicate that some have serious side effects.[72] Appropriately designed clinical trials for toxicity and efficacy have not been performed. Randomized clinical trials are considered unethical because they involve the assessment of banned substances.[72]

The abuse of drugs or substances that are not approved is a threat to the athlete's health.[72] Doping also threatens the integrity of athletics. The use of performance-enhancing drugs or techniques to gain an advantage over others in competition is fundamentally unfair to athletes who train and compete legally. All participating in athletics should be educated with guidance from physicians and relevant athletic organizations regarding the risks of illicit drugs.[72] The use of performance-enhancing drugs and substances such as anabolic-androgenic steroids, growth hormone, and red cell–boosting agents, as well as medications such as diuretic agents, β_2-adrenergic agonists, and glucocorticoids, jeopardizes athletic eligibility. These drugs and substances, including some commercially available nutritional supplements, can be harmful and result in athletic disqualification. Athletes should disclose all prescription medication and supplement use to health care providers and governing organizations. A therapeutic use exemption can be obtained as an official authorization from a governing agency indicating that an athlete may take a medication that is otherwise considered a banned substance without jeopardizing athletic eligibility.[70]

Recently, multiple specific recommendations related to drugs and performance-enhancing substances have been updated.[72] These include the recommendation that all athletes should have their nutritional needs

met through a healthy, balanced diet without dietary supplements. Additionally, governing bodies should develop policies and educate all athletics that performance-enhancing drugs and supplements should be prohibited by sponsoring or participating organizations as a condition for continued participation in athletic activities. Importantly, it is now explicitly stated that the principle of "unreasonable risk" (ie, the potential for risk in the absence of defined benefit) should be the standard for banning or recommending avoidance of substances being evaluated for permission to use by athletes. Finally, athletes should receive formal education and counseling by physicians and athletic department staff on the potential dangers of recreational drugs and performance-enhancing substances, including the risk of sudden death and myocardial infarction.

CONCLUSION

Cardiovascular disease potentially contributing to cardiovascular death in athletes presents several challenges to the medical professional and health care system, including diagnosis of cardiac abnormalities associated with sudden cardiac death, management of these cardiac disorders, and the evolution of universally applicable screening protocols aimed at reducing exposure of susceptible individuals to risk of death. The current clinical focus is on identification of underlying cardiac disease by screening strategies, appropriate treatment, and selective restriction from athletic participation. At the same time, it is important to recognize the limitations of this approach and also focus on preparation for cardiovascular emergencies caused by undetected cardiac disease that may manifest on the athletic field. Although significant advances have been made regarding identification, treatment, athletic restrictions, and emergency preparation regarding cardiovascular disease in the athlete over the last several years, it is evident that much remains unknown.

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CHAPTER 65

CARDIOVASCULAR DISEASE IN THE ELDERLY: PATHOPHYSIOLOGY AND CLINICAL IMPLICATIONS

Joshua M. Stolker, Dae H. Kim, and Michael W. Rich

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INTRODUCTION

Most cardiovascular diseases (CVDs) increase in prevalence and severity with age, and most clinicians provide care for a substantial number of elderly patients with disorders of the heart and vascular system. According to the American Heart Association, nearly 70% of all US adults ≥ 60 years old and more than 85% of those ≥ 80 years old have known CVD (Fig. 65–1).[1] Despite earlier treatment of risk factors and progressive improvements in therapies over the past several decades, heart disease remains the leading cause of death in the Medicare population. Furthermore, more than half of all cardiovascular procedures in the United States are performed in patients age 65 years and older, and the total cost for CVD in this population exceeded $115 billion in 2011.[1] With the progressive aging of our population,[2,3] these figures will continue to rise. For these reasons, an understanding of the effects of aging on the development of CVD and the utility of cardiovascular therapies in the context of other age-related medical concerns (eg, multimorbidity, polypharmacy, frailty) is critical for reducing risk and improving outcomes in older patients.

OVERVIEW OF CARDIOVASCULAR AGING PROCESSES

Normal aging is associated with diffuse changes in cardiovascular structure and function (Table 65–1).[4,5] These processes have important effects on the cardiovascular system with direct clinical implications (Table 65–2). Taken together, these changes contribute to the exponential rise in the incidence and prevalence of CVD in the geriatric population, including the marked increase in incidence of coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF), and stroke in older adults. In addition, cardiovascular aging promotes the emergence of many age-associated CVD syndromes, including isolated systolic hypertension (the dominant form of hypertension in older adults), HF with preserved ejection fraction (HFpEF), calcific aortic stenosis, and "sick sinus syndrome." Each of these conditions is discussed in subsequent sections of this chapter.

Aging is also associated with important changes in other organ systems that interact with the cardiovascular system and have implications for the clinical presentation and management of cardiovascular disorders (see Table 65–1). Renal function declines progressively with age, resulting in diminished capacity to maintain fluid and electrolyte homeostasis and predisposing to volume overload, cardiorenal syndrome, and electrolyte abnormalities (eg, in response to diuretics). Commonly used cardiovascular medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid antagonists (MRAs), and diuretics may contribute to worsening renal function. Conversely, advanced chronic kidney disease (eg, estimated glomerular filtrate rate < 30 mL/min/1.73 m^2) mandates cautious use or avoidance of many drugs that are the foundation of guideline-directed medical therapy.

Age-associated reductions in pulmonary reserve contribute to increased dyspnea, reduced exercise capacity, and impaired quality of life in older patients with CVD, particularly among those with HF. Alterations in the neurohormonal system contribute to increased risk for side effects from cardiovascular medications, especially lightheadedness, falls, and syncope. Age-related impairment in the thirst mechanism predisposes to intravascular volume contraction and prerenal azotemia.

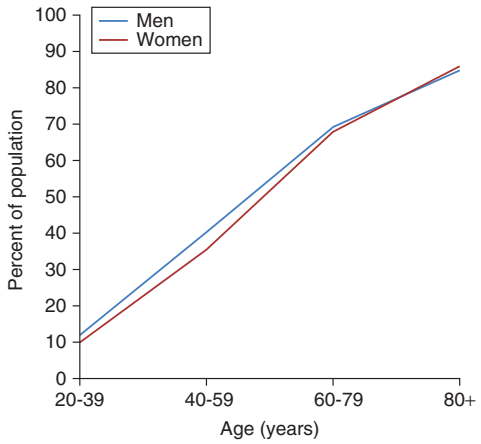

FIGURE 65–1. Prevalence of cardiovascular disease by age and sex, from the National Health and Nutrition Examination Survey (2009-2012). Data from the American Heart Association's 2016 Statistical Fact Sheet.

With increasing age, changes in the hemostatic system shift the intrinsic balance between thrombosis and fibrinolysis in the direction of thrombosis. As a result, older adults are at increased risk for both venous thromboembolic disease (ie, deep venous thrombosis and pulmonary embolism), as well as thrombosis in the arterial system, including myocardial infarction (MI), left atrial appendage thrombus in AF, and stroke. Despite these changes, and perhaps paradoxically, older adults are also at increased risk for bleeding complications with all antiplatelet, anticoagulant, and fibrinolytic agents, as exemplified by increased incidence of intracranial hemorrhage in older adults receiving prasugrel or fibrinolytic agents (see later Ischemic Heart Disease section). In addition, age-associated declines in muscular mass (sarcopenia) and bone mass (osteopenia) contribute to reductions in exercise tolerance, adversely affect balance, and predispose to injurious falls. Further, aging is associated with altered pharmacokinetics and/or pharmacodynamics of almost all medications, so that drug dosages tested in clinical trials involving predominantly younger and healthier patients may not be appropriate for the majority of older adults.

TABLE 65–1. Effects of Aging on the Cardiovascular System and Other Organ Systems

Gross anatomy of the heart
- Increased left ventricular wall thickness and decreased cavity size
- Endocardial thickening and sclerosis
- Increased left atrial size
- Valvular fibrosis and sclerosis
- Increased epicardial fat

Cardiac histology
- Increased lipid and amyloid deposition
- Increased collagen degeneration and fibrosis
- Calcification of fibrous skeleton, valve rings, and coronary arteries
- Shrinkage of myocardial fibers with focal hypertrophy
- Decreased mitochondria, altered mitochondrial membranes
- Decreased nucleus: myofibril size ratio

Biochemical changes of the myocardium
- Decreased protein elasticity
- Numerous changes in enzyme content and activity affecting most metabolic pathways; no change in myosin ATPase activity
- Decreased catecholamine synthesis, especially norepinephrine
- Decreased acetylcholine synthesis
- Decreased activity of nitric oxide synthase

Cardiac conduction system
- Degeneration of sinus node pacemaker and transition cells
- Decreased number of conducting cells in the atrioventricular node and His-Purkinje system
- Increased connective tissue, fat, and amyloid
- Increased fibrosis in and around the atrial conduction system
- Increased calcification around conduction system

Peripheral vasculature
- Decreased distensibility of large and medium-sized arteries
- Impaired endothelial function
- Aorta and muscular arteries become dilated, elongated, and tortuous
- Increased wall thickness
- Increased connective tissue and calcification

Autonomic nervous system
- Decreased responsiveness to β-adrenergic stimulation
- Increased circulating catecholamines, decreased tissue catecholamines
- Decreased α-adrenergic receptors in left ventricle
- Decreased cholinergic responsiveness
- Diminished response to Valsalva and baroreceptor stimulation
- Decreased heart rate variability

Kidneys
- Gradual decline in glomerular filtration rate, ~8 mL/min/decade
- Impaired fluid and electrolyte homeostasis

Lungs
- Reduced ventilatory capacity
- Increased ventilation/perfusion mismatching

Neurohumoral system
- Reduced cerebral perfusion autoregulatory capacity
- Diminished reflex responsiveness
- Impaired thirst mechanism

Hemostatic system
- Increased levels of coagulation factors
- Increased platelet activity and aggregability
- Increased inflammatory cytokines and C-reactive protein
- Increased inhibitors of fibrinolysis and angiogenesis
- Shift in balance between thrombosis and fibrinolysis in favor of thrombosis

Musculoskeletal system
- Decreased muscle mass (sarcopenia)
- Decreased bone mass (osteopenia), esp. in women

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TABLE 65–2. Major Clinical Implications of Cardiovascular Aging

Effect of Aging	Clinical Implications
Increased stiffness of large arteries	Increased impedance to LV ejection (afterload) with compensatory LV hypertrophy
	Increased systolic blood pressure with decline in diastolic blood pressure and increased pulse pressure
	Isolated systolic hypertension becomes dominant form of hypertension
Increased LV myocardial stiffness and impaired LV relaxation	Altered diastolic filling with shift to the left in LV pressure-volume relationship
	Predisposition to heart failure with preserved ejection fraction
	Left atrial enlargement and predisposition to atrial fibrillation
Impaired responsiveness to β-adrenergic stimulation	Decline in maximum HR (220 – age) and peak cardiac output (HR × SV)
	Decline in peak LV contractility in response to stress
	Decline in peripheral vasodilatation with reduction in peak blood flow to skeletal muscles and skin
Fibrosis of cardiac skeleton, conduction system, and valves; degeneration of sinus node pacemaker cells	Increased incidence and prevalence of supraventricular and ventricular arrhythmias (especially atrial fibrillation)
	Increased bradyarrhythmias, including "sick sinus syndrome," AV nodal block, and infranodal conduction disturbances
	Increased prevalence of calcific aortic stenosis
Impaired endothelial function	Decreased peak coronary blood flow and increased risk for "demand" ischemia
	Decreased flow-mediated vasodilation and peak blood flow to periphery, including exercising muscles
Impaired carotid baroreceptor responsiveness	Increased risk for orthostatic hypotension, lightheadedness, falls, and syncope
	Increased side effects from cardiovascular drugs, esp. diuretics and β-blockers
Net effect of age-related changes	Marked reduction in cardiovascular reserve (see section titled Cardiac Dysfunction and Heart Failure and Fig. 65–7)

Abbreviations: AV, atrioventricular; HR, heart rate; LV, left ventricular; SV, stroke volume.

Finally, as discussed in more detail in the next section, coexisting illnesses and geriatric syndromes greatly increase the complexity of managing cardiovascular disorders in older adults. Similarly, optimal management of older adults must consider a host of other factors including life expectancy, functional limitations, lifestyle and quality of life, psychosocial and behavioral issues (eg, depression, social support), and financial concerns.

In sum, older adults with CVD represent an extraordinarily heterogeneous population, often with considerable complexity, for which high-quality evidence from clinical trials is generally inadequate, and for whom standard guideline recommendations (which typically focus on a single cardiovascular disorder) may not be applicable. Hence, the approach to management of elderly patients is fundamentally different from that used in younger patients and must be individualized to ensure that care is well aligned with patient-centered goals.

GERIATRIC SYNDROMES IN CARDIOVASCULAR DISEASE

Geriatric syndromes refer to multifactorial problems of old age that do not fit into classical disease categories.[6] Key examples include frailty, cognitive impairment, delirium, functional decline, falls, and incontinence. The interrelationships of CVD with multimorbidity, polypharmacy, and geriatric syndromes are complex (Fig. 65–2). First, CVD is a risk factor for geriatric syndromes, and geriatric syndromes may in turn contribute to new onset or progression of CVD. Second, when CVD and noncardiovascular conditions coexist, the risk of geriatric syndromes and adverse health outcomes is higher than the risk associated with either condition alone (ie, disease-disease interaction). Third, a medication used to treat one condition may worsen another condition (drug-disease interaction) or increase the risk of drug-related adverse events (drug-drug interaction). Such interactions are more likely to occur as the number of medications increases. Fourth, the presence of geriatric syndromes is a poor prognostic marker for mortality, functional decline, and lack of treatment benefit in older adults with CVD. In particular, the degree of frailty may affect an individual's likelihood of positive and negative outcomes after cardiovascular procedures.[7,8] This section outlines how assessing common geriatric conditions can help individualize cardiovascular care in older adults.

MULTIMORBIDITY

Multimorbidity, the presence of two or more chronic conditions, affects over two-thirds of older adults[9,10] and is associated with an increased risk of mortality, disability, nursing home admission, and health care utilization.[9-11] Multimorbidity frequently involves CVD—coexistence

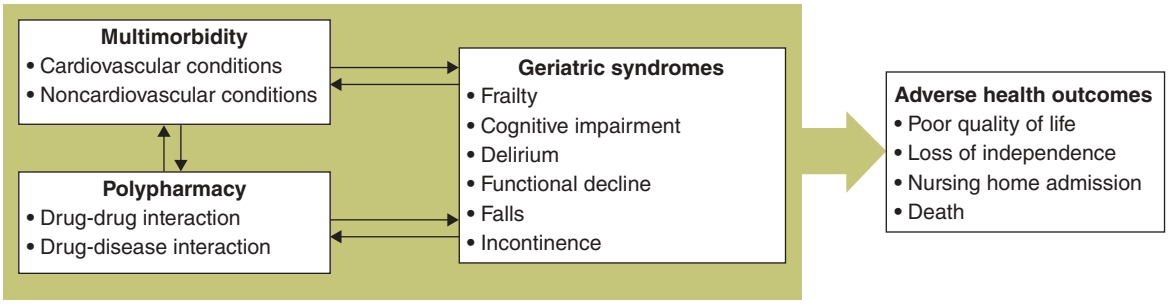


FIGURE 65–2. Relationship of cardiovascular disease with multimorbidity, polypharmacy, and geriatric syndromes.

of a cardiometabolic condition and osteoarthritis was the most common multimorbidity pattern in several population-based studies.[12] Among Medicare beneficiaries, the dyad of hypertension and hyperlipidemia was most prevalent (53%), and other common conditions were ischemic heart disease, diabetes, and arthritis.[10,13] In addition, over 50% of Medicare beneficiaries with HF, stroke, or AF have more than five chronic conditions.[9] Prevalent noncardiovascular conditions include arthritis, anemia, chronic kidney disease, cataracts, chronic obstructive pulmonary disease, dementia, and depression.[13] Furthermore, noncardiovascular conditions account for almost half of readmissions after HF or MI in older adults.[14] Therefore, identifying common patterns of multimorbidity may guide clinical decisions by helping clinicians prioritize interventions most likely to have a positive impact on overall outcomes.

When prescribing medications, clinicians should be aware that combining multiple evidence-based recommendations according to each disease-based guideline may not be feasible or may even be harmful in older adults with multimorbidity.[15] Because certain multimorbidity patterns may increase the risk of adverse drug-disease and drug-drug interactions,[10] trade-offs between different conditions are inevitable. There are three major domains of the equation required to make individualized treatment decisions: expected benefits, potential risks, and patient-level factors (Fig. 65–3). Personal goals and preferences should be incorporated into decision making by involving the patient to set priorities among competing treatments for different conditions.[16] The likelihood of benefit versus risk of a treatment should be assessed based on relevant evidence and the patient's prognosis. To maximize adherence, clinicians need to consider the feasibility of a proposed treatment regimen as well as overall treatment burden from pharmacologic and nonpharmacologic therapies for all chronic conditions.

POLYPHARMACY

Polypharmacy is typically defined as concomitant use of five or more medications.[17] Use of prescription medications and prevalence of polypharmacy have increased markedly over the past decade.[18] The number of chronic conditions and prescribing practices aligned with disease-based guidelines are directly correlated with polypharmacy.[17,19] Approximately 40% of community-dwelling older adults take at least five medications,[17] and 20% take medications that may exacerbate coexisting conditions.[20] For example, arthritis is often treated with nonsteroidal anti-inflammatory drugs, which antagonize the effects of many cardiovascular medications (ACEIs, ARBs, diuretics) and also increase risk for MI, HF, and worsening renal function. The number of medications and treatment complexity are associated with nonadherence, drug-related adverse events, financial burden, and caregiver stress.[15,17,20-25] Although evidence-based management of CVD often warrants therapeutic polypharmacy, CVD medications are responsible for 25% of preventable adverse events caused by medications.[26] Because the majority of clinical trials of CVD treatment excluded older adults with multimorbidity and polypharmacy, the incremental benefit and harm of a drug when added to an already complex treatment regimen remain unclear.[27]

Some evidence suggests that the benefit of guideline-recommended CVD treatments may be less in patients with certain multimorbidity patterns.[19] Clinicians should carefully weigh the benefit of prescribing a new medication against the risk of adverse events, reduced adherence to other essential treatments, and financial burden.[16] To justify prescribing, the expected time horizon to benefit needs to be shorter than the patient's life expectancy (eg, avoid statins for primary prevention if life expectancy is < 2 years). It is essential to periodically review the indications for each agent to decrease the risk of drug-drug and drug-disease interactions.[28] When the indication for a medication is unclear, a time-limited withdrawal trial may be useful (eg, discontinuing a proton pump inhibitor that was initiated for stress ulcer prophylaxis in the hospital). A gradual taper and careful monitoring for withdrawal symptoms or worsening chronic conditions may be needed when a CVD or psychoactive medication is reduced.[29] In addition, adopting a standard checklist (eg, the American Geriatrics Society Beer's list[30] or Screening Tool of Older People's Potentially Inappropriate Prescriptions [STOPP]/Screening Tool to Alert Doctors to the Right Treatment [START] criteria[31]) can effectively reduce use of potentially inappropriate medications and drug-related adverse events in older adults.[32,33]

FRAILTY

Frailty is a geriatric syndrome that is characterized by reduced physiologic reserve in multiple organ systems (eg, the brain or endocrine, immune, musculoskeletal, or cardiovascular systems) to maintain homeostasis after a stressful event and increased vulnerability to adverse health outcomes.[34] It is the most problematic manifestation of aging and contributes substantially to the heterogeneity in health status of the aging population. Several criteria for diagnosing frailty have been developed, yielding varying prevalence estimates in the general population, from < 5% using a specific physical performance-based definition to > 50% using a more comprehensive definition.[35] The *frailty phenotype*, derived from the Cardiovascular Health Study, is a widely accepted method for classifying older adults into robust, prefrail, or frail categories based on unintentional weight loss, weak handgrip strength, exhaustion, slow gait speed, and low physical activity.[36] Persons with three or more of these criteria are considered frail; those with one or two criteria are considered prefrail. Alternatively, frailty can be quantified using a continuous scale, known as the *frailty index*, based on accumulation of health deficits (eg, symptoms, signs, diseases, diagnostic test results, functional limitations) in multiple physiologic systems[37] or by standard comprehensive geriatric assessment.[38] The frailty phenotype may offer better clinical translation by allowing targeted interventions for and monitoring of each component, whereas the frailty index offers better prediction of adverse health outcomes.[39]

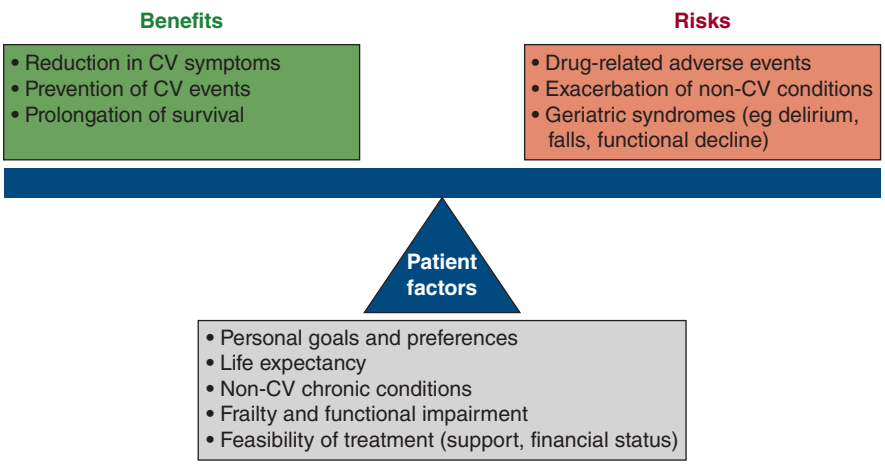


FIGURE 65–3. Factors to consider in assessing the benefits and risks of cardiovascular (CV) treatment.

The prevalence of frailty in older adults with CVD ranges from 21% in patients with CAD[40] to 51% in those with decompensated HF[41] and as high as 50% to 70% in those undergoing transcatheter aortic valve replacement (TAVR).[8,42,43] In the Cardiovascular Health Study, clinical and subclinical CVDs were strongly associated with frailty[44] and prolonged disability.[45] In particular, patients with HF were 7.5-fold more likely to have frailty than those without HF.[44] In the Health, Aging, and Body Composition Study, severe frailty was associated with a 1.9-fold increased risk for HF.[46] In addition, markers of frailty predicted hospitalizations,[47] disability,[48] and mortality[41] in older adults with HF. Mobility impairment, a hallmark of frailty,[49] is a strong predictor of postoperative complications, mortality, functional decline, and lack of improvement after cardiac surgery or TAVR.[7,50-54]

Although the relationship between CVD and frailty is bidirectional, it remains to be elucidated whether treating an advanced CVD (eg, TAVR for aortic stenosis) can reverse frailty or whether interventions targeting frailty can improve CVD-related outcomes. Nonetheless, frailty assessment is useful to predict prognosis and guide decision making about CVD management and procedures. If feasible, clinicians should consider using a validated screening instrument for frailty in patients of advanced age.[55,56] A brief mobility test, such as Timed Up-and-Go (Fig. 65–4) or gait speed, is a good alternative to more comprehensive tests, with high sensitivity (0.93-0.99) and moderate specificity (0.62-0.64) for identifying frailty.[57,58] A positive screening test for frailty should be followed with a comprehensive geriatric assessment comprising medical, psychosocial, and functional domains and development of an individualized care plan. Such a patient-centered approach can prevent functional decline and nursing home admissions in frail older adults.[59-61]

COGNITIVE IMPAIRMENT

Dementia affects 14% of adults age 70 years or older in the United States, and the prevalence increases with age, from 5% in patients age 71 to 79 years to 37% in those over 90 years of age.[62] Mild cognitive impairment, a less severe form of cognitive limitation with relative preservation of functional status, is present in 22% of people ≥ 70 years old.[63] The annual rate of progression from mild cognitive impairment to dementia is estimated to be about 12%.[63] The prevalence of cognitive impairment in older adults with CVD is higher than that in the general population: 35% in patients undergoing coronary artery bypass graft (CABG) surgery[64] and 47% in hospitalized patients with HF.[65] The underlying mechanisms include hypoperfusion, oxidative stress, and inflammation, which lead to diverse cerebrovascular pathologies, including large cerebral infarcts, white matter lesions, lacunes, microinfarcts, and microbleeds.[66]

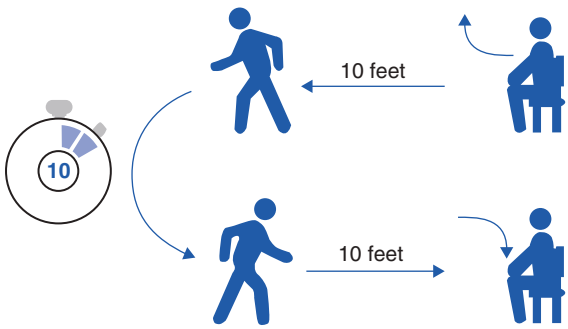
A unique clinical characteristic of cognitive impairment attributable to CVD is executive dysfunction that manifests as difficulty with complex daily activities required for independent living (eg, managing finances, taking medications, using transportation). Cognitive impairment is associated with poor adherence[67] and increased risk of readmissions and mortality in HF patients.[65,68] Thus, cognitive impairment presents a serious challenge in outpatient management of older adults with CVD, and it may be difficult to diagnose among higher functioning patients. Moreover, cognitive impairment is a strong risk factor for delirium in hospitalized patients.[69]

DELIRIUM

Delirium, an acute-onset disturbance in attention and awareness, is present in up to 35% of patients age 65 years or older on general medical wards[70] and up to 46% of patients age 60 years or older after cardiac surgery.[71] Evaluation for delirium requires a brief cognitive assessment, such as the Confusion Assessment Method algorithm comprised of the following four key features: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness.[72] Use of multiple drugs (ie, polypharmacy), psychoactive drugs (especially benzodiazepines), physical restraints, and bladder catheters are common precipitating factors of delirium in hospitalized patients.[69] Development of delirium is associated with prolonged hospitalization, functional decline, nursing home admission, and mortality.[69] Patients who develop delirium after cardiac surgery may have persistent cognitive decline for up to a year after hospital discharge.[71] Because there is no effective pharmacologic treatment for delirium, nonpharmacologic preventive interventions are the key to avoiding adverse consequences of delirium.[73] However, recognition and documentation of cognitive impairment and delirium by clinicians are poor.[65,68,74] Regular use of a validated screening instrument to assess cognitive function is recommended, particularly as a part of preoperative assessment before cardiac surgery or other major procedures.

FUNCTIONAL DECLINE

The risk of functional decline is greatest in hospitalized older adults. In addition to the debilitating effects of acute illness, hospitalization itself is associated with restricted mobility, enforced dependence, little encouragement of independence, limited access to food and liquids, disturbance of circadian rhythm, and polypharmacy.[75] These



Instructions to the patient:

When I say **"Go,"** I want you to:

1. Stand up from the chair
2. Walk to the line on the floor at your normal pace
3. Turn
4. Walk back to the chair at your normal pace
5. Sit down again

On the word **"Go"** begin timing.

Stop timing after patient has sat back down and record.

Time: _____ seconds

An older adult who takes ≥12 seconds to complete the TUG is at high risk for falling.

adapted from web and CDC brochure

FIGURE 65–4. Timed Up-and-Go (TUG) test for assessment of mobility and fall risk. Reproduced with permission from Centers for Disease Control and Prevention (http://www.cdc.gov/steadi/index.html).

perturbations may predispose patients to delayed recovery, functional decline, cognitive impairment, and falls after hospital discharge. The term *post-hospital syndrome* refers to an acquired, transient condition of increased vulnerability following hospital discharge.[76] To mitigate the risk of complications occurring in the early post-hospitalization period, clinicians treating hospitalized older patients with CVD should assess functional status, mobility, and cognition on admission to identify high-risk individuals and then assess these patients daily thereafter to detect functional decline. At discharge, adequate support systems and interventions that promote functional recovery and safety beyond CVD management should be instituted. Multidisciplinary care provided in a dedicated inpatient geriatric unit has been shown to increase home discharge and reduce functional decline in heterogeneous populations of hospitalized older adults with acute medical illness, although dedicated trials in older adults with CVD and multimorbidity are lacking.[77,78]

FALLS

One-third of community-dwelling adults ≥ 65 years of age fall at least every year, and 5% to 10% of them sustain a fracture, laceration, or head trauma. Risk factors for falls include gait and balance problems, decreased muscle strength, vision impairment, medications, orthostatic hypotension, functional limitations, cognitive impairment, and urinary incontinence.[79] Symptomatic CVD can contribute to slow gait, decreased muscle strength, functional limitations, and cognitive impairment. Use of psychoactive drugs,[80,81] antihypertensive drugs,[81,82] and loop diuretics[83] is common in those with CVD, and these agents have been linked to falls in older adults. In a population-based study, symptomatic HF was associated with a 1.9-fold higher risk of falls.[84] Falls and fear of falling are also barriers to participating in physical activity.[85] As such, falls may negatively influence adherence to evidence- based CVD treatments and lifestyle interventions. Fall screening can be done by asking about history of falls and self-reported difficulty with walking or balance or by performing the Timed Up-and-Go test (see Fig. 65-4).[86] High-risk patients should receive multidisciplinary evaluation and targeted interventions, including gait and balance training.[87]

URINARY INCONTINENCE

Urinary incontinence is an underdiagnosed and undertreated geriatric syndrome that causes significant psychological and physical challenges, including increased risk of falls.[88] In the community, 11% of men and 16% of women over the age of 60 experience urinary incontinence at least weekly, and the proportion increases considerably with age.[89] Like other geriatric syndromes, incontinence has multiple contributing causes, such as atrophic vaginal tissue, infection, delirium, increased urine volume, medications, and mobility impairment,[90] many of which are affected by CVD and common CVD treatments. Cough from ACEI medications may cause or exacerbate stress incontinence, whereas increased urine volume from diuretics may precipitate urge incontinence. Calcium channel blockers may worsen urinary retention, voiding difficulty, and constipation, leading to urge incontinence. Given the negative impact of urinary incontinence on quality of life and risk of falling, clinicians should ask about urinary incontinence and consider the patient's preferences and mobility before prescribing medications that may contribute to incontinence. Nonpharmacologic treatment (eg, lifestyle interventions, Kegel exercises, bladder training) should be offered to all incontinent patients.[91]

IMPLICATIONS FOR CARDIOVASCULAR DISEASE MANAGEMENT

The ultimate goal of treating CVD in older adults is to reduce symptoms and prevent future CVD events, thereby improving quality of life, functional status, and survival. Because of the complex interactions among multimorbidity, polypharmacy, and geriatric syndromes (see Fig. 65–2), treatments to improve CVD-related outcomes may not necessarily lead to proportional improvements in quality of life and functional status in older adults comparable to those seen in clinical trials. To maximize the benefits in CVD-related outcomes as well as global outcomes, cardiologists should assess the burden of coexisting noncardiovascular conditions, polypharmacy, and geriatric syndromes, and recognize their significance when considering options for CVD management (Table 65–3). Given the short clinic visit time and fragmented care provided to many patients with multiple medical problems, involvement of a multidisciplinary team that consists of experts in geriatrics, pharmacology, rehabilitation, and social work is encouraged whenever possible to facilitate comprehensive assessment and optimal selection of interventions.

ISCHEMIC HEART DISEASE

EPIDEMIOLOGY AND RISK FACTORS

The American Heart Association reports that 20% of men and 10% of women between 60 and 79 years of age have ischemic heart disease (IHD), and approximately half of these patients have experienced a previous MI.[1] These proportions increase markedly with age, such that one of every four individuals age 80 years and older has clinically evident CAD. In autopsy studies, the prevalence of obstructive coronary atherosclerosis increased from 10% to 20% for patients in their 40s to 50% to 70% among patients in their 80s.[92] In patients referred for CABG in a large clinical trial, older age was associated with more diffuse coronary atherosclerosis, substantially higher rates of left main and triple-vessel disease, and greater degrees of left ventricular wall motion abnormalities and systolic dysfunction.[93] In the United States, the average age of first MI is 65 years for men and 72 years for women, with approximately 80% of all coronary-related deaths occurring in the Medicare-aged population.[1] Furthermore, nearly half of the 7 million deaths attributed to IHD across the globe each year occur in the small subgroup of patients ≥ 80 years old.[3] For these reasons, a thorough understanding of the nuances in patient presentation, prognosis, and management of IHD among elderly patients is imperative for treating acute and chronic CAD in daily clinical practice.

Risk assessment is the cornerstone of CVD management, and multiple studies have demonstrated the prominent role of age in predicting adverse outcomes in patients with IHD. For example, increasing age is the strongest predictor of IHD events in the Framingham Risk Score,[94] and the impact of age on IHD risk is substantially greater than for other traditional risk factors such as hypertension, smoking, or lipid profiles. Similarly, in updated algorithms such as the Reynolds Risk Score, age provides nearly threefold more statistical weight to the final risk estimate than any other risk factor.[95,96] Older age also consistently identifies patients at higher risk for short-term clinical events after acute coronary syndrome (ACS), as noted in the Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) risk models espoused by national guidelines.[97,98] For example, age ≥ 80 years has nearly twice the prognostic significance in the GRACE ACS algorithm (91-100 points) than any other risk factor (46-59 points for the most severe clinical presentations, including profound hypotension or tachycardia, pulmonary edema, cardiac arrest, or renal failure).[99]

Taken together, the structural and functional changes that occur with increasing age, along with the increasing prevalence of most atherosclerotic risk factors and a progressively sedentary lifestyle, all contribute to higher likelihood of developing IHD with increasing age.

TABLE 65–3. Implications of Common Geriatric Conditions in Managing Cardiovascular Disease in Older Adults

Geriatric Condition	Significance	Assessment	Management
Multimorbidity	• Older patients with multimorbidity excluded from clinical trials of CVD treatments • Guideline-based CVD treatments may not be feasible or effective • CVD treatment may worsen coexisting conditions • Non-CVD conditions account for almost half of readmissions after CVD admissions	• Identify coexisting non-CVD conditions requiring treatments that may compete with CVD treatments	• Adopt patient-centered care that aligns treatments with personal goals and preference • Consider the following aspects: - Likelihood of benefits vs harms - Prognosis (life expectancy) - Functional impairment and frailty - Treatment feasibility
Polypharmacy	• CVD medications are responsible for 25% of preventable drug-related adverse events. • ↑ Risk of drug-drug interactions • ↑ Risk of drug-disease interactions • ↓ Treatment adherence • ↑ Financial burden • ↑ Caregiver stress	• Assess total treatment burden from - Nonpharmacologic treatment - Pharmacologic treatment (total number of medications and treatment complexity) • Assess treatment adherence	• Identify medications with high likelihood of harms and questionable benefits using an expert consensus checklist (eg, Beers criteria) • Discontinue nonessential treatments to maximize adherence to essential treatments
Frailty	• Underdiagnosed • CVD is a risk factor for frailty • ↑ Risk for hospitalization, nursing home admission, functional decline, and mortality • Useful for risk stratification before invasive procedure (eg, transcatheter aortic valve replacement)	• Use a validated frailty assessment: - Timed Up-and-Go test - Gait speed - Short physical performance battery - Frailty phenotype - Comprehensive geriatric assessment	• No effective pharmacologic interventions exist for prevention or treatment of frailty • Comprehensive geriatric assessment and exercise program can prevent functional decline and nursing home admission • Use frailty assessment to predict prognosis and guide individualized treatment decisions
Cognitive impairment	• Underdiagnosed • CVD is a risk factor for cognitive impairment • ↓ Treatment adherence and disease monitoring • ↑ Risk for hospitalization and mortality in heart failure	• Use a validated cognitive screening tool: - Mini-Mental State Examination - Montreal Cognitive Assessment - Mini-Cog test	• Simplify CVD treatments for better adherence • Use support system to improve adherence and disease monitoring
Delirium	• Underdiagnosed • ↑ Risk for hospitalization, nursing home admission, functional decline, and mortality • May lead to persistent cognitive impairment after cardiac surgery	• Use the Confusion Assessment Method (CAM) for diagnosis in hospitalized older patients	• Use nonpharmacologic interventions to prevent delirium • No effective pharmacologic interventions exist for prevention or treatment of delirium
Functional decline	• Underdiagnosed • CVD can cause functional decline • ↓ Treatment adherence and disease monitoring • ↑ Risk for hospitalization, nursing home admission, and mortality	• Use a validated instrument: - Katz index of activities of daily living - Lawton index of instrumental activities of daily living	• Use support system to improve adherence and disease monitoring
Falls	• Underdiagnosed • Symptomatic heart failure and certain CVD medications may contribute to fall risk • ↓ Adherence to exercise intervention	• Use a validated screening tool: - Number of falls in the past year - Self-reported difficulty in gait or balance - Timed Up-and-Go test	• Start CVD medications at low dose and gradually increase • Refer high-risk patients to gait and balance training program or to a fall specialist for multidisciplinary assessment and targeted interventions
Incontinence	• Underdiagnosed • CVD medications may contribute to the risk (especially diuretics and ACEI cough) • ↓ Quality of life	• Ask about urinary incontinence	• Discuss the impact of worsening incontinence by CVD treatments • Initiate nonpharmacologic interventions for incontinent patients • Refer selected patients to a specialist if nonpharmacologic interventions are not effective

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CVD, cardiovascular disease.

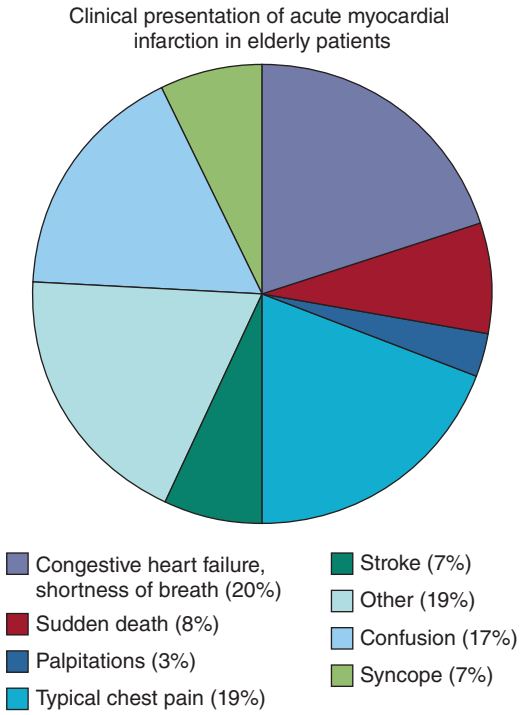


FIGURE 65–5. Clinical presentation of acute myocardial infarction in elderly patients. Reproduced with permission from Arenson C, Busby-Whitehead J, Brummel-Smith K, et al: *Reichel's Care of the Elderly: Clinical Aspects of Aging*, 7th ed. New York: Cambridge University Press; 2016.

Furthermore, subclinical cardiovascular and other medical diseases are highly prevalent among older patients.[100] As a result, older patients with IHD often present later and with more severe disease, resulting in substantially higher risks of adverse outcomes.

CLINICAL PRESENTATION

Typical angina has been described most often in cohorts of middle-aged patients, the majority of whom are male and white. However, older patients with acute MI are more likely to be female and to present with dyspnea, nausea, diaphoresis, altered mental status, or other nonspecific symptoms such as malaise and fatigue (Fig. 65–5).[5,101-103] As a result, the proportion of patients presenting with typical angina decreases with age, which makes the diagnosis of ACS more challenging and often more delayed than in younger individuals. Reduced functional capacity, competing diagnoses with similar symptoms (eg, chronic lung disease or indigestion), and cognitive impairment may further obscure the diagnosis.

Although physical examination has limited utility for the diagnosis of IHD at all ages, the delayed recognition of ACS in elderly patients likely contributes to the higher proportion of patients with more advanced disease and complications at presentation, including signs of pulmonary edema or cardiogenic shock.[5,101] Other findings of more advanced IHD in elderly ACS patients may include altered mental status or confusion, rales, tachycardia, hypoxia, jugulovenous distension, or peripheral edema. Electrocardiographic diagnosis of ACS may be confounded by pre-existing electrical abnormalities, including left bundle branch block, left ventricular hypertrophy, prior MI, repolarization changes from antiarrhythmic drugs, or the presence of ventricular paced rhythm[5,104]—again contributing to later recognition of MI in older patients.

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

In conjunction with age-related differences in clinical presentation, increasing age is associated with higher complication rates after MI, including striking increases in short-term mortality after age 65 (Fig. 65–6).[101,102,105,106] This increase in risk with age has been demonstrated for both ST-segment elevation MI (STEMI)[107-109] and for non–ST-segment elevation ACS (NSTE-ACS).[99,110,111] Of note, quantifiable indices of MI size, such as peak biomarkers or severity of electrocardiographic changes at presentation, are not substantially different between younger and older patients.[102,107,109] Nonetheless, older patients experience markedly higher rates of HF, AF, and cardiogenic shock, which in part reflects age-related cardiovascular changes and diminished cardiovascular reserve.[107,111]

With improvements in short-term survival following acute MI during the coronary reperfusion era, postinfarction HF affects a large proportion of elderly ACS patients and is associated with poor outcomes[112] (see Chaps. 39 and 42). Right ventricular ischemia or infarction in patients with inferior STEMI is associated with particularly high mortality in elderly patients.[113] Mechanical complications of acute MI (eg, left ventricular free wall rupture, papillary muscle dysfunction with acute mitral regurgitation, ventricular septal rupture, left ventricular aneurysm or pseudoaneurysm formation) have declined in frequency during the reperfusion era, but older age continues to be a risk factor for developing each of these potentially life-threatening complications.[114] Electrical events also occur more commonly in older populations, particularly AF and heart block, perhaps as a result of having

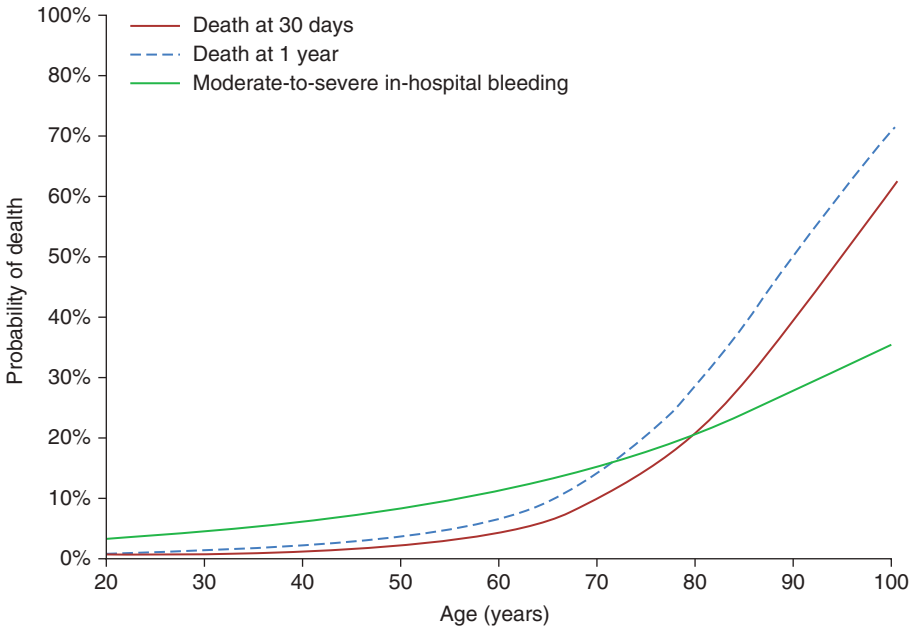


FIGURE 65–6. Increasing risk of death and in-hospital bleeding with increasing age after acute myocardial infarction in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial. Modified with permission from White HD, Barbash GI, Califf RM, et al: Age and outcome with contemporary thrombolytic therapy: results from the GUSTO-I trial. *Circulation*. 1996 Oct 15;94(8):1826-1833.

more extensive CAD and left ventricular dysfunction at the time of ACS presentation.

Overall, the mechanisms underlying worse outcomes among older ACS patients are likely independent of the acute coronary occlusion itself, but instead are related to pathophysiologic changes with age, greater severity of CAD and left ventricular dysfunction at the time of diagnosis, and concomitant medical comorbidities and frailty. Additional aging processes, such as diminished collateral circulation to occluded coronary arteries and lower number and lesser function of endothelial progenitor cells to facilitate myocardial recovery after MI, also contribute to adverse outcomes in older patients.[115-117]

PHARMACOLOGIC CONSIDERATIONS IN OLDER PATIENTS

Older patients, women, and racial/ethnic minorities have been underrepresented in randomized clinical trials of ACS therapies,[118] despite the high incidence of ACS in the elderly[119] and substantially worse outcomes among older patients.[101] In general, elderly patients have more advanced atherosclerotic risk factors, more prolonged exposure to these risk factors, and multiple other medical problems that may impact the benefits and risks of all interventions, both pharmacologic and nonpharmacologic. Older patients are also more likely to present with NSTE-ACS than STEMI, which may significantly impact initial therapy.[101,102,106] A large proportion of ACS presentations in older adults is caused by supply-demand mismatch in the setting of fixed coronary obstruction (ie, type II MI according to the World Health Organization classification).[120] In these cases, there may be less benefit from anticoagulation therapies as a result of lack of intracoronary thrombus. Thus, treatment of older patients with NSTE-ACS often requires greater focus on the underlying factors precipitating the event, such as infection, uncontrolled hypertension, anemia, tachycardia, or other systemic insults (eg, noncardiac surgery, thyroid disease, cancer).[5] Conversely, the value of aggressive pharmacologic and invasive management in this population is less well established.

Antiplatelet Therapy

Oral Agents In the largest randomized comparison of aspirin versus placebo in patients with suspected acute STEMI, the benefit of aspirin increased with increasing age, from 1% absolute reduction in 5-week vascular mortality for patients under age 60, to 4.7% absolute reduction among patients ≥ 70 years old.[121] More than a decade later, clopidogrel was shown to reduce the composite end point of MI, stroke, or cardiovascular death by 20% when added to aspirin for 1 year after ACS, with similar benefits among patients older or younger than 65 years of age.[122] Subsequently, prasugrel and ticagrelor were each compared with clopidogrel and demonstrated additional benefits for ACS patients. However, these more potent antiplatelet therapies had disparate effects on elderly patients. Specifically, prasugrel reduced recurrent MI more effectively than clopidogrel in patients younger than age 75 years,[123] but there was loss of benefit for patients ≥ 75 years and a significant increase in major bleeding complications (including intracranial hemorrhage) in this age group. In contrast, ticagrelor reduced recurrent MI and cardiovascular death when compared with clopidogrel during the first year after ACS, and ticagrelor was not associated with higher bleeding rates in the elderly. However, there was a somewhat attenuated benefit among the 15% of the 18,000 trial participants over age 75 years.[124,125] In a follow-up trial evaluating ticagrelor versus placebo in patients with prior MI, the 12% of the trial patients ≥ 75 years old had similar benefits and bleeding risks as the overall trial population.[126]

An additional medication, vorapaxar, was recently approved in the United States for patients with prior MI (> 2 weeks previously) or peripheral arterial disease at high risk of ischemic events. In a large trial, vorapaxar added to aspirin and clopidogrel reduced thrombotic events but was associated with higher bleeding rates.[127] Because most patients with recent MI are already treated with aspirin and another oral antiplatelet medication, the principal role for vorapaxar in the geriatric population may be in select patients with peripheral arterial disease at low risk of bleeding.

Intravenous Agents The role of intravenous antiplatelet therapy in ACS is more difficult to define, both for younger and older patients. Glycoprotein IIb/IIIa inhibitors appear to reduce reinfarction and overall infarct size at the time of NSTE-ACS, with patients at higher risk deriving the most benefit, but few studies have enrolled patients over age 75, and the risk of bleeding complications increases with age.[5,128] One study of ACS patients demonstrated higher event rates in octogenarians randomized to glycoprotein IIb/IIIa inhibitor therapy,[129] and current guidelines recommend avoiding these medications entirely in the setting of fibrinolytic therapy for STEMI in patients ≥ 75 years of age.[98] Because these drugs are associated with greater bleeding risks in the elderly, use of glycoprotein IIb/IIIa inhibitors should probably be limited to select older individuals with high thrombosis risk and low bleeding risk. The intravenous platelet inhibitor cangrelor has a different mechanism of action than the glycoprotein IIb/IIIa inhibitors, and clinical trials evaluating cangrelor demonstrated similar benefits among patients older and younger than age 75 years.[130] However, the magnitude of bleeding risk associated with cangrelor remains unclear[131]; thus, the safety of this drug in elderly patients requires further study.

Duration of Oral Antiplatelet Therapy In recent years, multiple studies have demonstrated benefit from continuing dual antiplatelet therapy beyond the first year after acute MI.[126,132] However, the risk of bleeding during long-term therapy must be carefully weighed against the diminishing anti-ischemic benefit beyond the first year. For example, in the largest randomized trial to date evaluating prolonged dual antiplatelet therapy after drug-eluting stent placement, approximately 10% of the 10,000 study patients were ≥ 75 years old.[133] These individuals appeared to have somewhat less benefit but also lower bleeding rates than the overall study population during the 18 additional months of clopidogrel therapy (perhaps representing a selection bias for enrolling "healthier" elderly patients eligible for prolonged antiplatelet therapy). Although the optimal duration of dual antiplatelet therapy requires further study, at present, it seems reasonable to limit extended use beyond 1 year to elderly patients with prior MI at lower risk of bleeding.

Antithrombotic Therapy

Intravenous unfractionated heparin has been a standard ACS therapy for decades, but recent guidelines have espoused the use of enoxaparin, bivalirudin, and related compounds as alternatives to heparin.[97,98] Although these newer agents appear to provide more predictable or better targeted antithrombotic activity than heparin, nearly all of them are cleared through renal mechanisms. This is problematic in elderly ACS patients, given the age-related decline in renal function, thus contributing to the substantially higher risks of bleeding with age.[134,135] Despite these risks, older and younger subjects in clinical trials derived similar benefits from the newer antithrombotic therapies.[136,137] Thus, these agents appear to be reasonable choices as long as dosing is carefully adjusted to account for renal function, weight, and other factors (eg, frailty) in the elderly.

Long-term oral antithrombotic medication (eg, warfarin, apixaban, rivaroxaban, dabigatran, edoxaban) in combination with dual antiplatelet therapy further increases bleeding risks, especially in older patients. Because the prevalence of AF, heart valve replacement, venous thromboembolism, and other indications for anticoagulation increases

with age, the dilemma of "triple therapy" becomes more common when treating older patients with IHD. In an observational study, nearly 5000 older patients with AF undergoing percutaneous coronary intervention (PCI) for acute MI had substantially higher rates of major bleeding with triple therapy (vs those receiving dual antiplatelet therapy alone), with no difference in ischemic events.[138] The concept of temporarily withholding aspirin is controversial and requires further study, but it appears to be a reasonable option for elderly patients at higher risk of bleeding. Alternatively, bare metal stents may be considered for these higher risk individuals,[139,140] particularly when performing PCI for stable coronary disease, to provide shorter exposure to triple therapy (acknowledging that the risk of restenosis is higher with bare metal stents).

β-Blockers

As noted previously, older patients with acute MI often present later, with a greater burden of medical comorbidities, and with more extensive complications from the infarct. Increasing age is also associated with higher risk of complications from β-blocker therapy, including hypotension, bradycardia, HF, and cardiogenic shock.[141] Nonetheless, when administered judiciously, β-blockers reduce mortality, recurrent ischemia, and arrhythmias in acute MI, and the 23% reduction in mortality among elderly patients (in a pooled analysis of multiple β-blocker trials) was significantly greater than the effect in younger patients.[5] The same analysis demonstrated 6 lives saved per 100 older patients treated, whereas younger patients had only 2 lives saved per 100 treated. Furthermore, subgroup analyses from β-blocker trials suggest that the majority of the long-term survival benefit after MI occurs in patients age ≥ 65 years.[142,143] However, all of these studies were conducted prior to the reperfusion era, and the value of early β-blocker therapy in contemporary practice is less clear. To minimize side effects and complications associated with β-blocker therapy in the elderly, these drugs should be started at low doses and titrated slowly,[5,98] and immediate intravenous β-blocker injection should be avoided in most elderly MI patients.[141]

Angiotensin and Aldosterone Inhibitors

A large meta-analysis of ACEI therapy for acute MI confirmed a significant reduction in mortality for older patients, particularly for those age 65 to 74 years.[144] The absolute benefit of ACEI was nearly three times greater for older patients than for younger patients, with most trials demonstrating 17% to 34% relative risk reductions in the geriatric subgroups.[145-147] ARBs are reasonable alternatives to ACEIs in HF, but ACEIs are the preferred agents after acute MI in both younger and older populations.[148] Because most of the benefits occur in MI patients with HF or left ventricular systolic dysfunction,[144] more judicious use of these medications may be warranted in elderly patients with preserved systolic function. Both ACEIs and ARBs must be titrated carefully in older individuals, as the risk of medication-induced hypotension, renal failure, and hyperkalemia increases with age and comorbidity burden.

The MRAs spironolactone and eplerenone reduce fibrosis and adverse remodeling after myocardial injury.[149,150] In patients with acute MI and left ventricular dysfunction or HF treated with MRAs, those older or younger than age 65 experience similar reductions in morbidity and mortality.[151] However, an analysis from Canada demonstrated much higher rates of hospitalization for hyperkalemia and renal failure after the widespread adoption of spironolactone for treating HF.[152] Thus, given the increased prevalence of renal dysfunction in the geriatric population, the use of MRAs in elderly individuals requires meticulous monitoring of serum creatinine and potassium levels.

Statins

In the absence of major contraindications, statins are indicated for all patients with established vascular disease, and particularly those with IHD or prior ACS.[97,98,104,153] Numerous studies have confirmed the benefits of statins in older patients,[154-157] although few patients over age 80 have been enrolled in clinical trials.[158,159] Because elderly individuals are at increased risk for myalgias, fatigue, and both functional and cognitive impairment related to statin therapy,[160-163] older patients should be monitored for these adverse drug effects. In addition, the use of statins in patients of advanced age should consider life expectancy, overall cardiovascular risk, and patient preferences. Nonetheless, the greatest benefits from statins occur in high-risk patients following vascular events,[164] so statins are indicated in almost all older patients with established IHD and life expectancy of at least 1 to 2 years (although lower doses may be considered).

Other Anti-Ischemic Medications

Nitrates, calcium channel blockers, morphine, and other anti-ischemic medications have not reduced mortality in ACS clinical trials; thus, the primary indication for these agents is to alleviate symptoms, with similar recommendations for older and younger patients.[97,98,104,153] As always, careful titration is important in elderly patients, given the potential for increased side effects (eg, hypotension, bradycardia, mental status changes). Ranolazine is indicated for management of chronic stable angina, with patients older or younger than age 65 years deriving similar benefits in exercise duration, frequency of angina attacks, and number of nitroglycerin tablets needed per week.[165-167] However, side effects such as dizziness, constipation, nausea, headache, and abdominal discomfort were more common in patients over age 65. In patients with NSTE-ACS, ranolazine is safe but does not improve clinical outcomes, and effects were similar in patients older or younger than age 75 years.[168]

REPERFUSION AND REVASCULARIZATION

Acute Reperfusion for ST-Segment Elevation Myocardial Infarction

Although the absolute benefit of fibrinolytic therapy is greatest in older patients at high risk for complications from STEMI, the risk of catastrophic bleeding also increases markedly after age 75 years (see Fig. 65–6).[105,169] In clinical trials of fibrinolysis for STEMI, intracranial hemorrhage occurred in approximately 1% to 2% of patients over age 75 years versus 0.5% to 1% of younger patients.[170,171] Thus, although older age is not a contraindication to fibrinolytic therapy, the risk-benefit ratio must be carefully evaluated in patients with frailty or advanced age, particularly because few patients over age 85 were enrolled in the fibrinolytic trials for acute MI.[172-174]

Recent guidelines have moved toward recommending primary PCI over fibrinolysis in most patients with STEMI as a result of clinical trials showing greater efficacy and fewer serious bleeding events with contemporary PCI techniques.[98] In particular, elderly patients enrolled in these studies had improved survival with primary PCI for STEMI,[175,176] and a small trial limited to patients ≥ 75 years of age also demonstrated superiority of PCI over fibrinolysis.[171] To minimize bleeding risks in patients of advanced age, an additional 30-minute delay beyond the standard 90-minute "door-to-balloon time" is permitted when the delay allows for primary PCI instead of thrombolysis in the geriatric population.[104]

Reperfusion in Non–ST-Segment Elevation Acute Coronary Syndrome

Older age is a major risk factor for adverse ACS outcomes, as well as for procedural complications, both from cardiovascular issues (eg, access

site problems, complex vascular anatomy, coronary calcification precluding adequate stent delivery) and from other medical comorbidities (eg, renal dysfunction, cognitive impairment or agitation with sedation, bleeding risks in frail patients). Despite these concerns, in most studies, older patients treated with an early invasive approach to NSTE-ACS experienced reductions in death or recurrent MI.[177,178] In a recent unblinded trial of 457 patients ≥ 80 years of age with NSTE-ACS, early coronary angiography and revascularization were associated with a significant reduction in urgent revascularization or recurrent MI over a median follow-up time of 1.5 years when compared with initial medical therapy alone.[179] Of note, the benefit of invasive management declined with age and was no longer evident among patients ≥ 90 years of age. With these competing concerns in mind, the decision to pursue an invasive approach among patients with advanced age must be individualized, with consideration of anticipated benefits, potential risks, and patient preferences. Among elderly patients with lower risk ACS characteristics, intensification of medical management alone is often a reasonable option.

Revascularization in Cardiogenic Shock

In a clinical trial evaluating revascularization therapy for patients with ACS complicated by cardiogenic shock, patients under age 75 had lower mortality with early PCI or CABG, whereas patients over age 75 did not.[180,181] However, patients enrolled in the trial registry (and thus removed from the randomization process) had improved outcomes with early revascularization, including elderly individuals.[182] Newer data suggest higher rates of cardiogenic shock after STEMI during the past decade, with greater utilization of early PCI and circulatory support devices, along with lower in-hospital mortality over time.[183] Of note, patients over age 75 years continued to have lower utilization of early revascularization and support devices, and despite gradual reductions in mortality that mirrored the improvements seen in younger patients, overall mortality rates remained nearly twice as high in older patients. Larger support devices such as Impella (Abiomed, Danvers, MA) may help stabilize some of these patients while awaiting myocardial recovery after revascularization, but the impact of these interventions on clinical outcomes is uncertain, and optimal patient selection remains challenging (see Chap. 42).[184,185] Nonetheless, with continued technological advancements and greater clinical experience, these devices may play an important role in managing select elderly patients with shock physiology complicating ACS.

STABLE ISCHEMIC HEART DISEASE

As with ACS, chronic angina may manifest differently or at a later stage in older patients. Prolonged exposure to risk factors, concomitant medical diseases, and aging processes likely contribute to the more advanced atherosclerosis discovered in older patients at the time of IHD diagnosis. For example, chronic lung disease, diabetic neuropathy, cognitive impairment, and sedentary lifestyle may contribute to delayed recognition of IHD in older patients.[5] Medical therapies for chronic IHD are similar in older and younger patients, with emphasis on relief of symptoms and prevention of disease progression using statins, aspirin, and appropriate blood pressure and diabetes management (see Chap. 43). Dual antiplatelet therapy beyond the first year after ACS or coronary stent implantation appears to primarily benefit patients with prior MI—at a cost of higher bleeding rates—and should be considered for select elderly patients at higher risk of recurrent ischemic events and lower risk of bleeding.[186,187]

Coronary revascularization should be considered for elderly patients with chronic IHD and either high-risk coronary anatomy or persistent ischemic symptoms despite optimal medical therapy.[188] Complications of PCI and CABG are more common among patients ≥ 80 years old,[189,190] but hospital mortality rates have continued to decline over the past two decades in both younger and older patients despite substantial increases in comorbidity.[1] Increasing age is a potent risk factor for arrhythmias after CABG (especially AF; see Chap. 44), as well as for postoperative delirium and cognitive impairment.[191]

Despite these concerns, revascularization is associated with excellent clinical outcomes among appropriately selected patients of advanced age (ie, octogenarians and nonagenarians), including fewer symptoms and improved quality of life compared with medical therapy alone.[188,192-194] Thus, advanced age alone should not be considered a contraindication to either PCI or CABG. In the past decade, several studies have compared PCI and CABG in patients with left main or multivessel CAD, demonstrating higher rates of repeat revascularization after PCI but similar rates of other clinical outcomes (MI, stroke, and death) between the two approaches.[195,196] As a result, many elderly patients with severe IHD choose multivessel PCI over CABG, thus trading the higher perioperative risk and longer recovery time for the greater likelihood of needing repeat PCI during short-term follow-up. Coupled with additional improvements in PCI (ie, radial artery access, newer stents with lower restenosis and thrombosis rates, smaller catheters, and lower contrast volumes), these trends likely explain why CABG rates in the United States have continued to decline since 1997, whereas PCI rates in the geriatric population have remained relatively constant.[1]

NONPHARMACOLOGIC THERAPY

Medication adherence and polypharmacy may challenge efforts to reduce the risk of recurrent cardiovascular events in older patients with established IHD. Cognitive impairment may lead to missed doses of medications, inability to recall instructions, or confusion about the multiple therapies prescribed. Substantial effort has been devoted to discussing these issues in contemporary guidelines[188]; instructions must be discussed clearly, caregivers should also receive these instructions, and close surveillance for drug-drug interactions or medication side effects should be implemented. These concerns are particularly relevant for antiplatelet therapies after ACS or stent placement, as premature discontinuation of these medications is the primary cause of short-term stent thrombosis, reinfarction, and cardiovascular death.[197]

Other supportive measures during and after IHD events are important as well. For example, hospitalized patients with STEMI commonly receive narcotics and are relatively bedbound while recovering in the intensive care unit, so implementation of a bowel regimen is important for these individuals, many of whom already have impaired bowel function.[188] Cardiac rehabilitation is markedly underused in the geriatric population, despite proven reductions in mortality and improvements in quality of life,[198] although referral rates have increased in recent years.[199] Older patients unable to attend formal cardiac rehabilitation for logistical or transportation reasons should be referred for a home-based rehabilitation program if available.

CARDIAC DYSFUNCTION AND HEART FAILURE

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Approximately 10% of all individuals age ≥ 80 years have an established diagnosis of HF, and half of the HF hospitalizations each year in the United States occur in patients age 75 years and older.[1] At 40 years of age, the lifetime risk of developing HF is nearly 20%, and this remains true at age 80 despite a much shorter life expectancy in octogenarians. In addition, mortality from HF increases with age, and HF is the most

common and costly reason for acute hospitalization in the Medicare program.

Although the high prevalence of HF in elderly patients is partly related to improved survival from acute MI and other CVDs, other age-related factors contribute to the development of HF including long-standing hypertension (present in 75% of patients with HF), vascular stiffness, left ventricular diastolic dysfunction, sinus node dysfunction, progressive valvular heart disease, coronary ischemia, and reduced responsiveness to β-adrenergic stimulation.[5] As a result, a gradual erosion in cardiovascular reserve with age results in an exponential rise in HF among older individuals. Studies in healthy older adults have confirmed that the effects of normal aging lead to altered preload, afterload, heart rate, and contractility—the four major determinants of cardiac output—thus resulting in a progressive decline in peak cardiopulmonary performance, even in the absence of clinically evident CVD (Fig. 65–7).[200] Stated another way, an otherwise healthy 90-year-old individual is likely to have exercise capacity and cardiovascular reserve equivalent to a younger person with New York Heart Association functional class III HF.

HEART FAILURE PREVENTION

In populations with stage A or stage B HF, clinical guidelines recommend preventative measures, such as lowering blood pressure,[201] particularly in elderly patients.[202] Generalized deconditioning is pervasive in elderly patients with HF, and exercise physiology studies have demonstrated that nearly half of dyspnea in HF patients is related to skeletal, diaphragmatic, and intercostal muscle weakness, beyond cardiopulmonary dysfunction alone.[201] This suggests that breathing exercises and interventions designed to strengthen respiratory muscles may be beneficial in reducing symptoms, but studies testing this hypothesis in older patients with HF are lacking. As with IHD, older patients with HF also need extensive support and counseling to avoid medication and dietary nonadherence, which are leading causes of rehospitalization in this population.

CLINICAL PRESENTATION AND EVALUATION IN OLDER PATIENTS

Although dyspnea and exercise intolerance are the cardinal symptoms of HF, exertional symptoms may be less prominent in sedentary older patients, and atypical symptoms such as anorexia and mental status changes become more prevalent with increasing age.[5] In addition, concomitant noncardiac conditions such as anemia, renal dysfunction, or lung disease often contribute to exercise intolerance in older adults, and it may be difficult to determine the primary etiology of patients' symptoms. Similarly, physical examination findings associated with HF may be lacking or nonspecific in older adults. For example, pulmonary crackles may be a result of chronic lung disease or atelectasis, and dependent edema may be secondary to malnutrition (hypoalbuminemia), venous insufficiency, or medications (especially calcium channel blockers).

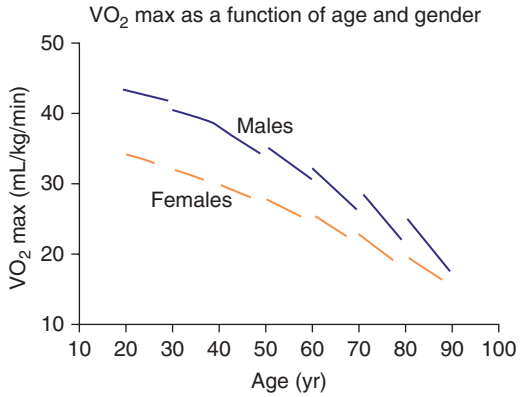


FIGURE 65–7. Peak oxygen consumption (VO_2 max) in healthy adults enrolled in the Baltimore Longitudinal Study of Aging. Patients were rigorously screened to exclude cardiovascular disease, and in this substudy, VO_2 max decreased with increasing age in both men and women. Data from Fleg JL, Morrell CH, Bos AG, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation*. 2005 Aug 2;112(5):674-682

As in younger patients, older individuals with suspected HF should have an echocardiogram to evaluate systolic and diastolic function, chamber size and wall thickness, valve function, the pericardium, and pulmonary arterial pressure. B-type natriuretic peptide (BNP) and N-terminal pro-BNP may be helpful in distinguishing HF from noncardiac sources of dyspnea among patients presenting to the emergency department,[203] but these levels tend to increase with age and other comorbidities (eg, renal dysfunction, pulmonary hypertension, cardiac arrhythmias).[204] As a result, the predictive accuracy of natriuretic peptides decreases with increasing age, especially in women.[205] Careful assessment for changes in medications (eg, initiation of a nonsteroidal anti-inflammatory drug) or recent procedures or surgeries (in which intravenous fluid may have been administered) may help elucidate the cause of an HF exacerbation.

PHARMACOTHERAPY OF HEART FAILURE

Because the majority of HF trials have enrolled few elderly patients, there is uncertainty about the benefits of medical and procedural therapies in older patients.[206] Nonetheless, guidelines generally extrapolate from effects demonstrated in younger patient populations.[201] As a result, most guideline recommendations for HF therapy are similar across age groups, including hemodynamic stabilization after hospital admission, correction of volume overload, careful surveillance of renal function and electrolytes while titrating medications, and implementing therapeutic interventions based on results of large-scale clinical trials (see Chaps. 70 and 71).

Diuretics

Although the long-term risks and benefits of loop diuretics remain controversial,[207-209] these medications are essential for reducing pulmonary congestion and peripheral edema during HF exacerbations, and they also play a key role in maintaining normal volume status during long-term HF management.[201] Older patients are generally more prone to develop renal dysfunction and electrolyte abnormalities during diuretic therapy, so close monitoring is imperative.[5]

Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Neprilysin Inhibitors

In clinical trials of ACEIs for HF with reduced ejection fraction (HFrEF), similar improvements in mortality, quality of life, and HF hospitalizations were noted in older and younger patients,[210] although the benefit may be attenuated above age 75 years.[211] Older patients experience higher rates of hypotension and renal dysfunction (likely related to pre-existing renal impairment), but other adverse effects such as ACEI-associated cough and angioedema are unrelated to age. In general, in the absence of contraindications, elderly patients with HFrEF should undergo ACEI titration to dosage levels achieved in clinical trials, with close monitoring for side effects or complications of therapy.[201,212,213]

In HF patients intolerant to ACEIs, ARBs are an effective alternative, with comparable benefits across the age spectrum.[214,215] In three large

HF trials of candesartan that included 1736 subjects age ≥ 75 years, candesartan was associated with a 14% reduction in death or HF hospitalization, which was similar to findings in younger patients.[216] As with ACEIs, older age confers higher risk for adverse hemodynamic and renal complications. In addition, combined ACEI and ARB therapy is not recommended as a result of increased risk for adverse events without incremental benefit.[201,217]

Recently, the combination of valsartan with the neprilysin inhibitor sacubitril was compared to enalapril in patients with HFrEF.[218] In this study, valsartan-sacubitril reduced the composite end point of HF hospitalization or death, with similar reductions in each component end point. Furthermore, benefits were similar among the 49% of trial subjects over age 65 years, as well as the 19% of subjects over age 75 years. Side effects were generally mild, although there was a higher rate of symptomatic hypotension with the combination drug. Additional studies are needed to evaluate the effects of neprilysin inhibition in older patients with multimorbidity or frailty.

β-Blockers and Ivabradine

β-Blockers improve left ventricular function and reduce mortality in patients with cardiomyopathy and HF,[219,220] including older patients with HFrEF.[221,222] However, elderly patients are more prone to developing symptomatic bradycardia, hypotension, fatigue, or fluid retention during titration of therapy. Therefore, starting at a low dose and titrating gradually is imperative in these individuals.

Recently, ivabradine was approved in the United States for patients with symptomatic HFrEF and continued heart rates above 70 bpm despite maximally tolerated β-blocker therapy.[223] Although the primary clinical trial of ivabradine demonstrated reductions in mortality and HF hospitalizations beyond conventional medical therapy, the effect was somewhat blunted in patients over age 65 years (borderline statistical significance for the interaction with age). In addition, clinically important bradycardia was more common in the ivabradine group. Nonetheless, ivabradine may provide an additional therapeutic option for older adults with HFrEF who are unable to tolerate β-blockers or who have higher heart rates on maximally tolerated doses of β-blockers.

Aldosterone Antagonists

Although the indications for MRA therapy in patients with symptomatic HFrEF are similar in younger and older patients,[201,224] older patients are more susceptible to worsening renal function and hyperkalemia, as noted previously.[152] In addition, the overall benefits of MRAs may be reduced in elderly patients, with one registry study suggesting no mortality benefit and higher rates of 30-day readmission for hyperkalemia in Medicare patients (mean age 78 years).[225] Thus, judicious patient selection and close monitoring of renal function and electrolytes are essential for older patients receiving MRA therapy.

Hydralazine and Nitrates

The combination of hydralazine and nitrates provided additional benefit in a clinical trial of African American HF patients with functional class III or IV symptoms treated with concomitant ACEIs and β-blockers.[226] However, patients in this trial were relatively young (mean age 57 years), so it is unclear whether the findings can be extrapolated to older patients. In addition, dosing of hydralazine/nitrates is three times daily, which can be problematic in older patients, with polypharmacy or cognitive dysfunction affecting medication adherence.

Digoxin

Although post hoc subgroup analysis of the Digitalis Investigation Group suggested that digoxin may have favorable effects on mortality when serum levels are maintained < 1.0 ng/mL,[227] use of digoxin is generally limited to patients with persistent symptoms despite optimal therapy, as described earlier.[201,228] The risks and benefits of digoxin are similar in older and younger patients, including those ≥ 80 years of age.[229] Nonetheless, elderly patients have higher rates of symptoms attributed to digoxin, and other factors associated with digoxin toxicity (renal dysfunction, electrolyte disturbances, drug-drug interactions, bradycardia, cardiac amyloid) are more prevalent in older patients. Thus, treatment must be individualized, and low doses should be used to maintain trough serum digoxin concentrations < 1.0 ng/mL.[5]

HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

Nearly half of the geriatric HF population has preserved or only mildly reduced left ventricular systolic function (ie, HFpEF),[230,231] and HF in these patients is generally related to long-standing hypertension, diabetes, renal dysfunction, and vascular and ventricular stiffening. Current guidelines recommend similar approaches to younger and older patients with HFpEF, including management of volume status, and minimizing factors known to promote HF exacerbations such as uncontrolled hypertension, arrhythmias (especially AF), myocardial ischemia, worsening renal function, dietary indiscretion, or medication nonadherence.[201] Of note, no studies to date have demonstrated mortality benefit for any pharmacological treatments for HFpEF, and effects on other outcomes have been modest (Table 65–4; see Chap. 70 for further details).

NONPHARMACOLOGIC THERAPIES

Lifestyle Modifications

HF is a chronic illness that requires substantial self-care by patients in order to optimize outcomes, especially with regard to reducing HF exacerbations and recurrent hospitalizations—irrespective of whether the phenotype is HFrEF or HFpEF.[5,201] Although adherence to medications and dietary restrictions is essential for HF patients of all ages, older patients are often additionally challenged by limited access to HF-healthy meals, social isolation with limited travel options (eg, to shop for food and obtain medications), complex medication regimens, and financial constraints. Older patients with HF at increased risk for adverse outcomes should be referred to a multidisciplinary HF management program, if available.[201,232] Similarly, exercise training and structured cardiac rehabilitation are associated with improved health status and reductions in HF hospitalizations,[233] so cardiac rehabilitation should be prescribed when possible for older patients who fulfill criteria for participation.

Implantable Device Therapies

The role of device therapy in the contemporary management of HF is discussed elsewhere (see Chap. 70). Only a small fraction of patients enrolled in trials evaluating cardiac resynchronization therapy (CRT) were over age 80 years, but patients above and below the median age in the trials (approximately 65 years) derived equivalent benefits.[234-236] In addition, observational data have demonstrated improvements in quality of life among octogenarians,[237] suggesting that CRT is a reasonable option in elderly HF patients who meet criteria for device implantation.

In contrast to CRT, the use of implantable cardioverter-defibrillators (ICDs) in elderly patients with HFrEF often poses a difficult quandary. Whereas CRT improves quality of life, ICDs may prolong life without improving quality of life[236,238,239]—an effect not always considered desirable in elderly patients with symptomatic HF or poor quality of life as

TABLE 65–4. Pharmacotherapy Trials for Heart Failure With Preserved Ejection Fraction

Trial Name[a]	No. of Patients	Treatment	LVEF (%)	Age (years)	Outcomes vs Placebo[b]
PEP-CHF	850	Perindopril	65 (56-66)	75 (72-79)	Death/hospitalization by 1 year – HR 0.69 (0.47-1.01, $P = 0.055$) HF hospitalization by 1 year – HR 0.63 (0.41-0.97, $P = .033$)
CHARM-Preserved	3023	Candesartan	54 ± 9	67 ± 11	CV death/HF admission – HR 0.89 (0.77-1.03, $P = .118$) HF admission – HR 0.85 (0.72-1.01, $P = .072$)
I-PRESERVE	4128	Irbesartan	60 ± 9	72 ± 7	Death/hospitalization – HR 0.95 (0.86-1.05, $P = .35$)
SENIORS (LVEF > 35% subgroup)	643	Nebivolol	49 ± 10	76 ± 5	All cause death/CV hospitalization – HR 0.81 (0.63-1.04)
TOPCAT	3445	Spironolactone	56 (51-62)	69 (61-76)	CV death/HF hospitalization/aborted SCD – HR 0.89 (0.77-1.04, $P = .14$) HF hospitalization – HR 0.83 (0.69-0.99, $P = .04$)
Aldo-DHF	422	Spironolactone	67 ± 8	67 ± 8	Reduced E/e' avg 1.5 ($P < .001$)
RELAX	216	Sildenafil	60 (56-65)	69 (62-77)	No difference Δ VO_2 peak at 24 weeks
ESS-DHF	192	Sitaxsentan	61 ± 12	65 ± 10	Median 43-second relative increase in Naughton treadmill time ($P = .03$)
DIG Ancillary	988	Digoxin	55 ± 8	67 ± 10	HF hospitalization – HR 0.79 (0.59-1.04, $P = .09$) Hospitalization for unstable angina – HR 1.37 (0.99-1.91, $P = .06$)
NEAT-HFpEF	110	Isosorbide mononitrate	63 ± 8	69 ± 9	Trend toward lower daily activity (−381 accelerometer units [−780 to +17], $P = .06$) and significant decrease in hours of activity per day (−0.30 hours [−0.55 to −0.05], $P = .02$)

Note: Patient characteristics are reported as mean ± standard deviation or median (interquartile range). Outcome variables are reported as hazard ratios (95% confidence interval).

Abbreviations: CV, cardiovascular; E/e' avg, ratio of average echocardiographic mitral inflow velocity to tissue Doppler velocity; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

[a]Trial acronyms: PEP-CHF (Perindopril in Elderly People With Chronic Heart Failure), CHARM-Preserved (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Preserved LVEF), I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Study), SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure), TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure), RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction), ESS-DHF (Effectiveness of Sitaxsentan Sodium in Patients With Diastolic Heart Failure), DIG Ancillary (Digitalis Investigation Group Ancillary Trial), NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction).

[b] Of note, all-cause mortality was not significantly reduced in *any* trial.

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a result of other medical comorbidities. Again, few patients over age 80 years were enrolled in clinical trials evaluating ICDs in HF, and the mortality benefit of ICD placement declines with age as a result of competing causes of death.[240] Thus, selection of elderly patients for ICD placement must include a realistic appraisal of the potential benefits and risks, with inclusion of the patient and family in the decision-making process. There should also be a discussion of clinical scenarios in which the patient might want to consider disabling the ICD function (eg, terminal illness or unacceptably poor quality of life).[241] Similar discussions should occur prior to "routine" generator changes caused by battery end-of-life.

Heart transplantation is a therapeutic option for small numbers of patients with advanced HF up to age 75 years, with similar outcomes in younger and older individuals.[242] However, a substantially larger number of patients with refractory HFrEF may be considered for ventricular assist devices (VADs). Newer generation devices have led to less invasive surgical implantation procedures, acceptable complication rates, and favorable effects on cardiovascular health status in elderly subjects.[243] Although experience in patients ≥80 years old remains limited, VAD implantation in this population is likely to increase as a result of technological advances, lower complication rates, and more refined criteria for patient selection. Nonetheless, consideration of a VAD as destination therapy requires a detailed discussion of all available options through a process of shared clinical decision making.

PROGNOSIS AND END-OF-LIFE CARE

Nearly half of all patients discharged with a primary diagnosis of HF are readmitted to the hospital within 6 months, and 20% to 25% are readmitted within 30 days. Multidisciplinary programs reduce readmissions by 20% to 25%,[244] but repeat admissions remain problematic, and well over 50% of readmissions occur for diagnoses other than HF. In addition, repetitive admissions are a marker for declining prognosis and contribute to deterioration in functional status and quality of life, especially in elderly patients with multimorbidity and frailty.

The overall prognosis for elderly HF patients is poor, with 1-year mortality rates close to 25% and 5-year survival rates of only 20% to 25% (ie, worse than for most forms of cancer). Older age and dementia are potent predictors of adverse outcomes; other prognostic factors include renal dysfunction, hyponatremia, and worse functional status.[245] End-of-life discussions, including patient-centered goals of care and preferences regarding resuscitation status, should be undertaken early after diagnosis, particularly among patients with advanced age or other high-risk characteristics for early mortality.[246] Because the course

of HF is unpredictable, patients should be encouraged to develop a living will and designate durable power of attorney for health care. Consultation with palliative or hospice care specialists is recommended in patients with short estimated life span (eg, < 6 months) as a result of refractory functional class IV symptoms, advanced age, frailty, or poor overall health.[5,247]

VALVULAR HEART DISEASE

The prevalence of most acquired cardiac valve disorders increases with age. Furthermore, because medical therapies for valvular heart disease are limited, procedural and surgical treatments play a prominent role in management. In this context, the ability of an elderly patient to recover from such procedures must be weighed against the severity of symptoms and prognosis related to the underlying disease process. With refinements in surgical and anesthetic techniques, plus the shift toward less invasive or percutaneous valve procedures in recent years, more geriatric patients are becoming eligible for repair or replacement.

AORTIC STENOSIS

The prevalence of symptomatic aortic stenosis (AS) increases from 0.2% in patients under age 60 to nearly 10% in those ≥ 80 years of age.[5,248] As a result, over 70% of all aortic valve procedures are performed in the geriatric population, and AS is the most common valvular abnormality requiring surgical or percutaneous intervention. Symptoms may not be as prominent in elderly patients with sedentary lifestyle, resulting in delayed presentation or incidental diagnosis of severe AS at the time of presentation for other medical problems.[5] In addition, although physical findings are generally similar in younger and older patients, older individuals with severe AS are less likely to exhibit delayed upstroke of the carotid pulse wave (pulsus tardus et parvus) as a result of increased arterial stiffness.

Because older patients are more likely to have left ventricular systolic dysfunction, the prevalence of low-flow, low-gradient AS increases with age. Paradoxical low-flow, low-gradient AS with normal systolic function is more common in older individuals as well. Assessing the response to dobutamine infusion may be helpful in distinguishing severe AS from "pseudo" severe AS (ie, low calculated aortic valve area in the absence of severe obstruction to flow), but in some cases, cardiac catheterization with hemodynamic studies is needed to clarify AS severity. In addition, almost all older patients with AS who are being considered for a valve procedure require coronary angiography to evaluate for IHD, which has shared pathophysiology with AS and is present in at least 50% of geriatric patients with significant AS.[249]

Until recently, surgical aortic valve replacement (SAVR) has been the only effective treatment for severe AS, with limited roles for medical therapy or balloon valvuloplasty (see Chap. 47). Elderly patients deemed to be reasonable surgical candidates have excellent outcomes in observational SAVR registries, with average survival similar to actuarial tables of the general population (ie, nearly 7 years for patients age 80-84 and more than 6 years among patients ≥ 85 years old).[250] Predictors of adverse outcomes after SAVR are similar to those in younger patients, including severe left ventricular dysfunction, AF, more complex surgery (eg, requiring concomitant CABG or multivalve surgery), cerebrovascular disease, and the need for emergency surgery. Age is not usually considered a major risk factor for perioperative mortality, but multimorbidity and frailty portend less favorable outcomes.

The development of TAVR has revolutionized the treatment of elderly and frail AS patients who are not considered suitable candidates for SAVR. Clinical trials and observational studies have demonstrated the feasibility and equivalence (and sometimes superiority) of TAVR when compared with medical or surgical therapy for intermediate-risk, high-risk, or "inoperable" patients with severe AS.[251-254] Importantly, TAVR has been evaluated in patients with extensive medical comorbidities or other high-risk features for SAVR, and thus, the clinical trials included substantial numbers of patients over age 80 years and a large number over age 90 years (mean age 83-84 years). Because patients in this age range with complex morbidity and frailty have been systematically excluded from most clinical trials, the development and testing of TAVR represent a significant advancement both in the management of patients with AS and, more broadly, for the general population of elderly patients with CVD. However, despite the manifest benefits of TAVR for many elderly patients with severe AS, up to 25% of patients who undergo the procedure do not survive 1 year, and another 20% to 30% do not experience clinically meaningful improvements in quality of life.[255] Thus, careful patient selection is imperative, partly to minimize procedural complications, but also to ensure that these procedures are not overused in patients with low likelihood of deriving meaningful benefit.[256]

MITRAL REGURGITATION

The prevalence of significant mitral regurgitation (MR) increases with age, partly as a result of progression of chronic mitral valve disorders such as rheumatic or myxomatous valve disease, but also as a consequence of myocardial ischemia or mitral annular dilation from dilated cardiomyopathy.[5,249] As a result, most mitral valve surgeries are performed in the Medicare age group. Observational data suggest that mitral valve surgery is associated with better outcomes when performed prior to left ventricular dilation,[257] but as with other cardiac conditions, older patients may present with more advanced disease as a result of sedentary lifestyles or confounding medical comorbidities.

When surgery for MR is performed prior to ventricular dilation and dysfunction, outcomes are favorable, with survival rates in the elderly similar to those predicted for the general population.[258] However, recovery following mitral valve surgery in elderly patients tends to be slower when compared with aortic valve surgery.[5,249] As noted for SAVR, many older individuals are considered too high risk for mitral valve surgery as a result of severe ventricular dysfunction or other medical problems. In recent years, the development of transcatheter mitral repair has allowed select older individuals to undergo nonsurgical mitral valve therapy with favorable clinical outcomes.[259,260]

OTHER VALVE DISORDERS

In geriatric patients, the etiology of aortic insufficiency is likely to be related to chronic diseases such as hypertension, myxomatous degeneration of the aortic valve leaflets, or aneurysmal dilation of the ascending aorta. Some older patients may also develop complications from aortic dissection, endocarditis, long-standing rheumatic valve deformities, or autoimmune processes. Management is similar to that for younger patients,[249] and operative mortality is generally favorable in older patients with preserved left ventricular systolic function (see Chap. 47).

Some elderly patients (particularly those with advanced chronic kidney disease) may experience progressive valvular and mitral annular calcification leading to mitral stenosis. This process rarely leads to stenosis severe enough to warrant surgical intervention, but pulmonary venous congestion and pulmonary hypertension may develop over time.

Tricuspid regurgitation in the geriatric population usually occurs as a consequence of right ventricular dilation, commonly attributable to pulmonary hypertension, chronic lung disease, or left HF.[249] Surgical intervention is generally reserved for patients with severe tricuspid regurgitation who are undergoing simultaneous CABG or other valvular surgery. As with aortic and mitral valve disease, percutaneous

techniques for treating severe tricuspid regurgitation are under development. Stenotic lesions of the tricuspid or pulmonic valves are rare in older patients, although carcinoid heart disease may occasionally present in the geriatric age group.

Infective endocarditis, once a condition predominantly affecting younger patients, is now primarily a disorder of older adults. Progressive valvular calcification and degeneration in older patients contribute to a higher risk of structurally abnormal heart valves and thus higher rates of potential infections. Older individuals are also at higher risk for developing bacteremia as a result of increased prevalence of immune deficiencies (ie, cancer, malnutrition, autoimmune diseases, and their associated medical therapies), periodontal disease, other infections such as pneumonia, or iatrogenic complications (eg, indwelling catheters, hemodialysis, noncardiac surgeries or procedures).[5] Elderly patients with endocarditis may not manifest typical symptoms of infection or heart valve dysfunction, leading to delayed diagnosis at a more advanced stage of disease. As a result, major complications such as valve destruction and HF, or perivalvular abscess with progressive heart block, may be present at the time of endocarditis diagnosis, thus necessitating operative intervention.[249] Management of endocarditis is similar in older and younger patients, but outcomes are worse in older patients with both medical and surgical treatments, largely because of higher complication rates and the impact of medical comorbidities.

ARRHYTHMIAS AND CONDUCTION SYSTEM DISEASE

Progressive fibrosis and calcification along with degeneration of the cardiac electrical system contribute to high rates of arrhythmias and conduction disturbances in older adults. At a cellular level, electrical impulse generation is slower, and there are more competing impulses from non-nodal atrial and ventricular tissues. At the clinical level, these changes explain why > 75% of pacemakers and > 50% of ICDs are placed in the Medicare population.[1] Because these processes increase the incidence of both bradyarrhythmias and supraventricular tachyarrhythmias, many elderly patients develop "sick sinus syndrome" or "tachy-brady syndrome," in which symptoms such as fatigue, dyspnea, palpitations, dizziness, or falls may occur as a result of either slow or rapid ventricular heart rates.[5] Short-term ambulatory monitoring (24-48 hours) or event monitoring is commonly used to identify these syndromes and verify the association of symptoms with arrhythmia. Exercise treadmill tests may be used to evaluate for stress-induced arrhythmias or chronotropic incompetence, and implantable loop recorders may be considered for patients with infrequent symptoms or falls.

BRADYCARDIA, HEART BLOCK, AND PACEMAKERS

The progressive degeneration of sinus node pacemaker cells results in only 10% continuing to function normally by age 75.[5] Similar processes occur in the tissues surrounding the sinus node and within the conduction pathways, contributing to the development of sinoatrial exit block or atrioventricular nodal block. Simultaneously, autonomic input to the heart may change with advancing age, resulting in carotid sinus hypersensitivity, vagally mediated bradycardia, and lack of compensatory sympathetic upregulation. As a result, elderly patients experience high rates of symptomatic bradyarrhythmias, with symptoms ranging from lightheadedness, exertional intolerance, or syncope to more subtle presentations such as confusion, fatigue, or falls.

In older patients with symptoms that may be attributable to a bradyarrhythmia, evaluation for potentially reversible causes is essential (see Chap. 86). Reduction in dosage or withholding of cardiac medications such as β-blockers, diltiazem, verapamil, digoxin, clonidine, or antiarrhythmic drugs may be necessary to improve symptoms. Other medications and medical conditions may contribute to bradycardia as well, such as anticholinergic effects of donepezil and related drugs, drug-drug interactions, or worsening of hepatic or renal clearance of medications. In addition, hypothyroidism, hypoglycemia, electrolyte disorders, and coronary ischemia may cause bradycardia (or mimic symptoms of bradycardia) and should be considered in the differential diagnosis. Indications for pacemaker placement in the geriatric population are similar to those recommended for younger patients.[236]

SUPRAVENTRICULAR TACHYARRHYTHMIAS

The prevalence of supraventricular arrhythmias increases with age, and initial evaluation should include assessments for electrolyte disturbances, thyroid dysfunction, anemia, infection, pulmonary embolus, or structural cardiac disease, according to the patient's clinical presentation. In the Baltimore Longitudinal Study of Aging, short runs of supraventricular arrhythmias were common in healthy older subjects rigorously screened to exclude those with overt CVD. These arrhythmias were not associated with coronary events, but 15% of these individuals developed AF during follow-up, as compared with < 1% of those without atrial runs.[261] Similar findings were noted among patients with nonsustained supraventricular arrhythmias during exercise, with 10% developing sustained tachyarrhythmias versus 2% of those without atrial runs on exercise testing.[262] In addition, the incidence of exercise-induced tachycardia increased from near zero among the youngest patient subgroup to approximately 10% in patients ≥ 90 years of age. In elderly patients, sinus node dysfunction may result in prolonged sinus pauses and associated symptoms after termination of a supraventricular tachyarrhythmia. When the tachy-brady syndrome occurs (as noted earlier), treatment of bradycardia may require a pacemaker to facilitate more intensive suppression of tachycardia.

Atrial Fibrillation and Flutter

AF is the most common sustained and clinically important supraventricular arrhythmia in the geriatric population. Nearly one in four adults will develop AF during their lifetime, with a marked increase with age from < 1% prevalence before age 40 to approximately 10% after age 80 (Fig. 65–8).[263] In another study, the incidence of AF in men increased more than 50-fold with increasing age, from 21 per 100,000 people annually among individuals under age 45 years to 1077 per 100,000

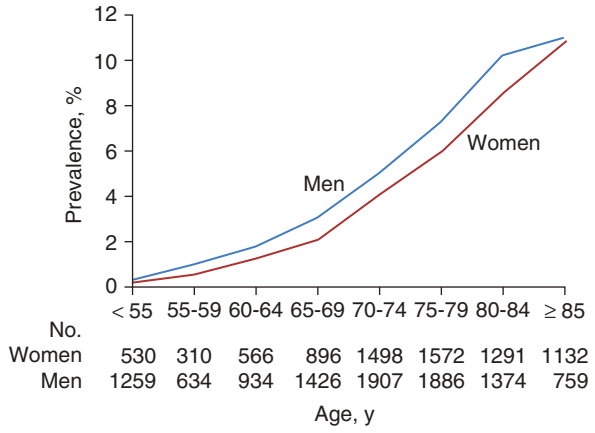

FIGURE 65–8. Prevalence of atrial fibrillation by age and sex in a large health maintenance organization in 1996 to 1997. Based on data from Go AS, Hylek EM, Phillips KA, et al: Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA* 2001 May 9;285(18):2370-2375.

people annually among those age 85 years and older.[1] In women, the increase was more than 150-fold, from 7 to 1204 per 100,000 people annually among those age < 45 versus ≥ 85 years. The increase in AF incidence and prevalence is in part attributable to age-related atrial fibrosis, atrial remodeling, and electrical signaling abnormalities. In addition, the increasing prevalence of hypertension, IHD, valve disease, lung disease, chemotherapy, cardiac or noncardiac surgery, diabetes, and other common medical comorbidities associated with the onset of AF contributes to the higher rates of AF with increasing age.

Presentation and Evaluation As with other CVDs, elderly patients with AF may not experience typical symptoms such as palpitations or dizziness. These individuals frequently describe exertional intolerance, fatigue and malaise, altered cognition, or no symptoms at all.[5] Some patients present with acute pulmonary edema as a result of the sudden loss of the atrial contribution to end-diastolic volume and cardiac output at the onset of AF, whereas others may experience syncope or falls. Unfortunately, AF is occasionally first recognized when a patient presents with a stroke, transient ischemic attack, or other systemic embolic event, or during monitoring following such an event.

The evaluation of new or recurrent AF is similar in geriatric patients as for younger populations and includes thyroid and electrolyte assessments plus echocardiography to identify valvular heart disease, cardiomyopathy, pulmonary hypertension, or pericardial disease.[264] Pulmonary embolism should be considered in sedentary older patients, as well as those recovering from recent surgery, especially in those with obesity or other risk factors for venous thromboembolic disease. In addition, obstructive sleep apnea is a common and often unrecognized cause or contributing factor to the development of AF in older patients.

Rate and Rhythm Management Several randomized trials comparing rate-control and rhythm-control strategies have failed to show a significant difference between the 2 approaches with respect to major clinical outcomes, including stroke, other thromboembolic events, or death.[264,265] In one large trial involving older patients, the rhythm control strategy was associated with more frequent hospitalization for management of recurrent AF, although the use of ablation therapy in this study was uncommon.[265] Despite these findings, maintenance of sinus rhythm (regardless of the strategy chosen) appears to be associated with better quality of life when compared with persistent or permanent AF,[266,267] and there is preliminary evidence to suggest that chronic AF is a risk factor for cognitive impairment in older adults.[268] For these reasons, many clinicians recommend at least one attempt to restore sinus rhythm in patients with recent-onset AF, even in those who are minimally symptomatic.[264] In addition, patients with persistent moderate or severe symptoms despite efforts to control the heart rate with medical therapy should be considered for rhythm control or, alternatively, ablation of the atrioventricular node with pacemaker implantation. Amiodarone is the most effective agent currently available for maintaining sinus rhythm in patients with AF, but it has an adverse side effect profile, particularly during long-term use, and interacts with a wide range of other medications commonly used by older adults[5,264] (see Chap. 87 for further discussion).

The use of catheter ablation procedures for management of AF in older patients is evolving. Few older patients were enrolled in the clinical trials evaluating catheter ablation, and older patients tend to have more adverse prognostic factors for ablation when compared to younger patients, including persistent or permanent rather than paroxysmal AF, large left atrial size, and more atrial fibrosis and scarring. Nonetheless, catheter ablation of AF appears to have similar efficacy and safety in carefully selected older patients.[269,270] Surgical ablation of AF using a modification of the Maze procedure is associated with long-term maintenance of sinus rhythm in up to 90% of patients, including older adults.[271] Although surgical ablation can be performed as a stand-alone procedure, it is usually performed in conjunction with CABG and/or valve surgery in patients with indications for those interventions.

Regardless of the approach taken to treat AF symptoms, prevention of thromboembolism is a critical component of AF management. Indeed, as noted in one survey of patients with CVD, older individuals wish to avoid stroke more than any other common adverse event, even death.[272] Not only does older age increase the risk of developing AF, but increasing age is also a potent risk factor for stroke among AF patients. In the Framingham Heart Study, approximately 1.5% of strokes in patients younger than age 50 years were attributed to AF, whereas 23.5% of strokes were related to AF among patients ≥ 80 years.[273] Accordingly, age > 75 years is incorporated as a major risk factor for stroke in the $CHADS_2$ score (congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke),[274] and the more recent CHA_2DS_2-VASc algorithm (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category) assigns 1 point for age 65 to 74 years and 2 points for age 75 and older.[275] Systemic anticoagulation therapy is recommended for all patients with CHA_2DS_2-VASc scores of 2 or greater,[264] and because female sex adds an additional point to the overall score, all men ≥ 75 years old and all women ≥ 65 years old should be considered for anticoagulation.

Anticoagulation One of the most common reasons for withholding anticoagulation in elderly patients with AF is concern about falls and fall-related bleeding. Several studies have demonstrated that the reduction in stroke risk is substantially greater than the risk of serious fall-related bleeding complications in patients with AF.[276,277] Furthermore, a meta-analysis of patients ≥ 75 years of age enrolled in 10 randomized trials of the new oral anticoagulant agents demonstrated no significant difference in bleeding risk with the new drugs when compared with warfarin and similar efficacy for reduction of thromboembolic events as in younger patients.[278] Although clinical trial patients are generally "healthier" than the broader population of older adults seen in clinical practice, the preponderance of evidence suggests that most elderly patients are candidates for anticoagulation therapy for AF, including those with frailty or perceived fall risk. Reduction in medication dosage should be strongly considered in elderly patients with increased bleeding risk (eg, apixaban 2.5 mg twice daily, rivaroxaban 15 mg daily, or dabigatran 75-110 mg twice daily).[279]

In patients at high risk for stroke but with prohibitively high bleeding risk (eg, prior life-threatening bleeding or intracranial hemorrhage), several devices have been developed for reducing thromboembolism originating from the left atrial appendage (see Chap. 83). The Watchman device appears to be noninferior to warfarin therapy in selected patients younger and older than age 75 years.[280] The Lariat device cinches closed the mouth of the left atrial appendage using a transpericardial approach. Surgical amputation of the appendage is also an option for patients undergoing cardiac surgery for other indications. Although studies are needed in elderly patients, these procedural approaches provide an alternative to anticoagulation therapy in selected individuals with AF.

Atrial Flutter Management of atrial flutter is similar in older and younger patients (see Chap. 83). The general approach is analogous to that discussed earlier for AF, except that catheter-based ablation of the flutter pathway has greater efficacy than for AF, and it is also more effective than antiarrhythmic drugs.[5,264,281] Thus, elderly individuals with isolated atrial flutter should be considered for catheter ablation, although periprocedural complication rates may be somewhat higher in older patients.

VENTRICULAR ARRHYTHMIAS

Aging is associated with progressive fibrosis and degeneration of the infranodal electrical conduction pathways.[5] As a result, isolated

premature ventricular depolarizations, nonsustained runs of ventricular tachycardia, and sustained ventricular arrhythmias increase in frequency with age. In addition, chronic cardiac conditions such as IHD, cardiomyopathy, and left ventricular hypertrophy contribute to the higher incidence of these arrhythmias. In the Baltimore Longitudinal Study of Aging, in which individuals with ischemic ST-segment changes with exercise were excluded, isolated premature ventricular complexes were found in 0.5% of men age 20 to 40 years versus 8.6% of men age ≥ 60 years.[282] The age-related increase in ventricular ectopy was not associated with subsequent coronary events and was not observed in women.[261] Findings were comparable for exercise-induced ventricular arrhythmias.[283] Management of ventricular arrhythmias is similar in older and young patients, including treatment of underlying HF, ischemia, valve disease, and electrolyte disorders (see Chap. 85).

SUMMARY

The pervasive theme regarding CVD in the geriatric population is quite simple: elderly patients undergo structural and functional changes over time, which—in conjunction with long-standing exposure to cardiovascular risk factors and noncardiovascular comorbidities—result in higher prevalence, more advanced clinical presentations, and worse prognosis of nearly all forms of CVD. On the other hand, management becomes more complex with age, as most CVDs occur in the context of multiple other competing medical conditions, and medical and procedural therapies are associated with higher risks of complications. As a result, choosing the appropriate treatment often requires shared decision making, beginning at the onset of therapy and continuing throughout the disease course. Because most clinical trials failed to enroll the oldest and frailest subjects, benefits and risks are uncertain in these patients, and treatment must be individualized according to patient and family preferences, particularly when quality of life is deemed to be more important than long-term survival.[284] As our population continues to age, substantial additional research into CVD prevention and management in older adults is imperative.

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CHAPTER 66

PERICARDIAL DISEASES

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INTRODUCTION

Disorders of the pericardium constitute a diverse group of pathologies, ranging from benign congenital structural abnormalities, such as pericardial cyst, to life-threatening entities, such as cardiac tamponade and constrictive pericarditis. Although pericardial diseases are not uncommon in daily practice, physicians including cardiologists tend to be less familiar with managing these diseases. This can lead to a delay in the diagnosis (patients with constriction might have been treated for "refractory" heart failure for years) or incomplete or inadequate treatment. We provide herein a concise and practical approach to pericardial diseases for cardiovascular practitioners. We have also incorporated the recommendations from the 2015 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Management of Pericardial Diseases[1] (a summary of the most relevant recommendations is also provided in the chapter).

ANATOMY OF PERICARDIUM

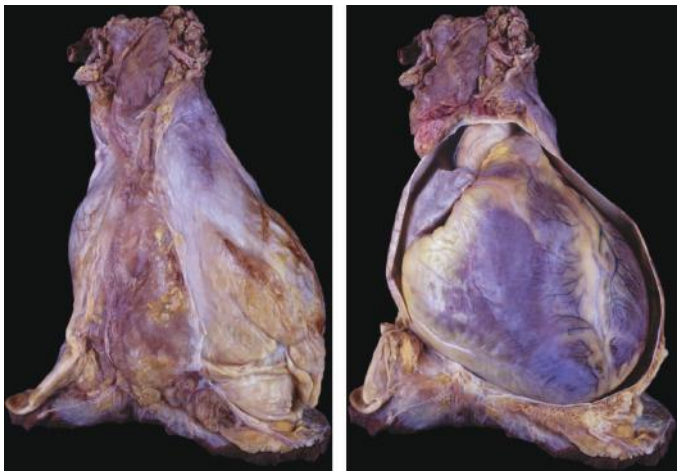
The human pericardium has two distinct layers; the *serosa* is composed of a single column of mesothelial cells that surrounds all four cardiac chambers and the proximal great vessels and reflects on itself to form the inner surface of the *fibrosa*, a fibrocollagenous structure (Figs. 66–1 and 66–2). This monolayer of serosal cells covering the surface of the heart and epicardial fat is also called the *visceral pericardium*, whereas the fibrosa and the reflection of the serosa make the *parietal pericardium*. Pericardial fluid, an ultrafiltrate of the plasma, accumulates between the serosal layers; normal pericardial fluid volume ranges from 15 to 50 mL. As opposed to the visceral pericardium, the fibrosa does not cover the cardiac surface in its entirety; pericardial reflections at the level of great vessels give origin to the *pericardial sinuses*. The two most important are the *transverse sinus*, which lies between the great arteries (aorta and pulmonary artery) and the great veins (pulmonary veins and vena cavae), and the *oblique sinus*, which has the shape of an inverted U and lies behind the left atrium as the fibrosa reflects around the pulmonary veins. Pericardial fluid can accumulate in these sinuses, increasing pericardial volume if necessary, and therefore, constituting the *pericardial reserve* (Fig. 66–3).

Most of the innervation of the pericardium occurs via the phrenic nerves (C4-C6), which course anteriorly; this is particularly relevant during pericardiectomy. Blood supply to the pericardium is provided by small branches from the aorta or the internal thoracic artery.

PHYSIOLOGY OF THE PERICARDIUM

The pericardium is not essential for life; no adverse consequences follow congenital absence or surgical removal of the pericardium.[1-4] However, the pericardium serves many important (although subtle) functions (Table 66–1).[1-4] It limits distension of the cardiac chambers and facilitates interaction and coupling of the ventricles and atria. Thus, changes in pressure and volume on one side of the heart can influence pressure and volume on the other side. Limitation of cardiac filling volumes by the pericardium may also limit cardiac output and oxygen delivery during exercise.[2] The pericardium also influences quantitative and qualitative aspects of ventricular filling; the thin-walled right ventricle and atrium are more subject to the influence of the pericardium than is the more resistant, thick-walled left ventricle.

Although the magnitude and importance of pericardial restraint of ventricular filling at physiologic cardiac volumes remain controversial,



A B

FIGURE 66–1. Anatomy of the pericardium. Gross anatomy specimens showing the intact pericardium (A) and post excision of the anterior pericardial surface (B) and exposure of the pericardial cavity. Used with permission from Dr. William D. Edwards, Mayo Clinic, Rochester, MN USA.

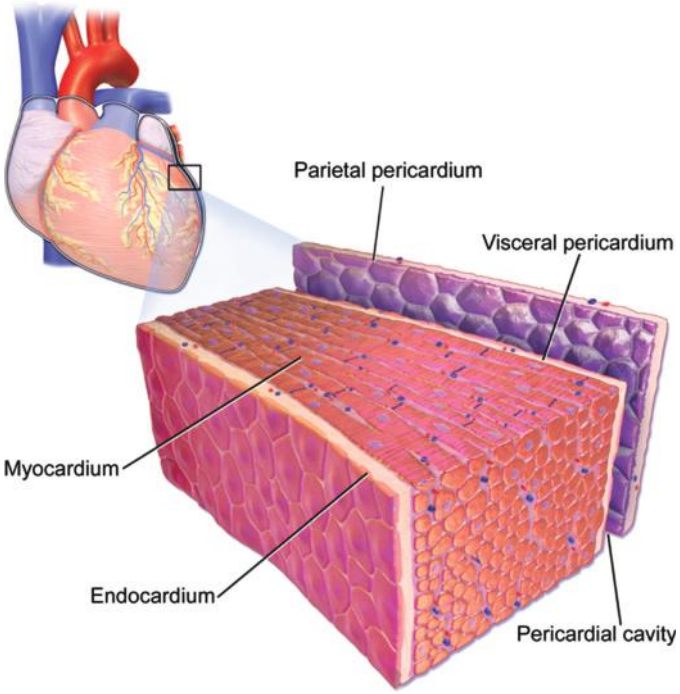


FIGURE 66–2. Pericardial layers. Illustration showing a detailed view of the pericardium and its layers in relationship to the myocardium. Reproduced with permission from from Blausen.com staff, "Blausen gallery 2014," *Wikiversity Journal of Medicine*. DOI: 10.15347/wjm/2014.010.

there is general agreement that pericardial reserve volume (ie, the difference between unstressed pericardial volume and cardiac volume) is relatively small and that pericardial influences become significant when the reserve volume is exceeded. This may occur with rapid increases in blood volume and in disease states characterized by rapid increases in heart size (eg, acute mitral and tricuspid regurgitation, pulmonary embolism, right ventricular infarction). In contrast, chronic stretching of the pericardium results in "stress relaxation"; this explains why large but slowly developing effusions do not produce tamponade. In addition, the pericardium adapts to cardiac growth by "creep" (ie, an increase in volume with constant stretch) and cellular hypertrophy.

The pericardium serves a variety of other important functions. It prevents excessive torsion and displacement of the heart, minimizes friction with surrounding structures, and is an anatomic and immunologic barrier to the spread of infection from contiguous structures. The thin layer of pericardial fluid reduces friction on the epicardium and equalizes gravitational, hydrostatic, and inertial forces over the surface of the heart; therefore, transmural cardiac pressures do not change during acceleration or differ regionally within cardiac chambers. The pericardium also has immunologic, vasomotor, paracrine, and fibrinolytic activities.[5] The mesothelium of the pericardium is metabolically active and produces prostaglandin E_2, eicosanoids, and prostacyclin; these substances modulate sympathetic neurotransmission and myocardial contractility and may influence epicardial coronary arterial tone. Epicardial mesothelial cells may modulate myocyte structure and function and gene expression. The level of brain natriuretic peptide in the pericardial fluid is a more sensitive and accurate indicator of ventricular volume and pressure than is either plasma brain natriuretic peptide or atrial natriuretic factor; it may play an autocrine-paracrine role in heart failure. Finally, the pericardial space has been used as a vehicle for drug delivery and gene therapy[1]; studies using radiolabeled growth factors indicate that substances more consistently and reproducibly gain access to the coronary arteries via pericardial fluid than via endoluminal delivery.[5]

ETIOLOGY AND PATHOLOGY OF THE PERICARDIUM

Pericardial diseases may be caused by either infectious or noninfectious agents (Table 66–2) and typically may be either an isolated process or a part of a systemic disease (eg, systemic inflammatory disease).[1-4] The pericardial response to an infectious or noninfectious noxa is rather nonspecific and is usually manifested as pericardial inflammation

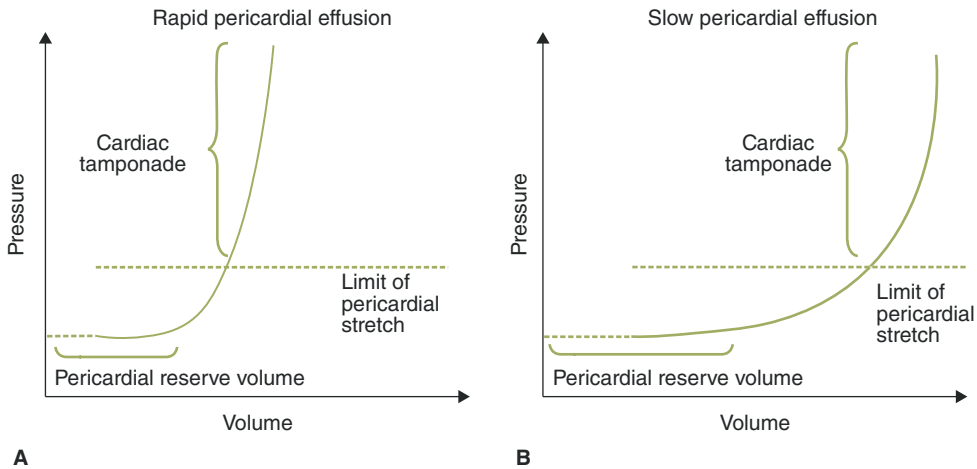


FIGURE 66–3. Pericardial reserve and pericardial pressure-volume curves in cardiac tamponade. **A.** The pressure-volume curve observed in acute cardiac tamponade; note the much steeper curve at smaller pericardial volumes compared to the pressure-volume curve observed in slowly developing pericardial effusions (**B**). Reproduced with permission from Imazio M, Adler Y: Management of pericardial effusion. *Eur Heart J*. 2013 Apr;34(16):1186-1197.[3]

TABLE 66–1. Functions of the Pericardium

Mechanical
Effects on chambers
Limits short-term cardiac distention
Facilitates cardiac chamber coupling and interaction
Maintains pressure-volume relationship of the cardiac chambers and output from them
Maintains geometry of left ventricle
Effects on whole heart
Lubricates, minimizes friction
Equalizes gravitation and inertial hydrostatic forces
Mechanical barrier to infection
Immunologic
Vasomotor
Fibrinolytic
Modulation of myocyte structure and function and gene expression
Vehicle for drug delivery and gene therapy

(*pericarditis*) with the possible increased production of pericardial fluid giving rise to *pericardial effusion*. If the pericardial inflammation persists, the evolution may be toward fibrosis and calcification with the development of *constrictive pericarditis*. On this basis, in clinical practice, pericardial diseases are usually manifested as the following "pericardial syndromes": *pericarditis* (acute and recurrent), *pericardial effusion*, *cardiac tamponade*, *constrictive pericarditis*, *congenital diseases of the pericardium*, and *pericardial masses*[1]; these conditions will be reviewed in this chapter.

Treatment of pericardial disease is also challenging in that there is a paucity of randomized, placebo-controlled trials (Level of Evidence: A) from which appropriate therapy may be selected and important clinical decisions assisted. Table 66–3 summarizes the main recommendations of the 2015 ESC guidelines.[1]

ACUTE PERICARDITIS

Acute pericarditis is an inflammatory pericardial syndrome with or without pericardial effusion that can be caused by infectious or noninfectious causes (see Table 66–2). The following description refers to viral and idiopathic pericarditis without significant effusion. Specific forms of pericardial heart disease are reviewed later in this chapter.

HISTORY

Acute pericarditis is usually characterized sharp retrosternal pain (> 85% of cases) that is aggravated by lying down and relieved by sitting up; its onset is frequently heralded by a prodrome of fever, malaise, and myalgia. The pain of pericarditis is often worse with inspiration and is difficult to distinguish from pleurisy; in some cases, it may radiate to the shoulders, arms, and jaw and may simulate "ischemic chest pain" (Fig. 66–4).

PHYSICAL EXAMINATION

The most specific physical sign can be the presence of a *pericardial rub*, which is identifiable in no more than a third of cases. It is a superficial scratchy or squeaking sound best heard with the diaphragm of the stethoscope applied firmly and with respiration suspended over the left sternal border and the cardiac apex and is heard better with the patient sitting up and leaning forward.[2,4] It is likened to the sound of walking on dry snow or the squeak of a leather saddle (see Fig. 66–4). Most pericardial friction rubs are independent of the respiratory cycle, but on occasion, they are louder during inspiration. The pericardial rub may be confined to ventricular systole but most often includes a component during atrial systole and occasionally during ventricular diastolic filling, resulting in biphasic and triphasic rubs, respectively. Frequent examinations are necessary to detect a rub because of its evanescent nature; pericardial fluid does not prevent a friction rub.

TABLE 66–2. Etiology of Pericardial Diseases

Infectious Causes:

Viral (common): Enteroviruses (coxsackieviruses, echoviruses), herpesviruses (Epstein-Barr virus, cytomegalovirus, human herpesvirus-6), adenoviruses, parvovirus B19 (possible overlap with etiologic viral agents of myocarditis)

Bacterial: *Mycobacterium tuberculosis* (common, other bacterial rare), *Coxiella burnetii*, *Borrelia burgdorferi*, rarely: *Pneumococcus* spp., *Meningococcus* spp., *Gonococcus* spp., *Streptococcus* spp., *Staphylococcus* spp., *Haemophilus* spp., *Chlamydia* spp., *Mycoplasma* spp., *Legionella* spp., *Leptospira* spp., *Listeria* spp., *Providencia stuartii*

Fungal (rare): *Histoplasma* spp. (more likely in immunocompetent patients), *Aspergillus* spp., *Blastomyces* spp., *Candida* spp. (more likely in immunocompromised host)

Parasitic (rare): *Echinococcus* spp., *Toxoplasma* spp.

Noninfectious Causes:

Autoimmune (common): Systemic autoimmune and autoinflammatory diseases (systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma), systemic vasculitides (eg, eosinophilic granulomatosis with polyangiitis or allergic granulomatosis, previously named Churg-Strauss syndrome, Horton disease, Takayasu disease, Behçet syndrome), sarcoidosis, familial Mediterranean fever, inflammatory bowel diseases, Still disease

Neoplastic: Primary tumors (rare; especially pericardial mesothelioma), secondary metastatic tumours (common; especially lung and breast cancer, lymphoma)

Metabolic: Uremia, myxedema, anorexia nervosa, other rare

Traumatic and iatrogenic:

Early onset (rare):

- Direct injury (penetrating thoracic injury, esophageal perforation)
- Indirect injury (nonpenetrating thoracic injury, radiation injury)

Delayed onset:

- Pericardial injury syndromes (common) post–myocardial infarction syndrome, postpericardiotomy syndrome, post-traumatic, including forms after iatrogenic trauma (eg, coronary percutaneous intervention, pacemaker lead insertion, radiofrequency ablation).

Drug-related (rare):

- Lupus-like syndrome (procainamide, hydralazine, methyldopa, isoniazid, phenytoin);
- Antineoplastic drugs (often associated with a cardiomyopathy; may cause a pericardiopathy): doxorubicin and daunorubicin, cytosine arabinoside, 5-fluorouracil, cyclophosphamide
- Hypersensitivity pericarditis with eosinophilia: penicillins, amiodarone, methysergide, mesalazine, clozapine, minoxidil, dantrolene, practolol, phenylbutazone, thiazides, streptomycin, thiouracils, streptokinase, p-aminosalicylic acid, sulfa drugs, cyclosporine, bromocriptine, several vaccines, GM-CSF, anti-TNF agents

Other (common): Amyloidosis, aortic dissection, pulmonary arterial hypertension, chronic heart failure

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating hormone; TNF, tumor necrosis factor.

TABLE 66–3. Summary of the 2015 European Society of Cardiology Guidelines on the Diagnosis and Management of Pericardial Diseases

	Indication	Evidence
Acute and recurrent pericarditis		
A triage is recommended to identify high-risk patients who should be admitted to hospital. Low-risk patients can be managed as outpatients.	Class I	Level B
Colchicine is now a first-choice drug to be used as adjunct to aspirin/NSAID or corticosteroids to treat and prevent pericarditis either in acute or recurrent pericarditis (weight-adjusted doses are recommended without a loading dose; eg, 0.5 mg twice a day for 3 months in acute pericarditis and 6 months in recurrent pericarditis; colchicine should be given only as 0.5 mg once for patients > 70 kg).	Class I	Level A
Levels of C-reactive protein are useful to guide the treatment duration and assess the response to treatment in acute and recurrent pericarditis; anti-inflammatory therapy should be maintained until symptom resolution and C-reactive protein normalization.	Class IIa	Level C
Corticosteroids should not be prescribed as first choice in patients with acute pericarditis since it may favor chronicization.		
Pericardial effusion	Class III	Level C
The essential indications to drain a pericardial effusion include: (1) cardiac tamponade (therapeutic pericardiocentesis), (2) a suspicion of bacterial or neoplastic aetiology, and (3) persistent moderate to large pericardial effusion without response to medical therapy.	Class I	Level C
A triage system is proposed also for the management of pericardial effusion and is essentially based on the following: (1) recognize cardiac tamponade and possible bacterial of neoplastic etiologies, (2) exclude concomitant pericarditis or treat as pericarditis, (3) identify associated underlying diseases, and (4) if chronic and large (> 20 mm), consider pericardial drainage to prevent cardiac tamponade during follow-up.	Class I	Level C
Treatment of pericardial effusions should be tailored as much as possible to the underlying etiology.	Class I	Level C
Cardiac tamponade		
In a patient with clinical suspicion of cardiac tamponade, echocardiography is recommended as the first imaging technique to evaluate the size, location, and degree of hemodynamic impact of the pericardial effusion.	Class I	Level C
Urgent pericardiocentesis or cardiac surgery is recommended to treat cardiac tamponade.	Class I	Level C
A judicious clinical evaluation including echocardiographic findings is recommended to guide the timing of pericardiocentesis.	Class I	Level C
Vasodilators and diuretics are not recommended in the presence of cardiac tamponade.	Class III	Level C
Constrictive pericarditis		
CT and CMR are indicated for the evaluation of a suspected constrictive pericarditis as second-level imaging techniques after echocardiography.	Class I	Level C
Cardiac catheterization is indicated only in complex cases when noninvasive imaging does not provide a clear-cut diagnosis or provides conflicting results.	Class I	Level C
The mainstay of therapy for chronic constriction is radical pericardiectomy, but it is acknowledged that there is a need to assess the possible presence of pericardial inflammation (eg, elevation of C-reactive protein, pericardial inflammation on CT/CMR) as precipitating cause in new-onset cases in order to treat with empiric anti-inflammatory therapy.	Class I	Level C
Diagnostic workup of pericardial diseases		
First diagnostic evaluation in a patient with a clinical suspicion of pericardial disease should include: focused history and physical examination, ECG, chest x-ray, and routine blood tests, including markers of myocardial inflammation and lesion and renal function.	Class I	Level C
Echocardiography is the first essential diagnostic imaging tool, whereas CT and CMR are second-level imaging techniques for specific indications.	Class I	Level C
Additional diagnostic testing should be targeted and clinically guided.	Class I	Level C
Main specific forms		
Tuberculosis		
Empiric antituberculous therapy is only recommended in countries where tuberculosis is endemic and the disease is highly probable in the setting of a patient with pericarditis and pericardial effusion.	Class I	Level C
In cases with an established diagnosis of tuberculous pericarditis, standard antituberculous therapy is recommended for 6 months and prevents the evolution to constrictive pericarditis.	Class I	Level C
In patients with tuberculous pericarditis with features of constriction and not responding to antituberculous therapy, pericardiectomy is recommended after 4-8 weeks of medical therapy.	Class I	Level C
Neoplastic pericardial diseases		
The definite diagnosis of neoplastic pericardial disease relies on the evidence of neoplastic cells on cytology of pericardial fluid.	Class I	Level B
Pericardial biopsy should be considered for the final etiologic diagnosis in selected cases.	Class IIa	Level B
Tumor markers in pericardial fluid may be helpful to differentiate a benign vs a malignant pericardial effusion.	Class IIa	Level B
In cases with a confirmed diagnosis of neoplastic pericardial disease, systemic antineoplastic treatment is indicated.	Class I	Level B
Extended pericardial drainage is recommended to prevent recurrent cardiac tamponade and pericardial effusion and to provide a way for intrapericardial therapy.	Class I	Level B
Intrapericardial therapy with cytostatic agents should be considered to treat neoplastic pericardial disease.	Class IIa	Level B

Abbreviations: CT, computed tomography; CMR, cardiac magnetic resonance; ECG, electrocardiography; NSAID, nonsteroidal anti-inflammatory drugs.

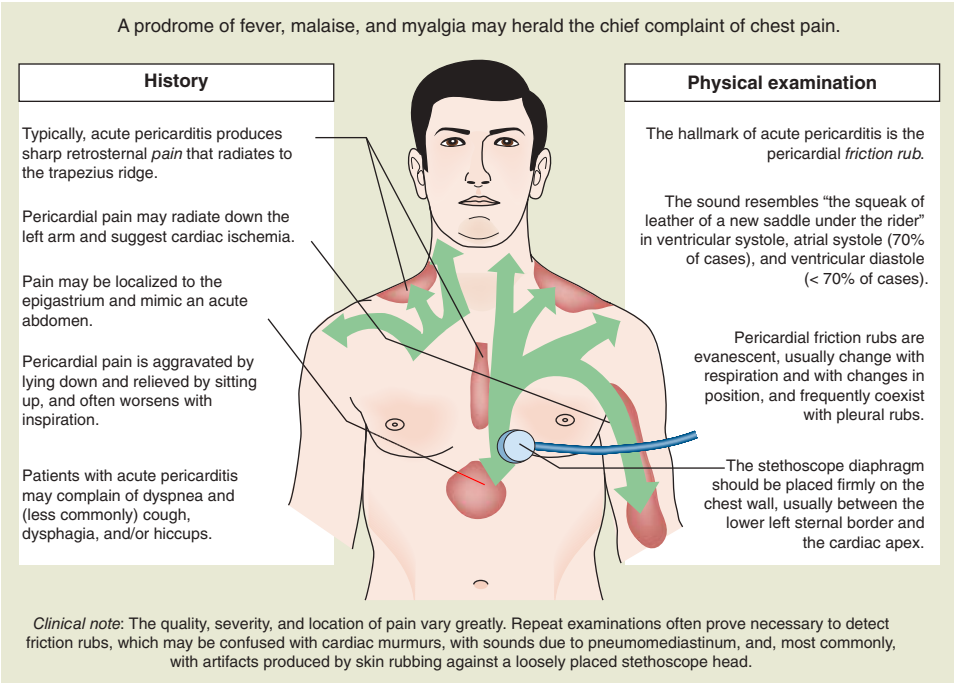


FIGURE 66–4. Clinical features of acute pericarditis: history and physical examination. Reproduced with permission from Hoit BD. Acute pericarditis: diagnosis and differential diagnosis. *Hosp Pract*. 1991;27:23-43.

In uncomplicated pericarditis, the jugular venous pressure usually remains normal. Ventricular third and fourth heart sounds indicate coexisting myocardial disease. The history and physical examination are also helpful in recognizing complications and in identifying underlying diseases associated with pericarditis. Depending on the etiology, there may be fever and other signs of inflammation or systemic illness.

EVALUATION AND TESTING

Electrocardiography

On electrocardiography (ECG), the classical reported feature of acute pericarditis is *widespread ST-segment elevation* (Fig. 66–5), although either this sign or the earlier *PR depression* (as an atrial current of injury that is the earliest ECG sign) are an expression of concomitant subepicardial involvement and not "pure pericarditis" because the pericardium is electrically silent.[6-8] As opposed to other leads, aVR will show *PR elevation* ("knuckle sign"), another ECG sign of acute pericarditis.[9]

Presentation times and therapies may affect the ECG presentation; early presentation may show ST-segment elevation, whereas a normal ECG or an ECG with negative T waves (reflecting an ECG in evolution) can be seen in late presentations or chronic forms. In patients with a fast response to medical therapy and in mild forms, the ECG may be absolutely normal; thus, a normal ECG does not exclude pericarditis.[6,7]

The ECG may either confirm the clinical suspicion of pericardial disease or first alert the clinician to the presence of pericarditis. Serial tracings may be needed to distinguish the ST-segment elevations caused by acute pericarditis from those caused by acute myocardial infarction or normal early repolarization. The ST-T wave changes in acute pericarditis are diffuse and have characteristic evolutionary changes.

The ECG evolves according to the classical four stages reported by Imazio et al[8] in no more than 60% of patients. In the first stage,

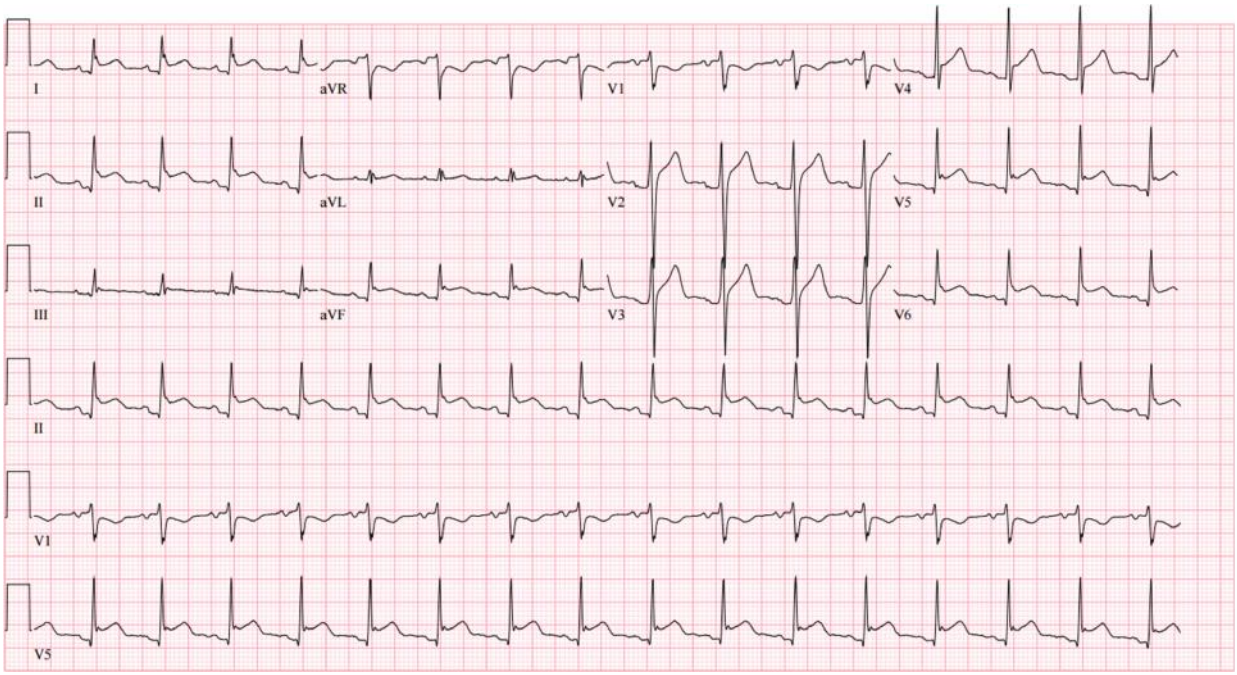


FIGURE 66–5. Electrocardiography findings in a patient with acute pericarditis. Note the widespread ST-segment elevation. This electrocardiogram also demonstrates PR-segment change with PR depression (best seen in lead II) and PR elevation in lead aVR.

TABLE 66–4. Differential Diagnosis of Acute Pericarditis Versus Early Repolarization and ST-Segment Elevation Myocardial Infarction (STEMI)

Electrocardiographic Feature	Acute Pericarditis	Early Repolarization	STEMI
PR depression	Possible	No	No
ST elevation	Concave up	Concave up	Usually convex
Localization of ST elevation	Widespread	Usually precordial, inferior leads	Localized
Reciprocal ST changes	No	No	Common
T-wave inversion	Yes but after ST segment normalization	No	Yes before ST segment normalization
ST/T ratio in lead V_6	> 0.25	< 0.25	Variable
Presence of Q waves	No	No	Possible
QT prolongation	No	No	Possible

ST-segment elevations (which differ from ischemic ST-segment elevations by their upward concavity and seldom exceed 5 mm in height) typically occur within a few hours of the onset of chest pain and persist for hours or days. Depression of the PR segment (except in lead aVR) occurs in this stage and differentiates acute pericarditis from early repolarization variants. In the second stage, the ST segments return to baseline; at this point, the T waves may appear normal or exhibit a loss of amplitude. In the third stage, tracings show inversion of T waves. T-wave inversions may persist indefinitely, particularly with chronic pericarditis. The ECG normalizes in the variably present fourth stage.

Atrial arrhythmias complicate 5% to 10% of cases of acute pericarditis. The risk of cardiac arrhythmias is very low in simple acute pericarditis, that is, in the absence of myocarditis or structural heart diseases.[6,7,10,11]

The ST-segment elevation seen in acute pericarditis can usually be distinguished from that of acute myocardial infarction by several differential features, which are reported in Table 66–4.

Although the ST-segment elevation in the early repolarization variant (common in young individuals, especially blacks, athletes, and psychiatric patients) may simulate the ECG of acute pericarditis, the former is distinguished by the absence of PR-segment depression and evolutionary ST-T wave changes. Moreover, the height of the J-point can be used to differentiate early repolarization from acute pericarditis: if the ratio between the height of the J-point and the height of the T wave is < 0.25, early repolarization is diagnosed.[4]

Laboratory Studies and Imaging

Nonspecific blood markers of inflammation, such as the erythrocyte sedimentation rate, C-reactive protein, and white blood cell count, usually increase in cases of acute pericarditis. Patients with extensive epicarditis and/or concomitant myocarditis occasionally have increases in serum cardiac isoenzymes (eg, troponins).

The chest-x-ray may be completely normal in the absence of concomitant pleuropulmonary disease or large pericardial effusion (> 300 mL); in such cases, the heart may assume a water bottle–shaped configuration (Fig. 66–6).[1] The chest radiograph may provide evidence of concomitant pleuropulmonary diseases (eg, tuberculosis, fungal disease, pneumonia, neoplasm).

The use of echocardiography for the evaluation of all patients with suspected pericardial disease was given a Class I recommendation by a 2003 task force of the American College of Cardiology, the American Heart Association, and the American Society of Echocardiography[12] and 2015 ESC guidelines on the diagnosis and management of pericardial diseases.[1] Echocardiographic identification of pericardial effusion confirms the clinical diagnosis of acute pericarditis (Fig. 66–7) but is not necessary for the diagnosis because pericarditis may occur without pericardial effusion ("dry pericarditis").

A semiquantitative assessment of pericardial effusion is recommended by the 2015 ESC guidelines.[1] The assessment is performed by the end-diastolic distance of the echo-free space between the epicardium and parietal pericardium: small (< 10 mm), moderate (10-20 mm), and large (> 20 mm). A large (> 20 mm) pericardial effusion or cardiac tamponade identifies high-risk patients with an increased risk of a nonviral etiology or complications during follow-up.[13]

The clinical diagnosis of acute pericarditis is established when two of four clinical criteria are satisfied (Table 66–5). In atypical cases, additional supporting criteria are provided by elevation of markers of inflammation and evidence of pericardial inflammation by an imaging technique (eg, computed tomography [CT] or

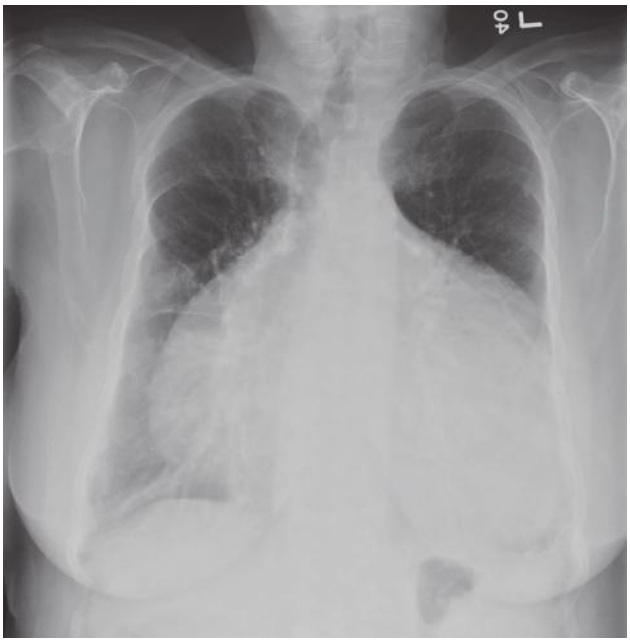


FIGURE 66–6. Chest radiography in a patient with a large pericardial effusion. Note the marked enlargement of the cardiac silhouette with a "water bottle–shaped" configuration in this patient with a large pericardial effusion. Used with permission from Dr. Nandan S. Anavekar, Mayo Clinic, Rochester, MN USA.

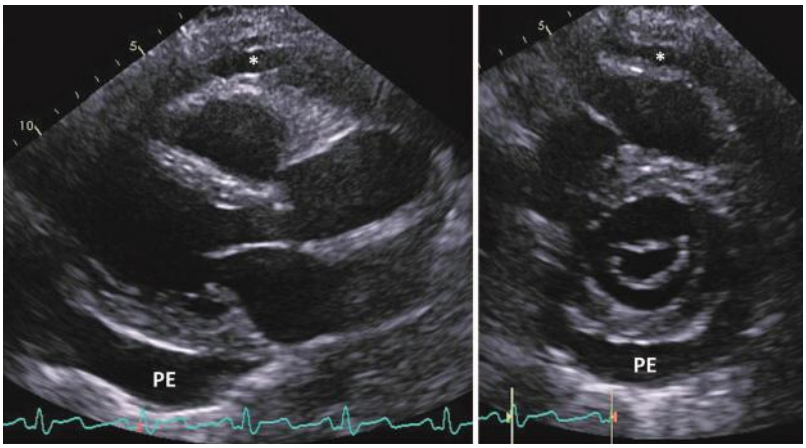


FIGURE 66–7. Two-dimensional echocardiography findings in a patient with pericardial effusion. Parasternal long-axis view (*left*) reveals a circumferential pericardial effusion (PE), also seen in the parasternal short axis view (*right*). Please note that the effusion can also be identified anteriorly (*asterisk*).

cardiac magnetic resonance [CMR]). The inflamed pericardium may be contrast enhanced on CT and show increased signal on T2-weighted imaging on CMR (as evidence of pericardial edema) and late enhancement after administration of gadolinium (as evidence of increased extracellular space that may be caused by edema and/or organizing pericarditis).[14,15]

TREATMENT

Hospitalization is warranted for many patients who present with an initial episode of acute pericarditis and high-risk features such as elevated temperature (> 38°C), subacute onset, large pericardial effusion, cardiac tamponade, immunosuppression, recent trauma, oral anticoagulant therapy, and aspirin or nonsteroidal anti-inflammatory drug (NSAID) failure[13] to determine the etiology and for monitoring (Table 66–6 and Fig. 66–8); close follow-up is important in the remainder of patients, and outpatient management is warranted.[10]

Establishing the exact cause of acute pericarditis is especially important in patients with high-risk features, a suspicion of a bacterial or neoplastic etiology, or failure of empiric anti-inflammatory therapy. An extensive evaluation is generally unnecessary in a young, previously healthy adult who presents with a viral syndrome, typical pericardial chest pain, and a pericardial friction rub and has a prompt response to empiric anti-inflammatory therapy.

The mainstay of therapy of simple uncomplicated pericarditis is aspirin or a NSAID plus colchicine to fasten the response to anti-inflammatory therapy and prevent recurrences.[16-23] Colchicine is now a well-established therapy even for the first episode of pericarditis.[17-19,24] It is recommended without a loading dose using weight-adjusted dosing (eg, colchicine 0.5-0.6 mg once daily for patients < 70 kg and 0.5-0.6 mg twice a day for patients > 70 kg with a duration of therapy of 3 months) (Class I recommendation; Level of Evidence [LOE]: A).[1] These recommendations are based on randomized data from the Colchicine for Acute Pericarditis (COPE)[18] and Investigation on Colchicine for Acute Pericarditis[24] trials, which showed that the use of colchicine in addition to anti-inflammatory therapy reduces recurrence rates as well as persistence of symptoms at 72 hours after initiation of therapy.

Proposed therapeutic schemes for acute pericarditis are reported in Table 66–7. The attack dose should be maintained until symptom resolution and normalization of markers of inflammation (eg, C-reactive protein).[21,22] Tapering is recommended after initial clinical remission according to 2015 ESC guidelines.[1]

Corticosteroids should be prescribed only as second-line therapy in case of contraindication or failure of aspirin and NSAID and for specific indications (eg, pregnancy, systemic inflammatory disease already on steroids, renal failure, need to prevent interactions with other drugs, especially oral anticoagulants).

Prophylaxis against gastrointestinal bleeding with proton pump inhibitors is warranted in all patients to allow a safe therapy with high-dose aspirin or NSAID.

As a nonpharmacologic measure, avoidance of physical exertion and exercise is recommended until remission in nonathletes and for an arbitrary defined time of 3 months in athletes,[25,26] also according to the 2015 ESC guidelines.[1]

TABLE 66–5. Definition and Diagnostic Criteria for Acute Pericarditis

Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria:
(1) pericarditic chest pain
(2) pericardial rubs
(3) new widespread ST elevation or PR depression on ECG
(4) pericardial effusion (new or worsening)
Additional supporting findings:
Elevation of markers of inflammation (ie C-reactive protein, erythrocyte sedimentation rate, and white blood cell count);
Evidence of pericardial inflammation by an imaging technique (Computed tomography, cardiac magnetic resonance).

TABLE 66–6. Indicators of Poor Prognosis or Nonviral Etiology in Acute Pericarditis

Major
Fever > 38°C
Subacute onset
Large pericardial effusion (> 20 mm on echocardiography)
Cardiac tamponade
Lack of response to aspirin or NSAID after at least 1 week of therapy
Minor
Pericarditis associated with myocarditis
Immunodepression
Trauma
Oral anticoagulant therapy

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

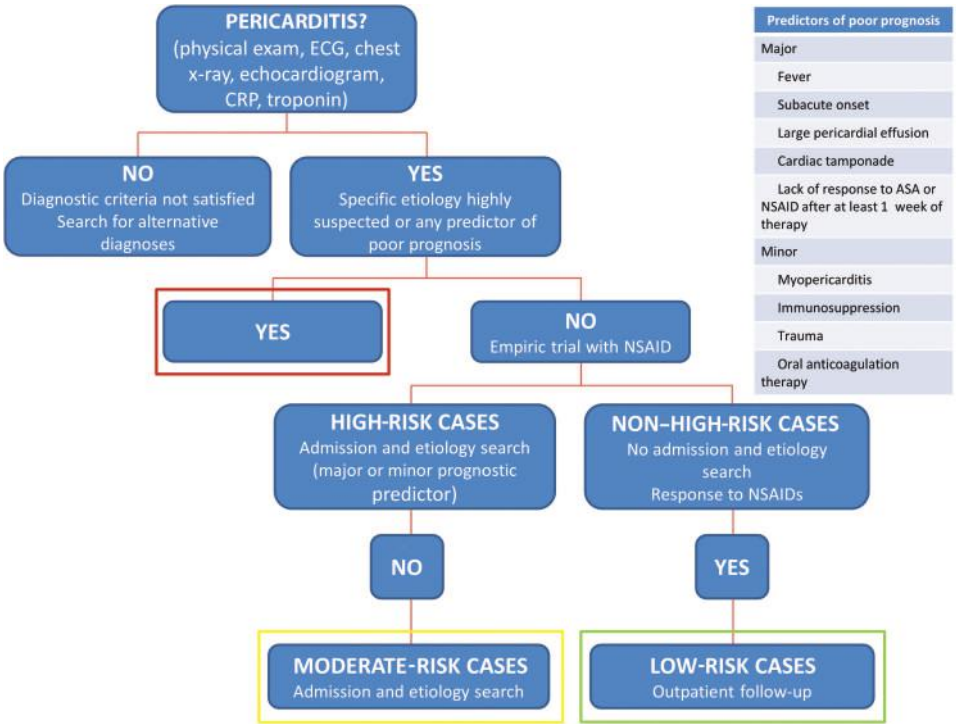


FIGURE 66–8. Algorithm for evaluation and triage of patients with acute pericarditis. ASA, acetylsalicylic acid; CRP, C-reactive protein; ECG, electrocardiogram; NSAID, nonsteroidal anti-inflammatory drug.

PROGNOSIS

The overall prognosis is related to the etiology.[27] Recurrences are reported to occur in 20% to 50% of patients, but the recurrence rate may be halved if empiric anti-inflammatory therapy of pericarditis is provided with the adjunct of colchicine.[18,24]

The most feared complication is the evolution toward constrictive pericarditis that rarely occurs in idiopathic and viral pericarditis (< 1%), and it is usually more common for specific etiologies, such as autoimmune and neoplastic pericarditis (2%-5%) and especially tuberculous and purulent pericarditis (20%-30%).[27]

TABLE 66–7. Empiric Anti-inflammatory Therapy for Acute Pericarditis

Drug	Usual Dosing	Duration	Tapering
Aspirin	750-1000 mg every 8 hours	1-2 weeks	Decrease doses every week: eg, 750 mg TID for 1 week, then 500 mg TID for 1 week, then stop
Ibuprofen	600 mg every 8 hours	1-2 weeks	Decrease doses every week: eg, 600 mg plus 400 mg plus 600 mg for 1 week, then 600 mg plus 400 mg plus 400 mg for 1 week, then 400 mg TID for 1 week, then stop
Colchicine	0.5 mg once (< 70 kg) or 0.5 mg BID (≥ 70 kg)	3 months	Not mandatory; alternatively, 0.5 mg every other day (< 70 kg) or 0.5 mg once (≥ 70 kg) in the last weeks

Abbreviations: BID, twice a day; TID, three times a day.

RECURRENT PERICARDITIS

Recurrent pericarditis is one of the most troublesome complications of pericarditis, occurring in one-third of cases. Use of colchicine and restriction of corticosteroid use in acute pericarditis may help to reduce the recurrence rate.

Most recurrences remain "idiopathic" without a definite etiology, although most recurrences are considered to be immune mediated. In clinical practice, a significant number of cases are related to the inappropriate therapy of the first episode of pericarditis, including low anti-inflammatory doses, short courses, nonprescription of colchicine, or use of corticosteroids, especially high doses (eg, prednisone 1.0 mg/kg/d).

A true recurrence occurs when there is a symptom-free interval from the previous episode of pericarditis. This time is usually 4 to 6 weeks in order to allow the completion of the anti-inflammatory therapy of pericarditis. In the absence of this symptom-free interval, the term *incessant pericarditis* is proposed rather than *recurrent pericarditis* because incessant pericarditis is characterized by continuous symptoms without remission. Such forms may directly progress to constrictive pericarditis. The term *chronic* is generally referred, especially for pericardial effusions, to disease processes lasting for > 3 months, and *chronic pericarditis* is an arbitrary term used by experts for disease lasting > 3 months, according to 2015 ESC guidelines (Table 66–8).[1]

The mainstay of the therapy for recurrences is similar to that of acute pericarditis: aspirin or a NSAID plus colchicine at the same doses recommended for acute pericarditis, but in this case, colchicine is recommended for 6 months (Class I recommendation; LOE: A).[1]

Colchicine as adjunct to aspirin or a NSAID has been demonstrated to be safe and efficacious to improve the response to conventional anti-inflammatory therapy (aspirin/NSAID) and halve the recurrence rate either in first recurrences (data from Colchicine for Recurrent Pericarditis [CORE] and Colchicine for Recurrent Pericarditis [CORP] trials)[20,28] or in patients with multiple recurrences.[29]

Corticosteroids should be considered as a second-line therapy for patients with contraindications for or failure of aspirin/NSAID or patients with specific indications (eg, pregnant patients, patients with a

TABLE 66–8. Definitions of Recurrent, Incessant, and Chronic Pericarditis

	Definition
Incessant	Pericarditis lasting for > 4-6 weeks but < 3 months[a] without remission
Recurrent	Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4-6 weeks or longer[b]
Chronic	Pericarditis lasting for > 3 months[a]

[a]Abitrary term defined by experts.

[b]Usually, recurrences occur within 18 to 24 months for the index attack.

TABLE 66–9. Tapering of Corticosteroids in Recurrent Pericarditis

Prednisone dose[a]	Starting dose 0.25-0.50 mg/kg/d[a]	Tapering[b]
Prednisone daily dose	> 50 mg	10 mg/d every 1-2 weeks
	50-25 mg	5–10 mg/d every 1-2 weeks
	25-15 mg	2.5 mg/d every 2-4 weeks
	< 15 mg	1.25 to 2.5 mg/d every 2-6 weeks

[a]Avoid higher doses except for special cases, and only for a few days, with rapid tapering to 25 mg/d. Prednisone 25 mg is equivalent to methylprednisolone 20 mg.

[b]Every decrease in prednisone dose should be done only if the patient is asymptomatic and C-reactive protein is normal, particularly for doses < 25 mg/d.

Calcium intake (supplement plus oral intake; 1200-1500 mg/d) and vitamin D supplementation (800-1000 IU/d) should be offered to all patients receiving glucocorticoids. Moreover, bisphosphonates are recommended to prevent bone loss in all men ≥ 50 years old and postmenopausal women in whom long-term treatment with glucocorticoids is initiated at a dose ≥ 5.0 to 7.5 mg/d of prednisone or equivalent.

systemic inflammatory disease already on corticosteroids, patients with renal failure, patients on oral anticoagulant therapies to avoid interference with aspirin/NSAIDs). If used, low to moderate doses (eg, prednisone 0.2-0.5 mg/kg/d or equivalent) are indicated because high doses (eg, prednisone 1.0-1.5 mg/kg/d) are associated with a high rate of severe side effects (up to 25%) with more drug withdrawals, drug-related hospitalization, and recurrences. A slow tapering is also critical in order to allow corticosteroid withdrawal after remission (Table 66–9).[30]

In more difficult cases, aspirin or NSAID, colchicine, and corticosteroids may be used together as a triple therapy to achieve a better control of symptoms.[31]

A small subset of patients with recurrent pericarditis (also called *refractory recurrent pericarditis*) develop corticosteroid dependence (ie, unable to withdraw or taper corticosteroids without a new relapse) and do not respond to colchicine. In such cases, anecdotal evidence supports the use of alternative drugs (eg, azathioprine, but especially human intravenous immunoglobulins and anakinra; Table 66–10).[32-35]

After failure of medical therapy, the last option is pericardiectomy, which should be performed in centers with specific expertise in such surgery to achieve the best outcomes.[36]

SPECIFIC FORMS OF PERICARDIAL DISEASE

IDIOPATHIC PERICARDITIS

In North America and western Europe (countries with a low prevalence of tuberculosis), acute pericarditis is most often idiopathic (80%-55% of unselected cases) and is typically a self-limited disease usually lasting 2 to 6 weeks. Small pericardial effusions occur commonly (up to 60% of cases), but cardiac tamponade is unusual (< 5% of cases). Heart failure caused by associated myocarditis and constrictive pericarditis is uncommon. These complications usually can be detected by clinical and echocardiographic evaluation. The clinical course and prognosis of individuals with pericarditis are otherwise largely determined by the presence and nature of any underlying disease.

INFECTIOUS PERICARDITIS

Viral Pericarditis

Viral pericarditis is the most common infectious type, although a definitive diagnosis from acute and convalescent (3 weeks) viral neutralizing antibodies is generally not helpful in a sporadic case of pericarditis. Viral isolation from pericardial fluid and in situ hybridization techniques have been used to identify a specific etiology. However, viral infection is often presumed rather than proved, and many cases are classified as idiopathic. Common viral infections causing acute pericarditis are those resulting from echovirus and coxsackievirus; however, several other viruses may cause pericarditis (see Table 66–2).

TABLE 66–10. Common Therapeutic Options for Recurrent Pericarditis

Therapy	Dosing	Duration[a]	Tapering	Monitoring[b]	LOE[c]
Aspirin[d]	750-500 mg 3 times daily	1-2 weeks	Weekly in 3-4 weeks	Needed	A
Ibuprofen[d]	600-800 mg 3 times daily	1-2 weeks	Weekly in 3-4 weeks	Needed	A
Indomethacin	50 mg 3 times daily	1-2 weeks	Weekly in 3-4 weeks	Needed	B
Colchicine[d]	0.5 once (< 70 kg or chronic kidney disease) or 0.5 mg twice daily	6 months	May be considered	Needed	A
Prednisone	0.2-0.5 mg/kg/d	2-4 weeks	Several months	Needed	B
Azathioprine	Starting with 1 mg/kg/d, then gradually increased to 2-3 mg/kg/d	Several months	Several months	Needed	C
IVIG	400-500 mg IV daily for 5 days	5 days	Not required	Needed	C
Anakinra	1-2 mg/kg/d up to 100 mg/d in adults	Several months	To be determined	Needed	C
Pericardiectomy	NA	NA	NA	Needed	C

Abbreviations: IV, intravenous; IVIG, intravenous immunoglobulin; LOE, level of evidence; NA, not applicable.

[a]Therapy duration as initial dosing

[b]Monitoring is essentially based on the assessment of blood count, creatinine, creatinine kinase, transaminases, C-reactive protein, and echocardiography.

[c]LOE A, data derived from multiple randomized clinical trials or meta-analyses; LOE B, data derived from a single randomized clinical trial or large nonrandomized studies (in this review, a study with at least 100 patients is considered large); LOE C, consensus of opinion of the experts and/or small studies, retrospective studies, or registries.

[d]Aspirin and ibuprofen are common first-level treatments for the first episode of pericarditis (acute pericarditis) associated with colchicine for 3 months.

However, in immunocompetent patients, there are no proven antiviral therapies to offer, and the disease is usually self-limiting and resolving, while pericardial inflammation and pain are treated by aspirin or a NSAID and colchicine. Thus, it is absolutely not necessary to reach a specific viral etiology in clinical practice.

Bacterial Pericarditis

The most common cause of bacterial pericarditis is tuberculous pericarditis. Tuberculosis is the leading cause of pericardial diseases in developing countries and all over the world. Purulent pericarditis is now relatively rare, especially in countries with a low prevalence of tuberculosis.[37]

Bacterial (purulent) pericarditis was most often caused by streptococci, staphylococci, gram-negative rods, and, increasingly, anaerobic bacteria.[38] *Haemophilus influenzae* is an important cause in children. The increasing frequency of cardiac surgery and percutaneous interventions, selection-induced changes in the flora responsible for hospital-acquired infections, and prolonged survival of immunocompromised hosts (eg, human immunodeficiency virus [HIV], steroids) have changed the incidence and bacterial spectrum of purulent pericarditis. Predisposing factors include pericardial effusion, immunosuppression, chronic diseases (eg, alcohol abuse, rheumatoid arthritis, chronic kidney disease, malignancy), cardiac surgery, and chest trauma. Pericardial involvement often is unrecognized when it complicates systemic infection; unusually high fever and high white blood cell counts are clues to the presence of pericarditis. Children and immunosuppressed patients of all ages are most vulnerable, and the characteristic features of acute pericarditis are frequently absent. The course of bacterial pericarditis is fulminant, often presenting with cardiac tamponade; adhesive and constrictive pericarditis are common sequelae in survivors and may develop suddenly and early. Less common complications of purulent pericarditis include mycotic aneurysms (most often *Staphylococcus* and *Salmonella* species in the thoracic aorta) and left ventricular and submitral pseudoaneurysms.[38] Pericarditis complicating systemic infection and sepsis may go unrecognized and misdiagnosed. Many patients lack the typical findings of pericarditis, and the diagnosis of purulent pericarditis often is made either at autopsy or after cardiac tamponade develops; empyema is a common antecedent. The threshold for echocardiography in the septic patient should be low, and whenever purulent pericarditis is suspected, the pericardial space should be explored and fluid and blood sent for extensive microbiologic testing. Bacterial pericarditis is treated with surgical exploration and drainage and appropriate systemic antibiotics. Fibrinolytics may be used to lyse fibrous adhesions, liquefy purulent exudate, and prevent constrictive pericarditis. Pericardiectomy may be required for dense adhesions, loculated and thick effusions, persistent infection, recurrence of tamponade, and constriction. Although fatal if untreated, mortality remains high (~40%) in those receiving proper therapy.[37,38]

Legionella infections account for approximately 10% of community-acquired pneumonias and may be associated with pericarditis more often than previously was appreciated. Studies suggest that patients with pericardial involvement tend to be younger and healthier than those without it. Recurrent pericarditis, effusion, and chronic constriction occur in approximately 20% to 30% of cases.[27] Pericarditis may be an early complication of Lyme disease.

Tuberculous Pericarditis

Tuberculosis is a major cause of pericarditis in nonindustrialized countries but an uncommon cause in developed countries with a low prevalence of tuberculosis.[1] Nevertheless, its incidence is increasing because of HIV infection; consequently, tuberculosis should be considered in the differential diagnosis of pericardial heart disease.[1,39]

Tuberculous pericarditis results from hematogenous spread of primary tuberculosis or from the breakdown of infected mediastinal lymph nodes, with the result that affected individuals generally lack the typical symptoms and signs of pulmonary tuberculosis. A delayed hypersensitivity response to protein antigens of the bacilli that penetrate the pericardium is responsible for the morbidity associated with tuberculous pericarditis.

Fever, weight loss, and night sweats occur early; pericardial pain and friction rubs are often absent. Enlargement of mediastinal lymph nodes is not routinely seen on chest radiography (CT or magnetic resonance imaging [MRI] is required), although an enlarged cardiac silhouette is common. Patients may present with tamponade or constriction, which may be subacute. A fibrinous pericarditis with caseating necrosis and mononuclear infiltrate gives rise to an effusive phase, which is often voluminous and hemodynamically significant. An adhesive phase follows resolution of the effusion and eventuates in dense, calcific adhesions with clinical constriction in > 30% of patients.[1,39]

A *definite diagnosis* of tuberculous pericarditis is based on the demonstration of the presence of tubercle bacilli in the pericardial fluid or tissue. However, a *probable diagnosis* of tuberculous pericarditis can be achieved with evidence of the disease elsewhere (eg, pulmonary tuberculosis) and concomitant pericarditis, a lymphocytic pericardial exudate with elevated unstimulated interferon-gamma, adenosine deaminase, or lysozyme levels. An *ex juvantibus diagnosis* is admitted only in countries with a high prevalence of tuberculosis with the demonstration of the response to empiric antituberculous therapy.[1,39,40] A presumptive diagnosis generally requires a history of contact and/or purified protein derivative conversion (although the latter lacks sensitivity and specificity).

A regimen consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol for at least 2 months, followed by isoniazid and rifampicin (total of 6 months of therapy), is effective in treating extrapulmonary tuberculosis. Treatment for 9 months or longer gives no better results and has the disadvantages of increased cost and increased risk of poor compliance. Tuberculous pericarditis has a high risk of evolving in constrictive pericarditis, usually within 6 months in effusive forms. Prompt antibiotic therapy is essential to prevent this progression, which occurs in 20% (especially in developed countries) to 40% of cases. Additional treatments that may be useful to prevent constriction include intrapericardial urokinase and adjunctive prednisolone for 6 weeks, which may halve this complication (to be avoided in HIV-infected patients because it increase the risk of HIV-associated malignancies).[1,39-41]

Pericardiectomy is recommended if the patient's condition is not improving or is deteriorating after 4 to 8 weeks of antituberculosis therapy (Class I recommendation; LOE: C).[1]

Human Immunodeficiency Virus Pericarditis

HIV is an important cause of pericardial heart disease. The presence of pericardial effusion was considered a negative prognostic predictor in past years. However, today, patients with HIV who are treated with highly active antiretroviral therapies (HAART) may have an etiologic spectrum of pericardial diseases that is similar to that of a non–HIV-infected population.[42]

Pericardial involvement may be a result of associated malignancies (eg, lymphoma and Kaposi sarcoma), viruses (including HIV), and opportunistic infections (eg, mycobacteria, cytomegalovirus, *Nocardia*, and cryptococci) and, irrespective of its cause, predicts a poor prognosis in patients with HIV infection if they are not treated by HAART. Large symptomatic pericardial effusion in patients with HIV infection should be aggressively investigated because two-thirds of these

cases have an identifiable cause. Tamponade in patients with HIV is mycobacterial (*Mycobacterium tuberculosis* or *Mycobacterium avium-intracellulare*) in origin in approximately one-third of patients.[42] Tuberculous pericarditis in those with HIV infection is associated with a lower risk of constriction.[1]

NEOPLASTIC PERICARDITIS

Neoplastic pericardial involvement is manifested by pericarditis or simple pericardial effusion (usually moderate to large, cardiac tamponade) related to metastatic lymphatic involvement (especially for lung cancer) or hematogenous spread (especially for breast cancer). In addition, lymphomas, leukemias, melanoma, and cancer of contiguous organs (eg, esophageal cancer) may also affect the pericardium. Only rarely is neoplastic disease primary (usually pericardial mesothelioma).[1,43-45]

Neoplastic pericardial disease may be manifested as pericarditis, pericardial effusion, effusive-constrictive pericarditis, or constrictive pericarditis. Masses may be diagnosed by imaging techniques.

The definite diagnosis is based on the confirmation of the malignant infiltration within the pericardium by cytology or pericardial biopsy. A probable diagnosis may be achieved by the detection of tumor markers in pericardial fluid (eg, carcinoembryonic antigen [CEA], cytokeratin 19 fragment [CYFRA 21-1]), although none of the tumor markers has been proven to be accurate enough for distinguishing malignant from benign effusions. Evidence of malignant disease elsewhere and concomitant pericarditis or pericardial effusion are also suggestive, although in almost two-thirds of patients with documented malignancy, pericardial effusion is caused by nonmalignant diseases (eg, radiation pericarditis, other therapies, opportunistic infections). The management of these patients require a multidisciplinary approach with oncologists, radiotherapists, and other subspecialty experts.[43]

PERICARDIAL DISEASES IN SYSTEMIC INFLAMMATORY DISEASES AND POST–CARDIAC INJURY SYNDROMES

Systemic inflammatory diseases (especially systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma, systemic vasculitides, Behçet syndrome, sarcoidosis, and inflammatory bowel diseases) are common causes of pericarditis or "apparently" isolated pericardial effusion. Up to 10% of patients with pericarditis (often recurrent) have a known systemic inflammatory disease, but rarely, pericarditis/pericardial effusion may be the first manifestation of the systemic disease. Usually the degree of pericardial involvement is related to the activity of the systemic disease. Moreover, concomitant myocarditis may be present as well, because it is also a cause of myocardial inflammatory involvement.[43,46]

A specific subgroup of these patients, especially children, may be affected by *periodic fevers* or *autoinflammatory diseases*. Periodic fevers are genetic disorders characterized by mutations of genes involved in the regulation of the inflammatory response, without involvement of specific T cells or autoantibodies. The most common autoinflammatory syndromes include familial Mediterranean fever, in which serositis episodes last only 1 to 3 days, and tumor necrosis factor receptor–associated periodic syndrome, in which the episodes last weeks. Mutations associated with these disorders are rare in recurrent pericarditis. A positive family history for pericarditis or periodic fevers, a poor response to colchicine, and the need for immunosuppressive agents are clues to the possible presence of an autoinflammatory disease. Genetic testing is required for the definitive diagnosis.[43]

The term *post–cardiac injury syndromes* includes a group of inflammatory pericardial syndromes (post–myocardial infarction pericarditis, post-pericardiotomy syndrome, and post–traumatic pericarditis). Such syndromes are presumed to have an autoimmune pathogenesis triggered by an initial damage to pericardial and/or pleural tissues, caused by either myocardial necrosis (late post–myocardial infarction pericarditis or Dressler syndrome), surgical trauma (post-pericardiotomy syndrome), accidental thoracic trauma (traumatic pericarditis), or iatrogenic trauma with or without bleeding (pericarditis after invasive cardiac interventions).[2,47] Such forms are increasing, especially in developed countries, as a result of the aging of the population and the widespread use of percutaneous coronary intervention.

Treatment of these forms is similar to that of idiopathic pericarditis, with use of aspirin/NSAID plus colchicine as a first-line therapy and corticosteroids as a valid option especially when patients are on oral anticoagulants and interaction with anti-inflammatory drugs is not wanted.[43,47]

RADIATION-INDUCED PERICARDIAL DISEASE

Prior chest radiation is an important cause of pericardial disease. Radiation therapy may affect not only the pericardium, but also the myocardium, heart valves, coronary arteries, and all mediastinal structures inducing fibrosis. Most cases are secondary to radiation therapy for Hodgkin lymphoma or breast or lung cancer, and serious radiation-induced pericardial disease was most often a result of radiation therapy of Hodgkin lymphoma. Today, lower doses and modern radiation therapy (shielding and dose calculation) have reduced the complications; radiation pericarditis has now dropped from 20% to 2.5% of cases.

Radiation can induce an early disease, with pericarditis with or without effusion, and a late disease, with constrictive pericarditis after 2 to 20 years and not necessarily preceded by pericarditis. This late disease may affect a variable number of patients (4%-20% of patients) and appears to be dose dependent and related to the presence of late pericardial effusion in the delayed acute phase. The effusion may be serous or hemorrhagic and has a high probability to develop fibrous adhesions. Therapies are similar to those employed in pericarditis and pericardial effusion.

The concomitant possible myocardial damage affects the prognosis because radiation-induced constrictive pericarditis has a worse outcome after pericardiectomy.[1,43,48]

TRAUMATIC PERICARDIAL DISEASE

Blunt and penetrating traumas are important causes of pericarditis, particularly among young men. Acute tamponade beginning very soon after trauma (pericardial injury syndrome), recurrent pericardial effusion, recurrent acute pericarditis (postpericardial syndrome), and chronic constrictive pericarditis are well-recognized complications.

Severe blunt trauma, as with a fall from a considerable height, can rupture the pericardium, resulting in the potentially fatal complication of herniation of the heart. This event should be suspected if the chest radiography shows pneumothorax or air in the mediastinum distributed between the heart and diaphragm.

The application of echocardiography in the trauma unit rapidly and accurately diagnoses hemopericardium in patients with potentially penetrating cardiac wounds. Failure to repair the injury responsible for tamponade is associated with a poor clinical outcome. Constrictive pericarditis may be delayed, presenting weeks or years after the injury.

CHYLOPERICARDIUM

Chylopericardium is a milky-white pericardial effusion comprised of chyle, the normal content of the lacteals (lymphatics of the small

intestine) and thoracic duct; the composition is variable but generally has a high content of chylomicrons, protein, and lymphocytes. The disorder is rare, but morbidity (a result of nutritional, metabolic, and immunologic abnormalities) and mortality are considerable. Although the majority of cases are asymptomatic, cardiac tamponade can occur. Acute pericarditis and chronic constriction may result from the irritant effects of chyle.

Chylous pericardial effusions generally follow traumatic (blunt or penetrating) or surgical injury (thoracic or cardiac) to the thoracic duct but may result from neoplastic obstruction of the duct (secondary chylopericardium); less commonly, they may be idiopathic (primary). Drainage and dietary manipulation are effective in approximately 55% of cases. Failure to respond to a diet rich in medium-chain triglycerides and pericardiocentesis warrants ligation of the thoracic duct and pericardiectomy. In cases deemed inappropriate for aggressive therapy, implantation of a valved pericardioperitoneal conduit has been helpful.

PERICARDIAL DISEASES IN RENAL FAILURE

Pericardial diseases in renal failure have been become less common than in the past but should be considered in the differential diagnoses for pericarditis and pericardial effusion. There are three main presentations of pericarditis in renal failure: (1) uremic pericarditis, occurring before renal replacement therapy or within 8 weeks from its initiation and related to retention of toxic metabolites; (2) dialysis pericarditis, occurring on dialysis (usually ≥ 8 weeks after its initiation); and (3) constrictive pericarditis, occurring only rarely.[1,4,49,50]

MYXEDEMA PERICARDIAL DISEASE

Pericarditis with effusion (sometimes containing cholesterol) occurs in approximately one-third of patients with myxedema. Effusions develop slowly and may reach a prodigious size; slow resolution usually follows the institution of thyroid replacement therapy. Pericardial drainage is generally not indicated because myxedema effusions seldom cause tamponade.[1]

PERICARDIAL EFFUSION

Pericardial effusions are commonly encountered in routine cardiovascular practice, with clinical presentation ranging from an incidental finding to cardiac tamponade. The incidence of pericardial effusion is unknown; it has been reported to be present in 9% of echocardiograms performed at a European tertiary care center specializing in diseases of the pericardium.[51] The differential diagnosis of a pericardial effusion is extensive, and the management of pericardial effusion depends on disease progression and its hemodynamic consequences.

CLINICAL PRESENTATION AND ETIOLOGIES

Pericardial effusions can be classified according to their temporal development: acute, subacute, and chronic (typically longer than 3 months).[3] Pericardial fluid accumulates when there is an increase in its production as a result of inflammation of the serosal layers; alternatively, pericardial effusions can occur in the setting of impaired lymphatic drainage of the pericardial space as a result of increased central venous pressure (as observed in heart failure or severe pulmonary hypertension). Effusions will have characteristics of an exudate in the former and of a transudate in the latter. The anatomy of pericardial lymphatics and their communication with other thoracic structures, such as the pleura and the breasts, explain pericardial involvement in pulmonary/pleural disorders and malignancies.

The volume of a pericardial effusion can range from trivial to large. The assessment of the size of pericardial effusions is most frequently done by transthoracic echocardiography. Quantification of pericardial effusion size is subjective and varies as the pericardial fluid shifts according to the patient's body position (for example, increase in the size of a posterior pericardial effusion in the supine positon). The size of the pericardial effusion has prognostic implications; a large effusion in the setting of acute pericarditis is associated with a high risk of developing cardiac tamponade.[13] Echocardiography also differentiates circumferential from loculated effusions.

Data from multiple studies suggest that idiopathic pericardial effusions are the most common (approximately 50% in some series) in developed countries, followed by infectious causes and cancer (15%-20% each) and connective tissue disorders.[52-54] In developing countries, tuberculosis continues to be the predominant etiology, accounting for 50% to 60% of the cases.[54] Essentially all causes of pericarditis (as depicted in Table 66–2) can manifest as pericardial effusion. Additional causes include iatrogenic causes (after intervention or device placement); postinjury causes (following myocardial infarction, postpericardiotomy syndrome), and less commonly, drugs or systemic disorders (such as hypothyroidism). Transudative effusions might also occur as a result of hypoalbuminemia in the setting of liver or kidney diseases or as a result of high hydrostatic pressure, as seen in heart failure. The presence of pericardial effusions in patients with pulmonary hypertension should be noted because it has been described as a poor prognostic feature in that population.[55]

The clinical presentation of patients with pericardial effusion will vary according to the underlying process, rate of accumulation, and hemodynamic effect. Patients presenting with acutely developing pericardial effusion, as in thoracic trauma, cardiac perforation, or aortic dissection, might present with rapid hemodynamic deterioration secondary to cardiac tamponade despite relatively small pericardial effusions. Conversely, in chronic pericardial effusions, symptoms might develop over weeks or even months, and patients might be entirely asymptomatic, with the effusion being an incidental finding during thoracic imaging or transthoracic echocardiography. Symptoms may include atypical chest pain or fullness, exertional dyspnea, orthopnea (rarely), or other less specific findings such as cough, malaise, or fatigue. Compression of local structures can lead to dysphagia, hoarseness, or hiccups.

PHYSICAL EXAMINATION

The diagnosis of pericardial effusion at the bedside is difficult and essentially of historical interest. The roles of physical exam in patients with pericardial effusion are, first, to assess the hemodynamic consequences of the pericardial effusion and, second, to identify signs suggestive of underlying causes (such as signs of myxedema). Heart rate and blood pressure should be manually recorded, and the presence of pulsus paradoxus (Fig. 66–9) should be sought. A thorough examination of the jugular veins is mandatory to determine whether cardiac tamponade is present (the details of the physical examination in the diagnosis of cardiac tamponade are discussed below). In uncomplicated pericardial effusions, distant heart sounds might be present, but cardiac examination might be otherwise unremarkable. Lastly, pericardial rubs may be auscultated in patients with concomitant pericarditis.

EVALUATION AND TESTING

The chest radiograph reveals enlargement of the cardiac silhouette in large effusions, but chest radiographs might be entirely normal in patients with pericardial effusions. ECG findings include low QRS

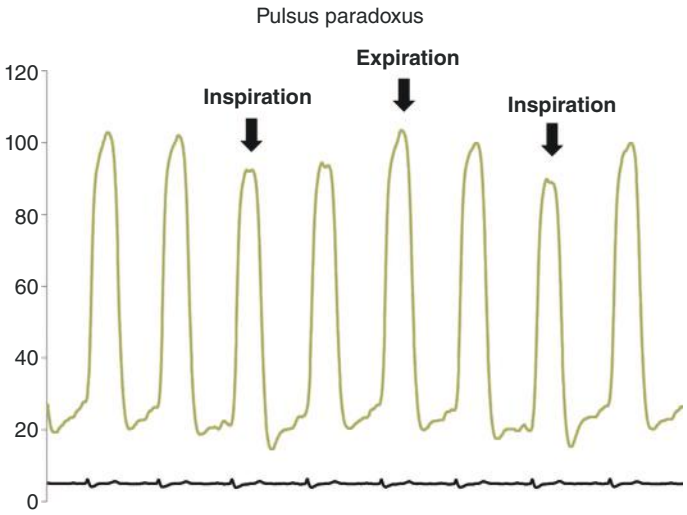


FIGURE 66–9. Pulsus paradoxus in a patient with cardiac tamponade. Note the marked drops in left ventricular systolic pressures upon inspiration; similar findings will be observed during noninvasive blood pressure measurement.

voltage and *electrical alternans* (Fig. 66–10; beat-to-beat variations in the QRS amplitude as a result of changes in cardiac position in the setting of the effusion). In patients with pericardial effusion related to acute pericarditis, typical ECG changes of pericarditis might be present. Some patients with pericardial effusions might have entirely normal ECGs.

Pericardial effusions are most often identified by transthoracic echocardiography but might also be incidentally found during radiologic thoracic imaging (for example, during staging or follow-up of patients with known cancer). Echocardiography is the main diagnostic tool in the evaluation of pericardial effusion and should be performed in all patients (Class I recommendation; LOE: C)[1] because it allows the assessment of its size, location, and hemodynamic consequences (presence of tamponade physiology). The presence of trivial effusions (only noticeable during ventricular systolic) is not uncommon and of no clinical consequence ("physiologic" effusions). Although objective quantitation of the size of the pericardial effusion is recommended[1] (free pericardial space in diastolic < 10 mm in small, 10-20 mm in moderate, and > 20 mm in large effusions), estimation of the size of pericardial effusion is mainly qualitative in clinical practice. Echocardiography is also indicated during pericardiocentesis.

The determination of the cause of the pericardial effusion might be challenging, and additional testing should be performed, taking into account the clinical scenario and the patient's social and travel history. Given the prevalence of tuberculosis in developing countries (and among immigrants in developed countries), its diagnosis should always be considered and ruled out in those patients; HIV testing should also be performed. If bacterial pericarditis is suspected, prompt diagnostic pericardiocentesis is mandatory. Serum inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) should be measured (Class I recommendation; LOE: C).[1] The need for pericardiocentesis in the evaluation of the etiology should be individualized. A diagnostic algorithm is proposed in Fig. 66–11.[3] Patients presenting with acute pericarditis, elevated inflammatory markers, and no signs of cardiac tamponade might be medically managed. Patients with small and moderate effusions can be safely observed. Diagnostic pericardiocentesis should be reserved for patients with large pericardial effusions or where the diagnosis of pericardial involvement would have management implications (such as in some malignancies).

Table 66–11 summarizes routine pericardial fluid testing and accompanying etiologies. Analysis of pericardial fluid can discriminate exudates from transudates, but this distinction has limited diagnostic implications. Low glucose levels are more frequently encountered in infectious or malignant effusions. Total white blood cell count and differential white blood cell count rarely have meaningful diagnostic or management implications. A pericardial fluid–to–serum hemoglobin ratio ≥ 0.5 of the plasma hemoglobin is diagnostic of hemopericardium.

Bacterial and mycobacterial cultures should be performed if bacterial infection or tuberculosis is suspected, respectively. Acid-fast bacilli

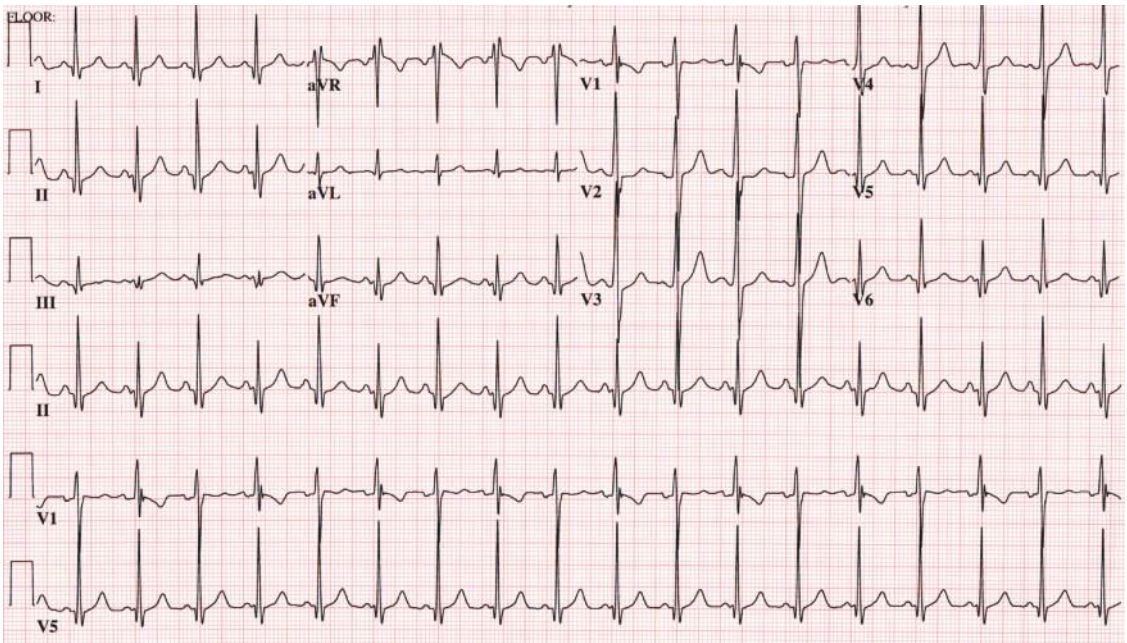


FIGURE 66–10. Electrocardiogram demonstrating features of electrical alternans. Electrocardiographic findings in a patient with a large pericardial effusion; please note the beat-to-beat variation in QRS amplitude. Changes in QRS axis are also evident, best appreciated in lead V_1. Used with permission from Dr. Peter A. Brady, Mayo Clinic, Rochester, MN USA.

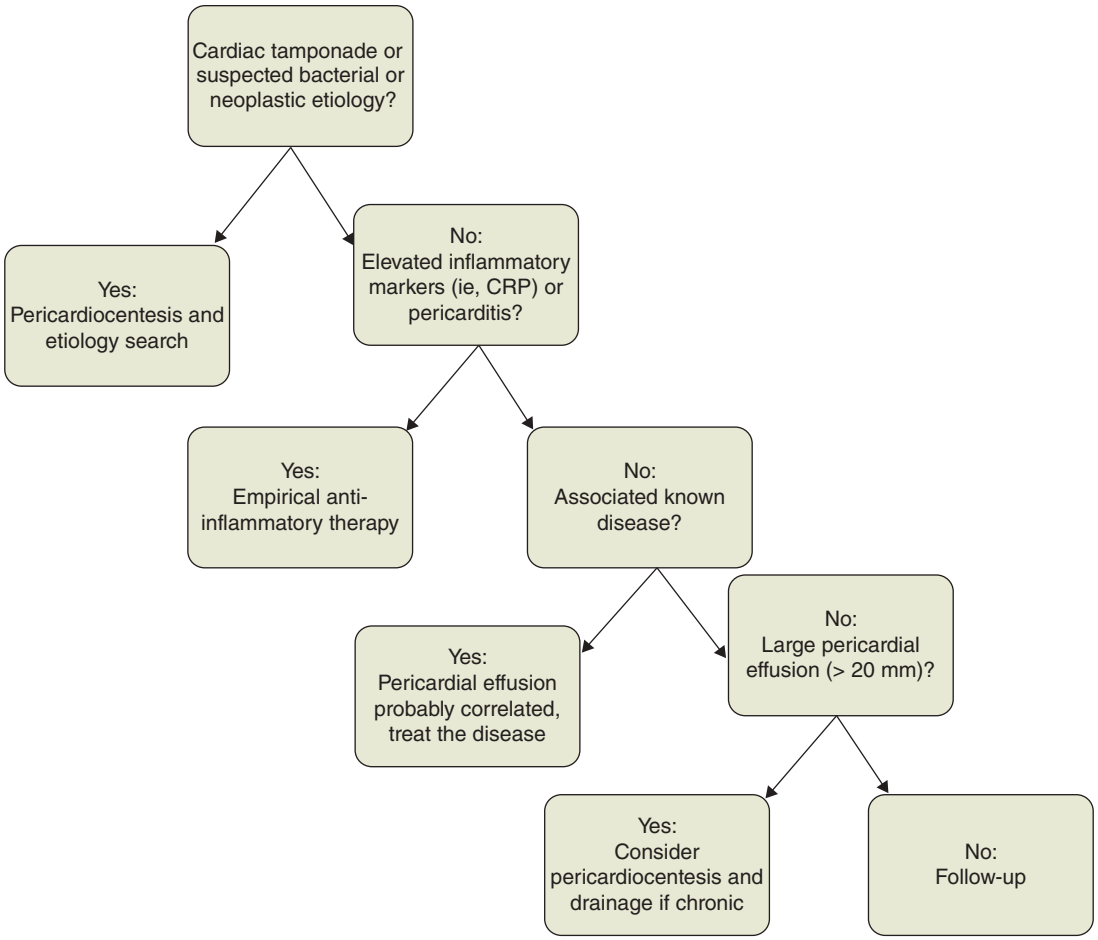


FIGURE 66–11. Simplified algorithm for the triage and management of patients with pericardial effusion. CRP, C-reactive protein. Reproduced with permission from Imazio M, Adler Y. Management of pericardial effusion. *Eur Heart J.* 2013 Apr;34(16):1186-1197.

TABLE 66–11. Pericardial Fluid Analysis

Analysis	Test	Etiology
Chemistry	Specific gravity > 1015, protein level > 3 g/dL, protein fluid/serum ratio > 0.5	Exudate
	LDH > 200 mg/dL, fluid/serum ratio > 0.6[a]	
	Glucose, blood cell count	
Cytology	Cytology (higher volumes of fluid, centrifugation, and rapid analysis improve diagnostic yield)	Cancer
Biomarkers	Tumor markers (ie, CEA > 5 ng/mL or CYFRA 21-1 > 100 ng/mL)	Cancer
	Adenosine deaminase > 40 U/L, interferon-γ	Tuberculosis
Polymerase chain reaction (PCR)	PCR for specific infectious agents (eg, tuberculosis)	Tuberculosis
Microbiology	Acid-fast bacilli staining, *Mycobacterium* cultures, aerobic and anaerobic cultures	Tuberculosis Other bacteria

Abbreviations: CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase.

[a]These chemical features have been especially validated for pleural fluid and not pericardial fluid, although generally used also for pericardial effusion

staining, adenosine deaminase, pericardial lysozyme, and interferon-γ levels, as well polymerase chain reaction testing, should be added in the evaluation of tuberculous pericarditis.[56] Patients with tuberculous pericarditis have a high risk of developing constrictive pericarditis (30%-50% in some series[57,58]); thus, a high index of suspicion is needed in those at risk.

Pericardial effusion cytology should be performed (the largest volume possible sent to increase its yield) when malignancy is either known or suspected. Specific tumor marker levels (eg, CEA, cancer antigen [CA]-125) can also be measured in the pericardial fluid if malignant effusion is a possibility. Lastly, although some groups include pericardioscopy and pericardial biopsy in the workup of pericardial effusions, this is rarely performed by our group.

Additional imaging can also provide further information in the workup of patients with pericardial effusions (Class IIa recommendation; LOE: C).[1] CT allows additional assessment of the size and location of the fluid collection, as well as differentiation between pericardial fluid versus pericardial thickening (which can be challenging echocardiographically). It also permits detection of associated thoracic abnormalities (such as tumors) or identification of pericardial masses. CMR has the advantage of assessing the presence and degree of pericardial inflammation and concomitant myocardial involvement in the case of myopericarditis. The cost and availability of MRI (especially in the acute setting) are potential limiting factors; the use of gadolinium is required to assess inflammation; however, this is contraindicated in some patients (as in those with advanced renal insufficiency).

TREATMENT

Therapy should be directed at the underlying cause (Class I recommendation; LOE: C)[1]; if pericarditis is present, treatment of pericarditis is the goal. For patients with idiopathic effusions (especially if inflammatory markers are elevated), a combination of a NSAID and colchicine is recommended (Class I recommendation; LOE: C)[1]; viral pericardial effusions are also often responsive to this regimen. In cases of relapsing pericardial effusions, a longer treatment course should be prescribed. Corticosteroids should not be used as first-line therapy and should be limited to special situations (treatment of concomitant systemic disease) or in patients for whom NSAID are contraindicated.[1] The use of other immunosuppressant agents (eg, azathioprine) should be reserved to a multidisciplinary team (eg, cardiologists, rheumatologists) with expertise in the management of refractory pericarditis. Limited data are available on the use of topical (intrapericardial) steroid therapy, and it is currently not routinely recommended.

Aspirin is recommended as first-line therapy in post–acute myocardial infarction pericarditis (Class I recommendation; LOE: C)[1] given the risk of impaired myocardial healing and expansion of the infarct zone seen with other agents.[59] Corticosteroids should be reserved for refractory cases because it might affect myocardial healing.

The details regarding pericardiocentesis are described in the section on cardiac tamponade; postprocedurally, the intrapericardial catheter should be kept in place until output is lower than 30 mL over 24 hours; this promotes adhesion of pericardial layers, limiting fluid reaccumulation and reducing the need for repeat pericardiocentesis. Pericardial window or balloon pericardiostomies can be performed in patients with refractory recurrent pericardial effusions and cardiac tamponade (most commonly secondary to malignant effusions).[3] Pericardiectomy might also be an option in selected cases but should only be performed in centers with surgical expertise.

The prognosis of pericardial effusions is related to its underlying etiology. It has been suggested that large pericardial effusions carry a 30% chance of cardiac tamponade[60]; close follow-up is recommended in those circumstances. The risk of developing constrictive pericarditis is very small in idiopathic pericarditis,[27] even if relapse is present. Given the higher risk in bacterial or tuberculous pericarditis, those patients also require more frequent re-evaluation. Pericardial guidelines do not provide specific recommendations regarding follow-up. Patients with small effusions who respond to therapy do not need long-term follow-up. Patients with moderate to large effusions should be evaluated at the end of their therapy course with repeat imaging; at that point, the need for continuous follow-up (every 3 or 6 months) is reassessed.

CARDIAC TAMPONADE

Cardiac tamponade corresponds to a corollary of hemodynamic derangements that are secondary to increased intrapericardial pressure and impaired cardiac filling. Essentially any form of disease that affects the pericardium can potentially lead to cardiac tamponade. Although normally associated with pericardial fluid (effusion), tamponade may also occur when blood, pus, or clots occupy the pericardial space.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

Although usually considered in the differential diagnosis of patients presenting with shock and acute hypotension, the clinical presentation of cardiac tamponade depends on the *tempo* with which pericardial fluid accumulates and intrapericardial pressures rise. Intrapericardial pressures will directly reflect pericardial compliance, as illustrated in pericardial pressure-volume curves (see Fig. 66–3). When the pericardial volume changes acutely (eg, cardiac perforation secondary to a procedure or as a result of aortic dissection), a small amount (as little as 150 mL) of fluid in the pericardial space results in a significant, abrupt elevation in intrapericardial pressure and can lead to sudden hemodynamic decompensation. Conversely, in the setting of chronic pericardial effusions, the pericardium "stretches out" and is sometimes able to accommodate liters of fluid without major hemodynamic consequences. As illustrated on curve B in Fig. 66–3, the pressure-volume curve is much less steep if the increase in pericardial pressure develops subacutely or chronically.

A good understanding of the pericardial pressure-volume curves is not merely academic; it is critical for the proper management of patients with pericardial effusion. First, it shows that cardiac tamponade is part of a clinical spectrum. Patients might present acutely, but cardiac tamponade can also be an insidious process, where subtle, subclinical hemodynamic abnormalities develop as patients approach the steep part of the curve (*decompensated* cardiac tamponade). Second, it illustrates that once at the steepest portion of the pressure-volume curve, very small changes in pericardial volume can lead to profound changes in intrapericardial pressure and overall hemodynamics. This is of extreme clinical importance; patients presenting with decompensated cardiac tamponade who "stabilize" with vasopressors or intravenous fluids are not truly stable, and pericardiocentesis should not be delayed. A positive clinical response to removal of a small amount of pericardial fluid is not a reassuring finding; the pericardial space should be fully drained. If the former approach is pursued, prompt reaccumulation of a small volume of pericardial fluid might have catastrophic consequences.

As intrapericardial pressure rises in patients with cardiac tamponade, elevated pericardial pressure is transmitted to all four chambers, affecting diastolic filling. As a result, right atrial transmural pressure decreases markedly and systemic venous pressure increases. As a result of pericardial restraint from a now distended, inelastic pericardium, right ventricular filling occurs at the expense of left ventricular filling—the so-called *enhanced ventricular interaction* or *ventricular interdependence*. Although some degree of ventricular interdependence is always present, the changes that occur in cardiac tamponade correspond to marked, pathologic exaggeration of normal pericardial physiology. As a result, with inspiration, right ventricular stroke volume increases (secondary to increased venous return) while left ventricular stroke volume decreases (this is the origin of pulsus paradoxus); the opposite occurs during expiration. As right ventricular diastolic filling is further compromised, both ventricles become underfilled, and cardiac output decreases. Tachycardia and increased peripheral vascular resistance initially compensate for the reduction in stroke volume, but as pericardial pressures increase further, the reduction in cardiac output leads to hypotension, shock, and ultimately death unless the pericardial effusion is drained.

Cardiac tamponade should always be considered in patients presenting with shock and elevated venous pressure, unexplained hypotension, clinical decompensation in the setting of known pericardial effusion, recent intracardiac manipulation (cardiac catheterization, transseptal puncture, pacemaker implantation, electrophysiology ablation) or intrapericardial (pericardial access) procedures, or after trauma or cardiac or thoracic surgery. Its diagnosis can be challenging, particularly when several other possible causes for hypotension/shock are present (eg, following trauma or cardiac operation). Thus, a high index of suspicion is needed, and the diagnosis of cardiac tamponade should be actively sought by clinical and imaging techniques. Conversely, patients with insidious development of cardiac tamponade might complain of reduced functional capacity, nonspecific chest pain, or simply fatigue. We discourage the use of the terms *medical cardiac tamponade* and *surgical cardiac tamponade* because they generate confusion and have no etiologic or management implications.

PHYSICAL EXAMINATION

Tachycardia (heart rate > 100 bpm in adults) is usually present, but some patients might have heart rates at the upper end of normal (90-100 bpm). Hypotension is a classic sign of cardiac tamponade, but relative hypotension might be present in patients who are hypertensive at baseline (*hypertensive tamponade*). Blood pressure should be manually measured in patients with possible tamponade with special attention to the presence of pulsus paradoxus (see Fig. 66–9). In normal patients, systolic blood pressure should not drop more than 10 mm Hg upon inspiration. The presence of "pulsus" might be subtle, and proper technique needs to be applied. The blood pressure cuff should be inflated to 15 to 20 mm Hg above the systolic blood pressure (determined by palpation and then auscultation). The cuff should then be slowly deflated and the Korotkoff sounds meticulously auscultated while the patient breathes normally; the sounds will show respirophasic changes, decreasing (or even disappearing) with inspiration. At a certain pressure, these respirophasic changes will be no longer noticeable, and the expiratory and inspiratory Korotkoff sounds will be similar. The "pulsus" will correspond to the pressure difference between the two points and should be recorded (eg, 12 mm Hg).

Inspection of the jugular veins will show elevation in central venous pressure; venous distention may or may not be present. Analysis of the venous wave contour will reveal absence or blunting of the *y* descent, representing impaired ventricular diastolic filling. If pericardiocentesis is performed, pre- and post-estimated venous pressure and venous contour should be recorded. Persistence of elevation in central venous pressure following pericardial effusion drainage suggests that the cardiac tamponade has not been totally relieved or that effusive-constrictive pericarditis is present (in this case, blunting will be replaced by deepening of the *y* descents).[61]

The apical impulse might not be palpable or might be hyperkinetic. Cardiac auscultation might reveal distant heart sounds. Because early diastolic filling is profoundly impaired, a third heart sound should never be present; its occurrence suggests an alternative diagnosis. For unclear reasons, tamponade does not lead to pulmonary edema; the lungs should be clear on auscultation in patients with isolated cardiac tamponade.

Although classically described as a sign of cardiac tamponade, *Beck's triad*—hypotension, distended neck veins, and distant heart sounds—is rarely present, and therefore, its absence should not influence the evaluation of patients with suspected cardiac tamponade.[62]

EVALUATION AND TESTING

ECG frequently shows sinus tachycardia; electrical alternans (see Fig. 66–10) might be present, where QRS amplitude will vary with each cardiac beat as a result of the swinging motion of the heart in the large effusion; changes in P and QRS axes might also be present. Low QRS amplitude might be seen and can be caused by the effusion or underlying myocardial disease. Lastly, ST-T changes associated with underlying pericarditis might be also be noted.

Chest radiography might reveal a very enlarged cardiac silhouette in the setting of a large pericardial effusion but might be entirely normal. In isolated cardiac tamponade, pulmonary parenchymal abnormalities should not be seen; pleural effusions might be found in the case of a pleuropericarditic process.

Two-dimensional and Doppler transthoracic echocardiography is the key diagnostic tool in the evaluation and management of patients with cardiac tamponade (Class I recommendation; LOE: C).[1] First, echocardiography confirms the presence of pericardial fluid (or clots; Fig. 66–12). Although the size and location of an effusion are

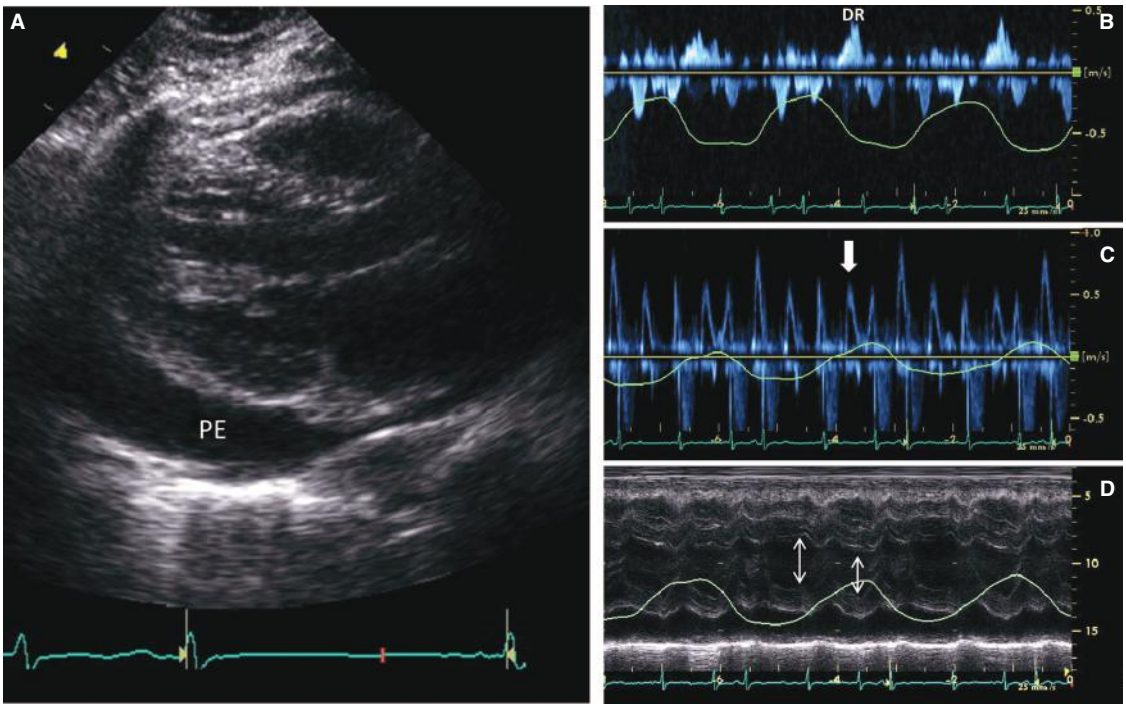


FIGURE 66–12. Two-dimensional and Doppler echocardiographic findings in a patient with cardiac tamponade. **A.** Parasternal long-axis view shows a large pericardial effusion (PE). **B.** Characteristic hepatic vein pulsed-wave Doppler findings are shown with prominent expiratory diastolic reversal (DR); marked variations in mitral inflow pulsed-wave Doppler are also present (**C**; inspiration marked by the *thick arrow*). Respirophasic shifts in the interventricular septum (increased ventricular interdependence) are shown by M-mode at the midventricular level (**D**); note the respirophasic changes in left ventricular size (*thin arrows*). A simultaneous respirometer (*light green tracing*) was used during echo-Doppler data acquisition; upstroke (movement away from the electrocardiogram) occurs during inspiration, and down stroke occurs during expiration.

important for planning and feasibility of pericardiocentesis, the size of the effusion (small vs large) does not favor or exclude the presence of cardiac tamponade. An important part of the echo-Doppler examination in patients with suspected tamponade is the evaluation of the inferior vena cava; it is typically dilated (*plethoric)* and shows diminished (< 50%) or absent collapse with "sniffing maneuver." An entirely normal inferior vena cava makes tamponade unlikely. Signs of impaired diastolic filling can be evidenced by two-dimensional echocardiography, illustrated by collapse of the right ventricular or right atrial walls during diastole (collapse of the left atrium is less common). The hallmark of pericardial restraint, ventricular interdependence is manifested as respirophasic changes in the interventricular septum motion (see Fig. 66–12). Doppler signs of tamponade physiology included respirophasic changes in mitral inflow (see Fig. 66–12) and left ventricular stroke volume (echocardiographic equivalent of pulsus paradoxus). The most specific finding, however, is the presence of expiratory flow reversals in the hepatic veins (see Fig. 66–12).[63-65] The use of a respirometer facilitates timing of inspiratory and expiration and should always be performed in the evaluation of patients suspected of having tamponade or constriction.

Cardiac catheterization will show elevation in right- and left-sided filling pressures with equalization of end-diastolic pressures. In acute tamponade, however, left-sided filling pressures might be lower as a result of significant underfilling of the left ventricle. Although discordance of right and left ventricular systolic pressures might be present, as opposed to constrictive pericarditis, rapid filling waves will not be seen on ventricular tracings. The main diagnostic feature of cardiac tamponade is blunting or absence of *y* descents on right atrial tracings (Fig. 66–13) as a result of impaired right ventricular early diastolic filling[66]; the *y* descents should normalize after pericardiocentesis.

Classical teaching states that cardiac tamponade is a clinical diagnosis and should not be based on testing alone. Once the clinical diagnosis is made, patients should undergo pericardiocentesis. However, cardiac tamponade is part of continuum and not an all-or-none phenomenon; patients in earlier stages may have "tamponade physiology" (typically by echocardiography) on complementary testing before overt (decompensated) clinical signs develop. This can also be the case in chronic cardiac tamponade. The management of those patients should be individualized, and intervention should be based on clinical status, risks of the pericardiocentesis (location and size of the effusion), and expertise of the proceduralists.

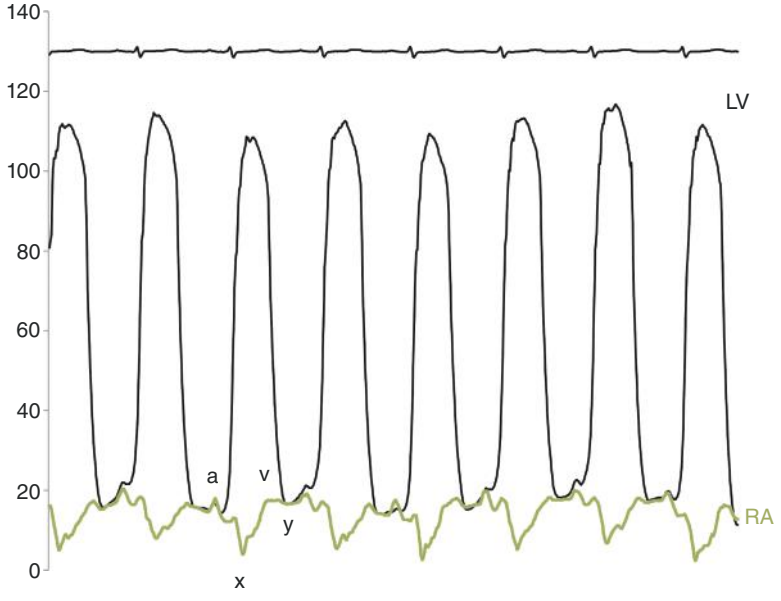


FIGURE 66–13. Cardiac catheterization hemodynamic tracing from a patient with cardiac tamponade. Right atrial (RA, *red line*) pressure tracings show prominent *x* descent and blunting of the *y* descent, representing impaired ventricular diastolic filling, which is the hallmark of cardiac tamponade. Please also note the elevated filling pressures and the presence of pulsus paradoxus on the left ventricular (LV) pressure tracings (*black*).

TREATMENT

Cardiac tamponade is a cardiac emergency and should be treated with prompt needle pericardiocentesis unless it is caused by aortic dissection. The procedure should be done with transthoracic echocardiographic guidance by an experienced operator. Blind pericardiocentesis should only be performed in extreme, life-threatening circumstances. If proper technique is applied, complications rates are low.[51] The goal should be aspiration of all pericardial fluid. The use of simultaneous right atrial pressure measurement is not mandatory and varies between groups; at our institution, invasive pressure recording is not routinely performed during pericardiocentesis.

During echo-guided pericardiocentesis, the largest collection of fluid in closest proximity to the chest wall should be identified, defining the optimal site for needle entry. Echocardiography also confirms the absence of interposed lung or liver tissue. The angle of the transducer should orient the trajectory of the needle. In our published experience, major complications occurred in 3% of cases; the most common site of entry was para-apical (70% of cases).[44] Complications include cardiac or coronary perforation, hemothorax or liver injury, pneumothorax, and pneumopericardium.[67]

The daily output of pericardial fluid is recorded. The pigtail catheter should not be removed until the output is less than 30 mL over a 24-hour period. It is our practice to repeat a limited echocardiogram to reassess the effusion size and areas of loculation before the intrapericardial catheter is removed. The need for surgical pericardiocentesis is rare and involves less common circumstances (eg, removal of clots or pus) or simultaneous repair of damaged cardiac structures.

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis results from inflammation and/or scarring of the pericardium, leading to impairment of cardiac filling.[68] Therefore, constrictive pericarditis is a form of diastolic heart failure. The importance of the diagnosis lies in the fact that pericardial constriction is a potentially curable disease and carries a very poor prognosis if left untreated.[69]

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

Constrictive pericarditis develops after an injury to the pericardium results in ongoing pericardial inflammation and ultimately fibrosis. This process might be acute (over the course of days), subacute, or chronic; in acute cases, inflammation prevails, whereas fibrosis tends to be predominant in chronic forms of the disease. Pericardial inflammation may resolve spontaneously or with anti-inflammation therapy, but the pericardium typically becomes fibrotic or scarred if not resolved within 3 months. The reason why some patients will evolve to have constrictive pericarditis after an acute event is unclear; however, certain etiologies (eg, tuberculous pericarditis) are associated with higher risk of developing

constrictive pericarditis.[27,58] The disease also appears to favor men over women (2:1 ratio).[68] Although, constrictive pericarditis is primarily a pericardial disease, subepicardial myocardial atrophy might be present[70] (particularly in long-standing cases), leading to concomitant myocardial systolic and diastolic dysfunction. A mixed pattern is also seen in patients who develop constriction after cardiac surgery or radiation therapy.

Given the abnormal pericardial compliance, diastolic filling is significantly impaired in patients with constrictive pericarditis (steeper increase in pressure per change in volume in the pressure-volume curve). As a consequence, cardiac filling pressures increase and cardiac output falls as stroke volume decreases. The thickened pericardium (Fig. 66–14) has limited expansion, and cardiac chambers "compete" for pericardial space during diastolic filling. With respiration, an increase in preload in one ventricle occurs at the expense of filling in the other (ventricular interdependence). The abnormal pericardium insulates the heart from respirophasic changes in intrathoracic pressures, and negative pressures generated by inspiration are not transmitted to cardiac chambers. This contributes to decreased filling of the left atrium and ventricle upon inspiration as a result of decreased pressure gradient between pulmonary veins and left atrium (pulmonary veins are located outside the pericardium). These physiologic changes can be appreciated by both invasive hemodynamic and noninvasive hemodynamic assessment and are used for the diagnosis of constrictive pericarditis.

Patients with constrictive pericarditis typically present with features of right-sided heart failure right-sided heart failure, manifested by elevated venous pressure, ascites, and leg edema. Pericardial constriction must also be considered when right heart failure is disproportional to the degree of pulmonary congestion or in patients presenting with heart failure following cardiac surgery. For unknown reasons, patients with constrictive pericarditis are more prone to the development of ascites than other patients with right heart failure; the ascites is often more striking than lower extremity edema. Additional common complaints are fatigue, decreased functional capacity, and head fullness. Orthopnea and paroxysmal nocturnal dyspnea are not usually observed and suggest another etiology. In more advanced stages, liver and renal dysfunction might be present.

ETIOLOGIES

Causes of constrictive pericarditis are illustrated in Table 66–12. The epidemiology of the disease has substantially changed over the past 50 to 60 years, with the advances in and increased use of cardiac surgery. Data from the Mayo Clinic showed that the 72% of cases of constrictive pericarditis seen between 1936 and 1982 were idiopathic, whereas only 2% involved patients with prior cardiac surgery.[71] Between 1996 and 2006, postoperative cases accounted for 34%, whereas the prevalence of idiopathic cases decreased to 18%.[72] This shift in epidemiology has also been shown by other US and European centers.[73-75] Constrictive pericarditis occurs in 0.2% to 0.4% of patients undergoing cardiac surgery and, on average, occurs 2 years after the surgical procedure.[76,77]

In areas where tuberculosis is still prevalent (such as Africa and India), tuberculous pericarditis continues to be most common cause of pericardial constriction.[78,79] Thus, a thorough travel and social history should be obtained in the evaluation of patients with constrictive pericarditis. A history of radiation therapy is also of great importance, given the risk of concomitant myocardial and valvular disease, which has diagnostic and therapeutic implications.

TABLE 66–12. Etiologies of Constrictive Pericarditis

Idiopathic
Post–cardiac surgery
Connective tissue disorders
Radiation induced
Tuberculous
Neoplastic
Purulent
Uremia
Other (rare)
Trauma, sarcoid, parasites, drug induced (procainamide, methylsergide), asbestos

PHYSICAL EXAMINATION

General examination will typically reveal muscle wasting, increased abnormal girth, and leg edema, with patients usually appearing ill. In patients with a subacute course, those findings can be absent, and the complaints will appear out of proportion to the patient's "healthy" appearance. Abdominal exam will show signs of liver enlargement and ascites; signs of cirrhosis should be noted because the presence of liver failure has implications regarding surgical risk. Pleural effusions are commonly present, but rales should not be expected.

Detailed assessment of jugular venous pressure is mandatory in the evaluation of constrictive pericarditis. Elevated central venous pressure is essentially always present, unless the patient has been aggressively diuresed. If the venous pulse cannot be seen with the patient sitting, he or she should be asked to stand; failure to do this will preclude proper analysis of venous pressure and contour in patients with very elevated filling pressures. The *Kussmaul sign* corresponds to an increase in venous pressure associated with inspiration; however, this is not pathognomonic of constriction and can be seen in other situations where severe elevation in right atrial pressure is present. Jugular venous waveforms will show prominent *y* descents or sometimes prominent *x* and *y* descents (if sinus rhythm is present and there is absence of significant concomitant myocardial disease)—the *W* or *M* pattern. It should be noted that if constrictive pericarditis

A B

FIGURE 66–14. Pericardial thickness. **A.** Normal parietal pericardium (< 1 mm thick). **B.** Abnormally thickened parietal pericardium in the setting of pericardial constriction. The pericardium may or may not be calcified and, in some instances, may be near 1 cm thick. Used with permission from Dr. Joseph J. Maleszewski, Mayo Clinic, Rochester, MN USA.

is present, the predominant waves are the descents (down strokes), which is the opposite of normal. In severe tricuspid regurgitation, although a deep *y* descent will be present, the predominant wave is a positive one, the large *v* wave. Restrictive cardiomyopathy can be associated with deep *y* descents, and the distinction between restriction and constriction at the bedside can be extremely challenging.

Auscultation might reveal the presence of low-pitched third heart sounds, and these can sometimes only be heard during inspiration or expiration. The presence of a high-pitched early diastolic sound (slightly earlier than a typical third heart sound)—the *pericardial knock*—is specific but not a sensitive sign that constrictive pericarditis is present. A loud pulmonary component of the second heart sound is not usually heard and should suggest the presence of a concomitant myocardial process.

FIGURE 66–15. Chest radiograph demonstrating pericardial calcification. Posteroanterior (*left*) and lateral (*right*) chest radiography in patient with calcific constrictive pericarditis showing extensive pericardial calcification.

EVALUATION AND TESTING

ECG usually shows nonspecific ST-T wave abnormalities; atrial fibrillation occurs commonly in patients with constrictive pericarditis. *P mitrales* (broad, notched P waves in lead II) in the absence of mitral disease has also been described as a sign of constrictive pericarditis.[80] Chest radiography may reveal pericardial calcification (Fig. 66–15), although this is not a sensitive or specific sign and is seen in only 25% to 30% of cases.[81] Pleural effusions are frequently present. Plasma brain natriuretic peptide levels appear to be lower in patients with constrictive pericarditis compared to patients with myocardial restrictive disease.[82]

Echocardiography is now the main diagnostic tool in the evaluation of constrictive pericarditis; it also helps to assess the patient for classic mimickers of constrictive physiology, such as severe tricuspid regurgitation and myocardial restrictive disease. Guidelines recommend transthoracic echocardiography to be performed in all patients with suspected constrictive pericarditis (Class I recommendation; LOE: C).[1] In our practice, transthoracic echocardiography can diagnose constrictive pericarditis in 75% of cases.[72] Echocardiographic features of constrictive pericarditis[15,68,83] include septal notching and flattening of the posterior left ventricular wall seen on M-mode, diastolic bounce (or shudder) of the interventricular septum, respirophasic variations in tricuspid and mitral inflow echo-Doppler (Fig. 66–16), restrictive mitral valve inflow pulse-wave Doppler, and "annulus reversus" (medial e′ velocity greater than lateral e′ on mitral annular tissue Doppler) (see Fig. 66–16). Given the multitude of echocardiographic findings and with the aim of simplifying the diagnosis of constrictive pericarditis, our group proposed the use of the following three echocardiographic criteria for its diagnosis (Mayo Clinic Echocardiographic Diagnostic Criteria[84]) (Fig. 66–17): diastolic respirophasic shift of the interventricular septum, medial mitral annulus e′ ≥ 9 cm/s, and diastolic expiratory hepatic vein flow ratio > 0.8 as well as plethoric inferior vena cava and restrictive mitral inflow velocities. If septal shift is present in conjunction with one of the other two criteria, sensitivity and specificity approach 90%. If all three criteria are present, specificity increased to 97%, but sensitivity decreased to 67%. A proposed algorithm of the echocardiographic diagnosis of constrictive pericarditis is illustrated in Fig. 66–18.

Cardiac catheterization findings[85,86] (Fig. 66–19) include elevated filling pressures with equalization of end-diastolic pressures (within 5 mm Hg). Right atrial pressures typically show prominent *x* and *y* descents with no drop in mean right atrial pressure with inspiration (Kussmaul sign). Other classic findings include right ventricular systolic pressures < 55 mm Hg (ie, absence of pulmonary hypertension), presence of rapid

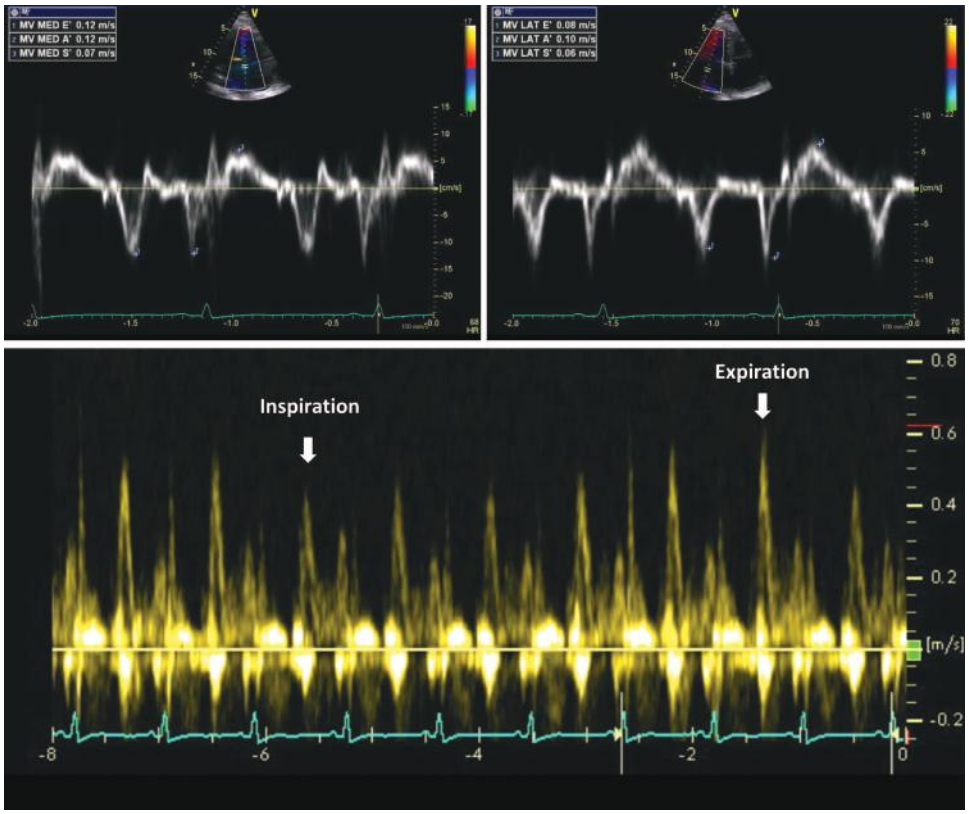


FIGURE 66–16. Echo-Doppler findings in a patient with constrictive pericarditis. Tissue Doppler shows medial e′ (*left upper panel*) greater than lateral e′ velocities (*right upper panel*)—the so-called *annulus reversus*. Mitral inflow pulse-wave Doppler (*lower panel*) revealed marked respirophasic changes in E velocity; note reduction in mitral E velocity during inspiration.

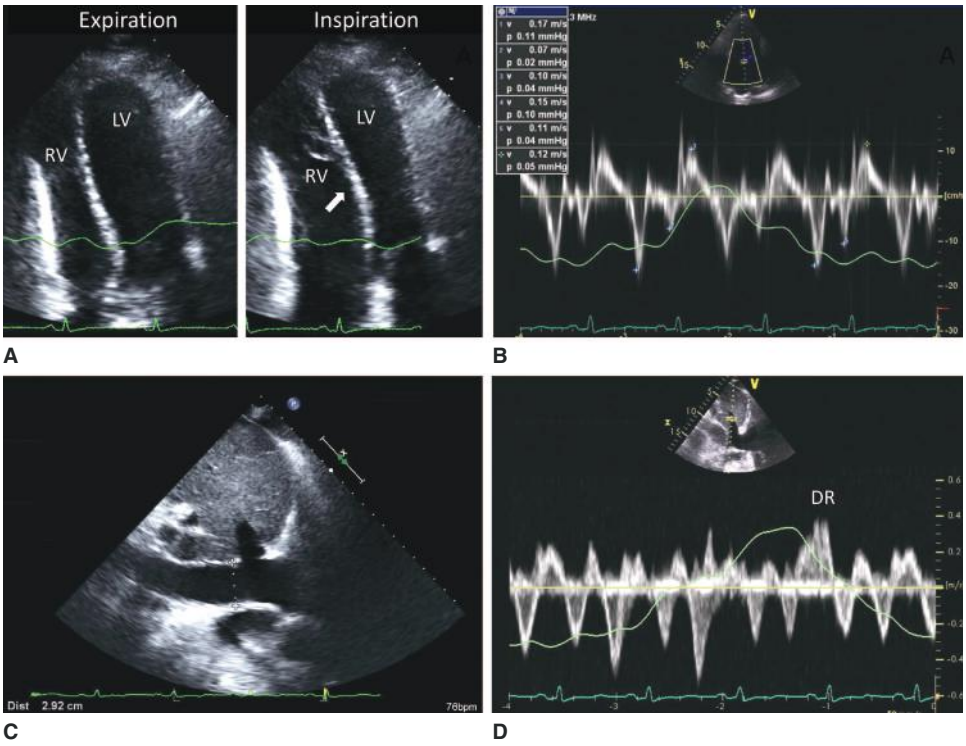


FIGURE 66–17. Two-dimensional and Doppler echocardiographic findings illustrating the Mayo Clinic constrictive pericarditis criteria: (1) respirophasic interventricular septal shift (*arrow*, A); (2) medial e′ velocity ≥ 9 cm/s on tissue Doppler (B); (3) dilated inferior vena cava (C); and (4) hepatic vein expiratory end-diastolic reversal (DR)/forward flow ≥ 0.8 (D). LV, left ventricle; RV, right ventricle.

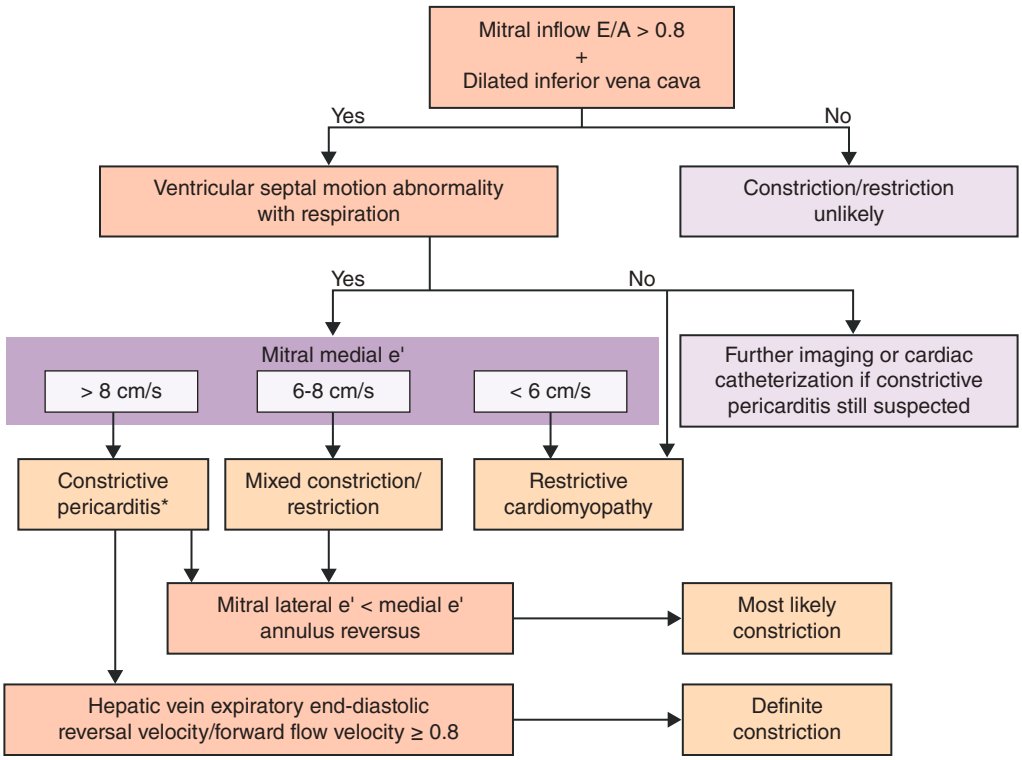


FIGURE 66–18. Algorithm for the evaluation of patients with constrictive pericarditis based on echocardiographic findings. Reproduced from *Nat Rev Cardiol*. 2015;12(12):682.[68] *In patients with obstructive airways disease or increased respiratory effort, ventricular interaction occurs and can be high especially in a young patient. In that situation, increased flow in the superior vena cava during inspiration is also seen and the hepatic vein also shows markedly increased flow with inspiration.

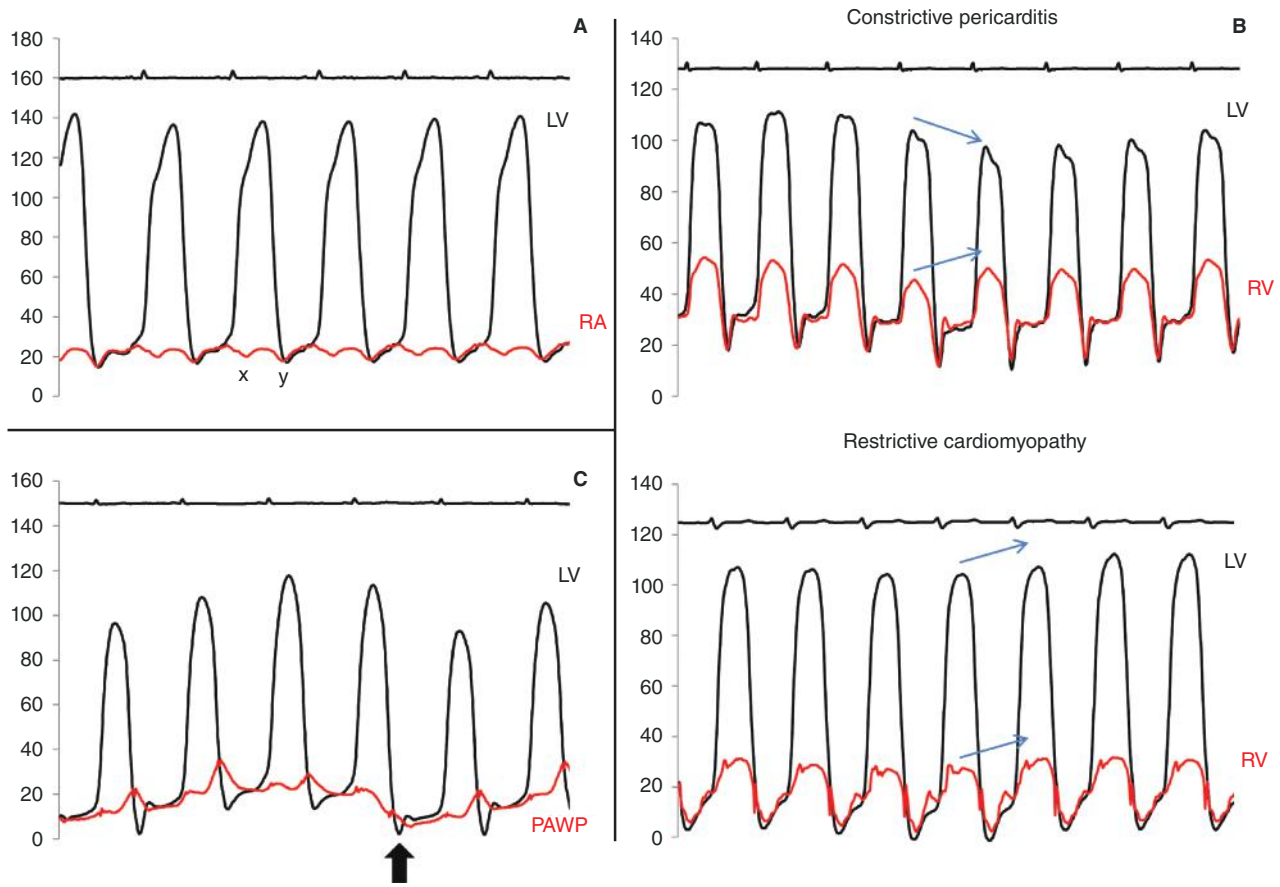


FIGURE 66–19. Cardiac catheterization findings in constrictive pericarditis (**A-C**). **A.** Right atrial (RA, *red*) pressure tracings show prominent *x* and *y* descents; elevation in filling pressures is also present. **B.** Tracings show discordance (*converging blue arrows*) between left ventricular (LV, *black*) and right ventricular (RV, *red*) pressure tracings upon inspiration, representing enhanced ventricular interdependence; this finding is compared to findings in a patient with restrictive cardiomyopathy, where concordance between left and right ventricular pressure tracings (*parallel blue arrows*) is present (*lower right panel*). Please note the rapid filling waves in both ventricular tracings (*dip-and-plateau* or *square root* sign). **C.** Tracings illustrate the dissociation of intrathoracic and intracardiac pressures; on inspiration (*arrow*), there is marked decrease in the pulmonary artery wedge pressure (PAWP) to left ventricular gradient. As a result of scarred pericardium, respirophasic changes in intrathoracic pressures can be transmitted to the pulmonary veins (PAWP) but not to the cardiac chambers.

ventricular filling waves (≥ 5 mm Hg; so-called *square root sign*), and right ventricular end-diastolic pressures greater than a third of right ventricular systolic pressures. However, in more than a third of the contemporary patients with constriction, pulmonary artery systolic pressure is greater than 50 mm Hg, and the classic hemodynamic features are probably correct only in patients with pure constrictive pericarditis, but not in patients with concomitant myocardial disease or additional diastolic dysfunction. A normal cardiac output argues against the presence of clinically significant constrictive pericarditis. Simultaneous left ventricular and pulmonary artery wedge pressures can show evidence of dissociation of intrathoracic and intracardiac pressures. Lastly, discordance between right and left ventricular tracings during inspiration is of great diagnostic importance given its sensitivity and specificity.[87,88] If atrial fibrillation is present, temporary pacing might be necessary during the catheterization procedure to appreciate respirophasic changes. Lastly, it should be noted that most of these findings are load dependent and might not be present if filling pressures are normal or only mildly elevated; fluid challenge (rapid infusion of 1 L of fluid) should be considered in patients with right atrial pressures < 15 mm Hg.

Additional imaging with cardiac CT or MRI might be performed to assess pericardial thickness (Fig. 66–20). A thickened pericardium, defined as more than 2 mm in maximal thickness, is present is approximately 80% of the patients with constrictive pericarditis.[89] Thus, normal pericardial thickness makes the diagnosis of constrictive pericarditis less likely but does not exclude the diagnosis. CMR imaging provides valuable incremental

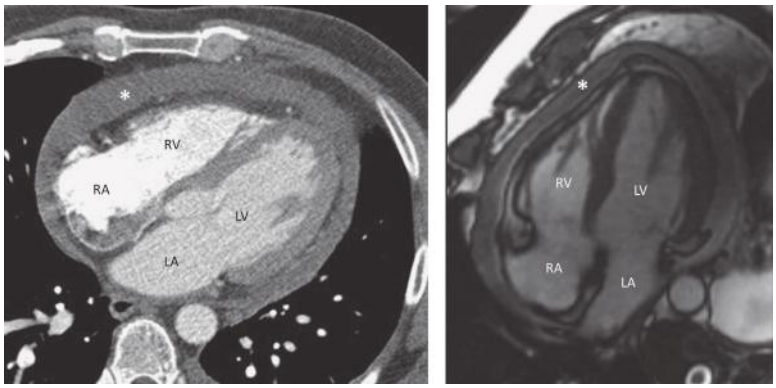


FIGURE 66–20. Computed tomography and magnetic resonance imaging findings in a patient with constrictive physiology. Cardiac computed tomography (**A**) and magnetic resonance imaging (**B**) showing increased pericardial thickness with the pericardial space being occupied by semisolid material (*asterisk*). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

information regarding the presence of pericardial inflammation, which has therapeutic implications, as well the presence of constrictive physiology (based on septal motion).

The evaluation of patients with constrictive pericarditis can be rather complex, in particular in patients with previous cardiac surgery, severe concomitant myocardial/valvular disease, or radiation heart disease. The workup should be individualized, and the threshold to intervene (most often with therapeutic pericardiectomy) will depend on concordant/discordant data. If the history, physical exam, and echocardiogram findings are typical for the disease, no additional testing is typically required. However, this requires familiarity with bedside and echocardiographic assessment of constrictive pericarditis. If necessary, additional imaging (CT and MRI) and/or cardiac catheterization are the next steps (Class I recommendation; LOE: C). In our practice, cardiac catheterization is only performed in one-third of patients undergoing pericardiectomy. If the diagnosis is still unclear despite extensive evaluation, exploratory surgery and surgical inspection of the pericardium (gold standard in the hands of an experienced surgeon) can be performed; today, the need for diagnostic thoracotomy is rare.

TREATMENT

Although patients presenting with constrictive pericarditis and evidence of active pericardial inflammation (either by CMR or elevated inflammatory markers) might respond to anti-inflammatory therapy (Class IIb recommendation; LOE: C),[1] therapeutic pericardiectomy is the recommended treatment for symptomatic patients with constrictive pericarditis (Class I recommendation; LOE: C).[1]

Pericardiectomy

Pericardiectomy is the surgical removal of the pericardium, and the procedure is applicable to all variants of pericardial disease.[75,90-97] Successful operation is predicated on two fundamental caveats: obtain adequate operative exposure and remove the appropriate amount of pericardium. Although median sternotomy and thoracotomy both allow for safe removal of the pericardium, thoracotomy exposure may require extension across the midline into the right chest to allow for resection of all right-sided pericardium (Fig. 66–21).[90,92,98] The Mayo Clinic Rochester experience includes 513 patients operated with isolated pericardiectomy from 1993 through 2013. During that time period, the majority (n = 412, 80%) of operations were performed through a median sternotomy.[99]

From a surgical perspective, pericardiectomy can be classified as either radical or complete (also referred to as total). The nomenclature is controversial and can be confusing.[98] It is probably best to frame the discussion about amount of pericardial resection in the context of the underlying disease process. For example, effusive and relapsing pericarditis represent inflammatory pathologies that can involve the entire pericardium.[93] Therefore, when operation is undertaken, total or complete pericardiectomy is indicated.[90] Constrictive pericarditis, on the other hand, is a disease of the ventricles.[68,90] Operation in that setting mandates resection of the

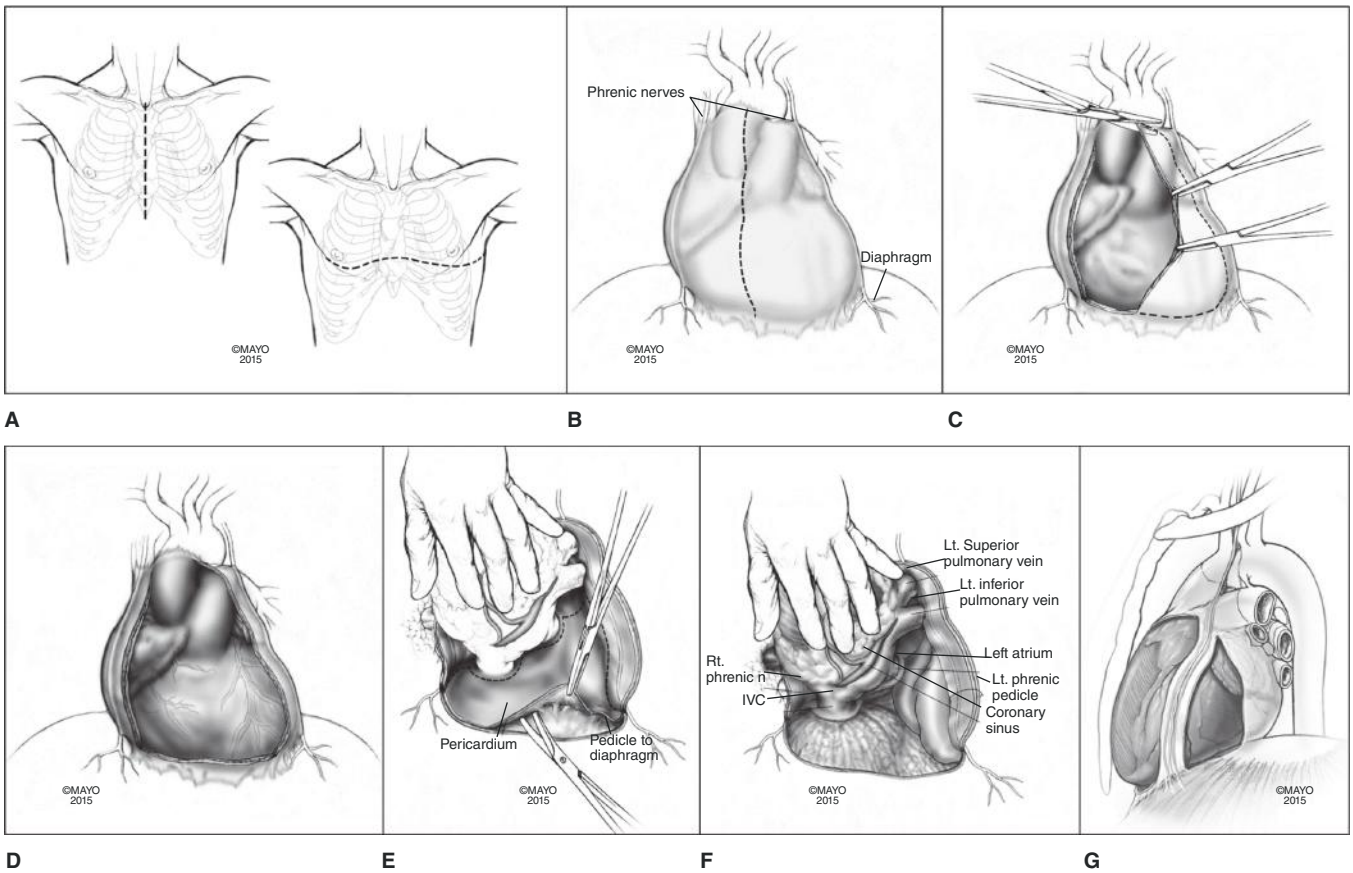


FIGURE 66–21. Schematic of surgical pericardiectomy. **A.** Surgical approaches to pericardiectomy. **B.** Exposure of anterior pericardium. **C.** Resection of anterior pericardium. **D.** Completed anterior or "phrenic-to-phrenic" pericardiectomy. **E.** Removal pericardium off diaphragm. **F.** Completed diaphragm and posterior pericardiectomy. **G.** Left lateral view of completed pericardiectomy showing pedicle along left phrenic nerve. IVC, inferior vena cava.

pericardium overlying the ventricles (ie, radical pericardiectomy).[90] In the Mayo Clinic Rochester experience, operation was more commonly performed for constrictive (n = 355, 69%) rather than for inflammatory etiology (n = 158, 31%).[99]

The key procedure-related elements of pericardiectomy are to remove the pericardium and to preserve phrenic nerve function. From the median sternotomy approach, the pericardial resection typically begins up near the great vessels, where the pericardium is usually less inflamed and less scarred to the underlying cardiac structures (see Fig 66–21). The "anterior" pericardium is resected from the great vessels to the diaphragm, and from the left phrenic nerve to the atrioventricular groove (at a minimum for constriction) or right phrenic nerve (for inflammatory etiologies), as needed or allowed (see Fig 66–21). To prevent injury to the phrenic nerves, a 1- to 2-cm pedicled strip of pericardium should be left undisturbed along the course of the nerves.

Resection of the anterior pericardium is also referred to as a "phrenic-to-phrenic" pericardiectomy. Specific attention is brought to this nomenclature to make the point that such limited resection (see Fig 66–21) is inadequate surgical therapy for essentially all pericardial disease processes; furthermore, it puts the patient at risk of treatment failure and disease recurrence.[90,98,100] As such, it is imperative that the pericardium be removed off the diaphragm and posterior to the left phrenic nerve (see Fig 66–21). Exposure to facilitate removal of that pericardium can require cardiopulmonary bypass support and sometimes even aortic occlusion (ie, aortic cross-clamp).[75,97,100] In the Mayo Clinic Rochester experience, 207 patients (40%) received cardiopulmonary bypass support during pericardiectomy, but only 4 patients (0.8%) received aortic occlusion.[99]

Constrictive pericarditis is a surgical disease that is best treated with pericardiectomy.[1,68] For this condition, the ESC recommends removal of as much of the pericardium as possible.[1,68] This is ideally and theoretically correct, but in practice, it can be misguided thinking because the constricting peel often is densely fibrosed to the heart and calcification may even penetrate into the myocardium. This is especially true in the area of the atria, inferior vena cava, and atrioventricular groove. Attempts to resect the densely adhered pericardium can be dangerous, and injury to the thin-walled structures can even prove fatal. The pathophysiology requires release of the ventricles (see Fig 66–21), which must include the visceral pericardium.[98,101] Tricuspid valve regurgitation can be a confounding condition and should be addressed prior to the completion of the operation.[102]

Pericardiectomy can be performed with an associated low operative morbidity and mortality and results in significant improvement in quality of life out to 10 years.[99] In the Mayo Clinic Rochester experience, overall mortality was 2.3%; for the constrictive pericarditis group, mortality was 2.5%, and for the inflammatory group, it was 1.9%.[99] Variables associated with an increased operative mortality have been well described by several investigators and commonly include a delay in treatment, advanced heart failure (eg, increased New York Heart Association class or reduced ejection fraction), and need of completion pericardiectomy (ie, for inadequate first operation or recurrence of disease).[75,96,97,100,103,104] The take-home message is that early and adequate pericardiectomy is both life changing and life saving. Referral for operation should not be denied.

EFFUSIVE-CONSTRICTIVE PERICARDITIS

Most patients with constrictive pericarditis present with the classic, chronic form of the disease. However, other "uncommon" presentations have been recognized.[105] Although typically described as two separate entities,[106,107] transient and effusive-constrictive pericarditis are most likely part of a clinical spectrum, and distinction between the two might be academic.

Some patients presenting with cardiac tamponade demonstrate features of constrictive pericarditis immediately after pericardiocentesis is performed and tamponade relieved[61] (Fig. 66–22). This is felt to be secondary to decreased pericardial compliance in the setting of acute inflammation. The reported incidence of effusive-constrictive pericarditis has varied according to the population analyzed and the most common etiologies (ranging from 8% in developed countries to more than 50% in African patients with tuberculous pericarditis).[106,108] Echocardiography shows features of constrictive pericarditis with a small amount of fluid or after resolution of tamponade. Therapy should be focused on treating active inflammation[61]; a subset of patients might develop chronic constrictive pericarditis and require pericardiectomy. Therefore, we suggest close follow-up of patients with effusive-constrictive pericarditis.

TRANSIENT CONSTRICTIVE PERICARDITIS

The definition of transient constrictive pericarditis has been variable in the literature. Initially described by Sagrista-Sauleda et al,[107] this group included patients presenting initially with acute pericarditis (not necessarily tamponade) that developed constrictive features when the acute process was resolving and the pericardial effusion was small or absent. The long-term prognosis for affected patients was good, with none requiring surgical treatment. Others have described transient constriction as constrictive pericarditis that resolved with corticosteroids or anti-inflammatory therapy.[109] Pericardial effusions are common in patients with transient constriction, reported in two-thirds of cases. Affected patients tend to have signs of inflammation with elevated

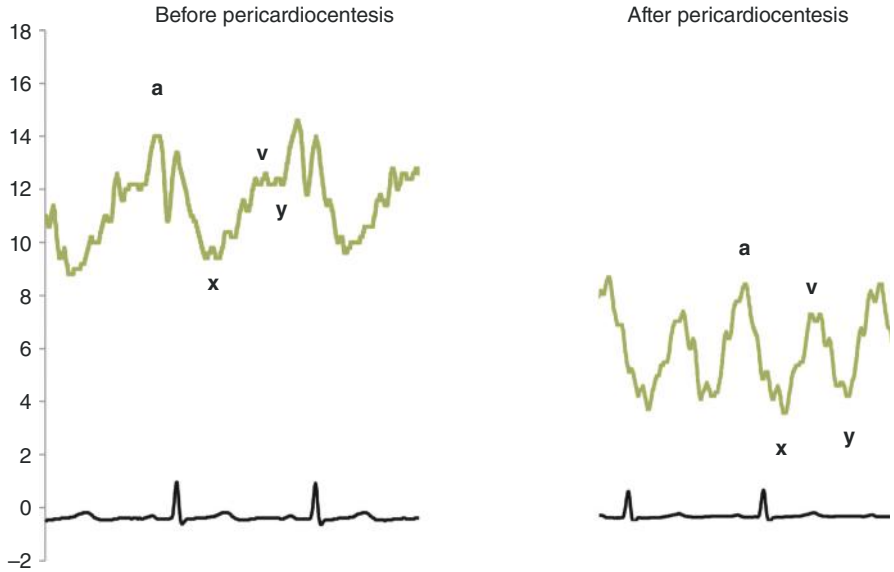
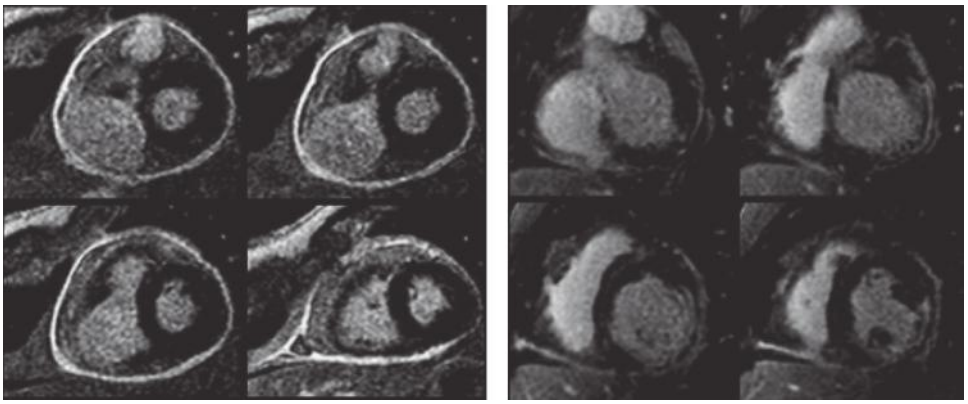


FIGURE 66–22. Hemodynamic pressure tracings in effusive-constrictive pericarditis. Right atrial pressure tracings before and after pericardiocentesis. Before pericardiocentesis, there is blunting of the *y* with a prominent *x* descent in the setting of elevated right atrial pressures, findings consistent with cardiac tamponade. After pericardiocentesis, although mean right atrial pressure drops, it remains slightly elevated with the development of deep *x* and *y* descents; this finding is diagnostic of effusive-constrictive pericarditis.



A B

FIGURE 66–23. Cardiac magnetic resonance findings in a patient with transient constrictive pericarditis before and after anti-inflammatory therapy. Severe pericardial delayed enhancement is present before therapy (A). With anti-inflammatory therapy, there was clinical and echocardiographic resolution of constrictive pericarditis. Post-treatment images (B) show improvement in the degree of pericardial delayed enhancement. Reproduced with permission from Feng D, Glockner J, Kim K, et al: Cardiac magnetic resonance imaging pericardial late gadolinium enhancement and elevated inflammatory markers can predict the reversibility of constrictive pericarditis after antiinflammatory medical therapy: a pilot study. *Circulation*. 2011 Oct 25;124(17):1830-1837.[110]

inflammatory markers and gadolinium enhancement on MRI at the time of the diagnosis of constrictive pericarditis (Fig. 66–23).[110] Optimal type and duration of NSAID versus corticosteroids with or without colchicine for transient constrictive pericarditis are still unknown. However, our experience has taught us that clinical response to medical therapy is relatively quick (within a week), and at least 3 months of medical therapy are required for a complete or clinically satisfactory response.

OCCULT CONSTRICTIVE PERICARDITIS

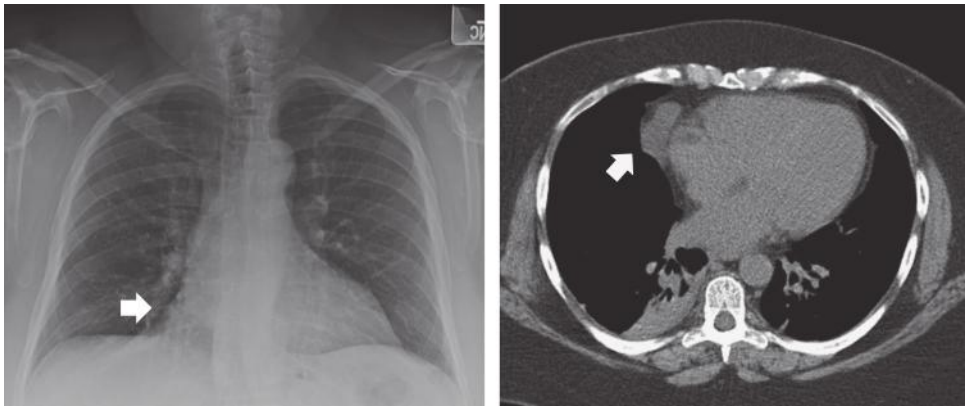
Occult constrictive pericarditis was described in a group of patients in whom constrictive features were only noticeable after fluid challenge.[111] Although we do use rapid saline infusion in the catheterization laboratory for patients with suspected constrictive pericarditis and low filling pressures related to overdiuresis, we do not use fluid challenge routinely to identify occult constrictive pericarditis. Given the lack of data, we would not recommend the diagnosis and management of constrictive pericarditis solely based on post–saline infusion changes for patients who do not otherwise have diagnostic features of the constrictive pericarditis.

CONGENITAL ABNORMALITIES OF THE PERICARDIUM

Congenital abnormalities of the pericardium are rare. The two most common abnormalities encountered are pericardial cysts and congenital absence of the pericardium (typically partial); other rarer abnormalities include pericardial diverticula and pericardial bands. These abnormalities are usually found incidentally when chest radiography or other cardiac imaging is performed. Although most patients remain entirely asymptomatic, a small group of patients might require percutaneous or surgical intervention for symptomatic relief.

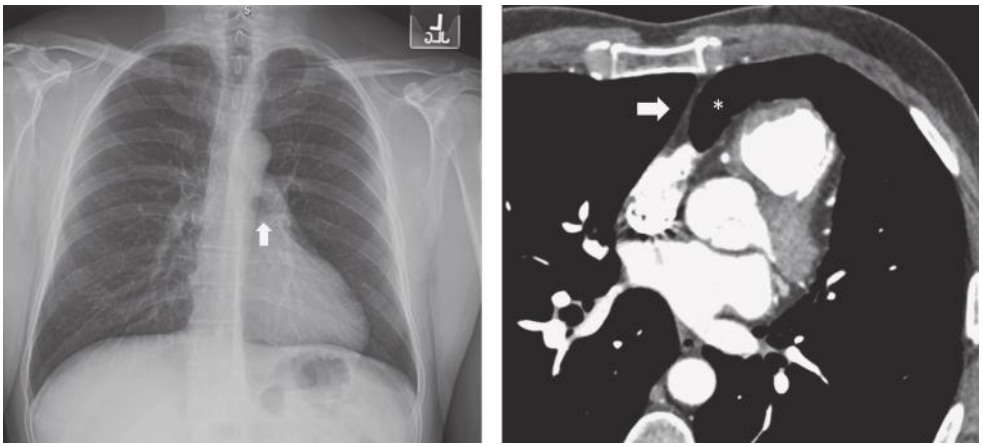
PERICARDIAL CYSTS

Pericardial cysts are smooth, thin-walled structures filled with clear fluid (hence the term *spring water cysts*). If there is a communication between the cavity and the pericardial space, a pericardial diverticulum is said to be present. Although typically found in the right costophrenic angle[112] (Fig. 66–24), they can be located at the left costophrenic angle or anteriorly. Pericardial cysts usually measure 3 to 4 cm in diameter, but larger cysts can also be seen, mimicking large pericardial effusions on chest radiography. The diagnosis is usually made incidentally when imaging of the chest is performed. If the diagnosis is unclear, CT of the



A B

FIGURE 66–24. Pericardial cyst. Posteroanterior chest radiography (A) shows a mass (*arrow*) in the right costophrenic angle; computed tomography (B) findings on the same patient show a pericardial cyst as the cause of the radiographic abnormality.



A B

FIGURE 66–25. Partial congenital absence of the pericardium. Posteroanterior chest radiography (**A**) shows deviation of the cardiac silhouette to the left of the spine; the silhouette has the appearance of a "Snoopy dog"; computed tomography (**B**) on the same patient at the level of the aortic valve shows interposed lung tissue (*asterisk*), a finding suggestive of congenital absence of the pericardium; this can be also appreciated on chest radiography as an area of radiolucency (*vertical arrow*). Please also note the prominence of the sternopericardial ligament (*horizontal arrow*).

chest is a helpful diagnostic tool and is preferred over transthoracic echocardiography.

Patients with pericardial cysts are usually asymptomatic, and the cysts tend not to increase in size. Rarely, there is resolution of the cyst, which may be related to spontaneous rupture. Some patients with pericardial cysts complain of atypical chest pain or dyspnea, most likely as a result of compression of contiguous structures. Because the symptoms are often nonspecific, it is difficult to attribute them to the pericardial cyst.

For patients with symptoms related to the pericardial cyst, percutaneous drainage or surgical removal can be performed.[113] However, given the risks associated with both procedures and the benign, well-tolerated course of the disease, we would recommend observation for most patients with pericardial cysts.

CONGENITAL ABSENCE OF THE PERICARDIUM

Congenital absence of the pericardium can be divided into partial (most common) or total (ie, bilateral) congenital absence of the pericardium. Although a wide spectrum can be found, including absence of the right portion and diaphragmatic components of the pericardium, the most typical presentation is total absence of the left portion of the pericardium. The diagnosis is usually made by chest radiography, when there is leftward displacement of the cardiac silhouette and aortic knob with no distinct right heart border seen to the left of the thoracic spine.[114] As a result of the absence of the pericardium, lung tissue may be visible between the pulmonary artery and the aorta, appearing as the ear of a "Snoopy dog" (Fig. 66–25). As a result of the abnormal location of the heart within the chest, congenital absence of the pericardium should be suspected in patients with "very unusual" echocardiographic windows.[115] CT nicely illustrates the displacement of the heart and shows elongation of the sternopericardial ligament with the presence of lung tissue interposed between the pulmonary artery and the sternum.

Patients with congenital absence of the pericardium are typically asymptomatic; rarely herniation or incarceration of cardiac structures might occur, leading to arrhythmias, angina, or syncopal spells. These symptoms might be precipitated by a change in body position; however, the most common complaint is vague chest pain. The need for surgical repair of congenital defects of the pericardium is extremely rare.[116]

PERICARDIAL MASSES

Although some autopsy studies reported pericardial metastatic involvement in 10% to 20% of patients with known malignancies,[117] pericardial masses are rare in clinical practice. Primary pericardial tumors are even less common, with mesothelioma being the most frequently encountered. Others include sarcomas and malignant teratomas. Nonmalignant tumors include lipomas, hamartomas, and benign teratomas.

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CHAPTER 67

INFECTIVE ENDOCARDITIS

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ANTIBIOTIC PROPHYLAXIS FOR THE PREVENTION OF INFECTIVE ENDOCARDITIS / 1643

Infective endocarditis (IE) is a disease caused by a microbial infection involving the endothelial lining of intracardiac structures such as the heart valves. The infection is invariably fatal if untreated. Infection commonly resides on one or more of the heart valve leaflets but may involve mural endocardium, chordal structures, deeper layers of the myocardium, and/or the pericardium. The presence of an intracardiac or endovascular device provides a nidus for infection, as well as a barrier to eradication. Despite significant advances in the diagnosis and treatment of IE, 6-month mortality rates still approach 25%.[1,2] Changes in both patient demographics and microbial biology involving an increased incidence of antibiotic-resistant organisms create challenges for contemporary physicians. Prompt recognition and diagnosis, triggered by a high index of clinical suspicion in susceptible patients, trigger aggressive treatment and represent the critical components of a successful management strategy. Combined medical and surgical intervention leads to improved outcomes for selected patients. However, recent years have not seen improved clinical outcomes despite medical and surgical advances.[3] Patient education, attention to general oral-mucosal hygiene, and the appropriate limited use of prophylactic antibiotics are the mainstays of a preventive strategy. IE is often a complex disease with abnormal function in a number of organ systems. Management by a team of physicians and allied healthcare providers is usually required.[3,4]

HISTORY

Our current understanding of IE began with the observations of Sir William Osler who made several important advances in the understanding of this illness, as summarized in his famed Gulstonian lectures of 1885.[5,6] Osler defined IE as a primary "mycotic" process and provided the first formal description of two clinical variants of the disease—the acute and fulminating form versus the chronic and insidious form. Despite his extensive knowledge of the disease, Osler acknowledged the reality of diagnostic uncertainty in many cases.

EPIDEMIOLOGY

In the first half of the 20th century, IE was predominantly a complication of rheumatic heart disease and poor dentition. In developing countries, rheumatic heart disease remains the most frequent predisposing cardiac condition.[7] However, the epidemiologic features of IE in developed countries have changed considerably in recent decades. The aging of the population has been paralleled by increases in the prevalence of degenerative heart valve disease and in the use of prosthetic heart valves and other intracardiac devices. The numbers of patients with chronic, predisposing medical comorbidities, such as diabetes, human immunodeficiency virus (HIV) infection, end-stage renal disease, and immunosuppressive therapy, have markedly increased, as has the commensurate risk of exposure to nosocomial bacteremia, often with antibiotic resistance.[8-10] A recent prospective study of 2781 adults with IE found that 25% of cases were associated with recent health care exposure.[2] These changing demographics are reflected in two observations. First, the median age of patients with IE has gradually increased from 30 to 40 years in the preantibiotic era to 47 to 69 years in the late 20th century.[2,11,12] Second, the incidence of IE in developed countries has remained unchanged, despite the dramatic reduction in the incidence of rheumatic heart disease over the last half century. The Nationwide Inpatient Sample database for the years 2000 to 2011 for the United States found 457,052 IE-related hospitalizations, with a steady increase in incidence.[12,13] The number of cases of staphylococcal IE per million population was stable, but cases of streptococcal IE increased during this time period perhaps as a result of altered recommendations for antibiotic prophylaxis. This report also noted an increasing rate of valve replacement for patients with IE.

The incidence of IE has been difficult to estimate due principally to the challenges of accurate case definition and identification of representative populations at risk (eg, urban vs rural, injection drug users, young vs elderly). Over recent years, a number of well-designed epidemiologic studies have attempted to address these problems[9-15] and are summarized in Table 67–1. A number of these studies suggest that the incidence of IE is increasing among the elderly.[16,17] Increased patient longevity and the increased use of health care interventions predict that the incidence of IE throughout the world will continue to rise.[18]

TABLE 67–1. Studies of IE Incidence

Study	Population Studied	IE Incidence (cases per 100,000 person-years)	Comments
Pant et al[12]	US Nationwide Inpatient sample database; 2000-2011	11-15	The trend in IE hospitalizations in the United States from 2000-2007 and from 2008-2011 was not significantly different.
Hogevik et al[10]	Well-defined urban population in Goteborg, Sweden, followed prospectively from 1994-1998	5.9	IE incidence was age- and sex-adjusted. Crude incidence was 6.2. In the oldest age group (80-89 years), the annual incidence was 22.
Berlin et al[13]	Retrospective analysis of IE cases in metropolitan Philadelphia from 1988-1990	11.6	The population studied had a high proportion of injection drug users, a population whose rate of IE was 5.2 cases/100,000 person-years.
Delahaye et al[14]	Retrospective analysis of 415 IE cases collected from a combined urban and rural population from 3 regions in France in 1991	2.4	IE incidence was age- and sex-adjusted. The study population had only 5% injection drug users.
Tleyjeh et al[15]	Retrospective analysis of 107 IE cases occurring in Olmsted County, MN, between 1970 and 2000	5.0-7.0	IE incidence was age- and sex-adjusted. Increasing temporal trend was observed for PVE and for cases associated with mitral valve prolapse.
Hoen et al[9]	Retrospective analysis of 390 IE cases in 6 regions of France in 1999	3.1	IE incidence was age- and sex-adjusted. There was a high incidence of IE in the elderly of 14.5 cases per 100,000 patient-years.
Cabell et al[16]	Retrospective analysis of IE incidence in the US Medicare database, reflecting more than 16,000 cases from 1986-1991	20.4	This study reported a 13.7% increase in IE incidence in the Medicare population from 1986 to 1998.
Morellion and Que[17]	Review of 26 publications between 1993 and 2003 encompassing 3784 cases of IE	Median incidence of IE among all studies of 3.6.	In subjects older than 65 years, the median incidence was > 15 cases per 100,000 person-years, nearly 3 times that of subjects less than 50 years of age.

Abbreviations: IE, infective endocarditis; PVE, prosthetic valve endocarditis.

INFECTIVE ENDOCARDITIS IN SELECTED PATIENT POPULATIONS

The Elderly

The incidence of IE among the elderly, often due to nosocomial infection, appears to be rising.[19] A heightened index of suspicion is required to make the diagnosis in this population because the presentation may be atypical.[20] There is a higher incidence of degenerative, calcific valve disease, usually aortic, which can decrease the specificity of echocardiographic imaging for the lesions of IE. Transesophageal echocardiography (TEE) imaging is often required for more accurate delineation of valve pathology.[21] IE caused by *Enterococcus faecalis* may be more common among the elderly.[22] Although there are conflicting reports, advanced age appears to predict mortality in IE,[19,23-25] particularly with *Staphylococcus aureus* infection.[26]

Injection Drug Users

IE is a dreaded complication of injection (ie, intravenous or subcutaneous) drug use. The incidence of IE among injection drug users (IDUs) is approximately 2% to 5% per year, and IE is responsible for 5% to 20% of hospital admissions and 5% to 10% of overall mortality in this group.[27] The incidence of IE and the causative agents in this population are related to contaminated injection technique (eg, sharing or licking of hypodermic needles), the injection of unsterile particulate material (eg, talcum), and the high prevalence of HIV infection. *Staphylococcus aureus* is the most common etiologic agent, causing more than 60% of IE cases in IDUs.[27] IE caused by gram-negative bacilli (notably *Pseudomonas aeruginosa*) and fungi is also more common among IDUs. The distinctive feature of IE in IDUs is that it frequently involves the right heart, with 60% to 70% of cases involving the tricuspid valve. The tricuspid valve may be particularly susceptible to bacterial infection as a result of chronic degenerative changes caused by the repetitive injection of irritants (eg, talcum) into peripheral veins. Septic pulmonary emboli are common in IDUs with IE. Despite the high frequency of *Staphylococcus aureus* infection, isolated right heart involvement in IDUs partially explains the lower mortality in this population (4%) compared with other IE patient subsets. Nevertheless, left-sided infection does occur and can result in major complications, such as systemic emboli, paravalvular abscess, and severe valvular destruction. IDUs with uncomplicated right-sided IE may be eligible for short-course parenteral antibiotic therapy (2-4 weeks), a regimen that would not be considered in patients with left-sided IE.[28] Because the administration of a 4-week parenteral antibiotic regimen in IDUs can be challenging, combination oral therapy with ciprofloxacin plus rifampin can be used safely and effectively in selected patients with uncomplicated right-sided staphylococcal IE.[29] Given the relative efficacy of antibiotic cure for isolated right-sided IE in IDUs, surgical therapy is infrequently indicated and is reserved for cases of severe right heart failure caused by tricuspid regurgitation, refractory bacteremia, and persistent tricuspid vegetations > 20 mm with recurrent septic pulmonary emboli or left-sided valve involvement.[30] IDU is not an absolute contraindication to surgery for patients with IE, and studies have shown that surgery can be performed in these patients safely and with acceptable outcomes.[31]

Human Immunodeficiency Virus Infection and the Immunocompromised Host

Although HIV infection and intravenous drug use commonly coexist, HIV infection appears to be an independent risk factor for the development of IE.[32] Patients with low CD4 counts (< 200 cells/mL) tend to have an increased risk of IE,[33] as well as a higher associated mortality.[27,34] IDUs who are HIV positive have a higher incidence of left-sided valvular involvement and complications compared with HIV-negative IDUs.[34] Although they rarely cause IE, *Bartonella* species can cause opportunistic infections, including IE, in patients with acquired immunodeficiency syndrome (AIDS).[35] There is a paucity of data on the characteristics of IE in the non–HIV-infected immunocompromised host. However, immunocompromised patients with gram-negative bacteremia or fungemia may be at risk for IE as a result of these organisms.

Hemodialysis Patients

There are more than 300,000 patients in the United States who are receiving hemodialysis (HD). Infectious complications of vascular access are a major cause of morbidity and mortality in HD patients. In this population, there is an alarming rate of bacteremia, approaching nearly 1.0 episode per 100 patient-care months. Few other medical conditions, with the exception of chemotherapy-induced neutropenia and intravenous drug use, are associated with such high rates of bacteremia. As a result, IE occurs in approximately 2% to 6% of patients receiving HD. Staphylococcal species are the predominant organisms and gain access to the bloodstream via infected central venous catheters, arteriovenous (AV) grafts, or AV fistulae. Primary AV fistulae have the lowest rates of infections and are the access of choice if vascular anatomy allows for this approach. Indwelling central venous catheters have the highest rate of infection and are often associated with more serious metastatic complications.[36] Access-related infections are the most common cause for the loss of dialysis vascular access, causing nearly 10% of deaths (second only to ischemic heart disease) in this patient population.[37] Patients with end-stage renal disease have a high incidence of calcific degeneration of the aortic and mitral valves,[38] which may predispose to bacterial colonization of the endocardium. Such degenerative valvular disease may render echocardiographic detection of vegetations extremely challenging.[21] Vancomycin is often used as a first-line agent because of the high incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) in this population and the ease of administration of this drug with HD. Treatment of catheter-related bloodstream infections with antibiotics alone yields poor results, and removal of infected catheters or grafts is necessary in most circumstances.[39] Effective prevention of bacteremia in the HD population hinges on early referral for primary AV fistula placement (preferably before dialysis is needed) and strict adherence to sterile technique with access catheter manipulation.

Cardiac Device–Related Infective Endocarditis

The rates of pacemaker and implantable cardiac defibrillator (ICD) placement have markedly increased over the past 10 years, given the growing number of evidence-based indications for their use. However, the increasing rate of device infection appears to be disproportionate to the increased rate of device implantation.[40] The overall incidence of cardiac device–related infective endocarditis (CDRIE) lies between that of native valve endocarditis and prosthetic valve endocarditis.[41,42] Staphylococcal species are the causative organism in more than 70% of cases.[43,44] Infection with coagulase-negative staphylococci can be particularly difficult to eradicate. The vast majority of cardiac device infections are apparently a result of pocket site contamination at the time of device placement. Hematogenous seeding from a distant focus of infection, particularly when due to *Staphylococcus aureus*, can cause late-onset infection. The clinical presentation may be misleading initially, with prominent respiratory or rheumatologic symptoms, as well as local signs of infection.[44] Septic pulmonary embolism is a frequent complication and contributes to the high mortality associated with CDRIE.[45] CDRIE is one of the most difficult forms of IE to diagnose; the Duke criteria in this setting lack adequate sensitivity. Modifications of the Duke criteria have been proposed to include signs of local (generator pocket, subclavian vein) infection and septic pulmonary embolism as major criteria.[44,46]

There are several important imaging considerations in patients with suspected intracardiac device infections. With transthoracic echocardiography (TTE), it can be difficult to differentiate infected vegetations from noninfected device-related thrombus. TEE is often required for adequate visualization, and it is essential that echocardiographic data be integrated with clinical and microbiologic data. The device and leads should be imaged throughout their entire course within the cardiac chambers and proximal veins, with special attention to their relationship to the tricuspid valve. Device leads that track through the superior vena cava should be visualized as close to the origin of the generator as possible.[18] In addition to TEE, preliminary experience with intracardiac echocardiography for the detection of lead vegetations has recently been reported.[47] Although no prospective studies have been conducted, management with parenteral antibiotics and complete device removal are the standards of care.[43] Cardiac device extraction can be performed percutaneously without the need for surgical intervention in the majority of patients, although percutaneous approaches may be more difficult when the device has been in place for a number of years. Pulmonary embolism of vegetative material during extraction occurs frequently, particularly when vegetations are large.[46,48] However, these episodes are frequently asymptomatic, and percutaneous extraction remains the procedure of first choice, even in cases with large vegetations,[45,46,48] because the overall risks are even higher with surgical extraction.[30,44] Increased experience with evolving percutaneous lead-extraction techniques may aid in the management of infected devices.[49] When there is documented valvular IE in a patient with an implanted device, there is a high likelihood of concomitant device infection, which usually necessitates extraction of the device at the time of valve surgery. The American Heart Association has recently published a scientific statement that provides recommendations for the prevention, diagnosis, and management of cardiovascular implantable electronic device (CIED) infections.[50] Decisions regarding optimal timing and site of device reimplantation are complex and must be adapted to the individual patient.[40-51] A retrospective analysis of patients undergoing pacemaker implantation suggests that antibiotic prophylaxis before device implantation can prevent infectious complications.[52] The current scientific statement recommends that prophylaxis with an antistaphylococcal agent should be administered at the time of CIED placement.[50] Antimicrobial prophylaxis for the prevention of CIED infections is not recommended for dental or other invasive procedures not directly related to device manipulation.[50]

ADDITIONAL ASPECTS OF INFECTIVE ENDOCARDITIS EPIDEMIOLOGY

Patients who recover from an episode of IE are unfortunately still at risk for late complications.[53] In this study, Shih et al[53] observed that patients with successfully treated IE were at higher risk for the late occurrence of ischemic and hemorrhagic stroke, myocardial infarction, hospitalization for heart failure, and sudden death compared with a cohort of matched controls without IE. The diagnosis of IE is also a substantial marker for the presence of occult cancer.[54]

PATHOGENESIS

Normal vascular endothelium resists colonization by bacteria. Damaged vascular endothelium can be colonized by circulating bacteria with specific adhering qualities.[55] The hallmark of IE is persistent endocardial or endovascular infection causing continuous bacteremia. Importantly, IE is a relatively uncommon consequence of transient bacteremia, and not all organisms can effectively colonize or invade the endovascular space. It is apparent that a complex series of host-pathogen interactions conspire in the development of IE lesions, including the integrity of the vascular endothelium, the host immune system, hemostatic mechanisms, cardiac anatomical characteristics, microbial properties, and the peripheral events that cause the bacteremia.[18,55] There are substantial experimental data to suggest that host endothelial damage is the key predisposing insult, with subsequent platelet and fibrin deposition and

creation of a receptive milieu for bacterial colonization during episodes of transient bacteremia. That endothelial damage is the inciting event is further supported by the observation that vegetations are most likely to form in areas where blood-flow injury is likely to occur—on the ventricular side of semilunar valves and the atrial side of AV valves.[56,57] Jet lesions from regurgitant valves or intracardiac shunts may also damage endothelium, and vegetations may form on such sites of injury, including the mitral chordae with aortic regurgitation, the mural left atrial endocardium with mitral regurgitation, or the septal leaflet of the tricuspid valve with ventricular septal defect.[18,53] Figure 67–1 illustrates the classic locations of endocardial flow injury that are associated with vegetation formation in IE.[57]

Once endothelial injury has occurred, bacteria must gain access to the intravascular space to seed the lesion. Common sources of bacteremia include skin, surgical wounds, the periodontal space, indwelling intravascular catheters, and the urinary and gastrointestinal tracts. Bacteremia is common after both toothbrushing and tooth extraction. More bacteria are released into the bloodstream after extraction than after toothbrushing. However, because toothbrushing is so much more common than extraction, it may well be a common source for the initiation of IE.[58] Bacteria that have entered the bloodstream must be able to adhere to the damaged endothelium, exposed extracellular matrix, or areas of fibrin deposition.[59] This adherence is mediated by microbial surface components recognizing adhesive matrix molecules, which, in turn, recognize a variety of host proteins such as fibronectin, collagen, and integrins. Certain organisms appear to preferentially express these molecules, enabling them to adhere more effectively and colonize the injured endocardium.[52,60] The fact that *Staphylococcus aureus* can induce endothelial tissue factor expression may partially explain why this organism can adhere to relatively normal heart valves.[60] Particulate material that may be injected may also promote *Staphylococcus aureus* adherence by stimulating matrix protein expression on valvular endothelium.[59] In a *Streptococcus* rat model of endocarditis, extracellular neutrophil "traps" form with the aid of activated platelets and specific immunoglobulin G. Pathogens, in this case streptococci, actually promoted the formation of these extracellular traps, which form part of the characteristic vegetation. These neutrophil traps actually aid in promoting and expanding the vegetations of IE.[61]

A factor in the pathogenesis of device-related intravascular infections is biofilm formation, which impedes microbial clearance by host mechanisms, and thus often mandates device removal for eradication of the infection. *Staphylococcus epidermidis* and *Staphylococcus aureus* have been studied most extensively in this regard, with characterization of a responsible intercellular adhesin and its gene cluster.[62] Once adherent, certain strains of bacteria are able to evade the host immune system, destroy host tissue, or occasionally enter the cytosolic compartment of endothelial cells. Repetitive cycles of bacterial proliferation, fibrin-platelet deposition, and host tissue destruction create an infected vegetation, within which bacteria can reach extremely high concentrations (10^9-10^{11} organisms per gram of tissue; Fig. 67–2). These dense vegetations are a source of continuous bacterial seeding of the bloodstream. Figure 67–3 shows a gross pathologic specimen of the heart with a large, complex vegetation attached to the left atrial surface of the anterior mitral leaflet. After successful antimicrobial therapy, vegetations will resolve completely or contract in size and persist indefinitely as a sterile and frequently calcified mass adherent to valve tissue.

The various systemic manifestations of IE are the result of showers of bacteria-laden emboli that often result in satellite areas of infection with subsequent abscess formation. Osler and Janeway lesions are the result of these infected emboli and not the result of immunologically induced vasculitis.[63] That small, often clinically unnoticed, embolic phenomena are occurring with considerable frequency was documented by Cooper et al[64] who observed with magnetic resonance imaging (MRI) scans that the majority of their patients with definite left-sided IE had subclinical brain lesions highly suggestive of embolic events.

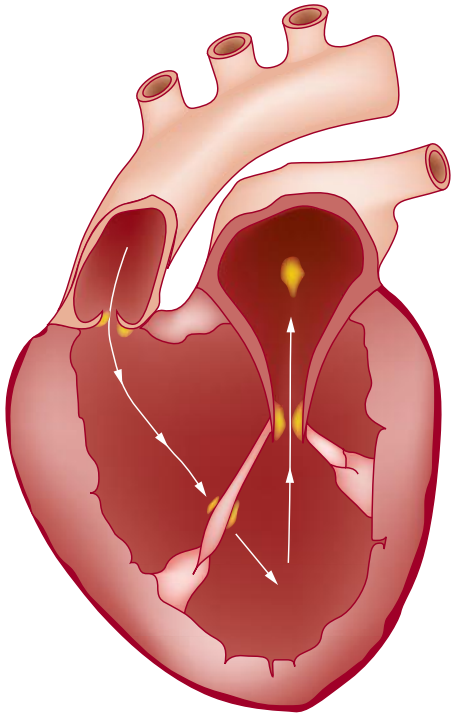


FIGURE 67–1. Sites of typical endocardial flow-related injury and associated vegetation formation in infective endocarditis (IE). Flow injury from aortic regurgitation is typically associated with vegetations on the ventricular side of the aortic valve or on the anterior mitral leaflet and its subvalvular apparatus. Flow injury from mitral regurgitation is associated with vegetation formation on the left atrial surface of the mitral leaflets or on the mural surface of the left atrial endocardium (MacCallum patch). Flow injury from a ventricular septal defect (not shown) with left-to-right shunting is associated with vegetation formation on the septal leaflet of the tricuspid valve. Adapted with permission from Rodbard S. Blood velocity and endocarditis. *Circulation*. 1963 Jan;27:18-28.[56]

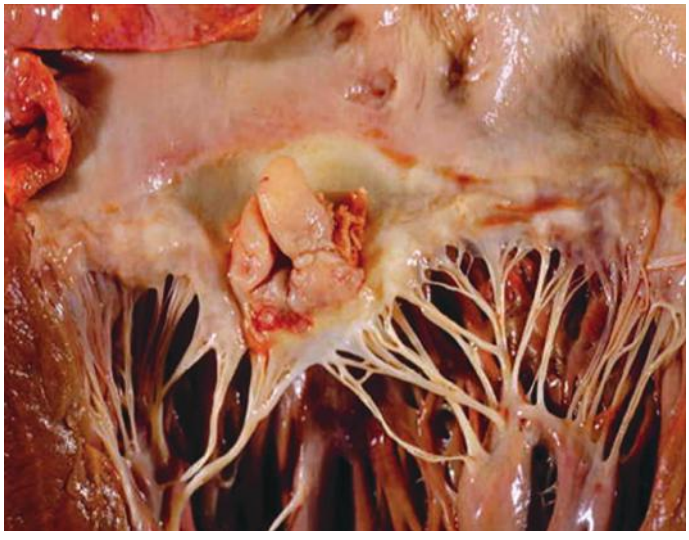


FIGURE 67–2. Large, complex vegetation attached to the left atrial surface of the anterior mitral valve leaflet from a patient with *Staphylococcus lugdunensis* infective endocarditis. Used with permission from Richard Mitchell, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston, MA.

FIGURE 67–3. Cutaneous purpura fulminans in a patient with *Abiotrophia* native valve endocarditis of the mitral and aortic valves.

MICROBIOLOGY OF INFECTIVE ENDOCARDITIS

A wide range of microorganisms can cause IE, but only a few species account for the vast majority of cases. Streptococci and staphylococci are the cause of greater than 80% of IE cases in which a responsible organism is identified. Streptococcal species were historically the most common group of pathogens, but more recent data identify *Staphylococcus aureus* as the most frequently isolated microbial agent worldwide.[26] Moreover, the rate of antibiotic resistance among causative organisms is increasing.[26,65]

NATIVE VALVE ENDOCARDITIS

Streptococci

Viridans group streptococci, or α-hemolytic streptococci, are a frequent cause of community-acquired native valve endocarditis (NVE). Viridans streptococci are responsible for 30% to 65% of cases of NVE in older children and adults.[65,66] They are normal residents of the oropharynx and easily gain access to the circulation after dental or gingival trauma. The viridans streptococci comprise several species, of which *Streptococcus sanguinis*, *Streptococcus gallolyticus* (formerly *bovis*), *Streptococcus mutans*, and *Streptococcus mitior* are most commonly isolated in cases of IE. The viridans streptococci are usually highly sensitive to penicillin, as defined by a minimum inhibitory concentration of < 0.1 μg/mL, and thus can often be eradicated with penicillin monotherapy.[66]

S gallolyticus, a normal inhabitant of the human gastrointestinal (GI) tract, is noteworthy because IE caused by this organism is strongly suggestive of GI malignancy,[67] polyp formation, or diverticular disease. Colonoscopy should be performed when this organism is detected in the blood. When meticulously investigated, GI pathology is discovered in as many as 60% of patients with *S bovis* IE.[60]

Nutritionally deficient streptococci, now known as *Abiotrophia* species and *Granulicatella* species, require specialized isolation and culture techniques for growth (supplemental thiol compounds or active forms of vitamin B_6) and now account for approximately 5% to 7% of streptococcal IE cases.[68] IE caused by these organisms is virtually always indolent in onset and associated with pre-existing heart disease. Therapy remains difficult, and prognosis is poor because these organisms are generally less sensitive to penicillin than the viridans group streptococci.[69] Treatment often requires synergistic therapy with an aminoglycoside.

The *Enterococcus* species, formerly classified as group D streptococci, are now defined as a distinct genus. They are responsible for 5% to 18% of cases of native valve IE, the vast majority of which are caused by *E faecalis* (80%) or *Enterococcus faecium* (10%). These organisms are normal inhabitants of the GI and genitourinary tracts and may enter the bloodstream after manipulation of the colon, urethra, or bladder (eg, Foley catheterization, colonoscopy). The incidence of enterococcal endocarditis appears to be rising, likely as a result of the increased genitourinary and GI instrumentation in older adults and the increased use of indwelling central venous catheters and prosthetic implants. These organisms can infect both normal and diseased heart tissue, as well as prosthetic materials. Indeed, among the most relevant risk factors for development of enterococcal IE is the presence of an implanted device. The pathogenesis of such infections is poorly understood, but several virulence factors have been proposed. The ability to form biofilm has recently been shown to be one of the most prominent features of this microorganism, allowing colonization of inert and biological surfaces and preventing antibiotic penetrance. The disease typically runs an indolent course, and cure is challenging because the organism has limited susceptibility to many antibiotics, including β-lactam drugs. There is an alarming incidence of nosocomial bacteremia with these organisms and a growing problem with drug resistance (to both vancomycin and aminoglycosides). Although synergistic antibiotic therapy, as predicated by susceptibility testing, should be considered,[69] there is some debate regarding its efficacy.[69]

Group A *Streptococcus* rarely causes IE. *Streptococcus pyogenes*, the causative organism in childhood pharyngitis, scarlet fever, impetigo, cellulitis, erysipelas, fasciitis, and myositis, is not associated with IE in adults. Before 1945, *Streptococcus pneumoniae* caused approximately 10% of IE cases; however, the current incidence of pneumococcal IE is very low. *Streptococcus pneumoniae* bacteremia often begins with respiratory infection, and nearly half of patients with pneumococcal IE suffer from chronic alcoholism.[70] *Streptococcus pneumoniae* can infect normal valve tissue and usually results in an acute, fulminant illness often associated with severe valve damage, perivalvular extension, embolic complications, pericarditis, meningitis, and high mortality (25%-50%).[63]

Group B streptococci (eg, *Streptococcus agalactiae*) are chiefly responsible for infections in the neonate and parturient, although these organisms can be isolated from diabetic foot ulcers. Risk factors for group B streptococcal bacteremia in adults include obstetric complications,[71] diabetes, carcinoma, liver failure, alcoholism, and IDU.[72] These organisms are generally less sensitive to penicillin than group A isolates and require higher doses for treatment.

Staphylococci

Staphylococcus aureus causes 80% to 90% of staphylococcal IE and is the most common cause of acute IE. Recent prospective data from the International Collaboration on Endocarditis (ICE) suggest that *Staphylococcus aureus* has become the leading cause of IE worldwide and more often presents as an acute disease.[2,26] The mucous membranes of the anterior nasopharynx are the most common sites of colonization, and approximately 30% of normal persons carry *Staphylococcus aureus*. Carrier rates are higher among persons with more frequent exposures to the organism and those who are at risk for breakdown of the normal mucocutaneous barrier. Rates of *Staphylococcus aureus* infection, particularly bacteremia associated with health care contact, have increased in hospitalized patients and among those receiving outpatient medical therapy.[73,74] Although only a fraction of patients with *Staphylococcus aureus* bacteremia will develop NVE,[75] populations at increased risk include patients on dialysis,[37] patients with type 1 diabetes, burn victims, persons with HIV,[32] IDUs,[27] patients with certain chronic dermatologic conditions, and patients with recent surgical incisions (including median sternotomy for valve replacement).

Despite the frequency of nosocomial *Staphylococcus aureus* acquisition, community-acquired infection appears to be an independent risk factor for the development of IE and metastatic disease.[76,77] *Staphylococcus aureus* is respected as a highly virulent organism and has the capacity to infect and destroy normal endocardial surfaces (see Fig. 67–2). A number of virulence factors help this organism enter the bloodstream, adhere to endothelial and prosthetic surfaces, and evade host defense.[55] *Staphylococcus aureus* IE is frequently fulminant when it involves left-sided cardiac valves and often results in major complications such as valve destruction, heart failure, perivalvular extension with conduction disturbances, embolization, and metastatic infection.[78] Not surprisingly, *Staphylococcus aureus* as a causative organism is an independent predictor of poor prognosis in IE[78] and is associated with a 25% to 30% mortality.[1,26] As many as 50% of patients with left-sided NVE as a result of *Staphylococcus aureus* will require surgery. Right-sided (tricuspid valve) IE with *Staphylococcus aureus*, by contrast, is most frequently associated with IDU and is associated with a high incidence of septic pulmonary embolization but only a 2% to 4% case fatality rate.

The detection of *Staphylococcus aureus* bacteremia should prompt echocardiography to look for evidence of IE, especially if bacteremia is persistent. Although most patients undergo TTE first, an initial TEE should be considered for patients with catheter-associated *Staphylococcus aureus* bacteremia as a cost-effective means of determining the duration of antibiotic therapy (ie, 2 weeks vs 4 weeks).[79] A semisynthetic, β-lactamase–resistant penicillin (eg, nafcillin) is preferred for initial treatment of susceptible *Staphylococcus aureus* in non–penicillin-allergic individuals, often with a short course of an aminoglycoside. Antibiotic resistance can be a particular challenge with *Staphylococcus aureus* because more than 90% of clinical isolates produce β-lactamase and are thus penicillin resistant. Semisynthetic penicillin analogs that are unaffected by β-lactamase, such as methicillin, oxacillin, and nafcillin, are first-line agents. Increasing rates of MRSA in both hospital and community settings[26] and the recovery of clinical *Staphylococcus aureus* isolates resistant to vancomycin[80] have complicated the treatment of *Staphylococcus aureus* IE. Increasing hospital use of vancomycin for the treatment of MRSA is likely one additional reason for the growing incidence of vancomycin resistance among enterococci. Vancomycin, although the best available antibiotic for treatment of MRSA, is only weakly bactericidal and predominantly bacteriostatic. Recently, *Staphylococcus aureus* isolates with varying levels of vancomycin resistance have been cultured from infected patients and have been associated with IE treatment falures.[81] The new lipopeptide antistaphylococcal agent daptomycin has been approved for treatment of *Staphylococcus aureus* bacteremia and right-sided IE[82] and may have promise for the treatment of left-sided IE caused by resistant organisms. Cases of resistant *Staphylococcus aureus* IE should always be managed in close collaboration with an infectious diseases specialist.

The coagulase-negative staphylococci (CoNS) are constituents of normal human skin flora and are much less likely to infect normal endocardial surfaces. *Staphylococcus epidermidis* is an important causative agent in prosthetic valve and device-related endocarditis. NVE caused by CoNS occurs mainly in patients with pre-existing valvular heart disease,[83] although exceptions to this generalization do occur (see Fig. 67–3). NVE caused by CoNS has historically been regarded as an indolent disease; however, recent data from the ICE have demonstrated equal rates of heart failure and death for CoNS and *Staphylococcus aureus* NVE.[83] *Staphylococcus epidermidis* infections of intracardiac devices are extremely difficult to eradicate, and the addition of adjunctive course of rifampin therapy is often recommended. Rare cases of IE caused by other CoNS (eg, *Staphylococcus saprophyticus*, *Staphylococcus capitis*) have been reported,[84,85] including a growing number of reports of IE caused by community-acquired *Staphylococcus lugdunensis*.[86] *S lugdunensis* may cause a more virulent form of IE with high morbidity despite uniform in vitro susceptibility to most antibiotics.

Gram-Negative Bacilli

IE caused by gram-negative bacilli is uncommon and tends to occur in IDUs, immunocompromised patients, patients with advanced liver disease, and prosthetic heart valve recipients. The fastidious gram-negative rods of the HACEK group (*Haemophilus* species, *Actinobacillus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) reside normally in the oropharynx and are responsible for a very small (approximately 1%) proportion of cases of NVE, usually involving abnormal valve tissue. Because of their growth requirements (carbon dioxide), they may take 3 to 4 weeks to grow in culture and have gained notoriety for their implicated role in certain cases of culture-negative IE. The *Haemophilus* species (*Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus*) are the most common etiologic agents from this group. They typically form large and friable vegetations that have a tendency to embolize. There are numerous case reports of IE caused by other members of the HACEK group.[87] The Enterobacteriaceae (eg, *Escherichia coli, Klebsiella, Enterobacter, Serratia*) are rare causes of IE. *Salmonella* species have a particular predilection for atherosclerotic plaque and may infect arterial aneurysms.[88] The vast majority of patients with *P aeruginosa* endocarditis are IDUs.[89] The source of *Pseudomonas* appears to be from standing water that contaminates needles and other drug paraphernalia. Left-sided endocarditis caused by *P aeruginosa* is difficult to eradicate with antibiotics alone, has a high rate of complications, and often requires early surgery.[89]

The rickettsial organism *Coxiella burnetii* is the causative agent of Q fever and is a relevant cause of IE in areas where cattle, sheep, and goat farming are common. Cases of IE caused by *C burnetii* are well documented in the developed world.[90] The aortic valve is affected in more than 80% of cases, and the infection is difficult to eradicate with antibiotics. Because the organism is extremely difficult to culture, the diagnosis is best made serologically using antibody titers.[90] *Bartonella* species (*Bartonella quintana, Bartonella henselae, Bartonella elizabethae*), the etiologic agents in cat scratch disease, have been recently described as an important cause of IE among both homeless men and HIV-infected patients. The diagnosis can be suspected serologically and confirmed with special culture techniques or by polymerase chain reaction.[91] Brucellae have been implicated in approximately 4% of cases of IE in Spain. These organisms are usually ingested in unpasteurized milk or cheese and are occupational hazards for veterinarians, shepherds, and livestock handlers. IE is the most common cause of death in patients with brucellosis, and surgery is usually required for cure.[92]

Fungal Infective Endocarditis

Fungal endocarditis is a relatively new syndrome associated with exceedingly high mortality (survival rates of < 20%). Patients who develop fungal IE have multiple predisposing conditions that include an immunocompromised state, the use of endovascular devices, and previous reconstructive cardiac surgery. *Candida* and *Aspergillus* species are the most common causes of fungal IE and are associated with large, bulky vegetations that can obstruct valve orifices and can also embolize to large vessels (eg, the femoral artery). Blood cultures are usually positive in cases of *Candida* IE, whereas they are rarely positive with *Aspergillus*. Fungal endocarditis is an indication for surgical replacement of an infected valve. Cure usually requires combination fungicidal (amphotericin) and surgical treatment, followed by long-term suppressive therapy with an oral antifungal agent.[93-95]

Culture-Negative Infective Endocarditis

Blood cultures are negative in up to 20% of patients with IE diagnosed by strict criteria.[93,94] Failure to isolate a microorganism may be the result of inadequate culture technique, a highly fastidious organism or a nonbacterial pathogen as the causative agent, or previous administration of antimicrobial therapy before blood culture acquisition. The latter is an extremely important consideration because the administration of antibiotics before drawing blood cultures can reduce the recovery rate of bacterial pathogens by nearly one-third.[93-96] There are numerous noninfectious causes of endocarditis that may behave like culture-negative IE, including those that are related to neoplasia (nonbacterial thrombotic endocarditis), autoimmune diseases (antiphospholipid antibody syndrome, systemic lupus erythematosus), or the postcardiac surgical state (thrombi, sutures).[88,93-95] Empiric therapy for culture-negative IE remains extremely challenging because the patient may be exposed to potentially toxic antimicrobial therapy while awaiting what is often delayed identification of a causative organism, if one is identified at all. Consultation with an infectious disease specialist to define the most appropriate therapy is recommended.

PROSTHETIC VALVE ENDOCARDITIS

Prosthetic valve endocarditis (PVE) represents approximately 10% to 30% of all IE cases.[9,15,65] Although many of the general principles applicable to native valve IE are relevant, there are important considerations specific to PVE. After valve replacement, the incidence of PVE is approximately 1% to 3% at 1 year and 3% to 6% at 5 years. Although the current evidence is not definitive, PVE can be broadly divided into two groups based on the time of onset of the infection after valve surgery—early PVE and late PVE. Early PVE is defined as endocarditis that develops within the first 2 months to 1 year after valve surgery. During this period, the vast majority of causative organisms are nosocomially acquired, with a predominance of staphylococci, notably coagulase-negative species (*Staphylococcus epidermidis*). Gram-negative bacilli, diphtheroids, and fungal species, although uncommon causes of IE overall, have a predilection to cause PVE during this early period. Late PVE is defined as that occurring beyond 1 year postoperatively. In contrast to early PVE, the spectrum of causative organisms in late PVE resembles that of NVE. In late PVE, cases are predominantly a result of streptococci and enterococci, with a significant decrease in the rate of coagulase-negative staphylococci and a continued rate of infection with *Staphylococcus aureus*. Between 2 and 12 months after valve replacement surgery, there is a gradual transition between the early and late microbiologic causes of PVE.

TEE imaging is recommended in cases of suspected PVE (see below). In some cases, both TTE and TEE are performed to provide optimal characterization of the infection, prosthetic valve function, and cardiac performance. Empiric therapy for suspected PVE is similar to that for NVE; however, staphylococcal coverage should always be provided until definitive culture data are available, with particular attention to the likelihood of antibiotic resistance (MRSA). Complication rates with PVE are high, and surgery is often required even in the absence of documented perivalvular extension. For example, *Staphylococcus aureus* PVE is rarely eradicated with antibiotics alone, and retrospective analyses suggest that combined medical and surgical therapy is more effective than medical therapy alone.[95,96] With proper timing of antibiotic therapy and surgery, the imputed risk of early reinfection of a newly implanted valve is only 2% to 3%.[97]

APPROACH TO THE PATIENT WITH SUSPECTED INFECTIVE ENDOCARDITIS

The history in patients with suspected IE should focus on predisposing factors such as intravenous drug use, a prior history of IE, recent exposures, the presence of an intracardiac device or indwelling central venous catheter, congenital or acquired valvular heart disease, and other congenital or structural heart disease. The patient may report fever, fatigue, anorexia, weight loss, night sweats, joint pain, or back pain. Often, the nature of the presenting symptoms reflects the severity and type of infection. Patients with *Staphylococcus aureus* infection, for example, are likely to have a fulminant course with high fever and systemic sepsis, whereas some infections with streptococcal organisms may have a more protracted course. Features on clinical examination that raise suspicion for IE include fever, a new heart murmur indicative of valvular insufficiency, signs of heart failure, and peripheral vascular phenomena. Examples of classic IE-related findings include major arterial emboli with pulse deficits, septic pulmonary emboli (with right-sided IE), mycotic brain aneurysms with intracranial hemorrhage, mucosal or conjunctival petechiae, splinter hemorrhages of the nail beds, palpable purpuric skin rashes (Fig. 67–4), Janeway lesions (small, flat, irregular erythematous spots on the palms and soles), Osler nodes (tender, erythematous nodules occurring in the pad portion of the fingers), Roth spots (cytoid bodies and associated hemorrhage caused by microinfarction of retinal vessels), and urinary red cell casts suggestive of glomerulonephritis (Fig. 67–5).

Although the history and physical examination are useful, the diagnosis of IE rests on the ability to demonstrate endocardial involvement and persistent bacteremia. The proper acquisition of blood cultures before initiation of antimicrobial therapy is essential. In hospitalized patients, the presence of bacteremia with a typical causative organism (eg, *Staphylococcus aureus*) often provides initial suspicion for IE and prompts further diagnostic evaluation. Echocardiography should be used to seek the presence of endocardial involvement (vegetations, abscess formation, and new valvular regurgitation). These clinical, microbiologic, and echocardiographic features are the foundation for the modified Duke criteria, a set of integrated findings that has become the standard for diagnosis of IE (Tables 67–2 and 67–3).[98] These criteria are discussed in detail later in this chapter.

Once the diagnosis has been made and appropriate therapy initiated, the patient should be monitored closely for complications, especially during the first week of therapy. All patients should have repeat blood cultures after institution of antibiotics to ensure sterility of the blood. Persistent fever beyond 1 week of appropriate therapy should raise the suspicion for intracardiac extension, satellite abscess formation, or an antibiotic-resistant organism. In the absence of complications, the first several days of intravenous antibiotics are administered in the hospital and the remaining course provided via a central venous catheter (eg, peripherally inserted central catheter) as an outpatient with careful follow-up. Patients should be maintained on telemetry while in hospital; the need for surveillance electrocardiograms (ECGs) during outpatient therapy is dictated by the location of the infection and the predicted likelihood of conduction disturbances. Patients should be monitored for antimicrobial toxicity, particularly with aminoglycoside use. Routine surveillance echocardiography during therapy is not necessary unless complications develop or cardiac surgery is being considered (see later section Echocardiography in Infective Endocarditis). At the completion of therapy, TTE may be performed to establish a new "post-IE baseline."[65] After successful therapy, patients with IE should be followed longitudinally for the possible development of progressive valvular and/or ventricular dysfunction. Patients with successfully treated IE are at high risk for the development of future episodes of IE and should receive antibiotic prophylaxis before specific dental procedures, as recommended by current guidelines (see later section Antibiotic Prophylaxis for the Prevention of Infective Endocarditis).[3,4,99,100]

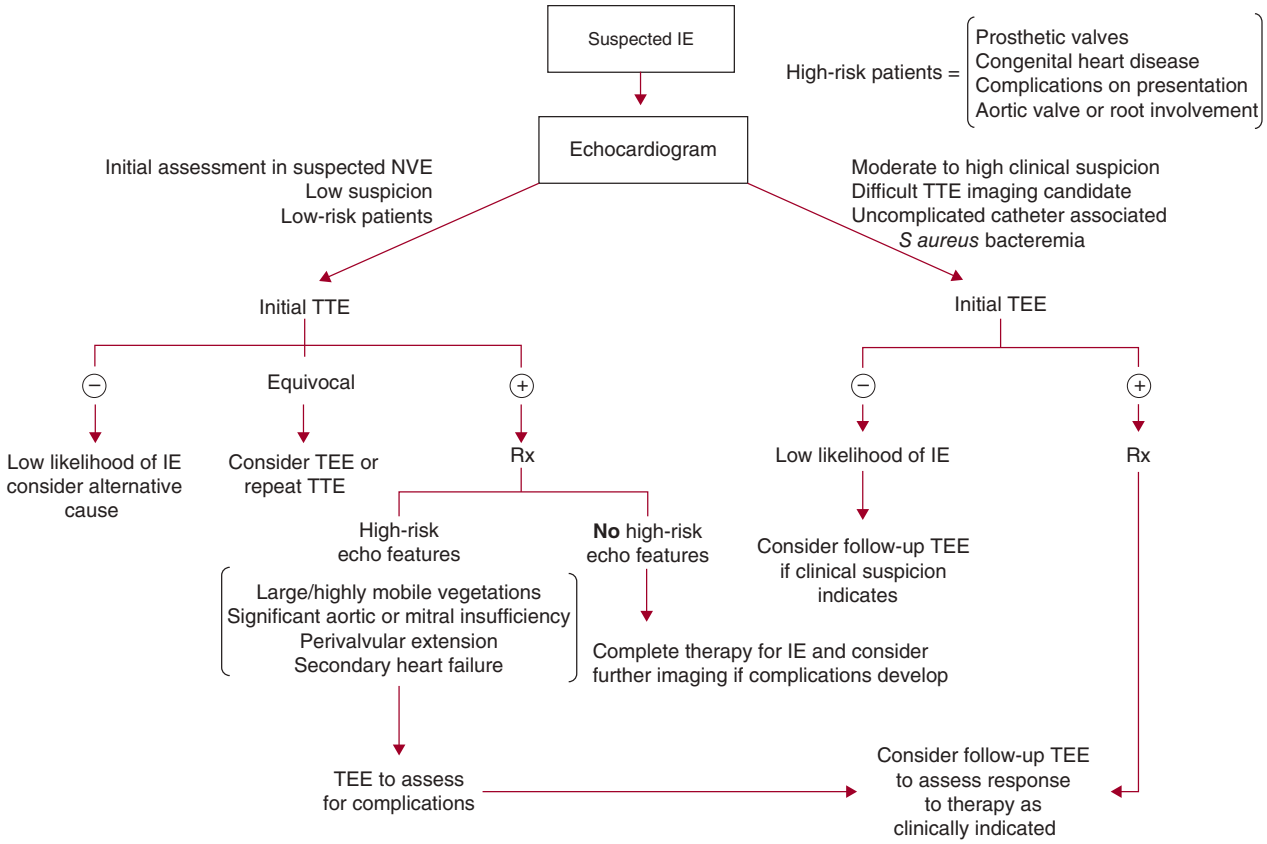
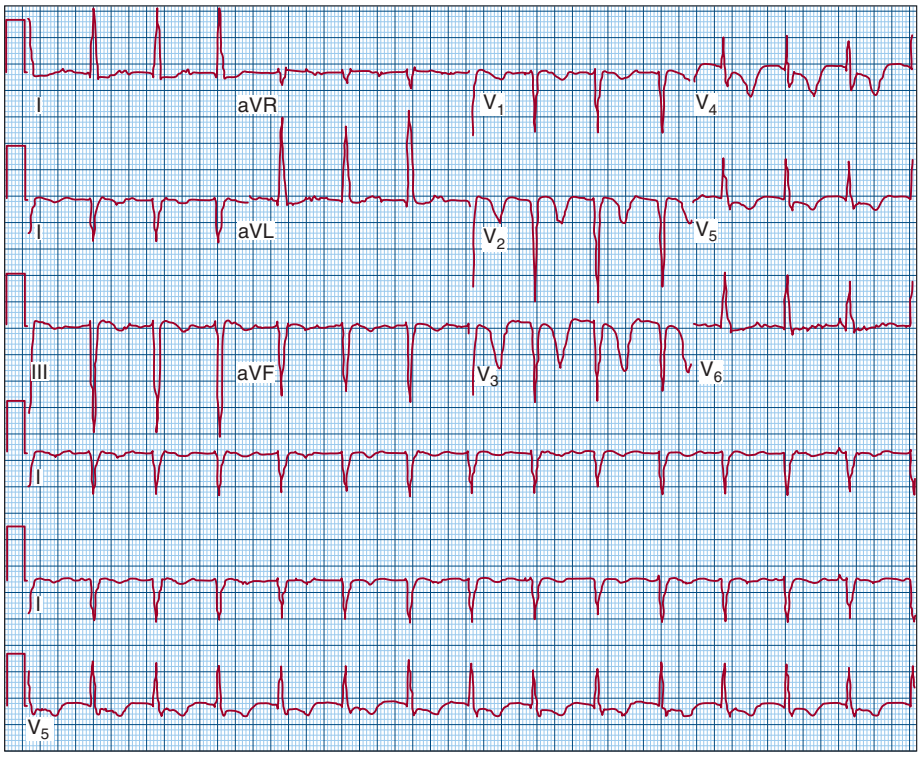
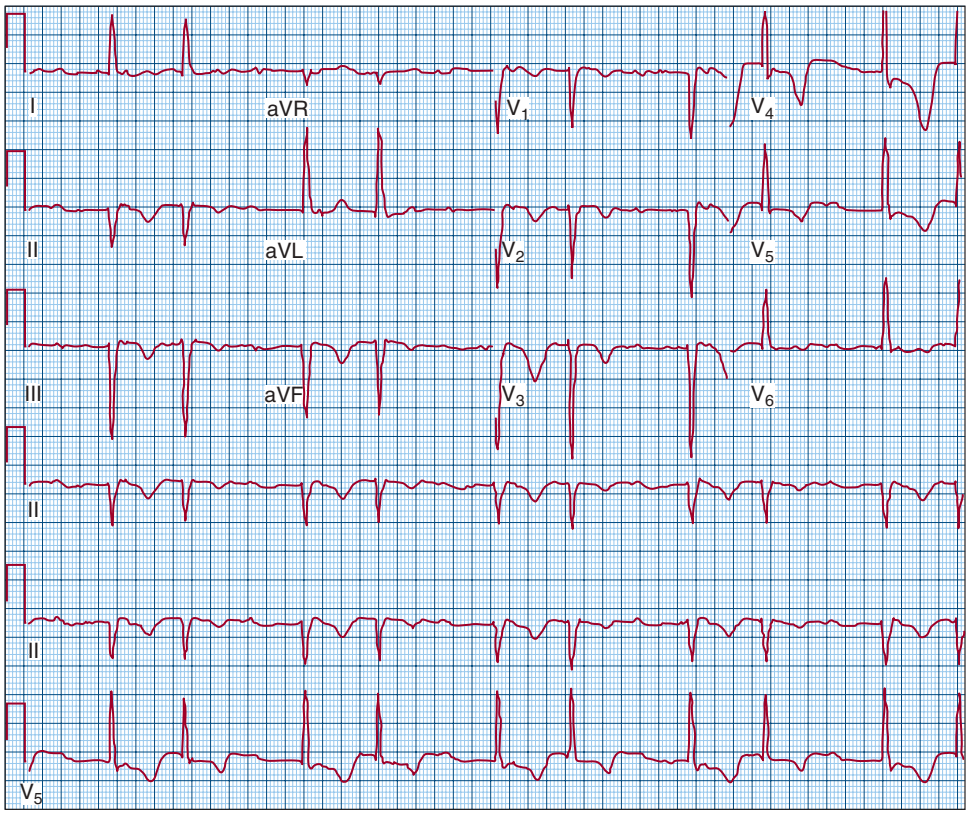


FIGURE 67–4. Use of echocardiography in diagnosis and management of infective endocarditis (IE). NVE, native valve endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. Adapted with permission from Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation*. 1998 Dec 22-29;98(25):2936-2948.



A

FIGURE 67–5. Serial electrocardiograms obtained in a patient with methicillin-resistant *Staphylococcus aureus* (MRSA) aortic valve endocarditis complicated by root abscess and ventricular septal rupture. Note progressive degrees of high-grade atrioventricular (AV) block. **A.** First-degree AV block. **B.** Second-degree AV block. **C.** Complete heart block.



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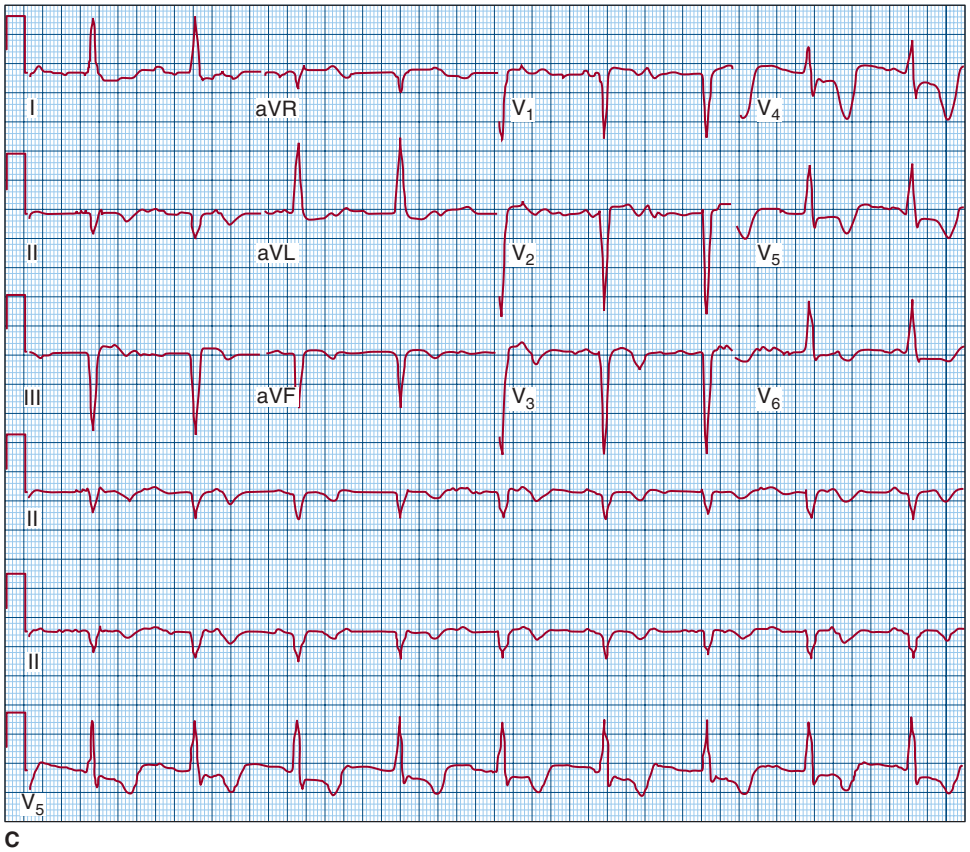


C

FIGURE 67–5. (*Continued*)

TABLE 67–2. Definition of Terms Used in the Proposed Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures:
Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus*; or
Community-acquired enterococci in the absence of a primary focus; or
Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
At least 2 positive cultures of blood samples drawn more than 12 h apart; or
All of 3 or a majority of greater than 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for *Coxiella brunetti* or anti–phase 1 IgG antibody titer greater than 1:800
Evidence of endocardial involvement
Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
Abscess; or
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition, or injection drug use
Fever, temperature > 100.4°F (38°C)
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunologic phenomena; glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
Microbiologic evidence: positive blood culture but does not meet a major criterion,[a] or serologic evidence of active infection with organism consistent with IE
Echocardiographic minor criteria eliminated

Abbreviations: HACEK, *Haemophilus* species, *Actinobacillus, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species; IE, infective endocarditis; Ig, immunoglobulin; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

Reproduced with permission from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000 Apr;30(4):633-638.

TABLE 67–3. Definition of Infective Endocarditis According to the Proposed Modified Duke Criteria

Definite infective endocarditis
Pathologic criteria
(1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
(2) Pathologic lesions, vegetation, or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria
(1) 2 major criteria; or
(2) 1 major criterion and 3 minor criteria; or
(3) 5 minor criteria
Possible infective endocarditis
(1) 1 major criterion and 1 minor criterion; or
(2) 3 minor criteria
Rejected
(1) Firm alternate diagnosis explaining evidence of infective endocarditis; or
(2) Resolution of infective endocarditis syndrome with antibiotic therapy for less than 4 days; or
(3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for less than 4 days; or
(4) Does not meet criteria for possible infective endocarditis, as noted above

Reproduced with permission from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000 Apr;30(4):633-638.

DIAGNOSIS OF INFECTIVE ENDOCARDITIS

IE is defined as an infection on any structure within the heart, including normal or damaged endothelial surfaces, prosthetic heart valves, and implanted devices (eg, pacemakers, ICDs, ventricular assist devices, surgical shunts).[18] The diagnosis of IE relies chiefly on the following factors: (1) an initial clinical suspicion, especially in a patient with identifiable risk factors, for example, fever without obvious etiology; (2) microbiologic data (blood cultures demonstrating continuous bacteremia or cultures of vegetative emboli removed surgically); and (3) the results of echocardiographic imaging. Diagnosis is straightforward in only a minority of patients who present with a defined predisposing condition and the classic manifestations of fever, evidence of active valvulitis, peripheral emboli, renal immunologic or peripheral vascular phenomena, and bacteremia. In the majority of patients, IE has an extremely variable clinical presentation.[2,66]

CLINICAL CRITERIA

Pelletier and Petersdorf[101] published the first formal case definition based on their 30-year experience caring for patients with IE in Seattle, Washington. Although this first case definition was specific for the diagnosis of IE, it lacked sufficient sensitivity. Subsequently, von Reyn and colleagues[102] developed the first stratified diagnostic schema in which cases were placed into four categories (rejected, possible, probable, and definite). This approach eventually proved inadequate because of overclassification of cases as "possible" and "probable," over-reliance on pathologic specimens, and the lack of incorporation of echocardiographic data. In 1994, Durack and colleagues published the Duke criteria[103] for the diagnosis of IE that incorporated additional clinical factors as well as echocardiographic data. These criteria were revised in 2000 to increase the sensitivity for detection of cases related to *Staphylococcus aureus* bacteremia, as well as to account for culture-negative IE.[98] The modified Duke criteria (see Tables 67–2 and 67–3) have become the current standard for diagnosis and clinical research and have been validated in numerous subsequent studies.[104-106] A diagnosis of *definite IE* is established clinically by evidence of two major criteria, one major plus three minor criteria, or five minor criteria. Patients identified with *possible IE* (one major criterion plus one minor criterion or three minor criteria) should be treated for IE until the diagnosis is satisfactorily excluded. Application of these criteria in clinical practice will capture the vast majority of cases of IE and render quite remote the possibility

of missing a potential case. The modified Duke criteria are both clinically and biologically sound, relying on microbiologic data and evidence of endocardial involvement, with attention to predisposing factors and early complications of a vascular or immunologic nature. Definitions of specific criteria and terms used in the modified Duke criteria are detailed in Table 67–2.[98,100]

The importance of obtaining blood cultures by appropriate methods, before the institution of antibiotics, cannot be overemphasized. Three separate sets of blood cultures obtained from different venipuncture sites over 24 hours are recommended. For the most commonly encountered bacterial pathogens (staphylococci, streptococci, enterococci), the first two sets of blood cultures will be positive in the vast majority of cases.[107] Culture-negative IE is most commonly associated with antecedent antibiotic use but may be caused by fastidious (eg, HACEK) or intracellular organisms that are not readily detected using standard culture techniques,[87] especially if the laboratory has not been alerted to the possibility of IE and the need to perform additional testing. Identification of the offending pathogen may require special culture media and prolonged incubation times (> 2 weeks).[17] Other indirect measures of active infection with difficult-to-culture organisms (eg, *Bartonella, Brucella, Legionella*) include positive results of serology, agglutination, immunofluorescence, and polymerase chain reaction amplification assays.[66,87] It should be noted that many of these indirect diagnostic tests may be nonspecific, and careful interpretation is needed to avoid erroneous or false-positive results.

ECHOCARDIOGRAPHY IN INFECTIVE ENDOCARDITIS

All patients with suspected IE should undergo prompt echocardiographic assessment. There are several TTE findings suggestive of endocarditis, including vegetations, evidence of periannular tissue destruction (ie, abscess formation), aneurysms or fistula formation, leaflet perforation, or prosthetic valve dehiscence.[18] Specific definitions of these findings are outlined in Table 67–4.[108] The echocardiographic definition of a vegetation is an irregular-shaped, discrete echogenic mass that must be adherent to, yet distinct from, the endothelial surface to which it is attached. The presence of a vegetation is strongly supportive of the diagnosis of IE if the suspected mass oscillates at a high frequency, independent of other intracardiac structures.

Although there remains some debate regarding the optimal approach, the vast majority of patients should initially undergo transthoracic (TTE) imaging because of its immediate availability and ease of use. A low threshold to pursue transesophageal (TEE) imaging is appropriate, as dictated by the clinical circumstances, the adequacy of the TTE images, and the potential need for early surgical planning and intervention. It is well established that TTE has limited sensitivity for the detection of vegetations (approximately 65%) and intracardiac abscesses (approximately 30%).[21,109] The technique, however, is safe, portable, readily available, and provides useful information regarding ventricular size and function, estimated pulmonary artery systolic pressure, and the appearance and function of uninvolved valves. Another important strength of TTE is its high specificity for the detection of vegetations (approaching 98%).[109] When visualized, vegetations can be characterized further by their size, mobility, texture, and point of attachment. Any associated valvular dysfunction (regurgitation or stenosis) can be assessed with Doppler interrogation and a baseline established against which future comparisons can be made. Nevertheless, as many as one-fifth of patients have technically inadequate TTE images for proper resolution of valvular and endocardial structures.[18] TTE does not provide adequate visualization of prosthetic heart valves (especially in the mitral position) as a result of acoustic shadowing, a situation in which its diagnostic sensitivity is reduced to 15% to 35%.[110] Finally, TTE has limited ability to delineate perivalvular extension of infection under most clinical circumstances.[21,110,111]

TEE is now performed with increasing frequency in the assessment of patients with suspected or proven IE. Although TEE is invasive and requires conscious sedation, the procedure is generally well tolerated, with low complication rates.[111] Compared with TTE, TEE has excellent specificity and offers better sensitivity for the detection of vegetations (85%-95%) and intracardiac abscesses (87%) as well as greater spatial resolution.[21,109,110] The sensitivity of TEE for the detection of vegetations in patients with suspected PVE is 82% to 96%,[110] and TEE should be considered a first-line imaging modality in cases of suspected PVE. TEE, combined with spectral and color flow Doppler analysis, also provides excellent definition of intracardiac fistulas, valve leaflet perforations, and false aneurysms. The performance characteristics of TTE and TEE are summarized in Table 67–5. TEE should be performed expeditiously in patients with high-risk clinical features at presentation (eg, suspected *Staphylococcus aureus* infection of the aortic valve and root), known congenital heart disease, or suboptimal TTE images. For patients undergoing cardiac surgery for IE, intraoperative TEE is routine. TEE should also be considered for patients

TABLE 67–4. Typical Echocardiographic Findings in Infective Endocarditis

Finding	Description
Vegetation	Irregularly shaped, discrete echogenic mass.
	Adherent to, yet distinct from, endocardial surface.
	High-frequency oscillation of the mass with motion that is independent of that of normal cardiac structures is a supportive, but not mandatory, finding.
Abscess	Thickened area or mass within the myocardium or annular region.
	Appearance is nonhomogeneous, often with both echogenic and echolucent areas in the lesion.
	Evidence of flow (by Doppler interrogation) within the area is strongly supportive, but not mandatory.
Aneurysm	Echolucent space that is contiguous with the cavity of origin and that is completely bounded by a thin layer of tissue extending from the cavity of origin.
Fistula	Connection between 2 distinct cardiac blood spaces through a nonanatomic channel.
Leaflet perforation	Defect in the body of a cardiac valve leaflet with evidence of blood flow through the defect.
Prosthetic valvular dehiscence	Rocking motion of a prosthetic valve with excursion of more than 15 degrees in any single plane.

Data from Sachdev M, Peterson GE, Jollis JG. Imaging techniques for diagnosis of infective endocarditis. *Cardiol Clin*. 2003 May;21(2):185-195.

TABLE 67–5. Aggregate Performance Characteristics of TTE and TEE in the Diagnosis of IE

	Sensitivity (%)	Specificity (%)
TTE	60-65	98
TEE	85-95	85-98

Abbreviations: IE, infective endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
Data compiled.[103-106,110]

with catheter-associated *Staphylococcus aureus* bacteremia to predict the indicated duration of antibiotic therapy (ie, 2 weeks vs 4 weeks).[79] Other analyses have suggested that in patients with an intermediate pretest likelihood of IE, an initial TEE is cost-effective.[112]

Because of its superior performance characteristics, it is tempting to pursue TEE in all cases of suspected or proven IE. In several circumstances, however, TTE is sufficient for both diagnosis and clinical decision making. For example, in a patient with mitral valve endocarditis caused by a penicillin-sensitive viridans streptococcal species, an isolated posterior leaflet vegetation of less than 1 cm in length, and mild mitral regurgitation, antibiotic therapy can be initiated with careful follow-up. If clinically indicated, a repeat TTE can be performed to assess for complications or response to therapy. A similar approach could be adopted for a patient who has used intravenous drugs with resultant tricuspid valve IE and no clinical or TTE evidence of left-sided involvement at presentation. Thus, the choice of echocardiographic modality can be tailored to the clinical situation. The indications for TTE and TEE in patients with IE are shown in Tables 67–6 and 67–7.[100] An algorithm for the use of echocardiography in IE is presented in Fig. 67–6.[66]

Although diagnostic echocardiography is recommended for all patients with suspected IE, some studies have suggested that in very low-risk subgroups, echocardiography may be avoided without loss of diagnostic accuracy. Kuruppu and colleagues[113] have shown that 53% of echocardiograms could have been avoided without loss of diagnostic accuracy by using a simple algorithm in patients with a low pretest probability of disease. In another analysis, Greaves and colleagues[114] have shown that the negative predictive value of TEE was 1.0 in the absence of five simple clinical criteria: vasculitic/embolic phenomena, presence of central venous access, recent history of intravenous drug use, presence of a prosthetic valve, and positive blood cultures. These studies suggest that routine echocardiographic imaging may not be indicated in a subset of low-risk patients.

The findings on echocardiography alone do not definitively establish or exclude the diagnosis of IE. Infective vegetations may be difficult to distinguish from other intracardiac masses, such as calcified debris, torn chordae, thrombus, fibroelastoma, and the nonbacterial lesions associated with healed IE, nonbacterial thrombotic endocarditis in the setting of systemic malignancy, antiphospholipid antibody syndrome, and systemic lupus erythematosus (Libman-Sacks endocarditis). In addition, an initially nondiagnostic TEE (despite its high negative predictive value) does not exclude the possibility of IE, and a repeat study is indicated in 3 to 5 days if the clinical index of suspicion remains high.[115] Accurate diagnosis, therefore, relies on an integrated assessment of the clinical, microbiologic, and echocardiographic data.

In uncomplicated cases of IE, a single echocardiographic study is usually sufficient. However, with complex IE, serial echocardiographic examinations may help determine prognosis and guide surgical intervention.

TABLE 67–6. Indications for Transthoracic Echocardiography in Endocarditis

Class I

1. Transthoracic echocardiography to detect valvular vegetations with or without positive blood cultures is recommended for the diagnosis of infective endocarditis. *(Level of Evidence: B)*
2. Transthoracic echocardiography is recommended to characterize the hemodynamic severity of valvular lesions in known infective endocarditis. *(Level of Evidence: B)*
3. Transthoracic echocardiography is recommended for assessment of complications of infective endocarditis (eg, abscesses, perforations, and shunts). *(Level of Evidence: B)*
4. Transthoracic echocardiography is recommended for reassessment of high-risk patients (eg, those with a virulent organism, clinical deterioration, persistent or recurrent fever, new murmur, or persistent bacteremia). *(Level of Evidence: C)*

Class IIa

Transthoracic echocardiography is reasonable to diagnose infective endocarditis of a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur. *(Level of Evidence: C)*

Class IIb

Transthoracic echocardiography may be considered for the re-evaluation of prosthetic valve endocarditis during antibiotic therapy in the absence of clinical deterioration. *(Level of Evidence: C)*

Class III

Transthoracic echocardiography is not indicated to re-evaluate uncomplicated (including no regurgitation on baseline echocardiogram) native valve endocarditis during antibiotic treatment in the absence of clinical deterioration, new physical findings, or persistent fever. *(Level of Evidence: C)*

Data from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

TABLE 67–7. Indications for Transesophageal Echocardiography in Endocarditis

Class I

1. Transesophageal echocardiography is recommended to assess the severity of valvular lesions in symptomatic patients with infective endocarditis, if transthoracic echocardiography is nondiagnostic. *(Level of Evidence: C)*
2. Transesophageal echocardiography is recommended to diagnose infective endocarditis in patients with valvular heart disease and positive blood cultures, if transthoracic echocardiography is nondiagnostic. *(Level of Evidence: C)*
3. Transesophageal echocardiography is recommended to diagnose complications of infective endocarditis with potential impact on prognosis and management (eg, abscesses, perforation, and shunts). *(Level of Evidence: C)*
4. Transesophageal echocardiography is recommended as first-line diagnostic study to diagnose prosthetic valve endocarditis and assess for complications. *(Level of Evidence: C)*
5. Transesophageal echocardiography is recommended for preoperative evaluation in patients with known infective endocarditis, unless the need for surgery is evident on transthoracic imaging and unless preoperative imaging will delay surgery in urgent cases. *(Level of Evidence: C)*
6. Intraoperative transesophageal echocardiography is recommended for patients undergoing valve surgery for infective endocarditis. *(Level of Evidence: C)*

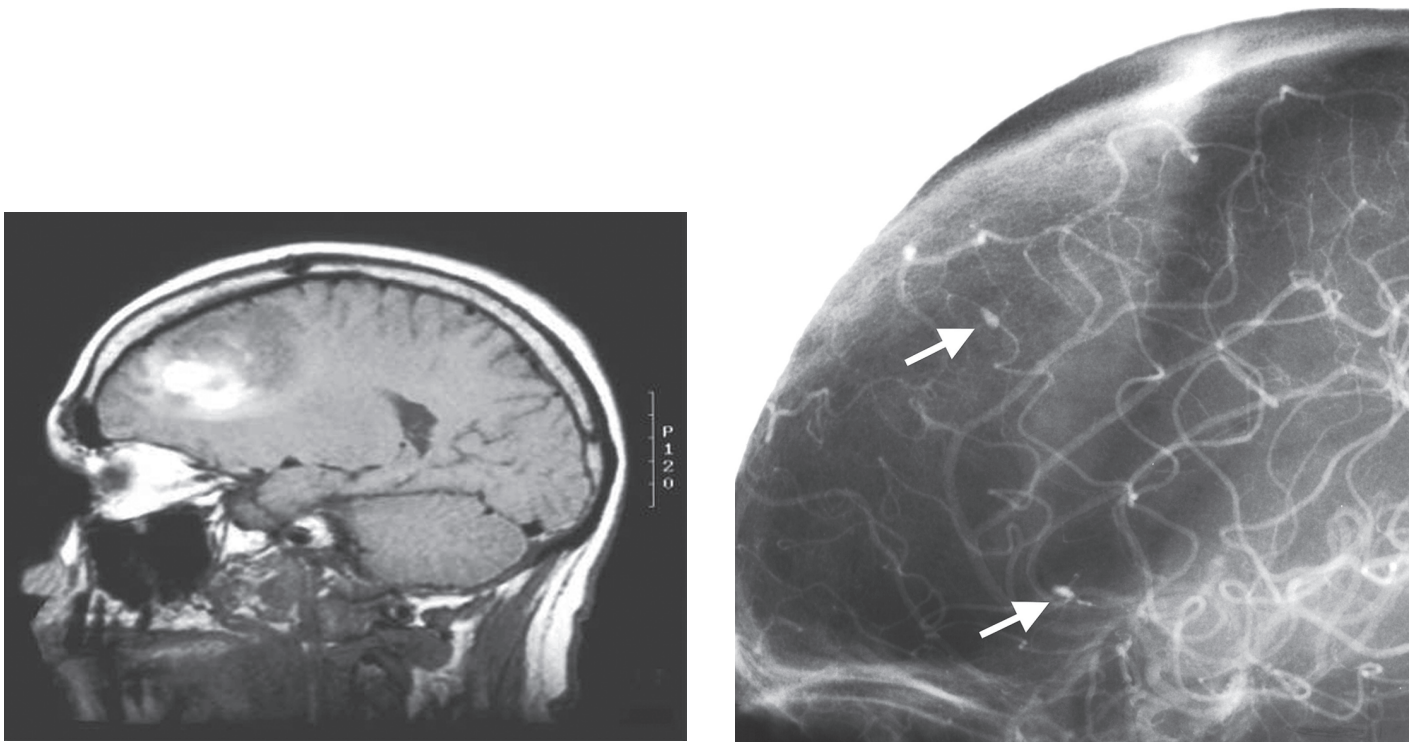
Class IIa

Transesophageal echocardiography is reasonable to diagnose possible infective endocarditis in patients with persistent staphylococcal bacteremia without a known source. *(Level of Evidence: C)*

Class IIb

Transesophageal echocardiography might be considered to detect infective endocarditis in patients with nosocomial staphylococcal bacteremia. *(Level of Evidence: C)*

Data from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.



A B

FIGURE 67–6. A. Large right frontal hemorrhage in a patient with *Staphylococcus aureus* mitral valve endocarditis. **B.** Mycotic aneurysms (*arrows*) along the course of the branches of the middle cerebral artery. Reproduced with permission from Mauri L, de Lemos JA, O'Gara PT. Infective endocarditis. *Curr Probl Cardiol*. 2001 Sep;26(9):562-610.

Rohmann and colleagues[116] performed serial TEE studies in 83 patients with echocardiographic evidence of IE and followed them prospectively for a mean duration of 6 months and found that vegetations that increased in size were associated with significantly increased risk of complications. Similarly, Thuny et al[117] reported that vegetation length was a strong predictor of the occurrence of both embolic events and mortality. Re-evaluation echocardiographic studies should be performed in patients with complex IE defined as infection with a virulent organism (eg, *Staphylococcus aureus*), severe hemodynamic compromise, aortic valve involvement, persistent fever or bacteremia, clinical change during therapy, or symptomatic deterioration. The use of re-evaluation studies in uncomplicated IE is less well established.[111] In the vast majority of cases, no additional diagnostic information is provided with a second echocardiogram.[118] Cerebral imaging with MRI can be useful in many patients with IE because it may disclose evidence of brain embolization, leading to possible alteration in the clinical approach to such individuals.[119]

BIOMARKERS IN THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS

Recently, a number of blood biomarkers have been described for increasing diagnostic accuracy in patients with suspected IE. Mueller et al[120] and Knudsen et al[121] observed that blood procalcitonin levels were elevated in patients with documented IE. Unfortunately, sepsis without endocarditis can also raise blood procalcitonin levels, so the specificity of IE with this test is not high. C-reactive protein (CRP) has also been measured in patients with IE. CRP is a nonspecific marker of inflammation that is elevated in patients with IE. Normalization of CRP levels in patients with documented IE is a good predictor of a favorable outcome for these individuals.[122] N-terminal pro-B-type natriuretic peptide along with troponin levels also predict the outcome for patients with IE.[123]

ACUTE COMPLICATIONS

Complication rates with IE have remained relatively unchanged despite advances in diagnosis and antimicrobial therapy. Complications can generally be related to local extension of infection (eg, valve ring abscess, fistulae, conduction block), destruction of or interference with intracardiac structures (eg, leaflet perforation or valvular obstruction), embolization (eg, stroke, septic pulmonary emboli), bacteremia/sepsis (eg, multisystem organ failure), and immune complex disease (eg, glomerulonephritis).

HEART FAILURE

Heart failure, the most frequent major complication of IE,[124] was found to occur in 32% of patients in a recent prospective study.[2] Its development portends an adverse prognosis with medical therapy alone[1,2] and is an indication for surgical intervention in most instances.[100,125] Reduced left ventricular (LV) systolic function is a powerful predictor of an adverse outcome after surgery.[126] Heart failure in IE is most often related to acute, severe valvular dysfunction as a result of either leaflet destruction or interference with normal leaflet coaptation. Heart failure may also develop secondary to rupture of infected mitral chordae, obstruction caused by bulky vegetations, development of intracardiac shunts, or prosthetic valve dehiscence.[66] Heart failure may also develop more gradually, over the intermediate to long term, as a function of continued valve incompetence with concomitant worsening of ventricular function after otherwise successful antibiotic treatment.

Heart failure is most commonly associated with aortic valve IE (29%), followed by mitral valve (20%) and tricuspid valve (8%) involvement.[127] In acute severe aortic regurgitation, the LV operates on the steep portion

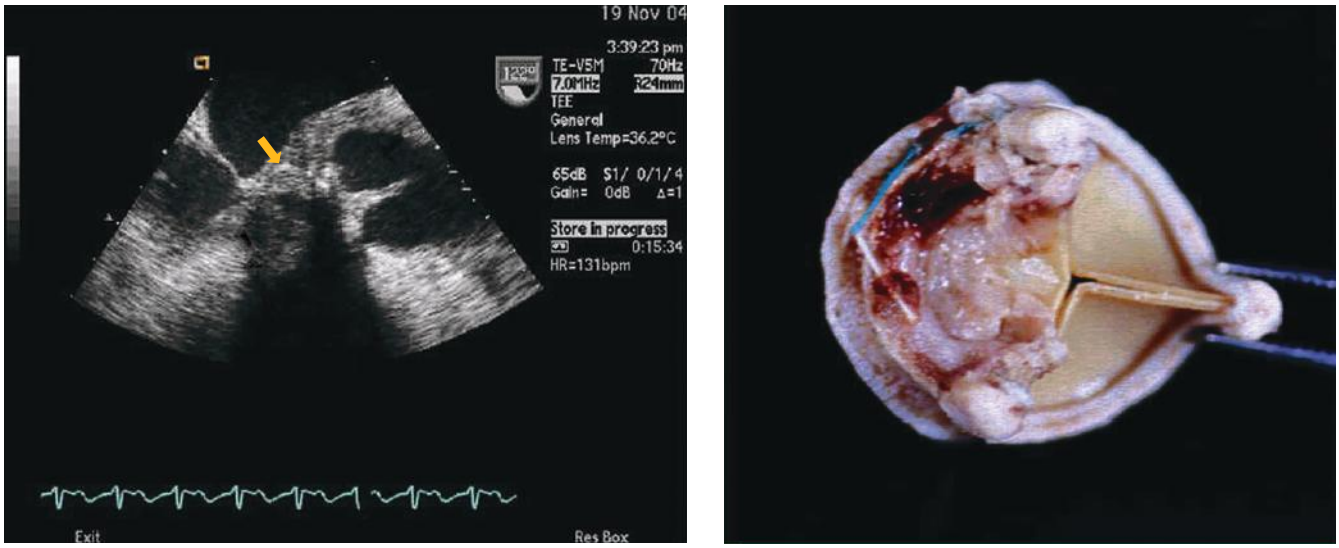


FIGURE 67–7. A. Transesophageal echocardiographic image of bioprosthetic aortic valve with annular abscess (*arrow*) from a patient with *Staphylococcus aureus* prosthetic valve endocarditis. **B.** Excised surgical specimen.

of its diastolic pressure-volume relationship. The sudden delivery of a large regurgitant volume into an unprepared LV is met with a marked increase in LV diastolic and left atrial pressures. Forward stroke volume falls, in part because of the inability of the left ventricle to dilate acutely. Tachycardia develops but is usually not enough to maintain cardiac output. Such patients may present with pulmonary edema and shock. Examination findings may be masked by the severity of the heart failure. The pulse pressure is not widened, the first heart sound is soft, and the diastolic murmur is of relatively short duration. The rapid decrease in coronary driving pressure, represented by the aortic-LV pressure gradient, may result in diminished coronary blood flow and myocardial ischemia, even with normal epicardial coronary arteries. Inappropriate bradycardia, which can develop if the infection extends into the conduction system, is often accompanied by atrioventricular block (Fig. 67–7). If the patient is receiving a β-blocker, this can lead to catastrophic cardiogenic shock. Patients with acute severe mitral regurgitation may present with pulmonary edema, low cardiac output, and/or rapid atrial fibrillation. These latter patients can usually be stabilized with intensive medical therapy and, in contrast to patients with acute severe aortic regurgitation, surgery can be deferred temporarily. Patients with acute tricuspid regurgitation may show signs of right heart failure; medical management is the rule here rather than the exception. Premorbid heart disease, including antecedent valvular disease, coronary artery disease, cardiomyopathy, and/or arrhythmia, may also increase the likelihood that heart failure will develop, even with lesser degrees of acute valvular dysfunction.

EMBOLISM

Embolization is a frequent complication of IE. The brain and the spleen are the most common sites of embolization in left-sided IE, whereas septic pulmonary emboli are common in right-sided IE.[2-4,64] A recent prospective study of 2781 patients from ICE found the incidence of stroke to be 17% and that of embolization other than stroke to be 23%.[2] Central nervous system (CNS) embolization can present without any neurologic symptoms or findings or with subtle neurologic abnormalities (headache), focal motor or sensory defects caused by branch vessel occlusion, or sudden hemiplegia and obtundation, as seen with a ruptured mycotic aneurysm with resultant intracranial hemorrhage (Fig. 67–8). Up to 90% of CNS emboli lodge in the distribution of the middle cerebral artery and carry a high mortality rate.[128] Any patient with suspected or definite IE who develops neurologic symptoms should undergo immediate neurologic imaging and be considered to have CNS embolization until proven otherwise.

Emboli may also end in other organ systems, including the liver, spleen, kidneys, and lungs. Metastatic sites of infection may appear in the spine and/or paraspinous space and may be the cause of prolonged fever or bacteremia despite appropriate antimicrobial therapy. Septic pulmonary emboli are present in the majority of cases of right-sided IE related to intravenous drug use.[129,130] Rarely coronary embolism can cause myocardial infarction. Although coronary embolization is relatively rare, it has long been appreciated that patients with IE can develop scattered areas of myocardial *microinfarction* in the absence of epicardial vessel occlusion. Such areas have been attributed to microembolization, hypoperfusion, and immunologic phenomena with microembolization the most likely culprit.[130] Janeway and Osler lesions are vascular phenomena indicative of embolization of vegetative material[63] (see Fig. 67–5D).

Given the varied incidence of systemic embolization among patients with IE, the ability to assess patients for embolic risk is important and

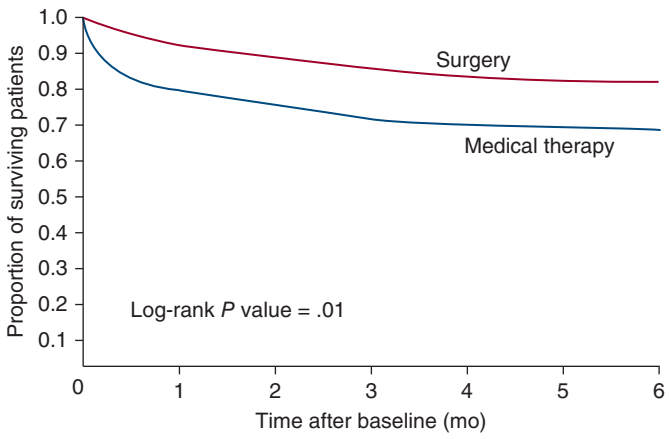


FIGURE 67–8. Survival curves for patients with complicated left-sided native valve endocarditis and moderate to severe heart failure managed with medical therapy alone or combined medical/surgical therapy. In this retrospective propensity analysis, there was a clear advantage with surgical therapy for this indication (hazard ratio 0.22; 95% confidence interval, 0.08-0.53; $P = .01$).

may help identify patients who might benefit from an earlier surgical intervention. However, the prediction of individual patient risk for embolization has proven difficult. Embolization risk appears to decrease precipitously after 2 weeks of appropriate antibiotic therapy, from 13 to 1.2 embolic events per 1000 patient-days in a Mayo Clinic report[131] and from 4.8 to 1.7 embolic events per 1000 patient-days in a more recent report from the ICE group.[132] A prior embolic event has generally not been a predictor for recurrent embolization. An exception to this observation was noted in the report from Vilacosta and colleagues.[133] In many series, the risk of embolization appears to be higher with mitral than with aortic valve endocarditis (approximately 25% vs 10%, respectively), particularly with anterior mitral valve leaflet involvement.[134-136] A number of echocardiographic studies have demonstrated a trend toward higher embolic rates with left-sided vegetations that are > 1 cm in diameter,[137,138] and more recent work suggests that vegetation size > 1.5 cm is a predictor of IE-related mortality.[139] Increasing or unchanged vegetation size during antimicrobial therapy as seen on serial TEE studies may be associated with higher embolic rates.[140] It has been suggested that there exists an interaction between vegetation size and the presence of patient-specific antiphospholipid antibodies.[116,117,139] The risk of embolization may also be related to microbial-specific features and is consistently higher with *Staphylococcus aureus*, *S lugdunensis*, certain streptococcal strains, *H influenzae*, and fungi.

MYCOTIC ANEURYSMS

Mycotic aneurysms (MAs) represent a small but extremely dangerous subset of embolic complications. They occur most frequently in the intracranial arteries and have a particular predilection for the middle cerebral artery and its branches (see Fig. 67–8).[140] MAs result from septic embolization to the arterial vasa-vasorum, with subsequent spread of infection and weakening of the vessel wall. MAs tend to develop at arterial branch points, which are a common site of embolic impaction. The overall mortality rate among IE patients with intracranial MAs is 60% and approaches 80% if rupture occurs.[141] The presenting symptoms of intracranial MAs are highly variable and can range from a localized headache (as seen with a small sentinel bleed) to dense neurologic deficits resulting from sudden intracranial hemorrhage.[142] Routine screening of patients with definite IE for the presence of intracranial MAs is not currently recommended, and neurologic imaging is reserved for symptomatic patients. In such patients, a contrast-enhanced computed tomography (CT) scan is highly sensitive for the detection of intracranial hemorrhage and may thus indirectly identify the location of an MA.[66] CT angiography and magnetic resonance angiography are evolving techniques for the detection of intracranial MAs, although their sensitivity for small aneurysms remains inferior to that of invasive four-vessel cerebral angiography.[142] Although many intracranial MAs often heal with medical therapy,[143] a subset may rupture unpredictably. There are no good predictors of whether an asymptomatic intracranial aneurysm will rupture, although enlargement on antibiotic therapy is usually an indication for invasive intervention.[143] Given the complex risks of prophylactic neurosurgical intervention, decisions concerning medical versus surgical therapy must be individualized.[66] Percutaneous neuroradiologic intervention is preferred when anatomically appropriate.[144] MAs may develop in other arteries (eg, splenic, mesenteric) and remain clinically silent or rupture spontaneously. These MAs are sometimes detected incidentally during abdominal imaging obtained for another indication.

PERIANNULAR EXTENSION OF INFECTION

Extension or spread of infection beyond the valve annulus is a potentially very dangerous development that usually presages the need for surgical therapy. Findings such as persistent fever and bacteremia despite antibiotic therapy, heart failure, or new conduction block should raise an immediate suspicion for this complication. Although a relatively insensitive sign, the development of new atrioventricular block on a 12-lead ECG in the setting of aortic valve IE has a high positive predictive value for the presence of perivalvular abscess formation.[145] Periannular extension may occur in 10% to 40% of all native valve IE and complicates aortic valve IE more commonly than either mitral or tricuspid valve IE. Periannular extension is more common with PVE (occurring in > 50% of patients),[145] as the interface between the prosthetic sewing ring and native annular tissue is often the initial site of infection (Fig. 67–9).[146] Perivalvular extension sets the stage for abscess formation, perforation, fistula development, and hemodynamic deterioration. The aortic annular segment adjacent to the membranous septum and the atrioventricular node is particularly vulnerable to abscess formation and may explain the occurrence of conduction block seen in some patients with aortic valve IE (see Fig. 67–7).[145,147] Patients with suspected periannular extension of infection and intracardiac abscess formation should undergo prompt TEE, which is both sensitive and specific for detection of this complication.[147-149] Surgical therapy is directed toward complete eradication of the infection and correction of the anatomical abnormalities. Valve replacement with reconstruction or replacement of the supporting annular structures is usually required.

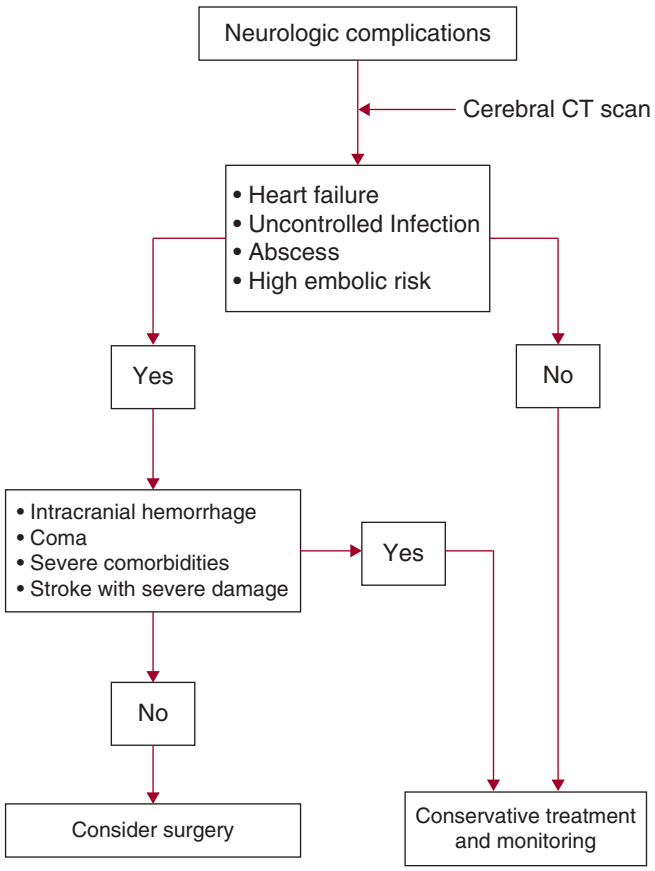


FIGURE 67–9. Therapeutic strategy for patients with infective endocarditis and neurologic complications. CT, computed tomography. Adapted with permission from Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J*. 2009 Oct;30(19):2369-2413.

RENAL DYSFUNCTION

Renal dysfunction is a common complication of IE and is often multifactorial in nature given the high incidence of pre-existing renal disease, acute immune complex disease, drug-induced nephrotoxicity, and hemodynamic perturbations. A recent necropsy and biopsy study of 62 patients with IE revealed that localized renal infarction (often caused by septic emboli) was present in 31%, acute glomerulonephritis in 26%, acute interstitial nephritis (likely antibiotic related) in 10%, and renal cortical necrosis in 10%.[150] Glomerulonephritis, as suggested by the appearance of red cell casts in the urine, is caused by immune complex deposition and complement activation. Similar examples of immune complex disease include nonseptic arthritis, and palpable purpuric skin lesions with findings of leukocytoclastic vasculitis on biopsy (see Figs. 67–4 and 67–5).

ANTIMICROBIAL THERAPY

GENERAL PRINCIPLES

Rapid institution of appropriate parenteral antibiotic therapy is the single most important initial intervention in the treatment of suspected or proven IE. Given the rising rate of antimicrobial resistance among causative organisms,[58] therapy is predicated on the identification of the responsible pathogen and delineation of its antibiotic sensitivities. An infectious disease specialist should supervise the dose, duration, and method of delivery of antimicrobial therapy during and after hospitalization. Serum antibiotic levels should be monitored where appropriate and renal and hepatic function assayed when indicated. A recent American Heart Association Scientific Statement[58] has addressed antimicrobial therapy for IE, and specific recommendations are provided in Tables 67–8 through 67–14.

TABLE 67–8. Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus gallolyticus* (formerly known as *Streptococcus bovis*)

Regimen	Dosage[a] and Route	Duration (wk)	Comments
Aqueous crystalline penicillin G sodium	12-18 million U per 24 h IV either continuously or in 4-6 equally divided doses	4	Preferred in most patients > 65 y of age or patients with impairment of 8th cranial nerve function or renal function Ampicillin 2 g IV every 4 h is an alternative if penicillin not available
Or			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose Pediatric dose[b]: penicillin 200,000 U/kg per 24 h IV in 4-6 equally divided doses or ceftriaxone 100 mg per 24 h IV/IM in 1 dose	4	
Aqueous crystalline penicillin G sodium	12-18 million U per 24 h IV either continuously or in 6 equally divided doses	2	Two-week regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of < 20 mL/min, impaired 8th cranial nerve function, or *Abiotrophia, Granulicatella*, or *Gemella* spp. infection. Gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 µg/mL and trough serum concentration of < 1 µg/mL when 3 divided doses are used; nomogram used for single-daily dosing.
Or			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose	2	
Plus			
Gentamicin sulfate[c]	3 mg/kg per 24 h IV/IM in 1 dose Pediatric dose: penicillin 200,000 U/kg per 24 h IV in 4-6 equally divided doses or ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses[d]	2	
Vancomycin hydrochloride[e]	30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g per 24 h unless concentrations in serum are inappropriately low Pediatric dose: 40 mg/kg per 24 h IV in 2-3 equally divided doses	2	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to a trough concentration range of 10-15 µg/mL

Minimum inhibitory concentration ≤ 0.12 µg/mL.

Abbreviations: IM, intramuscular; IV, intravenous.

[a]Dosages recommended are for patients with normal renal function.

[b]Pediatric dose should not exceed that of a normal adult.

[c]Other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

[d]Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.

[e]Vancomycin dosages should be infused during course of at least 1 hour to reduce risk of histamine-release "red man" syndrome.

Modified with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

TABLE 67–9. Therapy of Native Valve Endocarditis Caused by Strains of Viridans Group Streptococci and *Streptococcus gallolyticus* (*bovis*) Relatively Resistant to Penicillin

Regimen	Dosage[a] and Route	Duration (wk)	Comments
Aqueous crystalline penicillin G sodium	24 million U per 24 h IV either continuously or in 4-6 equally divided doses	4	Patients with endocarditis caused by penicillin-resistant (MIC > 0.5 μg/mL) strains should be treated with regimen recommended for enterococcal endocarditis
Or			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose	4	If isolate is susceptible to ceftriaxone
Plus			
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 1 dose Pediatric dose[b]: penicillin 200,000-300,000 U per 24 h IV in 4-6 equally divided doses or ceftriaxone 100 mg/kg per 24 h IV/IM divided every 12 h; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses	2	
Vancomycin hydrochloride[c]	30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g per 24 h, unless serum concentration are inappropriately low Pediatric dose: 40 mg/kg per 24 h in 2 or 3 equally divided doses	4	Vancomycin therapy is recommended only for patients unable to tolerate penicillin or ceftriaxone therapy

[c]Minimum inhibitory concentration > 0.12 μg/mL to ≤0.5 μg/mL.

Abbreviations: IM, intramuscular; IV, intravenous; MIC, minimum inhibitory concentration.

[a]Dosages recommended are for patients with normal renal function.

[b]Pediatric dose should not exceed that of a normal adult.

Modified with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

CHOICE OF ANTIBIOTICS

The lesions of IE are extremely difficult to eradicate because the infection exists in a sequestered area of impaired host defense. Thus IE requires weeks of parenteral antibiotic therapy, preferably with a drug that has bactericidal activity against the offending organism. Combination antimicrobial therapy may provide more rapid bactericidal effect, and in certain circumstances, acts synergistically to accelerate sterilization of the blood.[139,151] All patients should have surveillance blood cultures obtained 2 to 3 days after the initiation of antibiotic therapy to ensure efficacy. Most patients will require long-term venous access via a peripherally inserted central catheter or Hickman line for a 4- to 6-week course of antibiotics. Patients should remain in an inpatient setting during the initial phase of treatment when complications are most likely to occur, after which appropriate patients can be considered for outpatient parenteral antibiotic therapy.[140,152]

EMPIRIC ANTIBIOTIC THERAPY

Initial empiric antibiotic therapy (ie, before blood culture results are available) should cover *Staphylococcus aureus* and the many species of streptococci that can cause IE, with consideration of *E faecalis* in certain circumstances. Thus, a combination of a β-lactamase–resistant penicillin (nafcillin), or vancomycin for penicillin-allergic patients, and gentamicin is often used. The tempo of infection can be a valuable clue to the identity of the causative organism; *Staphylococcus aureus* endocarditis often presents with an acute, fulminant course with high-grade bacteremia. Other risk factors for *Staphylococcus aureus* IE include chronic hospitalization, indwelling central venous catheters or prosthetic devices, surgical wounds, and intravenous drug use. Vancomycin should be used if the patient is at significant risk for MRSA infection. Oral rifampin is added to nafcillin and gentamicin for staphylococcal infections of prosthetic materials (see Table 67–12). The duration of gentamicin therapy will vary as a function of the offending organism but is usually 2 weeks or less.

ANTIPLATELET AND ANTITHROMBIN THERAPY

Despite their theoretical benefit, there are no human studies that support the use of either antiplatelet or antithrombin agents to prevent embolic complications or hasten antibiotic cure.[153] Moreover, small uncontrolled studies suggest that antithrombin therapy actually increases the risk of intracranial hemorrhage after CNS embolization.[154,155] For patients who require anticoagulation for either chronic atrial fibrillation or a mechanical heart valve, warfarin should be discontinued on admission and unfractionated intravenous heparin substituted. Because of their extended therapeutic effect and attenuated response to protamine reversal, low-molecular-weight heparins should be avoided when anticoagulation is needed in hospitalized patients with IE. Warfarin should not be resumed until (1) it is clear that the patient has not had a CNS complication and (2) all invasive procedures are completed. For patients with mechanical valves, there is a small risk of thromboembolism when anticoagulation is withheld for a short period of time. Thus, even when anticoagulation is indicated, it should be administered with caution because the acute phase of IE is a period of high hemorrhagic risk. If neurologic symptoms develop, anticoagulant therapy should be stopped until CNS imaging can be performed. A CNS or major visceral bleed may necessitate the discontinuation of all forms of anticoagulation for a longer period of time, depending on the clinical course and the risk-benefit analysis regarding the timing of re-exposure. In the event of a CNS bleed, neurosurgical and interventional neuroradiologic consultation should be sought, especially because major intracranial hemorrhage is often caused by rupture of an

TABLE 67–10. Therapy for Endocarditis Caused by *Enterococcus*

Regimen	Dosage[a] and Route	Duration (wk)	Comments
Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin and gentamicin and in patients who can tolerate β-lactam therapy			
Ampicillin sodium	2 g every 4 h IV in 6 equally divided doses	4-6	Native valve: 4-wk therapy recommended for patients with symptoms of illness ≤ 3 mo; 6-wk therapy recommended for patients with symptoms > 3 mo
Or			
Aqueous crystalline penicillin G sodium	18-30 million U per 24 h IV either continuously or in 6 equally divided doses	4-6	Prosthetic valve or other prosthetic cardiac material: minimum of 6-wk therapy recommended
Plus			
Gentamicin sulfate[b]	3 mg/kg per 24 h IV/IM in 3 equally divided doses Pediatric dose[c]: ampicillin 200-300 mg/kg per 24 h IV in 4-6 equally divided doses up to 12 g daily or penicillin 200,000-300,000 U/kg per 24 h IV in 4-6 equally divided doses; gentamicin 3-6 mg/kg per 24 h IV/IM in 3 equally divided doses	4-6	
Or			
Ampicillin	2 g IV every 4 h		
Plus			Recommended for patients with creatinine clearance < 50 mL/min before or after gentamicin therapy
Ceftriaxone	2 g IV every 12 h		
Therapy for endocarditis involving a native or prosthetic valve or other prosthetic material resulting from *Enterococcus* species caused by a strain susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patient able to tolerate β-lactams			
Ampicillin	2 g IV every 4 h	6	
Plus			
Ceftriaxone	2 g IV every 12 h	6	
For streptomycin-susceptible, gentamicin-resistant patients			
Ampicillin sodium	2 g IV every 4 h	4-6	
Or			
Aqueous penicillin G	18-30 million U per 24 h IV either continuously or in 6 divided doses		
Plus			
Streptomycin sulfate	15 mg/kg per 24 h IV or two doses IM		
Vancomycin-containing regimens for vancomycin- and aminoglycoside-susceptible penicillin-resistant *Enterococcus* species for native or prosthetic valve IE in patients unable to tolerate β-lactams			
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6	
Plus			
Gentamicin	3 mg/kg per 24 h IV or IM in 3 doses	6	
Penicillin resistance; intrinsic or β-lactamase producer			
Vancomycin plus aminoglycoside	30 mg/kg per 24 h IV in 2 equally divided doses		
Therapy for endocarditis involving a native or prosthetic valve or other prosthetic material resulting from *Enterococcus* species caused by strains resistant to penicillin, aminoglycosides, and vancomycin			
Linezolid	600 mg IV or orally every 12h	> 6	
Or			
Daptomycin	10-12 mg/kg per dose	> 6	

Abbreviations: IE, infective endocarditis; IM, intramuscular; IV, intravenous.

[a]Dosages recommended are for patients with normal renal function.

[b]Dosage of gentamicin should be adjusted to achieve peak serum concentration of 3 to 4 μg/mL and a trough concentration of less than 1 μg/mL. Patients with a creatinine clearance of < 50 mL/min should be treated in consultation with an infectious diseases specialist.

[c]Pediatric dose should not exceed that of a normal adult.

Modified with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

TABLE 67–11. Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage[a] and Route	Duration (wk)	Comments
Oxacillin-susceptible strains: Nafcillin or oxacillin[b]	12 g per 24 h IV in 4-6 equally divided doses	6	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk
For penicillin-allergic (nonanaphylactoid type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin	6 g per 24 h IV in 3 equally divided doses	6	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases
Oxacillin-resistant strains: Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses Pediatric dose: 40 mg/kg per 24 h IV in 2 or 3 equally divided doses up to 2 g/day	6	Adjust vancomycin dosage to achieve trough concentration of 10-20 μg/mL
Daptomycin	≥ 8 mg/kg dose		

Abbreviations: IE, infective endocarditis; intravenous.

[a]Dosages recommended are for patients with normal renal function.

[b]Pediatric dose should not exceed that of a normal adult.

Modified with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

TABLE 67–12. Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci

Regimen	Dosage[a] and Route	Duration (wk)	Comments
Oxacillin-susceptible strains			
Nafcillin or oxacillin	12 g per 24 h IV in 6 equally divided doses	At least 6	Penicillin G 24 million U per 24 h IV in 4-6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤ 0.1 μg/mL) and does not produce β-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics; cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins
Plus			
Rifampin	900 mg per 24 h IV/PO in 3 equally divided doses	At least 6	
Plus			
Gentamicin[b]	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses Pediatric dose[c]: nafcillin or oxacillin 200 mg/kg per h IV in 4-6 equally divided doses; +/– rifampin 20 mg/kg per 24 h IV/PO in 3 equally divided doses if prosthetic material present; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses	2	
Oxacillin-resistant strains			
Vancomycin	30 mg/kg per 24 h in 2 equally divided doses Pediatric dose: vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; +/– rifampin 20 mg/kg per 24 h IV/PO in 3 equally divided doses if prosthetic material present (up to adult dose); gentamicin 3 mg/kg per 24 h IV or IM in 3 equally divided doses	At least 6	Adjust vancomycin to achieve 1-h serum concentration of 30-45 μg/mL and trough concentration of 10-15 μg/mL

Abbreviations: IM, intramuscular; IV, intravenous; PO, by mouth.

[a]Dosages recommended are for patients with normal renal function.

[b]Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing.

[c]Pediatric dose should not exceed that of a normal adult.

Modified with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

TABLE 67–13. Therapy for Both Native and Prosthetic Valve Endocarditis Caused by HACEK[a] Microorganisms

Regimen	Dosage and Route	Duration (wk)	Comments
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose[b]	4	Cefotaxime or another third- or fourth-generation cephalosporin may be substituted
Or			
Ampicillin-sodium	2 g IV every 4 h	4	
Or			
Ciprofloxacin[c,d]	1000 mg per 24 h PO or 800 mg per 24 h IV in 2 equally divided doses	4	Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted; fluoroquinolones generally not recommended for patients < 18 y old. Prosthetic valve: patients with endocarditis involving prosthetic cardiac valve or other prosthetic cardiac material should be treated for 6 wk
	Pediatric dose[e]: Ceftriaxone 100 mg/kg per 24 h IV/IM every 12 h; or ampicillin-sulbactam 200-300 mg/kg per 24 h IV divided into 4 or 6 equally divided doses		

Abbreviations: IM, intramuscular; IV, intravenous; PO, by mouth.

[a]*Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*.

[b]Patients should be informed that intramuscular injection of ceftriaxone is painful.

[c]Dosage recommended for patients with normal renal function.

[e]Pediatric dose should not exceed that of a normal adult.

Modified with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

TABLE 67–14. Therapy for Culture-Negative Endocarditis Including *Bartonella* Endocarditis

Regimen	Dosage[a] and Route	Duration (wk)	Comments
Native valve			
Ampicillin-sulbactam	12 g per 24 h IV in 4 equally divided doses	4-6	Patients with culture-negative endocarditis should be treated with consultation with an infectious diseases specialist
Plus			
Gentamicin sulfate[b]	3 mg/kg per 24 h IV/IM in 2 equally divided doses	4-6	
Vancomycin[c]	30 mg/kg per 24 h IV in 2 equally divided doses	4-6	Vancomycin recommended only for patients unable to tolerate penicillins
Plus			
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	4-6	
Plus			
Ciprofloxacin	1000 mg per 24 h PO or 800 mg per 24 h IV in 2 equally divided doses	4-6	
	Pediatric dose[d]: ampicillin-sulbactam 200-300 mg/kg per 24 h IV in 4-6 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; vancomycin 60 mg/kg per 24 h in 2 or 3 equally divided doses; ciprofloxacin 20-30 mg/kg per 24 h IV/PO in 2 equally divided doses		
Prosthetic valve (early: ≤ 1 y)			
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6	
Plus			
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2	

(*continued*)

TABLE 67–14. Therapy for Culture-Negative Endocarditis Including *Bartonella* Endocarditis (*Continued*)

Regimen	Dosage[a] and Route	Duration (wk)	Comments
Plus			
Cefepime	6 g per 24 h IV in 3 equally divided doses	6	
Plus			
Rifampin	900 mg per 24 h PO/IV in 3 equally divided doses	6	
	Pediatric dose: vancomycin 60 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; cefepime 150 mg/kg per 24 h IV in 3 equally divided doses; rifampin 20 mg/kg per 24 h PO/IV in 3 equally divided doses		
Prosthetic valve (late: > 1 y)		6	Same regimens as listed above for native valve endocarditis
Suspected Bartonella, culture negative			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose	6	Patients with *Bartonella* endocarditis should be treated in consultation with an infectious diseases specialist
Plus			
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2	
With/without			
Doxycycline	200 mg/kg per 24 h IV/PO in 2 equally divided doses		
Documented *Bartonella* culture positive			
Doxycycline	200 mg per 24 h IV or PO in 2 equally divided doses	6	If gentamicin cannot be given, then replace with rifampin 600 mg per 24 h PO/IV in 2 equally divided doses
Plus			
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2	
	Pediatric dose: ceftriaxone 100 mg/kg per 24 h IV/IM every 12 h; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; doxycycline 2-4 mg/kg per 24 h IV/PO in 2 equally divided doses; rifampin 20 mg/kg per 24 h PO/IV in 2 equally divided doses		

Abbreviations: IM, intramuscular; IV, intravenous; PO, by mouth.

[a]Dosages recommended are for patients with normal renal function.

Data from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

MA. CNS hemorrhage will delay the performance of cardiac surgery (if indicated) for up to 1 month in most circumstances. If cardiac surgery is eventually performed, a tissue valve is preferable in order to avoid the need for postoperative anticoagulation.[156]

SURGICAL THERAPY

The decision for surgical intervention in the treatment of IE can be extremely challenging, and there are no randomized clinical trials to guide practice. The most recent American College of Cardiology/American Heart Association guidelines for surgery in IE are summarized in Tables 67–15 and 67–16.[100] Perioperative morbidity and mortality vary according to the type of infection, the extent of destruction of cardiac structures, the degree of LV dysfunction, and hemodynamic status of the patient at the time of surgery.[31,100] Operative mortality in IE ranges between 5% and 15%.[157-166]

For NVE, the primary indication for surgery in the active phase of infection is the development of clinical heart failure from either acute valve regurgitation or, less commonly, stenosis (Fig. 67–10). Evidence of elevated LV end-diastolic or left atrial pressures by either invasive (catheter) or noninvasive (echo/Doppler) assessment may also prompt surgery. Valve surgery is indicated for treatment of fungal or other highly resistant organisms and for treatment of intracardiac abscess, perforation, fistulous tracts, and false aneurysms. Surgery is reasonable for patients with recurrent emboli and persistent vegetations and for patients with persistent bacteremia despite several days (5-7 days) of appropriate antibiotic therapy in the absence of a metastatic focus of infection. Surgery to prevent embolization can be considered for treatment of large (> 1.0 cm), mobile vegetations, particularly in high-volume cardiac surgical centers with expertise in primary valve repair. This latter issue remains controversial, although improvements in repair techniques and surgical outcomes would seem to warrant this recommendation. Most echocardiographic studies have shown a relationship

TABLE 67–15. Indications for Surgery for Native Valve Endocarditis

Class I

1. Early surgery (during initial hospitalization and before completion of a full course of antibiotics) is indicated in patients with IE who present with valve dysfunction resulting in symptoms of heart failure. CLASS I
2. Early surgery should be considered particularly in patients with IE caused by fungal or highly resistant organisms (eg, vancomycin-resistant *Enterococcus*, multidrug-resistant gram-negative bacilli). CLASS I
3. Early surgery is indicated in patients with IE complicated by heart block, annular or cardiac or aortic abscess, or destructive penetrating lesions. CLASS I
4. Early surgery is indicated for evidence of persistent infection (manifested by persistent bacteremia or fever lasting > 5-7 days and provided that other sites of infection and fever have been excluded) after the start of appropriate antibiotics. CLASS I

Class II

5. Early surgery is reasonable in patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy. CLASS IIa
6. Early surgery is reasonable in patients with severe valve regurgitation and mobile vegetations > 10 mm. CLASS IIa
7. Early surgery may be considered in patients with mobile vegetations > 10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery. CLASS IIb

Valve Surgery in Patients With Right-Sided IE

1. Surgical intervention is reasonable for patients with certain complications (eg, heart failure, recurrent emboli, resistant organisms). CLASS IIa
2. Valve repair rather than replacement should be performed when feasible. CLASS I
3. If valve replacement is performed, then an individualized choice of prosthesis by the surgeon is reasonable. CLASS IIa
4. It is reasonable to avoid surgery when possible in patients who are IV drug users. CLASS IIa

Valve Surgery in Patients With Prior Emboli/Hemorrhage/Stroke

1. Valve surgery may be considered in IE patients with stroke or subclinical cerebral emboli and residual vegetation without delay if intracranial hemorrhage has been excluded by imaging studies and neurologic damage is not severe. CLASS IIb
2. In patients with major ischemic stroke or intracranial hemorrhage, it is reasonable to delay valve surgery for at least 4 weeks. CLASS IIa

Abbreviations: IE, infective endocarditis; IV, intravenous.

Data from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

between vegetation size and the risk of embolization, particularly for lesions affecting the anterior mitral valve leaflet. In these studies, embolization risk increases significantly for vegetation size greater than 1.0 cm.[137-161] Because embolization risk appears to decrease precipitously after institution of appropriate antibiotic therapy,[131] prophylactic surgery to prevent embolization should be performed early in the course of the infection. Before undertaking such surgery, the members of an experienced medical/surgical team should concur that the likelihood of successful repair is high. In many instances, repair constitutes vegetectomy and pericardial patch repair of the underlying defect. Leaflet resection, placement of an annular ring, or both may be required, as dictated by the intraoperative findings.

It has been extensively documented in many recent trials that early valve surgery for patients with IE results in decreased early and late mortality. This is particularly true for patients with any complication such as heart failure, heart block, large vegetation size, recurrent embolization, perivalvular extension of infection, infection with a resistant organism, and other signs or symptoms of clinical instability[160-167] (see Table 67–15).

Indications for surgery in patients with PVE are similar to those for patients with native valve IE. Heart failure, a poorly responsive microorganism, perivalvular extension, or an unstable prosthesis are class I indications for surgery. Prosthetic valve dehiscence is defined as a rocking motion of the valve with excursion of 15 degrees or more in at least one plane. As noted, perivalvular abscess formation is more common with PVE than with NVE because the infection typically involves the interface between the sewing ring and surrounding tissue (see Fig. 67–9).[145] Early surgery may be considered for selected patients with PVE without perivalvular extension or heart failure. For example, *Staphylococcus aureus* PVE is rarely eradicated with antibiotics alone, and retrospective analyses suggest that combined medical and surgical therapy is more effective than medical therapy alone.[96,166] Relapse of PVE after appropriate antibiotic therapy should

TABLE 67–16. Indications for Surgery for Prosthetic Valve Endocarditis (PVE)

Class I

1. Early surgery is indicated in patients with symptoms or signs of heart failure resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction. CLASS I
2. Early surgery should be done in patients who have persistent bacteremia despite appropriate antibiotic therapy for 5 to 7 days in whom other sites of infection have been excluded. CLASS I
3. Early surgery is indicated when IE is complicated by heart block, annular or aortic abscess, or destructive, penetrating lesions. CLASS I
4. Early surgery is indicated in patients with PVE caused by fungi or highly resistant organisms. CLASS I

Class II

5. Early surgery is reasonable for patients with PVE who have recurrent emboli despite appropriate antibiotic therapy. CLASS IIa
6. Early surgery is reasonable for patients with relapsing PVE IE. CLASS IIa
7. Early surgery may be considered in patients with mobile vegetations > 10 mm. CLASS IIb.

Abbreviation: IE, infective endocarditis.

lead to a careful search for perivalvular extension or for metastatic foci of infection.[3,4] Some patients with relapsed PVE may respond to a second course of antimicrobial therapy, but the majority will require surgery for cure. Despite the frequent need for surgery, medical cure with antibiotic therapy should be initially attempted for uncomplicated PVE caused by first infection with a sensitive organism (eg, enterococci, streptococci).

The timing of surgery after CNS embolization in either NVE or PVE is problematic because of the risk of hemorrhagic transformation. The clinical spectrum of neurologic complications in IE is wide and includes ischemic or hemorrhagic stroke, transient ischemic attack, silent cerebral embolism, symptomatic or asymptomatic MA, brain abscess, meningitis, toxic encephalopathy, and seizure.[134,135,162] Furthermore, there is a high prevalence of asymptomatic findings on head CT in patients with IE.[162] It should be re-emphasized that rapid diagnosis and initiation of appropriate antibiotic therapy are of major importance to prevent a first or recurrent neurologic complication. After a neurologic event, many patients will still have at least one indication for which surgery should be considered.[162] One prospective study found that the risk of postoperative neurologic deterioration is low after silent cerebral embolism or a transient ischemic attack, and surgery for such cases is recommended without delay if an indication remains.[3,4,162] After an ischemic stroke, cardiac surgery is not absolutely contraindicated unless the neurologic prognosis is deemed to be poor. There is conflicting evidence regarding the optimal time interval between stroke and cardiac surgery.[3,4,156,162-173] If cerebral hemorrhage has been excluded by head CT imaging and neurologic damage is not severe (eg, coma or severe neurological dysfunction), and surgery is indicated for heart failure, uncontrolled infection, or abscess, the intervention should not be delayed and can be performed with relatively low neurologic risk (3%-6%) with a reasonable probability of a favorable neurologic outcome.[165,166] Conversely, in cases with intracerebral hemorrhage, the neurologic prognosis is worse, and surgery is usually postponed for at least 1 month.[163] In all cases of IE with neurologic complications, early neurologic and neurosurgical consultation is advisable. Before contemplating cardiac surgery in a patient with neurologic complications, MAs may require attention with extirpation by either percutaneous or surgical techniques.[153,166,167] Recent guidelines from the European Society of Cardiology provide recommendations for management of neurologic complications and the timing of surgery (Table 67–17 and Fig. 67–11).[4]

TABLE 67–17. Management of Neurologic Complications of Infective Endocarditis (IE)

1. After a silent cerebral embolism or transient ischemic attack, surgery is recommended without delay if an indication still remains. CLASS I
2. Neurosurgery or endovascular therapy is indicated for very large, enlarging, or ruptured intracranial aneurysms. CLASS I
3. After a stroke, surgery is indicated for heart failure, uncontrolled infection, abscess, or persistent high embolic risk and should not be delayed. Surgery should be considered as long as coma is absent and cerebral hemorrhage has been excluded by cranial CT or MRI. CLASS IIa
4. Intracranial aneurysm should be looked for in patients with IE and neurologic symptoms—CT or MRI angiography should be considered for diagnosis. If noninvasive techniques are negative and the suspicion of intracranial aneurysm remains, conventional angiography should be considered. CLASS IIa
5. After intracranial hemorrhage, surgery must be postponed for at least 1 month. CLASS IIa

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

Data from Habib,G, Lancellotti P, Antunes MJ, et al: 2015 ESC guidelines for the management of infective endocarditis. *Eur Heart J*. 2015 Nov 21;36(44):3075-3128.

PROGNOSIS

Patients with IE are an extremely heterogeneous group, with varying comorbidities, causative organisms, and complications. Accurate prognostic classification may help inform individual treatment decisions. Chu and colleagues[78] analyzed 267 consecutive cases of definite IE with an overall mortality of approximately 20% and found the following factors to be independently predictive of death: diabetes mellitus, *Staphylococcus aureus* as the causative organism, an embolic event, and increased Acute Physiology and Chronic Health Evaluation (APACHE) II score. Data obtained from ICE have supported the finding that diabetes mellitus is independently associated with higher mortality in IE.[174] Hasbun and colleagues[1] derived an externally validated prognostic classification system for adults presenting with complicated left-sided NVE. The 6-month mortality rate was approximately 25%. Five clinical features were associated with 6-month mortality: increased Charlson comorbidity score, abnormal mental status, moderate to severe heart failure, causative organism other than viridans streptococci, and medical therapy without valve surgery. Using these prognostic features, the authors derived a weighted integer scoring system that classified patients into four groups with progressively increasing 6-month mortality risk, ranging from 5% to 59%.

In a separate analysis, Fowler and colleagues[26] analyzed 300 patients with definite IE caused by *Staphylococcus aureus* unrelated to intravenous drug use who were enrolled in the ICE Prospective Cohort Study. They found the following factors to be independently associated with in-hospital death: advanced age, stroke, and persistent bacteremia. Another study of *Staphylococcus aureus* NVE from the ICE-merged database found advanced age, heart failure, periannular abscess formation, and absence of surgical therapy to be associated with higher mortality.[175] Thuny and colleagues[117] performed TEE in 384 consecutive patients with IE. Embolism occurred in 34.1% of patients before and 7.3% of patients after initiation of antibiotics. In addition to age, female sex, serum creatinine > 2.0 mg/dL, moderate or severe heart failure, and infection with *Staphylococcus aureus*, vegetation length > 1.5 cm was an independent predictor of 1-year mortality. Total mortality at 1 year was 20.6%. Most recently, the ICE Prospective Cohort Study of 2781 cases of IE found the following characteristics to be associated with an increased risk of in-hospital death: PVE, increasing age, pulmonary edema, *Staphylococcus aureus* infection, coagulase-negative staphylococcal infection, mitral valve vegetation, and paravalvular complication.[2] Lopez et al[176] found that persistently positive blood cultures after the initiation of antibiotic therapy were an independent risk factor for in-hospital mortality in patients with left-sided native valve IE. Also of interest was the nationwide population study from Taiwan by Yang et al[177] that demonstrated that patients with IE who were concomitantly taking a statin agent had a reduced risk of in-hospital and subsequent mortality. One observational study demonstrated that the implementation of a standardized diagnostic and therapeutic protocol was associated with an improvement in outcomes.[178] Although the decision to undertake early surgery for the treatment of IE must be made on an individual basis, these data provide a useful approach for aggressive medical and surgical intervention in high-risk patient groups.[179]

ANTIBIOTIC PROPHYLAXIS FOR THE PREVENTION OF INFECTIVE ENDOCARDITIS

The use of antibiotic prophylaxis before dental, endoscopic, or surgical procedures for the prevention of IE has changed significantly over the past few years since the publication of the revised 2007 American Heart Association Guidelines.[92] The rationale for the revisions is based

TABLE 67–18. Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Infective Endocarditis (IE) for Which Antibiotic Prophylaxis Is Recommended

A. Prosthetic cardiac valve
B. Previous IE
C. Specific patients with congenital heart disease (CHD) (except for the conditions listed below, antibiotic prophylaxis is no longer recommended for any other form of CHD):
   1. Unrepaired cyanotic CHD, including palliative shunts and conduits
   2. Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after the procedure (prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure)
   3. Repaired CHD with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
D. Cardiac transplant recipients who develop cardiac valvulopathy

Data from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

on four principles including the recognition that previous recommendations lacked a robust evidence base. Accordingly, the emphasis has shifted from providing antibiotic prophylaxis to patients at high risk for the lifetime acquisition of IE to providing antibiotic prophylaxis to patients at highest risk for the development of an adverse outcome from IE. High-risk patient groups are listed in Table 67–18.[180] The specific procedures for which antibiotic prophylaxis is recommended in the absence of an intercurrent infection are listed in Table 67–19. With regard to IE prevention, there is general agreement between the American Heart Association Guidelines[92] and those more recently released by the European Society of Cardiology.[30] Recommended antibiotic regimens are listed in Table 67–20.

The revised guidelines have narrowed the procedures for which antibiotic prophylaxis is recommended. In particular, antibiotic prophylaxis solely to prevent IE is no longer recommended for GI/genitourinary tract procedures (including diagnostic esophagogastroduodenoscopy or colonoscopy), as no published data demonstrate a conclusive link between these procedures and the development of IE.[160] Antibiotic prophylaxis for high-risk patients is currently recommended only for the procedures listed in Table 67–19. In the unique scenario in which a high-risk patient requires elective urinary tract manipulation (eg, cystoscopy) and has an established enterococcal urinary tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure may be reasonable. If the urinary tract procedure is not elective, it is reasonable that the empiric or specific antimicrobial regimen administered to the patient contain an active antienterococcal agent.[92] All patients who undergo heart valve replacement or who receive an intravascular graft or intracardiac device should receive periprocedural prophylaxis with an antistaphylococcal agent. Antibiotic prophylaxis for IE prevention before dental procedures is not recommended for patients who have undergone coronary artery bypass grafting, percutaneous coronary intervention (with or without a stent), or implantation of a pacemaker/ICD.

Prophylactic antibiotics for IE prevention should be administered in a single dose before the procedure. If the dosage is inadvertently not administered before the procedure, it may be given up to 2 hours after the procedure.[92] Prophylactic antibiotic recommendations for dental procedures are directed against viridans group streptococci and are listed in Table 67–20. Prophylaxis for respiratory procedures is identical. Amoxicillin is the first choice for oral therapy because it is well absorbed in the GI tract and provides high and sustained

TABLE 67–19. Procedures for Which Antibiotic Prophylaxis Is Recommended for High-Risk Patients

A. Dental: All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. The following procedures and events do not need antibiotic prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.
B. Respiratory tract: Invasive procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa, such as tonsillectomy or adenoidectomy. Routine prophylaxis for bronchoscopy is not recommended unless the procedure involves incision of the respiratory tract mucosa.
C. Infected skin or musculoskeletal: Surgical procedures that involve infected skin, skin structure, or musculoskeletal tissue.

Data from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

TABLE 67–20. Prophylactic Regimens for a Dental Procedure

		Regimen: Single Dose 30-60 min Before Procedure	
Situation	**Agent**	**Adults**	**Children**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	or		
	Cefazolin or Ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin–oral	Cephalexin[a,b]	2 g	50 mg/kg
	or		
	Clindamycin	600 mg	20 mg/kg
	or		
	Azithromycin	500 mg	15 mg/kg
	or		
	Clarithromycin		
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or Ceftriaxone[b]	1 g IM or IV	50 mg/kg IM or IV
	or		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

Abbreviations: IM, intramuscular; IV, intravenous.

[a]Or other first- or second-generation cephalosporin in equivalent adult or pediatric dosage.

[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

Data from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-1486.

serum concentrations. For patients who are allergic to penicillins or amoxicillin, a first-generation cephalosporin is recommended.[92] There are a few special circumstances in which different microbial coverage is recommended. For high-risk patients with established genitourinary tract colonization or infection with enterococci, it is reasonable that anti-enterococcal prophylaxis be administered before cystoscopy.[92] In centers with high prevalence of methicillin-resistant staphylococci, prophylaxis before valve replacement surgery or cardiac device implantation with vancomycin is reasonable but has not been shown to be superior to prophylaxis with a cephalosporin.[92] Prophylaxis should be initiated immediately preoperatively, repeated during prolonged procedures to maintain serum concentrations intraoperatively, and continued for no more than 48 hours postoperatively to minimize emergence of resistant organisms.[92]

It is recognized that patients and providers may find that these revised guideline recommendations depart too radically from previously accepted standards. Many remain uncomfortable with their execution in patients with mitral valve prolapse with severe mitral regurgitation, hypertrophic obstructive cardiomyopathy, and bicuspid aortic valve disease. Accordingly, individual judgment respectful of patient preference is advised.

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Heart Failure

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CHAPTER 68

PATHOPHYSIOLOGY OF HEART FAILURE

Hanna K. Gaggin and G. William Dec

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Heart failure (HF) is a complex clinical syndrome associated with increased mortality and morbidity.[1] It is also common and becoming more prevalent with the aging population and improvement in survival of patients with cardiovascular diseases such as coronary artery disease. Although coronary artery disease is the most common cause of HF, patients can develop HF from any number of different cardiovascular diseases (Table 68–1); HF appears to be the final common pathway of ventricular dysfunction that share some important clinical characteristics and pathophysiology. Although the molecular biology and integrated physiology behind HF remain incompletely understood, several fundamental concepts and principles have evolved and are described here. In addition, many of the same proteins found in key HF pathophysiologic pathways have been evaluated as potential biomarkers in HF (some are well established in their clinical utility for diagnostic and prognostic purposes) and are important targets of therapeutic applications and exploration. An important caveat is that many of the proven concepts in HF were derived from HF models with reduced ejection fraction (HFrEF), and relatively little is known about the mechanisms involved in the development of HF with preserved ejection fraction (HFpEF). A special section on the pathophysiology of HFpEF is presented near the end of this chapter. Again, some of the concepts are shared between HFrEF and HFpEF.

A key feature of HF is the impaired ability of the heart to move blood forward to meet the needs of the body, whether it is a result of a dysfunction in its ability to fill, contract, or coordinate with the rest of the body. However, many of the body's responses to cardiovascular abnormalities, which are initially adaptive and maintain short-term circulatory function, eventually become maladaptive; these changes ultimately result in further cardiovascular injury and contribute to the progression of HF. Adaptations, in response to HF, occur not only within the heart, but also in the peripheral circulation, kidneys, skeletal muscle, and almost all organs of the body. There is some suggestion that maladaptive response of the extracardiac structures may contribute to HF development and progression, as may happen in HFpEF. A better understanding of how these changes occur may provide important insight into the complex pathophysiology of the HF syndrome and may help to identify specific therapeutic targets.

DEFINING HEART FAILURE

HF is generally defined as a complex clinical syndrome in which an abnormality of cardiac function and connected systems is responsible for the failure of the heart to move blood forward at a rate commensurate with the requirements of the metabolizing tissues.[2]

Starting in 2001, the American College of Cardiology (ACC)/American Heart Association (AHA) working group[3] introduced and continued to define a broadened concept of HF to include two additional groups of patients before they develop functional or structural heart disease and symptoms: patients at high risk for developing HF with a structurally normal heart and patients with an abnormal cardiovascular system who have not developed clinical symptoms. A broadened definition, such as this, more accurately describes the spectrum of HF and can potentially lead to earlier interventions based on the specific molecular and hemodynamic abnormalities present before symptoms develop. As a matter of fact, a recent meta-analysis showed that the presence of asymptomatic left ventricular systolic or diastolic dysfunction was associated with a substantial risk for incident HF.[4]

Once the diagnosis of HF has been determined, the following descriptive categorizations are available with significant overlap and coexistence within the groups: (1) acute versus chronic; (2) left, right, or biventricular; and (3) reduced or preserved ejection fraction (also commonly described as systolic or diastolic dysfunction).

ACUTE VERSUS CHRONIC HEART FAILURE

Acute decompensated HF is defined as a relatively rapid change in HF symptoms and signs resulting in a need for urgent therapy (Fig. 68–1).[5] These symptoms can develop in a progressive manner over a short period of time (hours, days, or weeks), sometimes with a defining event (eg, during acute myocardial ischemia, acute myocardial infarction, onset of atrial fibrillation, or a sudden development of mitral regurgitation caused by rupture of a papillary muscle or chordae tendineae) and sometimes with a more nonspecific event such as dietary or medication noncompliance. Regardless of cause, the transition to acute decompensated state is typically preceded by a rise in filling pressures several days to weeks beforehand even in the absence of significant weight changes (Fig. 68–2).[6,7] Acute shift of blood volume from the systemic to the pulmonary circulation (sometimes referred to as *flash pulmonary edema*) can occur before significant salt or water retention has ensued. Acute HF is distinguished from chronic HF, which refers to a relatively more stable but symptomatic condition, in many cases being considered as "compensated." In chronic HF, fatigue can occur because of a limited cardiac output and neurologic signals from underperfused skeletal muscle. Fluid accumulation can occur, leading to pulmonary congestion and peripheral edema (ie, "congestive" failure).

TABLE 68–1. Disease Processes That Can Lead to Heart Failure

Disease processes that can lead to myocardial and extramyocardial abnormalities
- Myocardial necrosis such as myocardial infarction
- Myocarditis
- Dyssynchronous contraction such as right ventricular pacing
- Reduced contractile force such as cardiomyopathy (acquired or genetic) or cardiotoxicity (substance, chemotherapy)
- Disarray of myocardial cells such as hypertrophic cardiomyopathy
- Infiltrative disease such as sarcoidosis, amyloidosis
- Arrhythmogenic right ventricular cardiomyopathy (desmosome gene abnormalities, genetic)
- Peripartum cardiomyopathy
- HIV infection
- Connective tissue disease
- Restrictive cardiomyopathy such as endocardial fibroelastosis
- Left ventricular noncompaction
- Cirrhotic cardiomyopathy
- Stress-induced cardiomyopathy
- Idiopathic

Excessive pressure or afterload
- Hypertension with or without left ventricular hypertrophy
- Aortic, subaortic, supra-aortic stenosis
- Pulmonary hypertension from pulmonary embolism or chronic lung disease for predominantly right-sided heart failure

Excessive volume
- Valvular regurgitation
- Atrial or ventricular septal defect

Arrhythmia
- Tachycardia

Pericardial abnormalities
- Pericardial constriction
- Tamponade from pericardial effusion

Comorbidities
- Aging
- Diabetes
- Obstructive and central sleep apnea syndrome
- Obesity
- Kidney disease
- Chronic lung disease
- Anemia and iron deficiency

Abbreviation: HIV, human immunodeficiency virus.

LEFT, RIGHT, OR BIVENTRICULAR FAILURE

HF can also be described by the predominant ventricle affected, although this is in part an artificial division because the ventricles are functionally and structurally related to each other; left-sided dysfunction can contribute to the right-side dysfunction and vice versa, and the two often coexist. HF with left ventricular dysfunction is classically associated with signs and symptoms of pulmonary congestion, whereas HF with right ventricular dysfunction is typically associated with signs and symptoms of venous congestion such as abdominal bloating and lower extremity edema. Again, a typical patient presents with both types of symptoms.

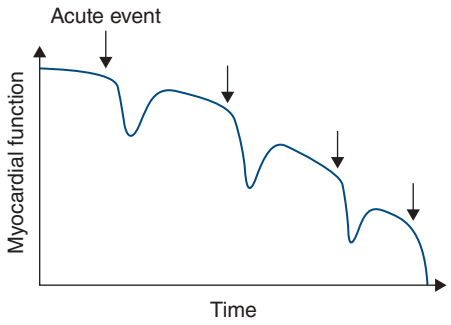

FIGURE 68–1. Contribution of acute decompensated heart failure events to the progression of heart failure. Myocardial function tends to decrease over time, in particular in response to acute decompensated heart failure events. Reproduced with permission from Gheorghiade M, De Luca L, Fonarow GC, et al: Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol*. 2005 Sep 19;96(6A):11G-17G.[5]

HEART FAILURE WITH REDUCED OR PRESERVED EJECTION FRACTION

Approximately half of HF patients have HFrEF and half have HFpEF. This is typically based on the ejection fraction of the left ventricle (LV) on cardiac imaging. The cutoff left ventricular ejection fraction (LVEF) by which to distinguish HFrEF from HFpEF is not well established, but clinical trials (the same trials that have either supported or refuted a specific HF therapy for use) have used LVEF ≤ 35% to 40% to define HFrEF[8,9] and LVEF ≥ 40% to 50% to define HFpEF.[10-15] It is unclear how exactly to categorize patients with LVEF between 40% and 50%. The only study to include a significant number of such patients, as a part of LVEF ≥ 40% criteria, was the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial,[12] which showed a small and almost significant reduction in the incidence of the primary end point of cardiovascular death or hospitalization for HF with candesartan for the overall study. With any cardiomyopathies, especially for those with LVEF in the lower range between 40% and 45%, it may not be unreasonable to treat patients as having HFrEF, but some have called for these patients to be defined as HFpEF instead, because development of symptomatic HF symptoms at a relatively normal LVEF may suggest a pathophysiology closer to HFpEF. However, definitive evidence is lacking. More recent trials of HFpEF are using higher cutoff values of ≥ 45% to 50% in order to have a more streamlined cohort of HFpEF, but perhaps even more so than with HFrEF patients, patients with HFpEF appear to be a heterogeneous group of HF patients, and a better understanding of different HFpEF phenotypes may be needed.[10,14]

Distinction between HFpEF and HFrEF is important because therapies that have a proven mortality and morbidity benefit in patients with HFrEF do not appear to be effective in patients with HFpEF,[10,12,14,16,17] and to some extent, these conditions may have fundamentally different pathophysiologic mechanisms and phenotypes. However, some believe that negative or neutral results from these trials are more reflective of the heterogeneity of the HFpEF population (some of whom may respond to therapy) more than lack of benefit. For example, the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial randomized 3445 chronic HF patients with LVEF ≥ 45% to spironolactone or placebo over 3 years. Although the study was overall negative for the primary composite end point (death from cardiovascular causes,

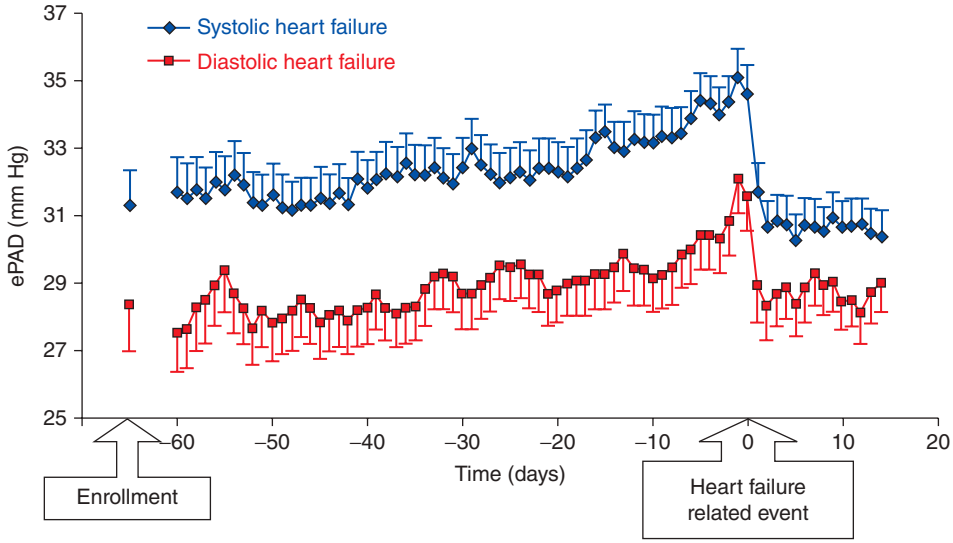

FIGURE 68–2. Daily median pulmonary artery diastolic pressures as estimated by intracardiac implantable continuous hemodynamic monitor beginning 60 days before acute decompensated heart failure episode and continuing for 14 days after the event: results from the Chronicle Offers Management to Patients With Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial. ePAD, estimated pulmonary artery diastolic pressure. Reproduced with permission from Zile MR, Bennett TD, St John Sutton M, et al: Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008 Sep 30;118(14):1433-1441.[6]

aborted cardiac arrest, or hospitalization for the management HF), there was a significant reduction in the primary composite end point in the subgroup of 981 patients (28.5%) who were enrolled based on the criterion of B-type natriuretic peptide (BNP) ≥ 100 pg/mL or N-terminal pro-BNP (NT-proBNP) ≥ 360 pg/mL rather than a history of HF hospitalization within 12 months (hazard ratio of 0.65 with spironolactone compared with placebo, $P = .003$). These patients were significantly different from those enrolled based on the hospitalization criterion and tended to be older, were less likely to be current smokers, had worse renal function, had lower potassium levels, and were less likely enrolled in Russia and Georgia. Results of the TOPCAT trial bring to light the fact that many of these negative trials have failed to comprehensively phenotype the HFpEF cohort, and the negative result may in fact be more reflective of the failure to appropriately phenotype HFpEF patients rather than actual lack of efficacy.

Patients with HFpEF have commonly been described as having diastolic HF. Although diastolic ventricular dysfunction is an important contributor to the pathophysiology of HFpEF in many cases, not all cases of HFpEF are driven by diastolic ventricular dysfunction. In addition, diastolic dysfunction is often present in patients with HFrEF.

There is also a group of patients with HFrEF who have partially or fully recovered their LVEF into the normal range with or without treatment. Because the original etiology of the cardiomyopathy is caused by a pathophysiologic process resulting in HFrEF, together with evidence of reversal of benefits to some extent on imaging and biomarker studies when these medical therapies for HFrEF are withdrawn, it is reasonable to continue to treat these patients as having HFrEF unless a new pathophysiologic process occurs.

PATHOPHYSIOLOGIC CONCEPTS IN HEART FAILURE

HF can be caused by a number of different cardiovascular disease processes (see Table 68–1), and the interplay between the causative *injury* and development and progression of HF is complex. However, several important concepts have emerged with the latest developments in genetics and molecular biology. In addition, these index cardiac or extracardiac injuries can stimulate responses that can be roughly grouped into categories of *neurohormonal activation* for cellular and molecular responses and *remodeling* for hemodynamic responses with much overlap and redundancy (Fig. 68–3). Although initially adaptive, continued neurohormonal activation and adverse remodeling can, in turn, result in further cardiac and extracardiac injury (eg, vascular, pulmonary, renal) in a vicious cycle. Relatively little is known regarding what exactly precipitates the transition from a chronic, compensated state to acute decompensated state in many cases. Interestingly, some patients can spontaneously resolve their HF through mechanisms that are not well understood and remain a focus of active exploration.

MECHANISM OF CARDIOVASCULAR INJURY AND PROGRESSION

Altered Cellular Proteins

Alterations are found in the failing heart in numerous contractile proteins, especially in heredity-based dilated cardiomyopathies. In the latter situation, these alterations can interact with additional injuries or abnormal loading conditions to result in HF. Such alterations found in the contractile proteins (myosin and actin), regulatory proteins (troponins and tropomyosin), and cytoskeletal proteins (myosin-binding protein C and titin) are likely to contribute to diminished myocardial performance. In the failing human heart, many changes in gene expression at the messenger ribonucleic acid (mRNA) or protein level have

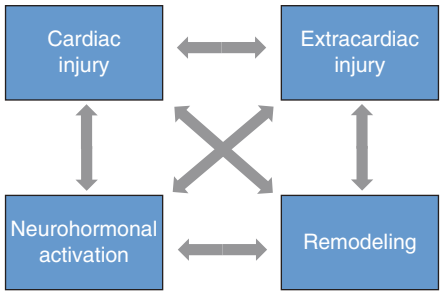

FIGURE 68–3. The interconnected relationship between cardiac injury, extracardiac injury, neurohormonal activation, and cardiac remodeling.

been found in hearts explanted at the time of cardiac transplantation. However, interpretation of end-stage HF findings may be complicated by many factors (eg, receiving multiple inotropic drugs) that can obscure the initial pathogenesis.

Sarcomere Proteins The fact that more than half of the volume of cardiac myocytes is comprised of contractile proteins speaks volumes about the importance of contractile proteins in cardiac function. Briefly, a myocardial cell contains bundles of myofibril, which is made of functional units of sarcomere. A sarcomere contains myosin (thick) and actin (thin) filaments (Fig. 68–4).[18] Hydrolysis of adenosine triphosphate (ATP) causes myosin and actin to slide past each other, shortening myofibrils and ultimately producing myocyte contraction; this is the foundation of the power of myocardium. Myosin contains both heavy and light chains. Two myosin heavy-chain (MHC) isoforms are present in mammalian heart, α- and β-MHC. The α-MHC is cardiac specific and is more enzymatically active. The less active β-MHC is present in the heart and in slow-twitch skeletal muscle. The distribution of α- and β-MHC is developmentally and hormonally regulated. Mechanical stress, such as pressure overload, induces an α- to β-MHC transition in the ventricles of experimental animals, thus imparting a slower but more economical type of work for the overloaded heart.

There is a general agreement that myofibril function is decreased in the failing human heart, but its causative role remains controversial. Downregulation of α-MHC and upregulation of β-MHC using mRNA measurements from right ventricular endomyocardial biopsies from non-HF and HF patients has been demonstrated, and their sequential changes can be observed with recovery of cardiac performance.[19,20] This alteration, if translated into protein expression, would decrease myosin adenosine triphosphatase (ATPase) enzyme velocity and slow the speed of contraction. Although such adaptive changes may provide a survival advantage in the face of increased load, slower contraction and relaxation could also contribute to abnormal myocardial relaxation (also known as lusitropy). In addition, isoform changes involving both the heavy and the light chains, as have been suggested, can play a role in HF. However, in contrast to smaller mammalian species such as mouse, rat, and rabbit, in which many of mechanistic experiments have been performed, the human ventricle contains a large amount of slow β-MHC to begin with (at least 90%). An isoform shift to increase the large amount of β-MHC already present in the cell may not translate to a significant difference in its function. In addition to myosin heavy- and light-chain isoform switches, other well-understood pathologic events also contribute to altered cardiac function in various forms of HF. Point mutations of virtually all of the sarcomere proteins cause hypertrophic cardiomyopathy. Similarly, mutations in the cytoskeletal proteins that provide the molecular scaffolding for the sarcomere have been found in both dilated and hypertrophic cardiomyopathies. Echocardiographic studies have demonstrated that 20% of first-degree relatives of patients with idiopathic dilated cardiomyopathy have enlarged LV cavities. In addition, some of the circulating autoantibodies specific to the heart and its contractile proteins been linked to development of HF[21]; a high incidence of circulating anti-heart antibodies is observed among first-degree relatives with dilated cardiomyopathy and can precede development of cardiomyopathy.[22,23]

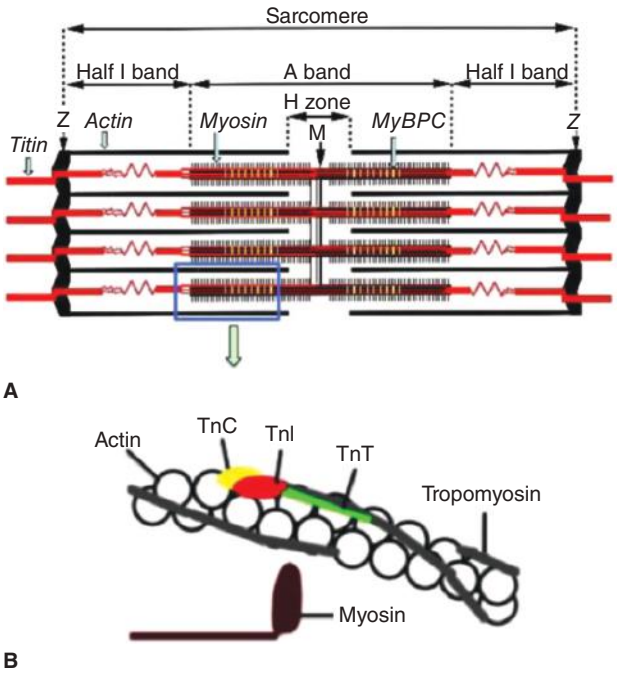

FIGURE 68–4. The sarcomere is the basic unit of the contractile proteins in the cardiomyocyte that allows the cardiomyocyte to contract. Tn, troponin. Reproduced with permission from Yin Z, Ren J and Guo W. Sarcomeric protein isoform transitions in cardiac muscle: a journey to heart failure. *Biochim Biophys Acta*. 2015 Jan;1852(1):47-52.[18]

Cell Membrane Ion Channels and Intracellular Calcium Kinetic Proteins Plasma membrane ion channels initiate excitation-contraction by generating and propagating the action potentials that depolarize the myocardium (Fig. 68–5).[24] These ion channels contain several subunits that surround the ion-selective pore. The intracellular calcium (Ca^{2+}) release channels are found in the sarcoplasmic reticulum (SR) and are quite different from those of the plasma membrane. The SR Ca^{2+} release channels are referred to as ryanodine receptors (RyRs) and interact with the ligand inositol triphosphate (IP_3). The Ca^{2+} pump ATPases are found in both the plasma membrane and SR. Both calcium pumps are activated by cytosolic Ca^{2+}. The sodium-calcium exchanger transports calcium out of the cytosol into the extracellular space, using the osmotic energy of the sodium gradient across the plasma membrane to generate active transport. The sodium-potassium (Na^+, K^+)-ATPase pump uses energy derived from ATP hydrolysis to exchange sodium that enters the cell for potassium lost from the cytosol during repolarization. Also, calcium-binding storage proteins (eg, calsequestrin) maintain a calcium store that can be readily used during excitation-contraction coupling. The heart's voltage-gated ion channels (especially inward sodium channels) are altered in the failing heart, as are outwardly rectifying potassium channels.[25,26] A common feature of both animal and human models of HF is prolongation of the action potential. Both decreased sodium influx and potassium efflux are contributory and are mediated by reduced activity of the myocardial membrane (also known as sarcolemma) sodium and potassium channels, respectively. This aberrant channel behavior contributes to the arrhythmias, which are the second most common cause of death of patients with HF.

Excitation-Contraction Coupling Proteins Excitation-contraction coupling links plasma membrane depolarization to the release of calcium into the cytosol, where it binds to troponin C, permitting the force-generating interaction between myosin and actin and ultimately contraction (see Fig. 68–5). Relaxation is also an energy-dependent process but is not simply a reversal of the steps in excitation-contraction coupling. During relaxation, Ca^{2+} is actively transported out of the cytosol by entirely different molecular pumps. The basic mechanism of cardiac excitation-contraction coupling involves Ca^{2+} entry from the extracellular fluid by means of the voltage-dependent L-type calcium channel to produce a trigger in increasing $[Ca^{2+}]_i$ and opening of the intracellular SR Ca^{2+} release channel or RyR. Key defects in SR Ca^{2+} uptake and release are present in HF including dysregulation of RyR, RyR2/Ca^{2+} release channel macromolecular complexes, and the SR calcium transport proteins, especially the sarcoplasmic-endoplasmic reticulum calcium

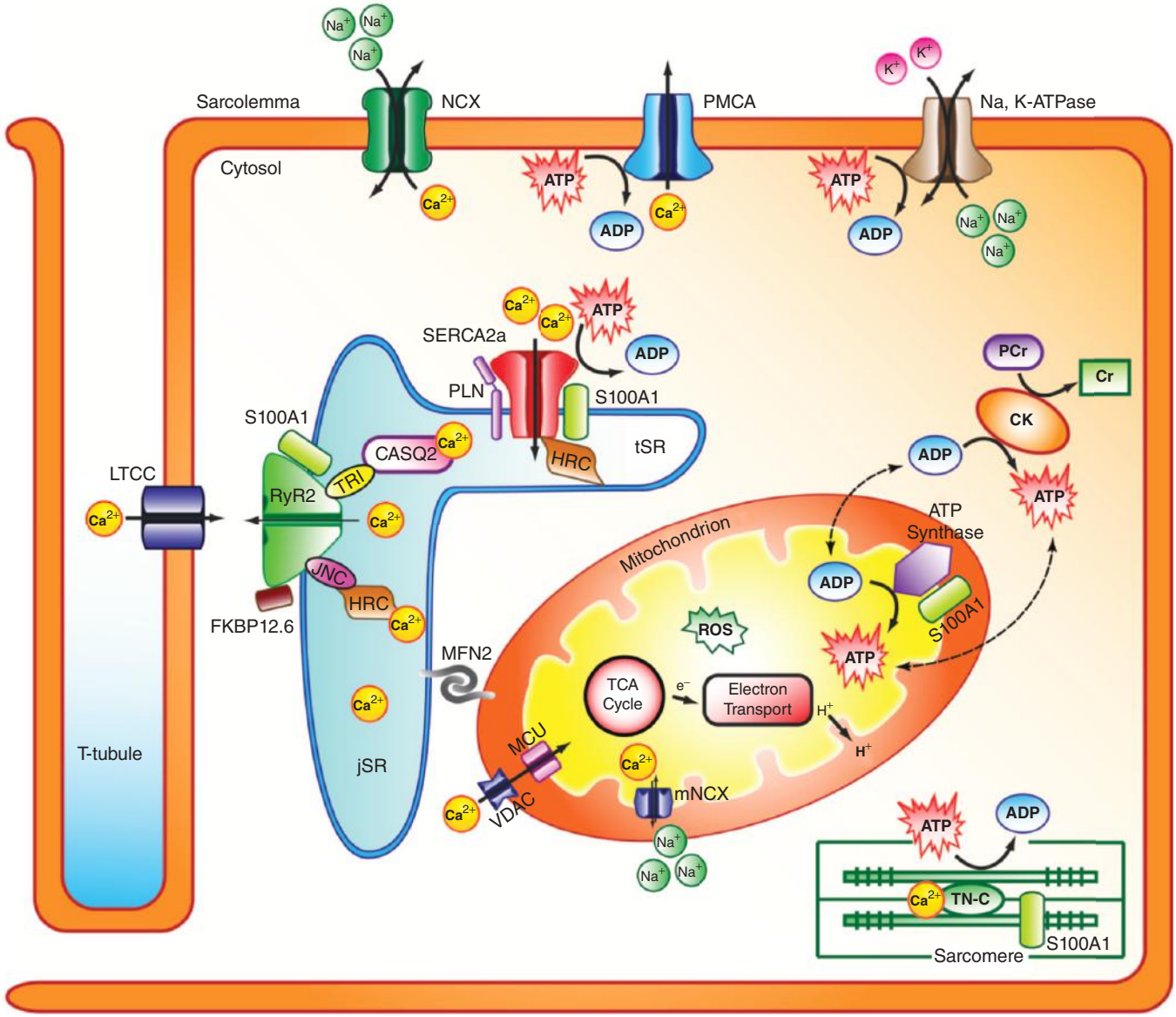

FIGURE 68–5. Cell membrane ion channels and intracellular calcium kinetic proteins initiate excitation-contraction, generating and propagating the action potentials that depolarize the myocardium. ADP, adenosine diphosphate; ATP, adenosine triphosphate, CASQ2, calsequestrin isoform 2; CK, creatine kinase; Cr, creatine; FKBP12.6, RyR2 accessory-binding protein; HRC, histidine-rich calcium-binding protein; JNC, junction; MCU, mitochondrial calcium uniporter; MFN2, mitofusin isoform 2; mNCX, mitochondrial sodium-calcium exchanger; Na,K-ATPase, sodium-potassium ATPase; NCX, sodium calcium exchanger; PCr, phosphocreatine; PLN, phospholamban; PMCA, plasma membrane calcium ATPase; ROS, reactive oxygen species; RyR2, ryanodine receptor isoform 2; SERCA2a, sarco(endo)plasmic reticulum calcium ATPase; S100A1, S100 calcium-binding protein A1; TCA, tricarboxylic acid; TN-C, troponin-C; TRI, triadin; VDAC, voltage-dependent anion channel. Reproduced with permission from Gorski PA, Ceholski DK and Hajjar RJ. Altered myocardial calcium cycling and energetics in heart failure-a rational approach for disease treatment. *Cell Metab.* 2015 Feb 3;21(2):183-194.[24]

ATPase (SERCA) and phospholamban, a reversible inhibitor of cardiac SR Ca^{2+}-ATPase activity.[27] Other calcium-cycling proteins such as Na^{+}-Ca^{2+} exchanger proteins can also be altered in HF.[28] Hyperphosphorylation of phosphokinase A, oxidation, or nitrosylation of RyR2 can lead to SR Ca^{2+} depletion, increased risk of arrhythmias, and impaired contractility. HF is characterized by reduced myosin-actin myofibril activation and decreased Ca^{2+} available for activation as well as heightened cytosolic calcium levels in diastole. Some studies have shown increased myosin-actin myofibril Ca^{2+} sensitivity and altered Ca^{2+} kinetics.[29] These abnormalities of Ca^{2+} metabolism can affect HF manifestation to varying degrees. Several potential therapeutic strategies to improve utilization of Ca^{2+} are being tested in humans, including those targeting SERCA2a and RyR2, and many more are being tested in animal models.[30,31]

Metabolic Adaptations and Maladaptations

The healthy heart works incredibly hard in maintaining forward blood flow every day; it pumps more than 7000 L/d and extracts energy from more than 6000 g of ATP daily.[32] Not surprisingly, many abnormalities and inefficiencies in myocardial energy metabolism have been shown to occur in HF; these include altered energy substrate with an increased dependence on glucose, decreased oxidative phosphorylation, and high-energy phosphate and mitochondrial dysfunction.[33] This is a potentially valuable area of therapeutic exploration because decreased myocardial metabolism and resulting dysfunction can result in adverse compensatory remodeling in the rest of the heart. Improving myocardial metabolism, in particular, of stunned or hibernating myocardium (as happens with chronic oxygen deprivation from coronary artery disease) may break this cycle of adverse remodeling.

Substrate Use The primary substrate of energy in the normal myocardium is fatty acid with a small contribution by glucose, lactate, amino acids, and ketones.[34] Although the myocardial uptake of fatty acids and glucose appears to be preserved in HF, there is a shift from primarily fatty acid metabolism to glucose metabolism through changes in enzymatic regulation. Interestingly, this increased dependence on glucose metabolism is similar to the fetal heart's use of glucose as the primary energy substrate in the relatively hypoxic environment.[35] This is likely an initially adaptive mechanism as energy extraction from glucose is much more efficient than from fatty acids; in addition, abnormalities of glucose transport in this setting have been shown to be harmful to the myocardium.[36] However, insulin resistance is common in HF and may limit the benefits of a shift in metabolism to glucose.

Energy Production and Storage Oxidative phosphorylation is the mitochondrial process by which ATP is produced in the myocardial cells. In HF, there is a reduction in oxidative phosphorylation capacity, as evidenced by reduced high-energy phosphate levels, such as phosphocreatine and ATP, and an altered phosphocreatine-to-ATP ratio.[37] This reduction in dilated cardiomyopathy has been closely associated with future mortality.[38]

Mitochondrial ATP production is linked to myocardial need by highly efficient shuttling of high-energy phosphates via creatine kinase, adenosine monophosphate (AMP)–activated protein kinase and adenylate kinase, and glycolysis. Dysregulation of any of these enzymatic pathways is associated with myocardial dysfunction; for example, creatine kinase activities are reduced in HF, which results in a decrease in shuttling of high-energy phosphate.

Mitochondrial Dysfunction Mitochondria are the driving power source of the cell; the majority of ATPs are produced by the mitochondria. There is evidence that suggests that abnormalities in mitochondria may contribute to the development and progression of HF, but many of the areas are incompletely evaluated.[39] Genetic mutations affecting key mitochondrial structures such as mitochondrial ATP synthase and acylglycerol kinase have been shown to result in myocardial dysfunction.[40,41] Some of the proven HF medications such as angiotensin-converting enzyme (ACE) inhibitors are associated with an improvement in mitochondrial function as evidenced by an increase in high-energy phosphate such as ATP and creatine phosphate, the mitochondrial oxygen consumption rate,[42] and viable but metabolically stunned myocytes.[33] Dysfunction of the mitochondria includes abnormalities in the production of new mitochondria, enhanced generation of reactive oxidative species in the mitochondria, and dysregulation of mitochondrial iron handling.

Neurohormonal Activation

The neurohormonal system is one of the first activated responses to myocardial injury or to alternations in cardiac loading. Decreased cardiac output (any combination of decreased blood pressure, pulse pressure, and perfusion) is sensed by various mechanoreceptors throughout the body including the LV, carotid sinus, aortic arch, and afferent renal arterioles. When there is diminished activation of these receptors, as in HF, the neurohormonal system is activated in an attempt to maintain cardiac output and vital organ perfusion.

The sympathetic nervous system is activated early, followed by the renin-angiotensin-aldosterone system (RAAS). Nonosmotic release of AVP (also known as vasopressin or antidiuretic hormone)[43] and underfilling of renal arterial bed result in sodium and water retention. Heightened peripheral vasoconstriction, increased myocardial contractility and heart rate, and increased blood volume restore cardiac output and arterial pressure in the short term.

However, sustained and unopposed neurohormonal activation has many important adverse consequences at the cellular level, including facilitation of myocyte hypertrophy, collagen synthesis, and fibrosis, as well as promoting apoptosis and return to fetal isoforms of contractile proteins.[44-48] Cardiac myocyte necrosis also occurs in response to pathophysiologic levels of endogenous and low-dose exogenous angiotensin II infusion.[49] Activation of the sympathetic nervous system contributes to tachycardia and arrhythmias and can be directly toxic to the myocardium.[50,51] With increased sympathetic tone in HF, increased phosphorylation of the ryanodine component of the L-type calcium channel can lead to abnormalities of Ca^{2+} activation.

Although neurohormonal activation is typically in balance with vasodilatory and natriuretic effects of counter-regulatory pathways such as natriuretic peptides, nitric oxide, prostaglandins, and bradykinin, as HF progresses, there is impaired cardiosensory activity that fails to keep unopposed neurohormonal activation in check.[52]

For unclear reasons, cardiac afferent activity to the central nervous system is reduced, leading to unhindered, efferent excitatory responses from the brain to the periphery. Reflex vasoconstrictor responses to unloading the heart are paradoxically blunted.[53] HF parasympathetic (vagal) tone is decreased, and heart rate variability is markedly reduced. Furthermore, decreased heart rate variability can provide independent prognostic value in the identification of patients at risk for cardiac death.[54] Beat-to-beat QT interval variability on surface electrocardiograms (given relatively stable heart rate) is thought to be closely related to the subtle variations in ventricular repolarization duration as well as sympathetic nervous system activation, most likely through SR Ca^{2+} release.[55] Increased QT interval variability has been associated with the presence of coronary artery disease, LV hypertrophy, and LV systolic dysfunction, as well as increased risk of mortality, sudden cardiac death, and ventricular tachycardia or fibrillation shocks in patients with implantable cardiac defibrillators. However, these data are largely based on retrospective analysis, and prospective studies are needed in a well-defined population before routine use can be recommended.

A large number of these neurohormones and their inert counterparts circulate in increased concentrations in HF or with altered activity levels and have been evaluated as potential biomarkers (Table 68–2). Because some of these biomarkers are quite intimately linked with key pathophysiologic processes in the development and progression of HF, they constitute a fertile field for potential diagnostic, prognostic, and therapeutic targets.

As a matter of fact, neurohormonal mechanisms are the targets of several important and successful therapeutic interventions in HF and hypertension and have a key role in determining prognosis.[56,57] ACE inhibitors, β-adrenergic blockers, and aldosterone antagonists now have a prominent role in the treatment of HF, and new, more innovative neurohormonal-blocking agents (eg, neprilysin inhibitors) are being rapidly developed, adding strong support to the neurohormonal hypothesis.[58-60]

Autonomic Nervous System Imbalance Normally, the balance between the sympathetic and parasympathetic system is tightly regulated and maintained. In HF, one of the earliest activated pathways is the sympathetic nervous system, and the withdrawal of parasympathetic tone results in a predominantly sympathetic milieu.[61] Vascular constriction, tachycardia, increased myocardial contractility, diaphoresis, and oliguria are manifestations of increased sympathetic drive, but often at the expense of increased myocardial oxygen demand.

In addition, HF is characterized by abnormal reflex control mechanisms. Peripheral vascular resistance (systemic vascular resistance) is increased; this is likely caused by a combination of locally active heightened vasoconstrictors (norepinephrine [NE], angiotensin II,

TABLE 68–2. Biomarkers in Heart Failure

- Myocardial insult
  - Myocyte stretch
    - NT-proBNP, BNP, MR-proANP
  - Myocardial Injury
    - Troponin T, troponin I, myosin light chain I, heart-type fatty acid protein, CK-MB
  - Oxidative stress
    - Myeloperoxidase (MPO), uric acid, oxidized low-density lipoproteins, urinary biopyrrins, urinary and plasma isoprostanes, plasma malondialdehyde
- Neurohormonal activation
  - Renin-angiotensin system
    - Renin, angiotensin II, aldosterone
  - Sympathetic nervous system
    - Norepinephrine, chromogranin A, MR-proADM
  - Arginine vasopressin system
    - Arginine vasopressin, copeptin
  - Endothelins (ET)
    - ET-1, big proET-1
- Remodeling
  - Inflammation
    - C-reactive protein, LpPLA2, TNF-α, soluble TNF receptors, Fas, interleukins (1, 1β, 6, and 18), osteoprotegerin, adiponectin
  - Hypertrophy/fibrosis
    - Soluble ST2, galectin-3, matrix metalloproteinases, collagen propeptides
  - Apoptosis
    - GDF-15
- Comorbidities
  - Renal biomarkers
    - Renal function
      - Creatinine, BUN, eGFR, cystatin C, β-trace protein
    - Renal injury markers
      - NGAL, KIM-1, NAG, liver-type fatty acid binding protein, IL-18
  - Hematologic biomarkers
    - Hemoglobin, RDW, iron deficiency (ferritin, transferrin sat)
  - Liver function tests, albumin
  - Metabolic
    - orexin, leptin
- Miscellaneous
  - MicroRNAs

Abbreviations: BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CK-MB, creatine kinase-MB; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; KIM-1, kidney injury molecule-1; $LpPLA_2$; lipoprotein-associated phospholipase A_2; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, MR-pro-atrial natriuretic peptide; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase associated lipocalin; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RDW, red cell distribution width; TNF, tumor necrosis factor.

endothelin, vasopressin, neuropeptide Y) and by structural changes in blood vessels from fluid retention and reduced endothelial-dependent vasodilatation. These later changes are closely associated with limitations of exercise in HF.[62] There is also defective cardiac parasympathetic control and altered baroreceptor function and reduced cardiac sympathetic activity in response to a variety of stimuli.[53,63-66] β-Blockers, shown to improve clinical outcomes in HF, reduce β_1-receptor–related catecholamine activity and oppose sympathetic activation.[67] In animal models, renal sympathetic denervation, which aims to reduce renal sympathetic activation, was shown to improve survival and LV function as well as decrease myocardial fibrosis.[68]

Norepinephrine Sympathetic nervous system activation and subsequent increase in plasma NE levels are noted in patients with HF.[69] Plasma NE levels correlate with functional class and extent of hemodynamic dysfunction.[70-72] Although early studies of plasma NE level showed promise as a useful research and prognostic marker for patients with HF, contemporary analyses failed to show incremental benefit of NE use for prognosis beyond other established biomarkers and clinical models such as the Seattle Heart Failure Model.[73] Moxonidine, an imidazoline agonist that decreases NE levels in HF patients, failed to improve HF clinical outcomes and, in fact, was associated with increased risk of death and HF hospitalizations.[74,75] Interestingly, myocardial stores of NE were found to be depleted in advanced HF patients, and severe New York Heart Association (NYHA) class IV HF patients may be quite dependent on catecholamine support (ie, continuous dobutamine infusion) to maintain suitable organ perfusion. However, there is no question that high circulating levels of NE are toxic to the myocardium and are partly responsible for progressive adverse LV remodeling.[76] NE is thus a double-edged sword in HF.

Myocardial Receptor Dysfunction The failing heart commonly demonstrates a decreased responsiveness to inotropic stimuli. A reduction in myocardial β-adrenergic receptors and the subsequent second messenger cyclic adenosine monophosphate (cAMP) plays an important role.[77] β-Adrenergic stimulation contributes importantly to the cardiac response to exercise, and β-adrenergic desensitization and uncoupling can be at least partially responsible for the reduced chronotropic and inotropic response to peak exercise commonly found in patients with HF. The β-adrenergic receptor abnormalities in HF appear to be caused by desensitization and uncoupling of the β_1-receptor produced by local rather than systemic alterations in catecholamines. In severe HF, the NE stores in sympathetic nerve endings are depleted. In a sense, the failing myocardium becomes functionally denervated. cAMP responses are reduced by approximately 30% to 35%, leading to further contractile dysfunction. Despite downregulation of the β_1-receptor, a relatively high proportion of β_2-receptors remains to mediate chronotropic and inotropic responses.[78] However, there is some uncoupling of the β_2-receptor from its G protein and a modest upregulation of the $G\alpha_i$ subunit, further contributing to a depressed response to chronotropic and inotropic stimuli.[79] There is also a marked decrease in cardiac β-adrenergic responsiveness with aging, which has clinical implications because HF is heavily concentrated in the elderly population.[80]

The desensitization and uncoupling of β-adrenergic receptors that occurs early with mild to moderate ventricular dysfunction is related to the degree of HF and is associated with a reduced response to β-adrenergic stimulation with drugs such as dobutamine. Long-term stimulation of β-adrenergic receptors can enhance myocardial β-adrenergic receptor kinase activity, leading to further desensitization and uncoupling of the β-adrenergic receptor.[81]

Of great therapeutic interest, β-adrenergic blockade with metoprolol and bisoprolol, relatively cardioselective β_1-blockers, upregulates the β_1-receptor, but carvedilol, a nonselective β_1 and β_2-blocker with additional α_1-blocking activity, does not increase β_1-receptor density.[82,83] These drugs improve LV function substantially in approximately two-thirds of patients. The ventricular improvement seen with chronic

β-blocker use may not be caused by upregulation of β-adrenergic receptors alone, and the beneficial effects of β-adrenergic receptor blockade in HF remains incompletely explained. Moreover, high plasma NE levels do not predict benefit from carvedilol,[84] suggesting that there is not a simple relationship between activation of the sympathetic nervous system and response to β-adrenergic blocking drugs in patients with HF.

The Renin-Angiotensin-Aldosterone System The RAAS plays a pivotal role in the pathogenesis of HF (see Fig. 68–4),[59] and consistent benefit has been derived from ACE inhibitor, angiotensin II receptor blocker (ARB), and aldosterone antagonist therapy in HF patients.[58,85] Mechanisms responsible for the release of renin from the renal cortex have been exhaustively studied and include increased sympathetic drive in the kidneys, β-adrenergic receptor activation, and actual or perceived hypovolemia with hyponatremia or hypochloremia at the level of renal macular densa or arteriole.[86-88] Renin proteolytic enzyme has little biologic activity, but it interacts with angiotensinogen to split off two amino acids to form angiotensin I. This is then cleaved by ACE (distributed widely in the vascular system, especially the lungs) to produce angiotensin II, a peptide with a vast range of biologic activities. Angiotensin II in turn stimulates release of aldosterone from the adrenal cortex, which also has an array of biologic effects, including sodium and water retention, renal salt excretion through increased urinary potassium loss by affecting the sodium-potassium exchange, and enhanced collagen turnover and organ remodeling.

There are at least four recognized angiotensin II receptors, but much of the activity is promoted by the AT_1 receptor. AT_1 receptor actions include arterial vasoconstriction, hypertrophy, apoptosis in myocytes, polydipsia, NE release, sensitization of blood vessels to NE, AVP release, and aldosterone release. The AT_2 receptor appears to have somewhat counter-regulatory effects, including antigrowth and antiremodeling, antiapoptosis, vasodilatation, and activation of the kinin–nitric oxide–cyclic 3′,5′-guanosine monophosphate system.[89] Because AT_1 receptor–blocking drugs (ARBs) increase angiotensin II levels, they can indirectly activate unoccupied AT_2 receptor activity. Angiotensin II levels tend to escape the pharmacologic effects of chronic ACE inhibition irrespective of dosage and can stimulate AT_2 receptor activity.[90] Although all of these components of the RAAS can be measured peripherally, local tissue activities may have a greater impact on the RAAS and reflect true biological activity of these components. Both ACE inhibitors and ARBs reduce cardiovascular events, and the role of the RAAS in the pathogenesis of heart and vascular disease, including progressive HF, is quite significant and remains an active area of investigation for therapeutic options.

Arginine Vasopressin HF is frequently characterized by water retention in excess of sodium retention, leading to hyponatremia. The hyponatremia is caused in part by the nonosmotic release of AVP (also known as vasopressin or antidiuretic hormone) from the neurosecretory cells located in the hypothalamus; AVP acts on the kidneys to reduce free water clearance and to promote vasoconstriction. Release of AVP in HF probably occurs by means of activation of carotid baroreceptors.[91] Plasma AVP levels are often but not always increased in patients with LV dysfunction and HF.[92,93] AVP acts on the V_2 receptors in the collecting duct of the kidney via adenylate cyclase to translocate aquaporin-2 water channels from cytoplasmic vesicles to the apical surface of the collecting duct. AVP also increases aquaporin-2 synthesis. Activation of V_1 receptors in vascular tissue contributes to heightened vascular resistance and myocardial dysfunction in HF.[94] Hyponatremia is a powerful predictor of poor outcome in HF, and elevated AVP levels in HF patients are associated with severe HF. Reliable measurement of circulating AVP is challenging because of a short half-life, but the C-terminal portion of the precursor of pro-vasopressin, copeptin, has been shown to be a strong predictor of cardiovascular outcomes in HF.[95] Despite its association with HF prognosis, therapeutic effects from modulation of AVP may be challenging. For example, tolvaptan, an oral AVP antagonist that improves hyponatremia, failed to improve HF mortality.[96,97]

Natriuretic Peptides A family of natriuretic peptides, including atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide (CNP), is encoded by separate genes, each with a tissue-specific distribution, regulation, and biologic activity.[98] ANP and BNP are often increased in patients with HF, and this has been leveraged to assist in the diagnosis of acute HF.[99] ANP is a 28-amino-acid peptide that is normally synthesized and stored in the atria and to some extent in the ventricles. It is released into the circulation during atrial distension. BNP is synthesized mainly by the ventricles and is released in LV dysfunction or early HF after cleavage (presumably by a protease, corin or furin) from the propeptide to BNP and NT-proBNP (Fig. 68–6).[100] For the most part, these peptides act via guanylate cyclase receptors to promote vasodilatation (ANP, BNP, CNP) and natriuresis (ANP, BNP). The natriuretic peptides, ANP and BNP in particular, are considered counter-regulatory because they tend to reduce right atrial pressure, systemic vascular resistance, aldosterone secretion, sympathetic nerve stimulation, RAAS activity, and hypertrophy of cells and can enhance sodium excretion when infused.[52]

BNP is removed from circulation by a number of mechanisms, including passive clearance by high-flow organs such as kidneys; membrane-bound, receptor-mediated clearance; and enzymatic processes including neutral endopeptidases, meprin-A, and dipeptidylpeptidase-4.[101,102]

Interestingly, data suggest that patients with HF may in fact have low circulating levels of biologically active BNP despite elevated detected levels of BNP and NT-proBNP; this is because commercially available BNP and NT-proBNP assays detect a mixture of the intended target BNP or NT-proBNP, pro-BNP, and degraded BNP fragments in the overall measured level.[103] Regardless, both BNP and NT-proBNP have proven diagnostic and prognostic value in HF as biomarkers (ACC/AHA HF guideline recommendation Class I), and their potential role in guiding HF therapy is being evaluated.[99,104-106]

Recently, drugs designed to inhibit degradation of natriuretic peptides (neutral endopeptidase or neprilysin inhibitor), among other effects, have been combined with ARBs (sacubitril/valsartan) and have shown mortality and morbidity benefit in HF.[58]

Endothelin Endothelins are a family of vasoconstrictor peptides produced by vascular endothelial cells and may play a role in HF and pulmonary hypertension. Although blood levels are increased in patients with HF,[107] endothelin-1 (ET-1) is more of a paracrine than an endocrine hormone.[108] Myocardial tissue ET-1 levels may be increased in HF more as a result of decreased clearance rates rather than as a result of increased synthesis. Endothelial cells synthesize ET-1 rapidly and convert so-called big ET-1 into ET-1 by an endothelin-converting enzyme. Both elevated ET-1 and big ET-1 have been shown to be associated with adverse clinical outcomes in chronic HF patients,[109] but the incremental role of adding ET to established markers of prognosis remains unclear. The synthesis of ET-1 is enhanced by angiotensin II, NE, growth factors, insulin, hypoxia, oxidized low-density lipoproteins, shear stress, and thrombin.[110] Its synthesis is antagonized by ANP and prostaglandins.

Endothelin acts on at least two types of G protein–coupled receptors, A and B. The ET-A receptor increases smooth muscle vasoconstriction, cell proliferation, and hypertrophy and mainly resides on vascular smooth muscle cells. The ET-B receptor, which is mainly endothelial, promotes vasodilatation that is probably mediated by a

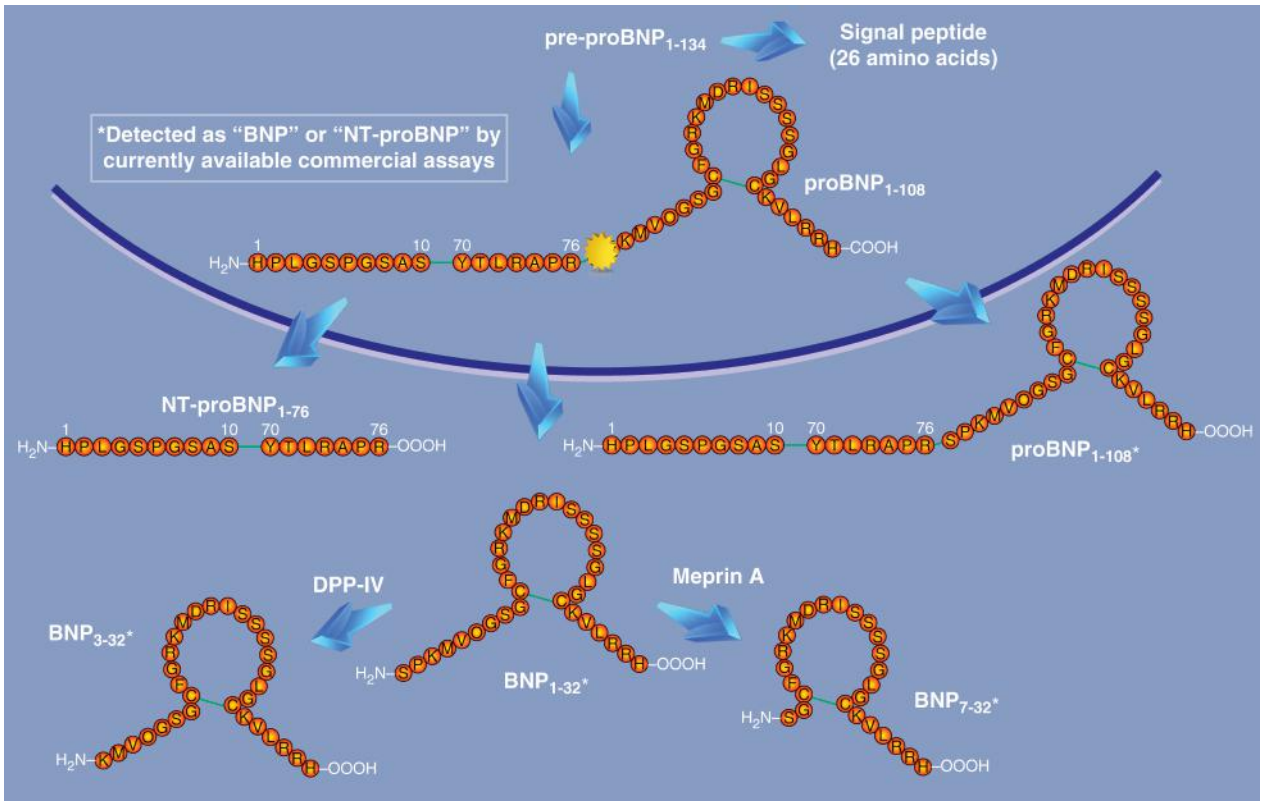

FIGURE 68–6. Synthesis and degradation of B-type natriuretic peptide (BNP). Neutral endopeptidase breaks down the biologically active BNP into inactive fragments. DPP, dipeptidyl peptidase; NT-proBNP, N-terminal pro–B-type natriuretic peptide. Reproduced with permsision from Kim HN and Januzzi JL, Jr. Natriuretic peptide testing in heart failure. *Circulation*. 2011 May 10;123(18):2015-9.[100]

variety of mechanisms, including increased production of nitric oxide (NO) and prostaglandins and activation of potassium channels. ET-1 can also act on the heart to cause hypertrophy, on the adrenal gland to release aldosterone, and on the kidney to promote sodium and water retention. However, blocking the effects of ET-1 has not been shown to improve symptoms or prognosis in HF in contrast to its beneficial effects in patients with pulmonary arterial hypertension.[111,112]

Inflammatory Responses and Remodeling

Cellular Responses and Cytokines It is now widely recognized that there is a strong association between inflammation and cardiovascular diseases. Many of the biomarkers of inflammation, such as erythrocyte sedimentation rate, C-reactive protein, tumor necrosis factor-α (TNF-α), Fas, and interleukins (IL) 1, 6, and 18, are recruited after myocardial injury, such as myocardial infarction, and are thought to be involved in the initiation of the repair process and remodeling as well as cardiac cachexia in certain subgroups of patients with injury.[113-117] These same biomarkers are also elevated in HF and associated with poor HF prognosis independent of traditional risk factors and baseline characteristics.[118] There is increasing evidence that a systemic inflammatory state caused by comorbidities may be intricately involved, especially in HFpEF, but more information is needed before a causative statement can be made.[119] Practical application of these biomarkers is challenging because of the nonspecific nature of inflammation and difficulty in adjusting for potential covariables that may affect them.

Elevated circulating levels of TNF-α can mediate cell growth, negative inotropy, and apoptosis. In cachectic HF patients, TNF-α has been associated with a marked activation of the RAAS.[115] Disappointingly, inhibitors of circulating TNF-α have not been shown to alter the outcome of HF in humans despite the beneficial effects in animal studies.[120] Another potential target of interest is the inflammasome. The inflammasome is a macromolecular structure that plays a central role in the inflammatory response to injury by first sensing the injury and then amplifying the inflammatory response by activating powerful cytokines. This activation of the inflammasome in the heart in the setting of injury may promote adverse ventricular remodeling and HF.[121] In a mouse acute myocardial infarction model, infusion with Nod-like receptor P_3 ($NLRP_3$) inhibitor resulted in > 40% reduction in infarct size and > 70% reduction in troponin I levels (Fig. 68–7), but no clinical trials have been done to date.[122]

Nitric Oxide, Endothelial Dysfunction, and Oxidative Stress Reactive oxygen species (ROS) are produced as a byproduct of normal aerobic metabolism and are involved in a variety of key cellular signaling and immune responses such as myocardial excitation-contraction coupling and myocardial growth. Typically, free ROS are scavenged and neutralized by antioxidants, but when this balance between ROS and antioxidants is thrown off, these species can promote progressive cellular injury or oxidative stress.[123] Prolonged exposure of ROS can lead to activation of specific pathways of oxidant stress with available substrates such as NO, leading to enzyme activation and deactivation, DNA breakage, and lipid peroxidation, which are ultimately responsible for subsequent myocyte apoptosis and pathologic remodeling seen in HF. Growing evidence has supported the role of heightened oxidative stress in the pathophysiology of HF.[124]

Biomarkers of oxidative stress such as myeloperoxidase, albeit nonspecific, are often elevated in patients with chronic HF.[125,126] Markers of oxidative stress were positively correlated to HF severity irrespective of its underlying cause.[124] However, the precise mechanisms contributing

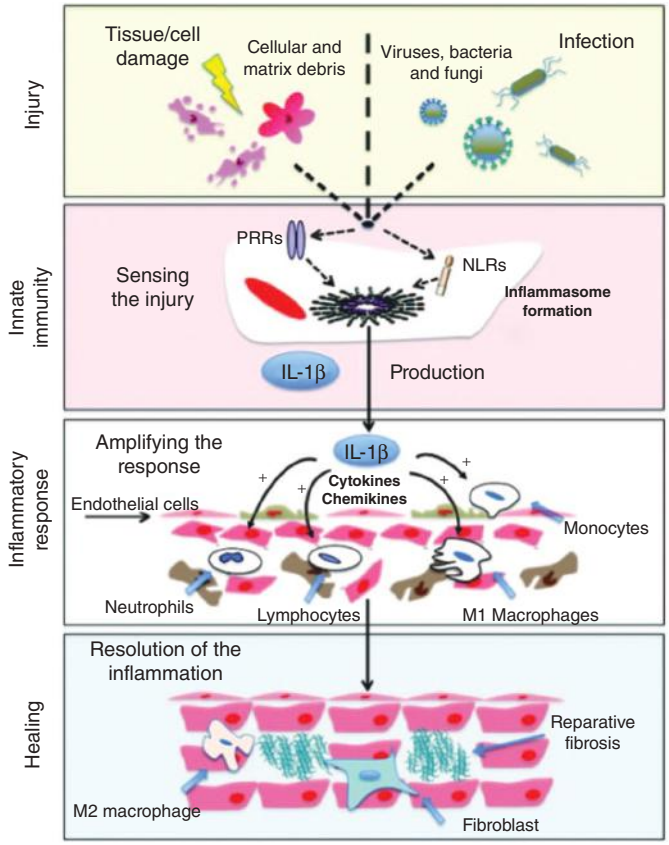

FIGURE 68–7. Acute inflammatory response. Infectious pathogens as well as noninfectious tissue injury producing cellular debris activate the pattern recognition receptors, which is a part of the innate immune response. Innate immunity is activated in resident cells that express membrane or intracellular pattern recognition receptors and/or Nod-like receptors. The resident cells initiate and sustain the inflammatory response by activating the inflammasome, producing interleukin-1β (IL-1β) and secondary cytokines and chemokines, and by recruiting immune cells (neutrophil, monocytes, macrophages, and lymphocytes). Immune cells clear the matrix and cellular debris produced by the injury and coordinate all the phases of healing. The healing process is then completed with the transition of macrophages from M1 to M2 phenotype and the collagen deposition by fibroblasts to form the reparative scar. Reproduced with permission from Toldo S, Mezzaroma E, Mauro AG, Salloum F, et al: The inflammasome in myocardial injury and cardiac remodeling. *Antioxid Redox Signal*. 2015 May 1;22(13):1146-1161.[121]

to oxidative stress in HF are multifactorial. Catecholamines and angiotensin II promote pro-oxidant activities within the myocardium, including enhanced superoxide (O_2^-) formation and generation of NO-derived oxidants, as a necessary consequence of increased myocardial oxygen consumption. Several studies have also observed an association between insulin resistance and HF in the absence of overt diabetes.[127,128] Animal and human studies indicate that endothelium-dependent vasodilatation is abnormal in a number of disease states, including atherosclerosis, hypertension, HF, hyperhomocysteinemia, insulin resistance, and hypercholesterolemia. Endothelial dysfunction has been demonstrated in patients with HF.[129] As already discussed briefly, such endothelial dysfunction in HF (ie, failure to vasodilate in response to a specific endothelial-dependent vasodilator or exertion) can be caused by a reduced release of NO during stimulation. The basal release of NO can be preserved or even enhanced in HF and can be compensatory by antagonizing neuroendocrine vasoconstrictor forces.[130] However, impairment of endothelium-dependent peripheral vasodilatation can be a factor contributing to exercise intolerance in patients with chronic HF, perhaps by limiting nutritive skeletal muscle flow during exercise.[131] This dysfunction of the endothelium can be related to deconditioning in later stages of HF, and with training, it can be largely reversible. The roles of NO and NO synthase (NOS) in the failing heart are much more complex, and new data are emerging.[132,133] NO has been considered to be present as a freely diffusible molecule, which inhibits the positive inotropic response to β-adrenergic stimulation in the failing heart.[134] Smaller physiologic amounts of NO produced by constitutive NOS (cNOS or NOS3) are necessary for normal function and have an antioxidant effect that can protect cells. The inducible isoform of NOS (iNOS or NOS2) is overexpressed in human HF and, therefore, can contribute to worsening HF because high levels of NO in the heart can induce proapoptotic and cytotoxic effects.[135] NO can act in subcellular signaling compartments or modules. Furthermore, covalent modification of cysteine thiol moieties of proteins (*S*-nitrosylation) can be an important second messenger signaling process, working in parallel with ROS and nitrogen species.[136] Therefore, disruption of this cyclic guanosine monophosphate signaling process can lead to nitroso-redox imbalance by either increased formation of ROS or decreased production of reactive nitrogen species.[137]

As HF progresses, there are important changes in the peripheral circulation, particularly downregulation of the NO system. Under normal conditions, NO permits peripheral arteriole dilatation and increased peripheral blood flow in response to exercise. As this system downregulates, peripheral dilatation does not occur with exercise; the lack of appropriate blood flow limits exercise and decreased functional capacity. With exercise training, this system can be restored and clinical status improved.

Extracellular Matrix Changes The extracellular matrix in the heart provides the scaffolding within which contractile cardiomyocytes are housed; it contains a basement membrane, collagen network, proteoglycans, and glycosaminoglycans. Of the different types of collagens, type I and III collagens are the predominant forms found in fibrils deposited in scar tissue after myocardial injury, more specifically demonstrated in myocardial infarction models. These collagens are initially synthesized by cardiac fibroblasts as procollagen precursors before both the N-terminal and the C-terminal are cleaved by proteinases, and then the resulting tropocollagen is assembled into mature fibrils. Markers of collagen turnover such as serum N-terminal type III collagen peptide (PIIINP) have been associated with increased mortality and hospitalization rates, and procollagen type I and PIIINP levels appeared to decrease following aldosterone antagonist therapy in chronic HF paitents.[138] In the 967 Framingham subjects without HF, PIIINP levels were not independently associated with LV mass, fractional shortening, end-diastolic dimensions, or left atrial size.[139] The role of PIIINP in the pathophysiology of HFpEF has not been evaluated to date.

The extracellular matrix is a rather dynamic system that is constantly turned over. In the setting of cardiac or extracardiac injury, regulation of extracellular matrix likely plays an important role in ventricular remodeling and fibrosis. For example, bone morphogenetic protein 1, a C-proteinase, plays a crucial role in the processing of extracellular matrix proteins and collagen deposition and regulation of excessive collagen deposition in fibrosis after tissue injury.[140] Recent studies have found that gene expression of tissue inhibitor of metalloproteinases 1 (TIMP-1) and matrix metallopeptidase 9 (MMP-9) was significantly increased in the border zone of myocardial infarct models as well as ischemic HF models in rats and that treatment with antifibrotic therapy can prevent the upregulation of MMP-9, ultimately leading to suppression of collagen deposition.[141,142] Interestingly, concentrations of TIMP-1 appeared to correlate with diastolic LV dysfunction,[143] In a multimarker analysis of HF patients, a panel that included TIMP-1 as well as NT-proBNP, hs-TnT, growth differentiation factor 15, and insulin-like growth factor-binding protein 4 had the best performance in predicting all-cause mortality at 3-year follow-up.[144]

Soluble ST2 Soluble ST2 (sST2) initially gained attention as a marker of inflammation, cell proliferation, and autoimmune diseases involving T-helper type 2 lymphocyte responses. Since then, the close relationship between the failing heart and sST2 has come to light. In response to the biomechanical stretch of cardiomyocytes and cardiac fibroblasts, the *ST2* gene is strongly upregulated, and circulating sST2 levels increase. sST2 interacts with circulating IL-33, a protein with antifibrosis and antiremodeling effects when it binds to the membrane-bound ligand receptor (ST2L), and appears to mediate the heart's ability to adapt to biomechanical stress. In experimental models, interruption of ST2L expression or infusion of high concentrations of sST2 leads to unchecked ventricular hypertrophy, fibrosis, remodeling, and higher risk for death.[145] Elevated concentrations of sST2 have been closely associated with the phenotype of cardiac decompensation and remodeling and very strongly linked to adverse clinical outcomes in HF. sST2 testing for risk prediction in both acute and chronic HF recently received a Class IIb recommendation in the recent ACC/AHA HF guidelines.[3] Studies have shown that sST2 adds independent and additive information to clinical assessment and natriuretic peptides.[146]

Galectin-3 A member of the lectin family closely involved in immune modulation, galectin-3 is found in a variety of cells and tissues, including the heart. Galectin-3 is involved in the initiation of the inflammatory cascade following cardiac insult and contributes to ventricular remodeling by the way of tissue repair, myofibroblast proliferation, and fibrogenesis. The galectin-3 gene is induced in animal HF models, and when galectin-3 is instilled in the pericardium, there is a considerable increase in collagen deposition.[147] Murine gene knockout models showed that lack of galectin-3 offered partial protection from LV pressure and volume overload with a slower progression to ventricular dysfunction and HF. Circulating values of galectin-3 are elevated in acute and chronic HF, and data suggest that they may identify a high-risk HF phenotype resistant to conventional HF management.[148-150] Galectin-3 testing also received a Class IIb recommendation in the ACC/AHA HF guidelines for risk prediction in HF,[85] but in a head-to-head analysis, galectin-3 testing failed to show independent and additive value to sST2 in a multivariable model; when sST2 was added to a baseline model that included age, sex, LVEF, estimated glomerular filtration rate, NYHA class, diabetes mellitus, ischemic etiology HF, hemoglobin, sodium, β-blocker treatment, ACE inhibitors or ARB, and NT-proBNP for all-cause mortality at 5 years, there was a significant improvement in the C-statistic from 0.757 to 0.770 (P = .004), whereas addition of galectin-3 did not significantly change the C-statistic in a discrimination analysis (C-statistic 0.760, P = .14).[151]

Myocyte Regeneration and Apoptosis

The heart of a normal human weighs approximately 300 g and contains approximately 2×10^{10} myocytes. Until recently, the accepted understanding was that myocyte cell division in the human heart ceased a few weeks after birth.[152] Thereafter, enlargement of the heart was a result of cell hypertrophy or the laying down of collagen in the extracellular space. That view was based on the observations that cancer in the heart is extremely rare, DNA turnover is almost undetectable except in pathologic states, and pathologists disputed whether mitotic figures of myocytes had ever been seen. Approximately 20% of myocytes in the human heart have two nuclei, so that cell separation, rather than mitosis, could bring about a small increase in the total cell number. The precise mechanism for the suppression of cell division in the human heart is unknown. What is established is that damage to human heart muscle results in fibrosis and any repair process, if it were to exist, is insufficient to overcome the rate of loss of cells. In some species such as the salamander and zebra fish, damage to myocardium is repaired by the generation of new myocardial cells, and the process is under genetic control. If the major problem in the worsening of HF is the continuing loss of myocytes, then a new approach is to either inhibit the loss of cells through the processes of apoptosis or necrosis or to promote the growth of new cells.

Apoptosis is increased in pressure overload LV remodeling and post–myocardial infarction animal models as well as in humans (over 200-fold increase in explanted hearts).[153,154] Rodent models appeared to show some promise in apoptosis as a potential target for therapy.[155] However, the extent to which apoptosis contributes to progressive LV dysfunction in HF patients is unclear because the absolute apoptosis rates are quite low at 0.08% to 0.25%, compared with 0.001% to 0.002% in controls.[156]

Growth Differentiation Factor-15 A member of the transforming growth factor-β family, growth differentiation factor-15 (GDF-15) is involved in regulating response to injury in a broad array of tissues including the heart. In the setting of ischemia or pressure overload, the gene for GDF-15 is strongly induced, and the resulting protein appears to modulate myocardial strain, remodeling, and apoptosis.[157] Circulating GDF-15 levels are increased in HF patients and correlate with prognosis, but their ability to add independent information over existing biomarkers and clinical variables was minimal.[158]

Stem Cell and Gene Therapy For the past few decades, much effort has been spent in an effort to increase the number of myocytes in human myocardium either by introducing other cells (eg, cells derived from bone marrow, induced pluripotent stem cells), which are intended to transform into cardiac myocytes, or by the stimulation of resident primitive cells within cardiac muscle. Most of the randomized controlled stem cell trials to date have been limited by their small size. Recent meta-analyses evaluating stem cell trials in post–myocardial infarction and HF patients showed a small improvement in ejection fraction in post–myocardial infarction patients but overall failed to show significant improvement in mortality or morbidity (reinfarction, hospitalization, restenosis, and target vessel revascularization) with stem cell therapy.[159-161] However, results are limited by the heterogeneity of individual trials, including stem cell types, cell modification, and dose, frequency, and method of delivery. Several studies published after these meta-analyses appear to show promise. A recent promising study demonstrated individual and synergistic benefit of bone marrow–derived mesenchymal stem cells and c-kit–positive cardiac stem cells in a swine ischemia/reperfusion injury model. Both cardiosphere-derived cells via intracoronary injection and mesenchymal stem cells via transendocardial stem cell injection also showed regenerative effects in patients with ischemic cardiomyopathy.[162,163]

Experts continue to encourage further exploration in stem cell therapy because the potential benefit from targeting specific mechanisms contributing to progressive LV dysfunction is large. In addition, the primary benefit of stem cell therapy may not be from the adult stem cell differentiating and regenerating into the target tissue, but rather from their paracrine activities such as secretion of numerous cytokines and growth factors, including those that modulate inflammation, adverse LV remodeling, collagen deposition, angiogenesis, apoptosis, mitochondrial dysfunction, and microvascular dysfunction.[164-171]

In the largest gene transfer study to date in the HF population, intracoronary injection of adeno-associated virus 1 (AAV1)/SERCA2a failed to improve clinical outcomes in patients with HFrEF despite promising previous studies. However, the gene therapy was not associated with serious safety issues and may assist in future gene therapy trial designs.[172]

CARDIAC REMODELING

Cardiac remodeling is defined as cardiac structural changes that happen in response to cardiovascular injury, neurohormonal activation, or abnormal hemodynamic loading conditions. Although initially adaptive, when sustained, remodeling can contribute to the development and progression of HF.

Physiologic Adaptations and Maladaptations

Oxygen deprivation, which is most often caused by coronary artery disease, results in impaired relaxation and weakened contraction, as can be seen in transient angina pectoris. This is readily reversible. With prolonged ischemia, decreased contraction (hypokinesis or akinesis) can persist for hours beyond return of blood flow (stunning). If coronary blood flow is chronically reduced, the myocardium can fail to contract normally even if there is no myocardial necrosis (hibernation). With a more serious loss of flow, infarction can occur; the time to infarction can be quite variable as a result of factors such as collateral coronary artery blood flow and myocardial oxygen requirement (also called myocardial demand). All of these stages can produce significant myocardial dysfunction for which the unaffected myocardium will sustain this load. The result is myocardial hypertrophy (increase in myocardial cell size with or without an increase in myocardial mass) of the nonaffected portion of the ventricle; if this is inadequate, an increase in ventricular volume and pressure occurs using the Frank-Starling mechanism to sustain stroke volume (Fig. 68–8).

In HF, myocardial demand may be increased for a variety of reasons including increased myocardial wall tension caused by myocardial hypertrophy and inefficient contractile energy metabolism. This increase can result in extraction of a greater amount of oxygen from each unit of coronary blood flow and widened coronary arteriovenous oxygen differential. Although significant reduction in coronary perfusion as the primary etiology of HF (in the absence of obstructive coronary artery disease) has not been documented, coronary microvascular flow is often impaired in acute dilated cardiomyopathy.[173]

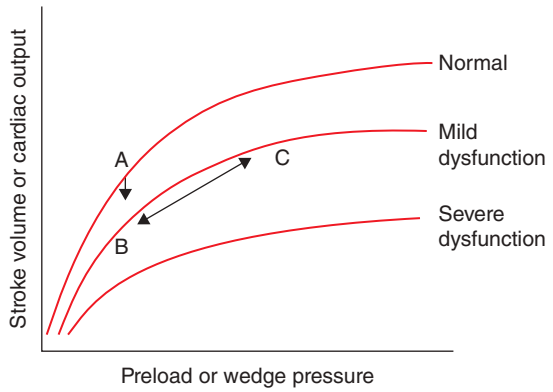

FIGURE 68–8. Frank-Starling relation in heart failure. Idealized family of Frank-Starling curves produced by worsening ventricular function in heart failure. In ventricles with normal cardiac performance, there is a steep and positive relationship between increased cardiac filling pressures (as estimated from the left ventricular end-diastolic or pulmonary capillary wedge pressure) and increased stroke volume or cardiac output (top curve). By comparison, during progression from mild to severe myocardial dysfunction, this relationship is right shifted (ie, a higher filling pressure is required to achieve the same cardiac output) and flattened so that continued increases in left heart filling pressures lead to minimal increases in cardiac output at the possible expense of pulmonary edema. The onset of mild heart failure results in an initial reduction in cardiac function (from point A to point B), a change that can be normalized, at least at rest, by raising the left ventricular end-diastolic pressure (LVEDP) via fluid retention (point C). Diuretic therapy reduces left ventricular filling pressure at the expense of mildly decreased cardiac output (moving from point C to point B). By comparison, normalization of stroke volume is not attainable in severe heart failure (bottom curve). Reproduced with permission from: Cohn JN. Cardiac remodeling: Basic aspects. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 28, 2017.) Copyright ©2017 UpToDate, Inc. For more information visit www.uptodate.com.

Even when myocardial perfusion is normal at rest, exercise can bring out significant impairment in HF patients including widened coronary arteriovenous oxygen difference caused by exercise-induced LV dilatation, impaired coronary vascular bed dilation during reactive hyperemia in the setting of LV hypertrophy and elevated filling pressures (which can normally increase up to five times), and tachycardia-induced reduction in diastolic filling time for coronary arteries.[174]

Force-Frequency Response in Heart Failure Normally, an increase in the frequency of stimulation and heart rate is accompanied by an increased rate of force development, a decreased duration of contraction, and an enhanced rate of relaxation (Bowditch effect). This tends to preserve or increase contractile force while preserving diastolic filling time. In the setting of HF, an increase in stimulation and heart rate is accompanied by a decrease in the rate of myocardial performance; some impairment of systolic function can be related to impaired LV filling as well as negative inotropic effect as a result of alterations in intracellular Ca^{2+} handling. Further reduction in contractile force and inability to decrease duration of contraction can worsen myocardial performance during exercise.[175,176]

Hemodynamic Perturbations: The Hemodynamic Hypothesis In the early stages of HF, the ventricular end-diastolic pressure (EDP) and cardiac output can be normal at rest. However, with exercise or stress (and the accompanying increase in cardiac output and afterload caused by increased blood pressure and heart rate), there is an increase in EDP. The ability to increase cardiac output in response to the increase in oxygen consumption is also reduced. As HF progresses, the resting EDP increases and end-diastolic and end-systolic volumes increase. This results in reduced elastic recoil of the ventricle during diastolic relaxation and is reflected in loss of rapid early diastolic ventricular filling (as revealed by a reduced E wave of the echocardiogram). This helps to further increase the mean diastolic pressure. The elevated ventricular diastolic pressure increases pulmonary venous and capillary pressures and decreases pulmonary compliance. These changes, in combination with increased volume status, can result in pulmonary edema and clinical symptoms of dyspnea.

HF can develop from pressure or volume overload. In pressure overload, myocytes hypertrophy to overcome the increased demands of the excess load. Hypertrophied cells contract and relax more slowly and can be subject to metabolic limitations. In addition, hypertrophied myocardial cells can have a shortened life span. This is of considerable prognostic importance because cardiac myocytes appear to have a reduced capacity to proliferate. When age-related myocyte loss is added to the picture, particularly in association with a decrease in myocyte contractile activity, diastolic dysfunction can occur. As the process continues, ventricular dilatation can occur with systolic dysfunction as well. Loss of myocytes—whether segmental, as in acute myocardial infarction, or diffuse, as in dilated cardiomyopathy—sets up a vicious cycle that leads to reactive hypertrophy in the remaining myocytes. As compensatory hypertrophy becomes more marked in some disease states, the contractility unit of the myocardium often declines because of molecular changes in the heart's contractile proteins and activation system. This is especially likely to occur in response to pressure overload, as in systemic arterial hypertension or aortic stenosis, but also ensues when myocytes are lost from any mechanism.

The Frank-Starling Law and Heart Failure Hemodynamics The volume of blood that the heart moves forward can be described as cardiac output (usually described as liters per minute), which depends on both the stroke volume (SV; the base unit of the volume of blood moving forward per

heartbeat and usually described as liters per beat or milliliters per beat) and heart rate (beats per minute). Although many factors contribute to SV for a given heart, in general, SV depends on three major factors: preload, contractility, and afterload. Preload describes the end-diastolic ventricular volume (EDV) and is determined by the volume of the blood circulating as well as the ability of the ventricle to relax and fill. Contractility describes the force generated by shortening of sarcomere or the ability to pump blood forward. Afterload is the opposing force to flow, such as peripheral arterial pressure, that the moving blood encounters once it is pumped out of the heart. LV hemodynamics are described next, but several of the concepts can be applied to the right ventricle with some important differences; for example, the right ventricle is not meant to withstand a high-pressure system, and its ability to compensate for acute changes in pressure is much more limited.

The Frank-Starling law describes the increase in SV when EDV is increased and is critical for the response to LV systolic dysfunction (see Fig. 68–8). Inadequate emptying of the LV leads to increased EDV (also referred to as increased preload), sarcomere lengthening as a result of LV stretch from increased EDV, and an increase in SV during the next contraction. For any given amount of Ca^{2+} released into the myocyte, there is increased cross-bridge formation and enhanced sensitivity of the myofilament to Ca^{2+} as the sarcomeres lengthen.

In systolic LV dysfunction, the extent of shortening for a given diastolic fiber length and afterload is reduced. The LV can initially maintain a normal or near-normal SV with an increased EDV and thus maintain end-diastolic fiber length. Eventually, the filling pressure increases inordinately, limiting this compensatory mechanism. The dilated LV requires more tension in the LV walls to generate the same pressure as per the Laplace relationship, which describes that the pressure inside the ventricle is inversely related to the radius of the ventricle and directly related to the tension in the LV wall. Furthermore, the dilated LV can lose elasticity, like an overstretched elastic band, and EDV can increase somewhat without an increase in LV EDP, reflecting a shift in the passive pressure-volume curve to the right. An obligatory reduction in ejection fraction occurs when SV is maintained in the face of a large EDV (ejection fraction = SV/EDV). Eventually, further increases in EDP produce little change in EDV, thus flattening the SV-EDP curve. There is no true descending limb to the Frank-Starling curve because increasing preload indefinitely will ultimately lead to mitral regurgitation, displacing the increased pressure. As the heart dilates, the increase in wall stress according to the Laplace relationship will also increase afterload, which can account for any observed reduction in SV as the heart dilates further (ie, the perception of a descending limb). It is important to keep in mind that LV performance depends not only on systolic pump function but also on active relaxation, diastolic elastic recoil, passive diastolic properties, and vascular loading conditions. It is likely that at high LV EDP, valvular incompetence (mitral regurgitation) is a major cause of a decrease in cardiac output. Thus, in end-stage HF in the intact circulation, the Frank-Starling curve flattens.

Loading Conditions and the Concept of the Laplace Relationship A characteristic feature of the dilated, failing heart is that it gradually becomes less sensitive to preload (EDV and fiber length) and more sensitive to afterload stress. At very high LV filling pressures (> 30 mm Hg), when the sarcomeres are fully stretched and the preload reserve is exhausted, the SV becomes exquisitely sensitive to alterations in the afterload. The impedance to ejection includes blood viscosity, vascular resistance, vascular distensibility, and myocardial wall tension. Much of the afterload is made up of ventricular myocardial wall tension. In the ventricle, the tension on the walls increases as ventricular chamber volume increases even if intraventricular pressure remains constant. As the ventricle empties, tension is reduced, even as pressure increases. Calculations of myocardial wall tension are defined by the Laplace equation and are expressed in terms of tension, *T*, per unit of cross-sectional area (dynes per centimeter [dyn/cm]).

Within a cylinder, the law of Laplace states that wall tension is equal to the pressure within a thick-walled cylinder times the radius of curvature of the wall:

$$T = P \times R/h$$

where *T* is wall tension (dyn/cm), *P* is pressure (dyn/cm^2), *R* is the radius (cm), and *h* is wall thickness. Wall tension is proportional to the radius. Because the heart has thick ventricular walls, wall tension is distributed over a large number of muscle fibers, thereby reducing tension on each.

Because the geometry of the ventricles is more complex than that of a cylinder, ventricular wall tension cannot be measured with precision. Wall stress, the force distributed across an area, is actually more correct but is seldom measured.

Two fundamental principles stem from the relationship between the geometry of the ventricular cavity and the tension on its muscular walls: (1) dilatation of the ventricles leads directly to an increase in tension on each muscle fiber, and (2) an increase in wall thickness reduces the tension on any individual muscle fiber. Therefore, ventricular hypertrophy reduces afterload by distributing tension among more muscle fibers.

The wall tension is highest in the inner surface of the heart. The endocardial surfaces must do more work and, therefore, are more vulnerable to reductions in coronary blood flow. Dilatation of the heart decreases cardiac efficiency as measured by myocardial oxygen consumption unless hypertrophy is sufficient to normalize wall stress. In HF, wall tension (or stress) is high, and thus, afterload is increased. The energetic consequences of the law of Laplace can have some role in progressive deterioration of energy-starved cardiac myocytes in the failing heart.

Another major disadvantage of the dilated ventricle is the inability to decrease the average radius during contraction. In the normal heart, wall tension falls during ventricular ejection as the volume decreases, even though pressure is rising. In HF, given the dilated heart with reduced ejection, the average tension in the myocardial fibers actually can continue to increase from the beginning of the ejection until peak systolic pressure is reached, adding additional afterload during ejection. The rate of myocardial fiber shortening is reduced, further contributing to diminished myocardial performance. It is difficult to overstate the importance of the law of Laplace when considering the syndrome of HF. This contrast is apparent in mitral insufficiency. With preserved contractility and a relatively small EDV, mitral insufficiency leads to rapid unloading of volume and reduced tension. When ventricular dilatation occurs with decreased ventricular contractility, ejection is reduced, and tension remains high during systole, leading to an unsteady state that cannot be maintained for long.

Overstretched myocardial cells can induce programmed cell death (apoptosis), thereby contributing to further disease progression.[177,178] The plasticity of progressive dilatation is now more apparent, with remarkable reversal of dilatation observed in response to ACE inhibitors and β-blockers, cessation of alcohol use in patients with alcoholic cardiomyopathy, and spontaneous improvement in patients with inflammatory myocarditis.

Myocyte Response to Altered Loading Conditions In response to increased load, whether created by increased pressure or loss of myocytes, hypertrophy occurs and tends to normalize the load per cell. With an increased volume load, myocytes elongate and, to a small extent, may undergo division.[179] Hyperplasia and apoptosis of myocytes occur with abnormal loading but involve less than 1% of the cardiac myocytes.

Reprogramming of the cardiac myocytes occurs, resulting in a more fetal-like state. More BNP is synthesized. Metabolism begins to favor glucose over free fatty acids. The myocytes enlarge, presumably rendering a short-term structural and functional advantage.[180] The reprogramming requires altered signals, both mechanical and chemical, to reach the nucleus of the cardiac myocyte to set into motion *new* gene transcription.[46] Contractile proteins are altered and improve energetic efficiency. Ultimately, there is a transition from hypertrophy to HF,[181] which has been recognized for a long time but is still not well understood. In a sense, myocyte hypertrophy leads to the structural changes of LV remodeling, thus creating a large, dilated, and poorly functioning heart. The processes of cellular remodeling and subsequent architectural changes in cell and chamber size and shape are highly complex and include many components other than myocardial cell hypertrophy.[46] Myocardial fibrosis and cell dropout occur, and perhaps myocyte slippage can occur, increasing dilatation. As cardiac output falls, multiple neurohormones, including renin and NE, are released in an attempt to preserve blood pressure and organ perfusion,[182] and atavistic counter-regulatory natriuretic peptides (such as BNP) are released in an attempt to offset vasoconstriction, hypertrophy, and volume conservation.[52] Multiple molecular mechanisms,[46,183] some of which primarily affect the cardiac interstitium and others the cardiac myocytes, are involved in the process.

Maladaptive remodeling of cardiac myocyte size and shape begins long before clinical HF begins.[184,185] Alterations in myocyte proteins and mitochondria size, as well as changes in myocardial interstitium and collagen content and architecture, are seen in response to a variety of injuries, including pressure overload, volume overload, and myocardial ischemia.[185,186] Additional phenotypic changes in HF include apoptosis.[153,187] It is important to recognize that much of the neuroendocrine activation that occurs in a primordial attempt to conserve organ perfusion appears to facilitate this myriad of pathologic changes in the heart at the cellular level, thereby possibly contributing to the success of neuroendocrine blockers as therapy for HF. Lastly, there is no single phenotypic change, protein expression, or signal transduction pathway that is dominant. Rather, there is extraordinary redundancy in these mechanisms. This observation has important implications for therapy. For example, blocking one neuroendocrine system can lead to enhanced overactivity of other neuroendocrine systems.

Table 68–3. Differential Diagnosis of Heart Failure With Preserved Left Ventricular Ejection Fraction

Heart failure with preserved ejection fraction
Cardiomyopathy with preserved ejection fraction
• Restrictive cardiomyopathy
• Hypertrophic cardiomyopathy
• Noncompaction cardiomyopathy (can also be with left ventricular systolic dysfunction)
Valvular disease
Right-sided heart failure
Pericardial disease
High-output heart failure
Obstructive
• Atrial myxoma
• Pulmonary vein stenosis

SPECIAL SECTION: PATHOPHYSIOLOGY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

There are many etiologies where a patient may have the clinical syndrome of HF and preserved ejection fraction (Table 68–3). For this section, we will concentrate on the first category of HF where there are no clear etiologic drivers such as aortic stenosis and the diagnosis is currently primarily a diagnosis of exclusion. Not surprisingly, a growing body of evidence suggests that this category of HFpEF may in fact be a rather heterogeneous collection of different HFpEF phenotypes (Fig. 68–9). Many trials did not phenotype the patient cohort well, and this may, in part, explain the lack of demonstrated therapeutic benefit in large phase III trials of nontargeted therapies to date.[188] Incomplete understanding of the pathophysiology of HFpEF and lack of clear diagnostic criteria further add to the challenges surrounding HFpEF, and better understanding is direly needed. Nonetheless, some of the known and shared pathophysiologic features are discussed. Two of the most important, and best studied, aspects of HFpEF are diastolic LV dysfunction and LV stiffness, but other contributing factors include LV systolic dysfunction, extracardiac vascular dysfunction, incoordination of the LV and the vascular system, and impaired reserve system and volume status.

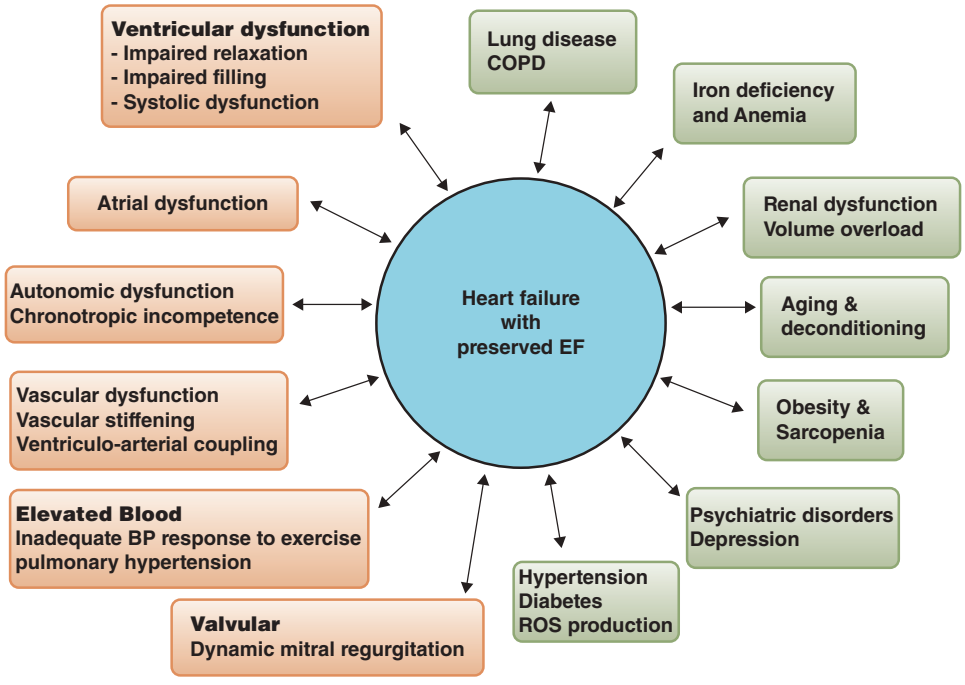

FIGURE 68–9. Contributing factors in heart failure with preserved ejection fraction (EF). Hypertension and diabetes are the most common factors in heart failure with preserved EF. BP, blood pressure; COPD, chronic obstructive pulmonary disease; ROS, reactive oxygen species. Reproduced with permission from Senni M, Paulus WJ, Gavazzi A, et al: New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. *Eur Heart J.* 2014 Oct 21;35(40):2797-2815.[188]

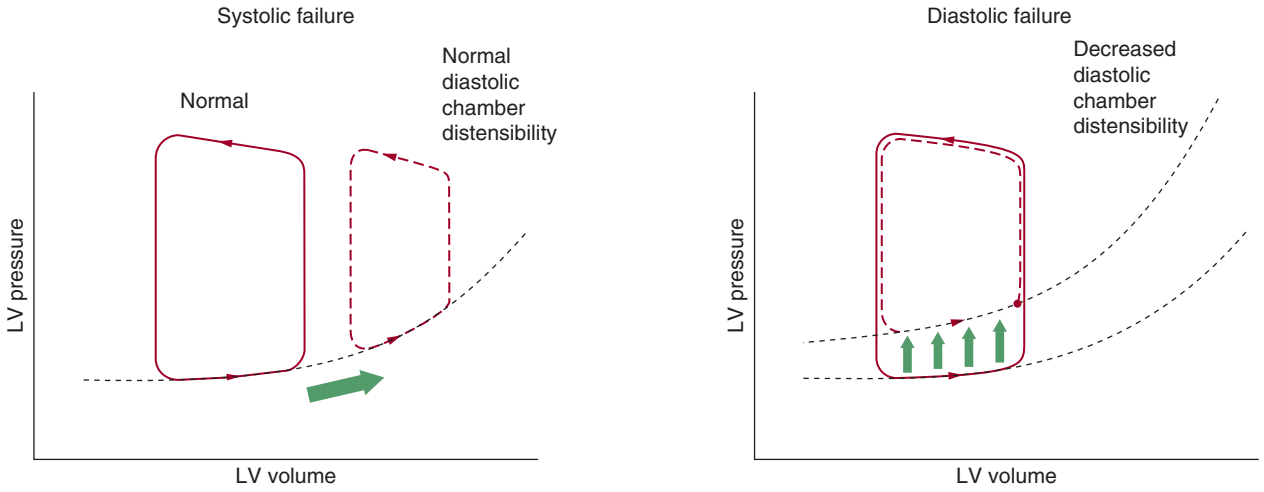

FIGURE 68–10. The *left* panel shows a schematized left ventricular (LV) pressure-volume loop from a patient with primary systolic failure. A normal LV pressure–volume loop (*solid loop*) is shown on the left portion of the curve; the transition to inotropic failure (*dashed loop*) is shown on the right. Systolic failure is manifest as an increase in LV end-systolic volume and as a reduction in the extent of shortening (stroke volume). LV end-diastolic pressure (LVEDP) is increased because LV volume is increased. As indicated by the *arrow*, the diastolic portion of the pressure–volume loop has simply shifted to the right, along the same diastolic pressure-volume relationship; thus, no change in the distensibility of the left ventricle has occurred. The right panel shows an LV pressure-volume loop from a patient with primary diastolic failure (*dashed loop*). In this setting, LV volume may be smaller than in systolic failure. Note that the LVEDP is the same as that in the patient with primary inotropic failure, as denoted by the heavy dots on both pressure-volume loops. In the *right panel*, however, this is caused by an upward shift of the LV diastolic pressure-volume relationship (*arrows*), which indicates a decrease in LV diastolic distensibility such that a higher diastolic pressure is required to achieve the same diastolic volume. In this patient, no change in end-diastolic volume or systolic shortening has occurred. Reproduced with permission from Lorell BH. Left ventricular diastolic pressure-volume relations: understanding and managing congestive heart failure. *Heart Failure* 1988;4:206-223.

DIASTOLIC LEFT VENTRICULAR DYSFUNCTION

The term diastolic HF was initially used to describe HFpEF, but not all HFpEF has etiologic origin in diastolic LV dysfunction. Having said that, diastolic LV dysfunction is quite common in HFpEF. Studies of diastolic function in HFpEF showed that it may be the primary factor responsible for hemodynamic abnormalities and symptoms in HFpEF, primarily in hypertrophic cardiomyopathy, marked LV hypertrophy, and restrictive cardiomyopathy.

The ventricle fills during diastole, and diastole can be divided into isovolemic relaxation and ventricular filling phases (Fig. 68–10). The ventricular filling phase is further made up of early rapid filling, diastasis, and atrial systole. The early rapid filling makes up the majority of the ventricular filling normally (70%-80%) and is driven by the pressure gradient between LV and left atrium (LA). Other contributing factors to the pressure gradient includes myocardial relaxation, ventricular stiffness, ventricular elasticity, systolic function, LA pressure, ventricular interaction, pericardium, LA stiffness, pulmonary vein status, and mitral valve. As a person gets older, the early rapid filling does not make up as much of the ventricular filling. Atrial systole further contributes 15% to 25% of ventricular filling followed by diastasis at another 5% in normal individuals without HF (Fig. 68–11).

LEFT VENTRICULAR RELAXATION

LV relaxation, or lusitropy, begins during end systole and isovolemic relaxation and through the rapid filling phase. It is one of the most important determinants of diastolic LV dysfunction in HFpEF.[189] The process of LV relaxation can be assessed by either an invasive or noninvasive measurement. By using a special manometer-tipped LV catheter to measure LV pressures at various stages of LV relaxation, one can derive tau, the time constant of relaxation that describes the rate of LV pressure changes during isovolemic relaxation.

$$\text{LV pressure} = P_0 e^{-t/\tau}$$

where P_0 = LV pressure at end ejection; t = time, and τ = tau.

Normally, tau is less than 40 milliseconds, and the larger the tau, the more impaired is the relaxation. More commonly, LV relaxation is estimated from echocardiographic data. Depending on LA pressure, LV pressure, and the gradient between LA and LV pressures, the transmitral Doppler flow velocity pattern during diastole is reflective of various degrees of diastolic dysfunction (Fig. 68–12). Mitral annular velocity during early diastole (e′) with tissue Doppler also provides more preload-independent information regarding LV relaxation. E/e′ ratio correlates reasonably with filling pressures; high E/e′ ratio is suggestive of elevated filling pressures. Transmitral flow velocity pattern,

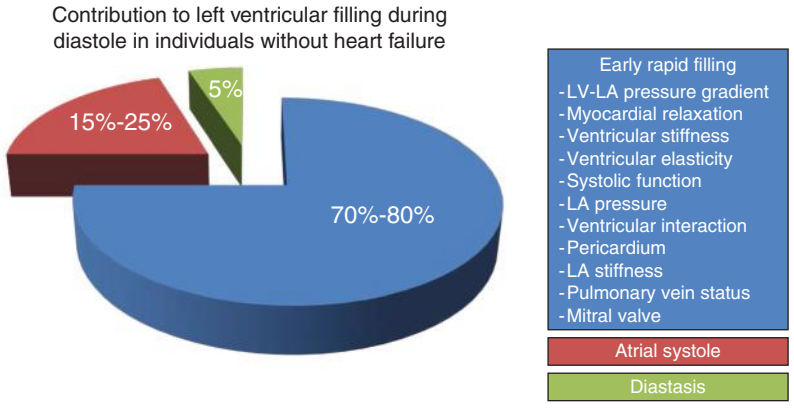

FIGURE 68–11. Contribution to left ventricular (LV) filling during diastole in individuals without heart failure. In addition, there are many determinants of early rapid filling. LA, left atrial.

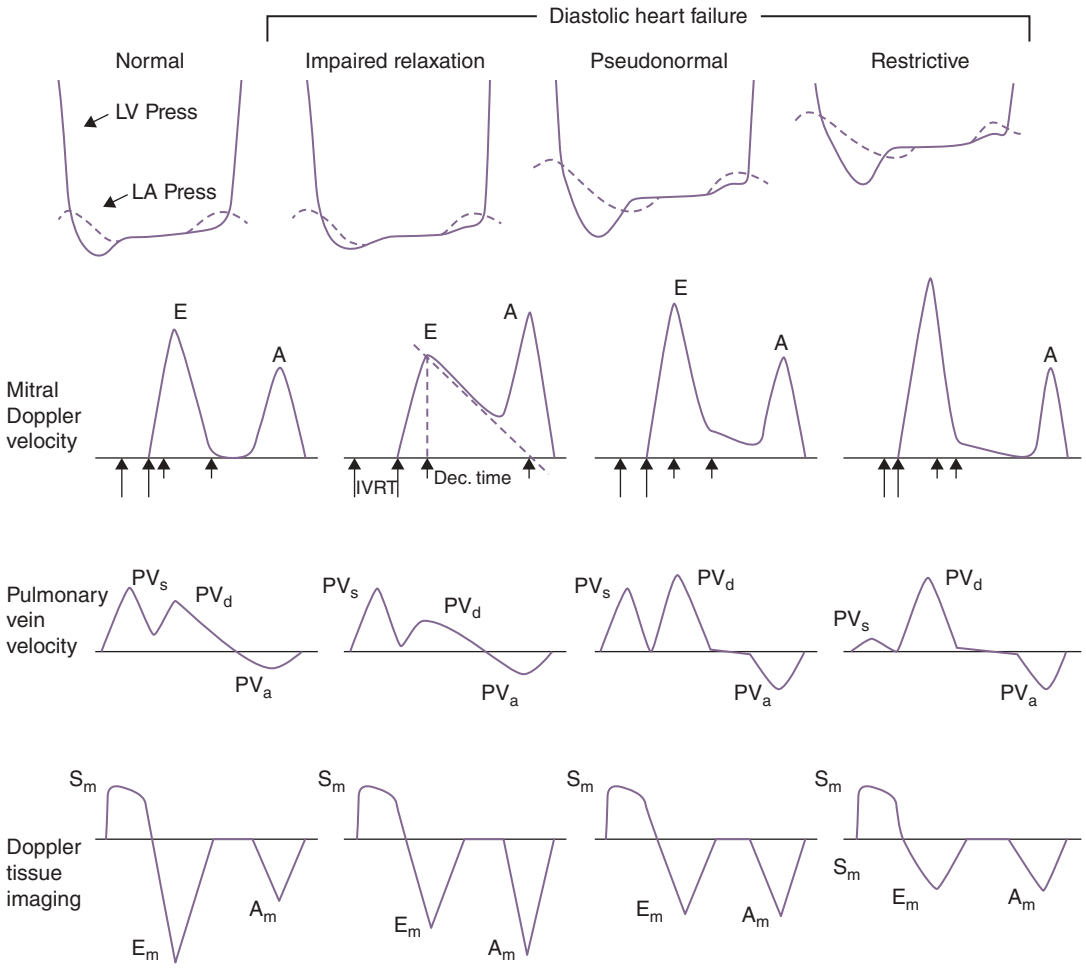

FIGURE 68–12. Doppler echocardiographic evidence of diastolic dysfunction. A_m, atrial mitral annulus velocity; E_m, early mitral annulus velocity; IVRT, isovolemic relaxation time; LA, left atrium; LV, left ventricle; PV_a, atrial pulmonary vein flow velocity; PV_d, diastolic pulmonary vein flow velocity; PV_s, systolic pulmonary vein flow velocity; S_m, systolic mitral annulus velocity. Reproduced with permission from Faggiano P, Vizzardi E, Pulcini E, et al: The study of left ventricular diastolic function by Doppler echocardiography: the essential for the clinician. *Heart international*. 2007;3(1-2):42-50.

mitral annular tissue velocity values, E/e′ ratio and E/A reversal with Valsalva maneuver, pulmonary venous inflow velocity patterns, LA dilation, and elevated pulmonary pressures can help to assess diastolic dysfunction. An isolated finding has limited diagnostic performance, and there is no gold standard definition of diastolic dysfunction; therefore, the final determination of diastolic dysfunction is ultimately based on gathering as much information as possible and making the most likely diagnosis.

There are several factors that impact LV relaxation with a number of potential mechanisms contributing to the pathophysiology of HFpEF, including afterload, the rate and extent of detachment of actin-myosin cross-bridges, and the timing and distribution of intraventricular pressure (Table 68–4).

For the myofiber to lengthen during diastole, the actin-myosin cross-bridges have to detach in an active, ATP-dependent process. This process involves close and rapid regulation of cytosolic Ca^{2+}. In animal models of HFpEF, there appears to be reduced Ca^{2+} reuptake into the SR via decreased SERCA activity, impaired β-adrenergic signaling leading to reduced protein kinase A activity, increased protein kinase C via protein phosphatases, and elevated catecholamine activation.[190,191] Myocardial injury, such as from myocardial ischemia, can directly impact ATP metabolism via reduced ability to cross-bridge detachment and ultimately myocardial relaxation.

These cellular abnormalities in LV relaxation contribute to hemodynamic abnormalities by increasing filling pressures, and these changes become even more apparent during exercise. In the normal heart, there is enhanced relaxation during exercise mediated by an increase in the LA-LV pressure gradient without increasing LA pressures. In the setting of impaired LV relaxation, there is evidence of chronotropic incompetence and impaired myocardial reserve during exercise as well as an increase in LV diastolic pressures when heart rate and blood pressure increase in response to exercise.[192,193]

Because patients with HFpEF and abnormal LV relaxation are increasingly dependent on atrial contraction for filling, atrial fibrillation along with its tachycardia can contribute to elevated filling pressure and onset of acute HF.[194]

LEFT VENTRICULAR DIASTOLIC STIFFNESS

LV diastolic stiffness is also one of the biggest contributors to diastolic dysfunction in HFpEF patients.[189,195-197] With increased stiffness of the LV or impaired elastance, there is an increase in LA pressures, pulmonary venous pressure, and congestion. Elastance is the ability of the LV to stretch and recoil with the distending intraventricular force on the myocardium. Estimation of LV diastolic stiffness requires formation of pressure-volume curves while varying preload invasively or by Doppler

TABLE 68–4. Potential Mechanisms in HFpEF

Cardiomyocyte

- Abnormal calcium homeostasis (↑ diastolic calcium or ↓ rate of calcium reuptake → incomplete or impaired relaxation)
  1. Sarcolemmal calcium channels (sodium/calcium exchanger and calcium pump)
  2. Sarcoplasmic-endoplasmic reticulum calcium ATPase (SERCA) abundance and function
  3. Proteins modifying SERCA activity
     1. Phospholamban, calmodulin, calsequestrin abundance, and phosphorylation state
     2. Sarcoplasmic reticulum calcium release channels

Extracellular matrix

- Increased extracellular matrix (collagen)
- Increased collagen stiffness (advanced glycation end products)

Myofilaments

- Energetics (↓ ATP or ↑ ADP slows actin-myosin cross-bridge release)
  1. ADP/ATP ratio, ADP and P_i concentration, phosphocreatine shuttle function
- Proteins regulating cross-bridge formation and calcium sensitivity
  1. Troponin C calcium binding
  2. Troponin I phosphorylation state
- Cytoskeletal proteins
  1. Microtubules (increased density) → ↑ diastolic stiffness
  2. Titin isoforms (↑ noncompliant isoform and phosphorylation state) → ↑ diastolic stiffness

Whole heart

- Asynchrony of relaxation due to regional infarction, ischemia, hypertrophy, fibrosis, conduction disease
- Concentric remodeling and other geometric changes
- Ischemia as a result of epicardial and microvascular disease
- Atrial systolic and diastolic dysfunction
- Rate and rhythm abnormalities (chronotropic incompetence, atrial fibrillation, supraventricular tachycardia)

Extracardiac

- Vascular dysfunction (arterial stiffening; endothelial dysfunction; impaired coronary, pulmonary, and peripheral flow reserve), abnormal ventriculoarterial coupling
- Extrinsic forces (RV-LV interaction and pericardial constraint)
- Peripheral muscle and ergoreflex dysfunction
- Pulmonary hypertension (secondary to chronic pulmonary venous hypertension)
- Neurohumoral activation
- Comorbidities (renal dysfunction, anemia)

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; RV, right ventricular.

Reproduced with permission from Mann DL, Zipes DP, Libby P, et al: Braunwald's Heart Disease: *A Textbook of Cardiovascular Medicine*, 10th ed. Philadelphia: Saunders; 2014.

evidence of elevated filling pressures in the setting of normal LV dimension, decreased deceleration in early diastolic transmitral flow velocity in the setting of impaired relaxation, and rapid equalization of LA and LV pressures during early diastolic filling.

Extracellular matrix surrounding myofibers contains fibrillar proteins such as collagen type I and III, elastin, proteoglycans, and the basement membrane proteins laminin and fibonectin and contributes significantly to LV diastolic stiffness.[198] Extracellular matrix, while acting as the scaffolding of the heart, is a rather dynamic system with close interdependence and regulation by myocardial injury, neurohormonal activation, and remodeling. There are close ties between extracellular matrix and fibrosis with a close association between interventions that affect extracellular matrix formation/removal and LV diastolic stiffness and relaxation.

Another factor affecting LV diastolic stiffness is titin, a large protein that acts as a spring in the heart's scaffolding. Change in titin isoforms or decreased phosphorylation of titin can raise resting tension of biopsied human myocytes.[199,200]

INFLAMMATION

Patients with HFpEF have increased frequency of comorbidities including hypertension, obesity, diabetes mellitus, chronic obstructive pulmonary disease, and iron deficiency. Although a definitive link is lacking, studies to date suggest that these comorbidities may be interconnected with the pathophysiology of HFpEF through increased inflammation found in patients with these comorbidities.[201] Human models of HFpEF have shown increased biomarkers of inflammation such as C-reactive protein, sST2, and tissue inhibitor of metalloproteinase.[197] One of the working hypotheses is that the inflammatory state may result in altered coronary microvascular endothelial function and increased ROS; reduced NO bioavailability, cyclic guanosine monophosphate content, and protein kinase G activity; hypophosphorylation of titin; and increased interstitial fibrosis, ultimately resulting in HFpEF (Fig. 68-13).[119] A study of mineralocorticoid receptor antagonism appeared to improve obesity-associated cardiac diastolic dysfunction as documented by echocardiography in mice with a reduction in cardiac fibrosis and restoration of endothelium-dependent vasodilation of isolated coronary arterioles via an NO-independent mechanism.[202] A promising therapy, the phosphodiesterase-5 inhibitor sildenafil, appeared to benefit systemic vasculature and endothelium but was found to be deleterious on ventricular function in HFpEF patients.[203]

EXERCISE TOLERANCE IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

Normally cardiac output can increase dramatically in response to exercise, and this increase is accomplished by an increase in heart rate and SV, decreased peripheral vascular resistance, increased LV contractility, and increased filling rate. However, to increase cardiac output during exercise, both the force-frequency relationship and the Frank-Starling mechanism have to be intact to compensate for the shortening of diastolic filling time during exercise. In the setting of HFpEF, there is an impaired force-frequency relationship and a prerequisite of a normal LV elasticity in order for the Frank-Starling mechanism to result in an increase in end-diastolic volume without increasing filling pressures. Cardiopulmonary exercise testing suggests that reduced cardiac output responses, such as impaired chronotropic responses and reduced peak SV likely influenced by LV diastolic dysfunction, and pulmonary vascular dysfunction mainly limit exercise capacity in HFpEF patients, rather than limitations in peripheral oxygen extraction.[192,204] Factors beyond the heart, such as impaired skeletal muscle vasodilation during exercise, likely contribute to exercise intolerance in HFpEF.[205] Fascinatingly, exercise training and even caloric restriction in obese HFpEF patients appeared to improve exercise tolerance in small randomized trials, with the greatest effect when combined.[206] Despite multiple therapeutic trials, the only intervention shown to improve exercise tolerance and quality of life in HFpEF patients is exercise training.[207] To date, no medications have been shown to improve hard clinical outcomes such as mortality or HF hospitalizations in HFpEF patients.

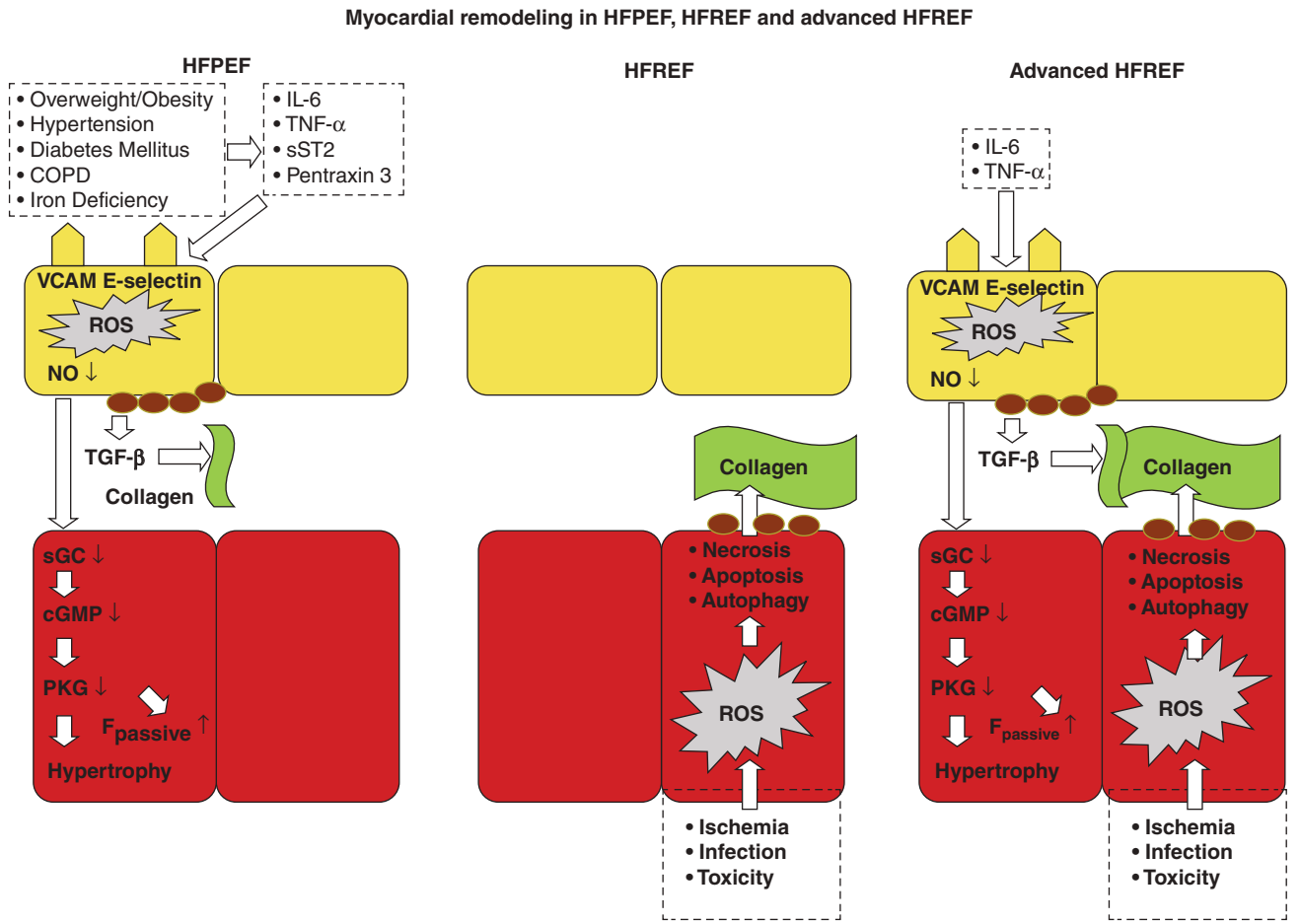

FIGURE 68–13. The role of endothelial oxidative stress in myocardial remodeling in heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and advanced HFrEF. cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; IL, interleukin; NO, nitric oxide; PKG, protein kinase G; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; sST2, soluble ST2; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule. Reproduced with permission from Paulus WJ and Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013 Jul 23;62(4):263-271.

INTEGRATIVE PATHOPHYSIOLOGY WITH OTHER ORGAN SYSTEMS

It is important to note that LVEF does not correlate well with exercise tolerance, and impaired cardiac output alone is not the dominant reason for exercise intolerance. Many factors limit increased cardiac output during exercise in patients with HF, including a reduced myocardial force-frequency response, an inability to fully use the Starling effect, and chronotropic incompetence. These limitations of cardiac performance are combined with endothelial dysfunction in the peripheral arterioles, leading to impaired vasodilatation and reduced nutritive skeletal muscle blood flow. Disuse atrophy of skeletal muscles also occurs. The latter effects appear to be excessively dependent on a glycolytic metabolism, partly because of reduced metabolic efficiency in performing external work.[208] Additional mechanisms include changes in muscle fiber recruitment, selective atrophy of oxidative fibers, and physical deconditioning. The mitochondrial content of skeletal muscle is reduced in HF.[209] Increased expression of the inducible isoform of NOS in skeletal muscle is correlated with reduced mitochondrial creatine kinase expression and exercise intolerance.[210] Apoptosis is frequently found in skeletal muscle of patients with HF and is also associated with exercise impairment.[211] This crosstalk between the heart and the peripheral organs is gaining increasing attention as new evidence comes to light.

INFLAMMATION

Myocardial injury such as from myocardial ischemia, or LV volume or pressure overload, results in recruitment of inflammatory cytokines such as IL-1β, IL-6, IL-18, and TNF-α. However prolonged inflammatory pathway activation can cause these factors to circulate in elevated concentrations.[212] These changes may be an attempt to repair injury or increased exposure to endotoxin as a result of altered gut permeability in patients with edema.[213] When elevated, these cytokines are associated further injury as well as poor clinical outcomes in HF. TNF-α in particular has garnered attention because it is elevated in patients with HF, the degree of elevation closely mirrors NYHA class, and elevated values are associated with worse clinical outcomes.[115,212] In murine models, overexpression of TNF-α resulted in dilated cardiomyopathy with biventricular fibrosis suggesting an etiologic role in the development of HF.[214] However, treatment with anti–TNF-α did not alter clinical outcomes in HF.

Furthermore prolonged exposure to elevated inflammatory cytokines may even result in peripheral organ damage. Inflammation and the nucleotide-binding oligomerization domain-like receptors with

pyrin domain ($NLRP_3$) inflammasome have been implicated in playing a central role in the connection between the heart and the peripheral organs in HF.[201]

CARDIOMETABOLIC CONNECTIONS: CARDIAC CACHEXIA

Obesity is a known risk factor for cardiovascular disease and for the development of chronic HF. However, recent data suggest that increased body mass index is associated with a more favorable prognosis once HF is established.[215-217] Negative energy balance and unintentional, nonedematous weight loss, or cachexia, occur in an estimated 13% to 35% of patients with HF.[218] Cachexia is also associated with increased risk of adverse clinical outcomes.[219,220] Studies suggest that there may be multiple factors involved in the development of cachexia in HF, such as altered nutritional absorption, neurohormonal activation, and immunologic activation.[221] Both human and animal models of cachexia have revealed that elevated levels of TNF-α correlate with sarcopenia and fat, although the mechanism is not well understood.[115,221] Adipose tissue secretes a number of cytokines, including adiponectin. Elevated adiponectin level is associated with increased mortality and is probably a marker of wasting.[222] Moreover, low rather than high cholesterol levels are associated with a poor outcome in patients with chronic HF. In HF, whole-body protein synthesis seems to be suppressed, and breakdown of myofibrillar protein, principally leg skeletal muscle, is increased. A significant decrease in LV mass also occurs in patients with cardiac cachexia.[223]

CARDIORENAL CONNECTIONS

The interaction between the heart and the kidney is bidirectional, with the heart affecting the renal function and the kidneys affecting the cardiac function.[224] A number of mechanisms may be involved including neurohormonal activation, reduced renal perfusion, and increased renal venous pressures. Activation of the neurohormonal system, including the activation of the sympathetic nervous system and RAAS system, release of vasopressin, and ET-1 lead to excessive salt and water retention and vasoconstriction and overwhelm the counter-regulatory systems. However such vasoconstriction also results in increased afterload and reduces cardiac output. Decreased cardiac output can further contribute to reduced renal perfusion in a vicious cycle. However, the relationship between decreased cardiac output and decreased renal perfusion may not be a simple one; evidence suggests that invasive measure of cardiac output does not correlate well with estimated glomerular filtration rate at baseline, and a change in cardiac output did not correlate with a change in renal function at moderate cardiac dysfunction, but may correlate in severely reduced cardiac output states.[225] More importantly, both animal and human models have shown that increased renal venous pressures resulting in a decreased perfusion gradient across the glomerular capillary network in accordance with the Poiseuille law may cause a reduction in renal function.[226-230] Right ventricular dilation and systolic dysfunction have also been suggested as other mechanisms of cardiorenal syndrome through elevated central venous pressure as well as interventricular interaction impeding LV filling caused by increased right-sided pressures.[231]

CONCLUSION

HF is a heterogeneous clinical syndromes composed of several phenotypes. The pathophysiology is complex, and our understanding of it is still emerging. Rather than the heart as an isolated organ, the intricate relationship between the heart and the rest of the body needs to be better understood. Treatment for HFrEF has improved over the years but is not curative. The prevalence of HFpEF is rapidly increasing, and no medical therapy has been shown to benefit the clinical status of affected patients. In addition, there is no question that prevention of HF must be given a higher priority. We now know that most coronary heart disease, the number one cause of HF, can be prevented by control of coronary risk factors. Because 60% to 65% of all HF in Western civilization is associated with advanced coronary disease, it is clear that controlling blood pressure, reducing plasma lipids, maintaining an ideal weight (and thus reducing the chance of developing diabetes mellitus), staying physically fit, and avoiding cigarettes can have a substantial prevention effect on the development of HF. More precise understanding of varying pathophysiologic mechanisms is needed in order to identify a more precise, targeted therapy for HF phenotypes, thus allowing for a rational, aggressive, and cost-effective prevention strategy before patients reach the late stages of the syndrome.

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CHAPTER 69

THE EPIDEMIOLOGY OF HEART FAILURE

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INTRODUCTION

Heart failure is a clinical syndrome caused by abnormalities of cardiac structure or function that result in impaired cardiac filling, ejection of blood, or both and, consequently, an inability to meet the circulatory needs of the body. There is substantial variation in its etiology, associated comorbidities, prognosis, and response to therapy. Heart failure carries a significant burden on society, accounting for approximately 1 million hospitalizations and 65,000 deaths at a cost of $31 billion annually in the United States alone. In this chapter, we review the epidemiology of HF, with a specific focus on chronic HF.

HISTORICAL PERSPECTIVE

Commonly encountered symptoms and signs of HF, such as dyspnea and edema, have been recognized for more than 2,500 years dating back to ancient Greece and Rome.[1] However, pathophysiologic understanding of HF was not well understood. Two millennia lapsed before William Harvey, in 1628, identified the heart as the pulsatile driver of blood through the vascular circulatory system.[2] This discovery set the stage for understanding hemodynamic abnormalities in HF. In 1918, Starling described the relationship between cardiac volumes and output in the normal and failing heart.[3] The advent of cardiac catheterization in the 1940's brought hemodynamic assessments into clinical medicine, but even then therapies for HF were limited to palliation of symptoms with digitalis and the toxic mercurial diuretics.[4]

Around World War II, cardiovascular disease was recognized as the leading cause of death in the United States, and in 1944, Franklin D. Roosevelt was diagnosed with hypertensive heart disease and cardiac failure.[5] In the context of increasing awareness of the public health burden of cardiovascular disease, the National Heart Act was signed in 1948, establishing what is now known as the National Heart, Lung, and Blood Institute and initiating a new epidemiologic study (the Framingham Heart Study).[5] In 1953, the cardiologist Inge Edler and physicist Hellmuth Hertz (Lund University, Sweden) developed echocardiography, which enabled a noninvasive estimation of cardiac structure and function.[6] In the late 1950s, thiazide diuretics were introduced to alleviate congestive symptoms in HF. The 1950s and 1960s also marked a time when knowledge about the cellular and molecular basis of HF was increasing, with seminal observations implicating inflammation, adrenergic and neurohormonal activation, abnormal energetics, myocyte hypertrophy, and altered excitation-contraction coupling.[7-10] A new era in HF therapy was also ushered in by the first heart transplant in 1967.[11]

A major barrier to understanding the risk factors and natural history of HF was a lack of uniform diagnostic criteria. Therefore, investigators at the Framingham Heart Study developed a set of clinical criteria for the diagnosis of HF that was first reported in 1971 (Fig. 69–1).[12] Other algorithms for the diagnosis of HF, such as the Boston and Gothenburg criteria, were developed in the mid to late 1980s (see Fig. 69–1).[13,14] In each of these algorithms, specificity for the diagnosis of HF is enhanced by combining several diagnostic criteria.

Following the introduction of standardized criteria for HF, clinical research into understanding its risk factors, etiologies, prognosis, and therapies accelerated. In the Framingham Heart Study, hypertension and coronary artery disease were identified to be the major risk factors for HF, and the poor survival among patients with HF was demonstrated.[12] In the 1980s, large-scale randomized clinical trials began not only for treatment, but also prevention of symptomatic HF.[15-17] In 1990, a genetic cause for dilated cardiomyopathy was first described.[18] The first clinical guidelines on HF management were published in 1995.[19] By the mid-1990s, recognition that HF could occur in the setting of a preserved left ventricular ejection fraction was gaining traction.[20,21] The efficacy of mechanical (ventricular assist) and electrical (implantable cardioverter-defibrillators and cardiac resynchronization) devices were demonstrated in the early to mid-2000s. Nonetheless, despite the remarkable advances in the pathophysiologic understanding and treatment of HF over the last half century, it remains a leading cause of morbidity and mortality.

EPIDEMIOLOGIC DEFINITIONS AND STAGES

Criteria for the diagnosis of HF have not substantially changed in the four to five decades since the Framingham, Boston, and Gothenburg criteria were developed. In 2002, circulating natriuretic peptide levels were demonstrated to be robust markers for the differentiation of cardiac versus noncardiac causes of dyspnea, particularly in the acute setting (such as the emergency department), that may aid in the diagnosis of HF.[22,23] However, to date, neither the American Heart Association (AHA)/American College of Cardiology (ACC), nor European Society of Cardiology (ESC) guidelines have incorporated natriuretic peptide levels into the diagnostic criteria for HF. The current ESC guidelines do, however, require objective evidence of cardiac dysfunction (typically obtained noninvasively from echocardiography) in the setting of symptoms and signs to diagnose HF.[24]

Framingham	Boston	Gothenburg
Major criteria Paroxysmal nocturnal dyspnea Orthopnea Jugular venous distension Pulmonary rales Radiographic cardiomegaly Acute pulmonary edema S3 gallop Increased venous pressure (≥ 16 cm H_2O) Circulation time ≥ 25 seconds Hepatojugular reflux Minor criteria Ankle edema Nocturnal cough Dyspnea on exertion Hepatomegaly Pleural effusion Vital capacity 1/3 of maximum Tachycardia (≥ 120 bpm) Major or minor criteria Weight loss ≥ 4.5 kg in 5 days with therapy Heart failure diagnosed if either A) 2 major B) 1 major and 2 minor	Category I: Symptoms Paroxysmal nocturnal dyspnea (4 pts) Resting dyspnea (4 pts) Orthopnea (4 pts) Dyspnea while walking level (2 pts) Dyspnea while walking incline (1 pts) Category II: Signs Wheezing (3 pts) S3 gallop (3 pts) Heart rate abnormality (1-2 pts) Elevated jugular venous pressure (1-2 pts) Pulmonary rales (1-2 pts) Category III: Chest radiography Alveolar pulmonary edema (4 pts) Interstitial pulmonary edema (3 pts) Bilateral pleural effusions (3 pts) Cardiothoracic ratio (≥ 0.50) Upper zone flow redistribution (2 pts) Heart Failure diagnosed as: Definite if 8-12 pts Possible 5-7 pts Unlikely ≤ 4 pts	Cardiac score Self-reported heart disease (1-2 pts) Self-reported angina (1-2 pts) Self-reported edema (1 pt) Self-reported nocturnal dyspnea (1 pt) Rales (1 pt) Atrial fibrillation on ECG (1 pt) Pulmonary score Self-reported chronic bronchitis/asthma (1-2 pts) Self-reported cough, phlegm, or wheezing (1 pt) Rhonchi (2 pts) Therapy score Digoxin (1 pt) Diuretic (1 pt) Scoring: 1 pt for past history 2 pts if within past yr Max 2 pts if both heart disease & angina Heart failure if 1 point from each category

FIGURE 69–1. Framingham (1971), Boston (1985), and Gothenburg (1987) criteria for the diagnosis of heart failure.[12-14]

Few studies have compared the performance and agreement of the various criteria for HF.[25-27] Although no accepted gold standard for the diagnosis of HF currently exists, the Framingham Heart Study criteria are among the most commonly used criteria for the evaluation of HF in both population-based studies and clinical practice.[12,28-30] Population-based cohort studies and/or clinical trials have used the different diagnostic criteria described above to variable extents (some with expert physician panel review, others with automated algorithms or use of administrative claims data, eg, International Classification of Diseases Ninth Revision codes), thereby limiting comparability of the absolute rates for incident and prevalent HF across studies. Geographic variation in the use of diagnostic criteria for HF also has implications on inclusion/exclusion in clinical trials.[31,32] Other factors that influence the estimates of the incidence, prevalence, and prognosis in HF include use of inpatient hospitalized events, outpatient diagnoses, or both; variation in statistical methodology; and ability to apply consistent diagnostic criteria over time. Nonetheless, despite the lack of uniform criteria for defining HF, prior studies of the epidemiology of HF still yield reasonably consistent patterns of disease occurrence and associations with risk factors.

Heart failure is typically a progressive syndrome resulting from risk factors (stage A) that lead to asymptomatic abnormalities of cardiac structure and function (stage B), then eventually transitioning to symptomatic HF (stage C) and decompensations/refractory symptoms (stage D) (Fig. 69–2).[33] This staging system formulated by the AHA and the ACC highlights the potential importance of risk factor modification through lifestyle and pharmacologic means to prevent progression to symptomatic HF. In 2007, the prevalence of each HF stage was estimated in a population-based sample of 2029 residents of Olmsted County, Minnesota, over the age of 45 years, all of whom underwent standardized testing with symptom questionnaires, electrocardiogram (ECG), and echocardiography. In this study, 32% of individuals were classified as stage 0 (no risk factors and normal ventricular structure and function), 22% stage A, 34% stage B, 12% stage C, and 0.2% stage D.[34] It should be recognized that estimates of the prevalence of each stage will vary according to the definitions for and the methods used to detect abnormalities of cardiac structure and function (stage B) and the assessment of symptoms (stages C and D). In the Olmsted County study, stage B was defined as asymptomatic individuals with one or more of the following: a prior history of myocardial infarction, regional wall motion abnormalities, left ventricular ejection fraction (LVEF) < 50%, left ventricular hypertrophy by ECG or echocardiography, left ventricular enlargement, diastolic dysfunction, or moderate or severe valvular heart disease.

For epidemiologic studies and clinical practice, HF can be classified according to other characteristics as well, including the degree of functional limitation, the LVEF, and whether the left, the right, or both ventricles are failing. The New York Heart Association (NYHA) classification is used to characterize functional capacity in patients with HF, ranging from no limitation (class I) to slight limitation during ordinary activities (class II), moderate limitation as a result of symptoms with less than ordinary activity (class III), or severe limitation with symptoms at rest (class IV).[35] For patients with advanced HF (ie, NYHA class III and IV with persistent limiting symptoms despite optimal medical therapy), the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) profile further refines classification of disease severity classification to inform risk assessment and the choice and the timing of mechanical circulatory support (Table 69–1).[36] For example, a HF patient with NYHA class III limitations may be further categorized as INTERMACS 5, 6, or 7, whereas a NYHA class IV patient could be further classified into INTERMACS categories 1, 2, 3, or 4.

The most common categorization based on cardiac structure and function, and one of substantial clinical importance, is whether the individual patient with HF has a preserved or a reduced LVEF. Heart failure with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) were previously referred to as systolic and diastolic HF, respectively. The terms systolic and diastolic HF were attempts to

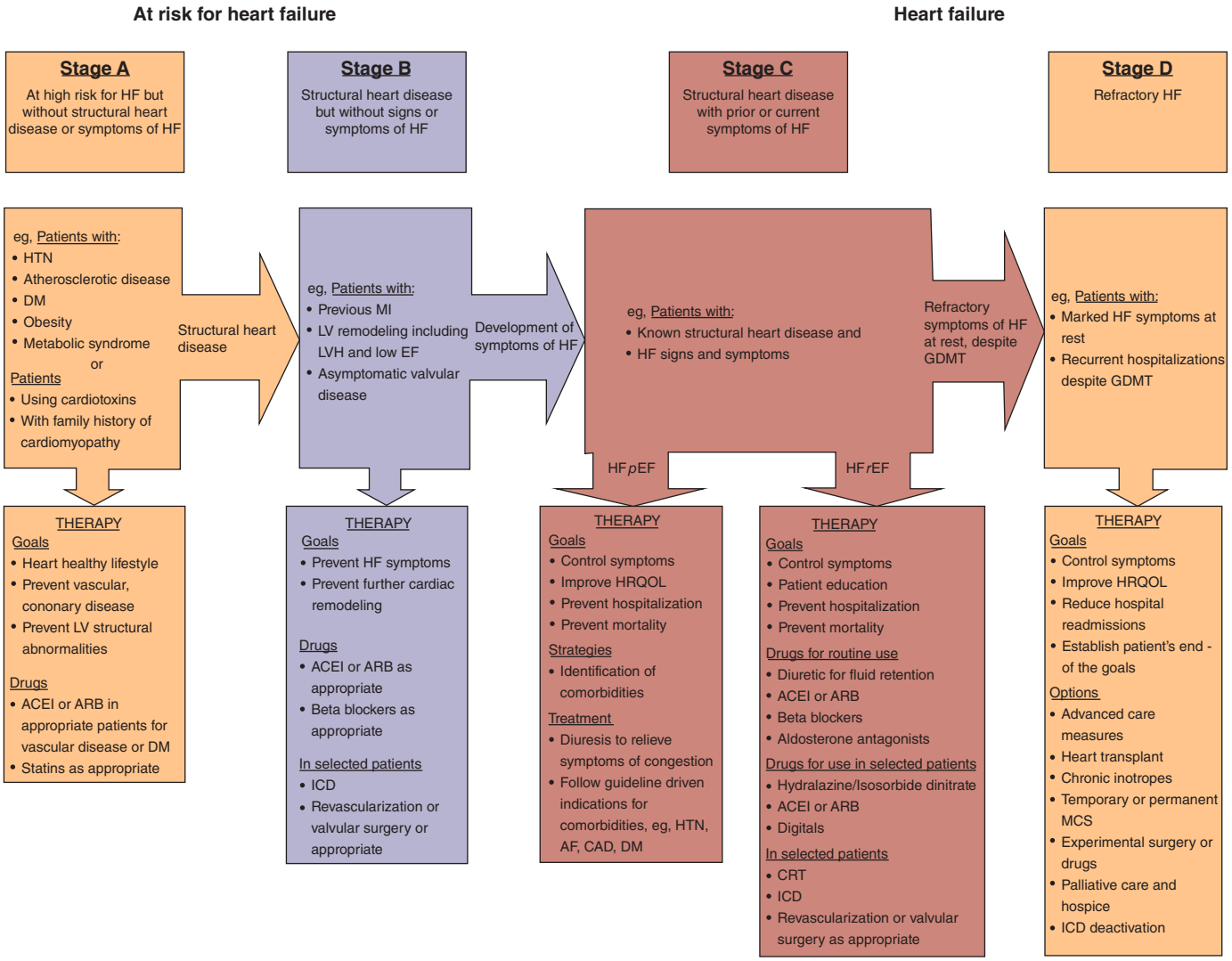

FIGURE 69–2. American Heart Association/American College of Cardiology stages of heart failure (HF). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; GDMT, guideline-directed medical therapy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRQOL, health-related quality of life; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVH, left ventricular hypertrophy; MCS, mechanical circulatory support. MI, myocardial infarction. Reproduced with permission from Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-e239.[33]

describe what was thought to be the primary underlying causal abnormality, namely, reduced pump function versus impaired ventricular filling, respectively. However, the terms have fallen out of favor because it is now well established that abnormalities of systolic function are present in HF patients even within the range of "normal" LVEF.[37] Similarly, patients with HFrEF have both systolic and diastolic dysfunction.

Recognition of HFpEF did not appear in the literature until the mid-1980s. In a study of 188 patients with symptomatic HF, approximately one in three had a "normal" LVEF (≥ 45%) quantified by radionuclide ventriculography.[20] Abnormal left ventricular filling, or diastolic dysfunction, was present in all 188 patients regardless of LVEF. At that time, LVEF was equated with systolic function; therefore, among the patients with normal LVEF, HF was attributed to diastolic dysfunction and labeled diastolic HF.

Transthoracic echocardiography is the preferred imaging modality for quantifying LVEF in individuals with HF because of its wide availability, lack of radiation, and ease of use.[33] According to the American Society of Echocardiography guidelines, the normal range of LVEF is 52% to 72% in men (average 62%) and 54% to 74% in women (average 64%), which is a slight change from prior guidelines in which the lower limit of normal LVEF was 55% for both men and women.[38,39] The threshold for defining preserved LVEF is controversial. The AHA, ACC, and ESC recommend differentiating a preserved from a reduced LVEF at a cut point of 50%, which is below the lower limit of the normal ranges in men and women.[24,33] Thus, preserved LVEF is not synonymous with normal LVEF. Clinical trials and community-based studies have used a variety of thresholds for defining preserved or reduced LVEF.[33,40,41] Clinical trials of HF tend to use lower LVEF values (≥ 40% or ≥ 45%) for defining preserved LVEF to include a broader range of eligible patients and to cover the LVEF spectrum for which medical therapies have not been demonstrated to improve morbidity and mortality, as described later in the chapter.[42] Slightly higher LVEF thresholds (≥ 45%, ≥ 50%, or ≥ 55%) have typically been used in community-based registries.[40,41] There is also a consideration of individuals with HF with LVEF of 40% to 50% as a distinctive entity, although this view is not universally accepted.[43]

TABLE 69–1. Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) Profiles for Disease Severity Classification in Advanced Symptomatic Heart Failure

		Possible profile modifiers		
Profile	Description	Temporary circulatory support (TCS)	Arrhythmia (A)	Frequent flyer (FF)
1.	Critical cardiogenic shock	X	X	
2.	Progressive decline on intropic support	X	X	
3.	Stable but inotrope dependent	X (in hosp)	X	X (if home)
4.	Resting symptoms home on oral therapy		X	X
5.	Exertion intolerant		X	X
6.	Exertion limited		X	X
7.	Advanced NYHA Class III symptoms		X	

NYHA, New York Heart Association Classification.

INTERMACS scores of 5 to 7 apply to New York Heart Association class III, whereas scores of 1 to 4 apply to NYHA class IV.

Reproduced with permission from Stevenson LW, Pagani FD, Young JB, et al: INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transplant*. 2009 Jun;28(6):535-541.[36]

The clinical importance of the distinction between reduced versus preserved LVEF relates to prognosis and therapy. This is addressed later in the chapter, but briefly, no specific therapy to date has been demonstrated in randomized clinical trials to be efficacious in reducing HF hospitalizations or risk of death among patients with HFpEF. This is in stark contrast to HFrEF, in which a number of pharmacologic and device-based therapies significantly improve morbidity and mortality. It is also noteworthy that a subset of patients with HFrEF may improve their LVEF over time, referred to as *HF with recovered ejection fraction*, an observation that suggests a possible dynamic nature of the condition instead of its classification into two distinctive subsets based on LVEF assessed at a single time point.[44,45]

Another classification system for cardiac dysfunction is based on whether the left, right, or both sides of the heart are failing. Heart failure is most commonly a result of left ventricular dysfunction, but right ventricular dysfunction is not uncommon among patients with HF.[46,47] Pulmonary venous hypertension secondary to left HF is the most common cause for right HF. Cor pulmonale, or isolated right-sided HF, typically occurs as a consequence of pulmonary arterial hypertension (which can be of various etiologies). Because cor pulmonale is a distinct entity, and substantially less common than left-sided or biventricular HF, it will not be discussed further in this chapter (see Chap. 76).

INCIDENCE, PREVALENCE, COST, AND HOSPITALIZATIONS

INCIDENCE

In absolute numbers, incident HF afflicts a large number of individuals. Based on data from 2005 to 2012, investigators from the Atherosclerosis Risk in Communities (ARIC) study estimated that approximately 915,000 individuals in the United States are newly diagnosed with HF annually.[48] Estimates of HF incidence rates vary markedly, from 1.0 to 32 cases per 1000 person-years (Table 69–2).[49] Factors contributing to this variation include the population studied and the diagnostic criteria used.[49] Incidence rates in northern and central Europe appear to be similar to that of the United States, whereas reliable data from the rest of the world are lacking.[49] In general, incidence rates increase with age and are higher in men than in women and in blacks compared to white individuals.[49] Older individuals consistently have the highest incidence rates, with an approximate two- to threefold higher incidence for each decade after age 55 years (Table 69–3).[48,50-52]

Studies of recent trends demonstrate a rise followed by a fall in the incidence of HF in the United States, Canada, and Scotland.[53-58] Advances in the care of coronary artery disease, hypertension, valvular heart disease, arrhythmias, and congenital heart disease over the last half a century have substantially improved cardiovascular mortality rates.[59] The consequence is a larger population of individuals at risk for the development of HF. Accordingly, an increasing incidence of HF was observed from the 1970s to 1990s among elderly individuals and in patients following myocardial infarction.[54] However, since the late 1990s, HF incidence rates have declined in the United States, suggesting that primary prevention approaches, including better recognition and treatment of hypertension and acute myocardial infarction, for HF may be effective. Among Medicare beneficiaries, the incidence rate for HF following an acute myocardial infarction significantly declined by approximately 15%, from 16.1 to 14.2 per 100 person-years, in 1998 to 2010.[55,60] Over a similar time period, from 2000 to 2010, the age- and sex- adjusted HF incidence rate in Olmsted County, Minnesota, declined nearly 40%, from 3.2 to 2.2 per 1000 person-years.[56] Temporal trends in HF incidence from Ontario, Canada, Scotland, Denmark, and Sweden are congruent with the decline seen in the United States that began in the late 1990s to early 2000s.[57,58,61,62] Whether this trend applies to other parts of the world is largely unknown. Higher incidence rates for HF might be expected in developing countries as a result of "Westernization," with increasing contributions of modifiable risk factors, such as obesity, diabetes mellitus, and systemic hypertension.[63]

The proportion of incident HF cases with preserved compared with reduced LVEF appears to be increasing over time.[64,65] Depending on the cutoff value for defining preserved LVEF, the proportion of individuals with HFpEF ranges from 44% to 72%.[41,66] The increasing contribution of HFpEF may be related to several factors. First, there is a greater awareness that HF can occur in individuals with a "normal" ejection fraction, which may increase the frequency with which HFpEF is diagnosed. Second, improved care for patients with acute and chronic ischemic heart disease has decreased the prevalence of reduced LVEF. Third, there is a rising burden of obesity, diabetes mellitus, and physical inactivity, compounded by the aging of the population, all risk factors for HFpEF.[30,67]

PREVALENCE

Approximately 26 million individuals worldwide (5.7 million in the United States) have HF.[48] In developed countries, the prevalence is approximately 1% to 2% of the overall population.[49] However, the distribution of individuals with prevalent HF substantially differs by age, affecting approximately 1% of individuals < 65 years old and approximately 10% of individuals ≥ 65 years old.[49] In the United States, the prevalence of HF is similar between men and women at 2.3% and 2.2%, respectively, but is more common in black (~3.0%) compared with white (~2.2%) individuals.[48] Forecasts in the United States estimate a 25% to 46% increase in the prevalence of HF by

TABLE 69-2. Heart Failure Incidence, Prevalence, and Mortality in Selected Studies

Diagnostic Criteria	Author	Years	Incidence	Prevalence	Population Source	Mortality
Nonvalidated criteria						
Self-report	Schocken et al	1971–1975	…	1%–2%	NHANES I Ages 1–74 y, not adjusted	At 10 y: 43%
Self-report	Go et al	2007–2010	…	2%	NHANES 2007–2010 Age ≥20 y	…
First hospitalization for heart failure	Croft et al*	1986	White: 22.4/1000 person-years	…	Medicare beneficiaries (age ≥65 y)	In hospital
			Black: 22.4/1000 person-years		Age adjusted	1986: White: 13% Black: 11%
		…				…
		1993	White: 24.6/1000 person-years Black: 26.1/1000 person-years			1993: White: 10% Black: 9%
First hospitalization for heart failure	Jhund et al	1986	Men: 1.2/1000 persons Women: 1.3/1000 persons	…	Scotland Age adjusted	1-y age adjusted 1986 Men: 33% Women: 31%
		…				…
		2003	… Men: 1.1/1000 persons Women: 1.0/1000 persons			2003 Men: 28% Women: 27%
Hospital discharge or death certificate with ICD code for HF	Loehr et al	1987–2002	White women: 3.4/1000 person-years White men: 6.0/1000 person-years Black women: 8.1/1000 person-years Black men: 9.1/1000 person-years	…	Atherosclerosis Risk in Communities Study Age adjusted	Overall 1-y mortality: 22% (similar for blacks and whites)
Hospital discharge diagnosis	Stewart et al*	1990–1996	Women: 1.3–1.9/1000 persons Men: 1.3–2.2/1000 persons	…	Scotland All ages, not adjusted	At 1 y 1990: ≈40% 1996: ≈36%
Administrative database: CMS	Curtis et al	1994	32/1000/person-years	9%	Medicare beneficiaries (age ≥65 y)	1-y risk adjusted
		1994	…	…	Age adjusted	1994: 29%
		…	29/1000 person-years	12%		2002: 28%
		2003				
Administrative database	Yeung et al	1997	4.5/1000 persons	…	Ontario, Canada	1-y risk adjusted
		…	…		Age and sex standardized	1997
		2007	3.1/1000 persons			Outpatients: 18% Inpatients: 36% 2007 Outpatients: 16% Inpatients: 34%

(*continued*)

TABLE 69-2. Heart Failure Incidence, Prevalence, and Mortality in Selected Studies (*Continued*)

Diagnostic Criteria	Author	Years	Incidence	Prevalence	Population Source	Mortality
Standardized criteria						
Framingham criteria	Levy et al*	1950–1999	≈5/1000 person-years	. . .	Framingham Heart Study All ages, age adjusted, mostly whites	At 1 y age adjusted 1950–1969 Men: 30% Women: 28% 1990–1999 Men: 28% Women: 24%
Framingham criteria	Barker et al	1970–1974 . . . 1990–1994	Women: 8.6/1000 person-years Men: 11.7/1000 person-years . . . Women: 11.8/1000 person-years Men: 12.7/1000 person-years	. . .	Kaiser Permanente Age adjusted, mostly whites	1- year age-adjusted mortality 1970–1974: Men: 47% Women: 27% 1990–1994: Men: 33% Women: 28%
Framingham criteria	Roger et al*	1979–2000	≈3/1000 persons	. . .	Olmsted County Age adjusted, mostly whites	At 1 y (75-year-olds) 1979–1984: Men: 30% Women: 20% 1996–2000: Men: 21% Women: 17%
Framingham criteria	McCullough et al*	1989–1999	Women: 3.7–4.2/1000 persons Men: 4.0–3.7/1000 persons	Women 0.4%–1.4% Men 0.4%–1.5%	REACH Study Henry Ford Health System 50% whites; age adjusted	Per year: 17%
Framingham criteria	Goldberg et al	2000	≈2/1000 persons	. . .	Worcester, MA hospitals Not age adjusted	Hospital case fatality rate: 5%
Boston criteria	Remes et al	1986–1988	Women: 1.0/1000 persons Men: 4.0/1000 persons	. . .	Eastern Finland In and out patient national registries Age adjusted	. . .
Boston criteria	Nielsen et al	1993–1995	. . .	0.5%–12%	Denmark General practice population Ages ≥50 y, not adjusted	. . .
European Society of Cardiology criteria	Bleumink et al	1989–2000	Women: 12.5/1000 person-years Men: 17.6/1000 person-years	1998: 7%	The Rotterdam Study Not age adjusted	At 1 y: 37%
European Society of Cardiology criteria	Cowie et al	1995–1996	Women: 1.2/1000 persons/y Men: 1.4/1000 persons/y	. . .	Geographically defined in United Kingdom In- and outpatient All ages, not adjusted	. . .

(*continued*)

TABLE 69-2. Heart Failure Incidence, Prevalence, and Mortality in Selected Studies (*Continued*)

Diagnostic Criteria	Author	Years	Incidence	Prevalence	Population Source	Mortality
European Society of Cardiology criteria	Davies et al	1995–1999	. . .	2%–3%	UK population Random sample Ages ≥45 y, not adjusted	. . .
Cardiovascular Health Study criteria	Gottdiener et al	1990–1996	Nonblack: 19/1000 person-years Black: 19/1000 person-years Women: 15/1000 person-years Men: 26/1000 person-years		Cardiovascular Health Study Age 65–100 y, age adjusted	. . .
Multi-Ethnic Study of Atherosclerosis criteria	Bahrami et al	Enrolled from 2000 to 2002; Median follow-up 4.0 y	Blacks: 4.6/1000 person-years Hispanic: 3.5/1000 person-years White: 2.4/1000 person-years Chinese Americans: 1.0/1000 person-years	. . .	Multi-Ethnic Study of Atherosclerosis Not age adjusted	. . .

CMS indicates Centers for Medicare and Medicaid Services; HF, heart failure; ICD, *International Classification of Diseases*; NHANES I, National Health and Nutrition Examination Survey; and REACH, Resource Utilization Among Congestive Heart Failure.

*Denotes studies reporting on time trends.

Data from Roger VL. Epidemiology of heart failure. *Circ Res*. 2013 Aug 30;113(6):646-659.[49]

2030, with 8 million adults afflicted.[48,68] In the setting of declining incidence rates for HF, the predicted increase in prevalence reflects an aging population as well as anticipated reductions in mortality rates following the onset of HF.[49]

COST

The global economic cost of HF is high. It was estimated that 108 billion US dollars were spent in 2012 on HF worldwide, with approximately 60% coming from direct costs (hospital care, medications, physician costs, outpatient care, and follow-up) and 40% from indirect costs (lost productivity, illness benefits, and social support programs).[69] Higher income countries spend a greater amount on direct costs, whereas low- to middle-income countries spend more on indirect costs. In the United States, annual spending on HF ranges from $30 to $40 billion, with direct costs accounting for nearly 70%.[48,70] Estimates suggest that HF–related costs will double in the United States by 2030.[68]

HOSPITALIZATIONS

Hospitalizations are a major driver of costs. Approximately 1 million primary hospitalizations for HF occur within the United States each year, with a similar number reported in Europe.[48] Data from Olmsted County, Minnesota, indicate that over a mean follow-up of 4.7 years 83% of HF patients are hospitalized at least once and 43% are hospitalized four or more times (Fig. 69–3).[71] Heart failure remains

TABLE 69–3. Annual Incidence Rates (per 1000 Person-Years) for Acute Decompensated Heart Failure in the Atherosclerosis Risk in Communities Study[48]

	Incidence Rate		
	Age 55-64 Years	Age 65-74 Years	Age ≥ 75 Years
White men	3.8	10.7	30.5
Black men	11.0	17.4	31.0
White women	2.7	7.5	25.9
Black women	8.2	14.8	28.4

The Atherosclerosis Risk in Communities study includes population-based community surveillance from four sites in the United States: Minneapolis, MN; Jackson, MS; Forsyth County, NC; and Washington County, MD. Hospitalizations in these communities are abstracted and adjudicated for heart failure.

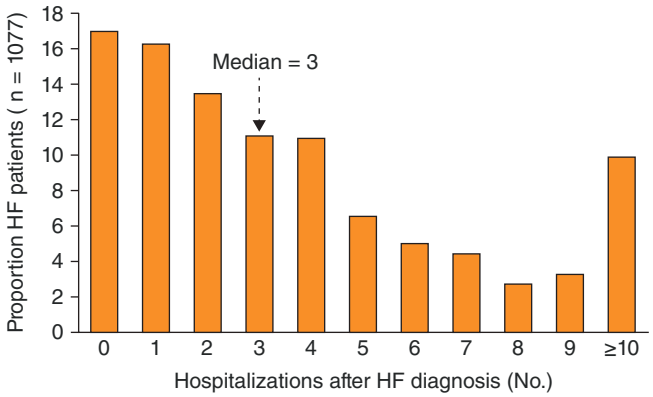

FIGURE 69–3. Number of hospitalizations per person over a mean of 4.7 years of follow-up after the diagnosis of heart failure (HF). Reproduced with permission from Dunlay SM, Redfield MM, Weston SA, et al: Hospitalizations after heart failure diagnosis a community perspective. *J Am Coll Cardiol*. 2009 Oct 27;54(18):1695-1702.[71]

the leading cause for hospitalization among Medicare beneficiaries, although the primary hospitalization rate for HF has declined from 1998 to 2008.[72] This may be, in part, a result of increased intensity of outpatient HF management. However, it is also worth noting that hospitalizations of patients with chronic HF as a secondary diagnosis are stable to increasing, with more than half of all hospitalizations being attributable to noncardiovascular causes, reflecting the rising prevalence of HF and the impact of multiple comorbidities in these patients.[71,73-76]

ETIOLOGY AND RISK FACTORS

ETIOLOGY

A number of etiologies for HF have been defined (Table 69–4). Coronary artery disease is often cited as the most common cause of HF.[77] Recent data from Norway indicate that 15% to 25% of patients with an acute myocardial infarction develop HF over a 3-year period, with the highest risk in the first 6 months after infarction.[78] However, there is race- and sex-related variation in the etiologies for HF. For example, in the Health, Aging, and Body Composition study, among white individuals, the population-attributable risks for incident HF were 23.9% and 21.3% for coronary artery disease and hypertension, respectively. Among black individuals, hypertension accounted for 30.1% of incident HF, whereas coronary artery disease accounted for 29.5%.[79] In the Framingham Heart Study, hypertension, rather than coronary artery disease, was the most common risk factor for HF in both men and women, accounting for approximately 60% of HF cases in women and approximately 40% in men.[80] Findings from Olmsted County, Minnesota, support sex-related differences in HF risk factors, with coronary artery disease being a major contributor for HF risk in men, whereas hypertension was a greater risk factor in women.[81]

The relative contributions of different etiologies for HF also vary geographically. The International Congestive HF Study included nearly 6000 individuals with prevalent HF from South America, Africa, the Middle East, and Asia (Table 69–5).[82] In South America, coronary artery disease and hypertension were the etiologies for HF in 26% and 21% of cases, respectively. Chagas disease is also an important cause for HF in South America.[83] In contrast, in Africa, hypertension was a major etiologic factor for HF in 35% of cases, whereas coronary artery disease accounted for 20%.[82] In Asia and the Middle East, half of HF cases were attributed to coronary artery disease, whereas hypertension caused 10% to 15% of cases. Rheumatic valvular disease was the etiology for HF in 6% to 9% of cases in Asia and the Middle East, accounting for a larger proportion than seen in North America and Europe.[82]

Although coronary artery disease and hypertension may be the leading causes of HF worldwide, individual patients frequently have multiple comorbidities that contribute to the syndrome of HF.[67,84] Cardiometabolic disorders such as obesity and diabetes mellitus are increasing in prevalence, with greater contributions to HF incidence.[67,84] Although modifiable cardiometabolic risk factors account for the majority of causes of HF, less common causes include dilated cardiomyopathy, hypertrophic cardiomyopathy, hemochromatosis, amyloidosis, and human immunodeficiency virus (HIV) infection, among others (see Table 69–4). An increasingly recognized cause of HF is cardiotoxic medications, such as some cancer chemotherapies (eg, anthracyclines and novel biologics).[85]

TABLE 69–4. Selected Etiologies of Heart Failure

Ischemic	Atherosclerotic coronary artery disease
	Coronary artery dissection
	Thromboembolism
	Anomalous coronary arteries
	Kawasaki disease
Hypertension	
Valvular heart disease	Degenerative
	Rheumatic
	Congenital
	Infectious (endocarditis)
	Carcinoid
Dilated cardiomyopathy	Idiopathic
	Familial
Arrhythmia	Tachycardia-mediated cardiomyopathy
	Pacemaker-mediated cardiomyopathy
Metabolic	Diabetes mellitus
	Thyroid disorders
	Paget disease
	Thiamine deficiency
	Obesity
	Selenium
Infectious	Viral myocarditis
	Rheumatic
	Endocarditis
	Human Immunodeficiency Virus
	Chagas' disease
Inflammatory	Systemic lupus erythematosus
	Sarcoidosis
	Scleroderma
	Rheumatoid arthritis
	Vasculitis
	Giant cell myocarditis
	Hypereosinophilic syndrome
	Endomyocardial fibrosis
Toxin	Alcohol
	Cocaine
	Chemotherapy (eg, anthracyclines, trastuzumab)
	Radiation
	Medications (eg, fenfluramine)
Genetic	Hypertrophic cardiomyopathy
	Arrhythmogenic right ventricular dysplasia
	Amyloid (transthyretin)
	Noncompaction
	Hemochromatosis

(*continued*)

TABLE 69–4. Selected Etiologies of Heart Failure (*Continued*)

Peripartum	
Storage diseases	Fabry
	Pompe
	Gaucher
Pericardial	Pericarditis
	Tamponade
Congenital	Shunt (eg, atrial septal defect, ventricular septal defect, fistulas, patent ductus arteriosus)
	Cyanotic heart disease
	Valvular disease (stenotic or regurgitant)
	Sub- and supravalvular stenosis
	Conduit obstruction or leak
	Intrinsic myocardial dysfunction
	Pulmonary hypertension
	Systemic hypertension (eg, coarctation or the aorta)
	Arrhythmias (primary or secondary to surgery)
	Post-Fontan procedure
High output	Anemia
	Thiamine deficiency
	Arteriovenous fistula
Neoplasm	Primary cardiac
	Metastatic disease
	Light chain (AL) amyloidosis

RISK FACTORS

Heart failure appears to cluster within families. For instance, parental HF has been associated with greater left ventricular mass, internal dimension, systolic dysfunction, and incident HF in offspring.[86] Nonetheless, no robust genetic variant has, as yet, been identified for "common" HF, or that caused by typical risk factors such as hypertension, diabetes mellitus, and coronary artery disease.[87] Some of the familial risk may be mediated through modifiable risk factors, particularly those present in middle age, which contribute substantially to the development of HF later in life. Modifiable risk factors include blood pressure, body mass, cholesterol, diet, glucose, physical activity, and smoking. The greatest cardiovascular impact of blood pressure lowering in hypertensive individuals is on the reduction in risk of HF, even more so than stroke or atherosclerotic coronary artery disease.[88] Higher body mass index and obesity are associated with increased risk of HF, and weight loss reduces this risk.[89-91] Alcohol, when chronically consumed in large amounts, is a recognized etiology for cardiomyopathy. However, recent observations from the ARIC study suggest that light to moderate alcohol consumption (seven or fewer drinks per week) lowered the risk of HF in men and, to a lesser extent, in women.[92] Similar findings were reported from the Norwegian Nord-Trøndelag Health Study.[93] Hyperglycemia and insulin resistance, even in the absence of overt diabetes mellitus, have been associated with increased risk for incident HF.[94,95] Diabetes mellitus is also an established risk factor for incident HF.[96-99] However, glucose-lowering therapies for diabetes mellitus have demonstrated mixed results regarding the risk of HF. A number of medications for the treatment of diabetes mellitus have been associated with increased risk of HF, such as the thiazolidinediones (rosiglitazone and pioglitazone) and the dipeptidyl peptidase-4 inhibitor (saxagliptin).[100,101] In contrast, glucose lowering with the sodium-glucose cotransporter 2 inhibitor empagliflozin was recently demonstrated to reduce the risk of HF among individuals with prevalent diabetes mellitus.[102] Higher amounts of physical activity have been associated with reduced risk of incident HF.[103,104] Further, among middle-aged to elderly individuals, smoking is an established risk factor for incident HF.[97,98]

The AHA recognized the importance of modifiable risk factors to cardiovascular risk and developed a concept known as the Simple 7 (blood pressure, body mass, cholesterol, diet, glucose, physical activity, and smoking). In the ARIC study, individuals with high Simple 7 scores (indicating more healthy behaviors) were at lower lifetime risk for incident HF (14%), compared with individuals with average (27%) or poor (49%) scores.[105] These findings were corroborated by recent observations from the Framingham Heart Study.[106] Data from the Physicians' Health Study suggest that optimal modifiable risk factor profiles can lower the lifetime risk of HF by as much as 50%.[107]

Modifiable risk factors and comorbidities contribute to the risk of HF, regardless of LVEF. However, the relative risk associated with risk factors for HF with a preserved versus a reduced LVEF may differ. In the Framingham Heart Study, a history of hypertension, diastolic dysfunction, atrial fibrillation, female sex, and lower ratio of forced expiratory volume in 1 second to forced vital capacity were associated with greater risk for symptomatic HFpEF compared with HFrEF.[76,108] Patients with HFpEF often demonstrate exaggerated blood pressure responses to exercise, increased vascular stiffness, chronotropic incompetence, and increased baroreceptor sensitivity, and are exquisitely sensitive to excess preload reduction. In this context, atrial fibrillation appears to be a particularly strong risk factor for HFpEF.[109] In the Framingham Heart Study, prior myocardial infarction, left bundle branch block, asymptomatic left ventricular systolic dysfunction, higher serum creatinine, and lower total blood hemoglobin concentration were significantly associated with greater risk for HFrEF.[76,108]

Asymptomatic abnormalities of cardiac structure and function are associated with increased risk for the development of HF. Several population-based studies from the United States, Europe, and Australia have examined the prevalence of asymptomatic left ventricular systolic dysfunction, typically defined by LVEF, with estimates ranging from 1% to 12.9% (pooled 4.8%) (Fig. 69–4).[110-120] The risk of incident HF associated with asymptomatic left ventricular systolic dysfunction compared with preserved left ventricular function has been reported from the Cardiovascular Health Study, Framingham Heart Study, and Multi-Ethnic Study of Atherosclerosis, with hazard ratios of 1.60 (95% confidence interval [CI], 1.35-1.91), 4.7 (95% CI, 2.7-8.1), and 8.69 (95% CI, 4.90-15.45), respectively.[110,111,114] In a meta-analysis of older (≥ 60 years) adults, the median prevalence of asymptomatic left ventricular diastolic dysfunction was 36%.[121] The presence, severity, and progression of diastolic dysfunction have been demonstrated in both clinical and community-based populations to be associated with increased risk for incident HF.[108,122-124] In the Framingham Heart Study, left ventricular hypertrophy was associated with increased risk of incident HF, with eccentric hypertrophy portending a greater risk for HFrEF, whereas concentric hypertrophy was associated with greater risk for HFpEF.[125,126] Increased arterial stiffness and vascular remodeling have also been associated with greater risk of HF.[127-129]

TABLE 69–5. Characteristics of Heart Failure Patients by Region in the International Congestive Heart Failure (INTER-CHF) Study

	Africa N = 1294	Asia N = 2661	Middle East N = 1000	South America N = 858
Demographics				
Age, mean (SE)	53.4 (0.4)	60.0 (0.3)	56.4 (0.5)	67.1 (0.5)
Male (%)	51.8	59.1	72.3	61.2
Rural (%)	31.8	46.2	26.2	21.0
Inpatient (%)	48.6	34.9	30.6	26.1
Social history				
Absence of health insurance (%)	65.8	46.9	24.8	14.7
Absence of medication insurance (%)	67.3	61.3	27.3	15.5
Illiterate (%)	42.7	14.9	36.1	4.2
Heart failure history				
NYHA functional class I (%)	7.2	12.9	15.4	19.6
Functional class II (%)	36.8	44.7	46.2	49.4
Functional class III (%)	35.5	28.9	31.0	26.4
Functional class IV (%)	20.9	12.8	6.4	4.7
< 1 year since of HF diagnosis (%)	53.9	44.0	26.5	32.3
Preserved LVEF (%)	28.8	40.7	11.1	29.0
HF hospitalization in past year (%)	36.4	27.7	22.1	26.9
Risk factors				
BMI, mean (SE)	25.5 (0.2)	24.4 (0.1)	30.0 (0.2)	28.5 (0.2)
Hypertension (%)	61.6	59.0	68.4	73.6
Diabetes mellitus (%)	17.1	27.9	56.0	21.9
Dyslipidemia (%)	21.1	26.1	57.1	48.7
Chronic kidney disease (%)	3.8	7.1	11.7	11.6
Tobacco use (ever) (%)	14.7	31.1	22.6	34.3
Alcohol use (any) (%)	10.8	9.1	2.5	14.9
Valve disease (%)	57.0	40.4	48.0	47.4
Prior stroke (%)	5.0	10.2	3.3	4.1
History of myocardial infarction (%)	8.2	22.3	19.1	18.3

$P < .0001$ for all.

Abbreviations: BMI, body mass index; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SE, standard error.

Reproduced with permission from Dokainish H, Teo K, Zhu J, et al: Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study. *Int J Cardiol*. 2016 Feb 1;204:133-141.[82]

LIFETIME RISK AND RISK PREDICTION MODELS

The lifetime risk for the development of HF is high. In the Framingham Heart Study, the overall lifetime risk among white men and women was 20%.[130] Even among individuals without a history of myocardial infarction, the lifetime risk of HF was substantial, estimated at one in nine men and one in six women.[130] Estimates for lifetime risk using data pooled from the Chicago Heart Association, ARIC, and Cardiovascular Health Studies corroborated the high lifetime risks of HF observed in the Framingham Heart Study and extended the findings to black individuals.[131] The lifetime risks for HF ranged from 30% to 42%, 20% to 29%, 32% to 39%, and 24% to 46% in white men, black men, white women, and black women, respectively.[131] The lifetime risk of HF also differed according to the presence of modifiable risk factors in the ARIC study, as previously mentioned.[105]

Heart failure risk prediction models from community cohorts have been developed (Table 69–6). Factors included in the risk prediction models vary by study, but typically include age, sex, heart rate, systolic blood pressure, body mass index, and diabetes mellitus. Other factors, such as smoking status, serum creatinine, coronary heart disease, antihypertensive medication use, left ventricular hypertrophy, and valvular disease, are included to varying extents. The c-statistics for model performance are good, ranging from 0.73 to 0.87.[96-98,132,133] Further attention has been given to the use of circulating biomarkers for risk prediction. Although a number of candidate biomarkers have been studied, the natriuretic peptides (eg, B-type natriuretic peptide [BNP] and N-terminal pro-BNP [NT-proBNP]) are the most

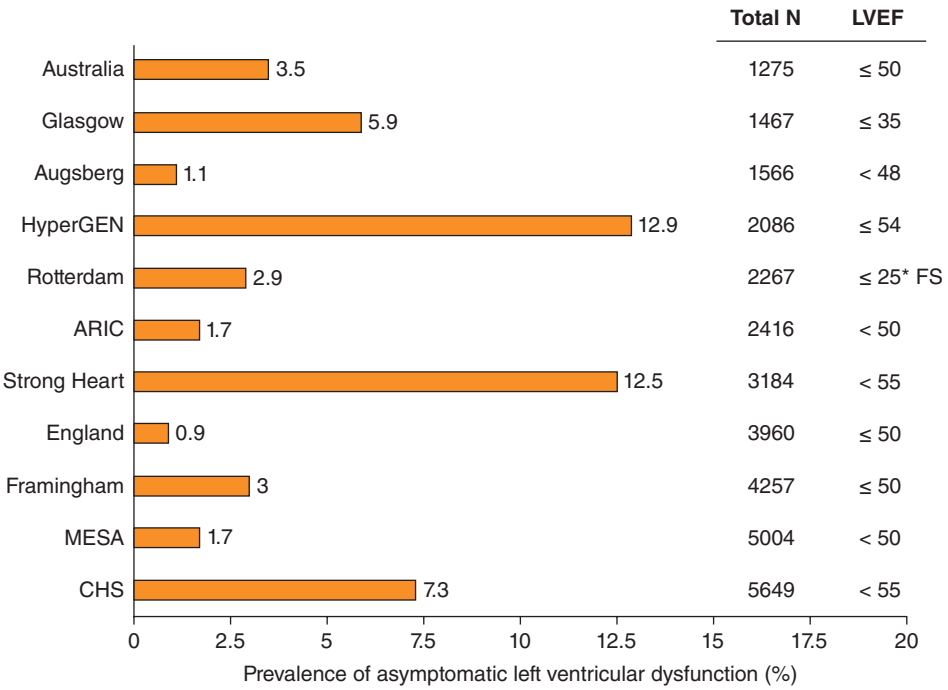

FIGURE 69–4. Prevalence of asymptomatic left ventricular dysfunction. Reported prevalence of asymptomatic left ventricular systolic dysfunction, based on left ventricular ejection fraction (LVEF), from different studies around the world.[110-120] *In the Rotterdam Study, fractional shortening (FS) was used rather than LVEF. A FS value of 25% corresponds to a LVEF of approximately 45%. ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; HyperGEN, Hypertension Genetic Epidemiology Network; MESA, Multi-Ethnic Study of Atherosclerosis.

robust biomarker predictors of incident HF after adjusting for clinical factors.[97,98,134,135] It is also noteworthy that prediction algorithms that can quantify risk of developing cardiovascular disease incidence in general seem to work reasonably well for predicting incidence of HF.[136]

TABLE 69–6. Factors Included in Community-Based Incident Heart Failure Risk Prediction Models

Framingham Heart Study[99]	Health, Aging, and Body Composition Study[96]	Atherosclerosis Risk in Communities Study[97]	Multi-Ethnic Study of Atherosclerosis[98]
Age	Age	Age	Age
Sex	Sex	Sex	Sex
LVH (ECG)	LVH (ECG)	Heart rate	Heart rate
Heart rate	Heart rate	Systolic BP	Systolic BP
Systolic BP	Systolic BP	CAD	Diabetes mellitus
CAD	CAD	Diabetes mellitus	Body mass index
Valve disease	Plasma glucose	Body mass index	Current, former, never smoker
Diabetes mellitus	Serum albumin	Current, former, never smoker	NT-proBNP
Body mass index	Serum creatinine	Race	
Vital capacity		Antihypertensive therapy	
Cardiomegaly		NT-proBNP	

Abbreviations: ECG, electrocardiogram; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

PROGNOSIS

OUTCOMES IN PREVALENT HEART FAILURE

Morbidity

Once HF develops, morbidity and mortality are high. The adverse impact of HF on quality of life is well established, with substantial reductions in both physical function and mental health compared with the general population.[137-139] The impairment in quality of life experienced by individuals with HF is comparable to or worse than patients on chronic dialysis and those with chronic lung disease.[137,138] Quality of life is similar between patients with HFrEF and HFpEF and declines with worse NYHA classification.[137,138,140] The syndrome of HF is complex with many systemic effects, as patients are at increased risk of stroke, atrial fibrillation, diabetes, chronic kidney disease, and venous thromboembolism.[141-146] Recent attention has also focused on the increased burden of cognitive impairment among patients with HF, specifically with HF as a risk factor for dementia and with cognitive impairment as a risk factor for adverse outcomes among patients with HF.[147,148]

The most commonly used end point for HF–related morbidity is hospitalizations, which are frequent for both cardiovascular and noncardiovascular causes (see Fig. 69–3).[48,71,75,149-153] For HF hospitalizations, length of stay varies substantially worldwide, with median times ranging from 4 to 20 days.[154] Prior hospitalization for HF is a strong predictor of future HF hospitalization, with 90-day readmission rates approaching 30%.[154,155]

Mortality

Survival among individuals with symptomatic HF (AHA/ACC stages C and D) is generally poor, with approximately 50% alive at 5 years following diagnosis.[56,156] However, there is variation in this risk according to disease severity and other factors. Mortality risk is directly proportional to NYHA class among patients with both preserved and reduced ejection fraction and in hospital and outpatient settings. The elderly are at particularly high risk, with 1-year mortality rates among Medicare beneficiaries approaching 30%.[72] In meta-analyses, the mortality rates in ambulatory patients with HFrEF (deaths per 1000 person-years 159; 95% CI, 154-165) exceed those of patients with HFpEF (deaths per 1000 person-years 146; 95% CI, 138-154).[157,158] The highest risk period appears to follow a hospitalization for HF, with 28-day and 1-year case fatality rates of 10% and 30%, respectively.[159-161] Indeed in the post–HF hospitalization setting, mortality rates may be similar between patients with HF with reduced and preserved ejection fraction.[64,162,163] Other factors reported to influence post–HF survival include blood pressure, right ventricular dysfunction and pulmonary hypertension, diabetes, anemia, chronic kidney disease, chronic obstructive pulmonary disease, and sleep apnea.[46,164-167]

The association between body mass index and prognosis in HF is particularly noteworthy. Obesity, a prominent risk factor for the development of HF, paradoxically appears to be related to better

outcomes among individuals with prevalent HF.[168-173] Thus, in the setting of acute or chronic HF, individuals with low body mass index are at increased risk of adverse cardiovascular outcomes and death compared with overweight or obese individuals. The obesity paradox has been consistently observed across a number of HF populations and does not appear to be solely attributable to cardiac cachexia, although the mechanisms underlying the relationship between body mass and composition, HF, and outcomes are not completely understood.[168-173] It has also been proposed that the obesity paradox seen in observational studies may not be biologically driven, but rather a statistical phenomenon caused by unmeasured confounders.[174]

Despite HF portending a poor prognosis with high mortality rates, risk prediction for the individual patient remains challenging.[175] Survival may differ according to etiology of HF, with ischemic heart disease, particularly in the setting of reduced LVEF, consistently reported to have the lowest survival compared with nonischemic etiologies.[77,176] To aid prognostication, risk prediction models for mortality in HF, such as the Seattle Heart Failure Model and Heart Failure Survival Score, have been derived and validated largely from cohorts of individuals with reduced ejection fraction and advanced HF (Table 69–7).[177,178] In a recent meta-analysis, these scores were found to be fair to modest in their discriminatory capacity for predicting death in HF, with c-statistics ranging from 0.56 to 0.81.[179] More recently, another model for predicting mortality in chronic ambulatory HF was developed by the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) using data from 39,372 patients largely enrolled in clinical trials.[180] A scoring system was developed based on 13 predictors, including age, LVEF, NYHA class, serum creatinine, diabetes, β-blocker use, systolic blood pressure, body mass, time since diagnosis, current smoking, chronic obstructive pulmonary disease, male sex, and angiotensin-converting enzyme inhibitor or angiotensin receptor blockers use. The advantages of the MAGGIC model are that it spans the spectrum of LVEF and uses readily available clinical predictors. The disadvantage is that it was largely derived from clinical trial populations.

The mode of death among HF patients is not always related to HF or even cardiovascular causes, with noncardiovascular causes accounting for 34% and 54% of deaths among HF patients in the Framingham Heart Study and Olmsted County, Minnesota, study respectively.[56,181] Noncardiovascular causes of death are particularly frequent among patients with HFpEF.[56,181] Cardiovascular causes of death in chronic HF include sudden death (36.4%), worsening of pump failure (27.5%), or death caused by a vascular event such as myocardial infarction (5.3%) or stroke (4.7%).[182]

TABLE 69-7. Factors Included in the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) and Seattle Heart Failure Models for Predicting Survival in Heart Failure[178,180]

MAGGIC	Seattle Heart Failure Model
Left ventricular ejection fraction, %	Age, years
Age, years	Sex
Systolic blood pressure, mm Hg	NYHA Class
Body mass index, kg/m^2	Weight, kg
Creatinine, μmol/L	Left ventricular ejection fraction, %
NYHA class	Systolic blood pressure, mm Hg
Sex	Ischemic etiology
Current smoker	ACEI, yes or no
Diabetes mellitus	β-Blocker, yes or no
Chronic obstructive pulmonary disease	ARB, yes or no
First diagnosis of HF in past 18 months	Statin, yes or no
β-Blocker, yes or no	Allopurinol, yes or no
ACEI/ARB use, yes or no	Aldosterone antagonist, yes or no
	Furosemide, yes (dose, route) or no
	Bumetanide, yes (dose, route) or no
	Torsemide, yes (dose, route) or no
	Metolazone, yes (and dose) or no
	Hydrochlorothiazide, yes (and dose) or no
	Chlorothiazide, yes (dose, route) or no
	Hemoglobin, g/dL
	Lymphocyte, %
	Uric acid, mg/dL
	Total cholesterol, mg/dL
	Sodium, mmol/L
	Biventricular pacemaker, yes or no
	Implantable cardioverter-defibrillator, yes or no
	Biventricular pacemaker with implantable cardioverter-defibrillator, yes or no
	Left bundle branch block, yes or no
	QRS duration > 150 ms, yes or no
	IABP, ventilator, or ultrafiltration, yes or no
	Number of pressors or inotropes

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; IABP, intra-aortic balloon pump; NYHA, New York Heart Association.

THERAPY

A full discussion of HF therapies is described in Chapters 70 to 73. Tremendous advances in the treatment of HF have been made over the past several decades. More attention has been given to HFrEF compared with HFpEF, despite a similar proportion of patients of each type. Many landmark trials have defined the therapeutic approach to HFrEF (Fig. 69–5).[15-17,183-205] In contrast, the few phase III randomized clinical trials in HFpEF have been neutral. With the increasing percentage of cases of HFpEF, it is reasonable to anticipate a larger number of future clinical trials in this population. A critical factor in trial design and interpretation will be to ensure the HF population studied meets standardized criteria for diagnosing HF both with regard to inclusion criteria and event adjudication. Additionally, matching clinical trial populations with those identified from community-based studies remains an important aim.

FUTURE

The prevalence of HF is forecast to increase substantially over the next 10 to 15 years as a result of changing risk factor profiles, Westernization of developing countries, reductions in mortality rates, and the aging of the population.[48,49] Modifiable risk factors underlie the majority of cases of HF; therefore, HF prevention strategies may greatly reduce the global burden of HF. Similarly, improved adherence to evidence-based guidelines for patients with chronic HFrEF may limit morbidity and reduce the risk of death.[24,33,152,206] However, efficacious therapies for acute decompensated HF and HFpEF are lacking. Because HF is a heterogeneous syndrome with considerable

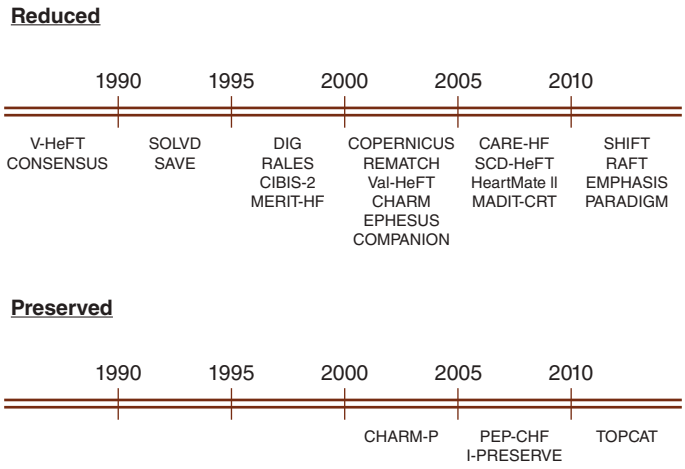

FIGURE 69–5. Timeline of selected landmark randomized clinical trials in heart failure, according to reduced or preserved left ventricular ejection fraction.[15-17,183-205]

interindividual variability, detailed phenotyping and personalized medicine that includes genomics, proteomics, and metabolomics may refine HF diagnosis, etiologic classification, prognostication, and therapeutic approaches.[207-209]

CONCLUSIONS

Heart failure is a major public health problem. Despite tremendous advances in the prevention and treatment of cardiovascular disease, HF remains highly prevalent, morbid, and lethal. It is also a complex syndrome that can be difficult to diagnose, often because of comorbidities, such as obesity, chronic obstructive pulmonary disease, and anemia, that are themselves associated with dyspnea. Although recent data indicate a possible decline in the incidence rates of HF in developed countries, an overall increase in the number of individuals with HF is anticipated in the coming years. In a large number of cases, HF may be preventable as a result of modifiable risk factors. The morbidity and mortality associated with HF remain high, with a substantial proportion of patients undergoing repeated hospitalizations and succumbing to death as a result of cardiovascular and noncardiovascular causes. Adherence to existing evidence-based therapies for HFrEF may further limit the burden of this syndrome. HFpEF is becoming the dominant form of HF over time; however, efficacious therapies for this condition, as we all as for acute decompensated HF, are currently lacking.

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CHAPTER 70

THE DIAGNOSIS AND MANAGEMENT OF CHRONIC HEART FAILURE

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INTRODUCTION

The syndrome of heart failure has existed at least as far back as when humans first began to document disease. Clinical texts attributable to Hippocrates describe patients with shortness of breath, edema, and anasarca, in a manner not too varied from contemporary accounts.[1] It has also long been realized that heart failure is not caused by a single disease; rather, it an amalgamate of several diseases that have unique etiologies, natural histories, and treatments.[2] The shared feature of this cluster of illnesses is damage to the cardiac tissue. Initially, the heart compensates in various manners to a loss in reserve; however, once there is a critical degree of impairment in its structure and function, a final common pathway emerges that shares similarities in symptoms and findings.

Over the past several decades, dramatic improvements in management of valvular and ischemic heart disease have decreased mortality from these illnesses and consequently led to an increase in the incidence and prevalence of heart failure. This, coupled with the aging of the population, has led to the growth of heart failure prevalence to epidemic proportions. Currently, heart failure affects more than 23 million people globally, of which over five million are Americans.[3] Heart failure is a difficult disease to manage and is associated with high rates of morbidity and mortality and high costs, both in terms of direct financial costs as well as indirect cost of patient and caregiver suffereing.[4] Therefore, it is imperative that we recognize and manage the syndrome using the best currently available information and make concerted efforts to find novel ways to further improve its management.

DEFINING HEART FAILURE

According to the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) heart failure guidelines:

> Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of heart failure are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue. Because some patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over "congestive heart failure." There is no single diagnostic test for heart failure because it is largely a clinical diagnosis based on a careful history and physical examination.[5]

The definition provided by the 2012 European Society of Cardiology (ESC) heart failure guidelines is as follows: "Heart failure can be defined as an abnormality of cardiac structure or function leading to the failure of the heart to deliver oxygen at a rate commensurate with the requirement of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures)."[6]

While previously thought of as simply a syndrome of disordered hemodynamics and fluid balance caused by alterations in the structure of the heart, our understanding of heart failure has progressed to a systemic illness that involves complex interplay between myocardial factors, systemic inflammation, renal abnormalities, and neurohormonal dysfunction (Fig. 70–1).[2,7,8] As a result, there is an evolution in our assessment and treatment from a focus solely on examination findings and improving hemodynamics to measuring and modifying the maladaptive molecular processes that contribute to disease progression.[9] In the absence of universally agreed upon objective biological descriptors of the syndrome, however, we must rely on an assortment of clinical descriptors to diagnose the syndrome that vary in their ability to adequately phenotype heart failure.[10]

CLASSIFICATION OF HEART FAILURE

Several constructs have been created for the purpose of describing heart failure such that there is greater uniformity in its diagnosis and treatment. The most common of these is the New York Heart Association (NYHA) functional classification that was first introduced in 1928 and still persists due to its ease of use and clinical relevance (Table 70–1).[11] Furthermore, currently approved therapies are anchored in this

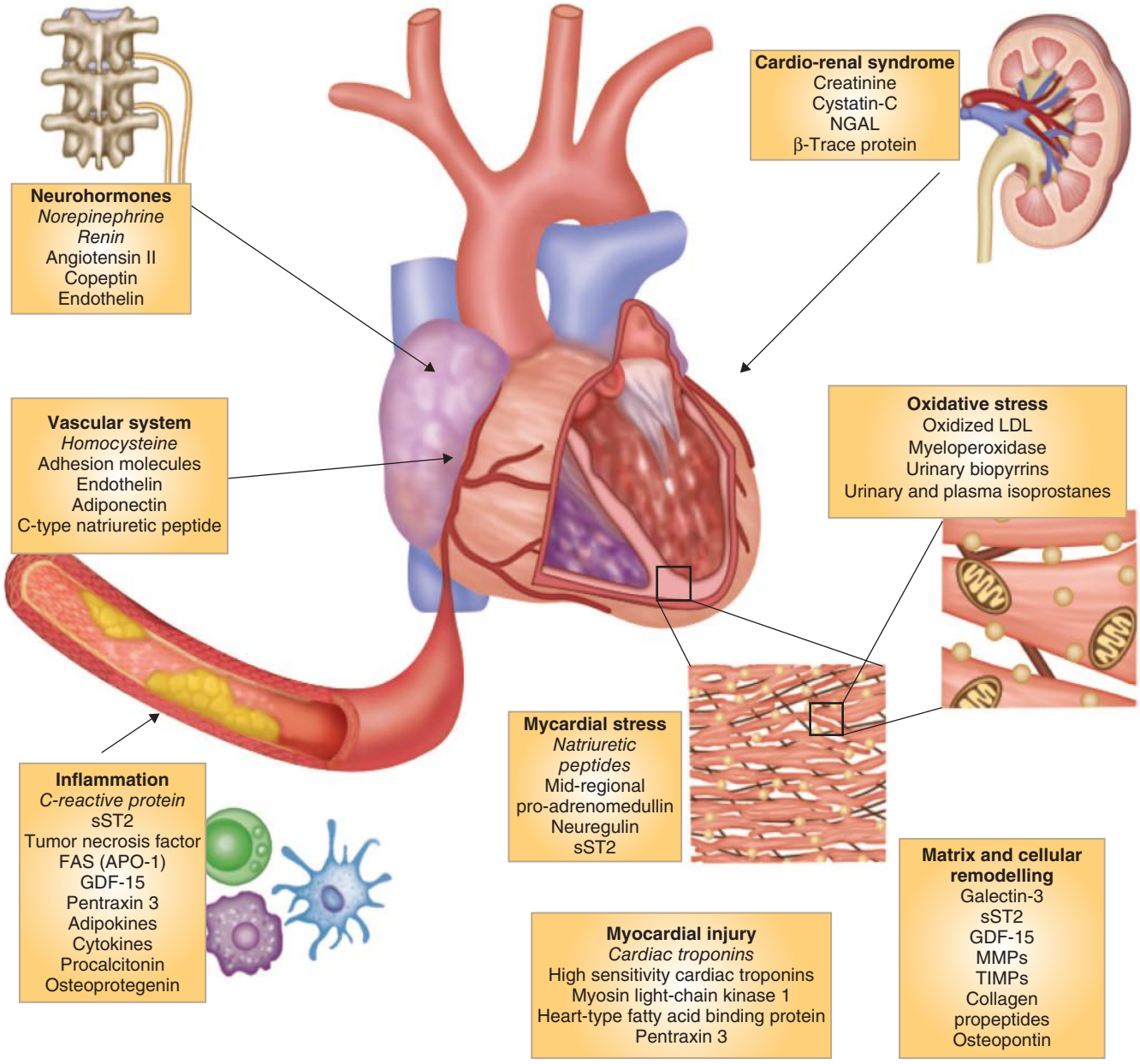

FIGURE 70–1. Heat failure involves an interplay between myocardial factors, systemic inflammation, renal dysfunction, and neurohormonal activation. Biomarkers can be classified according to broad categories of processes that are involved in the development and progression of heart failure. Several biomarkers have been characterized for each of these processes; these vary greatly in their ease of measurement, cost, turnaround time, and evaluation in the clinical setting. Traditional biomarkers that have been studied fairly rigorously appear in italics. APO, apoptosis antigen; GDF, growth differentiation factor; HF, heart failure; ICAM, intercellular adhesion molecule; LDL, low-density lipoprotein; MMPs, matrix metalloproteinases; NGAL, neutrophil gelatinase-associated lipocalin; TIMPs, matrix metalloproteinase tissue inhibitors. Reproduced with permission from Ahmad T, Fiuzat M, Felker GM, O'Connor C. Novel biomarkers in chronic heart failure. *Nat Rev Cardiol*. 2012 Mar 27;9(6):347-359.[7]

classification, as it was used to select patients for almost all randomized clinical trials in heart failure. Patients with NYHA class I have no symptoms attributable to heart disease; those in NYHA classes II, III, or IV have mild, moderate, and severe symptoms, respectively. It is important to note that this classification has numerous limitations: it correlates poorly with objective measures of heart failure, it is not a static measure, and there is significant intraobserver variability in assignment of class.[12]

Another classification introduced by the ACC/AHA is the heart failure staging approach that emphasizes the importance of development and progression of disease (see Table 70–1).[5] These stages are progressive and associated with prognosis, and interventions can vary based on stage, including modifying risk factors (stage A), treating structural heart disease (stage B), or reducing morbidity and mortality (stages C and D).

Another key classifier of heart failure is left ventricular (LV) ejection fraction (LVEF), principally because this was a fundamental variable used in clinical trials and there is a belief that it captures a distinct phenotypes of heart failure.[13-15] Mathematically, it is LV stroke volume divided by the end-diastolic volume. In patients with reduced contraction and emptying of the left ventricle due to systolic dysfunction, output is maintained by the heart ejecting a smaller percentage of a larger end-diastolic volume.[6] As systolic function decreases, this is generally paralleled by reduction in ejection fraction and greater end-diastolic

TABLE 70–1. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; NYHA, New York Heart Association.

Note: INTERMACS classification is used in patients needing left ventricular assist devices, and they can be in stage C and D

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and end-systolic volumes. In patients with heart failure symptoms in whom reductions in ejection fraction do not occur, there is generally an increase in thickness of the LV suggestive of chronically high filling pressures, as well as increased left atrial size.

A commonly used clinical classification of heart failure relies on bedside physician assessment of perfusion and volume status (see below).[16] Indicators of congestion include history of orthopnea and/or physical exam evidence of jugular venous distention, rales, hepatojugular reflux, ascites, peripheral edema, leftward radiation of the pulmonic heart sound, or a square wave blood pressure response to the Valsalva maneuver. Compromised perfusion is assessed by the presence of a narrow proportional pulse pressure ([systolic – diastolic blood pressure]/systolic blood pressure < 25%), pulsus alternans, symptomatic hypotension (without orthostasis), cool extremities, and/or impaired mentation.[16]

Heart failure itself is not synonymous with a certain degree of LV dysfunction, and similar abnormalities can exist across the spectrum of LVEF.[17,18] However, important clinical decisions hinge on a dichotomous classification of ejection fraction because, to date, only randomized clinical trials that enrolled patients with LVEF ≤ 35% to 40% have shown efficacious results (Table 70–2).[19,20] Therefore, one of the most common ways to describe heart failure is as heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The prevalence of HFrEF and HFpEF is approximately 50% each.[21] Of note, the descriptors "systolic" and "diastolic" are often used in place of HFrEF and HFpEF, but from a purist's perspective, these are incorrect, because systolic dysfunction and diastolic dysfunction coexist in the majority of patients with heart failure, irrespective of ejection fraction.[15]

Finally, there are a few other terminologies used. Patients who have had heart failure for some time are often said to have *chronic heart failure*. If symptoms in such patients are unchanged for some length of time, they are said to have *chronic stable heart failure*. If a chronic heart failure patient declines, they are said to have *worsening heart failure*, and in general, if this leads to hospitalization, it is referred to as *acute heart failure* or *acutely decompensated heart failure*. *Congestive heart failure* is a term still used and implies the symptoms of excessive volume retention that are frequent but by no means the sine qua non for heart failure.[6] Terms such as *right-sided heart failure* and *left-sided heart failure* attempt to isolate symptoms to a specific ventricle; for example, lower extremity edema and ascites are ascribed to a failing right ventricle, whereas dyspnea and low blood pressure are ascribed to the left.

DIAGNOSIS AND EVALUATION OF HEART FAILURE

SIGNS AND SYMPTOMS

It is often challenging to diagnose heart failure, especially in its early stages. Its signs and symptoms can be fairly nonspecific and may not prompt further testing that would lead to a more certain diagnosis.[22-24] In the acute setting, heart failure can be mistaken for disorders such as myocardial ischemia, chronic obstructive pulmonary disease, pulmonary embolism, or infections. In the more chronic setting, heart failure can be mistaken for diseases such as depression, asthma, cirrhosis, or hypothyroidism. Therefore, a high degree of mindfulness is required when a clinician encounters a patient with suspected heart failure such that the appropriate set of diagnostic and therapeutic interventions are performed. Once it is confirmed that abnormalities of the heart are driving the patient's symptoms, the diversity of causes for cardiomyopathy should be considered.[25] Another challenge is that criteria for early detection of heart failure in the community have not been well established at this time.

Table 70–3 outlines some of the findings noted in heart failure. As with many medical conditions, key information can be gleaned from a thoughtful history and physical exam.[26,27] Identification of risk factors such as prior myocardial infarction and a family history can provide important clues about etiology.[28] The duration and triggers of symptoms can identify potential drivers of cardiac dysfunction. Other clues might come from comorbid conditions and treatments. Social history might reveal use of cocaine, methamphetamine, or alcohol, all of which can cause cardiomyopathy.

Physical examination findings are generally ascribed to findings of increased total-body volume (edema, anasarca) or decreased cardiac output (fatigue, exercise intolerance, decreased urine output) and are

TABLE 70–2. Definitions of HF

Classification		EF (%)	Description
I	HFrEF	≤ 40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II	HFpEF	≥ 50	Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
	a. HFpEF, borderline	41-49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.
	b. HFpEF, improved	> 40	It has been recognized that a subset of HFpEF patients previously had HFrEF. These patients with improvement or recovery of EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.
III	Chronic stable HF	Any	A patient with HF symptoms and signs for quite some time that have remained generally unchanged for at least a month are said to have chronic stable HF.
	Acute decompensated HF	Any	If chronic stable HF deteriorates, the patient may be described as "decompensated," and this may happen suddenly (ie, "acutely,"), usually leading to hospital admission.

Abbreviations: EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
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useful for ruling in heart failure, rather than ruling it out.[16,29] Findings such as elevations in jugular venous pressure and third heart sound are strongly specific for heart failure but difficult to detect and suffer from lack of reproducibility.[30,31] Furthermore, they are dependent on the patient's body habitus and can be misleading in the presence of right ventricular dysfunction and/or tricuspid regurgitation. That said, the astute clinician can garner important clues by examination, especially when it is well integrated.[32] A proportional pulse pressure [(systolic – diastolic)/systolic)] of < 25% suggests a cardiac index < 2.2 $L \cdot min^{-1} \cdot m^{-2}$.[23] An elevated jugular venous pressure is the most important exam finding to identify congestion.[30]

The cardiovascular response to the Valsalva maneuver is a simple and highly sensitive bedside test for estimation of volume status and detection of LV systolic dysfunction. With the blood pressure cuff inflated 15 mm Hg over the systolic pressure, the patient is asked to perform a Valsalva maneuver. A normal response is when Korotkoff sounds are audible only at the onset of straining and at release. In patients with heart failure, Korotkoff sounds can be heard throughout the Valsalva maneuver (the square wave response), or there is a lack of reappearance of the sounds after release (the absent overshoot response).[29] The third heart sound (or gallop rhythm) is commonly present with tachycardia (but may be challenging to hear) and volume overload and signifies hemodynamic compromise and elevated left-sided filling pressures. Even in the absence of complaints, examination should be performed to determine the presence of ascites, hepatosplenomegaly, or a pulsatile liver. It is not uncommon for patients with advanced heart failure to present with severe right upper quadrant pain and to undergo cholecystectomy when the actual culprit is acute hepatic congestion.[33] Peripheral edema is common in heart failure but is nonspecific because it can result from a number of other disease states. The finding of cachexia in patients with end-stage heart failure is associated with a particularly poor prognosis.[34] Finally, it is important to remember that signs of pulmonary congestion such as rales and pulmonary edema are commonly lacking in patients with heart failure, even elevated pulmonary pressures.[26,27,35]

ROUTINE DIAGNOSTIC TESTING

Routine diagnostic testing generally starts with laboratory testing and electrocardiogram (ECG) analysis (Table 70–4).[36] Assessments of renal function and potassium can have therapeutic implications. Reversible causes of heart failure such as hypothyroidism, anemia, and hypocalcemia can be ruled out. The ECG can provide information about rhythm and conduction[37] and can help select therapies. Chest x-ray is commonly performed in patients with suspected or new-onset heart failure but is limited by low sensitivity and specificity,[38] and significant LV dysfunction and volume overload can exist in the presence of a normal chest x-ray.[39]

BIOMARKERS

Natriuretic peptides, specifically the B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), have revolutionized the diagnosis and prognostication of heart failure.[40] Before its activation, BNP is stored as a 108-amino acid polypeptide precursor, proBNP, in secretory granules in both ventricles and, to a lesser extent, in the atria. After proBNP is secreted in response to volume overload and resulting myocardial stretch, it is cleaved to the 76-peptide, biologically inert N-terminal fragment NT-proBNP and the 32-peptide, biologically active hormone BNP. The two fragments are secreted into the plasma in equimolar amounts, and both have been extensively evaluated for use in the management of heart failure. BNP has diuretic, natriuretic, and antihypertensive effects; furthermore, it may provide a protective effect against the detrimental fibrosis and remodeling that occurs in progressive heart failure. Normal natriuretic peptide level in an untreated patient virtually excludes significant cardiac disease, potentially making further testing unnessary.[36,41] Assays for BNP and NT-proBNP are reasonably correlated and either can be used clinically, except when the patient is taking LCZ696 (sacubitril/valsartan; Entresto) where neprilysin inhibition can elevate BNP levels.[42] Natriuretic peptides have an AHA/ACC Class I recommendation for the diagnosis of acute heart

TABLE 70–3. History and Physical Examination in HF

	Comments
History	
Potential clues suggesting etiology of HF	A careful family history may identify an underlying familial cardiomyopathy in patients with idiopathic DCM. Other etiologies should be considered as well.
Duration of illness	A patient with recent-onset systolic HF may recover over time.
Severity and triggers of dyspnea and fatigue, presence of chest pain, exercise capacity, physical activity, sexual activity	To determine NYHA class; identify potential symptoms of coronary ischemia.
Anorexia and early satiety, weight loss	Gastrointestinal symptoms are common in patients with HF. Cardiac cachexia is associated with adverse prognosis.
Weight gain	Rapid weight gain suggests volume overload.
Palpitations, (pre)syncope, ICD shocks	Palpitations may be indications of paroxysmal AF or ventricular tachycardia. ICD shocks are associated with adverse prognosis.
Symptoms suggesting transient ischemic attack or thromboembolism	Affects consideration of the need for anticoagulation.
Development of peripheral edema or ascites	Suggests volume overload.
Disordered breathing at night, sleep problems	Treatment for sleep apnea may improve cardiac function and decrease pulmonary hypertension.
Recent or frequent prior hospitalizations for HF	Associated with adverse prognosis.
History of discontinuation of medications for HF	Determine whether lack of GDMT in patients with HFrEF reflects intolerance, an adverse event, or perceived contraindication to use. Withdrawal of these medications has been associated with adverse prognosis.
Medications that may exacerbate HF	Removal of such medications may represent a therapeutic opportunity.
Diet	Awareness and restriction of sodium and fluid intake should be assessed.
Adherence to medical regimen	Access to medications; family support; access to follow-up; cultural sensitivity
Physical Examination	
BMI and evidence of weight loss	Obesity may be a contributing cause of HF; cachexia may correspond with poor prognosis.
Blood pressure (supine and upright)	Assess for hypertension or hypotension. Width of pulse pressure may reflect adequacy of cardiac output. Response of blood pressure to Valsalva maneuver may reflect LV filling pressures.
Pulse	Manual palpation will reveal strength and regularity of pulse rate.
Examination for orthostatic changes in blood pressure and heart rate	Consistent with volume depletion or excess vasodilation from medications.
Jugular venous pressure at rest and following abdominal compression	Most useful finding on physical examination to identify congestion.
Presence of extra heart sounds and murmurs	S_3 is associated with adverse prognosis in HFrEF. Murmurs may be suggestive of valvular heart disease.
Size and location of point of maximal impulse	Enlarged and displaced point of maximal impulse suggests ventricular enlargement.
Presence of right ventricular heave	Suggests significant right ventricular dysfunction and/or pulmonary hypertension.
Pulmonary status: respiratory rate, rales, pleural effusion	In advanced chronic HF, rales are often absent despite major pulmonary congestion.
Hepatomegaly and/or ascites	Usually markers of volume overload.
Peripheral edema	Many patients, particularly those who are young, may be not edematous despite intravascular volume overload. In obese patients and elderly patients, edema may reflect peripheral rather than cardiac causes.
Temperature of lower extremities	Cool lower extremities may reflect inadequate cardiac output.

Abbreviations: AF indicates atrial fibrillation; BMI, body mass index; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricular; NYHA, New York Heart Association.

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failure and establishment of prognosis in chronic heart failure.[5] Both BNP and NT-proBNP levels can be elevated from a variety of other causes as well (Table 70–5).[43]

An abundance of biomarkers can provide unique information about various aspects of heart failure pathophysiology, but only a few are approved for use in the clinical setting (see Fig. 70–1).[9,44] Cardiac troponin[45] elevations in heart failure are associated with more severe disease and prognosis, but the how treatments might be adjusted based on serum elevations remains unclear.[46] It is reasonable currently to measure levels in the hospital setting to rule out an ischemic trigger and establish prognosis. Soluble ST2 and galectin-3 are predictive of adverse outcomes in chronic heart failure and are additive in their value to natriuretic peptides.[47] Along with other prognostic factors, they can provide unique and objective information about the patient and are likely be included in future multimarker approaches to heart failure care.[48] In chronic heart failure, measurement of cardiac troponins, ST2, and galectin-3 has an AHA/ACC Class IIb recommendation for risk stratification.[49]

TRANSTHORACIC ECHOCARDIOGRAM

Transthoracic echocardiography plays an important part in the assessment of patients with heart failure (Table 70–6).[13,14,50,51] It can be performed at the bedside, is accurate and safe, and provides key

TABLE 70–4. Common Laboratory Test and Electrocardiogram Abnormalities in HF

Abnormality	Causes	Clinical Implications
Renal/kidney impairment (creatinine > 1.7 mg/dL, eGFR < 60 mL/min/1.73 m^2)	Renal disease	Calculate eGFR
	Renal congestion	Consider reducing ACE inhibitor/ARB or MRA dose (or postpone dose up-titration)
	ACE inhibitor/ARB/MRA	Check potassium and BUN
	Dehydration	Consider reducing diuretic dose if dehydrated, but if renal congestion, more diuresis may help
	NSAIDs and other nephrotoxic drugs	Review drug therapy
Anemia (< 13 g/dL in men, < 12 g/dL in women)	Chronic HF, hemodilution, iron loss or poor utilization, renal failure, chronic disease, malignancy	Diagnostic workup
		Consider treatment
Hyponatremia (< 135 mmol/L)	Chronic HF, hemodilution, AVP release, diuretics (especially thiazides) and other drugs	Consider water restriction, adjusting diuretic dosage
		Ultrafiltration, vasopressin antagonist
		Review drug therapy
Hypernatremia (> 150 mmol/L)	Water loss/inadequate water intake	Assess water intake
		Diagnostic workup
Hypokalemia (< 3.5 mmol/L)	Diuretics, secondary hyperaldosteronism	Risk of arrhythmia
		Consider ACE inhibitor/ARB, MRA, potassium supplements
Hyperkalemia (> 5.5 mmol/L)	Renal failure, potassium supplement, renin-angiotensin-aldosterone system blockers	Stop potassium supplements/potassium-sparing diuretic
		Reduce dose of/stop ACE inhibitor/ARB, MRA
		Assess renal function and urine pH
		Risk of bradycardia and serious arrhythmias
Hyperglycemia (117 mg/dL)	Diabetes, insulin resistance	Evaluate hydration, treat glucose intolerance
Hyperuricemia (8.4 mg/dL)	Diuretic treatment, gout, malignancy	Allopurinol
		Reduce diuretic dose
Albumin high (> 4.5 g/dL)	Dehydration	Rehydrate
Albumin low (< 3.0 g/dL)	Poor nutrition, renal loss	Diagnostic workup
Transaminase increase	Liver dysfunction	Diagnostic workup
	Liver congestion	Liver congestion
	Drug toxicity	Review drug therapy
Elevated troponins	Myocyte necrosis	Evaluate pattern of increase (mild increases common in severe HF)
	Prolonged ischemia, severe HF, myocarditis, sepsis, renal failure	Perfusion/viability studies
		Coronary angiography
		Evaluation for revascularization
Elevated creatine kinase	Inherited and acquired myopathies (including myositis)	Consider genetic cardiomyopathy (laminopathy, desminopathy, dystrophinopathy), muscular dystrophies
		Statin use
Abnormal thyroid tests	Hyper-/hypothyroidism	Treat thyroid abnormality
	Amiodarone	Reconsider amiodarone use
Urine analysis	Proteinuria, glycosuria, bacteria	Diagnostic workup
		Rule out infection, diabetes
International normalized ratio > 3.5	Anticoagulant overdose	Review anticoagulant dose
	Liver congestion/disease	Assess liver function
	Drug interactions	Review drug therapy
CRP > 10 mg/L, neutrophilic leukocytosis	Infection, inflammation	Diagnostic workup
Sinus tachycardia	Decompensated HF, anemia, fever, hyperthyroidism	Clinical assessment
		Laboratory investigation

(*continued*)

TABLE 70–4. Common Laboratory Test and Electrocardiogram Abnormalities in HF (*Continued*)

Abnormality	Causes	Clinical Implications
Sinus bradycardia	Beta-blockade, digoxin, ivabradine, verapamil, diltiazem	Review drug therapy
	Antiarrhythmics	Laboratory investigation
	Hypothyroidism	
	Sick sinus syndrome	
Atrial tachycardia/flutter/fibrillation	Hyperthyroidism, infection, mitral valve disease	Slow AV conduction, anticoagulation, pharmacologic cardioversion, electrical cardioversion, catheter ablation
	Decompensated HF, infarction	
Ventricular arrhythmias	Ischemia, infarction, cardiomyopathy, myocarditis, hypokalemia, hypomagnesemia	Laboratory investigation
	Digitalis overdose	Exercise test, perfusion/viability studies, coronary angiography, electrophysiology testing, ICD
Myocardial ischemia/infarction	Coronary artery disease	Echocardiography, troponins, perfusion/viability studies, coronary angiography, revascularization
Q waves	Infarction, hypertrophic cardiomyopathy	Echocardiography, perfusion/viability studies, coronary angiography
	LBBB, pre-excitation	
LV hypertrophy	Hypertension, aortic valve disease, hypertrophic cardiomyopathy	Echocardiography/CMR
AV block	Infarction, drug toxicity, myocarditis, sarcoidosis, genetic cardiomyopathy (laminopathy, desminopathy), Lyme disease	Review drug therapy, evaluate for systemic disease, family history/genetic testing indicated. Pacemaker or ICD may be indicated.
Low QRS voltage	Obesity, emphysema, pericardial effusion, amyloidosis	Echocardiography/CMR, chest x-ray, for amyloidosis consider further testing (CMR, 99mTc-DPD scan) and endomyocardial biopsy
QRS duration ≥120 ms and LBBB morphology	Electrical and mechanical dyssynchrony	Echocardiography
		CRT-P, CRT-D

Abbreviations: ACE, angiotensin-converting enzyme; ARB angiotensin-receptor blocker; AV, atrioventricular; BUN, blood urea nitrogen; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NSAIDs, nonsteroidal anti-inflammatory drugs.

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information on chamber size and volumes, systolic and diastolic function, wall thickness, and valve function. A two-dimensional echocardiogram with Doppler during an initial assessment of a patient with suspected heart failure, as well as patients with changes in symptoms, is a Class I recommendation.[5] The LVEF is measured using several different methods, with the recommended technique being the apical biplane method of disks (the modified Simpson rule). LVEF must be interpreted in its clinical context as it depends on several parameters such as heart rate, preload, afterload, and valvular function, and is not the same as stroke volume. Assessment of diastolic parameters is an important part of the assessment of patients with heart failure. No single echocardiographic parameter can make the diagnosis of diastolic dysfunction in heart failure; a comprehensive inclusion of two-dimensional and Doppler data is required (see Table 70–6). Other key echocardiographic measures in heart failure patients are assessments of right ventricular function, presence of pulmonary hypertension, inferior vena cava diameters, and collapsibility, which are useful in the estimation of right atrial pressure and severity of valve disease.[52]

OTHER NONINVASIVE IMAGING

Severe other imaging modalities are available that provide unique information about various aspects of myocardial dysfunction (Table 70–7 and Fig. 70–2).[53] Transesophageal echocardiography is useful when chest wall windows are inadequate, in patients with complex valvular or congenital heart disease, and to check for thrombus in the left atrial appendage.[6] Stress echocardiography is useful to identify ischemia and to gauge if the dysfunctional myocardium is viable.[52] It is also valuable for the evaluation of aortic stenosis severity or contractile reserve in the setting of reduced LVEF and low transvalvular gradient. Single-photon emission computer tomography (SPECT) or positron emission tomography (PET) may be used to assess ischemia and viability if coronary artery disease is present.

Cardiac magnetic resonance (CMR) can provide almost all the information gleaned from a comprehensive echocardiogram, as well as additional assessments.[54] It is considered the gold standard for assessment of myocardial volumes, mass, and wall motion. CMR can provide key input in regard to whether an inflammatory or infiltrative condition might be present. Furthermore, it is an extremely helpful tool for the understanding of potential sources of arrhythmias, pericardial disease, and anatomy in patients with congenital heart disease.

CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing measures a broader range of variables related to cardiorespiratory function, including expiratory ventilation ($\dot{V}E$) and pulmonary gas exchange (oxygen uptake [$\dot{V}O_2$] and carbon dioxide output [$\dot{V}CO_2$]), and helps quantitatively link metabolic,

TABLE 70–5. Selected Causes of Elevated Natriuretic Peptide Concentrations

Cardiac
- Heart failure, including RV syndromes
- Acute coronary syndrome
- Heart muscle disease, including LVH
- Valvular heart disease
- Pericardial disease
- Atrial fibrillation
- Myocarditis
- Cardiac surgery
- Cardioversion

Noncardiac
- Advancing age
- Anemia
- Renal failure
- Pulmonary: obstructive sleep apnea, severe pneumonia, pulmonary hypertension
- Critical illness
- Bacterial sepsis
- Severe burns
- Toxic-metabolic insults, including cancer chemotherapy and envenomation

Abbreviations: LVH, left ventricular hypertrophy; RV, right ventricular.
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cardiovascular, and pulmonary responses to exercise.[55] It objectively correlates the subjective findings in heart failure and helps understand the relative contributions of the heart, lungs, and peripheral muscles to symptoms of dyspnea and fatigue.[56] The test uses treadmill and bicycle protocols along with gas exchange analysis, and provides key information that can be used to gauge candidacy for advanced therapies such as left ventricular assist devices and transplantation. Cardiopulmonary exercise testing is the gold standard for risk stratification in patients being considered for cardiac transplantation.[57] Originally, a threshold of peak VO_2 of ≤ 14 $mL \cdot kg^{-1} \cdot min^{-1}$ had been suggested, but in the current era of improved therapies, a lower threshold of 10 to 12 $mL \cdot kg^{-1} \cdot min^{-1}$ has been suggested for consideration of advanced therapies. Some studies have suggested that the VE/VCO_2 slope is a better predictor of outcome than peak VO_2, LVEF, and NYHA class.[58]

GENETIC TESTING

Familial syndromes are thought to account for up to 20% to 35% of patients with apparent idiopathic dilated cardiomyopathy. Additionally, genetic testing in now readily available to assess for mutations in several other disease-causing genes that can lead to unexplained cardiomyopathies or syndromes with cardiac involvement (Table 70–8).

INVASIVE TESTING

Right heart catheterizations are commonly used to manage heart failure, but there are few data to help guide appropriate settings for when hemodynamic measurements are indicated. Based on expert consensus, invasive monitoring is recommended for patients with respiratory distress or evidence of impaired perfusion in whom clinical assessment falls short. It is also recommended for (1) presumed cardiogenic shock requiring escalating pressor therapy and consideration of mechanical circulatory support; (2) severe clinical decompensation in which therapy is limited by uncertain contributions of elevated filling pressures, hypoperfusion, and vascular tone; (3) apparent dependence on intravenous inotropic infusions; (4) persistent severe symptoms despite adjustment of recommended therapies; or (5) consideration for mechanical circulatory support or transplantation in a patient with advance disease. Routine use of right heart catheterization is not recommended in normotensive patients who are responding appropriately to diuretics and vasodilators.

Based on the premise that providing clinicians with continuous invasive data in heart failure patients could improve outcomes, an implantable device (CardioMEMS; St. Jude Medical, Saint Paul, MN) that allows therapeutic adjustment based on continuous measures of pulmonary artery pressures was tested in a randomized trial of 550 high-risk HF patients. The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial showed that the pulmonary artery pressure–guided treatment arm had a 37% reduction in HF hospitalizations compared with the control group.[59] Based on these results, the device is approved by the US Food and Drug Administration (FDA) for use in patients with heart failure and NYHA class III symptoms. The cost-effectiveness and appropriate subgroup of patients for this device remain unclear.[60] Left heart catheterizations or coronary angiography should be performed in patients who are candidates for revascularization in whom it is felt that ischemia is contributing to the development or worsening of heart failure.[61] Endomyocardial biopsy should be considered when seeking a specific diagnosis that would influence therapy, such as suspected giant cell myocarditis or cardiac amyloidosis.[62]

TREATMENT FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

SODIUM INTAKE

Despite the absence of credible data, dietary sodium restriction for the management of heart failure is widely recommended and is borne out of historical beliefs, putative mechanistic data, and observational studies.[63,64] No study to date has evaluated the effects of sodium restriction on outcomes in optimally treated patients,[65] and there are data showing that reduction in sodium intake might lead to adverse outcomes in heart failure,[66] underscoring the need for a randomized clinical trial in this area.[67]

EXERCISE

Both the ESC and the AHA/ACC guidelines give exercise training a Class I recommendation for treatment of HFrEF.[5,6] Several studies have shown that exercise has numerous benefits in heart failure.[68,69] The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial randomized 2331 patients with LVEF ≤ 35% to exercise training versus usual care[70] and showed improvements in quality of life, depression, physical fitness, and reduction in risk of heart failure hospitalizations. The Centers for Medicare and Medicaid Services has approved payment for cardiac rehabilitation for heart failure.[71]

TABLE 70–6. Common Echocardiographic Abnormalities in Patients With HF

Measurement	Abnormality	Clinical Implications
Parameters related to systolic function		
LV ejection fraction*	Reduced (< 50%)	LV global systolic dysfunction
LV fractional shortening	Reduced (< 25%)	LV radial systolic dysfunction
LV regional function	Hypokinesis, akinesis, dyskinesis	Myocardial infarction/ischemia
		Cardiomyopathy, myocarditis
LV end-diastolic size	Increased (diameter ≥ 60 mm, > 32 mm/m^2, volume > 97 mL/m^2)	Volume overload HF likely
LV end-systolic size	Increased (diameter > 45 mm, > 25 mm/m^2, volume > 43 mL/m^2)	Volume overload HF likely
LV outflow tract velocity time integral	Reduced (< 15 cm)	Reduced LV stroke volume
Parameters related to diastolic function		
LV diastolic dysfunction parameters	Abnormalities of the mitral inflow pattern, tissue velocities (e′) or the E/e′ ratio	Indicate LV diastolic dysfunction and suggest level of filling pressure
Left atrial volume index	Increased (volume > 34 mL/m^2)	Increased LV filling pressure (past or present)
		Mitral valve disease
LV mass index	Increased: > 95 g/m^2 in women and > 115 g/m^2 in men	Hypertension, aortic stenosis, hypertrophic cardiomyopathy
Parameters related to valvular function		
Valvular structure and function	Valvular stenosis or regurgitation (especially aortic stenosis and mitral regurgitation)	May be the cause of HF or a complicating factor or the result of HF (secondary mitral regurgitation)
		Assess dysfunction severity and hemodynamic consequences
		Consider surgery
Other parameters		
RV function (eg, TAPSE)	Reduced (TAPSE < 16 mm)	RV systolic dysfunction
Tricuspid regurgitation peak velocity	Increased (> 3.4 m/s)	Increased RV systolic pressure
Systolic pulmonary artery pressure	Increased (> 50 mmHg)	Pulmonary hypertension likely
Inferior vena cava	Dilated, with no respiratory collapse	Increased right atrial pressure
		RV dysfunction, volume overload
		Pulmonary hypertension possible
Pericardium	Effusion, hemopericardium, calcification	Consider tamponade, malignancy, systemic diseases, acute or chronic pericarditis, constrictive pericarditis
e′	Decreased (< 8 cm/s septal, < 10 cm/s lateral, or < 9 cm/s average)	Delayed LV relaxation
E/e′ ratio	High (> 15)	High LV filling pressure
	Low (< 8)	Normal LV filling pressure
	Intermediate (8-15)	Gray zone (additional parameters necessary)
Mitral inflow E/A ratio	"Restrictive" (> 2)	High LV filling pressure
		Volume overload
	"Impaired relaxation" (< 1)	Delayed LV relaxation
		Normal LV filling pressure
	Normal (1-2)	Inclusive (may be "pseudonormal")
Mitral inflow during Valsalva maneuver	Change of the "pseudonormal" to the "impaired relaxation" pattern (with a decrease in E/A ratio ≥ 0.5)	High LV filling pressure (unmasked through Valsalva)
A pulm–A mitral duration	> 30 ms	High LV filling pressure

*LV ejection fraction is not a good surrogate of systolic failure as many patients with hypertrophic cardiomyopathy may have systolic failure.

Abbreviations: HF, heart failure; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

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TABLE 70–7. Possible Applications of Various Imaging Techniques in the Diagnosis of HF

		Echocardiography	CMR	Cath	SPECT	MDCT	PET
Main advantages							
		Wide availability Portability No radiation Relatively low cost	Good-quality images No radiation	Good availability	Good availability	Reasonable availability High-quality images	Good-quality images
Main disadvantages							
		Echo window needed 3D, especially for the RV	Limited availability Contraindications Functional analysis Image quality limited if arrhythmia	Radiation Invasive	Radiation	Radiation Image quality limited if arrhythmia	Radiation Limited availability
Remodeling/dysfunction							
LV	EDV	++	+++	++	++	++	++
	ESV	++	+++	++	++	++	++
	EF	++	+++	++	++	++	++
	Mass	++	+++	–	–	++	–
RV	EDV	++	+++	+	–	++	–
	ESV	++	+++	+	–	++	–
	EF	++	+++	+	–	++	–
	Mass	++	+++	–	–	++	–
LV diastolic dysfunction		+++	+	+++	–	–	–
Dyssynchrony		++	+	–	+	–	–
Etiology							
CAD	Ischemia	+++	+++	+++	+++	–	+++
	Hibernation	+++	+++	–	+++	–	+++
	Scar	++	+++	–	++	–	++
	Coronary anatomy	–	–	+++	–	+++	–
Valvular	Stenosis	+++	+	+++	–	++	–
	Regurgitation	+++	++	++	–	–	–
Myocarditis		+	+++	+++	–	–	–
Sarcoidosis		+	+++	++	–	–	++
Hypertrophic cardiomyopathy (HCM)	HCM	+++	++	++	–	–	–
	Amyloidosis	++	+++	+++	–	–	–
Dilated cardiomyopathy	Myocarditis	+	+++	+++	–	–	–
	Eosinophilic syndromes	+	+++	+++	–	–	–
	Iron hemochromatosis	+	+++	–	–	–	–
	Iron thalassemia	+	+++	–	–	–	–
ARVC		++	+++	+++	–	+	–
Restrictive cardiomyopathy	Pericarditis	++	++	++	–	++	–
	Amyloidosis	++	+++	+++	–	–	–
	Endomyocardial fibrosis	+	+++	+++	–	–	–
	Anderson-Fabry	+	+	–	–	–	–
Unclassified cardiomyopathy	Takotsubo cardiomyopathy	++	++	+++	–	–	–

Abbreviations: 3D, three dimensional; ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; Cath, catheterization; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HF, heart failure; LV, left ventricular; MDCT, multidetector computed tomography; PET, positron emission tomography; RV, right ventricular; SPECT, single-photon emission computed tomography.

Data from McMurray JJ, Adamopoulos S, Anker SD, et al: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012 Jul;33(14):1787-1847.

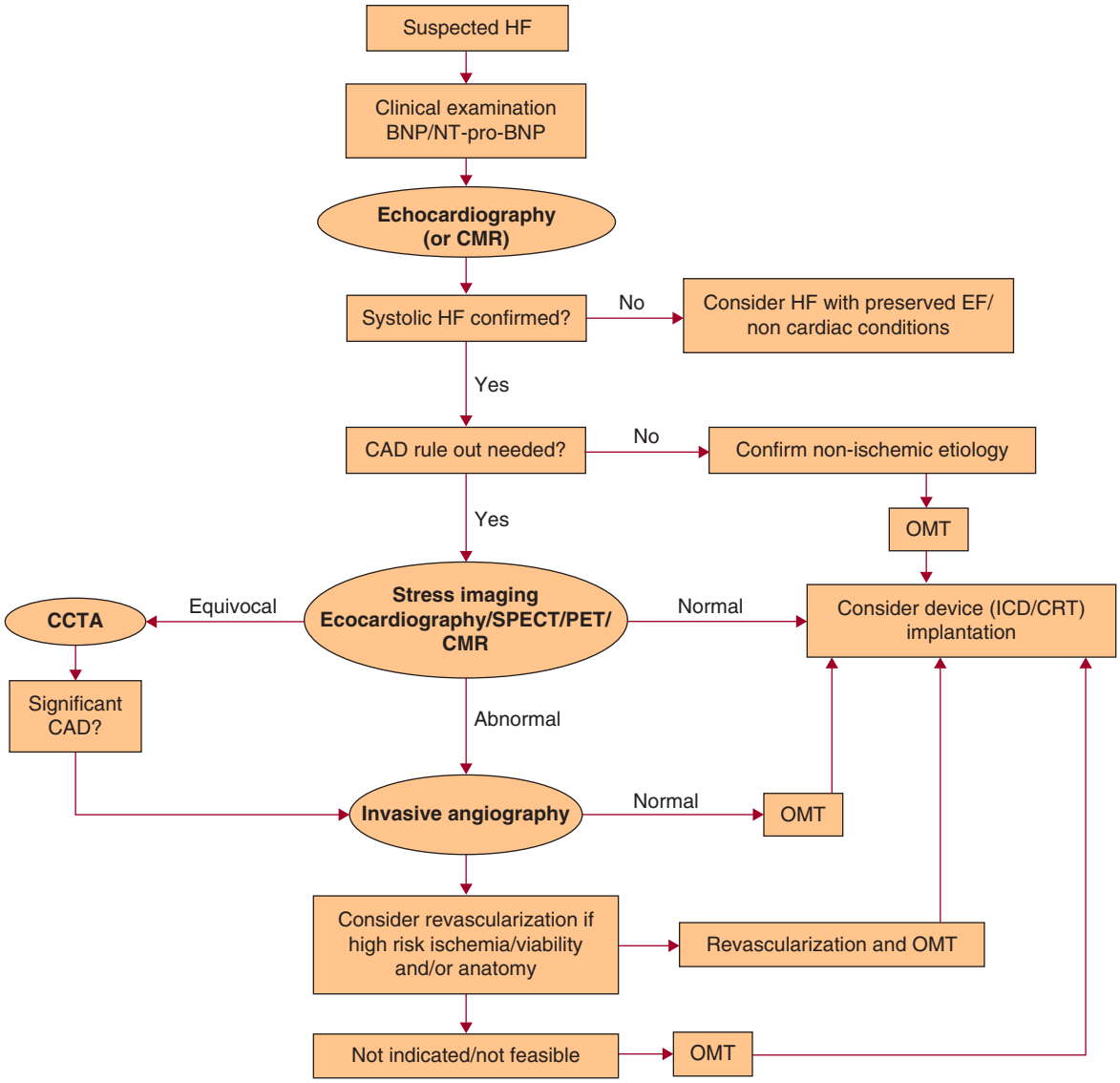

FIGURE 70–2. Use of cardiac imaging for the management of patients with chronic systolic heart failure (HF). BNP, brain natriuretic peptide; CAD, coronary artery disease; CCTA, cardiac computed tomographic angiography; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; NT-proBNP, N-terminal proBNP; OMT, optimal medical therapy; PET, positron emission tomography; SPECT, single-photon emission computed tomography. Reproduced with permission from Gimelli A, Lancellotti P, Badano LP, et al. Non-invasive cardiac imaging evaluation of patients with chronic systolic heart failure: a report from the European Association of Cardiovascular Imaging (EACVI). *Eur Heart J*. 2014 Dec 21;35(48):3417-3425.[53]

PHARMACOLOGIC TREATMENTS

The goal for pharmacologic treatment of heart failure is to help patients feel better, live longer, and stay out of the hospital. Until the evaluation of vasodilators in 1980s, no options were available to treat heart failure other than diuretics and digoxin.[72] Subsequently, hydralazine plus isosorbide dinitrate, angiotensin-converting enzyme (ACE) inhibitors,[73,74] β-blockers, and mineralocorticoid receptor antagonists have all been shown to improve outcomes in patients with HFrEF. Two novel therapies, sacubitril/valsartan and ivabradine, were recently approved for use in HFrEF (Fig. 70–3).

Diuretics

Many of the clinical manifestations of heart failure are related to excessive salt and volume retention and several downstream deleterious consequences.[75] Diuretics can restore salt and water homeostasis, relieve congestion and symptoms, and improve exercise capacity; however, no long-term studies examining the effects of diuretics on morbidity or mortality have been performed to date.[76] Figure 70–4 shows the tubular sites of action of commonly used diuretics, and Table 70–9 reviews usual dosage recommendations.

Proximal tubular diuretics act primarily by decreasing proximal tubular sodium reabsorption; include osmotic diuretics, such as mannitol, and carbonic anhydrase inhibitors, such as acetazolamide; and are not very effective when used alone. Although 50% to 70% of the glomerular filtrate is reabsorbed iso-osmotically in the proximal tubule, the distal nephron, particularly the ascending limb of Henle loop, has the capacity to increase its rate of sodium reabsorption substantially. Therefore, an increase in glomerular filtration or decrease in proximal tubular reabsorption alone may not be associated with a significant diuresis. Thus, these agents are rarely used.

Loop of Henle diuretics include ethacrynic acid, furosemide, bumetanide, and torsemide. Loop diuretics inhibit the $Na^+/2Cl^-/K^+$ cotransporter of the thick ascending loop of Henle, resulting in decreased

TABLE 70–8. Cardiomyopathy Panels

	Cardiomyopathy Panels (62 Genes)											
	Available Panels				Association							
Gene	Pan Cardiomyopathy Panel (62 Genes)	HCM Panel (20 Genes)	DCM/Arrythmogenic Cardiomyopathy Panel (53 Genes)	Inher.	HCM	DCM	ARVC	CPVT	LVNC	RCM	Other	Other diseases or syndromes
ABBC9	X		X	AD		X						
											X	Cantu Syndrome
ACTC1	X	X	X	AD	X	X			X	X		
ACTN2	X	X	X	AD	X	X						
ANKRD1	X			UNKN	X	X						
BAG3	X		X	AD	X	X				X		
						••					X	Myofibrillar myopathy
CASQ2	X		X	AD					X			
				AR				X				
CAV3	X			AD	X	X						
											X	Limb-girdle muscular dystrophy
											X	Long QT
CHRM2	X		X	AD		X						
CRYAB	X		X	Unkn		X						
				AD/AR		••					X	Myofibrillar myopathy
CSRP3	X	X	X	AD	X	X					X	Myopathy reported with HCM
DES	X		X	AD		X	X			X		
				AD/AR		••					X	Myofibrillar myopathy
											X	Limb-girdle muscular dystrophy
DMD	X		X	XL		••					X	Duchenne/Becker muscular dystrophy Female carriers may develop isolated DCM
DOLK	X		X	AR		X						
DSC2	X		X	AD		X	X					
DSG2	X		X	AD		X	X					
DSP	X		X	AD		X	X					
				AR		••	••				X	Carvajal syndrome
DTNA	X		X	AD					X			
EMD	X		X	XL		••					X	Emery-Dreifuss muscular dystrophy
FHL2	X			Unkn		X						
GATAD1	X		X	AR		X						
GLA	X	X	X	XL	••						X	Fabry disease
ILK	X			Unkn		X						
JPH2	X			Unkn	X							
JUP	X		X	AD			X					
				AR							X	Naxos disease
LAMA4*	X			Unkn		X						
LAMP2	X	X	X	XL	••	••					X	Danon disease
LDB3	X		X	AD	X	X			X			

(*continued*)

TABLE 70–8. Cardiomyopathy Panels (*Continued*)

Cardiomyopathy Panels (62 Genes)												
	Available Panels				Association							
Gene	Pan Cardiomyopathy Panel (62 Genes)	HCM Panel (20 Genes)	DCM/Arrythmogenic Cardiomyopathy Panel (53 Genes)	Inher.	HCM	DCM	ARVC	CPVT	LVNC	RCM	Other	Other diseases or syndromes
											X	Myofibrillar myopathy
LMNA	X		X	AD		X			X			
											X	Limb-girdle muscular dystrophy
												Charcot-Marie-Tooth disease
												Malouf Syndrome
												Partial lipodystrophy
				AD/AR		••					X	Emery-Dreifuss muscular dystrophy
MURC	X		X	AD		X						
MYBPC3	X	X	X	AD	X	X			X	X		
MYH6	X		X	AD	X	X						CHD
MYH7	X	X	X	AD	X	X			X	X		Myopathies
											X	Laing distal myopathy
											X	Myosin storage myopathy
MYL2	X	X	X	AD	X							
MYL3	X	X	X	AD	X					X		
MYLK2	X			Unkn	X							
MYOM1	X			AD	X							
MYOZ2	X	X	X	AD	X							
MYPN	X		X	AD	X	X						
NEBL	X		X	Unkn		X					X	Endocardial fibroelastosis
NEXN	X	X	X	Unkn	X	X						
PDLIM3	X			Unkn	X	X						
PKP2	X		X	AD		X	X					
PLN	X	X	X	AD	X	X	X					
PRDM16	X		X	Unkn		X			X			
PRKAG2	X	X	X	AD	••						X	Glycogen Storage Disease (with WPW)
PTPN11	X	X	X	AD	••						X	Noonan spectrum disorders
RAF1	X	X	X	AD	••						X	Noonan spectrum disorders
RBM20	X		X	AD		X						
RYR2	X		X	AD	X		X	X				Presentation can overlap with ARVC
SCN5A	X		X	AD		X	X				X	Brugada syndrome, Long QT syndrome
SGCD	X		X	AD		X						
				AR		••					X	Limb-girdle muscular dystrophy
TAZ	X		X	XL		••			••		X	Barth syndrome
TCAP	X		X	Unkn	X							
				AR		••					X	Limb-girdle muscular dystrophy
TMEM43	X		X	AD			X					

(*continued*)

TABLE 70–8. Cardiomyopathy Panels (*Continued*)

Cardiomyopathy Panels (62 Genes)												
	Available Panels				Association							
Gene	Pan Cardiomyopathy Panel (62 Genes)	HCM Panel (20 Genes)	DCM/Arrythmogenic Cardiomyopathy Panel (53 Genes)	Inher.	HCM	DCM	ARVC	CPVT	LVNC	RCM	Other	Other diseases or syndromes
TNNC1	X	X	X	AD	X	X						
TNNI3	X	X	X	AD	X	X				X		
TNNT2	X	X	X	AD	X	X			X	X		
TPM1	X	X	X	AD	X	X				X		
TRDN	X		X	AR				X				
TTN	X		X	AD	X	X	X					
											X	HMERF
				AD/AR							X	Tibial muscular dystrophy
				AR							X	Centronuclear myopathy
												Limb-girdle muscular dystrophy
TTR	X	X	X	AD	••						X	Amyloidosis
VCL	X		X	AD	X	X			X			

Inher. = Inheritance Pattern, AD = autosomal dominant, AR = autosomal recessive, XL = X-linked, HCM = hypertrophic cardiomyopathy, DCM = dilated cardiomyopathy, ARVC = arrhythmogenic right ventricular cardiomyopathy, CPVT = catecholaminergic polymorphic ventricular tachycardia, LVNC = left ventricular non-compaction, RCM = restrictive cardiomyopathy, Other = other disease or syndromes, ** = cardiomyopathy seen as part of other disease/syndrome
Used with permission from Laboratory for Molecular Medicine. Found at http://personalizedmedicine.partners.org/Assets/documents/Laboratory-For-Molecular-Medicine/Gene_Disease_Association/Cardiomyopathy_Website_Gene_Tables.pdf.

sodium and chloride reabsorption.[77] The potency of these agents depends on renal blood flow and proximal tubular secretion to deliver these agents to their site of action. Bioavailability of furosemide ranges from 40% to 70% of the oral dose; in contrast, the bioavailability of bumetanide and torsemide exceeds 80%.[78] Despite belief that continuous infusions of loop diuretics were superior to bolus dosing and that higher doses might be harmful, the Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE) trial showed that these therapeutic strategies largely made no difference, and it appeared to be beneficial to use higher doses of diuretics.[79] Loop diuretics also induce prostaglandin synthesis, resulting in renal and peripheral vascular smooth muscle relaxation and vasodilatation.

Thiazide diuretics include drugs like chlorthalidone and metolazone.[77] These agents are chemically different. Metolazone is an oral quinazoline that inhibits the Na^+/Cl^- transporter in the cortical portion of the ascending loop of Henle, prevents maximal dilution of the urine, and decreases the kidneys' ability to secrete free water. Thiazide diuretics may contribute to hyponatremia. They also increase Ca^{2+} and decrease Mg^{2+} resorption and may be associated with hypercalcemia and hypomagnesemia. Increased delivery of NaCl and H_2O to the collecting duct can trigger potassium secretion, causing hypokalemia. Metolazone and chlorothiazide can be used in conjunction with loop diuretics to overcome diuretic resistance.

The mineralocorticoid receptor antagonists spironolactone and eplerenone are the most relevant *potassium-sparing diuretics* in heart failure.[77] Spironolactone is a synthetic steroid that competes for the cytoplasmic aldosterone receptor. It increases the secretion of water and sodium, while decreasing the excretion of potassium, by competing for the aldosterone-sensitive Na^+/K^+ channel in the distal tubule of the nephron. Because sodium exchange in the distal tubule is low, potassium-sparing diuretics are generally relatively weak diuretics. As a nonselective aldosterone receptor antagonist, endocrine-related adverse effects (such as gynecomastia) are relatively common with spironolactone. The selective antagonist eplerenone has a similar mechanism of action but is associated with fewer endocrine-related side effects. These agents are weak diuretics and have a more essential role as neurohormonal modulators, discussed later.

Loop diuretics are the backbone for the treatment of volume overload, and most patients are on maintenance doses to preserve a euvolemic state. Their dosing is usually adjusted in response to disease progression, dietary changes, and concurrent therapies.[77] Although once-daily use of furosemide is common, more frequent dosing can limit the "rebound" period during which periods of subtherapeutic diuretic concentration in the tubule may lead to a "rebound" in sodium avidity by the kidney. Although furosemide is by far the most common oral loop diuretic, patients with resistance to oral furosemide therapy may benefit from bumetanide or torsemide, which may offer greater efficacy due to increased bioavailability and potency. All the available loop diuretics share similar toxicity, including the risk of ototoxicity in high doses. Ethacrynic acid may be used in patients with sulfa allergy, as it is the only loop diuretic that does not contain sulfa. Careful monitoring and supplementation of electrolytes, particularly potassium and magnesium, are crucial aspects of loop diuretic therapy.

Over time, some patients develop diuretic resistance. Once issues such as noncompliance and concomitant use of nonsteroidal anti-inflammatory drug have been ruled out, it is important to achieve an adequate dose of loop diuretics by requiring a higher dose in order to achieve the same level of sodium excretion (Fig. 70–5). This "breaking phenomenon" is felt to be a result of hemodynamic changes at the glomerulus, adaptive changes in the distal nephron, and stimulation of

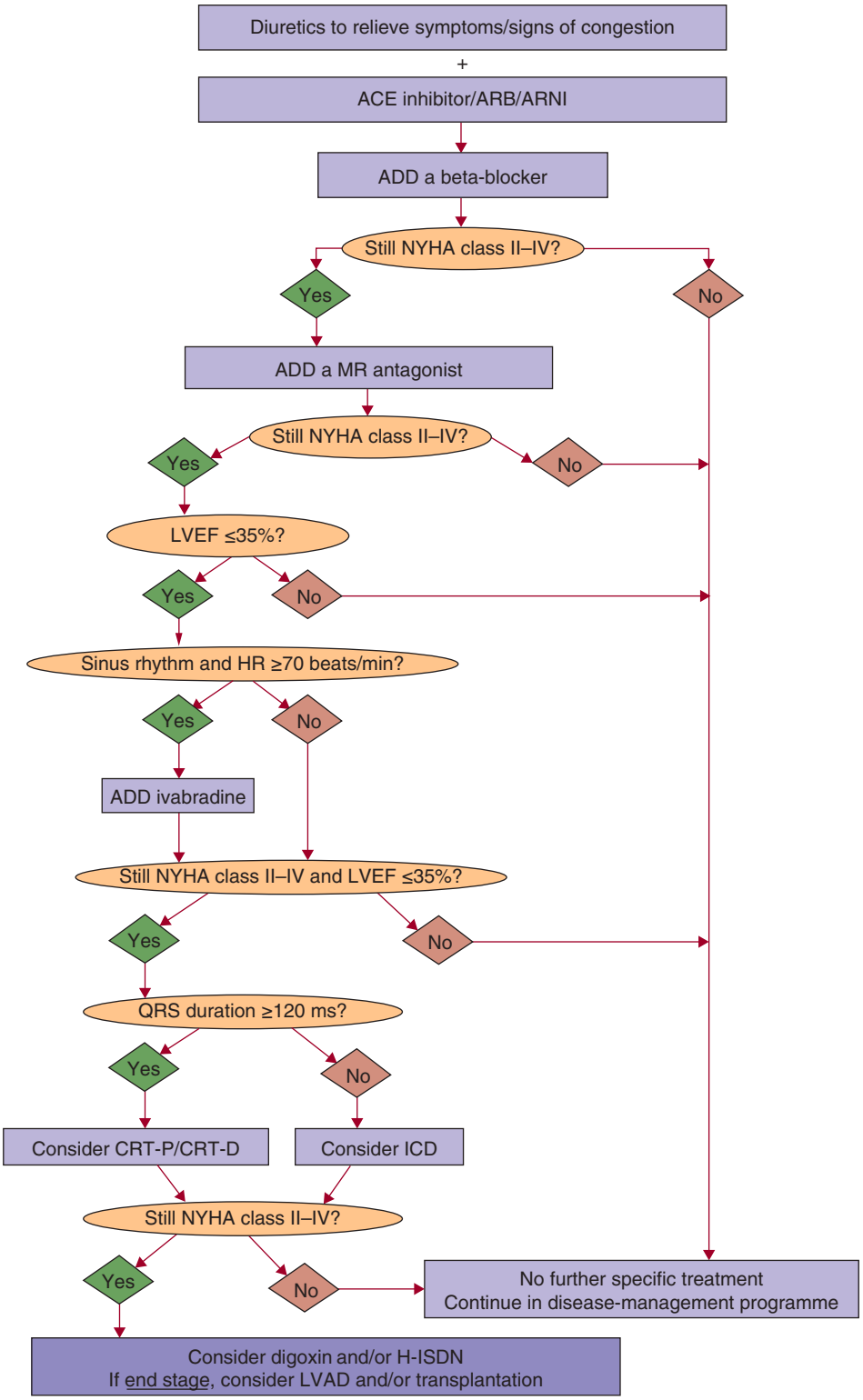

FIGURE 70–3. Treatment options for patients with chronic symptomatic systolic heart failure (New York Heart Association [NYHA] functional class II-IV). Reproduced with permission from McMurray JJ, Adamopoulos S, Anker SD, et al: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012 Jul;33(14):1787-1847.[6]

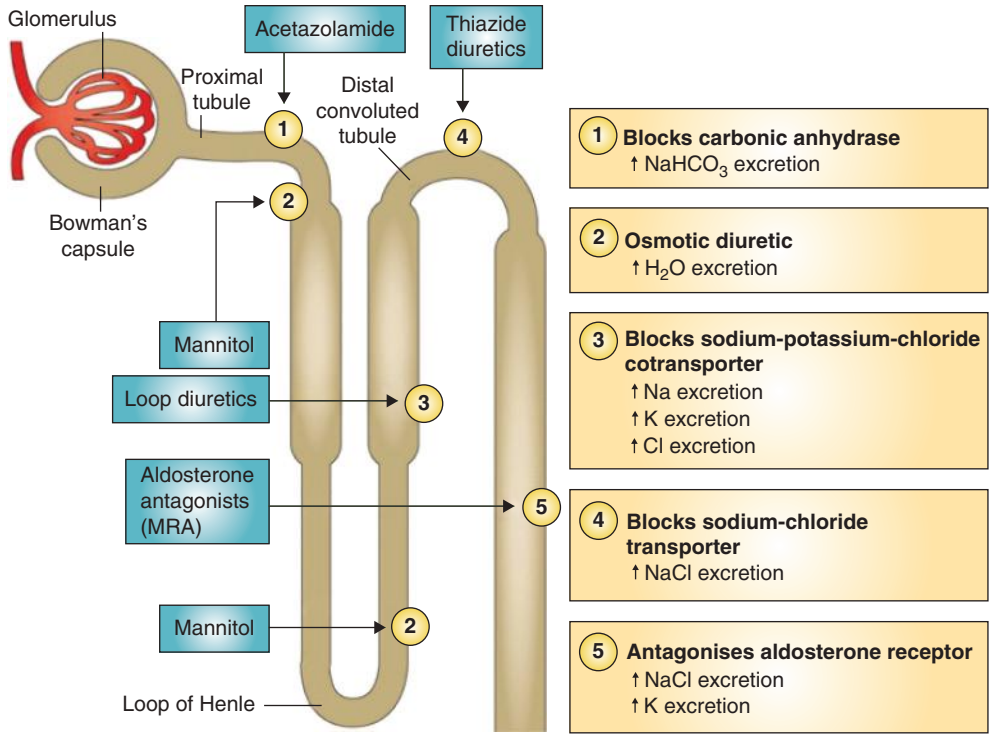

FIGURE 70–4. (1) Acetazolamide functions in the proximal tubule by blocking carbonic anhydrase and increasing $NaHCO_3$ excretion. (2) Mannitol functions in both the proximal tubule and the loop of Henle by increasing H_2O excretion. (3) Loop diuretics function in thick ascending limb of the loop of Henle by blocking the sodium-chloride-potassium cotransporter and increasing sodium, potassium, and chloride excretion. (4) Thiazide functions in the distal convoluted tubule by blocking the sodium-chloride transporter and increasing sodium chloride excretion. (5) Mineralocorticoid receptor antagonists (MRAs) function in the collecting duct of the distal tubule and antagonize the aldosterone receptor, hence increasing sodium excretion and potassium retention. Reproduced with permission from ter Maaten JM, Valente MAE, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure—pathophysiology, evaluation, and therapy. *Nat Rev Cardiol*. 2015 Mar;12(3):184-192.

TABLE 70–9. Oral Diuretics Recommended for Use in the Treatment of Chronic Heart Failure

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5-1.0 mg once or twice	10 mg	4-6 h
Furosemide	20-40 mg once or twice	600 mg	6-8 h
Torsemide	10-20 mg once	200 mg	12-16 h
Thiazide diuretics			
Chlorothiazide	250-500 mg once or twice	1000 mg	6-12 h
Chlorthalidone	12.5-25.0 mg once	100 mg	24-72 h
Hydrochlorothiazide	25 mg once or twice	200 mg	6-12 h
Indapamide	2.5 mg once	5 mg	36 h
Metolazone	2.5 mg once	20 mg	12-24 h
Potassium-sparing diuretics			
Amiloride	5 mg once	20 mg	24 h
Spironolactone	12.5-25.0 mg once	50 mg[a]	1-3 h
Triamterene	50-75 mg twice	200 mg	7-9 h
Eplerenone	25 mg once	50 once	12-24 h
Sequential nephron blockade			
Metolazone	2.5-10.0 mg once plus loop diuretic	NA	NA
Hydrochlorothiazide	25-100 mg once or twice plus loop diuretic	NA	NA
Chlorothiazide (IV)	500-1000 mg once plus loop diuretic	NA	NA

[a]Higher doses may occasionally be used with close monitoring.

Abbreviations: IV, intravenous; NA, not applicable.

Reproduced with permission from Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-e239.

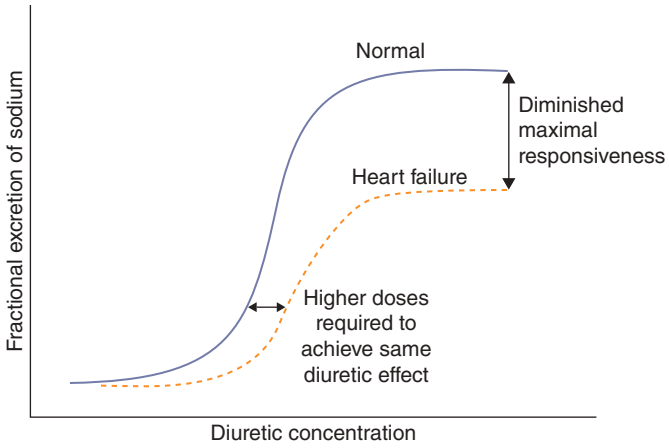

FIGURE 70–5. Schematic of dose-response curve of loop diuretics in heart failure patients compared with normal controls. In heart failure patients, higher doses are required to achieve a given diuretic effect, and the maximal effect is blunted. Reproduced with permission from Felker GM and Mentz RM. Diuretics and Ultrafiltration in Acute Decompensated Heart Failure. *J Am Coll Cardiol*. 2012 Jun 12;59(24):2145-2153.

the renin-angiotensin and sympathetic nervous systems. Chronically high amounts of sodium delivered to the distal nephron cause hypertrophy of distal convoluted tubule cells, leading to increased sodium reabsorption and negating the overall natriuretic effect of the loop diuretic. This occurs in a more pronounced manner in patients with renal insufficiency. The addition of either metolazone or chlorothiazide can also be helpful.

Finally, there is lingering concern about whether diuretics might cause some harm in heart failure (Figure 70–6).[80,81] For example, diuretics can upregulate neurohormonal activation, potentially worsening renal function, and cause electrolyte abnormalities. However, in the absence of randomized controlled data, it is difficult to separate causal association from confounding by indication.[82]

Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers

ACE inhibitors reduce the conversion of angiotensin I to angiotensin II and also upregulate bradykinin. The combination of these actions modifies adverse cardiac remodeling.[83] Several trials have shown that ACE inhibitors reduce the risk of death and hospitalization in patients with HFrEF, and ACE inhibitors are an ACC/AHA Class I recommendation for patients with current or prior symptoms of heart failure.[5] Two key randomized trials were the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and the Studies of Left Ventricular Dysfunction (SOLVD)-Treatment trial.[73,74] Both trials showed reductions in mortality, with a relative risk reduction of 27% in CONSENSUS and 16% in SOLVD-Treatment. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial randomized 3164 patients with moderate to severe heart failure to low- versus high-dose lisinopril and showed a 15% relative reduction in risk of death or hospitalization with the latter approach.[84] Furthermore, in 4228 patients with low LVEF but no symptoms of heart failure, enalapril in the SOLVD-Prevention trial showed a 20% reduction in risk of death or heart failure hospitalization.[85]

ACE inhibitors should be used with caution in patients with low systemic blood pressures, markedly elevated creatinine, bilateral

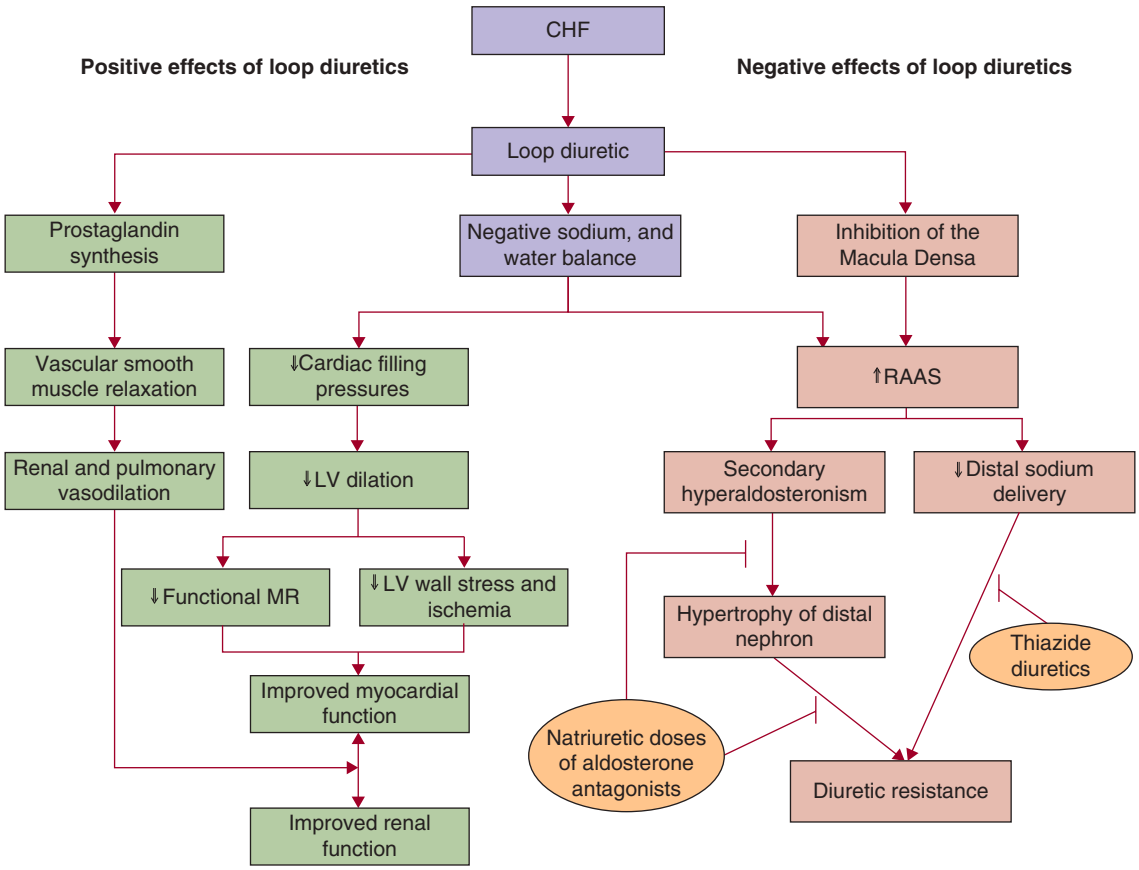

FIGURE 70–6. Proposed positive and negative effects of loop diuretics as well as sites of action for thiazide diuretics and natriuretic doses of aldosterone antagonists. CHF, congestive heart failure; LV, left ventricular; MR, mitral regurgitation; RAAS, renin-angiotensin-aldosterone system. Reproduced with permission from Felker GM and Mentz RM. Diuretics and Ultrafiltration in Acute Decompensated Heart Failure. *J Am Coll Cardiol*. 2012 Jun 12;59(24):2145-2153.[82]

renal artery stenosis, or elevated levels of serum potassium.[5] There are no differences among the various ACE inhibitors, and there is a Class I recommendation for their use (Table 70–10). Renal function and potassium should be monitored 1 to 2 weeks after initiation and at periodic time points afterward. Up to 20% of patients develop an ACE inhibitor–induced cough. In these patients and others who are intolerant of ACE inhibitors, angiotensin receptor blockers (ARBs) may provide an equally efficacious alternative.[5] These medications were developed with the rationale that much of the efficacy of ACE inhibition could be gained via blockade of the angiotensin type I receptor (AT1).[86] In several placebo-controlled studies, ARBs have been shown to yield similar long-term hemodynamic, neurohormonal, and clinical effects as those of ACE inhibition. Two key trials were the Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart Failure: Assessment of Mortality and Morbidity (CHARM)-Added trial, which randomized patients with mild to severe heart failure to placebo versus valsartan and candesartan, respectively.[87,88] Of note, the majority of patients in both trials were already on an ACE inhibitor. Treatment with an ARB improved symptoms and quality of life and reduced the risk of heart failure hospitalization. Further evidence of the sole benefit of ARB versus ACE inhibition came from the CHARM-Alternative trial that randomized ACE inhibitor–intolerant patients to placebo versus candesartan and showed a relative risk reduction of 23% for cardiovascular death and heart failure hospitalizations.[89] Other trials in acute myocardial infarction have continued to solidify the proposition that ARBs are worthy alternatives to ACE inhibitors in HFrEF.[6] Table 70–10 displays the recommended and target doses for ARBs in heart failure. Considerations for initiation of ARBs are similar to those of ACE inhibitors.

TABLE 70–10. Drugs Commonly Used for Stage C HFrEF

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
ACE inhibitors			
Captopril	6.25 mg three times	50 mg three times	122.7 mg/d
Enalapril	2.5 mg twice	10-20 mg twice	16.6 mg/d
Fosinopril	5-10 mg once	40 mg once	NA
Lisinopril	2.5-5 mg once	20-40 mg once	32.5-35.0 mg/d
Perindopril	2 mg once	8-16 mg once	NA
Quinapril	5 mg twice	20 mg twice	NA
Ramipril	1.25-2.5 mg once	10 mg once	NA
Trandolapril	1 mg once	4 mg once	NA
ARBs			
Candesartan	4-8 mg once	32 mg once	24 mg/d
Losartan	25-50 mg once	50-150 mg once	129 mg/d
Valsartan	20-40 mg twice	160 mg twice	254 mg/d
ARNI			
Sacubitril/valsartan	24/26 mg twice	97/103 mg twice	375 mg/d
I_f receptor antagonist			
Ivabradine	2.5 mg twice	7.5 mg twice	6.5 mg twice
Aldosterone antagonists			
Spironolactone	12.5-25.0 mg once	25 mg once or twice	26 mg/d
Eplerenone	25 mg once	50 mg once	42.6 mg/d
Beta-blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d
Carvedilol CR	10 mg once	80 mg once	NA
Metoprolol succinate extended release (metoprolol CR/XL)	12.5-25 mg once	200 mg once	159 mg/d
Hydralazine and isosorbide dinitrate			
Fixed-dose combination	37.5 mg hydralazine/20 mg isosorbide dinitrate three times daily	75 mg hydralazine/40 mg isosorbide dinitrate three times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate	Hydralazine: 25-50 mg three or four times daily and isosorbide dinitrate 20 to 30 mg three or four times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	NA

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CR, controlled release; HFrEF, heart failure with reduced ejection fraction; NA, not applicable.
Reproduced with permission from Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-e239.

β-Blockers

The use of β-blocker therapy was once considered counterintuitive in heart failure.[72,90] That belief was overturned by three landmark key clinical trials—Cardiac Insufficiency Bisoprolol Study II (CIBIS II), Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)—that randomized more than 9000 patients with mild to severe HFrEF to a β-blocker (bisoprolol, carvedilol, and metoprolol, respectively) or placebo.[91-93] In these trials, more than 90% of patients were on an ACE inhibitor or ARB. Each of these trials showed a significant reduction in risk of both mortality (including sudden cardiac death) and hospitalization by approximately 30%. Another randomized controlled trial, the Carvedilol or Metoprolol European Trial (COMET), showed that carvedilol increased survival compared with short-acting metoprolol.[94] It is now felt that β-blockers act by obstructing deleterious long-term effects of sustained sympathetic system activation in heart failure.

β-Blockers should be initiated in all stable heart failure patients except those who have a clear contraindication to their use. Types of β-blockers and target doses are shown in Table 70–10; the ones that have been shown to be efficacious in heart failure are bisoprolol and metoprolol succinate (β_1-antagonists) and carvedilol (α_1-, β_1-, and β_2-antagonists). They must be used cautiously in patients with recent decompensations. If a patient is admitted with acute heart failure, β-blockers can be continued, but in the setting of worsening clinical status, the dose should be lowered or the drug should be discontinued. Clinicians should attempt to achieve target doses suggested by clinical trials. Abrupt withdrawal can lead to clinical decompensation. Adverse effects such as hypotension and bradycardia might necessitate lowering dose or discontinuation; however, symptoms of fatigue or volume overload can be managed without medication discontinuation.

Mineralocorticoid Receptor Antagonists

Aldosterone is synthesized by the adrenal glands to preserve intravascular sodium, potassium, and water homeostasis. Aldosterone binds to mineralocorticoid receptors in the kidney, colon, and sweat glands and induces sodium reabsorption with concomitant potassium excretion. In heart failure, aldosterone levels increase as a response to perceived reductions in intravascular volume and cause several unfavorable effects including adverse remodeling of the heart.[95]

Two aldosterone receptor antagonists, spironolactone and eplerenone, block these deleterious effects and have been shown to have significant morbidity and mortality benefits in symptomatic heart failure. The Randomized Aldactone Evaluation Study (RALES) enrolled 1663 patients with severe heart failure (NYHA class III-IV) and LV systolic dysfunction to receive either spironolactone or placebo in combination with ACE inhibition and diuretics.[96] Only 11% of the patients were on β-blockers. Spironolactone led to a relative risk reduction in death of 30% and in heart failure hospitalization of 35%. The Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) trial randomized 2737 patients with NYHA class II symptoms and LVEF ≤ 30% (≤ 35% if QRS ≥ 130 milliseconds).[97] Treatment with eplerenone led to a relative risk reduction of 37% in cardiovascular death or heart failure hospitalization. The Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial enrolled 6632 patients with LV systolic dysfunction (LVEF ≤ 40%) within 2 weeks following an acute myocardial infarction and showed a 15% reduction in risk of all-cause mortality with eplerenone treatment.[98] Importantly, the majority of patients in both EPHESUS trials were on β-blockers and ACE inhibitors/ARBs.

It is recommended that spironolactone or eplerenone be used in all patients with HFrEF who are already on an ACE inhibitor (or ARB) and β-blocker but have suboptimal response to therapy and still have NYHA class II symptoms.[5,6] Table 70–10 shows the recommended target doses. The biggest concern is hyperkalemia, and therefore, these medications should not be used in patients with an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (serum creatinine of approximately 2.5 mg/dL in men and 2.0 mg/dL in women) and/or potassium > 5 mEq/L. Those with marginal renal function (glomerular filtration rate 30-50 mL/min/1.73 m^2) need every-other-day dosing. Even in the absence of these findings, patients on these medications require rigorous monitoring of their renal function and serum potassium levels. Patients should be advised to eat foods low in potassium and be taken off potassium supplementation. Men on spironolactone can experience gynecomastia or breast pain (~10%), in which case, they should be switched to eplerenone, because the major difference between the medications is selectivity of aldosterone receptor antagonism.

Hydralazine and Isosorbide Dinitrate

The effect of long-acting nitrates plus hydralazine on survival was evaluated in the First Veterans Heart Failure Trial (V-HeFT-I),[99] in which 642 men with mild to moderate heart failure were randomized to receive placebo, prazosin, or the combination of isosorbide dinitrate plus hydralazine. Compared with placebo, the mortality risk reduction in the group treated with isosorbide dinitrate plus hydralazine was 36% by 3 years. In contrast, the mortality in the prazosin group was the same as that seen in the placebo-treated patients. The V-HeFT-II trial published in 1991 directly compared the combination of isosorbide dinitrate plus hydralazine with enalapril in patients with predominantly NYHA class II or III heart failure.[100] Overall, 804 men were randomized to one of these two regimens for an average of 2.5 years. The study demonstrated the superiority of the ACE inhibitor in reducing cumulative mortality. The African American Heart Failure Trial (A-HeFT) tested the hypothesis that a fixed-dose combination of isosorbide dinitrate and hydralazine (BiDil) could improve outcomes in African Americans with systolic heart failure. In A-HeFT, 1050 African American patients with NYHA class III or IV heart failure were randomized to the fixed-dose combination or placebo. BiDil significantly improved the primary end point, a composite response including morbidity, mortality, and quality of life. Most impressively, a 43% reduction in all-cause mortality was seen in the treatment group. The results of this study led the US FDA to approve BiDil for African American patients with NYHA class III or IV heart failure and reduced ejection fraction.

Clinicians can use the combination of hydralazine and isosorbide dinitrate for African American patients with HFrEF who remain symptomatic while on ACE inhibitors, β-blockers, and aldosterone antagonists. These therapies are not a substitute for ACE inhibitors or ARBs but may be used in those who are intolerant of these medications and in non–African American patients as well (see Table 70–10). These therapies may not be well tolerated due to need for frequent dosing and numerous adverse reactions such as headache, dizziness, and gastrointestinal complaints.[101]

Digoxin

Digitalis has been used to treat heart failure for more than 200 years. The most commonly used preparation is digoxin.[102] Its mechanism of action is via inhibition of the Na-K-ATPase pump in myocardial cells, augmenting intracellular calcium, thus increasing inotropy. Digitalis also has an antiadrenergic effect and upregulates parasympathetic tone.[103] In the Digitalis Investigation Group (DIG) trial,[104] 6800 patients with LVEF ≤ 45% and NYHA class II to IV symptoms were randomized

to 0.25 mg of digoxin versus placebo. The patient population was on concomitant diuretics (82%) and ACE inhibitors (95%). Treatment with digoxin did not reduce all-cause or heart failure mortality but led to a 28% reduction in heart failure admissions. Digoxin was associated with a trend toward an increased incidence of sudden (presumed arrhythmic) death. A post hoc analysis showed a relationship between mortality and plasma digoxin concentration, with a serum concentration > 1 ng/mL associated with increased risk. Clinical improvements have been supported by smaller trials that suggest a role for digoxin in the improvement or prevention of clinical deterioration.[105,106]

Clinicians can consider adding digoxin if patients have persistent symptoms on guideline-recommended therapy. Generally, therapy is started at 0.125 to 0.25 mg/d, with lower or every-other-day dosing in patients with impaired renal function, elderly patients, or frail patients. Serum levels of 0.5 to 0.9 ng/mL should be targeted. The major side effects are arrhythmias (ectopic and reentry rhythms and heart block), gastrointestinal symptoms (anorexia, nausea, and vomiting), and neurologic symptoms (visual disturbances, disorientation, and confusion). Toxicity generally occurs at serum levels of > 2 ng/mL but may be potentiated at lower levels in the presence of hypokalemia, hypomagnesemia, and hypothyroidism. Several medications interact with digoxin, and interactions should be considered prior to initiation.

LCZ696 (Sacubitril and Valsartan)

A first-in-class of drug that involves dual inhibition of neprilysin and the angiotensin II receptor (angiotensin receptor-neprilysin inhibitor [ARNI]; LCZ696) was approved for use in HFrEF and NYHA class II to IV heart failure based on a trial that randomized 8442 patients to LCZ696 versus enalapril (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction [PARADIGM-HF] trial).[107] The trial was stopped early due to significant reductions in the primary end point after a median duration of follow-up of 27 months. LCZ696 reduced the primary composite end point of cardiovascular death or heart failure hospitalization by 20%. Similar results were observed for cardiovascular death, hospitalization, and all-cause mortality. Hypotension was more common in patients receiving LCZ696, although discontinuation because of hypotension was similar in both arms of the study. Elevations in serum creatinine and potassium and cough were less frequent in those assigned to LCZ696.

LCZ696 is composed of the ARB valsartan and the neprilysin inhibitor sacubitril. Valsartan blocks the AT1 receptor. Sacubitril is converted to the active neprilysin inhibitor LBQ657, which inhibits neprilysin, an enzyme that breaks down atrial natriuretic peptide, BNP, and C-type natriuretic peptide, as well as other vasoactive substances (Fig. 70–7). NT-proBNP is not a substrate for neprilysin and more appropriately reflects heart failure condition among patients on this therapy. The combined beneficial effects of ARBs in heart failure along with the natriuretic, vasodilatory, antisympathetic, and anti–adverse remodeling effects of natriuretic peptides likely account for the benefit with this agent.

Ivabradine

Ivabradine involves inhibition of the I_f node. It slows down the sinus node rate in patients who are in sinus rhythm. It is approved for stable patients with HFrEF who have a resting heart rate of at least 70 bpm

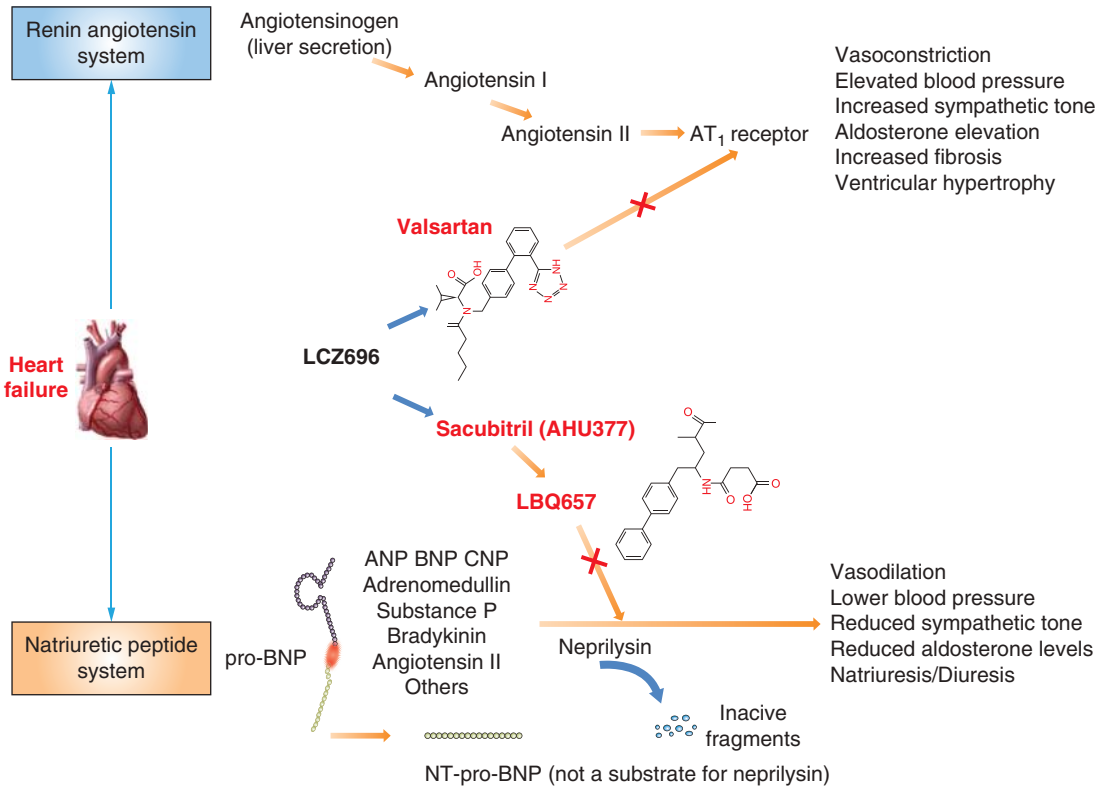

FIGURE 70–7. Schematic showing the mechanism of action of LCZ696. Heart failure stimulates both the renin-angiotensin system and the natriuretic peptide system. LCZ696 is composed of two molecular moieties, the angiotensin receptor blocker valsartan and the neprilysin inhibitor prodrug sacubitril (AHU377). Valsartan blocks the angiotensin type I (AT_1) receptor. Sacubitril is converted enzymatically to the active neprilysin inhibitor LBQ657, which inhibits neprilysin, an enzyme that breaks down the breakdown of atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), as well as other vasoactive substances. N-terminal pro-BNP (NT-proBNP) is not a substrate for neprilysin. Reproduced with permission from Vardeny O, Miller R, Solomon SD. Combined Neprilysin and Renin-Angiotensin System Inhibition for the Treatment of Heart Failure. *JACC Heart Fail*. 2014 Dec;2(6):663-670.[42]

on maximally tolerated β-blockers. The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) enrolled 6588 heart failure patients with NYHA functional class II to IV, sinus rhythm with a rate of ≥ 70 bpm, and an LVEF ≤ 35%.[108] Patients were randomized to ivabradine versus placebo, and ivabradine was associated with an 18% reduction in cardiovascular death or heart failure hospitalization. Ivabradine also improved LV function and quality of life. The major side effects were symptomatic bradycardia (5%) and visual disturbances (3%).

OTHER THERAPIES

Anticoagulation

Derangements in the clotting cascade are common in heart failure and the triad of prerequisites for thrombus formation (ie, endothelial dysfunction, hypercoagulopathy, and stasis) commonly coexist in heart failure.[109,110] Interruption of the clotting cascade to normalize its function can be a valuable therapeutic target in heart failure. However, large trials testing vitamin K antagonism in HFrEF without atrial fibrillation yielded no evidence of improvement in outcomes. The WASH (Warfarin/Aspirin Study in Heart Failure) and HELAS (Heart Failure Long-Term Anticoagulation Study) trials showed no benefit but noted an increased rate of major bleeding with warfarin.[111,112] The WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) trial (n = 1587) showed no difference in patients randomized to aspirin 162 mg versus clopidogrel 75 mg versus warfarin for the primary end point of death, myocardial infarction, or stroke.[113] The WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial enrolled 2305 patients with LVEF ≤ 35% and sinus rhythm and found no differences in the rates of the primary end point of death, ischemic stroke, or intracerebral hemorrhage for warfarin versus aspirin.[114] A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. Therefore, at this time, anticoagulants other than aspirin are recommended only for heart failure patients with atrial fibrillation.[5,6]

DEVICE-BASED THERAPIES

Three types of devices have been shown to reduce morbidity and mortality in select heart failure patients. They include implantable cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT), and left ventricular assist devices (LVADs). Chapter 73 discusses the use of LVADs in advanced heart failure.

Implantable Cardioverter-Defibrillators

Patients with HFrEF are at increased risk for ventricular arrhythmias and sudden cardiac death (SCD). Whereas therapy with neurohormonal blockade can decrease this risk of SCD, an unacceptable degree of residual risk remains. For these patients, an ICD can be life-saving. The benefits of these therapies have been evaluated in several clinical trials, both for primary and secondary prevention, leading to the current recommendations.

For primary prevention, current recommendations are largely based on three key trials: the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), and the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial.[115-117] SCD-HeFT enrolled 2521 patients with NYHA class II or III heart failure from ischemic or nonischemic etiologies and LVEF ≤ 35% and randomized them to placebo, amiodarone, or standard medical therapy. Amiodarone did not reduce mortality, but ICD was associated with a relative risk reduction of 23% over the follow-up period of approximately 5 years. The MADIT-II trial enrolled 1232 patients with ischemic cardiomyopathy and an LVEF ≤ 30% who were at least 40 days post–myocardial infarction. Follow-up was prematurely discontinued at 20 months due to a significant 31% reduction in all-cause mortality in the ICD group. The DEFINITE trial attempted to evaluate the role of primary prevention ICDs in 458 patients with a nonischemic etiology and LVEF ≤ 35%. A nonsignificant trend toward reduction in mortality was noted.

The following are Class I recommendations for ICD use in primary prevention, according to the ACC/AHA 2013 guidelines: (1) for the primary prevention of SCD to reduce mortality in patient with both ischemic and nonischemic cardiomyopathy and LVEF ≤ 35% with NYHA class II or III symptoms on guideline-recommended medical therapy for at least 3 months, and (2) for the primary prevention of SCD in patients who are at least 40 days post–myocardial infarction and with LVEF ≤ 30% and NYHA class I symptoms or more while receiving guideline-recommended medical therapy. For secondary prevention, ICDs are indicated for survivors of cardiac arrest and in patients with sustained ventricular arrhythmias, irrespective of LVEF. ICD therapy should only be offered to patients who have a reasonable expectation of survival beyond a year and lack of frailty and/or advanced comorbid conditions.

The decision to recommend an ICD is highly complex and should be approached with a high degree of contemplation, because an injudicious insertion can lead to significant suffering. Patients should be advised that the ICD is not a disease-modifying therapy, which is a common misconception. ICD shocks, whether appropriate or not, can lead to anxiety and even posttraumatic stress disorder. Patients with multiple comorbid conditions have far higher rates of device complications, and competing risks of death from noncardiac issues might blunt benefit from an ICD. There are unclear data on the benefit in patients > 75 years old and those with chronic renal disease. An ICD should not be implanted in patients with NYHA class IV symptoms who are not candidates for LVAD or cardiac transplantation. Finally, heart failure is a progressive disease, and patients with functional ICDs will eventually come to a point where the risk/benefit ratio from the device shifts to increased harm, in which case discussions with the patients and families about deactivation are challenging but obligatory.

Cardiac Resynchronization Therapy

Approximately a third of patients with HFrEF have prolongation of the QRS interval on ECG, inferring a degree of mechanical dyssynchrony of the failing heart, which is associated with worse clinical outcomes (Fig. 70–8).[118] CRT or biventricular pacing is accomplished through simultaneous pacing of both the left and the right ventricles and can lead to improvements in echocardiographic and hemodynamic parameters, functional status (average of 1-2 mL/kg/min increase in peak VO_2), and clinical outcomes (reduction in hospitalizations and all-cause mortality). CRT is recommended for patients in normal sinus rhythm with LVEF ≤ 35% and a left bundle branch block (LBBB) with QRS of ≥ 120 milliseconds. Less clarity exists for patients with non-LBBB patterns on ECG, those who are not in normal sinus rhythm, or those with wide QRS but ≤ 150 milliseconds.

Figure 70–9 presents an algorithm for the consideration of CRT in heart failure patients. Key among the studies for moderate to severe heart failure were the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization in Heart Failure Study (CARE-HF) trials, which together randomized 2333 patients with NYHA class III to ambulatory class IV symptoms, LVEF ≤ 35%, and QRS ≥ 120 milliseconds to CRT versus usual medical care.[119,120] Each of these two trials showed that CRT reduced the risk of death from any cause and hospital admission for

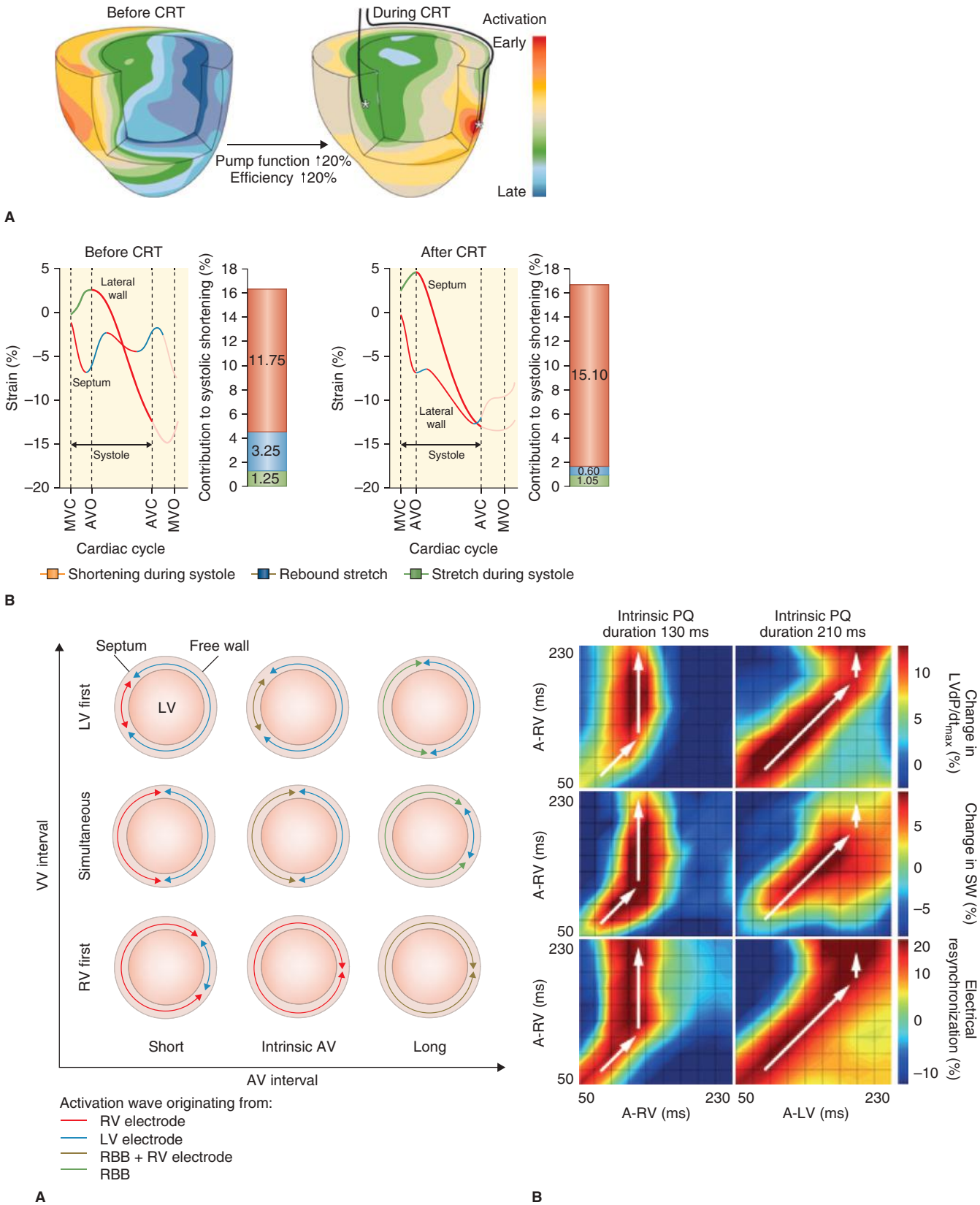

FIGURE 70–8. Three-dimensional representations of electrical activation indicate regions with early (*red*) or late (*blue*) activation. Before pacing, the electrical activation progresses slowly from the right to the left ventricle, but resynchronization is seen after biventricular pacing (*asterisks*). Myocardial strain curves are also shown (shortening indicated by negative values). Before CRT, the different strain curves in the septum and lateral wall indicate poor coordination of contraction, quantified by the sum of early systolic stretch (*green*) and rebound stretch (*blue*). After CRT, the contributions of early systolic stretch and rebound stretch to total systolic deformation are substantially reduced, which indicates improved coordination between the various regions. AV, atrioventricular; AVC, atrial valve closing; AVO, atrial valve opening; CRT, cardiac resynchronization therapy; LV, left ventricular; MVC, mitral valve closing; MVO, mitral valve opening; RBB, right bundle branch; RV, right ventricular. Reproduced with permission from Vernooy K, van Deursen CJM, Strik M, Prinzen FW. Strategies to improve cardiac resynchronization therapy. *Nat Rev Cardiol*. 2014 Aug;11(8):481-493.

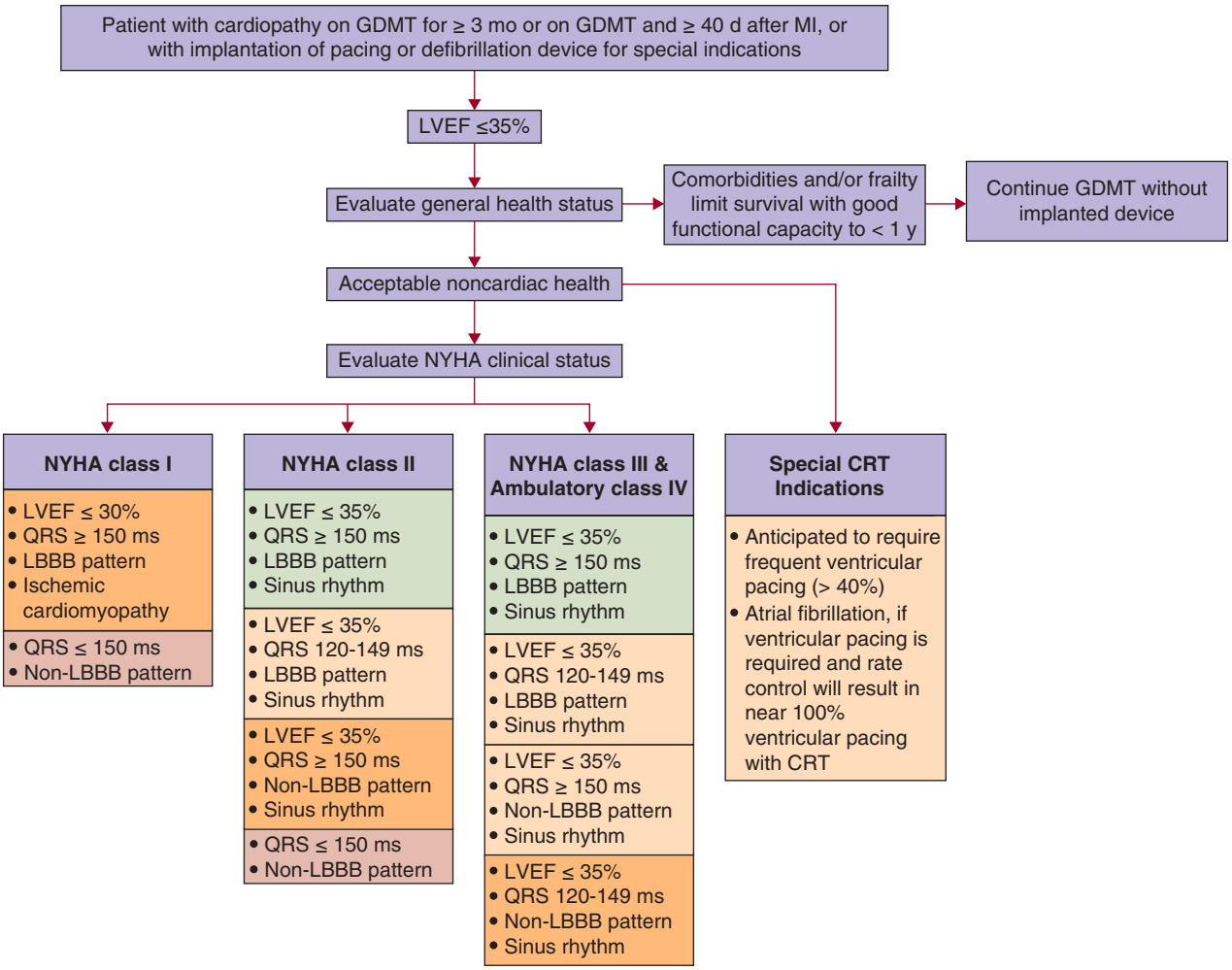

FIGURE 70–9. Indications for cardiac resynchronization therapy (CRT) algorithm. CRT-D, cardiac resynchronization therapy-defibrillator; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association. Please note that the colors in the figure correspond to the class of recommendations in the ACCF/AHA. Reproduced with permission from Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-239.

worsening heart failure (relative risk reduction for death of 24% with a CRT-pacemaker [CRT-P] and of 36% with CRT-defibrillator [CRT-D] in COMPANION and of 36% with CRT-P in CARE-HF). In CARE-HF, the relative risk reduction in HF hospitalization with CRT-P was 52%. These benefits were additional to those gained with conventional treatment, including a diuretic, digoxin, an ACE inhibitor/ARB, a β-blocker, and an aldosterone antagonist. These trials also showed an improvement in symptoms, quality of life, and ventricular function.

Two key randomized trials explored the data for CRT in 3618 patients with mild to moderate heart failure: the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) and Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT).[121,122] MADIT-CRT randomized NYHA class I (15%) and NYHA class II (85%) patients with LVEF ≤ 30%, a QRS duration ≥ 130 milliseconds, and normal sinus rhythm to optimal medical therapy plus an ICD or optimal medical therapy plus CRT-D. Each of these two trials showed that CRT reduced the risk of mortality and heart failure hospitalization by 25% to 35%. Only RAFT showed a decrease in all-cause mortality. In both studies, there was significant heterogeneity in treatment effect based on baseline QRS duration, diminishing the strength of recommendation of CRT in patients with mild heart failure to those with a QRS ≥ 150 milliseconds or ≥ 120 milliseconds plus an LBBB pattern. CRT is also indicated in heart failure patients who have an indication for conventional right ventricular pacing that alters cardiac activation in a manner similar to a native LBBB. Finally, because effective CRT requires high rates of biventricular pacing, the benefit of patients with underlying atrial fibrillation is greatest in patients who have undergone concomitant atrioventricular node ablation.[123,124]

Clinicians and their patients should have discussions about the pros and cons of CRT-D versus CRT. Similar discussions and recommendations as have been laid out for ICD apply to CRT-D. In addition, patients with CRT with or without ICD will need monitoring after device implantation for adjustment of parameters to maximize resynchronization, as is discussed in Chapter 89. The use of imaging, typically echocardiography, to adjust device parameters in an effort to reduce dyssynchrony is still the subject of research.[125,126] Potential complications include coronary sinus dissection or perforation, lead dislodgement, device infection, pneumothorax, and pocket erosion. High LV lead pacing capture thresholds can cause diaphragmatic pacing from stimulation of the phrenic nerve that runs parallel to the lateral LV free wall.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Approximately half of people with heart failure have HFpEF. The prevalence of HFpEF relative to HFrEF is growing by 10% per decade,[127] and the hospitalizations caused by HFpEF continue to increase at a high rate.[128] The increasing HFpEF epidemic is related to increasing rates of common comorbidities that are believed to drive the pathophysiology, including obesity, hypertension, and metabolic syndrome, along with aging of the population.[127-133] In striking contrast to HFrEF where numerous drugs and devices improve outcomes, there is no proven effective treatment that prolongs life in HFpEF.[134] The lack of efficacy of these therapies underscores the fundamental differences between these two phenotypically distinct forms of heart failure,[135,136] as well as our incomplete understanding of the pathophysiology.[137]

SIMILARITIES AND DIFFERENCES BETWEEN HEART FAILURE WITH PRESERVED EJECTION FRACTION AND HEART FAILURE WITH REDUCED EJECTION FRACTION

The traditional cutoff for defining HFpEF has been an ejection fraction of > 50% in the presence of clinical heart failure.[130] Patients with heart failure and an ejection fraction < 40% are defined as having HFrEF.[134] Patients with an ejection fraction from 40% to 50% have a borderline decrease in ejection fraction, which has been variably classified as either HFpEF or HFrEF in clinical trials, although emerging evidence supports the idea that this group is more accurately classified as HFrEF.[138-141] Although it should be obvious that the dichotomization of heart failure patients according to ejection fraction alone is arbitrary and flawed,[142,143] this method is unlikely to be replaced given the widespread use of echocardiography and the well-characterized risk factor profile, pathophysiology, and outcomes in the two heart failure phenotypes as defined according to this nosology.[130,137,141]

There are a number of key differences between HFpEF and HFrEF (Table 70–11), the most obvious of which is ventricular dilatation in HFrEF.[144] Eccentric LV remodeling in HFrEF increases wall stress, resulting in greater natriuretic peptide release.[145] As such, BNP or NT-proBNP levels are typically much lower in people with HFpEF, and among stable outpatients, they are often normal.[146,147] There are also important microscopic differences, including increased cardiomyocyte diameter, higher myofibrillar density, and increased cardiomyocyte stiffness in HFpEF as compared to HFrEF.[144] Patients with HFrEF have depressed contractility. Patients with HFpEF have stiffer ventricles and vasculature, which leads to much greater blood pressure lability with changes in loading associated with dietary indiscretion or physical exercise (Fig. 70–10).[135,148,149] Whereas vasodilator therapies are pushed aggressively in HFrEF despite low arterial pressure, it is unclear whether this practice is beneficial or even could be harmful in HFpEF.[135]

Despite the many differences in ventricular structure and function in HFpEF and HFrEF, there are many similarities. Hemodynamic derangements including elevation in filling pressures, pulmonary hypertension, and impaired cardiac output reserve are common to both, as are symptoms of severe exercise intolerance resulting in reduced aerobic capacity and poor quality of life.[135,150,151]

TABLE 70–11. Key Differences Between HFpEF and HFrEF

	HFrEF	HFpEF
Typical demographics	Any age, male > female	Older age, female > male
LV size	Dilated	Normal cavity size
LV systolic dysfunction	Severely depressed	Mildly depressed
LV diastolic dysfunction	May be severely impaired	Severely impaired
Pulmonary hypertension	Common (~80%)	Common (~80%)
BNP levels	Usually elevated, but can be normal	Lower, often normal
Exercise capacity	Severely impaired	Severely impaired
Response to therapy	Modest BP effect from vasodilators Multiple effective treatments	Marked BP reduction from vasodilators No effective medical treatment

Abbreviations: BNP, B-type natriuretic peptide; BP, blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular.

EPIDEMIOLOGY

The relative prevalence of HFpEF increased from 38% to 54% of all heart failure cases in Olmsted County, Minnesota, between 1987 and 2001.[127] This increase is likely related in part to increased recognition of the syndrome, but it also coincides with rising rates of comorbidities that are associated with the pathogenesis, including hypertension, obesity, atrial fibrillation, and diabetes.[133,152] A recent analysis of US data showed that among incident heart failure cases between 2005 and 2008, 52% of patients had HFpEF, 33% had HFrEF, and 16% had borderline systolic dysfunction (ejection fraction of 40%-50%).[131]

Comorbidities are common to both HFpEF and HFrEF, but patients with HFpEF are generally older, more hypertensive, obese, diabetic, and more likely to display atrial fibrillation.[137,153-156] Although comorbidities influence ventricular-vascular structure and function in HFpEF, fundamental disease-specific changes drive the disorder, indicating that HFpEF is not merely an amalgamation of comorbidities.[157] Furthermore, morbidity and mortality in patients with HFpEF greatly exceed what is observed in patients with the same comorbid conditions but who do not manifest heart failure.[158]

Risk factors for HFpEF are well established and include hypertension, older age, diastolic dysfunction, kidney disease, anemia, and diabetes.[159-161] LV diastolic compliance deteriorates as part of normal aging,[162,163] even in community-dwelling volunteers free of cardiovascular disease.[164] Age-related effects appear to accelerate in the presence of obesity.[164-166] Sedentary lifestyle is an independent risk factor for HFpEF, and increasing leisure time activity reduces that risk in a dose-dependent fashion.[167,168] Poor fitness is also associated with concentric ventricular remodeling and diastolic dysfunction,[169] which are common precursors of HFpEF. Prior myocardial infarction is more common in HFrEF than HFpEF,[170] but recent data have shown that coronary artery disease is common in HFpEF and associated with adverse outcome, independent of other predictors (Fig. 70–11).[171] Decreases in myocardial microvascular density are also present in HFpEF and may contribute to ischemia.[172]

Hospitalization and rehospitalization risk is similar in HFpEF and HFrEF.[153,154] Although some community-based studies have reported similar mortality in HFpEF and HFrEF,[127,173] others have reported better outcomes in HFpEF.[174] While mode of death is largely cardiovascular in HFpEF patients enrolled in trials,[175] noncardiovascular causes of death are common in HFpEF patients seen in the community.[176,177]

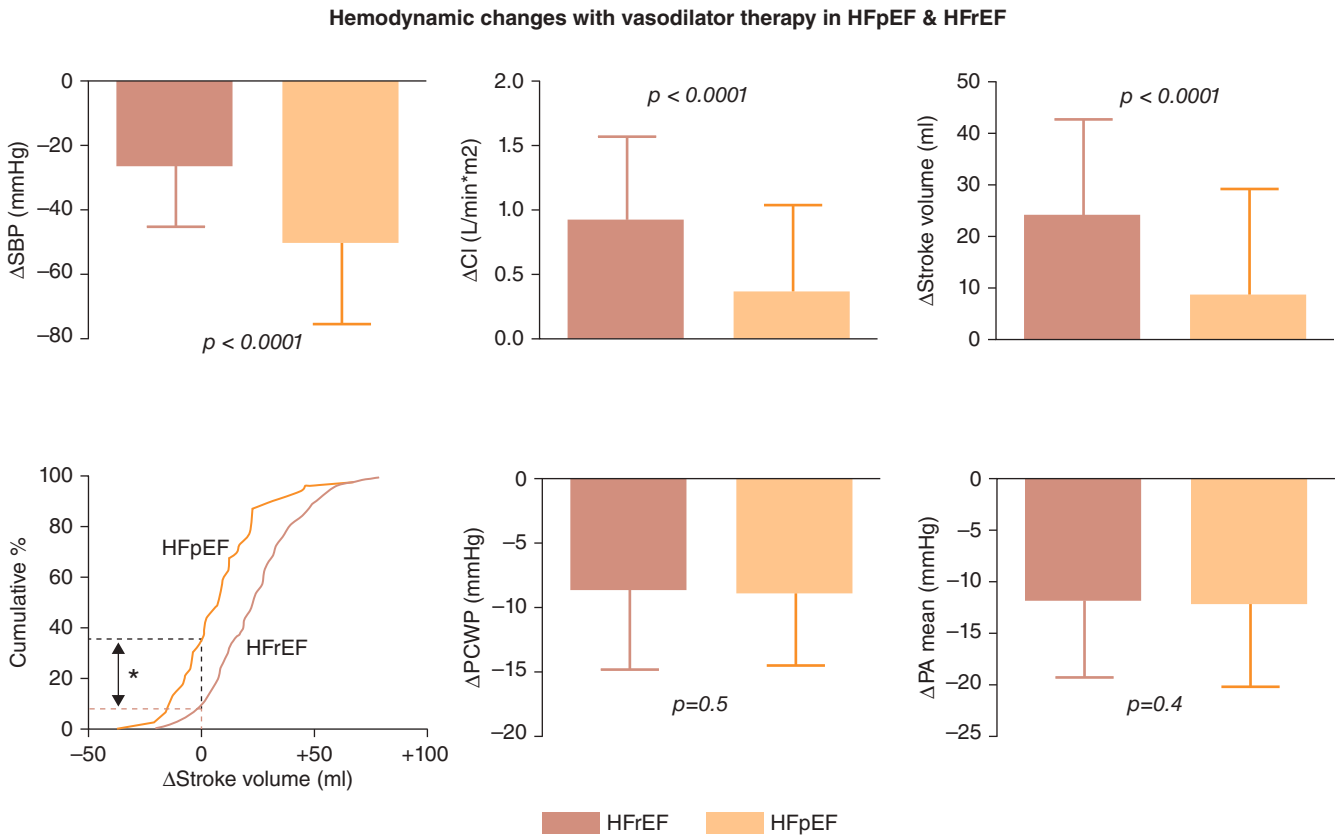

FIGURE 70–10. As compared to patients with heart failure with reduced ejection fraction (HFrEF), patients with heart failure with preserved ejection fraction (HFpEF) display greater reductions in systolic blood pressure (SBP), less improvement in cardiac index (CI) and stroke volume (SV), but similar reductions in pulmonary capillary wedge pressure (PCWP) and pulmonary artery (PA) pressure with nitroprusside. Despite the presence of high PCWP, patients with HFpEF are four-fold more likely to display a decrease in forward SV with nitroprusside ($P < .001$, *asterisk*), indicating greater vulnerability to preload reduction as compared to HFrEF patients. Reproduced with permission from Schwartzenberg, S. et al. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol*. 2012 Jan 31;59(5):442-451.[135]

PATHOPHYSIOLOGY

Diastolic dysfunction was formerly considered to be the sole pathophysiologic driver in HFpEF, but recent studies have shown far more complex abnormalities in LV systolic function, right heart function, the vasculature, endothelium, and periphery (including skeletal muscle) in HFpEF (Fig. 70–12).[178]

Left Ventricular Dysfunction

Elevated diastolic filling pressures at rest or with exercise are uniformly present in HFpEF (Fig. 70–13).[146,179] It is important not to equate diastolic dysfunction with HFpEF, as the former is quite prevalent in the general population and is essentially part of normal aging.[164,180] While echocardiographic indices have been established to estimate filling pressures as well as intrinsic chamber stiffness and compliance of the ventricle, these measures have greater variability than invasive assessments.[181-183] Indeed, echocardiography does not reveal substantial diastolic dysfunction at rest in up to a third of HFpEF patients.[184-186] On the other hand, invasive studies have generally shown diastolic abnormalities to be universal in patients with HFpEF, although in patients with earlier stages of disease, provocative maneuvers such as exercise or saline loading are required to elicit the pathologic changes.[146,179,187-193]

The normal enhancement of LV relaxation with increasing heart rates is lost in HFpEF, and this along with abnormalities in chamber compliance may lead to exercise-induced pulmonary venous hypertension and exercise intolerance.[179,194,195] Patients with progressively greater elevation in filling pressures have more advanced HFpEF as evidenced by greater multisystem reserve limitation and increased risk of death.[196,197]

Although the ejection fraction is normal or near-normal in HFpEF, LV systolic function is impaired, as shown using tissue Doppler imaging,[198,199] myocardial strain imaging,[200,201] and load-independent indices of chamber and myocardial contractility.[149] Patients with more profound impairments in systolic function and deformation display increased risk of death.[149,201] This may be related to abnormalities in

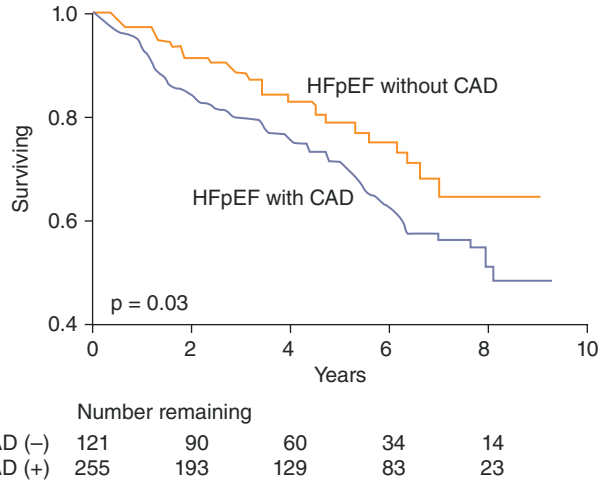

FIGURE 70–11. As compared to heart failure with preserved ejection fraction (HFpEF) patients with no coronary artery disease (CAD), patients with CAD dispay increased risk of death, independent of other predictors of outcome. Reproduced with permission from Hwang, S. J., Melenovsky, V. & Borlaug, B. A. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014 Jul 1;63(25 Pt A):2817-2827.[171]

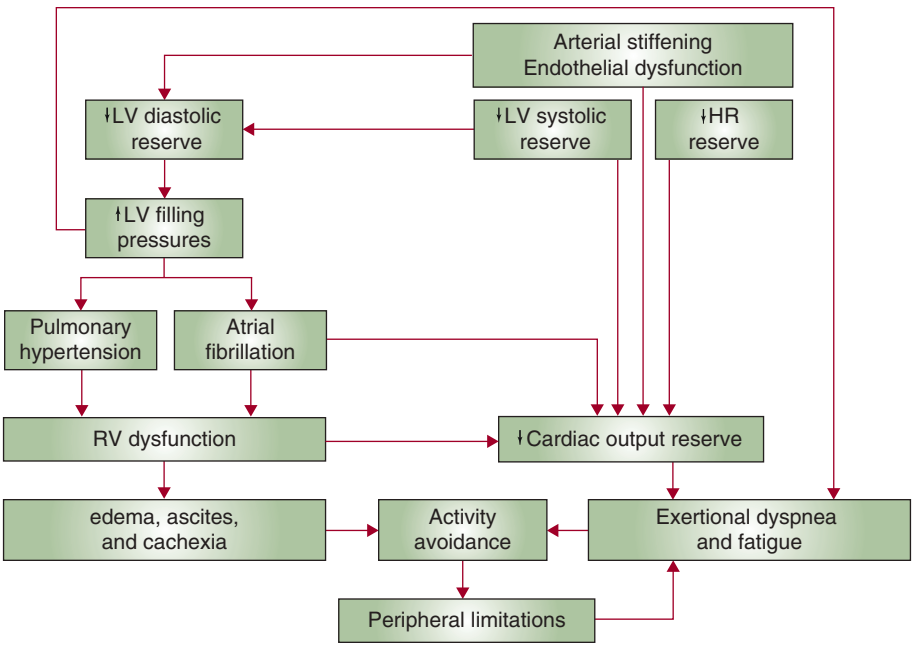

FIGURE 70–12. The pathophysiology of heart failure with preserved ejection fraction (HFpEF) is complex and highly interrelated, involving abnormalities in left ventricular (LV) systolic and diastolic reserve, arterial stiffening, endothelial dysfunction, chronotropic incompetence manifest by decreased heart rate (HR) reserve, and pulmonary hypertension and atrial fibrillation leading to right ventricular (RV) dysfunction. These abnormalities lead to hemodynamic perturbations developing in HFpEF (high filling pressures, cardiac output reserve limitations) that together with abnormalities in the periphery (skeletal muscle) produce typical symptoms including ascites, edema, and exercise intolerance. This leads to activity avoidance and worsening of muscle conditioning and additional peripheral limitations. Reproduced with permission from Borlaug, B. A. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014 Sep;11(9):507-515.[178]

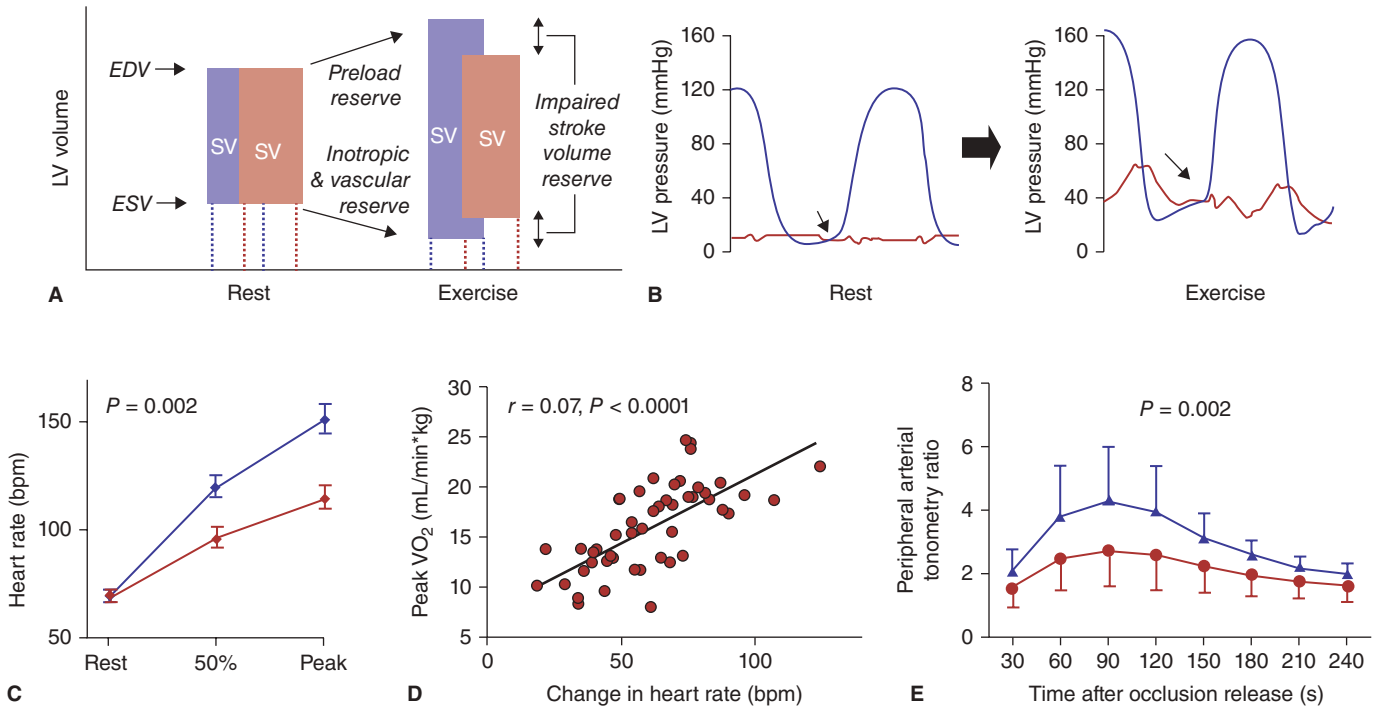

FIGURE 70–13. As compared to healthy individuals (*blue*), patients with heart failure with preserved ejection fraction (HFpEF; *red*) display less ability to increase left ventricular (LV) end-diastolic volume (EDV) and to decrease end-systolic volume (ESV), which leads to an impaired stroke volume (SV) response to exercise. Patients with HFpEF frequently present with normal LV filling pressures at rest (*arrow*, upper middle panel) that become very elevated during exercise (*arrow*, upper right panel). Compared to controls (*blue*), HFpEF patients (*red*) display blunted increases in heart rate that are correlated with poorer exercise capacity (peak oxygen consumption [VO_2]). The normal increase in peripheral blood flow with upper arm cuff occlusion related to endothelium-dependent vasodilation is also reduced in HFpEF patients as compared to age-matched controls (bottom right). Data from Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;117:2051-2060; Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2010;56:845-854.[15]

calcium handling,[202] β-adrenergic signaling,[203,204] myocardial energetics,[205,206] or tissue perfusion reserve.[171,172]

While systolic function at rest is only modestly impaired, a number of studies have also identified dramatic limitations in systolic reserve with stress that importantly contribute to decline in peak cardiac output and exercise intolerance in HFpEF (Fig. 70–12).[188,189,196,199,205,207-209] Systolic reserve limitations beget diastolic limitations, because inability to contract to a smaller LV end-systolic volume in HFpEF limits the amount of elastic recoil favoring diastolic suction of blood from left atrium to ventricle during the following diastole.[189,204,207,209]

Pulmonary Hypertension and Right Ventricular Dysfunction

Pulmonary hypertension (PH) has been reported to be present in over three-fourths of patients with HFpEF in some studies, initially developing as a form of "passive" PH related to elevated pulmonary capillary wedge pressure (PCWP).[150,210] Chronic elevations in PCWP induce pulmonary arteriolar and venous remodeling, resulting in increased pulmonary vascular resistance.[150,211] The presence and severity of PH in HFpEF are independently associated with increased mortality and represent a potential target for treatment.[210,212]

Depending on how it is defined, RV dysfunction is present in roughly one-third of patients with HFpEF.[213,214] Patients with RV dysfunction typically display more advanced heart failure, renal dysfunction, atrial fibrillation, tricuspid regurgitation, and LV dysfunction. The presence of right ventricular dilatation and dysfunction in HFpEF predicts increased risk of death, independent of the severity of PH and other covariates.[213-215]

Chronotropic Incompetence

Heart rate is the major determinant of cardiac output augmentation with exercise as opposed to stroke volume, with an increase of 200% to 400% at peak exercise.[216,217] Most studies in HFpEF have demonstrated chronotropic incompetence in the majority of studied pati ents.[188,189,207,208,218-220] This appears to be mediated more by reduced adrenergic sensitivity than decreased sympathetic outflow, since catecholamine levels increase similarly in patients with HFpEF and controls despite marked differences in chronotropic reserve.[208] There is additional evidence for autonomic dysregulation in HFpEF. Three studies have shown that the normal decrease in heart rate following exercise is blunted, and one study has observed that arterial baroreflex sensitivity is depressed in HFpEF.[207,208,220] Reduction in heart rate was recently shown to decrease exercise capacity in patients with HFpEF in a small trial.[221]

Peripheral Abnormalities

According to the Fick principle, decreased peak oxygen (O_2) consumption (VO_2) can be related to limitations in cardiac output reserve, limitations in arterial-venous O_2 content difference, or both.[178] The latter is related to how effectively O_2 is distributed, extracted, and used in the skeletal muscles during exercise.[222] Abnormalities in cardiac output reserve are clearly present in HFpEF.[188,189,191,207,208,223,224] Recent research has also identified abnormalities in peripheral O_2 extraction and utilization in a significant subset of patients with HFpEF.[192,225,226] The mechanism of inadequate peripheral utilization of O_2 may be related to impaired muscle O_2 extraction, impaired autonomic regulation of blood flow, or problems with macro- or microvascular perfusion to the muscular bed. Recent studies examining histopathologic changes in both skeletal and cardiac muscle have revealed that vascular rarefaction may be present in HFpEF patients, potentially contributing to impaired nutritive blood flow in the heart and periphery.[172,227-229] Exercise training, which improves aerobic capacity and quality of life in HFpEF,[230,231] appears to work mainly through beneficial effects in the periphery in people with HFpEF,[232] although one study did observe evidence of direct cardiac effects.[233]

Endothelial Dysfunction

Impaired flow-mediated vasodilation, a marker of abnormal endothelial function, has been observed in HFpEF, and the degree of dysfunction has been correlated with severity of symptoms, exercise impairment, pulmonary vascular disease, and risk of heart failure hospitalization.[207,234-236] However, not all studies in HFpEF have observed abnormal endothelial function, at least when examined in larger conduit vessels.[237-239] Nonetheless, there is substantial evidence that endothelial dysfunction plays a central role in the pathophysiology in a number of patients,[240] and numerous clinical trials have been or are being performed targeting this pathway, as discussed later.[223,241-246]

DIAGNOSIS

A patient with a low ejection fraction who is short of breath can be confidently diagnosed with an echocardiogram. In contrast, patients with a normal ejection fraction who are short of breath may have HFpEF, a non-HFpEF cardiac cause of symptoms (eg, valvular heart disease), or a noncardiac etiology. These patients often require a much more thoughtful evaluation to demonstrate objective evidence of elevated filling pressures and/or inadequate cardiac output. This is further complicated by the presence of early HFpEF where there may not be clinically detectable signs of congestion at rest, but there is marked elevation of filling pressures with exercise.[146]

The clinical diagnosis of HFpEF can be confidently performed at the bedside purely by physical examination and history, provided that the patient has demonstrable evidence of elevated filling pressures at rest and is in decompensated heart failure. Once a clinical diagnosis of heart failure is made in a patient with normal ejection fraction (≥ 50%), it is important to exclude alternative etiologies, such as pericardial or valvular disease, that would be treated differently.[247]

Elevated natriuretic peptide levels are strongly supportive of the diagnosis of HFpEF with a normal ejection fraction and have prognostic value.[134] However, it is important to remember that BNP levels are lower in obesity and that elevated BNP levels can occur with atrial fibrillation (even in the absence of heart failure), renal failure, or right ventricular strain from primary pulmonary arterial hypertension or pulmonary emboli. Importantly, a normal BNP (or NT-proBNP) level does not exclude the diagnosis of HFpEF.[146,147]

Echocardiography is essential in the evaluation of patients suspected of having HFpEF. Beyond measurement of ejection fraction, echocardiography provides assessment of LV diastolic function,[215,248] LV filling pressures (high E/e′ ratio),[249] systolic function and LV strain,[200,201] left atrial remodeling,[250,251] structural remodeling such as concentric LV hypertrophy, inferior vena caval dilatation (an assessment of right atrial pressure),[251,252] elevation in right ventricular systolic pressures (to estimate pulmonary artery pressure), and qualitative or quantitative impairments in right ventricular function.[210,213,214] In the proper clinical setting, identification of one or more of these echocardiographic abnormalities is highly supportive of the diagnosis of HFpEF (Table 70–12).

The gold standard diagnostic test remains direct measurement of intracardiac pressures by right and left heart catheterization.[253,254] Determination of filling pressures at rest may be inadequate if patients are euvolemic or if symptoms occur only with exercise.[146,188] In these situations, right heart catheterization with exercise stress should be considered. The presence of an elevated mean PCWP (≥ 15 mm Hg at rest or ≥ 25 mm Hg with exercise) is diagnostic of HFpEF.[130,146,188,191,192]

TABLE 70–12. Typical Findings in HFpEF

Symptoms	Exertional dyspnea and fatigue most common
Comorbid conditions	Hypertension (in 80%-90%), obesity (in 50%-60%), metabolic syndrome (prevalence not reported) or diabetes (in 30%-40%), coronary artery disease (in 50%-65%)
Examination	Ranges from normal to jugular venous distention, edema, and gallop sounds
Chest radiography	Ranges from clear to pulmonary edema
Plasma NP levels	Often normal, elevated values increase likelihood of HFpEF
Echocardiography	High E/e′ ratio High Doppler-estimated PA systolic pressure Increased left atrial volume Dilation of the inferior vena cava Increased LV relative wall thickness or hypertrophy
Invasive hemodynamics	High pulmonary capillary wedge pressure at rest (≥ 15 mm Hg) or during exercise (≥ 25 mm Hg)

Abbreviations: HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; NP, natriuretic peptide; PA, pulmonary artery.

TREATMENT

There is no proven effective treatment that improves mortality in HFpEF (Fig. 70–14). Current practice guidelines recommend control of volume overload with diuretics and management of comorbidities.[134] Although treatment of arterial hypertension clearly reduces the risk of incident HF,[255,256] prior trials testing antihypertensive agents in HFpEF have not been associated with improved outcomes,[257-259] and at this point, there is no clear answer as to which agents to use to treat hypertension or how aggressively to treat blood pressure in HFpEF. Recent studies have emphasized the importance of lifestyle interventions such as exercise and weight loss, which improve exercise capacity and quality of life.[231,260,261]

Diuretics

Diuretics decrease filling pressures to effectively treat acute decompensated heart failure, regardless of etiology, and are recommended to control fluid overload.[6,134] The CHAMPION trial has provided strong evidence supporting the treatment of elevated filling pressures in order to prevent fluid accumulation and decompensation of heart failure, including HFpEF.[262,263] In this trial, patients with recent heart failure hospitalization and NYHA class III symptoms underwent implantation of a pulmonary artery pressure monitor and were randomized to care based on investigator knowledge of invasive pressures versus standard care. The trial showed a significant reduction in heart failure hospitalizations overall and in ancillary analysis restricted to patients with HFpEF. The number needed to treat to prevent one HFpEF hospitalization over 18 months was 2. Although this was not a trial of diuretics per se, the vast majority of medication changes based on invasive pressure data were changes in diuretic dosing, and these data certainly reinforce the importance of control of congestion with diuretics in people with HFpEF. These data also reveal a new role for implantable hemodynamic monitors to help manage patients with advanced (NYHA class III) HFpEF with recent heart failure hospitalization.[262,263]

Renin-Angiotensin-Aldosterone System Inhibition

Three large, placebo-controlled, randomized trials testing ACE inhibitors and ARBs in HFpEF have been conducted to date.[257-259] There was a nonsignificant reduction in the composite outcome of cardiovascular death or heart failure hospitalizations with candesartan in the CHARM-Preserved study.[257] This trial defined HFpEF using an ejection fraction partition value of 40% and included more men and patients with coronary disease than are generally seen in HFpEF, suggesting that many of the participants had a phenotype resembling HFrEF. The larger Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) trial comparing irbesartan to placebo in a more typical HFpEF patient population was unequivocally neutral, overall and across all of the prespecified secondary analyses presented.[259] The Perindopril in Elderly People With Chronic Heart Failure (PEP-CHF) trial randomized older

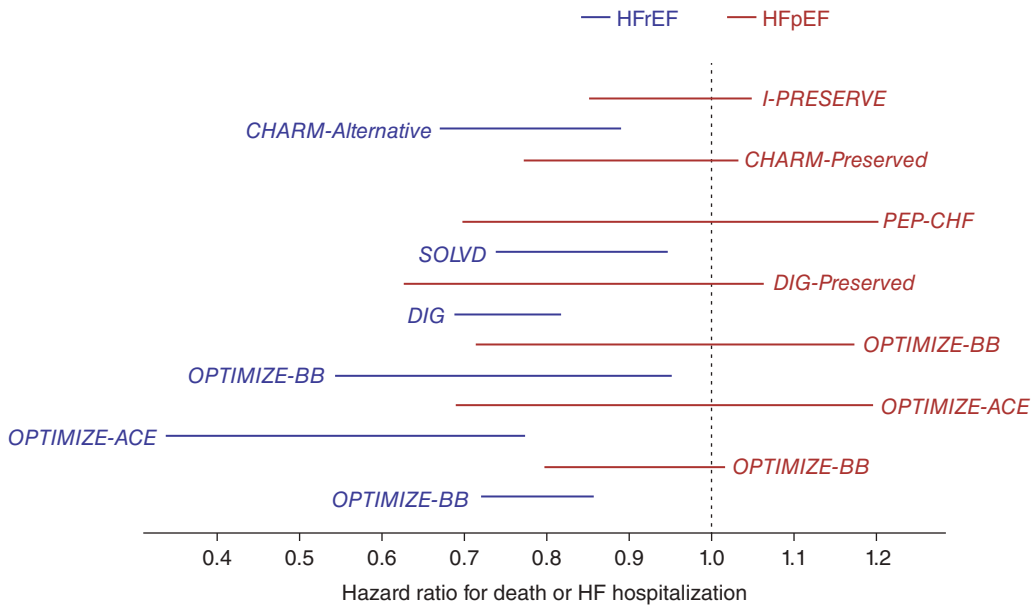

FIGURE 70–14. Forest plot showing the hazard ratios and 95% confidence intervals for neurohormonal antagonists tested in clinical trials and registry data in heart failure with preserved ejection fraction (HFpEF; *red*) and heart failure with reduced ejection fraction (HFrEF; *blue*) patients. Although angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, β-blockers, and digoxin have succeed in HFrEF, these approaches have failed to date in trials and observational studies in HFpEF. Reproduced with permission from Borlaug, B. A. & Redfield, M. M. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation*. 2011 May 10;123(18):2006-2013.[137]

patients (age ≥ 70 years) to perindopril or placebo and found that perindopril was associated with a trend toward decreased all-cause mortality and hospitalization for heart failure at 1 year, but over the entire 3-year study period, there was no reduction in the primary end point.[258] Thus, the available data do not support the use of ACE inhibitors/ARBs as a disease-modifying therapy in HFpEF, although they are clearly safe and still may be effective as antihypertensives in this population.

The mineralocorticoid receptor antagonist spironolactone was recently tested in a randomized controlled trial in HFpEF (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist [TOPCAT]), and there was no significant reduction in the composite primary end point of cardiovascular death, heart failure hospitalization, or aborted cardiac death as compared to placebo.[264] There was signal of benefit in higher risk populations, including patients enrolled on the basis of elevated natriuretic peptide levels. A post hoc subgroup analysis identified heterogeneity in response comparing subjects enrolled in the Americas as opposed to Russia and the Republic of Georgia, wherein spironolactone improved the composite end point of the trial in subjects enrolled in the Americas but not in Eastern Europe.[265] Notably, the event rate in the latter group was much lower as compared to participants in the Americas, raising concern over whether all of these patients truly had heart failure. In another ancillary study from TOPCAT, it was found that ejection fraction modified the treatment response to spironolactone.[140] Patients with lower ejection fraction (but still meeting the entry criteria) were observed to benefit from spironolactone as compared to placebo, whereas patients with higher ejection fraction (especially > 55%) did not.

A smaller trial observed that spironolactone improved estimated LV filling pressures (E/e′ ratio) in people with early-stage HFpEF, but the co-primary end point of exercise capacity and secondary end points including quality of life were not improved.[266] Given the signal of benefit in TOPCAT and the fact that filling pressures may improve, mineralocorticoid antagonists are reasonable choices in patients with HFpEF where azotemia and hyperkalemia are not problematic, particularly if there is additional role for more diuresis.

β-Blockers

β-Blockers are commonly prescribed for patients with diastolic dysfunction based on the notion that slowing the sinus rate will prolong diastole and promote ventricular filling.[267] Despite this theoretical benefit, there is little to no evidence that β-blockers improve exercise capacity or clinical outcomes, although data are quite limited in this regard.[268-272] A recent meta-analysis suggested a possible decrease in all-cause mortality associated with β-blockade in HFpEF,[273] and analysis of data from the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) trial showed no interaction between ejection fraction and the benefits of the β-blocker nebivolol, although the number of patients with "true HFpEF" (ie, ejection fraction ≥ 50%) in this trial was great.[269] One concern with β-blockers is the common presence of chronotropic incompetence in people with HFpEF, which will predictably worsen with initiation of a β-blocker.[208,268] A large multicenter trial testing β-blockers in HFpEF is urgently needed to better inform treatment decisions.

Digoxin

The Digitalis Investigators Group (DIG) trial included a cohort of 988 patients with heart failure and relatively preserved ejection fraction (> 45%) in sinus rhythm.[274] There was a trend to decreased heart failure hospitalizations, but this was negated by an increased number of admissions for unstable angina. There was no effect on mortality. Digoxin is often used for rate control in atrial fibrillation when low blood pressure limits rate-controlling medication, given its minimal hypotensive effects. Retrospective data suggest an increased mortality with digoxin use for atrial fibrillation in heart failure, but prospective trials are lacking.[275,276]

Organic Nitrates

Direct nitric oxide (NO) donors such as the organic nitrates increase cellular levels of cyclic guanosine monophosphate (cGMP), a key second messenger that activates kinases that may improve diastolic relaxation and compliance. Nitrates also decrease preload, allowing the ventricle to function at lower volumes, where operating stiffness may be lower as a result of the curvilinear end-diastolic pressure–volume relationship in HFpEF.[130] However, patients with HFpEF may display excessive reduction in blood pressure and stroke volume with nitrates.[135]

In a placebo-controlled crossover trial, isosorbide mononitrate was recently tested in 110 subjects with HFpEF.[245] The primary end point of the trial was chronic activity levels, assessed using hip-worn accelerometry devices, and key secondary end points included exercise capacity (6-minute walk distance), natriuretic peptide levels, and quality of life scores. Compared to placebo, isosorbide mononitrate tended to reduce activity levels, an effect that became more dramatic at higher doses. There was no improvement in exercise capacity and a numerical trend to worsening quality of life and natriuretic peptide levels.[245] These data do not support the use of organic nitrates for HFpEF, but they should not be interpreted to indicate that other NO-enhancing therapies will not be effective. Isosorbide mononitrate has been shown to worsen endothelial function in humans,[277] which is known to be problematic in HFpEF.[207] In addition, the exaggerated blood pressure–lowering effects might have contributed to decreased activity levels.[135] More targeted interventions that deliver NO at the time of greatest need, such as inorganic nitrite, might be more effective and are being evaluated in this population.[223]

Phosphodiesterase-5 Inhibitors

An alternative method to restore NO signaling is to decrease the degradation of its downstream second messenger (cGMP) using phosphodiesterase-5 inhibitors. In animal models of pressure-overload hypertrophy, sildenafil improves ventricular structure and function dramatically,[278] and a small pilot trial reported improvements in PH and right heart function with sildenafil.[279] However, in the Phosphdiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial, sildenafil did not improve exercise capacity, neurohormones, ventricular function, or quality of life.[242] There may also be untoward effects of sildenafil on ventricular contractility that offset any potential benefits on endothelial and vascular function.[280] A more recent trial testing sildenafil in patients with HFpEF and invasively proven PH again showed no improvement in hemodynamics or clinical parameters.[281]

Statins

In a prospective observational study of HFpEF, statin therapy was associated with significantly lower mortality (relative risk 0.20) over a median follow-up of 12 months, whereas ACE inhibitor, ARB, β-blocker, and calcium channel blocker therapy had no association with survival.[282] However, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure [GISSI-HF] trial, which tested the effects of rosuvastatin on death and death or cardiovascular hospitalization in patients with chronic heart failure, found no benefit in the subgroup of patients included with relatively preserved ejection fraction (> 40%).[283] More recent data from a Swedish registry and meta-analysis of

prior trials have suggested that statins may be beneficial in HFpEF.[284,285] As with β-blockers, a large-scale, multicenter, placebo-controlled trial is urgently needed to clarify the role of statins in patients with HFpEF.

Nonpharmacologic Interventions

Relatively small-sized trials have consistently shown that exercise training in HFpEF improves exercise capacity as well as quality of life.[230-233,237,260,261] It appears that these benefits are mediated by the periphery and are largely independent of the heart,[232] although one study did observe improvements in diastolic function.[233] Further study is needed to clarify the best modes and duration of training as well as better methods to optimize adherence and chronically sustain increases in activity levels.[261]

Dietary interventions may also prove effective. In a small, single-center trial, 3 weeks of treatment with a salt-restricted Dietary Approaches to Stop Hypertension (DASH) diet improved diastolic function, arterial stiffness, and ventricular arterial coupling in 13 subjects with HFpEF.[286] Kitzman et al[231] performed a randomized trial comparing exercise training, caloric restriction, or both to attention control. Both exercise training and caloric restriction improved exercise capacity, and the combination of both interventions was additive, supporting the concept that increases in activity levels and diet may be effective to at least improve morbidity in HFpEF.

Management of Comorbidities

Coronary artery disease is common in patients with HFpEF, seen in roughly 50% to 67% of patients defined angiographically or anatomically from postmortem exams.[171,172] Hwang et al[171] have recently shown that the presence of coronary disease is independently associated with increased mortality in HFpEF. Patients undergoing complete revascularization had better maintenance of ventricular function over time and improved survival as compared to patients not receiving complete revascularization (Fig. 70–15).[171] Intriguingly, stress testing identified the presence or absence of coronary disease poorly, with very high rates of false-positive and false-negative tests. At present, there are no prospective trial data to guide decisions regarding revascularization for patients with coronary disease and HFpEF, although consensus guidelines recommend revascularization if symptoms of heart failure are deemed to be related to coronary ischemia.[134]

Atrial fibrillation is common in HFpEF, seen in two-thirds of patients at some point during their lifespan.[287] Patients with HFpEF and atrial fibrillation are more likely to display right heart dilatation and dysfunction, tricuspid regurgitation, and exercise limitation, and they have a higher risk of death in long-term follow-up, independent of other confounders.[213,214,250,287,288] There is no clear-cut advantage for rhythm control as opposed to rate control in HFrEF,[289] but this has never been tested in patients with HFpEF. Recent studies have shown that aggressive efforts to restore and maintain sinus rhythm in patients with HFpEF and atrial fibrillation can be successful and may be associated with improvements in ventricular function if sinus rhythm can be maintained.[290] Further study is required to understand the management of atrial fibrillation in patients with HFpEF.

Given the high prevalence of obesity in HFpEF, diabetes, metabolic syndrome, and sleep apnea are also commonly observed in patients. There are no data evaluating the effects of treating these comorbidities in this population, and treatment is recommended according to their respective guidelines.

Future Directions

Numerous promising therapies are currently being studied in clinical trials for HFpEF. Sacubitril (a combined valsartan/neprilysin inhibitor) showed convincing superiority compared to enalapril in HFrEF,[291] and in the phase II Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trial, this treatment showed greater improvements in NT-proBNP as compared to ARB alone.[241] A larger pivotal trial (PARAGON [Efficacy and Safety of LCZ696 Compared with Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction]) is currently under way (NCT01920711) with intended enrollment of 4300 patients with an ejection fraction > 45%.

A recent double-blind, randomized trial demonstrated that acute administration of inorganic sodium nitrite markedly improved hemodynamic abnormalities developing during exercise, with substantial reduction in exercise LV filling pressures and improved cardiac output reserve.[223] Another acute crossover study testing inorganic nitrate (precursor to nitrite) delivered as beetroot juice also observed improvements in peak exercise capacity.[246] Larger scale studies testing this novel therapy are currently under way. The I_f current blocker ivabradine,

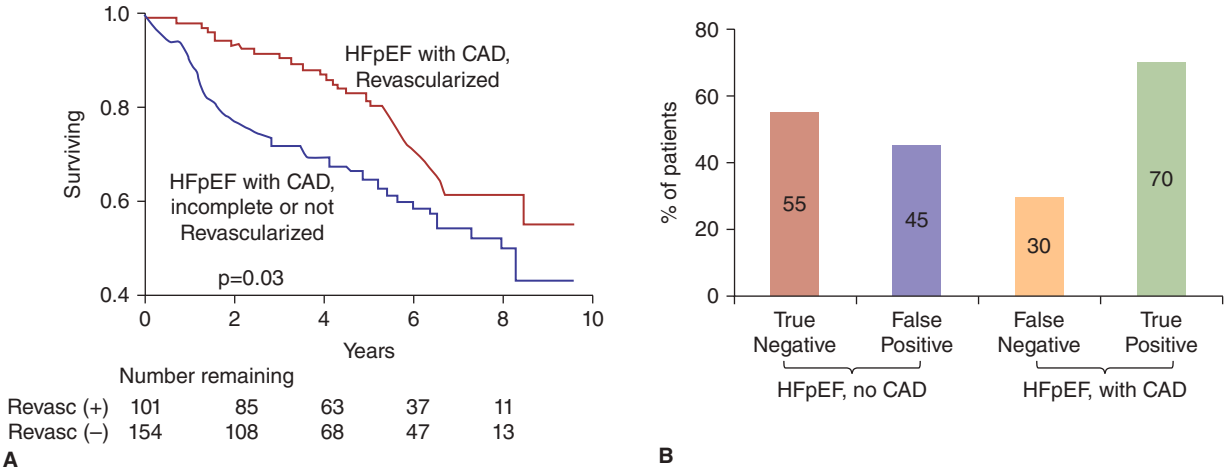

FIGURE 70–15. Patients with heart failure with preserved ejection fraction (HFpEF) and coronary artery disease (CAD) who underwent complete revascularization displayed lower mortality as compared to similar patients with HFpEF and CAD who were not revascularized (*left*). Noninvasive stress testing, using electrocardiography, perfusion imaging, or stress echocardiography, was associated with high false-positive and false-negative rates, suggesting that these modalities may have more limited value in HFpEF. Reproduced with permission from Hwang, S. J., Melenovsky, V. & Borlaug, B. A. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014 Jul 1;63(25 Pt A):2817-2827.[171]

which slows the heart rate in patients in sinus rhythm, has variably been shown to improve or worsen exercise capacity in patients with HFpEF.[221,292] A larger scale clinical trial is currently under way to help inform understanding regarding this novel approach. As described earlier, phase III studies testing β-blockers and statins remain a critical unmet need in our understanding regarding the treatment of HFpEF.

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CHAPTER 71

EVALUATION AND MANAGEMENT OF ACUTE HEART FAILURE

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EPIDEMIOLOGY OF ACUTE HEART FAILURE

PREVALENCE

Currently, the prevalence of heart failure (HF) in the United States is approaching 6 million, a number that will continue to grow as the population ages.[1] Despite advances in pharmacologic and device therapies, HF results in significant mortality and morbidity, including frequent emergency department visits and hospitalizations for decompensation. Acute heart failure (AHF) accounts for an estimated 700,000 emergency department visits[2] and over 1 million hospitalizations annually in the United States.[1] It is the leading cause of hospitalization in patients over 65 years of age, a population expected to grow considerably over the next 20 years.[1] Highlighting the prevalence of comorbid conditions in the HF population, an additional 3 million hospitalizations occur annually in which HF is listed as a secondary diagnosis.[3] In a large, community-based study, the incidence of AHF was as high as 11.6 cases per 1000 patients per year in those over the age of 55 years.[4] The economic impact of the HF epidemic is profound, and costs attributable to inpatient care are estimated to exceed 30 billion dollars annually.[5]

Data from large registries reveals that the typical AHF patient is > 70 years old, white (~80%), and equally likely to be female (~50%) compared to male.[6,7] Although most AHF patients are white, in the community setting, black males have the highest incidence of decompensation (15.7 per 1000 people per year), followed by black women (13.3 per 1000 people per year), white men (12.3 per 1000 people per year), and white women (9.9 per 1000 people per year).[4]

Although historically attention has focused on patients with systolic dysfunction (HF with reduced ejection fraction [HFrEF]), it is now clear that over 50% of AHF admissions occur in those with preserved ejection fraction (HF with preserved ejection fraction [HFpEF]).[8] Additionally, the proportion of hospitalizations in those with HFpEF is increasing considerably compared to those with HFrEF, likely a reflection of the aging population.[9] Several differences exist between these two groups, with HFpEF patients being more likely to be older and female, more likely to have less clinical coronary artery disease (CAD), and more likely to have atrial fibrillation, chronic kidney disease, higher blood pressure, and chronic pulmonary disease compared to their HFrEF counterparts.[9] Importantly, HFpEF patients with AHF have greater hospital lengths of stay and are more likely to be discharged to a skilled nursing facility.[9]

IMPORTANCE OF COMORBIDITIES

Comorbidities are common in patients presenting with acute HF (AHF), including systemic hypertension (> 70%),[10] CAD (57%),[2] diabetes mellitus (40%),[7] renal dysfunction (30%-67%),[11] anemia (50%-70%),[12] atrial fibrillation (31%),[7] and chronic obstructive pulmonary disease (COPD; 30%),[10] among others. These comorbidities are associated with higher inpatient mortality, regardless of the presence of preserved or reduced ejection fraction.[13,14] They may also confound the diagnosis of AHF (eg, COPD), reduce the effectiveness of treatments targeting decongestion (eg, renal dysfunction), and exacerbate an otherwise stable outpatient (eg, atrial fibrillation, uncontrolled hypertension). Thus, treatment of AHF almost universally involves management of comorbidities. An analysis of patients > 65 years old presenting with AHF revealed that 40% have greater than five comorbid conditions, leading to greater resource utilization and lengths of stay.[14]

OUTCOMES

AHF is a harbinger of poor outcomes and is associated with significant mortality after discharge. Recent trends suggest in-hospital mortality rates range from 2% to 5% and are similar when comparing HFpEF to HFrEF.[9,15] Postdischarge mortality for these two groups approaches 10% at 90-day follow-up,[16] whereas approximately 30% of patients die within 1 year of hospitalization (Fig. 71–1).[15,17] Despite concerted efforts to reduce rehospitalizations for AHF, nearly 25% of patients are readmitted within 30 days of discharge, and 50% are readmitted by 6 months.[18,19] Each subsequent hospitalization following the index stay is associated with increasing risk of death (Fig. 71–2).

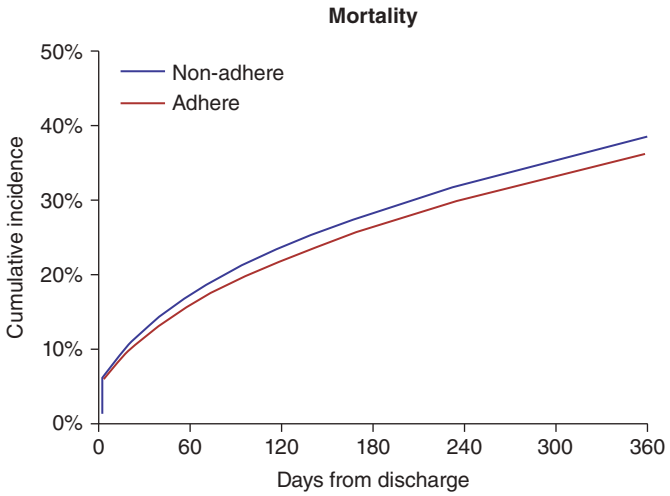

FIGURE 71–1. Incidence of mortality in patients over 65 years of age hospitalized with heart failure from both the Acute Decompensated Heart Failure National Registry (ADHERE) and a sampling of Medicare patients (non-ADHERE). Reproduced with permission from Kociol RD, Hammill BG, Fonarow GC, et al: Generalizability and longitudinal outcomes of a national heart failure clinical registry: Comparison of Acute Decompensated Heart Failure National Registry (ADHERE) and non-ADHERE Medicare beneficiaries. *Am Heart J*. 2010 Nov;160(5):885-892.[15]

PATHOPHYSIOLOGY

Although there is a tendency to treat patients with AHF as a homogenous group, it is clear that the syndrome of decompensated HF is complex and the "one size fits all" adage does not apply. Indeed, patients presenting with AHF are a heterogeneous group with a variety of underlying cardiac substrates and abnormalities. Additionally, the severity of AHF exists on a spectrum, ranging from mild fluid overload to overt cardiogenic shock, and therefore, no singular pathophysiologic model can account for the diversity of clinical presentations. Nevertheless, several key factors play varying roles in the initiation and propagation of AHF, including but not limited to: (1) acute or subacute worsening of cardiac dysfunction, either systolic or diastolic; (2) neurohormonal activation; (3) the cardiorenal syndrome resulting from the complex interplay between the kidney and the heart; (4) impaired vascular/endothelial function; (5) inflammation and oxidative stress; and (6) hemodynamic

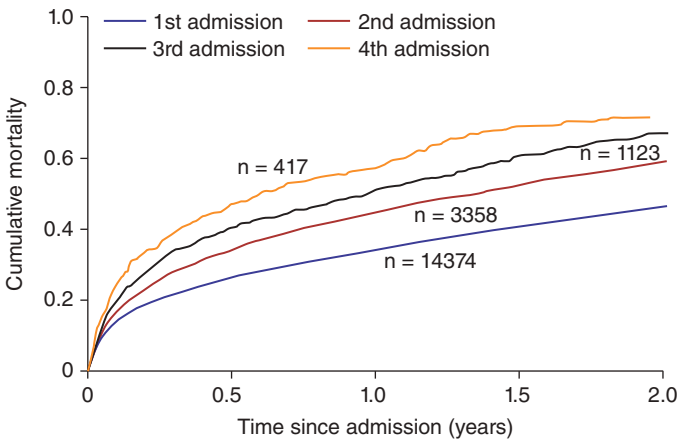

FIGURE 71–2. Kaplan-Meier survival curves for cumulative mortality after repeated acute decompensated heart failure hospitalizations. Reproduced with permission from Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J*. 2007 Aug;154(2):260-266.

factors. Ultimately, AHF is the end product of further comprise of an abnormal cardiac substrate, a precipitant that triggers instability, and a self-sustaining cycle of maladaptive mechanisms (Fig. 71–3).

ABNORMAL SUBSTRATE: ROLE OF CARDIAC DYSFUNCTION

HF is defined as a dysfunction of the heart that impairs its ability to maintain the metabolic needs of the body in the absence of elevated filling pressures. This dysfunction may manifest as impaired contractility (systolic dysfunction), impaired relaxation or decreased ventricular compliance (diastolic dysfunction), or more commonly, both. AHF in the setting of contractile dysfunction, often referred to clinically as acute systolic HF, may result from an abrupt insult (eg, myocardial infarction, myocarditis) or, more commonly, a worsening of a chronic, progressive process. The hallmark features of acute systolic HF include elevated left ventricular (LV) filling pressures, manifesting as congestion and dyspnea, and either subtle or overt impairments in systemic perfusion pressure ("arterial underfilling"), which may manifest as hypoperfusion or end-organ damage in extreme cases (eg, cardiogenic shock). When occurring abruptly as in the case of a myocardial infarction, cardiac output may be significantly reduced even with relatively small infarcts; however, when occurring progressively, systolic dysfunction typically does not lead to overt reductions in cardiac output until the late stages, related to the adaptive mechanisms at play to compensate for impaired ventricular function (ie, cardiac remodeling). Notably, even subtle abnormalities of systemic perfusion may result in upregulation of evolutionarily "protective" mechanisms to augment circulating blood volume and maintain mean arterial pressure, namely the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and pituitary vasopressin release. Although this so-called "neurohormonal activation" may serve to acutely augment perfusion pressures, it ultimately leads to volume overload, myocardial damage and fibrosis, and adverse ventricular remodeling, further amplifying the HF syndrome.

AHF in the absence of overt systolic dysfunction, termed acute diastolic HF, is largely a manifestation of the inability of the LV to effectively fill in diastole, be it passively or actively. This may occur abruptly (eg, acute onset atrial fibrillation with rapid ventricular response, accelerated hypertension) or progressively over time (eg, worsening hypertensive heart disease, progressive aortic stenosis). As diastolic dysfunction progresses (be it acute or chronic), left atrial pressure become increasingly elevated to facilitate ventricular filling. This escalating pressure is reflected upstream to the pulmonary capillary circulation, leading to pulmonary congestion and dyspnea. Although ejection fraction is preserved in acute diastolic HF by definition, the systolic function as measured by effective stroke volume at rest or exercise is often abnormal in many of these patients. Additionally, these patients often have evidence of increased ventricular systolic and arterial stiffness, which may manifest as lower stroke volume and contractile reserve.[20] The end product of these abnormalities is similar to patients with acute systolic HF: activation of RAAS, SNS, and vasopressin leading to worsening fluid overload and the ongoing propagation of the HF syndrome.

NEUROHORMONAL ACTIVATION IN ACUTE HEART FAILURE

The primary objective of the circulatory system is to maintain perfusion to vital organs by sustaining arterial pressure and circulating blood volume. Evolutionarily, a number of mechanisms that maintain organ perfusion have been identified, including the RAAS axis, the SNS, and the pituitary release of vasopressin (antidiuretic hormone [ADH]). Although acute upregulation of these systems is effective at restoring circulating blood volume and perfusion pressures in the short term, chronic activation leads to sodium and fluid overload as well as cardiac fibrosis and remodeling.[21]

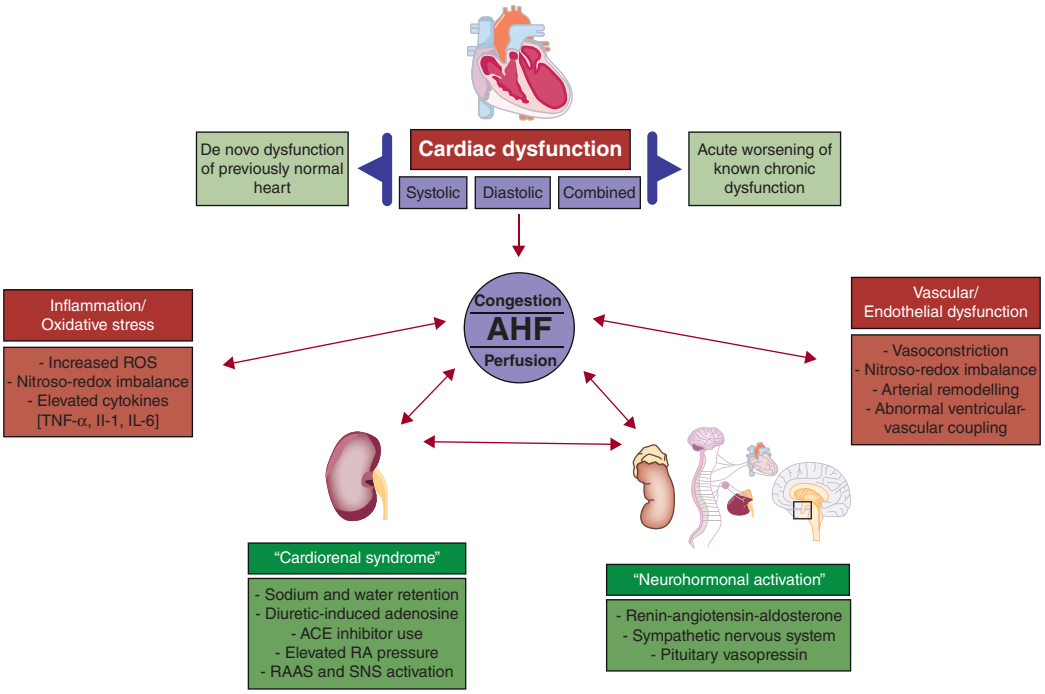

FIGURE 71–3. The basic pathophysiology of AHF. ACE, angiotensin-converting enzyme; IL, interleukin; RA, right atrial; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-α.

When perfusion pressures are reduced, whether as a result of acute blood loss or HF, the juxtaglomerular cells of the nephron release renin into the circulation. Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II has multiple downstream effects, including: (1) increased systemic vascular resistance through vasoconstriction; (2) volume expansion by promoting sodium reabsorption in the proximal tubule; (3) stimulation of adrenal aldosterone release; and (4) activation of the SNS. Aldosterone release from the adrenal glands leads to additional sodium resorption in the distal tubule and collecting duct, volume expansion, and ultimately myocardial fibrosis. Thus, RAAS activation plays a fundamental role in AHF through fluid retention and vasoconstriction while also contributing to chronic ventricular remodeling.

Reductions in perfusion pressure also lead to activation of the SNS, primarily through the suppression of cardioinhibitory baroreceptor reflexes and the augmentation of excitatory reflexes.[22] SNS activation results in increased cardiac output by increasing myocardial contractility and heart rate, while also increasing blood pressure through norepinephrine-mediated vasoconstriction. Additionally, heightened sympathetic activity leads to renin release from the kidney and the propagation of the RAAS axis, further exacerbating AHF. Much like the RAAS axis, the acute effects of SNS activation favorably support organ perfusion. However, chronic catecholamine exposure leads to myocyte death, myocardial fibrosis, and adverse cardiac remodeling.

Finally, ADH is released from the posterior pituitary in response to both osmotic and nonosmotic mechanisms. Angiotensin II triggers ADH release, as does a drop in perfusion pressure. ADH augments free water absorption in the kidney through aquaporin upregulation, stimulates thirst centers in the brain that trigger fluid intake, and increases vascular resistance through vasoconstriction. Ultimately this leads to free water overload, altered hemodynamics, and worsening AHF.

RENAL DYSFUNCTION

Renal dysfunction is common in AHF, affecting between 30% and 67% of patients in large registries.[11] Additionally, as many as 20% to 40% of patients experience worsening renal function (WRF) while being treated for AHF, a finding associated with worse prognosis.[11,23-25] Although many consider the kidneys the "barometer" of the heart in AHF, our understanding of the complex interactions between these two organs remains poor. The pathophysiology of renal dysfunction in HF likely incorporates hemodynamic factors, activation of the RAAS and SNS, inflammation and oxidative stress, and the iatrogenic effects of pharmacotherapy targeting decongestion, among other factors (Fig. 71–4).

While historically WRF in AHF was considered a consequence of reduced cardiac output ("underperfusion"), it has become increasingly apparent that right-sided congestion (eg, right atrial pressure) plays an important role. Multiple studies have failed to show a correlation between cardiac output and WRF in AHF,[26-28] with the exception of extreme reductions in output.[29] In contrast, several studies show a correlation between elevated right atrial pressure and intra-abdominal pressure with WRF.[26-28,30]

Neurohormonal activation plays a critical role in WRF in the setting of decompensation. The downstream effects of RAAS and SNS activation include angiotensin II and catecholamine-induced renal efferent arteriolar constriction, which increases glomerular filtration at the expense of renal blood flow. Additionally, stimulation of aldosterone secretion increases sodium resorption and exacerbates volume overload and congestion, which in turn promotes WRF. Chronic RAAS and SNS activation may lead to renal interstitial fibrosis and inflammation, resulting in chronic kidney disease.[31]

A number of pharmacologic treatments of AHF may result in WRF. ACE inhibitors have beneficial hemodynamics effects in AHF (reductions in preload and afterload) but are associated with a reduction in glomerular filtration rate as high as 30%.[32] Thus, they must be used with caution in those who already have considerable renal dysfunction, and further studies are needed to clarify the role of these agents specifically in AHF. Loop diuretics may also result in WRF. By increasing the delivery of sodium to the distal tubule, loop diuretics trigger adenosine release from the juxtaglomerular cells. The downstream effects of increased intrarenal adenosine include augmented sodium reabsorption in the proximal tubule (and therefore worsening congestion) and a reduction in glomerular filtration rate mediated by afferent arteriolar constriction. Unfortunately, treatments targeting adenosine receptors failed to prevent WRF in AHF in clinical trials.[33]

Regardless of the precise mechanisms at play, the kidneys play a crucial role in the syndrome of AHF, primarily through retention of sodium, leading to volume overload and congestion. This congestion can then cause WRF, triggering a vicious cycle that leads to further cardiac decompensation. Additionally, renal dysfunction leads to less utilization of standard HF pharmacotherapy (eg, ACE inhibitors,

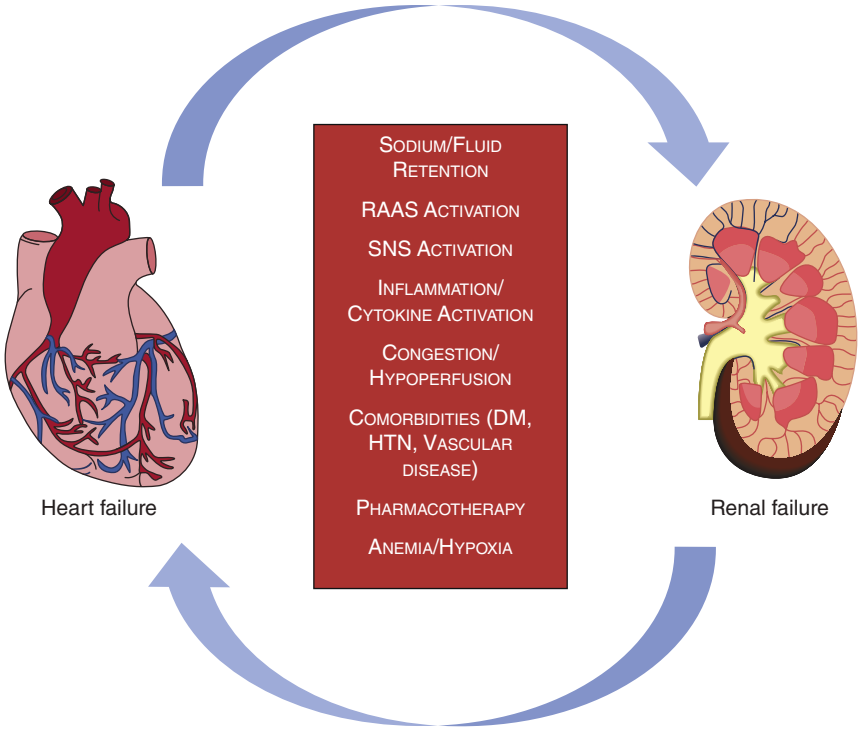

FIGURE 71–4. The cardiorenal syndrome results from a complex bidirectional relationship between the heart and the kidney. Many factors play a role in both worsening heart failure and worsening renal failure. DM, diabetes mellitus; HTN, hypertension; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system. Reproduced with permission from Cole RT, Masoumi A, Triposkiadis F, et al: Renal dysfunction in heart failure. *Med Clin North Am*. 2012 Sep;96(5):955-974.[11]

mineralocorticoid receptor antagonists [MRAs]), higher diuretic requirements to achieve effective decongestion, and a higher risk for adverse events.[11] However, it should be noted that WRF in the face of aggressive diuresis and hemoconcentration in a patient who is clinically improving may represents simply a delayed equilibration of fluid between the extra- and intravascular compartments and may be associated with improved and not worse outcomes.[34,35] Such transient WRF seems to result in better outcomes compared to those with persistent WRF during treatment for AHF.[36]

VASCULAR AND ENDOTHELIAL DYSFUNCTION

The role of the systemic vasculature in the pathophysiology of AHF has been known since the early 1960s, when studies showed elevations in afterload impair cardiac performance.[37,38] Many subsequent hemodynamic studies of both intravenous and oral vasodilator agents showed significant improvements in cardiac output and filling pressures in patients with AHF treated with these drugs.[37] Increased afterload, or systemic vascular resistance (SVR), is thought to result from endothelial dysfunction, common in both chronic and acute HF syndromes. Endothelial dysfunction, a by-product of an underlying nitroso-redox imbalance in HF,[39,40] leads to systemic vasoconstriction and elevated SVR. These mechanisms are amplified in AHF, resulting in greater cardiac work and higher LV filling pressures. Thus, vasodilator agents aimed at reducing afterload are prescribed commonly in the management of AHF.

INFLAMMATION AND OXIDATIVE STRESS

Inflammation plays a key role in the pathophysiology of AHF and also has important prognostic significance. Several inflammatory cytokines are upregulated in AHF, including tumor necrosis factor (eg, TNF-α), interleukins (eg, IL-1, IL-6), and acute-phase reactant C-reactive protein (CRP). Many of these factors directly suppress cardiac contractility and promote myocyte death, thereby worsening AHF. Higher levels also correlate with increased mortality.[41] Inflammation is associated with oxidative stress, manifest as an imbalance in nitric oxide (NO) and reactive oxygen species (ROS). This nitroso-redox imbalance leads to a variety of adverse effects that worsen the pathophysiology of AHF, including impairments in both ventricular and vascular function. Thus, there is a theoretical role for pharmacotherapy specifically targeting reductions in ROS (eg, hydralazine) and augmentation of NO (eg, isosorbide dinitrate) (Fig. 71–5).[42]

HEMODYNAMICS

The hemodynamics in AHF are highly variable and depend on the severity of the underlying substrate and the degree of decompensation. However, elevated filling pressures are the hallmark of hemodynamic aberrations in AHF. Increased LV end-diastolic pressure (LVEDP) results in elevated left atrial (LA) pressure, resulting in pulmonary congestion and dyspnea. Additionally, elevated right atrial pressure is common in AHF, accounting for lower extremity edema, ascites, liver congestion, and early satiety. Not uncommonly, secondary pulmonary hypertension may be present, initially reflecting passive hydrostatic forces from the LA to the pulmonary capillary bed. Over

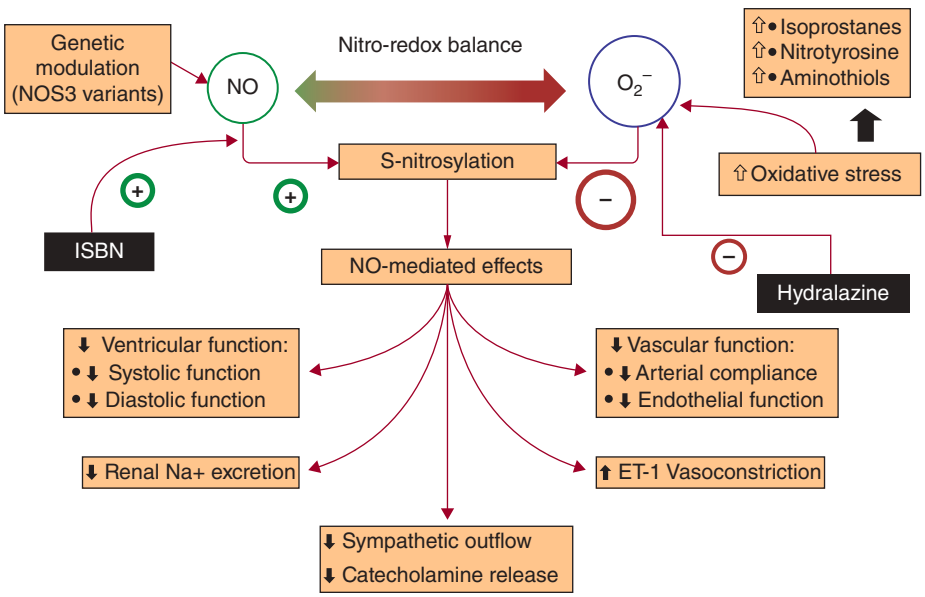

FIGURE 71–5. The nitroso-redox imbalance and acute heart failure (AHF); effects of hydralazine and isosorbide dinitrate on AHF pathophysiology. ET-1, endothelin-1; NO, nitric oxide. Reproduced with permission from Cole RT, Kalogeropoulos AP, Georgiopoulou VV, et al: Hydralazine and isosorbide dinitrate in heart failure: historical perspective, mechanisms, and future directions. *Circulation*. 2011 May 31;123(21):2414-2422.[42]

time, pulmonary vasoconstriction and adverse pulmonary arteriolar remodeling may occur, leading to pulmonary hypertension out of proportion to the LA pressure[43] and markedly elevated pulmonary vascular resistance.

In most cases of AHF, cardiac output (CO) is in the normal range or only mildly reduced at rest. In the case of an acute process, such as a myocardial infarction or fulminant myocarditis, CO may drop dramatically, leading to a low CO syndrome or shock characterized by end-organ underperfusion requiring inotropic or mechanical circulatory support. When AHF develops from a progressive exacerbation of chronic LV dysfunction, CO is typically not severely reduced in the absence of very late-stage or advanced disease. SVR may be normal or significantly elevated in AHF. In cases of systolic dysfunction and elevated SVR, vasodilator therapy may reduce SVR and lead to improvements in stroke volume and LV filling pressures. This may not be true in patients with decompensated HFpEF. Recent physiologic studies suggest that aggressive afterload reduction in the setting of HFpEF may actually reduce stroke volume.[44] This drop in stroke volume likely results from a reduction in LV end-diastolic volume (preload), although the mechanisms at play are not entirely clear. Therefore, afterload reduction should be used with caution in this setting.

RISK STRATIFICATION IN ACUTE HEART FAILURE

Although much progress has been made in the treatment of chronic HF, little has changed in the management of AHF in the last 40 years. As a result, mortality for patients with AHF remains unacceptably high.[9,15] However, not all patients face the same risk. A number of clinical variables may identify subgroups at risk for worse outcomes, and several risk scores have been developed to better facilitate stratification of patients with AHF (Table 71–1).[45-49] Additionally, several novel biomarkers have emerged that have shown considerable promise in the risk stratification of patients presenting with AHF or being discharged following a hospitalization for AHF. Biomarkers will be more comprehensively discussed later in this chapter.

The Acute Decompensated Heart Failure National Registry (ADHERE) "risk tree" was derived from an analysis of 39 admission variables in over 60,000 AHF patients.[45] Investigators found that the best predictors of inpatient mortality were markers of renal dysfunction (elevated blood urea nitrogen and creatinine) and lower blood pressure. A risk tree was developed incorporating these variables, enabling clinicians to estimate inpatient mortality ranging from low risk (~2%) to intermediate risk (~6%-13%) to high risk (~20%) (Fig. 71–6).[45]

The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) risk index uses a number of demographic, laboratory, and clinical variables at the time of admission to determine mortality risk at 30 days and 1 year of follow-up.[46] Developed from a retrospective study of over 4000 community-based AHF patients in Ontario, Canada, the EFFECT risk index can be used to categorize patients into low risk (mortality 0.4% at 30 days and 7.8% at 1 year) and high risk for death during follow-up (mortality 59% at 30 days and 79% at 1 year). The variables incorporated into this risk index may be found in Table 71–1.[46]

Finally, the Get With the Guidelines–Heart Failure (GWTG-HF) risk score was derived from a cohort of over 39,000 patients

TABLE 71–1. Risk Scores for Acutely Decompensated Heart Failure

Risk Score	Population	Outcome	Variables in Model	Utility
ADHERE risk tree	ADHERE registry (AHF admissions at 263 hospitals in United States); derivation cohort, n = 33,046; validation cohort, n = 32,229	Inpatient mortality	39 variables analyzed; 3 variables strongly associated with risk of death: BUN > 43 mg/dL; SBP < 115 mm Hg; Cr > 2.75 mg/dL	Stratify patients into low risk (~3%), low/intermediate (~6%), intermediate/high risk (~13%), and high risk (~20%) for inpatient death
EFFECT risk index	Over 4000 patients admitted with AHF to 24 hospitals in Ontario, Canada; derivation cohort, n = 2624; validation cohort, n = 1407	All-cause 30-day and 1-year mortality	Age, RR, SBP, BUN, sodium < 136 mEq/L, cerebrovascular disease, dementia, COPD, cirrhosis, cancer, hemoglobin < 10 g/dL	Categorize patients into low risk (score < 60): < 1% 30-day and ~8% 1-year mortality; or high risk (score > 150): 69% 30-day mortality and ~79% 1-year mortality
PROTECT risk score	2015 AHF patients with complete data enrolled in PROTECT study (AHF patients with renal dysfunction)	Risk of death, worsening HF, or readmission for HF at 7 days	BUN, albumin, SBP, RR, HR, cholesterol, HF hospitalization in last year, DM; incremental points awarded for increasing severity of each	Probability of an event ranges from 4.8% (lowest scores) to 39% (highest scores)
GWTG-HF risk score	GWTG-HF registry (AHF admissions to 198 participating hospitals); derivation cohort, n = 27,850; validation cohort, n = 11,933	Inpatient mortality	BP, BUN, sodium, age, HR, black race, COPD; incremental points awarded for increasing severity/presence of each	Discriminate mortality from < 1% in lowest decile of scores to ~10% in the highest decile of scores; valid for both HFpEF and HFrEF
ESCAPE discharge risk score	423 patients with complete data discharged during the ESCAPE study; validated by data from FIRST trial	6-month mortality following discharge	Age > 70, BUN > 40 or > 90 mg/dL, 6MWT < 300 ft, sodium < 30 mEq/L, CPR/ventilator use, D/C diuretic > 240 mg, no BB at D/C, D/C BNP > 500 or > 1300 pg/mL	D/C risk score discriminates mortality from 5% (score = 0) to 94% (score = 8) at 6 months

Abbreviations: 6MWT, 6-minute walk test; ADHERE, Acute Decompensated Heart Failure National Registry; AHF, acute heart failure; BB, β-blocker; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; Cr, creatinine; D/C, discharge; DM, diabetes mellitus; EFFECT, Enhanced Feedback for Effective Cardiac Treatment; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization and Effectiveness; FIRST, Flolan International Randomized Survival Trial; GWTG-HF, Get With the Guidelines–Heart Failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; PROTECT, Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy; RR, respiratory rate; SBP, systolic blood pressure.

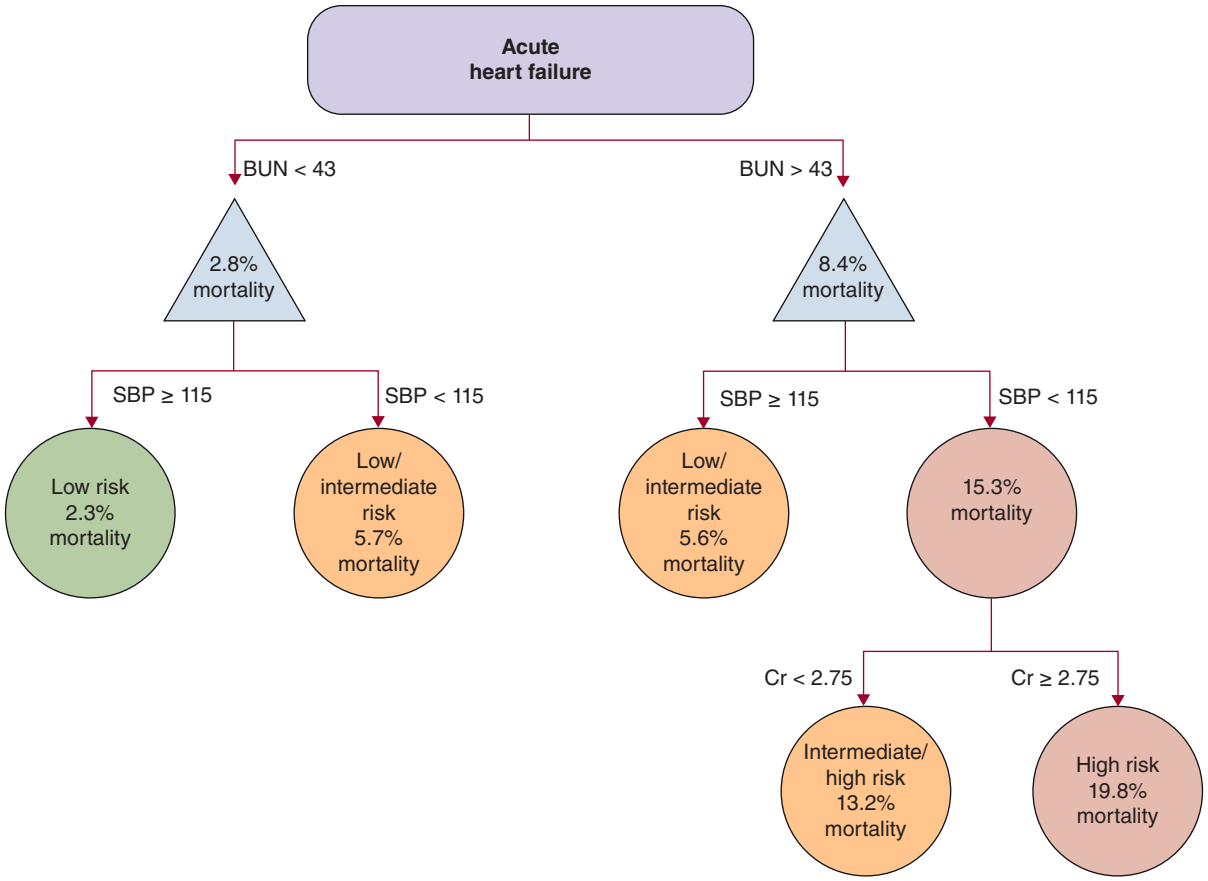

FIGURE 71–6. The Acute Decompensated Heart Failure National Registry (ADHERE) "risk tree" assessing inpatient mortality in patients admitted with acute decompensated heart failure in the ADHERE registry. Mortality varies based on admission blood urea nitrogen (BUN), systolic blood pressure (SBP), and serum creatinine (Cr).

admitted with AHF between 2007 and 2009.[49] This score incorporates a number of admission variables associated with mortality risk in a multivariable analysis: age, systolic blood pressure, blood urea nitrogen, heart rate, sodium, COPD, and nonblack race. This model has been validated for use across a wide spectrum of AHF patients and is effective in both HFpEF and HFrEF patients.[49] The above scores represent just a few of the many AHF risk scores available for clinical use. Additional information on scoring models is shown in Table 71–1.[45-49]

GENERAL APPROACH TO DIAGNOSIS AND TREATMENT

Therapeutic options for chronic HFrEF are well delineated and are founded in strong clinical trial evidence. In contrast, therapy for AHF has been met with largely negative or neutral clinical trials and less established treatment protocols. As new treatment options for AHF emerge, there is a critical need to identify patients appropriate for various therapies. Careful consideration should be paid to the need for inpatient management.[50] A general approach to the treatment of AHF is addressed in the American College of Cardiology (ACC)/American Heart Association (AHA)[51] guidelines, which include recommendations for the following: immediate determination of volume and perfusion status; addressing precipitating factors and comorbidities; recognition of acuity versus chronicity of the disease process; interpretation of contributing biomarker data; initiation or cautious uptitration of loop diuretic therapy without time delay; and initiation of intravenous inotropic or vasopressor drugs in those patients with systemic hypotension as indicated by acute kidney injury or change in mental status and severe elevation in cardiac filling pressures. Treatment of AHF centers on maintenance or restoration of systemic perfusion and preservation of end-organ performance and relieving congestion, while consideration of more definitive or advanced therapies takes place. In most patients admitted with AHF and HFrEF, chronic oral maintenance therapies, such as β-blocker (BB), ACE inhibitor (ACEI), or angiotensin receptor blocker (ARB), can be continued without interruption, assuming relative hemodynamic stability. In patients with HFrEF who are not already on neurohormonal antagonist medications, these agents should be initiated once hemodynamic stability and euvolemia have been achieved, because these therapies are known to improve outcomes[51] (Table 71–2). Hospitalization provides an opportunity for timely and comprehensive assessment.[52]

CLASSIFICATION

There is significant variability in patients who present with AHF, making appropriate classification paramount to appropriate triage and therapeutic targets. Although the majority of patients present with congestion, there is a significant variability in underlying cardiac and noncardiac comorbidities and variation in clinical presentation in AHF. There are many published classification systems for AHF (Table 71–3). The European Society of Cardiology (ESC) guidelines propose six clinical profiles, including: (1) worsening or decompensated chronic HF, (2) pulmonary edema, (3) hypertensive HF, (4)

TABLE 71–2. American College of Cardiology/American Heart Association Recommendations for Therapies in the Hospitalized HF Patient

Recommendations	COR	LOE	References
HF patients hospitalized with fluid overload should be treated with intravenous diuretics	I	B	310, 311
HF patients receiving loop diuretic therapy should receive an initial parenteral dose greater than or equal to their chronic oral daily dose; then dose should be serially adjusted	I	B	312
HF*r*EF patients requiring HF hospitalization on GDMT should continue GDMT except in cases of hemodynamic instability or where contraindicated	I	B	307–309
Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of intravenous agents	I	B	307–309
Thrombosis/thromboembolism prophylaxis is recommended for patients hospitalized with HF	I	B	22, 324–328
Serum electrolytes, urea nitrogen, and creatinine should be measured during titration of HF medications, including diuretics	I	C	N/A
When diuresis is inadequate, it is reasonable to	IIa		
a. give higher doses of intravenous loop diuretics; or		B	37, 312
b. add a second diuretic (eg, thiazide)		B	313–316
Low-dose dopamine infusion may be considered with loop diuretics to improve diuresis	IIb	B	317, 318
Ultrafiltration may be considered for patients with obvious overload	IIb	B	319
Ultrafiltration may be considered for patients with refractory congestion	IIb	C	N/A
Intravenous nitroglycerin, nitroprusside, or nesiritide may be considered an adjuvant to diuretic therapy for stable patients with HF	IIb	A	320–323
In patients hospitalized with volume overload and severe hyponatremia, vasopressin antagonists may be considered	IIb	B	330, 331

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; and N/A, not available.

Reproduced with permission fromYancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-e239.[51]

TABLE 71–3. Classification of Acute Heart Failure

Society or Authors	Description
European Society of Cardiology (ESC)[53]	Six clinical profiles 1. Worsening or decompensated chronic HF 2. Pulmonary edema 3. Hypertensive HF 4. Cardiogenic shock 5. Isolated right HF 6. ACS and HF
American College of Cardiology (ACC)/American Heart Association (AHA); Jessup et al[54]	Three clinical profiles for hospitalized HF patient: 1. Volume overload (pulmonary and/or systemic congestion and often precipitated by hypertension) 2. Hypotension and severe reduction in cardiac output 3. Signs and symptoms of both fluid overload and shock (hypotension, renal insufficiency, and/or shock syndrome)
Pang et al,[55] Gheorghiade and Braunwald[56]	Worsening chronic HF (75%) De novo or new onset (20%) Advanced or refractory (5%) Separated further into high, normal, or low blood pressure, preserved vs reduced EF, presence or absence of CAD
Gheorghiade and Braunwald[56]	Six-Axis Model 1. De novo vs worsening chronic heart failure 2. Blood pressure (low, normal, high) 3. Heart rate and rhythm 4. Severity of dyspnea (based on Likert scale) 5. Comorbidities 6. Precipitants
Vaduganathan et al[57A]	Classification for hospitalized HF patients: • LVEF • Medical or social precipitant • Chronicity (de novo vs worsening chronic)
Felker et al[57B]	Profiles in patients with AHFS AHFS with HTN AHFS with volume overload AHFS with hypotension AHFS due to other comorbid condition including: • AF • ACS • Acute valvular dysfunction • Myocarditis • Pulmonary Embolus Infection

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; AHFS, acute heart failure syndromes; CAD, coronary artery disease; EF, ejection fraction; HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fraction.

cardiogenic shock, (5) isolated right HF, and (6) acute coronary syndrome and HF.[53] The ACC/AHA describes three groups, including: (1) patients with volume overload (generally with pulmonary and/or systemic congestion and often hypertension), (2) those with hypotension and severe reduction in CO, and (3) those with combination cardiogenic shock and congestion.[54]

Pang et al[55] describe a classification framework combining both ACC/AHA and ESC guidelines, highlighting the need for optimization of management of known targets and the importance of recognizing "responders" to therapy.[55] Gheorghiade and Braunwald[56] propose a six-axis model in which severity informs immediate versus deferred therapy and inpatient management, using readily available intake parameters. This model takes into account de novo versus worsening chronic HF, blood pressure (low, normal, or high), heart rate and rhythm, severity of dyspnea, comorbidities,

and precipitants.[56] Felker et al[57B] highlighted a need for classification with respect to clinical trial design, proposing a clinically useful classification framework in this context. The authors recommend separation into clinical profiles of AHF based on patients with AHF and hypertension, hypotension, volume overload, and other precipitating factors.[57B]

IMMEDIATE ASSESSMENT

Signs, Symptoms, Physical Examination, and Hemodynamic Profiling

Dyspnea, or breathlessness, is the most common symptom reported by patients with AHF regardless of severity, followed by fatigue. In Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF),[58] 64% of enrolled patients had rales on exam, likely reflecting increased pulmonary capillary wedge pressure (PCWP). Dyspnea can be assessed by the provocative dyspnea assessment, which uses varying positions and maneuvers to assess level of dyspnea under stress, with and without oxygen.[59] Pang et al[60] proposed a dyspnea severity score, based on provocative dyspnea assessment performance using a 5-point Likert scale to standardize degree of dyspnea in clinical trials. Signs and symptoms in AHF vary based on clinical phenotype and inform treatment decisions.[57] For example, patients in AHF who present with hypertension may present with primarily pulmonary congestion with or without systemic congestion, with acute pulmonary edema in the most severe cases. AHF patients with worsening chronic HF and volume overload are likely to present with peripheral edema and less likely pulmonary or radiographic congestion. Patients with AHF and hypotension suggestive of a low CO state may have symptoms of poor end-organ perfusion, such as confusion, lethargy, and abdominal discomfort. A small subset of these patients present in cardiogenic shock.[57] Those with isolated right HF are likely to present with absence of pulmonary congestion with signs of low LV filling pressures with or without hepatomegaly.[53]

The physical exam in AHF must focus on vital signs (tachycardia, hyper- vs hypotension, narrow pulse pressure), heart and lung exam, neck veins, and assessment of volume overload in general.[51] The presence of jugular venous distention suggests elevated right-sided filling pressures, which in 80% of cases suggests elevated left-sided filling pressures.[61] In AHF, proportional pulse pressure ([systolic – diastolic blood pressure]/systolic blood pressure) < 25% is associated with low cardiac index (< 2.2 L/min/m^2) with high sensitivity and specificity and can therefore be an easy clinical marker.[62] Cardiac exam may reveal a third heart sound, suggestive of LV dilatation, or fourth heart sound, which may indicate poor LV compliance. The Valsalva maneuver may be used to indicate the presence of altered arterial pressures, suggesting LV systolic dysfunction,[63] but may be more challenging to perform in the acute setting. New or worsened murmur may indicate worsened ventricular dilatation or new valvular disease. Lung exam can reveal rales or wheezing. Abdominal exam may reveal hepatomegaly signifying passive congestion, or ascites. The presence of a hepatojugular reflux can indicate right ventricular dysfunction. Extremity exam can provide insight on both congestion (presence of lower extremity and dependent edema) and perfusion (poor capillary refill, cool temperature) (Table 71–4).[59]

TABLE 71–4. History and Physical Exam in Acute Heart Failure

History	Physical examination	Clinical/haemodynamic significance
Feature		
Establishment of diagnosis (ie, volume status and assessment of precipitating factors)		
Dyspnoea	Rales, dullness to percussion, cardiac wheezing, reduced oxygen saturation, accessory respiratory muscle use, elevated jugular venous pressure, peripheral oedema, hepatomegaly, ascites	Pulmonary oedema, left heart failure, right heart failure
Confussion, lightheadedness, dizziness	Systolic blood pressure (SBP) < 90 mm Hg, orthostatic hypotension, poor peripheral perfusion	Low output state, poor perfusion, possible hypovolaemia
Weakness, fatigue	SBP < 90 mm Hg, elevated jugular venous pressure, hepatomegaly, peripheral oedema, decreased strength and muscle mass	Low output state, right heart failure
Cold periphery	Cool extremities, anuria, oliguria	Low output state, poor perfusion, renal insufficiency, possible cardiogenic shock
Abdominal discomfort	Hepatomegaly, ascites	Right ventricular dysfunction
Palpitations	Tachycardia, bradycardia, irregular rhythm	Atrial fibrillation, heart block
Evaluation of comorbidities		
Hypertension	Blood pressure, fourth heart sound	Stiff left ventricle, impaired relaxation
Dyslipidaemia	Xanthomas	Suggestive of coronary artery disease or metabolic syndrome
Coronary artery disease, chest pain	Bruits, diaphoresis, visible discomfort	Acute coronary syndrome
Valvular abnormalities (ie, mitral regurgitation, aortic stenosis or regurgitation)	Systolic or diastolic murmur	Altered left ventricular geometry; elevated left ventricular diastolic and/or left atrial pressures
Arrhythmias (ie, atrial fibrillation)	Heart rate, irregular rhythm	Risk of stroke or sudden cardiac death

Reproduced with permission from Harinstein ME, Flaherty JD, Fonarow GC, et al: Clinical assessment of acute heart failure syndromes: emergency department through the early post-discharge period. *Heart*. 2011 Oct;97(19):1607-1618.[59]

Hemodynamic Profiling

The conventional approach to therapy in AHF begins with bedside determination of the hemodynamic profile. Nohria et al[64] described four patient profiles based on volume and perfusion status (Fig. 71–7). This simple classification has proven to be very useful in clinical practice.

Profile A: Patients without evidence of congestion with adequate perfusion ("dry-warm")

Profile B: Patients with congestion but adequate perfusion ("wet-warm")

Profile C: Patients with congestion and hypoperfusion ("wet-cold")

Profile L: Patients without congestion, with hypoperfusion ("dry-cold")[64]

Survival analysis revealed that clinical profiles predicted outcomes in HF, with profiles B and C portending increased risk of death or urgent transplantation, adding prognostic value even when limited to patients with New York Heart Association (NYHA) class III and IV symptoms. The presence of congestion was determined by orthopnea and/or physical exam evidence of jugular venous distention, pulmonary rales, hepatojugular reflux, ascites, peripheral edema, leftward radiation of the pulmonic heart sound, or a square wave blood pressure response to the Valsalva maneuver. Perfusion status was determined by the

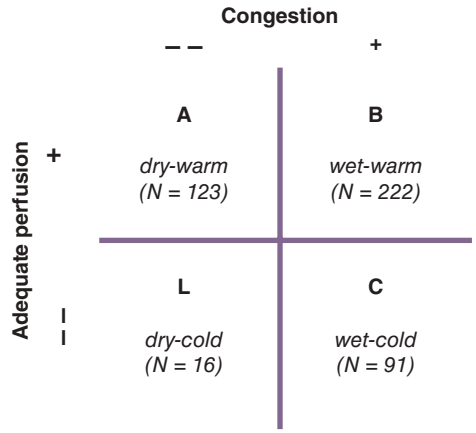

FIGURE 71–7. Hemodynamic assessment of clinical profiles. Congestion evaluated by orthopnea, jugular venous distention, rales, hepatojugular reflux, ascites, peripheral edema, leftward pulmonic heart sound, or square-wave blood pressure response to Valsalva maneuver. Poor perfusion determined by presence of narrow pulse pressure, pulsus alternans, symptomatic hypotension, cool extremities, and/or decreased mentation. Reproduced with permission from Nohria A, Tsang SW, Fang JC, et al: Reproduced from Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol*. 2003 May 21;41(10):1797-1804.[64]

presence of narrow pulse pressure ([systolic – diastolic]/systolic blood pressure < 25%), pulsus alternans, symptomatic hypotension, cool extremities, and/or impairment in mentation.[64]

Patients with profile A ("dry-warm") are compensated from a cardiac perspective, and presence of dyspnea in these patients should prompt evaluation for alternative causes of dyspnea. These patients, if not already taking a BB and ACEI/ARB should have these medications initiated and uptitrated as tolerated. Patients with profile B ("wet-warm") generally require diuresis with or without vasodilation. Importantly, profile B patients generally do not require lowering or discontinuation of their background HF medications. Profile C ("wet-cold") patients, in contrast, are generally a sicker group who may require inotropic support in order to achieve adequate diuresis and may require alteration in background HF medications such as holding or lowering BB and ACEI/ARB secondary to hypotension and/or WRF. This group may also require invasive hemodynamic monitoring, particularly if conventional therapy does not result in clinical improvement. Lastly, patients with profile L ("dry-cold") are not common but include those with severe limitation in cardiovascular reserve.[64] Along with symptom relief, careful consideration to more definitive therapies for HF or advanced planning should be considered for these patients.

Diagnostic Testing

Several diagnostic tests are essential as part of a workup for AHF. All patient should have an electrocardiogram in the emergency department.[51] Specific attention should be paid to signs of acute coronary syndromes and ischemia, QRS prolongation potentially indicating ischemia or ventricular dyssynchrony or dilatation, atrial and ventricular arrhythmias, and heart block. Chest radiography should be performed to assess for pulmonary congestion, cardiomegaly, pleural and pericardial effusions, and the other pulmonary processes that may be contributing factors such as infection or pulmonary disease.[59] Initial laboratory testing should include complete blood count, serum electrolytes, renal indices, liver function testing, and urinalysis. Specific attention should be paid to the presence of hyponatremia, anemia, and renal function. Evidence of hepatic abnormalities may signify passive congestion and right ventricular dysfunction. Measurement of natriuretic peptides is recommended for patients in whom the diagnosis of AHF is undetermined or for additional prognostic information.[51]

Other noninvasive testing includes echocardiogram and, in appropriate cases, assessment for the presence of ischemia and myocardial viability. Echocardiography can be useful for determining severity of valvular abnormalities, assessment of diastolic dysfunction, quantification of pulmonary hypertension by estimation of pulmonary artery systolic pressures, and other hemodynamic parameters noninvasively.[65] Most importantly, echocardiogram is often useful in providing estimated right atrial pressure using the inferior vena cava size and collapse index. Transesophageal echocardiography may be performed in AHF patients who have inadequate quality of transthoracic images, in cases of severe valvular disease for additional quantification, in suspected endocarditis, in patients with suspected source of cardiac thrombus, and in congenital disease.[66] Although the role of handheld echocardiography is still evolving, this imaging modality may aid in estimation of LV filling pressures as well.[67] There are several modalities that can be used for noninvasive assessment of myocardial ischemia and/or viability in suitable patients. These include stress echocardiography, nuclear imaging (single-photon emission computed tomography and positron emission tomography), as well as cardiac magnetic resonance imaging.[51]

Pulmonary Artery (Swan-Ganz) Catheterization: Use and Indications

Pulmonary artery catheters (PACs) have historically been used as part of a "tailored therapy" approach in AHF. More recently, routine use of PAC-guided management has been discouraged.[68] The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization and Effectiveness (ESCAPE) trial evaluated the use of PAC in patients hospitalized with HF in whom the use of a PAC was deemed to be of potential benefit but not essential.[69] The use of PAC was compared to clinical assessment alone in 433 patients with comparable baseline characteristics, including severe elevation in PCWP, diminished LV ejection fraction, and cardiac index 1.9 ± 0.6 L/min/m^2. The ESCAPE trial reported no differences between groups in the primary end point of days alive out of the hospital. Subgroup analysis showed a trend toward improved outcomes in the PAC group in the highest enrollment centers and a trend toward favor of PAC group for functional assessment (6-minute walk, Minnesota Living With Heart Failure testing), but also a trend toward higher adverse events.

It is important to note that the ESCAPE trial excluded patients whom physicians felt clearly required PAC for optimal management and involved physician investigators who were highly experienced in the evaluation and treatment of HF. With the bedside availability of astute physical exam skills, serum biomarkers and laboratory results, and point-of-care and advanced imaging techniques, PAC should be reserved for selective situations.[70] The ACC/AHA guidelines state that invasive hemodynamic monitoring should not be routinely used, but can play a role in carefully selected patients for whom hemodynamics are unclear or AHF symptoms are persistent.[51]

There may be a role for use of PAC, when performed by skilled operators knowledgeable in hemodynamic assessment, in identifying high-risk HF patients with persistent hemodynamic abnormalities, as well as in the trials for development of novel agents; however, improvement in education and guidelines are necessary to establish appropriate contemporary use of PAC.[71]

Biomarkers

Predicting individual risk in patients with AHF is challenging because of tremendous diversity in clinical presentation and underlying pathophysiology. The use of biomarkers can be additive in predicting risk after an AHF hospitalization[72] and inform decision making regarding treatment.[73] Different biomarkers for use in AHF relate

to the varied underlying pathophysiologic targets (Fig. 71–8).[73] Biomarkers reflecting myocardial stretch, the natriuretic peptides, are the most widely studied and used in AHF patients and are powerful predictors of outcome.[74] Both atrial natriuretic peptide and B-type natriuretic peptide (BNP) have vasodilatory, natriuretic, and diuretic properties.[75] N-terminal pro–B-type natriuretic peptide (NT-proBNP) is a part of the precursor peptide BNP and has a longer half-life.[76] BNP and NT-proBNP are similar for diagnosis of AHF,[77] but NT-proBNP is superior in predicting clinical outcome.[78] Serial measurement may add to prognostic prediction. The Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study showed that a 50% reduction in NT-proBNP correlated with a nearly 50% reduction in event rate.[79] Discharge value may be more predictive than admission value.[80,81]

Several biomarkers may be reflective of the underlying neurohormonal imbalance of AHF, including activation of SNS, RAAS, and ADH release. Adrenomedullin (ADM), a peptide hormone secreted by myocardial tissue and endothelial cells, may be reflective of neurohormonal activation. ADM, because of a short half-life, is difficult to measure. Midregional pro-adrenomedullin (MRproADM) is more stable and thus more useful in the clinical setting.[82-84] Elevated levels of MRproADM are associated with adverse outcome in AHF patient.[85] High levels of vasopressin reflect severity of HF but are difficult to measure as a result of instability and rapid clearance.[86] Copeptin is the C-terminal portion of the vasopressin prohormone and can be more easily measured. Copeptin is a marker for HF disease progression.[87] In patients with AHF, high levels of copeptin were predictive of mortality at 12 and 24 months.[88,89] Chromogranin A, a prohormone, is produced by adrenergic and neuroendocrine cells[90] and ultimately leads to vasoconstriction and catecholamine release.[91] Chromogranin A is found in higher levels in patients with HF. Similar to copeptin, higher levels are associated with HF severity and can be predictive of mortality.[92]

Another group of biomarkers is used to reflect the underlying pathophysiologic cardiac remodeling seen in HF, including myocardial hypertrophy, fibrosis, apoptosis, and necrosis. Soluble ST2, in response to volume overload and myocardial strain, is found in higher levels in patients with HF and is associated with poor prognosis.[93,94] ST2 levels can also add prognostic value to NT-proBNP and high-sensitivity troponin T.[95] Elevations in ST2 can aid in the identification of patients with decompensation and cardiac remodeling.[96] Galectin-3 is released by activated macrophages in response to cardiac stress and stimulates production of collagen, which leads to fibrosis and worsening ventricular dysfunction.[97-99] Galactin-3 has been shown to be an independent predictor of mortality[100] and rehospitalization[101] in patients with AHF.

Downstream myocyte necrosis and apoptosis may be a result of increased myocardial wall stress, elevated LVEDP, and decreased myocardial perfusion.[84] Biomarkers of myocyte injury, such as troponins T and I, have been shown to add to prognosis in patients with AHF,[102] although certain patient factors such as renal failure, sex, age, and the presence of LV hypertrophy can influence levels.[103] Patients with elevated troponin levels are generally sicker, with lower systolic blood pressure, lower ejection fractions, and higher inpatient mortality.[102]

WRF and acute kidney injury are correlated with worsened mortality[104] and are prevalent in patients with AHF. There has been growing interest in biomarkers reflecting renal injury, such as cystatin C and neutrophil gelatinase-associated lipocalin, to predict prognosis. Cystatin C is a cysteine protease inhibitor released from all kidney cells and filtered by the glomerulus.[105,106] High levels of cystatin C are associated with AHF outcome.[107] Neutrophil gelatinase-associated lipocalin is secreted by kidney cells in response to acute kidney injury, preceding creatinine elevation,[108] and predicts 30-day mortality after AHF hospitalization.[108]

AHF reflects a proinflammatory state. Levels of high-sensitivity CRP are elevated in AHF and associated with mortality.[109,110] Reliability of CRP levels may be diminished in patients with infections.[111]

Biomarker utilization may add to risk prediction, although which combination and in what capacity remain largely undefined. In the Multinational Observational Cohort on Acute Heart Failure (MOCA) trial,

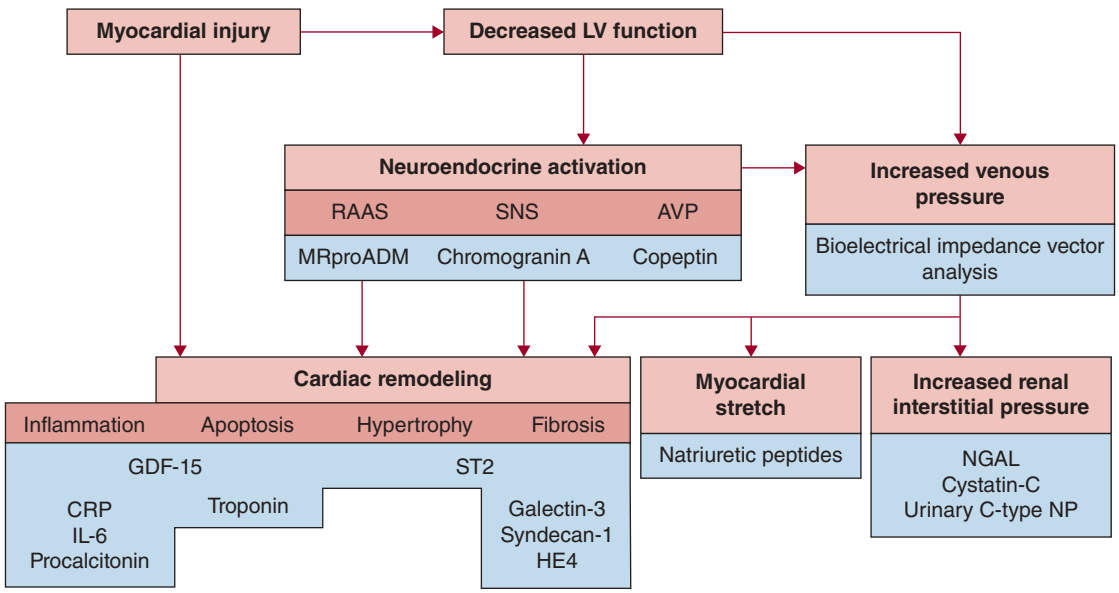

FIGURE 71–8. Biomarkers of heart failure as related to underlying pathophysiology. AVP, arginine vasopressin; CRP, C-reactive protein; GDF-15, growth differentiation factor-15; IL, interleukin; LV, left ventricular; MRproADM, midregional pro-adrenomedullin; NGAL, neutrophil gelatinase-associated lipocalin; NP, natriuretic peptide; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system. Reproduced with permission from van der Velde AR, Meijers WC, de Boer RA: Biomarkers for risk prediction in acute decompensated heart failure. *Curr Heart Fail Rep*. 2014 Sep;11(3):246-259.[73]

a multinational cohort of AHF patients that studied the value of adding biomarkers to a clinical prediction model, MRproADM had the highest 30-day mortality, and the combination of elevated CRP and ST2 had the highest 1-year mortality in risk prediction. The Biomarkers in Acute Heart Failure (BACH) trial, a prospective multicenter study of patients presenting with dyspnea, showed MRproADM to be the best predictor of mortality compared with BNP and NT-proBNP, but showed that BNP was still a superior predictor of rehospitalization.[112] In AHF, BNP was superior to troponin I and high-sensitivity CRP for mortality prediction, but the combination improved statistical significance.[109]

IDENTIFICATION AND MANAGEMENT OF PRECIPITATING FACTORS

Patients requiring hospitalization for HF exacerbation can often be characterized as having a precipitating event (Table 71–5). Data from OPTIMIZE-HF represent the most comprehensive identification of precipitants leading to hospitalization for AHF,[113] reporting that of the almost 50,000 patients included, roughly 60% had one or more identified precipitating factors. These precipitants independently predicted clinical outcomes, making early identification and targeted therapy critical. In the OPTIMIZE-HF registry, there were a number of factors found to precipitate hospital admission for AHF including ischemia or acute coronary syndromes, arrhythmia, uncontrolled hypertension, pneumonia, WRF, and noncompliance with diet or medications.[113]

Prompt identification and early medical management of precipitating factors in AHF are essential to improve outcomes of these patients.

MAINSTAYS OF THERAPY

Hospital management of AHF begins with immediate emergency department assessment followed by comprehensive in-hospital and predischarge management and planning (Table 71–6 and Fig. 71–9).[59,114] Two phases of AHF care have been described.[55,56] Phase I is the stabilization phase, often beginning with care in the emergency department, where the main goals include identification and improvement of signs and symptoms, hemodynamics, and correction of volume overload. Phase II continues into the hospitalization and through discharge planning. Primary goals include prevention of disease progression, focus on improving cardiac function, and following the evidence-based guidelines. Critical to phase I is early and appropriate identification of precipitating factors and determination of clinical profiles whereby therapies can be targeted appropriately based on patient selection. Paramount to phase II is appropriate incorporation of guideline-based therapy for both assessment and management, with careful attention to quality metrics to ensure safe discharge and optimize mortality benefit.

The presence of congestion is a leading factor in hospitalization for AHF. Multiple strategies for decongestion are used, including diuretics such as loop and thiazide and MRAs, vasodilators, ultrafiltration, vasopressin antagonists, and some novel agents.

TABLE 71–5. Phases of Acute Heart Failure Management

Phases	Goals	Available Tools
Initial or emergency department phase of management	Treat life threatening conditions	Examples: STEMI ⟶ reperfusion therapy
	Establish the diagnosis	History, physical exam, EKG, X-ray, natriuretic peptide level
	Determine the clinical profile	BP, HR, signs (eg pulmonary oedema), ECG, X-ray, laboratory analysis, echocardiography
	Identify and treat precipitant	History, physical exam, X-ray, ECG, laboratory analysis No universally accepted risk-stratification method
	Disposition	
In-hospitai phase	Monitoring and reassessment	Signs/symptoms, HR, SBP, ECG, orthostatic changes, body weight, laboratory analysis (BUN/Cr, electrolytes), potentially BNP
	Assess right and left ventricular pressures	SBP (orthostatic changes, valsalva manoeuvre), echocardiography, BNP/NT-pro BNP, PA catheter
	Assess and treat (in the right patient) other cardiac and non-cardiac conditions	Echo-Doppler, cardiac catheterization, electrophysiology testing
	Assess for myocardial viability	MRI, stress testing, echocardiography, radionu clear studies
Discharge phase	Assess functional capacity	6 min walk test
	Re-evaluate exacerbating factors (eg non-adherance, infection, anaemia, arrhythmias, hypertension) and treat accordingly	Examples: physical therapy, education for diet control and medication, evaluation for sleep apnoea
	Optimize pharmacological therapy	ACCF/AHA and ESC guidelines
	Establish post-discharge planning	Discharge instructions including body weight monitoring, smoking cessation, medication adherance, follow-up

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; ECG, electrocardiogram; ESC, European Society of Cardiology; HR, heart rate; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PA, pulmonary artery; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

Reproduced with permission from Gheorghiade M, Zannad F, Sopko G, et al: Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005 Dec 20;112(25):3958-3968.

TABLE 71–6. Precipitating Factors Leading to Acute Heart Failure

Medical Factors	Psychosocial Factors
CARDIAC:	Noncompliance with
Changes to cardiac meds (negative inotropes such as BB or non-DHPs)	Na restriction
Accelerated or uncontrolled HTN	Fluid restriction
Ischemia	Medications
Valvular	Daily weights
Unstable arrhythmia	Poor insight into illness
NONCARDIAC:	Poor access to medications or health care as a result of cost or physical condition
Endocrine abnormalities	ETOH or illicit drug use
Infection	OTC drugs such as NSAIDS, herbal, dietary
Anemia	
Pregnancy	
Pulmonary embolus	

Abbreviations: BB, β-blocker; DHP, dihydropyridine; ETOH, alcohol; HTN, hypertension; Na, sodium; NSAID, non-steroidal anti-inflammatory drug; OTC, over the counter.

DIURETICS (LOOP DIURETICS, THIAZIDES, MINERALOCORTICOID RECEPTOR ANTAGONISTS)

At the center of successful management of AHF is recognition and management of volume overload related to retention of salt and water in order to restore an euvolemic state. The mainstay of diuretic therapy is loop diuretics (furosemide, torsemide, bumetanide, and ethacrynic acid). In general, patients with AHF will require intravenous diuretics, with initial dose either equivalent to or exceeding their current home dose.[51] Diuretic therapy should be delivered without delay because early intervention has been shown to improve outcome in observational studies.[78,115] The Diuretic Optimization Strategies Evaluation (DOSE) trial randomized AHF patients to low-dose (equal to daily diuretic dose) or high-dose (2.5 times total daily dose) furosemide, administered as either an intravenous bolus every 12 hours or as a continuous infusion. The study found no significant difference between strategies in the patient-reported global assessment of symptoms and no change in serum creatinine from baseline to 72 hours.[116] However, there was a trend toward greater improvement in patients' global assessment of symptoms in the high-dose versus the low-dose group. In addition, the high-dose strategy was associated with more favorable outcomes in some secondary measures, including lower levels of BNP, higher levels of diuresis, and relief of dyspnea.

Certain patients with refractory volume retention may require higher doses of their current loop diuretic, a switch to an alternative loop diuretic, or addition of a diuretic with a different mechanism of action such as a thiazide diuretic (ie, metolazone or chlorthalidone). Thiazides may be useful as an addition in patients on chronic loop diuretics because they may overcome loop diuretic resistance, but they should be used with caution because they can cause severe electrolyte disturbances such as profound hypokalemia.

MRAs such as spironolactone and eplerenone have established mortality benefit in chronic HFrEF patients in low doses, secondary to their antifibrotic properties and beneficial effects on cardiac remodeling.[117-119] Higher doses can augment diuresis by blocking salt-retaining aldosterone receptors.[120] Thus far, high-dose spironolactone has only been evaluated in one trial, where it led to decreased edema, orthopnea, and NT-proBNP levels.[121] Further studies with MRA therapy in AHF are ongoing.

Mild elevations in blood urea nitrogen and creatinine should be monitored closely but should not prompt lowering or withholding of diuretic therapy. Intravenous loop diuretics can, however, reduce glomerular filtration rate and create a cycle of worsening neurohormonal activation and electrolyte disturbances. Excessive or incorrect use can lead to hypotension or renal dysfunction. In some patients in whom volume overload is accompanied by pre-existing renal impairment, response to diuretic therapy may be attenuated. In most cases, adequate diuretic dosing improves renal function as a result of venous decongestion.[122]

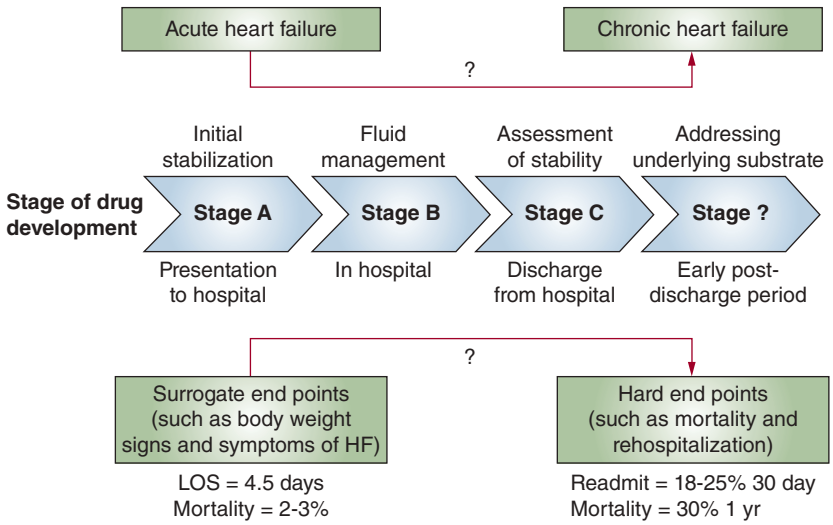

FIGURE 71–9. In-hospital assessment of acute heart failure from presentation through hospital discharge. HF, heart failure; LOS, length of stay. Reproduced with permission from Greene SJ, Fonarow GC, Vaduganathan M, et al: The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol*. 2015 Apr;12(4):220-229.[114]

Patients requiring an augmented diuretic strategy require frequent reassessment and monitoring of volume status by physical exam, measurement of daily weight, measurement of supine and standing vital signs, and daily serum laboratory testing. Hospital discharge should only be considered once euvolemia has been achieved and an appropriate diuretic strategy for maintenance therapy has been established. Roughly 50% of patients are discharged from the hospital with residual congestion after which they are at considerably higher risk of early readmission and poor outcomes.[123]

VASOPRESSIN ANTAGONISTS

Approximately 25% of patients admitted with AHF have low serum sodium, which is a strong predictor for postdischarge mortality and readmission.[124] Solute-free water diuretics, or "aquaretics," exert their effects through vasopressin antagonism. These agents include tolvaptan, conivaptan, and lixivaptan. They are most commonly used for the correction of hyponatremia but have been evaluated in the setting of AHF. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial revealed a clinical benefit with vasopressin, with significant weight reduction and dyspnea scores at 24 hours and decreased volume retention at day 7. Despite this, there were no observed differences in hospitalization or mortality at 10-month follow-up.[125] Lixivaptan effectively removes fluid in NYHA class II and III chronic HF patients.[126] The ongoing Treatment of Hyponatremia Based on Lixivaptan in NYHA III/IV Cardiac Patient Evaluation Study will aim to define the role of this "vaptan" in AHF patients with hyponatremia.[127] Conivaptan differs from others because of intravenous delivery and has been shown in a small pilot study to improve diuresis when added to a loop diuretic regimen,[128] although larger scale studies are needed.

ULTRAFILTRATION

If marked volume retention persists and more conservative strategies are limited by renal dysfunction, patients may require mechanical removal of volume with ultrafiltration (UF) or hemodialysis.[129,130] Ultrafiltration uses a volume removal strategy of moving water and small- to medium-weight solutes across a semipermeable membrane, using two peripheral venous catheters, thus avoiding complications of central venous access.[131] UF machines are relatively simple to use and do not require the same level of care as hemodialysis.[132] The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure trial was a 200-patient trial demonstrating the UF group to have greater weight loss and volume removal with no differences in dyspnea at 48 hours. By 90 days, the UF group had lower risk of HF hospitalization and fewer unscheduled clinic visits, without any difference in renal function or overall mortality.[133] The subsequent Cardiorenal Rescue Study in Acute Decompensated Heart Failure trial randomized 188 patients with AHF, WRF, and persistent intravascular congestion to receive either UF or high-dose loop diuretics (employing an aggressive strategy of addition of thiazide diuretics, inotropic agents, or vasodilators, as needed), and found no differences in mean weight loss at 96 hours. The UF group had more serious adverse events, mainly bleeding and worsened serum creatinine levels. As a result of uncertainty surrounding the results of these trials, a subsequent 800-patient trial, the Study of Heart Failure Hospitalizations After Aquapheresis Therapy Compared to Intravenous Diuretic Therapy, was undertaken but terminated prematurely secondary to slow patient recruitment.[134] The ACC/AHA guidelines currently state that UF is reasonable in certain patients with refractory congestion once other strategies have failed.[51]

VASODILATOR THERAPY

In patients with severe volume overload in the absence of systemic hypotension, intravenous vasodilators such as nitroglycerin, nitroprusside, or nesiritide may play a beneficial role when added to diuretic therapy.[51] These agents may be particularly suited in patients with adequate blood pressure experiencing refractory congestion with inadequate diuretic response. Intravenous nitroglycerin, primarily a venodilator, lowers preload, thereby relieving pulmonary congestion. Patients with hypertension, coronary ischemia, or severe mitral regurgitation are considered good candidates for nitroglycerin therapy.[135] Limitations include rapid development of tachyphylaxis, leading to drug resistance even at high doses.[136] Sodium nitroprusside is a balanced venous and arterial vasodilator that also provides some pulmonary vasodilation. Sodium nitroprusside can be used in markedly congested patients with hypertension or severe mitral regurgitation, although use is often limited by potential for systemic hypotension and potential thiocyanate toxicity, especially in patients with renal insufficiency.[135] Nesiritide reduces LV filling pressures and relieves dyspnea but may lead to hypotension. Nesiritide was shown to improve early hemodynamics in the Vasodilation in the Management of Acute Heart Failure trial.[137] However, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Subsequent trial failed to reach statistical significance for either relief of dyspnea or HF readmission or death at 30 days compared with placebo.[138] Furthermore, the Renal Optimization Strategies Evaluation in Acute Heart Failure trial with low-dose nesiritide versus low-dose dopamine in patients with AHF and renal failure also failed to show improvements in urine output, renal function, rehospitalization, HF symptoms, or mortality and showed nesiritide to be associated with more symptomatic hypotension than placebo.[139]

Endothelin receptor antagonist tezosentan was assessed in the Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies (VERITAS) study, which demonstrated no difference in tezosentan versus placebo in dyspnea, worsening HF, or death.[140] The Relaxin in Acute Heart Failure trial compared 48-hour serelaxin infusion versus placebo in patients presenting within 16 hours for AHF.[141] Serelaxin improved patient-reported dyspnea on a visual analog scale but not on a Likert scale and was associated with improvement in 6-month cardiovascular mortality risk.[142] Similarly, 24-hour infusion of ularitide was evaluated in the Safety and Efficacy of an Intravenous Placebo-Controlled Randomized Infusion of Ularitide in Symptomatic, Decompensated Chronic Heart Failure I and II trials.[143,144] Both serelaxin and ularitide are currently being investigated in ongoing phase III studies.

According to ACC/AHA guidelines, the use of vasodilators cannot be generalized because of lack of definitive data but may play a role in specific situations including relief, augmentation of blood pressure control complicating HF, and as an aid for the improvement in hemodynamic abnormalities while transitioning to oral medications.[51]

SODIUM AND FLUID RESTRICTION

Historically, based on neurohormonal imbalances leading to impaired excretion of sodium and water, HF patients have been advised to limit intake of both. Recent studies have questioned that high sodium intake correlated with development of AHF.[145] In the inpatient setting, sodium restriction may or may not be beneficial. In AHF patients randomized to a fluid- (800 mL/d) or sodium-restricted (800 mg/d) diet for 3 days of hospitalization, there were no differences in length of stay, renal function, body weight, congestion, or readmission, but perceived thirst was higher in the treatment group.[146] In a study of combination high-dose furosemide with high-dose hypertonic saline, patients randomized to the combination strategy versus high-dose diuretic alone had

improved diuresis, natriuresis, and renal function, with lower readmission and mortality rates.[147] The current ACC/AHA guidelines suggest that sodium restriction is reasonable in patients with symptomatic HF, and fluid restriction of 1.5 to 2 L/d can be considered in stage D patients, particularly with concurrent hyponatremia.[51]

ASSESSMENT OF PERFUSION AND HYPOTENSION

One of the strongest predictors of inpatient and postdischarge mortality in HF patients is low blood pressure.[148] Approximately 25% of patients at hospital presentation have low blood pressure, defined as systolic blood pressure ≤ 120 mm Hg, among which a subset has clinical signs and symptoms of low CO and systemic hypoperfusion. AHF patients with blood pressure < 110 mm Hg have an in-hospital mortality of 12% versus 4% for those who are normotensive.[149] OPTIMIZE-HF found in-hospital all-cause mortality to be highest for those with the lowest quartile BP (defined as SBP < 120 mm Hg).[148] EVEREST found patients with low blood pressure to be at high risk for rehospitalization from immediately after discharge to at least 18 months after discharge.[150] All oral agents known to improve long-term mortality in HF patients reduce blood pressure, greatly limiting use in this subset of patients for whom the therapeutic target is increased CO.[151]

Assessment of systemic perfusion is an essential component in management of AHF. A small subset of patients presents with a clinical scenario of low CO, manifested by low blood pressure (with or without congestion) accompanied by signs of diminished end-organ perfusion. Clinical manifestations may include cool or clammy skin, cool extremities, decreased urine output, and alterations in mental status. In patients considered to be "low output," consideration should be given to use of inotropic agents such as dopamine, dobutamine, and milrinone (Table 71–7). Milrinone, a phosphodiesterase-3 inhibitor, decreases the degradation of cyclic adenosine monophosphate, thus increasing protein kinase A, leading to phosphorylation of multiple myocardial targets downstream augmenting contractility. Milrinone is termed an *inodilator* because it effects contractility and decreases systemic and pulmonary vascular resistance. Because of its ability to improve pulmonary vascular resistance, milrinone administration may produce reversibility of marked pulmonary hypertension associated with poor CO.[152] The mechanism of action of milrinone is independent of β-adrenergic receptors, which are downregulated in HF. Because of this, the effect of the drug is independent of concomitant use of β-blocking agents and may influence a clinician's choice to choose milrinone over dobutamine. Milrinone has a half-life of roughly 2.4 hours and is renally cleared. Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure[153] evaluated the use of milrinone (0.5 μg/kg/min) versus placebo within 48 hours of hospital admission in all AHF patients not limited to the low-output group. Milrinone use did not result in decreased duration of hospitalization and was associated with a nonsignificant higher mortality both in hospital and after discharge, as well as higher rates of new-onset atrial arrhythmias and sustained hypotension requiring intervention. Thus, routine use of milrinone is not indicated in AHF.

Dobutamine is a sympathomimetic agent whose mechanism of action is through stimulation of β_1 receptors. The effect of dobutamine may be attenuated in patients who are concurrently taking BBs. Because it does not have direct pulmonary vasodilating properties, dobutamine typically does not affect pulmonary vascular resistance. Dobutamine has a half-life of 2 minutes with largely hepatic clearance. Both milrinone and dobutamine can cause a tachycardic response and are often arrhythmogenic, portending a higher risk of mortality. Observational analysis from the ADHERE registry suggested increased mortality with inotrope use in patients hospitalized with AHF, mostly in those with normal or elevated blood pressure.[154] ACC/AHA guidelines suggest that short-term inotropic support may be considered only for those patient with hypotension and signs of low CO, and long-term inotrope use may be considered for palliative treatment in stage D patient who are not candidates for advanced therapies. Guidelines also warn of harm in routine use of such parenteral agents.[51]

Levosimendan is a calcium sensitizer whose inotropic effect relates to its binding to calcium-saturated troponin C in the myocardial thin filament, which results in prolongation of actin-myosin coupling. In contrast to other inotropic agents, levosimendan does not cause an

TABLE 71–7. Intravenous Inotropic Agents Used in the Management of HF

Intropic Agent	Dose (mcg/kg)		Drug Kinetics and Metabolism	Effects				Adverse Effects	Special Considerations
	Bolus	Infusion (/min)		CO	HH	SVR	PVR		
Adrenergic agonists									
Dopamine	N/A	5 to 10	$t_{1/2}$: 2 to 20 min	↑	↑	↔	↔	T, HA, N, tissue necrosis	Caution: MAO-I
	N/A	10 to 15	R,H,P	↑	↑	↑	↔		
Dobutamine	N/A	2.5 to 5	$t_{1/2}$: 2 to 3 min	↑	↑	↓	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I; CI: sulfite allergy
	N/A	5 to 20	H	↑	↑	↔	↔		
PDE inhibitor									
Milrinone	N/R	0.125 to 0.75	$t_{1/2}$: 2.5 h H	↑	↑	↓	↓	T,↓BP	Renal dosing, monitor LFTs

BP indicates blood pressure; CI, contraindication; CO, cardiac output; F, fever; H, hepatic; HA, headache; HF, heart failure: HR, heart rate: LFT, liver function test; MAO-I, monoamine oxidase inhibitor; N, nausea; N/A, not applicable; N/R, not recommended; P, plasma; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; R, renal; SVR, systemic vascular resistance; T, tachyarrhythmias; and $t_{1/2}$, elimination half-life.

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increase in myocardial oxygen demand. Additionally, levosimendan also has vasodilatory, anti-inflammatory, and antiapoptotic properties.[155] In 2013, an expert panel reviewed potential uses for levosimendan in advanced HF patients and concluded there were several clinical scenarios in which the drug may be suitable to maintain clinical stability, although mortality data are lacking.[156] Levosimendan may also have a role in various types of cardiogenic shock including fulminant myocarditis, post–myocardial infarction, and Takotsubo cardiomyopathy, although prospective study is needed.[155] The second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy trial[157] and Survival of Patients With Acute Heart Failure in Need of Intravenous Inotrope Support trial[158] failed to show an overall mortality benefit in levosimendan compared with placebo or dobutamine, respectively, and currently the drug is not approved for use in AHF in the United States. The drug may have a role in select patients undergoing cardiac surgery, which is currently being studied in the Levosimendan in Patients With Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery on Cardiopulmonary Bypass trial (NCT02025621).

NEUROHORMONAL MODULATING THERAPIES

Numerous clinical trials have suggested that patients with chronic HFrEF respond as favorably to oral neurohormonal modulating therapies.[51] There is evidence to suggest that continuation or limited change in oral therapy in AHF is possible and positively affects outcomes.[159] In patients hospitalized with AHF with reduced ejection fraction not already being treated with oral therapies known to improve outcomes such as ACEI/ARBs, BBs, and MRAs, these agents should be initiated prior to discharge.[51] The decision to initiate (or reinitiate) BBs should be based on volume status optimization, generally after intravenous diuretics, vasodilators, and inotropic medications have been discontinued and hemodynamic stability has been established. Patients hospitalized with hypertension should have their medications uptitrated during hospitalization whenever possible. Importantly, the majority of patients with AHF should not have their oral HF therapy held because studies suggest that continuation is associated with improved outcomes and is well tolerated.[160,161]

There are certain scenarios during which therapy may require discontinuation or adjustment.[162] Patients with marked volume overload with marginal hemodynamics may require temporary disruption or lowering of BB dosing until further euvolemia is achieved. Patients with WRF, azotemia, or hyperkalemia may require cessation or downtitration of ACEI and/or aldosterone antagonist therapies, pending improvement in renal function. When starting or restarting ACEIs and BBs, initial dosing should be low, with careful attention to intolerance. Hospitalization for AHF often presents a unique opportunity to optimize oral HF medications in a more controlled setting with careful attention to blood pressure and renal function, which is often difficult to do with tenuous outpatients.

INVASIVE AND SURGICAL MANAGEMENT

There are certain hemodynamic conditions that require additional hemodynamic support. These clinical situations vary widely but result in compromised myocardial oxygen supply or demand. With acute myocardial infarction, reduced LV contractile function, increasing myocardial oxygen demand, and acute elevations in LV end-diastolic volume and pressure are coupled with diminished coronary blood flow. Cardiogenic shock is defined as systemic tissue hypoperfusion caused by inadequate CO despite adequate circulatory volume and filling pressure. Hemodynamic criteria include systolic blood pressure < 90 mm Hg for > 30 minutes, a drop in mean arterial pressure > 30 mm Hg below baseline with cardiac index < 1.8 L/min/m^2 without hemodynamic support, and a PCWP > 15 mm Hg.[163,164] For patients with advanced HF, the Interagency Registry for Mechanically Assisted Circulatory Support has defined seven clinical profiles with respect to acuity of hemodynamic deterioration, where profiles 1 and 2 refer to patients who either have acutely decompensated or are rapidly failing ionotropic therapy.[165] A consensus statement was published in 2015 to address the use of mechanical circulatory support in cardiovascular care.[166] The optimal timing for placement of mechanical circulatory support remains a source of debate, but the landscape of available options has evolved. Many factors influence the type of mechanical circulatory support to use, including the degree of hemodynamic instability, technical considerations, and acuity of need for implantation.

Intra-aortic balloon pump remains the most used temporary circulatory support device as a result of its widespread availability and familiarity. The intra-aortic balloon pump increases diastolic blood pressure, decreases myocardial oxygen consumption, improves coronary arterial perfusion, and provides up to 500 mL of additional CO. For patients requiring additional hemodynamic support, LA to aorta and LV to aorta assist devices can be considered. The Tandem heart is currently the only LA-aorta assist device commercially available and is inserted percutaneously via a trans-septal approach to pump extracorporeal blood from the LA to the iliofemoral artery, bypassing the left ventricle. The TandemHeart (TandemLife, Pittsburgh, PA) reduces LV preload, filling pressures, wall stress, and myocardial oxygen demand and, depending on cannula size, can provide up to 5 L of circulatory blood flow. Adequate right ventricular function or the use of simultaneous right ventricular assist device is necessary to maintain adequate LA preload. The Impella (Abiomed, Danvers, MA) is a nonpulsatile axial flow device that propels blood from the LV to the aorta and, depending on the specific device, can provide from 2.5 L/min (Impella 2.5) up to 5 L/min (Impella 5.0) of circulating blood volume. Similar to the TandemHeart, Impella decreases myocardial oxygen consumption, improves mean arterial blood pressure, and reduces PCWP. This device also relies on adequate preload for optimal functioning. Extracorporeal membrane oxygenation provides cardiopulmonary support either as veno-veno or veno-arterial support, with veno-arterial extracorporeal membrane oxygenation used as the mechanical circulatory support system of choice in patients requiring full biventricular support secondary to cardiogenic shock and inadequate oxygenation. Although veno-arterial extracorporeal membrane oxygenation can provide flows exceeding 6 L/min, the system often requires additional ventricular unloading (either by intra-aortic balloon pump or Impella) to reduced ventricular wall stress and myocardial oxygen demand. Bleeding, infection, limb ischemia, and hemolysis can complicate any of the aforementioned mechanical circulatory support devices. Extracorporeal devices can be used for short-term circulatory support in patients who are expected to recover from a major cardiac insult (eg, myocardial ischemia, postcardiotomy shock, or fulminant myocarditis).[166]

OTHER CONSIDERATIONS

Patients hospitalized with HF carry an increased risk of thromboembolic events and should receive prophylactic anticoagulation unless contraindicated.[167] Whenever possible, attempts should be made to transition patients from intravenous to oral medications, with careful attention to hemodynamic compromise once this occurs. Treating clinicians should assess and discuss overall prognosis with patients and

their caregivers, once functional status and precipitating factors have been addressed.[51] When indicated, discussions regarding advanced therapies and/or end-of-life care should ensue[133] (Table 71–8).

HOSPITAL DISCHARGE, PATIENT EDUCATION, AND TRANSITIONS OF CARE

Many registries suggest that patients with AHF are commonly discharged before euvolemia is achieved, without optimal BP control and without optimal use of life-saving medications such as ACEIs/ARBs and BBs.[59] To optimize posthospitalization outcomes, clinicians should follow published guidelines.[51] A critical performance measure set forth for HF hospitalization involves care coordination and transition of care, which includes written discharge instructions or educational materials provided to patients explaining discharge medications, activity level, diet, weight monitoring, follow-up visit instructions, and what to do if symptoms worsen.[168] Patients admitted with AHF should be evaluated prior to discharge for appropriateness for devices, including cardiac resynchronization therapy and implantable cardioverter-defibrillator.[169] Consideration should also be given to candidacy for implantable pressure sensors such as CardioMEMS (St. Jude Medical, St. Paul, MN), which may aid in decreasing rehospitalization compared with clinical assessment alone.[170] Patients should be provided with referral to a tertiary care centers with expertise in mechanical device support and/or orthotopic heart transplantation and other advanced surgical options as indicated for advanced disease.[51]

Early postdischarge assessment should include careful attention to congestion, the leading cause of readmission, optimizing diuretic doses, and other guideline-recommended drug- and device-based therapies, including uptitration of medications to recommended doses.[59] Recent data suggest that follow-up with a physician within 7 days of discharge[171] and follow-up with a cardiologist[172] can lower 30-day mortality. HF hospitalization is a well-recognized independent risk factor for mortality in patient with chronic HF, and the postdischarge period a particularly vulnerable phase for patients.[114] Comprehensive discharge planning ensuring compliance with guideline-recommended therapy can reduce readmissions and improve patient outcomes.[173]

TABLE 71–8. Clinical Events and Findings Useful in Identifying Patients With Advanced HF

Repeated ≥2) hospitalizations or ED visits for HF in trie past year
Progressive deterioration in renal function (eg, rise in BUN and creatinine)
Weight loss without other cause (eg, cardiac cachexia)
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
Intolerance to beta blockers due to worsening HF or hypotension
Frequent systolic blood pressure < 90 mm Hg
Persistent dyspnea with dressing or bathing requiring rest
Inability to walk 1 block on the level ground due to dyspnea or fatigue
Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose over 160 mg/d and/or use of supplemental metolazone therapy
Progressive decline in serum sodium, usually to < 133 mEq/L
Frequent ICD shocks

ACE indicates angiotensin-converting enzyme; BUN, blood urea nitrogen; ED; emergency department; HF, heart failure; and ICD, implantable cardioverter-defibrillator.

Adapted from Russell et al.[274]

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HEART FAILURE READMISSIONS

HF is the number one cause of hospitalization among Medicare beneficiaries, and each hospital readmission portends worse mortality risk subsequently than previous admission. Nearly 25% of patients are rehospitalized within 30 days, and 50% of HF patients are rehospitalized within 6 months of index hospitalization.[18,19] In observational registry data, mortality was reported to be approximately 40%, and readmission rate was nearly 70% at 1 year after index AHF admission.[174] With the aging population, HF rates and rehospitalizations are estimated to rise significantly. Several risk factors for rehospitalization have been identified, including but not limited to advanced age; ischemic etiology; low systolic blood pressure; increased heart rate; higher NYHA class at discharge; laboratory abnormalities such as low admission hemoglobin, admission and discharge creatinine, and increased blood urea nitrogen; other testing abnormalities such as prolonged QRS on electrocardiogram; echocardiographic parameters such as lower ejection fraction; higher systolic pulmonary artery pressure; and right ventricular tissue Doppler imaging.[18] Similarly, natriuretic peptide levels at admission and on discharge predict readmission risk, and postdischarge measurement also guides further risk stratification.[18] Both cardiac and noncardiac comorbidities increase risk of rehospitalization, as do patient-reported quality of life scores and psychosocial factors.[18] In addition, prolonged index hospitalization length of stay predicts higher risk of 30-day all-cause hospitalization.[175]

Currently, the 30-day postdischarge hospitalization rate is a metric that is associated with financial penalties by Medicare. Identification of low- and high-risk patient is necessary to risk stratify patients for likelihood of readmission in order to optimize prevention interventions. However, although several risk prediction models have been described for readmission risk, knowledge gaps in pathophysiology and heterogeneity of the patient population render these scores less accurate than risk prediction models for mortality. A recent scientific statement by the AHA summarizes available transitional care models with respect to interventions and outcomes, highlighting the need for further study in order to best integrate this approach. Key components included patient education prior to discharge focused on "teach back" to ensure patient engagement and understanding, early postdischarge follow-up and reassessment, and effective communication between in-hospital and outpatient providers.[176] Several strategies appear to be effective, especially when used in combination, to reduce HF readmissions, including partnering of inpatient teams with local physicians and local hospitals, medication reconciliation, assuring follow-up appointments before discharge, having discharge summaries sent to primary care physicians, and assigning team members to follow up on pending test results after discharge.[177] A "three-phase terrain" of HF readmission describes the predisposition of patients to early rehospitalization following admission and highlights this vulnerable period in the trajectory of a hospitalized HF patient, underscoring the need for tailored strategies targeted at preventing readmission.[178]

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CHAPTER 72

CARDIAC TRANSPLANTATION

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HISTORY AND OVERVIEW OF CARDIAC TRANSPLANTATION

Despite major advances in the treatment of end-stage heart disease, a sizable number of patients with refractory heart failure (HF), progressive angina, or uncontrolled ventricular arrhythmias cannot be stabilized with medical or interventional/surgical therapy and suffer significant morbidity and mortality.[1] In these patients, biological replacement of the heart (cardiac transplantation) has become standard therapy and is widely accepted to improve quality and quantity of life in carefully selected patients. As technologic and engineering advances occur, support or replacement of the heart by mechanical devices (mechanical circulatory support [MCS]) offers additional options for patients with end-stage heart disease as a bridge to recovery, bridge to transplantation, or destination therapy.

Early efforts to implant a functioning donor's heart into a recipient's circulation date back to the early part of the twentieth century. In 1905, Carrel and Guthrie[2] described the heterotopic transplantation of a functioning donor heart into the neck of a dog. The heart in that model functioned together with the recipient's heart in the circulation but was not capable of supporting the circulation. Although the exact anatomic connections were not described in detail in the original publication, this model of heterotopic transplantation beat regularly for approximately 2 hours before the blood clotted in all of the chambers. Carrel and Guthrie developed innovative surgical techniques for vascular anastomosis at the University of Chicago, and those advances set the stage for future organ transplantation.[3] These techniques included using ever-finer needles and sutures made slick with petroleum jelly, developing the triangulation method of small vessel anastomosis, and perfecting the everting anastomosis technique.[4] This work was partially responsible for Carrel's Nobel Prize for Physiology or Medicine in 1912.

It was not until 1933 that Mann and coworkers[5] at the Mayo Clinic published their seminal report of a technique for heterotopic heart transplantation. Because this was a canine working model, the chambers did not clot immediately, and the hearts beat for a mean of 4 days. Mann and coworkers established several important surgical principles or tenets, including the importance of avoiding ventricular distention and air embolism and the prevention of thrombosis by heparin. Their most incisive observation was that failure of a transplanted heart was not always caused by faulty surgical technique "but to some biologic factor which is probably identical to that which prevents survival of other homotransplanted tissues and organs."[5] In what was undoubtedly the first description of acute allograft rejection, Mann and coworkers recount: "When the heart was removed just before it became quiescent … the surface of the heart was covered with mottled areas of ecchymoses … histologically, the heart was completely infiltrated by large mononuclears and polymorphonuclears."[5] It took another 30 years to understand and manipulate the "biologic factor" these authors had described as limiting the survival of allograft organs.

In 1960, Lower and Shumway[6] performed orthotopic heart transplants in dogs using cardiopulmonary bypass and topical hypothermia for donor heart preservation. The dogs survived between 6 and 21 days and died of rejection. The main difference from the work of Mann and colleagues was that Lower and Shumway immersed the donor heart in cold saline, used cardiopulmonary bypass in the recipient, and combined the pulmonary venous and vena caval anastomoses into two atrial anastomoses. Lower and Shumway also recognized that "if the immunologic mechanisms of the host were prevented from destroying the graft, in all likelihood it would continue to function adequately for the normal lifespan of the animal."[6] Their technique remained the basis of cardiac transplantation technique through the 1990s.

In the early 1960s, the concept of pharmacologic immunosuppression was introduced; it ushered in the marriage of surgical and medical knowledge that characterizes the modern field of organ transplantation. Immunosuppression was viewed as a means to mitigate the "biologic factor" that otherwise limited organ graft survival. The first clinical transplants were of the kidney, which was a logical choice because hemodialysis was then available as a backup treatment if the graft failed, and the field has flourished since the early 1960s.[7]

The first human heart transplant was performed in South Africa in December 1967,[8] followed shortly thereafter by the first US heart

transplant by Shumway and colleagues at Stanford in January 1968. A flurry of transplant activity began at many centers, but the initial enthusiasm waned as it became evident that postoperative survival was limited by a variety of complex medical problems, including opportunistic infections and graft rejection. Most major centers discontinued their heart transplant programs in the early 1970s. It was not until the introduction of cyclosporine-based immunosuppression in 1980 and the demonstration of the attendant improvement in survival rates[9] that the procedure re-emerged as a widely accepted therapy for end-stage heart disease. By the 1990s, many tertiary care and academic centers had established programs for heart transplantation, and most medical care payers in the United States, including the federal government, provided coverage for such care. Currently, there are almost 6 million patients in the United States with HF, with an estimated 300,000 with end-stage HF who would be potentially eligible for heart transplantation or MCS.[10,11] However, because of limited donor availability, the number of heart transplantations performed worldwide is estimated to be more than 4000 procedures annually.[12]

RECIPIENT SELECTION AND MANAGEMENT

INDICATIONS

Given the relative scarcity of donor organs, it is essential to determine if end-stage HF patients are truly refractory to maximal medical therapy and merit transplant evaluation. The commonly acceptable indications for heart transplantation are shown in Table 72–1. Generally, the three major indications for heart transplantation are severe functional limitations, refractory angina, and ventricular arrhythmias refractory to maximal medical therapy.[13] The most common indication for heart transplantation is intractable HF. Patients with severe angina in the absence of HF are often not considered, since the survival benefit is unclear. Intractable ventricular arrhythmias, commonly referred to as "VT storm," may merit heart transplant evaluation and often urgent listing given the associated hemodynamic compromise and mortality.

Although these indications for cardiac transplantation are generally well accepted, identifying the subgroup of patients that is most likely to derive a benefit from transplantation can be challenging. Optimization of medical therapy is a crucial part of determining if a patient would benefit from heart transplantation. Standard of care for patients with HF with reduced systolic function includes an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker, β-receptor antagonist, and mineralocorticoid antagonists to improve symptoms and survival.[14] A new class of medication, the angiotensin receptor–neprilysin inhibitor combination sacubitril/valsartan, has proven superior to an ACE inhibitor alone in reducing HF hospitalization and mortality and will likely become standard of care instead of ACE inhibitors in HF patients.[15] Digoxin reduces rehospitalization in HF patients.[16] In addition to optimal medical therapy, device therapy with implantable defibrillators saves lives.[17] In appropriate candidates with increased QRS duration > 120 milliseconds, especially in those with left bundle branch block, cardiac resynchronization improves symptoms and survival.[18-20] For patients with ischemic cardiomyopathy, surgical revascularization may also be indicated to improve long-term survival.[19] Aggressive medical therapy has led to significant improvement in stable HF patients, with a survival of close to 75% at 5 years. However, in patients refractory to medical management, survival is estimated at 20% at 5 years.[1] It is in these end-stage patients that more advanced therapy should be considered.

Thus, the goal of a heart transplant evaluation is to determine if (1) the patient's cardiac status is limited enough, on optimal medical therapy, to benefit from heart transplantation (ie, "sick enough"); (2) the patient does not have comorbidities that would preclude heart transplantation (ie, "well enough"); and (3) the patient demonstrates compliance and possesses adequate social support ("can adapt to new transplant lifestyle"). At an advanced HF center, patients may undergo right heart and pulmonary arterial catheterization for optimization of filling pressures and cardiac output and to ensure absence of severe pulmonary hypertension, revascularization of coronary artery disease, or ablation of ventricular tachycardia, before considering heart transplantation. As a result, most heart transplant centers have evolved into centers for advanced HF management in addition to providing the opportunity for transplantation or mechanical support.

TABLE 72–1. Commonly Accepted Indications for Cardiac Transplantation

Systolic heart failure with severe functional limitations or refractory symptoms despite optimal medical and device therapy
NYHA functional class IIIb-IV
LVEF usually < 35%[a]
Maximal oxygen uptake (VO_2 max) of ≤ 12-14 mL/kg/min and/or VO_2 max < 50% predicted and/or VE/VCO_2 slope > 35 on cardiopulmonary exercise stress testing[b]
Cardiogenic shock not expected to recover
Acute myocardial infarction
Acute myocarditis
Ischemic heart disease with intractable angina not amenable to surgical or percutaneous revascularization and refractory to maximal medical therapy
Intractable ventricular arrhythmias, uncontrolled with standard antiarrhythmic, device, or ablative therapy
Severe symptomatic hypertrophic or restrictive cardiomyopathy
Congenital heart disease in which severe, fixed pulmonary hypertension is not a complication
Cardiac tumors with a low likelihood of metastasis

Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VE/VCO_2, minute ventilation/carbon dioxide production slope.

[a]Low LVEF alone is not an adequate indication for heart transplantation.

[b]Abnormal cardiopulmonary exercise testing in the absence of functional limitations is not a sufficient criteria for transplantation.

Role of Exercise Testing

In ambulatory patients, evaluation often includes cardiopulmonary exercise stress testing to determine if a patient is limited enough to merit heart transplant evaluation.[21,22] The cardiopulmonary exercise stress test measures maximal oxygen consumption (VO_2 max), which is proportional to cardiac output. Patients with a peak VO_2 of more than 14 mL/kg/min have 1- and 2-year survival rates that are comparable or better than those achieved with transplantation, and these patients should be managed medically and undergo serial exercise testing.[21,22] In the original publication, the threshold of 14 mL/kg/min was not based on a sensitivity/specificity analysis. Instead, this threshold was selected as a criterion for acceptance for cardiac transplant based on the investigators' prior experience that patients with peak VO_2 levels below this threshold had significant functional limitations and based on exercise data in the literature. The literature at the time suggested that peak VO_2 level was an independent predictor of death[23] and that an exercise capacity under 4 metabolic equivalents (equivalent to a peak VO_2 under 14 mL/kg/min) was a stronger predictor of death in patients with HF after myocardial infarction.[24]

Patients with a peak VO_2 between 10 and 14 mL/kg/min constitute an intermediate-risk group in which continued medical therapy may offer a survival benefit similar to heart transplantation among selected patients who are able to tolerate β-blockers and have the protection of an internal defibrillator.[25,26] In patients tolerating β-blockers, a peak VO_2 of less than 12 mL/kg/min has been suggested as an appropriate threshold to identify individuals who are likely to derive a survival benefit from transplantation.[27] Patients with a peak VO_2 of 10 mL/kg/min or less, regardless of β-blocker use, have significantly reduced survival rates with medical therapy compared with cardiac transplantation, and these patients should be listed for transplantation.[24,28] Adequate effort is defined as the patient's achievement of anaerobic threshold, at which point CO_2 production exceeds O_2 consumption (indicated by the respiratory exchange ratio > 1.10).[29-31] Other parameters of cardiopulmonary exercise testing that are also associated with increased mortality include a predicted VO_2 max < 50%[32] and minute ventilation/carbon dioxide production slope > 35[33] and may be considered in the evaluation for heart transplantation. A score developed by Myers and colleagues[34] may offer further refine the use of cardiopulmonary exercise testing in HF. Based on their score, which combines ventilator efficiency, VO_2 max, heart rate recovery, oxygen uptake efficiency slope, expired carbon dioxide, and chronotropic response, a score > 15 portends a high 1-year mortality rate in excess of 40%.

At an advanced HF center, end-stage patients may also be evaluated for MCS. MCS is considered for patients with end-stage HF as (1) a bridge to recovery, for those individuals who require temporary circulatory support and are expected to recover; (2) a bridge to transplantation, for those patients with progressive decline in organ perfusion on escalating inotropic therapy while awaiting transplantation; and (3) destination therapy, for those individuals with contraindications to heart transplantation, include advanced age.[35] The decision to proceed with MCS in the form of a left ventricular assist device, biventricular assist device, or total artificial heart as a bridge to transplantation will vary from center to center, depending on the patient's projected wait time to transplantation, degree of hemodynamic compromise, and anatomic consideration (for total artificial heart). In general, heart transplantation is usually the preferred option for end-stage HF patients, and MCS is reserved for patients who are not candidates for transplantation or who cannot survive until a heart becomes available. The options considered for patients may also vary by regions as donor wait time may be significantly different.

CONTRAINDICATIONS

Appropriate candidates for cardiac transplantation should have severe functional limitations, limited life expectancy from their heart disease, and a limited number of established contraindications (Table 72–2). Many of these factors are not absolute and need to be considered in the context of the severity of the patient's heart disease and associated comorbidities. The degree to which they are interpreted and applied may vary considerably among transplant programs.

Advanced Age

In general, patients are considered for heart transplantation if they are 70 years of age or less, since advances in post-transplant care have shown that survival in the older age group is comparable to that of younger recipients.[12] Patients over the age of 70 years have also been reported to have acceptable outcome, but careful consideration of associated comorbidities is essential in these cases. At some centers, such patients are offered nonstandard donor hearts, including those with coronary artery disease, mildly decreased left ventricular ejection fraction, left ventricular hypertrophy, or donor age older than 55 years.

TABLE 72–2. Contraindications to Heart Transplantation

Age	Over 70 is an relative contraindication depending on associated comorbidities
Obesity	BMI < 30 kg/m^2 is recommended; most centers will tolerate BMI < 35 kg/m^2[a]
Malignancy	Active neoplasm, except nonmelanoma skin cancer, is an absolute contraindication; cancers that are low grade or in remission may be acceptable in consultation with an oncologist
Pulmonary hypertension	The inability to achieve PVR < 2.5 Wood units with vasodilator or inotropic therapy is a contraindication; such patients may benefit from unloading with a ventricular assist device
Diabetes	Uncontrolled diabetes or that associated with significant end-organ damage is an absolute contraindication
Renal dysfunction	If caused by diabetes, may be an absolute contraindication (unless combined heart-kidney transplantation is considered)
Cirrhosis	May be secondary to cardiac disease and is an absolute contraindication in most centers (unless combined heart/liver transplant is considered)
Peripheral vascular disease	Severe disease not amenable to revascularization is an absolute contraindication, especially if associated with ischemic ulcers
Infection	HIV and hepatitis C are absolute contraindications at most centers; with novel hepatitis C therapy, some centers may consider such patients
Substance use	6 months of abstinence from smoking, alcohol, and illicit drugs are required; in critically ill patients, consultation with psychiatry and social work is essential
Psychosocial issues	Noncompliance, lack of caregiver support (either provided by family or agencies), and dementia are absolute contraindications; mental retardation may be a relative contraindication

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; PVR, pulmonary vascular resistance

[a]Higher BMI may be acceptable in certain populations with larger body habitus, such as patients of Pacific Island descent

Adapted with permission from Kittleson MM, Kobashigawa JA: Management of advanced heart failure: the role of heart transplantation. *Circulation*. 2011 Apr 12;123(14):1569-1574.

This practice allows older patients to undergo heart transplantation without denying the scarce resource to younger potential recipients, with comparable outcomes.[36] Physiologic age may be more important than chronologic age with respect to survival and rehabilitation potential. As a result, many programs are moving away from fixed upper age limits and instead focus on a patient's functional status, integrity of major organ systems, and the presence of comorbidities that might impact survival, rehabilitation potential, and quality of life.

Pulmonary Hypertension

Pulmonary hypertension from chronic elevation of left ventricular end-diastolic pressure is a common complication of long-standing HF and can result in irreversible changes to the pulmonary vasculature over time if left unrecognized and untreated.[37] In the early years of heart transplantation, it was discovered that a normal donor right ventricle (RV) is unable to increase its external workload acutely to overcome elevated pulmonary vascular resistance (PVR), resulting in acute RV failure and cardiogenic shock postoperatively.[38] Elevated PVR remains a strong risk factor for RV failure and early postoperative mortality in the modern era. Potential heart transplant candidates must therefore undergo measurements of pulmonary artery pressures and

calculation of PVR in the cardiac catheterization laboratory or in the intensive care unit as part of their transplant evaluation.

A pulmonary artery systolic pressure above 50 to 60 mm Hg, a PVR value above 5 Wood units, or a transpulmonary gradient above 15 to 20 mm Hg is usually considered prohibitive of successful heart transplantation. A vasodilator challenge should be administered when the pulmonary artery systolic pressure is ≥ 50 mm Hg and either the transpulmonary gradient is ≥ 15 or the PVR is > 3 Wood units. Pharmacologic interventions for reducing PVR include administration of intravenous agents such as nitroprusside, prostaglandin E_1, nesiritide, milrinone, and dobutamine or use of inhaled nitric oxide. The use of oral phosphodiesterase-5 inhibitors (sildenafil) has been shown to improve pulmonary hypertension caused by left ventricular systolic dysfunction sufficiently to allow heart transplantation.[39]

A vasodilator challenge is considered successful if the PVR can be reduced below 2.5 Wood units with a vasodilator while maintaining a systolic arterial blood pressure over 85 mm Hg. If the PVR cannot be reduced below 2.5 Wood units or if the systolic blood pressure falls below 85 mm Hg with reduction in the PVR, the patient remains at high risk of right HF and mortality after cardiac transplantation. In this situation, hospitalization with continuous hemodynamic monitoring should be performed, as often the PVR will decline after 24 to 48 hours of treatment consisting of diuretics, inotropes, and vasoactive agents. If this strategy is unsuccessful, longer-term unloading with an intra-aortic balloon pump or left ventricular assist device may be considered.[22] In one study, after 6 months of left ventricular assist device support, mean PVR decreased from 3.5 to 1.5 Wood units.[40] In another study, mean PVR decreased from 5 to 2.1 Wood units after 3 months of left ventricular assist device support.[13,22,41]

Infections

Patients must be free of active infection before transplantation because infections can be exacerbated by the immunosuppression that is required after transplantation to prevent rejection. The presence of an active systemic infection or severe localized infection is often considered a temporary contraindication to transplantation. Patients with a history of infection should not be activated or reactivated on the transplant waiting list until there is sufficient evidence that the infection is resolved or under control, as demonstrated by absence of fever for a minimum of 72 hours on appropriate antibiotics, a normal white blood cell count, negative blood culture results, and resolving signs or symptoms of infection.

The evaluation of patients with chronic viral infections such as hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) remains controversial, and such patients are considered poor transplant candidates by many centers.[42,43] Whether the use of the new nucleotide polymerase inhibitors that may achieve a sustained virologic response in patients with hepatitis C will change this relative contraindication is not yet clear but is changing practice at many centers. At some centers, HIV infection is no longer considered a contraindication to heart transplantation as long as the patient has no opportunistic infections, acceptable CD4 count, and an undetectable viral load and acceptable outcomes have been achieved in selected patients.[44-46] Chagas disease, while uncommon in the United States, is a common indication for transplantation in South America, and reactivation of disease can occur.[47] The decision to proceed with transplantation in these situations must be made in collaboration with an infectious disease specialist well-versed in transplantation.

Malignancy

In general, patients with active malignancies, with the exception of nonmelanoma cutaneous cancers, primary cardiac tumors restricted to the heart, and low-grade neoplasms of the prostate, should be excluded from cardiac transplantation. However, pre-existing neoplasms are diverse with respect to their response to immunosuppressive therapy and risk of recurrence. Consultation with an oncologist should be obtained for any patient with a history of previous or active malignancy to assess the risk of tumor recurrence. Cardiac transplantation should be considered when the risk of tumor recurrence is low based on the tumor type, response to therapy, and negative metastatic workup. The specific amount of time to wait before transplantation after neoplasm remission should depend on the aforementioned factors, and no arbitrary time period for observation should be used.

Other Comorbidities

Potential cardiac transplant recipients are screened for the existence of other conditions or systemic diseases that may independently limit their survival or rehabilitation potential. Obese patients have a greater risk of poor wound healing, infections, and pulmonary complications after cardiac surgery, although the outcomes in heart transplant recipients are less clear.[12] Nevertheless, it is recommended that patients achieve a body mass index < 30 kg/m^2 before listing. This may be difficult to achieve in patients with poor functional status, and most centers will consider patients with a body mass index < 35 kg/m^2 or slightly higher thresholds in patients of African or Pacific Islander race.

The presence of pre-existing insulin-requiring diabetes mellitus was once considered a relative contraindication to heart transplantation because of concerns regarding diminished survival, increased infection rates, and worsening glycemic control with the initiation of corticosteroid immunosuppression. However, several reports have demonstrated similar short- and long-term survival rates in diabetic and nondiabetic groups, as well as similar rates of infection, rejection, renal function, and cardiac allograft vasculopathy.[48-50] Although the safety and efficacy of heart transplantation in these very carefully selected patients have been documented in the literature, most transplant programs continue to consider the presence of diabetes with end-organ damage (proliferative retinopathy, neuropathy, or nephropathy) a relative contraindication to transplantation. Corticosteroid therapy may worsen glycemic control in patients with preexisting diabetes, and thus the presence of poorly controlled diabetes is also considered a relative contraindication for transplantation. At most centers, patients are expected to achieve control with a hemoglobin A1c under 7.5% before listing for transplantation; ongoing collaboration with an endocrinologist is helpful in achieving this goal. In patients with poorly controlled diabetes mellitus, early weaning of steroids before 6 months is sometimes considered.

Other comorbid conditions must be considered on an individual basis, but irreversible organ dysfunction such as pulmonary fibrosis, severe emphysema, and hepatic or renal dysfunction out of proportion to that predicted as a consequence of severe HF are strong relative contraindications. Selected patients with irreversible renal or hepatic dysfunction may be considered for multiorgan transplantation.[51-54] The presence of cardiac cirrhosis has been considered a contraindication to heart transplantation as a result of concern for progressive liver failure and increased mortality, although data are sparse.[55]

Advanced noncardiac vascular disease, in the form of symptomatic cerebrovascular disease or peripheral vascular disease that is not amenable to revascularization, is considered a relative contraindication to transplantation if the condition is expected to limit survival or impair rehabilitation after transplantation.

Experience has shown that pulmonary infarcts have a high probability of becoming pulmonary abscesses after the institution of immunosuppression. For this reason, potential recipients who sustain

a pulmonary infarction are usually temporarily removed from the waiting list until the infarct resolves as shown radiographically.

Psychosocial Factors

All cardiac transplant candidates should undergo a careful psychosocial assessment with emphasis on current and previous substance abuse history, compliance with medical therapy and follow-up, comprehension of and ability to follow a complex medical regimen, and adequacy of social support. Active cigarette smoking is a contraindication to heart transplantation, and smoking during the previous 6 months before transplant is a risk factor for poor outcomes.[13,22] At most centers, patients must display abstinence from smoking for 6 months, documented by urine nicotine screens, prior to listing. Addiction to alcohol or illicit drugs is an absolute contraindication, as it suggests that these patients will have poor compliance after transplantation, and 6 months of abstinence with participation in counseling programs are required. This assessment may be difficult to make in the critically ill patient in whom transplantation cannot be delayed for 6 months. In this scenario, consultation with social workers and psychiatrists is essential to gauge the patient's commitment to abstinence.

In addition to freedom from dependence on cigarettes, alcohol, and illicit substances, patients must be able to demonstrate the ability to comply with medications and follow-up after transplantation, which includes social support with a dedicated caregiver. Patients have been denied transplantation as a result of lack of compliance and social support. Mental retardation and dementia are relative contraindications to heart transplantation; the former because of concerns of compliance and the latter because of overall poor prognosis.

SPECIAL CONSIDERATIONS

A small but substantial proportion of patients with advanced HF are affected by diseases expressing a phenotype not characterized by left ventricular dilation and hypokinesis and are usually unresponsive to traditional pharmacologic and device therapy. These diseases include hypertrophic cardiomyopathy, restrictive cardiomyopathies, and infiltrative cardiomyopathies such as sarcoidosis or amyloidosis.[56] These diseases represent a challenge to the traditional management of end-stage systolic HF. Prognosis, therapeutic strategies, and indications for heart transplantation in these patients require disease-specific considerations and often assessment of extracardiac organ involvement. Furthermore, experience with MCS is limited in patients with restrictive or infiltrative cardiomyopathies[57] and not currently recommended.[22]

CHANGING FACE OF HEART TRANSPLANTATION

Although heart transplantation has become standard of care for the management of end-stage HF, the role of heart transplantation is changing as the characteristics of heart transplant candidates continue to evolve.[58] Heart transplant candidates are increasingly more complex: they are older, recipients of MCS, and sensitized.

The proportion of candidates age 65 years or older has increased; in 2013, 18.2% of candidates in the United States were age 65 years or older, compared with 10.8% in 2003.[59] The proportion of candidates with MCS (most commonly ventricular assist devices) at listing has also increased dramatically, from 7.5% in 2003 to 27.4% in 2013.[59] Furthermore, the number of heart transplant candidates with antibodies to human leukocyte antigens (HLA), so-called "sensitization," has increased over the past decade.[60]

The heart transplant candidates of the modern era—older, sensitized, with MCS—are at higher risk for poor outcomes, including primary graft dysfunction and antibody-mediated rejection.[12,59,61] Strategies to mitigate this risk are ongoing, including proposed changes in heart transplant allocation policy for more equitable organ distribution,[62,63] a better understanding of the definition and management of primary graft dysfunction,[64] and advances in the management of sensitized heart transplant candidates.[65,66] Developments in these areas could result in more equitable distribution and expansion of the donor pool and improved quality of life and survival for heart transplant recipients.

DONOR SELECTION AND MANAGEMENT

Acceptance of the concept of irreversible brain death, both legally and medically, has been integral to the emergence of organ transplantation in the modern era. Brain death is defined as irreversible cessation of all functions of the entire brain.[67] The heart does not need to stop for a valid declaration of death, and this definition has facilitated heart transplantation. Criteria for brain death have been adapted from the Harvard Ad Hoc Committee (1968)[68] and codified into law in the Uniform Determination of Death Act (1981) following the President's Commission Report. Fundamental requirements for brain death are summarized in Table 72–3.[69]

The most common causes of brain death include intracranial hemorrhage, blunt traumatic injury to the head, penetrating traumatic injury, and anoxic brain injury. Patients with irreversible brain injury accompanied by the intent to withdraw life support are also considered potential organ donors. The complete absence of brainstem function is not required; many patients who meet all the criteria for brain death do not, in fact, have irreversible cessation of all functions of the entire brain, because some of the brainstem's homeostatic functions remain, such as temperature control and water and electrolyte balance.[70]

DONOR EVALUATION

After a potential donor is identified, the procurement process is initiated by contacting the local, or "host," organ procurement organization (OPO). The host OPO is responsible for obtaining consent for organ donation, verifying pronouncement of brain death, evaluating and managing the donor, and equitably allocating the donor organs. The process of donor evaluation begins with a detailed history and physical examination, focusing on cause of death, past medical history, donor height and weight, and clinical course. Basic laboratory studies, including a complete blood count, metabolic panel, ABO blood typing, and viral serologies (hepatitis B and C, HIV, human T-cell leukemia virus, Ebstein-Barr virus [EBV], and cytomegalovirus), are ordered; in addition, other serologies may be obtained in the presence of outbreaks such as West Nile virus or in donors considered high risk for infections such as Chagas disease. Additional studies include chest radiography, 12-lead electrocardiography (ECG), and echocardiography.

To be considered suitable donors for cardiac transplantation, brain-dead individuals must meet certain minimum criteria (Table 72–4). Most cardiac donors are younger than age 55 years, although older donors may be used selectively in critically ill or older recipients. There should be no evidence of severe cardiothoracic trauma or cardiac puncture. An initial echocardiogram is performed to identify significant structural heart disease such as left ventricular hypertrophy or dysfunction, occlusive coronary artery disease, valvular dysfunction, and congenital lesions. Donors with these conditions are typically excluded, although selected marginal organs may be allocated to higher risk recipients. Angiography is performed to exclude significant coronary artery disease in male donors older than age 45 years and in female donors older than age 50 years but may also be performed in younger patients with multiple risk factors for coronary artery disease. Patients

TABLE 72–3. Criteria for Determining Brain Death

Clinical evaluation
Mechanism of brain injury is sufficient to account for irreversible loss of brain function
Absence of reversible causes of CNS depression
CNS depressant drugs[a]
Hypothermia (< 32°C)
Hypotension (MAP < 55 mm Hg)
Absence of neuromuscular blocking drugs that may confound the results of the neurologic examination
No spontaneous movements, motor responses, or posturing
No gag or cough reflexes
No corneal or pupillary light reflexes
No oculovestibular reflex (cold calorics)
Confirmatory tests
Apnea test for minimum of 5 min showing:
No respiratory movements
pCO_2 > 55 mm Hg
pH < 7.40
No intracranial blood flow

Abbreviations: CNS, central nervous system; MAP, mean arterial pressure; pCO_2, partial pressure of carbon dioxide.

[a]Removal of CNS-depressing drugs may take several days to take effect.

TABLE 72–4. More Favorable Donor Characteristics

Age < 55 y
Absence of significant structural abnormalities such as:
LV hypertrophy (wall thickness > 13 mm by echocardiography)[a]
Significant valvular dysfunction
Significant congenital cardiac abnormality
Significant coronary artery disease
Adequate physiologic function of donor heart
LVEF ≥ 45%[b] or
Achievement of target hemodynamic criteria after hormonal resuscitation and hemodynamic management
MAP > 60 mm Hg
PCWP 8-12 mm Hg
Cardiac index > 2.4 L/min·m^2
CVP 4-12 mm Hg
SVR 800-1200 dyne/s·cm^5
No inotrope dependence
Donor-recipient body size match (usually within 20%-30% of height and weight)[c]
Negative hepatitis C antibody,[d] hepatitis B surface antigen, and HIV serologies Absence of active malignancy (except nonmelanoma skin cancers and certain primary brain tumors) or overwhelming infection

Abbreviations: CVP, central venous pressure; HIV, human immunodeficiency virus; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

[a]Echocardiograms are often reviewed by the accepting center to confirm the accuracy of the reported left ventricular dimensions.

[b]LVEF may be reduced as a result of catecholamine-induced myocardial stunning and may resolve in a period of days to hours.

[c]Mainly guided by weight matching; donor weight mismatch is more concerning with female donors given the likelihood of a greater contribution of fat to overall body weight.

[d]Hepatitis C donors may not be absolutely contraindicated at all centers with the advent of antiviral therapy that offers the chance of cure.

with active malignancy (excluding nonmelanocytic skin cancers and certain isolated brain tumors) or severe systemic infections are typically excluded. HIV and hepatitis B and C infections would preclude organ donation, although whether hepatitis C donors will be considered with the advent of new nucleotide polymerase inhibitors that offer a potential for cure remains to be seen.[71]

DONOR MANAGEMENT

After brain death has been determined and the patient has been identified as a potential organ donor, the main goals of organ donor management are to ensure optimal organ function by providing volume resuscitation; optimizing cardiac output; normalizing systemic vascular resistance; maintaining adequate oxygenation; correcting anemia, acid-base, and electrolyte abnormalities; and correcting hormonal imbalances that occur after brain death and that can impair circulatory function. Standardized algorithms incorporating early use of invasive hemodynamic monitoring along with aggressive hemodynamic management and hormonal resuscitation with insulin, corticosteroids, triiodothyronine, and arginine vasopressin have been proposed to improve cardiac donor management and maximize organ utilization, particularly in patients with a left ventricular ejection fraction below 45% on initial echocardiography.[72] In brain death, particularly in cases of subarachnoid hemorrhage, there is a catecholamine surge that can result in left ventricular dysfunction and regional wall motion abnormalities.[73] This dysfunction is often not associated with structural abnormalities and may be reversible, so such donors may ultimately be acceptable for transplantation.[74,75]

Most donor hearts are currently harvested locally from the donor by an organ procurement team from the transplant center and transported back to the center for implantation. A cold ischemic period of less than 4 to 6 hours in adult hearts is generally considered optimal. This requirement for short ischemic times leads to the rationale for geographic subdivision into OPOs for cardiac allografts despite the drive for a national list for other organs.

Currently, fewer than 50% of potential organ donors in the United States become actual donors.[76] Despite ongoing efforts to increase the identification of potential donors, increase the consent rate among eligible donors, expand donor selection criteria, and maximize potential donor organ function, heart transplantation will likely remain a donor-limited field for the foreseeable future.

In an effort to expand the donor pool, recently donation after circulatory death (DCD) has been successfully employed for heart transplantation.[77] In DCD, retrieval of organs for the purpose of transplantation occurs from patients whose death is diagnosed and confirmed using cardiorespiratory criteria. Asystole must be confirmed for at least 5 minutes for declaration of death. This may occur following cardiac arrest awaited after planned withdrawal of life support in patients who are not brain dead. The challenge for heart transplantation using DCD donors is the minimization of ischemic injury of the donor organs.

One way to minimize ischemic injury would be to limit cold ischemic time through use of an ex vivo heart perfusion platform that maintains the donor heart in a warm, beating state for transplantation. In a trial to assess the safety of an ex vivo platform, 130 patients were randomized to receive donor hearts preserved with either the Organ Care System or standard cold storage. There was no difference in 30-day patient and graft survival rates or serious adverse events.[78] An ongoing phase III clinical trial, the EXPAND trial (International Trial to Evaluate the Safety and Effectiveness of the Portable Organ Care System [OCS"] Heart for Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation; NCT02323321), will offer further insight into the utility of this platform.

ORGAN MATCHING AND ALLOCATION

Donor-recipient matching is performed based on ABO blood group compatibility and overall body size. Although the benefit of matching donor organs and recipients with respect to HLA has been well established in renal transplantation, HLA matching is not performed in potential heart transplant recipients because of the relative scarcity of donor organs. However, heart transplant candidates who are sensitized (those with preformed anti-HLA antibodies related to prior pregnancy, transplant, blood transfusions, or MCS) will undergo crossmatching to determine if there are potentially cytotoxic antibodies against the donor HLA. This can be performed with a prospective crossmatch whereby donor cells are mixed with recipient serum to assess for cell-dependent cytotoxicity prior to heart transplantation. Although this is the gold standard, a prospective crossmatch constrains the donor pool to OPOs where recipient serum can be banked for comparison. The "virtual crossmatch" is a relatively newer advance where the recipient's HLA antibodies are compared to the donor's HLA type. Donors with HLA types that correspond to the presence of HLA antibodies in the recipient are avoided. This major advance in antibody management expands the donor pool and has been found to be comparable in accuracy and safety to the prospective crossmatch in many cases.[79] However, a prospective crossmatch is still employed for heart transplant candidates with multiple high-level HLA antibodies for which potential cytotoxicity cannot be adequately predicted, and thus a virtual crossmatch is considered less reliable.[80]

Allocation of thoracic organs in the United States is made according to the recipient's priority on the United Network for Organ Sharing (UNOS) waiting list and geographic distance from the donor. Priority on the recipient waiting list is determined by a recipient's assigned status code and time accrued within a status code. In general, patients with the highest medical urgency and lowest expected short-term survival are assigned a higher status code (Tables 72–5 and 72–6). Donor hearts are first offered to local Status 1 patients and then extended to Status 1 patients within a 500-mile radius of the donor hospital (Zone A). If no eligible recipients are identified, the organ is offered to local Status 2 patients. This process repeats in a sequence of "zones" delineated by subsequent concentric circles of 1000- and 1500-mile radii from the donor hospital.[59]

As a result of the emerging MCS population and need to further reduce waitlist mortality, changes to the current US donor heart allocation scheme are being planned by the UNOS Thoracic Committee. These changes include options for improved geographic sharing and altering the status of potentially disenfranchised groups, which may result in a new multi-tiered allocation scheme. The new allocation scheme will prioritize patients with end-organ dysfunction who have increased short-term mortality.[62]

TABLE 72–5. Recipient Prioritization for Heart Transplantation in the United States

Status 1A
Mechanical circulatory support
VAD until clinically stable (≤ 30 d) or with objective medical evidence of significant device-related complications (thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias)
Total artificial heart as an inpatient
IABP
ECMO
Mechanical ventilation
Continuous infusion of single high-dose inotrope or multiple inotropes in addition to continuous hemodynamic monitoring of LV filling pressures
Exceptional provision for patients with medical urgency not meeting above criteria
Status 1B
VAD beyond 30 d
Total artificial heart as an outpatient
Continuous infusion of IV inotropes not meeting criteria in IA
Status 2
Any candidate not meeting criteria for status 1A or 1B
Status 7
Inactive as a result of a change in condition, such as infection; patients do not lose time they have already accrued

Abbreviations: ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic balloon pump; IV, intravenous; LV, left ventricular; VAD, ventricular assist device.

SURGICAL TECHNIQUE

The donor heart is explanted, or "harvested," by a surgical team at a hospital usually remote from the transplant center, and the procedure must be coordinated with the surgical teams procuring other organs for transplantation. The donor heart is first arrested with cardioplegic solution. The original surgical technique for orthotopic heart transplantation, or biatrial technique, was described by Lower and Shumway in 1960.[6] In this procedure, both the donor and recipient hearts are removed by transecting the atria at the midatrial level, leaving the multiple pulmonary venous connections to the left atrium intact in the posterior wall of the left atrium, and then transecting the aorta and pulmonary artery just above their respective semilunar valves. The explanted heart is cooled topically by being placed in an iced preservation solution; it is then placed in a secure container and transported expeditiously to the transplant center. Ischemic times average 3 to 4 hours.

Implantation of the heart in the orthotopic position begins with reanastomosis at the midatrial level, beginning with the atrial septum (Fig. 72–1). Efforts are made to include a generous cuff of donor right atrium so the sinoatrial node will be included. The great vessels are connected just above the semilunar valves. Commonly seen with the biatrial technique is the presence of two asynchronous P waves on ECG. One P wave emanates from the sinus node of the donor heart and the other from the sinus node in the right atrial remnant of the native heart. In recent years, the biatrial technique has been modified by leaving the donor atria intact and making anastomoses at the level of the superior and inferior vena cavae and

TABLE 72–6. Recipient Prioritization for Heart Transplantation in Canada

Status 4
Mechanically ventilated patient on high-dose single or multiple inotropes ± mechanical support (eg, intra-aortic balloon pump, extracorporeal membrane oxygenation [ECMO], Abiomed BVS5000, or Bio-Medicus), excluding long-term ventricular assist devices (VAD)
Patient with VAD malfunction or complication, such as thromboembolism, systemic device-related infection, mechanical failure, or life-threatening arrhythmia
Status 4S
High panel reactive antibody (> 80%)
Status 3.5
High-dose or multiple inotropes in hospital, and patients not candidates for VAD therapy or no VAD available
Acute refractory ventricular arrhythmias
Status 3
VAD not meeting Status 4 criteria
Patients on inotropes in hospital, not meeting above criteria
Heart/lung recipient candidates
Cyanotic congenital heart disease with resting saturation < 65%
Congenital heart disease, arterial shunt dependent
Adult-sized complex congenital heart disease with increasing dysrhythmic or systemic ventricular decline
Status 2
In-hospital patient, or patient on outpatient inotropic therapy not meeting the above criteria
Adult with cyanotic congenital heart defect: resting oxygen saturation 65%-75% or prolonged desaturation to < 60% with modest activity (eg, walking)
Adult with Fontan palliation with protein-losing enteropathy
Patients listed for multiple organ transplantation (other than heart-lung)
Status 1
All other out-of-hospital patients

Data from, Isaac D, Chan M, Haddad H, et al: Cardiac Transplantation: Eligibility and Listing Criteria in Canada 2012. Canadian Cardiac Transplant Network, December 2011.

pulmonary veins.[81] This *bicaval* technique (Fig. 72–2) results in less distortion of atrioventricular geometry, resulting in improved atrial and ventricular function, less atrioventricular regurgitation, decreased incidence of atrial arrhythmias, and decreased incidence of donor sinus node dysfunction and heart block requiring permanent pacemaker implantation.[82-84]

Immediate postoperative care differs little from that after more routine heart surgery except for the institution of immunosuppression (described later) and the need for chronotropic support of the donor sinoatrial node for the first 2 to 3 postoperative days, usually with temporary pacemaker support or with β-agonist intravenous infusions. Postoperative bradycardia usually results from sinus node dysfunction because of surgical trauma, ischemia to the sinus node, or pretransplant use of amiodarone.[85] Most cases resolve within a few weeks to months. The incidence of refractory bradycardia requiring permanent pacemaker implantation is between 10% and 20% with the biatrial technique and less than 10% with the bicaval technique.[84] Patients with uncomplicated postoperative courses are discharged from the hospital as early as 7 to 10 days after heart transplantation.

PHYSIOLOGY OF THE TRANSPLANTED HEART

LACK OF INNERVATION

When the donor heart is placed into the recipient, both afferent (from the heart to the central nervous system) and efferent (from the central nervous system to the heart) nerve supply is lost. The loss of afferent nerve supply means that the recipient will not experience angina with the exception of a small subgroup that may have reinnervation.[86] Therefore, chest discomfort in a heart transplant recipient, especially early after transplantation, is likely not caused by coronary ischemia, and coronary ischemia will likely not present with chest discomfort. The standard practice of annual angiograms for surveillance of transplant coronary artery disease is a direct consequence of the lack of afferent nerves supplying the transplanted heart and required for early detection of allograft vasculopathy.

The consequences of the loss of efferent nerves are related to the loss of vagal tone and the postganglionic direct release of norepinephrine stores in response to exercise. With the loss of vagal tone, heart transplant recipients have a higher than normal resting heart rate, usually around 90 to 110 bpm. The lack of efferent nerves also means that the transplant recipient must rely on circulating catecholamines to respond to exercise, so there is a blunting of the heart rate's response to exercise. Similarly, after exercise, the heart rate returns to baseline more slowly because of the gradual decline of circulating catecholamine concentrations to baseline.

Heart transplant recipients lack the baroreceptor reflex, which relies on intact baroreceptors and sympathetic and parasympathetic innervation. Thus, heart transplant recipients are more susceptible to orthostasis, and carotid sinus massage will not break a re-entrant tachycardia in these patients.

Nevertheless, heart transplant recipients often experience reinnervation of the heart, with possible angina, an improvement in exercise tolerance, and a decrease in resting heart rate. This process is variable among patients, although it tends to increase over time. Restoration of sympathetic innervation correlates with improved responses of heart rate and contractile function to exercise.[87]

RESPONSE TO MEDICATIONS

Some cardiac drugs are not effective in the denervated heart. As a result of the lack of vagal tone, digoxin will have little effect on sinoatrial and atrioventricular conduction velocity and will not achieve rate control if the transplanted heart develops atrial fibrillation. However, the inotropic effects of digoxin persist after transplantation. Similarly, the parasympatholytic effect of atropine will not increase heart rate in transplanted hearts. As a result of the lack of baroreceptor reflexes, vasodilators such as nifedipine and hydralazine will not cause reflex tachycardia.

The lack of postganglionic sympathetic nerves in the transplanted heart results in increased receptor density and thus more sensitivity to sympathetic agonists and antagonists.[88] Clinically, this is most often seen with β-blockers; heart transplant recipients will often have exaggerated fatigue in response to administration of β-blockers, especially with exercise.

POST-TRANSPLANT OUTCOMES

SURVIVAL

Survival after heart transplantation has steadily improved in the past three decades (Fig. 72–3). In the 1980s, 1-year survival was 70%, and the conditional half-life, the time at which 50% of patients who survived the first year are still alive, was 9.4 years. In the 2015 report from the

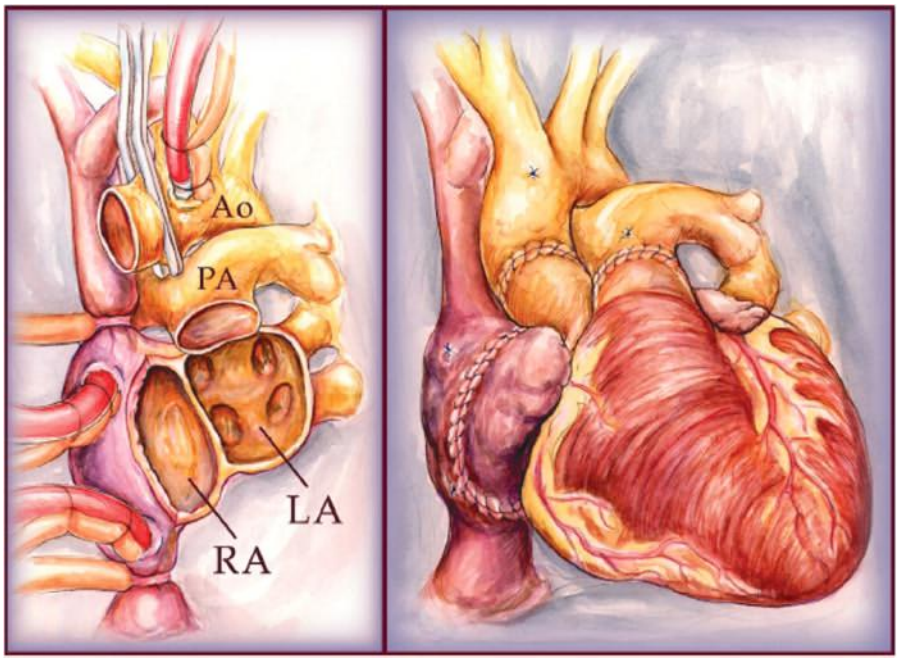

FIGURE 72–1. Original biatrial technique for orthotopic heart transplantation. The *left panel* shows the completed recipient cardiectomy with the recipient atria transected at the midatrial level. The *right panel* shows the completed reanastomosis of the donor heart. Ao, aorta; LA, left atrium; PA, pulmonary artery; RA, right atrium. Reproduced with permission from Pahl E, Backer CL, Mavroudis C. *Heart transplantation at Children's Memorial*. The Children's Doctor: Journal of Children's Memorial Hospital, Chicago. Fall 1999.

International Society of Heart and Lung Transplantation (ISHLT) registry,[12] 1-year survival was almost 90% with a conditional half-life of 14 years. Notably, the mortality rate beyond 1 year after transplant has improved only marginally for patients who received allografts after 1992, and there has been no statistically significant improvement in the past two decades. This stable annual mortality rate of approximately 3% to 4% is higher than that of the general population and likely exists because the processes responsible for long-term mortality, including cardiac allograft vasculopathy and malignancy, remain a challenge of detection and treatment. Thus, future improvements in post-transplant survival may result from interventions aimed at the detection and treatment of cardiac allograft vasculopathy and malignancy.

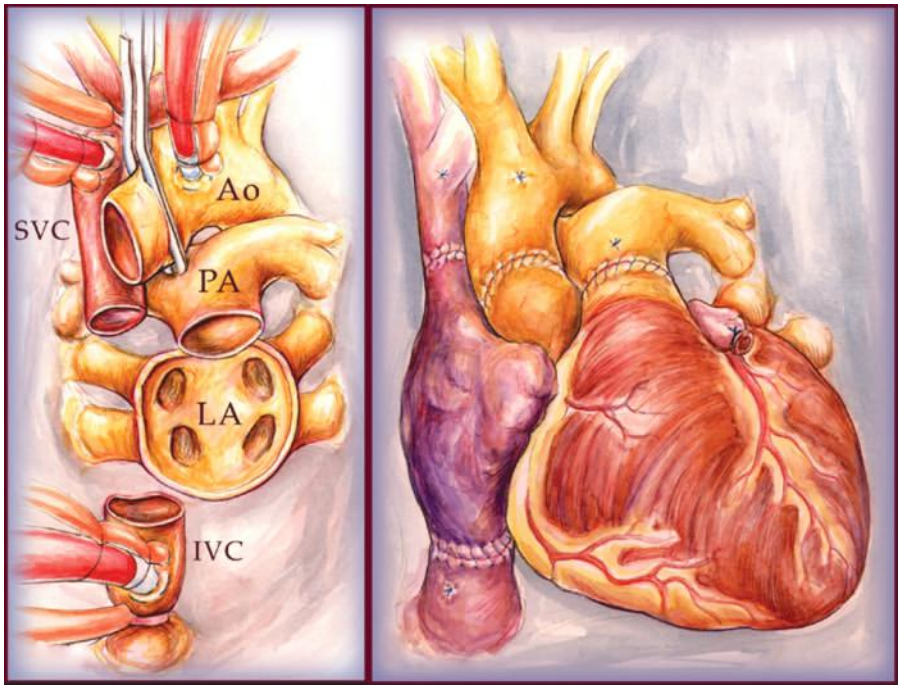

FIGURE 72–2. Bicaval technique for orthotopic heart transplantation. The *left panel* shows the completed recipient cardiectomy. The recipient atria are completed removed except for a cuff of tissue around the pulmonary vein orifices. The superior and inferior vena cavae are transected at their junction with the right atrium. The *right panel* shows the completed anastomoses of the donor heart at the level of the superior and inferior venae cavae and pulmonary veins. Ao, aorta; IVC, inferior vena cava; LA, left atrium; PA, pulmonary artery; SVC, superior vena cava. Reproduced with permission from Pahl E, Backer CL, Mavroudis C. *Heart transplantation at Children's Memorial*. The Children's Doctor: Journal of Children's Memorial Hospital, Chicago. Fall 1999.

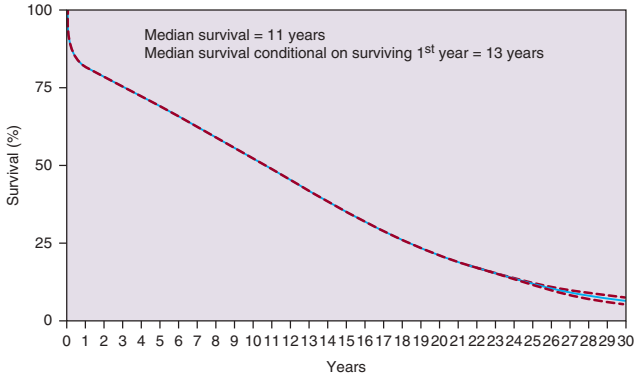

FIGURE 72–3. Actuarial survival for adult and pediatric heart transplants patients performed between January 1982 and June 2013. The half-life is the time at which 50% of those transplanted remain alive, and the conditional half-life is the time to 50% survival for recipients surviving the first year after transplantation. Reproduced with permission from International Society for Heart and Lung Transplantation. 2015 Registry. 2015 [Accessed 10 May 2016]. Available from: https://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry.

An in-depth analysis of risk factors for survival at 1, 5, 10, 15, and 20 years after transplantation is provided in the ISHLT registry report.[12] The strongest risk factors for 1-year mortality, associated with a 50% or more increase in the risk of 1-year mortality, are mainly related to technical issues and the underlying disease responsible for transplantation, including the use of temporary circulatory support, congenital cardiomyopathy versus nonischemic cardiomyopathy, prior transplant, and pretransplant ventilatory support or dialysis. Risk factors for 5- and 10-year mortality, on the other hand, are most referable to immunologic issues and toxicity related to immunosuppression, including dialysis or infection after transplant, rejection during the first post-transplant year, and lack of immunosuppression therapy with a combination of at least two of the following classes: cell cycle inhibitors, calcineurin inhibitors, and PSIs.

Transplant era influences 20-year survival; patients transplanted in 1990 have better 20-year survival than those transplanted in 1985.[12] Other factors affecting 20-year survival include etiology for transplantation, sex, age, ischemic time, and center volume. Patients receiving retransplant and those receiving transplant for ischemic heart disease or valvular heart disease have a lower likelihood of survival past 20 years after transplant compared with patients who receive an allograft for nonischemic cardiomyopathy. The reasons for this are unclear and may be related to progression of the underlying disease or older age of recipients with ischemic or valvular disease versus nonischemic cardiomyopathy. Women also have a somewhat higher risk of death compared with their male counterparts. Younger donor age, younger recipient age, lower allograft ischemic time, and higher center volume are additional factors associated with long-term survival, and these risk factors appear consistent across countries.

QUALITY OF LIFE

Patients not only gain increased quantity of life after transplantation, but quality of life is improved as well. In the first years after heart transplant, approximately 75% of recipients report having a normal healthy lifestyle or only few disease symptoms, an additional 15% participate in normal activities with some difficulty, and less than 10% report a higher degree of limitations.[12]

In-depth analysis of a smaller cohort of transplant patients indicates that the most frequently reported long-term symptoms after heart transplantation, at moderate rates of 50% to 65%, were fatigue, sexual dysfunction, memory problems, bruising, and cramps.[89] These symptoms are less common in recipients who are married and those with a higher educational level.

Based on information from the international registry, many patients return to work after transplant. Among recipients aged 25 to 55 years old, approximately 50% were employed 5 years after transplantation.[12] On the basis of the functional data reviewed above, it is apparent that additional recipients could return to the workplace; however, in the United States the structure of disability benefits and health insurance considerations may represent a barrier to this process.

POSTOPERATIVE MANAGEMENT

IMMUNOSUPPRESSION

General Principles

Most of the immunosuppressive regimens used in clinical transplantation consist of a combination of several agents used concurrently and use several general principles. The first general principle is that immune reactivity and tendency toward graft rejection are highest early (within the first 3-6 months) after graft implantation and decrease thereafter over time. Thus, most regimens use the highest levels of immunosuppression immediately after surgery and decrease those levels over the first year, eventually settling on the lowest maintenance levels of immune suppression that are compatible with preventing graft rejection and minimizing drug toxicities. The second general principle is to use low doses of several drugs without overlapping toxicities in preference to higher (and more toxic) doses of fewer drugs whenever feasible. The third principle is that excessive immunosuppression is undesirable because it leads to a myriad of undesirable effects, such as susceptibility to infection and malignancy. Finding the right balance between over- and under-immunosuppression in an individual patient is truly an art that uses science.

Induction Therapy

Currently, about 50% of transplant programs use a strategy of augmented immunosuppression, or "induction" therapy, with antilymphocyte antibodies or interleukin-2 receptor antagonists during the early postoperative period. The goal of induction therapy is to provide intense immunosuppression during a time when the risk of allograft rejection is highest. Additionally, induction therapy allows delayed initiation of nephrotoxic immunosuppressive drugs in patients with compromised renal function after surgery. Agents used for induction therapy include polyclonal antithymocyte antibodies derived by immunization of horses (ATGAM) or rabbits (thymoglobulin) with human thymocytes. These agents may reduce the risk of early rejection but have been associated with an increased risk of infection.[90,91] Anti–interleukin-2 (IL-2) receptor antagonists such as daclizumab result in reduced rates of moderate or severe cellular rejection among heart transplant patients treated with standard immunosuppression (cyclosporine, mycophenolate mofetil [MMF], and corticosteroids) without increasing the incidence of opportunistic infection or cancer at 1 year. However, among patients receiving daclizumab induction, there was an increased risk of fatal infection when cytolytic therapy was concomitantly used.[92] Although induction therapy is commonly used, there have been no large randomized trials or studies based on UNOS registry data demonstrating benefit of induction therapy versus no induction therapy.

Maintenance Immunosuppression

Most maintenance immunosuppressive protocols use a three-drug regimen consisting of a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite agent (MMF or azathioprine), and tapering

doses of corticosteroids over the first year after transplantation. The commonly used drugs and their toxicities are outlined in Table 72–7. Recent trends in the use of these drugs are presented in Fig. 72–4.

The calcineurin inhibitors exert their immunosuppressive effects by inhibiting calcineurin, which is responsible for the transcription of IL-2 and several other cytokines, including tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor, and interferon-β. The result is blunting of T-lymphocyte activation and proliferation in response to alloantigens. The two available agents, cyclosporine and tacrolimus, inhibit calcineurin by forming complexes with different intracellular binding proteins. Since the introduction of cyclosporine in the early 1980s,[9] the calcineurin inhibitors have remained the cornerstone of maintenance immunosuppressive therapy in patients undergoing solid organ transplantation. Tacrolimus is favored over cyclosporine based on evidence from clinical trials suggesting that tacrolimus-based immunosuppression is associated with decreased rates of acute rejection.[93,94] Although nephrotoxicity is seen with both agents, there is more hypertension and dyslipidemia observed with cyclosporine and a higher incidence of new-onset insulin-requiring diabetes observed with tacrolimus.[95,96]

MMF has replaced azathioprine as the preferred antimetabolite agent in recent years based on a clinical trial demonstrating a significant reduction in both mortality and in the incidence of treatable rejection at 1 year with MMF versus azathioprine.[97] Mycophenolate sodium is an enteric-coated, delayed-release formulation developed to improve the upper gastrointestinal tolerability of MMF. It is therapeutically similar to MMF with respect to the prevention of both biopsy-proven and treated acute rejection episodes, graft loss, or death.[98]

Proliferation signal inhibitors (PSIs), or mammalian target of rapamycin inhibitors, are relatively more recent advances in standard immunosuppression. The two agents in this class, sirolimus and everolimus, inhibit the proliferation of T cells, B cells, and vascular smooth muscle cells in response to growth factor and cytokine signals. Compared with azathioprine, both sirolimus and everolimus reduce the incidence of acute rejection and prevent the development of cardiac allograft vasculopathy (CAV) when used in conjunction with cyclosporine and prednisone in de novo heart transplant recipients.[99,100] Compared to MMF, everolimus is noninferior with respect to the combined end point of rejection, graft loss, and death[101] and demonstrates less CAV progression as measured by intravascular ultrasound (IVUS) at 1 year.[102] Other benefits of sirolimus include slowing of CAV progression and reduction in the incidence of clinically significant cardiac events.[103] Also, when used in heart transplant recipients with significant renal impairment, sirolimus permits minimization or complete withdrawal of the calcineurin inhibitors, resulting in notable improvements in renal function without an associated increased risk of rejection.[104-106]

Sirolimus is generally not initiated de novo after transplantation because of an increased risk of sternal wound dehiscence,[107] but based on the benefits observed in clinical trials, it can be initiated later after transplantation for specific indications. The PSIs are often used in place of MMF in patients with rejection, allograft vasculopathy, malignancy, and viral infections such as cytomegalovirus[108] to prevent recurrence or progression. When used in place of the calcineurin inhibitor, the PSIs may prevent progression of renal dysfunction.

Corticosteroids are nonspecific anti-inflammatory agents that interrupt multiple steps in immune activation, including antigen presentation, cytokine production, and proliferation of lymphocytes. Although steroids are highly effective for the prevention and treatment of acute rejection, their long-term use is associated with a number of adverse effects, including new-onset or worsening diabetes mellitus, hyperlipidemia, hypertension, fluid retention, myopathy, osteoporosis, and a predisposition toward opportunistic infections. Thus, although most programs use corticosteroids as one of the three maintenance immunosuppressive agents, they are used in relatively high doses in the early postoperative period but are then tapered to low doses or discontinued altogether within the first 6 to 12 months.

Although dual- and triple-drug therapy are the most commonly used strategies for maintenance immunosuppression after heart transplantation, single-drug therapy using tacrolimus following early withdrawal of corticosteroids and MMF has also been shown to be safe and efficacious.[109] However, this strategy required higher tacrolimus trough levels, which resulted in higher serum creatinine levels at 1 year.

DRUG INTERACTIONS

In managing patients on immunosuppressive drug therapy, clinicians should be aware of the potential for drug interactions when other agents are added to or deleted from the patient's regimen.[110] A list of the most common and clinically important drug interactions is shown in Table 72–8. The calcineurin inhibitors and PSIs are predominantly metabolized by the cytochrome P450 3A4 pathway in the liver. Drugs that induce the P450 3A4 pathway, such as phenytoin, rifampin, and St. John's wort, enhance the metabolism of the calcineurin inhibitors and PSIs, thus lowering their blood levels and clinical effectiveness. Alternatively, drugs that inhibit the enzyme pathway such as calcium channel blockers, antifungal agents, and HIV protease inhibitors, decrease the metabolism of cyclosporine, tacrolimus, or sirolimus, thus increasing their drug levels and potentiating their nephrotoxic effects. Finally, the lipid-lowering agents lovastatin, atorvastatin, and simvastatin have decreased clearance and increased drug concentrations when used concurrently with the calcineurin inhibitors. Therefore, the use of higher doses of these statins may lead to an increased risk of myopathy or rhabdomyolysis. When a drug with the potential to interact with the immunosuppressive agents is added to or deleted from a patient's regimen, immunosuppressive drug levels and renal function should be carefully monitored.

RECOGNITION AND TREATMENT OF ACUTE REJECTION

DIAGNOSIS

Transplant rejection remains one of the major causes of death after heart transplantation[12] and is classified as hyperacute rejection, acute cellular rejection, or antibody-mediated rejection. Hyperacute rejection is rare but may occur in the setting of circulating preformed antibodies to the ABO blood group (in cases of ABO blood group incompatibility) or to major histocompatibility antigens in the donor. Possible risk factors include presensitization after blood transfusions, multiparity, and previous organ grafts.[111] Hyperacute rejection manifests as severe graft failure within the first few minutes to hours after transplantation. Without inotropic agents and MCS, plasmapheresis, and intense immunosuppression, the recipient usually does not survive.

Whereas the presentation of hyperacute rejection is dramatic, the signs and symptoms of acute rejection are generally nonspecific and may only manifest in the late stages. Patients may present with fatigue, low-grade fevers, HF symptoms, or hypotension. Occasionally, rejection will manifest as atrial arrhythmias or new pericardial effusions. On examination, patients may have an elevated jugular venous pressure or a new S_3 gallop. However, the majority of patients with acute cellular or antibody-mediated rejection are asymptomatic without signs of allograft dysfunction.

Because symptoms are often vague, routine testing for rejection is standard practice. Unlike renal or liver transplantation, there are no

TABLE 72–7. Immunosuppressive Agents Used in Heart Transplantation

Drug	Typical Dose	Major Toxicities
Calcineurin inhibitors		
Cyclosporine	3-6 mg/kg/d in two divided doses titrated to keep therapeutic 12-h trough levels[a]	Renal dysfunction Hypertension Dyslipidemia Hypokalemia and hypomagnesemia Hyperuricemia Neurotoxicity (encephalopathy, seizures, tremors, neuropathy) Gingival hyperplasia Hirsutism
Tacrolimus	0.02-0.04 mg/kg/d in two divided doses titrated to keep therapeutic 12-h trough levels	Renal dysfunction Hypertension Hyperglycemia and diabetes mellitus Dyslipidemia Hyperkalemia Hypomagnesemia Neurotoxicity (tremors, headaches)
Antimetabolite agents		
Azathioprine	1.0-3.5 mg/kg/d, titrated to keep WBC ~3000K	Bone marrow suppression Hepatitis (rare) Pancreatitis Malignancy
Mycophenolate mofetil	2000-3000 mg/d in two divided doses titrated to tolerance	GI disturbances (nausea, diarrhea) Leukopenia
Proliferation signal inhibitors		
Sirolimus	0.5-2 mg daily titrated to keep therapeutic 24-h trough levels	Oral ulcerations Hypercholesterolemia and hypertriglyceridemia Poor wound healing Lower extremity edema Pleural and pericardial effusions Pulmonary toxicities (interstitial pneumonitis, alveolar hemorrhage) Bone marrow suppression (leukopenia, anemia, and thrombocytopenia) Potentiation of calcineurin inhibitor–mediated nephrotoxicity
Everolimus	1.5 mg/d in two divided doses	Similar to sirolimus with less marked impairment in wound healing
Prednisone	$\leq$ 1 mg/kg/d in two divided doses, usually rapidly tapered to 0-0.05 mg/kg/d by 6-12 mo	Weight gain Hypertension Hyperlipidemia Osteopenia Hyperglycemia Poor wound healing Salt and water retention Proximal myopathy Cataracts Peptic ulcer disease Growth retardation

Abbreviations: GI, gastrointestinal; WBC, white blood cell.

[a]Two-hour peak cyclosporine levels are more reliable but are not practical and not routinely performed.

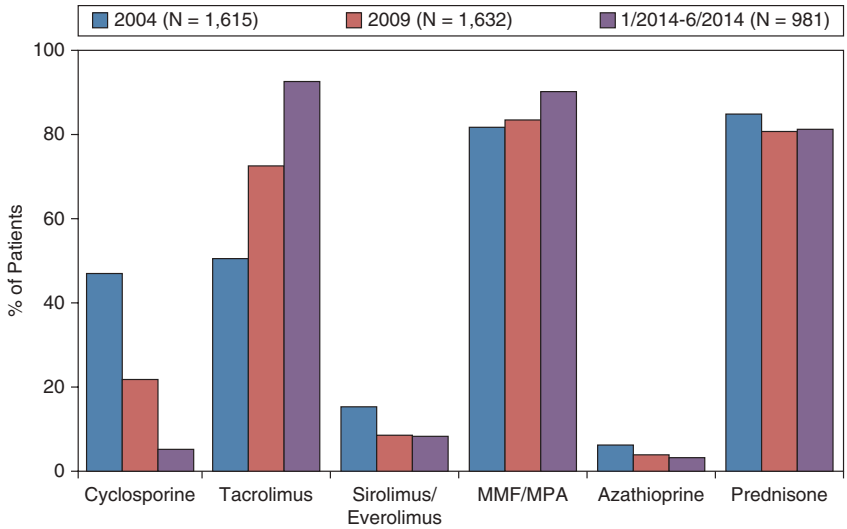

FIGURE 72–4. Trends in maintenance immunosuppression at 1 year in adult heart transplant recipients. MMF, mycophenolate mofetil; MPA, mycophenolic acid. From the International Society for Heart and Lung Transplantation. 2015 Registry. https://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry. Accessed May 10, 2016.

TABLE 72–8. Important Drug Interactions

Drugs that increase levels of CNIs and PSIs (inhibitors of cytochrome P450 3A4)	
Calcium channel blockers	Diltiazem
	Nifedipine
	Nicardipine
	Verapamil
Antifungal drugs	Itraconazole
	Fluconazole
	Ketoconazole
	Voriconazole
	Posaconazole
Macrolide antibiotics	All
Fluoroquinolone antibiotics	Ciprofloxacin
HIV protease inhibitors	All
Antiarrhythmic agents	Amiodarone
Gastrointestinal agents	Metoclopramide
Miscellaneous	Grapefruit juice
Drugs that decrease levels of CNIs and PSIs (inducers of cytochrome P450 3A4)	
Antitubercular drugs	Rifampin
Antiseizure drugs	Phenytoin
	Phenobarbital
Miscellaneous	St. John's wort
Drugs with synergistic nephrotoxicity when used with CNIs	
Aminoglycoside antibiotics	
Amphotericin B	
Colchicine	
NSAIDs	
Drugs whose concentrations are increased when used with CNIs	
Lovastatin	
Simvastatin	
Atorvastatin	
Ezetimibe	

Abbreviations: CNI, calcineurin inhibitor; GI, gastrointestinal; HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug; PSI, proliferation signal inhibitor.

laboratory markers for rejection in heart transplantation, and the endomyocardial biopsy remains the cornerstone of rejection surveillance. Despite its limitations (sampling error and interobserver variability of interpretation among pathologists), endomyocardial biopsy has remained the gold standard for the diagnosis of acute allograft rejection. It is performed via the right internal jugular vein or femoral vein by introducing a bioptome into the right ventricle and obtaining three to five pieces of endomyocardium, typically from the right ventricular septum (Fig. 72–5).

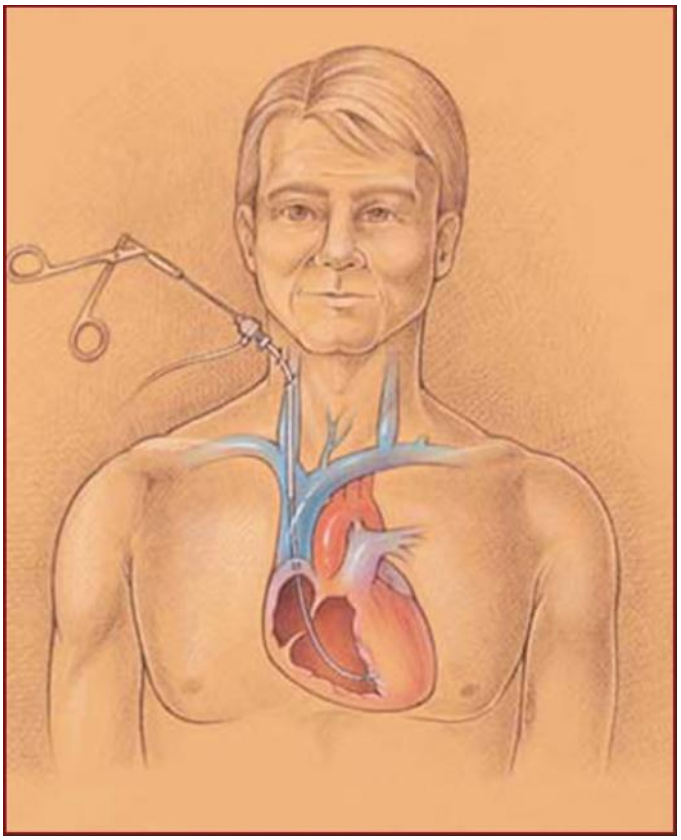

FIGURE 72–5. Endomyocardial biopsy via the right internal jugular vein.

Although the timing of biopsies will vary from center to center, in general, biopsies are performed frequently early after transplantation and less frequently over time. Most programs perform surveillance biopsies on a weekly basis for the first 4 to 6 postoperative weeks and then with diminishing frequency in a stable patient, but at a minimum of every 3 months for the first postoperative year. The need for continued surveillance biopsies after the first year in clinically stable patients has been questioned,[112,113] but many centers continue to perform them every 4 to 6 months during the first 5 years after transplantation.[114]

The purpose of the endomyocardial biopsy is to assess for myocardial damage in the form of acute cellular rejection (ACR; Fig. 72–6) or antibody-mediated rejection (AMR; Fig. 72–7). The diagnosis of ACR is made in accordance with the revised ISHLT grading scale shown in Table 72–9.[115,116] The diagnosis of AMR achieved standardization after a consensus conference in 2010 (Fig. 72–8).[66,117]

Although not required for the diagnosis of AMR, many centers also perform screening for antibodies against HLAs after transplantation. Strong, and especially complement-binding, donor-specific anti-HLA antibodies (DSA) are considered potentially cytotoxic.[118,119] Their presence may merit a change in treatment, depending on the clinical situation, as discussed below.

Although performing an endomyocardial biopsy is straightforward, the morbidity associated with this invasive procedure has led to attempts to identify other means of diagnosing rejection, and the gene expression profile (GEP) test (AlloMap®, CareDx, San Francisco, CA), an 11-gene expression signature derived from peripheral blood mononuclear cells, has emerged as a noninvasive test with a high negative predictive value for the presence of ACR.[120] In a randomized trial, GEP was shown to be noninferior to biopsy in the diagnosis of ACR[121] and also useful early after transplantation.[122] One role of the GEP is to screen low-risk patients at predetermined intervals, with biopsies performed only if the GEP score is abnormal. However, it must be emphasized that patients with a history of or risk factors for AMR are not candidates for GEP screening, as the test has only been validated for ACR.

Another emerging technology in the noninvasive diagnosis of rejection involves cell-free DNA technology. Cell-free donor-derived DNA is detectable in both the urine and blood of transplant recipients.[123,124] This cell-free DNA may be a candidate marker for noninvasive diagnosis of graft injury, because increased levels of donor-derived DNA correlate with ACR events as determined by endomyocardial biopsy in early studies.[125,126]

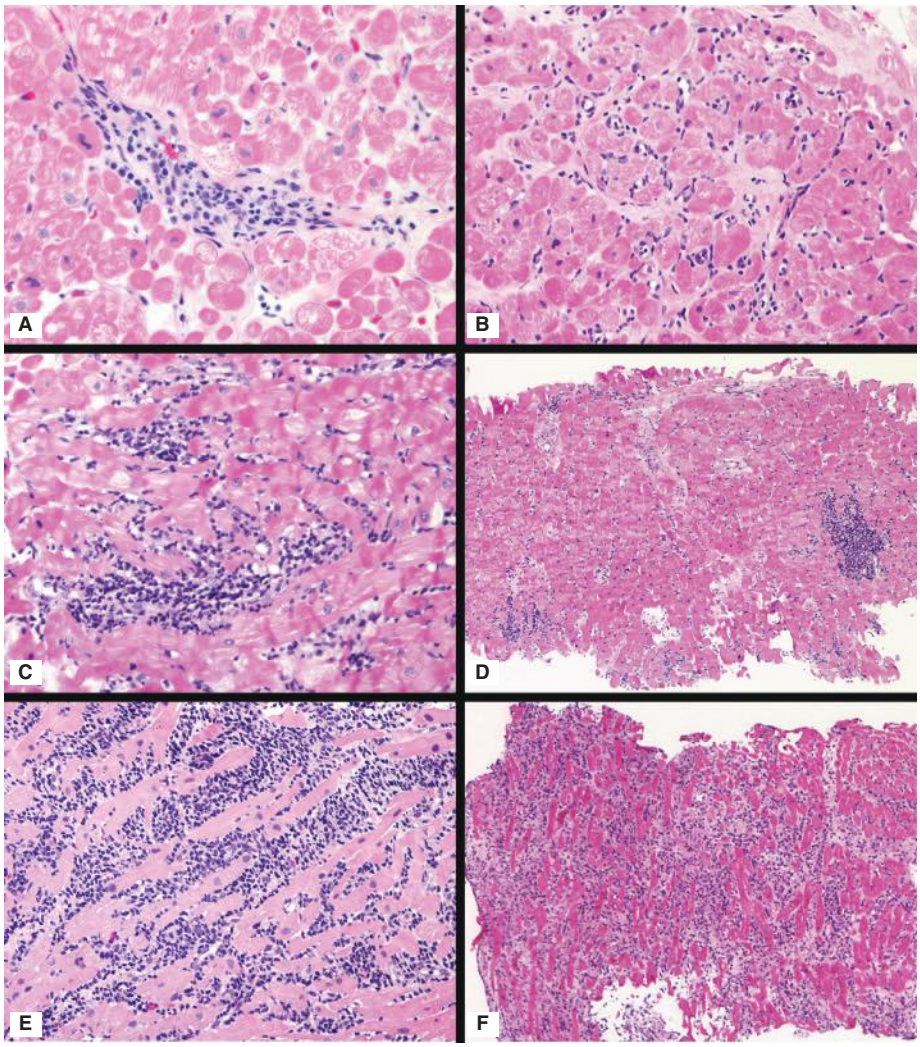

FIGURE 72–6. 2004 International Society for Heart and Lung Transplantation (ISHLT) acute cellular rejection grading scheme. **A.** Mild acute rejection characterized by a perivascular cuff of mononuclear inflammatory cells without myocyte damage. This corresponds to focal mild grade 1R. **B.** Mild acute rejection characterized by a diffuse interstitial pattern. This corresponds to diffuse mild grade 1R. **C.** Mild acute rejection characterized by a solitary focus of mononuclear cells with rare myocyte damage. This corresponds to focal moderate 1R. **D.** Moderate acute rejection characterized by multiple foci of inflammation and myocyte damage. This corresponds to multifocal moderate 2R. **E.** Severe acute rejection showing dense interstitial infiltrates and myocyte damage. This corresponds to diffuse moderate, borderline severe grade 3R. **F.** Severe acute rejection corresponding to grade 3R.

TREATMENT

The management of rejection proceeds in a stepwise fashion based on the severity of rejection detected on biopsy and the patient's presentation (Table 72–10). Biopsies with grade 1R or AMR 1, in the absence of clinical or hemodynamic compromise, generally merit no intervention.

More serious findings on the biopsy, including grade 2R or higher and AMR 2 or higher warrant treatment. As shown in Table 72–10, the intensity of treatment depends on the patient's presentation. If the patient is asymptomatic (no HF symptoms and normal left ventricular ejection fraction), treatment options include oral pulse steroids, targeting higher levels of immunosuppressive medications, switching from cyclosporine to tacrolimus,[94,127] or switching from MMF to a PSI.[99,100,103] Given the equivalent success of intravenous and oral corticosteroid therapy for the treatment of asymptomatic ACR,[128] an outpatient course of oral corticosteroids is often the first-line treatment.

Asymptomatic AMR is more challenging. It may be associated with poor outcomes,[129-131] but it is unclear whether treatment affects outcomes. At some centers, such patients will receive an oral corticosteroid bolus, consideration of intravenous immune globulin, and monitoring of donor-specific anti-HLA antibodies.[66]

For patients with HF symptoms or reduced ejection fraction, treatment is more aggressive, with intravenous corticosteroids and cytolytic

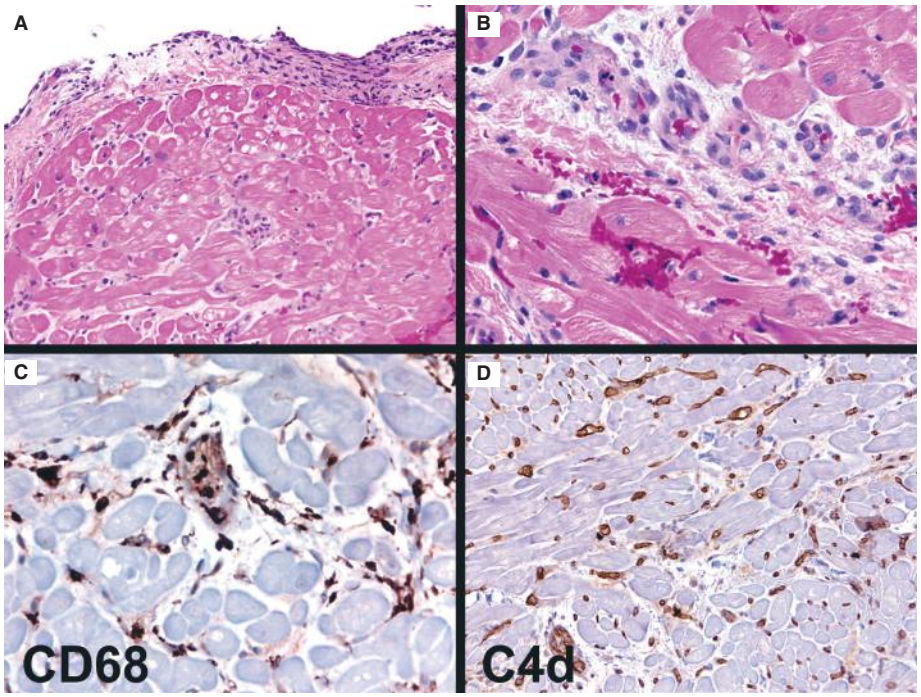

FIGURE 72–7. Acute antibody-mediated (humoral) rejection. **A.** Scanning magnification of endomyocardial biopsy specimen showing a mononuclear cell infiltrate within the endocardium. In the central part of the figure, the small vessel displays prominent endothelial cells. **B.** High-power magnification showing endothelial cell hyperplasia and perivascular edema. **C.** CD68 staining of interstitial and intravascular histiocytes. **D.** Strong, uniform staining of the microvascular for C4d, a marker of complement activation and deposition.

therapy with antithymocyte globulin. If there is evidence of grade AMR 2 or higher, patients will also often receive intravenous immunoglobulin. If donor-specific anti-HLA antibodies are present in the setting of AMR, patients may receive more intensive therapy with rituximab or bortezomib. Plasmapheresis may also be used in this setting.

Finally, in patients presenting with cardiogenic shock, empiric aggressive treatment includes intravenous corticosteroids, cytolytic therapy, plasmapheresis, intravenous immunoglobulin, heparin (as patients often have thrombotic occlusion of the cardiac microvasculature on postmortem examination[132,133]), and hemodynamic support with intra-aortic balloon counterpulsation or even extracorporeal membrane oxygenation.[134]

Any rejection episode should prompt an investigation for precipitating causes such as infection, noncompliance, or drug interactions resulting in subtherapeutic immunosuppressive drug levels. A biopsy should be repeated 2 weeks after completion of treatment to document improvement or resolution of the rejection episode.

TABLE 72–9. International Society for Heart and Lung Transplant Standardized Cardiac Biopsy Grading: Acute Cellular Rejection

Grade	Description	Prior Classification
0R	No rejection	0
1R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage	1A, 1B, 2
2R, moderate	Two or more foci of infiltrate with associated myocyte damage	3A
3R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis	3B, 4

LONG-TERM MANAGEMENT

Whereas ACR is often successfully treated with corticosteroids and cytolytic therapy, resulting in a resolution of HF and normalization of the ejection fraction,[135] management of AMR is often more complicated. Patients may have a persistent reduction in ejection fraction, restrictive physiology with recurrent HF, and accelerated progression of transplant coronary artery disease.[135]

The management of such patients with a persistent drop in ejection fraction after treatment of symptomatic rejection is not well established. Some centers rely on therapies to reduce the levels of donor-specific anti-HLA antibodies, including rituximab and bortezomib, as well as photopheresis to alter the function of T cells.[66] In small case series, such therapies have shown benefit,[136,137] although often such patients go on to require redo heart transplantation.

CARDIAC ALLOGRAFT VASCULOPATHY

INCIDENCE AND CLINICAL PRESENTATION

The incidence of CAV varies widely as a result of differences in definition of disease and patient populations, but by various estimates, it ranges from 42% at 5 years to 50% at 10 years.[138,139] CAV can occur as early as 1 year after transplantation, and this accelerated form of disease is more aggressive and associated with a worse prognosis.[140] Even in patients without apparent angiographic epicardial disease, microvascular abnormalities may be present and are associated with adverse outcomes.[141] Despite improvements in immunosuppression over the past three decades, the incidence of CAV has not significantly decreased, and its development continues to limit long-term survival in patients undergoing cardiac transplantation.

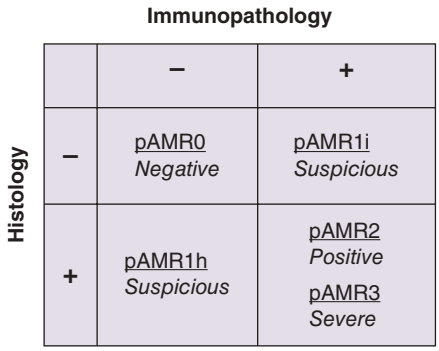

FIGURE 72–8. Diagnosis of antibody-mediated rejection. Histologic findings include endothelial activation with intravascular macrophages and capillary destruction. Immunologic findings encompass complement and human leukocyte antigen deposition. The grading scheme stratifies biopsies based on: no histologic or immunologic evidence of antibody-mediated rejection (negative, pAMR0); either histologic or immunologic evidence of antibody-mediated rejection (suspicious, pAMR1h or pARMi, respectively), both histologic and immunologic evidence of antibody-mediated rejection (positive, pAMR2), and a final category for severe findings of myocardial destruction (pAMR3). Reproduced with permission from Kittleson MM, Kobashigawa JA: Antibody-mediated rejection. *Curr Opin Organ Transplant*. 2012 Oct;17(5):551-557.

TABLE 72–10. Treatment of Acute Cellular and Antibody-Mediated Rejection

	Asymptomatic	Reduced EF	Heart Failure/Shock
Cellular rejection	• Target higher CNI levels • Oral steroid bolus + taper • MMF ⟶ PSI	• Oral steroid bolus/taper *or* • IV pulse steroids	*Treat based on clinical presentation; do not await biopsy findings* • IV pulse steroids • Cytolytic therapy (ATG) • Plasmapheresis (before ATG dose) • IV immunoglobulin • Inotropic therapy • IV heparin • IABP or ECMO support
Antibody-mediated rejection with no/↓ DSA	• Target higher CNI levels • MMF ⟶ PSI	• IV pulse steroids • Consider IV immunoglobulin	
Antibody-mediated rejection with ↑DSA	• Oral steroid bolus + taper • MMF ⟶ PSI • Consider IV immunoglobulin and rituximab	• IV pulse steroids • IV immunoglobulin • Consider ATG, rituximab, or bortezomib	

Patients receiving augmented immunosuppression with high-dose steroids or ATG should also be given prophylaxis against *Pneumocystis* pneumonia and cytomegalovirus.

Abbreviations: ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; DSA, donor-specific anti–human leukocyte antigen antibodies; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; IABP, intra-aortic balloon pump; IV, intravenous; MMF, mycophenolate mofetil; PSI, proliferation signal inhibitor;

Adapted with permission from Chang DH, Kittleson MM, Kobashigawa JA. Immunosuppression following heart transplantation: prospects and challenges. *Immunotherapy*. 2014;6(2):181-194.

Given the denervation of the transplanted heart, patients do not experience typical angina, and the presentation of CAV differs from that of nontransplant coronary artery disease (Table 72–11).[142] However, over time, patients may develop cardiac reinnervation, and chest pain caused by ischemia and infarction in transplant patients has been documented.[86,143,144] In general, the atypical presentation often leads to lower utilization for revascularization therapies and worse outcomes,[145,146] including HF, arrhythmia, or sudden death. Thus, routine surveillance angiography is performed in cardiac transplant recipients, usually at 1-year intervals.

TABLE 72–11. Cardiac Allograft Vasculopathy Versus Coronary Artery Disease in Nontransplant Patients

Nontransplant Atherosclerosis	Cardiac Allograft Vasculopathy
Mainly epicardial disease	Panvascular disease (may include microvasculature)
Slower progression	Rapid progression
Eccentric lesions	Concentric lesions (usually)
Lipid rich	Generally lipid poor
Early calcification	Late calcification

Adapted with permission from Kittleson MM, Kobashigawa JA. Management of the ACC/AHA Stage D patient: cardiac transplantation. *Cardiol Clin*. 2014 Feb;32(1):95-112.

MORPHOLOGIC FEATURES

In CAV, the major epicardial vessels, their branches, and often the intramyocardial divisions display uniform, diffuse involvement extending along their entire length (Fig. 72–9). The asymmetric and calcified plaques or lesions composed of cholesterol that are characteristic of conventional atherosclerosis are not found in uncomplicated lesions of vessels affected by CAV. Histopathologic sections show a concentrically thickened intimal layer composed of modified smooth muscle cells, foamy macrophages, and variable numbers of histiocytes and lymphocytes within a connective tissue matrix that ranges from loose, edematous, and myxoid in early lesions to densely hyalinized and fibrotic in older lesions.[147] Intraluminal thrombosis is uncommon.

DIAGNOSIS

CAV is usually beyond therapeutic intervention by the time symptoms develop, so surveillance is essential to monitor the development of CAV. Coronary angiography remains the mainstay of CAV detection, although it has limitations. Coronary angiography relies on the ability to compare normal segments of the vessel with diseased segments. The diffuse nature of CAV often results in underestimation of disease because there is no reference segment in which the normal diameter of the vessel can be assessed. Comparison with prior studies may help but requires the use of the same angiographic protocol at each study to avoid confounding by technical factors.

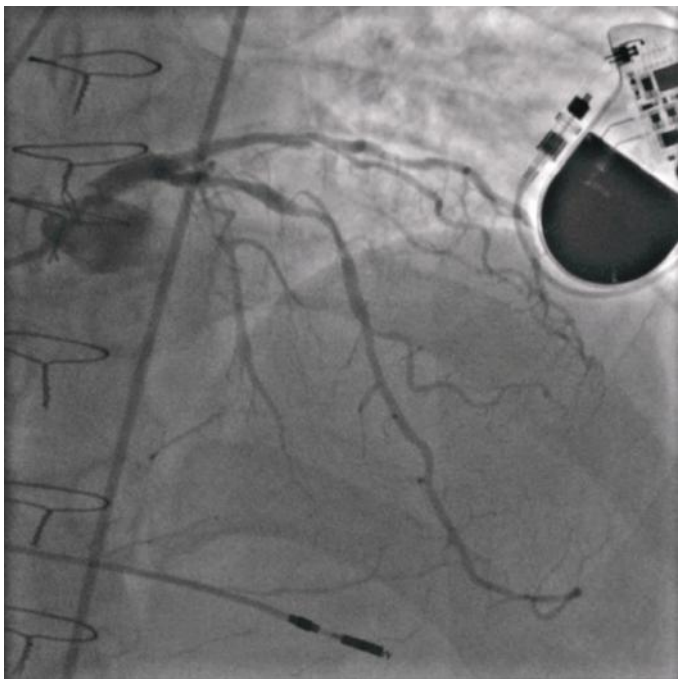

FIGURE 72–9. Coronary angiogram in a patient with severe cardiac allograft vasculopathy showing diffuse disease of the left anterior descending coronary artery, occlusion of the left circumflex coronary artery, and obliteration of the obtuse marginal branches.

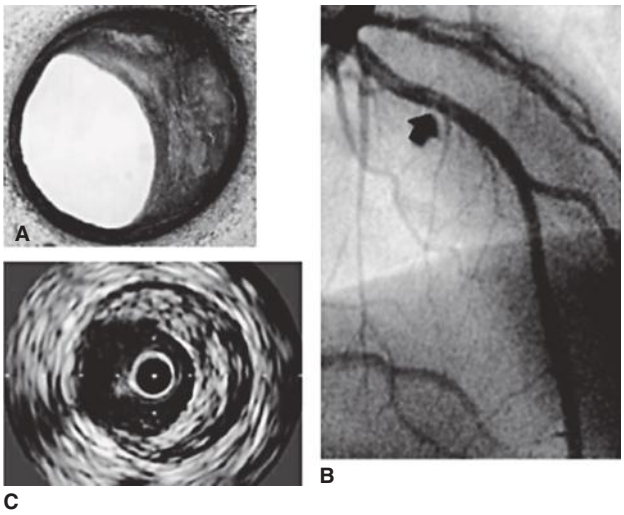

FIGURE 72–10. Concentric or eccentric subintimal proliferations in cardiac allograft vasculopathy seen histologically (**A**) are underestimated in lesion severity angiographically (**B**) but are better appreciated by intravenous ultrasound (**C**). Reproduced with permission from Ahsan N: Chronic allograft failure: natural history, pathogenesis, diagnosis and management. Austin, TX: CRC Press; 2007.

IVUS is currently the only technique that offers cross-sectional images of the coronary vessel wall comparable to histologic sections to detect even early plaque burden (Fig. 72–10). IVUS is more sensitive than angiography in detecting CAV[148-151] and has prognostic value: progression of intimal thickening greater than 0.5 mm in the first year after transplantation is associated with an increased risk of death and development of angiographic CAV up to 5 years later.[140] Nevertheless, IVUS has limitations. It is invasive and requires anticoagulation and the use of expensive single-use catheters, and evaluation is limited to the major epicardial vessels.

TREATMENT

Clinically apparent CAV is associated with a poor prognosis, and therefore, prevention is an important strategy. Aspirin is given because its established role in nontransplant coronary disease. Control of hypertension and hyperlipidemia is paramount. 3-Hydroxy-3-methyl-glutaryl–coenzyme A reductase inhibitors are particularly important because they also prevent allograft rejection in addition to reducing CAV development.[152] The PSIs also show significant promise in reducing the progression of intimal thickening by IVUS.[99-102]

Once clinically significant CAV is apparent, percutaneous coronary intervention is successful for focal disease, although restenosis is common and there is no evidence to date that percutaneous coronary intervention alters the prognosis of CAV.[153] Drug-eluting stents may help, but restenosis rates continue to be higher than in the nontransplant population.[154-156] Patients with multivessel focal disease with adequate distal target vessels may be candidates for surgical revascularization with coronary artery bypass grafting, although limited efficacy data are available.

Retransplantation may be considered for patients with advanced CAV. After retransplantation, patients have comparable survival and CAV incidence to patients undergoing a first transplant.[157] The scarcity of donor hearts, however, creates an ethical dilemma. Some argue that it is better to maximally distribute organs, rather than to allocate two organs to the same individual. Others contend that patients needing a second transplant should be considered on the same basis as those being evaluated for a first transplant.

COMPLICATIONS OF IMMUNOSUPPRESSION

Hypertension, hyperlipidemia, and the development of post-transplant diabetes mellitus are the most common metabolic complications associated with calcineurin inhibitor and corticosteroid use (see Table 72–7). Renal dysfunction occurs in up to one-third of individuals and is related to the direct effects of the calcineurin inhibitors on the kidney tubules and from calcineurin inhibitor–mediated vasoconstriction of the afferent arteriole, leading to decreased kidney perfusion. In addition to experiencing drug- and class-specific toxicities, heart transplant patients have a higher risk of developing opportunistic infections and malignancies compared with the general population.

INFECTION

Infections are the major cause of death during the first postoperative year and remain a threat throughout the life of a chronically immunosuppressed patient. Infections in the first postoperative month are commonly bacterial and typically related to indwelling catheters and wound infections. They involve nosocomial organisms such as *Legionella, Staphylococcus, Pseudomonas, Proteus, Klebsiella*, and *Escherichia coli*. These infections typically present in the form of pneumonias, urinary tract infections, sternal wound infections and mediastinitis, and bacteremia. Late infections (those that occur 2 months to 1 year after transplantation) are more diverse. In additional to typical pathogens, transplant patients are susceptible to viruses (particularly cytomegalovirus), fungi (*Aspergillus*, *Candida*, and *Pneumocystis* spp.), and *Mycobacterium*, *Nocardia*, and *Toxoplasma* species. Effective therapy requires an extremely aggressive approach to obtaining a specific diagnosis and a background of experience in recognizing the more common clinical presentations of cytomegalovirus, *Aspergillus* species, and other opportunistic infectious agents. Infection surveillance is mainly clinical, but routine chest radiography often detects infections, especially fungal and mycobacterial pulmonary infections, that may be at an early and asymptomatic stage.

Balancing the risks of infection and rejection with immunosuppression relies on an understanding of the patient's global immune state. An immune-monitoring assay (ImmuKnow®; Vircor-IBT, Lee's Summit, MO) performed on peripheral blood, which measures adenosine triphosphate (ATP) release from activated lymphocytes, may offer some guidance in profoundly immunosuppressed patients.[158,159] In the largest study to date in heart transplant recipients, the average immune monitoring score was significantly lower in patients who developed an episode of infection within 1 month after the measurement compared with steady-state patients.[160] An immune monitoring score of less than 200 ng ATP/mL was associated with future infection. Thus, centers may target lower calcineurin inhibitor (CNI) trough levels or reduce MMF doses in patients with scores less than 200 ng ATP/mL, especially those with recurrent infections or malignancy.

Given the degree of immunosuppression, all transplant recipients receive antimicrobial prophylaxis for oral candidiasis, toxoplasmosis and pneumocystis, and cytomegalovirus over the first post-transplant year. The use of vaccines in heart transplant recipients remains controversial. Live vaccines are definitely contraindicated because of the patients' immunosuppressed states. Even dead vaccines may pose a risk because they can promote activation of the immune system and cause rejection.[161] At some centers, dead vaccines such as the influenza or pneumococcal vaccines are recommended only to patients more than 6 months after transplant and with no history of rejection within the previous 6 months.

MALIGNANCY

Incidence

Malignancy is one of the most common causes of late mortality in heart transplant recipients.[162] Malignancies are approximately two- to four-fold more common in heart transplant compared with renal transplant recipients.[163-166] The enhanced risk of cancer among cardiac transplant recipients is thought to reflect the greater degree of immunosuppression that heart transplant recipients receive, possibly because of inherent immunologic requirements.[167]

All immunosuppressive agents are believed to contribute to the cumulative risk of malignancy, with the possible exception of corticosteroids. However, the PSIs sirolimus and everolimus may have a decreased incidence and progression of malignancy compared with CNIs and antimetabolites.[168-170]

Clinical Presentation

Cancer in solid organ transplant recipients usually presents at least 3 to 5 years after transplantation. Cutaneous malignancies are the most common type after heart transplantation, mainly squamous cell and basal cell carcinomas.[171] Risk factors common to the general population for the development of skin cancers include fair skin, previous history of skin cancer, and geographic location (in areas of high sun exposure).[172] Specifically in heart transplant recipients, increased intensity of immunosuppression and long-term voriconazole use for treatment of fungal infections such as aspergillosis are associated with a higher increased risk of developing skin cancer.[173]

Post-transplant lymphoproliferative disorder (PTLD), most commonly a B-cell lymphoma related to EBV infection, may occur after transplantation.[174,175] More than 50% of patients with PTLD present with extranodal masses involving the gastrointestinal tract, lungs, skin, liver, central nervous system, and the allograft itself. Risk factors for the development of PTLD include the use of cytolytic therapy for induction[175] and EBV serostatus (with EBV-seronegative recipients of EBV-seropositive donors being at the highest risk).[176]

Neoplasms common in the general population also occur in heart transplant recipients, including breast, lung, and prostate. Lung cancer is more common in heart and lung transplant recipients than in recipients of other solid organs, likely because smoking, a strong risk factor for lung cancer, may also contribute to end-stage heart and lung disease requiring transplantation.[177]

Prevention and Treatment

The most critical point of treatment of malignancies is prevention. Heart transplant recipients should undergo routine health maintenance screenings with their primary care physicians, including mammograms, pap smears, prostate exams, and colonoscopies as indicated for nontransplant patients. In addition, patients are instructed to use sun protection and to establish care with a dermatologist for routine skin exams.

The initial approach to malignancy is reduction of immunosuppression, and this may be the only treatment required for some forms of PTLD. Patients with newly diagnosed malignancy are often switched to a PSI such as sirolimus or everolimus, because of its possible beneficial effect in malignancies,[168,169] in place of a CNI or MMF.

GENERAL MEDICAL MANAGEMENT

Heart transplant recipients should receive regular care from an internist for routine health maintenance. Such patients require the same general medical surveillance as nontransplant patients, including age-appropriate cancer screening. Internists also manage the long-term complications of heart transplant recipients, including renal dysfunction, hypertension, dyslipidemia, diabetes, osteoporosis, and gout. However, it is essential that patients inform the transplant center of any new medication recommended by another physician, as there may be unforeseen interactions (see Table 72–8).

Renal insufficiency is a common adverse effect of the CNIs and often worsens over time, such that up to 8% of heart transplant recipients will develop end-stage renal disease at 5 or more years after transplantation.[162,178,179] "Renal-sparing" immunosuppressive regimens are often used in such patients, including a reduction in CNI dose or substitution of the CNI with a PSI.[180] CNI withdrawal should not be performed prior to 6 months as rejection risk is high. To be successful, the timing is important; if the renal dysfunction has progressed, the damage may be irreversible. When replacing CNIs with PSI, the key to preventing rejection is to withdraw CNIs gradually over a period of 2 to 4 weeks while awaiting therapeutic PSI levels.[181]

Hypertension after cardiac transplantation is primarily a result of CNI use and occurs in up to 80% of patients.[167] Post-transplant hypertension is often difficult to control and often requires a combination of several antihypertensive agents.[182,183] No agent has proven superior in clinical trials of renal transplant[184-186] or heart transplant recipients.[187] However, β-blockers are often avoided because the denervated heart relies on circulating catecholamines to maintain cardiac function during exercise, and thus heart transplant recipients often experience significant fatigue from β-blockers. ACE inhibitors and angiotensin receptor blockers may not be tolerated because of renal dysfunction or hyperkalemia. Dihydropyridine calcium channel blockers such as amlodipine and nifedipine are often effective, but may result in troublesome dependent edema and will increase levels of CNIs, which should be monitored after initiation.

Elevated lipid levels are common after heart transplantation, as a result of the use of steroids, CNIs, and PSIs.[188] Statins are effective in reducing total and low-density lipoprotein cholesterol in heart transplant recipients. Notably, treatment initiated within 2 weeks of transplantation with statins is also associated with a lower frequency of hemodynamically compromising rejection episodes and improved survival over the first transplant year.[152] Pravastatin is the statin of choice, because it is hydrophilic and is not metabolized by the cytochrome 3A4 system, reducing the possible interactions with CNIs.[110]

Diabetes is common before transplantation because it increases the risk of cardiovascular disease. Furthermore, the use of steroids and tacrolimus after transplantation may cause or worsen diabetes; up to 32% of patients are diabetic by 5 years after transplantation.[162] Although diabetes is associated with poorer long-term survival,[189] optimal treatment is not clear. Because renal insufficiency is common, metformin is often avoided. Sulfonylureas may be the agents of choice for heart transplant recipients.[110]

Osteoporosis resulting in vertebral compression fractures is a common and debilitating problem after heart transplantation, exacerbated by steroid use. We recommend screening bone density examinations on an annual basis. To prevent osteoporosis, patients should receive supplemental calcium and vitamin D, engage in weight-bearing exercises, and receive bisphosphonates as recommended by the primary care physician.

Gout is common after heart transplantation. In these patients, causes of gout include CNI use, diuretic use, and renal insufficiency. Nonsteroidal anti-inflammatory agents are often avoided in heart transplant recipients because of the potential of renal insufficiency. Colchicine may be used to treat acute attacks, although there is a risk of myoneuropathy when colchicine is combined with CNIs. Thus, for acute flares, systemic or intra-articular steroids may be considered.

Allopurinol is useful as suppressive therapy, as long as the patient is not receiving azathioprine, since the combination may result in severe myelosuppression.

CONCLUSION

Over the last four decades, cardiac transplantation has become the preferred therapy for select patients with end-stage heart disease. Improvements in immunosuppression, donor procurement, surgical techniques, and post-transplant care have resulted in a substantial decrease in acute allograft rejection, which had previously significantly limited survival of transplant recipients. However, major impediments to long-term allograft survival exist, including rejection, infection, CAV, and malignancy. Nevertheless, through careful balance of immunosuppressive therapy and vigilant surveillance for complications, we can expect further advances in the long-term outcomes of heart transplant recipients over the decades to come.

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CHAPTER 73

MECHANICALLY ASSISTED CIRCULATION

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Advanced heart failure is characterized by the clinical signs and symptoms of congestion, low cardiac output, and progressive organ dysfunction with an annualized mortality rate of 80% to 90% despite optimal medical and electrical therapies.[1] Cardiac transplantation remains the gold standard treatment for stage D heart failure, but the worldwide donor shortage has resulted in highly selective criteria and long waiting times for a suitable organ. The option of mechanically assisted circulation as a viable treatment alternative for this population has gained gradual acceptance over the past decade. The original mechanical blood pumps were designed to replicate the human heart, resulting in large, pulsatile devices with a normal adult stroke volume. The conceptual model of assisted circulation has evolved to smaller, less complex continuous flow pumps. The Interagency Registry for Mechanically Assisted Circulation (INTERMACS) has documented the growth of the field with detailed clinical information on > 15,000 individual patients treated with mechanical circulatory support (MCS) in the United States.[2]

INDICATIONS FOR MECHANICAL CIRCULATORY SUPPORT

Patients considered for treatment with MCS have severely depressed left ventricular (LV) systolic function, New York Heart Association (NYHA) functional class III or IV limitations, systemic hypotension, frequent heart failure hospitalizations, and intolerance to standard heart failure therapy secondary to hypotension or worsening renal function. Objective evidence of functional limitations includes a peak oxygen consumption of ≤ 14 mL/kg/min or a 6-minute walk distance < 300 m. Hemodynamic assessment typically demonstrates elevated left-sided cardiac filling pressures and a cardiac index < 2 L/min/m^2.

Standard contraindications to MCS therapy include ongoing systemic infection, irreversible end-organ dysfunction, severe untreated carotid artery disease, recent stroke, inability to take anticoagulation or antiplatelet therapy, a mechanical aortic valve without plans for replacement or exclusion from the circulation, and a life expectancy related to another disease process of < 2 years. Medical noncompliance, ongoing substance abuse, and inadequate social support are also important predictors of adverse outcomes and typically exclude patients from this complex therapy. Advanced age, medical frailty, and malnutrition are considered to be relative contraindications.

The growing number of devices and population heterogeneity necessitate matching patient characteristics with device capability and anticipated support duration. Assisted circulation descriptors are LV assist device (LVAD), right ventricular (RV) assist device, biventricular assist device, and total artificial heart (TAH). The most common ventricular assist device (VAD) implant indications are bridge to transplantation (BTT) in patients listed for transplantation at high priority who are failing optimal medical therapies or as permanent cardiac replacement in patients ineligible for transplant (destination therapy [DT]). The latter group have NYHA class IIIb or IV functional limitations on maximally tolerated medical therapy, an LV ejection fraction < 25%, and a peak oxygen consumption of < 14 mL/kg/min. In less stable patients, treatment with continuous infusion of inotropic medications for at least 14 days or need for acute circulatory support for at least 7 days are also indications for durable LVAD therapy.

SHORT-TERM MECHANICAL CIRCULATORY SUPPORT

Short-term MCS is indicated in instances of acute heart failure or cardiogenic shock when the degree of reversibility is unclear or suitability for durable MCS cannot be completely determined at the time of implantation.[3] Most acute circulatory support strategies are used for days to weeks, so attempts to wean the device and/or transition to durable circulatory support should begin at the time of short-term device placement.

INDICATIONS FOR ACUTE CIRCULATORY SUPPORT

The most common indication for short-term MCS is hemodynamic instability or shock following acute myocardial infarction. These cases may also include papillary muscle rupture with acute mitral insufficiency and infarct-related ventricular septal defects. Although ruptured papillary muscle and postinfarct ventricular septal defects require surgical correction, MCS can immediately improve end-organ perfusion and better prepare the patient for cardiac surgery. There is a range of MCS options for patients with cardiogenic shock after myocardial infarction from intra-aortic balloon pump (IABP) counterpulsation to venoarterial (VA) extracorporeal membrane oxygenation (ECMO). The degree of hemodynamic compromise and anticipated duration of MCS are important variables in device choice (Table 73–1).

Ventricular failure necessitating short-term MCS may follow cardiac surgery when severe ventricular dysfunction preceded the operation or unexpected myocardial injury occurs during the conduct of the procedure. In either instance, circulatory support with high-dose inotropic agents and vasopressors alone may be inadequate, and termination of cardiopulmonary bypass results in cardiogenic shock. The best immediate strategy in these cases is restoration of cardiopulmonary bypass with reassessment and correction of residual valvular and coronary lesions. If ventricular dysfunction does not resolve, initiation of short-term MCS is indicated.

Acute viral myocarditis resulting in profound myocardial dysfunction is another indication for short-term MCS. Unlike chronic heart failure, patients with acute viral myocarditis often have normal ventricular diameters and a higher incidence of ventricular functional recovery. Therefore, short-term devices that can be more easily implanted, weaned, and explanted should be considered in this condition. Specific device choice should depend on the severity of shock and the presence of pulmonary dysfunction. The duration of support prior to ventricular recovery can range from days to months.

Hemodynamic compromise necessitating short-term MCS may occur in patients with reduced LV function undergoing a variety of cardiac interventions including percutaneous coronary interventions (PCIs), catheter ablations, and valve replacement. Periprocedural support is generally well tolerated and required for only a few hours. The most common device for these procedures is IABP, but percutaneous VADs have also been used for this indication.[4]

Graft dysfunction after cardiac transplantation is commonly treated with short-term MCS therapy. Typically, graft function recovers during the first several days following transplantation. Late graft dysfunction related to acute rejection and coronary artery vasculopathy may also be treated with short-term MCS; the former condition is more likely to recover than the latter.

Finally, a less common application for short-term VADs is as a bridge to cardiac transplantation. Typically, prolonged waiting times require treatment with durable LVADs rather than short-term MCS. The disadvantage of the durable LVAD, however, is the requirement for two major operations and a more technically difficult transplant procedure. In some instances, bridging with percutaneous devices such as IABP or percutaneous VADs may be preferable. Short-term MCS strategies are more appropriate in smaller patients with favorable blood types for whom the anticipated wait for a suitable donor is reduced. Outcomes from bridging with short-term devices in select patients appear to be equivalent to outcomes after bridging with durable LVADs.[5]

TABLE 73–1. Anticipated Duration of Support Based on Condition and Likelihood of Reversibility

Condition	Reversibility of Ventricular Dysfunction	Anticipated Duration of Support
Acute MI with shock	++	Days to weeks
Postcardiac surgery inability to wean CPB	++	Days to weeks
Viral myocarditis	+++	Weeks
High-risk PCI	++++	Hours
High-risk ventricular arrhythmia ablation	++++	Hours
High-risk catheter valve procedure	++++	Hours
Post–heart transplant graft dysfunction	Early ++++	Days
	Late ++++	Days
RV failure from acute PE	++++	Days
Ventricular dysfunction from drug overdose or electrolyte disturbance	++++	Days
Decompensated chronic heart failure support	+	Weeks

Abbreviations: CPB, cardiopulmonary bypass; MI, myocardial infarction; PCI, percutaneous coronary intervention; PE, pulmonary embolism; RV, right ventricular.

SPECIFIC DEVICE TYPES AND APPLICATION FOR SHORT-TERM MECHANICAL CIRCULATORY SUPPORT

Short-term MCS devices can be subdivided into percutaneously and peripherally inserted pumps and those implanted centrally through a thoracic incision. A subset of short-term VADs are designed and applied uniquely for right heart support. ECMO is another category of short-term MCS capable of circulatory support and gas exchange.

PERCUTANEOUS SHORT-TERM LEFT VENTRICULAR ASSIST DEVICES

Intra-Aortic Balloon Pumps

The simplest and most commonly applied percutaneous MCS device is the IABP. This is a catheter with a pressure transducer and an elongated balloon that is inflated during ventricular diastole and deflated during ventricular systole (Fig. 73–1). A lumen within the catheter delivers and removes helium gas from the balloon. IABPs are typically inserted via the femoral artery utilizing a Seldinger technique. The device is inserted into the arterial system over a wire with fluoroscopy, but intraoperative guidance with transesophageal echocardiography is also possible. Optimal balloon position is in the descending thoracic aorta, just distal to the ostium of the left subclavian artery. The balloon volume is typically 40 mL, but a newer design features a 50-mL "mega" balloon and also smaller sizes for adult or pediatric patients.

Direct effects of counterpulsation include increased diastolic pressure, improved coronary and cerebral blood flow, and decreased afterload. Indirect benefits may include increased stroke volume, reduced LV end-diastolic pressure and volume, and reduced wall stress. The effectiveness of IABP support is dependent on the presence of organized native heart rhythm and LV ejection. Relative contraindications to use of the IABP support include significant aortic valve insufficiency and severe atherosclerotic vascular disease between the femoral artery and the aortic arch. Complications include arterial bleeding, vascular

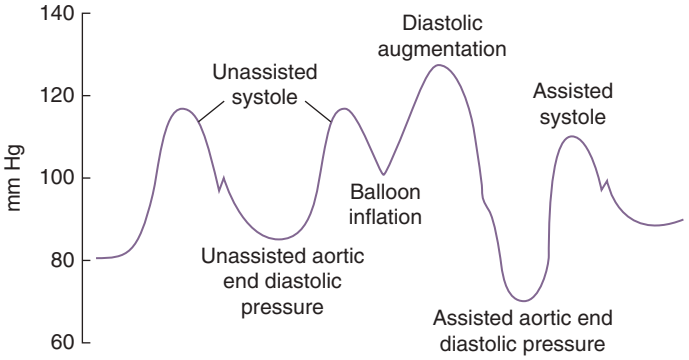


FIGURE 73–1. Optimal timing of inflation for intra-aortic balloon pump (IABP) support. Timing of inflation for the IABP can be determined from the electrocardiogram or arterial pressure waveform. Optimal timing consists of initiation of inflation just after closure of the aortic valve and completion of deflation just prior to opening of the aortic valve during the next cardiac cycle. Therefore, the initiation of balloon inflation should occur at the dicrotic pressure notch on the arterial pressure tracing. In this manner, augmentation of the mid-diastolic pressure is achieved with reduction of the end-diastolic pressure compared with the nonaugmented cycle. Adapted with permission from Trost JC, Hillis LD. Intra-aortic balloon counterpulsation. *Am J Cardiol*. 2006 May 1;97(9):1391-1398.

complications, gas embolus, and stroke. Given the low rates of adverse events, IABP support is considered first-line MCS and, in many cases, should be trialed before more invasive forms of MCS are deployed. Weaning IABP support is achieved by decreasing the frequency of counterpulsation or reducing the degree of augmentation. Although IABP is most commonly inserted percutaneously in a retrograde manner up the femoral artery into the descending aorta, other approaches may be used in special circumstances, including direct insertion into the ascending aorta with antegrade delivery into the descending aorta, which has been described in conditions of severe peripheral vascular disease, or insertion into the axillary or subclavian artery enabling ambulation.[6] Although short-term support is most common, multiple weeks of IABP support have been used to bridge chronic heart failure patients to cardiac transplantation.[5]

Impella

The Impella (Abiomed, Danvers, MA) is a catheter-mounted, axial flow VAD demonstrated to provide more hemodynamic support than IABP. The catheter is inserted into the LV using an over-the-wire technique. The device draws blood from the LV and ejects it into the aortic root. In addition to housing the electrical power cord, the catheter also contains a lumen for delivery of a heparin dextrose solution that protects the motor from blood contact.

The Impella product line includes four left-sided support devices that differ in maximal pump output (Table 73–2). The PROTECT II trial randomized nearly 500 patients to either the Impella 2.5 or IABP during high-risk PCI.[7] There was no difference in major adverse events during the 30 days following the procedure despite the Impella-supported patients receiving more extensive coronary revascularization. The most common application of the Impella 2.5 device remains high-risk PCI, with great variability in rates of utilization between institutions.[4]

The Impella LD and 5.0 are intended for surgical insertion through a 10-mm Dacron vascular graft and are capable of 5 L/min of blood flow under ideal circumstances. The Impella LD device was designed for utilization after cardiac surgery in the setting of inability to wean from cardiopulmonary bypass.[8]

Device malposition may occur over time and requires careful assessment. The inlet is ideally located 3.5 cm below the aortic valve and outlet cannula just above the valve. Impella features a position monitoring screen that simultaneously displays aortic pressure and motor current tracings (Fig. 73–2). Proper device positioning is confirmed by a normal aortic pressure tracing and motor current phasic with the native cardiac cycle. Abnormal positioning results in changes in motor current and ventricular pressure tracing that can be used in diagnosis. Echocardiographic or fluoroscopic imaging can be used to confirm and guide positioning. Device weaning can be accomplished by turning down pump speeds while monitoring ventricular function on echocardiography and examining hemodynamics.

Adverse events related to use of the Impella devices include arterial insertion site complications, ventricular perforation, ventricular arrhythmias, mitral insufficiency related to the device impinging on the anterior mitral valve leaflet or chordal attachments, and hemolysis. Further, patients with advanced LV failure may not receive adequate flow rates and may remain in a low-output state, particularly with the smaller device.

HeartMate PHP

The HeartMate PHP (St. Jude Medical, St. Paul, MN) is another electrical axial flow pump mounted on a catheter (Fig. 73–3). The ongoing SHIELD II trial in the United States will randomize patients undergoing high-risk PCI to receive either the HeartMate PHP or the Impella 2.5 with the end point being freedom from major adverse events at 90 days. This device has many similarities to the Impella devices,

TABLE 73–2. Specifications of 4 Impella Products for Left Ventricular Support

	Device		
	Impella 2.5	Impella CP	Impella 5.0/LD
Maximum output	2.51 pm	4.01 pm	5.01 pm
Maximum RPM	51,000	46,000	33,000
Guiding catheter size	9 Fr	9 Fr	9 Fr
Guide wire	0.018	0.018	0.018
Motor size	12 Fr	14 Fr	21/22 Fr
Introducer size	13 Fr	14 Fr	Dacron graft, 10 mm
Access	Percutaneous femoral	Percutaneous femoral	Surgical

Abbreviation: RPM, revolutions per minute.

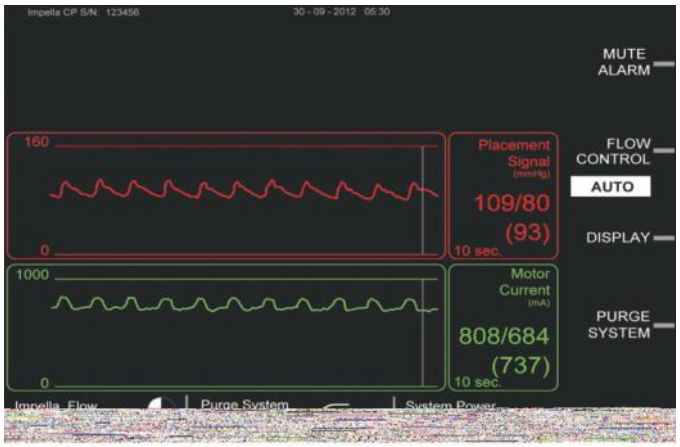


FIGURE 73–2. Positioning screen for Impella device. The device is optimally positioned 3.5 cm below the aortic valve, and the outlet area is approximately 1 cm above the aortic valve. With the device in place, the red tracing represents a pressure being transduced near the outlet area, and thus proper positioning is suggested by the aortic pressure tracing. The green trace represents the motor current, which is typically phasic with the cardiac cycle provided that the inlet and outlet portions of the device are on either side of the aortic valve. Used with permission from Abiomed, Inc.

including insertion technique. After insertion, the inlet component expands to 24 Fr, and the device is capable of 4 L/min of blood flow under ideal loading conditions. The adverse event profile for this device is likely to mimic the Impella devices.

TandemHeart Pump and Cannula System

The TandemHeart Pump and Cannula System (CardiacAssist, Pittsburgh, PA) is another percutaneous device for LV support. This extracorporeal centrifugal pump is attached by blood tubing to two percutaneously inserted cannulas. The left heart drainage cannula is inserted from the femoral vein into the left atrium across the intra-atrial septum. Outflow from the pump is into the femoral artery and descending aorta. Use of this percutaneous device has been less common relative to the Impella device probably related to technical considerations. Cannulas for this device can also be placed surgically directly into the left atrium or ventricle.

SURGICALLY IMPLANTED SHORT-TERM VENTRICULAR ASSIST DEVICES

The most common indication for surgically implanted short-term VAD support is ventricular failure following cardiac surgery. Historically, these devices were extracorporeal, pulsatile devices based in part on the theory that pulsatile blood flow was advantageous for end-organ recovery from shock state.

FIGURE 73–3. Newer transaortic acute circulatory support devices. The St. Jude HeartMate PHP device is inserted through a 14-Fr femoral sheath and is positioned across the aortic valve in the left ventricle. After insertion, the cannula inlet area expands to 24 Fr. Used with permission from Thoratec.

Pulsatile Extracorporeal Blood Pumps

Older, pulsatile devices such as the paracorporeal ventricular assist device (PVAD; St. Jude Medical, St. Paul, MN) can be used for right, left, or biventricular support. Right heart drainage is achieved with a surgically attached right atrial or RV cannula, whereas the left heart is drained with a surgically attached LV apical cannula. Outflow from the right heart PVAD pump consists of a graft cannula sewn to the main pulmonary artery, whereas outflow from the left heart PVAD consists of a graft cannula attached to the ascending aorta. The cannulas exit the body below the sternotomy incision and are attached to pneumatic pumps that rest on the anterior abdominal wall. These pumps have fill signal indicators that activate delivery of compressed air into a hard shell surrounding a flexible blood sac that is compressed, resulting in ejection of the pump stroke volume. The AB5000 pump (Abiomed, Danvers, MA) is similar to the PVAD in that it is a pneumatically driven, pulsatile device used for either right- or left-sided support. Like the PVAD, the AB5000 lies on the anterior abdominal wall and is attached to the heart via surgically placed tunneled cannulas (Fig. 73–4). These pumps both feature active assisted drainage since suction of compressed air from the pump creates a vacuum force that facilitates filling. In cases of ventricular recovery, surgical exploration is required to explant the cannulas. The pulsatile extracorporeal VADs have experienced reduced application for several reasons including blood stagnation predisposing to pump thrombus, the large air compressor required for pump function, and the trend toward continuous flow devices.

Centrifugal Extracorporeal Blood Pumps

In the present era, extracorporeal surgically implanted VADs are more commonly rotary flow devices that provide continuous blood flow. Two examples of this type of device are the CentriMag pump (St. Jude Medical, St. Paul, MN) and the Rotaflow pump (Maquet, Wayne, NJ). Like the pulsatile devices, rotary flow systems provide right heart and/or left heart support and use surgically attached cannulas tunneled out of chest onto the upper abdomen (see Fig. 73–4).

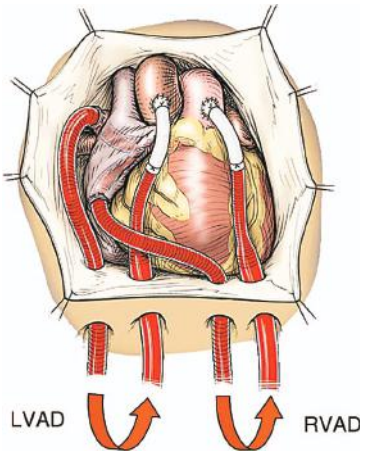


FIGURE 73–4. Configuration of cannulas for biventricular support with surgically implanted acute circulatory support device. Blood is drained from the left heart to the left ventricular assist device (LVAD) via a cannula inserted into the left atrium at the interatrial groove. The LVAD then returns blood to a cannula inserted into the ascending aorta. Blood is drained from the right heart to the right ventricular assist device (RVAD) via a cannula inserted into the right atrium, and then returned to a cannula inserted into the main pulmonary artery. These cannulas are attached via blood tubing to either pulsatile or centrifugal blood pumps. More commonly used in the current era are centrifugal pumps that contain a central rotor activated by an electromagnetic driver that is external to the pump. Copyright IHC 2004.

Pump speed can be altered to change cardiac output and is typically higher for left-sided than right-sided support. Since there is no "pump diastole," pump thrombus is uncommon in the setting of adult pump flows (3-6 L/min). Flow is measured with an ultrasonic flow probe attached to the blood tubing that provides reliable measurement. Total systemic blood flow consists of the pump blood flow plus residual blood flow ejected from the native heart. If required, an oxygenator can be spliced into the circuit leading back to the patient, creating a hybrid strategy between VAD and ECMO. Weaning from these devices involves decreasing pump speeds with simultaneous echocardiography to determine ventricular functional recovery. Device removal requires general anesthesia and sternal reentry to de-cannulate and achieve hemostasis at the cannulation sites. In fact, when LV apical cannulation is used, cannula removal and repair of the site may require cardiopulmonary bypass support.

Management of patients supported on these centrifugal pumps includes heparin anticoagulation to achieve an activated partial thromboplastin time between 60 and 80 seconds and antiplatelet therapy with aspirin. Ambulation is generally safe with these devices and should be encouraged to promote skeletal muscle reconditioning.

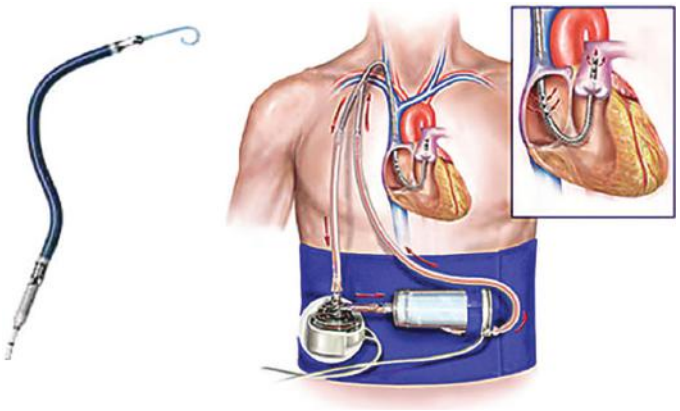


FIGURE 73–5. Percutaneous devices designed for right ventricular support. The left panel is the Impella RP device. The outlet portion of the device located at the pigtail portion is delivered above the pulmonary valve. The right panel is the PROTEK Duo Cannula consisting of an outer proximal lumen that is positioned at the right atrium and an inner distal lumen positioned in the main pulmonary artery. The two independent lumens are attached via blood tubing to an extracorporeal centrifugal blood pump. Used with permission from Abiomed, Inc.

RIGHT VENTRICULAR ASSIST DEVICES

Indications for Right Ventricular Assist Devices

RV failure most commonly results from LV failure, but other important causes include RV infarct, primary RV myocardial diseases, and cardiac surgery. Each of these conditions may lead to need for isolated RV mechanical support.

Extracorporeal Right Ventricular Assist Devices

The extracorporeal centrifugal pumps described for left heart support can also be surgically implanted for RV support. Most typically, standard cannulas used for cardiopulmonary bypass can be used to cannulate the right atrium and the main pulmonary artery (see Fig. 73–4). Potential adverse events include bleeding and device thrombosis that may cause pulmonary embolism. Other pulmonary complications include development of edema and hemoptysis. These events can result from supraphysiologic pulmonary artery pressures or flows and emphasize the need for caution when increasing the pump speeds, particularly when LV performance is not normal.

Percutaneous Right Ventricular Assist Devices

Recently, percutaneous devices have become available that provide RV mechanical support. An example is the Impella RP (Abiomed, Danvers, MA). Like the other Impella devices, the right-sided device is an axial flow, electrically driven pump placed through a 23-Fr sheath inserted in the right femoral vein and guided over a 0.025-inch wire into the right heart. The inlet is positioned at the junction between the right atrium and the inferior vena cava with the device outlet positioned in the main pulmonary artery (Fig. 73–5). This device was studied in the Recover Right Trial, a single-arm outcomes study that enrolled patients with RV failure following LVAD implantation, with an acute RV infarct, or who had postcardiotomy RV failure. Patients supported with the Impella RP demonstrated a significantly reduced central venous pressure, increased cardiac output, and reduction in intravenous inotropic or vasopressor support. The primary end point was survival to 30 days, discharge, or transition to a durable RV assist device; 73% of the patients supported with the Impella RP achieved the primary end point compared to a predetermined performance measure of 50%.[9] On the basis of this trial, the device was approved by the US Food and Drug Administration. Adverse events experienced in the trial included device malposition, hemolysis, and bleeding either at the insertion site or related to lung injury.

Another device used for percutaneous RV mechanical support is the TandemHeart Centrifugal Pump System and PROTEK Duo Cannula (CardiacAssist, Pittsburgh, PA) (see Fig. 73–5). The PROTEK Duo Cannula is a two-lumen catheter positioned to draw blood from the right atrium and deliver it to the main pulmonary artery (see Fig. 73–5). The catheter interfaces with a Centrifugal TandemHeart Blood Pump. An oxygenator can be inserted to provide gas exchange, creating a ventrovenous (VV) ECMO circuit. One potential advantage of this device is the ability for ambulation. Potential adverse events include hemolysis, bleeding complications, and inadequate blood flows as a result of either the cannula size or malposition.

EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO is another temporary MCS strategy capable of supporting the cardiovascular and respiratory systems. VV ECMO drains and oxygenates venous blood prior to returning it to the venous system and is primarily used for severe pulmonary insufficiency and impaired gas exchange. VA ECMO consists of a circuit in which blood is drawn from the venous circulation, oxygenated, and returned to the arterial system. VA ECMO has been adopted for management of cardiogenic shock, and its utilization in the United States is increasing.[4]

VA ECMO deployment requires venous and arterial access and systemic anticoagulation with heparin. There are many potential components to a VA ECMO circuit, but most commonly, venous blood is drawn into a centrifugal pump and then delivered out of the pump through a membrane oxygenator into an arterial cannula. A flow probe is attached to the circuit to measure flow, and bubble detector locking mechanisms are placed on the circuit as a safeguard against air being introduced into the arterial system.

VA ECMO for management of cardiogenic shock has a number of advantages. First, hospital systems have developed teams for emergency ECMO deployment. Although VA ECMO can be established within an operating room or catheter lab, emergency cannula placement and initiation can also take place in intensive care unit settings, in the emergency department, and in patients experiencing cardiac arrest and undergoing active cardiopulmonary resuscitation. VA ECMO provides RV and LV replacement as well as gas exchange support.

Therefore, VA ECMO is particularly useful in the setting of profound biventricular dysfunction associated with pulmonary edema or other lung injuries. A final advantage of this technology is that newer circuits have miniaturized the system and are portable. CARDIOHELP (Maquet, Wayne, NJ) is a highly condensed circuit and allows greater patient mobility within a hospital but also facilitates hospital-to-hospital transfers

Adverse events associated with VA ECMO are related to the cannulation and artificial blood circuit as well as the underlying shock state that prompted treatment. Peripheral arterial complications associated with VA ECMO include bleeding, arterial obstruction, and distal extremity ischemia. When femoral arterial cannulation is used, ipsilateral lower extremity perfusion must be monitored. Insertion of a small antegrade limb perfusion catheter or surgical cutdown and graft arterial cannulation enables antegrade lower extremity perfusion. Central aortic cannulation for VA ECMO is appropriate when the patient has had recent heart surgery and a previous incision can be reopened to place the arterial aortic cannula. In other instances, cannulas can be inserted into the aorta and right atrium through a small right anterior thoracotomy.

VA ECMO does not directly unload the LV, and blood return from an incompetent aortic valve or from pulmonary venous return may cause LV distention resulting in progressive ventricular distention and hydrostatic pulmonary circulatory injury. Placement of an LV vent via the apex or right superior pulmonary vein with return of blood to the ECMO circuit can prevent this complication.

ECMO support is associated with blood component abnormality coagulopathies. Hemolysis related to blood contact with the ECMO tubing is usually not clinically significant as long as appropriate cannulas and pump speeds are used. Thrombocytopenia may result from platelet consumption or clumping. Exposure of the blood volume to the artificial surfaces may trigger inflammatory responses manifested as fever, leukocytosis, or peripheral arterial vasodilation requiring vasopressors.

DURABLE CIRCULATORY SUPPORT DEVICES

Contemporary durable LVADs have similar conceptual design. Access to the circulation is obtained via an inflow cannula inserted in the LV apex. The pump housing contains a rotor that draws blood from the LV and delivers it to the ascending aorta via an outflow graft. Devices receive power via a driveline tunneled subcutaneously across the anterior abdomen that attaches to a controller that drives the pump and collects information on device performance. The driver is powered by either direct current (battery) or alternating current. Devices for durable mechanically assisted circulation have two configurations: axial flow devices in which the impeller is in line with the direction of blood flow and centrifugal flow devices in which the direction of the blood path is perpendicular to the rotor (Fig. 73–6).

HEARTMATE II LEFT VENTRICULAR ASSIST DEVICE

The HeartMate II LVAD (St. Jude Medical, Minneapolis, MN) is an axial flow LVAD implanted in the left upper quadrant of the abdomen. HeartMate II has US approval for BTT and DT (see Fig. 73–6). The pivotal BTT trial was a 133-patient, single-arm study that used objective performance criteria as a comparator.[10] Seventy-five percent of patients who received the HeartMate II successfully achieved a combined end point of transplantation, alive on device support, or device explanation for myocardial recovery at 12 months. The HeartMate II DT trial randomized 200 patients in a 2:1 ratio to receive either a HeartMate II LVAD or the HeartMate I, an older pulsatile device.[11] The primary end point of the HeartMate II trial was survival without disabling stroke or the need for surgical repair or replacement of the device at 24 months. Patients randomized to HeartMate II had a four-fold higher likelihood of successfully achieving the primary end point compared to the control group (Fig. 73–7). When the components of the primary end point were examined, there were statistically significant reductions in mortality and device repair/replacement. The stroke rate was not

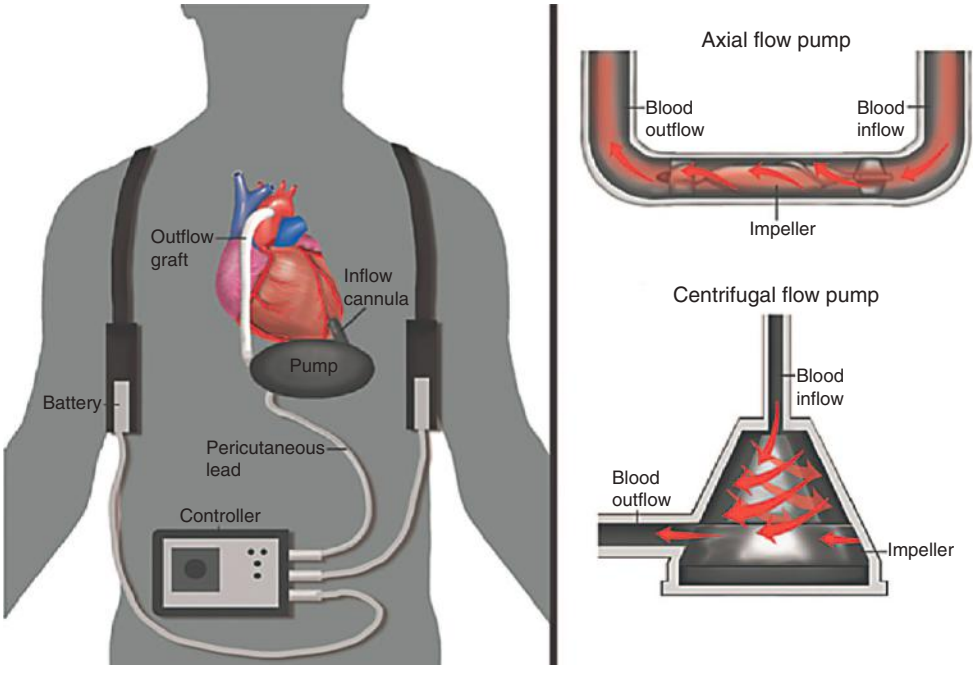


FIGURE 73–6. Configuration of current-era durable left ventricular assist devices (LVADs). Durable LVADs are implanted with the inflow cannula of the pump positioned at the left ventricular apex connected to either an axial flow or centrifugal flow device. The outflow graft is positioned in the aorta to provide flow via a continuous flow mechanism. Reproduced with permission from Mancini D, Colombo PC. Left ventricular assist devices: a rapidly evolving alternative to transplant. *J Am Coll Cardiol*. 2015 Jun 16;65(23):2542-2555.

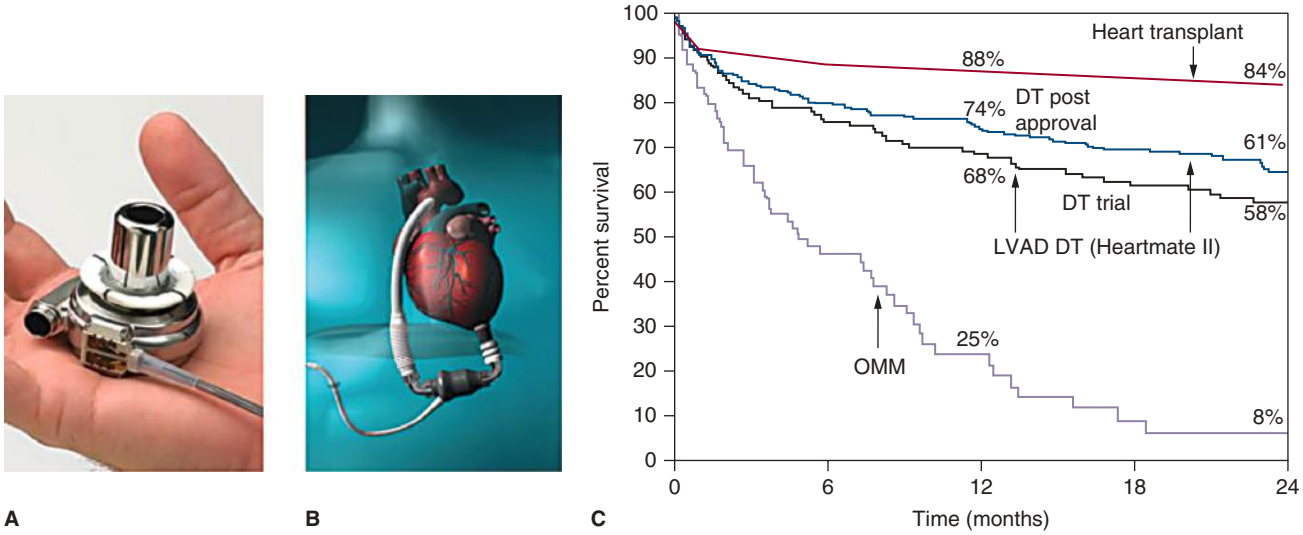


FIGURE 73–7. Contemporary outcomes after left ventricular assist device (LVAD) implantation. With current-generation LVADs (**A**, HeartWare HVAD; **B**, HeartMate II), there has been gradual improvement of survival outcomes. In the destination therapy (DT) population, 1-year survival rates now exceed 70% and have improved in the postmarket surveillance phase. OMM, optimal medical management. **C**, reproduced with permission from Mancini D, Colombo PC. Left ventricular assist devices: a rapidly evolving alternative to transplant. *J Am Coll Cardiol*. 2015 Jun 16;65(23):2542-2555.

significantly different between devices. Adverse events were also examined and found to be less common in the HeartMate II cohort.

HEARTWARE HVAD

The HeartWare HVAD (HeartWare, Framingham, MA) is a centrifugal flow device that is smaller than HeartMate II and is implanted in the pericardial space (see Fig. 73–7). The rotor of the HVAD is suspended magnetically and on a blood bearing preventing contact with the interior surface of the pump housing. The HVAD has US approval for BTT based on a 140-patient trial that compared HVAD outcomes to a contemporaneously enrolled INTERMACS cohort that received an approved LVAD. HVAD was statistically similar to the comparator for the primary end point of survival to 180 days on the originally implanted pump, transplantation, or explantation for myocardial recovery.[12] The HVAD DT trial was a multicenter, randomized, noninferiority trial that compared HVAD to HeartMate II in 445 patients ineligible for transplantation. The primary end point was survival to 24 months on the originally implanted device without a disabling stroke (measured 6 months after the event), transplantation, or explantation for recovery. The two groups had similar outcomes for the primary end point.[13] Quality of life and functional outcomes were also similar between devices. Adverse event analysis demonstrated a higher rate of stroke with HVAD relative to HeartMate II. Secondary analysis demonstrated that mean arterial blood pressure > 90 mm Hg was a risk factor for stroke, as were aspirin dosing and international normalized ratio (INR). More aggressive blood pressure management is the focus of an ongoing clinical trial assessing its impact on postimplant stroke.

SYNCARDIA TOTAL ARTIFICIAL HEART

The Syncardia Total Artificial Heart (Syncardia, Tucson, AZ) is the only commercially available TAH that has achieved BTT approval in patients with severe biventricular heart failure. This device is manufactured in 50- and 70-mL sizes to accommodate a range of body sizes. The device was approved based on a prospective study comparing TAH with medical therapy or IABP. Patients supported with TAH had a superior survival to transplantation than the control cohort (79% vs 46%).[14]

EXCOR PEDIATRIC VENTRICULAR ASSIST DEVICE

The Excor Pediatric VAD (Berlin Heart, Woodlands, TX) is a miniaturized, pneumatically driven, extracorporeal LVAD manufactured with stroke volumes from 10 to 60 mL to fulfill the hemodynamic needs of children from newborn through adolescence. The Excor was tested in a single-arm trial in pediatric patients ranging in weight from 3 to 60 kg using historical outcomes with ECMO as a control group.[15] Children treated with the Excor had a statistically lower likelihood of death, withdrawal of support for stroke with serious neurologic injury, or inability to wean from the device than controls. Based on the results of this trial, Excor is approved as a BTT for children in the United States.

OTHER DEVICES

Several other devices are in various stages of development and investigation. The Jarvik 2000 (Jarvik Heart, New York, NY) is an intracardiac axial flow device being studied as BTT in both children and adults. The CARMAT TAH (CARMAT, Velizy Villacoublay, France) has been implanted in a small cohort of patients in Europe. This novel device has a biological blood contacting surface made from bovine pericardium. The BiVACOR TAH (BiVACOR, Houston TX) is a magnetically levitated centrifugal flow pump currently in development.

A common feature of the clinical trials in chronic MCS is improvement in quality of life and functional capacity. Data from the HeartMate II clinical trials program demonstrated that both continuous and pulsatile flow devices resulted in significant improvements in 6-minute walk distance and NYHA functional class that occurred within 3 months of implantation and remained stable through 24 months of follow-up.[16] Quality of life measured by the Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires had a similar pattern of improvement to functional study. There were no differences between patients who received continuous flow and pulsatile flow pumps, suggesting that reduction of LV filling pressures and improvement in cardiac output are important drivers of these changes. Neurocognition studies measured over 24 months have shown sustained improvements in executive cognitive function.[17]

DEVICE MANAGEMENT

MEASURING BLOOD PRESSURE

The unique physiology of continuous flow LVADs poses interesting challenges in seemingly simple medical tasks such as measuring blood pressure or obtaining peripheral pulse oximetry, both dependent on detection of a peripheral pulse (Fig. 73–8). Use of a Doppler and a peripheral blood pressure cuff is the most effective means to measure blood pressure. When compared to an automated blood pressure, palpation, and auscultation, Doppler was more highly correlated with the blood pressure obtained simultaneously from direct measurement with an arterial catheter.[18] The narrow pulse pressure observed with continuous flow LVADs minimizes the distinction between systolic and diastolic pressure, often making them imperceptible. If the peripheral pulse is not detectable, the first sound detected with a Doppler can be considered the mean arterial pressure. Detection of a palpable pulse should prompt consideration for device malfunction or insufficient pump speed. It is common for the pulse oximeter to provide inaccurate data. The pulse oximeter may not display a clinically accurate value or may read a value that is lower than obtained by blood gas analysis.

ANTICOAGULATION AND ANTIPLATELET THERAPIES

Contemporary LVADs are managed with both an anticoagulant and an antiplatelet agent. During the peri-implant period, heparin and aspirin are started after surgical bleeding slows, with heparin continuing until the INR is therapeutic. Recent data suggest that anti–factor Xa levels are a more accurate reflection of anticoagulation status than activated partial thromboplastin times in the MCS population.[19] Recommendations regarding chronic antiplatelet drug dosing and target INR are device specific and largely empiric. Data from the HeartWare ADVANCE trial demonstrated that patients with an INR > 3.0 were at risk for hemorrhagic stroke, whereas those with an INR < 2.0 were at risk for ischemic stroke.[20] In the same analysis, patients on low-dose (81 mg) aspirin were at higher risk for both ischemic and hemorrhagic stroke, raising the possibility that some hemorrhagic strokes evolve from ischemic injury. Use of the new anticoagulants, such as the direct thrombin inhibitors and factor Xa inhibitors, is not currently endorsed for use in the VAD population. There are no clinical data supporting the use of these agents, and concern has been raised about the risks for thrombosis, significant mucosal bleeding, and lack of an antidote.

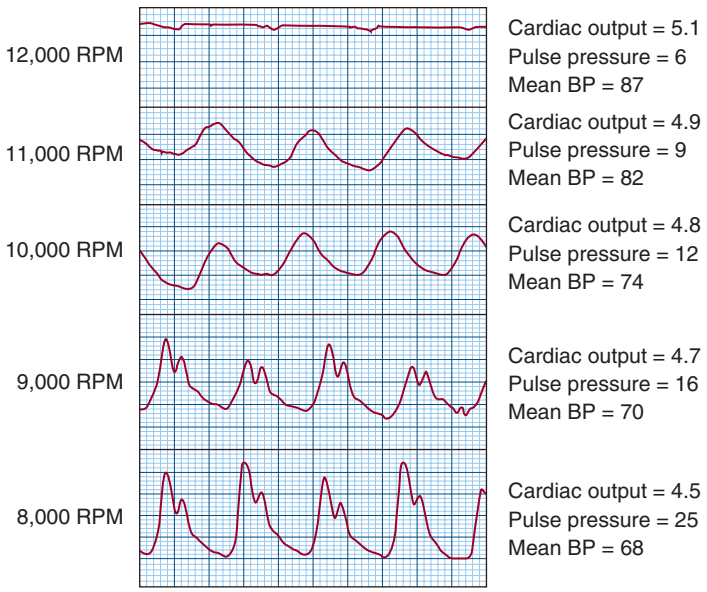


FIGURE 73–8. Arterial pressure tracings after left ventricular assist device implantation. With increasing speed, there is reduced pulse pressure as a larger volume of blood is removed from the left ventricular apex. Aortic valve opening is gradually reduced until it closes completely to provide continuous systemic blood flow. BP, blood pressure; RPM, revolutions per minute. Reproduced with permission from Frazier OH, Myers TJ, Gregoric ID, Initial clinical experience with the Jarvik 2000 implantable axial-flow left ventricular assist system. *Circulation*. 2002 Jun 18;105(24):2855-2860.

HYPERTENSION MANAGEMENT

Blood pressure management is an important aspect of normal LVAD function and postimplant care. Elevated systemic blood pressure reduces cardiac output and increases LV filling pressures in continuous flow LVADs. The HeartWare Clinical Trials Program identified systemic hypertension as an important contributor to both ischemic and hemorrhagic stroke.[20] Therefore, it is recommended that the mean arterial pressure is maintained < 90 mm Hg with the HeartWare HVAD. To date, it is less clear that the same relationship exists with the HeartMate II device.

SETTING DEVICE SPEED

Regardless of the specific MCS device implanted, there are several general goals of mechanically assisted circulation including reduction of heart failure symptoms, ventricular unloading, reduction of LV diameter and mitral regurgitation, and maintenance of the interventricular septum in a neutral position. Excessive device speeds with excessive lowering of the LV end-diastolic pressure will cause septal shift toward the lateral wall of the LV, resulting in secondary tricuspid regurgitation as well as RV enlargement and dysfunction.

IMAGING

The only adjustment that a clinician can make with the continuous flow LVADs is speed alteration, and transthoracic echocardiography plays a key role in optimizing this parameter.[21] Prior to discharge, many programs assess the adequacy of LVAD support using a ramp study. This technique involves reducing the LVAD speed to a level nominal support and then incrementally increasing the speed with simultaneous assessment of the patient symptoms, ventricular size, septal position, mitral regurgitation, and aortic valve opening. The ramp study has been shown to be beneficial in both setting the most optimal speed and assessing for VAD malfunction.[22] In instances in which speed increases do not reduce ventricular size, consideration should be given to obstruction of flow into or out of the pump.

Other imaging techniques are intermittently used to assess the positioning of the LVAD inflow cannula. Routine chest x-ray is useful to serially evaluate the angulation of the inflow cannula of the HeartMate II. The cannula should be positioned in the long axis of the LV and directed at the mitral valve. Positioning toward the ventricular septum or lateral wall may lead to suboptimal device function. Gated computed tomography (CT) angiography is another technique that is useful to determine positioning of the inflow cannula, particularly its relationship to ventricular myocardium.

HEMODYNAMICS

Certain clinical scenarios should prompt measurement of central hemodynamics using a pulmonary artery catheter. Patients with secondary pulmonary hypertension awaiting transplantation should have a measurement of pulmonary artery pressures after a period of device support to ensure the pulmonary hypertension has resolved with

mechanical unloading. Recent data suggest that once normalization of pressures has been demonstrated, repeated invasive hemodynamic studies are not required.[23] Patients with residual signs or symptoms of low-output or congestion despite attempts at a ramp study should have a right heart catheterization. A recent report suggests that combining an invasive hemodynamic assessment with an echocardiographic ramp study frequently results in changing LVAD speed.[24] Patients with moderate to severe aortic insufficiency may also require an invasive hemodynamic evaluation to determine LV filling pressures.

ADVERSE EVENTS

The 2015 INTERMACS report showed that within the first year after LVAD implantation, approximately 70% of patients experienced a major adverse event, including bleeding, infections, arrhythmia, stroke, or death.[2]

NEUROLOGIC EVENTS

Neurologic complications after LVAD therapy can have devastating consequences for patients and negatively impact survival and transplant candidacy. Ischemic and hemorrhagic strokes have been observed following LVAD implantation, with an incidence of 5% to 29%.[11,25-27] Ischemic events are likely thromboembolic, resulting from complex interactions of blood components with the device. However, concomitant atherosclerotic disease in the intracranial or extracranial head and neck vasculature should be excluded. Hemorrhagic cerebrovascular accidents have been postulated to result from elevated blood pressure in fully anticoagulated patients, higher velocity flow, or hemorrhagic conversion from thromboembolic ischemic strokes.[20] Female sex has also been implicated in stroke risk after LVAD.[28]

AORTIC INSUFFICIENCY

Continuous flow LVADs can both exacerbate pre-existing aortic insufficiency (AI) and prompt development of de novo aortic valve disease. The incidence of de novo AI 1 year after implantation ranges from 6% to 14.3% and is caused by limited opening of the valve that promotes commissural fusion and deformation.[29-33] Additional risk factors for the development of AI after LVAD placement include female sex, smaller body surface area, and greater aortic root diameter.[29,30] The hemodynamic consequence of AI is the generation of a closed loop circulation that reduces LVAD efficiency, worsens heart failure symptoms, and perpetuates AI. Management includes AV suture closure or repair/replacement at the time of LVAD implant to prevent progression of AI.[34] Postimplant strategies include surgical repair or replacement, although percutaneous approaches have been attempted in select patients with hemodynamically significant AI without surgical options.[35-37]

RIGHT VENTRICULAR FAILURE

RV failure is an important cause of morbidity and mortality in LVAD-supported patients. Preimplant prediction is best accomplished by integrating multiple data elements. A ratio of central venous pressure to pulmonary capillary wedge pressure > 0.63 is a risk factor for early RV failure.[38] Other predictive hemodynamic parameters include RV stroke work index and the pulmonary artery pulse index, which provide measures of RV systolic function relative to filling pressures. Echocardiographic factors correlated to RV failure include qualitative and quantitative RV function, ratio of RV to LV size, and tricuspid annular plane systolic excursion.[39,40] Echocardiographically derived strain indices are associated with postoperative RV failure and may be an important prognostic indicator.[41] Many other clinical variables have been identified in multivariate analyses to be associated with the development of early RV failure. These include the lack of hemodynamic stability, use of inotropic or vasopressor support, and markers of liver injury.[42] Furthermore, although the focus of many analyses has been on early RV failure, there is increasing evidence that a syndrome of late RV failure can develop months to years after LVAD implantation. This may be in part a result of residual RV dysfunction that manifests later in the clinical course, ongoing myocyte injury leading to declining contractility of the unsupported RV, or a new insult to the RV myocardium. Similar to early RV failure, management of this clinical syndrome requires careful consideration of relative right- and left-sided filling pressures, which can be concordant or discordant. In patients with concordant elevation in left- and right-sided filling pressures, diuretic therapy and LVAD speed adjustment may be key therapeutic interventions. However, elevated right-sided pressures in the setting of low or normal left-sided pressures may require consideration of inotropic support to improve RV contractility. Other therapeutic considerations include pulmonary vasodilators or mechanical fluid removal to lower right-sided filling pressures. In severe cases, right-sided mechanical support may be required to directly augment pulmonary blood flow. INTERMACS has demonstrated the negative survival implications of patients requiring biventricular mechanically assisted circulation.[2]

TRICUSPID REGURGITATION

Tricuspid regurgitation (TR) associated with advanced heart failure and secondary pulmonary hypertension usually improve following isolated LVAD implantation. LVAD support reduces LV end-diastolic and pulmonary venous pressures, decreases RV afterload, and improves RV performance and venous pressures, leading to decreased RV end-diastolic diameter and decreased TR.[43] However, TR may worsen if the pulmonary vascular resistance remains elevated, there is excessive RV preload from the VAD, or the septum shifts leftward.[44] Patients with moderate or greater TR at time of LVAD placement have worse outcomes including decreased survival.[45-47] Thus, the possibility of improving outcomes, including decreasing the incidence of RV failure, by correcting TR remains a therapeutic option for select patients that may result in improved RV performance.[48]

VENTRICULAR ARRHYTHMIAS

Ventricular tachycardia (VT) and ventricular fibrillation (VF) occur in 30% to 55% of patients supported with LVAD therapy.[49,50] Ventricular arrhythmias are often related to the underlying cardiomyopathy but can be induced by ongoing ischemia or originate from areas of myocardial scarring or fibrosis, including the apical cannulation site. Ventricular arrhythmias may also be caused by contact of the LVAD with the myocardium. Preimplant arrhythmias are associated with postimplant VT/VF, suggesting a role for targeted antiarrhythmic therapy, intraoperative surgical ablation, biventricular assist device support, or heart transplantation.[51] Catheter ablation for postimplant refractory VT/VF is often well tolerated as a result of the hemodynamic stability provided by the LVAD.[52,53] Following LVAD implantation, strategies to reduce ventricular arrhythmias and antitachycardia therapies include careful volume management and device speed adjustment to avoid interaction between the myocardium and LVAD as well as careful reprogramming of implantable cardioverter-defibrillator (ICD) parameters to limit defibrillator therapies. Post hoc analysis of clinical trial databases and the INTERMACS registry have demonstrated a higher than desirable rate of sudden death in LVAD patients without an ICD; therefore, it is recommended that these patients have an ICD implanted as prophylaxis if they are candidates and are known to have hemodynamic

compromise with their clinical arrhythmia.[48] Finally, many LVAD patients have cardiac resynchronization therapy. There are no data to support biventricular pacing in an LVAD-supported patient, so LV lead deactivation should be considered to maximize battery life.

SYSTEMIC BLEEDING

Both surgical and nonsurgical bleeding are common adverse events associated with LVAD therapy. Bleeding in LVAD recipients results from hematologic alterations including acquired von Willebrand disease, impaired platelet aggregation, and the requisite use of antiplatelet agents and anticoagulation.[54,55] Acquired von Willebrand disease, a consequence of high shear stress generated in the LVAD, exposes enzymatic cleavage sites on the von Willebrand protein with resultant proteolysis to smaller molecular weight fragments that are less effective at platelet binding.[56,57] LVAD patients have measurable reductions of large-molecular-weight von Willebrand factor multimers within 30 days after implantation but restoration following heart transplantation, suggesting a primary role of the device.[58-60]

MUCOSAL BLEEDING

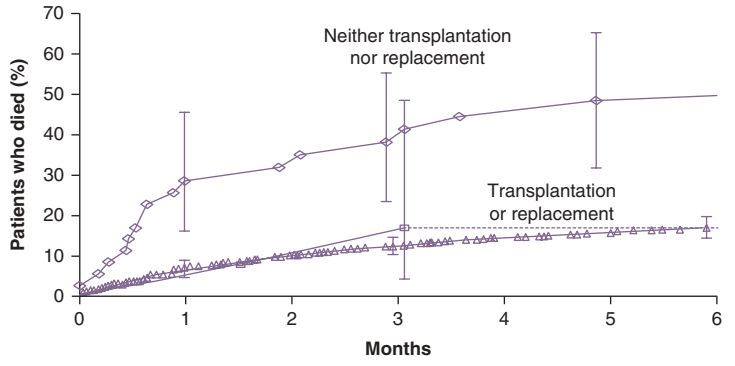
Nasal and gastrointestinal (GI) bleeding occur in 10% to 30% of LVAD patients, with 21% to 44% experiencing recurrence that often leads to readmission and invasive diagnostic and therapeutic procedures.[61-66] It is postulated that GI bleeding is a consequence of continuous blood flow physiology. High shear stress on blood elements causes hematologic alterations in von Willebrand factor, as described earlier. Reduced pulse pressure leads to alterations in microcirculatory flow, promoting proliferation of arteriovenous malformations (AVMs) in the GI tract.[55] AVMs have been identified as the bleeding source in up to one-third of GI bleeding events and are most commonly identified in the small bowel.[67] The proposed pathophysiologic mechanisms by which continuous flow support promotes formation of AVMs are (1) elevated intraluminal pressures and smooth muscle alterations causing arteriovenous dilatation and (2) decreased pulse pressure causing hypoperfusion, regional hypoxia, and vascular dilatation.[55,61,68] Patients with mucosal bleeding require interruption of standard anticoagulation and antiplatelet treatments. In addition to endoscopic evaluation/treatment and modification of anticoagulation targets, novel strategies to reduce the incidence GI bleeding are being explored, including restoration of pulsatility and novel pharmacologic therapies to reduce AVM formation or stabilize von Willebrand factor multimers.

THROMBOSIS

Balancing the risks of thromboembolic events and bleeding represents a difficult clinical decision-making process.[69,70] Multicenter analyses suggest that thrombosis risk is the highest in the first few months following implant[71] (Fig. 73–9). There are no clear risk factors for the development of LVAD thrombosis, and some risk may be device specific. The clinical spectrum of pump thrombosis ranges from asymptomatic hemolysis to overt heart failure and device malfunction. Thrombus within the pump increases shear force, resulting in turbulent flow and red blood cell destruction (Fig. 73–10). Elevated levels of lactate dehydrogenase, plasma free hemoglobin, and hemoglobinuria associated with alterations in consumed pump power help confirm the diagnosis. Other imaging modalities such as echocardiography, CT scan, or angiography provide supporting information. Medical management strategies include hemodynamic stabilization, enhanced anticoagulation, and systemic or intraventricular thrombolysis.[72,73] Most patients, however, will require LVAD exchange; this recommendation is based largely on the observation of improved survival for the patient cohort managed with device removal versus noninvasive management.[73]

INFECTION

Device-related infections are a frequent adverse event and may present as a driveline infection, a deep tissue infection, or sepsis. The importance of driveline infections cannot be underestimated; the majority of LVAD-related infections begin at the driveline, and 64% are associated with invasive disease.[74] Major predisposing factors for percutaneous site infections include young age and exit site trauma. The most common bacteria involved in LVAD-related infections are *Staphylococcus* and *Pseudomonas* species, whereas most other infections are fungal involving *Candida* species.[74] Fungal infections are difficult to eradicate and carry a high risk of mortality.[75,76] Infections in this population require active microbiologic and imaging diagnoses as well as aggressive antibiotic therapy and possibly surgical treatment.[77,78] In general, LVAD-related bloodstream infections are difficult to eliminate and frequently require pump exchange or transplantation.[79]



No. at risk							
HeartMate II support without thrombosis	895	790	709	652	612	576	531
Thrombosis with transplantation or replacement	32	13	13	13	10	10	10
Thrombosis with neither transplantation nor replacement	40	25	23	20	18	15	15

FIGURE 73–9. Outcomes after left ventricular assist device (LVAD) thrombosis. Mortality according to management strategy after confirmed pump thrombosis (axial flow LVAD). Patients with pump thrombosis who were managed with device replacement or transplantation experienced survival outcomes that were similar to the cohort who did not have pump thrombosis. Survival is diminished for the cohort with pump thrombosis who did not undergo replacement or transplantation. Adapted with permission from Starling RC, Moazami N, Silvestry SC, et al: Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med*. 2014 Jan 2;370(1):33-40.[71]

DURABLE LEFT VENTRICULAR ASSIST DEVICE EXCHANGE

The transition from pulsatile to continuous flow LVADs was driven in part by improved durability. Although this change has resulted in reduced need for LVAD exchange, device replacement is still occasionally required. Indications for LVAD exchange include device thrombosis, driveline electrical fault, and infection. The incidence of

FIGURE 73–10. Left ventricular assist device (LVAD) thrombosis. HeartMate II LVAD pump with inflow elbow and pump housing removed. Thrombus is seen near the inlet portion of the impeller mechanism. Reproduced with permission from Uriel N1, Morrison KA, Garan AR, et al: Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. *J Am Coll Cardiol.* 2012 Oct 30;60(18):1764-1775.[22]

pump replacement for all causes in the ENDURANCE trial was 10% per patient-year for the Heartmate II LVAD versus 6% per patient-year for the HVAD pump.[13] In many instances, LVAD exchange can be performed without redo sternotomy, particularly if the outflow graft to the ascending aorta is free of thrombus or malalignment (Fig. 73–11). Therefore, a preoperative contrasted chest CT scan may be helpful in planning the approach to exchange. For the Heartmate II axial flow LVAD, there have been multiple reports of successful replacement with a subcostal approach.[80] This approach replaces the impeller, where thrombus is most commonly encountered (see Fig. 73–10). Schechter et al[80] reported a survival and morbidity advantage when this approach was utilized rather than redo sternotomy (see Fig. 73–11). For the centrifugal LVADs, device replacement can be performed through an anterior thoracotomy. In both instances, peripheral cardiopulmonary bypass is established and the old outflow graft is retained and attached to the new LVAD pump. This strategy may also be appropriate in cases of ascending power cord infections or electrical fault involving the power cord. Although short-term survival for replacement procedures approaches 100%, long-term outcomes may be diminished relative to primary implants. The exact reasons for this are unclear, but recurring pump thrombosis has been report, and reinfection can occur when replacement is required for infections. More studies are required to truly understand the long-term success of replacement procedures.

SPECIAL POPULATIONS

BIVENTRICULAR HEART FAILURE

At present, there are no VADs designed for chronic, out-of-hospital treatment of RV failure with the exception of the TAH. Post-LVAD RV failure is associated with decreased survival.[81] Further, the use of biventricular mechanical support in the INTERMACS registry has an attendant 40% mortality rate in 6 months compared to the isolated LVAD cohort.[2] The use of LVADs in a biventricular configuration has been described.[82]

RESTRICTIVE AND INFILTRATIVE CARDIOMYOPATHIES

LVADs have been evaluated in patients with dilated cardiomyopathies. Patients with primarily restrictive physiology have limited options for mechanical support. Computer modelling suggests that an appropriately designed LVAD would provide important and clinically meaningful hemodynamic advantages for this patient population.[83] A small experience from the Mayo Clinic described the outcomes of eight patients with restrictive and infiltrative cardiomyopathy.[84] The hemodynamic benefits of LVAD were less pronounced in the restrictive/hypertrophic cardiomyopathy cohort compared to patients with dilated cardiomyopathy, but 12-month survival was similar. The surgical technique was varied and included LV myocardial resection to accommodate the device inflow cannula and promote more normal flow characteristics.

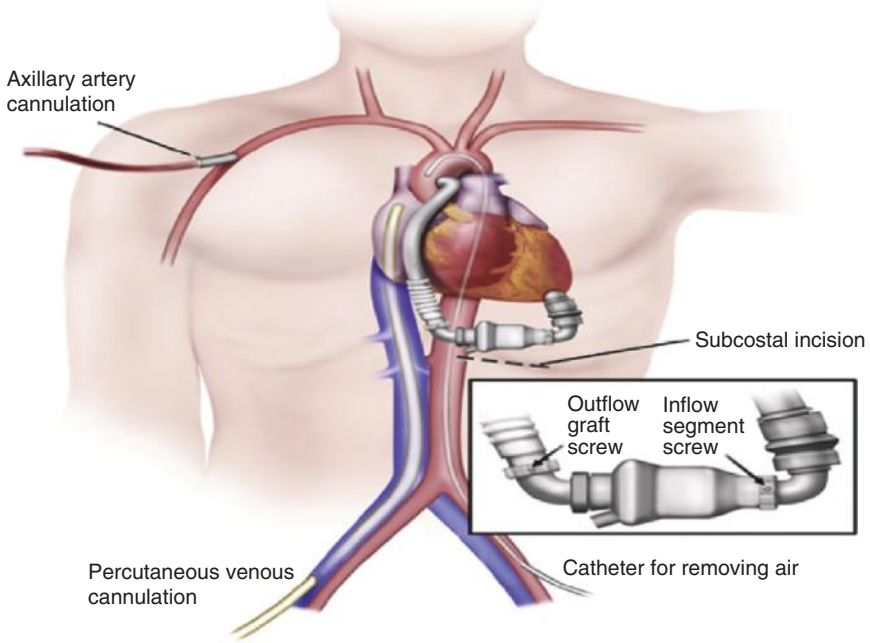


FIGURE 73–11. Surgical approach for replacement of axial flow left ventricular assist device. Peripheral cardiopulmonary bypass is established via right axillary artery and right percutaneous femoral venous cannulation. Through a left subcostal incision, the pump and power cord are replaced, while retaining the old inflow elbow and outflow graft. A separate arterial catheter introduced via the femoral artery can be positioned in the ascending aorta for the purpose of de-airing. Reproduced from Rogers JG, Jollis JG, Milano CA. Replacement of continuous-flow left ventricular assist device via left subcostal incision. *J Thorac Cardiovasc Surg.* 2012 Apr;143(4):975-976.

MECHANICAL CIRCULATORY SUPPORT IN CHILDREN

Device technology has limited the use of mechanical blood pumps in children. The complexity of childhood heart failure, including structurally abnormal hearts previously treated with palliative cardiac surgeries, the need to account for the variability in body size and growth, the duration of support, and the special challenges associated with childhood device management, necessitated innovative and durable solutions to mechanically assisted circulation. ECMO has been the most common mechanical support strategy in children.[85] This approach has the advantages of being easily deployed, providing support of both the cardiac and pulmonary systems, and being relatively simple. The risk of ECMO complications is dependent on support duration. In the Extracorporeal Life Support Organization registry, 16% of children supported on ECMO experienced a stroke.[86] Mortality risk factors included low birth weight, gestational age < 34 weeks, acidosis, and the need for cardiopulmonary resuscitation. The Berlin Heart EXCOR (Berlin Heart, The Woodlands, TX) is an alternative for pediatric patients with left or right heart failure. This extracorporeal device is manufactured in multiple sizes to match the circulatory requirements of this diverse population. The EXCOR received approval for use in children based upon a clinical trial of 48 subjects with body surface area as low as 0.23 m^2. Compared to a propensity-matched historical control group treated with ECMO, children bridged to transplant with the EXCOR had statistically superior survival.[87]

FUTURE DIRECTIONS

Evolution of mechanically assisted circulation therapies in the next 10 years is likely to focus on further refinement of patient selection and management strategies, enhanced engineering to reduce adverse events, miniaturization of the devices, and development of totally implantable systems that eliminate the need for an external driveline. It is important to note that each of these goals may not be achieved in mutual fashion. For example, although miniaturization and/or earlier implantation may reduce short-term mortality, adverse events related to reduced pulsatility may result in longer term morbidity. Prioritization of these future goals will be paramount to the ongoing success of MCS and will be developed from clinical experience. Indeed, clinicians will play a pivotal role in improving outcomes through continued evaluation of predictors of right heart failure, management of common comorbid conditions, and thoughtful application of innovative medical therapies. A contemporary example of engineering innovation is integration of an artificial pulse in the computer software of the HeartMate III LVAD that speeds and slows the rotor at intervals to allow the native ventricle to fill and eject several times each minute. It is hoped that restoration of ventricular ejection will reduce the risk of some adverse events including aortic valve stenosis and mucosal bleeding.

Approximately 70% of LVAD patients experience an adverse event in the first year after implant.[2] These events cross a wide spectrum of severity but often require hospital days to manage. The next generation of devices will be more biocompatible in an attempt to reduce blood trauma and platelet activation and potentially reduce the need for anticoagulation and antiplatelet therapies.

Another critically important innovation required in this field is the development of the totally implantable system. In conceptual form, a capacitor will be implanted subcutaneously that can be charged across the skin and will provide sufficient power to the device that allows several hours of untethered time.

ADJUVANT THERAPIES

The ultimate goal of transplantation is to use LVAD therapy as a means to support critically ill patients while an adjuvant therapy is administered that will allow myocardial recovery and VAD removal. Prior work has demonstrated favorable improvements in myocardial energy utilization, myocardial interstitium, downregulation of proinflammatory cytokines, and improvements in cardiac structure and function.[88] To date, however, these favorable changes have not commonly resulted in sufficient improvement in native cardiac function that implanting centers remove the device. In fact, clinical trials and registries demonstrate that only approximately 3% of LVADs are explanted as a result of recovery.[87] Factors associated with the likelihood of recovery are short duration of heart failure, nonischemic etiology, and younger patient age.[89] One of the most important challenges faced in the field of recovery is lack of a validated biomarker that assists the clinician and patients predict durability of recovery.

Adjuvant therapies have been used to promote myocardial recovery. Birks and colleagues[90] reported a cohort of patients with nonischemic cardiomyopathy treated with adjuvant clenbuterol, a β_2-receptor agonist to enhance cardiac performance. Following a period of treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists, β-blockers, and mineralocorticoid receptor antagonists, clenbuterol was initiated and patients were monitored with serial imaging studies, exercise tests, and hemodynamic assessment. Seventy-three percent of patients treated with clenbuterol were weaned off their device with stable cardiac size and function through 48 months.[90]

Another approach to myocardial recovery is cell based. Ascheim and colleagues[90] recently reported the results of an early-phase, placebo-controlled, randomized trial examining the role of allogeneic mesenchymal stem cells injected directly into the myocardium at the time of LVAD implant. The primary end point of the study was safety of this technique, and neither excessive adverse events nor allosensitization occurred with this approach. A secondary end point was ability to tolerate short-term device weaning, and patients who received cells were more tolerant of transient reductions of LVAD speed (more reliant on native heart function) than those who received placebo.[91]

Mechanically assisted circulation has evolved over the past 10 years from a niche therapy used for short periods to support unstable patients awaiting transplantation to a viable long-term treatment for advanced heart failure. Clinical trials have demonstrated that MCS prolongs survival and simultaneously improves functionality and quality of life in carefully selected patients. The therapy remains imperfect, with a higher than desirable rate of important adverse events that result in morbidity, mortality, and cost. However, this field has entered a new phase of rapid change in which critical feedback loops between patients, clinicians, and engineers are being leveraged to improve devices, peripheral components, and adjuvant management. With continued progress, the ultimate goal of the field may be realized—widespread availability of a treatment that rivals cardiac transplantation.

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CHAPTER 74

PULMONARY HYPERTENSION

Lewis J. Rubin

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Pulmonary hypertension (PH) is a hemodynamic abnormality common to a variety of conditions that is characterized by increased right ventricular (RV) afterload and work. The clinical manifestations, natural history, and reversibility of PH depend heavily on the nature of the pulmonary vascular lesions and the etiology and severity of the hemodynamic disorder, although individual variability exists. For example, subacute or chronic hypoxia predominantly causes increased muscularization of the small muscular pulmonary arteries and arterioles with the intima relatively intact. Relief of the hypoxia improves or occasionally reverses the process with little or no pathologic residue.[1,2] In contrast, the lesions of systemic sclerosis (scleroderma), mostly confined to the intima of the small pulmonary arteries and arterioles, are usually progressive and irreversible. Unlike these two examples, which spare the pulmonary capillary bed, the pulmonary capillaries are the primary site of involvement in pulmonary capillary hemangiomatosis.[3]

Because of its large capacity, its great distensibility, its low resistance to blood flow, and the modest amounts of smooth muscle in the small arteries and arterioles, the pulmonary circulation is not predisposed to become hypertensive. In normal individuals lying supine, systolic pressure is approximately 15 to 25 mm Hg; the corresponding diastolic pressure is 5 to 10 mm Hg. The mean driving pressure (ie, the difference between the mean blood pressure in the pulmonary artery and in the left atrium, the transpulmonary gradient) is usually < 10 mm Hg. Because blood flow (cardiac output) is the same in both circulations in the absence of any systemic to pulmonary communications, the pulmonary vascular resistance (PVR) is approximately one-eighth of systemic vascular resistance. The large cross-sectional surface area of the pulmonary circulation, coupled with the distensibility of its thin-walled vessels and the large recruitable vascular reserve, account for these unique characteristics. During exercise, as pulmonary blood flow increases, new regions of the pulmonary vascular bed are open and existing vasculature dilates; accordingly, the pulmonary circulation is capable of accommodating a fourfold or greater increase in resting blood flow with virtually no change in pulmonary artery pressure, with a concomitant decrease in PVR.

When total cross-sectional area is decreased by destruction or obliteration of lung tissue or occlusive lesions in the resistance vessels, pulmonary arterial pressures increase. The degree of PH that develops is a function of the amount of the pulmonary vascular tree that has been eliminated. PH is most often associated with cardiac or pulmonary diseases. Although idiopathic pulmonary arterial hypertension (IPAH; formerly known as primary pulmonary hypertension [PPH]) is uncommon, it is well recognized as a distinctive clinical entity in which intrinsic pulmonary vascular disease is free of the complicating features of PH contributed by diseases of the heart and/or lungs. Mild PH can exist for a lifetime without becoming evident clinically. For example, native residents at high altitude, in whom mild to moderate PH is a natural result of sustained exposure to hypoxia, can adapt and function normally. When PH does become manifest clinically, the symptoms tend to be nonspecific (Table 74–1).

DEFINITIONS

PH is defined as a mean pulmonary arterial pressure at least 25 mm Hg at rest measured by invasive monitoring. Pulmonary *arterial* hypertension (PAH) is defined as PH with normal left-sided filling pressure (ie, pulmonary capillary wedge pressure [PCWP] < 15 mm Hg) and an increased PVR (> 3 units). PAH can be either acute or chronic. The acute form is usually a result of either pulmonary embolism (see Chap. 75) or the acute respiratory distress syndrome. This chapter deals with *chronic* PAH.

Pulmonary *venous* hypertension is usually encountered as a consequence of left ventricular (LV) dysfunction or mitral valve disease. Occasionally, it may occur in the course of fibrosing mediastinitis or as a complication of catheter ablation for supraventricular tachyarrhythmias. The hallmarks of pulmonary venous hypertension are pulmonary congestion and edema. For practical purposes, pulmonary venous hypertension exists when pulmonary venous (or left atrium [LA]) pressure rises above 15 mm Hg. To maintain forward blood flow, pulmonary arterial pressure increases; however, this does not necessarily result in an increase in PVR. Additionally, PH can be *mixed pulmonary vasculopathy*, defined as PH with a PCWP > 15 mm Hg and an increased PVR.

TABLE 74–1. Symptoms of Pulmonary Hypertension

Dyspnea	Palpitations
Fatigue	Orthopnea
Dizziness	Cough
Syncope	Hoarseness
Chest pain	

Cor pulmonale signifies the presence of PH and cardiac dysfunction in the setting of diseases affecting the structure or function of the lung.[4] PH in patients with chronic lung disease tends to be less severe than in connective tissue diseases, chronic thromboembolic disease, or IPAH. PH may be severe, however, in some patients with interstitial lung disease.

NORMAL PULMONARY CIRCULATION

STRUCTURE

Immediately before birth, pulmonary and systemic arterial blood pressures are near equal and approximately 70/40 mm Hg, with a mean of 50 mm Hg. Immediately after birth, with closure of the ductus arteriosus and initiation of ventilation, pulmonary arterial pressure falls rapidly to approximately one-half of systemic levels. Thereafter, pulmonary arterial pressures gradually decrease over several weeks to reach adult levels.[5]

In some neonates, the normal PH of the fetus fails to recede normally, generally as a result of either a developmental anomaly or a relentless increase in pulmonary vascular tone. In such infants, the persistent PH and RV failure may become life threatening. Surgical intervention or temporizing measures, such as the use of inhaled nitric oxide (NO) or extracorporeal membrane oxygenation, have improved the outcome for many infants with reversal of the pulmonary vascular abnormalities.[6]

In the normal adult at sea level, the small muscular arteries and arterioles in the lungs are thin-walled and contain very little smooth muscle. In contrast, in the fetus or the adult who has lived under hypoxic conditions (eg, native residents at high altitude), the media of the arterioles are thickened, and the muscle extends distally into precapillary vessels that are ordinarily devoid of muscle; that is, the precapillary vessels undergo *remodeling*.[7]

ENDOTHELIUM AND ENDOTHELIUM–SMOOTH MUSCLE INTERACTIONS

In addition to its role as a semipermeable barrier between blood and interstitium, the endothelium provides many biologically important functions, the net effect of which is the processing of blood flowing through the lungs. Among these functions are the synthesis, uptake, storage, release, and metabolism of vasoactive substances; transduction of bloodborne signals; modulation of coagulation and thrombolysis; regulation of cell proliferation; engagement in the local inflammatory and proliferative reactions to injury; involvement in immune reactions; and angiogenesis (see Chap. 5). Some of the enzymes involved in these processes, such as the angiotensin-converting enzyme, are found on the surface of endothelial cells; others, such as 5-nucleotidase, are found within the cell. Hence it is appropriate to regard the endothelium as an organ with diverse metabolic and endocrine functions, one that is unique because of its strategic location as a continuous, monolayered lining of blood vessels throughout the body. Importantly, the lungs contain the largest expanse of endothelium in the body.

The cells that make up the monolayered endothelial lining communicate not only with each other by anatomic junctions and bridges, but also with the underlying smooth muscle by way of biologically active substances. This interaction participates in regulating normal vasomotor tone as well as responding to the administration of vasoactive substances. Thus damage to the lining cells, proliferation of the intima, or hypertrophy of the smooth muscle will each upset the normal interplay.

HEMODYNAMIC PARAMETERS

For the adult pulmonary circulation, the definition of *normal* depends on the altitude. Table 74–2 compares the normal pulmonary hemodynamics of adults residing at sea level and above sea level. At *sea level*, a cardiac output of 5 to 6 L/min is associated with a pulmonary arterial pressure of approximately 20/12 mm Hg, with a mean of approximately 15 mm Hg. At an altitude of 15,000 ft, the same level of blood flow is associated with somewhat higher pressures (see Table 74–2). Pulmonary arterial pressures also tend to increase somewhat with age.

A pressure drop of only 5 to 10 mm Hg between the pulmonary artery and LA accompanies the cardiac output of 5 to 6 L/min (see Table 74–2). Determination of PVR, calculated as the ratio of the difference in mean pressure at the two ends of the pulmonary vascular bed (pulmonary arterial pressure minus LA pressure) divided by the cardiac output (see Table 74–2), is a practical clinical tool for assessing the hemodynamic state of the pulmonary circulation and for distinguishing between active and passive changes in the pulmonary resistance vessels (eg, the effect of administering a vasodilator agent to a patient with PH). In practice, because the LA may not be readily accessible, PCWP is generally substituted for LA pressure.

Another approach to defining certain characteristics of the pulmonary arterial tree and its behavior—that is, elastic properties and geometry—is the calculation of pulmonary arterial input impedance. This approach has more physiologic than clinical value. It takes into account the pulsatile nature of pulmonary arterial pressures and flow. Like vascular resistance, it is defined as a ratio. But instead of a ratio involving *mean* pressures and blood flow, the ratio uses the amplitudes of pulsatile pressure to oscillatory flow near the beginning of the pulmonary artery at a particular frequency. Values for the ratio are calculated by compartmentalizing the pulsatile pressure and flow curves into their sinusoidal components.

PVR has proved useful in assessing the state of the normal and abnormal pulmonary circulation, but reliance on the calculated resistance

TABLE 74–2. Values for Normal Pulmonary Circulation at Sea Level and High Altitude

	Sea Level	Altitude (~15,000 ft)
Pulmonary arterial pressure (P_{PA}), mm Hg	20/12, 15	38/14, 25
Cardiac output (Q), L/min	6	6
Left atrial pressure (P_{LA}), mm Hg	5	5
Pulmonary vascular resistance (PVR),[a] (mm Hg/L)/min (R units)	1.7	3.3

[a] $PVR = \frac{P_{PA} - P_{LA}}{Q} = \frac{15-5}{6} = 1.67$ R units

To convert R units to CGS (centimeter-gram-second) units (dynes/s/cm^5), multiply R units by 80.

must be done with caution. For example, PVR may decrease despite an *increase* in pulmonary arterial pressure if cardiac output increases to a greater degree than the increase in pulmonary arterial pressure as a result of a drug-induced primary effect on cardiac contractility or heart rate with little direct effect on pulmonary vasomotor tone. It is unlikely that this pattern of hemodynamic response will be beneficial. Also, a clinical shortcut, such as the substitution in the numerator of the pulmonary arterial pressure for the pressure drop between the pulmonary artery and LA, may be useful empirically but deprives the calculation of any physiologic meaning. Finally, the clinical significance of a value calculated for PVR depends heavily on the implications of the hemodynamic changes on the work of the RV. For example, the same decrease in calculated PVR brought about by two different pulmonary vasodilators may affect the work of the RV differently: Should one agent elicit a *decrease* in pulmonary arterial pressure along with an increase in cardiac output (an ideal response), it is more apt to be of long-term benefit than another agent that, although increasing the cardiac output, fails to decrease the pulmonary arterial pressure.

In the normal lung, a considerable increase in cardiac output, that is, three to five times that at rest, generally increases pulmonary arterial pressure by only a few millimeters of mercury with a concomitant decrease in PVR. On the other hand, in pulmonary hypertensive states, in which the distensibility and recruitability of the pulmonary vascular bed are restricted by disease, pulmonary arterial pressure increases along with even small incremental increases in pulmonary blood flow. Changes in pulmonary blood volume are much more subtle than changes in blood pressure or flow in their hemodynamic effects; they are also much more difficult to quantify. Clinical clues can be helpful in recognizing that the pulmonary blood volume has increased. Often a fullness of the pulmonary vascular pattern on the chest radiograph along with evidences of interstitial edema suggest that pulmonary blood volume has increased acutely. In chronic mitral stenosis or LV failure, the pulmonary blood volume is not only increased, but also redistributed toward the apices of the lungs, that is, *cephalization* (see Chap. 14).

Autonomic innervation of the pulmonary vascular tree plays a lesser role in modulating vasomotor tone than do local stimuli, particularly hypoxia. Indeed, hypoxia can exert its pulmonary pressor effect in the denervated lung. The mechanism by which hypoxia exerts its local pressor effect is not fully characterized, but appears to involve altered smooth muscle cell membrane ion channel activity.[2] Acidosis potentiates the hypoxic pressor effect. Hypercapnia also exerts a pulmonary pressor effect as a result of the respiratory acidosis that it generates.

PULMONARY HYPERTENSION

PH is a final common hemodynamic consequence of multiple etiologies and diverse mechanisms. Among the underlying causes of PH are mechanical compression and distortion of the resistance vessels of the lungs (eg, by diffuse pulmonary fibrosis), hypoxic vasoconstriction (eg, in severe obstructive airways or diffuse parenchymal diseases), intravascular obstruction (eg, thromboemboli or tumor emboli), and combinations of mechanical and vasoconstrictive influences. The significance of PH, however, is that the increased afterload compromises RV function. Once pulmonary arterial pressures reach systemic levels, RV failure becomes inevitable.

CLASSIFICATION

The classification of PH has gone through a series of changes since the first classification was proposed in 1973 at an international conference on PPH endorsed by the World Health Organization (WHO). The most recent classification, the Nice 2012 5th World Symposium on Pulmonary Hypertension,[8] is based on shared pathologic, pathobiologic, and clinical features (Table 74–3). PH patients can belong to more than one group; additionally, patients in group 1 PAH can have more than one risk factor or associated condition. The terms *PPH* and *secondary PH* have been replaced with more specific and descriptive terms.

TABLE 74–3. Updated Classification of Pulmonary Hypertension[a]

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
     - 1.2.1 BMPR2
     - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
     - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 Human immunodeficiency virus (HIV) infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
   - 1.5 Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   - 1.6 Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension as a result of left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension as a result of lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

Reproduced with permission from Simonneau G, Gatzoulis MA, Adatia I, et al: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013 Dec 24;62(25 Suppl):D34-41.[8]

EPIDEMIOLOGY

In adults, the most common cause of PH is lung disease (eg, chronic obstructive pulmonary disease [COPD]). An estimated 30,000 persons die each year from COPD, many of whom have PH and resulting RV failure as a contributing cause of death. Patients with interstitial lung disease, cystic fibrosis, sleep apnea syndrome, and lung disorders caused by occupational and other exposures also frequently develop PH.[4] In the United States, approximately 200,000 patients die annually from acute pulmonary embolism, often with acute RV failure as a result of sudden onset of severe PH. PH is also seen in patients with chronic or recurrent pulmonary embolism, regardless of the source of the embolic material.[4]

Estimates of the incidence of IPAH (formerly termed PPH) range from one to two newly diagnosed cases per million people per year. Its prevalence is approximately 0.1% to 0.2% of all patients who have postmortem examinations. The prevalence of pulmonary vascular disease in patients with other illnesses is not known, but it appears to occur in 2% to 4% of patients with portal hypertension and approximately 0.5% of patients with HIV infection. The incidence of PAH in patients with systemic sclerosis (which includes limited systemic sclerosis and diffuse systemic sclerosis) ranges from 8% to 12%. PAH has been reported to occur in 23% to 53% of patients with mixed connective tissue diseases and in 1% to 14% of patients with systemic lupus erythematosus, but it is rare in patients with rheumatoid arthritis, Sjögren syndrome, or dermatomyositis.

Pulmonary vascular obstructive disease associated with congenital heart disease, and in particular associated with unrepaired large, unrestrictive congenital systemic-to-pulmonary shunts (ie, the Eisenmenger syndrome), develops after a period of decreased PVR and increased pulmonary flow. The high rates of pulmonary vascular obstructive disease in uncorrected congenital heart disease (Table 74–4)[9] demonstrate that even if all other causes of death could be eliminated, approximately one-third of patients with congenital heart disease would die from pulmonary vascular disease. Why some patients develop irreversible pulmonary vascular obstructive disease in the first year of life and other patients remain "operable" from a pulmonary vascular disease standpoint into the second or third decade of life or later with the same congenital cardiac defect remains unknown.

TABLE 74–4. Risk for Pulmonary Vascular Disease in Persons With Congenital Heart Disease[a]

Lesion	%	Total No.	No. at Risk
Ventricular septal defect	30	9000	3000
Patent ductus arteriosus	9	2700	900
Atrial septal defect	7	2100	700
Atrioventricular septal defect	3	900	800
Aortic stenosis	5	1500	0
Pulmonic stenosis	7	2100	0
Coarctation	6	1800	0
Tetralogy of Fallot	5	1500	200
Transposition of the great arteries	5	1500	500
Truncus arteriosus	1	300	300
Hypoplastic right heart	2	600	50
Hypoplastic left heart	1	300	0
Double-outlet right ventricle	0.2	60	60
Total anomalous pulmonary venous connection	1	300	300
Univentricular heart	0.3	90	90
Miscellaneous	17.5	5250	2625
Total	100.0	30,000	9525 (32%)

[a]Assumptions: 3,000,000 live births per year; 1% incidence of congenital heart disease.

Reproduced with permission from Friedman WF, ed. Proceedings of the National Heart, Lung, and Blood Institute Pediatric Cardiology Workshop. Pulmonary hypertension. *Pediatr Res*. 1986 Sep;20(9):811-824.[9]

RISK FACTORS FOR PULMONARY ARTERIAL HYPERTENSION

Risk factors are categorized based on the strength of the association with PAH and a possible causal role (Table 74–5; see also Tables 74–3 and 74–4). These include genetic predispositions, comorbid conditions, and drug exposures.

GENETIC BASIS OF PULMONARY ARTERIAL HYPERTENSION

Heritable PAH (HPAH) represents approximately 15% of cases previously considered IPAH. HPAH is inherited as an autosomal dominant disorder with incomplete penetrance and genetic anticipation, in which disease development may skip generations.

Mutations in three receptors of the transforming growth factor-β family (ie, bone morphogenetic protein receptor 2, activin receptor-like kinase type 1, and endoglin) have been identified in HPAH, indicating a critical role for transforming growth factor superfamily ligand-receptor interactions in vascular homeostasis and in embryologic development (Fig. 74–1). Exonic mutations in *BMPR2* are found in approximately 75% of patients with HPAH, and *ALK-1* or endoglin mutations are found in a minority of patients with hereditary hemorrhagic telangiectasia and coexistent PAH. *BMPR2* mutations are also seen in approximately 25% of patients who were previously classified

TABLE 74–5. Risk Factors and Associated Conditions for Pulmonary Arterial Hypertension From the 2008 Dana Point 4th World Symposium on Pulmonary Hypertension

1. Definite
   - Aminorex
   - Fenfluramine
   - Dexfenfluramine
   - Toxic rapeseed oil
2. Likely
   - Amphetamines
   - L-Tryptophan
   - Methamphetamines
3. Possible
   - Cocaine
   - Phenylpropanolamine
   - St. John's wort
   - Chemotherapeutic agents
   - Selective serotonin reuptake inhibitors
4. Unlikely
   - Oral contraceptives
   - Estrogen
   - Cigarette smoking

Data from Simonneau G, Gatzoulis MA, Adatia I, et al: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013 Dec 24;62(25 Suppl):D34-41.[8]

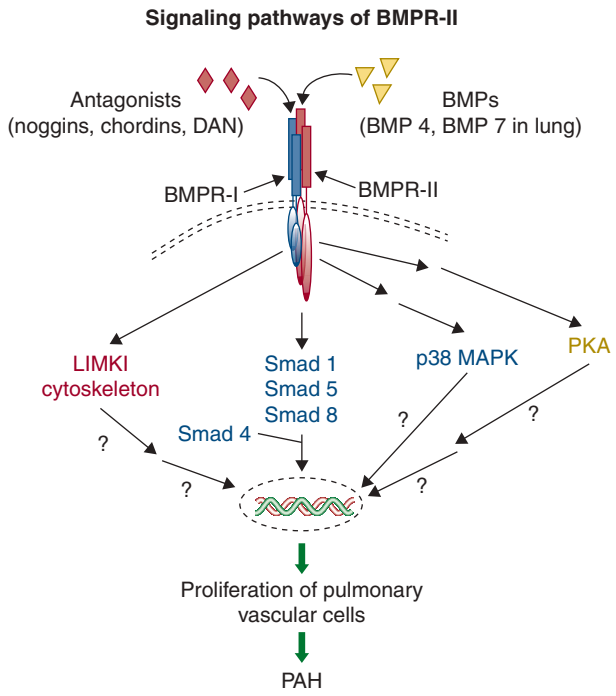


FIGURE 74–1. Signaling pathways of the bone morphogenetic protein (BMP) receptor type II (BMPR II). In the extracellular space, the receptor ligands BMPs bind directly to the BMPR-II on the cell membrane. The bioavailability of BMPs is regulated by the presence of BMPR-II receptor antagonists such as noggins, chordins, and DAN (differential screening-selected gene aberrative in neuroblastoma). The binding of ligands to BMPR-II leads to the recruitment of BMPR-I to form a heteromeric receptor complex at the cell surface. This complex results in the phosphorylation and activation of the kinase domain of BMPR-I. The activated BMPR-I subsequently phosphorylates and activates cytoplasmic signaling proteins Smads (Smad 1, 5, and 8). Phosphorylated Smads bind to the common mediator Smad 4, and the resulting Smad complex moves from the cytoplasm into the nucleus and regulates gene transcription. Other downstream signaling pathways that can be activated after the engagement of BMPR-I and BMPR-II by BMPs include cell type–dependent activation of p38 mitogen-activated protein kinase (p38 MAPK) and protein kinase A (PKA). In addition, the cytoplasmic tail of BMPR-II has been shown to interact with the LIM motif-containing protein kinase 1 (LIMK1) that is localized in the cytoskeleton. Germline mutations of the gene encoding BMPR-II underlie heritable pulmonary arterial hypertension (HPAH), which is characterized by the abnormal proliferation of pulmonary vascular cells. However, the specific cytoplasmic proteins and nuclear transcription factors that are involved in the development of HPAH have not been identified.

as IPAH without a family history of PAH. IPAH is now reserved for patients without a family history and without an identified genetic abnormality. Mutations in *BMPR2* confer a 10% to 20% chance of developing PAH in a carrier's lifetime. Hence, gene-gene or gene-environmental interactions appear to be involved to promote or prevent pulmonary vascular disease. *BMPR2* mutations have also been identified in other PAH cohorts, including appetite suppressant–induced PAH and PAH associated with congenital systemic-to-pulmonary shunts. To date, *BMPR2* mutations have not been reported in PAH related to connective tissue disease, human immunodeficiency virus (HIV), or portal hypertension.

EVALUATION OF SUSPECTED PULMONARY HYPERTENSION

The gold standard for the confirmation of suspected PH is right heart catheterization. This enables the direct determination of right atrial and ventricular pressures, pulmonary arterial pressure, PCWP (as an approximation of pulmonary venous pressure), pulmonary blood flow (cardiac output when there are no systemic-to-pulmonary shunts), and the responses of these parameters to interventions (eg, acute vasodilator testing, oxygen supplementation, rapid intravenous volume loading, exercise). However, the skilled clinician can often suspect PH on the basis of the assessment of an elevated jugular venous pressure pulsation and a loud P_2 (see Chap. 11). PVR is calculated from the measurements and samples obtained during cardiac catheterization (see Table 74–2).

Chest Radiography

The findings on the chest radiograph depend on the duration of the PH and its etiology (see Chap. 14). The characteristic findings of PH are enlargement of the pulmonary trunk and hilar vessels in association with attenuation (pruning) of the peripheral pulmonary arterial tree (Fig. 74–2). Right-sided heart enlargement can best be detected radiographically on the lateral view as fullness in the retrosternal airspace. In PH caused by pulmonary diseases, changes in the lungs (eg, hyperinflation, fibrosis) and in the position of the heart and diaphragm often mask the radiologic changes of PH. Contrast angiography has a role in the workup for PH when chronic thromboembolic disease, which may be treated surgically, is suspected.[10]

Electrocardiogram

The electrocardiogram (ECG) can disclose hypertrophy of the RV and is more reliable in nonrespiratory etiologies than in obstructive airways disease or parenchymal lung disease (see Chap. 12).

Echocardiography

The amount of reliable information obtained by Doppler and two-dimensional echocardiography depends greatly on the commitment of individual clinics to standardizing and perfecting these noninvasive techniques (see Chap. 15). In general, echocardiographic techniques have proved useful in providing a measure of RV thickness as an index of RV hypertension (Fig. 74–3). Estimates of RV systolic pressure can be obtained by determining regurgitant flows across the tricuspid valves using continuous-wave Doppler echocardiography.[11] However, the diagnosis of PH should not be made without confirmatory right heart catheterization because echocardiography not infrequently overestimates or underestimates RV systolic pressure as a result of poor visualization of the tricuspid regurgitant jet. Although echocardiography is an attractive alternative to repeated cardiac catheterization in following the course of the disease and assessing the effects of therapeutic interventions in some patients, the optimal parameters to monitor have not been well characterized. Furthermore, a reduction in estimated or directly measured pulmonary artery systolic pressure may be caused by either hemodynamic improvement or deterioration, since the pressure may decrease as pulmonary blood flow decreases as a result of progressive right heart failure (see Chap. 15).

Lung Scans

Ventilation-perfusion scans are of most value in the diagnosis and exclusion of chronic thromboembolic disease (see Thromboembolic Disease below; see also Chap. 71).

Radionuclide Studies

The response of the RV to exercise can be assessed by calculating the change in RV ejection fraction with exercise using radionuclide angiography. Scintigraphy using thallium-201 also has been useful in detecting hypertrophy of the RV caused by PH (see Chap. 18). Magnetic resonance imaging has more recently been useful in assessing disease severity (eg, RV mass, RV ejection fraction) and effects of therapeutic interventions.

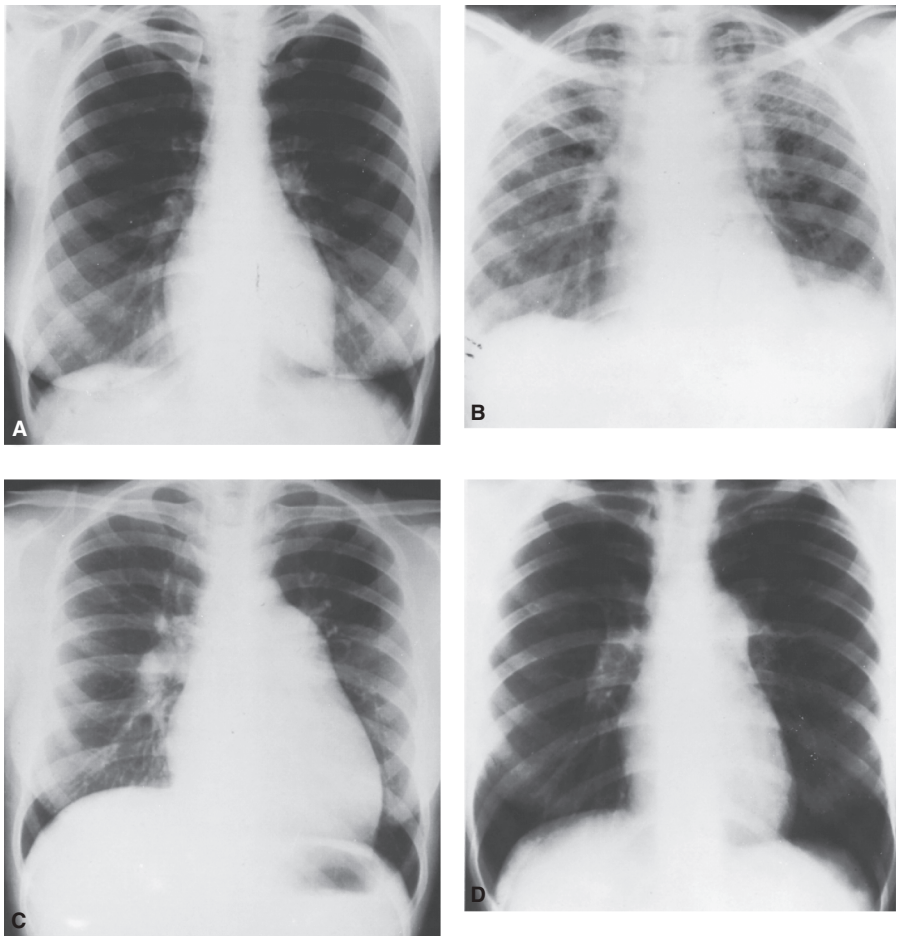


FIGURE 74–2. Cardiac silhouette in four patients with severe pulmonary hypertension on admission to the hospital. **A, B.** Idiopathic pulmonary arterial hypertension (IPAH) showing different stages in the evolution of right-sided heart failure. **C.** Widespread pulmonary fibrosis. **D.** Systemic lupus erythematosus proven by lung biopsy. This radiograph is indistinguishable from that of IPAH.

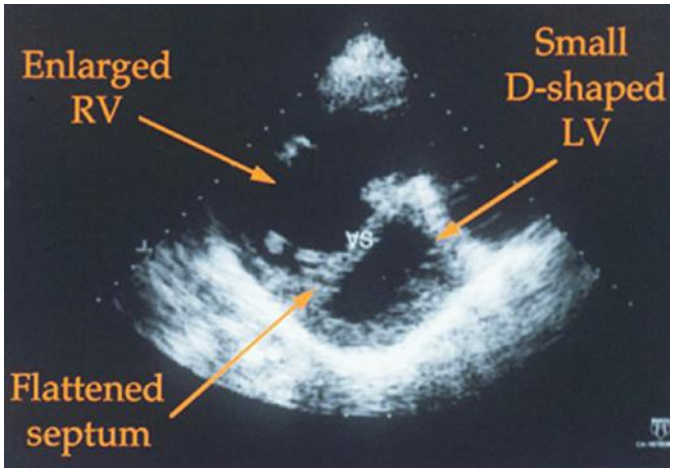


FIGURE 74–3. Echocardiographic image from a patient with pulmonary arterial hypertension. The right ventricle (RV) is enlarged, the interventricular septum (IVS) is flattened, and the ventricular cavity is small. LV, left ventricle.

Lung Biopsy

The sampling of lung tissue by open thoracotomy or thoracoscopy is rarely needed to make an accurate diagnosis. There are, however, exceptions such as confirming suspected pulmonary vasculitis. Furthermore, the procedure carries substantial risk in these hemodynamically compromised individuals. Attempts to predict responsiveness to vasodilators on the basis of lung biopsy have had limited success,[12] most likely because of significant heterogeneity in the pulmonary vasculature. Thus, the hemodynamic assessment by cardiac catheterization gives a more overall assessment of the degree of pulmonary vascular disease as opposed to an isolated piece of lung tissue. Lung biopsy had been previously considered a necessary component of the diagnostic workup for patients suspected of having pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; however, both conditions can now be diagnosed by chest CT when performed and interpreted by radiologists who are attuned to these diseases, thereby avoiding an invasive procedure that carries significant risk.

PULMONARY HYPERTENSION ASSOCIATED WITH CARDIAC OR PULMONARY DISORDERS

Cardiac and/or respiratory diseases are the most common causes of PH. Cardiac disease leads to PH by increasing pulmonary blood flow (eg, large left-to-right shunts) or by increasing pulmonary venous pressure (eg, LV failure). Invariably, secondary influences such as intimal proliferation in the pulmonary resistance vessels add a component of obstructive pulmonary vascular disease.[13] In respiratory disease, the predominant mechanism for the PH is an increase in resistance to

pulmonary blood flow arising from perivascular parenchymal changes coupled with pulmonary vasoconstriction and remodeling because of hypoxia. In pulmonary thromboembolic disease, clots in various stages of organization and affecting pulmonary vessels of different size increase resistance to blood flow.[14]

CARDIAC DISEASE

The mechanisms of PH are often quite different in acquired disorders of the left side of the heart than in those of congenital heart disease.

Acquired Disorders of the Left Side of the Heart

LV failure is one of the most common causes of PH. Among the various etiologies, myocardial disorders and lesions of the mitral and aortic valves predominate. Both categories of lesions lead to an increase in pulmonary venous pressure that, in turn, evokes an increase in pulmonary arterial pressure. Presumably, the increase in pulmonary arterial pressure is reflex in origin. In time, three types of morphologic changes supervene: (1) occlusive intimal and medial changes not only in pulmonary venules and veins, but also in the precapillary vessels; (2) perivascular interstitial edema and fibrosis that, under the influence of gravity, cause vascular and perivascular changes to be most marked in the dependent portions of the lungs; and (3) occlusion of small pulmonary vessels by emboli or thrombi in situ when the RV fails and cardiac output decreases. Chapter 70 discusses the medical management of myocardial failure. The treatment of congenital heart disease and of mitral valvular disease is usually mechanical (eg, surgical or interventional, such as closure of an atrial septal defect or balloon mitral valvuloplasty). When the PH is caused by pulmonary venous hypertension, relief of the pulmonary venous hypertension, as by mitral valve commissurotomy or replacement, will reverse the pulmonary vascular disease in virtually all cases, and even if the PVR does not return to normal, PVR will decrease in virtually all instances to a level that is not clinically significant. An elevated PVR should not be a contraindication to surgery or an interventional procedure to eliminate a discrete site of obstruction causing pulmonary venous hypertension. However, this does not mean that the patient is not without risk for acute pulmonary hypertensive crises, which can be life-threatening, at the time of the intervention. LV failure is the most common cause of RV failure; the level of PH that accompanies LV failure is infrequently sufficient to account for RV failure. RV failure, secondary to LV failure, is usually attributed in part to failure of the muscle in the shared ventricular septum. It turns out, for reasons that remain unclear, that it is the degree of RV hypertension (ie, PH) and the RV ejection fraction that are prognostic for LV failure and not the degree of LV failure.

Heart failure is a growing public health problem, with a prevalence of approximately 5 million patients in the United States, and an incidence of more than 555,000 patients.[15] Heart failure can be a result of abnormalities in systolic and/or diastolic function.[16] The incidence of heart failure resulting from diastolic dysfunction with normal systolic function has increased to more than 50% of heart failure patients overall.[16-20]

Diastolic heart failure, also known as heart failure with preserved ejection fraction, has emerged as a distinct entity, with clear differences in its pathophysiology, diagnostic evaluation, and prognosis compared with heart failure with decreased systolic function.[21] The clinical syndrome includes limitations in exercise capacity and fluid retention, with peripheral edema, ascites, and pulmonary congestion.[22] It is largely a clinical diagnosis based on history and physical examination. Patients with heart failure with preserved ejection fraction tend to be older females and have a history of systemic hypertension, LV hypertrophy, obesity, lipid abnormalities, diabetes, myocardial ischemia, coronary artery disease, and/or atrial fibrillation.[16,19,20,23] Although the prognosis for these patients was previously considered better than for patients with a decreased LV ejection fraction,[20,23-24] recent data suggest otherwise.[25,26] Pulmonary venous hypertension caused by diastolic dysfunction[27,28] is often more severe than expected. A history of conditions associated with diastolic abnormalities and evidence on diagnostic testing with ECG, chest radiography, computed tomography, and/or echocardiography consistent with left heart disease (eg, LA enlargement, LV hypertrophy, or infiltrative disease) should raise suspicion of heart failure with preserved ejection fraction. In some patients, LV end-diastolic pressure is normal at rest but increases with exercise. Testing with agents that increase inotropy (eg, dobutamine, rapid intravenous volume loading, or exercise heart failure with preserved ejection fraction) may identify compliance abnormalities.

There is currently no strong evidence to support the use of any targeted PAH therapies in patients with heart failure with preserved ejection fraction, although studies are ongoing.

Congenital Heart Disease

The Eisenmenger syndrome represents an advanced stage of structural and functional changes in the pulmonary vasculature that lead to a progressive increase in PVR.[29] The Eisenmenger syndrome is frequently seen in developing countries where infant cardiac surgery is largely unavailable. Until recently, the absence of specific treatment options for pulmonary vascular disease associated with congenital cardiac defects resulted in varying degrees of therapeutic nihilism, and little structured management was available.

All congenital cardiac defects with an increased pulmonary blood flow have a propensity to develop pulmonary vascular disease. The likelihood and rate of development of vascular disease is determined by a number of variables that include the quantum of left-to-right shunt, the nature of the underlying defect, and duration of exposure of the pulmonary vascular bed to increased flow. Left-to-right shunts at the level of the ventricles or great arteries (post-tricuspid) have a greater chance of developing pulmonary vasculopathy as compared with shunts at the atrial level (pre-tricuspid). Cyanotic cardiac defects with increased pulmonary blood flow (eg, transposition of the great arteries with ventricular septal defect or patent ductus arteriosus, truncus arteriosus) are particularly prone to develop early vasculopathy, often during infancy. Additional variables appear to contribute but are poorly understood: The response of the pulmonary vasculature to a high pulmonary blood flow is not uniform from patient to patient and does not occur in a predictable fashion. There appears to be a spectrum in the development of pulmonary vascular disease, with a subset of patients with high PVR and advanced pulmonary vascular occlusive lesions in early infancy at one end of the spectrum and adults who remain operable with large left-to-right shunts at the other end of the spectrum. Conditions such as trisomy 21, thoracic and spinal skeletal deformities, and lung parenchymal disease are often associated with a higher likelihood of developing pulmonary vascular disease. Increased pulmonary blood flow results in endothelial dysfunction with impaired relaxation and increased vasomotor tone accompanied by histologic changes in the vessel wall. In addition to the signs and symptoms seen with other forms of PAH, patients with Eisenmenger syndrome have additional comorbid conditions (Table 74–6).

Until recently, PAH therapy had been considered potentially harmful in patients with PAH associated with unrepaired congenital heart disease because of the potential to increase right-to-left shunting by reducing systemic vascular resistance to a greater degree than its pulmonary counterpart. However, a number of newer agents now appear promising for patients with Eisenmenger syndrome, including endothelin receptor antagonists and phosphodiesterase-5 (PDE-5) inhibitors. The short-term benefits in exercise endurance and hemodynamics

TABLE 74–6. Clinical Features in Eisenmenger Syndrome

Abnormalities	Clinical Manifestations
Elevated and fixed pulmonary vascular resistance	Exercise intolerance, dyspnea, syncope, sudden death
Secondary erythrocytosis	Hyperviscosity, relative iron, folic acid, and vitamin B_{12} deficiency
Bleeding diathesis	Hemoptysis, cerebral hemorrhage, menorrhagia, epistaxis
Right ventricular failure	Liver enlargement, edema
Arrhythmias	Syncope, sudden cardiac death
Altered red cell rheology and thrombotic diathesis	Cerebrovascular events (stroke or transient ischemic attacks), intrapulmonary thrombosis
Renal dysfunction	Increased blood urea nitrogen, hyperuricemia, and gout
Hepatobiliary dysfunction	Calcium bilirubinate gallstones, cholecystitis
Infections	Endocarditis, cerebral abscess
Skeletal disease	Scoliosis and hypertrophic osteoarthropathy

may not be predictive of long-term improvement in outcomes; long-term follow-up is needed. With improved intensive care units and the availability of targeted drugs for PAH (eg, inhaled NO use in the perioperative period), more patients with what had been previously thought to be inoperable pulmonary vascular disease are now being repaired either surgically or interventionally in the cardiac catheterization laboratory. However, long-term outcome could be affected by eliminating their "pop off" valve with closure of the systemic-to-pulmonary shunts.

CONNECTIVE TISSUE DISEASES

Pulmonary vascular disease is an important component of certain connective tissue diseases, most commonly systemic lupus erythematosus (SLE), the scleroderma spectrum of diseases, and dermatomyositis.[30] The lesions may take the form of interstitial inflammation and fibrosis, obliterative disease, or vasculitis, either singly or in combination. Although PH can complicate many connective tissue diseases, it has been documented most often in SLE and progressive systemic sclerosis (scleroderma) and its variant syndromes. The possibility has been raised that IPAH is an inflammatory, or autoimmune, disease. The high frequency of both connective tissue disease and IPAH in women and the occurrence of Raynaud phenomenon in up to 20% of patients with IPAH has been used as additional evidence.[31] Additionally, the increased incidence of thyroid abnormalities, and in particular hyperthyroidism, further support the role of autoimmune dysfunction in the pathobiology of PAH. Finally, there is a high incidence of positive serologic tests for antibodies (antinuclear antibody, anti-Ku), particularly in women with IPAH.

The lungs and pleura are frequently involved in SLE, with a reported frequency of up to 70%. Patients with PH and SLE are predominantly women; most of these patients also exhibit Raynaud phenomenon.

The histopathologic lesions in these patients resemble those of IPAH. PH in these patients may originate in thrombi secondary to the hypercoagulable state caused by lupus anticoagulant or anticardiolipin antibodies in the blood. Unfortunately, treatment of PH associated with SLE using either anticoagulants or pulmonary vasodilators has had only modest success. However, patients with active pulmonary vasculitis may either improve or stabilize their vascular disease with immunosuppressive agents.

In progressive systemic sclerosis (which includes limited systemic sclerosis [previously termed the CREST syndrome] and diffuse systemic sclerosis) and in overlap syndromes (eg, mixed connective tissue disease), the incidence of pulmonary vascular disease is estimated to be between 8% and 12%. In these patients, PH is the cause of considerable morbidity and mortality.[32] The pulmonary vascular disease may be independent of pulmonary or other visceral disease. As in the case of SLE, the pathology of these lesions is often indistinguishable from that of IPAH. Newer therapies, such as continuous intravenous epoprostenol, endothelin receptor antagonists, and PDE-5 inhibitors, have been shown to improve hemodynamics and exercise endurance,[33,34] although their impact on survival in this population is less clear.

THROMBOEMBOLIC DISEASE

Thromboembolic disease is a form of occlusive pulmonary vascular disease that may be acute or chronic. In the United States and Europe, clots originating in peripheral veins represent a common cause of chronic occlusive pulmonary vascular disease. Elsewhere in the world, other intravascular particulates may cause pulmonary vascular occlusive disease. For example, in Egypt, where schistosomiasis is endemic, pulmonary vascular disease stemming from ova lodged in pulmonary vessels and hypersensitivity reactions to the organism (usually situated outside the lungs) is common. In some parts of Asia, filariasis is reputed to be an important cause of PH. Tumor emboli to the lungs from extrapulmonary sites (eg, the breast) can cause PH by invading the adjacent minute vessels of the lungs. Intravenous drug use may be associated with talc or cotton fiber embolism to the lungs, which can result in a granulomatous pulmonary arteritis.

The *syndromes of thromboembolic pulmonary hypertension* can be categorized according to the segments of the pulmonary arterial tree that are primarily affected: (1) small vessels (muscular pulmonary arteries and arterioles), (2) intermediate arteries, and (3) large central arteries. Some overlap is inevitable because clots lodged in large vessels are fragmented by the churning motion of the heart, and both the parent clot and its derivatives tend to move peripherally for final lodging.

Occlusion of Small Muscular Arteries and Arterioles by Organized Thrombi

At autopsy, small thrombi, predominantly recent in origin, are common in the small pulmonary vessels of patients with PH who have developed heart failure preterminally. In contrast is the syndrome of widespread pulmonary vascular occlusion by organized thrombi in the small pulmonary arteries and arterioles. Once attributed to multiple pulmonary emboli, these lesions are now regarded as organized, in situ thrombi.[14] The syndrome is rare and indistinguishable during life from IPAH except by lung biopsy. However, histologic identification of these lesions serves little purpose in management. After a ventilation-perfusion scan has excluded chronic proximal thromboembolism (see below), treatment consists of long-term anticoagulation using warfarin or related agents, antiplatelet agents, or both to prevent further clotting.

Occlusion of Intermediate Pulmonary Arteries by Emboli

This syndrome is by far the most common of the three.[14] It is thought to be caused by multiple emboli released from vessels in the upper legs and thighs that progressively amputate the pulmonary arterial tree. Ventilation-perfusion scans and selective angiography demonstrate the pulmonary vascular occlusion, although both studies tend to underestimate the degree of obstruction compared with direct inspection of the vascular tree at surgery or postmortem (see Chap. 75). The major

therapeutic concern in these patients is to exclude chronic proximal pulmonary thromboembolism (see below) and to prevent recurrent thromboemboli. Treatment involves the use of anticoagulants of the warfarin type and antiplatelet agents.

Chronic Proximal Pulmonary Thromboembolism

In some patients who have survived large to massive pulmonary emboli, resolution fails to occur, and the clots become organized and incorporated into the walls of the major pulmonary arteries, leading to PH (Fig. 74–4). Overwhelming the capacity of the local fibrinolytic mechanisms also allows the clot to propagate, to obstruct large segments of the pulmonary vascular bed, and to decrease the compliance of the central pulmonary vessels. By the time the diagnosis is made, the obstructing lesions in the central pulmonary arteries have become an integral part of the vascular wall through the processes of endothelialization and recanalization.[14]

The importance of recognizing *proximal* pulmonary thromboembolism as a cause of PH is the possibility of relieving the PH by surgical intervention, that is, by pulmonary thromboendarterectomy. Ventilation-perfusion lung scanning is the critical diagnostic test. As a rule, patients with proximal pulmonary thromboembolism show two or more segmental perfusion defects. If the perfusion defects are segmental or larger, selective pulmonary angiography is called for to define the location, extent, and number of pulmonary vascular occlusions.[35,36] Although contrast CT may demonstrate chronic thromboembolic PH, it has a 7% false-negative rate. Cardiac catheterization for selective pulmonary angiography also enables hemodynamic assessment. Fiberoptic angioscopy, helical computed tomographic scanning, and magnetic resonance imaging may be helpful in defining the lesions of proximal thromboembolic PH (see Chap. 75).[37]

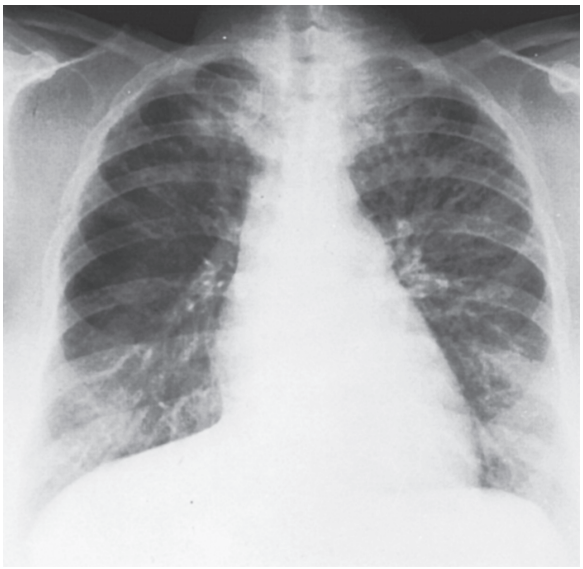
Surgery is advocated for patients with PH who have persistent clots in lobar or more proximal pulmonary arteries after at least 6 months of anticoagulation. Pulmonary endarterectomy is done using a median sternotomy and deep hypothermic cardiopulmonary bypass with intermittent periods of circulatory arrest. Postoperatively, hemodynamic improvement is often quite dramatic.[10,36] Reperfusion pulmonary edema can be a severe complication immediately after the obstruction has been relieved. In experienced hands, mortality is approximately 5%. After the operation, patients are placed on lifelong anticoagulants. In some centers, a filter is also placed in the inferior vena cava to further prevent recurrence.

RESPIRATORY DISEASES AND DISORDERS

In addition to intrinsic pulmonary diseases, disturbances in respiratory muscle function or in the control of breathing also can cause PH. Among the intrinsic lung diseases are those affecting the airways (eg, chronic bronchitis), as well as those affecting the parenchyma (ie, emphysema, pulmonary fibrosis). Among the ventilatory disorders are the syndromes of alveolar hypoventilation caused by respiratory muscle weakness and sleep-disordered breathing.

Intrinsic Diseases of the Lungs and/or Airways

Diseases that affect the parenchyma of the lungs or the tracheobronchial tree can elicit PH in different ways, depending on the underlying disease (Fig. 74–5). In obstructive airways disease, ventilation-perfusion abnormalities cause vasoconstriction because of hypoxemia. In diffuse fibrosis, several mechanisms act in concert: loss of vascular surface area because of lung destruction, loss of vascular compliance because of hyperinflation-induced vascular compression, and vascular remodeling caused by hypoxic vasoconstriction.



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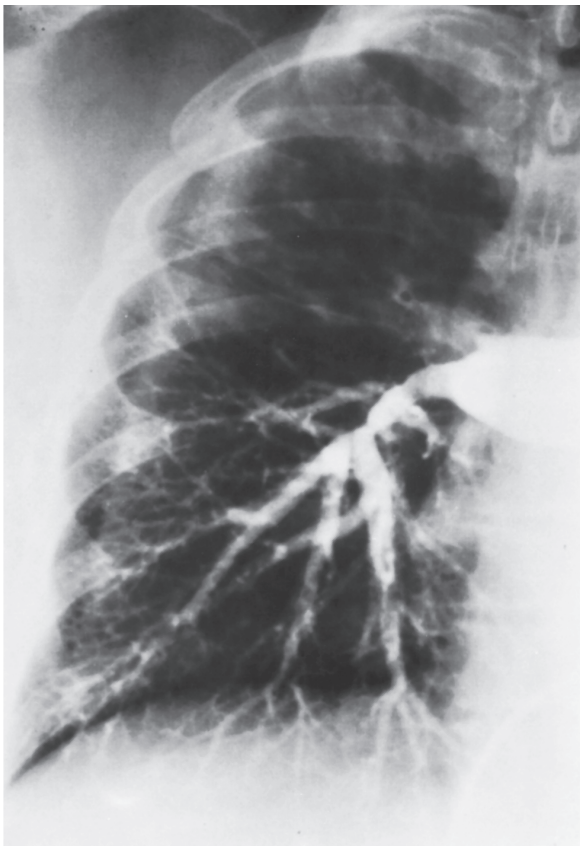

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FIGURE 74–4. Pulmonary hypertension as a result of an organized clot in central pulmonary arteries. Dramatic relief after pulmonary thromboendarterectomy. **A.** Chest radiograph. The right upper lobe is strikingly hypoperfused, and the vasculature on the left is quite prominent, reflecting redirection of the pulmonary blood flow to open vessels. **B.** Angiogram. The flow to the right upper lung is interrupted by the large central clot.

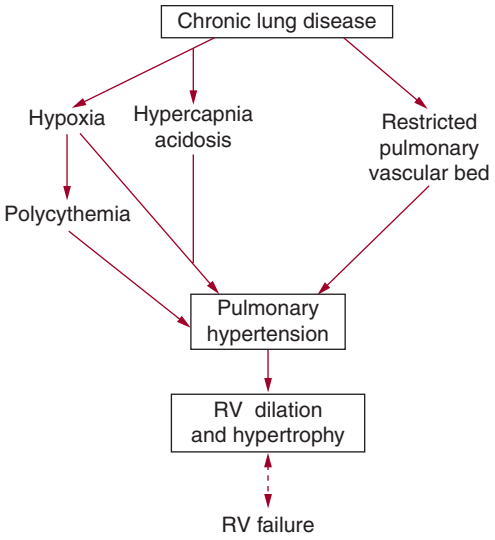


FIGURE 74–5. The evolution of right ventricular (RV) failure in chronic obstructive airway disease (chronic bronchitis and emphysema; chronic obstructive pulmonary disease). The factors on the left arise primarily from the bronchitis; those on the right from emphysema.

Interstitial Fibrosis

Pulmonary sarcoidosis, asbestosis, and idiopathic and radiation-induced fibrosis commonly cause widespread pulmonary fibrosis that result in cor pulmonale. Dyspnea and tachypnea dominate the clinical picture of interstitial fibrosis; cough may also be prominent. Usually, severe PH occurs toward the end of the illness, when hypoxemia and hypercapnia are present at rest (see Fig. 74–2B).

Systemically administered vasodilators have no proven place in treating the PH associated with interstitial fibrosis and may worsen intrapulmonary gas exchange. Recent experience with inhaled vasodilators, such as the prostacyclin analogue iloprost, is encouraging and suggests the possibility of producing selective pulmonary vasodilation and/or antiproliferative effects in this population.[38] Oxygen therapy, particularly during daily activity or sleep, can be important in attenuating the hypoxic pulmonary pressor response. Glucocorticoids and other potent immunosuppressive and antifibrotic agents are the mainstay of therapy and often effect some symptomatic relief. The advent of lung transplantation has widened greatly the therapeutic horizons for dealing with widespread interstitial fibrosis.

Chronic Obstructive Airway Disease

Chronic bronchitis and emphysema (COPD) are the most common causes of cor pulmonale in patients with intrinsic pulmonary disease.[39,40] Cystic fibrosis is an example of a mixed airways and parenchymal lung disease in which PH plays a significant role in outcome. Additionally, with improved neonatal care, increasing numbers of premature infants are developing bronchopulmonary dysplasia, and many are now surviving into adulthood, with, not infrequently, persistent PH.

Cor pulmonale is encountered in two different settings: *acutely* in the setting of decompensation, which is often caused by an acute respiratory infection, and *chronically*, when progressive lung disease and worsening gas exchange lead to unremitting vascular remodeling.

The gold standard for diagnosing PH in patients with COPD, as for other forms of PH, is right-heart catheterization. Noninvasive studies, such as echocardiography, have proved useful in some centers[41,42]; however, echocardiography frequently overestimates or underestimates the true pulmonary artery systolic pressure. Additionally, RV enlargement, the cardinal sign of PH, can be difficult to discern in obstructive airways disease because of hyperinflation and cardiac rotation resulting in poor echo windows.[43] Once suspicion is raised that the clinical picture of RV failure stems from gas exchange abnormalities, an arterial blood sample will confirm that the partial pressure of oxygen (PO_2) is low (PO_2 < 50 mm Hg) and the partial pressure of carbon dioxide (PCO_2) is high (PCO_2 > 50 mm Hg). Derangement in gas exchange to this degree is rare in LV failure unless overt pulmonary edema is present.

Electrocardiogram evidence of RV hypertrophy is also often equivocal in patients with chronic obstructive airways disease (chronic bronchitis and emphysema, COPD) because of rotation and displacement of the heart, widened distances between electrodes and the cardiac surface, and the predominance of right-sided heart dilatation over hypertrophy. Because of these limitations, standard ECG criteria for RV enlargement apply in approximately one-third of patients with COPD who have cor pulmonale at autopsy. Consecutive changes in the ECG are often more useful than a single ECG in detecting RV overload. As the arterial PO_2 drops to abnormal levels (eg, < 60-70 mm Hg while awake), T waves tend to become inverted, biphasic, or flat in the right, precordial leads (V_1 to V_3); the mean electrical axis of the QRS shifts 30 degrees or more to the right of the patient's usual axis; ST segments become depressed in leads II, III, and aVF; and right bundle branch block (incomplete or complete) often appears. These changes tend to reverse as arterial oxygenation improves (see Chap. 12).

In the patient with COPD with acute cor pulmonale precipitated by a bout of bronchitis or pneumonia, the goal of therapy is to maintain tolerable levels of arterial oxygenation while waiting for the upper respiratory infection to subside. Considerable improvement also may be accomplished even in the individual who has chronic PH by sustained (> 18 h/d) breathing of oxygen-enriched air. Once the RV has failed, inotropic agents should be used cautiously because of the threat of arrhythmias posed by arterial hypoxemia and respiratory acidosis. Moreover, after adequate oxygenation has been achieved, the need for digitalis and diuretics often decreases because the hemodynamic burden on the RV decreases. Even though acute cor pulmonale is largely reversible, each bout appears to leave behind a slightly higher level of PH after recovery.[39]

Arterial blood gas composition is the therapeutic compass to the control of PH in COPD. The degree of hypoxia may be underestimated by blood sampling while the patient is awake and at rest, as hypoxemia is more marked during sleep and with physical activity. Determinations of the oxygen saturation during sleep or with ambulation using pulse oximetry are helpful in optimally prescribing supplemental oxygen.

Polycythemia is rarely severe enough to be a serious problem in cor pulmonale associated with bronchitis and emphysema; when it is present, it is usually indicative of suboptimal use of supplemental oxygen. Vasodilators have been evaluated in PH associated with COPD[44,45]; however, there currently are no data to support treatment of COPD with costly (and possibly ineffective) therapies indicated for the treatment of PAH. They may aggravate arterial hypoxemia by exaggerating ventilation-perfusion abnormalities. To date, the safest and most effective approach to pulmonary vasodilatation in obstructive lung disease with arterial hypoxemia is the use of supplemental oxygen.[44]

Alveolar Hypoventilation in Patients With Normal Lungs

In patients who hypoventilate despite normal lungs (alveolar hypoventilation), the primary pathogenetic mechanism is alveolar hypoxia potentiated by respiratory acidosis.[46] The alveolar hypoxia and respiratory acidosis play the same role in eliciting PH in patients with alveolar hypoventilation as in patients with ventilation-perfusion abnormalities. In individuals with normal lungs, the alveolar hypoventilation

generally originates from an inadequate ventilatory drive (eg, after encephalitis or in central sleep apnea), covert obstruction of the upper airways (eg, in obstructive sleep apnea), an ineffective chest bellows (eg, after poliomyelitis or polymyositis), lungs entrapped by neoplasm or fibrosis (eg, in trapped lung caused by asbestosis), or in morbid obesity.

Regardless of etiology, whether PH will occur in patients with alveolar hypoventilation and normal lungs depends on whether there is sufficient alveolar and arterial hypoxia to raise pulmonary arterial pressures considerably. In the sleep apnea syndromes, severe arterial hypoxemia and PH that develop initially only during sleep may become self-perpetuating and carry over into wakefulness, although PH tends to be mild and only occurs in those with severe disturbances in respiration during sleep.[47]

For the patient with alveolar hypoventilation with combined respiratory and cardiac (RV) failure, the highest therapeutic priority is to improve oxygenation. Assisted ventilation, particularly during sleep (eg, continuous positive airway pressure), may be particularly helpful in improving oxygenation and reducing hypercapnia. Pharmacologic therapy is rarely needed for patients with alveolar hypoventilation because of the efficiency of assisted ventilation coupled with oxygen therapy in promoting pulmonary vasodilatation.

PULMONARY ARTERIAL HYPERTENSION

GENERAL FEATURES

Idiopathic pulmonary arterial hypertension (IPAH) and heritable pulmonary arterial hypertension (HPAH) are disorders intrinsic to the pulmonary vascular bed that is characterized by sustained elevations in pulmonary arterial pressure and vascular resistance that generally lead to RV failure and death.[31] The diagnosis of IPAH requires the exclusion on clinical grounds of other conditions that can result in PAH (see Table 74–3).[8]

The clinical diagnosis of IPAH rests on three different types of evidence: (1) clinical, radiographic, and ECG manifestations of PH; (2) hemodynamic features consisting of abnormally high pulmonary arterial pressures and PVR in association with normal left-sided filling pressures and a normal or low cardiac output; and (3) exclusion of the other causes for the PH.

Females predominate, regardless of age, with an overall ratio of approximately 3:1. The typical picture of a patient with IPAH is that of a woman who develops one or more of the symptoms listed in Table 74–1 without discernible cause. Sex and age are sometimes useful in distinguishing clinically between the likelihood of IPAH and pulmonary thromboembolic disease or portal PH. The latter generally favor men, particularly in their later years.[24] Females also predominate with a similar approximately 3:1 ratio in associated PAH (APAH) with connective tissue disease or congenital heart disease.

NATURAL HISTORY

IPAH historically has exhibited a course of relentless deterioration and early death. Newer pharmacologic and surgical treatments have demonstrably altered not only symptomatic status, but also the progression of the disease and duration of survival. Until the 1990s to early in the 21st century (with the advent of PAH-specific therapies), the survival of patients with IPAH who did not undergo transplantation was 68% to 77% at 1 year, 40% to 56% at 3 years, and 22% to 38% at 5 years; patients presenting with more advanced symptoms had a shorter subsequent survival, with a median survival of 59 months for patients diagnosed in WHO functional class I or II (Table 74–7) compared with 32 months for class III and 6 months for class IV.[31] Survival for several decades has been reported, as have rare cases of apparent regression of the disease.

TABLE 74–7. World Health Organization Functional Classification for Pulmonary Hypertension (PH)

Class I	Patients who have PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Slight limitation of physical activity; no discomfort at rest; ordinary activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class III	Marked limitation of physical activity; no discomfort at rest, but less than ordinary physical activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class IV	Inability to perform any physical activity without symptoms; signs of right ventricular failure or syncope; dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

Prognosis is also dependent on the underlying etiology of the disease. The prognosis for patients with APAH with connective tissue disease is worse than for IPAH. Survival in patients with HIV-APAH is similar to that of patients with IPAH. With current HIV therapies, most of the deaths in patients with HIV and APAH are attributed to PAH. Patients with PAH and coexisting portal hypertension have a worse prognosis as IPAH. However, the natural history of the Eisenmenger syndrome was markedly better than for IPAH, with an overall 75% 5-year survival and a 40% 25-year survival.

Similarly, the natural history of patients who have only mild PH as a result of underlying pulmonary diseases, such as COPD, is also much better than for IPAH. In most cases, it is the natural history of the COPD that determines the patient's ultimate prognosis. In patients with pulmonary venous hypertension, the picture is often mixed and varies depending on the severity of the pulmonary vasoreactivity (which determines the magnitude of the PH and whether the PVR is increased), as well as the degree of pulmonary venous hypertension with or without left-sided heart failure. When PAH is the predominant abnormality, the natural history can still vary substantially as a result of the wide range of biologic variability of progressive pulmonary vascular disease.

PATHOBIOLOGY

The common denominator in the pathobiology of PAH appears to be "injury" to the layers of the vascular wall of the small muscular pulmonary arteries and arterioles (Table 74–8; Fig. 74–6).[48] The intima of these vessels proliferates, perhaps in response to injury, so that the endothelium changes from a single flat layer to a piled-up projection that narrows the caliber of the vascular lumen. Also, both the media and the adventitia of the affected vessels undergo hypertrophy.[49]

The primary site of injury in PAH remains uncertain, although accumulating evidence supports damage to the endothelium as a prerequisite for the development of pulmonary vascular disease. An intrinsic defect in ion channel function and calcium homeostasis in vascular smooth muscle has been implicated.[50] Other studies show that endothelial function is disturbed, leading to altered production or handling of a variety of endothelium-derived vasoactive substances, including endothelin-1, thromboxane A_2, NO, and prostacyclin.[48] These abnormalities, coupled with altered platelet-endothelial interactions that predispose to intravascular thrombosis in situ and release of growth factors (eg, vascular endothelial growth factor, platelet-derived growth factor), lead to an inexorable course of enhanced vascular reactivity, proliferation and remodeling, and progressive obliterative

TABLE 74–8. Suggested Pathobiology for Pulmonary Arterial Hypertension

Proposed Mechanism	Evidence
Endothelial proliferation and dysfunction	Altered smooth muscle cell calcium
	Vasodilator/antiproliferative and vasoconstrictor/proliferative imbalance
	Vascular smooth muscle hypertrophy
	Endothelial dysfunction
Genetic predisposition	Familial disease; genetic mutations: *BMPR2*, *ALK-1*, endoglin
	Susceptibility with exposures, eg, anorexigens, human immunodeficiency virus, portal hypertension, hepatic toxins, other exogenous toxins
Coagulation abnormalities	Widespread occlusion of arteries/arterioles; thrombosis in situ
	Altered endothelial-platelet interaction
Autoimmune dysfunction	Raynaud phenomenon; antinuclear antibodies; female sex predilection; thyroid disorder
Shear stress	Congenital systemic to pulmonary shunts

vasculopathy. Certain associations of PAH have attracted interest because of their prospects for shedding light on some etiologies. These include HPAH, HIV-APAH, and portal PH.[51-54] An epidemic of PAH in Europe between 1967 and 1970 that was linked to the use of aminorex, an anorectic agent, raised the prospect of hereditary predisposition, because only 1 in 1000 who took the drug developed PH. In the 1990s, the appetite suppressants fenfluramine and dexfenfluramine were shown to cause PAH and valvular heart disease.[52,55] The toxic oil epidemic in Spain has reinforced the concept of individual susceptibility to pulmonary vasotoxic agents.[56]

In each of these, the clinical findings and the histologic appearance of the lungs at autopsy are identical to those characterizing IPAH. This diversity in associations underscores the likelihood that so-called IPAH is the final common expression of heterogeneous etiologies.

It has now become clear that in at least a number of PAH patients, the disease is genetically linked.[57] Additionally, it appears that PAH develops in subjects who are genetically predisposed with subsequent or concomitant exposure to a "vascular insult." One major insight provided by the families with HPAH is the diversity of pulmonary vascular lesions in members of the same family.[57] With the most recent classification (see Table 74–3), IPAH is now defined as a patient without a family history or without having had a genetic mutation identified. HPAH includes patients with a family history (with or without a genetic mutation identified) and sporadic PAH in which there is no family history but the patient has had a genetic mutation identified. The natural history and response to therapy have been considered similar, although there are recent studies to suggest that patients with HPAH may have a worse outcome than IPAH patients.

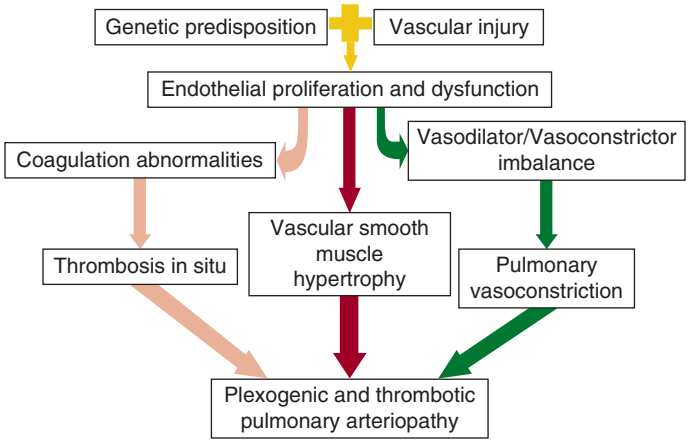


FIGURE 74–6. Schematic representation of postulated pathobiology in pulmonary arterial hypertension.

PATHOLOGY

The evolution of IPAH depends on progressive attenuation of the pulmonary arterial tree, which gradually increases PVR to the point of eliciting RV strain and failure. The seat of the disease is in the small pulmonary arteries (between 40 and 100 μm in diameter) and arterioles. The obliterative lesions can affect one or more layers of these vessels. In some instances, medial hypertrophy predominates; in others, it is the intima that proliferates. In addition, evidence of inflammation may be present (Fig. 74–7).[58]

Histologic examination of the lung identifies a constellation of pulmonary precapillary lesions that are consistent with the clinical diagnosis of PAH—that is, plexiform lesions, angiomatoid lesions, concentric intimal fibrosis, and necrotizing arteritis. The pathologist is often hard pressed to distinguish between organized clots in small vessels that initiate the PH and those that result from the obliterative pulmonary vascular disease. Recent clots in small pulmonary arteries and arterioles are common at autopsy in patients with IPAH, particularly when the RV has failed and cardiac output falls. Although similar clots may not have initiated the PH process in IPAH, it seems reasonable that more often they are complicating features that aggravate and exaggerate pulmonary vascular obstruction.

PATHOPHYSIOLOGY

The hemodynamic hallmarks of IPAH in the resting patient were discussed earlier: a combination of high pulmonary arterial pressure, a normal or low cardiac output, and normal LA or left-sided filling pressures. Calculated PVR is high, generally leading to the logical conclusion that the resistance vessels, that is, the small muscular arteries and arterioles,

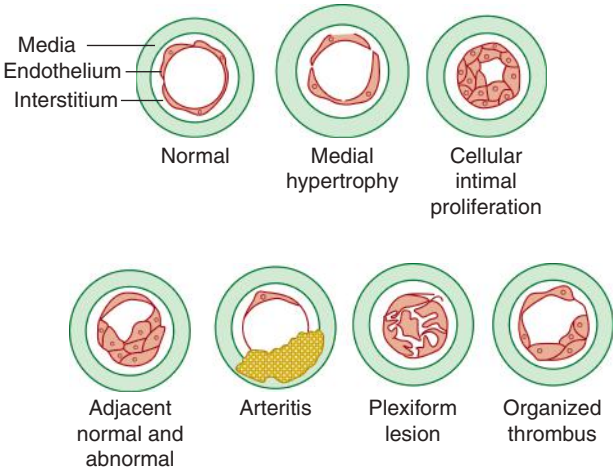


FIGURE 74–7. Vascular lesions in idiopathic pulmonary arterial hypertension. The plexiform lesion, once believed to be the histologic hallmark of idiopathic pulmonary arterial hypertension, has emerged as only one feature of a constellation of lesions.

are the predominant sites of vascular obstruction. During exercise, as cardiac output increases, pulmonary arterial pressures increase further; the increments in pressure in the pulmonary hypertensive circuit are much more striking than in the normotensive pulmonary circulation, as a result of the inability of the existing vasculature to dilate or recruit unused vessels to accommodate the rise in pulmonary blood flow. In normal subjects, although the pulmonary arterial pressure may increase slightly with exercise concomitant with the increase in cardiac output, the PVR decreases with exercise. This is in contrast to the patient with PAH in whom PVR increases with exercise; in the patient with pulmonary venous hypertension, PVR remains unchanged with exercise (unless there is "mixed" pulmonary vasculopathy).

Based on the limited ability to increase cardiac output in the face of increased PVR, treatment that will increase cardiac output will result in (1) improved oxygen delivery to peripheral organs and tissues; (2) a decrease in the level of PAH, with evidence of regression of RV hypertrophy and or dilatation; and (3) a decrease in calculated PVR; optimally, this decrease should entail an increase in cardiac output (with minimal increase in heart rate) accompanied by a substantial decrease in pulmonary arterial pressure. These changes should result in an increase in exercise capacity and an improved quality of life.

Right-heart catheterization is useful not only for defining the hemodynamic state of the patient, but also in providing a hemodynamic baseline for future invasive and noninvasive studies, such as serial echocardiograms. Acute vasodilator testing is also useful in identifying whether the patient has significant acute pulmonary vasoreactivity (which can be helpful in selecting initial therapy).

CLINICAL PICTURE

Symptoms

In its early stages, the disease is difficult to recognize. With mild PH, the earliest complaints are often fatigue and vague chest discomfort. These symptoms are often ignored unless the patient has another underlying condition, such as COPD, interstitial lung disease, alveolar hypoventilation, or sleep apnea. Easy fatigability and dyspnea are frequently attributed to being "out of shape," except when the index of suspicion is high, as with a history of ingestion of anorectic agents or HPAH.

When the PH is advanced, the clinical manifestations include cyanosis, dyspnea on exertion, hemoptysis, atypical chest pain or angina pectoris, syncope, heart failure, arrhythmias, cerebral vascular accidents from paradoxical emboli, and gout. Dyspnea, the most common symptom of IPAH, is also the most frequent symptom of the Eisenmenger syndrome. Syncope is an exceedingly rare symptom in unoperated patients with the Eisenmenger syndrome because of the ability to decompress the right heart via an open atrial septal defect, ventricular septal defect, or patent ductus arteriosus. In contrast, patients with IPAH with an intact atrial septum (ie, without a patent foramen ovale) and patients with elevated PVR after complete surgical repair of congenital shunts may present with syncope. Angina, a common symptom that is often underappreciated, most often results from RV ischemia (although LV ischemia can also occur, as discussed above). Edema is generally a reflection of RV failure and is more likely to be associated with advanced pulmonary vascular disease.

Physical Examination

Each underlying or associated condition affects the clinical presentation. For example, COPD is usually associated with hyperinflation of the lungs, and this hyperinflation often shifts the position of the heart so that heart sounds are more difficult to hear. With interstitial lung disease, tachypnea invariably occurs. Nevertheless, certain physical findings (eg, an increased intensity of P_2, a palpable P_2, a right-sided third heart sound, and, as the PH progresses, murmurs of pulmonary and tricuspid insufficiency) typically develop. Ultimately, the neck veins are distended and the liver is pulsatile, and the patient may develop peripheral edema, pleural effusions, and ascites. In patients with pulmonary venous hypertension, the presentation is frequently overshadowed by signs of left-sided heart disease (eg, mitral stenosis, systemic hypertension, or heart failure). In IPAH, there is no evidence of underlying pulmonary or cardiac disease. The cardiac examination will show RV overload as for any cause of PH.

Physical examination in a patient with Eisenmenger syndrome demonstrates central cyanosis, clubbing of the digits, RV lift, palpable P_2, increased intensity of P_2 (frequently with a single loud second heart sound), a pulmonic ejection sound associated with a dilated pulmonary trunk, and a diastolic murmur of pulmonary insufficiency. In the presence of heart failure, patients develop edema, ascites, and hepatosplenomegaly. In patients who have undergone corrective surgery for congenital heart disease when the PVR was already elevated, the physical examination is similar to that seen with IPAH (ie, an increase in the pulmonic component of the second heart sound, a right-sided fourth heart sound, and tricuspid regurgitation); an RV third heart sound and pulmonary insufficiency generally reflect advanced disease. Peripheral cyanosis and edema are common. Clubbing, which is common with the Eisenmenger syndrome, is typically not seen in IPAH or in patients who have undergone repair of the congenital heart defect(s) after PVR was already increased.

When the disease is advanced, increasing nonspecific discomfort progressively reduces the activities of daily life. Dyspnea, the most frequent presenting complaint in patients with PH, is a result of impaired oxygen delivery during physical activity as a result of an inability to increase cardiac output in the presence of increased oxygen demands; during physical activity, the dyspnea can become incapacitating. Some patients develop an anginal type of chest pain along with breathlessness. The chest pain most often results from RV ischemia because coronary blood flow is impaired in the setting of increased RV mass and elevated systolic and diastolic pressures; however, left main coronary artery compression by an enlarged main pulmonary artery can cause LV ischemia. Syncope, which is often exertional or postexertional, implies a severely restricted cardiac output and diminished cerebral blood flow, which may be exacerbated by peripheral vasodilatation during physical exertion. Other common symptoms are weakness, fatigue, and exertional or postexertional syncope (see Table 74–1). Infrequently, an enlarged pulmonary artery causes hoarseness because of compression of the left recurrent laryngeal nerve. Although the LV is not directly affected by pulmonary vascular disease, progressive RV dilatation can impair LV filling, leading to modestly increased LV end-diastolic pressure and PCWP.

Patients with congenital heart disease and PH who become pregnant are at increased risk of sudden death, both in the course of delivery and in the immediate postpartum period, because of acute exacerbations of PH and RV decompensation that may result from intravascular volume shifts and worsening hypoxemia caused by atelectasis, infection, thromboembolism, and other factors.

The two most frequent mechanisms of death are progressive RV failure and sudden death, the latter being more common in patients who have Eisenmenger syndrome. Death has occurred unexpectedly during normal activities, cardiac catheterization, and surgical procedures and after the administration of anesthetic agents. The mechanisms of sudden death are not clear and may include arrhythmias or acute pulmonary thromboembolism. Pneumonia may cause alveolar hypoxia, which worsens pulmonary vasoconstriction with a resultant inability to maintain adequate cardiac output, followed by cardiogenic shock and

death. Arterial hypoxemia and acidosis can precipitate life-threatening arrhythmias. Other causes of sudden death include bradyarrhythmias and tachyarrhythmias, acute pulmonary embolus, rupture of a pulmonary artery aneurysm, massive pulmonary hemorrhage, and sudden RV ischemia. In patients with right-to-left cardiac shunts, complications can result from brain abscesses, bacterial endocarditis, volume changes associated with pregnancy, and ill-advised attempts at surgical repair in patients with Eisenmenger syndrome.

DIAGNOSTIC EVALUATION AND ASSESSMENT OF PULMONARY HYPERTENSION

Direct determination of pulmonary circulatory pressures by right-heart catheterization is the only way to definitively establish the diagnosis of PH; however, other studies that are less direct can strongly suggest that it is present. Because the diagnosis of IPAH is one of exclusion, a number of tests are undertaken, usually in the hope of identifying a more treatable disease.[58]

Chest Radiography and Electrocardiography

In the early stages, the chest radiograph is generally normal. Later it shows cardiac enlargement in association with enlargement of the pulmonary trunk, whereas the peripheral pulmonary arterial branches are attenuated; the lung fields appear oligemic (see Fig. 74–2). Although fullness of the central pulmonary arterial trunks and peripheral "pruning" are distinctive, appearances vary somewhat from patient to patient in accord with the level and pace of the PH and the age of the patient. Radiographic evidence of RV enlargement usually becomes overt only late in the course of the PH (see Chap. 14). Pleural effusions, especially right pleural effusions, are most frequently seen with right heart failure. Similarly, pericardial effusions, suggestive on the chest radiograph by a globular-shaped cardiac shadow, signify severe disease. The ECG usually shows right axis deviation, RV hypertrophy, and right atrial enlargement (Fig. 74–8; see Chap. 12). However, it is important to appreciate that patients can have significant PAH with a normal-appearing ECG and a normal-appearing chest radiograph.

Echocardiography

Transthoracic echocardiography confirms the enlargement and hypertrophy of the right atrium and RV, tricuspid regurgitation, and pulmonic valvular regurgitation (see Fig. 74–3). At the same time, LV structure and function are normal. The magnitude of the velocity of the tricuspid regurgitant jet using Doppler techniques can provide a noninvasive estimate of RV peak systolic pressure. On occasion, transesophageal echocardiography is helpful to search for intracardiac shunts or other congenital abnormalities. Contrast echocardiography is also helpful in assessing for intracardiac shunts; additionally, the clearance suggests a qualitative assessment of RV function. The presence of a pericardial effusion (as stated above) should suggest severe disease.

Perfusion Lung Scans

Perfusion lung scans are particularly helpful in suggesting the possibility of large, long-standing organized clots in the major pulmonary arteries that may be amenable to surgical removal (thromboendarterectomy). The lung scan in IPAH fails to disclose major perfusion defects. Selective pulmonary angiography is done in cases where the scan is equivocal. Scanning over the brain or kidneys may disclose the presence of an intracardiac or intrapulmonary right-to-left shunt.

Cardiac Catheterization

Right heart catheterization is invaluable in quantifying the hemodynamic abnormalities, excluding cardiac causes of PAH, and assessing the hemodynamic responses of the heart and pulmonary circulation to acute vasodilator agents.[33,42] If an accurate assessment of left-sided filling pressures by measuring the PCWP is questionable, a left heart catheterization should be performed to accurately measure LV end-diastolic pressure. Angiography may also be indicated to evaluate for possible bronchial collaterals that may be responsible for hemoptysis with consideration of embolization. Pulmonary angiography is indicated in the patient with chronic thromboembolic PH in whom surgical operability (ie, thromboendarterectomy) may be possible. In patients with hereditary hemorrhagic telangiectasia, pulmonary arterial venous malformations may also be visualized by pulmonary angiography. For the rare patient with an enlarged pulmonary artery causing dynamic compression of the left anterior descending coronary artery, angiography is useful, with consideration of stent intervention therapeutically.

The diagnosis of IPAH (Fig. 74–9) rests on two pillars: (1) the detection of PH and (2) the exclusion of known causes of high pulmonary arterial pressure. The history is of utmost importance. Before categorizing PH as idiopathic, due regard must be paid to the exclusion of known etiologies (see Table 74–3), particularly thromboembolic disease and connective tissue disorders. Account also should be taken of the likelihood of familial disease. Pulmonary function tests are useful in excluding diffuse pulmonary disorders,

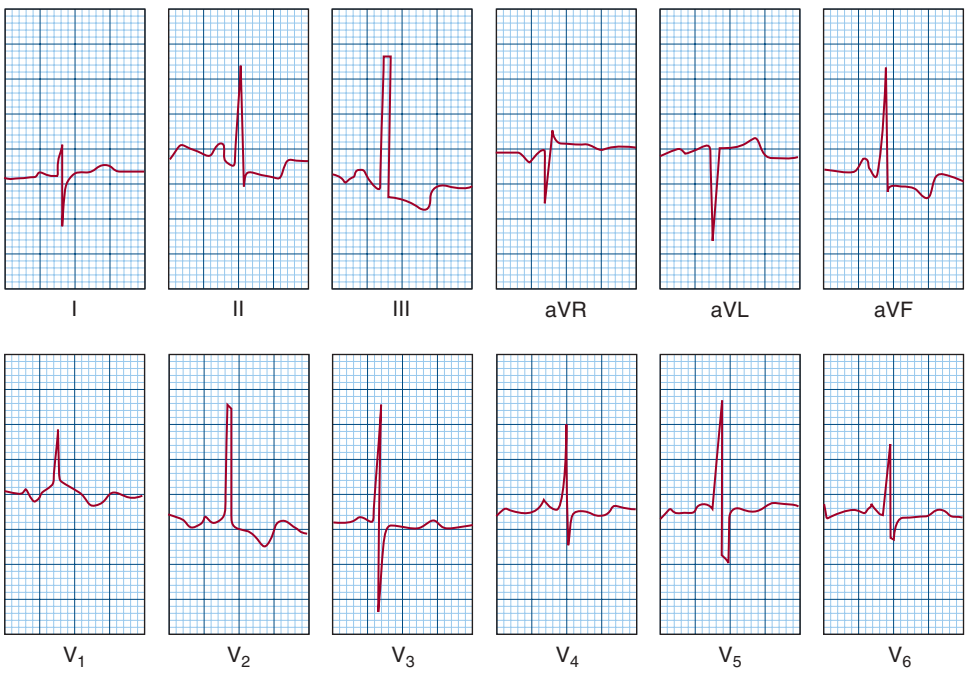


FIGURE 74–8. Electrocardiogram in patients with idiopathic pulmonary arterial hypertension.

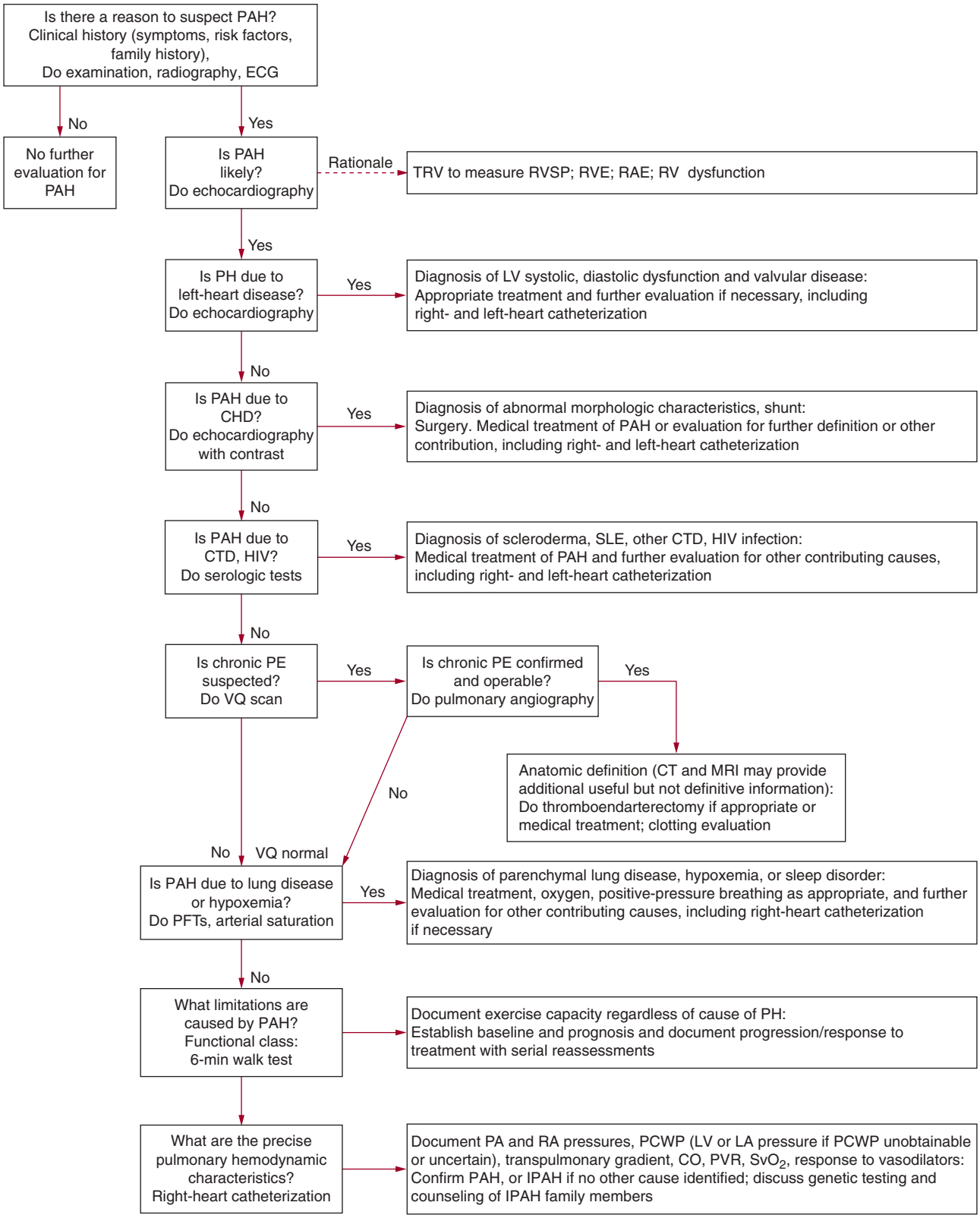


FIGURE 74–9. Guideline for approaching the differential diagnosis of pulmonary hypertension. CHD, congenital heart disease; CO, cardiac output; CT, contrast-enhanced computed tomography of the chest; CTD, connective tissue disease; ECG, electrocardiogram; Echo, transthoracic Doppler echocardiogram; IPAH, idiopathic pulmonary arterial hypertension; FPAH, familial pulmonary arterial hypertension; LA, left atrial; LV, left ventricular; MRI, magnetic resonance imaging; PA, pulmonary arterial; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PE, pulmonary embolism; PFTs, pulmonary function tests; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RAE, right atrial enlargement; RV, right ventricular; RVE, right ventricular enlargement; RVST, right ventricular systolic pressure; SLE, systemic lupus erythematosus; SvO_2, mixed venous oxygen saturation; TRV, tricuspid regurgitant velocity; V/Q, ventilation/perfusion. Adapted with permission from Rubin LJ, Badesch DB. Evaluation and management of the patient with pulmonary arterial hypertension. *Ann Intern Med*. 2005 Aug 16;143(4):282-292.

particularly interstitial lung disease. Serologic testing can point the way to connective tissue disorders and occult HIV infection. Abnormal liver function tests can signal the coexistence of portal hypertension and PH. The value of cardiac catheterization in eliminating acquired or congenital heart disease was indicated earlier. However, unless congenital heart disease is specifically looked for, the diagnosis may remain undetected. Contrast echocardiography was discussed earlier as being helpful in ruling out an intracardiac shunt; differential pulse oximetry (between the right upper extremity and a lower extremity) may also help identify a systemic to pulmonary shunt at the level of the great vessels. Unfortunately, by the time PH complicating congenital heart disease is recognized, the anatomic lesions are often too far advanced for the obliterative pulmonary vascular disease to be reversible with corrective surgery.

Screening High-Risk Patients

Screening may lead the early identification of PAH in asymptomatic or minimally symptomatic individuals with scleroderma, who have high prevalence of PAH, as compared with the much lower prevalence in patients with SLE, rheumatoid arthritis, and other connective tissue diseases. Screening is also recommended for first-degree relatives of patients with documented IPAH. A transthoracic echocardiogram is performed in all patients with portal hypertension when they are evaluated for liver transplant. There is no definitive recommendation regarding routine screening for PH in patients with pulmonary disease such as COPD unless there are also signs or symptoms suggestive of PH.

INCIDENTAL DISCOVERY OF PULMONARY HYPERTENSION

The clinical significance and natural history of asymptomatic or mild PAH is unclear; thus the implications for further assessment and/or treatment when discovered incidentally, as a result of screening or during evaluation of nonspecific symptoms, remain uncertain. Moreover, the criterion of clinically significant PH when detected under these circumstances by Doppler echocardiography, which in itself is an isolated estimate of RV systolic pressure, is not precisely defined. Commonly used definitions of PH are pulmonary artery systolic pressure > 35 mm Hg or mean PAH > 25 mm Hg at rest. However, a pulmonary artery systolic pressure > 40 mm Hg is present in 6% of otherwise normal individuals older than 50 years and in 5% with a body mass index > 30 kg/m^2. In general, any degree of PH should prompt an attempt to define or exclude possible causes, because it may be the first evidence of a modifiable substrate. However, the severity of PH and the reliability of the measurement should temper the aggressiveness of the evaluation. Confirmation by right heart catheterization is warranted before embarking on extensive evaluation for an underlying cause or considerations of prognosis or treatment.

Although most studies report a high correlation (0.57-0.93) between transthoracic echocardiography and right heart catheterization measurements of pulmonary artery systolic pressure, underestimation as well as overestimation of pulmonary artery systolic pressure by Doppler echocardiography is not infrequent. Reported sensitivity of transthoracic echocardiographic estimated pulmonary artery systolic pressure for detecting PH ranges from 79% to 100% and specificity from 60% to 98%. However, these figures are strongly influenced by the value used to define PH. The range of RV systolic pressure among healthy controls has been well characterized. Among a broad population of male and female subjects ranging from 1 to 89 years of age, RV systolic pressure was reported as 28 ± 5 mm Hg (range 15-57 mm Hg). The RV systolic pressure increases with age and body mass index. Athletically conditioned men also have higher resting RV systolic pressure. Defining the normal distribution of RV systolic pressure does not ipso facto define the point at which an elevated RV systolic pressure is clinically important or predictive of future consequences. Mild PH is defined as a pulmonary artery systolic pressure of approximately 36 to 50 mm Hg or a resting tricuspid regurgitant velocity of 2.8 to 3.4 m/s. Possible explanations for mildly elevated pulmonary artery systolic pressure suggested by echocardiography include (1) overestimation of the RV systolic pressure in a patient with truly normal pulmonary pressure; (2) serendipitous observation of a rare transient pressure elevation in an otherwise healthy individual; (3) discovery of stable mild PH, possibly of long duration; or (4) discovery of early progressive PH in an individual with PAH. In addition, PAH differences may be observed in different populations and conditions, including age, level of conditioning, exercise, or stress. No clear guidelines are available that delineate normal from pathologic in all circumstances.

TREATMENT

Treatment for PH depends on an accurate assessment of the cause of the PH (Fig. 74–10).[34,42] Although there is no cure or a single therapeutic approach that is uniformly successful for PAH, therapy has improved substantially over the past two decades.

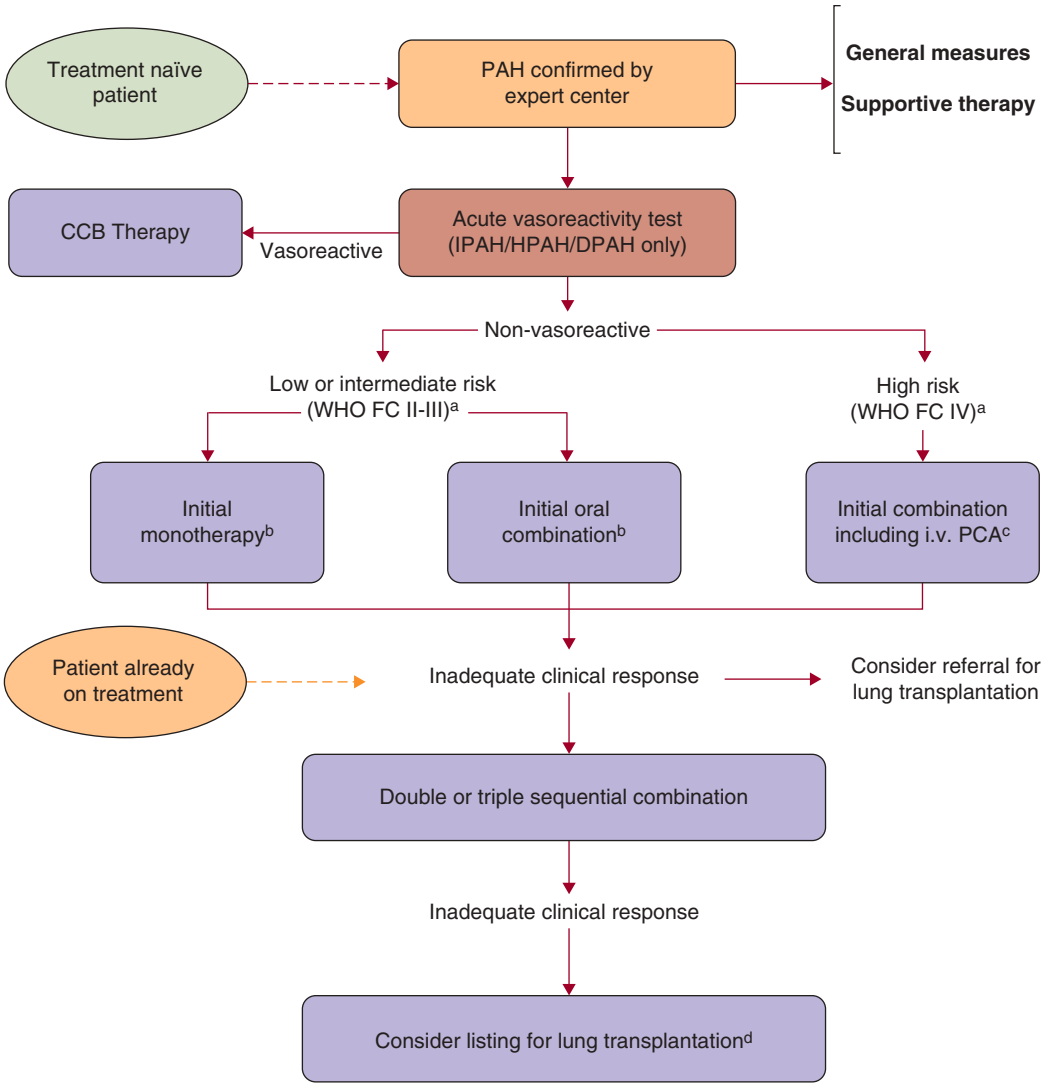
Clinical drug development for PAH began in the late 1980s initially as a palliative bridge to transplantation. The first drug approved for PAH was continuous intravenous infusion of epoprostenol in 1995.[58-60] In 2002, the prostacyclin analogue treprostinil was approved for subcutaneous infusion,[61] and in 2004, it was approved for intravenous administration.[62,63] In addition, use of the prostacyclin analogue iloprost via inhalation was approved in 2004. In 2001, bosentan, a dual endothelin (endothelin receptor type A [ET_A]/endothelin receptor type B [ET_B]) receptor antagonist (ERA),[64,65] was the first oral therapy approved for the treatment of PAH, and sildenafil citrate, an oral PDE-5 inhibitor, was approved in 2005.[66] In 2007, the oral ET_A selective ERA ambrisentan[67,68] was approved. The oral PDE-5 inhibitor tadalafil[69] was approved in 2009, as was the inhaled formulation of treprostinil.[70] More recently, oral treprostinil, the dual ET_A and ET_B receptor antagonist macitentan,[71] and riociguat, a guanyly cyclase activator, have also been approved for PAH.

General Measures

General measures for patients with all forms of PAH include the avoidance of circumstances or substances that may aggravate the disease state. Exercise should be guided by symptoms, and exposure to high altitude may worsen PAH by producing hypoxia-induced pulmonary vasoconstriction. Pregnancy, oral contraceptives, and appetite suppressants should be avoided. Because anesthesia and surgery of any type pose an increased risk of hemodynamic instability and death, elective procedures should be carefully considered, and emergent operations should ideally be performed at a center where multidisciplinary expertise is available to assist in management. Phlebotomy with replacement of fluid (eg, plasma or albumin) is helpful in patients with pulmonary vascular disease and cyanotic congenital heart disease in whom severe hypoxemia has evoked substantial polycythemia. Phlebotomy is recommended for symptoms of hyperviscosity as a result of severe polycythemia, such as headache or blurry vision, or if the hematocrit is greater than 65% to 70%. Caution is required to avoid depletion of iron stores and to avoid reduction in the circulating blood volume. Cerebrovascular events are more often related to iron deficiency anemia; however, plasma exchange appears to relieve symptoms for patients with severe polycythemia.

Treatment of Underlying Conditions

Before initiating treatment for a patient's PAH, treatment should be started for any underlying or associated conditions. After these other



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.
[a]Some WHO-FC III patients may be considered high risk (see Table 13).
[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.
[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.
[d]Consider also balloon atrial septostomy.

FIGURE 74–10. Evidence-based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only).

disorders have been optimally treated, additional treatment for the PAH itself should be considered.

Conventional Medical Therapy

Anticoagulation Since 1984, when Fuster and coworkers,[72] in a retrospective study, showed that long-term survival was improved in patients with IPAH by anticoagulant therapy (warfarin in low doses), the use of anticoagulants has been incorporated into the therapeutic regimens of patients with PAH. This practice is supported by the high incidence of antemortem clots found at autopsy in the small pulmonary arteries and arterioles of patients with IPAH. Moreover, in a nonrandomized trial that separated responders from nonresponders to calcium channel blockers, survival was significantly better in the nonresponders given warfarin than in the nonresponders who did not receive anticoagulation.[73] The usual goal of anticoagulation is to achieve and maintain an international normalized ratio (INR) of 1.5 to 2.5[74]; however, certain clinical circumstances may require a higher INR, and a lower INR is often appropriate for patients at a higher risk for bleeding. Heparin subcutaneously (5000-10,000 units twice daily) or low-molecular-weight heparin (1 mg/kg subcutaneously twice daily) may be suitable alternatives in patients with adverse effects to warfarin. Patients with chronic thromboembolic disease are treated with higher doses of warfarin (ie, to achieve an INR of 2.5-3.5). Whether chronic anticoagulation is useful in patients with other forms of PAH remains unknown, although recent data suggest that patients with PAH as a result of connective tissue disease may not benefit.

Inotropic Agents/Diuretics The efficacy and toxicity of cardiac glycosides in PAH remain unknown. Diuretics can reduce the increased intravascular volume and hepatic congestion that occur in patients with right heart failure, although care should be taken to avoid excessive diuresis that decreases cardiac output in patients who are dependent on preload.

Supplemental Oxygen Supplemental low-flow oxygen alleviates the arterial hypoxemia and attenuates the PH in patients with chronic pulmonary parenchymal disease. In contrast, most patients with Eisenmenger syndrome appear to derive little hemodynamic benefit from supplemental oxygen; data conflict regarding whether supplemental oxygen with sleep improves outcome in Eisenmenger syndrome.[75,76] However, patients with other forms of PAH, including IPAH, may benefit from supplemental ambulatory oxygen if they have oxygen desaturation with activity. Supplemental oxygen with sleep is recommended for patients who desaturate with sleep to less than 92% in whom supplemental oxygen can restore the oxygen saturation to above the mid-90s.

Drugs That Block Calcium Transport Before the advent of targeted PAH disease-specific therapies (as discussed below), other than supportive therapy (eg, cardiotonic medications for right heart failure and supplemental oxygen), the only other therapy available was the use of calcium channel blockers. The designation calcium channel blocker refers to a heterogeneous group of agents of different structural, pharmacologic, and electrophysiologic properties. The agents used as pulmonary vasodilators are nifedipine, diltiazem, and amlodipine.

These drugs may have significant direct negative inotropic effects, although this may not immediately become manifest clinically if reflex sympathetic stimulation of the heart is present. They are used for therapy of patients who manifest acute vasoreactivity when tested with short-acting agents (ie, inhaled NO or intravenous epoprostenol) under hemodynamic monitoring. Unfortunately, fewer than 10% of IPAH patients are acute responders, defined as a decrease in mean pulmonary arterial hypertension of at least 10 mm Hg to an absolute nadir of less than 40 mm Hg with a normal or increased cardiac output.[73] For these acute responders, chronic calcium channel blockade can be very efficacious. Sustained-release preparations are preferred, with the dosage generally titrated to the maximal tolerable level based on avoiding untoward systemic effects, that is, hypotension, headache, dizziness, and flushing. Considerable caution is necessary in administering the higher dosages, however, because side effects can occur precipitously and be extremely serious. Calcium channel blockers should never be used empirically, even if a patient is an acute responder. If the patient is in significant right heart failure, calcium channel blockers are not recommended because they can precipitate life-threatening events. The likelihood of an acute responder in APAH patients is significantly less than for IPAH patients.

Targeted Pulmonary Arterial Hypertension Therapy

Before 1995, there were no approved therapies for PAH. However, since then, numerous randomized controlled trials (RCTs) of monotherapy have been completed in PAH patients.[59-62,65-71,77] In addition, RCTs testing combinations of agents (eg, ERA and PDE-5 inhibitor, or prostanoid and ERA or PDE-5 inhibitors) have been completed.[71,78-82] Approximately 5000 patients have participated in these studies aimed at developing effective treatments for PAH. The conclusions derived from clinical trials over the past 15 years have permitted us to develop an evidence-based treatment algorithm. This algorithm can be used worldwide, subject to the availability of specific drug therapies (see Fig. 74–10).[34]

Treatment of IPAH initially focused on the use of vasodilators in the hope that an increase in pulmonary vascular tone contributed importantly to the high pulmonary arterial pressures. Although the bulk of the pulmonary vascular obstruction was clearly anatomic, vasodilators offered the prospect not only of decreasing pulmonary arterial pressures somewhat, and therefore the hemodynamic burden on the RV, but also of prompting reversibility of the anatomic lesions. Unfortunately, the use of vasodilators, which could affect the systemic as well as the pulmonary circulation, led to progressive disenchantment with one agent after another.

Because fewer than 10% of IPAH patients and even fewer patients with PAH associated with other conditions such as connective tissue disease respond acutely with vasodilator testing and are therefore candidates for whom treatment with calcium channel blockade can be considered, a landmark development for patients who failed to satisfy the criteria for a good hemodynamic response to acute vasodilator testing was the demonstration that such patients respond to continuous infusion of epoprostenol. Indeed, a substantial number of such patients have been treated in this way for years or have used continuous intravenous epoprostenol as a transition to transplant or newer drug therapies. During this evolution, heart-lung and then lung transplantation became increasingly feasible and available, although the donor supply is still a limiting factor. More recently, oral medications that block the receptors for endothelin or that augment the effects of endogenous NO by inhibiting PDE-5 (the enzyme responsible for breakdown of cyclic guanosine monophosphate) have been shown to be effective therapy and may obviate the need for prostacyclin therapy in many patients. Alternative forms of delivery of longer acting prostacyclin analogues, including subcutaneous, aerosolized, and oral medications, have also been developed and may prevent the need for parenteral prostacyclin therapy in some patients.

As a result of these advances, a patient with PAH has several therapeutic options. However, none of these modalities are free of complications. Endothelin receptor antagonists can cause hepatic injury. The continuous infusion of prostacyclin analogues runs the risks of a permanently placed intravenous catheter, with risk of bacteremia, sepsis, or thromboembolic events.[83,84] Transplantation offers the substitution of immunosuppression and its attendant risk of infection as a better option than chronic cor pulmonale and RV failure.[85] Despite the limitations of each of these therapeutic modalities, together they provide a graduated therapeutic approach that has provided, at each stage, a better quality of life for many individuals with PAH.

Prostacydin and Its Analogues Epoprostenol (prostacyclin, prostaglandin I_2), a metabolite of arachidonic acid, and its analogues continue to be a major focus of attention as treatments for a variety of forms of PAH. The pulmonary endothelium elaborates prostacyclin into the bloodstream, where it has a short biologic half-life (2-3 minutes). In principle, it is attractive for the treatment of PAH on several accounts: (1) it is a pulmonary vasodilator, (2) it inhibits platelet aggregation, (3) it inhibits proliferation of vascular smooth muscle, (4) it improves endothelial dysfunction, and (5) it appears to be a cardiac inotrope. Unfortunately, it requires continuous intravenous infusion, which is accomplished using portable pumps.[83,84] Treprostinil, a longer acting prostacyclin analogue, is approved for continuous subcutaneous, continuous (AMBITION) trial, oral, or inhaled (administered four times daily) use.[62-64,71] Aerosolized iloprost, another stable prostacyclin analogue approved for the treatment of PAH, is administered six to nine times daily.[77,81]

Endothelin Receptor Antagonists Endothelin (ET-1) is a potent mitogen and vasoconstrictor that is produced in excess by the hypertensive pulmonary endothelium. Circulating levels of endothelin are increased in patients with PAH, and the magnitude of elevation correlates with survival. Bosentan, an oral twice-daily active dual ET_A and ET_B receptor antagonist, improves hemodynamics and exercise tolerance and delays the time to clinical worsening (ie, reduces morbidity and mortality) in PAH.[65,66,86] Although the drug is generally well tolerated, liver function must be monitored monthly because it produces significant hepatic dysfunction in approximately 5% of patients. Selective ET_A receptor antagonists have also been investigated in PAH, with the once-daily selective ET_A receptor antagonist ambrisentan[68,69] and the

dual antagonist macitentan[70] approved. Although the risk of increased hepatic transaminases appears to be less with ambrisentan and macitentan than with bosentan, all ERAs to date carry a risk of hepatic injury.

Nitric Oxide and Phosphodiesterase Inhibitors NO is synthesized in endothelial cells from one of the guanidine nitrogens of L-arginine by the enzyme NO synthase. It has proved to be the endothelium-derived relaxing factor that contributes to the low initial tone of the pulmonary circulation. It has the advantage over other vasodilators of selectively relaxing pulmonary vessels without affecting systemic arterial pressure. It is currently being used as an acute test of vasoreactivity in a wide variety of pulmonary hypertensive states and is approved for persistent PH in the newborn.[87-89]

Sildenafil (orally three times daily) and tadalafil (orally once daily), both PDE-5 inhibitors that enhance NO activity by inhibiting PDE-5, the enzyme responsible for catabolism of cyclic guanosine monophosphate, are approved for the treatment of PAH.[67,70] Sildenafil is also available intravenously. Riociguat is a guanyly cyclase activator that is approved for the treatment of PAH and inoperable chronic thromboembolic PH. Riociguat should not be used in combination with a PDE-5 inhibitor because of the risk of hypotension.

Interventional Therapy

Congenital Heart Disease Most patients with PH caused by systemic to pulmonary shunts will have had surgical repair as infants or children (unless the surgery is not available where the patient lives) to prevent the development of irreversible pulmonary vascular disease. New approaches to evaluation and perioperative or peri-interventional (via interventional cardiac catheterization) management now make repair of congenital heart defects possible in many patients who present later in life with elevated PVR. For example, inhaled NO, intravenous epoprostenol, or inhaled iloprost can unmask reversible pulmonary vasoconstriction and determine the minimal PVR that can be achieved. Temporary balloon occlusion of congenital heart defects or a patent foramen ovale with subsequent remeasurement of pressures can predict postrepair hemodynamics. In contrast, PH caused by pulmonary venous hypertension is reversible whenever the left-sided obstructive lesion is relieved, although the PH may take months to decrease.

These newer approaches to the evaluation of surgical operability or repair via an interventional cardiac catheterization in patients with congenital heart disease are also being applied to treating perioperative and postoperative acute pulmonary hypertensive crises in patients with PAH undergoing noncardiac operations. If a patient with elevated pulmonary resistance is being considered for surgery, there is an increased risk of postoperative pulmonary hypertensive crises. Knowing whether the pulmonary circulation will respond favorably to inhaled NO, intravenous epoprostenol, inhaled iloprost, or intravenous sildenafil will help in the management of this potential life-threatening perioperative complication. However, it remains to be determined whether closing all systemic-to-pulmonary shunts, just because we can now get these patients through surgery and the immediate perioperative period, is beneficial long-term. "Benign neglect" may remain the preferred therapy for some of these patients.

Atrial Septostomy Atrial septostomy has been performed in patients with severe RV pressure and volume overload refractory to maximal medical therapy.[90] The goal of this approach is to decompress the overloaded right heart and improve systemic output of the underfilled LV. Improvements in exercise function and signs of severe right-heart dysfunction, such as syncope and ascites, have been observed. Because the creation of an interatrial communication will result in an increased venous admixture, worsening hypoxemia is an expected outcome. The size of the septostomy that is created should be monitored carefully to achieve the ideal balance of optimizing systemic oxygen transport and reducing right-heart filling pressures without overfilling a noncompliant LV or producing extreme degrees of venous admixture.

Heart-Lung or Lung Transplant Fewer than 10% of patients with IPAH, and even fewer with other forms of PAH, are responsive to long-term oral calcium channel blockade vasodilator therapy. Of the remainder, approximately 75% can maintain sustained clinical improvement for at least several years with the newer oral therapies and/or long-term inhaled, continuous intravenous, or subcutaneous prostanoid therapy. When pulmonary hypertensive disease has progressed, or threatens to progress, to the stage of RV failure, the physician and patient are left with few therapeutic options other than transplant. Transplant is currently being done at specialized centers and is almost invariably handicapped by a shortage of donor lungs, which can lead to long delays. Single- or double-lung transplant has largely replaced heart-lung transplant. Hemodynamic improvement is often dramatic,[91] but transplant for PAH poses both a considerable surgical risk and the prospect of opportunistic infections that accompany lifelong immunosuppression.[92] Rejection phenomena, notably bronchiolitis obliterans, are the major limiting factors to prolonged survival.

Since 1981, more than 3000 patients have undergone a single-lung, double-lung, or heart-lung transplant for progressive PH worldwide. The operative mortality ranges between 15% and 30% and is affected by the primary diagnosis. The 1-year survival is reported at 61% to 83%, 3-year survival at 52% to 61%, 5-year survival at 38% to 49%, and 10-year survival at approximately 25% (www.unos.org). Timing a referral for transplant depends on the patient's prognosis with optimal medical therapy, the anticipated waiting time for transplant in the region, and the expected survival after transplant. The time on the waiting list depends on the lung allocation score.

Combination Therapy

More recently, combination treatment has been evaluated to address the multiple pathobiologic mechanisms present in PAH (Fig. 74–11). The combination of oral bosentan and intravenous (IV) epoprostenol was investigated in one small study, with inconclusive results.[78] Several additional RCTs have evaluated sequential combination therapy in PAH. The addition of inhaled iloprost to background oral bosentan demonstrated improved hemodynamic status and clinical events in one RCT[81]; however, these results were not confirmed in an open trial.[80] In another study, the addition of oral sildenafil to background IV epoprostenol demonstrated improved exercise capacity, hemodynamic status, and clinical events; furthermore, in a post hoc analysis, the addition of oral sildenafil to background IV epoprostenol increased survival versus IV epoprostenol alone.[82] In the pivotal tadalafil RCT, 53% of the patients were on background oral bosentan; in that study overall, tadalafil improved exercise capacity, hemodynamic status, and clinical events.[69] Inhaled treprostinil has also been studied as add-on therapy to either background bosentan or background sildenafil; in both combinations, the addition of inhaled treprostinil improved exercise capacity.[71] These studies support the efficacy of combination treatment in patients who remain symptomatic on monotherapy. The Ambrisentan and Tadalafil in Patients With Pulmonary Arterial Hypertension (AMBITION) trial demonstrated that initial combination therapy with ambrisentan and tadalafil in treatment-naïve PAH patients resulted in delay in disease progression and improved exercise capacity to a greater degree than with monotherapy using ambrisentan or tadalafil alone.[69] The optimal combination on the basis of overall risk-benefit considerations remains unknown.

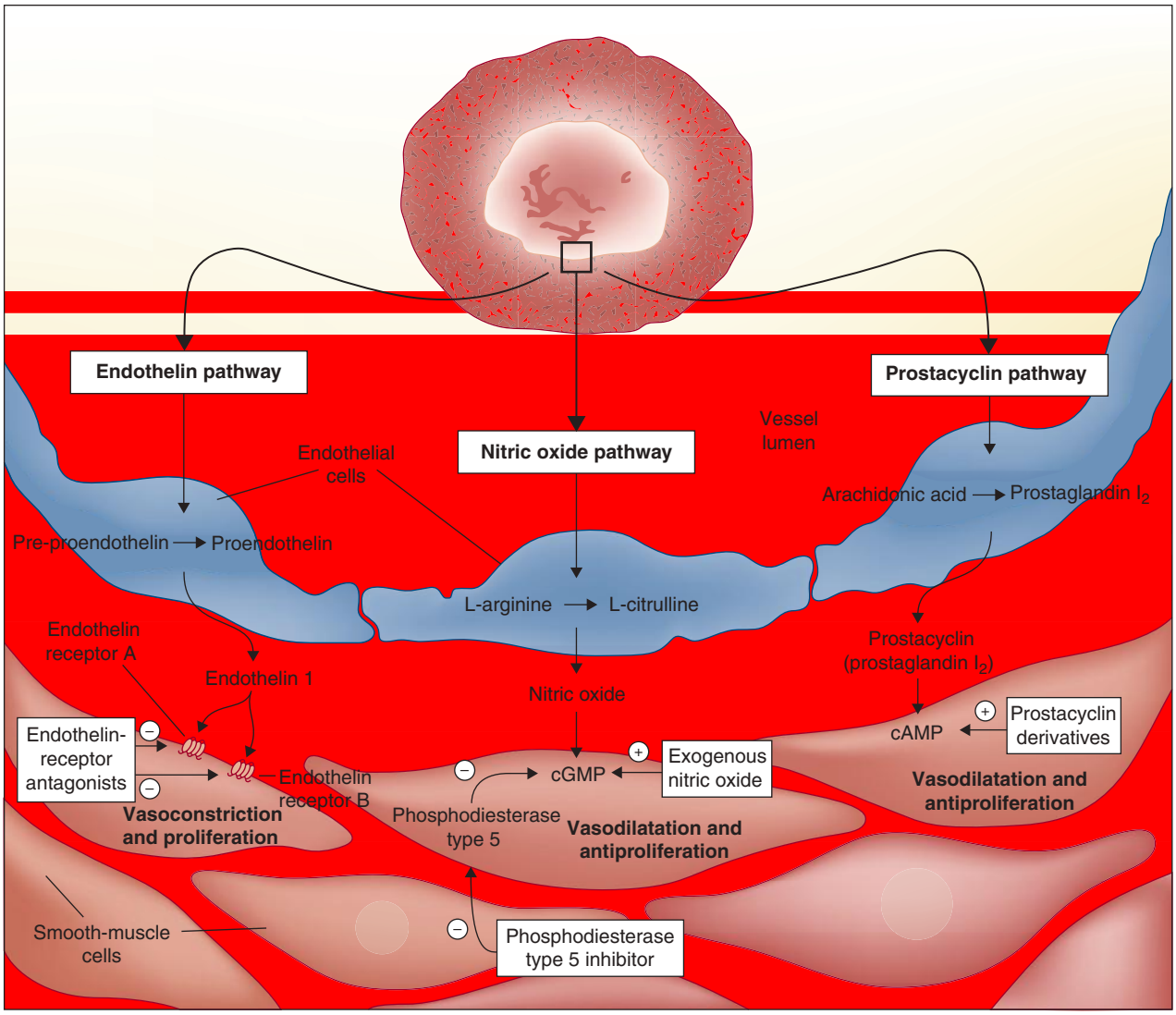


FIGURE 74–11. Three major pathways involved in abnormal proliferation and contraction of the smooth muscle cells of the pulmonary artery in patients with pulmonary arterial hypertension are shown. These pathways correspond to important therapeutic targets in this condition and play a role in determining which of four classes of drugs—endothelin receptor antagonists, nitric oxide, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives—will be used. At the top of the figure, a transverse section of a small pulmonary artery (< 500 μm in diameter) from a patient with severe pulmonary arterial hypertension shows intimal proliferation and marked medial hypertrophy. Dysfunctional pulmonary artery endothelial cells (*blue*) have decreased production of prostacyclin and endogenous nitric oxide, with an increased production of endothelin-1—a condition promoting vasoconstriction and proliferation of smooth muscle cells in the pulmonary arteries (*red*). Current or emerging therapies interfere with specific targets in smooth muscle cells in the pulmonary arteries. In addition to their actions on smooth muscle cells, prostacyclin derivatives and nitric oxide have several other properties, including antiplatelet effects. +, Increase in the intracellular concentration; –, blockage of a receptor, inhibition of an enzyme, or a decrease in the intracellular concentration; cGMP, cyclic guanosine monophosphate.

A treatment algorithm based on a consensus of the PH community is presented in Fig. 74–10. The recommendations in this guideline are based on a grading system in which the strength of the recommendation results from the interaction of two components: the quality of the evidence and the net benefit of the therapy. Because treatments have been evaluated primarily in IPAH, HPAH, and PAH associated with scleroderma or anorexigen use, extrapolation of these recommendations to other PAH subgroups should be done with caution.

In summary, the current approach to treating PAH patients after the diagnosis has been made is to treat patients with oral anticoagulant drugs if no contraindication exists, diuretics in cases of fluid retention, and supplemental oxygen in cases of hypoxemia, even though RCTs with these compounds are lacking. Patients should be referred without delay to centers experienced in the treatment of pulmonary vascular diseases. Acute vasoreactivity testing should be performed in all patients with PAH, although patients with IPAH, HPAH, and PAH associated with anorexigen use are the most likely to exhibit a positive response. Vasoreactive patients, as defined in the preceding text, should be treated with optimally tolerated doses of calcium channel blockers; maintenance of response, defined as WHO functional class I or II with near-normal hemodynamic status, should be confirmed by repeat right heart catheterization and clinical assessment after 3 to 6 months of treatment. Nonresponders to acute vasoreactivity testing or responders who remain in WHO functional class III should be considered candidates for treatment with an oral PDE-5 inhibitor, an oral ERA, both in combination, or riociguat. Among prostacyclin analogues, treprostinil can be administered subcutaneously, intravenously, orally, or by inhalation; iloprost can be given intravenously (available in the European Union) or by inhalation; beraprost (approved in Japan and Korea) is administered orally; and

epoprostenol is administered intravenously. The choice of drug is dependent on a variety of factors, including the approval status, route of administration, side effect profile, patient preference, and the physician's experience and clinical judgment. Continuous IV epoprostenol remains first-line therapy for PAH patients in WHO functional class IV because of its demonstrated survival benefit in IPAH/HPAH, with extrapolation to associated PAH patients in WHO functional class IV. Its short half-life and apparent inotropic effect are advantageous in treating functional class IV patients. Combination therapy should be considered for patients who fail to show improvement or who deteriorate with monotherapy. The goal in treating PAH is to improve WHO functional class III and IV patients to functional class I or II and to improve all functional class II patients to functional class I or at least to maintain functional class II in patients presenting in that functional class. Finally, both atrial septostomy and lung transplant are indicated in carefully selected patients for refractory PAH or in cases where medical treatments are unavailable. These procedures should be performed only in experienced centers. Major therapeutic advances for PAH patients have been achieved in the last decade; however, none of the currently approved therapies represents a cure for this progressive disease. The search for such treatments continues, with promising new concepts arising from a better understanding of the pathobiology of pulmonary vascular diseases. Patients and physicians should be encouraged to foster such research by participating in RCTs conducted at specialized PH centers.

DISEASE SEVERITY AND PROGNOSIS

The diagnosis of PAH carries with it a poor prognosis unless medical or surgical therapy succeeds in decreasing PVR. Assessment of disease severity has been evaluated using noninvasive studies and invasive tests. As no one test has been shown to be highly sensitive and highly specific, multiple tests are used. These include assessment of functional classification and exercise capacity using either the 6-minute walk test to assess exercise endurance or cardiopulmonary exercise testing to evaluate exercise tolerance. Although cardiopulmonary exercise testing may be more sensitive to changes in less ill patients, it can be technically challenging. Assessment of right heart function is evaluated qualitatively and quantitatively by echocardiographic parameters as well as by magnetic resonance imaging, with the presence of a pericardial effusion of any size carrying a poor prognosis. Brain natriuretic peptide appears to be a reasonable biomarker for disease severity. In addition to being used to confirm the diagnosis of PAH, repeat cardiac catheterization remains extremely valuable in assessing prognosis and response to therapy (Table 74–9). The prognosis is largely determined by the severity of right heart dysfunction and the hemodynamic and clinical response to therapy.[93,94]

TABLE 74–9. Pulmonary Arterial Hypertension[a]: Determinants of Prognosis

Risk Factors	Better Outcome	Worse Outcome
PAH group I classification	PAH-CHD, IPAH	PAH-CTD, PoPH, HPAH, PCH, PVOD
Rate of disease progression	Gradual	Rapid deterioration over several months
Syncope	Without	Recurrent
Right heart failure	No	Yes
WHO functional class[b]	I, II	IV
Resting systolic blood pressure		< 100 mm Hg
Resting heart rate		> 100 bpm
Chest radiograph		Pleural effusions
Echocardiography	Normal RV function to minimal RV dysfunction; no effusion	Pericardial effusion (any size); significant RV dilation/dysfunction; right atrial enlargement; IVS encroachment into the LVOT; IAS encroachment into LA; decreased right-sided clearance with cavitation study
6-Minute walk distance[c]	> 4 00 m	< 320 m
CPET	Peak VO_2 > 10.4 mL/kg/min; peak systolic blood pressure > 120 mm Hg	Peak VO_2 < 10.4 mL/kg/min; peak systolic blood pressure < 120 mm Hg
Platelet count	> 150,000	< 50,000
Uric acid	< 7 mg/dL	> 11 mg/dL
Renal insufficiency	No	Yes
BNP	Normal to minimal increase, ie, < 180 pg/mL	Significantly increased, ie, > 180 pg/mL
Troponin	Negative	Positive
RHC	Normal/near normal RAP and CI, ie, RAP < 10 mm Hg, CI > 2.5 L/min/m^2; PVR < 10 Wood units	High RAP, low CI, ie, RAP > 20 mm Hg, CI < 1.8 L/min/m^2; severe elevation in PVR, ie, PVR > 24 Wood units

Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; CPET, cardiopulmonary exercise testing; IAS, interatrial septum; IVS, interventricular septum; LA, left atrium; LVOT, left ventricular outflow tract; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; peak VO_2, peak oxygen uptake during exercise; PoPH, portal pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RAP, right atrial pressure; RHC, right heart catheterization; RV, right ventricle; WHO, World Health Organization.

[a]Note: One should not rely on any single factor to make risk predictions.

[b]WHO class is the functional classification for PH (modification of the New York Heart Association functional class).

[c]Six-minute walk distance is affected by age, sex, and height.

Data from McLaughlin V, McGoon M. Pulmonary arterial hypertension. *Circulation*. 2006 Sep 26;114(13):1417-1431.

PULMONARY VENO-OCCLUSIVE DISEASE AND PULMONARY CAPILLARY HEMANGIOMATOSIS

These are the least common of all types of unexplained PH.[95] Not infrequently, the patient is thought to have IPAH until manifestations inconsistent with pulmonary precapillary disease, such as pulmonary congestion and edema or severe hypoxemia, redirect attention to the vascular bed distal to the arterioles. The pathogenetic mechanism of pulmonary veno-occlusive disease (PVOD) is unknown, but the disease may begin as an inflammatory-thrombotic process in the small pulmonary veins and venules and end in fibrous obliteration of the venous and venular lumens. Presumably as a secondary phenomenon, the distal pulmonary arterial tree also develops obstructive lesions that are generally proliferative ("reactive") rather than inflammatory in nature; the intervening capillary bed is generally normal. The pulmonary veno-occlusive lesions have been attributed to an inflammatory response to vascular injury, followed by thrombosis and scarring. Among the postulated etiologies are viral illness, chemotherapy, toxins, autoimmune disease, and mediastinal fibrosis.[49]

Both PVOD and capillary hemangiomatosis can be familial. PVOD can also be associated with systemic sclerosis. When the PH is suspected of originating distal to the pulmonary capillary bed, mitral valve

disease, myocardial dysfunction, or even LA myxoma has a greater likelihood of being the cause than does PVOD.

CLINICAL PICTURE

Predominantly children and young adults are affected, but the age has been reported to range from infancy to the late 40s. Clinical suspicion of this disorder generally arises when a patient with congested and edematous lungs proves to have a normal mitral valve and LV.

The cardinal signs are dyspnea and fatigue on exertion in conjunction with evidence of PH; the pulmonary venous rather than pulmonary arterial etiology is suggested by radiologic evidence of postcapillary PH without evidence of involvement of the left side of the heart (Fig. 74–12A). Pleural effusions are common. Cyanosis, syncope, hemoptysis, and finger clubbing have been inconsistent findings. Moderate to severe hypoxemia, caused by intrapulmonary shunting through the abnormal capillary network, is a hallmark of capillary hemangiomatosis. Rarely, systemic embolization may occur.

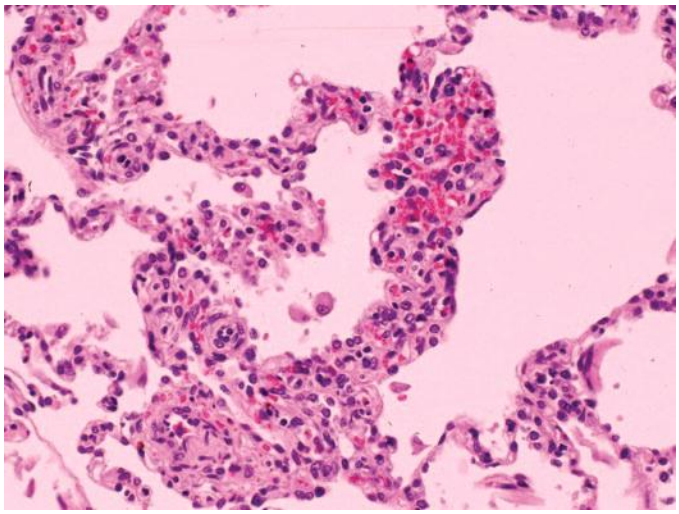


FIGURE 74–12. Pulmonary veno-occlusive disease (PVOD) proven by open lung biopsy. **A.** Computed tomography scan from a patient with PVOD showing a patchy mosaic pattern consistent with pulmonary edema. **B.** Photomicrograph of the lung from a patient with PVOD and pulmonary capillary hemangiomatosis, showing occlusion of small pulmonary veins and proliferation of the capillary network.

HEMODYNAMIC PARAMETERS

Cardiac catheterization discloses a high pulmonary arterial pressure with a normal pulmonary wedge and LV end-diastolic pressure. Although one might expect the PCWP to be elevated, the reason that it is usually normal is as follows: Inflation of the balloon at the tip of a pulmonary artery catheter creates a downstream *stop-flow* phenomenon that extends to same-diameter veins and therefore generally gives a satisfactory estimate of LA or end-diastolic LV pressure. When epoprostenol is administered to a patient with PVOD, a pulmonary edema pattern may ensure, most often acutely (although it may not occur for several days in some patients), resulting from increasing pulmonary blood flow in the face of downstream vascular obstruction.[96] This response, when present, is virtually diagnostic of PVOD. Patients with capillary hemangiomatosis may experience worsening hypoxemia with epoprostenol, attributable to increased shunting through the low-resistance capillary meshwork.

PATHOLOGY

At autopsy, both lungs are involved. The lungs are the seat of congestion, edema, and focal fibrosis, which may become extensive. The venous lesions may be more marked in one region than in another. Although both the small pulmonary arteries and the small pulmonary veins are affected, the lesions are different (see Fig. 74–12B). Most striking are the morphologic changes in the pulmonary veins and venules, which are narrowed or occluded by intimal proliferation and fibrosis; up to 95% of the veins and venules may be affected in this way, but complete occlusion is uncommon. Bronchial veins and bronchopulmonary anastomoses share in the occlusive process. Hypertrophy in the walls of the pulmonary arteries may be quite striking. PVOD, to varying degrees, may also coexist with capillary hemangiomatosis. Thrombi in the pulmonary arteries are common.[49]

TREATMENT

Medical management has been disappointing, because the lesions generally are irreversible. An occasional patient has been reported to do well with medical therapy, although most experienced clinicians consider both PVOD and capillary hemangiomatosis to be contraindications to the use of oral PAH medications or intravenous epoprostenol. The usual duration of life after recognition ranges from a few weeks in infants to several years in adults, with 7 years being the maximum reported. The treatment of choice is probably lung transplant.

FUTURE DIRECTIONS

Future developments in vascular biology will improve our understanding of the pathobiology of PAH and provide rationale and proof of concept for more disease-specific targeted therapies. With the advent of genomic technologies and methodologies, the necessary tools are already pinpointing the genes that contribute to disease susceptibility and progression. Candidate gene discovery, involving gene analysis using microarrays, can identify genes that may provide valuable insight into disease biology and may represent an initial step toward the identification of genetic polymorphisms that may help predict efficacy, or lack thereof, with various disease-specific targeted PAH therapeutic modalities. By identifying the genes and gene variants that determine individual disease susceptibility, we might one day be able to identify patients in preclinical stages of disease as well as allow for individualized therapies that are most efficacious and least likely to cause side effects. Furthermore, although RV function appears to be the most significant prognostic parameter in PAH, comparatively little attention

has been devoted to how RV function and dysfunction can be detected and measured, what specific molecular and cellular mechanisms contribute to the maintenance or failure of RV function, how RV dysfunction evolves structurally and functionally, or what interventions might best preserve RV function. In addition, RV-LV interaction and RV–pulmonary arterial coupling have largely been overlooked as potential targets for investigation and therapy.

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CHAPTER 75

PULMONARY EMBOLISM

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Treatment of Isolated Distal Deep Vein Thrombosis and Upper Limb Thrombosis / 1828
Pulmonary Embolism in Pregnancy / 1829
Pulmonary Embolism in Cancer Patients / 1829

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). It is the third most frequent cardiovascular disease with an overall annual incidence rate between 75 and 270 cases per 100,000 inhabitants.[1] The risk of VTE approximately doubles with each subsequent decade after the age of 40; therefore, a larger number of patients are expected to be diagnosed with VTE in aging societies in the coming future.[1] PE is the most serious clinical presentation of VTE with 1- and 3-month mortality rates between 9% and 11% and up to 17%, respectively.[2-4] Following the acute PE episode, resolution of emboli is frequently incomplete despite optimal anticoagulant therapy,[5] which may lead to the development of chronic thromboembolic pulmonary hypertension (CTEPH).[6] Although a number of patients die of comorbidities that predispose them to the thromboembolic event, approximately one-third of patients die from PE within the first hours of presentation, often before the diagnosis can be confirmed and therapy initiated or because the diagnosis was overlooked.[7] Despite advances in diagnostic imaging tests and therapeutic interventions, PE remains underdiagnosed, and prophylaxis continues to be dramatically underused. Globally, improvements in length of stay and changes in the initial treatment are being accompanied by a reduction in short-term all-cause and PE-specific mortality.[8,9]

Over the past decade, a number of valuable insights into the natural history of venous thrombosis and PE have enhanced our diagnostic and therapeutic approaches.[10] One such insight is the awareness that patients hospitalized for medical problems face a thromboembolic risk similar to that of their surgical counterparts. Another is an understanding of the substantial thromboembolic recurrence risk among patients with idiopathic or unprovoked venous thrombosis.[11] Yet another insight is the awareness that the presence of right ventricular (RV) dysfunction and increased levels of troponins and/or natriuretic peptides in the setting of PE may be associated with an increased risk of adverse consequences, including subsequent cardiovascular collapse and death.[12] Anticoagulation with heparin, low-molecular-weight heparin (LMWH), or fondaparinux as a "bridge" to oral anticoagulation is still considered the standard treatment for PE. The spectrum of anticoagulant drugs has been expanded recently with the new generation of oral direct thrombin inhibitors and factor Xa inhibitors.

RISK FACTORS AND PATHOGENESIS OF VENOUS THROMBOEMBOLISM

In 1856, Virchow proposed his triad of factors leading to intravascular coagulation, including stasis, vessel wall injury, and hypercoagulability. Risk factors for VTE are based on these processes (Table 75–1). VTE is considered to be provoked in the presence of a temporary or reversible, usually acquired, risk factor (eg, surgery, trauma, immobilization, pregnancy) within the last 3 months before the diagnosis and unprovoked in the absence thereof.[13] The presence of a persistent, sometimes inherited, risk factor may affect the decision of the duration of anticoagulation therapy after a first episode of VTE. The overwhelming majority of emboli originate from the deep veins of the lower extremities, although any venous bed can be involved. Although thrombi may form at any point along the vein wall, most originate in valve pockets. The veins of the calf are the most common site of origin, with subsequent extension of the clot prior to embolization.[14] Eventually, the thrombus may expand to fill the vessel entirely, with both retrograde and proximal extension. If embolization does not occur, the thrombosis can partially or completely resolve via three mechanisms: recanalization, organization, and lysis. Post-thrombotic syndrome occurs in 20% to 50% of patients and involves chronic pain, swelling, edema, and skin changes, which reduce quality of life and incur significant health care costs.[15]

ACQUIRED RISK FACTORS

Frequently, more than one risk factor for venous thrombosis is present; knowledge of these risk factors provides the rationale for both

TABLE 75–1. Risk Factors for Venous Thromboembolism

Acquired factors
Age older than 40 y
History of venous thromboembolism[a]
Prior major surgical procedure
Major trauma[a]
Hip or lower limb fracture[a]
Hip or knee replacement[a]
Spinal cord injury[a]
Immobilization or paralysis
Blood transfusion
Varicose veins and superficial vein thrombosis
Hospitalization for congestive heart failure or atrial fibrillation/flutter (within previous 3 months)[a]
Congestive heart or respiratory failure
Myocardial infarction (within previous 3 months)[a]
Obesity
Pregnancy or postpartum period
In vitro fertilization
Hormone replacement and oral contraceptive therapy (depends on formulation)
Cerebrovascular accident
Malignancy and chemotherapy
Central venous line
Severe thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Antiphospholipid antibody syndrome (including lupus anticoagulant)
Inherited factors
Antithrombin III deficiency
Factor V Leiden (activated protein C resistance)
Prothrombin gene (G20210A) defect
Protein C deficiency
Protein S deficiency
Dysfibrinogenemia
Disorders of plasminogen
Hyperhomocysteinemia

[a]Strong risk factors for venous thromboembolic disease.

prophylaxis and clinical suspicion. Comorbidities enhance the risk of VTE. In the DVT FREE prospective registry of 5451 patients with ultrasound-confirmed DVT, the most common comorbidities were systemic hypertension (50%), surgery within 3 months (38%), immobility within 30 days (34%), cancer (32%), and obesity (27%).[16]

Although studies to date have yielded inconsistent results, long automobile or airplane trips appear to be risk factors for VTE. The proportion of subjects who develop acute PE during or after airplane travel appears to be associated with other thrombotic risk factors, such as the presence of the factor V Leiden mutation or the use of oral contraceptive agents and correlates with the flight distance. The risk of PE significantly increases with a flight distance of greater than 3107 miles (5000 km) or a duration longer than 8 hours.[17]

Obesity merits further investigation because recent studies implicate obesity as a risk factor for VTE, particularly in developed countries, where obesity represents a major health issue.[18-20] The Nurses' Health Study explored risk factors for PE in women and found that a body mass index of 29 kg/m^2 or greater was an independent risk factor.[21] The Framingham Study has confirmed that obesity is a risk factor for PE, particularly in women.[22] In addition to increased venous stasis, obesity may also increase the risk for VTE as a consequence of elevated plasma levels of certain clotting factors, such as fibrinogen, factor VII, and plasminogen activator inhibitor-1, and as a result of platelet activation caused by enhanced lipid peroxidation.[23]

An abundance of literature documents that the risk of VTE and its mortality increases with age, with a relative risk for those 70 years of age approximately 25-fold greater than the risk for those 20 to 29 years of age.[24]

Prior VTE substantially increases the risk of subsequent events. Surgical patients with a previous history of VTE who do not receive prophylaxis are at particularly high risk for DVT. Surgery itself significantly enhances the risk. The risk of VTE is highest during the first two postoperative weeks but remains elevated for 2 to 3 months. Spinal surgery, pelvic surgery (and joint replacement in general), and neurosurgery place patients at a particularly high risk for VTE.[25,26] Prophylactic anticoagulation may be initiated either before surgery or shortly thereafter to prevent the development of intraoperative and early postoperative thrombosis. The incidence of VTE is reduced with increasing duration of thromboprophylaxis after major orthopedic surgery and cancer surgery, whereas this association has not been observed for general surgery.[27] Trauma, particularly major trauma and trauma of the lower extremities and pelvis, heightens the risk of DVT.[25,26]

Upper extremity DVT has become more important because of an increasing use of pacemakers; implantable defibrillators; and long-term, indwelling, central venous catheters.[28] Symptomatic PE may originate from upper extremity thrombi, although this appears much less common than embolization from lower extremity DVT. Upper extremity DVT poses the risk of superior vena cava syndrome and loss of vascular access.[29] Effort-related, upper extremity axillosubclavian thrombosis (Paget-von Schroetter syndrome) may occur spontaneously or be associated with an underlying thrombophilic tendency and may result in significant, long-term functional impairment.[28]

Epidemiologic analyses suggests that patients with cardiac disease are predisposed to VTE.[30] Myocardial infarction and heart failure increase the risk of PE[31]; conversely, patients with VTE are at increased risk of subsequent myocardial infarction and stroke.[32] Cancer clearly augments the risk of VTE, although the precise pathogenesis of thromboembolism in cancer is not well understood. Numerous mechanisms, including intrinsic tumor procoagulant activity and extrinsic factors such as chemotherapeutic agents and indwelling access catheters, contribute to this process. The thrombophilic tendency associated with cancer is often amplified by clinical factors such as patient weakness and immobility. An analysis based on data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study found that of 399 patients with PE, 73 (18.3%) had cancer.[33] The risk of VTE varies with different types of cancer.[34] Hematologic malignancies, lung cancer, gastric and pancreatic malignancies, brain cancer, genitourinary tract cancer, and breast malignancies are associated with a particularly high risk of DVT and PE.[35,36] About half of all cancer patients and approximately 90% of those with metastases exhibit abnormalities of one or more coagulation parameters.[37] After the administration of various chemotherapeutic agents, changes in the levels of coagulation factors, suppression of anticoagulant and fibrinolytic activity, and direct endothelial damage have been documented clinically and experimentally.[38] Hormonal therapy, particularly tamoxifen in breast cancer adjuvant therapy, is also associated with an increased risk of thromboembolism, particularly when combined with chemotherapy.[39]

Neutropenia and sepsis, which often accompany chemotherapeutic regimens, often necessitate hospitalization and bedrest, which contribute further to the risk of VTE. A subsequent malignancy has been reported to occur within 2 to 3 years in approximately 5% to 10% of patients presenting with idiopathic venous thrombosis.[40] Although some data suggest that a limited approach (abdominal/pelvic computed tomography [CT], mammography, sputum cytology) to search for cancer may be cost effective,[41] it does not appear to be routinely warranted in patients presenting with unprovoked VTE.[42]

Oral contraception, pregnancy and the postpartum period are the most common settings in which women younger than age 40 years acquire thromboembolic disease. Venous thrombosis develops in these settings three to six times more often than in age-matched women not on oral contraceptives.[43] When occurring during pregnancy, VTE is a major cause of maternal mortality.[44] The risk is highest in the third trimester of pregnancy and over the 6 weeks of the postpartum period,[44] but the risk is considerable throughout pregnancy.[45] Cesarean section further augments the risk. In vitro fertilization further increases the risk of pregnancy-associated VTE, particularly during the first trimester of pregnancy.[46] Oral contraceptives are associated with an increased relative risk of VTE, although the absolute risk (approximately 1-3 cases per 10,000 woman-years) remains small.[43] Third-generation agents (agents containing desogestrel or gestodene as the progestogen component) appear to cause acquired resistance to activated protein C and double the risk of VTE. Oral contraceptive use should be avoided by women with protein C, protein S, and antithrombin III deficiency, as well as those who are homozygous carriers of the factor V Leiden mutation. Results from a clinical trial evaluating hormone replacement therapy indicated that such therapy increased the incidence of VTE in women 45 to 64 years of age. The best available evidence suggests a two- to four-fold increased relative risk of VTE among oral hormone replacement therapy users compared with nonusers,[43] although the risk of VTE varies widely depending on the formulation used in postmenopausal women who receive hormone replacement.[47] The risk of VTE also appears to be highest during the first year of exposure to hormone replacement. Although such therapy is associated with quality-of-life benefits in women who require postmenopausal symptom control, physicians must balance this benefit against the risk of VTE, cardiovascular disease, and breast cancer before prescribing hormone replacement therapy. Whether routine screening should be performed before the initiation of oral contraceptive agents or hormone replacement therapy remains controversial.[48] Given the low absolute risk, especially among users of oral contraceptive agents, the general consensus is that such an approach would not be cost effective.[49]

Antiphospholipid antibodies represent a diverse family of immunoglobulins that includes anticardiolipin antibodies and the lupus anticoagulant and are targeted against anionic surfaces such as β_2-glycoprotein I and prothrombin. Antiphospholipid antibodies, notably the lupus anticoagulant and high-titer anticardiolipin antibodies, are associated with both arterial and venous thrombi.[50]

INHERITED RISK FACTORS

Inherited thrombophilias result in variable degrees of VTE risk.[51,52] Antithrombin III deficiency was first described in 1965 and was the first inherited trait associated with thrombophilia. Functional and quantitative abnormalities of protein C and protein S were subsequently described. The factor V Leiden mutation, a single base mutation (substitution of A for G at position 506), is a far more common genetic polymorphism associated with activated protein C resistance. It is present in approximately 4% to 6% of European populations and is less common among those of Asian, Indian, or African descent.[53,54] The relative risk of a first idiopathic DVT among men heterozygous for the mutation is three- to seven-fold higher than that of those not affected.[53] This genetic mutation is also a risk factor for recurrent pregnancy loss, probably because of placental thrombosis.[55] Oral contraceptive use in patients with heterozygous factor V Leiden mutation is associated with a 10-fold higher risk of VTE.[56]

Another less frequent thrombophilic mutation has been identified in the 3′ untranslated region of the prothrombin gene (substitution of A for G at position 20210).[57] This mutant allele is present in 2% to 4% of the general population and causes increased levels of prothrombin. This prothrombin gene defect increases the risk of DVT by a factor of 2.7 to 3.8.[57,58] It appears that carriers of *both* factor V Leiden and the prothrombin G20210A defect have an increased risk of recurrent DVT after a first episode and are candidates for lifelong anticoagulation.[59]

Homocysteine has potential thrombogenic effects, including injury to vascular endothelium and antagonism of the synthesis and function of nitric oxide.[60] Coexisting hyperhomocysteinemia has been shown to increase the risk for thrombosis in patients with factor V Leiden.[61] However, the thermolabile methylenetetrahydrofolate reductase gene variant is not independently associated with thrombosis, emphasizing that the precise role of homocysteine in venous thrombosis is unclear. Thus, interactions between the genetic factors (defects in enzymes) that control homocysteine metabolism and nutritional factors (folate, vitamin B_6, and vitamin B_{12} deficiencies) that affect homocysteine metabolism warrant additional investigation with regard to VTE.[62]

Recently, elevated levels of clotting factors VII, VIII, IX, XI, and XII have been associated with an increased risk for venous thrombosis. In particular, elevated factor VIII levels have been demonstrated to be a strong and independent risk factor for both acute and recurrent venous thrombosis.[63,64] Factor VIII, may, however, be an acute phase reactant, so if used to determine treatment duration, it should be repeated at some point months after the acute PE episode.

PATHOPHYSIOLOGY OF ACUTE PULMONARY EMBOLISM

GAS-EXCHANGE ABNORMALITIES

The effect of PE on oxygenation and hemodynamics depends on the extent of obstruction of the pulmonary vascular bed and the severity of underlying cardiopulmonary disease.[12] Hypoxemia develops in the preponderance of patients with PE and has been attributed to various mechanisms, including intrapulmonary or intracardiac right-to-left shunting, elevated alveolar dead space, ventilation-perfusion (V/Q) inequality, and decreases in the mixed venous oxygen level, thereby magnifying the effect of the normal venous admixture. The two latter mechanisms are proposed to account for the majority of hypoxemia and hypocarbia associated with acute embolism. Shunt may occur as a consequence of atelectasis related to loss of surfactant, alveolar hemorrhage, or bronchoconstriction related to regional areas of hypocarbia. Hypoxemia leads to an increase in sympathetic tone with systemic vasoconstriction and may actually increase venous return with augmentation of stroke volume, at least initially, if there is no significant underlying cardiac or pulmonary pathology already present.

HEMODYNAMIC ALTERATIONS

The hemodynamic effects of embolism are related to three factors: the degree of reduction of the cross-sectional area of the pulmonary vascular bed, the pre-existing status of the cardiopulmonary system, and the physiologic consequences of both hypoxic and neurohumorally

mediated vasoconstriction.[12] Obstruction of the pulmonary vascular bed by embolism acutely increases the workload on the RV, a chamber ill-equipped to deal with high-pressure load. In patients without preexisting cardiopulmonary disease, obstruction of less than 20% of the pulmonary vascular bed results in a number of compensatory events that minimize adverse hemodynamic consequences. Recruitment and distension of pulmonary vessels occur, resulting in a normal or near-normal pulmonary artery pressure and pulmonary vascular resistance; cardiac output is maintained by increases in the RV stroke volume and increases in the heart rate. As the degree of pulmonary vascular obstruction exceeds 30% to 40%, increases in pulmonary artery pressure and modest increases in right atrial pressure occur. The Frank-Starling mechanism maintains RV stroke work and cardiac output. When the degree of pulmonary artery obstruction exceeds 50% to 60%, compensatory mechanisms are overcome, cardiac output begins to decrease, and right atrial pressure increases dramatically. With acute obstruction beyond this amount, the right heart dilates, RV wall tension increases, RV ischemia may develop, the cardiac output decreases, and systemic hypotension develops. In patients without prior cardiopulmonary disease, the maximal mean pulmonary artery pressure capable of being generated by the RV appears to be 40 mm Hg. The correlation between the extent of pulmonary vascular obstruction and the pulmonary vascular resistance appears to be hyperbolic, reflecting, at its lower end, the expansible nature of the pulmonary vascular bed and, at its upper end, the precipitous decline in cardiac output that may occur as the RV fails.[65]

The hemodynamic response to acute PE in patients with preexisting cardiopulmonary disease may be considerably different.[66] Patients with prior cardiopulmonary disease demonstrate degrees of pulmonary hypertension that are disproportionate to the degree of pulmonary vascular obstruction. As a result, severe pulmonary hypertension may develop in response to a relatively small reduction in pulmonary artery cross-sectional area. Thus, evidence of RV hypertrophy (rather than RV dilatation) associated with a mean pulmonary artery pressure in excess of 40 mm Hg should suggest an element of chronic pulmonary hypertension resulting from a potentially diverse group of etiologic possibilities (eg, CTEPH, left ventricular [LV] failure, valvular disease, right-to-left cardiac shunts).

DIAGNOSIS OF DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

HISTORY AND PHYSICAL EXAMINATION

Erythema, warmth, pain, swelling, and tenderness are not specific for DVT but suggest the need for further evaluation. PE must always be considered when unexplained dyspnea is present. Pleuritic chest pain and hemoptysis are also common in patients with PE. Coughing may be present, and although it is sometimes caused by PE, it more commonly occurs with bronchitis or pneumonia. Anxiety and lightheadedness are symptoms that may be caused by PE but may also be caused by a number of other entities that result in hypoxemia or hypotension. Severe dyspnea and syncope are the principal symptoms that may suggest massive, life-threatening PE.[67-69] Tachypnea and tachycardia are the most common signs of PE, but they are also nonspecific. A pleural rub may suggest pulmonary infarction, and accentuated pulmonic component of the second heart sound may suggest PE but can also be explained by other disorders. With embolism of sufficient magnitude to cause RV dysfunction, a murmur of tricuspid regurgitation, systemic hypotension, or jugular venous distension might be present.

A major advance in the diagnostic approach to both venous thrombosis and PE has been a transition from a technique-oriented approach to one that uses Bayesian analysis. In doing so, the pretest probability of the disease, calculated independently of a particular test result through either empiric means or through a standardized prediction rule, is calculated. This pretest probability aids in the selection and interpretation of further diagnostic tests to create a post-test probability of the disease. This post-test probability can then be used as a basis for clinical decision making. For PE, three such scores have been developed and validated. Wells and coworkers[70] prospectively tested a rapid seven-item bedside assessment to estimate the clinical pretest probability for PE. An alternative scoring system, the Geneva score, involved seven variables and required gas exchange and radiographic information.[71] Recently, a revised Geneva score requiring eight clinical variables without gas exchange or radiographic information was validated and published.[72] Although such scoring systems have not proven to be more accurate than implicit assessment, they have been adequately validated[73-75] and do provide a means of standardization that compensates for variability in physician experience and judgment. Both the Wells score and the revised Geneva rule were simplified in an attempt to increase their adoption into clinical practice,[76,77] and these simplified versions have been adequately validated as well.[74,78] Thus, in the absence of hemodynamic instability at presentation, the diagnostic workup of a patient with suspected PE should begin with the assessment of the clinical or pretest probability. Table 75–2 summarizes clinical prediction rules for PE.

DIFFERENTIAL DIAGNOSIS

PE may mimic a large spectrum of diseases. The most common differential diagnoses are pneumonia, musculoskeletal pain, pneumothorax, costochondritis, congestive heart failure, chronic lung disease, asthma/bronchitis, acute myocardial infarction, aortic dissection, pericarditis, and anxiety states.

NONIMAGING STUDIES FOR PULMONARY EMBOLISM

D-Dimer

The plasma D-dimer is a specific derivative of cross-linked fibrin. Measurement of circulating plasma D-dimer has been comprehensively evaluated as a diagnostic test for acute VTE.[79] A normal enzyme-linked immunosorbent assay (ELISA) or ELISA-derived assays result is highly sensitive in excluding PE and DVT. When an ELISA D-dimer level is below an established cutoff level, the sensitivity and negative predictive value for VTE are 95% or above.[79] Therefore, it can be used to exclude PE in patients with either a low or a moderate pretest probability. Importantly, D-dimer measurement is not recommended in patients with high clinical probability, because a normal result does not safely exclude PE. Increased levels of cross-linked fibrin degradation products are an indirect but suggestive marker of intravascular thrombosis, indicating endogenous fibrinolysis. An increased D-dimer level is nonspecific for PE and may be seen with advancing age and in patients with various conditions, including infections and other inflammatory states, cancer, myocardial infarction, the postoperative state, and the second and third trimesters of pregnancy. Thus, the specificity of D-dimer in suspected PE decreases steadily with age, to almost 10% in patients older than 80 years.[80] Recent evidence suggests using age-adjusted cutoffs (instead of the standard 500 μg cutoff) to improve the performance of D-dimer testing in the elderly.[81,82] In a contemporary meta-analysis, age-adjusted cutoff values (age × 10 μg/L above 50 years) resulted in increased specificity while retaining sensitivity above 95%.[83] Similar results were obtained in a recent prospective study that showed

TABLE 75–2. Clinical Prediction Rules for PE

Items	Points Assigned: Original version[70]	Points Assigned: Simplified version[76]
Wells score		
Previous PE or DVT	1.5	1
Heart rate ≥ 100 bpm	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0-1	N/A
Intermediate	2-6	N/A
High	≥ 7	N/A
Two-level score		
PE unlikely	0-4	0-1
PE likely	≥ 5	≥ 2
Revised Geneva score	**Original version[72]**	**Simplified version[77]**
Previous PE or DVT	3	1
Heart rate ≥ 100 bpm		
75-94 bpm	3	1
≥ 95 bpm	5	2
Surgery or fracture within the past month	2	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral edema	4	1
Age ≥ 65 years	1	1
Clinical probability		
Three-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	≥ 11	≥ 5
Two-level score		
PE unlikely	0-5	0-2
PE likely	≥ 6	≥ 3

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Adapted with permission from Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014 Nov 14;35(43):3033-3069.

increased specificity and no additional false-negative results after using an age-adjusted cutoff.[84] In addition, it has been suggested that the height of D-dimer level correlates with the likelihood of PE[85] and with increased mortality, especially in noncancer patients.[86]

It is important to recognize that the usefulness of D-dimer testing in inpatients is still limited as a result of comorbidities in this population that elevate D-dimer levels. However, the negative predictive value of a (negative) D-dimer test remains high in these situations.

Arterial Blood Gas Analysis

Although hypoxemia is common in acute PE, some patients, particularly young individuals without underlying cardiopulmonary disease, may have a normal arterial oxygen partial pressure (PaO_2). In a retrospective study of hospitalized patients with PE, the PaO_2 was greater than 80 mm Hg in 29% of patients who were younger than 40 years compared with 3% in the older group.[68] However, the alveolar-arterial difference was elevated in all patients. An important tenet should be that unexplained hypoxemia, particularly in the setting of risk factors for DVT, suggests the possibility of PE.

Electrocardiography

Electrocardiography (ECG) findings in acute PE are generally nonspecific and include T-wave changes, ST-segment abnormalities, incomplete or complete right bundle branch block, right-axis deviation in the extremity leads, and clockwise rotation of the QRS vector in the precordial leads. The changes that do occur are likely caused by right-heart dilation. In milder cases, the only anomaly may be sinus tachycardia, present in approximately 40% of patients. Atrial arrhythmias, most frequently atrial fibrillation, may be associated with acute PE. Approximately 20% of patients with PE have no ECG changes. Therefore, ECG cannot be relied upon to rule in or rule out PE, although ECG proof of a clear alternative diagnosis, such as myocardial infarction, is useful when PE is among the possible diagnoses. The "classic" $S_1Q_3T_3$ pattern described by McGinn and White[87] in 1935 in seven patients with acute cor pulmonale secondary to PE was subsequently demonstrated to be present in approximately 10% of PE cases.[88] In patients without underlying cardiac or pulmonary disease from the Urokinase Pulmonary Embolism Trial, ECG abnormalities were documented in 87% of patients with proven PE.[89] These findings were not specific for PE, however. In this clinical trial, 26% of patients with massive or submassive PE and 32% of those with massive PE had manifestations of acute cor pulmonale, such as the $S_1Q_3T_3$ pattern, right bundle branch block, a P-wave pulmonale, or right-axis deviation. The low frequency of specific ECG changes associated with PE was confirmed in the PIOPED study.[68]

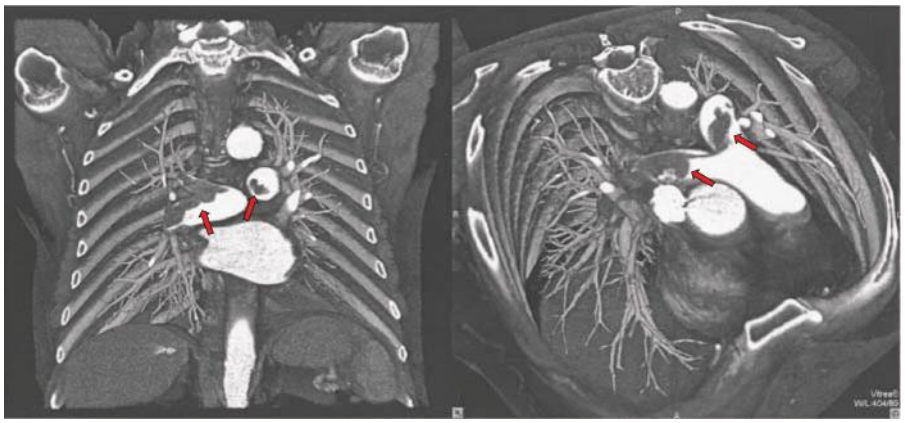
Despite its lack of diagnostic accuracy, ECG may be helpful in predicting adverse clinical outcomes in patients with PE. It was recently suggested that a T-wave inversion in V_2 or V_3 is the most frequent ECG sign of massive PE.[90] In another PE study, both the pseudoinfarction pattern (Qr in V_1) (Fig. 75–1) and T-wave inversion in V_2 were closely related to the presence of RV dysfunction and were independent predictors of adverse clinical outcome.[91] In a recent trial, an abnormal ECG at presentation proved to be an independent predictor of an adverse outcome, although no individual abnormality appeared capable of predicting such an outcome after being adjusted for the patients' clinical symptoms and findings on admission and for the presence of pre-existing cardiac or pulmonary disease.[92]

IMAGING STUDIES FOR PULMONARY EMBOLISM

Chest Radiography

The chest radiograph is abnormal in the majority of patients with PE, but the findings are nonspecific and often subtle. Atelectasis, cardiomegaly, pulmonary infiltrates, small pleural effusions, and mild elevation of a hemidiaphragm may be present.[68,93] Classic radiographic evidence of pulmonary infarction (Hampton hump) or decreased vascularity

(Westermark sign) is suggestive but uncommon. A normal chest radiograph in the presence of significant dyspnea and hypoxemia without evidence of bronchospasm or anatomic cardiac shunt is strongly suggestive of PE. In most situations, however, the chest radiograph cannot be used to definitively diagnose or exclude PE. Although exclusion of other processes such as pneumonia, congestive heart failure, pneumothorax, or rib fracture (which may cause symptoms similar to acute PE) is important, it is crucial to recognize that PE often coexists with other underlying lung diseases.



A B

FIGURE 75–1. Contrast-enhanced 16-slice computed tomography scan in a 72-year-old man with extensive, acute central pulmonary embolism showing a "saddle embolus" (*arrows*) extending into both central pulmonary arteries. Colored volume-rendering technique seen from an anterocranial (**A**) and anterior (**B**) perspective allows intuitive visualization of location and extent of embolism.

Computed Tomography of the Chest

Since the introduction of multidetector computed tomographic (MDCT) angiography, contrast-enhanced CT of the chest has become the most useful imaging test in patients with clinically suspected acute PE. It allows adequate visualization of the pulmonary arteries down to at least the segmental level.

First-generation scanners had poor resolution in the segmental pulmonary arteries and a limited sensitivity for subsegmental clots. However, a negative scan appeared to predict a benign clinical course over the ensuing 3 months.[94]

Second-generation scanners involve continuous movement of the patient through the scanner with concurrent scanning by a constantly rotating gantry and detector system.[95] A helix of projecting data is obtained. Continuous volume acquisitions can be obtained during a single breath. Rapid scans can be obtained, facilitating imaging in critically ill patients.

The latest generation of MDCT scanners (Figs. 75–1 and 75–2) permits image acquisition of the entire chest with 1-mm or submillimeter resolution with a breath hold of less than 10 seconds.[96]

Limitations of chest CT in early clinical studies included poor visualization of horizontally oriented vessels in the right middle lobe and lingula because of volume averaging.[95] The peripheral areas of the upper and lower lobes were inadequately scanned, and the presence of intersegmental lymph nodes resulted in false-positive study results. Multiplanar reconstructions in coronal, sagittal, or oblique planes aid in distinguishing lymph nodes from emboli. Based on studies with earlier generation scanners, CT was capable of revealing emboli in the main, lobar, or segmental pulmonary arteries with more than 90% sensitivity and specificity.[95,96] However, for subsegmental emboli, the sensitivity and specificity were, and still remain, lower. The incidence of isolated subsegmental emboli with first- and second-generation scanners appeared to be approximately 6% to 30%.[97]

When MDCT is used for PE diagnosis, it is ideal to incorporate the scan into an overall diagnostic strategy that includes pretest probability, D-dimer testing, and in certain specific settings, ultrasound examination of the deep leg veins.[96] An additional advantage of MDCT is the ability to evaluate a patient for the entire spectrum of VTE in one imaging session by scanning the legs and pelvis as well as the lungs. In PIOPED II, combining CT venography with CT angiography increased sensitivity for PE from 83% to 90% and had a similar specificity (around 95%)[98,99]; however, the corresponding increase in negative predictive value was not clinically significant. CT venography adds a significant amount of irradiation, which may be a concern, especially in younger women.[100] As CT venography and ultrasonography yielded similar results in patients with signs or symptoms of DVT in PIOPED II,[98] ultrasonography should be used instead of CT venography if indicated.

Outcome studies have demonstrated that PE can be safely excluded using a clinical assessment tool, D-dimer testing, and MDCT except in patients who present with a high clinical likelihood of embolism.[99,101-103] In the PIOPED II trial, the sensitivity of CT was 83%, a finding somewhat at odds with published outcome data.[99] PIOPED II did confirm the usefulness of clinical assessment in that the negative predictive value of a normal CT scan was 96% in patients with a low probability of embolism and 89% for those with an intermediate probability, but only 60% in those with a high clinical probability. In 2016, MDCT alone, with "wide detectors" of 256 to 320 rows, appears to be highly sensitive and specific for acute PE, and additional studies to confirm or refute the diagnosis are rarely required unless the quality of the CT is suboptimal. As demonstrated in the initial PIOPED trial, a negative V/Q scan or contrast pulmonary angiogram would also achieve this end.[104] Sequential, noninvasive, lower extremity examinations in patients with adequate cardiopulmonary reserve, although not confirming that embolism did not occur, would render the probability of

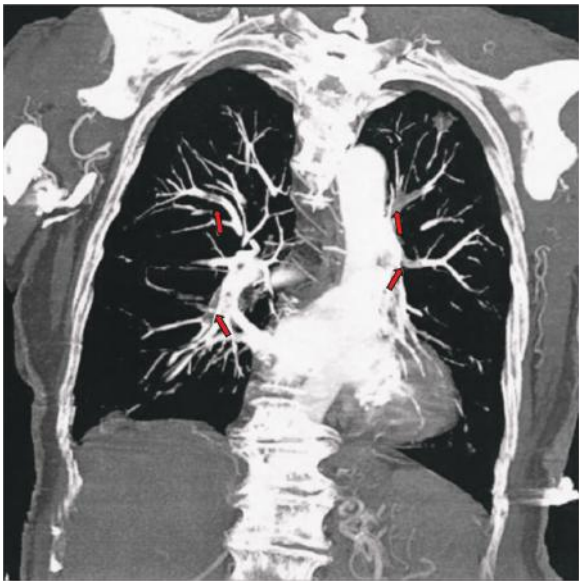


FIGURE 75–2. Contrast-enhanced 16-slice computed tomography (coronal reconstruction) in a 63-year-old man with multiple segmental pulmonary emboli (*arrows*). As an incidental finding, the examination also revealed a focal lung lesion in the left upper lobe, which was later confirmed to be stage I small-cell lung cancer.

recurrence unlikely. This approach is exceedingly impractical nowadays. Additional testing can be considered in patients with a low clinical probability of PE and a CT scan that is suggestive but not clearly diagnostic of PE. Another important advantage of chest CT is the concomitant ability to define nonvascular and vascular structures such as airway, parenchymal, and pleural abnormalities; lymphadenopathy; and cardiac and pericardial disease. This is very important for rapid detection of alternative diagnoses (eg, aortic dissection, pneumonia, pericardial tamponade) in patients with acute "chest syndromes" in the emergency setting. Disadvantages of MDCT include the potential for contrast-induced renal failure in patients with renal disease. Patients with a history of allergy to contrast agents should receive preprocedure treatment with steroids administered at least 6 hours before the procedure if possible. H_1 and H_2 histamine blockers may be used in addition to corticosteroids.

CT can expose patients to clinically significant doses of radiation. Younger women who have a known elevated incidence of PE are particularly at risk from radiation damage to the breast and lungs. In addition, the amount of contrast required for CT scanning (100-150 mL) poses a substantial risk of radiocontrast-induced nephropathy for patients with pre-existing renal disease (serum creatinine ~2 mg/dL or creatinine clearance < 60 mL/min), especially when it is associated with diabetes mellitus.[105] In such patients, a strategy using duplex ultrasonography and V/Q scanning would appear prudent followed by selective conventional pulmonary angiography if the noninvasive techniques do not yield a diagnosis. Although multiple pharmacologic agents have been used, only periprocedural hydration; the use of nonionic, iso-osmolar contrast agents; and perhaps *N*-acetylcysteine are of proven benefit in preventing dye nephropathy.[105]

Ventilation-Perfusion Scanning

V/Q scanning was the pivotal diagnostic test for suspected PE for many years. Although clinical indications for the study remain (contrast allergy, renal insufficiency, pregnancy), chest CT has now virtually replaced lung scanning. When the chest radiograph is normal or near normal, a V/Q scan can be performed; any perfusion defect in this situation will be considered to be a mismatch. Otherwise (eg, in the common clinical scenario involving an abnormal baseline chest x-ray), CT should be obtained. An additional advantage of the V/Q scan is that a portable study can be done in very ill patients who are too unstable to undergo CT.

The test is based on the intravenous injection of technetium (Tc)-99m–labeled albumin particles, which block a small fraction of the pulmonary capillaries and thereby enable scintigraphy assessment of lung perfusion. Perfusion scans are combined with ventilation studies, for which multiple tracers can be used. The purpose of the ventilation scan is to increase specificity; in acute PE, ventilation is expected to be normal in hypoperfused segments (mismatch). The radiation exposure from regular lung V/Q scanning is significantly lower than that of CT angiography.[106]

V/Q scanning is nondiagnostic in up to 70% of patients with suspected PE, which has been a cause for criticism, since this necessitates further diagnostic testing. Normal and high-probability scans are considered diagnostic. A normal perfusion scan excludes the diagnosis of PE with enough certainty that further diagnostic testing is unnecessary.

In the PIOPED study, the usefulness of lung scanning combined with clinical assessment of patients with suspected PE was prospectively evaluated.[104] Patients with PE had scans that were of high, intermediate, or low probability, but so did most individuals without PE. Although the specificity of high-probability scans was 97%, the sensitivity was only 41%. Of interest, 33% of patients with intermediate-probability scans and 12% of those with low-probability scans were diagnosed definitively with PE by pulmonary arteriography. Forty percent of low-probability scans in patients with high clinical suspicion were followed by documentation of PE at angiography. When the clinical suspicion of PE was considered very high, the positive predictive value of high-probability scans for PE was 96%. In patients with nondiagnostic lung scans, further diagnostic testing for PE should be undertaken. Recent studies suggest that data acquisition in single-photon emission CT imaging may reduce the frequency of nondiagnostic scans[106]; however, large-scale prospective studies are lacking and are needed to validate these new approaches.

Pulmonary Angiography

Standard contrast pulmonary arteriography (Fig. 75–3) has been considered the established "gold standard" imaging test for the diagnosis of PE. However, it is rarely performed now because MDCT offers similar diagnostic accuracy. Contrast injections may be useful, however, as a guide to percutaneous catheter-directed treatment of acute PE. The risk of subsequent VTE in patients with a negative test result and without anticoagulation has been shown to be less than 2%. In the current era when pulmonary arteriography is so rarely done, it is unclear whether this technique still remains this accurate.

Pulmonary angiography is not free of risk, with estimated rates of procedure-related mortality, major nonfatal complications, and minor complications of 0.5%, 1%, and 5%, respectively,[107] with the majority of deaths occurring in patients with hemodynamic compromise or respiratory failure.

Magnetic Resonance Imaging

Gadolinium-enhanced magnetic resonance angiography (MRA) is also occasionally used to evaluate clinically suspected PE.[108] Earlier studies demonstrated that when MRA was performed under optimal conditions, it appeared to be highly sensitive and specific even for segmental PE compared with pulmonary angiography.[108,109] MRA has several attractive

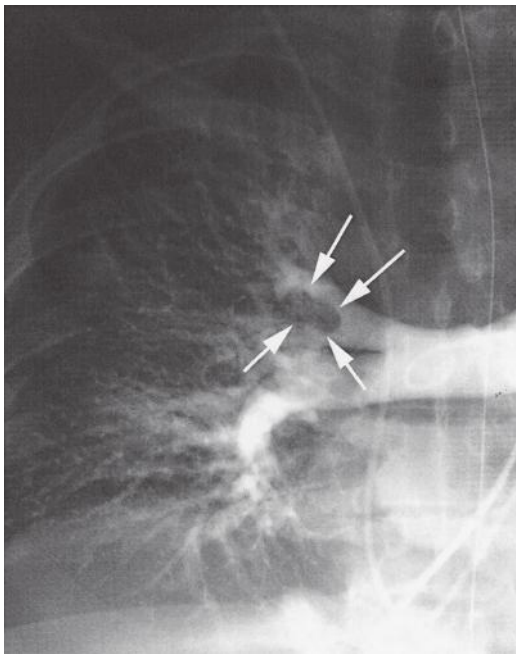


FIGURE 75–3. Selective conventional angiography of the right pulmonary artery in a 67-year-old woman with acute onset of dyspnea and chest pain, an elevated D-dimer enzyme-linked immunosorbent assay level, and an inconclusive ventilation-perfusion scan. The right upper lobe artery is obstructed with visualization of the tail of the embolus in the proximal right upper lobe artery (*arrows*).

advantages over chest CT, including no requirement of ionizing radiation or iodinated contrast agents. Furthermore, magnetic resonance technology also allows detailed assessment of RV size and function, which is potentially important for the risk stratification of PE patients. Large-scale studies have been recently published.[110,111] The results show that MRA, although promising, is not ready for current clinical practice in suspected PE as a result of its low sensitivity, the high proportion of nondiagnostic scans, required scanning time, cost, and low availability in most emergency settings. Notably, the substantially longer time required for image acquisition is an important limitation with current MRA sequences. This is especially relevant in the acute setting when acutely ill patients may not be able to tolerate the imaging protocol.

Echocardiography

Transthoracic echocardiography (Fig. 75–4A-C) has emerged as a potentially important tool for risk assessment and treatment guidance in patients with acute PE. Acute PE may lead to RV pressure overload and dysfunction, which can be detected by echocardiography. Because of the reported negative predictive value of 40% to 50%, a normal result cannot exclude PE.[112,113] On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE and be a result of concomitant cardiac or respiratory disease.[114] The presence of RV dysfunction on a baseline echocardiogram in normotensive patients appears to represent an independent predictor of an adverse outcome or early death.[112,115,116] Patients with severe RV dysfunction may demonstrate McConnell's sign, which is severe hypokinesis of the RV free wall combined with preserved systolic contraction of the RV apex.[117] A disturbed RV ejection pattern ("60/60 sign") consisting of an RV acceleration time ≤ 60 milliseconds in the presence of a tricuspid insufficiency pressure gradient ≤ 60 mm Hg may suggest PE but is not highly sensitive or specific. When combined, the two latter signs were 94% specific and 36% sensitive in diagnosing acute PE even in the presence of pre-existing cardiorespiratory disease.[118]

Approximately 40% of normotensive patients with symptomatic PE have echocardiographic evidence of RV dysfunction. Echocardiography is also useful to diagnose patent foramen ovale in patients with suspected paradoxical embolism, directly visualizing thrombi in the main pulmonary artery (Fig. 75–4D), right heart chambers, and vena cava.[115] In hemodynamically unstable (hypotensive) patients with suspected acute PE, the absence of echocardiographic signs of RV overload or dysfunction significantly reduces the likelihood of acute PE as the cause of the hemodynamic instability.[113] In the latter case, echocardiography may be of further help in the differential diagnosis of the cause of shock, by detecting pericardial tamponade, acute valve dysfunction, severe global or regional LV dysfunction, aortic dissection, or hypovolemia. In a carefully evaluated hemodynamically compromised patient with suspected PE, unequivocal signs of RV pressure overload and dysfunction may justify the consideration of aggressive therapy for PE if immediate CT angiography is not feasible.[119]

IMAGING STUDIES FOR DEEP VENOUS THROMBOSIS

In the majority of cases, PE originates from lower extremity DVT. A number of diagnostic techniques can be used to evaluate patients with suspected DVT. Compression ultrasonography (duplex ultrasonography) is the most commonly used technique. Impedance plethysmography is rarely used now even though number of important clinical trials have been performed using this now-outdated technique. Magnetic resonance imaging (MRI) appears to be very accurate but has not generally been used as a first-line test because of cost and inconvenience. CT venography used alone or in conjunction with CT angiography appears to have a sensitivity and specificity equivalent to that of duplex ultrasonography but exposes the patient to additional radiation. Contrast venography remains the gold standard but is rarely used. Each diagnostic technique has advantages and limitations. Although diagnostic algorithms may be suggested for suspected DVT, these are institution specific, depending on resources and available expertise with certain techniques.

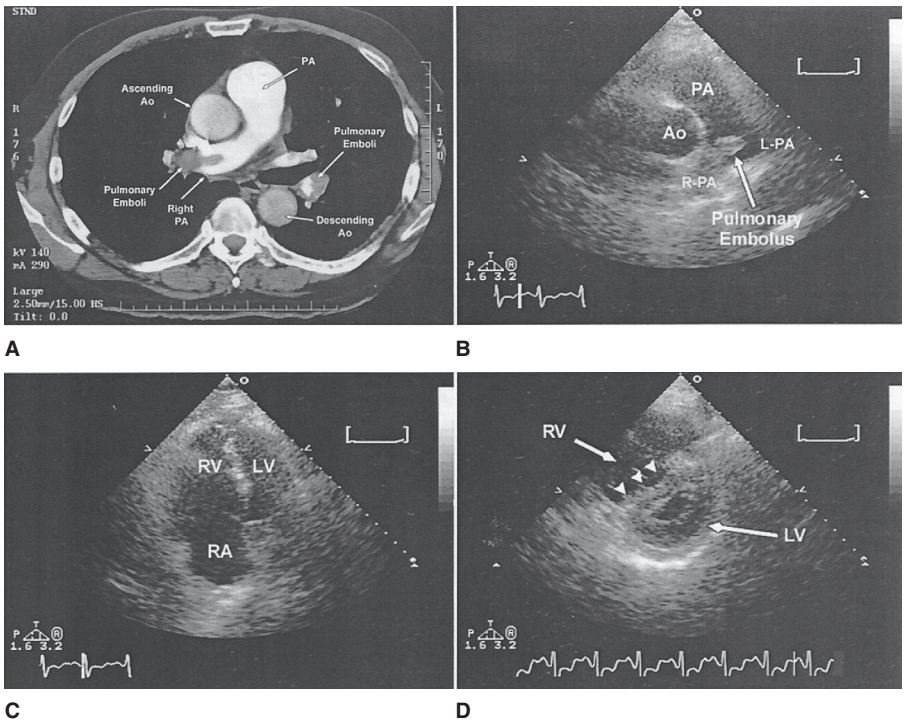


FIGURE 75–4. Chest computed tomography and echocardiographic findings in a 55-year-old man with submassive pulmonary embolism. **A.** Chest computed tomography scan demonstrating multiple segmental emboli, including a central embolus in main pulmonary artery and extending into right pulmonary artery (R-PA). **B.** Transthoracic apical four-chamber view with severe right ventricular (RV) dilatation. **C.** Transthoracic parasternal short-axis view showing flattening of interventricular septum ("D-shaped" left ventricle [LV], *arrowheads*). **D.** Transthoracic short-axis view demonstrating the central clot in the main and R-PAs. Ao, aorta; L-PA, left pulmonary artery; PA, pulmonary artery; RA, right atrium. Reproduced with permission from Garg RK, Bednarz J, Spencer KT, Lang RM. Acute pulmonary embolism. *Circulation*. 2000 Nov 7;102(19):2441-2442.

Ultrasonography

Compression ultrasonography with venous imaging is a portable, accurate, and widely available diagnostic technique for DVT.[120] The primary criterion to diagnose DVT by ultrasonography is the noncompressibility of the vein. Combined with a Doppler reading, this technique is referred to as *duplex ultrasonography*. Ultrasound technology has been further improved by the development of color duplex instrumentation that displays Doppler frequency shifts as color superimposed on the grayscale image. The color duplex images display both mean blood flow *velocity*, expressed as a change in hue or saturation, and *direction* of blood flow, displayed as red or blue. Ultrasound imaging techniques can also identify or suggest the presence of pathology other than DVT such

as Baker cysts, hematomas, lymphadenopathy, arterial aneurysms, superficial thrombophlebitis, and abscesses.[121] The sensitivity and specificity of ultrasonography for symptomatic proximal DVT has been well above 90% in most recent clinical trials.[122-125] However, there are limitations, including lower sensitivity for asymptomatic DVT, operator dependence, the inability to accurately distinguish acute from chronic DVT in symptomatic patients, and the lower sensitivity for calf vein thrombosis. Compared with other technologies, ultrasonography is relatively inexpensive and is the preferred diagnostic modality for symptomatic suspected proximal DVT.

Proven DVT by ultrasonography is strongly suggestive of PE in patients with symptoms suggesting PE, but it is not diagnostic. However, approximately 50% of patients with CT-confirmed embolism have no imaging evidence of residual lower extremity venous thrombosis.[122,123,126] Thus, PE cannot safely be ruled out in patients with suspected PE on the basis of a negative lower extremity duplex ultrasonography. In patients with suspected PE and a negative multidetector-row CT examination of the chest, the addition of duplex ultrasonography appears to only minimally increase diagnostic yield. Recent evidence suggests that multiorgan (lung, heart, and leg vein) ultrasonography might increase the accuracy of clinical pretest probability estimation in patients with suspected PE and may safely reduce the need for MDCT.[127] This strategy seems to be especially helpful for patients with multiorgan ultrasonography negative for PE plus an alternative ultrasonographic diagnosis or a negative D-dimer result.

Contrast Venography

Contrast venography is a costly and invasive procedure that may result in superficial phlebitis or hypersensitivity reactions, but it is generally safe and accurate. Although contrast venography is the gold standard for DVT diagnosis, it is now rarely performed except in clinical trials because of its higher sensitivity in detecting asymptomatic thrombi than duplex ultrasonography.[128] Venography is far more often done during procedures such as insertion of an inferior vena cava (IVC) filter than to simply diagnose suspected DVT.

Impedance Plethysmography

Impedance plethysmography has been used in patients presenting with suspected acute DVT but is rarely obtained in the era of ultrasonography. It measures the change in blood volume in the calf while a thigh cuff is inflated and deflated. Its sensitivity for proximal DVT ranges around 65%. Impedance plethysmography may not detect nonocclusive proximal DVT or occlusive proximal DVT present in parallel venous systems, such as duplicated femoral or popliteal veins, and cannot detect DVT isolated to the calf veins.[120]

Magnetic Resonance Imaging

Magnetic resonance venography (MRV) has clear advantages as a diagnostic test for suspected DVT and appears to be an accurate, noninvasive alternative to venography.[129] A major feature of this technique is excellent resolution of the IVC and pelvic veins.[108] Preliminary experience with MRV suggests that it is at least as accurate as contrast venography or ultrasound imaging and more sensitive than ultrasonography for pelvic vein and calf-limited thrombosis.[129,130] Simultaneous bilateral lower extremity imaging can be accomplished, and MRV appears to accurately distinguish acute from chronic DVT. This technique is also useful in differentiating other entities such as cellulitis or a Baker cyst from acute DVT. As with many other diagnostic techniques, its usefulness depends to a certain degree on the experience of the reader. As is the case with PE diagnosis, required scanning time and expense lessen its utility.

DIAGNOSTIC STRATEGIES

The overall diagnostic approach depends on the hemodynamic presentation of the patient. Although rapid diagnosis and therapeutic intervention are required in patients with shock and suspected massive PE, there is sufficient time to obtain imaging tests in hemodynamically stable patients with suspected PE.

PATIENTS WITH SUSPECTED PULMONARY EMBOLISM AND SHOCK OR HYPOTENSION

In patients with hypotension or cardiogenic shock associated with suspected massive PE, rapid initiation of therapy is potentially lifesaving. The definition of massive PE should be based on hemodynamic considerations (systolic blood pressure < 90 mm Hg or a drop in systolic blood pressure by ≥ 40 mm Hg from baseline) rather than purely anatomic considerations.[12] Irrespective of the degree of vascular obstruction, patients with PE who present with shock have a mortality rate that approaches 30%, but those with cardiopulmonary arrest have a mortality rate that exceeds 70%. Ideally, PE should be proven with imaging whenever possible.

While in patients with suspected massive PE and evidence of severe acute RV dysfunction by echocardiography, thrombolysis or embolectomy may be considered, extreme caution is advised in the absence of a firm diagnosis. Clues to the chronicity of RV dysfunction include a history of chronic rather than acute dyspnea, the presence of RV hypertrophy rather than simple dilation, or estimated pulmonary artery systolic pressures by echocardiography that are greater than approximately 70 mm Hg. A diagnostic algorithm in patients presenting with shock or persistent hypotension is summarized in Fig. 75–5.

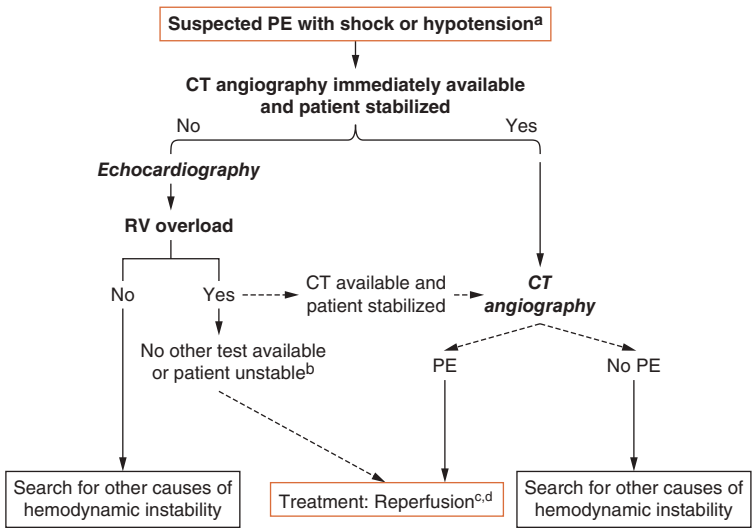


FIGURE 75–5. Diagnostic algorithm for patients with suspected pulmonary embolism (PE) with shock or hypotension. [a]Hypotension defined as systolic blood pressure < 90 mm Hg (or needing vasopressor drugs to maintain a systolic blood pressure ≥ 90 mm Hg) or a systolic pressure drop by ≥ 40 mm Hg, for > 15 minutes, if not caused by new-onset arrhythmia, hypovolemia, or sepsis. [b]If available, consider the possibility of utilizing a portable ventilation-perfusion scan in the setting of hemodynamic instability to confirm diagnosis. [c]Thrombolysis; alternatively catheter-based therapies or surgical embolectomy. CT, computed tomography; RV, right ventricle. [d]If PE is highly suspected in a critically ill patient, and a firm diagnosis cannot be established, empiric aggressive, therapy may be considered. Adapted with permission from Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014 Nov 14;35(43):3033-3069.

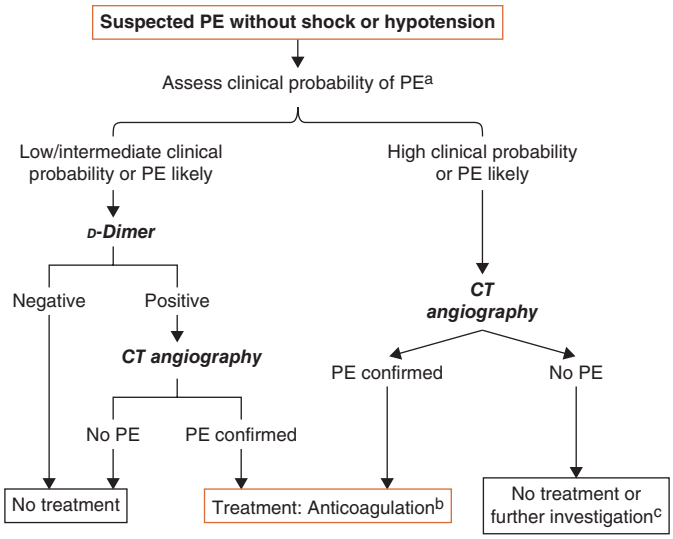


FIGURE 75–6. Diagnostic algorithm for patients with suspected pulmonary embolism (PE) without shock or hypotension. [a]Clinical judgment or prediction rule. [b]Close monitoring for intermediate-/high-risk patients; in case of hemodynamic instability, reperfusion therapy should be considered. [c]In patients with high clinical probability of PE and negative computed tomography (CT) angiography, further testing may be considered as shown in Figure 75–8. Adapted with permission from Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014 Nov 14;35(43):3033-3069.

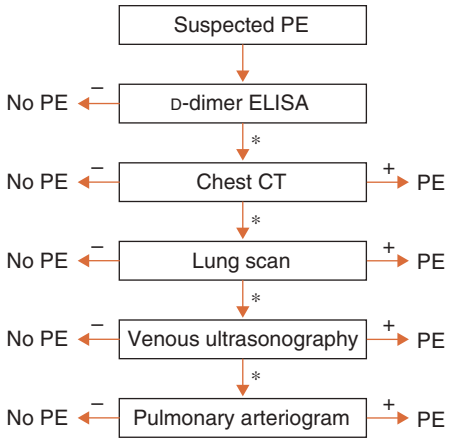


FIGURE 75–7. Diagnostic strategy for patients with suspected pulmonary embolism (PE) without shock or hypotension. In this strategy, chest computed tomography (CT) is used as the principal imaging test. *Further testing should be considered if the test is inconclusive or negative, with a persistent suspicion of PE. ELISA, enzyme-linked immunosorbent assay.

PATIENTS WITH SUSPECTED PULMONARY EMBOLISM WITHOUT SHOCK OR HYPOTENSION

PE cannot be excluded without objective testing. The history, physical examination, and diagnostic studies (eg, chest radiography, ECG, arterial blood gas analysis) can raise or lower the clinical suspicion of PE but are incapable of excluding or confirming it unless a clearly identifiable condition (eg, pneumothorax) is identified to account for the patient's complaints. Noninvasive strategies have been investigated and algorithms constructed that are capable of confirming or excluding the diagnosis of embolism under most circumstances. A diagnostic algorithm in patients presenting with shock or persistent hypotension is summarized in Fig. 75–6. In emergency department patients and other outpatients, the clinical pretest probability for PE should be calculated by implicit assessment or, preferably, through a standardized technique.[70-72,89] PE can be excluded by a highly sensitive D-dimer result below the assay-specific cutoff level except in patients with a high pretest clinical probability. In patients with elevated D-dimer levels or a high clinical probability of embolism, MDCT should be obtained (see Fig. 75–7). In patients with significant impairment of renal function, pregnancy, or allergy to contrast agents, V/Q perfusion scanning is preferred as the primary chest imaging test, particularly when the chest radiograph is normal or near normal. A V/Q scan can also be performed in patients with a nondiagnostic or negative chest CT when the clinical suspicion of PE persists. A normal V/Q is capable of excluding the diagnosis, and a high-probability scan is capable of confirming the diagnosis in patients with a high or intermediate probability of disease. If a high clinical suspicion for PE persists, leg ultrasonography and even pulmonary angiography can be performed (Fig. 75–7). This strategy is safe and requires pulmonary angiography in fewer than 10% of patients.[131] In conclusion, as of 2016, a negative MDCT alone can exclude PE under most circumstances. Although comparative studies of modern-day MDCT with standard pulmonary angiography are lacking, MDCT is recognized as extremely accurate and a stand-alone test, unless the images are suboptimal in quality. When uncertainty remains after a negative MDCT, a V/Q scan can be considered. If both tests are nondiagnostic, a negative lower extremity ultrasound may offer more reassurance. Because many patients with acute PE have no residual DVT, when the MDCT is inconclusive, a negative ultrasound cannot guarantee the absence of PE.

In hospitalized patients, clinical findings suggestive of PE may be more likely to be misleading as a result of comorbid conditions. At present, the safe exclusion of PE in inpatients using a clinical prediction rule and D-dimer result remains to be established. D-Dimer testing may have even less clinical utility in inpatients because of its poor specificity. Furthermore, translation of a standardized clinical prediction rule validated in outpatients to an inpatient population is problematic.

At present, PE can be safely excluded in patients with a low or intermediate probability of PE by a normal, highly sensitive D-dimer assay, a normal or near-normal V/Q scan result, a negative MDCT angiography result, or a negative contrast pulmonary angiography result. In patients with a high probability of PE, the clinical outcome appears to be acceptable after a negative MDCT angiography alone if the quality of the study is adequate. A normal V/Q scan or negative contrast pulmonary angiography is also acceptable. Under this circumstance, clinical judgment must come into play with the risk of possible recurrence balanced against the risk of additional diagnostic procedures.[75,113]

PE can be confirmed in patients with an intermediate or high probability of PE by a high-probability V/Q scan or a positive MDCT angiography result.[113] Finally, the diagnostic utility of "triple rule-out" CT angiography (for coronary artery disease, PE, and aortic dissection) is under debate. This technique has recently shown to be associated with slightly higher yield of PE and aortic dissection, specifically in the emergency department, but comes with higher nondiagnostic image quality, radiation, and contrast doses.[132] The appropriate use of "triple rule-out" CT needs to be further defined.

MANAGEMENT

RISK STRATIFICATION

An important advance in the therapeutic approach to PE has been the development of predictive models capable of stratifying patients by mortality risk. In-hospital mortality associated with PE depends on clinical features at admission and increases significantly when RV dysfunction

TABLE 75–3. Clinical Prediction Rule for 30-Day Mortality (Pulmonary Embolism Severity Index [PESI])[2]

Predictor	Points Assigned
Demographic characteristics	
Age	Age, in years
Male gender	+10
Comorbid illness	
Cancer	+30
Chronic heart failure	+10
Chronic lung disease	+10
Clinical findings	
Pulse rate ≥ 110/min	+20
Systolic blood pressure < 100 mm Hg	+30
Respiratory rate ≥ 30/min	+20
Temperature < 36°C	+20
Altered mental status	+60
Arterial oxygen saturation < 90%	+20

PESI score: ≤65, class I, very low 30-day mortality risk (0-1.6%); 66-85, class II, low mortality risk (1.7-3.5%); 86-105, class III, moderate mortality risk (3.2-7.1%); 106-125, class IV, high mortality risk (4.0-11.4%); >125, class V, very high mortality risk (10.0-24.5%).

Adapted with permission from Konstantinides SV, Torbicki A, Agnelli G, et al: 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014 Nov 14;35(43):3033-3069.[2]

is present. Accurate risk stratification in patients with PE is important in selecting the optimal management strategy for each individual patient and to potentially improve patient outcome. A bedside prediction rule based on 11 simple patient characteristics capable of classifying patients with PE into classes of increasing risk has been devised—the PE Severity Index (PESI) (Table 75–3).[2,133] A simplified version known as sPESI has also been developed and validated (Table 75–4).[134,135]

TABLE 75–4. Clinical Prediction Rule for 30-Day Mortality (Simplified Pulmonary Embolism Severity Index [sPESI])[134]

Predictor	Points Assigned
Demographic characteristics	
Age	+1 (if age > 80 y)
Comorbid illness	
Cancer	+1
Chronic heart failure or lung disease	+1
Clinical findings	
Pulse ≥ 110/min	+1
Systolic blood pressure < 100 mm Hg	+1
Arterial oxygen saturation < 90%	+1

sPESI score: 0 points, low 30-day mortality risk (1%, 95% CI 0 to 2.1%); ≥1 point(s), no low 30-day mortality risk (10.9%, 95% CI 8.5 to 13.2%).

Adapted with permission from Konstantinides SV, Torbicki A, Agnelli G, et al: 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014 Nov 14;35(43):3033-3069.

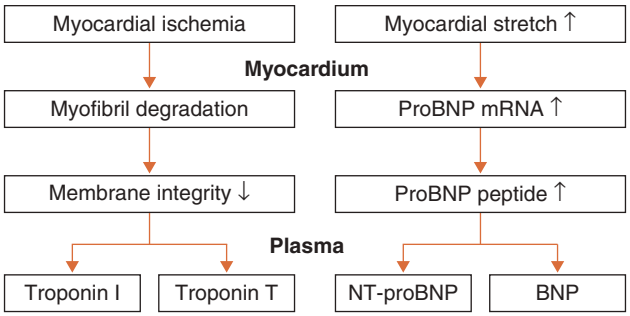


FIGURE 75–8. Mechanism of cardiac biomarker release in patients with acute pulmonary embolism. Right ventricular pressure overload with increased myocardial shear stress is responsible for myocardial synthesis and secretion of natriuretic peptides. Troponin release is a result of myocardial ischemia and microinfarction (see also the discussion under Pathophysiology of Acute Pulmonary Embolism: Hemodynamic Alterations). BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide.

ECHOCARDIOGRAPHY

Transthoracic echocardiography is the most important tool for risk stratification in PE because RV dysfunction on the echocardiogram is a powerful and independent predictor of mortality.[3,136] From a prognostic point of view, echocardiography helps to classify PE into three groups: (1) low-risk PE (no RV dysfunction) with a hospital mortality of less than 4%, (2) submassive PE (RV dysfunction and a preserved systemic arterial pressure) with a hospital mortality of 5% to 10%, and (3) hemodynamically massive PE (RV dysfunction and cardiogenic shock) with a hospital mortality of approximately 30%. A major limitation of echocardiography is its poor discriminative value. Approximately 40% to 50% of patients with symptomatic PE have echocardiographic evidence of RV dysfunction. Additional limitations are its limited availability on a 24-hour, 365 days per year basis and its cost. Another problem is the occasional poor imaging quality of the RV, particularly in obese patients and those with chronic lung disease.

Cardiac Biomarkers

Troponins and natriuretic peptides are similarly accurate in identifying low-risk PE patients (Figs. 75–8 through 75–10).[137] RV pressure overload is associated with increased myocardial stretch, which leads to the release of brain natriuretic peptide (BNP) or N-terminal

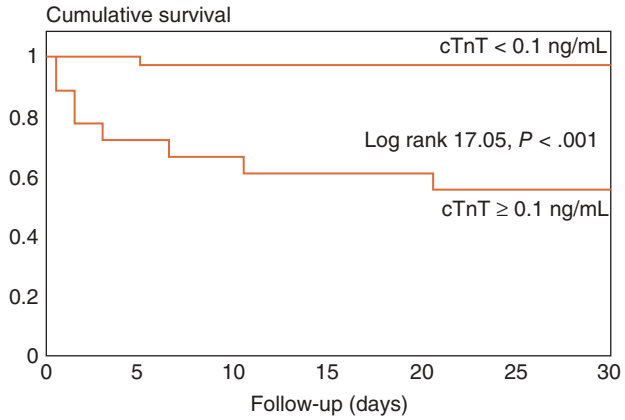


FIGURE 75–9. Cumulative survival rate at 30 days in patients with acute pulmonary embolism according to the level of cardiac troponin T (cTnT). A level above 0.1 ng/mL identifies patients at high risk for adverse clinical outcomes. Reproduced with permission from Giannitsis E, Muller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. *Circulation*. 2000 Jul 11;102(2):211-217.

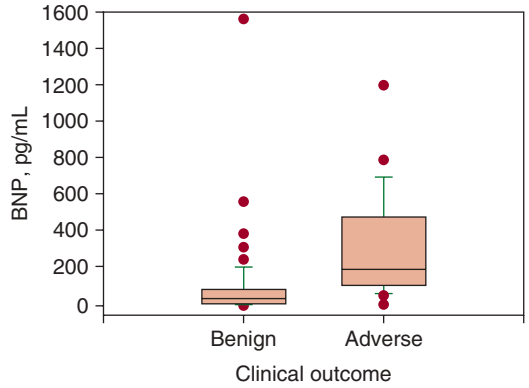


FIGURE 75–10. Brain natriuretic peptide (BNP) levels (median, confidence interval, and outliers) in patients with acute pulmonary embolism according to clinical outcome. Although BNP levels between patients with benign and adverse outcome overlap, the negative predictive value for the absence of adverse outcomes for BNP triage levels below 50 pg/mL was 97%. Data from Kucher N, Printzen G, Doernhoefer T, et al. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. *Circulation*. 2003 Apr 1;107(12):1576-1578.

(NT)-proBNP. Thus, the plasma levels of natriuretic peptides reflect the severity of hemodynamic compromise and RV dysfunction in acute PE.[138] The plasma cutoff values for the identification of elevated risk appear to be around 50 to 100 pg/mL and 500 to 600 pg/mL for BNP[139] and NT-proBNP,[140] respectively. The positive predictive value of elevated BNP or NT-proBNP concentration for early mortality is low. Conversely, low levels can identify patients with a favorable short-term clinical outcome based on their high negative predictive value.[139,141]

Similar findings have been reported with troponins. Thus, elevated plasma troponin concentrations on admission have been shown in connection with PE as associated with poor prognosis. Similarly, the reported positive predictive value of troponin elevation for PE-related early mortality is low, while the negative predictive value of normal levels is high. The cutoff levels for troponins are the lower detection limits for myocardial ischemia reported by the manufacturer. Recently developed high-sensitivity assays have further improved the prognostic performance of this biomarker, particularly with regard to normal values of troponin and the exclusion of patients with an adverse short-term outcome.[142,143]

Computed Tomography

A number of methods have been proposed to quantify the extent of vascular obstruction and RV enlargement/dysfunction by CT scanning. Following a number of early retrospective studies with divergent results,[144] the prognostic value of an enlarged RV on MDCT (RV to LV ratio ≥ 0.9) was confirmed by a prospective multicenter cohort study.[145] In this study, RV enlargement was an independent predictor for an adverse in-hospital outcome, both in the overall population and in hemodynamically stable patients. Interventricular septal bowing on CT has been shown to have the same prognostic value. Additional recent publications have confirmed these findings.[146,147]

At present, both the PE-related risk and the patient's clinical status and comorbidities should be taken into consideration for prediction of early (in-hospital or 30-day) outcome in patients with acute PE. The definition for level of clinical risk (early mortality) and the risk-adjusted therapeutic strategies recommended on the basis of this classification are summarized in Table 75–5. Hemodynamically unstable patients with shock or persistent hypotension should immediately be identified as high-risk patients; they require an emergency diagnosis and, if PE is confirmed, pharmacologic (or alternatively, surgical or interventional) reperfusion therapy.

TABLE 75–5. Classification of Patients With Acute PE According to Early Mortality Risk and Risk-Adjusted Therapeutic Strategies

	Early Mortality Risk			
		Intermediate		
Risk Parameters	High	High	Low	Low
Shock or hypotension	+	–	–	–
PESI class III-IV or sPESI ≥ I	(+)[a]	+	+	–
Signs of RV dysfunction/ enlargement on imaging tests	+	+	(–/+)[b]	(–)[c]
Elevated troponin, BNP or NT-proBNP	(+)[a]	+	(–/+)[b]	(–)[c]
Treatment	Reperfusion	A/C Close monitoring Rescue reperfusion	A/C Hospitalization	A/C Early discharge

Abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RV, right ventricular; sPESI, Simplified Pulmonary Embolism Severity Index; A/C, anticoagulation.

[a]Neither calculation of PESI/sPESI nor assessment of cardiac biomarkers is considered necessary in patients presenting with high-risk mortality PE (with shock or hypotension). If performed, both should be positive, but their assessment should not delay immediate treatment.

[b] Either one or none among signs of RV dysfunction/enlargement and elevated cardiac biomarkers should be positive.

[c]Assessment optional; if assessed, both should be positive. Patients in PESI class I or II or with an sPESI of 0 and elevated cardiac biomarkers or signs of RV dysfunction/enlargement on imaging tests are also to be classified into the intermediate-/low-risk group.

Patients without shock or hypotension are not at high risk of adverse early outcomes, and further risk stratification should be considered after diagnosis of PE has been confirmed, as this may influence the therapeutic strategy and the duration of hospitalization. In these patients, risk assessment should begin with the evaluation of the PESI or sPESI clinical prognostic score to distinguish between intermediate-risk and low-risk patients. Accordingly, normotensive patients in PESI class ≥ III or with an sPESI ≥ 1 are considered as being in the intermediate-risk group. In these patients, further risk assessment should be considered, focusing on the status of the RV (by echocardiography or CT) and cardiac biomarkers level. Patients who display evidence of both RV dysfunction and elevated cardiac biomarker levels (particularly cardiac troponin) should be classified into an intermediate-/high-risk category. These patients should be closely monitored to permit early detection of hemodynamic decompensation and the need of rescue reperfusion therapy.[148] On the other hand, patients in whom the RV is normal on echocardiography or CT and/or in whom cardiac biomarker levels are normal belong to an intermediate-/low-risk group.

Finally, routine performance of imaging or laboratory tests in the presence of PESI class I or II or an sPESI of 0 is not considered

necessary at present since it has not been shown to have therapeutic implications. If performed, available data suggest that patients in PESI class I-II or with an sPESI score of 0, but with elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, should be classified into the intermediate-/low-risk category.[143,149]

SUPPORTIVE MEASURES

When massive PE associated with hypotension or severe hypoxemia is suspected, supportive treatment is immediately initiated. Intravenous (IV) saline can be infused rapidly, but caution is recommended. Excess fluid may result in further RV dilatation, increased RV wall tension, and a decreased cardiac output that may result in RV ischemia.[12] Dopamine and norepinephrine appear to be the favored choices of vasoactive therapy in massive PE and should be administered if the blood pressure is not rapidly restored.[150] Death from massive PE results from RV failure, and dobutamine may augment RV output.[150] A vasopressor, such as norepinephrine, combined with dobutamine might offer optimal results. However, there is a lack of large randomized data evaluating the use of vasopressor/inotropic drugs in the setting of massive PE.

Hypoxemia and hypocapnia are frequently encountered in patients with PE, in most cases of moderate severity, and are usually reversed with administration of oxygen. Mechanical ventilation may be instituted to decrease systemic oxygen demands or manage respiratory failure. Intubation in the setting of a decompensated RV, however, is fraught with risk. Premedications may cause systemic vasodilatation, and positive-pressure ventilation may abruptly reduce preload and cardiac output. Therefore, positive end-expiratory pressure should be applied with caution, and low tidal volumes (approximately 6 mL/kg lean body weight) should be used in an attempt to keep the end-inspiratory plateau pressure < 30 cm H_2O.

ANTICOAGULATION

In patients with acute PE, anticoagulation is recommended with the objective of preventing early death and recurrent VTE. The standard duration of anticoagulation should be at least 3 months. Acute-phase treatment consists of parenteral anticoagulation (unfractionated heparin [UFH], LMWH, or fondaparinux) over the first 5 to 10 days overlapped with a vitamin K antagonist (VKA), or, after 5 days of parenteral therapy, initiation of dabigatran, or edoxaban. A simpler alternative in stable patients is oral anticoagulation initiated immediately with rivaroxaban or apixaban alone instead of the standard parenteral/VKA regimen. Often, parenteral therapy is used for 24 to 48 hours until it is clear that surgery or other invasive procedures are not necessary. Extended anticoagulation beyond the first 3 months, or even indefinitely, may be necessary for secondary prevention, after weighing a patient's risk of recurrence and bleeding. If a VKA is used, it may be initiated as soon as the activated partial thromboplastin time (aPTT) is therapeutic or after the administration of a LMWH. The parenteral agent should be maintained at therapeutic levels for at least 5 days and until a therapeutic international normalized ratio (INR) of 2.0 to 3.0 has been achieved for 2 consecutive days. This initial anticoagulation approach applies to both acute DVT and PE.[151]

Parenteral anticoagulation should be initiated while awaiting the results of diagnostic tests in patients with intermediate or high clinical probability for PE. LMWH or fondaparinux is preferred over UFH for initial anticoagulation in PE, except for patients in whom primary reperfusion is considered and those with creatinine clearance < 30 mL/min or severe obesity, in whom UFH is recommended.

TABLE 75–6. Nomogram for Heparin Therapy in Acute Venous Thromboembolism

aPTT		
Seconds	Times Control	Heparin Dose Adjustment
< 35	< 1.2	80 U/kg bolus, then increase infusion rate by 4 U/kg/h
35-45	1.2-1.5	40 U/kg bolus, then increase infusion rate by 2 U/kg/h
46-70	1.5-2.3	No change
71-90	2.3-3.0	Decrease infusion rate by 2 U/kg/h
> 90	> 3	Stop infusion 1 h, then decrease rate by 3 U/kg/h

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Standard Unfractionated Heparin

Heparin is generally favored when anticoagulation is deemed safe but when the bleeding risk is still potentially higher than usual, and when invasive procedures are definitely or potentially planned. Heparin is cleared within 4 hours of stopping the infusion and is reversible with protamine. When IV UFH is instituted, the aPTT should be aggressively followed at 6-hour intervals until it is consistently in the therapeutic range of 1.5 to 2.0 times control values. Heparin can be administered by several protocols, but a weight-based approach substantially enhances the chances of attaining the therapeutic range quickly. Heparin can be administered as an IV bolus of 5000 U followed by a maintenance dose of at least 30,000 U every 24 hours by continuous infusion.[152] This aggressive approach decreases the risk of subtherapeutic anticoagulation and, although excessive levels are sometimes achieved initially, bleeding complications do not appear to be increased.[152] An alternative regimen consisting of a bolus of 80 U/kg followed by 18 U/kg/h has been recommended.[153] Subsequent adjusting of the heparin dose should also be weight based (Table 75–6).

Low-Molecular-Weight Heparin

LMWHs are commonly used for acute VTE. These agents differ in a number of respects from standard UFH (Tables 75–7 and 75–8). A major advantage of these preparations over UFH is substantially enhanced bioavailability, and thus, they are more predictable than standard UFH.

TABLE 75–7. A Comparison of Low-Molecular-Weight Heparin with Unfractionated Heparin

Characteristic	UFH	LMWH
Mean molecular weight	12,000-15,000	4000-6000
Protein binding	Substantial	Minimal
Anti-Xa activity	Substantial	Substantial
Anti-IIa activity	Substantial	Minimal
Platelet inhibition	Substantial	Minimal
Vascular permeability	Moderate	None
Microvascular permeability	Substantial	Minimal
Elimination (predominant)	Hepatic/macrophages	Renal

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

TABLE 75–8. Potential Advantages of Low-Molecular-Weight Heparins Over Unfractionated Heparin

Efficacy: Comparable or superior[a]
Safety: Comparable or superior[b]
Bioavailability: Superior
Subcutaneous administration
Once- or twice-daily dosing
No laboratory monitoring[c]
Less phlebotomy
Earlier ambulation
Home therapy in certain patient subsets

[a]Based on objectively documented recurrence rates in clinical trials.

[b]Based on rates of major and minor bleeding in clinical trials.

[c]In certain patient populations (significant obesity, renal insufficiency), monitoring is suggested.

TABLE 75–9. Doses of Low-Molecular-Weight Heparin and Fondaparinux for Prevention and Treatment of Venous Thromboembolism

Compound	Prevention	Treatment
Enoxaparin	30 mg bid, 40 mg qd	1 mg/kg bid, 1.5 mg/kg qd
Dalteparin	2500-5000 IU qd	100 IU/kg bid, 200 IU/kg qd
Tinzaparin	75 IU/kg qd	175 IU/kg qd
Nadroparin	41-62 IU/kg qd	86 IU/kg bid, 171 IU/kg qd
Fondaparinux	2.5 mg qd	< 50 kg: 5 mg qd 50-100 kg: 7.5 mg qd > 100 kg: 10 mg qd

Abbreviations: bid, twice a day; qd, once a day.

Numerous clinical trials have demonstrated the efficacy and safety of LMWHs for the treatment of patients with acute proximal DVT, using recurrent symptomatic VTE as the primary outcome measure.[154] Treatment with LMWHs is more convenient for the patient and the nursing staff. A continuous IV line is not required because these agents can be administered once or twice per day subcutaneously at fixed therapeutic doses, usually without laboratory monitoring.

In certain settings, therapy can be monitored by measuring anti-Xa levels.[155] Prophylactic doses of LMWH usually result in anti-Xa levels of 0.1 to 0.3 U/mL. The therapeutic target peak anti-Xa level drawn 4 hours after administration should be in the range of 0.6 to 1 IU/mL for twice-daily administration and 1 to 2 IU/mL for once-daily administration. The peak anti-Xa level is useful for monitoring heparin therapy under the following circumstances: (1) a baseline elevated aPTT because of antiphospholipid antibodies or other circulating anticoagulants in patients being treated with UFH, (2) extremes of body weight (< 40 kg and ≥ 150 kg), (3) renal failure or insufficiency (creatinine clearance < 30 mL/min), (4) pregnancy, and (5) the occurrence of an unexpected bleeding or clotting event during therapy.[155]

Unlike regimens for prophylaxis, in which a fixed dose of LMWH is used, a weight-based dosing regimen is used for the treatment of patients with established VTE. In addition to being more convenient, the LMWH preparations appear to be cost effective, particularly when outpatient therapy is used. Table 75–9 lists some of the different LMWH products and their prophylaxis and treatment regimens. The advent of newer oral anticoagulants has reduced the use of LMWH preparations.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor Xa. It is approved by the US Food and Drug Administration (FDA) and in Europe for the initial treatment of VTE, including PE. In hemodynamically stable patients with acute symptomatic PE, fondaparinux is as safe and effective as IV UFH.[156] Fondaparinux is administered subcutaneously on a once-daily basis in fixed doses of 5 mg for patients weighing less than 50 kg, 7.5 mg for those weighing 50 to 100 kg, and 10 mg for those weighing greater than 100 kg. Like LMWH, fondaparinux is administered in a fixed dose and does not require dose adjustment with laboratory coagulation tests. Also like the LMWHs, fondaparinux is cleared via the renal route and is contraindicated in patients with severe renal disease (creatinine clearance < 30 mL/min). In patients with creatinine clearance of 30 to 50 mL/min, the dose should be reduced by 50%.[151] In contrast to heparin compounds, fondaparinux does not cause heparin-induced thrombocytopenia (HIT).

Complications of Heparin

Heparin-Induced Thrombocytopenia HIT typically develops 5 or more days after the initiation of heparin therapy and occurs in 5% to 10% of patients.[157] If a patient is placed on heparin for VTE and the platelet count progressively decreases either by 50% or to 100,000/μL or less, heparin therapy should be discontinued and another agent initiated. Although the risk of HIT appears to be lower with LMWH, it is important for clinicians to realize that HIT can occur with the use of either form of heparin.[157]

Prolonged administration of UFH may cause asymptomatic osteopenia, osteoporosis, and (rarely) pathologic bone fractures. After discontinuation of heparin, bone metabolism by densitometry usually improves within 1 year. Epidural catheter placement should be delayed for at least 12 hours after LMWH injection, because of the risk of epidural or spinal hematoma, which can cause permanent paraplegia. LMWH should be delayed for at least 2 hours after epidural catheter removal.

Vitamin K Antagonists

VKA therapy should be initiated with concomitant UFH or LMWH; otherwise, the first few days of VKA administration may lead to a prothrombotic state because of rapid depletion of anticoagulant proteins C and S. The procoagulant effect of VKA can be prevented by overlapping heparin with warfarin for at least 5 days.

Warfarin can be started at a dose of 10 mg for 2 days, with monitoring performed daily, in younger (eg, 60 years of age), otherwise healthy outpatients.[151] A dose of 5 mg is recommended for older patients (> 60 years of age) and in those who are hospitalized, debilitated, or malnourished.[151,158] A standardized nomogram has been developed and can be used to make dose adjustments based on INR values obtained on days 3 and 5.[158] A small percentage of patients have extremely low daily warfarin dose requirements of 1 to 2 mg, with an increased bleeding risk because of *CYP2C9* and *VKORC1* variant alleles.[159] At present, however, data indicate that pharmacogenetic-based dosing, used on top of clinical parameters, does not improve the quality of anticoagulation (more effective and/or less risky than empiric, clinically based dosing).[160-162]

In selected patients, self-management of VKA therapy using INR measurement with point-of-care devices may be effective and safe.[163]

Adverse Effects of Vitamin K Antagonists VKAs have a narrow therapeutic window, and the risk of bleeding increases with increasing INR. A large retrospective survey of more than 42,000 patients who were taking VKAs suggested that an INR of 2.2 to 2.3 has the highest benefit-to-risk ratio.[164] In this study, a two-fold increase in the hazard of mortality per unit INR elevation greater than 2.5 was observed. Risk factors for VKA-related bleeding include hepatic disease, renal dysfunction, alcoholism, drug interactions, trauma, cancer, and a history of gastrointestinal bleeding. The risk of bleeding is greatest in the first month after initiation of anticoagulation.[165]

Depending on the extent and site, patients with major bleeding can routinely be treated with fresh-frozen plasma or prothrombin complex concentrates. Although vitamin K should be administered, it can take many hours to take effect. In patients with excessive INR values without bleeding, withholding one or two doses of warfarin with elective administration of oral vitamin K 2.5 mg is an effective strategy.

Rare complications of VKAs are skin necrosis and cholesterol microembolization, causing the "purple toes" syndrome by enhancing crystal release from ulcerated plaques.[166]

Reliable contraception and patient education are mandatory in women of childbearing potential because VKAs are teratogenic, particularly during weeks 6 to 12 of gestation.[45]

Direct-Acting Oral Anticoagulants

The latest generation of oral anticoagulants was initially called novel oral anticoagulants, or NOACs. However, an Institute for Safe Medication Practices safety alert noted that "NOAC" had been interpreted as "no anticoagulation" and thus designated "NOAC" a potentially dangerous abbreviation, discouraging its use. The acronym DOAC, for direct-acting oral anticoagulant, provides a reasonably short, easily pronounced, accurately descriptive abbreviation that distinguishes the class from warfarin, which acts indirectly. This has also been advocated by the International Society of Thrombosis and Haemostasis. Several phase III clinical trials on the acute-phase treatment and duration of anticoagulation after VTE (DVT or PE) with DOACs have been recently published.[167-172] The overall results of these trials indicate that these agents are noninferior (in terms of efficacy) and possibly safer (particularly in terms of major bleeding) than the standard parenteral/VKA regimen.[173] Although experience with DOACs is still limited, at present, they can be viewed as an alternative to standard treatment. Four DOACs have been approved for the treatment of VTE in United States and Europe: rivaroxaban, dabigatran, apixaban, and edoxaban. Rivaroxaban and apixaban allow for single-drug therapy, eliminating the need for initial parenteral anticoagulation, whereas dabigatran and edoxaban are initiated after a short course of parenteral anticoagulation regimen. Practical recommendations for their dosing and for the handling of their bleeding complications are summarized in Table 75–10. Importantly, some reversal agents for DOACs are under investigation. Recent data suggest that the monoclonal antibody idarucizumab, which binds dabigatran, is effective in emergency situations, and it is now FDA approved[174]; however, phase III clinical trials are currently ongoing with other compounds that may serve as universal antidotes for a broad range of oral factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban).[175] Andexanet is likely to be approved in the near future for Xa inhibitor reversal.[176]

New Anticoagulation Strategies

Recent preclinical and preliminary clinical data suggest that reduction of factor XI levels might be a promising strategy to achieve effective thrombosis prevention and/or treatment without significant increase in the risk of bleeding.[177,178] These results need confirmation in larger trials for further prophylactic or therapeutic indications of this new target.

THROMBOLYTIC THERAPY

Systemic Thrombolysis

Thrombolytic therapy of acute PE restores pulmonary perfusion more rapidly than anticoagulation alone, leading to a prompt reduction in pulmonary vascular resistance and a concomitant improvement in RV function.[179,180] Thrombolytic therapy seems to reduce total mortality, PE recurrence, and PE-related mortality in patients with acute PE, particularly in hemodynamically unstable patients or patients with massive PE. However, it has not been clearly proven that these agents decrease overall mortality in hemodynamically stable patients with acute PE.[181,182]

FDA- and European-approved thrombolytic agents include recombinant tissue plasminogen activator (rtPA), streptokinase, and urokinase. Table 75–11 presents thrombolytic regimens for the treatment of PE. Accelerated regimens administered over 2 hours with rtPA are preferable to prolonged infusions of first-generation thrombolytic agents over 12 to 24 hours. Thrombolytic therapy is associated with an increase in major and fatal or intracranial hemorrhage.[181] Primary contraindications for thrombolytic therapy include medical conditions that increase the possible risk of bleeding complications, such as recent bleeding, surgery, stroke, or gastrointestinal hemorrhage. Table 75–12 lists the contraindications to thrombolysis in PE.[151] Most contraindications to thrombolysis should be considered relative in patients with life-threatening PE. In these cases, an alternative approach may consist of local, catheter-delivered therapy, using reduced doses of a thrombolytic agent (rtPA).

Heparin should be withheld until the thrombolytic infusion is completed if streptokinase or urokinase is used; it can be continued during rtPA infusion. The aPTT is then determined, and heparin is initiated without a loading dose if this value is less than twice the upper limit of normal. If the aPTT exceeds this value, the test is repeated every 4 hours until it is safe to proceed with heparin. Given the bleeding risk associated with thrombolysis, it appears reasonable to continue with anticoagulation with UFH for several hours after the end of thrombolytic therapy before switching to LMWH or fondaparinux. In patients receiving LMWH or fondaparinux at the time thrombolysis is initiated, infusion of UFH should be delayed until 12 hours after the last LMWH injection (if given twice daily) or until 24 hours after the last LMWH or fondaparinux injection (given once daily).

In the absence of hemodynamic compromise, the clinical benefits of thrombolysis have remained controversial for many years. Recent evidence suggests that hemodynamically stable patients with evidence of RV enlargement/dysfunction and elevated troponins and no contraindications may benefit from thrombolytic therapy,[116,148,183] but potentially at a cost of higher rates of major hemorrhage.[148] Some of these trials used tenecteplase as the thrombolytic agent,[148,183] which is not approved yet for the treatment of PE. Accordingly, systemic thrombolysis is not routinely recommended as primary treatment for patients with intermediate-/high-risk or submassive PE, but should be considered if clinical signs of hemodynamic decompensation appear. The efficacy of reduced-dose systemic fibrinolysis has been recently explored in small trials with preliminary modest positive results[184,185]; however, the 50-mg dose of IV tissue plasminogen activator is not FDA approved for use. Therefore, if anticipated bleeding risk under systemic thrombolysis is high in these cases, surgical pulmonary embolectomy or percutaneous catheter-directed treatment should be considered.

TABLE 75–10. Direct-Acting Oral Anticoagulants (DOACs) for the Treatment and Secondary Prevention of Venous Thromboembolism

Compound	Dosage		Contraindicated or Caution	Handling of Bleeding Complications (common for all DOACs)
	Initial Phase	Long-Term Phase		
Dabigatran exilate	Parenteral anticoagulation for 5-10 days before initiation	150 mg bid 110 mg bid[a]	CrCl < 30 mL/min Concomitant treatment with P-glycoprotein inhibitors/inducers	Supportive measures (local hemostatic, fluid replacement, and RBC substitution if necessary) Platelet substitution (in case of thrombocytopenia ≤ 60×10^9/L or thrombopathy) FFP as plasma expander (not useful as reversal agent) Tranexamic acid In case of *life-threatening bleeding*: PCC 25 U/kg; activated PCC 50 U/kg; activated factor VII (90 µg/kg); idarucizumab (5 g, only if dabigatran-related bleeding)
Edoxaban	Parenteral anticoagulation for 5-10 days before initiation	60 mg qd 30 mg qd[b]	CrCl < 15 mL/min Moderate/severe hepatic impairment Concomitant treatment with rifampin	
Rivaroxaban	15 mg bid for 21 days	20 mg qd	CrCl < 30 mL/min Moderate/severe hepatic impairment Concomitant treatment with P-glycoprotein and strong CYP3A4 inhibitors/inducers	
Apixaban	10 mg bid for 7 days	5 mg bid	CrCl < 15 mL/min Severe hepatic impairment Concomitant treatment with strong dual inhibitors or inducers of P-glycoprotein/CYP3A4	

Note. Apart from the specific conditions listed above, all DOACs are contraindicated in patients: (1) expected to be treated with thrombolysis or embolectomy; (2) receiving concomitant treatment with another anticoagulant; (3) requiring dialysis; (4) with active bleeding or at very high risk of bleeding; and (5) who are pregnant or breast-feeding. In general, all DOACs should be administered with caution in patients with an increased risk of bleeding, including those receiving concomitant treatment with nonsteroidal anti-inflammatory drugs and antiplatelet agents. A full updated list of drug interactions and tables of inducers and inhibitors of P-glycoprotein and CYP can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency.

Abbreviations: bid, twice a day; CrCl, creatinine clearance; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; qd, once a day; RBC, red blood cells.

[a]Dabigatran 110 mg bid may be considered in elderly patients (≥ 80 years); those receiving concomitant treatment with moderate P-glycoprotein inhibitors (ie, amiodarone, verapamil, quinidine); those at higher risk of bleeding; or those with CrCl 30 to 50 mL/min.

[b]Edoxaban 30 mg qd may be considered in patients with at least one of the following factors: CrCl 15 to 50 mL/min; concomitant use with strong P-glycoprotein inhibitors; or body weight ≤ 60 kg.

Adapted with permission from Konstantinides SV, Barco S, Lankeit M, et al: Management of Pulmonary Embolism: An Update. *J Am Coll Cardiol*. 2016 Mar 1;67(8):976-990.

TABLE 75–11. Regimens for Systemic Thrombolytic Therapy in Pulmonary Embolism

Lytic Agent	Dose Regimen
Streptokinase	Loading dose: 250,000 IU IV
	Continuous infusion: 100,000 U/h for 24 h
Urokinase	Loading dose: 4400 IU/kg IV over 10 min
	Continuous infusion: 4400 IU/kg/h for 12-24 h
Alteplase (rtPA)	Loading dose: None
	Continuous infusion: 100 mg over 2 h

Abbreviations: IV, intravenous; rtPA, recombinant tissue plasminogen activator.

CATHETER-BASED THERAPIES

Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed, if appropriate expertise and resources are available on site.[186-188] Interventional options include the following: thrombus fragmentation with a pigtail or balloon catheter; rheolytic thrombectomy with hydrodynamic catheter devices; suction thrombectomy with aspiration catheters; and rotational thrombectomy. If the bleeding risk is not exceedingly high, catheter fragmentation/embolectomy may be combined with local thrombolysis. Recent small studies suggest that a catheter-directed ultrasound-assisted delivery of a reduced dose of rtPA may be beneficial and safe when compared to heparin alone in patients with PE at intermediate/high and high risk.[187,189-192] Most of the devices appear to be effective, safe, and potentially lifesaving in the presence of large "fresh" clots. However, none of the devices has been investigated in a large controlled trial, and all commercially available devices have important limitations.[193]

TABLE 75–12. Absolute and Relative Contraindications to Thrombolysis in Pulmonary Embolism

Absolute contraindications
Hemorrhagic stroke or stroke of unknown origin at any time
Ischemic stroke in preceding 6 months
CNS damage or neoplasm
Recent major trauma, surgery, or head injury (within preceding 3 weeks)
GI bleed within the past month
Known bleeding
Relative contraindications
Transient ischemic attacks in the preceding 6 mo
Oral anticoagulant therapy
Pregnancy or within 1 wk postpartum
Noncompressible punctures
Traumatic resuscitation
Refractory hypertension (systolic blood pressure ≥ 180 mm Hg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer

Abbreviations: CNS, central nervous system; GI, gastrointestinal.

SURGICAL EMBOLECTOMY

Urgent surgical embolectomy should be considered in patients with hemodynamically massive PE or right-heart thrombus who have an absolute contraindication to anticoagulant or thrombolytic therapy; in patients with impending paradoxical embolism; and in patients in whom aggressive medical therapy, including the use of thrombolysis, has proven ineffective. Aortic cross-clamping and cardioplegic cardiac arrest should be avoided.[194] Current mortality rates with a rapid multidisciplinary approach, including the use of peripheral extracorporeal membrane oxigenators,[195] and individualized indications before hemodynamic collapse have been reported to be less than 10%.[196,197] Preoperative thrombolysis increases the risk of bleeding, but it is not an absolute contraindication to surgical embolectomy.

VENA CAVA FILTERS

Routine use of vena cava filters in patients with PE is not recommended. The essential indications for filter placement include contraindications to anticoagulation, recurrent embolism while on adequate therapy, and significant bleeding complications during anticoagulation in the acute phase.[151]

Although IVC filters can be potentially lifesaving by preventing early recurrence of PE, patients with filters may be at higher mid- and long-term risk for recurrent VTE but appear to be at lower risk of PE-related death.[198]

Consequently, anticoagulation is generally continued when a filter is placed unless it is contraindicated. These devices can be inserted via the jugular or femoral vein and are usually placed in the infrarenal portion of the IVC. Complications associated with IVC filters are common, although rarely fatal.[199,200] Possible mechanisms of IVC filter failure include filter migration; improper filter positioning, allowing thrombi to bypass the filter; and formation of thrombosis proximal to the filter or on the proximal tip of the filter with subsequent embolization. Rare complications include clinically significant perforation of the IVC, migration to the heart, and displacement of the filter during insertion. Occasionally, these devices may erode into the wall of the IVC. In some cases, IVC obstruction caused by thrombosis at the filter site may occur. The use of temporary filters can obviate the problems associated with permanent filter insertion. Depending on the filter type, retrievable filters can be removed within weeks to months of placement or can remain permanently if necessary because of a trapped large thrombus or a persistent contraindication to anticoagulation. However, when nonpermanent IVC filters are used, it is recommended that they be removed within the first few months after placement. Although some studies have suggested that IVC filters may be associated with significantly lower rates of mortality in patients with PE who were hemodynamically unstable whether or not they were treated with fibrinolysis,[201,202] several recent studies have investigated the use of retrievable filters with no convincing data.[198,203] Therefore, the use of cava filters beyond the indications listed above is not supported by evidence at present and is a matter of great controversy.[204,205]

Finally, in the meta-analysis by Becattini and colleagues, concomitant/residual DVT had a significant association with 30-day all-cause mortality in all patients.[206] Thus, although IVC filter placement has not yet been proven to improve mortality in this setting, some clinicians feel that placement of an IVC filter in patients with extensive residual DVT is justified. The clot burden in the legs and in the lungs, together with the overall stability of the patient, may help clinicians to make this decision.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

A small percentage of patients with acute PE progress to CTEPH.[207] Estimates of the incidence of CTEPH range from 0.5% to 3.8% after an initial episode of embolism and 13.4% after recurrent episodes of PE, with an estimated incidence of five individuals per million population per year.[207,208] Approximately 30% of patients who develop CTEPH have no documented history of acute DVT or PE, and this feature greatly impedes the diagnosis. Anticardiolipin antibodies or a lupus anticoagulant has been detected in approximately 10% of patients, and elevated factor VIII levels have been detected in 40%.[209] Apart from major pulmonary vascular obstruction, the pathophysiology of CTEPH includes pulmonary microvascular disease, pulmonary vascular remodeling, immune phenomena, and inflammation.[210]

The median age of patients at diagnosis of CTEPH is 63 years, and both genders are equally affected.[211] Clinical symptoms and signs are nonspecific or absent in early CTEPH, with signs of right heart failure only becoming evident in advanced disease. As in other forms of pulmonary hypertension (PH), progressive exertional dyspnea and exercise intolerance are characteristic. Later in the course of the disease, exertional chest pain, presyncope, or syncope may occur. Diagnostic delay, particularly in the absence of a history of acute VTE, occurs commonly.[211]

The chest radiograph usually reveals RV enlargement and enlarged main pulmonary arteries. ECG changes are consistent with RV hypertrophy. Arterial blood gases generally reveal hypoxemia with a widened alveolar-arterial difference, although some patients may demonstrate only exercise-induced hypoxemia. Echocardiography documents the presence of PH, as well as RV hypertrophy.

V/Q lung scanning represents a simple, noninvasive means of differentiating disorders of the peripheral pulmonary vascular bed from those of the central vascular bed and remains the first-line imaging modality for patients with PH being evaluated for CTEPH since

V/Q lung scanning has been shown to have superior sensitivity compared with CT imaging for the diagnosis of CTEPH.[212,213] In chronic thromboembolic disease, at least one segmental or larger mismatched perfusion defect is present. For CTEPH to occur, however, there are generally more extensive perfusion abnormalities. In disorders of the distal pulmonary vascular bed, perfusion scans either are normal or exhibit a "mottled" appearance characterized by subsegmental defects. Mismatched segmental or larger defects in patients with PH may also arise from other processes that result in obstruction of the central pulmonary arteries or veins, such as pulmonary artery sarcoma, large-vessel pulmonary vasculitides, extrinsic vascular compression by mediastinal adenopathy or fibrosis, and pulmonary veno-occlusive disease.[214] MDCT angiography has become an established imaging technique for CTEPH after an intermediate- or high-probability V/Q scan. A variety of CT abnormalities have been described in patients with chronic thromboembolic disease, including right-sided cardiac enlargement, enlargement of the pulmonary arteries, a mosaic perfusion pattern, intraluminal thrombi, webs/bands, poststenotic pulmonary artery dilation ("pouch defects"), subpleural densities, and dilated bronchial arteries.[215] Right-heart catheterization is an essential diagnostic tool since it provides important diagnostic and prognostic information. Finally, contrast pulmonary arteriography can be performed to establish the diagnosis with certainty and to determine operability. The angiographic findings in CTEPH are distinct from those encountered in acute embolism and considerable experience is required for accurate angiographic interpretation (Fig. 75–11).

Thus, the diagnosis of CTEPH is based on following findings obtained after at least 3 months of anticoagulation in order to discriminate this condition from subacute PE: mean pulmonary arterial pressure ≥ 25 mm Hg with pulmonary arterial wedge pressure ≤ 15 mm Hg plus at least one segmental or large-sized defect detected by V/Q or MDCT scan.

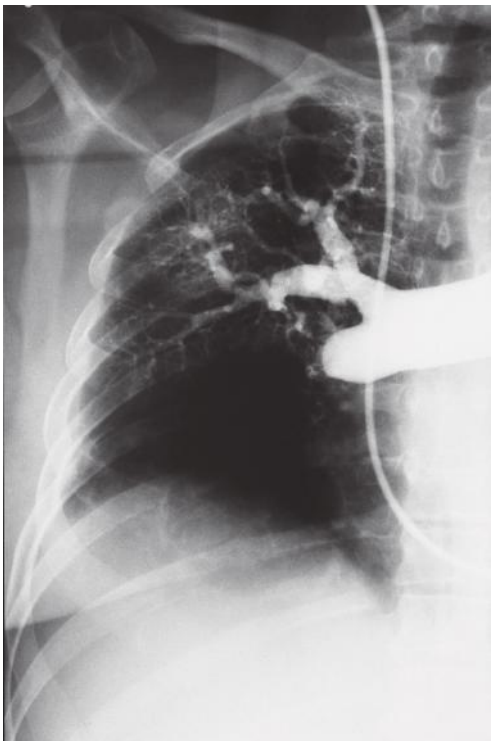

FIGURE 75–11. Representative right-sided pulmonary angiogram in a patient with chronic thromboembolic pulmonary hypertension demonstrating classic "pouch" defect with absent flow to the right middle and lower lobes.

Pulmonary endarterectomy is the treatment of choice for CTEPH. General criteria for the operability of patients include New York Heart Association functional class II to IV and the surgical accessibility of thrombi up to the segmental level. There is no particular age, pulmonary vascular resistance, or RV dysfunction thresholds that absolutely preclude pulmonary endarterectomy because patients who do not undergo surgery or suffer from persistent residual pulmonary hypertension after surgery face a very poor prognosis. However, all these parameters constitute important prognostic factors after surgery. Pulmonary endarterectomy is performed via median sternotomy on cardiopulmonary bypass with periods of deep hypothermic circulatory arrest and is technically quite distinct from pulmonary embolectomy for acute embolic disease. The procedure is a true endarterectomy, which requires careful dissection of chronic endothelialized material from the native intima to restore pulmonary arterial patency (Fig. 75–12). The use of pulmonary balloon angioplasty has been explore in selected patients with inoperable CTEPH or rescue therapy after surgery, with promising results but at the cost of potentially periprocedural complications.[214,216-218] However, this has not been investigated in large controlled trials.

Optimal medical treatment for CTEPH consists of anticoagulants, diuretics, and oxygen. Lifelong anticoagulation is recommended, even after pulmonary endarterectomy. Riociguat, a soluble oral stimulator of guanylate cyclase, has been approved by the FDA for symptomatic patients who have been classified as having inoperable CTEPH by an experienced group/center or have persistent/recurrent CTEPH after surgical treatment.[207,219] The temptation to use riociguat or other drugs approved for pulmonary arterial hypertension, as a therapeutic bridge to endarterectomy in patients considered to be at high risk as a result of poor hemodynamics, should be resisted, except in advanced cases in whom endarterectomy cannot be done or is substantially delayed. It is worthwhile reiterating that pulmonary endarterectomy remains the first-line intervention for CTEPH. At present, the hemodynamic and symptomatic benefits to be accrued from medical therapy, although often positive, are modest compared with those resulting from surgery.

FIGURE 75–12. Example of chronic thromboembolic material obtained from the right pulmonary artery at the time of pulmonary thromboendarterectomy. Note the chronic fibrotic material that must be meticulously dissected from the native intima to achieve an optimal outcome.

PREVENTION OF VENOUS THROMBOEMBOLISM

BACKGROUND

Prophylaxis for DVT is effective. Evidence-based clinical guidelines for the prevention of thromboembolism in a wide range of patient populations have been published by the American College of Chest Physicians.[220-222]

A substantial reduction in the incidence of DVT can be accomplished when individuals at risk receive appropriate preventive care; however, such measures have historically been grossly underused. A recent review confirmed that prophylaxis can be administered safely, with major bleeding complications occurring in only 0.2% of surgical patients.[223] Several risk assessment models have been proposed to estimate VTE risk in hospitalized medical patients, such as the Padua Prediction Score,[224] among others.[225] Despite some shared limitations of these risks models (small number of events, suboptimal validation), they may provide some basis for judging such a hospitalized patient's risk.

Prophylaxis can be pharmacologic or nonpharmacologic. Pharmacologic prophylaxis options include low-dose UFH, LMWH, fondaparinux, warfarin, and new oral anticoagulants.[220-222] LMWHs are increasingly used in clinical practice for both the prevention and treatment of established VTE. The LMWH preparations are advantageous in that they have a more predictable dose-response relationship and are administered subcutaneously only once or twice daily (without monitoring), depending on the preparation (see Table 75–9). Aspirin has a slight benefit but not enough to be used alone as a standard therapy to prevent VTE.[226] Early ambulation whenever possible is always recommended in postoperative patients.

GENERAL MEDICAL PATIENTS

Prophylactic measures to prevent VTE are not widely implemented among patients with medical illnesses. In the DVT FREE Registry of 5451 DVT patients, 59% of those who did not receive prophylaxis were medical patients.[16] Recent trials have demonstrated that medical patients have a thrombosis risk equivalent to that of moderate-risk surgical patients and that the use of prophylaxis can significantly reduce the rate of VTE events with an acceptable rate of bleeding.[227,228]

Patients should be stratified according to DVT risk, and certain prophylactic measures are more appropriate for some patients than for others. The intensity of a prophylactic regimen should take into account the relative risk for thrombosis. Generally, low-dose anticoagulation with standard UFH, LMWH, or fondaparinux is indicated in medical patients who are deemed to be at risk for DVT. In patients requiring prophylaxis who are bleeding or are at high risk of major bleeding, mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression can be used. Hospitalized patients with cancer are at high risk for VTE, and prophylaxis in this population should follow the recommendations outlined for medical patients.[222] In outpatients with cancer and no additional risk factors for VTE, routine thromboprophylaxis is not recommended. Anticoagulation together with graduated compression stockings or intermittent pneumatic compression is appropriate in patients who are deemed to be at exceptionally high risk and for those who have multiple risk factors for DVT. Extensive evidence-based recommendations for prevention of VTE in general medical patients (including hospitalized medical patients, outpatients with cancer, the chronically immobilized, long-distance travelers, and those with asymptomatic thrombophilia) can be found elsewhere.[222]

GENERAL SURGICAL PATIENTS

In general surgical patients, a number of prophylactic strategies have been used.[220,221] Approximately one-third of the 150,000 to 200,000 VTE-related deaths per year in the United States occur following surgery.[229,230] The high incidence of postoperative VTE and the availability of effective methods of prevention mandate that thromboprophylaxis be considered in every surgical patient. Thus, an overview of the results of randomized trials in surgical patients demonstrated the substantial benefit of DVT prophylaxis.[220,221] For patients undergoing minor operations who are younger than age 40 and who have no additional risk factors for DVT, no prophylaxis other than early ambulation is recommended. Older patients who are undergoing major operations without additional risk factors should receive standard low-dose UFH twice daily or three times daily, LMWH, fondaparinux, or intermittent pneumatic compression. For patients with a high risk of bleeding, mechanical prophylaxis in the form of graduated compression stockings or intermittent pneumatic compression should be substituted for pharmacologic prophylaxis. Extensive evidence-based recommendations for prevention of VTE in general nonorthopedic surgical patients can be found elsewhere.[221]

OTHER HIGH-RISK PATIENTS

Total hip arthroplasty and total knee arthroplasty are performed with increasing frequency. The risk for VTE in major orthopedic surgery, in particular total hip or knee arthroplasty and hip fracture surgery, is among the highest for all surgical specialties. For patients undergoing elective total hip or knee arthroplasty, approved regimens include fondaparinux initiated 6 to 8 hours after surgery, LMWH initiated 12 hours before or 12 to 24 hours after surgery, adjusted-dose VKA initiated on the evening of the surgical day, low-dose UFH, aspirin, dabigatran, apixaban, or rivaroxaban (total hip arthroplasty or total knee arthroplasty but not hip fracture surgery). The duration of prophylaxis depends on whether the patient is ambulatory and on additional risk factors, although at least 10 days and as many as 35 days of therapy are recommended.[220]

Direct-acting oral anticoagulants (DOACs), including direct thrombin inhibitors (dabigatran etexilate) and factor Xa inhibitors (rivaroxaban, apixaban) appear as effective as enoxaparin in reducing the risk of VTE in patients undergoing total hip or total knee arthroplasty with a similar safety profile, although some studies suggest a trend of increased major bleeding when compared to LMWH.[231] The introduction of oral, once-daily forms of thromboprophylaxis that do not require monitoring represents a substantial advance in both pre- and potentially postembolic prophylaxis. Current evidence-based guidelines still recommend the use of LMWH in preference to the other alternative agents in major orthopedic surgery and suggest the use of DOACs in patients who decline injections.[220]

In summary, given the effective options available, few patients at risk for venous thrombosis cannot be protected. Optimal use of prophylaxis must occur if a substantial impact is to be made on the considerable and often unnecessary morbidity and mortality associated with PE. Not only must prophylaxis be applied, but it also must also be applied in a manner proportionate to the patient's risk of thromboembolism.

SPECIFIC ISSUES

EARLY DISCHARGE AND OUTPATIENT TREATMENT

Early discharge and outpatient treatment in patients with acute PE is a matter of debate. The crucial issue is to select patients who are at low risk of adverse early outcome. A number of risk-prediction models

have been developed.[232] Among them, the PESI and the Hestia score are the most extensively validated scores to date. The value of the simplified form of the PESI score (sPESI) for selecting candidates for early discharge and home treatment has not yet been directly evaluated. Several recent multicenter clinical trials (randomized and nonrandomized) have investigated the 3-month clinical outcome of patients with PE, who were discharge early or treated entirely at home using different prediction rules with divergent results.[233-236] Meta-analysis suggests that pooled incidences of recurrent VTE, major bleeding, and total mortality did not differ significantly between early discharge patients and those treated as inpatients.[237]

Although further research is needed,[238] current clinical guidelines recommend that early discharge (within the first 24 hours) and outpatient treatment should be considered in patients with DVT and in those with PE and low risk of adverse early outcomes (PESI class I or II and probably those with sPESI score of 0) plus low bleeding risk, if it appears feasible based on the patient's anticipated compliance and family/social background.[151,239] The recent approval of DOACs for use in patients with PE may extend the number of patients treated out of the hospital in the future.[240] Finally, it should be realized that there are patients who might meet criteria based on PESI, the Hestia criteria, or both who may not be ideal candidates for outpatient PE therapy. An example might be a patient with an extensive PE burden but who retains normal RV size and function, particularly when extensive residual DVT remains.

FOLLOW-UP AND OPTIMAL DURATION OF ANTICOAGULATION

The duration of outpatient anticoagulation for patients with VTE remains controversial, especially in patients with a first episode of acute unprovoked VTE (ie, occurring in the absence of reversible risk factors such as surgery, trauma, immobilization, or contraception/hormonal therapy).[13,151,241] The incidence of recurrent VTE does not depend on the clinical manifestation of the first event (ie, it is similar after PE compared with after DVT); however, in patients who have suffered PE, VTE more frequently recurs as symptomatic PE, whereas in patients who have suffered DVT, it tends to recur more frequently as DVT.[242]

Patients with a clearly defined initial predisposition whose initial thromboembolic risk factors have resolved ("provoked" PE; ie, temporary or reversible risk factors) should receive at least 3 months of anticoagulation. Consideration should be given for a longer course of therapy in those with persistent V/Q or CT scan defects or abnormal lower extremity test results. Treatment beyond this initial period with VKA reduces the risk of recurrent VTE up to 90%, but this benefit is partially offset by at least 1% higher risk of major bleeding.[243,244] Therefore, in patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed on a regular basis.

Patients without a clearly defined initial predisposition to thromboembolism (unprovoked PE) should be treated for at least 3 months, although extended oral anticoagulation should always be strongly considered in these patients if the bleeding risk is low.[245] Certain patients, such as those with recurrent spontaneous or unprovoked episodes of VTE (two or more episodes), an irreversible clinical risk factor, combined thrombophilic tendencies, antithrombin III deficiency, deficit of protein C or protein S, homozygous factor V Leiden or homozygous prothrombin G20210A, or presence of a lupus anticoagulant, should be treated with an indefinite period of anticoagulation even though such a strategy is associated with an increased risk of bleeding complications. It has been proposed that D-dimer testing, alone[246] or integrated in recurrence risk scores,[247-249] might identify patients in whom anticoagulation can be and cannot be safely discontinued after a first unprovoked VTE. However, a recent prospective study has questioned the utility of this strategy.[250] In patients who refuse or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prevention.[251,252]

Finally, four DOACs (dabigatran, rivaroxaban, edoxaban, and apixaban) have been evaluated for the extended treatment of patients with VTE.[168,169,253,254] The results of these trials indicate that DOACs are both effective (in terms of prevention of recurrent VTE) and safe (particularly in terms of major bleeding). One trial with apixaban (AMPLIFY-EXT) has shown that for patients already treated for 6 to 12 months, extended therapy at a lower dose (2.5 mg every 12 hours) is effective at preventing recurrences and potentially safer than higher dose therapy.[253] The EINSTEIN-CHOICE study is now under way, in which patients already treated for 6 to 12 months are randomized to two once-daily doses of rivaroxaban (20 and 10 mg) or aspirin (100 mg daily).[255]

SIGNIFICANCE OF SUBSEGMENTAL PULMONARY EMBOLISM AND OVERDIAGNOSIS

The diagnostic value and clinical significance of subsegmental defects on MDCT are still under debate.[256] A single subsegmental defect probably does not have the same clinical relevance as multiple, subsegmental emboli. A recent analysis showed similar outcomes (3-month recurrence and mortality rates) between patients with subsegmental and more proximal PE, but outcomes were largely determined by comorbidities.[257] Compression ultrasound of the lower limbs may be helpful in this situation, as the exclusion of proximal DVT in a patient with isolated subsegmental PE could support anticoagulation discontinuation.[151] However, this decision should be made on an individual basis, particularly taking into account the patient's VTE risk factors and bleeding risk.

There is also growing evidence suggesting overdiagnosis of PE.[258] Data from the United States show an 80% rise in the apparent incidence of PE after the introduction of MDCT, without a significant impact on mortality.[259,260] Most experts advocate that patients with incidental (unsuspected) PE on CT should be treated with anticoagulants, especially if they have cancer and a proximal clot,[261] but solid evidence in support of this recommendation is lacking.

TREATMENT OF ISOLATED DISTAL DEEP VEIN THROMBOSIS AND UPPER LIMB THROMBOSIS

The optimal treatment of patients with isolated distal DVT remains controversial. Although posing a substantially lower embolic risk than proximal vein thrombosis, calf-limited thrombi may extend into the proximal veins. Furthermore, the symptomatic outcome may be worse in the absence of therapy.[262] If a contraindication to anticoagulation exists, noninvasive testing over 10 to 14 days should be performed to detect possible extension into the popliteal vein.

The spectrum of upper extremity venous thrombosis is variable and includes patients with peripherally and centrally placed IV catheters, as well as those with underlying malignancy. Patients with documented upper extremity DVT should be anticoagulated.[28] Prophylactic anticoagulation in patients with long-term indwelling catheters is controversial.[263] Effort-related upper extremity venous thrombosis (Paget-Schroetter syndrome) usually affects young, active men and is related to extrinsic compression of the subclavian vein at the thoracic inlet.[28] A multidisciplinary approach to management is often required to avoid long-term consequences, including recurrence, embolism, and symptomatic sequelae.

PULMONARY EMBOLISM IN PREGNANCY

PE is a leading cause of pregnancy-related maternal death in developed countries; the risk of PE is higher in the postpartum period, particularly after a cesarean section.[264,265] Symptoms should be interpreted with caution since pregnant women often complain of breathlessness, and data on clinical prediction rules for PE in pregnancy are scarce. Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods.[266] If the suspicion for acute PE is high, then lung imaging should be performed directly. When the chest radiograph is normal or near normal, a V/Q scan can be performed. Otherwise, chest CTA should be obtained. When PE is suspected and there are symptoms and signs of DVT, bilateral leg ultrasound followed by anticoagulation treatment (if positive) is recommended. A normal D-dimer value has the same exclusion value for PE in pregnant women as for other patients with suspected PE but is found more rarely, because plasma D-dimer levels physiologically increase throughout pregnancy.[267] In general, D-dimer testing is not recommended as part of the diagnostic evaluation in pregnancy.

The treatment of PE in pregnancy is based on heparin anticoagulation, because heparin does not cross the placenta and is not found in breast milk in significant amounts. Weight-adjusted dose of LMWH is the preferred treatment given its safety profile.[264,268] Adaptation according to anti-Xa monitoring may be considered in women at extremes of body weight or with renal disease, but routine monitoring is generally not justified.[264] Fondaparinux should not be used in pregnancy because of the lack of data. VKAs should not be administered throughout pregnancy, especially during the first and third trimesters. DOACs are not approved for use in pregnancy; rivaroxaban, edoxaban, and dabigatran have been graded as FDA pregnancy category C and apixaban as category B.

Thrombolytic treatment during pregnancy and the peripartum period should be used only in life-threatening situations.[264]

The management of labor and delivery requires particular attention. Epidural analgesia cannot be used unless LMWH has been discontinued at least 12 hours before delivery. Treatment can be resumed 12 to 24 hours after removal of the epidural catheter. After delivery, heparin treatment may be replaced by VKAs, including in breast-feeding mothers, which should be continued for at least 3 months.

PULMONARY EMBOLISM IN CANCER PATIENTS

The overall risk of VTE in cancer patients is four times greater than in the general population. The risk of VTE varies with different types of cancer.[34] Hematologic malignancies, lung cancer, gastric and pancreatic malignancies, brain cancer, genitourinary tract cancer, and breast malignancies are associated with a particularly high risk of DVT and PE.[35,36] The risk is higher in patients receiving chemotherapy; nevertheless, prophylactic anticoagulation is not routinely recommended during ambulatory anticancer chemotherapy, with the exception of thalidomide- or lenalidomide-based regimens in multiple myeloma.[269] Bevacizumab has also been shown to be clearly associated with increased risk.[270] The risk of VTE is particularly increased after cancer surgery, especially in the first 4 to 6 weeks, although it may remain elevated beyond the third month after surgery.[271] Continued vigilance is therefore necessary, as currently recommended prophylactic anticoagulation regimens only emphasize the first 1 month after surgery.

Malignancy should be considered when estimating the clinical probability of VTE. A negative D-dimer test has the same diagnostic value as in noncancer patients; therefore, a normal value excludes the diagnosis of VTE in patients with low or intermediate clinical probability of PE. On the other hand, D-dimer levels are nonspecifically increased in many patients with cancer. Thus, in patients with suspected PE and elevated D-dimer or those with high clinical probability of PE, further imaging tests should be performed as in the general population.

Cancer is a risk for adverse outcome in PE, which is mainly a result of the increased bleeding risk during anticoagulation therapy and the high rate of recurrence of VTE.[272,273] LMWH administered in the acute phase (except for high-risk PE) and continued over the first 3 to 6 months should be considered as first-line therapy.[274-276] Evidence with fondaparinux or DOACs is limited. Based on a recent meta-analysis, DOACs seem to be as effective and safe as conventional anticoagulation for the treatment of VTE in patients with cancer.[277] Further clinical trials in patients with cancer-associated VTE should be performed to confirm these results.

The decision of chronic anticoagulation (continuation of LMWH, transition to VKAs, or discontinuation of anticoagulation) should be assessed individually based on the success of anticancer therapy, estimated risk of recurrence of VTE, bleeding risk, and patient's preference. In general, treatment with LMWH or VKA beyond the 3- to 6-month initial period is recommended as long as the disease is considered active.

Recurrence of VTE in cancer patients on VKA or LMWH treatment may be managed by changing to the highest permitted dose of anticoagulation or opting for vena cava filter placement. Complications such as filter thrombosis in the absence of anticoagulation can occur in cancer patients, making this solution less ideal. In these cases, the placement of a retrievable filter and its prompt removal may reduce this potential complication.[278] These decisions are often difficult based on the continued risk in cancer patients.

Finally, up to 10% of patients with VTE may be diagnosed with cancer within 1 year following the "unprovoked" index event. However, an extended occult cancer screening does not seem superior to a limited-screening strategy based on clinical, exploratory, and laboratory parameters.[42]

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CHAPTER 76

COR PULMONALE: THE HEART IN PARENCHYMAL LUNG DISEASE

Ori Ben-Yehuda

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INTRODUCTION

Cor pulmonale, or "pulmonary heart," describes the pathological changes and associated signs and symptoms of right ventricular failure resulting from pulmonary hypertension in the setting of parenchymal lung disease such as chronic obstructive pulmonary disease (COPD).[1]

The pulmonary circulation (with the exception of the bronchial arteries, which deliver oxygenated blood from the left heart) is characterized not only by the delivery of venous deoxygenated blood to the alveoli for oxygen uptake but also by low resistance and large capacitance. The pulmonary circulation in the absence of right-to-left shunts has to accept the entire cardiac output, approximately 5 L/min at rest and up to fivefold during maximal exercise. Normal mean pulmonary pressure is less than 20 mm Hg at rest, with a level greater than 25 mm Hg diagnostic of pulmonary hypertension (PH).[2] Although pulmonary pressures do rise with exercise, pulmonary vascular resistance (PVR) normally drops further with exercise to accommodate the marked increase in cardiac output. In PH, although there is an exaggerated increase in pulmonary pressures during exercise without an appropriate decrease in PVR, criteria for exercise-induced PH have not been established.[2] To accommodate the large amount of blood flow, the pulmonary circulation provides a large cross-sectional area. Reduction in the cross-sectional area by up to 50% as with a pneumonectomy is well tolerated without PH at rest. Further reductions as may occur with advanced pulmonary disease can lead to PH both on exertion and at rest with resultant pressure overload on the right ventricle.

The term *cor pulmonale* originated over two centuries ago and has been applied variably in the past to right heart failure as a result of various lung conditions, both parenchymal and vascular in origin, as well as a result of pulmonary emboli. Indeed, from a pathophysiologic and clinical standpoint, any disease in which pulmonary arterial pressures increase sufficiently to affect right ventricular function results in a similar clinical syndrome of right heart failure. In 1963, the World Health Organization (WHO) defined cor pulmonale as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs."[3] Strictly speaking, therefore, the term should be applied only to group III PH and excludes group I (pulmonary arterial hypertension, including idiopathic pulmonary arterial hypertension, connective tissue diseases, and congenital heart disease), group II (secondary to left heart failure), group IV caused by chronic thromboembolic disease, and group V (miscellaneous conditions such as sarcoidosis) based on the 2013 Updated Clinical Classification of Pulmonary Hypertension.[4] PH is discussed in detail in Chap. 74.

Chronic cor pulmonale is typically a manifestation of various parenchymal lung diseases. Acute pulmonary embolism, if large, leads to acute right heart failure, which has been termed by some as *acute cor pulmonale*. Pulmonary embolism is not an intrinsic lung disease, and as such, the term is not strictly within the definition used here for cor pulmonale. The cardiac response to "acute cor pulmonale" also differs from the typical cor pulmonale syndrome, which is characterized by right ventricular hypertrophy with right ventricular dilatation as a late phenomenon. In contrast, in acute pulmonary embolism, the right ventricle dilates acutely without intervening hypertrophy, leading to a volume overload rather than pressure overload right ventricular failure.

EPIDEMIOLOGY AND INCIDENCE

The sine qua non of cor pulmonale is the presence of significant PH. Lung diseases that are associated with PH include the obstructive lung diseases, with COPD being by far the most prevalent; restrictive lung diseases including pulmonary fibrosis and kyphoscoliosis; and diseases associated with hypoventilation such as obstructive sleep apnea. A listing of lung diseases that have been associated with cor pulmonale is provided in Table 76–1. All of these have chronic hypoxemia in common, and indeed without significant hypoxemia, cor pulmonale does not typically develop.

Given the worldwide smoking epidemic, COPD is by far the most important disease causing cor pulmonale. COPD risk factors include not only smoking, however, but also outdoor, occupational, and indoor air pollution, with burning of wood and other biofuels being a major risk factor, and nonsmokers accounted for 23.3% of COPD with moderate or greater disease severity in the Burden of Obstructive Lung Disease (BOLD) study.[5] COPD is also a disease of aging, with a higher prevalence among men. COPD is considered the fourth leading cause of death in the world and is predicted to become the third leading cause by 2020. There is significant underdiagnosis of COPD as well as different criteria used for diagnosis, creating uncertainty as to the burden of disease. The BOLD study reported a prevalence of 10.1% for moderate or above disease (11.8% for men and 8.5% for women), a higher disease burden than previously appreciated, with every decade of life associated with almost a doubling in the odds ratio of having the disease.[6]

TABLE 76–1. Major Lung Diseases Associated With Cor Pulmonale

Obstructive lung diseases
Chronic obstructive pulmonary disease
Cystic fibrosis
Bronchiectasis
Bronchiolitis obliterans
Restrictive lung diseases
Sarcoidosis
Neuromuscular diseases
Kyphoscoliosis
Sequelae of pulmonary tuberculosis
Pneumoconiosis
Drug-related lung diseases
Extrinsic allergic alveolitis
Connective tissue diseases
Idiopathic interstitial pulmonary fibrosis
Interstitial pulmonary fibrosis of known origin
Hypoventilation syndromes
Obstructive sleep apnea
Obesity-hypoventilation syndrome (formerly Pickwickian syndrome)
Central sleep apnea
Hypoxic vasoconstriction
Mountain sickness

The presence of cor pulmonale markedly increases the risk of mortality in COPD, but its exact contribution is difficult to separate from the almost invariable severe COPD and respiratory failure found in patients at the stage when cor pulmonale is diagnosed.

PATHOPHYSIOLOGY

Various mechanisms contribute to increased pulmonary vascular disease in parenchymal lung disease, including inflammation, destruction of lung parenchyma as in emphysema, obliteration as a result of fibrosis as in idiopathic pulmonary fibrosis, endothelial dysfunction, and hypoxemia[7] (Fig. 76–1). In COPD, hypoxia plays a central role and is usually manifest when patients become symptomatic with cor pulmonale, but it is preceded in the pathogenesis of PH by a much earlier inflammatory process. In the case of COPD, this inflammatory process is even induced by smoking itself, even while lung function is still normal.[8,9]

INFLAMMATION

Changes in the structure and function of the arterial wall (arterial remodeling) have been studied extensively in smokers and patients with COPD. Intimal thickening, with an increase in both cellular proliferation with smooth muscle cell migration and proliferation, as well as an increase in extracellular matrix occur early in the disease process and are present even in patients with mild COPD, whereas the severity of pulmonary vascular remodeling correlates with the severity of inflammation.[9] Remodeling occurs in arteries of different sizes, although it affects small muscular arteries the most, with intimal thickening being the most pronounced pathologic abnormality, while the muscular layer does not show significant changes. The resultant decrease in cross-sectional area and vasodilatory capacity leads to an increase in PVR.

The inflammatory process in COPD is characterized by an increase in activated T lymphocytes, mostly $CD8^+$ cells,[10] and correlates with the extent of airflow obstruction. Even smokers with normal lung function have an increased number of $CD8^+$ T cells in their pulmonary arteries, with a reduction in the $CD4^+/CD8^+$ ratio, similar to patients with COPD.[11]

ENDOTHELIAL DYSFUNCTION

As in the systemic circulation, the endothelium plays a key role in mediating vascular dilation. Unlike the systemic circulation, endothelial cells in the pulmonary circulation respond to hypoxia with signaling leading to vasoconstriction as opposed to vasodilation, so that the endothelium may also mediate the response to hypoxia, which is a major contributor to development of PH. COPD and other lung diseases associated with PH have been shown to have impairment in the three major pathways that regulate pulmonary vascular tone: the two vasodilatory pathways, the nitric oxide pathway and the prostacyclin pathway, and the vasoconstrictive pathway, the endothelin pathway. Impairment of nitric oxide synthesis (reduction in endothelial nitric oxide synthase) as well as prostacyclin synthase has been shown in patients with COPD along with upregulation in the expression of endothelin-1 receptors.

HYPOXIA

Hypoxia has been considered as a key mediator in PH associated with various parenchymal lung diseases including COPD. That hypoxemia

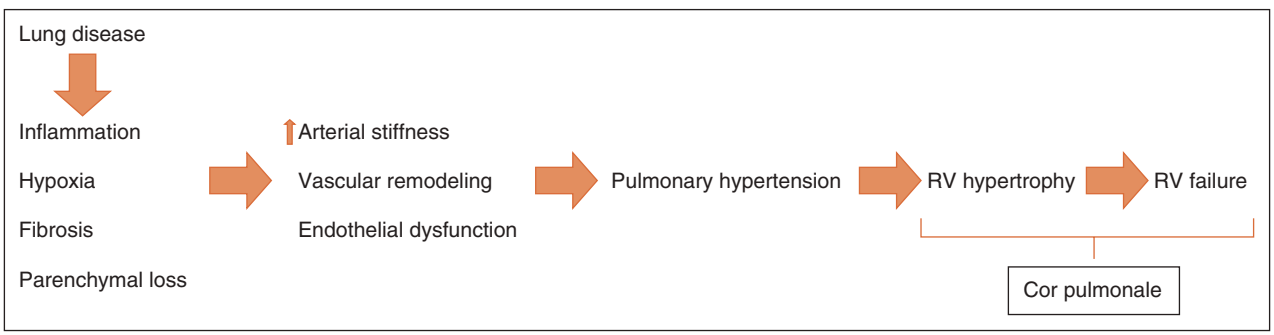

FIGURE 76–1. The pathophysiology of cor pulmonale. RV, right ventricular.

can indeed be a cause of PH is seen in both subacute mountain sickness (seen in sea-level dwellers who move to high altitude) and in chronic mountain sickness (seen after many years at high altitude). In both conditions, the PH is relieved by relief of the hypoxia. In COPD patients, when cor pulmonale develops, significant hypoxia is usually evident with arterial partial pressure of oxygen (PO_2) < 55 mm Hg, but whether the hypoxemia is the key mediator in causing the PH or simply a marker of more advanced disease is controversial. Although oxygen therapy does ameliorate the associated PH, its effect is limited. Most importantly, changes in the pulmonary vasculature, specifically pulmonary vascular remodeling and endothelial dysfunction, have been documented in early COPD without overt hypoxemia and even in smokers with normal lung function.[12,13]

The acute effects of hypoxia on the pulmonary vasculature also need to be distinguished from chronic effects. Acute hypoxemia causes vasoconstriction in the resistance pulmonary vessels. When caused by localized (eg, a segmental or lobar pneumonia) hypoxemia, this vasoconstriction may serve to improve the matching of ventilation and perfusion. In contrast, in the presence of diffuse lung disease, such vasoconstriction is deleterious because it increases right ventricular afterload.

CLINICAL MANIFESTATION

The clinical manifestations of cor pulmonale are nonspecific and reflect the signs and symptoms of right heart failure. Typically, the underlying lung disease is long-standing and has been diagnosed already, and although subtle changes in the pulmonary vasculature may have occurred much earlier in the disease process, overt signs and symptoms of cor pulmonale are a late phenomenon and often overshadowed by the signs and symptoms of the underlying pulmonary disease. Thus, a patient with severe COPD may present with an exacerbation with respiratory failure, which appropriately becomes the focus of treatment.

SIGNS AND SYMPTOMS

Signs and symptoms attributable to cor pulmonale include peripheral edema, hepatic congestion presenting as early satiety, presyncope, and when pulmonary pressures are significantly elevated, frank syncope. On physical exam, the patient may appear plethoric as a result of accompanying polycythemia (a response to chronic hypoxemia). The cardiac exam may reveal jugular venous distention, a prominent jugular V wave caused by tricuspid regurgitation, a parasternal lift caused by right ventricular hypertrophy (this may be obscured by significant hyperinflation in the COPD patient), and a prominent P_2 sound. As PH progresses, pulmonic valve regurgitation may develop (Graham-Steele murmur), along with a right-sided third heart sound. Signs of right-sided volume overload include hepatojugular reflux, ascites, and in severe cases, anasarca.

ELECTROCARDIOGRAM

Electrocardiographic findings in cor pulmonale include evidence of right axis deviation, right ventricular hypertrophy, right ventricular strain, P pulmonale secondary to right atrial enlargement, and hypertrophy. Common accompanying arrhythmias include atrial fibrillation, atrial flutter, and multifocal atrial tachycardia in addition to premature atrial and ventricular contractions.[14]

ECHOCARDIOGRAPHY

Echocardiography is particularly useful for the detection of cor pulmonale and its antecedent PH. Because of the anterior location of the right ventricle, transthoracic echocardiography is sufficient and often superior to transesophageal echocardiography in assessing the right ventricle. The assessment of right ventricular function differs from assessment of left ventricular function as a result of the complex crescent-like shape of the right ventricle, different fiber orientation, and contraction (the septum normally contracting toward the left ventricle). The salient features on transthoracic echocardiography include right ventricular hypertrophy, right ventricular enlargement, elevated tricuspid regurgitation velocity indicative of increased gradient between the right ventricle and right atrium, increased right ventricular/left ventricular ratio and eccentricity index, and decreased tricuspid annular plane systolic excursion (TAPSE), as detailed further below.

Because cor pulmonale is invariably preceded by PH, assessment of pulmonary artery pressure is an essential part of the evaluation of patients with suspected cor pulmonale. Although right heart catheterization is the gold standard for measurement of pulmonary artery pressures, the presence of tricuspid regurgitation, which is almost universally present in patients with PH, allows the calculation of the gradient between the right ventricle and right atrium by measuring the peak tricuspid regurgitation velocity by Doppler and adding the estimated right atrial pressure. The latter can be obtained from physical examination or from echocardiographic assessments. Since the description of the technique by Yock and Popp,[15] it has become the standard for assessing PA pressures noninvasively, but various correlations with invasive measurements have been reported, with correlations varying from a low of $r = 0.23$[16] to a high of $r = 0.97$.[17] A recent comprehensive assessment of the correlation in 307 patients who underwent echocardiography and right heart catheterization within 5 days of each other showed a strong correlation when the tricuspid regurgitation signal was interpretable (which was found in approximately two-thirds), with an area under the curve for classifying PH of 0.97 for right ventricular systolic pressure. When tricuspid regurgitation signals were uninterpretable, eccentricity index and right ventricular size were independently associated with PH classification (area under the curve, 0.77).

TAPSE reflects the longitudinal myocardial shortening of the right ventricle and accurately represents global right ventricular function. TAPSE is assessed with M-mode in the apical four-chamber view, with normal value being at least 16 mm and severe RV dysfunction when TAPSE is less than 10 mm.

Right ventricular dimensions are increased in cor pulmonale and are accompanied by increases in wall thickness, usually assessed by the long-axis view on the subcostal view. Normally the right ventricle appears to be smaller than the left ventricle on the four-chamber view, with the apex being formed by the left ventricle. With the development of cor pulmonale, the right ventricle enlarges, the right ventricular/left ventricular ratio increases to greater than 1, and the right ventricle forms the apex. When pressure and volume overload of the right ventricle develop, the left ventricle assumes a D shape as the intraventricular septum flattens. This leads to an abnormal ratio (> 1; sometimes significantly > 1, normal ~1) between the left ventricular anteroposterior and septolateral dimensions (eccentricity index). Other parameters of right ventricular function include right ventricular dP/dt assessed by measuring the time required for the tricuspid regurgitation jet to increase in velocity from 1 to 2 m/s on continuous wave Doppler and right ventricular fractional area change, a measure of the right ventricular ejection fraction in the apical four-chamber view.

The assessment of ventricular myocardial function (for the left ventricle but particularly for the right ventricle) by two-dimensional echocardiography is limited by high subjectivity as well as the inability to accurately differentiate movement from contraction. Newer techniques that assess deformation of the muscle (tissue Doppler imaging and two-dimensional speckle tracking) can provide strain and strain rate data. Assessment of myocardial strain can provide early evidence of myocardial dysfunction, is often abnormal in the early stages of the development of cor pulmonale, and can better predict hemodynamic abnormalities than traditional echocardiography parameters.[18-20]

RADIOGRAPHY, NUCLEAR SCAN, COMPUTED TOMOGRAPHY, AND MAGNETIC RESONANCE IMAGING

Beyond the characteristic findings of the underlying lung diseases (eg, honeycombing in pulmonary fibrosis and hyperinflation in emphysema) and skeletal abnormalities (eg, kyphoscoliosis) that lead to cor pulmonale, the characteristic radiologic findings are of right ventricular hypertrophy, which is best assessed in the lateral projection with filling of the retrosternal space. This sign, however, may be obscured by the vertical emphysematous heart. PH may be suspected when there is enlargement of the descending pulmonary arteries (> 16 mm in the right pulmonary artery and > 18 mm in the left pulmonary artery). Nuclear scanning and magnetic resonance imaging may be used to assess right ventricular function and obtain an accurate ejection fraction.

Computed tomography scans are particularly useful to screen for associated lung abnormalities such as pulmonary fibrosis, bronchiectasis, and chronic thromboembolic PH. Perfusion/ventilation nuclear scans are also helpful in excluding chronic thromboembolic PH and predicting response to pulmonary thromboendarterectomy surgery.

Magnetic resonance imaging of the heart (cardiac magnetic resonance) and of the lung vasculature has emerged as a useful tool in the assessment of PH and, by extension, cor pulmonale. Magnetic resonance assessments of patients with PH has shown close correlations with findings on invasive right heart catheterization.[21] In addition, magnetic resonance imaging can assess pulmonary arterial compliance. Increased pulmonary artery stiffness is not only a characteristic and relatively early sign of PH, but may also play a role in the progression of the disease.[22,23]

COR PULMONALE IN SPECIFIC LUNG DISEASES

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is an inflammatory disease characterized by a combination of small airway disease (obstructive bronchiolitis) and destruction of the parenchyma (emphysema), with variable contribution of each component in an individual patient.[24] The hallmark of the disease is a chronic limitation in airflow, which can be objectively quantified by spirometry. Smoking is the most recognized and studied risk factor, but the disease can also occur in nonsmokers. Genetic factors (eg, α_1-antitrypsin deficiency), age, male gender, impaired lung growth and development, and exposure to various air pollutants (both indoor and outdoor) have been clearly linked to the development of COPD, whereas asthma, bronchial hyperreactivity, and chronic bronchitis have been variably linked.

In the majority of COPD patients, PH is present only during exercise, but resting PH is almost invariably present in Global Initiative for Chronic Obstructive Lung Disease stage IV disease, with up to 5% of patients having mean pulmonary artery pressure (mPAP) > 35 mm Hg.[25-27]

The effect of PH in COPD has been controversial. Vonbank et al[28] studied 42 patients with moderate to very severe COPD. Resting mPAP was elevated in 32 patients with PH (mPAP = 26.8 ± 5.9 mm Hg) and normal in 10 nonhypertensive patients (mPAP = 16.8 ± 2 mm Hg). Exercise capacity was evaluated by maximum oxygen uptake during exercise and was significantly lower in PH patients (785 ± 244 mL/min) than in nonhypertensive patients (1052 ± 207 mL/min, $P = .004$). Similar findings were found by Sims et al,[29] who evaluated 362 patients with severe COPD being evaluated for lung transplantation with both 6-minute walk test and right heart catheterization. They documented a decrease in 6-minute walk test of 11 m for every 5-mm Hg rise in mPAP. In contrast, a smaller study by Pynnaert et al[30] did not demonstrate a correlation between PH and exercise parameters in COPD, with respiratory exhaustion being the key variable.

The traditional "blue bloater" phenotype, in contrast with the "pink puffer," has traditionally been associated with cor pulmonale. A recent analysis from the Multi-Ethnic Study of Atherosclerosis (MESA)[31] investigating COPD surprisingly found lower right ventricular end-diastolic volumes (RVEDV) with no change in right ventricular mass in COPD patients compared with controls. The findings may have been mediated partly by more emphysema rather than chronic bronchitis in the population, perhaps reflecting a shift in the presentation of COPD in the United States. Indeed, a greater percentage of emphysema and presence of centrilobular and paraseptal emphysema were associated with lower RVEDV. Possible mechanisms for this lack of overt cor pulmonale (termed *parvus cor pulmonale* by the MESA authors) in these patients include decreased venous return as a result of lung hyperinflation and compression of the inferior vena cava. Alternatively, the decreased RVEDV may be a reflection of right ventricular diastolic dysfunction accompanying concentric hypertrophy, akin to the small left ventricular volume often seen in aortic stenosis[32] with marked left ventricular hypertrophy.

The treatment of cor pulmonale in COPD is geared to addressing hypoxia when arterial PO_2 is below 60 mm Hg and treating the underlying inflammatory process that may exacerbate arterial thickening and PH. Loop diuretics are appropriate when edema develops. Attention needs to be paid to potential acid-base alterations. The associated contraction alkalosis with loop diuretics may be beneficial to counteract the respiratory acidosis caused by carbon dioxide retention in COPD, but may lead to significant alkalosis if the patient is ventilated with correction of the carbon dioxide retention.

Small studies have evaluated the role of specific PH treatments such as the phosphodiesterase-5 inhibitor sildenafil[33-35] and the endothelin receptor antagonist bosentan[36,37] A meta-analysis demonstrated significant increases in exercise capacity and reductions in pulmonary pressures with these targeted therapies, but hypoxemia and quality of life were not affected.[25]

SLEEP APNEA AND OBESITY HYPOVENTILATION SYNDROME

Both obstructive sleep apnea (OSA) and central sleep apnea have been associated with cor pulmonale. OSA is common and underdiagnosed, with moderate to severe OSA affecting up to 10% of the adult population in the United States.[38] Abnormalities in right ventricular function, decreased strain and ejection fraction, increased dyssynchrony,[39] right ventricular dilatation, hypertrophy of the interventricular septum, and reduced tissue Doppler–determined systolic and diastolic velocities[40] have been documented in patients with OSA. Importantly, improvements in all these parameters have been observed with treatment of the OSA with continuous positive airway pressure during sleep.[41]

Although OSA is characterized by hypoventilation during sleep and is associated with obesity, morbid obesity is associated by alveolar

hypoventilation during both sleep and wakefulness as a result of the obesity hypoventilation syndrome, previously termed the Pickwickian syndrome (named after the character in the Charles Dickins novel *The Pickwick Papers*). The disorder involves a complex interaction between impaired respiratory mechanics, decreased ventilatory drive, and obstructive sleep apnea and is associated with significant mortality and morbidity. Continuous positive airway pressure treatment and bariatric surgery are the mainstays of therapy.

SARCOIDOSIS

Sarcoidosis is a disease characterized by the presence of noncaseating granulomas in multiple organs, with the lungs being most commonly affected. Overt cardiac involvement, clinically manifest with heart failure, conduction system disease, and arrhythmias is relatively uncommon, and autopsy data suggest cardiac involvement in up to a quarter of cases.[42] The right ventricle may be affected both directly with sarcoidosis and indirectly as a result of lung involvement. Right ventricular function by free wall longitudinal strain was found to be abnormal in over half of patients with pulmonary sarcoidosis,[43] with PH being a common finding. Overt cor pulmonale, however, is uncommon. Therapy of sarcoidosis is mainly anti-inflammatory with steroids.

COR PULMONALE IN INTERSTITIAL LUNG DISEASE INCLUDING PULMONARY FIBROSIS

Interstitial lung disease, also known as diffuse parenchymal lung disease, is a heterogeneous group of lung diseases affecting the interstitium of the lung and is characterized by a restrictive pattern on pulmonary testing. Interstitial lung disease may be associated with inhaled substances such as asbestos or beryllium, hypersensitivity pneumonitis, drugs, or connective tissue diseases, as well as idiopathic presentations. In idiopathic pulmonary fibrosis (IPF), typical radiographic (basal and pleural-based fibrosis with honeycombing) and pathologic (temporally and spatially heterogeneous fibrosis findings) findings accompany an often progressive clinical course. PH is found in a third of patients with severe IPF and is associated with worse prognosis.[44] There is no specific treatment for PH in IPF, with oxygen therapy being the mainstay of therapy. Recently both pirfenidone, a small-molecule anti-inflammatory drug, and nintedanib, a tyrosine kinase inhibitor, were approved for treatment of IPF. Although a rare disease, IPF is now the leading cause for lung transplantation.[45] A trial (Randomized Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF [ARTEMIS]) using the endothelin-1 antagonist ambrisentan for IPF, including a subset with PH (ARTEMIS-PH), was halted prematurely[46] because of an increase in disease progression. An increase in ventilation/perfusion mismatch may be the underlying cause for the adverse effects of ambrisentan.

CONCLUSION

Right ventricular dysfunction is common in patients with lung diseases, but overt cor pulmonale is relatively uncommon. Therapy (Table 76–2) is mostly aimed at the underlying lung disease with oxygen therapy when arterial oxygen is below 60 mm Hg. Diuretic therapy is indicated in volume overload. The role of specific PH therapies remains inadequately studied and should be used judiciously with attention to possible ventilation/perfusion mismatch and increasing hypoxemia.

TABLE 76–2. Treatment Principles of Cor Pulmonale

Treat underlying disease
Chronic obstructive pulmonary disease: smoking cessation, bronchodilators, steroids (inhaled for maintenance therapy/systemic for exacerbations)
Sarcoidosis: steroids
Sleep apnea: continuous positive airway pressure, weight loss, corrective surgery
Pulmonary fibrosis: perfinidone, nintedanib, lung transplantation
Oxygen supplementation if arterial PO_2 < 60 mm Hg
Loop diuretics for volume overload
Consider torsemide if gut edema suspected/diuretic resistance
PH-specific therapies: unproven
Endothelin receptor antagonists contraindicated in pulmonary fibrosis

Abbreviations: PH, pulmonary hypertension; PO_2, partial pressure of oxygen.

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CHAPTER 77

SLEEP-DISORDERED BREATHING AND CARDIAC DISEASE

Martin R. Cowie

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INTRODUCTION

Sleep-disordered breathing (SDB), or sleep apnea, is common in patients with cardiovascular disease, and its presence is associated with a poorer prognosis and high health care costs.[1,2] Increasingly, international guidelines suggest it is worthwhile to screen for this condition and that appropriate treatment may not only improve the patient's quality of life, but may also reduce the risk of cardiovascular events. However, recent evidence suggests that the relationship between SDB and the underlying cardiovascular condition may be complex, particularly in heart failure, and further research is required to clarify the most appropriate treatment pathway for the individual patient.

WHAT IS SLEEP-DISORDERED BREATHING?

Sleep-disordered breathing (SDB) includes obstructive sleep apnea (OSA), central sleep apnea (CSA), or a combination of both. In OSA (the most common form of SDB in the general population), there is collapse of the pharynx during sleep with consequent upper airway obstruction, often with snoring (Fig. 77–1).[3] Predisposing factors include obesity, a short neck, and retrognathism. In heart failure (HF), rostral fluid shift during sleep can lead to pharyngeal edema, which may exacerbate the tendency to obstruction.[4]

CSA is usually associated with HF, although it has also been observed in patients with stroke, especially in the acute phase, and in those with renal failure.[5] In CSA, the underlying abnormality is in the regulation of breathing in the respiratory centers of the brainstem. In normal physiology, minute ventilation during sleep is primarily regulated by chemoreceptors in the brainstem and carotid bodies, which trigger an increase in respiratory drive in response to a rise in partial pressure of arterial carbon dioxide ($PaCO_2$), thus maintaining $PaCO_2$ within a narrow range. Patients with HF and CSA tend to have an exaggerated respiratory response to carbon dioxide, associated with excess sympathetic nervous activity, so that modest rises in $PaCO_2$ that may occur during sleep result in inappropriate hyperventilation.[5-7] This drives the $PaCO_2$ below the "apneic threshold," at which point the neural drive to respire is too low to stimulate effective inspiration and an apnea (complete pause in breathing) or hypopnea (partial reduction in airflow) ensues. $PaCO_2$ subsequently rises, and the cycle is repeated. This overshoot of the homeostatic feedback loop is exacerbated by the prolonged circulation time between the alveoli and the brainstem seen in more severe HF, so that the $PaCO_2$ sensed in the brainstem may not accurately reflect the $PaCO_2$ at the lung. CSA is associated with lower resting $PaCO_2$, increased sympathetic nervous activity, and more severe cardiac dysfunction.[8] The more prolonged the circulation time, the longer the duration of the hyperpneic phase of CSA.[9,10] In addition, pulmonary congestion and edema lead to stimulation of J receptors in the lungs, triggering reflex hyperventilation. A particular form of CSA is a periodic pattern of hyperventilation followed by hypoventilation, termed *Cheyne-Stokes respiration* (CSR). The physiology of CSA is shown in Fig. 77–2.[11]

A tendency to progress from OSA to CSA over the course of the night has been observed in patients with HF. This is thought to be secondary to progressive pulmonary congestion and deteriorating hemodynamics, which may be exacerbated by the SDB.[8]

Interestingly, periodic breathing (CSR) is not limited to sleep but can occur at rest or develop during exercise in patients with advanced HF.[12,13] Recently, it has been suggested that CSR may be a compensatory mechanism in patients with HF.[14,15]

Apnea is currently defined as a reduction in airflow by at least 90% of pre-event baseline for at least 10 seconds; hypopnea is defined as a reduction in airflow by at least 30% from baseline for at least 10 seconds, associated with a fall in arterial oxygen saturation of at least 3% or an arousal from sleep.[16] In OSA, there is evidence of ongoing respiratory effort throughout the apneic-hypopneic event, often with paradoxical movement of the chest and abdomen as breathing against

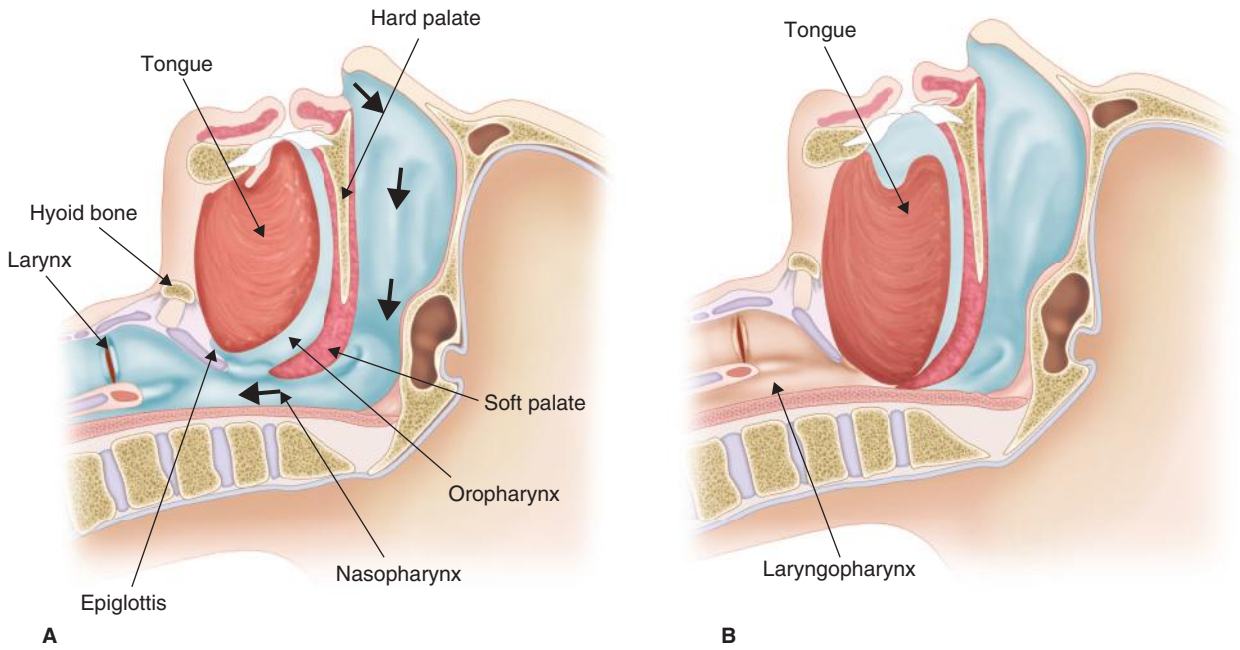


FIGURE 77–1. Normal airflow during respiration (**A**) and common points of obstruction in a patient with obstructive sleep apnea (**B**). Modified with permission from Levitsky MG. Using the pathophysiology of obstructive sleep apnea to teach cardiopulmonary integration. *Adv Physiol Educ*. 2008 Sep;32(3):196-202.[3]

a closed airway is attempted. In contrast, apneas and hypopneas in CSA are accompanied by a marked reduction or cessation of respiratory effort.

The severity of SDB is generally described by the average number of apneic and hypopneic events per hour of sleep, or the *apnea-hypopnea index* (AHI). Normal is defined as up to 5 events per hour, mild as 5 to 15 events per hour, moderate as 15 to 30 events per hour, and severe as > 30 events per hour. The number and severity of oxygen desaturations may also be used as a metric of the severity of SDB. Additionally, those in whom > 50% of events are obstructive are labeled as having predominantly OSA, and those in whom > 50% of events are central are labeled as having predominantly CSA.

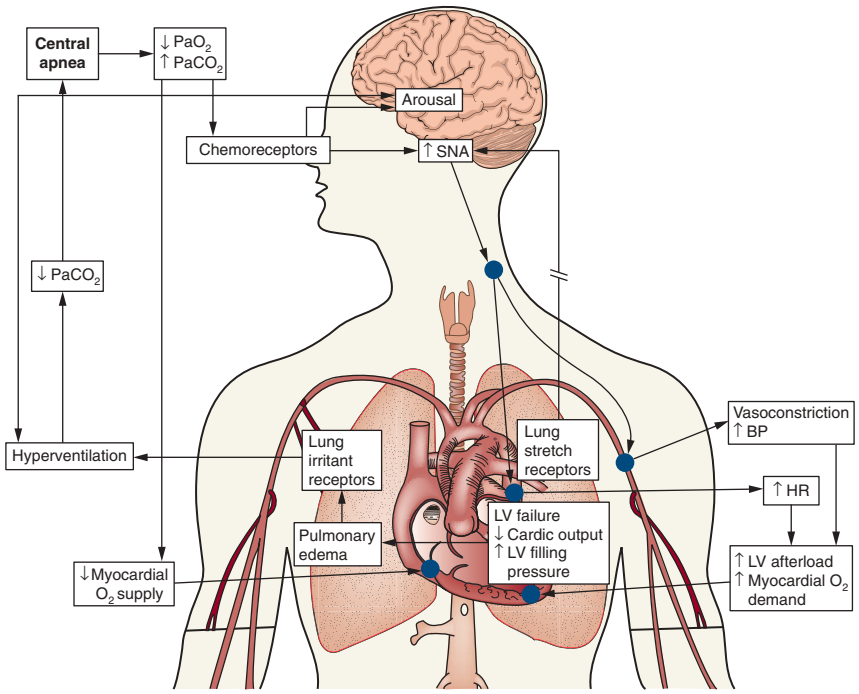


FIGURE 77–2. Pathophysiology of central sleep apnea in heart failure. BP, blood pressure; HR, heart rate; LV, left ventricular; O_2, oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SNA, sympathetic nerve activity. Reproduced with permission from Bradley TD, Floras JS. Sleep apnea and heart failure: part II: central sleep apnea. *Circulation*. 2003 Apr 8;107(13):1822-1826.[11]

HOW IS SLEEP-DISORDER BREATHING DIAGNOSED?

In patients without cardiovascular disease (CVD), typical symptoms of SDB include excessive daytime sleepiness including drowsy driving, insomnia, morning headaches, depression, cognitive dysfunction, nocturnal dyspnea, nocturia, and erectile dysfunction. However, there is wide interindividual variation in symptoms, especially between male and female patients.[17]

At least 50% of patients with severe OSA do not report symptoms of unrestful sleep. This proportion is even higher in patients with OSA and CVD, who often primarily report the symptoms of the underlying CVD, such as chest pain or breathlessness, rather than the typical symptoms of OSA.[18,19]

Patients with HF and SDB do not tend to complain of daytime sleepiness, possibly because of the high sympathetic tone found in HF. Screening questionnaires that include questions about daytime sleepiness (such as the Epworth Sleepiness Scale used to screen for OSA in non-HF populations) are therefore not useful.[20]

Attended in-hospital polysomnography (PSG), including assessment of respiratory movement, oxygen saturation, nasal and oral airflow, snoring, electroencephalography, electrocardiography, electromyography, and ocular movement, has long been considered the gold standard test for sleep disorders. This provides comprehensive data, but it is expensive, laborious and not available in all centers. More limited, multichannel sleep polygraphy with oxygen saturation, nasal airflow, and chest and abdominal movement recorded is more widely available and can be set up by the patient at home. It is comfortable to wear and less expensive than in-hospital PSG, and the data produced are relatively simple to analyze (Fig. 77–3).[21] Studies comparing the diagnostic accuracy of home polygraphy with gold standard PSG have shown that polygraphy has a sensitivity and specificity of 90% to 100% for the diagnosis of significant SDB, at least in patients with HF.[22,23] An advantage of PSG is that periods of wakefulness are easily identified, and therefore, AHI can be recorded during sleep only, whereas in polygraphy, AHI is calculated throughout the recording period regardless of sleep pattern, and this may lead to an underestimation of the severity of the SDB.

Even simpler screening for SDB may be performed by recording nocturnal oxygen saturation via a finger probe. For the diagnosis of moderate to severe SDB in patients with HF, a sensitivity of 93% and specificity of 73% compared to PSG when using a cutoff of 12.5 desaturations of ≥ 3% per hour for patients have been reported, implying that few patients with clinically important SDB would be missed by this simple first-stage approach.[24] Oxygen saturation monitoring is a simple and inexpensive method for screening for SDB, but it cannot determine the phenotype of SDB, and further investigation with (at least) polygraphy is mandatory in those who test positive and in anyone who tests negative but in whom clinical suspicion remains high.

Nocturnal heart rate variability, whether on a 24-hour tape or from an implanted device, reflects autonomic tone but does not appear to be a useful approach to screening, although more sophisticated analytical algorithms show promise.[25]

In the past 10 years, there has been increasing interest in whether algorithms could be developed in cardiac implantable electronic devices (such as pacemakers and defibrillators) to accurately detect and quantify SDB.[26] It is possible to continually measure thoracic impedance between the right ventricular lead tip and the generator. On inspiration, the increased volume of air in the chest increases thoracic impedance with the inverse occurring on expiration, with consequent proportional changes in detected potential difference. SDB diagnostic algorithms are now commercially available. The DREAM study reported a sensitivity of 89% and specificity of 85% for the diagnosis of moderate to severe SDB by a pacemaker algorithm using transthoracic impedance and minute ventilation sensors.[27] Studies on other device platforms are currently under way (including NCT02204865 [ClinicalTrials.gov identifier]). With the additional facility to download implanted device data remotely, it is hoped that changes in SDB severity might be useful as an early marker of HF decompensation, providing a window of opportunity to optimize treatment. Further research, including prospective validation studies, is required.

RISK FACTORS FOR SLEEP-DISORDERED BREATHING

AGE

The prevalence of SDB varies considerably by age group, with one peak occurring in children ages 4 to 8 years, related to adenotonsillar hypertrophy or craniofacial abnormalities, after which there is a declining prevalence until early adulthood, when the rates of SDB progressively increase into older age,[28] perhaps related to reduced pharyngeal caliber, increased pharyngeal length and parapharyngeal fat pad volume, or impairment of protective pharyngeal reflexes.[29-31] Among older individuals, the prevalence of SDB is at least 20%.[32-34] The high prevalence of SDB in older individuals, the population group at highest risk for CVD, underscores the importance of determining the link between this comorbidity and morbidity and mortality in cardiovascular practice.[33]

SEX

Most population-based data indicate that the prevalence of SDB is two- to three-fold higher in men compared with women.[35,36] Men also experience a more rapid progression of the AHI with age than women,[28,37] although sex differences decrease after women reach menopause. Women tend to have less severe OSA than males as a result of milder episodes of upper airway resistance and flow limitation that do not meet the criteria for apnea. This is likely a result of differences in the upper airways geometry, parapharyngeal fat distribution, and respiratory stability.[35] These gender differences tend to decrease with age.[17]

ETHNICITY

Differences in the prevalence of SDB among individuals of varied racial and ethnic backgrounds likely reflect genetic factors that influence craniofacial shape, body fat distribution, and physiologic risk factors for SDB, as well as the influence of environmental factors. In the United States, the prevalence of SDB among African Americans has been reported to be between two- and six-fold higher than European American populations.[38-41] Race-based differences in chemoreceptor and baroreceptor responses also may predispose African Americans to development of SDB.[42] Several studies of Asian populations, with lower rates of obesity than in many Western societies, also have identified a relatively high prevalence of SDB, which is likely attributable to race-based differences in craniofacial morphology.[43,44] In an elderly US cohort of men, the highest prevalence of SDB was among the Asian American sample, who, after considering the effects of obesity, had a two-fold higher SDB prevalence compared with whites.[33]

OBESITY

Approximately 40% to 60% of cases of SDB are attributable to being overweight.[35] It is estimated that a 1% increase in body mass index (BMI; kg/m^2) is associated with a 3% increase in AHI.[45] Excess body weight increases susceptibility to upper airway collapsibility by increased mechanical loading of the upper airway, which causes the upper airway to assume an elliptical, relatively collapsible shape, and by reducing resting lung volume, resulting in a loss of caudal traction on

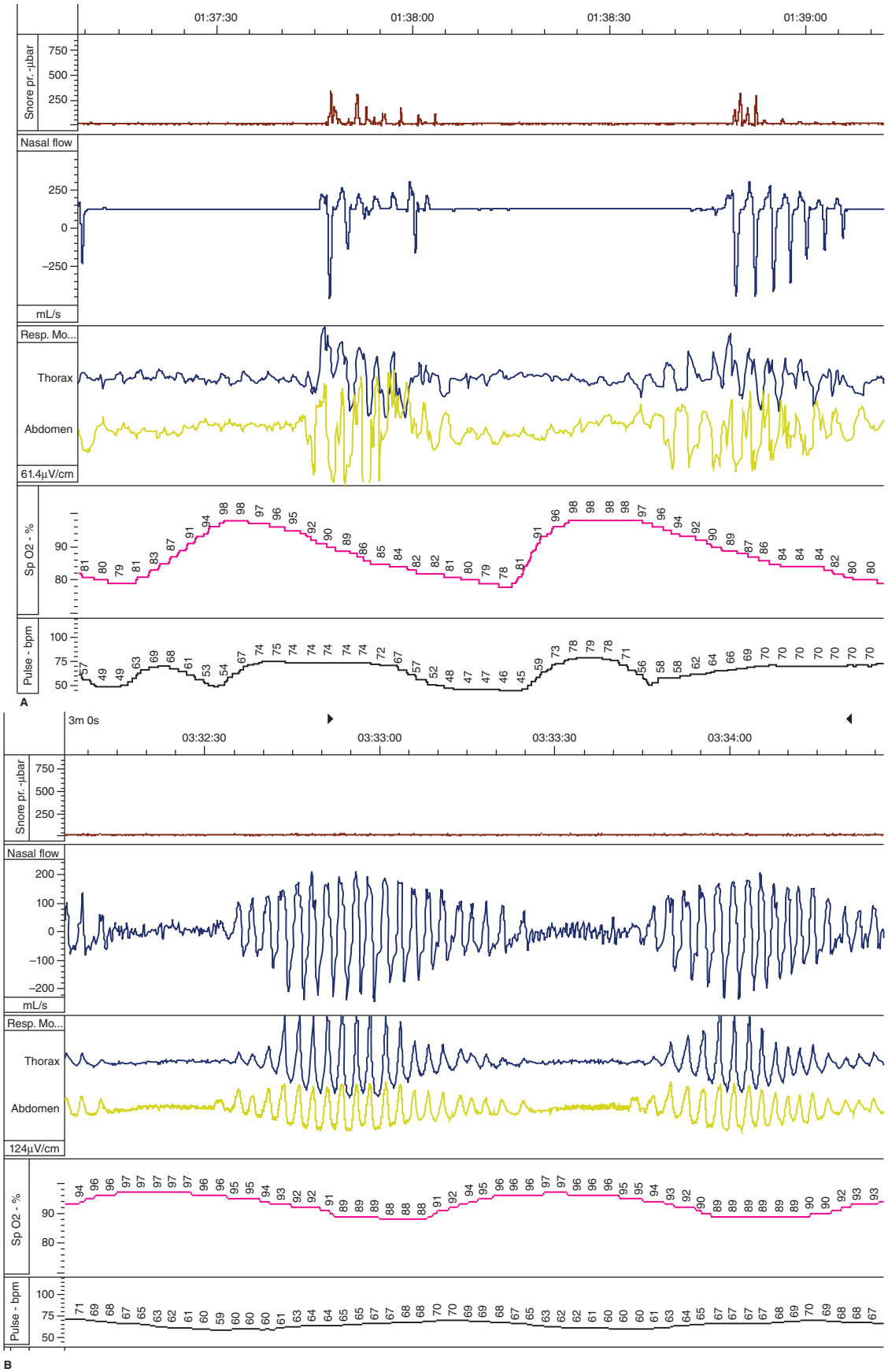


FIGURE 77–3. Polygraph recordings from a patient with (**A**) obstructive sleep apnea and a patient with (**B**) central sleep apnea. Reproduced with permission from Pearse SG and Cowie MR. Sleep disorderd breathing in heart failure. *Eur J Heart Fail*. 2016 Apr;18(4):353-361.[21]

upper airway structures. Additional effects may be related to release of adipokines such as leptin, which can affect ventilatory control.[46]

SMOKING AND ALCOHOL USE

Although exposure to tobacco smoke may increase upper airway inflammation and snoring, smoking is not a firmly established risk factor for SDB. Alcohol use may exacerbate SDB, especially during the first 2 hours after ingestion, as a result of a decrease in upper airway muscle tone and perhaps a reduction in central respiratory drive.[47,48] In patients with SDB treated with positive airway pressure, alcohol use may increase the required pressure needed to maintain airway patency.[47]

HEART FAILURE

There is likely a bidirectional relationship between congestive HF and SDB, particularly CSA. Significant risk factors identified for CSA in HF in patients referred to a sleep laboratory include male sex (odds ratio [OR] = 3.50), atrial fibrillation (OR = 4.13), age > 60 years (OR = 2.37), and hypocapnia (partial pressure of carbon dioxide [PCO_2] < 38 mm Hg during wakefulness; OR = 4.33).[49] HF may contribute to SDB development by precipitating periodic breathing and upper airway neuromotor instability as well as through effects that include accumulation of fluid or edema of the upper airway, thereby enhancing collapsibility and thus the tendency to obstruction. A recent study of more than 6500 patients in Germany with systolic HF confirmed the strong association between obesity, male sex, atrial fibrillation, age, and poorer left ventricular systolic function and the presence of SDB.[50]

PHYSIOLOGIC CONSEQUENCES OF SLEEP-DISORDERED BREATHING

INTERMITTENT HYPOXEMIA

Cyclical episodes of hypoxemia-reoxygenation occur in patients with SDB and result in increased inflammation and production of oxygen-derived free radicals with likely resultant tissue damage.[51] The apnea-related recurrent hypoxemia-reoxygenation in SDB may be analogous to ischemia/reoxygenation injury.[52-55] The severity of oxygen desaturation is associated with levels of vascular endothelial growth factor, a stimulator of neoangiogenesis.[56] Intermittent hypoxia and reoxygenation may also result in activation of the proinflammatory transcription factor nuclear factor-κB.[57] Atherogenesis may result as a consequence of endothelial cell and leukocyte activation and increased expression of adhesion molecules.[58-62] Endothelial damage may also result from intermittent blood pressure and heart rate surges associated with marked sympathetic activation.[63] Other adverse responses to hypoxia include activation of "stress" genes[64] that influence oxygen delivery, such as hypoxia-inducible factor-1.[65]

SYMPATHETIC NERVOUS SYSTEM ACTIVATION

Sympathetic nervous system activity is heightened in SDB, with increased muscle sympathetic nervous system activity (measured by peroneal microneurography)[66-68] and elevated urinary norepinephrine concentrations.[68] Urinary norepinephrine increases in parallel with the severity of SDB, the number of arousals, and the degree of oxygen desaturation.[69] The mechanism for the increased SNS activation remains unclear, but appears to be related to upper airway closure, hypoxemia, hypercarbia, and arousals associated with the respiratory events.[70,71] SDB treatment with positive airway pressure (PAP) therapy lowers urinary norepinephrine excretion[68,72,73] and plasma norepinephrine, vanillylmandelic acid, and metanephrine levels.[74] Similarly to hypoxemia, enhanced sympathetic nervous system activity may stimulate the expression of inflammatory cytokines.[75]

ALTERATIONS IN INTRATHORACIC PRESSURE

The repetitive inspiratory efforts during the apneas and hypopneas in SDB lead to exaggerated negative intrathoracic pressure swings (up to -65 mm Hg intrathoracic pressure in OSA), causing a cardiac load unique to SDB,[76,77] including increased left ventricular transmural pressure, increased afterload and right ventricular venous return, and an abnormal leftward shift of the interventricular septum.[78] This leads to increased myocardial oxygen demand, impaired myocardial relaxation, and reduced cardiac output. Progressive increases in intra-atrial pressures lead to atrial myocardial overstretching and dilation, causing cardiac volumetric changes and electrical remodeling that may lead to atrial fibrillation.[79,80] Adverse effects on intrathoracic pressure may worsen the hemodynamic status in patients with HF. Several studies have reported that left ventricular diastolic function declines in association with SDB, especially with aging.[81-83]

CARDIAC REMODELING

Animal models have shown the development of hypertension, left ventricular hypertrophy, and reduced left ventricular ejection fraction as a result of experimentally manipulated long-term SDB.[84,85] In humans, a progressive increase in left ventricular mass index with AHI level, independent of BMI, has been reported in the Sleep Heart Health Study, an observational cross-sectional study investigating cardiovascular outcomes in SDB.[86] More severe SDB, as defined by higher AHI and more hypoxemia, was associated with greater left ventricular systolic dimensions and lower left ventricular ejection fraction. Left ventricular diastolic dysfunction also appears to be poorer in patients with more severe SDB, independently of obesity, diabetes mellitus, and hypertension.[87] SDB may more adversely affect myocardial function in patients with underlying coronary artery disease than in those without coronary artery disease.[88] Mechanisms of such harm are likely to include marked swings in preload and afterload, sympathetic nervous system activity, increased myocardial oxygen demand and decreased myocardial oxygen supply, and direct effects of hypoxemia.[89]

SLEEP REDUCTION AND FRAGMENTATION

SDB likely exerts its negative physiologic effects in part as a result of reduced quantity of sleep and excessive sleep fragmentation caused by repetitive upper airway obstruction-induced sleep disruption. Reduced sleep duration has been associated with cardiovascular morbidity and all-cause mortality in several epidemiologic surveys.[90-94] The proposed pathophysiologic mechanisms likely include increased inflammation as evidenced by research showing elevations in interleukin (IL)-6,[95] high-sensitivity C-reactive protein,[96] and leukocyte counts[97,98] occurring with sleep deprivation. Because sleep is a complex neurophysiologic process, reductions in specific stages of sleep, as may occur in SDB, may be particularly deleterious. For example, reduction in rapid eye movement sleep may contribute to activation of lipid peroxidation and inhibition of antioxidants,[99] and reduction in slow-wave sleep, a state highly associated with endocrine functions, may decrease insulin sensitivity, increase cortisol, and increase central body fat deposition.[100,101]

METABOLIC DYSREGULATION

Several observational studies have demonstrated associations between sleep apnea and insulin resistance that are independent of obesity.[102] An uncontrolled interventional study demonstrated improved insulin sensitivity in patients with moderate to severe sleep apnea with

treatment, with the best responses occurring in those with a BMI < 30 kg/m^2.[103] Using frequently sampled intravenous glucose tolerance testing, SDB was found to be associated with reduction in insulin sensitivity, glucose effectiveness, and pancreatic β-cell function.[104] Glucose intolerance and insulin resistance in SDB may be mediated by upregulation of inflammatory cytokines.[104] Intermittent hypoxia associated with SDB may lead to glucose intolerance and insulin resistance by promoting the release of proinflammatory cytokines, such as IL-6 and tumor necrosis factor (TNF)-α. IL-6 levels have been correlated with indices of insulin resistance, and higher levels have been associated with an increased risk of type 2 diabetes mellitus.[105-107] Increased levels of TNF-α also likely contribute to the development of insulin resistance.[108-111] Two clinic-based studies have shown that plasma levels of IL-6 and TNF-α are higher in patients with SDB than in control subjects.[112,113] Animal studies showing an increase in insulin levels with exposure to hypoxemic conditions provide further evidence implicating SDB in the pathogenesis of metabolic dysfunction.[114-116]

Increased sympathetic activity associated with SDB also may affect glucose homeostasis by increasing glycogen breakdown and gluconeogenesis.[67,117,118] Further predisposition toward metabolic dysfunction may occur through effects of SDB on the hypothalamic-pituitary-adrenal axis. Experimental partial or total sleep deprivation has been shown to increase levels of plasma cortisol on the following evening at a time when the circadian rhythm of the hypothalamic-pituitary-adrenal axis is at its nadir.[119] The increase in evening cortisol can result in pronounced increases in serum glucose levels and insulin concentrations and increased insulin secretion.[120]

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction may occur in SDB as a result of systemic inflammation, oxidative stress, and sympathetic nervous system activation. Individuals with SDB have impaired resistance-vessel endothelium-dependent dilation.[121] A controlled study in normotensive men with SDB demonstrated that endothelium-dependent, flow-mediated dilation significantly increased in men who were compliant with 6 months of SDB treatment with PAP.[122] Two studies suggested that the effects of SDB on endothelial function may be stronger in women than men.[123,124]

THROMBOSIS

There is some evidence for a hypercoagulable state in sleep apnea, which may contribute to the increased risk of vascular events. Sleep apnea has been associated with increased levels of plasminogen activator inhibitor-1 (PAI-1),[125] fibrinogen,[126] activated coagulation factors XIIa and VIIa, thrombin/antithrombin III complexes, and soluble P selectin.[127] PAI-1, a molecule that inhibits fibrinolysis by inactivation of tissue plasminogen activator, has been shown to contribute to atherothrombotic events and an increased risk of recurrent myocardial infarction.[128-130] PAI-1 levels have been shown to vary with measures of hypoxia[131,132] and sympathetic nervous system activation.[133] PAI-1 levels have been reported to be elevated in individuals with SDB and to improve with SDB treatment.[134] Fibrinogen plays a role in clot formation and has been identified as a predictor of coronary artery disease.[135] Several small studies have identified an association between fibrinogen and SDB[136,137]; however, potential confounders such as obesity were not considered in these studies.

SLEEP-DISORDERED BREATHING AND CARDIAC DISEASE

The potential links between SDB and cardiac disease are illustrated in Fig. 77–4.

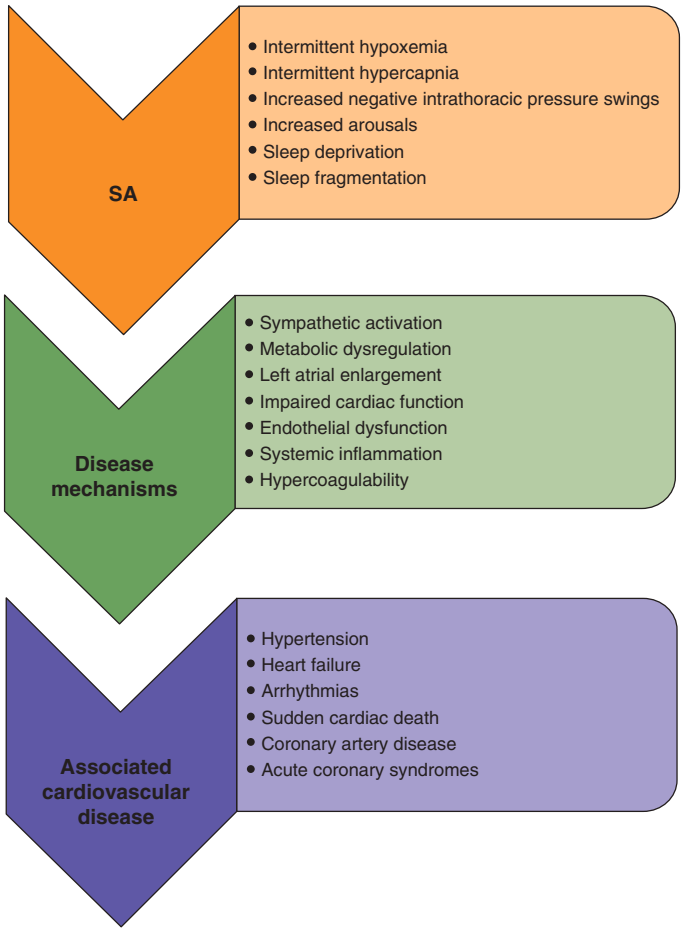


FIGURE 77–4. Schematic of pathophysiologic components of obstructive sleep apnea (SA), activation of cardiovascular disease mechanisms, and consequent development of cardiovascular disease. Modified with permission from Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol*. 2008 Aug 19;52(8):686-717.[18]

OVERALL MORTALITY

Observational studies of clinic-based patients have reported that patients with SDB have a higher mortality risk and that treatment with continuous positive airway pressure (CPAP) therapy may reduce this risk.[32,138-149] Many of these studies were small and did not fully consider confounding factors such as obesity, hypertension, and CVD, and changes in other treatment. However, three larger population-based cohort studies have confirmed that after attempting to account for such confounders, SDB appears to be independently associated with all-cause mortality.[150-152]

The Australian Busselton Study of 397 participants followed for a mean period of 13.4 years reported an adjusted hazard ratio for mortality of 4.4 to 6.2 for moderate to severe SDB (AHI ≥ 15).[150])The Wisconsin Sleep Cohort Study involving 1522 participants, with follow-up over a period of 18 years, demonstrated no significant increase in all-cause mortality in individuals with an AHI between 15 and 30 but demonstrated a significant hazard ratio of 2.7 to 3.8 for severe SDB (AHI ≥ 30).[152] In the much larger Sleep Heart Health Study, which included 6441 middle-aged and older adults with an average follow-up time of 8.2 years from several US communities, SDB was associated with increased all-cause and CVD-related mortality (Fig. 77–5). The association was strongest in men age 40 to 70 years with severe disease (AHI ≥ 30), with an adjusted hazard ratio of approximately 2.[151]

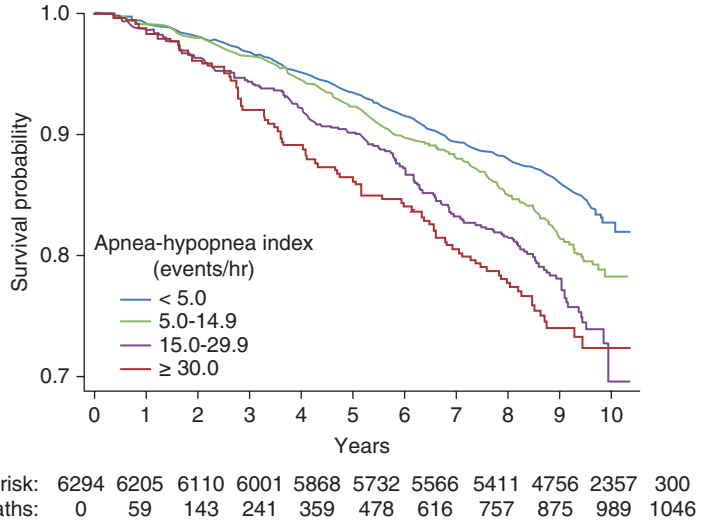


FIGURE 77–5. Kaplan-Meier survival curves across categories of sleep disordered breathing in 6441 men and women in the Sleep Heart Health Study. Modified with permission from Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med*. 2009 Aug;6(8):e1000132.[151]

HYPERTENSION

Animal studies suggest a central role of hypoxemia occurring with upper airway obstruction in the pathogenesis of hypertension,[84,153] whereas a human study suggests a critical role of upper airway-associated arousal.[154] Increases in blood pressure and heart rate occur approximately 5 to 7 seconds after the termination of an apnea or hypopnea, coincident with arousal, peak ventilation, and the nadir of oxygen saturation.[155,156] The hemodynamic profile of blood pressure patterns in SDB is characterized by a nondipping blood pressure pattern,[153] a profile also associated with an increase in CVD.[157]

Repetitive upper airway obstruction-associated sympathetic nervous system activation, intermittent negative intrathoracic pressure swings, sleep deprivation, and recurrent episodes of hypoxemia and hypercapnia resulting in arterial chemoreceptor activation and increased sympathetic activity, which individually or interactively may result in acute blood pressure increases, may also contribute to sustained sympathetic activation and chronically elevated blood pressure even during nonsleep periods.

Abundant cross-sectional data support an association between SDB and hypertension independent of obesity,[34,158-165] including data from large cohorts such as the Wisconsin Sleep Cohort Study and the Sleep Heart Health Study. In a cross-sectional analysis of 709 Wisconsin Sleep Cohort participants, an independent association between blood pressure and SDB (AHI ≥ 5) was observed.[34] In a Pennsylvania-based study involving 1741 participants, a dose-response pattern was observed for SDB and hypertension (ie, the ORs for hypertension were 6.8, 2.3, and 1.6 for moderate or severe SDB, mild SDB, and snoring, respectively). Additionally, this association was strongest among individuals who were young and of normal weight.[166] In a cross-sectional analysis of data from 6132 participants in the Sleep Heart Health Study, mean systolic and diastolic blood pressure and prevalence of hypertension increased significantly with increasing severity of SDB, measured by the AHI and percentage of sleep time spent below 90% oxygen saturation, and a 40% to 50% increased adjusted odds of hypertension was observed for those with an AHI ≥ 30 or upper quartile of hypoxemia.[165]

In a sample of 2677 adults referred to a sleep clinic with suspected SDB, the mean blood pressure level and prevalence of hypertension were reported to increase linearly with severity of SDB; each additional apneic event per hour of sleep was estimated to increase the odds of hypertension by approximately 1%, and each 10% decrease in nocturnal oxygen saturation increased the odds by 13%.[163] Overall, these studies demonstrate associations between SDB and hypertension even with mild levels of SDB, show dose-response relationships between hypertension and increasing SDB severity, and demonstrate persistence of statistical significance of these associations even after taking into account measures of obesity.

A causal association between SDB and hypertension is supported by longitudinal data from the Wisconsin Sleep Cohort Study, which showed significant dose-response relationships, such that relative to the reference category (baseline AHI = 0), the ORs for the presence of hypertension at the 4-year follow-up were 1.42 for an AHI of 0.1 to 4.9, 2.03 for an AHI of 5.0 to 14.9, and 2.89 for an AHI of ≥ 15.0.[167] Recent findings from the Sleep Heart Health Study also demonstrated a significant longitudinal relationship between SDB and the development of hypertension among individuals who were normotensive at baseline examination; however, this relationship was attenuated to borderline significance after taking obesity into account.[168,169]

Randomized clinical trials have assessed the effects of CPAP treatment on OSA in more than 1600 patients with hypertension.[170] In the majority of studies, the effect on blood pressure has been favorable. The results of two meta-analyses, including studies that were conducted largely in normotensive patients, suggest that the reduction in blood pressure during CPAP therapy is in the region of 1.5 to 2.5 mm Hg[171,172]; the magnitude of effect varied from zero up to a 10-mm Hg reduction in blood pressure.[173,174] Regression analysis estimated that 24-hour mean blood pressure would decrease by 1.39 mm Hg for each 1-hour increase in effective nightly use of a CPAP device.[172]

In the most recent meta-analysis of published data, which included 29 randomized controlled trials, mean reductions in daytime systolic and diastolic blood pressures with CPAP (vs no treatment) were 2.6 and 2.0 mm Hg, respectively; corresponding nighttime reductions were 3.8 and 1.8 mm Hg.[175] Another interesting finding of this systematic review was that there was an association between the severity of OSA at baseline and the beneficial effects of CPAP on blood pressure: The higher the baseline AHI, the greater the reduction in systolic BP, suggesting that patients with more severe OSA may benefit the most from CPAP therapy in terms of blood pressure reduction.

The greatest benefits of CPAP therapy for OSA have been seen in patients with resistant hypertension.[164,176-178] In such patients, treatment of OSA with CPAP reduced daytime blood pressure by 6.5 mm Hg, compared with a 3.1-mm Hg increase in untreated patients over the study period.[177]

It is important to mention that compliance to CPAP therapy by patients with resistant hypertension plays a key role in achieving optimal blood pressure reduction. Decreases in 24-hour blood pressure were documented in patients with resistant hypertension who used CPAP for at least 5.8 hours per night, but not in those with lower usage,[178] and another study of CPAP treatment for OSA in patients with resistant hypertension reported a significant correlation between hours of CPAP use and decreases in 24-hour systolic and diastolic blood pressure.[179]

It may take 3 to 6 months to achieve the maximum reduction in blood pressure associated with CPAP therapy.[180,181] OSA is recognized as the most prevalent risk factor contributing to resistant hypertension,[182] and an American Heart Association (AHA) scientific statement recommends that OSA in patients with resistant hypertension should be treated with CPAP.[183]

CARDIAC ARRHYTHMIA

Bradycardia and Atrioventricular Block

Bradycardia and atrioventricular block are commonly observed in association with SDB and most likely are mediated by vagal stimulation accompanying apneas and hypopneas.[184,185] Atrioventricular block has been noted to be frequent in SDB and tends to occur during rapid eye movement sleep and improve with CPAP treatment.[186,187]

Atrial Fibrillation

Sleep apnea is highly prevalent in patients with atrial fibrillation (AF). More than 50% of those with persistent AF or with paroxysmal AF with a high AF burden have been shown to have clinically relevant SDB.[188] The prevalence of CSA (as opposed to OSA) in patients with AF is not well described. One study has reported a prevalence of 79% for CSA in pacemaker recipients with permanent AF[189]; this was probably a result of a high prevalence of underlying HF and reduced systolic left ventricular function in this study population. A study in AF patients with normal left ventricular systolic function reported prevalence rates of 31% for CSA/CSR and 43% for OSA.[190]

Among participants in the Sleep Heart Health Study, moderate to severe SDB, as compared with minimal SDB, was associated with a four-fold increased adjusted odds of AF on overnight PSG. Among elderly individuals, stronger associations have been reported between AF and CSA compared with OSA.[191]

Patients with AF with untreated SDB have a higher recurrence of AF after cardioversion than patients without a known SDB diagnosis or patients with treated SDB.[192] Data from a meta-analysis reported that the risk ratio for recurrent AF after pulmonary vein isolation was 1.25 in patients with, versus without, OSA.[193] Prevention of obstructive respiratory events in OSA using CPAP reduces the risk of AF recurrence after ablation therapy.[194,195] In a study of 426 patients,[195] CPAP therapy in patients with OSA and AF undergoing pulmonary vein isolation was associated with a higher AF-free survival rate at 12 months (71.9% vs 36.7% in OSA patients not treated with CPAP), a rate only slightly higher than found in the group of patients without OSA. In AF management guidelines, OSA is mentioned as being associated with AF and as a factor contributing to a reduction in the success of ablation procedures.[196] Consideration of screening for sleep apnea in such patients is reasonable, and if OSA is diagnosed, treatment with CPAP may maximize the effectiveness of other rhythm control strategies.

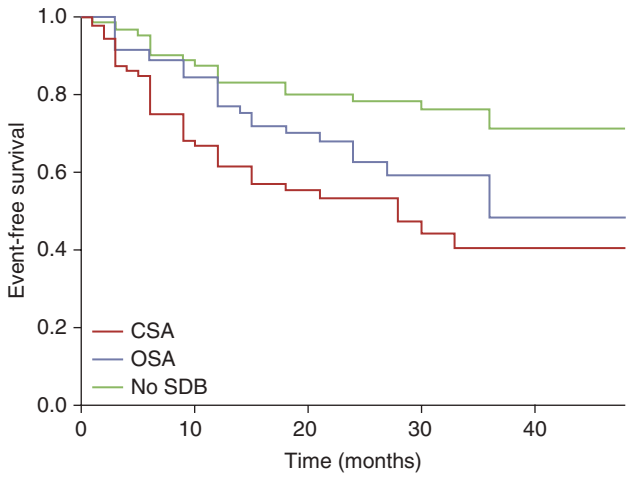
An increased occurrence of AF after coronary artery bypass graft surgery also has been reported to occur in patients with SDB compared with those without SDB, suggesting the importance of untreated SDB in modifying post-cardiac surgery cardiovascular outcomes.[197]

Several mechanisms may contribute to the development of arrhythmia (such as AF) in sleep apnea.[198] In animal studies and in clinical observation, the negative thoracic pressure during obstructive respiratory events in particular was identified as the most relevant factor for the perpetuation and initiation of AF. Negative thoracic pressure changes result in increased occurrence of atrial premature contractions, potentially triggering AF episodes.[199,200] In a pig model of OSA, application of negative tracheal pressure during tracheal occlusion, but not tracheal occlusion without applied negative tracheal pressure, reproducibly and reversibly shortened the atrial refractory period and strongly enhanced the inducibility of AF. These arrhythmogenic electrophysiologic changes were largely driven by combined sympathovagal activation as it could be modulated by sympathetic as well as vagal inhibition.[199-201] Additionally, repetitive obstructive respiratory events resulted in an arrhythmogenic structural substrate for AF characterized by local conduction disturbances as a result of increased atrial fibrosis and distribution of connexins in a rat model of sleep apnea.[202]

Ventricular Arrhythmia

An increase in ventricular arrhythmias in association with SDB was demonstrated in the Sleep Heart Health Study, which reported that after adjusting for age, sex, BMI, and prevalent coronary heart disease, individuals with SDB had a three-fold increased odds of nonsustained ventricular tachycardia and almost twice the odds of complex ventricular ectopy based on electrocardiographic data from overnight PSG.[203] An attenuated association of SDB and ventricular cardiac arrhythmias was observed with increasing age, with potential reasons including survivorship bias, competing risk factors, and/or age-related alterations in the cardiac conduction system altering risk profiles in older adults.[203] A large community-based cohort of older men, the Outcomes of Sleep Disorders in Older Men Study, identified stronger associations of OSA and hypoxia with nocturnal ventricular arrhythmias compared with CSA.[191] Several clinic-based studies also have examined the association between arrhythmias and SDB. In a study of 400 patients with severe SDB, almost half demonstrated cardiac arrhythmias after evaluation by PSG and 24-hour Holter monitoring.[204] Two other studies, however, yielded conflicting results as a result of attenuation of associations after adjustment for confounders.[205,206] Improvement in ventricular ectopy with CPAP treatment has been shown in HF patients[207] and in general SDB patients,[208] with one study showing concomitant improvement in sympathetic activity.[207]

An AHI of > 20/h was a significant and independent risk factor for incident sudden cardiac death in a study of more than 10,000 patients with HF referred for PSG.[209] Coexisting HF and SDB (both OSA and CSA) increase the risk of developing malignant ventricular arrhythmia in patients with implanted cardioverter-defibrillators[210] (Fig 77–6). Severe OSA also increases the risk of ventricular premature beats, nonsustained ventricular tachycardias, and nocturnal sudden cardiac death.[203,211] It has been shown that an episode of AF or nonsustained ventricular tachycardias was almost 18 times more likely to occur within 90 seconds of an apnea or hypopnea compared with normal breathing.[212]



No. at risk	0	6	12	18	24	30	36	42	48
CSA	87	61	39	30	16	13	8	5	5
OSA	82	57	43	31	13	10	7	6	6
No SDB	86	70	50	42	37	32	26	25	24

FIGURE 77–6. Kaplan-Meier plot on appropriate cardioverter-defibrillator therapies, arranged according to no sleep-disordered breathing (no SDB), obstructive sleep apnea (OSA), and central sleep apnea (CSA) with a cut off apnea-hypopnea index ≥ 5. Reproduced with permission from Bitter T, Westerheide N, Prinz C, et al. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. *Eur Heart J*. 2011 Jan;32(1):61-74.[210]

Registry data show that treatment of SDB with servo-assisted positive airway pressure (adaptive servo-ventilation [ASV]) in HF patients with implantable cardioverter-defibrillator devices is associated with less use of defibrillatory therapies and improvements in cardiac function and respiratory stability.[213] However, in light of the increased mortality in a large randomized trial of ASV in patients with HF and reduced ejection fraction and predominantly CSA (SERVE-HF study), discussed further below, mask-based therapy for CSA should be avoided at the present time.

CORONARY ARTERY DISEASE

Animal studies support the occurrence of myocardial ischemia in settings of limited coronary artery flow and SDB, with SDB-associated physiologic stressors causing reductions in myocardial oxygen delivery and increased myocardial oxygen consumption in regions of vulnerable myocardium.[214,215] Similar mechanisms for myocardial ischemia have been identified in studies of SDB patients; increased myocardial oxygen consumption associated with increased diastolic pressure and decreased oxygen supply have been observed to occur during peak changes in hemodynamics during the rebreathing phase of the OSA.[216] It has also been shown that coronary artery disease (CAD) patients with OSA have a higher frequency of noncalcified/mixed atherosclerotic plaques, along with more serious stenosis and a higher number of affected vessels.[217]

The prevalence of OSA in patients with CAD is high (up to 87% in CAD patients referred for coronary artery bypass graft surgery) and is significantly increased compared with healthy controls.[218-223] In a cohort of patients who had undergone revascularization for CAD, the prevalence of OSA was higher than that of obesity, hypertension, diabetes, and AF.[224]

Case-control studies have shown associations between CAD and SDB, with one study showing the persistence of this association even after taking into account potential confounding factors.[221,222,225] In a cross-sectional analysis of the Sleep Heart Health Study data, SDB was marginally associated with self-reported coronary heart disease (upper vs lower AHI quartile: OR = 1.27; 95% confidence interval [CI], 0.99-1.62).[226] Prospective analyses showed a 70% increased 8-year incidence of CAD in men younger than age 70 years in the Sleep Heart Health Study cohort.[227] Over a 7-year study of the Gothenburg Sleep Cohort, CAD was observed in 16% of patients with SDB (defined as ≥ 30 oxygen desaturation events) compared with 5.4% of patients without SDB, with reduced rates of CAD among those with SDB who used CPAP.[228] A Spanish observational study involving solely male patients assessed incidence of fatal and nonfatal cardiovascular events over a 10-year period and reported that patients with untreated severe SDB had a 2.9-fold increased risk of fatal and 3.2-fold increased risk of nonfatal cardiovascular events compared with healthy participants, even after taking into account potential confounders. The authors concluded that, in men, severe SDB significantly increases the risk of fatal and nonfatal cardiovascular events.[139]

In a study in which cardiovascular mortality was prospectively investigated in consecutive patients with known CAD during a follow-up period of 5 years, cardiovascular death occurred in 38% of those with SDB compared with 9% of the non-SDB group ($P = .02$).[140] In another prospective cohort study involving 408 patients ≤ 70 years old with verified coronary disease who were followed for a median of 5.1 years, there was a significant 70% relative increase and a 10.7% absolute increase in the primary composite end point of death, cerebrovascular event, and myocardial infarction in patients with SDB defined as an oxygen desaturation index of ≥ 5 (risk ratio = 1.70). Patients with an AHI ≥ 10 had a significant 62% relative increase and a 10% absolute increase in the composite end point (risk ratio = 1.62).[229] These results suggest that individuals with CAD and SDB have a worse cardiovascular prognosis compared with individuals with CAD without SDB and may benefit from SDB treatment, in addition to more aggressive treatment of their vascular risk factors. The Sleep Apnea Cardiovascular Endpoints Trial is due to report in 2016[230]; this international, multicenter, open, blinded end point randomized trial recruited more than 2700 patients with CVD and OSA and is designed to determine the effect of CPAP therapy on cardiovascular end points (ClinicalTrials.gov identifier: NCT00738179). The average duration of follow-up by the time the trial reports results is likely to be more than 4 years.

Few reports have documented the association between SDB events and symptomatic ischemia.[231] One study reported a high prevalence of ST-segment depression in patients with SDB during sleep, even in the absence of documented CAD, with a reduction in periods of ST-segment depression occurring with initiation of CPAP therapy.[232] Another study noted that patients with SDB have a higher frequency of cardiac rhythm disturbances and ST-segment depression episodes than controls and that the ST-segment changes were related to heightened sympathetic tone and sleep fragmentation.[233] Cardiac ischemia may also disrupt sleep. In one study, more frequent and more severe arousals were observed during periods with myocardial ischemia than during control episodes, suggesting a vicious cycle where apneas may induce ischemia, which then further disrupts sleep.[234]

In patients with CAD, SDB treatment with CPAP has been reported to reduce rates of nocturnal ischemia in one nonrandomized study[216] and reduce rates of cardiovascular death, acute coronary syndrome, hospitalization for HF, and need for coronary revascularization in another observational study.[235]

ACUTE CORONARY SYNDROME

The prevalence of SDB in the setting of acute coronary syndrome has been reported to be high. Specifically, of 104 patients admitted with acute coronary syndrome to one center in the United States, 66% had mild to moderate SDB (AHI ≥ 10), and 26% had moderate to severe SDB (AHI ≥ 30), with the predominant apnea pattern being obstructive (72%).[236] In the first few days after an acute myocardial infarction (MI), the prevalence of moderate to severe sleep apnea (AHI > 15) was as high as 55% in one German center.[237] AHI has been shown to be independently associated with less myocardial salvage and a larger infarct size at 3 months,[238] and the presence of OSA appears to inhibit the recovery of left ventricular function after MI.[223] In the acute setting, the presence of OSA has been shown to be an independent predictor of cardiovascular events in patients with non-ST-segment elevation coronary syndromes in a study from a Brazilian center (OR = 3.4; 95% CI, 1.3-9.0; $P = .0002$).[239] Cardiovascular event rates over a 5-year follow-up were 37.5% and 9.3% in CAD patients with and without OSA, respectively ($P = .018$).[239] A randomized trial of CPAP in patients with acute coronary syndrome and nonsleep OSA is being conducted in 15 teaching hospitals in Spain, with plans to recruit more than 1250 patients (ClinicalTrials.gov identifier: NCT01355087).[240] Until the results are available (likely in 2017), patients should be managed on an individual basis.

HEART FAILURE

The Sleep Heart Health Study identified OSA as an independent risk factor for the development of HF,[226] with more impact in men than in women.[227] Prospective data from the Wisconsin Sleep Cohort Study in a cohort of 1131 adults (men and women) age 30 to 60 years and followed for 24 years show a 2.6-fold increase in the incidence of coronary heart disease and (self-reported) HF, after adjustment for age, sex, BMI, and smoking.[241]

SDB is common in patients with HF, with prevalence rates of 50% to 75%.[242,243] SDB has been documented in patients with both HF with reduced ejection fraction[244,245] or HF with preserved ejection fraction (HFpEF),[246,247] with no difference in prevalence between the two groups,[248] and in patients with acute decompensated HF, where the prevalence can be even higher (44%-97%).[249-251]

The prevalence of CSA/CSR appears to increase as the symptomatic severity of the HF syndrome increases[242,246] (Fig. 77–7), and the severity of CSA/CSR seems to mirror underlying cardiac dysfunction.[252-254] Furthermore, CSA is independently associated with a worse prognosis in patients with HF, including increased mortality.[210,255-259] Approximately 20% to 45% of patients with chronic HF have OSA,[242,243] and the predominant type of SDB in HFpEF appears to be OSA (70%-80%), which occurs more often than CSA in these patients.[246,260] OSA is independently associated with a worse prognosis in HF patients,[255] even in those who are receiving maximal and optimal HF therapy, including cardiac resynchronization.[261]

One of the interesting features of SDB in patients with HF compared to general SDB patients is a relative lack of symptoms, especially of daytime somnolence,[262,263] which could contribute to the lack of recognition and detection of SDB in HF patients.[264] One possible explanation for a lack of daytime sleepiness in HF patients with SDB is the increased sympathetic nervous system activity in HF patients compared with healthy subjects,[265,266] which is increased even further in the presence of OSA.[7,267] Increased sympathetic stimulation could stimulate alertness to counteract the effects of sleep fragmentation and sleep deprivation.[265] A significant inverse correlation between the degree of subjective daytime sleepiness and daytime muscle sympathetic nervous system activity has been documented in patients with HF and OSA.[20] Furthermore, patients with HF are often taking a variety of medications that cross the blood-brain barrier, and these could also impact on sleep and SDB.[268] One such group of agents is β-blockers, which have been shown to reduce daytime sleepiness and the prevalence of CSA.[269]

Although effective treatment of HF may improve CSA/CSR,[253,270] its negative prognostic impact persists even in patients who are receiving maximal and optimal HF therapy, including cardiac resynchronization.[210,261] In addition, when present, CSA in acute decompensated HF patients is usually severe (AHI > 30)[250] and has been shown to be a predictor of hospital readmission and mortality.[271] It is important to note that even with optimal medical management, resolution of acute decompensation, and return to baseline cardiopulmonary status, the severity of CSA may not change.[13,250,272,273] The effect of the specific treatment of SDB in HF is discussed later in this chapter.

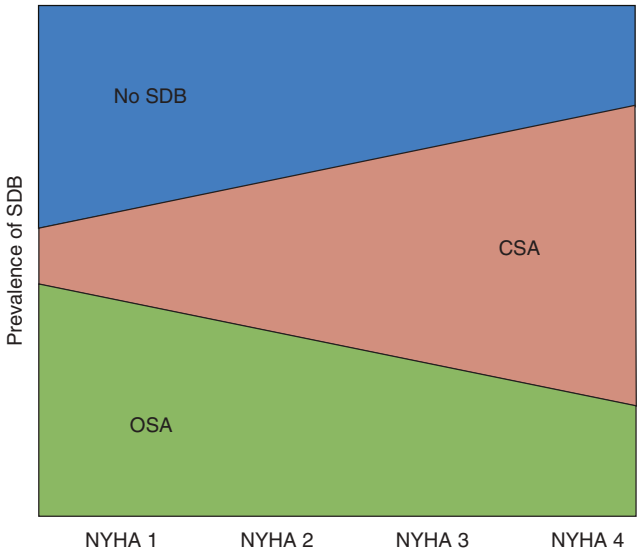


FIGURE 77–7. Prevalence of sleep-disordered breathing (SDB) by symptomatic severity of heart failure. CSA, central sleep apnea; NYHA, New York Heart Association; OSA, obstructive sleep apnea. Modified with permission from Jing J, Huang T, Cui W, et al: Effect on quality of life of continuous positive airway pressure in patients with obstructive sleep apnea syndrome: a meta-analysis. *Lung*. 2008 May-Jun;186(3):131-144.

PULMONARY ARTERIAL HYPERTENSION

Pulmonary hypertension, defined as a mean pulmonary arterial pressure of > 25 mm Hg at rest or > 30 mm Hg during exercise, is characterized by a progressive and sustained increase in pulmonary vascular resistance that may lead to right ventricular failure. Acute changes in pulmonary arterial pressures have been observed to occur during apneas.[274] The primary mechanism likely to be involved with pulmonary hypertension development in SDB is hypoxemia, which reflexively increases pulmonary arterial pressures.[275]

Several studies have shown pulmonary hypertension in 20% to 40% of patients with SDB in the absence of other known cardiopulmonary disorders.[276-278] The pulmonary hypertension associated with SDB appears to be mild to moderate in severity and is thought to be a result of a combination of precapillary and postcapillary factors, including pulmonary arteriolar remodeling and hyperreactivity to hypoxia, left ventricular diastolic dysfunction, and left atrial enlargement.[279] In a study involving 220 consecutive patients with moderate SDB, pulmonary arterial hypertension (mean arterial pressure > 20 mm Hg) was found in 17% of patients; however, the degree of pulmonary hypertension was relatively mild, and only 5% of patients had a pulmonary artery pressure > 35 mm Hg.[280] Individuals with SDB and pulmonary hypertension tended to be more obese and to have hypoxemia and hypercapnia while awake, and some may have had underlying pulmonary disease.[280] Severe SDB is independently associated with pulmonary hypertension in direct relationship with disease severity and presence of diastolic dysfunction.[81] Although measurable changes in the structure and function of the right ventricle have been reported in association with SDB, the clinical significance of these changes is uncertain. Right ventricular failure in SDB appears to be uncommon and is more likely if there is coexisting left-sided heart disease or chronic hypoxic respiratory disease.[279]

In a study of patients with moderate SDB and mild pulmonary hypertension, CPAP treatment resulted in a significant decrease in pulmonary artery pressure, from an average of 16.8 mm Hg before CPAP to an average of 13.9 mm Hg after 4 months of CPAP, and a significant decrease in total pulmonary vascular resistance from 231.1 to 186.4 dyn/s/cm^5.[280] A randomized crossover trial demonstrated that effective CPAP induced a significant reduction in the values for pulmonary systolic pressure (from a mean of 28.9 to 24.0 mm Hg).[281] The reduction was greatest in patients with either pulmonary hypertension or left ventricular diastolic dysfunction at baseline. Another study also reported that CPAP was associated with a reduction in pulmonary systolic pressure levels,[282] including reduced hypoxic pulmonary vascular reactivity. The clinical relevance of these small changes in pulmonary artery pressure is not known.

TREATMENT

LIFESTYLE MEASURES

Lifestyle modifications to improve activity and diet are important in the management of SDB. Weight loss significantly reduces AHI in obese patients with OSA; a meta-analysis of seven randomized controlled trials showed that weight loss programs resulted in a mean

reduction in AHI of 6.04 events per hour (95% CI, -11.18 to -0.90).[283] However, patients with HF and OSA are less likely to be obese, and the impact in this group is not known.

Patients in whom SDB occurs either exclusively or predominantly in a supine sleep position should be counseled regarding positional therapy. Using a wedge or cushion or sewing a pocket filled with tennis balls on the back of a pajamas shirt can discourage sleep in the supine position. Such an approach appears to work for patients with SDB caused by HF.[284]

Alcohol, sedatives, narcotics, and muscle relaxants should be avoided because they may reduce upper airway muscle tone. Drowsy driving precautions should be reviewed with the patient and advice documented.

GENERAL MEDICAL OPTIMIZATION

For patients with HF, optimal medical management is likely to improve the SDB. This should include the use of diuretics, disease-modifying therapy such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, sacubitril-valsartan, β-blockers, and aldosterone antagonists.[269,270,272,285] Cardiac resynchronization therapy for patients with HF with reduced ejection fraction, a broad QRS complex, and CSA significantly reduces AHI[286]; meta-analysis of trials investigating the effect of cardiac resynchronization therapy on CSA reported a mean reduction in AHI of 13.05/h (95% CI, −16.74 to −9.36; $P < .00001$), whereas cardiac resynchronization therapy had no effect on AHI in patients with predominantly OSA[287] (Fig. 77–8).

ORAL APPLIANCES

In patients with retrognathism, mandibular advancement devices may also significantly improve AHI in OSA.[288-290] Oral appliances, worn during sleep and usually fitted by a dentist, may be used to extend the dimensions of the airway and may be effective in select patients, such as those with mild SDB, with positional SDB, or without marked obesity.

SURGERY

Bariatric surgery, increasingly used to treat multiple obesity-related comorbidities, also may benefit patients with OSA and a BMI > 35 kg/m^2.[291] Upper airway or craniofacial surgical interventions may be an option for SDB treatment; however, they require careful assessment and evaluation including a nasopharyngoscopic examination by an experienced otolaryngologist. Outcomes are often suboptimal, with < 50% of patients achieving a 50% reduction in the AHI and reduction to less than critical thresholds.[292] Procedures such as those involving injection of the soft palate resulting in stiffening, radiofrequency ablation, laser-assisted uvulopalatoplasty, and palatal implants can improve snoring, but minimal data exist to support their use for SDB.

POSITIVE AIRWAY PRESSURE

Obstructive Sleep Apnea

PAP therapy delivered through a nasal or nasal-oral mask stabilizes the airway and thus prevents collapse and is the standard treatment for SDB.[293,294] There are a variety of different treatment modalities, as illustrated in Fig. 77–9.[295]

An overnight PAP titration study is required to determine the optimal pressure setting that reduces the number of apneas/hypopneas during sleep, improves hypoxia and sleep architecture, and reduces arousals. Additional beneficial cardiovascular effects of CPAP include

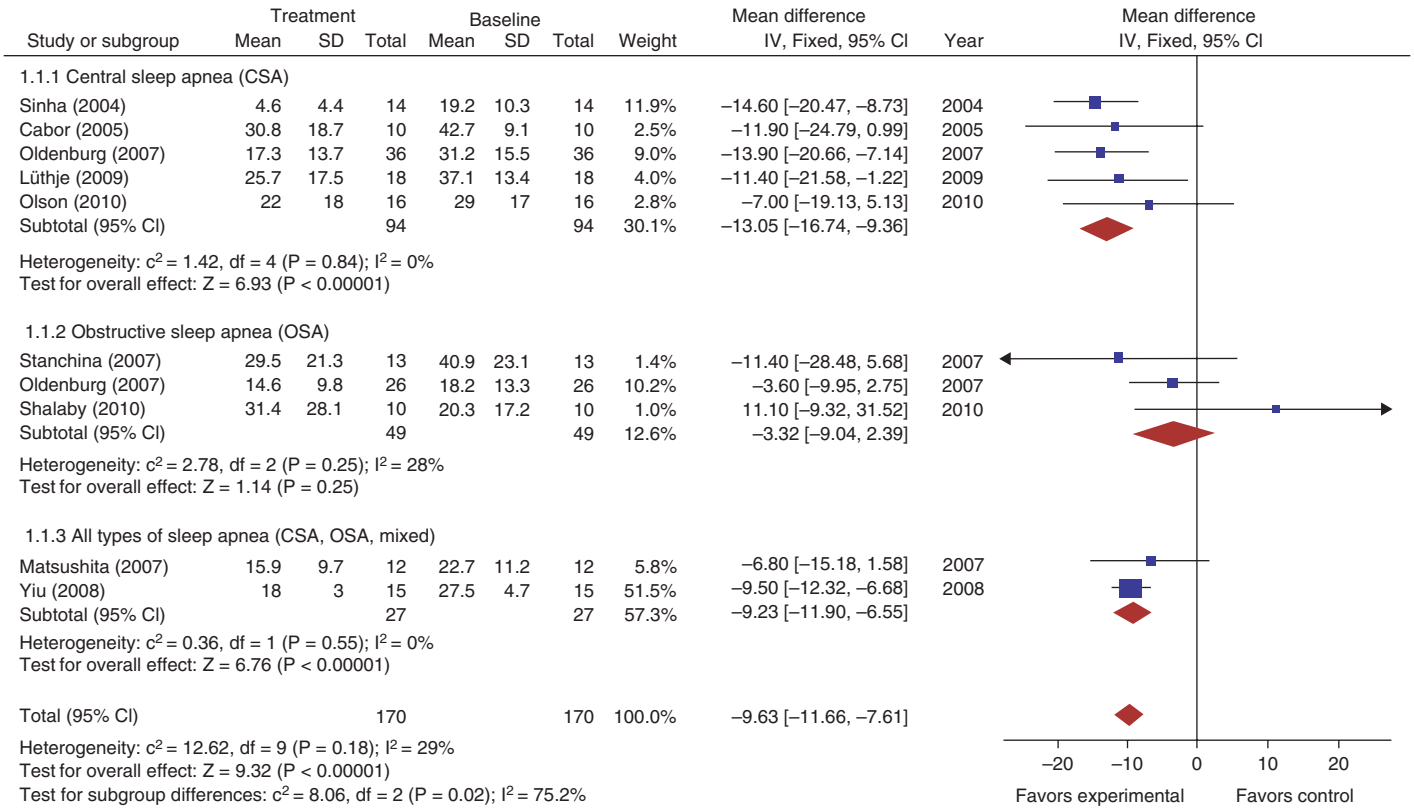


FIGURE 77–8. Reduction in sleep apnea with the use of cardiac resynchronization therapy: meta-analysis of published studies. CI, confidence intervals; IV, inverse variance; SD, standard deviation. Reproduced with permission from Lamba J1, Simpson CS, Redfearn DP, et al: Cardiac resynchronization therapy for the treatment of sleep apnoea: a meta-analysis. *Europace*. 2011 Aug;13(8):1174-1179.

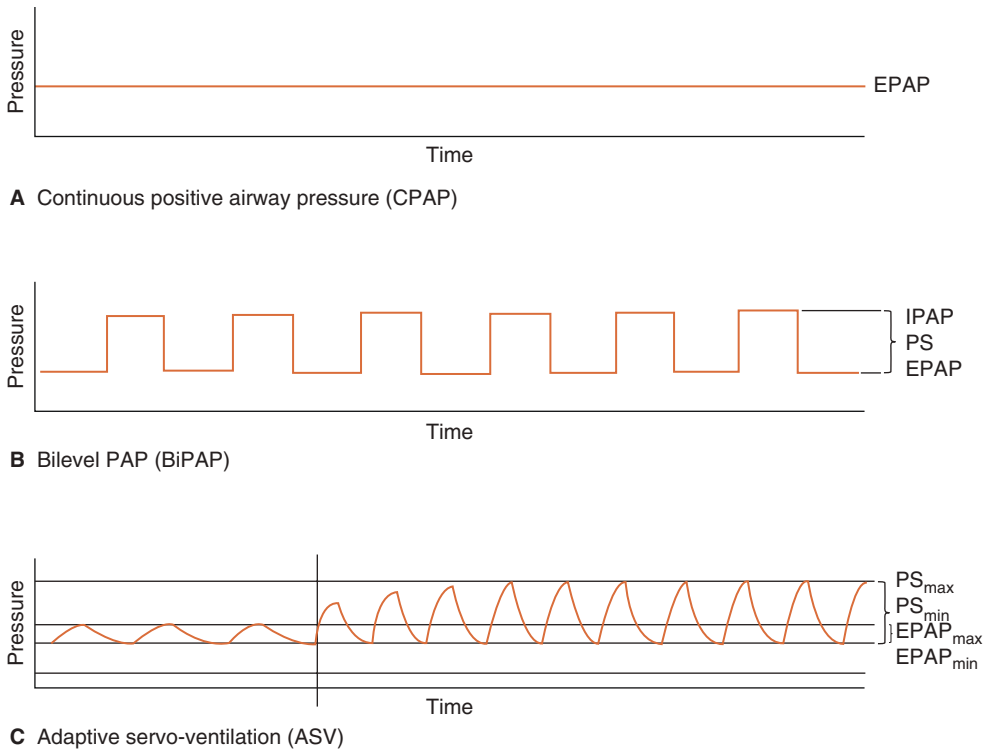


FIGURE 77–9. Different positive airway treatment modalities: (**A**) continuous positive airway pressure (CPAP) with fixed or automatically adjusted expiratory pressure (EPAP) to maintain upper airway patency; (**B**) bilevel positive airway pressure (BiPAP) with fixed EPAP and pressure support (PS) at inspiration (inspiratory pressure [IPAP]), usually with a fixed back-up rate to trigger breathing in respiratory insufficiency; and (**C**) adaptive servo-ventilation (ASV) with fixed or automatically adjusted expiratory pressure (minimal [$EPAP_{min}$] and maximal [$EPAP_{max}$]) and adaptive pressure support (minimal [PS_{min}] and maximal [PS_{max}]) at inspiration with servo-controlled backup rate to stabilize unstable breathing such as central sleep apnea/Cheyne-Stokes respiration. Reproduced with permission from Linz D, Woehrle H, Bitter T et al. The importance of sleep-disordered breathing in cardiovascular disease. *Clin Res Cardiol*. 2015 Sep;104(9):705-718.

increased intrathoracic pressure, reduced left ventricular preload and afterload, and reduced transmural cardiac pressure gradients, all of which can ameliorate impaired cardiac function.[296,297] CPAP improves daytime somnolence, some measures of quality of life, and physical vitality scores.[298]

Adherence with this therapy is highly variable, with average levels ranging from 50% to 80%,[299] but with around 70% of patients still regularly using treatment after 5 years.[300] Adherence is positively influenced by patient education, reviewing the health and quality-of-life benefits of SDB treatment, careful selection of PAP masks that best fit the patient, and supportive management of adverse effects such as nasal congestion or dryness and pressure intolerance. Patient perception of symptoms and improvement in sleepiness and daily functioning may be more important in determining patterns of use than physiologic aspects of disease severity.[299]

In a randomized controlled trial of 55 patients with HF and OSA, nocturnal CPAP for 3 months improved left ventricular ejection fraction (by 5.0% ± 1.0% vs 1.0% ± 1.4%, $P = .04$) and reduced urinary noradrenalin excretion.[301] Kaneko and colleagues[302] demonstrated that even one night of CPAP lowers systolic blood pressure (from 126 ± 6 to 116 ± 5 mm Hg, $P = .02$), reduces heart rate (from 68 ± 3 to 64 ± 3 bpm, $P = .007$), and improves left ventricular end-systolic diameter (from 54.5 ± 1.8 to 51.7 ± 1.2 mm, $P = .009$) in those with OSA and HF, compared to standard medical therapy. Another study, with echocardiographic and cardiac magnetic resonance follow-up, demonstrated that CPAP improves right ventricular function, left ventricular mass, and pulmonary hypertension after 3 months of treatment. These improvements persisted at 1 year.[303] An observational study (88 patients) of CPAP versus medical therapy for those with HF and moderate to severe OSA demonstrated a significantly higher rate of hospitalization or death in the non-CPAP group (hazard ratio = 2.03; 95% CI, 1.07-3.68; $P = .03$) compared to those treated with CPAP.[304] Patients who were not compliant with CPAP also had a higher risk of the composite end point. Two other large registry studies found similar results.[305,306]

The 2010 Heart Failure Society of America Comprehensive HF guidelines recommend screening for SDB and CPAP therapy in those with confirmed OSA.[307] The 2013 American College of Cardiology Foundation/AHA guidelines state that treating OSA with CPAP in patients with HF does have benefit.[308]

Central Sleep Apnea

A number of treatments for CSA/CSR have been studied, including oxygen, carbon dioxide, CPAP, bilevel positive airway pressure (BiPAP), and ASV (see Fig. 77–9).

Although it does not trigger inspiration during CSA, CPAP improves CSA/CSR probably by increasing functional residual capacity (and, as a result, oxygen stores), decreasing blood volume in the lungs and upper airway when lying down,[309] and reducing hyperventilation via a direct effect on the paravasal J-receptors of the lung.[253] In addition, CPAP reduces preload and afterload and the cardiac transmural pressure and may benefit cardiac function in some patients.[11] It may have additional benefits in HF, as positive end-expiratory pressure prevents alveoli collapsing secondary to pulmonary edema and maintains alveoli at a greater diameter, thus reducing the work of breathing. It also increases alveolar recruitment, improves gas exchange, and reduces right-to-left intrapulmonary shunting of blood.

Early small trials of CPAP in CSA with HF demonstrated an improvement in AHI, reduced daytime plasma natriuretic peptide and

catecholamine concentrations, and improved left ventricular ejection fraction, and in one small study of 29 patients, there was a trend toward improved survival with CPAP.[310] A larger randomized controlled trial (the CANPAP study) was designed to evaluate the effect of CPAP on transplant-free survival in patients with CSA and HF.[311] This trial was stopped early after 258 patients had been randomized and followed up for over 2 years; there was no difference in transplant-free survival between CPAP and the optimal medical therapy alone arm. CPAP did result in an improved AHI (-21 ± 16 vs -2 ± 18, $P < .001$), left ventricular ejection fraction (2.2% ± 5.4% vs 0.4% ± 5.3%, $P = .02$), and 6-minute walk test distance and reduced plasma noradrenaline concentrations, but this did not translate into a survival advantage. Post hoc subgroup analysis suggested that there was a survival advantage in those in whom the AHI was suppressed by the CPAP therapy to < 15/h,[312] suggesting a possible role for more efficacious ventilatory techniques, such as ASV.

Some patients with HF and OSA develop CSR during CPAP administration, a finding labeled *complex sleep apnea*.[313-315] BiPAP with backup rate has been shown to be more effective than CPAP at controlling CSA/CSR,[316] but it can also worsen CSA.[317] This is because BiPAP (with a backup rate) is designed to provide ventilation and reduce carbon dioxide (CO_2) levels, which does not ameliorate the hyperventilation and low CO_2 levels associated with CSA/CSR. For this reason, BiPAP is not considered an adequate treatment for CSA/CSR.

However, a high proportion of patients with CSA have residual apnea events despite CPAP therapy, suggesting that a more effective intervention is required.[318] ASV has been shown to be the most effective intervention for controlling (central) SDB in patients with HF.[319] ASV is a more sophisticated mode of noninvasive ventilation in which the ventilator increases inspiratory support during hypopnea, withdraws support during hyperventilation, provides mandatory breaths during apnea, and generates background positive airway pressure. Therefore, it is effective in both CSA and OSA and can suppress complex sleep apnea.[314] Teschler and colleagues[316] showed that ASV is more effective than CPAP or oxygen therapy in suppressing CSA events and is better tolerated by patients than CPAP (Fig. 77–10). ASV has also been shown by others to be more effective than BiPAP for treating CSA/CSR in HF[320] and is better tolerated than CPAP,[321] resulting in improved compliance with therapy, which is an important part of successful treatment.[322]

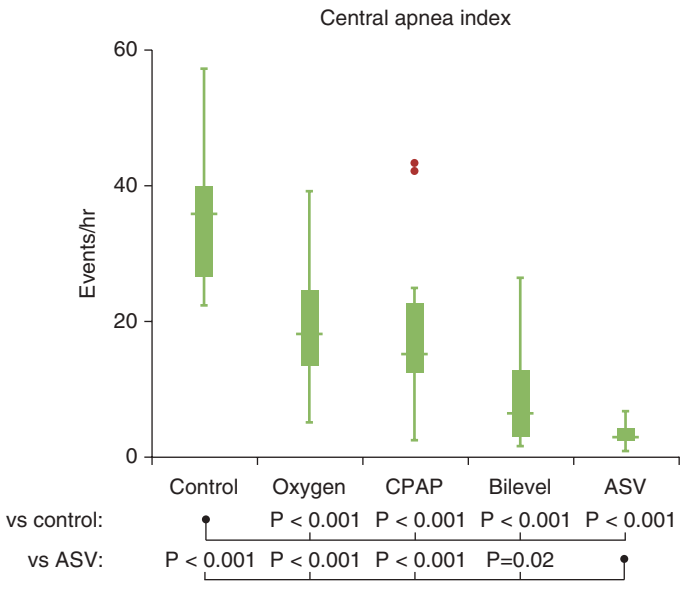


FIGURE 77–10. Relative effects of different treatments on sleep-disordered breathing in patients with central sleep apnea. ASV, adaptive servo-ventilation; CPAP, continuous positive airway pressure. Reproduced with permission from Teschler H, Dohring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med*. 2001 Aug 15;164(4):614-619.[316]

Small studies of ASV have documented improvements in AHI, sleep quality, quality of life, left ventricular ejection fraction, New York Heart Association class, oxygen uptake, serum natriuretic peptide concentrations, inflammatory markers, and exercise capacity.[323-329]

In randomized controlled clinical trials, beneficial effects of ASV treatment of CSA/CSR in HF patients include significant reductions in AHI,[322,330-334] N-terminal pro-brain natriuretic peptide concentrations,[322,333-336] urinary catecholamine release,[333] and left ventricular end-systolic diameter[322]; increases in 6-minute walk distance[322] and left ventricular ejection fraction[330-332]; and improved New York Heart Association class.[331]

Given these beneficial effects, a large randomized controlled trial, SERVE-HF, was undertaken to assess the impact of ASV on hospitalization, life-saving cardiovascular intervention, or death in those with HF and CSA.[337,338] A total of 1325 patients with a left ventricular ejection fraction of 45% or less and moderate to severe (predominantly) CSA were enrolled. At 12 months, ASV was highly efficacious at reducing AHI (from a mean of 31.2 events per hour at baseline to 6.6 per hour). Despite the good control of the CSA, there was no difference in the primary end point (of all-cause mortality, unplanned HF hospitalization, or life-saving cardiovascular intervention) between the two groups, and the study demonstrated a higher overall mortality and cardiovascular mortality in those treated with ASV (hazard ratio for all-cause mortality, 1.28; 95% CI, 1.06-1.55; $P = .01$; and hazard ratio for cardiovascular mortality, 1.34; 95% CI, 1.09-1.65; $P = .006$) (Fig. 77–11). This trial did not find differences in plasma B-type natriuretic peptide concentration, 6-minute walk test, or health-related quality of life between the two randomized groups. Further analyses of the mode of death and data from the patients who had an implanted device with defibrillator capacity are awaited, but initial results suggest that the excess mortality is driven by an increase in sudden death. There was no difference in deaths from pump failure or admissions to hospital with HF decompensation. Various explanations have been proposed for these results, including chance, a direct toxic effect of PAP on patients with poor left ventricular function and a low pulmonary capillary wedge pressure,[339] and the fact that CSA may be at least partially adaptive for patients with severe HF, as has been suggested previously.[14] Further data will emerge from another randomized trial of an ASV device in patients with HF and reduced ejection fraction and either predominantly OSA or CSA (ADVENT-HF; ClinicalTrials.gov identifier: NCT01128816). In the meantime, the use of ASV for the treatment of predominantly CSA in patients with HF and reduced ejection fraction cannot be recommended. Patients already on ASV should be counseled about the potential risks of continuing with this therapy.

CSA is found in the majority of patients with acute decompensated (as opposed to chronic) HF, is usually severe, and is associated with an increased risk of readmission and mortality.[340] A randomized trial of ASV in this patient group was initiated, but was terminated after the results of SERVE-HF became available (CAT-HF; ClinicalTrials.gov identifier: NCT01953874). The results will be presented in late 2016.

Another area of interest is the use of ASV in patients with HFpEF and CSA/CSR. Early results show that ASV can improve cardiac diastolic function, improve symptoms, and decrease B-type natriuretic peptide concentrations in this group of patients.[341,342] In addition, the proportion of HFpEF patients treated with ASV who were free of cardiac events was significantly higher than that in untreated patients.[343]

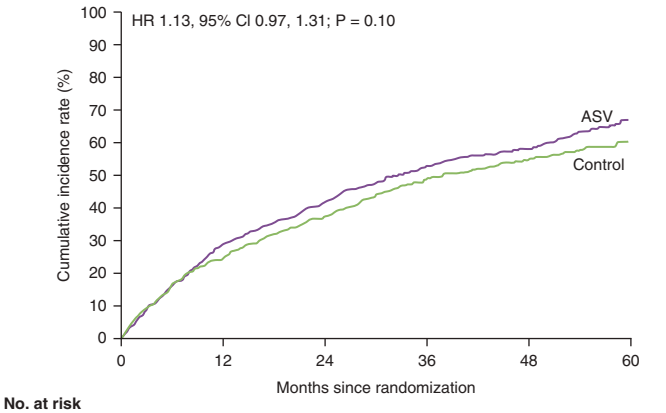


FIGURE 77–11. Cumulative incidence curves for (**A**) the primary end point, (**B**) death from any cause, and (**C**) cardiovascular death in the SERVE-HF trial. The primary end point was a composite of death from any cause, lifesaving cardiovascular intervention, and unplanned hospitalization for worsening chronic heart failure. ASV, adaptive servo-ventilation; CI, confidence interval; HR, hazard ratio. Reproduced with permission from Cowie MR, Woehrle H, Wegscheider K et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med*. 2015 Sep 17;373(12):1095-1105.[338]

OXYGEN THERAPY FOR CENTRAL SLEEP APNEA/CHEYNE-STOKES RESPIRATION

Oxygen therapy for CSA has been the subject of a few small-scale trials. Its use during sleep reduces the severity of CSA/CSR by approximately 50%, reduces nocturnal norepinephrine levels, and attenuates apnea-associated hypoxemia over time frames ranging from 1 night to 1 month,[344-346] but only one study has reported clinical improvements.[346] The CHF-HOT trial randomized a small number of patients with CSA and HF to standard medical therapy with or without home oxygen therapy. Meta-analysis of the results from 97 patients demonstrated a decrease in AHI (–11.4 ± 11.0 vs –0.2 ± 7.6, $P < .01$) and an improvement in left ventricular ejection fraction (36.1% ± 11.8% vs 46.3% ± 16.2%, $P = .014$) in those with severe CSA treated with home oxygen at 3 L/min via an oxygen concentrator, at least out to 12 weeks.[347] There was also an improvement in mean New York Heart Association class but no overall improvement in ventricular ectopy or plasma catecholamine concentrations. The impact on prognosis is unknown. A meta-analysis of 14 studies concluded that oxygen therapy does reduce overnight desaturations, but prolongs apneas and hypopneas.[348]

CARBON DIOXIDE THERAPY FOR CENTRAL SLEEP APNEA/CHEYNE-STOKES RESPIRATION

Administration of CO_2 reduces AHI in CSA but at the expense of hyperventilation and poor sleep quality and, thus, is not used clinically.[349]

EXPERIMENTAL THERAPIES FOR SLEEP-DISORDERED BREATHING

Phrenic Nerve Stimulation

Phrenic nerve stimulation is a new approach to the treatment of CSA/CSR, with initial results showing that it may improve central respiratory events by about 50%.[350-352] This device is similar to a pacemaker, with an electrode that stimulates the phrenic nerve via the left pericardiophrenic or right brachiocephalic vein (Fig. 77–12). It can be implanted percutaneously under sedation in the catheter laboratory. The device unilaterally stimulates the phrenic nerve when no impulse is sensed

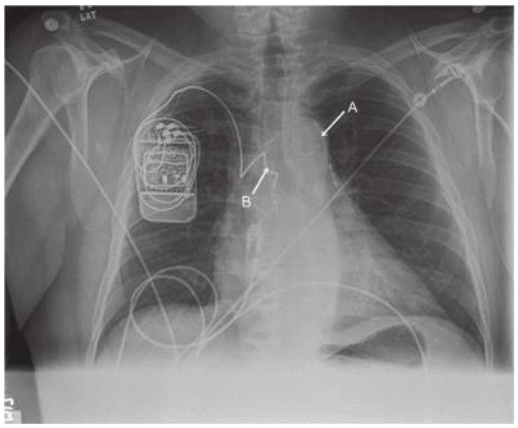


FIGURE 77–12. Chest radiograph of an implantable phrenic nerve stimulator therapy. The neurostimulator has been implanted in the right pectoral area, and the right subclavian approach was used to place the stimulation lead (*A*) in the left pericardiophrenic vein and the sensing lead (*B*) in the azygos vein. Reproduced with permission from Abraham WT, Jagielski D, Oldenburg O, et al: Phrenic nerve stimulation for the treatment of central sleep apnea. *JACC Heart Fail*. 2015 May;3(5):360-369.[350]

for a predetermined time period, inducing a breath. A nonrandomized study of 57 patients showed a mean reduction of 55% in AHI over 3 months (49.5 ± 14.6 to 22.4 ± 13.6, $P < .0001$), with the effect being largely confined to prevention of apnea and with little effect on hypopneas, as well as reductions in arousals and oxygen desaturation index and improved quality-of-life indices.[350] Device- or procedure-related adverse events occurred in 26% of patients, predominantly as a result of lead displacement. A somewhat larger randomized study has completed recruitment to further evaluate the effect of this technology on the reduction in CSA events but is not powered to determine the effect on hospitalization or mortality (ClinicalTrials.gov identifier: NCT01816776).

Hypoglossal Nerve Stimulation

For those with OSA, a similar device exists that stimulates the hypoglossal nerve in response to apnea and hypopnea. An uncontrolled study has shown a significant mean reduction of 68% in AHI over 12 months in those treated with this stimulator.[353] The impact on cardiovascular outcomes is not known.

Acetazolamide

Two small trials of medical therapy with acetazolamide have been reported, showing reductions in AHI and improved oxygen saturation in patients with HF and CSA, which may be a result of its respiratory-stimulating properties as well as diuretic action.[354,355] A slightly larger (n = 85) randomized study addressing the effect of acetazolamide on the severity of SDB in HF is currently being conducted (Predicting Successful Sleep Apnea Treatment With Acetazolamide in Heart Failure Patients; ClinicalTrials.gov identifier: NCT01377987). Whether furosemide achieves the same effect is unknown, although reduction in pulmonary congestion might be expected to lessen CSA by reducing pulmonary J-receptor stimulation.

SUMMARY

SDB causes chronic episodic exposure to intermittent hypoxemia, sympathetic nervous system activation, intrathoracic pressure swings, and sleep fragmentation, which exert profound effects on the heart and vasculature. There is strong evidence for the association of SDB with systemic hypertension, glucose intolerance, obesity, CAD, AF, and HF, and SDB may be an independent risk factor for these conditions. Much of the evidence for the benefit of treatment of SDB comes from observational data sets or small randomized trials, but there is much circumstantial evidence to suggest that the diagnosis and treatment of OSA are worthwhile and may improve cardiovascular prognosis in addition to improving symptoms, including daytime sleepiness. A recent randomized trial of the treatment of CSA with noninvasive pressure support reported an unexpected increase in cardiovascular mortality, largely driven by an increase in sudden death. The explanation for this is unclear, but currently there is no therapeutic imperative to diagnose and treat CSA. Further research is ongoing to establish a stronger evidence base for the diagnosis and treatment of SDB in patients with, or at risk of, CVD.

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SECTION 13

Rhythm and Conduction Disorders

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CHAPTER 78

ELECTROPHYSIOLOGIC ANATOMY

Jonathan P. Piccini, Siew Yen Ho, and Anton E. Becker

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CONCLUSION / 1879

Although the study of cardiac electrophysiology centers around the initiation of electrical impulses and their propagation, it is also very much an "anatomic specialty." The study of electrophysiology requires critical appreciation and understanding of the anatomy of the heart and its relationship to electrophysiologic function. Over the past two decades, advances in electroanatomic mapping and cardiovascular imaging and innovations in both catheter ablation and device-based interventions have led to an improved understanding of cardiac anatomy, normal electrophysiologic function, and mechanisms behind heart rhythm disorders. Accordingly, describing cardiac structures in terms of their function and relationship to cardiac conduction[1] is much more useful to the clinical electrophysiologist than the conventional approach[2] of describing the heart in a purely anatomic and geographic fashion. This chapter on electrophysiologic anatomy highlights features of particular relevance in heart rhythm disorders.

THE HEART IN THE CHEST

For the clinician, the heart must be viewed in the context of its location and relationship to surrounding structures (Fig. 78–1). The frontal silhouette of the heart is nearly trapezoidal. The right border of the heart is more or less a vertical line just to the right of the sternum. It is formed exclusively by the right atrium, with the superior and inferior caval veins joining at its upper and lower margins. The inferior border lying horizontally on the diaphragm is marked by the right ventricle. The sloping left border is often described as having three to four "moguls" on the chest x-ray, which correspond to the aortic arch, pulmonary artery, and left ventricle (superior to inferior). Occasionally, the left atrial appendage is visible between the pulmonary artery and the left ventricle. The aortic knob appears above the pulmonary trunk. In the hilum, the aortic knob is superior and rightward and the main pulmonary artery (or pulmonary trunk) is inferior and leftward. The pulmonary trunk crosses over the root of the aorta anteriorly such that the aorta ascends behind or posterior to it. On the frontal silhouette, the left atrium is barely seen; only its appendage curling round the edge of the pulmonary trunk is visible. The left atrium is the most posterior cardiac chamber (closest to the spine), and the esophagus is immediately behind the left atrium (Fig. 78–2). Understanding this spatial relationship is crucial to ablationists in order to reduce the risk of the postprocedural complication of atrioesophageal fistula.[3]

The heart is enclosed in the fibrous pericardium, which is a protective sac that separates the surface of the heart from adjacent structures and creates a low-friction environment to facilitate cardiac motion. The mediastinal pleura is the outermost lining of the fibrous pericardium. Within the fibrous pericardium, there is a thinner double-layered membrane, the serous pericardium. One layer of the serous pericardium is fused to the inner surface of the fibrous pericardium, whereas the other layer lines the outer surface of the heart as the epicardium. The pericardial cavity is the space between the layers of the serous pericardium. Two recesses are found within the pericardial cavity. These recesses have particular importance for interventional pericardial procedures. The first is the transverse sinus, which is a passage between the superior and posterior reflections of the pericardium, anterior to the superior vena cava, posterior to the arterial trunk, and superior to the left atrium. The second is the oblique sinus, which separates the left atrium from the esophagus. The oblique sinus is a blind cul-de-sac formed by the right pulmonary veins and inferior vena cava on the right side and by the left pulmonary veins on the left side.[4,5] The vein of Marshall is contained within the left margin of the oblique sinus.

The phrenic nerves descend over the pericardial sac. The right phrenic nerve courses along the right anterolateral surface of the superior vena cava down across the intercaval aspect of the right atrium and crosses the diaphragm at the lateral border of the inferior vena cava.[6] Along this course, the right phrenic nerve can be less than 2 mm from the anterior wall of the right superior pulmonary vein (Fig. 78–3A) and thus can be injured during catheter ablation for pulmonary vein isolation.[7] The left phrenic nerve descends on the left side close to the aortic arch and onto the pericardium over the left atrial appendage and the left ventricle. It takes one of three courses over the left ventricle, passing over the anterior surface, leftward over the obtuse margin, or more posteriorly over the left atrial appendage and the basal lateral wall. Most commonly, the course of the left phrenic nerve is close to the lateral branches of the great cardiac vein and thus can be stimulated during left ventricular pacing for cardiac resynchronization therapy (Fig. 78–3B).[6,7]

THE ATRIA

The relationship between the right and left atria is highlighted in Figure 78–4. When viewed from the frontal plane (see Fig. 78–4A), the right atrium is rightward and anterior, whereas the left atrium is leftward and posterior (see Fig. 78–4B). The left atrium is also more superior (cephalad) relative to the right atrium. As mentioned earlier, the roof of the left atrium (including the Bachman bundle) forms the inferior aspect of the transverse pericardial sinus. The posterior wall of the left atrium is just in front of the tracheal bifurcation and esophagus. When looking at the right atrium from the right lateral view, one can

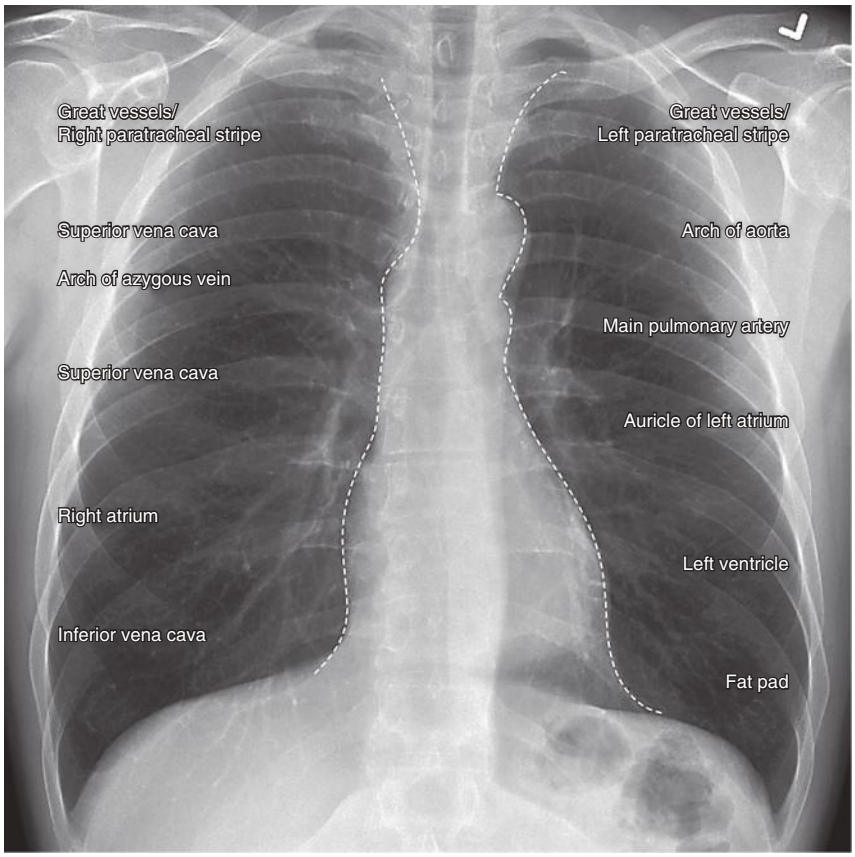
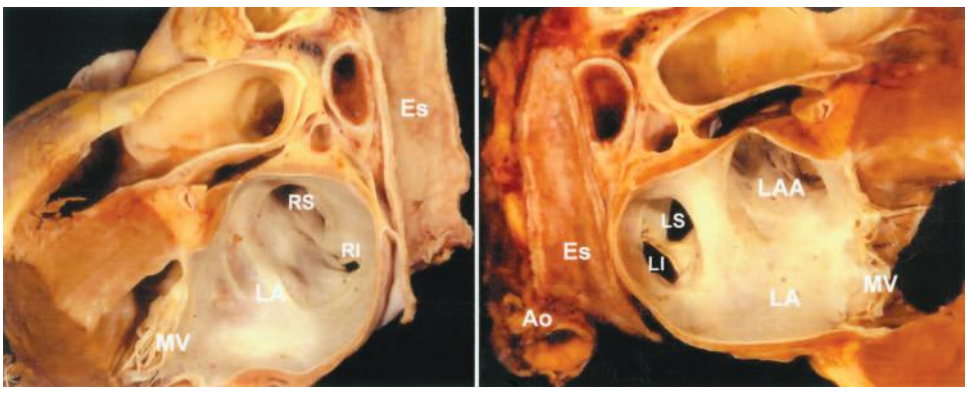


FIGURE 78–1. Chest x-ray illustrating the frontal view and associated anatomy of the heart and mediastinum. The right heart border is dominated by the right atrium. The left heart border is marked by a series of prominences or "moguls." These moguls correspond to the aortic knob, pulmonary artery, left atrial appendage (auricle), and left ventricle (superior to inferior). Reproduced with permission from Knipe H and Gaillard F. Normal contours of the cardiomediastinum on chest radiography. (Accessed from http://radiopaedia.org/articles/normal-contours-of-the-cardiomediastinum-on-chest-radiography). Case courtesy of A. Prof Frank Gaillard, Radiopaedia.org.

see Waterston's groove, which is the sulcus between the pulmonary veins (posterior) and the vena cava (anteriorly) (see Fig. 78–3A).

The atrial septum runs obliquely from the front extending backward and to the right. The posterior part of the left atrium receives the pulmonary veins. The orifices of the left pulmonary veins are more superiorly located than those of the right pulmonary veins. Typically, there are four pulmonary veins (left superior, left inferior, right superior, and right inferior). Sometimes, there is a fifth pulmonary vein (usually a right middle pulmonary vein), and sometimes, two of the veins will share a common antrum (eg, a left common antrum).[8] Coursing close to the lateral and posterior mitral annulus is the coronary sinus/great cardiac vein (see Fig. 78–4). The oblique vein of Marshall enters the coronary sinus; it passes superiorly to inferiorly, between the left atrial appendage and the left superior pulmonary vein. This vein is obliterated in the majority of individuals, and the remnant of this vein (also termed the ligament of Marshall) is contained in the Coumadin ridge.



A B

FIGURE 78–2. Two halves of the same specimen bisected longitudinally to show the relationship between the posterior wall of the left atrium and the esophagus. Ao, aorta; Es, esophagus; LA, left atrium; LAA, left atrial appendage; LI, left inferior pulmonary vein; LS, left superior pulmonary vein; MV, mitral valve; RI, right inferior pulmonary vein; RS, right superior pulmonary vein.

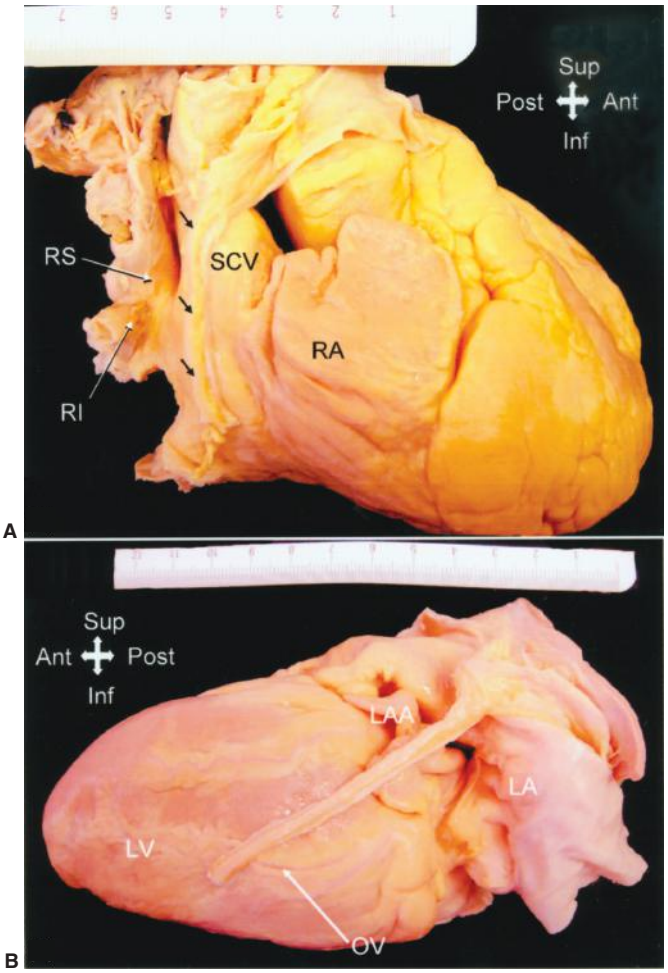


FIGURE 78–3. A. The right phrenic nerve (*arrows*) descends along the pericardium, in close proximity to the right pulmonary veins as they enter the left atrium. **B.** The descent of the left phrenic nerve is commonly related to the great cardiac vein and anterior descending coronary artery or, as in this specimen, over the course of the obtuse marginal or lateral vein. Abbreviations as before, and OV, obtuse vein; RA, right atrium; SCV, superior caval vein (superior vena cava).

This muscular ridge separates the os of the left superior pulmonary vein (or both left-sided veins) and the left atrial appendage. The mitral valve orifice and left atrial appendage are the anterior structures of the left atrium (Fig. 78–5B).

THE RIGHT ATRIUM

The right atrium is best considered in terms of its three components: the appendage, the venous part, and the vestibule.[9] A fourth component, the septum, is shared by the atria and is discussed later (see section titled "The Atrial Septum"). During embryonic development, the crista terminalis separates the sinus venosus from the heart. Therefore, the crista terminalis separates the smooth-walled posterior or venous atrium from the anterior trabeculated atrium (Fig. 78–6).[10] The crista terminalis is a muscular ridge that is frequently the source of atrial tachycardia. It also has a critical role in atrial flutter as it is a site of functional block, which is necessary to facilitate reenty in cavotriscupid-dependent flutter. The trabeculated anterior portion of the right atrium includes the pectinate muscles. In between these muscles, the wall is very thin.

From the epicardial aspect, the right atrium is dominated by its large, triangular-shaped appendage, which extends anteriorly and laterally. Usually, a fat-filled groove (*sulcus terminalis*) that corresponds internally to the crista terminalis can be seen along the lateral wall demarcating the junction between appendage and venous components. The sinus node is a subepicardial structure in the cephalad aspect of this groove, at the anterolateral aspect of the superior vena cava–right atrial junction.[11,12] Right atrial musculature often extends a short distance into the superior vena cava and can be another source of focal atrial arrhythmias (Fig. 78–7). The pectinate muscles do not reach the tricuspid valve. There is a smooth muscular vestibule surrounding the tricuspid orifice, with the musculature inserting into the tricuspid leaflets (see Fig. 78–6).

The eustachian valve guards the entrance of the inferior vena cava and is variably developed between individuals. In most hearts, it appears as a triangular flap of fibrous tissue. The eustachian valve is a fibrous extension from the inferior margin of the crista terminalis that inserts medially to the eustachian ridge (Fig. 78–8). In some cases, the eustachian valve is particularly large and muscular and can pose

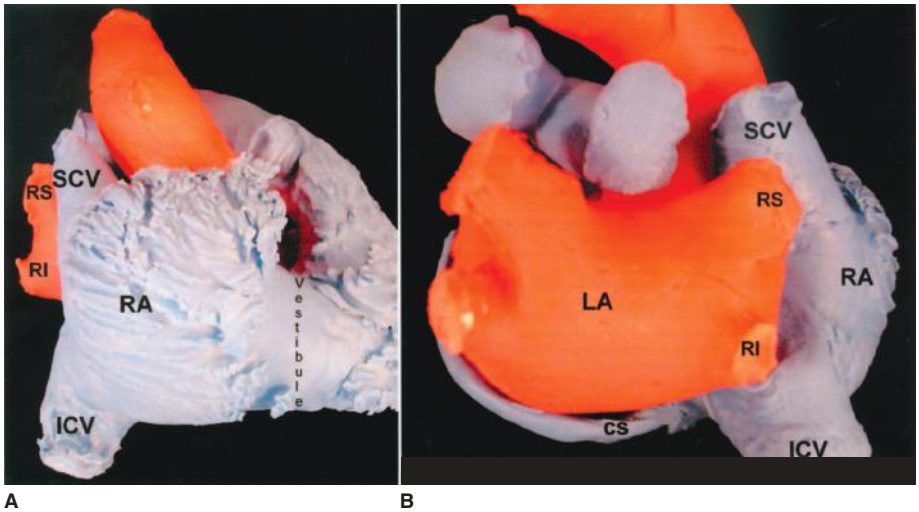


FIGURE 78–4. A. A view of the endocast from the right lateral view shows the characteristically extensive pectinate muscles of the right atrial wall contrasting with the smooth vestibule. The right superior pulmonary vein is posterior to the superior vena cava. **B.** The endocast viewed from the back or posterior view shows the right pulmonary veins passing behind the superior vena cava and the intercaval area. The coronary sinus is inferior to the left atrium. Abbreviations as before, and, CS, coronary sinus; ICV, inferior caval vein (inferior vena cava).

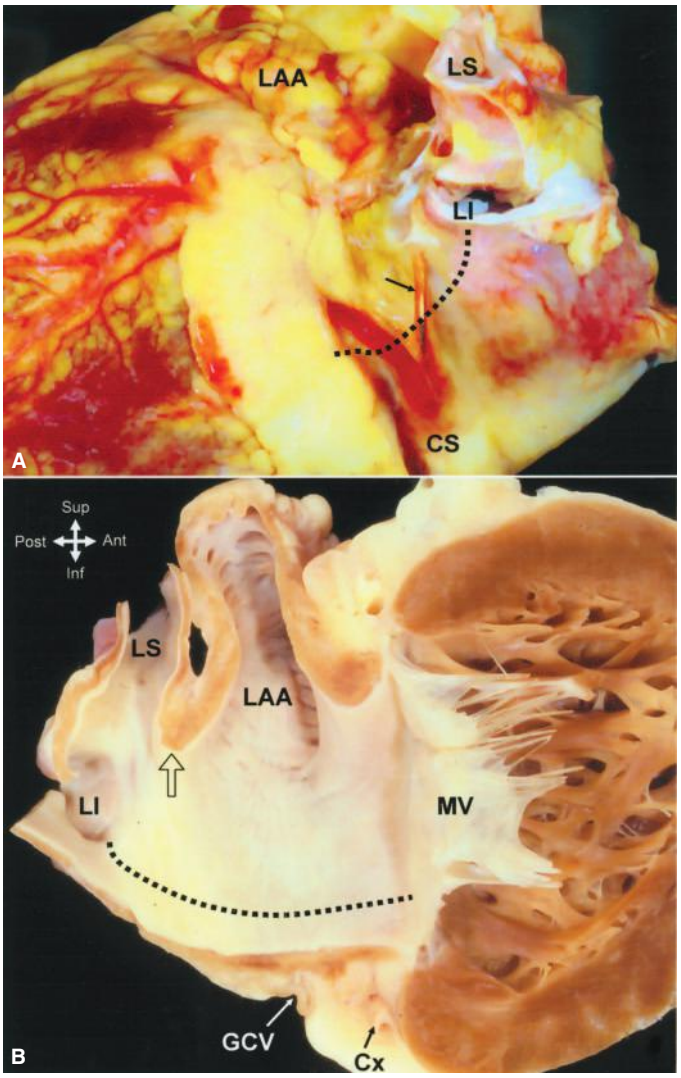


FIGURE 78–5. A. The heart viewed from the left and inferior aspect shows a small remnant of the vein of Marshall (*arrow*) descending along the atrial wall in between the left atrial appendage and the left pulmonary veins to enter the coronary sinus. The left atrial isthmus between the left inferior pulmonary vein and the mitral valve is indicated by the dotted line. **B.** The long axis cut through the left atrium and left ventricle shows the orifices of the left pulmonary veins and the left atrial isthmus (*dotted line*). Note the narrow fold (*arrow*) between the os of the left atrial appendage and the orifice of the left superior pulmonary vein in the heart. It may be challenging to keep the ablation catheter stable along this narrow fold without dropping inadvertently into the vein or the appendage. Abbreviations as before, and GCV, great cardiac vein.

an obstacle to passage of catheters from the inferior vena cava to the inferior part of the right atrium. Sometimes, the valve is perforated or net-like and is often described as a Chiari network.

The free border of the eustachian valve continues as the eustachian ridge and then the fibrous tendon of Todaro. The tendon of Todaro penetrates the musculature of the sinus septum, which separates the fossa ovalis from the os of the coronary sinus.[13] It is one of the borders of the triangle of Koch, which marks the location of the atrioventricular nodal tissue. As shown in Figure 78–9, the other borders of the triangle of Koch include the septal leaflet of the tricuspid valve anteriorly and the coronary sinus os inferiorly. The apex of the triangle of Koch marks the location of the central fibrous body and its associated structures: the compact atrioventricular node and penetrating bundle of His (see Fig. 78–8).[14,15] The region between the coronary sinus os and tricuspid valve, also known as the paraseptal isthmus (see Fig. 78–8), is the area often targeted for ablation of the slow pathway in atrioventricular nodal reentrant tachycardia. Inferior extensions of the atrioventricular node have been observed in this area (see Fig. 78–8). The so-called fast pathway, which usually forms the retrograde limb in patients with slow-fast atrioventricular nodal tachycardia (eg, typical atrioventricular nodal reentrant tachycardia), corresponds to the area of musculature immediately posterior and adjacent to the apex of the triangle of Koch.[15,16]

The coronary sinus is a structure of critical importance in cardiac electrophysiology, with particular relevance in cardiac mapping, catheter ablation, and placement of leads for cardiac resynchronization. A small crescentic flap, the thebesian valve, often guards the orifice of the coronary sinus.[17] Frequently, the thebesian valve is fenestrated. A complete and imperforate thebesian valve is rare but can be a cause of inability to cannulate the coronary sinus. The atrial wall inferior to the orifice of the coronary sinus is usually pouch-like and is termed the subeustachian sinus of Keith (or subeustachian pouch). The area between the inferior caval vein and the tricuspid valve (Fig. 78–10B)[18] is the cavotricuspid isthmus. The cavotricuspid isthmus is a region of slow conduction in common or typical atrial flutter.[19,20] When targeting the cavotricuspid isthmus during catheter ablation of typical flutter, ablationists target the central aspect of the isthmus in order to avoid the trabeculated ridges of the lateral isthmus and the pouch-like aspect of the septal or medial isthmus. This approach also avoids injury to the compact atrioventricular node medially and the right coronary artery laterally. Although injury to these structures is rare, it can occur.[21]

THE ATRIAL SEPTUM

During transseptal catheterization, the left atrium is accessed from the right atrium. Transseptal catheterization requires an appreciation of the extent of the true atrial septum (see Fig. 78–8). Although inspection of the septum from the right atrium suggests an extensive septal area, the true septum separating the right and left atrial cavities is much smaller. The difference between the apparent septum and the true septum is a result of a deep fold between the caval connections and the right atrium and the right pulmonary veins to the left atrium (Fig. 78–11). Enclosed within this fold is epicardial fat. The left aspect of the atrial septum lacks the crater-like feature of the right side. The true septum that interventionalists can cross safely is limited to the fossa ovalis and the immediate muscular rim that surrounds it on the right atrial aspect (**see** Fig. 78–11). Most hearts have a well-defined muscular rim on the right atrial aspect, allowing the operator to "feel" and observe (in the left anterior oblique view) the "jump" from firm muscular rim to tenting of the fossa ovalis as the transseptal access sheath is withdrawn from the superior vena cava to the right atrium.

In approximately 20% to 25% of normal hearts, the fossa is patent, even though on the left atrial side the valve is large enough to overlap the rim. This is because the adhesion of the valve to the rim is incomplete, leaving a gap usually in the anterosuperior margin corresponding to a C-shaped mark in the left atrial side just behind the anterior atrial wall (Fig. 78–12). The gap in adhesion allows a probe, or catheter, in the right atrium to slip between the rim and the valve into the left atrial chamber. A catheter lodged in this crevice will have its tip directed toward the anterior wall of the left atrium. The anterior aspect of the fossa ovalis is adjacent to the noncoronary cusp, an important relationship to appreciate in order to avoid inadvertent puncture of the aortic root. The use of intracardiac ultrasound helps facilitate accurate and safe crossing of the true septum.

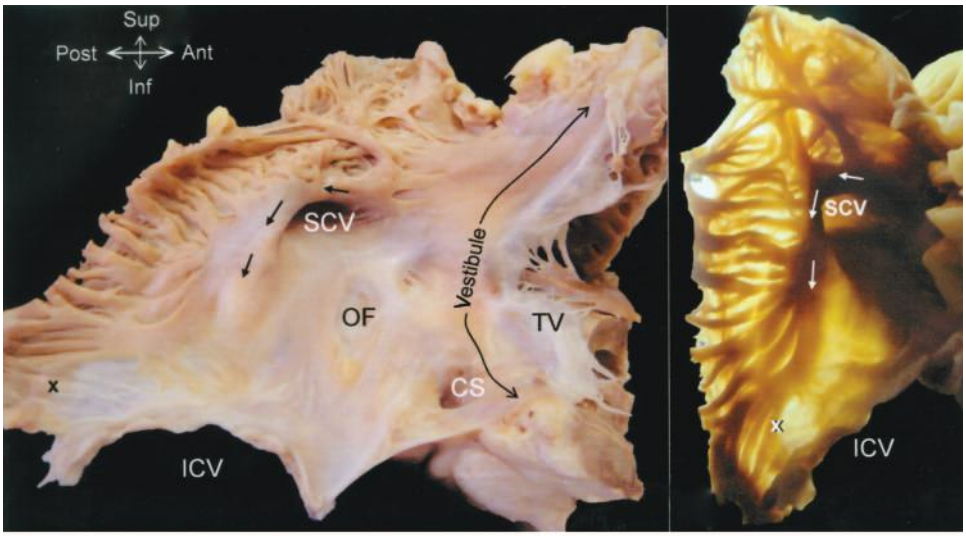


FIGURE 78–6. **A.** The parietal wall of the right atrium has been cut and deflected posteriorly to show the crista terminalis (*arrows*). X indicates the distal ramifications of the crista terminalis that lead into the cavotricuspid isthmus. **B.** A similar display with transillumination reveals the thin areas in between the pectinate muscles, at the inferior isthmus, and the posteroinferior part of the intercaval atrial wall. Abbreviations as before, and, TV, tricuspid valve.

THE LEFT ATRIUM

As with the right atrium, the left atrium has three components and shares its septum. The left atrial appendage arises from the anterolateral primordial atrium. The atrial appendage is a highly crenellated structure of variable shape, frequently resembling a chicken wing, windsock, cactus, or cauliflower.[22,23] In fibrillating atria, thrombi may form in the appendage as a result of low flow and stasis. Unlike the right atrium, virtually all the pectinate muscles in the left atrium are confined to the appendage. The lumen of the appendage is lined by a complicated network of muscular ridges and intervening membranes

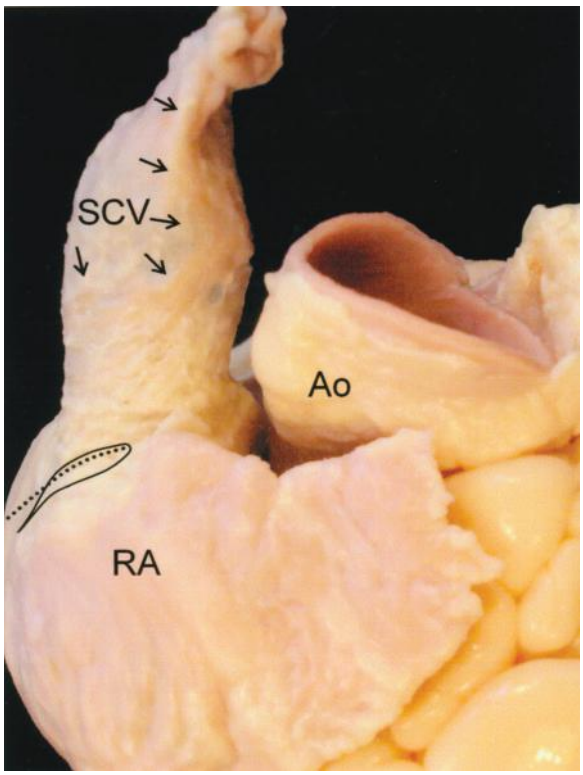


FIGURE 78–7. This anterior view of the superior cavoatrial junction shows the location of the sinus node (*ovoid shape*) in the terminal groove (*dotted line*), and muscular extension around the outside of the venous wall (*arrows*). Abbreviations as before.

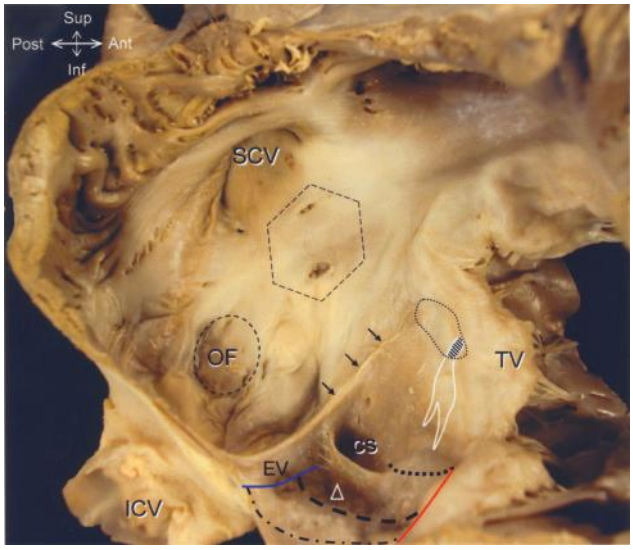


FIGURE 78–8. Simulating a right anterior oblique projection, the right atrium is opened to show the septal aspect that appears extensive, but the area marked by the hexagon is not septal. Termed the *aortic mound*, it is the anterior wall of the right atrium that abuts the non- and right coronary aortic sinuses. The true septum is limited to the valve of the fossa ovalis/oval foramen (OF) and its immediate muscular rim. The triangle of Koch is delineated posteriorly by the tendon of Todaro (*arrows*) running in the eustachian ridge, anteriorly by the septal leaflet of the tricuspid valve, and inferiorly by the coronary sinus. The apex of the triangle is marked by the central fibrous body (*dotted shape*) through which the atrioventricular conduction bundle penetrates (*hatched*). The atrioventricular node and its inferior extensions are depicted by the white shape. The cavotricuspid isthmus is bordered posteriorly by the eustachian valve (*blue line*) and anteriorly by the tricuspid valve (*red line*). Within this area are marked three isthmuses: paraseptal isthmus (dots), inferior or central flutter isthmus (*dashes*), and inferolateral isthmus (*dots and dashes*). The inferior isthmus passes through the sinus of Keith (*triangle*). The coronary sinus is guarded by a crescentic thebesian valve. Abbreviations as before, and ER, eustachian ridge; EV, eustachian valve.

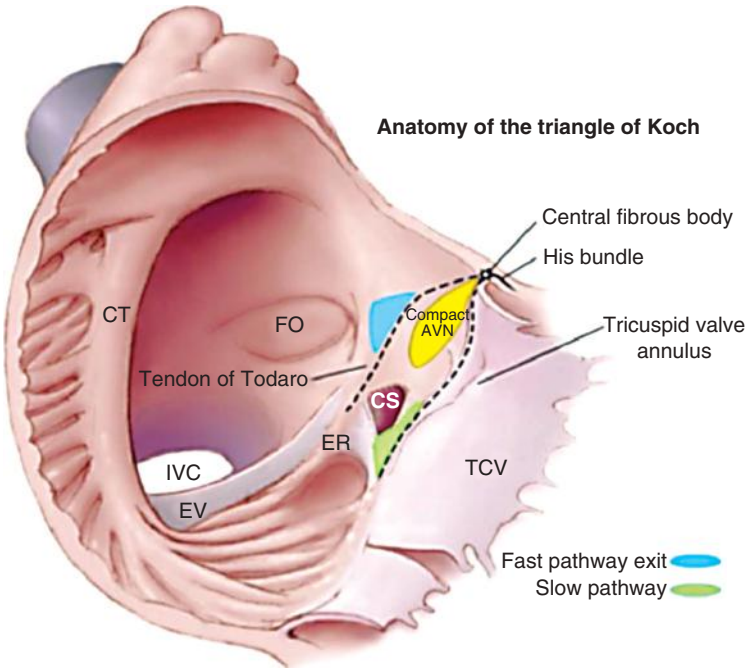


FIGURE 78–9. Schematic of the right atrium illustrating the triangle of Koch (see anatomic specimen in Fig. 78–8). The slow pathway region, the target of ablation in the treatment of atrioventricular nodal reentrant tachycardia, is just anterior to the os of coronary sinus (CS). AVN, atrioventricular node; CT, crista terminalis; ER, eustachian ridge; EV, eustachian valve; FO, fossa ovalis; IVC, inferior vena cava; TCV, tricuspid valve. Reproduced with permission from Macedo PG, Patel SM, Bisco SE, Asirvatham SJ. Septal accessory pathway: anatomy, causes for difficulty, and an approach to ablation. *Indian Pacing Electrophysiol J*. 2010 Jul 20;10(7):292-309.

that form its wall. Its tip can be directed anteriorly overlying the pulmonary trunk, superiorly behind the arterial pedicle, or posteriorly. When its tip is directed anteriorly, the body of the appendage usually also overlies the main stem of the left coronary artery. As described previously, the remnant of the vein of Marshall or ligament of Marshall runs on the lateral epicardial aspect of the neck of the appendage, anterior to the left pulmonary veins (see Fig. 78–5).

The venous component of the left atrium receives the pulmonary veins posteriorly (Fig. 78–13). The orifices of the right pulmonary veins are directly adjacent to the plane of the atrial septum (see Fig. 78–11). The venous orifices are oval shaped with a longer superoinferior diameter than anteroposterior diameter. The musculature of the atrial wall extends into the veins to varying lengths, with the longest sleeves along the upper or superior veins.[8,24-26] Close to the venous insertions, the sleeves are thicker and completely surround the epicardial aspect of the vein. The veins often have electrical continuity with bridging muscle fibers between the superior and inferior veins, which are present in approximately half of left vein pairs and one-third of right vein pairs.[27] The distal margins of the sleeves, however, are usually thinner and irregular as the musculature fades out. The muscle sleeves are composed predominantly of circularly orientated myocardial fibers with interdigitating longitudinally and obliquely orientated fibers (see Fig. 78–13B).[8,25] Triggered activity from the pulmonary vein muscle sleeves can initiate atrial fibrillation,[28] and these sources of ectopic activity are targeted during pulmonary vein isolation procedures for the treatment of drug-refractory atrial fibrillation.[29]

The anterior vestibular component leads to the mitral valve. There are no surface anatomic landmarks that separate the venous left atrium from the vestibule. The region between the left inferior pulmonary vein and the mitral valve annulus is the mitral isthmus and is frequently a zone of slow conduction that favors the development of atypical left atrial flutter, particularly in patients with prior left atrial ablation (see Fig. 78–5).[30,31] The mitral isthmus is occasionally targeted in substrate ablation during ablation procedures in patients with advanced atrial fibrillation. The tissue of the mitral isthmus is very thick, and therefore, complete transmural ablation can be difficult to achieve.

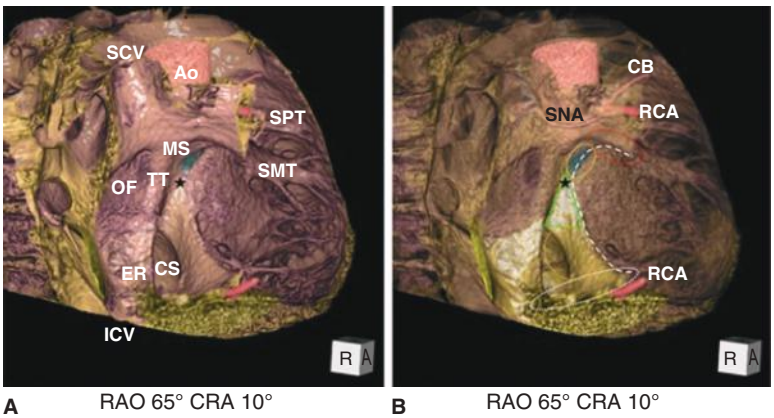


FIGURE 78–10. Computed tomography images of the paraseptal region. **A.** Volume-rendered image viewed from the right anterior oblique (RAO) 65-degree and cranial (CRA) 10-degree view. The membranous septum (MS) is shown in *blue*, and the *star* indicates the location of the compact atrioventricular node at the apex of the triangle of Koch. In part **B**, the transparency has been increased. The *red dotted circle* indicates the caudal portion of the superior paraseptal area, and the *yellow dotted circle* indicates the septal part of the superior paraseptal area. The *green dotted triangle* indicates the mid-paraseptal area corresponding to the triangle of Koch. The *orange dotted circle* indicates the inferior paraseptal area. The *white dotted oval* indicates the cavotricuspid isthmus extending from the tricuspid annulus to the inferior vena cava. Ao, ascending aorta; CB, conus branch; CS, coronary sinus; ER, Eustachian ridge; ICV, inferior caval vein; OF, oval fossa (fossa ovalis); RCA, right coronary artery; SCV, superior caval vein (superior vena cava); SMT, septomarginal trabecula; SNA, sinus node artery; SPT, septoparietal trabecula; TT, tendon of Todaro. Reproduced with permission from Mori S, Fukuzawa K, Takaya T, et al. Clinical structural anatomy of the inferior pyramidal space reconstructed within the cardiac contour using multidetector-row computed tomography. *J Cardiovasc Electrophysiol*. 2015 Jul;26(7):705-712.

THE ATRIOVENTRICULAR JUNCTIONS

In the normal heart, the fibrous rings of tissue surrounding the atrioventricular valves provide electrical separation of the atrial and ventricular tissue with the exception of the atrioventricular nodal tissue. However, anomalous muscular atrioventricular connections at the atrioventricular junctions (accessory pathways or bypass tracts) can lead to atrioventricular reentry and pre-excitation, including the Wolff-Parkinson-White syndrome.[32] Description of the location of accessory pathways in the literature and clinical arena has been complicated by the use of heterogeneous terminology. This terminology has been particularly complicated by the interchangeable use of the terms *anterior* and *superior* and the terms *posterior* and *inferior*.[1] Anatomically, the term *superior* is more accurate and is preferred to *anterior*, whereas *inferior* is more accurate and preferred to *posterior*.

The true septal component is limited to the area of the central fibrous body and immediate musculature. The so-called *anterior septum* is contiguous with part of the supraventricular crest of the right ventricle, whereas the *posterior septum* is formed by the muscular floor of the coronary sinus overlying the diverging posterior walls of the ventricular mass and the vestibule of the right atrium overlapping ventricular myocardium (the atrioventricular septum). Anatomically, the atrioventricular junction can be described as comprising

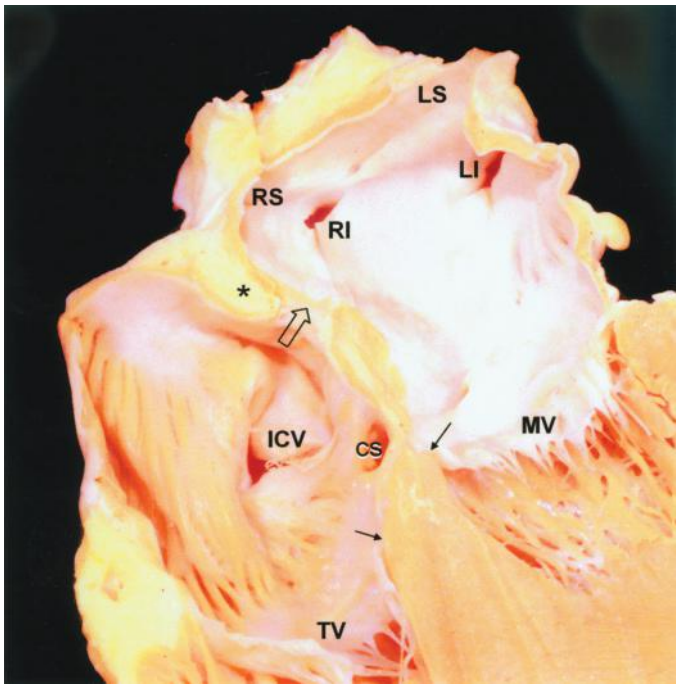


FIGURE 78–11. A long-axis section through the heart profiles the cardiac septum to show the thin valve of the fossa ovalis (*open arrow*) on the left atrial side and the muscular rim on the right atrial side. The cut reveals the infolding of the right atrial wall at the superior rim that is filled with epicardial fat (*asterisk*) to form the interatrial groove. At the ventricular septum, the leaflets of the tricuspid and mitral valves are hinged at different levels (*small arrows*) producing offset between the right and left atrioventricular junctions. Thus, the vestibule of the right atrium overlies the ventricular septum. Abbreviations as before.

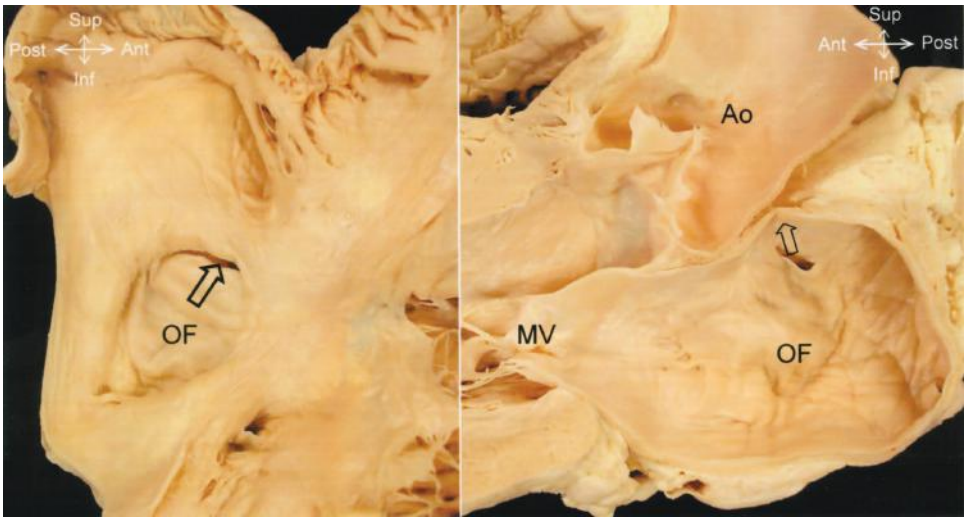
extensive right and left parietal junctions that meet with a small true-septal component (Fig. 78–14). The right parietal junction is relatively circular and occupies a near vertical plane in the heart marked by the course of the right coronary artery in the atrioventricular groove. The superior and most medial part of the junction abuts directly on the membranous septum.

The left parietal junction surrounds the orifice of the mitral valve, and part of it is the area of fibrous continuity between the mitral and aortic valves (see Fig. 78–14). On the left side, because of the nature of the aortomitral continuity, accessory atrioventricular connections are mainly limited to the mitral annulus supporting the posterior leaflet of the mitral valve. This portion of the mitral annulus runs from posterosuperior to posterior and inferior when the heart is viewed in left anterior oblique projection. The inferior area harbors the coronary sinus and its tributary, the great cardiac vein (see Fig. 78–5). The inferior paraseptal region, the so-called *posterior septum*, is the inferior pyramidal space that contains epicardial fibrofatty tissues together with the artery supplying the atrioventricular node (Fig. 78–15).[33,34] The floor of the pyramidal space is formed by the pericardium, and the four walls of the pyramidal space include the triangle of Koch in the right atrium, the left atrium, the right ventricle, and the left ventricle. The central fibrous body forms the peak of the pyramid.

Maintaining a more ventricular position when ablating septal pathways is important to avoid injury to the compact atrioventricular node and subsequent complete heart block. Because the tricuspid valve is more caudal than the mitral valve, there is a tiny portion of the right atrium that shares a common wall with the left ventricle—the atrioventricular membranous septum. The atrioventricular membranous septum is immediately adjacent to the pyramidal space. More extensive than the atrioventricular membranous septum is the so-called *atrioventricular muscular septum*, which is formed by the right atrial wall overlying the basal left ventricular wall in the medial portion of the atrioventricular junction, and sandwiched in between is epicardial fat of the pyramidal space inferiorly and central fibrous body superiorly. Appreciation of the "atrioventricular septum" is important because a catheter at this location may record a large ventricular signal from the basal left ventricle, leading an ablationist to think he or she is more ventricular with little risk of heart block during attempted ablation of a septal accessory pathway.[35] In fact, a catheter on the "atrioventricular septum" is on the atrial side of the junction, with significant risk of iatrogenic heart block.

THE VENTRICLES

Each ventricle has three components: the inlet containing the atrioventricular valve, the outlet leading to the arterial valve, and the apical trabecular component. The ventricular septum curves as it is traced from inlet toward the outlet portions, allowing the right ventricle to lie anterosuperiorly over the left ventricle. The curvature places the right ventricular outflow tract anteriorly and slightly leftward to that of the left ventricle, resulting in a characteristic "crossover" relationship between right and left ventricular outflow tracts (Fig. 78–16).



A B

FIGURE 78–12. A. Displayed in right anterior oblique view, the anterocephalad margin (*open arrow*) of the fossa ovalis will allow a probe to pass into the left atrium behind. **B.** The left atrial view of the same heart shows the crevice through which the probe will exit and its proximity to the thin part of the left atrial wall anteriorly (*open arrow*). Abbreviations as before.

THE RIGHT VENTRICLE

The right ventricle is the most anteriorly situated cardiac chamber in the normal heart. It is located immediately behind the sternum. This anatomic relationship is important to recognize when performing pericardiocentesis. Using an anterior approach, if the needle continues through and past the pericardial space, the needle will encounter the right ventricular free

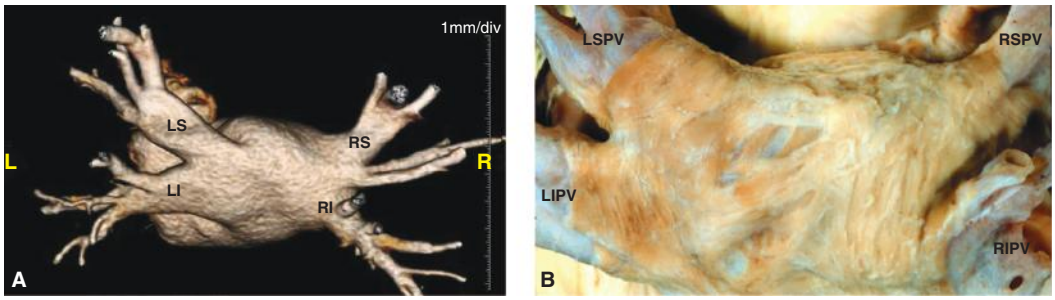


FIGURE 78–13. A. Posterior view of the left atrium from a computed tomography scan. Shown are the four pulmonary veins draining into the posterior left atrium. Note that the left superior and left inferior veins share a common antrum in this heart. LI, left inferior pulmonary vein; LS, left superior pulmonary vein; RI, right inferior pulmonary vein; RS, right superior pulmonary vein. **B.** Posterior view of an anatomic specimen showing atrial fiber orientation around the pulmonary vein sleeves and posterior wall of the left atrium. LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

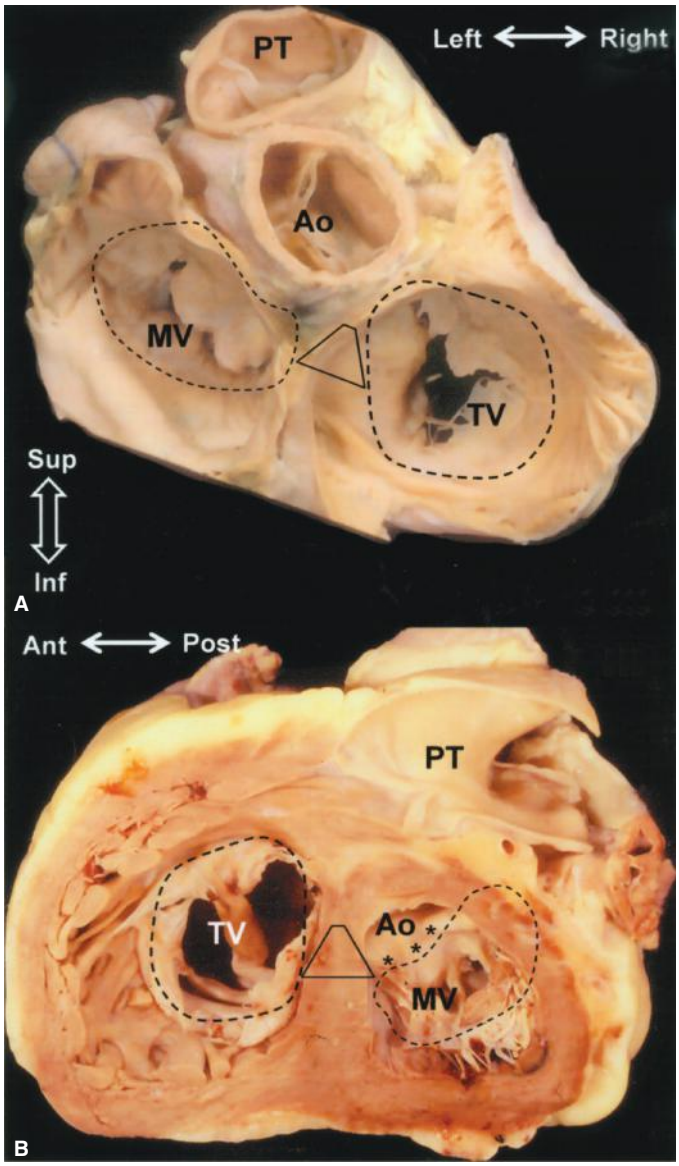


FIGURE 78–14. A. A view of the cardiac base with the broken lines representing the annuli of the mitral and tricuspid valves and the box representing the extent of the septum at the atrioventricular junction illustrates how much of the junction is not septal. **B.** Viewed from the ventricular aspect and in attitudinal orientation, the atrioventricular junction is represented by the *broken lines*. Note the area of aortomitral continuity indicated with *asterisks*, which is clearly not a septal area. Abbreviations as before.

wall, thus creating potential for right ventricular puncture or laceration. When viewed from the front, the right ventricle has a triangular shape. The right ventricular inlet extends from the annulus of the tricuspid valve to the papillary muscles. The leaflets of the tricuspid valve can be distinguished as septal, anterosuperior, and inferior or mural. The septal leaflet, with its cords inserting directly to the ventricular septum, is characteristic of the tricuspid valve. The medial papillary muscle, a small out-budding from the septum, supports the junction (commissure) between the septal and anterosuperior leaflets (Fig. 78–17). A larger papillary muscle, the anterior papillary muscle, supports the extensive anterosuperior leaflet and its junction with the inferior leaflet. The junction between anterosuperior and inferior leaflets is supported by a group of small papillary muscles, the inferior papillary muscles.

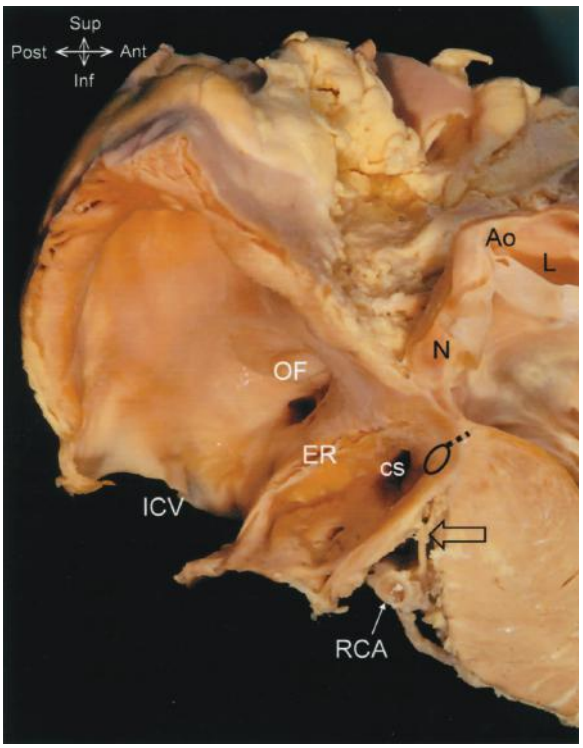


FIGURE 78–15. A longitudinal section through the inferior pyramidal space reveals the right atrial wall overlying the right coronary artery (RCA) and the arterial branch (*open arrow*) supplying the atrioventricular node (*oval*). Note the proximity of the noncoronary aortic sinus (N) to the right atrial wall and the His bundle (*dots*). Abbreviations as before.

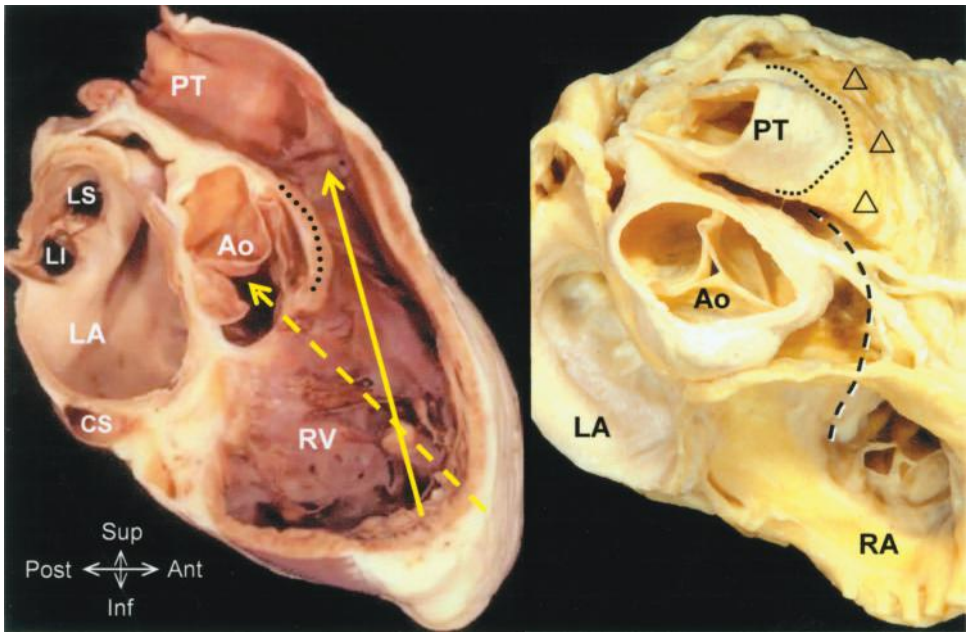


FIGURE 78–16. A. A sagittal section through a heart shows the aortic root in the middle. From the cardiac apex to the pulmonary valve, the right ventricular outflow tract (*solid arrow*) overlies the left ventricular outflow tract (*broken arrow*), which is behind the ventricular septum. The subpulmonary muscular infundibulum (*dots*) that lies anterior to the aortic valve is not septal. **B.** The dissection shows the relationship between the pulmonary and aortic valves. Note the musculature forming the freestanding subpulmonary infundibulum (*triangles*) that is proximal to the ventriculoarterial junction (*dotted line*). The deeper location of the ventricular septum is indicated by the *broken line*. Abbreviations as before.

Coarse muscular trabeculations crisscross the apical portion. One of them, the moderator band, is characteristic of the right ventricle (see Fig. 78–17). This bridges the ventricular cavity between the body of the septomarginal trabeculation and the parietal wall, giving rise to the anterior papillary muscle along the way. Within its musculature runs a major fascicle of the right bundle branch. The septomarginal trabeculation itself is a y-shaped muscular band that is adherent to the septal surface. In between its limbs lies the infolding of the heart wall forming the ventricular roof, an area also known as the supraventricular crest (see Fig. 78–17). This crest separates the two right heart valves and is an integral part of the outlet, continuous with the freestanding subpulmonary muscular infundibulum, which is a tube-like structure supporting the pulmonary valve. The right ventricular outflow tract is a frequent origin of adenosine-sensitive triggered ventricular extrasystoles and ventricular tachycardia in patients without structural heart disease. Most outflow tract ventricular tachycardias arise in the perivalvular tissue. Although ablationists frequently refer to septal and free wall portions of the right ventricular outflow tract, it should be noted that the infundibulum does not have a true septal component (see Fig. 78–17) because the pulmonary valve can be resected surgically for the Ross procedure without entering the left ventricle.[36] The septal component of the right ventricular outlet is only in its most proximal part, where it continues into the supraventricular crest. Furthermore, the right ventricular outlet curves to pass anterior and cephalad to the left ventricular outlet (see Fig. 78–16). Thus, the aortic root is immediately posterior to the "septal" right ventricular outflow tract (see Fig. 78–17). Two of the pulmonary sinuses are adjacent to the right and left coronary sinuses of the aortic valve, although the planes of the aortic and pulmonary valves are at an angle to one another (see Fig. 78–16). Thus, the main coronary arteries can also be at risk when ablating in the so-called septal part of the right ventricular outflow tracts (see Figs. 78–16 and 78–17).

THE LEFT VENTRICLE

The left ventricle is conical in shape. When the heart is viewed from the front, most of the left ventricle is behind the right ventricle. Its outlet overlaps its inlet. The mitral valve annulus at the entrance to the inlet has limited attachment to septal structures (see Fig. 78–14). Compared to that of the tricuspid valve, the mitral valve annulus is further away from the apex and does not have a septal leaflet (see Fig. 78–11). The larger portion of the valve is hinged to the parietal atrioventricular junction, whereas a third is the span of fibrous continuity with the aortic valve (see Fig. 78–14). The aortomitral continuity is a structure of particular importance and is another site from which triggered idiopathic ventricular arrhythmias can originate.[37] At the septal end of valvar fibrous continuity is the right fibrous trigone, and at the parietal end is the left fibrous trigone (Fig. 78–18; see also Fig. 78–14). The right trigone in continuity with the membranous septum forms the central fibrous body. The two leaflets of the mitral valve are disproportionate in size. The *anterior* leaflet in continuity with the aortic valve is deep, whereas the *posterior* (or mural) leaflet is shallow. The mitral leaflets are attached via tendinous cords exclusively to two groups of papillary muscles: anterolateral and posteromedial papillary muscles. The papillary muscles can also be sources for ventricular arrhythmias that are often difficult to ablate given their location and motion within the left ventricular cavity as well as the thick nature of the papillary muscles.

The apical component of the left ventricle extends from the papillary muscles to the ventricular apex. At the apex, the muscular wall tapers to a thickness of 1 to 2 mm in normal hearts. The trabeculations are finer than those found in the right ventricle. Occasionally, fine muscular strands, or so-called *false tendons*, extend between the septum and the papillary muscles or the parietal wall.[38] Often, they carry the distal ramifications of the left bundle branch and have been implicated in idiopathic left ventricular tachycardia.[39]

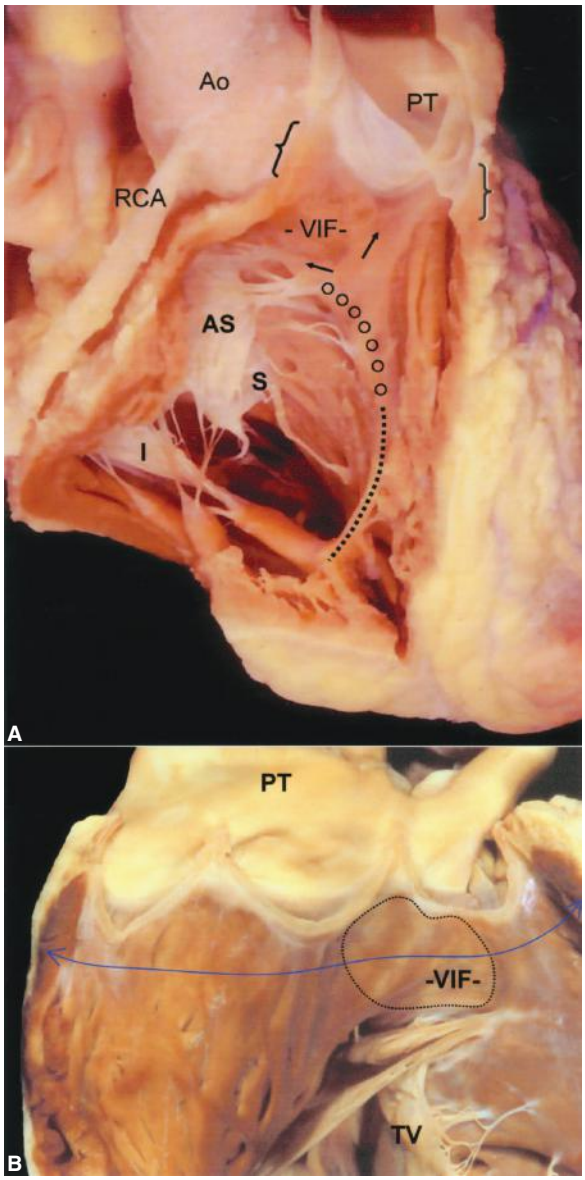


FIGURE 78–17. A. The inside of the right ventricle is displayed to show the supraventricular crest in between the pulmonary and tricuspid valves. The limbs (*arrows*) of the septomarginal trabeculation cradle the ventriculoinfundibular fold at the crest. The braces indicate the subpulmonary infundibulum. The course of the right bundle branch in the subendocardium of the septomarginal trabeculation is indicated by *circles*. One of its fascicles passes into the moderator band (*broken line*). **B.** The right ventricular outflow tract is displayed. The leaflets of the pulmonary valve have been removed to show the semilunar hinge lines crossing the ventriculoarterial junction. Each sinus thus includes a crescentic segment of ventricular wall (*dark areas*). *Double-headed arrow* indicates the free wall of the subpulmonary infundibulum. The area within the *dotted line* represents the so-called *septal* or *high septal* component but is actually free wall also. Abbreviations as before, and AS, anterosuperior; I, inferior; PT, pulmonary trunk; RCA, right coronary artery; S, septal leaflet of tricuspid valve; VIF, ventriculoinfundibular fold.

The left ventricular outlet is bordered by the muscular ventricular septum anterosuperiorly and the anterior leaflet of the mitral valve posteroinferiorly (see Fig. 78–18). The upper part of the ventricular septum leading to the aortic valve is smooth. The common atrioventricular conduction bundle emerges from the central fibrous body to pass between the membranous septum and the crest of the muscular ventricular septum (see Fig. 78–18). The landmark for the site of the atrioventricular conduction bundle is the fibrous body that adjoins the crescentic hinge lines of the right and noncoronary cusps of the aortic valve. From here, the left bundle branch descends in the subendocardium and usually branches into three main fascicles that interconnect and further divide into finer and finer branches as the *Purkinje* network (see section titled "The Cardiac Conduction System").

In the outlet, two leaflets of the aortic valve have muscular support, these being the ones adjacent to, or facing, the pulmonary valve (the right and left coronary sinuses). The third sinus, the noncoronary sinus, does not have muscular support. The facing aortic sinuses give rise to the right and left coronary arteries. Like the pulmonary valves, these two sinuses contain small segments of ventricular myocardium within (see Fig. 78–18).[40] Thus, ventricular arrhythmias emanating from the aortic sinuses are limited to the right and left coronary sinuses. As a result of the spatial relationship of the subpulmonary infundibulum and the left ventricular outlet (Fig. 78–19), the foci may be ablated from within the part of the right ventricular outlet that overlies the adjacent aortic sinuses.[41] Since the main coronary arteries arise from the arterial part of the sinuses, they are not in the immediate field, and thus ablations can be performed safely without significant risk of injury to the coronaries.[42] The noncoronary aortic sinus, being immediately adjacent to the paraseptal region of the left and right atriums and close to the superior atrioventricular junction, may be used to map and ablate focal atrial tachycardias that have earliest activation in the vicinity of the His bundle area—so-called "parahisian" atrial tachycardias (see Fig. 78–15).[43]

THE CORONARY VEINS

The venous return from the myocardium either is channeled via small thebesian veins that open directly into the cardiac chambers or, more significantly, is collected by the greater coronary venous system, which drains 85% of the venous flow.[44,45] The main coronary veins in the greater system are the great, middle, and small cardiac veins. The great cardiac vein is a continuation of the coronary sinus and is also continuous with the anterior interventricular vein, which runs parallel to the anterior descending artery. The middle cardiac vein runs alongside the posterior descending coronary artery. The great cardiac vein and middle cardiac vein (usually) drain into the coronary sinus. The small cardiac vein receives tributaries from the right atrium and the inferior wall of the right ventricle before coursing in the right atrioventricular junction to open to the right margin of the coronary sinus orifice or into the middle cardiac vein. Several other veins from the anterior surface of the right ventricle drain directly into the right atrium. The coronary veins may be surrounded by a cuff of myocardium that gives the potential for accessory atrioventricular connection as the vein passes through the atrioventricular groove.[46]

The coronary sinus is a critical structure in electrophysiology. Its ostium is usually between 5 and 15 mm in diameter. Its transition to the great cardiac vein is marked by several structures including the valve of Vieussens and the vein of Marshall. The entrance to the vein of Marshall, or oblique left atrial vein, marks the venous end of the tube-shaped coronary sinus. The vein is an embryonic remnant of the left superior vena cava and is a fibrous ligament in most individuals. Even when a lumen is present in the remnant vein, it is narrow, rarely exceeding 2 cm in length before tapering to a blind end (see Fig. 78–5). If adequately wide, this channel may be used for ablating the left atrial wall, including the use of alcohol instillation. The other structure that marks the transition from the coronary sinus to the great cardiac vein is the valve of Vieussens. Found in 80% to 90% of hearts, this flimsy valve can provide some resistance to potential catheter placement.[47] Once past Vieussens valve, a sharp bend in the great cardiac vein can cause

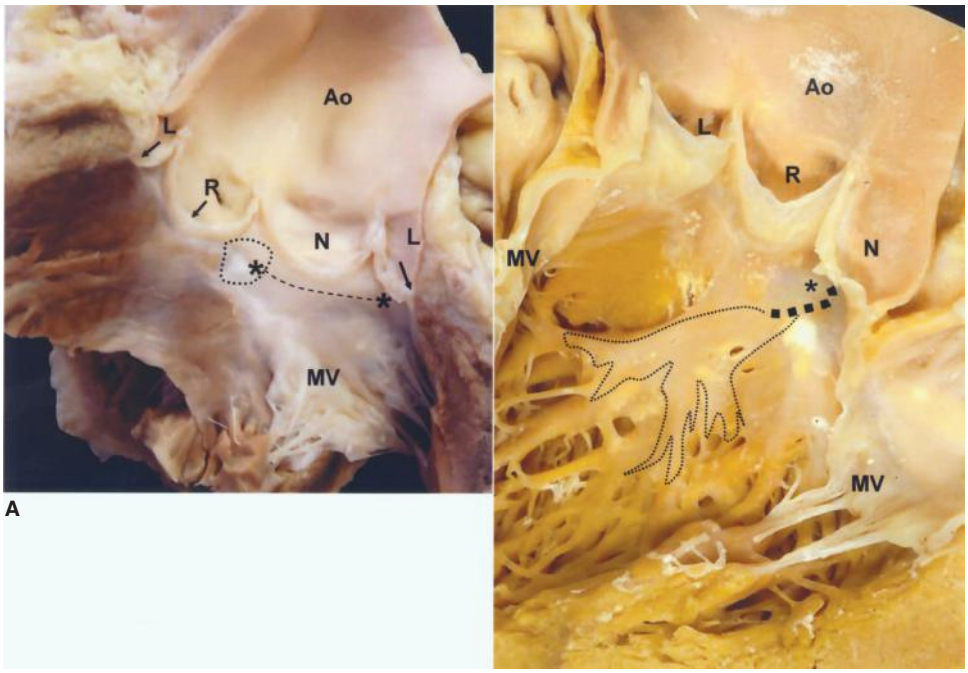


FIGURE 78–18. A. The left ventricular outflow tract incised through the left coronary aortic sinus is displayed to show the location of the membranous septum (*dotted shape*) and aortic-mitral fibrous continuity (*broken line*) with the fibrous trigones (*asterisks*) at each end. The aortic leaflets have been removed to show the muscular components (*arrows*) in the right (*R*) and left (*L*) coronary aortic sinuses that may be the source of aortic cusp ventricular tachycardia. **B.** The aortic root is displayed by cutting through the "anterior" leaflet of the mitral valve. The atrioventricular conduction bundle (*broken line*) passes between the membranous septum (*asterisk*) and the muscular septum. The irregular shape represents the left bundle branch and its three fascicles. Abbreviations as before, and N, noncoronary aortic sinus.

further obstruction in 20% of patients.[47] There is a muscular sleeve around the proximal portion of the coronary sinus. Bundles from the sleeve sometimes run into the left atrial wall and also cover the outer walls of adjacent coronary arteries (Fig. 78–20).[48]

As the great cardiac vein ascends in the atrioventricular groove, it collects tributaries draining the left ventricle, including the lateral (obtuse marginal) veins and posterior veins, which are important targets for left ventricular pacing in cardiac resynchronization therapy (Fig. 78–21). The distribution, courses, and calibers of the left ventricular veins vary from individual to individual. When using these veins for pacing lead implants, it is worth noting that the left phrenic nerve running in the pericardium may pass across or very close to the lateral or posterolateral veins (see Fig. 78–3).[7] Thus, pacing from these veins can cause phrenic capture and diaphragmatic stimulation. The great

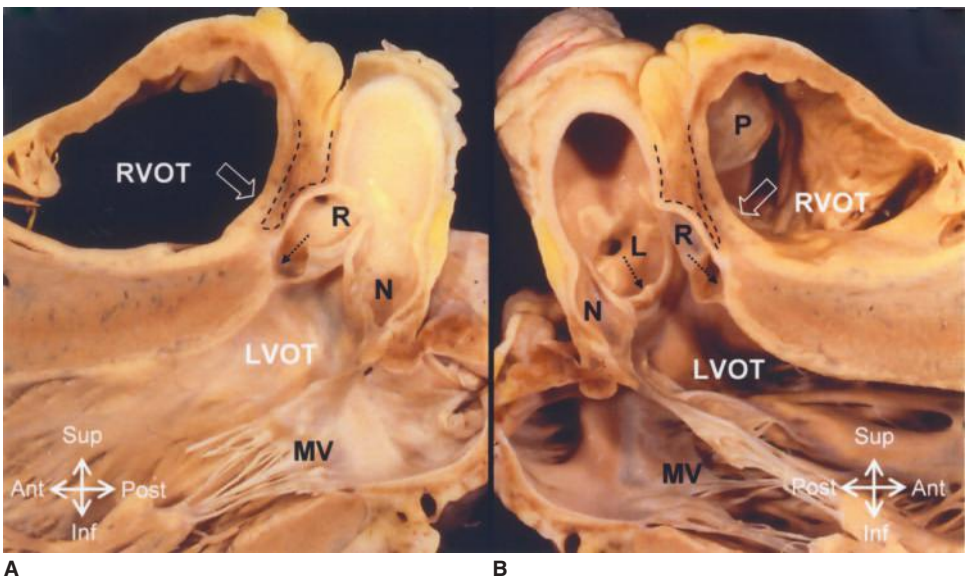


FIGURE 78–19. These are two halves of a heart cut longitudinally to show the relationship between left and right ventricular outflow tracts and why ablation of foci within the so-called septal component (*open arrows*) of the subpulmonary infundibulum may be approached from the adjacent aortic sinuses. Ablation of aortic sinus ventricular tachycardia targets the muscle enclosed within the right and left coronary aortic sinuses (*arrows*). Note the epicardial fat (*within broken lines*) between the subpulmonary infundibulum and the aortic root. Abbreviations as before, and LVOT, left ventricular outflow tract; P, pulmonary valve; RVOT, right ventricular outflow tract.

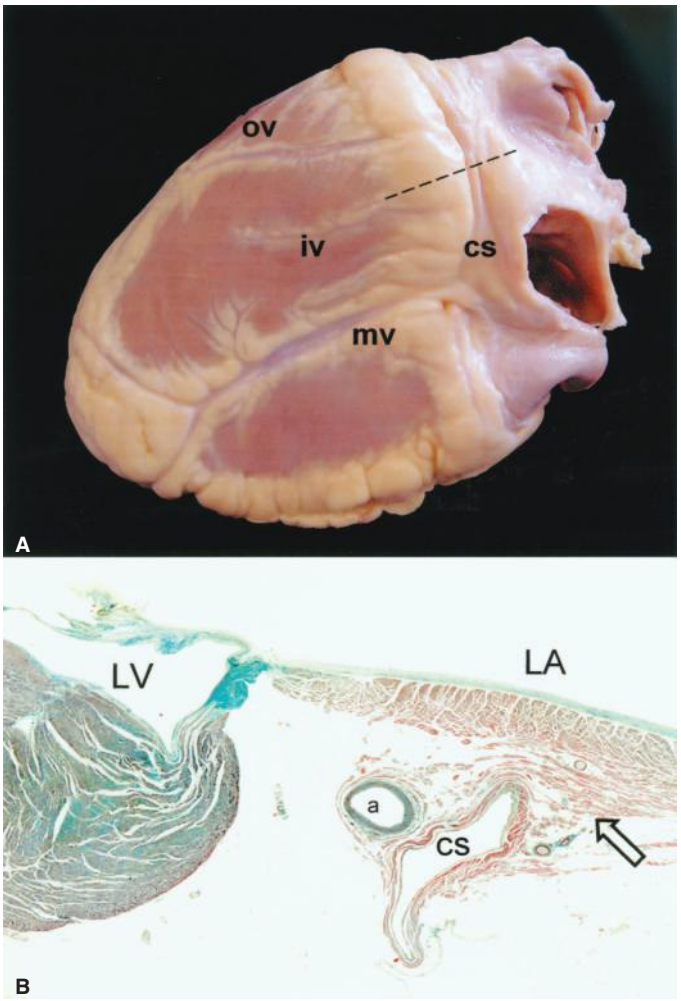


FIGURE 78–20. A. View of the diaphragmatic aspect showing cardiac veins draining into the coronary sinus. *Broken line* indicates plane of histologic section shown in panel **B**. **B.** The coronary sinus has a muscular wall (tissue stained *pink*). This section shows muscular continuity (*arrow*) between the coronary sinus and the left atrial wall. The muscle has also surrounded the coronary artery. Abbreviations as before, and a, circumflex artery; iv, inferior left ventricular vein; mv, middle cardiac vein; ov, left obtuse marginal vein.

cardiac vein continues to the interventricular groove where it becomes the anterior interventricular vein. In most hearts, it passes under the cover of the left atrial appendage. The left ventricular veins may be accessed for ablating ventricular tachycardia from a source close to the epicardium.[49] When deploying catheters or wires in superficial veins, it is important to note that venous walls are thin and "unprotected" by muscle on the epicardial side.

The middle cardiac vein drains into the coronary sinus just within the sinus os. Occasionally the middle vein enters the right atrium directly via its own separate os. The middle cardiac vein passes just superficial to the right coronary artery at the cardiac crux. It is a useful portal for ablating epicardial posteroseptal accessory atrioventricular pathways located in the inferior pyramidal space.[50] Ablation at this site can cause injury to the posterior descending artery given its close proximity.[51] Rarely, the entrance of the middle vein is dilated (or aneurysmal) and surrounded by a cuff of muscle, giving the potential for accessory atrioventricular connections.[52,53] Tributaries from the middle cardiac vein with a lateral course can also be used to access the lateral wall for lead placement in biventricular pacing.

THE CARDIAC CONDUCTION SYSTEM

THE SINUS NODE

The key components of the cardiac conduction system include the sinus node, the atrioventricular node, and the His-Purkinje system. The sinus node is a subepicardial structure, crescent-like in shape, with a mean length of 13.5 mm in the adult heart.[11,12] The "head" of the sinus node is located at the superior margin of the terminal groove near the anterolateral aspect of the junction between the right atrium and superior vena cava. The "tail" of the sinus nodal tissue can extend down more than 50% of the length of the crista terminalis toward the inferior vena cava. The node is richly supplied with nerves from both the sympathetic chains and the vagus nerve. Nodal tissues are penetrated by the sinoatrial nodal artery, which arises from the right coronary artery in 65% of individuals.[54] The tissue surrounding the sinus node is dominated by calcium channel activation (as opposed to Na^+), and therefore, sinus node exit conduction is slow and decremental, similar to the atrioventricular node.[54] The borders of the node are irregular with frequent interdigitations between nodal and ordinary atrial myocytes, facilitating communication between the node and right atrial wall.[11,12] Figure 78–22 shows the area of early endocardial activation as a result of sinus node activity.

Although much has been written about *specialized internodal tracts* (anterior, middle, and posterior) connecting the sinus node to the atrioventricular node, their existence in the form as originally defined by early anatomists has never been demonstrated.[55] There are several muscular interatrial connections that are important in normal cardiac conduction and have relevance in a number of heart rhythm disorders. Bachmann's bundle is a prominent interatrial muscle bridge that extends across the roof of the atria anterosuperior to the fossa ovalis (Fig. 78–23). Conduction over Bachmann's bundle leads to early endocardial activation in the anterior left atrium in order to help facilitate interatrial synchrony.[56] Multiple smaller interatrial bridges are frequently present, giving the potential for macroreentry. Some cross Waterston's groove and connect the muscular sleeves of the right pulmonary veins and the superior caval vein to the left atrium (see Fig. 78–23).[8,9] Finally, as previously mentioned, muscular bridges from the left atrial wall often overlie and run into the wall of the coronary sinus.

THE ATRIOVENTRICULAR CONDUCTION SYSTEM

In the normal heart (without accessory pathway connections), the atrioventricular conduction system provides the only pathway of muscular continuity between atrial and ventricular myocardium. There is an interface of transitional cells between ordinary atrial myocardium and the histologically specialized cells that make up the atrioventricular node. The compact atrioventricular node was described by Tawara[57] in 1906 and is located near the apex of the triangle of Koch (see Figs. 78–8 and 78–9). In the adult, the compact atrioventricular node is approximately 5 mm long and wide. The atrioventricular node receives its blood supply from the atrioventricular nodal artery, which arises from the right coronary artery in 80%, the left circumflex artery in 10%, and both in 10% of hearts. Most of the time, extensions from the compact node pass to the right and left sides of the artery.[58] The right extension courses parallel and adjacent to the tricuspid annulus, whereas the left extension projects toward the mitral vestibule. The distance of the right inferior extension to the endocardial surface is approximately 1 to 5 mm. With reference to the triangle of Koch, the compact node (see Fig. 78–8) is near the apex, but the right inferior extensions reach to the mid-level of the triangle and may even extend to the vicinity of

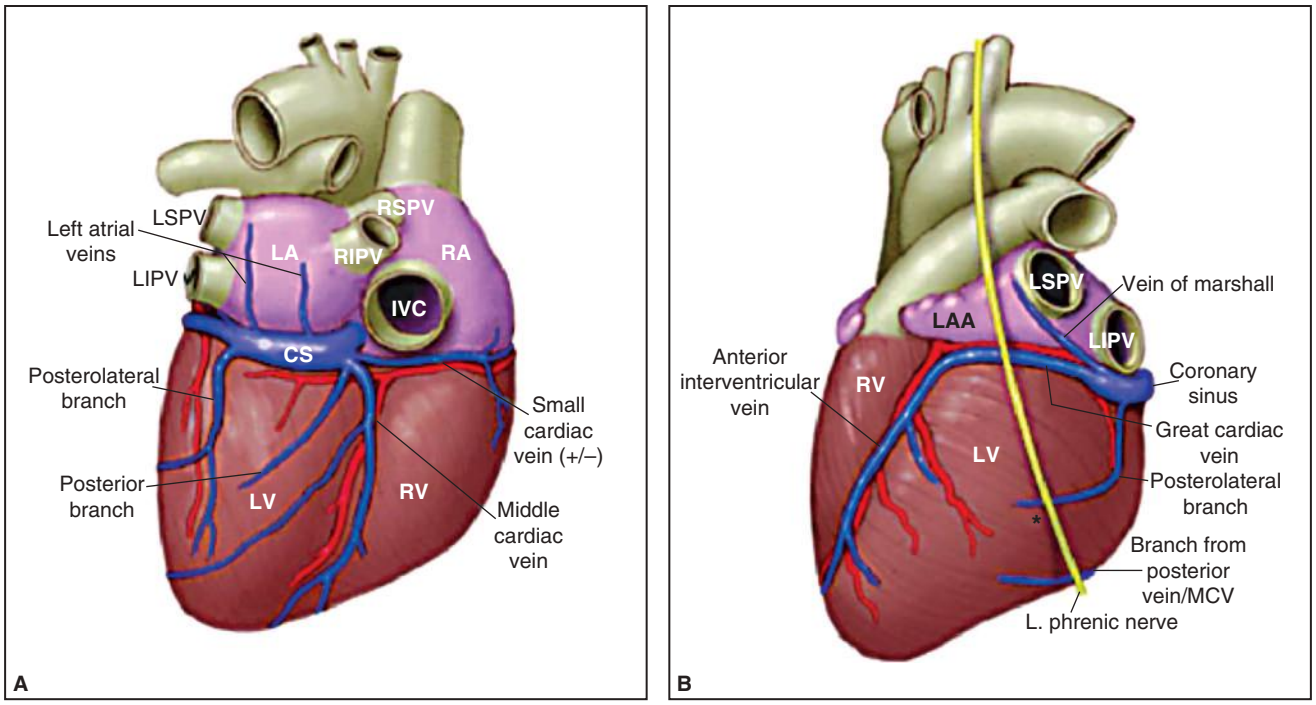


FIGURE 78–21. **A** and **B.** The course of the coronary venous system is shown. The coronary sinus gives rise to the middle cardiac vein and the great cardiac vein. Branches off the great cardiac vein include the left atrial veins, vein of Marshall, the posterolateral branch, lateral branches (not shown), and the anterior interventricular veins. The left phrenic nerve course near the left-sided coronary veins; thus, pacing from these veins can lead to diaphragmatic stimulation. Abbreviations as before, and LA, left atrium; LV, left ventricle; MCV, middle cardiac vein; RA, right atrium; RV, right ventricle. Reproduced from Noheria A, DeSimone CV, Lachman N, et al. Anatomy of the coronary sinus and epicardial coronary venous system in 620 hearts: an electrophysiology perspective. *J Cardiovasc Electrophysiol*. 2013 Jan;24(1):1-6.

the coronary sinus.[59] This area is the location at which catheter ablation targets the slow pathway in patients with evidence of dual atrioventricular nodal physiology and evidence of atrioventricular nodal reentrant tachycardia, the most common form of supraventricular tachycardia.

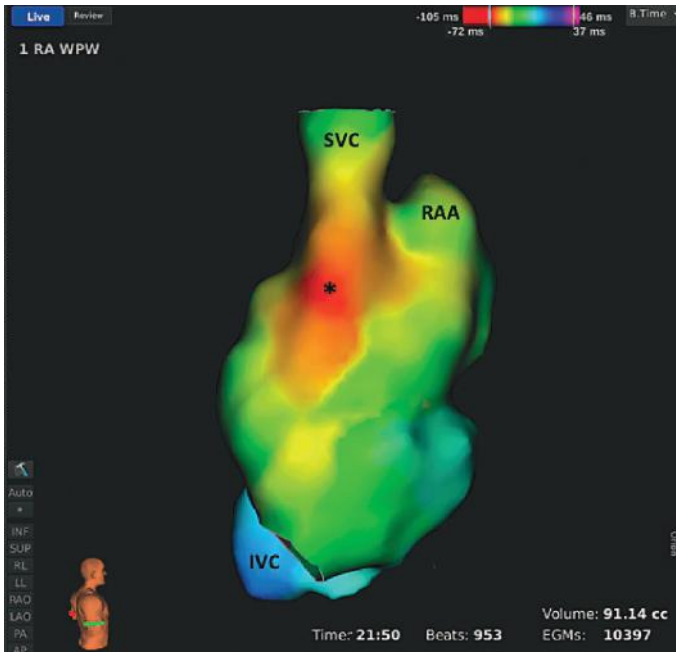


FIGURE 78–22. Shown here is a three-dimensional electroanatomic map of the right atrium from a right lateral view. Note that the location of the sinus node is close to the right atrial–superior vena caval junction in the anterolateral right atrium. The *red* area labeled with an *asterisk* represents the earliest endocardial activation as a result of sinus node depolarization. IVC, inferior vena cava; RAA, right atrial appendage; SVC, superior vena cava.

THE HIS-PURKINJE SYSTEM

Superiorly, at the apex of the triangle of Koch, the penetrating bundle of His passes through the central fibrous body coursing leftward. This short bundle of specialized myocardium encased in a fibrous sheath is a direct extension of the compact atrioventricular node, enabling atrial activity to be conveyed to the ventricles. The emergence of the bundle in the ventricles is directly related to the membranous septum and the aortic outflow tract. In relationship to the aortic valve, the landmark for the atrioventricular conduction bundle is immediately inferior to the fibrous area between the right and noncoronary aortic sinuses. The bundle is sandwiched between the membranous septum and the crest of the ventricular septum. After a short distance, the bundle bifurcates into the left and right bundle branches. The left bundle branch fans out as it descends in the subepicardium of the septal surface the left ventricle (see Fig. 78–18). In contrast, the right bundle branch is cord-like and descends through the musculature of the ventricular septum to emerge in the subendocardium at the base of the medial papillary muscle to run in the septomarginal trabeculation (see Fig. 78–17). Along its descent, a prominent branch crosses to the parietal wall within the moderator band. Both bundle branches are insulated as they descend toward the apical parts of the ventricles. The branches then ramify as the Purkinje fibers, running in the subendocardium and into the myocardium in a net-like fashion (Fig. 78–24).

FAT PADS AND INNERVATION

The heart is heavily influenced by autonomic innervation. Moreover, cardiac innervation includes both extrinsic innervation as well as influence from the intrinsic cardiac nervous system. The intrinsic cardiac nervous system is largely an atrial network of neural ganglia.[60]

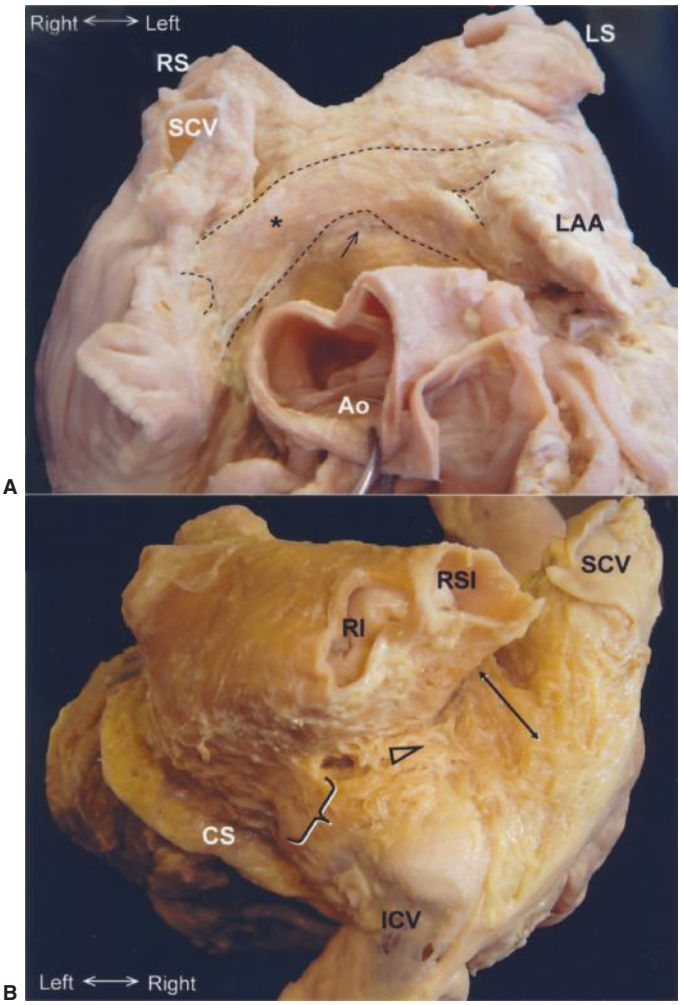


FIGURE 78–23. A. The aortic root is retracted forward to show the anterior wall of the atria. Bachmann's bundle (*between broken lines*) is displayed crossing the anterior aspect of the interatrial groove (*asterisk*). The *arrow* indicates a thin area of the anterior left atrial wall that is frequently found inferior to Bachmann bundle. Abbreviations as before. **B.** A heart tilted forward and viewed from the back shows muscle bridges in addition to Bachmann bundle. A muscle bundle (*double-headed arrow*) connects the anterior wall of the left atrium with the posterior right atrial wall inferior to the superior vena cava (or superior caval vein [SCV]). Further bridges are present posteriorly and inferiorly (*triangle and brace*). Abbreviations as before.

The vagal inputs to the heart arise from various nuclei in the medulla. Sympathetic inputs come from the paravertebral, superior cervical, middle cervical, cervicothoracic (stellate), and thoracic ganglia. The stellate ganglion is the primary source of cardiac sympathetic innervation. Generally speaking, the innervation of the atria is predominantly parasympathetic, while the innervation of the ventricles is predominantly sympathetic. The extrinsic cardiac nerves course through the hilum at the base of the heart and branch into different autonomic ganglia. These ganglionated plexuses contain neuronal inputs from the atrial myocardium and the extrinsic cholinergic and adrenergic neurons. Between 6 and 10 collections of ganglia or ganglionated plexuses have been described in the human heart.[61,62] Approximately half of the plexuses are located on the atria and the other half on the ventricles. Occasional ganglia are located in other atrial and ventricular regions of the epicardium.[63] The ganglionated plexuses are generally associated with islands of adipose tissue

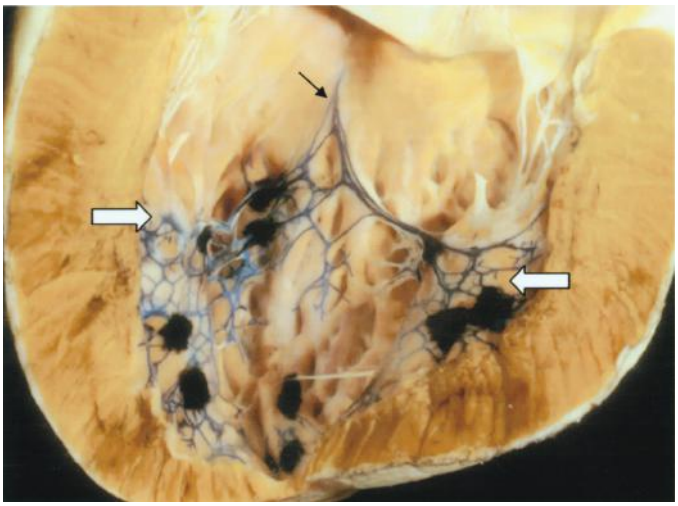


FIGURE 78–24. This preparation of a sheep heart shows the left bundle branch (*small arrow*) fanning out into interconnecting fascicles and *false tendons* carrying the distal ramifications across the cavity to the papillary muscles (*white arrows*).

referred to as fat pads that serve as visual landmarks to cardiac surgeons.[62] The atrial fat pads are located in the interatrial groove, at the cavoatrial junctions, and on the left atrial wall in the vicinity of the venoatrial junctions (Fig. 78–25). The ligament of Marshall is densely innervated with both parasympathetic and sympathetic inputs. During catheter ablation of atrial fibrillation, ablation of ganglionated plexi in the ligament of Marshal often results in vagal events during

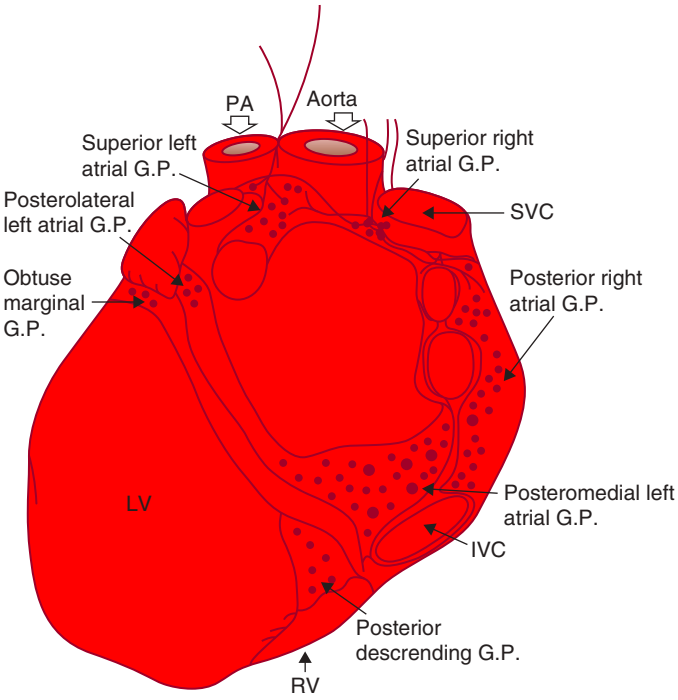


FIGURE 78–25. Posterior view of the heart illustrating the locations of the cardiac ganglionated plexi. The mediastinal nerves descend the aortic root and join the two superior atrial ganglionated plexi (G.P.). IVC, inferior vena cava; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; SVC, superior vena cava. Adapted with permission from Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec.* 1997 Feb;247(2):289-298.

radiofrequency application. Pauza et al[61] found up to 50% of all cardiac ganglia on the posterior and posterolateral surfaces of the left atrium, whereas Singh et al[62] reported that the largest populations of ganglia are adjacent to the sinus and atrioventricular nodes, reflecting different methodologies of studies. The ganglia within each plexus are interconnected by thin nerves, whereas ganglia of adjacent plexuses are also interconnected, forming the meshwork of the epicardiac neural plexus.[64] Further nerves penetrate into the myocardium to become thinner and thinner and devoid of ganglia.[65] Autonomic influences from cardiac ganglia are known to exert important roles in both atrial and ventricular arrhythmogensis.[66-68] For example, surgical left thoracic stellate ganglionectomy is often employed to treat ventricular arrhythmia storm refractory to medical therapy.[69]

CONCLUSION

Whereas the structure of the human heart has not changed, understanding of its anatomy has evolved over time as electrophysiologic diagnostic and therapeutic strategies have evolved, each calling for a revisit of cardiac anatomy. In recent decades, the development of electrophysiologic mapping and catheter ablation techniques has outpaced the work of cardiac anatomists in many ways. Nevertheless, better understanding of detailed anatomy is relevant to clinical electrophysiologists not only to improve outcomes and therapeutic efficacy and avoid or minimize complications during interventional procedures, but also to provide the anatomic background for different substrate and mechanisms behind many heart rhythm disorders.

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CHAPTER 79

MECHANISMS OF CARDIAC ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Peng-Sheng Chen and Charles Antzelevitch

ABNORMAL IMPULSE FORMATION / 1881
Normal Automaticity / 1881
Automaticity as a Mechanism of Cardiac Arrhythmias / 1885
Parasystole and Modulated Parasystole / 1886
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REMODELING AND THE MECHANISMS OF CARDIAC ARRHYTHMIA / 1901
Myocardial Remodeling / 1901
Neural Remodeling and Cardiac Nerve Sprouting / 1901

NEUROMODULATION FOR ARRHYTHMIA CONTROL / 1903

SUMMARY / 1903

Recent years have witnessed important advances in our understanding of the molecular and electrophysiologic mechanisms underlying the development of a variety of cardiac arrhythmias (Table 79–1) and conduction disturbances. Progress in our understanding of these phenomena has been fueled by innovative advances in our understanding of the genetic basis and predisposition for electrical dysfunction of the heart. These advances notwithstanding, our appreciation of the basis for many rhythm disturbances is incomplete. This chapter examines our present understanding of cellular, ionic, and molecular mechanisms responsible for cardiac arrhythmias, placing them in historical perspective whenever possible.

Cardiac activation and repolarization are controlled by movement of ions across channels in the cell membrane of cardiomyocytes, which in turn are strongly influenced by the activity of the autonomic nervous system. Abnormal activity of these ionic movements is important in cardiac arrhythmogenesis.[1-3] Arrhythmic activity can be categorized as passive (eg, atrioventricular [AV] block) or active. The mechanisms responsible for active cardiac arrhythmias are generally divided into two major categories: (1) enhanced or abnormal impulse formation, and (2) reentry (Fig. 79–1). Reentry occurs when a propagating impulse fails to die out after normal activation of the heart and persists to reexcite the heart after expiration of the refractory period. Evidence implicating reentry as a mechanism of cardiac arrhythmias stems back to the turn of century.[4-6] Multichannel mapping studies subsequently documented that reentrant wavefronts may underlie the mechanisms of atrial and ventricular tachyarrhythmias.[7-9] Phase 2 reentry,[10] spiral waves of excitation,[11] mother rotors, and fibrillatory conduction[12] are interesting concepts advanced to explain the development of atrial as well as ventricular fibrillation. Mechanisms responsible for abnormal impulse formation include enhanced automaticity and triggered activity. Automaticity can be further subdivided into normal and abnormal. Triggered activity consists of (1) early afterdepolarizations (EADs), (2) late phase 3 EAD, and (3) delayed afterdepolarizations (DADs).[13-15] Although traditionally automaticity and triggered activity were thought to be two distinct mechanisms of arrhythmogenesis, more recent studies suggest that they might share similar mechanisms.

ABNORMAL IMPULSE FORMATION

NORMAL AUTOMATICITY

Automaticity is the property of cardiac cells to generate spontaneous action potentials. Spontaneous activity is the result of diastolic depolarization caused by a net inward current during phase 4 of the action potential, which progressively brings the membrane potential to threshold. The sinoatrial (SA) node normally displays the highest intrinsic rate. All other pacemakers are referred to as subsidiary or latent pacemakers because they take over the function of initiating excitation of the heart only when the SA node is unable to generate impulses or when these impulses fail to propagate. There is a hierarchy of intrinsic rates of subsidiary pacemakers that have normal automaticity: atrial pacemakers have faster intrinsic rates than AV junctional pacemakers, and AV junctional pacemakers have faster rates than ventricular pacemakers.

Wit and Cranefield[16] defined automatic activity as activity that arose in the absence of an external cause (ie, activity that did not have to be triggered by a stimulated action potential). The prototypical example of automaticity is the spontaneous beating of the SA node. On the other hand, triggered activity was the activity in which nondriven action potentials were initiated by one or more driven action potentials. The authors used the term "triggered" to explain the mechanisms by which quiescent fibers remained quiescent until driven at fast rate. However, more recent studies have shown that automaticity and triggered activity may share a common mechanism (ie, activation of the sodium-calcium exchange current [I_{NCX}]).[17]

The Voltage Clock and Automaticity

Lakatta and colleagues[17] used the terms *membrane clocks* and *calcium (Ca) clocks* to describe the mechanisms of SA node automaticity. These two clocks were mutually entrained to form a robust, stable, coupled-clock system that drives normal cardiac pacemaker cell automaticity. The membrane clock is formed by voltage-sensitive membrane currents, such as the hyperpolarization-activated pacemaker current (I_f).[18,19] This current is also referred to as a "funny" current because, unlike the majority of voltage-sensitive currents, it is activated by hyperpolarization (from –40/–50 mV to –100/–110 mV) rather than depolarization. At the end of the action potential, the I_f is activated and is responsible for early diastolic depolarization that gradually depolarizes the sarcolemmal membrane.[20,21] The I_f is a mixed Na-K inward current modulated by the autonomic nervous system through cyclic adenosine monophosphate.[22] Sympathetic stimulation (isoproterenol) increases the I_f, whereas parasympathetic stimulation (acetylcholine) reduces I_f. These findings suggest that I_f is responsible for heart rate control by the autonomic nervous system. The depolarization activates L-type Ca current ($I_{Ca,L}$), which provides Ca to activate the type 2 (cardiac) ryanodine receptor (RyR2). The activation of RyR2 initiates sarcoplasmic reticulum Ca release (Ca-induced Ca release),

TABLE 79–1. Characteristics and Presumed Mechanisms of Cardiac Arrhythmia

Tachycardia	Mechanism	Origin	AV or VA Conduction
Sinus tachycardia	Automatic (normal)	Sinus node	1:1
Sinus node reentry	Reentry	Sinus node and right atrium	1:1 or variable
Atrial fibrillation	Reentry, automatic, triggered activity	Atria, thoracic veins, pulmonary veins, SVC, vein of Marshall	Variable
Atrial flutter	Reentry	RA, LA (infrequent)	Variable
Atrial tachycardia	Reentry, automatic, triggered activity	Atria	1:1, 2:1, or variable
AV nodal reentry tachycardia	Reentry	AV junction	1:1 or variable
AV reentry (WPW or concealed accessory AV connection)	Reentry	Circuit includes accessory AV connection, atria, AV node, His-Purkinje system, ventricles	1:1
Accelerated AV junctional tachycardia	Automatic	AV junction (AV node and His bundle)	1:1 or variable
Accelerated idioventricular rhythm	Abnormal automaticity	Purkinje fibers	Variable, 1:1, or AV dissociation
Ventricular tachycardia	Reentry, automatic, triggered	Ventricles	AV dissociation, variable
Bundle branch reentrant tachycardia	Reentry	Bundle branches and ventricular septum	AV dissociation, variable, or 1:1
RVOT	Automatic, triggered activity	RVOT	AV dissociation, variable, or 1:1
TdP tachycardia	Reentry, triggered activity	Ventricles	AV dissociation
Bidirectional tachycardia	Triggered activity	Purkinje cells	AV dissociation

Abbreviations: AV, atrioventricular; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; SVC, superior vena cava; TdP, torsades de pointes; VA, ventriculoatrial; WPW, Wolff-Parkinson-White.

leading to contraction of the heart, a process known as excitation-contraction coupling. The intracellular Ca (Ca_i) is then pumped back into sarcoplasmic reticulum by the sarcoplasmic reticulum Ca-ATPase (SERCA2a), which completes the Ca cycle. In addition to I_f, multiple time- and voltage-dependent ionic currents have been identified in cardiac pacemaker cells, which contribute to diastolic depolarization. These currents include (but are not limited to) the $I_{Ca,L}$, T-type Ca current, and various types of delayed rectifier K currents.[23] Many of these membrane currents are known to respond to β-adrenergic stimulation. All these membrane ionic currents contribute to the regulation of SA node automaticity by changing the membrane potential. In addition to the contribution of voltage-gated ionic currents, the small conductance Ca-activated K (SK) current also plays an important role in modulating automaticity both in the SA node and in the AV node.[24] Overexpression of subtype 2 of SK (SK2) channels in mice results in the shortening of the spontaneous action potentials of the AV node cells and an increase in the firing frequency. However, ablation of the SK2 channel results in the opposite effects. Because the SK current is activated by the Ca_i, this current may play an important role in the interaction between the membrane clock and the Ca clock.

The Calcium Clock and Automaticity

The I_f is not the only depolarizing current active in late phase 3 or phase 4 of the action potential. Another important ionic current that can depolarize the cell is the Na-Ca exchanger current (I_{NCX}). In its forward mode, the I_{NCX} exchanges three extracellular Na^+ with one intracellular Ca^{2+}, resulting in a net intracellular charge gain. This electrogenic current is active during late phase 3 and phase 4 because the Ca_i decline outlasts the SA node action potential duration (APD). Multiple studies have shown that I_{NCX} may participate in normal pacemaker activity.[25-30] The sequence of events includes spontaneous rhythmic sarcoplasmic reticulum Ca release, Ca_i elevation, the activation of I_{NCX}, and membrane depolarization.[17] This process is highly regulated by cyclic adenosine monophosphate and the autonomic nervous system.[31] According to findings, sympathetic stimulation accelerates heart rate by phosphorylation of proteins that regulate Ca_i balance and spontaneous sarcoplasmic reticulum Ca cycling. These proteins include phospholamban (a sarcoplasmic reticulum membrane protein regulator of SERCA2a), L-type Ca channels, and RyR2. Phosphorylation of these proteins controls the phase and size of subsarcolemmal sarcoplasmic reticulum Ca releases. The resultant I_{NCX} is crucial for both basal and reserve cardiac pacemaker function.

Many of the elegant studies on automaticity were performed in isolated SA node cells. However, the SA node is a complex structure, and many factors interact with each other to ensure the initiation of the heart beats. Activation maps in intact canine right atria have shown that the SA node impulse origin is multicentric,[32,33] and sympathetic stimulation predictably results in a cranial (superior) shift of the pacemaking site in humans and dogs.[32,34] Based on evidence from isolated SA node myocytes, late diastolic Ca_i elevation prior to the membrane action potential upstroke is a key signature of pacemaking by the Ca clock. Simultaneous mapping of the membrane potential and Ca_i transient in a Langendorff-perfused canine right atrium preparation[35] showed changes consistent with the Ca clock mechanism of impulse generation (Fig. 79–2). In that study, sympathetic stimulation (isoproterenol) induced spontaneous sarcoplasmic reticulum Ca release during phase 4 depolarization of intact canine SA node. The spontaneous Ca release then induced upward (cranial) shift of the leading pacemaker site and heart rate acceleration. Studies performed in human electrophysiologic laboratories have confirmed the presence of multiple early sites in the right atrium during sinus rhythm, consistent with multicentric origin of SA nodal rhythm.[36] Heart failure is associated with sinus node dysfunction and a reduction of the number of early sites. Another more recent study confirmed the multicentric origin of SA node rhythm.[37] The authors also confirmed that sympathetic stimulation resulted in cranial shift of pacemaking site in patients without SA nodal diseases. In contrast, unresponsiveness of superior SA node to sympathetic stimulation is a characteristic finding in patients with atrial fibrillation (AF) and symptomatic bradycardia (Fig. 79–3).

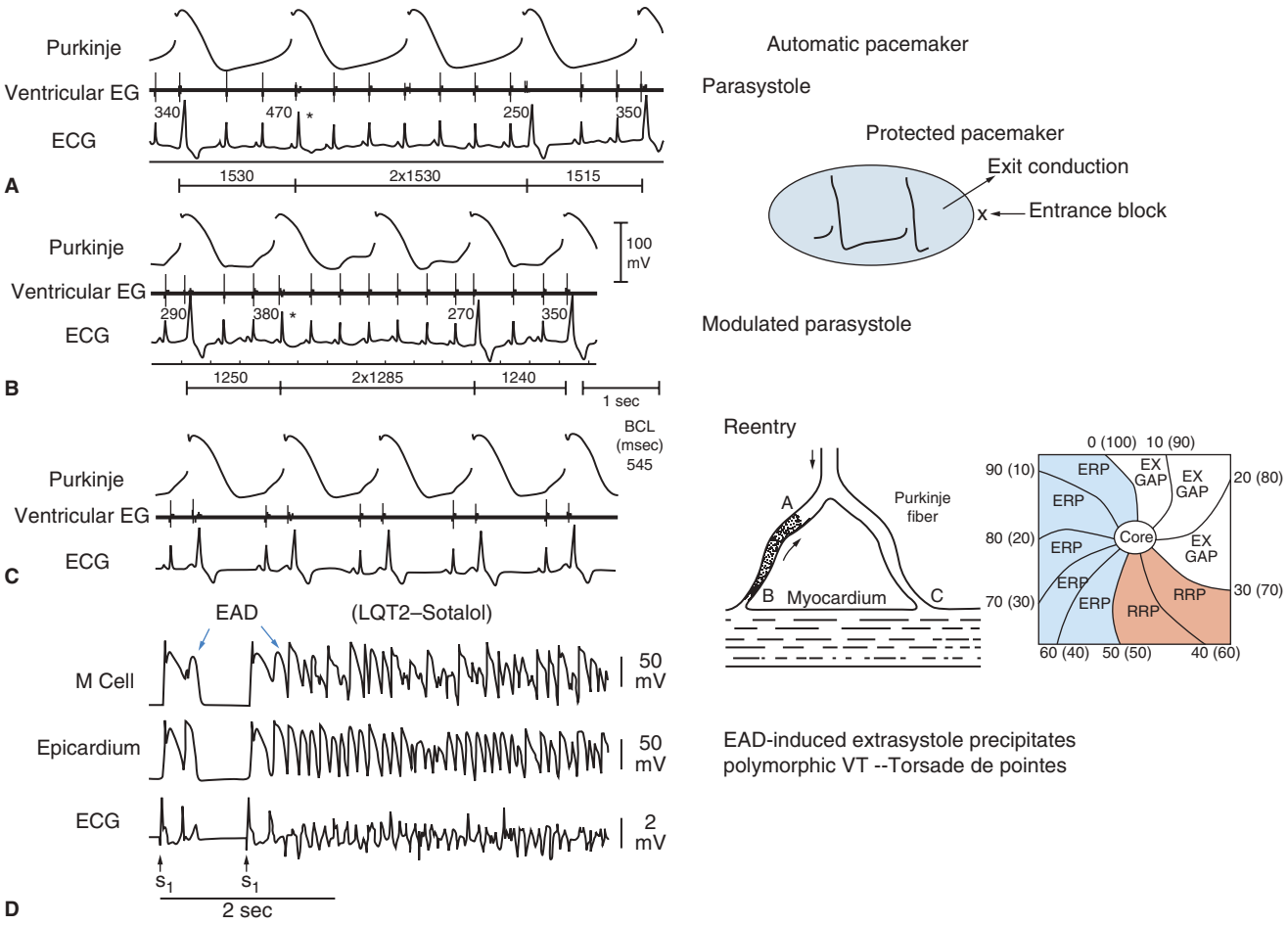

FIGURE 79–1. Examples of the main classes of active cardiac arrhythmias. **A.** Automaticity. Shown is an example of an automatic pacemaker firing independently of ventricular activity. This classical parasystolic behavior is characterized by variable coupling intervals of the ectopic extrasystoles and interectopic intervals that are multiples of the pacemaker cycle length (1530 milliseconds). Complete entrance block into the pacemaker focus is seen but unencumbered exit conduction out of the protected focus. **B.** The pacemaker activity in the protected focus is electrotonically modulated by ventricular activity in this example. This modulated parasystolic activity is characterized by variable couple intervals at some rates (panel **B**) and fixed coupling intervals at select rates (panel **C**) as a result of the incomplete entrance block. **C.** Reentry. Reentrant activity is characterized by fixed coupling intervals of the premature extrasystoles to the beat of sinus origin. Such activity can be a result of modulated parasystole, circus movement reentry with or without an anatomical obstacle, reflection, or phase 2 reentry. The first schematic to the right illustrates reentry around an anatomical obstacle, in the Purkinje fiber–muscle junction. The schematic on the far right shows reentry around a functional obstacle. The numbers in the latter schematic represents the times (in milliseconds) of activation, whereas the numbers in the parentheses are the times (in milliseconds) of recovery. The reentry may be associated with an excitable gap (EX GAP), a relative refractory period (RRP), or an effective refractory period (ERP). **D.** Triggered activity. Shown is an example of sotalol-mediated early afterdepolarization (EAD)–induced triggered extrasystole giving rise to a polymorphic ventricular tachycardia characteristic of torsade de pointes. In this experimental model of long QT syndrome 2 (LQT2; coronary-perfused wedge), the EAD generally arises from the M-cell layer in the deep subendocardium of the ventricular wall. ECG, electrocardiogram; EG, electrogram; VT, ventricular tachycardia. **A-C**, reproduced with permission from Antzelevitch C, Bernstein MJ, Feldman HN, et al: Parasystole, reentry, and tachycardia: a canine preparation of cardiac arrhythmias occurring across inexcitable segments of tissue. *Circulation*. 1983 Nov;68(5):1101-1115. **D**, reproduced with permission from Shimizu W, Antzelevitch C: Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol*. 2000 Mar 1;35(3):778-786.

Subsidiary Pacemakers

In addition to SA node, AV nodes and the Purkinje system are also capable of generating automatic activity. The contribution of the I_f and potassium channel (I_K) differs in SA node/AV nodes and Purkinje fiber because of the different potential ranges of these two pacemaker types (ie, –70 to –35 mV and –90 to –65 mV, respectively). The contribution of other voltage-dependent currents can also differ among the different cardiac cell types. Similar to the SA node, the Ca clock also contributed significantly to the automaticity of the AV node.[38] Cells in the SA node possess the fastest intrinsic rates. Thus, the SA node is the primary pacemaker in the normal heart. When impulse generation or conduction within or out of the SA node is impaired, latent or subsidiary pacemakers within the atria or ventricle are capable of taking control of pacing the heart. The intrinsically slower rates of these latent pacemakers result in bradycardia. Subsidiary atrial pacemakers with more negative diastolic potentials (–75 to –70 mV) than SA nodal cells are located at the junction of the inferior right atrium and the inferior vena cava, near or on the Eustachian ridge.[39,40] Other atrial pacemakers have been identified in the crista terminalis[41] as well as at the orifice of the coronary sinus[14] and in the atrial muscle that extends into the tricuspid and mitral valves.[40,41] The cardiac muscle sleeves that extend into the cardiac veins (venae cavae and pulmonary veins) can also have the property of normal automaticity.[42] Latent pacemaking cells in the AV junction are responsible for AV junctional rhythms.[43] Both atrial and

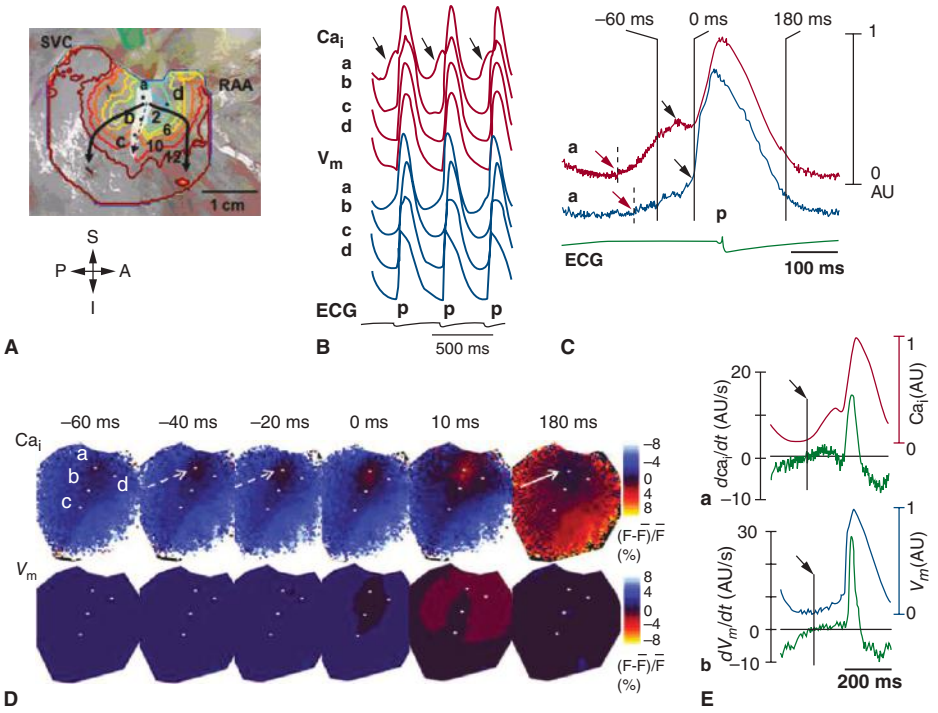

FIGURE 79–2. Activation pattern of sinoatrial (SA) node and surrounding right atrium (RA) during isoproterenol infusion of 0.3 µmol/L. This study was done in isolated Langendorff-perfused RA preparation. **A.** Isochronal map of V_m. The number on the each isochronal line indicates time (milliseconds). *White shaded area* is the SA node identified by the presence of spontaneous phase 4 depolarization. **B.** The V_m (*blue*) and Ca_i (*red*) recordings from the superior (*a*), middle (*b*), inferior (*c*) SA node and RA (*d*) presented in **A**. **C.** Magnified view of Ca_i and V_m tracings of superior SA node. Note the robust late diastolic Ca elevation before phase 0 of action potential (0 milliseconds), which in turn was much earlier than onset of the p wave on electrocardiogram (ECG). **D.** The V_m and Ca_i ratio maps at times from –60 milliseconds before to 180 milliseconds after phase 0 of action potential of **C**. The late diastolic Ca^{2+} elevation (*broken arrows* in frame –40 and –20 milliseconds) was followed by the Ca_i sinkhole during early diastole (*solid arrow* in frame 180 milliseconds). **E.** (*a*) Ca_i and dCa_i/dt. (*b*) V_m and dV_m/dt. The onset of late diastolic Ca^{2+} elevation and diastolic depolarization were (*arrows*) identified by the time when dCa_i/dt and dV_m/dt, respectively, crossed the baseline. Ca_i, intracellular calcium; RAA, right atrial appendage; SVC, superior vena cava. Reproduced with permission from Joung B, Tang L, Maruyama M, et al: Intracellular calcium dynamics and acceleration of sinus rhythm by beta-adrenergic stimulation. *Circulation*. 2009 Feb 17;119(6):788-796.[35]

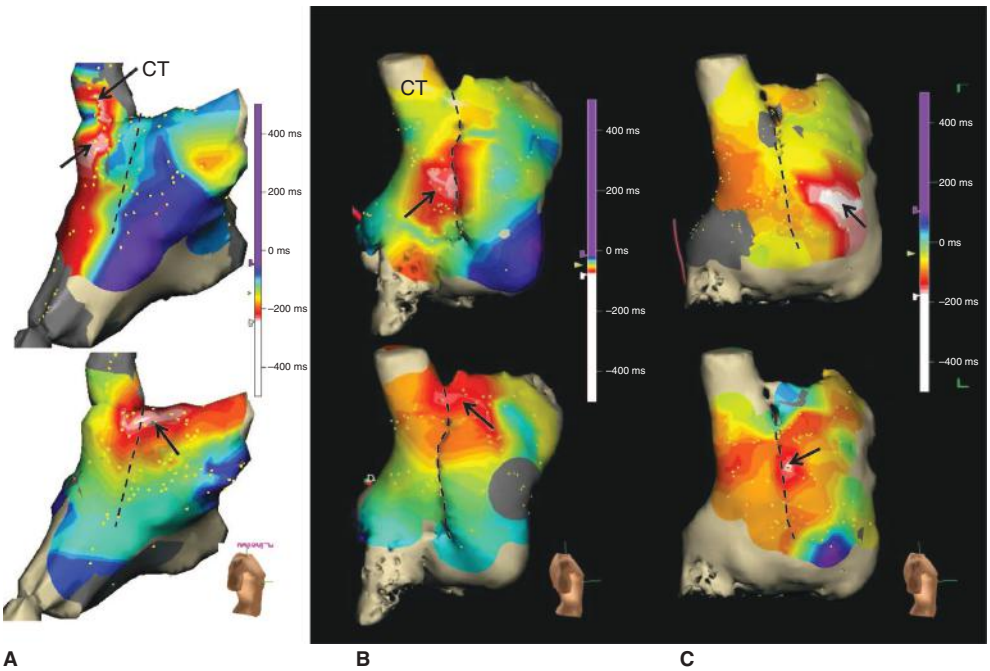

FIGURE 79–3. Effects of isoproterenol infusion on early activation site (EAS) in humans. **A.** Patient without sinoatrial (SA) nodal disease. The most cranial EAS at baseline (*a*) was in the superior vena cava (*arrows*). The EAS during isoproterenol infusion (*b*) was at the superior one-third of crista terminalis (CT), consistently with cranial shift of pacemaking site. **B.** Cranial shift of the EAS in a patient with atrial fibrillation (AF) but no symptomatic bradycardia. The EASs at baseline (*a*) and during isoproterenol infusion (*b*) were at the mid and superior part of CT, respectively. **C.** Impaired cranial shift of the EAS in a patient with AF and symptomatic bradycardia. The EAS at baseline (*a*) was ectopic (at the right atrial free wall). The EAS during isoproterenol infusion (*b*) was located at the mid one-third of CT. The superior SA node in this patient was inactive with or without isoproterenol. The *dashed line* in each panel marks the CT.

AV junctional subsidiary pacemakers are under autonomic control, with the sympathetic system increasing and parasympathetic system slowing the pacing rate.

The slowest subsidiary pacemakers are found in the His-Purkinje system in the ventricles of the heart.[44] In the His-Purkinje system, parasympathetic effects are less apparent than those of the sympathetic system. Although acetylcholine produces little in the way of a direct effect, it can significantly reduce Purkinje automaticity by means of inhibition of the sympathetic influence, a phenomenon termed *accentuated antagonism*.[45-47] Simultaneous recording of cardiac sympathetic and parasympathetic activity in ambulatory dogs confirmed that sympathetic activation followed by vagal activation may be associated with profound bradycardia.[48,49] Accentuated antagonism is also important in abnormal automaticity in the His-Purkinje system.[50] Adenosine has no effects on His-Purkinje System activation rate at baseline, but reduces its activation rate during isoproterenol infusion. These findings suggest that adenosine's effects on the human His-Purkinje system are primarily antiadrenergic and are thus consistent with the concept of accentuated antagonism. These effects of adenosine may serve as a counterregulatory metabolic response that improves the oxygen supply-demand ratio perturbed by enhanced sympathetic tone. Some catecholamine-mediated ventricular arrhythmias that occur during ischemia or enhanced adrenergic stress may be a result of an imbalance in this negative feedback system.

Biological Pacemakers

Changes of ionic component of cardiac cells by gene transfer can convert ordinary myocytes into cardiac pacemakers. One approach is to suppress inward rectifier current (I_{K1}) and enhance automaticity of ventricular myocytes.[51] A second approach is to insert a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel into cells using viral gene transfer, cell fusion, or stem cell technologies.[52-55] Successful HCN expression in the myocytes leads to the activation of I_f, enabling nonpacemaking cells to generate automaticity. These studies further confirm the importance of I_f in the mechanisms of automaticity. A more recent approach is to alter the gene expression during embryonic stem cell development to upregulate the pacemaker gene program and enhance automaticity.[56,57] Although these preliminary studies are exciting, more will need to be done before this approach can be useful in humans.

AUTOMATICITY AS A MECHANISM OF CARDIAC ARRHYTHMIAS

Abnormal automaticity includes both reduced automaticity, which causes bradycardia, and increased automaticity, which causes tachycardia. Arrhythmias caused by abnormal automaticity can result from diverse mechanisms (see Table 79–1). Alterations in sinus rate can be accompanied by shifts of the origin of the dominant pacemaker within the sinus node or to subsidiary pacemaker sites elsewhere in the atria. Impulse conduction out of the SA mode can be impaired or blocked as a result of disease or increased vagal activity leading to development of bradycardia. AV junctional rhythms occur when AV junctional pacemakers located either in the AV node or in the His bundle accelerate to exceed the rate of SA node or when the SA nodal activation rate is too slow to suppress the AV junctional pacemaker.

Hereditary Bradycardia

Bradycardia can occur in structurally normal hearts as a result of genetic mutations that result in abnormalities of either the membrane clock or Ca clock mechanism of automaticity. One example is the mutation of subtype 4 of HCN channel (*HCN4*), which is part of the channels that carry I_f. Mutations of *HCN4* cause changes in HCN4 channel expression and kinetics,[58] leading to familial bradycardia.[59-61] However, the bradycardia caused by *HCN4* mutations may be entirely asymptomatic. Although *HCN4* mutations cause baseline bradycardia, the heart rate responses to exercise may be either suboptimal, with a maximum rate of 100 bpm,[60] or entirely normal, with maximum rates of > 150 bpm.[61] The presence of normal heart rate response in patients with *HCN4* mutation can be explained by the intact Ca clock, which can accelerate the sinus rate during sympathetic activation.[17,35]

Secondary Sinoatrial Node Dysfunction

Common diseases, such as heart failure and AF, may be associated with significant SA node dysfunction.[36,62] Malfunction of membrane voltage clocks and Ca clocks might both be present in these common diseases. Zicha et al[63] reported that downregulation of HCN4 expression contributes to heart failure–induced sinus node dysfunction and that upregulation of atrial HCN4 may help to promote atrial arrhythmia formation. Heart failure is also known to be associated with significant abnormalities of Ca_i regulation.[64] It is likely that abnormalities of both the membrane voltage clock and Ca clock are responsible for the SA node dysfunction in heart failure. Similarly, AF is also associated with malfunction of both membrane and Ca clocks.[35,65] The SA node malfunction is reversible after successful radiofrequency catheter ablation of AF.[66]

Enhanced Automaticity

Atrial and ventricular myocardial cells do not display spontaneous diastolic depolarization or automaticity under normal conditions but can develop these characteristics when depolarized, resulting in the development of repetitive impulse initiation, a phenomenon termed *depolarization-induced automaticity*.[67] The membrane potential at which abnormal automaticity develops ranges between –70 and –30 mV. The rate of abnormal automaticity is substantially higher than that of normal automaticity and is a sensitive function of resting membrane potential (ie, the more depolarized the resting potential, the faster the rate). Similar to normal automaticity, abnormal automaticity is enhanced by β-adrenergic agonists and by reduction of external potassium. Depolarization of membrane potential associated with disease states is most commonly a result of: (1) an increase in extracellular potassium, which reduces the reversal potential for I_{K1}, the outward current that largely determines the resting membrane or maximum diastolic potential; (2) a reduced number of I_{K1} channels; (3) a reduced ability of the I_{K1} channel to conduct potassium ions; or (4) electrotonic influence of neighboring depolarized zone. Because the conductance of I_{K1} channels is sensitive to extracellular potassium concentration, hypokalemia can lead to major reduction in I_{K1}, leading to depolarization and the development of enhanced or abnormal automaticity, particularly in Purkinje pacemakers. A reduction in I_{K1} can also occur secondary to a mutation in *KCNJ2*, the gene that encodes for this channel, leading to increased automaticity and extrasystolic activity presumably arising from the Purkinje system.[68,69] Interestingly, because β-adrenergic stimulation is effective in augmenting I_{K1},[70] sympathetic stimulation can produce a paradoxical slowing of automaticity and ectopy in this setting. Because of the importance of I_{K1} in maintaining membrane depolarization and preventing automaticity, suppression of Kir2 and reduce I_{K1} can enhance automaticity of ventricular myocytes. The latter approach has been used as an approach to develop biological pacemakers.[51]

Autonomic Mechanisms in Sinoatrial Nodal Tachycardia and Atrial Tachycardia

Normal or subsidiary pacemaker activity also can be enhanced, leading to sinus tachycardia or a shift to ectopic sites within the atria, giving rise to atrial tachycardia. One cause can be enhanced autonomic nerve

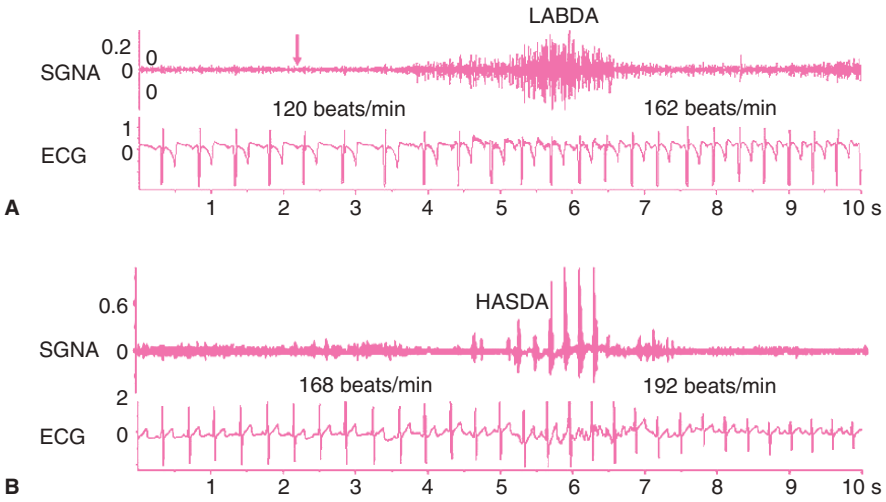

FIGURE 79–4. Sympathetic control of heart rate. Stellate ganglion nerve activity (SGNA) was recorded simultaneously with electrocardiogram (ECG) in a normal ambulatory dog with an implanted radiotransmitter. **A.** Low-amplitude burst discharge activity (LABDA), which induced heart rate acceleration. **B.** High-amplitude spike discharge activity (HASDA) that occurred during LABDA. HASDA further accelerated the heart rate. The unit for SGNA and ECG is mV. Reproduced with permission from Zhou S, Jung BC, Tan AY, et al: Spontaneous stellate ganglion nerve activity and ventricular arrhythmia in a canine model of sudden death. *Heart Rhythm*. 2008 Jan;5(1):131-139.[71]

activity. Direct recording from the stellate ganglion and vagal nerves show that stellate ganglion nerve activity (SGNA) and vagal nerve activity are both important in controlling sinus rate and in triggering atrial tachycardia in ambulatory dogs. Figure 79–4 shows an example of heart rate acceleration induced by SGNA. The SGNA consists of two types of activity. The vast majority of activity was in the form of low-amplitude burst discharge activity. A second form of activity is the high-amplitude spike discharge activity, which occurs less than 10 times daily in normal dogs, and the incidence may more than double in dogs with heart failure or myocardial infarction.[48,49,71] In this and in all dogs studied, there was no latency between the onset of nerve activity and the shortening of the next P-P interval. Vagal nerve activation, on the other hand, induces sinus bradycardia.[48] Figure 79–5 shows an example of bradycardia associated with increased vagal nerve activity. The same figure shows that simultaneous sympathovagal discharges are common triggers of atrial tachyarrhythmia.

Overdrive Suppression of Automaticity

The automaticity of all pacemakers within the heart is inhibited when they are overdrive paced.[72] This inhibition is called *overdrive suppression*. Under normal conditions, all subsidiary pacemakers are overdrive-suppressed by SA nodal activity. The mechanisms of overdrive suppression are thought to be related to pacing-induced intracellular accumulation of Ca and Na.[73,74] The Na accumulation leads to enhanced activity of the sodium pump (sodium-potassium adenosine triphosphatase [Na^+-K^+ ATPase]), which generates a hyperpolarizing electrogenic current that opposes phase 4 depolarization.[74] The faster the overdrive rate or the longer the duration of overdrive, the greater is the enhancement of sodium pump activity, so that the period of quiescence after cessation of overdrive is directly related to the rate and duration of overdrive.

PARASYSTOLE AND MODULATED PARASYSTOLE

Latent pacemakers throughout the heart are generally reset by the propagating wavefront initiated by the dominant pacemaker and are therefore unable to activate the heart. An exception to this rule occurs when the pacemaking tissue is protected from the impulse of sinus origin. A region of entrance block arises when cells exhibiting automaticity are surrounded by ischemic, infarcted, or otherwise compromised cardiac tissues that prevent the propagating wave from invading the focus, but which permit the spontaneous beat generated within the automatic focus to exit and activate the rest of the myocardium. A pacemaker region exhibiting entrance block and exit conduction defines a parasystolic focus. The ectopic activity generated by a parasystolic focus is characterized by premature ventricular complexes with variable coupling intervals, fusion beats, and interectopic intervals that are multiples of a common denominator.

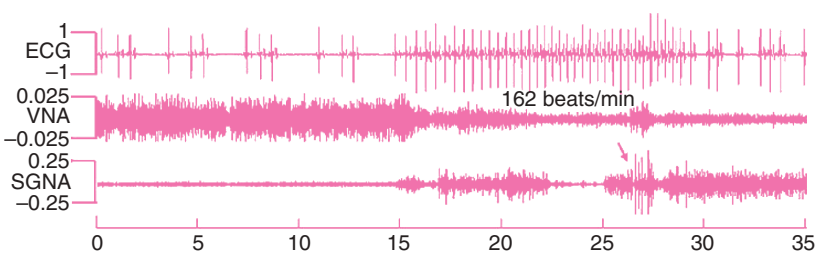

FIGURE 79–5. Vagal control of heart rate. This figure was obtained from a normal ambulatory dog with implanted transmitter. Vagal nerve activity (VNA) is associated with slow heart rate response (left part of the figure), whereas sympathovagal co-activation was associated with atrial tachycardia, followed by irregular heartbeats and sinus bradycardia toward the end of the tracing. *Arrows* point to an episode of high-amplitude spike discharge activity amid continuous low-amplitude burst discharge activity. ECG, electrocardiogram; SGNA, stellate ganglion nerve activity. Reproduced with permission from Ogawa M, Zhou S, Tan AY, et al: Left stellate ganglion and vagal nerve activity and cardiac arrhythmias in ambulatory dogs with pacing-induced congestive heart failure. *J Am Coll Cardiol*. 2007 Jul 24;50(4):335-343.[48]

AFTERDEPOLARIZATION AND TRIGGERED ACTIVITY

Oscillatory depolarizations that attend or follow the cardiac action potential and depend on preceding transmembrane activity for their manifestation are referred to as afterdepolarizations. Two subclasses are traditionally recognized: (1) early and (2) delayed. EADs interrupt or retard repolarization during phase 2 and/or phase 3 of the cardiac action potential, whereas DADs occur after full repolarization. When EAD or DAD amplitude suffices to bring the membrane to its threshold potential, a spontaneous action potential, referred to as a triggered response, is the result. These triggered events can be responsible for extrasystoles and tachyarrhythmias that develop under conditions predisposing to the development of afterdepolarizations.

Early Afterdepolarizations and Triggered Activity

EADs are observed in isolated cardiac tissues exposed to injury, altered electrolytes, hypoxia, acidosis, catecholamines, and pharmacologic agents, including antiarrhythmic drugs. Ventricular hypertrophy and heart failure also predispose to the development of EADs.[75] However, because of source-sink mismatch in well-coupled cardiac tissues, it is unlikely that the EAD of a single cardiomyocyte will be able to generate propagated wavefronts. Rather, a critical mass of literally thousands of myocytes to develop an EAD synchronously on the same beat is needed for an overt EAD to trigger a premature ventricular contraction. Weiss et al[76] proposed that the chaotic EAD behavior combined with the smoothing effect of electrotonic gap junction coupling permits normally irregular EADs to synchronize regionally, producing macroscopic "EAD islands" next to areas without EADs. This synchronization mechanism produces shifting focal activations, mixed with reentry, which arise suddenly from normal or bradycardic heart rates and produce characteristic features of polymorphic and torsades de pointes ventricular tachycardia (VT).

EAD characteristics vary as a function of animal species, tissue or cell type, and the method by which the EAD is elicited. Although specific mechanisms of EAD induction can differ, a critical prolongation of repolarization accompanies most, but not all, EADs. Drugs that block potassium currents may reduce repolarization reserve and predispose the cells to EADs.[77] Figure 79–6 illustrates the two types of EADs generally encountered in Purkinje fiber. Oscillatory events appearing at potentials positive to –30 mV are generally referred to as phase 2 EADs. Those occurring at more negative potentials are termed phase 3 EADs. Phase 2 and phase 3 EADs sometimes appear in the same preparation.

EAD-induced triggered activity is sensitive to stimulation rate. Antiarrhythmic drugs with class III action generally induce EAD activity at slow stimulation rates and totally suppress EADs at rapid rates.[78,79] In contrast, β-adrenergic agonist–induced EADs are fast rate dependent.[80,81] In the presence of rapidly activating delayed rectifier current (rapid outward potassium current [I_{Kr}]) blockade, β-adrenergic agonists and/or acceleration from an initially slow rate transiently facilitate the induction of EAD activity in ventricular M cells, but not in epicardium or endocardium and rarely in Purkinje fibers.[82] This biphasic effect is thought to be caused by an initial priming of I_{NCX}, which provides an electrogenic inward current that facilitates EAD development and prolongs APD. This early phase is followed by recruitment of slowly activating delayed rectifier current (slow outward potassium current [I_{Ks}]), which abbreviates APD and suppresses EAD activity.

Cellular Origin of Early Afterdepolarizations

EADs develop more in midmyocardial M cells and Purkinje fibers than in epicardial or endocardial cells when exposed to APD-prolonging agents. This is in part a result of the presence of a weaker I_{Ks} in M cells.[83] In addition, a recent study showed that apamin-sensitive SK current (I_{KAS}) is deficient in the M-cell layer in failing human ventricles.[84] Because I_{KAS} current is low, the M-cell myocytes are not able to shorten the APD in conditions associated with increased Ca_i. The reduced SK current can therefore contribute to the development of EADs in the M cells. Chromanol 293B, which blocks both the I_{Ks},[85] and the I_{KAS},[86] permits the induction of EADs in canine epicardial and endocardial tissues in response to I_{Kr} blockers such as E-4031 or sotalol.[87] The predisposition of cardiac cells to the development of EADs depends principally on the reduced availability of I_{Kr}, I_{Ks}, and I_{KAS} as occurs in many forms of cardiomyopathy and heart failure. Under these conditions, EADs can appear in any part of the ventricular myocardium.

Ionic Mechanisms Responsible for Early Afterdepolarizations

An EAD occurs when the balance of current active during phase 2 or 3 of the action potential shifts in the inward direction. If the change in current-voltage relation results in a region of net inward current during the plateau range of membrane potentials, it leads to a depolarization or EAD. Most pharmacologic interventions or pathophysiologic conditions associated with EADs can be categorized as acting predominantly through one of four different mechanisms: (1) a reduction of repolarizing potassium currents (I_{Kr}, class IA and III antiarrhythmic agents; I_{Ks}, chromanol 293B or I_{K1}); (2) an increase in the availability of calcium current (Bay K8644, catecholamines); (3) an increase in the sodium-calcium exchange current (I_{NCX}) caused by augmentation of Ca_i activity or upregulation of the I_{NCX}; and (4) an increase in late Na current (I_{NaL}) (aconitine, anthoplexurin-A, and ATX-II). Combinations of these interventions (eg, calcium loading and I_{Kr} reduction) or pathophysiologic states can act synergistically to facilitate the development of EADs.

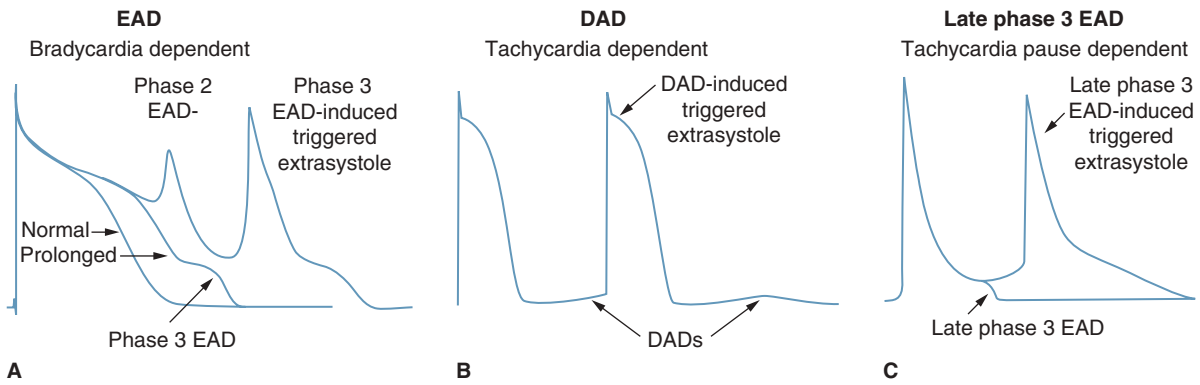

FIGURE 79–6. Examples of (**A**) early afterdepolarization (EAD), (**B**) delayed afterdepolarization (DAD), and (**C**) late phase 3 EAD.

A sustained component of sodium channel current (I_{Na}) active during the action potential plateau, originating from channels that fail to inactivate and a nonequilibrium component arising from channels recovering from inactivation during phases 2 and 3, has been shown to contribute prominently to the APD and induction of EADs.[88,89] Reactivation of $I_{Ca,L}$ may contribute to the development of EADs when there was persistent late I_{Na} and reduced repolarization reserve.[88] Calcium-calmodulin kinase II has been linked to the development of EAD in mouse models of cardiac hypertrophy.[90] Ranolazine, which suppresses late I_{Na}, is a promising antiarrhythmic agent, especially in the atria.[91,92]

Delayed Afterdepolarization–Induced Triggered Activity

DADs occur because of the spontaneous sarcoplasmic reticulum Ca release, which activates the I_{NCX} and results in oscillations of transmembrane potentials that occur after full repolarization of the action potential.[93,94] When there is spontaneous sarcoplasmic reticulum Ca release, it activates the I_{NCX} and depolarizes the cell membrane. DADs may reach the threshold and give rise to spontaneous action potentials generally referred to as triggered activity. However, whether or not spontaneous sarcoplasmic reticulum Ca releases can cause a DAD depends in part on the cell type. Maruyama et al[95] used the term *diastolic Ca_i-voltage coupling gain* to describe membrane potential (V_m) responses to elevated Ca_i during diastole. This concept is based on the finding that the same magnitude of sarcoplasmic reticulum Ca release may induce DADs in the Purkinje fibers but not in the epicardial cells. The reduced I_{K1} in the Purkinje cells[96] was thought to underlie the higher diastolic Ca_i-voltage coupling gain compared with other myocardial cells. As discussed earlier, recent studies suggest that rhythmic spontaneous sarcoplasmic reticulum Ca release (Ca clock) is also a mechanism of SA nodal automaticity. Specifically, the rhythmic sarcoplasmic reticulum Ca releases in the SA node cause DADs and triggered activity, which underlies the mechanism of sinus rhythm.[97] Therefore, although spontaneous sarcoplasmic reticulum Ca release is an arrhythmogenic mechanism, it also contributes significantly to the normal automaticity.

Role of Delayed Afterdepolarization–Induced Triggered Activity in the Development of Cardiac Arrhythmias

An excellent example of DAD-induced arrhythmia is catecholaminergic polymorphic ventricular tachycardia (CPVT), which may be caused by the mutation of *RyR2*, calsequestrin (*CSQ2*), *CALM1*, and *CALM2*.[98-101] The fundamental mechanism of these arrhythmias is the "leaky" ryanodine receptor, which is aggravated during catecholamine stimulation to induce DADs.[102,103] A typical clinical phenotype of CPVT is bidirectional VT, which is also seen in digitalis toxicity[104,105] and long QT syndrome type 7 (*KCNJ2* mutation).[106] Alternans of Ca_i may play a role in the development of bidirectional VT.[107] Because the genetic defects of CPVT have been well described, it is possible to generate transgenic mice that duplicate the human genotype. One of the transgenic mice (RyR2/RyR2[R4496C]) was subjected to optical mapping studies.[103] The isolated cells were studied for DADs. The results showed that these mice exhibited both polymorphic VT and bidirectional VT and hence reproduced the most important phenotypes of CPVT. The in vitro studies documented that DADs underlie both polymorphic and bidirectional VT of these mice. In another study, mice carrying a human D307H missense mutation of calsequestrin (CASQ307/307)[108] also demonstrated frequent and prolonged sarcoplasmic reticulum Ca release events. If DADs and triggered activity underlie arrhythmias in CPVT syndrome, it follows that inhibition of spontaneous sarcoplasmic reticulum Ca release from the RyR2 might lead to successful mechanism-based therapy of cardiac arrhythmia. Wehrens et al[109] demonstrated that heterozygous mutation of *FKBP12.6* leads to leaky RyR2 and exercise-induced VT and ventricular fibrillation (VF), simulating the human CPVT phenotype. RyR2 stabilization with a derivative of 1,4-benzothiazepine (JTV519) increased the affinity of calstabin2 for RyR2, which stabilized the closed state of RyR2 and prevented the Ca leak that triggers arrhythmias. The authors postulated that enhancing the binding of calstabin2 to RyR2 may be a therapeutic strategy for common ventricular arrhythmias. RyR2 stabilization may also be useful in managing patients with heart failure, a disease condition associated with abnormal Ca_i handling.[110] Although RyR2 stabilizers are not yet approved for human use, Knollmann's laboratory[111] discovered that flecainide, a commonly used antiarrhythmic drug, prevented adrenergic stress–induced arrhythmias in a mouse model of CPVT and in humans with *CASQ2* or *RYR2* mutations. The latter study provided the first human data that support the efficacy of RyR2-based therapy in human patients. Subsequent clinical studies that showed flecainide effectively suppresses exercise-induced arrhythmias in patients with CPVT.[112]

Taken together, these human and transgenic model studies suggest that spontaneous sarcoplasmic reticulum Ca release, DAD, and triggered arrhythmias underlie the mechanisms of CPVT. However, in order for DAD to induce triggered activity, there is a need for Na channel activation. Therefore, the effects of flecainide in suppressing CPVT could also be explained by its action on Na channels.[113] Other studies indicate that the epicardial origin of these ectopic beats increases transmural dispersion of repolarization, thus providing the substrate for the development of reentrant tachyarrhythmias, which underlie the rapid polymorphic VT/VF.[114] In addition to CPVT, DADs may also contribute significantly to arrhythmogenesis in common arrhythmias, such as premature ventricular contractions from the peri-infarct zone in rabbit hearts with subacute myocardial infarction.[115] Heart failure is associated with structural and electrophysiologic remodeling, leading to tissue heterogeneity that enhances arrhythmogenesis and the propensity of sudden cardiac death. The mechanisms of arrhythmogenesis in heart failure may be attributed to the upregulation of I_{NCX} activity, abnormal intracellular calcium (Ca_i) handling, and non-reentrant ventricular arrhythmias as a result of triggered activity.[116] DADs occur in heart failure as a result of sarcoplasmic reticulum Ca overload and spontaneous sarcoplasmic reticulum Ca release that activates electrogenic I_{NCX} during phase 4 of the action potential.[117] Genetic suppression reduces both EADs and DADs.[118] Because DADs are often induced by rapid activation and Ca_i accumulation, the best time to observe DADs is at the cessation of rapid pacing or tachycardia such as immediately after ventricular defibrillation.[95,119] Figure 79–7 shows an example of spontaneous VF in a Langendorff-perfused failing heart. Panel A shows baseline recording. The arrow in Panel B shows spontaneous Ca_i elevation, associated with a DAD on the epicardium.

Late Phase 3 Early Afterdepolarizations and Their Role in the Initiation of Cardiac Fibrillation

Panels B and C of Figure 79–7 show V_m and Ca_i at termination and at the onset of spontaneous VF, respectively. Note the presence of short APD in the immediate postshock period (panel B) and that the first ectopic beat that initiated VF occurred from late phase 3 of the preceding action potential (panel C). The mechanism of VF is best explained by the late phase 3 EAD and triggered activity.[15,120,121] This arrhythmogenic mechanism combines properties of both EAD and DAD but has its own unique character (see Fig. 79–7C). Late phase 3 EAD-induced triggered extrasystoles occur because abbreviated repolarization permits normal sarcoplasmic reticulum Ca release to induce an EAD-mediated closely coupled triggered response, particularly under conditions permitting intracellular Ca

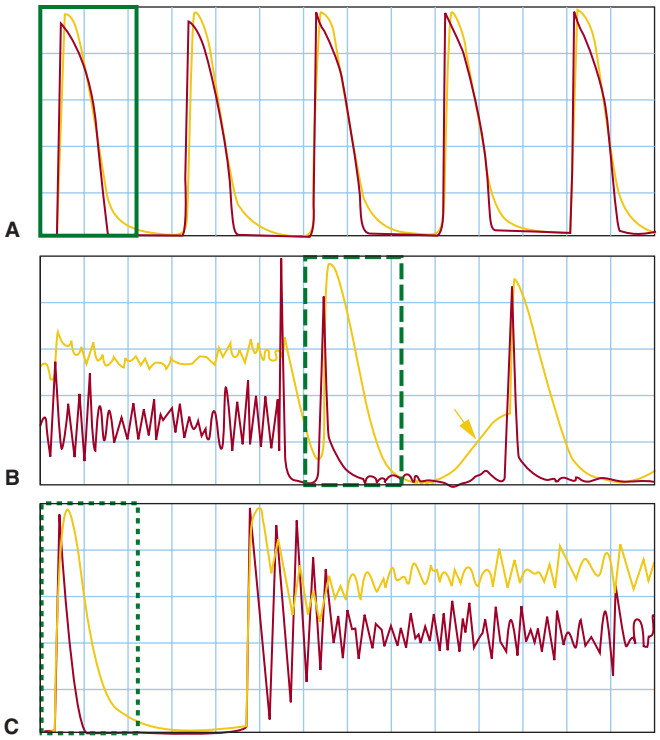

FIGURE 79–7. Delayed afterdepolarization (DAD) and late phase 3 early afterdepolarization (EAD) in the postshock period. The figure shows optical mapping of membrane potential (V_m, *red trace*) and intracellular Ca^{2+} (Ca_i, *yellow trace*). **A.** Baseline recording, where the action potential duration (APD) and Ca_i transient were of similar duration. **B.** Spontaneous Ca_i elevation after successful defibrillation (*arrow*), associated with an epicardial DAD on the V_m tracing. That DAD did not induce triggered activity from the epicardium. Subsequent beat originated from outside of the mapped region and is associated with very short APD. **C.** An episode of spontaneous ventricular fibrillation in the postshock period. Because of the short APD and long Ca_i transient, the mechanism of DAD is most consistent with the late phase 3 EAD. Reproduced with permission from Ogawa M, Morita N, Tang L: Mechanisms of recurrent ventricular fibrillation in a rabbit model of pacing-induced heart failure. *Heart Rhythm*. 2009 Jun;6(6):784-792.[119]

loading (such as AF and VF). These EADs are distinguished by the fact that they interrupt the final phase of repolarization of the action potential (late phase 3). In contrast to previously described DAD or intracellular calcium (Ca_i)–dependent EAD, it is normal, not spontaneous, sarcoplasmic reticulum Ca release that is responsible for the generation of the EAD. Late phase 3 EADs are observed when APD is markedly abbreviated as with acetylcholine (see Figs. 79–6C and 79–7B). Based on the time course of contraction, levels of Ca_i would be expected to peak during the plateau of the action potential (membrane potential of approximately –5 mV) under control conditions but during the late phase of repolarization (membrane potential of approximately –70 mV) when there is an abbreviated APD. As a consequence, the two principal Ca-mediated currents, I_{NCX} and $I_{Cl(Ca)}$, would be expected to be weakly inward or even outward ($I_{Cl(Ca)}$) when APD is normal (control), but strongly inward when APD is very short (such as during acetylcholine infusion).[15] Thus, abbreviation of the atrial APD allows for a much stronger recruitment of both I_{NCX} and calcium-activated chloride conductance ($I_{Cl(Ca)}$) in the generation of late phase 3 EADs.

In the isolated canine atria, late phase 3 EAD-induced extrasystoles have been shown to initiate AF, immediately following the termination of the arrhythmia.[15] The same mechanisms may play an important role in the development of triggered activity within the pulmonary veins, where the APD is short even at baseline.[120,121] Simultaneous sympathovagal activation is also known to be the primary trigger of paroxysmal atrial tachycardia and AF episodes in dogs with intermittent rapid pacing.[49] In addition to the atrial arrhythmias, late phase 3 EAD may also be responsible for the development recurrent VF in failing hearts.[119] As shown in Figure 79–7, Langendorff-perfused failing hearts develop acute and transient APD shortening immediately after successful defibrillation. Because of Ca_i accumulation during fibrillation, a combination of short APD and large Ca_i allows late phase 3 EAD to occur. Subsequently, studies showed that I_{KAS} is upregulated during heart failure[84,122] and may play an important role in modulating cardiac memory.[123] VF results in the Ca_i elevation, which activates I_{KAS} and shortens the postshock APD. A combination of high Ca_i and short APD results in spontaneous VF as shown in Figure 79–7. Apamin, a specific blocker of I_{KAS}, prevents the spontaneous recurrences of VF.[122] Therefore, in addition to recurrent atrial arrhythmias, late phase 3 EADs may also be the mechanism responsible for ventricular arrhythmias associated with heart failure.

REENTRANT ARRHYTHMIAS

Reentry is a fundamentally different mechanism of arrhythmogenesis than automaticity or triggered activity. The circus movement reentry occurs when an activation wavefront propagates around an anatomical or functional core and reexcites the site of origin. In this type of reentry, all cells take turns recovering from excitation and get ready to be excited again when the next wavefront arrives. In comparison, reflection and phase 2 reentry occur when there are large differences of recovery from one site to another. The site with delayed recovery serves as a virtual electrode that excites its already recovered neighbor, resulting in reentry. A circus movement is not observed. In addition, reentry can also be classified as anatomical and functional, although there is a gray zone in which both functional and anatomical factors are important in determining the characteristics of reentrant excitation.

CIRCUS MOVEMENT REENTRY AROUND AN ANATOMICAL OBSTACLE

The ring model is the prototypical example of reentry around an anatomical obstacle. It first emerged as a concept shortly after the turn of the last century when Mayer reported the results of experiments involving the subumbrella tissue of a jellyfish (*Sychomedusa cassiopeia*).[4] The muscular disk did not contract until ringlike cuts were made and pressure and a stimulus applied. This caused the disk to "spring into rapid rhythmical pulsation so regular and sustained as to recall the movement of clockwork."[4] Mayer demonstrated similar circus movement excitation in rings cut from the ventricles of turtle hearts, but he did not consider this to be a plausible mechanism for the development of cardiac arrhythmias. His experiments proved valuable in identifying two fundamental conditions necessary for the initiation and maintenance of circus movement excitation: (1) unidirectional block—the impulse initiating the circulating wave must travel in one direction only; and (2) for the circus movement to continue, the circuit must be long enough to allow each site in the circuit to recover before the return of the circulating wave. G. R. Mines[6] was the first to develop the concept of circus movement reentry as a mechanism responsible for cardiac arrhythmias. He confirmed Mayer's observations and suggested that the recirculating wave could be responsible for clinical cases of tachycardia.[124] The clinical importance of reentry was reinforced with the discovery by Kent of an accessory pathway connecting the atrium and ventricle of a human heart,[125] and that successful surgical ablation of the accessory pathway results in the cure of the paroxysmal supraventricular tachcardia.[126]

The following three criteria developed by Mines for identification of circus movement reentry remain in use today:

1. An area of unidirectional block must exist.
2. The excitatory wave progresses along a distinct pathway, returning to its point of origin and then following the same path again.
3. Interruption of the reentrant circuit at any point along its path should terminate the circus movement.

It was recognized that successful reentry could occur only when the impulse was sufficiently delayed in an alternate pathway to allow for expiration of the refractory period in the tissue proximal to the site of unidirectional block. Both conduction velocity and refractoriness determine the success or failure of reentry, and the general rule is that the length of the circuit (path length) must exceed or equal that of the wavelength, the wavelength being defined as the product of the conduction velocity and the refractory period or that part of the path length occupied by the impulse and refractory to reexcitation. The theoretical minimum path length required for development of reentry was therefore dependent on both the conduction velocity and the refractory period. Reduction of conduction velocity[127] or APD[128] can both significantly reduce the theoretical limit of the path length required for the development of reentry.

CIRCUS MOVEMENT REENTRY WITHOUT AN ANATOMICAL OBSTACLE

That reentry could be initiated without the involvement of anatomical obstacles and that "natural rings are not essential for the maintenance of circus contractions" was first suggested by Garrey in 1914.[129] Years later, Allessie and coworkers[130] provided direct evidence in support of this hypothesis in experiments in which they induced a tachycardia in isolated preparations of rabbit left atria by applying properly timed premature extra-stimuli. Using multiple intracellular electrodes, they showed that although the basic beats elicited by stimuli applied near the center of the tissue spread normally throughout the preparation, premature impulses propagate only in the direction of shorter refractory periods. An arc of block thus develops around which the impulse is able to circulate and reexcite its site of origin. Recordings near the center of the circus movement showed only subthreshold responses. The authors proposed the term *leading circle* to explain their observation.[7] They argued that the functionally refractory region that develops at the vortex of the circulating wavefront prevents the centripetal waves from short circuiting the circus movement and thus serves to maintain the reentry. The authors also proposed that the refractory core was maintained by centripetal wavelets that collide with each other. Because the head of the circulating wavefront usually travels on relatively refractory tissue, a fully excitable gap of tissue may not be present; unlike other forms of reentry, the leading circle model may not be readily influenced by extraneous impulses initiated in areas outside the reentrant circuit and thus may not be easily entrained. Although leading circle reentry was for a time widely accepted as a mechanism of functional reentry, there is significant conceptual limitation to this model of reentry. For example, the centripetal wavelet was difficult to demonstrate either by experimental studies with high-resolution mapping or with computer simulation studies.

First introduced by Wiener and Rosenblueth in 1946,[131] the concept of spiral waves (rotors) has attracted a great deal of interest. Originally used to describe reentry around an anatomic obstacle, the term *spiral wave reentry* was later adopted to describe circulating waves in the absence of an anatomic obstacle.[11,78,132,133] Because the concept of spiral waves of excitation is a well-described phenomenon in many excitable media,[132] the application of the spiral waves of excitation to cardiac tissues is met with great enthusiasm. Spiral wave theory has advanced our understanding of the mechanisms responsible for the functional form of reentry. Although leading circle and spiral wave reentry are considered by some to be similar, a number of distinctions have been suggested. The curvature of the spiral wave is the key to the formation of the core.[134] The curvature of the wave forms a region of high impedance mismatch (source-sink mismatch), where the current provided by the reentering wavefront (source) is insufficient to charge the capacity and thus excite a larger volume of tissue ahead (sink). The ability of impulse propagation to succeed depends critically on the ability of source current generated by already activated cells to excite the cells ahead that have not yet been activated, generally referred to as the sink. When the source current generated by a few cells is required to activate a large number of cells in the sink, the dilution of the current may lead to conduction failure or block. A prominent curvature of the spiral wave is generally encountered following a wave break, where the wavefront meets the wavetail and a large curvature (and short action potential) is present. As a result of a very small source in part related to a short action potential (wavefront and wavetail meets), the broken end of the wave moves most slowly. Figure 79–8 shows the formation of the spiral wave by wavefront interaction with the refractory tail of a previous activation.[135] This three-dimensional computer simulation study reproduced the wavebreak observed in the optical mapping studies of VF in swine ventricle.[136] The wavebreak occurs when the wavefront encountered the refractory tail of a previous activation, inducing two spiral waves (panel A). A three-dimensional view of the scroll wave is shown in panel B. Panel C is a close-up of the wavebreak. Note that the newly formed wavebreak has a very high curvature. As curvature decreases along the more distal parts of the spiral, propagation speed

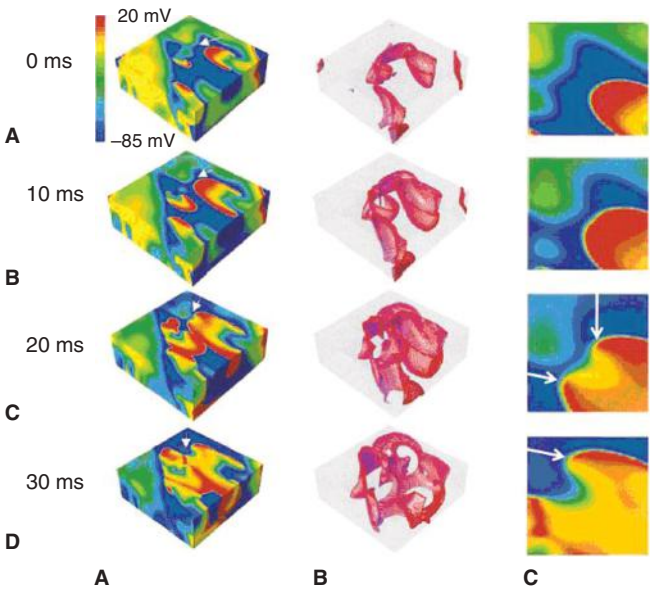

FIGURE 79–8. Three-dimensional simulation of wavebreak by a wavefront running into the trailing edge of refractoriness. **A.** Surface activation patterns (*red* = wavefront, *green* = waveback) at the times indicated. The *white arrows* indicate the region where this mechanism of wavebreak occurs. **B.** Corresponding scroll wavefronts in the tissue (*red* = rising membrane voltage). **C.** Blowup of the region of wave break on the upper surface (near the *white arrows* in **A**). Residual refractoriness (*green*) was left over by a previous wavefront, and when the next wave (*red*) encountered this refractory region, wave break occurred, generating two new scroll waves. *White arrows* point to the new wave breaks. At that site, the curvature of the wave is high and the source-sink ratio is low, preventing the wavefront from propagating. The wavefront (*red*) then circles around the wavebreak and forms circus movement. Reproduced with permission from Lee MH, Qu Z, Fishbein GA, et al: Patterns of wave break during ventricular fibrillation in isolated swine right ventricle. *Am J Physiol Heart Circ Physiol*. 2001 Jul;281(1):H253-H265.[136]

increases. The high curvature prevents the wave from propagating in the direction of wavebreak. The wavefront (red) then circles around the wavebreak site to form circus movement. In three dimensions, there are two new scroll waves formed by these interactions. Another difference between the leading circle and spiral wave is the state of the core; in the former, the core is refractory because of repetitive centripetal wavelet that invades the core. In the latter, the core remains unexcited because the source-sink mismatch prevents the propagation of the wavefront into the core.[137]

The term *spiral wave* is usually used to describe reentrant activity in two dimensions. The center of the spiral wave is called the *core*, and the distribution of the core in three dimensions is referred to as the *filament*. The three-dimensional form of the spiral wave forms a scroll wave (see Fig. 79–8B). In its simplest form, the scroll wave has a straight filament spanning the ventricular wall (ie, from epicardium to endocardium). Theoretical studies have described three major scroll wave configurations with curved filaments (L-, U-, and O-shaped), although numerous variations of these three-dimensional filaments in space and time are assumed to exist during cardiac arrhythmias.

Spiral wave activity has been used to explain the electrocardiographic patterns observed during monomorphic and polymorphic cardiac arrhythmias as well as during fibrillation. Monomorphic VT results when the spiral wave is anchored and not able to drift within the ventricular myocardium. In contrast, a meandering or drifting spiral wave causes polymorphic VT/VF-like activity.[138,139] VF seems to be the most complex representation of rotating spiral waves in the heart. VF is often preceded by VT. One of the theories suggests that VF develops when a single spiral wave responsible for VT breaks up, leading to the development of multiple spirals that are continuously extinguished and re-created.[140]

Stability of Circus Movement Reentry

The stability of reentry is critical to the understanding of the electrocardiographic manifestations of arrhythmias. If only a single stable reentrant wavefront is present, the electrocardiogram is likely to show consistent beat-to-beat QRS morphology (such as during monomorphic VT) or consistent beat-to-beat P-wave morphology (such as during cavotricuspid isthmus–dependent atrial flutter). However, if the reentrant circuit either meanders or breaks down into multiple reentrant circuits, then the electrocardiographic manifestation becomes polymorphic or fibrillatory. Many different factors independently determine the stability of the circus movement reentry.[138-140]

Size of the Anatomical Obstacle

Although circus movement reentry can be conveniently classified as anatomical and functional, there is a gray zone in which the features of these two mechanisms are both present. Ikeda et al[141] performed a study in isolated superfused canine atria. The authors punched holes with 2- to 10-mm diameters in the center of the tissue. Figure 79–9

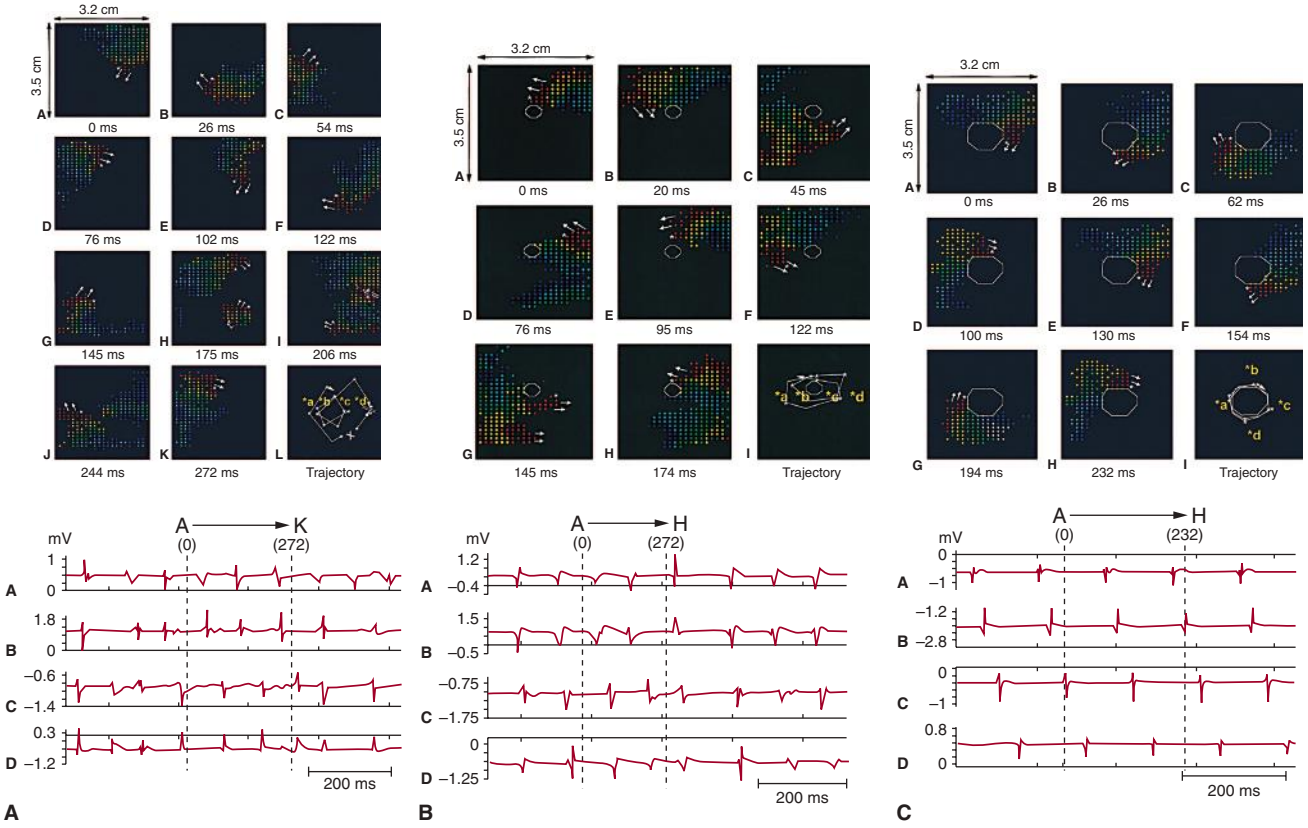

FIGURE 79–9. Functional and anatomical reentry in isolated superfused canine right atrium. Reentry was induced by electrical stimulation. The *red dots* represent activation wavefront. The color then changed every 10 milliseconds from yellow to green to light blue and purple before becoming black (background color). **A.** Reentry without a functional obstacle. The reentrant wavefronts (*spiral waves*) meandered in the preparation. Bipolar electrogram showed irregular activations. **B.** Reentry after a 4-mm-diameter hole was created in the middle of the preparation (*white circle*). There is less meandering, and the activation cycle length was irregular but slower. **C.** The effects of a 10-mm central hole on reentrant wavefront. The reentry is no longer meandering, and the bipolar electrogram showed regular activations consistent with sustained monomorphic tachycardia. Reproduced with permission from Ikeda T, Yashima M, Uchida T, Hough D, Fishbein MC, Mandel WJ, Chen PS, Karagueuzian HS. Attachment of meandering reentrant wave fronts to anatomic obstacles in the atrium. Role of the obstacle size. *Circ Res*. 1997 Nov;81(5):753-764.[141]

shows the effects of a central hole (anatomical obstacle) on reentrant wavefronts (spiral waves). In the absence of a lesion (see Fig. 79–9A), the induced single (functional) reentrant wavefront, in the form of a spiral wave, meandered irregularly from one site to another before terminating at the tissue border. Holes with 2- to 4-mm diameters (see Fig. 79–9B) had no effect on meandering. However, when the hole diameters were increased to 6 to 10 mm (see Fig. 79–9C), the tip of the spiral wave attached to the holes, and reentry became stationary. This model shows that a critically sized anatomic obstacle converts a nonstationary meandering reentrant wavefront to a stationary one. This electrical activation changed from irregular "fibrillation-like" activity into regular monomorphic activity. However, there was no abrupt transition from functional reentry to anatomical reentry. Rather, with a small anatomical obstacle, the reentrant wavefront exhibits the characteristics of both functional and anatomical reentry. Many previous studies showed that functional reentrant wavefronts tend to have a very short life span and are frequently unstable in whole hearts. For example, electrically induced reentry in the ventricles usually has a life span averaging a few seconds in the whole heart.[9,142] Under normal conditions, it is unlikely for the initial reentrant wavefronts to persist and continue to serve as the source of rapid excitation to induce sustained ventricular arrhythmia. To induce sustained arrhythmia in the whole heart, these initial spiral waves will need to break down and induce multiple spiral waves to induce VF or to anchor to a large anatomical barrier to induce VT.

Figure-Eight Reentry

Figure-eight reentry was first described by El-Sherif and coworkers in the surviving epicardial layer overlying infarction produced by occlusion of the left anterior descending artery in canine hearts in the late 1980s.[143,144] The same patterns of activation can also be induced by creating artificial anatomical obstacles in the ventricles[145] or during functional reentry induced by a single premature ventricular stimulation.[9] In the figure-eight model, the reentrant beat produces a wavefront that circulates in both directions around a long line of conduction block (Fig. 79–10) rejoining on the distal side of the block. The wavefront then breaks through the arc of block to reexcite the tissue proximal to the block. The reentrant activation continues as two circulating wavefronts that travel in clockwise and counterclockwise directions around the two arcs in a pretzel-like configuration. The diameter of the reentrant circuit in the ventricle can be as small as a few millimeters or as large as a several centimeters. When the line of block is short and functional, the reentrant circuits are unstable and the figure-eight pattern may soon terminate.[142] However, more sustained figure-eight reentry can be induced when large anatomical obstacles are present in the preparation.[145]

Critical Mass

A second factor that determines the stability of circus movement reentry is the tissue size. As first documented by Garrey,[129] a critical mass must be present for VF to be sustained. If the tissue mass reduces to below that critical mass, VF invariably terminates. Kim et al[146] induced VF in isolated and perfused swine right ventricular free wall. The tissue mass was then progressively reduced by sequential cutting. The critical mass to sustain VF in this preparation was around 20 g. As tissue mass was decreased, the number of wavefronts decreased, the life span of reentrant wavefronts increased, and the cycle length, diastolic interval, and duration of action potential lengthened. When the mass is small enough, the remaining wavefront might anchor to the papillary muscle and convert VF to VT.[147] Figure 79–11 shows typical examples of activation patterns after progressive tissue mass reduction. In addition, the APD progressively lengthened and the average activation rate progressively

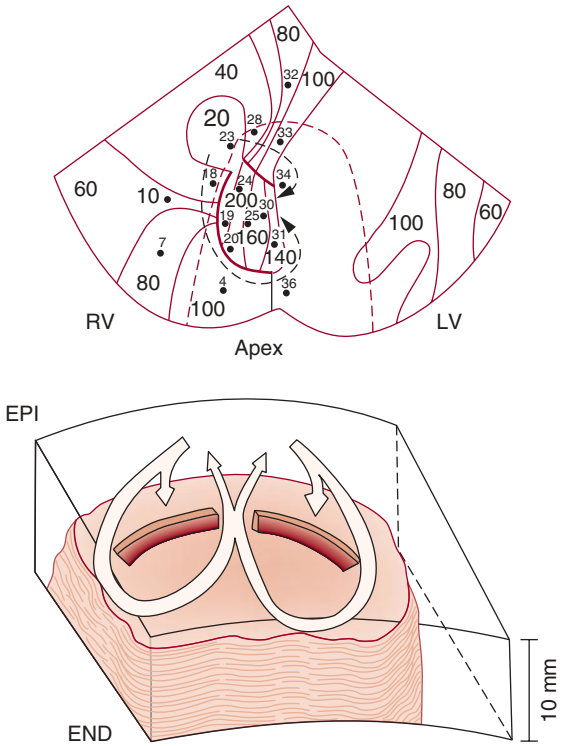

FIGURE 79–10. Figure-of-eight model of reentry. Isochronal activation map during monomorphic reentrant ventricular tachycardia occurring in the surviving epicardial layer overlying an infarction. Recordings were obtained from the epicardial surface of a canine heart 4 days after ligation of the left anterior descending coronary artery. Activation isochrones are drawn at 20-millisecond intervals. The reentrant circuit has a characteristic figure-of-eight activation pattern. Two circulating wavefronts advance in clockwise and counterclockwise directions, respectively, around two zones (*arcs*) of conduction block (*heavy solid lines*). The epicardial surface is depicted as if the ventricles were unfolded following a cut from the crux to the apex. A three-dimensional diagrammatic illustration of the ventricular activation pattern during the reentrant tachycardia is shown in the lower panel. END, endocardium; EPI, epicardium; LV, left ventricle; RV, right ventricle. Reproduced with permission from El-Sherif N. Reentry revisited. *Pacing Clin Electrophysiol*. 1988 Sep;11(9):1358-68.

reduced with the tissue size reduction. There was a parallel decrease in the dynamical complexity of VF as measured by Kolmogorov entropy and Poincaré plots. A period of quasiperiodicity became more evident before the conversion from VF (chaos) to a more regular arrhythmia (periodicity). Therefore, reducing tissue size is antifibrillatory. It causes a decrease in the number of wavefronts in VF by tissue mass reduction, which causes a transition from chaotic to periodic dynamics via the quasiperiodic route.[147] This observation might explain the ameliorative effects of the Maze procedure in the setting of AF.[148,149]

Action Potential Duration Restitution and Effective Refractory Period

A third important factor in determining the stability of circus movement reentry is the APD restitution properties of the cardiac tissue. The APD restitution describes the relationship between APD and the preceding diastolic interval. The slope of APD restitution in theory determines the stability of cardiac activation.[150,151] When the slope is less than 1.0, repeated pacing of the system will induce APD alternans and dynamic instability, leading to fibrillation. However, flattening the restitution might be an antifibrillatory strategy.[152] Figure 79–12 illustrates this concept with the help of computer simulation and a rabbit heart experiment. Panel A shows APD shortening and APD alternans as pacing cycle length decreases. Panel B shows two different APD

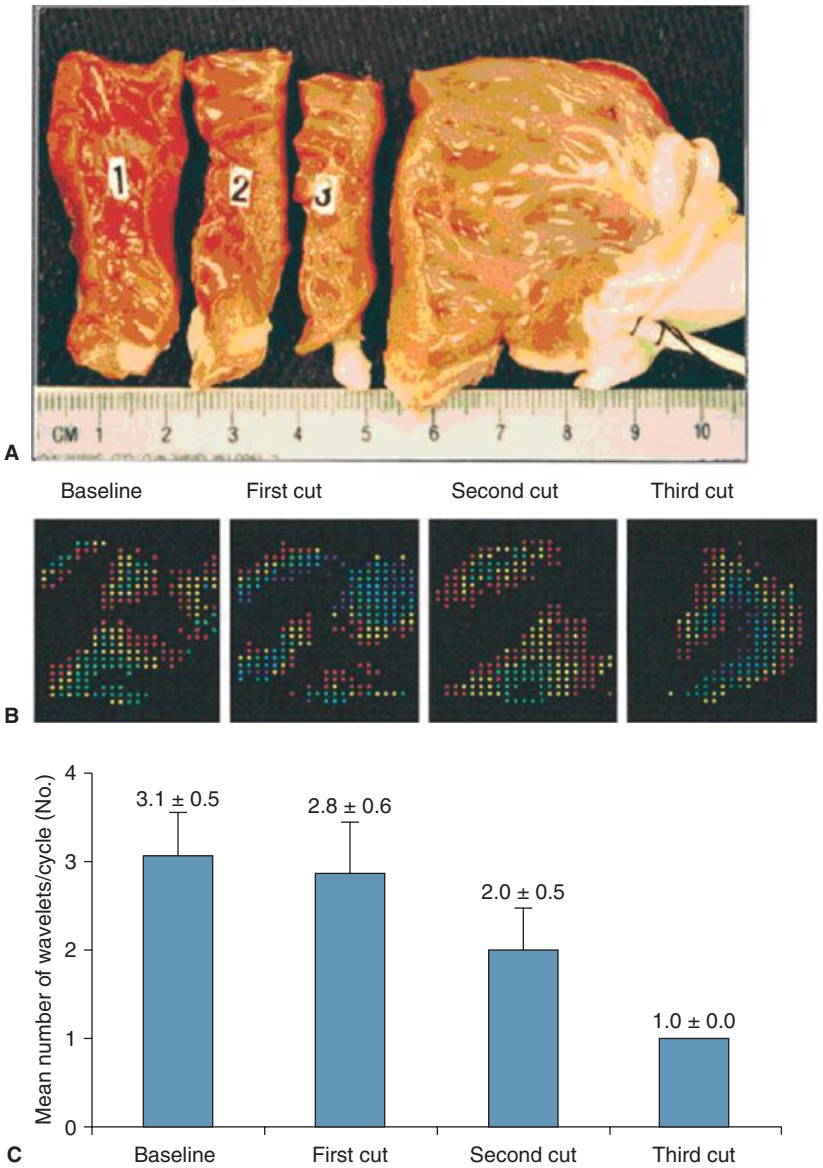

FIGURE 79–11. Effects of tissue mass reduction on reentrant wavefronts in ventricular fibrillation. **A.** An isolated perfused swine right ventricle preparation. **B.** The patterns of activation in the right ventricle at baseline and after first, second, and third cuts. **C.** The average number of wavefronts after each cut in six different preparations. After third cut, a single reentrant wavefront (spiral wave) is present. Reproduced with permission from Kim YH, Garfinkel A, Ikeda T, et al: Spatiotemporal complexity of ventricular fibrillation revealed by tissue mass reduction in isolated swine right ventricle. Further evidence for the quasiperiodic route to chaos hypothesis. *J Clin Invest*. 1997 Nov 15;100(10):2486-2500.[146]

restitution curves; one with slope > 1 (solid line) and one with slope < 1 (dashed line, obtained with 50% block of the calcium current). Panels C and D are results of computer simulation studies, whereas panels E and F are actual experimental data from a Langendorff-perfused rabbit heart. Flattening of the restitution curves in both simulation studies and in rabbit hearts resulted in the conversion of VF to VT.

In normal hearts, atrial effective refractory period (ERP) approximates APD at 70% repolarization in atria and at 90% repolarization in the ventricle (APD70-90).[153,154] Abbreviation of ERP is associated with increased susceptibility for development of reentry. In experimental models of AF, without cardiovascular disease, abbreviation of atrial ERP, secondary to pharmacologic interventions or sustained rapid atrial activation, is associated with a significant increase in AF vulnerability.[15,130,155,156] In structurally remodeled atria or following exposure to sodium channel blockers, ERP can outlast APD70-90 secondary to reduced excitability, leading to development of postrepolarization refractoriness. Prolongation of ERP, whether by prolongation of APD or development of postrepolarization refractoriness, can terminate and/or prevent the development of reentry and is an effective treatment for paroxysmal AF.[157]

In addition to APD restitution, the conduction velocity restitution is also an important factor that determines the stability of the reentrant wavefronts.[158,159] Figure 79–13 shows the primary findings of those studies. At baseline, the activation rate was fast, and the dominant frequency of VF was around 16 Hz. D600 flattened the APD restitution curve and converted baseline fast (type I) VF to VT. Further increasing the D600 concentration to 2.5 or 5.0 mg/L converted VT to slow (type II) VF with an average dominant frequency around 11 Hz. Because high concentrations of D600 block Na channels as well as Ca channels, the authors hypothesized that reduced excitability might underlie type II VF, which was not driven by steep APD restitution, but was a result of broad conduction velocity restitution. Whereas steep APD restitution drives wave instability by making the *waveback* sensitive to small changes in diastolic interval, conduction velocity can drive wave instability by making the *wavefront* sensitive to small changes in

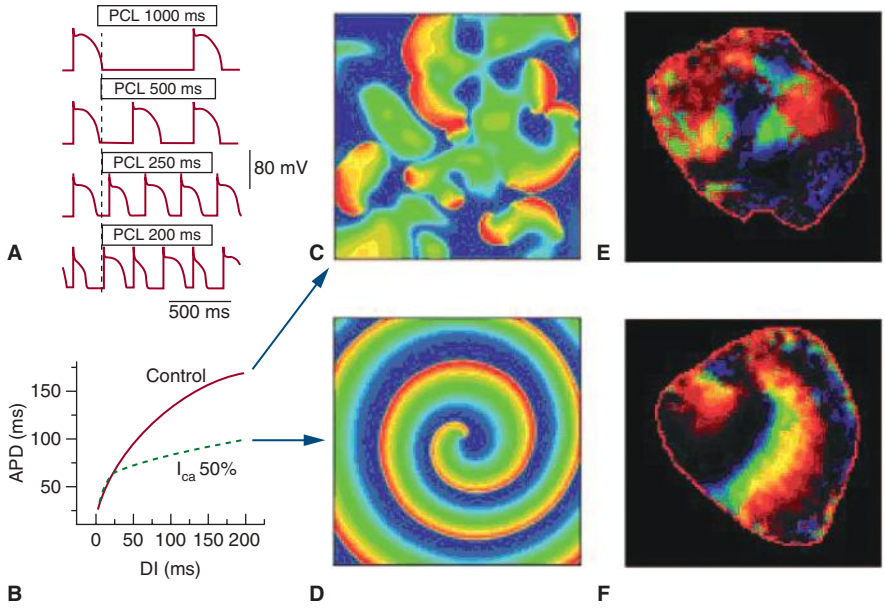

FIGURE 79–12. Action potential duration (APD) restitution and stability of reentrant. **A.** APD shortening and APD alternans as pacing cycle length (PCL) decreases (computer simulation). Diastolic interval (DI) is measured from the end of the preceding action potential to the onset of phase 0 of the present action potential. As shown in these examples, the shorter the preceding DI, the shorter is the APD. **B.** APD restitution curves with slope > 1 (*solid line*) or < 1 (*dashed line*, obtained with 50% block of the calcium current). **C** and **D.** Spiral wave behavior several seconds after initiating a spiral wave in homogeneous two-dimensional tissue. All cells are identical, with either a steep (**C**) or shallow (**D**) APD restitution slope. **E** and **F.** Optically measured surface voltage maps in an intact Langendorff rabbit heart before (**E**) and after (**F**) partially blocking the L-type calcium current with D600 (0.5 mg/mL) to flatten the APD restitution slope to > 1. In **E**, multiple wavefronts move in a complex ventricular fibrillation (VF) pattern. In **F**, VF has converted to ventricular tachycardia, manifested as a stable double-armed rotor. Reproduced with permission from Weiss JN, Qu Z, Chen PS, Lin SF, Karagueuzian HS, Hayashi H, Garfinkel A, Karma A. The dynamics of cardiac fibrillation. *Circulation*. 2005 Aug 23;112(8):1232-1240.

diastolic interval, especially if structural and electrophysiologic heterogeneities are present.

Calcium Dynamics

Electrical activation and calcium dynamics are closely coupled. However, the coupling between the two can be variable, which results in an additional complex dynamics that affect the APD restitution and the stability of the reentrant wavefronts.[151] Whereas voltage-Ca_i coupling is generally positive (ie, a longer APD produces a larger Ca_i transient), Ca_i-voltage coupling can be either positive or negative. Positive Ca_i-voltage coupling refers to the mode in which a larger Ca_i transient produces a longer APD. This occurs when the large Ca_i transient enhances net inward current during the action potential plateau by potentiating inward I_{NCX} to a greater extent than it reduces the $I_{Ca,L}$ (by facilitating Ca-induced inactivation). However, negative Ca-voltage coupling refers to the mode in which a larger Ca_i transient causes a shorter APD. This occurs when the reduction in $I_{Ca,L}$ predominates over the increased I_{NCX}. In addition to complex coupling, the cardiac Ca handling has its own dynamics. It is possible to have a large discrepancy between the Ca_i transient duration and the APD in pathologic conditions. The dynamic V_m-Ca_i coupling underlies the development of arrhythmogenic discordant alternans during rapid ventricular activation[160,161] and increases the probability that an ectopic beat will induce reentrant excitations.[151] This dynamic coupling could also affect the stability of the spiral waves and contribute to the degeneration of VT into VF.[162-164]

Reflection

Reentry may also occur without circus movement. One noncircus movement reentry is reflected reentry (or reflection). The concept of reflection was first suggested by studies of the propagation characteristics of slow action potential responses in K^+-depolarized Purkinje fibers.[165] In strands of Purkinje fiber, Wit and coworkers demonstrated a phenomenon similar to that observed by Schmitt and Erlanger in which slow anterograde conduction of the impulse was at times followed by a retrograde wavefront that produced a "return extrasystole."[165,166] They proposed that the nonstimulated impulse was caused by circuitous reentry at the level of the syncytial interconnections, made possible by longitudinal dissociation of the bundle, as the most likely explanation for the phenomenon but also suggested the possibility of reflection. Direct evidence in support of reflection as a mechanism of arrhythmogenesis was provided by Antzelevitch and coworkers in the early 1980s.[167,168] A number of models of reflection have been developed. The first of these involves use of ion-free isotonic sucrose solution to create a narrow (1.5-2 mm) central inexcitable zone (gap) in unbranched Purkinje fibers mounted in a three-chamber tissue bath (Fig. 79–14).[169] In the sucrose-gap model, stimulation of the proximal segment elicits an action potential that propagates to the proximal border of the sucrose gap. Active propagation across the sucrose gap is not possible because of the ion-depleted extracellular milieu, but local circuit current continues to flow through the intercellular low resistance pathways (an Ag/AgCl extracellular shunt pathway is provided). This local circuit or electrotonic current, very much reduced on emerging from the gap, gradually discharges the capacity of the distal tissue, thus giving rise to a depolarization that manifests as a either a subthreshold response (last distal response) or a foot potential that brings the distal excitable tissue to its threshold potential (Fig. 79–15).[170] Active impulse propagation stops and then resumes after a delay that can be as long as several hundred milliseconds. When anterograde (proximal to distal) transmission time is sufficiently delayed to permit recovery of refractoriness at the proximal end, electrotonic transmission of the impulse in the retrograde direction is able to reexcite the proximal tissue, thus generating a closely coupled reflected reentry. Reflection therefore results from the to-and-fro electrotonically mediated transmission of the impulse across the same inexcitable segment; neither longitudinal dissociation nor circus movement needs to be invoked to explain the phenomenon.

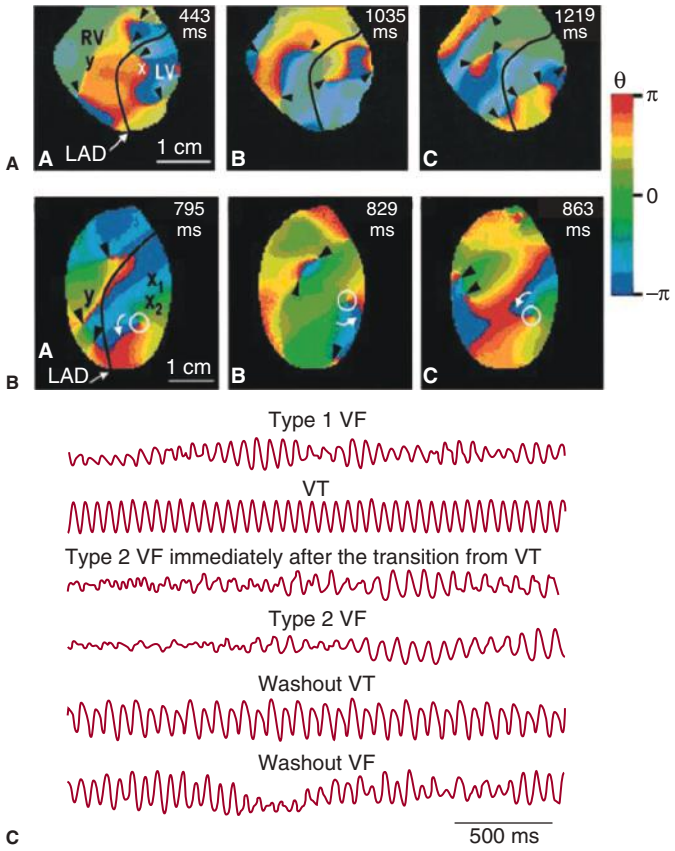

FIGURE 79–13. Two types of ventricular fibrillation (VF). **A.** Phase maps of type 1 VF, which is characterized by a steep action potential duration (APD) restitution but narrow conduction velocity (CV) restitution curve. **B.** Type 2 VF, with a single meandering mother rotor (*white circle*) that is meandering on the epicardium. This type of VF is characterized by flat APD restitution (which prevents spiral breakup) and broad CV restitution (which facilitates wavebreak). **C.** Electrograms corresponding to types 1 and 2 VF. Note that there is a period of monomorphic ventricular tachycardia between types 1 and 2 VF. LAD, left anterior descending artery. Reproduced with permission from Wu TJ, Lin SF, Weiss JN, Ting CT, Chen PS. Two types of ventricular fibrillation in isolated rabbit hearts: Importance of excitability and action potential duration restitution. *Circulation*. 2002 Oct 1;106(14):1859-1866.[158]

A second model of reflection involved the creation of an inexcitable zone permitting delayed conduction by superfusion of a central segment of a Purkinje bundle with a solution designed to mimic the extracellular milieu at a site of ischemia.[168] The gap was shown to be largely comprised of an inexcitable cable across which conduction of impulses was electrotonically mediated. Reflected reentry has been demonstrated in isolated atrial and ventricular myocardial tissues as well.[171-173] Reflection has also been demonstrated in Purkinje fibers in which a functionally inexcitable zone is created by focal depolarization of the preparation with long duration constant current pulses.[174] Reflection is also observed in isolated canine Purkinje fibers homogeneously depressed with high K^+ solution as well as in branched preparations of normal Purkinje fibers.[175]

PHASE 2 REENTRY

Another reentrant mechanism that does not depend on circus movement and can appear to be of focal origin is phase 2 reentry. Phase 2 reentry occurs when the dome of the action potential, most commonly epicardial, propagates from sites at which it is maintained to sites at which it is abolished, causing local reexcitation of the epicardium and the generation of a closely coupled extrasystole. Accentuated spatial dispersion of repolarization is needed for phase 2 reentry to occur.

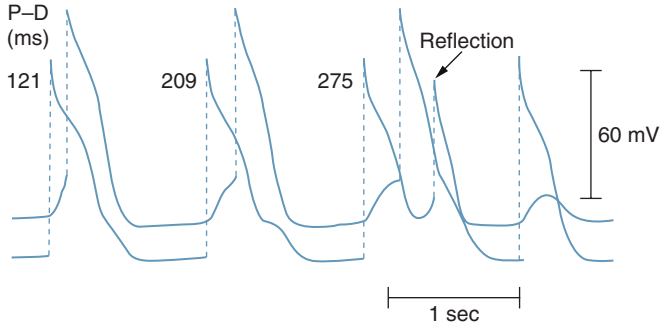

FIGURE 79–14. Delayed transmission and reflection across an inexcitable gap created by superfusion of the central segment of a Purkinje fiber with an ion-free isotonic sucrose solution. The two traces were recorded from proximal (P) and distal (D) active segments. P–D conduction time (indicated in the upper portion of the figure, in milliseconds) increased progressively with a 4:3 Wenckebach periodicity. The third stimulated proximal response was followed by a reflection. Reproduced wtih permission from Antzelevitch C: Clinical application of new concepts of parasystole, reflection, and tachycardia. *Cardiol Clin*. 1983 Feb;1(1):39-50.[169]

Spatial Dispersion of Repolarization

Studies conducted over the past 25 years have established that ventricular myocardium is not homogeneous but is comprised of at least three electrophysiologically and functionally distinct cell types: epicardial, M, and endocardial cells.[176,177] These three principal ventricular myocardial cell types differ with respect to phase 1 and phase 3 repolarization characteristics (Fig. 79–16). Ventricular epicardial and M, but not endocardial, cells generally display a prominent phase 1, because of a large 4-aminopyridine–sensitive transient outward current (I_{to}), giving the action potential a spike and dome or notched configuration. These regional differences in I_{to}, first suggested based on action potential data,[178] have now been directly demonstrated in ventricular myocytes from a wide variety of species including canine,[179] feline,[180] guinea pig,[181] swine,[182] rabbit,[183] and humans.[184,185] Differences in the magnitude of the action potential notch and corresponding differences in I_{to} have also been described between right and left ventricular epicardium.[186] Similar interventricular differences in I_{to} have also been described for canine ventricular M cells.[187] This distinction is thought to form the basis for why the Brugada syndrome, a channelopathy-mediated form of sudden death, is a right ventricular disease.

Recent optical mapping studies using normal and failing human ventricles confirmed the presence of M-cell islands in the midmyocardial layer.[84,188,189] These M-cell islands are characterized by long APDs. A large APD gradient is present between the APD within the island and the surrounding myocardium. Apamin, a specific SK current blocker, prolonged APDs in the surrounding myocardium to a greater extent than within the M-cell island.[84] Because apamin is a highly specific blocker of I_{KAS},[84] these findings suggest a highly heterogeneous transmural distribution of the I_{KAS}. The I_{KAS} deficiency may contribute to the long APD of the M cells.

Between the surface epicardial and endocardial layers are transitional and M cells. M cells are distinguished by the ability of their action potential to prolong disproportionately relative to the action potential of other ventricular myocardial cells in response to a slowing of rate and/or in response to APD-prolonging agents.[176,190,191] In the dog, the ionic basis for these features of the M cell include the presence of a smaller slowly activating delayed rectifier current (I_{Ks}),[83] a larger late sodium current (late I_{Na}),[89] and a larger Na-Ca exchange current (I_{NCX}).[192] In the canine heart, the rapidly activating

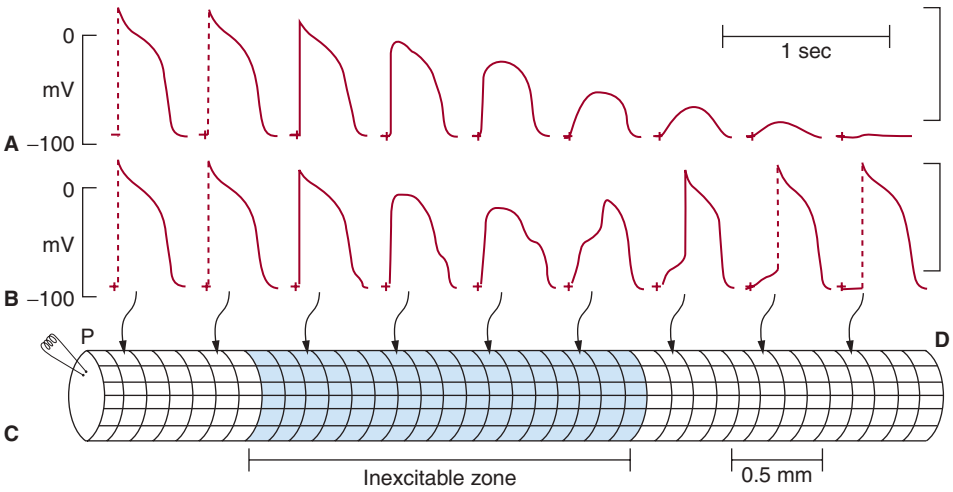

FIGURE 79–15. Discontinuous conduction (B) and conduction block (A) in a Purkinje strand with a central inexcitable zone (C). The schematic illustration is based on transmembrane recordings obtained from canine Purkinje fiber–sucrose gap preparations. An action potential elicited by stimulation of the proximal (P) side of the preparation conducts normally up to the border of the inexcitable zone. Active propagation of the impulse stops at this point, but local circuit current generated by the proximal segment continues to flow through the preparation encountering a cumulative resistance (successive gap junctions). Transmembrane recordings from the first few inexcitable cells show a response not very different from the action potentials recorded in the neighboring excitable cells, despite the fact that no ions may be moving across the membrane of these cells. The responses recorded in the inexcitable region are the electrotonic images of activity generated in the proximal excitable segment. The resistive-capacitive properties of the tissue lead to an exponential decline in the amplitude of the transmembrane potential recorded along the length of the inexcitable segment and to a slowing of the rate of change of voltage as a function of time. If, as in panel B, the electrotonic current is sufficient to bring the distal excitable tissue to its threshold potential, an action potential is generated after a step delay imposed by the slow discharge of the capacity of the distal (D) membrane by the electrotonic current (foot-potential). Active conduction of the impulse therefore stops at the proximal border of the inexcitable zone and resumes at the distal border after a step delay that can range from a few to tens or hundreds of milliseconds. Modified with permission from Antzelevitch C, Rosen MR, Janse MJ, et al: Electrotonus and reflection. *Cardiac Electrophysiology: A Textbook*. Mount Kisco, NY: Futura Publishing Company, Inc; 1990.

delayed rectifier (I_{Kr}) and inward rectifier (I_{K1}) currents are similar in the three transmural cell types. Transmural and apical-basal differences in the density of I_{Kr} channels have been described in the ferret heart.[193] Amplification of transmural heterogeneities normally present in the early and late phases of the action potential can lead to the development of a variety of arrhythmias, including Brugada, early repolarization, long QT, and short QT syndromes as well as catecholaminergic VT. The genetic mutations associated with these inherited channelopathies are listed in Table 79–2. Their resulting gain or loss of function underlies the development of the arrhythmogenic substrate and triggers.

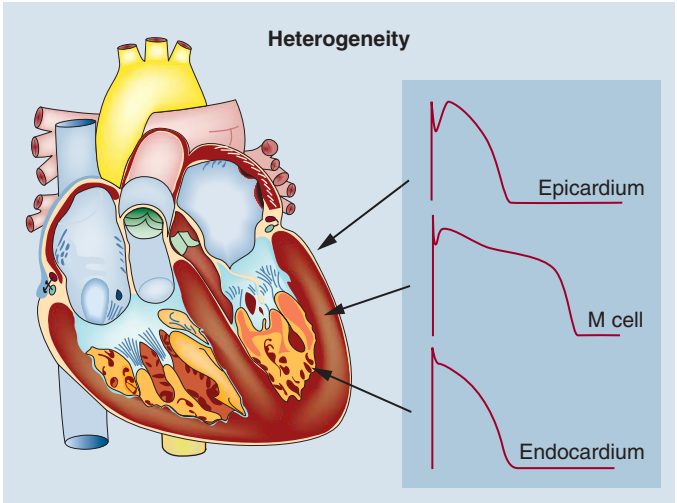

FIGURE 79–16. Action potential characteristics recorded from epicardial, M, and endocardial regions of the canine left ventricle.

J-WAVE SYNDROME AND PHASE 2 REENTRY

The J-Wave Syndromes and Phase 2 Reentry

The appearance of prominent electrocardiographic J waves has long been associated with hypothermia[194-196] and hypercalcemia,[197,198] and more recently with life-threatening ventricular arrhythmias.[199] Under these circumstances, the accentuated J wave is often so broad as to appear as an ST-segment elevation, as in cases of Brugada syndrome (BrS). A normal J wave in humans typically appears as a J-point elevation, with much of the J wave buried inside the QRS. An early repolarization (ER) pattern in the ECG, characterized by a distinct J wave, J-point elevation, and a notch or slur of the terminal part of the QRS with and without an ST-segment elevation, has traditionally been viewed as benign.[200,201] In 2000, this view was challenged[202] based on experimental data showing that this ECG manifestation predisposes to the development of polymorphic VT and VF in coronary-perfused wedge preparations.[1,202-204] This hypothesis was validated by seminal studies of Haïssaguerre et al,[205] Nam et al,[206] and Rosso et al.[207] These formative studies, coupled with many additional case-control and population-based studies, have provided clinical evidence for an increased risk for development of life-threatening arrhythmic events and sudden cardiac death (SCD) among patients presenting with an ER pattern, referred to as *early repolarization syndrome* (ERS).

An expert consensus statement recently published by MacFarlane and coworkers[208] has provided recommendations for measurement and reporting of ER and J waves. The taskforce recommends that peak of an end QRS notch and/or the onset of an end QRS slur be designated as J_p and that J_p should exceed 0.1 mV in two or more contiguous inferior and/or lateral leads of a standard 12-lead electrocardiogram for ER to be present.[208] It was further recommended that the start of the end QRS notch or J wave be designated as J_o and the termination as J_t.

BrS and ERS are both associated with vulnerability to development of polymorphic VT and VF leading to SCD[1,205,206,209] in young adults and

TABLE 79–2. Genetic Disorders Causing Cardiac Arrhythmias in the Absence of Structural Heart Disease (Primary Electrical Disease)

	Disorder	Rhythm	Inheritance	Locus	Ion Channel	Gene
LQTS (RW)	LQT1	TdP	AD	11p15	$\downarrow I_{Ks}$	*KCNQ1*, KvLQT1
	LQT2	TdP	AD	7q35	$\downarrow I_{Kr}$	*KCNH2*, HERG
	LQT3	TdP	AD	3p21	$\uparrow I_{Na\text{-}L}$	*SCN5A*, Nav1.5
	LQT4	TdP	AD	4q25		*ANKB*, ANK2
	LQT5	TdP	AD	21q22	$\downarrow I_{Ks}$	*KCNE1*, minK
	LQT6	TdP	AD	21q22	$\downarrow I_{Kr}$	*KCNE2*, MiRP1
	LQT7	TdP	AD	17q23	$\downarrow I_{K1}$	*KCNJ2*, Kir 2.1
	LQT8	TdP	AD	6q8A	$\uparrow I_{Ca}$	*CACNA1C*, $Ca_V1.2$
	LQT9	TdP	AD	3p25	$\uparrow I_{Na\text{-}L}$	*CAV3*, caveolin-3
	LQT10	TdP	AD	11q23.3	$\uparrow I_{Na\text{-}L}$	*SCN4B*, Navb4
	LQT11	TdP	AD	7q21-q22	$\downarrow I_{Ks}$	*AKAP9*, Yotiao
	LQT12	TdP	AD	20q11.2	$\uparrow I_{Na\text{-}L}$	*SNTA1*, α_1-syntrophin
	LQT13	TdP	AD	11q24.3	$(I_{K\text{-}ACh}$	*KCNJ5*, Kir3.4
	LQT14	TdP	AD	14q32.11	$\uparrow I_{Ca}$	*CALM1*, calmodulin1
	LQT15	TdP	AD	2p21.3-p21.1	$\uparrow I_{Ca}$	*CALM2*, calmodulin2
	LQT16	AVB	UN	19q13	UN	*CALM3*, calmodulin2
LQTS (JLN)		TdP	AR	11p15	$\downarrow I_{Ks}$	*KCNQ1*, KvLQT1
				21q22	$\downarrow I_{Ks}$	*KCNE1*, minK
BrS	BrS1	PVT	AD	3p21	$\downarrow I_{Na}$	*SCN5A*, $Na_V1.5$
	BrS2	PVT	AD	3p24	$\downarrow I_{Na}$	*GPD1L*
	BrS3	PVT	AD	12p13.3	$\downarrow I_{Ca}$	*CACNA1C*, $Ca_V1.2$
	BrS4	PVT	AD	10p12.33	$\downarrow I_{Ca}$	*CACNB2b*, $Ca_V\beta2b$
	BrS5	PVT	AD	19q13.1	$\downarrow I_{Na}$	*SCN1B*, $Na_V\beta1$
	BrS6	PVT	AD	11q13-q14	$\downarrow I_{Ca}$	*KCNE3*, MiRP2
	BrS7	PVT	AD	11q23.3	$\downarrow I_{Na}$	*SCN3B*, Navb3
	BrS8	PVT	AD	12p11.23	$\uparrow I_{K\text{-}ATP}$	*KCNJ8*, Kir6.1
	BrS9	PVT	AD	7q21.11	$\downarrow I_{Ca}$	*CACNA2D1*, $Ca_V\alpha2\delta1$
	BrS10	PVT	AD	1p13.2	$\uparrow I_{to}$	*KCND3*, $K_V4.3$
	BrS11	PVT	AD	17p13.1	$\downarrow I_{Na}$	*RANGRF*, MOG1
	BrS12	PVT	AD	3p21.2-p14.3	$\downarrow I_{Na}$	*SLMAP*
	BrS13	PVT	AD	12p12.1	$\uparrow I_{K\text{-}ATP}$	*ABCC9*, SUR2A
	BrS14	PVT	AD	11q23	$\downarrow I_{Na}$	*SCN2B*, $Na_V\beta2$
	BrS15	PVT	AD	12p11	$\downarrow I_{Na}$	*PKP2*, plakophillin2
	BrS16	PVT	AD	3q28	$\downarrow I_{Na}$	*FGF12*, FHAF1
	BrS17	PVT	AD	3p22.2	$\downarrow I_{Na}$	*SCN10A*, $Na_V1.8$
	BrS18	PVT	AD	6q	$\uparrow I_{Na}$	*HEY2* (transcriptional factor)
ERS	ERS1	PVT	AD	12p11.23	$\uparrow I_{K\text{-}ATP}$	*KCNJ8*, Kir6.1
	ERS2	PVT	AD	12p13.3	$\downarrow I_{Ca}$	*CACNA1C*, $Ca_V1.2$
	ERS3	PVT	AD	10p12.33	$\downarrow I_{Ca}$	*CACNB2b*, $Ca_V\beta2b$
	ERS4	PVT	AD	7q21.11	$\downarrow I_{Ca}$	*CACNA2D1*, $Ca_V\alpha2\delta1$
	ERS5	PVT	AD	12p12.1	$\uparrow I_{K\text{-}ATP}$	*ABCC9*, SUR2A
	ERS6	PVT	AD	3p21	$\downarrow I_{Na}$	*SCN5A*, $Na_V1.5$
	ERS7	PVT	AD	3p22.2	$\downarrow I_{Na}$	*SCN10A*, $Na_V1.8$
SQTS	SQT1	VT/VF	AD	7q35	$\uparrow I_{Kr}$	*KCNH2*, HERG

(*continued*)

TABLE 79–2. Genetic Disorders Causing Cardiac Arrhythmias in the Absence of Structural Heart Disease (Primary Electrical Disease) (*Continued*)

	Disorder	Rhythm	Inheritance	Locus	Ion Channel	Gene
	SQT2		AD	11p15	$\uparrow I_{Ks}$	*KCNQ1*, KvLQT1
	SQT3		AD	17q23.1-q24.2	$\uparrow I_{K1}$	*KCNJ2*, Kir2.1
	SQT4		AD	12p13.3	$\downarrow I_{Ca}$	*CACNA1C*, $Ca_v1.2$
	SQT5		AD	10p12.33	$\downarrow I_{Ca}$	*CACNB2b*, $Cav\beta_{2b}$
	SQT6		AD		$\downarrow I_{Ca}$	*CACNA2D1*, $Ca_v\alpha2\delta1$
CPVT	CPVT1	VT	AD	1q42-q43		*RYR2*, ryanodine receptor 2
	CPVT2	VT	AR	1p13-q21		*CASQ2*, calsequestrin 2
	CPVT3	VT	AR	6q22.31		*TRDN*, triadin
	CPVT4	VT	AD	14q32.11	$\uparrow I_{Ca}$	*CALM1*, calmodulin1

Note. Listed in chronological order of discovery.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AVB, atrioventricular block; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; JLN, Jervell and Lange-Nielsen; LQTS, long QT syndrome; LQT7, Andersen-Tawil syndrome; LQT8, Timothy syndrome; PVT, polymorphic ventricular tachycardia; RW, Romano-Ward; SQTS, short QT syndrome; TdP, torsades de pointes; UN, unknown; VF, ventricular fibrillation; VT, ventricular tachycardia.

occasionally to sudden infant death syndrome.[210-212] The region generally most affected in ERS is the inferior region of the left ventricle, and in BrS, it is the anterior right ventricular outflow tract.[205,207,213-217] BrS is characterized by accentuated J waves, appearing as a coved-type ST-segment elevation in the right precordial leads, V_1-V_3, whereas ERS is characterized by J waves, J_o elevation, notch or slur of the terminal part of the QRS, and ST-segment or J_t elevation in the lateral (type I), inferolateral (type II), or inferolateral plus anterior or right ventricular leads (type III).[199] ER pattern is often encountered in healthy individuals, particularly in young black individuals and athletes. ER pattern is also observed in acquired conditions, including hypothermia and ischemia.[1,218,219]

Mechanisms Underlying Electrocardiographic and Arrhythmic Manifestations of Brugada Syndrome and Early Repolarization Syndrome

The J-wave syndromes are so named because they involve accentuation of the electrocardiographic J wave.[199] The J wave is thought to be inscribed as a consequence of transmural differences in the manifestation of the action potential notch between epicardium and endocardium secondary to heterogeneous transmural distribution of the transient outward current (I_{to}).[220]

The ionic and cellular mechanisms underlying J-wave syndromes have been the subject of some controversy.[221,222] Two central hypotheses have been advanced to explain BrS: (1) The repolarization hypothesis maintains that an outward shift in the balance of currents in right ventricular epicardium leads to repolarization abnormalities that give rise to phase 2 reentry and the generation of closely coupled premature beats capable of precipitating VT/VF; and (2) the depolarization hypothesis suggests that slow conduction in the right ventricular outflow tract (RVOT) and other regions of the right ventricle, secondary to structural defects including fibrosis and reduced Cx43, leading to discontinuities in conduction, plays a key role in the development of the electrocardiographic (ECG) and arrhythmic manifestations of the syndrome. These theories are not mutually exclusive and may indeed be synergistic.

Apparently compelling evidence in support of the depolarization hypothesis was advanced by Nademanee et al[223] showing that radiofrequency ablation of epicardial sites displaying fractionated bipolar electrograms and late potentials in the RVOT of patients with BrS reduces the ECG and arrhythmic manifestations of the syndrome. Similar results have been reported by Brugada et al[224] and in a case report published by Sacher and coworkers.[225] Sacher et al[225] also observed that accentuation of the Brugada ECG by ajmaline was associated with increasing area of low-voltage and fragmented electrogram activity and a more prominent ST-segment elevation.[224] These authors concluded that the late potential and fractionated electrogram activity are caused by conduction delays within the RVOT and that ablation of the sites of slow conduction is the basis for the ameliorative effect of ablation therapy.[223-225]

A direct test of this hypothesis by Szél and coworkers[226] provided evidence for an alternative explanation. Using an experimental model of BrS, they showed that low-voltage fractionated electrogram activity nearly identical to that observed by Nademanee et al[223] in the RVOT of BrS patients develops as a result of desynchronization in the appearance of the second action potential upstroke, secondary to accentuation of the epicardial action potential notch and not to slow or delayed conduction (Fig. 79–17). They also showed that high-frequency late potentials develop in the right ventricular epicardium as a result of concealed phase 2 reentry and not as a result of delayed conduction as generally presumed.[226]

In another series of studies, Patocskai et al[227] targeted these regions of fractionated low-voltage electrogram activity and late potentials as a result of abnormal repolarization for ablation. Ablation of the right ventricular epicardium reduced the manifestation of J waves and ST-segment elevation and abolished all arrhythmic activity, a result identical to that obtained by Nademanee and coworkers (Fig. 79–18). They concluded that ablation ameliorates the BrS phenotype not by eliminating regions of delayed conduction but rather by eliminating the epicardial cells responsible for the repolarization abnormalities that give rise to phase 2 reentry and VT/VF.[1,227]

In an attempt to create an in vivo model of BrS, Park et al[228] genetically engineered Yucatan minipigs to heterozygously express a nonsense mutation in *SCN5A* (E558X), which was originally identified in a child with BrS. Atrial myocytes isolated from the $SCN5A^{E558X/+}$ pigs showed a loss of function of I_{Na}, and the minipigs displayed conduction abnormalities consisting of prolongation of the P wave, QRS complex, and PR interval. A BrS phenotype was never observed, not even after

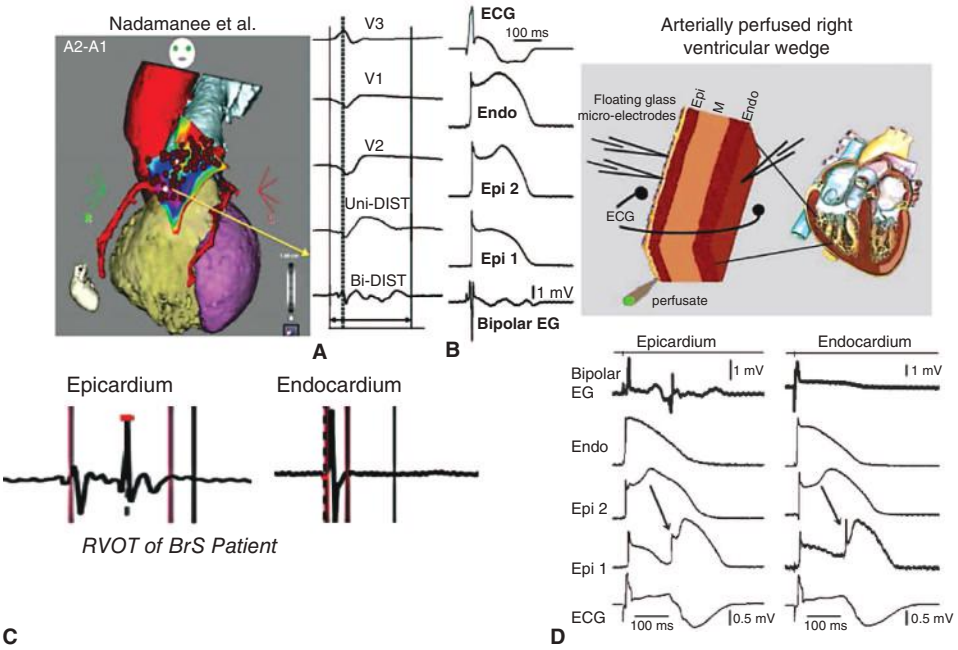

FIGURE 79–17. New interpretation of fractionated electrogram (EG) activity and late potentials. Desynchrony in the appearance of the epicardial action potential second upstroke gives rise to fractionated epicardial EG activity, and concealed phase 2 reentry gives rise to high-frequency late potentials in the setting of Brugada syndrome (BrS). **A.** Shown are right precordial lead recordings and unipolar and bipolar EGs from the right ventricular outflow tract (RVOT) of a BrS patient. **B.** Electrocardiogram (ECG), action potentials from endocardium (Endo) and two epicardial (Epi) sites, and a bipolar epicardial EG (Bipolar EG) all simultaneously recorded from a coronary-perfused right ventricular wedge preparation treated with the I_{to} agonist NS5806 (5 μM) and the calcium channel blocker verapamil (2 μM) to induce the Brugada phenotype. Basic cycle length = 1000 milliseconds. **C.** Bipolar EGs recorded from the epicardial and endocardial surfaces of the RVOT in a patient with BrS. The epicardial EG displays fractionated electrogram activity as well as a high-frequency late potential (130 milliseconds delay). **D.** Bipolar EGs recorded from the epicardium and endocardium of a coronary-perfused wedge model of BrS, together with action potential recordings from an endocardial and two epicardial sites and a transmural ECG. Slow or delayed conduction was never observed. **A** and **B**, reproduced with permission from Nademanee K, Veerakul G, Chandanamattha P, et al: Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation*. 2011 Mar 29;123(12):1270-1279. **C** and **D**, reproduced with permission from Szél T, Antzelevitch C, et al: Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome. *J Am Coll Cardiol*. 2014 May 20;63(19):2037-2045.

the administration of flecainide. These observations are expected as a result of the lack of I_{to} in the pig, which is a prerequisite for the development of the repolarization abnormalities associated with BrS. These observations were argued to provide strong evidence against the depolarization hypothesis and for the repolarization hypothesis.[227]

Additional evidence in support of the repolarization hypothesis derives from the observation that monophasic action potentials recorded from the epicardial and endocardial surfaces of the RVOT of a patient with BrS are nearly identical to transmembrane action potentials recorded from the epicardial and endocardial surfaces of the wedge model of BrS.[229,230] In both cases, the action potential displays a prominent accentuation of the notch in epicardium, but not endocardium, without any major transmural conduction delays.

Zhang et al[231] recently conducted noninvasive ECG imaging of 25 patients with BrS and 6 patients with right bundle branch block. The authors reported both slow discontinuous conduction and steep dispersion of repolarization in the RVOT of patients with BrS. ECG imaging was able to differentiate between BrS and right bundle branch block. Interestingly, in studying the response to an increase in rate, they found increased fractionation of the electrogram but reduced ST-segment elevation, again suggesting that conduction impairment was not the principal cause of the BrS ECG.

Using an experimental model of ERS, Koncz et al[215] recently provided evidence that the ECG and arrhythmic manifestations of ERS are similar to those of BrS. They reported that accentuation of transmural gradients in the left ventricular wall are responsible for the repolarization abnormalities underlying ERS, giving rise to J-point elevation, distinct J waves, or slurring of the terminal part of the QRS. The repolarization defect was accentuated by cholinergic agonists and reduced by quinidine, isoproterenol, cilostazol, and milrinone, accounting for the ability of these agents to reverse the repolarization abnormalities responsible for ERS.[215,232] Higher levels of I_{to} in the inferior left ventricle were shown to underlie the greater vulnerability of the inferior left ventricular wall to VT/VF.[215]

Using ECG imaging, Rudy and coworkers[233] provided additional evidence in support of the repolarization abnormalities by identifying abnormally short activation-recovery intervals in the inferior and lateral regions of the left ventricle and a marked dispersion of repolarization. Recent ECG image mapping studies performed in an ERS patient during VF demonstrated VF rotors anchored in the inferolateral left ventricular wall.[234]

Similarities and Differences Between Brugada Syndrome and Early Repolarization Syndrome

ERS and BrS display several phenotypic similarities, once again suggesting similar pathophysiologic mechanisms.[203,220,235-237] In both syndromes, (1) males strongly predominate[238,239]; (2) patients may be totally asymptomatic until presenting with sudden cardiac arrest; (3) the highest incidence of VF or SCD occurs in the third decade of life, perhaps tied to testosterone levels in males[240]; (4) appearance of accentuated J waves and ST-segment elevation are generally associated with bradycardia or pauses,[241,242] explaining why VF in both syndromes often occurs during sleep or at a low level of physical activity[243,244]; (5) phenotype is associated with mutations or rare variants in the same genes (see Table 9–2); (6) electrical storms and associated J-wave manifestations

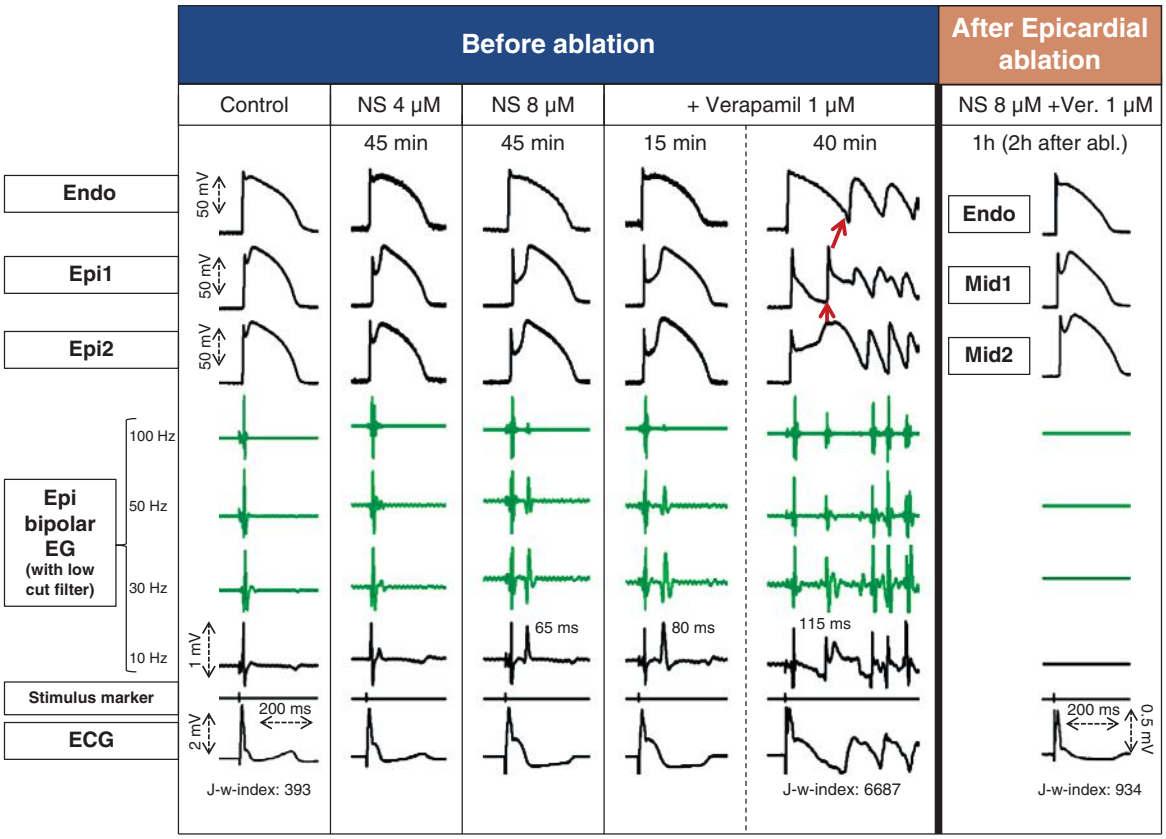

FIGURE 79–18. Radiofrequency ablation of the epicardial surface abolishes the Brugada syndrome (BrS) electrocardiogram (ECG) and suppresses arrhythmogenesis in coronary-perfused canine right ventricular wedge model of BrS. Transmembrane action potentials (APs) were simultaneously recorded from one endocardial (Endo) and two epicardial (Epi) sites together with epicardial bipolar electrograms (EGs) and a transmural pseudo-ECG. The epicardial bipolar EGs were recorded at 10- to 1000-Hz bandwidth (*black trace*) and were simultaneously band-pass filtered at 30 to 200 Hz, 50 to 200 Hz, and 100 to 200 Hz (*green traces*). *Column 1:* Control. *Column 2:* Recorded 45 minutes after the addition of the I_{to} agonist NS5806 (4 μM) to the coronary perfusate. *Column 3:* Recorded 45 minutes after the concentration of NS5806 was raised to 8 μM. High- and low-frequency late potentials (LPs) are apparent in the EG recordings resulting from progressive delay in the appearance of the second upstroke of the Epi AP secondary to accentuation of the AP notch. *Column 4:* Recorded 15 minutes after the addition of the I_{Ca} blocker verapamil (1 μM) to the coronary perfusate. *Column 5:* Recorded after 40 minutes of exposure to verapamil (1 μM). Loss of the AP dome at Epi1 but not Epi2 gives rise to a phase 2 reentrant beat, which precipitates polymorphic ventricular tachycardia. *Column 6:* Recorded 2 hours after radiofrequency ablation of the epicardial surface and 1 hour after reintroduction of the provocative agents to the perfusate (in the same concentration as before ablation). APs are now recorded from the deep subepicardium-midmyocardium (Mid1, Mid2) instead of the epicardial surface. Ablation markedly suppressed the BrS phenotype and abolished all arrhythmic activity by destroying the cells exhibiting the pronounced repolarization abnormalities. Slow or delayed conduction was not observed at any phase. Reproduced with permission from Patocskai B, Antzelevitch C: Novel Therapeutic Strategies for the Management of Ventricular Arrhythmias Associated with the Brugada Syndrome. *Expert Opin Orphan Drugs*. 2015;3(6):633-651.[227]

can be suppressed using β-adrenergic agonists[245-248]; and (7) chronic oral pharmacologic therapy using quinidine,[249,250] cilostazol,[245,247,251-255] denopamine,[245,251] and bepridil[247] suppresses the development of VT/VF secondary to inhibition of I_{to}, augmentation of I_{Ca} or I_{Na}, or both.[206,252,256]

Differences between the two syndromes include: (1) the region of the heart most affected (RVOT vs inferior left ventricle); (2) greater incidence of late potentials in signal-averaged ECGs in BrS (60%) versus ERS (7%)[244]; (3) greater inducibility of VF during electrophysiologic study in BrS than in ERS; (4) greater elevation of J_O, J_P, or J_t (ST-segment elevation) in response to sodium channel blockers in BrS versus ERS; and (5) higher prevalence of AF in BrS versus ERS.[257]

How Can We Distinguish Between a Depolarization Versus Repolarization Defect?[1]

When notches appear in the rising phase of the R wave, it is well established and accepted that these are a result of conduction defects within the ventricular myocardium. When the notch occurs at the terminal portion of the QRS, thus resembling a J wave, it may be a result of either a conduction or repolarization defect.[236,258] The response to prematurity or to an increase in rate may be able to differentiate between the two.[259] Delayed conduction invariably becomes more exaggerated at faster rates or during premature beats, thus leading to an accentuation of the QRS notch, whereas repolarization defects are usually moderated, resulting in a diminution of the J wave at faster rates. Although typical J waves are usually accentuated with bradycardia or long pauses, the opposite has also been described.[260,261] J waves are often seen in young males with no apparent structural heart diseases, whereas intraventricular conduction delay is often observed in older individuals or in cases of postmyocardial infarction or cardiomyopathy.[258,260] The prognostic value of a fragmented QRS has been demonstrated in BrS,[262,263] although fragmentation of the QRS is not associated with increased risk in the absence of cardiac disease.[264] Another factor that may aid in the differential diagnosis of J wave versus intraventricular conduction delay–mediated syndromes is gender, since the appearance of J waves is strongly male predominant.

Thoracic Veins as an Arrhythmogenic Structure

Because of the discovery that pulmonary veins are important sources of AF,[265] the arrhythmogenic mechanisms of the pulmonary veins and other thoracic veins deserve separate discussion. Although the original report showed that rapid activations in the pulmonary veins are responsible for triggering AF, rapid activations from other thoracic veins, such as the

superior vena cava and the vein of Marshall,[266,267] are also important for AF to occur and sustain. Both reentrant and non-reentrant mechanisms may underlie the rapid activations within these thoracic veins.[268,269] The embryologic development of the pulmonary veins is closely related to the development of the sinus venosus segment of the heart, which are known to be structures that can generate automaticity.[270-272] Brunton and Fayer[273] first demonstrated independent pulmonary vein contractions in rabbits and cats. They also noted that, although both atria subsequently ceased to beat, the pulmonary veins in both lungs continued to pulsate. These seminal observations have two important implications. The first is that the pulmonary vein has contractile muscle fibers. The second is that the pulmonary vein is capable of generating electrical activity independent of the atria. Findings by other investigators are compatible with these results. Masani et al[274] showed that node-like cells are present in the myocardial layer of the pulmonary vein of rats. Subsequent studies showed multiple different arrhythmogenic cell types are present in the pulmonary veins. These cell types include periodic-acid Schiff–positive cells,[275,276] Purkinje-like cells,[277] interstitial Cajal-like cells,[278,279] and melanocyte-like cells.[280] All of these cells are potentially electrically active and can contribute to the generation of either automaticity or triggered activity.

Cheung[281] demonstrated that ouabain infusion or norepinephrine infusion could trigger the onset of repetitive rapid responses from the distal pulmonary vein. Chen et al[282,283] performed transmembrane potential recording of isolated canine pulmonary vein myocytes using standard glass microelectrodes. They reported several types of electrical activity within the pulmonary veins, including silent electrical activity, fast response action potentials driven by electrical stimulation, and spontaneous fast or slow response action potentials with or without EADs. The incidence of action potentials with an EAD and of spontaneous tachycardias is much greater in dogs with chronic rapid pacing than in normal dogs. The authors concluded that pulmonary veins have arrhythmogenic ability through spontaneous activities or high-frequency irregular rhythms. Because of the short APD, the pulmonary veins are also prone to the development of late phase 3 EADs and triggered arrhythmias.[120,121,284] In addition to increased propensity for automaticity and triggered activity, the complex myocardial fiber orientation in the pulmonary veins and at the pulmonary vein–left atrial junction can cause conduction blocks and facilitate reentrant excitations in that region.[275] In addition, increased fibrosis at the pulmonary vein–left atrial junction in heart failure may play an important role in determining the characteristics of the reentrant wavefronts, thereby perpetuate AF.[285]

REMODELING AND THE MECHANISMS OF CARDIAC ARRHYTHMIA

Although genetic arrhythmias often occur in structurally normal hearts, most of the common cardiac arrhythmias (such as AF, VF, and SCD) occur primarily in diseased hearts. Therefore, the cardiac remodeling associated with heart diseases plays an important role in cardiac arrhythmogenesis. The remodeling in diseased hearts includes structural remodeling, electrophysiologic remodeling, and neural remodeling.[286] The neural remodeling may include both reduced innervation (denervation) and increased innervation through cardiac nerve sprouting.

MYOCARDIAL REMODELING

A common structural remodeling in diseased hearts is increased fibrosis, which occurs in both ischemic and nonischemic cardiomyopathy. Histologic studies of human hearts have shown a strong association between myocardial scars and VT.[287] Computerized mapping studies of human hearts with dilated cardiomyopathy[288] showed that reentrant wavefronts and transmural scroll waves were present during VF. Although the coronary arteries are open, these diseased hearts have increased fibrosis, and these fibrotic tissues provide a site for conduction block, leading to the continuous generation of reentry. Figure 79–19 shows an example of increased fibrosis in a human heart with nonischemic dilated cardiomyopathy. The patient underwent cardiac transplantation, and the heart was Langendorff perfused and mapped.[288] Trichrome staining showed significantly increased fibrosis, which was a consistent finding in all hearts at two different levels of sections. However, these fibrotic tissues were distributed unevenly. As shown in Figure 79–19, significant interstitial replacement and perivascular fibrosis are present in panels C and E. These fibrotic tissues corresponded to the area of conduction block shown panel B. In comparison, areas without conduction block showed either normal tissue (panel A) or mild fibrosis (panel D). Complete reentrant wavefronts have also been documented around the sites of fibrosis in that study.

Atrial fibrosis is a major substrate of AF.[289,290] One possible reason is that atrial fibrosis decreases the safety factor of propagation and promotes anisotropic reentry, similar to that shown in Figure 79–19. The increased anisotropic reentrant activity facilitates the development of AF.[285,291] In addition to synthesis and remodeling of extracellular matrix, fibroblasts have much broader functions in the myocardium. Some studies have suggested a "sentinel" role for fibroblasts that is intimately associated with the global myocardial response to mechanical, electrical, and chemical signals.[292] Standard microelectrode recordings showed that the atrial cardiac fibroblasts had resting V_m of –37 ± 3 mV, which oscillated during contraction and relaxation.[293] Through the functional coupling between the myocytes and fibroblasts,[294] the oscillating V_m of the fibroblasts could potentially modulate conduction[295] and promote cardiac automaticity and triggered activity by raising the diastolic V_m toward depolarization. Fibroblast $K(^+)$-current remodeling may be a new component of AF-related remodeling that contributes to arrhythmia dynamics.[296]

In addition to structural remodeling, electrophysiologic remodeling is also important in the development of cardiac arrhythmia. As described earlier in this chapter, reduction of I_{K1} significantly increases the incidence of DADs. Both chronic myocardial infarction[297] and heart failure[298] can result in significant reduction of I_{K1}. The mechanisms of I_{K1} reduction might be related to the elevated Ca_i.[299] In addition to I_{K1} downregulation, heart failure and myocardial infarction also significantly upregulate I_{NCX}.[116,298,300] The increased I_{NCX} contributes to the developments of DAD-mediated arrhythmias in these settings.[117] Heart failure is associated with increased I_{NaL},[301] which helps reduce repolarization reserve and is proarrhythmic. It may also contribute to the diastolic dysfunction in the failing hearts.[302] Complete AV block in canine models causes QT prolongation by downregulation of delayed rectifier potassium currents.[303,304] This ionic current remodeling helps reduce repolarization reserve and promotes arrhythmias in diseased conditions. However, recent findings indicate that heart failure, myocardial infarction, complete AV block, and hypokalemia can upregulate the I_{KAS}, which serves as a countermeasure to preserve the repolarization reserve.[84,122,305-309] Blocking I_{KAS} with apamin can further reduce repolarization reserve, leading to EADs and ventricular arrhythmias.[310]

In summary, myocardial remodeling in diseased states includes both structural and electrophysiologic remodeling. These changes significantly increase the propensity of arrhythmia through both reentrant and non-reentrant mechanisms.

NEURAL REMODELING AND CARDIAC NERVE SPROUTING

Static myocardial remodeling by itself does not provide a trigger for arrhythmia to occur. Additional remodeling of the autonomic nervous system in diseased states might also be important in triggering

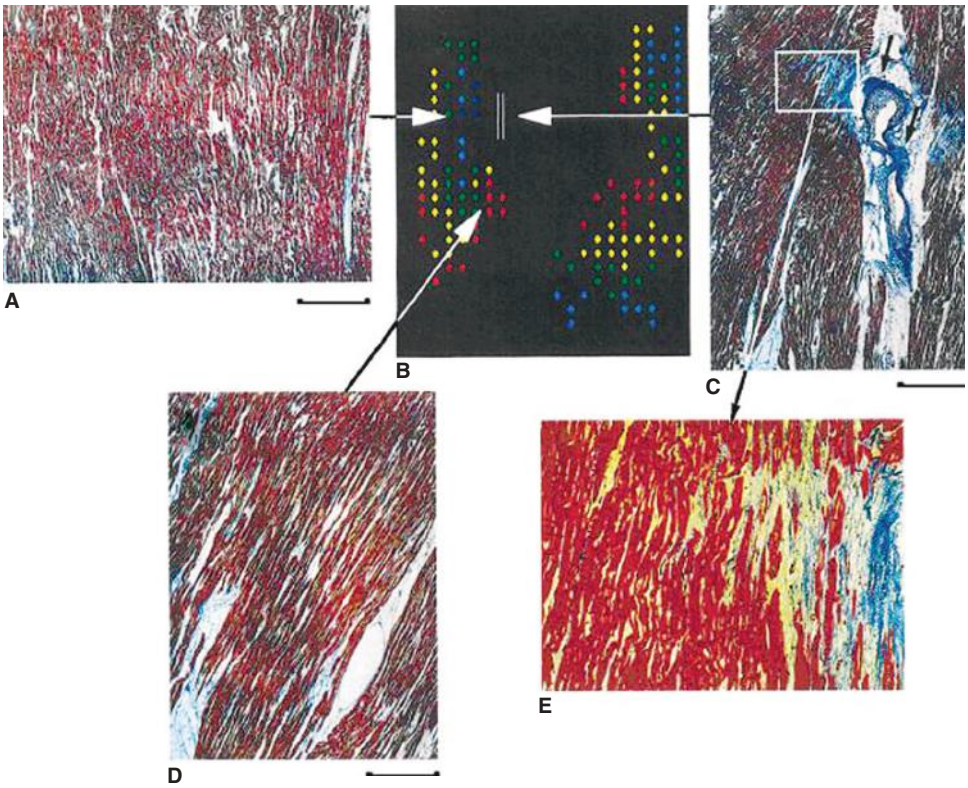

FIGURE 79–19. Fibrosis and conduction block in human hearts. **A, C, D,** and **E.** Sections of the left ventricular myocardium parallel to the epicardium in heart number 1. With trichrome stain, small veins with perivascular fibrosis (*blue areas*) were clearly seen in panel **C** (*arrows*). The magnified view (**E**) also showed interstitial and replacement fibrosis. The areas of fibrosis in panels **C** and **E** corresponded to the line of conduction block in panel **B**, which showed computerized mapping of wavefronts in ventricular fibrillation. The *red color* is the wavefront. The color then changed every 10 milliseconds to orange, yellow, green, blue, purple, and then black (*background*). It shows propagation block (*double white line segments*) and wavefront circling around the lower end of the block in a counterclockwise direction. The wavefront then continues to form a complete circus movement around the site of block (not shown). However, in the areas without conduction block, histologic examination showed either normal tissue (**A**) or mild fibrosis (**D**). Calibration line segments are 1 mm long.

cardiac arrhythmia.[3] In the central nervous system, nerve sprouting is an important mechanism of seizure disorder.[311,312] Vracko et al[313,314] demonstrated an increased number and complexity of cardiac nerve fibers in human myocardial scars and in animal models, suggesting that myocardial ischemia and infarction can also induce nerve sprouting. Compatible with this hypothesis, necrotic injury to the rat myocardium results in denervation followed by proliferative regeneration of both Schwann cells and nerve axons.[315] Cao et al[316] performed immunocytochemical studies of the native hearts of transplant recipients. In some patients, there was strong evidence of cardiac nerve sprouting and neural regenerative activity. Abundant nerve twigs are also present in tissues resected from the origin of VT (Fig. 79–20). There was a correlation between nerve density and a clinical history of ventricular arrhythmia. Subsequent studies in dogs confirmed that increased cardiac nerve sprouting and sympathetic hyperinnervation may be responsible for the initiation of VT, VF, and SCD.[317] In addition to histologic evidence, iodine-123–metaiodobenzylguanidine scanning showed that myocardial infarction can lead to both denervation and reinnervation of the heart.[318-322] A potential benefit of cardiac reinnervation is the improved hemodynamic performance, as has been demonstrated in the recipients of cardiac transplantation.[323-326] These latter studies suggest that nerve sprouting occurs and that sympathetic hyperinnervation after myocardial infarction and cardiac transplantation may contribute to the increased hemodynamic performance of the surviving myocardium. Excessive and heterogeneous nerve sprouting, however, may result in abnormal patterns of myocardial innervation, leading to cardiac arrhythmia and SCD.[316,317,327,328]

The mechanisms of nerve sprouting after myocardial infarction are not completely understood. However, it is known that multiple neurotrophic factors are overexpressed after myocardial infarction.[329] Among them, nerve growth factor (NGF) is known to promote the survival and differentiation of sympathetic nerves and maintains the catecholamine phenotype, as well as participates in axonal collateral sprouting after injury.[330] An increase in the number and size of

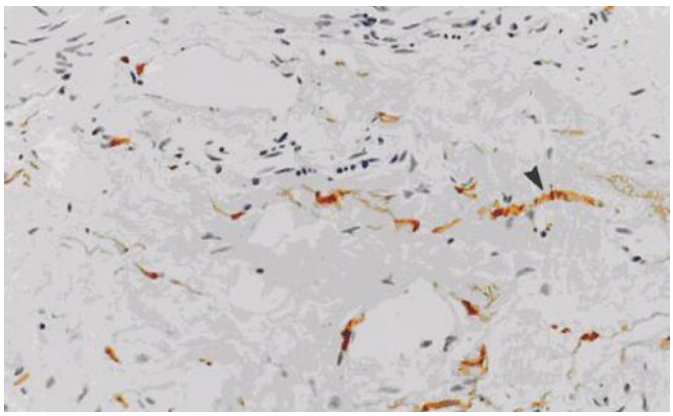

FIGURE 79–20. S100-positive nerve fibers in ventricular tachycardia (VT) origin of patients with coronary artery disease who underwent surgical ablation of VT. The S100 protein staining in the heart identifies Schwann cells. There are abundant positive stains located in perivascular area and areas with fibrosis. Reproduced with permission from Cao JM, Fishbein MC, Han JB, et al: Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. *Circulation* 2000;Apr 25;101(16):1960-1969.[316]

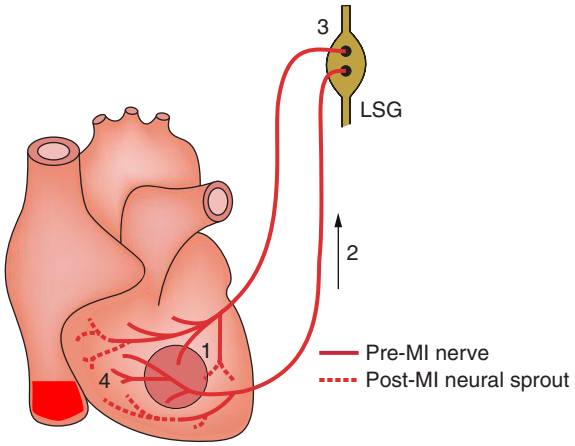

FIGURE 79–21. Cardiac nerve sprouting after myocardial infarction (MI). Myocardial injury results in the overexpression of multiple neurotrophic factors, including (but not limited to) nerve growth factor (NGF). After binding with the high-affinity NGF receptor (Trk A) on the axons, the NGF is transported to the stellate ganglia via axonal retrograde transport system. NGF then triggers cardiac nerve sprouting and sympathetic hyperinnervation that occur not only in the infarcted region but also throughout the heart. LSG, left stellate ganglion.

neurons in the sympathetic ganglia, as well as a marked elevation of the catecholamine level in the heart, were demonstrated in transgenic mice that overexpressed NGF.[331] Enlarged ganglion cells have also been observed in the stellate ganglia of human and canine models of myocardial infarction.[332,333] Zhou et al[334] demonstrated increased NGF both in the myocardium and in the left stellate ganglion after myocardial infarction, suggesting that retrograded axonal transport from the myocardium to the left stellate ganglion might be responsible for the increased growth associated protein 43 (GAP43) and nerve sprouting within the left stellate ganglion. Figure 79–21 illustrates the involvement of the stellate ganglia in cardiac nerve sprouting after acute myocardial infarction. The figure shows that the nerve sprouting is a process that involves not only the site of infarction but also the entire heart. Therefore, a small to medium-sized myocardial infarction in the left anterior descending artery distribution can cause nerve sprouting in the atria and increase the atrial vulnerability to arrhythmia.[335] In the latter study, atria were not involved in the ischemic injury. The structural remodeling of the nerve structures, such as the stellate ganglia, are associated with increased sympathetic nerve activities for at least 2 months after myocardial infarction.[332] The increased cardiac sympathetic outflow might contribute to the cardiac arrhythmia and sudden death after myocardial infarction.

NEUROMODULATION FOR ARRHYTHMIA CONTROL

Because autonomic nervous system activity is important in the generation and maintenance of cardiac arrhythmias,[3,336] neuromodulation may be helpful in arrhythmia control. Multiple preclinical and clinical studies suggested that the reduction of autonomic innervation or sympathetic outflow can reduce atrial arrhythmias.[49,337-343] Preliminary clinical studies showed that ganglionated plexi ablation may improve the AF ablation outcomes,[344,345] although elimination of vagal responses does not guarantee the absence of AF recurrences.[346] A recent prospective randomized clinical trial concluded that the ablation of ganglionic plexi had no benefit over simple isolation of pulmonary veins.[347] More studies will be needed in this area before translating these findings into patient care.

SUMMARY

In summary, the mechanism of cardiac arrhythmia includes automaticity, triggered activity, and reentry. Myocardial infarction, heart failure, and cardiac hypertrophy are associated with significant structural, electrophysiologic, and neural remodeling. The disease-induced cardiac remodeling may facilitate the development of both reentrant and non-reentrant arrhythmias. Understanding these arrhythmogenic mechanisms is important to providing mechanism-based therapy for cardiac arrhythmia.

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CHAPTER 80

GENETICS OF CHANNELOPATHIES AND CLINICAL IMPLICATIONS

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INTRODUCTION

The term *cardiac channelopathies* refers to a group of genetic diseases in which the primary dysfunction is an abnormal electrophysiologic substrate creating susceptibility to arrhythmias in the context of a substantially normal cardiac structure. Channelopathies are also referred to as *inherited arrhythmogenic diseases* (IADs).

IADs typically manifest with peculiar electrocardiographic patterns, syncope, and sudden death in young, otherwise healthy individuals. The common denominator of these disorders is a genetic mutation affecting either directly or indirectly the cardiac excitability.

It is now evident that the multiplicity of causes and the complex pathogenesis of IADs depict a framework with few "major" well-characterized conditions (ie, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia) and a number of entities that show up as typical Mendelian traits but more inconsistently (eg, lone atrial fibrillation or idiopathic ventricular fibrillation [VF]). In these cases, causative genetic mutations are seldom identified, suggesting a more heterogeneous pathogenesis. In other instances, overlap phenotypes presenting with features of two or more diseases (eg, long QT syndrome type [LQT] 3/Brugada syndrome) are recognized. In this chapter, we will review the clinical and genetic features of the most epidemiologically relevant cardiac channelopathies and will also overview the clinical presentation and genetics of less common disorders and overlap phenotypes that are emerging as a new clinical problem.

LONG QT SYNDROME

DEFINITION

The long QT syndrome (LQTS) encompasses abnormally prolonged QT interval with peculiar morphologic abnormalities of the T wave and syncope and/or cardiac arrest typically occurring in children or teenagers (Fig. 80–1). Two clinical signs (QT prolongation with or without syncope) define the most common LQTS presentation, the so-called Romano-Ward syndrome, which has autosomal dominant inheritance. Other clinical entities have been described, all sharing the presence of QT prolongation and arrhythmic risk but also including other features: Jervell and Lange-Nielsen syndrome (sensorineural deafness, autosomal recessive inheritance), Andersen syndrome (hypokalemic periodic paralysis, facial dimorphism, and autosomal dominant inheritance), and Timothy syndrome (syndactyly, autism spectrum disorders, congenital cardiac defects, and metabolic abnormalities, with sporadic presentation or parental mosaicism). The estimated prevalence of LQTS is between 1:7000 and 1:3000.[1,2]

GENETIC BASIS AND PATHOPHYSIOLOGY

Fifteen genes have been associated with LQTS (Table 80–1). Their common consequence is the disruption of one or more ionic currents that contribute to generate the cardiac action potential. It is interesting to note that similar electrophysiologic abnormalities may result from mutations of different genes. For example, an excess of sodium flowing into the cell (gain of function of the sodium channel current [I_{Na}]) causes LQTS, but this electrophysiologic defect can be achieved by mutations directly affecting the channel pore-forming proteins (*SCN5A*, LQT3), its β_4 regulatory subunit (*SCN4B*, LQT10), the caveolin 3 (*CAV3*, LQT9) gene that controls the channel localization in the plasmalemma, or syntrophin (*SNTA1*, LQT12), which modifies the channel nitrosylation. Thus, the genetic heterogeneity of LQTS can be reconciled in a reduced spectrum of physiologic functions that are affected by the dysfunctional gene products. Of note, however, three LQTS genetic variants (*KCNQ1* [LQT1], *KCNH2* [LQT2], and *SCN5A* [LQT3]) constitute approximately 90% of patients in whom a mutation is eventually identified.[2] Thus, the remaining genetic variants account for a minority of patients and are less well clinically characterized. In the following sections, we will describe the pathogenesis of LQTS according to the specific electrophysiologic function that is altered by the genetic mutation (Fig. 80–2).

Potassium Currents and Long QT Syndrome

There are four cardiac potassium currents involved in LQTS: the slow (I_{Ks}) and rapid (I_{Kr}) components of the delayed rectifier current, the inward rectifier current (I_{K1}), and the acetylcholine-dependent potassium current (I_{KAch}).

KCNQ1 is the gene of the I_{Ks} current (slow component of the delayed rectifier current). It represents the most common variant of LQTS (LQT1), which accounts for 45% to 55% of patients.[1,2] I_{Ks} is mostly

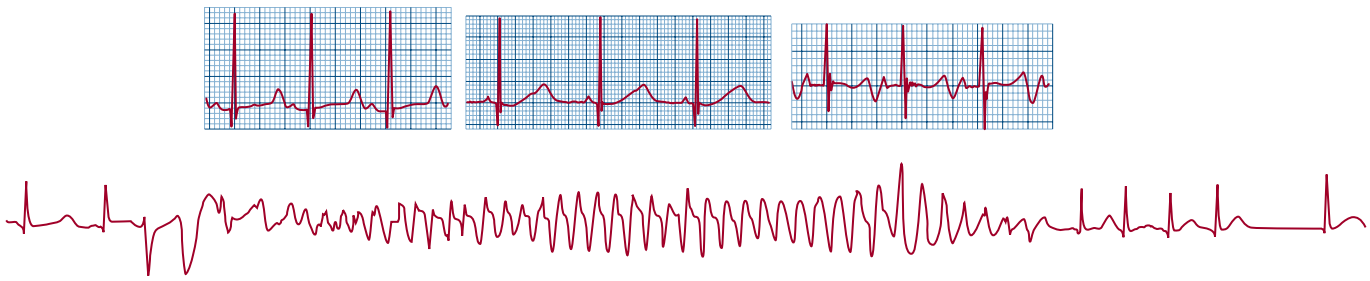

FIGURE 80–1. Electrocardiogram in long QT syndrome (LQTS). Upper row shows electrocardiogram (ECG) strips from three LQTS patients with marked QT prolongation and typical ST-T morphologic abnormalities: straight ST segment (*left*), wide T wave with late component (*center*), and biphasic T wave (*right*). The ECG shown in the lower row is an example of the typical polymorphic ventricular tachycardia that can lead to syncope and/or sudden cardiac death in LQTS.

TABLE 80–1. Long QT Syndrome Genes

Variant	Gene	Protein	Effect of Mutations
LQT1	*KCNQ1*	KvLQT1 (potassium channel α-subunit)	Reduced I_{Ks}
LQT2	*KCNH2*	HERG (potassium channel α-subunit)	Reduced I_{Kr}
LQT3	*SCN5A*	Nav1.5 (sodium channel α-subunit)	Increased I_{Na}
LQT4	*ANK2*	Ankyrin B, anchoring protein	Reduced membrane expression of Na^+ and Ca^{2+} channels
LQT5	*KCNE1*	MinK (potassium channel β-subunit)	Reduced I_{Ks}
LQT6	*KCNE2*	MiRP (potassium channel β-subunit)	Reduced I_{Kr}
LQT7 (ATS)	*KCNJ2*	Kir2.1 (potassium channel α-subunit)	Reduced outward I_{K1}
LQT8 (TS)	*CACNA1c*	Cav1.2 (L-type calcium channel α-subunit)	Increased I_{Ca} as a result of impaired voltage-dependent inactivation
LQT9	*CAV3*	Cardiac caveolin gene	Increased I_{Na} as a result of altered gating kinetic
LQT10	*SCN4B*	Sodium channel β4-subunit	Reduced subunit expression causing increased I_{Na}
LQT11	*AKAP9*	Yotiao (KvLQT1 regulating proteins)	Impaired I_{Ks} activation by catecholamines
LQT12	*SNTA1*	Syntrophin	Reduced NaV1.5 nitrosylation an increased current
LQT13	*KCNJ5*	Kir 3.4/GIRK4 potassium channel	Reduced I_{KAch} inward rectified acetylcholine-dependent current
LQT14	*CALM*	Calmodulin mutations in isoforms 1, 2, and 3 (three genes produce identical proteins)	Increased calcium current
LQT15	*TRDN*	Triadin (Trisk)	Reduced I_{Ca} inactivation (hypothesized but not experimentally verified)

Abbreviations: ATS, Andersen-Tawil syndrome; LQT, long QT syndrome type; TS, Timothy syndrome.

active during phase 3 of the action potential, but its role in the control of repolarization becomes more evident during adrenergic stimulation since the current is mainly activated by catecholamines. Thus, the consequences of *KCNQ1* mutations, leading to reduced I_{Ks}, become more evident during increased sympathetic tone (eg, exercise, acute emotions), with a failure to shorten action potential (ie, QT interval) and increased risk of arrhythmias. The second most common variant of LQTS, LQT2 is due to loss of function mutations in the *KCNH2* gene. *KCNH2* encodes for the α-subunit (pore-forming protein) of the I_{Kr} (rapid component of the delayed rectifier) channel, which participates in the control of cardiac repolarization during phase 3. Overall, LQT1 and LQT2 represent the majority of LQTS patients (~60%) with identified mutation. Interestingly, I_{Ks} and I_{Kr} currents are affected in two other LQTS variants: *KCNE1*-LQT5 (which co-assembles with *KCNQ1*) and *KCNE2*-LQT6 (which is thought to co-assemble mainly with *KCNH2*, but also with other potassium channels), which are β-subunits of I_{Ks} and I_{Kr}. LQT5 and LQT6 account for approximately 5% of cases and have similar pathogenesis (and clinical presentation) as LQT1 and LQT2, respectively, but with milder phenotype and lower penetrance.[3] *KCNQ1* and *KCNE1* mutations, when present in "double dose" (homozygosity) and inherited as a recessive trait, cause the Jervell and Lange-Nielsen syndrome. In rare cases, the I_{Ks} current can be reduced by mutations in the *AKAP9* gene (Yotiao; LQT11) that binds in the carboxyl-terminal region of the *KCNQ1* protein to transduce the adrenergic signal to the channel. Finally, *KCNJ2* causes the LQT7 variant, also known as Andersen-Tawil syndrome.[2] The gene encodes for the cardiac inward rectifier I_{K1} current gene (*Kir2.1*) that participates in the control of the late repolarization phase and resting membrane potential. LQT7 is a rare variant (< 1%) that can sometimes include extracardiac manifestations (periodic paralysis and dysmorphic features).

Sodium Current and Long QT Syndrome

The cardiac sodium current (I_{Na}) is the major determinant of phase 0 (depolarization) of the cardiac action potential and is involved in the pathogenesis of different LQTS variants but primarily of LQT3. LQT3 is caused by *SCN5A* gain-of-function mutations and represents the third most frequent LQTS variant. LQT3 mutations induce an increase of the late component of I_{Na}, leaving the peak (fast) component of the current unaffected or only mildly altered. This prototypical LQT3 defect can be accompanied by a spectrum of mutation-specific biophysical abnormalities, including loss-of-function defects that underlay the so-called *overlap syndromes*—a combination of LQT3 and Brugada syndrome and/or conduction defect (see below).[4] A gain of function of I_{Na} is also present in LQT9 as a result of the *CAV3* gene, LQT10 as a result of *SCN4B*, and LQT12 as a result of the syntrophin gene (*SNTA1*). Overall, mutations in these

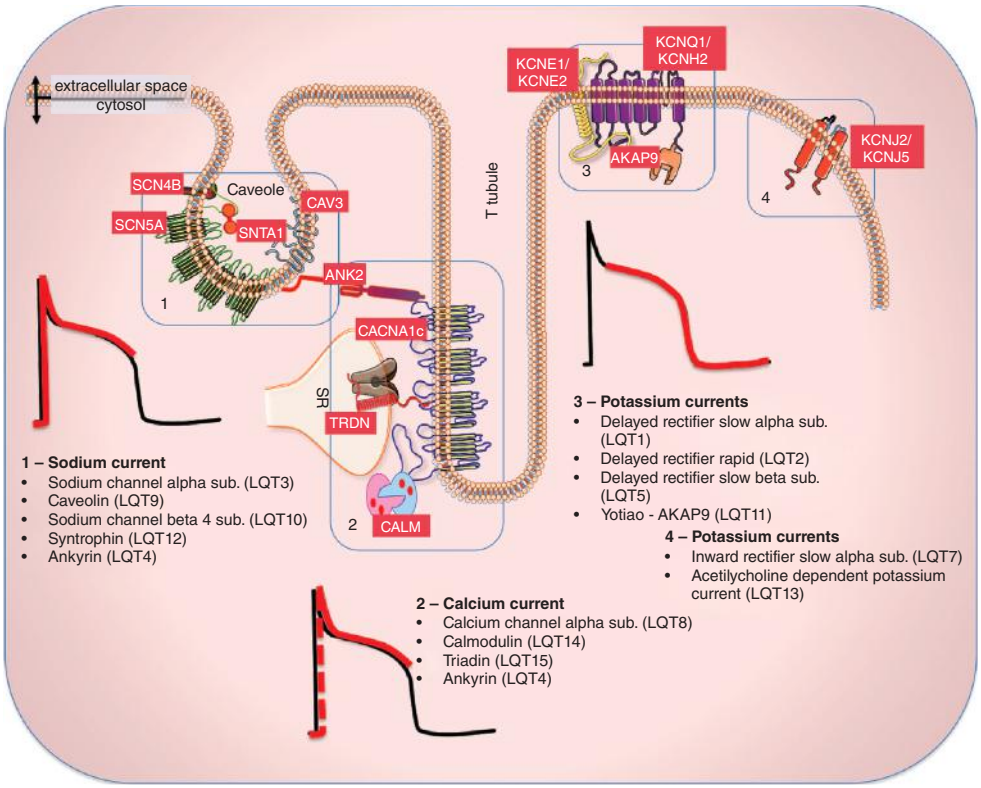

FIGURE 80–2. LQTS genes and proteins grouped by function. Four major groups can be identified: genes that alter the cardiac sodium current (group 1), genes affecting cardiac calcium channel and intracellular calcium handling (group 2), genes controlling the early repolarization (group 3) including phase 2 and 3 of the cardiac action potential, and genes that affect mainly the resting membrane potential (group 4). The action potential phases involved for each functional group are highlighted with a *red line* on the action potential. The *dotted line* indicates the fact that I_{Ca} is of limited force, albeit active, during phase 0.

latter variants are rare (< 5%), and it is currently unclear whether the associated outcome is similar to that of LQT3.[2]

Calcium Current and Long QT Syndrome

The role of the L-type voltage-dependent calcium current (I_{Ca}) in the pathogenesis of LQTS is being progressively recognized. The first mutations of the gene encoding for the pore-forming protein (*CACNA1c*) were identified in 2004 and 2005 in patients presenting with an extremely severe and rare phenotype, including QT prolongation, atrioventricular block, syndactyly, congenital heart defects, autism, reduced immune response, and developmental delay.[5] This disorder was defined as LQT8 and named Timothy syndrome. Timothy syndrome is a severe, often lethal condition, and therefore, it has a very low prevalence in the population (probably < 1:20,000 for patients with fully penetrant phenotype). Experimental studies have demonstrated that *CACNA1c* mutations cause a gain-of-function type of defect, with loss of voltage-dependent inactivation of the channel leading to an increase in I_{Ca}.[5] Accumulating evidence suggests that *CACNA1c* mutations can also cause QT prolongation in the absence of structural cardiac abnormalities and extracardiac manifestations.[6] In other cases, "mild"[7] or nontypical[8] extracardiac manifestations may occur, suggesting that calcium channel mutations can create a continuum of clinical manifestations between Timothy syndrome and nonsyndromic QT prolongation. Thus, the identification of a *CACNA1c* mutation in a patient with apparently isolated QT prolongation requires careful investigation to exclude the possibility of mild or subclinical immunologic, neurologic, or skeletal muscle involvement.

Infrequent Long QT Syndrome Variants

Other genes that account for a minority of cases have been reported, namely *ANK2* (LQT4), *CALM* (LQT14), and *TRDN* (LQT15) (see Table 80–1). The pathogenesis and the clinical manifestations of these "minor" LQTS variants are poorly elucidated. Of note, whenever a mutation in one of these genes is found, the possibility of overlap phenotypes should be considered. *ANK2* has been associated with mild QT prolongation but adrenergic-induced arrhythmias.[9] Similarly, *CALM* and *TRDN* mutations have been linked to catecholaminergic polymorphic ventricular tachycardia (CPVT) or a similar pattern of catecholaminergic arrhythmias (Fig. 80–2). An increased calcium current gain of function has been demonstrated for *CALM* and *TRDN* mutations associated with LQTS (see section on CPVT for further discussion of these variants).

DIAGNOSIS AND CARDIAC EVENTS

The diagnosis of LQTS is based on the evaluation of the electrocardiogram (ECG) and on the measurement of the QT interval. Current guidelines[10] indicate that LQTS can be diagnosed under the following conditions: (1) either QTc ≥ 480 milliseconds in repeated 12-lead ECGs or LQTS risk score > 3; (2) confirmed pathogenic LQTS mutation, irrespective of the QT duration; or (3) a QTc ≥ 460 milliseconds in repeated 12-lead ECGs in patients with unexplained syncope in the absence of secondary causes for QT prolongation. These new diagnostic criteria substantially facilitate the clinical diagnosis since they allow excluding patients with isolated (ie, with no family history, symptoms, or genetic mutation) and borderline QTc (440 to 460 milliseconds).

LQTS diagnostic score can be used in conjunction with QT measurements. The diagnostic score was proposed in 1993.[11] Besides QT, the score includes other variables such as history of syncope and family history. It is a probabilistic scoring system, and diagnosis has a high probability with a score > 3. LQTS score may be less sensitive for patients with reduced penetrance because it does not include genotype. Accurate assessment of QTc is important in LQTS because it is the single most important predictor of cardiac events. A QTc interval consistently ≥ 500 milliseconds is associated with a five-fold increased risk of events with a rate of 4% to 5% per year.[3] Events are due to the onset of rapid polymorphic ventricular tachycardia (VT) defined as torsade de pointes; the arrhythmias can cause syncope and degenerate into VF, leading to sudden death. Additional risk factors are female sex (approximately two-fold increased risk) and the occurrence of a first cardiac event in early childhood. In LQTS, cardiac arrhythmias are often precipitated by physical or emotional stress, although in 10% to 15% of patients, cardiac events occur at rest. Both the risk and the triggers for events are modulated by the genotype (see below). Additional increased risk is seen in the 9-month postpartum period.

THERAPY

Lifestyle and cautionary behavior are absolutely important for a correct approach to LQTS: avoidance of QT-prolonging drugs, correction of electrolyte disturbances (especially hypokalemia), and the avoidance of genotype-specific triggers have a class I indication. In parallel, β-blockers are recommended in all patients with a clinical diagnosis of LQTS[10] (Table 80–2). The most frequently used drugs are nadolol (1-2.5 mg/kg/d), propranolol (2-4 mg/kg/d), and metoprolol (2-4 mg/kg/d). A recent study[12] has suggested that the relative risk reduction for a first cardiac event is similar irrespective from the β-blocker used (on average, 0.63; 95% confidence interval, 0.47-0.86). However, nadolol was more effective than the other β-blockers among LQT2 patients, and propranolol was the least effective in preventing recurrences in patients with previous events on β-blockers. The use of β-blockers should also be considered (class IIa) in carriers of LQTS mutations with normal QT interval.[10]

The use of implantable cardioverter-defibrillators (ICDs), always in conjunction with β-blockers, is indicated in all patients surviving cardiac arrest (secondary prevention). ICDs should be also considered for the 20% to 30% of patients who experience recurrence of syncope despite β-blockade (class IIa) or for primary prevention of cardiac arrest in high-risk genotypes (class IIb; see Table 80–2).[10] The use of I_{Na} blockers like mexiletine and, more recently, ranolazine can be considered in LQT3 patients. Recent evidence demonstrates that mexiletine at an average daily dose of 8 mg/kg significantly reduces the risk of cardiac events among LQT3 patients.[13] Because the response to these approaches are not invariably positive (nonresponders), acute oral drug testing in the hospital setting may be advisable before chronic administration.[14] Finally, left cardiac sympathetic denervation may be used to reduce the burden of cardiac symptoms in highly symptomatic patients who are nonresponders to β-blockers, but it is not considered an alternative to ICD at this time.[10]

TABLE 80–2. LQTS Clinical Management and Therapy

Recommendations	Class	Level
LQTS is diagnosed with either QTc ≥ 480 ms in repeated 12-lead ECGs or LQTS risk score > 1.	I	C
LQTS is diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration.	I	C
ECG diagnosis of LQTS should be considered in the presence of a QTc ≥ 460 ms in repeated 12-lead ECGs in patients with an unexplained syncopal episode in the absence of secondary causes for QT prolongation.	IIa	1
The following lifestyle changes are recommended in all patients with a diagnosis of LQTS: (a) Avoidance of QT-prolonging drugs (b) Correction of electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) that may occur during diarrhea, vomiting, or metabolic conditions. (c) Avoidance of genotype-specific triggers for arrhythmias (strenuous swimming, especially in LQTS1, and exposure to loud noises in LQTS2 patients).	I	B
β-Blockers are recommended in patients with a clinical diagnosis of LQTS.	I	B
ICD implantation with the use of β-blockers is recommended in LQTS patients with previous cardiac arrest.	I	B
β-Blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.	IIa	B
ICD implantation in addition to β-blockers should be considered in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of β-blockers.	IIa	B
Left cardiac sympathetic denervation should be considered in patients with symptomatic LQTS when (1) β-blockers are not effective, not tolerated, or contraindicated; (2) ICD therapy is contraindicated or refused; or (3) patients on β-blockers with an ICD experience multiple shocks.	IIa	C
Sodium channel blockers (mexiletine, flecainide, or ranolazine) may be considered as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc > 500 ms.	IIb	C
Implant of an ICD may be considered in addition to β-blocker therapy in asymptomatic carriers of a pathogenic mutation in KCNH2 or SCN5A when QTc is > 500 ms.	IIb	C
Invasive EPS with PVS is not recommended for SCD risk stratification.	III	C

Note. An updated list of QT-prolonging drugs can be found at https://www.crediblemeds.org/.

Abbreviations: ECG, electrocardiogram; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator; LQTS, long QT syndrome; PVS, programmed ventricular stimulation; SCD, sudden cardiac death; VT, ventricular tachycardia.

GENOTYPE-PHENOTYPE CORRELATION AND CLINICAL MANAGEMENT

Genotype-phenotype correlations are available for the three most prevalent LQTS variants: LQT1, LQT2, and LQT3. The remaining variants account for a minority of patients, and their genotype-specific phenotypes are ill defined. Gene-specific repolarization morphology and triggers for cardiac events have been reported.[1] Most importantly, genotype plays a relevant role in determining the risk of events and the response to β-blocker therapy. LQT2 and LQT3 patients have worse long-term prognosis than LQT1 patients (two-fold risk increase for LQT2 and LQT3 vs LQT1). Therefore, genotype has entered the risk stratification scheme as independent predictor of events together with QT duration and sex (Fig. 80–3).[3] LQTS genotype not only influences prognosis but also response to therapy. Recurrences of life-threatening arrhythmias are infrequent among LQT1 patients, whereas a clinically relevant residual risk of events remains for LQT2 and LQT3 patients on β-blockers, with hazard ratios for recurrent event in patients with LQT2 and LQT3 versus LQT1 of 2.8 and 4.0, respectively[15] (see Fig. 80–3). Incomplete efficacy of β-blockers may suggest that ICD implant for primary prevention of cardiac arrest could be considered for LQT2 and LQT3 patients with QTc > 500 milliseconds, especially if there is evidence of a first event early in life (< 7 years).

The use of genotype information has significantly improved the risk stratification and management, but relevant intraindividual variability[16] hampers the possibility of individualized approaches. Several efforts in this direction have been pursued. Studies have suggested that mutations occurring in the pore region of the *KNCH2* gene or in the C-loop region of *KCNQ1* are associated with a more severe prognosis. On the other hand, C-terminal mutations of *KCNQ1* are often found in mild LQTS cases.[16,17] These additional markers of risk have not been included in specific risk stratification schemes so far; therefore, their systematic applicability is limited. More recently, the technique of electrocardiographic imaging (ECGI) is emerging as a possible means to overcome the current limitations in LQTS risk stratification. ECGI is a computational technique that allows reconstructing the pattern of epicardial electrical activation with the combined use of surface ECG mapping and anatomic data (cardiac computed tomography scan or

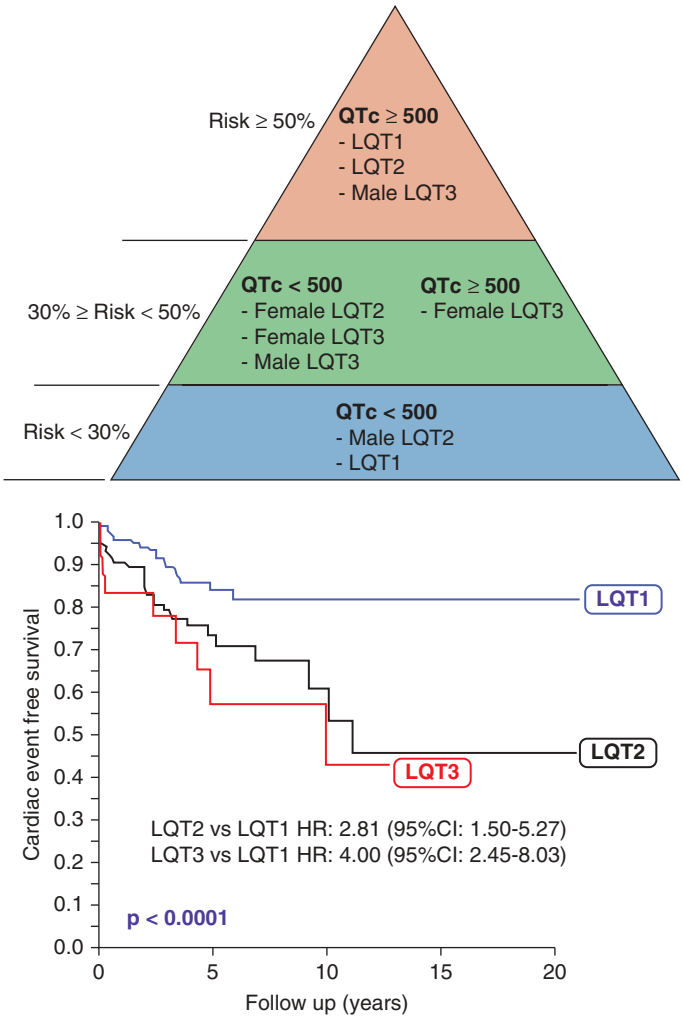

FIGURE 80–3. Risk stratification in long QT syndrome (LQTS). *Upper panel* shows the risk categories in LQTS according to QTc duration, genotype, and sex. Percentages on the left indicate the risk of a first cardiac event (syncope or cardiac arrest) in patients younger than 40 years of age in the absence of any LQTS active treatment. The *lower panel* shows the cardiac event-free survival in LQTS patients on active β-blocker therapy. The presence of an LQT2 or LQT3 mutation is an independent predictor of reduced efficacy: hazard ratio values are reported in the figure. Upper panel reproduced with permission from Priori SG, Schwartz PJ, Napolitano C, et al: Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003 May 8;348(19):1866-1874.

magnetic resonance imaging).[18] Preliminary observations suggest that the quantification of the dispersion of the activation recovery interval (a measure of the duration of local repolarization) can differentiate symptomatic from asymptomatic LQTS patients even if their QTc is not significantly different.[19]

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

DEFINITION

CPVT was described by Philippe Coumel in 1978, as an inherited disorder characterized by structurally normal heart, unremarkable resting ECG, and a typical and reproducible pattern of bidirectional adrenergic-dependent VT (Fig. 80–4). CPVT was found to be caused by mutations in two genes, namely *RyR2* and *CASQ2*, involved in the control of intracellular calcium handling. More recently, systematic testing of a larger cohort of patients with adrenergic-dependent arrhythmias, but not typical CPVT, has allowed the identification of mutations in other genes involved in the control of intracellular calcium (Fig. 80–5).

GENETIC BASIS AND PATHOPHYSIOLOGY

Genetic Variants Associated With Typical Catecholaminergic Polymorphic Ventricular Tachycardia Pattern

In 2001, two genes causing a typical (the one described by Coumel in 1978) CPVT phenotype were identified. We initially demonstrated that cardiac ryanodine receptor (*RyR2*) mutations cause the autosomal dominant CPVT type 1 (CPVT1).[20] RyR2 is a tetrameric Ca^{2+} release channel spanning the membrane of the sarcoplasmic reticulum (SR); it is required for excitation-contraction coupling. *RyR2* is the major CPVT gene, accounting for 50% to 60% of cases. Calsequestrin 2 (*CASQ2*) is the gene responsible for the autosomal recessive variant of CPVT (CPVT type 2 [CPVT2]).[21] Calsequestrin is a calcium-buffering protein located in the SR that controls the SR Ca^{2+} concentration, and it modulates the *RyR2* open probability (presumably through interaction with *RyR2* channels mediated by triadin and junctin that constitute parts of the SR calcium release macromolecular complex) (see Fig. 80–5).

Experimental evidence obtained in cellular models and transgenic mice engineered with both *RyR2* and *CASQ2* mutations demonstrates that the myocardium of CPVT patients is prone to the development of delayed afterdepolarizations (DADs), spontaneous membrane depolarizations due to the activation of the sodium-calcium exchanges that extrude the excess of Ca^{2+} ions in the cytosol (Ca^{2+} overload). DADs can generate spontaneous action potentials when they are large enough to reactivate the sodium current. This arrhythmogenic mechanism is called triggered activity, and it is favored by catecholamines (adrenergic stimulation) (see Fig. 80–5).[22]

The onset of DADs and triggered activity is the final effect of *RyR2* and *CASQ2* mutations and is a result of abnormal release from the SR. This mechanism is summarized in the concept of store overload-induced calcium release (SOICR) proposed by Wayne Chen.[22] The threshold for the release of calcium from the SR (the Ca^{2+} store) is reduced by the mutation, and therefore, the SR is "leaky." Adrenergic stimulation increases the SR calcium content; therefore, the threshold for uncontrolled release ("spillover") is more readily reached. The SOICR threshold can be altered by the CPVT mutations through different mechanisms, including altered calcium sensitivity, channel instability (the channel "unzipping" mechanism), or impaired *CASQ2/RyR2* interaction (for a detailed review of *RyR2* and *CASQ2* mutation pathogenesis, see Priori and Chen[22]). The *RyR2* leakage is a gain-of-function type of functional defect. However, few *RyR2* mutations can cause a reduced SOICR as a result of reduced *RyR2* calcium sensitivity. These mutations have been associated with idiopathic VF in the absence of typical CPVT phenotype, but their arrhythmogenic mechanisms are not fully elucidated.

Nontypical Catecholaminergic Polymorphic Ventricular Tachycardia Variants and Differential Diagnosis

At least four more genes have been linked to adrenergically induced arrhythmias with a CPVT-like phenotype but with a less reproducible pattern of arrhythmias: ankyrin (*ANK2*). Kir2.1 (*KCNJ2*), calmodulin (*CALM1*), and triadin (*TRDN*).

Ankyrins are adapter proteins with key modulatory and targeting roles in membrane protein targeting, including the cardiac sodium channel and the sodium calcium exchanger. Initially, an ankyrin-B

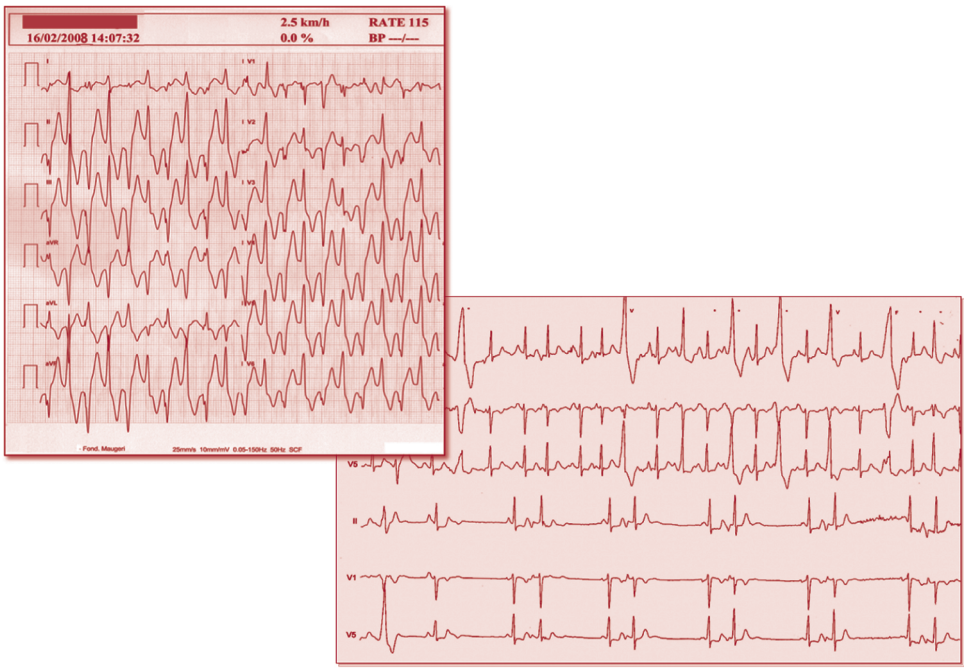

FIGURE 80–4. Arrhythmias in catecholaminergic polymorphic ventricular tachycardia (CPVT). The *upper panel* shows bidirectional ventricular tachycardia during exercise stress test at low workload and arising at a sinus heart rate of 115 bpm. An example of supraventricular arrhythmias is shown in the *lower panel*.

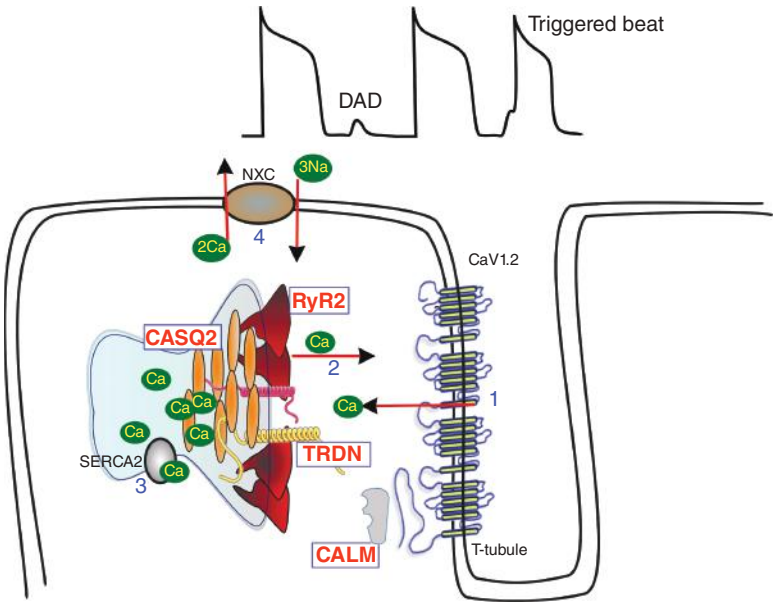

FIGURE 80–5. Pathophysiology of catecholaminergic polymorphic ventricular tachycardia (CPVT). The normal process of calcium-induced calcium release (CICR) includes three steps (blue numbers 1 to 3): (1) the calcium entering the cell through the voltage-dependent L-type channels triggers further calcium release from the sarcoplasmic reticulum (SR) (2) through the ryanodine receptors. After contraction, the calcium reuptake from the cytosol to the SR is an active process controlled by the calcium ATPase pump (SERCA) (3). In the presence of CPVT mutations, the ryanodine receptor releases an excessive amount of calcium, and it is "leaky" during the electrical diastole. This leads to cytosolic calcium overload that is removed from the cells by an abnormal hyperactivation of the sodium-calcium exchanger (NCX) that extrudes calcium (4). However, NCX generates a net inward current because it transports three sodium ions (three positive charges) for one calcium ion (two positive charges). This current is called *transient inward* current and is visible as a depolarizing "hump" (delayed afterdepolarization [DAD]) on the action potential. When large enough, DADs may trigger extrasystolic action potential(s) (triggered beat). The genes associated with CPVT (or CPVT-like; see text for details) phenotypes are also illustrated and shown in *bold red* type.

mutation was identified in LQTS (LQT4). LQT4 is a nontypical LQTS variant with mild QT prolongation and sinus node dysfunctional arrhythmias (ventricular and atrial).[23] Several mutations have subsequently been reported, including mutations associated with adrenergically induced arrhythmias and sudden death resembling CPVT.[23] *KCNJ2* is the gene involved in Andersen-Tawil syndrome (LQT7); it encodes for a two-transmembrane segment potassium channel (Kir2.1) that controls the I_{K1} (inward rectifier) current active during phase 4 of cardiac action potential. Many patients with Andersen-Tawil syndrome have bidirectional VTs, although the arrhythmias are unrelated with adrenergic stimulation.[2]

Nyegaard at al[24] reported two cardiac calmodulin 1 (*CALM1*) mutations associated with adrenergic-dependent arrhythmias and sudden death. Calmodulin is a small (140 amino acids) cytoplasmic protein that binds calcium in the cytosol; it transduces calcium-mediated signaling to a number of intracellular targets (including the ryanodine receptor). Both cases reported in this study did not show a typical CPVT phenotype with reproducible bidirectional VT. From an experimental standpoint, the mutations reduce the calcium-binding affinity of calmodulin[25] and lower the threshold for RyR2 activation (ie, reduced SOICR threshold) and the threshold for calcium release termination.[25] As outlined earlier in this chapter, other studies have associated *CALM1*, *CALM2*, or *CALM3* mutations with LQTS.[26] It is interesting to note that the three different genes (*CALM1*, *CALM2*, and *CALM3*) generate an identical calmodulin protein. Experimental studies have suggested that the effects of *CALM1* mutations associated with CPVT or LQTS are not substantially different.[25,27] Therefore, it is possible that overlap CPVT-LQTS phenotypes are generated in the presence of *CALM* mutations, irrespectively from the gene isoform. Overall, calmodulin is considered a rare cause of CPVT-like phenotype.

TRDN mutations were found in two families with cases of syncope and sudden death during exercise but without evidence of inducible typical bidirectional VT[28]; a third case was reported more recently by the same group.[29] This phenotype is observed only in homozygotes, with a recessive phenotype. Cardiac triadin gene encodes for multiple, tissue-specific regulated splice variants. Cardiac triadin, also known as Trisk32, has a single transmembrane segment spanning the SR membrane (see Fig. 80–5) where it participates in the formation of the SR calcium-releasing macromolecular complex (which also includes RyR2, junctin, and calsequestrin). *TRDN* knockout results in reduced SR Ca^{2+} release, impaired calcium current (I_{Ca}) inactivation, and intracellular Ca^{2+} overload. The reduced inactivation of the calcium channel is consistent with the identification of cases of QT prolongation with adrenergic arrhythmias related to *TRDN* recessive mutation.[30] Thus, it appears that *TRDN* mutations can create a clinical condition with intermediate phenotype between CPVT and LQTS, not dissimilar from the case of calmodulin. Overall, no typical CPVT patient has been identified as a carrier of *TRDN* mutations

CLINICAL PRESENTATION

CPVT patients have unremarkable resting ECGs with the exception of sinus bradycardia and a prominent U wave reported in some cases. A distinctive pattern of arrhythmias is observed during exercise or acute emotion: an alternating 180-degree QRS axis on a beat-to-beat basis, the so-called *bidirectional ventricular tachycardia* (see Fig. 80–4). Supraventricular arrhythmias (supraventricular tachycardia and atrial fibrillation) are also observed.[31] The reproducible arrhythmogenic effect of catecholamines is the second important diagnostic hallmark of the disease. However, it is important to recall that the pattern of arrhythmias can be less reproducible in the presence of mutations in the "minor" CPVT genes or with specific, uncommon *RyR2* mutations causing loss of function.

The mean age of onset of symptoms in CPVT patients is 12 years of age. Syncope, triggered by exercise or acute emotion, is the typical manifestation of the disease. Sudden death can be the first manifestation of the disease, leading to the diagnosis of idiopathic VF.[31] Available data show that 75% to 80% of patient experience at least one life-threatening event before the age of 40 years and are left without therapy.[31] The presence of a normal resting ECG is often the cause of a dangerous delay in the diagnosis of CPVT from the time of the first syncope. In 2002, we showed a mean time to diagnosis of 2.5 years.[31] Such delayed diagnosis, recently confirmed by the results of a multicenter registry,[32] may expose patients to unnecessary risk of life-threatening events and should be avoided. The exercise stress test is the most important diagnostic test for suspected CPVT (patients with normal ECG and syncope, presyncope, or dizziness triggered by exercise or acute emotions)

THERAPY

β-Blockers are the mainstay of treatment. Nonspecific β-blockers (nadolol and propranolol) have been empirically used, and their superior efficacy over selective compounds has been recently confirmed.[33] Nadolol is the drug of choice in our center at doses of 1.5 to 3 mg/kg/d; the dose should always be individualized to demonstrate the absence of repetitive arrhythmias during exercise stress testing. β-Blockers are indicated also for genetically positive family members even if phenotype negative (ie, negative off-drug exercise test).[10] Despite optimal use of β-blockers, there is a 25% to 35% risk of recurrent cardiac events.[31,32] The adjunctive antiarrhythmic effect of flecainide has been confirmed in recent years.[32] This drug should be considered in patients with recurrence of syncope and/or repetitive ventricular arrhythmia during exercise stress test in the presence of optimized (maximally tolerated dose) β-blockers (class IIa indication). The average dose is 100 to 200 mg/d.[32] Flecainide could also be considered as monotherapy in the few patients who are intolerant to β-blockers. The reported rate of side effects with this drug is 10% to 20%.[32] Recurrences of cardiac events are possible even in patients treated with an "optimized" combination of β-blockers and flecainide.

Finally, left cardiac sympathetic denervation (LCSD) has been proposed for CPVT with intractable arrhythmias; however, because events after LCSD are reported,[32,34,35] LCSD is to be considered a means to further abate the number of events but not as a replacement for ICD. Current guidelines recommend the use of ICD, in addition to β-blockers with or without flecainide, in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope, or polymorphic/bidirectional VT despite optimal therapy. ICD is always indicated for secondary prevention of cardiac arrest. A key component of CPVT treatment is therapy compliance, and patients should be made aware of its relevance.

BRUGADA SYNDROME

DEFINITION

Brugada syndrome (BrS) is characterized by a peculiar ECG pattern of ST-segment elevation in leads V_1 to V_3 (Fig. 80–6) and incomplete or complete right bundle branch block in the absence of signs of acute myocardial ischemia. Syncope and sudden death are the typical symptoms.

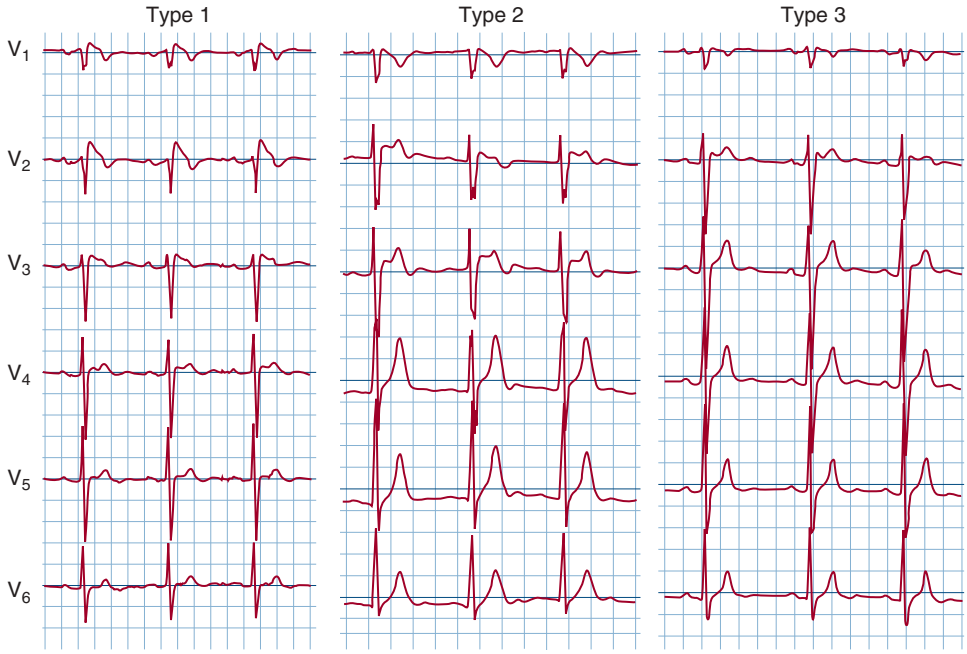

FIGURE 80–6. Electrocardiogram patterns in Brugada syndrome (BrS). Only type 1 ST-segment elevation either spontaneously present or induced by ajmaline/flecainide testing is considered diagnostic for BrS. Types 2 and 3 may lead one to suspect the presence of BrS, but drug testing with flecainide or ajmaline is required for diagnosis.

GENETIC BASIS AND PATHOPHYSIOLOGY

After the identification of the first mutations in the *SCN5A* gene (variant named as BrS1), which is still the most prevalent, several genes have been causally linked to the disease (Table 80–3). When considering the wide BrS gene list, it is clear that there are three main electrophysiologic functions that can be affected: the cardiac sodium current, the calcium current, and the transient outward potassium current. Besides *SCN5A*, which accounts for approximately 20% of cases, the remaining BrS genes explain a minority of cases. This impacts not only on the clinical utility of genetic testing but also the robustness of the interpretation of the results of genetic testing when mutations on "minor" and less well characterized genes are identified. Globally, no more than 30% to 35% of cases have a mutation in the known genes.

Sodium Current and Brugada Syndrome

At variance with LQT3 mutations (causing a gain of function), BrS1-associated *SCN5A* mutations cause loss of function with reduction of current density and/or multiple biophysical abnormalities (eg, faster inactivation rate).[14] Such electrophysiologic alteration often results in negative bathmotropic and dromotropic effects that contribute to the arrhythmogenic substrate (see below). As a consequence, sodium-dependent BrS presents with a high prevalence of atrioventricular and intraventricular conduction defects.[36] The corollary of this observation is that the presence of a conduction defect in a BrS patient increases the chance of identifying an *SCN5A* mutation.

Mutations in at least seven additional genes may lead to altered sodium current in BrS, namely, *GPD1-L, SCN1B, SCN3B, SLMAP, TRPM4, SCN2B*, and *RANGRF* (see Table 80–3, Fig. 80–7). The relative prevalence of these genes among patients has not been established yet, but on the basis of the current indirect evidence, it is likely to be low (< 1%) and thus has limited epidemiologic impact.

Calcium Current and Brugada Syndrome

Cardiac calcium channel mutations have been reported in a few BrS patients, and three genes have been involved: *CACNA1c*, *CACNB2*, and *CACNA2D1*. They all encode for subunits that co-operate to form the multimeric structure of the channel (see Fig. 80–7). *CACNA1c* mutations, causing BrS3, were found in 2 of 82 BrS patients, whereas *CACNB2*, causing BrS4, was found in 1 patient from the same cohort. The causal link of *CACNA2D1* with a Brugada phenotype has still to be definitely established; preliminary observations suggest a link with a BrS phenotype that also includes early repolarization.[37] *CACNA1c* and *CACNB2* constitute the α- and β-subunits of the cardiac voltage-dependent calcium channel, respectively, and in both cases, the mutations cause a loss of function with reduced calcium entry and shortening of the plateau (phase 2) of action potential. *CACNA2D1* produces a preprotein that is cleaved into multiple chains that compose the α2- and δ-subunits of the voltage-dependent calcium channel complex.

A common feature of BrS associated with calcium channel mutations is the presence of a short QT interval, which is reported to be constantly in the lower range of normal or even frankly below normal in some patients. Therefore, BrS and short QT syndrome may have instances of overlapping clinical manifestations.

Potassium Current and Brugada Syndrome

The cardiac transient outward potassium (I_{to}) current is emerging as another culprit in the pathogenesis of BrS. I_{to} is the current that controls phase 1 of the cardiac action potential (initial fast repolarization).

TABLE 80–3. Brugada Syndrome Genes

Variant	Gene	Protein	Functional Defect
BrS1	*SCN5A*	Cardiac sodium channel α-subunit (Nav1.5)	Loss of function/reduced Na^+ current
BrS2	*GPD1-L*	Glycerol-6-phosphate dehydrogenase	Loss of function/reduced Na^+ current
BrS3	*CACNA1c*	L-type calcium channel α-subunit (Cav1.2)	Loss of function/reduced Ca^{2+} current
BrS4	*CACNB2*	L-type calcium channel β_2-subunit	Loss of function/reduced Ca^{2+} current
BrS5	*SCN1B*	Cardiac sodium channel β_1-subunit	Loss of function/reduced Na^+ current
BrS6	*KCNE3*	Transient outward current β-subunit; transient outward current	Gain of function/increased K^+ I_{to} current
BrS7	*SCN3B*	Cardiac sodium channel β_3-subunit	Loss of function/reduced Na^+ current
BrS8	*HCN4*	Hyperpolarization activated potassium channel (I_f)	No functional studies available
BrS9	*RANGRF*	Guanine nucleotide release factor, control of NaV1.5 trafficking (*MOG1*)	Loss of function/reduced Na^+ current
BrS10	*KCND3*	SHAL potassium channel isoform 3 - transient outward current (Kv4.3)	Gain of function/increased K^+ I_{to} current
BrS11	*KCNH2*	Rapid component of the cardiac delayed rectifier current	Increased repolarizing current (gain of function)
BrS12	*KCNJ8*	ATP-dependent potassium current (Kir6.1)	Incomplete closing of the ATP-sensitive potassium channels
BrS13	*CACNA2D1*	L-type calcium channel δ_2-subunit	Loss of function/reduced Ca^{2+} current
BrS14	*KCNE5*	Potassium channel β_5-subunit; transient outward current (MiRP4)	Gain of function/increased K^+ I_{to} current
BrS15	*SLMAP*	Sarcolemmal membrane–associated protein	Reduced Na^+ current (impaired NaV1.5 trafficking)
BrS16	*TRPM4*	Calcium-activated cationic channel subfamily M isoform 4	Reduced sodium current
BrS17	*SCN2B*	Cardiac sodium channel β_2-subunit	Loss of function/reduced Na^+ current
BrS18	*ABCC9*	ATP-binding cassette transporter of I_K-ATP	Incomplete closing of the ATP-sensitive potassium channels; negative shift of I_{Na} inactivation

Abbreviations: ATP, adenosine triphosphate; BrS, Brugada syndrome; OMIM, Online Mendelian Inheritance in Man.

[a]OMIM-designated variants go from BrS1 to BrS8; other variants do not have OMIM designation.

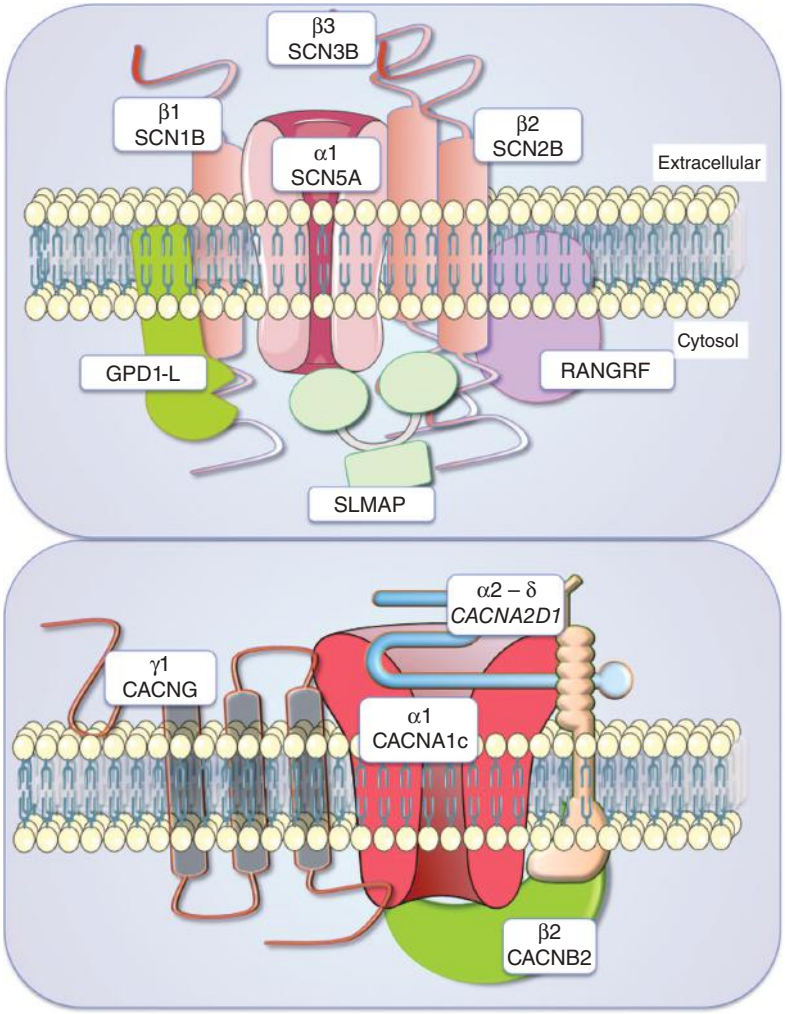

FIGURE 80–7. Multiplicity of genes causing Brugada syndrome (BrS) resulting from loss of function of sodium current (*upper panel*) or calcium current (*lower panel*). A reduced or abnormal sodium current can be a result of mutations in at least seven different genes. Three genes can cause BrS as a result of an abnormal calcium channel (*CACNA1c*, *CACNB2*, *CACNA2D1*), whereas no mutations have been identified so far in the calcium channel γ-subunit. Overall, both I_{Na} (sodium current) and I_{Ca} (calcium current) are generated and regulated by several proteins that aggregate in macromolecular complexes.

Three genes have been involved: *KCNE3*, *KCND3*, and *KCNE5*.[38] *KCND3* (Kv4.3) is a component of I_{to}, and the identified mutations cause increased current, leading to shortening of the action potential. *KCNE5* (MiRP4) and *KCNE3* (Kv4.3) are potassium channel β- and α-subunits involved in BrS; when mutated, they increase the I_{to} current. Furthermore, *KCNJ8* (Kir6.1)[39] and *ABCC9*[40] mutations induce a gain of function (incomplete closing) of the adenosine triphosphate–dependent potassium current. Of note, mutations in the potassium channel genes have been identified in less than 1% of the screened probands. Gain-of-function mutations have also been reported in *KCNH2*,[41] the LQT2 and short QT syndrome type 1 gene, and *HCN4*, the pacemaker channel,[37] although their pathogenesis is poorly understood. Overall, potassium-related BrS is considered a rare occurrence, but large-cohort studies are not available for a precise quantification of the prevalence.

Brugada Syndrome Electrocardiogram and Arrhythmias: Mechanistic Insights

Two hypotheses have been proposed to explain the link between ST-segment elevation and polymorphic VT in BrS.[42] The repolarization hypothesis proposes that BrS mutations cause the predominance of early depolarizing currents (transient outward current) over depolarizing currents (Na^+ and Ca^{2+} currents). This may be a result of either an increase in repolarizing current or a decrease in depolarizing currents leading to loss of the action potential dome and to action potential shortening in the epicardium of the right ventricular outflow tract (RVOT), where I_{to} is more expressed. This process generates a transmural repolarization gradient that causes ST-segment elevation. Arrhythmias can be generated by this abnormal dispersion of action potential duration, which causes the so-called phase 2 reentry. The depolarization hypothesis suggests that the ST-segment elevation in the precordial leads is attributable to slowing of conduction and delayed activation of the RVOT. This provides the substrate for the onset of reentry arrhythmias.

In a recent study by Zhang et al,[43] the two hypotheses have been unified. The analysis of ECGI mapping data obtained in 25 BrS patients provides evidence that the electrophysiologic abnormalities and the ST elevation are indeed localized in the RVOT. Delayed and fractionated electrograms and prolonged recovery time with steep repolarization gradients (dispersion of repolarization) have been simultaneously detected. Thus, the RVOT of BrS patients is prone to arrhythmias due to transmural dispersion of repolarization (the so-called phase 2 reentry) or due to epicardial reentry favored by localized slow conduction area.

DIAGNOSIS AND CLINICAL PRESENTATION

BrS can be diagnosed in the presence of a "type 1 ECG," consisting of a J-point elevation ≥ 2 mm with descending ST segment. In the presence of type 2 and type 3 patterns, it is indicated to perform a diagnostic test with the intravenous administration of sodium channel blockers (flecainide 2 mg/kg up to 150 mg or ajmaline 1 mg/kg). On the basis of electroanatomic studies, the current guidelines[2] suggest recording right precordial leads (V_1 and V_2) also in the third and second intercostal spaces to improve diagnostic sensitivity. The clinical usefulness of this approach has been recently demonstrated.[44] This should be done during drug testing (ajmaline/flecainide) and during 12-lead Holter monitoring. Holter has a relevant diagnostic role because the type 1 ECG is intermittent. BrS manifests with syncope and cardiac arrest occurring at rest or during sleep. Specific triggers for events are fever, abundant meals, and excessive alcohol consumption. Avoiding such conditions as much as possible is recommended (Table 80–4). The first manifestation typically occurs in the third or fourth decade of life, whereas pediatric manifestations are rare (Fig. 80–8). The epidemiologic data suggest that the percentage of clinically affected patients with at least one cardiac event (syncope and/or cardiac arrest) before age 60 is approximately 20%, and only 10% to 14% of patients experience cardiac arrest.[45] Several drugs can exacerbate the ECG pattern and potentially trigger arrhythmias: local anesthetics (bupivacaine), cocaine, α-adrenergic agonists (methoxamine), potassium channel activators (pinacidil), tricyclic antidepressants, opioid analgesics (propoxyphene), lithium, and propofol (www.brugadadrugs.org). Finally, some BrS patients may present with mild right ventricular enlargement and structural abnormalities[38] that may raise the issue of differential diagnosis with arrhythmogenic right ventricular cardiomyopathy.

RISK STRATIFICATION AND THERAPY

ICD is the only proven effective treatment to reduce mortality. Although ICD is clearly indicated in cardiac arrest survivors (class I), the challenge for the clinician is to define when the prophylactic implantation

TABLE 80–4. Brugada Syndrome Clinical Management and Therapy

Recommendations	Class	Level
Brugada syndrome is diagnosed in patients with ST-segment elevation with type 1 morphology ≥ 2 mm in one or more leads among the right precordial leads V_1 and/or V_2 positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after provocative drug test with intravenous administration of sodium channel blockers (such as ajmaline, flecainide, procainamide, or pilsicainide)	I	C
The following lifestyle changes are recommended in all patients with a diagnosis of Brugada syndrome: (a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org) (b) Avoidance of excessive alcohol intake and large meals (c) Prompt treatment of any fever with antipyretic drugs	I	C
ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who (1) are survivors of an aborted cardiac arrest and/or (2) have documented spontaneous sustained VT.	I	C
ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope.	IIa	C
Quinidine or isoproterenol should be considered in patients with Brugada syndrome to treat electrical storms.	IIa	C
Quinidine should be considered in patients who qualify for an ICD but present a contraindication or refuse it and in patients who require treatment for supraventricular arrhythmias.	IIa	C
ICD implantation may be considered in patients with a diagnosis of Brugada syndrome who develop VF during PVS with two or three extra stimuli at two sites.	IIb	C
Catheter ablation may be considered in patients with a history of electrical storm or repeated appropriate ICD shocks.	IIb	C

Abbreviations: ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; PVS, programmed ventricular stimulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

(primary prevention) is indicated (ie, when the benefits overtake the risk of complications). Agreement exists to support ICD use for patients with a history of syncope plus a spontaneously abnormal ECG (ie, a diagnostic ECG without the need to perform a drug challenge) (see Fig. 80–6). These patients have approximately a six-fold increased risk of cardiac arrest compared with the lowest risk category[46] (ie, asymptomatic patients with type 1 ECG only after provocative testing). In these latter cases, the risk of cardiac events is very low (< 1% year), and patients can be reassured with the only indication being regular follow-up to monitor the possible onset of a spontaneous pattern.

Patients with a spontaneous type 1 pattern without history of syncope represent the most difficult scenario. The risk of life-threatening events in these patients is two-fold compared with patients without spontaneous ST-segment elevation.[46] Approximately 40% of patients fall within this group. The inducibility of arrhythmias (VT/VF) at programmed electrical stimulation (PES) has been proposed for these patients, but conflicting results have been published. Overall, the most recent meta-analysis shows that inducibility of VT/VF at PES with up to two extra stimuli is associated with approximately three-fold increased risk of cardiac arrest at follow-up.[47] However, it is important to consider that negative PES patients still have a significant burden of events (approximately 1% year).[47] Thus, ICD implant based on PES has limitations. Among other proposed risk markers, the presence of QRS fragmentation is a promising approach. QRS fragmentation is rarely detected on surface ECG, but when present, it increases the risk of events more than four times (hazard ratio, 4.94; 95% confidence interval, 1.54-15.8).[45] The new ECGI technique may improve the identification of this marker of risk.[43]

Quinidine may prevent arrhythmia inducibility at PES and may prevent the occurrence of cardiac arrhythmias at follow-up.[48] Although encouraging, these results are to be considered preliminary. At present, quinidine is indicated only for the treatment of electrical storm (class IIa) or in patients with contraindications to ICD (class IIa).[10]

SHORT QT SYNDROME

DEFINITION

Short QT syndrome (SQTS) is a rare genetically determined disorder causing arrhythmias and sudden death in the setting of an abnormally short QT interval and structurally normal heart (Fig. 80–9).

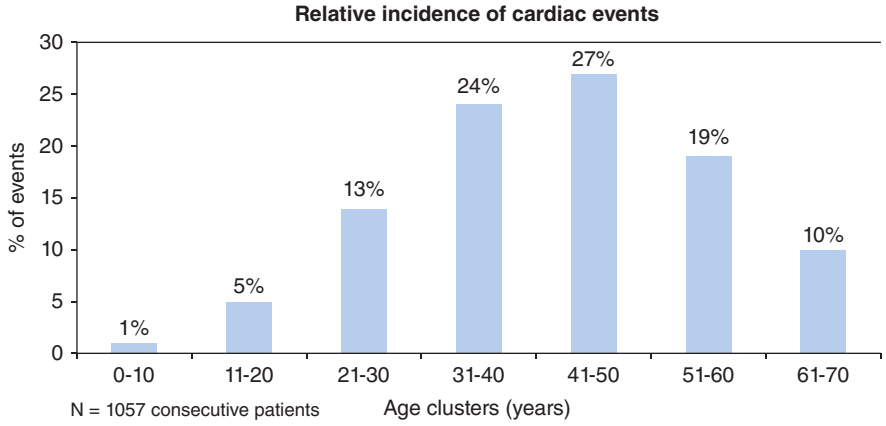

FIGURE 80–8. Age-dependent distribution of cardiac events in Brugada syndrome. The figure shows the relative incidence of combined end point of syncope and cardiac arrest in patients clustered by age (10-year intervals). Data have been obtained from a cohort of consecutive patients enrolled in the Pavia Brugada Syndrome Registry (n = 1057). Overall, there were 269 events (25.4%). Cardiac arrest occurred in 10.1% of patients with a similar age distribution.

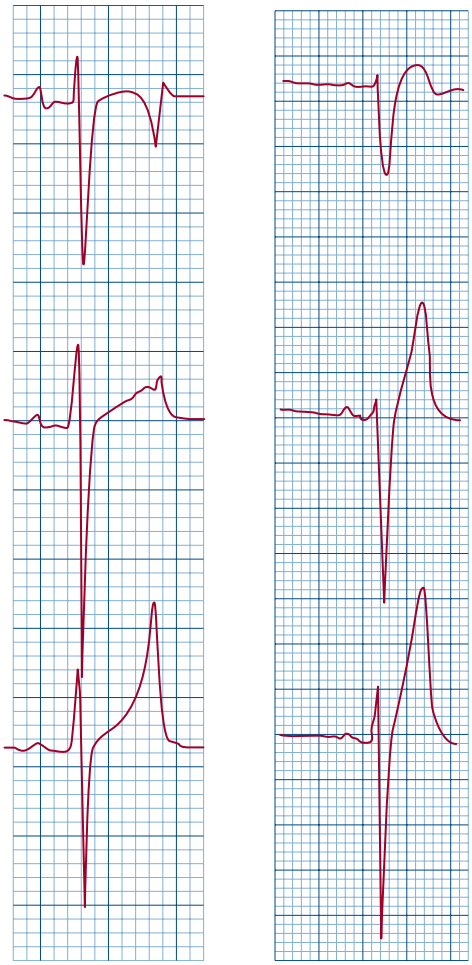

FIGURE 80–9. Examples of typical ST-T patterns in short QT syndrome (SQTS). Leads V_1 to V_3 are reported from a patient with SQTS3 (*left panel*) and SQTS2 (*right panel*).

GENETIC BASIS AND PATHOPHYSIOLOGY

Three SQTS variants manifest with "isolated" short ventricular repolarization. These variants are found in association with gain-of-function mutations in *KCNH2* (SQTS1), *KCNQ1* (SQTS2), and *KCNJ2* (SQTS3).[49] In other instances, short QT interval may coexist with ST-segment elevation in right precordial leads (Brugada ECG pattern). This is the case of loss-of-function mutations in the cardiac calcium channel *CACNA1c* and *CACNB2*. More specifically, *CACNA1c* mutations have been identified in patients with BrS and short QT interval and in patients with isolated SQTS.[49] A single family has been associated with *CACNA2D1* (calcium channel α2/δ subunit), with negative flecainide challenge suggesting that even calcium channel mutations can be associated with isolated short QT interval.[50] The yield of genetic screening in SQTS is limited, and no gene accounts for > 10% of cases. In unselected cohorts of consecutively diagnosed subjects, the mutation can be identified in 10% to 25% of subjects.[49]

The shortening of ventricular repolarization, the hallmark of SQTS, is the marker of action potential shortening at the cellular level. This results in a very short refractory period that has been recognized in patients as well as in experimental studies.[49] In silico three-dimensional modeling and in vitro expression of SQTS mutants has revealed increased tissue temporal vulnerability for initiating reentry and reduced minimal substrate size necessary to sustain reentry.[51] This may explain both the susceptibility to ventricular arrhythmias and atrial fibrillation observed in several SQTS patients.[51]

CLINICAL PRESENTATION AND MANAGEMENT

SQTS can be diagnosed in the presence of QTc < 340 milliseconds (class Ic)[10] and can also be considered (class IIa) in the presence of a QTc ≤ 360 milliseconds and one or more of the following: (1) confirmed pathogenic mutation; (2) family history of SQTS; (3) family history of sudden death at age < 40 years; or (4) survival from a VT/VF episode in the absence of heart disease.

The measurement of QT interval for SQTS diagnosis can be complicated by the lack of QT adaptation to heart rate changes, a common finding in SQTS (flat QT/R-R relationship). It is important to note that the steepness of the Bazett formula for calculating heart rate–corrected QT interval (QTc) may lead to bias with a tendency for overdiagnosis during bradycardia and underdiagnosis when the QT is measured during tachycardia. For this reason, diagnosis in children may be challenging. Ideally, QT interval measurements should be made at heart rates between 55 and 65 bpm and stable heart rate for the best diagnostic accuracy. Tall and peaked T waves (hyperkalemic-like pattern) or asymmetrical T waves with a normal ascending phase and a rapid descending limb are commonly observed (see Fig. 80–9). Furthermore, atrial fibrillation occurs in more than half of SQTS patients. Recent data suggest the presence of mild mechanical impairment (with no apparent clinical implications) in SQTS.[52] This may be a result of the abnormal function of stretch-activated ion channels (secondary to the shortened repolarization) that lead to a dissociation between ventricular repolarization and the end of mechanical systole.[53]

The average cardiac event rate in SQTS is around 1% per year,[49] but cardiac arrests and sudden cardiac death events seem to peak in the first 1 to 2 years of life and subsequently after 25 years of age. There are no predictors of cardiac events in SQTS. Therefore, ICD is indicated for secondary prevention of VF. Furthermore, with the high risk of sudden death and the lack of drugs with documented efficacy, some authors suggest the use of ICD for the primary prevention of VF in all patients. This approach is not justified at present. Alternatively, quinidine seems to be effective in normalizing the QT interval in several SQTS patients and prolonging the ventricular refractory period. More data are required to define whether quinidine can impact mortality in SQTS.

VARIABLE PENETRANCE AND MIXED PHENOTYPES IN CHANNELOPATHIES

Penetrance is defined as the ratio between the number of individuals showing the disease phenotype and the number of carriers of a given mutation. This is a common finding in all IADs. It is usually rather high in more severe conditions such as Timothy syndrome and CPVT, but it may be as low of 30% to 50% for some genes (eg, the average reported penetrance for LQT1 and LQT5 is 55% and 33%, respectively). Variable penetrance should always be considered when assessing families with suspected inherited arrhythmias, and it should prompt the use of genetic testing in all available family members whenever a mutation is identified in the proband. Variable penetrance can be the result of the presence of modulatory genetic factors, known as "genetic modifiers." Population studies demonstrated that the heritable component of various ECG parameters is between 25% and 45% of the total variance, and it includes the QT, RR, and PR intervals and RR variability.[54] Accordingly, QT interval and risk of events in LQTS patients are modulated by single nucleotide polymorphisms (SNPs). Specific data have been observed for few SNPs on the *NOS1AP* gene

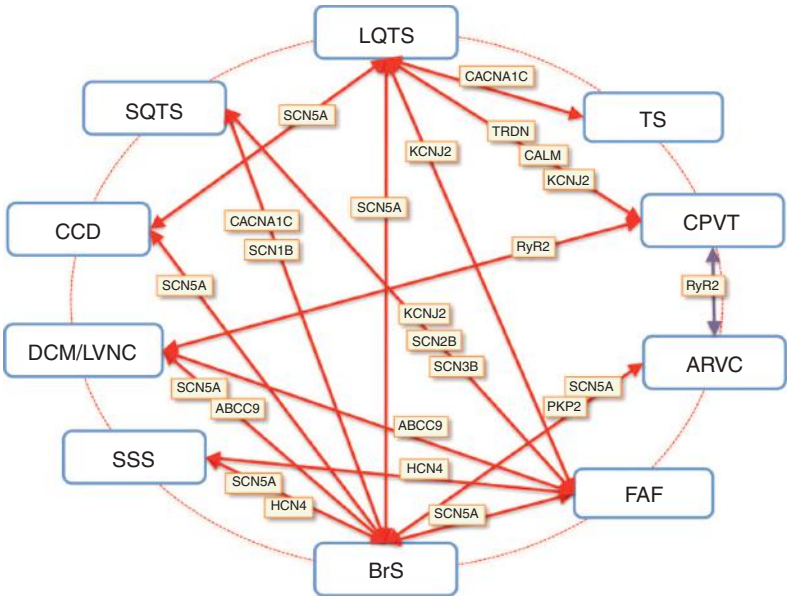

FIGURE 80–10. Schematic representation of overlap phenotypes that can be observed in inherited arrhythmogenic diseases. The connectors represent the combinations of phenotypes reported in the literature. The specific gene(s) involved in one or more cases of overlap phenotype are reported above each connector. ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CCD, cardiac conduction defect; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, Dilated cardiomyopathy; FAF, familial atrial fibrillation; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; SQTS, short QT syndrome; SSS, sick sinus syndrome; TS, Timothy syndrome.

that are associated with a two-fold increased risk of events in LQTS with QTc < 500 milliseconds.[16]

The role of common genetic variants has also been identified for BrS. The evidence that the yield of genetic testing in BrS is low and that familial distribution of the phenotype is less frequent than expected for a Mendelian disorder stimulated a genome-wide linkage study that identified three genetic loci (*SCN10A*-rs10428132, *HEY2*-rs9388451, and *SCN5A*-rs11708996) with an additive effect on the risk of BrS diagnosis. Patients carrying all of the risk alleles (singularly frequent in the population) had an odds ratio of 21.4 of being affected by BrS.[55] In other words, the probability of diagnosis is proportional to the number of common genetic variants concomitantly present in the same subject.

An additional clinically relevant issue is the presence of "overlap" phenotypes and clinical phenocopies. The prototype of these overlap syndromes is represented by *SCN5A* mutations that can cause LQT3, BrS, progressive conduction defects, and dilated cardiomyopathy, all coexisting in the same patient or family.[36] Figure 80–10 schematically outlines the interconnections between clinical entities with possible mixed clinical phenotypes; the figure highlights the web of interplays as a result of mutations of several genes, often causing complex and incompletely understood functional consequences.

Finally, it should be noted that irrespective of the specific clinical diagnosis approximately 4% to 8% of patients harbor two (or more) independently inherited mutations. This possibility should be always considered when dealing with mixed phenotypes or inconsistent cosegregation data within families.

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CHAPTER 81

APPROACH TO THE PATIENT WITH CARDIAC ARRHYTHMIAS

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INTRODUCTION

Cardiac arrhythmias are common in clinical practice,[1] yet their diagnosis and evaluation can be challenging because of diverse presentations[2] and their clinical impact can range from minor to potentially life-threatening. The evaluation must be comprehensive, but should focus initially on a detailed history of episodes and relevant comorbidities, and on ECG documentation of index episodes. Cardiac arrhythmias may present with cardiovascular symptoms such as palpitations or dizziness, but may also present with symptoms from secondarily affected organs such as cryptogenic stroke or peripheral thromboembolism. Important arrhythmias may also be asymptomatic,[3] so that the clinician must maintain a high index of suspicion for these conditions, particularly in individuals with structural heart disease or a family history of unexplained syncope. The purpose of this chapter is to provide a general approach to evaluate patients with arrhythmias, and those who require arrhythmia screening. Other chapters of this textbook will detail the management of specific arrhythmias.

HISTORY

The clinical history is often pivotal in deciphering cardiac arrhythmias. It is important to recognize that arrhythmia symptoms can be diverse and may include palpitations, lightheadedness, chest "discomfort," heart failure, fatigue, or neurological symptoms such as amaurosis fugax. The symptom complex in each individual should be defined for (1) onset, particularly whether sudden or gradual; (2) associated symptoms; (3) potential triggers of episodes; (4) the duration and frequency of episodes; (5) temporal patterns (eg, "Are they improving or not?"); (6) the effect of interventions such as Valsalva or vagal maneuvers such as coughing or swallowing ice,[4] which may terminate some arrhythmias; (7) the effect of prescribed therapy; and (8) family history of similar symptoms, cardiac disease, unexplained syncope, or sudden death.

The history should be pertinent while also considering potential predispositions. For instance, a past history of rheumatic valve disease or thyrotoxicosis may cause atrial fibrillation (AF) in a patient with intermittent palpitations or cryptogenic stroke; a history of myocardial infarction (MI) may cause ventricular arrhythmias[5] in a patient with palpitations or near-syncope; while medications that are known to prolong the QT interval or may produce hypotension may explain dizzy spells. Although alcohol[6] is linked with AF in some patients, this is inconsistent. The link between caffeine[7] and arrhythmias is less clear, and perhaps more clear for sinus tachycardia than supraventricular tachycardias (SVT). Neither alcohol nor caffeine is clearly linked with paroxysmal SVT or sustained ventricular tachycardias. Patients with AF and comorbidities such as obstructive sleep apnea or morbid obesity should be identified *a priori*, because they respond less well to traditional therapy[8] and may require risk factor modification[9] or therapy tailored to specific localized substrate mechanisms such as rotors.[10] Careful attention to descriptions by the patient and accompanying individuals, focused on the items above, provide critical clues to decipher an arrhythmic etiology and guide management.

In evaluating the plan of management for arrhythmia patients, it is critical to those at high risk of serious sequelae such as syncope, sudden cardiac arrest, or heart failure who require expedited evaluation, versus those in whom outpatient evaluation is appropriate. This often involves distinguishing between supraventricular and ventricular arrhythmias, which may differ in their "classical" presentations. Supraventricular tachycardia is likely in a patient with episodic palpitations such as few times per year, with no structural heart disease. SVT may be caused by AV reentry (AVRT), AV node reentry (AVNRT), and atrial tachycardia (AT), which may present differently. For example, tachycardia initiation by bending over or squatting often indicates AVRT or AVNRT rather than AT. Tachycardia with gradual onset or offset is classic for AT, rather than AVRT or AVNRT, which are typically abrupt. Demographic factors may provide clues. In paroxysmal SVT, studies show that older age of onset, female sex, and presence of neck palpitations during tachycardia (from "cannon A waves") favor the diagnosis of AVNRT,[11] while onset of symptoms in childhood favor AVRT. Typically, very fast tachycardia rates of ≥ 250 bpm favor AVNRT rather than AT or AVRT.[12] An irregularly irregular pulse is characteristic of AF, which is classically age-related but recognized in a wider population including athletes or very tall individuals,[13] but can be mimicked by frequent ectopic beats.

PHYSICAL EXAMINATION

The physical examination should focus on the suspected arrhythmia, yet be thorough enough to avoid missing unrecognized arrhythmic comorbidities. This commences with visual inspection, where a malar flush (associated with mitral stenosis) and signs of thyrotoxicosis may suggest atrial fibrillation as the cause of presenting symptoms, classically in a middle-aged woman.[14] A recent sternotomy scar suggests postoperative AF as a cause of palpitations. A patient with visible

shortness of breath and volume overload from heart failure may be at risk for ventricular as well as atrial arrhythmias.

Identification of orthostatic hypotension from the vital signs may explain symptoms in a patient with dizzy spells or syncope. The presence of a carotid bruit or decreased peripheral pulses may guide examination towards coronary artery disease. Detection of occasional cannon A waves in the jugular venous pulse, from near-simultaneous atrial and ventricular contraction, may reveal AV nodal echo beats in a patient with AVNRT or AV dissociation during complete heart block. Signs of cardiac failure and volume overload, such as elevated jugular venous pressure, a displaced apical impulse, S_3 gallop on cardiac auscultation, crackles on pulmonary auscultation, or peripheral edema indicate increased risk for ventricular arrhythmias as well as AF. An S_4 gallop suggests left ventricular hypertrophy associated with AF, but is also consistent with hypertrophic cardiomyopathy with increased risk for ventricular arrhythmias.

Specific arrhythmic syndromes may also be diagnosed, rarely, on physical examination. In a young person with palpitations or near syncope, particularly after squatting or exercise, a jerky pulse and mid-systolic ejection murmur suggest hypertrophic cardiomyopathy. A patient with woolly hair and plantar keratosis likely has Naxos disease,[15] a form of arrhythmogenic right ventricular cardiomyopathy (ARVC) with risk for ventricular arrhythmias; nerve deafness in a patient with syncope requires search for a prolonged QT on the ECG of Jervell and Lange-Nielsen syndrome[16]; while craniofacial abnormalities such as those associated with Noonan syndrome and HCM[17] may suggest ventricular arrhythmias as the cause of symptoms.

The chapter will now focus on some common arrhythmia presentations.

THE PATIENT WITH PALPITATIONS

Palpitations mean different things to different patients, including "strong heartbeats," skipped beats, a sudden thump, "fluttering" in the chest, a rapid pulse that may be detected on a treadmill monitor at the gym, or merely a vague feeling of irregular pulse. Patients often do not detect a premature beat, but instead feel the strong beat after the pause. Notably, patients with one predominant form of "palpitations" may be unable to distinguish it from others. For instance, a patient with palpitations from AF may not be able to distinguish this from atrial or ventricular ectopy,[18] and may even be asymptomatic during some paroxysms of AF.[19] It may be helpful for the physician to "tap out" rhythms—for instance, representing AF by an irregularly irregular cadence, SVT by a rapid regular cadence, extrasystoles by an early beat and then a pause—which are often meaningful to patients. Palpitations that are more prominent at night, especially when patients lie on their left side, are often sinus rhythm.[20] It has been shown that women may present with palpitations from supraventricular tachycardia at particular times during their menstrual cycle.[21] Although the mechanism of this phenomenon remains undefined, it illustrates the importance of dynamic processes on the propensity for arrhythmia initiation.

Patients with a diagnostic ECG rhythm strip or 12-lead ECG—which often can only be obtained from the emergency department—can proceed to risk factor modification, pharmacologic therapy, or ablation. However, in the absence of ECG diagnosis, the urgency of evaluation is determined both by the severity of the presentation and of comorbidities. Patients with structural heart disease, even if asymptomatic, are at increased risk of life-threatening ventricular arrhythmias,[22] and those with syncope and other substantial symptoms should be evaluated as inpatients. Patients with sustained ventricular arrhythmias should be evaluated promptly for the need for ICD implantation,[22] particularly if they have structural heart disease. Conversely, patients with palpitations but without structural heart disease may start with outpatient ambulatory ECG monitoring. In patients with recurrent unexplained palpitations, ambulatory ECG monitoring may provide a higher diagnostic yield more cost-effectively than a traditional evaluation with intermittent Holter monitoring even with invasive electrophysiological study.[23] Data increasingly support the use of extended ambulatory ECG monitoring to detect arrhythmias even in asymptomatic individuals.[24] Many patients are reassured once important causes of palpitations are excluded, even if the precise cause of intermittent symptoms is not known.

THE PATIENT WITH SYNCOPE, NEAR-SYNCOPE, OR DIZZINESS

Patients with syncope, near-syncope, lightheadedness, or dizziness are commonly referred for arrhythmia evaluation. A detailed history is essential. Evaluation must distinguish between true lightheadedness—the sensation that *the lights are going out* or that the patient is about to lose consciousness—versus neurological symptoms such as vertigo, in which the patient feels that the room is spinning. It is essential to document neurological prodromes or sequelae that may suggest the aura or postictal state of seizures, or focal neurological abnormalities that may point to a nonarrhythmic etiology, although stroke may be associated with AF. Although not pathognomic, syncope preceded by palpitations and syncope of sudden onset are often arrhythmic, while syncope with a prodrome may be neurocardiogenic ("vasovagal").[25] Table 81–1 illustrates a clinical scoring system to separate cardiac syncope from seizures.

ECGs from the time of events are often the only way to definitively invoke or exclude an arrhythmic cause of syncope. However, ECGs at other times may suggest causes of syncope such as the acute injury pattern of MI, sinus node dysfunction, forms of AV block or conduction disease, Wolff-Parkinson-White syndrome, long or short QT interval, Brugada syndrome, or hypertrophic cardiomyopathy. An echocardiogram is indicated in most patients (see below), and can identify or exclude reduced left ventricular ejection fraction or other forms of structural heart disease.

The urgency and intensity of evaluation depends upon the severity of comorbidities. A patient with syncope and reduced left ventricular

TABLE 81–1. Historical Criteria that Distinguish Syncope from Seizures (seizures likely for points ≥ 1)

Criteria	Points
Waking with cut tongue	2
Abnormal behavior noted	1
Loss of consciousness with emotional stress	1
Postictal confusion	1
Head turning to one side during loss of consciousness	1
Prodromal déjà vu	1
Any presyncope	−2
Loss of consciousness with prolonged standing or sitting	−2
Diaphoresis before a spell	−2

Modified with permission from Sheldon R1, Rose S, Ritchie D, et al: Historical criteria that distinguish syncope from seizures. *J Am Coll Cardiol*. 2002 Jul 3;40(1):142-148.

ejection fraction should be admitted for workup for ventricular arrhythmias[22] that may lead to ICD implantation or potentially ablation. However, in patients with syncope without structural disease, arrhythmia monitoring using implanted loop recorders (ILR) may be more revealing and cost effective than a traditional strategy even with invasive electrophysiological testing[26] and may improve therapy.[27]

Neurally mediated, or vasovagal syncope is the most common cause of syncope in patients without evidence of cardiac disease.[28] Vasovagal syncope is often associated with a prodrome of nausea, pallor, and diaphoresis, consistent with increased vagal balance. The supine position restores adequate blood flow to the brain and accelerates recovery. However, complete symptomatic recovery may be delayed—sometimes for several hours—as a result of persistent fatigue.

Syncope without prodrome is more common in patients with cardiac disease. Nevertheless, because noncardiac syncope is far more prevalent than cardiac syncope, most patients with sudden-onset syncope still have a noncardiac cause.[29] As a result, the cause of syncope is often not obvious, and 18% to 40% of patients may continue to have unexplained syncope despite a thorough workup.[30] Establishing a diagnosis for syncope is likely to improve with the adoption of ambulatory ECG monitoring[26,27,31] and more focused methods[32] as outlined below.

THE PATIENT WITH FATIGUE OR NONSPECIFIC SYMPTOMS

Arrhythmia patients often present with nonspecific symptoms such as fatigue, atypical chest pain, or dyspnea. This is particularly true for patients with AF, who often do not experience palpitations and present with fatigue or mild shortness of breath. Such patients often consider themselves asymptomatic, and ascribe their symptoms to aging or other factors. The true cause of their symptoms is often established only after a trial of sinus rhythm by cardioversion relieves their fatigue. Fatigue is a less common presentation for patients with sustained supraventricular or ventricular tachycardias, whose episodes are often shorter than in AF.

Fatigue and reduced exercise tolerance may also be harbingers of unrecognized cardiomyopathy. There is a close relationship between AF and cardiomyopathy, and patients with AF have an annual incidence of CHF of 3.3% per year[33] reflecting as yet undefined mechanisms. Cardiomyopathy may also result directly from tachycardia from AF as well as less common arrhythmias such as paroxysmal junctional reciprocating tachycardia in children, which is a form of AVRT with bypass tract located near the coronary sinus. In AF, acute control of ventricular rate[34] often improves heart function.[35] In the subacute setting once the patient is stabilized, there is evidence that ablation of AF may be preferable to restore LVEF and eliminate symptoms.[36]

PATIENTS WITHOUT ARRHYTHMIA SYMPTOMS

Asymptomatic patients may require arrhythmia evaluation if they have documented arrhythmias or are at heightened risk for arrhythmias. Asymptomatic arrhythmias are typically documented serendipitously and, depending upon the arrhythmia, evaluation may be similar to patients with symptoms. In patients with AF, for instance, goals for antithrombotic therapy to prevent thromboembolism[37] or ventricular rate control[38] are similar in patients with or without symptoms. Similarly, sustained VT may be treated similarly whether patients present with palpitations or no symptoms. In other cases, symptoms alter management. Patients with asymptomatic bradycardia or forms of AV block can be followed if daytime awake heart rates are > 40 bpm, but those with symptoms may be indicated for a pacemaker.[22]

Asymptomatic patients who require arrhythmia screening include scenarios such as preexcitation detected on an ECG, newly diagnosed left ventricular dysfunction, patients with documented structural disease such as prior MI or hypertrophic cardiomyopathy, patients with cryptogenic stroke, and patients with bradycardia who may have undetected AV block.

The evaluation and management of patient with asymptomatic preexcitation depends upon their age. For patients over 35 years of age who are truly asymptomatic, the probability of life-threatening arrhythmias is low and conservative management is recommended.[39] Conversely, patients under 35 years of age are more likely to have rapid accessory pathway conduction leading to ventricular arrhythmias and sudden cardiac arrest, and invasive electrophysiology study is recommended with ablation of pathways with a short refractory period (< 250 milliseconds).[40]

Patients with newly diagnosed left ventricular dysfunction are at high risk of malignant arrhythmias[22] and require rapid clinical evaluation by the cardiology service, for consideration of ICD implantation. Patients with recent acute myocardial infarction (MI) should also be screened for arrhythmias although ICD implantation is typically not indicated immediately,[41] but deferred for at least 40 days.[22] Patients in whom the concern of arrhythmic risk in this period is high may be considered for wearable cardioverter-defibrillator therapy.[42]

Asymptomatic patients with various inherited syndromes may require arrhythmia screening. Hypertrophic cardiomyopathy is the most common inherited arrhythmic syndrome, with an incidence of 1 in 500 individuals.[43] Guidelines for managing the risk of serious ventricular arrhythmias in such patients are well established and discussed below in Section Adjunctive Tests to Risk Stratify for Ventricular Arrhythmias on stratifying risk for ventricular arrhythmias. Patients without sustained ventricular arrhythmias should also be assessed for ICD therapy using a tiered approach based on high-risk features of left ventricular thickness > 3.0 cm, history of syncope or aborted sudden cardiac arrest, family history of syncope or sudden cardiac arrest, or other risk factors including nonsustained VT or a hypotensive response to exercise.[44] Scar detected by late gadolinium enhancement on magnetic resonance imaging, which is an interesting modality, may provide supplemental prognostic information.[45] Arrhythmia screening is warranted for other heritable syndromes with a clear structural phenotype, such as arrhythmogenic right ventricular cardiomyopathy, or those with primarily electrical phenotypes such as long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or Brugada syndrome. Family and genetic screening are part of the evaluation in such individuals.

Patients with cryptogenic stroke should be screened for arrhythmias, and are at particular risk for recurrent cerebrovascular events if they have AF. However, the optimal screening strategy in these patients is in flux. Recent work suggests that an ILR greatly improves the diagnostic yield for AF in such patients.[46] It is our practice to perform long-term ECG monitoring in such patients, and then prescribe anticoagulation and rate or rhythm control should AF be detected.[37]

Another important group of asymptomatic patients who require arrhythmia evaluation is those with bradycardia. Careful assessment of the ECG can often separate benign conditions such as sinus bradycardia or Mobitz I AV block from malignant conditions such as Mobitz II or complete AV block. Exercise or isoproterenol will worsen Mobitz II AV block yet classically improve Mobitz I or Wenckebach block. Conversely, atropine may improve Mobitz II block and worsen Wenckebach block. A diagnosis of Mobitz II or complete heart block typically warrants pacemaker therapy.[22] Patients with newly diagnosed high-grade AV block should also be evaluated for sarcoid, amyloid, and Lyme disease in endemic areas.

DIAGNOSTIC TESTS

12-LEAD ELECTROCARDIOGRAM

The electrocardiogram (ECG) is central in establishing the etiology of cardiac arrhythmias. When obtained during an arrhythmia episode, the ECG can be diagnostic (Fig. 81–1). Even if the arrhythmia is not captured, the ECG may help guide the diagnosis via critical data such as preexcitation, abnormal QT intervals, epsilon waves or J-point elevation, or evidence of conducting system disease. The ECG also provides supportive information on contributing factors such as ischemia, electrolyte abnormalities, and prior infarction. Nevertheless, the standard ECG records only 8 to 10 seconds of data, which provide limited sensitivity for episodic arrhythmias including AF, premature beats, or transient AV block. Ambulatory monitoring is often indicated in such patients.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Ambulatory ECGs are increasingly used both to detect and to establish the burden of episodic arrhythmias. Ambulatory ECGs improve sensitivity for detecting AF in patients with cryptogenic stroke[46] or for detecting ventricular arrhythmias in patients with comorbidities such as MI or left ventricular dysfunction at risk for future events.[22] Ambulatory ECGs can help titrate rate control therapy in patients with AF, or document burden or absence of AF after rhythm control strategies such as ablation. The ambulatory ECG can also be used to detect episodic myocardial ischemia from ST-segment shifts, although

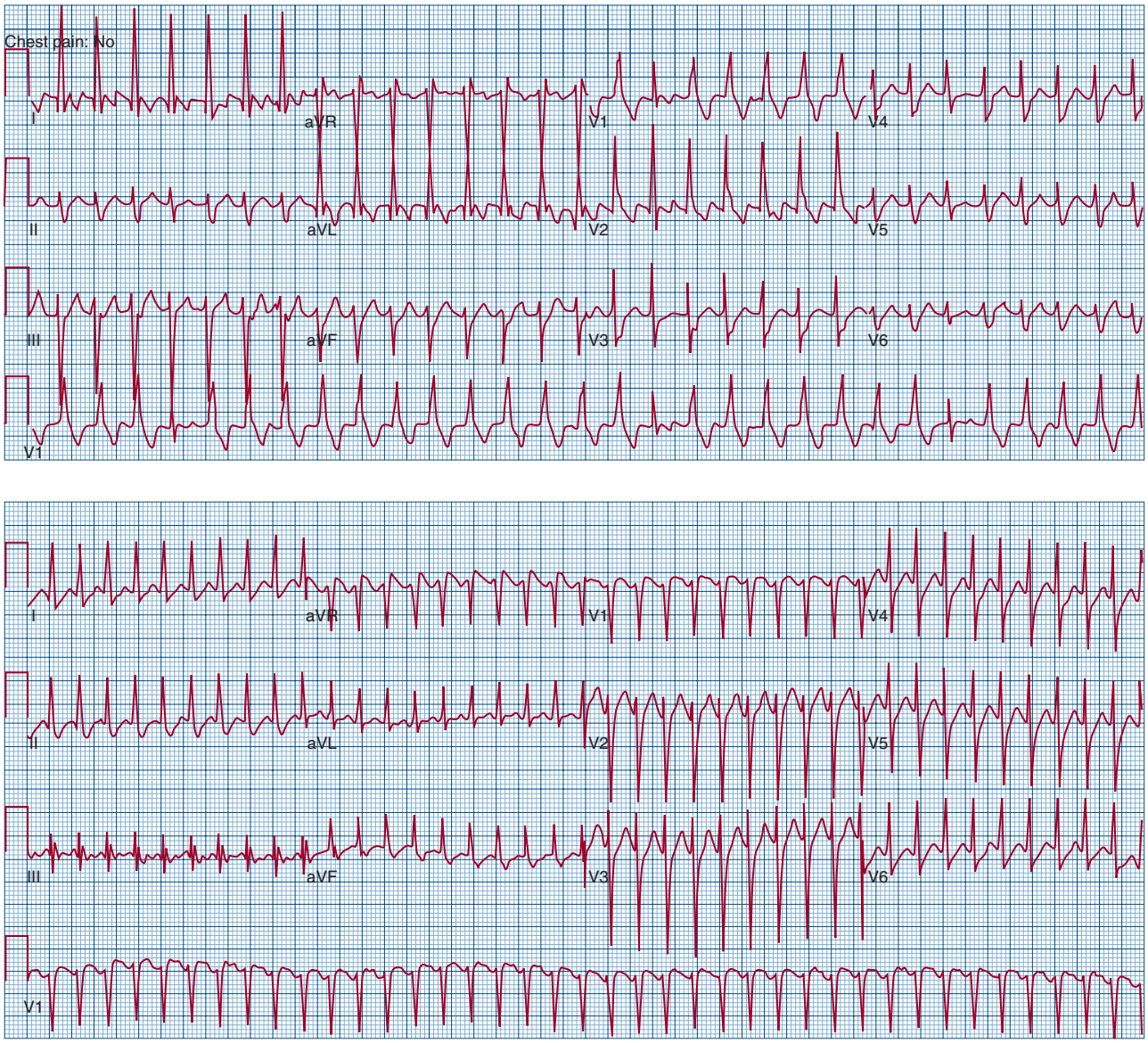


FIGURE 81–1. A. 12-Lead ECG establishes diagnosis of wide-complex tachycardia in a patient with palpitations and near-syncope. Despite QRS complexes that are not bizarre, this tachycardia shows evidence of AV dissociation, a key feature of VT. AV dissociation may manifest in several ways: lack of A–V relationship, fusion beats, or capture beats (capture beats shown in this tracing, particularly evident in lead V_1). Complexes 4, 17, and 25 are narrower than others, and represent capture beats, consistent with AV dissociation and VT. Fascicular tachycardia was diagnosed and subsequently treated by ablation. **B.** 12-Lead ECG can establish diagnosis during narrow-complex tachycardia. This narrow-complex tachycardia in a patient with troublesome palpitations demonstrates P waves at the J-point immediately after the QRS complex, especially in leads II, V_1, and aVF. This "pseudo-RSR" pattern is typical of AVNRT, could be atrial tachycardia with a prolonged PR interval, but largely excludes AV reentry through a bypass tract. Invasive electrophysiological study revealed AVNRT, and this patient was treated by slow pathway ablation.

this may be difficult because of technical factors (eg, nonstandard lead positions) and the fact that ST segments or T waves alter in response to ventilation, eating, anxiety, and medications.[47]

Four types of ambulatory ECG devices are currently available: continuous recorders, intermittent or event recorders, instruments for real-time recording and transmission of ECGs, and implantable recorders (Table 81–2).

Continuous Monitoring

The Holter monitor is a widely available tool that records the ECG continuously typically over 24 hours to 7 days, and improves the sensitivity for detecting arrhythmic events over a standard ECG or exercise testing.[48] Its monitoring duration makes the Holter ideal for daily, or several-times-per-week arrhythmias, whether they are symptomatic or asymptomatic (see Table 81–2). The device is typically physically returned for post-hoc analysis. In-patient telemetry is used to detect arrhythmias during hospitalization often for myocardial infarction (MI) or syncope, but can also document response to therapy, such as with antiarrhythmic medications. These techniques provide a rough estimate of the burden of AF,[49] premature ventricular contractions, and bradycardia. However, these devices are not ideally suited to detect infrequent events that are unlikely to occur during 1- to 7-day recordings, and post-hoc analysis delays the diagnosis, which may be problematic in patients with critical events.

Intermittent Monitoring

Intermittent event monitors can document arrhythmias at times of symptoms, in a patient-activated or patient-triggered mode, or potentially via auto-triggering based upon physiological parameters (eg, heart rate). In distinction, traditional loop recorders capture events that are then marked after the fact. Such intermittent devices can be worn for several weeks, and are thus useful in patients with events occurring every few days to weeks (see Table 81–2). Many event monitors now have automatic triggering, and others allow patients to activate the device retrospectively, ie, immediately after the event. Nevertheless, such noncontinuous recordings may miss events that occur at night, are asymptomatic, or do not meet triggering thresholds.[50] Thus, event monitors poorly estimate arrhythmia burden. Additional limitations include the inability of some patients to keep accurate diaries or transmit symptoms for each event, and missed events because of patient error in activating the device.[46]

The technology for event monitoring is rapidly advancing (see Table 81–2). A newer tool is event monitoring from wearable cardioverter defibrillators (WCDs), prescribed in the short-term to provide

TABLE 81–2. Clinically Available Forms of Ambulatory ECG Recording

Type	Typical Duration	Full ECG Disclosure, Analysis	Transmissibility	Clinical Utility
Continuous				
Holter	1-7 days	Yes. Automated analysis with technician over-read. Trends available.	Typically no. Device physically transferred for analysis.	ECG detection of frequent (near-daily) symptomatic or asymptomatic events, eg, bradycardia, SVT. Estimate burden.
Outpatient Telemetry	14-30 days	Yes. Automated analysis with technician over-read. Trends available.	Typically yes. Transmission is transtelephonic, periodic, or near real-time.	ECG detection of less frequent (weekly) symptomatic or asymptomatic events, eg, bradycardia, SVT. Estimate burden.
Intermittent				
Event Monitor	7-30 days	No. ECG at times of triggered, patient-activated events. Technician over-read. Trends available.	Typically yes. Transmission is transtelephonic, periodic.	ECG detection of symptomatic events that are relatively frequent, eg, bradycardia, SVT.
Wearable Cardioverter Defibrillator (WCD)	1-4 months	No. ECG at times of triggered, patient-activated events. Trends available.	Typically yes. Transmission is transtelephonic.	Patients for possible defibrillator use. ECG detection of infrequent symptomatic or asymptomatic events, eg, VT, bradycardia.
Consumer Devices (eg, Smartphone App)	Minutes, but available over years	No. Currently limited to time of patient activation. Fast changing technology.	Yes. Currently manual.	ECG detection of symptomatic events, eg, bradycardia, SVT.
Real-Time Telemetry				
Inpatient Telemetry	1-3 days	Yes. Automated algorithms. Technician over-read. Trends available.	Yes. Transmission is continuous, real-time.	During hospitalization. Arrhythmia detection, monitor response to therapy.
Outpatient Telemetry	14-30 days	Yes. Automated algorithms. Technician over-read. Trends available. Fast changing technology.	Yes. Transmission is continuous, near real-time (wireless dependent).	ECG documentation of less frequent events, eg, bradycardia, SVT. Estimate burden.
Implanted (Invasive)				
Implantable Loop Recorder (ILR)	2-3 years	No. ECGs at times of triggered parameters. Complete trends and burden assessment.	Yes. Transmission is transtelephonic, periodic.	ECG documentation of even rare events, eg, bradycardia, SVT. Gold standard to define burden, eg, AF, low-grade AV block.

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

life-saving defibrillation in patients at risk for ventricular arrhythmias who have yet to receive an implantable cardioverter-defibrillator (ICD). Such devices can detect ventricular tachycardia and bradyarrhythmias, and enable patient-triggered recordings.[42] Consumer devices are increasingly available as event monitors, including smartphone apps linked to sensors built into a modified phone case. At the time of writing, one device (Alivecor) is FDA-cleared for ambulatory ECG detection and diagnosis. Custom solutions such as this are available at modest cost, are intuitive for the general population, and have been shown to be effective at diagnosing AF.[51] Although formal clinical trial data are lacking, the wide ownership of mobile smart devices means that they are likely to play an increasing role in clinical practice in the near future.

Real-Time Telemetry Monitoring

New devices enable long-term ECG recordings by combining wearable ECG monitors with (near) real-time data transmission over a wireless network, analyzed automatically at a centralized center and over-read by a technician. Commercial systems may consist of three-electrode, two-channel sensors with recording device that intermittently uploads ECG data for near–real-time monitoring.[18] Significant arrhythmias, either symptomatic (patient-triggered) or asymptomatic (auto-triggered), are analyzed by trained personnel. In a randomized prospective trial, one commercial telemetry system was more effective than standard event recorders in diagnosing clinically significant arrhythmia (41% vs 15%, respectively).[24] This modality is likely to play an increasing clinical role in clinical management.

Implantable Continuous Electrocardiogram Monitors

Implantable monitors, also known as implantable loop recorders (ILR), provide long-term outpatient ECG recordings for periods of years, and are ideal to detect rare events missed by other modalities,[23-25,49] such as causes of recurrent infrequent syncope or detection of AF in patients with cryptogenic stroke. They also have value for the care of patients with chronic arrhythmias, or to define arrhythmia burden, eg, of AF after ablation. Such devices are implanted subcutaneously typically near the V_2-V_4 precordial lead positions where P waves can be detected (Fig. 81–2). Devices store summary trend data including heart rates, and record events that are patient-triggered but also auto-triggered based on heart rate and other threshold criteria. Many studies show the ability of very long-term recordings to improve the detection of AF and other arrhythmias compared to traditional recordings, even combined with invasive electrophysiological study, in patients with palpitations or syncope.[26,27,31,46] This modality is becoming more widespread thanks to the ease of inserting ever smaller devices, some of which can be "injected" through millimeter-sized incisions (see Fig. 81–2), and the lack of need for patient compliance with implanted devices. Nevertheless, although risks such as infection or bleeding are uncommon, careful assessment and patient discussion are mandatory before prescribing invasive monitoring.

Device Selection and Limitations

The choice of ambulatory ECG tool depends on individual patient needs (see Table 81–2). Although device functionality is rapidly improving, most are selected for their duration of monitoring. Although one day may be sufficient to assess ventricular rate control in an AF patient, weeks may be needed to titrate oral medications to control ventricular rate or determine if an antiarrhythmic medication has suppressed paroxysmal AF. A continuous monitor is preferable to estimate the burden of ectopy, eg, to ascertain if a patient with premature ventricular contractions merits ablation (often > 10% burden)[52] or to characterize paroxysmal AF. An ILR is required in patients with very infrequent events such as syncope.

Clinical judgement must recognize the limitations of ECG recordings such as artifacts. *Patient-related* artifacts may result from involuntary muscle contractions, such as the Parkinsonian tremor of 4 to 5 Hz that can be mistaken for atrial flutter, or movements such as brushing teeth that can be confused with ventricular tachycardia (Fig. 81–2).[53] *Data recording* artifacts (see Fig. 81–3) are mostly from loose skin-electrode contact, myopotentials, electrical noise, or mechanical stimulation of the electrode.[12] In earlier analog tape systems, battery or motor failure could slow tape speed which, when played back, mimicked tachycardia. This is recognizable by shortening of all ECG intervals (PR, QRS, QT, and R-R). *ECG noise* can result from various devices as a 60 Hz signal, digital ECG amplifiers (that may produce high-frequency artifact), or medical equipment such as infusion pumps and transcutaneous or implanted nerve stimulators. Many artifacts are readily identifiable as nonphysiological. For instance, one can "see through" artifacts for QRS complexes that appear periodically at similar rates before and after the potential event. A high index of clinical suspicion is needed to identify artifacts while avoiding misreading a potential artifact and thus rejecting a real arrhythmic event.

HEAD-UP TILT TABLE TESTING

The head-up tilt table test is a noninvasive study used in the evaluation of syncope. It may be useful in the evaluation of younger patients with a suspected diagnosis of vasovagal syncope, in the evaluation of postural orthostatic tachycardia syndrome (POTS), and to discriminate between reflex and orthostatic hypotension syncope.[54] It consists of footrest-supported head-up tilting to 60 or 70 degrees[55] for 30 to 45 minutes. In patients with vasovagal syncope, this position may lead to venous pooling and loss of consciousness, helping to establish the diagnosis. In some protocols, infusions of isoproterenol[56] or nitroglycerin are used to increase the study sensitivity, at the cost of decreasing specificity. At this time, the role of tilt table testing is not defined in many scenarios and the ideal protocol remains the subject of expert opinion. The clinical role of tilt table testing is outlined in guidelines[54,55] that recognize that the test has limited specificity, sensitivity, and reproducibility.

ECHOCARDIOGRAPHY

Echocardiography is central to evaluating arrhythmia patients.[57] Transthoracic echocardiography (TTE) is widely available, provides excellent anatomic and functional information, and is noninvasive. Transesophageal echocardiography (TEE) is invasive, yet can visualize structures that are poorly imaged by TTE such as left atrial appendage clot. Intracardiac echocardiography (ICE) is typically used intraprocedurally during catheter ablation of arrhythmias.

In patients with supraventricular tachycardias, TTE is important to screen for valvular disease in patients with AF, or other congenital abnormalities, such as Epstein anomaly in patients with right-sided accessory pathways. In patients with AF, left atrial volume enlargement indicates patients with advanced atrial remodeling likely to have a lower success from ablation.[58] TEE is central to discerning left atrial appendage thrombus, for instance in patients with AF being considered for cardioversion.[59] ICE is frequently used during ablation procedures for supraventricular arrhythmias to guide transseptal puncture and visualize catheter position.

In patients with ventricular arrhythmias or syncope, TTE is often used to define left ventricular ejection fraction (LVEF) and cardiac

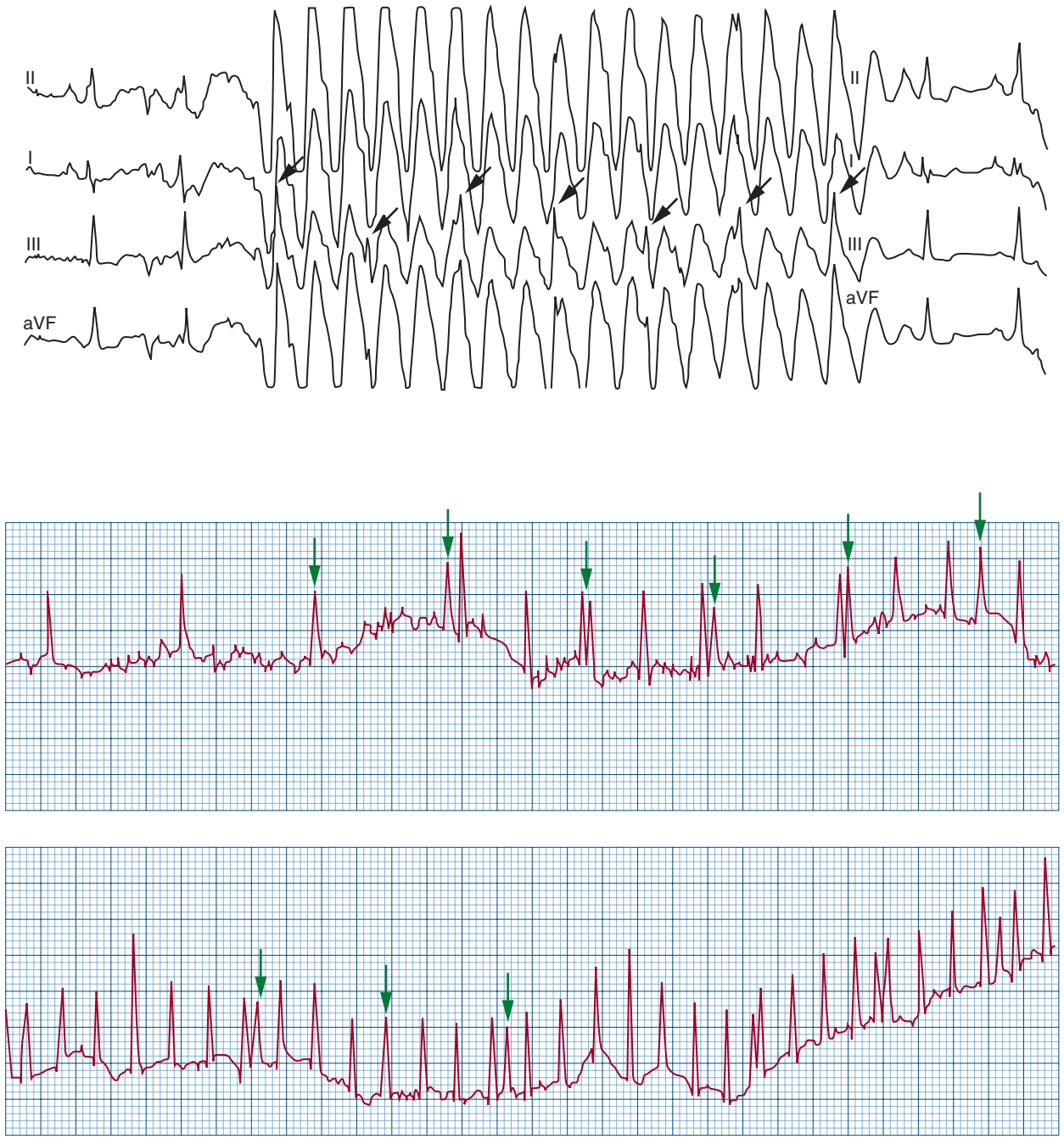


FIGURE 81–2. A. Artifact masquerading as monomorphic ventricular tachycardia. Close inspection reveals QRS complexes at the same rate as the preceding and succeeding sinus rhythm "marching through" the abnormal period. This figure represents sinus rhythm with mechanical artifact. **B.** Artifact that may be mistaken as ventricular tachycardia. Regular QRS complexes at 75 bpm are evident throughout the tracing, confirming the diagnosis of electronic artifact to explain the rapid spikes. **A**, reproduced with permission from Knight BP, Pelosi F, Michaud GF, et al: Clinical Consequences of Electrocardiographic Artifact Mimicking Ventricular Tachycardia. *N Engl J Med*. 1999 Oct 21;341(17):1270-4.

anatomy. Under current guidelines a reduced LVEF alone may be sufficient to prescribe ICD therapy,[22] although other clinical factors should be considered and additional tests are available as described below. TTE may reveal dyssynchrony between septal and lateral left ventricular contraction to help prescribe or tailor resynchronization therapy (eg, biventricular pacing).[57] TTE or TEE may identify LV thrombus[60] in patients with recent myocardial infarction or ventricular aneurysms, which is a contraindication to endocardial ablation or cardioversion. ICE is commonly used during VT ablation to visualize catheter position relative to intracardiac structures such as the papillary muscles, which may be VT sources.

A more thorough discussion of the uses of echocardiography in arrhythmia management can be found in other chapters in this textbook and in current guidelines.[57]

INVASIVE ELECTROPHYSIOLOGIC STUDY AND TESTING

Invasive electrophysiologic study (EPS) and testing is a powerful tool for evaluating tachycardias and bradycardias. EPS has been the cornerstone of diagnostic electrophysiology for decades,[61] and is an integral part of evaluating arrhythmia mechanisms in patients referred for ablative therapy of atrial and/or ventricular arrhythmias. Conversely, the purely diagnostic role of EPS has diminished in many practices, particularly in patients without structural heart disease presenting with palpitations and even syncope, as a result of studies in which extended ambulatory monitoring had a higher diagnostic yield.[26,27]

In a typical EPS, catheters are advanced via the bilateral femoral veins to the right atrium, coronary sinus, right ventricle, and Bundle of His. Electrical signals from the heart are displayed in real time and recorded on a computer for subsequent analysis. Electrophysiologists record baseline conduction characteristics and perform provocative testing with or without pharmacologic agents such as adenosine, isoproterenol, atropine, flecainide, and less commonly procainamide to determine arrhythmia etiology.

In patients with suspected bradycardia, invasive EPS may provide an important assessment of the cardiac conduction system. For SA nodal assessment, pacing is performed at a cycle lengths faster than the baseline heart rate for 30 seconds or more. Pacing is then terminated, and the amount of time for the sinoatrial node to resume pacing activity is measured. After correction for baseline heart rate, sinus node recovery indices can then be compared with normal values[62] to assess for the presence of significant disease. Similarly, in patients with possible atrioventricular node dysfunction, measurement of the His-ventricle (H-V) interval provides important prognostic information. H-V intervals greater than 70 milliseconds identify patients at increased risk of progression to complete heart block; those with H-V intervals greater than 100 milliseconds are at particularly high risk,[63] and pacemaker therapy is indicated.

In patients with suspected supraventricular tachycardia, EPS is performed immediately prior to ablation to evaluate SVT etiology.[39] Baseline characteristics, tachycardia characteristics, and the effect of specific pacing maneuvers are used to define the tachycardia type.[64] Following ablation, EPS is repeated to evaluate the effectiveness of the intervention.

In patients felt to be at risk for ventricular tachycardia, programmed ventricular stimulation may be performed to evaluate the need for an ICD, typically in patients with left ventricular ejection fractions from 35% to 40%.[65] In this context, single-, double-, and triple-extrastimulus pacing is performed at two different baseline rates and two different pacing locations to increase sensitivity. Induction of a sustained (> 30 seconds), monomorphic ventricular tachycardia is considered a positive result in patients with suspected VT, and ICD therapy is indicated.[66]

ADJUNCTIVE TESTS TO RISK STRATIFY FOR VENTRICULAR ARRHYTHMIAS

Patients at risk for life-threatening ventricular arrhythmias and sudden cardiac arrest have diverse profiles. A fundamental dichotomy is that most patients who suffer sudden cardiac arrest have no diagnosed cardiac disease, while current screening for ICD therapy mostly focuses on patients with reduced left ventricular ejection fraction and/or prior MI.[22] Accordingly, risk stratification for sudden cardiac arrest has both limited sensitivity and specificity, and improving this situation is a critical research area.

Expert guidelines recommend ICD therapy for patients with prior life-threatening ventricular arrhythmias, or as primary prevention in patients with structural heart disease, inducible VT on EPS (described earlier) or inherited arrhythmia syndromes.[22] Thus most patients referred for arrhythmic evaluation should have an assessment of left ventricular ejection fraction (LVEF), and those with LVEF < 35% to 40% may warrant ICD therapy. Some experts recommend ambulatory ECG screening for ventricular ectopy or nonsustained ventricular tachycardia, which may guide electrophysiological testing and ICD placement.[67]

It is increasingly recognized that patients with significant competing causes of mortality benefit less from ICDs even if covered by current indications. In particular, the presence of end-stage renal disease, wide QRS duration, advanced congestive cardiac failure, and AF reduce the benefit of the ICD over optimal medical therapy in traditional at-risk populations.[68,69] An inverted U-shaped curve has been reported,[70] in which patients with one or two of these risk factors have the most benefit from an ICD, while those with no risk factors or multiple risk factors benefit less (Fig. 81–3). These factors should be considered during clinical evaluation.

Screening for inherited syndromes is an expansive topic covered in another chapter, but should be considered in young individuals with unexplained syncope or sudden death, with a family history of these events, or with suspicious comorbidities such as dysmorphic features. Guidelines are well developed for some inherited syndromes such as hypertrophic cardiomyopathy,[71] as summarized in Fig. 81–4. Systematic testing can often uncover a diagnosis in patients with inherited arrhythmia syndromes.[32]

There is increasing general interest in the science and practice of improving risk stratification for ventricular arrhythmias. Although it is currently not possible to identify if individual patients will or will not suffer arrhythmias, some clinically available tools will be summarized here.[72] They include indices of abnormal conduction (signal-averaged ECG),

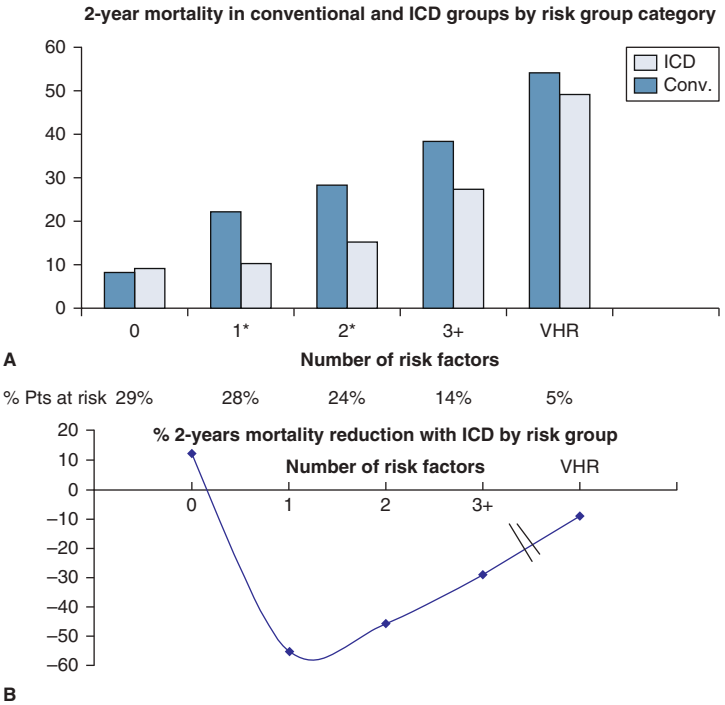
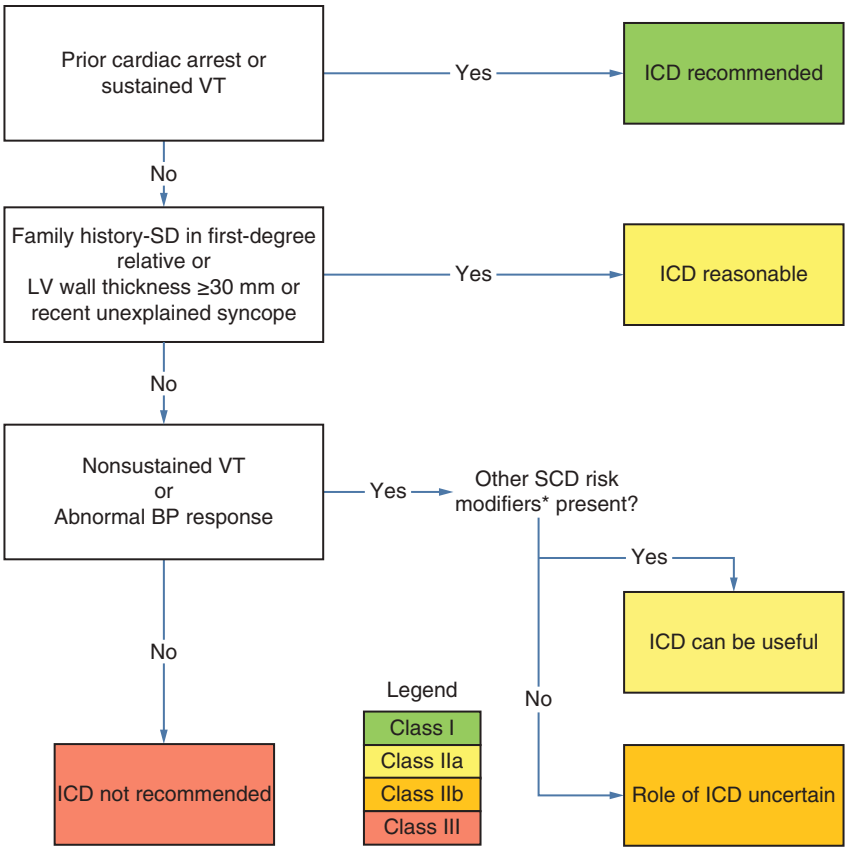


FIGURE 81–3. U-shaped curve for ICD efficacy. **A.** Two-year Kaplan-Meier mortality rates in the ICD and conventional therapy groups. **B.** The corresponding 2-year mortality rate reduction with an ICD, by risk score and in VHR patients. *$P < .05$ for the comparison between the conventional therapy and ICD groups. Reproduced with permission from Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol*. 2008 Jan 22;51(3):288-296.



Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, thorough discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.

FIGURE 81–4. Guideline recommendations in patients with hypertrophic cardiomyopathy for evaluating the need for ICD implantation. Reproduced with permission from Gersh BJ, Maron BJ, Bonow RO, et al: 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2011 Dec 13;58(25):e212-e260.

indices of abnormal repolarization (in particular microvolt changes in the T wave), and measures of unfavorable autonomic balance.

The Signal-Averaged Electrocardiogram

The signal-averaged ECG (SAECG) identifies abnormal and delayed ventricular conduction, that may indicate scar from MI or structural disease such as fibrofatty infiltration from ARVC.[73] The SAECG is measured in sinus rhythm, using signal averaging and filtering to identify small visually undetectable signals (Fig. 81–5). The SAECG detects low-amplitude signals occurring late in the QRS complex that may reflect slow conduction near diseased myocardium, which may predispose to reentry.[74] The three main criteria are prolonged filtered QRS duration, a small root-mean-square voltage of terminal 40 milliseconds of the QRS (RMS40), and prolonged duration of this small late signal (LAS) > 40 mV. The SAECG predicted ICD therapy in the MUSTT trial, but is currently of adjunctive value.[22,72]

T-Wave Alternans

T-wave alternans (TWA) is an ECG measure of beat-to-beat oscillations in the T wave on an alternating beat-to-beat basis.[75] Such oscillations have long been linked with arrhythmias (Fig. 81–6), and reflect dispersion of repolarization in animal models[75] and human heart[76] and risk for ventricular arrhythmias.

TWA can be assessed in many ways. In the long QT syndrome, visible T-wave alternans may occur. In patients with structural disease, subtle oscillations can be revealed as microvolt-level TWA, which has high negative predictive value for ventricular arrhythmias. In patients with ICD indications, ie, LVEF < 35%, individuals with negative TWA have a low (< 5%) risk of sudden cardiac arrest in a 1-year period. Patients with relatively preserved LVEF (35%-45%) with a positive TWA test may also be at higher risk for ventricular arrhythmias.[77] The use of TWA has a class II indication in managing patients at risk for ventricular arrhythmias.[22]

Autonomic Evaluation

Autonomic dysfunction may contribute to the initiation of arrhythmias, yet the extent to which current tools can alter clinical management is debated. Heart rate variability (HRV) is the prototype, which measures variability in sinus cycle length. Traditional methods calculate the R-R interval over prolonged periods (24 hours) and measure the standard deviation of normal-to-normal beats as SDNN. Several studies show that reduced HRV < 100 milliseconds is associated with increased mortality.[72]

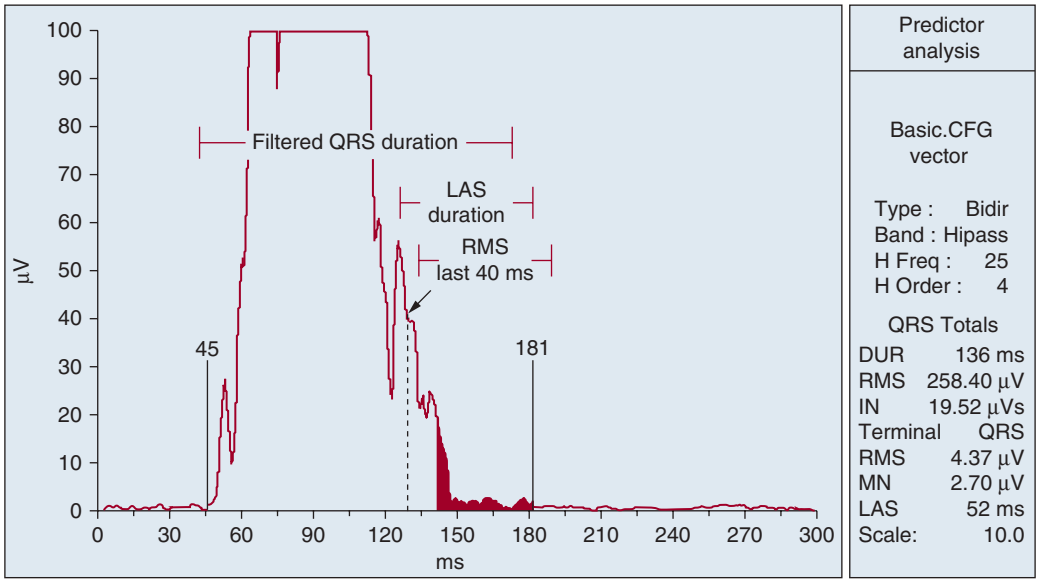


FIGURE 81–5. Signal-averaged ECG. The ECG is recorded from three orthogonal Frank leads, then averaged over > 200 beats and filtered. A representative tracing is shown and analyzed for a late small signal (late potential) as well as prolonged overall filtered QRS duration.

In one study, post-MI patients with SDNN < 50 milliseconds have a 5.3 times higher mortality risk than those with HRV > 100 milliseconds. This risk is maintained in post-MI patients with LVEF ≤ 40%.[78] An alternative test is to create a power spectrum of HRV. Three spectral components can be identified: (1) very low frequency (< 0.04 Hz), (2) low frequency (0.04-0.15 Hz), and (3) high frequency (0.15-0.40 Hz).[78] An increased ratio of low-frequency components (sympathetic balance) to high-frequency components (parasympathetic balance) is associated with unfavorable prognosis. HRV can be obtained from Holter monitors and contemporary implanted devices.

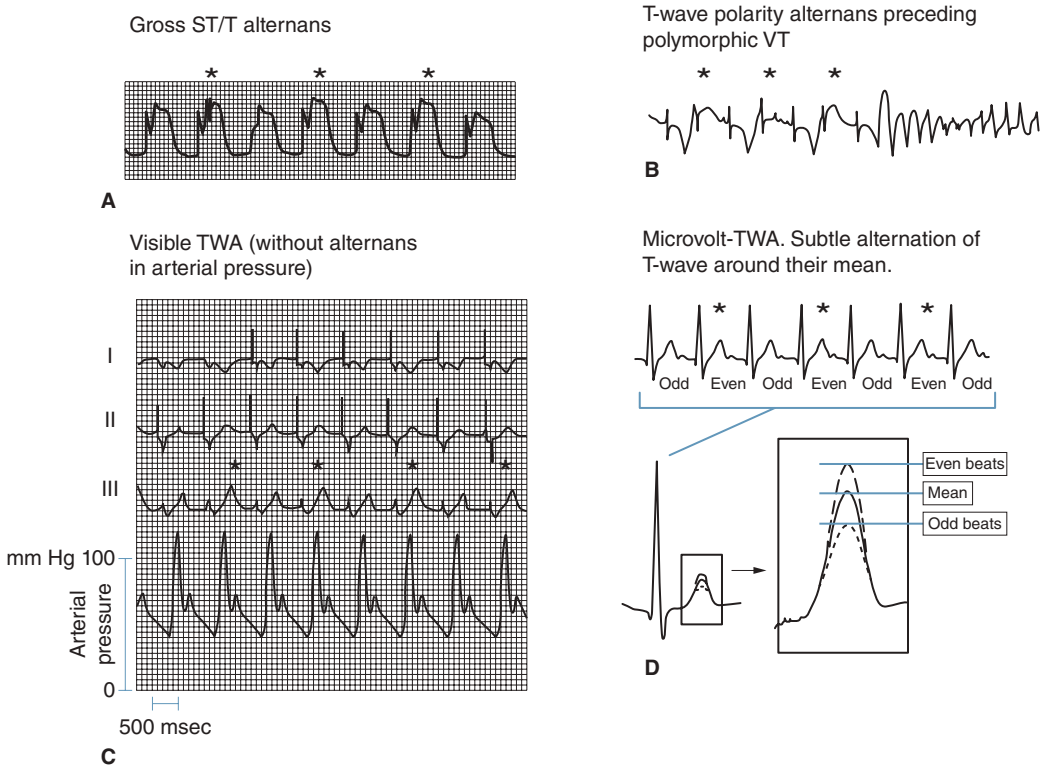


FIGURE 81–6. Clinical utility of T-wave alternans (TWA), documented in diverse scenarios over time. **A.** *Gross alternans* of elevated ST/T segments in a patient with angina pectoris preceding ventricular tachycardia. **B.** *Visible alternans* of T-wave polarity in a woman without angina, heralding polymorphic VT. **C.** *Subtle but visible TWA* after tachycardia termination, without arterial pressure alternans (bottom). **D.** *Visually inapparent microvolt-level TWA*, uncovered by digital signal processing. *The more positive T wave of each alternating pair. Reproduced with permission from Narayan SM: T-wave alternans and the susceptibility to ventricular arrhythmias. *J Am Coll Cardiol*. 2006 Jan 17;47(2):269-281.

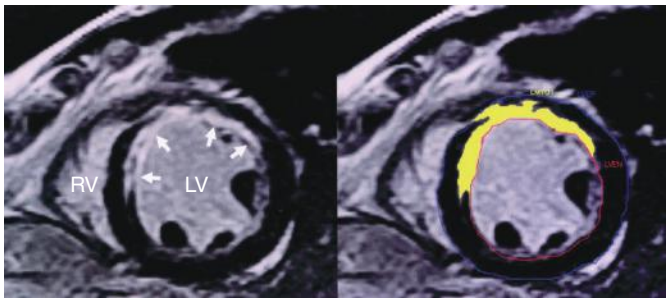
Autonomic tone can also be assessed by baroreflex sensitivity (BRS), which measures the reflex slowing in heart rate prompted by rises in blood pressure, typically measured in response to phenylephrine infusion. Reduced BRS may indicate risk for VF. In the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study of 1284 patients after MI, multivariate risk of cardiac mortality was 2.8 for BRS < 3 ms/mm Hg, and 3.2 for SDNN < 70 milliseconds. Mortality was 17% for patients with BRS < 3 ms/mm Hg and SDNN < 70 milliseconds, versus 2% for patients with BRS > 3 ms/mm Hg and SDNN > 70 milliseconds. In patients with CHF, depressed BRS is associated with a higher NYHA class and predicts cardiac events.

Baroreflex sensitivity can also be measured indirectly by heart rate turbulence (HRT), in which premature ventricular (or atrial) beats cause oscillations ("turbulence") in heart rates. Two metrics are turbulence onset and turbulence slope.[79] Both heart rate turbulence indices are associated with mortality in patients with prior MI[80] and dilated cardiomyopathy.[79] These indices are available from some ambulatory ECG and implanted devices, and are also adjuncts to clinical evaluation.

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging has an increasing role in arrhythmia management. In addition to detailed information regarding cardiac structure and function, CMR can quantify and localize myocardial scar. For patients with coronary disease, the presence of extensive ventricular scar may indicate increased risk for ventricular arrhythmias[81] via stabilization of arrhythmia-sustaining mechanisms.[82] Similarly, in patients with hypertrophic cardiomyopathy, CMR identification of ventricular scar may help determine eligibility for ICD therapy (Fig. 81–7A).[83] CMR may also assist in the diagnosis of conditions such as ARVC,[84] and may help risk stratify mutation carriers.[85]

In patients in whom electrophysiologic procedures are planned, CMR images may be incorporated into electroanatomic mapping



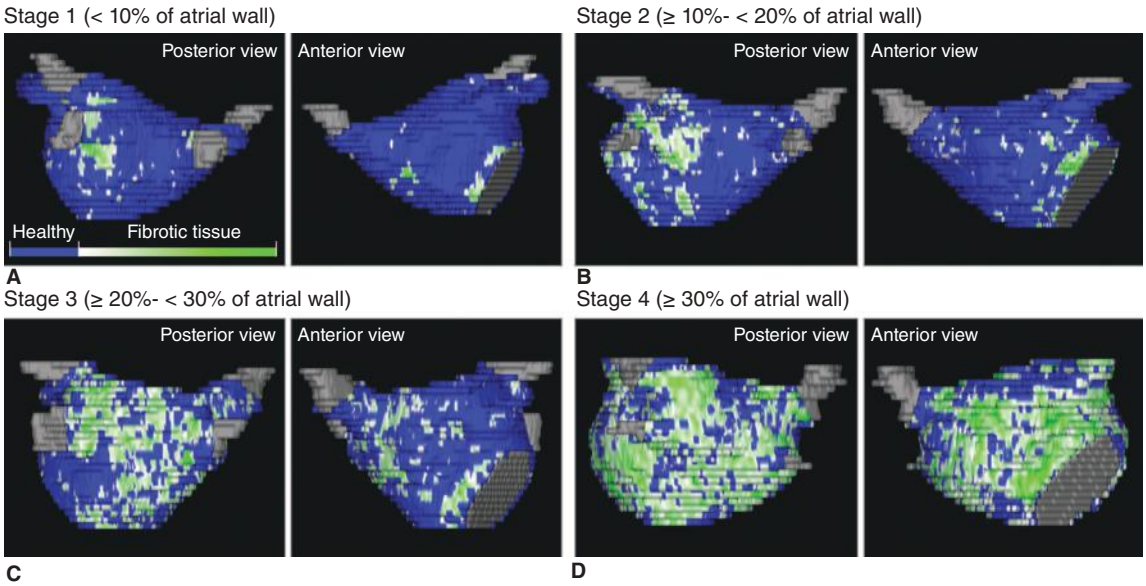


FIGURE 81–7. A. Left ventricular scar as late enhancement on cardiac magnetic resonance. Increasing LV scar is correlated with an increased risk of ventricular arrhythmias. (Reproduced with permission from Kwong RY, Chan AK, Brown KA, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation*. 2006 Jun 13;113(23):2733-2743.) **B.** Four stages of left atrial tissue fibrosis based on 3D delayed enhancement magnetic resonance imaging. Increasing percentages of LA fibrosis are correlated with progressively increasing risk of AF recurrence after AF ablation. Normal left atrial wall is displayed in *blue*; fibrotic changes are in *green* and *white*. (Reproduced with permission from Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF stud, JAMA. 2014 Feb 5;311(5):498-506.) **C.** Integration of coronary artery anatomy from computed tomography in commercially available electroanatomic map during epicardial ablation. Multimodality image integration is routinely used in electrophysiological studies and ablation, providing the advantages of structural/functional characterization of tissue, increasing safety during navigation of catheters within or external to the patient's heart, and decreasing use of traditional fluoroscopy. (Reproduced with permission from Zeppenfeld K, Tops LF, Bax JJ, et al: Images in cardiovascular medicine. Epicardial radiofrequency catheter ablation of ventricular tachycardia in the vicinity of coronary arteries is facilitated by fusion of 3-dimensional electroanatomical mapping with multislice computed tomography. *Circulation*. 2006 Jul 18;114(3):e51-e52.) (*continued*)

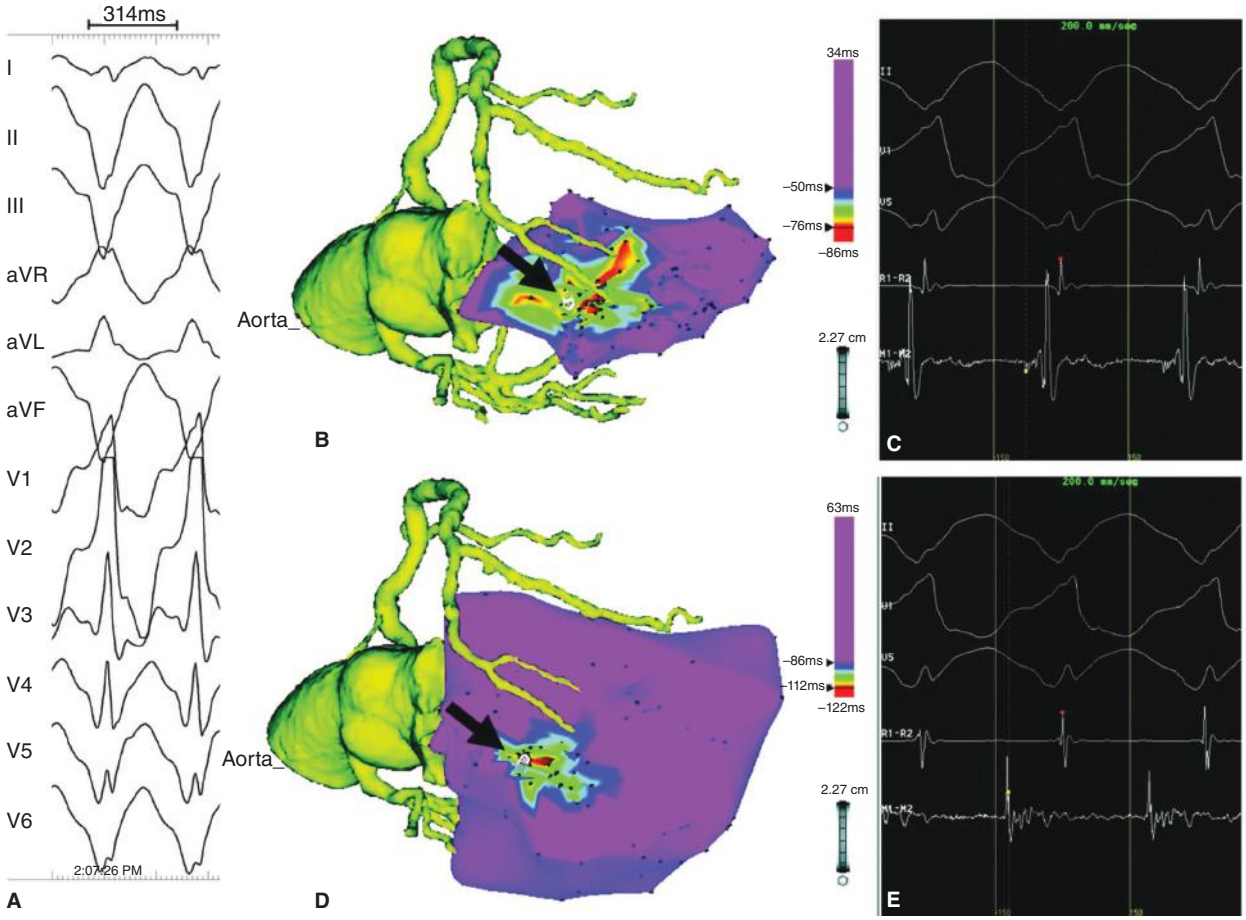


FIGURE 81–7. (*Continued*)

systems to facilitate catheter navigation and guide ablation.[86] Investigators have proposed the noninvasive identification of VT circuits with CMR to facilitate ablation.[87]

Individuals with AF often have structural atrial disease, and emerging data show that gadolinium enhancement on atrial CMR (Fig. 81–7B) may indicate atrial fibrosis or scar.[88] Such atrial structural abnormalities may predict the occurrence of atrial substrates remote from the pulmonary veins, potentially including rotors,[89] and may help to guide AF ablation.[88] CMR has also been used to analyze atrial function post ablation,[90] which may be pertinent in patients with shortness of breath or heart failure from suspected left atrial dysfunction.[91]

COMPUTED TOMOGRAPHY

Computed tomography (CT) is an increasingly helpful tool in evaluating patients with cardiac arrhythmias. The detailed images from CT can be used to help define patient-specific anatomy prior to invasive electrophysiology study and ablation. Images from adjoining "slices" are combined to form three-dimensional models that are then integrated into real-time mapping systems (Fig. 81–7C).[92] They may be particularly useful in understanding the complex anatomy in patients with congenital heart disease after surgical repair with arrhythmias undergoing ablation.[93] Additionally, defining the location of scar in patients undergoing ventricular tachycardia (VT) ablation,[92] and localizing the coronary arteries in patients having an epicardial VT ablation[94] (see Fig. 81–8C), may help reduce fluoroscopy use and increase procedural success.

INCREMENTAL VALUE OF MAGNETIC RESONANCE IMAGING AND COMPUTED TOMOGRAPHY IMAGING OVER ECHOCARDIOGRAPHY IN ARRHYTHMIA MANAGEMENT

CMR and cardiac CT provide data beyond those presently available from echocardiography. As noted above, MRI[81,83] and more recently CT with appropriate protocols[92,94] provide information regarding the presence and extent of myocardial scar, which may help risk-stratify patients with ischemic cardiomyopathy or hypertrophic cardiomyopathy. MRI may also be used to assess for infiltrative diseases or myocarditis. It is currently the test of choice for the diagnosis of cardiac sarcoidosis,[95] which may predispose patients for heart block and ventricular arrhythmias, and is useful in staging patients with Chagas disease,[96] who are susceptible to ventricular arrhythmias. Cardiac CT can provide important information regarding coronary sinus anatomy,[97] which may be important in left ventricular lead implantation. Both MRI and CT are recommended to assess for pulmonary vein stenosis following atrial fibrillation ablation.[98]

BIOMARKERS IN ARRHYTHMIA MANAGEMENT

Biomarkers are an emerging clinical tool to track pathophysiologic mechanisms for atrial and ventricular arrhythmias. Accordingly, biomarkers have the promise of identifying patients at high risk for arrhythmias, although they are currently the subject of clinical research.

For atrial arrhythmias, incident AF may be predicted by elevated B-type natriuretic peptide (BNP), which likely reflects stretch of the

atria or ventricles; or by C-reactive protein (CRP), which measures inflammation.[99] Increased galectin-3, a marker of atrial fibrosis, is also associated with an increased risk of AF.[100]

For ventricular arrhythmias, BNP may add to the predictive value of low LVEF for sudden cardiac arrest, with a cutpoint of BNP ≥ 23 pg/mL (lower than typical predictive cutpoints for heart failure), the most powerful predictor for ventricular arrhythmias in one prospective study.[101] Combinations of biomarkers may increase the specificity of testing; elevated sST2 and NT-proBNP concentrations are more predictive of sudden cardiac arrest in patients with HF than either alone.[102] Plasma osteopontin and galectin-3 are attracting attention as predictors for sustained ventricular tachycardia/ventricular fibrillation, as shown in many populations including ICD patients even after adjusting for clinical factors including reduced LVEF.[103]

Biomarkers may also have a role in evaluating the progression or regression of heart failure. In patients receiving cardiac resynchronization therapy (ie, biventricular pacing), elevated BNP levels following device implantation are more likely in nonresponders than in responders.[104] Recently, microRNA expression of factors that regulate cardiac fibrosis, apoptosis, and hypertrophy have been shown to indicate a favorable response to resynchronization therapy.[105]

At this time, the clinical role of biomarkers remains investigational. However, the development of biomarker panels, or their use in combination with other functional or imaging studies, may soon allow such tests to establish a clinical role.

SUMMARY

Patients with cardiac arrhythmias can present with diverse symptoms, ranging from palpitations, dizziness, or syncope, to stroke or sudden cardiac arrest. The main components of evaluating an arrhythmia patient include a detailed history and analysis of ECGs at the time of events. Further workup is based on the severity of the presenting condition and comorbidities, and may comprise noninvasive imaging, ambulatory ECGs, and various other modalities. Rapid technological advances, including developments in wearable technologies to detect arrhythmias, improved functional imaging, and novel biomarkers, may dramatically improve the evaluation of arrhythmia patients in coming years.

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CHAPTER 82

INVASIVE DIAGNOSTIC ELECTROPHYSIOLOGY

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INTRODUCTION

Electrophysiology studies (EPS) are minimally invasive procedures utilized for the diagnosis and treatment of cardiac arrhythmias. They can provide insight into the mechanism underlying a variety of cardiac rhythm disorders when noninvasive testing has been unrevealing. Abnormal findings often require device therapy or catheter ablation, which is often performed concomitantly with EPS.

INVASIVE DIAGNOSTIC ELECTROPHYSIOLOGY STUDIES

INDICATIONS FOR ELECTROPHYSIOLOGY STUDIES

EPS is recommended when noninvasive investigations do not establish the diagnosis or etiology of arrhythmia and the result will change the clinical management. It is indicated for the evaluation of documented or suspected bradyarrhythmias and tachyarrhythmias, syncope, and for risk stratification of individuals at risk for sudden cardiac death (SCD).[1,2] Indications are summarized in Table 82–1. EPS should not be performed in patients who have unstable angina, systemic infection, deep venous thrombosis in the region of venous access, or any other medical condition where the risks of the procedure outweigh the benefits derived from testing.

TECHNIQUE

EPS involves placing catheters equipped with electrodes at the tip in the right atrium, right ventricle, coronary sinus, and the His region. AV node activity cannot be measured directly, and therefore, His region conduction, which is situated immediately adjacent to the AV node, is used as an indirect way to measure conduction properties of the AV node.

Fluoroscopy is used for placement of catheters (Fig. 82–1), which are typically inserted into the venous system through femoral venous access but also can be inserted through the internal jugular or subclavian veins.

The electrodes at the catheter tips are used to sense and pace cardiac tissue so that the conduction properties of the heart can be studied at baseline, with pacing, following drug infusion, and during tachycardia.

COMPLICATIONS

In the present era, EPS is commonly performed concomitantly with catheter ablation, particularly for supraventricular or ventricular arrhythmias. Complications associated with EPS alone, without catheter ablation, include cardiac perforation (0.2%), vascular access complications (0.4%), thromboembolic events (~0.5%), thrombophlebitis (0.6%), and mortality (0.1%).[3,4] Nonetheless, patients should not be exposed even to this minimal risk if there is no benefit expected from EPS.

INTRACARDIAC ELECTROGRAMS

During EPS, intracardiac electrograms from various locations in the heart, along with the 12-lead surface electrocardiogram (ECG), are recorded and displayed to the physician. The AH interval is measured between the atrial and His electrograms on the His catheter and corresponds to conduction time from the low interatrial septum to the His, which is an indirect measure of AV node conduction (Fig. 82–2). The normal AH interval during sinus rhythm is approximately 55 to 130 msec.[5] The AH interval varies with autonomic tone. Increased vagal tone would increase the AH interval, whereas increased sympathetic or decreased vagal tone would shorten it.[6,7] Therefore, a prolonged AH measurement out of the normal range should not be seen as pathological but should rather increase the suspicion of AV node disease.

The HV interval is measured between the His deflection and the earliest ventricular signal, either on the surface ECG or ventricular electrogram recorded on the His catheter. The HV interval is not affected by autonomic tone and the normal range is 35 to 55 milliseconds.[5] Abnormal baseline intervals could suggest a pathology, for example in manifested preexcitation, Wolff-Parkinson-White syndrome (WPW), the HV interval is often noticed to be < 35 milliseconds (Fig. 82–3).

After assessment of baseline conduction intervals, programmed electrical stimulation is performed from the atrium and ventricle with or without drug infusion. Burst pacing at a fixed or decremental cycle length is performed followed by delivery of extrastimuli. This involves pacing at fixed rate for several beats (≥ 8 beats) followed by delivery of single or multiple premature extra stimuli at progressively earlier intervals. These maneuvers can distinguish between normal and pathological conduction and refractory properties of cardiac tissue and can also facilitate arrhythmia induction.

BRADYARRHYTHMIAS

The pathophysiology, diagnosis, and management of bradyarrhythmias are discussed in Chapter 86. The role of EPS in the diagnosis of sinus node dysfunction, AV node, and His-Purkinje disease will be discussed next. The normal conduction system and sites of electrical block along with sites of normal or abnormal automaticity are shown in Fig. 82–4.

TABLE 82–1. Indications for Diagnostic Electrophysiology Studies

Bradyarrhythmias: For the diagnosis and management of suspected or documented bradyarrhythmias when noninvasive testing has been inconclusive.

- Evaluation of sinus node function in patients with suspected sick sinus syndrome—suggested by the presence of a prolonged SNRT (> 1500 ms) and inappropriate sinus bradycardia.
- Assessment of the level of AV conduction abnormality in patients with bifascicular or intermittent AV block—induction of infra-nodal block (either intra- or infra-Hisian), or an HV interval > 100 ms are abnormal findings.

Tachyarrhythmias: For the diagnosis and management when noninvasive testing has been inconclusive.

- Delineate of the mechanism of narrow-complex tachycardia.
- Delineate the mechanism of wide-complex tachycardia.
- Define of the mechanism of narrow- or wide-complex tachycardia for catheter ablation.

Syncope

- Assessment sinus node function and AV conduction in patients with syncope.
- Evaluation for tachyarrhythmias (SVT or VT) as a potential cause of syncope in patients presenting with palpitations associated with syncope.
- Evaluation of syncope in patients with structural heart disease.
- Evaluation of syncope of unclear etiology.
- Evaluation of syncope in high-risk occupations—airline pilots, bus drivers, etc.

Risk Stratification

- Patients with coronary artery disease, depressed LVEF (< 40%), and nonsustained VT—induction of sustained VT or VF is an indication for ICD.
- Brugada syndrome—the role of electrophysiology study for VT/VF induction and risk stratification is controversial.
- Wolff-Parkinson-White syndrome—when pre-excitation persists with exercise on stress testing.

Other

- Assessment for VT or VF in patients with a suspected risk of arrhythmic sudden death.
- Survivors of sudden cardiac death without a clear cause.

AV, atrioventricular; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; SNRT, sinus node recovery time; SVT, supraventricular tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation.

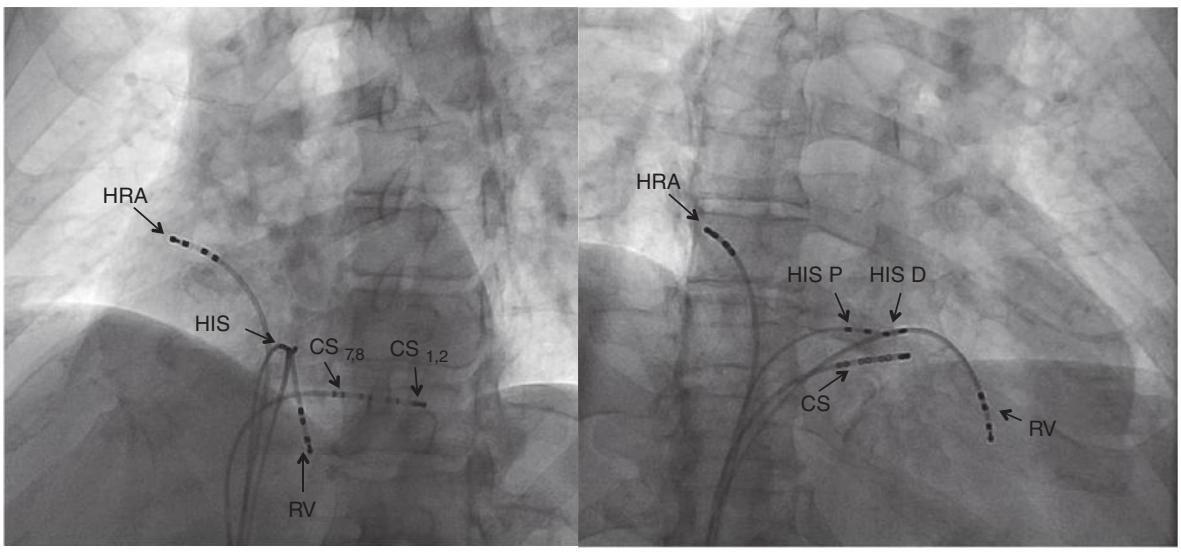

FIGURE 82–1. A. Left anterior oblique projection with catheters positioned in the high right atrium (HRA), His, right ventricular (RV) apex, and coronary sinus (CS) is shown in a patient undergoing comprehensive diagnostic electrophysiology study. $CS_{1,2}$ represents the distal poles of the CS catheter, which is located near the lateral mitral annulus, and $CS_{7,8}$ are the proximal poles, which are positioned near the CS ostium. **B.** The catheter positions are also seen in this right anterior oblique position. The proximal (HIS P) and distal (HIS D) poles of the His catheter are seen in this view.

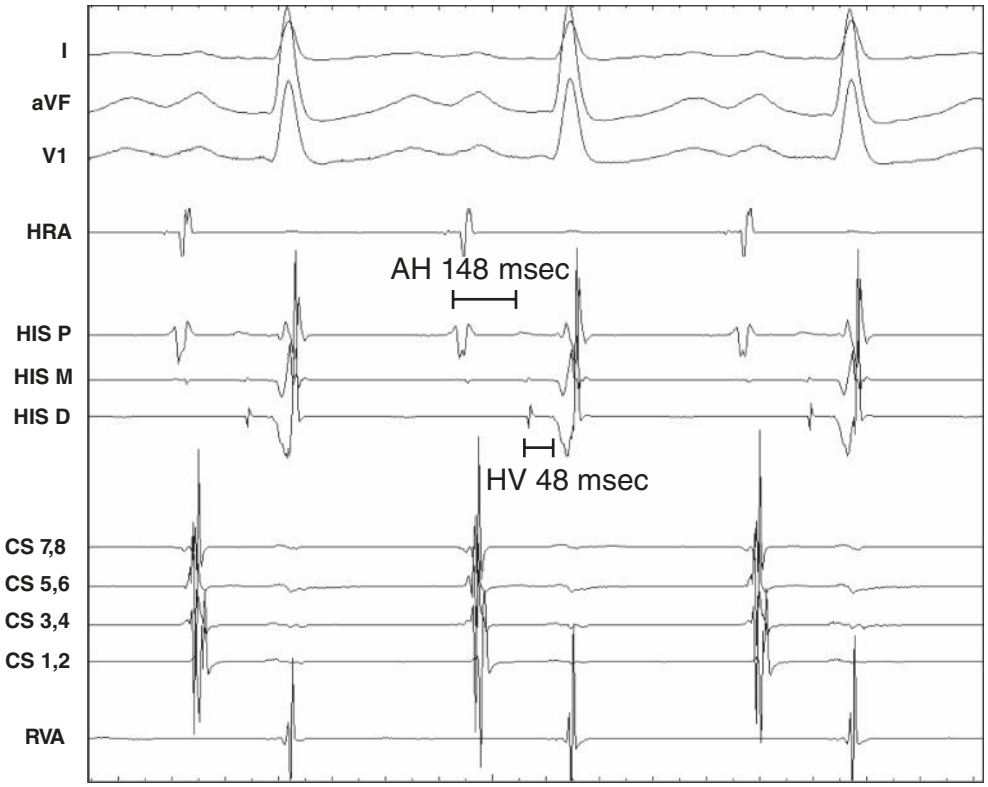

FIGURE 82–2. Normal baseline intracardiac electrograms are shown. There are three surface ECG leads seen (I, aVF, V_1) at the top of the tracing. Intracardiac electrograms are recorded from the high right atrium (HRA), His (proximal [P], mid [M], and distal [D] electrodes), coronary sinus (CS), and right ventricular apex (RVA). Atrial electrograms can be identified as they line up vertically with the surface P wave (seen on HRA, His, and CS). Similarly ventricular electrograms demonstrate vertical alignment with the surface QRS (seen on HIS, far-field electrograms on CS, and on RVA). The His electrogram is seen on the HIS catheter and is a sharp deflection located between the atrial and ventricular electrograms. In this patient, the intracardiac intervals are normal with an AH interval of 148 milliseconds and an HV interval of 48 milliseconds. CS 1,2 represents distal coronary sinus position near the lateral mitral annulus, and CS 7,8 represents proximal coronary sinus position near the ostium.

FIGURE 82–3. Baseline intracardiac electrograms of a patient with Wolff-Parkinson-White syndrome are shown. Preexcitation is evident in the surface ECG leads. The HV interval is negative (–16 milliseconds) and is consistent with ventricular preexcitation. The *dashed line* represents onset of QRS, and the *solid line* represents onset of the His electrogram. HRA, high right atrium; HIS, His electrodes (P, proximal; M, mid; D, distal); CS, coronary sinus; RVA, right ventricular apex.

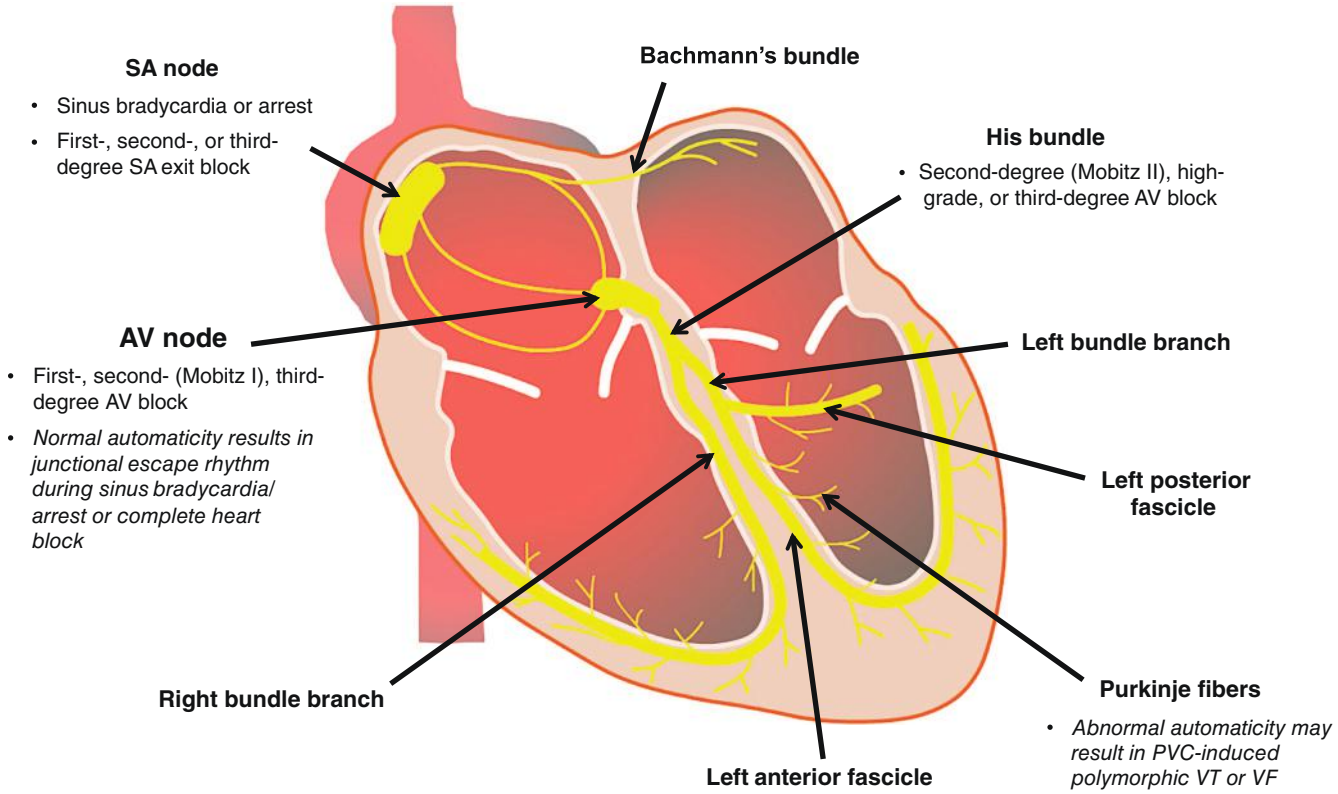

FIGURE 82–4. Cardiac conduction system with common sites of conduction block. AV, atrioventricular; PVC, premature ventricular contraction; SA, sinoatrial; VF, ventricular fibrillation; VT, ventricular tachycardia.

SINUS NODE DYSFUNCTION

Sinoatrial or sinus node dysfunction is usually observed in elderly patients. Sinus node dysfunction may accompany AV node disease in up to 12% of patients, suggesting a degenerative process involving the conduction system is present.[8] Sinus node dysfunction may also be present in patients with paroxysmal atrial fibrillation and prolonged conversion pauses.

Clinical examination and noninvasive testing usually are sufficient to diagnose sinus node dysfunction without the need for EPS. For example, a classical history of vasovagal syncope or carotid sinus massage in suspected patients may provide the diagnosis without the need for EPS. Ambulatory monitoring, in addition to treadmill stress testing, serve as a noninvasive means to assess for sinus node dysfunction.[9,10] In patients in whom the diagnosis of symptomatic sinus bradycardia is inconclusive despite noninvasive testing, EPS can be performed.

Sinus node recovery time (SNRT) and corrected sinus node recovery time (CSNRT) are the most common means of assessing sinus node function. The SNRT is measured after pacing the atrium at different rates up to 300 bpm for at least 30 seconds. The interval between the last atrial paced beat to the first sinus beat is the SNRT. The normal SNRT value is < 1500 milliseconds.[11,12] As SNRT may be influenced by the baseline sinus rhythm rate, the CSNRT (which corrects for this) is an alternative method for measuring sinus node function. The normal value for CSNRT is < 525 milliseconds.[13,14] The SNRT and CSNRT are repeated at different cycle lengths. If abnormal pauses are observed during the recovery phase after pacing or it takes > 5 seconds to recover to the baseline cycle length (total recovery time), that would also suggest sinus node dysfunction is present.

The sinoatrial conduction time (SACT), the time required for impulse propagation from sinus node to atrium, can be measured during EPS and represents another method to ascertain sinus node function. SACT is measured by direct (recording sinus node electrograms) and indirect (pacing maneuvers) methods. Pharmacologic evaluation of sinus node function can be performed as well, although this is rarely done in the present era (see Chap. 86).

ATRIOVENTRICULAR NODE AND HIS-PURKINJE SYSTEM DYSFUNCTION

Similar to sinus node disease, atrioventricular (AV) node dysfunction can be diagnosed on the basis of symptoms and ambulatory telemetry findings. Based on ECG findings, AV block is classified as first degree (prolonged conduction, PR > 200 milliseconds), second degree (intermittent conduction), and third degree or complete heart block (no conduction). Second-degree AV block is further classified as type I with gradual progression of PR interval before loss of conduction, whereas type II AV block has abrupt loss of conduction. During 2:1 AV block, short PR interval, wide QRS, worsening conduction with exercise, and improvement with carotid sinus massage suggests type II second-degree AV block. Second-degree type II AV block represents underlying infra-nodal (intra- or infra-Hisian) disease. Rarely, type II AV block can occur in the AV node during periods of high vagal tone and is seen with concomitant sinus rate slowing, which confirms that the mechanism of block is caused by increased vagal tone. During atrial fibrillation, pauses > 5 seconds are suggestive of high-degree AV block.

Type I second-degree AV nodal block is very commonly seen during an electrophysiology study with atrial pacing (Fig. 82–5). This is a normal physiological phenomenon and does not warrant any intervention. Resting type I second-degree AV block can be seen with high vagal tone in young athletes and with medications such as beta-blockers, calcium channel blockers, and digoxin.[15]

However, intra-Hisian and infra-Hisian block are indications for permanent pacing (Fig. 82–6). EPS can provide information vital

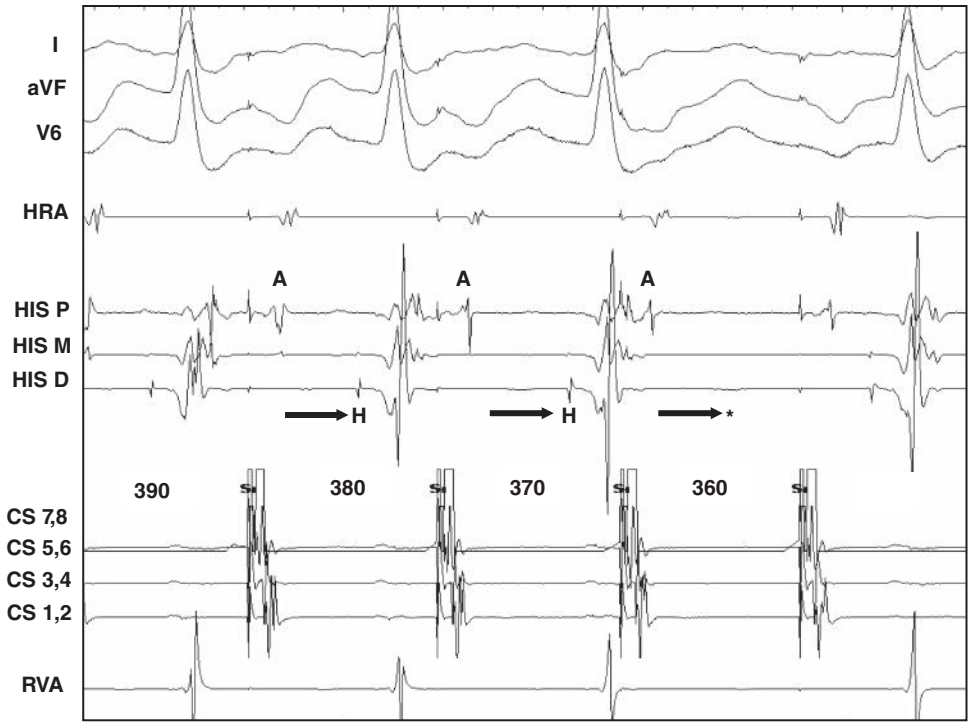

FIGURE 82–5. Demonstration of type I second-degree AV block during EPS. The atrium is paced from the proximal coronary sinus (CS) at progressively shorter cycle length (faster rate). The AH interval prolongs and then there is block in the AV node (*asterisk*). The subsequent paced beats again conduct to the ventricle. This is a normal finding and does not require any intervention.

to making decisions for permanent pacing. A baseline HV interval ≥ 70 milliseconds is considered high-risk for developing high-degree AV block in the future, whereas a HV interval ≥ 100 milliseconds would warrant permanent pacemaker placement.[16]

Second-degree AV block at the intra- or infra-Hisian level, which is most commonly associated with type II block, is also pathological and also indicates a need for permanent pacing. The manifestation of infra-nodal conduction disturbance at atrial pacing rates < 150 bpm (> 400 millisecond cycle length) is considered abnormal, and an indication for permanent pacemaker placement.[17]

It is important to recognize normal versus pathological AV conduction during EPS. During programmed electrical stimulation, delivery of single premature atrial extrastimuli at progressively shorter coupling intervals will ultimately result in failure to elicit a ventricular response. However, on occasion AV conduction will resume when extrastimuli are delivered at even shorter coupling intervals. This is a normal

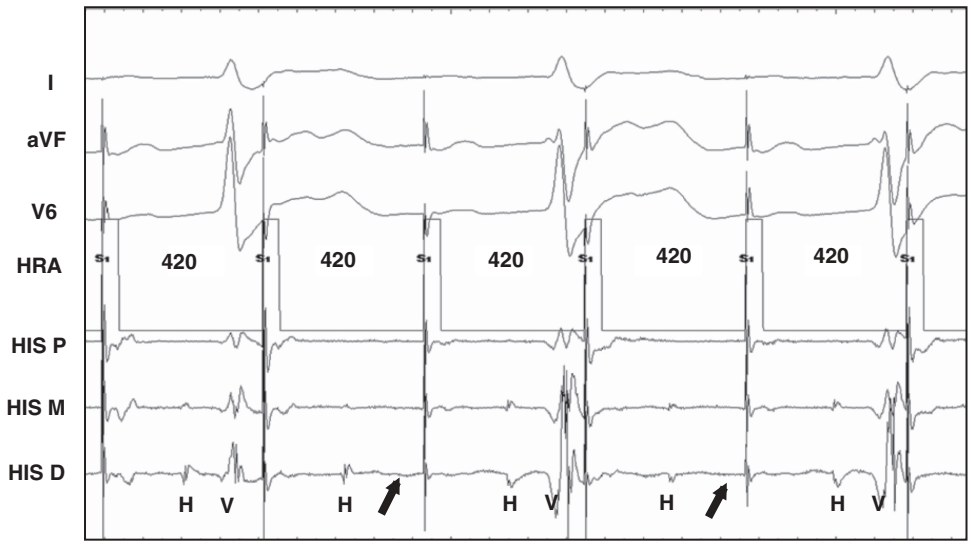

FIGURE 82–6. These tracings were obtained during evaluation of AV node and His-Purkinje system function in a patient with exercise-induced pre-syncope caused by abrupt decrease in heart rate during exertion. During atrial pacing from the high right atrium (HRA) at a cycle length of 420 milliseconds, there is 2:1 infra-Hisian block seen. With the first paced atrial beat, there is conduction to the His (H) and then ventricle (V). With the second paced beat, there is conduction to the His but then failure to conduct to the ventricle (*arrow*). This pattern is repeated throughout the tracing. This patient was implanted with a dual-chamber pacemaker leading to resolution of symptoms.

finding and is termed "gap phenomenon."[18] This occurs as a result of functional differences in conduction and refractory properties of at least two anatomically distinct locations in the AV conduction system. The initial site of block is distal and with progressively more premature atrial extrastimuli, proximal delay occurs allowing recovery of distal AV conduction. With progressively shorter coupled atrial extrastimuli, AV conduction is decremental and shows an exponential increase in the AH interval. However, on occasion there may be discontinuity in the AV conduction with progressively premature atrial extrastimuli resulting in a discontinuous AH curve.[18] This results from the presence of dual AV node physiology and is a normal finding even in those without atrioventricular nodal reentrant tachycardia (see Chap. 84).

Intraventricular conduction delay, defined as left bundle branch block, right bundle branch block, or bifascicular block, poses a unique challenge. Bifascicular block refers to conduction abnormality in the right bundle and either left anterior or posterior fascicle. Bifascicular block increases the risk of sudden death.[19] Syncope in patients with bifascicular block could be a result of intermittent infra-Hisian block or ventricular tachycardia. EPS may be useful in elucidating the mechanism in these patients.[20,21] In patients with symptoms that are related to bifascicular block, intravenous procainamide infusion can be used to risk stratify patients at high risk for high-degree AV block. Procainamide 10 mg/kg is administered intravenously. Observation of second- or third-degree block, or increase in HV interval by 100% or ≥ 100 milliseconds is considered abnormal and an indication for pacemaker.[22,23] As mentioned before, infra- or intra-Hisian block induced by atrial pacing would be considered abnormal. In addition to provoking infra- or intra-Hisian block, program ventricular stimulation (PVS) is necessary to evaluate for ventricular tachycardia susceptibility. In conclusion, EPS could identify some patients with symptomatic bifascicular block who would benefit from device therapy.

TACHYARRHYTHMIAS

In the present era, EPS for tachyarrhythmias is generally performed with ablation or device therapy as the goal. The mechanism of all tachyarrythmias is either macro-reentry or focal. Macro-reentrant arrhythmias are most common. Focal arrhythmias may be caused by automaticity, micro-reentry, or triggered activity.[24] Reentry requires (1) two functionally or anatomically separate pathways, (2) unidirectional block in one pathway, and (3) recovery of excitability in blocked pathway to initiate or maintain reentry.[25] In the present era, electrophysiology study for tachyarrhythmia is generally performed with ablation or device therapy as the goal.

For the purposes of EPS, all tachyarrhythmias can be classified as either narrow-complex or wide-complex tachycardias. The mode of tachycardia initiation and termination as well as tachycardia characteristics can provide clues for diagnosis of the mechanism of arrhythmia. Additionally, pacing maneuvers (such as entrainment) and activation mapping together with three-dimensional (3D) electroanatomic mapping can be utilized to confirm the diagnosis and subsequently be used to guide catheter ablation (see Chap. 88).

A detailed discussion of entrainment is beyond the scope of this chapter.[26,27] However, briefly, entrainment mapping involves overdrive pacing the tachycardia from a catheter. The tachycardia is paced at slightly faster than the tachycardia cycle length (TCL). If tachycardia is accelerated, then certain findings such as progressive fusion during overdrive pacing suggests entrainment and a reentrant mechanism. If pacing were performed from within the reentry circuit, then the interval between the last paced beat and the subsequent sensed electrogram (postpacing interval, or PPI) would be equal to TCL. The farther the catheter is from the circuit, the longer would be the PPI (Fig. 82–7).

Activation mapping is performed in a chamber using a roving catheter and timing the local electrogram relative to a reference electrogram. A focal arrhythmia would reveal a small area of earliest activation in the chamber from which the activation spreads centrifugally (Fig. 82–8). A macro-reentrant tachycardia would not have a focal area of early activation but would demonstrate *early meets late* activation, where the areas of earliest activation are adjacent to those with the latest activation times (Fig. 82–9). Electroanatomic mapping systems are utilized to record local electrical information (local activation time or voltage) in a 3D chamber reconstruction during mapping so that ablation can be targeted at the appropriate sites.

NARROW-COMPLEX TACHYCARDIA

Atrial fibrillation, atrial tachycardia or flutter, and supraventricular tachycardia (SVT), in the absence of aberrant ventricular conduction, are all narrow-complex tachycardias where the QRS duration is < 120 msec (see Chap. 84).

Atrial fibrillation is easily diagnosed on surface ECG. Pulmonary vein isolation continues to be the ablation strategy for both persistent and paroxysmal atrial fibrillation.[28] Hence, detailed EPS is generally not performed before atrial fibrillation ablation.

Atrial Tachycardia

Atrial tachycardia (AT) is a focal or micro-reentry arrhythmia, whereas atrial flutter is macro-reentrant (see Figs. 82–8 and 82–9). As described earlier, entrainment and activation mapping along with 3D electroanatomic mapping can be used to differentiate these arrhythmias. Atrial tachycardia or flutter is easily identified on intracardiac electrograms when there are more atrial than ventricular electrograms (Fig. 82–10). However, when a narrow-complex tachycardia has a 1:1 atrial to ventricular electrogram ratio, then EPS can help differentiate between atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and AT.

Atrial flutter can be classified as cavotricuspid isthmus dependent (typical) and nonisthmus dependent (atypical). Typical atrial flutter commonly occurs in patients that have no atrial scar and is often associated with atrial fibrillation. On the other hand, atypical atrial flutter is usually seen in patients with atrial scar resulting from prior ablation, cardiac surgery, and so on. EPS can differentiate between these two types and is typically performed with catheter ablation as the goal.[29]

Atrioventricular Nodal Reentrant Tachycardia

Atrioventricular nodal reentrant tachycardia (AVNRT) is a reentry arrhythmia involving the two pathways of the AV node. In typical AVNRT, antegrade conduction is via the slow pathway and retrograde conduction via the fast pathway. In contrast, atypical AVNRT has antegrade conduction through the fast pathway and retrograde conduction through the slow pathway. In those with multiple slow pathways, atypical AVNRT may also be the result of antegrade and retrograde conduction over different slow pathways.

During EPS, atrial pacing demonstrates evidence of dual AV node pathways as described above and isoproterenol is often required to induce tachycardia. In typical AVNRT, the AV node excites the ventricle and atrium in parallel; hence the VA relationship is 1:1 and often simultaneous (VA time ≤ 60 milliseconds).[30] As atrial activation is retrograde from the AV node, the atrial activation sequence is concentric and demonstrates earliest activation on the septum and later activity in the distal coronary sinus and high right atrium (Fig. 82–11). Rarely, AVNRT may demonstrate 2:1 AV block resulting from functional infranodal block.[31]

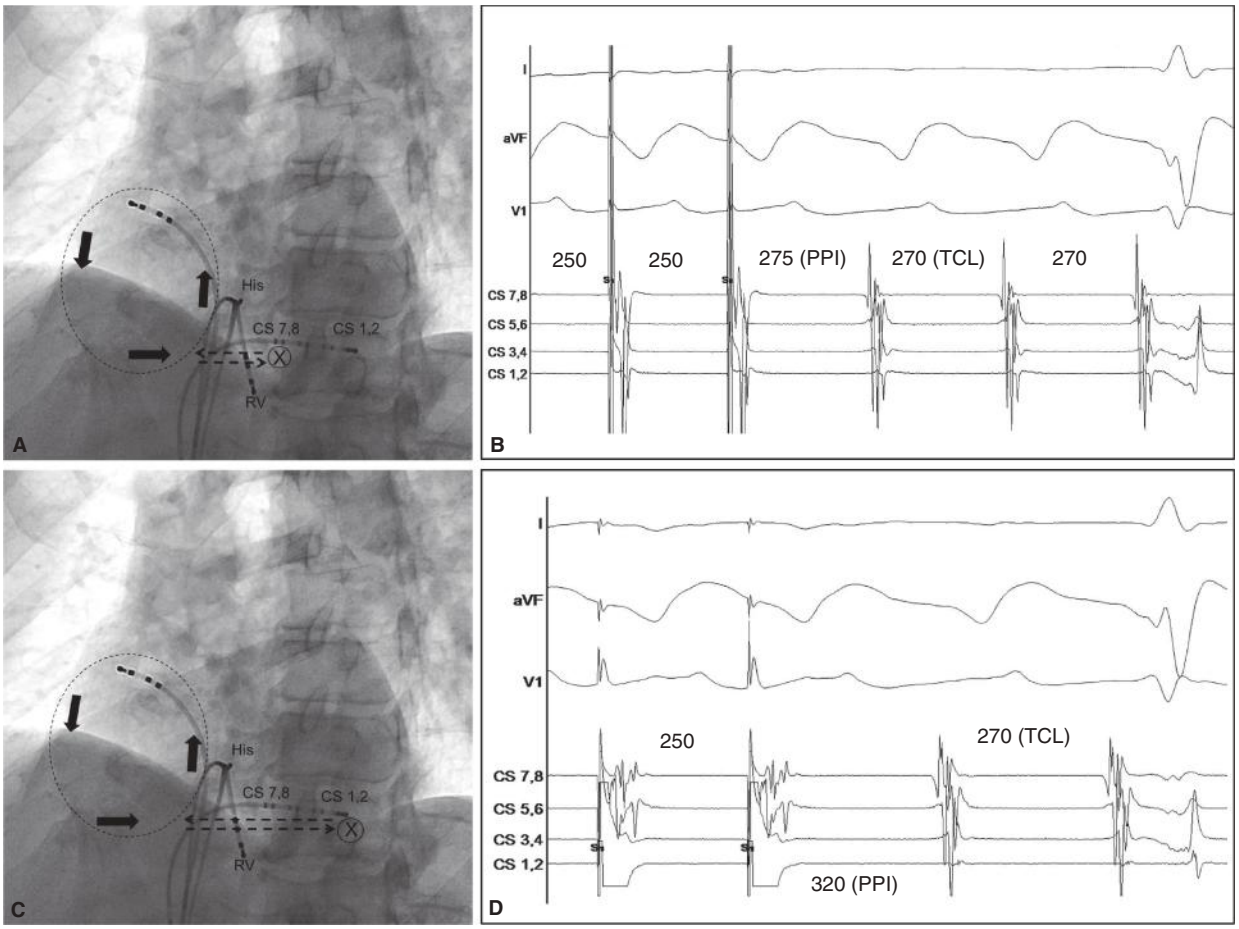

FIGURE 82–7. Entrainment of typical counterclockwise atrial flutter. **A.** Left anterior oblique fluoroscopic view is shown with catheters positioned at the His, in the right ventricle (RV), and coronary sinus (CS). The *circle* represents the atrial flutter circuit, and the *arrows* show the direction of the circuit in the right atrium. The time to travel around the circumference of the circle represents the tachycardia cycle length (TCL), which in this case is 270 milliseconds. Overdrive pacing from CS 7,8 (proximal CS, site X) is performed. The postpacing interval (PPI) is equal to the time to reach the circuit from the pacing site (*left-pointing dashed arrow*) + TCL + time to return to pacing site (*right-pointing dashed arrow*). **B.** In this case, the PPI is 275 milliseconds. **C.** Overdrive pacing is repeated from CS 1,2 (distal CS, site X). **D.** Overdrive pacing from this second site would be expected to yield a longer PPI as it is more remote from the tachycardia circuit than the proximal CS. This was indeed observed (320 milliseconds). Overdrive pacing from a site within the circuit would yield a PPI that is equal to TCL, and the further away the overdrive pacing is performed, the longer the PPI.

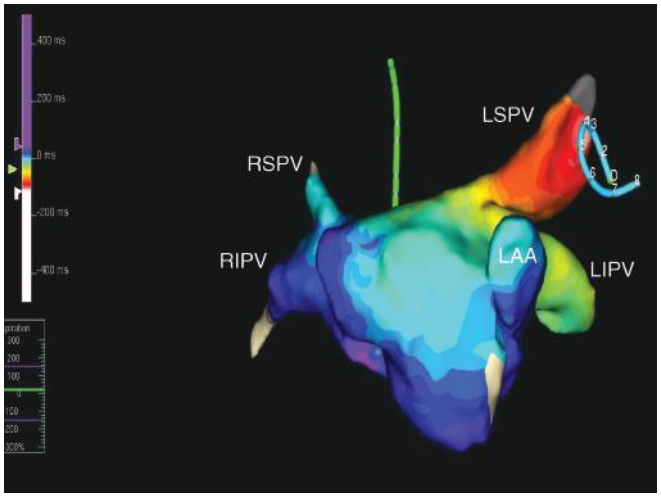

FIGURE 82–8. A three-dimensional activation map (left anterior oblique projection) of the left atrium is shown in a patient with focal atrial tachycardia. The *red area* represents the site of earliest activation, which is in the left superior pulmonary vein (LSPV). The *blue areas* represent the sites of late activation. A circular mapping catheter was used for mapping and is seen positioned in the distal LSPV. LAA, left atrial appendage; LIPV, left inferior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

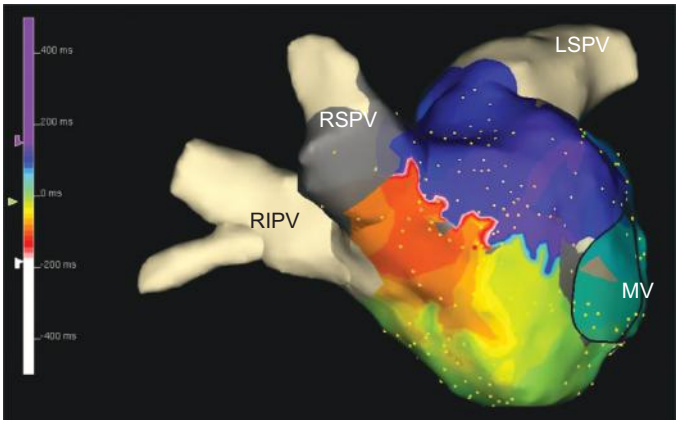

FIGURE 82–9. A three-dimensional activation map (anteroposterior projection) of the left atrium is shown in a patient with a macro-reentrant atypical atrial flutter. The *red area* represents the site of earliest activation and the *blue area* represents the site of latest activation. The activation pattern is consistent with a macro-reentrant circuit around the mitral annulus with appearance of early meets late activation. LSPV, left superior pulmonary vein; MV, mitral valve; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

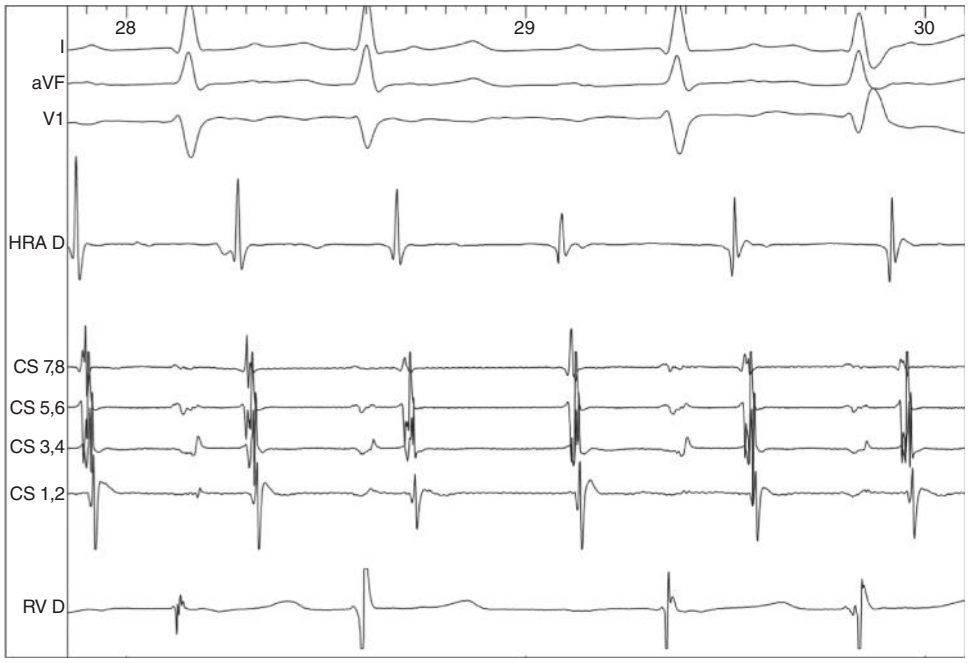

FIGURE 82–10. Atrial tachycardia is seen in this tracing of a patient undergoing EPS for supraventricular tachycardia. The intracardiac electrograms demonstrate that there are more atrial electrograms than ventricular electrograms, which is consistent with a diagnosis of atrial tachycardia. The atrial electrograms are seen in the high right atrium (HRA D) and coronary sinus catheters (CS). Ventricular electrograms are best appreciated in the right ventricular catheter (RV D).

In atypical AVNRT, retrograde VA conduction is via the slow pathway. Therefore, the VA relationship is not simultaneous (VA time > 60 milliseconds) although retrograde atrial activation remains concentric. A similar finding is seen with orthodromic AVRT utilizing a posteroseptal accessory pathway. Pacing maneuvers are required to differentiate between the two.[32]

Atrioventricular Reentrant Tachcyardia

In atrioventricular reentrant tachycardia (AVRT) or orthodromic reciprocating tachycardia, the reentry circuit is formed by antegrade conduction down the AV node and retrograde conduction over an accessory pathway that can be located anywhere along the tricuspid annulus, mitral annulus, and aortic cusps region. The accessory pathway may demonstrate antegrade conduction that is visible on ECG as ventricular preexcitation, ie, Wolff-Parkinson-White (WPW) pattern, or may demonstrate only retrograde conduction properties that is not appreciated on ECG, ie, concealed accessory pathway.

Similar to AVNRT, the approach to the tachycardia remains similar in AVRT. The tachycardia is induced either by burst pacing or program electrical stimulation in atrium and ventricle with or without isoproterenol. Tachycardia activation sequence is observed and entrainment

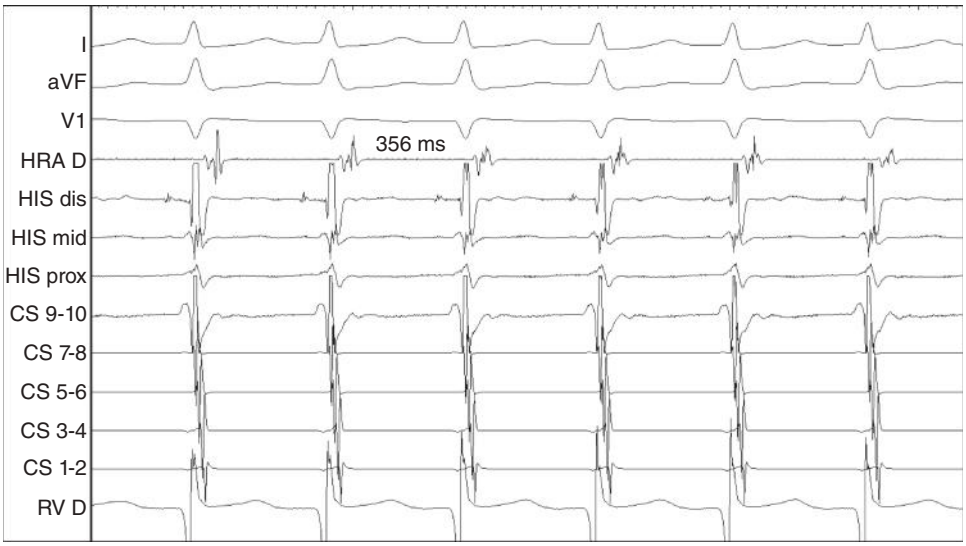

FIGURE 82–11. Typical AVNRT is associated with near simultaneous activation of the atrium and ventricle as demonstrated on intracardiac electrograms. Atrial electograms are evident on the high right atrium (HRA D) and coronary sinus (CS) catheters. Ventricular electrograms are seen on the His (HIS) and right ventricular (RV D) catheters. The tachycardia cycle length is 356 milliseconds, and retrograde atrial activation is concentric with earliest activity on the septum (CS 9-10) and later activity in the distal coronary sinus (CS 1-2) and high right atrium (HRA D).

FIGURE 82–12. Orthodromic AVRT using a left lateral accessory pathway. The surface ECG leads and intracardiac tracings demonstrate a narrow-complex tachycardia. Retrograde atrial activation is eccentric demonstrating earliest activation in the distal coronary sinus (CS 1,2), which is located at the lateral mitral annulus. The VA time during tachycardia is > 60 milliseconds.

maneuvers are performed. The VA relationship is 1:1 with a long VA time (VA > 70 milliseconds). Pacing maneuvers are required to differentiate AVRT from atypical AVNRT and atrial tachycardia. For accessory pathways that are not located near the septum, retrograde atrial activation during tachycardia may be eccentric, ie, earliest atrial activation may be in the distal coronary sinus or lateral mitral annulus for a left lateral accessory pathway (Fig. 82–12). If tachycardia cannot be initiated, the finding of nondecremental or eccentric retrograde VA conduction during ventricular pacing also suggests the presence of an accessory pathway. In contrast, retrograde AV node conduction is decremental and concentric.

Rarely, a narrow QRS ventricular tachycardia originating from the upper septal fascicular region can be observed. The HV interval during tachycardia is shorter than HV interval during sinus rhythm.[33] The mechanism described for this tachycardia is reentry. The antegrade limb is part of the left posterior fascicle and retrograde limb is septal Purkinje fibers. The simultaneous activation of left anterior fascicle and right bundle branch during antegrade conduction leads to narrow QRS.[34,35]

WIDE-COMPLEX TACHYCARDIA

SVT with aberrant conduction, antidromic reciprocating tachycardia, and ventricular tachycardia all represent wide QRS complex tachycardias.

Supraventricular Tachycardia with Aberrancy

Atrial fibrillation, atrial tachycardia or flutter, AVNRT, and AVRT could all present with aberrant conduction including left bundle branch or right bundle branch block aberrancy. It can be challenging to differentiate it from ventricular tachycardia using surface ECG alone. Various criteria have been developed to differentiate VT from supraventricular tachycardia (SVT) with aberrancy.[36,37]

EPS can differentiate VT from SVT with aberrancy. If the intracardiac electrograms reveal VA dissociation with more ventricular electrograms than atrial electrograms, then a diagnosis of VT is suggested. However, if VA association is seen, then VT cannot be ruled out, as retrograde conduction from the ventricle to atrium through the AV node may occur in a 1:1 manner. Additionally, aberrancy during SVT would demonstrate antegrade conduction through the His-Purkinje system. Therefore, intracardiac electrograms would demonstrate a His electrogram prior to every ventricular electrogram (Fig. 82–13), which is not seen during VT with the exception of bundle branch reentry VT. Even in the presence of abberancy, the mechanism of the supraventricular tachycardia can be further defined.[38,39]

Antidromic Tachycardia

Antidromic tachycardia is characterized by reentry utilizing a bypass tract for antegrade conduction and AV node for retrograde conduction in antidromic AVRT. Antidromic tachycardia would show maximum preexcitation as complete antegrade ventricular conduction is through the bypass tract. ECG during sinus rhythm can demonstrate a similar pattern of preexcitation as seen during tachycardia. Intracardiac electrograms would reveal retrograde ventricle to His activation followed by atrial activation. On rare occasions, bypass tracts may demonstrate decremental AV conduction properties and may be either atriofascicular or atrioventricular connections and are referred to as Mahaim fibers.[40] These are right-sided accessory pathways, and the associated tachycardias have left bundle branch block morphology.

Ventricular Tachycardia

Sustained ventricular tachycardia (VT) is defined as a tachycardia originating from the ventricle that lasts ≥ 30 seconds or that causes hemodynamic instability. The majority of VTs are scar-related in patients with structural heart disease. Idiopathic VT is seen in patients without structural heart disease. Reentry is the mechanism in scar-related VT and idiopathic VTs are commonly caused by triggered activity.

EPS for induction of ventricular arrhythmias is indicated (1) for syncope in those with structural heart disease and suspected

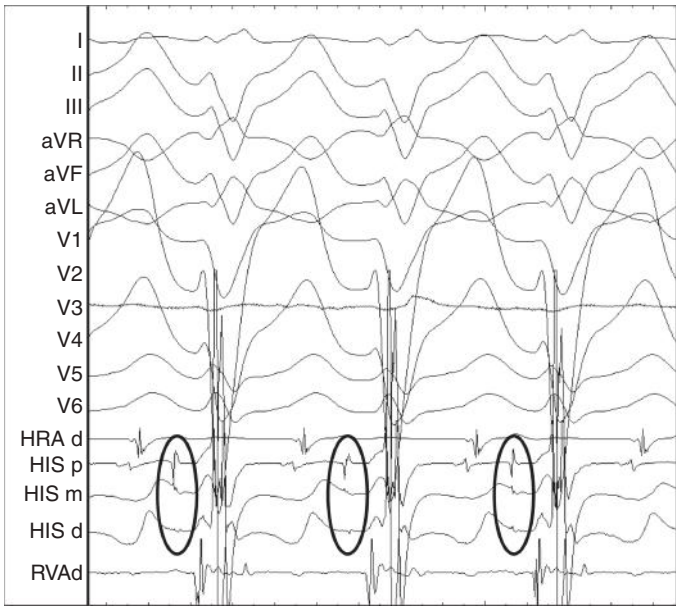

FIGURE 82–13. Orthodromic AVRT with left bundle branch aberrancy. The 12-lead electrocardiogram demonstrates a left bundle branch block. The diagnosis of supraventricular tachycardia with aberrancy is confirmed by the presence of His electrograms (*encircled*, HIS catheter) prior to the QRS and ventricular electrogram seen on the right ventricular catheter (RVAd).

ventricular arrhythmias; (2) for risk-stratification in asymptomatic patients with coronary artery disease, depressed LV function (ejection fraction ≤ 40%), and nonsustained VT (41); (3) to define the mechanism of wide-complex tachycardia; (4) to guide catheter ablation (see Chap. 88); and (5) for risk-stratification in Brugada syndrome.

EPS for induction of ventricular arrhythmias consists of burst pacing and programmed electrical stimulation (PES) with delivery of up to three ventricular extrastimuli during two paced cycle lengths and from two ventricular locations. Induction of sustained monomorphic VT anytime during the study or induction of VF or polymorphic VT with up to two premature stimuli is considered positive (Fig. 82–14). *A positive study would warrant ICD implantation in those who do not have one and potentially catheter ablation in those with an ICD.*

The role of EPS in Brugada syndrome remains a controversial topic (see Chap. 80). In asymptomatic patients with Brugada syndrome, whether the induction of VT/VF during EPS predicts future risk of sudden death is ambiguous, with studies both supporting and refuting this.[42,43] However, a history of syncope and spontaneous type 1 Brugada ECG pattern have been shown to be predictors of future sudden cardiac death.[44] As ECG findings in Brugada syndrome may be transient, in addition to recording the right precordial leads (V_1 and V_2) from higher intercostal (second or third) positions, sodium channel blockers (procainamide, flecainide, and ajmaline) can be administered to unmask a type 1 pattern in those with type 2 or 3 patterns (Fig. 82–15).[45-47]

SYNCOPE

Syncope is a transient loss of consciousness, which is rapid onset, short duration, and with spontaneous and complete recovery because of transient global cerebral hypoperfusion.

History and physical examination are crucial in diagnosis of syncope (see Chap. 90). Diagnostic electrophysiology study is indicated when syncope is suspected to be secondary to arrhythmia and undiagnosed by noninvasive testing such as ECG, ambulatory monitoring, and tilt table testing.

Certain characteristics of the patient history, ECG, and noninvasive testing should increase the suspicion for an arrhythmic etiology of syncope and prompt EPS.[2] These are summarized in Table 82–2.

If the clinical suspicion is of bradyarrhythmia, then a detailed EPS is performed with focus on sinus node, AV node, and infranodal conduction system. As discussed earlier, findings such as CSNRT > 525 milliseconds, HV interval ≥ 70 milliseconds, and second- or third-degree infranodal block would be considered abnormal

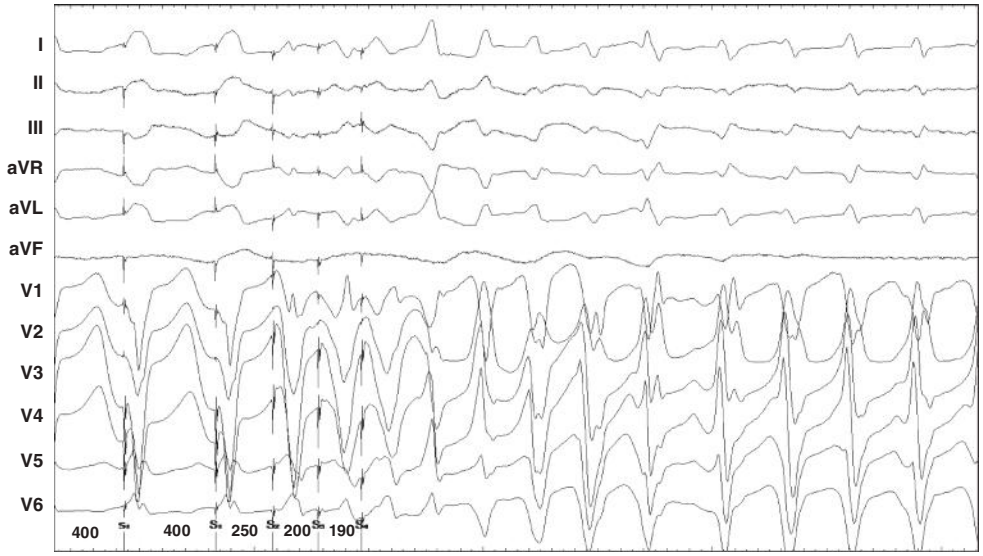

FIGURE 82–14. Programmed ventricular stimulation utilizing triple ventricular extra stimuli from the right ventricle was performed in a patient for risk stratification of sudden cardiac death. Sustained monomorphic ventricular tachycardia was induced that required defibrillation for termination. This patient subsequently underwent implantation of an implantable cardioverter-defibrillator.

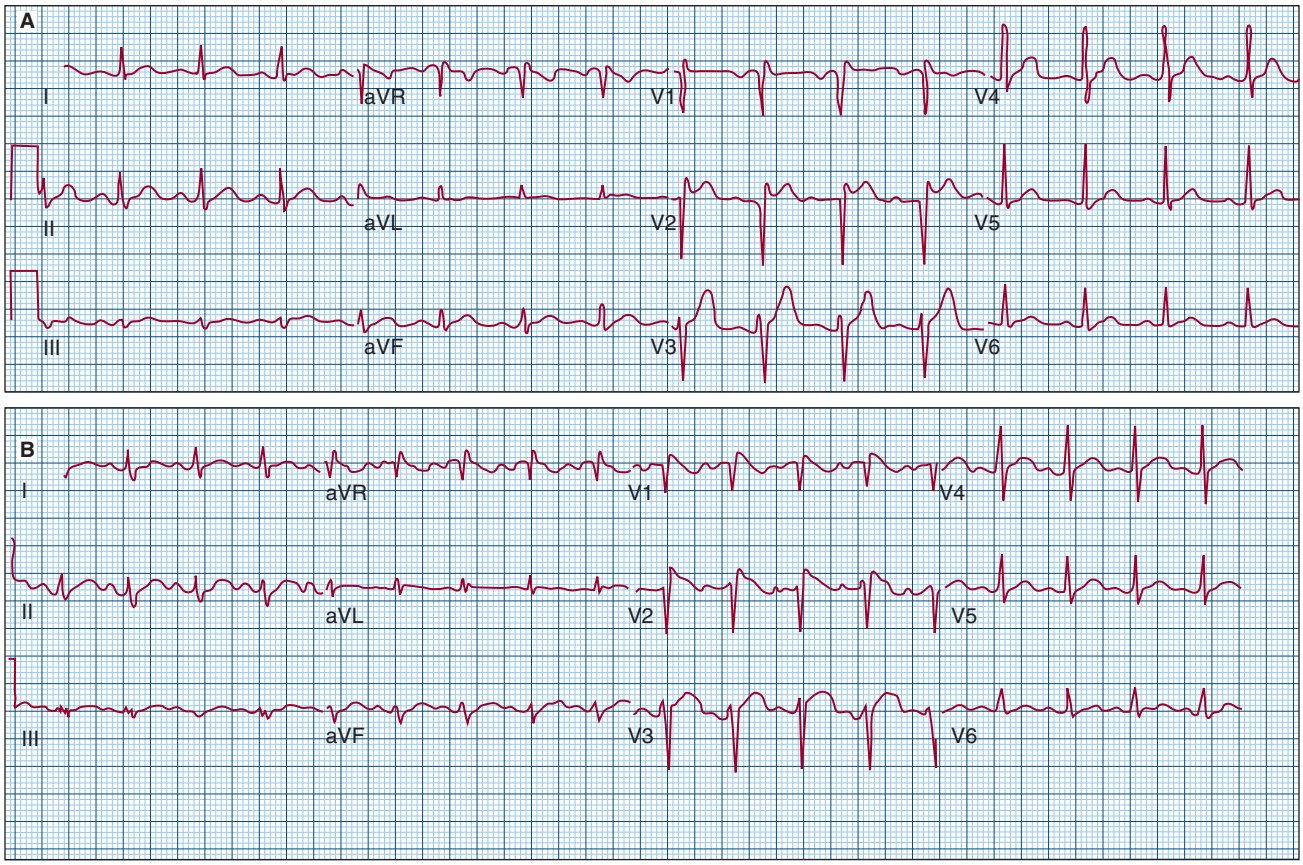

FIGURE 82–15. **A.** The baseline 12-lead ECG of a patient who presented with syncope is shown. A type 2 Brugada pattern is seen in lead V_2. **B.** Following administration of procainamide, a type 1 pattern is elicited.

TABLE 82–2. Findings Suggestive of an Arrhythmic Etiology of Syncope

History
• Syncope-related exertion or in supine position
• Structural heart disease (ischemic or nonischemic cardiomyopathy, ARVC, hypertrophic cardiomyopathy, etc.)
• Arrhythmogenic drugs
Electrocardiogram
• Severe sinus bradycardia
• Bundle branch block (left bundle branch or bifasicular block)
• Prolonged or short QT interval
• Type 1 Brugada pattern (Brugada syndrome)
• Pre-excitation pattern (Wolff-Parkinson-White syndrome)
• Epsilon waves, negative T waves in precordium, late potentials (ARVC)
Ambulatory Monitoring
• Nonsustained ventricular tachycardia, particularly in the setting of structural heart disease

Abbreviation: ARVC, arrhythmogenic right ventricular cardiomyopathy.

findings in patients with syncope and may require the placement of a permanent pacemaker.

SVT can rarely cause syncope, and EPS with ablation can be performed when this is clinically suspected or documented. In manifest preexcitation, ie, a WPW pattern, the objective of EPS is to ascertain the conduction properties of the bypass tract and the risk of sudden cardiac death. If EPS demonstrates that pathway conduction can occur faster than 240 bpm (< 250 milliseconds), it would be considered high risk, and catheter ablation is recommended.[48,49] The concern is that during atrial fibrillation, rapid conduction to the ventricle through the accessory pathway can lead to ventricular fibrillation and SCD.

In patients with syncope and structural heart disease, such as ARVC, hypertrophic cardiomyopathy, ischemic cardiomyopathy, and nonischemic cardiomyopathy, EPS is focused at induction of sustained monomorphic ventricular tachycardia, as previously detailed.

CONCLUSIONS

EPS can provide crucial mechanistic information in a variety of suspected or documented cardiac arrhythmias. They are indicated when the history, clinical examination, and noninvasive testing fail to provide conclusive information and therapy is dependent upon findings. Pacemaker implantation may be necessary when EPS reveals abnormal sinus node, AV node, or His-Purkinje system function, whereas ICD implantation is indicated for those who are found to be at high risk for SCD caused by inducible VT or VF. Finally, EPS provides insight into the mechanism of narrow- and wide-complex tachycardia that can be used to guide curative catheter ablative therapy. Thus diagnostic EPS has an important role in the diagnosis and management of patients with bradyarrhythmias, tachyarrhythmias, syncope, and for risk-stratification for SCD.

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CHAPTER 83

ATRIAL FIBRILLATION, ATRIAL FLUTTER, AND ATRIAL TACHYCARDIA

Eric N. Prystowsky, Jonathan Halperin, and Peter Kowey

ATRIAL FIBRILLATION / 1950
Classification / 1950
Epidemiology / 1950
Etiology / 1950
Pathophysiology / 1950
Clinical Manifestations / 1954
Treatment / 1955

ATRIAL FLUTTER / 1961
Classification and Mechanisms / 1961
Etiology / 1962
Diagnosis / 1962
Management / 1962

Atrial fibrillation and atrial flutter are common arrhythmias associated with a variety of cardiac conditions. Atrial fibrillation, the most common sustained cardiac arrhythmia encountered in clinical practice, is increasing in prevalence.[1-3] These arrhythmias may be associated with deterioration of hemodynamics, a wide spectrum of symptoms, and significant morbidity or mortality. Perhaps because no single therapy has been shown to be ideal for all patients, there are a variety of treatment strategies that may be applied to these arrhythmias. These include no therapy at all, anticoagulation, rhythm control, and rate control.[2,3] This chapter describes the epidemiology, electrophysiologic mechanisms, and approach to management of patients with atrial fibrillation and atrial flutter.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is characterized by temporally and spatially varying rapid disorganized atrial electrical activation and uncoordinated atrial contraction. The surface electrocardiogram (ECG) characteristically demonstrates rapid atrial fibrillatory waves with changing morphology and rate and a ventricular response that is usually irregularly irregular (Fig. 83–1).

CLASSIFICATION

AF has been classified into four categories: *paroxysmal, persistent, longstanding persistent*, and *permanent*.[3] Paroxysmal AF is characterized by self-terminating episodes that generally last < 7 days (most < 24 hours), whereas persistent AF generally lasts > 7 days and often requires electrical or pharmacologic cardioversion. Longstanding AF has been continuous for at least a year. It is recognized that many patients have both paroxysmal and persistent episodes of AF, and in general, we characterize such a patient by their more typical form of AF. AF is classified as permanent when it has failed cardioversion or when further attempts to terminate the arrhythmia are deemed futile. At the initial detection of AF, it may be difficult to be certain of the subsequent pattern of duration and frequency of recurrences. Thus a designation of *first detected* episode of AF is made on the initial diagnosis. When the patient has experienced two or more episodes, AF is classified as *recurrent*. The term *lone AF* refers to AF occurring in the absence of cardiac disease or other known etiologic factors, usually in relatively young individuals.[3] Most cases of AF occur in patients with evidence of structural heart disease, but there may be no evidence of concomitant disease in others, especially with paroxysmal AF.[3] In contrast, > 80% of patients with permanent AF have an identifiable underlying cause.[4] The definition of *chronic* AF varies greatly in the literature, and the terminology is best avoided.

EPIDEMIOLOGY

It is estimated that 2.2 to 5.0 million Americans and 4.5 million Europeans experience AF.[1-3,5] The incidence and prevalence of AF steadily increase with age, such that this arrhythmia occurs in about 1% of the population < 60 years of age, and more than one-third of AF patients are 80 years old or older.[3] Up to 12% who have AF are between 75 and 84 years old.[3] The age-adjusted prevalence of AF is higher for men than women and higher for whites than blacks.[3] Familial AF has been described.[3] Genetic abnormalities have been reported.[6-9] In several Chinese families, the defect has resulted in a gain in function of potassium channels and shortening of atrial refractoriness.[8,9]

ETIOLOGY

AF is associated with a wide variety of predisposing factors (Table 83–1). Reversible causes should be sought and treated, eg, hyperthyroidism, and risk factors such as obesity and obstructive sleep apnea should be modified.[2] In the developed world, the most common clinical diagnosis associated with AF is hypertension.[2,3] The presence of heart failure (HF) markedly increases the risk of AF. In developing countries, hypertension, rheumatic valvular heart disease, and congenital heart disease are the most commonly related conditions.[10,11]

PATHOPHYSIOLOGY

The mechanism of AF may be multifactorial, including electrophysiologic and structural abnormalities and even extrinsic factors such as autonomic perturbations.[2,3,12] Different mechanisms may initiate (trigger) and maintain AF in an individual. The most frequent triggers are rapid spontaneous activity arising in the pulmonary veins. Pulmonary vein ectopy is often transient, and persistence of AF after this mode of initiation likely depends on atrial substrate factors.

Atrial Fibrillation Triggers

Spontaneous ectopy from muscular sleeves of pulmonary veins can serve as triggers of AF. Rapidly firing ectopic foci in pulmonary veins have been shown to be the underlying mechanism of most paroxysmal AF (Fig. 83–2).[13,14] The pulmonary vein musculature of patients with paroxysmal AF demonstrates a markedly reduced effective refractory period and conduction delay.[15] Rapidly firing foci can often be recorded within the pulmonary veins with conduction block to the left atrium (LA) (Fig. 83–3).[13,14] Discontinuous properties of conduction within the pulmonary vein may also provide a substrate for reentry within the pulmonary vein itself.[16] Although most triggering foci that are mapped during electrophysiologic studies occur in the pulmonary

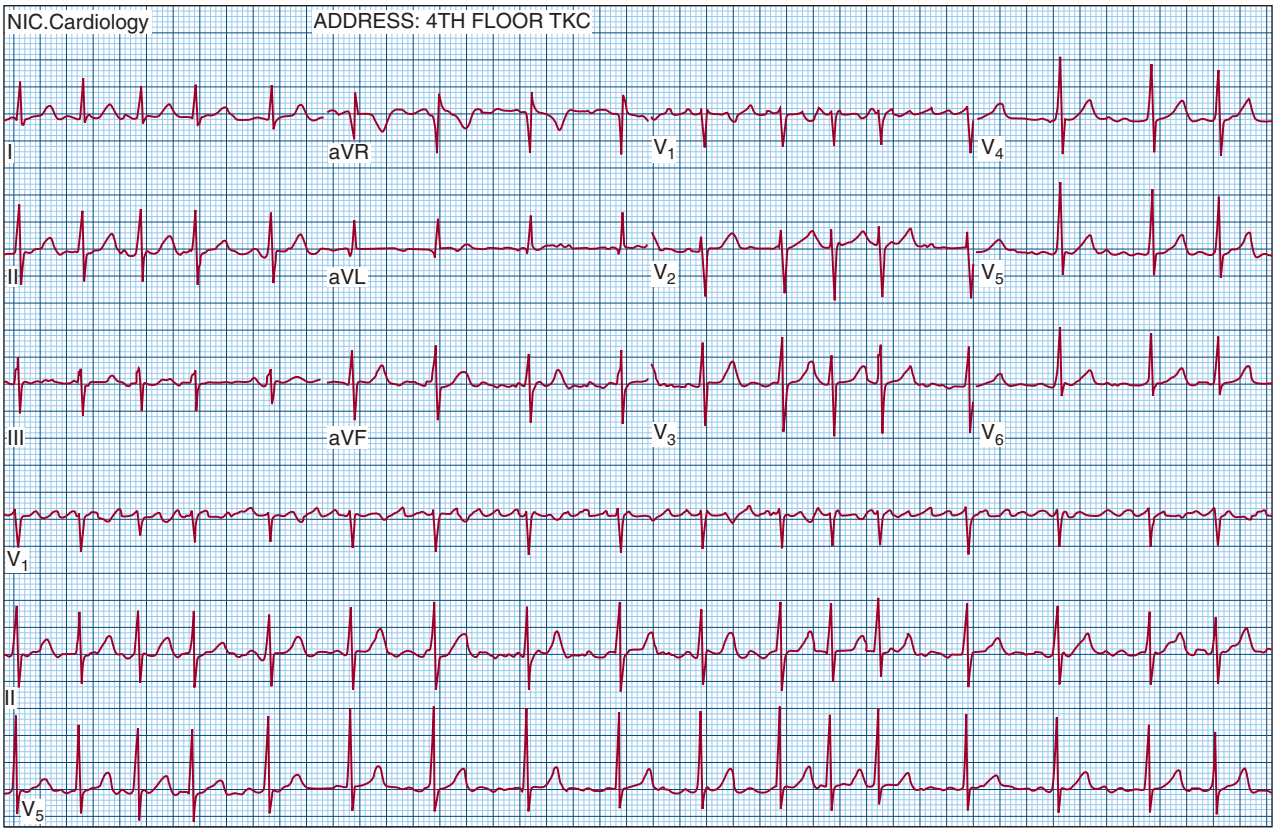


FIGURE 83–1. Twelve-lead electrocardiogram of atrial fibrillation. Note the rapid, irregular, low-amplitude fibrillatory waves with varying morphology and an irregularly irregular ventricular response.

TABLE 83–1. Anatomic and Electrophysiologic Substrates[a] Promoting the Initiation and/or Maintenance of Atrial Fibrillation

Diseases	Anatomic	Cellular	Electrophysiologic
Part A. Substrate Develops During Sinus Rhythm (Remodeling Related to Stretch and Dilatation). The Main Pathways Involve the RAAS, TGF-β, and CTGF.			
Hypertension	Atrial dilatation	Myolysis	Conduction abnormalities
Heart failure	PV dilatation	Apoptosis, necrosis	ERP dispersion
Coronary disease	Fibrosis	Channel expression change	Ectopic activity
Valvular disease			
Part B. Substrate Develops Because of Tachycardia (Tachycardia-Related Remodeling, Downregulation of Calcium Channel, and Calcium Handling).			
Focal AF	None or[b]	None or[b]	Ectopic activity
Atrial flutter	Atrial dilatation PV dilatation	Calcium channel downregulation	Microentry Short ERP[c]
	Large PV sleeves	Myolysis	ERP dispersion[d]
	Reduced contractility[e]	Connexin downregulation	Slowed conduction
	Fibrosis	Adrenergic supersensitivity	
		Changed sympathetic innervation	

[a] Substrate develops while in sinus rhythm, usually caused by ventricular remodeling, atrial pressure overload, and subsequent atrial dilatation (Part A), or because of the rapid atrial rate during atrial fibrillation (AF), according to the principle that "AF begets AF" (Part B).

[b] The listed changes may only occur with prolonged episodes of AF at high atrial rate.

[c] Short ERP and slow conduction may produce short wavelength, thereby promoting further AF.

[d] ERP dispersion together with spontaneous or stretch-induced ectopic activity may initiate AF. Long ERPs occur in Bachmann bundle among other tissues.

[e] The reduction of atrial contractility during AF may enhance atrial dilatation, leading to persistent AF.

Abbreviations: CTGF, connective tissue growth factor; ERP, effective refractory period; PV, pulmonary vein; RAAS, renin-angiotensin-aldosterone system; TGF-β, transforming growth factor β.

Data from Fuster V, Rydén LE, Cannom DS, et al: ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J*. 2006 Aug;27(16):1979-2030.

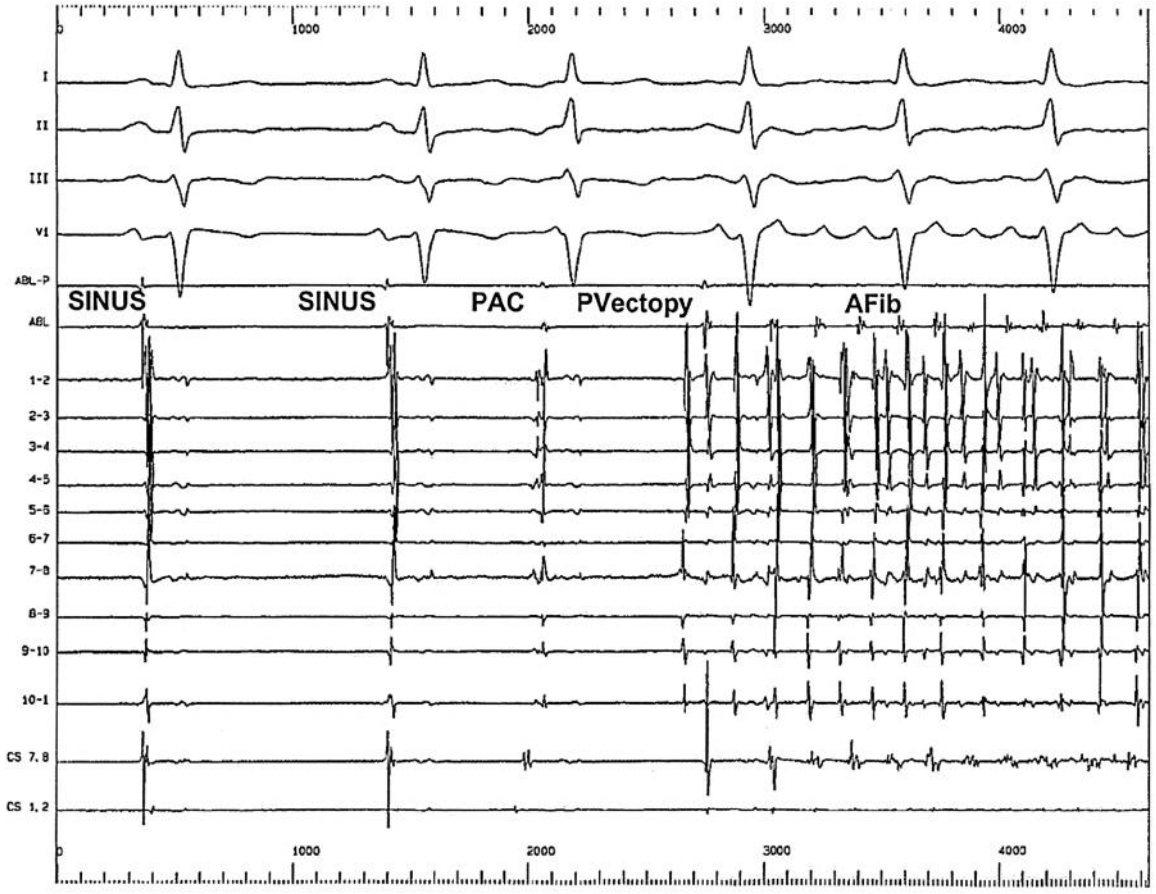


FIGURE 83–2. Rapid firing in a pulmonary vein (PV) with the spontaneous onset of atrial fibrillation (AFib). Two sinus beats are followed by a premature atrial complex (PAC) then rapid ectopy seen on a catheter positioned in a PV that starts AFib.

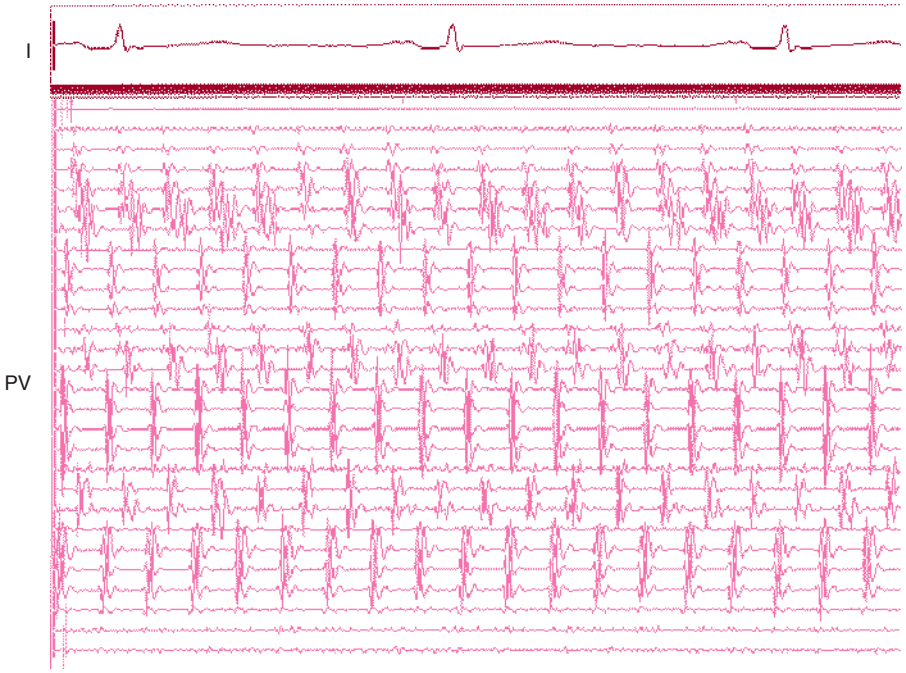


FIGURE 83–3. Simultaneous recordings of surface electrocardiographic lead I and bipolar electrograms from the right superior pulmonary vein (PV) of a patient after catheter ablation at the ostium of the vein produced conduction block from the vein into the left atrium. Note the rapid, irregular electrical activity recorded with a 64-electrode basket catheter within the pulmonary vein, with sinus rhythm in the remainder of the atria as recorded on the surface electrocardiogram.

veins in patients with paroxysmal AF, foci within the superior vena cava,[17] the ligament of Marshall,[18] and the musculature of the coronary sinus[19] have been identified. Other sites of initiating foci may be recorded in the left atrial appendage, left atrial wall, or along the crista terminalis in the right atrium.[3,20] For patients with pulmonary vein foci, a primary increase in adrenergic tone followed by a marked vagal predominance has been reported just before the onset of paroxysmal AF.[21] A similar pattern of autonomic tone has been reported in an unselected group of patients with paroxysmal AF and a variety of cardiac conditions.[22] Vagal stimulation shortens the refractory period of atrial myocardium but with a nonuniform distribution of effect. These factors support the importance of vagal stimulation in the induction of paroxysmal AF. In animal models, these pulmonary vein foci manifest delayed afterpotentials and triggered activity in response to catecholamine stimulation, rapid atrial pacing, or acute stretch.[11]

Atrial Fibrillation Maintenance

A variety of electrophysiologic and structural factors promote the perpetuation of AF. Moe and colleagues[23,24] proposed the multiple wavelet hypothesis as the mechanism of AF. Wavefronts traversing the atria fractionate into multiple daughter wavelets, the number of wavelets at any moment depends on the refractory period, conduction velocity, and anatomic obstacles in the atria. More recently, rotors or spiral wave reentry have shown importance as a perpetuating mechanism for AF in humans.[2,25-28] Ablation of these rotors can lead to termination of AF in some patients (Fig. 83–4).

Li and colleagues[29] demonstrated in a canine model of heart failure that interstitial fibrosis predisposed to intraatrial reentry and AF. Fibrosis of the atria may produce inhomogeneity of conduction within the atria, leading to conduction block and intraatrial reentry,[30] a mechanism that has been shown in animal models.[31,32] A variety of clinical studies have demonstrated that patients with AF have delayed interatrial conduction and inhomogeneous dispersion of atrial refractory periods.[33] Long-standing AF results in loss of myofibrils, accumulation of glycogen granules, disruption in cell-to-cell coupling at gap junctions,[34] and organelle aggregates.[35,36] Thus AF itself seems to produce a variety of alterations of atrial architecture that further contribute to atrial remodeling, mechanical dysfunction, and perpetuation of fibrillation, a concept of AF begetting more AF. Of note, recent data suggest the greater the atrial fibrosis, the less likely is success of catheter ablation using standard ablation approaches.[37]

In a population-based study of elderly patients without AF at baseline, Tsang and coworkers[38] demonstrated that AF developed in direct relation to the echocardiographic left atrial volume index. An even stronger predictor of the development of nonvalvular AF was a restrictive transmitral Doppler flow pattern. Thus clinical evidence for diastolic dysfunction strongly supports the concept that myocardial stretch is an important mechanism of AF in the elderly. Altered stretch on atrial

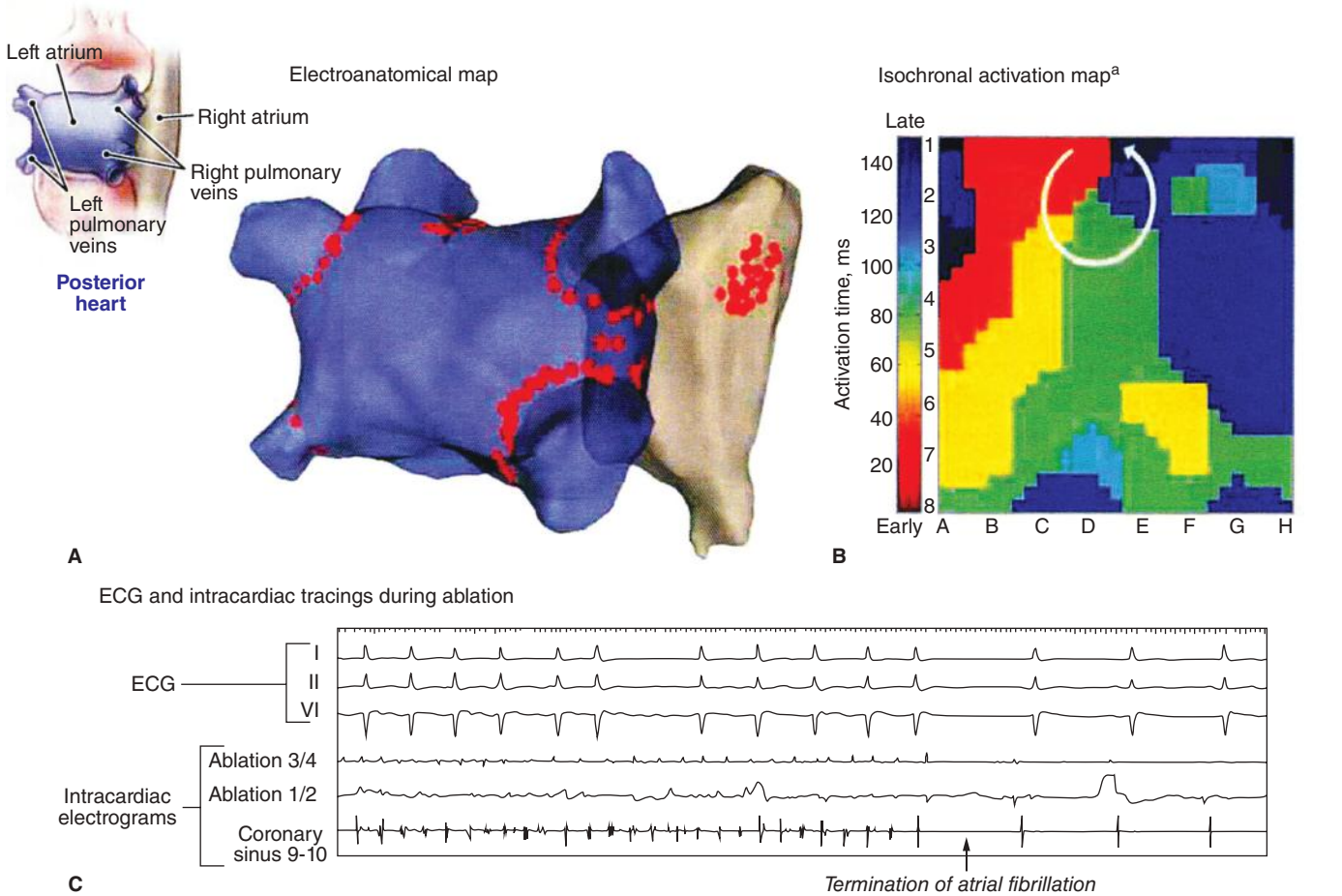


FIGURE 83–4. Catheter ablation to isolate the pulmonary veins and rotor mapping and ablation. **A.** Three-dimensional electroanatomic map of left (*blue*) and right (*gray*) atria in a patient with atrial fibrillation (AF). The *red dots* are ablation lesions that isolate the pulmonary veins in the left atrium, and target a rotor in the right atrium. **B.** A right atrial rotor activation sequence (*arrow*). **C.** Ablation of the rotor results in sudden termination of AF and restores sinus rhythm. Modified with permission from Prystowsky EN, Padanilam BJ, Fogel RI: Treatment of Atrial Fibrillation. *JAMA* 2015 Jul 21;314(3):278-288.

myocytes results in opening of stretch-activated channels.[11] Force transmitted to stretch-activated channels in the membrane or via cytoskeletal integrins produces opening of these channels as well as increasing local production of angiotensin II, which in turn increases L-type Ca^{2+} current and decreases the transient outward K^+ current. Stretch-activated channels increase G protein–coupled pathways, leading to increased protein kinase A and C activity and increased L-type Ca^{2+} current through the cell membrane and release of Ca^{2+} from the sarcoplasmic reticulum (promoting after depolarizations and triggered activity).[11]

CLINICAL MANIFESTATIONS

Clinical presentation of AF may relate to the disease itself or its consequences (thromboembolism and tachycardia-induced cardiomyopathy). Patients may exhibit none to disabling symptoms. Common symptoms include anxiety, palpitations, dyspnea, dizziness, chest pain, and fatigue. Several hemodynamic derangements, including rapid ventricular rates, loss of organized atrial contraction, irregularity of cardiac rhythm, and bradycardia (resulting particularly from sinus pauses when AF episodes terminate) may be the underlying cause of the symptoms. Many patients with symptomatic AF also have asymptomatic episodes.[2,39,40] Several studies have reported a marked reduction in quality of life in patients with AF.[41,42]

Evaluation of patients with AF starts with a complete history and physical examination. It is important to identify any reversible causes or contributory factors such as alcohol and obstructive sleep apnea. Electrocardiographic confirmation of AF is key, and capturing the onset may give valuable clues to therapy. In some patients AF may be caused by another arrhythmia (tachycardia-induced tachycardia,[43] for example, WPW reentry degenerating into AF (Fig. 83–5). Ablation of the accessory pathway responsible for AV reentry typically results in no recurrence of AF, especially in younger patients. Very frequent AF may be detected on a standard 12-lead ECG, but in many patients longer-term ECG monitoring with a 24-hour or multiple-day recorder is needed. It is suggested that patients also have a chest radiograph (if lung disease is suspected), echocardiogram, blood count, assessment of serum electrolytes, and assessment of renal, hepatic, and thyroid function.[3]

The ventricular rate during AF can be quite variable and depends on autonomic tone, the electrophysiologic properties of the atrioventricular (AV) node, and the effects of medications that act on the AV conduction system. The ventricular rate may be very rapid (> 300 bpm) in patients with the Wolff-Parkinson-White syndrome, with conduction over accessory pathways (wide preexcited QRS complexes) having short anterograde refractory periods (see Fig. 83–5). A regular, slow ventricular response during AF suggests an AV junctional rhythm, either as an escape mechanism with complete AV block or as an accelerated AV junctional pacemaker.

Thromboembolism

Stroke is the most common clinical thromboembolic event in AF, and approximately 36% of all strokes in individuals aged 80 to 89 years are attributed to AF.[44] Furthermore, strokes occurring in patients who have AF tend to have a higher degree of severity.[45] Individuals who have AF are not at equal risk for thromboembolic events and several predisposing clinical factors can identify those patients at high risk (discussed later). Most thrombi associated with AF arise within the left atrial appendage.[46] Flow velocity within the left atrial appendage is reduced during AF because of the loss of organized mechanical contraction.[47] Compared with transthoracic echocardiogram, the transesophageal echocardiogram offers a much more sensitive and specific means of assessing left atrial thrombi and spontaneous echo contrast, an indicator of reduced flow.[48] Several factors contribute to the enhanced thrombogenicity of AF. Nitric oxide (NO) production in the left atrial endocardium is reduced in experimental AF, with an increase in levels of the prothrombotic protein plasminogen activator inhibitor 1 (PAI-1).[49] The lowest levels of NO and the highest levels of PAI-1 were recorded in the left atrial appendage during AF. Patients with AF have elevated levels of β-thromboglobulin and platelet factor 4[50,51]; elevated plasma levels of von Willebrand factor (vWF), soluble thrombomodulin, and fibrinogen have been reported in patients with permanent AF with no evidence of diurnal variation in thrombogenicity.[52,53] In the Stroke Prevention in Atrial Fibrillation (SPAF) III study,[54] increased plasma levels of vWF were strongly correlated with the clinical predictors of stroke in AF (age, prior cerebral ischemia, HF, diabetes, and body mass index). There was a progressive increase in vWF with increasing clinical risk of stroke in this population.

Tachycardia-Induced Cardiomyopathy

In occasional patients, the first clinical manifestation of AF may be CHF related to a tachycardia-induced cardiomyopathy.[2,55,56] The left ventricular (LV) dysfunction develops as a result of sustained high

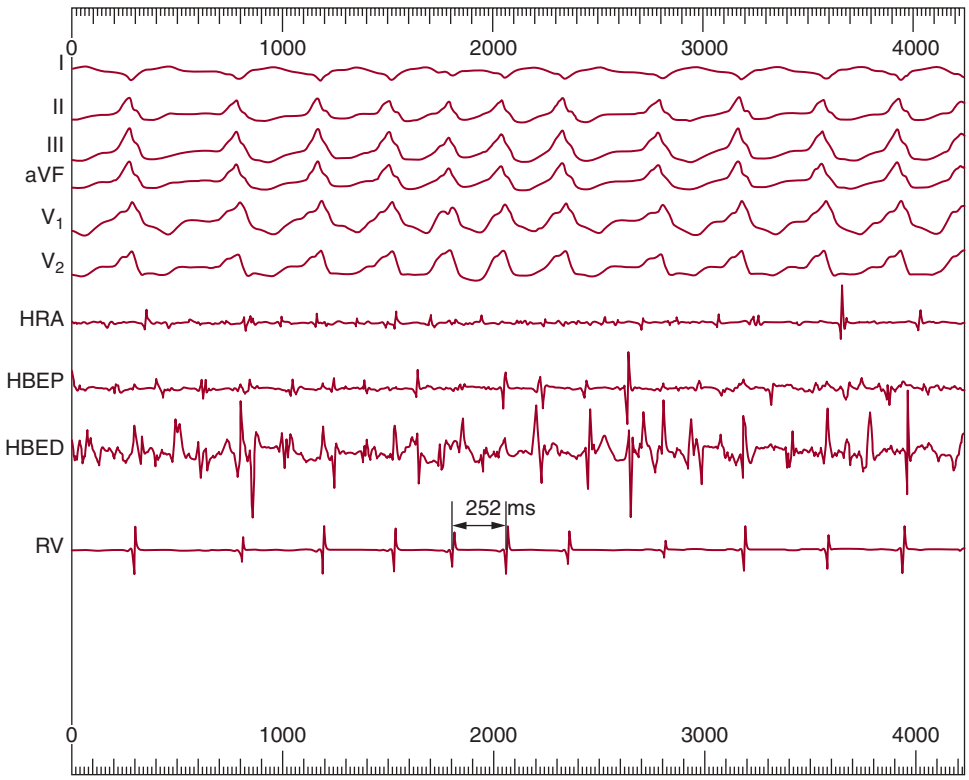


FIGURE 83–5. Atrial fibrillation with rapid ventricular response over an accessory pathway. HBED, distal His bundle electrogram; HBEP, proximal His bundle electrogram; HRA, high right atrium; RV, right ventricle.

ventricular rates during AF. This clinical syndrome generally occurs in patients who have minimal symptoms from AF and who present with shortness of breath. They typically have a sustained high ventricular rate (usually > 120 bpm) for prolonged time periods, often months to years.[57,58] However, the severity and temporal course of its onset varies significantly between individuals. Because the patients do not experience symptoms, they do not seek medical care initially. In these patients, control of the ventricular rate usually reverses the impaired LV function within weeks to months. In our experience, lack of fibrosis on cardiac MR augurs return to near or normal LV function.

Hemodynamic Effects

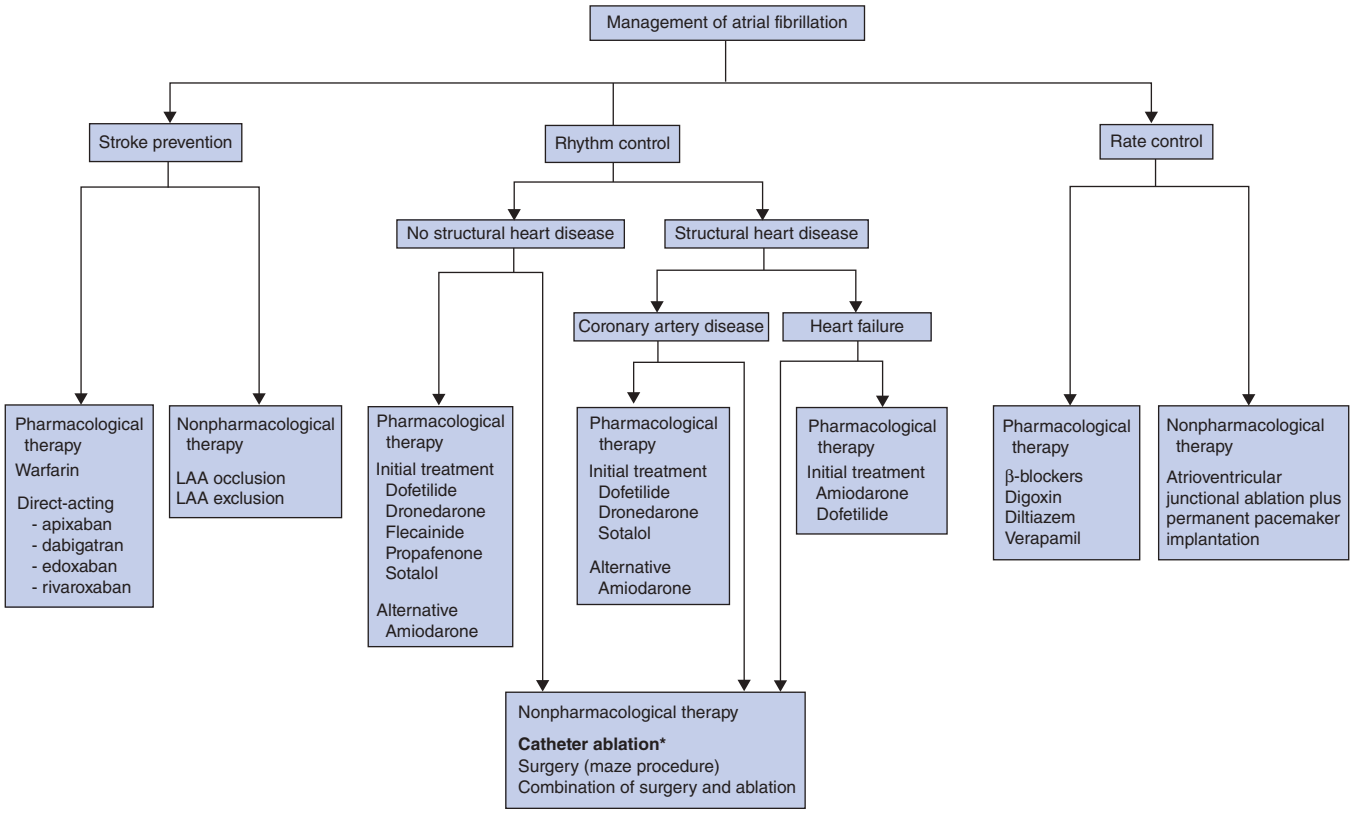
AF produces several adverse hemodynamic effects, including loss of atrial contraction, a rapid ventricular rate, and an irregular ventricular rhythm. The loss of mechanical AV synchrony may have a dramatic impact on ventricular filling and cardiac output when there is reduced ventricular compliance, as with LV hypertrophy from hypertension, restrictive cardiomyopathy, hypertrophic cardiomyopathy, or the increased ventricular stiffness associated with aging. In addition, patients with mitral stenosis, constrictive pericarditis, or right ventricular infarction typically experience marked hemodynamic deterioration at the onset of AF. The loss of AV synchrony results in a decrease in LV end-diastolic pressure (LVEDP) as the loading effect of atrial contraction is lost, thereby reducing stroke volume and LV contractility by the Frank-Starling mechanism. Although there is a reduction in the LVEDP, there is an increase in the left atrial mean diastolic pressure. Patients with significant restrictive physiology may experience pulmonary edema and/or hypotension with the onset of AF. In contrast, patients with dilated cardiomyopathy may experience minimal hemodynamic compromise with AF if their LV compliance is not significantly impaired. The inappropriately rapid ventricular rate during AF also limits the duration of diastole and reduces ventricular filling. The irregular ventricular rhythm has adverse hemodynamic effects that are independent of the ventricular rate. Irregular rhythm may significantly reduce cardiac output[59] and coronary blood flow[60] compared with a regular ventricular rhythm at the same average heart rate.

TREATMENT

Prevention of the disease-related complications (thromboembolism and tachycardia-induced cardiomyopathy) and control of symptoms may be considered the primary goals of AF management. The three major therapeutic strategies in managing AF include prevention of stroke, rate control, and rhythm control (Fig. 83–6). Anticoagulation with warfarin or the newer direct oral anticoagulants reduce the risk for stroke. Therapies to achieve symptom control and prevention of tachycardia-induced cardiomyopathy are often similar. For example, ventricular rate control during AF or maintenance of sinus rhythm may improve symptoms and prevent tachycardia-induced cardiomyopathy. When clinical goals are not met using one strategy, the alternate strategy can be pursued in the same patient. Primary prevention of AF is another area of great importance for research considering the high prevalence of the disease.

Anticoagulation

Risk Stratification Not all AF patients are at high risk for stroke. The recognized clinical markers predicting increased risk for stroke in AF are prior stroke or transient ischemic attack, hypertension, diabetes mellitus, HF, and age older than 75 years (Table 83–2).[3] Other less



*May be first-line therapy in paroxysmal AF in experienced centers.

FIGURE 83–6. Management of atrial fibrillation (AF). LAA, left atrial appendage. Modified with permission from Prystowsky EN, Padanilam BJ, Fogel RI: Treatment of Atrial Fibrillation, *JAMA* 2015 Jul 21;314(3):278-288.

TABLE 83–2. Stroke Risk in Patients with Nonvascular Atrial Fibrillation Not Treated with Anticoagulation According to the $CHADS_2$ Index

$CHADS_2$ Risk Criteria		Score
Prior stroke or TIA		2
Age > 75 y		1
Hypertension		1
Diabetes mellitus		1
Congestive heart failure		1
Patients (n = 1733)	**Adjusted Stroke Rate (%/y)[a] (95% CI)**	**$CHADS_2$ Score**
120	1.9 (1.2-3.0)	0
463	2.8 (2.0-3.8)	1
523	4.0 (3.1-5.1)	2
337	5.9 (4.6-7.3)	3
220	8.5 (6.3-11.1)	4
65	12.5 (8.2-17.5)	5
5	18.2 (10.5-27.4)	6

[a]The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage.

Abbreviations: $CHADS_2$, cardiac failure, hypertension, age, diabetes, and stroke (doubled); CI, confidence interval; TIA, transient ischemic attack.

validated stroke risk factors include coronary artery disease, thyrotoxicosis, female sex, LV dysfunction, and age older than 65 years.[3] Mitral stenosis is well known to be associated with high risk for stroke in AF patients and warfarin anticoagulation is indicated in all such patients.

The $CHADS_2$ stroke risk stratification scheme, which is based on analysis of 1773 patients in the National Registry for Atrial Fibrillation, gained considerable favor and was used in the ACC/AHA/ESC 2006 guidelines to tailor therapy for stroke prevention.[61] Each of the letters in this acronym represents a risk factor—congestive heart failure, hypertension, age, diabetes, and stroke. Previous stroke or transient ischemic attack is the strongest predictor of stroke and therefore carries 2 points, whereas the other risk factors carry 1 point each. The adjusted stroke rate per 100 patient-years increases from 1.9 with a score of 1 to 18.2 with a score of 6 (see Table 83–2). Although $CHADS_2$ provides a simple tool for predicting individual risk of stroke related to AF, it accounts for only part of the risk (c-statistic = 0.570).[62] Not all patients with a $CHADS_2$ score of 0 are at low risk and other risk factors have been identified that are not encompassed by this tool.[63,64]

The 2012 ESC guidelines and 2014 ACC/AHA/HRS guidelines recommended use of a more nuanced risk stratification schema (CHA_2DS_2-VASc), summarized in Table 83–3.[3] The CHA_2DS_2-VASc schema recognizes that stroke risk in patients with AF is related to age as a continuous variable, acknowledges the higher, albeit unequal, risk of stroke faced by women, and incorporates the less validated risk associated with vascular disease, prior MI, complex aortic plaque, and peripheral arterial disease, although these may contribute unequally. Because of its greater sensitivity, the CHA_2DS_2-VASc better excludes lowest-risk patients who may not benefit as much from anticoagulation, but it still fails to account for a considerable proportion of risk (c = 0.578). Oral anticoagulants are recommended for patients with a prior stroke, TIA, or CHA_2DS_2-VASc score of 2 or more; either oral anticoagulants, aspirin, or no antithrombotic therapy can be considered for CHA_2DS_2-VASc of 1; and antithrombotic therapy may be omitted for CHA_2DS_2-VASc score of 0.[3]

TABLE 83–3. CHA_2DS_2-VASc Scoring System for Stroke Risk in Atrial Fibrillation

	Score
Congestive HF	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease[a]	1
Age 65-74 years	1
Female gender (sex category)	1

[a]Prior myocardial infarction, peripheral artery disease, aortic plaque.

Abbreviations: HF, heart failure; TIA, transient ischemic attack; TE, thromboembolism.

There is widespread consensus that all patients with rheumatic valvular heart disease or prosthetic heart valves and AF require anticoagulation unless there is an absolute contraindication. There is no difference in the indications for antithrombotic therapy between paroxysmal, persistent, or permanent AF. The pathogenic mechanisms linking atrial fibrillation with ischemic stroke are incompletely understood. Clinical risk assessment instruments like the CHA_2DS_2-VASC score do not fully account for thromboembolic risk, and stroke can occur after sinus rhythm is restored by electrical or pharmacological cardioversion. Atrial fibrosis correlates with both the persistence and burden of AF, and gadolinium-enhanced magnetic resonance imaging is gaining utility for detection and quantification of the fibrotic substrate, but methodological challenges limit its use. There is increasing evidence that the fibrotic atrial cardiomyopathy associated with AF is thrombogenic and that AF is a marker of stroke risk regardless of whether or not the arrhythmia is sustained. Antithrombotic therapy should therefore be guided by a comprehensive assessment of intrinsic risk rather than the presence or absence of AF at a particular time.

Antithrombotic Therapy Warfarin is remarkably effective at reducing stroke risk in patients with AF (Fig. 83–7). This was demonstrated by a meta-analysis of five randomized, controlled clinical trials comparing warfarin versus placebo or no therapy. When analyzed according to intention-to-treat, there was a 68% risk reduction in stroke for patients taking warfarin compared with patients in the control groups who were not anticoagulated ($P < .001$).[65] Moreover, on-treatment analysis demonstrated an 83% risk reduction in stroke when patients were taking warfarin compared with placebo.[66] Warfarin should be administered to achieve an international normalized ratio (INR) between 2 and 3 for optimal efficacy and safety (Fig. 83–8).

Meta-analysis of studies comparing aspirin with placebo suggests a relative risk reduction of approximately 22% with aspirin. Comparisons of warfarin versus aspirin show superiority of warfarin (Fig. 83–9). Additional concerns using aspirin for stroke prevention in lieu of warfarin relate to severity of stroke.[68,69] Thus, warfarin with an INR ≥ 2 not only reduces the frequency of ischemic stroke, it also reduces the severity and risk of death from stroke compared with aspirin.

Several trials compared the safety and efficacy of alternative oral anticoagulants to reduce risk of stroke in patients with AF.[70-74] In a trial involving patients with AF at increased risk of stroke who were deemed unsuitable for warfarin, the combination of aspirin plus clopidogrel compared with aspirin alone had a small, but significant reduction in

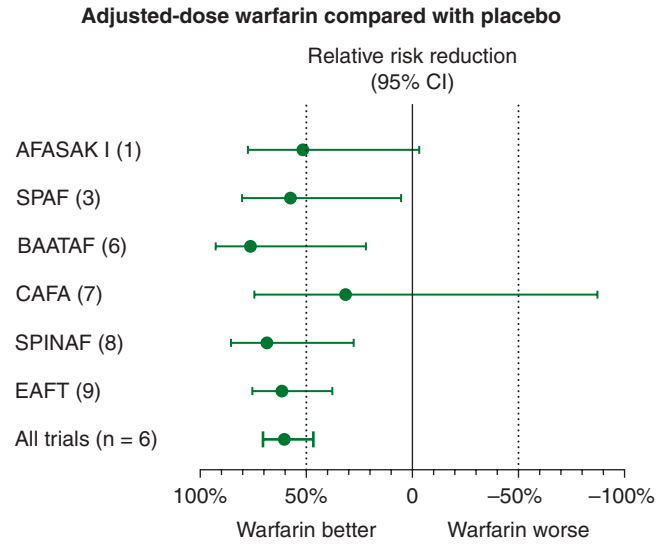


FIGURE 83–7. Effects of warfarin versus placebo on risk of stroke in six randomized, placebo-controlled clinical trials in nonvalvular atrial fibrillation. AFASAK I, The Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention in Atrial Fibrillation. Data from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. *Ann Intern Med*. 1999 Oct 5;131(7):492-501.

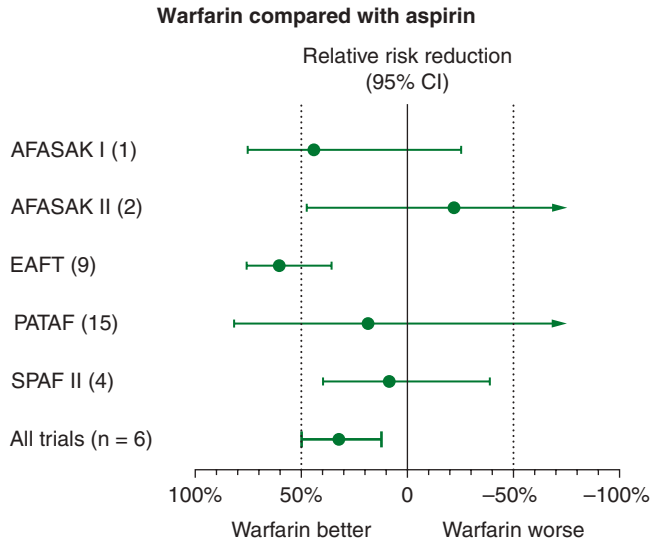


FIGURE 83–9. Effects of aspirin versus warfarin on risk of stroke in five randomized, controlled clinical trials in nonvalvular atrial fibrillation. AFASAK I and AFASAK II, The Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study; EAFT, European Atrial Fibrillation Trial; PATAF, Primary Prevention of Arterial Thromboembolism in Non-rheumatic Atrial Fibrillation; SPAF II, Stroke Prevention in Atrial Fibrillation. Data from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. *Ann Intern Med*. 1999 Oct 5;131(7):492-501.

the risk of major vascular events, especially stroke, but increased the risk of major hemorrhage.[70] Several target-specific novel oral anticoagulants (NOACs) act by direct inhibition of thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, and edoxaban). Unlike vitamin K antagonists, these anticoagulants do not require routine INR monitoring and possess favorable pharmacological properties. They act rapidly, and have a stable and predictable dose-related anticoagulant effect with few clinically relevant drug-drug interactions. Trials comparing these agents to warfarin for stroke prevention in patients with nonvalvular AF demonstrated that they are at least as efficacious and safe as warfarin.[75] Clinical practice guidelines have incorporated these anticoagulants for

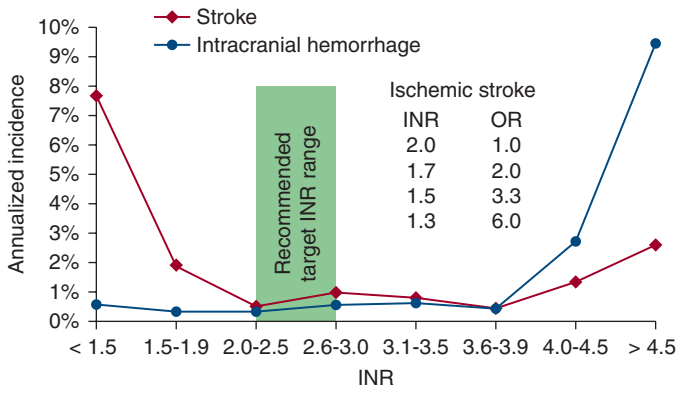


FIGURE 83–8. Effects of aspirin versus placebo on risk of stroke in five randomized, placebo-controlled trials in nonvalvular atrial fibrillation. AFASAK I, The Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; ESPS II, European Stroke Prevention Study; LASAF, Alternate-Day Dosing of Aspirin in Atrial Fibrillation Pilot Study Group; SPAF I, Stroke Prevention in Atrial Fibrillation; UK-TIA, United Kingdom Transient Ischaemic Attack Trial. Data from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. *Ann Intern Med*. 1999 Oct 5;131(7):492-501.

stroke prevention in nonvalvular AF, but safe and effective use requires understanding of their distinct pharmacological properties.

Dabigatran, a direct competitive inhibitor of thrombin (coagulation factor IIa), and rivaroxaban, apixaban, and edoxaban, which inhibit coagulation factor Xa, have shown noninferior or superior efficacy against all stroke (ischemic plus hemorrhagic) and systemic embolism with rates of major bleeding comparable to or lower than warfarin. The doses of each are modified according to renal function. Considered collectively, the NOACs have been associated with significantly lower risks of intracerebral hemorrhage than even well-adjusted warfarin in the trials leading to their approval for clinical use, generally better outcomes even in cases when major bleeding occurred, and lower rates of all-cause mortality when used for thromboembolism prevention in patients with nonvalvular AF. These agents have not been proven safe or effective in patients with AF associated with rheumatic mitral stenosis or mechanical heart valves, and experience in patients with AF who have undergone bioprosthetic heart valve replacement or valve repair is limited.

Despite several advantages, when introduced there were no readily available coagulation assays to measure anticoagulation effect of the NOACs, making it difficult to titrate dosage and identify causes of therapeutic failure and creating challenges in emergent situations including trauma, hemorrhage, or need for invasive procedures. There were initially no evidence-based strategies for rapid reversal of the anticoagulant effects of these agents for situations in which the relatively short half-lives were not sufficient. In contrast, anticoagulation induced by warfarin can be attenuated by administration of vitamin K and more rapidly reversed by fresh frozen plasma or four-factor prothrombin complex concentrate (PCC).[76] However, there is lack of evidence proving that the consequences of CNS hemorrhage occurring on warfarin can be favorably influenced by available reversal strategies, including four-factor PCC. A humanized antibody against dabigatran (idarucizumab) was introduced for clinical use in 2015,[77] and a decoy-based approach to reversal of anticoagulation induced by the factor Xa inhibitors is under accelerated clinical development.[78]

Although several risk stratification schemes have been proposed to assess the risk of bleeding during anticoagulant therapy, notably the HEMORR2HAGES,[79] HAS-BLED,[80] and ATRIA[81] scores, they are relatively limited, having been derived from historical cohorts anticoagulated with warfarin, and have not been validated for use in patients treated with NOACs. They are intended to predict major bleeding but not specifically intracranial or fatal bleeding, and have been incorporated in the European (ESC) practice guidelines but not the American (ACC/AHA/HRS) guidelines, which do not advise formal use of bleeding risk scores. It is important to bear in mind that a stroke prevention benefit of anticoagulation is preserved even in patients at increased risk of bleeding, and that in the process of clinical decision making, risk should generally be stratified first on the basis of stroke risk, with the risk of bleeding considered as a modifying factor.

A percutaneous closure device introduced into the left atrial appendage (LAA) may be an alternative for patients in whom long-term anticoagulation with warfarin is not considered optimum for stroke prevention.[82] The LAA occlusion strategy has not been compared with anticoagulation using the NOACs for stroke prevention in patients with nonvalvular AF, and clear indications for the device-based approach are in evolution.

Rate Control Versus Rhythm Control Strategies

Whenever possible, potential reversible causes of AF should be identified and treated, even if they may only ameliorate AF.[2,3] Hyperthyroidism is a very uncommon cause of AF, but therapy of it often leads to disappearance of AF. Treatment of obstructive sleep apnea and significant weight loss in obese patients can reduce AF episodes.[83-85]

Many factors should be considered when choosing a primary treatment strategy of rate or rhythm control. A rate control strategy assumes maintenance of sinus rhythm is not needed, but it is important to consider whether sinus rhythm may be needed in the future, for persistence of AF for years often results in the inability to restore and maintain sinus rhythm. An example is a patient with ventricular hypertrophy that may worsen over time in whom sinus rhythm may then be important. Age is another factor to consider, for although several prospective, randomized trials have been published comparing the strategies of rate control and rhythm control in patients with AF, most patients have been over 65 years old.[86-88]

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial enrolled 4060 patients aged older than 65 years (mean age 69.7 years) or with risk factors for stroke, randomizing them to rate versus rhythm control.[86] Over a mean follow-up period of 3.5 years, there was no significant difference in overall mortality between the two groups. Hypertension was present in 70.8% of patients and coronary artery disease in 38.2%. More than two-thirds of the patients in the rhythm control group received either sotalol or amiodarone.

The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial[87] randomly assigned 522 patients with persistent AF after electrical cardioversion to either a rate-control or a rhythm control treatment. The mean age was 68 years, and follow-up was a mean of 2.3 years. Hypertension was present in 55% compared with 43% in the rhythm and rate control groups, respectively ($P = .007$). There was no difference in the primary end point of the study (a composite of cardiovascular death, CHF, thromboemboli, bleeding, need for pacemaker, or serious drug side effects) between the two strategies.

There was no difference in any clinical outcomes in a recent meta-analysis of 10 studies that compared rhythm (drugs) versus rate control strategies.[89] An observation of an exploratory subanalysis showed that patients younger than 65 years had an advantage with rhythm control in the prevention of all-cause mortality. Although interesting, this observation requires confirmation in prospective studies.

Follow-up in AFFIRM and RACE was less than 4 years. Caution should be exercised extending the results to longer follow-up periods and to younger patients. In a large population-based database of patients with AF, no difference in mortality was noted in those treated with either rhythm or rate control drugs during the first 4 years, but for those who survived more than 5 years, a lower mortality was noted in the rhythm control group.[90]

Although stroke has been studied in detail in rate versus rhythm control trials, other neurologic consequences have not. Future studies should address the potential consequences of AF on cognitive impairment, silent cerebral infarcts, memory impairment, and Alzheimer disease, which have been reported with AF.[91,92] In summary, the choice of a rhythm or rate control strategy should be individualized for each patient, and the physician should be flexible and be willing to modify the strategy if the clinical situation changes.[2] If rate control is chosen and symptoms persist, rhythm control should be tried. In reality, many patients who have rhythm control using antiarrhythmic drugs will require AV node blockers to slow the ventricular rate if AF recurs. Selection of various drugs is shown in Fig. 83–6. Anticoagulation is needed in patients at high risk for stroke regardless of whether a rate or rhythm-control strategy is chosen.

Rate Control

Medical Therapy Control of the ventricular rate involves both acute and chronic phases. In the acute phase, intravenous metoprolol, esmolol, diltiazem, or verapamil have all been demonstrated to provide slowing of AV nodal conduction; these drugs are indicated for patients with severe symptoms related to a rapid ventricular rate.[2,3] Intravenous digoxin requires a longer duration to achieve rate control and is less useful. Intravenous amiodarone, usually employed for acute AF conversion, has the ability to slow the ventricular response via its beta-blocking and calcium channel blocking effects. Heart rate slowing may be seen within minutes of its acute administration.[93]

For patients with only mild or moderate symptoms, oral medications that slow AV nodal conduction should be prescribed. After control of the resting ventricular rate has been achieved, attention is paid to the ambulatory heart rate. There is no overall agreement on what constitutes optimum rate control.[94] One set of criteria is 60 to 80 bpm at rest and between 90 and 115 bpm during moderate exercise.[3] In a small randomized study, lenient rate control (less than 110 bpm) was not found to be inferior to more stringent rate control (less than 80 bpm).[95]

It is also uncertain which method is best to evaluate rate control, which has been done using a resting 12-lead ECG, 24-hour Holter monitor, exercise testing, and combinations of methods.[94] In essence, achievement of rate control for each patient during their usual daily activities seems reasonable, so titrating AV nodal blockers on an outpatient basis following the daily 24-hour heart rate plot as a guide appears useful.[94]

Digoxin may provide effective control of the resting heart rate but is often ineffective during exertion, making it less than ideal in young active patients. β-Adrenergic blockers or calcium channel blockers achieve much better control of the ventricular rate during exercise and should be considered for most patients. Digoxin is most useful in the setting of impaired systolic function, and also can be used in combination with β-blockers or calcium antagonists if these agents do not provide adequate rate control. Recent conflicting data have been developed regarding digoxin's effect on cardiovascular and total mortality. The prevailing opinion is that digoxin can be used safely at lower doses and with careful monitoring of renal function.[96]

Control of the ventricular rate can be especially challenging for patients with the tachycardia-bradycardia syndrome, who experience rapid ventricular rates during AF and sinus bradycardia or sinus pauses

when AF terminates. Ablation of AF or AV node ablation and permanent pacemaker implantation is indicated for many of these patients.

Atrioventricular Node Ablation Some patients may continue to experience significant symptoms from a rapid or irregular ventricular rhythm despite drug therapy. Catheter ablation of the AV conduction system and permanent pacemaker implantation is a highly effective means of establishing permanent control of the ventricular rate during AF in selected patients.[97-99] Despite the many favorable effects of this procedure, there are several limitations. First, AV nodal ablation does not change the long-term need for anticoagulation. Second, although an adequate junctional escape rhythm may be present after ablation, some patients may become pacemaker dependent as a result of an inadequate escape rhythm. Third, right ventricular pacing produces an abnormal LV contraction sequence, and acute worsening of hemodynamics has been observed in some patients. The development of a right-ventricular pacing-induced cardiomyopathy can occur.[2] In the Post AV Node Ablation Evaluation (PAVE) trial, patients who received biventricular versus right ventricular apical pacing, especially those with abnormal LV ejection fractions before ablation, had longer 6-minute walking distances and higher LV ejection fractions after ablation.[100]

Rhythm Control When a rhythm control strategy is chosen for patients with paroxysmal or persistent AF, prophylactic treatment with antiarrhythmic drugs is usually needed to maintain sinus rhythm. Although the ideal of pharmacologic therapy would be to prevent all recurrences of AF, this is unrealistic for many patients. Rather, marked reduction of the frequency, duration, and symptoms of AF may be a very acceptable clinical goal. In addition, the use of pharmacologic agents resulting in an apparent clinical resolution of AF does not change the indication for anticoagulation.

Some patients can be managed with intermittent antiarrhythmic drug therapy, the so-called pill-in-the-pocket approach (see "Pharmacologic Cardioversion" later in the chapter). This approach must be reserved for patients who have highly intermittent and terminable episodes of AF who are also motivated to keep drug supplies available over long intervals. A corollary is the "booster" approach in which patients are given permission to use supplemental doses of a safe and effective chronic therapy upon AF recurrence. Again, patient selection is the key to employing these strategies successfully.[3]

The choice of pharmacologic agent is largely determined by the potential side effects of a given drug in an individual patient rather than comparative efficacy. The first drug chosen is usually associated with a lowest risk of serious side effects for that patient. For most patients, a specific etiologic factor for the initiation of AF cannot be identified. Conversely, if such an inciting factor is uncovered, therapeutic efforts should be targeted to eliminating it. Examples include β-blockers for exercise-induced AF and avoidance of alcohol in particularly sensitive individuals.

Many agents have effectiveness to maintain sinus rhythm in patients with AF.[3] Because class IC drugs may suppress AF but promote atrial flutter, they are combined with a β-blocker or calcium channel blocker to decrease the risk of atrial flutter with 1:1 ventricular response, a potentially life-threatening situation. Monitoring the QRS duration and PR interval is important during class IC therapy. Sotalol, dofetilide, and amiodarone prolong ventricular refractoriness and the QT interval. Monitoring the QT interval during initiation of therapy is important. If possible, avoid corrected QT intervals of > 500 to 520 milliseconds with sotalol and dofetilide, but longer QT intervals may occur without a risk of proarrhythmia in patients receiving amiodarone. Periodic ECGs should be obtained on an outpatient basis in patients receiving antiarrhythmic drugs, and efforts to avoid hypokalemia and hypomagnesemia are important.

Amiodarone is the most effective drug for the treatment of atrial fibrillation despite the fact that it has not gained regulatory approval for this indication in the United States. It is a complex drug pharmacologically with protean toxicity that mandates careful clinical supervision. Its most feared and dangerous side effect is pulmonary fibrosis, which can be lethal if not diagnosed promptly.[101]

Dronedarone is the most recent oral antiarrhythmic drug approved for the treatment of patients with AF and atrial flutter.[102] It is a noniodinated benzofuran derivative of amiodarone.[103] Like amiodarone, it blocks multiple channels, including sodium, potassium, and calcium, and has noncompetitive antiadrenergic effects. Compared with placebo in two randomized controlled trials, dronedarone prolonged the median times to recurrence of arrhythmia.[104] In a multicenter randomized controlled trial of more than 4600 patients, dronedarone reduced the incidence of hospitalization from cardiovascular events or death in patients who had atrial fibrillation.[105] A follow-up study, PALLAS, failed to demonstrate a benefit on a similar endpoint when dronedarone was administered to patients with heart disease and permanent AF. Based on this study and ANDROMEDA, which enrolled recently hospitalized patients with heart failure,[106] dronedarone is contraindicated in patients with permanent AF, those with class II to IV heart failure, and those with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.

Recent data have emerged regarding the safety and efficacy of combining lower doses of dronedarone with ranolazine, a late sodium channel blocker that has been shown to be moderately effective in suppressing atrial fibrillation.[101] In a late phase II trial, the combination was superior to both placebo and to individual components in reducing AF burden in patients with devices, with an excellent safety profile.[107] We await phase III studies of this interesting formulation.

There are few studies of the safety of initiating drugs in the outpatient setting, but some general rules are useful. Flecainide and propafenone can be initiated in patients without heart disease who are in sinus rhythm, and safety is maximized if AV nodal blockers are given first. Amiodarone can be used in patients with or without sinus rhythm, but frequent ECG monitoring, for example, by using event recorders, is recommended to identify any potential bradycardia or tachycardia proarrhythmia. Sotalol may be administered to patients in sinus rhythm with minimal or no heart disease and normal QT interval and electrolyte status; the lowest dose should be used and an ECG should be obtained within days of starting sotalol to determine the QT interval. The same process should occur for any dose increase. Dofetilide must be started in hospital, and dronedarone is typically started out of hospital.

Antiarrhythmic Drug Selection As stated, antiarrhythmic drugs are selected on a safety-first basis (see Fig. 83–6). The ACC/AHA/HRS guidelines[3] suggest that patients with no structural heart disease start with dofetilide, dronedarone, flecainide, propafenone, or sotalol, agents with minimal noncardiac toxicity. Second-line therapy is either amiodarone or catheter ablation. Patients with hypertension who do not have substantial LV hypertrophy have a similar treatment algorithm, but those with substantial LV hypertrophy are considered at increased proarrhythmic risk with most drugs other than amiodarone, which becomes first-line therapy in this circumstance. Catheter ablation is second-line treatment in most clinical situations but may be considered first-line in some patients (discussed later). Safety of drugs in coronary artery disease has been demonstrated for dofetilide, dronedarone, and sotalol (first line) and amiodarone (second line), and catheter ablation is also a second-line treatment. For patients with heart failure, first-line treatment can be either amiodarone or dofetilide, but the authors prefer amiodarone in most circumstances, and ablation

as second-line therapy. Class IA agents quinidine, procainamide, and disopyramide are rarely used in clinical practice, although quinidine, by virtue of its effect on Ito, and other nonsodium channels, may be useful for rare patients with inherited channelopathies such as Brugada syndrome and the short QT syndrome.[108] Dronedarone appears to be a safe drug to use as first-line therapy in patients with normal or nearly normal hearts.

Nontraditional Antiarrhythmic Agents Several drugs used to treat other medical conditions have shown promise as adjuvant therapy in patients with AF including anti-inflammatory drugs. Drugs that modulate the rennin-angiotensin-aldosterone system—for example, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers—may decrease the incidence of AF when examined retrospectively in trials of other purpose.[3] These drugs can reduce atrial fibrosis and promote more favorable hemodynamics, but it is not clear if these actions are important to reduce AF. Prospective randomized trials have not proven benefit. Preliminary data also support the beneficial effect of statins to reduce AF without clear efficacy in controlled trials.[3]

Fish oils have also been touted as having a treatment effect in AF, although the largest and best controlled studies of these agents have failed to show benefit. At this time these is no evidence to support the routine use of nonmembrane-active antiarrhythmic drugs for the prevention or termination of AF.[109]

Cardioversion Cardioversion can be accomplished using either antiarrhythmic drugs or the direct-current approach. In situations in which urgent cardioversion is needed, such as marked hypotension, the direct-current approach is preferred. The need for anticoagulation before cardioversion must be considered. There is general consensus that AF that has been present for < 48 hours can be cardioverted without prior anticoagulation, but there are no randomized trial data to support this, and systemic emboli can potentially occur even in this situation.[110] Because it is often impossible to time accurately the onset of AF, if cardioversion is needed soon, transesophageal echocardiography and anticoagulation therapy are recommended for AF of uncertain duration.

There are two basic anticoagulation strategies before cardioversion: (1) oral warfarin with a therapeutic INR (2-3) for 3 to 4 weeks before cardioversion followed by continued warfarin therapy for a minimum of 4 weeks, or (2) transesophageal echocardiography (TEE) and intravenous heparin immediately before cardioversion followed by oral warfarin thereafter.[111] The recent AHA/ACC/HRS guidelines suggest use of a NOAC for 3 weeks before cardioversion is reasonable,[3] but there are few prospective data supporting this. The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) study randomized 1222 patients with AF undergoing direct-current cardioversion between these strategies and found no difference in the rate of embolic events (0.5% TEE vs 0.8% conventional) but a lower risk of bleeding complications (2.9% vs 5.5%) and a shorter interval to cardioversion (3.0 vs 31 days) in the TEE-guided group.[112] The left atrial mechanical function may be significantly impaired for up to several weeks after cardioversion from AF to sinus rhythm. This *stunning* effect on the atria may occur after either electrical or pharmacologic cardioversion[113-115] and is more marked with longer duration of AF. In patients without high-risk factors for stroke, anticoagulation can be discontinued approximately 4 weeks after cardioversion. If the patient has a standard indication for warfarin before cardioversion, anticoagulation should be continued indefinitely after cardioversion unless a clear reversible cause of AF has been corrected.

Direct Current Cardioversion Successful electrical cardioversion requires attention to details. Always be sure the patient is adequately anticoagulated. Rather than use handheld paddles, adhesive gel electrodes can be placed anteriorly over the sternum (with the upper edge at the sternal angle) and posteriorly (just to the left of the spine).[116] If cardioversion is not successful with this electrode position, a different electrode placement such as anterior-lateral configuration can be attempted. The shock must be synchronized to the QRS complex, and it is important to select an ECG lead that has a prominent R wave with no sensing of the T wave. Cardioversion shocks are painful and the patient requires adequate anesthesia. Biphasic waveforms clearly improve defibrillation efficacy at all energy settings as compared with monophasic shocks.[117,118] An initial shock energy of 200 J or more is recommended for both monophasic and biphasic waveforms.[119] However, in patients with smaller body habitus who have not had AF of long duration, we typically start with approximately 120 J using biphasic waveform shocks. Another theoretical reason for using higher initial shock energies is to avoid initiating ventricular fibrillation if by accident the shock falls on the T wave. A high-energy shock has a better chance of being above the lower limit of vulnerability to induce ventricular fibrillation. Consideration should be given to selected patients, for example, those with AF duration > 3 months, to receive an antiarrhythmic drug before cardioversion to avoid immediate or early recurrence of AF.

Pharmacologic Cardioversion The duration of AF is a major factor for cardioversion success using antiarrhythmic drugs, and AF lasting < 1 week has a substantial chance of cardioversion using oral flecainide, propafenone, dofetilide, and intravenous ibutilide.[3] For longer duration AF, only dofetilide seems to have a reasonable chance of success, but amiodarone and ibutilide may be useful.[3] A single oral dose of propafenone (eg, 600 mg) or flecainide (eg, 300 mg) can be useful to convert recent-onset AF to sinus rhythm.[120-123] A recent study demonstrated the safety of the *pill-in-the-pocket* approach to outpatient conversion of AF in some patients.[124] Select patients were observed in hospital while being given a single oral loading dose of either propafenone or flecainide to convert AF. Those with success were allowed to self-administer the drug if they had a recurrence of AF, and few complications occurred during follow-up. Because a type 1C drug may convert AF to atrial flutter with 1:1 conduction to the ventricle, an AV nodal blocking agent should be administered concomitantly, although the actual occurrence is very low.

Dofetilide is useful to convert AF of both short and long duration, although it is not commonly used expressly for this purpose.[125,126] Intravenous ibutilide has also been demonstrated to provide effective cardioversion of recent-onset AF or flutter and is one of the very few drugs that has gained regulatory approval for this indication.[127] The risk of nonsustained or sustained torsades de pointes ventricular tachycardia was 3.6% across studies. Thus, although effective, intravenous ibutilide requires continuous electrocardiographic monitoring for at least 4 hours after administration. Ibutilide is far more effective than intravenous procainamide (51% vs 21%) for the acute termination of AF.[128] Intravenous amiodarone has some efficacy, but onset of action is frequently delayed for several hours, which makes the drug less useful in clinical practice.[129]

Vernakalant is a multichannel blocker that was studied extensively in an intravenous formulation for this indication and was found to have a placebo-subtracted efficacy of > 40% in most studies. The drug is available in a few countries primarily in Europe, but not in the United States, where concern was registered regarding cases of hypotension and bradycardia following conversion to sinus rhythm.[130]

Nonpharmacologic Options of Rhythm Control

Catheter Ablation The observation that rapidly firing atrial impulses from the pulmonary veins could initiate AF led to the catheter ablation approach of pulmonary vein isolation (PVI) to cure AF[13] (see Fig. 83–3). Although the site of initiation of AF may be noted during

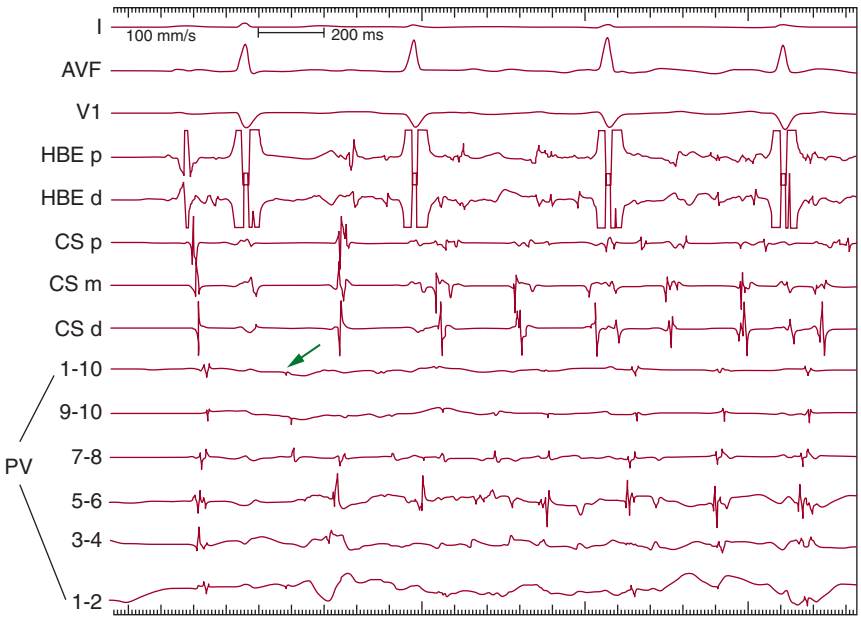


FIGURE 83–10. Spontaneous onset of atrial fibrillation (AF) by rapid firing from a pulmonary vein (PV). The onset of AF (*arrow*) is produced by rapid firing from the PV 1-10 electrode pair of a circular mapping catheter in the PV. Note that PV activity occurs before the coronary sinus (CS) electrograms. d, distal; HBE, His bundle electrogram; p, proximal.

the study (Fig. 83–10), the goal is usually to isolate all the pulmonary veins. PVI has had reasonably good success to cure patients with paroxysmal AF, but has shown limited efficacy in patients who have persistent or long-standing persistent AF.[2] Triggers can also originate in the right atrium, left atrial appendage, LA posterior wall, superior vena cava, crista terminalis, vein of Marshall, and coronary sinus.[3,131]

Atrial substrate is likely important to the maintenance of AF, especially in persistent AF. Various approaches have been tried to modify atrial tissue including linear atrial ablation lines and ablation of complex fractionated atrial electrograms, but with limited success.[2] More recently, rotors (spiral waves) have been shown to sustain AF and these can be located in various sites in the right and left atria.[27,28,132] Ablation of these rotors (see Fig. 83–4) can yield improved outcomes even in patients with persistent AF.[132] Using a noninvasive mapping technique, the concept of AF maintenance by focal drivers was validated during ablation of AF.[133] Radiofrequency energy is the most common energy source used for PVI, but cryoablation[134] is also effective to achieve PVI. In a recent multicenter randomized trial of patients with paroxysmal AF, efficacy was similar using cryoballoon ablation compared with radiofrequency ablation.[135] Using meta-analysis, the long-term success of AF ablation after a single procedure was 54.1% and 41.8% for paroxysmal and persistent AF, respectively.[2,136] The success improved to 79.8% with multiple procedures.[136] Further, data from multiple randomized clinical trials that compared medical therapy with catheter ablation showed the superiority of ablation to eliminate clinical AF symptoms and episodes.[134,137-144] Current guidelines state that catheter ablation in experienced centers may be performed as first-line therapy in symptomatic patients who have paroxysmal AF (see Fig. 83–6).[3,131] (In a worldwide survey of 85 institutions, major complications occurred in 4.5 % of ablations including stroke and cardiac tamponade, and rarely death or atrial-esophageal fistula.[145]

Surgical Options Based on the pioneering research of Cox and coworkers, several surgical treatments for the prevention of AF have been developed.[146] Success rates have ranged from 70% to 95%.[147,148] For patients with AF who are undergoing cardiac surgery, consideration should be given to concomitant AF surgery. Gillinov and colleagues randomized patients with persistent or long-standing persistent AF undergoing mitral-valve surgery to additional surgical ablation for AF or not.[149] Freedom from AF at 6 and 12 months was significantly better for those with surgical AF ablation (63.2% vs 29.4%, $P < .001$). However, permanent pacemaker use was significantly higher in the patients who had AF ablation. Otherwise, its role is typically for patients who require sinus rhythm for symptom relief and have failed to respond to antiarrhythmic drugs and catheter ablation.

Management of Special Clinical Scenarios

Postoperative Atrial Fibrillation AF may occur in approximately one-third of patients after open-heart surgery regardless of the technique used.[150] It is an important risk factor for postoperative stroke, and anticoagulation should be considered despite the increased bleeding risk inherent in this setting.[150-152] Several clinical trials have demonstrated a modest benefit of β-blockers for AF prevention and they are used routinely for patients undergoing cardiac surgery of all types.[153] Amiodarone likewise has efficacy but its toxicity profile has caused most to consider its use in patients at high risk for postoperative AF such as the elderly and those with heart failure.[3,154] A recent trial comparing rate control versus rhythm control for postoperative AF showed no difference in absence of AF at 60 days,[155] which confirms previous observations suggesting most patients without preoperative AF who develop AF after cardiovascular surgery will not need long-term antiarrhythmic drug therapy.

Atrial Fibrillation and Wolff-Parkinson-White Syndrome Wolff-Parkinson-White syndrome presents two specific clinical problems with AF. First, an accessory pathway–mediated AV reentrant tachycardia can degenerate into AF. Second, in some patients who have accessory pathways capable of rapid conduction to the ventricles (see Fig. 83–6), the AF may degenerate into ventricular fibrillation and cause sudden death.[156] Electrical cardioversion is necessary if patients are hemodynamically unstable. In stable patients, intravenous procainamide, ibutilide, or amiodarone can be used to block conduction over the accessory pathway. Intravenous β-blockers and calcium channel blockers could result in hypotension and accelerated conduction over the accessory pathway and are contraindicated in this setting. Digoxin also is contraindicated in this setting because of concerns of accelerated conduction over the accessory pathway and paradoxic effect of increased ventricular rates from AV node blockade.[3] Definitive therapy is radiofrequency ablation of the accessory pathway.

ATRIAL FLUTTER

The term *atrial flutter* is generally used to describe atrial arrhythmias with large reentrant circuits. The surface ECG is characterized by regular repetitive flutter waves with an undulating baseline. The undulation of the baseline occurs because of continuous electrical activation of the atria from the reentrant circuit. The atrial rate is usually 240 to 340 bpm.

CLASSIFICATION AND MECHANISMS

Typical atrial flutter, also called *counterclockwise atrial flutter*, is characterized by negative sawtooth flutter waves (Fig. 83–11); and reverse

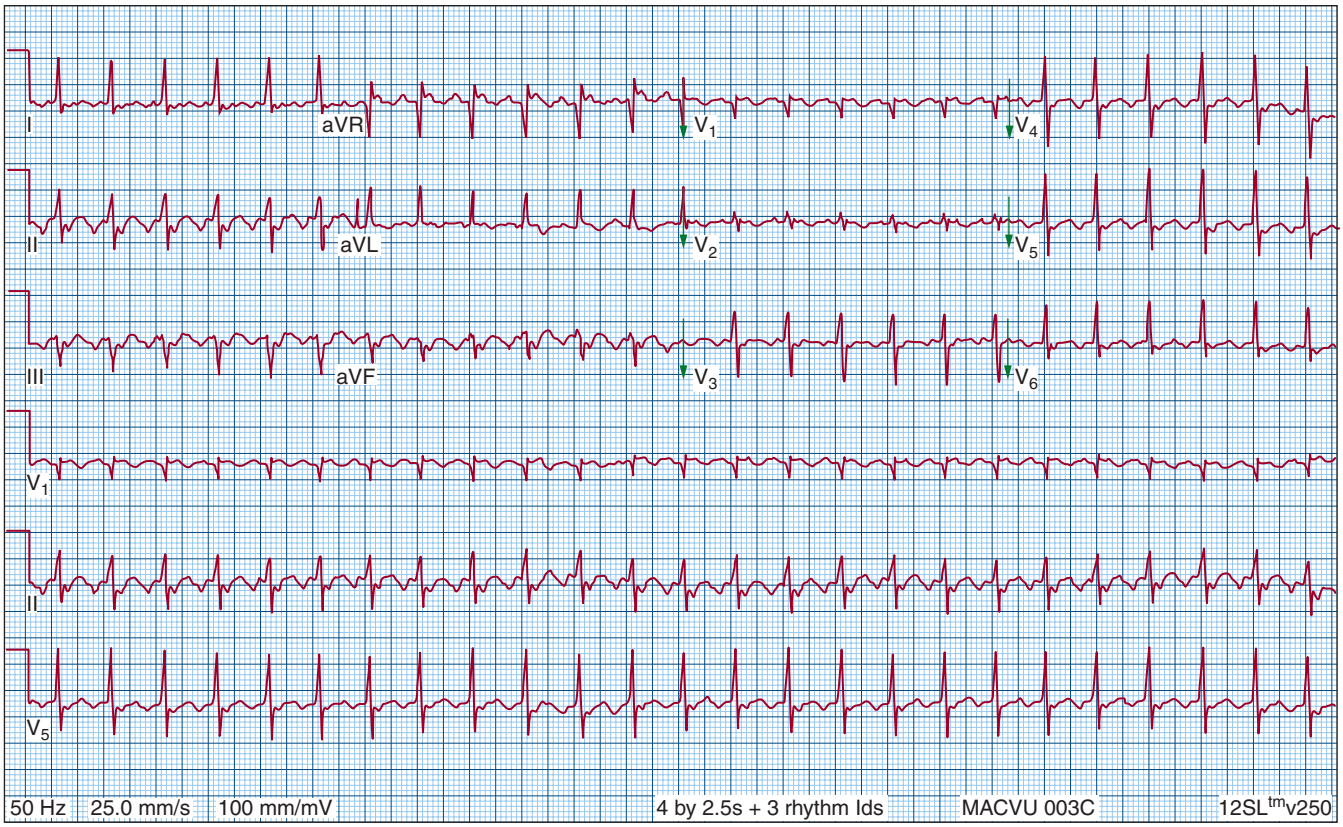


FIGURE 83–11. Twelve-lead electrocardiogram of typical atrial flutter. Note the negative flutter waves in leads II, III, and aVF and the upright flutter waves in lead V_1. This is characteristic of counterclockwise, isthmus-dependent atrial flutter.

typical atrial flutter, also called *clockwise atrial flutter*, is characterized by positive flutter waves in ECG leads II, III, and aVF.[157] These two atrial flutter types share the same right atrial reentrant circuit. In typical atrial flutter, the reentrant wavefront travels up the interatrial septum and down the right atrial free wall anterior to the crista terminalis and traverses the cavotricuspid isthmus to complete the circuit in a counterclockwise direction in the right atrium. The same circuit is completed in clockwise direction in reverse typical atrial flutter. Both types use the sub-Eustachian or cavotricuspid isthmus (ie, the isthmus between the tricuspid annulus on one side and the inferior vena cava–Eustachian ridge–coronary sinus on the other) as a critical part of the reentrant circuit.

Left atrial flutter, double wave reentry atrial flutter (two reentrant wave fronts simultaneously circulating in the same reentrant circuit),[158] lower loop and upper loop reentry right atrial flutter,[159] and atrial flutter caused by reentry around a surgical incision[160] have also been described. Left atrial flutter (Fig. 83–12) may be caused by reentry around the mitral valve annulus, the pulmonary veins, or a region of scar.[161] Reentry around a surgical lesion is common in patients after repair of congenital heart defects,[160] although most (approximately two-thirds) atrial flutter in patients after surgical repair of congenital heart defects uses the classic cavotricuspid isthmus-dependent reentrant circuit.[162]

ETIOLOGY

Atrial flutter often is initiated by AF. It is not surprising that it is also associated with chronic obstructive pulmonary disease, mitral or tricuspid valve disease, thyrotoxicosis, and postsurgical repair of certain congenital cardiac lesions (eg, atrial septal defect, the Mustard procedure, the Senning procedure, or the Fontan procedure),[163] as well as enlargement of the atria for any reason, especially the right atrium.[3,163] Atrial flutter occurs commonly in association with AF.

DIAGNOSIS

Atrial flutter usually can be diagnosed from the ECG (see Figs. 83–11 and 83–12) by the presence of atrial complexes of constant morphology and cycle length with an undulating baseline. Although these ECG features are essential to clinical diagnosis, atrial flutter can present with discrete P waves, especially in atria that have extensive scar. On occasion, the identification of atrial flutter complexes in the ECG may be difficult because of their temporal superimposition on other ECG deflections or because of their low amplitude. Use of vagal maneuvers or the intravenous administration of adenosine to transiently prolong AV conduction may reveal the atrial flutter complexes.

MANAGEMENT

Although the choice between rate and rhythm control is similar to that in AF, there is bias toward rhythm control in atrial flutter as a result of the relative ease and high success rate of catheter ablation, but also to the difficulty in many patients to achieve good rate control. The regular and slower atrial rate seen in atrial flutter compared with AF yields less concealed conduction in the AV node and often shows a 2:1 AV conduction pattern. Consistent adequate slowing of the ventricular response is harder to achieve in this situation. Selection of rate-control agents and antiarrhythmic drugs to treat atrial flutter mirrors that to treat AF[3] (see Fig. 83–6).

Initial management of atrial flutter is similar to treatment of AF. Urgent conversion to sinus rhythm or rapid control of the ventricular

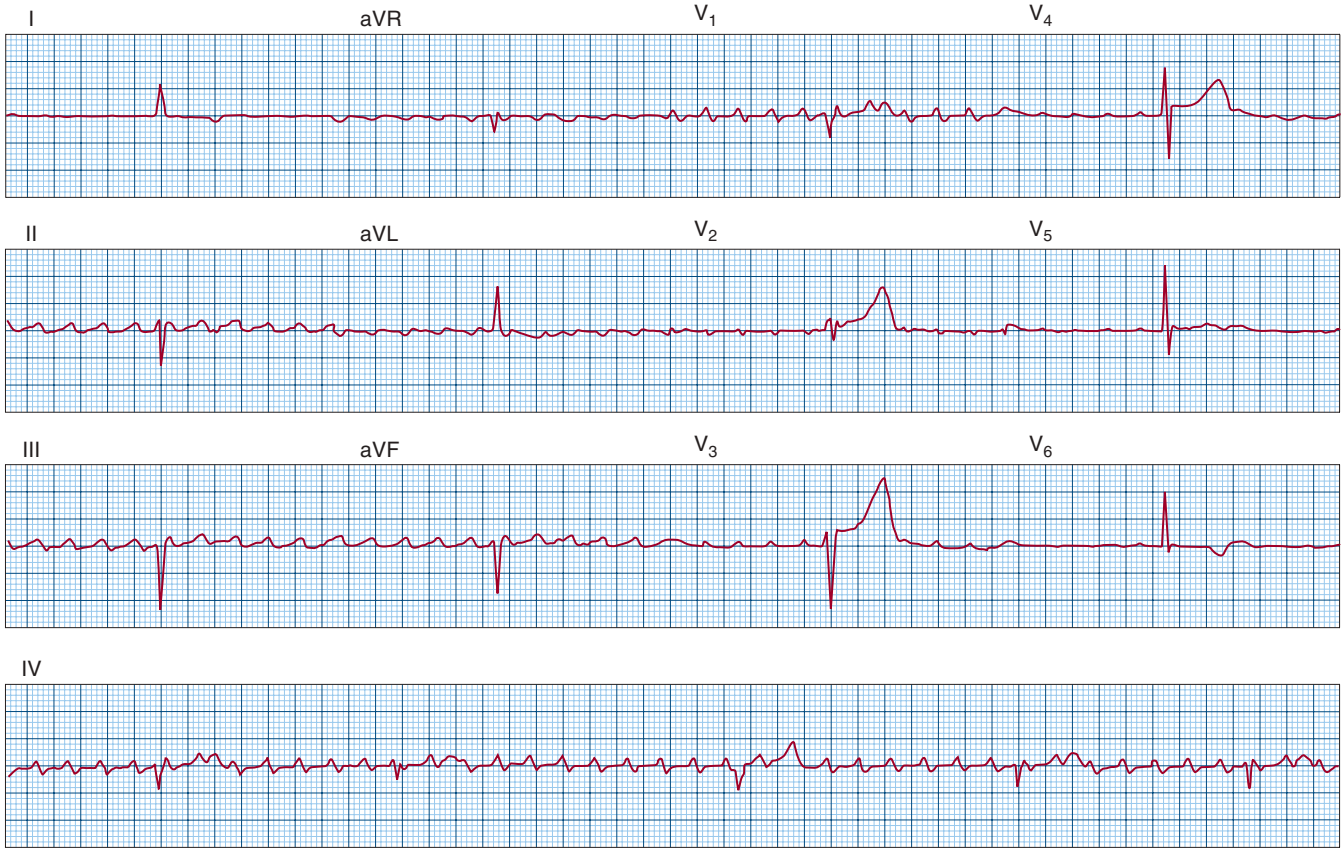


FIGURE 83–12. Twelve-lead electrocardiogram of a left atrial flutter that did not involve the usual cavotricuspid isthmus. Note the upright flutter waves in leads II, III, and aVF and the upright flutter waves in lead V_1.

response rate may be needed, depending on the patient's hemodynamic status. Options for cardioversion include transthoracic direct current (DC) cardioversion or chemical cardioversion using antiarrhythmic medications.[3,127] Rapid atrial pacing in patients with permanent or temporary pacemakers can also be used to restore sinus rhythm.[164] Drug therapy with β-blockers, calcium channel blockers, and digitalis may be used to slow the ventricular response rate. It is often difficult to achieve sufficient AV nodal block to slow adequately the ventricular response during atrial flutter, and 2:1 AV conduction frequently recurs. When using a class IC antiarrhythmic agent to treat atrial flutter, care must be taken to provide adequate AV block. These agents slow intraatrial conduction time by blocking sodium channels and slow the rate of atrial flutter. Slower atrial flutter may result in a 1:1 AV conduction of the flutter waves, resulting in very fast ventricular rates. This can degenerate into fatal ventricular tachycardia or ventricular fibrillation. It is important to remember that atrial flutter is often initiated by AF, which may become manifest after atrial flutter reverts to sinus rhythm.

Anticoagulant therapy

In patients with atrial flutter, anticoagulation using daily warfarin therapy to achieve an INR between 2 and 3 or use of one of the direct oral anticoagulants (NOAC) is recommended using the same criteria as for AF.[3] In addition, several studies indicate that the incidence of stroke associated with atrial flutter approaches that of AF.[165-167]

Catheter Ablation Therapy

Catheter ablation is highly successful, typically 90% or greater, to eliminate the typical atrial flutter.[3] This coupled with the recognized difficulty in achieving adequate long-term suppression with antiarrhythmic drug therapy make catheter ablation a first-line treatment option for many patients.[168] Because classical atrial flutter is usually preceded by a variable period of AF, successful ablation of the atrial flutter reentrant circuit per se does not prevent recurrence of AF. In fact, in our experience, the longer the follow-up after successful ablation of atrial flutter, the greater is the chance that atrial fibrillation will manifest, especially in more elderly patients.

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CHAPTER 84

SUPRAVENTRICULAR TACHYCARDIA: ATRIAL TACHYCARDIA, ATRIOVENTRICULAR NODAL REENTRY, AND WOLFF-PARKINSON-WHITE SYNDROME

Hugh Calkins

ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA / 1967
Pathophysiologic Basis of Atrioventricular Nodal Reentrant Tachycardia / 1967
Diagnosis / 1969
Management / 1971
Management Strategy / 1973

ATRIOVENTRICULAR REENTRANT TACHYCARDIA AND WOLFF-PARKINSON-WHITE SYNDROME / 1973
Pathophysiology / 1973
Diagnosis / 1977
Management / 1977
Management Considerations / 1980

ATRIAL TACHYCARDIA / 1982

Supraventricular tachycardias (SVTs) include all tachyarrhythmias that either originate from or incorporate supraventricular tissue in a reentrant circuit. The ventricular rate may be the same or less than the atrial rate, depending on the atrioventricular (AV) nodal conduction. The term *paroxysmal supraventricular tachycardia* (PSVT) refers to a clinical syndrome characterized by a rapid, regular tachycardia with an abrupt onset and termination. Approximately two-thirds of cases of PSVT result from AV nodal reentrant tachycardia (AVNRT). Orthodromic AV reciprocating tachycardia (AVRT), which involves an accessory pathway (AP), is the second most common cause of PSVT, accounting for approximately one-third of cases. The term *Wolff-Parkinson-White* (WPW) *syndrome* designates a condition comprising both preexcitation and tachyarrhythmias. Atrial tachycardias, which arise exclusively from atrial tissue, account for approximately 5% of all cases of PSVT.[1] The purpose of this chapter is to review the mechanism, clinical features, and approach to diagnosis and treatment of patients with AVNRT and AP-mediated tachycardias (including WPW syndrome). Particular attention is focused on reviewing management guidelines developed by the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (formerly known as the North American Society of Pacing and Electrophysiology).[1] We will also provide a brief overview of atrial tachycardia.

ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

AVNRT is an important arrhythmia for several reasons. First, AVNRT is extremely common. AVNRT occurs in approximately 10% of the general population and accounts for up to two-thirds of all cases of PSVT. Although AVNRT can occur at any age, it is extremely uncommon before age 5 years. The usual age of onset is beyond the fourth decade of life and is later than the usual age of onset of AP-mediated tachycardias. Women are affected twice as often as men. A second reason for the importance of AVNRT is the fact that it can result in significant debility and decreased quality of life.

PATHOPHYSIOLOGIC BASIS OF ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

Anatomic Considerations of the Atrioventricular Node

The AV node is located epicardially just underlying the right atrial epicardium anterior to the nodal artery and between the coronary sinus (CS) and medial tricuspid valve leaflet. It comprises three different components: the transitional cell zone, the compact node, and the penetrating bundle of His (Fig. 84–1). The *compact* AV node refers to the most easily histologically distinguishable tissue located at the apex of the triangle of Koch (TOK). A zone of transitional cells is interposed between the compact node and the atrial myocardium. Transitional cells enter the TOK to join the compact node superiorly, inferiorly, posteriorly, and from the left. At its distal extent, the AV node is distinguished from the penetrating bundle, not so much by cellular characteristics as by the presence of a fibrous collar surrounding the specialized cells. Systematic anatomic investigation of the AV node in patients with AVNRT is lacking. No obvious histologic abnormalities have been identified among patients with AVNRT versus patients without AVNRT. Several recent autopsy studies have reported that the sites of successful slow pathway ablation were clearly away from the histologic compact AV node, approximately 1 or 2 cm inferior and posterior to it.

Concept of Dual Pathways

The concept of dual AV nodal physiology was introduced in the 1950s in an effort to explain AVNRT. It was proposed that dual AV node physiology results from functional dissociation within the compact node into fast and slow pathways, and that AVNRT resulted from reentry within the AV node involving the fast and slow pathways. Subsequently, several investigators developed a catheter-based ablative technique that used direct current shocks or radiofrequency (RF) energy to eliminate the fast AV pathway and permanently eliminate AVNRT. Despite the excellent results of this procedure, it was complicated by a small but definite risk of AV block. A technique to interrupt slow pathway conduction without affecting normal AV conduction through the fast pathway by ablating small segments of myocardium in the posterior septum near the CS ostium was subsequently described.[2] This experience paved the way for the current approach using catheter ablation of this arrhythmia.

Types of Atrioventricular Nodal Reentrant Tachycardia

Three types of AVNRT have been described (Table 84–1).[3] Typical or slow/fast AVNRT is the most prevalent type, accounting for 85% to 90% of cases. Representing the other 10% to 15% of cases, atypical AVNRT can be further differentiated into fast/slow and slow/slow (or

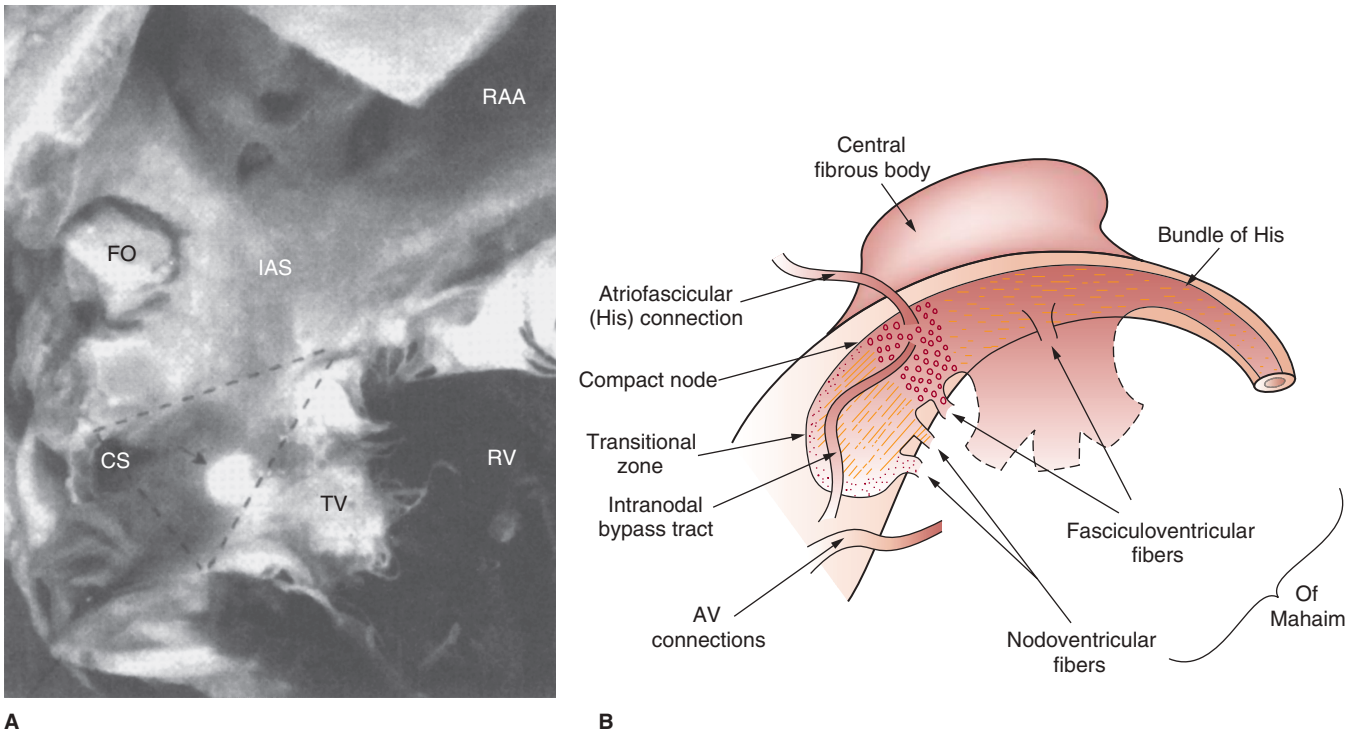


FIGURE 84–1. Structure of the atrioventricular (AV) node. **A.** Heart specimen from patient with atrioventricular nodal reentrant tachycardia (AVNRT). Koch triangle is formed by tendon of Todaro, coronary sinus (CS), ostium, and septal attachment of tricuspid valve (TV). *Arrow* represents site of successful ablation. **B.** Schematic drawing depicting the three zones of the AV node and various types of perinodal and atrioventricular bypass tracts. FO, fossa ovalis; IAS, interatrial septum; RAA, right atrial appendage; RV, right ventricle. **A**, reproduced with permission from Olgin JE, Ursell P, Kao AK, et al. Pathological findings following slow pathway ablation for AV nodal reentrant tachycardia. *J Cardiovasc Electrophysiol*. 1996 Jul;7(7):625-631; **B**, reproduced with permission from Singer I: *Interventional Electrophysiology*, 2nd ed. New York: Lippincott Williams & Wilkins; 2001.

intermediate) AVNRT. Induction of typical and atypical AVNRT in the same patient is possible but unusual. The typical or slow/fast AVNRT is thought to use the slow pathway for antegrade conduction and the fast pathway for retrograde conduction (Fig. 84–2). When an atrial premature complex blocks the fast pathway and proceeds slowly along the slow pathway, the fast pathway has enough time to recover from its refractoriness. This allows the impulse to activate the fast pathway retrogradely and return to the atrium, giving rise to an AV nodal reentrant echo beat. The impulse then travels down along the slow pathway again, continuation

TABLE 84–1. Differential Diagnosis for Types of Supraventricular Tachycardia Based on Electrocardiographic Characteristics

I. Long-RP tachycardia: RP ≥ PR
i. Atypical AVNRT
ii. Atrial tachycardia
iii. AVRT with a slowly conducting pathway (eg, PJRT)
iv. Sinus node reentry
v. Sinus tachycardia
II. Short-RP tachycardia RP < PR
i. Typical AVNRT
ii. AV reentry

Abbreviations: AV, atrioventricular; AVRT, atrioventricular reciprocating tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; PJRT, permanent junctional reciprocating tachycardia.

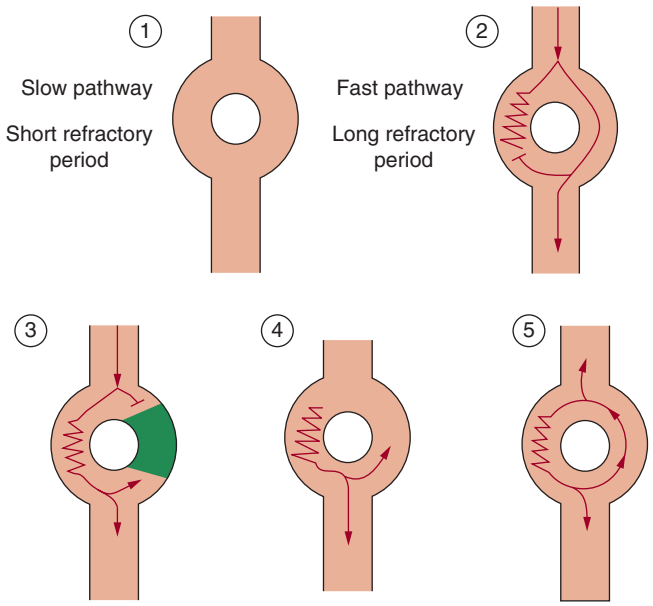


FIGURE 84–2. Schematic drawing showing dual atrioventricular (AV) nodal conduction. **1.** The two AV nodal pathways, one with fast conduction and a relatively long refractory period and a second with slower conduction and shorter refractory period. **2.** During sinus rhythm, impulses are conducted over both pathways but reach the bundle of His through the fast pathway. **3.** A premature atrial impulse finds the fast pathway still refractory and is conducted over the slow pathway. **4, 5.** If the fast pathway has enough time to recover excitability, the impulse may reenter the fast pathway retrogradely and establish reentry. Modified with permission from Podrid PJ, Kowey PR: *Cardiac Arrhythmia: Mechanisms, Diagnosis and Management*, 2nd edition. New York: Lippincott Williams & Wilkins; 2001.

giving rise to AVNRT. It has been proposed that the fast/slow AVNRT uses the fast pathway for anterograde conduction and the slow pathway for retrograde conduction. The slow/slow AVNRT, conversely, requires presence of two or more slow pathways with different conduction properties and refractory periods; one slow pathway is used for antegrade conduction and the other slow pathway for retrograde conduction.

DIAGNOSIS

Clinical Features

Patients with AVNRT typically present with the clinical syndrome of paroxysmal SVT. Episodes may last from seconds to several hours. Patients often learn to use certain maneuvers such as carotid sinus massage or the Valsalva maneuver to terminate the arrhythmia, but many patients require pharmacologic treatment to achieve this. There is no significant association of AVNRT with other types of structural heart disease. The physical examination is usually remarkable only for a rapid, regular heart rate. At times, because of the simultaneous contraction of atria and ventricles, cannon A-waves can be seen. Clinical variables that are predictive of AVNRT rather than APs as the cause of paroxysmal SVT include older age at onset of symptoms (> 30 years), the presence of palpitations in the neck during tachycardia, and female gender.

Electrocardiographic Characteristics

AVNRT is characterized by a tachycardia with a narrow QRS complex with sudden onset and termination generally at regular rates between 120 and 200 bpm. Uncommonly, the rate can be as low as 110 bpm; occasionally, especially in children, it may exceed 200 bpm. The rate of tachycardia may vary from episode to episode. In typical or slow/fast AVNRT, anterograde AV node conduction usually exceeds 200 milliseconds. Because the retrograde conduction is through the fast pathway, the VA interval is short, resulting in superimposition of the P wave onto the QRS complex on the surface electrocardiogram (ECG). Usually, the P wave is obscured by the QRS or may be seen slightly before or after the QRS complex. The presence of a pseudo r wave in lead V_1 or pseudo S wave in leads II, III, and aVF suggests typical AVNRT (Fig. 84–3). Because of fast retrograde conduction, the RP interval is shorter than the PR interval.

In atypical fast/slow or slow/slow AVNRT, the AH interval is relatively short and the HA interval long. The P wave on surface ECG hence can be well delineated and is inverted in II, III, and aVF. The RP interval is equal to or longer than the PR interval (Fig. 84–4). This is one of the causes of *long R–P* tachycardia (see Table 84–1).

Functional bundle branch block (BBB) may develop, producing a wide QRS tachycardia. However, functional BBB should not affect the rate of tachycardia. Less commonly, dual pathways can be manifest on the ECG during sinus rhythm by sudden prolongation of the PR interval, PR alternans, and two QRS complexes in response to a single P wave (Fig. 84–5).

Other ECG changes may be seen during or after the termination of AVNRT. Significant ST-segment depressions can be observed during tachycardia in nearly 25% to 50% of patients with AVNRT, and this is not predictive of ischemia.

Newly acquired T-wave inversions after termination of AVNRT, commonly in anterior or inferior leads, can be seen in nearly 40% of patients. They may be seen immediately after termination of tachycardia or may develop within 6 hours, and they can persist for a variable duration. This occurrence is also not related to rate or duration of tachycardia. This is also not the result of coronary artery disease but is caused by repolarization abnormalities, probably because of ionic current alterations resulting from the rapid rate.

A beat-to-beat oscillation in the QRS amplitude (ie, QRS alternans) can be observed, although uncommonly, during episodes of AVNRT. Studies have reported that QRS alternans is observed more frequently in association with AP-mediated tachycardias than during AVNRT.

Electrophysiologic Testing

Dual AV nodal physiology can be demonstrated by two pacing techniques. Atrial pacing with introduction of premature atrial contractions (PACs) with increasing prematurity shows a gradual and progressive conduction delay in the AH interval. At a critical atrial coupling interval, a 10-millisecond decrement in the A_1A_2 results in a marked (> 50-millisecond) prolongation of the A_2H_2 interval. It is a well-accepted convention that a 50-millisecond or greater increase in the AH interval in response to a 10-millisecond shortening of the A_1A_2 is considered evidence of dual AV node physiology. A plot of the A_1A_2 versus the A_2H_2 or

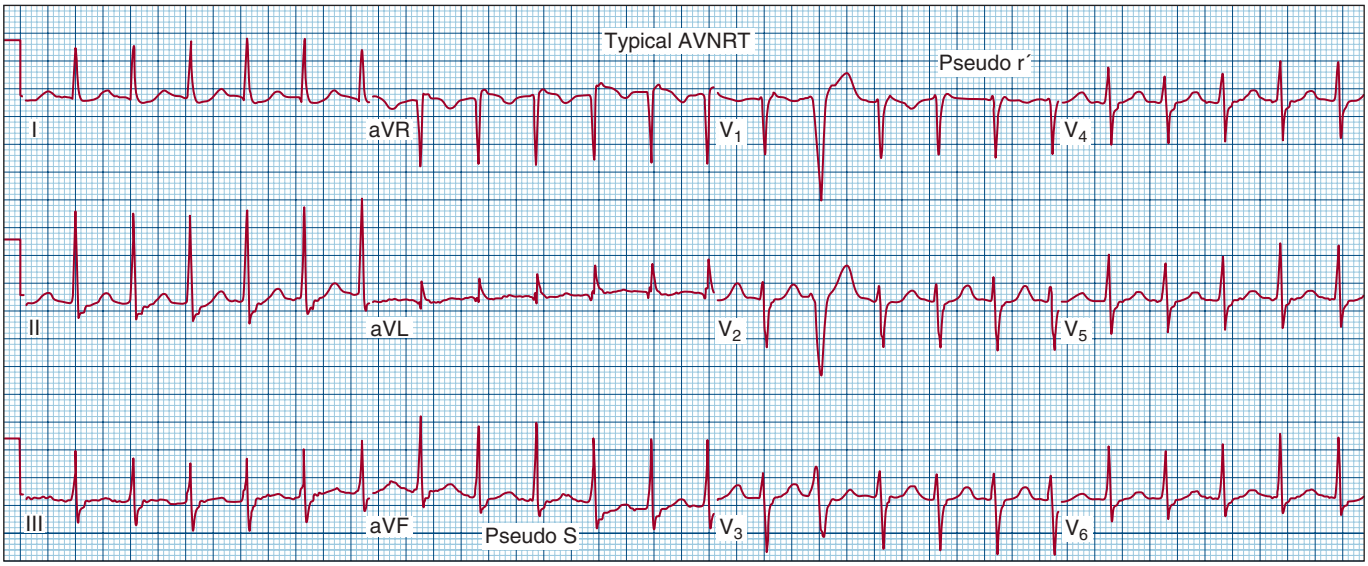


FIGURE 84–3. Twelve-lead electrocardiogram of a patient with typical atrioventricular nodal reentrant tachycardia. Note the pseudo r and pseudo S waves, which are very typical of this arrhythmia.

A

B

C

FIGURE 84–4. Surface electrocardiogram and intracardiac electrograms shown simultaneously in three different paroxysmal supraventricular tachycardias. The vertical line in each of the panels shows the onset of atrial depolarization to indicate the timing of the P wave relative to the QRS. **A.** Typical atrioventricular nodal reentrant tachycardia (AVNRT). **B.** AVRT involving an accessory pathway. **C.** Atypical AVNRT. *R* and *P* denote the corresponding waves on the surface ECG. A, atrial; HRA, high right atrium; V, ventricular deflection.

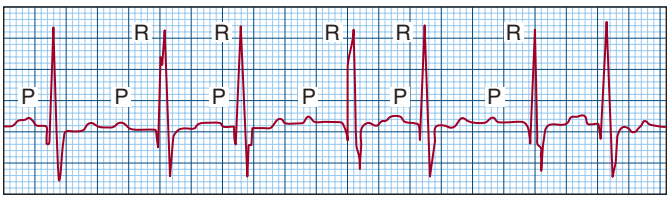


FIGURE 84–5. Rhythm strip of a patient during sinus rhythm. Note the sudden alternation of the PR interval from beat to beat. PR alternans is a manifestation of dual atrioventricular node physiology.

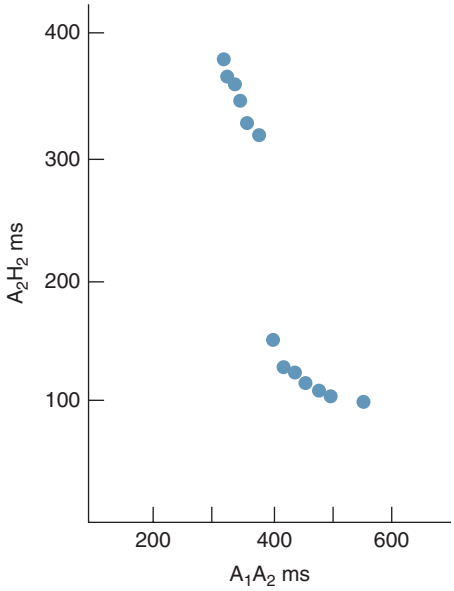


FIGURE 84–6. Atrioventricular (AV) nodal function curve in a patient with dual AV nodal physiology. As the coupling interval of A_1A_2 is progressively decreased, there is a progressive prolongation of A_2H_2 intervals. At a coupling interval of around 360 milliseconds, there is a large jump in the A_2H_2 interval. This is caused by the fast pathway effectively reaching refractoriness at 360 milliseconds and conduction proceeding over the slow pathway, which has a shorter refractory period but slower conduction. Modified with permission from Josephson M: *Clinical Cardiac Electrophysiology: Technique and Interpretation*, 3rd ed. New York: Lippincott Williams & Wilkins; 2002.

the A_2H_2 versus the H_1H_2 shows a discontinuous curve (Fig. 84–6). The fast pathway has a shorter conduction time and longer refractory period, and the slow pathway has a longer conduction time and shorter refractory period. The abrupt increase in AV nodal conduction time is caused by block in the conduction of fast pathway with a selective conduction over the slow pathway (Fig. 84–7). Some patients with AVNRT may not have discontinuous refractory period curves, and some patients without AVNRT exhibit discontinuous refractory period curves. It has been estimated that *dual AV node physiology* is present in approximately 10% of the general population. Such existence in the latter patients is a benign finding. Multiple AV nodal pathways can be demonstrated in occasional patients. More than one pathway may be involved in clinical tachycardia. The development of a PR interval that is greater than the atrial pacing cycle length during stable 1:1 AV conduction is a quite specific sign of slow AV nodal conduction.

Whereas typical AVNRT is usually not inducible with ventricular pacing, this is the rule with atypical AVNRT. Lack of reproducible arrhythmia induction is most often caused by block in retrograde fast pathway. Other causes include slow-pathway block and an inability to achieve a critical delay in the AH interval.

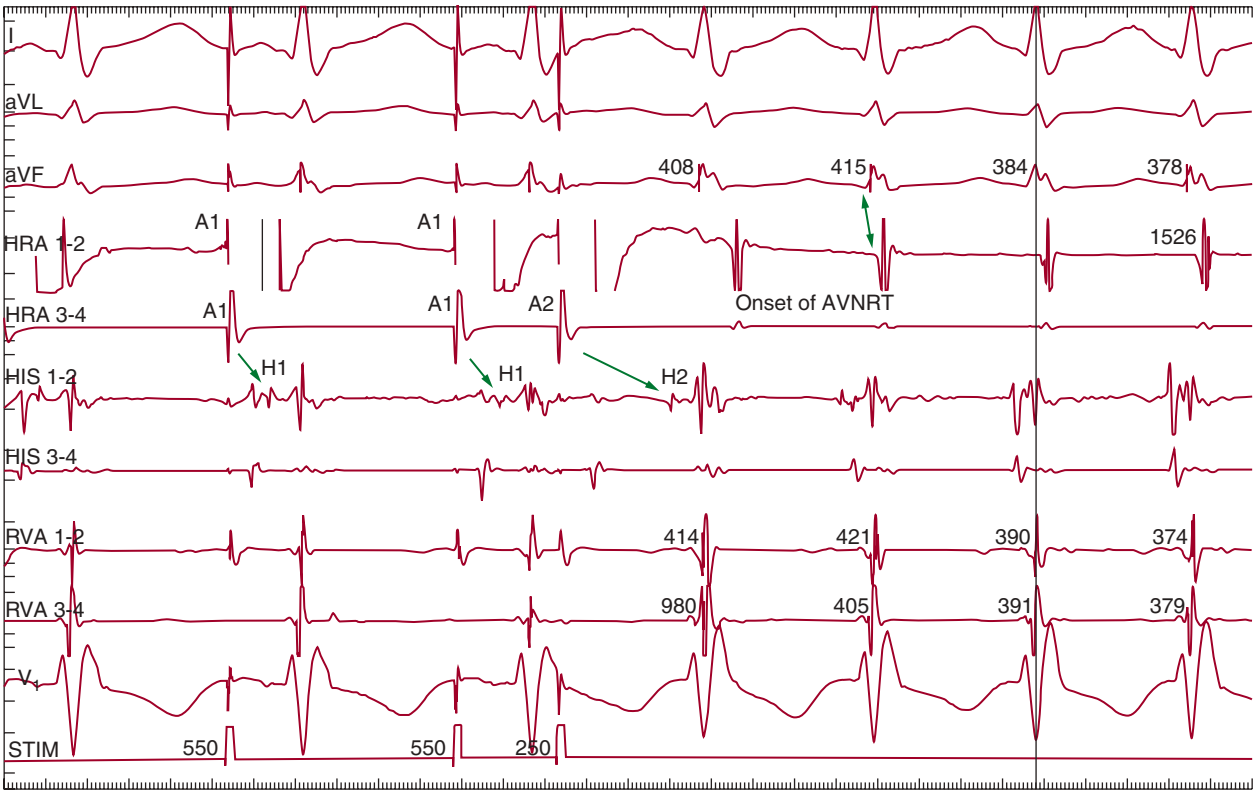


FIGURE 84–7. Electrophysiologic demonstration of dual atrioventricular nodal physiology and initiation of atrioventricular nodal reentrant tachycardia (AVNRT). At an A_1A_2 coupling interval of 350 milliseconds, there is a jump in the A_2H_2 interval (*arrows*). This is followed by initiation of tachycardia. Note the very short VA conduction time. A, atrial; HRA, high right atrium.

During typical AVNRT, the atrial and ventricular activation is nearly simultaneous, hence causing short HA intervals. An HA interval below 70 ms is virtually diagnostic of AVNRT (see Fig. 84–7). Differentiation of AVNRT, particularly of the atypical type, from other forms of SVT can be challenging, requiring the use of several maneuvers during the electrophysiologic study (EPS).

MANAGEMENT

Because AVNRT is generally a benign arrhythmia that does not influence survival, the main reason for treating it is to alleviate symptoms. The threshold for initiation of therapy varies based on patient preference and on the frequency and duration of the episodes of tachycardia as well as the associated symptoms. The threshold for treatment also reflects whether the patient is a competitive athlete, a woman considering pregnancy, or someone with a high-risk occupation such as scuba diving. The American College of Cardiology, American Heart Association, and the Heart Rhythm Society (ACC/AHA/HRS) have recently published updated guidelines on the management of supraventricular arrhythmias. The recommendations made by this task force are reviewed at the end of this section.[1]

Acute Management

The dependence of AVNRT on AV nodal conduction has important therapeutic implications. Because of the known influence of autonomic tone on AV nodal conduction, maneuvers that increase vagal tone, such as the Valsalva and Mueller maneuvers, gagging, carotid sinus massage, and occasionally exposing the face to ice water, can be used to terminate the tachycardia. The effect of vagal maneuvers is most pronounced on the slow pathway. Hence, in the slow/fast form of AVNRT, the tachycardia typically terminates in the anterograde direction; in the fast/slow type of AVNRT, the block is in the retrograde limb of the tachycardia circuit.

Adenosine, a purinergic blocking agent that causes acute and transient AV nodal blockade, is the drug of choice for acute termination of AVNRT. Adenosine is nearly 100% effective in terminating AVNRT. It has a rapid onset of action (seconds) and a short half-life (< 10 seconds); moreover, it does not impair contractility. When used for termination of a narrow-complex tachycardia, an initial dose of 6 mg may be followed by 12 mg if the first dose is ineffective. Because of its short duration of action, it is essential that adenosine be administered as a rapid bolus. This is best achieved by having a syringe with adenosine and a 5-mL flush attached to the patient using a stopcock. In this fashion, the dose of adenosine can be followed immediately by a saline flush to ensure rapid delivery of the drug. Minor side effects, including transient dyspnea or chest pain, are common with adenosine. Sinus arrest or bradycardia may occur but resolve quickly if appropriate upward dosing is used. Adenosine shortens the atrial refractory period, and atrial ectopy may induce atrial fibrillation. This may be dangerous if the patient has an AP capable of rapid antegrade conduction. Because adenosine is cleared so rapidly, reinitiation of tachycardia after initial termination may occur. Either repeat administration of the same dose of adenosine or substitution of a calcium channel blocker (CCB) will be effective. Adenosine mediates its effects via a specific cell-surface receptor, the A_1 receptor. Theophylline and other methylxanthines block the A_1 receptor. Caffeine levels achieved after beverage ingestion may be overcome by the doses of adenosine used to treat patients with PSVT. Dipyridamole blocks adenosine elimination, thereby potentiating and prolonging its effects. Cardiac transplant recipients are also unusually sensitive to adenosine. If adenosine is chosen in these latter

situations, much lower starting doses (ie, 1 mg) should be selected. Adenosine should also be used with great caution in patients with a history of asthma because it may trigger bronchospasm.

Several other drugs that affect the AV node can also be used for acute termination of AVNRT. Verapamil, a CCB, can terminate AVNRT and prevent induction. It slows conduction both in the slow and fast pathways, and termination is usually caused by anterograde block. A 5-mg bolus of verapamil may be followed by one or two additional 5-mg boluses 10 minutes apart if the initial dose does not terminate the tachycardia. Drugs that enhance vagal tone, such as digoxin, or that block the sympathetic effect, like β-blockers, can also be used to terminate AVNRT. Digoxin, which has a slower onset of action than the other AV nodal blockers, is not favored for the acute termination of AVNRT except if there are relative contraindications to the other agents. Class Ia and Ic sodium channel blockers can also be used in treating an acute event of AVNRT, a strategy that is rarely used when other regimens have failed. Unlike the other agents, the sodium channel blocking agents depress retrograde fast-pathway conduction. If a patient's tachycardia cannot be terminated with intravenous drugs, direct-current shock cardioversion can always be used. Energies in the range of 10 to 50 J are usually adequate.

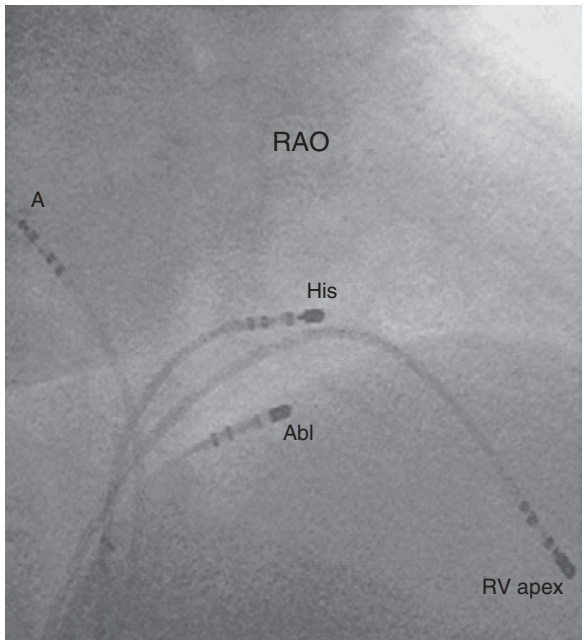
The recommendations for the acute management of patients with recurrent AVNRT, which were developed by the ACC/AHA/HRS, are shown in Table 84–2.[1] Catheter ablation is considered class 1 therapy for treatment of patients with symptomatic AVNRT. The indications for pharmacologic management are also provided.

Long-Term Management

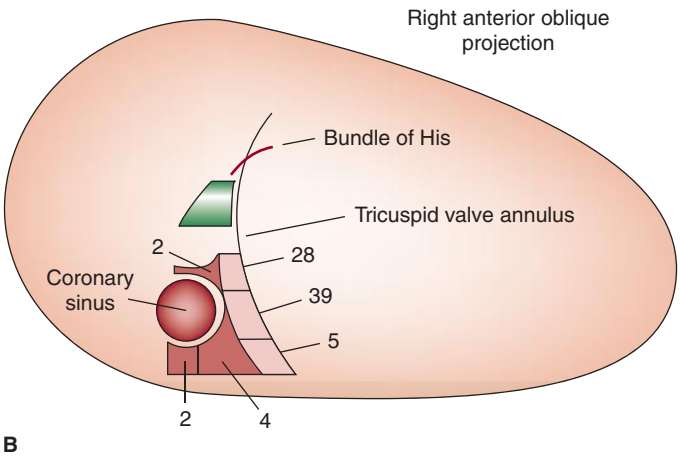
Catheter Ablation Catheter ablation of AVNRT is performed by ablating the slowly conducting portion of the AV node using the *posterior approach.* After the diagnosis of AVNRT has been established and the end point for ablation defined (either the presence of dual AV node physiology or reproducibly inducible AVNRT), the ablation catheter is positioned across the tricuspid valve at the level of the CS ostium (Fig. 84–8). The ablation catheter is then slowly withdrawn with clockwise catheter torque until a small multicomponent atrial electrogram is observed together with a large ventricular electrogram.[3] The most common site of successful ablation is at the level of the superior aspect of the CS ostium (see Fig. 84–8). In patients with unusual forms of AVNRT, the site of successful ablation is slightly inferior to the CS ostium or, at times, within the floor of the CS. After an appropriate site has been identified, RF energy is applied. The development of a junctional rhythm during RF application is a marker for a successful ablation site. If a junctional rhythm develops, VA conduction should be monitored carefully; if VA or AV conduction block is observed, RF

TABLE 84–2. AHA/ACC/HRS 2015 Recommendations for the Acute Treatment of AVNRT[1]

Class	
1	Vagal maneuvers are recommended for acute treatment in patients with AVNRT.
1	Adenosine is recommended for acute treatment in patients with AVNRT.
1	Synchronized cardioversion should be performed for acute treatment in hemodynamically unstable patients with AVNRT when adenosine and vagal maneuvers do not terminate the tachycardia or are not feasible.
1	Synchronized cardioversion is recommended for acute treatment in hemodynamically stable patients with AVNRT when pharmacologic therapy does not terminate the tachycardia or is contraindicated.
2A	Intravenous beta-blockers, diltiazam, and verapamil are reasonable for acute treatment in hemodynamically stable patients with AVNRT.
2B	Oral beta-blockers, diltiazam, or verapamil may be reasonable for acute treatment in hemodynamically stable patients with AVNRT.
2B	Intravenous amiodarone may be considered for acute treatment in hemodynamically stable patients with AVNRT when other therapies are ineffective or contraindicated.



A



B

FIGURE 84–8. Site of slow-pathway ablation for atrioventricular nodal reentrant tachycardia. **A.** Accessory pathway and left lateral fluoroscopic images showing the alignment of the catheters during slow-pathway ablation. Note that the site of the slow pathway is a considerable distance from the site of the His bundle or compact atrioventricular node. **B.** Schematic showing the orientation of heart during corresponding fluoroscopic projection. The numbers represent the sites of successful slow-pathway ablation in corresponding patients. A, atrial catheter; Abl, ablation catheter; RAO, right anterior oblique; RV, right ventricle. Part A, modified with permission from Meininger GR, Calkins H. One method to reduce heart block risk during catheter ablation of atrioventricular nodal reentrant tachycardia. *J Cardiovasc Electrophysiol.* 2004 Jun;15(6):727-728; part B, reproduced with permission from Jackman WM, Beckman KJ, McClelland JH, et al. Treatment of supraventricular tachycardia due to atrioventricular nodal reentry by radiofrequency catheter ablation of slow-pathway conduction. *N Engl J Med.* 1992 Jul 30;327(5):313-318.

energy should immediately be discontinued. Some centers, including ours, use an even more conservative strategy for RF energy delivery in an effort to further reduce the risk of AV block.[4]

Successful ablation of AVNRT with the posterior approach is usually characterized by an increase in the AV block cycle length and in the AV nodal effective refractory period; a normal PR interval on ECG and lack of inducibility of AVNRT both at baseline and during isoproterenol infusion are also seen. Retrograde conduction is generally not affected. The presence of more than one AV nodal echo beat or a PR prolongation that exceeds the paced atrial cycle length during stable 1:1 AV conduction suggests that the AVNRT is likely to recur and will require further RF applications.

Calkins and colleagues.[5] reported the largest multicenter experience with the posterior approach. In this trial of more than 1000 patients with AV tachycardias, 373 patients had AVNRT. The overall success rate of ablation was 97%. AV block is the most common complication, occurring in 0.5% to 1% of patients. The incidence of recurrence after successful ablation is approximately 3%. Because of the higher efficacy and lower incidence of AV block and arrhythmia recurrence and the greater likelihood of maintaining a normal PR interval during sinus rhythm, the posterior approach is now considered the preferred approach to ablation of AVNRT.[6]

Cryoablation has become available as an alternative energy source for creation of myocardial lesions that can be used for treatment of AVNRT.[6] The main advantage of cryoenergy as compared with RF energy is that the risk of heart block appears to be lower.[7-10] This potential, but unproven, benefit must be balanced against longer procedure times and lower acute and long-term efficacy. Because of the implications of heart block in children, cryoablation is used by an increasing number of pediatric electrophysiologists.[8] In contrast, RF energy has remained the dominant ablation energy source for treatment of AVNRT in adults.

Medical Therapy Most pharmacologic agents that depress AV nodal conduction may be demonstrated to reduce the frequency of recurrences of AVNRT. These pharmacologic agents include β-blockers, CCBs, class 1a antiarrhythmic agents such as procainamide and disopyramide, class 1c antiarrhythmic agents such as flecainide and propafenone, and class 3 antiarrhythmic agents such as sotalol (Betapace) and amiodarone. The best studied among these have been the class Ic antiarrhythmic agents. Although the 1c antiarrhythmic agents are effective for treatment of AVNRT, they are used rarely because of the curative nature of catheter ablation.

MANAGEMENT STRATEGY

Patients with AVNRT typically present with the clinical syndrome of PSVT. The diagnosis of PSVT can be made with a high degree of certainty based on the clinical history alone even if the tachycardia has never been documented by an ECG. Physicians may try to document the tachycardia with an ECG using either a 30-day event monitor or by instructing the patient to go to an emergency department (ED) or physician's office if another episode of tachycardia occurs. Because AVNRT is not a life-threatening arrhythmia, the primary indication for its treatment relates to its impact on the patient's quality of life. Patients who develop a highly symptomatic episode of PSVT, particularly if it requires an emergency room visit for termination, may elect to initiate therapy after a single episode. In contrast, a patient who presents with minimally symptomatic episodes of PSVT that terminate spontaneously or with a Valsalva maneuver may elect to be followed clinically without specific therapy.

After it has been decided to initiate treatment for AVNRT, the question arises of whether to initiate pharmacologic therapy or to use catheter ablation (Table 84–3). Because of its greater than 95% efficacy and low incidence of complications, catheter ablation is now considered first-line therapy. The ACC/AHA/HRS SVT Guidelines include catheter ablation of AVNRT using the posterior approach as a class 1 indication for catheter ablation.[1] It is therefore reasonable to discuss catheter ablation with all patients suspected of having AVNRT. Depending on the frequency and severity of tachycardia episodes as well as the patient's lifestyle and preferences, an individual may elect to be followed clinically without specific therapy, to begin a trial of pharmacologic therapy with a beta-blocker or CCB, or to undergo EPS and catheter ablation.

The recommendations for the long-term management of patients with recurrent AVNRT, which were developed by the ACC/AHA/HRS, are shown in Table 84–4.[1] Catheter ablation is considered class 1 therapy for treatment of patients with symptomatic AVNRT. The indications for pharmacologic management are also provided.

ATRIOVENTRICULAR REENTRANT TACHYCARDIA AND WOLFF-PARKINSON-WHITE SYNDROME

APs are important because they provide a substrate for antidromic and orthodromic AV reciprocating tachycardia, are associated with sudden cardiac death, and may be detected in asymptomatic patients on a routine screening ECG. The sections that follow cover the pathophysiology, diagnosis, and management of this fascinating clinical entity.

PATHOPHYSIOLOGY

APs are anomalous, typically extranodal connections that connect the epicardial surfaces of the atrium and ventricle along the AV groove. Accessory bypass tracts, which conduct antegrade from the atrium to the ventricle and therefore are detectable on an ECG, are reportedly present in 0.15% to 0.25% of the general population. A higher prevalence of 0.55% has been reported in first-degree relatives of patients with WPW syndrome.

Classification

APs can be classified based on their site of origin and insertion, location along the mitral or tricuspid annulus, type of conduction, and properties of conduction (decremental or nondecremental). APs usually exhibit rapid, nondecremental conduction, similar to that which is present in normal His-Purkinje tissue and atrial or ventricular myocardium. Approximately 8% of APs display decremental antegrade or retrograde conduction. Whereas APs that are capable only of retrograde conduction are referred to as *concealed*, those capable of antegrade conduction are referred to as *manifest*, demonstrating preexcitation on a standard ECG (Fig. 84–9). APs usually conduct both antegrade and retrograde. Antegrade-only APs are particularly uncommon. When present, they are usually right sided and frequently demonstrate decremental conduction (Mahaim fiber). Concealed APs are less common, accounting for approximately 15% of all APs. Patients with Ebstein anomaly who also have WPW syndrome frequently have more than one AP.

Variant APs include those that connect the atrium to the distal or compact AV node (James fibers), the atrium to the His bundle (the Brechenmacher fiber), and the AV node or His bundle to the distal Purkinje fibers or ventricular myocardium (the Mahaim fibers) (see Fig. 84–1B).

Concept of Preexcitation

The hallmark of an AP function during sinus rhythm is depolarization of all or part of the ventricles earlier than expected if conduction has

TABLE 84–3. Recommendations for Long-Term Management of Patients with Recurrent Atrioventricular Nodal Reentrant Tachycardia

Clinical Presentation	Recommendation	Classification	Level of Evidence
Poorly tolerated AVNRT with hemodynamic intolerance	Catheter ablation	1	B
	Verapamil, diltiazem, β-blockers	2a	C
	Sotalol, amiodarone	2a	C
	Flecainide, propafenone	2a	C
Recurrent symptomatic AVNRT	Catheter ablation	1	B
	Verapamil	1	B
	Diltiazem, β-blockers	1	C
	Digoxin	2b	C
	Verapamil, diltiazem, digoxin	3	C
Recurrent AVNRT unresponsive to β-blockade or CCB and patients not desiring RF ablation	Flecainide, propafenone, sotalol	2a	B
	Amiodarone	2b	C
AVNRT with infrequent or a single episode in patients desiring complete control of arrhythmia	Catheter ablation	1	B
Documented PSVT with only dual AV-nodal pathways or single echo beats demonstrated during EPS and no identified cause of arrhythmia	Verapamil, diltiazem, β-blockers	1	C
	Flecainide, propafenone	1	C
	Catheter ablation	1	B
Infrequent, well-tolerated AVNRT	No therapy	1	C
	Vagal maneuvers	1	B
	Pill in the pocket	1	B
	Verapamil, diltiazem, β-blockers	1	B
	Catheter ablation	1	B

Abbreviations: AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; CAD, coronary artery disease; CCB, calcium channel blocker; EPS, electrophysiology study; LV, left ventricle; PSVT, paroxysmal supraventricular tachycardia; RF, radiofrequency.

Adapted with permission from Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation*. 2003 Oct 14;108(15):1871-190.

TABLE 84–4. AHA/ACC/HRS 2015 Recommendations for Ongoing Management of AVNRT[1]

Class	
1	Oral verapamil or diltiazem is recommended for ongoing management in patients with AVNRT who are not candidates for, or prefer not to undergo, catheter ablation.
1	Catheter ablation of the slow pathway is recommended in patients with AVNRT.
1	Oral beta-blockers are recommended for ongoing management of AVNRT patients who are not candidates for, or prefer not to undergo, catheter ablation.
2A	Flecainide or propafenone is reasonable for ongoing management in patients without structural heart disease or ischemic heart disease who have AVNRT and are not candidates for, or prefer not to undergo catheter ablation and in whom beta-blockers, diltiazem, and verapamil are ineffective or contraindicated.
2A	Clinical follow-up without pharmacologic therapy or ablation is reasonable for ongoing management of minimally symptomatic patients with AVNRT.
2B	Oral sotolol or dofetiline may be reasonable for ongoing management in patients with AVNRT who are not candidates for, or prefer not to undergo, catheter ablation.
2B	Oral digoxin or amiodarone may be reasonable for ongoing treatment of AVNRT in patients who are not candidates for, or prefer not to undergo, catheter ablation.
2B	Self-administered ("pill-in-the-pocket") acute doses of oral beta-blockers, diltiazem, or verapamil may be reasonable for ongoing management in patients with infrequent, well-tolerated episodes of AVNRT.

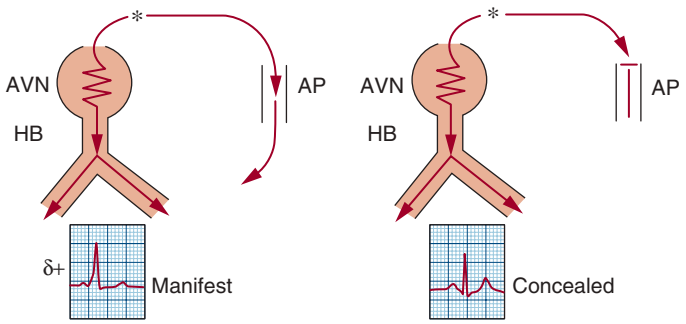


FIGURE 84–9. Atrioventricular conduction patterns and QRS morphologies during sinus rhythm for manifest and concealed accessory pathways (APs). AVN, atrioventricular node; HB, His bundle. Modified with permission from Cain ME, Luke RA, Lindsay BD. Diagnosis and localization of accessory pathway. *Pacing Clin Electrophysiol*. 1992 May;15(5):801-824.

occurred only over the normal AV conduction system, resulting in preexcitation (Fig. 84–10).

The degree of shortening of the PR interval and the extent of ventricular preexcitation depend on several factors, including location of the AP, the relationship between antegrade conduction times and refractory periods of the AV bypass tract, and the normal AV conduction system. A bypass tract that crosses the AV groove in the left lateral region may also result in inapparent preexcitation and minimal PR interval shortening during sinus rhythm because of greater interatrial distance for impulse propagation from the sinus node to this site of atrial input into the AP. Conversely, an AP on the right side is more likely to demonstrate marked preexcitation. Preexcitation may be less apparent during sinus tachycardia, when sympathetic tone is high and vagal tone low, resulting in faster AV node conduction time than that in the AP. On the other extreme, during conditions of slowed conduction through the AV node by intrinsic nodal factors, withdrawal of sympathetic tone, or increased vagal tone, the amount of preexcitation apparent on the 12-lead ECG is maximized because of relatively greater conduction through the AP. Rapid intravenous administration of adenosine causing blocking or slowing of AV node conduction and exposing the anterograde AP conduction has been used as a diagnostic maneuver. The degree of preexcitation can also be enhanced with atrial pacing directly over the AP, eliminating the intra-atrial conduction delay from the sinus node to the atrial insertion site of AP (Fig. 84–11).

Intermittent preexcitation is characterized by abrupt loss of delta wave, normalization of the QRS duration, and an increase in the PR interval during a continuous ECG recording, often despite only minor variations in resting sinus rhythm heart rate. This should be distinguished from day-to-day variability in preexcitation or inapparent preexcitation caused by factors described above. The presence of intermittent preexcitation has been considered to suggest that the refractory period in the AP is long, making them very unlikely to mediate a rapid, preexcited ventricular response during atrial fibrillation.

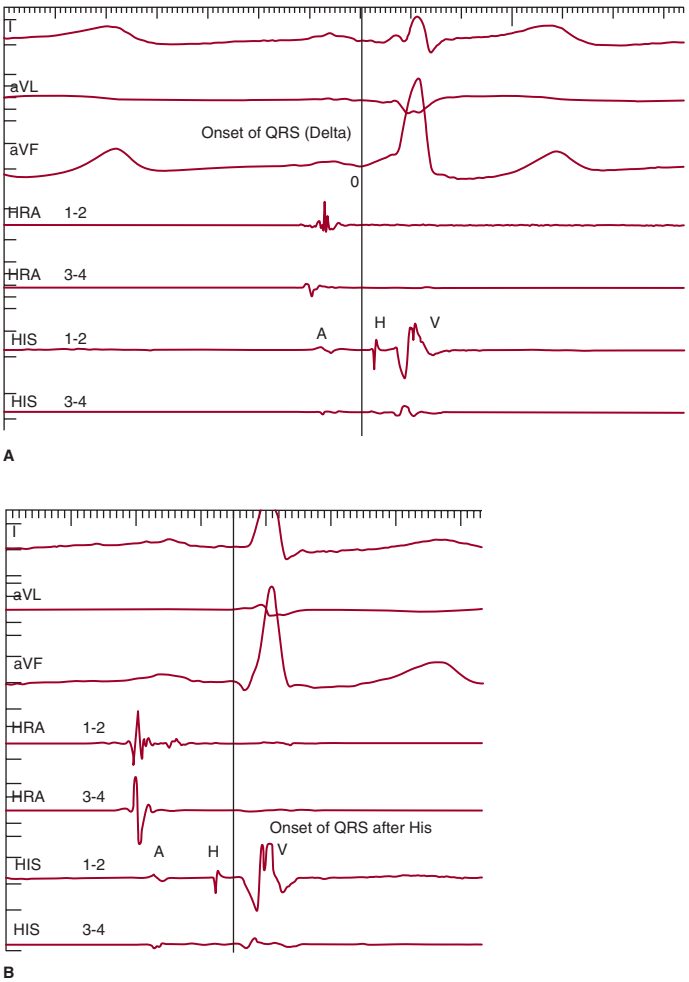


FIGURE 84–10. Electrophysiologic confirmation of preexcitation. **A.** Preexcited QRS complex in Wolff-Parkinson-White syndrome. Onset of QRS or delta wave is clearly before the His electrogram before ablation. **B.** Loss of preexcitation and shift of onset of QRS after His deflection postablation. A, atrial electrogram; H, His electrogram; HRA, high right atrium; HIS, His bundle electrogram; V, ventricular electrogram.

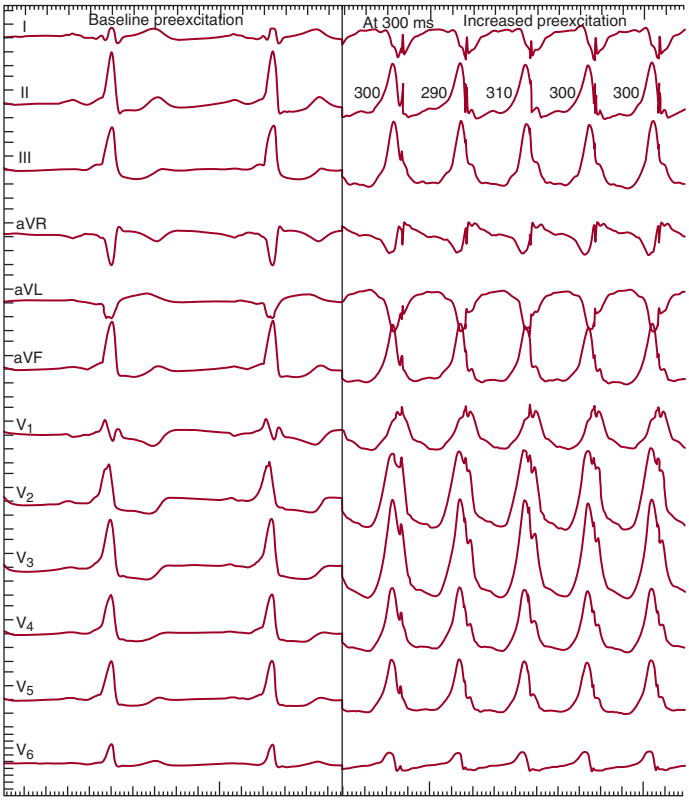


FIGURE 84–11. Increase in degree of preexcitation with atrial pacing. Left panel shows 12-lead electrocardiogram during sinus rhythm. Note the obvious increase in preexcitation in the right panel with atrial pacing at a cycle length of 300 milliseconds (200 bpm). Increase in atrial input causes decremental conduction in the atrioventricular node, resulting in increased conduction over the accessory pathway.

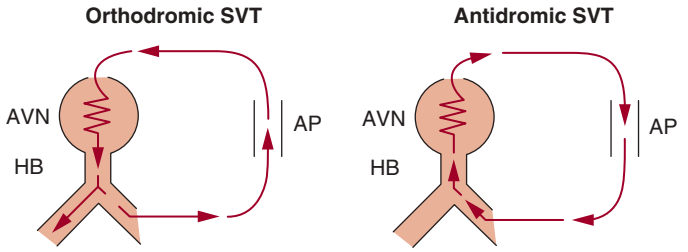


FIGURE 84–12. Schematic representation of the patterns of conduction through an accessory pathway (AP) and the normal conduction system (AVNHB) during orthodromic atrioventricular nodal reentrant tachycardia (AVRT) and antidromic AVRT. AVN, atrioventricular node; HB, His bundle; SVT, supraventricular tachycardia. Modified with permission from Cain ME, Luke RA, Lindsay BD. Diagnosis and localization of accessory pathway. *Pacing Clin Electrophysiol*. 1992 May;15(5):801-824.

Tachycardias Associated with Accessory Pathways

Tachycardias associated with APs can be subdivided into those in which the AP is necessary for initiation and maintenance of tachycardia and those in whom the AP acts as a bystander.

AVRT is a macro-reentrant tachycardia involving the atrium, the AP, the AV node, and the ventricle. AVRT is further subclassified into orthodromic and antidromic AVRT (Fig. 84–12). During orthodromic AVRT, the reentrant impulse uses the AV node and specialized conduction system for conduction from the atrium to the ventricle and uses the AP for conduction from the ventricle to the atrium. Orthodromic AVRT can be initiated by atrial or ventricular premature depolarizations (atrial premature beats [APDs] or ventricular premature beats [VPDs]). APDs initiating the tachycardia block antegradely in the AP and conduct relatively slowly over the AV nodal tissue to the ventricles. The impulse then retrogradely conducts over the AP reentering the atria at the atrial insertion site of the pathway, thus completing the reentrant loop (Fig. 84–13). A VPD, conversely, blocks in the His-Purkinje system and retrogradely reaches the atria through retrogradely conducting AP. The impulse then antegradely conducts through the AV nodal tissue, completing the circuit. The QRS complex during orthodromic AVRT hence is not preexcited.

During antidromic AVRT, however, the reentrant impulse travels in the reverse direction, with conduction from the atrium to the ventricle occurring via the AP. Antidromic AV reciprocating tachycardia is rare, occurring in only 5% to 10% of patients with WPW syndrome. APDs that occur at a coupling interval that is longer than the refractory period of the AP and shorter than the AV nodal refractory period can initiate the antidromic AVRT; the converse is true with a VPD. Susceptibility of antidromic AVRT appears to depend on the existence of adequate separation between the AP and the AV nodal tissue. Hence, most of the antidromic AVRTs seem to occur only with left-sided bypass tracts.

Other forms of SVTs, including atrial tachycardia, junctional tachycardia, AVNRT, and even ventricular tachycardia, may occur in patients with bypass tracts. Dual AV nodal physiology has been noted in nearly 12% of patients with WPW syndrome. Coexisting ventricular tachycardia is less likely because patients with WPW syndrome tend to present at a younger age and have less structural heart disease.

Atrial fibrillation is a less common but potentially more serious arrhythmia in patients with the WPW syndrome. If an AP has a short antegrade refractory period, atrial fibrillation may result in a rapid ventricular response with subsequent degeneration to ventricular fibrillation.[11-13] The risk of sudden death has been shown to be higher if the shortest R-R interval is less than 250 milliseconds during spontaneous or induced atrial fibrillation.[11] It has been estimated that one-third of patients with WPW syndrome also have atrial fibrillation. APs appear to play a pathophysiologic role in the development of atrial fibrillation in these patients because most are young and do not have structural heart disease. Furthermore, surgical or catheter ablation of APs usually results in elimination of atrial fibrillation as well.

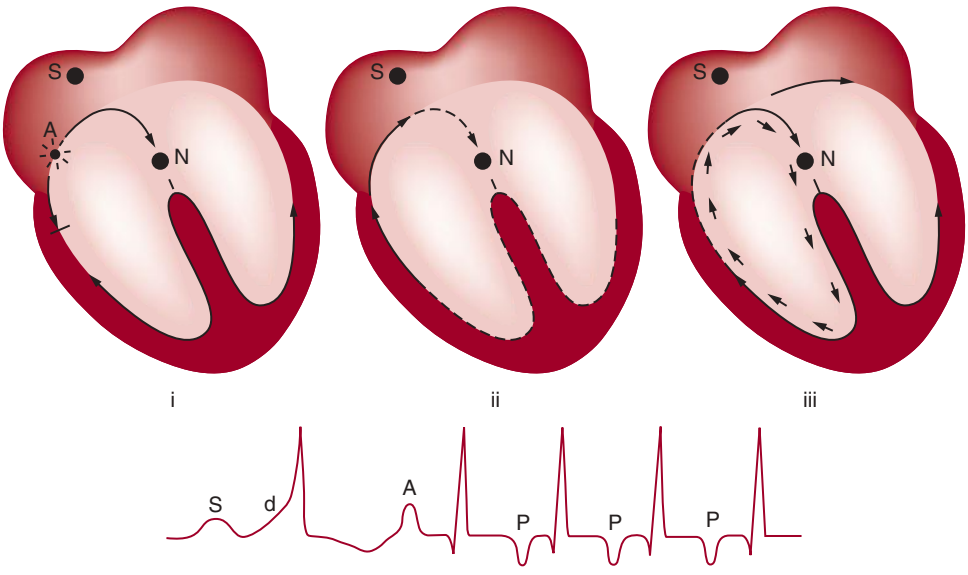


FIGURE 84–13. Schematic of initiation of orthodromic atrioventricular (AV) reentrant tachycardia. A diagrammatic electrocardiograph recording shows the first P wave of sinus node (S) origin yielding a preexcited QRS complex with a delta wave (*d*) and short PR interval (*I*). An ectopic atrial impulse (A) blocks antegradely in the bypass tract but still conducts over the AV node (N) and His-Purkinje system to the ventricles. This causes the second QRS complex to appear nonpreexcited (*ii*). The premature impulse continues to conduct retrogradely over the bypass tract because the latter had time recover excitability while the impulse was conducting over the node (*iii*). The retrogradely conducted impulse has activated the atria from the bypass tracts' atrial insertion point and generated the first retrograde P wave (*P*) of atrioventricular nodal reentrant tachycardia (AVRT). Reentrance of impulse through the node then occurs, causing AVRT to perpetuate. Modified with permission from Chung EK. Wolff-Parkinson-White syndrome: current views. *Am J Med*. 1977 Feb;62(2):252-266.

DIAGNOSIS

Clinical Features

Preexcitation occurs in the general population at a frequency of around 1.5 per 1000. Of these, 50% to 60% of patients become symptomatic. Approximately one-third of all patients with PSVT are diagnosed as having an AP-mediated tachycardia. Patients with AP-mediated tachycardias most commonly present with the syndrome of PSVT. Population-based studies have demonstrated a bimodal distribution of symptoms for patients with preexcitation, with a peak in early childhood followed by a second peak in young adulthood. Nearly 25% of patients will become asymptomatic over time. More than half the patients with an episode will experience a recurrence.

Symptoms range from palpitations to syncope. As in AVNRT, episodes of tachycardia may be associated with dyspnea, chest pain, decreased exercise tolerance, anxiety, dizziness, or syncope. Although syncope is often considered a bad prognostic sign, the evidence is not clear. Physical examination demonstrates a fast, regular pulse with a constant-intensity first heart sound. The jugular venous pressure waveform is usually constant, but it can sometimes be elevated. The incidence of sudden cardiac death in patients with WPW syndrome has been estimated to range from 0.15% to 0.39%.[11-13] It is distinctly unusual for cardiac arrest to be the first symptomatic manifestation of WPW syndrome. A recent report by Bunch et al compared the outcomes of 872 WPW patients who underwent ablation, 1461 WPW patients who did not have ablation, and 11,175 control patients.[14] Among all WPW patients the mortality and incidence of sudden death was no different than in the control population. However, the risk of AF was greater in WPW patients. It is also notable that patients with WPW who underwent ablation had a lower mortality than those who did not. Surprisingly, however, there was no difference in the incidence of sudden death in these two groups. Given the high prevalence of atrial fibrillation among patients with WPW syndrome and the concern for sudden cardiac death resulting from rapid preexcited atrial fibrillation, the low annual incidence of sudden death among patients with WPW syndrome is reassuring.

Patients with functioning AV bypass tracts tend to have certain congenital abnormalities, particularly Ebstein anomaly of the tricuspid valve. Nearly 10% of patients with Ebstein anomaly have preexcitation. APs also commonly occur in patients with corrected transposition of great vessels. In this case, the Ebstein anomaly of the left (tricuspid) valve is associated with APs to the functioning systemic ventricle (anatomic right ventricle). In addition, multiple bypass tracts are frequently seen in patients with Ebstein anomaly. Conversely, of patients with WPW syndrome presenting with SVT early in childhood, only 5% have Ebstein anomaly even though it is the most common from of congenital heart disease associated with WPW syndrome.

Electrocardiographic Characteristics

The ECG hallmark of an antegradely conducting AP is the delta wave along with a shorter than usual PR interval. Conversely, the presence of retrograde conduction only in an AP will not be apparent on a surface ECG during sinus rhythm. Whereas ECG during orthodromic AVRT has a normal QRS complex with retrogradely conducting P wave after the completion of the QRS complex in the ST segment or early in the T wave (see Fig. 84–4), the QRS during antidromic AVRT is fully preexcited.

Numerous algorithms have been described to localize the site of the AP using the axis of the delta wave and QRS morphology. The location of the AP along the AV ring is classified variously into five or ten regions, which can be broadly divided into those on the left and the right of the AV groove. Distribution along these lines is not homogenous. Some 46% to 60% of the pathways are found on the left free wall space. Nearly 25% are within the posteroseptal and midseptal spaces, 15% to 20% in the right free wall space, and 2% in the anteroseptal space. A simple algorithm that includes both the delta wave axis and the QRS axis is shown in Fig. 84–14.

ST-segment depression may also occur during orthodromic AVRT. It may occur even in young individuals, who are unlikely to have coronary artery disease. The location of the ST-segment depression may vary with the location of the AP. ST-segment depression in V_3 to V_6 is almost invariably seen with a left lateral pathway; a negative T wave in the inferior leads is associated with a posteroseptal or posterior pathway; and a negative or notched T wave in V_2 or V_3 with a positive retrograde P wave in at least two inferior leads suggests an anteroseptal pathway. However, ST-segment depression occurring during orthodromic AVRT episodes in older patients or associated with symptoms of ischemia mandate the consideration of coexisting coronary artery disease.

Electrophysiologic Testing

EPS in patients with AVRT is done to not only confirm the presence of an AP and differentiate this condition from other forms of SVT but also to find the pathway participating in the tachycardia and aid in ablative therapy.

By definition, if an AP is present and conducting antegradely, some part of the ventricle begins activation earlier than expected, so that the HV interval is less than normal at rest (see Fig. 84–10). Because the QRS complex is a fusion complex of conduction down both the AV node and the AP, slowing of conduction down the normal pathway results in an increasing degree of preexcitation.

Eccentric atrial activation with ventricular pacing makes it easy to identify the presence of an AP (Fig. 84–15). Retrograde conduction over most APs is nondecremental. Hence, in the absence of intraventricular conduction delay or the presence of multiple bypass tracts, the VA conduction time is the same over a range of pace cycle lengths (see Fig. 84–15). The exception to this is the slowly conducting decremental posteroseptal pathway found in the permanent form of junctional reciprocating tachycardia, in which the VA conduction time increases with increasing ventricular pacing rate.

It is important and often challenging to differentiate retrograde conduction over septal pathway from conduction over the normal AV system. One maneuver that can make this differentiation is *differential pacing* (ie, pacing both from the right ventricular apex and the RV base) and measuring the VA conduction time. Retrograde conduction over the normal AV conduction system is fastest when pacing from the apex because conduction can occur rapidly over the His-Purkinje system. VA intervals are longer when the pacing site is moved from the apex to the base. The converse is true in the presence of an AP, with VA intervals shortest when pacing from the base, closer to the site of pathway insertion, than from the apex. The technique of *para-Hisian pacing* is useful in differentiating the anteroseptal pathway from AVNRT.

Development of BBB aberration during tachycardia can be useful in determining both presence of and participation of an AP in tachycardia (Fig. 84–16). An increase in tachycardia cycle length caused by an increase in VA conduction time with functional BBB is consistent with the presence of an AP ipsilateral to the BBB.

MANAGEMENT

Catheter Ablation of Accessory Pathways

Catheter ablation of APs is performed in conjunction with a diagnostic EPS. After the AP has been localized to a region of the heart,

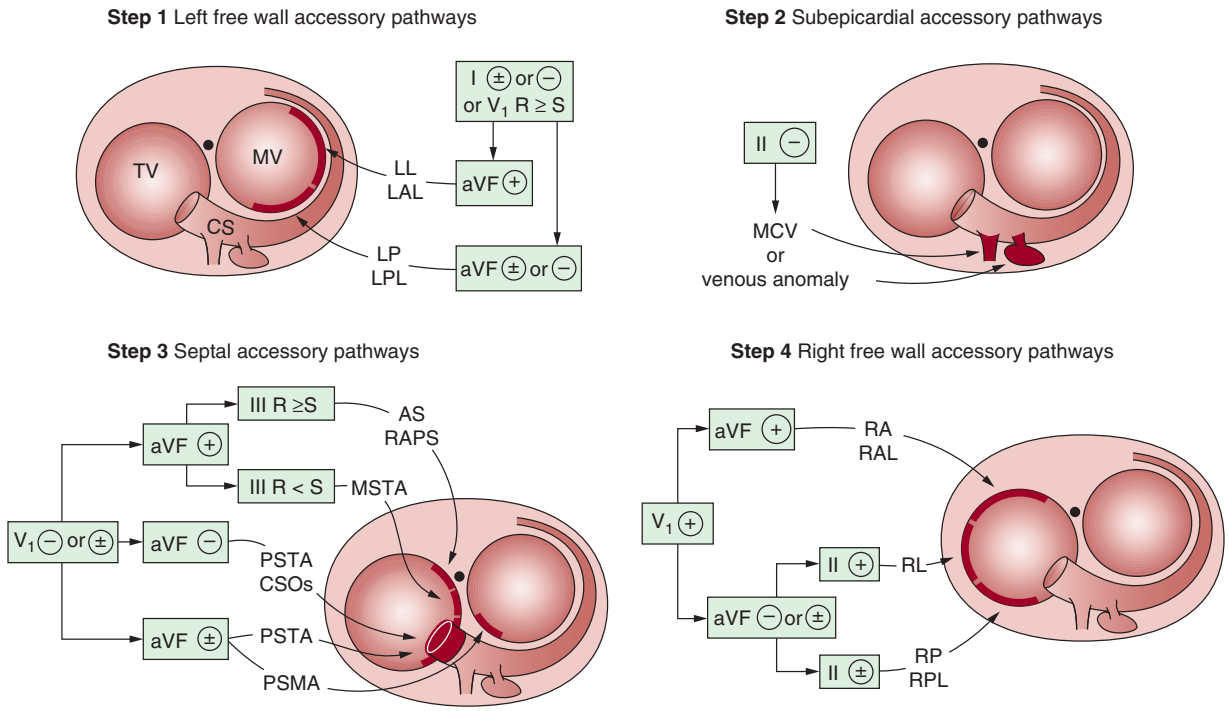


FIGURE 84–14. Localization of accessory pathways in patients with Wolff-Parkinson-White (WPW) syndrome. The line drawings illustrate the anatomic relationships between the tricuspid valve (TV), mitral valve (MV), coronary sinus (CS), atrioventricular conducting system, and accessory pathways. For each accessory pathway location indicated, the combination of QRS vectors most likely to result are shown based on upright (+) or inverted (–) QRS waveforms. These vectorial guidelines are generally useful but not necessarily precise because activation patterns from specific sites may vary in individual patients. AS, anteroseptal; CSOs, coronary sinus ostium; LAL, left anterolateral; LL, left lateral; LP, left posterior; LPL, left posterolateral; MCV, middle cardiac vein (coronary vein); MSTA, midseptal tricuspid annulus; PSMA, posteroseptal mitral annulus; PSTA, posteroseptal tricuspid annulus; RA, right anterior; RAL, right anterolateral; RAPS, right anterior paraseptal; venous anomaly (coronary sinus diverticulum); RL, right lateral; RP, right posterior; RPL, right posterolateral. Adapted with permission from Arruda MS, McClelland JH, Wang X, et al: Development and validation of an ECG algorithm for identifying accessory pathway ablation site in Wolff-Parkinson-White syndrome. *J Cardiovasc Electrophysiol*. 1998 Jan;9(1):2-12.

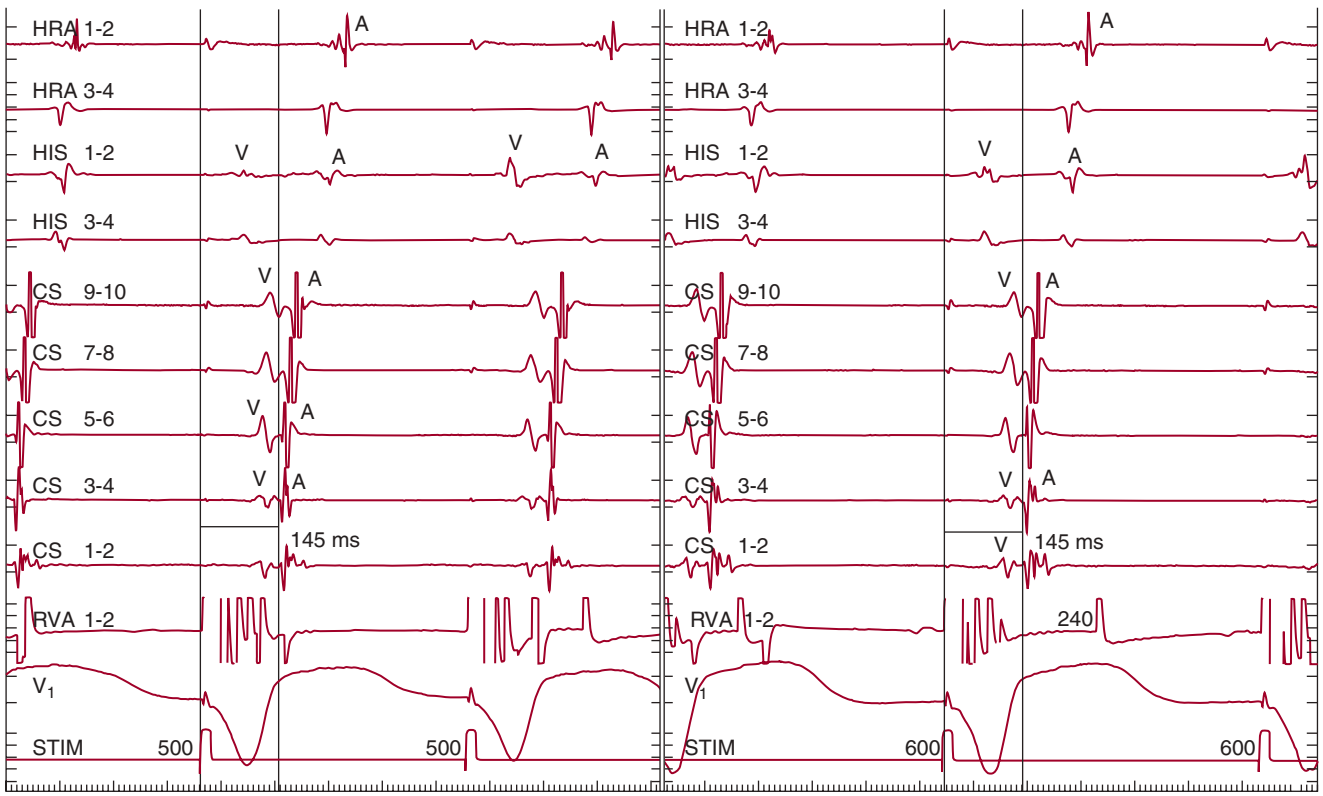


FIGURE 84–15. Nondecremental retrograde conduction in the accessory pathway. Note the eccentric activation of the atrium with pacing from the ventricle, with earliest atrial depolarization at the distal CS lead (CS 1-2). The left panel shows right ventricular pacing at a 120 bpm (cycle length, 500 milliseconds), and the right panel shows the same at 100 bpm (cycle length, 600 milliseconds). Note that the VA conduction time shown between the vertical lines remains the same with varying pacing rates. 1-2, distal electrodes; 3-4, proximal electrodes in each catheter; A, atrial electrogram; CS, coronary sinus; CS 9-20, the most proximal electrode in the CS catheter; HIS, His bundle electrogram; HRA, high right atrium; RVA, right ventricular apex; V, ventricular electrogram.

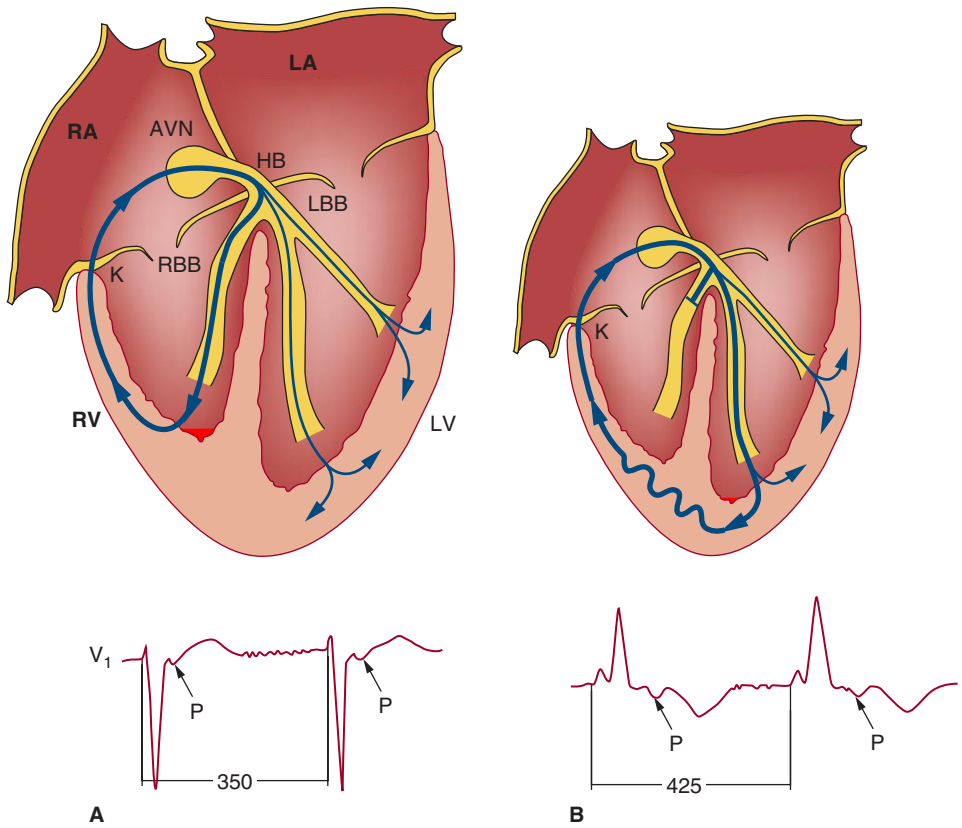


FIGURE 84–16. Effect of bundle-branch block (BBB) on atrioventricular nodal reentrant tachycardia (AVRT). **A.** AVRT involving a right-sided accessory pathway. Schematic at the bottom shows the electrocardiographic appearance of the tachycardia at a cycle length of 350 milliseconds. **B.** Appearance of BBB on the same side leads to increase the cycle length of the tachycardia to 425 milliseconds. See text for discussion. AVN, atrioventricular node; HB, His bundle; LA, left atrium; LBB, left bundle branch; LV, left ventricle; RA, right atrium; RBB, right bundle branch; RV, right ventricle. Modified with permission from Josephson M: *Clinical Cardiac Electrophysiology: Technique and Interpretation*, 3rd ed. New York: Lippincott Williams & Wilkins; 2002.

precise mapping and ablation are performed using a steerable electrode catheter. No prospective, randomized clinical trials have evaluated the safety and efficacy of catheter ablation of APs. However, the results of catheter ablation of APs have been reported in a large number of other trials.[5,8,9,15-21] The largest prospective, multicenter clinical trial to evaluate the safety and efficacy of RF ablation was reported by Calkins and colleagues.[5] This study involved analysis of 1050 patients, of whom 500 had APs. Overall success of catheter ablation in curing APs was 93%. The success rate for catheter ablation of left free wall APs was slightly higher than for catheter ablation of right-sided APs (95% vs 90%, $P = .03$). After an initially successful procedure, recurrence of AP conduction was found in approximately 5% of patients. The recurrence-free interval postablation was also best with left-sided pathways (Fig. 84–17). APs that recur can usually be successfully ablated again. Complications associated with catheter ablation of APs may result from obtaining vascular access (hematomas, deep venous thrombosis, perforation of the aorta, arteriovenous fistula, pneumothorax), catheter manipulation (valvular damage, microemboli, perforation of the CS or myocardial wall, coronary dissection or thrombosis), or delivery of RF energy (AV block, myocardial perforation, coronary artery spasm or occlusion, transient ischemic attacks, or cerebrovascular accidents).

Calkins and coworkers,[5] reported the incidence of major complications in their trial to be 3% and of minor complications around 8%. The procedure-related mortality associated with catheter ablation of APs has ranged from 0% to 0.2%. The two most common types

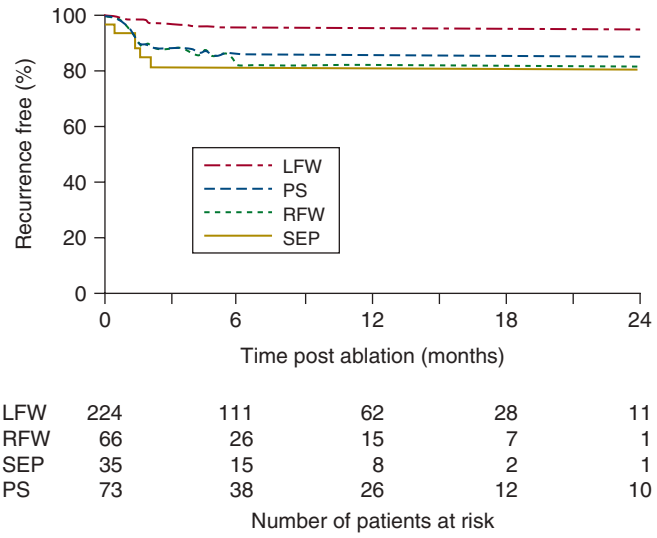


FIGURE 84–17. Kaplan-Meier curve showing freedom from arrhythmia recurrence among patients who underwent successful ablation of an accessory pathway subclassified by its location. This analysis was confined to patients in whom successful ablation was achieved with the investigational ablation system. LFW, left free wall; PS, posteroseptal; RFW, right free wall; SEP, septal. Reproduced with permission from Calkins H, Yong P, Miller JM, et al. Catheter ablation of accessory pathways, atrioventricular nodal reentrant tachycardia, and the atrioventricular junction: final results of a prospective, multicenter clinical trial. The Atakr Multicenter Investigators Group. *Circulation*. 1999 Jan 19;99(2):262-270.

of major complications reported during catheter ablation of APs are inadvertent complete AV block and cardiac tamponade. The incidence of inadvertent complete AV block ranges from 0.17% to 1.0%. Most instances of complete AV block occur in the setting of the ablation of septal and posteroseptal APs. The frequency of cardiac tamponade as a result of the ablation of APs varies between 0.13% and 1.1%.

In the past several years, cryoablation has become available as an alternative energy source for creation of myocardial lesions, which can be used for catheter ablation of APs. The main advantage of cryoenergy compared with RF energy is that the risk of heart block appears to be lower.[16] This potential benefit must be balanced against longer procedure times and lower acute and long-term efficacy.[16] Because of the lower acute and long-term success rates of catheter ablation of APs using cryoenergy, this energy source is generally used only for ablation of APs located in the anteroseptal and para-Hisian locations.

Medical Therapy

Antiarrhythmic drugs represent one therapeutic option for management of patients with AP-mediated arrhythmias (see Table 84–4). Antiarrhythmic drugs that primarily modify conduction through the AV node include verapamil, β-blockers, and adenosine. In contrast, the antiarrhythmic drugs, which primarily modify conduction across the AP, consist of class 1 drugs such as procainamide, propafenone, and flecainide as well as class 3 antiarrhythmic drugs such as sotalol and amiodarone. The approach to acute termination of these arrhythmias generally differs from that used for long-term suppression and prevention of further episodes of SVT. In general, the approach used does not vary based on the specific tachycardia mechanism, which generally is unknown when the patient first presents to an ED. Pharmacologic agents are in general more effective in terminating an acute episode of tachycardia than in preventing future recurrences. Verapamil or diltiazem should not be administered intravenously to patients with atrial fibrillation and preexcitation because they may accelerate conduction through the AP and precipitate a cardiac arrest.

There have been no controlled trials of drug prophylaxis involving patients with AV reentry. However, a number of small, nonrandomized trials have been performed which have demonstrated reasonable effectiveness of propafenone, flecainide, and amiodarone.

MANAGEMENT CONSIDERATIONS

Management of Asymptomatic Preexcitation

Most patients with asymptomatic preexcitation have a good prognosis. Because of the small but real risks associated with invasive procedures, EPS is not mandated for risk stratification or ablative therapy. The ACC/AHA/HRS Guidelines for Management of Patients with Supraventricular Arrhythmias gives electrophysiologic testing and catheter ablation when indicated a 2A classification for treatment of patients with asymptomatic preexcitation.[1] A 2A designation means that it is reasonable to offer EPS with or without ablation in selected patients after a thorough discussion of the risks and benefits of the procedure. Similar recommendations have been made in the PACES/HRS Expert Consensus Statement on the Management of Asymptomatic Young Patients with a WPW ECG Pattern.[14]

Several noninvasive and invasive tests have been proposed as useful in stratifying patients for the risk of sudden death.[1,17] The detection of intermittent preexcitation—which is characterized by an abrupt loss of the delta wave, normalization of the QRS complex, and an increase in the PR interval during a continuous ECG recording—is evidence that an AP has a relatively long refractory period and is unlikely to precipitate ventricular fibrillation. The loss of preexcitation after administration of antiarrhythmic drugs such as procainamide or ajmaline has also been used to indicate a low-risk subgroup. These noninvasive tests are generally considered inferior to EPS in the assessment of risk of sudden cardiac death. Because of this, they play little role in patient management at present.

When screening studies are performed in patients with asymptomatic preexcitation, approximately 20% of those who are asymptomatic will demonstrate a rapid ventricular rate during atrial fibrillation induced at EPS. Studies have identified markers that identify patients at increased risk. These include (1) a short preexcited R-R interval below 250 ms during spontaneous or induced atrial fibrillation, (2) a history of symptomatic tachycardia, (3) multiple APs, and (4) Ebstein anomaly.[1,17,18] A short preexcited R-R interval during atrial fibrillation above 250 ms has been reported to have a negative predictive value greater than 95%.

More recent evidence makes a stronger case for use of EPS in risk stratifying all asymptomatic patients with preexcitation.[23] Pappone and coworkers[24] studied 212 consecutive asymptomatic WPW patients after a baseline EPS over 5 years. After a mean follow-up of 37.7 months, 33 patients became symptomatic. Of these, 29 had inducible SVT on EPS, and only 4 were not inducible. More importantly, there were three sudden deaths in the entire population, and all of them occurred in patients in whom AVRT and atrial fibrillation were inducible during EPS. In a more recent study, Pappone and colleagues (24) examined the role of prophylactic catheter ablation in children with asymptomatic preexcitation. Of the 165 eligible children, 60 were determined to be at high risk of an arrhythmia based on their results of EPS. Of these 60 patients, 20 underwent prophylactic catheter ablation, 27 had no treatment, and 13 withdrew from the study. During a mean follow-up of 34 months, 1 child in the ablation group (5%) and 12 in the control group (44%) had arrhythmic events. Among these 12 patients in the control group, 2 experienced ventricular fibrillation, and one died suddenly.

Santinelli and coworkers[25,26] published two papers describing the natural history of asymptomatic preexcitation. Among 293 adults with asymptomatic preexcitation followed for a median of 67 months, 31 patients (10.6%) developed a first arrhythmic event. Among these patients, the event was classified as potentially life threatening in 17 patients. One of these patients experienced a cardiac arrest. Multivariate analysis identified inducibility, an anterograde effective refractory period shorter than 250 milliseconds as predictive of potentially life-threatening arrhythmias.[24] And among 184 children with asymptomatic preexcitation followed for a median of 57 months, 51 patients (28%) developed a first arrhythmic event. Among these patients, the event was classified as potentially life threatening in 19 patients. Three of these patients experienced a cardiac arrest. Multivariate analysis identified an anterograde effective refractory period shorter than 240 milliseconds and the presence of multiple APs as predictive of potentially life-threatening arrhythmias.[25,26] Pappone et al went on to publish an outcome registry involving 2169 WPW patients followed for 8 years[27] among this group, 1001 (550 asymptomatic) did not undergo ablation and 1168 (206 asymptomatic) did have ablation. VF occurred during follow-up in 1.5% of patients who

TABLE 84–5. AHA/ACC/HRS 2015 Recommendations for Management of Patients With Symptomatic Manifest or Concealed Accessory Pathways[1]

Class	
1	In asymptomatic patients with preexcitation, the findings of abrupt loss of conduction over a manifest pathway during exercise in sinus rhythm or intermittent loss of preexcitation during ECG or ambulatory monitoring are useful to identify patients at low risk of rapid conduction over the pathway.
2A	An EP study is reasonable in asymptomatic patients with preexcitation to risk stratify for arrhythmic events.
2A	Catheter ablation of the accessory pathway is reasonable in asymptomatic patients with preexcitation if an EP study identifies a high risk of arrhythmic events including rapidly conducting preexcited AF.
2A	Catheter ablation of the accessory pathway is reasonable in asymptomatic patients if the presence of preexcitation precludes specific employment (such as pilots).
2A	Observation, without further evaluation or treatment, is reasonable in asymptomatic patients with preexcitation.

did not have catheter ablation. In contrast, no patients with WPW who underwent ablation experienced VF during follow-up. Based on the results of these studies, as well as the well-established safety and efficacy of catheter ablation of APs, an increasing proportion of electrophysiologists, particularly pediatric electrophysiologists, now advocate screening EPS and prophylactic catheter ablation when a high-risk AP is uncovered. The recommendations made for management of asymptomatic preexcitation in the AHA/ACC/HRS 2015 SVT Guidelines are summarized in Table 84–5.

Management of Symptomatic Wolff-Parkinson-White Syndrome

The ACC/AHA/HRS Guidelines for Management of Patients with SVT states that catheter ablation is considered first-line therapy (class 1) and the treatment of choice for patients with WPW syndrome (ie, patients with manifest preexcitation along with symptoms).[1,19,20] It is curative in more than 95% of patients and has a low complication rate. It also obviates the unwanted side effects of antiarrhythmic agents. Catheter ablation is also considered first-line therapy (class 1) for patients with PSVT involving a concealed AP. However, because concealed APs are not associated with an increased risk of sudden cardiac death in these patients, catheter ablation can be presented as one of a number of potential therapeutic approaches, including pharmacologic therapy and clinical follow-up alone (see discussion of management of AVNRT). When pharmacologic therapy is selected for patients with concealed APs, it is reasonable to consider a trial of β-blocker therapy, CCB therapy, or a class 1C antiarrhythmic agent. It is important to note that β-blockers and CCBs generally are not recommended for the management of patients who have evidence of preexcitation.

The recommendations for the acute and long-term management of patients with AP-mediated arrhythmias developed by the ACC/AHA/HRS are shown in Tables 84–6 and 84–7.[1] Catheter ablation is considered class 1 therapy for treatment of patients with WPW syndrome and for those with AVRT in the absence of preexcitation.

TABLE 84–6. AHA/ACC/HRS 2015 Recommendations for Acute Management of Patients with AP-Mediated Arrhythmias[1]

Class	
1	Vagal maneuvers are recommended for acute treatment in patients with orthodromic AVRT.
1	Adenosine is beneficial for acute treatment in patients with orthodromic AVRT.
1	Synchronized cardioversion should be performed for acute treatment in hemodynamically unstable patients with AVRT if vagal maneuvers or adenosine are ineffective or not feasible.
1	Synchronized cardioversion is recommended for acute treatment in hemodynamically stable patients with AVRT when pharmacologic therapy is ineffective or contraindicated.
1	Synchronized cardioversion should be performed for acute treatment in hemodynamically unstable patients with preexcited AF.
1	Ibutlide or intravenous procainamide is beneficial for acute treatment in patients with preexcited AF who are hemodynamically stable.
2B	Intravenous diltiazem, verapamil, or beta-blockers can be effective for acute treatment in patients with orthodromic AVRT who do not have preexcitation on their resting ECG during sinus rhythm.
2B	Intravenous beta-blockers, diltiazem, or verapamil might be considered for acute treatment in patients with orthodromic AVRT who have preexcitation on their resting ECG and have not responded to other therapies.
3	Intravenous digoxin, intravenous amiodarone, intravenous or oral beta-blockers, and verapamil are potentially harmful for acute treatment in patients with pre-excited AF.

TABLE 84–7. AHA/ACC/HRS 2015 Recommendations for Management of Patients With Symptomatic Manifest or Concealed Accessory Pathways[1]

Class	
1	Catheter ablation of the accessory pathway is recommended in patients with AVRT and/or preexcited AF
1	Oral beta-blockers, diltiazem, and verapamil are indicated for ongoing management of AVRT in patients without preexcitation on their resting ECG.
2A	Oral flecainide or propafenone is reasonable for ongoing management in patients without structural heart disease or ischemic heart disease who have AVRT and/or preexcited AF and are not candidates for, or prefer not to undergo, catheter ablation.
2B	Oral dofetilide or sotolol may be reasonable for ongoing management in patients with AVRT and/or preexcited AF who are not candidates for, or prefer not to undergo, catheter ablation.
2B	Oral amiodarone may be considered for ongoing management in patients with AVRT and/or preexcited AF who are not candidates for, or prefer not to undergo, catheter ablation and in whom beta-blockers, diltiazem, flecainide, propafenone, and verapamil are ineffective or contraindicated.
2B	Oral beta-blockers, diltiazem, or verapamil may be reasonable for ongoing management of orthodromic AVRT in patients with pre-excitation on their resting ECG who are not candidates for, or prefer not to undergo, catheter ablation.
2B	Oral digoxin may be reasonable for ongoing management of orthodromic AVRT in patients without preexcitation on their resting ECG, who are not candidates for or prefer not to undergo catheter ablation.
3	Oral digoxin is potentially harmful for ongoing management in patients with AVRT or AF and preexcitation on their resting ECG.

ATRIAL TACHYCARDIA

Atrial tachycardia is an arrhythmia that arises from the left or right atrium or the musculature of the great cardiac veins.[1] There are many types of atrial tachycardias. Some are paroxysmal while others are continuous. The mechanisms of atrial tachycardias vary widely and include enhanced automaticity, triggered activity, and reentry. Although atrial fibrillation and atrial flutter can be considered under the broad umbrella of atrial tachycardias, in my opinion it is best to consider atrial flutter and atrial fibrillation as distinct arrhythmias in part because of the marked increase in stroke risk that accompanies atrial fibrillation and atrial flutter.

Atrial tachycardias are generally benign arrhythmias where the main indication for treatment is symptom relief. One important exception is incessant atrial tachycardia with a rapid rate. It is well established that incessant atrial tachycardia's that result in a persistently rapid ventricular response can lead to a rate related cardiomyopathy. It is important to recognize that this potentially serious condition is reversible once the atrial tachycardia is eliminated with an associated return of the ventricular rate to normal.

There are many approaches to treatment of atrial tachycardia. Pharmacologic therapy with beta-blockers or calcium channel blockers is effective in a proportion of patients. If these first-line medications fail, membrane active antiarrhythmic medications such as flecainide, propafenone, sotolol, or rarely amiodarone can be considered. Catheter ablation is an important treatment strategy that is appropriate to use first line based on patient's values and preferences. With the use of three-dimensional computerized mapping systems, the cure rate associated with ablation of atrial tachycardia exceeds 90%. One important exception to this rule is multifocal atrial tachycardia, which is far more difficult to approach with ablation because of its multifocal origin.

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CHAPTER 85

VENTRICULAR ARRHYTHMIAS

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INTRODUCTION

Ventricular arrhythmias occur commonly in clinical practice, and range from benign asymptomatic premature ventricular contractions (PVCs) to sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) resulting in sudden cardiac death (SCD). The presence of structural heart disease plays a major role in risk stratification; however, it is important to recognize potentially lethal arrhythmias can occur in structurally normal-appearing hearts. Management depends on the associated symptoms, underlying pathologic substrate, hemodynamic consequences, and associated long-term prognosis. Given the complexity of these arrhythmias, initial management, risk stratification, and treatment of ventricular arrhythmias pose a significant challenge to clinicians.

This chapter provides an overview of the clinical presentation, natural history, diagnosis, and therapeutic options for the ventricular arrhythmias encountered in clinical practice. Given the differences in management, this chapter has been divided into two major sections: ventricular arrhythmias in patients with structurally normal and abnormal hearts.

This chapter incorporates the recommendations from the most recent professional society guidelines, including the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities,[1] the 2012 ACC/AHA/HRS Focused Update Incorporated Into the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities,[2] the HRS/ACC/AHA Expert Consensus Statement on the Use of Implantable Cardioverter-Defibrillator Therapy in Patients Who Are Not Included or Not Well Represented in Clinical Trials[3], the 2013 HRS/European Heart Rhythm Association (EHRA)/Asia-Pacific Heart Rhythm Association (APHRS) Expert Consensus Statement on the diagnosis and Management of Patients with Primary Inherited Arrhythmia Syndromes,[4] the 2009 EHRA/HRS Consensus on Catheter Ablation of Ventricular Arrhythmias,[5] the 2014 EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias,[6] and the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[7] As with all guidelines, these documents provide specific categories of recommendation, according to the level of evidence available.

VENTRICULAR TACHYCARDIA DEFINITIONS

Sustained VT: Duration of VT is > 30 seconds or < 30 seconds associated with hemodynamic collapse.

Nonsustained VT: Duration > 3 beats and < 30 seconds not associated with hemodynamic collapse.

Repetitive Monomorphic VT: Episodes of nonsustained VT that continuously repeat.

VT Storm: More than three separate episode of VT in 24 hours requiring intervention to terminate.

Monomorphic VT: All beats have same QRS morphology (some variation may be seen at initiation).

Polymorphic VT: Continuously changing morphology of the VT is seen from beat to beat.

Pleomorphic VT: More than one distinct morphology during the same episode of VT.

VENTRICULAR TACHYARRHYTHMIAS IN THE SETTING OF A STRUCTURALLY NORMAL HEART

PREMATURE VENTRICULAR CONTRACTIONS/NONSUSTAINED VENTRICULAR TACHYCARDIA IN THE ABSENCE OF ORGANIC HEART DISEASE

Premature ventricular contractions (PVCs)/nonsustained ventricular tachycardia (NSVT) are commonly seen in clinical practice in patients with structurally normal hearts. The significance of PVCs/NSVT depends on the frequency, the presence and severity of structural heart disease, and the presence of associated symptoms.

PVCs occur frequently in the general population.[8] In patients without structural heart disease, PVCs are not associated with any excess risk of sudden death. Kennedy and coworkers[9] studied 73 patients with frequent ventricular ectopy and no structural heart disease on a 24-hour ambulatory (Holter) monitor. Patients were followed for an average of 6.5 years with no excess in mortality. A recent meta-analysis reaffirmed these findings.[10] PVCs that occur in patients with a structurally normal heart may not warrant therapy, unless significant symptoms are present or there is concern for PVC-induced cardiomyopathy. NSVT is also very common, occurring in up to 6% of patients in Holter studies.[11]

OUTFLOW TRACT PREMATURE VENTRICULAR CONTRACTIONS/ NONSUSTAINED VENTRICULAR TACHYCARDIA

The right ventricular outflow tract (RVOT) is the most common site of origin of idiopathic PVCs/NSVT. PVCs/NSVT originating from this region are characterized on the 12-lead electrocardiogram by a left bundle branch block pattern in V_1 and tall, monophasic R waves in the inferior leads (Fig. 85–1). Although most outflow tract PVCs/NSVT originate from the RVOT, in approximately 25% of cases the site of origin is from other sites (coronary cusps, mitral annulus, left ventricular (LV) summit, or within or adjacent to the epicardial coronary venous structures) based on mapping studies (Fig. 85–2).[12] For most patients with structurally normal hearts who have idiopathic outflow tract PVCs/NSVT, the prognosis is good.[13] This group of patients may manifest with frequent single PVCs, bigeminy, trigeminy, NSVT, or as repetitive salvos of nonsustained monomorphic VT.

PREMATURE VENTRICULAR CONTRACTIONS AS A CAUSE OF CARDIOMYOPATHY

Clinical evidence of an association between frequent PVCs and a dilated cardiomyopathy (CM) has been demonstrated.[14-18] A higher burden of PVCs over a 24-hour period is associated with higher risk, but development of CM associated with a burden as low as 10% has been described.[14]

In a study by Niwano and associates,[13] 239 patients with frequent PVCs and no evidence of primary CM by echocardiography and cardiac magnetic resonance imaging were followed for > 4 years. Forty-six patients had highly frequent PVCs (> 20,000/24 h), 105 patients had moderately frequent PVCs (5000-20,000/24 h), and 88 patients had less frequent PVCs (1000-5000/24 h). A significant negative correlation was observed between PVC frequency and left ventricular (LV) ejection fraction (EF) at 4 years and 5.6 years.

Several studies have further demonstrated that elimination of PVCs among patients with depressed LV function may improve EF.[19,20] In a series of 60 consecutive patients with frequent PVCs (> 10 PVCs/h), reduced LV function (mean LVEF 34% ± 13%) was present in 22 patients (37%).[19] Patients with depressed LV function had more frequent PVCs than patients with normal LV function (37% ± 13% vs 11% ± 10% of all QRS complexes, respectively; $P = .0001$). Radiofrequency catheter ablation was successful in eliminating PVCs in 48 (80%) of 60 patients. Among the 22 patients with abnormal LV function, LV function assessed 6 months after the procedure returned to normal in 18 (82%) of 22 patients (LVEF of 34% ± 10% to LVEF of 59% ± 7%; $P < .0001$). Among patients with LV dysfunction at baseline who were not successfully ablated, the LV function further declined (LVEF of 34% ± 10% to LVEF of 25% ± 7%; $P = .06$).[21]

In summary, current studies regarding the role of PVCs in the development of a CM demonstrate the following: (1) LV dysfunction can occur when PVCs are present for a prolonged period of time; (2) LV dysfunction occurs among patients with a high frequency of PVCs; and (3) among patients with a PVC-induced CM, LVEF improves in the majority of patients when the PVCs can be eliminated with radiofrequency catheter ablation.

A number of electrocardiographic and other factors have been associated with increased risk of PVC-induced CM, but further assessment is ongoing. A higher burden, retrograde ventriculoatrial (VA) conduction[15], PVC QRS duration,[16,22] site of origin,[22] interpolation,[18] male gender,[17] PVCs throughout the day,[17] epicardial origin,[23] and coupling interval dispersion[24] have been described as potential contributing factors.

MANAGEMENT OF PATIENTS WITH IDIOPATHIC PREMATURE VENTRICULAR CONTRACTIONS/NONSUSTAINED VENTRICULAR TACHYCARDIA

Patients with PVCs/NSVT should have an echocardiogram to assess LV function. If no significant structural abnormalities are noted on echocardiography, no further imaging studies are typically required.

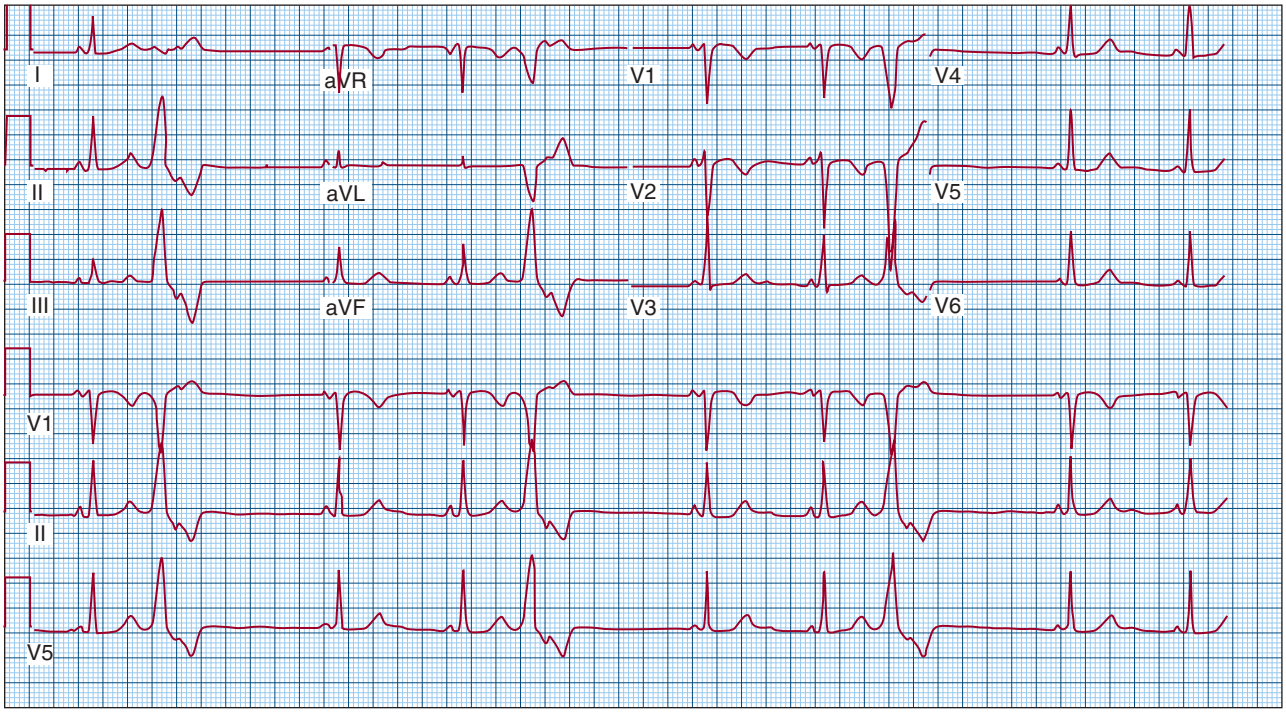

FIGURE 85–1. Outflow tract premature ventricular contraction (PVC). Thirty-year-old woman with symptomatic PVCs despite previous trial of beta-blockers and flecainide. The PVC morphology is a left bundle branch block (LBBB) pattern with inferior axis (tall positive R waves in leads II, III, and aVF), consistent with a focus in the right ventricular outflow tract (RVOT). The PVC was successfully ablated.

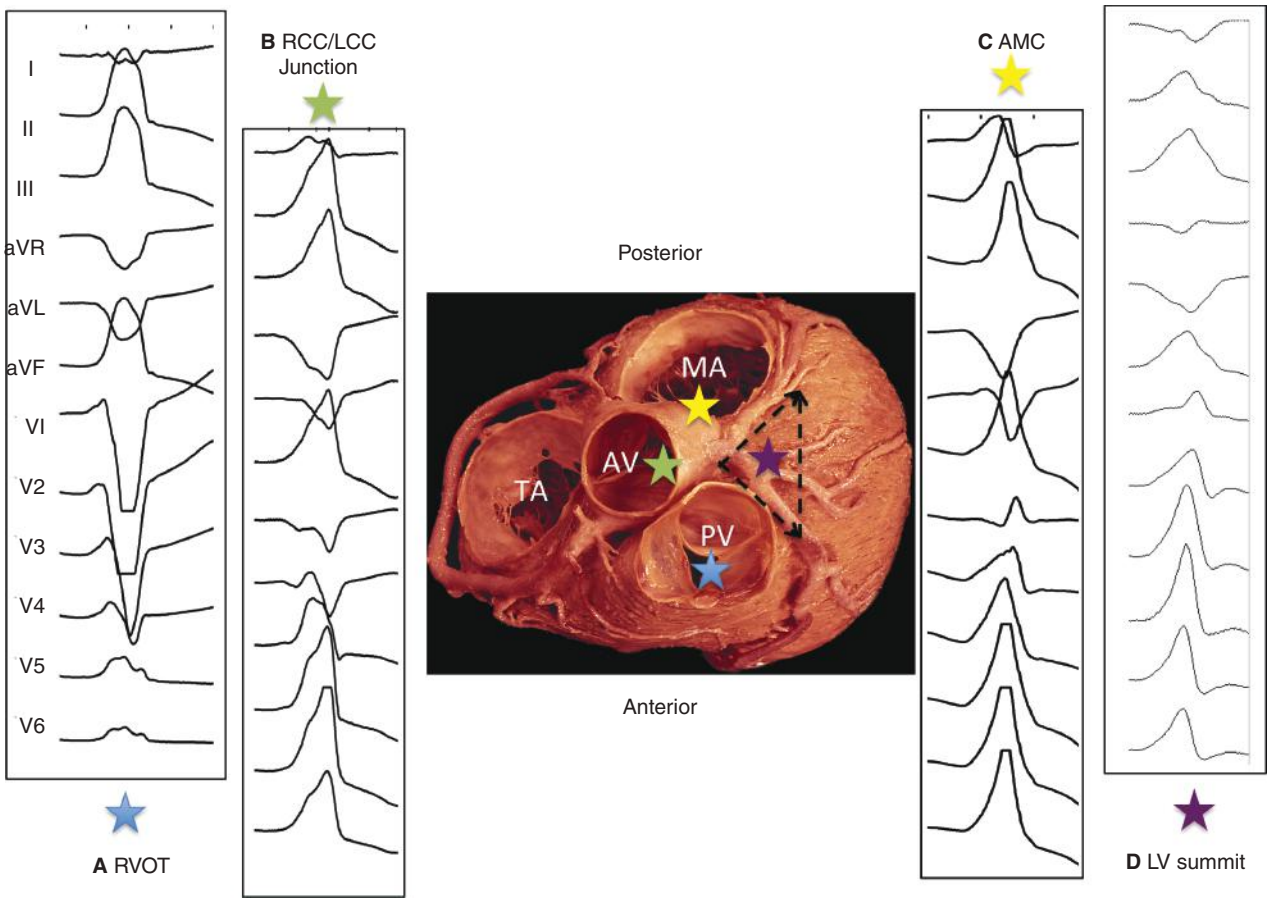

FIGURE 85–2. Idiopathic premature ventricular contractions (PVCs) of variable origin. **A.** Right ventricular outflow tract (RVOT) origin PVC with left bundle branch block (LBBB) morphology, inferior axis, and "late" transition (R > S after V_3) in precordial leads. **B.** A right coronary cusp/left coronary cusp (RCC/LCC) junction origin PVC with LBBB morphology with "W"-shaped V1, inferior axis, and earlier precordial transition then the RVOT PVC. **C.** Aorto-mitral continuity (AMC) orign PVC with a right bundle branch block (RBBB) morphology pattern, inferior axis, and "qR" V_1 morphology. **D.** A left ventricular (LV) summit origin PVC with RBBB morphology, inferior axis. Associated star colors show the anatomic location of these PVCs in an anatomic specimen from a superior view with the atria removed. RVOT-origin VT/PVCs typically originate below the valve but as in the LVOT can originate from strands of myocardium above the pulmonic valve. Black triangle demonstrates area of LV summit between the LAD and Cx arteries. AV, aortic valve; Cx, circumflex; LAD, left anterior descending; MA, mitral annulus; PV, pulmonic valve; TA, tricuspid valve. Used with permission from UCLA Cardiac Arrhythmia Center-Wallace A. McAlpine Collection.

The frequency of "outflow tract" PVCs/NSVT is often augmented by exercise; therefore, an exercise treadmill test may be a useful diagnostic test. Increased burden during recovery as opposed to peak exercise may be associated with increased risk.[25,26] Further exercise stress testing can help assess for catecholaminergic polymorphic VT (CPVT), which has a definitive bidirectional VT pattern during stress. In addition, cardiac magnetic resonance imaging (MRI) may have utility[27,28] when history or clinical findings raise concern for subtle underlying structural pathology (Table 85–1).

However, while further imaging studies are often not required, patients with PVCs from the right ventricle (RV), with RV dysfunction or enlargement on echocardiogram or multiform RV-origin PVCs, should be considered for further evaluation to exclude arrhythmogenic RV cardiomyopathy (ARVC) or cardiac sarcoidosis. This workup should include a cardiac MRI[29] and possibly a positron emission tomography-computed tomography (PET-CT) scan. Additional testing, including a signal-averaged electrocardiogram and electrophysiologic study with three-dimensional electroanatomic voltage mapping to assess for early endocardial scar, may be also considered.

Patients with structurally normal hearts and asymptomatic PVCs do not require specific therapy unless the PVC burden is high enough to raise concern for PVC-induced CM. In patients with symptomatic PVCs, therapy is aimed at alleviating symptoms. Initial treatment should the avoidance of potential exogenous stimulants (such as caffeine, excess alcohol, recreational drugs) or a trial of β-adrenergic blocking or calcium channel-blocking agents. However, the success rate for medical therapy is low (< 50%) in this population.[30,31]

Radiofrequency catheter ablation can be a curative treatment option for patients with symptomatic PVCs/NSVT when there is a predominant PVC/NSVT morphology and the PVCs are causing symptoms or possible risk of CM and drug therapy is proven ineffective, is not tolerated, or is not preferred (EHRA/HRS/APHRS guidelines) (Fig. 85–3).[6] Catheter ablation is more effective at decreasing PVC burden than antiarrhythmic medication,[32,33] and the success rate is consistently over 75% in studies on ablation of PVCs of various locations of origin.[34-39]

MALIGNANT PREMATURE VENTRICULAR CONTRACTIONS

Rarely, "idiopathic" PVCs thought to be benign, with no known underlying pathological substrate, can have a more malignant clinical course. Viskin and colleagues[40] reported "short-coupled" PVCs inducing polymorphic VT in three case studies; however, this concept requires further study. Patients developing recurrent syncope or seizures with frequent PVCs on ambulatory monitoring warrant closer evaluation. This should include longer-term monitoring and a careful evaluation to rule out inherited arrhythmia syndromes and subtle structural heart abnormalities.

TABLE 85–1. Appropriate Workup and Indications for Catheter Ablation of VT

Workup and Treatment

1. Obtain 12-lead ECG of the clinical VT when possible.
2. Obtain transthoracic echocardiogram to assess for evidence of structural heart disease.
3. If no definitive structural heart disease on echocardiogram, consider:
   - Exercise stress testing
   - Signal average ECG
   - Cardiac MRI
   - Cardiac CT/PET scan
4. Structural heart disease found:
   - Consider indication for ICD
   - When ICD implanted, ensure appropriate programming to minimize inappropriate shocks.
5. Consider need for additional intervention:
   - Antiarrhythmic medications
   - VT ablation
6. Consider catheter ablation in patients without structural heart disease:
   - Symptomatic sustained monomorphic VT in patient unresponsive to antiarrhythmics or when antiarrhythmics are not tolerated or not desired by the patient
   - When a monomorphic PVC trigger of PMVT or VF is present and refractory to antiarrhythmic
7. Consider catheter ablation in patients with structural heart disease:
   - Symptomatic sustained VT (with or without ICD therapy) despite antiarrhythmic therapy or when antiarrhythmic therapy is not tolerated or desired
   - VT storm without reversible cause
   - For PVCs/NSVT/VT thought to be the cause ventricular dysfunction
   - Bundle branch reentry VT or interfascicular VT
   - When a monomorphic PVC trigger of PMVT or VF is present and refractory to antiarrhythmics

Abbreviations: CT, computed tomography; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; MRI, magnetic resonance imaging; PET, positron emission tomography; PMVT, polymorphic VT; PVC, premature ventricular contraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Data from 2014 EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias,[6] 2009 EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: patients with structurally normal hearts,[5] and 2009 EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: patients with structural heart disease.[6]

Short-coupled PVCs independently are less likely to be a clinical risk unless occurring in patients with a predisposition to VF (ie, Brugada syndrome, long QT syndrome, short QT syndrome, CPVT, and idiopathic VF). In the setting of these clinical entities, the PVC may serve as an important triggering mechanism.[41,42] In a multicenter observational series of 27 patients who had suffered from recurrent VF, Haisseguerre and colleagues[43] reported that the initiating trigger for VF was a PVC in all patients. In this series, 23 patients had PVCs that were found to originate in the Purkinje fibers and the remaining patients had PVC triggers mapped to the RVOT. The PVCs were successfully mapped and eliminated with radiofrequency catheter ablation, and after a follow-up period of 24 ± 28 months, 89% had no recurrences of VF, off antiarrhythmic drug therapy. Therefore, when a monomorphic PVC is the trigger for VT or VF, catheter ablation is an excellent treatment option (Table 85–2). However, in another study (median follow-up 63 months) of 38 patients with idiopathic VF triggered by PVCs, 7 (18%) of 38 patients had recurrence of VF after catheter ablation of the PVC trigger. Therefore, patients with this and other inherited arrhythmia syndromes, unlike those with idiopathic PVCs without underlying pathology, may still need to be considered for an implantable cardioverter-defibrillator (ICD) despite successful ablation of the PVCs.[44]

OUTFLOW TRACT SUSTAINED VENTRICULAR TACHYCARDIA

Clinically, the percentage of patients presenting with idiopathic VT as compared to VT in the setting of structural heart disease will depend largely on the type of center evaluating the patient. Idiopathic VT likely represents the majority of VT cases in community hospitals and many tertiary care centers. In more specialized referral centers, structural heart disease–related VT may be more common.

The two main clinical entities of idiopathic VT include "outflow tract" VT and "idiopathic left ventricular" VT (also known as fascicular VT or verapamil-sensitive VT). The differentiation of these VTs from VTs associated with structural heart disease is important because they are associated with an excellent prognosis, and can be more easily treated with catheter ablation. However, the potentially subtle differences between an idiopathic VT that can potentially be managed conservatively and a VT with more substantial risk of SCD can be difficult to decipher.

"Outflow tract" VT occurs frequently in young to middle-aged patients without structural heart disease. This arrhythmia is often provoked by exercise and emotional stress. Recurrence may be associated with exercise, stress, or caffeine, and in women, it occurs more frequently during premenstrual, perimenopausal, and gestational periods.[45]

"Outflow tract" VT most commonly arises from the RVOT immediately inferior to the pulmonary valve. Outflow origin PVCs and VT have a characteristic pattern on the 12-lead electrocardiogram, with a left bundle branch block (LBBB) morphology and inferior axis.[46] This general description often leads physicians to assume all arrhythmias with this ECG morphology are of RVOT origin. However, because of the complex three-dimensional structure of the outflow tracts (Fig. 85–4), numerous sites of potential origin are possible and depending on the exit site of the PVC/VT, can have similar morphologies. Numerous other sites can be foci for idiopathic PVCs and VT, including, but not limited to, the LV outflow tract, aortic sinus of Valsalva/coronary cusps, LV summit (Fig. 85–5), mitral annulus, tricuspid annulus, coronary venous system, papillary muscles, moderator band, cardiac crux, para-Hisian region, and the pulmonary artery above the pulmonic valve.[35-38,47,48] Given the multiple sites of possible origin, it is important to have a consistent approach to localizing and mapping these arrhythmias when ablation is considered,[49] and to utilize available published criteria to help differentiate likely sites of origin.[50]

The proposed cellular mechanism of this tachycardia is cyclic adenosine monophosphate–mediated (cAMP) triggered activity from delayed afterdepolarizations.[51] This mechanism is supported by the sensitivity of the arrhythmia to adenosine infusion, which often terminates the arrhythmia. This is consistent with the finding that myocardial cells from RVOT, LV outflow tract, LV epicardium, and aortic sinus of Valsalva share a common embryologic origin in the neural crest.[52]

As with idiopathic PVCs/NSVT, idiopathic VT is associated with an excellent prognosis. Therefore, treatment is again aimed at the

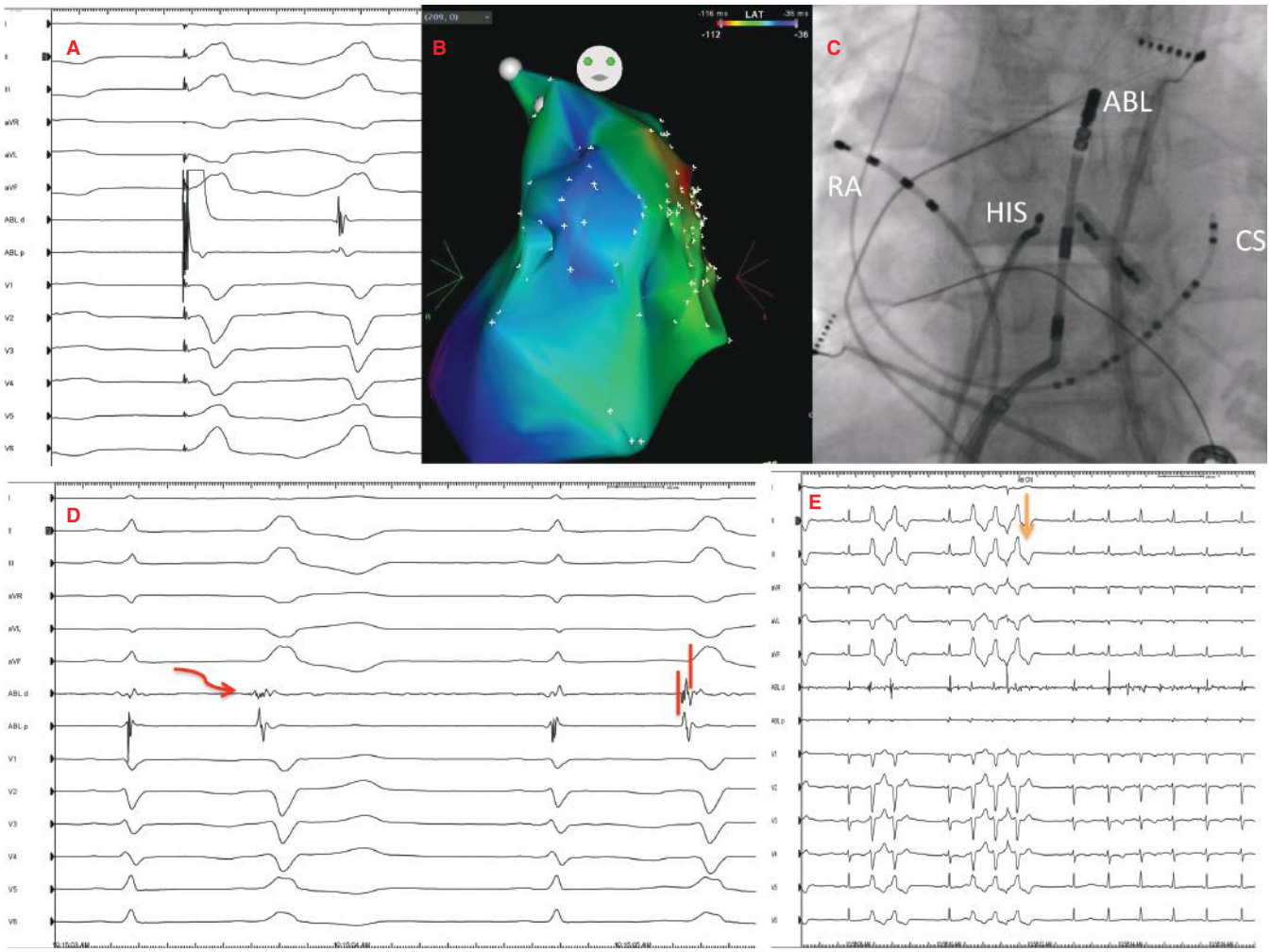

FIGURE 85–3. Thirty-two-year-old woman with drug-refractory symptomatic outflow PVCs referred for ablation. She was brought to the electrophysiology laboratory for an electrophysiology study and radiofrequency ablation procedure. **A.** A mapping catheter is placed in the anterior-septal RVOT at the site of origin of the PVC. Pacing from this site demonstrates a 12-lead QRS morphology that matches the spontaneously occurring PVC (subsequent beat). **B.** Three-dimensional electroanatomic map (Carto, Biosense, Diamond Bar, CA). AP view is shown. Earliest activation pre-QRS is noted in red, latest sites in blue. The earliest site is shown in the anterior RVOT. **C.** Left anterior oblique (LAO) fluoroscopic position of ablation catheter at the RVOT ablation site positioned by the Niobe magnetic navigation system (Stereotaxis, Inc.); also shown are right atrial (RA), His, and coronary sinus (CS) catheters. **D.** The electrogram at the site of earliest activation (*red arrow*) was 40 ms pre-QRS. **E.** A single radiofrequency ablation lesion successfully eliminates the PVC (*orange arrow*) after an initial increase in activity after RF was turned on. ABL, ablation catheter; CS, coronary sinus catheter; HIS, His bundle catheter; LBBB, left bundle branch block; PVC, premature ventricular contraction; RA, right atrial catheter; RV, right ventricular; RVOT, right ventricular outflow tract.

alleviation of symptoms. It remains important to consider the diagnosis of ARVC and sarcoidosis in the workup of patients presenting with VT from the RVOT.

Beta-adrenergic receptor blockers and calcium channel antagonists are usually the first choice for the treatment of symptomatic VT, but their efficacy in preventing arrhythmia recurrence is modest. In general, β-blockers are effective in approximately 25% to 50% of patients, whereas calcium channel blockers are effective in approximately 25% to 30%. Class I or III antiarrhythmic medications can also be considered,[53,54] but the potential side effects and risk of proarrhythmia is increased with the use of these medications compared to β-blockers and calcium channel blockers.

Radiofrequency catheter ablation of idiopathic VT is an excellent option (see Table 85–1). Originally described in the 1980s,[55] this technique has continued to evolve, with success rates ranging from 75% to 100%[54]; the major limitation of ablation is the potential lack of PVC activity or inducibility at the time of attempted ablation. Ablation of idiopathic VT originating from sites other than the RVOT such as the papillary muscles is more complex and has a lower success rate.[56,57]

FASCICULAR VENTRICULAR TACHYCARDIA

Fascicular VT is characterized by a right bundle branch block (RBBB) pattern with a left superior axis on a 12-lead ECG. Belhassen and Laniado[58] were the first to describe the sensitivity of this tachycardia to verapamil in 1981. Patients typically have a structurally normal heart, but may present with an incessant VT and a reversible tachycardia-mediated CM can develop. The site of origin of the tachycardia is usually in the region of the left posterior fascicle (inferior posterior LV septum).[59] Anterior fascicular,[60] upper septal[61] fascicular, and interfascicular[62] versions have been described, but are less common. The ability to induce fascicular VT using programmed stimulation and the ability to entrain this tachycardia support reentry as the mechanism for this arrhythmia.[63,64] The reentrant circuit encompasses the distal

TABLE 85–2. Disease-Specific Treatment by Sympathetic or Parasympathetic Modulation to Prevent Sudden Cardiac Death

Disease	Trigger	Treatment
Ischemia and MI	Sympathetic	BB, ARB, ACE-I, aspirin, RFCA, ICD, BCSD
Cardiomyopathy		
NICM	Sympathetic	BB, ARB, ACE-I, III, ICD, BCSD
HCM	Sympathetic	BB, Ca-B, III, ICD, BCSD
ARVC	Sympathetic	BB, ARB, ACE-I, III, ICD, BCSD
Inherited Arrhythmia Syndromes		
Long QT syndrome		
LQT1	Sympathetic	BB, LCSD
LQT2	Sympathetic	BB, LCSD?
LQT3	Parasympathetic	Mexiletine, pacemaker, ICD
Brugada syndrome	Parasympathetic	Quinidine, isoproterenol, ICD
Idiopathic VF	Sympathetic/ Parasympathetic	BB?, ICD Quinidine, isoproterenol, ICD
CPVT	Sympathetic	BB, flecainide, LCSD

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARVC, arrhythmogenic right ventricular cardiomyopathy; BB, beta-blocker; BCSD, bilateral cardiac sympathectomy; Ca-B, calcium channel blocker; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; III, class III antiarrhythmic medications; LCSD, left cardiac sympathectomy; NICM, nonischemic cardiomyopathy; RFCA, radiofrequency catheter ablation; VF, ventricular fibrillation.

Purkinje network of the left posterior fascicle, accounting for the relatively narrow QRS.[65]

The clinical features of this VT include (1) a structurally normal heart; (2) VT with a relatively narrow QRS (< 140 milliseconds), a RBBB pattern in V_1, and superior axis; (3) sensitivity to verapamil; and (4) induction with atrial pacing.[66] The arrhythmia usually presents in patients between 15 and 40 years of age. False tendons in the left ventricle are found in a most patients with fascicular VT, but their anatomic and functional significance is unknown.[67]

Patients with fascicular VT have a good prognosis,[68] responding well to verapamil for acute termination of VT as well as for long-term arrhythmia control.[68,69] Class I or III antiarrhythmic medications are rarely indicated in the treatment of this arrhythmia and are usually ineffective.[70] In patients with unresponsive to verapamil or preference not to take medications long-term, catheter ablation is an excellent option for treatment.[70-73]

VENTRICULAR TACHYCARDIA IN PATIENTS WITH STRUCTURAL HEART DISEASE

VENTRICULAR TACHYCARDIA IN PATIENTS WITH CORONARY ARTERY DISEASE/ISCHEMIC CARDIOMYOPATHY

Ventricular arrhythmias in patients with coronary disease range from PVCs to NSVT to sustained VT leading to hemodynamic compromise and SCD. The understanding of the pathophysiology of VT in patients with coronary artery disease has been greatly enhanced by animal studies, electrophysiologic studies in humans, and the results from multicenter randomized trials.

Pathophysiology

The anatomic substrate from which ischemic VT originates usually involves a healed scar after an acute MI (Fig. 85–6). The interplay of healthy, damaged (border zone), and scarred (fibrotic) myocardium serves as a setting for slowed conduction and reentry.[74,75] Evolution of the electrophysiologic substrate occurs over weeks to months after an MI and then remains indefinitely. The tissue may continue to be modified by subsequent ischemic insults as well as late ventricular remodeling and worsening pump function. These changes may lead to neurohormonal activation, sympathetic hyperinnervation, and progressive LV dilatation with regional and global elevations in wall tension, all of which may contribute to the proarrhythmic potential.[76]

Patients with VT have a high risk of recurrence even when heart failure and coronary ischemia are controlled. Early data demonstrated that the risk of VT is highest during the first year after an MI (3%-5%), but VT may occur many years later,[77] and the risk of SCD from ventricular arrhythmias may increase with time.[78,79]

Mechanism

Multiple findings support reentry as the mechanism of NSVT and sustained VT in most patients with previous myocardial infarction (see Fig. 85–6). Ischemic VT can be initiated, terminated, and reset with programmed electrical stimulation in the electrophysiology laboratory.[80] The reentry circuit most frequently exists within the border zone of the scar.[74, 81] However, reentrant scars are often three-dimensional and critical regions can exist deep within the infarcted or fibrotic regions. The presence of an infarct does not however preclude the possibility of a concomitant focal VT, with recent estimates that focal arrhythmias account for between 9% and 39% of VTs in patients with structural heart disease.[82,83]

Clinical Presentation and Management

Symptoms associated with ischemic VT are variable. The main determinants of hemodynamic tolerance are the rate of the VT and the degree of LV dysfunction.[84] Interestingly, the hemodynamic stability of sustained VT is not necessarily prognostic of mortality risk. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) registry, patients with hemodynamically tolerated VT at presentation had similar mortality to patients with syncopal/unstable VT.[85]

A 12-lead ECG should be obtained whenever possible to help localize the origin of the VT. Algorithms have been described to localize the origin[86] and help differentiate endocardial and epicardial sites of origin; however, there are limitations to such algorithms, especially in the presence of antiarrhythmic medications or when the VT is sufficiently fast, resulting in fusion of T waves with the initial component of the QRS complex.[87]

ECG Features for VT Exit Site Localization

LBBB pattern in V_1 suggests exit in RV or interventricular septum.

RBBB pattern with dominant R waves in V_1 indicates LV exit.

Superior axis → inferior wall exit.

Inferior axis → anterior wall.

Dominant S waves in V_3, V_4 → apical exit.

Dominant R waves in V_3, V_4 → basal exit.

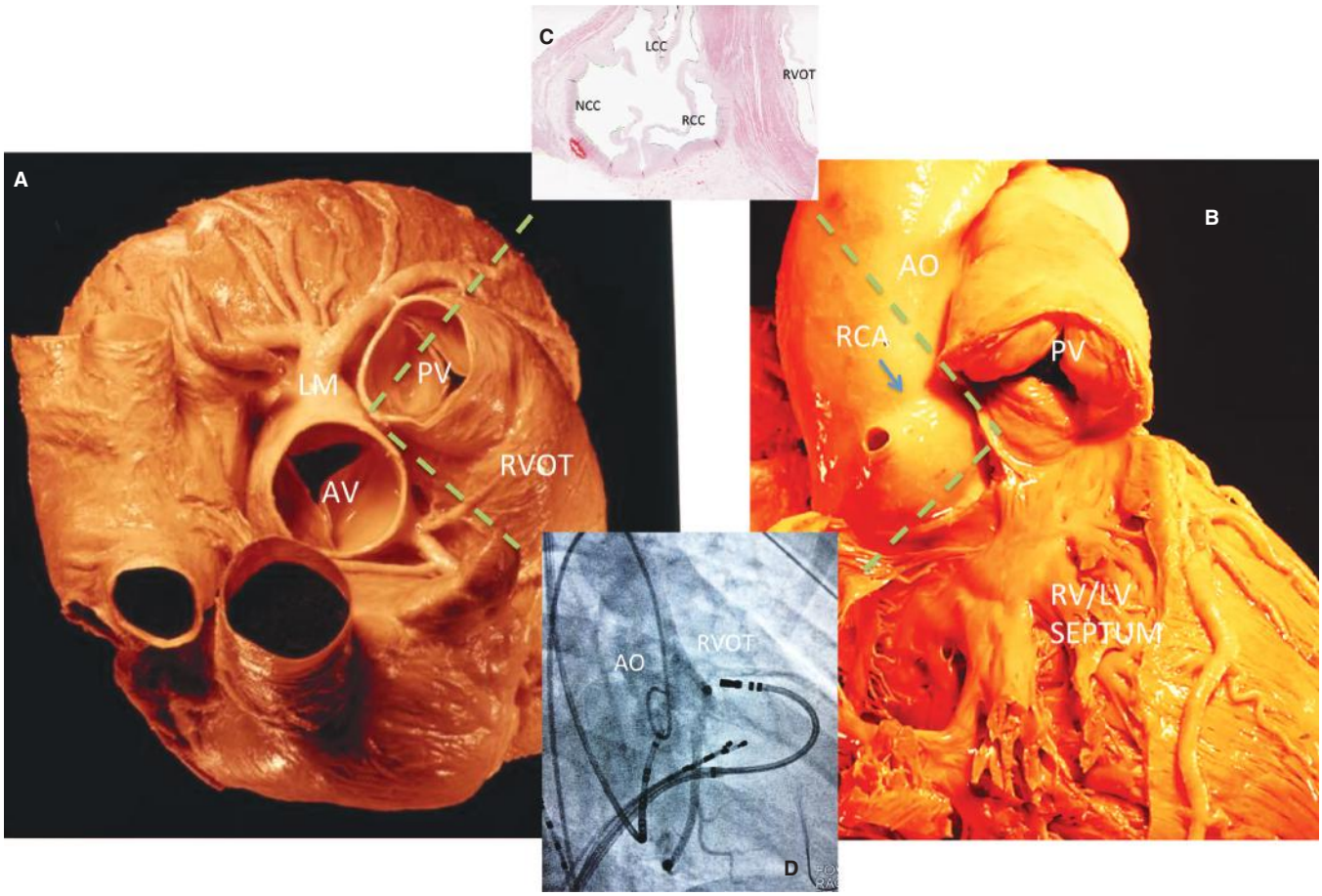

FIGURE 85–4. Superior (**A**) and right anterior oblique (RAO) (**B**) views demonstrating anatomic relationship between right ventricular outflow tract (RVOT) and left ventricular outflow tract (LVOT), and the close proximity of the two structures. The right ventricular (RV) free wall is removed in this image. (**C**) The pathologic relationship and (**D**) RAO fluoroscopic relationship between the coronary cusps and RVOT. Shown is a pigtail catheter in the aortic root with contrast outlining the aorta; an ablation catheter is positioned in the RVOT posteriorly. This further demonstrates how it may be difficult to distinguish the origin of premature ventricular contractions (PVCs)/ventricular tachycardia (VT) originating from these closely related anatomic regions and how a single PVC/VT can have highly variable QRS morphologies depending on the exit site. AO, aorta; AV, aortic valve; LM, left main; LV, left ventricle; PV, pulmonary valve; RCA, right coronary artery. Used with permission from UCLA Cardiac Arrhythmia Center-Wallace A. McAlpine Collection.

Premature Ventricular Contractions After Myocardial Infarction The relationship between PVCs after myocardial infarction (MI) and SCD has been studied extensively, and patients with larger MIs and lower left ventricular ejection fractions (LVEFs) are at the greatest risk of sudden death.[88-92] Early data from trials of the thrombolytic therapy era have also shown an association between PVCs and sudden death. In an analysis of Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2, Statters and colleagues[92] compared the prognostic value of PVCs among 680 patients who received or did not receive thrombolytics. They reported the greatest risk of sudden death among the patients who had > 10 PVCs per hour and did not receive thrombolytics. In contrast, PVCs did not predict sudden death in patients who received thrombolytics until the frequency of PVCs were > 25 per hour. These observations reflect the contribution of infarct size and, by association, EF to the prognosis of patients who have experienced an MI. However, these studies predate many current advances in management of acute myocardial infarction such as primary PCI, and therefore need to be understood in this context.[93]

While the association between PVCs after MI and adverse events has been established, there is no clear benefit to routinely treating PVCs with antiarrhythmics in this setting. The association of PVCs with SCD previously led to the routine use of intravenous lidocaine in patients following MIs.[94] Subsequent randomized controlled studies demonstrated poorer survival when PVCs were treated with antiarrhythmic agents.[95] Based on these findings, the routine prophylactic use of antiarrhythmic agents for patients after an MI is not recommended. The treatment of PVCs and NSVT with antiarrhythmics is also not recommended unless they are associated with hemodynamic compromise or refractory symptoms, or there is evidence of PVC-induced CM. In patients with frequent ventricular ectopy, electrolyte and acid-base imbalance should be corrected. If frequent and persistent ventricular ectopy results in hemodynamic instability (which is rare), a β-adrenergic blocking agent or amiodarone are the preferred pharmacologic interventions in this setting. Lidocaine may be considered temporarily when recurrent hemodynamically significant ventricular arrhythmias occur in the setting of acute MI.[96]

The use of amiodarone in patients during and after an acute MI is controversial. Amiodarone has unique pharmacologic properties beyond its effects on the cardiac sodium and potassium channels. It is also a β-adrenergic receptor blocker and a calcium channel blocker and has anti-ischemic effects.[97] The European Myocardial Infarction Amiodarone Trial (EMIAT) was a study that randomized 1486 patients with an EF of < 40% and prior MI to amiodarone or placebo. No difference in total mortality was observed after a mean follow-up

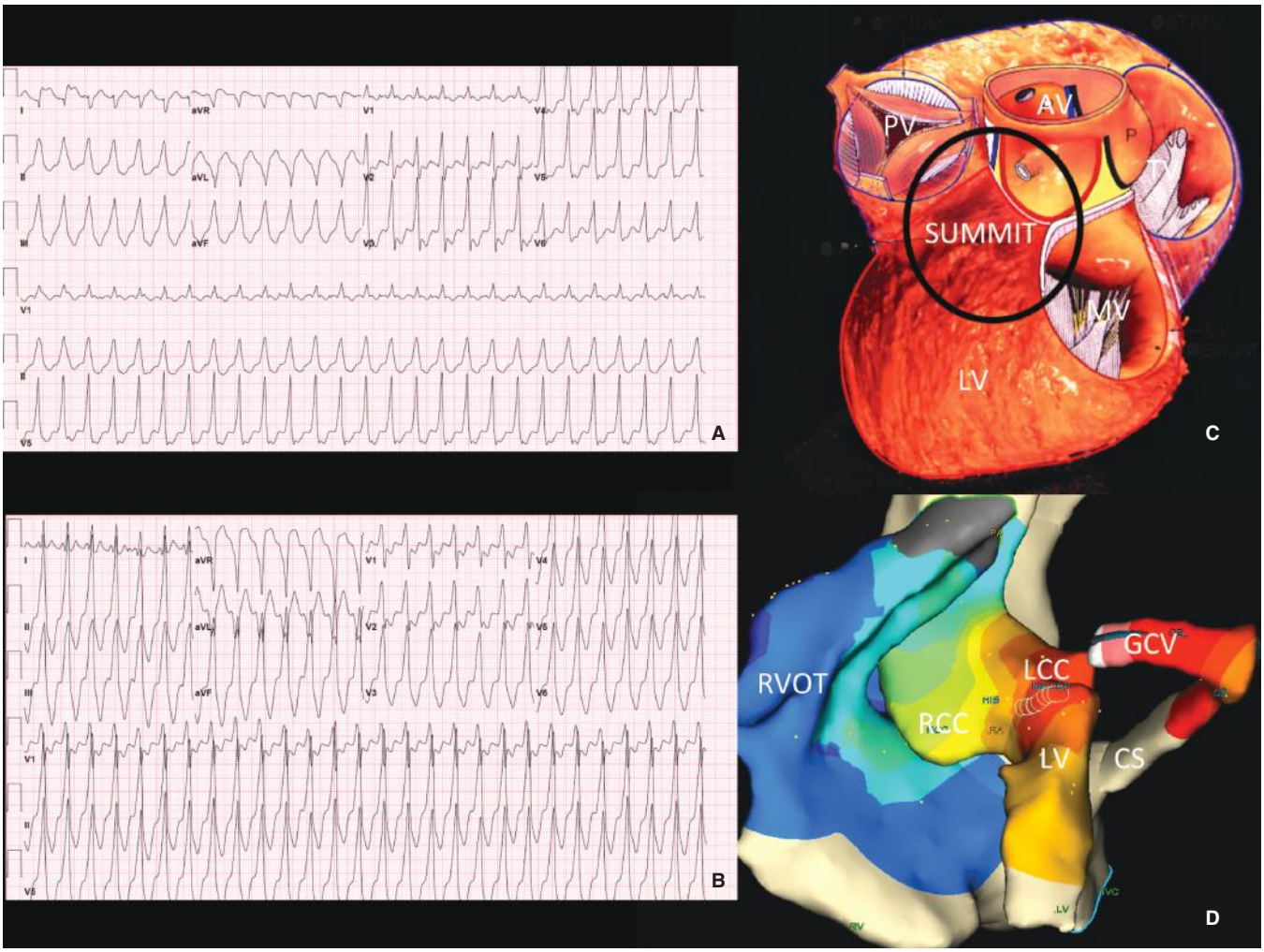

FIGURE 85–5. Twelve-lead ECGs of two patients who presented with symptomatic sustained VT originating from the LV summit (epicardial region bounded by the left anterior descending and circumflex arteries, which is the most superior portion of the left ventricle). Patient 1 (**A**) had a structurally normal heart, while patient 2 (**B**) had evidence of mid-myocardial scar based on delayed enhancement seen on cardiac MRI. (**C**) Pathologic specimen with overlying illustration demonstrating the anatomy of the LV summit and the close relation to the RVOT and aortic root. (**D**) Three-dimensional electroanatomic map (NavX, St. Jude Medical, Minneapolis, MN) of patient 1 demonstrating the earliest activation (*white region*) of PVCs with a similar morphology to the sustained VT shown in (**A**). The earliest site is between the anterior interventricular vein/great cardiac vein (AIV/GCV) junction and the left coronary cusp (LCC) within the LV summit. AV, aortic valve; CS, coronary sinus; LV, left ventricle; MV, mitral valve; PV, pulmonic valve; RCC, right coronary cusp; RVOT, right ventricular outflow tract. Used with permission from UCLA Cardiac Arrhythmia Center-Wallace A. McAlpine Collection.

of 21 months.[98] In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), patients with prior MI and frequent ventricular ectopy (> 10 PVCs/h) were randomized to amiodarone or placebo. The primary end point (combined arrhythmic death and resuscitated VF) was observed in 0.6% of the amiodarone group and 3.3% of the placebo group (P = .016). Most of the benefit was seen in patients who were treated concomitantly with β-adrenergic blockers. Although a significant benefit in arrhythmic death was observed in the amiodarone group, no significant difference in total mortality was observed in this study.[99] A meta-analysis of 13 trials of amiodarone after MI or in congestive heart failure reported a reduction in mortality and arrhythmic death in patients treated with amiodarone.[100] Based on the available information, the prophylactic use of amiodarone in patients after an MI is not recommended for primary prevention. However, the use of amiodarone for the treatment of hemodynamically significant ventricular arrhythmias or other arrhythmias, such as atrial fibrillation, in the postinfarct setting appears to be safe.

In patients with chronic ischemic cardiomyopathy (ICM) or nonischemic cardiomyopathy (NICM), there may be benefit to treatment of PVCs[101] in certain clinical circumstances. Patients with previous MI and presumed ICM may have appreciable EF improvement to the point of no longer requiring primary prevention ICD implant if a high burden of PVCs can be successfully reduced.[102-104] Further evidence suggests that in cardiac resynchronization therapy (CRT) nonresponders, decreasing a high burden of PVCs may allow for improved percentage of biventricular pacing and potentially improve response to CRT.[105]

Sustained Ventricular Tachycardia Patients who present in clinically stable VT may be treated with antiarrhythmic drugs, anti-tachycardia pacing (ATP) when available, or synchronized direct current (DC) cardioversion. Patients in VT with hemodynamic compromise,

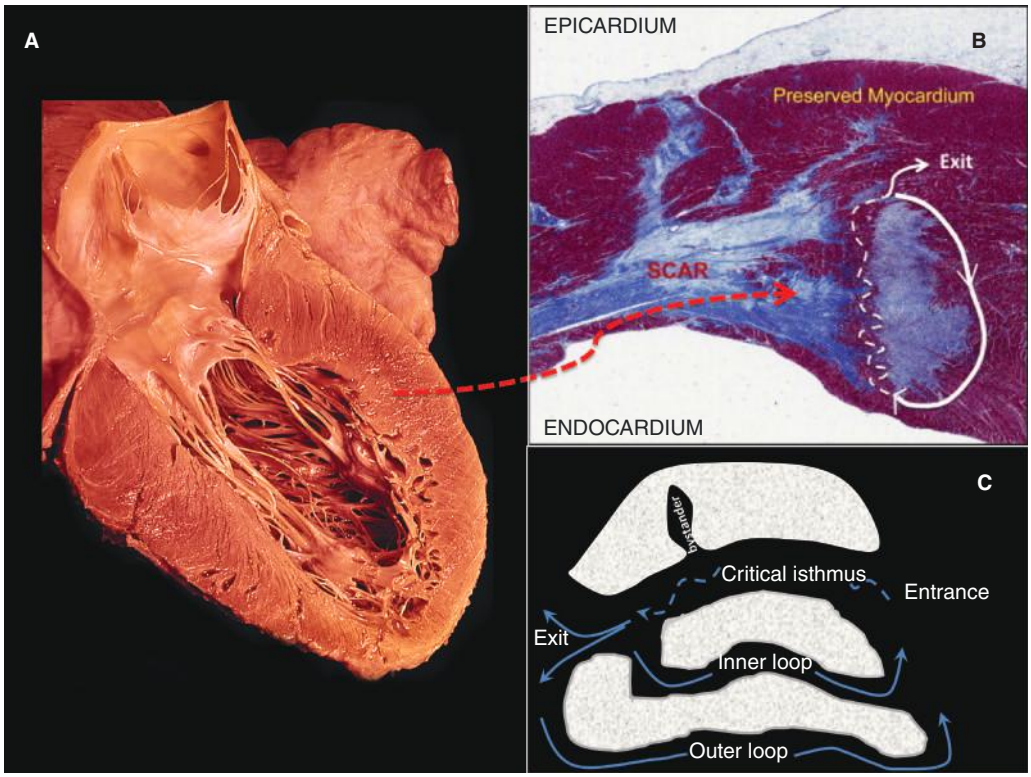

FIGURE 85–6. Schematic of reentry in patients with myocardial scar tissue/fibrosis. Regions of scar/fibrosis allow for conduction slowing and the potential for a reentrant circuit to form. The gross pathologic specimen (**A**) and representative histologic section (**B**) show scar tissue stained blue. The *white arrow* represents the potential reentrant circuit and the *dashed lines* the region of slow conduction within the scar. A schematic similar to that proposed by Stevenson et al.[141] (**C**) of a potential VT circuit including both critical (isthmus) and noncritical (inner loop, outer loop, bystander) locations is included. Used with permission from UCLA Cardiac Arrhythmia Center-Wallace A. McAlpine Collection.

congestive heart failure, chest pain, or ischemia should be treated promptly with synchronized DC cardioversion. When antiarrhythmic drug therapy is required, amiodarone is the treatment of choice. The efficacy of amiodarone is superior to lidocaine or procainamide in this setting.[106-108]

All patients with VT should be treated with a β-blocker unless prohibited by hypotension, bradycardia, or other clinical factors (ie, reactive airway disease, vasospastic coronary disease). Reversible factors contributing to VT, such as congestive heart failure exacerbation, acute ischemia, or electrolyte abnormalities, should be diagnosed rapidly and treated. However, while concerning in the setting of polymorphic VT, ischemia is rarely a cause of monomorphic VT. Monomorphic VT in the setting of structural heart disease suggests underlying myocardial fibrosis/scar. Whenever possible, a 12-lead ECG should be obtained of the clinical tachycardia. Algorithms can be utilized to localize the exit site of the VT.[86,109]

In the setting of VT storm (VT requiring more than 3 ICD therapies in a 24-hour period) that cannot be controlled by antiarrhythmics, consideration should be given to intubation and sedation and possibly neuraxial modulation to decrease the sympathetic surge that may be contributing to the electrical storm (see Table 85–2).[110-112] In patients who have refractory VT despite aggressive treatment, patients may be treated successfully with an emergent or elective radiofrequency catheter ablation procedure (Fig. 85–7, Table 85–1).[113] If this intervention fails, mechanical ventricular assist devices and/or cardiac transplantation may be treatment options in specialized centers.[114]

Management of VT/VF Storm

- Intensive care unit/coronary care unit admission
- ICD reprogramming to maximize use of ATP and minimize shocks
- Correct ischemia and electrolyte imbalance
- Consider potential for drug proarrhythmia
- Beta-blockade
- Antiarrhythmic drugs (amiodarone, lidocaine, procainamide)
- Sedation, intubation
- Hemodynamic support (intra-aortic balloon pump)
- Catheter ablation (anytime feasible)
- Neuraxial modulation (thoracic epidural anesthesia, cardiac sympathetic denervation)

The primary aim in patients who have presented with sustained VT is to reduce recurrence of VT and prevent SCD. LV function is a well-established independent risk factor for SCD in patients with ventricular arrhythmias.[115,116] In a subanalysis of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, evaluation of the impact of LVEF quartiles on long-term survival revealed a 39% increase in the hazard ratio for mortality for every 10% reduction in LVEF.[117]

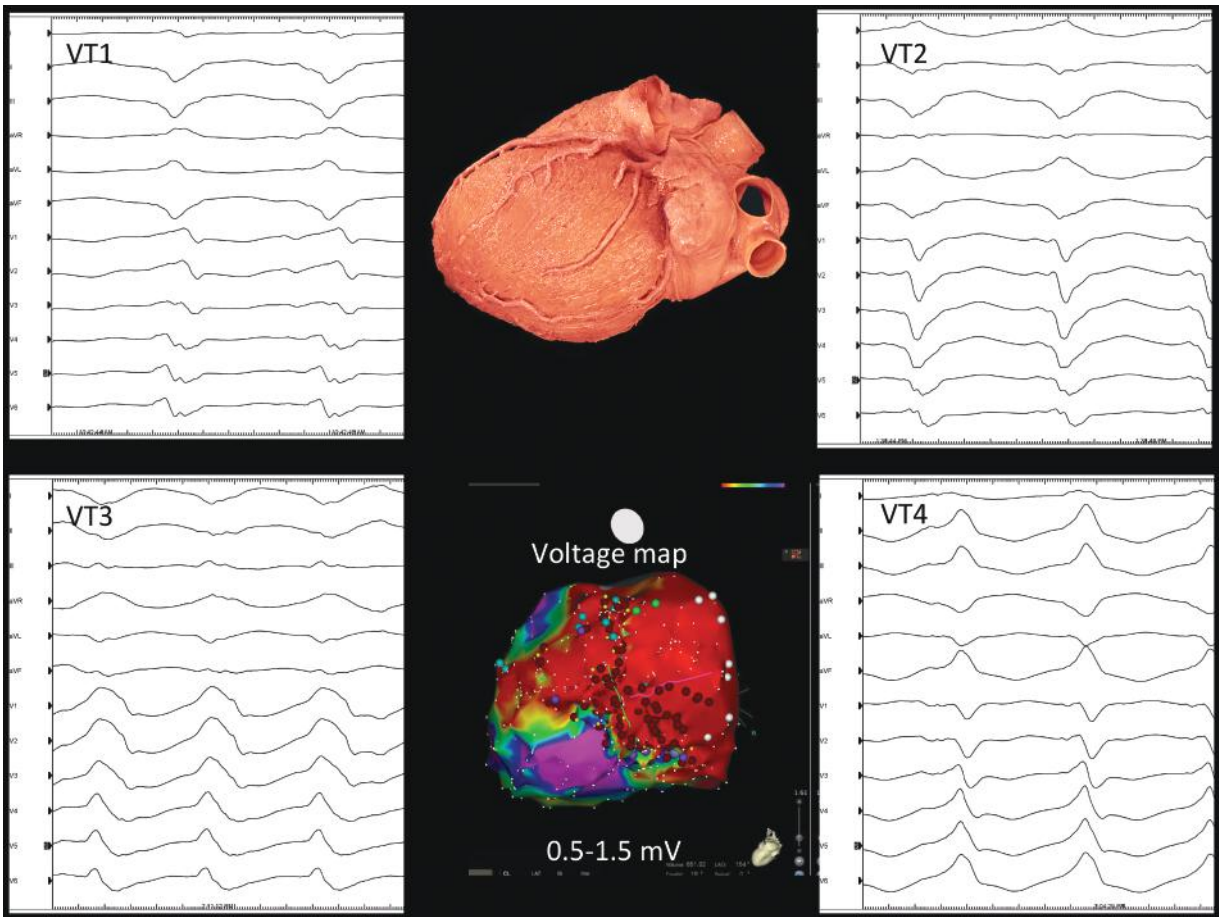

FIGURE 85–7. Seventy-two-year-old man with history of coronary artery disease status post-percutaneous coronary intervention with previous failed endocardial ablation referred for a combined endocardial-epicardial ablation. Four ventricular tachycardias (VTs) were induced during the procedure. A three-dimensional electroanatomic (CARTO, Biosense Webster, Diamond Bar, CA) voltage map was constructed to guide the delivery of ablation lesions (*red dots*). Red color signifies dense scar (< 0.5 V) located on the basal/inferior wall of left ventricle (LV), while the purple area denotes preserved myocardium (> 1.5 V) in the apical region. A pathologic specimen is provided for representative anatomy of the involved lateral LV. After ablation the patient was no longer inducible for VT. Used with permission from UCLA Cardiac Arrhythmia Center-Wallace A. McAlpine Collection.

Patients who present with sustained VT and a structural heart disease should be considered for an ICD (Table 85–3). Patients with a history of cardiac arrest have clear benefit from ICD implantation across many trials, as shown in a meta-analysis of secondary prevention ICD versus antiarrhythmic drug trials published by Connolly and colleagues.[118] In this meta-analysis there was a 50% reduction in arrhythmic death (25% all-cause mortality decrease). Before implantation of an ICD, it is important that VT is clinically well controlled to minimize the risk of multiple shocks from the ICD. Reversible causes of VT should be corrected. Continued episodes of VT despite correcting reversible causes should be considered for radiofrequency ablation therapy.

In patients with preserved LV function, the data for implantation of an ICD is less robust. A meta-analysis of the secondary-prevention ICD trials revealed that the patients who benefited from ICD therapy over amiodarone therapy had an EF < 35%. Amiodarone was equivalent to ICD in patients with EF > 35%.[118] However, most patients with sustained VT, not likely to be idiopathic in origin, should receive an ICD. In some patients with preserved LV function, antiarrhythmic therapy or catheter ablation alone can be considered. Long-term amiodarone toxicity (eg, pulmonary, hepatic, thyroid, neurological, and skin) and the high rate of drug cessation as a result of intolerance remain practical limitations for chronic amiodarone therapy. Improving success rates with acceptable complication rates[119] have led to the earlier utilization of catheter ablation as a primary therapy.

Once an ICD is implanted, numerous studies have demonstrated the efficacy of antiarrhythmic agents in reducing ICD shocks. In a randomized study of patients with ICDs implanted for inducible or spontaneously occurring VT or VF, 412 patients were randomized to β-adrenergic blockers alone (n = 140), sotalol alone (n = 134), or amiodarone plus β-blocker (n = 140). After a mean follow-up of 359 days, ICD shocks occurred in 38.5% of patients assigned to the β-blocker group, 24.3% of patients in the sotalol group, and 10.3% of patients in the amiodarone plus β-blocker group. Amiodarone plus β-blocker resulted in significantly fewer shocks compared with β-blocker alone (P = .006).[120] The decision for empiric therapy with antiarrhythmic agents at the time of ICD implantation depends on numerous clinical factors including recent VT burden and likelihood or recurrence. The current consensus is that β-adrenergic blocking agent should be administered in all patients unless contraindicated.

When antiarrhythmic agents are initiated in patients with an ICD, care must be taken in programming the device because antiarrhythmic medications can have varying effects on defibrillation thresholds and may slow the rate of the VT below a programmed detection zone. Further, both appropriate and inappropriate shocks can be detrimental[121,122] and associated with increased mortality. ICD programming with longer VT detection times and more ATP therapies can help minimize shocks for nonsustained episodes of VT or inappropriate shocks from supraventricular arrhythmias.[123-125]

TABLE 85–3. ICD Indications

Class I Indications

1. ICD therapy is recommended for or secondary prevention of SCD in patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamlcally unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. *(Level of Evidence: A)*
2. ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT whether hemodynamically stable or unstable. *(Level of Evidence: B)*
3. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibriation induced at electrophysiologic study. *(Level of Evidence: B)*
4. ICD therapy is recommended in patients with LVEF < 35% due to prior myocardial infarction who are at least 40 days post–myocardial infarction and are in NYHA functional class II or III. *(Level of Evidence: A)*
5. ICD therapy is recommended in patients with nonischemic dilated cardiomyopathy who have an LVEF ≤ 35% and who are in NYHA functional class II or III. *(Level of Evidence: B)*
6. ICD therapy is indicated in patients with LV dysfunction due to prior myocardial infarction who are at least 40 days post–myocardial infarction, have an LVEF < 30%, and are in NYHA functional class I. *(Level of Evidence: A)*
7. ICD therapy is indicated in patients with nonsustained VT due to prior myocardial infarction, LVEF < 40% and inducible ventricular fibrillation or sustained VT at electrophysiologic study. *(Level of Evidence: B)*

Class IIa Indications

1. ICD implantation is reasonable for patents with unexplained syncope. significant LV dysfunction, and nonischemic dilated cardiomyopathy. *(Level of Evidence: C)*
2. Implantation of an ICD is reasonable in patients with sustained VT and normal or near-normal ventricular function, *(Level of Evidence: C)*
3. ICD implantation is reasonable for patients with hypertrophic cardiomyopathy who have one or more major risk factors for SCD. *(Level of Evidence: C)*
4. ICD implantation is reasonable for the prevention of SCD in patients with arrhythmogemc right ventricular dysplasia/cardiomyopathy who have one or more risk factors for SCD. *(Level of Evidence: C)*
5. ICD implantation is reasonable to reduce SCD in patients with long QT syndrome who are experiencing syncope and/or VT while receiving β-blockers. *(Level of Evidence: B)*
6. ICD implantation is reasonable for nonhospitalized patients awaiting transplantation. *(Levet of Evidence. C)*
7. ICD implantation is reasonable for patients with Brugada syndrome who have had syncope. *(Level of Evidence: C)*
8. ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest. *(Level of Evidence: C)*
9. ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving β-blockers. *(Level of Evidence: C)*
10. ICD implantation is reasonable for patients with cardiac sarcoidosis, giant-cell myocarditis, or Chagas disease. *(Level of Evidence: C)*

Class IIb Indications

1. ICD therepy may be considered in patients with nonischemic heart disease who have an LVEF of < 35% and who are in NYHA functional class I. *(Level of Evidence: C)*
2. ICD therapy may be considered for patients with long QT syndrome and risk factors for SCD. *(Level of Evidence: B)*
3. ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause. *(Level of Evidence: C)*
4. ICD therapy may be considered in patients with a familial cardlomyopathy associated with sudden death. *(Level of Evidence: C)*
5. ICD therapy may be considered in patients with LV noncompaction. *(Level of Evidence: C)*

Class III Indications

1. ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the classes I, IIa, and IIb recommendations above. *(Level of Evidence: C)*
2. ICD therapy is not indicated for patients with incessant VT or VF. *(Level of Evidence: C)*
3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. *(Level of Evidence: C)*
4. ICD therapy is not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or implantation of a CRT device that incorporates both pacing and defibrillation capabilities. *(Level of Evidence: C)*
5. ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. *(Level of Evidence: C)*

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LV, left ventricle; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SCD, sudden cardiac death; VT, ventricular tachycardia.

Data from ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities[1] and 2012 ACC/AHA/HRS Focused Update.[2]

Patients with ICM and recurrent VT refractory to medications may be successfully treated with radiofrequency catheter ablation techniques.[6,126-131] ICM-related VT comprises approximately 60% of patients with structural heart disease referred for VT ablation.[132] It should be emphasized that such ablation is adjuvant to ICD therapy and cannot be expected to preclude the need for an ICD for most patients with structural heart disease. However, in the past, extended periods of attempted antiarrhythmic therapy have often been undertaken before considering ablation as an option. Recent data suggest that early intervention with ablation may improve patient outcomes.[133]

When considering scar-based VT ablation in a stable patient, preprocedure cardiac MRI should be considered.[134,135] Myocardial scar/fibrosis location on MRI can be correlated with three-dimensional electroanatomic mapping findings during the procedure to help guide ablation. When performed in experienced centers, the 1-year freedom from VT is approximately 70% in retrospective studies. Ablation has demonstrated benefit in the setting of electrical storm (VT requiring more than three ICD therapies in a 24-hour period).[113,136] Additionally, studies have shown that ablation decreases the risk of future ICD therapies[131,137] and is superior to antiarrhythmic therapy.[130] In a recent International VT Ablation Center Collaborative Group study, freedom from VT was associated with improved transplant-free survival.[138]

Ablation techniques for scar-based VT continue to evolve. However, techniques utilized largely depend on the hemodynamic tolerance of the clinical VT. Voltage mapping of myocardial scar and border zones and associated late potentials (Fig. 85–8) can help localize potentially

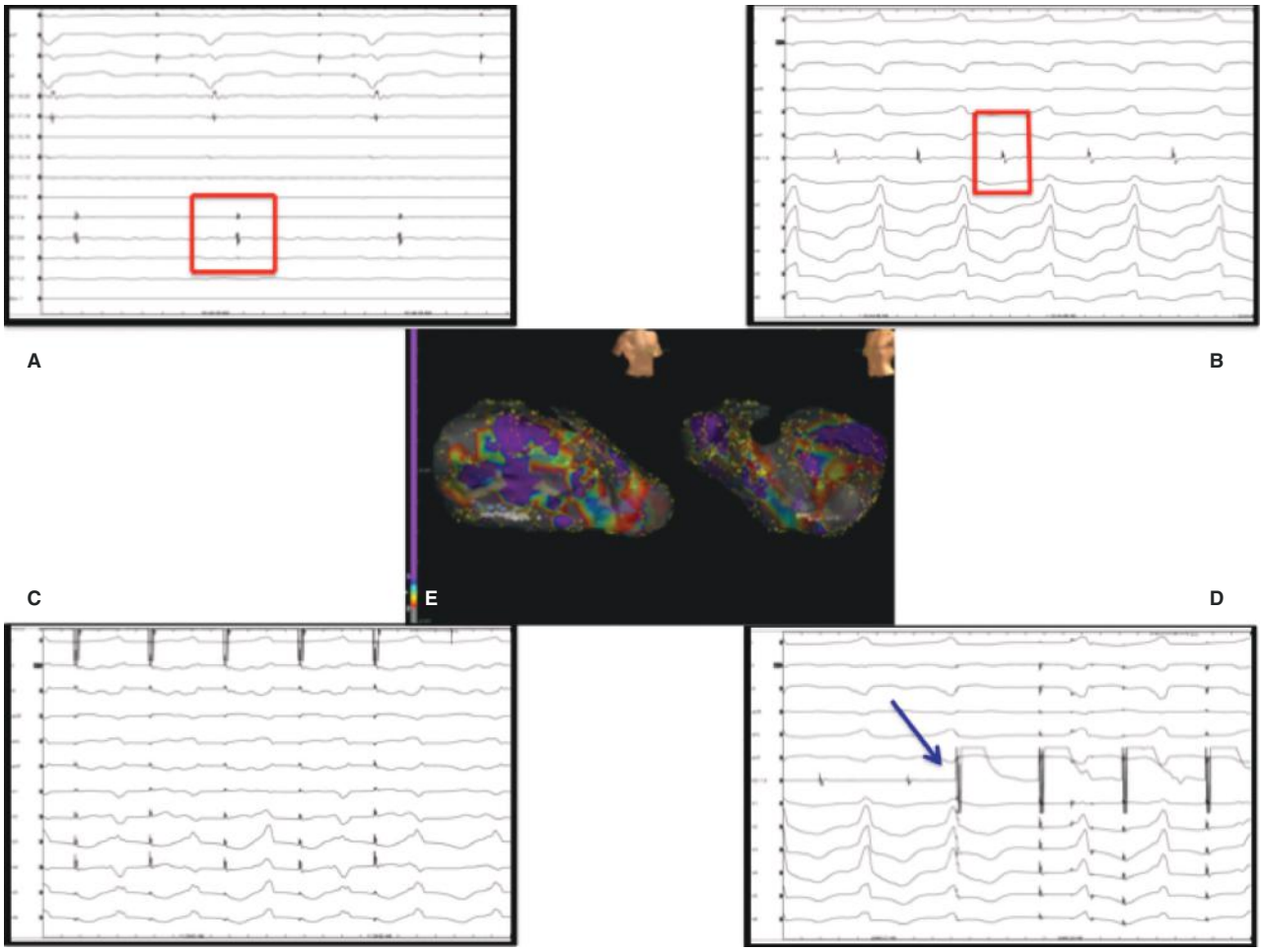

FIGURE 85–8. Sixty-five-year-old man with recurrent impantable cardioverter-defibrillator shocks referred for a combined endocardial-epicardial ablation. A three-dimensional electroanatomic (NavX, St. Jude, Minneapolis, MN) voltage map (**E**) was constructed. Gray color signifies dense scar (< 0.5 V) while the purple area denotes normal voltage (> 1.5 V). Late potentials (**A**) are demonstrated along the border zone of scar and multiple exit sites (changing QRS morphology while pacing from a stable site) (**C**) suggest the potential importance of this anatomic region. When ventricular tachycardia (VT) is induced, the site of previously seen late potentials demonstrates mid-diastolic potentials during VT (**B**), and a stimulus delivered during VT (**D**) at that site terminated VT without propagation, verifying this site is within the critical isthmus. Ablation at this site made the VT noninducible.

important sites during sinus or paced rhythm. Additionally, pace mapping of exit sites and evidence of multiple exits sites can provide additional important information during sinus rhythm without risk of compromising hemodynamic stability. When the spontaneous or induced VT is relatively slow and blood pressure is stable or can be adequately supported with pressors or mechanical hemodynamic support, diastolic potentials and nonpropagated stimuli may be seen at critical sites (see Fig. 85–8) and entrainment mapping[139-141] allows differentiation of the critical isthmus from other regions (inner loop, outer loop, bystander).

Nonsustained Ventricular Tachycardia The evaluation and management of patients with ischemic heart disease and asymptomatic NSVT begins with the evaluation of the patient's LVEF. Patients with preserved LV function are generally at low risk and often require no further treatment other than beta-blockers as part of optimal medical management. Patients with low EF are at risk of SCD. In patients with an LVEF of < 40%, annual mortality of patients post-MI is estimated to be 8% to 10%.[142] The importance of treating these patients with an angiotensin-converting enzyme inhibitor (ACEI), aspirin, and a β-adrenergic receptor blocker cannot be overemphasized.

Previously programmed electrical stimulation at electrophysiologic study has been advocated for risk stratification.[143] However, this technique has been demonstrated to be of limited utility except in specific circumstances. Spontaneous NSVT and/or inducible VT does not differentiate patients who would benefit from a primary prevention ICD in this setting. However, an analysis of the Multicenter Unsustained Tachycardia Trial (MUSTT) registry data demonstrated that patients with negative electrophysiologic study who were followed in a registry had a high risk of arrhythmic death (12% over 12 months).[144] The high mortality rate in the patients who were noninducible at electrophysiologic study in this study called into question the usefulness of programmed electrical stimulation as a risk stratification tool.

The need for documented NSVT to stratify patients who would benefit from an ICD was invalidated by the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II study. This study randomized 1232 patients with ischemic cardiomyopathy based on LV function alone (LVEF ≤ 30%) with no requirement for the documentation of NSVT. After an average follow-up of 20 months, a significant reduction in all-cause mortality was observed in patients who received an ICD (hazard ratio for risk of death from any cause comparing ICD therapy to conventional therapy, 0.69).[145] The Sudden Cardiac Death

in Heart Failure Trial (SCD-HeFT) is the largest randomized primary prevention trial (2521 patients) comparing ICD versus amiodarone versus optimal medical therapy in patients with LVEF < 35%. This study did not require the presence of NSVT for enrollment. Patients enrolled in SCD-HeFT also had New York Heart Association (NYHA) functional class II to III heart failure symptoms. After a 5-year follow-up period, this study demonstrated that (1) the annual mortality of patients on optimal medical therapy was 7% to 8% per year; (2) amiodarone, when used as a primary preventative agent, does not improve survival over optimal medical therapy for heart failure; and (3) addition of an ICD decreases mortality by 23% compared with optimal medical therapy alone (HR = 0.77; 95% CI, 0.62-0.96; $P = .007$).[146]

In patients who already have an ICD and are known to have frequent NSVT, changes in ICD programming should be considered to minimize the risk of inappropriate shocks for arrhythmias that are likely to self-terminate. The detection time should be increased in the VT zones to decrease the likelihood of ICD shocks for NSVT.[123,147]

Accelerated Idioventricular Rhythm Accelerated idioventricular rhythm (AIVR) is typically an automatic rhythm originating in the ventricle with rates between 40 and 120 bpm. It is often seen gradually accelerating beyond the sinus rate, resulting in isorhythmic atrioventricular dissociation.[148] Fusion beats may be seen at the onset and termination of the arrhythmia. AIVR may be associated with ischemic cardiomyopathy, acute coronary syndromes, rheumatic heart disease, dilated cardiomyopathy, and acute myocarditis.[149] Furthermore, AIVR has been described in patients with no apparent heart disease.[150] In the setting of acute coronary syndromes, AIVR is considered to be a noninvasive albeit nonspecific marker for successful reperfusion after thrombolytic therapy. The incidence of AIVR is not affected by the location of MI or the infarct size. The presence of AIVR after an MI is not associated with an increase in mortality.[151]

The mechanism of AIVR is thought to be increased automaticity in a region of the ventricle; however, in some instances, such as in myocardial ischemia and digitalis toxicity, the mechanism may be caused by triggered activity.[152] AIVR is a benign rhythm; no specific treatment is necessary. In the acute setting, when loss of atrioventricular synchrony results in hemodynamic compromise, atrial overdrive pacing or atropine may reestablish AV synchrony when the two rhythms are competing. However, one must consider that in the setting of patients with CM already on antiarrhythmic medications, reentry VT can be confused with an automatic rhythm.

VENTRICULAR TACHYCARDIA IN PATIENTS WITH NONISCHEMIC CARDIOMYOPATHY

NICM includes a heterogeneous group of conditions resulting in LV and/or RV dysfunction. Causes of NICM include idiopathic, valvular heart disease, chronic ethanol/drug abuse, viral infections, Chagas disease, and cardiac sarcoidosis, among others. Sudden death in dilated cardiomyopathy is usually caused by a VT/VF and may account for up to 30% of deaths in this population,[153] though bradyarrhythmias must also be a cause. In a report of 157 cases of SCD in NICM in which the rhythm preceding death was available from ambulatory monitoring, 62% of patients had organized VT that progressed to VF, 13% had primary VF, and 17% had bradyarrhythmias.[154]

Pathophysiology

The pathogenesis of ventricular arrhythmias in NICM is not well understood and may reflect a variety of mechanisms. In a study of the autopsy findings in 152 patients with NICM, subendocardial scarring was present in 33% of patients. Histologic sectioning revealed multiple patchy areas of fibrosis in 57% of patients. These patchy areas of fibrosis, intermingled with viable myocardium, may serve as the substrate for reentry and associated VT and were predominantly found in the LV basal lateral wall and anteroseptum. These patterns do not follow and coronary distribution, unlike fibrotic scars in ICM.[155] Subsequent studies have reinforced the predominance of basal lateral and septal scars in NICM,[156-158] and demonstrated frequent involvement of the mid-myocardium and epicardium.[159]

In an autopsy study comparing patients with ICM and NICM who underwent orthotopic heart transplant,[160] the extent of fibrosis, hypertrophy, and myolysis was comparable between groups. However, while myocardial scar is often present in NICM and may be predictive of VT inducibility,[161] the definitive scar burden in patients with VT is often less than in ICM based on electroanatomic mapping data.[81] This potential lack of clear modifiable substrate not only makes the mechanism of the arrhythmia less well defined, but also potentially decreases VT ablation success rates in this population.

Clinical Presentation and Management

Premature Ventricular Contractions and Nonsustained Ventricular Tachycardia in Nonischemic Cardiomyopathy The association between PVCs and NSVT in NICM and SCD is unclear. NSVT is common in patients with NICM and is seen on 24-hour ambulatory and telemetry monitoring in 50% to 60% of these patients. The prevalence of NSVT increases with worsening heart failure symptoms. In patients with class I to II congestive heart failure, the prevalence of NSVT is 15% to 20%; and in patients with class IV heart failure, the prevalence is 50% to 70%.[162,163]

Several large trials, including the Grupo de Estudio de la Sobrevida en la Insufficiencia Cardiaca en Argentina (GESICA) trial and the Vasodilator-Heart Failure Trial (VHeFT), have found that NSVT is a risk factor for SCD.[164,165] However, in contrast, Von Olshausen and coworkers[166] found that only the presence of a bundle branch block and depressed EF predicted SCD when they followed 73 patients with NICM and frequent PVCs for 3 years. In another study of ambulatory monitors performed in 674 patients with NICM, NSVT was not associated with a lower survival rate.[167] Therefore, based on available studies, the clinical significance of asymptomatic NSVT in patients with NICM remains uncertain.

Sustained Ventricular Tachycardia Patients with NICM should be treated with optimal medical therapy for LV dysfunction. If sustained VT or cardiac arrest occurs, the data for benefit from secondary prevention ICDs is clear from analysis of trials such as AVID,[78] CIDS,[168] and CASH.[169] In addition, the role of an ICD in the primary prevention of SCD in patients with NICM has been established. In the SCD-HeFT trial, in which there was a 23% relative reduction in mortality observed in the patients randomized to ICD compared to medical therapy only (HR = 0.77; 97.5% CI, 0.62-0.96; $P = 0.007$). This benefit was similar between the ICM and NICM subgroups.[146] Based on these findings, patients with NICM with an EF of < 35% and NYHA class II to III heart failure symptoms should be considered for implantation of an ICD for primary prevention of sudden death (seeTable 85–3).

Radiofrequency catheter ablation in patients with drug-refractory VT may offer an additional treatment option for patients with NICM suffering from recurrent VT and/or frequent ICD therapies[170,171] Most patients do not have hemodynamically tolerated VT and therefore a substrate-based approach can be undertaken with reasonable success.[172] Ablation is supported in several studies[81,156,158,170,173] and complete noninducibility of VT at the end of the procedure may lead to a decreased mortality rate.[174] As a result of the frequent epicardial substrates, a combined endocardial-epicardial approach is often required in NICM patients,[175] and is safe in experienced centers.[176]

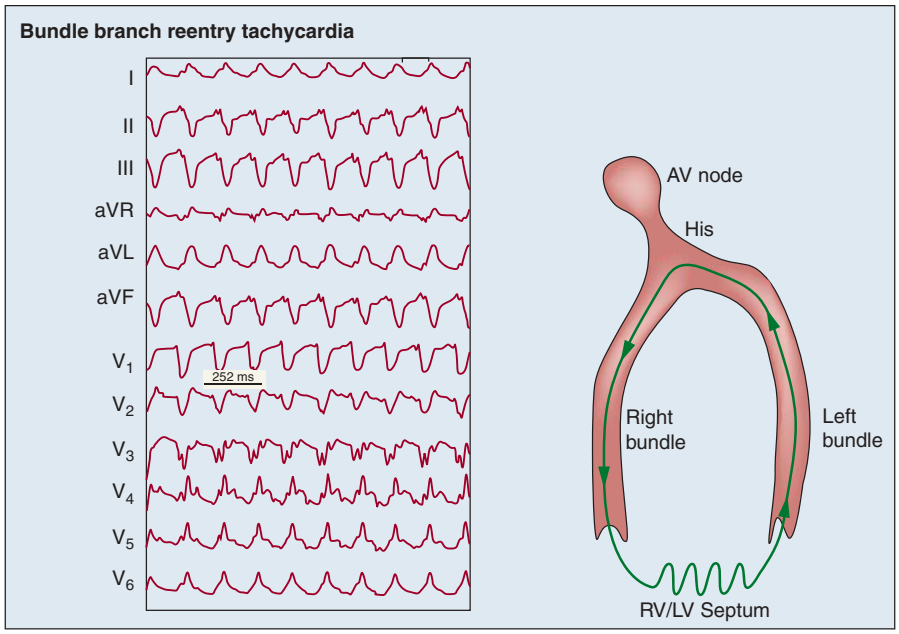

FIGURE 85–9. Representative 12-lead electrocardiogram and schematic of bundle branch reentry (BBR) VT. In typical BBR VT, the morphology is LBBB as the conduction blocks in the left bundle antegrade and is able to conduct antegrade down the right bundle and retrograde back up the left bundle to form the circuit. A right bundle branch block version has been described but is less common. LV, left ventricle; RV, right ventricle.

Bundle Branch Reentry VT

Bundle branch reentry VT is a reentrant ventricular arrhythmia utilizing the conduction system, most commonly with antegrade conduction over the right bundle fibers and retrograde conduction over the left bundle. The 12-lead electrocardiogram during VT typically has an LBBB configuration in lead V_1 (Fig. 85–9). Rarely, if anterograde conduction is over the LBB, then RBBB QRS morphology will be seen in V_1. The clinical recognition of bundle branch reentry (BBR) VT is essential because this arrhythmia can potentially be cured by a radiofrequency ablation procedure.[177] The rate of BBR VT is usually rapid and may be associated with syncope. The sinus rhythm 12-lead electrocardiogram usually demonstrates an intraventricular conduction delay or a left bundle branch block (LBBB). The treatment of choice for this arrhythmia is radiofrequency ablation of the right bundle branch. Antiarrhythmic drugs for BBR are associated with a high recurrence rate. Patients with BBR with an EF < 35% should receive an ICD even after successful ablation of the right bundle because they remain at risk for other lethal ventricular arrhythmias. The role of an ICD in patients with an EF > 35%, who have had a successful ablation for BBR, is less clear.

Ventricular Arrhythmias in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic CM and is associated with ventricular hypertrophy with or without outflow tract obstruction, atrial and ventricular arrhythmias, myocardial ischemia, stroke, heart failure, and SCD. HCM is discussed in detail in Chapter 59. SCD is relatively uncommon in patients with HCM, though HCM is the cause of SCD in approximately 10% of cases,[178, 179] and is among the most common causes of SCD among young athletes.[180]

Based on observational studies of patients with HCM, five clinical risk factors have been found to be associated with an increased risk of SCD: (1) a history of sudden cardiac arrest or spontaneous sustained VT, (2) unexplained syncope, (3) NSVT, (4) abnormal blood pressure response to exercise, and (5) extreme LV hypertrophy (septal thickness > 3.0 cm).[181] Antiarrhythmic agents do not appear to provide protection against sudden death,[182] and the only clinically proven primary and secondary treatment option against sudden death is an ICD.

In a large international registry of ICDs implanted in 506 patients with HCM at risk for SCD, appropriate ICD shocks were observed at a rate of 5.5% per year. In the secondary prevention cohort, appropriate ICD shocks occurred at a rate of 11% per year, and in the primary prevention cohort, it was 4% per year. An interesting observation in this study was that in the primary prevention group, the event rate was the same in the subset of patients with one, two, or three risk factors of SCD. Overall, 25% of patients experienced an appropriate ICD shock for ventricular arrhythmias after a follow-up of 5 years.[182]

For primary prevention, the decision to implant an ICD is individualized with the recognition that complications from inappropriate shocks caused by atrial arrhythmias and lead fractures may occur in up to 23% of patients,[183] and that given the young age of the population, many lead revisions may be required over time (Fig. 85–10). The ACC/AHA/HRS guidelines recommend implantation of an ICD in patients with HCM with a prior history of cardiac arrest, sustained VT (class I), or one or more major risk factors for SCD[1] (see Table 85–3). One promising risk stratification tool is scar quantification with delayed-enhancement cardiac MRI. Patients with larger areas of delayed enhancement on cardiac MRI have more ventricular arrhythmias.[184] Catheter ablation for the treatment of recurrent VT has also been performed successfully in this patient population.[185]

Ventricular Tachycardia in Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fatty infiltration, fibrosis, and thinning of the RV and less commonly the LV, and is associated with ventricular arrhythmias and SCD. It is the most common cause of exercise-induced SCD among young male athletes in Italy and may be responsible for up to 20% of SCD in men younger than age 30 years old.[186] Although most cases

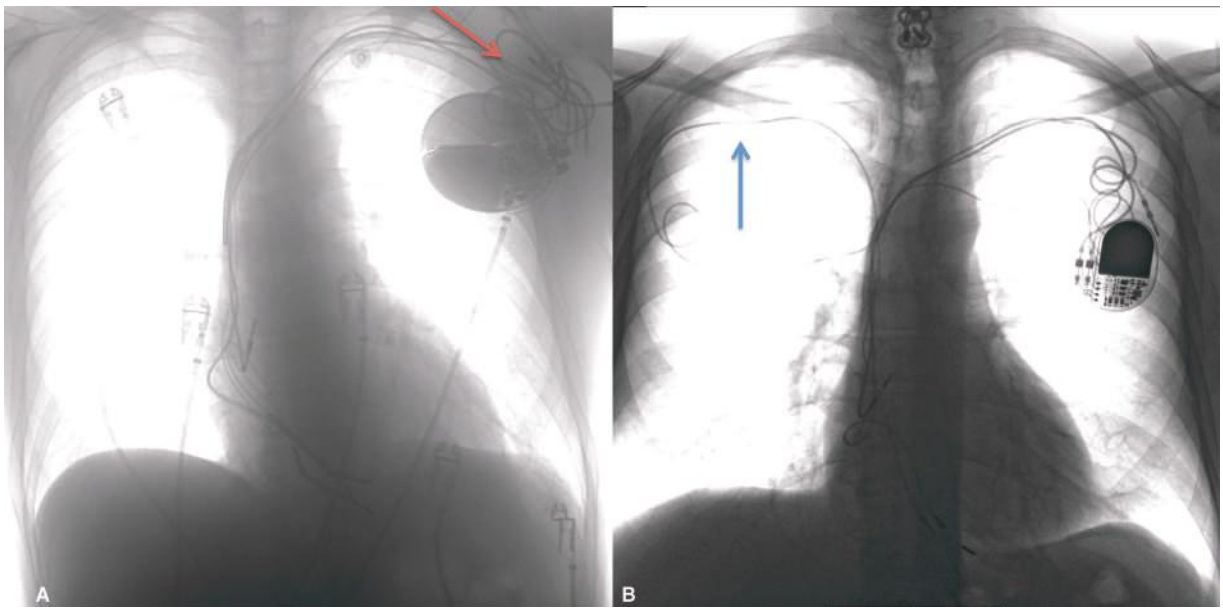

FIGURE 85–10. Two chest x-rays of patients with previous implanatable cardioverter-defibrillator (ICD) implants for primary prevention of sudden cardiac death. Each patient had appropriate ICD shocks for ventricular tachycardia/ventricular fibrillation. However, both patients required repeated lead revisions over time due to device upgrades and lead dysfunction. Neither patient had lead extractions at the time of needed revisions, leading to multiple abandoned intracardiac leads seen on fluoroscopy. The extra-cardiac portion of the abandoned leads are shown in the left chest pocket (**A**, *red arrow*) and on the right side (**B**, *blue arrow*).

appear to be sporadic, approximately 30% of patients have a family history of ARVC. Mutations in genes encoding for several cytoskeletal proteins such as plakoglobin, desmoplakin, and plakophilin-2 have been reported. The most frequently involved areas of the RV are the posterior base, apex, and the infundibulum. These areas are collectively called the *triangle of dysplasia*.[187]

The electrocardiogram during sinus rhythm in ARVC has some distinctive features. T-wave inversion may be present in electrocardiographic leads V_1 to V_3. Epsilon waves, or small high-frequency deflections found in the terminal portion of the QRS complex in leads V_1 to V_3, may be present, as shown in Fig. 85–11. When present, epsilon waves appear to be associated with significant conduction delays and scarring and may correlate with electrical activation of the subtricuspid region.[188]

The diagnosis of ARVC can be difficult. A task force proposed several criteria in 1994 for the diagnosis of ARVC, which were updated in 2015.[189] From this consensus of experts, several major and minor diagnostic criteria are described, and the presence of two major, or one major and two minor, criteria is needed to make a definite diagnosis of ARVC. Major and minor criteria fall into one of six categories: structural abnormalities on imaging (echo/MRI), tissue characterization on biopsy, repolarization abnormalities (ECG), depolarization and conduction abnormalities (ECG and single averaged ECG), documented arrhythmias, and family history.

Patients with ARVC may present with stable monomorphic VT. VT is typically characterized by a LBBB pattern in V_1 given the predominant origin from the right ventricle. However, left ventricular involvement has been described,[190] in which case a RBBB morphology VT pattern can occur. Multiple morphologies of VT are often present in a given individual. VT, which originates from the infundibulum or RVOT, may be difficult to distinguish from idiopathic RVOT VT, which is a benign disease in patients with structurally normal hearts. Among these patients with VT that has an LBBB pattern in V_1, the presence of multiple morphologies of VT, some with a superior QRS axis (negative in leads II, III, and aVF), should raise the suspicion for ARVC as the possible etiology.

Treatment of ventricular arrhythmias arising from ARVC is aimed at preventing SCD and palliation of the clinical burden of VT. Amiodarone, β-blockers, or sotalol may be used as first-line drug therapy for treatment of sustained VT. Data on the efficacy of antiarrhythmic agents is limited, however. Marcus et al[191] demonstrated that β-adrenergic blocking agents and sotalol do not seem to have a protective effect on recurrent VT and ICD shocks. However, patients on amiodarone had a significantly lower risk of clinically relevant ventricular arrhythmias (HR = 0.25; 95% CI, 0.07-0.95; P = .041).

Patients who have had sustained VT or a history of cardiac arrest from VF should receive an ICD. Recurrent VT, not responsive to antiarrhythmic medications, can be successfully ablated. Mapping guided by classic entrainment techniques can often be utilized as most patients with ARVC have preserved LVEF and therefore are more likely to have hemodynamically tolerated VT. If not, a substrate-based approach can be utilized. Although ablation of one clinical VT may be successful, an ICD is often implanted, as multiple VT morphologies typically occur with progression of disease. Evidence demonstrates that the arrhythmogenic substrate for reentry is more often accessible from the RV epicardium, as VT mapping studies demonstrate that many patients have VT mapped in the epicardium that is associated with normal adjacent endocardial voltages. Epicardial RF ablation at these sites can successfully eliminate and prevent long-term VT recurrence when endocardial ablation is unsuccessful.[192,193]

Ventricular Tachycardia in Cardiac Sarcoidosis

Sarcoidosis is a granulomatous disease involving multiple organ systems. The incidence of cardiac symptoms in patients with sarcoidosis is relatively low[194]; however, 20% to 30% of patients with sarcoidosis are found to have evidence of cardiac involvement. Myocardial

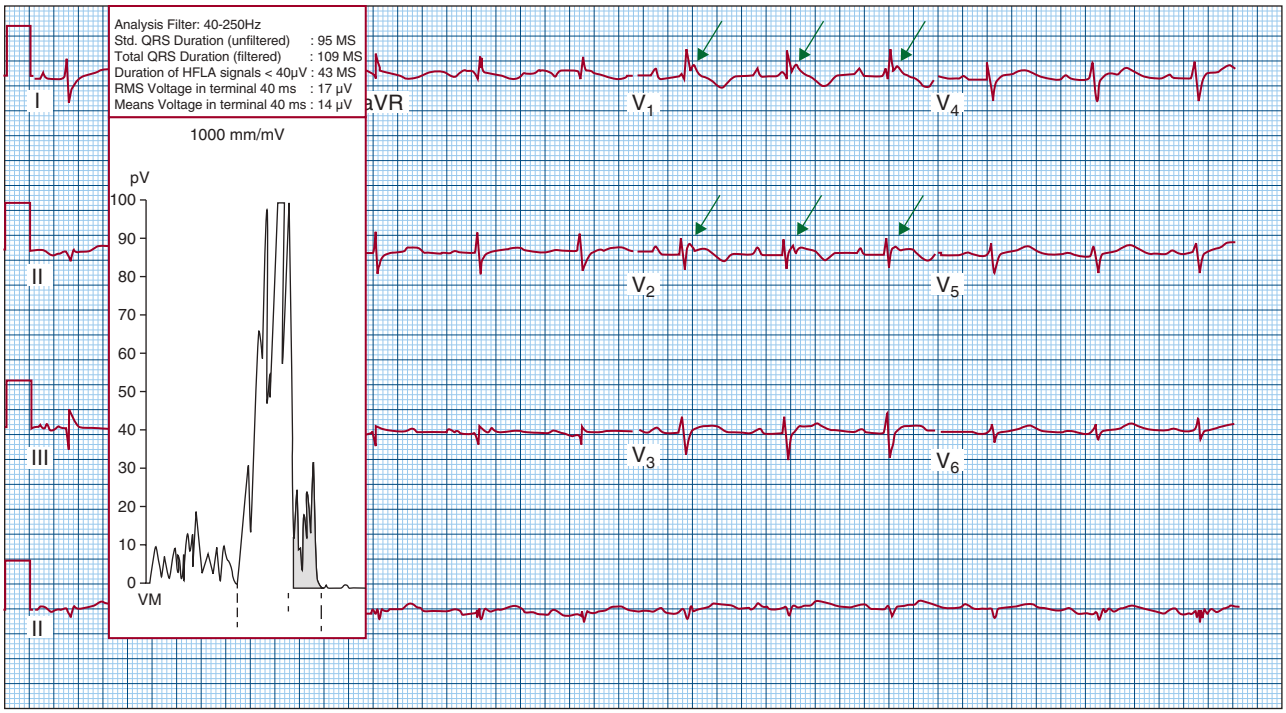

FIGURE 85–11. Epsilon waves (*arrows*) in a patient with arrhythmogenic right ventricular cardiomyopathy (ARVC). Epsilon waves meet a major criterion for the diagnosis of ARVC. Inset shows results from a signal-averaged electrocardiogram (SAECG) demonstrating a duration of the terminal < 40 μV, which was > 38 ms and the root-mean square voltage of the terminal 40 ms ≤ 20 μV. SAECG provides a minor criterion for ARVC.

involvement may be diffuse but is frequently focal or patchy with a propensity for the basal free wall and the anteroapical septum.[195,196] The most common cardiac arrhythmias associated with cardiac sarcoidosis are VT and heart block (LBBB, RBBB, hemi-blocks, and complete heart block). VT can be of left or right ventricular origin. The mechanism of VT is reentry within areas of patchy fibrosis, scarring, and granulomatous involvement of the myocardium. Diagnosis of cardiac sarcoidosis often relies on 18-FDG (fluoro-2-deoxyglucose) positron emission tomography (PET)/computed tomography scans and cardiac MRI, as tissue diagnosis is most often not available. However, recent data suggest that occult inflammation is often present in patients referred for VT ablation with NICM,[197] and therefore clinicians must differentiate patients with true cardiac sarcoidosis from those with an alternative etiology for their NICM.

Because of to the increased risk of sudden death from VT/VF in patients with sarcoidosis, the ACC/AHA/HRS 2008 guidelines give primary prevention with an ICD in patients with sarcoidosis a class IIA recommendation.[1] In addition to an ICD, patients with sustained VT may be treated initially with a β-adrenergic blocking agent with the potential addition of amiodarone or sotalol as needed.

Catheter ablation of VT is a reasonable option for those patients with VT recurrence refractory to antiarrhythmic medications. Because of the frequent RV involvement and associated RV-origin VTs, one must always consider the potential cross-over of electrophysiologic properties for VT resulting from sarcoidosis and that resulting from ARVC.[198] The success rate of VT ablation in sarcoidosis, however, may be mitigated by multiple morphologies and active inflammation and associated substrate progression occurring during active disease. Therefore, if evidence of active inflammation is present by PET scan, initial anti-inflammatory medical therapy in addition to antiarrhythmics should be considered. When catheter ablation is undertaken,[199,200] acute success rates in one study were 78%; however, freedom from VT at 1 year was lower at 37%. Because of the complexity of the arrhythmia substrate in sarcoidosis, a combined endocardial-epicardial approach may be needed and even when acutely successful, residual VTs may be present and require continued antiarrhythmic therapy.

Ventricular Tachycardia in Chagas Disease

Chagas disease is the major cause of CM and VT in Central and South America and is a growing problem in the United States[201] as a result of immigration patterns. The protozoan *Trypanosoma cruzi* is transmitted to humans via triatome insect vectors. The etiology of chronic Chagas CM and associated VT is likely a combined effect of direct-parasitism, autoimmune reaction, inflammatory effects, microvascular destruction, and autonomic dysregulation. Recurrent monomorphic VT is common in chronic Chagas CM. Most VTs can be induced with programmed stimulation and entrained during VT favoring reentry as the predominant mechanism.

Histologic examination of patients with Chagas disease reveals focal and diffuse fibrosis of the myocardium, predominantly in the subepicardium and interspersed with surviving myocardial fibers. Regional wall-motion abnormalities are present often in the inferolateral wall of the LV. Apical septal and apical inferior aneurysms also frequently occur. Sudden death is the most common cause of death in Chagas disease, accounting for 55% to 65% of deaths.[202] In a systematic review, Rassi and colleagues[203] demonstrated that EF, heart failure class, and NSVT predicted risk of cardiac events.

Chagas patients with sustained VT have a high mortality, and patients with Chagas disease and depressed EF or previous sustained

VT benefit from ICD insertion.[204] Cardiac MRI may have predictive value with regards to VT risk in this population; patients with two or more regions of transmural delayed enhancement are at increased risk of clinical VT.[205] The ACC/AHA/HRS 2008 guidelines recommend an ICD for primary prevention of sudden death in patient with Chagas disease.[1]

Amiodarone has modest benefit (62% suppression of VT at 1 year) in this patient population.[206] Radiofrequency catheter ablation may be considered for the treatment of recurrent VT. This often requires epicardial mapping and ablation,[207,208] as Chagas patients often have more epicardial substrate then endocardial.[209]

VENTRICULAR FIBRILLATION/POLYMORPHIC VENTRICULAR TACHYCARDIA/TORSADE DE POINTES

Ventricular fibrillation (VF) is characterized by rapid, chaotic, and asynchronous contraction of the LV. The surface electrogram of VF reveals a rapid, irregular, dysmorphic pattern with no clearly defined QRS complex. VF is associated with rapid hemodynamic collapse and is the most common arrhythmia resulting in out-of-hospital cardiac arrest. Furthermore, patients who suffer a cardiac arrest have significant risk of subsequent arrest.[210]

Polymorphic VT, unlike VF, has clearly defined QRS complexes, but they are constantly changing with no clear pattern. Torsade de pointes (TdP) is polymorphic VT, often self-terminating, in the setting of a prolonged QT interval. It is characterized by a rapid polymorphic VT that constantly changes (cycle length, axis, and morphology), in a pattern that appears to twist around a central axis.

MECHANISM

The exact mechanism underlying VF continues to be enigmatic.[211] Understanding of the mechanism of VF has been enhanced through animal and computer simulation models. Experimental studies in VF suggest functional reentry plays a role in VF and an excitable gap has been demonstrated in experimental models.[212,213] In mathematical models, these functional reentry wavelets have the appearance of nonstationary rotating spiral waves.[214] The ever-changing pathways of these wavelets through the complex three-dimensional geometry of the ventricle accounts for the chaotic appearance of this rhythm on a rhythm strip or 12-lead electrocardiogram.

Coronary artery disease and resultant MI is the most common etiology of VF, polymorphic VT, and cardiac arrest.[215] Other causes of VF/polymorphic VT include dilated cardiomyopathies,[216] hypertrophic cardiomyopathy,[217] myocarditis,[218] valvular heart disease,[219] congenital heart disease,[220] proarrhythmia from drugs, acid-base and electrolyte abnormalities, inherited arrhythmia syndromes, and atrial fibrillation in a patient with Wolff-Parkinson-White syndrome with an anterograde rapidly conducting bypass tract.[221]

Identification of the etiology of VF/polymorphic VT is essential in the risk stratification and prevention of further episodes. For example, revascularization of patients with myocardial ischemia caused by coronary disease, ablation of a bypass tract in a patient with VF as a result of Wolff-Parkinson-White syndrome, or elimination of proarrhythmic drugs decreases the risk of future VF episodes. However, even patients thought to have a reversible cause of cardiac arrest may continue to be at risk for further episodes of VF/polymorphic VT. In an analysis of the AVID trial for patients with sustained VT or VF, Wyse and coworkers[222] reported a similar mortality rate in patients with a reversible cause of arrest compared with patients considered to have a nonreversible cause of their VT or VF.

CLINICAL CHARACTERISTICS AND MANAGEMENT

In the early stages of cardiac arrest, VF is the most common arrhythmia encountered. Patients with VF require immediate defibrillation. Early defibrillation is an essential, as with every minute of delay in defibrillation for VF, the chance of survival decreases by 7% to 10%.[223] Determinants of successful defibrillation include time to defibrillation, energy delivered, defibrillation waveform, transthoracic impedance, shock electrode placement, surface area of the shock electrodes, and the patient's metabolic status (acid-base and electrolytes). Biphasic waveforms appear to have an advantage over monophasic waveforms in that less energy is required for defibrillation.[224] In the setting of VF, a nonsynchronized shock should be delivered.

The management of patients presenting with a resuscitated VF arrest is aimed at determining its cause and treating potential recurrence. As most cardiac arrests occur in patients with coronary artery disease, all patients should have serial cardiac enzymes monitored and be evaluated for the presence of epicardial coronary disease (usually via coronary angiography).[225,226] In addition, an echocardiogram should be performed to assess LV function. In patients with structurally normal-appearing hearts without evidence of ischemia or MI, other etiologies of VF should be considered, including coronary artery spasm, Wolff-Parkinson-White syndrome, proarrhythmia from medications, long QT syndrome, Brugada syndrome, short QT syndrome, and catecholaminergic polymorphic VT.

When VF occurs during an acute MI, it usually occurs within the first 4 hours following onset of coronary occlusion. In GISSI-2, the incidence of early VF (occurring in the first 4 hours after presentation) was 3.1%, whereas the incidence of late VF (occurring in the subsequent 4-48 hours) was only 0.6%. Patients with early VF had a more complicated in-hospital course than matched controls. Both early (odds ratio [OR] = 2.47; 95% CI, 1.48-4.13) and late VF (OR = 3.97; 95% CI, 1.51-10.48) were independent predictors of in-hospital mortality. Postdischarge to 6-month death rates were similar for both early and late VF subgroups and controls.[227] It is important to emphasize that all patients with an acute MI should undergo revascularization (if appropriate) and be treated with aspirin, a β-adrenergic receptor blocker, a statin, and an ACEI.

Identification and treatment of reversible causes of VF, such as removal of proarrhythmic medications and correcting electrolyte abnormalities, should be performed without delay. Patients with long QT syndrome should be treated with a β-adrenergic receptor blocker as a long-term treatment to decrease the risk of torsade de pointes; however for acute therapy for incessant torsades, isoproterenol infusion or temporary pacing should be considered to increase the heart rate and shorten the QT interval.

When the patient's evaluation is complete and all reversible causes or contributions to VF are corrected, most patients presenting with VF arrest should undergo implantation of an ICD. ICD implantation has become the mainstay of therapy for cardiac arrest survivors. Recent early data suggest the potential benefit of left[228-230] and bilateral[112,231,232] cardiac sympathetic denervation as an additional treatment modality, both for recurrent VF/polymorphic VT in channelopathies as well as for monomorphic VT in the setting of structural heart disease. In select cases, focal triggers of VF can be mapped and ablated (Fig. 85–12). These PVCs tend to originate in the border zones between scars and normal myocardium.[233]

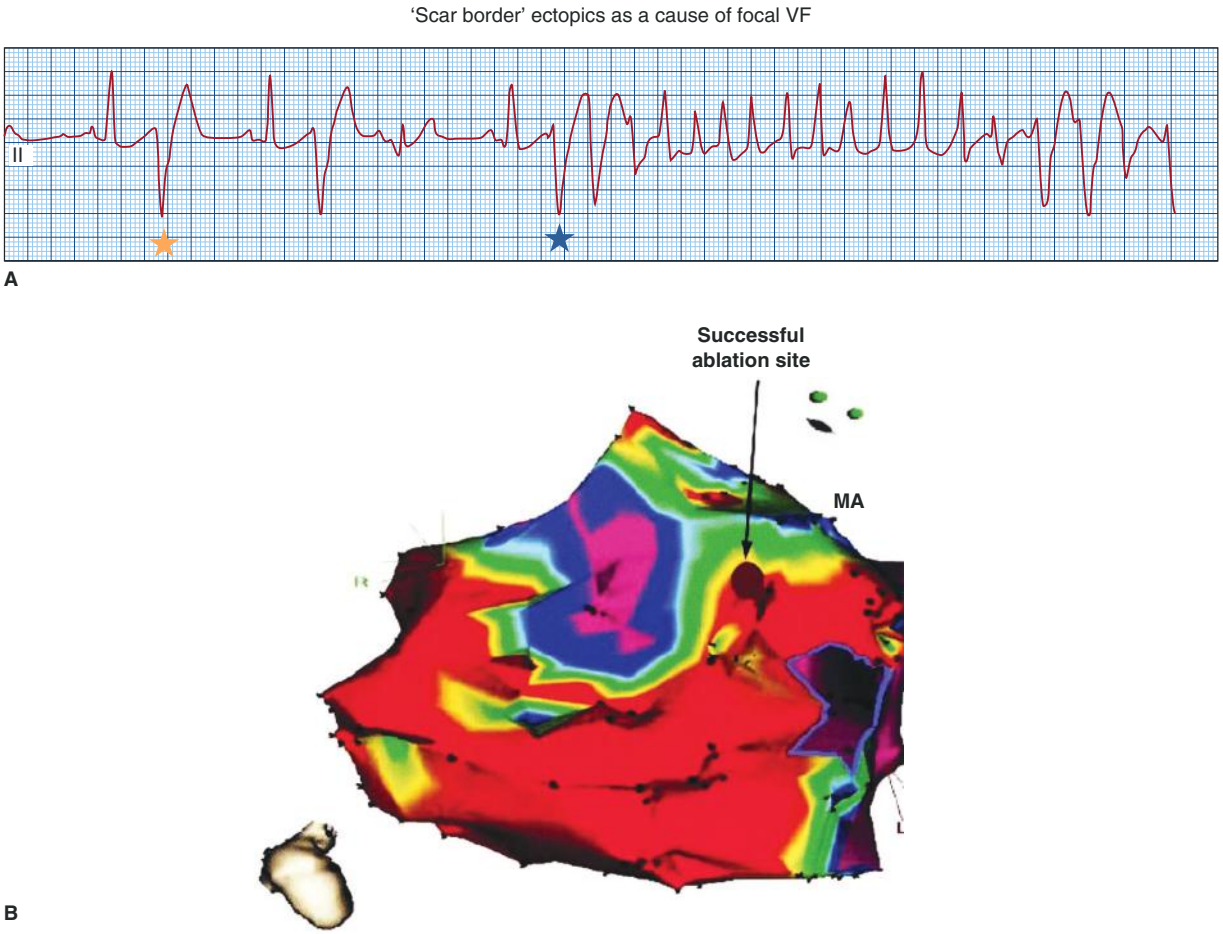

FIGURE 85–12. A. Rhythm strip of recurrent PVC that repeatedly triggered VF. (*Orange star* = PVC, and *blue star* = PVC-initiated VF.) **B.** Three-dimensional anatomic map (Carto, Biosense Webster, Inc., Diamond Bar, CA) of the site of origin of the PVC within the scar "border zone." Purple represents normal tissue, and red delineates dense scar. MA, mitral annulus; PVC, premature ventricular contraction; VF, ventricular fibrillation.

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CHAPTER 86

BRADYARRHYTHMIAS

Pugazhendhi Vijayaraman and Kenneth A. Ellenbogen

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Bradyarrhythmias are most commonly caused by failure of impulse formation (sinus node dysfunction) or by failure of impulse conduction over the atrioventricular (AV) node/His-Purkinje system. Bradyarrhythmias may be caused by disease processes that directly alter the structural and functional integrity of the sinus node, atria, AV node, and His-Purkinje system or by extrinsic factors (autonomic disturbances, drugs, etc) without causing structural abnormalities (Table 86–1).

ANATOMY OF THE SINUS NODE AND CONDUCTION SYSTEM

SINOATRIAL NODE

Normal electrical activation of the heart arises from the principal pacemaker cells that spontaneously depolarize, located laterally in the epicardial groove of the sulcus terminalis,[1] near the junction of the right atrium and the superior vena cava (Fig. 86–1). The sinus node in adults measures approximately 1 to 2 cm long and 0.5 mm wide. The central zone of the sinus node containing the principal central pacemaker cells is small and located within a fibrous tissue matrix. In the periphery of the node along the crista terminalis, transitional cells with pacemaker function are also present. In essence, the SA node has a complex three-dimensional tissue architecture with central and peripheral components made up of distinct ion channel and gap junction expression profiles. This heterogeneity is necessary to maintain normal automaticity and impulse conduction. The principal pacemaker site within this region may migrate, resulting in subtle alterations in P-wave morphology. Once the impulse exits the sinus node and the perinodal tissues, it traverses the atrium to the AV node. The conduction of impulses from right to left atrium has been postulated to occur preferentially via Bachmann bundle, and secondarily across the musculature of the coronary sinus.

ATRIOVENTRICULAR NODE

Once the sinus node impulse activates the atrium, electrical activation continues through the AV node, with a conduction delay ensuring complete atrial contraction before initiation of ventricular conduction. The AV nodal complex is considered to have three related regions: (1) the transitional cell zone, (2) the compact AV node, and (3) the penetrating AV bundle.[2] The transitional zone consists of the main atrial approaches to the compact AV node. The compact AV node is shaped like a half oval and is located beneath the right atrial endocardium at the apex of the triangle of Koch. The triangle of Koch is formed by the base of the septal leaflet of the tricuspid valve and the tendon of Todaro (formed by the extension of the eustachian valve into the central fibrous body). The coronary sinus ostium is located at the base of this triangle. The distal end of the compact AV node enters the central fibrous body to become the penetrating bundle and continues in the membranous septum as the bundle of His. The speed of conduction through the AV nodal complex is 0.03 m/s, whereas the His-Purkinje fibers conduct at 2.4 m/s.

HIS-PURKINJE SYSTEM

The penetrating part of the AV bundle continues through the annulus fibrosis into the membranous septum, along the crest of the left side of the interventricular septum for 1 to 2 cm, and then divides into the right and left bundle branches. The right bundle branch continues intramyocardially along the right side of the interventricular septum and emerges subendocardially beneath the anterior papillary muscle of the right ventricle. The left bundle begins as a sheet of fascicles and runs along the left side of the interventricular septum and soon separates into anterior and posterior sheets (most anatomists agree it is a trifascicular system with a substantial septal branch) corresponding to the anterior and posterior papillary muscles. In many hearts, the left bundle may appear more as a network rather than a well-defined bifascicular system. The terminal Purkinje fibers arising from the bundle branches form interweaving networks on the endocardial surface of both the right and left ventricles. The rapid conduction of electrical impulses across this network results in near simultaneous activation of both right and left ventricles.

The anatomy of the main His bundle has practical implications for permanent His bundle pacing. While early reports on permanent His bundle pacing demonstrated its feasibility, it had been technically challenging.[3] Recent studies have shown that routine permanent His bundle pacing is possible both in patients with AV nodal and proximal His bundle disease.[4] Understanding the anatomy of the His bundle is critical in achieving procedural success. The proximal part of the His bundle rests on the right atrial-left ventricular (RA-LV) part of the membranous septum, and the more distal part travels along the right ventricle-left ventricular (RV-LV) part of the membranous septum, immediately below the aortic root (Fig. 86–2). Kawashima and Sasaki[5] reported anatomical variations of the AV bundle from their macroscopic anatomical investigation of 105 elderly human hearts. They reported three distinct variations of the His bundle relative to the membranous part of the ventricular septum. The His bundle consistently coursed along the lower border of the membranous part

TABLE 86–1. Classification of Bradyarrhythmias

Sinus node dysfunction
Sinus bradycardia
Sinus pauses, sinus arrest
Sinoatrial exit block
Tachycardia-bradycardia syndrome
Chronotropic incompetence
Atrioventricular (AV) conduction abnormalities
First-degree AV block
Second-degree AV block
Mobitz type I (Wenckebach)
Mobitz type II
2:1 AV block
High-grade AV block
Third-degree (complete) AV block
Atrioventricular dissociation
Bundle branch block
Left bundle branch block
Right bundle branch block
Left anterior hemiblock
Left posterior hemiblock
Bifascicular block/trifascicular block
Nonspecific intraventricular conduction defect

of the interventricular septum (Fig. 86–3) but was covered with a thin layer of myocardial fibers spanning from the muscular part of the septum (type I, 46.7% of 105 cases). The His bundle was apart from the lower border of the membranous part of the interventricular septum and ran within the interventricular muscle (type II, 32.4%). The His bundle was immediately beneath the endocardium and coursed onto the membranous part of the interventricular septum (naked atrioventricular bundle, type III, 21%). These anatomical variations of the His bundle may have clinical implications for permanent His bundle pacing and to avoid His bundle injury during surgical reconstruction of membranous part of the ventricular septal defect.

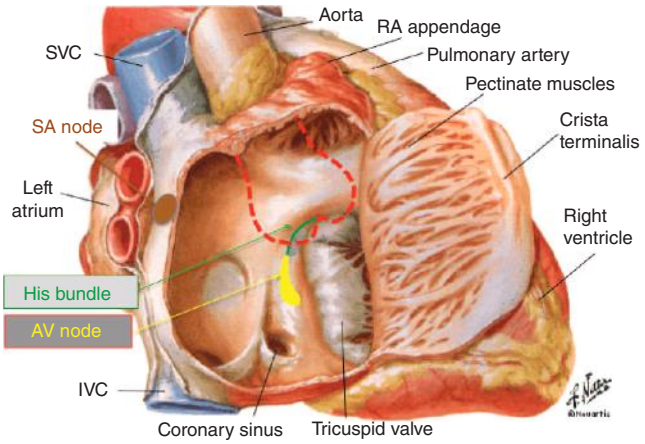


FIGURE 86–1. Schematic representation of the cardiac conduction system. AV, atrioventricular; IVC, inferior vena cava; RA, right atrial; SA, sinoatrial; SVC, superior vena cava. Copyright 2016, Elsevier Inc. All rights reserved. www.netterimages.com.

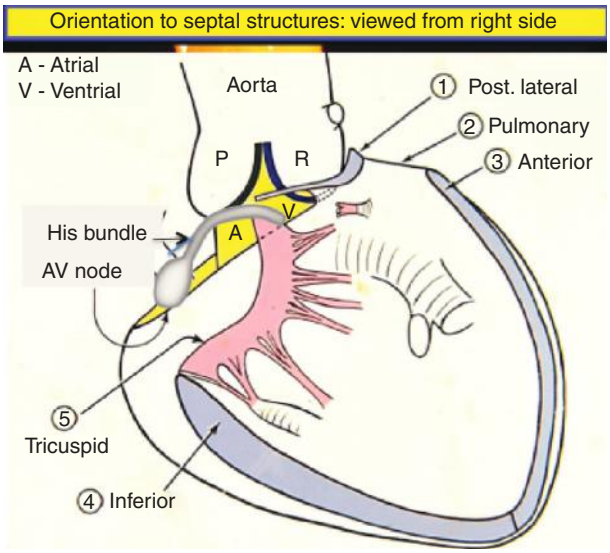


FIGURE 86–2. Schematic representation of atrial (A) and ventricular (V) aspect of the membranous septum (MS) and its relation to aortic root and valve cusps. AV node and the course of His bundle are superimposed on the membranous septum. The proximal portion of the His bundle is on the right atrial-left ventricular aspect of the MS. The distal portion of the His bundle is in the right ventricle-left ventricular aspect of the MS. Used with permission from Dr. K. Shivkumar, UCLA Arrhythmia Center.

BLOOD SUPPLY

The sinus node receives its blood supply from the sinoatrial (SA) nodal artery arising from the right coronary artery in 59% of patients, from the left circumflex artery in 38%, and from both arteries with a dual blood supply in 3%. The AV node is supplied by the AV nodal artery arising from the right coronary artery in 90% of patients, whereas the left circumflex artery provides it in the remaining 10% of patients. Both the AV nodal artery and branches of the left anterior descending artery supply the bundle of His. The left bundle has a rich blood supply from the AV nodal artery, posterior descending artery, and branches of the left anterior descending artery.

INNERVATION

The conduction system of the heart is significantly influenced by both the parasympathetic and sympathetic nervous systems. The sinus node is richly innervated with postganglionic adrenergic and cholinergic nerve terminals. Vagal stimulation slows the sinus node discharge rate and increases the intranodal conduction time, occasionally to the point of sinus node exit block. Adrenergic stimulation increases the sinus node discharge rate. Parasympathetic tone predominates at rest in healthy individuals, and parasympathetic withdrawal occurs with increased sympathetic discharge during exercise and emotion. The effects of sympathetic and parasympathetic stimulation on the AV node are more pronounced than they are on the His-Purkinje system. Although sympathetic stimulation shortens AV-nodal conduction time and refractoriness, vagal stimulation prolongs AV-nodal conduction time and refractoriness. Both sympathetic and vagal stimulation have minimal effect on normal conduction in the His bundle.

SINUS NODE DYSFUNCTION

Sinus node dysfunction (SND) is a common clinical syndrome, comprising a wide range of electrophysiologic abnormalities including failure of impulse generation, failure of impulse transmission to the atria,

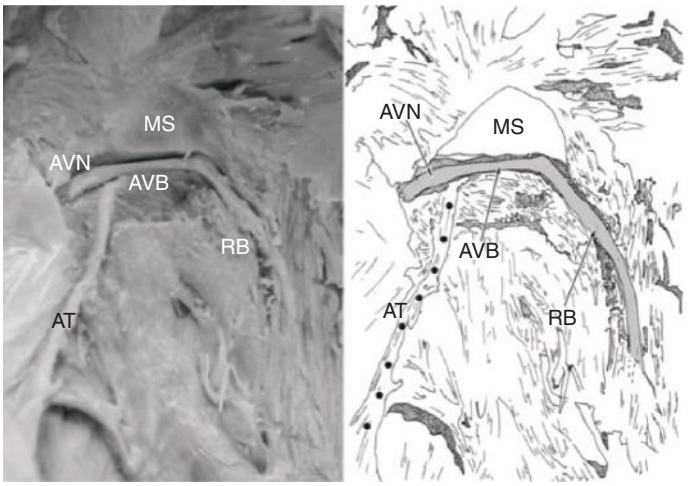


FIGURE 86–3. Type I His bundle. The His bundle runs under the membranous part of the interventricular septum (MS). Dots correspond with the line of the attachment of tricuspid valve (AT). AVB, atrioventricular bundle; AVN, atrioventricular node; RB, right bundle. Reproduced with permission from Kawashima T, Sasaki H: A macroscopic anatomical investigation of atrioventricular bundle locational variation relative to the membranous part of the ventricular septum in elderly human hearts. *Surg Radiol Anat*. 2005 Aug;27(3):206-213.

inadequate subsidiary pacemaker activity, and increased susceptibility to atrial tachyarrhythmias.[6] This disorder has also been variably termed the *sick sinus syndrome, tachycardia-bradycardia syndrome, SA disease,* and *SA dysfunction.*

SINUS NODE ELECTRICAL ACTIVITY

Normal myocardium has a stable hyperpolarized (negative) resting potential during phase 4 of the action potential. The sinoatrial node in contrast, displays phase 4 diastolic depolarization (Fig. 86–4). The cell membrane potential becomes gradually more positive until an action potential is triggered at the threshold potential. Alteration of this phase 4 slope changes the heart rate.[7] The current paradigm of sinoatrial node automaticity is modeled as mutual entrainment of two molecular

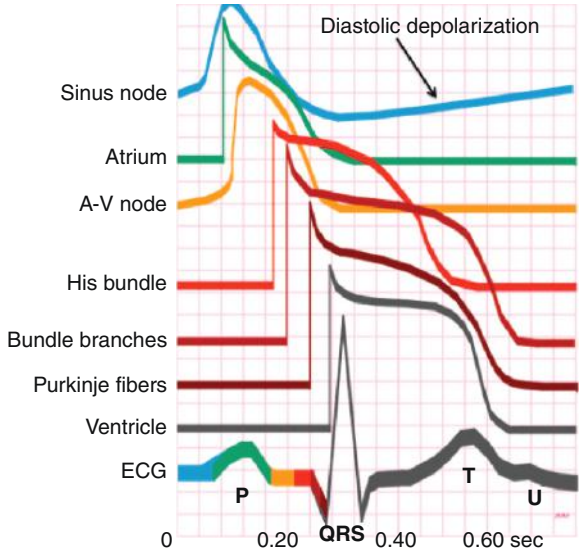


FIGURE 86–4. Cardiac conduction system. The sinus node action potential is different from the rest of the cardiac conduction tissue by the presence of diastolic depolarization, which is essential for its automaticity. A-V, atrioventricular; ECG, electrocardiogram. Used with permission from John Miller, Indiana University.

clocks, the "membrane voltage clock" and the "calcium clock."[8] The membrane clock is produced by the net disequilibrium between the hyperpolarizing outward potassium current (I_k) and the depolarizing inward current (principally the I_f). The pacemaker, or funny current, I_f, is generated by the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel.[9] The I_f is activated at hyperpolarized membrane potentials (between –65 and –40 mV) and this current contributes to diastolic depolarization. The subsarcolemmal calcium clock contributes significantly to late diastolic depolarization of SA node through the spontaneous rhythmic release of Ca^{2+} from the sarcoplasmic reticulum (SR) via the ryanodine type 2 receptor (RYR2).[10] The elevation of the local intracellular calcium drives the sodium-calcium exchange current (I_{NCX}) to substitute one intracellular Ca^{2+} for three extracelluar Na^+ leading to net gain in positive charge and resulting in membrane depolarization. Both the membrane and calcium clocks are modulated by cAMP and hence sensitive to adrenergic stimulation (Fig. 86–5). Human mutations affecting the membrane clock (SCN5A and HCN4), calcium clock (RYR2 and CASQ2), or both mechanisms (ANKB) have been identified to negatively affect sinus node function.[11]

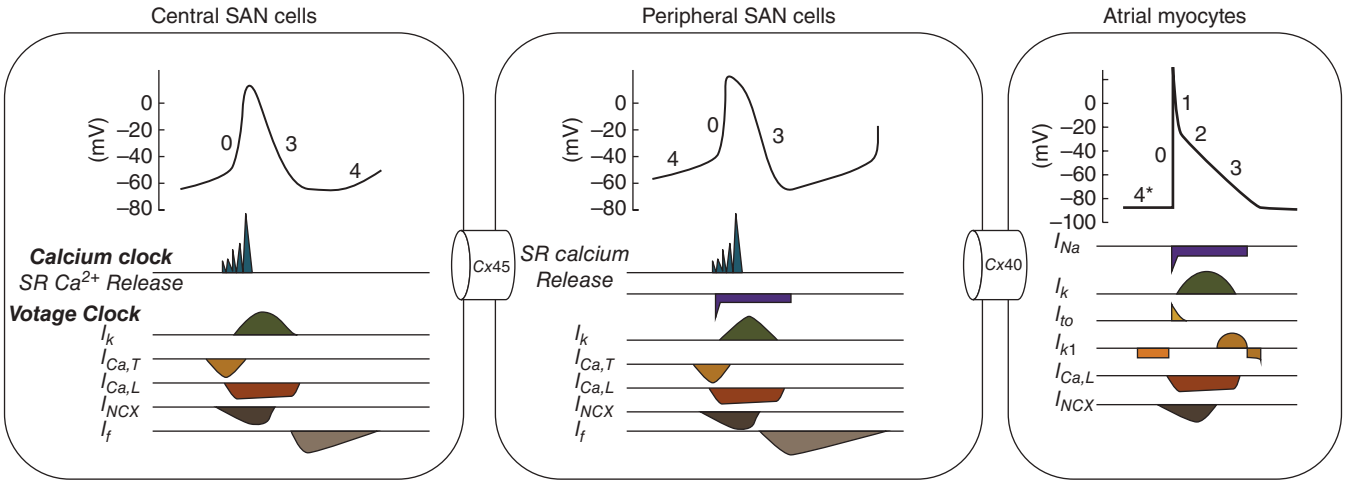
PATHOPHYSIOLOGY

Disorders of sinus node dysfunction may be caused by intrinsic (processes that directly affect the anatomy and physiology of the sinus node and/or the surrounding atrial tissue) or extrinsic factors (processes that affect sinus node function in the absence of structural abnormalities) (Table 86–2). However, in some patients a combination of intrinsic and extrinsic factors may be responsible for sinus node dysfunction. In patients with sinus node dysfunction, histopathologic evaluation has revealed the following patterns[12]: significant loss of nodal cells with replacement fibrosis, amyloid deposition in the nodal region, hypoplastic or atrophic sinus node, and no detectable morphologic abnormality.

Aging is associated with alterations in sinus node function, causing a decrease in the intrinsic HR, an increase in sinoatrial conduction time (SACT), and conduction slowing and voltage loss around the region of crista terminalis, and increases SACT. In the presence of clinically detectable sinus node dysfunction there is caudal shift of the leading pacemaker site within the SA node pacemaker complex. Decreased expression of Cx43 in the vicinity of SA node may lead to increase in SACT and SA exit block seen with aging.[13] While structural changes such as fibrosis and degeneration had been implicated in sinus node dysfunction, there is also evidence for reverse remodeling of the SA node. Electrical remodeling of the sinus node pacemaker complex and molecular remodeling of key ion channels and regulatory elements has been demonstrated in response to variety of conditions known to lead to SND.[14]

Sinus node dysfunction is a well-known association with recurrent atrial arrhythmia (atrial fibrillation, atrial flutter). Chronic overdrive of the SA node by a primary atrial arrhythmia leads to electrical remodeling and sinus node dysfunction. Rapid atrial pacing induces abnormalities of both membrane clock (reduction in HCN4 and HCN2 expression with reduction in I_f and $I_{k,s}$ currents) and Ca^{2+} clock (altered Ca^{2+} cycling and RYR expression).[15] Reverse remodeling of SND can be demonstrated after restoration of sinus rhythm following catheter ablation of atrial fibrillation.

Although an idiopathic degenerative disorder of the sinus node is the most common cause for intrinsic sinus node dysfunction, ischemic heart disease is responsible in a significant number of patients. Chronic ischemia from sinus node artery disease or acute myocardial infarction (MI), especially inferior wall MI, may result in sinus bradycardia, sinus arrest, and atrial tachyarrhythmias. Transient sinus bradycardia and



Current	Current name	Channel	Gene
I_{Na}	Sodium current	Nav1.5	SCN5A
I_k	Delayed rectifier (slow)	KvLQT1/minK	KCNQ1/KCNE1
	Delayed rectifier (fast)	HERG/MiRP	KCNH2/KCNE2
$I_{Ca,T}$	T-type calcium current	Cav3.1	CACNA1G
$I_{Ca,L}$	L-type calcium current	Cav1.2	CACNA1C
I_{k1}	Inward rectifier slow	Kir2.1	KCNJ2
I_f	Funny current	HCN4	HCN4
$I_{NCX}(I_{tf})$	Na^+–Ca^{2+} exchanger	NCX1	SLC8A1
I_{to}	Transient outward	Kv4.2/Kv4.3	KCND2/KCND3

Gap Junction	Gene	Conduction
Connexin 45 (Cx45)	GJA7	Slow
Connexin 40 (Cx40)	GJA5	Fast

Action potential (AP) phase	AP number
Diastolic depolarization	4
Resting membrane potential	4*
Depolarization	0
Fast repolarization	1
Plateau	2
Terminal repolarization	3

FIGURE 86–5. Electrophysiologic heterogeneity of the sinoatrial node (SAN). The central SAN, the site of dominant pacemaking, is electronically insulated from the hyperpolarizing atrial myocardium through the differential expression of connexins and ion channels. Peripheral SAN cells are electrophysiologically intermediate between central cells and atrial cardiomyocytes. SR, sarcoplasmic reticulum. Reproduced with permission from Park DS, Fishman GI. The cardiac conduction system. *Circulation*. 2011 Mar 1;123(8):904-915.

sinus arrest seen in acute myocardial infarction may in part be related to altered neurologic influences on the heart. Other potential causes include long-standing hypertension, cardiomyopathy (especially infiltrative disorders such as amyloidosis and sarcoidosis), inflammation, collagen vascular disease, and inherited neuromuscular disorders.

In some cases, the condition appears to be familial in origin.[16] SND can occur in children and young adults without structural heart disease. In addition to autosomal inheritance, polygenetic susceptibility to SND has been described. HCN4 mutations result in a lack of channel responsiveness to cAMP or reduction in I_f, leading to sinus bradycardia, chronotropic incompetence, and AF.[17] Mutations in Ca^{2+} channels and Ca^{2+} handling proteins (RYR or calsequestrin 2[CASQ2]) are also associated with SND.[18] Mutations in the cardiac sodium channel gene, *SCN5A,* have been reported in families to result in primary cardiac conduction disease. The mutations that are associated with conduction system disease result in reduced Na^+ current. The spectrum of these conduction diseases varies widely, but includes sinus node dysfunction, atrial standstill, AV block, and progressive cardiac conduction disease (PCCD). An inherited form of Lev-Lenégre disease is associated with loss of function mutations in *SCN5A* and can exist alone or as overlap syndromes with Brugada or long QT syndrome. Mutations in ankyrin-B (ANKB) are associated with long QT type 4 and familial sinus node dysfunction by disrupting the membrane and Ca^{2+} clocks.[19,20]

Rare cases of sinus node dysfunction requiring pacemaker therapy have been reported with Lyme disease (*Borrelia burgdorferi* infection).[21] In children and young adults, damage to the sinus node during atrial surgery (closure of atrial septal defects of the sinus-venosus type, Mustard procedure for transposition of great arteries) has been commonly associated with sinus node dysfunction. Sinus node dysfunction is also not uncommon in the donor hearts of patients with orthotopic cardiac transplantation.

The most important causes of sinus node dysfunction in patients without structural abnormalities are drugs and autonomic nervous system influences (see Table 86–2). Drugs may alter sinus node function by direct pharmacologic effects on nodal tissue or indirectly by neurally mediated effects. Antiarrhythmic drugs used to maintain sinus rhythm in patients with atrial fibrillation may cause significant sinus node dysfunction, especially in patients with underlying sinus node dysfunction. Other causes for sinus node dysfunction include electrolyte abnormalities, such as hyperkalemia, hypothermia, intracranial hypertension, hypoxia, hypercapnia, and hypothyroidism.

ELECTROCARDIOGRAPHIC MANIFESTATIONS

A variety of electrocardiographic (ECG) abnormalities have been described in patients with sinus node dysfunction. Many of the ECG abnormalities that define sinus node dysfunction may be asymptomatic, and these abnormalities by themselves do not warrant therapy.

Sinus Bradycardia

Sinus bradycardia is defined as a sinus rate < 60 bpm. In most instances sinus bradycardia is a benign arrhythmia. In healthy young adults and trained athletes, resting sinus bradycardia may be a normal phenomenon caused by increased vagal tone. Sinus bradycardia during sleep

TABLE 86–2. Etiology of Sinus Node Dysfunction

Intrinsic	Extrinsic
Idiopathic degenerative disorder	Drugs
Ischemic heart disease	Antiarrhythmic agents
Chronic ischemia	Class IA—quinidine, procainamide
Acute myocardial infarction	Class IC—propafenone, flecainide
Hypertensive heart disease	Class II—β-blockers
Cardiomyopathy	Class III—sotalol, amiodarone, dronedarone
Trauma	
Surgery for	Class IV—diltiazem, verapamil
Congenital heart disease	Ivabradine (I_f blocker)
Valvular heart disease	Cardiac glycosides
Heart transplant	Antihypertensive agents
Inflammation	Clonidine, reserpine, methyldopa
Collagen vascular disease	Antipsychotic agents
Rheumatic fever	Lithium, phenothiazines, amitriptyline
Pericarditis	
Infection	Autonomically mediated
Viral myocarditis	Vasovagal syncope (cardioinhibitory)
Lyme disease *(Borrelia burgdorferi)*	Carotid sinus hypersensitivity
	Hypothyroidism
Neuromuscular disorder	Intracranial hypertension
Friedreich ataxia	Hypothermia
X-linked muscular dystrophy	Hyperkalemia
Familial disorder	Hypoxia
Inherited channelopathy	
Atrial arrhythmias	

in elderly individuals is common. Inability to increase sinus rates adequately during exercise is considered abnormal (see below). Sinus bradycardia < 40 bpm (not associated with sleep or physical conditioning) is generally considered abnormal. Correlation of symptoms with sinus bradycardia is critical in the evaluation of these patients.

Sinus Pause and Sinus Arrest

Sinus pause or arrest means failure of sinus node discharge with lack of atrial activation of sinus origin. This results in absence of P waves and periods of ventricular asystole if lower pacemakers (junctional or ventricular) do not initiate escape beats (Fig. 86–6). The resulting pause in sinus activity should not be in multiples of preceding sinus cycle length (P-P interval), which would indicate that sinoatrial exit block is present (see below). Asymptomatic sinus pauses of up to 3 seconds in duration are not uncommon in trained athletes.[22] Pauses longer than 3 seconds need careful clinical correlation with symptoms and warrant further evaluation.

Sinoatrial Exit Block

In SA exit block, as the name implies, the impulse is formed in the sinus node but fails to conduct to the atria, unlike sinus arrest. This particular arrhythmia is recognized on ECG by pauses resulting from the absence of normal P waves and the duration of the pause, measuring an exact multiple of the preceding P-P interval (Fig. 86–7). SA block can also be described in the same way as AV block. In first-degree SA block, there is significant prolongation of the time for the sinus impulse to exit into the atria (SA conduction time). This cannot be identified clinically or electrocardiographically. Similar to AV block, second-degree SA block can be type I (Wenckebach) or type II. In type I there is progressive prolongation of SA conduction, manifested on surface ECG as progressive shortening of P-P interval, before the pause created by loss of a P wave. In type II SA exit block, the P-P intervals remain constant before the pause. Third-degree or complete SA block will manifest as absence of P waves, with long pauses resulting in lower pacemaker escape rhythm; it is impossible to diagnose with certainty without invasive sinus node recordings.

Tachycardia-Bradycardia Syndrome

Sinus bradycardia interspersed with periods of atrial tachyarrhythmias is a common manifestation of sinus node dysfunction. The atrial tachyarrhythmias usually range from paroxysmal atrial tachycardia to atrial flutter and atrial fibrillation. Apart from underlying sinus bradycardia of varying severity, these patients often experience prolonged sinus arrest and asystole upon termination of the atrial tachyarrhythmias, resulting from suppression of sinus node and secondary pacemakers (Fig. 86–8). Long sinus pauses that occur after electrical cardioversion of atrial fibrillation are another manifestation of sinus node dysfunction. Therapeutic strategies to control tachyarrhythmias often result in the need for pacemaker therapy. These patients are at increased risk for thromboembolism,[23] and the issue of long-term anticoagulation should be addressed to prevent strokes.

Chronic atrial fibrillation with a slow ventricular response in the absence of AV nodal-blocking drugs may also be a manifestation of sinus node dysfunction. These patients may demonstrate very slow ventricular rates at rest or during sleep and occasionally have long pauses. They may also conduct rapidly and develop symptoms caused by tachycardia during exercise. Occasionally they may develop complete AV block with junctional or ventricular escape rhythms.

Persistent Atrial Standstill

Atrial standstill is a rare clinical syndrome in which there is no spontaneous atrial activity and the atria cannot be electrically

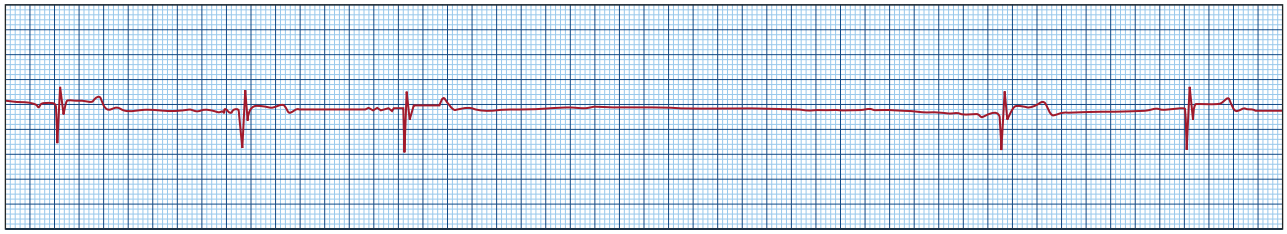


FIGURE 86–6. Telemetry strip demonstrating sinus bradycardia followed by a 4.6-second sinus pause.

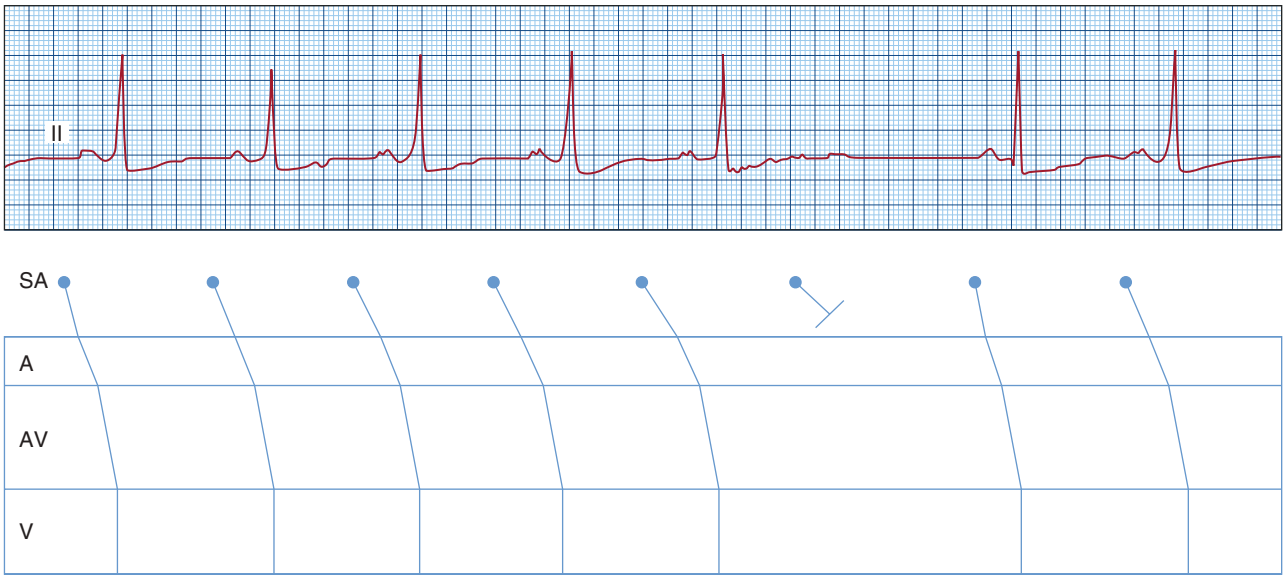


FIGURE 86–7. Telemetry strip demonstrating a sinus pause twice the length of the preceding P-P interval, suggesting sinoatrial exit block. Ladder diagram depicts sinoatrial (SA) nodal type I exit block.

stimulated.[24] The surface ECG usually reveals junctional bradycardia without atrial activity (Fig. 86–9). This must be differentiated from fine atrial fibrillation with complete heart block. Intracardiac electrograms fail to show any atrial activity. Atria are generally fibrotic and without any functional myocardium. Myocarditis, amyloidosis, and familial etiology have been recognized as causes in some cases. Lack of mechanical atrial contraction poses a high risk for thromboembolism in these patients.

Chronotropic Incompetence

Chronotropic incompetence (CI) is most commonly defined as the inability of the sinus node to achieve at least 85%, 80%, or less commonly 70% of the age-predicted maximal heart rate (APMHR, 220 –age) obtained during an incremental dynamic exercise test. CI has also been determined from change in HR from rest to peak exercise during an exercise test, commonly referred to as the HR reserve. Adjusted (percent) HR reserve is determined from the change in HR from rest to peak exercise divided by the difference of the resting HR and the APMHR. The majority of studies in the literature have used failure to attain > 80% of the HR reserve, measured during a graded exercise test, as the primary criterion for CI.[25] It is present in approximately 20% to 60% of patients with sinus node dysfunction. Although the resting heart rates may be normal, these patients may have either the inability to increase their heart rate during exercise or have unpredictable fluctuations in heart rate during activity. Some patients may initially experience a normal increase in heart rate with exercise, which then plateaus or decreases inappropriately. Chronotropic incompetence may be secondary to intrinsic sinus node dysfunction or secondary to drugs with negative chronotropic effects. Chronotropic incompetence is also common in patients with heart failure.[26]

CLINICAL PRESENTATION

Even though sinus node dysfunction may occur in any age group, more than half of the patients affected are older than 50 years of age at the time of diagnosis. The incidence of sinus node dysfunction is approximately equal in both men and women. Patients with sinus node dysfunction commonly present with symptoms of syncope, near syncope, or dizzy spells, predominantly related to prolonged sinus pauses. Patients with sinus bradycardia or chronotropic incompetence, however, may present with relatively nonspecifc symptoms, such as decreased exercise capacity, recurrent falls, or fatigue. Patients with atrial fibrillation may also present with palpitations or congestive heart failure. Elderly individuals may have unexplained confusion or memory loss. Occasionally, stroke may be the first manifestation of sinus node dysfunction in patients presenting with paroxysmal atrial fibrillation and thromboembolism.

DIAGNOSTIC EVALUATION

The diagnosis of sinus node dysfunction in patients who present with typical symptoms and ECG findings is straightforward. However, because of the intermittent nature of the symptoms and rhythm manifestations, the diagnosis can be time-consuming and frustrating.

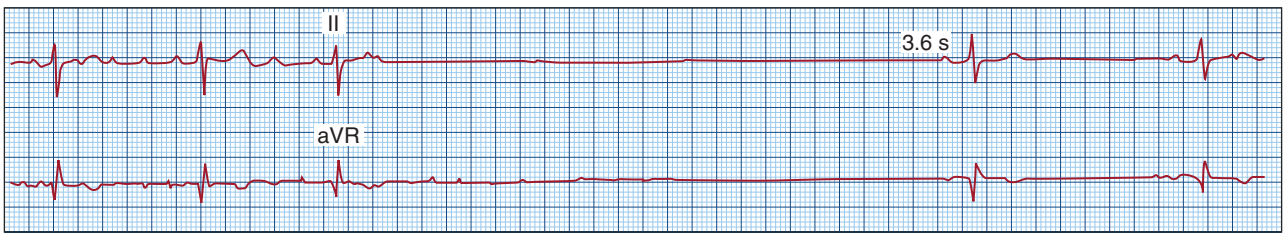


FIGURE 86–8. An example of atrial tachyarrhythmia terminating with a 3.6-second sinus pause.

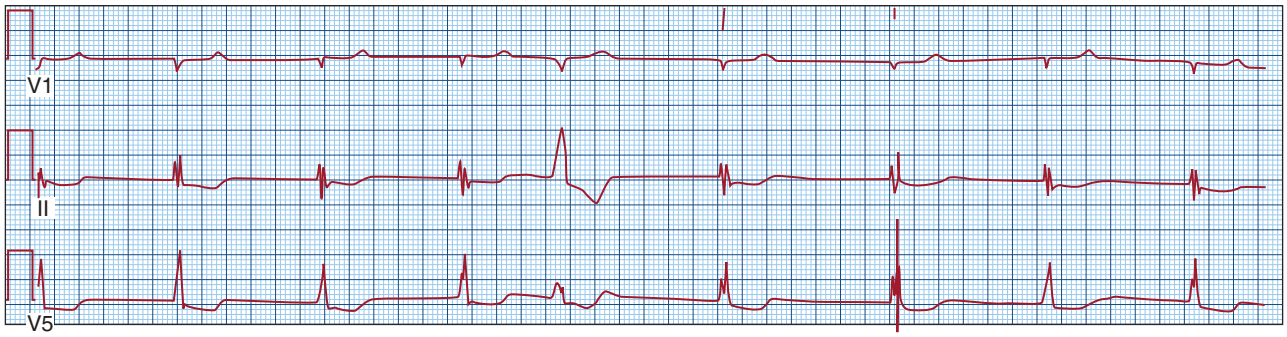


FIGURE 86–9. Atrial standstill. Rhythm strip demonstrates junctional rhythm with no anterograde or retrograde atrial activity. Atrial pacing in this patient could not achieve atrial capture, confirming atrial standstill.

A number of noninvasive and invasive tests are available to assist in the evaluation.

Electrocardiographic Recordings

Documentation of the various arrhythmias associated with sinus node dysfunction can be obtained with routine telemetric monitoring during hospitalization or with outpatient ambulatory 24- to 48-hour Holter recordings. If the symptoms are infrequent in nature, event recorders capable of intermittent or continuous monitoring can be used. Newer monitoring systems use remote real-time monitoring of patients' rhythm using wireless cellular technology as well as physician-defined triggers. If other noninvasive and invasive tests are inconclusive, patients may benefit from an implantable loop recorder, which has the ability to record both patient-triggered and automatic device-triggered events over a period of 18 to 36 months. Recently a miniaturized implantable monitor (Reveal LINQ, Medtronic, Minneapolis, MN) with wireless capability has become commercially available (Fig. 86–10). The implantation can easily be performed under local anesthesia in a subcutaneous location to the left of patient's fourth intercostal space.[27] The device transmits data to Medtronic's CareLink network automatically on a daily basis. Alerts are sent from CareLink to physicians when one of the following conditions is detected: patient-activated episodes, including episodes that occur within 20 minutes of a device-detected episode; device-detected tachycardia, asystole, bradycardia, and AF; AF burden above a threshold determined by the clinician; or ventricular rates (with or without ventricular fibrillation) above a threshold set by the clinician (Fig. 86–11). The storage capacity of the device allows for up to 59 minutes of ECG recordings from patient-activated episodes and automatically detected arrhythmias. Exercise testing to assess chronotropic incompetence can be valuable in select patients. Many patients with sinus node dysfunction may achieve peak heart rates similar to matched controls during specific exercise protocols; however, the time course of heart rate acceleration during activity and deceleration after activity may be markedly abnormal.

FIGURE 86–10. Miniaturized implantable cardiac monitor (Reveal LINQ, Medtronic, Minneapolis, MN) with wireless capability.

Autonomic Testing

Abnormalities of autonomic control of sinus node alone or in association with intrinsic sinus node disease can result in clinical symptoms and electrocardiographic findings of sinus node dysfunction. This can be assessed by observing the response of heart rate and rhythm with carotid sinus massage, head-up tilt testing, and Valsalva maneuver. Pharmacologic evaluation of the sinus node can be performed with atropine, isoproterenol, and propranolol. After injection of atropine 0.04 mg/kg intravenously, the heart rate increases by 15% and to more than 90 bpm. Isoproterenol infusion at 1 to 3 μg/min increases heart rate by 25%. Not all normal patients will respond as described. Patients with sinus node dysfunction show blunted heart rate responses to the preceding infusions. Another method to assess sinus node function is to measure the intrinsic heart rate (IHR) of the sinus node when the autonomic influence is negated by both atropine (0.04 mg/kg) and propranolol (0.2 mg/kg), using the following equation[28]:

$$\text{IHR} = 117.2 - (0.53 \times \text{age}) \text{ bpm}$$

Patients with sinus node dysfunction often demonstrate a decreased IHR.

Electrophysiology Study

Invasive electrophysiology study, in addition to assessing sinus node function, offers insight into other potential etiologies for symptoms of syncope and palpitations (AV block, supraventricular tachycardia, ventricular tachycardia [VT]) (see Chap. 82). The sinus node recovery time is a measure of sinus node automaticity and is measured as the longest pause after atrial overdrive pacing. SA conduction time is a measure of the interval from sinus node depolarization to activation of atrial muscle. With improved modalities for monitoring, it is less common to require electrophysiology studies to make this diagnosis.

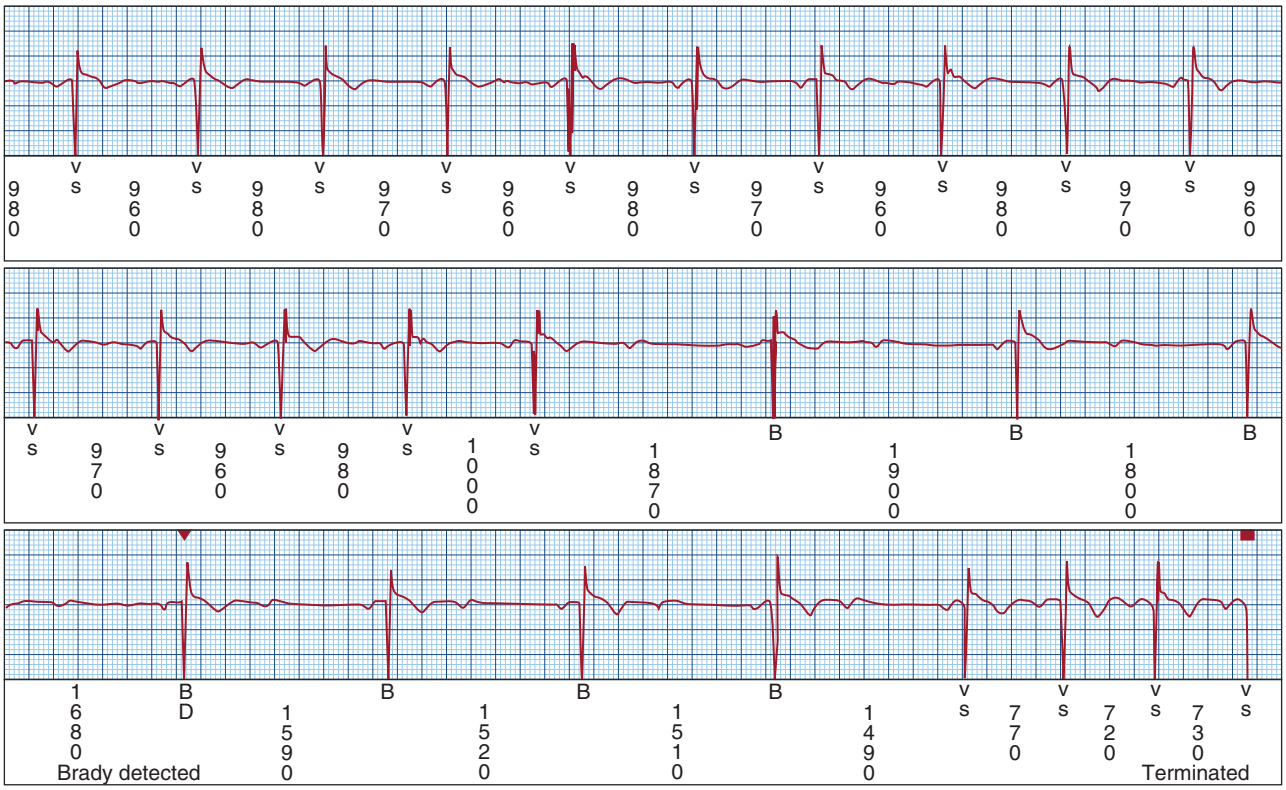


FIGURE 86–11. Electrograms obtained from the implantable monitor (LINQ) during an episode of near syncope shows sudden-onset 2:1 atrioventricular block with bradycardia.

MANAGEMENT

Pharmacologic Treatment

Theophylline and β-adrenergic agonists have been used to treat symptomatic bradycardia. Although they have been shown to increase the heart rate and reduce the duration of sinus pauses, they do not prevent recurrent syncope.[29] In patients with extrinsic causes for sinus node dysfunction, treatment should be directed toward the underlying etiology. Drugs known to depress sinus node function can be switched to other agents that lack effects on the cardiac conduction system. This is not possible, however, in many patients. Patients with paroxysmal atrial tachyarrhythmias either require drugs to maintain sinus rhythm or agents to control ventricular rate, both of which may have significant sinus node depressant effects. In many of these patients, pacemaker therapy becomes essential. At the time of diagnosis of sinus node dysfunction, the incidence of atrial fibrillation is reported to be approximately 8%, and the likelihood of developing new atrial fibrillation in this group of patients is approximately 5% per year.[30] The prevalence of thromboembolism was reported to be 15.2% in this group. This underscores the importance of monitoring for atrial fibrillation and the need for oral anticoagulation in intermediate- to high-risk patients.

Pacing Therapy in Sinus Node Dysfunction

The current indications for pacing in the setting of sinus node dysfunction are shown in Table 86–3. In this and subsequent tables, the format used for American Heart Association (AHA)/American College of Cardiology (ACC) guidelines is used, with class I to III indications denoting the degree of agreement for a given procedure or treatment that is useful and effective.[31]

Sinus node dysfunction is the most common indication for permanent pacemaker implantation in North America, accounting for more than 42% to 60% of new pacemaker implants. The optimal pacemaker choice is influenced by a number of factors. At the time of diagnosis of sinus node dysfunction, 17% of patients have been reported to have AV conduction abnormalities in the form of a PR interval > 240 ms, bundle branch block, H-V interval prolongation, AV Wenckebach rates < 120 bpm, and second- or third-degree AV block. The incidence of new AV block developing over time was reported to be < 2.7% per year.[32] Generally, if the patient has persistent atrial fibrillation, a single-chamber ventricular pacemaker (VVIR) is recommended. In all other situations, a rate-responsive dual-chamber pacemaker (DDDR) is used, whereas a single-chamber atrial pacemaker (AAIR) can be implanted if no evidence of AV conduction disease is present.

Clinical Trials and Pacing Mode

Many nonprospective, nonrandomized studies have suggested significant survival benefits with physiologic pacing compared with ventricular demand pacing (VVI mode) in patients with sinus node dysfunction. This led to randomized, large-scale prospective trials, the results of which are summarized in Table 86–4. The first randomized trial comparing atrial with ventricular pacing in 225 patients with sick sinus syndrome demonstrated significant reduction in the incidence of atrial fibrillation, thromboembolism, and cardiovascular mortality in the atrial pacing group.[33] Subsequent large-scale trials have not confirmed these mortality or stroke prevention benefits. The Canadian Trial of Physiologic Pacing (CTOPP)[34] randomized patients with symptomatic bradycardia without chronic atrial fibrillation to receive either a physiologic (atrial or dual-chamber) pacemaker or a ventricular pacemaker and showed no difference in stroke or cardiovascular mortality, but a decreased annual rate of atrial fibrillation in the physiologic pacing group (5.3%) compared with the ventricular pacing group (6.6%). Another large randomized trial of dual-chamber pacing versus ventricular pacing was MOST (Mode Selection Trial in Sinus Node Dysfunction),[35] which also confirmed the benefit of dual-chamber pacing

TABLE 86–3. Indications for Pacing in Sinus Node Dysfunction (ACC/AHA/HRS 2012 Revised Guidelines)[31]

Class I

1. Sinus node dysfunction with documented symptomatic bradycardia or sinus pauses. *(Level of Evidence: C)*
2. Symptomatic chronotropic incompetence. *(Level of Evidence: C)*
3. Symptomatic sinus bradycardia that results from required drug therapy for medical conditions. *(Level of Evidence: C)*

Class IIa

1. Sinus node dysfunction occurring spontaneously or as a result of necessary drug therapy, with heart rates < 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. *(Level of Evidence: C)*
2. Syncope of unexplained origin when major abnormalities of sinus node function are discovered or provoked in electrophysiologic studies. *(Level of Evidence: C)*

Class IIb

1. In minimally symptomatic patients, chronic heart rates < 40 bpm while awake. *(Level of Evidence: C)*

Class III

1. Sinus node dysfunction in asymptomatic patients. *(Level of Evidence: C)*
2. Sinus node dysfunction in patients with symptoms suggestive of bradycardia that are clearly documented as not associated with a slow heart rate. *(Level of Evidence: C)*
3. Sinus node dysfunction with symptomatic bradycardia caused by nonessential drug therapy. *(Level of Evidence: C)*

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society.

to reduce the risk for atrial fibrillation. The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial compared dual-chamber pacing with single-chamber ventricular pacing in patients older than 70 years of age with high-grade atrioventricular block.[36] Over a mean follow-up period of 4.6 years, there was no difference in annual mortality, atrial fibrillation, or heart failure between the groups. The DANPACE trial randomized 1415 patients with SND to AAIR mode or DDDR mode and followed them for a mean of 5.4 ± 2.6 years.[37] There was no difference in the primary outcome of all-cause mortality (29.6% vs 27.3%, $P = .53$). There was no difference in the secondary outcome of chronic atrial fibrillation, stroke, and heart failure. The incidence of paroxysmal atrial fibrillation (28.4% vs 23%, $P = .024$) and the need for pacemaker reoperation (22.1% vs 11.9%, $P < .001$) were higher in the AAIR group compared to the DDDR group. In a meta-analysis of randomized pacing modes, atrial-based pacing was associated with a significant reduction in atrial fibrillation of approximately 20% (95% confidence interval [CI], 0.77-0.89; $P = .00003$) and a borderline significant reduction in the risk of stroke of 19% (95% CI, 0.67-0.99; $P = .035$). The use of atrial-based pacing did not reduce mortality or the incidence of congestive heart failure.[38]

The failure to easily demonstrate clinical benefits of dual-chamber pacing has forced a rethinking of *physiologic pacing*. It is now well accepted that long-term right ventricular (RV) pacing causes a deterioration of left ventricular (LV) function through complex effects on regional ventricular wall strain and loading conditions. This deterioration is thought to result from intraventricular dyssynchrony between different regions of the left ventricle induced by RV apical pacing. Sweeney and coworkers demonstrated, by careful review of data from MOST, that an increase in the frequency of ventricular pacing in patients with sick sinus syndrome who had a narrow native QRS complex was associated with an increased incidence of atrial fibrillation and congestive heart failure.[39] These observations were confirmed by Wilkoff and colleagues in the Dual Chamber and VVI Implantable Defibrillator (DAVID) study, in which backup ventricular pacing and dual-chamber pacing were prospectively compared in patients with dual-chamber defibrillators.[40] The primary end point was a composite of congestive heart failure, hospitalization, and death, which was increased by a factor of 1.6 in patients with an increased frequency of ventricular pacing. Thus RV pacing is a double-edged sword, conferring atrioventricular synchrony but at the same time possibly negating its benefit by inducing ventricular dysfunction. Sweeney and associates[41] randomized 1065 patients with sinus node dysfunction and intact ventricular conduction to receive conventional dual-chamber pacing or dual-chamber minimal ventricular pacing with the use of new pacemaker features designed to promote atrioventricular conduction and prevent ventricular desynchronization. The hazard ratio for development of persistent atrial fibrillation in patients with dual-chamber minimal ventricular pacing as compared with those with conventional dual-chamber pacing was 0.60 (95% CI, 0.41-0.88; $P = .009$), indicating a 42% reduction in relative risk. We recommend that patients with sinus node dysfunction have the pacemaker programmed to either AAI(R) or DDD(R) with an algorithm that minimizes unnecessary ventricular pacing.

CAROTID SINUS HYPERSENSITIVITY AND VASOVAGAL SYNCOPE

The pathophysiology, diagnosis, and specific management of these disorders are discussed separately elsewhere in this textbook (see Chap. 90). A hypersensitive response to carotid sinus stimulation of 5 to 10 seconds is defined as asystole caused by sinus arrest or AV block of more than 3 seconds (cardio inhibitory), a substantial symptomatic decrease in systolic blood pressure of 50 mm Hg or more (vasodepressor), or both (mixed). The pathophysiology of carotid sinus syncope is complex and poorly understood and is hypothesized to result from abnormalities of neuromuscular structures surrounding the carotid sinus mechanoreceptors, a central defect of the autonomic nervous system, and association with atherosclerotic disease. Cardiac sympathetic neuronal activity is increased relative to age-matched controls in individuals with carotid sinus syndrome as measured using iodine-123-metaiodobenzylguanidine (123-I-MIBG) scanning.[42] Carotid sinus syncope predominantly occurs in elderly males with associated coronary artery disease. Although carotid sinus hypersensitivity is common, carotid sinus syncope is relatively rare, accounting for 11% to 19% of patients with syncope of undetermined cause. For patients with recurrent or severe carotid sinus syncope of the cardioinhibitory type, permanent pacemaker implantation is the accepted and proven modality of treatment as evidenced by many small randomized trials.[43] DDI or DDD pacemakers are generally the accepted mode of pacing for patients with carotid sinus syncope, whereas AAI pacing is contraindicated because many patients may demonstrate associated AV block. The current indications for pacing in hypersensitive carotid sinus syndrome and neurocardiogenic syncope are shown in Table 86–5.

Vasovagal syncope is a common condition caused by inappropriate reflex vasodilation and bradycardia and occasionally even asystole. Dual-chamber pacemakers with *rate-drop response* or *rate hysteresis* features are currently a treatment option in a select group of patients with recurrent syncope and refractory to conventional medical therapy.

TABLE 86–4. Randomized Trials of Pacing Modes in Patients with Sinus Node Dysfunction and/or Atrioventricular Block

Trial	Indication	Mode Comparison	No. of Patients	Follow-Up	End Points	Results
Danish[33]	SSS	AAI vs VVI	225	8 y	Total mortality, AF, thromboembolism	Atrial pacing significantly reduced mortality (RR 0.66), AF (RR 0.54), and stroke (RR 0.47).
PASE[35]	SSS and AVB	DDDR vs VVIR	427	30 mo	Primary: QOL Secondary: Total mortality, stroke, AF, HF	No change in QOL, mortality, stroke, or AF; improved QOL in SSS patients with physiologic pacing.
CTOPP[34]	SSS and AVB	DDDR/AAIR vs VVIR	2568	3 y	Primary: Stroke, CV mortality Secondary: Total mortality, AF, hospitalization for HF	No reduction in mortality or stroke; relative risk reduction of 18% for AF with physiologic pacing.
MOST[32]	SSS	DDDR vs VVIR	2010	33 mo	Primary: Total mortality, stroke Secondary: Composite of death, stroke, or hospital for HF, AF, QOL, HF score	No difference in primary or secondary end point except for AF; lower incidence of AF with DDD pacing (hazard ratio of 0.79).
UKPACE[36]	AVB	DDDR vs VVIR	2021	4.6 y	Primary: Total mortality Secondary: HF, AF, composite of stroke, TIA, or thromboembolic events	No difference in primary (mortality 7.4% vs 7.2%) or secondary end points.
SAVE PACe[41]	SSS	DDD vs DDD with minimal ventricular pacing	1065	1.8 y	Primary: Time to persistent AF Secondary: HF, mortality	42% relative risk reduction; 4.8% absolute risk reduction in AF.
DANPACE[37]	SSS	AAIR vs DDDR	1415	5.4 y	Primary: All-cause mortality Secondary: AF, stroke, HF, pacer reoperation	No difference in mortality or HF. No difference in mortality, chronic AF, stroke, HF. Increase in paroxysmal AF and need for reoperation in AAIR group.

Abbreviations: AF, atrial fibrillation; AVB, atrioventricular block; CTOPP, Canadian Trial of Physiologic Pacing; CV, cardiovascular; DANPACE, Danish Multicenter Randomized Trial on Single Lead Atrial Pacing Versus Dual Chamber Pacing in Sick Sinus Syndrome; HF, heart failure; MOST, Mode Selection Trial; PASE, Pacemaker Selection in the Elderly; QOL, quality of life; RR, relative risk; SAVE PACe, Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction Trial; SSS, sick sinus syndrome; TIA, transient ischemic attack; UKPACE, United Kingdom Pacing and Cardiovascular Events.

Three randomized but non–placebo-controlled trials have assessed the role of permanent pacemakers in patients with vasovagal syncope and cardioinhibitory response during tilt-table testing (Table 86–6).[44-45] The results of these trials are somewhat contradictory, and subsequent randomized, controlled trials[46,47] did not show a significant reduction in recurrent syncope. The Third International Study on Syncope of Uncertain Etiology (ISSUE-3) was a double-blind, placebo-controlled randomized study in patients > 40 years of age, three or more episodes of syncope in the previous 2 years, and ILR documented asystole of ≥ 3 seconds with syncope or ≥ 6 seconds without syncope. Of 89 patients, 77 were randomly assigned to dual-chamber pacing with rate drop response or to sensing only. There was a 32% absolute and 57% relative reduction of occurrence of syncope in patients with dual-chamber pacing compared to no pacing.[48] Cardiac pacing was effective in neurally mediated syncope patients with documented asystolic episodes in whom tilt table test was negative.[49] As a result, we recommend pacing therapy as a last resort for patients who are severely symptomatic and refractory to medical therapy.

DISORDERS OF ATRIOVENTRICULAR CONDUCTION

AV block occurs when atrial conduction to the ventricle is blocked at a time when the AV junction is not physiologically refractory. This can be caused by conduction block in the atrium, AV node, and/or His-Purkinje system. Using His-bundle electrogram recordings, three anatomic sites of AV block can be identified: AV nodal, intra-Hisian, or infra-Hisian. Block at the AV nodal level implies a favorable prognosis, whereas block at or below the His-bundle level implies an unfavorable prognosis. Surface ECGs often provide adequate information to make a diagnosis regarding the site of the block, whereas intracardiac recordings are often necessary to define the level of the block at or below the His.

PATHOPHYSIOLOGY OF ATRIOVENTRICULAR BLOCK

Transient or persistent AV block of varying degrees can occur in a variety of clinical situations (Table 86–7). Heightened vagal tone in

TABLE 86–5. Recommendations for Permanent Pacing in Hypersensitive Carotid Sinus Syndrome and Neurocardiogenic Syncope

Class I

1. Recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of more than 3 seconds. *(Level of Evidence: C)*

Class IIa

1. Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response of 3 seconds or longer. *(Level of Evidence: C)*

Class IIb

1. Significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing. *(Level of Evidence: B)*

Class III

1. A hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms or in the presence of vague symptoms. *(Level of Evidence: C)*
2. Situational vasovagal syncope in which avoidance behavior is effective. *(Level of Evidence: C)*

Abbreviation: AV, atrioventricular.

athletes or during sleep may be associated with first-degree or type I second-degree AV block and occasionally even complete heart block. The AV block in these situations is usually preceded by slowing of the heart rate. Increased vagal tone during sleep is often associated with obstructive sleep apnea and may lead to high grade AV block and long pauses (Fig. 86–12). This is a common occurrence and pacemaker therapy is rarely indicated in this situation. Vagally mediated AV block may occur in response to various stimuli such as carotid sinus hypersensitivity, coughing, swallowing, or micturition. Varying degrees of heart block have been described in a large variety of infectious diseases. Heart block associated with endocarditis may be transient or permanent. In patients with endocarditis and ring abscess, heart block may not resolve and pacing may be required. With Lyme disease, cardiac involvement may occur in 8% to 10% of patients. More than 50% of patients with cardiac involvement may develop advanced heart block requiring temporary pacing.[21] Even complete AV block generally resolves in 1 to 2 weeks, and permanent pacing is seldom necessary.[21] Chagas cardiomyopathy may be associated with persistent AV block.

Mutations in the cardiac-specific sodium channel gene (*SCN5A*) have been associated with progressive cardiac conduction system disease (PCCD), also referred to as Lev or Lenegre disease.[50] It is a relatively common cardiac conduction disorder characterized by age-dependent progressive delay in the propagation of cardiac impulse through the His-Purkinje system with right or left bundle branch block, eventually resulting in complete AV block. Patients with classic Lev disease demonstrate fibrosis within the proximal His bundle, whereas those diagnosed with Lenegre disease often demonstrate fibrosis within the more distal bundle branches and Purkinje fibers. *SCN5A* mutations can produce a variety of other phenotypes, including Brugada syndrome, congenital type 3 long QT syndrome (LQTS), idiopathic ventricular fibrillation, congenital sick sinus syndrome, atrial fibrillation, and dilated cardiomyopathy. Dominantly inherited mutations in the transient receptor potential melastatin 4 (*TRPM4*) gene are associated with isolated cardiac conduction disease (ICCD), giving rise to atrioventricular conduction block.[51] The TRPM4 channel mediates a Ca^{2+}-activated nonelective cationic current (I_{NSCca}) involved in cardiac conduction, pacemaking, and action-potential repolarization. Andersen-Tawil syndrome (LQT7) is caused by mutations in the

TABLE 86–6. Randomized Trials of Permanent Pacing in Patients with Recurrent Vasovagal Syncope

Trial	Inclusion Criteria	Treatment Groups	No. of Patients	Follow-Up	End Points	Results
VPS[44]	Syncope × 6, positive tilt-table test with relative bradycardia	DDD pacer with RDR vs no pacer	54	15 mo	First recurrence of syncope	85% relative risk reduction for recurrent syncope (22% in pacemaker vs 70% in no pacemaker arm)
VASIS[45]	> 3 syncope in last 2 y, positive tilt-table test with HR < 42 or asystole < 3 s, age > 42 y	DDI pacer with rate hysteresis vs no pacer	42	3.7 y (mean)	First recurrence of syncope	Significant reduction in recurrent syncope (5 % in pacemaker arm vs 61% in no pacer arm)
SYDAT[46]	> 3 syncope in last 2 y, positive tilt-table test with relative bradycardia, age > 35 y	DDD pacer with RDR vs atenolol	93	17 mo (mean)	First recurrence of syncope	Significant reduction in recurrent syncope, 4.3% in pacer group vs 25.5% in atenolol group
VPS II[47]	> 5 syncope/lifetime or > 2 syncope/2y, positive tilt-table test with relative bradycardia, age > 19 y	DDD pacer with RDR vs pacer in ODO mode	100	6 mo	First recurrence of syncope	Nonsignificant reduction in recurrent syncope (DDD-paced patients 30% vs 42% in ODO)
SYNPACE[48]	> 6 syncope/lifetime, positive tit-table test ≥ 3 syncope in 2 y, age > 40 y	DDD with RDR vs OOO	29	715 d (median)	First recurrence of syncope	No difference
ISSUE-3[49]	≥ 3 s asystole with syncope or ≥ 6 s asystole without syncope	DDD with RDR vs ODO	77	24 mo	First recurrence of syncope	32% absolute and 57% relative reduction of syncope

Abbreviations: HR, heart rate; ISSUE-3, International Study on Syncope of Uncertain Etiology 3; RDR, rate drop response; SYDIT, Syncope Diagnosis and Treatment Study; SYNPACE, Vasovagal Syncope and Pacing Trial; VASIS, Vasovagal Syncope International Study; VPS, vasovagal Pacemaker Study.

TABLE 86–7. Etiology of Atrioventricular Block

Reversible	Permanent
Physiologic	Idiopathic fibrosis
Heightened vagal tone (athletes, sleep apnea)	Lev disease
Autonomic mediated	Lenègre disease
Carotid sinus hypersensitivity	Congenital AV block
Neurocardiogenic syncope	Congenital heart disease
Coronary artery disease	Maternal systemic lupus erythematosus
Acute myocardial infarction	Coronary artery disease
Angina (Prinzmetal)	Acute myocardial infarction
Infectious disease	Ischemic cardiomyopathy
Infective endocarditis	Idiopathic cardiomyopathy
Myocarditis	Infiltrative disease
Viral, rickettsial, Lyme disease,	Amyloidosis
Rheumatic fever	Sarcoidosis
Metabolic	Hemochromatosis
Hyperkalemia	Infectious disease
Hypermagnesemia	Endocarditis
Addison disease	Syphilis
Traumatic	Tuberculosis
Catheter induced	Chagas disease
Radiofrequency energy	Collagen vascular disease
Surgery	Systemic lupus erythematosus
Drug induced	Rheumatoid arthritis
Digitalis	Scleroderma
β-Blockers	Traumatic
Calcium channel blockers	Surgery
Class III antiarrhythmic agents	Aortic, mitral, tricuspid valve surgery
Class I antiarrhythmic agents	Transcatheter aortic valve replacement (TAVR), ventricular septal defect repair
Adenosine	Septal myomectomy
Lithium	Radiofrequency ablation
Paroxysmal AV block	Radiation
Idiopathic paroxysmal AV block	Tumors
	Mesothelioma
	Rhabdomyoma
	Hodgkin lymphoma
	Melanoma
	Neuromuscular disease
	Myotonic dystrophy
	Kearns-Sayre syndrome
	Erb dystrophy
	X-linked muscular dystrophy
	Peroneal muscular atrophy

KCNJ2 gene encoding an inward rectifier potassium channel, *Kir2.1*. Patients may present with conduction abnormalities, such as AV block, BBB, or intraventricular conduction delay. This syndrome is characterized by potassium-sensitive periodic paralysis, ventricular arrhythmias, and dysmorphic features.[52] A variety of inherited heart disease has been recently reported to be associated with dilated cardiomyopathy and conduction system disease, including disorders of the nuclear envelope proteins lamin A and C.[35] Lamin A/C is necessary for the structural integrity of the nucleus; in the presence of *LMNA* mutation, myocardial cells exposed to mechanical stress undergo cell damage. *LMNA* mutations also are associated with dilated cardiomyopathy, with AV conduction defects referred to as "laminopathy."[53]

Acute Myocardial Infarction

AV block occurs in 12% to 25% of all patients with acute MI; first-degree AV block occurs in 2% to 12%, second-degree AV block in 3% to 10%, and third-degree AV block in 3% to 7%.[54] Ischemic injury can produce conduction block at any level of the AV or intraventricular conduction system. Second-degree type I AV block occurs more commonly in inferior than anterior MIs. Inferior infarctions are often associated early on with increased vagal tone causing sinus bradycardia and AV block. Most patients are asymptomatic, and rarely type I AV block may progress to complete AV block. Second-degree type II AV block occurs in 1% of patients with acute MI and predominantly occurs in patients with anterior infarctions. The risk of progression to complete AV block is high in these patients. Complete AV block can occur in both inferior and anterior infarction. In inferior MI, the block is typically at the level of the AV node and the escape rhythm generally arises from the AV junction, with a narrow QRS and an escape rate of 40 to 60 beats/min. The prognosis in these patients is generally good, as the AV block resolves in almost all patients within a few days and almost always by 1 week. Complete AV block resulting from anterior infarction is usually at the His or infra-Hisian level, and the escape rhythm is from the distal Purkinje fibers or the ventricle, with a wide QRS interval and a rate of 20 to 40 bpm. Because of the coexisting extensive infarction and pump failure, AV block resulting from anterior infarctions are associated with high mortality. In patients with acute MI, temporary pacing is generally indicated in patients with complete AV block at any level, type II second-degree AV block, and in patients with type I second-degree AV block if associated with symptomatic bradycardia. Although the incidence of complete AV block in acute MIs has decreased after thrombolytic therapy, the mortality still remains high. In the current era of percutaneous coronary intervention (PCI) for acute ST elevation MI, the incidence of second or third-degree AV block is significantly lower (3.2% in a retrospective study of 2073 patients).[55] In a recent study using the 2003 to 2012 National Inpatient Sample databases, the incidence of complete heart block complicating acute ST elevation MI was 2.2% and the in-hospital mortality was higher in patients with CHB compared to those without CHB (20.4% vs 8.7%).[56] The indications for permanent pacing in patients with acute MI are listed in Table 86–8. Patients with coronary artery disease and ischemic cardiomyopathy may develop persistent AV block. AV nodal block can occur transiently during episodes of ischemia, especially with Prinzmetal angina.

A variety of uncommon autoimmune, oncologic, infectious, and iatrogenic disorders can also lead to heart block and are listed in Table 86–7. Certain neuromuscular disorders (myotonic dystrophy, Kearns-Sayre syndrome, peroneal muscular atrophy, Erb limb-girdle dystrophy, Emory-Dreifuss muscular dystrophy, and X-linked muscular dystrophies) may give rise to progressive and insidiously developing conduction disorders of the His-Purkinje system. Myotonic dystrophy and Kearns-Sayre syndrome are associated with high incidence of unpredictable and rapidly progressive conduction system disease.[57] Complete heart block may occur after aortic or mitral valve replacement surgery and rarely after coronary artery bypass surgery. Preoperative right bundle branch block and multivalve surgery involving

FIGURE 86–12. Telemetry strip demonstrating an episode of high-grade atrioventricular (AV) block occurring during sleep. Note the sinus bradycardia associated with AV block suggesting increased vagal tone.

the tricuspid valve were shown to be strong independent predictors of postoperative heart block requiring permanent pacemaker implantation. Complete AV block is more common after surgical procedures to correct ventricular septal defects, tetralogy of Fallot, AV canal defects, or myectomy for hypertrophic obstructive cardiomyopathy. Transcatheter aortic valve replacement (TAVR) is a rapidly evolving technology for severe, calcific aortic stenosis. The incidence of complete heart block requiring permanent pacemaker following TAVR is significantly higher than the approximate 5% following surgical aortic valve replacement.[58,59] A recent meta-analysis of 41 studies including 11,210 patients undergoing TAVR showed that 17% required permanent pacemaker implantation (Fig. 86–13).[60] Two TAVR devices are most currently in clinical use in North America: the Edwards SAPIEN valve (ESV, Edwards Lifesciences Corp., Irvine, CA) and the CoreValve Revalving system (CV, Medtronics, Minneapolis, MN). The rate of PPM ranged from 2% to 51% in individual studies (with a median of 28% for the CV and 6% for the ESV). The rate of permanent pacemaker requirement is lower for the ESV compared to CV. The higher rate with CV may be a result of the design (self-expanding as compared to balloon expanding) and lower position in the LVOT.[61] Recent changes to the ESV (S3) were noted to be associated with a higher pacemaker implantation rate attributable to lower positioning of the valve in the left ventricular outflow tract.[61] Male sex, preexisting conduction abnormalities (first-degree AV block, right bundle branch block, left anterior hemiblock,) and intraprocedural AV block are predictors of need for permanent pacer post-TAVR.[62] Recent meta-analysis also suggests that new-onset LBBB post-TAVR is a marker of an increased risk of cardiac death and need for a permanent pacemaker at 1-year follow-up.[63]

Complete AV block can also occur in 0.5% to 2% of patients as a complication during radiofrequency catheter ablation of supraventricular arrhythmias, primarily AV node reentrant tachycardias and septal accessory pathways. Radiofrequency catheter ablation is also used to create permanent complete AV block in patients with paroxysmal and chronic atrial tachyarrhythmias (most frequently AF). This treatment option is reserved for the small group of patients in whom AV node–blocking drugs cannot control the heart rate or who are intolerant, unwilling, or unable to take drugs to maintain sinus rhythm or control the ventricular response during AF.

Congenital heart diseases such as corrected transposition of great arteries, ostium primum atrial septal defects, and ventricular septal defects may be associated with complete heart block. Congenital complete AV block is a rare anomaly that results from abnormal embryonic development of the AV node and is not associated with structural heart disease in 50% of cases. Congenital complete heart block is also associated with maternal lupus erythematosus. When congenital CHB is detected in utero in a child with a structurally normal heart, the condition is frequently associated with intrauterine exposure to maternal autoantibodies to Ro and La (ie, neonatal lupus); this situation has a

TABLE 86–8. Indications for Pacing in Atrioventricular Block Associated with Acute Myocardial Infarction

Class I

1. Persistent second-degree atrioventricular (AV) block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after acute myocardial infarction. *(Level of Evidence: B)*
2. Transient advanced (second- or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiology study may be necessary. *(Level of Evidence: B)*
3. Persistent and symptomatic second- or third-degree AV block. *(Level of Evidence: C)*

Class IIb

1. Persistent second- or third-degree AV block at the AV node level even without symptoms. *(Level of Evidence: B)*

Class III

1. Transient AV block in the absence of intraventricular conduction defects. *(Level of Evidence: B)*
2. Transient AV block in the presence of isolated left anterior fascicular block. *(Level of Evidence: B)*
3. Acquired left anterior fascicular block in the absence of AV block. *(Level of Evidence: B)*
4. Persistent first-degree AV block in the presence of bundle branch or fascicular block. *(Level of Evidence: B)*

better prognosis than when congenital heart disease is present.[64] Most children with isolated congenital complete AV block have a stable escape rhythm with a narrow complex. Pacing is generally indicated in children with complete heart block if the heart rate in the awake child is < 50 bpm or if associated with LV systolic dysfunction or ventricular arrhythmias. The indications for pacing in children, adolescents, and patients with congenital heart disease are outlined in Table 86–9.

Anti-Ro/SSA-associated AV block has been described in adults. Currently available data suggest two possible forms of anti-Ro/SSA-associated AV block in adults: (1) an acquired form and (2) a late progressive congenital form.[65] The acquired form is characterized by the presence of anti-Ro/SSA antibody in the affected subject. In these patients immunosuppressive therapy (methylprednisolone plus azathioprine) may normalize rhythm disturbances. In contrast, in the late progressive congenital form, anti-Ro/SSA antibodies are not detectable in the subjects while their mothers are seropositive. Immunosuppressive therapy has no clinical value in these patients. It is estimated that these two forms may represent at least 20% of all cases of isolated complete heart block of unknown origin in adults (10% of each form).

Cardiac sarcoidosis should be considered in the differential diagnosis in a young patient (20-40 years old) presenting with CHB.[66] Cardiac manifestations of sarcoidosis are present in at least 25% of patients with systemic sarcoidosis and can include Mobitz II, second-degree AV block, LBBB, RBBB, CHB (~30%), ventricular tachyarrhythmias, intracardiac masses, ventricular aneurysms, and dilated cardiomyopathy. Current expert consensus statement on arrhythmias associated with cardiac sarcoidosis recommends that in patients aged < 60 years presenting with unexplained Mobitz II second-degree AV block or complete heart block, further evaluation with high-resolution chest CT and/or cardiac MRI may be necessary to diagnose cardiac sarcoidosis.[67] Patients with conduction system disease and evidence of cardiac or sarcoidosis in other organs should undergo implantation of either a dual-chamber pacemaker or defibrillator.

Drug-induced bradycardia is a common and important clinical problem.[68] Many common drugs, including β-adrenergic blockers, calcium channel antagonists, digoxin, class I and III antiarrhythmic drugs, tricyclic antidepressants, phenothiazines, lithium, and donepezil (a cholinesterase inhibitor used to treat Alzheimer disease), can cause AV conduction disturbances. If the AV block is caused by drug toxicity, is expected to resolve, and is unlikely to recur, pacemaker implantation is generally considered unnecessary, according to current guidelines. However, if AV block occurs in the setting of drug use or toxicity, and the block is expected to recur even after the drug is withdrawn, pacemaker implantation may be considered (class IIb indication). In the majority of patients presenting with presumed drug-induced AV block, discontinuation of the offending medications does not obviate the need for pacemaker implantation.[69]

Paroxysmal AV block is defined as the sudden occurrence, during a period of 1:1 AV conduction, of a block of sequential atrial impulses resulting in a transient total interruption of AV conduction.[70,71] It is thus the onset of a paroxysm of high-grade AV block associated with a period of ventricular asystole before conduction returns or a subsidiary pacemaker escapes. It may occur in variety of clinical conditions associated with vagal stimulation (eg, coughing, swallowing, vomiting, micturition, during abdominal pain) or in the setting of His-Purkinje conduction system disease. Idiopathic paroxysmal AV block is a distinct form of syncope characterized by a long history of recurrent syncope as

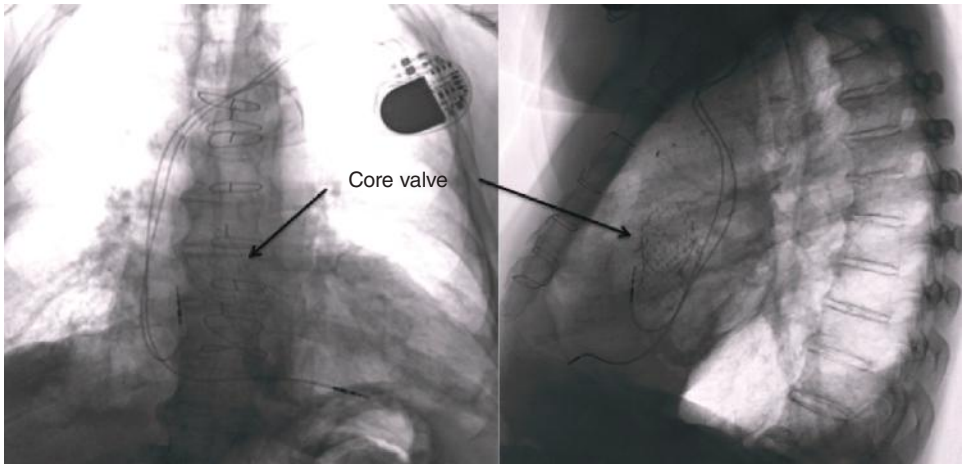


FIGURE 86–13. Transcutaneous aortic valve replacement (TAVR). Radiographs of a patient with Core Valve (Medtronic) and permanent pacemaker are shown. Complete heart block is a known complication of TAVR.

TABLE 86–9. Indications for Pacing in Children, Adolescents, and Patients with Congenital Heart Disease

Class I

1. Advanced second- or third-degree atrioventricular (AV) block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output. *(Level of Evidence: C)*
2. Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient's age and expected heart rate. *(Level of Evidence: B)*
3. Postoperative advanced second- or third-degree AV block that is not expected to resolve or persists at least 7 days after cardiac surgery. *(Level of evidence: B, C)*
4. Congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction. *(Level of Evidence: B)*
5. Congenital third-degree AV block in the infant with the ventricular rate < 55 bpm or with congenital heart disease and a ventricular rate < 70 bpm. *(Level of Evidence: C)*

Class IIa

1. Patients with sinus bradycardia for the prevention of recurrent episodes of intra-atrial reentrant tachycardia; sinus node dysfunction may be intrinsic or secondary to antiarrhythmic treatment *(Level of Evidence: C)*
2. Congenital third-degree AV block beyond the first year of life with an average heart rate < 50 bpm, abrupt pauses in ventricular rate that are two or three times the basic cycle length, or associated with symptoms resulting from chronotropic incompetence. *(Level of Evidence: B)*
3. Sinus bradycardia with complex congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 seconds. *(Level of Evidence: C)*
4. Unexplained syncope in the patient with prior congenital heart surgery complicated by transient complete heart block with residual fascicular block after a careful evaluation to exclude other causes of syncope. *(Level of Evidence: B)*
5. Patients with congenital heart disease and impaired hemodynamics resulting from sinus bradycardia or loss of AV synchrony. *(Level of Evidence: C)*

Class IIb

1. Transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block. *(Level of Evidence: C)*
2. Congenital third-degree AV block in the asymptomatic children or adolescents with an acceptable rate, narrow QRS complex, and normal ventricular function. *(Level of Evidence: B)*
3. Asymptomatic sinus bradycardia after biventricular repair of congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 seconds. *(Level of Evidence: C)*

Class III

1. Transient postoperative AV block with return of normal AV conduction. *(Level of Evidence: B)*
2. Asymptomatic postoperative bifascicular block with or without first-degree AV block after surgery for congenital heart disease in the absence of prior transient complete AV block. *(Level of Evidence: C)*
3. Asymptomatic type I second-degree AV block. *(Level of Evidence: C)*
4. Asymptomatic sinus bradycardia in the adolescent with longest R-R interval < 3 seconds and minimum heart rate > 40 bpm. *(Level of Evidence: C)*

a result of idiopathic paroxysmal AV block with long pauses, absence of cardiac and ECG abnormalities, absence of progression to persistent forms of AV block, and efficacy of cardiac pacing therapy.[72] These patients show an increased susceptibility to exogenous adenosine. Permanent pacemakers are effective in these patients to prevent symptoms such as syncope.

ELECTROCARDIOGRAPHIC MANIFESTATIONS

First-Degree Atrioventricular Block

Prolongation of the PR interval to > 200 ms constitutes first-degree AV block. It is most commonly caused by conduction delay within the AV node and occasionally caused by intra-atrial or infra-Hisian conduction delay. If the QRS duration is normal, the site of conduction delay is almost always within the AV node. If first-degree AV block occurs in the presence of bundle branch block, the conduction delay can be in the AV node (60% of cases), His-Purkinje system, or both. Patients with first-degree AV block have an excellent prognosis even when associated with chronic bifascicular block, as the rate of progression to third-degree AV block is low, and no specific therapy is indicated (Fig. 86–14).

Second-Degree Atrioventricular Block

Second-degree AV block is characterized by intermittent failure of conduction from the atria to the ventricles. If the AV block occurs with the atrial rate in the physiologic range, it is considered a primary arrhythmia. AV block in the setting of atrial tachyarrhythmias is generally a normal response. Based on the electrocardiographic patterns, second-degree AV block is classified into Mobitz types I and II.

Second-Degree Atrioventricular Block of the Wenckebach Type (Mobitz Type I)

Second-degree AV block of the Wenckebach type (Mobitz type I) is characterized by the following features: (1) progressive prolongation of the PR interval before a nonconducted P wave, (2) PR interval prolongation at progressively decreasing increments, (3) progressive shortening of R-R intervals, (4) pause encompassing the blocked P wave shorter than the sum of two P-P cycles, and (5) the last conducted PR interval before the blocked P wave longer than the next conducted PR interval (Fig. 86–15). Type I second-degree AV block often occurs with regularity leading to patterns of *group beating*. When type I second-degree AV block occurs in association with a normal QRS interval, block is almost always in the AV node. In the presence of a prolonged QRS interval, block may be in the AV node, His-Purkinje (rare), or both. Very long PR intervals are usually caused by a block in the AV node. Type I second-degree AV block occurs in a small percentage of normal people and not uncommonly in well-trained athletes. Most patients are asymptomatic, whereas some develop symptomatic bradycardia, near syncope, or occasionally syncope caused by progression to complete AV block.

Mobitz Type II Second-Degree Atrioventricular Block

Mobitz type II second-degree AV block is characterized by (1) constant P-P intervals and R-R intervals, (2) constant PR intervals before a nonconducted P wave, and (3) pause encompassing the nonconducted P wave equal to two P-P cycles. Type II AV block usually occurs in the presence of bundle-branch block and is almost always caused by a block in the His-Purkinje system (Fig. 86–16). Type II AV block rarely occurs in patients with normal QRS duration. Type II AV block frequently progresses to a complete AV block and may result in syncopal attacks.

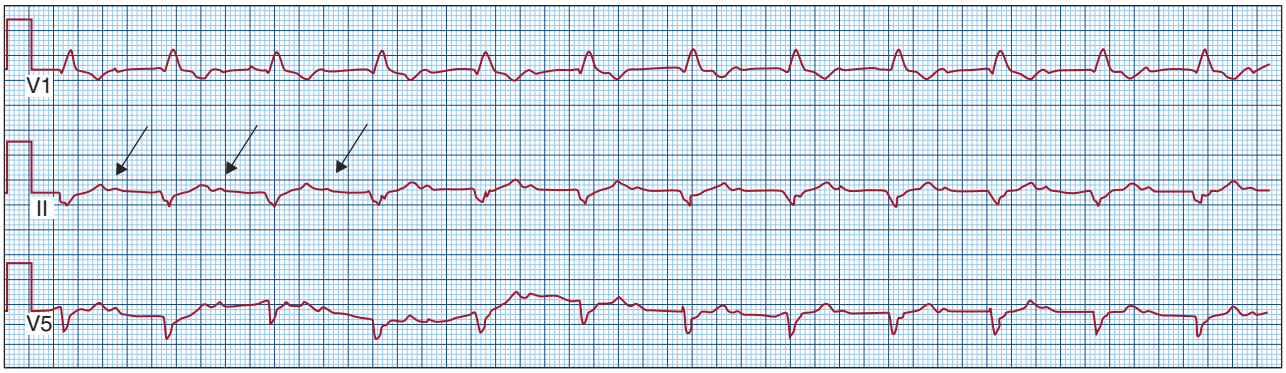


FIGURE 86–14. Rhythm strip of a patient with prolonged PR interval of 400 ms and bifascicular block (right bundle branch block and left anterior fascicular block) is shown.

2:1 Atrioventricular Block

In this form of second-degree AV block, every other P wave is not conducted, making it difficult to diagnose the level of AV block (Fig. 86–17). A 2:1 AV block pattern with normal QRS duration or with a very long PR interval generally suggests block in the AV node. A 2:1 AV block pattern in the presence of bundle branch block especially in the setting of normal PR interval favors block below the AV node, but is not diagnostic (Fig. 86–18). A prolonged electrocardiographic recording may sometimes reveal a transition to varying degrees of AV block (3:2 or 4:3), with type I or type II features that aid in the diagnosis. Rarely, Wenckebach conduction may be noted in the His-Purkinje system. Intracardiac recordings with a His-bundle catheter are sometimes necessary to determine the site of the block (Fig. 86–19). In patients with a 2:1 AV block, vagal maneuvers are helpful in diagnosing the level of AV block. Carotid sinus stimulation may worsen the degree of block if it is in the AV node, whereas slowing of the sinus rate may paradoxically improve the ratio of AV conduction and increase ventricular rate if the block is located in the His-Purkinje system. Similarly, atropine improves AV nodal conduction, but the increased sinus rate may worsen the ratio of AV conduction in patients with His-Purkinje block, resulting in worsened bradycardia. Hence atropine should be used with caution in patients with a 2:1 AV block and bundle branch block where His-Purkinje disease is strongly suspected.

High-Grade Atrioventricular Block

When two or more consecutive atrial impulses do not conduct to the ventricle, it is defined as high-grade AV block. It may be associated with a junctional or ventricular escape rhythm. Occasionally, runs of consecutive atrial impulses may fail to conduct to the ventricles for up to 10 to 20 s with or without an escape rhythm, resulting in ventricular asystole and syncope. The block is usually initiated by a conducted or blocked atrial or ventricular premature beat. The block persists until terminated by an escape beat. Unless a clearly defined reversible etiology is identified, permanent pacing is indicated.

Third-Degree Atrioventricular Block

Complete or third-degree AV block is characterized by failure of all P waves to conduct to the ventricle. This results in complete dissociation of P waves and QRS complexes. Complete AV block may occur as a result of block in the AV node or at the His-Purkinje level. In patients with block at the AV node level, the escape rhythm is usually junctional, with a narrow QRS complex (unless associated with preexisting bundle branch block), at rates of 40 to 60 bpm (Fig. 86–20). In complete heart block resulting from His-Purkinje disease, the escape rhythm is ventricular in origin, with a wide QRS interval and at rates of 20 to 40 bpm (Fig. 86–21).

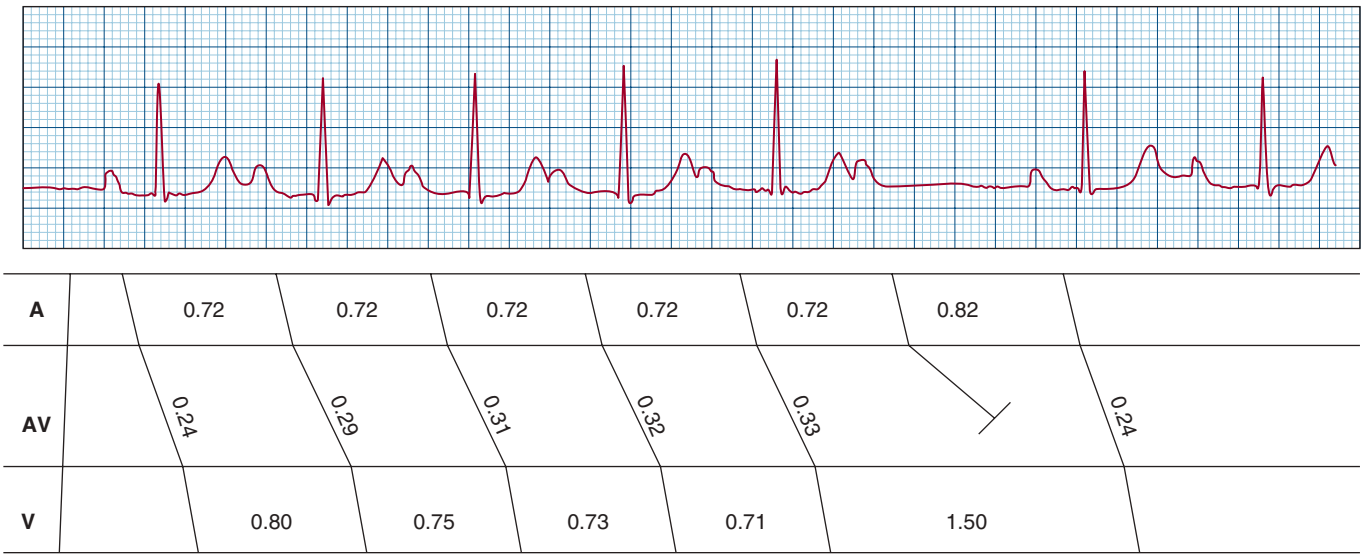


FIGURE 86–15. Type I second-degree atrioventricular (AV) block. A 6:5 AV Wenckebach periodicity is shown. Note that the PR interval progressively lengthens with a decreasing increment. This results in shortening of R-R intervals. The last conducted PR interval (0.33 seconds) is significantly longer than the next conducted PR interval (0.24 seconds).

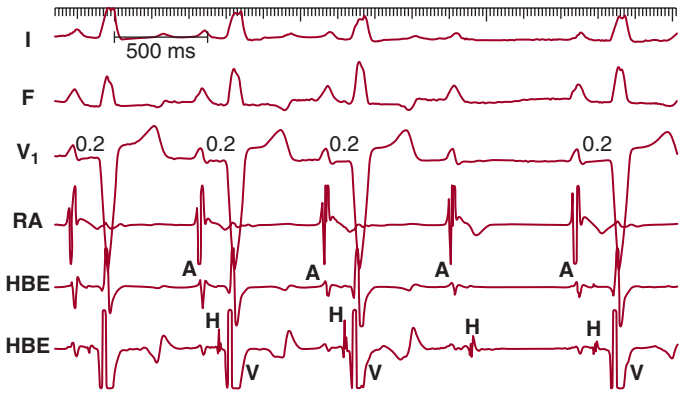


FIGURE 86–16. Type II second-degree atrioventricular block. Surface electrocardiogram, leads I, aVF, and V_1, and intracardiac electrograms from the right atrial (RA), proximal, and distal His bundle electrogram (HBE) catheters are shown. Surface ECGs show that the PR intervals are constant at 0.2 seconds with a left bundle branch block morphology of the QRS complex, and the fourth P wave is not followed by a QRS complex. The HBEs reveal that the site of block of the fourth P wave is below the His bundle.

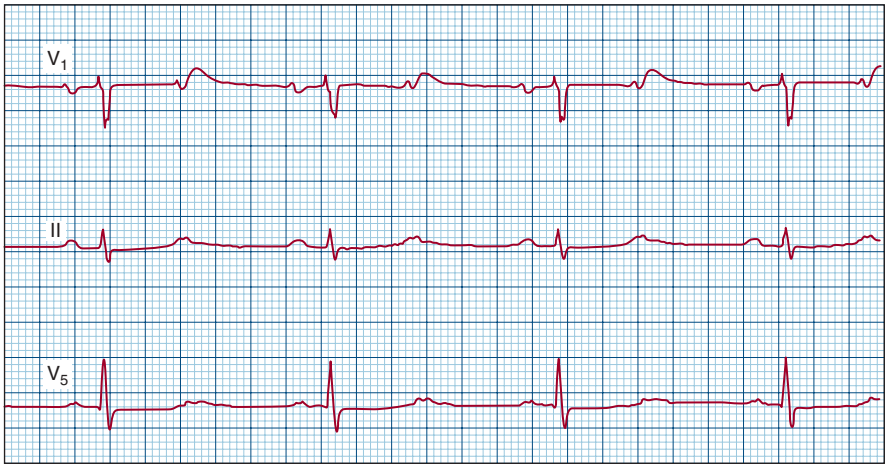


FIGURE 86–17. Surface electrocardiogram from leads V_1, II, and V_5 demonstrating 2:1 AV block with narrow QRS complexes. Although a definite diagnosis of type I or type II AV block cannot be made, longer rhythm strip recordings might reveal Wenckebach periodicity. Vagal maneuvers or exercise might assist further in the final diagnosis.

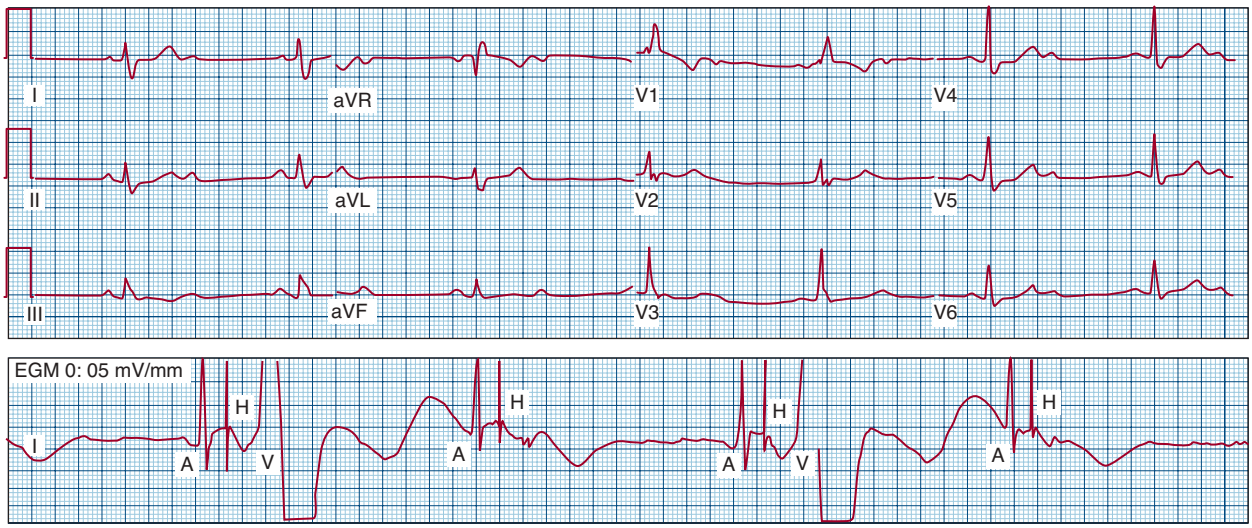


FIGURE 86–18. Twelve-lead surface electrocardiogram shows 2:1 AV block in the presence of normal PR interval and right bundle branch block. His bundle ECG in the lower panel shows 2:1 HV block. A, atrial; H, His; V, ventricle.

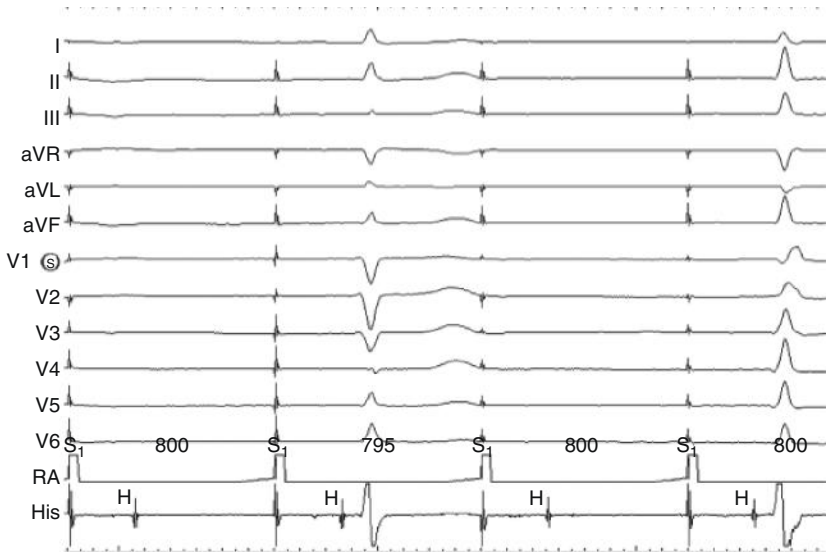


FIGURE 86–19. During atrial pacing at 75 bpm, 2:1 AV block is demonstrated. The first conducted QRS complex is narrow and the second conducted complex has right bundle branch block (RBBB). His bundle electrograms show 2:1 HV block. Pacing from His bundle location in this patient resulted in 1:1 conduction with narrow QRS complex suggesting intra-His block. A, atrial; H, His; V, ventricle; RA, right atrium.

Atrioventricular Dissociation

This rhythm is characterized by atrial and ventricular activity independent of each other. AV dissociation may be secondary to AV block (complete heart block) or physiologic refractoriness. AV dissociation can occur when the sinus rate is slower than the secondary junctional or ventricular pacemaker as in patients with sinus bradycardia. In contrast, AV dissociation can also occur in the presence of normal sinus rhythm and accelerated junctional (junctional tachycardia) or ventricular (ventricular tachycardia [VT]) rhythm with retrograde conduction block. In patients with complete heart block, the atrial rate is faster than the ventricular rate, whereas in AV dissociation, the ventricular rate is faster than the atrial rate. Although AV dissociation is present in complete heart block, it is not synonymous. AV dissociation is usually a manifestation of another rhythm abnormality, such as complete heart block, sinus bradycardia, or VT. Treatment is usually directed toward the underlying cause.

CLINICAL PRESENTATION

Symptoms in patients with AV conduction abnormalities are generally caused by bradycardia and loss of AV synchrony. Patients with significantly prolonged PR intervals may behave in a similar fashion to patients with pacemaker syndrome because of loss of AV synchrony. In patients with structural heart disease and LV dysfunction, this may result in worsening of heart failure. Symptoms caused by more advanced AV block may range from exercise intolerance, easy fatigability, dyspnea on exertion, dizzy spells, and near syncope to frank syncope. In patients with paroxysmal or intermittent complete heart block, these symptoms are episodic, and routine ECGs may not be diagnostic. Children and adolescents with isolated complete heart block may be generally asymptomatic, whereas some may develop symptoms later as adults because of chronotropic incompetence. Other late signs and symptoms include the development of congestive heart failure and nonsustained VT.

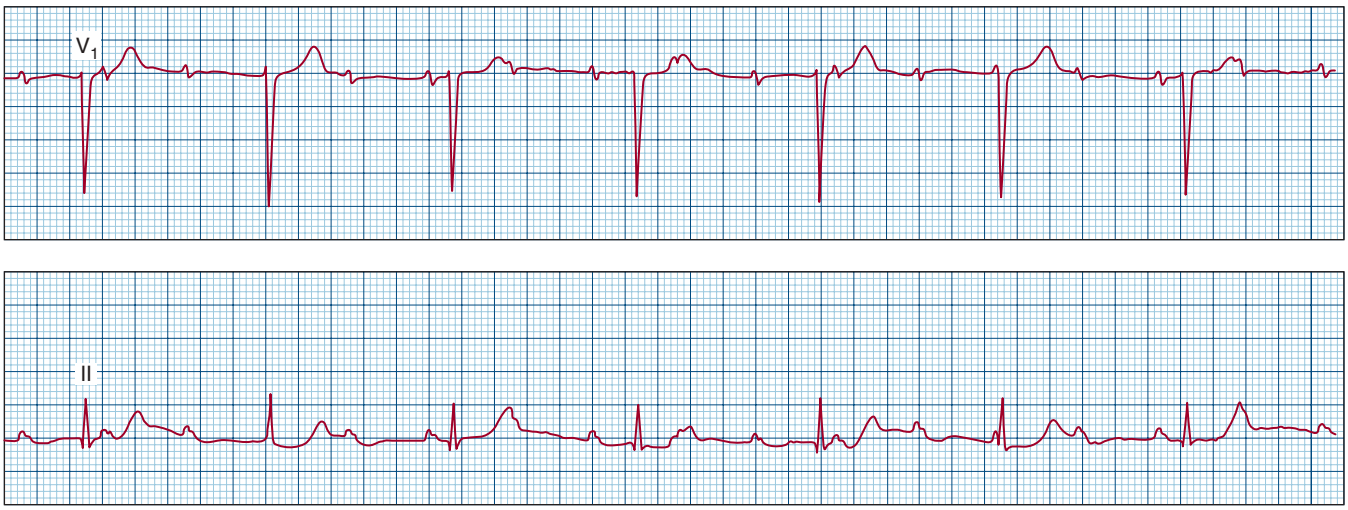


FIGURE 86–20. Complete heart block. Surface leads V_1 and II show sinus tachycardia at 120 bpm and are completely dissociated from a regular junctional (narrow QRS complexes) escape rhythm at 54 bpm. The site of atrioventricular (AV) block is most likely within the AV node.

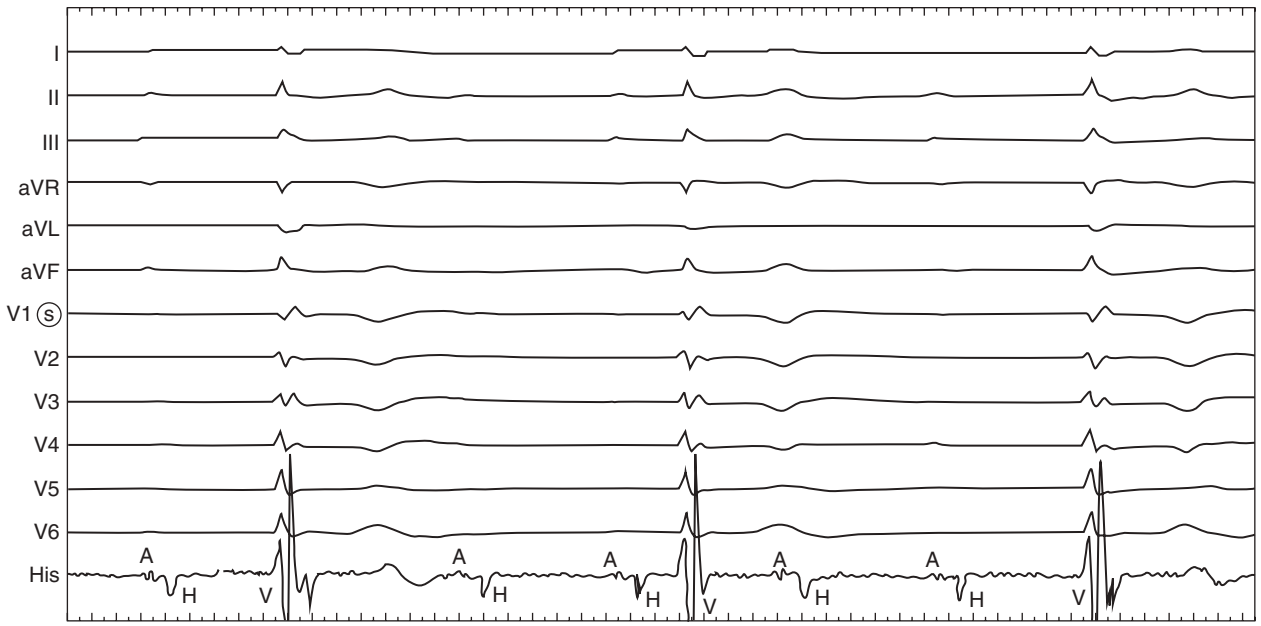


FIGURE 86–21. Complete heart block. Surface leads show complete heart block with right branch block morphology escape rhythm. Simultaneous His bundle electrogram demonstrates HV block. A, atrial; H, His; V, ventricle.

Children with complete heart block associated with structural heart disease are symptomatic very early on and have an increased risk for sudden death.

DIAGNOSTIC EVALUATION

The prognosis and treatment of AV block depends on its association with symptoms and the level of AV block. Routine 12-lead surface ECGs adequately establish the diagnosis of varying degrees of AV block in many patients. Analyzing the PR interval, QRS duration, Wenckebach phenomenon, and ventricular rates on the surface ECG provides important clues to the level of AV block. In certain situations such as 2:1 AV block, additional maneuvers may be necessary to establish the level of AV block. Responses to carotid sinus massage, atropine, and exercise are often very helpful.

In patients with complete heart block at the level of the AV node, the resultant junctional escape rhythm usually accelerates with exercise in contrast to the ventricular escape rhythm with infranodal block, which usually remains unchanged. Early studies using HB recordings have suggested that intra-His block contributes only 15% to 20% of patients with infranodal AV block.[73,74] However, recent observations suggest that in the majority of patients with infranodal AV block, the conduction disease is in the main His bundle, suggesting intra-His block.[4,75] In a consecutive series of 100 patients, AV nodal block was noted in 46% of the patients and infranodal (HV block) was observed in 54% of the patients.[4] Presence of split His potentials, narrow QRS in the setting of HV block, identification of distal His potential, and correction of His-Purkinje conduction by permanent His bundle pacing were used to identify a high (76%) percentage of patients with intra-His block (Fig. 86–22).

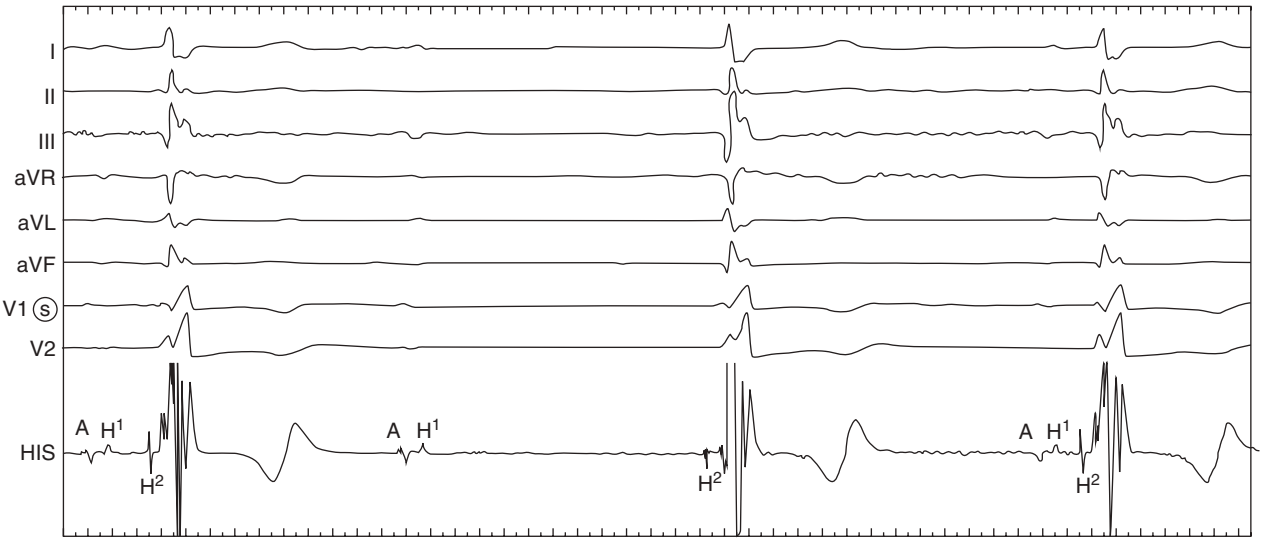


FIGURE 86–22. Second-degree atrioventricular (AV) block. Surface leads show second-degree AV block with right bundle branch block. His bundle electrograms demonstrate split His potentials (H1 and H2) and block in between the two His potentials suggesting intra-His block.

In patients with paroxysmal symptoms of near syncope or syncope and no significant conduction abnormalities on the surface ECG, prolonged electrocardiographic monitoring with 24- to 48-hour Holter recordings or 30-day event monitors may be helpful. Newer event monitors with automatic detection algorithms and cellular technology have increased the yield of these monitors. An implantable loop recorder may be necessary to establish the diagnosis, particularly in patients with infrequent symptoms. Electrophysiology study is indicated in patients with syncope or near syncope in whom high-grade AV block is suspected as the cause. In patients with structural heart disease, in addition to AV conduction disease, VT can also be a major etiology for syncope, and electrophysiology study can be very useful in establishing the diagnosis.

MANAGEMENT

Identifying transient or reversible causes for AV conduction disturbances is the first step in management. Withdrawal of any offending drugs, correction of any electrolyte abnormalities, or treatment of any infectious processes should be considered before permanent pacing therapy. If the drugs causing AV block are essential for treatment of other medical conditions, permanent pacing may be considered. However, it has become recently increasingly realized that many patients with AV block believed to be precipitated by drugs may develop recurrent heart block in follow-up even after discontinuation of the offending agent(s).[68] In patients with advanced AV block and hemodynamic decompensation unresponsive to drug therapy such as atropine or isoprenaline, as in digitalis toxicity, hyperkalemia, acute anterior MI, or Lyme myocarditis, temporary pacing should be instituted until AV block resolves or permanent pacing can be initiated. Temporary pacing can be accomplished by transcutaneous pacing systems in those patients at low to moderate risk for developing complete heart block or in patients with complete heart block and hemodynamically stable escape rhythms. Transcutaneous pacing for prolonged periods is very uncomfortable and transvenous pacing should be performed in patients with need for continuous active pacing.

Permanent pacemaker implantation is indicated in most patients with advanced heart block associated with symptoms. Permanent pacemakers are also indicated in asymptomatic patients with complete heart block and infra-Hisian second-degree AV block. Permanent pacing has clearly been shown to decrease mortality in patients with advanced heart block and syncope.[76] The indications for pacing in children with AV block and in adults with acquired heart block are described in Table 86–9 and Table 86–10, respectively.

Most patients with AV block require dual-chamber pacemakers, because this mode of pacing maintains AV synchrony and prevents development of pacemaker syndrome. In patients with associated sinus node dysfunction, dual-chamber pacemakers with a rate-responsive function (DDDR) are the preferred mode of choice. In patients with normal sinus node function and AV block, VDD pacing using a single lead with a series of electrodes for atrial sensing and ventricular pacing and sensing is an ideal mode of pacing, because it provides AV synchrony and rate responsiveness and is superior to single-chamber VVI pacing. In patients with chronic atrial fibrillation and bradycardia, rate-responsive single-chamber ventricular pacing (VVIR) is adequate. Early studies of comparison of pacing modes in a small number of patients with AV block had shown that physiologic pacing (DDD or VDD) enhanced survival compared with VVI pacing.[75,77] However, prospective, randomized, large-scale trials showed that dual-chamber pacing provided little benefit over ventricular pacing for the prevention of death (see Table 86–4). The incidence of

TABLE 86–10. Indications for Pacing in Acquired Atrioventricular Block in Adults

Class I

1. Third-degree and advanced second-degree atrioventricular (AV) block at any anatomic level, associated with any one of the following conditions:
   a. Bradycardia with symptoms (including heart failure) presumed to be caused by AV block. *(Level of Evidence: C)*
   b. Arrhythmias and other medical conditions requiring drugs that result in symptomatic bradycardia. *(Level of Evidence: C)*
   c. Documented periods of asystole ≥ 3.0 s or any escape rate < 40 bpm in awake, symptom-free patients. *(Level of Evidence: C)*
   d. Documented periods of pauses of 5 s or greater in symptom-free patients with atrial fibrillation. *(Level of Evidence: C)*
   e. After catheter ablation of the AV junction. *(Level of Evidence: C)*
   f. Postoperative AV block that is not expected to resolve after cardiac surgery. *(Level of Evidence: C)*
   g. Neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy, with or without symptoms, because there may be unpredictable progression of AV conduction disease. *(Level of Evidence: B)*
   h. Second-degree AV block with associated symptomatic bradycardia regardless of the type or site of block. *(Level of Evidence: B)*
   i. Asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 bpm or faster if cardiomegaly or left ventricular dysfunction is present or if the site of block is below the AV node *(Level of Evidence: B)*
   j. Second- or third-degree AV block during exercise in the absence of myocardial ischemia. *(Level of Evidence: C)*

Class IIa

1. Asymptomatic third-degree AV block with average awake ventricular rates of 40 bpm or faster in the absence of cardiomegaly. *(Level of Evidence: C)*
2. Asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiologic study. *(Level of Evidence: B)*
3. First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise *(Level of Evidence: B)*
4. Asymptomatic type II second-degree AV block with narrow QRS; when type II second-degree AV block occurs with a wide QRS, including isolated right bundle branch block, pacing becomes a class I recommendation. *(Level of Evidence: B)*

Class IIb

1. Neuromuscular diseases, such as myotonic muscular dystrophy, Erb (limb-girdle) dystrophy, and peroneal muscular atrophy, with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease. *(Level of evidence: B)*
2. AV block in the setting of drug use or drug toxicity when block is expected to recur even after drug is withdrawn. *(Level of evidence: B)*

Class III

1. Asymptomatic first-degree AV block. *(Level of Evidence: B)*
2. Asymptomatic type I second-degree AV block at the AV nodal level or not known to be intra- or infra-Hisian. *(Level of Evidence: C)*
3. AV block expected to resolve and/or unlikely to recur (eg, drug toxicity, Lyme disease, or during hypoxia in sleep apnea syndrome in absence of symptoms). *(Level of Evidence: B)*

pacemaker syndrome was as high as 26% in patients with ventricular pacing, necessitating cross-over to dual-chamber pacing in the pacemaker selection in the elderly trial.[35]

Growing recognition of the long-term adverse effects of RVA pacing has stimulated interest in strategies to promote physiologic pacing and to minimize or eliminate the deleterious effects.[78,79] There is controversy, however, regarding the optimal ventricular pacing sites and approach in patients undergoing permanent pacemaker implantation for AV block in whom ventricular pacing cannot be avoided.[80] Some investigators advocate LV or biventricular pacing, whereas others suggest a role for selective-site RV pacing. Alternative RV pacing sites (ie, non-RVA), including the His bundle, RV septum, RV outflow tract (RVOT), and dual-site right ventricle, have been investigated, but the benefits of alternative-site pacing remain unresolved.[81,82] In a recently published protect-pace study that randomized 240 patients with high-grade AV block to high septal or RV apical pacing (> 90% RV pacing), there was no significant difference in intrapatient change in LVEF between the two groups.[83]

Current guidelines indicate that cardiac resynchronization therapy (CRT) can be useful for patients with symptomatic HF and LVEF ≤ 35% who are expected to require frequent ventricular pacing (> 40%) after device implantation. However, the role of BiV pacing in patients with AV block and a normal LVEF or only modest depression of LV function remains unsettled. The Biventricular Versus RV Pacing in Heart Failure Patients With Atrioventricular Block (BLOCK HF) study was a prospective trial that randomized 691 patients with mild to moderate heart failure (NYHA Class I, II, or III), LV dysfunction (LVEF ≤ 0.50), and AV block to RV pacing versus BiV pacing with an average follow-up of 37 months.[84] Patients randomly assigned to biventricular pacing had a significantly lower incidence of the primary outcome (time to death from any cause, an urgent care visit for heart failure that required intravenous therapy, or a 15% or more increase in the left ventricular end-systolic volume index) over time than did those assigned to RV pacing (hazard ratio, 0.74; 95% credible interval, 0.60 to 0.90). The Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace) trial[85] randomized 1810 patients with AV block (mean age 73.5 years) to either RV pacing (n = 908) or BiV pacing (n = 902) and after a mean follow-up of 5.6 years, the groups had a similar rate of the composite end point that included time-to-death or first hospitalization as a result of heart failure, with a nonsignificant trend in favor of BiV (hazard ratio [HR] 0.87; $P = .08$). It is unclear which patients, if any, would benefit from biventricular pacing in the setting of normal LV function.

The His bundle is an ideal RV stimulation site from a hemodynamic standpoint. However, the technical challenge of long-term implementation of permanent His bundle pacing (HBP) had thus far been a major obstacle to its reliable application in routine clinical practice. By preserving normal electrical activation of the ventricles, HBP prevents ventricular dyssynchrony and its long-term consequences (Fig. 86–23). Recent studies have shown that permanent HBP is technically feasible and may be safe in routine clinical practice.[86,87] Preliminary data suggest that permanent HBP is associated with an improvement in exercise capacity, myocardial perfusion, ventricular synchrony, and LVEF compared to RV pacing.[88,89]

BUNDLE BRANCH BLOCK

Conduction disturbances that occur at various levels of the branches of the His-Purkinje system are described as bundle branch block or intraventricular conduction defects (IVCDs). In patients with isolated chronic right or left bundle branch block, the progression to advanced AV block is rare. Patients with bifascicular block (right bundle branch block and left anterior or posterior fascicular block) or left bundle branch block and left axis deviation have a 6% annual incidence of progression to complete heart block.[90] In patients with acute MI, the development of new bifascicular block and first-degree AV block is associated with a very high risk (42%) for progression to high-grade AV block. These patients are generally recommended to undergo prophylactic temporary pacing. Alternating bundle branch block, even in asymptomatic patients, is a sign of advanced conduction disturbance

FIGURE 86–23. Permanent His bundle pacing. Surface electrograms show sinus bradycardia and complete heart block. Intracardiac electrogram from the His bundle pacing (HBP) lead shows block at the atrioventricular nodal level. Pacing from the HBP electrode results in 1:1 His capture and narrow QRS complex.

TABLE 86–11. Indications for Pacing in Chronic Bifascicular and Trifascicular Block

Class I

1. Advanced second-degree or intermittent third-degree atrioventricular (AV) block. *(Level of Evidence: B)*
2. Type II second-degree AV block. *(Level of Evidence: B)*
3. Alternating bundle branch block. *(Level of Evidence: C)*

Class IIa

1. Syncope not demonstrated to be caused by AV block when other likely causes have been excluded, specifically ventricular tachycardia. *(Level of Evidence: B)*
2. Incidental finding at electrophysiology study of markedly prolonged HV interval (≥ 100 ms) in asymptomatic patients. *(Level of Evidence: B)*
3. Incidental finding at electrophysiology study of pacing-induced infra-His block that is not physiologic. *(Level of Evidence: B)*

Class IIb

1. Neuromuscular diseases such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of fascicular block with or without symptoms, because there may be unpredictable progression of AV conduction disease. *(Level of Evidence: C)*

Class III

1. Fascicular block without AV block or symptoms. *(Level of Evidence: B)*
2. Fascicular block with first-degree AV block without symptoms. *(Level of Evidence: B)*

in the His-Purkinje system and is considered a class I indication for permanent pacing. In patients with bundle branch block, His-bundle recordings can occasionally be helpful in identifying patients at high risk for progression to high-grade AV block. The incidental findings of markedly prolonged H-V interval (> 100 ms) or atrial-pacing–induced infra-Hisian block[91] that is not physiologic during an electrophysiology study are considered to indicate high risk for progression to advanced AV block, and prophylactic permanent pacing is recommended (Table 86–11). Intraventricular conduction disturbances are usually associated with significant structural heart disease, especially dilated (ischemic or idiopathic) cardiomyopathies, and are a marker of poor prognosis both in terms of advanced heart failure and increased mortality in these patients. Left bundle branch block (LBBB) in patients with cardiomyopathy is associated with significant ventricular dyssynchrony, worsening heart failure, and increased mortality. Biventricular pacing in these patients has been shown to improve heart failure and decrease mortality.[92,93] In a subgroup of patients with nonischemic cardiomyopathy, biventricular pacing can normalize LV function (hyperresponders), raising the possibility of LBBB-induced cardiomyopathy.[94] Recent evidence also suggests that bundle branch block is often caused by to disease in the proximal His bundle and may be amenable to correction by permanent His bundle pacing.[95,96]

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CHAPTER 87

ANTIARRHYTHMIC DRUGS

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PRINCIPLES OF ANTIARRHYTHMIC DRUG THERAPY

The treatment of patients with tachyarrhythmias has evolved dramatically over the last several decades. However, even with advances in catheter ablation and implantable cardioverter-defibrillators, antiarrhythmic drug therapy remains a cornerstone in the treatment of nearly every form of cardiac arrhythmia. An in-depth knowledge of the pharmacology of antiarrhythmic drugs, including their pharmacokinetics and pharmacodynamics, is essential to their successful and safe implementation (Table 87–1).

MECHANISMS UNDERLYING ANTIARRHYTHMIC AND PROARRHYTHMIC EFFECTS

The development of cardiac arrhythmias and drug-induced proarrhythmias can be a result of abnormal impulse formation (ie, enhanced automaticity and triggered activities) and/or reentry. This section provides a brief overview of ionic and cellular mechanisms underlying the antiarrhythmic and proarrhythmic effects of the drugs.

ION CHANNEL PHYSIOLOGY

Antiarrhythmic drugs exert their effects on cardiac electrical impulse formation and propagation via their interaction with ionic channels or with membrane receptors and cellular pumps that subsequently influence ionic currents across the cell membrane. Cardiac ionic currents commonly targeted by antiarrhythmic drugs include inward sodium current (I_{Na}), L-type calcium current ($I_{Ca,L}$), and delayed rectifier outward potassium current (I_K), which consists of two components—a rapidly activating component (I_{Kr}) and a slowly activating component (I_{Ks}). Although transient outward potassium current (I_{to}) is not commonly influenced by currently available antiarrhythmic drugs, it has been shown to contribute importantly to the genesis of polymorphic ventricular tachycardia and ventricular fibrillation.[1] Therefore, antiarrhythmic drugs with selective I_{to} blockade will be favored in future drug development.

Antiarrhythmic drugs that block the sodium channel appear to bind selectively to the channel during designated states and dissociate from the channel during the other states. Therefore, a sodium channel blocker will block the sodium channel differently depending on pathologic conditions. The maximal velocity of change in membrane potential during phase 0 (V_{max}) is correlated with influx of sodium ions through opened sodium channels and this is the major driving force for electrical conduction in atrial, His-Purkinje, and ventricular tissues. Drug binding occurs during phase 0 and phase 2 and dissociation occurs during phase 4. Class Ic drugs, which demonstrate slow dissociation kinetics, cause conduction slowing that manifests as P-wave and QRS widening on the surface electrocardiogram (ECG) during tachycardia because there is less time for dissociation and more opportunity for drug binding. Class Ib drugs have only a modest effect on action potential phase 0 under normal conditions. However, in ischemic myocardium with reduced membrane potential, voltage- and time-dependent recovery of the sodium channel from inactivation is delayed, such that binding of class Ib drugs to the channel is significantly increased. This explains the greater activity of class Ib antiarrhythmic drugs under conditions of myocardial ischemia. In contrast, atrial repolarization is faster compared with the ventricles and is associated with rapid transition of the atrial sodium channel from the inactivated to the resting state. Therefore, class Ib drugs play little role in atrial arrhythmias.

A few channels may remain open through sustained depolarization, the so-called *late* (or *slow*) $I_{Na\text{-}L}$,[2] and contribute to the action potential duration. Compared with the epicardium and endocardium, the submyocardium of the left ventricle (M cells) has a larger late $I_{Na\text{-}L}$.[3] Increasing evidence suggests that, as a result of its slow inactivation and recovery kinetics, $I_{Na\text{-}L}$ plays a central role in the rate dependence of the action potential duration (APD) and QT duration as well as in the reverse use-dependence of select APD/QT-prolonging agents.[4]

$I_{Ca,L}$ is responsible for the prolonged plateau phase (phase 2) of the action potentials of atrial, His-Purkinje, and ventricular cells and is the major inward current responsible for phase 0 depolarization in sinus and atrioventricular (AV) nodal cells. Consequently, calcium channel blockade causes slight action potential shortening in the atria, His-Purkinje system, and ventricles; depresses the slope of diastolic depolarization and action potential amplitude; and prolongs the effective refractory period in sinus and AV nodal cells. L-type calcium channels may reactivate during the action potential plateau under conditions of delayed ventricular repolarization (ie, long QT syndrome). This may lead to early afterdepolarization (EAD) capable of initiating a specific form of polymorphic ventricular tachycardia termed *torsade de pointes* (TdP).[5] In addition, a larger calcium influx via L-type calcium channel

TABLE 87–1. Vaughan-Williams Classification of Antiarrhythmic Drugs

	Action	Example Drugs
I	Sodium channel blockade	
Ia	Block sodium channel in open state with an intermediate recovery from block; also, inhibit I_{Kr} at relatively lower concentrations; moderate phase 0 depression and conduction slowing, prolonging of action potential duration.	Quinidine, procainamide, disopyramide
Ib	Block sodium channel in inactivated state with a fast time constant of recovery from block; minimal effect on phase 0 upstroke; no change or slight shortening of action potential duration.	Lidocaine, mexiletine
Ic	Block sodium channel in open state with slow recovery from block; marked phase 0 depression and conduction slowing; small or no effect on repolarization.	Flecainide, propafenone
II	β-Adrenergic receptor blockade.	Propranolol, metoprolol, atenolol, esmolol, acebutolol, pindolol, nadolol, carvedilol, labetalol, and bisoprolol
III	Potassium channel blockade and/or inward current enhancer.	*d,l*-Sotalol, dofetilide, amiodarone, bretylium, ibutilide, dronedarone
IV	Calcium channel blockade.	Verapamil, diltiazem

increases the likelihood of calcium overloading in the sarcoplasmic reticulum (SR) under certain pathologic conditions. Oscillatory release of calcium from SR increases Na/Ca exchange, resulting in the genesis of delayed afterdepolarization (DAD) and triggered activity.[6]

I_{Kr} and I_{Ks} are the major repolarizing currents in the heart, and their blockade leads to an increase in action potential duration and effective refractory period in the atria, AV node, His-Purkinje fibers, ventricles, and accessory pathways. Therefore, the drugs that inhibit I_{Kr} and/or I_{Ks}, such as sotalol and dofetilide, have value in the treatment of reentrant arrhythmias such as atrial fibrillation, atrial flutter, and monomorphic ventricular tachycardia. The majority of antiarrhythmic and noncardiac drugs that prolong the QT interval and induce TdP also block I_{Kr}.

The role of I_{to} in arrhythmogenesis has been highlighted in the past two decades. A prominent I_{to}-mediated action potential notch in the ventricular epicardium, but not endocardium, produces a transmural voltage gradient during early ventricular repolarization that could register as a J-wave or J-point elevation on the ECG.[7] If the I_{to}-mediated notch is deep enough, epicardial action potential dome at phase 2 is sensitive to a change in the net repolarization current. An increase in the net repolarization current, resulting from either a decrease in inward currents or augmentation of outward currents, may result in partial or complete loss of the dome, leading to a transmural voltage gradient that manifests as ST-segment elevation.[8] Heterogeneous loss of I_{to}-mediated action potential dome, particularly when it is complete, results in marked repolarization dispersion on the epicardium surface, leading to reentry at action potential phase 2 (ie, so-called *phase 2 reentry*). The extrasystole produced via phase 2 reentry occurs often on the down limb of the T wave (R-on-T phenomenon). This may, in turn, initiate polymorphic ventricular tachycardia or fibrillation.[8]

In structurally normal hearts, the I_{to}-mediated J wave is the intrinsic link for ST-segment elevation among early repolarization syndrome, idiopathic ventricular fibrillation, and Brugada syndrome. Therefore, these syndromes are now referred to as *J-wave syndromes*.[1,9-11] This explains why quinidine, a class IA drug that also exhibits an additional inhibitory effect on I_{to}, is effective in preventing ventricular fibrillations in J-wave syndromes.[12-14]

Use Dependence

Blockade of inward currents may be use dependent. The class Ic drugs dissociate from the sodium channels in the resting state very slowly, exhibiting strong use dependence that manifests as a marked increase in sodium channel blockade during tachycardia. This is thought to be responsible for the increased efficacy of the class Ic antiarrhythmic drugs in slowing and converting tachycardia with minimal effects at normal sinus rates. However, strong use dependence of a drug on I_{Na} may be proarrhythmic (eg, flecainide-induced atrial flutter or ventricular tachycardia) when the effect of the drug on conduction slowing is stronger than its effect on the effective refractory period.

Reverse Use Dependence

As opposed to the use dependence observed for drugs that block the sodium and calcium channels, inhibition of I_{Kr} is enhanced during bradycardia when the channel is "not frequently used," leading to more significant action potential prolongation at slow heart rates. The mechanism may be related to the dependence of I_{Kr} blockade on extracellular potassium concentration.[15] However, reverse use dependence does occur in an extracellular environment where K^+ concentration is unchanged, and it is likely a result of an effect on $I_{Na\text{-}L}$. Block of $I_{Na\text{-}L}$ blunts the normal rate dependence of APD/QT and abolishes reverse use dependence.[16]

REENTRY

Development of reentry using an anatomic circuit, for example around a scar tissue secondary to myocardial infarction, is determined by the wavelength of the reentrant wavefront and the size of the circuit. The wavelength of the reentrant wavefront is equal to the product of the conduction velocity times the effective refractory period of myocardial tissue in the pathway and should be significantly shorter than the length of the reentrant circuit for maintenance of circus movement. Conduction velocity of the electrical impulse in the atria, His-Purkinje, and ventricles is largely determined by the intensity of the fast inward sodium current that contributes to the rapid upstroke (V_{max}) of the action potential. Therefore, class Ic antiarrhythmic drugs may predispose to the development of monomorphic ventricular tachycardia in patients with coronary artery disease as a result of the drugs' reduction of V_{max} of the action potential and conduction velocity that surpasses the drugs' effects to prolong the effective refractory period.[17] However, antiarrhythmic drugs that prolong the effective refractory period without influencing conduction and thus the wavelength of a reentrant impulse are useful in suppressing reentrant arrhythmias.

ABNORMAL IMPULSE FORMATION

Abnormal Automaticity

Normal automaticity of cardiac cells is the consequence of spontaneous diastolic depolarization caused by a net inward current during phase 4 of action potential. Abnormal automaticity, which is caused by either enhanced normal automaticity or spontaneous activity in ventricular and atrial myocardium, may occur with heightened

β-adrenergic tone or reduced resting membrane potentials, such as ischemia or infarction.[18] β-Adrenergic receptor or calcium channel blockers are useful in treatment of arrhythmias caused by abnormal automaticity. The hyperpolarization-activated "funny" current (I_f, also called *pacemaker current*) may play an important role in enhanced automaticity such as in inappropriate sinus tachycardia. Blockade of this current is a promising treatment option for patients with inappropriate sinus tachycardia.[19]

Afterdepolarizations and Triggered Activity

Afterdepolarization can be divided into two subclasses: EADs and DADs. EADs often occur in M cells or endocardium because these action potentials prolong disproportionally with drugs that block I_{Kr}, an ionic current targeted by most QT-prolonging drugs.[5,20] Antiarrhythmic drugs that inhibit $I_{Ca,L}$ or shorten action potential duration by blocking the sodium current, such as mexiletine, suppress EADs. Calcium channel and β-adrenergic blockers suppress DADs, and therefore DAD-mediated arrhythmias, by reducing intracellular calcium overload.

PROARRHYTHMIA

Proarrhythmic and antiarrhythmic effects of a drug are two sides of the same coin. Antiarrhythmic drugs intended to suppress arrhythmias may potentially worsen a preexisting arrhythmia or cause a new arrhythmia. The mechanisms responsible for cardiac arrhythmias are complicated, and any intervention may be antiarrhythmic in some circumstances and proarrhythmic in others.

Atrial Proarrhythmia

When class Ic antiarrhythmic drugs are used for the treatment of supraventricular tachycardia, they can cause atrial flutter, often with slower rates (~200 bpm). This is seen in patients with atrial fibrillation treated with the class Ic drugs flecainide and propafenone. The slowed atrial flutter may be associated with 1:1 AV conduction with markedly rapid ventricular rates. Therefore, dosing with an AV nodal blocking agent should be considered with a sodium channel blocker in patients with atrial fibrillation and intact AV nodes.

Adenosine and digitalis occasionally promote the development of atrial fibrillation by shortening the atrial effective refractory period. Shortening of the refractory period reduces the wavelength of the reentrant wavefront, so that reentry can occur in smaller reentrant substrates.

Ventricular Proarrhythmia

Ventricular proarrhythmias can generally be divided into two categories based on mechanisms and ECG features: monomorphic ventricular tachycardia and TdP.

A key factor in the genesis of monomorphic ventricular tachycardia is the availability of an anatomic reentrant pathway such as scar tissue or tricuspid and mitral rings. Any drug that causes conduction slowing greater than effective refractory period prolongation has the potential to facilitate the development of reentrant arrhythmias. Class Ic drugs have the highest risk to cause this type of proarrhythmia and to increase mortality in patients with coronary artery disease and left ventricular systolic dysfunction.[21-23] Myocardial ischemia seems to play a pivotal role in the genesis of proarrhythmia with class Ic drugs. Conversely, proarrhythmia rates are nearly zero when class Ic drugs are used for atrial arrhythmias in patients with a structurally normal heart.[24]

TdP requires QT prolongation.[8] It is widely accepted that TdP is initiated by EAD-dependent triggered activity and maintains itself via functional reentry.[5] Class Ia and class III antiarrhythmic drugs that block I_{Kr} and/or increase late I_{Na} may facilitate the development of TdP. Interestingly, amiodarone, a commonly used class III antiarrhythmic drug, significantly prolongs the QT interval but rarely causes TdP. Amiodarone prolongs the action potential duration without producing EADs and reduces transmural dispersion of repolarization, probably as a consequence of its effects on multiple ionic channels and receptors.[25] Dronedarone, a noniodinated benzofuran derivative of amiodarone that was approved for treatment of atrial fibrillation in 2009, also causes QT prolongation without a significant risk of TdP.[26]

Marked QT prolongation and resultant TdP are more likely to occur in patients with reduced repolarization reserve. Clinical diseases or factors that are associated with reduced repolarization reserve include congenital long QT syndrome, bradycardia, female sex, ventricular hypertrophy, electrolyte disturbances such as hypokalemia and hypomagnesemia, and coadministration of other QT-prolonging agents or drugs that delay clearance of the drugs from the body.

PHARMACOKINETICS OF ANTIARRHYTHMIC DRUGS

Pharmacokinetics describes the relationship between drug administration and plasma concentration. It is assumed that the plasma concentration reflects, in a general sense, myocardial concentrations and thus the availability of the drug at its site of action. The pharmacokinetics of antiarrhythmic drugs are variable and not predictable by drug classification or by knowledge of the drug's chemical structure.

ABSORPTION/BIOAVAILABILITY

Absorption describes the movement of orally administered drug from the gut lumen to the systemic circulation, and the efficiency of this absorption is defined as *bioavailability*. Those factors that influence passage of the drug through the gut wall into the portal circulation and through the liver will have an effect on drug bioavailability. Thus diseases that affect bowel motility, bowel wall blood flow, gastric and bowel pH, and presystemic or "first-pass" hepatic clearance will, to some extent, influence the amount of drug that is available to the systemic circulation.

A common way to extend interdosing intervals during treatment with drugs that have a relatively short plasma half-life is to formulate them into a sustained-release preparation. These preparations can be particularly affected by changes in bowel pH and other conditions within the gut that influence the amount of drug that is absorbed from the gastrointestinal tract. Drugs can also have altered absorption because of intraluminal binding by other substances, such as milk and antacids. Finally, the physiochemical properties of the drug itself can have an effect on absorption.

Absorption of antiarrhythmic drugs is also dependent upon the solubility of the drug, which is affected by its intrinsic chemical and physical makeup, as well as the composition of the medium. Weak bases are rapidly dissolved in acid medium, and therefore, the use of antacids can slow the absorption of a weakly basic drug by increasing gut pH. In clinical situations, high intestinal pH, caused by such factors as bacterial overgrowth syndrome, can reduce the bioavailability of antiarrhythmic drugs. Thus, for patients with serious arrhythmias, especially those that are controlled by drugs that have a relatively narrow toxic-to-therapeutic ratio, reassessing plasma concentration or clinical efficacy during conditions of altered bowel physiology or pathology is relevant.

Finally, many antiarrhythmic drugs have a *food-fast effect*; that is, the bioavailability of a drug may be changed several-fold in the presence of

food or during fasting. A notable example is oral amiodarone, which is three times more bioavailable after a high-fat meal.[27] For such drugs, providing the patient with specific information as to the timing of drug ingestion with relationship to meals is important to maintain a predictable and reproducible plasma concentration over the course of therapy.

Generic antiarrhythmic drugs are approved by demonstration of *bioequivalence*. Thus, variations in formulation that can occur with generic drugs are permissible as long as there is a clear demonstration that the same amount of the generic drug is absorbed and available to the systemic circulation as the proprietary compound. Regulatory agencies have specified limits in the difference in bioavailability that may be allowed for the approval of new formulations.[28]

DISTRIBUTION

An understanding of distribution is key to appreciating both the intended and unintended effects of antiarrhythmic drugs. Following absorption, drug is distributed to various parts of the body, and the pattern of distribution is determined by the amount of blood flow to different tissues (Fig. 87–1). Organs with high blood flow, such as the heart, liver, brain, and kidney, are generally exposed to the drug early, and these organs are generally referred to as the *central compartment*. However, drugs nearly always redistribute from the central compartment to other tissues or sites of metabolism and elimination. They may distribute to muscle, skin, and adipose tissue, generally in a second phase. These less-perfused organs are considered to be the *peripheral compartment*. Finally, some drugs may distribute very slowly to tissues and organs that have low blood flow and may be referred to as the *deep compartment*. When the relative concentrations of drugs in all compartments reach equilibrium, *steady state* has been reached.

Volume of distribution is the term used to describe the virtual pool into which a drug is administered, and is affected by tissue perfusion and degree of protein binding. Therefore, patient characteristics and disease states may affect the volume of distribution. In congestive heart failure, reduced organ perfusion may decrease the volume of distribution of the central compartment, making more of the drug available to active binding sites in the heart. Consequently, patients with congestive heart failure have increased sensitivity to the electrophysiologic properties of commonly used agents.[29]

Critically important among the factors that modulate volume of distribution is protein binding, which can be influenced by changes in the concentration of binding proteins, fluctuations in drug concentrations, and interactions with drugs competing for the same protein-binding sites. Most antiarrhythmic drugs are bound to varying extents in plasma to α_1-acid glycoprotein. For example, when dosing lidocaine in a patient with myocardial infarction, potential increases in α_1-acid glycoprotein levels and subsequent increased lidocaine binding would lessen the proportion of unbound drug available for the expected pharmacologic effect.[30]

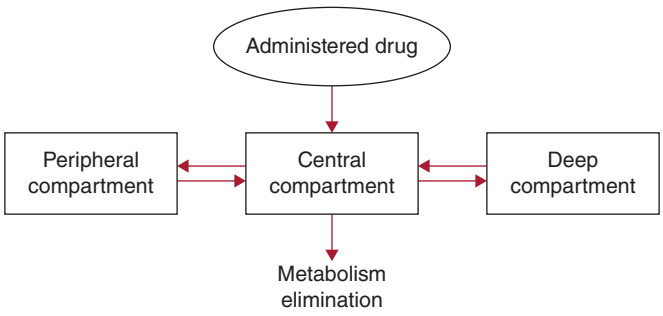

FIGURE 87–1. Pharmacokinetic compartments. Administered drug enters a highly perfused central compartment and then is redistributed to peripheral compartments and more slowly equilibrating deep compartments. Reproduced with permission from Mandel WJ: *Cardiac Arrhythmias: Their Mechanisms, Diagnosis and Management*. 3rd edition. Baltimore: Williams & Wilkins; 1995.

DRUG METABOLISM

The metabolism of drugs in general, as well as of antiarrhythmic drugs, can be divided into two phases. The first phase changes the drug into more polar metabolites via oxidation-reduction reactions. During the second phase, drugs are conjugated to endogenous ligands, such as glucuronide or sulfate. The majority of drug metabolism occurs in the liver, with oxidative metabolism usually occurring via the cytochrome P450 enzyme system. However, the metabolism of rapidly cleared drugs may occur in lung, plasma, vascular endothelium, or even red blood cells.

Knowledge of the relative concentration of active metabolites and their electrophysiologic action is critical to understanding the net pharmacologic effect of an antiarrhythmic drug. An example of an active metabolite is 5-hydroxypropafenone, a metabolite that has similar electrophysiologic effects to those of the parent compound but with slightly less potency.[31] The 5-hydroxy metabolite of propafenone possesses little β-adrenergic blocking activity. Thus, the presence of higher concentrations of the metabolite would be associated with less rate slowing in extensive metabolizers compared with a small percentage of individuals who are poor metabolizers of propafenone who manifest a greater β-blocking effect. Similarly, *N*-acetylprocainamide, the principal metabolite of procainamide, has a greater repolarization effect than the parent drug procainamide. *N*-acetylprocainamide (NAPA) is renally eliminated, and so in a rapid acetylator with renal impairment, a greater effect on QT interval might be expected compared with an individual who has lesser amounts of the metabolite in the circulation.[32]

The relative concentration of parent and metabolite in any individual is genetically determined.[27] Varying metabolic characteristics of antiarrhythmic agents is a major determinant of the utility of therapeutic drug monitoring, for example, measuring lidocaine or procainamide levels. Genetic polymorphisms have been most extensively described for the oxidative P450 enzyme system. Population studies demonstrate that this enzyme system is expressed in a bimodal pattern, with subjects having either "extensive" or "poor" metabolic capability. The poor metabolizer phenotype is expressed in approximately 10% of the population in whom parent drug plasma concentration is increased, clearance is reduced, and elimination half-life is prolonged. P450 enzyme isoforms have been identified that are responsible for the metabolism of specific agents and now can be identified by genotyping. Careful monitoring of patients during drug initiation to detect differences in response that may be caused by relative concentration of parent and metabolite is critically important for patient safety. As our understanding of pharmacogenetics continues to grow there may be a role for individually tailored antiarrhythmic drug strategies to achieve optimal drug levels.

CYP2D6 is the enzyme responsible for the metabolism of propafenone, flecainide, acebutolol, metoprolol, and propranolol. Most patients are *extensive metabolizers*, which means that a large percentage of the parent compound is transformed into a metabolite with activity that is identical to, similar to, or dissimilar from the parent. However, 5% to 10% are *poor metabolizers*, producing poor clearance with increased drug concentration, for which significant beta blockade can occur with an increased risk of asthma.

CYP3A4 is the most prevalent enzyme in the liver and plays a role in the metabolism of many antiarrhythmic drugs, including amiodarone,

quinidine, lidocaine, and many calcium channel blockers. This enzyme is inhibited by multiple agents, which include cimetidine, erythromycin, fluconazole, and grapefruit juice. Use of these agents causes accumulation of higher concentrations of the parent compound and thus an exaggerated electrophysiologic effect.

Metabolism issues are important in predicting the interaction of antiarrhythmic drugs with other agents, including other cardiac and noncardiac drugs that may be metabolized by the same pathways. These drugs may interfere with metabolism either by occupying the enzyme site or by having a direct effect on the activity of the enzyme. The relative affinity of the drug for the enzyme system is predictive, in many cases, of the potency of the drug interaction that might occur with commonly used agents such as digoxin and warfarin.[33]

ELIMINATION

Clearance is the term that describes removal of drug from plasma and is defined as the volume of plasma cleared of drug per unit of time. The sum of all individual clearances is called *total-body clearance* and is the most reliable indicator of the rate of metabolism and elimination of drug. Other methods of quantifying elimination are less satisfactory.

Clearance generally begins with *presystemic clearance*, which is the metabolism of the drug during its passage through the liver before reaching the systemic circulation, as previously described. A number of drugs, such as lidocaine,[34] undergo extensive first-pass clearance, which obviates their oral use. Other drugs with less extensive first-pass clearance may be given at high doses so as to make some of the drug available to the systemic circulation. Examples include propafenone, propranolol, and verapamil.

Half-life is defined as the time required for the plasma concentration to decrease by 50% (Fig. 87–2), and can be altered by changes in both clearance and volume of concentration. Despite its limitations, the concept of half-life can be used to describe the time required for drug elimination. For drugs that have more than one pharmacologic compartment, more than one half-life may be defined. For example, the decrease in plasma concentration after administration of an intravenous bolus of a drug can be divided into its *distribution period*, when the drug is distributed from the central to the peripheral compartments, and an *elimination period*, during which time the drug is cleared from the central compartment by metabolism and elimination. Conversely when a drug is administered by mouth, it is usually absorbed at a rate slower than the rate of distribution of the drug. Therefore, the distribution phase may be masked by the slow absorption of the drug.

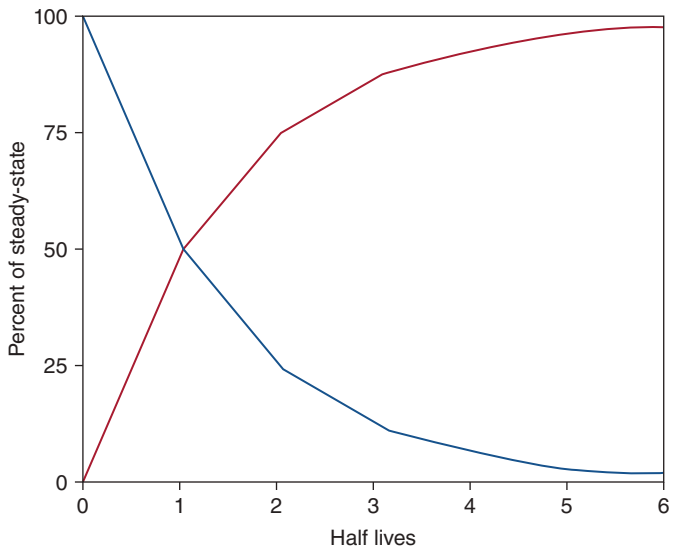

FIGURE 87–2. Time required for accumulation and elimination of drug. After initiation of drug therapy (*red line*), 50% of steady-state drug concentrations are achieved in 1 half-life and 90% are achieved in 3.3 half-lives. Similarly, after drug is stopped (*blue line*), concentration decreases by 90% after 3.3 half-lives. Reproduced with permission from Mandel WJ: *Cardiac Arrhythmias: Their Mechanisms, Diagnosis and Management*. 3rd edition. Baltimore: Williams & Wilkins; 1995.

As can be seen from Fig. 87–2, the time required to achieve a steady-state plasma concentration during chronic therapy can be estimated from the elimination half-life. After approximately 3.3 half-lives, 90% of the steady-state plasma concentration has been reached during loading or removed during washout. For example, sotalol has an elimination half-life of approximately 12 hours, and therefore takes 36 hours (or 2 to 3 days) to reach near steady state.

For drugs that have a longer half-life and therefore a longer time to achieve steady state, a *loading period* may be used to bring plasma concentrations into a desired range more rapidly. Lidocaine is an excellent example of this principle. Using fixed infusion rates without loading, the long elimination half-life of 1.5 to 2 hours in normal subjects would require > 6 hours for lidocaine to achieve a steady-state plasma concentration. In the setting of treatment of patients with severe arrhythmias, this time period is unacceptably long. Therefore, bolus doses are given to fill the central compartment and to replace the amount of drug leaving the plasma through distribution to peripheral compartments.[34] Once steady state has been achieved—that is, when there is no more movement of drug from central to peripheral compartments—the drug can be administered as a maintenance infusion that is given at the same rate at which the drug is eliminated.

Amiodarone represents the most complicated example of drug loading to balance distribution and elimination.[35] Amiodarone is generally considered to have three compartments, all of which need to be saturated to achieve steady state. Large doses of oral drug are given over several weeks to achieve saturation of the peripheral and deep compartments. However, because the myocardial half-life of the drug is significantly shorter than the half-life of deeper compartments, the drug is given daily to maintain equilibrium in the myocardium.

Knowledge of the elimination half-life is critical for designing proper interdosing intervals for most oral antiarrhythmic drugs. The main considerations in determining how frequently a drug has to be administered are half-life and *therapeutic range*, defined as the minimum and maximum plasma concentrations that will achieve clinical benefit without exposing patients to toxicity.[36] The larger the ratio of maximum to minimum therapeutic effect, the longer may be the intradosing interval, during which time high peak and low trough concentrations will be achieved. Reducing peaks and valleys requires shorter interdosing intervals.

For most drugs, knowledge of renal elimination kinetics is critical in formulating an effective interdosing interval and finding an adequate dose to achieve a therapeutic effect. A notable example of this principle is with dofetilide, which is predominantly excreted by the kidneys. Dofetilide has an elimination half-life of 8 to 10 hours in a patient with normal renal function, but prolongs with decreased creatinine clearance. Therefore, a determination of creatinine clearance is necessary to select an appropriate dose and dosing interval.

One caveat in designing dosing schedules is the problem of active metabolites. Metabolites may have pharmacokinetics that are distinct from the parent.[31,32] For drugs that have metabolites that are active and have longer half-lives than the parent, interdosing intervals might need to be extended to account for the metabolite's effect. Accumulation of a metabolite with higher than necessary dosing frequency can produce toxicity that may be life threatening.

Finally, drug half-life may be determined not only by the rate but also by the route of elimination. A prime example is adenosine, which is rapidly taken up and metabolized by erythrocytes and vascular endothelium and thus eliminated in prompt fashion.[37] Drugs with rapid offset of effect frequently are eliminated by routes other than the kidney, or they may be distributed quickly from the central compartment as in the case of ibutilide.[38]

DRUG INTERACTIONS

Antiarrhythmic drug interactions are ubiquitous and underappreciated, and therefore present a significant challenge to practicing physicians. Drug interactions may occur for a number of reasons, including inhibition or enhancement of drug metabolism and elimination, displacement of drug from plasma or tissue-binding sites, competition for receptor sites, and additive pharmacodynamic effects.[36] Table 87–2 outlines common drug interactions. The P450 enzyme system is responsible for an appreciable number of drug interactions in clinical practice.

Drug interactions resulting from interference with elimination also may occur. For example, digoxin is eliminated using a single pathway utilizing P-glycoprotein. P-glycoprotein activity is inhibited by many drugs, including amiodarone, quinidine, verapamil, and azithromycin.[39] Thus, the coadministration of these agents with digoxin can result in digoxin toxicity.

Among the assorted other mechanisms for kinetic interactions is reduced hepatic blood flow by β-adrenergic blockers, which can result in reduction of the clearance of high-extraction drugs such as lidocaine.

HEMODYNAMIC EFFECTS

A number of antiarrhythmic drugs have significant hemodynamic effects that may limit their usefulness under certain clinical situations. It is well known that class I drugs reduce myocardial contractility and may exacerbate congestive heart failure.[40] Among the sodium channel blockers, class Ic drugs and disopyramide exert the most potent negative inotropic effect; β-adrenergic and calcium channel blockers also are negative inotropic agents because of their inhibitory effect on inward L-type calcium current. Although β-adrenergic blockers, when used in patients with compensated heart failure, reduce symptoms of heart failure and improve survival, their use in patients with decompensated heart failure who need inotropic support of intravenous agents should be avoided. Quinidine also has α-blocking effect that can produce hypotension.

The majority of class III antiarrhythmic drugs are well tolerated hemodynamically in patients with heart failure. Data from clinical trials show that dofetilide and amiodarone do not significantly affect the hemodynamic state of patients with severe left ventricular dysfunction and heart failure.[41,42] However, *d,l*-sotalol should be used cautiously in patients with significant heart failure because its β-adrenergic blocking effect may exacerbate heart failure.

ANTIARRHYTHMIC DRUGS

Class I

According to the original schema, drugs that have an effect on sodium channels were placed in class I. It was later recognized that the relative potency of all of these drugs varied and that some had additional electrophysiologic effects differentiating them from others. For that reason, subclasses a, b, and c were used to designate these differences. The class Ia agents, including quinidine, procainamide, and disopyramide, exert an intermediate effect to block the fast sodium current and prolong the action potential duration by blocking outward potassium current. The class Ib agents, including lidocaine and mexiletine, are the weakest sodium blockers that produce little change in the QRS duration in normal cardiac tissues and have a negligible effect on repolarization. Class Ib drugs predominantly bind to the channel in the inactivated state. In ischemic myocardium with reduced membrane potential, voltage-dependent recovery of sodium channel from inactivation is delayed, so that binding of class Ib drugs to the channel is significantly increased. This explains the greater efficacy of class Ib antiarrhythmic drugs to inhibit ischemia-induced ventricular arrhythmias. The class Ic drugs, including flecainide and propafenone, have a more potent effect on the sodium current, leading to depression of phase 0 of the action potential and exhibiting more use dependence, that is, inhibiting the sodium current and slowing conduction during tachycardia. The varying sodium channel effects on the ventricular action potential of the three types of class I agents are illustrated in Fig. 87–3.

Class II

Class II agents act indirectly on ionic currents primarily by inhibiting sympathetic activity through β-adrenergic blockade, leading to sinus rhythm slowing and PR interval prolongation under physiologic conditions. Many of them have additional actions on the adrenergic receptors. For example, carvedilol and labetalol also have a strong

TABLE 87–2. Important Drug Interactions

	Digoxin	β-Blockers	Simvastatin	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Quinidine	↑[a]	–	–	↑	↑[a]	↑[a,b]	↑[a,b]
Flecainide	↑	–	–	–	–	–	–
Propafenone	↑	↑	–	↑	↑[a]	↑[a]	↑[a]
Amiodarone	↑[a]	↑	↑	↑	↑[a]	↑[a,b]	↑[a,b]
Verapamil	↑[a]	↑	–	–	↑[a]	↑[a,b]	↑[a,b]
Dronedarone	↑[a]	↑	↑	↑	↑[a]	↑[a]	↑[a]

↑ indicates increased serum concentration of one of the seven bolded reference drugs.

[a]Indicates drug interaction from P-glycoprotein transport inhibition.

[b]Indicates drug interaction from moderate CYP3A4 inhibition.

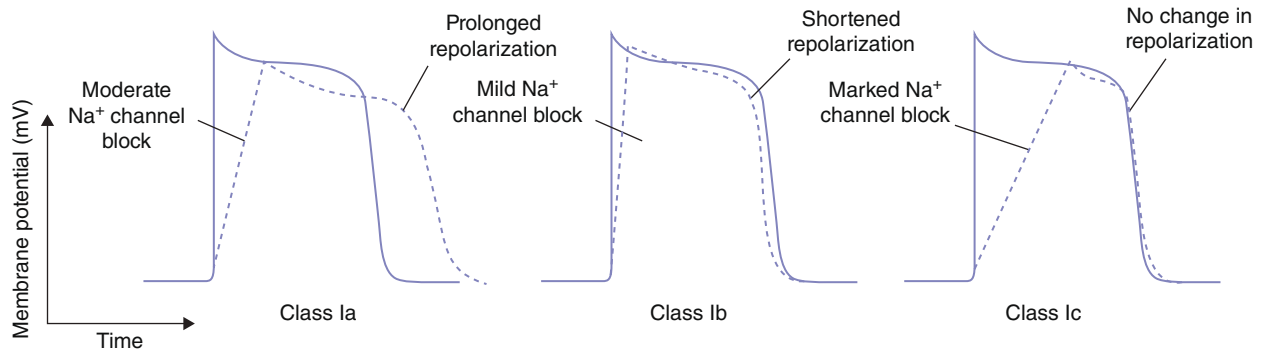

FIGURE 87–3. Effects of group I antiarrhythmic drugs on the ventricular action potential. Class Ia agents have an intermediate effect on the fast sodium current and prolong the action potential with blockade of the outward potassium current. Class Ib agents have less sodium channel blockade and bind to the sodium channel in inactivated state, having minimal effect on the action potential. Class Ic agents have a significant sodium channel blocking effect, which leads to the most marked depression of the initial phase (phase 0) of the action potential. Modified with permission from Golan DE, Tashjian, Jr. AH: *Principles of Pharmacology. The Pathophysiologic Basis of Drug Therapy*, 3rd Edition. Philadelphia: Lippincott Williams & Wilkins; 2012.

α-adrenergic blocking effect, whereas pindolol and acebutolol exhibit an intrinsic sympathomimetic activity.

Class III

Class III antiarrhythmic drugs are those that extend the action potential duration, thereby increasing the effective refractory period, which is shown in Fig. 87–4. There is a great deal of heterogeneity within this class because the drugs may act on any of several different ion channels, including sodium in addition to potassium channels, to reduce the net repolarizing current and prolong refractoriness. Most of the class III drugs demonstrate reverse use dependence, with their maximal effect on repolarization at slower heart rates, which may be counterproductive for effective arrhythmia termination. Amiodarone and ibutilide have a fairly homogeneous effect on refractoriness across a range of cycle lengths.

Class IV

Class IV antiarrhythmic drugs are L-type calcium channel blockers. Here again, there is substantial heterogeneity within the class. This may be particularly important because the calcium antagonists have a variable effect on slow channels in the heart versus the peripheral circulation.

The Vaughan-Williams classification schema (see Table 87–1) has been used as a conversational shorthand to facilitate exchange of information about the electrophysiologic properties of antiarrhythmic drugs. But it has a number of important drawbacks. First, many of the currently available drugs have multiple actions. Second, the metabolites of some of the drugs may be primarily responsible for at least some of the antiarrhythmic actions, such as procainamide and its metabolite NAPA. Third, the scheme does not account for important differences seen when the drugs are used in diverse patient populations, for example, the incidence and nature of proarrhythmia as it relates to presence, type, and severity of underlying structural heart diseases.

CLASS I ANTIARRHYTHMIC DRUGS

Class Ia Drugs

The common electrophysiologic feature of class Ia drugs is that the drugs block the rapidly activating delayed rectifier potassium current (I_{Kr}) at relatively lower concentrations than their effect on I_{Na}. Therefore, they cause QT prolongation that may lead to TdP. At higher doses, they inhibit I_{Na}, with an intermediate time constant of dissociation from the sodium channel, leading to conduction slowing and a decrease in myocardial contractility. Consequently, the class Ia agents are relatively contraindicated in structural heart disease.

Quinidine

Electrophysiology Among class Ia drugs, quinidine causes greater QT prolongation. Therefore, use of quinidine is associated with a higher incidence of TdP. Because quinidine has a larger concentration gap in blocking I_{Kr} and I_{Na}, TdP often develops when patients take lower doses of quinidine or just start to take the drug. Therefore, quinidine should be avoided in patients with heart failure or structural heart disease and in those with the congenital long QT syndrome, hypokalemia, or a history of TdP.[42] At higher doses, quinidine inhibits I_{Na}, leading to conduction slowing and a decrease in myocardial contractility.

Quinidine also inhibits I_{to} and may thereby prevent ventricular fibrillation in J-wave syndromes including idiopathic ventricular fibrillation with prominent J wave in ECGs leads excluding V_1 to V_3 and

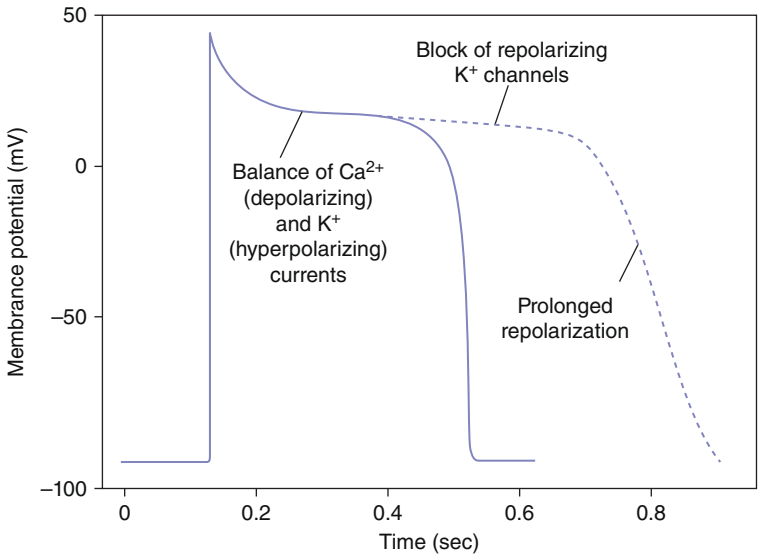

FIGURE 87–4. Effects of group III antiarrhythmic drugs on the ventricular action potential. Class III agents act on multiple ion channels including potassium channels, and extend the action potential duration. These changes prolong repolarization with an increase in the effective refractory period. Modified with permission from Golan DE, Tashjian, Jr. AH: *Principles of Pharmacology. The Pathophysiologic Basis of Drug Therapy*, 3rd Edition. Philadelphia: Lippincott Williams & Wilkins; 2012.

Brugada syndrome.[12,43] This is also the reason why quinidine, unlike other sodium channel blockers without an effect on I_{to}, cannot be used for unmasking ST-segment elevation in concealed Brugada syndrome.

Pharmacokinetics Quinidine can be rapidly absorbed; it reaches peak plasma concentrations in approximately 2 to 3 hours with the immediate-release formulations but takes much longer with the sustained-release formulations. Bioavailability varies from 50% to 100% with a mean value of 70% to 80%. The mean plasma half-life is 6 hours, but the half-life may vary from 3 to 19 hours. Therapeutic plasma concentrations of quinidine range between 2 and 6 μg/mL, and it is eliminated mainly by hepatic metabolism (~80%). The renal elimination of unchanged drug is approximately 20%.

Indications Quinidine has historically been used in the treatment of atrial fibrillation and ventricular arrhythmias.[44,45] Because quinidine is associated with a relative high incidence of TdP (5%-8%) leading to syncope (quinidine syncope) or sudden cardiac death, its role in the treatment of atrial fibrillation is limited and its overall used has diminished. However, quinidine has been shown to effectively prevent ventricular fibrillation in patients with J-wave syndromes because of its inhibitory effect on I_{to}.[12-14]

Adverse Effects Diarrhea is relatively common (~50% of patients). Less common adverse reactions include fever, rash, tinnitus, thrombocytopenia, and granulomatous hepatitis. Marked QT prolongation leading to TdP may occur, and is more commonly seen in females. Quinidine use simultaneously with another class Ia agent should be avoided because of an increased risk of death.[46]

Procainamide

Electrophysiology Because the concentration gap of procainamide to block I_{Kr} and I_{Na} is relatively narrower compared with quinidine, the risk that procainamide will prolong the QT interval and lead to TdP is smaller. Unlike quinidine, procainamide has no effect on I_{to}.

Pharmacokinetics Oral bioavailability of procainamide is approximately 83%, and drug can be administered orally or intraveneously. Procainamide is acetylated in the liver to an active metabolite, NAPA, which has a class III effect with a half-life of approximately 6 hours. The rate of acetylation varies in the population, with more than one half of the population being rapid acetylators. In rapid acetylators, NAPA levels usually exceed those of the parent compound. Therapeutic level for procainamide is 4 to 10 μg/mL and NAPA is 6 to 20 μg/mL. Short half-life of elimination (~3 hours) after oral administration in patients with normal renal function necessitates frequent dosing. Procainamide is contraindicated in patients with renal failure because the accumulation of the parent drug and its active metabolite can cause significant adverse effects including life-threatening proarrhythmias such as TdP.

Indications Procainamide suppresses both supraventricular and ventricular tachycardia. Intravenous procainamide can be used to convert supraventricular tachycardias, including atrial fibrillation, to normal sinus rhythm. In Wolff-Parkinson-White syndrome (preexcitation of the ventricles via accessory pathway(s) between the atria and ventricles), atrial fibrillation with rapid ventricular responses may mimic ventricular tachycardia, in which AV-blocking agents are relatively contraindicated. Intravenous procainamide inhibits conduction in the accessory pathway(s) and therefore effectively slows the ventricular response to atrial fibrillation. Intravenous procainamide can be also used to unmask the concealed type of Brugada syndrome as a result of its sodium channel blocking effect.

Adverse Effects Procainamide can cause nausea, anorexia, vomiting, rash, and granulocytosis. Intravenous administration of procainamide may result in hypotension. A systemic lupus erythematosus–like reaction is fairly common (10%-20%), particularly in slow acetylators who have a higher procainamide concentration and a lower NAPA level. Procainamide can cause QT prolongation likely via its active metabolite NAPA. However, the incidence of TdP is lower than with quinidine, and typically only occurs at high plasma concentrations (> 30 μg/mL).

Disopyramide

Electrophysiology Similar to procainamide, the concentration gap of disopyramide to block I_{Kr} and I_{Na} is relatively narrower than quinidine. Therefore, its effect on QT interval and conduction is comparable to procainamide. Among class Ia drugs, disopyramide has more negative inotropic and marked anticholinergic effects. Disopyramide also has a weak inhibitory effect on I_{to}.

Pharmacokinetics More than 90% of oral disopyramide is absorbed, and its bioavailability is approximately 83%. The rate of renal elimination of unchanged disopyramide is 55%. The half-life varies from 4 to 10 hours, with a mean value of 6 hours. In patients with renal failure and congestive heart failure, the plasma half-life is significantly increased. The therapeutic levels are between 2 and 5 μg/mL. In patients with renal and/or hepatic function insufficiency, the dosage needs to be adjusted.

Indications Disopyramide is used for treatment of ventricular and atrial arrhythmias. Because disopyramide has a strong vagolytic effect, it is useful in patients with vagally mediated atrial fibrillation. Its negative inotropic effect also makes it an effective treatment option in hypertrophic obstructive cardiomyopathy.

Adverse Effects The adverse effects of disopyramide are largely associated with its anticholinergic activity. These include bloating, constipation, urinary retention, oropharyngeal dryness, blurred vision, and worsening of glaucoma. Disopyramide may also cause headache, muscle weakness, nausea, and fatigue. Because of its relatively strong negative inotropic activity, disopyramide should be avoided in patients with left ventricular dysfunction and heart failure. Like other class Ia drugs, disopyramide may cause TdP.

Class Ib Drugs

Electrophysiology The common electrophysiologic feature of class Ib drugs is that the drugs block cardiac sodium channels in the inactive state with a rapid dissociation rate from the channels. Class Ib drugs increase the effective refractory period more significantly in the ventricles than in the atria because the action potentials of the ventricles have a relatively longer inactivated state. In addition, class Ib drugs have little effect on accessory pathways and those cardiac structures with calcium-dependent action potentials such as the sinus node and AV node. This explains why class Ib drugs are ineffective for treatment of supraventricular tachycardias and atrial fibrillation or flutter. However, class Ib drugs inhibit ventricular tachycardias more effectively under conditions of myocardial ischemia because shifting of resting potential to more positive potential in ischemic tissues markedly prolongs the inactivated state. Class Ib drugs have no significant effect on I_{Kr} and other repolarizing currents, and therefore have a minimal influence on the QT interval. Class Ib drugs have a smaller effect on hemodynamics and myocardial contractility than class Ia and Ic drugs and can be safely used in patients with heart failure.

Lidocaine

Pharmacokinetics Lidocaine is given intravenously for treatment of ventricular arrhythmias and has a half-life of 1.5 to 2.0 hours, with a mean value of 1.8 hours in normal adults. Because lidocaine is approximately

90% metabolized in the liver by CYP1A2, its half-life may be prolonged significantly in patients with hepatic impairment. Congestive heart failure may also increase the half-life of lidocaine. Lidocaine should be loaded with an intravenous bolus of 100 to 200 mg before continuous infusion is initiated. For ventricular tachycardia or fibrillation refractory to the drug, a repeat bolus of 100 mg can be given. Although the initial loading doses do not require adjustment, the maintenance doses should be reduced in patients with hepatic impairment or heart failure.

Indications Lidocaine is used to treat ventricular arrhythmias, particularly in setting of ischemia. However, amiodarone is now used as first-line treatment in ventricular arrhythmias in the setting of acute myocardial ischemia.

Adverse Effects The most common adverse reactions of intravenous lidocaine are central nervous system effects that are often dose related. They include tongue numbness, visual disturbances, tremor, seizure, drowsiness, hallucinations, and even coma. These adverse effects are particularly frequent in elderly patients and those with heart failure or liver function impairment. Cardiac effects of lidocaine are infrequent, but overdosing or rapid infusion may cause asystole, hypotension, and shock.

Mexiletine

Pharmacokinetics Mexiletine is well absorbed orally and has a bioavailability of approximately 87%. Mexiletine is largely (> 75%) metabolized in the liver, and the rest is excreted unchanged through the kidneys. The peak serum concentration occurs in 2 to 3 hours, with a half-life of 9 to 12 hours, and the therapeutic plasma concentration ranges from 0.5 to 2.0 μg/mL. Clearance of mexiletine is significantly delayed in patients with congestive heart failure and hepatic impairment. Therefore, the dose needs to be reduced in these patients.

Indications Mexiletine is considered as an oral form of lidocaine in terms of clinical application, and similarly is used in treating ventricular arrhythmia. In addition, mexiletine displays the unique property of blocking the late sodium current ($I_{Na,L}$).[47] This property of mexiletine is the basis for its use in preventing TdP in patients with acquired long QT syndrome.[48] Mexiletine can be used in patients with long QT3 syndrome because it blocks late sodium current, an inward current responsible for delayed ventricular repolarization and TdP in long QT3 syndrome.[49]

Adverse Effects Gastrointestinal adverse effects of mexiletine are relatively common (30%) and include nausea, vomiting, stomach cramps, and diarrhea or constipation. Other adverse effects include blurred vision, tremor, headache, ataxia, and confusion.

Class Ic Drugs

Electrophysiology Class Ic drugs block the sodium channels at their open state and dissociate from the channels with a relatively longer time constant. Therefore, class Ic drugs exhibit strong use dependence (ie, the blockade of the sodium channel is more prominent during tachycardia when the channels are "frequently used"). Class Ic drugs increase the effective refractory period in the atria, His-Purkinje system, ventricles, and accessory pathways. However, class Ic drugs slow conduction. Therefore, the effect of class Ic drugs on impulse wavelength, a key parameter that determines whether a reentrant tachycardia can occur, varies depending on the net effect of the drugs on effective refractory period and conduction velocity.[50] When class Ic drugs are used for the treatment of atrial fibrillation, atrial flutter may develop. Since class Ic drugs have minimal effect on the AV node, one-to-one AV conduction may occur during atrial flutter, leading to marked tachycardia. Sometimes atrial flutter with one-to-one AV conduction may resemble ventricular tachycardia because the QRS complex widens significantly as a result of strong sodium blockade at tachycardia. This is why an AV-blocking agent, such as a calcium channel blocker or β-blocker, should normally be used in conjunction with class Ic drugs for treatment of atrial fibrillation. Class Ic antiarrhythmics should be avoided in patients with ischemic and structural heart disease because of the significant proarrhythmic risk in these patients.

Flecainide

Pharmacokinetics Flecainide has an oral bioavailability of 60% to 86%, with a mean value of approximately 70%. The therapeutic levels range from 0.2 to 1.0 μg/mL. Although flecainide is mostly metabolized hepatically, renal clearance is important as well. Its half-life varies from 10 to 20 hours and can be significantly prolonged in patients with liver and renal impairment and congestive heart failure.

Indications Flecainide is indicated for treatment of atrial fibrillation in patients with structurally normal heart. Flecainide is useful for treating and preventing supraventricular tachycardia including AV nodal reentrant tachycardia, AV reentrant tachycardia, and atrial tachycardia. Because the action potential in the accessory pathways is I_{Na} dependent, flecainide is particularly effective to inhibit reentrant tachycardia using accessory pathway(s) like AV reentrant tachycardia and Wolff-Parkinson-White syndrome. Flecainide also has shown to be effective in preventing arrhythmic events in catecholaminergic polymorphic ventricular tachycardic (CPVT) when added to β-blocker therapy via inhibition of the ryanodine receptor.[51,52]

Adverse Effects Flecainide is usually well tolerated. However, it should be avoided in patients with ischemic cardiomyopathy and congestive heart failure.[15] Flecainide may cause ventricular tachycardia or fibrillation and worsen heart failure in these patients as a result of its strong use-dependent inhibition of I_{Na}. It also should be avoided in patients with J wave syndromes because it may induce ST-segment elevation and facilitate the development of ventricular fibrillation via its effect on I_{Na} in these patients. Flecainide may worsen sinus node dysfunction leading to sinus bradycardia, and in addition, it may slow conduction in His-Purkinje and cause AV block in patients with severe His-Purkinje system disease. Because flecainide blocks I_{Kr} at a concentration slightly lower than that at which it blocks I_{Na}, it may cause mild QT prolongation not related to its effect on QRS. However, TdP is extremely rare. Noncardiac adverse effects are dose related, including tremor, dizziness, blurred or double vision, headache, nausea, and dry mouth.

Propafenone

Pharmacokinetics Propafenone is almost completely absorbed and undergoes extensive first-pass hepatic clearance. The bioavailability of propafenone is dose dependent, ranging from 5% to 50%. The half-life of the parent compound is approximately 5.5 hours, although it may be prolonged to 14 hours in poor metabolizers (~10% of patients), who are determined by genetic factors. The major metabolites of propafenone include 5-hydroxypropafenone (active) and *N*-debutyl propafenone. Propafenone has a weak β-blocking effect. In poor metabolizers, a relatively higher level of propafenone and lower levels of its active metabolites may be associated with a greater β-blocking effect. Because propafenone is largely eliminated via the liver, its doses should be adjusted in patients with liver disease. Propafenone also exhibits saturable kinetics, resulting in a nonlinear increase in plasma concentration during increases in oral dosing. This also results in a change in the ratio of parent drug to metabolite when the oxidative enzyme in the liver becomes saturated.

Indications The indications of propafenone are similar to those of flecainide.[53]

Adverse Effects The majority of cardiac adverse effects are similar to those of flecainide. However, propafenone does not prolong ventricular repolarization and has not been reported to induce TdP. Propafenone should be avoided in advanced heart failure because of its proarrhythmic risk. Unusual taste, nausea or vomiting, constipation, dizziness, and headache are relatively common. Propafenone toxicity can present with cardiovascular effects of hypotension, ventricular arrhythmias or bradycardia, as well as CNS depression. Patients who are poor metabolizers or are taking CYP2D6 inhibitors would be more likely to experience symptoms of propafenone toxicity. Rash is also seen in 1% to 3% of patients on propafenone. Rarely, propafenone can cause profound neutropenia or lupus-like syndrome.

CLASS II DRUGS (β-BLOCKERS)

Electrophysiology

β-Agonists enhance $I_{Ca,L}$ and the pacemaker current (I_f). Therefore, β-receptor blockade prolongs the AV node effective refractory period and suppresses automaticity, resulting in depression of AV conduction and increase in sinus node recovery time, leading to slowing of the sinus rate. Although β-blockers per se have no clear effect on repolarization, they seem to prevent or blunt the changes in refractoriness at all levels in the heart.

Antiarrhythmic effects of β-blockers on supraventricular and ventricular tachycardias are largely a result of their counteracting action on arrhythmogenesis of catecholamines. In addition, β-blockers also increase ventricular fibrillation thresholds by reducing dispersion of repolarization, particularly in ischemic zones.

Pharmacokinetics

Pharmacokinetics and thus dosing differ significantly among β-blockers. β-Blockers are usually titrated based on resting heart rate.

Indications

β-Blockers effectively suppress arrhythmias in which catecholamines play an important role. These arrhythmias include catecholamine-sensitive polymorphic ventricular tachycardia and TdP in certain congenital long QT syndromes (long QT1 and long QT2 syndromes). β-Blockers slow AV nodal conduction and reduce the ventricular response to atrial fibrillation and atrial flutter. As a result of their antifibrillatory and anti-ischemic actions, β-blockers are also useful in the treatment of ischemia-related ventricular arrhythmias such as premature ventricular beats and nonsustained ventricular tachycardia and in prevention of sudden arrhythmic death in patients with ischemic cardiomyopathy. β-Blockers may be effective in terminating AV and AV nodal reentry or in preventing such arrhythmias. Multiple studies have demonstrated beta blockers having similar rates of prevention of atrial fibrillation recurrence as the class IA and class III antiarrhythmics.[46] β-Blockers, particularly when given intravenously, are contraindicated in patients with preexcitation during atrial fibrillation.

Adverse Effects

β-Blockers are generally well tolerated, but they are contraindicated in patients with moderate to severe asthma. β-Blockers also exacerbate sick sinus syndrome and AV block. β-Blockers may be associated with fatigue, depression, insomnia, hallucinations, and sexual dysfunction. Abrupt withdrawal of β-blockers in patients with coronary artery disease may lead to worsening angina, myocardial infarction, and even sudden death. β-Receptor blockade may mask signs of hypoglycemia in diabetics. Initiation of β-blockers should generally be avoided in acute decompensated heart failure requiring intravenous vasoactive medications.

CLASS III DRUGS

Ibutilide

Electrophysiology Ibutilide, a methanesulfonamide derivative, blocks the I_{Kr} current and enhances late slow inward sodium current, therefore exhibiting a strong effect to delay repolarization in both atrial and ventricular myocardium including accessory pathways.[54,55] ECG changes associated with use of ibutilide include prolongation of the QT interval. The QT interval normally returns to baseline within 3 to 4 hours after drug infusion is discontinued. Ibutilide has minimal effects on sinus node and AV conduction.

Pharmacokinetics Ibutilide is available only in an intravenous preparation because of extensive first-pass metabolism during oral administration. It has a half-life of 2 to 12 hours and is extensively metabolized by the liver to eight metabolites that are largely eliminated via the kidney. Weight-based dosing is required for patients weighing < 60 kg.

Continuous ECG telemetry monitoring during infusion and for at least 4 hours after infusion is strongly recommended because TdP can occur. The patient should not be discharged until the QT interval returns to baseline.

Indications The indication of ibutilide is for acute termination of atrial flutter and fibrillation. Its efficacy is higher in atrial flutter or fibrillation of short duration. It is also useful in converting atrial fibrillation to sinus rhythm in patients after cardiac surgery and in those with the Wolff-Parkinson-White syndrome.

Adverse Effects The primary adverse effect of ibutilide is TdP (4%-8%). TdP is more likely to occur in females or under conditions of hypokalemia, hypomagnesemia, bradycardia, or significant left ventricular dysfunction.

Sotalol

Electrophysiology *d,l*-Sotalol is a racemate of *d* and *l* isomers that both exhibit antiarrhythmic actions via blocking I_{Kr}.[56] In addition, the *l* isomer also exhibits nonselective β-blocking activity. Electrophysiologic effects of sotalol include an increase in action potential duration in both the atria and ventricles and a decrease in sinus rate and AV conduction.

Pharmacokinetics Sotalol is well absorbed with bioavailability of almost 100%. It is primarily eliminated in an unchanged form by the kidney. The half-life ranges from 10 to 16 hours. In patients with renal insufficiency, sotalol clearance is significantly delayed, and drug accumulation leading to serious toxic effects may occur. Therefore, sotalol dosage must be adjusted based on patients' creatinine clearance. Because of the risk of TdP, sotalol should be started in hospital with QT monitoring.

Indications Sotalol is effective in suppressing atrial and ventricular arrhythmias.[57] Its common clinical use is to prevent recurrence of atrial fibrillation and ventricular tachycardia particularly related to old myocardial infarction.

Adverse Effects Sotalol is contraindicated in patients with acquired or congenital long QT syndrome, symptomatic sinus node dysfunction, AV block, and moderate to severe asthma. β-Blocking activity can cause bradycardia and worsening of left ventricular function. Sotalol commonly causes fatigue, and may also cause insomnia, headache, mild diarrhea, nausea, or vomiting. QTc prolongation > 500 ms in

narrow QRS or a change in the QTc interval of > 15% in baseline wide QRS (> 120 ms) should prompt discontinuation of sotalol. TdP risk is approximately 2% to 4%.[58]

Amiodarone

Electrophysiology While amiodarone is designated as a class III agent, it has properties of all four classes of the Vaughan-Williams classification. The electrophysiologic effects of intravenous amiodarone differ from oral amiodarone; when given intravenously, amiodarone exhibits acute inhibitory effect on I_{Na} and $I_{Ca,L}$, whereas oral amiodarone has a delayed onset of action, which takes at least 2 to 3 days, that mainly targets outward currents. Chronic administration of amiodarone inhibits multiple outward potassium currents including I_{Kr}, I_{Ks}, I_{K1}, and I_{to}. Although amiodarone may cause marked QT prolongation, it rarely leads to TdP.[59] Amiodarone exerts its antiadrenergic effects by noncompetitive binding to β-adrenergic receptors and inhibition of agonist-induced increases in adenylate cyclase activity. These combined effects may lead to QT prolongation, a slight increase in QRS duration, and a profound inhibitory effect on sinus node and AV conduction.

Pharmacokinetics Amiodarone is highly lipid soluble and has complex pharmacokinetics. The effective volume of distribution of oral amiodarone is variable, but can be quite significant (range 18-148 L/kg), and therefore, it may take many weeks or months for amiodarone to reach equilibrium in the body. Similarly, its elimination half-life is also very long, ranging from many weeks to months.[60] Amiodarone is metabolized to desethylamiodarone, which has similar electrophysiologic effects to those of amiodarone.

The typical oral loading regimen is 800 to 1600 mg daily in divided doses, up to 2 to 3 weeks before dose adjustment to 200 to 400 mg per day. The goal of chronic amiodarone is to use a dose as low as possible for good efficacy and limited adverse effects. Because amiodarone is not eliminated by the kidney, dose adjustment in patients with renal insufficiency is not necessary.

Intravenous use of amiodarone typically starts with a 150-mg bolus. The standard intravenous loading regimen is then a continuous infusion of 1 mg/min for a period of 6 hours and then reduction to 0.5 mg/min for an additional 18 hours. Intravenous bolus can be repeated for refractory or recurrent arrhythmia. When given intravenously, amiodarone is distributed rapidly; its plasma level after discontinuing infusion diminishes quickly in 30 to 60 minutes.

Amiodarone may raise the plasma concentration of digoxin and warfarin, leading to serious toxicities. Therefore, doses of these two drugs often need to be adjusted when amiodarone is started.

Indications Amiodarone has a broad spectrum of antiarrhythmic actions in a variety of supraventricular and ventricular arrhythmias.[61,62] Of the currently available antiarrhythmic drugs, amiodarone has claimed supremacy in treatment and prevention of atrial fibrillation by its cardiac safety and efficacy in multiple randomized and nonrandomized trials.[46,57]

In addition, intravenous amiodarone has replaced intravenous lidocaine as the first-line drug for treatment and prophylaxis of ventricular fibrillation, particularly hemodynamically compromised ventricular arrhythmias refractory to other therapies.[61] Amiodarone has not been demonstrated to have a clear benefit on survival for ventricular arrhythmias in patients with LV dysfunction. Specifically, the SCD-HeFT (Sudden Cardiac Death in Heart Failure) trial, which looked at patients with ischemic or nonischemic cardiomyopathies, did not show a mortality benefit in either group with amiodarone therapy.[63] Intravenous amiodarone is also an excellent AV-blocking agent and is effective in slowing the ventricular responses to atrial fibrillation in critically ill patients.[64]

Adverse Effects Although amiodarone has an excellent efficacy and cardiac safety profile, it has potential adverse effects affecting nearly every organ system except the kidney. Even low-dose amiodarone (≤ 400 mg) has been shown to at least double a patient's likelihood of developing a thyroid, neurologic, ocular, skin, or bradycardic adverse event.[65] The odds of discontinuing amiodarone because of adverse events was almost 1.5 times that of the control group.[65] Additionally, amiodarone therapy, compared with other antiarrhythmic drugs, is more sustained because of its extended half-life, and the adverse effects of the drug increase as a function of time as a result of extensive tissue accumulation.

Iodine in the amiodarone molecule is the likely cause of its extracardiac adverse effects. With a daily maintenance dose of amiodarone between 100 and 600 mg, approximately 3.5 to 31 mg of iodide are released into the systemic circulation, which is equivalent to a 35- to 140-fold excess of daily intake. In a normal-functioning thyroid gland, further iodine transport and thyroid hormone biosynthesis are inhibited, leading to hypothyroidism. However, a preexisting autonomously functioning nodule escapes the Wolff-Chaikoff effect and produces excess amounts of thyroid hormones in response to large concentrations of iodine, leading to type 1 hyperthyroidism. Conversely, amiodarone itself and excess iodide can exert direct cytotoxic effects on thyroid follicles, leading to destructive inflammatory thyroiditis and a consequent leakage of a large amount of thyroid hormone, leading to type 2 hyperthyroidism.

Additionally, iodine also renders the amiodarone molecule more lipophilic, increasing its volume of distribution. The active metabolite of amiodarone, *N*-desethylamiodarone, significantly accumulates in adipose tissue and highly perfused organs. Besides the previously mentioned hyperthyroidism and hypothyroidism, relatively common adverse effects of amiodarone include anorexia, nausea, vomiting, constipation, altered taste, corneal microdeposits, blue-gray skin discoloration, and photosensitivity of the skin. Liver and pulmonary toxicities, which may be dose dependent, are important extracardiac adverse effects and include elevation of hepatic enzymes, hepatic cirrhosis, chronic interstitial pneumonitis or bronchiolitis obliterans, and relatively rare acute pneumonitis. Neurologic adverse effects including peripheral neuropathy and myopathy may occur with use of higher-dose amiodarone. Rarely, amiodarone may cause optic neuritis.

Amiodarone may cause marked sinus bradycardia or AV block. However, TdP is rare. Its minimal risk in increasing proarrhythmia also adds to its attractiveness and wide use.

Because amiodarone may cause significant extracardiac adverse effects, hepatic, thyroid, and pulmonary functions need to be assessed on a regular basis.

Dofetilide

Electrophysiology Dofetilide is a pure I_{Kr} blocker that prolongs action potentials in the atria and ventricles. On the ECG, QT prolongation is not accompanied by an increase in PR and QRS. The $T_{p\text{-}e}$ interval, an index of transmural dispersion of repolarization,[8] may increase as well when the baseline ECG is normal (ie, there are positive T waves).

Pharmacokinetics Dofetilide is well absorbed with a bioavailability of 92%.[66] The free therapeutic plasma concentration is approximately 0.8 ng/mL. The elimination half-life ranges from 8 to 10 hours in patients with normal renal function. Approximately 70% to 80% of the drug is excreted in the urine, so dosing must be adjusted based on creatinine clearance. The remaining 20% to 30% is metabolized in the liver by the CYP3A4 isoenzyme of the cytochrome P450 enzyme system. Compounds that inhibit the CYP3A4 isoenzyme, such as

amiodarone, erythromycin, ketoconazole, verapamil, and cimetidine, increase serum dofetilide level.

Dosage must be adjusted based on the change in the QT interval because of TdP risk, so the initiation of the drug therapy must be done in a hospital, where ECG recording and telemetry are available. QTc prolongation > 500 ms in narrow QRS or a change in the QTc interval > 15% in baseline wide QRS (> 120 ms) should prompt discontinuation of the drug.

Indications Dofetilide is used for treatment and prevention of atrial fibrillation and atrial flutter. Because dofetilide has no deteriorating effect on ventricular contractility, it can be safely used for conversion of atrial fibrillation and prevention of its recurrence in patients with congestive heart failure. It may also have value in suppressing reentrant ventricular arrhythmias such as monomorphic ventricular tachycardia resulting from myocardial scar.

Adverse Effects TdP is a major concern. The TdP incidence was approximately 3% to 4% in earlier clinical trials. When dofetilide is initiated in hospital and its dose is adjusted based on ECG changes, the TdP incidence appears to be lower. Dofetilide should be avoided in patients with marked renal insufficiency or baseline QT prolongation. Defetilife also has demonstrated safety in left ventricular dysfunction and recent history of myocardial infarction.[67]

Dronedarone

Dronedarone was approved for the treatment of atrial fibrillation and flutter by the US Food and Drug Administration in 2009. It is an analog of amiodarone but is a noniodinated benzofuran derivative with the most significant molecular modification being removal of iodine and the addition of a methane sulfonyl group.

Electrophysiology Although dronedarone displays similar electrophysiologic properties as its mother compound amiodarone and has effects on multiple cardiac ion channels, its efficacy in suppressing cardiac arrhythmias is inferior to amiodarone. It has potent class I to IV antiarrhythmic activity according to the Vaughan-Williams classification scheme.[26] However, dronedarone has stronger $I_{Ca,L}$ inhibition. In addition, dronedarone has a noncompetitive antiadrenergic action. On the ECG, dronedarone prolongs the R-R and QTc intervals and may also mildly increase QRS duration.

Pharmacokinetics Dronedarone is well absorbed after oral administration, with bioavailability of 15% to 20% that increases two- to three-fold when taken with food.[68] It undergoes extensive first-pass metabolism and is metabolized by CYP3A4. It is expected to interact with drugs such as digoxin, calcium channel blockers, erythromycin, and ketoconazole. Dronedarone is also a CYP2D6 inhibitor and causes a modest increase in bioavailability of metoprolol in CYP2D6 extensive metabolizers.[68] The clearance of dronedarone is principally nonrenal. With chronic administration at 400 mg twice daily, the steady-state plasma level is reached in approximately 2 weeks, and elimination half-life is approximately 24 hours.

Indications Dronedarone is used for the prevention of recurrent atrial fibrillation and flutter.

Adverse Effects Based on an adverse effect on mortality in ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease), dronedarone should be avoided in patients with advanced heart failure.[26,69] In addition, dronedarone should not be used in patients with permanent atrial fibrillation because of an increased risk for heart failure, stroke, and death with use in this population. This recommendation is based upon data from the PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) trial, which was terminated early as a result of excess mortality and morbidity in patients in the dronedarone treatment group versus control.[70]

Dronedarone is not associated with thyroid, neurologic, ocular, or pulmonary toxicity. Dronedarone leads to dose-dependent prolongation of QT interval, but no TdP has been reported. Like amiodarone, it has a very low proarrhythmic risk, differentiating it from most other antiarrhythmics. The most common adverse effects of dronedarone are gastrointestinal, including nausea, vomiting, and diarrhea. There was a reported incidence of serum creatinine elevation by about 0.1 mg/dL in approximately 2.4% of patients as a result of dronedarone-induced inhibition of tubular secretion.[71]

CLASS IV DRUGS

Nondihydropyridine Calcium Channel Blockers

Electrophysiology Unlike a large number of dihydropyridine calcium channel blockers, the nondihydropyridine calcium channel blockers verapamil and diltiazem specifically inhibit calcium-dependent slow action potentials in the sinoatrial and AV nodes. These two agents slow diastolic depolarization in both nodes, therefore slowing the pacemaker rate. They also prolong the refractory period of the AV node, reducing ventricular responses to atrial fibrillation. However, verapamil and diltiazem may cause peripheral vasodilation, which may partially offset their sinus and AV nodal slowing effects.

Pharmacokinetics When given intravenously with bolus, the peak effects of verapamil and diltiazem occur after approximately 15 minutes. Although both drugs are well absorbed, their bioavailability is approximately 35% (verapamil) and 45% (diltiazem) after their first-pass metabolism. Elimination by the kidney is not important. Their elimination half-life is similar, ranging from 3 to 7 hours.

Indications Verapamil and diltiazem are used for termination of supraventricular tachycardias and prevention of their recurrence. They are also used for ventricular rate control in atrial fibrillation and flutter. Calcium channel blockers can effectively suppress focal atrial tachycardia particularly related to pulmonary diseases. Some idiopathic ventricular tachycardias, particularly in the left ventricle, are verapamil sensitive and may be successfully treated with this agent. Verapamil and diltiazem reduce both resting and exercise heart rates in patients with atrial fibrillation. Verapamil and diltiazem may also effectively prevent ventricular tachycardia or fibrillation caused by coronary artery spasm.

Adverse Effects Both agents inhibits $I_{Ca,L}$ and should be avoided in patients with advanced heart failure or hypotension. Both agents can cause sinus bradycardia and AV block. Verapamil and diltiazem, particularly when given intravenously, should be avoided in the Wolff-Parkinson-White syndrome complicated by atrial fibrillation because they may facilitate conduction over the accessory pathway, resulting in ventricular fibrillation. Noncardiac adverse effects include dizziness, headache, nausea, constipation, and insomnia.

OTHER ANTIARRHYTHMIC DRUGS

Adenosine

Electrophysiology Adenosine is an important physiologic regulator in many organ systems. Rapid intravenous injection of adenosine has negative dromotropic and chronotropic effects mainly on the sinoatrial and AV nodes mainly via the A_1 adenosine receptor. Adenosine activates adenosine-induced inwardly rectifying K^+ current (I_{KAdo}) and inhibits the pacemaker current (I_f) in the atria, sinus, and AV nodes. These combined effects cause transient complete AV block and sinus

bradycardia. Adenosine has no significant effect on AV accessory pathways. Adenosine can produce coronary vasodilatation via its effects on A_2 receptors in the vascular smooth muscle cells.

Pharmacokinetics Adenosine is rapidly cleared by cellular uptake and metabolism, with an estimated elimination half-life of 1 to 5 seconds. Aminophylline antagonizes the negative chronotropic and dromotropic effects of adenosine, whereas dipyridamole, a strong adenosine uptake inhibitor, potentiates the effects of adenosine. The dose of adenosine is 6 to 12 mg by intravenous bolus.

Indications The main use of adenosine is to convert paroxysmal supraventricular tachycardias to normal sinus rhythm. Two common types of proximal supraventricular tachycardias (ie, AV nodal reentry and AV reentry tachycardias) use the AV node as part of the route for their circus (reentry) movement. Therefore, adenosine that transiently blocks AV conduction effectively terminates these two reentrant paroxysmal supraventricular tachycardias. Adenosine administration also has growing utility in guiding pulmonary vein isolation catheter ablations for atrial fibrillation. In this setting, adenosine testing has been utilized effectively to identify potentially at risk dormant pulmonary vein conduction during catheter ablation.[72]

Adverse Effects Adenosine should be avoided in patients with sick sinus syndrome or AV block. The common adverse effects are facial flushing, chest pressure, and dyspnea, but these effects are mild and brief. In patients with asthma, adenosine can trigger an acute attack caused by bronchoconstriction. Adenosine may induce atrial fibrillation.

Digoxin

Electrophysiology Digoxin augments vagal tone, leading to the prolongation of the AV node effective refractory period and a decrease in sinus rate and AV conduction. However, digoxin inhibits sarcolemmal Na^+-K^+-ATPase, leading to an increase in intracellular calcium that may promote triggered activities.

Pharmacokinetics Digoxin is fairly well absorbed, with an oral bioavailability of 60% to 80%. It is mainly eliminated by the kidney. The elimination half-life is approximately 36 hours in patients with normal renal function and up to a week in those with renal impairment. In patients with renal failure, hepatic metabolism becomes important in digoxin clearance. Many drugs, such as amiodarone, quinidine, and verapamil, increase serum digoxin concentration. Digoxin can be given orally or intravenously, and is initially given with a weight based loading dose followed by a maintenance dose. Intravenous and oral dosing is not equivalent, with 100 μg intravenous equaling 125 μg oral dose.

Indications Digoxin as an antiarrhythmic drug is mainly used to control the ventricular rate in atrial fibrillation/flutter or to prevent relapse of supraventricular arrhythmias using the AV node. Digoxin is particularly useful in pregnant patients with supraventricular tachycardias because many years of clinical experience has demonstrated that use of digoxin is safe during pregnancy. Digoxin has also been used routinely in ventricular rate control in atrial fibrillation in congestive heart failure. However, there is data that suggests a possible increased mortality risk with the use of digoxin in this group.[73] Future studies and ideally a randomized control study examining this issue will be critically important in guiding future clinical management with respect to digoxin use in heart failure patients with atrial fibrillation.

Adverse Effects Cardiac toxicities are sinus bradycardia, AV block, and triggered atrial and ventricular arrhythmias including paroxysmal atrial tachycardia, ventricular bigeminy, junctional tachycardia, and bidirectional ventricular tachycardia. Noncardiac adverse effects include anorexia, nausea, headache, halo vision, visual scotomas, and altered color perception. Hypokalemia enhances digoxin toxicity.

Digoxin levels are routinely measured to monitor for appropriate target drug concentration as a result of its narrow toxic to therapeutic window. In patients with left ventricular dysfunction, a lower digoxin level is recommended (0.5-0.8 ng/mL).[74] This is based on evidence of a possible reduced mortality at these lower digoxin levels, as well as increased mortality with a serum digoxin concentration ≥ 1.2 in this population.[75,76]

Ranolazine

Ranolazine is approved for treatment of chronic angina. However, this drug has potent antiarrhythmic activity.[77] Ranolazine inhibits I_{Kr}, I_{Ks}, late I_{Na}, I_{Ca}, and $I_{Na\text{-}Ca}$.[78] Animal data revealed marked atrial selectivity in its sodium channel blockade in a rate dependent manner, which may have particularly valuable characteristics in atrial fibrillation.[79] Oral bioavailability of ranolazine is 35% to 50% and it is eliminated primarily by the liver. The elimination half-life is approximately 7 hours with the extended-release formulation.

Ranolazine appears to be useful for treatment of both atrial fibrillation and ischemia-induced ventricular arrhythmias. In the MERLIN-TIMI 36 randomized controlled trial of 6351 patients with a non–ST-segment elevation acute coronary syndrome who were hospitalized and monitored with continuous ECG recording, ranolazine was associated with less ventricular tachycardia (5.3% vs 8.3%) and less new onset of atrial fibrillation (1.7% vs 2.4%) compared with the placebo group.[77] The HARMONY trial showed that the addition of ranolazine to reduced dose dronedarone had a synergistic effect in providing a reduced burden of atrial fibrillation in patients with paroxysmal atrial fibrillation.[80] However, there are no prospective trial data to support its usefulness to treat arrhythmias such as atrial fibrillation. Adverse effects include constipation, headache, dizziness, and nausea. Ranolazine may also cause bradycardia, orthostatic hypotension, and palpitations. QT prolongation may be present, but TdP has not been reported.

Ivabradine

Ivabradine is approved for treatment of stable symptomatic heart failure, specifically in patients with decreased systolic function who are in sinus rhythm with a heart rate of 70 bpm of greater. It works by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel causing a decrease in the spontaneous pacemaker activity of the sinus node through inhibition of the "f-current" (I_f). Its utilization has also been explored in management of inappropriate sinus tachycardia and postural tachycardia syndrome (POTS).[81,82] For inappropriate sinus tachycardia, there are initial data showing its efficacy in reducing heart rate as well as providing improvement in symptoms in this patient group.[83,84] Additional studies and clinical experience using ivrabadine are both necessary before being routinely used in this setting.

Ivabradine is metabolized by CYP3A4. Use of strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole, ritonavir) is contraindicated, with potential for high ivabradine concentrations and increased risk of severe bradycardia. It is contraindicated in patients with severe liver dysfunction. Adverse reactions include bradycardia, hypertension, atrial fibrillation, and visual disturbances. There are no effects on cardiac contractility.

Vernakalant

Vernakalant hydrochloride is a novel intravenous antiarrhythmic that is designed to rapidly terminate acute-onset atrial fibrillation.[85] Vernakalant's mechanism of actions is blockade of sodium channels and early activation of potassium channels. Its activity on the sodium channel is rate dependent, and therefore has weak activity blocking the I_{Na} channel at low heart rates but increases its I_{Na} channel blockade with increasing heart rates. Vernakalant also has an atrial selective

potassium channel blocking effect. Initial data examining electrophysiologic properties revealed prolongation of the atrial refractory period and AV nodal conduction.[86] Its elimination half-life is approximately two hours. It is predominantly cleared by the liver, and likely requires dose adjustments in advanced liver disease.

Vernakalant hydrochloride injection is under review for its use in rapid conversion of atrial fibrillation to sinus rhythm. Prior studies reveal an approximate 50% conversion rate from atrial fibrillation to sinus rhythm within 90 minutes from initial infusion.[87,88] Currently, vernakalant is not approved by the Food and Drug Administration for use in the United States.

SPECIAL POPULATIONS

THE ELDERLY

The elderly are particularly prone to both the adverse effects and overdosing of antiarrhythmic drugs. Elderly patients are more susceptible to common side effects of many antiarrhythmic drugs including bradycardia, orthostatic hypotension, and urinary retention. In addition, several physiologic changes associated with aging that make drug accumulation more likely. These include reduction in lean body mass, decrease in renal function, alterations in hepatic metabolism, and changes in receptor affinity.[89,90] The elderly also have increases in glycoprotein concentrations and reductions in serum albumin concentrations that may alter the ability of drugs to bind to plasma proteins, in effect raising free concentrations. Reduced receptor affinity and stimulation of adenylate cyclase attenuate the effects of catecholamines and may make these patients more susceptible to the depressant effects of β-adrenergic blocking agents. Reduction in the activity of the renin-aldosterone system and arterial wall elasticity make elderly patients more susceptible to the development of orthostatic hypotension.

Age affects the density of ion channels as well as likely alteration of the properties of certain ion channels. This was seen in animal data that that revealed alterations in L-type calcium ($I_{Ca,L}$) and outward potassium (I_K) currents from aged canine atrial myocytes.[88] As a result of these physiologic changes, elderly patients in general should be started on a smaller dose of an antiarrhythmic drug with slow upward dose titration to clinical effect or to tolerance.

OBESE PATIENTS

In general, patients with larger body size require higher doses of drugs to achieve a therapeutic plasma concentration. However, drugs may distribute differently in adipose tissue compared with muscle and other tissue. Thus, if adjustment in dose is made only on the basis of the patient's weight, some drugs will be overdosed.

UNDERWEIGHT PATIENTS

Patients with low lean body mass may require lower doses of certain drugs to achieve a therapeutic plasma concentration dependent upon the distribution of the drug. For example, digoxin, which distributes significantly into skeletal muscle, should be started at lower doses in this patient population to avoid potential toxicity.

CONGESTIVE HEART FAILURE

The central volume of distribution of an antiarrhythmic drug is generally reduced in congestive heart failure, necessitating reduction in the initial dose.[91] Congestive heart failure also gives rise to derangements of liver and renal blood flow with reduction in clearance of the drug and high extraction ratios. For all of these reasons, as well as altered sensitivity to drug and altered plasma protein binding, drugs should be administered in low dose to patients with congestive heart failure with slow upward dose titration, as in the elderly. Many antiarrhythmic drugs, including the majority of the class I agents, have negative inotropic activity, and therefore should be avoided or used cautiously in the heart failure population. Antiarrhythmic drugs that should be administered with caution or are contraindicated in heart failure and in various other conditions are listed in Table 87–3.

RENAL FAILURE

Drug and metabolites can accumulate in patients with renal failure, depending on the proportion of the drug that is eliminated by the kidney. Drugs such as sotalol and dofetilide, which are predominantly renally eliminated, are particularly important in this regard.[92] Fortunately, most drugs have other routes of elimination, which can at least partly compensate for reduced elimination because of renal failure. Antiarrhythmic drugs that are almost exclusively cleared via the liver, such as amiodarone and propafenone, can be safely administered to patients with advanced kidney disease including patients on renal replacement therapy. Specific antiarrhythmic drugs that mandate cautious use or dose reduction are listed in Table 87–3.

HEPATIC DISEASE

Fortunately, until hepatic disease is advanced, hepatic metabolism and elimination of most drugs is not significantly compromised. Short of liver cirrhosis, it can be assumed the drugs will be metabolized and eliminated normally, even in patients who have elevated transaminase and bilirubin concentrations.[93] In patients with end-stage liver disease, antiarrhythmic drugs with predominant hepatic clearance should be avoided or dose reduced on initiation. When used in this setting, these agents should be titrated carefully while observing for toxicities, and drug levels should be monitored if available.

TABLE 87–3. Special Populations and Antiarrhythmic Drug Selection

Populations	Use with Caution	Contraindicated
Congestive heart failure/structural heart disease	β-Blockers and nondihydropyridine calcium channel blockers *(use with caution in acute decompensated heart failure)* Sotalol Digoxin[a] *(decreased level in left ventricular dysfunction)*	Class Ia and Ic drugs Dronedarone *(avoid in advanced heart failure)*
Recent myocardial infarction	Sotalol	Flecainide
Renal failure	Dofetilide[a] Sotalol[a] Digoxin[a] Flecainide[a]	Dofetilide *(with advanced renal failure)*
Asthma/chronic obstructive pulmonary disease	Adenosine β-Blockers Propafenone	–

[a]Dose reduction may be necessary.

ANTIARRHYTHMICS IN PREGNANCY

Antiarrhythmic drugs have played a central role in the treatment of arrhythmias in the mother as well as the fetus. Increased arrhythmogenesis in pregnancy underscores the importance of the knowledge of safe use and key adverse effects in the various antiarrhythmic drugs that may be utilized in this population. Table 87–4 summarizes the use of antiarrhythmic drugs and their potential adverse effects in pregnancy. As seen in this table, the strong majority of antiarrhythmic drugs are US Food and Drug Administration Category C, meaning that risk to the fetus cannot be ruled out. This is because of the paucity of randomized control trials (animal or human) necessary to demonstrate a higher level of evidence-based safety.

The significant increase of 40% to 50% in intravascular volume may affect doses needed to reach therapeutic levels of concentration and loading doses. Altered absorption characteristics, reduced drug protein binding, and increased renal blood flow also may similarly affect drug blood levels. These changes underscore the importance of closely following drug levels (when possible), as well as monitoring for therapeutic effect and potential toxicities.

Quinidine and procainamide have been safely used for the treatment of maternal and fetal arrhythmias. For pregnant women who develop atrial fibrillation in pregnancy, both quinidine and procainamide can be used to try to pursue pharmacologic cardioversion.[62] Quinidine may cause thrombocytopenia and eighth nerve damage in the fetus; chronic administration of procainamide may be associated with autoimmune responses such as lupus-like syndrome. There is limited experience with the use of disopyramide, but it can cause uterine contraction and premature labor.

Lidocaine is well tolerated and widely used in pregnancy. Intravenous lidocaine is administrated primarily for the acute management of life-threatening ventricular arrhythmias. Flecainide appears to be a well-tolerated option for maternal arrhythmias, particularly atrial fibrillation, and has evidence of safety in data with its use in treating fetal tachyarrhythmias.[94] Experience with mexiletine and propafenone in pregnancy is more limited.[95,96] Because propafenone and flecainide have good transplacental passage, both have been used as second-line therapy for sustained fetal supraventricular arrhythmias, particularly in the presence of hydrops fetalis, that are refractory to digoxin.[94,96]

β-Adrenergic blockers are primarily used to treat hypertension and thyrotoxicosis in pregnancy. These agents are generally safe for the mother and the fetus. β-Adrenergic blockers are useful in the treatment of supraventricular tachycardia, atrial fibrillation or atrial flutter, idiopathic ventricular tachycardia, and long QT syndrome. Prophylactic treatment with β-adrenergic blockers significantly reduces the risk of cardiac events in patients with the congenital long QT syndrome, particularly in the postpartum period when patients are at the highest risk.[97]

The adverse effects of β-adrenergic blockers include bradycardia, hypoglycemia, fetal apnea, premature labor, and metabolic abnormalities, but these effects occur more frequently in high-risk patients.[98] Because β-adrenergic blockers may cause intrauterine growth retardation,[99] the use of β-adrenergic blockers in the first trimester of

TABLE 87–4. Antiarrhythmic Drugs and Pregnancy

Drug	FDA Class[a]	Indications	Possible Adverse Effects	Comments
Quinidine	C	SVT/CBT and VT	Maternal and fetal thrombocytopenia, eighth nerve toxicity, and TdP	Long record of safety
Procainamide	C	SVT/CBT, VT, or undiagnosed WCT	Lupus-like syndrome with long-term use and TdP	Long record of safety
Disopyramide	C	Limited experience Induction of labor	Uterine contractions, premature labor, and TdP	Limited experience
Lidocaine	B	VT	CNS adverse effects and bradycardia	Long record of safety
Mexiletine	C	VT	CNS adverse effects and fetal bradycardia	Limited usage
Flecainide	C	SVT/CBT and selected VT	?	Used in fetal SVT with hydrops fetalis; more recent evidence of safety
Propafenone	C	SVT/CBT and selected VT	?	Used in fetal SVT with hydrops fetalis
β-Blockers	B-D	SVT, AF/AFL, selected VT, and LQTS	Intrauterine growth retardation, fetal bradycardia, hypoglycemia, and apnea	Generally safe; avoid during first trimester
Sotalol	B	SVT and VT	Bradycardia and TdP	Limited experience
Amiodarone	D	Life-threatening VT	Fetal hyper- or hypothyroidism, growth retardation, prematurity, bradycardia, and malformation	Avoid during first trimester
Dronedarone	X	–	Fetal vascular and skeletal malformations	Absolutely contraindicated in pregnancy
Ibutilide	C	Acute termination of AF/AFL	TdP	Limited record of safety
Verapamil	C	SVT, AF/AFL, and selected VT	Maternal hypotension, fetal bradycardia, and AV block	Relatively safe
Diltiazem	C	SVT and AF/AFL	Maternal hypotension, fetal bradycardia, and AV block	Verapamil preferred
Digoxin	C	SVT and AF/AFL	Low birth weight and premature labor	Long record of safety
Adenosine	C	Acute termination of SVT	Transient dyspnea and fetal bradycardia	Short duration of effect

[a]FDA pregnancy categories: A, no risk demonstrated in well-controlled studies in humans; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.

Abbreviations: AF/AFL, atrial fibrillation/flutter; AV, atrioventricular; CNS, central nervous system; FDA, Food and Drug Administration; LQTS, long QT syndrome; SVT, supraventricular tachycardia; SVT/CBT, supraventricular tachycardia using concealed bypass tract; TdP, torsade de pointes; VT, ventricular tachycardia; WCT, wide complex tachycardia; ?, unknown.

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pregnancy should be avoided. Although some β-adrenergic blockers, such as propranolol, atenolol, labetalol, nadolol, and metoprolol, are excreted in breast milk, significant bradycardia in infants may be seen, although rarely.

There is relatively limited experience with the use of class III antiarrhythmic drugs in pregnancy. Sotalol has been used in the treatment of refractory maternal and fetal supraventricular and ventricular arrhythmia, including efficacy in terminating fetal atrial fibrillation.[94] Sotalol or flecainide is typically considered for ventricular arrhythmias that fail β-blocker therapy. Ibutilide has also been used safely in case reports for chemical cardioversion of atrial fibrillation, but its use in this setting has not yet been broadly demonstrated.[100,101]

Amiodarone should be totally avoided or used with extreme caution for arrhythmias that are refractory to other drugs and are life threatening. Amiodarone causes hypothyroidism or hyperthyroidism, congenital abnormalities, bradycardia, premature labor, low birth weight, and prematurity.[102,103] Amiodarone is excreted in breast milk and can cause hypothyroidism or hyperthyroidism, but not significant bradycardia, in breast-fed infants. Dronedarone is US Food and Drug Administration Category X and is absolutely contraindicated as it has animal data showing teratogenic effects, specifically vascular and skeletal malformations.

Calcium channel blockers, like verapamil and diltiazem, have been used for supraventricular tachycardia and control of the ventricular response to atrial fibrillation or flutter in pregnancy. These agents are also useful in the treatment of selected idiopathic ventricular tachycardias. Calcium channel blockers are considered to be relatively safe, although they have the potential to cause hypotension, heart block, bradycardia, and exacerbation of heart failure in mother and fetus.

Digoxin has a long record of safety for the treatment of supraventricular tachycardia including AV nodal reentrant tachycardia and atrial fibrillation or flutter in pregnancy.[104] Because digoxin can cross the placenta, it has been used to treat fetal supraventricular tachycardia. It is often administered in a relatively large dose to the mother to obtain a therapeutic plasma concentration in the fetus because transplacental passage of digoxin may be impaired by some pathologic conditions, such as hydrops fetalis.[96,104] Digoxin is associated with premature labor and low birth weight. Adenosine is used for the acute termination of supraventricular tachycardia and is not associated with adverse effects in the mother or fetus. Fetal bradycardia may occur occasionally but is usually very brief because of the drug's short half-life.

DRUG-DEVICE INTERACTIONS

Patients with devices may require concomitant drug therapy for a variety of reasons, the most common being to reduce arrhythmia frequency. An antiarrhythmic drug can cause excessive rate slowing that mandates placement of a permanent pacemaker. Drugs can also have an impact on the pacing threshold and the thresholds for arrhythmia termination, which can be seen in Table 87–5. In general, drugs that reduce the sodium current should be expected to raise pacing and defibrillation thresholds, whereas potassium channel blockers reduce the defibrillation threshold and exert little effect on capture threshold. Drugs can change ventricular tachycardia rate and thus the efficiency of detection and termination algorithms.[105] Slowing of ventricular tachycardia may be beneficial in improving hemodynamic stability and decreasing risk of degeneration to ventricular fibrillation, but may also lead to underdetection by the device.

TABLE 87–5. Threshold Effects of Some Antiarrhythmic Drugs

Drug	Pacing Threshold	Defibrillation Threshold
Quinidine	Increase	Increase
Procainamide	Increase	No change
Lidocaine	No change	Increase
Mexiletine	Slight increase	Increase
Flecainide	Increase	Increase
Propafenone	Increase	No change
β-Blockers	Variable	No change
Sotalol	No change	Decrease
Dofetilide	No change	Decrease
Ibutilide	No change	Decrease
Amiodarone	Variable	Increase
Dronedarone	No change	No change
Verapamil	Increase	No change
Digitalis	Decrease	No change or decrease

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SUMMARY

Arrhythmia management is a constantly evolving practice, which requires a comprehensive knowledge of antiarrhythmic drugs, ablation, device implementation and strategies to decrease arrhythmia burden, symptoms, and risk of adverse outcomes. An individualized antiarrhythmic strategy is integral to effective arrhythmia management. Knowledge of antiarrhythmic drug indications, pharmacokinetics, adverse effect profiles, and both contraindications and optimal use in specific patient populations is critically important in guiding safe and effective antiarrhythmic use.

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CHAPTER 88

CATHETER-ABLATIVE TECHNIQUES

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INTRODUCTION

Major advances have been made in the field of interventional cardiac electrophysiology (EP) over the past three decades. Catheter-based ablation enables minimally invasive therapeutic options in the management of various tachyarrhythmias. Ablation is often guided by EP study and mapping to diagnose the arrhythmia and localize the arrhythmogenic substrate that is to be targeted for ablation. Catheter ablation requires expertise and constitutes a major procedural component, in addition to implantation and management of cardiac electronic devices, within the subspecialty of clinical cardiac electrophysiology. In this chapter, we discuss (1) general technical considerations for catheter ablation, (2) specifics related to ablation of different arrhythmias, and (3) potential complications of ablation.

TECHNICAL CONSIDERATIONS

EP study and catheter ablation are performed in the clinical EP laboratory, yet prior review of the specific arrhythmia and medical background, especially cardiac function and anatomy, is fundamental. General anesthesia facilitates patient comfort and safety during the procedure, which typically require 4 to 8 hours without significant patient motion. Certain arrhythmias are driven in part by sympathetic/catecholaminergic axes and can be rendered noninducible by anesthetic agents. This can preclude identification of the culprit rhythm, and inhaled anesthetic gases, benzodiazepines, and opioids are commonly avoided, while propofol or ketamine are less suppressive of arrhythmia.

ACCESSING THE HEART

Most EP studies and ablation procedures require percutaneous access to the heart with multiple catheters. These catheters contain multiple electrodes for recording intracardiac electrical signals and in addition are capable of electrical stimulation of the myocardium (Fig. 88–1), and are inserted through sheaths placed in the femoral, jugular, or subclavian veins. Mapping of the relevant electrophysiologic substrate is performed by repositioning and recording of the constellation of electrical signals throughout the relevant sections of the heart. Current catheter technology typically provides a soft, deflectable 1- to 5-mm mapping electrode that can be maneuvered throughout the atria, ventricles, coronary sinus, pulmonary veins, and above and below the atrioventricular and semi-lunar valves. Left-sided chambers are accessed with a trans-interatrial septal puncture or femoral arterial access for retroaortic mapping of the left ventricle and/or the sinuses of Valsalva. Epicardial mapping is performed through the coronary vein branches of the coronary sinus, or by direct percutaneous access to the pericardial space from the subxiphoid region (Fig. 88–2).[1]

Catheter ablation is commonly performed by a single 3.5- to 8-mm electrode ablation catheter via the application of radiofrequency (RF) electrical energy that results in thermal injury to the adjacent myocardium. The procedural risks depend on the location of the arrhythmia in addition to the relevant anatomic and patient considerations. Thrombus formation on catheters and the ablated regions in the left heart chambers can result in systemic embolization and stroke. To mitigate this risk, it is necessary to use systemic anticoagulation (with intravenous heparin) during the procedure.[2] The use of anticoagulation, however, increases the risk of bleeding, including pericardial effusion and access-site vascular complications.

CATHETER POSITIONING AND IMAGING MODALITIES

Echocardiography, cardiac computed tomography (CT), and magnetic resonance imaging (MRI) allow for the appreciation of the cardiac anatomy prior to the ablation procedure. Catheters are positioned during the ablation procedure using fluoroscopy and guided by intracardiac chamber- and contact-specific electrogram recordings (Figs. 88–1 and 88–3). Fluoroscopy is supplemented by other real-time modalities like computerized mapping systems and intracardiac echocardiography.

Fluoroscopy

Fluoroscopy provides a two-dimensional projection of the cardiac anatomy and catheter orientation, yet is operator dependent, utilizing either a single plane of view or two orthogonal views to create a three-dimensional location of catheters. The right anterior oblique (RAO) and the left anterior oblique (LAO) are common views (Figs. 88–1, 88–2, and 88–4). The RAO is a profile view of the heart. This differentiates the atrial and the ventricular components; however, there is overlap of the left- and right-sided structures. The LAO view is an end-on view from the apex to base with foreshortening of the long axis of the

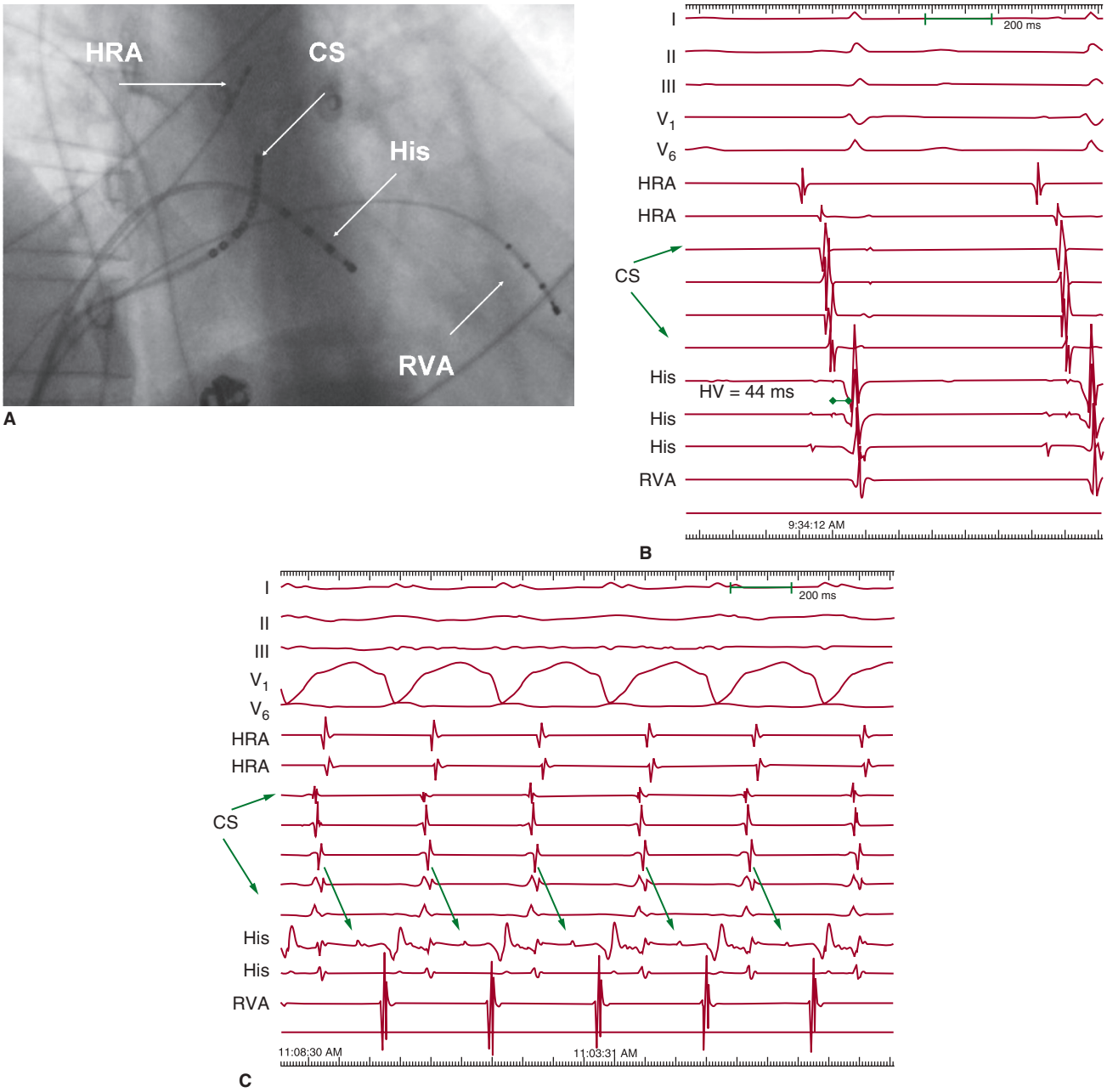


FIGURE 88–1. Standard intracardiac catheter positioning and recordings for an electrophysiology study and supraventricular tachycardia ablation. **A.** A right anterior oblique fluoroscopic image of a typical initial catheter setup. Catheters are placed via the femoral vein. There is a quadripolar catheter in the high right atrium (HRA) and in the right ventricular apex (RVA). There is another quadripolar catheter positioned to measure a His bundle (His) electrogram and a decapolar catheter in the coronary sinus (CS). **B.** Baseline conduction intervals in sinus rhythm with a normal HV interval of 44 ms. Note that atrial activation times with the P wave on the surface ECG and starts with the HRA catheter that is nearest to the sinus node. **C.** A patient in atrioventricular reentrant tachycardia with left bundle branch block. Note that on the surface leads, there is a wide complex with QS pattern in V_1. *Arrows* indicate the HB deflection preceding each QRS complex, indicating conduction down the His-Purkinje system producing the observed wide complex on the surface ECG.

heart. The LAO projection facilitates differentiating the left from the right side chambers, and the septal from the free wall aspect within a chamber. The location of catheters is inferred by relationship to various anatomic references including the cardiac silhouette, vertebral column, diaphragm, fat stripe along the atrioventricular groove, implanted lead, and intracardiac catheters. Iodinated contrast injections are used to characterize the anatomy of coronary arteries and veins, pulmonary veins, left atrial appendage, etc.

Intracardiac Echocardiography

Intracardiac echocardiography (ICE) is performed with an 8- or 10-French ultrasound transducer mounted at the tip of a catheter. Linear phased array and radial ICE catheters are available. ICE supplements fluoroscopy by allowing detailed real-time visualization of structures like the interatrial septum, Eustachian ridge, cardiac valves, papillary muscles, false tendons, coronary artery ostia, as well as confirming catheter position, tissue contact, and ablation lesion formation (Fig. 88–5).

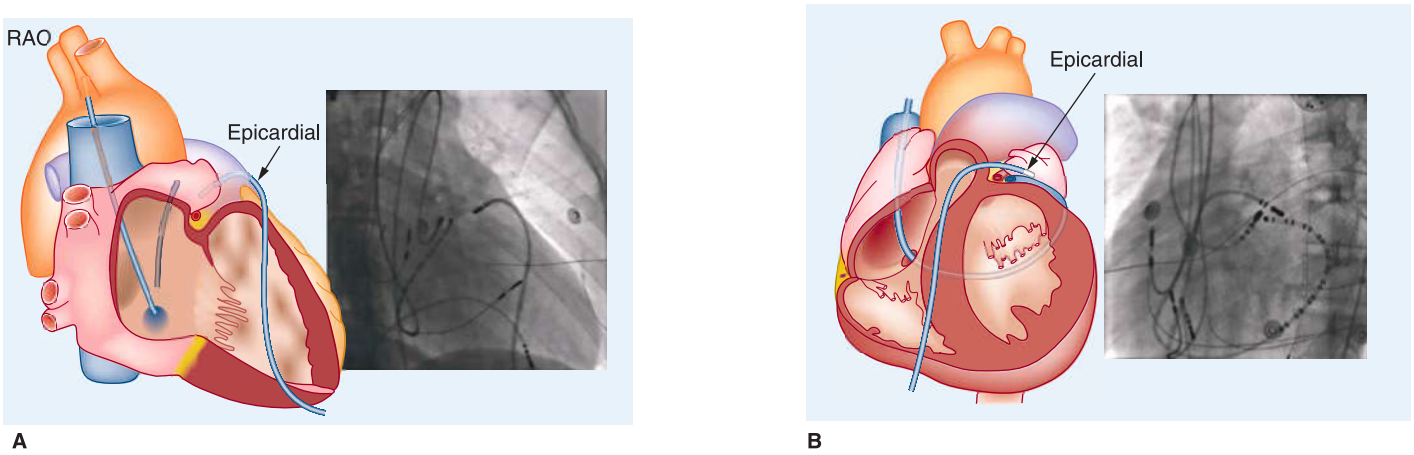


FIGURE 88–2. Epicardial ablation for ventricular tachycardia. Illustrations and correlated fluoroscopic images for ablation of ventricular tachycardia in a patient with previous failed endocardial ablation are shown **A.** Right anterior oblique (RAO) shows a side view of the heart with a multielectrode catheter placed in the coronary sinus. Note a catheter placed via subxiphoid pericardial access placed in the epicardial surface of the ventricular outflow tracts that in this patient represented the source of the arrhythmias. **B.** Left anterior oblique (LAO) in the same patient. Note the epicardial catheter, coronary sinus catheter, and an endocardial catheter placed near the aortic valve allow simultaneous mapping defining the true origin of tachycardia. Appreciation of exact anatomy and fluoroscopic correlation has allowed safer and more efficacious management of complex cardiac arrhythmia.

ICE allows quick assessment for complications like pericardial effusion or formation of thrombus.

Three-Dimensional Mapping Systems

Mapping systems construct a real-time representation of the mapping catheter position in relation to the chamber being mapped. They thereby facilitate less fluoroscopy use, and provide a mechanism to hallmark certain electrical and anatomical features/characteristics. These electroanatomic mapping tools receive electrophysiologic input from a large number of mapped points tagged with three-dimensional spatial localization to create computerized chamber geometries.[3,4] Activation times (in reference to a fiduciary electrical signal), recorded voltage, and other characteristics of local electrograms are depicted

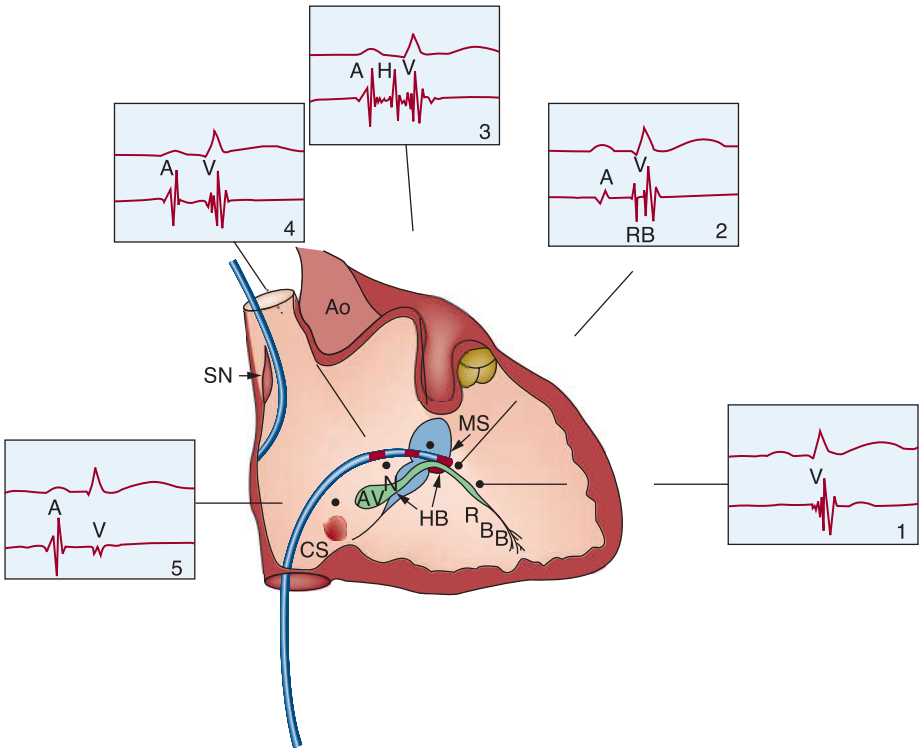


FIGURE 88–3. Intracardiac recordings from the specialized conduction system in the region of the atrioventricular (AV) junction. The recording of various electrograms along the right side of the interventricular septum with gradual withdrawal of the catheter across the tricuspid valve is shown. The intracardiac recordings are labeled. Numbers 1 through 5 refer to intracardiac location of catheters along with corresponding electrogram. A, atrial deflection; Ao, aorta; AVN, atrioventricular node; CS, coronary sinus; H and RB, His and right bundle potentials; HB, His bundle; MS, membranous septum; RBB, right bundle branch; SN, sinus node; V, ventricular deflection. Reproduced with permission from Grossman W: Cardiac Catheterization and Angiography. Philadelphia: Lea & Febiger; 1980.

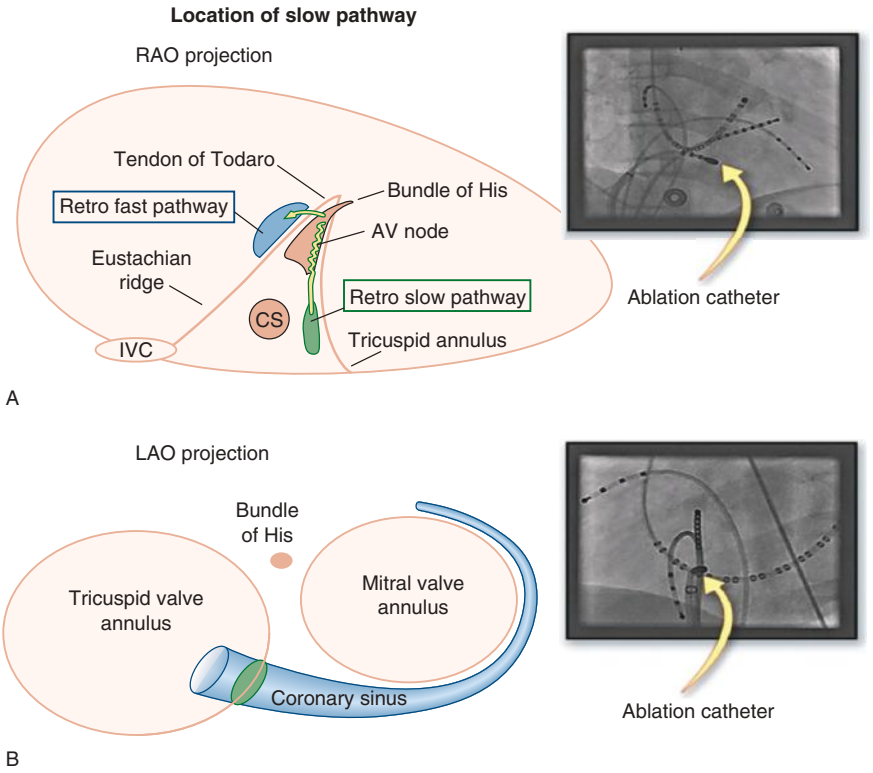


FIGURE 88–4. Atrioventricular (AV) nodal reentry tachycardia. Illustrations with correlated fluoroscopic images of the right anterior oblique (RAO; **A**) and left anterior oblique (LAO; **B**) projections. The ablation catheter is placed in the region of the coronary sinus (CS) ostium. This is the location of the slow pathway input to the AV node. Ablation at this site transects the AV node reentry circuit and is highly successful (success rates > 95%) in treating typical AV node reentry. The compact AV node is located close to the annulus near the septal leaflet of the tricuspid valve. Because of the complexity of the right atrium, the atrial connections to the AV node may be discrete in some patients, forming the fast and slow pathways—the limbs of the AV node reentry circuit. (IVC, inferior vena cava.)

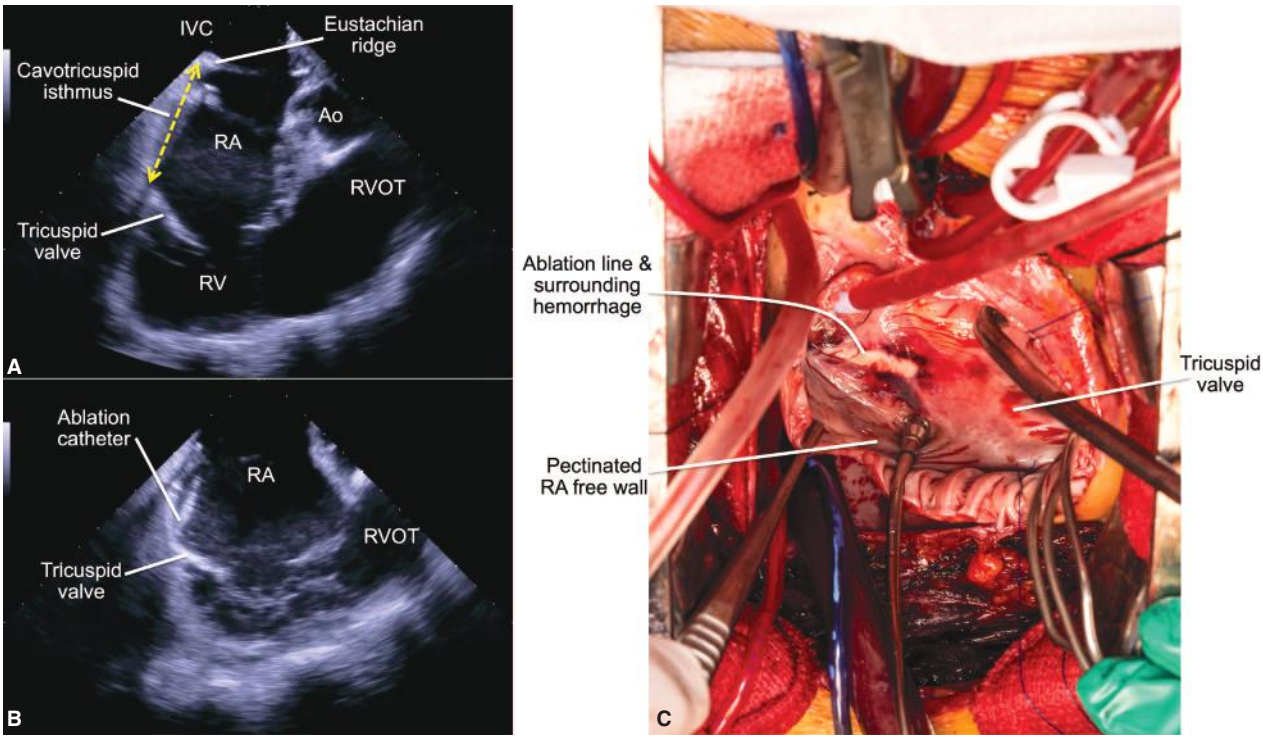


FIGURE 88–5. A. Intracardiac echocardiography (ICE) during linear cavotricuspid ablation for inducible typical right atrial flutter. Electrophysiology study was performed 1 day before cardiac surgery for tricuspid valve repair in this patient with Ebstein anomaly. The phased array ICE catheter is positioned in the right atrium with the imaging sector towards the tricuspid valve. **B.** ICE image during radiofrequency (RF) catheter ablation across the cavotricuspid isthmus. **C.** The linear RF ablation with surrounding hemorrhage is visible from the right atriotomy during surgery. Ao, aortic root; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract.

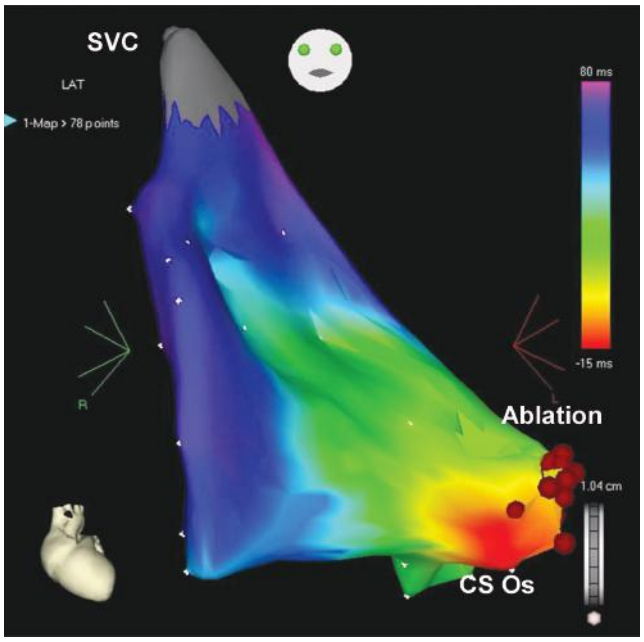


FIGURE 88–6. Activation map of focal atrial tachycardia originating from the coronary sinus ostium (CS Os). Shown here is an electroanatomic map of the right atrium created by moving a catheter point by point throughout the atrium. Sensing of a low-energy electromagnetic field is used to calculate the position of the catheter in three-dimensional space without the need for fluoroscopy, allowing monitoring of catheter position and creation of an anatomic shell. The superior vena cava (SVC) is marked in *gray*. *Colors* indicate activation times during tachycardia. The earliest area of activation appears *red*, and progressively later activation is indicated by *orange*, *yellow*, *green*, *blue*, and *purple*, respectively. In this case, activation originated at the ostium of the CS and spread rightward across the atrium from that site. Ablation lesions placed at the early region, indicated by the *small red spheres*, abolished the tachycardia.

with a color-coded display (Figs. 88–6 to 88–9). Mapping systems can also import and integrate the cardiac chamber anatomy from imaging modalities like cardiac CT, MRI, or ICE (Fig. 88–10).[5]

Magnetic field-based systems measure the field strength at the mapping electrode of the magnetic field emanated from a point source to deduce the relative distance. Distance of the mapping electrode from three point sources of time varying magnetic fields of different frequencies is used to triangulate the location in three-dimensional space (Carto 3 System, Biosense-Webster, Diamond Bar, CA).[3,4,6] *Electrical impedance-based systems* calculate the spatial location by sensing the voltage gradient of three orthogonal low-voltage electrical currents of specific frequencies applied across the patient's chest (EnSite NavX, St. Jude Medical, St. Paul, MN).[3]

CARDIAC MAPPING

Cardiac mapping is performed with acquisition of data during an arrhythmia and can be achieved in a point-by-point manner or via the use of multielectrode mapping of multiple points simultaneously.[7] In *activation mapping* the local activation time (electrogram) can be annotated compared to a fiducial reference point (surface electrocardiogram [ECG] or fixed intracardiac electrode). Compilation of the activation times at all sites within a chamber depicts the spread of the activation wavefront. Focal arrhythmias originate from a point-source and spread in a centrifugal manner, with the earliest site of activation of the myocardium correlating with the successful site of ablation (see Fig. 88–6).[8] Macroreentrant arrhythmias occur as a result of continuous repetitive activation around a reentry circuit. In this case cardiac activation is occurring at some site throughout the tachycardia cycle without any period of complete quiescence. These reentrant circuits are usually amenable to continuous resetting by pacing at a slightly faster

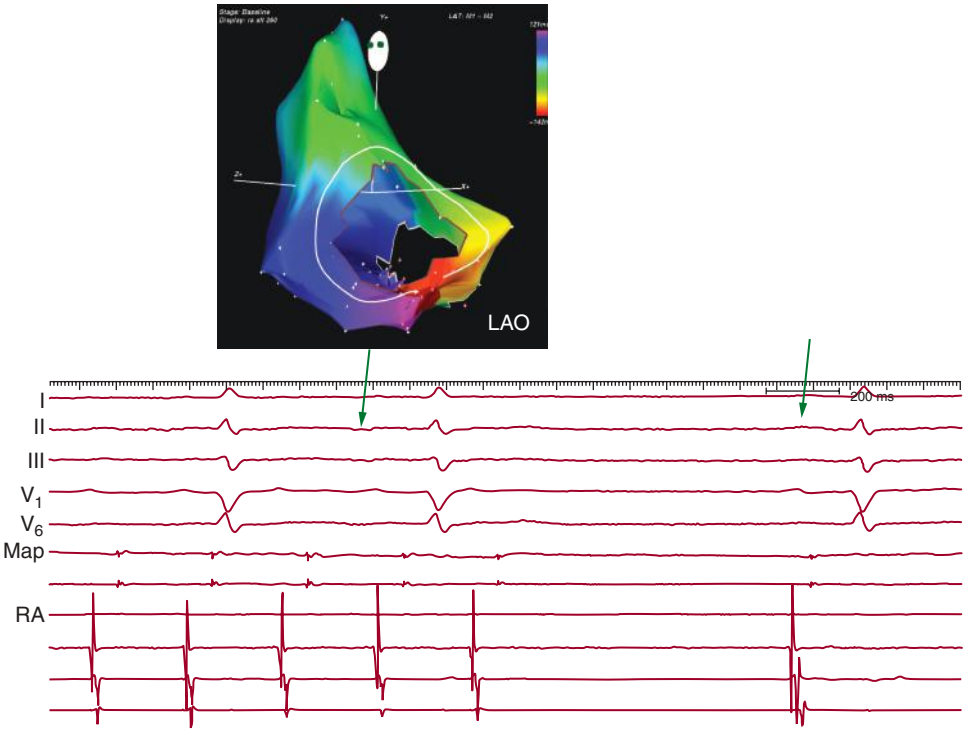


FIGURE 88–7. Mapping and ablation of typical counterclockwise atrial flutter. At the top is an activation map of the right atrium during counterclockwise atrial flutter created as described in Fig. 88–6. The atrium is viewed from a left anterior oblique (LAO) projection. Activation circulates up the interatrial septum, across the roof of the atrium, and down the free wall of the atrium and through the sub-Eustachean isthmus between the tricuspid valve annulus and inferior vena cava. A line of radiofrequency lesions was placed across this isthmus, which blocked conduction in the isthmus terminating atrial flutter. The tracing at the bottom shows surface electrocardiographic leads and intracardiac recordings from the mapping catheter (Map) and lateral right atrium (RA) during RF ablation. Atrial flutter terminates and is followed by sinus rhythm (*arrow*).

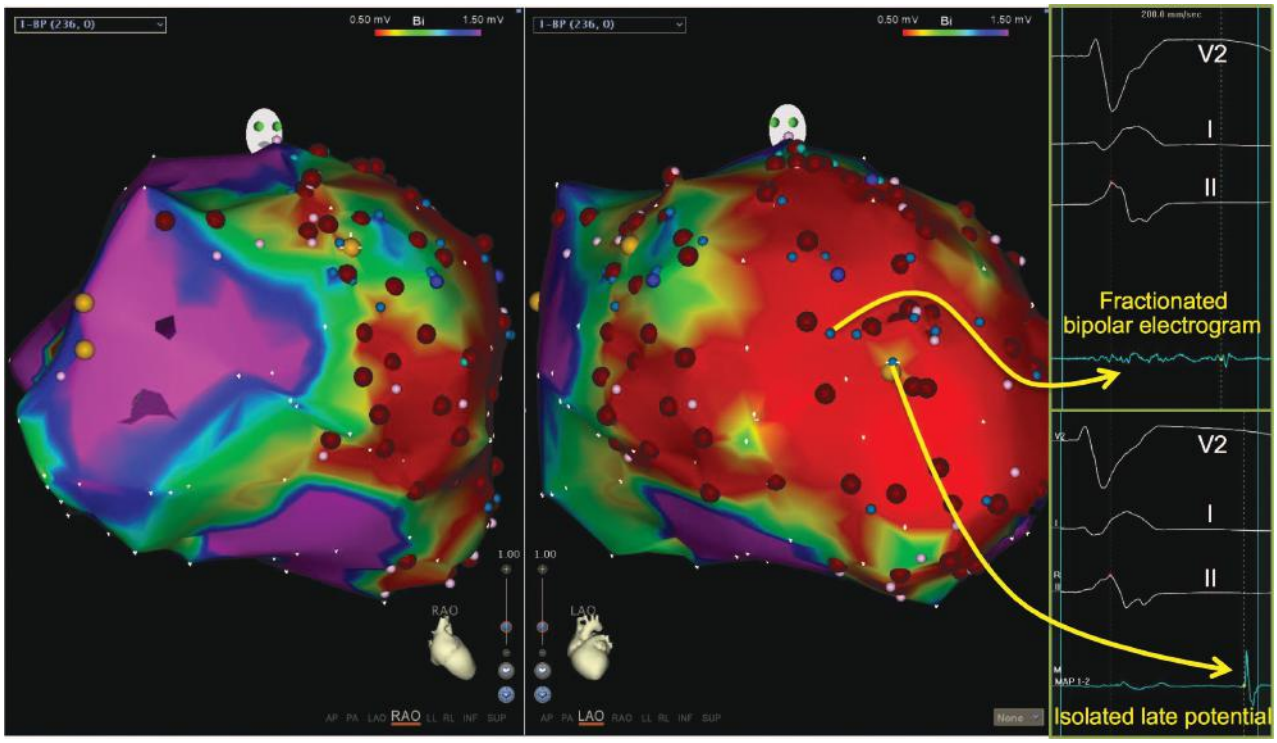


FIGURE 88–8. Electroanatomic voltage map of the left ventricle in a patient with sustained monomorphic ventricular tachycardia (VT) caused by an old anterior wall myocardial infarction. Right anterior oblique (RAO) and left anterior oblique (LAO) projections are shown. In contrast to the maps shown in Figs. 88–6 and 88–7, the color coding indicates the bipolar voltage acquired at each point in the map during sinus rhythm. Normal voltage is that above 1.5 mV and is *purple*. Voltage progressively decreases as colors proceed to *blue*, *green*, *yellow*, *orange*, and *red*. The large low-voltage region is consistent with a prior anteroseptal infarction. Sites with abnormal local electrograms during sinus rhythm mapping are labeled with *small blue spheres* (late activation) and *pink spheres* (fragmented signals). The prototypical abnormal sites shown in the right-hand panel were the arrhythmogenic substrate participating in the reentry circuit of the clinical VT, and ablation at the site labeled *isolated late potential* terminated the clinical VT. Further substrate ablation of the abnormal electrograms within the low-voltage region (*maroon spheres*) was performed and no VT was subsequently inducible.

rate than the tachycardia and insights can thereby be gained into mechanism and location of the reentry circuit (*entrainment mapping*).[9] Successful treatment of reentry relies on identifying and confirming with entrainment a critical isthmus necessary to maintain the circuit, that is then transected with ablation (see Figs. 88–5 and 88–7).

Substrate mapping can be performed during sinus rhythm or during an arrhythmia (along with activation mapping) to identify diseased myocardial sites. Arrhythmogenic sites may have low-voltage, fractionated or late activated electrograms that are targets for ablation (see Fig. 88–8).[10] *Pace mapping* is performed by pacing from various sites and comparing the generated surface ECG morphology to the template arrhythmia.[8] A pace match may identify regions close to the site of origin of a focal arrhythmia or exit site of a reentrant tachycardia.[11] Failure to electrically stimulate the tissue in contact depicts presence of electrically inert scar.

HEMODYNAMIC SUPPORT

It is optimal to study the mechanism and physiology of the arrhythmia by mapping while the patient is sustained in the pathologic rhythm. Ventricular tachycardias, especially in patients with structurally diseased hearts, are sometimes hemodynamically unstable despite treatment with vasopressors. This precludes detailed activation and entrainment mapping, with potential failure to appreciate the true arrhythmogenic substrate to ablate successfully. Substrate and pace mapping is important and often may be adequate. However, in some cases, mechanical hemodynamic support (eg, with percutaneous left ventricular assist device) is required to enable mapping and ablation.[12]

ROBOTIC NAVIGATION SYSTEMS

Robotic systems are sometimes used to maneuver catheters within the heart. Magnetic navigation systems (Niobe Magnetic Navigation System, Stereotaxis, St. Louis, MO) use large magnets to generate deflecting forces on the magnetized mapping catheter.[3] The catheter is robotically manipulated from a computer console. This allows controlled advancement or retractions, and precise rotations in all spatial coordinates. Other systems use regular mechanically deflectable catheters that are controlled with a robotic system that translates operator hand motion to catheter movements (Sensei X Robotic Catheter System, Hansen Medical, Mountain View, CA).

NONINVASIVE CARDIAC MAPPING

Major advancements have being made in the bioengineering for activation mapping of cardiac arrhythmias noninvasively to guide ablative therapy. Electric signals are recorded using numerous electrodes (eg, vest with 250 electrodes) from the body surface. High-resolution imaging (noncontrast CT) is used to obtain the atrial or ventricular epicardial geometry and its spatial relationship to the electrodes. Computerized computational analysis then uses this data to reconstruct the regional cardiac electrograms and activation maps (Fig. 88–11).[13,14]

ABLATION ENERGY SOURCES

A variety of techniques have been evaluated for cardiac tissue ablation and include electrical energy in the radiofrequency spectrum, cryoenergy, lasers, microwaves, high-intensity focused ultrasound,

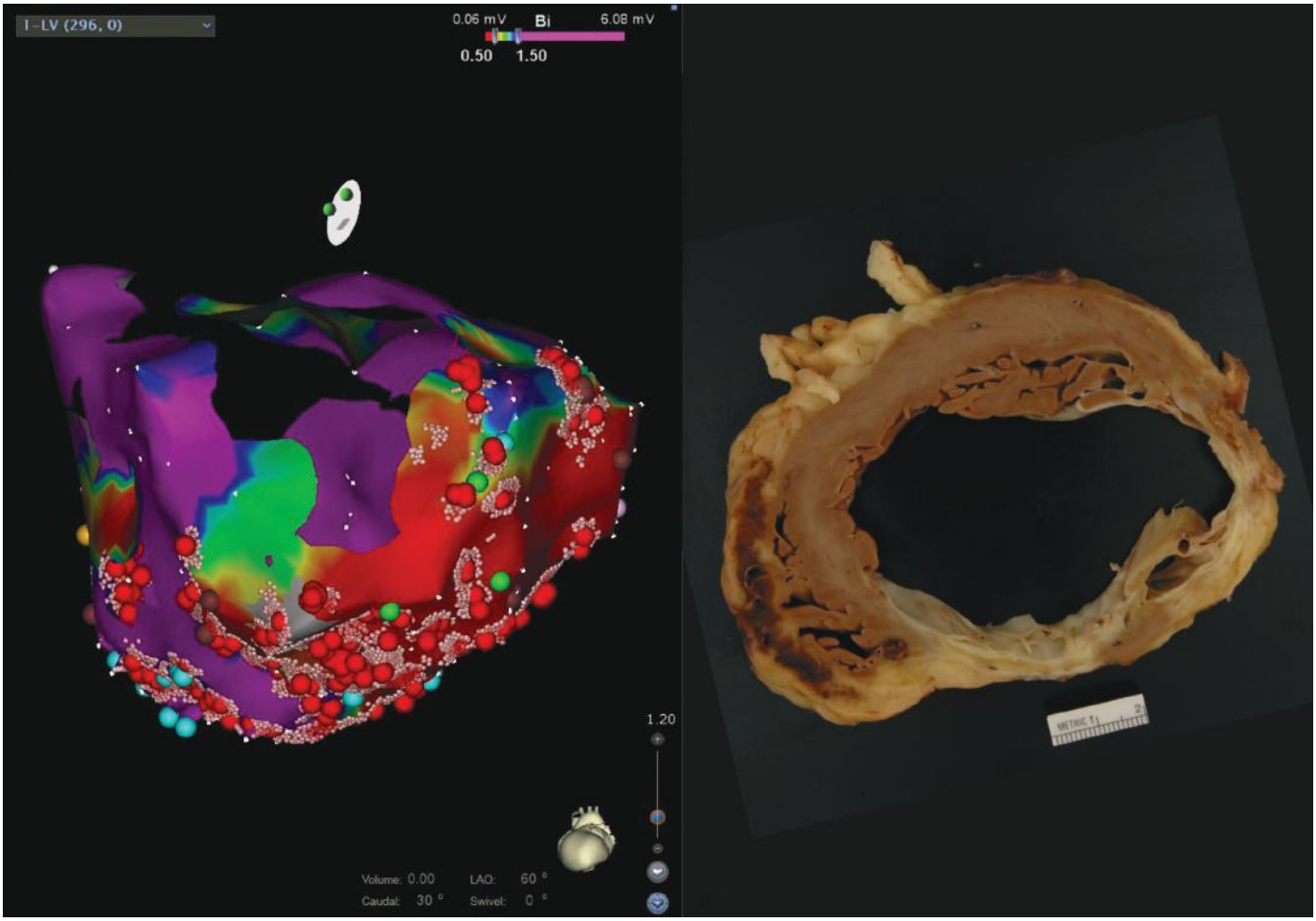


FIGURE 88–9. A patient with severe dilated nonischemic cardiomyopathy status post-mitral valve repair with recurrent ventricular tachycardia and ICD shocks. **A.** Electroanatomic endocardial left ventricle substrate map seen in left anterior oblique (LAO) caudal projection. Color coding shows regions of very low bipolar recorded voltage (< 0.5 mV) in *red*, and good voltages (> 1.5 mV) in *purple*. Substrate modification to treat multiple ventricular tachycardia morphologies was performed with ablation areas represented with *red spheres*. **B.** The patient subsequently underwent total artificial heart placement for refractory heart failure and the pathologic section of the resected heart is shown. Note correlation of regions of scarred fibrotic myocardium with red very low voltage areas in the electroanatomic substrate map. Also seen is iatrogenic hemorrhage in the right ventricular free wall sustained during attempted epicardial needle access.

radiotherapy, and chemical ablation with alcohol, with varying degrees of applicability in current clinical practice.

Radiofrequency Ablation

Initial attempts at catheter ablation of AV node for supraventricular tachycardias were with high-energy direct current (DC) shocks. These were painful and resulted in uncontrolled lesions with risk of life-threatening complications. The advent of radiofrequency (RF) energy in the ~500 kHz range has permitted more controlled and effective ablation by thermal injury. Reversible loss of myocardial excitability occurs between 43°C and 50°C, and cell death occurs at tissue temperatures above 50°C.[15] The RF current density is highest at the electrode-tissue interface, and a 1- to 2-mm rim of tissue in contact with the electrode is resistively heated (ohmic heating). Passive conductive heating of the surrounding tissue results in a larger lesion (Figs. 88–5 and 88–12).[16]

Lesion size is proportional to the RF power delivered to the tissue. However, power delivery is limited by excessive heating at the electrode-tissue interface, which causes formation of coagulum from blood proteins and subsequent char development. Convective cooling of the ablation electrode allows increase in power delivery without coagulum formation. Passive convective cooling increases with regional blood flow, increase in electrode size, and to-and-fro sliding of the electrode with cardiac and respiratory motion. Saline irrigation is often used to actively cool the ablation electrode to allow higher power delivery. In open irrigated catheters saline is driven through the lumen and cools the electrode as it is forced out of holes at the tip of the catheter. These measures allow increased power delivery without overheating of the ablation electrode; however, excessive heating of the myocardium can lead to tissue vaporization and subsequent injury secondary to steam generation (steam pop).[17]

Real-Time Assessment of Ablation Electrode temperature (measured with a thermistor or thermocouple in the electrode) is used as a surrogate of tissue temperature to ensure adequate heating during ablation. This is, however, not possible with actively cooled catheters. Tissue heating with onset of effective RF delivery results in a 5 to 10 Ω drop in impedance.[18] Loss of excitability of the local myocardium is seen as diminution of the recorded electrogram.[19] Lesion formation is seen in real-time with intracardiac echocardiography,[20] and better imaging techniques like MRI thermography have been developed.[21] Noninducibility of clinical arrhythmia is also an important end point of ablation.

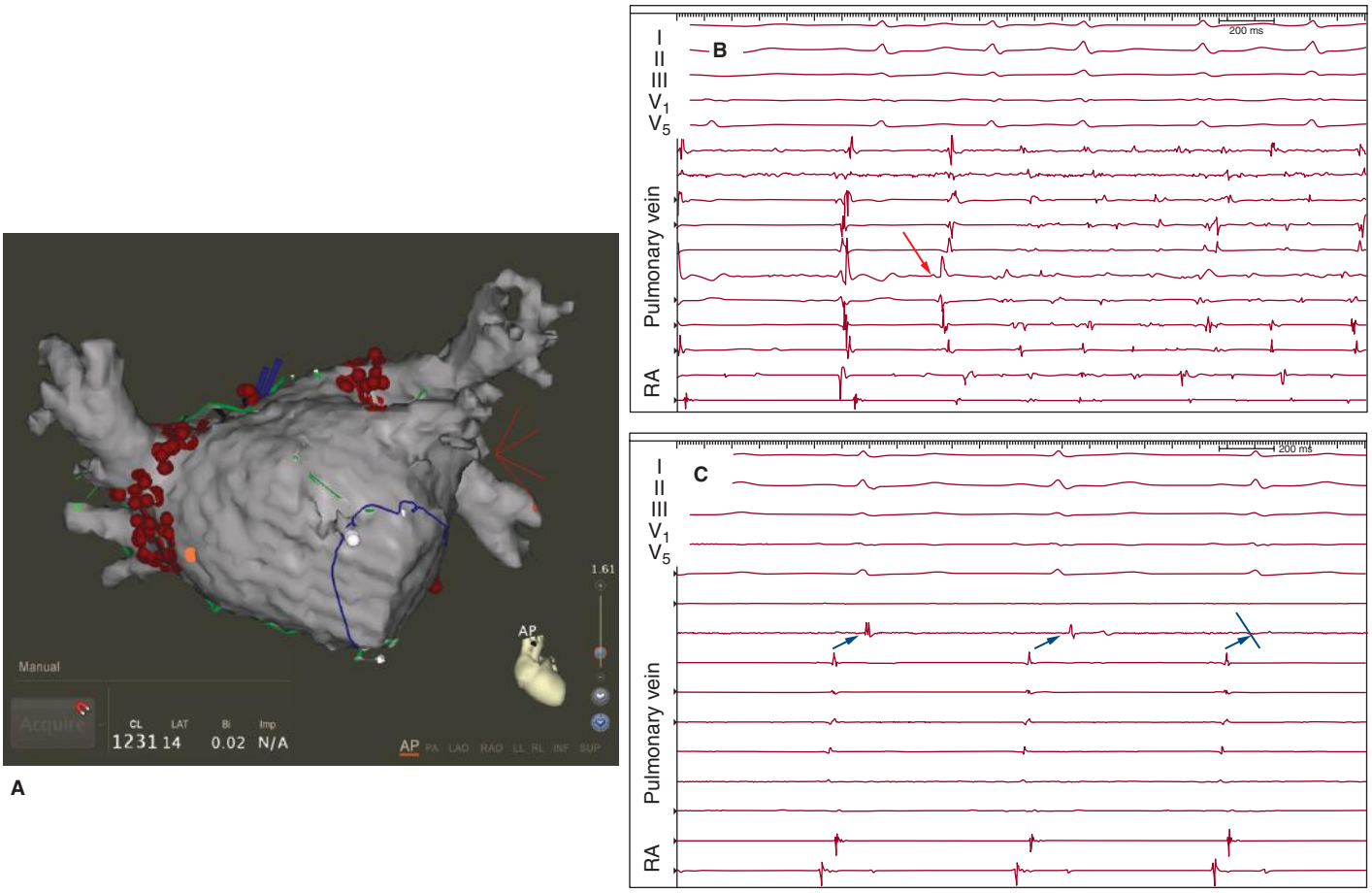


FIGURE 88–10. A. Magnetic resonance image (MRI) of the left atrium and pulmonary veins from a patient who underwent atrial fibrillation ablation, viewed from an anteroposterior posterior projection. Detailed MRI or computed tomography images of the anatomy are useful for guiding ablation and can be merged into three-dimensional mapping systems with intracardiac echocardiography data to guide ablation. **B, C.** Surface electrocardiographic leads and intracardiac recordings from a circular catheter placed in the left superior pulmonary vein and a separate catheter in the right atrium (RA). In **B**, the first beat is sinus rhythm that conducts into the sleeve of musculature around the vein, as indicated by the electrograms recorded from the vein. This is followed by a premature atrial beat that has earliest activation in the pulmonary vein (*arrow*) and that initiates atrial fibrillation, with rapid atrial electrical activity in the vein. In **C**, after radiofrequency (RF) ablation, lesions placed around the vein subsequently terminated atrial fibrillation (not shown), and sinus rhythm is again present. Note that the electrical signals recorded from the catheter in the vein are much reduced in amplitude compared to the sinus rhythm beat in **B**, and most are actually "far-field" signals from the left atrium outside the vein. A delayed pulmonary vein potential is potential at one electrode (*arrow*). During additional RF ablation, this final pulmonary vein potential (*arrow*) disappears after the third sinus beat, indicating block of conduction into the vein.

Contact Force Titrating the applied force with a force-sensing catheter has been shown to be associated with improved ablation efficacy.[22-24] Further greater force is counterproductive because it limits convective cooling and power delivery because of catheter wedging in the tissue, and increases risk of steam pop and myocardial perforation.[23,24]

Bipolar Radiofrequency Ablation Conventional RF ablation is delivered between an ablation electrode and a large grounding patch placed on the patient's skin. In this configuration, ablation of substrate deep within the thick ventricular myocardium may not be possible. Transmural ablation can be performed with bipolar delivery of RF current between electrodes on either side of the target tissue.[22] On the other hand, a continuous ablation line can be delivered with phased bipolar RF between respective electrode pairs on a linear or circular multielectrode ablation array.[25]

Needle Radiofrequency Ablation A novel needle-tip electrode is under development for accurate mapping and ablation of deep ventricular myocardial arrhythmogenic substrate. The needle is inserted within the myocardium and delivers RF with saline irrigation allowing for extension of the ablation lesion.[26]

Cryothermal Ablation

Cryoablation results in well-defined homogenous lesions preserving the ultrastructural integrity of the tissue (see Fig. 88–12). The mechanism of tissue injury includes freezing, thawing, inflammation, and fibrosis.[27,28] Commercially available cryocatheters use nitrous oxide as the refrigerant and achieve temperatures in the −80°C range. Cryoablation lesions take longer to deliver than RF and may be less durable.

Advantages of Cryoablation Cryoablation results in adhesion of the catheter to the target tissue during the freeze. This is advantageous in regions with poor catheter stability and in vicinity of critical structures like the AV node. Additionally, an initial period of reversible injury during the freeze provides an opportunity to assess safety and efficacy.[27] Cryoablation has a lower risk of thromboembolism, cardiac perforation, and coronary arterial injury compared to RF.[27,29] A cryoballoon-based ablation at the pulmonary vein ostium can electrically isolate the entire vein with a single freeze, and has been shown to be equivalent in terms of efficacy and safety to radiofrequency ablation for paroxysmal atrial fibrillation.[27,30]

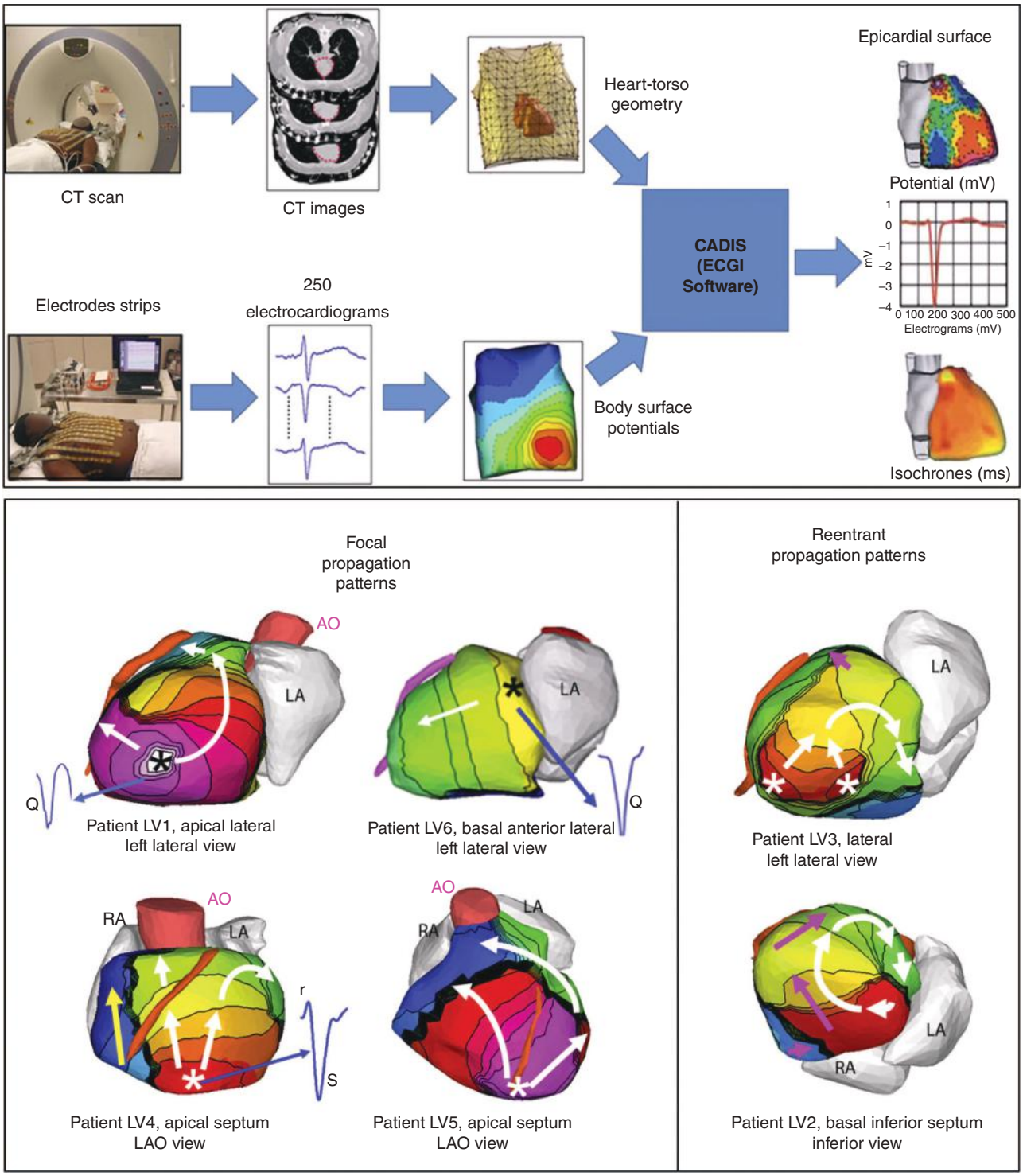


FIGURE 88–11. *Top Panel*. Noninvasive electrocardiographic imaging (ECGI) methodology: 250 carbon electrodes mounted in strips are applied to the patient's torso before a preprocedural thoracic computed tomography (CT) scan, which provides cardiac geometry and torso-electrode positions in the same reference frame. The electrodes are connected to a multichannel mapping system. The electrical and anatomical data are processed mathematically to obtain noninvasive ECGI epicardial images that include potential maps, electrograms, isochronal activation sequences, and repolarization patterns. *Bottom Panel*. ECGI-imaged propagation patterns, origins, and local electrograms for ventricular tachycardia (VT): Isochrone maps are shown for six patients, with earliest epicardial activation marked with an asterisk. Tachycardias that were determined to be focal during electrophysiologic (EP) studies demonstrate a radial spread (*white arrows*) away from the early activation point (*asterisk*). *Yellow arrows* indicate later phases of ventricular activation. Tachycardias that were determined to be reentrant during EP studies show a rotational activation pattern (*white arrows*). *Thick black lines* indicate conduction block. *Pink arrows* indicate later phases of ventricular activation. *Insets:* Several epicardial electrograms from sites of earliest activation are shown in *blue*, highlighting the presence or absence of r-wave; pure Q morphology indicates epicardial origin, rS morphology indicates intramural origin. Legend under each image indicates the location of VT initiation and identifies the displayed view of the heart. AO, aorta; LA, left atrium; LAO, left anterior oblique; RA, right atrium. Reproduced with permission from Wang Y, Cuculich PS, Zhang J, et al: Noninvasive electroanatomic mapping of human ventricular arrhythmias with electrocardiographic imaging. *Sci Transl Med*. 2011 Aug 31;3(98):98-84.

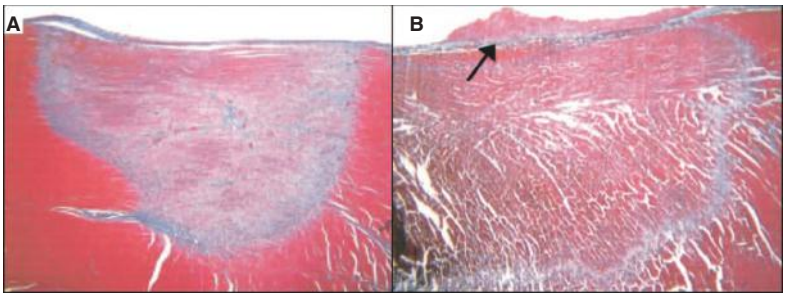


FIGURE 88–12. Histology of cryoablation and radiofrequency (RF) lesions. Typical characteristics seen 1 week after cryothermal (**A**) and RF (**B**) ablation when stained with Masson's trichrome and magnified 16-fold. Note the more homogeneous nature of cryolesion, with a smoother, sharper demarcation from intact myocardium (**A**). In contrast, RF lesion is less well circumscribed, with serrated edges (**B**). *Arrow* shows endocardial thrombus formation at ablation site. Reproduced with permission from Khairy P, Chauvet P, Lehmann J, et al: Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. *Circulation*. 2003 Apr 22;107(15):2045-2050.

Alcohol Ablation

Chemical ablation of the myocardium is achieved by selective injection of ethanol or phenol in a coronary vessel that is proximally occluded with a balloon. Alcohol septal ablation via a ventricular-septal perforator artery is used to alleviate outflow obstruction in patients with hypertrophic cardiomyopathy. Similar ablation can be performed for deep septal substrate of ventricular tachycardia.[31] This is limited by the availability of a suitable coronary arterial branch and difficulty in controlling the size of myocardial infarction. Alcohol ablation is also feasible to ablate the vein of Marshall for atrial fibrillation.[32]

Laser Ablation

A phase-coherent monochromatic high-intensity light beam in the visible, ultraviolet, or infrared frequency range is used to focus energy for thermally mediated ablation.[33] Carbon dioxide and argon lasers cause superficial lesions as a result of high energy absorption in water and myocardium, while Nd:YAG lasers result in deeper lesions because of higher scattering.[28] A variable inflatable balloon with an optical endoscope to visualize the adjacent tissue and a laser for point-to-point ablation have been used for durable electrical isolation of pulmonary veins.[34]

Microwave Ablation

Electromagnetic radiation in the microwave frequency range (300 MHz-300 GHz) causes dielectric heating by oscillation of polarized water molecules in the target tissue.[28,33] Adjacent tissue is heated by indirect conductive heating. Microwaves travel farther with less energy absorption in tissues with little water like fat, and have greater absorption in tissue with a high water content like myocardium. Ablation can be performed without direct tissue contact, across an intervening layer of adipose tissue, and results in deeper lesions compared to RF ablation. Microwave ablation is not available for commercial use.[35,36]

Noninvasive Radiation Therapy

Stereotactic body radiotherapy using x-rays and gamma spectrum radiation has been used for treatment of cancers. This modality is now being explored as a noninvasive technique for cardiac ablation. In vivo animal experiments have shown feasibility and safety for AV node ablation, right atrial flutter ablation, and pulmonary vein isolation with stereotactic body radiotherapy.[38,39] There have been case reports of successful noninvasive ablation of malignant ventricular tachycardia in humans.[40,41]

With x-rays and gamma radiation, DNA damage in active cancer cells is incurred largely indirectly through formation of hydroxyl ions, which interfere with cellular function and replication.[42] Direct ionizing effects of ionized particles like protons and alpha particles with high-energy absorption in tissue may be more effective for myocardial ablation. Heavy charged carbon-12 ions may allow for cardiac ablation with high precision without any exit dose.[43]

SPECIFIC ARRHYTHMIAS

SUPRAVENTRICULAR TACHYCARDIAS

The prevalence of supraventricular tachycardia (SVT) in the general population is ~2.25 per 1000 persons.[44] Paroxysms of SVTs, often with 1:1 AV relationship, can occur in the pediatric population and healthy adults in absence of overt structural heart disease. These include atrioventricular nodal reentry tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and focal atrial tachycardia (AT). Symptoms are often paroxysmal and include palpitations, chest pain, lightheadedness, and rarely syncope. Symptoms of SVT overlap with and are attributed to panic and anxiety disorders in a majority of patients. Macroreentrant atrial tachycardia (atrial flutter) tends to occur in older patients and those with structural heart disease, and often presents as a persistent arrhythmia that conducts 2:1 to the ventricles. Some incessant SVTs like AVRT using a decrementally conducting accessory pathway, incessant focal ATs, and persistent atrial flutter may present with tachycardia-mediated cardiomyopathy. EP study and catheter ablation is a suitable first-line option for management of SVT, though medical management with drugs can also be offered.[45] Overall risk of major complications with ablation is less than 1% to 3% depending on the specific SVT diagnosis.

ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

AV nodal reentrant tachycardia (AVNRT) is the most common regular paroxysmal SVT in adults and has a female preponderance. AVNRT is a reentrant tachycardia involving the AV node, the adjacent atrial tissue, and two distinct atrionodal connections (see Fig. 88–4). EP study often shows evidence of dual atrionodal pathways for conduction from atrium through the AV node to the His bundle, with a discontinuity in conduction times during atrial extra-stimulus testing.[46] AVNRT may be inducible with programmed atrial stimulation at baseline, or more commonly with administration of catecholaminergic drugs like isoproterenol. Typically, there is 1:1 relationship of V to A, with A being activated retrogradely through the "fast pathway" synchronously or immediately following the QRS (RP interval < 90 msec). In atypical forms of AVNRT, atrial activation occurs retrogradely through the "slow pathway" with a longer VA interval (long RP tachycardia). The diagnosis of AVNRT is confirmed by pacing maneuvers during tachycardia.[47]

As a result of inability of current techniques to record activation of the AV node, and the decremental conduction properties of the AV nodal tissue, use of entrainment maneuvers to define the tachycardia circuit is challenging. However, participation of any atrionodal connection can be inferred with resetting the tachycardia with late-coupled extra-stimuli from that site,[48] or terminating/resetting the tachycardia without global atrial capture, for example, with subthreshold stimulation or cryomapping.[49,50] Regardless, such maneuvers are largely unnecessary; and ablation is often performed solely anatomically, guided by local electrogram characteristics. This is possible because

AVNRT tends to be dependent on conduction through an anatomically distinct "slow pathway." This right inferior atrionodal connection is ablated in the inferoseptal region along the isthmus between the septal tricuspid leaflet and the coronary sinus ostium without undue risk of injury to the compact AV node and the essential AV conduction system (see Fig. 88–4).[51]

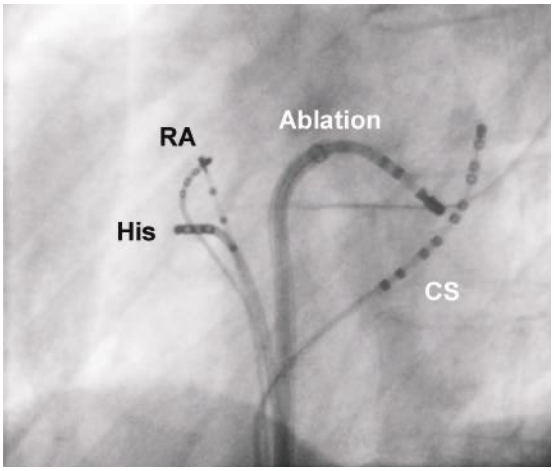
AVNRT ablation is acutely successful in more than 95% cases and has a 5% recurrence rate.[45,52] The major risk is inadvertent damage to the compact AV node producing heart block that requires permanent pacemaker implantation (~1%).[45,52] Cryoablation has a lower risk of heart block but also has lower long-term efficacy.[27,50] Slow pathway ablation in the inferoseptal region may result in elevation of sinus heart rates for up to 6 months, possibly related to ablation of adjacent autonomic nerve fibers.[53]

ACCESSORY PATHWAY–MEDIATED TACHYCARDIA

An extra–AV-nodal (accessory) atrioventricular pathway/connection that conducts antegradely from atrium to ventricle causes partial ventricular depolarization during sinus rhythm before normal ventricular activation through the His-Purkinje system catches up (ventricular preexcitation).[54] This is characterized by a short PR interval and a slurred onset of the QRS complex (delta wave). The presence of ventricular preexcitation on ECG along with paroxysmal tachypalpitations is called Wolff-Parkinson-White (WPW) syndrome. Antegrade conduction over an accessory pathway poses a potential risk of a very rapid ventricular response to atrial fibrillation that can cause ventricular fibrillation and sudden death.[55] Some accessory pathways have no antegrade conduction and only conduct from ventricle to atrium. These are termed "concealed" because preexcitation is absent during sinus rhythm, but atrioventricular reentry tachycardia can still occur.

Atrioventricular reentrant tachycardia (AVRT) is the second most common paroxysmal SVT after AVNRT, and tends to present at an earlier age with the prevalence being highest in adolescents.[45] The usual tachycardia circuit involves antegrade conduction over the AV node, producing a narrow QRS (or typical right or left bundle branch aberrancy) and retrograde conduction, from ventricle to atrium, over the accessory pathway (*orthodromic reentry tachycardia*). Sometimes reentry can proceed in the opposite direction with the entire ventricular activation occurring from the accessory pathway (completely preexcited) and retrograde conduction to the atrium over the AV node (*antidromic reentry tachycardia*). AVRT is usually inducible with programmed stimulation, and the mechanism is confirmed with additional pacing maneuvers.[47]

Accessory AV pathways occur anywhere along the tricuspid or the mitral annulus. The majority traverse the mitral annulus and are accessed by a transseptal approach through the fossa ovalis to the left atrium or retrogradely by inserting the catheter from the femoral artery across the aortic valve to the left ventricle (Fig. 88–13).[56] Many septal and all right free wall pathways are accessible by a standard venous approach to the right heart. The target of ablation is the accessory pathway potential,



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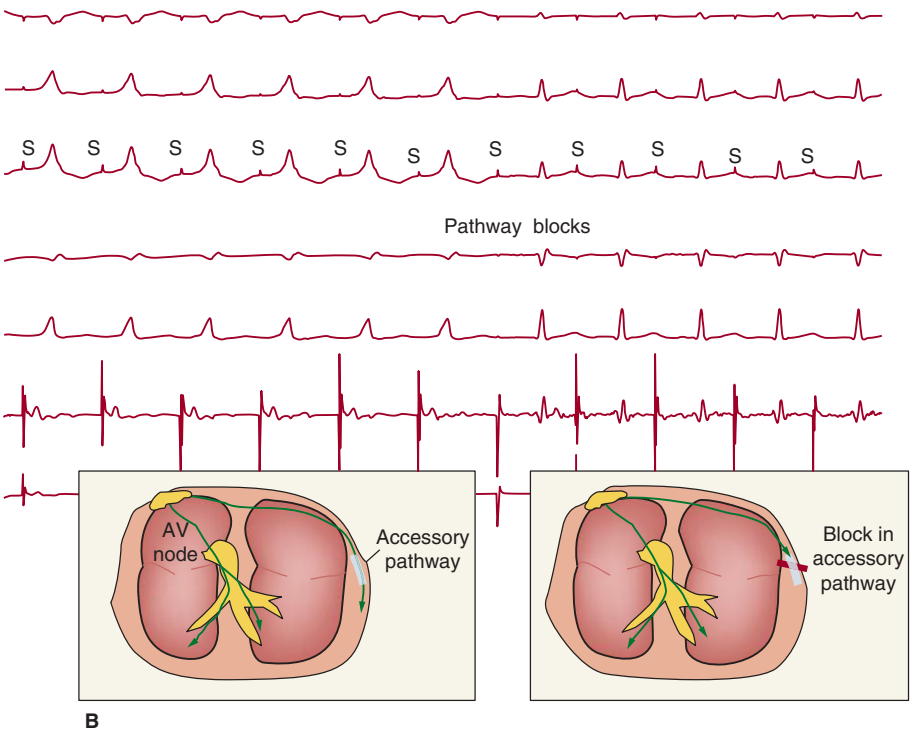

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FIGURE 88–13. A. Ablation of a left-sided accessory pathway in a patient with Wolff-Parkinson-White syndrome. Shown is a left anterior oblique fluoroscopic image depicting catheter position for transablation of a left-sided accessory pathway by a transeptal approach. A decapolar catheter is seen in the coronary sinus (CS). The ablation catheter (Ablation) is passed through a sheath, which crosses the fossa ovalis into the left atrium for mapping along the tricuspid valve annulus. **B.** Five surface electrocardiographic leads and two intracardiac leads depicting ablation of a left lateral accessory pathway during atrial pacing. The right atrium is being paced (pacing stimuli indicated by S). Pacing stimuli initially conduct from the atrium to the ventricles over the atrioventricular (AV) node and an accessory pathway producing a pattern of ventricular preexcitation with a wide QRS with a slurred initial delta wave as indicated by the left-hand schematic at the bottom of the figure. The pathway blocks within seconds of the application of radiofrequency energy with sudden narrowing of the QRS complex (Pathway blocks) indicating that conduction to the ventricles is occurring only over the normal conduction system of AV node and His bundle (right-hand schematic at the bottom of the figure). RA, right atrium.

yet this can be difficult to identify, and the onset of the earliest myocardial activation produced by conduction through the accessory pathway can also be considered.[57] Most accessory pathways are thin strands of myocardial tissue traversing the fibrous atrioventricular annulus, which are vulnerable to being inhibited temporarily with mechanical injury during catheter manipulation.[54] In absence of recurrent conduction, the region of a "catheter bump" may be a suitable site for ablation.

Approximately 25% of patients with overt WPW syndrome have pathways that place them at risk of ventricular fibrillation if atrial fibrillation occurs. Catheter ablation is the preferred treatment for AVRT, especially if preexcitation is present on baseline ECG (WPW syndrome) and for preexcited atrial fibrillation.[45] The management of asymptomatic patients who are found to have preexcitation on ECG is more controversial. Even though the odds of incident symptomatic tachyarrhythmia are high, the risk of sudden death is estimated to be 1 in 1000 per year.[55,58] Exercise testing or EP study may be helpful in risk stratification, and individualized consideration of the risks and benefits of ablation is warranted. Overall acute success in ablation of accessory pathway is 93%, with an 8% risk of recurrent conduction.[45,59] AV block can occur with attempted ablation of pathways that are located close to the AV node.

FOCAL ATRIAL TACHYCARDIA

Focal atrial tachycardia (AT) represents approximately 10% of SVTs referred for ablation. AT may be paroxysmal, occur in repetitive bursts, or may be incessant. It may respond to β-blockers, calcium channel blockers, and membrane-active antiarrhythmic drugs. Catheter ablation is an alternative to pharmacologic therapy.[45] AT foci tend to occur in specific anatomic locations, including the crista terminalis, tricuspid or mitral annulus, coronary sinus, atrial appendages, and the pulmonary veins. Foci in the left atrium often have a P wave that is negative in leads I and aVL, and positive in lead V_1; whereas those from the right atrium tend to have a negative terminal component in V_1. AT originating from the septum has narrow P waves whereas foci in the free walls have wider P waves, on account of simultaneous or sequential activation of the two atria.[45,60] The wide range of possible locations requires accurate mapping to identify the earliest site of activation to target ablation (see Fig. 88–6). Paroxysmal AT can, however, be difficult to induce in the EP lab, especially when sedation or anesthesia is used. Ablation is successful in more than 80% of patients with reported recurrence rate after successful ablation from 4% to 27%.[45]

Ectopic ATs arising from the peri-AV nodal region, verapamil- or adenosine-sensitive septal ATs, as well as junctional ectopic tachycardia (JET) have a higher risk of AV block with ablation. The noncoronary aortic sinus of Valsalva is an adjunctive region for mapping and ablation of these tachycardias (and anteroseptal accessory pathways) because of its anatomic apposition with the anteroseptum.[61]

INAPPROPRIATE SINUS TACHYCARDIA

Inappropriate sinus tachycardia (IST) is an uncommon disorder characterized by sinus tachycardia out of proportion to physiologic demand. IST is often associated with fatigue and palpitations that respond poorly to pharmacologic therapy.[62] Catheter ablation is feasible to target sinus node tissue along the crista terminalis. The septal portion of the crista has the most rapid automaticity and is initially targeted, often reducing the sinus rate.[63] Ablation can be difficult because of the epicardial location of the sinus node and epicardial ablation can be considered. The long-term success is limited, with frequent recurrences and persistent symptoms despite rate control in some patients.[63] Complications include superior vena cava obstruction, phrenic nerve paralysis, and sinus node dysfunction.[62,63] The role of ablation for IST is controversial and is infrequently recommended—even as a measure of last resort, with nonablative therapy being the accepted approach of choice.

MACROREENTRANT ATRIAL TACHYCARDIAS OR ATRIAL FLUTTER

The most common form of sustained macroreentrant AT (*typical atrial flutter*) consists of electrical reentry around the tricuspid valve. The circuit traverses the myocardium between the inferior vena cava and the tricuspid valve, and is also labeled as cavotricuspid isthmus flutter. This arrhythmia frequently presents with regular 2:1 atrioventricular conduction. The ECG pattern is highly characteristic and the P wave is negative with a "saw tooth" morphology in the inferior leads, positive in V_1, and negative in V_6—correlating with a *counterclockwise* activation around the tricuspid annulus viewed in the left anterior oblique (LAO) projection. Activation in the opposite direction (*clockwise* flutter) gives rise to positive flutter waves in the inferior leads, but this is not a distinctive and consistent pattern.

Atrial flutter is a marker for atrial disease; a third of patients will subsequently develop AF, though the risk of AF continues to increase with extended follow-up.[45,64] Antiarrhythmic drug therapy may suppress atrial fibrillation but lead to sustained atrial flutter. Ablation of the atrial flutter with continuation of antiarrhythmic medications to prevent atrial fibrillation can be useful to maintain sinus rhythm. Contiguous ablation lesions placed across the cavotricuspid isthmus to create a line of conduction block abolish the typical flutter with a success rate of 97% (see Figs. 88–5 and 88–7).[45,65]

Atypical atrial flutters (non–isthmus-dependent) are often caused by reentry around atrial scars from prior heart surgery, such as congenital heart disease repair, mitral valve surgery, surgical atrial maze, or after catheter ablation for atrial fibrillation. Inferring the circuit of atypical atrial flutters from ECGs can be extremely challenging.[66] Detailed activation and entrainment mapping and a thoughtful strategy to transect a critical limb of the circuit between two anatomic boundaries (or regions of scar/ablation) with linear ablation eliminates the circuit. Success rates of 80% to 85% are reported, and late recurrences are more frequent than for ablation of typical atrial flutter.[67]

ATRIAL FIBRILLATION

Atrioventricular Node Ablation for Rate Control

Catheter ablation of the AV node to create complete heart block with implantation of a permanent pacemaker is an option for controlling the heart rate in patients with atrial fibrillation (AF) and difficult-to-control ventricular rates.[68] This is typically a low-risk, relatively quick procedure with high efficacy. The heart rate is controlled without medications and the ventricular rate is regularized. This leads to improvements in quality of life, exercise tolerance, and ejection fraction.[69]

Several potential disadvantages require careful consideration before using this strategy. The atria usually continue to fibrillate, so patients remain at risk for thromboembolic complications. The abrupt restoration of a slower rate with ventricular pacing has been associated with occasional cases of sudden death possibly caused by polymorphic VT (torsades de pointes). This risk appears to be largely mitigated by setting the pacemaker lower rate to 90 bpm for the first several weeks and then gradually reducing the rate over time.[70] Further, chronic right ventricular (RV) apical pacing has important adverse hemodynamic consequences in some patients. Patients with poor left ventricular function and mitral regurgitation are at greatest risk for aggravation of

heart failure with RV pacing, and biventricular pacemaker for cardiac resynchronization therapy may be warranted.[69]

AV node ablation is usually considered for patients who already have a pacemaker inserted, are elderly, or those who cannot tolerate either rate control medications or antiarrhythmic drug therapy. The procedure is less attractive for younger patients because of dependency on permanent pacing for decades with need for multiple generator changes, risk of pacing lead complications, and the potential for deleterious consequences of chronic RV pacing.

Atrial Ablation to Maintain Sinus Rhythm

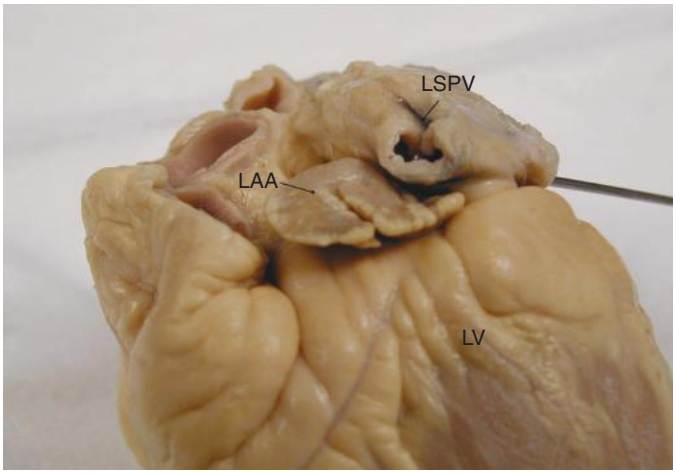
Maintenance of sinus rhythm is indicated to manage symptoms related to AF.[71] Sinus rhythm may have hemodynamic benefits especially in patients with diastolic dysfunction, as ventricular filling is improved with slower heart rates and restoration of atrial mechanical function.

Initiation of paroxysmal AF in humans by rapid firing of triggers in myocardial sleeves in the pulmonary veins was demonstrated in 1998, and the feasibility of preventing AF by ablating these foci was described.[72] It was soon recognized that focal triggers for AF could also occur in the atria outside the pulmonary veins, and RF ablation within the pulmonary veins was accompanied by a significant risk of pulmonary vein stenosis. This led to ablation approaches that encircle and electrically isolate the entire broader antral regions of the pulmonary veins (see Figs. 88–10 and 88–14).[73-75] Techniques have evolved to address both triggers that initiate AF, as well as the atrial substrate that allows perpetuation of the arrhythmia.[75] Pulmonary vein isolation (PVI) is effective for many patients with paroxysmal AF, but more extensive atrial ablation is often required for persistent AF, though the optimal technique has not been confirmed in a randomized trial.[76]

Post-AF ablation atrial tachycardia and fibrillation are common but typically dissipate spontaneously over a period of several weeks as ablation lesions heal and the atrium remodels. Antiarrhythmic medications may be continued for 1 to 3 months after ablation. It is also not uncommon for some patients to need a second procedure to ablate recurrent atrial tachyarrhythmias. These arrhythmias may be caused by recovery of conduction across ablation lines or may arise from areas that were not ablated at the first procedure.

Ablation success varies with the type of AF and severity of underlying heart disease. Young patients with paroxysmal AF and without structural heart disease have the best outcome; more than 70% to 80% have sinus rhythm after the initial healing phase after ablation.[77] Success rates are lower for patients with persistent or long-standing (> 1 year) persistent AF. A worldwide survey on outcomes of catheter ablation of AF suggests clinical benefit in about 80% of patients after an average 1.3 procedures per patient, with about 70% of patients not requiring antiarrhythmic drug therapy at a mean follow-up of 18 months.[75,78]

Oral anticoagulation is recommended for at least 2 to 3 months following AF ablation, and subsequent anticoagulation should not be dictated by apparent procedural success, but rather by the clinical assessment of the individual patient's stroke risk. The overall complication rate with AF ablation is approximately 5%, major complications around 2%, and in-hospital mortality less than 0.5%.[78,79] Myocardial perforation with tamponade occurs in 1% to 2% of procedures and can usually be managed by reversing anticoagulation and performing pericardiocentesis, although emergency surgery may be required. The intensive anticoagulation during the procedure and extensive ablation required are likely factors that increase this risk compared with other ablation procedures. Stroke or a transient ischemic attack occurs in 0.5% to 1% of patients. Severe pulmonary vein stenosis was reported in 2% to 6% of patients and may present months after the procedure with dyspnea, pneumonia, or pulmonary infiltrate, or may be asymptomatic.[80] Pulmonary vein stenosis appears to have become less frequent with the avoidance of ablating inside the pulmonary vein ostia. Rare but usually fatal atrial-esophageal fistulae, presenting days to a few weeks after the procedure with endocarditis, septic emboli, or gastrointestinal bleeding, have been reported (estimated ~0.1%).[75,80,109]



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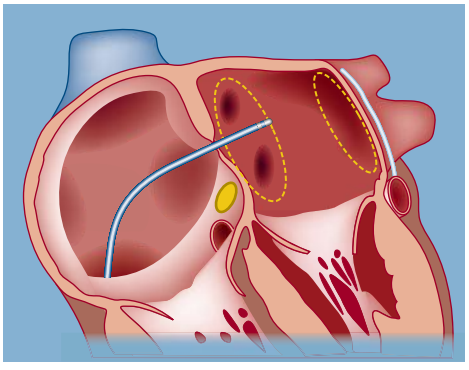

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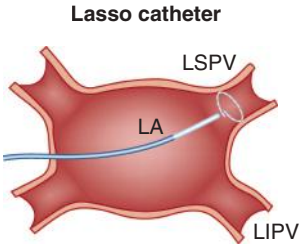

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FIGURE 88–14. Left atrial ablation for atrial fibrillation. **A.** Left lateral view of cardiac dissection demonstrating two important targets for arrhythmia therapy—the left atrial appendage (LAA) and the pulmonary veins. Shown is a catheter placed in the left superior pulmonary vein (LSPV). Myocardium of the pulmonary vein is an important location for triggers initiating paroxysms of atrial fibrillation. Ablation techniques involve electrical isolation of the pulmonary veins by ablating the left atrial tissue adjacent to the pulmonary vein ostia. The LAA is not a common ablation target because this structure is a common source for cerebral thromboembolism. **B.** Present ablation techniques to electrically isolate the pulmonary veins. The catheter is advanced to the left atrium via transseptal puncture. Large-area circumferential lesions are placed around the ostia of the left- and right-sided pulmonary veins. This procedure may be combined with linear ablation to prevent atrial flutters and possible targeted ablation of abnormal myocardium and the retroatrial ganglia. **C.** Catheters may be placed into the pulmonary vein, including circumferential mapping catheter depicted in this figure placed in the left superior pulmonary vein. Electrical signals retrieved from these catheters are characteristic of abnormalities associated with atrial fibrillation substrate. After circular left atrial ablation, these signals should no longer be seen. LV, left ventricle.

The feasibility of catheter ablation for maintaining sinus rhythm and improving symptoms in patients with AF has been well demonstrated. Data are largely from relatively young patients treated at experienced centers and followed-up for less than 3 years. The procedure is mainly reserved for symptomatic patients in whom the potential benefit is believed to justify the risks. Technologic advances and ongoing studies should continue to improve patient selection and outcomes.

Beyond Pulmonary Vein Isolation

Pulmonary vein isolation (PVI) alone as the first procedure has good results for paroxysmal AF. However, outcomes in persistent AF have been suboptimal. Additional ablation targets have been sought for AF recurrence after PVI and for ablation of persistent AF. Extrapulmonary vein triggers of AF can be mapped with testing on high-dose isoproterenol in the EP lab and targeted for ablation. These include the superior vena cava, vein of Marshall, coronary sinus, left atrial appendage, and other sites of focal AT.[75] Techniques to identify and ablate regions of presumed anchoring of rotors that sustain persistent AF are being evaluated, though clinical utility needs to be validated.[81] The role of cardiac autonomic nervous system in the pathogenesis of AF is well documented, and endocardial ablation at sites of epicardial cardiac ganglia has been demonstrated to improve outcomes.[82] Ablation of atrial regions with fibrosis as determined by MRI imaging has been proposed to eliminate the substrate that sustains AF.[83] These additional targets of ablation—autonomic ganglia, rotors, areas of fibrosis—are often localized to the pulmonary vein antra and the posterior left atrial wall, and empiric linear ablations to isolate the entire left atrial posterior wall in addition to wide area pulmonary vein antral isolation can be performed. Extrapolating from the surgical maze literature of compartmentalizing the atria to prevent atrial fibrillation, catheter-based maze with empiric linear ablations can be performed. However, empiric linear ablations can be proarrhythmic and lead to atypical atrial flutters if there are gaps in ablation lines. There is also evidence that extensive atrial ablation can affect interatrial conduction, atrioventricular synchrony, and atrial mechanical function.[84]

AF more commonly develops in the context of systemic inflammation and metabolic derangements related to sedentary lifestyle, unhealthy eating habits, obesity, sleep apnea, metabolic syndrome, hypertension, and increased left atrial pressures. Therefore ablation therapy for AF should be considered in context of such underlying aggravating factors; and aggressive lifestyle modification, weight reduction, and treatment of sleep apnea and hypertension markedly improve outcomes.[85]

Cryoballoon Ablation

A cryoballoon catheter has been specially designed for the ostial pulmonary vein and antral ablation to occlude and freeze the pulmonary vein ostium with a single freeze. The cryoballoon has a 70% success in preventing recurrent AF over 12 months in patients with paroxysmal AF, comparable to RF ablation.[86,87] Injury to the right phrenic nerve (coursing adjacent to right superior pulmonary vein) was the most frequently observed complication, reported in ~6%.[27,86] Monitoring of the diaphragmatic compound motor action potential (CMAP) using electrodes on the torso while electrically stimulating the phrenic nerve can be used to detect and avoid impending hemidiaphragmatic paralysis during cryoballoon ablation of right-sided pulmonary veins.[88,89]

VENTRICULAR TACHYCARDIAS

Premature Ventricular Complexes

Premature ventricular complexes (PVCs) can arise from any ventricular tissue, yet the outflow tracts and adjacent epicardial regions, papillary muscles, tricuspid and mitral valve annuli, and the fascicular conduction system are more common as sources of this form of arrhythmia.[8] Frequent PVCs can cause symptoms of palpitations, dyspnea, chest pain, lightheadedness, and anxiety. A very high burden of PVCs, typically more than 10,000 or 20,000 per 24 hours, can depress the left ventricular systolic function in a subset of patients. Analogous to tachycardia-mediated cardiomyopathy, suppression of PVCs can result in resolution of ventricular dysfunction.[8,90] PVC suppression may also be indicated when a consistent PVC triggers sustained ventricular fibrillation or tachycardia and results in syncope or implanted cardioverter-defibrillator (ICD) shocks.[8,91]

PVCs occasionally respond to β-blockers or calcium channel blockers, and antiarrhythmic drugs like flecainide, sotalol, or amiodarone may be effective. When one or two PVC morphologies predominate, PVC ablation can be performed when drug therapy is ineffective, not tolerated, or not desired.[8,92] Most commonly, PVCs arise from the right ventricular outflow tract (RVOT), and have a left bundle branch block configuration in lead V_1 with an inferiorly directed axis and tall positive QRS complexes in leads II, III, and AVF. PVCs may be suppressed with anesthesia, but are sometimes inducible with isoproterenol or rapid ventricular pacing resulting in calcium loading of cells and triggering of PVCs.[93] Activation mapping is critical to identify the earliest site of activation, and often a prepotential at the earliest site is the target of ablation. As a result of the complex anatomy of the outflow tracts, multiple sites like the right ventricular outflow tract, left ventricular outflow tract, supravalvar myocardium in the aortic sinuses of Valsalva, and the epicardial region accessible through the great cardiac and the anterior interventricular veins may need to be mapped. Intracardiac echocardiography is useful to visualize intracavitary structures like papillary muscles, moderator band, and false tendons to facilitate mapping of PVCs originating from these respective sites.[8]

Outflow Tract Ventricular Tachycardia

The most common region in the heart responsible for PVCs and ventricular tachycardia (VT) in the absence of structural heart disease is the right ventricular outflow tract (RVOT). Tachycardia may be sustained or present with repetitive bursts of nonsustained VT, and has an inferiorly directed QRS axis on ECG. The mechanism of idiopathic outflow tract VT is thought to be cyclic AMP-triggered automaticity.[93] Outflow tract VT is often exercise induced and may respond to vagal maneuvers, intravenous adenosine, β-blockers, or calcium channel blockers. Catheter ablation is an alternative to drug therapy, or can be performed when drugs fail to suppress VT.[8,92]

Ablation is performed at the area of earliest ventricular activation during the VT. Occasionally, the focus originates from the LV outflow tract, along the mitral annulus, or in sleeves of ventricular myocardium that extend above the aortic or pulmonic valves (Fig. 88–15). Catheter ablation successfully eliminates tachycardia in more than 80% of patients. An inability to induce the arrhythmia in the electrophysiology laboratory can prevent mapping and is a major cause of failed ablation.

Fascicular Ventricular Tachycardia

Idiopathic fascicular VT occurs typically related to micro-reentry in or near the fascicles of the left bundle,[94] though focal origin of fascicular PVCs and VT can also occur. Idiopathic fascicular VT has a right bundle branch block (RBBB) configuration in lead V_1 and usually a superiorly directed axis on ECG. Fascicular VT has a male preponderance and typically occurs during the young adulthood years. It is often provoked with exertion and responds to verapamil or adenosine. The sites of early fascicular activation or diastolic activation located along the left ventricular septum are targets for ablation. Difficulty in

inducing the VT during the ablation procedure and the risk of "catheter bump" suppressing the arrhythmia can limit mapping. Ablation may be successful in more than 80% of cases. There is a small risk of left fascicular block or even AV block if ablation is performed too proximally in the conduction system.

Ventricular Tachycardia in Structurally Diseased Hearts

In patients with structural heart disease, VT is most commonly caused by reentry through areas of myocardial scar. These scars are associated with areas of conduction block with intervening regions of slowly conducting diseased myocardium that can support reentrant circuits. VT can usually be induced with programmed stimulation. Most often, the scar is a late sequela of prior myocardial infarction, and VT in this setting is associated with a mortality risk that generally warrants an ICD to prevent sudden cardiac death. Although many VTs are nonsustained or terminated by antitachycardia pacing before significant symptoms develop, some patients experience lightheadedness or syncope, or sustain painful shocks for VT termination. Further, ICD shocks are associated with an increased risk of death despite effective termination of the VT.[95] Catheter ablation is an important alternative to antiarrhythmic drug therapy for preventing or reducing the frequency of VT episodes, and ablation can be lifesaving if VT becomes incessant.[92]

Any ventricular scar can lead to development of reentry and VT. Myocardial infarction is the most common cause but arrhythmogenic cardiomyopathy, cardiac sarcoidosis, Chagas disease, hypertrophic cardiomyopathies, and idiopathic dilated cardiomyopathies are all associated with scar-related VT. Ventricular scars from prior cardiac surgery such as tetralogy of Fallot repair can also cause VT.

Premature ectopic beats can induce VT that is typically regular and monomorphic. The morphology of the QRS helps to localize the exit site from the scar region to the healthy ventricular myocardium. VTs with a left bundle branch block (LBBB) configuration in V_1 on ECG often map to the right ventricle or interventricular septum. Those with a RBBB configuration originate from the left ventricle.

Most patients with scar-related VT possess several potential reentry circuits, creating VTs with different QRS morphologies and cycle lengths. These are often terminated promptly by ICDs, such that the QRS morphologies are unknown. In addition, VT often produces hypotension and is not tolerated to allow extensive mapping during VT. Substrate mapping approaches that facilitate identification of potential reentry circuits while mapping during sinus rhythm allow effective ablation of many of these VTs. Potential areas of scar can be identified on imaging as regions with hypokinesis, akinesis, or dyskinesis, or directly imaged with myocardial perfusion techniques, or late gadolinium enhancement on MRI. During the ablation procedure, areas of scar are identified as regions with very low voltage electrograms and inability to electrically capture with local stimulation.[92,96] Plotting the electrogram amplitude in three-dimensional anatomic maps identifies regions of very low voltage that

FIGURE 88–15. Three examples to demonstrate the complex regional anatomy of the outflow tracts: *Top Panel*. Angiography is being performed through a catheter engaging the left main coronary artery with a wire advanced into the left anterior descending (LAD) artery. Note the close proximity of catheters advanced to map outflow tract ventricular ectopy from different cardiac chambers. (E, epicardial space; G, great cardiac vein [GCV]; R, right ventricular outflow tract [RVOT]). This patient had a high burden of premature ventricular complexes (PVCs) resulting in left ventricular systolic cardiomyopathy. PVCs were mapped to close proximity of the LAD. After mapping the left ventricular outflow tract (LVOT) and left coronary cusp (LCC) in addition to the aforementioned sites, radiofrequency ablation was performed in the distal GCV, epicardial region, and the LCC with successful elimination of PVCs without injury or need for intervention on the LAD. *Middle Panel*. Anatomic chamber geometry to show the correlative anatomy of the outflow tracts generated with three-dimensional mapping using intracardiac ultrasound and mapping catheters. AIV, anterior interventricular vein; LCC/RCC/NCC, left, right, and noncoronary cusps (aortic sinuses of Valsalva); LM, left main coronary artery; LV, left ventricle; LVOT, left ventricular outflow tract; PA, pulmonary artery; RVOT, right ventricular outflow tract. PVC focus was mapped and ablated at the commissure between RCC and LCC (*maroon spheres*). *Bottom Panel*. Color-coded three-dimensional activation map of outflow tract ectopy with earliest site at the anterior interventricular vein (AIV)-great cardiac vein (GCV) junction (*red*) with subsequent activation in the endocardial LVOT/anterior mitral annular region and RVOT. Ablation lesions (*maroon spheres*) were delivered at the earliest site (cluster 1) and consolidation lesions on corresponding endocardial site at anterior mitral annulus (cluster 2) to sandwich the mid-myocardial arrhythmia focus. AIV, anterior interventricular vein; GCV, great cardiac vein; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract. Left hand panel shows the surface ECG leads of the mapped premature ventricular beat with presystolic bipolar (*cyan*) and unipolar (*orange*) electrogram noted at the earliest site. LAO, left anterior oblique; RAO, right anterior oblique.

coincide with myocardial disease and scar (see Figs. 88–8 and 88–9). Fragmented, delayed electrograms, and pace mapping help identify regions of abnormal conduction and potential exit sites.[11] Ablation then targets conducting channels through the scar region or the exit sites in the border region of the scar.[10] When VT is hemodynamically tolerated, additional mapping can be performed during VT to target the specific clinical VT.

Ablation of scar-related VT is more difficult than ablation for SVT and has lower success rates. Even so, over two-thirds of patients experience clinical benefit from a marked reduction in frequency of VT episodes. With improvements in ablation methods and techniques, freedom from VT recurrence at 1-year follow–up has improved to 70%, yet frequently the underlying cardiomyopathic process progresses, leading to the development of other VT.[97] Procedural mortality is approximately 3%, though the most common cause of death is uncontrollable VT from a failed procedure. Stroke, perforation with tamponade, femoral hematomas, and heart block can also occur.[59]

The presence of culprit substrate deep to the endocardium, or in the subepicardium, is a major reason for failure of endocardial ablation approaches. Epicardial VTs can be approached by a subxiphoid percutaneous puncture into the pericardial space for mapping and ablation (see Fig. 88–2).[1] Pericardial scarring from prior surgery, epicardial adipose tissue, and the presence of epicardial coronary arteries limit applicability of this approach in some patients.

Bundle Branch Reentry Ventricular Tachycardia Approximately 6% of patients with VT associated with structural heart disease are found to have reentry involving the bundle branches as the mechanism for at least one of their inducible VTs.[98] These patients often have a left intraventricular conduction delay or a pattern of LBBB during sinus rhythm and coexistent advanced ventricular dysfunction. A diseased Purkinje system supports a reentry circuit revolving up one bundle branch and down the contralateral bundle branch. Catheter ablation of the right bundle branch interrupts the reentry circuit and is curative.[99]

Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

Polymorphic VT and VF are generally not thought of as arrhythmias amenable to ablation. However, some patients with repetitive episodes of idiopathic VF, or VF associated with recent myocardial infarction or hereditary ion channel diseases, have episodes of arrhythmia triggered by ventricular ectopy from identifiable foci in the Purkinje system or RVOT that can be targeted for ablation.[100,101] Ablation in these circumstances can be lifesaving. Recently, ablation of the right ventricular outflow tract free wall to modify the substrate and susceptibility for VF in patients with Brugada syndrome has been described.[102]

Patients with malignant ventricular arrhythmias refractory to medical therapy or ablation can be considered for sympathetic denervation surgery.[103] Typically performed via a thoracoscopic approach by the thoracic surgeon, the technical details of cardiac denervation are beyond the scope of this chapter. Results of cardiac denervation are particularly encouraging in certain subsets of patients—with the most consistent salutary, anti-fibrillatory results in patients with genetic channelopathies.[104]

COMPLICATIONS AND THEIR PREVENTION

CARDIAC PERFORATION AND PERICARDIAL TAMPONADE

Any catheter-based intervention in the heart has risk of perforation with pericardial effusion and tamponade, especially in the atria and right ventricle. AF ablation may have a 3% risk of effusion.[78,79] Although intracardiac echocardiography is invaluable in the early recognition, tamponade can be fatal unless emergent pericardiocentesis is accomplished, whereas a minority may still require open thoracotomy to stabilize bleeding.

THROMBOEMBOLISM AND STROKE

Coagulum is formed during thermally mediated ablation by direct heating of blood near the electrode-endocardial interface causing denaturation of proteins, especially in absence of active electrode cooling with saline irrigation.[105] Coagulum formation may limit delivery of ablation energy. It is a nidus for further thrombogenesis and embolic complications, especially stroke, when ablating in left heart chambers. Limiting RF ablation power, open irrigation, and therapeutic heparin anticoagulation are important to reduce risk. In addition to clinical strokes, a high rate of silent cerebral ischemia is seen with MRI.[106] Additionally, the injured and inflamed endocardial surface can result in thromboembolic complications even weeks after ablation, and two to three months of systemic anticoagulation may be warranted after extensive ablation in left heart chambers.

COLLATERAL DAMAGE

Collateral injury to extracardiac structures occurs when lesion depth exceeds myocardial wall thickness. Depending on the ablation target, damage to the phrenic nerve, coronary arteries, esophagus, lung parenchyma, or aorta can occur. It is critical to understand the anatomical relationships of cardiac and extracardiac structures in vicinity of the ablation target. High-output pacing near anterior aspect of right superior pulmonary vein and along the right atrial free wall can detect the course of the right phrenic nerve by diaphragmatic stimulation, and diaphragmatic stimulation can be monitored with phrenic nerve pacing from the superior vena cava above the level of potential injury during ablation.[88,107,108] Coronary arteriography is useful to ensure ablation is not delivered in close proximity, especially during epicardial ablation or ablation in the epicardial coronary veins.

Atrioesophageal fistula is a rare (~0.1%) but highly fatal complication of atrial fibrillation ablation usually presenting a few weeks after ablation.[109] The mechanism of injury probably includes damage of the esophageal vasculature, inflammatory response with esophageal ulceration, and progressive erosion from the esophagus into the pericardium and eventually the atrium. Caution is needed when ablation is performed on the posterior left atrial wall, with limiting the power and duration of RF delivery, and avoiding ablation of atrial tissue in direct apposition to the esophagus. Monitoring luminal esophageal temperature near the ablation site is useful but does not guarantee safety.

ATRIOVENTRICULAR BLOCK

Ablation in proximity to the AV node, fast pathway, and the His bundle in the mid and anterior septal region has risk of complete heart block. AV block can occur during ablation for AVNRT, septal atrial tachycardias, mid and anteroseptal accessory pathways, junctional tachycardia, and para-Hisian or septal PVCs or VT. Injury to the essential AV conduction system can occur from the right heart chambers, aortic root, left ventricle, and left atrium. As there is no distinct electrogram signature for the AV node, safety relies on understanding the critical anatomic relationships of the conduction system, and close monitoring or AV conduction during ablation. Early recognition of rapid junctional beats is crucial, and cryoablation may be considered when risk of irreversible AV block with radiofrequency ablation is high.

ACCESS SITE COMPLICATIONS

Multiple venous cannulations and arterial access can result in vascular complications including venous thrombosis, arteriovenous fistula, pseudoaneurysm, hematoma, and retroperitoneal bleeding.

CONCLUSIONS

Catheter ablation is rapidly evolving and currently offers a more effective alternative to antiarrhythmic drug therapy for most tachyarrhythmias. Appropriate patient selection depends on an individualized assessment of risks and benefits. Ablation procedures have revolutionized the approach to the management of patients with tachycardias and have evolved to the point where ablation is a reasonable first-line therapy for symptomatic patients with accessory pathways, AVNRT, ATs, atrial flutter, PVCs, idiopathic VTs, and paroxysmal AF. Catheter ablation is an option for symptomatic persistent AF but is still an evolving procedure that requires careful assessment of risks and benefits. Ablation for VT and VF can be lifesaving in those with recurrent ICD shocks.

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CHAPTER 89

PACEMAKERS AND DEFIBRILLATORS

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Cardiac implantable electronic devices (CIEDs), notably pacemakers and implantable cardioverter-defibrillators (ICDs), represent dramatic technological advances that have become essential in addressing the problems of arrhythmia and heart failure (HF) in modern cardiovascular patients. Although similar in design, these technologies represent two distinct paradigms of treatment. Where conventional single or dual-chamber pacemakers are used to address the fundamental problem of bradyarrythmia, ICDs are designed to automatically detect and treat tachyarrhythmias, specifically hemodynamically unstable ventricular tachycardia (VT) or ventricular fibrillation (VF). In the past two decades, a third paradigm has also emerged—cardiac resynchronization therapy (CRT)—in which biventricular pacing is used to improve left ventricular pump function in patients with intraventricular conduction delay and systolic HF. Along with developments in fundamental approaches to pacing and defibrillation, recent years have also brought about exciting advances in design as well, with the development of leadless pacing and subcutaneous defibrillators. The purpose of this chapter is to provide an overview on pacing, defibrillation, and the indications for specific types of devices, and to review seminal clinical trials supporting their use in clinical practice.

INITIAL WORK

Although experimental use of short-term direct myocardial pacing for cardiac arrest had been described by 1932 by Dr. Albert Hyman,[1] Dr. Paul Zoll is credited with spurring widespread interest in cardiac pacing after his description of successful resuscitation through external subcutaneous electrical stimulation in 1952.[2] Pacing soon became indispensable to the nascent field of cardiac surgery when, in 1957, Dr. C. Walton Lillehei applied a direct myocardial electrode to the heart of a child undergoing a ventricular septal defect repair who developed complete atrioventricular (AV) block intraoperatively. He attached the electrode to an externalized transistor pacemaker developed by Earl Bakken.[3] The first description of a technique for transvenous pacing in humans came only 1 year later.[4] Subsequently, the field has undergone an explosion of development and miniaturization, although has remained astonishingly faithful in concept to these initial pioneering descriptions (Fig. 89–1). It was not until close to three decades of the seminal work of Dr. Michel Mirowski and Dr. Morton Mower that an "automatic" implantable defibrillator was used in humans for the termination of malignant ventricular arrhythmias.[5] Fast forward more than a decade later to the first case report of biventricular pacing in the treatment of dilated cardiomyopathy.[6] Both pacing and defibrillation CIED systems share similar components, consisting of an impulse generator—the "battery" that stores electrical charge—and a lead or leads which are used to deliver electrical energy to either pace or defibrillate myocardial tissue. Although with similarities in overall design, it has been the process of developing and refining indications in large trials that has led to the adaptation of these devices for the use of specific clinical needs and that informs their continuing evolution today. An overview of key indications and seminal trials will now be given prior to discussion of the mechanics of implant, management of complications, and troubleshooting.

INDICATIONS AND SEMINAL TRIALS

PACEMAKERS

Indications for Pacing

Cardiac pacing was initially developed to address the problem of bradyarrhythmia, particularly caused by AV block and sinus node dysfunction (SND). These continue to constitute the primary indications for consideration for pacing, although pacing for neurocardiogenic syncope and special situations (eg, postcardiac transplant, neuromuscular disease, sleep apnea, or infiltrative disease) has grown. Pacing for the termination of arrhythmia (or anti-tachycardia pacing [ATP]) is

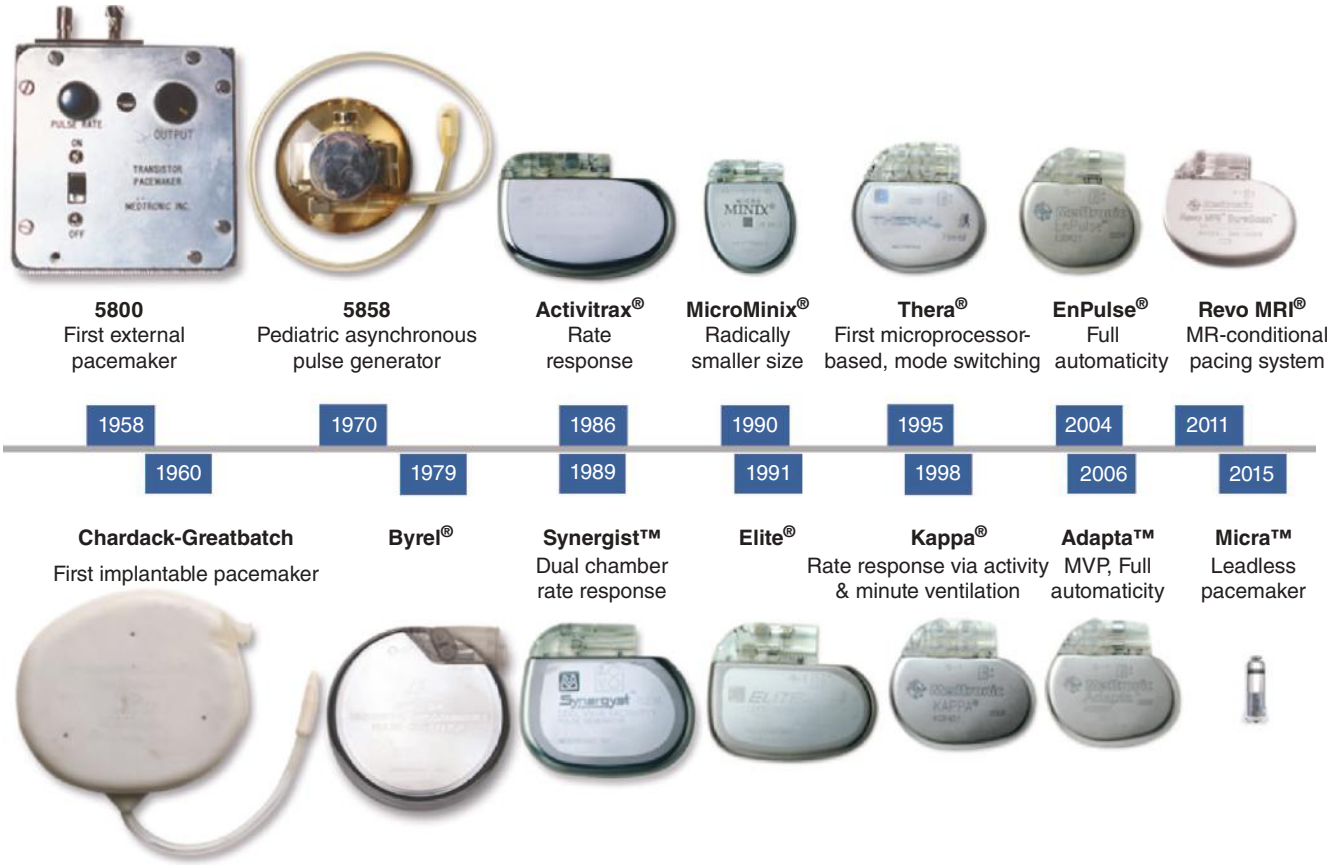


FIGURE 89–1. Evolution of pacemakers. Reproduced with permission from Medtronic, Inc.

almost exclusively employed in combination pacemaker-defibrillator devices in the modern setting. The clinical guidelines for consideration of pacing were recently outlined by a collaboration between the American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and Heart Rhythm Society (HRS).[7]

Pacing in SND Class I recommendations for pacing for SND hinge primarily on the presence of symptoms, along with class II consideration for pacing in patients with heart rate < 40 bpm while awake, with (class IIa) or without (class IIb) clear symptomology associated with bradycardia (Table 89–1). SND may be caused by either intrinsic

TABLE 89–1. Recommendations for Permanent Pacing in Sinus Node Dysfunction

Class I

1. Indicated for SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. (LOE: C)
2. Indicated for symptomatic chronotropic incompetence. (LOE: C)
3. Indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions. (LOE: C)

Class IIa

1. Reasonable for SND with heart rate less than 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. (LOE: C)
2. Reasonable for syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies. (LOE: C)

Class IIb

1. May be considered in minimally symptomatic patients with chronic heart rate less than 40 bpm while awake. (LOE: C)

Class III (No Benefit)

1. Not indicated for SND in asymptomatic patients. (LOE: C)
2. Not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. (LOE: C)
3. Not indicated for SND with symptomatic bradycardia resulting from nonessential drug therapy. (LOE: C)

Data from Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. Jan 22 2013;61(3):e6-75.

FIGURE 89–2. **A.** Telemetry strip demonstrating sinus bradycardia followed by 4.6-second sinus pause. **B.** Telemetry strip demonstrating a sinus pause twice the length of the preceding P-P interval, suggesting sinoatrial exit block. **C.** An example of atrial tachyarrhythmia terminating with 3.6-second sinus pause.

disease or sinoatrial exit block, and also includes sinus pause after cessation of atrial tachyarrhythmia (Fig. 89–2).

Pacing in AV Block Indications for pacing in acquired AV block attempt to discriminate between sites of block in the cardiac conduction system. Broadly, block above the AV node is considered lower risk than below the node (ie, infranodal block) (Fig. 89–3) because of the relative instability of escape rhythms emanating from below the AV junction. This is particularly salient in patients with stigmata of other His-Purkinje disease, such as bundle branch block or fascicular block. In addition, AV block at any level may contribute to the risk of ventricular arrhythmia through a pause-dependent mechanism. The indications for pacing in acquired AV block take into account the site of block, and similar to recommendations for SND, suggest pacing in patients with symptomatic bradycardia < 40 bpm (including heart failure), for those who require medical therapy and are at risk for bradycardia, and in those at risk for significant pauses (> 3 seconds). In contrast to indications for SND, however, pacing is recommended even in asymptomatic patients if infranodal block (ie, intra-His or infra-His) is suspected (Table 89–2). Patients with alternating bundle branch block (ie, right bundle branch block [RBBB] alternating with left bundle branch block [LBBB], or RBBB alternating with associated left anterior fascicular block and left posterior fascicular block), or with chronic bifascicular block associated and type 2 second-degree or advanced AV block, also meet a class I indication for pacing, irrespective of symptoms. AV block is also frequently a sequel of ST-segment elevation myocardial infarction (MI), and is associated with poorer prognosis overall. Generally, patients with inferior MI demonstrate nodal AV block that is transient, whereas anterior MI may cause direct infranodal and fascicular ischemia leading to higher degree of persistent AV block. An electrophysiology (EP) study may be necessary in differentiating site of block in patients where the site of block is uncertain (class I indication; level of evidence [LOE] B).

Pacing in Hypersensitive Carotid Sinus Syndrome or for Neurocardiogenic Syncope Pacing in these conditions is generally reserved for patients in whom a cardioinhibitory reflex (as opposed to vasodepressor response) predominates with respect to their syndromes. These include patients in whom carotid sinus stimulation induces ventricular asystole for > 3 seconds *and* is associated with syncope (class I indication; LOE C). The indications are downgraded in patients with a hypersensitive cardioinhibitory response without clear, provocative events (class IIa; LOE C), and for those with significantly symptomatic neurocardiogenic syncope and bradycardia documented spontaneously (as with event monitoring or implantable loop monitor) or during tilt table testing (class IIb; LOE B).

Pacing in Specific Conditions Specific conditions that merit indication for pacing include patients who have undergone cardiac transplant, patients with neuromuscular diseases such as myotonic dystrophy and Emery-Dreifuss syndrome, sleep apnea, cardiac sarcoidosis, and patients with hypertrophic cardiomyopathy (HCM) and evidence of dynamic left ventricular outflow tract (LVOT) obstruction. In addition to standard

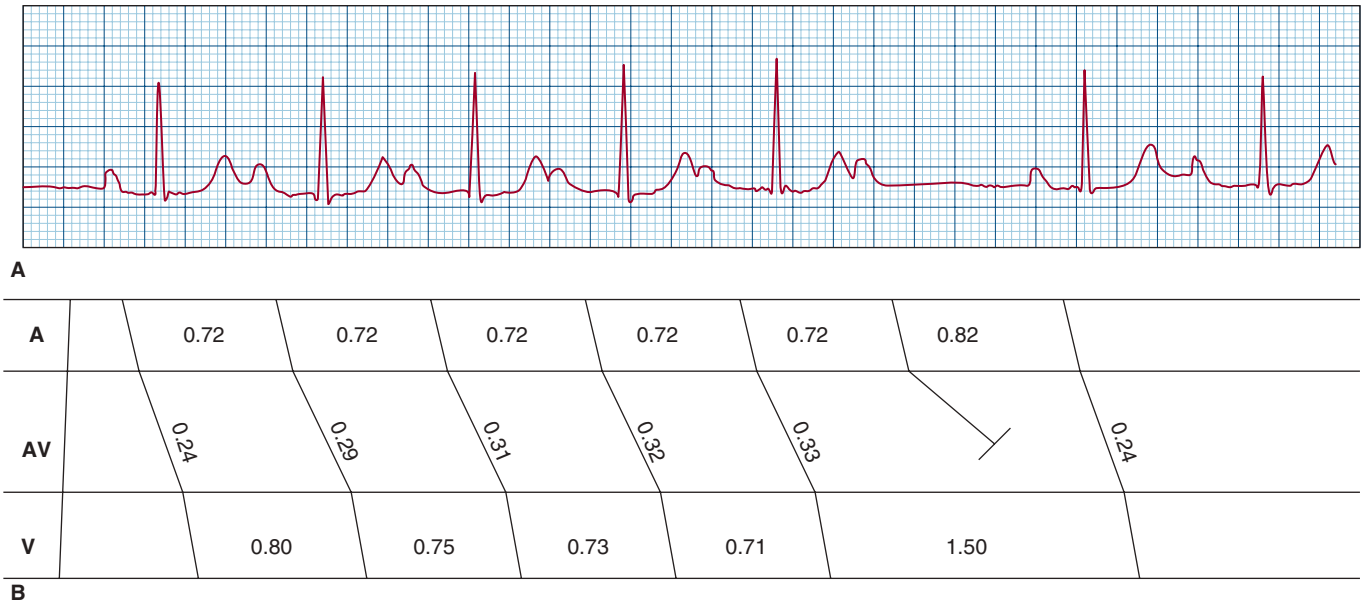


FIGURE 89–3. A. Type I second-degree atrioventricular (AV) block. A 6:5 AV Wenckebach periodicity is shown. Note that the PR interval progressively lengthens with a decreasing increment. This results in shortening of R-R intervals. The last conducted PR interval (0.33 seconds) is significantly longer than the next conducted PR interval (0.24 seconds). **B.** Type II second-degree atrioventricular block. Surface electrocardiogram (ECG), leads I, aVF, and V_1, and intracardiac electrograms from the right atrial (RA), proximal, and distal His bundle electrogram (HBE) catheters are shown. Surface ECGs show that the PR intervals are constant at 0.2 seconds with a left bundle branch block morphology of the QRS complex, and the fourth P wave is not followed by a QRS complex. The HBEs reveal that the site of block of the fourth P wave is below the His bundle.

indications, patients postcardiac transplant may benefit from pacing even for relative bradycardia if it is prolonged or recurrent (class IIb; LOE C), and asymptomatic patients with neuromuscular disease with prolonged His-Ventricular (HV) interval or abnormal resting ECG may also benefit from pacing. Pacing indications for nocturnal bradyarrhythmia in patients with sleep apnea that remains persistent despite continuous positive airway pressure have not been established.[7,8] With respect to cardiac sarcoidosis, a recent expert consensus statement of the Heart Rhythm Society (HRS) suggested that, in addition to the accepted guidelines, there is a class IIa indication for device implantation even in patients with transient AV block owing to the unpredictable nature of the disease and its variable response to immunosuppression.[9] After initial exuberance for the role of dual-chamber pacing to alter septal contraction timing and reduce LVOT gradients for obstructive HCM, subsequent randomized crossover studies have not shown consistent benefit. Permanent pacing is now reserved only for medically refractory patients with obstructive HCM in whom septal reductive therapy is not possible (class IIb; LOE B).[10]

Seminal Pacemaker Trials

Beginning in the late 1950s, the original indications for pacing consisted of treatment for malignant bradyarrhythmias. Given that the benefits of cardiac pacing were imminent and lifesaving (eg, pacing to prevent ventricular asystole), use of pacing versus sham was not studied for these indications in controlled trials. With the development of dual-chamber and multisite pacing systems, there has been randomized investigation with respect to pacemaker device type and mode selection. The evidence base to guide mode selection was recently reviewed in an expert consensus jointly released by the HRS and the American College of Cardiology Foundation (ACCF)[11] along with a systematic review commissioned by the National Institute for Health Research.[12] Observations regarding the seminal trials supporting these recommendations, as well as emerging technology in so-called "leadless" pacing, will briefly be reviewed here.

Pacing Mode Selection for SND There have been four major randomized trials comparing single or dual-chamber pacing for patients with bradycardia secondary to isolated sinoatrial dysfunction in the absence of AV block.[13-16] There are multiple possible approaches to pacing for these patients, including single-chamber atrial-only pacing, single-chamber ventricular-only pacing, or dual-chamber atrial and ventricular pacing (Fig. 89–4). The first large study seeking to answer this question was conducted by Andersen and associates at a single center in Denmark and has been referred to subsequently as the Danish Study.[16] In the study, 225 consecutive patients with sick-sinus syndrome were randomized to single-chamber atrial or single-chamber ventricular pacing. Mortality was not significantly different between the two groups at 40 months, but was significantly lower in patients receiving atrial-only pacing at 5.5 years (hazard ratio [HR] 0.66, $P = .045$).[17] Incidence of atrial fibrillation (AF) was also significantly less common in patients who were atrially paced, and interestingly, the rate of thromboembolic events—specifically stroke or peripheral arterial embolism—was lower in patients receiving single-chamber atrial pacing (17% vs 5%, $P = .0083$). In order to enroll, patients were required to demonstrate a PQ interval of less than 220 milliseconds and atrial pacing with 1:1 AV conduction was required at a rate of at least 100 bpm. With these criteria, a low rate of progression of AV block was noted (0.6% per year).[18] Single-chamber atrial versus dual-chamber atrial and ventricular pacing was next studied in another randomized study of 177 patients by Nielsen et al.[15] In contrast to ventricular-only pacing, there was no difference in this study with respect to morality, thromboembolism, or HF, but dual-chamber pacing was associated with increased left atrial (LA) size and reduced LV fractional shortening versus atrial-only pacing.

The matter of whether atrial-only or dual-chamber pacing is superior in SND was evaluated most comprehensively in DANPACE. Investigators at 20 European centers randomized 1415 patients with isolated SND and no AV block or bundle branch block (BBB) to single

TABLE 89–2. Recommendations for Pacing in Acquired AV Block

Class I

1. Indicated for advanced block[a] with bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be caused by AV block. (LOE: C)
2. Indicated for advanced block[a] with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia. (LOE: C)
3. Indicated for advanced block[a] in awake, symptom-free patients in sinus rhythm, with documented periods of asystole greater than or equal to 3.0 seconds or any escape rate less than 40 bpm, or with an escape rhythm that is below the AV node. (LOE: C)
4. Indicated for advanced block[a] in awake, symptom-free patients with AF and bradycardia with one or more pauses of at least 5 seconds or longer. (LOE: C)
5. Indicated for advanced block[a] after catheter ablation of the AV junction. (LOE: C)
6. Indicated for postoperative AV block that is not expected to resolve after cardiac surgery. (LOE: C)
7. Indicated for advanced block[a] with neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms. (LOE: B)
8. Indicated for second-degree AV block with associated symptomatic bradycardia regardless of type or site of block. (LOE: B)
9. Indicated for asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 bpm or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node. (LOE: B)
10. Indicated for advanced block[a] with during exercise in the absence of myocardial ischemia. (LOE: C)

Class IIa

1. Reasonable for persistent third-degree AV block with an escape rate greater than 40 bpm in asymptomatic adult patients without cardiomegaly. (LOE: C)
2. Reasonable for asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiological study. (LOE: B)
3. Reasonable for first- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise. (LOE: B)
4. Reasonable for asymptomatic type II second-degree AV block with a narrow QRS. When type II second-degree AV block occurs with a wide QRS, including isolated RBBB, pacing becomes a Class I recommendation. (LOE: B)

Class IIb

1. May be considered for neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease. (LOE: B)
2. May be considered for AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn. (LOE: B)

Class III (No Benefit)

1. Not indicated for asymptomatic first-degree AV block. (LOE: B)
2. Not indicated for asymptomatic type I second-degree AV block at the supra-His (AV node) level or that which is not known to be intra- or infra-Hisian. (LOE: C)
3. Not indicated for AV block that is expected to resolve and is unlikely to recur (eg, drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms).

[a]Advanced second-degree or third-degree block at *any* anatomic level.

Data from Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. Jan 22 2013;61(3):e6-75.

or dual-chamber rate-adaptive pacemakers.[13] The primary outcome of all-cause death was no different between the two groups, nor was there a difference with respect to secondary end points of incidence of stroke or HF. Surprisingly, and in stark contrast to prior randomized studies of atrial versus ventricular-only or dual-chamber pacing, atrial rate-adaptive pacing was associated with an *increased* risk of paroxysmal AF (HR 1.27, $P = .024$) in DANPACE, although permanent AF was not different. The mechanism for this difference is unclear; patients were programmed to paced AV delays of ≤ 220 milliseconds, which may have promoted better AV synchrony. Perhaps more importantly, however, the reoperation rate was significantly higher in this multicenter investigation of single-chamber devices (HR 1.99, $P < .0001$), and was driven by the need for change of pacing mode as a result of progression of heart block (at a mean rate of 1.7% per year, close to three times the rate of the Danish study). Any pacemaker reoperation is associated with a risk of infection or extraction, and these considerations factored into the class I recommendation for consideration of dual-chamber over single-chamber atrial pacing in SND.[11]

Importantly, the largest randomized pacemaker study for isolated SND was the Mode Selection Trial (MOST), although it did not look at atrial-only pacing systems. The trial randomized a total of 2010 patients to either dual-chamber (atrial and ventricular) or single-chamber (ventricular-only) pacing.[14] Neither the primary end point of death from any cause or nonfatal stroke, nor the secondary end point—a composite of death, stroke, or HF hospitalization—differed between patients assigned to dual-chamber versus ventricular-only pacing. Incidence of AF was less common with dual-chamber pacing (HR 0.79, $P = .008$), HF scores were better ($P < .0001$), as were quality of life metrics. Importantly, close to one-third of patients assigned to ventricular pacing crossed-over to dual-chamber pacing. This was driven by incidence of the pacemaker syndrome in half of all crossovers. Notable here is that MOST had a strict definition for pacemaker syndrome, requiring documentation of both symptoms of dyspnea or syncope along with demonstration of ventriculoatrial (VA) conduction or blood pressure (BP) reduction of 20 mm Hg or more during ventricular-only pacing. In addition, there was signal regarding the deleterious effect of RV pacing,

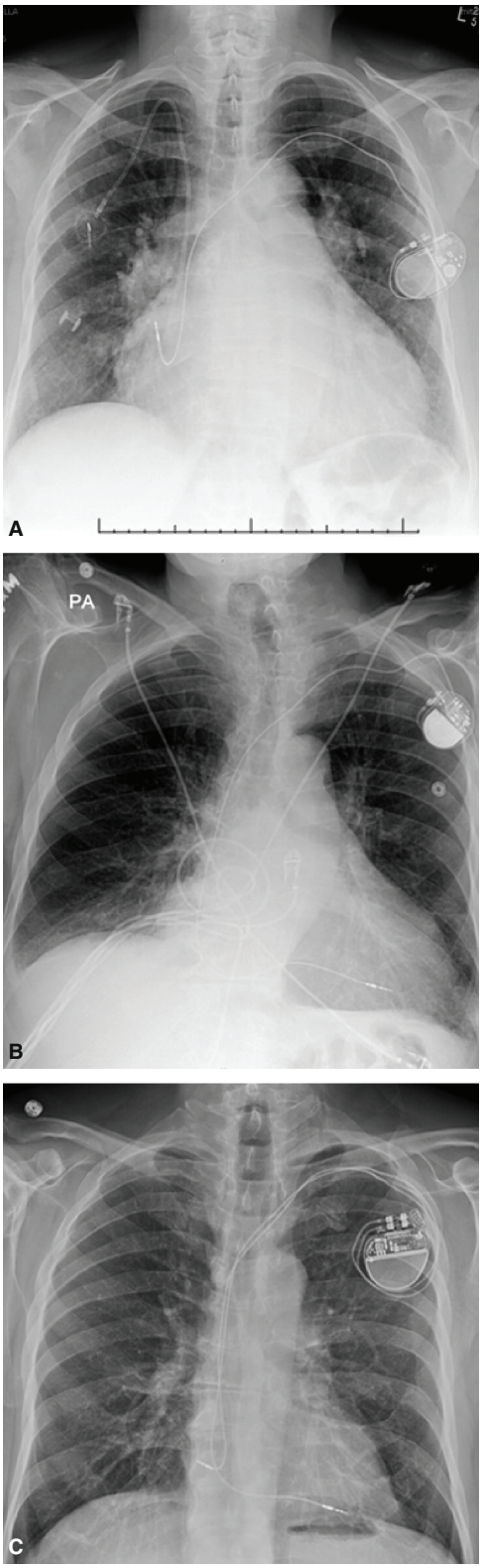


FIGURE 89–4. Types of pacemakers. **A.** Atrial-only single-chamber pacemaker. **B.** Ventricular-only single-chamber pacemaker. **C.** Atrial and ventricular dual-chamber pacemaker.

as cumulative percentage of right ventricular pacing (cum%VP) was associated with an increased risk of HF or AF in patients with both dual-chamber (HR 2.99, P = .024 for cum%VP > 40) and single-chamber (HR 2.56, P = .0007, cum%VP > 80) devices.[19] These findings were later further validated in the SAVE-PACe trial, which randomized 1065 patients with SND to dual-chamber devices programmed to deliver conventional AV pacing or to implement device-based algorithms to minimize ventricular pacing.[20] Conventional pacing systems with ~99% ventricular pacing versus those designed to minimize pacing (mean 9.1%) were associated with 40% increased risk of persistent AF (P = .0009), but no differences in mortality.

Pacing Mode Selection for AV Block There have been three large randomized trials investigating the role of pacing mode in patients with AV block.[21-23] Two of these trials, the Pacemaker Selection in the Elderly (PASE) study and the Canadian Trial of Physiologic Pacing (CTOPP), enrolled patients with SND and AV block. The largest and most recent, the United Kingdom Pacing and Cardiovascular Events (UKPACE) study, was focused on the question of how best to pace patients with AV block only.

PASE was a single-blind, randomized study of ventricular versus dual-chamber pacing in patients over the age of 65.[21] Of 407 patients studied, 201 demonstrated AV block (of which 59% had third-degree AV block). Importantly, all patients received dual-chamber devices and randomization was implemented based on programming only. Perhaps because of this, there was a high-degree of crossover in the trial (26%), attributed to the pacemaker syndrome (driven by symptoms of fatigue and dyspnea on exertion). There was no significant difference with respect to incidence of all-cause death, stroke, or HF hospitalization. The primary end point of the study, an assessment of health-related quality of life, reached significance only in patients with SND receiving dual-chamber programming. There was no difference among patients with AV block. Interestingly, incidence of AF was higher in patients with SND assigned to ventricular-only pacing but not in those with AV block.

The CTOPP investigators enrolled 2568 patients (with AV block present in 60%) at 32 Canadian centers and randomized them to a "physiologic pacing system" (either atrial-only pacing or dual-chamber) versus a ventricular-only pacemaker. The primary outcome, a composite of cardiovascular death and stroke, was not different the two groups. In subgroup analysis, and in contrast to PASE, there appeared to be greater benefit for physiologic pacing among patients with AV block, although this did not reach significance (P = .29). In addition, rates of crossover resulting from pacemaker syndrome were also considerably lower than PASE, with 99.2% of patients assigned to ventricular-pacing only maintaining that mode. Incidence of AF, however, appeared lower among patients with physiologic pacing (5.3% vs 6.6%, P = .05).

UKPACE was heralded as the definitive trial to guide mode selection among patients with AV block. In the trial, 2021 patients > 70 years of age undergoing implant for high-grade AV block were randomly assigned to a single-chamber ventricular pacemaker or a dual-chamber pacemaker. Over a median follow-up of 4.6 years, there was no difference in all-cause mortality. There was also no difference with respect to the secondary outcomes of rate of AF, HF, and a composite of stroke, transient ischemic attack (TIA), or other thromboembolism at 3 years. Surprisingly, there was an increase in incidence of AF among patients assigned to dual-chamber pacing in the initial 18 months, which may have reflected a systematic ascertainment bias, as dual-chamber devices could more readily detect AF. Similar to PASE, rate of crossover resulting from pacemaker syndrome at the end of the study was low (3.1%). Interestingly, median percentage of ventricular pacing was higher in patients assigned to dual-chamber pacing (99% vs 94%). There is speculation that—given that AV block may be intermittent—continuous RV pacing may have been unnecessary and diminished the possible benefits of a dual-chamber pacing system. Regardless, it has been these findings that leave open a class I recommendation that ventricular-only pacing is an acceptable alternative in patients with AV block who

have specific clinical situations (including but not limited to sedentary patients, those with significant medical comorbidities, or those with vascular access limitations) that make them less likely to benefit from dual-chamber systems (LOE B).[11]

Leadless Pacing There has been a resurgence of interest in ventricular-only pacing because of the development of integrated pulse generator and sensing/pacing systems that are fully self-contained (and are therefore "leadless"). These devices overcome some of the limitations of the conventional transvenous lead-based systems, including the early risk of acute complications such as pneumothorax, upper extremity thrombosis, or frozen shoulder, as well as mitigate longer-term risks such as lead-associated infection, fracture, or need for extraction. Indeed, some of have argued that the lead is the "Achilles' heel" of a pacing system.[24] Two fully integrated pulse generator and sensing/pacing systems have now been studied in human trials: the Nanostim leadless cardiac pacemaker (LCP, St. Jude Medical) and the Micra transcatheter pacing system (TCP, Medtronic) (Figs. 89–5 and 89–6). Both devices rely on a catheter-based deployment tool and are delivered to the RV for ventricular-only pacing.

The feasibility of LCP was tested in the LEADLESS trial, a prospective, nonrandomized single-arm multicenter study of safety and clinical performance in 33 subjects.[25] Indications for implant included permanent AF with slow response or AV block, normal sinus rhythm patients with high-degree block and low level of physical activity or short lifespan, or sinus bradycardia with infrequent pauses or unexplained syncope with abnormal findings at EP study. The overall complication-free rate acutely was 94%,[25] with no pacemaker-related adverse events, stable device sensing, and pacing thresholds between 3 and 12 months in follow-up.[26] Interim analysis of the LEADLESS II study was also recently reported.[27] Similar to LEADLESS, the study was a prospective, nonrandomized, multicenter analysis of 526 patients receiving LCP with a primary outcome of efficacy and safety. Pacemaker implant success was achieved in 95.8% of patients, with an average procedural time of 28.6±17.8 minutes and an average hospital stay of 1.1±1.7 days. Successful implant failure resulted predominantly from inadequately sensed R waves. Serious adverse events were observed in 6.7% over a 6-month period, and included device dislodgement (1.7%), cardiac perforation (1.3%), and vascular complications (1.3%).

FIGURE 89–5. Leadless pacemakers presently available for human use: the St. Jude Nanostim (*right*) and the Medtronic Micra (*center, next to ruler*). Reproduced with permission from Miller MA, Neuzil P, Dukkipati SR, Reddy VY. Leadless cardiac pacemakers: back to the future. *J Am Coll Cardiol*. 2015 Sep 8; 66(10):1179-1189.

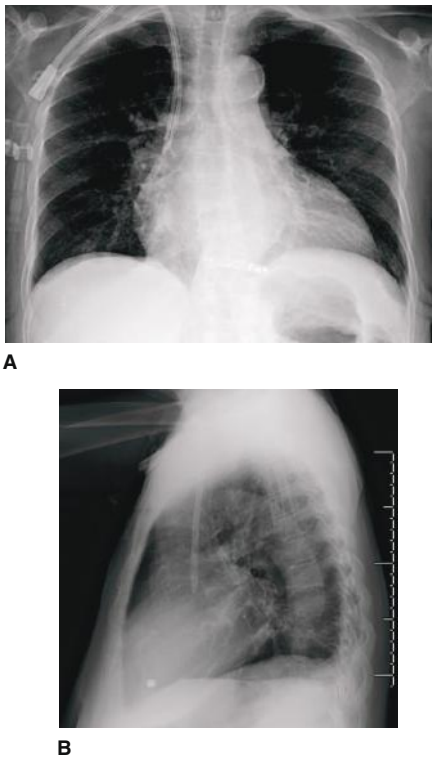


FIGURE 89–6. **(A)** Posteroanterior and **(B)** lateral chest films of patient with leadless cardiac pacemaker.

Early results of the Micra TCP trial have also been reported.[28,29] A prospective, nonrandomized investigation conducted at 56 centers, criteria for entry are broader than in LEADLESS, including all class I or class II guideline-based indications for pacing. A total of 725 patients underwent implant. The primary indication for enrollment was persistent or permanent atrial tachyarrhythmia (64%), SND (17.5%), and AV block (14.8%). Implant success was achieved in 99.2% and freedom from major complication of 96% at 6 months. Cardiac perforation or effusion (1.6%) and vascular access complication (0.7%) were the most common. No radiographic device dislodgements were noted, but three patients required system revision as a result of elevated pacing threshold, symptoms of pacemaker syndrome, or intermittent loss of capture.

With relatively short implant times, low rate of dislodgement, and projected longevity lasting 10 to14 years, there is growing enthusiasm with respect to the possible role of fully self-contained CIEDs for pacing. Although they do not expand the indication for pacing, they may be associated with fewer adverse events, particularly those resulting from late infection or extraction, as compared with conventional transvenous systems. Further randomized study will help clarify whether their role is that of niche player or whether they represent a new paradigm in the delivery of care.[30]

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Indications for ICDs

Defibrillation to treat VF was first reported in the surgical setting in 1947.[31] Less than a decade later, Zoll demonstrated that trans-chest countershock using paddles was a viable means for defibrillation for routine clinical practice.[32] Development of an internal, automatic defibrillator was first described and successfully tested by Dr. Mirowski and Dr. Mower in canines by 1970.[33] Misgivings regarding the safety

profile or appropriate patient population for the device delayed human clinical investigation.[34] Indeed, in the initial pilot study subjects were required to have survived two episodes of cardiac arrest on dual antiarrhythmic therapy in order to enroll.[5] Indications for ICDs have expanded since this period of initial work, and can broadly be categorized as (1) applying to patients who have survived prior cardiac arrest, sustained VT/VF, or syncope caused by ventricular arrhythmia (ie, secondary prevention); versus (2) individuals at risk, but who have not yet had a documented episode of sustained VT/VF, arrhythmic syncope, or cardiac arrest (ie, primary prevention).[7] A recent HRS/ACC/AHA expert consensus statement also comments on use of ICDs in patients who are not included or not well represented in clinical trials.[35] Both sets of secondary and primary prevention recommendations are made with the caveat that patients be maintained goal-directed medical therapy and have a reasonable expectation of survival for greater than 1 year with good functional status.

Secondary Prevention The fundamental principle guiding ICD therapy in secondary prevention is that patients who have survived sudden cardiac death (SCD) are at increased risk for subsequent events and therefore will usually meet the indications for ICD (Table 89–3). ICD therapy is not recommended in secondary prevention, however, among patients with completely reversible causes for malignant arrhythmia (eg, electrolyte abnormalities, drugs, trauma, or ventricular tachycardia amenable to cure with ablation) or those within 48 hours after a diagnosis of MI. Data regarding the 48-hour window of increased risk of VT/VF after MI was initially obtained from early trials of thrombolysis in which ventricular arrhythmia after MI was a marker of increased risk, particularly when occurring greater than 2 days after admission.[36,37] The increased mortality attributed to early VT/VF in these studies was incurred during the index hospitalization. In more recent trials of percutaneous coronary intervention (PCI), it was observed that the majority of VT/VF episodes occurred within 48 hours, frequently during or immediately after PCI.[38-40] Although both early (< 48 hours) and late VT/VF is associated with increased risk, patients with later VT/VF episodes sustained greater mortality in follow-up for both STEMI and non-STEMI populations.

Primary Prevention The indications to implant ICDs for primary prevention among patients with chronic ischemic heart disease (IHD) or nonischemic cardiomyopathy (NICM) are based on large randomized trials that have demonstrated reduction in mortality with ICD therapy. There are also recommendations for ICDs in select clinical situations that have been informed by limited prospective study and consensus opinion. These include inherited arrhythmia syndromes, HCM, arrhythmogenic right ventricular cardiomyopathy (ARVC), nonhospitalized patients awaiting cardiac transplant, sarcoidosis, giant cell myocarditis, and Chagas disease (Table 89–4).

The primary tool for risk assessment in clinical practice is assessment of left ventricular ejection fraction (LVEF), based on the landmark trials which led to the approval of ICD therapy for SCD prevention. The guidelines acknowledge that the determination of LVEF lacks a "gold standard" and there is variation among commonly used techniques for LVEF assessment (including echocardiography, nuclear study, or cardiac magnetic resonance [CMR]). The writing committee recommended the clinician use the LVEF determination that "they feel is the most clinically accurate and appropriate."[7] In patients who are NYHA class II or III, ICD therapy is indicated for patients with LVEF ≤ 35% resulting from IHD or NICMP; for patients who are NYHA functional class I, an LVEF ≤ 30% is recommended for patients with IHD (and *may be considered* [class IIb] for NICMP); among patients with a history of IHD and with inducible VT or VF, the LVEF criterion is relaxed to ≤ 40%, irrespective of etiology of LV systolic dysfunction. The waiting period of 40 days after acute MI or 90 days after revascularization draws in part from large-scale trials assessing efficacy of ICD therapy in these clinical settings and will be discussed further below.

Special Situations With regard to special situations, there have been increasing data regarding use of defibrillators among patients with inherited arrhythmia syndromes that have informed specific recommendations for these patients.[41] Given that syncope may portend malignant ventricular arrhythmias, there is a class IIa recommendation for primary prevention ICD among long QT syndrome patients who experience recurrent syncopal events while on beta-blocker therapy, among patients with Brugada syndrome with a type 1 ECG pattern and arrhythmic syncope, or among lamin A/C mutation-positive patients with progressive cardiac conduction disease (PCCD) with LV dysfunction or NSVT. The recommendation is upgraded to class I for catecholaminergic polymorphic ventricular (CPVT) patients who demonstrate polymorphic VT or bidirectional VT on medical therapy. There are also more modest class IIb indications to consider ICD for patients with Brugada syndrome who develop VF during programmed electrical stimulation, among asymptomatic patients with short QT syndrome and a family history of SCD, among asymptomatic patients with a high-risk early repolarization (ER) pattern or symptomatic family members of ER syndrome patients with inferolateral ER, and in first-degree relatives of patients with idiopathic ventricular fibrillation who experience unexplained syncope.

Specific recommendations have also been elaborated for patients with HCM.[10] In this group, there is a class IIa recommendation to proceed with ICD in patients with a family history of SCD in a first-degree relative or with LV wall thickness ≥30 mm or recent unexplained syncope. There is also class IIa recommendation to consider ICD in patients with NSVT and SCD risk factors, including LVOT obstruction (resting gradient ≥ 30 mm Hg), the presence of late gadolinium enhancement (LGE) on CMR, LV apical aneurysm, or malignant genetic mutations. In patients with HCM and only NSVT or abnormal blood pressure response during exercise without SCD risk factors, the recommendation is downgraded to class IIb.

Seminal ICD Trials

Secondary Prevention There have been three pivotal trials that led to the approval of ICDs for secondary prevention: Antiarrhythmics Versus Implantable Defibrillators (AVID),[42] the Canada Implantable Defibrillator Study (CIDS),[43] and the Cardiac Arrest Survival in Hamburg (CASH) trial.[44] AVID was the largest and was conducted first—enrolling 1016 patients who had either survived near-fatal VF or undergone cardioversion for sustained VT with syncope, or with sustained VT and an LVEF of ≤ 40% with symptoms of hemodynamic compromise from VT such as near-syncope, congestive heart failure, or angina. Patients were assigned to either ICD or antiarrhythmic therapy (amiodarone or sotalol). The trial was stopped early (before its original goal of 1200 patients) because of significance of the primary outcome—overall survival—which was improved in patients randomized to ICDs at 1 year (89.3% vs 82.3%), 2 years (81.6% vs 74.7%), and 3 years (75.4% vs 64.1%) (unadjusted estimates, $P < .02$). Incidence of tachycardia therapy with either ATP or shocks was common at 3 years (85% for VF patients and 69% for VT patients). Importantly, however, in subgroup analysis, it was found that patients with LVEF > 35% or nonischemic arrhythmia were less likely to benefit from ICD versus antiarrhythmic therapy.

CIDS and CASH were both smaller than AVID. Eligible patients for CIDS included those who were > 72 hours from MI and electrolyte imbalance and demonstrated documented VF, out-of-hospital arrest requiring defibrillation or cardioversion, sustained VT with syncope,

TABLE 89–3. Recommendations for ICD therapy in Secondary Prevention

Class I (Is Recommended)

1. Indicated in patients who are survivors of cardiac arrest caused by VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. (LOE: A)
2. Indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. (LOE: B)
3. Indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study. (LOE: B)
4. In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) ventricular tachyarrhythmias > 48 hours after an MI and in the absence of ongoing ischemia, implantation of an ICD ***is recommended***.
5. In patients within 90 days of revascularization who have previously qualified for secondary prevention ICD and have abnormal left ventricular function, implantation of an ICD ***is recommended***.
6. In patients within 90 days of revascularization who have previously qualified for secondary prevention ICD that is unlikely to be related to myocardial ischemia/injury and have normal left ventricular function, implantation of an ICD ***is recommended***.
7. In patients within 90 days of revascularization with structural heart disease and sustained (or hemodynamically significant) ventricular tachyarrhythmia that was not clearly related to acute myocardial infarction or ischemia, implantation of an ICD ***is recommended***.
8. In patients < 9 months from the initial diagnosis of NICM with sustained (or hemodynamically significant) ventricular tachyarrhythmia, implantation of an ICD ***is recommended***.

Class IIa (Can Be Useful)

1. Reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM. (LOE: C)
2. Reasonable for patients with sustained VT and normal or near-normal ventricular function. (LOE: C)
3. Reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta-blockers. (LOE: B)
4. Reasonable for patients with Brugada syndrome who have had syncope. (LOE: C)
5. Reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest. (LOE: C)
6. Reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta-blockers. (LOE: C)
7. In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) VT > 48 hours after an MI that can be treated by ablation, implantation of an ICD ***can be useful***.
8. In patients who, within 40 days of an MI, present with syncope that is thought to result from ventricular tachyarrhythmia (by clinical history, documented NSVT, or electrophysiologic study), implantation of an ICD ***can be useful***.
9. In patients within 90 days of revascularization who have previously qualified for secondary prevention ICD that was not related to acute myocardial ischemia/injury and who were subsequently found to have coronary artery disease that is revascularized with normal left ventricular function, implantation of an ICD ***can be useful***.
10. In patients who, within 90 days of revascularization, develop sustained (or hemodynamically significant) VT that can be treated by ablation therapy, implantation of an ICD ***can be useful***.
11. In patients within 90 days of revascularization present with syncope that is thought to result from ventricular tachyarrhythmia (by clinical history or documented NSVT, or EP study), implantation of an ICD ***can be useful***.
12. In patients < 9 months from the initial diagnosis of NICM with syncope that is thought to result from ventricular tachyarrhythmia (by clinical history or documented NSVT), implantation of an ICD ***can be useful***.

Class IIb (May Be Useful)

1. May be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause. (LOE: C)

Class III (Not Recommended)

1. Not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet other ICD implantation criteria (LOE: C)
2. Not indicated for patients with incessant VT or VF. (LOE: C)
3. Not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. (LOE: C)
4. Not indicated when VF or VT is amenable to surgical or catheter ablation (eg, atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). (LOE: C)
5. Not indicated for patients with ventricular tachyarrhythmias resulting from a completely reversible disorder in the absence of structural heart disease (eg, electrolyte imbalance, drugs, or trauma). (LOE: B)
6. In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) ventricular tachyarrhythmias where there is clear evidence of an ischemic etiology with coronary anatomy amenable to revascularization (and appropriately treated), implantation of an ICD ***is not recommended***.
7. In patients within 90 days of revascularization who were resuscitated from cardiac arrest caused by ventricular tachyarrhythmia that was related to acute myocardial infarction/injury, with normal left ventricular function, and who undergo complete coronary revascularization, an ICD ***is not recommended***.

Data from Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* Jan 22 2013;61(3):e6-75.

TABLE 89-4. Recommendations for ICD Therapy in Primary Prevention

Class I (Is Recommended)

1. Indicated in patients with LVEF less than or equal to 35% resulting from prior MI who are at least 40 days post-MI and are in NYHA functional class II or III. (LOE: A)[a]
2. Indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35% and who are in NYHA functional class II or III. (LOE: B)[a]
3. Indicated in patients with LV dysfunction resulting from prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30%, and are in NYHA functional class I. (LOE: A)[a]
4. Indicated in patients with nonsustained VT resulting from prior MI, LVEF less than or equal to 40%, and inducible VF or sustained VT at electrophysiologic study. (LOE: B)[a]
5. In patients with abnormal cardiac biomarkers that are not thought to result from an MI and who otherwise would be candidates for implantation on the basis of primary prevention or secondary prevention criteria, implantation of an ICD ***is recommended***.[b]
6. In patients who, within 40 days of an MI, require nonelective permanent pacing, who also would meet primary prevention criteria for implantation of an ICD, and recovery of left ventricular function is uncertain or not expected, implantation of an ICD with appropriately selected pacing capabilities ***is recommended***.[b]
7. In patients within 40 days of an MI and who have an ICD that requires elective replacement because of battery depletion, after careful assessment of comorbidities and the current clinical situation, replacement of the ICD generator ***is recommended***.[b]
8. In patients within 90 days of revascularization who require nonelective permanent pacing, who would also meet primary prevention criteria for implantation of an ICD, and in whom recovery of left ventricular function is uncertain or not expected, implantation of an ICD with appropriately selected pacing capabilities ***is recommended***.[b]
9. In patients within 90 days of revascularization with an ICD that requires replacement because of battery depletion, after careful assessment of comorbidities and the current clinical situation, replacement of the ICD generator ***is recommended***.[b]
10. In patients < 9 months from the initial diagnosis of NICM who require non-elective permanent pacing, who would meet primary prevention criteria for implantation of an ICD, and in whom recovery of left ventricular function is uncertain or not expected, implantation of an ICD with the appropriately selected pacing abilities ***is recommended***.[b]

Class IIa (Can Be Useful)

1. Reasonable for patients with HCM who have one or more major risk factors for SCD. (LOE: C)[a]
2. Reasonable for the prevention of SCD in patients with ARVD/C who have one or more risk factors for SCD. (LOE: C)[a]
3. Reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta-blockers. (LOE: B)[a]
4. Reasonable for nonhospitalized patients awaiting transplantation. (LOE: C)[a]
5. Reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. (LOE: C)[a]
6. In patients who are within 90 days of revascularization and who previously qualified for the implantation of an ICD for primary prevention of sudden cardiac death, and who have undergone revascularization that is unlikely to result in an improvement in LVEF > 0.35, and who are not within 40 days after an acute MI, implantation of an ICD ***can be useful***.[b]
7. In patients within 90 days of revascularization who have been listed for heart transplant or implanted with a ventricular assist device, and who are not within 40 days of an acute myocardial infarction, implantation of an ICD ***can be useful***.[b]
8. If recovery of left ventricular function is unlikely, implantation of an ICD for primary prevention ***can be useful*** between 3 and 9 months after initial diagnosis of NICM[b]
9. In patients < 9 months from the initial diagnosis of NICM who have been listed for heart transplant or implanted with a left ventricular assist device, implantation of an ICD ***can be useful***.[b]

Class IIb (May Be Useful)

1. May be considered in patients with nonischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional class I. (LOE: C)[a]
2. May be considered for patients with long-QT syndrome and risk factors for SCD. (LOE: B)[a]
3. May be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause. (LOE: C)[a]
4. May be considered in patients with a familial cardiomyopathy associated with sudden death. (LOE: C)[a]
5. May be considered in patients with LV noncompaction. (LOE: C)[a]

Class III (Not Recommended)

1. Not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. (LOE: C)[a]
2. Not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D. (LOE: C)[a]
3. Implantation of an ICD within the first 40 days following acute MI in patients with preexisting systolic ventricular dysfunction (who would have qualified for a primary prevention ICD) ***is not recommended***.[b]
4. ICD implantation in patients within 40 days of an MI who have been listed for heart transplant or implanted with a left ventricular assist device ***is not recommended***.[b]
5. Implantation of an ICD for primary prevention ***is not recommended*** within the first 3 months after initial diagnosis of NICM.[b]

[a]Data from Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. Jan 22 2013;61(3):e6-75.

[b]Date from Kusumoto FM, Calkins H, Boehmer J, et al. HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. *J Am Coll Cardiol*. Sep 16 2014;64(11):1143-1177.

sustained VT with presyncope in patients with LVEF ≤ 35%, or unmonitored syncope with subsequent documentation of spontaneous VT ≥ 10 seconds or sustained VT (≥ 30 seconds) induced at EP study. A total of 659 patients were randomized to either ICD or amiodarone. A *nonsignificant* 20% relative risk reduction was found in all-cause death and 33% reduction in arrhythmic mortality. Similarly in CASH, 288 patients with resuscitated from cardiac arrest from documented sustained VT or VF were randomized to amiodarone and beta-blockade versus ICD and a 23% nonsignificant reduction in all-cause mortality was noted. Meta-analyses combining the data from AVID, CIDS, and CASH have shown that, when taken together, the benefit of ICDs in secondary prevention does reach significance and is associated with 28% relative risk reduction of overall mortality, driven by a 50% reduction in arrhythmic death.[45,46]

Two additional trials bear mentioning with respect to secondary prevention. The first Multicenter Automatic Defibrillator Implantation (MADIT-I) trial evaluated 196 patients with LV systolic dysfunction (LVEF ≤ 35%), prior MI, and either documented asymptomatic NSVT and inducible nonsuppressible sustained VT or VF at EP study.[47] CABG within the past 2 months or percutaneous coronary intervention (PCI) within 3 months were exclusion criteria. Although distinct from secondary prevention in that patients enrolled in MADIT-I had no history of arrhythmic syncope or sustained VT, all patients demonstrated inducible and nonsuppressible (by procainamide or another antiarrhythmic) VT at EP study. These patients were allocated to either ICD or conventional medical therapy, and the trial revealed an impressive reduction in mortality (HR 0.46, $P = .009$). Also relevant to secondary prevention patients is the Multicenter Unsustained Tachycardia Trial (MUSTT) in which 704 patients with coronary artery disease (> 4 days from the most recent MI or revascularization procedure), LVEF ≤ 40%, and asymptomatic NSVT (lasting for ≥ 3 beats) underwent EP study.[48] Patients with sustained VT or VF at EP study were then randomized to either antiarrhythmic therapy with either ICD or EP-guided antiarrhythmic therapy versus no antiarrhythmic therapy. The trial showed that, although patients with EP-guided therapy demonstrated lower risk of arrhythmia, the risk of arrhythmic death was lowered only in patients assigned to ICD (RR 0.24 versus those who received EP-guided antiarrhythmic therapy, $P < .001$). Perhaps more than any other secondary-prevention trial, MUSTT makes a compelling argument for ICD among patients with CAD and inducible VT or VF, above and beyond medical therapy.

Primary Prevention Evidence supporting the use of ICDs in the primary prevention of SCD was comprehensively reviewed in a recent report commissioned by the Agency for Healthcare Research and Quality (AHRQ).[49] Their meta-analysis of 14 studies showed a significant reduction in all-cause mortality (HR 0.69, 95% CI 0.6-0.79) and an even stronger case for reducing SCD (HR 0.37, 95% CI 0.26-0.52). The seminal trials that led to the approval of ICDs for current indications include MADIT-II,[50] the Sudden Cardiac Death-Heart Failure (SCD-HeFT) trial,[51] and the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study.[52] In MADIT-II, 1232 patients with prior MI and LVEF ≤ 30% were randomly assigned (in a 3:2 ratio) to ICD or conventional medical therapy. Patients with MI within the past month or coronary revascularization within the prior 3 months were excluded. The trial was stopped early because of the superiority of ICDs. The primary outcome was all-cause death, and was significantly reduced for patients assigned to ICD versus usual care (HR 0.69, $P = .016$). SCD-HeFT was larger and more inclusive in enrollment than MADIT-II, including NYHA class II or II patients with stable HF and LVEF ≤ 35% from ischemic or nonischemic causes, and randomized subjects to placebo, amiodarone, or single-chamber ICD. The primary outcome was also death from any cause and was significantly reduced for patients assigned to ICD (HR 0.77, $P = .007$), and was similar for patients with ischemic or nonischemic HF. Finally, DEFINITE enrolled 458 patients exclusively with nonischemic dilated cardiomyopathy, LVEF < 36%, and presence of ambient arrhythmias (NSVT 3 to 15 beats at a rate ≥ 120 bpm) or at least 10 PVCs per hour on 24-hour Holter. Patients were randomized to either medical therapy or medical therapy supplemented with single-chamber ICD. The primary end point of all-cause death was better for patients assigned to ICD, but did not reach significance (HR 0.65, $P = .08$). A secondary end point of reduction in SCD, however, was significantly better for patients assigned to ICD (HR 0.20, $P = .006$).

Arguably even more informative than trials demonstrating benefit among primary prevention patients have been three large negative studies which have constrained use in patients after revascularization. These include the Coronary Artery Bypass Graft-Patch (CABG-Patch),[53] Defibrillator in Acute Myocardial Infarction Trial (DINAMIT),[54] and the Immediate Risk-Stratification Improves Survival (IRIS) study.[55] In CABG-Patch, patients scheduled for elective coronary bypass surgery were screened for age < 80 years, LVEF < 36%, and abnormalities on signal-averaged electrocardiogram; 1055 patients were enrolled and finally 900 assigned to either epicardial ICD or control (no ICD). The study was terminated early because of futility (HR 1.07 for all-cause death, $P = .64$) and was attributed to a perceived low rate of SCD among CABG patients, although this could not be ascertained with certainty because the majority of ICDs used lacked the ability to store electrograms. In addition, postoperative infection was significantly more common among patients assigned to ICD.

DINAMIT evaluated another high-risk group, patients between 6 and 40 days post MI. A total of 674 patients with LVEF ≤ 35% and evidence of reduced heart-rate variability or elevated average heart rate (HR) > 80 bpm on Holter monitoring were randomly assigned to ICD or no-ICD. The primary end point of all-cause mortality was not improved by ICD (HR 1.08, $P = .66$), whereas the risk of arrhythmic death was significantly reduced (HR 0.42, $P = .009$). Concerning, however, was that the risk nonarrhythmic death was significantly greater among patients assigned to ICD (HR 1.75, $P = .02$). Some commentators speculated that *inappropriate* device therapies might be harmful and have led to this difference.[56,57] The larger IRIS trial was meant to tackle the disappointing findings of DINAMIT head-on, enrolling 898 patients 5 to 31 days post MI with LVEF ≤ 40% and either high resting HR (≥ 90 bpm) or at least three beats of NSVT at a rate of ≥ 150 bpm. Patients were randomized to ICD or medical therapy alone. Results were in line with what had been found in DINAMIT—overall mortality was not reduced (HR 1.04, $P = .78$), SCD was reduced in patients assigned to ICD (HR 0.55, $P = .049$), but nonarrhythmic death was substantially greater for patients assigned to ICD (HR 1.92, $P = .001$). In part, it was the findings of DINAMIT and IRIS that primed investigators to the possible harm of ICDs, setting the stage for more contemporary trials of device programming to improve outcome (discussed further below).

Subcutaneous ICD Defibrillator systems have evolved from devices requiring an open-chest surgical approach to modern defibrillators that can be placed transvenously. The trials discussed above were conducted exclusively with either an epicardial or transvenous system. Indeed, as noted above in discussion regarding the rationale behind leadless pacing systems, the lead itself may be the weakest link in defibrillation systems—associated with greater risk of periprocedural complication and susceptible to later bacterial seeding and infection, insulations break, or fracture. Although subcutaneous arrays have been utilized to lower defibrillation threshold for a number of years, they have been used in accompaniment with transvenous or epicardial sensing leads for sensing. An entirely subcutaneous system was first

FIGURE 89–7. The Boston Scientific subcutaneous defibrillator (S-ICD). This is the second-generation, Emblem device. Image provided courtesy of Boston Scientific. ©2016 Boston Scientific Corporation or its affiliates. All rights reserved.

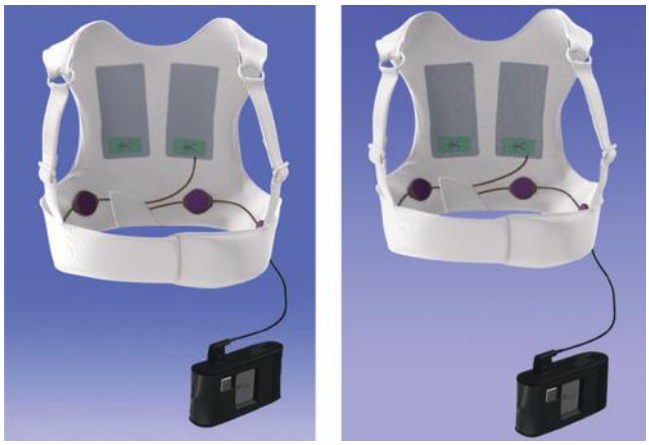


FIGURE 89–8. Zoll LifeVest wearable cardioverter-defibrillator.

conceptualized and demonstrated in canines in 1970,[58,59] but the idea largely went unnoticed. It was not until 2001 that the concept was pursued rigorously in human investigation (Fig. 89–7). The first study evaluated 78 patients in whom different configurations of a temporary subcutaneous ICD (S-ICD) were evaluated.[60] The best configuration (parasternal electrode and left lateral thoracic pulse generator) was then studied in 49 patients to determine appropriate defibrillation threshold, and then evaluated in longer-term use in a pilot study of 6 patients followed by a nonrandomized trial of 55 patients. Initial results were promising with the detection and treatment of 12 spontaneous episodes of arrhythmia.

A number of small cohort studies have now published safety and efficacy data regarding the S-ICD, which has been overall favorable.[61-65] The largest data set was pooled from two large registries: the S-ICD System IDE Clinical Investigation (IDE) study and the Boston Scientific Post Market S-ICD Registry (EFFORTLESS) trial, reporting on the results of 882 patients who were followed for close to 2 years.[66] Spontaneous VT or VF was detected in 111 discrete events in 59 patients with a first-shock success of 90.1% and 98.2% successful with 5 available shocks. The 3-year inappropriate shock rate was 13.1% and reduced with dual-zone programming. Device-related complications occurred in 9.6%, with device-related infection requiring revision or removal being the most common. Importantly, given that the device is subcutaneous, no bacteremia or device-related endocarditis occurred, and the complication rate was reduced with operator experience.[67] The ongoing Prospective, Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter-Defibrillator Therapy (PRAETORIAN; NCT01296022) trial seeks to compare the efficacy and safety of S-ICD versus conventional transvenous ICD systems head-to-head and will help answer questions regarding which type of system to implant for a primary prevention patient going forward.[68]

Wearable Cardioverter-Defibrillator Use of a wearable cardioverter-defibrillator (WCD) (Fig. 89–8) to terminate VF in humans was first described in 1998,[69] and has emerged as a viable option to "bridge" patients during a period of increased risk prior to eventual ICD implantation or to a point at which ICD implantation is no longer indicated. There are limited observational data available regarding the efficacy of WCDs leading to its general approval.[70,71] An ongoing study, Vest Prevention of Early Sudden Death Trial/Prediction of ICD Therapies Study (VEST/PREDICTS; NCT01446965) seeks to address the question of whether WCDs in patients with low LVEF (≤ 35%) after MI might benefit from additional protection with randomization to WCDs in addition to goal-directed medical therapy. PREDICTS will follow VEST as part of an ongoing observational study after 2 months (the completion of VEST). The largest real-world data regarding use comes from the WEARIT-II Registry, in which 2000 patients (40% ischemic, 46% nonischemic, and 12% with congenital or inherited arrhythmia) received WCDs for a median duration of 90 days.[72] Sustained VT/VF was detected in 2.1% of patients with therapy delivery required for 1.1% (and the remainder spontaneously terminating). Risk was higher for patients with ischemic cardiomyopathy or congenital/inherited disease than nonischemic cardiomyopathy. Similar findings were also seen in another large single-center cohort study.[73] The WCD therefore may be an option to cover the "gap" highlighted by DINAMIT and IRIS in patients at risk after MI. Importantly, rates of inappropriate therapy were low (0.5%). At the end of WCD use in WEARIT-II, less than half (42%) required ICD, with improvement in LVEF being the most common reason for deferral.

CARDIAC RESYNCHRONIZATION THERAPY

Indications for CRT

During the past two decades, cardiac resynchronization therapy (CRT) has emerged as a safe and efficacious device-based therapy for heart failure patients with severe systolic dysfunction and evidence of intraventricular conduction delay. CRT is the use of a pacemaker or defibrillator with three electrical leads to coordinate myocardial contraction. Two leads are endocardial, placed in the RA and RV, and a third lead is traditionally placed in a tributary of the coronary sinus overlying the epicardial surface of the LV (Fig. 89–9). CRT exerts its physiological impact via synchronizing ventricular contraction, leading to improved left ventricular filling, reduced mitral regurgitation, increased pumping efficiency, and improved cellular bioenergetics. Indeed, in marked contrast to traditional pacing systems, the goal in CRT is to pace every single beat. Multiple prospective randomized studies have shown that CRT yields long-term clinical benefits, including improved quality of life, increased exercise capacity, reduced heart failure hospitalization, and decreased all-cause mortality. Since the initial development of CRT as a modality, indications for therapy have been tailored to those with evidence of left-sided intraventricular conduction delay, with the strongest indication for patients in sinus rhythm with wide QRS secondary to LBBB (Table 89–5).

Seminal CRT Trials

Conventional Indications Since its first description in 1994, there has been an explosion of research directed towards elaborating the impact of CRT on ventricular performance as well as elucidating its clinical impact.

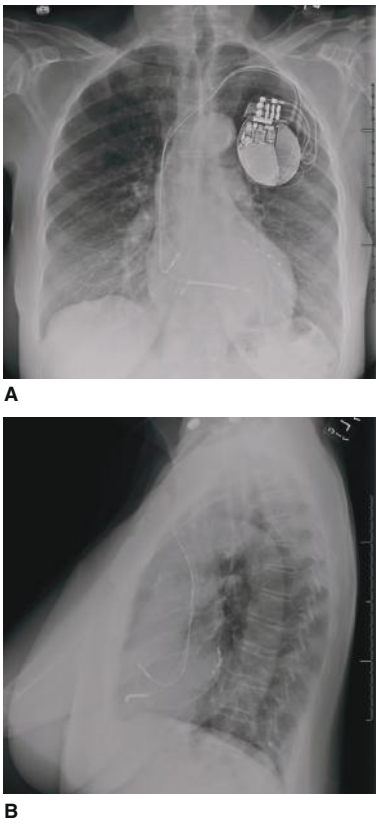


FIGURE 89–9. Posteroanterior (**A**) and lateral (**B**) chest film of patient with biventricular defibrillator (CRT-D device) with a quadripolar LV lead.

A recent comprehensive review commissioned by the AHRQ provides evidence regarding the efficacy and safety of CRT among Medicare beneficiaries.[74] Among the first controlled clinical trials of CRT was the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial,[75] in which 67 patients with severe heart failure (LVEF ≤ 35% and LV end-diastolic diameter > 60 mm), sinus rhythm, and QRS interval ≥ 150 milliseconds were implanted with CRT devices. The patients then underwent a single-blind, randomized, crossover study in which the study compared responses during 3-month periods of inactive pacing (or ventricular pacing only at heart rates < 40 bpm) versus aorto-biventricular (BiV) pacing for 3 months. Each patient acted as her or his own control, and the primary end point was 6-minute walking distance (6MWD). This distance was 23% greater with BiV pacing ($P < .001$); in addition, quality of life score as assessed by the Minnesota questionnaire ($P < .001$) and peak oxygen uptake were improved and two-thirds fewer hospitalizations occurred for those who received BiV pacing in the first 3 months ($P < .05$). These results were impressive and led the way for further trials exploring clinical and echocardiographic end points after the CRT.

Later, two seminal trials led to the initial approval for widespread use of CRT: the Comparison of Medical Therapy, Pacing, and Defibrillation on Heart failure (COMPANION) study[76] and the Cardiac Resynchronization-Heart Failure (CARE-HF) study.[77] In COMPANION, 1520 patients with NYHA class III or ambulatory class IV HF from ischemic or nonischemic cardiomyopathy, LVEF ≤ 35%, and QRS ≥ 120 milliseconds, were assigned to optimal pharmacologic therapy (OPT), OPT plus CRT pacemaker (CRT-P), or OPT plus a combined CRT-defibrillator (CRT-D). The primary end point was a composite of time to death or any-cause hospitalization and was significantly reduced by CRT-P (HR 0.81, $P = .014$) and CRT-D (HR 0.80, $P = .01$). The secondary end point of all-cause death was reduced by 24% in CRT-P patients in a trend that neared significance ($P = .059$) and was significant for CRT-D patients (36% reduction, $P = .003$). The CARE-HF study randomized 813 patients to medical therapy or medical therapy and CRT-P. The primary end point was a composite of death and cardiovascular hospitalization, and was significantly reduced by CRT-P (HR 0.63, $P < .001$). The secondary end point of mortality alone was also significantly reduced (HR 0.64, $P < .002$). CRT-P patients demonstrated better quality of life, less severe symptoms of heart failure, improved LVEF, reduced MR, and reduced N-terminal pro-brain natriuretic peptide (NT-proBNP).

Expanding the indication of CRT to less symptomatic patients were the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE),[78] the Multi-Center Automatic Defibrillator Implantation Trial-CRT (MADIT-CRT),[79] and the Resynchronization-Defibrillation for Ambulatory Heart Failure (RAFT) trial.[80] Briefly, REVERSE evaluated 610 patients with NYHA

TABLE 89–5. Recommendations for CRT

Class I

1. CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, III, or ambulatory IV; symptoms on GDMT. (LOE: A for NYHA class III/IV; LOE: B for NYHA class II)

Class IIa

1. CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT. (LOE: B)
2. CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT. (LOE: A)
3. CRT can be useful in patients with atrial fibrillation and LVEF less than or equal to 35% on GDMT if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT. (LOE: B)
4. CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (> 40%) ventricular pacing. (LOE: C)

Class IIb

1. CRT may be considered for patients who have LVEF less than or equal to 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of greater than or equal to 150 ms, and NYHA class I symptoms on GDMT. (LOE: C)
2. CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYHA class III/ambulatory class IV on GDMT. (LOE: B)
3. CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class II symptoms on GDMT. (LOE: B)

Class III (No Benefit)

1. CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 ms. (LOE: B)
2. CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year. (LOE: C)

Data from Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2013;61(3):e6-e75.

class I or II HF with QRS ≥ 120 milliseconds and LVEF ≤ 40%. Patients were randomized to CRT-ON or CRT-OFF. The primary end point was an HF clinical composite, which did not reach significance, but with greater improvement in LV remodeling and significantly reduced time to first HF hospitalization. Overall, the trial was felt to be underpowered. The larger MADIT-CRT study compared CRT-D with ICD only in 1820 patients with QRS ≥ 130 milliseconds, LVEF ≤ 30%, and NYHA class I (ischemic only) or II (ischemic or nonischemic) symptoms. The trial was terminated early because of efficacy (HR 0.66 for primary end point in CRT-D patients, $P < .001$), driven by a reduction in HF hospitalization. The annual mortality was low, at approximately 3% annually, and was not significantly different in the two groups. Improvement in LV volumes and LVEF was also noted. A few months later, the similarly sized (1798 patients) RAFT study evaluated CRT-D versus ICD in patients with LVEF ≤ 30%, NYHA class II or II HF, and a QRS duration ≥ 120 milliseconds. Results were quite similar, with reduction in the primary end point of all-cause death or HF hospitalization with biventricular pacing (HR 0.75, $P < .0001$). Mortality reduction was also achieved in this slightly more advanced HF population (HR 0.75, $P = .003$). Together, MADIT-CRT and RAFT led to a change of the guidelines, with approval for CRT for less symptomatic HF patients and earlier in the pathophysiologic disease process.

Narrow QRS Although initially developed to address the problem of electrical conduction delay (as evidenced by a wide QRS), there was initial enthusiasm that CRT might have a role in patients with narrower QRS and echocardiographic evidence of mechanical dyssychrony. An initial randomized controlled trial, the Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ),[81] showed no difference in a primary end point comparing increase in peak oxygen consumption, although patients with a QRS width of 120 to130 milliseconds did benefit. The largest and most comprehensive study evaluating the question of CRT in patients with narrow QRS with respect to hard clinical end points was the Echocardiography Guided Cardiac Resynchronization therapy (EchoCRT) trial.[82] Eligible patients demonstrated NYHA class III or IV HF, LVEF ≤ 35%, left ventricular end-diastolic dimension (LVEDD) ≥ 55 mm, QRS duration ≤ 130 milliseconds, and echocardiographic evidence of LV dyssynchrony (ie, opposing-wall delay of ≥ 80 milliseconds or speckle-tracking anteroseptal-to-posterior wall delay of ≥ 130 milliseconds). Patients were randomized to either CRT-on or CRT-off. The trial was terminated early because of futility, with no benefit found at a mean of 19.4 months. There was also a worrisome signal of increased mortality in CRT-on patients (HR 1.81, $P = .02$). Persistent or worsened dyssychrony was a marker of worse clinical outcomes.[83]

RV-Paced Patients In contrast, the use of CRT in patients with paced QRS complexes (even if the underlying native is narrow) has been shown to be successful at improving outcomes in select populations if pacing percentage is high. Putatively this is because RV pacing is analogous to a LBBB-like activation. The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial evaluated whether biventricular pacing would be superior to RV pacing in patients with high-degree atrioventricular block, NYHA class I to III symptoms, and LVEF ≤ 50%.[84] The primary outcome was a composite of time to death for any cause, HF visit requiring intravenous therapy, or increase in LVE end-systolic volume index by ≥ 15%. 691 patients were randomized and the primary outcome was reduced significantly (HR 0.74, 95% CI 0.60-0.90), and this effect was also seen when examining clinical end points of time to all-cause death and HF treatment alone (HR 0.73, 95% CI 0.57-0.92). Recent guidelines have taken BLOCK HF into account in consideration for BiV upgrade for patients with chronic RV pacing. The results of the larger Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace) trial[85] looked at a similar population, and preliminary results were presented at the European Society of Cardiology Congress in 2014. In it, any patient with high-degree AV block, or with first-degree block or slow AF with an expected high burden of pacing, could be eligible.[86] Patients with normal LVEF and no HF could also enroll, and a total of 1810 patients were randomized. Average ventricular pacing was > 85% in both groups at 1 month and the average LVEF in the study was 55%. Although there was a trend toward benefit for mortality and HF hospitalization reduction, it did not reach significance (HR 0.87, $P = .08$). Interestingly, there was no significant difference when stratified by LVEF greater or less than 50%. Implant failure was 14.8% among patients assigned to BiV devices and may have also confounded results. Even as fundamental indications expand, implementation of technology continues to be a moving target, particularly with respect to the LV lead in patients with CRT. Further discussion will be provided below to provide a perspective on pacing and defibrillation systems, their fundamental components and implant, as a general background to understanding indications and use.

PACING AND DEFIBRILLATION SYSTEMS

IMPULSE GENERATOR

A transvenous pacing system (used in both pacemakers and ICDs) consists of an implanted pulse generator and the leads through which it delivers electrical stimuli in the various chambers of the heart. The pulse generator houses complex electronic circuitry and the battery, or the power source. The pulse generator contains an output circuit, sensing circuit, timing circuit, and telemetry coil that sends and receives programming instructions and diagnostic information. Most current devices also have another circuit for the rate-adaptive sensor. In ICDs, in addition the pulse generator also includes a capacitor, to store and deliver the energy used in high-voltage shocks.

Lithium-iodine batteries are the most commonly employed batteries used for pacemakers, whereas ICDs utilize slightly different battery chemistries (eg, lithium-silver vanadium oxide, lithium-manganese dioxide, and lithium hybrids). The advantages of the lithium-iodine battery is that it has a high-energy density, long shelf-life, low battery life loss caused by internal self-discharge, and predictable characteristics that allow early warning of battery depletion. Most single-chamber pacemakers have expected battery longevity of 7 to 12 years, whereas dual-chamber pacemakers have an expected longevity of 6 to 10 years. Most pacemakers generate 2.8 V at the beginning of life. When the voltage nears the end of life (2.1-2.4 V), several elective replacement indicators in the pacemaker are activated. The common indicators of elective replacement can be found during routine device interrogation, including:

- Percent or fixed decrease in pacing rate on magnet application or free running rate
- Change to a simpler pacing mode (DDDR to VVI; VVIR to VOO)
- Reduced battery voltage
- Elevated battery impedance
- Restricted programmability

Once the elective replacement indicator (ERI) is activated, the pacemaker should generally be replaced within 1-3 months, or earlier if the patient is pacemaker dependent. When the battery reaches the end-of-service (EOS, < 2.1 V), the pacemaker changes to the simplest mode (VOO), fails to communicate or reprogram, fails to pace or sense, and may function erratically. If the pacemaker reaches EOS, it should be replaced immediately.

PACING AND DEFIBRILLATION LEADS

Permanent pacing leads have five major components: (1) electrodes, (2) conductors, (3) insulation, (4) connector pin, and (5) fixation mechanism. Pacing leads are identified as unipolar or bipolar based on the number of electrodes in contact with the myocardium, although all leads utilize a circuit with cathodal and anodal terminals. For example, unipolar leads carry a single conductor to a single electrode present at the lead tip (cathode), which is in contact with the myocardial tissue, and the surface of the pacemaker acts as the anodal terminal. Bipolar lead systems, on the other hand, house two conductors in the lead body leading to a cathodal tip electrode and an anodal ring electrode, 10 to 20 mm proximal to the tip electrode. Most modern pacing systems allow for bipolar leads to be "programmed unipolar" based on clinical scenario, such as to increase the field-of-view for sensing or possibly reduce the pacing output needed to capture the myocardium at a particular location. Downsides to the unipolar configuration are greater susceptibility to myopotential oversensing, far-field sensing, cross-talk (atrial stimulus sensed by ventricular channel or vice-versa), and skeletal muscle stimulation than the bipolar configuration.

Contemporary electrodes have a small tip surface area with a porous or roughened surface and steroid-eluting capability that reduces stimulation thresholds, decreases current drain, and improves sensing. The electrodes are connected to the connecter pin at the proximal end of the leads by the conductor wires, which are usually made of a nickel-composite alloy. The two primary materials utilized for insulation for leads are silicone rubber and polyurethane. Silicone demonstrates excellent biostability, flexibility, and resistance to thermal injury (as from electrocautery). Polyurethane insulation, on the other hand, has the advantage of having higher tear strength, lower friction coefficient, and smaller diameter.

Defibrillation leads are similar in design to pacing leads but with a multilumen design. In addition to conductors for pacing and sensing, defibrillator leads carry conducting cables for high-voltage output used during defibrillation. These are typically contained in distinct inner channels with a secondary insulator, usually composed of fluoropolymers (PTFE or ETFE).

The most commonly used transvenous endocardial leads have either a passive or an active fixation mechanism to avoid early dislodgement. Passive fixation mechanisms are limited to pacing leads only and include tines, fins, or wings that are entrapped within the trabeculae of the right-sided heart chambers and are subsequently covered by fibrous tissue. Contemporary active fixation leads are isodiametric, and use an extendable/retractable or exposed helix which is deployed in screw-like fashion into the myocardium. Active fixation allows for more precise positioning of the pacing lead in locations other than the right atrial appendage or right ventricular (RV) apex. They are also associated with reduced rates of acute dislodgement rates and greater ease in extraction, but slightly increased risk of perforation when compared with passive-fix leads.

TRANSVENOUS DEVICE IMPLANTATION

Approach

Transvenous pacemaker and defibrillator device implantations are usually performed under conscious sedation and local anesthesia targeting the cephalic, axillary, or subclavian veins. Cephalic or axillary vein access avoids the potential complication of compression damage to leads inserted via medial subclavian puncture by the costoclavicular ligament (also referred to as "subclavian crush"). The pulse generator is usually placed in the upper pectoral region subcutaneously, and occasionally the pacemaker is implanted behind the pectoral muscle or behind the breast via an inframammary approach, especially in young women. In patients who do not requiring pacing, an entirely subcutaneous defibrillation system, (the S-ICD) may be used, which is usually positioned in the left mid-axillary line between the fifth and sixth intercostal spaces (see further below).

Pacing Site

Atrial Lead The atrial lead is generally placed in the right atrial appendage; however, in patients with prior cardiopulmonary bypass (requiring an RA cannula), the atrial septum or the lateral wall is often utilized. It is preferable to avoid the atrial free wall with active fixation leads, because this has the potential to cause delayed pericardial effusion and/or cardiac tamponade. There has been interest in evaluating variable atrial pacing strategies to reduce the incidence of atrial fibrillation (AF), including atrial septal, coronary sinus (CS) ostium, Bachmann bundle, and biatrial pacing. No clear benefit for AF suppression has been demonstrated in randomized trials in patients with sinus node dysfunction,[87-89] although there may be utility for Bachmann bundle pacing in patients with documented interatrial conduction system delay,[90] or for biatrial pacing or Bachmann bundle pacing patients after coronary artery bypass graft (CABG) surgery.[91,92]

Right Ventricular Lead The RV lead is typically placed in the RV apex. However, attempts to maintain the normal sequence of ventricular activation by high septal pacing near the His-bundle and the RV outflow tract, especially in patients with cardiomyopathies, have suggested hemodynamic benefits by improving cardiac output compared with RV apical pacing. A randomized crossover trial of patients with congestive heart failure, LV dysfunction (ejection fraction [EF] < 42%), and chronic atrial fibrillation pacing from RV outflow tract (RVOT) or dual-site RV pacing (RVOT + RV apex) did not consistently improve quality of life or other clinical outcomes compared with RV apical pacing.[93] On the other hand, direct His-bundle pacing is a viable approach for permanent cardiac pacing in patients with dilated cardiomyopathy, which appears to better preserve LV function compared with RV apical pacing,[94,95] and with results comparable to biventricular pacing.[96] Indeed, recent data suggest that in patients with at least moderate pacing percentage (> 40% ventricular pacing), heart failure hospitalization can be significantly reduced in patients with His-bundle pacing relative to right ventricular pacing.[97] Although provocative, these findings need to be reproduced and verified in randomized study prior to effecting a change in the routine approach to RV lead placement.

Left Ventricular Lead In patients receiving biventricular pacing systems, an additional lead is placed for left ventricle (LV) pacing. The LV lead is typically targeted to a posterior or lateral tributary of the coronary sinus on the epicardial surface of the heart and requires use of specialized delivery systems. Direct epicardial LV lead placement pacing via thoracotomy may need to be considered in occasional patients with inadequate venous access, phrenic nerve stimulation, mechanical prosthetic tricuspid valve, or in patients with significant right-to-left shunting. Endocardial LV lead position may have theoretical advantage with respect to ventricular activation, but has been associated with an increased risk of stroke in an early study.[98] LV lead localization to improve outcome in CRT has been an area of active investigation. There are emerging data that targeting the LV lead to locations of either mechanical or electrical delay is associated with better outcome. Clinical trials have demonstrated that LV lead localization to areas either concordant or adjacent to mechanical delay, as assessed by echocardiographic strain mapping, is associated with better reverse LV remodeling and reduced HF hospitalization.[99,100] LV lead locations associated with longer LV lead electrical delay (LVLED) or surface QRS-to-sensed-LV time (QLV) have also been associated with better acute and longer-term success,[101-103] even in patients with nonideal anatomical location.[104-106]

Particularly as methods for LV lead delivery become more refined, intraprocedural assessment of optimal location will be a valuable means to improve CRT response. Recently, quadripolar LV leads (see example of quadripolar LV lead in Fig. 89–9) have made it possible to interrogate greater potential regions of the LV for pacing as well as develop strategies for "multisite" pacing in which sequential or simultaneous LV bipoles are utilized to increase LV recruitment to improve resynchronization and reduce dyssynchrony.[107-109] This may be particularly beneficial in non-LBBB patients in whom regions of electrical delay are difficult to predict from standard surface ECG analysis.[110]

Pacing Threshold and Sensing

Atrial and ventricular leads are placed into the appropriate chambers and sutured in place after ensuring adequate pacing and sensing thresholds. The basic premise in obtaining acute pacing and sensing thresholds during implant is that these thresholds may degenerate over time, and adequate safety margins must be maintained to ensure safe long-term pacing and sensing. It is essential to understand the strength-duration curve (Fig. 89–10). The strength-duration curve for stimulation is the quantity of voltage required to stimulate the heart at a series of pulse widths. As shown in Fig. 89–10, increasing the pulse width beyond 0.6 milliseconds usually does not decrease the voltage threshold. Ideally, at implant an atrial pacing threshold of < 1.5 V and ventricular threshold of < 1 V should be obtained. The threshold commonly increases over the next 2 to 4 weeks, reaches a peak, and then decreases to a chronic threshold level after 6 to 8 weeks. With steroid-eluting leads, the acute rise in threshold is ameliorated and the chronic threshold is significantly lower than in nonsteroid-eluting leads. During initial programming, the pacing output is programmed at three to five times the threshold voltage with a pulse width of 0.4 to 0.5 milliseconds. At the 2- to 3-month follow-up visit, the output is decreased to no less than twice the threshold to maintain an adequate safety margin and prevent battery drain. Some pacemakers have algorithms that enable the device to confirm capture. These algorithms may determine pacing threshold at programmed time intervals or on a beat-by-beat basis. Using algorithms to automatically check pacing-capture thresholds, these devices adjust pacing voltages to just above the pacing threshold to reduce current drain and prolong battery longevity. Automatic capture algorithms are available for atrial, right ventricular, and left ventricular leads.

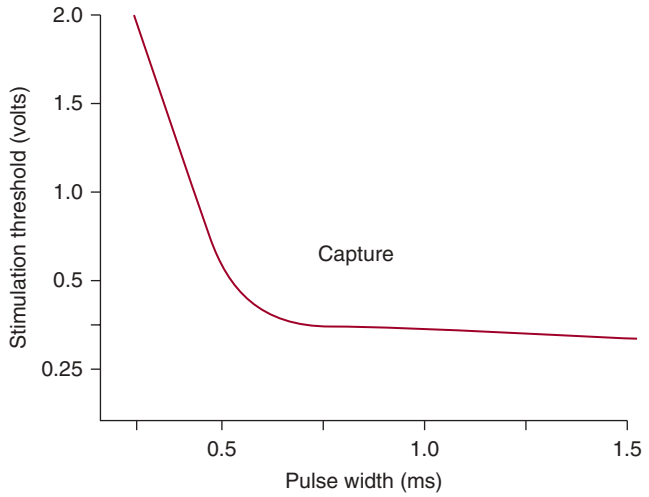


FIGURE 89–10. Strength-duration curve. This curve is obtained by plotting the voltage threshold obtained at various pulse widths. When programming the pacemaker output, this curve should be considered to ensure at least two times the safety margin. Increasing the pulse width beyond 0.6 ms generally does not decrease the voltage threshold.

Sensing is usually measured as the peak-to-peak or base-to-peak amplitude of the intracardiac electrogram in millivolts. The ventricular electrograms should measure at least 5 mV and frequently measure in excess of 10 to 20 mV. Ventricular sensitivity (the level in mV that the intracardiac electrogram must exceed to be sensed by the device) is generally programmed between 2 to 3 mV so that an adequate safety margin exists for sensing intrinsic ventricular depolarization without the risk of oversensing T waves or other artifacts. Atrial electrograms are smaller in amplitude than ventricular electrograms; however, a minimum atrial electrogram of 1 to 2 mV should be obtained. In patients with paroxysmal atrial fibrillation or flutter, the atrial electrogram during tachycardia might be smaller than during sinus rhythm. The atrial sensitivity is usually programmed at 0.5 mV; however, the sensitivity may have to be adjusted depending on the size of the far-field ventricular electrogram and associated atrial arrhythmias. Newer pacemakers also incorporate algorithms that automatically adjust sensitivity to the size of the atrial or ventricular signal.

Impedance

Lead impedance is the resistance to the flow of current from the generator to the myocardial tissue through the lead. Although there is a wide variability of normal lead impedances (250-1200 Ω), chronic lead impedances should not vary widely between outpatient follow-up visits. A fractured lead exhibits markedly elevated lead impedance. Insulation breaks manifest by reduced lead impedances. Lead fractures or insulation breaks often are intermittent problems. Therefore, normal lead impedances and pacing and sensing thresholds do not rule out these problems. The leads can be stressed by having the patient change position and do various provocative arm movements (eg, isometric exercise) to facilitate diagnosis of lead-related problems that are not otherwise observed. Many pacemakers intermittently monitor lead impedance and alert the physician to measured impedances that are out of the typical range.

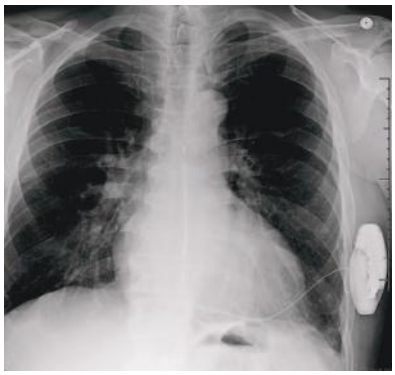
Leadless Pacemaker Implant

In contrast to traditional transvenous system implantation, deploying leadless cardiac pacing systems does not require the creation of a prepectoral pocket. Femoral venous access is obtained, preferably on the right side, and a delivery catheter is used to position the LCP or TCP into the appropriate RV position. The LCP utilizes an active helix fixation mechanism in an apicoseptal position whereas the TCP employs self-expanding nitinol tines delivered into the RV apex. Both devices are tethered to the delivery catheter and "tug-tested" before final release.

There has been also growing interest regarding endocardial LV lead positioning. This has been achieved either through use of transseptal access and use of active helix leads as well as with the development of leadless LV pacing. Traditional leads have been associated with a need for a higher degree of therapeutic anticoagulation and increased risk of stroke. On the other hand, the Wireless Stimulation Endocardiallly for CRT (WiSE-CRT) study utilized a system with a small LV lead receiver electrode powered by a subcutaneous ultrasound pulse generator.[111] This technique has generated interest, but was associated with increased risk of periprocedural complication resulting from pericardial effusion in early case series.[112] Continued research with a modified delivery system is under way.[113]

SUBCUTANEOUS DEFIBRILLATOR IMPLANT

Prior to implant, all patients who are candidates for S-ICD are screened with a three-lead surface ECG and the use of a template tool provided by the manufacturer. A patient "passes" only if a single lead consistently falls within a designated area in order to minimize the risk of T-wave



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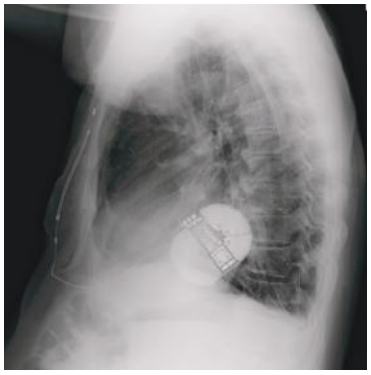

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FIGURE 89–11. Subcutaneous defibrillator in posteroanterior (**A**) and lateral (**B**) chest view.

oversensing in the S-ICD device.[114] This is particularly problematic for patients with HCM or congenital heart disease,[115-117] although a new software upgrade has included an algorithm that appears to reduce T-wave oversensing by 40%.[118] Template evaluation during rest and exercise testing has been advocated by some as a means to best identify a vector associated with lower risk.[119]

At the time of implant, multiple approaches have been used. Fluoroscopy is not required, although limited pre-procedural fluoroscopy may be useful in marking the patient. The implant procedure relies on use of anatomical landmarks utilizing either a three-incision (one for pulse generator, one for B-electrode, and one for A-electrode) or two-incision technique (which requires tunneling A-electrode from B-electrode incision).[120] Special attention paid to posterior placement of the pulse generator as well as accurate localization of the B electrode at the base of the heart (Fig. 89–11). Device testing is presently recommended for S-ICD systems at the time of implant, although as experience increases with the S-ICD and more data are acquired regarding its first shock success rate, this may well change as it has already for transvenous ICD systems.[121]

PROGRAMMING

PACEMAKER NOMENCLATURE

The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group established a five-letter pacemaker code to describe basic pacemaker mode and function (Table 89–6).[103,122] The first letter represents the chamber being paced and the second the chamber being sensed: A for atrium, V for ventricle, and D for both atrium and ventricle. The third position describes the response of the device to a sensed event: I for inhibition, T for triggered, and D for both inhibition and triggering. The device can either inhibit (I) pacing output from one or both of its leads, or it can trigger (T) pacing after the sensed event. In a DDD pacemaker, a sensed atrial event inhibits the atrial pacing channel and triggers ventricular pacing after a programmable AV delay. The fourth position refers to the programmability of the device: R for rate-responsive pacing. The fifth position refers to antitachycardia function for pacemakers only; with the evolution of implantable defibrillators, this position is rarely used.

PACING MODES

VVI Mode

As the code indicates, the ventricle is the chamber sensed and paced, with inhibition of ventricular pacing in response to a sensed ventricular event. A sensed or paced ventricular event initiates two timing cycles:

1. A refractory period that is programmable (ventricular refractory period) during which no ventricular sensing occurs to prevent inappropriate sensing of T waves. Any ventricular event occurring during this interval will also not reset the timing cycle.
2. A lower-rate interval (LRI), which corresponds to the programmed pacing rate. If there is no sensed ventricular event after the end of the ventricular refractory period and this interval expires, the pacemaker initiates a paced ventricular event. If a ventricular event is sensed after the ventricular refractory period (VRP), the pacemaker resets the timing cycle to begin a new LRI and VRP (Fig. 89–12).

TABLE 89–6. The Pacemaker Code

I	II	III	IV	V
Chamber-Paced	Chamber-Sensed	Response to Sensing	Programmability/Rate Response	Antitachycardia Function(s)
O (None)	O (None)	O (None)	O (None)	O (None)
A (Atrium)	A (Atrium)	I (Inhibit)	R (Rate responsive)	P (Antitachycardia pacing)
V (Ventricle)	V (Ventricle)	T (Triggered)	P (Simple programmable)	S (Shock)
D (Dual)	D (Dual)	D (I + T)	M (Multiprogrammable)	D (P + S)
S (Single chamber)	S (Single chamber)		C (Communicating)	

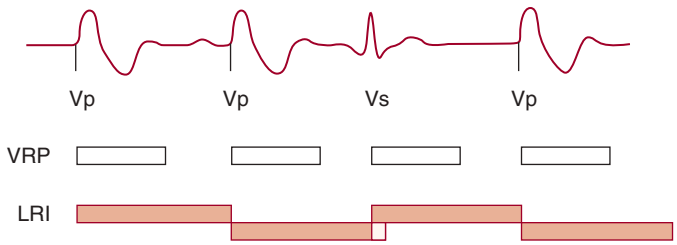


FIGURE 89–12. Single-chamber ventricular-inhibited pacing mode. The first two beats are ventricular-paced (Vp) events. The third beat is a ventricular-sensed (Vs) event. A Vs or Vp event starts a lower-rate interval (LRI), at the end of which ventricular pacing is initiated. A sensed or paced event also initiates a ventricular refractory period (VRP) during which no sensing will occur. The LRI after a sensed event can be separately programmed at a longer interval to allow for native rhythm. This is called *hysteresis.*

3. VVI pacing is the most commonly used pacing mode. Although it is a simple pacing mode and offers protection against bradyarrhythmias, loss of AV synchrony is not well tolerated in many patients and may lead to pacemaker syndrome (discussed later in this chapter). In patients with chronic atrial fibrillation, this is an ideal pacing mode, especially if rate responsiveness is available.

AAI Mode

Similar to VVI mode, sensing and pacing occur in the atrium, with the atrial pacing channel inhibited in response to a sensed atrial activity. An atrial refractory period (ARP) and an LRI are initiated in response to a sensed or paced atrial event. AAIR pacing with rate-responsiveness is an excellent pacing mode in patients with sinus node dysfunction and normal AV conduction. Patients with sinus node dysfunction may develop AV block, which may be a source of concern when using AAI pacing. However, with careful selection of patients, including normal PR intervals, absence of bundle branch block, and AV Wenckebach phenomenon occurring at atrial pacing rates of more than 120 bpm, the risk of development of second- or third-degree AV block may quite low (< 0.6% per year in the Danish study).[18]

VOO/AOO Modes

In these asynchronous pacing modes, there is no sensing. The chamber is paced asynchronously at the lower rate limit. The timing cycle consists of only an LRI and will not be reset by any intrinsic activity. Because there is no sensing, there are no refractory periods. This mode is rarely used except during procedures using constant electrocautery to avoid inhibition of pacing caused by sensing of the high-frequency impulses of electrocautery. When a magnet is applied over the pulse generator, the pacemaker switches to an asynchronous mode (VVI to VOO, DDD to DOO). The obvious disadvantage of this pacing mode is the possibility of asynchronous pacing during the vulnerable period and initiation of either atrial or ventricular fibrillation (although this is rare in patients in the absence of ischemia or prolonged QT). Importantly, magnet application to an ICD usually only disables tachyarrhythmia therapies (shocks and antitachycardia pacing), but does not switch to an asynchronous mode.

VDD Mode

In this mode the pacemaker paces only the ventricle, senses in both the atrium and the ventricle, and responds to atrial sensing with ventricular pacing. The ventricular channel is also inhibited by spontaneous ventricular activity. A sensed atrial event will start an atrioventricular interval (AVI) followed by ventricular pacing. If spontaneous AV conduction occurs before the termination of the AVI, ventricular pacing is inhibited. If there is no spontaneous atrial activity, ventricular pacing occurs at the lower-rate limit as in a VVI pacemaker. However, because there is no atrial pacing, this mode should not be used in patients with sinus node dysfunction. In patients with normal sinus node function and AV block, this is an excellent mode choice.

DDD Mode

A DDD pacemaker senses and paces in both the atrium and the ventricle, and the response to sensing involves both inhibition and triggered output. The DDD pacemaker uses numerous timing cycles. Most modern pacemaker timing cycles are ventricular-based (with some modifications) and are explained as follows:

- The LRI starts with a sensed or paced ventricular event and ends with a paced ventricular event, and consists of two portions.
- The ventricular event initiates an atrial escape interval (AEI) or VA interval at the end of which atrial pacing is initiated.
  - The atrial paced or sensed event initiates the AVI, at the end of which ventricular pacing is initiated. So, LRI = VA interval + AVI.
- A sensed atrial event occurring before the completion of the VA interval terminates this interval and starts the AVI.
- A sensed ventricular event occurring before the completion of the AVI will terminate this interval and the LRI and reinitiate the LRI.
- A sensed or paced ventricular event will also initiate the ventricular refractory period (VRP) to avoid T-wave oversensing and simultaneously initiates the postventricular atrial refractory period (PVARP).
  - Thus, the PVARP helps prevent the sensing and tracking of any retrograde P waves. This refractory period is programmable and is essential to the prevention of pacemaker-mediated, endless-loop tachycardia, which is an arrhythmia in which the dual-chamber pacemaker serves as the antegrade limb and the patient's retrograde conduction as the retrograde limb.
- The AV interval and the PVARP together constitute the total atrial refractory period (TARP), during which the atrial channel remains refractory and will not be tracked.
  - This in essence determines the upper rate interval (URI) or the maximal tracking rate interval (MTRI) in a DDD pacemaker.

In patients with DDD pacemakers, four different rhythm scenarios are possible, and many patients exhibit more than one scenario:

1. Normal sinus rhythm with no atrial or ventricular pacing: Here the patient's rate is faster than the programmed lower rate of the pacemaker, and the native PR interval is shorter than the programmed AV interval, as a result of which both the atrial and ventricular channels are inhibited (Fig. 89–13).
2. Atrial sensed, ventricular pacing: The patient's atrial rate is faster than the lower-rate limit, and the AV conduction interval is longer than the programmed AV interval, or there is no AV conduction, resulting in sensing of P waves and triggering of the ventricular channel after the programmed AV interval. In this situation, the

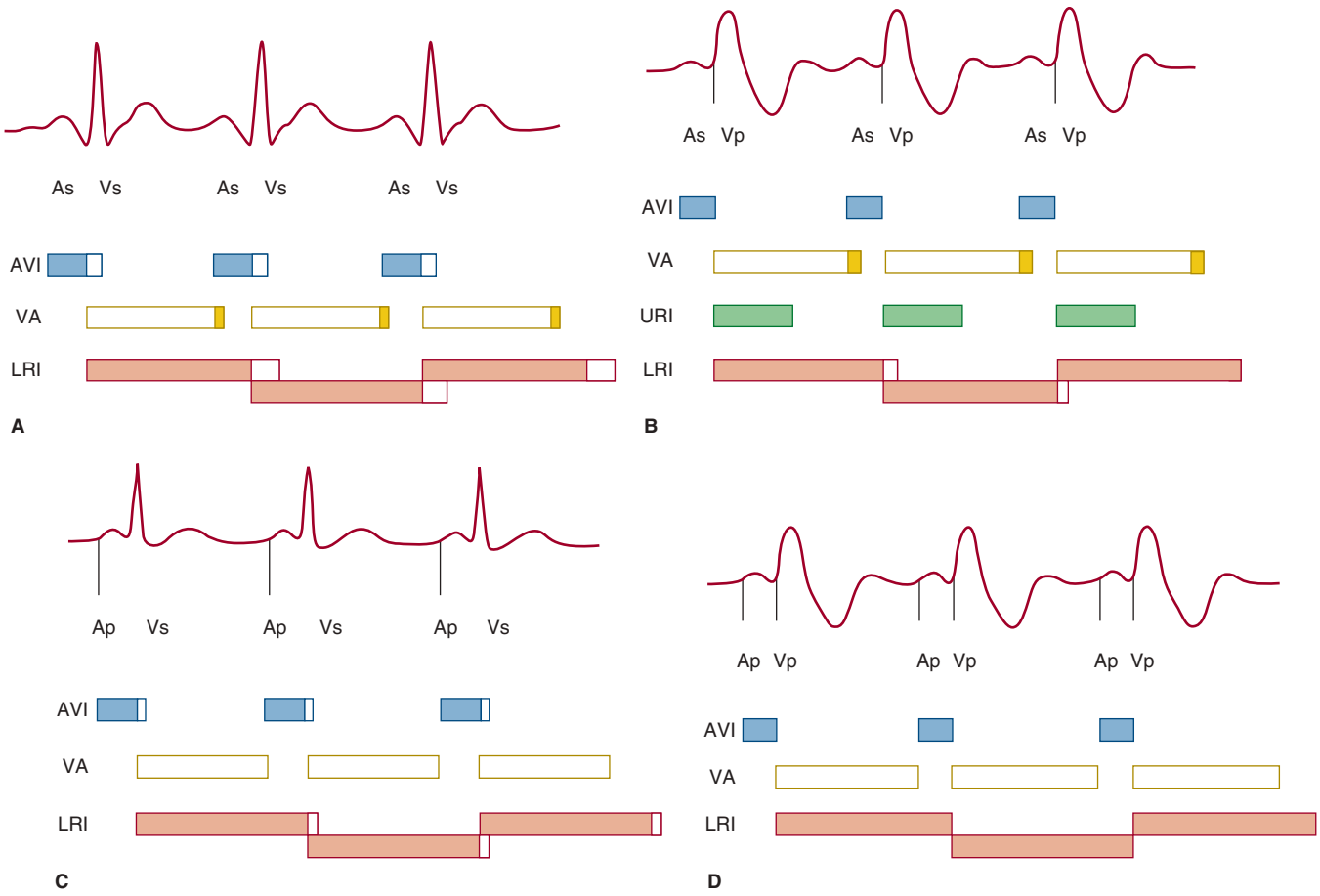


FIGURE 89–13. **A.** DDD pacing mode: atrial- and ventricular-sensed. In this example, atrial-sensed activity (As) initiates an atrioventricular interval (AVI), and normal conduction results in a ventricular-sensed (Vs) event that terminates the AV interval and the lower-rate interval (LRI) and initiates an LRI and the atrial escape interval (VA). Spontaneous atrial activity (As) again terminates the VA interval and starts a new AV interval. **B.** DDD pacing mode: As ventricular pacing. In this example the As event leads to Vp at the completion of the programmed AVI, because there is no native AV conduction to the ventricle. The Vp event starts the VA interval, the LRI, and the upper rate interval (URI). The VA and the LRIs are terminated by the spontaneous atrial activity that starts a new AV interval. **C.** DDD pacing mode: atrial-paced–ventricular-sensed. In this example, Ap starts the AVI but is terminated by the ventricular event that occurs before the completion of the AV interval. The Vs event initiates the VA and the LRI. If there is no spontaneous atrial activity, the VA interval times out and Ap occurs. **D.** DDD pacing mode: atrial- and ventricular-paced. The Ap event starts the AVI, at the completion of which the ventricle is paced because there is no spontaneous ventricular activity. The Vp event initiates the VA interval and results in atrial pacing, as there is no spontaneous atrial activity. Both Ap and Vp occur at the LRI.

patient is ventricularly paced at the patient's sinus rate until the upper rate limit (see Fig. 89–13).

3. Atrial paced and ventricular sensed: In this situation the patient's atrial rate is slower than the programmed lower rate and the patient's AV conduction interval shorter than the programmed AV interval. Here the patient is atrially paced at the lower-rate limit (see Fig. 89–13).
4. Atrial and ventricular pacing: Here the sinus rate is slower than the lower-rate limit, and AV conduction is longer or absent, resulting in atrial and ventricular pacing at the lower-rate limit (see Fig. 89–13).

ATRIOVENTRICULAR INTERVAL

The AV interval after a sensed atrial event is usually programmed to a shorter value than the AV interval after a paced atrial event and is termed the differential AV interval. Some DDD pacemakers also have the added capability of shortening the AV interval with increase in heart rates; this is called dynamic, or rate adaptive, AV interval. Another available feature increasingly incorporated into modern pacemakers is AV hysteresis in which the device periodically increases the AV interval to allow native AV conduction and intrinsic ventricular activation.

The paced AV interval is considered as a single interval with two subportions. The initial interval is the blanking period (12-50 milliseconds, programmable) during which the ventricular channel is blanked to avoid ventricular sensing of the atrial pacing artifact. If a spontaneous ventricular event occurs in this period, it will not be sensed. The second portion of the AV interval is the cross-talk sensing window during which a ventricular event is sensed if it occurs and leads to ventricular safety pacing with a shorter AV interval of 100 to 110 milliseconds. This is to avoid cross-talk, or inhibition of the ventricular channel by sensing of the atrial pacing artifact (Fig. 89–14).

UPPER RATE BEHAVIOR

In VDD and DDD modes, in addition to the programmed lower rate limit, there is an upper rate limit beyond which ventricular tracking of atrial events will not occur. When the atrial rate exceeds the programmed upper rate limit, the pacemaker will exhibit either Wenckebach or 2:1 AV block behavior. When the patient with complete heart block exercises to a sinus rate beyond the upper rate limit of the pacemaker, the P wave that is sensed is followed by ventricular pacing with

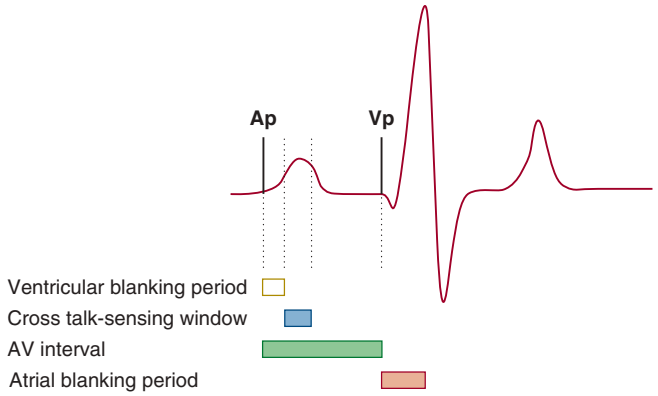


FIGURE 89–14. Atrioventricular (AV) interval and blanking periods. The AV interval after atrial pacing has two subportions. During the initial ventricular blanking period, sensing is suspended to avoid ventricular sensing of the leading edge of the atrial pacing artifact. During the second portion (cross-talk sensing window), if ventricular activity is sensed, ventricular pacing occurs with a shorter AV delay. The purpose of this safety feature (ventricular safety pacing) is to avoid inhibition of the ventricular channel by sensing of the atrial pacing artifact during this time window. Similar to the ventricular blanking period, there is an atrial blanking period after ventricular pacing, during which sensing is suspended in the atrial channel to avoid atrial oversensing of the far-field ventricular pacing artifact. Ap, atrial paced; Vp, ventricular paced.

prolongation of the AV interval beyond the programmed value to avoid violating the upper rate limit for pacing. When one subsequent P wave falls in the postventricular atrial refractory period, it will not be tracked, resulting in pacemaker Wenckebach behavior (Fig. 89–15). When the atrial rate increases further, such that every other P-wave falls in the total atrial refractory period (TARP), a 2:1 pacemaker AV block pattern occurs. The TARP should be programmed shorter than the upper rate interval to prevent sudden development of a 2:1 pacemaker AV block.

In young patients with complete heart block, the upper rate of the pacemaker should be programmed to faster rates corrected for the patient's age to prevent Wenckebach behavior of the pacemaker during exercise. Programming dynamic AV interval and dynamic PVARP allows the TARP to be shorter at higher pacing rates and avoid sudden slowing of ventricular pacing rates. Another option is rate-responsive features, where a separately programmable sensor rate allows the pacemaker to continue to pace at the sensor-driven rate during exercise.

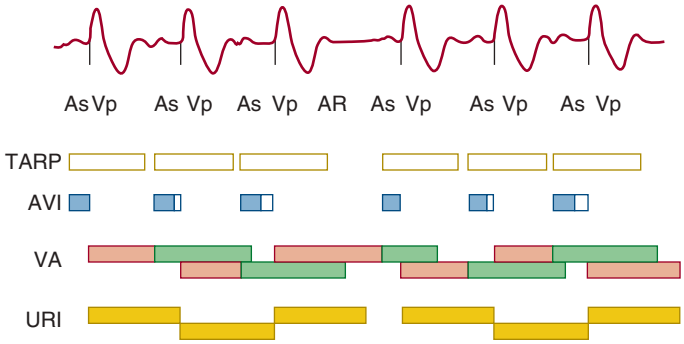


FIGURE 89–15. DDD pacemaker: Wenckebach behavior at upper rate limit. The first beat shows the ventricular-paced (Vp) event synchronized to the atrial-sensed (As) event at the programmed AV interval (AVI). The next atrial event initiates an AVI, but when the AVI times out, the upper rate limit has not been satisfied so the AVI is prolonged. When the upper rate limit is satisfied, ventricular pacing occurs. Because of the delayed ventricular pacing, the next P wave falls even earlier into the next cardiac cycle and the AVI extension is even greater. The next P wave falls within the total atrial refractory period (TARP) and is not sensed. This atrial event (AR) is not followed by ventricular pacing. The following P wave occurs before the VA interval expires, and tracking occurs at the programmed AV delay because the upper rate limit cannot be exceeded. URI, upper rate interval.

MODE SWITCH

When pacemaker patients with AV block (in DDD or VDD mode) develop atrial tachyarrhythmias (atrial tachycardia, flutter, or fibrillation), many atrial events are sensed and ventricular tracking occurs up to the programmed upper rate of the device. The surface ECG typically shows an irregular ventricular paced rhythm at rates close to the upper rate limit of the device. Occasionally in patients with slower atrial flutter, every other atrial electrogram may fall in the PVARP, resulting in a 2:1 AV block. In patients with intact conduction, the ventricular rates are determined by the patient's intrinsic AV conduction.

In patients with persistent atrial tachyarrhythmias, reprogramming the pacemaker to DDI(R) or VVI(R) mode avoids rapid ventricular tracking of the atrial arrhythmias. Automatic mode switching is a programmable option in all current-generation pacemakers for patients with paroxysmal atrial tachyarrhythmias (Fig. 89–16). When the atrial rate exceeds the programmed mode switch rate, the device automatically changes its mode to either the VVI or DDI, in which ventricular tracking of atrial-sensed events do not occur. Current devices can also provide a complete history of mode-switch episodes with regard to the duration and frequency of these episodes and may also provide electrograms to confirm their nature. During follow-up of these devices, it is important to monitor for mode-switch episodes and confirm by reviewing the electrograms that they truly represent atrial tachyarrhythmias. Arrhythmia logs from the device provide a very efficient way of assessing the effects of various drug therapies in patients with atrial fibrillation.

PACING MODES TO REDUCE RIGHT VENTRICULAR PACING

RV pacing leads to asynchronous activation and can cause deterioration of LV function through complex effects on regional ventricular wall strain and loading conditions. Most pacemakers now use a variety of different AV interval algorithms to search for intrinsic conduction and avoid unnecessary ventricular pacing. Electrocardiograms obtained during such pacemaker behavior may cause concern for the interpreting physicians unaware of these pacemaker functions. Unlike traditional mode switch from DDD to VVI or DDI mode during atrial tachyarrhythmias, newer pacemakers can switch pacing mode from AAI(R) to DDD(R) or VVI back-up. Algorithms used by various vendors to minimize RV only pacing include the Medtronic Managed Ventricular Pacing (MVP) mode, Boston Scientific RHYTHMIQ, St. Jude Ventricular Intrinsic Preference (VIP), Biotronik Vp Suppression, and Sorin SafeR.

The general approach to minimize ventricular pacing is to maintain the AAI mode and lengthen the AV interval to allow for intrinsic conduction. Some ventricular beats may be "dropped" during various algorithms, which falsely leads concern for pacemaker malfunction, but actually represents normal pacemaker behavior (Fig. 89–17).

RATE-RESPONSIVE PACING

Rate-responsive pacing refers to the ability of the pacemaker to increase its lower rate in response to physiologic stimuli. Simple VVI and AAI pacemakers do not have the ability to increase their pacing rates in response to exercise. In patients with normal sinus node function and DDD pacemakers, the ventricular pacing rate increases in response to an increase in sinus rate and is physiologic. However, in the presence of sinus node dysfunction, the pacing rate does not increase commensurate with the increase in physiologic need. Rate-responsive pacemakers provide the ability to increase pacing rates through special sensors incorporated in the pacing system that monitor various physiologic processes. Based on information from the sensors, the lower rate of the pacemakers constantly varies up to the upper sensor rate. At any point in time, the sensor rate overrides the programmed lower rate of

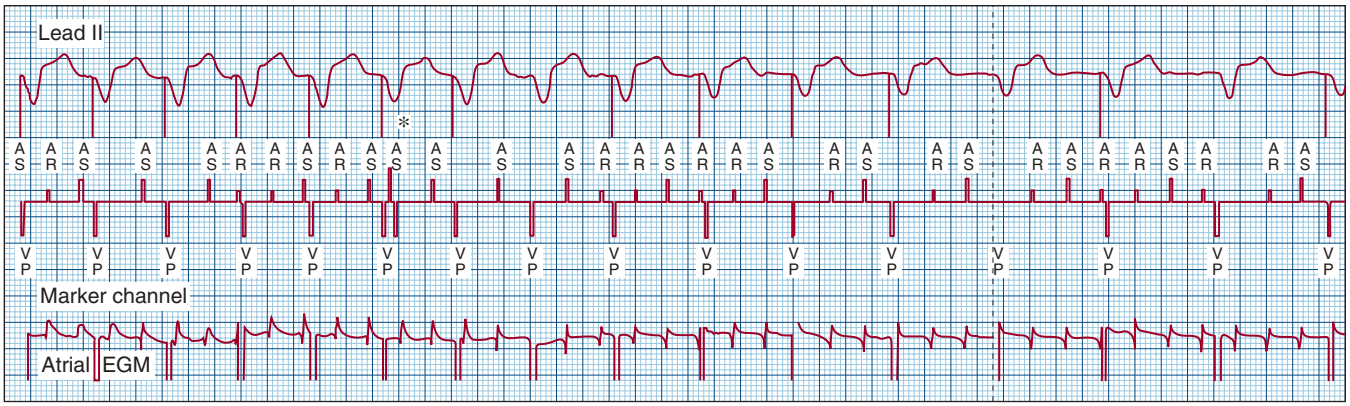
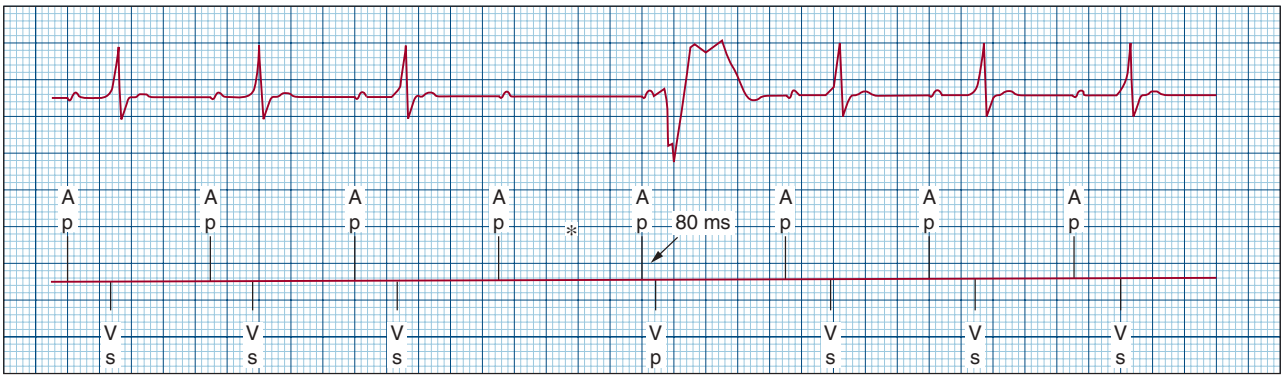


FIGURE 89–16. Mode switch behavior of DDD pacemaker during atrial flutter. Surface lead II, marker channel, and atrial electrograms (EGMs) are shown. In the beginning of the tracing, atrial flutter is sensed and the ventricle is paced at, but does not exceed, the upper rate limit of 110 bpm. Once atrial tachyarrhythmia detection criteria are met, mode switch occurs (*). Pacemaker switches mode to DDI (no atrial tracking) at 70 bpm with rate-smoothing function to avoid an abrupt change in pacing rate.

the pacemaker. Rate-responsive pacing is available in almost all current pacemakers in VVIR, AAIR, DDIR, and DDDR modes. In patients with sinus node dysfunction, rate-responsive pacing in AAIR, DDIR, or DDDR mode is preferable to non–sensor-driven pacing. Also, in patients with chronic atrial fibrillation and heart block, VVIR pacing is preferable to VVI pacing. In patients with severe coronary artery disease, it may be necessary to limit the programmed upper rate limit. The ideal mode for pacing is decided based on information regarding sinus node function, AV nodal function, atrial arrhythmias, heart rate response to exercise, and patient-specific clinical factors.



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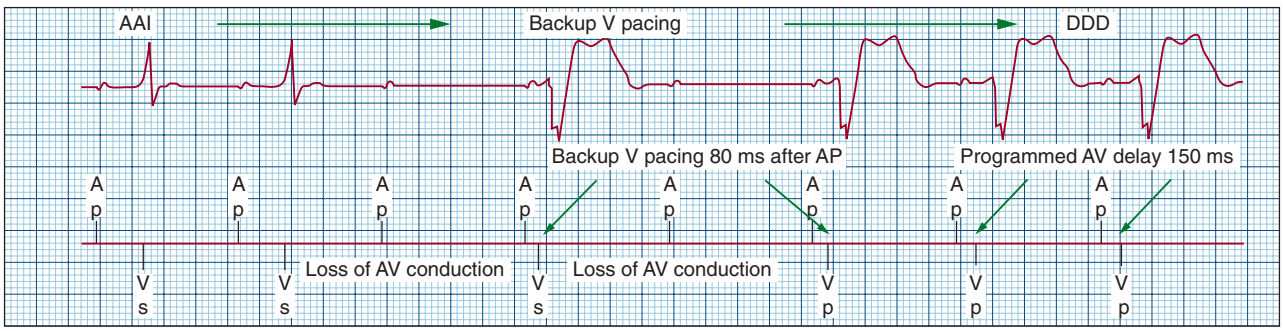

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FIGURE 89–17. Example of algorithm used to minimize right ventricular pacing—managed ventricular pacing (MVP). **A.** Primarily, MVP mode looks like AAI(R) mode, except that it allows for prolonged AV interval. It is an atrial-based pacing (Ap) mode that looks for any consecutive A-A intervals without associated ventricular events. For occasional, single, nonconducted normal atrial contractions, the device provides backup ventricular pacing to ensure ventricular support. The backup ventricular pace (Vp) is scheduled to occur after any A-A interval in which there is no Vp event (*). The Vp occurs 80 ms after the scheduled Ap (if pacing is occurring in the chamber), or after the inhibited atrial pace (ie, 80 ms after the escape A-A interval). **B.** MVP switches from AAI(R) operation to DDD(R) operation when there is evidence of persistent loss of AV conduction. The criterion to switch is loss of AV conduction for two of the last four pacing cycles (the four most recent A-A intervals). The strip illustration shows that immediately after the first A-A interval with no conducted ventricular sensed event (Vs), a backup Vp is delivered 80 ms after the scheduled Ap. Then a second A-A interval occurs with no conducted Vs event. Again, the backup Vp is delivered followed by a permanent switch to DDD(R) operation, wherein the AV delay is the programmed paced (or sensed) AV delay of 150 ms. AV, atrioventricular.

TABLE 89–7. Physiologic Classification of Sensors

Type	Description	Physiologic Parameters
Primary	Physiologic factors that modulate sinus function	Catecholamine level Autonomic nervous system activity
Secondary	Physiologic parameters that are the consequence of exercise	QT[a], respiratory rate[a] Minute ventilation,[a] temperature[a] pH, stroke volume Pre-ejection interval, O_2 saturation Peak endocardial acceleration
Tertiary	External changes that result from exercise	Vibration[a] Acceleration[a]

[a]Available clinically.

Rate-Responsive Sensors

An ideal rate-responsive pacing system should provide rate response appropriate for the metabolic demand during a wide range of activities. The optimal sensor should provide the following:

- Proportionate increase in heart rate to match increase in metabolic demand
- Appropriate rapid change in heart rate with exercise onset
- High sensitivity and specificity
- Appropriate slowing of heart rate after exercise

Sensors available or under development can be classified using a physiologic or technical classification system. In physiologic classification, the sensors are classified according to the physiologic level at which they sense (Table 89–7).

Activity Sensors

Activity-Based Sensors Using piezoelectric crystals or accelerometers to detect vibration are the most widely used sensors. Although the piezoelectric crystal senses vibration associated with up-and-down motion, the accelerometer detects anteroposterior motion of the body. Accelerometer-based sensors provide adequate and quick increases in heart rate during treadmill exercise as compared with piezoelectric crystals. Although both sensors have been shown to provide excellent rate-responsiveness, direct manual pressure, walking down stairs, horseback riding, or riding on a bumpy street can cause an inappropriate increase in heart rate with the piezoelectric crystal-based sensor. These activity-based sensors do not provide adequate heart rate response with emotional stress or isometric exercises. Currently, the accelerometer is the most widely used rate response sensor.

Minute-Ventilation Sensor The specificity and sensitivity of minute-ventilation sensing pacemakers for changes in metabolic workload are excellent. Current pulses are emitted from the pacemaker can, and the proximal ring electrode of the RV lead (or right atrial lead) and transthoracic impedances are measured. Measurement of phasic impedance changes provides respiratory rate and tidal volume information, thus determining the minute ventilation. The minute ventilation changes are used to calculate the pacing rate and have good correlation with exercise. Minute-ventilation sensing pacemakers can inappropriately increase pacing rates with hyperventilation, coughing, and mechanical ventilation and in patients with chronic obstructive pulmonary disease exacerbations.

Dual Sensors Most of the currently available sensors have an excellent track record, but they may occasionally respond to nonphysiologic stimuli. A multisensor rate-responsive pacemaker can improve specificity by having one sensor verify the other sensor (eg, sensor cross-checking). A combination of two sensors can better simulate the normal sinus node response. Pacemakers with dual sensors can provide patients with rapid responses during the start of exercise and then use a more physiologic sensor (minute ventilation) to provide more proportional heart rate responses during steady state (eg, sensor blending).

Contractility Sensors Attempts have been made to gauge cardiac contractility, which from first principles, would provide valuable data regarding physiologic status, including possible response to emotional or psychic stimuli. Closed loop stimulation (CLS) is a proprietary algorithm in which RV contractility is assessed by measuring multiple impedance values during the QRS in order to generate a reference waveform, which is then compared beat-to-beat in order to determine whether pacing rate should be increased. CLS appears to compare favorably to simple accelerometer based rate-adaptive pacing.[123] Another presently available CRT technology utilizes a pressure transducer as part of a specialized atrial lead which is used to detect the amplitude of heart sounds as a proxy LV maximal pressure generation and overall contractility. AV and VV intervals are then automatically adjusted by the device. Early data suggest this method may correlate well with other noninvasive methods of contractility assessment and randomized trial evaluating clinical outcomes are under way.[124]

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR PROGRAMMING

Pacing Programming

Although initial ICDs were not developed with pacing capabilities, modern transvenous devices were combined with pacemaker functionality and there was initial enthusiasm regarding the role of dual-chamber pacing to facilitate optimal medical therapy and improve hemodynamics. The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial was designed to test the hypothesis that DDD rate-adaptive pacing at 70 bpm (DDDR 70) was superior to ventricular back-up pacing at 40 bpm (VVI 40).[125] A total of 506 patients with LVEF ≤ 40% were enrolled who had *no indications for antibradycardia pacing*. Surprisingly, but in line with studies from patients receiving conventional pacemakers, patients with less RV pacing were significantly less likely to die or to be hospitalized for new or worsened HF (61% less; $P \leq .03$). In large part because of DAVID, most patients receiving primary prevention ICDs are programmed to back-up ventricular pacing at low rates to minimize unnecessary RV pacing.[126]

Anti-tachycardia Pacing and Shock Programming

More recently, there has been evolving investigation regarding the possible risks of ICD therapies with respect to delivery of ATP or shocks. The prevalence of "inappropriate" use (ie, device therapy for supraventricular arrhythmia) is common and has been associated with harm in large randomized controlled trials,[127-129] particularly in younger patients.[130] In addition, there is increasing recognition of therapy that, although appropriately directed toward VT or VF, may be avoidable. In addition to optimization of medical therapy or selective application of catheter ablation, device programming to reduce avoidable therapies and mitigate harms has been of growing interest. These were nicely summarized in a recent expert consensus document of the HRS.[131] There are three commonly used programming domains that can be manipulated to determine ICD therapies:

1. Duration and rate criteria for detection
2. Use of single or multizone programming
3. Use of SVT-VT discriminators

Multiple cohort studies[132,133] and three large randomized studies[134-136] support the use of high-rate cutoffs (between 185 and 200 bpm) and tachycardia duration of 30 intervals or at least 6 to 12 seconds before completing detection and initiating therapies for primary prevention patients. For secondary prevention patients, rate cutoff should be tailored to VT thresholds, if known. Discrimination algorithms (ie, SVT-VT discriminators) can also be safely used at rates up to 200 bpm. In general, there has been migration away from early treatment in order to allow for spontaneous termination of VT or VF. This strategy also appears effective for devices programmed for shock-only therapies, such as the S-ICD.

CARDIAC IMPLANTABLE ELECTRONIC DEVICE COMPLICATIONS

Patients undergoing a new CIED system implantation are generally monitored in the hospital for a day in anticipation of any untoward complications. The various complications associated with transvenous CIEDs are outlined in Table 89–8.

PNEUMOTHORAX

At the time of implantation, subclavian or axillary venous access can rarely result in pneumothorax, hemothorax, or hemopneumothorax. This can occur from inadvertent puncture and laceration of the subclavian vein or the subclavian artery or the lung. The use of venograms to locate the venous system in difficult cases and the routine use of axillary venous access have reduced these complications significantly. Occasionally, air embolism may occur during cephalic vein or subclavian vein cannulation. The use of safe sheaths with one-way valve mechanism minimizes this risk.

CARDIAC PERFORATION

Cardiac perforation resulting in pericardial effusion and occasionally cardiac tamponade is a rare but potentially life-threatening complication of pacemaker lead insertion. This may be recognized at the time of lead insertion by fluoroscopic position of the lead, right bundle branch block morphology of the paced QRS complex, diaphragmatic stimulation, or hypotension resulting from cardiac tamponade. If identified at the time of implantation, lead withdrawal and repositioning is usually not associated with tamponade. In patients with chest pain, friction rub, and a small pericardial effusion, serial echocardiograms may be performed to assess for hemodynamic deterioration. Cardiac perforation and pericarditis may also develop as a late complication and occasionally lead to tamponade weeks to months after the pacemaker implantation, especially with active fixation leads.

TABLE 89–8. Pacemaker Complications

Acute	Subacute or Chronic
Pneumothorax	Venous occlusion
Hemothorax	Infection
Air embolism	Pacemaker allergy
Cardiac perforation and tamponade	Twiddler syndrome
Coronary sinus dissection	Pacemaker syndrome
Pocket hematoma	Pacemaker-mediated arrhythmias
Lead dislodgement	Pacemaker-mediated tachycardia
Infection (pocket, sepsis)	Runaway pacemaker
Loose set screws	Lead failure
Diaphragmatic stimulation	Pacemaker malfunction
	Electromagnetic interference

HEMATOMAS

Hematomas occurring at the pacemaker pocket site can vary from a small ecchymosis to large and tense swelling. Most small hematomas can be managed conservatively with cold compresses and withdrawal of antiplatelet or antithrombotic agents. Occasionally, large hematomas that compromise the suture line or skin integrity may have to be surgically evacuated. In patients who require therapeutic anticoagulation, heparin should be delayed for at least 24 to 48 hours after implantation to avoid bleeding complications. A recent large randomized trial has confirmed that the risk of hematomas is lower if the procedure is performed while warfarin is continued at therapeutic levels.[137] There is a relative paucity of data regarding management of direct oral anticoagulants (DOACs) at the time of device implantation. Most operators will interrupt therapy at the time of implant,[138] with discontinuation at least 24 hours before procedure for dabigatran and 36 hours or longer for rivaroxaban.[139] With the recent availability of reversal agents for DOACs, however, practice may change going forward.

VENOUS OCCLUSION

Venous occlusion may result from acute subclavian or axillary vein thrombosis and lead to ipsilateral arm edema and thrombosis. Venous thrombosis is generally treated with heparin and 3 to 6 months of warfarin. Rarely, invasive surgical interventions may be required. Close to one-third of patients undergoing pacemaker implantation may develop partial to complete venous occlusion over time and may remain asymptomatic because of the development of venous collaterals.[140] Upper extremity deep vein thrombosis, when symptomatic, can be managed with anticoagulation in most cases.[141] Superior vena cava syndrome is a rare complication of transvenous devices, and may require device explant and endovascular stenting for definitive treatment.[142]

INFECTION

The use of prophylactic antibiotics and pocket irrigation with antibiotic solutions has decreased the rate of acute infections after pacemaker implantations to < 1% to 2% in most series. Periprocedural antibiotics has been validated in double-blinded clinical trials, and cefazolin is a commonly used agent.[143] Although early infections are generally caused by *Staphylococcus aureus* and may be aggressive, late infections associated with CIEDs may be associated with coagulase-negative staphylococci, and their course tends to be indolent.[144] The signs of infection include local inflammation and abscess formation, erosion of the pacer, and fever with positive blood cultures without an identifiable focus of infection. Occasionally the infected pacemaker tends to erode through the skin. Transesophageal echocardiography helps determine whether vegetations are present on the pacemaker leads. Incisional or superficial infection with no bacteremia or involvement of the CIED can usually be managed with oral antibiotic therapy. With that said, complete system removal if advocated for source control in patients with definite evidence of CIED system involvement (subcutaneous, transvenous, or epicardial) or lead-associated vegetation or valvular

endocarditis without definite involvement of the leads (class I indication).[144] Patients with bacteremia but no localizing evidence of generator-site or clear lead involvement are a challenging group. In patients with relapsing or occult staphylococcal bacteremia, system explant is recommended (class I) and may also be reasonable for gram-negative bacteremia (class IIa).

LEAD DISLODGEMENT

Leads may dislodge from the initial implant site in the first few days to few weeks after implantation. Active and passive fixation mechanisms of leads help prevent this complication. Atrial lead dislodgement is slightly more common than it is for ventricular leads. Although passive fixation leads are stable in the atrial appendage, active fixation leads are necessary to prevent dislodgment in patients with prior cardiac surgery. Lead dislodgment may result in an increase in pacing thresholds, failure to capture, or failure to sense. Lead dislodgment may be radiographically visible or it may be a microdislodgement, where there is no radiographic change in position, but there is significant increase in pacing threshold and/or decline in the electrogram amplitude.

DIAPHRAGMATIC/PHRENIC NERVE STIMULATION

Diaphragmatic/phrenic nerve stimulation may lead to significant discomfort. This phenomenon is most commonly observed in patients with LV coronary vein branch lead placement for biventricular stimulation. During implant, high-output pacing at maximal voltage and pulse width should be tested routinely to avoid diaphragmatic stimulation. With the advent of quadripolar LV leads, multiple pacing vectors are possible and allow the physician to avoid repeat surgery by reprogramming the stimulation vector.

TWIDDLER SYNDROME

First described in 1968,[145] Twiddler syndrome is a term applied to patients who intentionally or unintentionally manipulate their pulse generator, causing twisting of the entire pacemaker system (Fig. 89–18). This leads to lead dislodgment or lead fracture. Elderly age and obesity, along with a capacious pocket, have been identified as risk factors. Submuscular reimplant or use of reinforced tie-downs and use of an antibacterial pouch may be used prevent recurrence.[146]

PACEMAKER SYNDROME

The constellation of neurologic and cardiovascular signs and symptoms resulting from deleterious hemodynamics induced by ventricular pacing has been termed pacemaker syndrome. The basis for pacemaker syndrome is not only loss of AV synchrony but also the presence of ventriculoatrial (VA) conduction. Atrial contraction against closed AV valves leads to increases in jugular and pulmonary venous pressure, causing cough and malaise in patients with intact cardiac function and congestive heart failure in other patients with structural heart disease. The symptoms may vary from mild to severe and the onset of symptoms range from acute to chronic.

The exact incidence of pacemaker syndrome is unknown, but severe manifestations are expected to occur in 5% to 7% of ventricularly paced patients. Milder symptoms or significant drops in systolic blood pressure and cardiac output during ventricular pacing occur in > 20% of patients. In the Pacemaker Selection in the Elderly (PASE) trial, 26% of patients in the ventricular pacing arm crossed over to the DDD pacing mode because of symptoms caused by pacemaker syndrome.[21] The management of pacemaker syndrome usually requires restoration of AV synchrony. In many patients, an upgrade to a dual-chamber pacer is indicated. In some patients with intact sinus and AV conduction, lowering the pacing rate in VVI mode and using the hysteresis mode may promote sinus rhythm, lessening the symptoms associated with pacemaker syndrome.

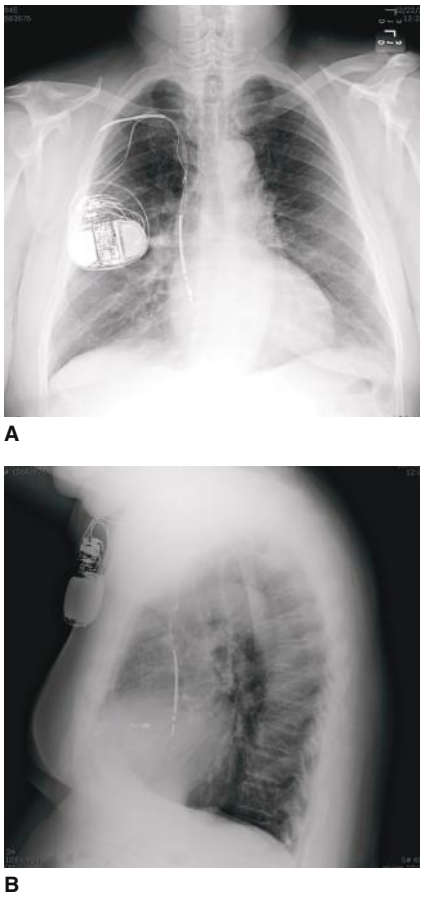

FIGURE 89–18. Twiddler syndrome in patient with CRT-D device. On posteroanterior (**A**) view, the RV and LV leads have been retracted to SVC. On lateral (**B**) view, the atrial lead is still seen in RA appendage.

PACEMAKER-MEDIATED ARRHYTHMIAS

Pacemaker-mediated tachycardia (PMT), or endless-loop tachycardia, is a well-recognized arrhythmia mediated by the pacemaker in patients with atrial-sensed ventricular pacing systems. In patients with intact VA conduction, a premature ventricular contraction may result in retrograde conduction to the atria, which, if outside the PVARP, is sensed and followed by ventricular pacing after the programmed AV interval. The paced ventricular event will again be followed by VA conduction, resulting in endless-loop tachycardia. PMT can be prevented by programming the PVARP to be longer than the native VA conduction time. However, if the VA interval is very long, the PVARP cannot be lengthened, as this will limit the upper rate. Modern pacemakers have several options to prevent or terminate PMT. One such feature is automatic extension of PVARP after a sensed premature ventricular beat to prevent tracking of retrogradely conducted P waves. If PMT is established (atrial-sensed ventricular pacing close to the upper rate limit with stable VA intervals), the PVARP is automatically extended to a longer interval of 500 milliseconds for one cycle, usually terminating the tachycardia (Fig. 89–19).

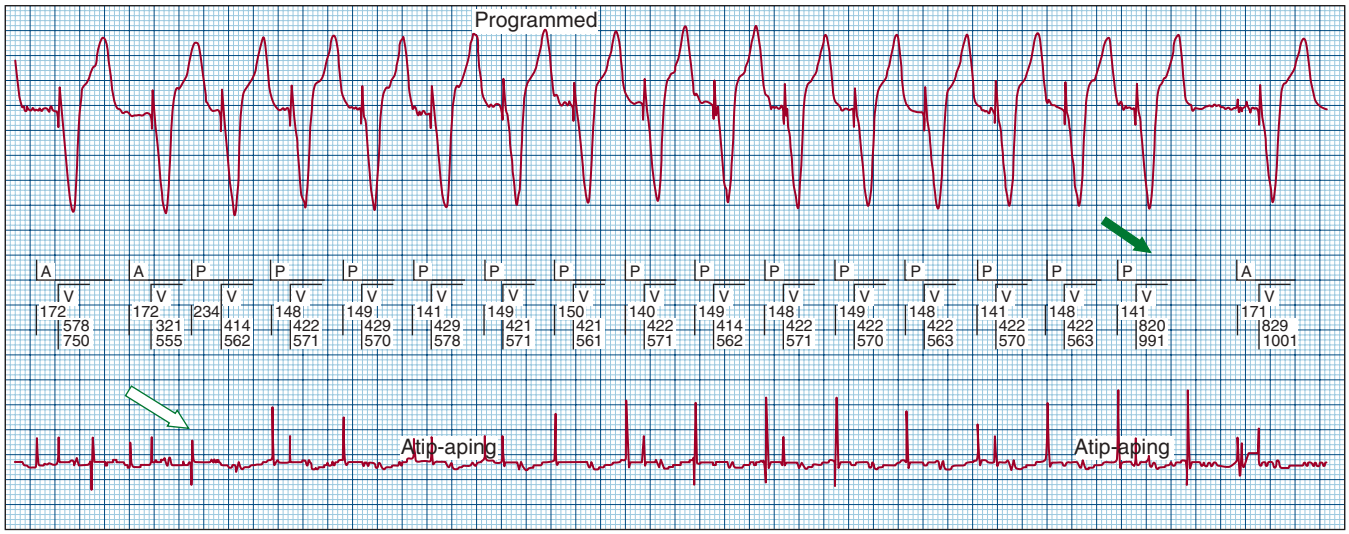

FIGURE 89–19. Pacemaker-mediated tachycardia. Surface electrocardiogram; marker channel with AV, VA, and VV intervals; and intracardiac atrial electrograms are displayed. The atrium is paced (**A**) at subthreshold output, leading to noncapture after the second ventricular paced beat, resulting in atrioventricular dissociation. The second-paced ventricular event is followed by a native P wave with a VA interval of 320 ms (PVARP 275 ms) and is sensed, leading to ventricular pacing. This is followed by a retrogradely conducted P wave (*open arrow*), with a VA interval of 420 ms, and sets up the endless-loop tachycardia. Because the ventricular pacing rate is above the programmed pacemaker-mediated tachycardia rate of 100 bpm, the device automatically extends the PVARP on the second-to-last ventricular paced beat to 500 ms (*arrow*), resulting in nonsensing of the retrograde P wave, terminating the tachycardia. PVARP, postventricular atrial refractory period.

LEAD FAILURE

Transvenous leads are subject to long-term complications. The insulation of the leads may break, leading to problems with oversensing (caused by electrical noise), undersensing, and failure to capture (caused by current leak). This problem often manifests intermittently and may be difficult to detect during a routine pacer check. The patient may complain of pectoral muscle stimulation caused by current leakage around an insulation break. An abnormally low impedance with demonstrable lead malfunction is diagnostic for insulation break. Leads may also fracture over time. Early lead fractures lead to increased impedances associated with failure to capture, oversensing, and undersensing. Lead damage can occur at the site of venous access (subclavian vein) in the costoclavicular space, causing the crush syndrome.

TROUBLESHOOTING AND SYSTEM MALFUNCTION

CIED system malfunction can be secondary to circuitry failure or to lead dysfunction. Not uncommonly, what appears to be device malfunction may actually represent normal functioning of the pacemaker: A pacing artifact may be delivered in the middle of the normal QRS and may represent pseudofusion (caused by late sensing) and not undersensing. Unexplained longer pauses after sensed, but not paced, complexes might suggest oversensing, but it may represent normal function caused by hysteresis. Major electrocardiographic abnormalities of pacemaker system malfunction are broadly categorized into the following: failure to capture, failure to output, undersensing, and oversensing.

FAILURE TO CAPTURE

The loss of pacemaker capture occurs when there is a visible pacing stimulus and no atrial or ventricular depolarization. The differential diagnosis of failure to capture is outlined in Table 89–9. Failure to capture may be intermittent or persistent. Lead dislodgment can cause obvious failure to capture. An increase in the pacing threshold above the programmed pacing output can occur as a result of the rise of the threshold within a few weeks after lead placement because of drug therapy, electrolytes, MI, or ischemia. Fracture of the lead, insulation breaks, and loose set screws are mechanical problems that can cause failure to capture (Fig. 89–20). Finally, battery depletion may cause the pacing output to decline sufficiently such that pacing failure occurs. Loss of capture requires a check of the pacing threshold and of pacing lead impedance and a chest radiograph. For instance, if the problem is an elevated pacing threshold, pacing outputs must be increased. Abnormal lead impedances may confirm a lead failure and the need for lead replacement. Functional noncapture occurs when a stimulus falls during the physiologic refractory period of a native depolarization. It may be secondary to undersensing or as a function of the pacing mode (AOO, VOO).

FAILURE TO OUTPUT

Another pacing system malfunction is the absence of pacing stimuli and hence no capture. In bipolar systems the pacing artifact is diminutive, especially if isoelectric in some surface leads. It is important to record multiple leads simultaneously. Failure to output is often

TABLE 89–9. Differential Diagnosis of Failure to Capture

Etiology	Pacing Threshold	Impedance
Lead dislodgement	Elevated	Normal
Lead insulator failure	Elevated	Decreased
Lead conductor fracture	Elevated	Increased
Loose set screw	Elevated	Increased
Battery depletion	Normal	Normal
Functional noncapture	Normal	Normal

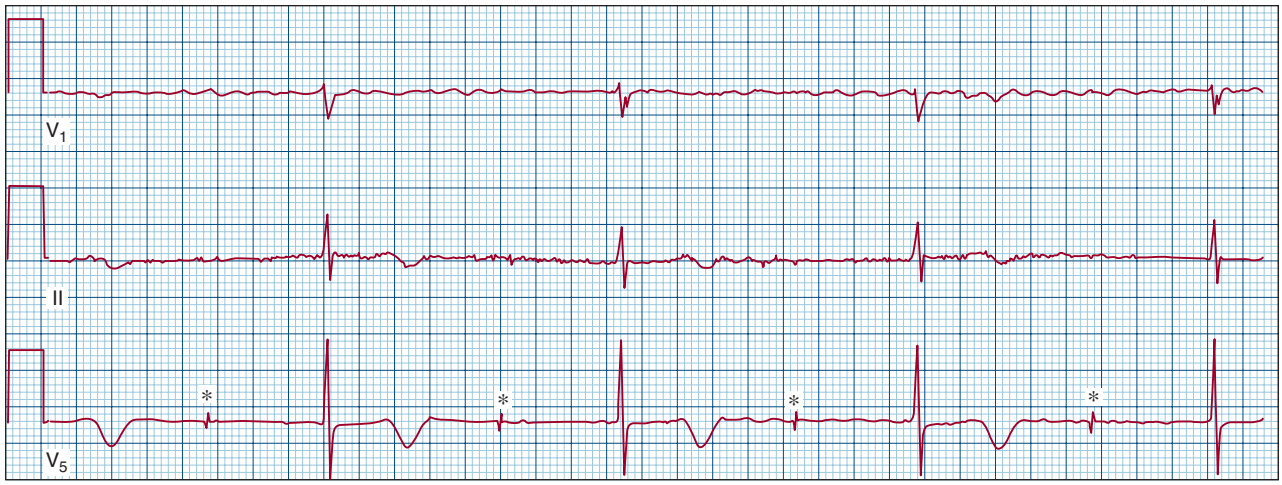

FIGURE 89–20. Failure to capture. Surface electrocardiogram of a patient with VVI pacemaker at a lower-rate limit of 60 ppm is shown at the bottom. The pacemaker spikes (*) are not followed by ventricular depolarization (no capture). Patient has spontaneous ventricular activity at 35 bpm. The device clearly senses the ventricular event because the pacemaker spike appears 1000 ms (60 ppm) after the sensed event. On interrogation of the device, His lead impedance was significantly lower (300 Ω) than the implant values, and the pacing threshold had increased significantly. These findings are consistent with lead failure secondary to insulation break. Chest radiograph revealed evidence of insulation break at the subclavian venous access site. VVI, ventricular demand pacing.

caused by oversensing and inhibition of pacing output and is less commonly caused by circuitry failure (Table 89–10). Oversensing may be caused by T waves, P waves, or far-field R waves and may cause inhibition of pacing output. In unipolar systems, oversensing of myopotentials is common. A loose set screw may cause noise and oversensing, leading to inhibition of pacing output. Electromagnetic signals from arc welding and electrocautery may be sensed by the pacemaker. Occasionally, the ventricular channel may be inhibited by oversensing the atrial channel output (cross-talk). If the absence of pacing output is caused by oversensing, a magnet application changes the pacemaker to an asynchronous mode to eliminate the pauses. In generator component malfunction, there is no delivery of pacing output by the device and magnet application does not restore pacing output. Systematic analysis of the pacing parameters, evaluation of lead impedances at rest, and provocative isometric exercises and chest radiograph may help identify the cause.

TABLE 89–10. Differential Diagnosis of Failure to Output

Etiology	Diagnosis/Management
Oversensing	Application of magnet eliminates pauses
T wave, P wave, R wave	Reduce sensitivity
Myopotential/diaphragmatic	
Electromagnetic interference	
Cross-talk	
Make-break potential	Change unipolar to bipolar sensing
Insulation failure	Pauses persist despite magnet application
	Impedance low; replace lead
Open circuit	Pauses persist despite magnet application
Conductor fracture	Impedance high
Loose set screw	Chest x-ray may show conductor deformity
	Loosely seated lead pin
Component malfunction	Pauses persist despite magnet application
	Replace pulse generator
Pseudo-normal function	Pauses follow only sensed beats
Hysteresis	Reassurance
Mode switching	
Pacemaker-mediated tachycardia intervention	

OVERSENSING

In a single-chamber pacemaker or defibrillator, oversensing leads to inhibition of the pacing channel and causes inappropriate pauses. However, in dual-chamber devices, oversensing elicits either inappropriate inhibition or triggering, depending on the channel in which oversensing occurs and the programmed pacing mode. Oversensing in the ventricular channel in the DDD or DDI mode results in inhibition of both atrial and ventricular outputs and resetting of timing cycles. In patients with complete heart block, this may result in ventricular asystole (Fig. 89–21). Oversensing in the atrial channel can lead to inappropriate triggering of ventricular output. The various etiologies of oversensing were discussed in the previous section. One example of oversensing peculiar to dual-chamber pacemakers is cross-talk. The atrial channel output can be sensed in the ventricular channel as a far-field signal and inhibits the ventricular pacing output. In patients with complete heart block, this can result in ventricular asystole. Although far more common with unipolar systems, cross-talk can also occur in bipolar pacing systems. To prevent this phenomenon, there is a programmable ventricular blanking period (51-150 milliseconds) after atrial pacing, during which the ventricular channel is refractory. Additionally, there is a cross-talk–sensing window after the blanking period, during which a ventricular event, if sensed, will lead to ventricular pacing with a shorter AV interval. Oversensing as a result of lead fracture, insulation break, or other electrode problems will usually be random and erratic. With early lead problems, the malfunction is typically intermittent and may be exacerbated by certain body positions or motions. In later stages, the combination of oversensing, undersensing, and failure to capture is almost always diagnostic of a lead-related problem. Programming to an asynchronous mode may temporarily control this problem while awaiting lead replacement, which should be carried out as promptly as possible.

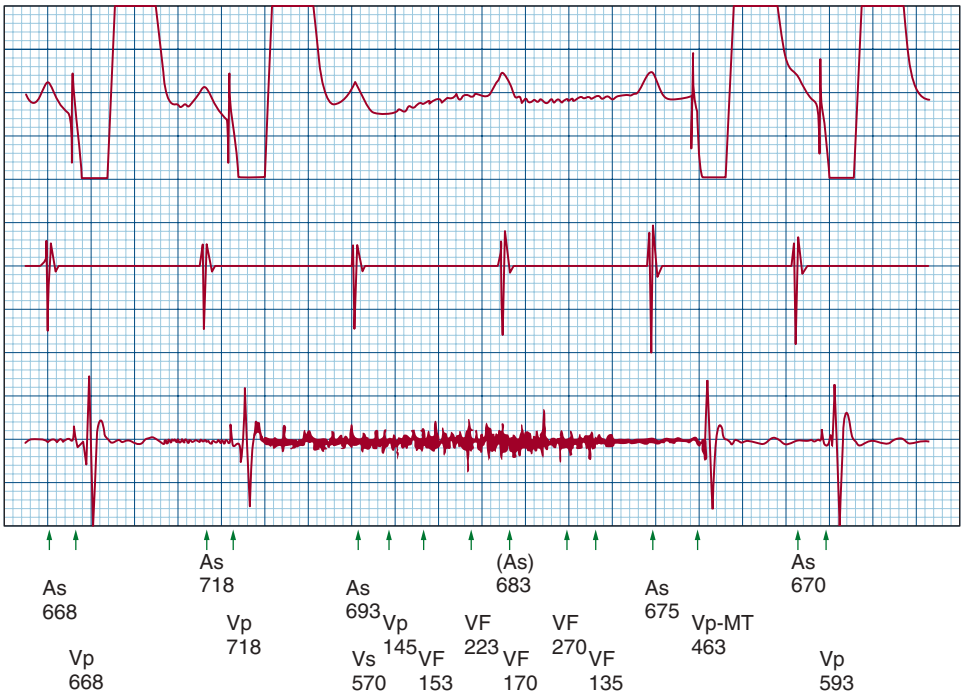

FIGURE 89–21. Oversensing of diaphragmatic myopotentials. Surface electrocardiogram and atrial and ventricular electrograms with event markers are shown. In this patient with a dual-chamber defibrillator, deep respiration reproduced the diaphragmatic myopotentials, resulting in inhibition of ventricular output. The patient developed dizzy spells caused by underlying complete heart block and inhibition of pacing because of oversensing. The ventricular lead was repositioned in the RV outflow tract eliminating the diaphragmatic oversensing. As, atrial sensed; VF, ventricular fibrillation; Vp, ventricular paced; Vs, ventricular sensed.

UNDERSENSING

An inadequate intracardiac signal can lead to undersensing. The intracardiac electrograms can deteriorate because of inflammation or scar formation at the tissue lead interface. Additionally, some drugs, electrolyte abnormalities, infarction, ischemia, lead fracture, or insulation breaks can all lead to undersensing. Cardioversion or defibrillation can also cause attenuation of intracardiac electrograms. Usually, undersensing is a greater problem in the atrium than the ventricle. The atrial electrograms are typically significantly lower in amplitude during atrial fibrillation than they are during sinus rhythm. The optimal solution is to program an enhanced sensitivity (decreased sensing level, eg, from 1.5 to 0.55 mV). With bipolar systems, the programmed sensitivity can usually be reduced to as low as 0.18 mV in the atrium in some devices, without oversensing of myopotentials or other extraneous signals. Other etiologies for undersensing occur when intrinsic atrial or ventricular complexes fall within one of the programmed refractory periods. Undersensing can also result when a pacemaker is inadvertently programmed to an asynchronous mode (occasionally occurring with battery depletion or pacemaker generator reset).

ELECTROMAGNETIC INTERFERENCE

Electromagnetic interference (EMI) is defined as any nonphysiologic electrical signal that interferes with pacemaker function. EMI can originate from a variety of sources both within the hospital environment and outside. EMI can result in the inhibition of the pacemaker, inappropriate triggering, noise reversion, resetting of the pacemaker parameters, and occasionally damage to the circuitry or electrode-myocardial interface; unipolar pacemakers are more susceptible to EMI than bipolar pacemakers. EMI has become an increasingly important problem because sources of interference are ubiquitous in the hospital and workplace.

In the hospital environment, the most common sources of EMI include electrocautery and defibrillation. Electrocautery can cause inhibition of the pacemaker, and in a pacemaker-dependent patient, this may result in severe bradycardia or asystole. Specific perioperative management of a device includes the following[147]:

- Identify the type of the device and its manufacturer; identifying the manufacturer is essential.
- Identify whether the patient is dependent on the device for antibradycardia pacing; this may be obtained from the history of syncope, complete heart block, or AV node ablation requiring pacemaker placement. Interrogating the device may help identify whether the patient has a stable underlying escape rhythm.
- Determine whether EMI is likely to occur during the procedure. The device should be reprogrammed to asynchronous mode (VOO or DOO) or triggered mode (VVT), especially if the patient is dependent. Rate-adaptive pacing function should be turned off. Antitachyarrhythmia functions should be suspended (if an ICD). The surgeon should be advised to use a bipolar electrocautery (if possible) to minimize EMI.
- Place a magnet over the pacemaker to convert this device to function in an asynchronous mode (VVI to VOO or DDD to DOO) for as long as the magnet remains over the device. Removing the magnet returns the device to its original mode. In patients with ICDs, placing a magnet disables its antitachycardia therapies. However, this will not alter its pacemaker function. Magnets should be used when reprogramming options are not immediately available. All operating room personnel, including the surgeon, anesthesiologist, and nursing staff, must be aware of the presence of the device, the potential for electromagnetic interference encountered in the operating room, and corrective techniques. An external defibrillator with transcutaneous pacing capabilities should be readily available.

- Intraoperatively, electrocardiographically monitor all patients to assess for device inhibition and with peripheral pulse evaluation (plethysmography or arterial pressure, etc.) in case of electrocautery-induced artifact on telemetry. Individuals performing the procedure should be advised to avoid electrocautery in the immediate field of the device generator and leads. Electrocautery should be used in short, intermittent, and irregular bursts.
- If the patient requires electrical cardioversion, deliver the shock as far as possible from the pulse generator and place the defibrillation pads on an axis perpendicular to that of the leads and pulse generator (to avoid transient undersensing or pacing inhibition).
- Interrogate devices after the procedure to assess for threshold changes and to reprogram the device to its original function if necessary.

Other potential sources of EMI in the hospital include extracorporeal lithotripsy, radiation therapy, and MRI. Traditionally, MRI has been avoided in patients with pacemakers because of concerns for rapid pacing triggered by the pulsing of the magnetic field, device reprogramming, reed switch closure, heating at the myocardial-lead interface, or mechanical movement of the device. MRI "safe" (or conditional) pacemakers, ICDs, and now CRT devices are available, however. In addition, there is growing robust evidence regarding the use of protocols to image patients with CIEDs that are not conditionally approved (although abandoned leads are an absolute contraindication).[148,149] Approaches to minimize the risk of MRI to patients consist of programming the device to asynchronous mode, reducing the pacemaker output, limiting the MRI to areas remote from the device, and monitoring blood pressure and ECG during the MRI scanning.

Lithotripsy can also result in inappropriate inhibition or oversensing, especially in rate-responsive pacemakers with piezoelectric crystals. The pacemaker should generally be programmed to VVI or VOO mode with the rate-responsive feature turned off before lithotripsy. Radiation therapy should be avoided directly over the field of the pacemaker. If shielding the pacemaker and limiting the field of radiation cannot be performed with safety, repositioning of the pacemaker before radiotherapy should be considered. Other possible EMI sources in the hospital include therapeutic diathermy, radiofrequency catheter ablation, transcutaneous electric nerve stimulation (TENS) units, and spinal cord stimulators.

Daily sources of EMI include digital cellular phones, electronic article surveillance devices, metal detectors, and electric razors, and work or industrial environment sources include high-voltage power lines, transformers, welding, and electric motors. Activated digital cell phones should not be placed in the breast pocket ipsilateral to the pacemaker, and the phone should be held to the ear contralateral to the pacemaker. Electronic surveillance devices or antitheft devices present in most stores and libraries can cause transient asynchronous pacing, atrial oversensing with tracking, and ventricular oversensing and inhibition. Patients with pacemakers should quickly walk through these devices and avoid lingering near them. Common household appliances such as electric can openers, stereos, televisions, video recorders, power tools, electric blankets, electric shavers, microwave ovens, and electric lawnmowers do not cause any pacemaker interference.

DEVICE RECALLS, ADVISORIES, AND ALERTS

As the number of implantable cardiac devices has increased, device alerts and advisories have become a part of routine clinical practice. Recent lead recalls that have captured national and international attention has been the Medtronic Sprint Fidelis lead and the St. Jude Riata lead, both with implications regarding device efficacy and thus prompting discussion regarding extraction. When a physician is faced with the management of a patient with an implanted device that has been the subject of a recall or advisory, the major concern facing the clinician is how to manage the patient and whether the device must be replaced. Compared with other medical devices, these devices are unique because they are often implanted for life-threatening problems for which device failure may be causally linked to death or poor outcome. A review by Maisel and colleagues of device manufacturer performance reports issued between 1990 and 2002 found that > 17,000 devices were explanted during this timeframe for confirmed malfunction.[150] The explanted devices were evenly split among pacemakers and ICDs, but when comparing the number of implants in each category, ICDs appeared to be four times more likely to malfunction and require explantation. A meta-analysis of device registries found that pacemaker reliability has improved markedly and consistently over the past 20 years.[151]

There are a wide variety of malfunctions that have been reported with pacemakers and ICDs. These include both hardware component malfunction and software problems. In general, hardware malfunction tends to be far more common than software malfunction and is also more problematic for physicians and patients. Among hardware problems, battery/capacitor and electrical issues account for more than half of the reported malfunctions. Gould and Krahn reported the results from a multicenter Canadian study of the consequences of various ICD advisories.[152] From approximately 18% (533 of 2915 patients) of devices electively replaced because of advisories, complications were observed in 8.1% of cases within 2.7 months after ICD generator replacement (5.8% were major complications requiring reoperation, including two deaths). In contrast, there were only three (0.1%) device malfunctions from the devices that were included in advisories but no clinical complications from these malfunctions. In some centers, very low rates of complications have been observed, emphasizing the importance of individualizing patient management and knowing an individual center's risk of complications.[153]

The HRS has proposed a series of recommendations for physicians and industry.[154] Device manufacturers and the FDA notify physicians and patients after determining a device problem by an advisory; however, decisions about management are left to physicians. All patients with devices affected by recall, advisories, or alerts should be seen in the office for immediate device interrogation and discussion of the implications of the notification to the patient and their immediate and long-term device management and clinical status. The patient's indication for device implantation and relative device dependence should be discussed, and well as potential consequences of device failure. The decision regarding which patients affected by the advisory/recall should undergo device replacement may be difficult for both the patient and the physician. Pacemaker dependence, ICDs implanted for secondary prevention, and high likelihood of device failure are some of the factors that lead to consideration for device replacement. Alternatively, patients may be scheduled for more frequent in-clinic follow-up or by transtelephonic or computer-based remote monitoring based on a careful review of the company, FDA, and any outside physician panel recommendations. Patients should be instructed to present to the device clinic or use remote follow-up whenever any symptoms (eg, syncope, presyncope, palpitations, angina, etc.) or other symptoms that suggest possible device malfunction are experienced. Device self-monitoring capabilities and the ability to do intensive remote follow-up allow for more reliable device follow-up in the future. Remote automatic checks with wireless or Internet-based physician notification schemes may improve monitoring of device performance, but currently office interrogations remain the most commonly used modality for follow-up. Diagnostic tools are also being developed to help detect potential hardware problems that could lead to malfunction.[155]

LEAD EXTRACTION

Particularly as use of CIEDs has risen, the need for device and lead removal, because of infection, lead fracture, or recall has become an area of investigation for which specialized tools and methods have been developed. In particular, the field of transvenous lead extraction (TLE) has evolved beyond methods of simple extraction, to include the development of tools such as specialized locking stylets, snares, and mechanical, rotating threaded tip, electrosurgical, telescoping, and laser excimer sheaths.[156] In 2009, the HRS released an expert consensus statement on facilities, training, indications, and patient management for TLE.[157] The statement comments on the importance of having a multidisciplinary team in order to care for patients, including a primary operator properly trained in lead extraction, an immediately available cardiothoracic surgeon for backup during cases, anesthesia support, "scrubbed" and "nonscrubbed" assisting personnel (eg, nurses, technicians, as well as other physicians), and trained echocardiography support. When performed at high-volume centers, lead extraction can be associated with high acute procedural success, include complete lead removal 96.5% of the time, and have a 97.7% overall clinical success rate.[158] Overall in-hospital mortality approaches 2%, however, and risk factors for major adverse events include length of time leads have been implanted (particularly > 10 years), type of lead (with dual-coil defibrillator leads associated with higher risk), lower body mass index, presence of chronic kidney disease or diabetes, LVEF, and extraction for infection, among others.[158,159] Taken together, the decision on whether or not to pursue extraction should be made after careful assessment of risks and benefits in conjunction with the patient and family members.

FUTURE DIRECTIONS

The indications for CIED use in the care of the cardiovascular patient are rapidly expanding. In addition to the treatment of bradyarrhythmia and tachyarrhythmia (pacemakers and ICDs), devices are being employed in the treatment of symptomatic heart failure to reduce hospitalization (CRT devices). Furthermore, complementary to their role in therapy, devices also provide diagnostic data through evaluation of real-time heart rate, patient activity, and arrhythmia burden. Indeed, device-based diagnostics have already been correlated with HF hospitalization and mortality.[160,161] In concert with wider networks of patient management such as telemonitoring and remote patient care, the future use of CIEDs will be invaluable in providing additional insight into patients' dynamic disease state, and as a means to help tailor and direct real-time care. There is also growing interest in providing device-based data stored online to patients to help facilitate greater engagement in health care as well as improve the patient-physician interaction. These areas of active investigation are expanding the fundamental paradigms of these tools, from devices that go well beyond arrhythmia or HF care, to overall cardiovascular disease management and patient-centered fitness.

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CHAPTER 90

DIAGNOSIS AND MANAGEMENT OF SYNCOPE

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INTRODUCTION

Syncope is a sudden loss of consciousness and postural tone caused by transient decreased cerebral blood flow; it is associated with spontaneous recovery. The occurrence of syncope in the general population, as reflected in the Framingham Study, is 3.0% in men and 3.5% in women.[1] As a general rule, the incidence of syncope increases with age. In the United States, 1 to 2 million patients are evaluated for syncope annually; 3% to 5% of emergency department visits and 1% to 6% of urgent hospital admissions are for syncope.[2-5] As a result, management of syncope is associated with significant resource use and expense.[6-8]

Syncope can occur suddenly, without warning, or may be preceded by a prodrome of presyncope, including lightheadedness, dizziness but not true vertigo, nausea, a feeling of warmth, diaphoresis, and blurred or tunnel vision. Self-limited episodes of presyncope can occur in the absence of loss of consciousness.

CAUSES OF SYNCOPE

The causes of syncope include *cardiovascular disorders, disorders of vascular tone or blood volume,* and *cerebrovascular disorders.* The relative incidence of these categories varies with the clinical site from which the patients are selected; in hospitalized patients, syncope is most often a result of a cardiovascular disorder, whereas in the emergency room, other causes of syncope predominate.[4] In many cases, the cause of syncope may be multifactorial. Furthermore, in up to 50% of cases, the cause of syncope cannot be determined with certainty even after a rigorous evaluation.

Recent studies document the widely divergent mortality risks associated with an episode of syncope, ranging from those that are benign to cardiac arrhythmias that are potentially lethal.[9] Syncope caused by cardiovascular disorders is associated with the highest risk for mortality, approaching 50% over 5 years and 30% in the first year after diagnosis.[4] Furthermore, among patients with certain cardiac diseases, including hypertrophic cardiomyopathy, the long QT syndrome, and others, those with syncope are at greater risk for mortality.[10] The mortality rate is lower among patients with syncope from other causes (30% over 5 years and < 10% in the first year) but still substantial. Syncope that is not associated with cardiac disease and is of undetermined cause is usually associated with the lowest mortality risk (6%-10% over 3 years and 24% over 5 years).[2,4,7] Syncope can impact quality of life for patients and their families, particularly when it occurs abruptly without warning and is recurrent or when it is likely to occur in relationship to certain activities. In such cases, patients may need to adjust their lifestyle or change occupation.

For prognostic and therapeutic reasons, it is important to distinguish syncope from other causes of trsnsient loss of consciousness, including seizures, psychogenic seizures, hypoglycemia, pharmacologic agents, and trauma. In some cases, this may prove difficult because reduced cerebral blood flow associated with syncope can cause tonic-clonic movements similar to those that occur with certain seizures. In one study, syncope had been misdiagnosed as seizures in 38% of patients who continued to have episodes despite adequate anticonvulsant therapy.[11]

CARDIOVASCULAR DISORDERS

Syncope can occur from either severe obstruction of cardiac output or disturbances of cardiac rhythm.[4,12-24] Obstructive lesions and arrhythmias frequently coexist; indeed, one abnormality may accentuate the effects of the other. Table 90–1 lists the cardiovascular disorders that may be associated with syncope.

Syncope Related to Obstruction of Cardiac Output

Obstruction to cardiac output in the left or right side of the heart may cause syncope. The relationship of syncope to exertion may provide clues to the etiology. Loss of consciousness during or immediately after exertion can occur with any of the cardiac causes of syncope but is particularly common and may be the presenting symptom in patients with certain obstructive lesions, including aortic stenosis and hypertrophic cardiomyopathy. Studies suggest that in such patients, failure of cardiac output to increase adequately during exercise together with a reflex decrease in peripheral vascular resistance may play a role.[25] Nonexertional syncope related to acute decreases in preload or afterload or to inotropic stimulation may also occur in either aortic stenosis or hypertrophic cardiomyopathy (see Chaps. 47 and 59). Transient arrhythmias can also induce syncope in patients with obstructive lesions. Syncope is an ominous sign in patients with hypertrophic cardiomyopathy, portending a significant risk for sudden cardiac death.[10,25-27] Syncope in patients with aortic stenosis suggests that the obstruction is severe.

Malfunction of a left-sided prosthetic heart valve can produce transient and profound obstruction to blood flow resulting in syncope (see Chap. 52). Mitral stenosis can produce cardiac syncope but usually does so only when tachycardia or other arrhythmias occur (see Chap. 50). A left atrial myxoma may cause syncope by obstructing left ventricular filling. In some cases, the obstruction of left ventricular inflow is posturally induced.

Obstruction in the pulmonary vasculature as a result of pulmonary artery hypertension, pulmonary stenosis, or pulmonary embolism can cause syncope. Pulmonary embolism as a cause of syncope should be suspected in paraplegic patients and in those who have been at prolonged bedrest.[28,29] In tetralogy of Fallot, because the right ventricular

TABLE 90–1. Cardiac Disorders Associated with Syncope

Obstructive
Aortic stenosis
Hypertrophic cardiomyopathy
Mitral stenosis
Prosthetic mitral or aortic valve malfunction
Atrial myxoma
Pulmonary embolism
Pulmonary hypertension
Tetralogy of Fallot
Cardiac tamponade
Arrhythmic
Sinoatrial disease
Atrioventricular block
Supraventricular tachyarrhythmias
Ventricular tachycardia
Pacemaker disorders

outflow obstruction is often fixed, the magnitude of flow through the right-to-left shunt increases when systemic resistance falls during exertion. This shunting can result in marked arterial hypoxia, which may precipitate syncope. Cardiac tamponade, which affects both the right and the left sides of the heart, rarely causes syncope. The likelihood of syncope is increased by concomitant arrhythmias.

Syncope Related to Cardiac Arrhythmia

Arrhythmias are a common cause of syncope and must be considered in any patient, particularly when cardiac disease is present. Either extreme of ventricular rate (bradycardia or tachycardia) can depress cardiac output to the point of critical hypotension with cerebral hypoperfusion and syncope. The arrhythmias that produce syncope most often are caused by sinoatrial disease (bradycardia, exit block, or pauses), high-grade atrioventricular (AV) block, and ventricular tachycardia. Although arrhythmias are usually secondary to disorders such as ischemic heart disease, cardiomyopathy, valvular heart disease, and primary conduction system disease, they can on occasion occur in the absence of apparent heart disease.

Primary degenerative disease of the sinus node and the specialized conduction tissue is the most common cause of sinoatrial disease (*sick sinus syndrome;* see Chap. 86). The sick sinus syndrome may be manifested by persistent or episodic sinus bradycardia or sinoatrial exit block, often with impaired junctional escape rhythm. The presence of alternating sinus bradycardia or sinoatrial block with atrial tachyarrhythmias is referred to as the *bradycardia-tachycardia syndrome*. Syncope often occurs with asystole or bradycardia at the termination of tachycardia because of overdrive suppression of the sinoatrial and junctional pacemakers.[30] AV and intraventricular conduction defects are more prevalent in the sick sinus syndrome and, along with ventricular tachyarrhythmias, may be responsible for syncope in these patients.[21]

High-grade AV block may be a result of disease of either the AV node or the His-Purkinje system. Conduction block in the AV node is usually associated with a junctional pacemaker, a normal QRS complex, and a heart rate that can sustain blood pressure adequate to maintain consciousness, whereas AV block as a result of His-Purkinje system disease is usually associated with a wide-complex idioventricular escape rhythm that may be too slow to maintain adequate blood pressure. Bifascicular block in the presence of a prolonged PR interval suggests that His-Purkinje system disease is present and is associated with a substantial risk of developing high-grade AV block and syncope. Progression to high-grade AV block in patients with bifascicular block and a normal PR interval is less common.

Sinus bradycardia, AV block, or cardiac asystole may be mediated by reflex vagal mechanisms and have been observed in a variety of disease states or during diagnostic procedures. Transient sinus bradycardia or AV block also can occur in apparently healthy young individuals, certain of whom may have mitral valve prolapse.[22]

Supraventricular tachyarrhythmias rarely cause syncope unless they occur in the presence of other abnormalities that decrease cerebral perfusion (decreased cardiac output because of structural heart disease, a neurocardiogenic reaction, disorders of vascular control, or reduced blood volume). As is the case for other causes of syncope, a neurocardiogenic reaction may be precipitated by the hemodynamic effects of arrhythmias.[31] In such cases, syncope may be related to vasomotor factors and not be solely a result of heart rate.[30,31] Syncope can occur in patients with Wolff-Parkinson-White (WPW) syndrome who experience atrial fibrillation and a very rapid ventricular rate as a consequence of conduction across an accessory atrioventricular connection.

Ventricular tachycardia is the most common arrhythmic cause of syncope and often occurs in the setting of structural heart disease. In the United States, ventricular tachycardia is usually associated with previous myocardial infarction and depressed left ventricular ejection fraction, but it can occur also in nonischemic cardiomyopathy.

Ventricular tachycardia may also cause syncope in patients with normal left ventricular (LV) function (ie, long QT syndrome, Brugada syndrome, right ventricular outflow tract ventricular tachycardia, arrhythmogenic right ventricular cardiomyopathy [ARVC], and idiopathic left ventricular tachycardia).[32-35] Syncope is considered to be an ominous sign, portending a high risk for sudden cardiac arrest in patients with long QT syndrome, Brugada syndrome, and ARVC.

Torsade de pointes can cause syncope in patients with either congenital or acquired long QT syndrome (see Chap. 85). A normal QT interval does not preclude the diagnosis of long QT syndrome, because prolongation of repolarization can be intermittent. In some heritable forms of the syndrome, QT prolongation and ventricular tachycardia can be triggered by exercise or a startle response.[36,37] Although a number of drugs can prolong ventricular repolarization, the most frequent causes of acquired long QT syndrome are antiarrhythmic drugs (types Ia and III) and electrolyte disorders (hypokalemia and hypomagnesemia). A pause preceding the onset of tachycardia is common, because the early afterdepolarizations thought to be responsible for torsade de pointes in some long QT syndrome patients are bradycardia dependent.[23,37,38]

A variety of other drugs may produce or aggravate arrhythmias, resulting in syncope or presyncope. Type Ic antiarrhythmic drugs may cause ventricular arrhythmias in patients with structural heart disease. β-Adrenoceptor antagonists, calcium-channel blockers, digoxin, sotalol, and amiodarone are some of the agents that most commonly cause significant sinus bradycardia or AV block. Theophylline and β agonists, used for therapy of chronic obstructive pulmonary disease, may precipitate ventricular or supraventricular arrhythmias. Therapy with diuretics can cause hypokalemia and hypomagnesemia. Both caffeine and alcohol may precipitate either atrial or ventricular tachyarrhythmias.

In the patient who has an artificial ventricular pacemaker, near syncope or syncope may be secondary to pacemaker malfunction or to the pacemaker syndrome (see Chap. 89). Dual-chamber pacemakers can

produce pacemaker-mediated tachycardias when there is retrograde conduction of the ventricular impulse to the atria. Improvements in technology have reduced the incidence of this complication.[39,40]

DISORDERS OF VASCULAR CONTROL OR BLOOD VOLUME

Disorders of vascular control or blood volume that can cause syncope include the reflex syncopes and a number of causes for orthostatic intolerance (Table 90–2).[41,42] Under normal circumstances, systemic blood pressure is regulated by a complex process that includes the musculature, the venous valves, the autonomic nervous system, and the renin-aldosterone-angiotensin system. Knowledge of these processes is a prerequisite to understanding the disorders of vascular control or blood volume that can cause syncope.

TABLE 90–2. Disorders of Vascular Control and Blood Volume

- Reflex syncope
  - Neurocardiogenic (vasovagal)
  - Situational
  - Carotid sinus hypersensitivity
- Orthostatic intolerance
  - Autonomic nervous system disorders
    - Primary autonomic failure
      - Pure autonomic failure
      - Multiple system atrophy
      - Postural orthostatic tachycardia syndrome
        - Peripheral or partial dysautonomic
        - Hyperadrenergic
      - Acute autonomic failure
    - Secondary autonomic failure
      - Amyloidosis
      - Diabetes
      - Sarcoidosis
      - Renal failure
      - Cancer
      - Nerve growth factor deficiency
      - β-Hydroxylase deficiency
    - Pharmacologic agents
  - Certain heavy metals
    - Mercury
    - Lead
    - Arsenic
    - Iron
- Intravascular volume depletion
  - Anemia
  - Blood loss
  - Dehydration
  - Diuretics
- Venous pooling/vasodilation
  - Prolonged bed rest
  - Prolonged weightlessness
  - Pregnancy
  - Venous varicosities
  - Pharmacologic agents
  - Hyperbradykininism
  - Mastocytosis
  - Carcinoid syndrome

Maintenance of Postural Blood Pressure

A principal stress imposed while standing is produced by gravity displacing venous blood downward to a level below the heart. Although the renin-aldosterone-angiotensin system regulates long-term blood pressure responses to upright posture, the autonomic nervous system provides the majority of the short- and medium-term responses to postural change.[43]

In the normal supine individual, approximately one quarter of the blood volume is in the thorax. On standing, there is a gravity-mediated displacement of between 300 and 800 mL of blood to both the dependent extremities and the inferior mesenteric area.[44] Approximately 50% of this displacement occurs within the first few seconds of standing, resulting in a drop in venous return to the heart and a mean fall in stroke volume of approximately 40%.[44] In the normal subject, accommodation to this change in posture occurs in less than 1 minute.

Immediately on standing, muscle contractions in the legs, abdomen, and arms, in concert with the venous valvular system, support blood pressure by facilitating venous return.[44,45] However, this alone is insufficient to maintain venous return and systemic blood pressure. The reduction in venous return with upright posture is followed by a slow progressive fall in arterial pressure and cardiac filling that produces less stretch and reduces the discharge rate of aortic arch and carotid sinus baroreceptors. Fibers from these mechanoreceptors travel with unmyelinated vagal fibers from the atria and the ventricles to the nucleus tractus solitarii and other areas of the medulla that modulate vascular tone. In the resting supine position, impulses from these fibers increase efferent parasympathetic activity and have an inhibitory effect on efferent sympathetic activity to the heart. After standing, the drop in arterial pressure receptor firing in the carotid sinuses decreases efferent vagal activity and increases efferent sympathetic activity, producing a reflex increase in heart rate and peripheral vasoconstriction. As a result, assumption of upright posture results in a 10 to 15 bpm increase in heart rate, minimal change in systolic blood pressure, and an approximately 10 mm Hg increase in diastolic blood pressure.[46]

Any inability of this complex process to respond adequately or in a coordinated manner may result in varying degrees of postural hypotension and ultimately loss of consciousness. Failure of one component may be compensated for by increased action of another component. For example, a failure of the peripheral vasculature to constrict during upright posture may be compensated for by increased heart rate and myocardial contractility sufficient to maintain blood pressure. Nonetheless, compensatory mechanisms may not be sufficient, or may not be sustainable over long periods of time. Furthermore, compensatory mechanisms, if not modulated, may result in orthostatic hypertension and inappropriate sinus tachycardia.

Reflex Syncope

In each of the reflex syncopes, there is a sudden failure of the autonomic nervous system to maintain sufficient vascular tone during periods of gravitational stress resulting in hypotension (and sometimes bradycardia). The two types most commonly encountered are neurocardiogenic (vasodepressor or vasovagal) syncope and the carotid sinus syndrome.[47] The other forms of reflex syncope are frequently grouped together under the term *situational* because they occur in association with specific activities or conditions (such as micturition, defecation,

swallowing, coughing, postprandial). It is important to realize that the reflexes responsible for neurocardiogenic syncope are normal; healthy individuals will experience neurocardiogenic syncope in the setting of a stimulus that is sufficiently strong and prolonged. However, some individuals develop neurocardiogenic syncope frequently and with relatively little provocation, suggesting that disorders of autonomic control exist.

Neurocardiogenic syncope can be quite diverse in presentation and tends to occur more often in young people.[48] The episodes often include three stages: a prodrome (nausea, sweating, lightheadedness, or visual alterations), abrupt loss of consciousness, and rapid recovery without a postictal state. However, close to one-third of patients (often elderly) experience little if any prodrome and report a sudden loss of consciousness (drop attack).

The etiology of neurocardiogenic syncope is poorly understood. It can be provoked by prolonged standing, warm environments, emotional distress, and pain, although episodes can occur also without an identifiable trigger.[48] Many episodes of neurocardiogenic syncope are provoked by prolonged orthostatic stress.[49-51] Gravity-mediated displacement of blood and venous pooling in dependent areas decreases venous return to the heart, resulting in a reflex-mediated increase in myocardial contractility that activates ventricular mechanoreceptors that would normally fire only during stretch.[50] This sudden increase in neural traffic to the medulla appears to mimic the conditions seen in hypertension, resulting in a "paradoxic" decrease in sympathetic activity that results in hypotension (vasodepressor response), and in some cases, an increase in vagal efferent activity that results in bradycardia.[51] Other nonorthostatic stimuli (such as fear, fright, or epileptic discharges) can provoke virtually identical responses, suggesting that these patients may have an inherent predisposition to these events.[48] During head upright tilt-table testing, individuals susceptible to neurocardiogenic syncope demonstrate a precipitous fall in blood pressure that is frequently (but not always) followed by a fall in heart rate (on occasion to the point of asystole).[47]

Carotid Sinus Hypersensitivity

Syncope caused by carotid sinus hypersensitivity is most common in men ≥ 50 years old and is precipitated by pressure on the carotid sinus baroreceptors, typically in the setting of shaving, a tight collar, or turning the head to one side. Activation of carotid sinus baroreceptors gives rise to impulses to the medulla oblongata that, in turn, activate efferent sympathetic nerve fibers to the heart and blood vessels, cardiac vagal efferent nerve fibers, or both. In patients with carotid sinus hypersensitivity, these responses may cause sinus arrest or AV block (a cardioinhibitory response), vasodilatation (a vasodepressor response), or both (a mixed response). The underlying mechanisms responsible for the syndrome are not clear, and validated diagnostic criteria do not exist.

Some investigators have noted that the hemodynamic responses observed in neurocardiogenic syncope and carotid sinus hypersensitivity are similar, suggesting that the two syndromes may represent different aspects of the same condition.[52] Others have proposed that each of the reflex syncopes may occur in predisposed individuals when rapid activation of neuroreceptors from multiple sites (esophagus, bladder, rectum, or cough) activates a similar response.[51] Recent observations concerning defecation syncope support this.[47] What seems to distinguish the reflex syncopes from the other autonomic syndromes is that between episodes of syncope these patients rarely complain of symptoms referable to the autonomic nervous system. Consequently, in the reflex syncopes the autonomic nervous system functions normally, despite being at times "hypersensitive," in contrast to other conditions wherein the autonomic system appears to "fail," operating at a level insufficient for the body's needs, and thereby resulting in drawing levels of orthostatic intolerance.[47]

Syndromes of Orthostatic Intolerance

Orthostatic hypotension may occur as a result of hypovolemia or disturbances in vascular control (see Table 90–2). The latter may occur because of agents that affect the vasculature directly or to primary or secondary abnormalities of autonomic control. During the last two decades, several autonomic disorders have been identified that can impact vascular control and cause syncope.[47] The system presented here corresponds with that developed by the American Autonomic Society and the Heart Rhythm Society and attempts to present these disorders in a clinically useful framework.[41,42] Primary autonomic disorders that affect vascular control are often idiopathic, occur in the absence of other disease states that affect the autonomic nervous system, and may follow either an acute or chronic course. In contrast, the secondary forms occur in conjunction with another illness (such as amyloidosis or diabetes), in the setting of a known biochemical or structural alteration, or following exposure to various drugs or toxins (heavy metals, alcohol, or some chemotherapeutic agents) (Tables 90–2 and 90–3).[41,42]

Primary Causes of Autonomic Failure

Pure Autonomic Failure Bradbury and Eggleston first reported an autonomic failure syndrome in 1925, coining the term *idiopathic orthostatic hypotension* to describe the disorder.[53] In the interim, it has become apparent that this term insufficiently describes the diffuse state of autonomic failure present in these patients, as evidence by impaired bladder, bowel, thermoregulatory, motor, and sexual function (all in the absence of somatic nerve involvement). Currently the condition is referred to as *pure autonomic failure* (PAF).[54] Onset of symptoms in PAF is usually between ages 50 and 75 years and affects twice as many men as women.[55] PAF is manifested by orthostatic hypotension, syncope, and near syncope, neurocardiogenic bladder, constipation, heat intolerance, inability to sweat, and erectile dysfunction. Typically, the onset of symptoms is gradual and insidious, often with sensations of positional weakness, lightheadedness, and dizziness.[56] Male patients often report that the earliest signs of PAF were erectile dysfunction

TABLE 90–3. Pharmacologic Agents That May Cause or Worsen Orthostatic Intolerance

Angiotensin-converting enzyme inhibitors
α-Receptor blockers
Calcium channel blockers
β-Blockers
Phenothiazines
Tricyclic antidepressants
Bromocriptine
Opiates
Diuretics
Hydralazine
Ganglionic-blocking agents
Nitrates
Sildenafil citrate
Monoamine oxidase inhibitors
Chemotherapeutic agents
Vincristine
Vinblastine

and diminished libido; women often report that their earliest symptoms were urinary retention and incontinence.[57] Although not the initial symptom, syncope may be the event that prompts the patient to seek medical attention. Whereas PAF may result in severe functional impairment, it infrequently leads to death.[57]

Multiple System Atrophy Multiple system atrophy (MSA) is a more severe form of autonomic failure, first reported by Shy and Drager in 1960.[58] In contrast to PAF, these patients display not only significant orthostatic hypotension, but also urinary and rectal incontinence, anhidrosis, iris atrophy, external ocular palsy, erectile dysfunction, rigidity, and tremor. As with PAF, the condition is twice as common in men as women and usually starts in the fifth and sixth decades of life.[55] Although MSA may initially be indistinguishable from PAF, patients with MSA eventually experience somatic nervous system involvement.[59]

MSA is subclassified into three groups according to the somatic system involvement.[55,56] Group I patients exhibit a muscle tremor similar to that seen in Parkinson disease (also referred to by some as suffering from striatonigral degeneration).[60] As opposed to patients with true Parkinson disease, MSA patients display more rigidity than tremor and the tremor usually lacks the "lead pipe" or "cogwheel" rigidity observed in Parkinson disease.[61,62] Patients with the parkinsonism form of MSA often show a loss of facial expression as well as limb akinesia.

Group II (olivopontocerebellar degenerative atrophy) patients demonstrate pronounced cerebellar and/or pyramidal signs and symptoms.[63] These patients display both gait disturbance and a truncal ataxia severe enough to prevent standing without assistance. They may have a mild intention tremor and severe slurring of speech with impaired diction. Group III (mixed) patients display features of both the parkinsonian and cerebellar groups.[59]

The frequency of MSA may be underappreciated, as an autopsy study found that between 7% and 22% of patients thought to have Parkinson disease during life had neuropathologic changes consistent with the disorder.[61] MSA is relentlessly progressive, with the vast majority of patients dying within 5 to 8 years after onset of the illness (although occasional patients have been reported to have lived up to 20 years).[56] Aspiration, apnea, and respiratory failure are the most frequent terminal events.

Postural Orthostatic Tachycardia Syndrome Postural orthostatic tachycardia syndrome (POTS) is a somewhat less severe autonomic insufficiency in which heart rate increases excessively in response to upright posture.[64] There are two primary forms of the disorder. The more common type is referred to as the peripheral (or partial) dysautonomic form.[65] These individuals appear to suffer from an inability to increase adequately peripheral vascular resistance in the face of continuing orthostatic stress. This leads to a greater than normal amount of blood pooling in the dependent areas of the body (including the mesenteric vasculature), which is then compensated for by an excessive increase in both heart rate and myocardial contractibility.

Patients with dysautonomic POTS experience constant tachycardia (up to 160 bpm) while standing, and often complain of palpitation, exercise intolerance, fatigue, lightheadedness, cognitive impairment, visual disturbances, dizziness, near syncope, and syncope. Patients may complain of heat intolerance and that they constantly feel cold. Heart rate increases greater than 30 bpm or to a rate greater than 120 bpm, usually with minimal drop in blood pressure during the first 10 minutes of upright tilt.[66] Approximately 10% of dysautonomic POTS patients progress to PAF. Dysautonomic POTS often occurs following a viral infection, surgery, or trauma. Recent studies suggest a link between dysautonomic POTS and the joint hypermobility syndrome.[47,67]

A second primary form of POTS is referred to as the *hyperadrenergic*, *β-hypersensitivity*, or *central* form. This form is thought to be associated with a failure of normal feedback mechanisms above the level of the baroreflex. Whereas the initial heart rate response to postural changes is adequate, the brain appears to be unable to discontinue the response, allowing heart rate to continue to rise. These patients may also be noted to have significant orthostatic *hypertension*. Although supine serum catecholamine levels are normal, upright levels are often quite elevated (over 600 mg/dL) and these patients often display an excessive response to an infusion of isoproterenol (a greater than 30 bpm increase in response to 1 μg/min). In contrast to patients with the peripheral dysautonomic form, patients with hyperadrenergic POTS complain more often of tremor, hyperhidrosis, diarrhea, panic attacks, and severe migraines headaches. Recent studies in a family with several affected members identified genes that appear to be responsible for hyperadrenergic POTS.[68] A defect was found in the genetic code for a protein that functions to recycle norepinephrine in the intra-synaptic cleft, allowing for excessively high serum levels of norepinephrine. Additional studies suggest that there may be several different genetic forms of the disorder.[69]

Acute Autonomic Failure Although less common than the other autonomic disorders, acute autonomic failure is dramatic in presentation.[70] The onset is surprisingly rapid and is characterized by severe widespread failure of both parasympathetic and sympathetic components of the autonomic nervous system, while the somatic system is unaffected. Patients may have such profound orthostatic hypotension that merely attempting to sit up in bed causes syncope.[71] Many suffer from complete anhidrosis and disturbances in bowel and bladder function that result in abdominal pain, cramping, bloating, nausea, and vomiting. Cardiac denervation is common, resulting in a fixed heart rate of 45 to 50 bpm and chronotropic incompetence.[72] Most of these patients have high circulating levels of antibodies to adrenergic receptors within the ganglia of the autonomic nervous system, supporting the idea that the disorder is autoimmune in nature.[73]

Secondary Causes of Autonomic Dysfunction

A wide variety of conditions may cause orthostatic hypotension by disturbing normal autonomic function (see Table 90–2).[41,42] Almost any systemic illness that affects multiple organ systems (such as diabetes mellitus, amyloidosis, sarcoidosis, renal failure, and certain cancers) may disrupt autonomic function sufficiently so as to result in orthostatic hypotension and syncope. A subgroup of patients with autonomic failure syndrome (especially diabetic patients) have a combination of supine hypertension and orthostatic hypertension, thought to be caused by a failure to properly vasoconstrict when upright or properly vasodilate when supine.[74] It is not uncommon for these patients to exhibit a 100-point fall in systolic blood pressure on standing. In some hypertensive patients, a rapid fall in blood pressure may exceed the brain's autoregulatory ability to maintain perfusion, causing syncope even though the systemic blood pressure may at the time be in a relatively normal range.[75] Some investigators suggest that there may be an association between Alzheimer disease and orthostatic hypotension as a consequence of effects on autonomic control.[76] Isolated enzyme abnormalities may also cause orthostatic hypotension, examples of which are nerve growth factor deficiency and β-hydroxylase deficiency.[74] In addition, certain pharmacologic agents may either produce or contribute to orthostatic hypotension by interfering with autonomic control (sew Table 90–3).

Additional Causes of Orthostatic Intolerance

Intravascular volume depletion, venous pooling, certain pharmacologic agents, and a number of endogenous vasodilators may cause orthostatic hypotension and syncope. Anemia, acute blood loss, and dehydration may cause intravascular volume depletion. Venous pooling is more

common in older individuals who have incompetent venous valves in the lower extremities. Individuals subjected to prolonged periods of bedrest or weightlessness often experience orthostatic hypotension. In addition to those pharmacologic agents that interfere with autonomic vascular control, a number of pharmacologic agents can cause orthostatic hypotension by reducing intravascular volume or causing vasodilatation. Certain endogenous vasodilators may cause syncope when they are present in high concentrations.

Clinical Presentation

The principal feature shared by the syndromes of orthostatic intolerance is a disturbance in cardiovascular regulation sufficiently profound so as to result in orthostatic hypotension. Symptoms, the response to tilt testing (see "Diagnostic Tests" later in the chapter), and the company they keep may assist in differentiating among the disorders. Symptoms are related to both the rate and magnitude of change in blood pressure.

On occasion it may be difficult to fully distinguish between the various autonomic nervous system disorders, as there is a considerable degree of overlap between them and because our understanding of mechanisms remains incomplete. In addition, these disorders should be distinguished from neurocardiogenic syncope. Patients with neurocardiogenic syncope tend to experience an abrupt fall in blood pressure that is commonly associated with definitive prodrome. In dysautonomic syncope the drop in blood pressure tends to be slow and may not be perceived, resulting in a "drop attack" with little or no warning, particularly in older patients.[74] Those who experience a prodrome report feeling lightheaded, dizzy, and blurred or tunnel vision. In contrast to reflex syncope, dysautonomic syncope is seldom associated with either bradycardia or diaphoresis.[56] Patients with the dysautonomic forms of syncope find that symptoms are more common in the morning after awaking from sleep and are made worse by situations that enhance peripheral venous pooling (extreme heat, fatigue, dehydration, and alcohol). Patients suffering from PAF and MSA may display severe chronotropic incompetence with a relatively fixed heart rate (usually around 50 to 70 bpm).[57]

CEREBROVASCULAR DISORDERS

A number of cerebrovascular disorders can cause syncope. Syncope can occur in patients with extensive occlusive disease of the origins of the brachiocephalic vessels, such as pulseless disease (eg, aortic arch syndrome and Takayasu arteritis).[4,77] With lesser degrees of cerebral occlusive disease, as with atherosclerotic narrowing, transient lowering of arterial pressure such as that immediately following assumption of the upright posture may be followed by vague symptoms suggesting impaired cerebral blood flow. In patients with cerebrovascular occlusive disease, a transient decrease in cardiac output and arterial pressure may provoke syncope at levels of arterial pressure that would otherwise be tolerated (see "Multifactorial Syncope" later in the chapter).

Impairment in or loss of consciousness in relation to changing positions of the head, particularly hyperextension and lateral rotation, has been attributed to mechanical narrowing of the vertebral arteries by skeletal deformities of the cervical spine. Such symptoms have been observed in patients with Klippel-Feil deformity, cervical spondylosis, and severe cervical osteoarthritis. Altered consciousness is often preceded by vestibular symptoms. However, when vertigo is a predominant symptom, the syndrome of benign postural vertigo must be considered.

Syncope in the *subclavian steal syndrome* is caused by major occlusive disease of the subclavian artery proximal to the origin of the vertebral artery. During upper extremity exercise, blood flow is shunted retrograde, by the circle of Willis, to the distal subclavian artery. The consequent decrease in cerebral circulation induces cerebral ischemia.[77] This syndrome is suggested by the findings of diminished brachial arterial pressure on the affected side, a bruit that is maximal over the supraclavicular area adjacent to the origin of the vertebral artery, and the induction of symptoms by exercise of the involved extremity.

Although focal neurologic symptoms and signs are the usual neurologic manifestations of cerebral emboli, transient loss of consciousness can be a primary presenting symptom. Syncopal episodes are more likely to occur when atherosclerotic occlusive disease involves the vertebrobasilar system, with compromised perfusion to the medullary arousal center. In vertebrobasilar vascular insufficiency, syncope or presyncope is nearly always preceded by symptoms of vertigo, diplopia, dysarthria, and ataxia. The episodes are generally attributed to microemboli arising from an atherosclerotic plaque, although vasospasm or postural hypotension may contribute.

SYNCOPE OF UNDETERMINED CAUSE

Despite careful diagnostic evaluation, the cause of syncope cannot be defined in as many as 50% of patients.[4] Unexplained syncope has a broad spectrum of etiologies. The varying mortality rate among patients with syncope of undetermined cause likely reflects the varying incidence of undetected cardiac syncope. A certain number of these patients may have experienced syncope from multiple causes.[78,79]

MULTIFACTORIAL SYNCOPE

The cause of syncope is often multifactorial. Patients with structural heart disease or cerebrovascular disease may be predisposed to lose consciousness when blood pressure is compromised because of other causes, such as orthostatic hypotension, a neurocardiogenic reaction, cerebrovascular disease, or an arrhythmia. In addition, patients may have more than one abnormality that alone can cause syncope. In these patients the history may provide clues that enable the clinician to identify the cause of a particular event.

APPROACH TO THE PATIENT

The diagnosis of syncope can be challenging, in part because the cause, like the event, may be only transiently apparent. One of the most important goals is to determine if the patient has a cause for syncope that is potentially life-threatening. This is particularly important because many of the life-threatening causes for syncope can be treated effectively to prolong and improve the quality of life. However, exclusion of a life-threatening cause is not the only goal. The efficacy of therapy depends to a great extent on an accurate diagnosis.

HISTORY AND PHYSICAL EXAMINATION

The history and physical examination remain of paramount importance and may alone diagnose the etiology or distinguish syncope from other causes of loss of consciousness.[80-92]

History

The history should include questions about when the first event occurred, how often and in what settings syncope has occurred, and external factors that can contribute to syncope including medications, diet pills, dietary supplements, and illicit drugs. Symptoms, the patient's posture, and activities preceding the event may provide clues to the cause. Elderly patients who experience lightheadedness or syncope immediately after assuming upright posture may have orthostatic hypotension. Bradycardia, caused by sinus node dysfunction or atrioventricular block, should be suspected in the elderly who experience abrupt loss of consciousness

without warning. Neurocardiogenic syncope should be suspected in young patients without apparent structural heart disease who lose consciousness after standing for a prolonged period or after venipuncture. Neurocardiogenic syncope rarely occurs in individuals when they are supine. Syncope while shaving or after turning one's head to the side suggests that carotid sinus hypersensitivity may be the cause.

Whenever possible, the history should include observations of the patient during an episode. Video recordings of the patient made by bystanders using "smart phone" technology during an event can be particularly useful. Tonic-clonic movements may accompany loss of postural tone if cerebral anoxia is prolonged. Although trauma can occur with syncope, tongue biting and incontinence are more commonly associated with seizures.[92] The time course of the event may suggest an etiology of syncope. Most episodes of syncope are brief, seconds to minutes, though episodes in patients with dysautonomias may be more prolonged. Typically, neurocardiogenic syncope is associated with spontaneous recovery of consciousness within seconds when the patient becomes supine. Unlike seizure disorders, patients rarely experience prolonged confusion or disorientation after an episode of syncope. Patients should be asked whether a family history exists for cardiovascular disease, neurologic disorders, and early sudden death. A thorough list of prescription and nonprescription medications, supplements, and herbal remedies should be obtained.

Physical Examination

The physical examination should include evaluation of blood pressure and heart rate in the supine, sitting, and upright positions, and again in the upright position 3 to 5 minutes after standing to determine if abnormal changes in orthostatic control are present. Blood pressure should be determined with the arm extended horizontally so as to diminish the hydrostatic effect that occurs when the arm is in a dependant position.[55] Traditionally, orthostatic hypotension has been defined as a fall in systolic blood pressure of at least 20 mm Hg or at least 10 mm Hg fall in diastolic blood pressure during the first 2 minutes of standing. It should be kept in mind, however, that in some patients, a less dramatic fall in blood pressure may be associated with symptoms.[47]

Cardiac auscultation, especially when combined with appropriate physical maneuvers, may reveal evidence for structural heart disease. When the cause of syncope is unknown, an attempt to reproduce the event may assist in determining the cause. A Valsalva maneuver may reproduce cough syncope; hyperventilation for 2 to 3 minutes may reproduce episodes that are related to anxiety. Although carotid sinus massage may induce significant bradycardia in susceptible individual, it is not recommended for those who may have carotid atherosclerotic disease because the procedure may cause plaque to embolize. The absence of a carotid bruit does not exclude the presence of an atheroma that could be dislodged during carotid sinus massage. In a patient with syncope, a pause of longer than 3 seconds during carotid sinus massage suggests that carotid sinus hypersensitivity may be the cause.

DIAGNOSTIC TESTS

The history and physical examination guide the choice of diagnostic tests. Blood tests that may sometimes contribute to diagnosis include a complete blood count to evaluate for anemia, serum electrolytes, including potassium and magnesium, to evaluate for abnormalities that might cause or aggravate arrhythmias, supine and upright serum catecholamine levels when hyperadrenergic postural orthostatic tachycardia is suspected, and drug levels when the patient's medication or an illicit drug has the potential to precipitate an arrhythmia.

Although it is unlikely alone to provide a diagnosis, almost all patients should undergo a 12-lead surface electrocardiogram because it may identify abnormalities that can predispose to syncope, including prior infarction, ventricular preexcitation (WPW syndrome), AV or bundle-branch block, short or long QT interval, incomplete right bundle-branch block with right precordial ST-segment elevation (Brugada syndrome), epsilon waves, or right precordial T-wave inversion suggestive of ARVC. A transthoracic echocardiogram should be performed whenever heart disease is considered to be in the differential diagnosis.

Transthoracic echocardiography can identify a number of structural abnormalities that are associated with obstructive and arrhythmic causes for syncope. An echocardiogram should be performed whenever the diagnosis of structural heart disease is considered to be significantly likely. Gated blood pool scanning measures left ventricular ejection fraction, but does not provide as much information about cardiac valvular abnormalities.

Patients who are at risk for coronary artery disease should undergo a stress test. In patients who are at high risk for or who are known to have coronary artery disease, cardiac catheterization may be indicated. The use of new high-fidelity computed axial tomography scans to identify coronary artery disease and anomalous coronary arteries is evolving.

Because of their transient nature, arrhythmic causes of syncope may be very difficult to diagnose. Testing for structural heart disease is important to identify patients at risk for arrhythmia and to determine prognosis when an arrhythmia is diagnosed. Figure 90–1 lists the various diagnostic tests used for the evaluation of arrhythmic syncope. The 12-lead surface electrocardiogram (ECG) is usually of limited use other than to reveal cardiac abnormalities that predispose to arrhythmia. The signal-averaged ECG, which was developed to detect late potentials following myocardial infarction, is rarely used for that purpose in light of the several clinical trials that demonstrated that left ventricular ejection fraction ≤ 35% and the presence of heart failure predict benefit from an implantable cardioverter-defibrillator.[93-96] Patients with arrhythmogenic right ventricular cardiomyopathy may also have an abnormal signal-averaged ECG.[97] Cardiac magnetic resonance imaging (MRI) may also be useful in establishing the diagnosis of arrhythmogenic right ventricular cardiomyopathy.

In addition to its use to detect myocardial ischemia, an exercise stress test should be performed when exertional arrhythmias are suspected and ambulatory monitoring has failed to document arrhythmia.[98,99] Continuous ECG monitoring (Holter monitor) is a widely used screening test for suspected arrhythmic syncope but it has a low yield in unselected patients. One 24-hour monitoring period may not be sufficient for detecting transient rhythm disturbances. However, the diagnostic yield increases only slightly with more prolonged monitoring.[98-100] When a Holter monitor does not document an arrhythmia, a patient-activated ECG device (event recorder) may prove efficacious, particularly if the episodes are infrequent (days to weeks). In patients without implantable defibrillators, event recorders should not be used when life-threatening arrhythmias are thought to be the likely cause of symptoms.[101-103]

Patients in whom syncope is very infrequent (weeks to months between episodes) may benefit from an implantable loop recorder, a small device that is surgically placed subcutaneously in the chest, can store up to 45 minutes of retrospective electrocardiographic data, and can record automatically or be activated by the patient. Implantable loop recorders provide diagnostic information in up to two-thirds of patients with syncope of undetermined cause.[104,105] A diagnostic strategy beginning with the implantable loop recorder may be more cost-effective than the traditional approach (external event recorder, tilt-table and electrophysiologic testing) in some patients.[106]

When noninvasive testing does not diagnose arrhythmic causes, an electrophysiologic study may be useful in high-risk patients (those with structural heart disease, suspicious arrhythmia by ECG monitoring,

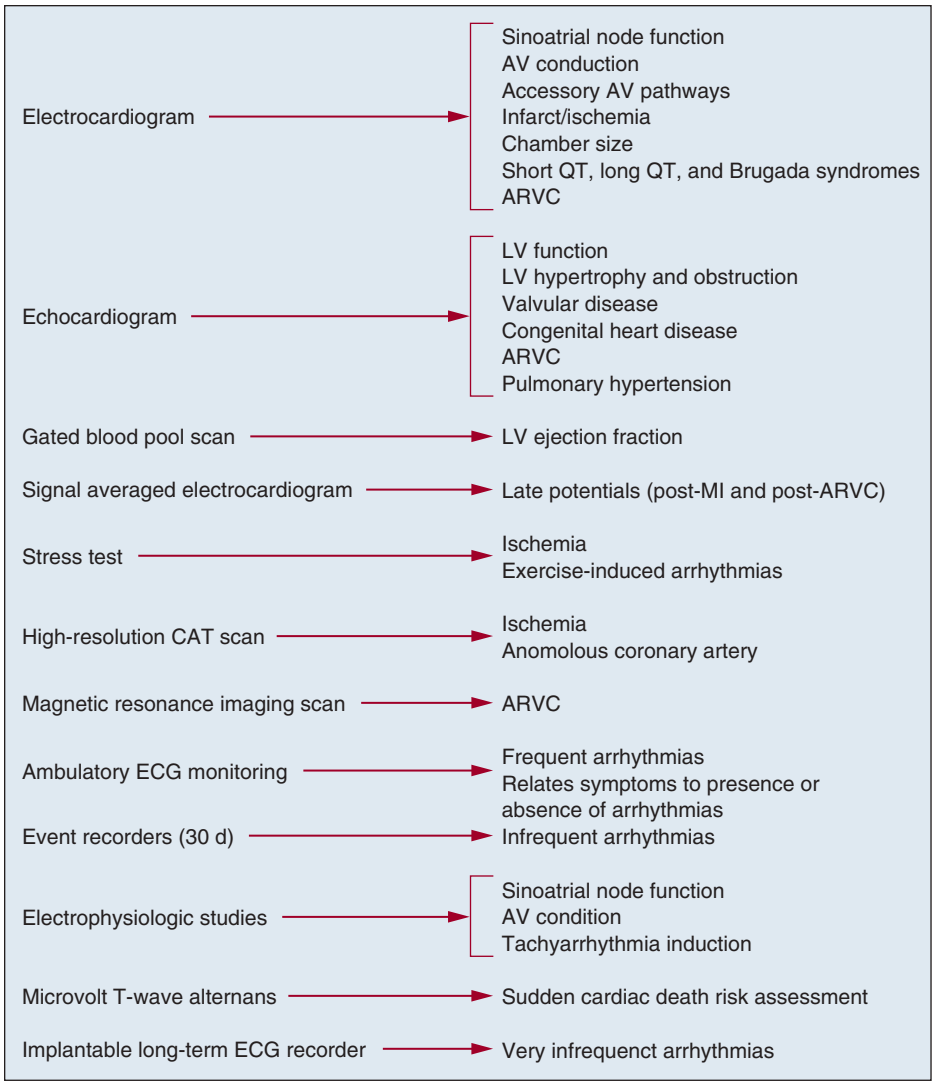

FIGURE 90–1. Diagnostic tests for arrhythmic syncope. ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; ECG, electrocardiogram; LV, left ventricular; MI, myocardial infarction.

or recurrent syncope) to assess sinus and AV node function and susceptibility to supraventricular and ventricular tachyarrhythmias (see Chap. 82). The yield of electrophysiologic testing in patients with an otherwise normal evaluation for syncope is approximately 3%.[106] Furthermore, the sensitivity of electrophysiologic testing for bradyarrhythmias is low.[107] However, electrophysiologic testing can be useful in stratifying risk among symptomatic patients with bundle-branch block and in those with bifascicular block. Patients who receive a permanent pacemaker on the basis of electrophysiologic testing also have a favorable prognosis, with a low rate of symptom recurrence.[108-113]

Patients without identifiable heart disease are less likely to have the cause of syncope identified by electrophysiologic study. In patients with coronary artery disease, particularly those with previous myocardial infarction, the cause of syncope most commonly identified by electrophysiologic study is ventricular tachycardia.[107]

The use of the microvolt T-wave alternans test to stratify risk for ventricular arrhythmias is evolving. The test is most useful when performed during exercise and appears to have a strong negative predictive value.[114-117]

Tilt-table testing is the only method employed for the diagnosis of neurocardiogenic syncope that has undergone extensive evaluation.[118-121] Tilt-table testing is based on the principle that orthostatic stress, such as that provided by a period of prolonged upright posture, can produce venous pooling and thus provoke the aforementioned responses in susceptible individuals. As opposed to standing, the patient is placed on a table that can incline up to an angle of 60° to 70°. In this position, the skeletal muscle pump is inhibited and the autonomic nervous system must function alone to maintain blood pressure. The absence of compensatory mechanisms in the presence of a stimulus (prolonged upright posture) may provide the opportunity to observe heart rate and blood pressure patterns that provoke syncope.

Table 90–4 lists the indications for tilt-table testing. A positive test is one that provokes a hypotensive episode (or in the case of POTS, a tachycardic episode) that reproduces the patient's symptoms.[121] A young, otherwise healthy individual with a history that strongly suggests neurocardiogenic syncope and no evidence of life-threatening condition may not require tilt-table testing after an initial episode of syncope.[122] The specificity of tilt-table testing is reported to be near 90%, but lower when pharmacologic provocation is employed. The sensitivity of the test is reported to be between 20% and 74%, the variability a result of differences in study populations, protocols, and the absence of a true "gold standard" to which the results of the test can be compared.[118,120,123-132] The reproducibility of the test (in a time frame ranging from several hours to weeks) is 80% to 90% for an initially positive response, but less for an initially negative response (ranging from 30% to 90%).

It is important to remember that the type of autonomic stress provided by tilt-table testing is different from that which the patient encounters

TABLE 90–4. Head-Up Tilt-Table Testing

Indications for head-up title-table testing

1. Unexplained recurrent syncope or single syncopal episode associated with injury (or significant risk of injury) in absence of organic heart disease.
2. Unexplained recurrent syncopal episodes or a single syncopal episode associated with injury (or significant risk of injury) in setting of organic heart disease after exclusion of potential cardiac cause of syncope.
3. After identification of a cause of recurrent syncope in situations in which determination of an increased predisposition to neurocardiogenic syncope could alter treatment.

Conditions in which tilt-table testing may be useful

1. Differentiating conclusive syncope from epilepsy.
2. Evaluation of recurrent near syncope or dizziness.
3. Evaluation of syncope in autonomic failure syndromes.
4. Exercise- or postexercise-induced syncope in absence of organic heart disease in whom exercise stress testing cannot reproduce an episode.
5. Evaluation of recurrent unexplained falls.

clinically. The International Study of Syncope of Unknown Etiology (ISSUE) compared heart rates during syncopal episodes induced during tilt-table testing with those that occurred spontaneously (as documented by an implantable loop recorder) and showed that spontaneous events were more likely to be associated with significant bradycardia.[119]

Abnormal tilt-table responses can be classified into five groups.[118] The first is referred to as a *classic neurocardiogenic response*, which is characterized by an abrupt drop in blood pressure. When accompanied by a significant drop in heart rate, this is referred to as a *vasovagal response*; in the absence of a decrease in heart rate, a *vasodepressor response*. A second pattern referred to as a *dysautonomic* (or *delayed orthostatic*), is characterized by a gradual progressive fall in blood pressure with relatively little change in heart rate. This pattern is often noted in the autonomic failure syndromes. The third pattern, termed a *postural tachycardic response*, is associated with a > 30 bpm increase in heart rate (or a heart rate of > 120 bpm) during the first 10 minutes of the baseline tilt. The fourth pattern is called *cerebral syncope*. These patients experience syncope in the absence of systematic hypotension concomitant with intense cerebral vasoconstriction (as determined by transcranial Doppler), as well as cerebral hypoxia (as determined by electroencephalogram). The fifth response pattern is *psychogenic*. These patients are noted to experience loss of consciousness in the absence of systemic hypotension or any observable change in electroencephalogram or transcranial Doppler recording.[132] These patients are often found to suffer from psychiatric disorders that range from conversion reactions to severe depression.[133] Patients suffering from conversion reactions are not consciously aware of these events.[134] Many patients with psychogenic syncope are young women who have been victims of sexual abuse.[133]

TREATMENT

Treatment of syncope depends to a great extent on the cause. However, regardless of the etiology, patients should be counseled to minimize exposure to factors that have or are likely to provoke a syncopal episode. This is particularly important for individuals with neurocardiogenic syncope in whom prolonged standing or specific environmental factors have played a role in initiating syncope. Patients should be counseled to avoid situations in which they or others could be injured were they to lose consciousness, particularly when syncope occurs frequently, abruptly, and without warning. Finally, patients should be counseled to take measures (ie, lie down) to minimize or avoid syncope should they experience prodromal symptoms.

A patient who has lost consciousness should be placed in a position that maximizes cerebral blood flow, offers protection from trauma, and secures the airway. Whenever possible, the patient should be placed supine with the head turned to the side to prevent aspiration and the tongue from blocking the airway. Assessment of the pulse and direct cardiac auscultation may assist in determining if the episode is associated with a bradyarrhythmia or tachyarrhythmia. Clothing that fits tightly around the neck or waist should be loosened.

Syndromes of Orthostatic Intolerance

Therapies for the syndromes of orthostatic intolerance target the various components of the complex mechanisms responsible for control of systemic blood pressure including blood volume, the skeletal muscle pump, heart rate, and central and peripheral components of the autonomic nervous system. Table 90–5 lists therapies and the syndromes

TABLE 90–5. Orthostatic Intolerance Syndrome Therapies

		Form Effective In				
Treatment	Application	NCS	PD	HA	OH	Problems
Reconditioning	Aerobic exercise 20 min 3 times/wk	X	X	X	X	If done too vigorously may worsen symptoms
Physical maneuvers (tilt training, etc.)	30 min 3 times/d	X				Noncompliance is common
Sleeping with head tilted upright	During sleep	X		X	X	
Hydration	2 L PO/d	X	X		X	Edema
Salt	2-4 g/d	X	X		X	Edema
Fludrocortisone	0.1-0.2 mg PO qd	X	X		X	Hypokalemia, hypomagnesemia, edema
Metoprolol	25-100 mg bid	X				Fatigue
Labetalol	100-200 mg PO bid			X		Fatigue
Midodrine	5-10 mg PO tid	X	X		X	Nausea, scalp itching, supine hypertension
Methylphenidate	5-10 mg PO tid	X	X	X		Anorexia, insomnia, dependency
Bupropion	150-300 mg XL/qd		X	X	X	Tremor, agitation, insomnia
Clonidine	0.1-0.3 mg PO bid			X		Dry mouth, blurred vision
	0.1-0.3 mg patch qwk					
Pyridostigmine	30-60 mg PO/d		X		X	Nausea, diarrhea
SSRI-escitalopram	10 mg PO/d	X	X		X	Tremor, agitation, sexual problems
Erythropoietin	10,000-20,000 µg SC qwk	X	X		X	Pain at injection site, expensive
Octreotide	50-200 µg SC tid		X	X	X	Nausea, diarrhea, gallstone
Permanent pacing		X				
Ivabradine	5-7.5 mg PO BID	X	X			Nausea, flashing lights
Droxidopa	100-600 mg PO TID				X	Nausea, supine hypertension

Abbreviations: HA, hyperadrenergic postural orthostatic tachycardia syndrome; NCS, neurocardiogenic syncope; OH, orthostatic hypotension; PD, partial dysautonomia; SSRI, selective serotonin reuptake inhibitor.

for which they are used. Moderate aerobic and isometric exercises are of paramount importance as these therapies enhance skeletal muscle pump function and thereby venous return to the heart. Patients with orthostatic hypotension should be instructed to move their legs prior to rising in order to facilitate venous return and to rise slowly and systematically (supine to seated, seated to standing) from the bed or a chair. Whenever possible, medications that aggravate the problem (eg, vasodilators, diuretics) should be discontinued.

A variety of physical maneuvers have been employed to treat the syndromes of orthostatic intolerance. Tilt training has been advocated; for neurocardiogenic syncope, however, long-term compliance is often poor.[135-137] Isometric countermaneuvers, such as tensing of the arm and leg muscle, can sometimes prevent neurocardiogenic syncope if used at the first onset of symptoms.[138,139] Sleeping with the head of the bed elevated 6 inches above the feet is reported to be useful in neurocardiogenic syncope and the autonomic failure syndromes. Elastic support stockings can be helpful in some patients; to be truly effective, however, they must be waist high and provide a minimum of 30 mm Hg of ankle counterpressure.

In some patients, salt and water loading increase intravascular volume and are effective in controlling syncope. However, many patients require pharmacologic therapy. β-Adrenoceptor antagonists were one of the first agents used to prevent neurocardiogenic syncope.[140] Theoretically, the negative inotropic effect of these drugs reduces the degree of cardiac mechanoreceptor activation provoked by a sudden drop in venous return. However, randomized trials of β-blockers have yielded mixed results. In the Prevention of Syncope Trial (POST), metoprolol was ineffective in patients who were younger than 42 years of age, but decreased the incidence of syncope in patients who were older than 42 years of age, raising the possibility that there may be important age-related differences in response to pharmacotherapy.[141]

The mineralocorticoid, fludrocortisone, in addition to promoting sodium and fluid retention, appears to enhance peripheral α-receptor sensitivity (promoting vasoconstriction).[142] Its role in treating neurocardiogenic syncope is not well defined.

Several vasoconstrictive agents have been employed as treatments. The first of these were ephedra alkaloids such as Dexedrine and methylphenidate, both of which are α-receptor stimulants.[143] Midodrine, another α-agonist, has been approved by the US Food and Drug Administration for the treatment of symptomatic orthostatic hypotension and was shown to be effective in preventing neurocardiogenic syncope in two randomized trials.[144,145] Bupropion is a norepinephrine and dopamine reuptake inhibitor that has been useful in certain patients. It tends to have fewer sexual side effects but may aggravate hypertension. Other vasoconstrictive substances, such as theophylline, ephedrine, and yohimbine, also are reported to be effective; however, tolerance of these agents is often poor.

The α_2-receptor agonist clonidine causes a paradoxic increase in blood pressure in patients with autonomic failure and a high degree of postganglionic sympathetic impairment. These individuals appear to have reduced peripheral sympathetic stimulation but increased density of postjunctional α_2 receptors throughout the vasculature. Whereas clonidine causes a reduction in central sympathetic output with subsequent blood pressure reduction in normal subjects, in patients with autonomic failure, the vasoconstrictive effects of the drug seem to predominate.[74] Clonidine may be most useful in patients with both hyper- and hypotensive episodes.

Recent investigations suggest that the acetylcholinesterase inhibitor pyridostigmine may be an effective agent for both orthostatic hypotension and postural tachycardia syndrome. Randomized, double-blind, placebo-controlled trials show that the agent is safe and effective and seems to be able to prevent falls in blood pressure without exacerbating supine hypertension.[146-148]

Evidence that serotonin plays a vital role in regulation of heart rate and blood pressure and the postulated role of serotonin in neurocardiogenic syncope has led to the investigation of selective serotonin reuptake inhibitors as a treatment for the disorder. Several open-label trials and one double-blind, randomized, placebo-controlled trial have demonstrated that the serotonin reuptake inhibitors prevent recurrent neurocardiogenic syncope.[149-152]

It has been observed that many patients suffering from the autonomic failure syndromes have some degree of anemia. In 1993, Hoeldtke and Streeten published a landmark study demonstrating that erythropoietin given by subcutaneous injection would not only raise red cell counts but would also prevent orthostatic hypotension.[153] Other studies have confirmed these findings, demonstrating that erythropoietin is an effective treatment for orthostatic hypotension.[154-156] Erythropoietin has vasoconstrictive effects (related to its effects on peripheral metric oxide) that are independent of its effect on red cell production.[155]

Octreotide, a synthetic somatostatin analogue, causes splanchnic mesenteric vasoconstriction, thus enhancing venous return to the heart.[157] Ivabradine, a selective sinus node slowing agent, can reduce heart rate without affecting blood pressure. Studies have reported that ivabradine may be useful in the management of both POTS and neurocardiogenic syncope.[158,159] Droxidopa is a synthetic amino acid precursor that acts as a prodrug to the neurotransmitter norepinephrine, resulting in peripheral vasoconstriction.[160] It has been approved in the United States for the treatment of neurogenic orthostatic hypotension. Biofeedback therapy also has been useful in preventing neurocardiogenic syncope provoked by a variety of psychogenic stimuli.[48]

Despite several trials evaluating its efficacy, the role of permanent cardiac pacing for neurocardiogenic syncope remains somewhat controversial. Initial randomized trials reported that pacing was effective in preventing syncope.[161-163] However, because all patients who received a pacemaker were paced and patients in the control group did not receive a pacemaker, there were concerns that the observed benefit could be a result of placebo effect. In two ensuing studies pacemakers were implanted in all patients who were then randomized to having the pacemaker programmed to an "on" or "off" mode. The Vasovagal Pacemaker Study II (VPS 2) reported no significant reduction in the time to a first recurrence of syncope during dual-chamber pacing over 6 months of follow-up.[164] The Vasovagal Syncope and Pacing Trial (SYNPACE) also reported that there was no significant difference between the "on" and "off "groups.[165] However, they did observe that the subgroup of patients who had demonstrated asystole during tilt-table testing had a significant increase in time to first syncope recurrence compared to those with bradycardia alone (91 vs 11 days). The ISSUE II trial reported that permanent pacing in patients with periods of asystole had a significant reduction in the frequency of syncope.[166] This observation lead to the ISSUE III trial, in which implantable loop recorders were used to identify asystole during the patients syncopal events. Each patient with documented asystole then received a dual-chamber pacemaker, with half of them being randomly assigned to the pacemaker being "on" and half being "off."[167] After one year the patients were crossed over (the ones who had pacing "off "were converted to "on" and vice versa. They reported a 57% relative risk reduction of syncope for pacemaker "on" patients at 2 years, with 25% of "on" versus 57% of "off" patients having had syncope recurrence. In many patients, however, a fall in blood pressure precedes the decline in heart rate; therefore by the time the pacemaker is activated, an episode can be well underway, providing "too little too late." Newer systems using continuous right ventricular impedance measurements have been developed that can provide an indirect measurement of blood pressure by the pacemaker.[168] Preliminary observational studies have suggested that this technology may be superior

to standard pacing methods in patients suffering from vasovagal syncope.[169-170] Further studies are underway comparing these new systems to standard pacing modalities. Patients with the cardioinhibitory or mixed forms of carotid sinus hypersensitivity may also benefit from permanent pacing. In SAFE PACE, permanent pacing reduced falls, recurrent syncope, and injuries in elderly patients with frequent nonaccidental falls and cardioinhibitory carotid sinus hypersensitivity.[171]

For patients who suffer from syncope with little or no prodrome, in whom other forms of therapy have failed, permanent pacing can potentially reduce the frequency of syncope or prolong the time from onset of symptoms to loss of consciousness. This may allow the patient sufficient time to take evasive action (ie, lie down) and prevent injury if not loss of consciousness.

In contrast to reflex syncope, the autonomic failure syndromes can be associated with symptoms in addition to hypotension some of which are easier to control then others. In addition, some of the autonomic disorders are chronic and progressive necessitating treatment alterations to meet the patient's changing needs. The patient with a severe form of autonomic neuropathy may encounter a wide range of both personal and social difficulties that may include psychosocial problems that necessitate a multidisciplinary approach, including social work, psychological therapy, and physical therapy.

Cerebrovascular Disorders

The treatment of recurrent syncope in cerebrovascular disease is predicated on an accurate diagnosis. In this regard, it is essential to segregate the potential contribution of cardiac and vascular factors and their interplay. Anticoagulants and/or platelet antiaggregant agents are recommended for the prevention of embolic disease from the heart or central vessels. Endarterectomy or percutaneous dilatation should be considered in carotid arterial occlusive disease.

Cardiovascular Disorders

Obstructive Heart Disease Cardiac surgery is often the treatment of choice for patients with syncope caused by obstructive heart disease. Patients with hypertrophic cardiomyopathy and syncope may respond well to pharmacologic therapy but certain patients may respond to A-V sequential pacing.[172-180] However, in patients with severe obstruction and persistent symptoms, surgery should be considered. High-risk patients with hypertrophic cardiomyopathy benefit from placement of an implantable cardioverter-defibrillator.[181,182] Among all patients with obstructive heart disease and recurrent syncope, the diagnosis of fixed pulmonary hypertension is most difficult to treat because effective therapeutic options are limited (see Chap. 74).

Arrhythmic Syncope Detailed discussions of therapy for cardiac arrhythmias are presented in Chapters 78 to 92 of this book. General principles of arrhythmia management as they apply to patients with syncope are summarized here. Treatment of arrhythmic syncope requires accurate definition of the arrhythmia associated with syncope or presyncope.

The bradycardic rhythm disturbances responsible for syncope, primarily AV and sinoatrial pauses or exit block, usually require the implantation of a permanent pacemaker. However, patients who are receiving drugs that cause or contribute to the bradyarrhythmia may benefit from withdrawal or substitution of the offending agent. Patients with bradycardia-tachycardia syndrome usually require pacemaker therapy, because the antiarrhythmic agents required for control of the tachycardia often further suppress sinoatrial function. A select group of patients with symptomatic sick sinus syndrome may benefit from oral theophylline.[183]

Implicit in the approach to the tachycardias causing syncope is the accurate diagnosis of a specific tachycardia. The definition of the tachycardia and the response to antiarrhythmic therapy are often achieved best in the electrophysiologic laboratory. Patients with syncope caused by supraventricular tachycardia associated with an atrioventricular accessory pathway are most often treated with catheter ablation.[184,185] Catheter ablation is also a successful mode of therapy in patients with AV nodal reentry supraventricular tachycardia, atrial flutter, and some atrial tachycardias (see Chap. 88).

Implantable cardioverter-defibrillators (ICDs) are the first-line therapy for ventricular tachycardia in the setting of structural heart disease. It is important to recognize that some patients may continue to experience presyncope or even syncope if cerebral hypoperfusion occurs before the ICD terminates the arrhythmia. Some patients may require additional antiarrhythmic drugs to reduce the frequency of shocks from the ICD. Ventricular tachycardia ablation may be palliative for ventricular tachycardia, which requires frequent ICD shocks. Catheter ablation may be effective also for right ventricular outflow tract tachycardia, bundle-branch reentrant tachycardia, fascicular tachycardias, and idiopathic left ventricular tachycardia.

In patients with polymorphic ventricular tachycardia in the setting of a long QT interval (torsade de pointes), the potential offending drug(s) (usually an antiarrhythmic drug) should be stopped. Acute therapy includes intravenous magnesium and measures to increase the heart rate and shorten electrical diastole (ie, cardiac pacing). Long-term therapy for congenital long QT syndrome may include β-blockers, permanent pacing, an implantable defibrillator, and lifestyle changes.

Pacemaker-induced hypotension and syncope are rectified by changing from ventricular pacing to AV sequential pacing when hypotension is a result of loss of atrial transport or neurocardiogenic response is responsible for symptoms. Pacemaker-mediated tachycardia can usually be corrected by reprogramming the pacemaker. Pacemaker malfunction or myopotential inhibition requires a change in programming or replacing the defective system component.

Patients who are known to have a normal heart and for whom the history strongly suggests vasovagal or situational syncope may be treated as outpatients if the episodes are neither frequent nor severe. Patients with syncope should be hospitalized with continuous electrocardiographic monitoring if there is a reasonable likelihood that the episode resulted from a life-threatening abnormality or if recurrence with significant injury seems likely. In the Syncope Evaluation in the Emergency Department Study (SEEDS), a syncope unit in the emergency room reduced hospital admission and total length of hospital stay without affecting recurrent syncope or mortality.[186]

Syncope of Unknown Cause

Treatment of syncope can be particularly challenging when the cause is unknown. Often, treatment must be targeted to the most likely cause and to prolong life. This is particularly true for patients in whom an arrhythmia is the likely (but undocumented) cause of syncope. Certain patients who are at high risk for sudden cardiac arrest may benefit from an implantable cardioverter-defibrillator even when it is not clear that a ventricular arrhythmia caused syncope. Patients with certain cardiac conduction abnormalities may benefit from a permanent pacemaker.

CONCLUSIONS

Syncope, transient loss of consciousness and postural tone as a result of decreased cerebral blood flow with spontaneous recovery, is common and can occur as a result of a number of underlying mechanisms and disorders, some of which may be normal or benign and do not require therapy (a single episode of neurocardiogenic syncope), and others that are life-threatening and require intervention (eg, ventricular

arrhythmias, aortic stenosis). Identifying the cause for syncope is important for establishing a prognosis and to guide therapy. In addition, syncope must be distinguished from other causes of loss of consciousness (eg, seizures, trauma, metabolic abnormalities, certain drugs). Syncope can be classified as cardiac, noncardiac, unknown origin, or multifactorial. The history, physical examination, and certain tests can be used to identify the likely cause and guide therapy in many cases. Yet in many cases, the cause may remain obscure, more than one explanation may exist, or syncope may have occurred as a result of more than one process. In these cases, clinical judgement and assessment of the risks and benefits of therapies are required for effective management.

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CHAPTER 91

SUDDEN CARDIAC DEATH

Jonathan W. Waks and Mark E. Josephson

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DEFINITION OF SUDDEN CARDIAC DEATH

Sudden cardiac death (SCD) describes an unexpected natural death resulting from a cardiac cause within a short time period after the onset of symptoms in a person without a prior condition that would appear imminently fatal. It is most often caused by a sustained ventricular tachyarrhythmia (ventricular tachycardia [VT] and ventricular fibrillation [VF]). Although many cardiovascular disorders increase the risk of SCD, the presence of preexisting cardiovascular disease is not necessary, and SCD may be the first manifestation of overt cardiac disease.[1,2] Prodromal symptoms, such as palpitations, chest pain, or dyspnea, may suggest a cardiovascular etiology such as arrhythmia, ischemia, or congestive heart failure, but are not specific.

The definition of SCD includes the time interval between onset of symptoms and death, the unexpected nature of the event, and the specific cause of death which, unfortunately, can be difficult to verify in all cases. Recent definitions have focused on time intervals between symptom onset and death of 1 hour or less, which normally identify populations having a 90% or more proportion of arrhythmic death.[3,4] However, because 80% of sudden deaths occur in the home environment and up to 40% are unwitnessed, the interval between symptom onset and death, and the cardiac rhythm that precipitated onset of symptoms, are frequently unknown. Therefore, precise measurement of SCD rates is difficult.[5,6] For this reason, in some studies, time intervals of up to 24 hours have been used to allow capture of events in persons that were unexpectedly found dead but who were alive and well during the prior day [6,7]

EPIDEMIOLOGY

INCIDENCE

SCD accounts for between 180,000 and over 450,000 deaths yearly in the United States, with exact numbers depending on the data source and SCD definition used.[1,8,9] When the definition of SCD is restricted to deaths less than 2 hours from onset of symptoms, 12% of all natural deaths are sudden and 88% of these are a result of cardiac disease. In autopsy-based studies, a cardiac etiology of sudden death has been reported in 60% to 70% of sudden death victims.[5] More recent data from the United States, Europe, and Asia have demonstrated an incidence of approximately 40 to 100 SCDs per 100,000 persons,[6,7,10-13] with significant geographical variation (Fig. 91–1). The majority of cardiac arrest victims are male, and the average age is > 60 years.[6,7,14]

In the United States, several population-based studies have documented an age-adjusted decline in SCD rates of more than 8% over the last 15 years.[1] SCD rates in other developed countries are comparable to those in the United States: The World Health Organization reported an annual incidence of SCD of 1.9 per 1,000 persons in men and 0.6 per 1,000 persons in women.[15] SCD rates in developing countries are considerably lower, paralleling the rates of ischemic heart disease, the most common substrate for SCD in developed nations. Population-based studies evaluating SCD incidence and risk factors in developing nations are ongoing.[16]

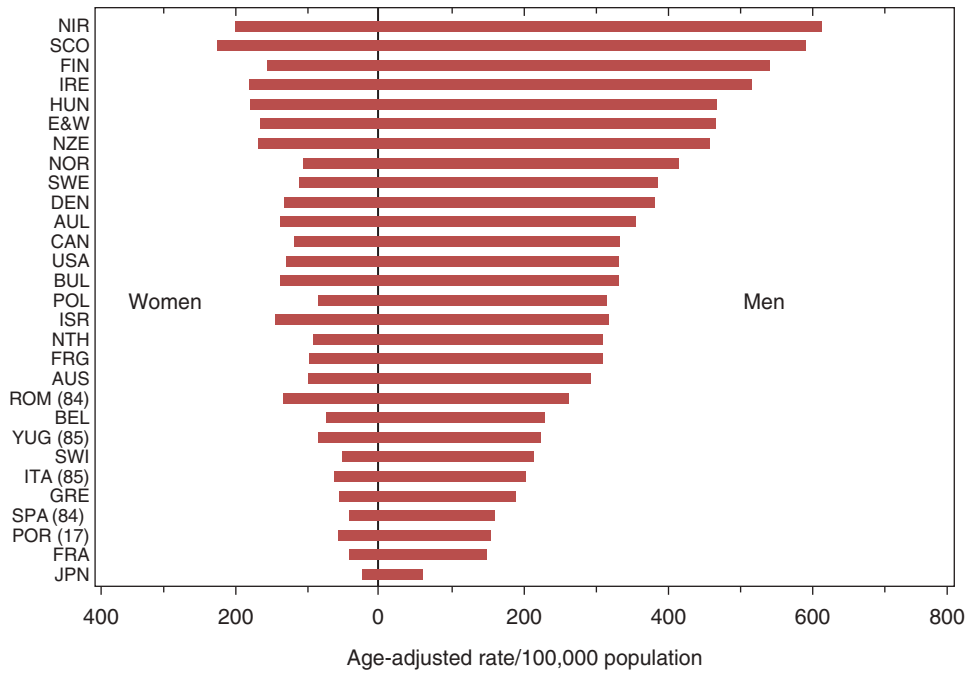

FIGURE 91–1. Sudden cardiac death (SCD) rates by sex and country, ages 35 to 74 years, compiled from death certificates by the World Health Organization, Geneva, 1986. Reproduced with permission from Manolio TA, Furberg CD. Epidemiology of SCD. In: Akhtar M, Myerburg RJ, Ruskin JN, eds. *SCD*. Baltimore, MD: Williams & Wilkins; 1994.

INFLUENCE OF AGE, RACE, AND SEX

Age

The incidence of SCD increases along with the prevalence of ischemic heart disease at older ages (Fig. 91–2).[1,17] This trend is independent of gender or race. Among sudden natural deaths, the proportion with cardiac causes also increases with advancing age. Among patients with coronary heart disease (CHD), however, the proportion of cardiac deaths that are sudden decreases from more than 74% of deaths in those aged 35 to 44 years to < 60% of those aged 75 to 84 years.[1,17] SCD accounts for approximately 20% of all sudden deaths in patients younger than age 20.[18] Structural cardiac abnormalities can be identified in the majority of young victims of SCD[19]; however, autopsy-based studies suggest that 20% to 35% of sudden deaths in young adults occur in the absence of identifiable structural abnormalities.[20,21] Many of these deaths are likely caused by genetically based arrhythmogenic disorders. These topics are discussed in further detail later (also see Chap. 80).

Racial Differences

The annual incidence of SCD has been shown to be higher in African Americans than whites in numerous studies.[1,22-24] An analysis of cardiac death rates in the United States between 1989 and 1998 showed that the age-adjusted rates of SCD per 1,000 persons were 5.0 for black men, 4.1 for white men, and 2.1 for Asian men. Similar trends have been observed in women of various races.[1] Hispanic men and women tend to have lower rates of SCD overall.[1] Likewise, in a analysis of sudden deaths in young female military recruits, African American women were found to have a risk ratio of 10.2 compared with other races.[25] In the Oregon Sudden Unexpected Death Study, African American men and women had an approximately twofold increase in age-adjusted SCD incidence.[23]

The reasons for these observed racial variations in SCD incidence are unclear, but they may be partially because of variations in SCD risk factors.

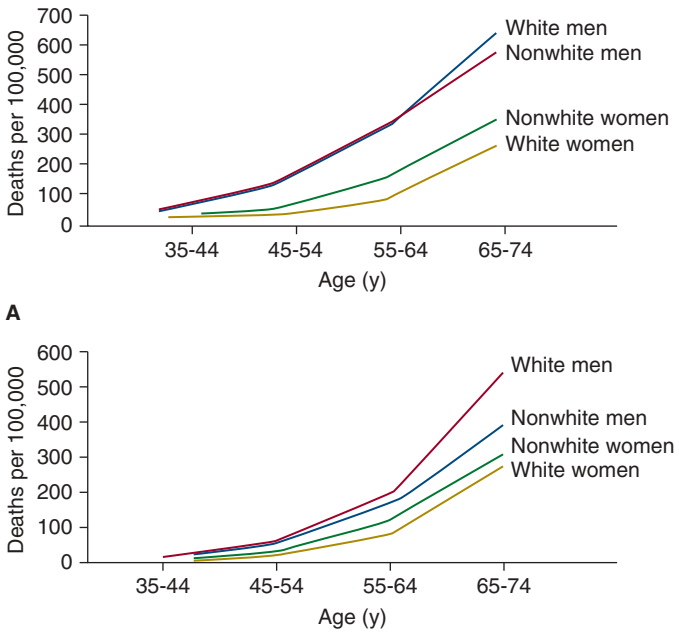

FIGURE 91–2. Plots of mortality rates (deaths per 100,000 persons) for ischemic heart disease occurring (**A**) out of hospital or in an emergency department (an estimate for sudden cardiac death rate) and (**B**) occurring in the hospital, by age, sex, and race in 40 states during 1985. From the National Center for Health Statistics. Reproduced with permission from Gillum RF. Sudden coronary death in the United States: 1980-1985. *Circulation*. 1989 Apr;79(4):756-765.

Postmortem studies show that differences in rates of sudden death may be the result of an increased prevalence of hypertension, left ventricular hypertrophy, diabetes, and tobacco use.[26] Other factors that must be considered include limitations in access to preventive care,[27] prehospital delays in patient activation of emergency medical services,

and disparities in health system quality that disproportionately affect minorities.[28] These issues warrant further investigation.

Gender

Age-adjusted SCD rates are significantly higher in men than in women, reflecting sex-related differences in the incidence of CHD, although men continue to have higher rates of SCD even after correcting for CHD.[1,17] As is the case with coronary artery disease (CAD), however, this gender disparity decreases with advancing age, with a male:female ratio for SCD incidence of 7:1 in 45- to 64-year-olds but only 2:1 in 65- to 74-year-olds. Women are more likely than men (64% vs 50%) to suffer SCD without prior evidence of coronary heart disease.[17] Among survivors of cardiac arrest, women are more likely than men to have structurally normal hearts or forms of structural heart disease other than CAD/infarct-related cardiomyopathy (including valvular heart disease, and nonischemic dilated cardiomyopathy)[29] (Fig. 91–3).

SCDs in women are more likely to occur outside the hospital than in men, and the aforementioned decline in sudden death rates has been noted to be smaller in women (6%) than men (12%). In fact, the rate of sudden death has actually increased by 21% in women aged 35 to 44 years. The reasons for these findings are myriad and may include less aggressive treatment for cardiac conditions,[27,30] patients' lack of awareness of the importance of cardiovascular signs and symptoms, and the greater likelihood of atypical cardiac symptoms in women.

RISK FACTORS FOR SCD

Only a fraction of patients survive a cardiac arrest, and there has been considerable interest in identifying populations at risk for sustained ventricular arrhythmias. More than 80% of SCDs occur in patients with underlying coronary disease. The risk factors for SCD, therefore, largely reflect those for CHD, with hypertension, hypercholesterolemia, smoking, and diabetes appearing as significant risk factors in multiple studies (Table 91–1). The majority of SCDs occur in persons with multiple risk factors (Fig. 91–4).

Despite the fact that studies have shown a strong relationship between risk factors for CHD and SCD, no clear modifiable risk factors that are specific for SCD have been identified once CHD is established.[17,31] Rather, the likelihood of SCD once CHD is established is most strongly related to the degree of cardiac damage, as reflected by structural and electrocardiographic abnormalities, and the severity of clinical heart failure. The inability to determine epidemiologic risk factors specific for SCD reflects the fact that these factors are linked to chronic disease processes that create the structural basis for sustained arrhythmia. These structural abnormalities may be necessary but are not sufficient to cause an episode of SCD, and the events that trigger SCD are probabilistic and unpredictable. In the future, genotypic and other biomarkers may improve the stratification of risk for sudden death. Hemostatic factors,[32,33] inflammatory markers,[34] polymorphisms in cardiac β-receptors,[35,36] and novel electrocardiographic parameters[37] show promise as novel markers of SCD risk.

Lifestyle Factors

Observations suggest that lifestyle factors such as alcohol consumption, cigarette smoking, diet, exercise, and stress are significantly correlated with the risk of sudden death.[17,38,39]

Alcohol Individuals who consume large amounts of alcohol (more than five drinks per day) have increased risks of ventricular arrhythmia and SCD.[40] However, a prospective analysis of 21,537 subjects in the Physicians' Health Study demonstrated a decreased risk of SCD in men who consumed light to moderate amounts of alcohol (two to six drinks per week) compared with those who drank rarely or never.[38]

Cigarette Smoking Cigarette smoking is one of the few coronary risk factors associated with a disproportionate increase in the risk of SCD. In the Framingham Study, the annual incidence of SCD increased from 13 per 1000 persons in nonsmokers to 31 per 1000 persons in those smoking more than 20 cigarettes per day.[41] Smoking has been shown to induce physiologic changes that predispose to SCD, such as increased platelet adhesiveness and catecholamine release, decreased VF threshold, acceleration of heart rate, increased blood pressure, coronary spasm, reduced oxygen-carrying capacity by accumulation of carboxyhemoglobin, and impairment of myoglobin utilization.[41] Those who stop smoking have a prompt reduction in CHD mortality rate irrespective of the duration of previous tobacco use.[42] In addition, recent studies have documented significant reductions in rates of acute myocardial infarction and SCD after the institution of public smoking bans.[43,44]

Diet Diet may also play a role in modifying SCD risk. Omega-3 fatty acids (such as those found in fish) have been shown to have antiarrhythmic properties in experimental animal models,[45] and administration of omega-3 fatty acids has been associated with reduced inducibility for monomorphic VT in patients with CAD undergoing ICD implantation.[46] In a substudy of the Physicians' Health Study, increased levels of omega-3 fatty acids were associated with reduced risk of SCD,[47] and men who consumed fish at least once per week also

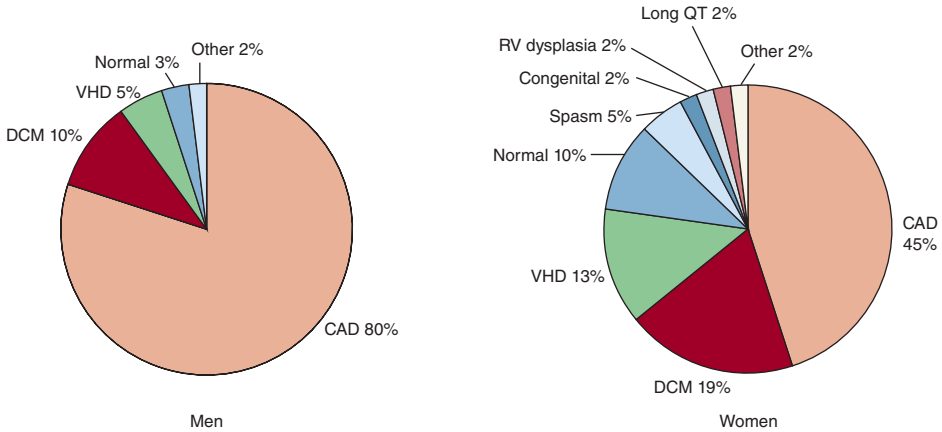

FIGURE 91–3. Proportion of underlying structural heart disease in male and female survivors of cardiac arrest. CAD, coronary artery disease; DCM, dilated cardiomyopathy; RV, right ventricular; VHD, valvular heart disease. Reproduced with permission from Albert, CM et al. Sex differences in cardiac arrest survivors. *Circulation*. 1996 Mar 15;93(6):1170-1176.

TABLE 91–1. Age-Adjusted Risk Factors for Sudden Cardiac Death in Population-Based Studies

Study	Study Population	Risk Factors for SCD
Kannel et al[17,394] (Framingham study)	5128 men and women, age 30-62, no CHD at entry: 546 CHD deaths over 26 y, 46% (men) and 35% (women) SCD	Men LVH (by ECG) Cholesterol Systolic blood pressure Relative body weight Cigarette smoking Women Vital capacity Cholesterol Serum glucose
Hinkle et al[31]	269,755 men, age 20-65: 1839 CHD deaths over 5 y, 60% SCD	Hypertension Cigarette smoking Alcohol History of CHD LVH (by ECG) Enlarged heart (CXR) CHF PVCs
Wannamethee et al[395]	7735 British men, age 40-59: 488 CHD events, 117 SCD over 8 y	History of CHD Physical inactivity Systolic blood pressure Cholesterol Cigarette smoking Arrhythmia Resting heart rate > 90 Alcohol Diabetes mellitus
Albert et al[396]	121,701 women age 30-55: 1110 CV deaths, 244 SCD over 12 y	Hypertension Cigarette smoking Family history CHD Obesity

Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; CXR, chest x-ray; LVH, left ventricular hypertrophy; PVCs, premature ventricular complexes; SCD, sudden cardiac death.

had a significant reduction in SCD risk. Fish intake and omega-3 fatty acid levels had no association with myocardial infarction or total cardiovascular mortality.[48] Frequent consumption of fish was also associated with a reduction in arrhythmic death in the Cardiovascular Health Study[49] and other population-based studies.[50]

Despite these favorable observational data, randomized trials evaluating the benefit of omega-3 fatty acid supplementation on SCD risk have demonstrated mixed results. In the GISSI-Prevenzione trial, survivors of recent MI who were randomized to 1 gram of omeaga-3 fatty acid daily had a 45% reduction in sudden death risk.[51] The Alpha-Omega trial[52] and OMEGA[53] trials evaluating the effect of dietary supplementation of omega-3 fatty acids in survivors of MI, and the JELIS trial evaluating efficacy of dietary supplementation of omega-3 fatty acids in Japanese participants with hypercholesterolemia,[54] however, failed to demonstrate a reduction in ventricular-arrhythmic events or SCD. In patients with ICDs, fish oil supplementation had no effect on time to first implantable cardioverter-defibrillator (ICD) therapy for VT/VF,[55,56] and may have actually contributed to increased rates of recurrent VT/VF in some patients.[56]

Stress There are many reports linking stress, particularly emotional stress, to SCD. Patients experiencing intense anger tend to have higher rates of ICD discharges,[39] and an estimated sevenfold greater relative risk of appropriate ICD discharge occurs during mental and physical stress.[57] ICD discharge rates in New York City remained elevated for up to 30 days after the 2001 terrorist attack.[58]

Physical Activity There is increasing evidence that regular physical activity may help prevent CHD and its complications, although the benefits of vigorous exercise in patients with known CHD is controversial. Several clinical and autopsy-based studies have reported exercise as a trigger for SCD.[59,60] Emergency medical records have shown that 11% to 17% of adults with CHD and SCD collapse during or immediately after exertion, but the amount of exertion is rarely quantified.[61] Cardiac arrest rates of 1 per 12,000 to 15,000 persons in cardiac rehabilitation programs and 1 per 2,000 persons during cardiac stress testing have been reported.[62] These rates are at least six times higher than those for patients not known to have heart disease.[61]

Although the absolute risk of sudden death during any particular episode of vigorous exertion is low (1 sudden death per 1.51 million episodes of exertion), the Physicians' Health Study estimated that the risk of sudden death increases more than 16-fold in the first 30 minutes of vigorous activity.[59] Nevertheless, there is ample experimental evidence that regular exercise may prevent ischemia-induced VF and death,[63] and habitual vigorous exercise attenuates the relative risk of sudden death associated with vigorous exertion.[59] It therefore appears that regular participation in moderate-intensity physical activity is associated with reduced rates of cardiovascular morbidity and mortality, but the risks of SCD and myocardial infarction are transiently increased during acute bouts of high-intensity activity.

SCD in competitive athletes is rare (see Chap. 64). Unfortunately, SCD is often the first manifestation of the underlying cardiac disease that is present in the majority of these patients.[64] Age has been shown to be the most useful variable in predicting the type of underlying cardiac disease in athletes with SCD (Fig. 91–5). In athletes younger than 35 years of age, the majority of SCDs arise from a variety of congenital cardiovascular diseases, most commonly hypertrophic cardiomyopathy and congenital coronary artery anomalies.[65] Less common structural conditions include myocarditis, aortic dissection (eg, related to Marfan syndrome), aortic stenosis, dilated cardiomyopathy, and arrhythmias associated with mitral valve prolapse. Other disorders such as arrhythmogenic right ventricular cardiomyopathy (ARVC) may be more frequent in endemic areas.[66] SCD among young athletes without structurally identifiable cardiac abnormalities is historically thought to be rare,[64] but was more recently found to be much more common among young active-duty military members.[20] These cases are likely to be related to inherited arrhythmia disorders such as long QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, and others (see Chap. 80 and the discussion below). Obstructive coronary artery disease is an uncommon cause of SCD in athletes younger than 35 years.[67]

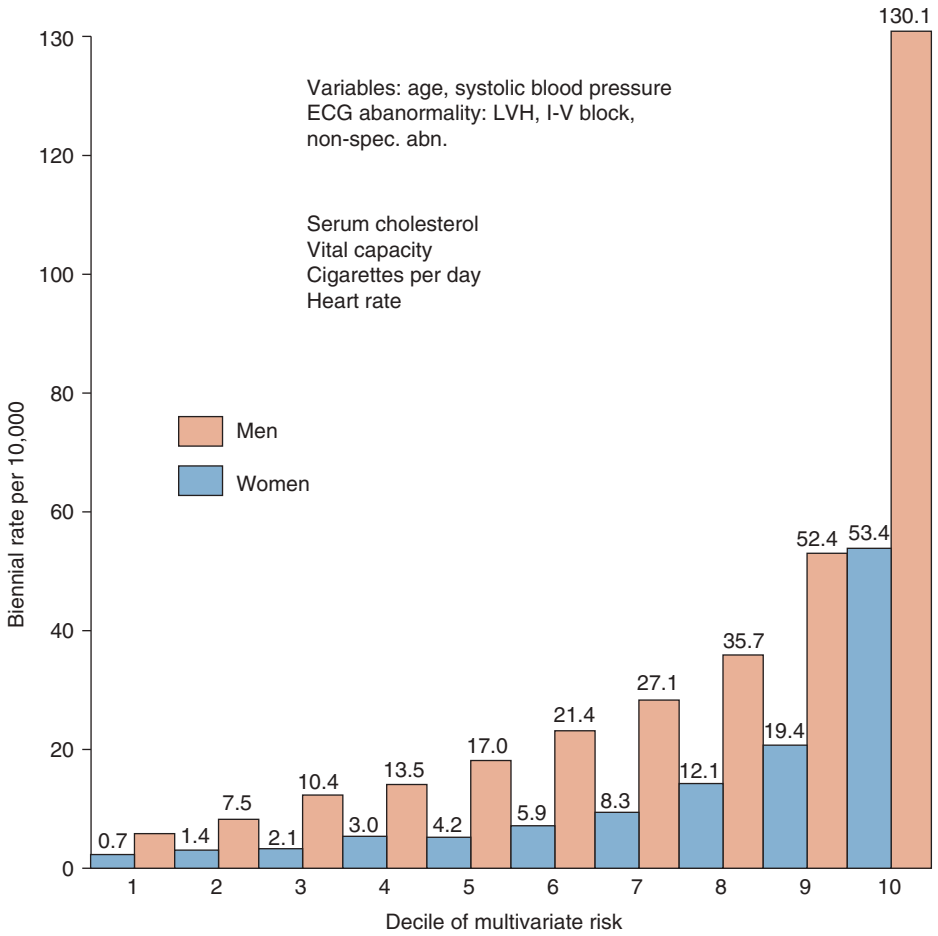

FIGURE 91–4. Risk of sudden cardiac death by decile of multivariate risk: 26-year follow-up from the Framingham Study. ECG, electrocardiographic; I-V, intraventricular; LVH, left ventricular hypertrophy; non-spec. abn., nonspecific abnormality. Reproduced with permission from Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. *J Am Coll Cardiol*. 1985 Jun;5(6 Suppl):141B-149B.

Because of the dramatic and often public nature of SCD in athletes and the medical-legal climate, the need for extensive preparticipation screening of athletes for cardiac conditions has been debated. US guidelines for such screening have been published and they focus on detailed personal and family history and physical examination.[68] A long-standing screening program in Italy has credited the use of routine electrocardiography with identifying cardiomyopathies and significantly reducing the rate of SCD during athletic activities,[69,70] but the necessity of routine electrocardiography has been questioned.[71] US and European guidelines have also been published outlining which

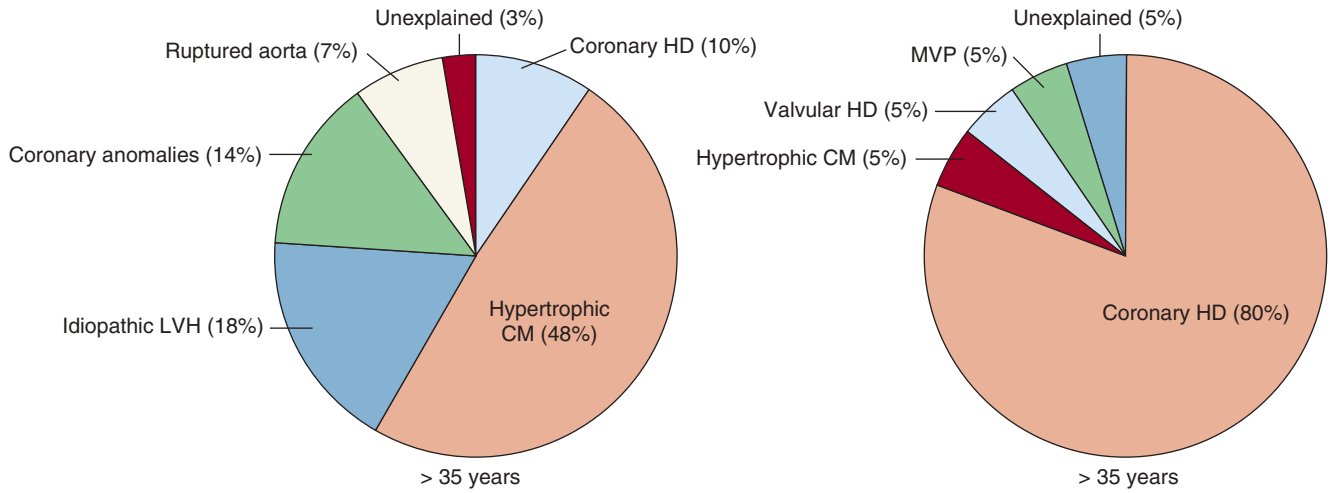

FIGURE 91–5. Causes of sudden cardiac death in competitive athletes by age group. There is evidence for structural heart disease in nearly all athletes who die suddenly of cardiac causes. In athletes younger than 35 years, hypertrophic cardiomyopathy is more prevalent, whereas in those older than 35 years, coronary heart disease is the most frequent cause. CM, cardiomyopathy; HD, heart disease; LVH, left ventricular hypertrophy; MVP, mitral valve prolapse. Reproduced with permission from Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. *J Am Coll Cardiol*. 1986 Jan;7(1):204-214.

athletes with cardiac arrhythmias can participate in competitive athletics[72-74] (see Chap. 64).

Blunt, nonpenetrating, and usually innocent-appearing chest blows leading to ventricular arrhythmia and sudden death have also been reported as causes of SCD in young persons.[75] Termed *commotio cordis,* these events often occur during organized sports but also occur in other settings. Most deaths occur with low energy and velocity projectiles striking the chest.

MECHANISMS OF SCD

RELATIONSHIP BETWEEN STRUCTURE AND FUNCTION IN SCD

The vast majority of patients who have experienced SCD have cardiac structural abnormalities. In the adult population, these consist predominantly of CHD, cardiomyopathies, valvular heart disease, and abnormalities of the conduction system. These structural changes provide the substrate for ventricular tachyarrhythmias, the cause of SCD in most cases. It is important to recognize the role of triggering factors such as ischemia, hemodynamic changes, fluctuations in the autonomic nervous system, electrolyte abnormalities, and proarrhythmic effects of drugs in the initiation of ventricular arrhythmias resulting in SCD (Fig. 91–6).[76,77] Strategies aimed at eliminating or reducing the triggers of arrhythmias may prove to be effective short- and midterm solutions at reducing the risk of SCD because most structural abnormalities, once present, usually cannot be reversed.

TACHYARRHYTHMIAS AND BRADYARRHYTHMIAS IN SCD

As the majority of patients who experience SCD do not have cardiac rhythm monitoring at the time of their event, it is frequently difficult to determine the cardiac rhythm that initiated SCD. Ventricular fibrillation is the first recorded rhythm in approximately 75% of patients who have cardiac arrest.[78] Sustained VT is only rarely (< 2%) documented as the initial rhythm, but it is unknown how often it precedes and precipitates ventricular fibrillation. In a series of 157 ambulatory patients who were wearing an ECG monitor at the time of their cardiac arrest, primary VF was documented in 8%, VT degenerating into VF in 63%, and torsade de pointes in 13%.[79] Similarly, in patients with ICDs, 90% of appropriate arrhythmia detections are for VT rather than VF.[80]

Electromechanical dissociation and asystole are found in approximately 30% of patients experiencing cardiac arrest, and this finding is usually related to the time interval from collapse to first monitoring of the rhythm, suggesting that it is often a later manifestation of cardiac arrest.[78] The incidence of bradycardia as the first documented rhythm varies according to the population studied. In patients who have died suddenly while wearing an ambulatory ECG monitor, bradyarrhythmias as the initial rhythm were documented infrequently, and ventricular tachyarrhythmias were most often the mode of cardiac arrest, even in patients with preexisting atrioventricular or intraventricular conduction defects.[79] In a small group of patients with severe congestive heart failure awaiting cardiac transplant, bradycardia or electromechanical dissociation at the time of death was more frequent than ventricular tachyarrhythmia.[81] In this population, bradycardia likely reflects the unrelenting failure of the severely impaired heart and is not a primary cause of sudden death unless the bradyarrhythmia allows for the development of a tachyarrhythmia. An understanding of the mechanisms responsible for ventricular arrhythmia is essential in its prevention and treatment (see Chaps. 79 and 85).

ELECTROPHYSIOLOGIC EFFECTS OF ISCHEMIA

Acute myocardial ischemia leads to intracellular and extracellular acidosis and loss of myocellular membrane integrity with efflux of potassium and influx of calcium. These biochemical abnormalities have electrophysiological consequences, including decreases in the amplitude and upstroke velocity of the cardiac action potential, inhomogeneous depolarization of the resting membrane potential, and shortening of action potential duration.[82] Fast sodium and slow calcium channels in partially depolarized fibers may remain inactive, thereby prolonging refractoriness even after completion of repolarization. This may further contribute to electrical inhomogeneities within and around the ischemic zone, causing conduction delays, unidirectional block, and reentrant arrhythmias.[83]

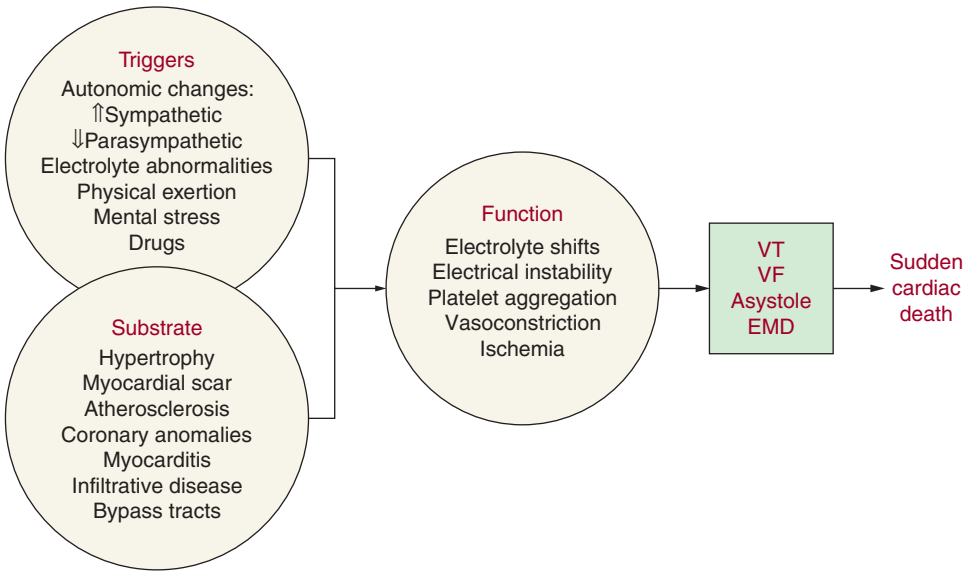

FIGURE 91–6. Interaction between structural cardiac abnormalities, functional changes, and triggering factors in the pathophysiology of sudden cardiac death. The role of triggering factors, such as changes in autonomic tone or reflexes, is increasingly being recognized. EMD, electromechanical dissociation; VF, ventricular fibrillation; VT, ventricular tachycardia.

Ventricular arrhythmias during experimental coronary occlusion occur in two peaks. The first peak in arrhythmogenesis occurs between 2 and 8 minutes (phase IA) and the second at 15 to 45 minutes (phase IB) after coronary occlusion. Rapid polymorphic VT and VF are the characteristic arrhythmias during the early stages of ischemia.[84] Activation mapping during VF has demonstrated that the initial arrhythmias result from reentry, which is facilitated by the inhomogeneous conduction velocities and refractory periods in and around the ischemic zone. The second peak of ventricular arrhythmias coincides with a peak in catecholamine release. Automatic and triggered rhythms have been implicated in these arrhythmias. Reentrant rhythms, attributed to cellular uncoupling related to impaired function of gap junctions, may also occur.[85]

Within the first 3 days of myocardial infarction, SCD may occur as a result of VF initiated by frequent, early, premature ventricular complexes (PVCs). Such PVCs have been shown in experimental models to be predominantly the result of impulse formation consistent with abnormal automaticity. Other manifestations of abnormal automaticity are accelerated idioventricular rhythms associated with reperfusion. These arrhythmias appear to arise, for the most part, from surviving Purkinje fibers in the subendocardial border zone of a transmural infarction. They have no prognostic significance for development of late arrhythmias and usually subside after 2 to 3 days at approximately the same time that the resting membrane potential and action potential duration of Purkinje fibers normalize.[82]

In the late phases after MI, when the infarction is healed, reentrant excitation is the principal mechanism of ventricular arrhythmias. Critical areas of the reentrant circuit are formed by surviving myocardial cells in the epicardial and endocardial border zone of a healed infarction, as well as surviving intramural fibers within the infarct zone.[86] It appears that the rate, time, and degree of myocardial reperfusion influence the incidence, rate, and duration of these arrhythmias. More work is needed to further define these relationships (see Chap. 79).

MECHANOELECTRICAL FEEDBACK

Although it is an imperfect marker of SCD risk, left ventricular dysfunction has been identified as the strongest independent predictor of SCD.[87] Despite the clinical recognition that acute heart failure can precipitate ventricular tachyarrhythmias, the mechanism by which this occurs is incompletely understood. Besides mechanisms related to acute and chronic ischemia, it has been shown that acute changes in the mechanical state of the heart related to altered preload and contractility can have direct electrophysiologic effects that may precipitate arrhythmias; this relationship is referred to as mechanoelectrical feedback. Myocardial stretch has been implicated in arrhythmogenesis in animal models,[88,89] and increased right ventricular pressure has been shown to shorten action potential duration in humans.[90] An increase in both left ventricular preload and contractility has been shown to shorten action potential duration and refractoriness in the canine ventricle as well, and there is some evidence that these changes may be mediated through the β-adrenergic receptor.[91] Downstream effects leading to fluctuation of intracellular calcium levels or to an increase in cyclic AMP-mediated potassium current may serve as the cellular mechanism by which this phenomenon occurs.[91]

Mechanistic evidence has also pointed to calcium handling in the sarcoplasmic reticulum, mediated by defective regulation of the cardiac ryanodine receptor.[92] Levels of B-type natriuretic peptide (BNP) have also been associated with SCD in patients with heart failure,[93,94] but whether BNP is involved in the causal pathway of arrhythmogenesis or if it is simply a marker for increased mechanical stress or more advanced heart failure is unclear and will require further prospective evaluation.

CARDIAC DISEASES ASSOCIATED WITH SCD

Table 91–2 summarizes cardiac abnormalities associated with sudden death.

ISCHEMIC HEART DISEASE

Coronary Atherosclerosis

In survivors of cardiac arrest, CHD is present in 40% to 86% of patients, depending on the age and sex of the population being evaluated.[95] Patients with known CHD accounted for 20% to 34% of SCDs in the Framingham cohort, and SCD was the first symptom of CHD in approximately 10% of all coronary events.[17]

Although many who suffer SCD have severe multivessel CAD, fewer than half of the patients resuscitated from SCD evolve evidence of significant myocardial infarction as determined by elevated cardiac biomarkers, and less than 20% of these patients have transmural myocardial infarction.[78] Holter monitoring at the time of cardiac arrest has infrequently shown evidence of ischemic ECG changes prior to the event.[76,96]

In catheterization studies, although approximately 70% of patients with SCD had significant CAD (defined as at least one stenosis > 50%), only 37% to 48% of patients had angiographic evidence of an acute coronary syndrome with either acute vessel occlusion or evidence of ruptured plaque. In these patients with acute coronary syndrome, revascularization had had mixed effects on survival.[95,97] Detailed pathologic studies have confirmed the presence of acute coronary arterial lesions (plaque fissure, plaque hemorrhage, and thrombosis) in up to 95% of patients dying suddenly, but only about half had total occlusion of a coronary artery.[98,99]

Coronary collateralization may play an important role in the presentation of coronary artery disease as SCD. It has been hypothesized that chronic ischemia may be a stimulus for development of coronary collaterals, which in turn could have a protective effect during acute coronary occlusion. The mitigating effect of coronary collateralization is supported by a study of exercise testing in 894 healthy men followed up for a mean of 12.7 years. In this study, the initial coronary event was acute myocardial infarction or SCD in 73% of those with a normal stress test result, as opposed to 20% of those with an abnormal result.[100] These findings might also be related to ischemic preconditioning, which is associated with reductions in VF in animal models.[101]

Nonatherosclerotic Disease of the Coronary Arteries

Several nonatherosclerotic diseases of the coronary arteries are associated with increased risk of SCD precipitated by cardiac ischemia. Congenital coronary artery anomalies, found in approximately 1% of all patients undergoing angiography and in 0.3% of patients at autopsy, have been associated with SCD. These SCDs are often exercise-related, and are present in up to approximately 17% of competitive athletes with confirmed cardiovascular sudden death.[65] Origin of the left main coronary artery from the right aortic sinus, or origin of the right coronary artery from the left coronary sinus, are the variants most frequently associated with SCD.[102] Percutaneous stenting or surgical reimplantation of these anomalous coronary arteries may reduce the risk of SCD.[103]

Life-threatening ventricular arrhythmias and SCD have been described in patients with coronary artery spasm (Prinzmetal or variant angina). Significant arrhythmias during attacks of vasospasm have been documented in these patients.[104] Calcium channel blockers are effective in many patients in preventing coronary spasm and also

TABLE 91–2. Cardiac Abnormalities Associated With Sudden Cardiac Death

Ischemic heart disease
Coronary atherosclerosis
Acute myocardial infarction
Chronic ischemic cardiomyopathy
Anomalous origin of coronary arteries
Hypoplastic coronary artery
Nonischemic heart disease
Cardiomyopathies
Idiopathic dilated cardiomyopathy
Hypertrophic cardiomyopathy
Hypertensive cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Left ventricular noncompaction
Infiltrative and inflammatory heart disease
Sarcoidosis
Amyloidosis
Hemochromatosis
Myocarditis
Valvular heart disease
Aortic stenosis
Aortic regurgitation
Mitral valve prolapse
Infective endocarditis
Congenital heart disease
Tetralogy of Fallot
Transposition of the great vessels (post–Mustard-Senning)
Ebstein anomaly
Pulmonary vascular obstructive disease
Congenital aortic stenosis
Primary electrical abnormalities
Long QT syndrome
Short QT syndrome
Wolff-Parkinson-White syndrome
Congenital AV block
Brugada syndrome
Catecholaminergic polymorphic VT
Idiopathic ventricular fibrillation
Early repolarization syndrome
Coronary artery spasm
Coronary artery dissection
Coronary arteritis
Small vessel disease
Drug-induced and other toxic agents[a]
Antiarrhythmic drugs (classes Ia, Ic, and III)
QT prolonging antibiotics (macrolides, fluoroquinolones, pentamidine, azole antifungals, and many others)
QT prolonging pain medications (methadone)
Antihistamines (astemizole, terfenadine)
Psychotropic drugs (tricyclic antidepressants, haloperidol, phenothiazines)
Prokinetic agents (cisapride)
Cocaine
Antimalarial drugs (chloroquine)
Alcohol
Phosphodiesterase inhibitors
Organophosphates
Electrolyte abnormalities
Hypokalemia
Hypomagnesemia
Hypocalcemia
Anorexia nervosa and bulimia
Liquid protein dieting
Diuretics

Abbreviations: AV, atrioventricular; VT, ventricular tachycardia.

[a] The drug classes and/or individual drugs listed here are not inclusive of all drugs that have been associated with sudden cardiac death.

appear to protect from malignant ventricular arrhythmias if the attacks can be completely abolished. Predictors of major coronary events in this population include systemic hypertension, luminal irregularities on coronary arteriography, and QT dispersion.[104]

SCD has been described as a rare complication of coronary artery dissection in Marfan syndrome, during the puerperium, secondary to trauma or coronary catheterization, as a consequence of syphilitic aortitis, or as an extension of aortic dissection. Myocardial bridges have been reported in association with SCD during exercise, but they are also an incidental finding at autopsy in up to 25% of patients dying of other causes.[105] Coronary arteritis and subsequent infarction have been reported in Kawasaki disease, giant-cell arteritis, Behçet disease, systemic lupus erythematosis, and Churg-Strauss syndrome. Coronary occlusion can also occur as a complication of infective endocarditis, particularly involving the aortic valve (see Chap. 35).

CARDIOMYOPATHIES

Idiopathic/Nonischemic Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy is the substrate for approximately 10% of SCDs in the adult population. The total mortality rate for idiopathic dilated cardiomyopathy is high, reaching 10% to 50% annually, and is most closely tied to the severity of left ventricular dysfunction.[106] Mortality rates are higher among patients with advanced heart failure, but the proportion of sudden to nonsudden cardiac deaths in these patients is not increased.[107] In an overview of 14 studies including 1432 patients with idiopathic dilated cardiomyopathy, the mean mortality rate after a follow-up of 4 years was 42%, with 28% of deaths classified as sudden.[106] SCD in idiopathic dilated cardiomyopathy is usually attributed to both polymorphic and monomorphic ventricular tachyarrhythmias occurring in the setting of a high frequency of complex ventricular ectopy.[108] However, the terminal event may also be caused by pump failure with asystole or electromechanical dissociation, especially in patients with advanced left ventricular dysfunction.[81]

Risk stratification of patients with idiopathic dilated cardiomyopathy is difficult because there are few clinical predictors specific for SCD as opposed to total mortality. The only clinical variable that identifies patients with a higher risk of SCD is unexplained syncope,

and these patients should undergo further electrophysiologic (EP) evaluation. The prognostic value of simple and complex PVCs as well as nonsustained ventricular tachycardia (NSVT) is limited by the extremely high prevalence of these arrhythmias in patients with idiopathic dilated cardiomyopathy.[108] The induction of polymorphic VT or VF during EP testing is also nonspecific, and the probability of inducing sustained monomorphic VT in this population is less than 10%.[109] Therefore, an EP study is not considered a useful screening tool in patients with nonischemic dilated cardiomyopathy. However, when sustained monomorphic VT does occur in patients with nonischemic dilated cardiomyopathy, the mechanism is usually reentry. Although patients with nonischemic cardiomyopathy tend to have more epicardial arrhythmic involvement than patients with infarct related cardiomyopathy, these arrhythmias are still potentially amenable to catheter ablation[110] (see Chaps. 58 and 88).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM), caused by a variety of autosomal dominant mutations in genes encoding cardiac sarcomere proteins, is classically associated with asymmetric septal hypertrophy and myofibrillar disarray,[111,112] but recent evidence has demonstrated that it may have more diverse clinical presentations. More than 1,400 mutations in 11 genes have been implicated in HCM.[113] Historically, approximately 1 in 500 people in the United States are affected. Many affected individuals, however, have a mild phenotype that does not come to clinical attention, and based on modern genetic testing and recent cohort studies, the true incidence may be higher than previously thought.[114] HCM is present in both men and women, and can present at any age.

HCM is one of the most common causes of SCD in young individuals, especially among athletes.[67,115] The incidence of SCD in selected families with HCM treated at large referral centers has been reported as high as 2% to 4% per year in adults and 4% to 6% per year in children and adolescents,[116] but it is probably closer to 1% per year in unselected populations.[111,117]

A number of factors have been studied to aid in distinguishing the minority of HCM patients at high risk for SCD from the majority of patients at much lower risk. The highest-risk features include a clinical history of spontaneous ventricular arrhythmias, sudden death in family members,[116,118] onset of symptoms in childhood,[119] and syncope or near-syncope, especially when exertional or recurrent and unrelated to neurocardiogenic mechanisms.[120] Other risk factors with a lower predictive value include extreme left ventricular wall thickness (≥ 3.0 cm),[121] hypotensive response to exercise,[122] and significant (≥ 30 mm Hg) resting left ventricular outflow tract gradient, although a significant outflow tract gradient without any other risk factors was associated with a low overall risk.[123] The importance of NSVT during ambulatory monitoring (particularly repetitive or prolonged bursts) is unclear. Although early studies found an association between NSVT and SCD,[124] NSVT and PVCs are quite common in patients with HCM, and other studies have found that nonsustained ventricular arrhythmias/ectopy is associated with a low positive predictive value and a high negative predictive value for SCD.[125] The SCD risk associated with NSVT may be especially increased in younger patients.[126] Late gadolinium enhancement of the left ventricle during cardiac magnetic resonance imaging (MRI) may also have utility in identifying patients at increased risk of SCD.[127]

Although none of these factors have a high positive predictive value when taken alone, patients with multiple risk factors do appear to have a higher risk of SCD[118] and patients without any risk factors have a low incidence of SCD.[111] Current consensus guidelines give a class IIa (level of evidence C) recommendation for ICD implantation in patients with HCM and one or more major risk factors for SCD (defined as prior cardiac arrest, spontaneous sustained VT, NSVT, family history of SCD, high-risk syncope, abnormal blood pressure response to exercise, and left ventricular wall thickness ≥ 3.0 cm),[128] and ICDs appear to be effective at aborting ventricular arrhythmias in these patients.[129]

Because of the clinical heterogeneity of HCM, there is hope that genotypic analysis will provide further guidance on SCD risk. For example, some mutations of the β-myosin heavy chain appear to be associated with a benign prognosis, whereas mutations in cardiac troponin T have been associated with a mild degree of hypertrophy but a high incidence of SCD in selected kindreds.[130,131] As with most genetic disorders, however, the phenotypic expression of the same genetic abnormality is highly variable in HCM, and clinical decisions cannot be reliably made at this time based solely on genotype[132] (see Chaps. 59 and 55).

Hypertensive Cardiomyopathy

Left ventricular hypertrophy (LVH) has been identified as one of the strongest independent risk factors for acute myocardial infarction, congestive heart failure, and sudden death.[133] In the Framingham Study, ECG evidence of LVH was associated with an eightfold increased risk of SCD.[134] Echocardiographic studies have demonstrated a relative risk for cardiovascular death of 1.7 in men and 2.1 in women for each 50-g increment in the left ventricular mass index.[135] Decreased coronary blood flow, decreased flow reserve, and endothelial dysfunction may all be factors favoring the development of transient ischemia in the setting of LVH, and long-term, repeated transient ischemic episodes can lead to interstitial fibrosis, which may underlie the arrhythmias in this population.[136] Other potential contributing factors to the increased risk of SCD in hypertensive cardiomyopathy are electrolyte disturbances associated with diuretic therapy.[137]

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fatty or fibrofatty replacement of myocardium, primarily in the right ventricle, and ventricular tachyarrhythmias, usually of right ventricular origin.[138] It has been recognized, however, that the left ventricle can also be involved.[139] It is a rare cause of SCD except in a few endemic regions and is a familial disorder in approximately 30% to 50% of cases.[140]

Multiple genetic mutations have now been reported as causing ARVC. The first reported mutation involved the cardiac ryanodine receptor (*RyR2*), the major calcium release channel on the sarcoplasmic reticulum in cardiomyocytes.[141] More recently, mutations have been reported in genes encoding proteins associated with desmosomes[142] which anchor intermediate filaments to the cell membrane in adjoining cells. An autosomal-recessive mutation of the plakoglobin gene causes Naxos disease, characterized by ARVC and skin and hair abnormalities.[143] Desmosomal proteins are now thought to be involved in approximately half of ARVC cases,[144,145] but mutations of unrelated proteins, including transforming growth factor-β3,[146] have also been reported. Genetic penetrance is variable,[147] and specific mutations may have prognostic importance in terms of disease severity and risk of ventricular arrhythmias.[144]

Recurrent VTs with multiple left bundle branch block morphologies typify ARVC. Patchy myocarditis, programmed cell death, and/or congenital abnormalities of development appear to lead to myocardial atrophy and repair by fibrofatty replacement, which forms the basis for ventricular reentry. The left ventricle and ventricular septum can be

involved, especially later in the course of the disease, and such involvement confers a poor prognosis.[148]

The electrocardiographic manifestations of ARVC in sinus rhythm include T-wave inversion in V_1 to V_3 or complete or incomplete right bundle branch block. Intraventricular conduction delay may produce a terminal notch on the QRS complex of leads V1-V3, called an epsilon wave, in approximately 50% of patients or an abnormal signal-averaged ECG (SAECG). Patients with ARVC often have ventricular ectopy with a left bundle branch pattern, typically with a more leftward axis than the usually benign ectopy that arises in the RV outflow tract.[149,150]

The diagnosis of ARVC is based on consensus guidelines which include noninvasive assessment of RV size and function with echocardiography or cardiac MRI, histopathology (if available), ECG abnormalities (T-wave inversions in the right precordial leads, epsilon waves, and/or an abnormal SAECG), presence of ventricular arrhythmias of appropriate morphology, and family history of ARVC.[149] Immunohistochemical analysis of endomyocardial biopsy specimens revealing diffusely reduced plakoglobin signal at intercalated discs has also been found to be both sensitive and specific for ARVC.[151]

The course and prognosis of ARVC are highly variable and difficult to predict even in patients with overt disease and significant ventricular arrhythmias. ICDs are the primary therapy for prevention of SCD and have been shown to improve survival in patients with sustained VT/VF or as a primary prevention therapy.[152-154] Sustained, tolerated VT can also be treated successfully with catheter ablation,[155] but recurrent VT is common,[156] and because ARVC tends to be a progressive condition, these patients are usually treated with ICDs as well. More data are required to define which asymptomatic patients with ARVC benefit from ICD implantation or catheter ablation (see Chap. 55).

VALVULAR HEART DISEASE

Aortic Valve Disease

The risk of SCD in asymptomatic patients with aortic stenosis or regurgitation appears to be low.[157,158] In contrast, there appears to be an increased risk of SCD after aortic valve replacement for aortic stenosis or regurgitation. In 831 patients receiving a Bjork-Shiley prosthesis in the aortic (341 patients), mitral (345 patients), or double-valve (145 patients) position, the incidence of SCD in the subgroups was 1.8%, 3.5%, and 4%, respectively, over a follow-up period of 7 years.[159] Malignant tachyarrhythmias have been suggested as the cause of SCD in such patients. Transient complete heart block is relatively common after both surgical aortic (17.6%) and mitral (13%) valve replacement, pointing to bradyarrhythmias as another potential precipitating factor for SCD[160] (see Chap. 47).

NSVT, severe bradycardia, and heart block are often observed after transcatheter aortic valve replacement (TAVR) as well.[161-163] In a meta-analysis of 11,210 patients undergoing TAVR, 17% of patients required pacemaker implantation after their procedure.[163] In another study of 75 patients with severe aortic stenosis and without prior pacemakers undergoing TAVR, 14.7% of patients developed new AV block during the index hospitalization. Importantly, 4% of patients developed AV block after hospital discharge, when the risks associated with acute development of heart block would be presumed to be significantly higher.[162] Among 3726 patients who underwent TAVR, 5.6% of all deaths during a follow-up period of 22 months were the result of SCD, and reduced LVEF, new onset left bundle branch block, and QRS duration > 160 milliseconds were independent predictors of SCD.[164] In another study of 3934 patients who underwent TAVR, SCD was an infrequent case of death within the first 30 days after the procedure (4% of all deaths), but 11% of deaths after 30 days were SCDs.[165] Better risk stratification tools for both SCD and heart block after TAVR are needed as this procedure becomes more widespread.

Mitral Valve Prolapse

The association between mitral valve prolapse (MVP) and SCD is controversial. The prevalence of MVP is sufficiently high that its presence may just be a coincidental finding in victims of SCD. In a prospective 8-year study of 237 asymptomatic or minimally symptomatic patients with echocardiographically documented MVP, survival was not significantly different from that of a matched control population.[166] On the other hand, MVP may not always be benign. Patients with MVP associated with mitral regurgitation and left ventricular dysfunction clearly carry a risk for such complications as infective endocarditis, cerebroembolic events, and SCD.[167] In a significant number of victims of SCD, especially young women, MVP is the only structural cardiac disease identified.[168] In the Oregon Sudden Unexpected Death Study, 2.3% of patients with SCD had MVP detected on a pre-SCD echocardiogram, although this was a somewhat selected population given that all of these people with MVP and SCD had some indication for an echocardiogram prior to their SCD event.[169]

Several echocardiographic risk factors for SCD have been identified in asymptomatic or mildly symptomatic MVP patients without significant mitral regurgitation, including increased mitral valve annular circumference, thickness of the anterior and posterior mitral valve leaflets, presence and extent of endocardial plaque, and presence or absence of redundant mitral valve leaflets on M-mode echocardiography.[166,170] Late gadolinium enhancement of the papillary muscles and inferobasal left ventricle by cardiac MRI in patients with MVP has been associated with complex ventricular arrhythmias,[171,172] and fibrosis in similar areas has been detected in patients with MVP and without any other structural heart disease who died suddenly.[172] It remains unclear if this fibrosis is directly related to abnormal leaflet motion. The most important prognostic indicators for sudden death in MVP are a history of syncope, and family history of sudden death at a young age, as well as significant mitral regurgitation, abnormal left ventricular function, and a prolonged QT interval[170] Women with significant bileaflet MVP and frequent complex ventricular ectopy may also be at increased risk for SCD[173] (see Chaps. 48 and 49).

INFLAMMATORY AND INFILTRATIVE MYOCARDIAL DISEASE

Any inflammatory disease can cause SCD as a result of either ventricular tachyarrhythmias or complete heart block. Histologic findings suggestive of myocarditis have been reported in 10% to 44% of young victims of SCD.[174] In adults, the diagnosis of myocarditis is made much less frequently, perhaps because of concurrent structural heart disease or because the late manifestations of the disease are indistinguishable from idiopathic dilated cardiomyopathy (see Chap. 63). In South America, however, myocarditis resulting from specific pathogens, such as Chagas disease, is the most frequent cause of cardiomyopathy and related SCD.[175] Patients with infective endocarditis may also be at risk for SCD as a result of acute coronary emboli from valvular vegetations. Intramyocardial abscesses can also precipitate heart block or VT and lead to SCD. Most often, however, cardiovascular death in patients with infective endocarditis is caused by acute hemodynamic deterioration resulting from progressive valvular failure.

Infiltrative cardiomyopathies, such as primary or secondary amyloidosis, hemochromatosis, or sarcoidosis, have been associated with predominantly cardiac conduction defects but also ventricular tachyarrhythmias and SCD. In older autopsy studies, up to two-thirds of patients with cardiac sarcoid died from sudden cardiac death.[176] VT,

which may be the mode of presentation of cardiac sarcoidosis, can usually be reproduced by programmed electrical stimulation, and is associated with a high rate of recurrent arrhythmia and SCD.[177,178] Cardiac MRI may be useful in risk stratification of patients with cardiac sarcoidosis, as patients with late gadolinium enhancement have an elevated risk of ventricular arrhythmias[179,180] (see Chap. 61). Current guidelines state that it is "reasonable" to implant ICDs in patients with confirmed cardiac sarcoidosis[128] although high-quality, prospective data to support this recommendation are lacking, and it remains unclear how risk stratification with imaging and/or programmed stimulation can be used to refine patient selection for ICDs.

CONGENITAL HEART DISEASE

Tetralogy of Fallot, transposition of the great arteries, congenital aortic stenosis, and pulmonary vascular obstruction have been associated with a 25- to 100-fold increased risk of SCD resulting from arrhythmia, increasing primarily in the second postoperative decade.[181] In patients who have undergone reparative surgery for tetralogy of Fallot, a QRS duration of ≥ 180 milliseconds was found to be the most sensitive predictor of SCD and ventricular tachyarrhythmias in 793 adults and was correlated with other parameters of right ventricular volume overload. Older age at repair also increased the risk of arrhythmia.[182] Electrophysiology testing has recently been found to be useful in evaluating the risk of ventricular arrhythmias in patients late after surgical repair of tetralogy of Fallot,[183] as these patients can be uniquely susceptible to reentrant VT.

Transposition of the great arteries (post-Mustard or Senning procedures) is associated with a > 6% risk of late SCD, which can be the result of sinus node dysfunction or ventricular tachyarrhythmias[184] (see Chap. 56). Arterial-switch surgery for transposition may result in fewer late-term arrhythmias.

SCD is often (45%-60%) the mode of death in patients with primary or secondary pulmonary hypertension (see Chap. 74). Death can be precipitated by general anesthesia, dehydration, exertion, or pregnancy. Any process that decreases systemic vascular resistance increases right-to-left shunting and decreases pulmonary flow. The resultant peripheral desaturation may trigger lethal arrhythmias and SCD.[185]

The SCD risk in congenital aortic stenosis is estimated to be 1% and occurs predominantly in symptomatic patients with severe left ventricular hypertrophy. Ebstein anomaly is frequently (up to 25%) associated with the presence of accessory pathways and the Wolff-Parkinson-White syndrome, which carries a small risk of SCD (discussed later). Congenital heart block without associated structural heart disease occurs in 1 of 20,000 infants and is associated with maternal systemic lupus erythematosus. In these patients a moderate decrease in heart rate is usually well tolerated. As previously noted, patients with severe bradycardia, however, have a tendency to develop ventricular arrhythmias. Pacemaker therapy has virtually eliminated the risk of SCD in this population.[185]

CHRONIC KIDNEY DISEASE AND SUDDEN CARDIAC DEATH

SCD is a common cause of mortality in patients with end-stage renal disease (ESRD). Between 2011 and 2013, cardiac arrest accounted for approximately one-fourth of all deaths in patients with ESRD, with an estimated rate of 35 per 1,000 person-years. This risk increases significantly with increasing age and in patients who are on dialysis, who have an estimated fatal cardiac arrest rate of approximately 50 per 1,000 person-years.[186] Chronic kidney disease is an independent risk factor for cardiovascular disease and CHD.[187] Factors beyond worse coronary artery disease likely contribute to this elevated risk, however, because the risk of SCD remains significantly elevated in patients on dialysis even after surgical revascularization with coronary artery bypass grafting,[188] and treatment of patients with diabetes and ESRD on hemodialysis with statins had no effect on cardiovascular mortality or SCD despite approximately 40% reductions in median low-density lipoprotein cholesterol.[189,190]

Shifts in electrolytes and the dialysis procedure itself may also contribute to SCD risk. SCD risk is elevated 1.7-fold in the first 12 hours after initiation of chronic dialysis and is elevated threefold in the 12 hours prior to initiation of chronic dialysis after a 72-hour intradialytic interval.[191] Autonomic dysfunction, hypertension and LVH, uremia, and endothelial dysfunction may also contribute to myocardial fibrosis and the increased risk of SCD in patients with ESRD.[192]

Patients with severe renal dysfunction and patients on dialysis have been excluded from most ICD trials. Retrospective analysis of the National Cardiovascular Data Registry ICD registry has revealed that despite primary prevention ICDs, patients with chronic kidney disease have a two to fivefold elevated risk of total mortality (with risk proportional to the severity of renal dysfunction) compared to those with normal renal function.[193] Smaller studies have found similar findings.[194-196] In a meta-analysis of patients in the MADIT-I, MADIT-II, and SCD-HeFT studies, primary prevention ICD implantation was not associated with survival benefit in patients with an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 (stage 3 chronic kidney disease).[197] However, in a retrospective study of 6042 dialysis patients, ICD implantation for secondary prevention of SCD was associated with a 42% reduction in total mortality.[198] Studies evaluating rates of appropriate ICD therapies in patients with renal dysfunction have revealed mixed results, with some studies demonstrating an increased risk of ventricular arrhythmias in patients with renal dysfunction[199,200] and others finding no such association.[201] Renal dysfunction is also associated with increased procedural complications during ICD implantation.[202] Patients with ESRD, therefore, may derive less overall benefit from ICD implantation, although prospective studies evaluating ICD use specifically in this population are lacking. A prospective randomized trial evaluating implantation of primary prevention ICDs in dialysis patients aged 55 to 80 years is currently under way.[203]

PRIMARY ELECTRICAL ABNORMALITIES (SEE ALSO CHAP. 80)

LONG QT SYNDROME

Sudden cardiac death is one of the hallmarks of the congenital long QT syndrome (LQTS), a group of genetically distinct disorders resulting from mutations in 1 of 15 genes (with more likely to be discovered in the future) encoding cardiac ion channels or auxiliary ion-channel subunits[204-206] (see also Chap. 80). The long QT interval reflects abnormal prolongation of repolarization caused predominantly by defects in outward currents (potassium) or impaired inactivation of inward currents (sodium). Prolonged repolarization enhances the propensity to develop early after-depolarizations, leading to triggered activity that is the initiating mechanism for torsade de pointes (see Chap. 79). Other characteristics of this disorder, in addition to the prolonged QT interval (> 440 milliseconds for men or > 460 milliseconds for women, corrected for heart rate), include abnormal T-wave contours, relative sinus bradycardia, a family history of early sudden death, and a propensity for recurrent syncope and sudden cardiac death as a result of polymorphic ventricular tachycardia (torsade de pointes) and VF. The autosomal recessive Jervell-Lange-Nielsen syndrome is a rare condition associated with SCD and congenital deafness.

More than 90% of the congenital forms of LQTS have been linked to specific chromosomal defects, resulting in a genetically based classification (LQTS1 through LQTS15) with important functional and prognostic implications.[206] Multiple mutations have been identified in each gene, and this locus heterogeneity appears to be prognostically important. LQTS1 is caused by loss-of-function mutations in *KCNQ1* gene, which encodes a subunit of the slow delayed rectifier potassium channel, I_{Ks}. LQTS2 is caused by loss-of-function mutations in *KCNH2* (or *hERG*), which encodes a subunit of the rapid component of the delayed rectifier potassium channel, I_{Kr}. LQTS1 and LQTS2 therefore prolong the QT interval by reducing the amount of repolarizing potassium currents. LQTS3 is caused by a gain-of-function mutation in *SCN5A*, which encodes the cardiac sodium channel and which results in persistence of a late depolarizing sodium current.

The risk of sudden death in LQTS is influenced by the duration of the QT interval corrected for heart rate (QTc), the specific genetic defect, sex, family history, and possibly other factors.[207,208] Torsade de pointes can be triggered by different stimuli, typically involving high adrenergic states such as exercise or sudden arousal. Irregular rhythms with "long-short" R-R intervals are frequent triggers of torsade de pointes. Cardiac events associated with exercise, especially with swimming, dominate the clinical picture of LQTS1 patients, and auditory stimuli tend to be a trigger for arrhythmic events in LQTS2 patients.[209,210] Cardiac events associated with LQTS3 are frequently associated with rest or sleep.[210] The frequency with which sudden deaths attributed to electrolyte or drug effects actually occur in unrecognized or subclinical carriers of LQTS genetic mutations is unknown, but these factors can precipitate torsade de pointes in known LQTS patients. Registry data suggest a > 50% risk of syncope, cardiac arrest, or sudden death for LQTS1, LQTS2, and male LQTS3 gene carriers with QTc intervals > 500 milliseconds by age 40.[207] Lower levels of risk have been reported for other mutations and for patients with shorter QT intervals.

β-blockers are a mainstay of treatment for LQTS patients, and nonrandomized data suggest these drugs reduce mortality. Among the three most common types of LQTS (LQTS1-3), genotype modifies the efficacy of β-blockers, which are most effective in LQTS1 and least effective in LQTS3.[210-212] Left-sided sympathectomy has also been used in selected cases, especially in patients with recurrent symptoms while on β-blockers.[213] Implantable defibrillators are clearly indicated for sudden death survivors (class I, level of evidence A) and may also be appropriate for LQTS patients with syncope and other high-risk features (class IIb, level of evidence B), particularly when symptoms persist despite β-blocker therapy (class IIa, level of evidence B).[128]

SHORT QT SYNDROME

Different mutations in some of the same genes previously shown to cause long QT syndrome have recently been identified as causing a distinct syndrome characterized by shorter than normal corrected QT intervals (< 300-320 milliseconds) and a propensity for both atrial fibrillation and SCD at very young ages.[214,215] The first familial analysis identified gain-of-function mutations in the KCNH2 (*hERG*) gene, which codes for the potassium channel responsible for the rapidly activating delayed rectifier (I_{Kr}) current.[214] Although loss-of-function mutations in this gene cause LQTS2, the gain-of-function mutations in these families were associated with short QT intervals and unusually short atrial and ventricular refractory periods at electrophysiologic study.[216] Since this first description, two additional genetic mutations have been reported: a de novo gain-of-function mutation in the *KCNQ1* gene (responsible for the α subunit of the *KvLQT1* protein [I_{Ks}]),[217] and a mutation in the *KCNJ2* gene (coding the inwardly rectifying *Kir2.1* [I_{k1}] channel), associated with a unique T-wave morphology.[218] Based on these preliminary data, short QT syndrome appears to be another uncommon genetically based condition responsible for some sudden deaths in infancy, childhood, and early adulthood.[215] The frequency, full range of genotypes and phenotypes, and optimal therapy of this condition will require further study to define (see Chap. 80). ICD implantation is recommended in patients with short QT syndrome who survive cardiac arrest or have sustained VT.[219]

IDIOPATHIC POLYMORPHIC VENTRICULAR TACHYCARDIA AND IDIOPATHIC VENTRICULAR FIBRILLATION

Several additional types of idiopathic polymorphic VTs have been described and are associated with an unfavorable prognosis. These arrhythmias include idiopathic VF, torsade de pointes with normal QT interval and a short initiating coupling interval,[220] and catecholaminergic polymorphic ventricular tachycardia (CPVT). These disorders can occur in sporadic or familial forms and are frequently though not uniformly associated with catecholamine release during physical or emotional stress.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic VT (CPVT), characterized initially by a pattern of bidirectional VT first described in children, has been linked to mutations in the cardiac ryanodine receptor (*RyR2*)[221] and calsequestrin (*CASQ2*)[222] genes, both of which encode proteins involved in the handling of calcium by the sarcoplasmic reticulum. Patients with *RyR2* mutations have also presented with polymorphic VT and VF in adulthood. These arrhythmias are at least partly responsive to β-blockers, which are the first-line treatment for CPVT.[219,221] Left cardiac sympathetic denervation may also be useful.[223] Patients with CPVT should avoid strenuous exercise or competitive sports. ICD implantation is recommended only in patients who experience cardiac arrest, recurrent syncope, or polymorphic/bidirectional VT despite use of β-blockers and or sympathetic denervation, as ICD shocks can increase sympathetic tone and trigger worsening arrhythmias.[219]

Idiopathic Polymorphic Ventricular Tachycardia and Idiopathic Ventricular Fibrillation

The pathophysiologic mechanisms underlying short-coupled polymorphic ventricular tachycardia (PMVT) and other forms of idiopathic VF have not yet been characterized. Although the list of potential causes of SCD continues to grow, a definite cause cannot be established in a minority of patients suffering cardiac arrest. These instances of SCD without evident cause are sometimes attributed to idiopathic VF. The incidence of idiopathic VF is higher in selected populations such as younger patients (up to 14% in patients < 40 years of age[224]) or female survivors of SCD unrelated to myocardial infarction (10%[29]). The risk of recurrent VF in this young and otherwise healthy patient population ranges between 22% and 37% at 2 to 4 years.[225] In survivors of cardiac arrest caused by idiopathic VF, the diagnosis is made by exclusion if extensive cardiac workup reveals no diagnostic abnormality. An intriguing study found that an early repolarization pattern—heretofore believed to be a benign or "normal variant"—is present on ECGs in an unexpectedly high number of "idiopathic VF" cases, mostly men.[226] Because most people with these ECG findings do not die suddenly, the mechanistic implication of these findings is not presently clear.

In a recent analysis of 63 survivors of cardiac arrest with no evident cardiac disease, investigators followed a systematic evaluation that included advanced imaging, SAECG, exercise testing, provocative drug testing, and focused genetic testing. Using this approach, 24 patients

were definitively diagnosed with primary electrical disease. The highest yield tests were pharmacologic challenge and exercise testing, particularly in establishing the diagnoses of long QT syndromes and catecholaminergic polymorphic VT. This type of thorough systematic testing may help establish diagnoses in cases of sudden death presumed to be a result of idiopathic VF.[227]

BRUGADA SYNDROME

Brugada syndrome (BrS) refers to the syndrome of SCD associated with complete or incomplete right bundle-branch block and ST-segment elevation in V_1 to V_3 in patients without demonstrable structural heart disease.[228] Three ST-segment morphologies have been described, as detailed in Chap. 80, although type II and type III are considered clinically distinct from type I.

BrS is an autosomal dominant genetic disorder that has been associated with various mutations in multiple genes. The most commonly affected gene, *SCN5A*, encodes the α-subunit of the cardiac sodium channel, and loss-of-function of *SCN5A* is implicated in BrS. Mutations in *SCN5A*, however, account for < 30% of BrS.[219] Mutations in *SCN5A* can also lead to LQTS3 and other forms of conduction disease. Loss-of-function mutations in other sodium channel subunits or L-type calcium channels, and gain-of-function mutations affecting the transient outward current (I_{to}), have also been implicated in BrS.[229] Only approximately 30% of patients with BrS are found to have a known mutation, and genetic testing for BrS is not recommended without a diagnostic type I ECG or for family members of affected individuals who have been successfully genotyped.[219,230]

By the most recent consensus guidelines, the diagnosis of BrS is made by the presence of type I pattern ST-segment elevations > 2 mm in at least one lead (V_1-V_2) positioned in the second, third, or fourth intercostal space that is observed spontaneously or after administration of a class I antiarrhythmic drug.[219] BrS is also diagnosed in patients who have type II or type III pattern ST-segment elevation in least one lead (V_1-V_2) positioned in the second, third, or fourth intercostal space when a class I antiarrhythmic drug induces a type I ECG morphology.[219] Recent changes in consensus guidelines have removed the need for prior PMVT/VF, syncope, nocturnal agonal respiration, or family history of sudden death addition to ECG manifestations to make the diagnosis of BrS.

BrS is more common and tends to be more severe in men.[231,232] Because of the dynamic nature of the BrS pattern on ECG, the true prevalence of BrS is difficult to determine. Prevalence in Southeast Asia is particularly high, reaching 0.5 to 1 per 1,000 people, and BrS is now thought to be the explanation behind sudden, unexpected nocturnal death syndromes described before Brugada's work in young, apparently healthy men from Southeast Asia.[233-236] Prevalence in the United States and Europe is estimated to be significantly lower.

The mutations in the Brugada syndrome are not associated with structural heart disease and seem to lead to an acceleration of recovery of the sodium channel or nonfunctional sodium channels leading to transmural dispersion of repolarization and refractoriness. Local reexcitation via a phase 2 reentry mechanism can occur, leading to the development of very closely coupled premature ventricular contractions that trigger VT and VF.[151,152]

Symptomatic patients have a high incidence of SCD; those who have syncope thought to be caused by ventricular arrhythmias, spontaneous VT, or a prior history of cardiac arrest should be treated with ICD implantation (class I, level of evidence A).[128,219] ICD implantation is not recommended for asymptomatic patients with a drug-induced type I ECG and a positive family history of SCD alone.[219,237] All patients with BrS should avoid certain drugs that can worsen ECG manifestations and increase the risk of ventricular arrhythmias, including class I antiarrhythmic agents (with the exception of quinidine-see below), certain psychotropic drugs (especially tricyclic antidepressants), and excessive alcohol.[219] Fever can induce the ECG manifestations of BrS and lead to life-threatening ventricular arrhythmias, and patients with BrS must aggressively treat any febrile illness with antipyretic medications.[238]

High rates of inducible polymorphic VT/VF have been reported during EP studies of patients with BrS. It has therefore been proposed that family members of symptomatic patients who also have spontaneously abnormal ECGs undergo EP studies for risk stratification and consider ICD implantation if VF is induced.[232] However, the clinical benefit of this strategy is unproven, and in the France, Italy, Netherlands, and Germany (FINGER) BrS registry, inducibility of ventricular arrhythmias was not associated with future arrhythmic events.[239] Recent data have suggested that quinidine, due its inhibitory effects on the transient outward (I_{to}) current, may be beneficial in BrS with reductions in inducible ventricular arrhythmias and clinical events[240-243] (see Chaps. 80 and 55). Recent data have also suggested that the manifestations of BrS arise from electrophysiological abnormalities in the right ventricular outflow tract epicardium, and that catheter ablation of abnormal signals in this area can normalize the ECG manifestations of BrS and prevent future ventricular arrhythmias.[244] Future study of this novel treatment of BrS will be needed before it can be adopted into clinical practice.

WOLFF-PARKINSON-WHITE SYNDROME

The risk of SCD in patients with Wolff-Parkinson-White (WPW) syndrome is less than 1 per 1,000 patient-years of follow-up.[245] Although SCD is a rare event, it is important to consider, because it usually occurs in otherwise healthy individuals and is preventable. The mechanism of SCD in most patients with WPW is development of atrial fibrillation with extremely rapid ventricular rates because of antegrade conduction over an accessory pathway and subsequent degeneration into VF. The best predictor for development of VF during atrial fibrillation is the spontaneous occurrence of a rapid ventricular response over the accessory pathway, with the shortest interval between preexcited ventricular beats (eg, those conducted over the accessory pathway) being less than 250 milliseconds, but the specificity of this finding is low.[246,247] Spontaneous or exercise-induced intermittent loss of preexcitation is helpful in identifying patients who will have a slower ventricular response in atrial fibrillation and may be at lower risk for sudden death.[248,249]

In symptomatic patients, an electrophysiology study offers the opportunity to assess conduction properties of the accessory pathways, the propensity to develop tachyarrhythmias, and the possibility of cure with minimal risk using catheter ablation. In patients with preexcited atrial fibrillation, catheter ablation of the accessory pathway has a class I indication in the most recent guidelines, and ablation of the accessory pathway often prevents recurrence of AF (especially in young patients).[250]

Diagnostic electrophysiology study may also be helpful in identifying patients with asymptomatic preexcitation at high risk for arrhythmic complications. One randomized study[251] assessing catheter ablation in asymptomatic adults found a reduction in symptomatic arrhythmias—mainly atrioventricular reentrant tachycardia (AVRT)—with no difference in mortality. Further study in this area is needed,[252] and EP study for asymptomatic patients with preexcitation on ECG, with selective prophylactic ablation for patients with high-risk findings, is therefore considered a class IIa intervention by consensus guidelines. Ablative therapy of asymptomatic preexcitation may be especially appropriate in patients with high-risk occupations such as pilots. Careful observation of asymptomatic patients who have intermittent loss of

preexcitation during ambulatory monitoring or abrupt loss of preexcitation during an exercise stress test, and therefore have low SCD risk overall, is considered a class I recommendation; careful observation of asymptomatic patients without "low-risk" features is considered a class IIa recommendation given the overall low rate of SCD and potential complications of catheter ablation.[250]

EARLY REPOLARIZATION SYNDROMES

Early repolarization (elevation of the QRS complex-ST segment (J-point) above the baseline, or slurring of the terminal part of the QRS complex into the ST segment) is present on the ECG in up to 19% of the population, with variation based on age and race.[253] It is present in approximately 6% of middle-aged European adults.[254] Although early repolarization has been historically considered a benign electrocardiographic finding, recent data have suggested that it may be associated with an increased risk of SCD.

In a community-based cohort of 10,864 Finnish participants, after adjustment for SCD confounders, J-point elevation of ≥ 0.1 mV in the inferior leads was associated with a 43% increased risk of arrhythmic death (95% CI 6%-94%, P = .03), and a small group of participants with J-point elevation ≥ 0.2 mV in the inferior leads had an almost threefold increase in the risk of arrhythmic death (relative risk 2.92, 95% CI 1.45-5.89; P = .01). J-point elevation in the lateral leads was not associated with arrhythmic death.[254] In a retrospective case-control study evaluating patients who had cardiac arrest resulting from idiopathic ventricular fibrillation, early repolarization of ≥ 0.1 mV was more frequent in survivors of cardiac arrest than in controls (31% vs 5%, P < .001), and patients with early repolarization had higher rates of recurrent VF detected with ICDs (HR 2.1, P = .008).[226]

A meta-analysis of over 31,000 subjects and over 726,000 person-years of follow-up revealed that early repolarization was associated with a relative risk of 1.70 (95% CI 1.19-2.42, P = .003) for arrhythmic death, a very small increased absolute risk of arrhythmic death of 70 cases per 100,000 person-years, and no significant difference in cardiac death or total mortality.[255]

Various ion channel mutations have been associated with the "early repolarization syndrome" defined as the presence of early repolarization ECG pattern and idiopathic VF.[256-258] In patients with early repolarization but no ventricular arrhythmias, no specific treatment is recommended, as the ECG finding is highly prevalent and benign in the vast majority of cases.[259] Secondary prevention of SCD in patients with early repolarization and VF/cardiac arrest is managed the same way as in patients without early repolarization. Further study of the interplay between early repolarization and SCD is needed.

DRUGS AND OTHER TOXIC AGENTS

PROARRHYTHMIA

The paradox that antiarrhythmic agents can cause arrhythmias has been recognized since the introduction of quinidine in 1918.[260] The most common form of proarrhythmia, seen with Vaughan-Williams class IA and class III antiarrhythmics, stems from QT interval prolongation resulting from blockade of repolarizing potassium currents (primarily I_{Kr}) and is accordingly sometimes referred to as the "acquired" long QT syndrome. In these cases, the initiation of the arrhythmia is often triggered by bradycardia or a characteristic "long-short" coupling interval that initiates a pause-dependent prolongation of the QT interval. The VT in this setting is usually of the typical torsade de pointes morphology. This form of proarrhythmia, seen in a dose-dependent manner in 2% to 5% of patients treated with quinidine, sotalol, or dofetilide, may be precipitated by electrolyte abnormalities such as hypokalemia or hypomagnesemia. It usually occurs within 3 days of drug initiation, has greater prevalence in women than men,[261,262] and concomitant therapy with digitalis and diuretic agents may predispose patients to this complication[263] (see Chaps. 79 and 87).

Besides antiarrhythmic drugs, many other commonly used medications with diverse actions have been implicated in ventricular proarrhythmia. Common examples include erythromycin, terfenadine, astemizole, pentamidine, and certain psychotropic drugs, such as tricyclic antidepressants, methadone, and antipsychotics. Most of these drugs produce toxicity by prolonging repolarization and QTc, leading to torsade de pointes; some do so by interacting with the metabolism of other QT-prolonging agents. A few drugs (cisapride, terfenadine, astemizole) have been withdrawn from the US market because of such concerns. The list of medications reported to cause this complication is constantly growing (Table 91–2), and a registry of drugs associated with this complication has been developed. An updated list of these drugs can be found online at www.torsades.org.

Proarrhythmia with different underlying mechanisms has been seen with other drugs that do not prolong the QT interval. For example, the Cardiac Arrhythmia Suppression Trial (CAST) showed an increase in mortality in postinfarction patients treated with the class IC antiarrhythmic drugs encainide or flecainide compared with placebo, despite the documented suppression of PVCs.[264] It is believed that these potent sodium channel blockers exacerbate ischemia-induced myocardial conduction delays and promote reentrant VTs.[265] Class IC antiarrhythmic agents can also lead to by proarrhythmia by converting atrial fibrillation to atrial flutter at slower than usual atrial rates, allowing one-to-one conduction of the flutter waves (referred to as "enhanced atrioventricular [AV] nodal conduction"). For this reason, AV nodal blocking agents should be administered concomitantly with these medications in atrial fibrillation patients. Phosphodiesterase inhibitors and other positive inotropic agents may promote arrhythmias by increasing intracellular calcium levels. These medications have been shown to be proarrhythmic and to increase the risk of SCD, despite their beneficial effects on hemodynamic parameters.[266]

COCAINE AND ALCOHOL

Widespread use of cocaine in the United States led to the realization that this drug can precipitate life-threatening cardiac events, including SCD. The combination of alcohol and cocaine is especially dangerous because of the generation of a unique metabolite, cocaethylene, that has significant cardiotoxicity.[267] Cocaine causes coronary vasoconstriction, increases cardiac sympathetic tone, increases action potential duration, slows conduction, and precipitates cardiac arrhythmias irrespective of the amount ingested, prior use, or whether there is an underlying cardiac abnormality.[268] The combination of increased oxygen demand because of sympathetic stimulation and diminished coronary flow caused by vasoconstriction may precipitate ischemia-induced arrhythmias and SCD.

ELECTROLYTE ABNORMALITIES

Hypokalemia is often found in patients during and after resuscitation from a cardiac arrest. Although it can be a secondary phenomenon resulting from catecholamine-induced potassium shift into the cells, primary hypokalemia is clearly arrhythmogenic. There is an almost linear inverse relationship between serum potassium concentration and the probability of VT in patients with acute myocardial infarction.[269] Electrolyte abnormalities are thought to play a role in the sudden death of patients treated with non–potassium-sparing diuretics[270], those with severe eating disorders,[271] or those who abuse diuretics.

A decrease in the extracellular potassium level hypopolarizes the resting membrane potential, shortens the plateau duration, prolongs the phase of rapid repolarization in ventricular fibers, and causes an increase in pacemaker activity in Purkinje cells, triggering ventricular arrhythmias.[272] These changes may increase the dispersion of repolarization and facilitate reentrant ventricular arrhythmias.[272] Many of the electrophysiologic effects of hypokalemia are similar to those caused by digitalis and catecholamine stimulation, explaining the high risk of ventricular arrhythmias when a combination of these factors is present.

Magnesium deficiency and changes in intracellular concentration of calcium may also be arrhythmogenic.[272,273] Increased intracellular calcium is believed to play a significant role in arrhythmias associated with digitalis glycosides, catecholamine-induced VT, reperfusion arrhythmias, and the proarrhythmic effect seen with phosphodiesterase inhibitors and other positive inotropic agents (see Chap. 79).

CLINICAL PRESENTATION AND MANAGEMENT OF THE PATIENT WITH CARDIAC ARREST

OUT-OF-HOSPITAL CARDIAC ARREST

Approximately 75% of cardiac arrests occur at home, and approximately 60% are witnessed.[6] Because most patients are found in VF, the time to successful defibrillation is a key element in the acute management of the cardiac arrest victim (see Chap. 92). The importance of early intervention is reflected in the *chain of survival* concept of emergency cardiac care systems: early access, early cardiopulmonary resuscitation (CPR), early defibrillation, and early advanced cardiac life support.[274]

Cardiopulmonary Resuscitation

Initiation of bystander CPR is a critical element of early intervention and improves the chances of successful resuscitation. Retrospective studies have shown that high-quality bystander CPR more than doubles the odds of survival after cardiac arrest.[275,276] The earlier CPR is performed, the greater the proportion of patients who are found in VF as opposed to bradycardia or asystole, and there is an increased rate of successful defibrillation in these patients. Data from two studies suggests that a period of effective CPR before defibrillation when emergency response times are greater than 4 to 5 minutes may improve survival.[277,278] Recent studies have shown that effective chest compressions without interruption are the most critical aspect of CPR in out-of-hospital cardiac arrest,[279,280] and compression-only CPR (where lay rescuers do not interrupt chest compressions to administer rescue breathing) may be associated with higher rates of use and improved outcomes.[281,282] Initiatives to increase layperson training in CPR have also improved the survival of cardiac arrest victims.[283]

Automated External Defibrillators

In order to improve the time to initial defibrillation, early defibrillation by nonmedical personnel before Emergency Medical Services arrive is recommended. Automated external defibrillators (AEDs) have significantly expanded the availability of early defibrillation in many community settings, in some cases with demonstrable improvements in SCD survival.

One study evaluating the use of AEDs in casinos demonstrated a 74% survival rate for those who received their first defibrillation no later than 3 minutes after a witnessed collapse and 49% for those who received their first defibrillation after more than 3 minutes.[284] Improvements in other settings, such as on airplanes, have also been noted.[285] In the Piacenza region of Italy, 173,114 persons were instructed in the use of AEDs, and survival to hospital discharge after cardiac arrest improved from 3.3% to 10.5%.[286] Likewise, a large North American multicenter study found an improvement in survival to hospital discharge after cardiac arrest from 14% to 23% when training in the use of AEDs was added to traditional CPR education for lay volunteers.[287]

Despite these successes, AEDs have not improved survival in all settings: a recently completed randomized trial of myocardial infarction survivors not eligible for ICDs failed to show a survival benefit from deploying AEDs in patients' homes.[288]

SURVIVAL AND PROGNOSIS AFTER CARDIAC ARREST

Marked differences in survival rates after out-of-hospital cardiac arrest have been reported in different communities. Survival rates are lowest in large cities such as New York (1.4%) and Chicago (4.0%)[289] and highest in Seattle (29%), a midsized urban community where many early-intervention concepts have been pioneered.[290] The in-hospital mortality rate after successful resuscitation outside the hospital remains as high as 90% in some populations[290,291] (Fig. 91–7). Important factors associated with increased in-hospital mortality rates after out-of-hospital resuscitation are cardiogenic shock after defibrillation, age 60 years or greater, requirement of four or more shocks for defibrillation, absence of an acute myocardial infarction, and coma on admission to the hospital.[292]

Survival depends largely on the initial recorded rhythm. Some 40% to 60% of patients who are found in VF are successfully resuscitated, but only a fraction will survive to be discharged from the hospital. The outcome is much better in the smaller (< 7%) group of patients where VT is the initial documented rhythm, for whom the survival rate is more than 85% to hospital admission and more than 75% to hospital discharge. Bradycardias and electromechanical dissociation as the presenting rhythms are associated with the worst prognosis, and very few (< 5%) of these patients survive to discharge from the hospital.[293] A higher burden of comorbid conditions as well as recent symptoms before the event are associated with worse outcomes.[294]

MANAGEMENT OF CARDIAC ARREST SURVIVORS AND RISK STRATIFICATION FOR SCD

INITIAL ASSESSMENT AND TREATMENT

The initial management after successful resuscitation from cardiac arrest consists of stabilizing the patient's cardiopulmonary status and quickly addressing obvious potential triggers such as electrolyte

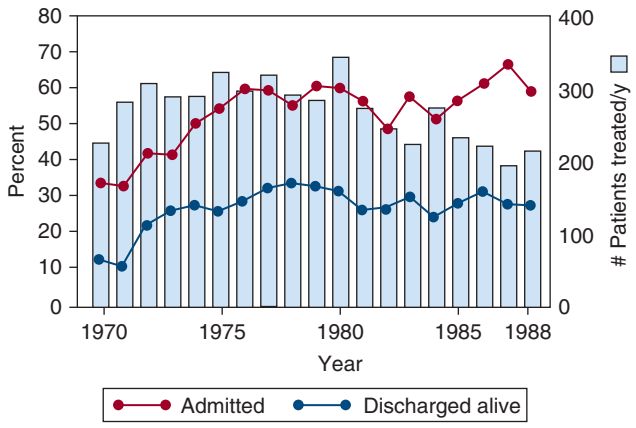

FIGURE 91–7. Percentage of out-of-hospital cardiac arrest victims admitted to the hospital by emergency medical service personnel and subsequently discharged alive during the period from 1970 to 1988. Reproduced with permission from Cobb LA, Weaver WD, Fahrenbruch CE, et al. Community-based interventions for sudden cardiac death. Impact, limitations, and changes. *Circulation*. 1992 Jan;85(1 Suppl):I98-102.

disturbance or coronary ischemia. After this initial period, strong consideration should be given to the use of therapeutic hypothermia (reduction of core body temperature to 32-34°C for 12-24 hours) based on randomized evidence showing substantially improved odds of favorable neurologic recovery.[295,296] Data supporting use of therapeutic hypothermia is strongest for patients who have an out-of-hospital cardiac arrest and a shockable initial rhythm, although this benefit has been extended to patients who have in-hospital cardiac arrest or who have cardiac arrest resulting from nonshockable rhythms.[297] Current guidelines recommend that adult patients who are comatose after successful resuscitation have a class I indication for therapeutic hypothermia regardless of their presenting cardiac rhythm.[298]

During and after initial stabilization, every effort should be made to determine the cause of cardiac arrest and likelihood of recurrence. For this, the presence of underlying cardiac disease should first be determined. History, physical examination, and the electrocardiogram may provide the first clues. Certain genetic channelopathies such as LQTS or BrS may be apparent on the electrocardiogram. Abnormal ECG findings immediately following arrest must be interpreted with caution, as some findings (such as repolarization abnormalities and QT prolongation) may be transient and related to metabolic derangement, defibrillation, induced hypothermia, or medications for hemodynamic support. If abnormalities are present immediately following arrest, they should be reconfirmed once the patient's physiology has normalized.[299] Myocardial infarction must be excluded by serum biomarker measurements and electrocardiography, although low-level troponin elevation can be seen as a consequence of prolonged hypotension and does not necessarily reflect myocardial ischemia or infarction as the inciting event. Echocardiographic studies can assess left ventricular function, regional wall motion abnormalities, and valvular heart disease. Stress-imaging studies can demonstrate inducible ischemia. Cardiac catheterization may be recommended to evaluate the coronary anatomy and hemodynamic parameters. Other tests, such as radionuclide studies, MRI, cardiac biopsy, genetic testing, and/or drug challenge may be necessary in selected patients. As discussed earlier, an underlying cardiac disease can be found in most patients.

PRIMARY VERSUS SECONDARY CARDIAC ARREST

One of the important questions after cardiac arrest is whether it was primarily because of acute circulatory/respiratory failure or an arrhythmia. Although all of these events are usually present during the arrest, it is important to distinguish whether the arrhythmia preceded or followed the hemodynamic collapse. Although several clinical and historical clues can help to answer this question (Table 91–3), the distinction sometimes cannot be made with certainty.

Separating primary from secondary cardiac arrest has important prognostic and therapeutic consequences. Patients who present with cardiac arrest secondary to (and within 48 hours of) an acute transmural myocardial infarction have a prognosis similar to that of patients who have an acute myocardial infarction without an arrhythmia.[78] Specific antiarrhythmic therapy is therefore usually not recommended if cardiac arrest occurs during or within 2 days of an acute ST-segment elevation myocardial infarction. In contrast, if the arrhythmia is the primary event and only low-level biomarker evidence of MI develops secondary to the acute hemodynamic deterioration during the arrhythmia, then antiarrhythmic therapy is recommended unless a transient or reversible cause is identified.

Every effort should be made to exclude potentially reversible causes of SCD, including transient ischemic episodes in patients who are candidates for revascularization and in whom the onset of the arrhythmia is clearly preceded by ischemic ECG changes or symptoms.

TABLE 91–3. Differences in Clinical Status Immediately Before Death in Patients Dying Primarily of Arrhythmia Versus Circulatory Failure

Clinical Status Immediately Before Death	Arrhythmic Deaths (n = 82)	Circulatory Failure Deaths (n = 59)
Comatose	0/82 (0%)	56/59 (95%)
Standing or actively moving	39/82 (48%)	0/59 (0%)
Terminal arrhythmia		
Ventricular fibrillation	15/18 (83%)	3/9 (33%)
Asystole	3/18 (17%)	6/9 (67%)
Duration of terminal illness		
< 1 h	53/82 (65%)	4/59 (7%)
> 24 h	17/82 (21%)	48/59 (81%)
Nature of terminal illness		
Acute cardiac events	80/82 (98%)	8/59 (14%)
Noncardiac events	1/82 (1%)	51/59 (86%)

Data from Hinkle LE, Jr., Thaler HT: Clinical classification of cardiac deaths. *Circulation*. 1982 Mar;65(3):457-464.

Other reversible etiologies for cardiac arrest include transient severe electrolyte disturbances and proarrhythmic effects of antiarrhythmic drugs and other pharmacologic agents (discussed earlier). It should be recognized that mild hypokalemia after cardiac arrest is common (because of catecholamine-induced shifts), usually corrects within 4 to 6 hours, and should not necessarily be considered a reversible cause of cardiac arrest. It can be difficult to establish a causal relationship between the proarrhythmic agent and the malignant ventricular arrhythmia in some cases. Pathologic prolongation of the QTc interval preceding initiation of the arrhythmia and return of the QTc interval to normal after discontinuation of the presumed proarrhythmic agent are strongly suggestive.

Another setting in which a reversible etiology for cardiac arrest is often present is in the hemodynamically unstable patient in the early postoperative period after cardiac surgery. Infusion of positive inotropic and pressor agents, electrolyte imbalances, acidosis, and hypoxia are often precipitating factors. Nevertheless, in the patient with structural heart disease, the underlying anatomic substrate should be considered the primary disorder, and eliminating transient perturbations such as drug effects, hypoxia, and ischemia may not be sufficient in eliminating the risk for recurrent arrest. In fact, patients from the Amiodarone Versus Implantable Defibrillator (AVID) registry who were thought to have arrested from a transient or correctable cause (and were therefore excluded from the trial) had a mortality rate that was similar to that of the general population of patients with VF arrest.[300]

RISK STRATIFICATION FOR SCD

A great effort has been put forth to assist in prospectively identifying individuals at high risk for SCD in order to target them for preventative therapies. Such methods have most often been applied to patients with dilated cardiomyopathy and/or prior myocardial infarction, as these are the most common and highest-risk conditions associated with SCD. Risk scores for screening the general population for SCD risk have also been developed.[37] At present there is no universal agreement on the optimal approach to sudden death risk stratification, in part because all currently available methods possess, at best, moderate

sensitivity and specificity for predicting future events, and in part because only a few of the techniques have been used in prospective clinical trials of effective interventions. The use of different risk stratification methods in the selection of candidates for prophylactic ICD implantation remains a point of controversy.

CLINICAL HISTORY

Syncope in patients with reduced left ventricular ejection fraction is associated with increased risk of SCD. In patients with unexplained syncope and structural heart disease, the induction of sustained VT or VF at electrophysiology study is considered a class I (level of evidence B) indication for ICD implantation.[128]

Post-hoc analyses from several primary prevention ICD trials have shown that total mortality risk can be stratified within the trial populations based on readily available clinical factors and that ICD benefit varies substantially, with evidence of reduced ICD benefit particularly in the patients with the greatest burden of comorbidities.[301-304] In subanalyses of the MADIT-II trial, five risk factors (NYHA functional class > II, age > 70 years, blood urea nitrogen > 26 mg/dL, QRS duration > 120 millseconds, and atrial fibrillation) were associated with reduced survival benefit from an ICD. In patients with three or more of these risk factors, there was no mortality benefit associated with ICD implantation.[304] Likewise, in a post-hoc analysis of the MUSTT trial, multiple variables beyond left ventricular ejection fraction (NYHA functional class, NSVT not related to bypass surgery, age, ventricular conduction abnormalities, inducible VT, and atrial fibrillation) were associated with the risks of arrhythmic death and total mortality.[301]

LEFT VENTRICULAR FUNCTION

Left ventricular dysfunction is a major independent predictor of total and sudden cardiac mortality rates in patients with ischemic as well as nonischemic cardiomyopathy and has become the most critical criterion in the selection of patients for prophylactic ICDs.[128] Unfortunately, detection of severe left ventricular dysfunction serves to predict the total cardiac mortality rate but does not distinguish patients who will die suddenly from those who will die of progressive congestive heart failure.[305,306]

ELECTROCARDIOGRAPHIC ABNORMALITIES

In survivors of out-of-hospital cardiac arrest, the presence of AV block or intraventricular conduction defects on ambulatory ECG (72 hours) is associated with a higher recurrence rate of cardiac arrest.[293] Other ECG parameters reported to be associated independently with an increased risk of SCD are prolongation of the QT interval,[307] increased dispersion of the QT interval,[308] atrial fibrillation, left bundle-branch block, and LVH.[133]

Detection of NSVT by ambulatory ECG monitoring has been reported to be of value in the risk stratification of patients for SCD, particularly after myocardial infarction.[87,309] The incidence of SCD in the 2 years after myocardial infarction in 766 patients enrolled in a prospective multicenter study increased with the frequency of PVCs detected during 24-hour ECG monitoring from 3% for less than 1 per hour to 14% for greater than 30 per hour; similarly, patients with NSVT had a higher (17%) incidence of SCD than did those with single PVCs (6%).[309] Suppression of PVCs in patients with prior myocardial infarction with class IC antiarrhythmic drugs in the CAST trial was associated with increased mortality.[264] The prognostic value of ambulatory ECG monitoring in patients with congestive heart failure is limited by the high incidence of these arrhythmias (up to 88%) in this population, resulting in low specificity.[310]

AUTONOMIC MARKERS

There is increasing evidence that cardiac abnormalities associated with a high risk of SCD are accompanied by changes and abnormalities in autonomic function. Myocardial infarction, for instance, has been shown to cause regional cardiac sympathetic and parasympathetic denervation.[311] Mathematical analyses of ambulatory ECG recordings have generated several measurements related to autonomic function associated with an increased risk of sudden and total cardiac death in post–myocardial infarction and heart failure populations. Reported measures include depressed baroreceptor sensitivity (BRS), heart rate variability (HRV), and heart rate turbulence.

Reduced BRS and HRV reflect impairment in the vagal efferent component of the autonomic nervous system and may help to predict cardiovascular mortality rates and arrhythmic events, particularly in patients after myocardial infarction. In one prospective study of 6693 unselected patients who underwent 24-hour ECG monitoring, those with reduced HRV had a fourfold higher risk of SCD than patients with higher variability.[312] The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study compared the relative utility of these measures alone and in combination by measuring BRS, HRV, 24-hour ECG recordings, and left ventricular ejection fraction in 1071 patients after MI. In that study, NSVT, abnormal HRV, and BRS were each independently predictive of worse outcomes. The combination of all three risk factors signified a 22-fold increased risk of death, but the positive predictive value was only approximately 20%.[313] An analysis from the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial showed very low mortality rates in nonischemic cardiomyopathy patients with preserved HRV, suggesting that these patients may not derive as much benefit from ICD implantation.[314]

SIGNAL-AVERAGED ELECTROCARDIOGRAPHY

Late potentials, which are microvolt waveforms extending the duration of a filtered QRS complex detected by signal-averaged electrocardiography (SAECG), have been shown to be helpful in the risk stratification of patients after myocardial infarction. The prognostic significance of late potentials has been demonstrated in several studies, which reported a 17% to 29% incidence of SCD, VF, or sustained VT in patients with an abnormal SAECG, in contrast to 0.8% to 3.5% in those without.[315] Although the negative predictive value of a normal SAECG is good, the application of SAECG in risk stratification for SCD is limited by a low positive predictive value in patients after myocardial infarction, as well as by its poor sensitivity in patients with nonischemic cardiomyopathies.[316] For additional information, please see Chapter 81.

MICROSCOPIC T-WAVE ALTERNANS

Macroscopic T-wave changes with an alternating-beat pattern have been observed in patients with long QT syndrome before onset of VF as well as in the setting of mechanical alternans, as is sometimes present during cardiac tamponade. Studies have indicated that T-wave alternans that is discernible only by computer-averaging techniques may be a more ubiquitous phenomenon that can identify patients at risk for ventricular arrhythmias.[317]

Techniques for computer-assisted detection of microvolt-level T-wave alternans have been developed and commercialized. The presence of sustained microvolt-level T-wave alternans, typically measured noninvasively during exercise, was shown in several early series to be associated with a two- to fourfold increased risk for SCD and/or total mortality, after adjusting for other factors.[318-320] In these series, abnormal test results had a roughly 80% sensitivity for serious arrhythmic

events over 1 to 2 years of follow-up, with negative predictive values consistently greater than 95%. However, more recent studies have failed to show consistently strong predictive accuracy for the test in predicting arrhythmic events,[321-323] possibly because many of the events were ICD therapies rather than true sudden death events.[324] The role of microvolt T-wave alternans testing in clinical practice remains uncertain. For additional information please see Chapter 81.

ELECTROPHYSIOLOGIC STUDIES

Electrophysiologic studies have advanced our understanding of life-threatening ventricular arrhythmias and facilitated the development of new therapies for their prevention and treatment. Induction of sustained monomorphic VT is the generally accepted end point for programmed ventricular stimulation, whereas induction of nonsustained ventricular arrhythmias, polymorphic VT, or VF may be nonspecific findings, depending on the aggressiveness of the stimulation protocol.[325,326] Information obtained during EPS, such as VT rate, morphology, origin, mechanism, and hemodynamic stability, is valuable in planning appropriate therapy.

In patients who present with sustained monomorphic VT, the clinical rhythm is reproducibly inducible in the majority of patients, especially in those with prior myocardial infarction.[325] Electrophysiologic testing is also useful in patients with structural heart disease who present with unexplained syncope. VT is the most common abnormal finding in these patients, but demonstration of His-Purkinje conduction disease or hemodynamically unstable supraventricular tachycardia can also be important. The role of electrophysiologic testing in selection of patients for primary prevention with ICDs has diminished in recent years. Although EP testing does predict future arrhythmic events independent of left ventricular ejection fraction in the presence of prior myocardial infarction, concern has been raised regarding the poor negative predictive value of electrophysiolgic studies in patients with severely compromised ejection fraction (< 30%).[327]

Electrophysiologic study inducibility (as well as nonsustained VT on ambulatory monitoring) was an entry criterion for the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT), the first major clinical trials to demonstrate a survival benefit for ICDs over drug therapy in the primary prevention of SCD (Table 91–4).[328,329] MUSTT and MADIT included post–myocardial infarction patients with left ventricular ejection fractions below 40% and 35%, respectively. More recent ICD trials, which enrolled post–myocardial infarction patients with ejection fractions less than 30% to 35%, did not require inducibility at an electrophysiologic study for enrollment.[330,331] Although these trials did show survival benefit for ICD implantation compared with control therapy, the magnitude of this benefit was significantly smaller than in the earlier trials that used electrophysiologic studies for risk stratification/entry criteria (see Chap. 81).

TREATMENT OPTIONS FOR PATIENTS AT RISK FOR SCD

PHARMACOLOGIC THERAPY

Several medications have been shown to reduce the risk of SCD in patients known to have cardiac disease. Some, such as the statins and aspirin, reduce sudden death by reducing the incidence of coronary plaque rupture or platelet aggregation and thrombosis. β-blockers stabilize autonomic balance, improve pump function, and help reduce ischemia, whereas angiotensin-converting enzyme (ACE) inhibitors reduce the incidence of sudden death through similar and probably other mechanisms as well (see Chap. 70).

β-Blockers

Of all the therapies currently available for the prevention of SCD, none are better established or more universally applicable in patients with CHD than β-blockers.[332] In a review of 19,000 post–myocardial infarction patients who were randomized to β-blockers or placebo, active treatment was associated with a 20% decrease in total mortality, a 30% reduction in SCD, and a 35% to 40% reduction in reinfarction.[333] The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) demonstrated a 34% decrease in all-cause mortality rate, a 38% decrease in cardiovascular mortality rate, and a 41% decrease in sudden death rate in 3991 patients who were randomized to β-blockers while being treated with standard medical therapy, including ACE inhibitors, digitalis, and diuretics.[334]

β-Blockers are effective in the setting of ventricular arrhythmias provoked by a high sympathetic tone, as in patients with congenital long QT syndrome, arrhythmogenic right ventricular dysplasia, or CHF. Importantly, the beneficial effects of β-blockers on cardiac mortality are most pronounced in patients who are at higher risk for sudden cardiac death, such as those with CHF, atrial and ventricular arrhythmias, post-myocardial infarction, and diabetes.[332]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Reduced total mortality rates have been proven with the use of ACE inhibitors in patients with impaired left ventricular ejection fraction with or without mild heart failure symptoms after myocardial infarction[335] and with established heart failure.[336-338] Although the mortality benefit from ACE inhibitors is thought to stem primarily from a reduction in pump failure, a specific reduction in the incidence of sudden death may be present as well. Although data from individual trials have conflicted on this issue, a meta-analysis including more than 15,000 post–myocardial infarction patients reported a 20% reduction in SCD in ACE inhibitor–treated subjects (odds ratio 0.80; 95% confidence interval, 0.70-0.92).[339] ACE inhibitor use has also been associated with reduction in appropriate ICD therapies.[340] Similar reductions in SCD have been seen with use of ARBs: in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) program, candesartan reduced sudden death by 15% (hazard ratio 0.85, 95% confidence interval 0.73-0.99, $P = .036$). Activation of the renin-angiotensin-aldosterone axis appears to be proarrhythmic, and ACE inhibitors and ARBs may exert antiarrhythmic properties via effects on multiple ion channels, cellular signaling pathways, and modulation of oxidative stress.[341]

The protection afforded by ACE inhibitors may extend to patients with vascular disease in general. A trial of patients with preserved left ventricular function who were 55 years or older and had vascular disease or diabetes and one other coronary risk factor found significantly fewer patients treated with ramipril had a cardiac arrest (relative risk, 0.62; $P = .02$).[342]

Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors (Statins)

The beneficial effects of statins for patients with atherosclerotic heart disease, and vascular disease in general, continue to mount. Recent reports suggest that, in addition to preventing vascular events, statins reduce SCD and appropriate shocks in patients with ICDs.[343] A report from the MADIT II trial found that time-dependent exposure to statins was associated with a nearly 30% reduction in appropriate ICD therapy for VT/VF or cardiac death, after adjustment for other factors,[344] and a recent meta-analysis demonstrated that statin use was associated with

TABLE 91–4. Trials for Primary Prevention of Sudden Cardiac Death

	N	CAD	Low EF	PVCs	NSVT	Therapy	Follow-Up (months)	Findings	Comments
Coronary artery disease									
Class IC									
CAST, 1989	1498	+	+	+	–	Encainide or flecainide vs placebo	10	7.7% mortality (treatment) vs 3.0% (placebo)	Terminated prematurely because of excess mortality in treatment group.
CAST II, 1992	1325	+	+	+	–	Moricizine vs placebo	14 d	2.6% death or cardiac arrest (treatment) vs 0.5% (placebo)	Terminated prematurely because of excess mortality in treatment group.
Amiodarone									
BASIS, 1990	312	+	–	+	–	Amiodarone vs mexiletine or quinidine vs placebo	72	5% mortality (amiodarone) vs 10% (class I) vs 13% (placebo)	Amiodarone improved survival, nonsignificant trend with Holter-guided PVC suppression.
EMIAT, 1997	1486	+	+	–	–	Amiodarone vs placebo	21	7.2% mortality (both groups), 35% RR in arrhythmic death	Amiodarone reduced arrhythmic death rate without affecting total survival.
CAMIAT, 1997	1202	+	–	+	–	Amiodarone vs placebo	21	3.3% VF/SCD (amiodarone) vs 6.0% (placebo), RR 21.2%	Prophylactic amiodarone improved survival for frequent/repetitive PVCs.
ICD									
MADIT, 1996	196	+	+	+	+	ICD vs conventional therapy	27	15.7% mortality (ICD) vs 38.6% (no ICD), RR 46%	Terminated prematurely because of significant ICD benefit.
CABG-Patch, 1997	900	+	+	–	–	ICD vs no ICD at time of CABG	36	No difference in all-cause mortality	All patients had abnormal SAECG; no benefit of prophylactic ICD.
MUSTT, 1999	704	+	+	+	+	EP-guided or ICD vs no antiarrhythmic therapy	60	25% mortality (EP-guided or ICD) vs 32% (no therapy)	EP-guided therapy with ICDs, but not with antiarrhythmic drugs, reduces the risk of SCD.
MADIT-II, 2002	1232	+	+	–	–	ICD vs conventional therapy	20	15.7% mortality (ICD) vs 19.8% (no-ICD), RR 31%	Patients on average were 3 y postinfarction.
DINAMIT, 2004	674	+	+	–	–	ICD vs conventional therapy	30	18.7% mortality (ICD) vs 17.0% (no ICD); HR 1.08	ICDs reduced arrhythmic death, but increased nonarrhythmic death.
IRIS, 2009	898	+	+	–	+	ICD vs conventional Rx	37	26.1% mortality (ICD) vs 25.8% (no ICD); HR 1.04	Findings confirmed results of DINAMIT.
Sotalol									
Julian et al, 1982	1456	+	–	–	–	*d,l*-Sotalol vs placebo	12	7.3% mortality (sotalol) vs 8.9% (placebo), RR 18%	*d,l*-Sotalol may reduce mortality by up to 25%.
SWORD, 1996	3121	+	+	–	–	*d*-Sotalol vs placebo	5	5.0% mortality (sotalol) vs 3.1% (placebo)	Trial terminated because of excess mortality in the treatment group.
CHF trials (nonischemic or mixed population)									
GESICA, 1994	516	~1/3	+	–	–	Amiodarone vs standard therapy	24	33.5% mortality (amiodarone) vs 41.4% (control)	Amiodarone improved survival in symptomatic heart failure.

(*continued*)

TABLE 91–4. Trials for Primary Prevention of Sudden Cardiac Death (*Continued*)

CHF-STAT, 1995	674	~2/3	+	–	–	Amiodarone vs placebo	45	30.6% mortality (amiodarone) vs 29.2% (placebo)	No survival benefit with amiodarone; trend to improved survival in DCM.
DEFINITE, 2004	458	–	+	+	+	ICD vs standard therapy	29	7.9% mortality (ICD) vs 14.1% (no ICD) at 2 y: HR 0.65 (0.40-1.06), $P = .08$	Statistically significant reduction in SCD from arrhythmia.
COMPANION, 2004	1520	~1/2	+	–	–	Med Rx vs CRT-P vs CRT-D	16	1-y mortality 19% (med Rx) vs 15% (CRT-P) vs 12% CRT-P	Mortality a secondary end point. CRT-D vs med Rx, $P = 0.003$.
SCD-HeFT, 2005	2521	~1/2	+	–	–	ICD vs amiodarone vs placebo	45	22% mortality (ICD) vs 28% (amiodarone) and 29% (placebo). HR (ICD vs placebo) 0.77	Amiodarone of no benefit vs placebo. Single-lead, shock only ICDs used.

Abbreviations: +, Inclusion criterion; –, not inclusion criterion; CAD, coronary artery disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; CHF, congestive heart failure; DCM, dilated cardiomyopathy; EF, ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; NSVT, nonsustained ventricular tachycardia; PVCs, premature ventricular contractions; RR, risk reduction; SCD, sudden cardiac death; VF, ventricular fibrillation. See text for clinical trial abbreviations.

Modified with permission from Welch PJ1, Page RL, Hamdan MH: Management of ventricular arrhythmias: a trial-based approach. *J Am Coll Cardiol*. 1999 Sep;34(3):621-630.

a 10% reduction in SCD.[345] Whether this beneficial effect of statins is mediated through prevention of coronary ischemic events, or through some other mechanism, is currently unknown.

Antiarrhythmic Agents

The efficacy and safety of antiarrhythmic drugs in preventing sudden death has been disappointing (see Table 91–4). In fact, for patients with advanced heart failure and/or prior myocardial infarction, only two antiarrhythmic drugs—amiodarone and dofetilide—lack evidence of *increased* mortality compared with placebo.

Class I Antiarrhythmic Agents The landmark CAST I and CAST II trials revealed increased mortality in post–myocardial infarction patients with frequent ventricular ectopy treated for primary prevention with Vaughn-Williams class I-C agents encainide, flecainide, and moricizine.[264,346,347] Likewise, the propafenone arm of the secondary prevention Cardiac Arrest Hamburg Study (CASH) trial was terminated early because of excess mortality compared with the other groups.[348]

A meta-analysis of lidocaine in acute myocardial infarction suggested an increase in in-hospital mortality rate despite a reduction in the prevalence of ventricular fibrillation.[349] Empiric use of class IA drugs for long-term management in cardiac arrest survivors was also shown to increase mortality in a nonrandomized series.[350] No other class I antiarrhythmic drug has been shown to prolong survival in any patient group studied (see Chap. 87).

Sotalol The effect of the class III agent sotalol on sudden death in high-risk patients is somewhat uncertain, in part because the commercially available preparation of the drug is a racemic mixture of *d*- and *l*-stereoisomers. The *d*-isomer is a potent class III antiarrhythmic agent, whereas the *l*-isomer has nonselective β-blocking effects. Separating potentially detrimental and beneficial effects of sotalol is therefore difficult. In the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) study, which enrolled patients with sustained VT (75%), syncope, or cardiac arrest, sotalol appeared to be both safer and more effective than a variety of class I agents.[351]

However, when the class III effects of *d*-sotalol are isolated from the β-blocking properties of *l*-sotalol, the drug appears less safe. *d*-Sotalol was compared with placebo in more than 3000 patients in the Survival With Oral *d*-Sotalol (SWORD) trial of post–myocardial infarction patients with ejection fractions ≤ 40% and was associated with a statistically significant *increase* in total mortality.[352] Sotalol prolongs the QT interval and can cause torsade de pointes, which has been reported to occur in up to 8% of treated patients.

Amiodarone Amiodarone is widely considered the most effective antiarrhythmic agent for therapy of supraventricular and ventricular arrhythmias[353,354] (see Chap. 87). It is a class III antiarrhythmic agent with additional class I, II, and IV properties and has unusual pharmacokinetics, with a delayed onset of action and long elimination half-life after chronic therapy. Both oral and intravenous versions are available.

Amiodarone was shown to significantly reduce SCD rates among post–myocardial infarction and heart failure patients in several placebo-controlled randomized studies, but its effects on total mortality are questionable, with some individual trials showing improved survival,[355,356] but others not[357-360] (see Table 91–4). Unlike with other antiarrhythmic drugs, however, no study has shown increased mortality associated with use of amiodarone in these populations. Two meta-analyses of all placebo-controlled amiodarone trials before the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was published both concluded that amiodarone reduced the total mortality of post–myocardial infarction and heart failure populations by approximately 10%.[361,362] Therefore, amiodarone is often the drug of choice when antiarrhythmic drug treatment is required in patients with left ventricular dysfunction and congestive heart failure. Amiodarone also served as an active control against ICD implantation in multiple randomized trials for both secondary and primary prevention of sudden death.[331,363-365] In all cases, amiodarone was inferior to ICD therapy for the end point of total mortality (see the next section).

In contrast to the oral amiodarone, relatively strong evidence supports the use of intravenous amiodarone for out-of-hospital cardiac arrest and recurrent unstable ventricular arrhythmias. The efficacy of intravenous amiodarone in patients with recurrent, hemodynamically

unstable VT refractory to lidocaine, procainamide, and bretylium was approximately 40% in one prospective study, with suppression of approximately 80% of the arrhythmias within 48 hours.[366] The use of intravenous amiodarone in out-of-hospital cardiac arrest was studied in two important randomized trials. In the first, community patients receiving a 300-mg bolus of intravenous amiodarone for VT/VF refractory to three external shocks had an improved rate of survival to hospital admission compared with placebo-treated patients.[291] In the second trial, intravenous amiodarone proved superior to intravenous lidocaine for the same indication.[367] Neither trial was sufficiently powered to detect a difference in survival to hospital discharge.

DEVICE THERAPY

Implantable Cardioverter-Defibrillator

The implantable cardioverter-defibrillator (ICD) was initially developed to recognize VF or rapid VT and terminate it automatically by delivering one or more high-energy shocks[368] (see Chap. 89). The first generation of defibrillators required a thoracotomy to epicardially place the sensing and defibrillator leads, and the generator size mandated implantation of the device in an abdominal pocket. The reduced size of defibrillators now allows for transvenous, endocardial lead systems that integrate pacing, sensing, and high-voltage defibrillation abilities. Current-generation defibrillators have the additional ability to deliver low-energy cardioversion, antitachycardia pacing for VT, antibradycardia pacing, and have all the features of the most sophisticated pacemakers, including the capacity to provide cardiac resynchronization therapy.[369] Given the excellent safety of current ICD implantation techniques and performance of ICD systems, a major challenge has been the identification of patient populations most appropriate for this potentially lifesaving therapy.

Secondary Prevention of Sudden Cardiac Death Three major trials of ICDs for secondary prevention of SCD have been conducted (see Chap. 89). Each enrolled patients successfully resuscitated from VF arrest or hemodynamically nontolerated VT without a transient reversible cause, and all three trials compared ICDs with amiodarone (the CASH trial had additional propafenone and metoprolol arms[348]). The Canadian Implantable Defibrillator Study (CIDS)[363] randomized 659 patients to ICD or amiodarone. After 3 years of follow-up, ICDs were associated with a 33% reduction in arrhythmic death and a 20% reduction in total mortality that did not reach statistical significance. The CASH trial reported a nonsignificant 23% reduction of all-cause mortality at 2 years in the ICD arm compared with the drug arm (metoprolol or amiodarone).[364] The Antiarrhythmics Versus Implantable Defibrillator (AVID) trial, the largest and most recent secondary prevention ICD trial,[365] randomized 1,016 patients to ICD or amiodarone and found a significant improvement in survival at 3 years for ICD patients (75% vs 64%, $P = .02$). Thus, although the CIDS and CASH trials did not reach statistical significance, the treatment effect was in the same direction, and the three trials were generally regarded as consistent. ICDs are therefore considered by consensus guidelines a class I (level of evidence A) indication for patients with cardiac arrest from VF or VT not caused by a transient or reversible cause and for patients with spontaneous sustained VT in association with structural heart disease.[128]

Primary Prevention of Sudden Cardiac Death A number of randomized studies looking at primary prevention of SCD (prophylactic use of defibrillators in high-risk populations) have been published as well (see Table 91–4) (see also Chap. 89). These studies varied considerably in patient population, entry criteria, and nature of control group therapy, but in aggregate supported an expansion in the use of ICDs for primary prevention of SCD.

The Coronary Artery Bypass Graft (CABG) Patch Trial found no significant difference in the primary end point of total mortality in patients with ejection fractions of < 30% and an abnormal SAECG randomized to ICD or no ICD at the time of CABG.[370] These negative findings were attributed to the benefit of complete revascularization and possibly to the poor positive predictive value of the SAECG. Two studies—MADIT[329] and MUSTT[328]—enrolled patients with left ventricular ejection fractions less than 35% or 40%, respectively, because of prior myocardial infarction who also had nonsustained VT on ambulatory monitoring and inducible VT at the time of invasive EP studies. In both MADIT and MUSTT, ICD therapy was associated with significant relative risk reductions (51%-59%) in total mortality over 3 to 5 years of follow-up, compared with no antiarrhythmic therapy (MUSTT) or "standard" therapy consisting primarily of amiodarone (MADIT).

The MUSTT/MADIT entry criteria remained the standard of care for selecting post-MI patients for ICDs until the publication of the MADIT II trial, which included patients with ejection fractions less than 30% as a result of prior MI, *without* further risk stratification with an electrophysiology study.[330] MADIT II patients were randomized to ICD implantation or standard medical therapy without antiarrhythmic drugs. MADIT II reported an absolute 6% decrease in total mortality from 20% to 14% over 20 months in favor of the ICD group.[330] The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which comprised a roughly even split between ischemic and nonischemic cardiomyopathy patients, similarly found a 7% absolute mortality difference (22% vs 29%) between ICD and standard medical therapy, respectively, over 45 months for patients with ejection fractions below 35% and NYHA class II or III heart failure.[331]

ICDs do not appear to be of benefit immediately after large myocardial infarctions. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) randomized 674 patients with recent (6-40 days) myocardial infarction, left ventricular ejection fraction less than 35%, and depressed heart rate variability on 24-hour monitoring to ICD or no ICD. In contrast to other trials that excluded patients with very recent infarcts, the DINAMIT found no benefit from prophylactic ICD implantation.[371] These findings were confirmed in the Immediate Risk Stratification Improves Survival (IRIS) trial, which also found no benefit on total mortality from ICDs in 898 patients enrolled between 5 and 31 days after an acute myocardial infarction.[372]

Based on results from the above trials, consensus guidelines have classified ICD implantation as a class I intervention under one of the three following scenarios: (1) left ventricular ejection fraction ≤40% as a result of prior myocardial infarction, nonsustained VT, and inducible VF or sustained VT at electrophysiological study (MADIT/MUSTT criteria—level of evidence B); (2) left ventricular ejection fraction ≤ 35% resulting from any cause with NYHA functional class II or III (SCD-HeFT criteria—level of evidence A for patients with prior MI who are > 40 days post MI, and level of evidence B for patients with nonischemic cardiomyopathy); or (3) left ventricular ejection fraction ≤ 30% as a result of prior myocardial infarction with NYHA functional class < IV (MADIT-II criteria—level of evidence A). In general, ICDs are not implanted in patients who have an expected lifespan of < 1 year or NYHA class IV heart failure (an exclusion criterion from most ICD trials), unless the patient is ambulatory and also a candidate for cardiac resynchronization therapy or ventricular assist device/cardiac transplant (class III, level of evidence C).[128]

Several ICD primary prevention trials in patients with nonischemic cardiomyopathy and heart failure have also been conducted, but the results have not been as consistently positive as in the post-MI population. Two early trials (the Cardiomyopathy Trial [CAT][373] and the Amiodarone Versus Implantable Cardioverter Defibrillator Trial [AMIOVIRT][374]) compared ICDs versus either standard medical

therapy or amiodarone, respectively, in nonischemic cardiomyopathy patients, but were too small to find differences between groups. The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFNITE) trial enrolled 458 nonischemic cardiomyopathy patients with ejection fraction ≤ 35%, symptomatic heart failure, and either nonsustained VT or frequent PVCs on Holter monitoring and randomized them to standard medical therapy with or without ICDs. All-cause mortality at 2 years was 13.8% with standard medical therapy versus 8.1% for medical therapy plus ICD, a result that fell just short of statistical significance ($P = .06$).[375]

Finally, the aforementioned SCD-HeFT trial enrolled more than 2500 patients with class II (70%) and III heart failure and left ventricular ejection fraction ≤ 35% as a result of either ischemic or nonischemic cardiomyopathy and randomized them to ICD, amiodarone, or placebo, in addition to standard medical therapy. After a median of 45 months, all-cause mortality in the ICD, amiodarone, and placebo arms was 22%, 28%, and 29%, respectively. The benefit of ICDs in the trial was highly statistically significant and appeared similar between ischemic and nonischemic subgroups, but was greater for patients with class II than for those with class III heart failure—an observation not seen in other ICD trials.[331] (Fig. 91–8).

ICDs have also been used in less common conditions associated with a high risk of SCD, including hypertrophic cardiomyopathy, congenital long QT syndrome, Brugada syndrome, and ARVC. Nonrandomized series suggest a salutary effect on survival in carefully selected patients with these disorders. Because of a lack of evidence from randomized trials, primary prevention ICD implantation in these cases is presently a class IIa or IIb recommendation (Table 91–5).[128]

The feasibility and safety of combining defibrillation with cardiac resynchronization therapy (CRT) pacing in a single device has also been established.[376] Although both CRT pacemakers and CRT defibrillators have been shown to reduce mortality in patients with left ventricular systolic dysfunction, severe heart failure symptoms, and wide

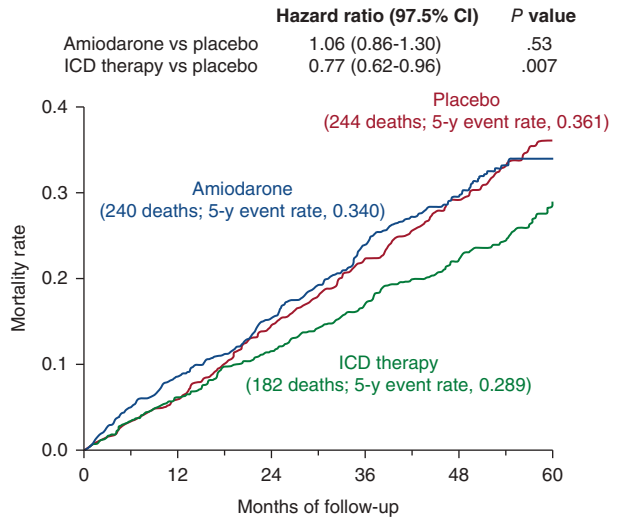

FIGURE 91–8. Kaplan-Meier estimates of overall mortality in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). For patients with left ventricular ejection fractions of ≤ 35% and New York Heart Association class II or III heart failure, implantable cardioverter-defibrillator therapy reduced all-cause mortality over 5 years by an absolute margin of 7% versus placebo (*red line*), whereas amiodarone (*green line*) provided no benefit. Reproduced with permission from Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005 Jan 20;352(3):225-237.

TABLE 91–5. Guidelines and Level of Evidence for ICD Implantation in Select Cardiac Disorders Associated With Ventricular Arrhythmias and Sudden Cardiac Death

Disorder	Indication for ICD	Recommendation Class/ Level of Evidence (LOE)
Long QT syndrome	Survivors of cardiac arrest	Class I/LOE A
	Recurrent syncope on beta-blockers	Class IIa/LOE B
	High risk factors for SCD[a]	Class IIb/LOE B
	Asymptomatic patients not on beta-blockers	Class III
Hypertrophic cardiomyopathy	Survivors of cardiac arrest/ sustained VT	Class I/LOA A
	1 or more SCD risk factors[b]	Class IIa/LOE C
Brugada syndrome	Survivors of cardiac arrest	Class I/LOA A
	Spontaneous Type I ECG and syncope likely caused by ventricular arrhythmia	Class IIa/LOE C or Class IIb
	Spontaneous VT without cardiac arrest	Class IIb/LOE C
	VF induced during EP study	Class IIb
	Asymptomatic patients with drug-induced type I Brugada pattern on the basis of only a family history of SCD	Class III
ARVC	Survivors of cardiac arrest/ sustained VT	Class I
	Patients at "high risk" for SCD[c]	Class IIa/LOE C
Short QT syndrome	Survivors of cardiac arrest/ spontaneous VT	Class I
	Asymptomatic patients with family history of SCD	Class IIb
CPVT	Survivors of cardiac arrest/ spontaneous VT/syncope despite medical therapy	Class I
	Syncope and/or sustained VT on beta-blockers	Class IIa/LOE C
	Asymptomatic patient not on medical therapy	Class III

[a] Including symptomatic patients with > 1 mutations, Jervell and Lange-Nielsen syndrome, extremely prolonged QT interval.

[b] Syncope, family history of SCD, nonsustained VT, LV outflow tract gradient > 30 mm Hg, hypotensive response to exercise, LV thickness > 30 mm. Other risk factors exist and may be important as well.

[c] Syncope, extensive RV involvement, LV involvement, Naxos disease, and other high-risk mutations, age < 5 years at presentation, VT induced at EP study, nonsustained VT.

Data from Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart rhythm : *the official journal of the Heart Rhythm Society*. 2013;10(12):1932-1963; and Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Journal of the American College of Cardiology*. 2008;51(21):e1-62.

QRS duration on ECG, the incremental benefit of CRT defibrillators over CRT pacemakers remains uncertain.[369,377]

Subcutaneous Implantable Cardioverter-Defibrillator

The subcutaneous defibrillator, which uses a single sensing and defibrillation lead placed in the subcutaneous tissue of the thorax and thus avoids the need for intravascular leads, has recently become available. The subcutaneous ICD may therefore be an attractive option for patients who meet criteria for ICD implantation, but who are at high risk for infection, have vascular access issues, or are young and at high risk for transvenous lead complications over time. The subcutaneous ICD has the ability to provide post-shock backup pacing, but cannot deliver antitachycardia pacing as treatment for ventricular tachycardia.[378] Data have suggested that the subcutaneous ICD is highly effective for treating ventricular arrhythmias, although inappropriate shocks are frequent (up to 13.1% at 3 years) and often caused by T-wave oversensing, with a trend towards a reduction in inappropriate shocks over time and with increased experience with use of the device.[379] As technology improves and experience with the subcutaneous defibrillator increases, the role for this device in primary and secondary prevention of SCD may increase. It should be noted, however, that because subcutaneous ICD technology is relatively new, there are no formal society guidelines supporting use of the subcutaneous ICD as opposed to a transvenous ICD, and the breadth of data supporting use of the subcutaneous ICD is limited.

Wearable Cardioverter-Defibrillator

Some patients who do not meet guidelines for ICD implantation (such as patients with a recent myocardial infarction within 40 days and severely reduced left ventricular function, cardiac revascularization within 90 days, or those in whom LV systolic dysfunction is likely to be reversible) have an elevated risk of ventricular arrhythmias and SCD. In these patients, a wearable cardioverter defibrillator (WCD) has been studied as a way of reducing SCD risk. The device consists of a vest-like garment with built in ECG and defibrillation electrodes that connects to a battery and monitoring unit.[380,381] The device contains algorithms to detect ventricular arrhythmias based on rate, template matching (comparing the QRS complex of the tachyarrhythmia to the QRS complex in sinus rhythm), and duration. The device delivers up to 150 J biphasic external shocks. To minimize the risk of inappropriate shocks, the device has an alarm to alert the patient prior to delivering therapy, and the patient can abort shocks if he or she is asymptomatic and/or conscious. The wearable cardioverter defibrillator has no pacing (either bradycardic or antitachycardia) capabilities[380].

Various iterations of the wearable cardioverter defibrillator have been evaluated for their ability to reduce SCD in multiple studies. In initial studies (WEARIT and BIROAD), 289 patients with symptomatic heart failure and LVEF < 30% (WEARIT) and patients deemed high risk for SCD after myocardial infarction or coronary artery bypass grafting (BIROAD) who did not meet criteria for ICD implantation, were waiting for ICD implantation at a later date, or had refused ICD implantation, were treated with the wearable cardioverter defibrillator. The studies (which were carried out simultaneously) were terminated early due to meeting prespecified efficacy and safety criteria. Seventy-five percent of defibrillation attempts were successful, and over 901 months of use, only six inappropriate shocks occurred. Six SCDs occurred, all in patients who were either not wearing the device or wearing it incorrectly.[382]

In a registry of 3,569 patients treated with a WCD, slightly more than half of patients were compliant with wearing the device (defined as wearing the WCD > 90% of the time). Inappropriate shocks occurred in 1.9% of patients. Only 1.7% of patients experienced VT/VF, and the device was successful at terminating VT/VF in 99% of cases. Overall, patients survived 90% of VT/VF events, but post-shock asystole and pulseless electrical activity were important causes of mortality that the WCD could not treat.[383]

In a study of 8,453 patients who had a WCD prescribed within the first 3 months after myocardial infarction, 133 (1.6%) patients received appropriate shocks, and 91% of these patients survived their arrhythmic event. The median time from index myocardial infarction to appropriate WCD therapy was only 16 days, and 75% of WCD therapies occurred within the first month.[384] In the WEARIT-II registry of a mixed population of 2,000 patients with ischemic cardiomyopathy, nonischemic cardiomyopathy, and congenital heart disease who were prescribed the WCD, approximately 1% of patients received appropriate therapy for VT/VF, and only 0.5% of patients received inappropriate shocks.[380] The first randomized trial evaluating use of the WCD in patients with recent MI and LVEF ≤ 35% (the Vest prevention of Early Sudden death Trial [VEST]—clinicaltrials.gov identifier NCT01446965) is currently recruiting patients.

The WCD is not indicated for long-term use—rather it should be considered for use in patients who have an indication for ICD implantation that may be temporary (such as early on in peripartum cardiomyopathy or myocarditis), an indication for ICD implantation but a temporary contraindication to therapy (such as after ICD extraction for a device related infection), or in those in whom additional testing will determine candidacy for permanent ICD implantation. Thus, the WCD should be used as a "bridge" to ICD implantation or the decision for ICD implantation rather than as "destination" therapy to reduce the risk of SCD. The most recent guidelines from the European Society of Cardiology give the WCD a class IIb (level of evidence C) recommendation for use in patients with reduced LV function at an elevated risk for SCD but who are not candidates for ICD implantation.[259] As randomized control trial data supporting use of the WCT becomes available (VEST trial) the indications for WCT use will likely expand.

ROLE OF SURGERY

REVASCULARIZATION

There is a reduced prevalence of SCD after CABG,[385] and attempts should be made to identify and revascularize ischemic myocardium in order to mitigate arrhythmic risk. Although it is accepted that CABG reduces ventricular arrhythmias, the effect is unpredictable. Among the 13,476 patients in the Coronary Artery Surgical Study (CASS) registry, all of whom had significant coronary artery disease, operable vessels, and no significant valvular disease, the mean incidence of SCD during the 4.6-year average follow-up was 5.2% in patients treated medically and 1.8% in those treated surgically. The beneficial effect of CABG was even more pronounced in the subgroup of patients with reduced left ventricular ejection fraction and multivessel disease, where the SCD free survival rate at 5 years was 91% for the surgical group versus 69% in the medical group.[385]

The protective effect of CABG against recurrent cardiac arrest appears to be best in patients with reversible ischemia as the major pathophysiologic factor in SCD. These patients are characterized by critical coronary artery disease, significant regions of myocardium at risk for ischemia, and no inducible monomorphic ventricular arrhythmias at electrophysiologic study.[386,387] Despite the encouraging results of CABG in survivors of cardiac arrest, it should be noted that only a minority of these patients are candidates for operative revascularization and that scar-mediated, monomorphic VT is often not controlled by myocardial revascularization alone.[388] The relative benefits of partial

or complete percutaneous revascularization compared with CABG in this setting are also unclear.

ANTIARRHYTHMIA SURGERY

Electrophysiologically guided subendocardial resection and cryoablation are potentially curative surgical options in patients with recurrent monomorphic VT in whom areas of slow conduction around myocardial scars are critical for sustaining VT. Long-term follow-up of this operative technique has yielded a clinical success rate of nearly 90% in eliminating the presenting rhythm in patients who survive surgery. This approach was limited by the high surgical mortality rate of 10% to 15% in early series[389]; however, these data, gathered in the 1980s, may exaggerate the operative risk, given improvements in surgical technique over time. The best candidates for electrophysiologically guided subendocardial resection are patients who require coronary revascularization and have a well-defined left ventricular aneurysm.

CATHETER ABLATION THERAPY

Catheter ablation of arrhythmias has emerged as a curative approach for many supraventricular arrhythmias and a few specific forms of VT. The role of catheter ablation in the prevention of SCD is less well established, but this therapy has been successfully used in selected cases. Rarely, supraventricular tachycardias with a rapid ventricular response may degenerate into fatal ventricular tachyarrhythmias and cardiac arrest.[390] Radiofrequency catheter ablation can eliminate the risk of a rapid ventricular response by abolishing conduction over an accessory pathway in patients with Wolff-Parkinson-White syndrome,[247] or it can slow or completely block conduction over the atrioventricular node in patients with atrial arrhythmias and rapid, medically uncontrolled atrioventricular conduction. Radiofrequency catheter ablation can potentially prevent SCD in patients with documented and inducible bundle-branch reentrant VT as the only mechanism of cardiac arrest.[391]

In the Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) randomized study, VT ablation significantly reduced the incidence of subsequent defibrillator therapies in patients with prior MI and spontaneous ventricular arrhythmias,[392] but high rates of recurrent VT after apparently successful VT ablations suggest that few of these patients can safely be managed without ICDs.[393] Improved imaging and mapping techniques, new types of catheters, and novel energy sources may help improve the efficacy of catheter ablation for VT and potentially expand its future role in the prevention of SCD (see Chap. 88).

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CHAPTER 92

CARDIOPULMONARY AND CARDIOCEREBRAL RESUSCITATION

Eyal Herzog, Lee Herzog, and Emad Aziz

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DEFINING SUDDEN CARDIAC ARREST

Cardiac arrest is defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. Cardiac arrest is traditionally categorized as being of cardiac or noncardiac origin. An arrest is presumed to be of cardiac origin unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination, or any other noncardiac cause as best determined by rescuers.[1]

It is challenging to define what "unexpected" or "sudden" death is. Current practice defines sudden cardiac death as unexpected death without an obvious noncardiac cause that occurs within 1 hour of symptom onset (witnessed) or within 24 hours of last being observed in normal health (unwitnessed).[2]

EPIDEMIOLOGY OF OUT-OF-HOSPITAL CARDIAC ARREST

The following is based on American Heart Association (AHA) statistical data from 2015[1]:

- Each year 326,000 people experience EMS-assessed out-of-hospital cardiac arrests in the United States.
- Approximately 60% of out-of-hospital cardiac arrests are treated by EMS personnel.[3]
- Twenty-five percent of those with EMS-treated out-of-hospital cardiac arrest have no symptoms before the onset of arrest.[4]
- Among EMS-treated out-of-hospital cardiac arrests, 23% have an initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) or are shockable by an automated external defibrillator.[5]
- The incidence of cardiac arrest with an initial rhythm of VF is decreasing over time; however, the incidence of cardiac arrest is not decreasing.[6]
- The median age for out-of-hospital cardiac arrest is 66 years.[7]
- Cardiac arrest is witnessed by a bystander in 38.7% of cases, by an EMS provider in 10.9% of cases, and is unwitnessed in 50.4% of cases.[7]
- In the Cardiac Arrest Registry to Enhance Survival (CARES) registry, 31,127 out-of-hospital cardiac arrests were treated in 2013. Survival to hospital discharge was 10.6% and survival with good neurological function (Cerebral Performance Category 1 or 2) was 8.3%. For bystander witnessed arrest with a shockable rhythm, survival to hospital discharge was 33.0%.[7]
- According to the CARES registry, in 2013 the majority of out-of-hospital cardiac arrests occurred at a home or residence (69.5%).[7]
- A family history of cardiac arrest in a first-degree relative is associated with a twofold increase in risk of cardiac arrest.[8,9]

EPIDEMIOLOGY OF IN-HOSPITAL CARDIAC ARREST

Based on the AHA Statistical Data from 2015[1]:

- Each year, 209,000 people are treated for in-hospital cardiac arrest in the United States.[10]
- According to the Get With The Guidelines (GWTG)-Resuscitation database from 2014, 25.5% of adults who experienced in-hospital cardiac arrest with any first recorded rhythm in 2013 survived to discharge.[1]
- In the United Kingdom National Cardiac Arrest Audit database between 2011 and 2013, the overall unadjusted survival rate was 18.4%. Survival was 49% when the initial rhythm was shockable and 10.5% when the initial rhythm was not shockable.[11]

CPR GUIDELINE EVOLUTION

The initial attempts to treat cardiac arrest focused on chest compressions. Closed chest defibrillation and closed chest cardiac massage were first described in the 1960s.

In the initial publication, some patients were treated with chest compression without positive pressure. However with time, ventilation gradually became an essential pillar of cardiopulmonary resuscitation.

Given the prevalence and lethality of cardiac arrest, the American Heart Association (AHA) disseminated cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) information to health care professionals and the lay public in the 1970s.

The International Liaison Committee on Resuscitation (ILCOR) was formed in 1993. It currently includes representatives from the American Heart Association (AHA), the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Australian and New Zealand Committee on Resuscitation, the Resuscitation Council of Southern Africa, the InterAmerican Heart Foundation, and the Resuscitation Council of Asia.[12]

In 1999, the AHA hosted the first ILCOR conference to evaluate resuscitation science and develop common resuscitation guidelines. The conference recommendations were published in the *Guidelines 2000 for CPR and ECC*. Since 2000, researchers from the ILCOR member councils have evaluated and reported their International Consensus on CPR and ECC Science with Treatment Recommendations (CoSTR) in 5-year cycles.[12]

HIGHLIGHTS OF THE 2015 AMERICAN HEART ASSOCIATION GUIDELINES UPDATED FOR CPR AND ECC

BASIC LIFE SUPPORT

Systems of Care

The 2015 AHA Updated Guidelines highlighted a new perspective on systems of care, differentiating in-hospital cardiac arrests (IHCAs) from out-of-hospital cardiac arrests (OHCAs).[13]

The care for all post–cardiac arrest patients, regardless of the location of the arrests, converges in the hospital, generally in an intensive care unit where post–cardiac arrest care is provided. The systems of care before that convergence are very different for the two settings. Patients who have an OHCA depend on their community for support. Lay rescuers must recognize the arrest, call for help, initiate CPR, and provide defibrillation (ie, public-access defibrillation [PAD]) until EMS assumes responsibility and transports the patient to an emergency department and/or cardiac catheterization lab. The patient is ultimately transferred to a critical care unit for continued care.

In contrast, patients who have an IHCA depend on a system of appropriate surveillance (rapid response or early warning system) to prevent cardiac arrest. If cardiac arrest occurs, patients depend on the smooth interaction of the institution's various services and a multidisciplinary team of professional providers, including physicians, nurses, and respiratory therapists, among others.

Community Lay Rescuer AED Programs

It is recommended that PAD programs for patients with OHCA be implemented in public locations where there is a relatively high likelihood of witnessed cardiac arrest (ie, airports, casinos, sports facilities). There is clear and consistent evidence of improved survival from cardiac arrest when a bystander performs CPR and rapidly uses an AED. Thus, immediate access to a defibrillator is a primary component of the system of care. The implementation of a PAD program requires four essential components: (1) a planned and practiced response, which ideally includes identification of locations and neighborhoods where there is high risk of cardiac arrest, placement of AEDs in those areas, ensuring that bystanders are aware of the location of the AEDs, and, typically, oversight by an HCP; (2) training of anticipated rescuers in CPR and use of the AED; (3) an integrated link with the local EMS system; and (4) a program of ongoing quality improvement. Figure 92–1 outlines the 2015 guideline recommendations for the initial approach to a patient who is unresponsive.

Chest Compressions

Untrained lay rescuers should provide compression-only (Hands-Only) CPR, with or without dispatcher guidance, for adult victims of cardiac arrest. The rescuer should continue compression-only CPR until the arrival of an AED or rescuers with additional training. All lay rescuers should, at a minimum, provide chest compressions for victims of cardiac arrest. In addition, if the trained lay rescuer is able to perform rescue breaths, he or she should add rescue breaths in a ratio of 30 compressions to 2 breaths. The rescuer should continue CPR until an AED arrives and is ready for use, EMS providers take over care of the victim, or the victim starts to move.

Chest Compression Rate In most studies, more compressions are associated with higher survival rates, and fewer compressions are associated with lower survival rates. New to the 2015 Guidelines Update are upper limits of recommended compression rate and compression depth, based on preliminary data suggesting that excessive compression rate and depth adversely affect outcomes.

For the critical outcome of survival to hospital discharge, evidence exists from two observational studies[14,15] representing 13,469 adult patients. They compared chest compression rates of greater than 140/min, 120 to 139/min, less than 80/min, and 80 to 99/min with the

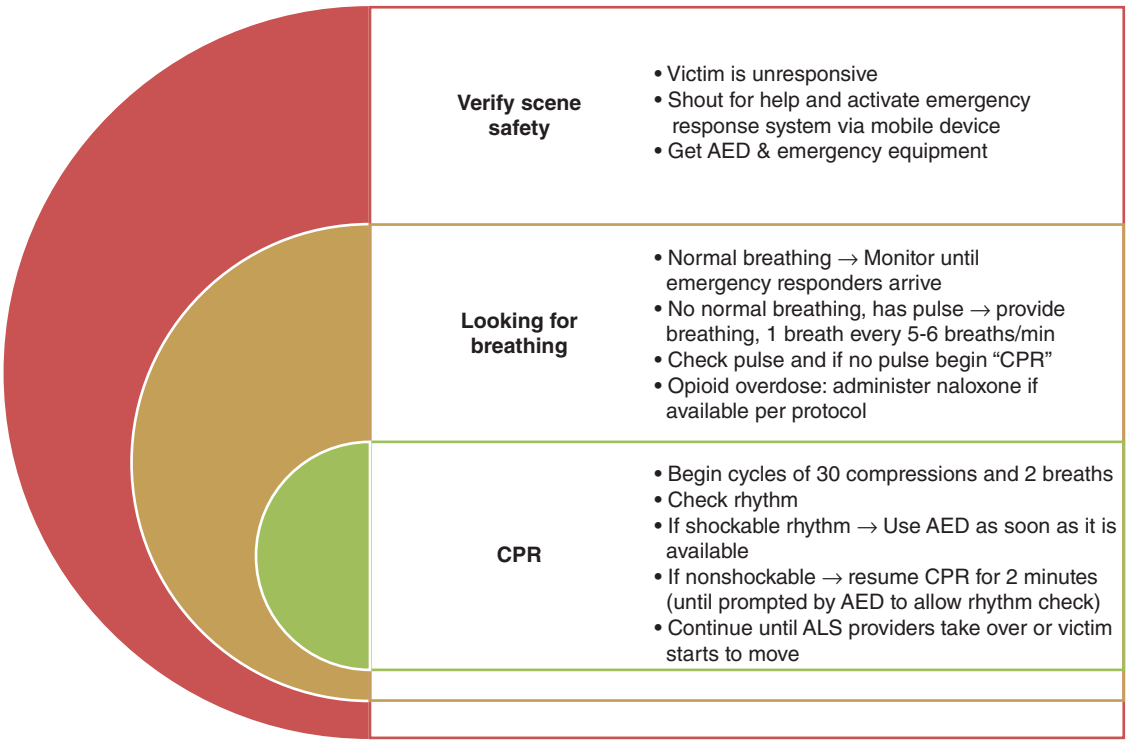


FIGURE 92–1. Updated 2015 guideline recommendations for unresponsive patient management. AED, automatic external defibrillator; CPR, cardiopulmonary resuscitation; ALS, advanced life support.

control rate of 100 to 119/min. When compared with the control chest compression rate of 100 to 119/min, there was a 4% decrease in survival to hospital discharge with compression rates of greater than 140/min, a 2% decrease in survival to hospital discharge with compression rates of 120 to 139/min, a 1% decrease in survival to hospital discharge with compression rates of less than 80/min, and a 2% decrease in survival to hospital discharge with compression rates of 80 to 99/min.

The study showed chest compression depth declined with increasing chest compression rate. The relationship of reduced compression depth at different compression rates was as follows: for a compression rate of 100 to119/min, 35% of compressions had a depth less than 3.8 cm; for a compression rate of 120 to 139/min, 50% of compressions had a depth less than 3.8 cm; and for a compression rate of 140/min or greater, 70% of the compressions had a depth less than 3.8 cm.

Treatment Recommendations The 2015 guidelines recommend a manual chest compression rate of 100 to 120/min.

Chest Compression Depth During manual CPR, rescuers should perform chest compressions to a depth of at least 2 inches (5 cm) for an average adult, while avoiding excessive chest compression depths (greater than 2.4 inches [6 cm]).

The reason for emphasis on accurate chest compression depth is the following: compressions create blood flow primarily by increasing intrathoracic pressure and directly compressing the heart, which in turn results in critical blood flow and oxygen delivery to the heart and brain. Rescuers often do not compress the chest deeply enough despite the recommendation to "push hard." Although a compression depth of at least 2 inches (5 cm) is recommended, as noted above the 2015 Guidelines Update incorporates new evidence about the potential for an upper threshold of compression depth (greater than 2.4 inches [6 cm]) beyond which complications may occur. Compression depth may be difficult to judge without use of feedback devices, and identification of upper limits of compression depth may be challenging.

For the critical outcome of survival to hospital discharge, three observational studies[16-18] suggest that survival may improve with increasing compression depth. In the largest study (9136 patients), a covariate-adjusted spline analysis showed a maximum survival at a mean depth of 4.0 to 5.5 cm (1.6 to 2.2 inches), with a peak at 4.6 cm (1.8 inches).[18]

Another important study showed injuries were reported in 63% with compression depth more than 6 cm (more than 2.4 inches) and 31% with compression depth less than 6 cm. Injuries were reported in 28%, 27%, and 49% with compression depths less than 5 cm (less than 2 inches), 5 to 6 cm (2 to 2.4 inches), and more than 6 cm (more than 2.4 inches), respectively.[19]

Treatment Recommendations The 2015 guidelines recommend a chest compression depth of approximately 5 cm (2 inches) while avoiding excessive chest compression depths (greater than 6 cm [greater than 2.4 inches] in an average adult) during manual CPR.

Compression-Ventilation Ratio

The critical outcome of survival with favorable neurologic outcome at discharge was studied in two observational studies.[20,21] Of the 1711 patients included, those who were treated under the 2005 guidelines with a compression-ventilation ratio of 30:2 had slightly higher survival than those patients treated under the 2000 guidelines with a compression-ventilation ratio of 15:2 (8.9% vs 6.5%; RR 1.37 [95% CI, 0.98–1.91]).

The critical outcome of survival to hospital discharge was tested in four observational studies.[20-23] Of the 4183 patients included, those who were treated under the 2005 guidelines with a compression-ventilation ratio of 30:2 had slightly higher survival than those patients treated under the 2000 guidelines with a compression-ventilation ratio of 15:2 (11.0% vs 7.0%; RR 1.75 [95% CI, 1.32–2.04]).

For the critical outcome of survival to 30 days, one observational study[24] found that patients treated under the 2005 guidelines had slightly higher survival than those patients treated under the 2000 guidelines (16.0% vs 8.3%; RR 1.92 [95% CI, 1.28–2.87]).

For the critical outcome of any return of spontaneous circulation (ROSC), two observational studies[20,21] found that patients treated under the 2005 guidelines had a ROSC more often than those patients treated under the 2000 guidelines (38.7% vs 30.0%; RR 1.30 [95% CI, 1.14–1.49]).

Treatment Recommendation The 2015 guidelines suggest a compression-ventilation ratio of 30:2 compared with any other compression-ventilation ratio in patients in cardiac arrest.

Ventilation During CPR with Advanced Airway

The 2015 guideline suggest that it may be reasonable for the provider to deliver 1 breath every 6 seconds (10 breaths per minute) while continuous chest compressions are being performed (ie, during CPR with an advanced airway).

Bystander Naloxone in Opioid-Associated Life-Threatening Emergencies

New for the 2015 guideline is that for patients with known or suspected opioid addiction who are unresponsive with no normal breathing but a pulse, it is reasonable for appropriately trained lay rescuers and BLS providers to administer intramuscular (IM) or intranasal (IN) naloxone in addition to providing standard BLS care. In 2014, the naloxone autoinjector was approved by the US Food and Drug Administration for use by lay rescuers and HCPs.[3]

Shock First Versus CPR First

Numerous studies have addressed the question of whether a benefit is conferred by providing a specified period (typically 1.5 to 3 minutes) of chest compressions before shock delivery, as compared to delivering a shock as soon as the AED can be readied. No difference in outcome has been shown. For witnessed adult cardiac arrest when an AED is immediately available, it is reasonable that the defibrillator be used as soon as possible. For adults with unmonitored cardiac arrest or for whom an AED is not immediately available, it is reasonable that CPR be initiated while the defibrillator equipment is being retrieved and applied and that defibrillation, if indicated, be attempted as soon as the device is ready for use. CPR should be provided while the AED pads are applied and until the AED is ready to analyze the rhythm.

Chest Recoil

Based on the 2015 guidelines it is reasonable for rescuers to avoid leaning on the chest between compressions, to allow full chest wall recoil for adults in cardiac arrest. Figure 92–2 summarizes the new 2015 guidelines recommendations for a high-quality CPR.

ADVANCED LIFE SUPPORT

Mechanical CPR Devices

The 2015 updated guidelines suggest against the routine use of automated mechanical chest compression devices to replace manual chest compressions.[24] For the critical outcome of survival to 1 year, one randomized controlled trial (RCT)[25] using the Lund University Cardiac Arrest System (LUCAS) device showed no benefit or harm when compared with manual chest compressions (5.4% vs 6.2%; RR, 0.87; 95% CI, 0.68-1.11). For the critical outcome of survival to 180 days, one RCT[26] using a LUCAS device enrolling 2589 OHCA patients showed no benefit or harm when compared with manual chest compressions when quality of chest compressions in the manual arm was not measured (8.5% vs 8.1%; RR, 1.06; 95% CI, 0.81-1.41).

Consideration in performing high-quality CPR
Perform chest compressions at a rate of 100-120/min
Compress to a depth of at least 2 inches (5 cm)
Allow for full recoil after each compression
Minimize pauses in compressions
Ventilate adequately (2 breaths after 30 compressions, each breath delivered over 1 second, each causing chest rise)

FIGURE 92–2. 2015 Guideline recommendation for high-quality CPR.

Drugs During CPR

Epinephrine Versus Vasopressin A single RCT[27] (n = 336) compared multiple doses of single-dose epinephrine (SDE) with multiple doses of standard-dose vasopressin in the ED after OHCA. For the critical outcome of survival to discharge with favorable neurologic outcome (CPC 1 or 2), there was no advantage with vasopressin (RR, 0.68; 95% CI, 0.25-1.82; P = .44). For the important outcome of ROSC, there was no observed advantage with vasopressin (RR, 0.93; 95% CI, 0.66-1.31; P = .67). The 2015 guidelines suggest vasopressin should not be used instead of epinephrine in cardiac arrest.[24]

Epinephrine Versus Vasopressin in Combination with Epinephrine For the critical outcome of survival to hospital discharge with CPC of 1 or 2, three RCTs[28-30] (n = 2402) comparing SDE with vasopressin and epinephrine combination therapy showed no superiority with vasopressin and epinephrine combination (RR, 1.32; 95% CI, 0.88-1.98). For the important outcome of ROSC, six RCTs[28-33] showed no ROSC advantage with vasopressin and epinephrine combination therapy (RR, 0.96; 95% CI, 0.89-1.04; P = .31). The 2015 guidelines suggest against adding vasopressin to SDE during cardiac arrest

SDE Versus HDE In adult patients in cardiac arrest in any setting, high-dose epinephrine (HDE) (at least 0.2 mg/kg or 5-mg bolus dose) was compared with SDE (1-mg bolus dose). For the critical outcome of survival to hospital discharge with CPC 1 or 2, two RCTs comparing SDE with HDE[34,35] (n = 1920) did not show advantage with HDE (RR, 1.2; 95% CI, 0.74-1.96). For the critical outcome of survival to hospital discharge, five RCTs comparing SDE with HDE (n = 2859) did not show any survival to discharge advantage with HDE (RR, 0.97; 95% CI, 0.71-1.32). The 2015 guidelines suggest against the routine use of HDE in cardiac arrest (weak recommendation, low-quality evidence).

Timing of Administration of Epinephrine

In-Hospital Cardiac Arrest For IHCA, for the critical outcome of survival to hospital discharge, one observational study[36] in 25,095 IHCA patients with a nonshockable rhythm showed an improved outcome with early administration of adrenaline. Compared to the reference interval of 1 to 3 minutes, adjusted OR for survival to discharge was 0.91 (95% CI, 0.82-1.00) when epinephrine was given after 4 to 6 minutes, 0.74 (95% CI, 0.63–0.88) when given after 7 to 9 minutes, and 0.63 (95% CI, 0.52-0.76) when given at more than 9 minutes after onset of arrest.

For IHCA, for the critical outcome of neurologically favorable survival at hospital discharge, an improved outcome was observed from early administration of adrenaline: compared with a reference interval of 1 to 3 minutes, adjusted OR was 0.93 (95% CI, 0.82-1.06) with epinephrine given after 4 to 7 minutes, 0.77 (95% CI, 0.62-0.95) when given after 7 to 9 minutes, and 0.68 (95% CI, 0.53-0.86) when given at more than 9 minutes after onset of arrest.

For IHCA, for the important outcome of ROSC, an improved outcome from early administration of adrenaline adjusted OR compared with a reference interval of 1 to 3 minutes of 0.90 (95% CI, 0.85-0.94) when given after 4 to 7 minutes, 0.81 (95% CI, 0.74-0.89) when given after 7 to 9 minutes, and 0.70 (95% CI, 0.61-0.75) when given after 9 minutes.

Out-of-Hospital Cardiac Arrest For the critical outcome of neurologically favorable survival at hospital discharge (assessed with CPC 1 or 2), four observational studies[37-40] involving more than 262,556 OHCAs showed variable benefit from early administration of epinephrine.

For the important outcome of ROSC, there was very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from four observational studies[38,41-43] of more than 210,000 OHCAs showing an association with improved outcome and early administration of adrenaline. One study[42] showed increased ROSC for patients receiving the first vasopressor dose early (less than 10 vs more than 10 minutes after EMS call; OR, 1.91; 95% CI, 1.01-3.63).

The 2015 guidelines recommendations for cardiac arrest with an initial nonshockable rhythm are that if epinephrine is to be administered, it is given as soon as possible after the onset of the arrest.

Antiarrhythmic Drugs for Cardiac Arrest Antiarrhythmic drugs can be used during cardiac arrest for refractory ventricular dysrhythmias. Refractory VF/pVT is defined differently in many trials but generally refers to failure to terminate VF/pVT with three stacked shocks or with the first shock.

For the important outcome of ROSC, one RCT involving 504 OHCA patients showed higher ROSC with administration of amiodarone (300 mg after 1 mg of adrenaline) compared with no drug (64% vs 41%; P = .03; RR, 1.55; 95% CI, 1.31-1.85).[44]

The 2015 guideline recommendations for antiarrhythmia drugs for cardiac arrest suggest the use of amiodarone in adult patients with refractory VF/pVT to improve rates of ROSC. The guidelines also suggest the use of lidocaine or nifekalant as an alternative to amiodarone in adult patients with refractory VF/pVT. The 2015 guidelines recommend against the routine use of magnesium in adult patients.

CARDIOCEREBRAL RESUSCITATION

BRIEF HISTORY OF THERAPEUTIC HYPOTHERMIA

The use of therapeutic hypothermia (TH) to mitigate various types of injury, in particular posthypoxic injury to the brain, has been studied since the late 1930s.[45] Interest was initially kindled by reports of survival after prolonged exposure to cold, or submersion in ice-cold water, indicating a possible protective effect of low temperature on hypoxic injuries.[46]

Use of hypothermia after cardiac arrest was first described in the late 1950s,[47,48] but proof that hypothermia could improve outcome in these patients remained elusive.[49,50] At the time it was thought that protective effects of TH were purely a result of hypothermia-induced lowering of metabolism; therefore, it was presumed that very low temperatures (25-28°C) were needed to provide significant neuroprotection.

This perception changed in the late 1980s, when animal studies demonstrated that significant protective effects also occurred with mild hypothermia (30-34°C), with far fewer side effects, and that a variety of destructive mechanisms were moderated by hypothermia rather than just reductions in brain metabolism.[49] In the late 1990s a number of small nonrandomized, clinical trials provided better evidence for the efficacy of TH.[51-54] This led to the initiation of two landmark multicenter RCTs to test TH treatment, the results of which were published side-by-side in 2002.[55,56] Both reported clear and significant improvements in outcome in cardiac arrest (CA) patients treated with therapeutic cooling.

The largest study, performed in 11 centers in Europe, enrolled 275 patients with witnessed CA and an initial rhythm of VF or pulseless VT. The authors observed a 15.8% absolute (35.1% relative) improvement in outcome in the hypothermia group ($P < .01$).[55] The other RCT enrolled 77 patients across four centers in Australia, reporting an absolute improvement of 22.3% (relative improvement 43.7%) in patients with witnessed VT/VF treated with hypothermia compared with controls ($P < .05$).[56] A meta-analysis calculated that one additional case of good neurological outcome would be gained for every six patients treated with TH.[57] Guidelines from various medical societies such as the American Heart Association (AHA), European Resuscitation Council (ERC), and Neurocritical Care Society (NCS) began recommending cooling after CA.[58,59]

A larger RCT, the Therapeutic Temperature Management (TTM) study, compared temperature management at 33.0°C to maintaining a core temperature of 36.0°C.[60] The study enrolled 939 patients with witnessed CA regardless of initial rhythm, including those with persistent hypoxia and hypotension who had been excluded from previous studies, with predefined subgroup analyses to correct for various risk factors. The results of this study were negative.[60] Rates of survival with good neurological outcome were 46.5% in the 33°C group versus 47.8% in the 36°C group ($P = .78$). The rate of survival with excellent outcome (no neurological residual) was 41.6% versus 39.4%, whereas survival with mild neurological impairment was 4.9% versus 8.4%.[60] The authors concluded that maintaining core temperature at 36°C has equally good outcomes as cooling to 33°C.

PATHWAYS FOR THE MANAGEMENT OF SURVIVORS OF OUT-OF-HOSPITAL AND IN-HOSPITAL CARDIAC ARREST

At our institution, similar to many tertiary medical centers, algorithms for the management of patients post cardiac arrest have been developed. Our first algorithm was published in 2010.[61] We continue to update it, as new scientific information and updated guidelines are published.[62] The term "therapeutic hypothermia" has now been replaced with targeted temperature management (TTM). Our 2015 updated TTM pathway is divided into three steps.

Step I. From the field through the emergency department (ED) into the cardiac catheterization laboratory and to the critical care unit (Fig. 92–3A).

Step II. Induced hypothermia protocol in the critical care unit (Fig. 92–3B).

Step III. The management following the rewarming phase including the recommendation for out-of-hospital therapy and the ethical decision to define goals of care (Fig. 92–3C).

Step I: Presentation to the Emergency Department, Proceeding to the Cardiac Catheterization Laboratory and to the Critical Care Unit

Upon arrival of a survivor of OHCA to the ED, the initial assessment (see Fig. 92–3A) includes vital signs, physical examination, and neurologic examination with Glasgow Coma Score. Immediate 12-lead EKG is obtained and laboratory testing performed.

Initial laboratory testing includes complete blood count (CBC) with differential, basic metabolic panel, cardiac marker (troponin, CPK, CPK-MB), B-type natriuretic peptide (BNP), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), lipid profile, phosphorus, calcium, magnesium, lactate, β-HCG (for women), TSH, and toxicology screening. We recommend a head CT without contrast only if it is clinically indicated and will not delay transfer to the cardiac catheterization laboratory.

The patient is stabilized in the ED where antiarrhythmic and vasopressor therapy may be administered, in addition to ventilator support.

The ED physician receives the emergency medical services (EMS) report of the primary rhythm and duration of cardiopulmonary resuscitation (CPR). This reported arrhythmia is the key decision point in our pathway.

The prognostically important distinction is between patients with documented ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) who had a restoration of spontaneous circulation (ROSC) in < 30 minutes and patients with reported asystole or pulseless electrical activity (PEA).

1. If the initial rhythm was VF or VT with an ROSC of ≤ 30 minutes, the cardiac arrest team is activated, and the patient will proceed to the cardiac catheterization laboratory.
2. If the initial reported arrhythmia was PEA or asystole, the next step will depend on the ECG performed in the ED. If the ECG performed in ED is suggestive of priority ACS (including ST elevation MI, left bundle branch block, or acute posterior wall MI), the MI team should be activated, and the care is similar to those patients with reported VF or VT arrest.
3. If priority ECG findings are not seen but the etiology of the arrest is most likely owing to primary cardiac disease, the cardiology fellow will admit the patient to the cardiac care unit. We recommend an emergency echocardiogram.
4. If the etiology is likely noncardiac, the patient will be admitted to the medical intensive care unit.

The *cardiac arrest team* includes the following 10 people. The traditional (acute coronary syndrome) ACS-MI team comprises the following members:

1. Interventional cardiologist on-call team leader
2. CCU director
3. Cardiology fellow on call
4. Interventional cardiology fellow on call
5. Cath lab nurse on call
6. Cath lab technician on call
7. CCU nurse manager on call

In addition, the following personnel form the team:

8. The neurologist on call
9. The critical care attending on call
10. The medical resident screener

The MI team is activated by a single page to the central call center by the ED physician.

Steps in the emergency department:

1. Decision to initiate induced hypothermia is made jointly by the ED physician and the cardiology or critical care physician. It is very important to review the hospital center's inclusion and exclusion criteria and decide whether the patient is a candidate for the therapeutic hypothermia protocol.
2. The physician places an order to initiate hypothermia protocol.

Our goal is to transfer the patient to the PCI center as soon as possible with a target door-to-balloon time of < 90 minutes.

The management of the patient at this point is according to our *P*riority risk, *A*dvanced risk, *I*ntermediate risk, and *N*egative/low risk (PAIN) pathway following the priority ACS algorithm.[63]

Following cardiac catheterization, several steps occur while the patient is still in the catheterization laboratory:

1. The femoral arterial sheath can be maintained as an arterial catheter, which may be necessary to obtain blood pressure readings and arterial blood gas analyses.
2. The intravascular hypothermia catheter is inserted under strict aseptic technique (if it was not done earlier).

All patients are then transferred from the catheterization laboratory to the CCU where invasive hypothermia is initiated.

Step II: Induced Therapeutic Hypothermia Protocol in the Critical Care Unit

The clinicians review the case and confirm the appropriateness of induced hypothermia (see Fig. 92–3B). In summary, we recommend induced hypothermia for patients > 18 years of age, who sustained a cardiac arrest and remain in coma. Patient must be comatose, not following commands or demonstrating purposeful movements. Patients excluded from the hypothermia protocol include patients who are awake, suffered prolonged ischemic times, experience refractory shock, demonstrate multiorgan failure, or have severe underlying illnesses, including terminal illnesses and do-not-resuscitate (DNR) status.

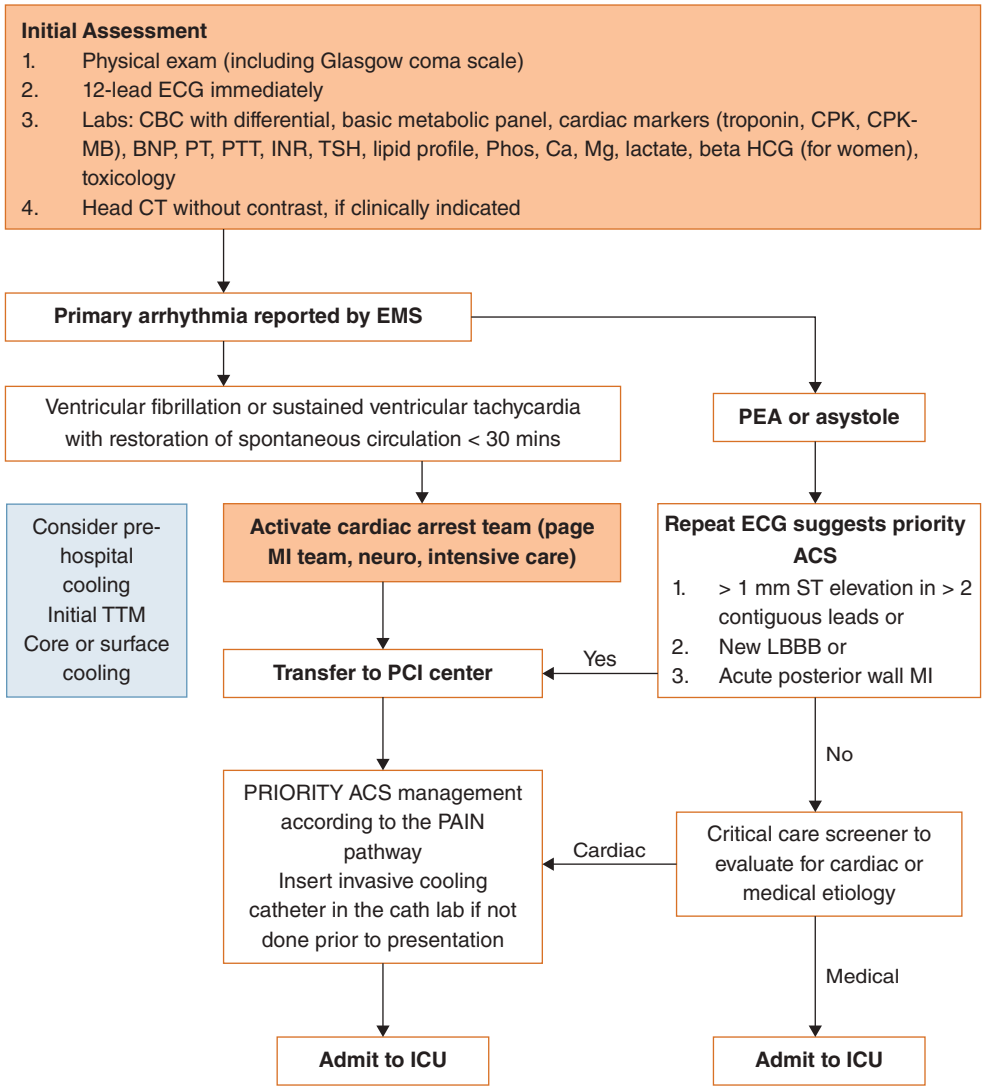
The hypothermia protocol is divided into three phases as seen in Fig. 92–3B:

Phase 1: Cooling phase for the first 24 hours

Phase 2: Rewarming phase

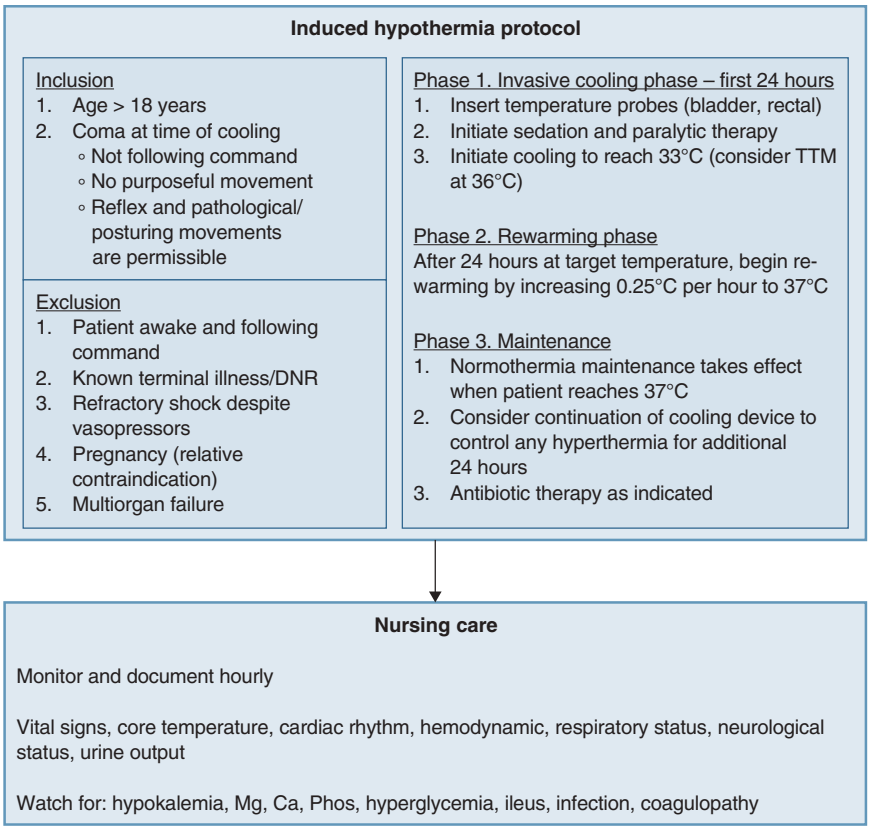
Phase 3: Maintenance phase

Phase 1: Cooling Phase for the First 24 Hours We recommend 24 hours of the cooling therapy at a temperature goal of 33°C. As will be discussed later in this chapter, the dose of the temperature management is controversial and some centers cool patients to 36°C. Endovascular catheters are an effective method of inducing therapeutic hypothermia (if a core cooling method is chosen). The catheters are usually inserted into the inferior vena cava through the femoral vein.



A

FIGURE 92–3. Pathway for management of survivors of out-of-hospital and in-hospital cardiac arrest. **A.** Step I. From the field, through the emergency department (ED) into the cardiac catheterization laboratory, and to the critical care unit. **B.** Induced hypothermia protocol in the critical care unit. **C.** The management following the rewarming phase, including the recommendation for out-of-hospital therapy and the ethical decision to define goals of care.



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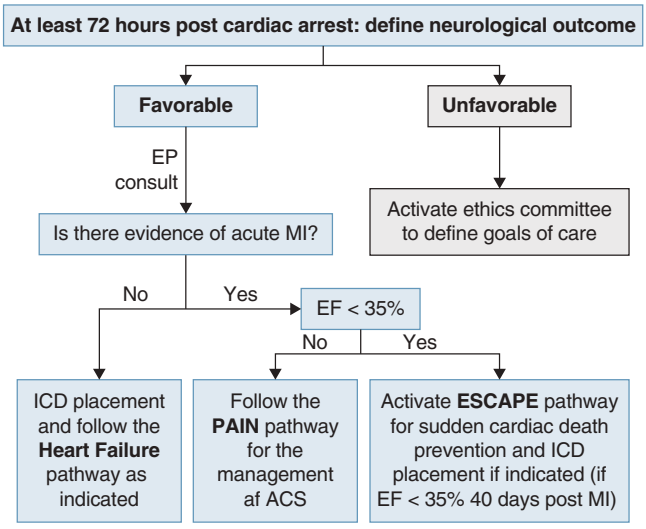

C

FIGURE 92-3 (*Continued*)

Continuous core temperature monitoring is required and generally accomplished using a temperature probe in the bladder (urinary catheter) or the rectum.

Monitoring of clinical condition and potential complications during the cooling phase As there are many physiologic effects of hypothermia, we recommend continuous monitoring and hourly documentation of vital signs; core temperature; cardiac rhythm; hemodynamic, respiratory, neurology status; and urine output. Common hemodynamic changes observed with cooling include hypertension, decreased cardiac output, and increased systemic vascular resistance. The hypertension and the increased systemic vascular resistance are believed to result from the cold-induced vasoconstriction.

Serum electrolyte imbalance is common during the cooling phase and results from the cooling-induced intracellular shifts of potassium, magnesium, calcium, and phosphate, resulting in low levels of all these electrolytes. During the rewarming phase these electrolytes shift back to the extracellular space. Our protocol therefore recommends measurements of the basic metabolic panel every 4 hours for a total of 48 hours, measuring electrolytes (calcium, magnesium, and phosphate), PT, PTT, and INR, and a CBC every 12 hours up to 48 hours.

Additional possible side effects of cooling to be monitored include the following:

1. *Coagulopathy*. Coagulopathy is generally not significant with careful temperature monitoring and avoiding temperature of < 33°C. If active bleeding occurs during the cooling phase, evaluation of coagulation factors and platelets should be performed and deficiencies corrected.
2. *Hyperglycemia*. Hypothermia suppresses insulin release and causes insulin resistance. Our insulin infusion protocol for the management of hyperglycemia in critical care unit is used.[64]
3. *Infection*. Infection is usually multifactorial including emergency intubation and intravenous catheter insertion and aspiration pneumonia at the time of arrest. Furthermore, the hypothermia itself can suppress white blood cell production and impairs neutrophil and macrophage function. All measures to reduce ventilator associated pneumonia are employed including elevating the head of the bed.
4. *Shivering*. Our protocol aims to prevent shivering by administration of sedation and neuromuscular blocking agents on induction of hypothermia.

Phase 2: Rewarming Phase After 24 hours of the target temperature, the rewarming phase starts. Controlled rewarming is a very important phase of this protocol. Rewarming should be slow; we recommend a rate of 0.25°C per hour; therefore it typically requires 16 hours to rewarm to 37°C. Potential complications during the rewarming phase include the following:

1. Hypotension—owing to peripheral vasodilatation during the rewarming phase.
2. Electrolyte imbalance—increased levels of potassium, magnesium, calcium, and phosphate owing to intracellular shifting of these ions back to the serum during the rewarming phase.

Phase 3: Maintenance of Normothermia Phase The maintenance phase is the last phase of the therapeutic hypothermia protocol. Normothermia maintenance takes effect when the patient's temperature reaches 37°C. We recommend continuation of the cooling device to maintain a temperature of 37°C and avoid fever, which can potentially worsen a cerebral injury. The duration of the additional maintenance phase is usually between 24 and 48 hours.

Step III

The management following hypothermia and rewarming depends on the neurologic prognosis (see Fig. 92–3C). At least 72 hours after cardiac arrest, the neurologic examination is performed by the neurology team. The neurologic examination may be affected by the hypothermia protocol, including requirements for sedation and therapeutic paralysis, so that the formulation of a neurologic prognosis may be delayed. In general, we defer neurologic prognostication until 6 days after arrest in patients undergoing hypothermia protocol.

Pathways for the patients will divide based on whether the patient has a favorable neurologic prognosis or an unfavorable neurologic prognosis. An unfavorable neurologic prognosis would be defined as expectation for a persistent coma or vegetative state, or severe disability. If the prognosis appears unfavorable, we recommend activating the ethics committee to meet with the family and clinicians to define the goals of care. From our experience, in most instances, life support is limited or withdrawn in such patients.

If the neurological prognosis appears favorable, then the key question regarding further therapy is based on whether the cardiac arrest was because of MI. If there is no evidence of acute MI (negative cardiac markers), then we recommend electrophysiology service consultation for consideration of implantable cardioverter-defibrillator (ICD) placement and treatment of heart failure based on our heart failure pathway.[65] If acute MI is confirmed by positive cardiac markers we advise care based on the LV ejection fraction (LVEF), as it is defined by echocardiography or other imaging modalities. If LVEF ≤ 35%, we recommend activation of the ESCAPE pathway for sudden cardiac death prevention[66] and to consider ICD placement if EF ≤ 35% at 40 days post-MI. Also we recommend managing heart failure according to our heart failure pathway.[65] If EF > 35%, we recommend following our PAIN pathway for the management of ACS[63] including the following:

Lifestyle modification

Cardiac rehabilitation

Secondary prevention medication (dual oral antiplatelet, β-blocker, high-dose statin, ACE inhibitor/ARB)

UNRESOLVED PRACTICAL QUESTIONS REGARDING TTM

How Low Should We Go?

As mentioned earlier, the Therapeutic Temperature Management (TTM) study compared temperature management at 33°C to maintaining a core temperature of 36°C.[60] and concluded that maintaining core temperature at 36°C has equally good outcomes as cooling to 33°C. This observation seems to contradict the findings of all previous studies and may have been a result of selection bias. Our group hypothesizes that a potential difference in outcome based on degree of cooling will depend on the severity of brain injury. Our group opinion regarding this difference in outcome depending on the selection of patients for TTM appears in Figure 92–4. As seen in this figure, we can divide patients who survive cardiac arrest into five groups based on the degree of their post-arrest brain injury.

1. Very severe brain injury
2. Severe brain injury
3. Moderate brain injury

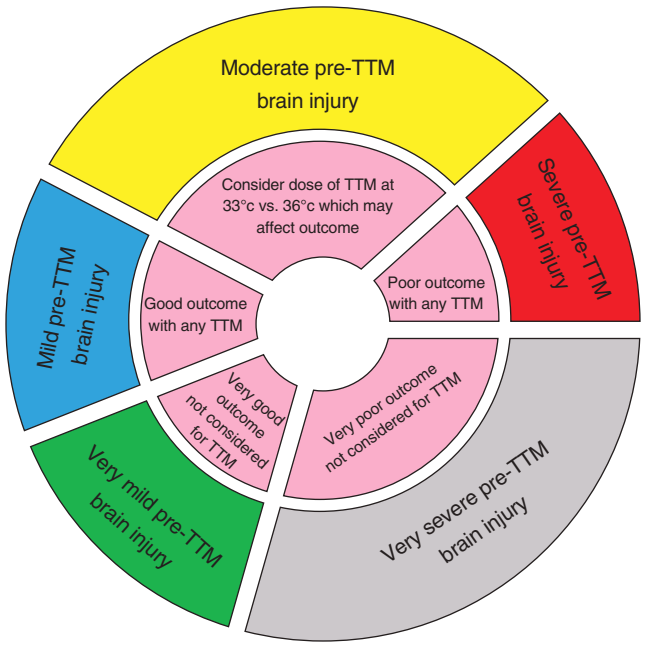

FIGURE 92–4. Degree of postarrest brain injury and proposed decision for TTM.

4. Mild brain injury
5. Very minimal brain injury

Patients who fall into the first or the last category are unlikely to be considered for TTM in any health care system (as seen in the lower half of our figure). Patients who fall into groups 2, 3, and 4 are expected to have variable outcome. Patients in group 2, with severe brain injury, are expected to have poor outcome with any TTM. Patients in group 4 with mild brain injury are expected to have a good outcome with any TTM. However, for patients in group 3, with moderate brain injury, the dose of TTM may affect outcome.

Our hypothesis is derived by applying Bayes' Theorem to the relationship between post-TTM degree of brain injury and pre-TTM degree of brain injury. Our hypothesis is seen in Fig. 92–5. In this figure we have plotted the pre-TTM degree of brain injury on the x-axis with score of 0 to 100 and the post-TTM degree of brain injury on the y-axis with score of 0 to 100, where a score of 0 means no brain injury and a score of 100 means irreversible brain injury.

As outlined earlier, we have five groups of patients based on their severity of brain injury: very minimal, mild, moderate, severe, and very severe.

The equivocal line (Z) represents where the pretreatment group brain injury is exactly the same as the posttreatment group brain injury.

The other two lines represent the different temperature doses of 33°C and 36°C.

It is the delta (Δ) between these lines that defines if the therapy has a potential benefits.

On the left end of this figure, the delta is very small for patients with very minimal or mild brain injury. This is the same case for patients with severe or very severe brain injury where the delta between the two doses of therapy is very small. However, for patients with moderate brain injury, the delta is quite large. In our hypothesized algorithm there is a potential to reduce the post-TTM degree of brain injury from a high to a low score. Based on this hypothesis, our group suggests that the dose of temperature management should be 33°C because it is difficult prognostically to determine moderate brain injury level. We have to remember that this is only a hypothesis and larger studies enrolling solely patients with moderate brain injury should be conducted. Our group believes that the Achilles heel of the field of TTM is our current limitations in the prognostication of postarrest brain injury.

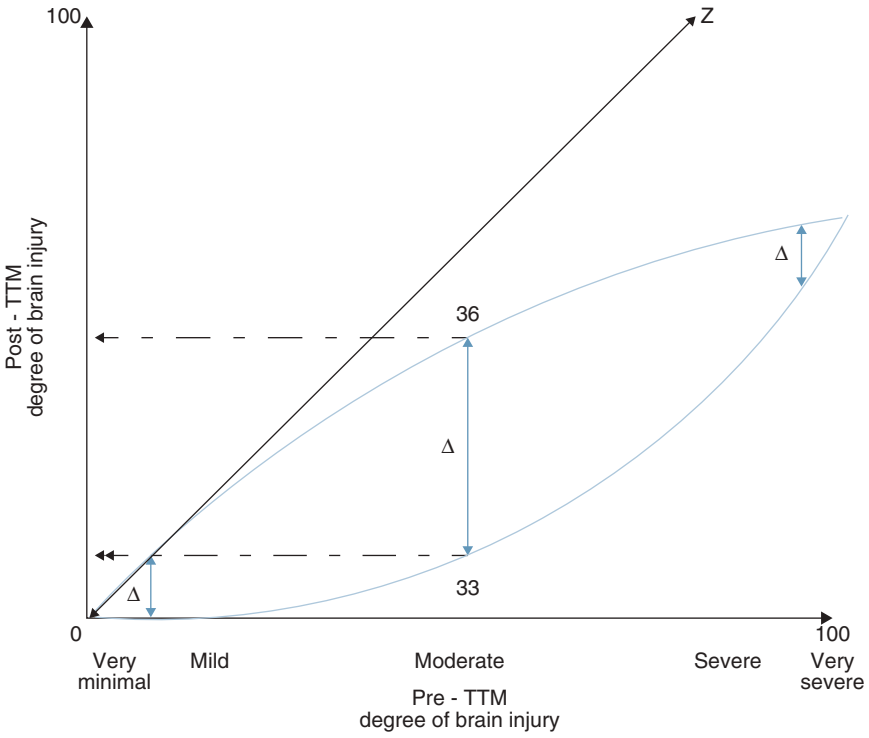

FIGURE 92–5. Applying Bayes' Theorem to the relationship between post-therapeutic temperature management (TTM) degree of brain injury and pre-TTM degree of brain injury.

Endovascular Versus Surface Cooling

Technologies can be broadly divided into invasive (core cooling) and noninvasive (surface cooling) methods.[67] There is no evidence for a difference in outcome based on cooling method.

The advantages of invasive cooling over surface cooling are:

1. Greater speed of hypothermia/normothermia induction when core cooling is used; however, it is unclear whether more rapid induction improves outcome.
2. Fewer and smaller temperature fluctuations in the maintenance phase.
3. Continuous central temperature measurement in some types of endovascular catheter is possible.
4. No risk of surface cooling-induced skin lesions.
5. Ease of accessibility to patient, that is, no need to cover large areas of the skin to achieve cooling.
6. Less medication may be needed to control shivering because there is more effective shivering suppression with skin counter warming (ie, the entire surface area can be warmed using warm air, leading to a significantly diminished shivering response).[49,68,69]

The advantages of surface cooling over invasive cooling are:

1. Ease of use; can be applied by nurses without a physician being present.
2. No invasive procedure required; therefore, no risk of mechanical complications.
3. Can be started immediately, without waiting for catheter insertion procedure, so potentially less delay in initiation of cooling.
4. No risk of catheter-induced thrombus formation.
5. Can be more easily applied outside the ICU setting.

A study by Deye and coworkers compared endovascular to surface cooling in a prospective, multicenter RCT.[70] The authors enrolled 400 patients; 203 were treated with endovascular cooling (using Zoll femoral Icy catheters) and 197 with external cooling (ice packs, fans, and a home-made tent). The main findings were as follows: significantly shorter time to target temperature (33°C), greater stability of temperature (defined as time within target ± 1°C) in the maintenance phase, and reduced nursing workload (10 vs 38 minutes, $P < .001$) in the endovascular group; more minor side effects in the endovascular group ($P = .009$); a nonsignificant trend toward more favorable outcome at 28 days (36.0% vs 28.4%, OR 1.41 [95% CI, 0.93-2.16], $P = .107$; for shockable rhythm 53.7% vs 37.1%, OR 1.97 [95% CI, 0.99-3.9], $P = .269$) and at 90 days (34.6% vs 26.0%, OR 1.51 [95% CI, 0.96-2.35], $P = .07$) in the endovascular group; and fewer cases of severe overshoot (below 30°C) in the endovascular group (n = 0 vs n = 3).[70] Strict fever control was maintained for a minimum of 3 days

following rewarming in both groups. This study had some limitations, especially the fact that newer and more powerful surface cooling devices such as the Arctic Sun system were not used and surface cooling was accomplished using fairly basic tools and devices. We believe that the cooling method should be determined by institutional protocol.

HIGHLIGHTS FROM THE 2015 GUIDELINE RECOMMENDATION FOR POST–CARDIAC ARREST CARE

Out-of-Hospital Cooling

Based on the 2015 guidelines, the routine prehospital cooling of patients with rapid infusion of cold IV fluids after ROSC is not recommended.[24]

Hemodynamic Goals After Resuscitation

It may be reasonable to avoid and immediately correct hypotension (systolic blood pressure less than 90 mm Hg, mean arterial pressure less than 65 mm Hg) during post–cardiac arrest care.[24]

Why? Studies of patients after cardiac arrest have found that a systolic blood pressure less than 90 mm Hg or a mean arterial pressure of less than 65 mm Hg is associated with higher mortality and diminished functional recovery, while systolic arterial pressures of greater than 100 mm Hg are associated with better recovery. Although higher pressures appear superior, specific systolic or mean arterial pressure targets could not be identified, because trials typically studied a bundle of many interventions, including hemodynamic control. Also, because baseline blood pressure varies from patient to patient, different patients may have different requirements to maintain optimal organ perfusion.

Early Coronary Angiography

Based on the 2015 guidelines, coronary angiography should be performed emergently (rather than later in the hospital stay or not at all) for OHCA patients with suspected cardiac etiology of arrest and ST elevation on ECG. Emergency coronary angiography is reasonable for select (eg, electrically or hemodynamically unstable) adult patients who are comatose after OHCA of suspected cardiac origin but without ST elevation on ECG. Coronary angiography is reasonable in post–cardiac arrest patients for whom coronary angiography is indicated, regardless of whether the patient is comatose or awake.[24]

Targeted Temperature Management

All comatose (ie, lacking meaningful response to verbal commands) adult patients with ROSC after cardiac arrest should have TTM, with a target temperature between 32°C and 36°C selected and achieved, then maintained constantly for at least 24 hours.[24]

Continuing Temperature Management Beyond 24 Hours

Actively preventing fever in comatose patients after TTM is reasonable. In observational studies, fever after rewarming from TTM is associated with worsened neurologic injury, although studies are conflicting. Because preventing fever after TTM is relatively benign and fever may be associated with harm, preventing fever is suggested.[24]

Prognostication After Cardiac Arrest

The earliest time to prognosticate a poor neurologic outcome using clinical examination in patients not treated with TTM is 72 hours after cardiac arrest, but this time can be even longer after cardiac arrest if the residual effect of sedation or paralysis is suspected to confound the clinical examination.[24]

Why? Clinical findings, electrophysiologic modalities, imaging modalities, and blood markers are all useful for predicting neurologic outcome in comatose patients, but each finding, test, and marker is affected differently by sedation and neuromuscular blockade. In addition, the comatose brain may be more sensitive to medications, and medications may take longer to metabolize after cardiac arrest. No single physical finding or test can predict neurologic recovery after cardiac arrest with 100% certainty. Multiple modalities of testing and examination used together to predict outcome after the effects of hypothermia and medications have been allowed to resolve are most likely to provide accurate prediction of outcome.

Organ Donation

All patients who are resuscitated from cardiac arrest but who subsequently progress to death or brain death should be evaluated as potential organ donors. Patients who do not achieve ROSC and who would otherwise have resuscitation terminated may be considered as potential kidney or liver donors in settings where rapid organ recovery programs exist.[24]

Why? There has been no difference reported in immediate or long-term function of organs from donors who reach brain death after cardiac arrest when compared with donors who reach brain death from other causes. Organs transplanted from these donors have success rates comparable to organs recovered from similar donors with other conditions.

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SECTION 14

Diseases of the Great Vessels and Peripheral Vessels

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CHAPTER 93

DISEASES OF THE AORTA

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THE NORMAL AORTA

The aorta has complex biological and mechanical properties involving intrinsic relaxation and contraction that interact with left ventricular ejection to enhance hemodynamics. The major conductance vessel of the body, the aorta is an elastic artery with a trilaminar wall: the tunica intima, tunica media, and tunica adventitia (Fig. 93–1).[1,2] The innermost lining of the tunica intima is the endothelium, resting on a thin basal lamina. The subendothelial tissue is comprised of fibroblasts, collagen fibers, elastic fibers, and mucoid ground substance. An internal elastic membrane forms the outer lining of the tunica intima. The tunica media is approximately 1 mm thick, comprised of elastin, smooth muscle cells, collagen, and ground substance. The predominance of elastic fibers in the aortic wall and their arrangement as circumferential lamellae distinguish it from the smaller muscular arteries. A lamellar unit is made up of two concentric elastic lamellae containing smooth muscle cells, collagen, and ground substance.[3,4] The thoracic aorta incorporates 35 to 56 lamellar units and the abdominal aorta about 28 units.[5] Surrounding the tunica media is the tunica adventitia, which is composed of loose connective tissue, including fibroblasts, relatively small amounts of collagen fibers, elastin, and ground substance. The adventitia strengthens the aorta and is essential to aortic surgeons for secure suturing of tissues. Within the tunica adventitia lie the nervi vasorum and vasa vasorum. The arteries arising along the course of the aorta give rise to the vasa vasorum, which develop into a capillary network supplying the adventitia and media of the thoracic aorta. The vasa vasorum do not supply the media of the abdominal aorta. Unlike the elastic fibers of the arterial wall, which are highly distensible, collagen is inelastic and provides the tensile strength required to prevent deformation and rupture of the aortic wall. Sophisticated biaxial strength testing of the human thoracic aorta has permitted new, detailed understanding of the tensile properties of the aorta (contributed by elastin and collagen) and permitted mechanical modeling of dissection and rupture events.[6]

The ascending aorta is approximately 3 cm in diameter, depending on age, sex, and body surface area. Among approximately 3500 individuals in the Multi-Ethnic Study of Atherosclerosis, the mean diameter of the ascending aorta was 3.2 ± 0.4 cm,[7,8] and in none of these normal individuals exceeded 5 cm. The diameter of the aortic arch is similar. Descending in the posterior mediastinum, the aorta tapers slightly to about 2 to 2.3 cm and the abdominal aorta narrows further to 1.7 to 1.9 cm in its distal portion. The aortas of males are larger than those of females. Aortic root dimension increases with age, height and weight, but the sex-based difference in aortic root dimension is not entirely explained by body surface area.[5]

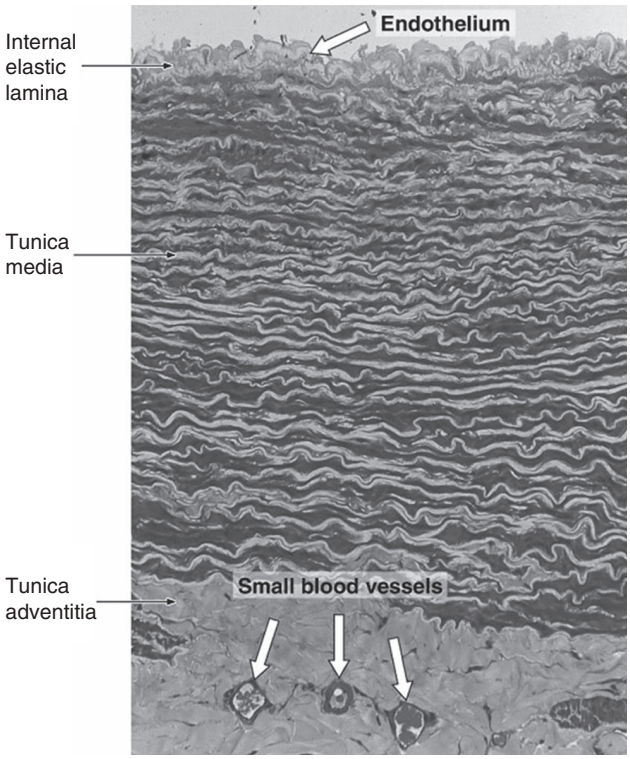


FIGURE 93–1. Transverse section of the wall of a large elastic artery demonstrating the well-developed tunica media containing elastic lamellae. Pararosaniline–toluidine blue stain; medium magnification. Reproduced with permission from Junqueira LC, Carneiro J: *Basic Histology: Text and Atlas*, 11th ed. New York, NY: McGraw-Hill; 2005.[1]

HEMODYNAMIC FUNCTION OF THE AORTA

The force of left ventricular (LV) ejection creates a pressure wave that traverses the aorta, producing radial expansion and contraction of the arterial walls.[9] Potential energy derived from myocardial contraction and stored in the aortic wall during systole is transformed during diastolic recoil into kinetic energy, which drives blood into the peripheral vessels.[10] The pressure wave is conducted at a velocity of approximately 5 m/s, increasing in amplitude along its course though the aorta.

Forward blood flow in the aorta begins when the aortic valve opens, and systolic pressure increases as the pressure wave courses along the length of the aorta. Flow velocity increases rapidly to a peak and then gradually decreases. With aortic valve closure, there is transient backward flow before forward flow resumes during diastole, particularly in the descending thoracic and abdominal aorta, albeit at considerably less than systolic velocity. The incisura in the arterial waveform in the proximal portion of the thoracic aorta gradually disappears and is usually absent in the abdominal aorta.[11]

CHANGES WITH AGE AND DISEASE

Each of the four components of the aortic wall—elastic tissue, collagen fibers, smooth muscle cells, and mucoid ground substance—change with age (Fig. 93–2).[11] Elastic fibers fragment, collagen content increases at the expense of smooth muscle cells, and glycosaminoglycans accumulate. As a result, the aorta becomes less distensible, reducing its capacity to absorb the forces derived from LV contraction.[12] The increased stiffness of the aortic wall with aging contributes to hypertension.[13] Concurrently, weakening of the aortic wall leads to dilation of the lumen and elongation and uncoiling of the aortic arch, collectively producing ectasia. Accompanying

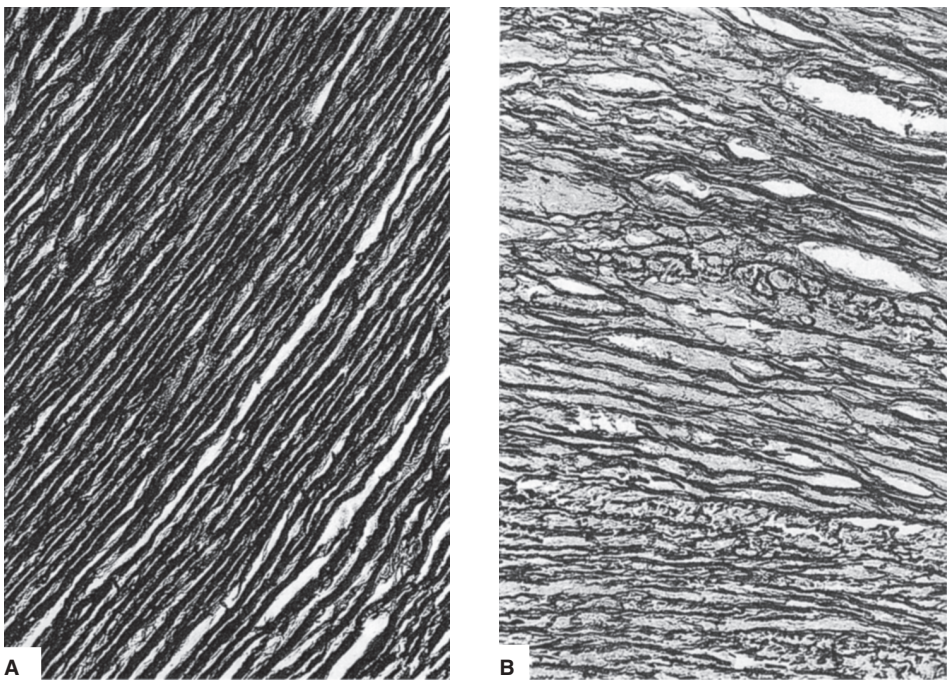


FIGURE 93–2. Histology of the normal aorta of a child (**A**) and an elderly adult (**B**). With aging, elastic fibers fragment, collagen becomes more prominent, smooth muscle cells diminish, and acid mucopolysaccharide ground substance accumulates. Weakening of the aortic wall leads to dilatation of the lumen as well as elongation and uncoiling of the aortic arch. Orcein and van Gieson stain, magnification × 414. Reproduced with permission from Nichols WW, O'Rourke MF, McDonald DA: *McDonald's blood flow in arteries: theoretic, experimental, and clinical principles*, 3rd ed. Philadelphia: Lea & Febiger; 199.[11]

these changes are alterations in aortic wall structure, fragmentation of elastic fibers, loss of smooth muscle cell nuclei (medionecrosis), accumulation of collagenous tissue, and deposition of basophilic ground substance.

When the aorta dilates due to disease of the medial layer, wall stress increases. This is accelerated by hypertension, particularly when pulsatile forces are high (see "Precipitation of Aortic Dissection" later in the chapter). When peripheral vascular resistance is high, the impact of the reflected pressure wave adds to that of antegrade pulsatile flow. The combination of inherited, degenerative, mechanical, and hemodynamic factors adversely affects the medial layer of the aortic wall, leading to dilation and setting the stage for the catastrophes of dissection or rupture.

DEFINITIONS AND CATEGORIES

The aorta can be affected by a variety of pathologic processes leading to *aneurysm*, *dissection*, or *ischemic* syndromes (Fig. 93–3A). The term *aneurysm*—derived from the Greek *aneurysma*, referring to dilation—is distinguished from *ectasia*, which refers to the modest generalized dilation and elongation of the aorta that occurs with aging.[14] Although the size of the normal aorta varies with gender and body size, most agree that the maximum diameter of the thoracic aorta should not exceed 4 cm. For the abdominal aorta, which normally has a smaller diameter than the thoracic segments, it has been suggested that the term *aneurysm* be restricted to situations in which the diameter exceeds 3 cm.[15] Another proposed definition depends on the affected segment having a diameter more than 1.5 to 2 times normal.[16]

Aneurysms may be classified according to morphology, location, or etiology. In *true* aneurysms, the wall of the aneurysm is composed of the normal histologic components of the aorta. A *false* aneurysm, on the other hand, represents a contained rupture in which the wall is a fibrous peel around a small perforation of the aorta, initially controlled by adherence of surrounding tissue and gradually enlarging over time.

A gross morphologic classification distinguishes true aneurysms as *fusiform* (most common) or *saccular*. A fusiform aneurysm is roughly cylindrical and affects the entire circumference of the aorta; a saccular aneurysm is an outpouching of only a portion of the aortic circumference. Frequently, a small neck provides continuity between the aortic lumen and the saccular aneurysm.

Aortic dissection refers to splitting of the medial layer of the aortic wall, permitting longitudinal propagation of blood between the components of the aortic wall (Fig. 93–3B). Aortic dissection is the most common cause of death due to human aortic disease.[17] *Atherosclerosis of the aorta* can narrow the ostia of the great vessels or produce mobile atheromatous masses capable of embolism to the brain or other organs.

Several additional types of aortic pathology are illustrated in Fig. 93–4. *Acute aortic transection,* a consequence of trauma, involves localized disruption of an intrinsically normal aortic wall, which is resistant to propagating dissection. A *ruptured* aortic aneurysm is self-explanatory. *Acute aortic dissection* refers to separation of the layers of the aortic wall discussed below. *Intramural hematoma* represents a concentric, circumferentially oriented collection of thrombus in the aortic wall, without the discrete transluminal flap typical of aortic dissection. *Penetrating aortic ulcer* involves localized perforation of the medial layer of the aortic wall beneath an atherosclerotic plaque.

Aortic aneurysms may also be classified according to the segment involved as thoracic, thoracoabdominal, or abdominal. Aneurysm formation can involve a greater portion of the aorta (Fig. 93–5) than obstructive atherosclerotic disease, potentially affecting almost the

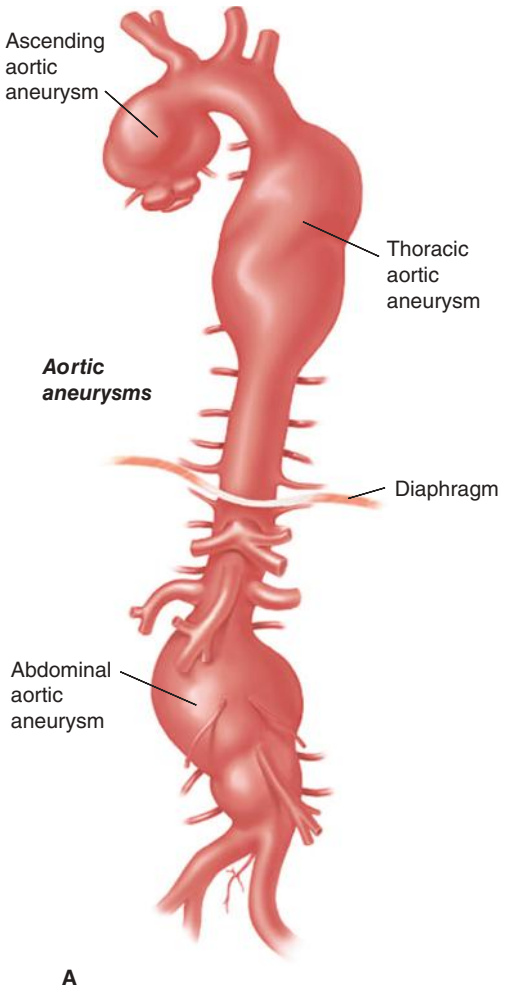


FIGURE 93–3. Artist's rendition of aortic aneurysms at various locations (A) and type B aortic dissection (B).

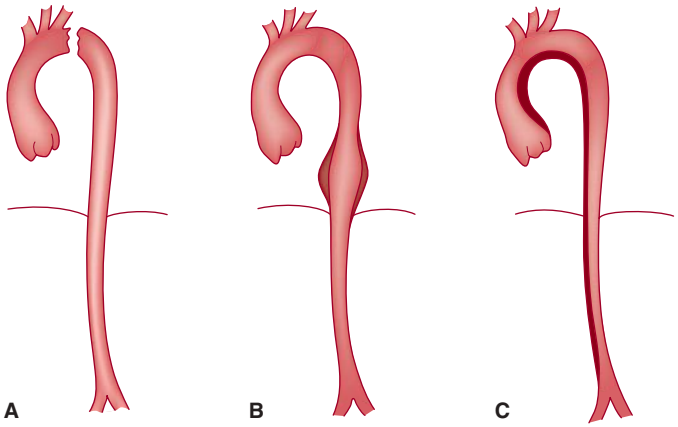


FIGURE 93–4. Three commonly confused aortic disorders. **A.** Acute aortic transection. **B.** Degenerative aneurysm of the descending aorta. **C.** Type A acute aortic dissection. Reproduced with permissionfrom Elefteriades JA, Geha AS, Cohen LS: *House Officer Guide to ICU Care*. Raven Press; 1994.

entire vessel, while atherosclerotic obstruction tends to involve mainly the abdominal portion of the aorta when the iliac arteries are often affected as well. Dilation of the aorta may occur as a consequence of atherosclerosis, aging, infection, inflammation, trauma, congenital anomalies, medial degeneration, or combinations of pathologic states. These conditions may cause the aorta to thicken, thin, bulge, tear, rupture, narrow, dissect, or be altered by combinations of these conditions.

With normal aging, degenerative changes occur throughout the aorta, leading to a mild form of *cystic medial necrosis*, in which the normal lamellar structure of the media is locally destroyed, leaving lakes of amorphous material. Although essentially a normal physiologic process, cystic medial necrosis develops more rapidly in patients with bicuspid aortic valve, during pregnancy, and very markedly in people with Marfan syndrome. The mechanism by which the medial layer of the aorta is subject to this accelerated degeneration is a subject of active molecular genetic investigation. Severe elastic fiber degeneration, necrosis of muscle cells, and cystic spaces filled with mucoid material are most often encountered in the ascending aorta from just above the aortic valve to the brachiocephalic artery (see Fig. 93–5). Because of accompanying dilation of the aortic root, aortic regurgitation may be a secondary feature, although the valve leaflets themselves are histologically unaffected.

Cystic medial necrosis is the most common cause of ascending aortic aneurysm,[17] and although this type of aortic pathology is typical of patients with the Marfan syndrome, it may also occur in the absence of other clinical stigmata.

ANEURYSMS

ASCENDING AORTIC ANEURYSMS

Ascending aortic aneurysms occur more frequently in men than in women, are typically fusiform, and usually extend into the aortic arch. Consequently, aneurysms of the aortic arch are often contiguous with aneurysms in the ascending aorta. Ascending aortic aneurysms are categorized according to the pattern of involvement of the aortic root (Fig. 93–6), with direct implications for surgical treatment. In the most common type, *supracoronary aneurysm*, the aortic annulus is normal in diameter, as is the short segment of aorta between the annulus and the coronary ostia. This type of aneurysm is treated by replacement with a tube graft, starting above the coronary arteries and extending cephalad to the end of the aneurysm. The second category, termed *annuloaortic ectasia*, is characterized by enlargement of both the aortic annulus and the proximal portion of the aorta. This type of aneurysm is typical of Marfan syndrome and related disorders characterized by cystic medial necrosis of the aortic wall.[14] Because the annulus and proximal aorta are the most dilated portions, the aneurysmal ascending aorta has a "flask-like" shape, requiring replacement of the entire aortic root and valve, usually with a prefabricated composite graft that includes a prosthetic valve and aortic graft in an integrated unit. The third category, the *tubular* type of ascending aortic aneurysm, shares features of the other two configurations. In patients with tubular aortic aneurysms, the annulus and proximal aorta are mildly dilated, and the caliber of the ascending aorta is more uniform. When surgical repair is necessary, either a supracoronary tube graft or total aortic root replacement may be appropriate based on considerations that include the patient's age. In younger individuals, composite grafting may confer greater protection against late dilation of the proximal portion of the aortic root, while in older patients more limited approaches may be advantageous.

DESCENDING THORACIC AORTIC ANEURYSMS

In contrast to the ascending aorta, the majority of aneurysms of the descending thoracic aorta are atherosclerotic.[18] These are typically fusiform, often begin distal to the origin of the left subclavian artery, and may extend to the level of the abdominal aorta. Descending thoracic aneurysms may also develop in patients with aortic coarctation.

ABDOMINAL AORTIC ANEURYSMS

In more than 90% of cases, the superior margins of abdominal aneurysms are distal to the origins of the renal arteries. Atherosclerosis is present in the majority, although some authors suggest that atherosclerosis may be a secondary phenomenon in aneurysmal disease.

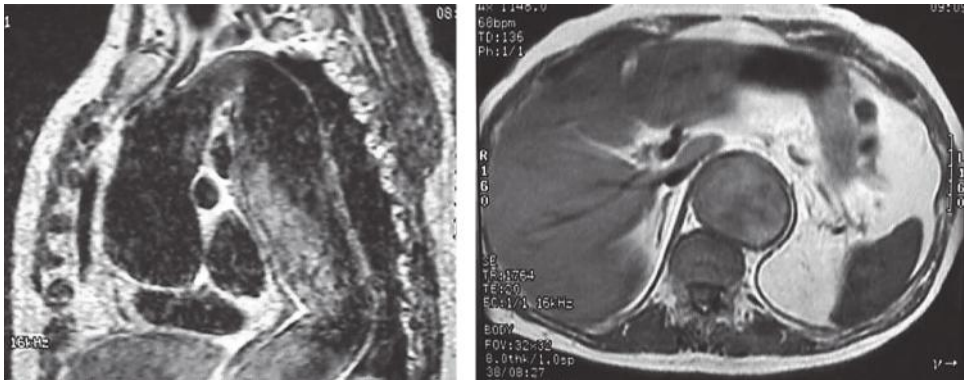


FIGURE 93–5. Magnetic resonance imaging demonstrating aneurysm of the entire aorta viewed in the sagittal thoracic and axial abdominal views.

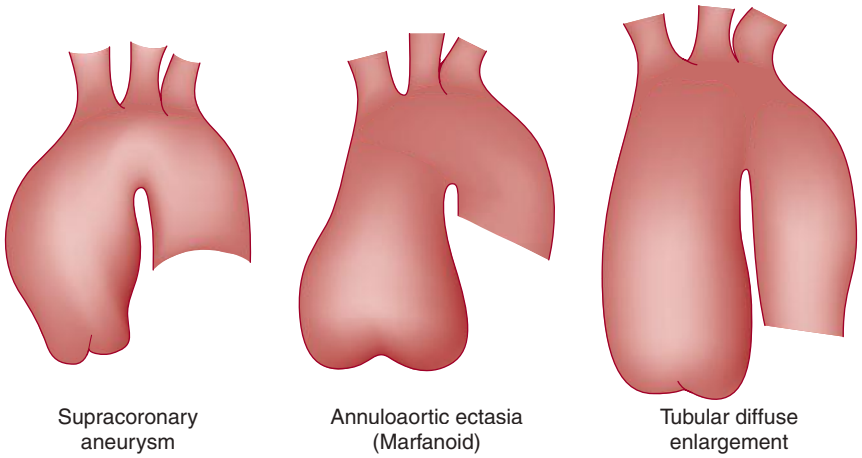


FIGURE 93–6. Three common patterns of ascending aortic aneurysmal disease: supracoronary, annuloaortic ectasia, and tubular. See text for details.

THORACOABDOMINAL AORTIC ANEURYSMS

As the nomenclature indicates, thoracoabdominal aortic aneurysms have features of both thoracic and abdominal aortic aneurysms (Fig. 93–7). Although they constitute only approximately 3% of all aortic aneurysms, thoracoabdominal aneurysms are classified separately because of the diffuse and extensive nature of the aortic disease process (usually atherosclerosis) and special considerations for surgical repair, which may entail reimplantation of visceral arteries.[19] Crawford and Coselli[20] delineated four types of thoracoabdominal aortic aneurysms according to the segment and extent of aorta involved, as described in Fig. 93–7.[20]

EPIDEMIOLOGY OF ANEURYSMAL DISEASE

The epidemiology of aortic aneurysms and the corresponding acute aortic syndromes present challenges because of confusion in terminology, referral bias, unknown incidence of asymptomatic cases, misdiagnosis of aortic rupture or dissection as myocardial infarction (MI), and limitations of administrative databases.[21-23] The Centers for Disease Control and Prevention (CDC) list aneurysmal disease as the 19th most common cause of death and 15th most common in those older than 65.[22]

The advent of routine postmortem computerized tomography in victims of out-of-hospital cardiac arrest brought to emergency departments (a growing trend in Europe and Japan) promises to improve understanding of the epidemiology of aortic dissection. These studies point to acute Type A aortic dissection as the cause of as many as 8% of cases of out of hospital cardiac arrest, and suggest that Type A aortic dissection is a more frequent cause of unexpected death than previously recognized.[24,25]

Abdominal aortic aneurysm affects approximately 5% of individuals over age 65 years, and the prevalence is considerably higher in men than women.[23] The annual incidence of ruptured abdominal aortic aneurysm is approximately 10 per 100,000 population and is similar in men and women, though the age at diagnosis is a decade higher among

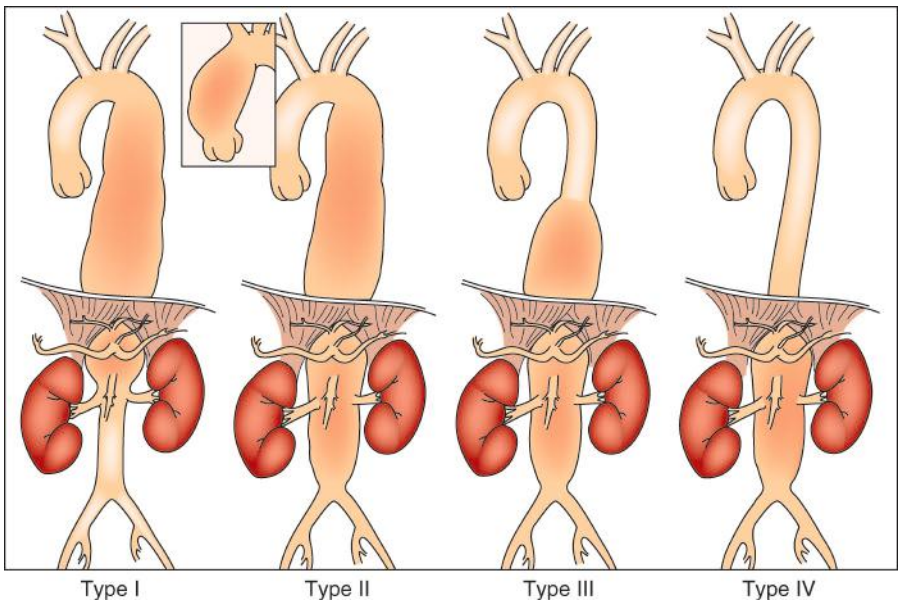


FIGURE 93–7. Classification of thoracoabdominal aortic aneurysms. **Type I** aneurysms involve most of the descending aorta from near the origin of the left subclavian artery to the abdominal vessels, but the renal arteries are not involved. **Type II** aneurysms also begin near the origin of the left subclavian artery but extend below the origins of the renal arteries. **Type III** aneurysms arise more distally and involve less of the descending thoracic aorta but often more of the abdominal aorta than types I and II aneurysms. **Type IV** aneurysms arise at the level of the diaphragm and typically extend below the origins of the renal arteries. Reproduced with permission from Crawford ES, Coselli JS. Thoracoabdominal aneurysm surgery. *Semin Thorac Cardiovasc Surg*. 1991 Oct;3(4):300-322.[20]

women.[26,27] The rate increases to approximately 50 per 100,000 for men in the seventh decade of life and each year more than one in 1000 men in the eighth decade experiences rupture of an abdominal aortic aneurysm.

The incidence of thoracic aortic aneurysm is also approximately 10 per 100,000 population and similar in women and men, but the age at diagnosis is a decade higher in women (70s). The yearly incidence of rupture or dissection of existing thoracic aortic aneurysms is approximately 7%, divided equally between these two types of events. A curious and as yet unexplained finding is that 79% of ruptures of thoracic aortic aneurysms occur in women.[27-29]

Aortic aneurysm and its acute complications are recognized with increasing frequency. These trends during the past three decades have been confirmed by the Centers for Disease Control for the United States, Scotland, Sweden, the Netherlands, England, and Wales.[28,30] Clinical data suggest a true increase in incidence rather than more frequent diagnosis due to wider availability of aortic imaging.

SCREENING FOR ABDOMINAL AORTIC ANEURYSM

The epidemiologic implications of screening for abdominal aortic aneurysms have been extensively studied.[23,31-33] Screening programs based on abdominal ultrasonography effectively detect aneurysms prior to rupture and reduce the frequency of aneurysm-related deaths. The cost of medical care per single aneurysm-related death prevented is about $10,000. One important benefit of screening is that a single negative ultrasonogram at 65 years of age suffices; patients without aneurysms at this age will not die of aneurysm rupture.[23,31-33]

Cost-effective screening of the general population is focused on family history of aneurysmal disease, age, male sex, history of cigarette smoking, coronary artery disease, cerebrovascular disease, and hypercholesterolemia as factors linked with incremental risk of aneurysm development. Abdominal aortic aneurysm is five times more common in smokers, in whom 89% of all aneurysm ruptures occur.[23]

The US Preventive Services Task Force recommends[31,33] one-time screening for abdominal aortic aneurysm by ultrasonography in men aged 65 to 75 years who have ever smoked. There is no recommendation (for or against) screening in men age 65 to 75 years who have never smoked, and an explicit recommendation against routine screening for abdominal aortic aneurysm in women based on the relatively low yield. The Society for Vascular Surgery recommends one-time screening for all men older than 65 (and at 55 if family history is positive) and screening for women older than 65 who have smoked or have a positive family history of aortic disease.[34]

CLINICAL MARKERS OF ANEURYSM DISEASE

Aneurysms are often clinically silent until rupture or dissection occurs, and these catastrophes are most often fatal. Thus detection of asymptomatic aneurysms is paramount. "Guilt by association" has been proposed as a strategic approach to aneurysm detection,[35] capitalizing on eight clinical correlates of thoracic aortic aneurysm: intracranial aneurysm, bovine aortic arch configuration, bicuspid aortic valve, renal cyst, abdominal aortic aneurysm, positive thumb-palm sign, family history, and temporal arteritis (Fig. 93–8). The association of intracranial

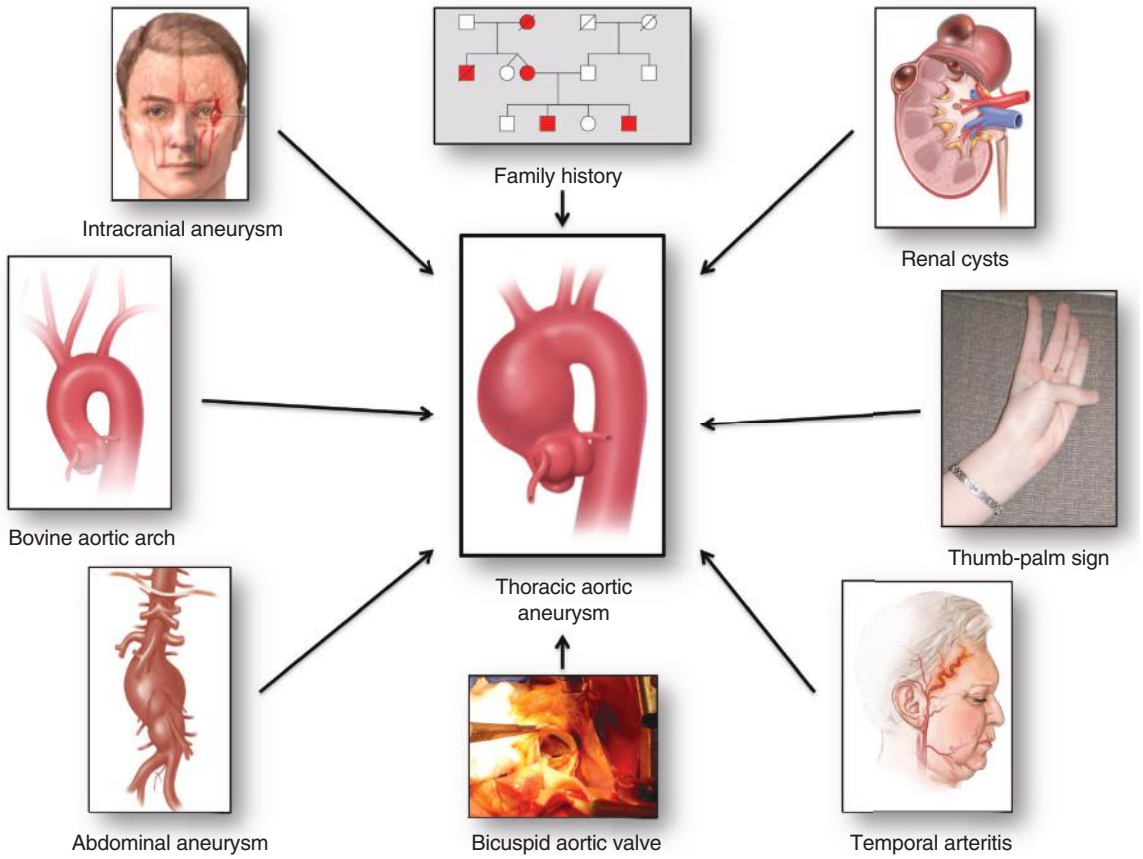


FIGURE 93–8. Paradigm of "guilt by association" for detection of silent thoracic aortic aneurysm. Reproduced with permission from Elefteriades JA, Sang A, Kuzmik G, Hornick M. Guilt by association: paradigm for detecting a silent killer (thoracic aortic aneurysm). *Open Heart*. 2015 Apr 24;2(1):e000169.[35]

or abdominal aneurysms with thoracic aortic aneurysms illustrates the coincidence of aneurysms in multiple vascular beds. Patients with thoracic aneurysms have an approximately 10% likelihood of concurrent intracranial aneurysm (higher for those with descending than ascending aneurysms),[36] probably as a consequence of common genetic and pathophysiologic mechanisms. Because of the prognostic significance and available catheter-based interventions to prevent rupture, routine screening for intracranial aneurysms may be warranted in patients with thoracic aortic aneurysms.

Bovine aortic arch and other arch anomalies like direct origin of the left vertebral artery from the aortic arch or aberrant right subclavian artery were previously considered benign variants, but these anomalies occur more frequently in patients with thoracic aortic aneurysm than in the general population.[37,38]

The association of renal cysts and thoracic aortic aneurysm may reflect excess matrix metalloproteinase (MMP) activity.[39]

The significance of family history of aortic aneurysmal disease, the thumb-palm sign, and arteritides are addressed below.

The emerging conclusion is that, if one of these "associates" or "markers" of thoracic aortic aneurysm is discovered in the history, physical exam, or imaging of a patient, the propensity toward a thoracic aortic aneurysm should be kept in mind.

ETIOLOGY AND PATHOPHYSIOLOGY

AORTIC ANEURYSM AS AN INHERITED DISEASE

Thoracic aortic aneurysms can be subdivided into two main categories: (1) *syndromic*, associated with abnormalities of other organ systems; and (2) *nonsyndromic*, with manifestations restricted to the aorta. Patients with syndromic thoracic aortic aneurysm may have Marfan syndrome, Loeys-Dietz syndrome, aneurysm-osteoarthritis syndrome, arterial tortuosity syndrome, Ehlers-Danlos syndrome (EDS), cutis laxa syndrome, or mutations affecting transforming growth factor beta (TGF-β). Nonsyndromic thoracic aortic aneurysm includes familial (affecting more than one family member) and sporadic forms.[40-42]

Marfan Syndrome

This inherited disorder, described in 1896, is characterized by dolichostenomelia (long, thin extremities), ligamentous redundancy or laxity, ectopia lentis, ascending aortic dilation, and incompetence of the aortic or mitral valves (or both).[43] A large number of specific mutations (> 600) produce the Marfan phenotype, thus reducing the clinical usefulness of genetic testing in diagnosis.[44] Diagnosis is established largely on clinical grounds using the criteria summarized in Table 93–1.[45] The syndrome is linked to an autosomal dominant anomaly in the gene regulating synthesis of fibrillin type 1, a large glycoprotein that directs and orients elastin in the developing aorta.[46] Marfan syndrome was widely attributed to structural abnormalities and weaknesses of the aortic wall until dysregulation of TGF-β signaling was identified as a more reliable correlate.[47-49] TGF-β controls a panoply of cell functions. As fibrillin 1 binds TGF-β in an inactive complex, increased TGF-β signaling develops as a compensatory mechanism and plays a role in the pathogenesis of the degeneration of elastic fibers, accumulation of mucoid material within the medial layer of the aortic wall, and accelerated cystic medial necrosis that characterize this disease.

In patients with the Marfan syndrome, the aortic root tends to enlarge in fusiform fashion in association with aortic valve regurgitation, and about half of patients also have mitral insufficiency (Fig. 93–9). Aneurysms characteristically involve the sinuses of Valsalva and the tubular portion of the ascending aorta, producing annuloaortic ectasia (Fig. 93–10). Over time, abnormalities associated with Marfan syndrome typically affect the entire length of the aorta, although dissection most often involves the thoracic portion.[50]

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome is an inherited connective tissue disorder less frequent than Marfan syndrome but also associated with aneurysm formation.[51,52] Although aneurysm formation and aortic dissection may occur in most types of Ehlers-Danlos syndrome, they are more frequent in the vascular type (Type IV), which results from a mutation of the *COL3A1* gene.[53]

Loeys-Dietz Syndrome

Loeys-Dietz syndrome, which is caused by mutations in the TGFBR1 and TGFBR2 genes, is associated with aortic and arterial aneurysms that enlarge rapidly and are prone to rupture; in one series, the mean age at death was 26 years.[54,55]

Bicuspid Aortic Valve

Patients with congenital bicuspid aortic valve have structural abnormalities of the ascending aorta predisposing to aneurysm and dissection.[56-59] Some have aortic coarctation as part of this syndrome as well. Aneurysmal enlargement of the aorta in patients with bicuspid aortic valve may occur independent of valvular stenosis or regurgitation and is not, therefore, predominantly a consequence of poststenotic dilation, although the aorta expands more rapidly when valvular dysfunction is present. Because bicuspid valves occur in ~2% of the population, the associated aortopathy is responsible for more cases of aortic dissection than the Marfan syndrome (which affects one in 10,000 people) (Table 93–2).

It is estimated that bicuspid valve disease accounts for more morbidity and mortality than all other congenital cardiac lesions combined.[60] Many authorities believe that this disease is so virulent that every individual with a bicuspid aortic valve will, given enough time, develop aortic stenosis, aortic insufficiency, or aortic aneurysm or dissection related to the bicuspid valve disease. Ascending aortic aneurysm in patients with bicuspid aortic valve is currently considered nearly as serious as ascending aortic aneurysm in patients with Marfan disease, and operation is often offered earlier than in nonbicuspid patients. Evidence now points to a congenital pattern of inheritance, and the fundamental embryology is being elucidated in animal models. The specific genetic mutations in humans with bicuspid valve have proven complex and multifactorial; abnormalities in the *NOTCH1* gene have been documented, but only in some bicuspid patients.[61] Evidence shows that excess matrix metalloproteinase (MMP) activity characterizes both the valve tissue and the aortic wall in bicuspid patients. The aorta grows more rapidly in bicuspid patients. Especially when there is associated valvular dysfunction, the current trend favors aggressive aortic resection in bicuspid patients with ascending aortic aneurysms (although specific criteria have varied in different editions of standard guidelines).

The histology and mechanical properties of the ascending aorta in patients with bicuspid aortic valves may predispose to dissection at smaller diameters than in patients with structurally normal (tricuspid) aortic valves.[62-64]

Familial Thoracic Aortic Aneurysm

Many cases of thoracic aortic aneurysm once classified as atherosclerotic, hypertensive, or idiopathic are now traced to hereditary metabolic abnormalities affecting the aortic wall. There is a family history of aneurysmal disease in one of five patients with aortic aneurysm.[65] Probands with ascending aortic aneurysm are more likely to have family members with ascending aneurysm, and those with aneurysms

TABLE 93–1. Quick Guide to Diagnosis of Marfan Disease

	Cardiovascular	Skeletal System	Ocular System	Pulmonary System	Skin and Integument	Dura	Family History/ Genetics
Major Criteria	One required: Dilatation of Asc A(+ AI), involving sinuses of Valsalva AAD	Four required: Pectus carinatum Pectus excavatum (requiring surgery) Reduced upper-to-lower segment ratio or increased arm span-to-height ratio Positive wrist and thumb signs Elbow extension reduced < 170° Pes planus Protrusion acetabulae	Ectopia lentis	None	None	Dural ectasia	Parent, child, or sibling with Marfan disease *FBN1* mutation
Minor Criteria	MVP (± prolapse) Dilatation of the main PA (patients younger than 40 y)	Pectus excavatum (moderate) Hypermobile joints Crowding of teeth or highly arched palate	Flat corneas Increased axial length of globe Hypoplastic iris or ciliary muscles, causing decreased meiosis	Spontaneous pneumothorax Apical blebs	Striae Recurrent or incisional hernias	None	None
Involvement (required to say organ system involved)	One major or one minor criterion	Two major or one major and one minor criteria	One major or two minor criteria	One minor criterion	One minor criterion	Major criterion	Major criterion

Diagnosis requires:

• For index case (without documented mutation)

> Major criteria in two organ systems, plus

> Involvement of another organ system

• For index case (with documented mutation)

> Major criterion in one organ system, plus

> Involvement of another organ system

• For a relative of a known case

> Major criterion in the family history, plus

> Major criterion in one organ system, plus

> Involvement of another organ system

Definitions and reference ranges:

Upper-to-lower segment = Distance from top of head to symphysis pubis/distance symphysis pubis to floor (reference range, 0.89-0.95) arm span-to-height ratio (reference range < 1.05).

Wrist sign = Positive if a person's thumb and little finger overlap when gripping own wrist.

Thumb sign = Positive if the entire nail of a person's thumb projects beyond the border of the hand when their fist is closed around the thumb.

Abbreviations: AAD, ascending aortic dissection; AI, aortic insufficiency; Asc, ascending; MVP, mitral valve prolapse; PA, pulmonary artery.

Data from Tsipouras P, Silverman DI. The genetic basis of aortic disease: Marfan syndrome and beyond. *Cardiol Clin*. 1999;17:683-696, and from National Library of Health of National Health Services. Available at http://www.library.nhs.uk/genepool/ViewResource.aspx?resID=126262.

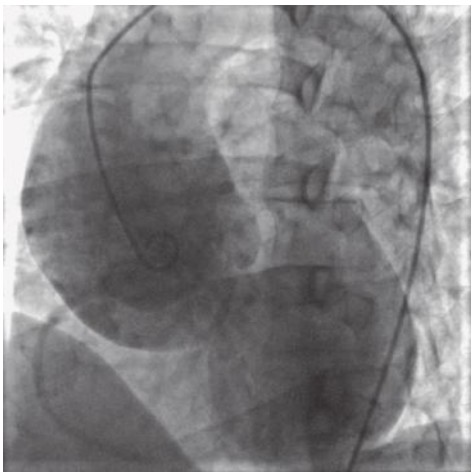


FIGURE 93–9. Aortogram of a patient with Marfan syndrome. Aortic aneurysms in this disorder are characterized by annuloaortic ectasia involving the sinuses of Valsalva and the ascending aorta produced by degeneration of elastic fibers and the accumulation of mucoid material within the medial layer of the aortic wall, grossly resembling cystic medial necrosis.

involving the descending aorta are more likely to have family members with abdominal aneurysms.[66] Although there are several patterns of inheritance, autosomal dominance with reduced penetrance predominates (Fig. 93–11).

Genetic Testing for Thoracic Aortic Aneurysm

To date, as many as 21 genes have been linked with familial or syndromic thoracic aortic aneurysms and dissection (Fig. 93–12),[67] and discovery of additional candidate genes is likely. These encode molecules that regulate extracellular matrix (*FBN1*, *FBN2*, *COL1A1*, *COL1A2*, *COL3A1*), the cytoskeleton of smooth muscle cells (*ACTA2*, *MYH11*, *MYLK*), and the TGF-β signaling pathway (*TGFβ2*, *TGFBR1*, *TGFBR2*, *SMAD3*, *SLC2A10*). Most known mutations predispose to aortic aneurysm formation. However, there are certain genes that are either exclusively involved in aortic dissection (the *MYLK* gene[68]), or cause aortic dissection at small aortic sizes (the *ACTA2* gene[69,70]). This near-exclusive dissection diathesis poses additional challenges in terms of counseling the patients regarding the most appropriate time for preventive surgical intervention, as aneurysm size is not useful in these small patient subgroups.

Certain genetic mutations influence the natural history of thoracic aortic disease, so the results of genetic testing may have implications for individualized management strategies in patients with thoracic aortic aneurysm. Genetic testing of patients with thoracic aortic disease can be accomplished using panels of genes or whole-exome sequencing. A potential benefit of routine whole-exome sequencing has been reported in patients with thoracic aortic aneurysm and dissection,[67] and genetic testing may lead to detection of asymptomatic aortic disease in the families of those with thoracic aortic disease, but the relative value of genetically based and imaging strategies for prevention of death related to aortic disease remains unsettled.

MOLECULAR PATHOPHYSIOLOGY

After genetic mutations establish the propensity for aneurysm development, lytic MMP enzymes degrade the structural proteins of the aortic wall, leading to aneurysm formation and dissection (Fig. 93–13). These enzymes are normally regulated by tissue inhibitors of metalloproteinases (TIMPs), which antagonize the lytic action of the MMPs. An uncertain

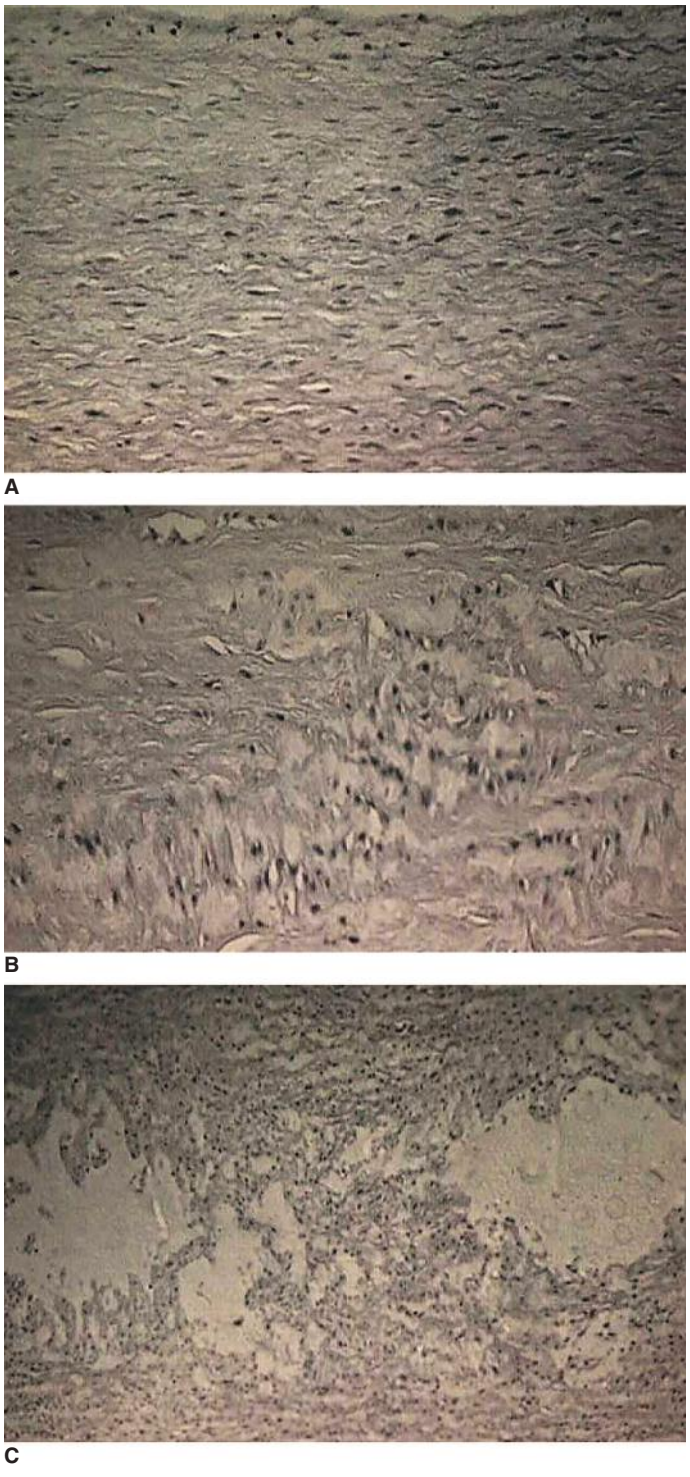


FIGURE 93–10. Cystic medial necrosis of progressive severity (A to C). Blood gaining access to one of the cystic spaces through a defect in the intimal layer of the aortic wall can propagate longitudinally along the aorta, initiating dissection.

proportion of patients with aortic aneurysms manifest excessive MMP activity, but such activity has been documented in cases of abdominal aortic aneurysm[71,72] as well as in cases of ascending aortic aneurysm and aortic dissection.[73] Several dozen specific MMP enzymes and certain TIMPs have been implicated in the pathogenesis of aneurysm disease.[74]

In addition to proteolysis of the extracellular matrix, the pathogenesis of aortic aneurysms involves inflammation, cytokine activity, and loss of

TABLE 93–2. Comparison of Epidemiology of Marfan Disease and Bicuspid Aortic Valve with Special Reference to Number of Cases of Aortic Dissection Brought on by Disease[a]

	Incidence	AAD Likelihood (Lifetime) (%)	AAD Caused (as % of Population)
Marfan disease	1/10,000 (0.01%)	40	0.004
Bicuspid aortic valve	2/100 (2%)	5	0.1

Abbreviation: AAD, acute aortic dissection.

[a]Note that bicuspid aortic valves cause 25 times more acute aortic dissections than Marfan disease.

smooth muscle cells. Together, these processes undermine the integrity of the aortic wall and set the stage for aneurysm formation, growth, and rupture. Inflammatory cells participate in the genesis of aneurysms.[74-76] Smooth muscle cells of the aortic wall are charged with repairing damaged proteins, and a substantial (~75%) reduction in the number of smooth muscle cells in the walls of abdominal aortic aneurysms impairs this function. Aneurysmal smooth muscle cells display a threefold increase in apoptosis and impaired growth capacity. Figure 93–14 illustrates the interaction of proteolysis, inflammation, cytokine activation, and deficient smooth muscle cell function in the pathophysiology of aneurysm formation.

Many patients with ascending aortic aneurysms, which are typically nonatherosclerotic, display relatively little evidence of systemic atherosclerotic disease. A study comparing patients with ascending aortic aneurysm associated with annuloaortic ectasia or aortic dissection with age- and gender-matched control subjects found significantly less arterial calcification as detected by computed tomography (CT) imaging in those with aneurysms.[77] Subsequent follow-up investigations showed that patients with ascending aortic aneurysm have lower intimal-medial carotid artery wall thickness (IMT) than control subjects.[78] A related study found a low incidence of myocardial infarction among patients with ascending aortic aneurysm.[79] Among the possible explanations for these observations are that mutations responsible for ascending aortic aneurysm protect against atherosclerosis, that the MMPs that lead to aortic aneurysm development have anti-atherogenic properties, or that the biophysics of atherogenesis is influenced by changes in pressure or flow dynamics resulting from aneurysmal disease.[80]

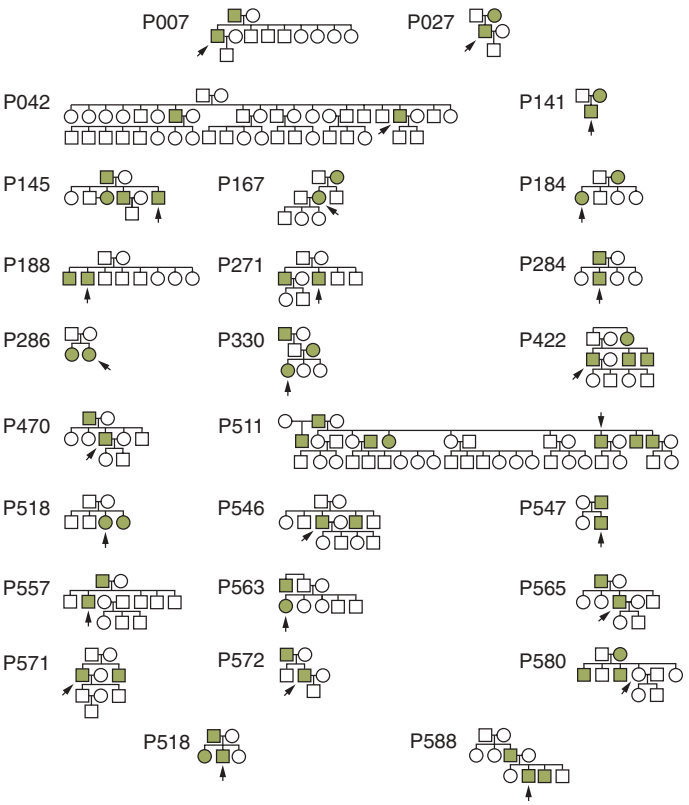


FIGURE 93–11. In a series of 100 family pedigrees of patients with thoracic aortic aneurysm or dissection, 21 suggested genetic transmission. Autosomal dominant inheritance predominates, but other patterns of transmission also are evident.

CLINICAL MANIFESTATIONS

AORTIC ANEURYSMS

Unfortunately, the vast majority of thoracic and abdominal aortic aneurysms are clinically silent, with rupture constituting the first manifestation.[81] A minority of patients (5%–10%) experience symptoms, permitting earlier detection of the aneurysm. Aneurysms of any kind can produce pain arising from stretching of the aortic tissue or impingement on adjacent structures. Pain originating in the ascending aorta is usually felt retrosternally. Pain from the descending aorta is characteristically located between the scapulae. Pain in the lateral or posterior chest may occur when the aneurysm compresses surrounding structures or erodes into adjacent ribs or vertebrae. Pain from the abdominal aorta may occur in the abdomen, left flank, or lower part of the back. It is often difficult to distinguish aneurysm pain from that resulting from other causes, but patients may be able to distinguish deep visceral pain from superficial or musculoskeletal pain. The interscapular location of pain caused by descending aortic enlargement or dissection is less often caused by musculoskeletal disease.

Rupture of the aorta in any location produces acute symptoms, usually severe pain followed by loss of consciousness or death as a result of internal hemorrhage. Rupture of an abdominal aortic aneurysm usually produces the clinical picture of extreme distress as a result of an abdominal catastrophe. Despite surgical advances, mortality is still the most frequent outcome because abrupt circulatory collapse prevents timely intervention except in unusual circumstances. Patients frequently have severe abdominal or back pain, but the pattern varies considerably. The aneurysm may rupture into the retroperitoneum or into the peritoneal or pleural cavities, leading to tachycardia, hypotension, diaphoresis, pallor, or shock, depending on the extent of rupture and associated blood loss into the extravascular space. On occasion, rupture occurs directly into the duodenum, causing an aortoduodenal fistula and acute gastrointestinal bleeding. This possibility should be considered when gastrointestinal bleeding is evident along with signs of an aneurysm on physical examination. Rupture may also occur into the inferior vena cava or iliac veins, producing an arteriovenous fistula; this is suggested by rapid development of leg swelling or high-output heart failure in the presence of an abdominal aortic aneurysm. Rupture of a descending or thoracoabdominal aortic aneurysm produces similar physiologic derangements, with the associated pain typically located higher in the trunk, consistent with the anatomical location of the disease process.

Aside from pain, ascending aortic aneurysms may produce heart failure on the basis of incompetence of the aortic valve. As the aortic root enlarges, diastolic coaptation of the aortic valve leaflets progressively falters, causing regurgitation of blood through the resultant central gap. Aneurysms of the sinuses of Valsalva may rupture directly

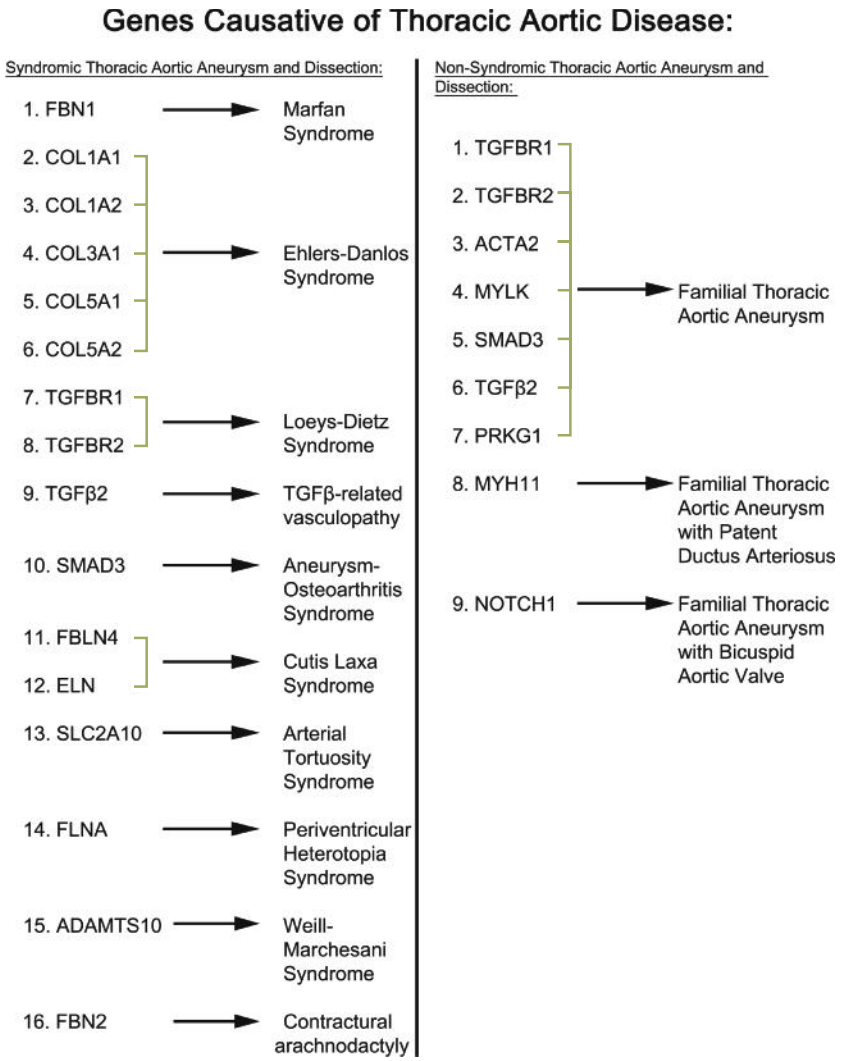


FIGURE 93–12. Genes that are currently known to cause syndromic and nonsyndromic thoracic aortic aneurysm and dissection. **COL3A1* is the gene responsible for Type IV (vascular type) Ehlers-Danlos syndrome, which is most often associated with aneurysm and/or dissection. Reproduced with permission from Ziganshin BA, Bailey AE, Coons C, et al: Routine Genetic Testing for Thoracic Aortic Aneurysm and Dissection in a Clinical Setting. *Ann Thorac Surg*. 2015 Nov;100(5):1604-1611.[67]

into the right ventricular cavity, right atrium, or pulmonary artery, causing heart failure associated with a continuous murmur. Ascending aortic aneurysms can distort or obstruct the trachea, producing respiratory symptoms. Compression of the superior vena cava may produce venous congestion in the head, neck, and upper extremities. Aortic arch aneurysms or descending thoracic aortic aneurysms may produce hoarseness or dysphagia ("dysphagia lusoria") from distortion of the recurrent laryngeal nerve or direct impingement on the esophagus. Descending thoracic aortic aneurysms may cause hemoptysis from direct erosion into the lung parenchyma or bronchi or hematemesis from esophageal erosion. Because mural thrombosis is so common in atherosclerotic aneurysms, they may be the source of peripheral embolism of thrombus or atherosclerotic debris causing occlusion of distal vessels or clinical features of atheroembolism. Occasionally, patients with abdominal aortic aneurysms may become aware of prominent abdominal pulsation. Nausea and vomiting may occur if an aneurysm compresses the duodenum. Compression of the left iliac vein may cause left leg swelling, compression of the left ureter may cause hydronephrosis, compression of the testicular veins may cause varicocele, or compression of the bladder may cause urinary frequency or urgency.

Thoracic or abdominal aortic aneurysms are most commonly diagnosed not on the basis of symptoms but incidentally by imaging procedures carried out for another reason. Occasionally, chest radiographs obtained to evaluate pulmonary symptoms or for general screening suggest an aortic aneurysm, which may then be confirmed by CT or magnetic resonance imaging (MRI).

AORTIC DISSECTION

Aortic dissection typically produces sudden intense pain, often described as tearing or shearing in quality. Whereas ascending aortic dissection usually causes anterior,

FIGURE 93–13. The proteins in the wall of this ascending aortic aneurysm were degraded, presumably by matrix metalloproteinase–related activity, to the extent that the aortic wall became so thin that the markings on a ruler are visible through the aortic wall.

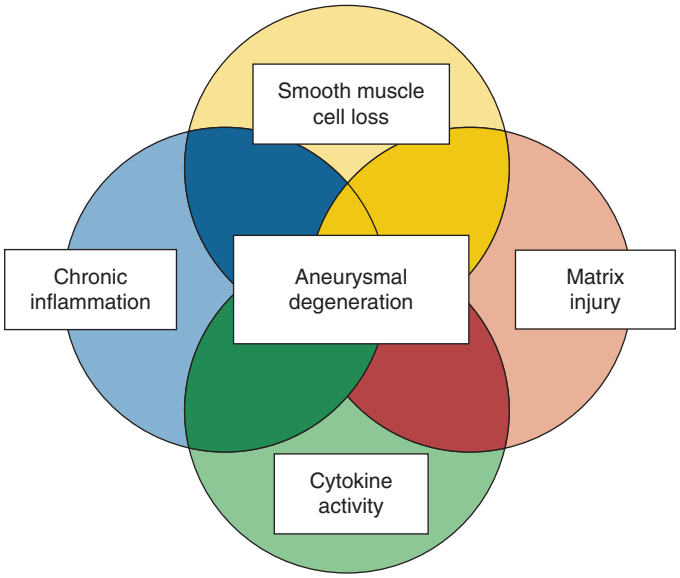


FIGURE 93–14. Factors involved in the pathogenesis of aortic aneurysms.

substernal chest pain, dissection of the descending aorta causes posterior, interscapular pain. Pain may migrate inferiorly to the flank or pelvis as the dissection propagates distally. Impending aortic rupture should be considered when pain subsides and later recurs.[76]

Painless dissection occurs in as many as 4% to 15% of patients[81-84] and is commonly detected as an asymptomatic finding on elective CT scans obtained for another purpose. By convention, aortic dissection is considered acute when identified within 2 weeks of onset and chronic when symptoms or other markers of dissection have been present longer.

Clinically, the inciting event responsible for aortic dissection is an intimal tear that permits blood to pass from the true lumen into the middle or outer layer of the aortic media, forming a second or false lumen separated by an intimal flap.[85] In some cases, intramural hematoma precedes perforation of the intima, possibly related to rupture of a vasa vasorum.[86] The dissection may propagate distally (antegrade) or proximally (retrograde) to narrow or occlude the origin of any branch artery arising from the aorta. Antegrade propagation is more common, and the dissection usually has spiral morphology, leaving some aortic branches supplied by the true lumen and others in continuity with the false lumen. Because any branch of the aorta can be affected, dissection can present as disease of any organ system—stroke, paraplegia, abdominal visceral catastrophe, renal failure, or lower limb ischemia. For this reason, aortic dissection has been given the well-earned moniker of "the great masquerader."

The intimal tear originates in the ascending aorta in 65% of cases, transverse arch in 10%, upper descending aorta just beyond the origin of the left subclavian artery in 20%, and more distally in 5% of cases. The false lumen may terminate at any point along the length of the aorta or in the iliac or femoral arteries, and there are sometimes multiple flaps and several sites of reentry. The false lumen can undergo retrograde dissection, thrombotic occlusion, pseudoaneurysm formation, compression, or rupture.

Aortic dissection occurs more often in men than in women, with a 2:1 to 5:1 preponderance,[81] usually in the sixth or seventh decade of life. Systemic hypertension is the major predisposing risk factor. In the International Registry of Aortic Dissection (IRAD) database, 74.4% of 2952 patients with proximal aortic dissections and 80.9% of 1476 with distal dissections had a history of hypertension.[87] Other predisposing conditions include Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, bicuspid aortic valve, aortic aneurysm, and annuloaortic ectasia associated with cystic medial necrosis. The most common causes of aortic dissection in patients younger than 40 years old are Marfan syndrome and pregnancy. Iatrogenic trauma resulting from intravascular catheterization is the cause in approximately 5% of dissections and may involve any segment of the aorta. Cocaine abuse is increasingly recognized as a factor predisposing to acute aortic dissection, possibly mediated by acute hypertension.[88,89]

Aortic dissection is often fatal unless recognized early and aggressively treated. Because the presenting symptoms and signs are myriad and nonspecific, dissection may be initially overlooked in up to 40% of cases. The diagnosis is first apparent at postmortem examination in a disturbingly large fraction of cases. The mortality rate associated with untreated aortic dissection approaches 1% to 2% per hour during the first 48 hours, reaching 90% at 3 months; most deaths related to dissection occur within 14 days after onset.[2,90] Up to 20% of victims die before reaching hospital.[90] With expert care, however, survival rates of more than 70% have been reported for patients reaching the hospital with acute aortic dissection. Most require intensive medical therapy, either as the sole treatment or in conjunction with surgical intervention. Even if the patient survives aortic dissection, expansion of the dissected portion of the aorta (dissecting aortic aneurysm) contributes to mortality beyond the acute phase.

Dissection may occur in the ascending (type A) or descending (type B) segments of the thoracic aorta, defined by the location of the inciting intimal tear. Tears in the ascending aorta generally occur 2 to 3 cm above the coronary ostia, and in the descending aorta typically originate 1 to 2 cm beyond the origin of the left subclavian artery. The first type produces ascending (Type A) dissection and the second descending (Type B) dissection, but dissections originating in the ascending aorta commonly extend along the aortic arch to involve the descending and abdominal portions of the aorta as well.

Aortic dissection can cause death in four main ways (Fig. 93–15): (1) hemopericardium with cardiac tamponade caused by retrograde dissection; (2) acute aortic valve insufficiency caused by retrograde dissection; (3) hemothorax caused by rupture of a descending aortic dissection into the pleural space; and (4) tissue ischemia caused by occlusion of a branch artery. Figure 93–16 illustrates the mechanism of branch occlusion and benefits of spontaneous, catheter-based, or surgical fenestration.

Most patients with aortic dissection present with hypertension, but 3% to 18% present with shock, sometimes secondary to extension of dissection into the coronary arteries, acute MI, LV failure, acute severe aortic insufficiency, cardiac tamponade, or aortic rupture. Coronary perfusion may be compromised by retrograde dissection, compression by the false lumen, or hypotension. In one series, differential pulse volume and blood pressure between the right and left upper extremities was detected in 38% of patients with ascending aortic dissection. An abrupt loss of pulse may affect the carotid, subclavian, axillary, radial,

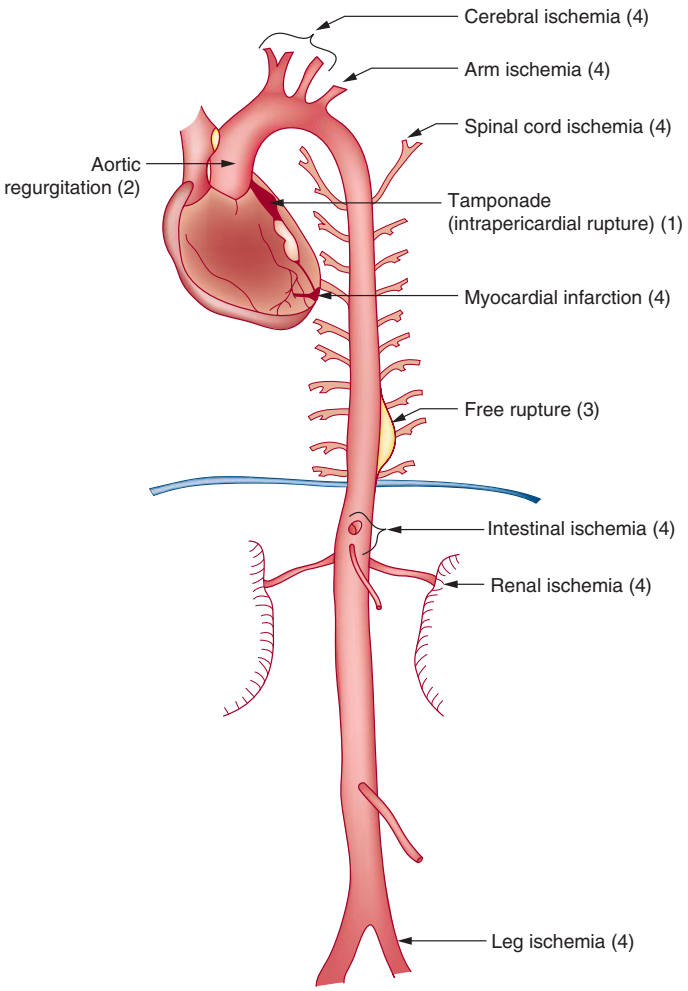


FIGURE 93–15. The mechanisms by which acute aortic dissection cause death: (1) intrapericardial rupture and tamponade, (2) acute aortic insufficiency, (3) free rupture into left pleural space, or (4) occlusion of a branch of the aorta.

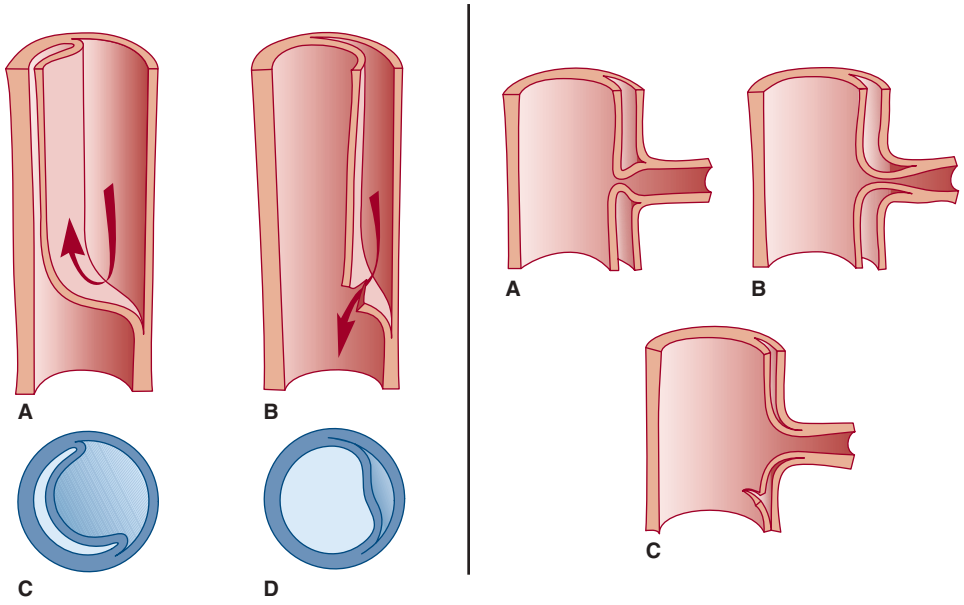


FIGURE 93–16. Schematic representation of the distended false channel in a case of aortic dissection impinging on the lumen of a branch vessel. **Left**. Main aortic trunk, with **A** and **B** before fenestration and **C** and **D** after fenestration. **Right**. Anatomic events at branch vessel; **A** and **B** show impingement by a false lumen, and **C** shows relief by fenestration. Reproduced with permission from Crawford ES, Coselli JS. Thoracoabdominal aneurysm surgery. *Semin Thorac Cardiovasc Surg*. 1991 Oct;3(4):300-22.[20]

ulnar, or femoral arteries, and acute limb ischemia has been reported in 20% of patients. Branch vessel occlusion results from compression by the distended false lumen of the true lumen of the branch vessel.

Approximately 15% to 20% of patients with aortic dissection develop neurologic deficits, with transient cerebral ischemia or stroke in up to 10% of patients resulting from extension of dissection into the carotid or vertebral arteries. In such cases, brain imaging and neurologic or neurosurgical consultation may be helpful to determine whether cerebral infarction has occurred; surgery is best avoided in such cases for fear of inducing intracerebral bleeding or otherwise extending the zone of infarction. When cerebral infarction is absent or incomplete, urgent operation is generally indicated because repair of the dissection may restore brain perfusion. Similarly, urgent surgical intervention is indicated when interruption of spinal circulation by a dissection of the descending aorta threatens to cause paraplegia.

Aortic rupture is the most common cause of death in patients with aortic dissection. The second most common cause of death in these patients is acute, severe aortic regurgitation, which has been reported in 44% of patients with dissection of the ascending aorta and is poorly tolerated hemodynamically, compared with chronic aortic insufficiency; because sudden volume overload allows no time for LV adaptation, cardiogenic shock typically ensues.

VARIANTS OF AORTIC DISSECTION: INTRAMURAL HEMATOMA AND PENETRATING AORTIC ULCER

Intramural aortic hematoma differs from typical dissection in that there is no flap delineating the true and false lumens, and the hematoma is located circumferentially around the aortic lumen, rather than obliquely (Fig. 93–17).[91] Whether the intramural hematoma arises from a small intimal tear that is not radiographically detected or from a rupture of a vasa vasorum within the aortic wall remains controversial. The clinical course is variable; the hematoma may persist, resorb (returning the aorta to a normal appearance), leave an aneurysm with the possibility of rupture, or later result in dissection.[92] Penetrating aortic ulcer involves disruption of the internal elastic lamina and erosion of the medial layer of the aortic wall, resulting in local penetration at the site of an atherosclerotic plaque. This lesion may mimic or result in aortic dissection, pseudoaneurysm formation, intramural hematoma, or rupture (Figs. 93–17, 93–18, and 93–19).[93]

It is important to recognize that intramural hematoma and penetrating aortic ulcer are diseases associated with advanced age, characteristically occurring in patients older than those with type B aortic dissection. In addition, although branch vessel occlusion is commonly associated with aortic dissection, this does not occur as a consequence of penetrating aortic ulcer or intramural hematoma.[92]

The management of patients with penetrating aortic ulcer or intramural hematoma is controversial.[92] When the descending aorta is involved, most authorities advocate medical management with pharmacologic therapy aimed at plaque stabilization and reducing systolic arterial wall stress. Others take a more aggressive stance, operating on

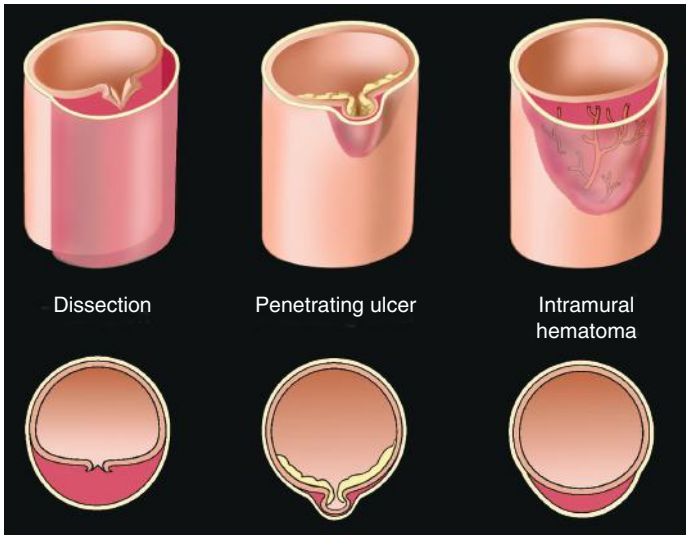


FIGURE 93–17. Variant forms of aortic dissection. Typical dissection, penetrating aortic ulcer, and intramural hematoma.

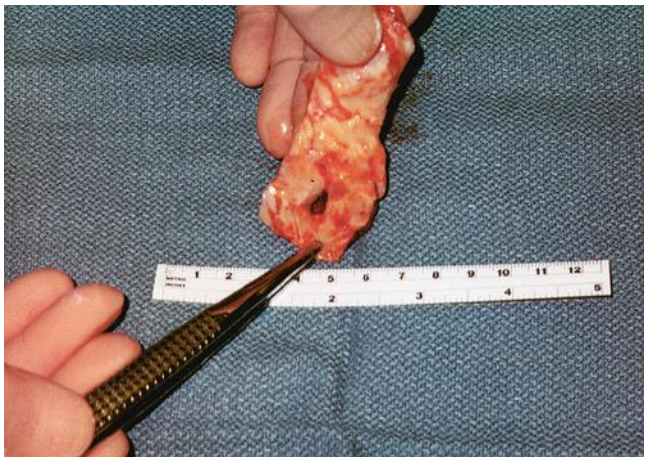


FIGURE 93–18. Gross specimen of a removed segment of aortic wall harboring a penetrating aortic ulcer.

all patients except very old and infirm ones, based on observational follow-up of unoperated patients, many of whom die of aortic rupture within 1 to 2 years.

For intramural hematoma involving the ascending aorta, there is more unanimity favoring immediate surgical intervention, although the Japanese literature challenges the need for routine surgery even in this anatomic location.[94] Penetrating aortic ulcers usually involve the descending aorta distal to the origin of the left subclavian artery, and for those associated with persistent pain, stent grafting is the treatment of choice. Figure 93–18 illustrates a dramatic case in which a penetrating ulcer ruptured through the posterior wall of the ascending aorta, mimicking "cryptogenic" pericardial effusion until surgical exploration made the diagnosis clear. Aortic intramural hematomas and penetrating ulcers rarely improve, and late surgery is commonly needed. Patients with penetrating ulcers may benefit from initial surgical management, but whether this applies to intramural hematomas is less clear (Fig. 93–20).[92] Endovascular therapy is an alternative to medical or open surgical management of intramural hematoma and penetrating aortic ulcer, and the appropriate role for endovascular therapy is currently under investigation.

FIGURE 93–19. Magnetic resonance angiogram with surface-shaded rendering demonstrating a penetrating aortic ulcer in the distal portion of the descending thoracic aorta. Note the severe generalized aortic arteriosclerosis.

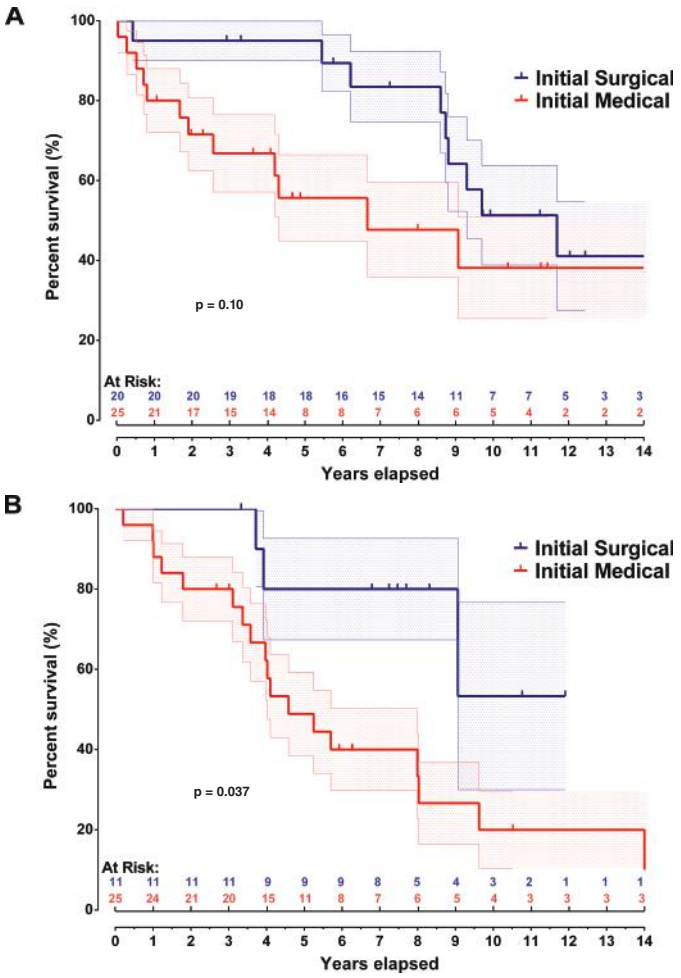


FIGURE 93–20. A. Kaplan-Meier survival curve for nonruptured intramural hematoma patients comparing long-term survival between initial surgical and initial medical cohorts. B. Kaplan-Meier survival curve for patients with nonruptured penetrating ulcers comparing long-term survival between initial surgical and initial medical cohorts. Reproduced with permission from Chou AS, Ziganshin BA, Charilaou P, et al: Long-term behavior of aortic intramural hematomas and penetrating ulcers. *J Thorac Cardiovasc Surg*. 2016 Feb;151(2):361-372.[92]

PHYSICAL EXAMINATION

Ascending aortic aneurysms are usually not detected by physical examination unless they produce the characteristic diastolic blowing murmur of aortic regurgitation, which is heard best at the upper right or left sternal border at end-expiration with the patient seated and leaning forward. Descending aortic aneurysms are seldom detectable on physical examination, except in rare instances when they can be palpated through an attenuated chest wall. In contrast, the abdominal aorta is easily palpable in most patients.

Dissection of the aorta is typically associated with physical signs, including the murmur of aortic regurgitation or decrement or loss of peripheral pulses (most commonly one of the femorals). Of course, a substantial difference in blood pressure between the two arms in the appropriate clinical setting should raise suspicion of acute or chronic aortic dissection as well.

DIAGNOSTIC STUDIES

For evaluation of patients with known or suspected aortic disease, imaging studies should be selected to identify aneurysm formation

and delineate zones of dissection or rupture. The challenge in the emergency department is to identify the relatively few patients with aortic dissection among the larger number presenting with signs and symptoms suggestive of acute MI—requiring continuous awareness of the three life-threatening causes of acute chest pain (MI, pulmonary thromboembolism, and aortic dissection) and judicious use of CT and echocardiographic imaging for diagnosis. Plain chest radiography is useful for screening for thoracic aortic disease. In the IRAD database abnormal chest radiography results are common in aortic dissection patients. The general contour of the ascending aorta, the aortic knob, and the stripe of the descending aorta can usually be identified well and evaluated even on a plain chest x-ray.[87]

Multiple three-dimensional imaging modalities are applicable to patients with aortic aneurysmal disease, including transesophageal echocardiography (TEE), CT, and MRI, each of which offers high sensitivity and specificity. Although CT and MRI show the three-dimensional structure of the aorta along its entire course, TEE may not fully delineate the aortic arch[95] or the abdominal aorta; conversely, TEE provides more detailed information about the pericardium, aortic valve, and LV function. Both the ascending and descending portions of the aorta are well visualized by TEE. The abdominal aorta can be examined by surface ultrasonography or by CT or MRI. The primary advantage of TEE is that it can be rapidly performed in the emergency department while the patient receives intensive medical support, but adequate sedation is required to avoid hypertension, which could extend dissection or instigate rupture.

The primary criterion for diagnosis of aortic dissection by CT is demonstration of two contrast-filled lumens separated by an intimal flap.[96] Inaccuracy may result from inadequate contrast opacification, nonvisualization of the intimal flap, artifacts extending across the aortic lumen that simulate an intimal flap, misinterpretation of adjacent vessels or a prominent sinus of Valsalva as a flap, atelectasis or pleural thickening, or thrombosis of the false lumen. Modern multidetector-row CT scanners offer rapid image acquisition, ECG gating, variable-section thickness, three-dimensional rendering, diminished helical artifacts, and smaller contrast requirements, overcoming many of these pitfalls. The sensitivity and specificity of CT and MRI for diagnosis of aortic dissection currently approach 100%, and TEE does not lag far behind. Contrast aortography is more invasive and does not provide the three-dimensional anatomic information afforded by CT, MRI, or TEE imaging. Intravascular ultrasonography using high-frequency transducers, though not widely available, may be a useful adjunct when other imaging studies are not definitive. It can provide an accurate determination of the location and extent of aortic dissection and assessment of branch vessels.

WHAT IS THE TRUE AORTIC SIZE?

It is important to know the true size of the aorta because key decisions regarding management of aortic aneurysms depend on the size of the aneurysm. However, determining the true size of the aorta in a given modality or with multiple or discrepant modalities is not a trivial matter.

Multiple specific sources of error or confusion in aortic measurement are encountered regularly in the clinical practice of aortic care.[97]

Inherent Level of Resolution of Current Imaging Technologies

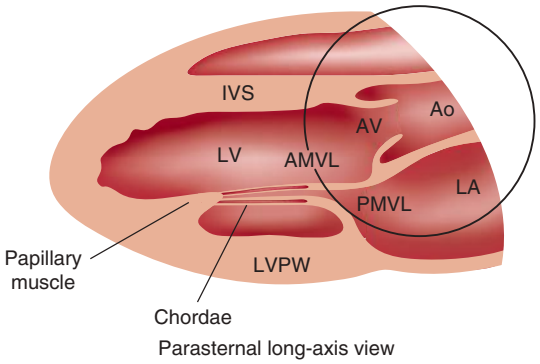
Although aortic size is commonly read to the millimeter, the technology does not satisfy that level of precision; one can have confidence in a measured change of 3 or 4 mm, provided careful review is made to ascertain that similar levels of the aorta are being measured.

Include or Exclude the Aortic Wall Itself in the Measurement?

There is no consensus on whether the aortic wall should be included or excluded in the aortic diameter, whether the test is made by echocardiography, CT, or MRI. This may make a difference of several millimeters in the calculated measurements. On a noncontrast CT image, for example, it is most comfortable to measure the entire aortic wall, including the lumen and wall; on the other hand, on a contrast image, it may be more comfortable to measure the luminal shadow alone. Echocardiographic images may be measured for the internal or external diameter of the aortic wall.

Limitations of Specific Imaging Modalities

Echocardiography Echocardiography images of the ascending aorta are often beautifully crisp. However, a transthoracic echocardiogram (TTE) can only visualize the proximal several centimeters of the ascending aorta, perhaps to just above the sinotubular junction in a patient with good echo windows (Fig. 93–21). Thus a TTE will miss an aneurysm of the mid-portion of the ascending aorta. Also, if the aneurysm is predominantly in the mid-ascending aorta, the TEE will "see" only the beginning of the aneurysm and will, consequently, underestimate its size. Even TEE is limited by the interposed tracheal



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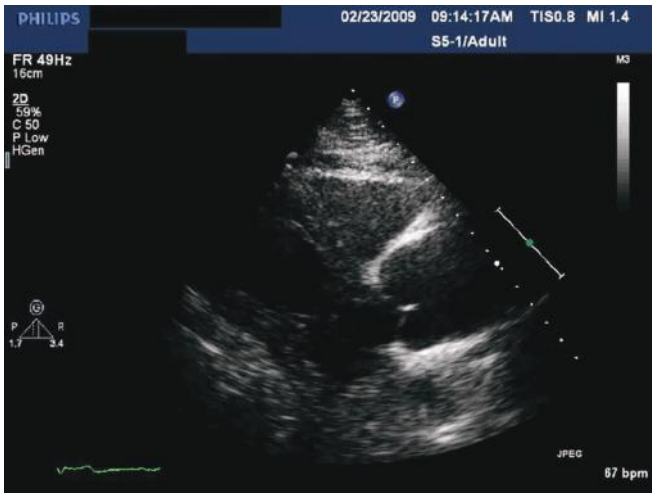
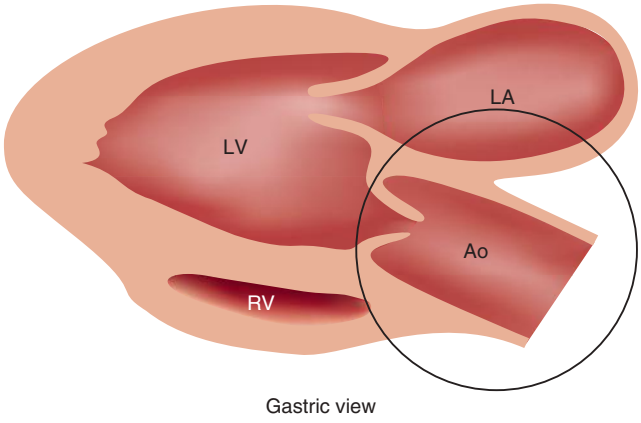


B

FIGURE 93–21. Limited distance above the aortic valve for which the ascending aorta can be seen on transthoracic echocardiography. A. Schematic. B. Echocardiographic image. Ao, aorta; AMVL, anterior leaflet of mitral valve; AV, aortic valve; IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVPW, left ventricular posterior wall; PMVL, posterior mitral valve leaflet. Reproduced with permission from Elefteriades JA, Farkas EA: Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol*. 2010 Mar 2;55(9):841-857.[97]



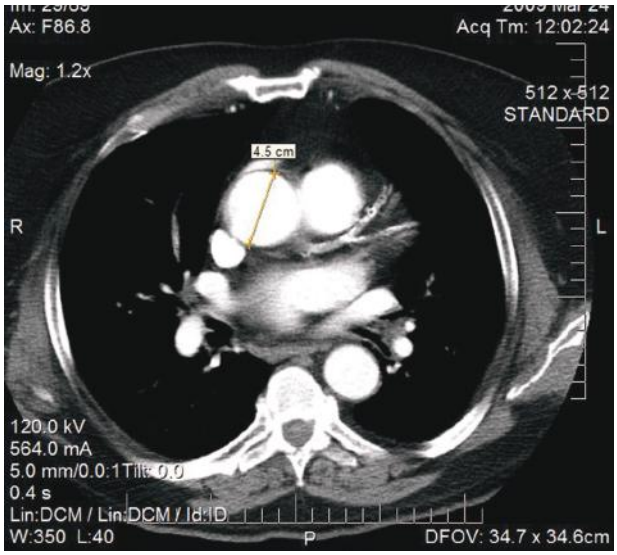
A

B

FIGURE 93–22. Limited distance above the aortic valve for which the ascending aorta (Ao) can be seen on transesophageal echocardiography; the tracheal air column interferes with visualization of the upper ascending aorta. A. Schematic. B. Echocardiographic image. LA, left atrium; LV, left ventricle; RV, right ventricle. Reproduced with permission from Elefteriades JA, Farkas EA: Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol*. 2010 Mar 2;55(9):841-857.[97]

air column and can be "blinded" to the upper portion of the ascending aorta (Fig. 93–22).

Computed Tomography Scan CT scan with axial images cannot properly evaluate the very proximal portion of the ascending aorta. The entire portion of aorta between the annulus and the coronary arteries usually represents only a centimeter or two of distance. Axial imaging planes may miss an aneurysmal dilatation in this location. Also, it can be exceedingly difficult to be certain if a given axial cut is above or below the aortic valve—a key distinction if one is to take a diameter measurement based on that cut (Fig. 93–23). Furthermore, it is naïve to believe that the plane of the aortic valve is confined to the plane of the axial images (perpendicular to the longitudinal axis of the body). Even the normal annulus may be skewed. Furthermore, as the ascending aorta elongates, the aortic valve plane is forced into a more vertical orientation, rendering even more difficult the assessment of size on axial images (Fig. 93–24). In modern CT scanners, reconstructions are done not only in axial but also in sagittal and coronal planes, but the resolution in the nonaxial reconstructions is often insufficient to permit precise assessment of the aortic shape or diameter. Also, the aorta changes in size, depending on the phase of the cardiac cycle in which an image is acquired, potentially affecting diameter measurement by as much as 17.5%.[98]



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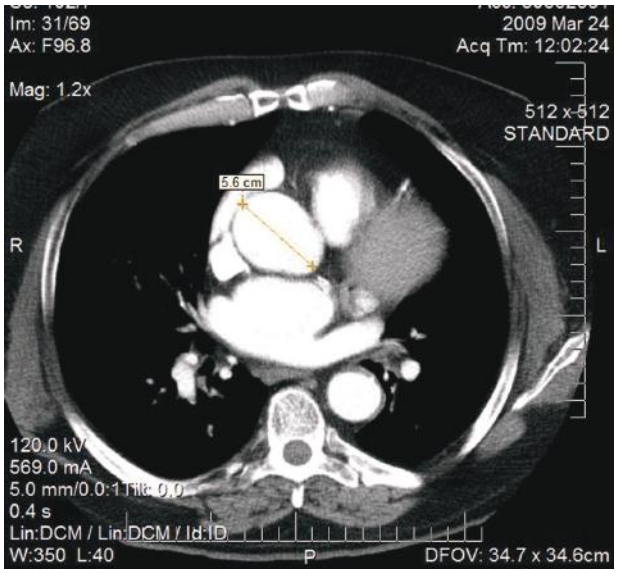
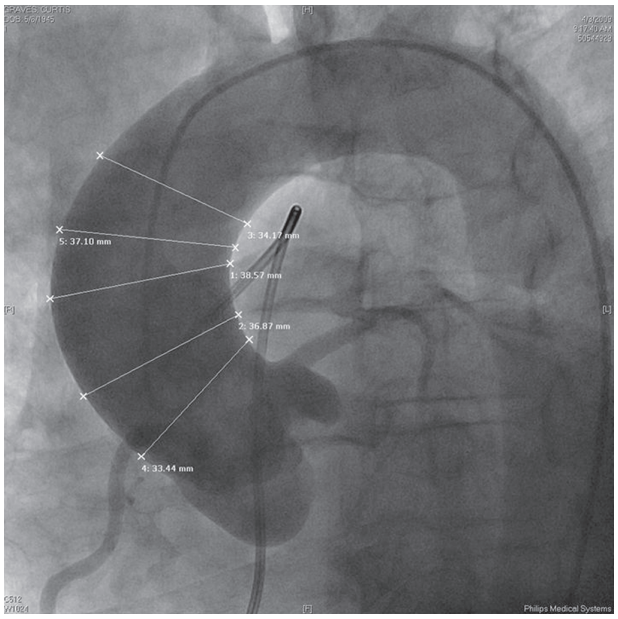


B

FIGURE 93–23. Difficulty in determining if a given axial computed tomographic (CT) image is still in the aorta or passing partially through the aorta and the left ventricular outflow tract. This factor can lead to gross misinterpretations of aortic diameter. A and B differ by only one CT level, yet they yield markedly different diameters. Is the lower frame still in the aorta? Does it represent the dimension of the sinuses, or does it run obliquely through both aorta and left ventricular outflow tract? It can be difficult or impossible to ascertain these answers on a purely axial technique. Reproduced with permission from Elefteriades JA, Farkas EA: Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol*. 2010 Mar 2;55(9):841-857.[97]

Gated Computed Tomography Gating of CT imaging—synchronizing image acquisition with the cardiac cycle, as determined by the ECG—mitigates motion artifact in aortic CT scan images and substantially improves diagnostic accuracy (Fig. 93-25).

Centerline Method of Measurement The centerline method of analysis of CT images of the aorta enhances precision in assessment of aortic wall morphology and measurement of aortic diameter (Fig. 93–26).[99] Commercial software programs automatically set the viewing plane perpendicular to the long axis of the aorta. It is important to bear in mind, however, that centerline methods may lead to smaller measurements



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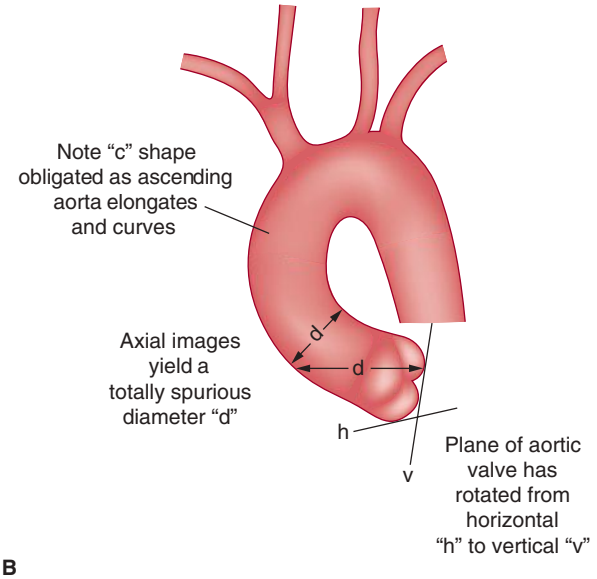


B

FIGURE 93–24. Aortogram (**A**) and schematic (**B**) showing gross elongation of the ascending aorta, forcing the aorta into a "C" shape and obligating the aortic valve to take a nearly vertical plane of orientation. On an axial computed tomography image, this common anatomy would markedly confound measurement of proximal aortic size. Note the difference between a horizontal diameter (as in an axial image) and a diameter perpendicular to the long axis of the aorta. Reproduced with permission from Elefteriades JA, Farkas EA: Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol.* 2010 Mar 2;55(9):841-857.[97]

of aortic diameter than traditional observer-based image analysis, and most criteria for selection of patients for aortic surgery have not been based on centerline methods. There is reason for concern, therefore, that the adoption of automated, computerized methods of measurement may underestimate the risk of aneurysmal dissection and rupture.

MRI is an inherently multiplane modality that provides axial, sagittal, and coronal images. Depending on resolution, accurate measurements may be feasible, potentially overcoming some of the limitations of echocardiography or CT imaging related to imaging windows, planar projection, and vascular calcification.

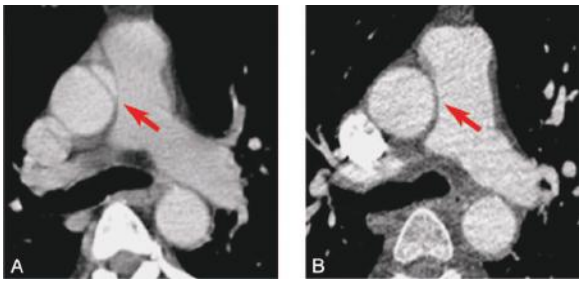


FIGURE 93–25. Nongated (**A**) and gated (**B**) contrast computed tomography angiography demonstrating an imaging artifact suspicious for an intimal flap in a Type A dissection. Reproduced with permission from Chou AS, Ziganshin BA, Elefteraides JA. Computed Tomography Imaging Artifact Simulating Type A Aortic Dissection, Aorta (Stamford). 2016 Apr 1;4(2):72-73.

Geometric Complexity

The human aorta is geometrically complex. The ascending aorta is not truly or totally vertical. The *aortic arch* poses an additional challenge because an axial image through the aortic arch will produce an oblong rather than a circular contour; measuring the long axis of this oblong contour is misleading because this does not represent the true aortic diameter. The same holds true for any other portion of the aorta that takes a sharp curve, as often happens at the peridiaphragmatic portion.

Furthermore, in comparing measurements over time, one can easily be misled by diameters taken from even slightly different longitudinal levels of the aorta. Also, even in a given cross-section, the aorta will not be a true circle. The measured girth may vary depending on which particular geometric diameter is selected. This can be especially true even on good-quality transesophageal echocardiograms, which do not "see" all diameters of the aortic annulus and aortic root; asymmetric dilatation of one sinus, for example, may escape detection.

In some cases, it may be difficult to reconcile discrepant studies or to achieve an ultimate measurement that encompasses the separate "realities" of different imaging modalities.

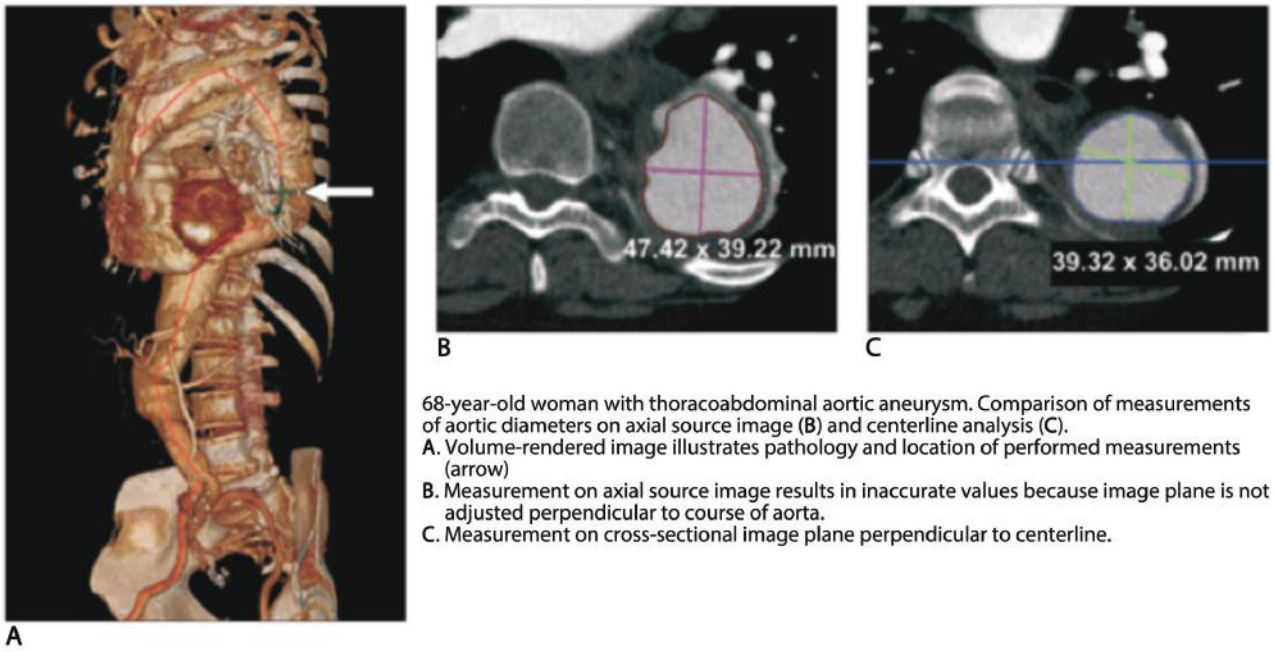
In comparing serial imaging studies, it is important to avoid the temptation to compare with the last prior image. The aneurysmal aorta grows slowly, about 1 mm per year on average.[100] Thus, looking at closely spaced images may miss even inexorable growth. Rather, it is *imperative* to compare to the very first available image, even if it means searching or sending for early studies.[101]

It is important to remember as well that size is not the only important imaging criterion; shape matters as well, especially loss of the normal "waist" of the aorta at the sinotubular junction (as seen in Fig. 93–27). Loss of this normal indentation is an indication of intrinsic aortic disease that should raise attention and stimulate concern about future aortic events.

BIOMARKERS IN AORTIC DISEASE

Thoracic aortic aneurysm is a virulent, potentially lethal disease. Also, it is a predominantly silent disease. This combination of circumstances cries out for discovery of biomarkers for this disease—blood tests that can detect aneurysm in the general population, monitor the progress of an aneurysm, and predict complications in patients known to be affected (Table 93–3).[102,103]

D-dimer is a byproduct of fibrin degradation. D-dimer is a useful biomarker in acute aortic dissection. It is 99% sensitive in the detection of acute aortic dissection.[104] If the D-dimer is not elevated, the patient does not have aortic dissection. However, D-dimer is extremely nonspecific, being elevated in patients with pulmonary embolism and coronary thrombosis, essentially in any state in which thrombosis and thrombolysis proceed. The extent of D-dimer elevation reflects the longitudinal



68-year-old woman with thoracoabdominal aortic aneurysm. Comparison of measurements of aortic diameters on axial source image (**B**) and centerline analysis (**C**).
A. Volume-rendered image illustrates pathology and location of performed measurements (arrow)
B. Measurement on axial source image results in inaccurate values because image plane is not adjusted perpendicular to course of aorta.
C. Measurement on cross-sectional image plane perpendicular to centerline.

FIGURE 93–26. Comparison of measurements of aortic diameters on axial source image and centerline analysis. Reproduced with permission from Rengier F, Weber TF, Giesel FL, et al: Centerline analysis of aortic CT angiographic examinations: benefits and limitations. *AJR Am J Roentgenol*. 2009 May;192(5):W255-W263.[99]

extent of aortic dissection, predicts the mortality of patients with aortic dissection, and differentiates dissection from MI. However, because D-dimer elevation occurs *after* the dissection, it is not useful as a predictor.

MMPs are known to be intimately involved in the pathogenesis of aortic aneurysm and dissection. Their use in the monitoring of aortic disease is in the earliest stages. It has been shown that MMP elevation signals recurrent blood flow in an aneurysm after endovascular therapy.[105,106]

Inflammation and collagen degradation are also known to be involved in the pathogenesis of aortic aneurysms. Accordingly, inflammatory markers and indicators of collagen turnover are being investigated as potential biomarkers in aortic diseases. CD4+CD28- T cells and elastin peptide are being investigated, in those two categories, respectively. Smooth muscle heavy chain myosin has also shown some promise.

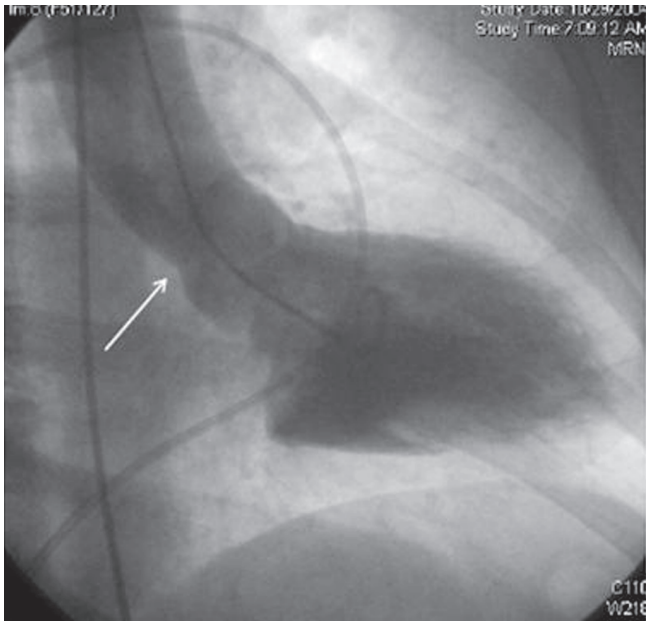
Measurement of aneurysm-related RNA signatures shows promise as a marker of aneurysm activity that may prove helpful for detection and monitoring.[107] Ideally, this RNA panel would detect aneurysms and predict rupture and dissection (Fig. 93–28). Another potential tool employs advanced glycation end products (AGE) and their soluble receptors (sRAGE), which may be involved in the pathogenesis of thoracic aortic aneurysm. Low levels of sRAGE and high levels of AGEs seem related to the risk of thoracic aortic aneurysm development and progression.[108] Other promising biomarkers under investigation, alone or in combination, include D-dimer, C-reactive protein, neutrophil/lymphocyte ratio, DAO (diamine oxidase), IL-6 (interleukin 6), TNF-α (tumor necrosis factor alpha), α-SMA (alpha smooth muscle actin), smMHC (smooth muscle heavy chain), and ncRNAs (noncoding RNAs).[109-112] However, most of these markers do not *predict* dissection, but rather, *detect* dissection after it has occurred.

DIFFERENTIAL DIAGNOSIS

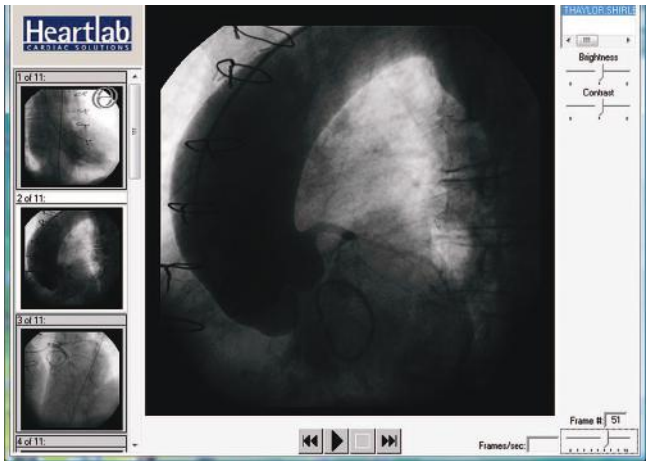
The imaging studies discussed above provide specific information that may establish or exclude the diagnosis of aortic aneurysm or dissection. Aortic dissection may masquerade as other acute cardiovascular, pulmonary, musculoskeletal, neurologic, or gastrointestinal disorders because it can produce symptoms related to almost any organ. The diagnosis is most strongly suggested by migratory chest and back pain of less than 24 hours in duration arising in a patient with a history of hypertension. Prompt diagnosis is essential because the clinical course may evolve rapidly to a catastrophic outcome unless appropriate therapy is instituted. In particular, aortic dissection should be considered in all patients presenting with chest pain without another obvious cause, and the thoracic aorta should be imaged routinely in such cases. The IRAD database has for over two decades described the presentation and differential diagnosis of aortic dissection and emphasized its protean potential clinical features.[87,113]

Other conditions frequently confused with aortic dissection are musculoskeletal chest pain, mediastinal tumors, pericarditis, pleuritis, pneumothorax, pulmonary embolism, cholecystitis, ureteral colic, appendicitis, mesenteric ischemia, pyelonephritis, stroke, transient ischemic attack, and primary limb ischemia. Especially troublesome are patients with abdominal symptoms and signs who display no apparent abdominal cause; it is important to consider aortic dissection in this situation. Given the extensive differential diagnosis, prompt objective diagnostic testing is necessary when the possibility of aortic dissection is raised. Aortic dissection and ruptured thoracic or abdominal aneurysm should be considered in the differential diagnosis of chest, abdominal, or back pain.

- *Obtain appropriate imaging to exclude acute aortic pathology (triple rule-out CT scan):* 256-row multidetector CT angiography can effectively exclude the major forms of life-threatening thoracic pathology, including coronary atherosclerosis, pulmonary thromboembolism, and aortic aneurysm or dissection (including intramural hematoma and penetrating aortic ulcer), but the threshold at which this technology can be most cost effectively applied has not yet been established.[114]
- *Use appropriate biomarkers indicating activation of the coagulation system:* The D-dimer assay not only helps evaluate patients with



A



B

FIGURE 93–27. Aortograms depicting normal aortic contour with a "waist" (*arrow*) above the coronary arteries (**A**) and the abnormal aortic contour (with no "waist) of Marfan-like annuloaortic ectasia (**B**). Reproduced with permission from Elefteriades JA, Farkas EA: Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol.* 2010 Mar 2;55(9):841-857.[97]

suspected acute pulmonary embolism but, when results are negative, also effectively excludes acute aortic dissection. Thrombosis of the false lumen in cases of aortic dissection typically raises D-dimer levels substantially in the peripheral blood.[115]

- *Examine the aorta carefully* whenever a CT scan is obtained in search of other thoracic or abdominal pathology.

NATURAL HISTORY, PROGNOSIS, AND CLINICAL DECISION MAKING

Studies of the natural history of thoracic aortic aneurysms using large databases involving thousands of patient-years of observation have established that thoracic aortic aneurysm is associated with approximately 50% mortality over 5 years, but not all deaths in these cohorts are directly attributable to aneurysm. On average, aneurysms of the aorta expand at a rate of about 0.1-0.2 cm annually, the descending aorta enlarging somewhat more rapidly than the ascending aorta. Such aneurysms usually develop over decades, so imaging is seldom necessary more often than once a year, and often only every 2 or 3 years, depending on the initial diameter and other factors. Rapid expansion of a thoracic aneurysm in the absence of aortic dissection is rare and usually reflects measurement error. One common source of error is oblique measurement of the aorta at the arch or near the diaphragm, where an ectatic aorta may take a sharp turn (Fig. 93–29). Current CT and MR technology can correct for most of these problems in measurement. More important than frequent imaging is to compare the most recent images with the *earliest* image available for a given patient to avoid underestimation of total growth over time.[97,101]

TABLE 93–3. Potential Biomarkers in Aortic Diseases (for Diagnosis and Monitoring)

Indicators of Ongoing Thrombosis
D-dimer
Plasmin
Fibrinogen
Matrix metalloproteinases
Inflammatory markers
Cytokines
CD4+CD28 T cells
C-reactive protein
Markers of collagen turnover
Elastin peptide
Other
Endothelin
Hepatocyte growth factor
Homocysteine
Genetic markers
RNA signature

INDICATIONS FOR SURGERY

Asymptomatic, Intact Thoracic Aortic Aneurysms

When viewed in terms of cumulative lifetime risk, the natural history of thoracic aortic aneurysms is characterized by an abrupt increment in the incidence of dissection or rupture at a maximum diameter of 6 cm for the ascending aorta; these events tend to occur at a larger dimension at the level of the descending aorta (Fig. 93–30). Yearly risks of rupture, dissection, or death reflect a stepwise increment in risk as the aorta expands, rising most dramatically to 14.1% at a dimension of 6 cm.[116-118] Based on this observation, patients without overwhelming comorbidities should undergo resection of thoracic aortic aneurysm before the maximum diameter reaches 5.5 to 6.0 cm (Table 93–4). For patients with Marfan syndrome or a family history of this disease, a criterion of 5 cm is usually applied because these patients are more prone to rupture or dissection.[116-118]

There are limited data regarding the aortic diameter at which the risk of dissection is high enough to warrant operative intervention in patients who do not fulfill criteria for aortic valve replacement (AVR) because of severe aortic stenosis or aortic regurgitation. Specifically, it is not clear whether patients with bicuspid aortic valves should

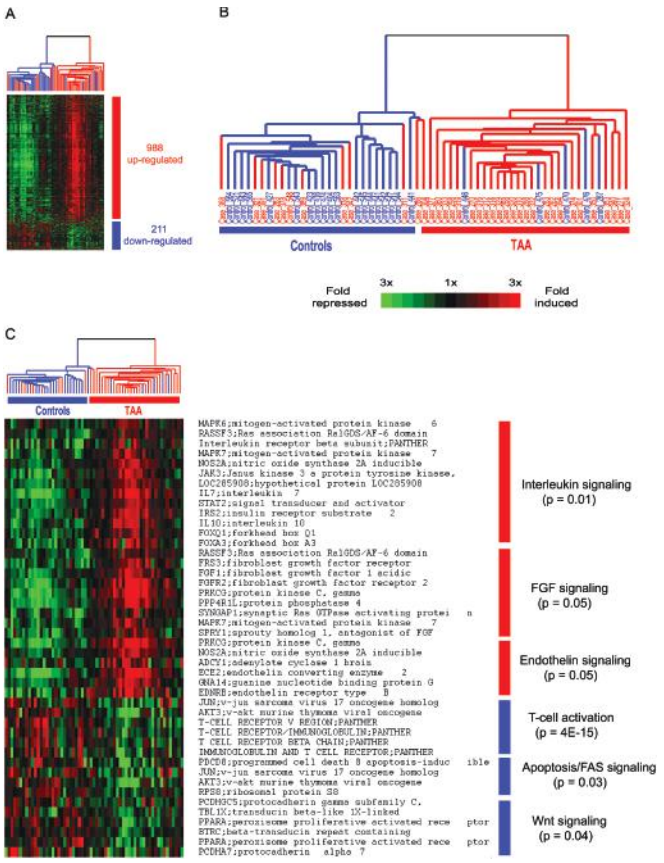


FIGURE 93–28. The RNA signature test for thoracic aortic aneurysm. In the hierarchical cluster diagram on the left, each *vertical line* represents a patient, and each *horizontal line* represents an RNA. In the grid, the *green* indicates underexpression, and *red* indicates overexpression. Note in the diagram on the left how the overexpression and underexpression cluster, depending on phenotype. In the figure on the right, note that if all the blues were together and all the reds were together, the test would have been 100% accurate. As it turns out, the overall accuracy was more than 82%. Reproduced with permission from Wang Y, Barbacioru CC, Shiffman D, et al. Gene expression signature in peripheral blood detects thoracic aortic aneurysm. *PLoS One*. 2007 Oct 17;2(10):e1050.[107]

undergo surgical intervention for aortic repair at diameters smaller than recommended for patients with tricuspid aortic valves and ascending aortic aneurysms. In general, aortic dissection develops in patients with bicuspid aortic valves at younger ages than in those with tricuspid aortic valve,[119-121] but in some studies, the diameters of the aortic root or ascending aorta in patients presenting with acute type A dissection were larger in those with bicuspid than tricuspid valves.[119,120]

Lacking evidence from prospective trials, surgical repair of aortic root or ascending aortic aneurysms in patients with bicuspid aortic valves is generally recommended at diameters ≥ 5.5 cm.[122] Surgical intervention may be considered when the aortic diameter reaches ≥ 5.0 cm, when aortic expansion occurs at a rate in excess of 0.5 cm annually, or in those with a family history of aortic dissection.[122,123] It remains controversial whether the anatomical location at which enlargement is greatest (ie, at the level of the sinuses of Valsalva or the tubular portion of the ascending aorta) or body surface area should be considered in determining the threshold for surgical intervention.

Asymptomatic, Intact Thoracoabdominal Aortic Aneurysms

No randomized trials have addressed the size at which suprarenal, juxtarenal, or Type IV thoracoabdominal aortic aneurysms should be repaired to prevent rupture. Because of the high risk of postoperative death, renal insufficiency, and other surgical complications, however, elective intervention is generally recommended for these aneurysms at slightly larger diameter than for infrarenal abdominal aortic aneurysms. In the absence of contraindications to surgery or comorbidities associated with a life expectancy less than 2 years, intervention is generally indicated in patients with suprarenal or type IV thoracoabdominal aortic aneurysms larger than 5.5 to 6.0 cm.

As for aortic aneurysms confined to the chest or abdomen, the dimensional criteria for surgical intervention apply only to asymptomatic aneurysms. *Symptomatic aortic aneurysms at any level should be resected regardless of size*. The development of symptoms frequently portends rupture and mandates surgical or endovascular repair.

Asymptomatic, Intact Abdominal Aortic Aneurysms

Multiple studies have addressed the appropriate size for resection of abdominal aortic aneurysms, including randomized trials in the United Kingdom and the United States[124,125] and meta-analyses (Table 93–5). Small aneurysms (< 4 cm in diameter) pose a low risk of rupture and should be managed with periodic surveillance for enlargement and symptoms. Abdominal aortic aneurysms between 4 and 5 cm in diameter are associated with a 1% per year risk of rupture, and decisions regarding surveillance or surgery should be individualized based on age, familial features, and an assessment of surgical risk. Aneurysms 5.5 cm in diameter or larger carry a substantial risk of rupture and should be repaired. As for thoracic aneurysms, the occurrence of symptoms supersedes diameter as a basis for intervention. In general, patients with infrarenal or juxtarenal abdominal aortic aneurysms measuring 4.0 to 5.4 cm in diameter should be monitored by ultrasonography or CT scans every 6 months to detect expansion. Repair may be beneficial in selected patients with aneurysms

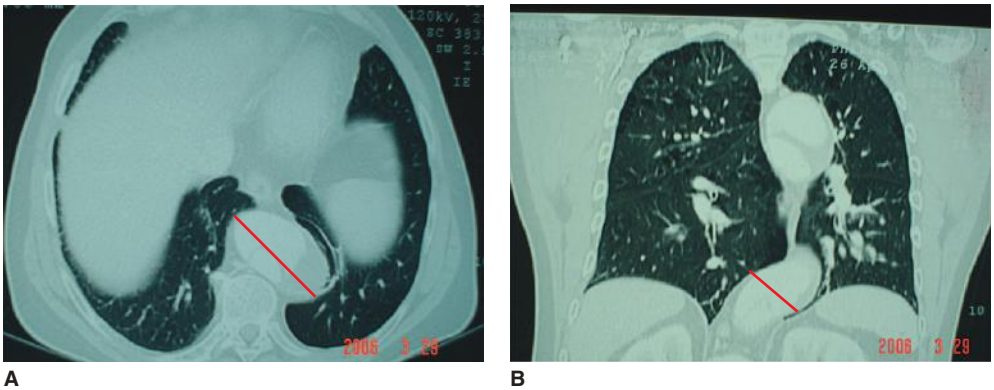


FIGURE 93–29. Spurious calculation of large aortic dimension (A) caused by measuring an oblique cross-section across a tortuous portion of the thoracic aorta (B).

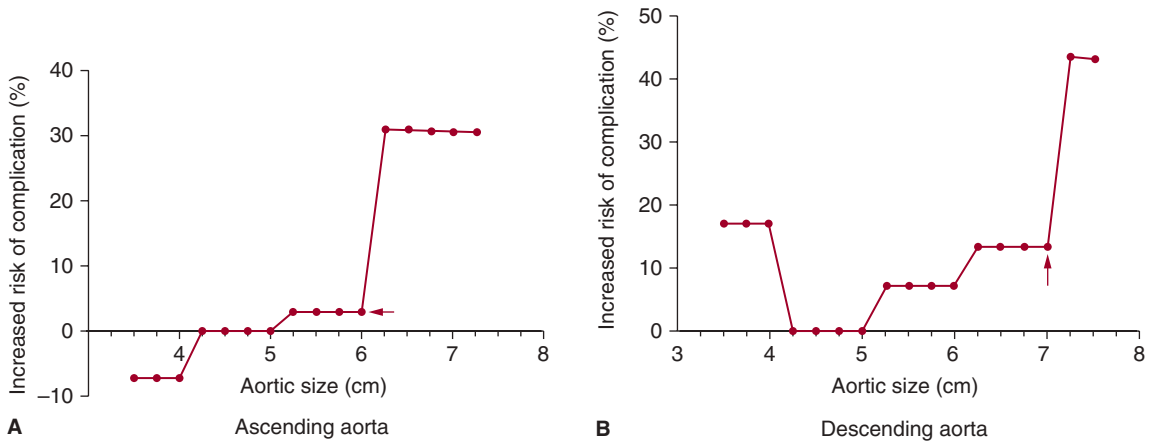


FIGURE 93–30. Depiction of "hinge points" for lifetime natural history complications at various sizes of the aorta. The y-axis lists the probability of complication; *complication* refers to rupture or dissection. The x-axis shows aneurysm size. **A**. The ascending aorta. **B**. The descending aorta. Reproduced with permission from Coady MA, Rizzo JA, Hammond GL, et al. What is the appropriate size criterion for resection of thoracic aortic aneurysm? *J Thorac Cardiovasc Surg*. 1997 Mar;113(3):476-491.

TABLE 93–4. The Yale Center for Thoracic Aortic Disease Recommended Surgical Intervention Criteria for Thoracic Aortic Aneurysms

1. Rupture
2. Acute aortic dissection
   a. Ascending requires urgent operation
   b. Descending requires a "complication-specific approach"
3. Symptomatic states
   a. Pain consistent with rupture and unexplained by other causes
   b. Compression of adjacent organs, especially the trachea, esophagus, or left mainstem bronchus
   c. Significant aortic insufficiency in conjunction with ascending aortic aneurysm
4. Documented enlargement
   a. Growth ≥ 1 cm/y or substantial growth and aneurysm is rapidly approaching absolute size criteria
5. Absolute size (cm)

	Marfan (cm)	Non-Marfan (cm)
Ascending	5.0	5.5
Descending	6.0	6.5

TABLE 93–5. Decision Making for Abdominal Aortic Aneurysms

HSTAT Meta-Analysis of Surgical Intervention Criteria for AAA Leads to the Following Conclusions

3.0-3.9 cm AAA	Very low risk of rupture	Yearly ultrasound
4.0-5.4 cm AAA	Yearly rupture rate = 1%	Ultrasound every 6 months
5.5 cm or larger AAA	Substantial rupture risk	Endovascular or open surgery advised

Abbreviations: AAA, abdominal aortic aneurysm; HSTAT, Health Services/Technology Assessment Text.

Data from Elefteriades and Rizzo[21] and Health Services/Technology Assessment Text.[23]

of 5.0 to 5.4 cm in diameter at this level. For patients with aneurysms smaller than 4.0 cm in diameter, monitoring by ultrasonography examination yearly is reasonable. Intervention is not recommended for patients with asymptomatic infrarenal or juxtarenal aneurysms smaller than 5.0 cm in diameter in men or 4.5 cm in women. A meta-analysis found that these criteria should be employed as well for *endovascular* treatment of abdominal aortic aneurysms, and that similar size indications for intervention should apply to both endovascular and surgical therapy.[126]

Some Dissections Can Occur at Small Sizes

We have known for some years that dissections do occasionally occur at small aortic sizes. This can be seen in Fig. 93–31. A paper from IRAD noted that a good number of the aortic dissections in their registry occurred at sizes below our recommended intervention criterion of 5.5 cm[127] (Fig. 93–32). Insightfully, the IRAD authors recognized the dangers of amending size criteria for surgical intervention downward, and they did *not* recommend any such change for fear of promoting surgical harm in operating on small aortas.

The key to reconciling our observational studies that small aortas pose only low risk with the IRAD observation that a substantial number of dissections occur at small sizes lies in recognition of the "at-risk" *denominator* pool of patients. The observational studies (enumerated above in discussing evidence-based criteria for aortic resection) present danger rates for patients *under observation* with small aortas at Yale University; indeed, their risk of aortic events, although not zero, is low—too low to justify surgical intervention. For the IRAD patients with dissection, however, the dissectors were drawn from the general population at large. Whether the distribution of aortic sizes is normal or paranormal, the number of at-risk patients increases dramatically as one moves toward normal from the largest aortic sizes in the distribution curve (Fig. 93–33). In fact, it is likely that there are millions of patients in the United States with aortas between 4 and 5 cm. One could certainly cause harm by operating on all of them prophylactically. In fact, if one were to divide the numerator of observed dissections in IRAD by a denominator of millions, the observed *yearly percentage rate* of dissection in the small sizes would be very small.

Analysis of the normal distribution of aortic diameters in the MESA[7] and IRAD database in relation to the risk of aortic dissection[127] revealed that although dissection can occur at smaller diameters, patients with aortas ≥ 4.5 cm are at 6000-fold greater risk of dissection than those with aortas ≤ 3.4 cm (Fig. 93–34).[8] These studies support the current criteria for surgical intervention.

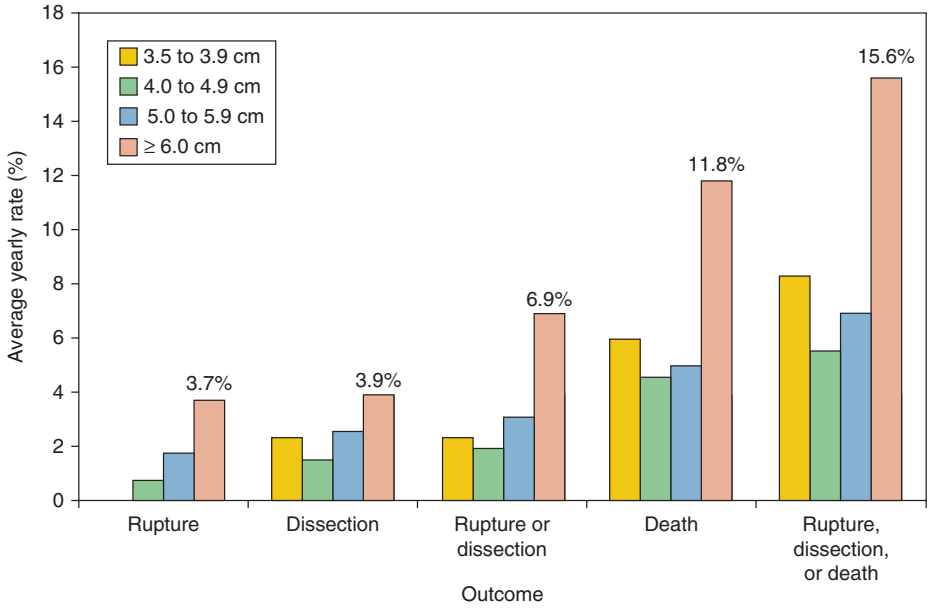


FIGURE 93–31. Yearly rates of rupture, dissection, or death related to aortic size. Note that the likelihood of rupture, dissection, or death within the coming year also jumps sharply for aneurysms that reach 6 cm or higher. (The rates indicated for "Rupture or Dissection" and for "Rupture, Dissection, or Death" are lower than the sum of the rates in individual categories because patients with multiple complications were counted only once in the combined categories.) These data underlie the conclusion that aneurysms in the ascending aorta need corrective surgery when the artery balloons to 5.5 cm. Used with permission from Alison Kendall.

This posture is supported by longitudinal follow-up of at-risk patients triaged to medical management based on the size paradigms described above (no symptoms and aortic size < 5.5 cm). Not a single patient triaged to medical therapy died of rupture during follow-up (Fig. 93–35). On the other hand, among patients triaged algorithmically to the surgical arm who were too ill for surgery or who refused surgery, the rate of aortic events leading to death was indeed very high, validating surgical therapy for patients meeting the algorithm criterion.[97]

PRECIPITATION OF AORTIC DISSECTION

MMPs and other pathophysiologic factors leading to degeneration of the aortic wall play an important role in aneurysm formation.[73]

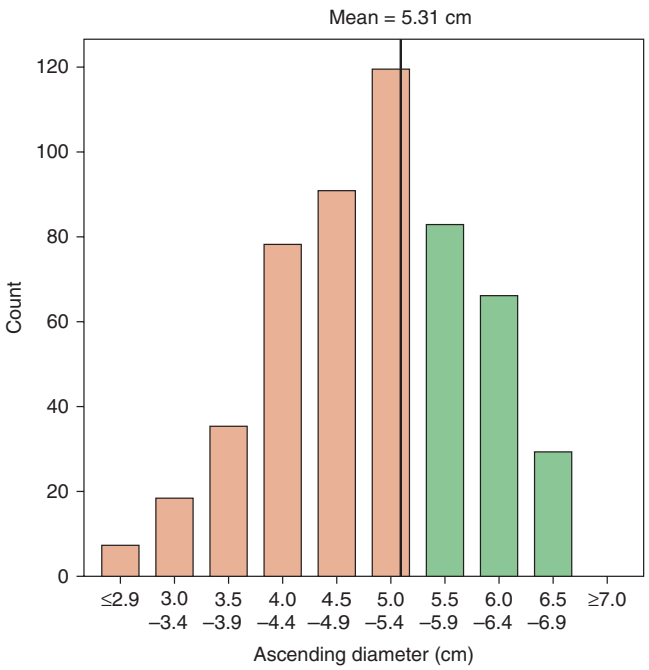


FIGURE 93–32. Distribution of aortic size at the time of presentation with acute type A aortic dissection (cm). *Orange bars* indicate 50% of patients with diameters smaller than 5.5 cm. Reproduced with permission from Pape LA, Tsai TT, Isselbacher EM, et al. Aortic diameter > or = 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2014 Sep 9;130(11 Suppl 1):S45-S50.[127]

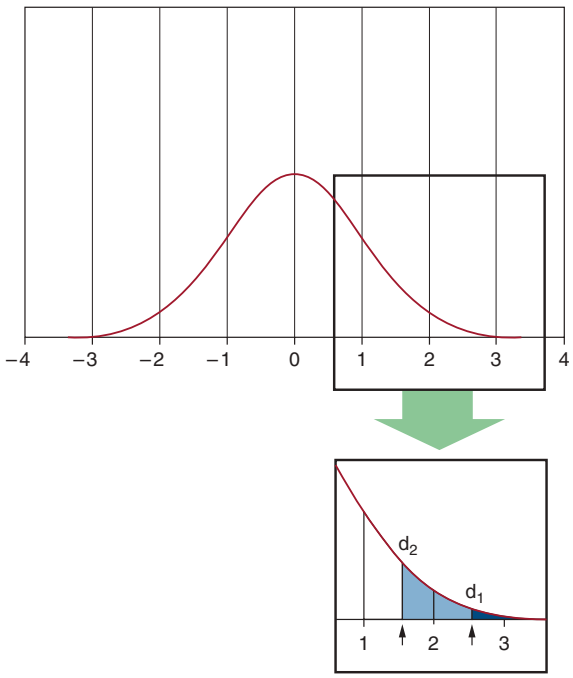


FIGURE 93–33. Huge general population at risk explains occurrence of some dissections at small sizes. Note how the number of patients increases dramatically if the intervention diameter criterion is shifted from d1 to d2. Reproduced with permission from Elefteriades JA, Farkas EA: Thoracic aortic aneurysm clinically pertinent controversies and uncertainties, *J Am Coll Cardiol*. 2010 Mar 2;55(9):841-857.[97]

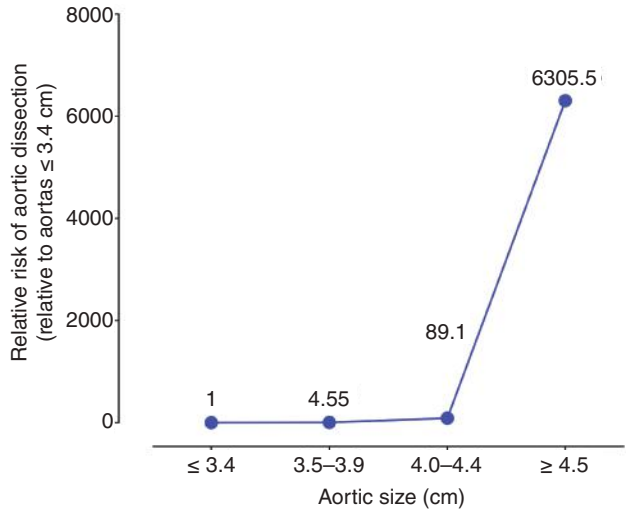


FIGURE 93–34. Relative risk of aortic dissection by comparison of observed instances of aortic dissection to the population at risk in each size range. The relative risk is > 6000-fold higher for large aortas than for small ones. This vindicates traditional intervention criteria. Reproduced with permission from Paruchuri V, Salhab KF, Kuzmik G, et al. Aortic Size Distribution in the General Population: Explaining the Size Paradox in Aortic Dissection. *Cardiology*. 2015;131(4):265-272.[8]

Mechanical studies of human aortas in vivo have shown loss of elasticity when expanded to a diameter of 6 cm, beyond which systolic forces cannot be dissipated by further aortic distension and instead accelerate disruption of the integrity of the aortic wall.[128] In addition to diameter, blood pressure plays a major role in determining wall tension. Without aortic enlargement, hypertension alone cannot generate sufficient wall stress to overcome the tensile strength of aortic tissue.

There are case reports of young, ostensibly healthy, athletic men experiencing aortic dissection during isometric weight training or other extreme exertion.[129] All had unknown moderate enlargement of the aorta, and all experienced acute onset of dissection pain during effort. Aortic dissection proved fatal in one-third of these cases. The magnitude of hypertension during weight lifting contributes excess wall stress that exceeds the tolerable aortic load limit, resulting in acute dissection. Nearly three-fourths of patients report either extreme emotion or exertion at the onset of symptomatic dissection, again suggesting a link with hemodynamic forces. Based on these considerations, some authors recommend that individuals embarking on programs involving heavy weight lifting or extreme physical training first undergo echocardiography to exclude ascending aortic aneurysm.

Based on these observations, the following sequence of events is postulated to cause aortic dissection (Fig. 93–36)[97]:

- *Genetic predisposition* sets the stage for development of aortic aneurysm or dissection.
- *Medial degeneration*. Genetic predisposition results in activation of mechanisms of inflammation, injury to the medial layer of the aorta, loss of smooth muscle cells, and histologic damage by cytokines. As a result, the aortic wall is damaged and weakened.
- *Aneurysm formation* results from progressive dilation, increasing mechanical stress on the aortic wall.
- *Hypertensive episode*. At a moment of extreme exertion or emotion, an abrupt rise in blood pressure increases aortic wall stress beyond the tensile strength of aortic tissue.
- *Aortic dissection*. The aorta dissects (and/or ruptures).

These steps hinge on the assumption that dissection originates from an intimal tear, which in turn leads to splitting of the medial layer and creation of the false lumen. However, Humphrey et al.[130] proposed that a pooling of glycosaminoglycans and proteoglycans within the medial layer of the aorta may have a delaminating effect due to localized loss of tensile strength, local stress concentration, and increased swelling pressures—all of which promote dissection.[130,131] Dissection may start with an initial delamination process within the media, which propagates proximally or distally to create an intimal tear. Pooling of glycosaminoglycans and proteoglycans may be related to the dysregulation of TGF-β[131-133] based on the hypothesis that aortic smooth muscle cells increase production of glycosaminoglycans and proteoglycans in response to increased TGF-β activity.[130,131]

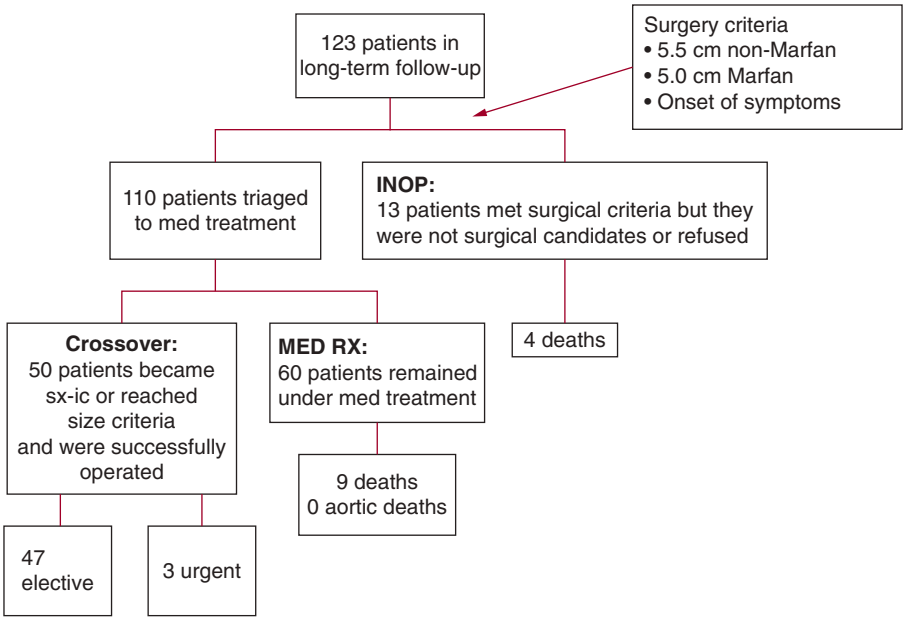


FIGURE 93–35. Flow diagram of medically treated patients. INOP, inoperable; crossover, crossed over from med rx to surgery; MED RX; medical therapy. Reproduced with permission from Elefteriades JA, Farkas EA: Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol*. 2010 Mar 2;55(9):841-857.

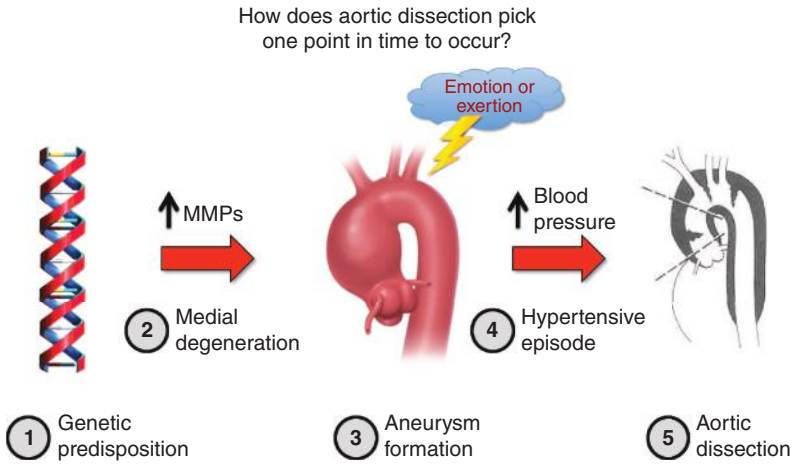


FIGURE 93–36. Schematic presentation of possible relationships underlying the instigation of an acute aortic dissection at one particular time. Adapted with permission from Hatzaras IS, Bible JE, Koullias GJ, et al: Role of exertion or emotion as inciting events for acute aortic dissection. *Am J Cardiol*. 2007 Nov 1;100(9):1470–1472.

TREATMENT OF ANEURYSM AND DISSECTION

The modern era in the treatment of aneurysms and dissections was ushered in by the pioneering innovations of Cooley and DeBakey, which were first reported in 1952.[134]

MEDICAL TREATMENT OF CHRONIC ANEURYSMS

Patients with aortic aneurysms are commonly treated with β-adrenergic antagonist drugs to decrease systolic arterial wall stress, but the effectiveness of this strategy has been validated only in one long-term study of 70 patients with clinical features of Marfan syndrome.[135,136] The value of β-adrenergic antagonist drugs in patients with and without Marfan syndrome is controversial.[137-141] Among the concerns, in addition to the potential for side effects, is evidence that β-blockers decrease the elasticity of the aortic wall. The overall effectiveness of β-blockers for thoracic aortic aneurysm has recently been reviewed.[139-141] As can be seen in Table 93–6, the evidence that β-blockers delay aortic dilatation in Marfan patients is quite equivocal and there is, further, simply no evidence of effectiveness in preventing the vital clinical end-points of aortic dissection or death (see Table 93–6).[141]

Angiotensin receptor blocking drugs (ARBs) represent a potential alternative to β-blockers in patients with Marfan syndrome,[142-144] based on groundbreaking work by Dietz and colleagues, which showed benefit of losartan in a mouse model and in infants with Marfan disease.[142-144] The concept was developed that ARBs (acting on the TGF-β pathway) can attenuate progression of aortic disease in Marfan patients. However, a randomized clinical trial comparing the losartan to atenolol showed no difference in rates of progressive aortic root dilation among children and young adults with Marfan syndrome,[145] but the issue remains unresolved in part because of concerns about dose selection.

The antibiotic agent doxycycline, an MMP inhibitor, has shown promise in large-scale clinical trials in patients with abdominal aortic aneurysms.[74] Other drugs that have undergone animal or clinical testing, including cyclooxygenase (COX) 2 inhibitory anti-inflammatory agents, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), the immunosuppressive agent rapamycin, and the angiotensin receptor inhibitor losartan,[146,147] have not been associated with consistent clinical benefit. A retrospective study in large numbers of patients with thoracic aortic aneurysm suggested substantial benefit in meaningful clinical end points from statin therapy for thoracic aortic aneurysm, most pronounced for descending and thoracoabdominal aneurysms.[148]

Observational data from IRAD raise the possibility the β-blockers might be beneficial in some patients with Type A aortic dissection and calcium-channel blockers might be useful in those with Type B aortic dissection, but additional studies are needed to verify these preliminary findings before these agents can be recommended for routine clinical use in these situations.[149,150]

MEDICAL TREATMENT OF ACUTE AORTIC SYNDROMES (DISSECTION, RUPTURE, AND IMPENDING RUPTURE)

Aortic dissection propagates more vigorously when either blood pressure or the force of cardiac contraction is elevated.[2,151,152] Accordingly, control of blood pressure is an important aspect of treatment in patients with acute aortic syndromes, including dissection, rupture, or impending rupture. Intravenous nitroglycerin or sodium nitroprusside are commonly used for this purpose. Lowering blood pressure by administration of vasodilator drugs alone may increase the sheer stress on the aortic wall; however, this can be ameliorated by decreasing the force of cardiac contraction pharmacologically. The objective is to reduce the rate of rise of arterial pressure (dP/dt), reflected in attenuation of the upslope of the aortic pulse wave,[151] by administering a short-acting β-blocking drug such as esmolol or the β- and α-adrenergic antagonist labetalol by intravenous infusion. When β-blocking drugs are contraindicated, the nondihydropyridine calcium channel blockers diltiazem and verapamil are reasonable alternatives. Table 93–7 presents specific drug options for the medical management of acute aortic syndrome.

SURGICAL THERAPY

Specific surgical procedures have been developed for resection and graft replacement of aneurysms involving the ascending aorta, transverse (arch), descending thoracic, thoracoabdominal, and abdominal aortic segments. The Dacron grafts are durable and do not require long-term anticoagulant therapy. The risks of such surgery include bleeding, stroke, paralysis, MI, renal failure, death, and other complications; safety is greatest when surgery is performed electively before aortic rupture or dissection. Due to advances in surgical techniques

TABLE 93–6. Literature on the Effectiveness of Beta-Blockers in Patients with Marfan Syndrome

			Beta-Blocker Group			Control Group			Study Results	
Author Name	Year of Publication	Designed to Evaluate Beta-Blocker Effect?	No. Patients[#]	Mean Age (years)	No. Clinical End Points*	No. Patients	Mean Age (years)	No. Clinical End Points*	Do BBs Slow Aortic Dilatation?	Do BBs Prevent Clinical End Points?*
Randomized Clinical Trial:										
Shores et al.[135]	1994	Yes	32	15.4	5/32 (15%)	38	14.5	9/38 (24%)	Yes	No ($P = 0.399$)
Observational Studies:										
Tahernia[a]	1993	Yes	3	10.0 ± 1.0	0/3 (0%)	3	8.3 ± 4.9	0/3 (0%)	Yes	No ($P = 1.0$)
Roman et al.[b]	1993	No	79	28 ± 15	18/79 (23%)	34	28 ± 15	3/34 (9%)	N/A	No ($P = 0.080$)
Salim et al.[c]	1994	Yes	100	11.1 ± 3.4	5/100 (5%)	13	10.2 ± 4.6	0/13 (0%)	Yes	No ($P = 1.0$)
Silverman et al.[d]	1995	No	191	33 ± 14	58/191 (30%)	226	31 ± 17	54/226 (24%)	N/A	No ($P = 0.137$)
Legget et al.[e]	1996	No	28	21 (median)	9/28 (32%)	55	21 (median)	8/55 (15%)	N/A	No ($P = 0.060$)
Rossi-Foulkes et al.[f]	1999	Yes	15	11.2 ± 5.3	4/15 (27%)	27	8.0 ± 5.2	0/16 (0%)	Yes	No ($P = 0.043$)
Tierney et al.[g]	2007	Yes	29	9.2 ± 4.0	1/29 (3%)	34	8.8 ± 4.8	3/34 (9%)	No	No ($P = 0.617$)
Ladouceur et al.[h]	2007	Yes	77	6.1 ± 3.2	3/77 (4%)	78	7.4 ± 5.2	8/78 (10%)	Yes	No ($P = 0.123$)
Meta-analyses:										
Gersony et al.[137]	2007	*Includes studies by Tahernia, Roman et al., Shores et al., Salim et al., Silverman et al., Legget et al.* ***Conclusions****: On the basis of this meta-analysis, there is no evidence that beta-blockade therapy has clinical benefit in patients with Marfan syndrome.*							N/A	No
Gao et al.[138]	2011	*Includes studies by Tahernia, Salim et al., Rossi-Foulkes et al., Tierney et al., Ladouceur et al.* ***Conclusion****: There is evidence that beta-blockade therapy can slow down the rate of dilatation of the aorta and has clinical benefits on children and adolescents with MFS.*							Yes[†]	No

[#]Please note that four of the eight studies involved fewer than 30 patients.

*Clinical end points included death or related cardiovascular events.

N/A – Data not available in study

[†]Although the meta-analysis included the Tierney et al. study, the calculations on aortic growth rates did not include their findings.

[a]Tahernia AC. Cardiovascular anomalies in Marfan's syndrome: the role of echocardiography and beta-blockers. *South Med J* 1993;86:305-310.

[b]Roman MJ, Rosen SE, Kramer-Fox R, Devereux RB. Prognostic significance of the pattern of aortic root dilation in the Marfan syndrome. *J Am Coll Cardiol* 1993;22:1470-1476.

[c]Salim MA, Alpert BS, Ward JC, Pyeritz RE. Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. *Am J Cardiol* 1994;74:629-633.

[d]Silverman DI, Burton KJ, Gray J, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol* 1995;75:157-160.

[e]Legget ME, Unger TA, O'Sullivan CK, et al. Aortic root complications in Marfan's syndrome: identification of a lower risk group. *Heart* 1996;75:389-395.

[f]Rossi-Foulkes R, Roman MJ, Rosen SE, et al. Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. *Am J Cardiol* 1999;83:1364-1368.

[g]Selamet Tierney ES, Feingold B, Printz BF, et al. Beta-blocker therapy does not alter the rate of aortic root dilation in pediatric patients with Marfan syndrome. *J Pediatr* 2007;150:77-82.

[h]Ladouceur M, Fermanian C, Lupoglazoff JM, et al. Effect of beta-blockade on ascending aortic dilatation in children with the Marfan syndrome. *Am J Cardiol* 2007;99:406-409.

Reproduced with permission from Ziganshin BA, Mukherjee SK, Elefteriades JA. Atenolol versus Losartan in Marfan's Syndrome. *N Engl J Med*. 2015 Mar 5;372(10):977-978.

(specifically myocardial and brain protection), graft materials (impervious), cardiopulmonary bypass, and anesthetic and postoperative care, these operations can be performed electively with outcomes at experienced centers rivaling those of coronary artery bypass and valve replacement surgery.[153]

Ascending aortic (type A) dissection requires urgent surgery to avoid death as a consequence of intrapericardial rupture, aortic regurgitation, or MI. Repair involves reapproximation of the aortic wall between layers of Teflon felt. At experienced centers, survival is approximately 85%.[154] Patients with descending aortic (type B) dissections face a better prognosis with initial medical management ("anti-impulse" therapy with β-blockers and vasodilator drugs), withholding surgery unless specific complications develop.[155] Medical management of uncomplicated type B aortic dissections offers long-term survival comparable to that of the general population, whereas patients with an initially complicated course face unfavorable long-term outcomes (Fig. 93–37).[155]

After corrective surgery for type A aortic dissection or stabilization on medication therapy for type B dissection, close observation is necessary, with serial aortic imaging during the first month and periodically thereafter. Some patients eventually develop enlargement of the dissected aorta requiring resection,[156] and in these cases, the dimensional criteria for surgical intervention are the same as those used for intact aneurysms.

AORTIC ROOT

The morphology of the aortic root dictates the surgical procedure required for correction of aneurysmal pathology (see Fig. 93–6). For supracoronary aneurysms, tube graft replacement is typically

TABLE 93–7. Intravenous Agents for Treatment of Ascending Aortic Dissection

Name	Category	Loading Dose	Maintenance Dose	Adverse Effects	Caution
Sodium nitroprusside	Vasodilator	0.3 µg/kg/min to 3 µg/kg/min; max. limit for an adult is 10 µg/kg/min for 10 min	1-3 µg/kg/min	Nausea, vomiting, agitation, muscle twitching, sweating, cutis anserine, cyanide toxicity, tachycardia	In patients with hepatic or renal dysfunction
Propranalol	β-blocker	1-3 mg (given at 1 mg intervals over 1 min). Can be repeated in not less than every 4 hours	1-3 mg every 4 hours	Hypotension, nausea, dizziness, cold extremities, reversible hair loss, bradycardia	In patients with bradycardia or history of CHF and bronchospasm. Max. initial dose should not exceed 0.15 mg/h
Esmolol	β-blocker	500 µg/kg bolus	Continuous 50 µg/kg/min up to 200 µg/kg/min	Hypotension, nausea, dizziness, bronchospasm, dyspepsia, constipation, increases digoxin level	In patients with CHF or asthma or on concomitant CCB therapy
Labetolol	α- and β-blocker	20 mg over 2 min, then 40-80 mg every 10-15 min (max. 300)	Continuous IV at 2 mg/min and titrate up to 5-10 mg/min	Vomiting, nausea, scalp tingling, burning in throat, dizziness, heart block, orthostatic hypotension	In patients with lung disease, concomitant CCB therapy
Diltiazem	CCB	0.25 mg/kg IV bolus (up to 25 mg)	5-10 mg/h by continuous infusion	Heart block, constipation, liver dysfunction	In patients with heart failure, concomitant β-blocker therapy
Enalapril	Vasodilator ACE inhibitor	0.625-1.25 mg bolus	0.625-5 mg every 6 hours	Precipitates fall in BP in high renin states, variable response, renal failure	In patients with high possibility of MI, renal dysfunction
Fenoldopam	Dopamine D1 receptor agonist	0.03-0.1 µg/kg/min initially	0.1-0.3 µg/kg/min, max. 1.6 µg/kg/min	Tachycardia, hypotension, headache, nausea, flushing, hypokalemia, elevation of IOP	In patients with glaucoma
Nicardipine	CCB	5 mg/hour; may increase by 2.5 mg/h every 5 minutes (for rapid titration) to every 15 minutes (for gradual titration) up to a maximum of 15 mg/h	For rapidly titrated patients, consider reduction to 3 mg/h after response is achieved	Flushing, pedal edema, exacerbation of angina pectoris, hypotension, palpitations, tachycardia, headache, dizziness, nausea, vomiting, dyspepsia	In patients with mild to moderate aortic stenosis, severe left ventricular dysfunction (particularly with concomitant β-blockade), hepatic impairment, hypertrophic cardiomyopathy, renal impairment
Clevidipine	CCB	Initial 1-2 mg/h; dose may be doubled at 90-second intervals toward blood pressure goal. As blood pressure approaches goal, dose may be increased by less than double every 5-10 minutes. For every 1-2 mg/h increase in dose, an approximate reduction of 2-4 mm Hg in systolic blood pressure may occur	4-6 mg/h; maximum: 21 mg/h	Atrial fibrillation, fever, insomnia, nausea, headache, vomiting, post-procedural hemorrhage, acute renal failure, pneumonia, respiratory failure	In patients with heart failure and pheochromocytoma. Avoid abrupt withdrawal of concomitant β-blocker therapy.

Abbreviations: ACE, angiotensin converting enzyme; BP, blood pressure; CCB, calcium channel blocker; CHF, congestive heart failure; IV, intravenous; IOP, intraocular pressure; MI, myocardial ischemia.

Data from Feldman M, Shah M, Elefteriades JA. Medical management of acute type A aortic dissection. *Ann Thorac Cardiovasc Surg*. 2009 Oct;15(5):286-293.

used unless stenosis or insufficiency of the aortic valve requires concomitant valve replacement. In patients with annuloaortic ectasia, composite graft replacement of the aortic root and the aortic valve with a prefabricated unit is preferred. This more complex procedure requires meticulous reimplantation of the coronary arteries with "buttons" of surrounding aortic tissue. Yacoub and associates[157] and David and coworkers[158] have advocated techniques for "valve-sparing" aortic root replacement. Accumulating data suggest that patient survival and aortic valve function are generally well maintained following valve-sparing procedures in appropriately selected cases,[159] but caution is warranted because recurrent or progressive aortic insufficiency can occur.[160]

AORTIC ARCH

Surgery for aneurysms of the aortic arch requires methods for cerebral protection during attachment of the cerebral arteries (great vessels) to the aortic graft. For attachment of the great vessels, Carrel patches (with a rim of aorta carrying the innominate, left carotid, and left subclavian arteries) are commonly used or, alternatively, prefabricated branched grafts that permit individual anastomosis of each great vessel. At 64.4°F (18°C), the temperature commonly used, the metabolic rate is below 15% of normal, permitting 30 to 45 minutes for manipulation of the aortic arch. When longer periods of circulatory arrest are necessary, direct cerebral perfusion can be provided through cannulae placed individually in the great vessels. An "elephant trunk" placed in the descending aorta facilitates subsequent procedures to address associated disease in the descending or thoracoabdominal aorta (Fig. 93–38).

THORACOABDOMINAL AORTA

The key issues in surgery of the thoracoabdominal aorta involve protection of the lower body organs and spinal cord during the period of aortic cross-clamping and attachment of the visceral arteries (superior

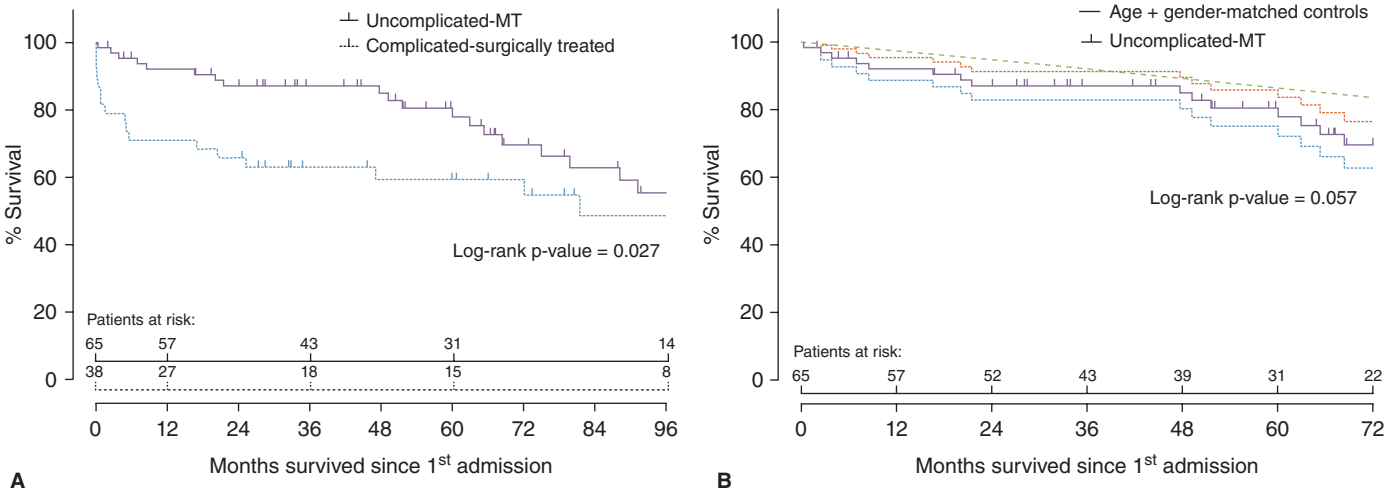


FIGURE 93–37. **A.** Kaplan-Meier curves comparing an 8-year follow-up between uncomplicated medically treated patients and complicated surgically treated patients with acute type B aortic dissection (complication-specific approach). **B.** Kaplan-Meier curves comparing 6-year survival between uncomplicated medically treated patients and age- and gender-matched control group. Reproduced with permission from Charilaou P, Ziganshin BA, Peterss S, et al: Current Experience With Acute Type B Aortic Dissection: Validity of the Complication-Specific Approach in the Present Era. *Ann Thorac Surg*. 2016 Mar;101(3):936-943.

mesenteric artery, celiac axis, and renal arteries). The arterial supply of the spinal cord is segmental, and viability of spinal cord cells is highly dependent on the artery of Adamkiewicz or arteries arising from the low intercostal or lumbar territory (T8-L2), which are excluded (at least transiently, and at times permanently) during thoracoabdominal aortic surgery. Intraoperative perfusion of the lower body by blood aspirated from the left atrium helps prevent paraplegia,[161,162] one of the most worrisome complications of this procedure. Other protective techniques include mild systemic hypothermia, aspiration of cerebrospinal fluid to decrease ambient pressure on the spinal cord, and reimplantation of the intercostal arteries.

The technical challenge of attaching all the important branch vessels of the abdominal aorta has been met by technical advances, most specifically by the implementation of reimplantation of the branch arteries on pedicles of surrounding aorta, often by the inclusion technique (in which the pedicle is not mobilized completely from its bed). Current rates of mortality or paraplegia for this type of surgery at experienced centers are below 10%, reflecting technical improvements in graft technology, surgical techniques, perfusion, anesthesia, and perioperative care.[163]

CONCOMITANT CORONARY ARTERY DISEASE

The most important risk factor for cardiac events and death in patients undergoing abdominal aneurysm surgery is coronary artery disease. Because operative mortality is related mainly to myocardial ischemia, it has been suggested that coronary revascularization be performed in

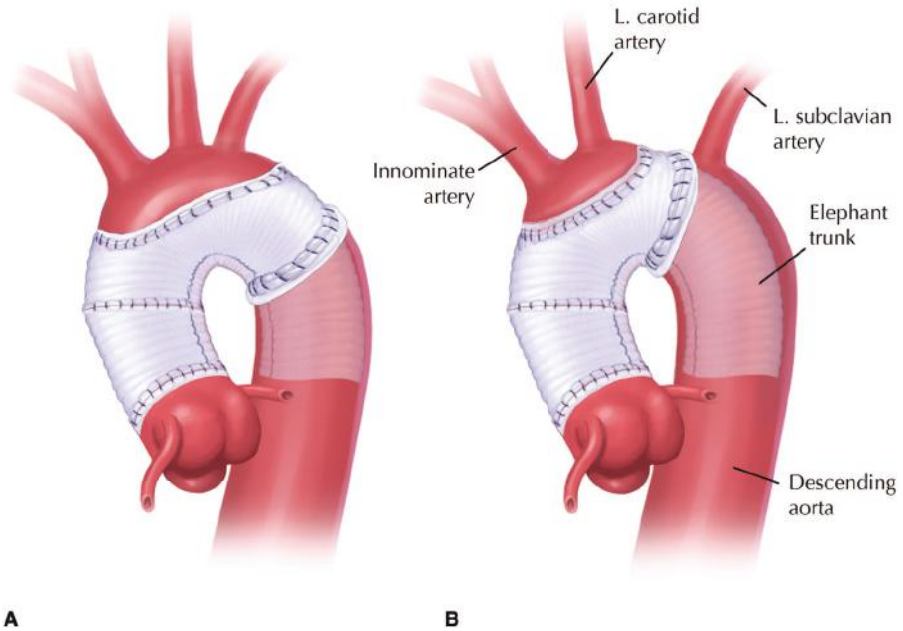


FIGURE 93–38. During aortic arch replacement procedures, an "elephant trunk" is placed in the descending aorta to facilitate any future interventions on the descending or thoracoabdominal aorta, should such be necessary. Reproduced with permission from Ziganshin BA, Rajbanshi BG, Tranquilli M, Fang H, Rizzo JA, Elefteriades JA. Straight deep hypothermic circulatory arrest for cerebral protection during aortic arch surgery: Safe and effective. *J Thorac Cardiovasc Surg*. 2014 Sep;148(3):888-898.

selected patients before abdominal aortic aneurysm resection.[164-166] No well-designed studies are available, however, comparing the outcome of serial myocardial revascularization and abdominal or thoracic aortic aneurysm repair with aneurysm surgery alone. Even so, an effort should be made to identify preoperatively patients at highest cardiac risk using noninvasive diagnostic methods. Findings of extensive myocardial ischemia may prompt angiography to define the coronary pathoanatomy and LV function. Thereafter, decisions regarding coronary revascularization must be based on symptoms, angiographic findings, and other elements of risk. One anticipates a survival advantage imparted by surgical revascularization in patients with left main coronary artery disease or stenosis greater than 70% involving each of the three major coronary arteries in patients with substantial zones of myocardial ischemia. In those with severe discrete proximal stenosis of a first-order coronary artery and symptomatic or extensive ischemia or reversible LV dysfunction amenable to catheter-based myocardial revascularization, clinical decision making must balance the long-term advantages of drug-eluting intracoronary stents against the need for potent platelet inhibitor therapy that may be difficult to administer in the days before and after aortic aneurysmectomy. Furthermore, in patients soon to undergo aortic reconstructive surgery, coronary balloon angioplasty or bare-metal stenting may be preferred, even though the potential for coronary restenosis may later require a second revascularization procedure after aortic surgery has been completed.

Diagnostic cardiac catheterization and angiography are routinely performed as part of the preoperative evaluation of patients undergoing surgical repair of ascending aortic aneurysms to evaluate the morphology of the ascending aorta, function of the aortic valve, and coronary anatomy. Based on the angiographic findings, myocardial revascularization can be readily incorporated into the reparative surgical procedure if warranted. For descending aortic aneurysms, if severe proximal coronary artery disease is found, then options include staged percutaneous or surgical coronary revascularization followed after an interval of several weeks by resection of the aneurysm. Results of such aggressive revascularization via a staged approach were recently reported with favorable outcomes.[167]

ENDOVASCULAR THERAPY FOR AORTIC ANEURYSMS

In 1991, Parodi and colleagues[168] first reported the technique of transfemoral catheter-based repair of infrarenal abdominal aortic aneurysms as an alternative to open repair for patients at high risk of complications with conventional surgical treatment. Over the ensuing years, a variety of stent grafts and delivery systems have been introduced, and endovascular repair has become a valuable alternative for elderly patients and those with advanced cardiopulmonary disease.

Most stent graft devices involve a modular construction consisting of a metallic exoskeleton surrounding an intimal fabric graft to maintain linear stability and prevent kinking.

Stent-graft therapy has a valid role in the management of patients with ruptured aortic aneurysm,[169] traumatic transection of the aorta,[170] and penetrating aortic ulcers.[171] The role of endograft therapy in typical, fusiform degenerative aneurysms is more controversial. An important limiting complication of stent-graft therapy is the propensity for *endoleak*,[172] in which blood flow continues into the excluded aneurysm sac after stent graft deployment. Endoleaks may lead to rupture of treated aneurysms.[173] Type I endoleaks are caused by incompetent proximal or distal attachments, producing high intrasac pressures that can lead to rupture and require repair using intraluminal extension cuffs or open surgery. Type II endoleaks resulting from retrograde flow from branch vessels (eg, intercostal, lumbar, or inferior mesenteric arteries) occur in as many as 40% of patients after endograft implantation. More than half of these seal spontaneously. Generally, type II endoleaks are followed with surveillance imaging and as long as the aortic sac does not enlarge, no treatment is necessary. However, if the aortic sac enlarges, type II endoleaks can usually be corrected by selective arterial embolization. Type III endoleaks are caused by fabric defects, tears, or disruption of modular graft components. These carry the same potential for aneurysm rupture as type I endoleaks and should be promptly repaired. Type IV endoleaks, the least common variety, result from graft porosity and diffuse leakage through interstices and usually develop within 30 days of implantation. Type IV endoleaks do not occur with the device technology that is currently used. Types I and III endoleaks seem the most dangerous and prompt repair is generally recommended.

Other complications of stent-graft repair of abdominal aortic aneurysms include occlusion of the iliac limbs of bifurcation endografts and migration from the proximal attachment as a result of progressive aortic expansion, which can be detected in at least one in five cases. Technical improvements in graft design and deployment techniques are reducing implant complications, but because of the potential for endoleak, graft migration, or graft limb occlusion, periodic follow-up imaging at intervals of 6 to 12 months is recommended after endovascular stent-graft repair.[172,174]

The effectiveness of endograft therapy in preventing aneurysm growth, rupture, and aneurysm-related mortality compared with open surgical repair remains controversial.[175] Although often ultimately lethal, thoracic aortic aneurysm is an indolent disease, and even without therapy years may elapse between diagnosis of a small- or moderate-size aneurysm and aneurysm-related death. The EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair (EUROSTAR) survey of endograft repair of abdominal aortic aneurysms exposed cases of late mortality and rupture even after initially successful intervention. Information regarding late outcomes after endograft repair of abdominal aortic aneurysms is more comprehensive than for thoracic aortic aneurysm, but it appears that the risk of endoleak is ongoing over at least 5 years (Fig 93–39). Endoleak predicted rupture, surgical intervention, or death in 13%, 14%, and 27% of patients, respectively, by 5 years postprocedure in patients originally presenting with large aneurysms (Fig. 93–40). These concerns about long-term effectiveness supported the original view that endograft therapy should be reserved for patients in whom comorbidity precludes direct open surgical repair and emphasize the need for lifelong surveillance.[176-179] However, more recent data support an even wider

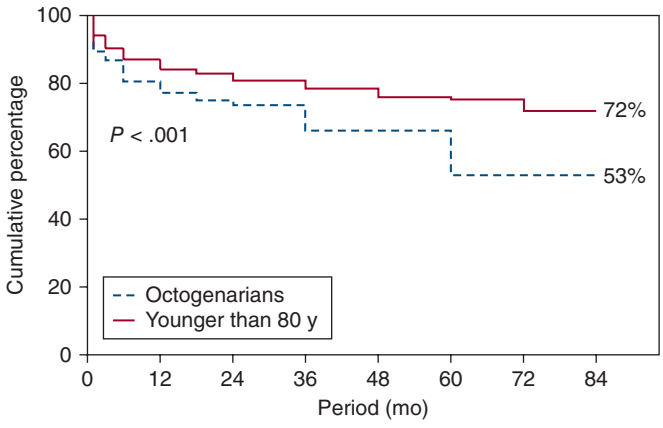


FIGURE 93–39. Kaplan-Meier graph represents cumulative freedom from any endoleak in patients operated on for abdominal aortic aneurysm with endovascular aneurysm repair. Reproduced with permission from Lange C, Leurs LJ, Buth K, et al. Endovascular repair of abdominal aortic aneurysm in octogenarians: an analysis based on EUROSTAR data. *J Vasc Surg*. 2005 Oct;42(4):624-630.

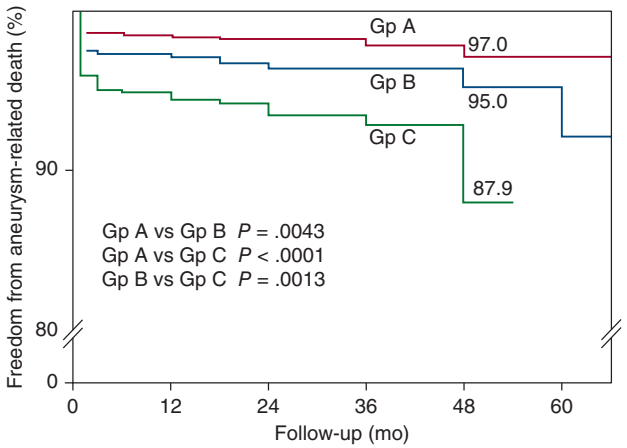


FIGURE 93–40. Cumulative freedom from aneurysm-related death after endovascular repair of abdominal aortic aneurysm in the EUROSTAR registry. Note low attrition during first 3 years of follow-up followed by rapid attrition in the fourth year. Gp denotes groups defined by increasing initial aneurysm size: Gp A = 4.0 to 5.4 cm; Gp B = 5.5 to 6.4 cm; Gp C = 6.5 cm or larger. Reproduced with permission from Peppelenbosch N, Buth J, Harris PL: Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR. *J Vasc Surg*. 2004 Feb;39(2):288-297.[178]

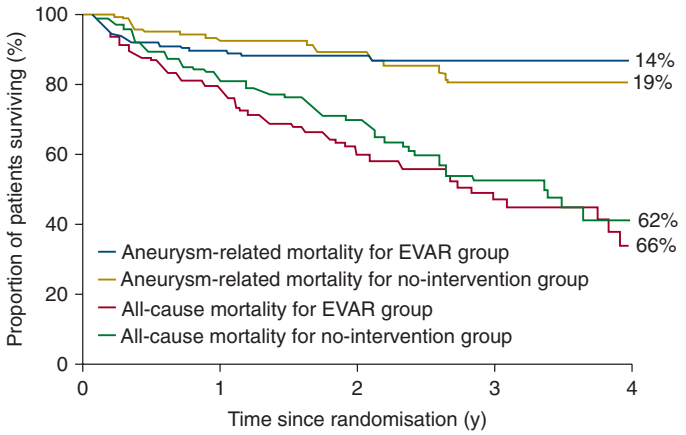
application of endograft therapy, although long-term survival is poor and has not improved much over the years.[180,181] Randomized trials of thoracic endografting versus open surgical repair will be required to provide conclusive evidence regarding the relative merits. Some midterm randomized studies are now coming to fruition:

1. **EVAR-2** (Endovascular Aneurysm Repair Trials). EVAR-2 compared endovascular aneurysm repair (EVAR) with no specific therapy ("medical therapy"). The key finding from EVAR-2[182] (presented in Fig. 93–41) shows no benefit from stent grafting of abdominal aortic aneurysm compared with no therapy. The all-cause mortality curves for EVAR and medical therapy are superimposable, as are the curves for aneurysm-related mortality. There is no evidence of benefit from EVAR in this trial.
2. **DREAM** (Dutch Randomized Endovascular Aneurysm Management). The DREAM trial compared EVAR for abdominal aortic aneurysm with traditional surgical therapy. The midterm follow-up in the DREAM trial found that at 2 years, the survival curves cross, and from that point on, stent treated patients have poorer survival than surgically treated patients. That is, EVAR shows an early advantage because surgery has some mortality, but this advantage is lost because EVAR did not show durable benefit.
3. **INSTEAD** (INvestigation of STEnt grafts in patients with type B Aortic Dissection). INSTEAD investigated stent therapy for patients doing well beyond 2 weeks after uncomplicated type B aortic dissection. The hope was that "tacking down" the dissection flap would lead to later benefit. Contrary to expectations, INSTEAD found early mortality and complications subsequent to stent therapy. There was no survival advantage over medical therapy alone.[183,184]
4. **INSTEAD XL**. Later follow-up (up to 5 years) from the INSTEAD trial has recently been reported, under the moniker "INSTEAD XL."[185] A retrospective "landmark analysis" was applied. This showed lower all-cause and aortic-related mortality and better aortic morphology in the stented group. Methodologic concerns have been raised (including the "landmark" analysis, which ignores all events occurring before the "landmark" time, and also the study's being "underpowered" for mortality assessments).[186-188]
5. **IRAD**. An analysis of the IRAD data also suggested better survival for type B dissection patients treated by TEVAR, but interpretation is difficult due to potential referral and selection biases.[189,190] More medium-term follow-up is needed to assess the durability of stent therapy. In the meantime, open surgical repair remains (debatably) the current standard in terms of both efficacy and durability, and it is essential that the same strict criteria for open surgery be applied in the decision to perform the less invasive endovascular therapies.

ATHEROSCLEROSIS OF THE AORTA

PATHOLOGIC ANATOMY

Atherosclerosis of the aorta is common in Western society. The usual risk factors are tobacco smoking, diabetes mellitus, hypertension, hypercholesterolemia, obesity, and a sedentary lifestyle, and the contribution of elevated levels of plasma homocysteine and C-reactive protein has more recently been suggested.[191] The pathogenesis of atherosclerosis is discussed in Chapter 32.



Number at risk

No intervention	172	139	71	29	9
EVAR	166	129	58	23	6

FIGURE 93–41. Mortality curves in EVAR-2 (Endovascular Aneurysm Repair Trial 2), showing no benefit from endovascular therapy of abdominal aortic aneurysm. Reproduced with permission from EVAR Trial Participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet*. 2005 Jun 25-Jul 1;365(9478):2187-2192.[177]

Atherosclerosis most commonly develops in the infrarenal aorta and may be asymptomatic or produce intermittent claudication, critical limb ischemia, or atheromatous embolism. Atherosclerosis typically also may involve the aortic arch and the origins of the brachiocephalic, carotid, and subclavian vessels, and the descending thoracic aorta. In this era, we usually detect atherosclerosis and calcification on CT scans done for other reasons, or on CT scans done deliberately as screening studies for calcium score. The thoracic aorta is so large that it is distinctly uncommon for calcified atherosclerotic lesions to cause stenosis of the aorta itself. Branch vessels (innominate, left carotid, and left subclavian arteries) are commonly involved and may produce brain or arm symptoms.

ATHEROMATOUS EMBOLISM

Embolism of cholesterol-laden atheromatous material and thrombus from the surface of the aorta occurs commonly in patients with severe aortic atherosclerosis.[192] Atheroembolism may be spontaneous, although it more frequently occurs after surgical or arteriographic manipulation, such as catheter-based coronary or peripheral interventions. In a retrospective study of 71 autopsies, the incidence of cholesterol embolism in patients who had undergone arteriography before death was 27% compared with 4.3% in an age- and disease-matched control group that did not undergo angiography.[193]

Whether or not anticoagulant and thrombolytic drugs can exacerbate atheroembolism associated with the "blue-toe syndrome" is controversial.[194-196] Few cases of this complication were reported in clinical trials of anticoagulation in high-risk patients with atrial fibrillation despite the frequent finding of morphologically complex aortic plaque in this population.[197]

Patients with atheromatous embolism typically have a history of angina pectoris, MI, transient ischemic attack, stroke, intermittent claudication, or peripheral gangrene. Clinical signs and symptoms are variable, depending on the amount, size, and location of origin of the atheromatous material as well as on the tissue affected. Whereas macroembolism may present catastrophically as an acute ischemic limb, patients with microembolism may have milder localized signs or a clinical picture suggesting systemic illness, including fever, weight loss, anorexia, myalgia, headache, nausea, vomiting, or diarrhea. Occasionally, the presentation may suggest vasculitis, infective endocarditis, or malignancy. Cutaneous manifestations are the most frequent findings[198] and include cyanotic toes, gangrenous digits, livedo reticularis, or nodules (Fig. 93–42).[199] When atheroembolism affects both lower extremities, the source is generally the aorta, but when only one extremity is involved, it may be difficult to determine whether the origin is the diseased ipsilateral iliofemoral artery or a more proximal or distal site.

Atheroembolism originating from the suprarenal aorta may involve the kidneys, producing occlusion of multiple small arteries and segmental ischemic atrophy. This small-vessel occlusive disease may cause accelerated hypertension, microscopic hematuria, or renal failure. Pathologically, biconvex cholesterol crystals occlude the interlobular and afferent arterioles (150-200 μm in diameter). A foreign-body reaction leads to small vessel occlusion, reducing glomerular filtration rate, activating the renin–angiotensin–aldosterone system, and accelerating hypertension. Various patterns of renal insufficiency may develop and progress over weeks or months to irreversible renal failure, requiring dialysis.[200] The differential diagnosis includes renal artery stenosis, renal artery thrombosis, infective endocarditis, vasculitis such as polyarteritis nodosa, and other causes of acute renal failure. No single laboratory test is diagnostic because acceleration of the erythrocyte sedimentation rate, leukocytosis with eosinophilia, and anemia are common in many systemic illnesses.[200] Blood urea nitrogen and creatinine elevations may be early manifestations of renal involvement, and the urine sediment may be abnormal.

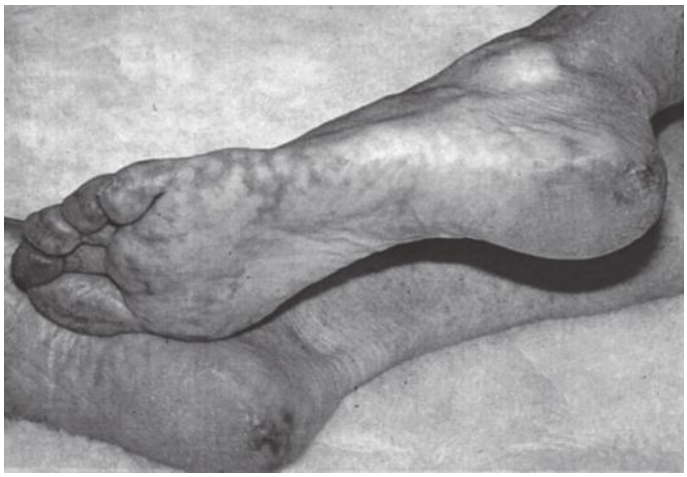


FIGURE 93–42. Typical appearance of atheromatous embolism involving the feet. The patient has cyanotic toes, livedo reticularis along the lateral portion of the foot, and ischemic lesions on both heels, indicating that the source of embolism is proximal to the aortic bifurcation. Reproduced with permission from Bartholomew JR: *Peripheral Vascular Diseases*, 2nd ed. St. Louis, MO: Mosby; 1996.

Elevated serum amylase or hepatic transaminase levels may indicate pancreatic or hepatic involvement, and creatine phosphokinase and aldolase arise from affected muscle. Renal biopsy is rarely required but may reveal pathognomonic needle-shaped cholesterol clefts within small vessels. Atheroembolic renal disease carries a poor prognosis, with a mortality rate of 81% (179 of 221 patients) in one series; the most common causes of death were cardiac, renal, or multiorgan failure.[200]

ATHEROSCLEROSIS OF THE AORTIC ARCH

Atherosclerosis of the thoracic aorta is a strong predictor of initial and recurrent stroke, coronary events, and death.[201] The thickness and morphology (protrusion, ulceration, or mobility) of atheromatous plaque correlate with the prevalence of stroke. Whether this association has a direct atheroembolic mechanism or reflects associated cerebrovascular pathology has not been conclusively determined.

Atheromatous embolism arising from the aortic arch or the carotid and vertebral arteries may cause stroke, transient ischemic attack, amaurosis fugax, blindness, headache, confusion, organic brain syndromes, dizziness, or spinal cord infarction. Retinal artery occlusion may be identified by Hollenhorst plaque visible on ophthalmoscopic examination as yellow, highly refractile atheromatous material at an arteriolar bifurcation.

Treatment

Because treatment of atheroembolism seldom reverses damage, emphasis is on prevention of subsequent ischemic events. When the source of embolism can be confirmed, it is often feasible to isolate or replace a discrete segment of the aorta by surgery, angioplasty and stent, or stent-graft insertion. Treatment should include symptomatic care of affected ischemic tissue and risk factor modification to prevent progression of atheromatous disease and promote plaque stabilization. If embolism affects the lower extremities, this involves local care of ischemic ulcers; when gangrene is present, amputation may be required. The role of sympathectomy is controversial, but this may be helpful when pain is intractable. In cases of renal atheroembolism, dialysis should be performed as necessary and blood pressure controlled pharmacologically.

Optimum antithrombotic therapy (anticoagulants, platelet inhibitors, or a combination of both) for atheromatous embolism has not been defined, but platelet inhibitor drugs generally lessen the risk of cardiovascular ischemic events. Anticoagulation therapy is far from protective, however, with a recurrence rate of cerebral events of 26% in patients with plaques more than 4 mm in thickness despite antiplatelet or warfarin therapy. Case reports of improvement with lipid-lowering therapy are supported by observations in nonrandomized series and evidence in coronary disease that HMG-CoA-reductase inhibitor ("statin") drugs improve plaque stabilization.[202,203]

The role of surgical therapy for patients with localized atheromata in the aortic arch and cerebral ischemia is controversial because it is seldom possible to determine conclusively whether the cause of symptoms is the aorta or associated cerebrovascular disease.[204,205]

AORTOILIAC OCCLUSIVE DISEASE

Atherosclerotic occlusive disease of the infrarenal aorta and iliac arteries may occur with or without atherosclerosis of the infrainguinal vessels.[206,207] When isolated, aortoiliac atherosclerosis typically occurs in younger individuals who smoke cigarettes. Almost half the cases are women, many of whom angiographically exhibit the "hypoplastic aortic syndrome," with small-caliber aortic, iliac, and femoropopliteal arteries. The disease in these cases is usually confined to the aortic bifurcation. Disease localized to the distal aorta and common iliac arteries (type I) rarely produces limb-threatening ischemia because of extensive collateral vessels. The classic presentation is Leriche syndrome, a clinical triad of intermittent claudication involving the low back, buttocks, hip, or thigh, which is often mistaken for degenerative joint disease of the low back or hips, impotency (which occurs in 30%-50% of men with aortoiliac occlusive disease), or "global atrophy" of the lower extremities, reflecting the chronicity of low-grade ischemia.[208] The femoral pulses are often weak or absent, but the ankle-brachial index may be normal at rest. A decline in ankle systolic pressure after exercise confirms hemodynamically significant stenosis.

Management

Treatment of patients with occlusive atherosclerosis of the aorta should include measures directed at improving symptoms (eg, claudication or limb ischemia) and thus quality of life, as well as reduction of overall cardiovascular risk. The latter involves the same measures as management of other manifestations of systemic atherosclerosis or peripheral artery disease (see Chaps. 32 and 96).[209] Catheter-based interventions to relieve aortic obstruction should be considered in lifestyle-interfering claudication or critical limb ischemia.

Patients with aortoiliac occlusive disease should be instructed on a supervised exercise program. The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial was a randomized prospective trial comparing optimal medical therapy (OMT) alone, supervised exercise plus OMT, and stenting plus OMT. At 6 months and 18 months, those assigned to exercise responded as well as those who received stents.[210,211] If the patient is not satisfied with the results of an exercise program, revascularization should be performed. In the past, decisions on the type of treatment the patient was offered was based on the location and extent of obstruction as assessed by *The Transatlantic Inter-Societal Consensus (TASC) II* classification.[212] However, the ESC and ACC/AHA guidelines now recommend an endovascular first approach in patients with aortoiliac occlusive disease, independent of the TASC classification.[213,214] The BelgianeItalian tRial Vascular Iliac StentS In the treatMent of TASC A, B, C, & D iliac lesiOns (BRAVISSIMO) reported a 24-month primary patency rate of 87.9% and a technical success of 100% in 325 patients with aortoiliac lesions.[215] Neither TASC category nor lesion length was predictive of restenosis. At the current time, open surgery is rarely performed for aortoiliac occlusive disease.

ACUTE OBSTRUCTION OF THE TERMINAL AORTA

ETIOLOGY

Sudden occlusion of the terminal aorta may result from a large "saddle" embolus,[216] trauma, dissection, or in situ thrombosis superimposed on aneurysmal or atherosclerotic disease. Most emboli large enough to occlude the terminal aorta (saddle embolism) originate in the heart in patients with mitral stenosis, atrial fibrillation, acute anterior MI, infective endocarditis, or paradoxical embolism through a right-to-left intracardiac shunt from a peripheral venous source. When thrombotic occlusion of the aorta develops at a point of atherosclerotic narrowing, collateral perfusion is usually sufficient to prevent acute limb ischemia. Acute aortic occlusion related to thrombosis of an abdominal aortic aneurysm is considerably less common than thrombosis of popliteal aneurysms.

CLINICAL FEATURES

Unlike gradually progressive obstruction, abrupt total or near-total interruption of flow through the terminal aorta or common iliac arteries poses an immediate threat to life and limb. Although the clinical picture varies depending on the collaterals, the full-blown syndrome is characterized by an abrupt onset of pain, typically severe, in the lumbar area, buttocks, perineum, abdomen, and legs. Diffuse cyanosis may be present from the umbilicus to the feet, and the lower limbs may be pale and cold. Numbness, paresthesia, and paralysis dominate the picture. Pulses are absent in the lower limbs and, unless circulation is restored promptly, muscle necrosis may produce myoglobinuria, renal failure, acidosis, hyperkalemia, and death.

MANAGEMENT

In contrast to chronic aortoiliac occlusion, acute aortic occlusion calls for immediate revascularization. The optimum procedure depends on the cause and the strategy for prevention of recurrent embolism. Transfemoral catheter-based embolectomy can extract even large amounts of embolic material from the distal aorta. Even after circulation has been restored, however, mortality is high, related to the underlying disease.

AORTITIS

Inflammation of the aortic wall may occur in noninfectious diseases, such as Takayasu disease, giant-cell arteritis, IgG-related diseases, the spondyloarthropathies, Behçet syndrome, relapsing polychondritis, Cogan syndrome, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, idiopathic retroperitoneal fibrosis, as isolated aortitis, and other disorders.[217,218] Only the most common of these uncommon entities are discussed in detail.

A possible role for infectious agents—including bacteria, viruses, and mycobacterium—in instigating arteritides of various sorts has been postulated.[219]

TAKAYASU DISEASE

The prototypical nonspecific aortitis, Takayasu arteritis was named for the Japanese ophthalmologist who first called attention to the funduscopic findings.[220,221] Because of its predilection for the brachiocephalic vessels, this arteritis has been labeled *pulseless disease* and *aortic arch syndrome*.

The classic form occurs with greatest frequency in Asian countries, but patients with a similar nonspecific aortitis are encountered worldwide. The etiology is unknown; no infectious agent has been identified, and identification of endothelial antibodies in 18 of 19 patients with this disease supports an autoimmune mechanism. This finding is nonspecific.

Recently, a genetic underpinning for Takayasu disease has been discovered, with mutations in the *HLA-B* and *IL12B* genes.[222,223] Continued progress in genetic understanding promises to clarify whether Takayasu and other, nonspecific arteritidies are one and the same or different diseases.

Histopathology

Histologic examination during active stages of the disease discloses a granulomatous arteritis similar to giant-cell arteritis and to the aortitis associated with the seronegative spondyloarthropathies and Cogan syndrome. In later stages, medial degeneration, fibrous scarring, intimal proliferation, and thrombosis result in narrowing of the vessel, yet there remains a lack of adequate histopathologic criteria for the differential diagnosis of noninfectious arteritides, including Takayasu disease and giant-cell aortitis.[224] Aneurysm formation is less common than stenosis, but aneurysm rupture is an important cause of death in patients with Takayasu arteritis. Angiographically, the left subclavian artery is narrowed in approximately 90% of patients. The right subclavian artery, left carotid artery, and brachiocephalic trunk follow closely in frequency of stenosis. Thoracic aortic lesions occur in 66% of patients, the abdominal aorta is involved in 50%, and aortoiliac involvement is seen in approximately 12%. Pulmonary arteritis occurs in about half of patients and may be associated with pulmonary hypertension.

Clinical Features

In 70% to 80% of patients, clinical manifestations of the illness appear during the second or third decade of life, but onset in childhood and in middle life has been reported. Women are affected eight to nine times more often than men.[225]

During the early or "prepulseless" phase, symptoms include fever, night sweats, malaise, nausea, vomiting, weight loss, rash, arthralgia, and Raynaud phenomenon. Splenomegaly may occur, and laboratory findings may include acceleration of the erythrocyte sedimentation rate, elevated levels of C-reactive protein, anemia, and plasma protein abnormalities. However, it should be recognized that a minority of patients may not experience any of the signs or symptoms listed above and may present with discrepancy of arm blood pressures, absent pulse(s), the presence of a supraclavicular or cervical bruit, or incidental findings on imaging performed for another reason.

When arterial obstruction develops, upper-extremity claudication may occur as a consequence of subclavian artery stenosis. Stroke, transient cerebral ischemia, dizziness, or syncope usually indicate stenosis of the brachiocephalic arteries or subclavian steal. The retinopathy that first drew the attention of Takayasu is believed to result from retinal ischemia. Hypertension, observed in more than 50% of the cases, may be severe and occurs due to stenosis of the aorta proximal to the renal arteries or involvement of the renal arteries themselves.[226]

Cardiac manifestations result from severe hypertension, dilatation of the aortic root producing valvular insufficiency, or coronary artery stenosis (Fig. 93–43). Angina pectoris, MI, and heart failure have been reported. Clinical pericarditis has been observed infrequently, but healed pericarditis is often encountered at necropsy. Involvement of the visceral arteries may result in splanchnic ischemia, and aortoiliac obstruction may produce intermittent claudication in the lower limbs.

Patients in whom severe aortitis is evident at the time of diagnosis face a 25% to 30% risk of ischemic events or death over the next 5 years. Those without ischemic complications at presentation tend to fare better over 5 to 10 years. Severe hypertension and cardiac involvement are associated with a shortened life expectancy.

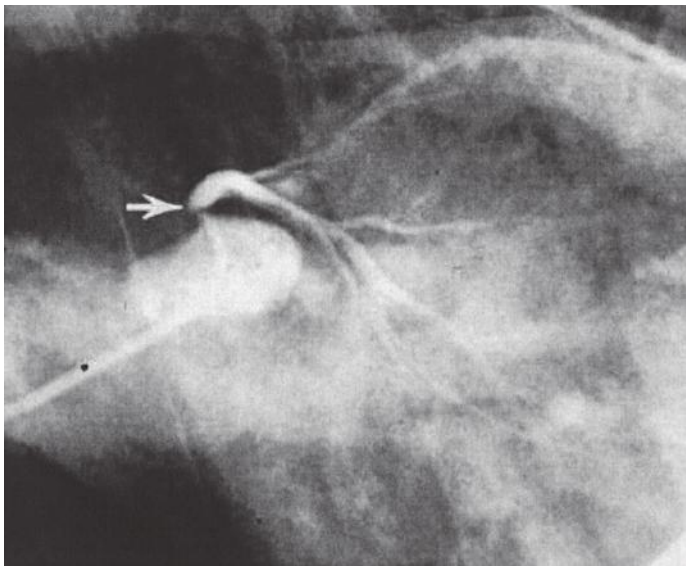


FIGURE 93–43. Typical angiographic appearance of Takayasu arteritis, showing focal ostial stenosis (*arrow*) of the left main coronary artery. Reproduced with permission from Jolly M, Bartholomew JR, Flamm S, Olin JW. Angina and coronary ostial lesions in a young woman as a presentation of Takayasu's arteritis. *Cardiovasc Surg*. 1999 Jun;7(4):443-446.

Diagnosis

The American College of Rheumatology has identified six major criteria for the diagnosis of Takayasu arteritis.[227] Onset of illness by age 40 years avoids overlap with giant-cell arteritis. Other criteria include upper-extremity claudication; diminished brachial pulses; greater than 10 mm Hg difference between systolic blood pressure in the arms; subclavian or aortic bruit; and narrowing of the aorta or a major branch. The presence of three of these six criteria carries high diagnostic accuracy.

Arteriography typically shows long areas of smooth narrowing interspersed with areas that appear normal. Aneurysm and occlusions are also common. Duplex ultrasound MRA or CT scans may show wall thickening resulting from inflammation and edema of the media and adventitia. MR or CT angiography of the entire aorta and iliac vessels is recommended for all patients with suspected Takayasu disease to define the extent of disease, identify aneurysms, and estimate the activity of disease. A "macaroni sign" on echocardiographic evaluation has recently been described, signifying the thick wall of the vessel with the small, linear residual lumen.[228] Positron emission tomography (PET) scanning is showing promise for diagnosis by identifying "hot spots" at sites of active Takayasu lesions.[229]

Management

Corticosteroid therapy appears effective in suppressing inflammation during the active phase, and favorable results have been reported with immunosuppressive and cytotoxic agents.[230] The mainstay of medical treatment continues to be administration of corticosteroids.[230] However, the use of biologic targeted treatments (infiximab, rituximab, toclizumab) has been quite effective and safe in patients refractory to standard therapy or in those who are glucocorticoid dependent.[231] Operative treatment may be used to relieve symptoms caused by arterial obstruction, and percutaneous angioplasty and stenting are associated with mixed results. When performed for stenosis, the restenosis rate is substantial in both open and endovasculuar surgery.[232-234] These procedures

are best reserved for patients in whom the acute inflammatory stage of the disease has been controlled.[217]

GIANT-CELL ARTERITIS

Giant-cell arteritis (temporal arteritis, polymyalgia rheumatica) involves extracranial arteries, including the aorta, in 10% to 13% of cases. A peak incidence late in life sets giant-cell arteritis apart from other nonspecific arteritides. Recent evidence suggests that giant-cell arteritis is occurring even later in life than in prior decades.[235] Similar to Takayasu disease, giant-cell arteritis may produce narrowing of the brachiocephalic arteries, aneurysms of the ascending aorta, aortic dissection, and aortic regurgitation.[236] Despite clinical, angiographic, and pathologic similarities to Takayasu arteritis, giant-cell arteritis almost always occurs in individuals older than 50 years of age. Although the most common presentation involves polymyalgia rheumatica with temporal arteritis, any large artery may be involved.

Treatment of giant-cell arteritis usually involves oral prednisone in an initial dose of 40 to 60 mg/d. Induction therapy with intravenous steroids has been found beneficial in a randomized trial. During clinical follow-up, CTA, MRA or [18F]-fludeoxyglucose positron emission tomography/magnetic resonance imaging[237] can be of value in monitoring improvement in arterial abnormalities with therapy. In unresponsive cases (< 10%) and in those who relapse as the dose is tapered, cytotoxic agents such as cyclosporine, azathioprine, and methotrexate may be helpful. One randomized, double-blind trial found a significant reduction in the rate of relapse and the cumulative mean dose of corticosteroid medication with methotrexate compared with placebo in corticosteroid-treated patients,[238] but another study did not.[239,240]

For patients with symptomatic ascending aortic involvement in giant-cell arteritis (pain, inflammation), we have, anecdotally, had excellent results with surgical aortic resection—often permitting dramatic reduction or elimination of corticosteroid treatment.

IgG4-RELATED DISEASES

IgG-related diseases are a relatively recently recognized immune-mediated condition that may involve nearly every organ system.[241,242] Hallmarks of this disease are tumor-like swelling of the involved organs, dense lymphoplasmacitic infiltrate that contains IgG4-positive plasma cells, and storiform fibrosis. Usually there are elevated IgG levels in the serum. A number of conditions are considered part of IgG-related diseases such as autoimmune pancreatitis, sclerosing mesenteritis, Mikulicz syndrome (salivary and lacrimal glands), Riedel thyroiditis, eosinophilic angiocentric fibrosis, Küttner tumor (submandibular glands), inflammatory pseudotumor, mediastinal fibrosis, and hypocomplementemic tubulointerstitial nephritis.[242] The vascular involvement includes IgG4-related retroperitoneal fibrosis, IgG4-related abdominal aortitis, and IgG4-related perianeurysmal fibrosis or inflammatory aortic aneurysms.[243] It is now recognized that IgG4-related disease may be the cause of idiopathic retroperitoneal fibrosis (previously called Ormonds disease) in up to two-thirds of cases.[244]

Presentations of periaortitis may be nonspecific, leading to a delay in the diagnosis. The most common symptoms are pain in the lower abdomen, flanks, and back. The aorta may be extremely tender to palpation. The thoracic aorta may also be involved leading to aneurysm or dissection.[245] Although Takayasu arteritis and giant-cell arteritis affect the primary aortic branches, IgG4-related disease generally spares the branches off the aortic arch.[242]

It is important to diagnose IgG4-related diseases early, as effective therapy is available. Glucocorticoids are first-line agents. There are no studies that have evaluated the usual steroid-sparing agents (methotrexate, azathioprine). There are no randomized trials using B-cell depletion therapy (targeting a subset of plasma cells that produce the IgG4) with agents such as rituximab, but this agent seems to be quite effective in treating some patients with IgG4-related diseases who do not respond to glucocorticoids.[242]

HLA-B27–ASSOCIATED SPONDYLOARTHROPATHIES

Aortitis is present in a substantial portion of patients with ankylosing spondylitis and Reiter syndrome; more than 90% have the histocompatibility antigen HLA-B27. Aortic involvement is most common in those with spondylitis of long duration, peripheral joint complaints in addition to spondylitis, and iritis.[246] Inflammation of the aortic root and surrounding tissues, manifest by aortic valve regurgitation or cardiac conduction abnormalities in patients with the HLA-B27 histocompatibility antigen, may also occur without spondyloarthropathies. Although the majority of cases occur in the aortic root and ascending aorta, occasionally isolated abdominal aortitis may occur.[247] Histologically, the aortic lesion in this setting resembles the inflammation seen in syphilis, with focal destruction of medial elastic tissue and thickening of the intima and adventitia. Aortic dissection has been reported.[248]

INFECTIOUS AORTITIS

Primary infection of the aortic wall is a rare cause of aortic aneurysms, which are more often saccular than fusiform. Infectious or "mycotic" aneurysms may arise secondarily from an infection occurring in a preexisting aneurysm of another cause. *Staphylococcus*, *Salmonella*, and *Pseudomonas* species are the most frequent pathogens causing primary aortic infections.[248] Many cases arise as complications of infective endocarditis or arterial catheterization. An intrinsically abnormal aorta, however, may become infected as a consequence of bacteremia. Such infection produces suppurative aortitis, leading to weakness of a portion of the aortic wall. In these cases, aneurysms are typically saccular, yet there is a comparatively high propensity to rupture. Infection of the aorta related to endovascular stents is a new and increasing clinical entity that is difficult to treat.[49,250]

SYPHILITIC AORTITIS

Treponemal infection produces chronic aortitis in approximately 10% of patients with untreated tertiary syphilis and is the primary cause of death in about the same proportion of cases, but there is evidence of the process at autopsy in about half of patients who have had untreated syphilis for more than 10 years.[251] During the spirochetemic phase of primary syphilis, *Treponema pallidum* organisms lodge in the adventitia of the vasa vasorum and initiate an inflammatory response characterized by perivascular lymphocytic and plasma cell infiltrate. This is followed by obliterative endarteritis, resulting in patchy medial necrosis, elastic fiber fragmentation, weakening of the aortic wall, and aneurysm formation. The intima of the aorta has a characteristic wrinkled appearance, frequently with superimposed atherosclerotic plaques. Because the infection is seeded through the vasa vasorum, the process is most severe in the ascending aorta and the arch, where the density of these vessels is greatest. Luetic aneurysms are typically saccular and involve the ascending aorta whether or not the transverse and descending portions are also affected. Aortic aneurysms resulting from cardiovascular syphilis follow interruption of the elastic fibers as a result of periaortitis and mesoaortitis, which thicken but weaken the aortic wall. Rupture is the major complication, but the enlarging aneurysm may also compress or erode adjacent structures of the mediastinum. Because the inflammatory process tends to interrupt the medial layer by transverse scars, dissection is distinctly uncommon.

Aortic involvement may be asymptomatic or associated with aortic regurgitation, coronary ostial stenosis, or aortic aneurysm. Asymptomatic aortitis may sometimes be identified by linear calcification of the ascending aorta, evident on chest radiographs. Valvular regurgitation, present in 20% to 30% of patients with syphilitic aortitis, is mainly a consequence of aortic root dilatation. Syphilitic coronary ostial stenosis, only a century ago more common than coronary atherosclerosis as a cause of angina pectoris, occurs in 25% to 30% of such patients, most of whom also have aortic regurgitation. Myocardial infarction is rare. The least frequent manifestation of syphilitic aortitis is aneurysm formation, which occurs in 5% to 10% of affected patients. Although the prognosis for patients with uncomplicated syphilitic aortitis is comparable to that of the general population, the outlook is poor when syphilitic aneurysms of the aorta are large enough to produce symptoms. The diagnosis of cardiovascular syphilis may be difficult in patients older than age 50 years, when hypertensive and atherosclerotic disease often coexist.

The frequency of cardiovascular syphilis has fallen dramatically over recent decades as a consequence of early identification and treatment of the disease. However, a recent report indicates that syphilitic ascending aortic aneurysm is still surprisingly common and must remain in the consciousness of the caring medical and surgical teams.[252]

Adequate antimicrobial therapy of early syphilis is the most important preventive measure, although whether such treatment retards the progression of disease once aortitis has developed has not been clearly established. Without surgical intervention, symptomatic syphilitic aortic aneurysms are associated with a high mortality rate.

Recently Roberts and colleagues[253] have described the features of syphilitic aortitis at surgery in hopes of permitting intraoperative identification and prompt institution of treatment. The distinguishing features include sparing of the aortic root, involvement of the tubular portion of the ascending aorta, uniform involvement of all of the surface area of the affected aortic portions, and inflammation in all three layers of the aortic wall. The aorta is said to have a "tree bark" appearance characteristic of syphilitic aortitis.

TUBERCULOUS AORTITIS

Tuberculous aneurysms usually result from direct extension of infection from hilar lymph nodes and subsequent granulomatous destruction of the medial layer, leading to loss of aortic wall elasticity. The posterior or posterolateral aortic wall is usually the site of saccular aneurysm formation in these cases. Caseating granulomatous lesions affecting the medial layer of the aortic wall characterize the histology. Pseudoaneurysm formation,[254] perforation, or aortoenteric fistula may result. Infection may occasionally invade the aortic valve ring and adjacent structures, producing a caseating paravalvular abscess. Rupture of tuberculous aortic lesions may occur. It is important to recognize that miliary tuberculous may manifest in a manner very similar to Takayasu arteritis. Therefore, if there is any suspicion that tuberculosis is present, testing should be performed before starting immunosuppressant medications.

FUTURE PROSPECTS

This is an exciting time in the care of the thoracic aorta. Although clinical trials of angiotensin receptor blocking drugs (ARBs) have not revealed the hoped-for medical panacea, other exciting advances are being made.

As the familial nature of aneurysmal diseases becomes familiar to a broader array of physicians, radiologic testing of relatives of affected individuals is likely to become standard practice and reimbursable by insurers. Recognizing an aneurysm in advance of symptoms is the optimal method to enhance survival, and family members represent the most cost-effective candidates for diagnostic testing.

Surgical therapy for the thoracic aorta has become safer and safer, approaching the low mortality rates of conventional cardiac surgical procedures, like coronary artery bypass and valve replacement. This trend is likely to continue, becoming more widespread and proliferating beyond leading large-volume centers.

Endovascular devices and technologies are advancing at a rapid rate, providing alternative options, especially for elderly and infirm patients. It is hoped that these endovascular therapies will advance further, perhaps even mimicking the success and durability of open techniques.

The aorta is being understood more and more thoroughly from an engineering standpoint. Engineering calculations are currently on the way towards becoming an integral part of surgical decision making.[255]

Once a thoracic aortic aneurysm has been identified, we can keep the patient safe by following algorithms based on patient symptoms and aortic size. Perhaps the biggest problem in thoracic aortic disease is the silent nature of thoracic aortic aneurysms. Via a "guilt by associaton" paradigm, we can identify more and more asymptomatic patients with thoracic aortic aneuryms.

The most significant advances in aneurysm disease of recent years have been on the genetic front. We are starting to understand thoracic aortic aneurysm at the genetic level. Now that whole-exome sequencing (WES) has become a relatively inexpensive clinical reality, our genetic understanding of these diseases will advance by leaps and bounds. New genes and new variants in known genes are being discovered on a regular basis. This genetic revolution holds promise in numerous areas. Genetic screening tests for the general population (and for family members) are in the process of becoming a clinical reality. Furthermore, knowledge of the specific genetic mutation borne by an individual thoracic aortic aneurysm patient permits *personalized* care at the genetic level. That is to say, not all aneurysms behave similarly. Certain mutations (eg, *ACTA2* and *MYLK*) produce aortic dissection at small aortic sizes. Affected patients violate the standard size algorithms for surgical intervention. The personalized mutation is now being invoked into the surgical decision-making process. The future will see this genetic incorporation increase steadily, with the specific mutation becoming an integral factor in the decision-making algorithm.

As our genetic understanding is enhanced, new pathogenic pathways will be identified, with direct potential correlates in terms of promising avenues for novel drug development. Directed drug development will be feasible when enhanced genetic and proteomic profiling of affected individuals leads to better appreciation of exactly how aortic wall proteins are deficient.

The 1960s saw "disruptive" advances in aneurysm care via the development of bold, novel surgical techniques. Today, we find ourselves on the threshold of similar "disruptive" insights and advances at the genetic level.

More than 100 years ago, Sir William Osler stated: "There is no disease more conducive to clinical humility than aneurysm of the aorta." This is still true today because aneurysms and dissections remain virulent processes that challenge the skill and experience of physicians and surgeons. However, advances in progress at the present time promise to tame this virulent disease.

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CHAPTER 94

CEREBROVASCULAR DISEASE AND NEUROLOGIC MANIFESTATIONS OF HEART DISEASE

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Many vascular diseases affect both the heart and the brain. Cardiac diseases often lead to lesions and dysfunction within the brain, and central nervous system (CNS) diseases can influence the heart and its function.

BRAIN AND CEREBROVASCULAR COMPLICATIONS OF HEART DISEASE

Stroke is a common and devastating disease, the fifth leading cause of death and the leading cause of disability in the United States. On average, one American dies from a stroke every 4 minutes. Cardiogenic stroke can occur when (1) the heart pumps unwanted material into the circulation that reaches the brain (embolism), (2) pump function fails and the brain is hypoperfused, or (3) drugs given to treat cardiac disease have adverse neurologic effects.

DIRECT CARDIOGENIC BRAIN EMBOLISM

Etiology

Cardiogenic cerebral embolism is responsible for approximately 20% of ischemic strokes.[1-5] Because many patients have coexisting cardiac and extracranial vascular disease,[5] criteria for the diagnosis of cardiac embolism remain controversial even today. As more advanced diagnostic techniques have been developed, more causative cardiac abnormalities (and their association with stroke) have been recognized. Cardiac sources of brain emboli can be divided into several groups[6]:

1. Arrhythmias
2. Cardiac wall and chamber abnormalities
3. Valve disorders
4. Cardiac tumors
5. Aortic arch disease

Some cardiac sources have much higher rates of initial and recurrent embolism. The more common sources will be reviewed. The Stroke Data Bank[7] in 1992 divided potential sources of brain embolism into *strong sources* (prosthetic valves, atrial fibrillation [AF], endocarditis, sick sinus syndrome, ventricular aneurysm, akinetic segments, mural thrombi, cardiomyopathy, and diffuse ventricular hypokinesia) and *weak sources* (myocardial infarct > 6 months old, aortic and mitral stenosis and regurgitation, congestive failure, mitral valve prolapse, mitral annulus calcification, and hypokinetic ventricular segments). Patients who have these weak sources are now often lumped within a category called *cryptogenic stroke* or *cryptogenic embolism*. The sources then deemed weak were frequent findings in patients who did not have brain embolism. Research is now directed into defining the frequency of these sources and identifying ways to determine in which patients they are the embolic source and in whom they are incidental findings. The risk of embolism varies within individual cardiac abnormalities depending on many factors. For example, in patients with AF, associated heart disease, patient age, duration, chronic versus intermittent fibrillation, and atrial size all influence embolic risk. The presence of a potential cardiac source of embolism does not mean that a stroke was caused by an embolus from the heart. Coexistent occlusive cerebrovascular disease is common. In the Lausanne Stroke Registry, among patients with potential cardiac embolic sources, 11% of patients had severe cervicocranial vascular occlusive disease (> 75% stenosis) and 40% had mild to moderate stenosis proximal to brain infarcts.[5]

Atrial Fibrillation Persistent and paroxysmal AF is a potent predictor of first and recurrent stroke, affecting more than 2.7 million Americans. The principal adverse consequence of AF is ischemic stroke, with AF patients being five times more likely to have a stroke than those without AF. In patients with brain emboli caused by a cardiac source, there is a history of nonvalvular AF in roughly one-half of all cases, of left ventricular thrombus in almost one-third, and of valvular heart disease in one-fourth.[1,8] Stroke prevention in patients with AF and other heart diseases is discussed later in this chapter.

Intracavitary Thrombus Patients with large anterior myocardial infarctions (MIs) associated with a left ventricle (LV) ejection fraction < 40% and anteroapical wall-motion abnormalities are at increased risk for developing mural thrombus caused by stasis of blood in the ventricular cavity as well as endocardial injury with associated inflammation.[2,8] Ventricular thrombi can also occur in patients with chronic ventricular dysfunction caused by coronary disease, hypertension, and dilated cardiomyopathy. Stroke is less common among uncomplicated MI patients but can occur in up to 12% of patients with acute MI complicated by a left ventricular thrombus. The rate of stroke is higher in

patients with anterior rather than inferior infarcts and may reach up to 20% in those with large anteroseptal MI. The incidence of embolism is highest during the period of active thrombus formation during the first 1 to 3 months, with substantial risk remaining even beyond the acute phase in patients with persistent myocardial dysfunction, congestive heart failure, or AF.[8,9]

Congestive Heart Failure Current data indicate that congestive heart failure affects an estimated 5.1 million Americans. Patients with ischemic and nonischemic dilated cardiomyopathy have a similarly increased stroke risk by a factor of 2 to 3, accounting for an estimated 10% of ischemic strokes.[3,8,10] Stroke rates may be higher in certain subgroups, including patients with prior stroke or trasient ischemic attack (TIA), lower ejection fraction, LV noncompaction, peripartum cardiomyopathy, and Chagas heart disease.[8] The 5-year recurrent stroke rate in patients with cardiac failure has been reported to be as high as 45%.[8,11]

Valvular Heart Disease The magnitude of risk for brain embolism from a diseased heart valve depends on the nature and the severity of the disease. Atrial fibrillation often coexists with valve disease.

Mitral Stenosis/Rheumatic Mitral Valve Disease Mitral stenosis is most commonly caused by rheumatic fever. The main proximate cause for embolic stroke in mitral stenosis of any cause is atrial fibrillation. Other factors associated with increased stroke risk in mitral stenosis patients include older age, left atrial enlargement, reduced cardiac output, and prior embolic event. In older studies prior to the era of chronic anticoagulation, recurrent embolism was reported in 30% to 60%.[8,11-14] Between 60% and 65% of these recurrences developed the first year, many within the first 6 months.[8,12,13] The majority of patients in these studies did have AF. Mitral valvuloplasty does not appear to eliminate the risk of embolism.[8,15]

Mitral Valve Prolapse Mitral valve prolapse (MVP) is the most common form of valve disease in adults and is generally benign.[17,18] MVP as a source of embolic stroke continues to be controversial.[6,19] Several small clinical series have reported cerebral embolism in MVP patients who lacked other possible embolic sources.[19-22] In the absence of AF, MVP/mitral regurgitation is probably not associated with a significant increase in the risk of first or recurrent stroke.[8,21,22]

Mitral Annulus Calcification Several series suggest a relation between mitral annulus calcification (MAC) and brain emboli and stroke.[3,6,23-25] In the Framingham Heart Study, MAC was associated with an increased risk for all types of stroke over 8 years of observation; however, only 63% were embolic and a portion of those were also associated with AF. Other population-based studies did not reveal a significant association. The association between MAC and increased risk of stroke may be the result of shared risk factors rather than direct causation. For example, AF can occur 12 times more often in patients with MAC than in those without MAC.[18,26]

Aortic Valve Disease Neither aortic regurgitation nor aortic stenosis is associated with an increased risk of first or recurrent stroke. Additionally, studies of lesser degrees of aortic valve disease, including aortic annular calcification and aortic valve sclerosis, have also not confirmed an association with an increased risk of stroke.[27,28]

Other Causes of Embolism Stroke in many patients remains cryptogenic, and more patients may have cardiogenic embolism than are recognized. Clinical features and brain investigations such as computed tomography (CT), magnetic resonance imaging (MRI), and angiography (CT, magnetic resonance [MR], and digital subtraction angiography) may suggest emboli, but often a clear source is unidentified. These cases, which are termed *infarcts of unknown causes* in the Stroke Data Bank,[29-31] include as many as 40% of all stroke patients.

TABLE 94–1. Embolic Materials

Cardiac	Intra-Arterial
1. Red fibrin-dependent thrombi	1. Red fibrin-dependent thrombi
2. White platelet-fibrin nidi	2. White platelet-fibrin nidi
3. Material from marantic endocarditis	3. Combined fibrin-platelet and fibrin-dependent clots
4. Bacteria from vegetations	4. Cholesterol crystals
5. Calcium from valves and mitral annulus calcification	5. Atheromatous plaque debris
6. Myxoma cells and debris	6. Calcium from vascular calcifications
	7. Air
	8. Mucin from tumors
	9. Talc or microcrystalline cellulose from injected drugs

Fibrous and fibrinous lesions of the heart valves and endocardium are associated with certain medical conditions, with the specific stroke risk depending on the underlying medical condition.[6] Valve lesions occur in patients with systemic lupus erythematosus (Libman-Sacks endocarditis[32]), antiphospholipid antibody syndrome,[33] cancer, and other debilitating diseases (nonbacterial thrombotic endocarditis). Mobile fibrous strands are also often found during echocardiography.[6,34-36] Fibrin-platelet aggregates may attach to these fibrous and fibrinous lesions.

Embolic complications are common in patients who have *infective endocarditis*.[6,37] Mycotic aneurysms can cause fatal subarachnoid bleeding. Bleeding can also result from vascular necrosis as a result of an infected embolus.[37] Embolization usually stops when infection is controlled.[34] Warfarin does not prevent embolization and is contraindicated in patients with endocarditis and known cerebral embolism unless there are other important lesions such as prosthetic valves or pulmonary embolism. In children and young adults with congenital heart defects, especially those with right-to-left shunts and polycythemia, brain abscess is an important complication.

Emboli often arise from sources other than the heart, such as the aorta, proximal arteries (*intra-arterial* or so-called *local embolism*), leg veins (*paradoxical emboli*), fat in the liver or bones (*fat embolism*), and materials introduced by the patient or physician (drug particles or air).[6] The types of embolic materials vary (Table 94–1).[6,38] *Atheromatous plaques in the aortic arch and ascending aorta* are an important source of embolism to the brain (Figs. 94–1 and 94–2). Ulcerated atheromatous plaques are often found at necropsy in patients with ischemic strokes, especially in those in whom the stroke etiology was not determined during life.[39] Transesophageal echocardiography (TEE) often shows these atheromas, but technical factors limit visualization of the entire arch.[40] Large (> 4 mm), protruding mobile aortic atheromas are especially likely to cause embolic strokes and are associated with a high rate of recurrent strokes.[41,42] Use of oral anticoagulants rather than antiplatelet agents is recommended in these patients.[18,43,44]

Clinical Onset and Course

Warning signs of stroke can include sudden hemiparesis, hemisensory loss, confusion, trouble speaking or understanding, visual loss, diplopia, ataxia, vertigo, or sudden severe headache with no known cause. Most embolic events occur during activities of daily living, but some embolic strokes have their onset during rest or sleep. Sudden coughing, sneezing, or nighttime micturation can precipitate embolism.[6,45] Although the deficit is most often maximal at outset, 11% of embolic

FIGURE 94–1. Descending aorta at necropsy from a patient whose transesophageal echocardiography before surgery showed severe disease of the ascending aorta and aortic arch with mobile protruding plaques. This patient died after coronary artery bypass grafting surgery having never awakened after the procedure. Used with permission from Denise Barbut, MD, Cornell University Medical College and the New York Hospital.

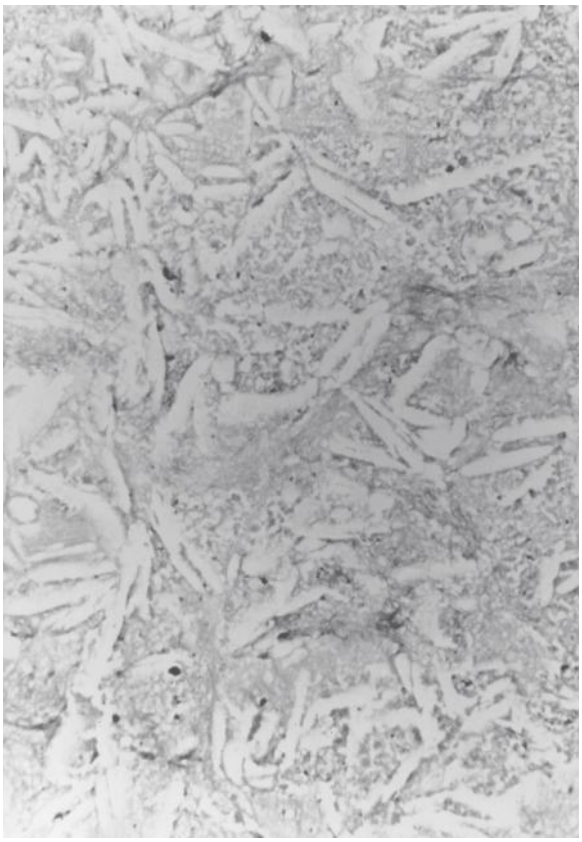

FIGURE 94–2. Cholesterol crystals and other particulate debris are caught in a filter placed in the aorta at the time that aortic clamps are removed. Used with permission from Denise Barbut, MD, Cornell University Medical College and the New York Hospital.

stroke patients in the Harvard Stroke Registry had a stuttering or stepwise course, whereas 10% had fluctuations or progressive deficits. Later progression, if it occurs, is usually within the first 48 hours. Progression is usually caused by distal passage of emboli. As in all large infarcts, brain edema and swelling may develop during the 24 to 72 hours after stroke with headache, decreased alertness, and worsening of neurologic signs. The edema is often cytotoxic (inside cells) and usually does not respond to corticosteroid treatment.

Diagnostic Testing

Emboli usually cause occlusion of distal branches and produce surface infarcts that are roughly triangular, with the apex of the triangle pointing inward. CT and MRI findings can suggest that an ischemic stroke was cardioembolic by the location and shape of the lesions on imaging[46]; eg, finding the presence of superficial wedge-shaped infarcts in multiple different vascular territories, hemorrhagic infarction, as well as visualization of thrombi within arteries. Among 60 patients with cardiogenic sources of embolism studied by CT in whom occlusive atherosclerotic cerebrovascular disease had been excluded, 56 had superficial large or small cortical or subcortical infarcts and only 4 had deep infarcts.[46] Emboli can also block the middle cerebral artery leading to solely deep infarcts, as a result of collateral flow preservation of superficial cerebral arterial flow.[6,45,47] Tiny emboli may also cause small deep or superficial infarcts.

MRI, particularly with the use of MR diffusion-weighted and MR gradient recall echo (GRE) imaging, is much more sensitive for detection of acute brain infarcts than is CT. MR is also superior in detecting hemorrhagic infarction by imaging hemosiderin. Hemorrhagic infarction has long been considered characteristic of embolism, especially when the artery leading to the infarct is patent.[48] The mechanism of hemorrhagic infarction is reperfusion of ischemic zones after iatrogenic opening of an occluded artery (eg, endarterectomy, fibrinolytic treatment) or after restoration of the circulation after a period of systemic hypoperfusion. Hemorrhage then occurs into proximal reperfused regions of brain infarcts.[6,45,49] At times, it is also possible to image the acute embolus on CT and also via MRI.[6,50-52]

In unselected series of stroke patients, transthoracic echocardiography (TTE) has been variably useful in detecting sources.[6,53-55] TTE is useful in patients with known cardiac disease to clarify potential embolic sources and heart function,[45] in young patients without stroke risk factors, and in stroke patients who do not have lacunar infarction or ultrasound or CTA evidence of intrinsic atherostenosis of a major extracranial and intracranial artery. TEE provides much better visualization of the aorta, atria, cardiac valves, and septal regions. Reports of TEE suggest that the diagnostic yield is 2 to 10 times that of TTE.[56-59] Aortic plaques, atrial septal aneurysms, and atrial septal defects are also much better seen with TEE (Fig. 94–3). The use of an echo-enhancing agent such as agitated saline or echogenic contrast helps detect intracardiac shunts.

Echocardiography has definite limitations. Particles the size of 2 mm can block major brain arteries but are beyond the imaging resolution of current echocardiographic technology.[60] Also, thromboembolism is a dynamic process. When a clot forms in the heart and embolizes, there may be no residual evidence unless a clot reforms.[6,38] Cardiac thrombi are imaged differently on sequential echocardiograms[6,64]; even large thrombi once seen on one echocardiogram can disappear later.[61]

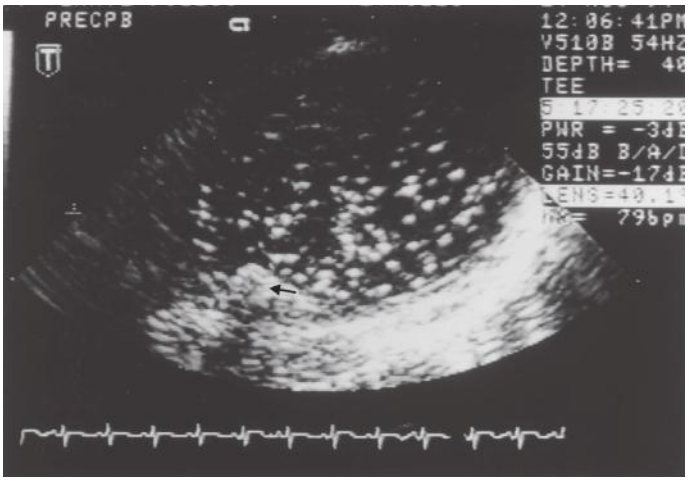

FIGURE 94–3. Transesophageal echocardiography recording during cardiac surgery from the aorta at the level of the origin of the left subclavian artery. A mobile plaque is seen protruding into the aortic lumen (*small black arrow*). This recording was taken after the release of aortic clamps and shows a shower of emboli within the aortic lumen beyond where the aorta was previously clamped. Used with permission from Denise Barbut, MD, Cornell University Medical College and the New York Hospital.

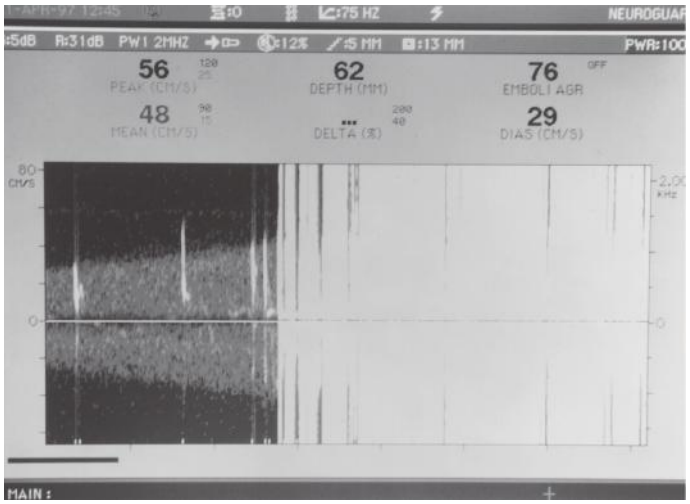

FIGURE 94–5. Transcranial Doppler recording from the middle cerebral arteries during cardiac bypass surgery. A few distinct emboli (*white streaks* in the left of the figure) are followed by a massive shower of emboli (*whiteout*) at the time of the release of aortic clamps. Used with permission from Denise Barbut, MD, Cornell University Medical College and the New York Hospital.

Cerebral embolic signals can also be detected by monitoring with transcranial Doppler (TCD).[6,62,63] Embolic particles passing under TCD probes produce transient, short-duration, high-intensity signals referred to as *HITSs* (high-intensity transient signals). Examples of HITSs are shown in Figs. 94–4 and 94–5. TCD monitoring of patients with AF,[64] cardiac surgery,[65] prosthetic valves, left ventricular assist devices,[66] carotid artery disease, during carotid endarterectomy, and in stroke patients with a patent foramen ovale have shown a relatively high frequency of embolic signals.[67] Monitoring of emboli with TCD may help guide treatment decisions.

Prevention and Treatment of Direct Cardiogenic Brain Embolism

Atrial Fibrillation: Treatment Options

Warfarin Multiple studies have showed warfarin to be effective in preventing brain embolism in patients with both rheumatic mitral stenosis and AF. Anticoagulation reduces the risk of ischemic stroke (and other embolic events) by about two-thirds irrespective of baseline risk. The intensity of anticoagulation was higher in early studies than that currently used, and brain hemorrhages and other bleeding complications were common. Trials have now shown that lower-dose warfarin (international normalized ratio [INR] 2.0-3.0) is effective in preventing brain emboli in patients with nonrheumatic AF.

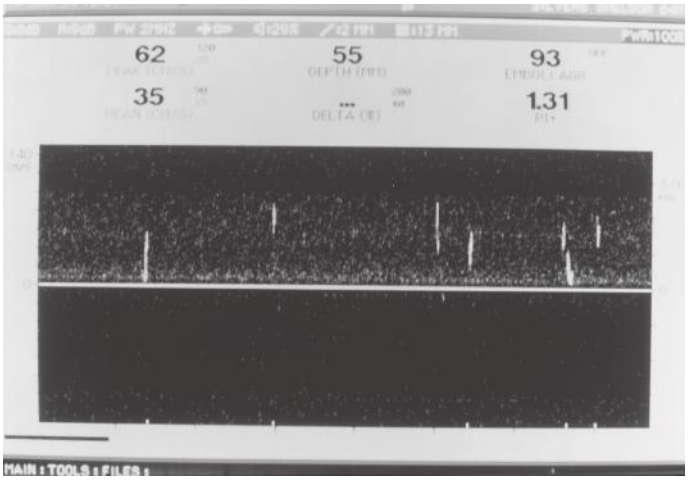

FIGURE 94–4. Transcranial Doppler recording from the middle cerebral arteries during steady-state cardiac bypass surgery at a time when the aorta was manipulated. The white streaks represent microemboli. Used with permission from Denise Barbut, MD, Cornell University Medical College and the New York Hospital.

In the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (AFASAK) study, 1007 patients (median age, 74.2 years) with chronic, nonrheumatic AF were assigned to warfarin (INR 2.8-4.2), aspirin (75 mg/d), or placebo.[68] The study was halted prematurely when analysis of effectiveness reached a predetermined level of significance in favor of warfarin treatment. The principal outcome was the composite of ischemic or hemorrhagic stroke, TIA, and systemic embolism. The observed reduction for warfarin compared with placebo was 64%, an absolute risk reduction of 3.5% per year. An analysis by intention to treat, which excluded TIA and minor stroke, indicated a risk reduction of approximately 50% ($P < .05$) and an absolute reduction of approximately 1.5% per year.

The Stroke Prevention in Atrial Fibrillation (SPAF) study investigators evaluated warfarin and aspirin in patients with nonrheumatic AF.[69,70,71] The study evaluated two groups of patients based on their eligibility for warfarin. In the first group, 627 patients judged eligible for warfarin were randomized to open-label warfarin (INR 2.8-4.5; prothrombin time [PT], 1.3-1.8 times control) or, in a double-blinded fashion, to either aspirin (325 mg daily, enteric coated) or a matching placebo. In the second group, 703 patients considered ineligible for warfarin were randomized (double blind) to aspirin (325 mg daily, enteric coated) or placebo. The principal outcome, a composite of ischemic stroke and systemic embolism, was significantly decreased during a mean follow-up of 1.3 years. The outcome of disabling ischemic stroke or vascular death was reduced by warfarin by 54% ($P = .11$), an absolute reduction of 2.6% per year. The outcome of disabling stroke or death was reduced 22% by aspirin ($P = .33$), an absolute reduction of approximately 1% per year. The SPAF investigators later compared low-intensity, fixed-dose warfarin (INR 1.2-1.5) plus aspirin (325 mg/d) with adjusted-dose warfarin (INR 2.0-3.0) in elderly patients with one or more risk factors for embolism.[71] Ischemic stroke and systemic embolism were present in 7.9% of patients on fixed-dose warfarin

plus aspirin versus only 1.9% of patients on adjusted-dose warfarin. SPAF investigators later studied the effectiveness of aspirin 325 mg in patients with low risk and found that the rate of ischemic stroke was low (2% per year).[72]

The SPAF study identified three risk factors for thromboembolism: (1) recent congestive heart failure, (2) history of hypertension, and (3) previous thromboembolism.[73,74] The study also suggested that anticoagulation with warfarin was not indicated in patients with none of the three risk factors who were at low risk for thromboembolism (2.5% per year). SPAF investigators concluded that in such patients, the dangers of anticoagulant therapy may outweigh its benefits. Aspirin (325 mg daily) is probably reasonable and safe therapy for patients with lone, nonrheumatic AF, who are younger than 60 years of age, and have none of the three identified risk factors.[73-75] In all other patients with AF, long-term oral warfarin therapy (INR 2.0-3.0) is recommended unless contraindicated.[72,75]

In the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), 420 patients with nonrheumatic AF (mean age, 68 years) were randomized unblinded to warfarin (target PT ratio, 1.2:1.5 × control; INR 1.5-2.7) or to a control group who were allowed to take aspirin.[76] The principal outcome was ischemic stroke or systemic embolism, and the mean follow-up time was 2.2 years. The incidence of stroke was reduced by 86% in the warfarin group compared with the control group (P = .002), equivalent to an absolute risk reduction of 2.6% per year. There was no demonstrable benefit of aspirin, but the study was not designed to test aspirin.

Although many trials showed the superiority of adjusted-dose warfarin over antiplatelet therapy for stroke prevention, participants in those trials tended to be younger (typically 70 years old) than the AF patients now commonly encountered in clinical practice (typically late 70s with a substantial fraction of octogenarians). The Birmingham Atrial Fibrillation Treatment in the Aged (BAFTA) trial addressed this issue, randomizing 973 AF patients with age ≥ 75 years to adjusted-dose warfarin versus aspirin 75 mg/d. The stroke rate was 5% on aspirin and nearly halved by warfarin. Surprisingly, major hemorrhage rates were similar in both groups, but 40% of patients had received warfarin previously, potentially biasing toward lower bleeding rates. The investigators concluded that "these data lend support to the use of anticoagulation for all people aged over 75 years who have AF, unless there are contraindications or the patient decides that the size of the benefit is not worth the inconvenience of treatment."[77]

Warfarin is approximately 50% more effective than aspirin in preventing stroke in patients with AF who do not have valvular disease. Data suggest that the optimal intensity of oral anticoagulation for stroke prevention in patients with AF appears to be a target INR of 2.0 to 3.0. However, the narrow therapeutic margin of warfarin, in addition to associated food and drug interactions, requires frequent INR testing and dosage adjustments. These liabilities likely contribute to underuse of warfarin, and alternative therapies are needed.

Antiplatelet Agents The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) evaluated the safety and efficacy of the combination of aspirin plus clopidogrel in AF patients who were unsuitable candidates for vitamin K antagonist therapy. In those patients, the addition of clopidogrel to aspirin did reduce the risk of major vascular events, especially stroke, but also increased the risk of major hemorrhage.[78]

Novel Oral Anticoagulants (NOACs)

1. *Oral direct thrombin inhibitors: Dabigatran etexilate*
2. *Oral direct factor Xa inhibitors: Apixaban, rivaroxaban, otamixaban, betrixaban, and edoxaban*

Direct thrombin inhibitors (DTIs) prevent thrombin from cleaving fibrinogen into fibrin. They bind to thrombin directly, rather than by enhancing the activity of antithrombin, as is done by heparin. The only oral DTI available for clinical use is dabigatran etexilate. Another oral agent, ximelagatran, was tested but development was discontinued in 2006 because of hepatotoxicity and cardiovascular events.

Dabigatran has been compared with warfarin in the landmark RE-LY trial, which was an open, prospective, randomized study, with blinded adjudication of events. In this trial, 18,113 patients with AF were assigned to dabigatran 110 mg twice a day, dabigatran 150 mg twice a day, or adjusted-dose warfarin. There was a trend for less myocardial infarction with warfarin. Compared to warfarin, dabigatran 110 mg twice a day had similar efficacy in terms of stroke rates, with fewer major bleeds and fewer hospitalizations. Dabigatran given at 150 mg twice a day had a lower stroke rate compared with coumadin, with less mortality but similar major bleeding rates. Of note, dyspepsia, dysmotility, and gastrointestinal reflux were twice as common in those who received dabigatran.[79]

Direct factor Xa inhibitors prevent factor Xa from cleaving prothrombin to thrombin. They bind directly to factor Xa, rather than enhancing the activity of antithrombin III. Examples of oral direct factor Xa inhibitors include apixaban, rivaroxaban, otamixaban, betrixaban, and edoxaban. The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study was a prospective, randomized, double-blind, multicenter, event-driven, noninferiority study comparing the efficacy and safety of rivaroxaban, an oral, once-daily, direct factor Xa inhibitor with adjusted-dose warfarin in patients with nonvalvular AF.[80] Additionally, a different factor Xa inhibitor, apixaban, was also compared with warfarin in the ARISTOTLE trial.[81]

Ruff and colleagues (2014) performed the first meta-analysis of four novel oral anticoagulants: dabigatran, rivaroxaban, apixaban, and edoxaban.[82] Anticoagulation with each of these NOACs led to similar or lower rates both of ischemic stroke and major bleeding compared to adjusted-dose warfarin (INR 2.0-3.0) in patients with nonvalvular AF. Important additional advantages of the NOAC agents are convenience (no requirement for routine testing of the INR), a high relative but small absolute reduction in the risk of ICH, lack of susceptibility to dietary interactions, and reduced susceptibility to drug interactions. Disadvantages include lack of efficacy and safety data in patients with chronic severe kidney disease, lack of easily available monitoring of blood levels and compliance, higher cost, variable availability of agents that can reverse NOAC anticoagulation, as well as the potential for unanticipated side effects, which will subsequently become evident.[79-82]

Additional meta-analyses have pooled the results from the RE-LY, ARISTOTLE, ROCKET AF, and ENGAGE AF-TIMI 48 trial and come to similar conclusions.[79-86] More recently, a 2014 Cochrane review compared the following factor Xa inhibitors to warfarin in patients with AF: apixaban, betrixaban, darexaban, edoxaban, idraparinux, and rivaroxaban. A lower rate of stroke and systemic embolic events was found with the NOACs as well a lower rate of death and ICH.[87] A second 2014 Cochrane review evaluated studies that compared direct thrombin inhibitors to warfarin and found no significant difference in the odds of vascular death and ischemic events.[88] Fatal and nonfatal major bleeding events, including hemorrhagic strokes, were less frequent with these agents.

These meta-analyses support the broad concept that NOAC agents (direct thrombin and factor Xa inhibitors) are preferable to warfarin use in patients with AF. However, they cannot directly compare the relative advantages and disadvantages of the individual agents nor can they demonstrate whether the agents are equal in safety and efficacy.

Also, the NOACs were studied in nonvalvular AF, and as a result, they are only approved for use in nonvalvular AF.

Summary There is no single perfect medication choice for patients with atrial fibrillation. The authors assert that a variety of factors should influence a physician's selection of therapy for their patient. Assessing a particular patient's risk of ischemic stroke with CHA2DS-VASc scoring can assist in making a treatment decision between antiplatelet, warfarin, and a NOAC.[89] For example, current 2014 ACC/AHA/HRS guidelines note that for patients with a CHA2DS2-VASc score of 0, antithrombotic therapy may be omitted (class IIa, level of evidence B).[90] Additionally, assessing the patient's risk of significant bleeding with HAS-BLED scoring can also influence medication choice.[91] We recommend that therapy should be tailored to the individual patient and their specific needs, including making an assessment of other comorbid medical issues, cost of the particular agent selected, history of patient compliance with medications, as well as patient preference.

Other Cardiac Causes The effectiveness of anticoagulation on embolic stroke prevention from other cardiac conditions has not been well studied. Current AHA/ASA guidelines recommend the following in patients with ischemic stroke or TIA in the setting of MI with left-ventricular thrombus or apical wall-motion abnormality[8]:

1. Treatment with warfarin (target INR, 2.5; range, 2.0-3.0) for 3 months is recommended in most patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation identified by echocardiography or another imaging modality *(class I; level of evidence C)*. Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the ACCP.
2. Treatment with warfarin (target INR, 2.5; range, 2.0-3.0) for 3 months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging modality *(class IIb; level of evidence C)*.
3. In patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation or anterior or apical wall-motion abnormalities with an LV ejection fraction < 40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA *(class IIb; level of evidence C)*.

Warfarin may not be effective in preventing calcific, myxomatous, bacterial, and fibrin-platelet emboli, and warfarin has been posited to worsen cholesterol crystal embolization.[92]

Timing of Warfarin Initiation After Embolic Stroke: Additionally the timing of the initiation of warfarin anticoagulation after embolic stroke remains controversial. Embolic brain infarcts often become hemorrhagic, and serious brain hemorrhage has occurred after anticoagulation.[93-95] Large infarcts, hypertension, large bolus doses of heparin, and excessive anticoagulation have been associated with hemorrhage. Because most hemorrhagic transformations occur within 48 hours, the recommendations of the Cerebral Embolism Task Force were to avoid early anticoagulation in patients with large infarcts or hemorrhagic transformation on repeat CT.[96,97] Studies of patients with cerebral and cerebellar hemorrhagic infarction show that, in the vast majority, the cause is embolic, with hemorrhagic infarction occuring equally with and without anticoagulation. The development of hemorrhagic infarction is rarely accompanied by clinical worsening.[98,99] Patients with hemorrhagic transformation who were continued on anticoagulants in general did not worsen. The risk of re-embolism must be balanced against the small but definite risk of important bleeding. However, if the patient has a large brain infarct, heparin should be delayed, and bolus heparin infusions should be avoided. If the risk for re-embolism is high, immediate heparinization is advisable; whereas if the risk seems low, it is prudent to delay anticoagulants for at least 48 hours. One study showed that patients with AF with embolic strokes who were treated with well-controlled heparin anticoagulation soon after stroke onset fared better than did patients treated later.[100,101]

PARADOXICAL EMBOLISM

Cryptogenic strokes, or strokes without a clear determined cause, remain a major challenge. Paradoxical embolism has been strongly implicated as one potential cause of cryptogenic stroke. Although once considered rare, emboli entering the systemic circulation through right-to-left shunting of blood are now often recognized with the advent of newer diagnostic technologies. By far the most common potential intracardiac shunt is a residual patent foramen ovale (PFO). The high frequency of PFOs in the normal adult population has made it difficult to be certain in an individual stroke patient with a PFO whether paradoxical embolism through the PFO was the cause of the stroke or whether the PFO was merely an incidental finding. Autopsy series have shown that approximately 30% of adults have a probe PFO at necropsy.[102] Echocardiographic studies have shown that PFOs are more common in patients with an undetermined cause of stroke than in those in whom another etiology has been defined.[103,104] Lechat and coworkers,[103] using TTE with contrast injection during Valsalva maneuver, demonstrated right-to-left shunting through a PFO in 56% of patients with cryptogenic stroke, in comparison to 10% of the patients in the control group. Webster and colleagues,[105] in a study of stroke patients younger than 40 years of age, found a PFO in 50% of patients with stroke using contrast echocardiography.

Neuroimaging studies are not conclusive with regard to the link between PFO and embolic stroke. However, in 1998, Steiner and colleagues[106] reported on a series of 95 patients with first stroke and who had PFOs. Those with large PFOs had more features of embolic strokes with brain imaging than did patients with small PFOs.

Review of series of patients with paradoxical embolism[107-109] through a PFO and the authors' experience allow the derivation of *five* criteria that, *when four or more are met*, establish the presence of paradoxical embolism with a high degree of certainty[6]:

1. Situations that promote thrombosis of the deep veins of the leg or pelvis (eg, long sitting in one position, such as prolonged airplane flight, or recent surgery).
2. Increased coagulability (eg, the use of oral contraceptives, presence of factor V Leiden, dehydration, and other inherited or acquired thrombophilia).
3. The sudden onset of stroke during Valsalva or other maneuvers that promote right to left shunting of blood (eg, sexual intercourse, straining at stool).
4. Pulmonary embolism within a short time before or after the neurologic ischemic event.
5. The absence of other putative causes of stroke after thorough evaluation.

But the question remains: While a PFO may have contributed to the development of an ischemic stroke, is an isolated PFO capable of causing the stroke alone? The presence of an atrial septal aneurysm along with a PFO increases the risk of stroke. Among 581 patients the stroke risk was 2.3% in patients with PFO and 15.2 % in those with both PFO and atrial septal aneyrysm.[109a] The Risk of Paradoxical Embolism (RoPE) study performed a patient-level meta-analysis of 12

cryptogenic stroke cohorts.[110,111] Among 3023 patients with cryptogenic stroke, the prevalence of PFO, and the likelihood that PFO was the cause of the stroke (the PFO-attributable fraction), correlated with the absence of vascular risk factors (ie, hypertension, diabetes, smoking, prior stroke or transient ischemic attack, older age) and the presence of a cortical (as opposed to subcortical) cryptogenic infarct on imaging.[110] Using multivariate modeling, the investigators devised the RoPE score, which estimates the probability that a PFO is either incidental or pathogenic in a patient with cryptogenic stroke.[110] High RoPE scores, as found in younger patients who lack vascular risk factors and have a cortical infarct on neuroimaging, suggest pathogenic PFOs, while low RoPE scores, as found in older patients with vascular risk factors, suggest incidental PFOs. For each RoPE score stratum, the corresponding PFO prevalence was used to estimate the PFO-attributable fraction: the probability that the index event was related to the PFO. In a subsequent analysis, *stroke recurrence was associated with the following three variables only in the high RoPE score group*: a history of prior stroke or TIA, a hypermobile interatrial septum (atrial septal aneurysm), and a small shunt.[111] The RoPE data did not include activity at onset; strokes that develop suddenly during sex, straining at stool, and Valsalva maneuvers and sudden exertion are often embolic.

In the author's opinion, the following evaluation should be done in patients with acute stroke who are also found to have PFO to attempt to ensure there are no other causes for the stroke:

1. Brain imaging: MRI of brain without contrast if possible, CT of head without contrast if obtaining an MRI is prohibitory.
2. Vascular imaging: CTA of head and neck *or* MRA of head and neck *or* Duplex of the carotid arteries and TCD of head.
3. TEE with bubble study.
4. Hypercoagulable work-up: protein C, protein S, APC resistance (if positive, test for factor V Leiden), DRVVT, cardiolipin Ab (if positive, test beta-2 glycoprotein 1 Ab), prothrombin gene mutation, antithrombin III, homocysteine
5. Other laboratory work-up: cholesterol panel, HBA1C, PT, INR, PTT, CBC, Chem7, troponin × 3, ESR. If patient is febrile or there is risk for endocarditis: blood cultures × 3.
6. ECG.
7. Holter monitor, and if negative, longer monitoring as an outpatient for occult arrhythmia.

Current treatment options for future stroke prevention in patients with PFO and cryptogenic ischemic stroke include medical therapy, open or minimally invasive cardiac surgical closure, and transcatheter closure. Before any treatment option is selected, it is again important to confirm that the stroke is indeed cryptogenic. The treating physician should exclude all other possible contributing causes to the stroke, including a coexisting hypercoagulable state and deep venous thrombosis (with or without May-Thurner syndrome).[113,114] If there is concomitant hypercoagulability or DVT, anticoagulation is the treatment of choice for these conditions as well as to prevent further ischemic stroke.

Once this has been done, with regard to medical therapies, antiplatelet therapy has always been considered reasonable for future stroke prevention in cryptogenic stroke patients with a first ischemic stroke/TIA plus an isolated PFO. In patients with a cryptogenic stroke and an atrial septal aneurysm, evidence had been insufficient to determine whether warfarin or aspirin is superior in preventing recurrent stroke or death. Warfarin is considered to be an appropriate treatment option in the subgroup of PFO/ischemic stroke patients with concomitant hypercoagulable state or venous thrombosis.

An alternative option is transcatheter PFO closure, a minimally invasive endovascular procedure during which a closure device is guided utilizing catheters to seal the PFO. Recently, transcatheter closure demonstrated a benefit compared to medical therapy for future stroke prevention. The RESPECT trial was a multicenter, prospective, randomized clinical trial designed to investigate whether percutaneous PFO closure, using the AMPLATZER PFO Occluder, is superior to current standard of care medical treatment in the prevention of recurrent embolic stroke. Investigators enrolled 980 patients (aged 18 to 60 years) with a PFO who experienced a cryptogenic stroke in the preceding 270 days. Patients were randomly assigned to receive either a PFO occluder (Amplatzer, AGA Medical, Golden Valley, MN; n = 499) or guideline-directed medication (n = 481). RESPECT represents the largest randomized trial on PFO closure ever conducted, with the longest-term follow-up, with a mean of 5 years and a duration of more than 10 years.[115]

Initial intent-to-treat analysis results revealed no significant difference in all-cause stroke between groups ($P = .16$): similar to prior PFO closure device studies. However, when strokes were restricted to cryptogenic strokes alone, Carroll and colleagues reported a 54% relative risk reduction in the PFO occlusion arm ($P = .042$), although the number of these strokes remained small (10 vs 19). Among patients under the age of 60 years, researchers found a 52% relative risk reduction in the PFO closure arm ($P = .035$). Furthermore, a 75% relative risk reduction in cryptogenic stroke was observed among PFO closure patients who had PFO characteristics of substantial shunt or atrial septal aneurysm ($P = .007$). In safety analysis, there were no cases of device erosion, embolization, or thrombosis, and no intra-procedure strokes. Additionally, the rate of atrial fibrillation was not significantly different between groups. Extended follow-up data from the RESPECT trial suggests that compared with medical management, a PFO closure device significantly decreases recurrent cryptogenic ischemic stroke in patients with PFO who had a cryptogenic stroke in the last 270 days.[115]

With regard to surgical closure of symptomatic PFO, there is no clear evidence at present that it is superior to medical or endovascular therapy for secondary stroke prevention. More recently, widespread use of intraoperative TEE during cardiac surgery has resulted in frequent discoveries of incidental asymptomatic PFOs. A recent survey by Sukernik and associates[116] suggests that a number of cardiac surgeons in the United States alter their planned procedure to include closure of the PFO. This is concerning in light of recent data published by Krasuski and coworkers,[117] who investigated the prevalence of intraoperative PFO diagnosis and the relationship that the incidental repair had on perioperative outcome and long-term survival. Surgeons were more likely to repair PFOs in patients who were younger, female, undergoing tricuspid or mitral surgery, had left atrial dilation, or with prior stroke and TIAs. Repair also tended to occur in patients with fewer comorbidities. Patients with incidental PFO were no more likely to have had a preprocedural stroke than patients without PFO. Postoperatively, the patients with an incidentally repaired PFO had 2.47 times greater odds of having an in-hospital, symptomatic postoperative stroke compared with those with unrepaired PFO (there was no difference in long-term survival).[117] These findings of increased short-term postoperative stroke risk should discourage the routine closure of incidentally detected PFO for now. Further studies to assess whether any subgroup of PFO patients may benefit from closure will be important in the future.

BRAIN HYPOPERFUSION (CARDIAC PUMP FAILURE)

After cardiopulmonary resuscitation (CPR), the heart often recovers in individuals whose brain has been irreversibly damaged by ischemic-anoxic damage.[118] Cardiologists must become very familiar with the pathology, signs, and prognosis of brain dysfunction after periods of circulatory failure.

Different brain regions have selective vulnerability to hypoxic-ischemic damage. Regions that are most remote and at the edges of major

vascular supply are more liable to sustain hypoperfusion injury. These zones are usually referred to as *border zones* or *watersheds*. The cerebral cortex and hippocampus are particularly vulnerable to injury.[119-122] In the cerebral cortex, the border zone regions are between the anterior cerebral artery (ACA) and middle cerebral artery (MCA), and between the MCA and posterior cerebral artery (PCA). The basal ganglia and thalamus are most involved if hypoxia is severe but some circulation is preserved. This situation applies most to hanging, strangulation, drowning, and carbon monoxide exposure.[123] Cerebellar neurons may also be selectively injured.[124]

When circulatory arrest is complete and abrupt, brainstem nuclei are especially vulnerable to necrosis in young humans and experimental animals.[125] When hypoxia and ischemia are especially severe, the spinal cord may also be damaged.[126,127] When cortical damage is severe and protracted, cytotoxic edema causes massive brain swelling, with cessation of blood flow and brain death.

Clinical Findings

Very severe hypoxic-ischemic damage can lead to mortal injury to the cortex and brainstem, irreversible coma, and brain death. When initially examined, such patients have no brainstem reflexes and no response to stimuli except perhaps a decerebration response. These findings do not improve, and respiratory control is absent or lost.

When cerebral cortical damage is very severe but brainstem reflexes are preserved, there is no meaningful response to the environment. Automatic facial movements such as blinking, tongue protrusion, and yawning usually persist. The eyes may rest slightly up and move from side to side. When this state does not improve, it is referred to as the *persistent vegetative state*[118,121,128,129] or *wakefulness without awareness*. Laminar cortical necrosis can cause seizures (multifocal myoclonic twitches or jerks of the facial and limb muscles), which are difficult to control with anticonvulsants.

With severe hypoperfusion ACA-MCA border zone injury, there is weakness of the arms and proximal lower extremities with preservation of face, leg, and foot movement (the "man in a barrel" syndrome). With MCA-PCA ischemia, the symptoms and signs are predominantly visual. Patients describe difficulty seeing and inability to integrate the features of large objects or scenes despite retained capacity to see small objects in some parts of their visual fields. Reading is impossible. There are features of Balint syndrome.[118,130] Apathy, inertia, and amnesia are also common. Patients cannot make new memories and have patchy, retrograde amnesia for events during and before hospitalization. This Korsakoff-type syndrome is caused by hippocampal damage and may not be fully reversible. Amnesia may be accompanied by visual abnormalities, apathy, and confusion, or may be isolated.

Prognosis

Shortly after resuscitation or arrest, patients with less severe cerebral injuries show some reactivity to the environment. Eye opening and restless limb movements develop. The eyes may fixate on objects. Noise, a flashlight, or a gentle pinch may arouse patients to react to stimuli. Soon patients awaken fully and may begin to speak. Cognitive and behavioral abnormalities may be detected after the patient awakens, depending on the degree of injury.

Prognostic signs and variables have been extensively studied.[118,131-134] The initial neurologic findings and their course are helpful in predicting outcome. Among patients who have meaningful responses to pain at 1 hour, almost all survivors have preserved intellectual function. Patients who do not respond to pain by 24 hours typically either die or remain in a vegetative state. Being comatose predicts a poor prognosis.[133,134] *Two simple observations—the presence or absence of coma and the response to pain—predict neurologic outcome very early.*[134] Recurrent myoclonus is also a poor prognostic sign.[135]

In a study in Seattle of out-of-hospital cardiac arrests, patients who did not awaken died on average 3.5 days after arrest.[136,137] Of 459 patients, 183 never awakened (40%). Among those who did awaken, 91 (33%) had persistent neurologic deficits.[136] Prognosis could be made by analysis of pupillary light reflexes, eye movements, and motor responses.[137] It is unclear whether bystander initiation of CPR is significantly related to awakening.[137,138] After in-hospital CPR, pneumonia, hypotension, renal failure, cancer, and a housebound state before hospitalization were significantly related to death in the hospital.[139]

Diagnostic Testing

Neuroimaging and other tests have proved to be relatively unhelpful in contrast to the neurologic examination.[118] CT is used to exclude other causes of coma such as brain hemorrhage. Electroencephalography is helpful in studying cortical activity in unresponsive patients. TCD may be helpful in the evaluation of brain death, but is not a requirement to determine brain death.[140-142]

Treatment

Other than maintaining adequate circulation and oxygenation, treatment has not helped improve outcome. Increased blood sugar correlates with poor outcome.[143] A multifaceted approach to therapy has been most successful.[144]

NEUROLOGIC EFFECTS OF CARDIAC DRUGS AND CARDIAC ENCEPHALOPATHY

Drugs given to patients with cardiac disease often have neurologic adverse effects.[145] Digoxin can cause visual hallucinations, yellow vision, and general confusion.[146,147] Digoxin levels need not be excessively elevated; the symptoms disappear with drug cessation. Quinidine can cause delirium, seizures, coma, vertigo, tinnitus, and visual blurring.[148] Similar toxicity has been seen with lithium. Patients may become acutely comatose while being treated with intravenous lidocaine. This effect has been associated with the accidental administration of very large doses; more common CNS effects of less extreme toxicity include sedation, irritability, and twitching. The latter may progress to seizures accompanied by respiratory depression. Amiodarone can cause ataxia, weakness, tremors, paresthesias, visual symptoms, a Parkinsonian-like syndrome, and occasionally delirium.[145] The neurological side effects with amiodarone can occur even at normal doses.

Patients with congestive heart failure often develop an encephalopathy characterized by decreased alertness, sleepiness, decrease in all intellectual functions, asterixis, and variability of alertness and cognitive functions from hour to hour.[145] These patients may not have pulmonary, liver, or renal failure or electrolyte abnormalities. This cardiac encephalopathy is probably multifactoral.[145]

NEUROLOGIC AND CEREBROVASCULAR COMPLICATIONS OF ENDOVASCULAR CARDIAC PROCEDURES AND CARDIAC SURGERY

Patients with heart disease are diagnosed, treated, and at times even cured with a variety of cardiac procedures. Although the implicit goal with any cardiac intervention (diagnostic or therapeutic) is to improve a patient's quality of life, these procedures often carry risk as well as the possibility of benefit.

ENDOVASCULAR CARDIAC DIAGNOSTIC AND THERAPEUTIC PROCEDURES

Cardiac Catheterization

Stroke and TIA are known complications of heart catheterization. In 1977, Dawson and Fischer[149] reported cerebrovascular complications in 10 of 1000 consecutive cardiac catheterizations. Nine out of 10 of these events were determined to be embolic.[149,150] Similarly, Mendez Dominguez and colleagues[151] reported thromboembolic neurologic complications in seven patients in a series of 2178 consecutive cardiac catheterizations. In all cases, the cerebrovascular impairment occurred either during or within several minutes following the cardiac catheterization. All strokes were confirmed with CT or MRI, and the clinical profile in most cases supported an embolic mechanism.[151] Central retinal artery occlusion has been reported in association with cardiac catheterization.[152] More recently, Liu and coworkers[153] reported six ischemic strokes and one intracerebral hemorrhage in a series of 3648 cardiac catheterizations in children. In this study, the suspected catheterization-related stroke mechanisms included intracranial hemorrhage caused by intraprocedure anticoagulation as well as cerebral embolism from local clot.[153] Other potential mechanisms for cerebrovascular events during cardiac angiography may include catheter tip thromboembolism, atherosclerotic plaque or cholesterol embolism, air emboli, arterial vasospasm, and/or hypotension.[150,154-157]

Coronary Artery Angioplasty and Stenting

The stroke rate in patients undergoing percutaneous coronary interventions for both stable and unstable coronary artery disease (including angioplasty for acute MI) has been reported to be between 0% and 4%.[158-165] A combined analysis of data from four double-blind, placebo-controlled, randomized trials (EPIC, CAPTURE, EPILOG, and EPISTENT) conducted between 1991 and 1997 assessed 8555 patients undergoing various percutaneous coronary interventions. Among the 8555 patients, there were 33 strokes in 31 patients (0.36%) within 30 days. Stroke occurred in 9 (0.29%) of 3079 patients receiving percutaneous coronary interventions alone; six strokes were ischemic, and three were hemorrhagic. Stroke was diagnosed in 22 (0.41%) of 5476 patients who underwent percutaneous treatment in conjunction with abciximab treatment, of which there were 13 ischemic strokes and 9 hemorrhages.[158-163]

Galbreath and colleagues[164] reported a 0.2% rate of focal central neurologic complication in their series of 1968 percutaneous transluminal coronary angioplasties; three were ischemic strokes, and one was a TIA. The mechanism in these cases was considered embolic in three patients; one patient had air inadvertently injected through the guide catheter, and two had events after the ascending aorta was scraped with the guide catheter in search of a graft ostium. The remaining patient had an event during a period of hypotension.[164]

Electrophysiologic Procedures and Electrical Cardioversion

Thromboembolic stroke can be a complication of cardiac electrophysiologic procedures, including radiofrequency catheter ablation of arrhythmia. Multicenter data are limited; however, the stroke risk appears to be < 2%.[150,166-169] Additionally, electrical cardioversion may be used in the treatment of AF and atrial flutter. Stroke caused by direct current cardioversion has been estimated to occur in 1.3% of cardioverted patients.[170] Anticoagulation before and after cardioversion lowers the risk of embolism.[150,170]

Percutaneous Closure of the Left Atrial Appendage

In patients with nonvalvular AF, embolic stroke is thought to be associated with left atrial appendage (LAA) thrombi. One multicenter, randomized, noninferiority trial found that percutaneous closure of the LAA was noninferior to warfarin treatment. In the future, closure of the LAA might provide an alternative to chronic warfarin for stroke prevention in patients with nonvalvular AF.[171] The PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) study investigated percutaneous closure of the LAA in patients who were not warfarin candidates. At the 5-year follow-up, the annualized stroke/TIA rate was 3.8% per year, which was lower than predicted.[172] More recent trials such as PROTECT AF found that after 3.8 years of follow-up among patients with nonvalvular AF at elevated risk for stroke, percutaneous LAA closure met criteria for both noninferiority and superiority, compared with warfarin, for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality.[173]

Intra-Aortic Balloon Pump

Intra-aortic balloon pumps (IABPs) are used in patients with severe left ventricular failure or cardiogenic shock. The IABP is inserted into the patient's midthoracic aorta to maintain adequate perfusion. Spinal cord infarcts can occur in patients with IABPs caused by local thromboembolism, aortic dissection, aortic atherosclerotic plaque rupture, or local hypoperfusion.[150,174]

Percutaneous Valvuloplasty

Surgical treatment, specifically valve replacement, are generally the treatment of choice for both aortic and mitral valve diseases in patients who are at acceptable risk for surgery. Aortic valvuloplasty, at present, provides only transient and modest benefit for aortic stenosis, with a significant risk of stroke and vascular injury. However, it can stabilize patients who require additional attention prior to undergoing surgery.[175] Additionally, over the last 5 years, percutaneous approaches to valve implantation have improved. Technical and device issues are being refined, and some percutaneous treatments are showing promise in ongoing clinical trials.[176] Percutaneous balloon aortic and mitral valvuloplasties have been complicated by stroke.[150,177-180] Sudden coma has also been reported after percutaneous balloon mitral valvuloplasty.[181] With regard to when the neurologic events occur, the 1988 series of Letac and coworkers[177] of 218 patients undergoing transcutaneous balloon aortic valvuloplasty indicates that one stroke occurred during the intraprocedure period, whereas three additional strokes occurred during the postprocedure period.[150,177-180]

Transcatheter Aortic Valve Replacement

Transcatheter aortic valve replacement (TAVR) is a minimally invasive catheter-based surgical procedure for patients with severe symptomatic aortic stenosis, who are either high-risk or inoperable candidates for traditional cardiac surgery. Samim and colleagues (2015) investigated the occurrence and distribution of TAVR-related silent acute ischemic brain lesions using diffusion-weighted magnetic resonance imaging (DWI). Clinically silent cerebral infarcts occurred in 90% of patients following TAVR, most of which were small (< 20 μL) and located in the cortical regions of the cerebral hemispheres: 47% of lesions were detected in the cortical regions, 35% in the subcortical regions, and 18% in the cerebellum or brainstem. An independent association was also found between age, hyperlipidaemia, and balloon postdilatation and the number of post-TAVR ischemic brain lesions. Only peak transaortic gradient was independently associated with postprocedural total infarct volume.[182]

The Placement of Aortic Transcatheter Valves (PARTNER) B trial found the rate of symptomatic stroke at 1 year among TAVR patients to be double that of patients assigned to medical therapy alone.[183] Initial presentation of the data caused concern; however, follow-up data

from the same trial have demonstrated that the risk of stroke or TIA was similar between those randomized to TAVR versus surgical aotic valve replacement (AVR): 15.9% in the TAVR group compared to 14% in the surgical AVR group.[184] It is important to note that the incidence of symptomatic stroke post-TAVR is improving over time. A more recently published registry with 12,182 patients noted the stroke rate at 1 year to currently be 4.1%.[185] The mechanism for stroke in TAVR is thought to be showering of atheroemboli or calcific material during balloon predilation, valve positioning, or valve implantation.[186]

Decreasing the TAVR risk of stroke in the future may include improving risk prediction, valve system technology, periprocedural medical therapy, and potentially through embolic protection devices.[186] The Embrella embolic deflection device for cerebral protection during TAVR was assessed in one small series of 15 patients (and compared to 37 patients who had previously undergone TAVR without a protection device). Use of this device actually was noted to increase the number of cerebral ischemic lesions on MR Imaging, but there was a significant reduction in single lesion volume as well as an absense of large total infarct volumes.[187] Whether this reduction in lesion size correlates to improved neurological outcomes is as yet uncertain. Additional embolic protection devices have been developed, with clinical trials currently under way.[186]

CARDIOVASCULAR SURGERY

Every year, an estimated 1 million patients undergo cardiac surgery throughout the world. Coronary artery bypass graft (CABG) surgery is the most common major cardiovascular operation performed.

The frequency of abnormalities of intellectual function and behavior after cardiac surgery is high.[188] Preoperative diagnoses of diabetes, history of prior stroke, older age, female sex, smoking, hypertension, left main coronary disease, mild renal impairment (defined as serum creatinine 1.47-2.25 mg/dL), and high-sensitivity preoperative C-reactive protein (defined as high-sensitivity C-reactive protein concentration ≥ 3.3 mg/L) have all been identified to increase perioperative stroke risk.[189-192] Additionally, preoperative stroke and TIA are also risk factors for in-hospital mortality.[191]

Bucerius et al's prospective data on 16,184 consecutive patients indicate that the cerebrovascular risk depends on the procedure performed.[193] In that study, the overall incidence of stroke was 4.6% and varied between surgical procedures (CABG 3.8%; beating-heart CABG 1.9%; aortic valve surgery 4.8%; mitral valve surgery 8.8%; double or triple valve surgery 9.7%; CABG and valve surgery 7.4%). Additional studies have also estimated stroke risk for isolated CABG range as less than 3.8%.[193-195] A particular patient's risk of perioperative stroke can be estimated using the Society of Thoracic Surgeons 2008 cardiac surgery risk models, which include outcomes for stroke, as well as deep sternal wound infection, reoperation, prolonged ventilation, and renal failure, among other morbidities. Several variables were forced into each model to ensure face validity (eg, the permanent stroke model includes AF as a variable).[196-198]

Early reported studies suggested a decrease in postoperative stroke rates in patients undergoing off-pump CABG compared with patients undergoing the traditional on-pump operation, but conflicts in the literature do exist.[199-203] One potential explanation for the discrepancy is that the temporal pattern of stroke after CABG was not distinguished in all studies. One single-center study of 2516 consecutive patients has noted that off-pump CABG reduced the incidence of early postoperative stroke (symptoms noted just after emergence of anesthesia). However, the risk of delayed stroke (normal neurologically emerging from anesthesia, but symptoms presenting within 30 days after surgery) was no different between the on- and off-pump CABG patients.[203] Perhaps the difference in the early stroke etiology between off- and on-pump CABG could be explained by the difference in aortic clamp use between these CABG procedures.

Another reason for the discrepancies in data may be that many of the above studies also did not differentiate between clampless and partial clamp off-pump techniques. One study of 700 consecutive patients undergoing multiple-vessel off-pump CABG demonstrated a decreased incidence of stroke (0.2% vs 2.2%) in the aortic no-touch group. Additionally, logistic regression identified partial aortic clamping as the only independent predictor of stroke, increasing this risk 28-fold.[204] Interestingly (and perhaps also a result of the difference in clamp use between on- and off-pump CABG procedures), one study also found that off-pump CABG provided a decreased risk of stroke and mortality advantages, especially for women.[202]

More recently in 2013, a larger trial by Lamy and colleagues reported effects of off-pump versus on-pump CABG at 1 year. The CORONARY (CABG Off or On Pump Revascularization Study) trial enrolled 4752 patients, randomly assigning them to on-pump versus off-pump CABG. Stroke rates did not differ significantly between the two groups. Quality of life and cognitive function were assessed at 30 days and 1 year. There was no significant difference in either of these two measures at 1 year.[205]

In one multicenter study, the incidence of stroke plus severe intellectual dysfunction from CABG has been reported to be 6%.[206] With regard to combined procedures, one multicenter investigation assessing 273 patients undergoing combined CABG and left-sided cardiac procedure (such as aortic or mitral valve replacement) estimated that 15.8% of patients had neurologic complications (8.5% with stroke or TIA and 7.3% with new intellectual deterioration).[207] This combined procedure appears to carry a higher stroke risk than CABG performed in isolation.

It is unclear whether minimally invasive cardiac surgical procedures may potentially have a lessened stroke risk because further data are needed. One study suggests that minimally invasive CABG may lessen the risk of major adverse cerebrovascular and cardiac events compared with traditional off-pump CABG.[208] Another center's result with direct-access, minimally invasive mitral valve surgery in 106 patients demonstrated a low rate of stroke and TIA, with a total of 0.28% of patients having either stroke or TIA. However, a second center's results with minimally invasive, reoperative, isolated valve surgery did not show a lower stroke rate compared with patients undergoing sternotomy.[209,210]

Overall, in prospective studies, transient complications have been noted in 61% of cardiac surgery patients.[211] In one series in CABG patients, 16.8% had stroke or encephalopathy postoperatively; the encephalopathies usually cleared, and only 2% of patients had severe strokes.[212] The potential mechanisms of cerebral impairment in the cardiac surgery population will be explored in the following sections.

Atherothrombotic, Hemodynamically Mediated Brain Infarcts

An estimated 12% of patients requiring CABG also have significant carotid artery disease.[209] Whether or not symptomatic of carotid atherosclerosis, patients with high-grade carotid artery stenosis undergoing CABG surgery face a higher risk of stroke than patients without carotid disease, but most strokes are mechanistically unrelated to carotid disease.[213] One major concern regarding cardiac surgery patients has been whether the hemodynamic stress of heart surgery leads to underperfusion of areas supplied by already stenotic or occluded arteries, resulting in brain infarcts. This concern underlies neck auscultation for bruits, ultrasound carotid artery testing, and cerebral angiography prior to CABG. However, hemodynamically induced infarction related to preexisting atherosclerotic occlusive cervicocranial arterial disease is a rare complication of heart surgery. Asymptomatic patients with

carotid bruits have a very low rate of stroke after elective surgery.[214,215] However, the risk of perioperative stroke does increase with increasing severity of carotid stenosis.[190,216,217] In a retrospective study of CABG patients with known carotid disease, ipsilateral strokes occurred in 1.1% of arteries with 50% to 90% stenosis, in 6.2% of arteries with > 90% stenosis, and in only 2% of vessels with carotid occlusion.[216,217]

Uncertainty exists about whether carotid endarterectomy (CEA) performed simultaneous or prior to CABG improves perioperative stroke risk.[213] Stroke rates vary greatly in those undergoing combined CEA-CABG as opposed to staged procedures.[213,218] Limited published data of 324 patients suggested that early outcomes after synchronous CEA plus off-pump CABG were better than those following staged or synchronous CEA plus on-pump CABG. It is unclear whether these findings were caused by publication bias, case selection, or, as we discussed earlier in the chapter, the fact that the aorta was not manipulated or cannulated.[219]

Definitive management of combined cervicocerebral and coronary artery disease awaits the outcome of clinical trials. One systematic review of 97 published studies of staged versus synchronous operations found no significant difference in outcomes between these two surgical groups. Unfortunately in this study, there were no comparable data for patients with combined carotid stenosis and cardiac disease *not* undergoing either staged or synchronous surgery.[220] A different retrospective study of 4335 patients undergoing cardiac surgery found that undergoing a combined CEA-CABG increased the risk of postoperative stroke compared with patients with similar degrees of carotid stenosis who underwent CABG without a carotid revascularization.[221]

Carotid artery stenting (CAS) has been recently introduced as an alternative revascularization modality in high-risk patients. Although some studies suggest that endovascular CAS for both symptomatic and asymptomatic carotid artery disease prior to CABG is safe and without an increased risk of stroke, conflicts again arise in the literature.[222-226] Whether CAS should be performed prior to CABG is still a point of debate at this time.

Most studies have relied on clinical localization of focal deficits and inference about their mechanisms. A neuroradiology study reviewed neuroimaging results from 30 patients with acute strokes in relation to CABG.[227] Only one had evidence of a hemodynamic atherostenotic mechanism, which supports the data suggesting that hemodynamically induced infarction during cardiac surgery is rare. Embolism arising from cardiac and aortic sources is much more common than atherothrombotic infarcts and is of a much greater concern.[182]

Brain Embolism

One point against a hemodynamic or hypoperfusion cause of many strokes is their timing. It appears that strokes may occur more frequently *after* recovery from the anesthetic.[205,228,229] If the mechanism of stroke were hemodynamic, the major circulatory stress would be intraoperative and patients would at least awaken from anesthesia with the deficit. In two studies in which the authors record the timing of coronary artery bypass surgery–related strokes, only 16%[228] and 17%[229] of patients had deficits noted immediately postoperatively. The distribution of infarcts and their multiplicity on neuroimaging scans were most consistent with embolism. Embolic infarcts may involve either the anterior or the posterior circulation.[182,213,227,228] In one series of postoperative, posterior circulation strokes, most were embolic and followed cardiac surgery.[229]

In cardiac surgery patients, the preponderance of evidence suggests that macroemboli (> 200 μm in diameter) and microemboli are responsible for most neurologic complications.[207,213,220,230,231] Macroemboli (associated with atherosclerotic plaque disruption or rupture) are believed to precipitate focal deficits, whereas particulate microemboli (white blood cell and platelet aggregates, fat, or air) may be implicated in more subtle diffuse cognitive dysfunction.[207,232]

Emboli may arise from preexisting cardiac abnormalities (such as hypofunctioning ventricles, dilated atria, and aortic atheromas) or from postoperative arrhythmias.[172] Evidence links operative and postoperative embolism to aortic ulcerative atherosclerotic lesions. Cross-clamping of the ascending aorta and aortotomy liberate cholesterol or calcific plaque debris.[182,233] Data from a series of 2641 consecutive cardiac surgery patients showed that left-body symptoms (right hemispheric stroke) were twice as common as right-body symptoms, suggesting that aortic manipulation and anatomic mechanisms in the aortic arch were more likely to cause cerebrovascular accidents than effects from aortic cannula stream jets.[234] Figure 94–1 shows the aorta of a patient who died having never awakened after CABG. Figure 94–2 shows cholesterol crystals and other debris trapped within a filter placed in the aorta at the time of unclamping.

Given that atherosclerosis of the ascending aorta is a significant risk for perioperative stroke,[235] it was postulated that avoiding direct manipulation of this area may improve neurologic outcome postoperatively. Epiaortic ultrasound scanning is thought to be superior to both manual palpation of the ascending aorta and TEE in detecting atherosclerosis, particularly noncalcified plaque. It has led to modifications in surgical management in patients undergoing CABG, such as modification of cannulation, clamping, or anastomotic technique, and temperature management.[236-238] One study suggested that the application of aortic clamping or cardiopulmonary bypass was not a risk when the ascending aorta was evaluated using epiaortic ultrasound.[236] A second study of 6051 patients also noted that the overall stroke risk was lower in patients who had intraoperative epiaortic ultrasound, compared with all patients undergoing cardiac surgical procedures.[239] Why the stroke risk is lower is not yet clear; a separate study found that the use of this imaging technique did not lead to a reduced number of TCD ultrasound–detected cerebral microemboli before or during bypass.[237] One might theorize that this technique reduces macroemboli and not microemboli.

In another series in which embolic signals were monitored during CABG surgery, 34% of signals were detected as the aortic cross clamps were removed, and another 24% were detected as aortic partial occlusion clamps were removed.[233] The number of microemboli detected correlated with abnormalities of cognitive function after surgery.[182,240] Figure 94–3 shows microemboli within the aorta shown by TEE after release of aortic clamps. Figures 94–4 and 94–5 are TCD recordings during manipulation of the aorta and after release of aortic clamps.

In a similar study within a Chinese population of 227 patients, off-pump CABG surgery was noted to significantly decrease the number of cerebral microembolic events detected by TCD. This also could be explained by the aortic clamping technique required for traditional CABG. Interestingly, though, this study also found that the incidence of postoperative cognitive dysfunction was not decreased by off-pump CABG, which suggests that microemboli may not be the responsible culprit for this phenomenon.[241]

Thromboembolic infarction often occurs in the days following surgery when cessation of anticoagulation is necessary. Postoperative activation of coagulation factors in cardiac surgery patients can promote hypercoagulability. Disseminated intravascular coagulation, acquired antithrombin III deficiency, and acquired protein C deficiencies are not uncommon. Activation of the coagulation-fibrinolytic system can persist for 2 months after cardiopulmonary bypass surgery.[242,243] In some patients, hypercoagulability related to surgery can precipitate occlusive thrombosis in atherostenotic arteries, and the newly formed thrombus can lead to intra-arterial embolism. Cardiac, aortic, and

intra-arterial embolism accounts for the vast majority of cardiac surgery–related focal neurologic deficits.

With regard to interventional treatment of cardiac surgery patients with an acute embolic stroke, unfortunately, given their recent surgery, these patients are not candidates to receive intravenous tissue plasminogen activator (t-PA). However, these patients may still be candidates for endovascular acute stroke treatment. The MR CLEAN trial recently demonstrated that patients with acute ischemic stroke caused by intracranial large vessel occlusion clearly benefit from intra-arterial therapy.[244] In this trial, intra-arterial therapy consisted of intra-arterial thrombolysis with alteplase or urokinase, mechanical treatment or both. Mechanical treatment refers to retraction, aspiration, sonolysis, or use of a retrievable stent (stent-retriever). Several other positive trial results confirmed these findings at the International Stroke Conference in 2015.

There was still uncertainty about the effect of intra-arterial therapy in patients with contraindications for treatment with intravenous alteplase treatment (such as the cardiac surgery population). A recent 2016 MR CLEAN subgroup analysis demonstrated that in those patients with acute ischemic anterior circulation stroke caused by intracranial large vessel occlusion, who have contraindications for intravenous alteplase, intra-arterial treatment is not less effective or less safe than in patients who receive the treatment after intravenous alteplase.[245]

Postoperative Encephalopathy: Microemboli and Other Causes

Gilman[246] described a diffuse CNS disorder following open heart surgery (characterized by altered levels of consciousness and activity and confusion) that is now referred to as *encephalopathy*. Clinical and imaging studies usually do not show important focal neurologic signs or large focal infarcts. The incidence of encephalopathy varies. In one series, 57 (3.4%) of 1669 CABG patients had postoperative mental state changes including delirium and encephalopathy.[247] In the Cleveland Clinic prospective series, 11.6% of patients were encephalopathic on the fourth postoperative day.[200] Additionally, the incidence of encephalopathy also varies depending on the cardiac procedure itself. Compared with conventional on-pump CABG, off-pump CABG has been shown to reduce postoperative neuropsychological dysfunction in elderly patients with severe systemic atherosclerosis.[248]

Encephalopathy has multiple causes. A necropsy study of patients who died after cardiopulmonary bypass or angiography has awakened interest in this subject.[249] Focal, small capillary and arteriolar dilatations (SCADs) were commonly found in the brain.[249] Approximately one-half of the SCADs show birefringent crystalline material within the dilated capillaries. SCADs could, at least in part, explain the decreased cerebral blood flow found during cardiopulmonary bypass. SCADs are iatrogenically generated microemboli, but as yet, their origin is unknown. Their morphology is most consistent with air or fat.[249]

Other causes of encephalopathy are common. Diffuse hypoxic-ischemic insults from hypotension and hypoperfusion do occur. Postoperative cognitive dysfunction at 1 week after surgery has been associated with increasing age and shorter duration of hospital stay.[241] Cognitive dysfunction at 3 months after CABG has also been associated with increasing age and with diabetes mellitus.[241] Lastly, drugs are a common cause of encephalopathy in the postoperative period. Particularly important are haloperidol, narcotics, and sedatives. Morphine is sometimes used heavily intraoperatively, and opiate withdrawal with restlessness and hyperactivity can result. Agitation and restlessness are often early signs of organic encephalopathy and may lead to the administration of haloperidol, barbiturates, phenothiazines, or benzodiazepines for calming and sedation. When these drugs wear off and the patient begins to awaken, agitation may occur, and more sedatives may be given. Haloperidol causes rigidity, restlessness, agitation, hallucinations, and confusion. In experimental animals, haloperidol delays recovery from strokes by months, and its use is not advised.[250,251] Phenothiazines and sedatives are also problematic; *in general, use of sedatives and narcotics should be minimized, and they should be tapered as soon as possible.*

Postoperative Intracranial Hemorrhage

Intracerebral or subarachnoid hemorrhages have occasionally been reported after cardiac surgery, most commonly in children who had repair of congenital heart disease[252] or in cardiac transplantation patients.[253] The postulated mechanism involves an abrupt increase in brain blood flow with rupture of small intracranial arteries unprepared for the new load. Usually, there is a prolonged period when cardiac output is low, and this output is suddenly increased by the surgery. Abrupt increases in brain blood flow or pressure in other situations have also been associated with intracerebral hemorrhage.[254]

Stroke Mimics: Postoperative Peripheral Nerve Complications

Brachial plexus and peripheral nerve lesions frequently develop after cardiac surgery and can be confused with CNS complications.[255] In one series, new peripheral nervous system deficits occurred in 13% of patients.[255] The most common deficit is a unilateral brachial plexopathy characterized by shoulder pain and usually weakness and numbness of one hand. It is probably caused by either sternal retraction or positioning of the arm during surgery, with traction on the lower trunk of the brachial plexus. Ulnar, peroneal, and saphenous nerve injuries are also common and are also related to positioning. Diaphragmatic and vocal cord paralyses are likely related to local effects of the cardiac surgery on the recurrent laryngeal and phrenic nerves. Postoperative Horner syndrome may be caused by manipulation of the sympathetic chain, but carotid dissection (particularly in surgical patients undergoing aortic dissection repair) should be excluded.

CARDIAC EFFECTS OF BRAIN LESIONS

Information is beginning to emerge on cardiac muscle changes (myocytolysis), arrhythmias, pulmonary edema, electrocardiogram (ECG) changes, and sudden death caused by brain disease and sudden emotional stresses.[256,257]

CARDIAC LESIONS

The two most common lesions found in the hearts of patients dying with acute CNS lesions are patchy regions of myocardial necrosis and subendocardial hemorrhage. The abnormalities range from eosinophilic staining of cells with preserved striations to transformation of myocardial cells into dense eosinophilic contraction bands. These changes have been referred to as *myocytolysis*.[256,257] One study found a high incidence of myocardial abnormalities in patients dying of brain lesions that increase intracranial pressure rapidly.[258] Stress-related release of catecholamines and possibly corticosteroids may be responsible, in part, for the cardiac lesions found in patients with CNS lesions.[256,259-264] Adrenoreceptor polymorphisms can explain increased catecholamine sensitivity and thus increased risk of cardiac injury in patients with subarachnoid hemorrhage and acute ischemic stroke.[265]

ELECTROCARDIOGRAPHIC AND ENZYME CHANGES

In stroke patients, especially those with subarachnoid hemorrhage (SAH), ECGs may show a prolonged QT interval; giant, wide, roller coaster–inverted T waves; and U waves.[266] These changes are often called *cerebral T waves*. Patients with stroke undergoing continuous

ECG monitoring have a high incidence of T-wave and ST-segment changes, various arrhythmias, and cardiac enzyme abnormalities. ECG changes may include a prolonged QT interval, depressed ST segments, flat or inverted T waves, and U waves.[256,266-269] Less often, tall, peaked T waves and elevated ST segments are noted. Myocardial enzyme release and echocardiographic regional wall motion abnormalities are associated with impaired left ventricular performance after SAH. In severely affected patients, reduction of cardiac output may elevate the risk of vasospasm-induced cerebral ischemia.[270] Cardiac and skeletal muscle enzymes, including the MB isoenzyme of creatine kinase (MB-CK), are often abnormal in stroke patients.[269,271-274] During days 4 to 7 after stroke, there is usually a slow increase and later decrease in serum MB-CK levels, a pattern quite different from that found in acute MI; the temporal pattern of cardiac isoenzyme release is more compatible with smoldering low-grade necrosis, such as patchy, focal myocytolysis.[275,271] The ST-segment and T-wave abnormalities and cardiac arrhythmias correlate significantly with increased levels of MB-CK in stroke patients.[275]

ARRHYTHMIAS

Various cardiac arrhythmias have been found in stroke patients, most frequently sinus bradycardia and tachycardia and premature ventricular contractions.[256,267-269] Some arrhythmias are manifestations of primary cardiac problems, but others are undoubtedly secondary to the brain lesions. The incidence of sinus tachycardia and bradycardia is maximal on the first day after intracerebral hemorrhage.[274] Ventricular bigeminy, atrioventricular dissociation and block, ventricular tachycardia, AF, and bundle-branch blocks are found less often.[276] Arrhythmias are more common in patients who have primary brainstem lesions or brainstem compression.

ECHOCARDIOGRAPHIC CHANGES

Takotsubo cardiomyopathy is also known as *broken heart syndrome*, as well as *transient left ventricular apical ballooning*. The name *takotsubo* cardiomyopathy was initially coined because the shape of the end-systolic left ventriculogram was thought to resemble an octopus catcher used in Japan.[277,278] It has been found after severe emotional stress, especially in postmenopausal women, and has been identified in both SAH and ischemic stroke patients.[277,279] In ischemic stroke patients, it occurs soon after stroke onset, is commonly asymptomatic, and is associated with insular damage.[280]

Echocardiography can show a hyperkinetic basal region and an akinetic apical half of the ventricle, traditionally in the setting of minimal cardiac enzyme release and normal coronary arteries on angiography. However, there are actually multiple patterns of takotsubo.[277-279]

Stimulation of the limbic system, including the insula, can result in marked sympathetic activation.[281] With this unifying pathophysiology of excessive sympathetic discharge, the broken heart syndrome may represent a variant of the regional wall motion abnormality phenomenon associated with SAH.[282] Prognosis is generally very good, with full recovery in most patients; however, there may be increased morbidity in patients with SAH.[282] Thus, it may be reasonable to consider TTE in SAH patients with ECG abnormalities.[282]

NEUROGENIC PULMONARY EDEMA

Acute pulmonary edema may complicate strokes, especially SAH, subdural hemorrhage, primary spinal cord hemorrhage, and posterior circulation ischemia and/or hemorrhage.[275,283-285] Pulmonary edema has been found in 70% of patients with fatal SAH and correlates with the development of increased intracranial pressure.[286] The pulmonary edema can develop despite normal cardiac function.[275,287] The most relevant imaging method is the chest x-ray, where diffuse hyperintensive infiltrates in both lungs are apparent. Although the levels of some substances such as brain natriuretic peptide, blood C-reactive protein, and interleukin-6 are increased, unfortunately, none of these tests is a specific marker for neurogenic pulmonary edema.[284,285]

SUDDEN DEATH

Sudden death associated with stressful situations, including so-called *voodoo death*, must involve CNS mechanisms.[264,288-293] However, the role that the CNS plays in precipitating sudden cardiac death is still uncertain. In particular, establishing a cause-effect relationship in the setting of a stroke has been complicated because these patients usually have risk factors for coronary disease as well.[294] However, it is notable that patients with lateral medullary and lateral pontine infarcts die unexpectedly and also have a high incidence of autonomic dysregulation (eg, labile blood pressure, tachycardia).

ECG alterations predictive of sudden death, such as QT prolongation, late ventricular potentials, premature ventricular beats, nonsustained ventricular tachycardia, and the R on T phenomenon, have been described in patients with SAH, intracerebral hemorrhage, and ischemic stroke. Additionally, a higher incidence of ventricular arrhythmias, particularly ventricular fibrillation (the presumed mechanism of sudden death), has been noted in acute stroke patients.[294-296] Ventricular fibrillation can be reliably elicited by stimulation of cardiac sympathetic nerves in both the normal and the ischemic heart.[292] Postmortem analysis of patients who died suddenly and without any evidence of coronary disease often shows myocytolysis and myofibrillar degeneration (which is observed also in experimental models of hearts subjected to sympathetic overstimulation).[294,297] Sudden vagotonic stimulation can cause bradycardia and cardiac standstill; however, the effects of vagal stimulation on the development of ventricular arrhythmias are uncertain.[292]

COEXISTENT VASCULAR DISEASES AFFECTING BOTH HEART AND BRAIN

ATHEROSCLEROSIS

The most common and important vascular disease that affects both the brain and the heart is atherosclerosis. The most frequent cause of death in stroke patients is coronary artery disease,[290] and extra- and intracranial arterial atherosclerosis is common in patients with coronary artery disease.[291]

Pathology and Predominant Sites of Disease

In white men, the predominant atherosclerotic lesions involve the origins of the internal carotid artery (ICA) and the vertebral artery (VA) origins in the neck.[45,298-300] Fatty streaks and flat plaques first affect the posterior wall of the common carotid artery (CCA).[301,302] Atherosclerotic plaques at this site do not differ from plaques in the aorta or coronary arteries. At first, plaques expand gradually and encroach on the lumen of the ICA and sometimes the CCA. Atheromatous plaques often develop concurrently at the VA origin or spread from the parent subclavian artery to involve the VA origin.[44,303] When plaques reach a critical size, they affect turbulence, flow, and motion of the arteries, causing complications to develop within the plaques. Cracking, ulcerations, and mural thrombi develop, and the overlying endothelium is damaged with the development of occlusive thrombi.[304] Fresh thrombi loosely adherent to vascular walls rapidly propagate and embolize. Because the ICA has no nuchal branches, the clot often propagates cranially. In the initial 2 to 3 weeks after the development of an occlusive

thrombus, the clot gradually organizes and is much less likely to propagate or embolize. The reduction in cranial blood flow caused by severe stenosis or occlusion of the ICA or VA stimulates development of collateral circulation that usually becomes adequate.

Figure 94–6 shows diagrammatically the sites of predilection for development of atherosclerosis in the cervicocranial circulation. Note the concentration of these sites at branch points and flow dividers. There are important race and sex differences in the distribution of cerebral atherosclerosis.[305-308] White men usually develop lesions of the ICA and VA origins. Patients with ICA-origin disease have a high frequency of hypercholesterolemia, coronary artery disease, and peripheral vascular occlusive disease. Blacks and individuals of Chinese, Japanese, and Thai ancestry have a much higher incidence of intracranial occlusive disease and a rather low frequency of extracranial disease.[305-309] Intracranial disease is more prevalent in women and diabetics. Interestingly, patients with intracranial occlusive disease do not have a high incidence of coronary or peripheral vascular occlusive disease.

Mechanisms of Ischemia

Ischemia in patients with atherosclerotic occlusive lesions is caused by two different mechanisms: hypoperfusion and embolism.[45,310,311] Hypoperfusion develops only when a critical reduction in luminal diameter causes reduced distal perfusion. When flow is reduced slowly, the brain vasculature has a remarkable capacity to develop collateral circulation. Patients with severe ICA-origin occlusive disease can remain asymptomatic despite marked decrease in blood flow.[312,313] Even when vascular occlusion is abrupt—as in tying neck arteries to treat brain aneurysms—surprisingly few patients develop persistent brain ischemia. In most patients, within a few days or at most 2 weeks following an arterial occlusion, collateral circulation stabilizes.

Intra-arterial embolism from atherosclerotic lesions is probably a much more frequent and important cause of brain infarction than hypoperfusion. However, decreased perfusion probably limits clearance (washout) of emboli.[311] In patients with anterior circulation infarcts, angiography shows a very high frequency of intra-arterial intracranial emboli distal to an ICA thrombosis.[314] These emboli most often involve the MCA and its branches. If angiography is repeated or performed later than 48 hours after stroke, MCA occlusion is usually not present.[29,45] Intra-arterial emboli often fragment and move distally. Intra-arterial embolism is also common in the posterior circulation, where the most common donor sites are the VA origin and intracranial VA.[315]

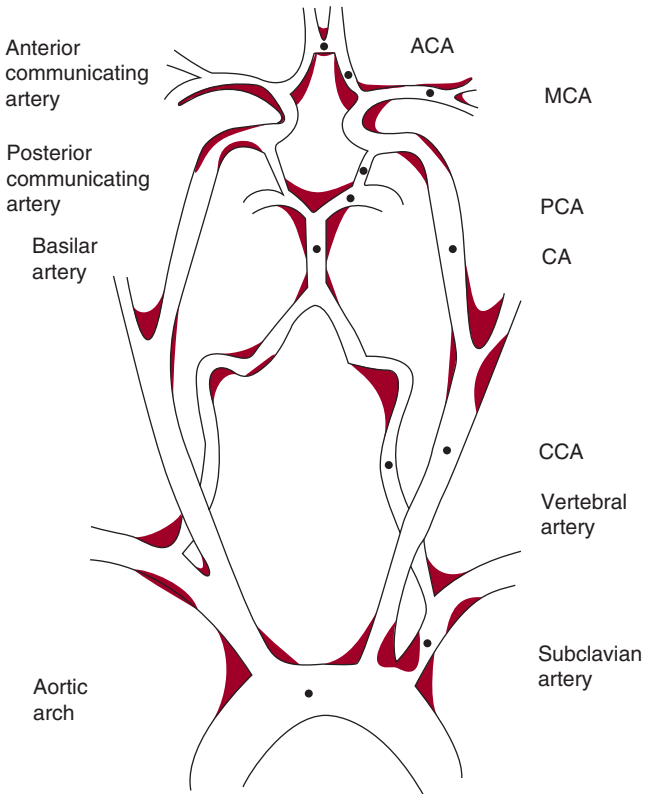

FIGURE 94–6. Sites of predilection for atherosclerotic narrowing; dark areas represent plaques. ACA, anterior cerebral artery; CA, carotid artery; CCA, common carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery. Reproduced with permission from Caplan LR: *Stroke: A Clinical Approach*, 3rd ed. Boston: Butterworth-Heinemann; 2000.

Clinical Findings

Many patients with atherosclerotic occlusive disease are asymptomatic. The most frequent symptoms of hypoperfusion or embolism are headache, TIAs, and focal neurologic signs from brain infarction. Headaches are caused by vascular distension or brain swelling secondary to infarction. Unaccustomed headaches often precede strokes.[45,316] TIAs are caused by hypoperfusion or intra-arterial emboli. Frequent, very brief stereotyped TIAs precipitated by postural changes, also known as *limb-shaking TIA*, can suggest a hemodynamic mechanism. In contrast, emboli cause longer, less frequent attacks.[310,317] In many patients with clinical TIAs (spells < 24 hours in duration with no lasting symptoms or signs), neuroimaging tests show brain infarcts.[318,319]

Neurologic symptoms and signs depend on the region of brain that is ischemic. Table 94–2 outlines the most frequent clinical patterns resulting from occlusions of the major extracranial and intracranial arteries.[45,300]

TABLE 94–2. Common Signs in Cerebrovascular Occlusive Disease at Various Sites

ICA origin	Ipsilateral transient monocular blindness; MCA and ACA signs
ICA siphon (proximal to ophthalmic artery)	Same as ICA origin
ICA siphon (distal to ophthalmic artery)	MCA and ACA signs
ACA	Contralateral weakness of the lower limb and shoulder shrug
MCA	Contralateral motor, sensory, and visual loss
	Left: Aphasia
	Right: Neglect of left space, lack of awareness of deficit, apathy, impersistence
AChA	Contralateral motor, sensory, and visual loss, usually without cognitive changes
Subclavian artery (proximal to VA)	Lack of arm stamina, cool hand, transient dizziness, veering, diplopia
VA origin	Same as subclavian, but no ipsilateral arm or hand findings
VA intracranially	Lateral medullary syndrome; staggering and veering (cerebellar infarction)
BA	Bilateral motor weakness; ophthalmoplegia and diplopia
PCA	Contralateral hemianopia and hemisensory loss
	Left: Alexia with agraphia
	Right: Neglect of left visual space

Abbreviations: ACA, anterior cerebral artery; AChA, anterior choroidal artery; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; VA, vertebral artery.

Diagnostic Testing

In most patients, the nature and severity of the brain and vascular lesions causing the stroke can be defined. CT and MRI should localize brain lesions, distinguish between infarcts and hemorrhages, and determine the location, extent, and size of the processes. CT or MRI is usually the first test in patients with suspected stroke because the information allows clinicians to exclude nonvascular disease such as tumor or abscess, differentiate hemorrhage from ischemia, identify the vascular territory involved, and define the extent of brain damaged.

The vascular territory involved should be inferred by the nature of the neurologic symptoms and signs and the location of brain lesions on CT or MRI. Echocardiography, especially TEE, has dramatically improved the ability to detect potential cardiac sources of emboli. Ultrasound techniques can be used to screen for obstructive lesions in the major extracranial and intracranial arteries in both anterior (carotid) and posterior (vertebrobasilar) circulation arteries. For extracranial use, the two most important are *B-mode scans* and *Doppler spectra*, both pulsed and continuous-wave (CW) Doppler. The anatomy of the carotid bifurcation (the CCA, proximal ICA, and external carotid artery) and the proximal VAs can be imaged by high-frequency, 5- to 10-MHz, B-mode ultrasound systems, which provide images of the vessels in real time both longitudinally and in cross-section (Fig. 94–7). Plaque calcifications and clot are often difficult to image. Pulsed Doppler registers frequency shifts from moving columns of blood. Doppler analysis can show the direction and velocity of blood flow. Multigated Doppler and B-mode scanning are now used together in so-called *duplex systems*.[45,320,321] The duplex system is probably > 90% effective in differentiating arteries that are normal or minimally narrowed from those that have moderate disease (30%-70% narrowing) and from those with severe narrowing (> 70% stenosis). B-mode scanning sometimes suggests the presence of ulceration or hemorrhage in plaques that show heterogeneous images.[321] CW Doppler uses a movable probe to measure flow velocities along the carotid and vertebral arteries; the technique is less time consuming and less expensive than the duplex system and, in expert hands, is very accurate in detecting high-grade stenosis.[321,322] Ultrasound techniques cannot reliably separate complete occlusion from very high degrees of stenosis. Color flow and power Doppler can show turbulence and altered flow dynamics.

TCD ultrasound is used to analyze the presence of intracranial arterial stenoses and provide information about the intracranial effects of extracranial occlusive lesions. The technique takes advantage of the soft spots in the temporal bones and natural foramina (the orbit and foramen magnum) that provide windows for ultrasound recording. The depth and angle of the probe recording can be varied, allowing the recording of velocities and sound spectra from all the major intracranial arteries.[45,140,323] Major obstructive lesions are reliably shown by both extracranial ultrasound and TCD. Continuous recording of intracranial arteries with TCD is a very sensitive and accurate method of detecting microemboli passing under the probes.[182,233,324,325] Examples of microembolic signals are shown in Figs. 94–4 and 94–5.

Magnetic resonance angiography (MRA) provides an additional method of imaging both the extracranial and intracranial arteries for areas of stenosis and occlusion.[326,327] CT angiography (CTA), using a spiral (helical) CT machine and dye injected intravenously, can also image the major large craniocervical arteries.[327] Standard catheter angiography is warranted when ultrasound and CTA or MRA have not sufficiently defined the vascular lesion and treatment is clinically feasible.[45,309]

Treatment

For rational treatment, know the following:

- Location, nature, and severity of the occlusive lesion
- Location, extent, and reversibility of the brain lesion
- Blood constituents and coagulability[45,328]

Treatment should *not* be guided solely by the temporal pattern of the symptoms, such as TIA, progressing stroke, or so-called *completed stroke*.[45,318,328,329] These time courses do not predict the cause and mechanism of ischemia, identify whether an infarct is present, or identify patients who will have further or recurrent ischemia.[329]

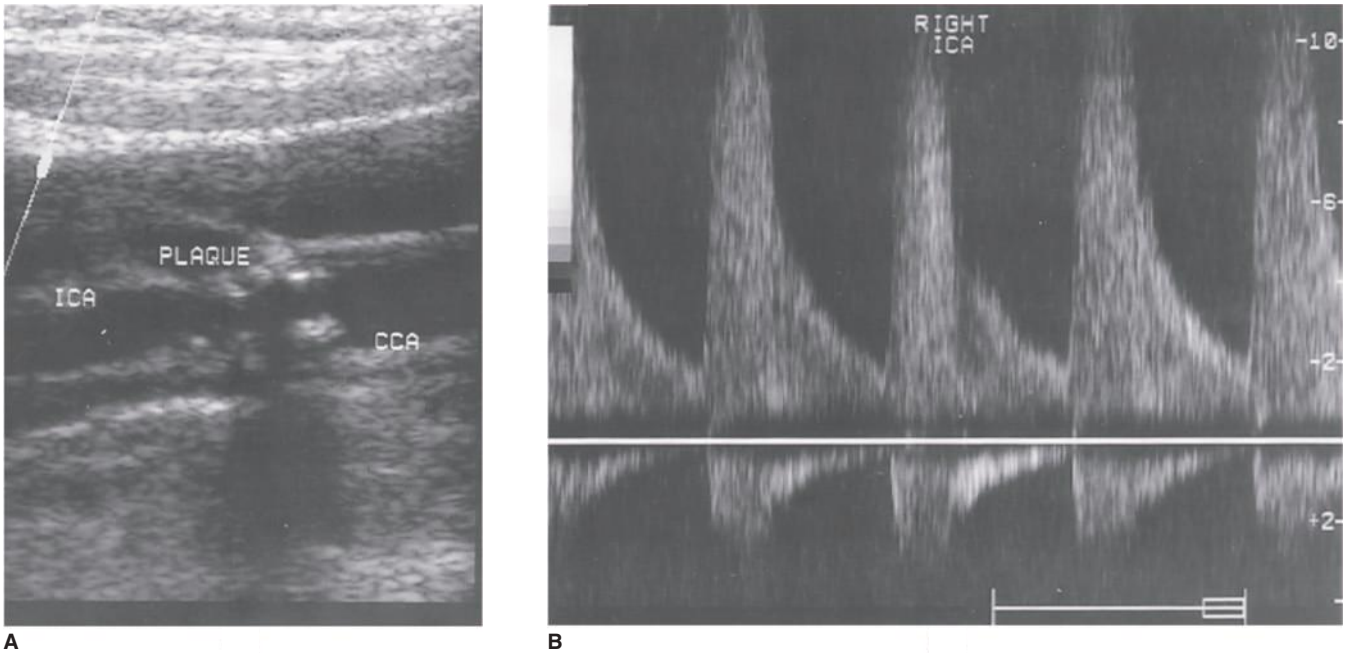

FIGURE 94–7. Duplex scan of carotid artery plaque. **A.** B-mode ultrasonic image showing plaque protruding into internal carotid artery (ICA) lumen. **B.** Doppler spectra at level of plaque showing high voltage related to stenosis.

Physicians should first decide whether or not any specific therapy is indicated. Very severe neurologic deficits, serious intercurrent illnesses (eg, dementia, cancer), and psychosocioeconomic considerations may make patients unsuitable for specific treatments. If treatment is feasible, two questions should be considered next: What brain tissue is at risk for further ischemia? What is the benefit-to-risk ratio of specific treatments? To determine the tissue at risk, clinicians consider the cause and the deficit. For example, a man with a slight hemiplegia caused by a small lacunar infarct in the anterior limb of the internal capsule may have infarcted the entire tissue supplied by an occluded small artery. In that case, treatment consists of controlling hypertension, the cause of the microvasculopathy. If, however, that same patient has a small cortical infarct in the precentral gyrus caused by ICA disease, the rest of the ICA territory is at risk for further ischemia, and aggressive treatment is warranted. Newer MRI techniques, such as diffusion-weighted and perfusion MRI, along with MRA, can show, even very soon after symptoms begin, brain tissue that is already infarcted and brain tissue that is underperfused but not yet infarcted.[45,327,330,331]

Patients who have little tissue at risk are not candidates for specific interventional therapy. If there is considerable residual at-risk tissue, the guidelines in Table 94–3 are used to direct treatment, which depends on the location and severity of the causative vascular lesions. CEA is effective in symptomatic patients with severe ICA stenosis (> 70%). For patients with carotid stenosis < 50%, these trials showed there was no significant benefit from CEA. For those with carotid stenosis in the moderate category (50%-69%), the relative and absolute risk reductions were less impressive than for those in the severely stenotic group.[332-335]

TABLE 94–3. Suggested Use of Anticoagulants and Platelet Antiaggregants

Heparin (Standard Dose)

Short term, 2-4 wk. Usually given by intravenous infusion, keeping APTT between 60 and 100 s (1.5-2 × control APTT).

1. Immediate therapy for definite cardiac-origin cerebral embolism (large cerebral infarct, hypertension, bacterial endocarditis, or sepsis would delay or contraindicate this use).
2. Patients with severe stenosis or occlusion of the ICA origin, ICA siphon, MCA, vertebral artery, or basilar artery with less than a large clinical deficit. Subsequent treatment could consist of warfarin or surgery.

Heparin (Subcutaneous Minidose)

For prophylaxis of deep vein occlusion in patients immobilized by stroke (unless contraindicated; see Chap. 84).

Warfarin

Usually overlapped with heparin; keeping prothrombin time around INR of 2.0-3.0 (~1.3-1.5 × control).

1. Long term (> 3 mo)
   a. Patients with cardiogenic cerebral embolization and rheumatic heart disease, atrial fibrillation with large atria or prior cerebral embolism, prosthetic valves, and some hypercoagulable states.
   b. Patients with severe stenosis of the ICA origin, ICA siphon, MCA stem, vertebral artery, and basilar artery. Used until studies show artery has been occluded for at least 3 wk.
2. Short term (3-6 wk)
   a. Patients with recent occlusion of the ICA, MCA, vertebral artery, or basilar artery.

Platelet Antiaggregants (Aspirin, Ticlopidine, Clopidogrel)

1. Patients with plaque disease of the extracranial and intracranial arteries without severe stenosis.
2. Patients with polycythemia or thrombocytosis and related ischemic attacks.

Abbreviations: APTT, activated partial thromboplastin time; ICA, internal carotid artery; INR, international normalized ratio; MCA, middle cerebral artery.

The Asymptomatic Carotid Artery Study (ACAS) suggested that CEA is slightly better than medical therapy in asymptomatic patients with severe carotid stenosis when the operation is executed by surgeons who have records of very low surgical morbidity and mortality.[336] To be effective, the operative mortality and morbidity of CEA must be ≥ 2% to 4%.[332-336] Surgery is also feasible on the extracranial VA in selected patients with intra-arterial embolism from this site or with intractable posterior circulation hemodynamic ischemia, which is a rare occurrence.[337]

Data on carotid (artery balloon) angioplasty and stenting (CAS) is emerging. The Wallstent Trial randomized 219 symptomatic patients with 60% to 90% stenosis to either CEA or CAS. In this early study, CAS was performed without distal protection and without antiplatelet prophylaxis, and the study design also allowed operators with limited experience to participate. The risk of perioperative stroke or death was 4.5% for CEA and 12.1% for CAS; 1-year risk of major stroke and death was 0.9% for CEA and 3.7% for CAS. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which compared CAS with CEA, did not find a difference in the rate of ipsilateral ischemic stroke up to 3 years after randomization. Several randomized comparisons of CAS versus CEA have helped to clarify the relative benefits and risks of these two procedures. Differences in the inclusion criteria of these three studies, use of embolic protection devices, and operator experience all need to be considered in interpreting their results.[294]

1. The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized 334 patients to CAS or CEA. Distal protection devices were used, and study operators had a periprocedural stroke, death, or MI complication rate of ≤ 4%. Thirty percent of the study population was symptomatic with a stenosis > 50%. The remainder (and the majority of) the study's patients had an asymptomatic carotid stenosis > 80%. Results revealed that CAS did not appear to be inferior to CEA, with a benefit of lower MI risk being detected in the CAS group.[8,338-340] In the 3-year follow-up from the SAPPHIRE trial published in 2008, 15 patients in both treatment groups had experienced stroke, for an estimated stroke rate of 2.3% per year.[341]
2. The Stent-supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial assessed 1200 symptomatic patients with ipsilateral carotid stenosis > 50% and a history of stroke or TIA. The average degree of stenosis in this study was between 80% and 89%. Ipsilateral ischemic stroke and death within 30 days were the primary outcomes observed and were found to be roughly equal. Rates of stroke and death 2 years after treatment were also similar. Multiple types of cerebral protection devices and stents were used.[342]
3. The Endarterectomy Versus Angioplasty in Symptomatic Severe Carotid Stenosis (EVA-3S) study followed 520 symptomatic patients with a prior ischemic stroke or TIA as well as a carotid stenosis of > 60%. The average degree of stenosis was similar to that in the SPACE trial at approximately 85%. Primary outcome was stroke or death within 30 days of randomization. This trial was stopped early because of futility and safety concerns; a higher risk of stroke was seen early in the trial with CAS when distal protection devices were not used, and the protocol was amended to recommend their use. The risk of stroke or death at 30 days was significantly lower in the CEA group (4%) than the CAS group (10%) and thought, in part, to reflect the issues with distal cerebral protection in the CAS group and operator inexperience at certain sites.[343]
4. The CREST study (Carotid Revascularization Endarterectomy versus Stenting Trial), which followed 2502 patients, initially found no significant difference between the stenting group and the

endarterectomy group with respect to the primary composite end point of stroke, myocardial infarction, or death during the periprocedural period or any subsequent ipsilateral stroke during 4 years of follow-up. Those results now extend to 10 years. With respect to the primary long-term end point, postprocedural ipsilateral stroke over the 10-year follow-up occurred in 6.9% of the patients in the stenting group and in 5.6% of those in the endarterectomy group; the rates did not differ significantly between the groups. No significant between-group differences with respect to either end point were detected when symptomatic patients and asymptomatic patients were analyzed separately. Over 10 years of follow-up, the investigators did not find a significant difference between patients who underwent stenting and those who underwent endarterectomy with respect to the risk of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke. The rate of postprocedural ipsilateral stroke also did not differ between groups.[344]

A consistent finding in the first three trials listed above was that after the first 30 days, the long-term ipsilateral stroke rate was < 1% per year with either procedure.[294] Despite these trials, there is still much debate regarding the optimal role of CAS versus CEA in stroke prevention. However, a recent large sample of US hospitals, identifying a total of 121,157 CEA and 18,503 CAS procedures performed at 445 medical centers, demonstrated that performance of CAS significantly increased after the publication of the CREST study.[345]

With regard to medical therapy, for minor and moderate degrees of stenosis in extra- and intracranial arteries, agents that alter platelet aggregation and adhesion are recommended. The most likely mechanism of ischemia in these patients is *white clot*, or platelet fibrin emboli. Aspirin,[346] ticlopidine,[347] clopidogrel,[348] and Aggrenox (a tablet containing aspirin 25 mg and modified-release dipyridamole 200 mg given two times a day)[349] have all proven effective in randomized trials in preventing a recurrent stroke after an initial noncardioembolic stroke. There is debate about which individual or antiplatelet therapy should be selected. The results of the Management of Atherothrombosis With Clopidogrel in High-Risk Patients with TIA or Stroke (MATCH) trial assessed patients with a prior stroke or TIA (n = 7599) who were assigned to either clopidogrel 75 mg daily or combination therapy (clopidogrel 75 mg daily plus aspirin 75 mg daily). Primary outcomes observed included ischemic stroke, MI, vascular death, and rehospitalization caused by ischemic event. There was no significant benefit observed in the combination group compared with clopidogrel alone; the risk of major hemorrhage was also increased in the combination therapy group. Thus, although clopidogrel plus aspirin is recommended over aspirin alone for acute coronary syndromes, the MATCH results do not suggest a similar benefit for stroke and TIA patients.[18,350] Clopidogrel is as effective as ticlopidine and has fewer serious hematologic complications.[348]

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial compared the efficacy and safety of aspirin plus extended-release dipyridamole with the efficacy and safety of clopidogrel among patients who had experienced a recent noncardioembolic ischemic stroke. Treatment with the combination therapy was associated with a reduction of 25 ischemic strokes compared with clopidogrel but with an increase of 38 hemorrhagic strokes and four strokes of unknown etiology. Despite the increase in bleeds, when stroke recurrence and major hemorrhage were combined into one end point reflecting a benefit-risk relationship, no statistical difference between the two groups was noted. So which drug should a physician choose while we are waiting for guideline committees to review the data and make a formal recommendation? There is a range of reasonable conclusions, and the decision should depend on factors such as adverse effects (eg, headache with the combination drug), medical history (eg, angina or stenting, which may warrant clopidogrel), and cost. All factors being equal, our personal preference is clopidogrel.[351]

For patients with severe stenosis of large intracranial arteries, we previously recommended warfarin if there were no contraindications. The randomized, double-blind, multicenter Warfarin-Aspirin Recurrent Stroke Study (WARSS) compared the efficacy of aspirin with warfarin (INR 1.4-2.8) for the prevention of secondary ischemic stroke caused by noncardioembolic sources (n = 2206). Various subgroups, including large-artery atherosclerotic lesions, were evaluated. No significant differences between aspirin and warfarin for secondary stroke prevention or death were found. However, patients treated with warfarin in whom the INRs were in the target range had significantly fewer strokes than patients treated with aspirin. Given the cost of monitoring warfarin and the potential increase in bleeding risk with warfarin use, the authors recommended that antiplatelets be chosen over anticoagulants for stroke prevention in patients with prior noncardioembolic strokes.[8,352] This study predated introduction of NOACS.

The state of the intracranial arteries can be monitored using TCD and/or MRA or CTA.[327] For patients with complete occlusions and with stump emboli–induced ischemic strokes, we still recommend heparin and then warfarin for 2 to 3 months.[45] Heparin should be used without a bolus, and target INR with warfarin should be 2.0 to 3.0.

Thrombolytic drugs, especially recombinant tissue-type plasminogen activator (rt-PA) and streptokinase, have been given intravenously and intra-arterially in patients with acute brain ischemia. In a study in which the arterial lesions were undefined, intravenous therapy with rt-PA given within 90 minutes and 3 hours of ischemia onset, in the aggregate, provided a statistically significant benefit.[353] Additionally, in a more recent study, intravenous t-PA was found to be of overall benefit even when given 3 to 4.5 hours after ischemic stroke symptom onset.[354] Unfortunately, in these and other studies, approximately 6% to 12% of patients treated with thrombolytic agents developed important intracranial bleeding. Uncontrolled studies show that patients with distal intracranial arterial embolic occlusions do well with intravenous thrombolytic therapy.[355-360] Patients with ICA occlusions in the neck and intracranially rarely reperfuse after intravenous thrombolytic therapy, especially if collateral circulation is poor. Intra-arterially administered prourokinase thrombolysis has also been proven to be very effective in opening blocked intracranial arteries within the anterior circulation.[361] The dose, timing, mode of delivery, and target group for therapy remain unsettled. The authors believe vascular imaging should precede administration of thrombolytic agents. Brain and vascular imaging can guide physicians as to who should receive thrombolytics and by what route.[362]

Because all patients with atherosclerosis are at risk of developing more lesions, control of risk factors is very important and should be begun in the hospital. Risk factors include smoking, hyperlipidemia, obesity, inactivity, and hypertension. Blood pressure should not be excessively lowered during the acute ischemic period because this may decrease flow in collateral arteries. Blood pressure control can be instituted 3 to 4 weeks after the stroke. Rehabilitation must also begin early.

MANAGEMENT OF COEXISTING CORONARY AND CEREBROVASCULAR DISEASE

In patients considered for cardiac surgery who have symptoms of brain ischemia, it is important to define the extent of cerebrovascular disease preoperatively by noninvasive means (ultrasound and/or MRA), as well as to define cardiac and coronary artery anatomy and function. In some patients with excessive surgical risks, anticoagulation may represent an alternative treatment. Clearly, optimal medical therapy should be instituted preoperatively and continued after surgery.

SYSTEMIC ARTERIAL HYPERTENSION

High blood pressure, both acute and chronic, damages deep, penetrating small intracranial arteries; accelerates the development of atherosclerosis in the extracranial and large intracranial arteries; and results in ischemic syndromes of lacunar infarction,[45,360,361] diffuse ischemic changes in white matter and basal gray matter structures (Binswanger disease[45,362]), and intracerebral hemorrhage. Hypertension is also frequent in patients with aneurysmal SAH and may contribute to enlargement and rupture of aneurysms.

Hypertension especially damages the deep arteries that penetrate perpendicularly from the major intracranial arteries (Fig. 94–8).

The two major patterns of brain ischemia in patients with hypertension are *discrete lacunar infarcts* and a more *diffuse, patchy, white and gray matter degeneration with gliosis*. Both are caused by sclerotic changes in deep intracerebral arteries and arterioles. The term *lacune* (hole) refers to a small, deep infarct caused by lipohyalinosis of the penetrating artery feeding the ischemic brain tissue.[363,364] Amyloid angiopathy can also cause small, deep infarcts in normotensive and hypertensive patients. Single lacunes cause discrete clinical syndromes.[45,365] The most common syndromes are pure motor hemiparesis,[366] pure sensory stroke,[367] ataxic hemiparesis,[368] and the dysarthria–clumsy hand syndrome.[369]

Since the advent of CT and MRI, it has become widely appreciated that hypertensive patients with lacunes often have more diffuse changes in the white matter of the brain, referred to as *leukoariosis*.[362,370] The clinical picture consists of acute strokes; subacute progression of neurologic signs; dementia; slow shuffling gait disorder; and parkinsonian, pyramidal, and pseudobulbar signs.[362,371,372] The clinical signs and gross pathology are identical to those partially described by Otto Binswanger in 1894 and 1895[371] and by his students Alzheimer and Nissl.[371] The deep arteries are thickened and hyalinized and show lipohyalinosis and sometimes amyloid angiopathy in regions of white matter atrophy and gliosis. Invariably, lacunar infarcts are also found. The diagnosis is made based on the clinical findings, the CT and MRI abnormalities, and the absence of cortical infarcts, larger artery occlusive disease, or cardioembolic sources.

Hypertensive Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) accounts for approximately 10% of all strokes.[29,45] Head trauma, vascular malformations, bleeding diatheses, drugs (especially anticoagulants, amphetamines, and cocaine), amyloid angiopathy, and intracranial aneurysms account for some cases.[326,342] Traditionally, spontaneous ICH has usually been equated with hypertensive hemorrhage. Many patients, however, have no history of hypertension or associated changes of hypertensive vasculopathy at necropsy.[257,373,374] Acute elevations of blood pressure and/or blood flow to the brain (Table 94–4) can cause ICH by the sudden increase in blood pressure, causing vessel breakage.[254]

TABLE 94–4. Causes of Acute Changes in Blood Pressure or Blood Flow That Can Result in Intracerebral Hemorrhage

Drugs, especially cocaine and amphetamines
Recent onset of arterial hypertension
Pheochromocytoma
Cold hemorrhages (exposure to freezing ambient temperatures)
Dental chair hemorrhages
Intracranial operations on the fifth cranial nerve
Stereotactic treatment of the fifth cranial nerve for trigeminal neuralgia
Carotid endarterectomy (reflex hypertension and reperfusion)
Cardiac transplantation, especially in children
Surgical repair of congenital heart disease in children
Migraine

Hypertensive ICH issues from the deep penetrating arteries, so the locations parallel the distribution of these arteries. Hypertensive hematomas develop in the same sites as lacunes; the most frequent locations are the putamen/internal capsule (30%-40%), caudate nucleus (8%), lobar white matter (20%), thalamus (15%), pons (10%), and cerebellum (10%). In fatal hematomas, microaneurysms and lipohyalinosis are prevalent in penetrating arteries, but the hematomas obscure findings in the middle of the lesions.[375] Arterioles or capillaries rupture in the center of the lesion, suddenly increasing local tissue pressure and leading to pressure on adjacent capillaries, which then rupture. As the hematoma gradually grows on its periphery (Fig. 94–9), local tissue pressure and finally intracranial pressure increase until the hematoma is contained. Alternatively, the pressure is decompressed by the lesion, emptying into the ventricular system or into the subarachnoid space on the brain surface.[45]

Clinical Findings Patients with ICH most often have a gradual evolution of neurologic signs. The first neurologic signs are related to the

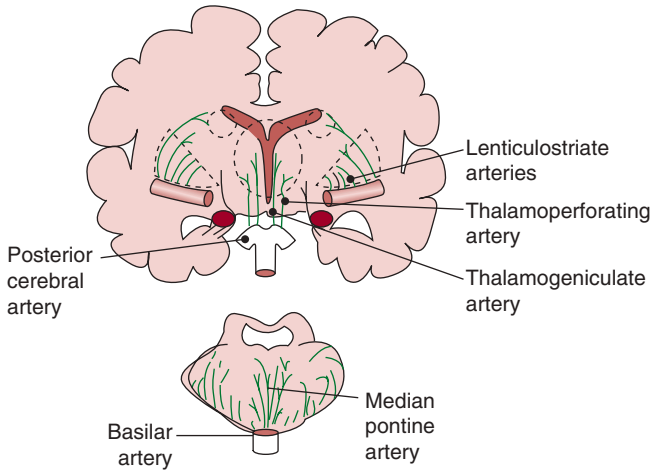

FIGURE 94–8. Deep penetrating arteries prone to the development of lipohyalinosis and microaneurysms (*green*). Occlusion of these arteries causes lacunar infarcts, and rupture of these arteries causes intracerebral hemorrhage. Reproduced with permission from Caplan LR: Stroke: *A Clinical Approach*, 3rd ed. Boston: Butterworth-Heinemann; 2000.

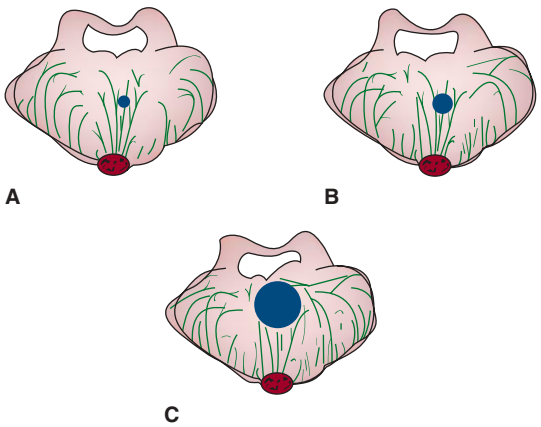

FIGURE 94–9. Gradual evolution of a hypertensive pontine intracerebral hematoma. **A.** The earliest leakage of blood from a paramedian penetrating artery. **B, C.** The hematoma has grown. Reproduced with permission from Caplan LR: Stroke: *A Clinical Approach*, 3rd ed. Boston: Butterworth-Heinemann; 2000.

bleeding site (eg, left putaminal hematoma patients might first notice right arm weakness or numbness).[376] As the hematoma grows, focal signs worsen. When and if the hematoma increases in size to increase intracranial pressure, headache, vomiting, and decreased levels of alertness develop.[376] In the presence of small, restricted hemorrhages, headache is absent, and the patient remains alert. Headache is absent or not a very prominent symptom in more than half of patients with ICH. Loss of consciousness is a bad prognostic sign when present.

Diagnosis Noncontrast CT, MR-GRE, and MR susceptibility imaging accurately show the location, size, and shape of acute ICHs.[377] Routine MRI (without MR susceptibility or GRE sequences) in the patient with an acute hematoma is more difficult to interpret. MRI is superior to CT in imaging arteriovenous malformations and cavernous angiomas. Lumbar puncture is seldom warranted. Atypical location, absence of hypertension, and abnormal vascular echoes on MRI are indications for angiography.

Prognosis and Treatment Coma, increased intracranial pressure, and large hematoma size (> 3 cm in one dimension on CT) all indicate a poor prognosis.[378] Ordinarily, severe systemic hypertension is reduced but not excessively. Patients with ICH can die from increased intracranial pressure. To perfuse the brain and maintain an arteriovenous pressure gradient, the systemic arterial pressure must increase. Overzealous reduction of systemic blood pressure can cause clinical deterioration. The patient's state of alertness and neurologic signs should be carefully monitored, together with the blood pressure.

Recent hematomas in the cerebral lobes, cerebellum, and right putamen are sometimes drained surgically without leaving a major deficit, at times using stereotactic equipment with CT guidance. The indications for drainage are increased intracranial pressure and the presence of lesions that require removal (eg, tumor, arteriovenous malformations, aneurysm).[378] When hematomas resolve, they leave a cavity disconnecting but not destroying the overlying cortex.

Small hematomas usually resolve well without specific therapy except blood pressure control, whereas massive hematomas usually kill or maim patients before they can be treated. Medium-sized hematomas (2-4 cm) that increase intracranial pressure and cause worsening signs or decreased consciousness while patients are under observation are indications for drainage if the hematoma is favorably located.

SUBARACHNOID HEMORRHAGE

SAH is not directly caused by hypertension in most cases, although an abrupt increase in blood pressure (eg, caused by cocaine or amphetamines) can sometimes lead to SAH, as can a bleeding diathesis, trauma, and amyloid angiopathy. The most frequent lesions causing SAH are abnormal vessels such as aneurysms and vascular malformations on or near the surface of the brain. SAH describes bleeding directly into the subarachnoid space with rapid dissemination into the cerebrospinal fluid (CSF) pathways. Usually blood is suddenly released under systemic arterial pressure, causing an abrupt increase in intracranial pressure and producing headache, vomiting, and interruption of conscious behavior and memory, at least temporarily.[45,379] In some patients, the jet and spread of blood cause neckache, backache, or sciatica instead of headache. Patients are usually agitated and restless or sleepy and have a stiff neck.

The most frequent cause of SAH is leakage from a berry aneurysm. Often there has been a past history of a *warning leak or sentinel hemorrhage*, presenting as a sudden-onset headache unusual for the patient that lasts days and prevents normal activities.[379,380] Aneurysms are usually located at bifurcations of major intracranial arteries. CT can often suggest the site of rupture if blood is pooled locally near a typical site.[381] Large aneurysms are occasionally visible on contrast-enhanced CT or MRI. CTA and MRA are useful tests for screening for aneurysms.[327] Lumbar puncture is very important in the diagnosis of SAH.[382] The absence of blood in the CSF effectively excludes the diagnosis of SAH if the fluid is examined within 24 hours of the onset of the headache, but bleeds that are very small in volume or older than 72 hours can be missed. The CSF pressure, presence of xanthochromia, and quantification of the hemoglobin and bilirubin content of the CSF by spectrophotometry can help establish and date the bleeding and document increased intracranial pressure.[383]

The two most important neurologic complications of aneurysmal SAH are rebleeding and brain ischemia caused by vasoconstriction (so-called vasospasm). Once an aneurysm has ruptured, either a tiny cap of platelets and fibrin seals the point of rupture or continued bleeding leads to death. Lysis of the fibrin cap initiates rebleeding. Surgical clipping of the aneurysmal sac or obliteration of the aneurysm by endovascular use of balloons or other devices should be attempted before rebleeding occurs.

Vasoconstriction of arteries is thought to be caused by blood or blood products that bathe the adventitia of arteries.[383-386] In the presence of a large accumulation of blood, there is a much higher incidence of arterial vasoconstriction and resultant brain ischemia and infarction. Delayed ischemia can also develop after surgery, as manipulation of vessels can precipitate vasoconstriction. The clinical findings in patients with vasoconstriction are often those of diffuse brain swelling, such as headache, decreased alertness, and confusion. When vasoconstriction is focal, the clinical findings are those of focal ischemia, such as hemiparesis, aphasia, hemianopia, and so on. Vasoconstriction usually has its onset 3 to 5 days after hemorrhage. The peak time for constriction is on days 5 to 9; vasoconstriction usually improves after the second week unless rebleeding occurs.[387]

Vasoconstriction is detected by angiography in 30% to 70% of patients with SAH, depending on the timing of the study.[383,384] TCD is effective in monitoring for the presence of vasoconstriction.[388,389] Single-photon emission CT (SPECT) can also show regions of poor perfusion and delayed ischemia.[390]

Many treatments have been tried to prevent or treat vasoconstriction after SAH,[386] including removal of blood by lumbar puncture and at the time of early surgery, pharmacologic agents such as calcium channel blockers to minimize vasospasm, and hypervolemia to prevent ischemia by maintaining perfusion. At present, the most popular approaches are early surgery, nimodipine (a calcium channel blocker), and hypervolemic therapy, especially after aneurysmal clipping. Hypovolemia is common after SAH, as is hyponatremia. Hypervolemia does not reverse the vasoconstriction but helps maintain brain perfusion.

COAGULOPATHIES

Hypercoagulability and bleeding caused by decreased coagulability affect most body organs, including the brain and heart. An increased tendency for clotting can be caused by abnormalities of the formed blood elements or serologic factors.[45,391-393] Increased numbers of red blood cells and platelets and qualitative abnormalities such as sickle cell disease can cause intravascular clotting, especially in the presence of dehydration. Excessive platelet activation, or so-called *sticky platelets*, can also explain increased coagulability.[394,395] The level of β-thromboglobulin is a good marker for platelet activation. Serologic abnormalities may be congenital or acquired. Decreased amounts of natural anticoagulants (antithrombin III, protein C, and protein S), resistance to activated protein C, and prothrombin gene mutations can cause hypercoagulability.[391-393,396] These proteins may be decreased in patients with hypoproteinemia, especially that caused by the nephrotic syndrome and urinary protein loss. Fibrinogen levels and the levels of the various coagulation factors

such as factors VIII and XI may also be high in patients with a prothrombotic state. In many of these patients—those on high-dose estrogen birth control pills, pregnant women, and patients with cancer—serologic and standard coagulation tests (in vitro) do not clarify the mechanism of the excessive clotting in vivo. Stroke patients may have serologic evidence of platelet activation and increased fibrin formation but decreased natural fibrinolytic and anticoagulant activity.[392,396]

Measurement of various serum antiphospholipid antibodies (APLAs) elicited considerable interest. The usually measured substances are the so-called *lupus anticoagulant*,[397-399] anticardiolipin antibodies, and β_2-glycoprotein 1 antibodies. Increased activity of APLAs is found in patients with systemic lupus erythematosus, acquired immunodeficiency syndrome (AIDS), giant cell arteritis, and Sneddon syndrome[399-402] (livedo reticularis and strokes), as well as in association with the use of some drugs (eg, phenytoin, phenothiazines, procainamide, hydralazine, quinidine). When the APLAs are not associated with other conditions and the patient has clinical evidence of excess clotting, the disorder is considered to be primary and is referred to as the *primary APLA syndrome*.[390-393] Patients with APLAs can have an increased incidence of spontaneous abortions, venous occlusive disease of the legs and pulmonary embolism, brain infarcts (often multiple), thrombocytopenia, and false-positive syphilis serologic tests. Older patients with APLAs often also have important risk factors for stroke.[403-406]

Patients with systemic illnesses often have elevated erythrocyte sedimentation rates, and strokes and pulmonary emboli often follow and complicate MI. Customarily, such brain infarcts have been attributed to cardiogenic embolism, but some undoubtedly are related to thromboses precipitated by increased levels of acute-phase reactant coagulation proteins. Cancer, especially mucinous adenocarcinoma, has been associated with multiple vascular occlusions, large and tiny brain infarcts, and venous and arterial occlusions.[407]

Deficient coagulability can lead to serious intracranial bleeding. The hemorrhage can be into the brain (ICH), CSF (SAH), or subdural and epidural compartments. Thrombocytopenia, hemophilia, and leukemia are common conditions leading to intracranial hemorrhage. The most common iatrogenic cause of bleeding is anticoagulation with heparin or warfarin.[408] Brain hemorrhage has also been described after fibrinolytic treatment of patients with coronary artery disease[409,410] and after rt-PA infusion to treat cerebrovascular occlusive disease.[353-360]

Anticoagulant-related ICH, a catastrophic complication with high morbidity and mortality, is relatively rare considering the frequency of anticoagulant use. Anticoagulant-related hemorrhages develop more insidiously and evolve more slowly and more often than do other causes of ICH.[360,404] Many are erroneously attributed to brain ischemia. Any patient taking anticoagulants who develops CNS symptoms should be considered to have anticoagulant-related ICH until CT or MRI excludes the diagnosis. Many patients require surgical drainage of their hematomas to ensure survival. Anticoagulants should be stopped immediately and their effect reversed by fresh frozen plasma or vitamin K. It is probably safe to resume anticoagulation with heparin 7 days to 2 weeks after the ICH if indicated, such as for prophylaxis in patients with mechanical heart valves.[411] In patients treated with fibrinolytic agents, hemorrhages are most often lobar or cerebellar and may be multiple. ICH is more common when there is a past stroke, when heparin or other agents that affect coagulation are given with or after fibrinolytic agents, and when there is a hemostatic defect secondary to treatment.[410,411]

ARTERIAL DISSECTION

Aortic dissections involving the innominate or common carotid arteries are a well-known cause of stroke and TIA. Less well known are the syndromes produced by dissections of the extracranial and intracranial cervicocephalic arteries, which are especially likely to occur in young, active individuals without risk factors for atherosclerosis or stroke but after trauma or chiropractic or other neck manipulations. They are also associated with fibromuscular dysplasia, α_1-antitrypsin deficiency, Marfan syndrome, pseudoxanthoma elasticum, and migraine.

Dissections start with a tear in the media and spread longitudinally (Fig. 94–10), often disrupting adventitial fibers or even rupturing through the adventitia to produce an extravascular hematoma and a false aneurysm, or pseudoaneurysm, within muscle and connective tissue. Intracranially, such a rupture can produce SAH. Other dissections cause arterial obstruction and secondary thrombosis of the narrowed vascular lumen. Most cerebrovascular dissections occur in the extracranial vessels, particularly the pharyngeal portion of the ICA and the nuchal VAs.[45,412-417]

Extracranial dissections produce sharp pain and throbbing headache; brain and retinal ischemic episodes, which may occur in rapid-fire attacks (*carotid allegro*[417]); and pressure on adjacent structures, especially cranial nerves X through XII, which exit at the skull base. Strokes, usually from embolization of clots, are common but may have a benign course. Intracranial dissections have a poorer prognosis, often with vascular rupture and SAH. The diagnosis is confirmed by angiography, CT, or MRI. Ultrasound studies can be helpful in suggesting the diagnosis of dissection in the neck.[418]

There is debate regarding the appropriate treatment for cervicocephalic arterial dissection. The Cervical Artery Dissection in Stroke Study (CADISS-NR) was a small trial enrolling 250 participants with cervicocephalic dissection (118 carotid, 132 vertebral), who were randomly assigned to receive antiplatelet or anticoagulants. The CADISS trial concluded that there was no difference in secondary stroke prevention provided by antiplatelet and anticoagulant agents in patients with carotid or vertebral artery dissections.[419] It is important to note that the mean time of treatment after symptom onset was 10.8 days (standard deviation 7.0, range 1-31 days) in this study. Extensive published data[420,421,422] as well as our personal experience show that most strokes develop within the first 7 days after brain ischemia and the rate of stroke thereafter is very low. In addition, strokes are uncommon in patients whose presentation does not include brain ischemia (neck pain, Horner syndrome, compression of nerve roots, or lower cranial nerves). These patients were also included in the trial. In CADISS-NR, only two patients had strokes within 3 months. In the meta-analysis included in the report, almost all of the patients were enrolled beyond 5 days after onset. Physicians must not take the

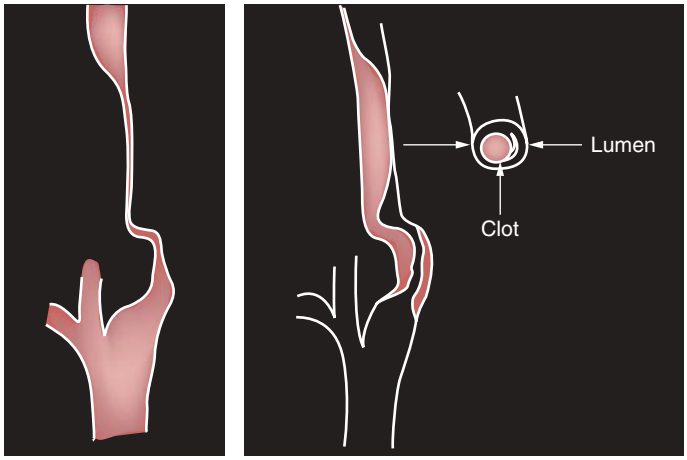

FIGURE 94–10. Diagrams of a carotid artery dissection. **A.** The intramural clot encroached on the lumen. **B.** The dissection (*cross-hatched*). Reproduced with permission from Caplan LR: Stroke: *A Clinical Approach*, 3rd ed. Boston: Butterworth-Heinemann; 2000.

results of this trial and the meta-analysis to conclude anything about treatment during the very acute period after brain symptom onset. This time period was not a part of the trial or the meta-analysis. In patients with brain ischemia, we generally would recommend that treatment consist of the use of heparin acutely, followed by warfarin. In patients in whom the dissected artery is initially occluded and remains occluded, warfarin can be stopped after 6 to 12 weeks, and an antiplatelet agent should then be initiated. The authors continue warfarin in other patients until severe luminal narrowing is no longer present, monitoring the dissected arteries with serial noninvasive techniques (ultrasound, CTA, or MRA) every few months. Intracranial dissections with SAH have been treated surgically.[413,423,424]

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CHAPTER 95

CAROTID ARTERY STENTING

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INTRODUCTION

Stroke is the fifth[1] leading cause of death in the United States and represents the single most important cause of long-term physical and intellectual disability. Each year in the United States, approximately 795,000 people experience a new or recurrent stroke (87% ischemic, 13% hemorrhagic), and roughly 610,000 (75%) of these strokes are first events. On average, every 40 seconds someone in the United States experiences a stroke; there are close to 130,000 annual deaths related to stroke, and the cost of managing stroke patients in the United States in 2012 was approxinately $33 billion.[1] Unfortunately, despite important advances and progress in several areas of medicine, the treatment options for an *established stroke* are limited and the expectation for reversibility or improvement of stroke-related neurological deficits is both guarded and unpredictable.

Extracranial (cervical) carotid disease ("carotid stenosis") is responsible for up to 20% of strokes[2,3] and the intent of treatment for carotid stenosis (medical, surgical, or stenting) is to prevent a future ipsilateral stroke. In the past, carotid stenting (CAS) was considered to be investigational or experimental and outcomes of this new procedure were constantly compared and benchmarked with the outcomes of carotid endarterectomy (CEA), long considered the gold standard for treatment of carotid stenosis. The results of three large prospective multicenter randomized trials with head-to-head comparisons of CAS and CEA are now available[4-9] and provide Level 1 evidence to support treatment recommendations in both symtpomatic and asymptomatic patients (Table 95–1). Although the US Food and Drug Administration (FDA) provided regulatory device approvals for CAS in high surgical risk and standard surgical risk patients in 2004 and 2011, respectively,[10] as of 2016, the Centers for Medicare and Medicaid Services (CMS) only reimburse CAS when the procedure is performed in symptomatic patients with > 70% stenosis and who are at high risk for CEA.

In this chapter, we will review invasive treatment approaches for the treatment of carotid stenosis, address the critical issue of how to identify the standard-risk CAS patient, summarize key aspects of the stenting technique, and provide analysis of the clinical trial data that support the current indications for this procedure.

INVASIVE TREATMENTS FOR EXTRACRANIAL CAROTID STENOSIS

SURGICAL CAROTID ENDARTERECTOMY

CEA is the most frequently performed surgical procedure to prevent stroke. Although the first surgical procedure for treating carotid stenosis was reported in the early 1950s,[11] it took another 30 years before large prospective randomized trials (with the intent of testing the benefit of CEA for stroke reduction) were initiated. These studies, including the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[12-15] the European Carotid Surgery Trial (ECST),[16] the Asymptomatic Carotid Atherosclerosis Study (ACAS),[17] and the Asymptomatic Carotid Surgery Trial (ACST),[18,19] confirmed the benefits of CEA for stroke reduction when compared to best available medical treatment during the trial period, in both symptomatic (NASCET, ECST) and asymptomatic (ACAS, ACST) patients.

It is important to recognize that the patients included in these surgical studies were carefully selected and subjects who were at high risk for CEA were excluded from participation, and medical therapy in this time period was not nearly as good as it is in 2016. The types of high CEA risk patients excluded from these trials were those over 80 years of age, patients with recurrent stenosis following prior ipsilateral

TABLE 95–1. Key Features of the Three Largest Randomized Trials Comparing CAS and CEA

Trial	Year	Type	Sites	Clinical Status	No.	CAS/CEA	Median FU (years)	Reference
ICSS	2001-2008	Prospective	European Union, Australia,	Symptomatic	1713	855/858	4.2	4,5
		Randomized	New Zealand, Canada	Asymptomatic	–			
CREST	2000-2008	Prospective	North America	Symptomatic	1321	668/653	2.5	6,7
		Randomized	Canada	Asymptomatic	1181	594/587	7.4	
ACT I	2005-2013	Prospective	North America	Symptomatic	–		5	9
		Randomized		Asymptomatic	1453	1089/364		

1. The CREST and ICSS trials randomized patients to CAS or CEA in a 1:1 ratio.

2. In ACT I, patients were randomized to CAS or CEA in a 3:1 ratio. Data is available for 328 patients at the 5-year follow-up time point.

3. Median FU = Median Follow-up.

endarterectomy, intracranial stenosis that was more severe than the surgically accessible lesion in the neck, patients with severe/symptomatic CAD, those on long-term anticoagulation therapy, and patients with surgically inaccessible lesions.[12,17] The rates of CEA have decreased over the past 15 years, and in 2010 approximately 100,000 endarterectomy procedures were performed in the United States.[1]

ENDOVASCULAR APPROACHES TO TREAT CAROTID STENOSIS

Carotid Angioplasty

Initial clinical reports of carotid angioplasty involved small series of patients and were limited to single centers.[20] Kachel[21] summarized the results of carotid angioplasty published through 1995 and noted that 503 of the 523 (96%) procedures were technically successful. There were no deaths, major strokes occurred in 2.1%, and minor complications were in the single digits (6.3%).[21]

Two complications most feared among patients undergoing carotid stenting in the 1990s included acute vessel closure (resulting from dissection caused by the barotrauma of balloon dilatation plus vessel recoil following deflation of the balloon) and distal embolization. The introduction of stents and embolic protection devices (EPD's) provided effective solutions to both of these key limitations and plain balloon angioplasty for treating extra-cranial carotid disease has been essentially reduced to a historical footnote.

Carotid Artery Stenting

The contemporary, percutaneous, interventional approach for the treatment of extracranial, cervical, bifurcation carotid stenosis centers around the use of a device that can capture and remove emboli generated during the procedure—embolic protection devices (EPDs)—and the practice of primary elective stenting, ie, stenting independent of the angiographic results of balloon angioplasty.

Balloon expandable stents are rarely used during carotid intervention because these stents are prone to deformation or "stent crush." This occurs in approximately 15% of the cases and is a consequence of the superficial location of the carotid artery and the associated movements of the neck.[22,23] This led to testing and rapid adoption of self-expanding stents such as the Wallstent (Elgiloy) and a variety of nitinol stents. Primary stenting has virtually eliminated the risk of acute carotid closure and fortunately acute stent thrombosis and in stent restenosis are not significant issues.

Indications for Carotid Artery Stenting The indications for carotid artery revascularization are well described in the Guidelines for the Management of Patients with Extracranial Carotid and Vertebral Artery Disease[24] and are guided by two important variables: the symptomatic or asymptomatic status of the patient and the severity of stenosis in the target carotid artery. Before providing a recommendation for intervention (CEA or CAS), it is critically important for patients and their physicians to understand the individual operator's experience as well as the center's procedural outcomes.

SYMPTOMATIC PATIENTS

The term "symptomatic carotid stenosis" refers to ischemia or infarction in the distribution of the internal carotid artery resulting in neurological abnormalities that include, but are not limited to contralateral motor and/or sensory events and speech and/or visual problems (monocular blindness, field defects). "Amaurosis fugax" refers to transient monocular visual loss typically described by the patient as a "shade being drawn down or across the eye" (amaurosis = fleeting in Latin; fugax = dark in Greek). The symptomatic event may present as a transient ischemic attack (TIA) or a major or minor stroke. A TIA is the most common symptomatic presentation and approximately 15% of strokes are heralded by a TIA.[25] By definition, a TIA lasts for less than 24 hours (typically under 30 minutes) and following resolution of the episode there are no clinically recognizable neurological deficits. A recent meta-analysis[26] reported that the risk of recurrence of cerebrovascular events in patients with symptomatic carotid stenosis within 2 weeks of the index event is 26%. The stroke risk may be lower in patients presenting with amaurosis as the sole symptom in comparison to patients who present with a hemispheric TIA. A patient is considered symptomatic for 6 months after the initial event.

It is important to distinguish ischemic symptoms caused by vertebrobasilar insufficiency (VBI) from those secondary to carotid origin. VBI symptoms include transient cranial nerve dysfunction, diplopia, vertigo, and dysarthria. Motor deficits are ipsilateral and visual symptoms may be bilateral.[27] Dizziness and problems with balance are symptoms that typically result from ischemia or infarction in the vertebrobasilar system; dizziness is very rarely a symptom of carotid artery disease.

In symptomatic patients, the periprocedural (CAS or CEA) risk of stroke or death should be under 6%.[28] The NASCET study[12] demonstrated the benefit of CEA over medical treatment for reducing the risk

TABLE 95–2. Stenosis Thresholds for Carotid Artery Revascularization

Recommendation	Characteristics	Symptomatic	Asymptomatic
Proven/acceptable	Stenosis severity[a]	70%–99%	> 80%
	Procedure-related risk	< 6%	< 3%
	Other considerations		Life expectancy > 5 y
May be acceptable	Stenosis severity[a]	50%–69%	> 70%
	Procedure-related risk	< 3%	< 3%
	Other considerations	Additional unfavorable features on the angiogram, eg, ulceration or a filling defect	Planned CABG Contralateral occlusion Clinical trial participant
Unacceptable	Stenosis severity[a] OR	< 49%	< 70%
	Procedure-related risk	> 6%	> 3%

Abbreviation: CABG, coronary artery bypass graft surgery.

[a] Angiographic stenosis severity is based on the NASCET methodology, which computes the ratio between lumen diameter at the point of maximal stenosis and the lumen diameter of the nontapered segment of the internal carotid artery distal to the stenosis.[68] (See Fig. 95–10).

of a stroke in symptomatic patients with carotid stenosis between 70% and 99%. Hence, it is well accepted that revascularization should be offered to all symptomatic patients with a 70% or greater ICA stenosis. The NASCET results also showed that the magnitude of the benefit is less for patients with a stenosis between 50 and 70% and revascularization is typically not recommended unless there are additional unfavorable features on the angiogram (Table 95–2). Although stroke risk in symptomatic patients scales with the degree of stenosis, there is no such definite correlation in asymptomatic patients.[24]

An important issue in the treatment of symptomatic patients relates to the timing of the revascularization procedure after the index, symptomatic event.[26,29-33] The risk of a recurrent neurological event after a TIA or stroke is estimated to be between 15% and 20% and this elevated risk persists for approximately 6 months after the initial event (hence the 6-month time limit when defining symptomatic patients). An important reason underlying the reluctance of operators to perform revascularization (CEA or CAS) soon after a stroke is the concern that "early treatment" increases the risk of hemorrhagic transformation of the culprit, nonhemorrhagic infarct. The practice of waiting and thereby delaying intervention in symptomatic patients has been challenged.[29] Proponents of "early intervention," ie, treatment within a few days of the symptomatic event, argue that the highest risk of a recurrent event is during this early period. Therefore any delay in treatment will significantly diminish its therapeutic value because a substantial portion of the patients would have already experienced a neurological event during the waiting period. Meschia and colleagues[34] analyzed 1180 symptomatic patients in the CREST trial who received their assigned procedure and had clearly defined timing of symptoms. Patients were classified into three groups based on time from symptoms to procedure: < 15, 15 to 60, and > 60 days. For both CEA and CAS, the risk of periprocedural stroke or death was not significantly different for the two later time periods relative to the earliest time period, leading the authors to conclude that time from symptoms to CEA or CAS did not alter periprocedural safety, supporting early revascularization regardless of modality. In the United States, the percentage of patients undergoing CEA within 2 weeks of the onset of stroke increased from 13% in 2007 to 47% in 2010.[35]

ASYMPTOMATIC PATIENTS

The detection of a carotid bruit during a clinical exam often leads to the diagnosis of asymptomatic carotid stenosis. However, neither the presence nor the severity of the bruit correlate with the severity of the stenosis.[36-38] The absence of symptoms in patients with severe, hemodynamically significant stenosis signals the presence of robust collaterals to the culprit hemisphere—most often from the contralateral carotid artery via a patent anterior communicating artery or from the VB circulation via a posterior communicating artery. The stroke risk in these patients is mainly from embolization from the stenotic plaque in the extracranial ICA to the intracranial vessel(s) rather than from complete occlusion of the carotid artery in the neck.

Two important issues impact treatment decisions in a patient with asymptomatic carotid stenosis:

1. *The severity of stenosis*. Per current guidelines, it is reasonable to consider revascularization for patients with > 80% asymptomatic stenosis and low periprocedural risk (see Table 95–2).[24]
2. *Choice of treatment*. In the event revascularization is to be performed, should the patient be referred for CEA or CAS? The CREST[6,7] and ACT I[9] trials provide prospective, randomized comparative outcomes of CEA and CAS in asymptomatic patients (see Table 95–1).

MEDICAL TREATMENT VERSUS INTERVENTION (CAROTID ENDARTERECTOMY OR CAROTID STENTING) FOR ASYMPTOMATIC CAROTID DISEASE

The Case for Medical Treatment

Because the annualized risk of a stroke in patients with asymptomatic carotid artery disease treated with contemporary medical treatment is likely around 2% to 3%, and treatment with CEA or CAS is always prophylactic—ie, a procedure done with the *intent of preventing a future stroke*, based on the ACC/AHA guidelines, the peri-procedural complications should be < 3%.[24] Not surprisingly, there has been intense debate, controversy, scrutiny, and oversight surrounding the issue of selection of the asymptomatic patient appropriate for carotid revascularization.

Proponents of medical treatment for asymptomatic disease argue that asymptomatic carotid stenosis is essentially a medical condition, and should be treated as such[39]; revascularization treatment subjects the patient to periprocedural risks that are immediate as opposed to the small risks with medical treatment that happen in the future and are spread out over time[40,41]; and there are too many carotid interventions being performed on patients who have a small risk of stroke on contemporary medical therapy. Therefore, in addition to the procedurally related risks, an interventional approach (CEA or CAS) is not cost effective.[41]

Proponents of "only medical treatment for asymptomatic patients" point out that in the past 20 years (since the publication of the ACAS results in 1995), the stroke risk in asymptomatic patients managed solely with medical treatment using antihypertensives,[42] antiplatelet agents,[43] and statins[44-46] together with smoking cessation, has shown a gradual but appreciable reduction.

Further, because statin treatment was infrequently used during the ACAS trial, the stroke outcomes in the early trials may not be representative of contemporary medical treatment outcomes. For example, in ACAS,[17] with best medical therapy, the annual ipsilateral stroke was 2.2% and incidence of any stroke was 3.5%. In the HOPE-3 trial,[44] treatment with rosuvastatin at a dose of 10 mg per day for a period of 5.6 years in intermediate-risk patients who did not not have cardiovascular disease and who had baseline lipid levels within the normal range resulted in signficantly lower risks of stroke and myocardial infarction compared

to those treated with placebo. Many invesstigators argue that there is an urgent need for a three-arm, randomized clinical trial for asymptomatic carotid disease that includes not only CEA and CAS but also a well-controlled medical treatment arm. The CREST II study, currently enrolling patients, is a two-arm study comparing best medical treatment with CEA and best medical treatment with CAS in asympomatic patients with 70% or greater carotid stenosis.

The Case for Intervention

Even though the ACAS and ACST trials included patients with 60% carotid stenosis, today most physicians will only consider interventional treatment for asymptomatic patients with ≥ 80% stenosis, the diagnosis based on appropriate duplex ultrasound velocities and corroborated by angiography (see Table 95–2). Important considerations supporting the case for intervention include:

1. Extracranial carotid stenosis accounts for approximately 12% to 21% of all anterior circulation ischemic strokes.[2,3] A TIA is a heralding symptom only in approximately 15% of patients.[25]
2. Treatment of an acute stroke essentially consists of supportive therapy, institution of pharmacological and/or interventional measures to contain the initial event, secondary prevention measures to prevent a recurrence, and rehabilitation. Unfortunately, none of these measures can guarantee recovery of any or all of the lost neurological function. Because the first presentation in a patient with asymptomatic disease can be a major devastating stroke, there is no active treatment that will predictably reverse the neurological deficit of a stroke, and response to treatment of an established stroke is unpredictable, significant efforts have been directed at primary stroke prevention.
3. The cornerstone of this primary preventative approach is centered on control and/or modification of risk factors. An equally important aspect of this primary prevention approach involves prescribing revascularization treatment for a subset of asymptomatic patients with significant (usually accepted to mean ≥ 80%) carotid stenosis because these patients represent a major treatable cause of ischemic stroke.
4. The management of an established stroke is expensive and is connected to the direct costs of hospitalization and rehabilitation and indirect costs stemming from loss of wages.[1]
5. Although risk-factor modification as part of the overall management strategy is important for all patients with atherosclerotic vascular disease, adopting the extreme position that all asymptomatic patients—including those with severe (≥ 80%) stenosis—should be managed exclusively with conservative medical treatment and not offered intervention should be tempered by the following observations:
   a. Lipid-lowering drugs have been used and studied extensively in patients with coronary artery disease, less so in patients with asymptomatic carotid disease.[47] A number of studies have shown beneficial effects of statins on plaque composition, plaque morphology, and plaque progression.[48-51] Although there are no studies demonstrating a decrease in major stroke in asymptomatic patients administered a statin, the SPARCL[45] study randomized 4731 patients who had a stroke or TIA within 1 to 6 months before study entry and no known CAD to 80 mg daily of atorvastatin or placebo. There was a significant reduction in the primary end point of fatal and nonfatal stroke (hazard ratio [HR] 0.84, $P = 0.03$), fatal stroke (HR 0.57, $P = 0.003$), stroke or TIA (HR 0.77, $P = 0.001$), and major cardiovascular (CV) events (HR 0.80, $P = 0.002$). There was no difference in nonfatal stroke or all-cause mortality. A meta-analysis[52] of randomized trials in asymptomatic patients found that statins were effective in decreasing the total number of strokes but not fatal strokes.
   b. Only a small proportion (< 30%) of the patients in the ACAS study[17] had severe (> 80%) stenosis—the current threshold[24] for treatment with intervention (see Table 95–2). Hence the low stroke risks in the medically treated arms of the ACAS and ACST trials must be interpreted with caution. It is not clear that the annualized stroke risk of < 3% applies equally to all degrees of stenosis, especially to patients with > 80% stenosis.
   c. Medical treatment requires a lifelong patient commitment and hence its value and impact on outcomes are completely dependent on shared decision making between the patient and physician and ultimately on patient compliance. Medication cost, side effects, and a perceived lack of any immediate benefit (because patients are asymptomatic) all compromise patient compliance. Because the dropout from medical treatment is random, it is entirely possible that the patients who need treatment the most, may end up not receiving it, compromising and undermining the value of this approach.
6. Revascularization: A critical message from the asymptomatic CEA trials[17] was that for surgical revascularization to be beneficial in reducing the future stroke risk in asymptomatic patients (Table 95–3), the periprocedural risk of the revascularization should not exceed 3%. If the risk breaches this threshold, the difference in stroke risk between the medically treated arm and the surgical arm will not be significant, ie, the benefit of stroke reduction from the intervention no longer accrues to the patient. This low tolerance for periprocedural complications constitutes what the authors have framed as the 3% Rule of Carotid Stenting.[53] How to avoid breaching this rule is central to the theme of patient selection for carotid stenting and underlies the critical, all important task of identifying the standard risk patient for carotid stenting. It is equally important to recognize that all patients considered high risk for CEA (Table 95–4) do not automatically become standard risk for stenting.

Identifying the Asymptomatic Patient at High Stroke Risk on Medical Treatment

Much of the controversy surrounding the treatment of asymptomatic carotid stenosis could be resolved if physicians had a method of reliably identifying the subset of asymptomatic patients who are at high risk for a stroke on medical treatment; interventional treatment could then be selectively directed at these patients.[54] Such an approach would greatly improve the justification, the yield, as well as the cost effectiveness of prophylactic invasive treatment with either CEA or CAS.[55] Some of the metrics that have been proposed as predictors of increased risk of ipsilateral ischemic events in asymptomatic patients with carotid stenosis include severity of stenosis, progression to a higher grade,[56,57] unfavorable plaque characteristics/composition including

TABLE 95–3. Event Rates from the Two Early Randomized Trials Comparing Carotid Endarterectomy to Best Medical Therapy in Asymptomatic Patients

			5-Year Stroke Risk		
Study	No.	Year	CEA	Medical Therapy	Hazard Ratio (CEA vs Medical Therapy)
ACAS[17]	1662	1995	5.1%	11%	0.46
ACST[18]	3120	2004	3.8%	11%	0.29

Abbreviation: CEA, carotid endarterectomy.

TABLE 95–4. High Risk for Carotid Endarterectomy (CEA)

Anatomical	Comorbidities
High lesion (at or above C2)	Unstable angina
Low lesion (at or below the clavicle)	
Restenosis following prior CEA	MI within last 30 days
Prior neck radiation	Functional class III/IV
Prior radical neck dissection	Low EF, severe aortic stenosis
Permanent tracheostomy	≥ 2 coronary vessels with ≥ 70% stenosis
Recurrent laryngeal nerve injury	Severe lung disease (DLCO < 50% predicted, FEV_1 < 30%)
Cervical spine immobility	Medical condition(s) that significantly increase risk of surgery/anesthesia

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; EF, ejection fraction; FEV_1, forced expiratory volume in 1 second; MI, myocardial infarction.

plaque ulceration and echolucency,[58,59] and verifying the presence or absence of microemboli by transcranial Doppler.[60-62] Other clinical and radiological markers for predicting an increased stroke risk in asymptomatic patients include occult cerebral infarction on brain imaging studies,[63] patients with contralateral carotid occlusion,[64] and detection of intraplaque hemorrhage by MRI.[65] Nicolaides and colleagues[66] have suggested that combining clinical risk factors such as diabetes and smoking together with high-risk ultrasound features such as the presence of an echolucent plaque may also help identify the high-risk asymptomatic patient (Table 95–5).

Although one cannot dispute the clinical importance and practical usefulness of being able to identify the asymptomatic patient at high risk for a stroke, none of the approaches outlined above have been validated to justify using them in making clinical decisions. Hence at the present time the degree of severity of carotid stenosis continues to remain the basis for deciding whether or not to treat asymptomatic patients.

In contemporary practice, most clinicians will (should) only consider interventional treatment options for an angiographically ≥ 80%, unilateral, incidentally discovered asymptomatic carotid stenosis, ie, diagnosed on routine duplex ultrasound screening or diagnosed following the identification of a carotid bruit. Patients with stenosis less than 60% are managed medically, with periodic, usually annual, ultrasound surveillance to monitor stenosis progression. Although stenosis between 60% and 80% is typically managed with conservative medical treatment, this recommendation may need to be altered (see Table 95–2) based on individual circumstances. Examples include the following:

1. Contralateral carotid occlusion and a stenosis between 60% and 80% in the index carotid artery, which also supplies the territory of the occluded carotid artery via collaterals.
2. MRI or CT findings of "clinically silent" (asymptomatic) prior ipsilateral stroke(s).

The decision to treat based on the degree of stenosis is an approach supported and validated by the large prospective clinical trials (see Table 95–3). Although standard risk-factor modification approaches should be implemented in all these patients, there is no convincing evidence to date that these risk-modifying measures by themselves will reduce the stroke risk in patients with severe degrees of stenosis, and invasive/interventional approaches should be considered in these patients, assuming, of course, that the periprocedural risk is 3% or less. Hopefully the ongoing CREST II trial will enroll an adequate number of patients with > 80% stenosis to test the value of medical versus invasive treatments. On the other hand, if the majority of patients in CREST II have only a modest degree of stenosis (70%-80%), the trial may fail in its mission.

TABLE 95–5. Metrics That Have Been Used to Identify the Asymptomatic Patient at High Risk of Stroke

Criteria	Observations
Anatomic features	High grade (> 80%) carotid stenosis
	Progression of stenosis severity observed on surveillance ultrasound
	Isolated hemisphere
	Contralateral occlusion
Plaque characteristics	Unfavorable plaque composition ("lipid rich"), ulceration, or echolucency
	Intraplaque hemorrhage
Imaging	Microembolization signals on transcranial Doppler
	Incidental finding of ipsilateral occult cerebral infarction on MRI/CT

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

PATIENT SELECTION FOR CAROTID STENTING

Prior to recommending carotid stenting, it is important for the physician and the patient to understand the natural history of the condition without intervention; the procedure-related risks, which can immediately erode the benefits of a procedure done purely with the intent of future benefit, and the durability of the stenting procedure.

NATURAL HISTORY

Our understanding of the natural history of extracranial carotid artery disease is based on the stroke outcomes of patients in randomized clinical trials, performed more than 15 years ago and assigned to the medical or conservative arm in the symptomatic NASCET and ECST studies,[12,16] and the stroke outcomes in the asymptomatic ACAS and ACST trials.[17-19] The risk of stroke is approximately 15% in the first 6 months following a symptomatic event and between 2% to 3% per year in asymptomatic patients,[17] translating into a 5-year cumulative risk of around 11%; approximately half of these events will be major strokes (Table 95–3).

PROCEDURE-RELATED RISKS

Perhaps the most important advance in the past 15 years relates to our understanding of what constitutes "high stent risk."[53] It is important to remember that CEA was first performed in the 1950s, and over the course of three decades, surgeons defined high CEA risk patients by identifying anatomical features and comorbidities that would increase the risk of CEA. These high CEA risk patients were excluded from the major randomized CEA trials.

Evolution in Our Understanding of the Concept of "High and Standard Stent Risk"

To help the interventionist decide whether stenting is the appropriate treatment choice for a particular patient, it is important for the operator to understand, recognize, and differentiate the standard-risk from the high-risk CAS patient (Table 95–6). This determination based on an individualized analysis is the single most important element of the CAS risk-stratification process, and should be performed for every patient.

TABLE 95–6. Standard Risk for Carotid Stenting: Patient and Lesion Characteristics

Ideal Patient	Ideal Lesion (for Distal Embolic Protection)
Male/female; < 70 y of age	Favorable arch anatomy
Asymptomatic	Duplex EDV > 120 cm/s (stenosis > 80%)
Preserved brain function	Minimal tortuosity in artery cephalad to the stenosis
Good LV function, no aortic stenosis	Minimal calcification
Known coronary anatomy	No ulceration
Normal renal function	Lesion located on a straight segment and not on a bend
No contraindication to DAPT	Angle between ICA and CCA is less than 90 degrees

Abbreviations: CCA, common carotid artery; DAPT, dual antiplatelet therapy; EDV, end-diastolic velocity; ICA, internal carotid artery; LV, left ventricular.

The attributes that define high CEA risk are distinct from those that define high stent risk; hence a patient who is high risk for CEA does not automatically become suitable (ie, standard risk) for CAS.

The designation of high stent risk has evolved over time as operators became more experienced. The high event rates observed in the early CAS stent registries that enrolled high CEA risk patients (Table 95–7) resulted in large part from the unintentional inclusion of high stent risk patients; exclusion of these high-risk patients from later clinical trials resulted in a corresponding improvement in procedural outcomes. The protocol for the CREST study was developed in 1998 and did not specifically call out high stent risk exclusions. By 2005, halfway through the trial enrollment, the concept of high stent risk was better established, and in the second half of the CREST study, many of these high stent risk patients were excluded, with corresponding better outcomes.

Standard Stent Risk

Age is a very important determinant of risk in patients undergoing CAS (see Table 95–6). Similar to patients with poor LV function, patients with poor "brain reserve" and brain function are more likely to clinically manifest neurological events related to periprocedural embolization. Embolization is a universal occurrence during CAS procedures and happens despite the routine use of EPDs. Examples of patients with poor brain reserve include those who have experienced a prior large stroke, multiple small strokes or lacunar infarcts, and those with dementia. In patients with dementia, there are anecdotal reports wherein despite having a perfectly acceptable angiographic and acute clinical result (ie, no procedure related events), in the follow-up period, there is a marked deterioration in memory and other cognitive functions. The reason(s) for this is unclear but dementia should be at least a relative contraindication for CAS.

Figures 95–1 to 95–4 illustrate lesion and vessel features that are ideal for stenting using *distal* embolic protection. These features include:

1. A narrow, acute angle between the ICA and the ECA. The wider this bifurcation (ie, approaching or exceeding 90°), the greater is the anticipated technical difficulty in advancing a distal embolic protection filter device with a fixed-wire system (Figs. 95–5 and 95–6). This difficulty imparted by an open ICA/ECA angle is compounded if there is additional tortuosity in the ICA distal to the stenosis.
2. Minimal calcification and no ulceration. Some degree of calcification is nearly always found at the carotid bifurcation, but heavy concentric calcification in association with a severe stenosis is a major problem. Although the diagnosis of carotid calcification is straightforward and requires only fluoroscopy (Fig. 95–7), the distinction between deep, vessel-wall calcium and superficial calcium encroaching on the vessel lumen may be challenging, and the decision to declare the case unsuitable for CAS is largely subjective. We arbitrarily define heavy calcification as calcification ≥ 3 mm in width with concentricity defined by imaging in two orthogonal views. The unyielding nature of calcium along with the stiffness it imparts to the involved vessel segment makes it very difficult to pre-dilate and advance the EPD and stent delivery system through the lesion. Forcing these devices in an attempt to "cross" the stenosis not only increases the chances of prolapsing the sheath out of the common carotid artery, it also increases the risk of embolization, spasm, and dissection. Inability to completely dilate and expand a deployed

TABLE 95–7. CAS: Registry Outcomes in High CEA Risk Patients

Trial	Year (Last Patient Enrolled)	Sponsor	Stent	EPD	Death/Major Stroke Rate	Death/Stroke/MI Rate	Asymptomatic
SAPPHIRE	2002	Cordis	Smart/Precise	Angioguard	na	6.90%	71.2%
ARCHeR	2003	Abbott	Acculink	Accunet	2.90%	8.30%	76.2%
SECuRITY	2003	Abbott	Xact	Emboshield	3.00%	7.20%	na
BEACH	2003	Boston	Wallstent	Filterwire EZ	2.50%	5.40%	76.7%
MAVErIC	2004	Medtronic	AVE	GuardWire	3.00%	5.40%	na
CAPTURE	2006	Abbott	Acculink	Accunet	2.60%	6.10%	86.2%
EXACT	2007	Abbott	Xact	Emboshield	1.80%	4.60%	90.1%
EMPiRE	2008	Gore	Not specified	Gore Flow Reversal	1.60%	3.70%	68%
CAPTURE 2	2009	Abbott	Acculink	Accunet	1.40%	3.50%	86.9%
PROTECT	2009	Abbott	Xact	Emboshield	0.50%	2.30%	> 80%
CHOICE	2012	Abbott	Xact/Acculink	Emboshield/Accunet	1.80%	3.90%	> 80%

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; EPD, embolic protection device; MI, myocardial infarction; na, not applicable.

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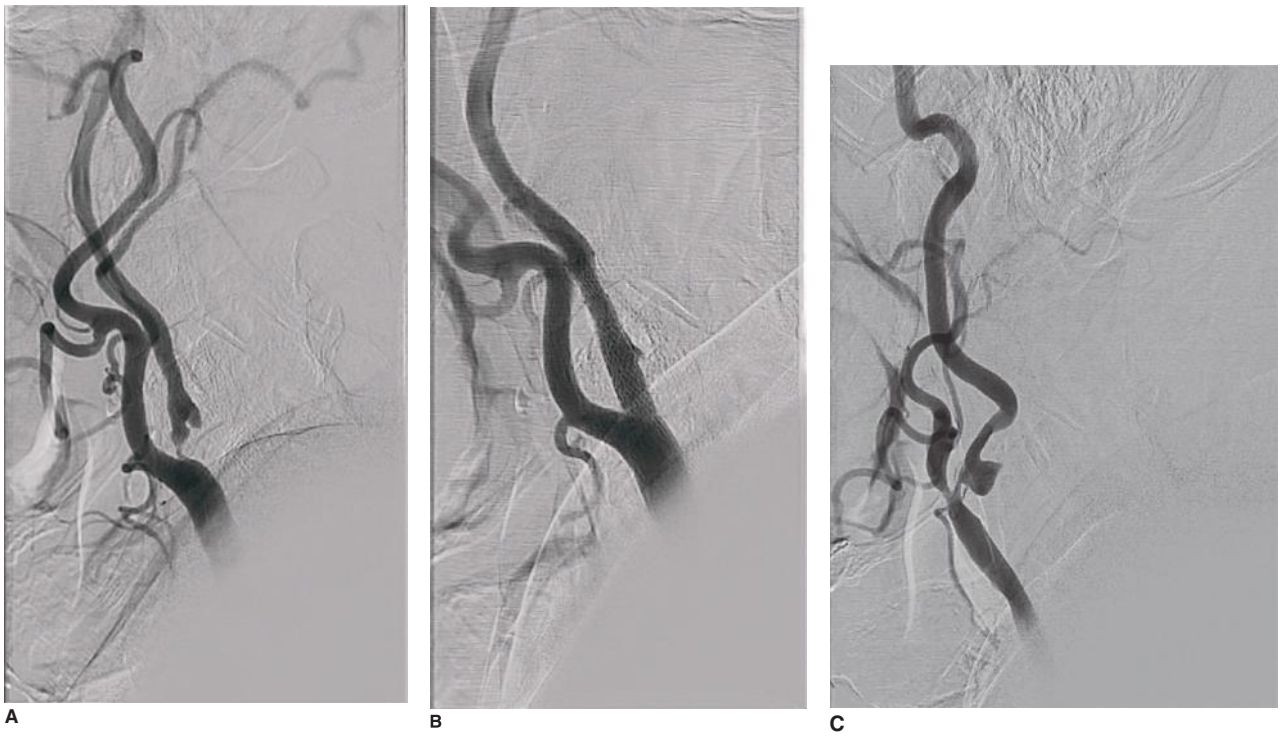


FIGURE 95–1. Severe bilateral carotid stenosis (suitable for both CEA and CAS). **Case Summary:** 72y male with T2DM, HTN, HPL; former heavy smoker. Right hemispheric TIA, 1 month prior to referral. **Noninvasive evaluation:** Carotid US (PSV/EDV): Right: 599/344. Left: 324/131. MRI negative for recent stroke. (**A**) **Invasive Angiography:** Arch: Type 2. **Assessment/Plan:** Symptomatic high grade RICA stenosis, suitable for CAS with distal embolic protection. (**B**) **Treatment:** RICA Stented with 10 × 8 X-ACT (self expanding, closed cell) nitinol stent with NAV-6 distal EPD (Both devices from Abbott Vascular). Postdilated with 5.0-mm balloon, uncomplicated. (**C**) Asymptomatic > 80% LICA stenosis. **Follow-up:** At 12 months RICA—Patent stent, normal flow velocities on US. LICA—managed conservatively (Dual antiplatelets, statins and RF modification) because of multiple interim medical and cardiovascular issues. Remains asymptomatic.

stent, despite using larger and/or high-pressure balloons, results in a stent with a "hourglass" appearance, leading to accelerated velocities of blood flow and turbulence through the stented areas.

3. The artery cephalad to the stenosis should be free of any significant kinks or bends. The presence or absence of this unfavorable feature is extremely important to note on the pre-procedure MRA, CTA, or invasive angiogram because it increases the degree of difficulty when attempting to place a distal EPD. Excessive vascular tortuosity is defined as two or more bend points that are 90 degrees or greater. At times the tortuosity is in the carotid artery proximal to the stenosis, and when extreme may impart a hairpin bend to the carotid artery (Fig. 95–8). Such severe tortuosity makes it impossible to position a sheath in the common carotid artery. Milder degrees of tortuosity in the common carotid artery may be straightened with a stiff wire; however, once the sheath is placed in the common carotid, the kink is transferred more cephalad and introduces an iatrogenic tortuosity in the internal carotid artery. Worsening grades of tortuosity increase the difficulty when attempting to cross the stenosis and may make device delivery difficult or impossible. Additionally, the straightening of the tortuous vessel segment by stiff wires or devices may result in vessel spasm and reduce antegrade flow. Thus, despite filter placement, the patient does not receive the benefit of brisk antegrade flow, and in the absence of adequate collaterals may manifest ischemic symptoms. Additionally, slow flow increases the risk of fibrin deposition within the filter. The longer the dwell time of the EPD, the higher the risk of an "iatrogenic thrombus." Iatrogenic tortuosity can be introduced by the placement of the sheath in a redundant carotid artery—hence tortuosity should be reassessed after the sheath is in place below the carotid bifurcation.

The degree of stenosis severity and eccentricity/concentricity are not problems as long as the flow in the vessel is normal (TIMI grade III). A severe stenosis in association with less than TIMI III flow ("string sign," Fig. 95–9) and an occluded carotid artery are contraindications for CAS. Ulceration is often noted—even on angiograms from asymptomatic patients—and although not a contraindication, operators should be aware that the risk of embolization may be higher, particularly during stent post-dilatation. Angiographic filling defects that are consistent with a thrombus are a contraindication to CAS.

Although both calcium and thrombus may appear as filling defects, the differentiation is based on the clinical presentation. Whereas a filling defect in a symptomatic patient should be presumed to be thrombus, filling defects in asymptomatic patients are frequently a result of calcium encroaching on the vessel lumen (see Fig. 95–7).

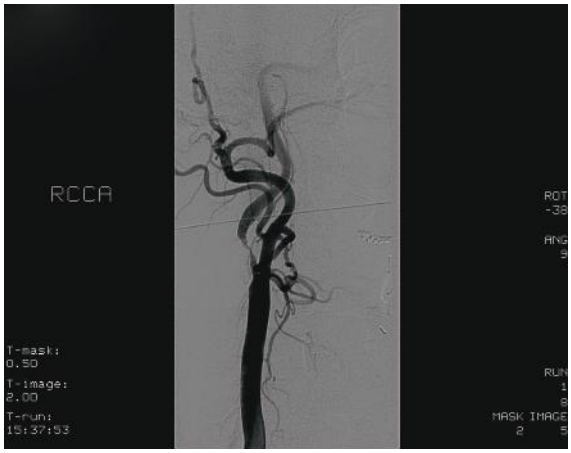
These unfavorable anatomical features—heavy calcification, visible thrombus, string sign, and carotid occlusion (see Figs. 95–7 and 95–9)—as a rule should be considered contraindications for CAS. Although special techniques (eg, use of a heavy gauge buddy wire to straighten tortuous vessel segments, use of cutting balloons to dilate unyielding lesions) may result in a satisfactory angiographic outcome, the risk of a procedure-related neurological event will likely be higher and can breach the acceptable periprocedural complication threshold.

PROCEDURAL CONSIDERATIONS IN CAROTID STENTING

INITIAL EVALUATION

Most if not all carotid revascularization procedures are elective and there is no justification for an ad hoc carotid procedure, ie, proceeding

A

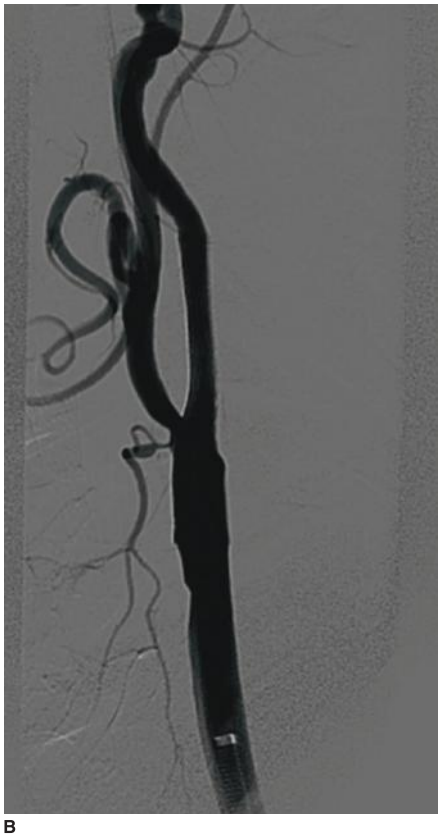


B

C

FIGURE 95–2. Severe RICA stenosis at the level of C-2 (anatomical high risk for CEA). **Case Summary:** 88y male with T2DM, HTN and s/p Left CEA several years earlier. One week prior to referral admitted with weakness of left upper and lower extremities and speech abnormalities. Made a full recovery. **Non invasive evaluation:** Carotid US (PSV/EDV): Right: 344/135. Left: Patent carotid artery with normal velocities. MRI positive for recent right hemispheric stroke. **Invasive Angiography:** Arch: Type 2. Isolated Right Hemisphere (absent anterior and posterior communicating arteries). **Assessment/Plan:** Symptomatic high-grade RICA stenosis, high risk for CEA (lesion at level of C-2) suitable for CAS with distal embolic protection (**A,** Lateral Projection; **B,** RAO). Increased risk in view of age > 80 years. **Treatment:** RICA Stented with 10 × 8 X-ACT with NAV-6 distal EPD. Postdilated with 4.5-mm balloon, uncomplicated (**C**). In view of the clinical circumstances (age, symptomatic stenosis) a single post inflation with a slightly undersized balloon (4.5 mm instead of 5.0 mm) was performed. Persistent hypotension and bradycardia post procedure recovered and discharged home on day 3. **Follow-up:** At 12 months RICA, patent stent, normal flow velocities on US. Asymptomatic.

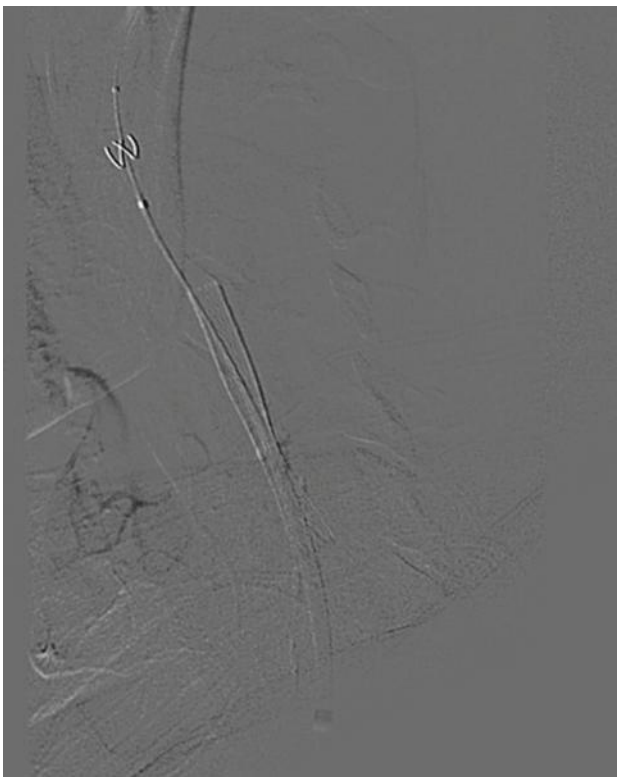
A



B

FIGURE 95–3. Ideal lesion and vessel morphology for carotid stenting. Note the ICA/ECA angle is acute and the artery cephalad to the stenosis is free of significant tortuosity. This was an asymptomatic stenosis in a 65-year-old male with type 1 DM, HTN, HPL, and 3V CAD. The contralateral carotid had been stented a few years earlier (outline of this self-expanding stent is seen in **A**) and was patent without restenosis. The severe stenosis was treated using a distal embolic protection device. Uncomplicated. Discharged the following day with instructions to be on aspirin and clopidogrel for 2 months. Pre (**A**) and post (**B**) images are shown.

A



B

C

FIGURE 95–4. Bilateral > 80% asymptomatic stenosis. **Case Summary:** 71y right-handed female with T2DM, HTN, HPL, obesity, and known CAD. Duplex velocities suggested bilateral > 80% stenosis (asymptomatic). Refused MRA because of claustrophobia. Offered medical treatment with strict control of risk factors. Elected to proceed with invasive angiography with CAS if appropriate. **Invasive Angiography:** Arch: Type 1. Bilateral > 80% stenosis (**A**). Neither anterior nor posterior communicating arteries were opacified (isolated hemispheres). **Treatment:** LICA stented with 10 × 8 X-ACT with NAV-6 distal EPD (**B**). Post dilated with 5.0-mm balloon, uncomplicated. Note that a closed cell stent was used for this treatment (preference of SI, GR). Cephalad to the stented segment there is a tortuosity/kink noted in the carotid artery. This is a result of redundancy of the carotid artery and the placement of the closed cell stent. No treatment is indicated. Withdrawal of the sheath from the carotid artery will further relax the artery and reduce the severity of the kink. The origin of the ECA has a severe stenosis. At the conclusion of the procedure, the ECA was open with TIMI 3 flow, despite a residual high-grade stenosis. There is no indication for treating this stenosis in an asymptomatic patient. On rare occasion, occlusion of the external carotid artery produces jaw claudication and treatment may be indicated in this instance. Discharged home the following day. **Follow-up:** At 6 months LICA—Patent stent, normal flow velocities on US. Asymptomatic. Treatment (CAS) of the high-grade asymptomatic RICA stenosis is planned.

FIGURE 95–5. High-grade tandem stenosis involving the distal common carotid and the proximal segment of the ICA. The ECA is occluded; this poses a challenge, because anchoring the wire in the distal ECA to facilitate placement of the sheath in the common carotid artery is not an option. A heavy-gauge anchor wire should be placed in the distal common; the operator needs to have excellent wire control to avoid traumatizing these soft plaques with the wire tip. The stenosis is fairly long, which increases the embolic burden and the chances of an intraprocedural event. Note the stenosis extends to the bottom of C-2 and such high lesions are considered high risk for CEA. This anatomy will be technically challenging and should be a contraindication for the beginner and low- and medium-volume operators.

to perform a carotid intervention during another scheduled invasive procedure (eg, coronary angiography). A comprehensive history and physical, including a detailed neurological exam, is a mandatory first step when evaluating a patient for a possible carotid intervention. Often patients referred for treatment of "symptomatic" carotid artery stenosis have other reasons for their symptoms including posterior circulation (vertebrobasilar) disease, or the culprit may be a cardioembolic source (eg, a patient with atrial fibrillation with thrombus in the atrial appendage). These patients have incidental, ie, asymptomatic, carotid disease and their risk assessment and treatment differs from the patient with true, symptomatic carotid artery stenosis. Another frequently encountered problem relates to suboptimal images resulting in unreliable noninvasive diagnostic studies.

The standard noninvasive method for the evaluation of carotid artery stenosis is duplex ultrasonography. Despite the overall high sensitivity and specificity, diagnostic accuracy varies widely between laboratories.[67] Therefore, trained, certified sonographers working in a quality-accredited laboratory are important for reliable and consistent diagnostic studies. Although ultrasound criteria corresponding to a > 80% stenosis on angiography (NASCET,[68] Fig. 95–10) vary considerably among different vascular laboratories, as a general rule if the peak systolic velocity is > 300 cm/s, end diastolic velocity is > 120 cm/s and ICA/CCA ratio is > 4,[69] the stenosis will typically qualify to be labelled > 80%.

The quality of the MRA study is influenced not only by the generation of the equipment but also by the scanning protocol (with or without gadolinium), the correct timing sequence, as well as the skill and the experience of the interpreting physician. CT angiography is less operator dependent; however, it exposes the patient to iodinated contrast and radiation. Moreover, the majority of carotid bifurcations are calcified, which may interfere with accurate interpretation of stenosis severity on CTA. Noninvasive diagnostic accuracy and

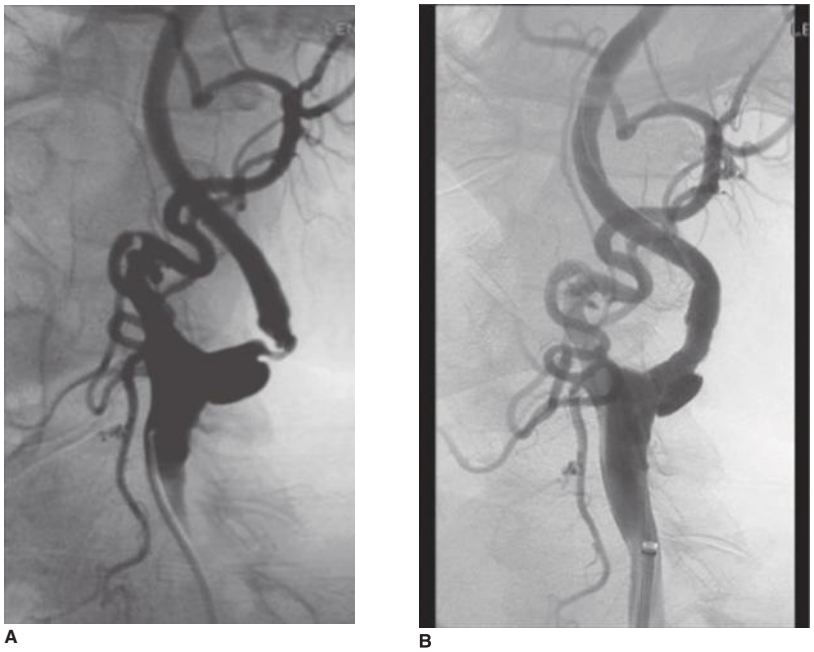
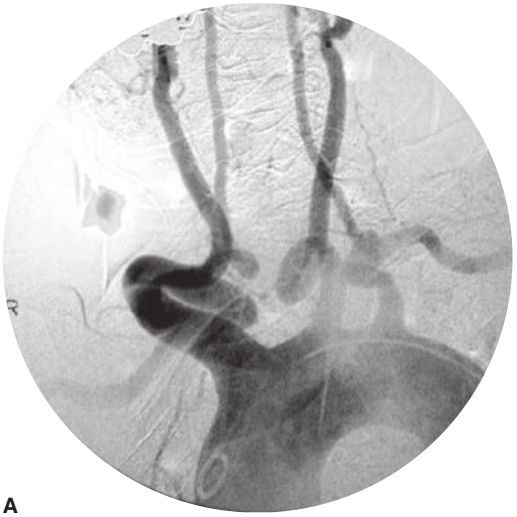


FIGURE 95–6. **A.** Greater than 90-degree (obtuse) ICA/ECA angle, a high-grade eccentric stenosis immediately distal to bifurcation and an ulcer proximal to the stenosis near the carotid bulb. Type 3 arch (not shown). The vessel distal to the stenosis is straight. **B.** Treatment result using an Emboshield (Abbott Vascular, USA) filter. The wire is independent of the filter, and this feature makes it easier to negotiate the unfavorable bifurcation as well as the severe eccentric stenosis. Predilatation may be needed. An open cell stent was used to treat the lesion on the bend; this stent design conforms to the ICA bend and does not introduce any additional bends in the ICA post stenting. Care should be taken to place the proximal end of the stent flush with the origin of the ICA—if it protrudes between the ICA origin and the CCA, the stent edge can cause problems in advancing the post-dilatation balloon as well as the filter-retrieval catheter. Note the ulcer is excluded and not obliterated, and no attempt should be made to obliterate the ulcer by using larger balloons. Flow to the ulcer crater will seal off in time. This anatomy will be technically challenging and should be a contraindication for the beginner and low- and medium-volume operators. Reproduced with permission from Creager MA, Beckman JA, Loscalzo J: *Vascular Medicine: A companion to Braunwald's Heart Disease*, 2nd edition. Philadelphia: Elsevier; 2013.

FIGURE 95–7. Extensive circumferential calcification of the internal carotid artery makes this lesion unsuitable for CAS. Subtraction imaging *without contrast* shows calcification of both the internal and common carotid arteries.

FIGURE 95–9. Severe ICA stenosis with "string sign" (flow less than TIMI III). Note the relatively complete filling of the ECA in comparison. The thrombus burden in such cases is high (even if it is not angiographically visible) and increases the risk of periprocedural embolization. These considerations should be incorporated into the risk analysis, especially in asymptomatic patients.



A

B

FIGURE 95–8. Even though the arch is type I, marked proximal tortuosity of the proximal segment of the innominate (**A**) or proximal common carotid artery (**B**) renders the anatomy unfavorable for carotid stenting. Although use of flow reversal with direct carotid access (System from Silk Road) may be an option, in general, such types of anatomy are contraindications for stenting.

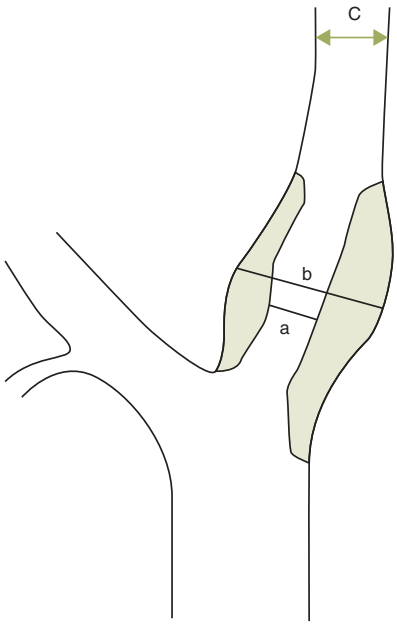


FIGURE 95–10. North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria for determining the degree of carotid stenosis. Luminal diameter at the site of greatest narrowing is recorded in three planes and is used as the numerator (a). A reference diameter is measured across a plaque-free section of the internal carotid artery distal to the stenosis (c) and is used as the denominator. The percentage stenosis is then calculated. The method used in the ECST trial compared luminal diameter at the site of greatest narrowing and compared it to the diameter of the carotid bulb (b). Reproduced with permission from Neale ML, Chambers JL, Kelly AT, et al: Reappraisal of duplex criteria to assess significant carotid stenosis with special reference to reports from the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial. *J Vasc Surg*. 1994 Oct;20(4):642-649.

reliability are important, especially in the patient with asymptomatic carotid stenosis.

The goal of the clinical exam and diagnostic testing is to provide answers to the following questions:

1. Is the patient symptomatic or asymptomatic?
2. If symptomatic, are symptoms referable to the stenosis at the carotid bifurcation?
3. What is the severity of the stenosis?
4. Risk assessment:
   a. Is the patient suitable for carotid stenting?
   b. Is the patient suitable for CEA?
   c. Overall recommendation: CAS, CEA, or continued medical management?

PREPROCEDURE ISSUES

Patients are admitted the day of the procedure and consented for brachiocephalic angiography and possible stent placement. An independent neurologist should document preprocedure neurological status and functional scores (typically using NIH and Rankin scales). All symptomatic patients, those with a prior history of stroke, and patients with an abnormal neurological examination should have a brain CT or MRI scan.

It is preferable to schedule the interventional procedure during the early part of the day. Patients are usually NPO overnight, and prolonging this state, especially in the elderly, can exaggerate the hemodynamic disturbances resulting from carotid sinus stimulation. Since these hemodynamic perturbations are treated by prophylactic administration of atropine and volume expansion with isotonic fluids, a preprocedure 2D echocardiogram to help define left ventricular function and exclude significant aortic stenosis is advised. Likewise, knowledge of the coronary anatomy is very helpful. In the absence of prior evaluation of the coronary arteries, diagnostic coronary angiography at the time of the carotid study should be considered. Often, especially in the elderly, asymptomatic patient, diagnostic carotid and cerebral angiography is performed as a stand-alone, first-stage procedure. This approach, although not convenient to the patient and the family, provides the operator an opportunity to more accurately assess the anatomy, compute the risks, and discuss the findings with the patient and the family before electively scheduling the intervention.

ANTIPLATELET AGENTS AND ANTICOAGULANTS

In the clinical protocol, great emphasis is placed on dual antiplatelet therapy before and after carotid stenting. The nonevent of stent thrombosis and the low rates of periprocedural and postprocedural embolic events are predicated upon the administration of the correct doses of adjunctive antiplatelet therapy. All patients should receive aspirin 81 mg and clopidogrel 75 mg orally for a week prior to the procedure, and both of these medications are continued for a minimum of 8 weeks after procedure to allow healing and stent endothelialization. If a patient has not received aspirin and clopidogrel before the procedure for a week, a 600-mg loading dose of clopidogrel should be given at least 4 hours prior to the procedure. If this is not possible, the procedure should be rescheduled. There is no experience using prasugrel or ticagrelor in patients undergoing carotid stenting. The approach to patients who are on chronic anticoagulation with warfarin should be individualized, with the recognition that in some cases the bleeding risk on triple therapy may be prohibitive and CAS may be contraindicated.

ANTIHYPERTENSIVE AGENTS AND BETA-BLOCKERS

In general, these medications are withheld the day of the procedure to avoid exaggerating the bradycardia and hypotension resulting from carotid baroreceptor stimulation. After the procedure, the blood pressure and heart rate need to be followed closely and these medications can be given as soon as the clinical situation permits. In patients with restenosis following prior carotid endarterectomy (denervated carotid bulb) or in cases where the location of the stenosis is such that balloon inflations and stent deployment are clearly cephalad to the carotid bifurcation, there may not be a need to discontinue these medications, and blood pressure in the postprocedure period needs to be carefully managed to minimize the risk of cerebral hyperperfusion syndrome.

PROCEDURAL CONSIDERATIONS

Table 95–8 lists the 10 steps in the CAS procedure.

Diagnostic Angiographic Evaluation

It is important to have a high-quality, complete diagnostic cerebral and extracranial carotid angiogram prior to initiating the stenting procedure. State-of-the art digital subtraction angiography with the ability to vary the field of view is available in all modern-day catheterization laboratories; neurovascular procedures should not be performed in angiography suites equipped solely with a C-arm. Aortic arch angiography is not routinely performed at our center; the amount of contrast required to perform this single angiogram is equivalent to what is needed to complete the entire selective angiographic study. Many of our patients have had MRA, which helps identify not only the degree of stenosis at the carotid bifurcation but also tortuosity of the carotid

TABLE 95–8. The 10 Steps in the Carotid Artery Stent Procedure

Vascular access
Angiographic evaluation
Carotid sheath placement
Lesion crossing and placement of an embolic protection device (EPD)
Predilatation
Stent deployment
Postdilatation
EPD Withdrawal and Final Angiographic Assessment
Sheath Removal, achieving hemostasis
Management of hemodynamics and treatment of complications

vessels. MRA can also define issues such as anomalous origins of the vessels (eg, independent origin of the left vertebral artery from the arch and origin of the left carotid artery from the innominate artery). However, neither MRA nor CTA can accurately define the extent of unfolding and elongation of the aortic arch and posterior displacement of the origin of the great vessels. This assessment of unfavorable aortic arch anatomy is best made during the invasive angiographic procedure, one important advantage of separating the diagnostic procedure from the intervention (see Fig. 95–11 for classification of the aortic arch).

A complete cerebral angiogram requires anatomical definition of both intracranial as well as extracranial arterial anatomy as well as the dominant vertebral artery (usually the left vertebral artery). Although in our center we often selectively image the dominant vertebral artery, the decision to perform selective cannulation and angiograms of the vertebral artery should be individualized. The vertebral arteries not infrequently have a tortuous course and the vessel is prone to spasm—features that can predispose to dissection with potentially catastrophic sequalae. Brachiocephalic angiography has several advantages in that it is a reliable and reproducible method for measuring the degree of carotid stenosis. Anatomical conditions that would increase the risk of carotid stenting, such as a dilated aortic arch, heavily calcified stenosis, and marked vessel tortuosity, can be easily identified. This approach allows accurate assessment of the cerebral circulation along with collaterals.

The term "isolated hemisphere" describes the anatomical situation where the cerebral hemisphere of interest is entirely dependent on the ipsilateral internal carotid artery for its blood supply because of the absence of the anterior and posterior communicating arteries. Angiography reliably demonstrates significant flow limiting stenosis distal to the carotid bifurcation. Although the bifurcation stenosis may be treatable, the ultimate benefit of stroke reduction may not accrue to the patient because of this additional disease and may influence the decision to proceed with CAS for bifurcation disease.

In the event there is an intraprocedural neurological event, the post-event intracranial angiograms can be compared with the baseline images. The main risks of invasive cerebral angiography relate to the use of contrast and the risk of a neurological event which in experienced hands is very small (0.1%).

The typical sequence of acquisition of the angiographic images is described next. We first selectively image the left subclavian artery in a PA view. The ostium of the left vertebral artery is usually seen well in the frontal projection; if not, the RAO-cranial projection is recommended. If a selective angiogram of the left vertebral artery is to be acquired, a roadmap to facilitate entry and selective placement of the catheter is recommended. Selective or nonselective intracranial views of the vertebrobasilar system are acquired in the lateral and steep AP cranial views. Next the left carotid artery is imaged. The bifurcation is imaged in LAO 45 as well as lateral projections. If the bifurcation is "over-rotated," an AP caudal view usually separates the external and internal carotid arteries very well. Intracranial images of the left carotid artery are acquired in the lateral and AP cranial (15-30 degree) views. An innominate angiogram is performed in the RAO caudal view. This view is optimal for separating the common carotid and the right subclavian arteries and hence very useful for defining the origin of the right subclavian artery. Finally, selective angiograms of the Right carotid artery are acquired. The bifurcation is imaged in the RAO 45 as well as the lateral projections. Intracranial images of the right carotid artery are obtained in the lateral and AP cranial (15-30 degree) projections.

Emboli Protection Devices

In 1984, Vitek and his neuroradiology colleagues from the University of Alabama at Birmingham[70] reported angioplasty of the innominate artery aided by distal occlusion balloon protection of the common carotid artery. This early report represents the first percutaneous

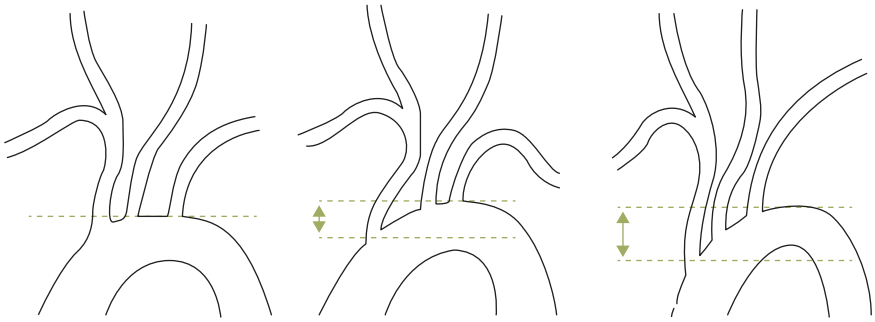


FIGURE 95–11. Classification of the aortic arch. In the frontal projection, a horizontal line is drawn across the origin of the left subclavian artery. **TYPE I**. All the great vessels originate at the same level and meet this line. Access to the left carotid and the innominate artery is easiest with this aortic arch configuration. **TYPE II** and **TYPE III**. As the aorta becomes more unfolded and elongated (a function of increasing age and hypertension) the origin of the great vessels becomes displaced more posterior, and on the frontal projection, the origins are progressively displaced inferior to the horizontal line referenced above. Access becomes increasingly difficult because a catheter approaching from the descending aorta tends to prolapse into the ascending aorta. Reproduced with permission from Madhwal S, Rajagopal V, Bhatt DL et al. Predictors of difficult carotid stenting as determined by aortic arch angiography. *J Invasive Cardiol*. 2008 May;20(5):200-224.

supra-aortic intervention performed with the benefit of distal embolic protection. Because placement of the sheath occurs prior to the deployment of the EPD and release of emboli occurs to some degree during all stages of the carotid intervention, all steps of the carotid intervention can never be completely "emboli protected." The risk of embolization appears to be highest during stent deployment and post-stent balloon dilatation.[71]

A number of EPDs are available and can be broadly categorized as flow-interrupting (occlusive) and flow-preserving devices. Flow-interrupting EPDs can be subdivided into distal occlusion and proximal occlusion types. An example of a distal flow-interrupting EPD is the Percusurge GuardWire (Medtronic, Minneapolis, MN. Proximal occlusion devices include those developed by Gore (Flagstaff, AZ) and the Mo.Ma device (Medtronic). Although flow-interrupting, occlusive-type embolic protection devices are intuitively appealing (no blood flow = no emboli), there have been some issues with their use. For example, it is mandatory to demonstrate a robust collateral circulation to the hemisphere that is being treated to permit occlusion and interruption of antegrade flow in the ipsilateral carotid artery. Device preparation and testing of the GuardWire is very different from that of a coronary balloon. Infrequent use of the Percusurge wire as well as occasional device failure resulting from inadequate balloon inflation and suboptimal seal of the carotid artery and/or premature deflation, has resulted in virtual abandonment of this device for carotid intervention. The rationale for use of the proximal occlusion devices is based on interruption of antegrade flow and "flow-reversal" in the ipsilateral internal carotid artery. This combination is achieved by balloon occlusion of the common carotid as well as the external carotid arteries. The multicenter ARMOUR Trial[72] evaluated the 30-day safety and effectiveness of the MO.MA proximal cerebral protection device (Medtronic) for CAS in 262 high surgical risk patients. Mean age was 75 years, 29% were older than 80 years, and 15% were symptomatic. The 30-day incidence of stroke, death, or myocardial infarction was 2.7%, with a 30-day major stroke rate of 0.9%

The system from Silk Road Medical involves introduction of a sheath via a small incision made in the common carotid artery, low down in the neck, just above the clavicle. The sheath is connected to a system that will reverse blood flow from the ipsilateral carotid artery and any embolic debris will be captured in a filter outside the body. The filtered blood is then returned through a second sheath placed in the femoral vein in the groin. Thus the system allows stenting and balloon angioplasty to be performed while blood flow is reversed (TCAR, or transcarotid artery revascularization procedure). After the stent has been deployed, flow reversal is turned off and blood flow to the brain resumes in its normal direction. This device and strategy was tested in the Roadster multicenter trial.[73] Of the 141 patients enrolled in the pivotal study, 25% were symptomatic. Stroke and death were noted in 2.8% (4 of 141). Strokes were seen in 1.4% (2 of 141), and stroke, death, and MI occurred in 3.5% (5 of 141). Cranial nerve injury was observed in one patient.

Although procedural outcomes using these devices appear favorable,[72-74] since the catheters are larger or require surgical incision of the carotid artery (TCAR), these will likely be used as "niche devices." They are particularly useful in cases with tortuous distal ICA and/or unfavorable aortic arch anatomies as well as for lesions with filling defects that may embolize during wire passage, prior to deployment of distal EPDs.

The nonocclusive, flow-preserving devices are the filters. Depending on their construction, the body of the filter can be supported by a nitinol frame or it may be unsupported and resemble a windsock. The underlying principle and rationale of use is the same for all filter EPDs: preserving antegrade flow while preventing passage of the embolic debris. As may be expected, each of these EPDs has certain unique features and familiarity with their construction and attributes will allow rational selection of the device most appropriate for use with a particular anatomy.

EPDs are standard of care for carotid stenting procedures in clinical practice. Given the wide choices, devices are selected based on operator familiarity, preference, experience, and compatibility with the clinical situation and vascular anatomy.

BRIEF REVIEW OF THE TECHNIQUE

The procedure is performed under local anesthesia; we do not recommend sedation. The heart rate, rhythm, blood pressure, and neurological status should be closely monitored throughout the intervention. The femoral approach is preferred, and either unfractionated heparin (target ACT around 250) or bivalirudin[75] is used for systemic anticoagulation. A 6-Fr, 90-cm-long sheath is placed in the common carotid artery below the bifurcation, and accomplishing this step in a safe and expeditious manner is critically important. Recognizing and responding appropriately to difficult access situations (which may include procedure termination prior to a complication) constitute a large and important part of the learning curve.

Wires ranging from soft, atraumatic 0.014-inch coronary wires to 0.038-inch stiff Amplatz wires may be needed in various stages of the procedure. The operator and the assistant must exercise excellent wire control and should be aware of the position of the distal wire tip at all times. This will minimize the risk of wire-induced perforation, spasm, and dissection. A suitable distal embolic protection device (our preference) is placed cephalad to the stenosis, and the dwell time of the embolic protection device should be tracked. The median dwell time in an experienced lab should be approximately 7 minutes. The longer the EPD is in the body, the higher the chance of fibrin accumulation and (iatrogenic) thrombus formation within the filter. The lesion is dilated with a small-diameter (generally 3.0 mm) low-profile coronary balloon; the goal is to create enough room to allow easy passage of a 5- or 6-Fr stent delivery system without major plaque disruption and creation of a flow-limiting dissection. A self-expanding nitinol stent (typically closed cell, 40 mm in length and 8-10 mm in diameter) is deployed across the bifurcation. The stent is postdilated using a 5.0-mm balloon, restricting this step to a single inflation. Balloon deflations should be performed gradually, typically over 30 to 45 seconds. The EPD device is retrieved, and control extracranial and intracranial angiograms in views comparable to baseline images are performed using the 90-cm sheath, which is then exchanged for a short 6Fr sheath, sutured in place, and removed when the ACT is subtherapeutic. Routine prophylactic placement of a temporary pacing wire is not necessary except in patients with severe aortic stenosis, left main disease, or severe LV dysfunction. Use of glycoprotein IIb/IIIa inhibitors is contraindicated.

Patients are monitored in a telemetry unit, and although we have reported the feasibility and safety of ambulatory carotid stenting,[76] our routine practice is to admit patients post-procedure for an overnight stay to allow periodic neurological evaluation and close hemodynamic monitoring. Although "low blood pressure" is not unusual in the post-procedure period, other causes such as retroperitoneal hemorrhage related to access site bleeding should be excluded as a cause of any unexplained, persistent hypotension. Before discharge, the patient should be reevaluated by the same neurologist who examined the patient pre- procedure and the NIH and Rankin stroke scale scores should be calculated. More than 95% of patients will be ready for discharge approximately 24 hours following the procedure. Follow-up visits for clinical evaluation and carotid duplex ultrasound are scheduled for 1 month, 6 months, and 12 months after the procedure.

Subsequently, the patient is followed on an annual basis with a carotid duplex ultrasound.

STENTS

To eliminate the risk of deformation and crushing[22,23] seen with balloon expandable stents, self-expanding stents are exclusively used for carotid stenting with the following notable exceptions:

1. When treating an aorto-ostial stenosis of the common carotid artery.
2. When the stenosis and treatment involves the distal portion of the cervical carotid artery (close to the skull base). There is minimal risk of stent deformation of a balloon expandable stent deployed at this level and advancing the bulkier 5- or 6-Fr self-expanding stent delivery systems to the distal internal carotid artery can be technically difficult.
3. On rare occasion, if despite predilatation with a 5.0-mm balloon the self-expanding stent cannot be advanced without resistance through the stenosis (eg, when dealing with a rigid, heavily circumferentially calcified stenosis of the carotid artery), a 5.0-mm balloon expandable stent is first deployed at the bifurcation. This prevents recoil at the lesion site and permits passage of a self-expanding stent. The latter functions as the definitive stent and the constant, externally directed radial force of nitinol prevents deformation of the balloon expandable stent.

Although the elgiloy (a cobalt chromium alloy) tracheobronchial Wallstent (Boston Scientific, Natick, MA) was initially used, currently most operators worldwide use nitinol (an alloy of nickel and titanium) self-expanding stents.

MANAGEMENT OF HEMODYNAMICS

The carotid sinus baroreceptor, innervated by the glossopharyngeal nerve (cranial nerve IX), is located in the adventitia of the carotid artery and is stimulated by balloon inflation and stent expansion stretching the vessel wall. The physiological role of this baroreceptor is to detect, respond, and thereby regulate the systemic blood pressure. Stretching of the carotid sinus baroreceptor stimulates the glossopharnygeal nerve, which in turn stimulates the vasomotor center in the medulla via the tractus solitarius, which then modulates the activity of the autonomic nervous system (suppresses sympathetic and stimulates parasympathetic output). The net effect of stimulation of the carotid baroreceptor is bradycardia (negative chronotropy) as well as some reduction in cardiac contractility. Additionally, the decreased sympathetic output results in vasodilatation, causing hypotension. As might be expected, carotid sinus stimulation with the resultant hemodynamic perturbations are most profound when the lesion and the stretch from the postdilatation balloon involves the carotid bifurcation, less so if the stenosis is cephalad to the bifurcation; these changes are not seen (or occur with much less intensity and frequency) in the post CEA patient whose carotid bulb is denervated. The bradycardia and hypotension can be profound and worse in younger patients as well as in patients with highly calcified stenosis (where higher pressures are used for postdilating the stent).

Beta-blockers, diuretics, and other antihypertensive agents are typically withheld on the morning of the procedure. The patient must be well hydrated, and procedure-related hypotension and bradycardia are treated with fluids 1.0 mg of prophylactic atropine, and small aliquots of alpha agonists. Close attention should also be paid to the management of the blood pressure after the procedure. Although the hemodynamic effect of the atropine and any alpha agonists used during the procedure will wear off quickly, in the postprocedure phase, unless the patient is symptomatic (which is the exception), there is usually no need to treat bradycardia or hypotension even though the blood pressures may be as low as 70 or 80 mm Hg. The systolic blood pressure will typically increase by 15 to 30 points by next morning. There are two main problems with persistent hypotension: (1) on occasion, patients with a periprocedural embolic event or a severe contralateral carotid stenosis can become symptomatic; and (2) patients with baseline renal insufficiency typically have an elevation of creatinine. Even though on average less than 30 mL of contrast is used for the stenting procedure, the combination of contrast exposure and persistent postprocedure hypotension results in worsening of renal function.

On the other hand, if the drop in blood pressure is less than expected and continues to be high following postdilatation (eg, in the post-endarterectomy patient with severe post-CEA restenosis), this situation increases the risk of hyperperfusion syndrome. Unfortunately, it is difficult to provide precise recommendations at what level the BP needs to be maintained, and it is not clear as to what medications should be used to dial down the blood pressure. In the poststenting period, patients are very sensitive to nitroglycerine because it overcomes the compensation and/or exaggerates the vasodilatation mediated via the autonomic system in the stented patient.

MANAGEMENT OF NEUROLOGICAL COMPLICATIONS

During the procedure, the neurological status of the patient should be monitored at frequent intervals. In our interventional suite, we follow a simple protocol—asking the patient to squeeze a toy placed in the contralateral hand. Conversing with the patient and judging the speed and the appropriateness of the response to simple questions is also very useful. Any departure from baseline, including frequent yawning in a nonsedated patient, all point to a neurological event (which at times can be very subtle) that should not be ignored.

In our experience, corroborated by the outcomes of the large prospective randomized trials like CREST, the risk of a major stroke during CAS is low, a benefit of using EPDs to trap the "larger" emboli. TIAs and minor strokes may be the result of embolic particles that are able to evade the filters, or the result of embolization that occurs during the "unprotected" phases of the procedure.

If the patient develops a neurological deficit during the procedure, the procedure should be completed, the EPD removed, and normal flow established. Patients should be hydrated with isotonic fluids and adequate blood pressure should be maintained (both hypotension and relative dehydration worsen the effects of small emboli that otherwise may be clinically silent). At the conclusion of the procedure, the patient should be reassessed clinically and intracranial angiograms should be repeated in views comparable to baseline projections. The angiographer should look for any occlusion of a proximal vessel segment, which requires intervention to lessen the likelihood of a major stroke; distal occlusion of a small branch, which can usually be managed with observation; and slow flow and/or identification of emboli in multiple branches, which generally has a poor prognosis.

In circumstances where neurovascular rescue is required, mechanical recanalization techniques may be utilized in an attempt to restore flow in the involved area of the brain. It is generally not advisable to use IA thrombolysis as the risk of intracranial bleeding is quite high.

On rare occasions, a patient may develop ipsilateral partial or complete loss of vision as a result of retinal infarction. Unless there is spontaneous recovery of the vision soon after the event, the prognosis for full recovery of vision is poor.

The risk of a clinically significant intracerebral bleed is approximately 0.5%—a complication that cannot be prevented by the best embolic protection devices. Downward modulation of the dose of anticoagulants targeting a lower ACT (around 250 seconds), recognizing that the use of glycoprotein IIb/IIIa inhibitors during carotid stenting is contraindicated, and with careful monitoring of the hemodynamics, the chances of an intracerebral bleed can be minimized.

CEREBRAL HYPERPERFUSION SYNDROME

Cerebral hyperperfusion is defined as an increase in blood flow of more than 100% from baseline and cerebral hyperperfusion syndrome (CHS) is hyperperfusion associated with a neurological deficit. Although CHS does not occur frequently, its consequences can be devastating. An increase in ipsilateral blood flow to the affected cerebral hemisphere may occur after carotid stenting (or endarterectomy); it is usually asymptomatic.[77] Although there are a host of possible mechanisms responsible for the failure of auto-regulation at the cerebral microcirculatory level (the basic mechanism underlying cerebral hyper-perfusion),[78-82] the pathophysiology is not completely understood.

Patients with severe (> 90%, subocclusive stenosis) and limited collateral supply (isolated hemisphere) are at the greatest risk for hyperperfusion.[83] Baseline severe hypertension and persistence of this increased blood pressure in the postprocedure period (not uncommon in patients after endarterectomy) can result in hyperperfusion that can last several days after the procedure.[83] Hyperperfusion resulting in a major intracerebral bleed is a concern. The most common clinical symptom of cerebral hyperperfusion is headache; several patients report this symptom on the table soon after the procedure is completed and it never progresses beyond this symptom. The headache may last a few days and is typically unilateral with a nonfocal neurological exam. A more serious presentation, possibly related to cerebral edema, is seizure activity, again with an otherwise normal exam. Patients with CHS can present with a variety of neurological deficits including isolated speech disturbance. In patients who develop neurological symptoms following carotid revascularization, a number of etiologies must be considered in the differential diagnosis. Differentiation must be made between procedure-related embolic complications, resulting in an ischemic infarct—a manifestation of a low-flow state, and a high-flow state characteristic of CHS. The diagnosis of CHS is best confirmed with MRI.[78]

Lowering blood pressure and anticonvulsant therapy are the most important treatments to reduce the degree of cerebral edema and seizures. As vasorelaxation may further increase cerebral blood flow, calcium antagonists and nitrates are contraindicated in the treatment of CHS. Hence, the operator must resist the urge to administer nitrates to relieve spasm; for example, at the site of deployment of the EPD noted on the postprocedure angiogram. The spasm will resolve gradually with time, and although nitrates will rapidly resolve the spasm, they can also predispose to the development of hyperperfusion. Because of their ability to reduce cerebral perfusion pressure, labetalol and clonidine[78,84] are the preferred agents. The duration of therapy may be for several days or even months after procedure.[85] There is no evidence to support the treatment of cerebral edema, although corticosteroids and barbiturates have been used to good effect. Prophylactic anticonvulsant treatment is not recommended but should be introduced if seizures occur.[78] As a result of the relative infrequency of this condition and the heterogeneity of presentations, it is hard to generalize the outcomes following CHS. However, the limited data from the CEA literature suggest that one-third of the patients may have some residual disability following CHS,[86] with others reporting mortality rates of up to 50%.[87]

RESULTS OF CAROTID STENTING WITHOUT EMBOLIC PROTECTION

As was the case with other arterial percutaneous interventions, the availability of stents for treatment of carotid disease resulted in predictable outcomes and soon stenting became the standard of care. Prospective observational studies of carotid stenting were initiated in the mid 1990's,[88] and even during this early period, the outcomes were good when assessed in terms of outcomes of disabling stroke or death. Nondisabling neurologic events were more frequent in patients with advanced age, complex aortic arch and internal carotid artery anatomies, and severe internal carotid artery stenosis.[89,90]

Numerous case reports and clinical series of carotid stenting without embolic protection have been published.[89-102] These were mixed series of symptomatic and asymptomatic patients, with varying degrees of arterial stenosis. Asymptomatic patients were generally required to have more severe stenosis or additional evidence of compromised cerebral circulation.[89,94,99] Some reports included common carotid artery lesions, which are not easily accessible by surgical techniques.[89,94,100,101] These early studies reported procedural success of > 95% with periprocedural minor stroke rates of 1.6% to 4.8% and major stroke and mortality rates between 1% and 1.5%.

Reviews of the status of carotid artery stent placement prior to the introduction of embolic protection devices were published in 1998[102] and 2000.[92] Thirty-six centers participated in the survey, which included 5210 stenting procedures with a technical success rate of 98.4%. The 30-day rates of TIAs, minor strokes, major strokes, and mortality were 2.6%, 2.5%, 1.4%, and 0.8%, respectively.[92] Technical failures were usually related to inability to access the common carotid artery (2%-7% of patients) and prolonged procedural time was associated with increased morbidity.[102] It is important to note that these were observational studies and the outcomes were not audited, and so the reported results were probably better than the outcomes obtained when a neurologist examined each patient after carotid stenting.

RESULTS OF CAROTID STENTING USING EMBOLIC PROTECTION

Neurologic events related to embolization during CAS were not unexpected. Transcranial Doppler studies showed that the majority of particles were released from the atheromatous plaque during stent deployment and postdilation of the stent; however, it should be recognized that embolization can occur during any phase of the procedure.[71] The embolized fragments consist of plaque debris, fibrin and platelet aggregates, lipid vacuoles, and calcium fragments.[103,104] Evidence of embolization on TCD provided the rationale for use of embolic protection systems during carotid stenting.[105,106]

CAROTID STENTING IN HIGH CAROTID ENDARTERECTOMY RISK PATIENTS

Table 95–4 lists anatomical characteristics and comorbidities that are used to define high CEA risk. In the NASCET study involving symptomatic patients, contralateral occlusion was not an exclusion for entry, and 30-day risk of stroke and death in this cohort was 9.4% (approximately 2.2 times the risk without contralateral occlusion).[15] The surgical outcomes in high CEA risk patients have never been tested in a large multicenter prospective trial with independent neurological assessment and event adjudication, rendering conclusions about benefit of CEA in this population unclear.

Initial studies of CAS with embolic protection were not randomized (registry data) trials and only included patients who were at high risk for CEA. The large number of registries of CAS in high-risk CEA patients was a result of the fact that the FDA required reporting the results of each carotid stent and embolic protection device as a condition of marketing approval (see Table 95–7).[107-113] The study design, study hypothesis, and statistical approach were largely similar for all the registries: the goal was to determine whether outcomes in high CEA

risk patients treated with a particular sponsor's stent in conjunction with their embolic protection device were less than or equal to those of an objective performance criteria (OPC) derived from historic controls undergoing CEA. An OPC of 15% for patients with comorbidities and 11% for patients with anatomical risk factors was negotiated a priori and agreed to by the FDA. The SAPPHIRE study[110] was the only one that included a randomized arm comparing outcomes of CAS and CEA in patients at high risk for CEA.

THE SAPPHIRE STUDY

This multicenter, *noninferiority*, randomized study was conducted in 29 centers across the United States and enrolled symptomatic patients (≥ 50% stenosis on duplex ultrasound, 29% of the patient population) and asymptomatic patients (≥ 80% stenosis on duplex ultrasound). The primary end point was the cumulative incidence of death, stroke, and MI within 30 days of treatment or death and ipsilateral stroke between day 31 and 1 year from the time of the procedure. Although the inclusion criteria included high CEA-risk patients, prior to randomization, all members of the team (neurologist, vascular or neurosurgeon, and interventionalist) had to agree that the patient was a suitable candidate for either endarterectomy or stenting. If the surgeon assessing the patient concluded that endarterectomy could not be safely performed but the interventional physician judged that stenting was feasible, the patient was not randomized but entered into a stent registry (n = 406). Likewise, if the surgeon deemed the patient suitable for surgery but the interventional physician did not think that stenting was feasible, the patient was entered into a surgical registry (n = 7).

Between August 2000 and July 2002, 747 patients were enrolled in the study, and 334 patients underwent randomization. Of the 167 patients randomly assigned to stenting, 159 received the assigned treatment; of the 167 patients assigned to surgery, 151 received the assigned treatment; all 334 patients were followed. Patients undergoing CAS received the nitinol self-expanding Precise stent and the Angio-Guard filter (Cordis, Johnson and Johnson, New Brunswick, NJ). In early 2002, the pace of enrollment abruptly slowed because several carotid-stent registries (nonrandomized) had become available and were competing for the same group of patients. The trial was therefore terminated (original goal was 600 randomized patients) and the primary end point was analyzed with respect to the noninferiority of CAS compared with CEA, using interval-censored survival data at 1 year.

By intention to treat (ITT) analysis, the primary end point at 1 year occurred in 20 CAS patients (12.2%) and 32 CEA patients (20.1%; $P = 0.05$). Cranial nerve injuries were seen in 5% of the patients undergoing CEA. The investigators concluded that carotid stenting with embolic protection was not inferior to CEA in a high surgical-risk population. The clinical durability of carotid stenting in this patient group (freedom from stroke during follow-up) was demonstrated by the 3-year follow-up data, which showed that there was no significant difference in long-term outcomes between patients who underwent CAS using an embolic protection device and those who underwent CEA.[114]

POSTAPPROVAL REGISTRIES

Postapproval studies are required by the FDA as part of the condition for marketing approval of stents and embolic protection devices. The purpose of this is to identify any unanticipated events related to the devices. Additionally these studies allow the assessment of stenting in the "real-world environment" as opposed to a controlled study environment. Gray and colleagues[107] reported the outcomes of two such prospective multicenter (280 US sites, 672 operators) postmarket surveillance studies wherein CAS was performed with distal embolic protection using filters in high CEA risk patients (CAPTURE 2 and EXACT). These studies had pre- and postprocedure neurological evaluation and independent adjudication of neurological events. There were 3500 patients in CAPTURE,[111] 4175 in CAPTURE-2,[107] and 2145 in EXACT.[107] Among these three postsurveillance studies, 86% to 90% of the patients were asymptomatic. The 30-day stroke and death rate for symptomatic patients was 12.1%, 6.2%, and 7.0% in CAPTURE, CAPTURE-2, and EXACT, respectively. The 30-day stroke and death rate for asymptomatic patients was 5.4%, 3.0%, and 3.7% in CAPTURE, CAPTURE-2, and EXACT. Symptomatic patients 80 years and older had a 30-day stroke and death rate of 10.5% (compared to 5.3% in younger patients), and asymptomatic octogenarians (or older) had a 4.4% risk compared to 2.9% in the younger cohort.

In subjects with anatomical features unfavorable for surgery, *independent of age*, the 30-day death and stroke rates were 1.7% among 60 symptomatic patients and 2.7% among 371 asymptomatic patients.

In patients with physiological factors unfavorable for surgery, the combined 30-day rate of death and stroke for 574 symptomatic patients was 6.4%, and for the 4603 asymptomatic patients it was 3.3%.

OPERATOR EXPERIENCE

The CAPTURE-2[115] investigators analyzed the carotid stenting outcomes of 3388 patients (representing 64% of the total number of patients) to determine if physician or site-related factors impacted outcomes of CAS.

Two-thirds of the sites (118 of 180, 66%) had no death and stroke events. Within the remaining sites, an inverse relationship between adverse event rates and hospital patient volume as well as individual operator volume was observed. The German registry analysis[116] and a meta-analysis of published studies[117] reported similar findings. In the CAPTURE 2 study, it was shown that site and operator volume were the most important determinants of perioperative events, and defined a threshold of 72 cases for consistently achieving a 30-day death and stroke rate of < 3%. This 72-case number is higher than the entry threshold for operators who participated in randomized trials like the CREST[6] or ACT I[9] (Carotid Stenting versus Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients) trials.

ANALYSIS

1. With the exception of SAPPHIRE, all studies testing CAS in high CEA risk patients were designed as registry studies. Unlike the majority of registry studies which are characterized by self-reported events with no opportunity for adjudication, the "high-risk CAS registries" were performed under FDA scrutinized clinical protocols, with prospective data collection and event adjudication. The importance of prospective, independent clinical review was demonstrated by Rothwell and Warlow,[118] who looked at adverse event rates following CEA. They found a threefold difference in neurological events between operator self-reported and independent neurologist-assessed events.
2. Individually and collectively, a large number of patients, mainly asymptomatic, have been studied within the context of these registries and provide a robust data set for analysis of high CEA risk patients undergoing CAS in the United States. Cumulatively, a total of more than 10,000 patients were included and analyzed in the three post-marketing studies (90% asymptomatic), and analysis of the data has helped provide answers to important questions concerning carotid stenting in a "real-world" setting.
3. Carotid stenting outcomes have shown a steady and continuous improvement since the initial introduction of these devices in US

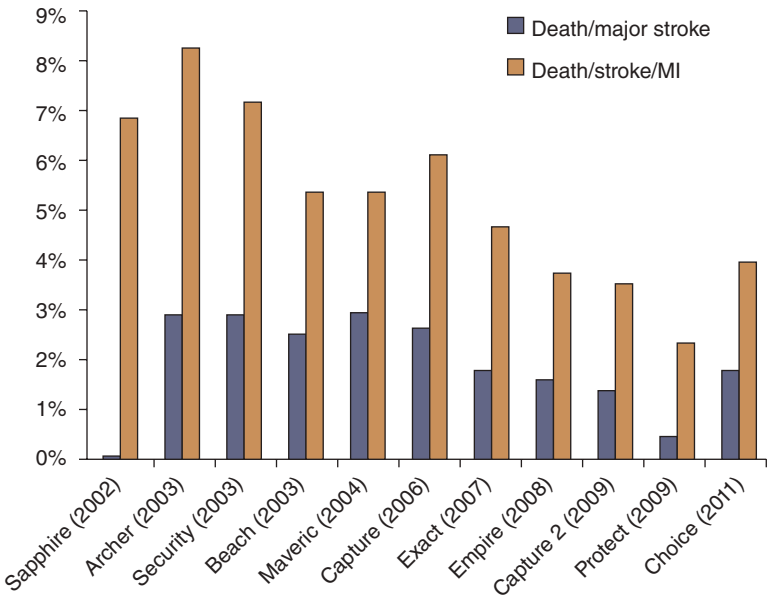


FIGURE 95–12. Published adverse event rates for carotid artery stent studies in high CEA risk registries over 10 years. Note the progressive decline in events over time. The year in parenthesis is the time of last patient enrollment. MI, myocardial infarction. Reproduced with permission from Creager MA, Beckman JA, Loscalzo J: *Vascular Medicine: A companion to Braunwald's Heart Disease*, 2nd edition. Philadelphia: Elsevier; 2013.

trials (Fig. 95–12). For example, compared with outcomes in the ARCHeR and the original CAPTURE registries, the combined results of the CAPTURE 2 and EXACT studies showed improvement in 30-day death and stroke outcomes: 6.9%, 5.7%, and 3.6%, respectively, and these improved outcomes meet AHA guidelines in the < 80 years age group. In the CREST study, the majority of the neurological events were "minor strokes" with substantial resolution of the neurological deficits during the follow-up period.[6,7]

4. Factors contributing to the improvement in the results of carotid stenting include:
   a. The recognition of the features that define the "high stent risk patient." This was not appreciated at the time these registry studies were initiated in the year 2000, and stenting with distal embolic protection was attempted in most if not all high CEA risk patients, a subset of whom had high stent risk features who were excluded from studies later in the decade. Exclusion of these patients resulted in better outcomes.
   b. The pool of qualified, experienced operators increased as multiple specialties now perform carotid stenting.
   c. There have been improvements in the devices such as smaller embolic protection devices and the use of nitinol stents. Additionally, changes in the procedure itself, such as limiting post-inflation to a single inflation, may have contributed to improved outcomes.
5. Carotid artery stenting outcomes in nonoctogenarian, high surgical risk patients, both symptomatic and asymptomatic, are within the acceptable thresholds of American Heart Association standards. Additionally, in patients deemed high CEA risk because of unfavorable anatomic features, the outcomes meet the AHA guidelines in symptomatic as well as asymptomatic patients, irrespective of age.
6. The higher event rates in the pre-2005 high CEA risk carotid stent registries may explain the lack of CMS reimbursement for asymptomatic patients undergoing carotid stenting, despite FDA approval for this indication. The outcomes of the CAPTURE-2 and the EXACT postmarketing registry are compelling because at least in the nonoctogenarian high CEA risk population (both symptomatic and asymptomatic), the death and stroke outcomes were within the AHA guidelines. The results of large prospective randomized trials in standard CEA risk patients (ICSS, CREST, and ACT I) are all directionally similar and should hopefully help support a favorable coverage decision from CMS when the issue comes up next for review.
7. The octogenarian and older population continues to be a challenge, and the decision to recommend and perform carotid stenting (or CEA), *especially in the asymptomatic patient older than 80 years of age, has to be individualized.*

CAROTID STENTING IN SYMPTOMATIC STANDARD CAROTID ENDARTERECTOMY RISK PATIENTS

There are four completed randomized trials in patients with symptomatic carotid disease: the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Cartoid Stenosis (EVA-3S) trial[119,120]; the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterctomy (SPACE) trial[121,122]; the International Carotid Stenting Study (ICSS)[4,5]; and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).[6,7] The CREST study also included asymptomatic patients.

EVA-3S,[119] a noninferiority study, was conducted in 30 centers across France and recruited and randomized standard CEA risk patients. These patients were within 120 days of either a TIA or a nondisabling stroke and had a ≥ 60% internal carotid artery stenosis in symptomatic carotid artery. The primary end point was any stroke or death within 30 days of treatment. Although the enrollment target was 872 patients, the trial was stopped prematurely by the data safety monitoring board after 527 patients had been enrolled for reasons of safety and futility. The primary end point was seen in 9.6% of patients in the stenting group compared to 3.9% in those undergoing endarterectomy ($P = 0.01$). Later analyses demonstrated that the difference between the two groups persisted out to 4 years, the difference being driven by procedural events.[120]

SPACE[121] was a multicenter (n = 35), multinational (German, Austrian, and Swiss) noninferiority study. This trial recruited and randomized standard CEA risk patients within 180 days of either a TIA or moderate stroke (Rankin score < 4). Patients had a stenosis severity of 70% or greater by ECST criteria (≥ 50% by NASCET) in the index carotid artery determined by catheter angiography or by duplex ultrasound. The primary end point was ipsilateral stroke and death within 30 days of treatment. The trial was stopped after data from 1183 patients had been analyzed, which led to the conclusion that a larger sample size (almost 2500 patients) would be needed; however, additional funding was not available. Event rates were 6.84% in the stenting group compared with 6.34% in patients undergoing endarterectomy. Although the outcome rates were similar between the two groups, the trial failed to demonstrate the noninferiority of CAS (ie, the study failed to prove that the outcomes in patients undergoing stenting were no worse when compared to the outcomes of CEA).

The International Carotid Stenting Study (ICSS),[4,5] a multicenter (n = 50), multinational (Europe, Australia, New Zealand, and Canada participation) *superiority* study, recruited and randomized 1713 standard

CEA risk patients to either CAS (n = 855) or CEA (n = 858) within 12 months of symptoms. Patients older than 40 years of age with a stenosis severity of 50% or greater (by NASCET criteria) in the index carotid artery were eligible for enrollment. Stenosis severity and study entry eligibility were determined by duplex ultrasound or other noninvasive imaging of the carotid artery; approximately 90% of patients in both groups had > 70% stenosis. Patients were followed for a median of 4.2 years. The median time from the symptomatic event to CAS and CEA was 35 and 40 days, respectively ($P < 0.013$), and 25% of CAS patients and 18% of the CEA patients underwent treatment within 14 days of the event.

The primary end point was long-term incidence of death or disabling stroke in any territory. The number of fatal or disabling strokes (52 vs 49) and cumulative 5-year risk did not differ significantly between the CAS and CEA groups (6.4% vs 6.5%; hazard ratio [HR] 1.06, $P = 0.77$). Although any stroke was more frequent in the stenting group than in the endarterectomy group (119 vs. 72 events; ITT population, 5-year cumulative risk 15.2% vs 9.4%, $P < 0.001$), *this difference was contributed by nondisabling strokes*. The distribution of modified Rankin scale scores at 1 year, 5 years, or final follow-up did not differ significantly between treatment groups. The ICSS study, the largest randomized study comparing CAS and CEA in symptomatic patients, concluded that long-term functional outcomes and the risk of fatal or disabling strokes are similar for stenting and endarterectomy.[5]

ANALYSIS

Inclusion and Exclusion Criteria

For the outcomes comparison between the two treatment strategies, CAS and CEA, to be valid, the two patients groups should be comparable. Specifically, for the patients enrolled in these studies it should not matter if they were in the CAS or CEA arms since, in a well-designed, adequately enrolled clinical trial, the process of randomization should "cancel the noise" and even out the imbalances between the two arms. However, despite randomization, an important imbalance continued to persist between the two treated groups related to the inclusion and exclusion criteria that handicapped the outcomes in the CAS arm. For example, in each one of these trials, patients with known anatomical characteristics that would render them "high risk" for CEA (tandem lesions, additional intracranial high grade stenosis, "hostile necks" as a result of prior surgery or radiation) were all excluded from trial participation. On the other hand the trial protocol did not specify exclusions for high stent risk. Additionally, when the trial protocol permits trial entry and randomization on the basis of duplex imaging, anatomical features that render stenting high risk (extended, type III aortic arch, tortuous extracranial carotid anatomy, obvious lesion filling defect(s) as a result of a fresh, friable, and loose thrombus) cannot be identified/excluded. Whereas inclusion of these patients made little or no difference to the outcomes for CEA, it negatively impacts CAS outcomes, and this imbalance cannot be corrected by the randomization process. In their defense, it is important to recognize that the EVA-3S, SPACE, and ICSS studies developed their protocols and started recruiting patients during a period wherein the concept of high stent risk was not well understood.

Antiplatelet Regimen

Contemporary carotid stent results are predicated on mandatory administration of adequate doses of dual antiplatelet medications in all patients prior to initiation of the stenting procedure and continuing them for around 8 weeks post-CAS.[123,124] In all three of the above trials, dual antiplatelet agent use was recommended but not mandated. Approximately 20% of patients in the EVA-3S and SPACE studies did not receive adequate antiplatelet medications.

Inconsistent Use of Embolic Protection Devices

In EVA-3S, during the first 3 years of enrollment (2000-2003), EPDs were used in approximately three-quarters of the procedures. In 2003, after a DSMB review, EPD use became mandatory. Analysis of the outcomes with and without use of EPDs reveals much higher complication rates for CAS performed without EPDs. In SPACE, EPDs were used in only 27% of the cases. In ICSS, use of EPDs was recommended but not mandatory. Less than three quarter of the cases were performed using an EPD. Since the protocol was silent with respect to the need for familiarity with these devices prior to use within the trial, experience and expertise with the use of these devices was very variable and in some centers, minimal if any. In contemporary carotid stenting practice, careful, critical analysis of the carotid anatomy as it relates to its suitability for placing a distal EPD is an important component of the risk stratification process. If the anatomy cephalad to the stenosis is markedly tortuous and/or there is no "adequate" landing zone (ie, there is insufficient room between the caudal extent of the EPD and the area where the distal tip of the stent delivery system is expected to land), unless the case is suitable for a proximal (flow reversal) EPD, the case should be considered high stent risk, and the operator should not proceed with "unprotected" carotid stenting.

Operator Experience

Among practitioners of CAS, a major concern with these studies has been the lack of experience of the investigators. Whereas the surgeons were experienced CEA operators and needed to have performed a minimum of 25 CEA surgeries in the year preceeding study participation (EVA-3S and SPACE), the entry barrier for CAS operators was much lower.[125,126] In EVA-3S, for example, a total stenting experience of 12 CAS procedures or 5 CAS procedures plus 30 non-CAS supra-aortic stent procedures was sufficient for entry qualification.[127] Surprisingly, first-ever CAS cases in the presence of a proctor in the room were allowed within the trial. In the ICSS study,[5] randomization was suspended at two centers; one of them enrolled 11 CAS patients but had 5 disabling strokes or deaths. In ICSS, the hazard ratio for the combined outcomes of procedural stroke or procedural death or ipsilateral stroke during follow-up was lower for centers that enrolled 50 or more patients. A disproportionately high number of patients underwent CAS using general anesthesia or conscious sedation, a reflection of operator inexperience and unfamiliarity with the CAS procedure and contrary to contemporary CAS practice. This has led many investigators[128,129] to question the validity of establishing clinical criteria and guidelines for carotid artery stenting on the basis of these trials.

THE CREST TRIAL

The CREST study[6,7] was conducted in 107 US and 9 Canadian centers and randomized standard risk CEA patients to either CAS or CEA. The trial, which commenced in 2000, started by enrolling symptomatic patients, ie, patients with TIA, amaurosis fugax, or nondisabling stroke, who were within 6 months from the index event. In 2005, enrollment criteria were modified to include asymptomatic patients. Symptomatic patients needed to have a stenosis severity of ≥ 50% on conventional angiography (NASCET criteria) or ≥ 70% stenosis on duplex ultrasonography, CTA, or MRA in the index carotid artery. For asymptomatic patients, the stenosis eligibility criteria were ≥ 60% on conventional catheter angiography, ≥ 70% by duplex ultrasonography, or ≥ 80% stenosis on CTA or MRA. The trial was sponsored by the NIH as well as Abbott Vascular, whose devices, the Accunet filter and Acculink stent, were utilized in the study. Secondary end points included all death, any stroke, or MI at 30 days (periprocedural); a

1-year composite end point stratified by symptomatic status and age (octogenarian status), acute procedural success, target lesion revascularization at 12 months, access site complications requiring treatment, cranial nerve injury unresolved at 1 and 6 months, and a prespecified interaction analyses involving gender and symptomatic status.

Data analysis was performed with four prespecified analysis populations: intent to treat (ITT), as treated (AT), modified as treated (MAT), and per protocol (PP).

The sample size of 2500 symptomatic patients in the initial proposal was based on a noninferiority analysis for a study with 80% power and one-sided alpha of 0.05, assuming a composite end point rate of 7.48% and a noninferiority margin of 2.6. When asymptomatic patients were added in 2005, the assumption was that 50% of the patient population would be asymptomatic. The assumed composite event rate was ratcheted down to 6.76%, and the study power increased marginally to 82% with a one-sided alpha of 0.05.

Of the 2307 patients in the per-protocol population, 1219 (52.8%) were symptomatic and 1088 (47.2%) were asymptomatic. The demographics of the two groups were well matched; approximately 9% of the patients were octogenarians, 30% were diabetic, and cardiovascular disease was present in about 45% of the patients.

The primary end point of the CREST study was the composite of any stroke, myocardial infarction, or death from any cause during the periprocedural period or ipsilateral stroke within 4 years after randomization. The data were also analyzed using a composite end point that included any stroke, myocardial infarction, and all death within 30 days of the procedure plus ipsilateral stroke between day 31 and day 365 (Table 95–9). This end point was used by the industry sponsor for FDA submission for device approval. CAS was shown to be noninferior to CEA based on a prespecified noninferiority margin of 2.6%. There were no significant differences between CAS versus CEA by symptomatic status for the primary CREST end point.[8]

During the periprocedural period, there was a greater risk of stroke with stenting (4.1% vs 2.3%; $P < 0.01$), a difference that was driven by the increased number of minor strokes in the CAS group (3.2% vs 1.7%; $P = 0.01$). It is worth noting and emphasizing that for the end points of death and major stroke, not only was there no significant difference between the two groups, the event rates for these two key end points was low with both CEA and CAS.[6] For both CAS and CEA, the overall stroke and death rates were below or comparable to those of previous randomized trials and were within the complication thresholds suggested in current guidelines for both symptomatic and asymptomatic patients.[8]

Minor Strokes

All interventions for extracranial carotid artery disease (CEA or CAS) are prophylactic and the specific goal of the procedure is to reduce the patient's future risk of a stroke. Although survival free of a major stroke is the principal goal of the therapeutic intervention, minor strokes cannot be simply ignored. In fact, especially when treating asymptomatic patients, operators should have an extremely low tolerance for any procedure-related neurological event, be it major or minor stroke or cranial nerve injuries. In the CREST study, an increased incidence of minor strokes contributed to the excess stroke hazard in the CAS arm. Analysis of the NIH stroke scale data of patients suffering a periprocedural minor stroke reveals that although residual defects were disproportionately higher in the CAS arm at 1 month (1.10% vs 0.60%), this difference was no longer evident at the 6-month time point (0.62% vs 0.6%). A similar trend to equalization was noted when objective classification of the residual deficits was performed using the Rankin scale. Importantly, the occurrence of a minor stroke did not negatively impact the patients' long-term survival.

Myocardial Infarction (MI)

In CREST, MI was defined by biomarker elevation (CK-MB or troponin > twice the upper limit of normal) plus either chest pain or ECG evidence of ischemia (> 1 mm ST elevation or depression in two contiguous leads). An additional prespecified category included biomarker elevation without chest pain or ECG abnormality (biomarker positive only). When compared to patients without biomarker elevation, mortality was higher over 4 years for those with a MI (HR 3.40) or biomarker positive only (HR 3.57). After adjustment of baseline risk factors, the occurrence of MI or the elevation of biomarkers only remained independently associated with increased mortality.[130]

The negative impact on survival in patients experiencing a periprocedural MI is consistent with observations from other cardiac and noncardiovascular procedures. It has been previously shown that small periprocedural elevations of cardiac enzymes were associated with increased future mortality.[131-134]

Cranial Nerve Injuries and Their Sequalae

Cranial nerve (CN) injuries occur in 4.9% to 7.7% of patients undergoing carotid endarterectomy. Although uncommon, CN deficits can be permanent and cause significant morbidity. In the ICSS study, two of the cranial nerve injuries (out of 857 endarterectomies) were classified as disabling—both patients required gastrostomies. In the CREST study, 5.3% of patients undergoing CEA had a CN injury. Two percent of the cranial nerve injuries were unresolved at 6-month follow-up. In future trials, consideration should be given to the inclusion of cranial nerve injuries as part of a composite primary end point together with death, stroke, and myocardial infarction.

Durability of Carotid Stenting

Clinical durability, ie, freedom from an ipsilateral stroke during long-term follow-up in both symptomatic and asymptomatic patients with extracranial carotid artery disease undergoing CEA, was established by the NASCET[12] and ACAS[17] trials.

The 10-year follow-up results from the CREST study were recently reported[7] (see Table 95–9). Postprocedural ipsilateral stroke over the 10-year follow-up occurred in 6.9% (95% CI, 4.4%-9.7%) of the patients in the CAS group and in 5.6% (95% CI, 3.7%-7.6%) of those in the CEA group; these rates were not significantly different (hazard ratio, 0.99; 95% CI, 0.64-1.52). There were no between-group differences when symptomatic and asymptomatic patients were analyzed separately. These results are similar to the observations in the EVA-3S[120] and SPACE[122] trials, suggesting excellent durability on longer-term follow-up. The durable benefits of carotid stenting, ie, freedom from ipsilateral stroke, in these large randomized studies reinforce the long-term results published by the authors (SI, GR) almost 15 years ago.[89]

Restenosis Following Carotid Stenting

Although duplex ultrasound is an excellent noninvasive method of following these patients, as a result of mechanical changes in the carotid artery following stenting, velocity criteria conventionally applied to diagnose stenosis in nonstented arteries are not the same in stented carotid arteries. It has been suggested that a peak systolic velocity greater than 300 cm/s be used to define a stenosis > 70%[135-137] in the stented patient. Although CT angiography may be used for noninvasive imaging,[138] MRA is not useful in a stented patient because of metallic interference from the implanted stent.

In the CREST trial,[7] restenosis was defined as the time from the procedure to either ipsilateral revascularization or the detection of a 70% to 99% stenosis or occlusion on a duplex exam performed annually

TABLE 95–9. CREST Trial Results: Stenting Versus Endarterectomy

	Periprocedural Period				Periprocedural Period + 10-Year Follow-Up				Postprocedural Period Only			
End Point	No. of Events	Rate (95% CI)	Hazard Ratio (95% CI)	*P*	No. of Events	Rate (95% CI)	Hazard Ratio (95% CI)	*P*	No. of Events	Rate (95% CI)	Hazard Ratio (95% CI)	*P*
Primary Composite End Point												
Stenting	66	5.2 (4.0-6.4)	1.18 (0.82-1.68)	.38	108	11.8 (9.1-14.8)	1.10 (0.83 to 1.44)	.51	–	–	–	
CEA	56	4.5 (3.3-5.7)			97	9.9 (7.9 -12.2)			–	–		
Stroke or Periprocedural Death												
Stenting	55	4.4 (3.2-5.6)	1.90 (1.21-2.98)	.005	98	11.0 (8.5-13.9)	1.37 (1.01-1.86)	.04	–	–	–	
CEA	29	2.3 (1.5-3.1)			71	7.9 (5.9-10)			–	–		
Death (% ± SE)												
Stenting	09	0.7±0.2		.18								
CEA	04	0.3±0.2										
All Strokes												
Stenting	52	4.1 (2.9-5.3)	1.79 (1.14-2.82)	.01	95	10.8 (8.3-13.7)	1.33 (0.98-1.80)	.07	42	6.9 (4.4-9.7)	0.99 (0.64-1.52)	.96
CEA	29	2.3 (1.5-3.1)			71	7.9 (5.9-10)			41	5.6 (3.3-7.6)		
Major Strokes												
Stenting	11	0.9 (0.3-1.5)	1.35 (0.54-3.36)	.52	24	3.5 (1.8-5.6)	1.53 (0.80-2.92)		12	2.7 (1.0-4.8)	1.91 (0.71-5.10)	.20
CEA	08	0.6 (0.2-1.0)			15	2.0 (0.9-3.5)			06	1.1 (0.2-2.4)		
Minor Strokes												
Stenting	41	3.2 (2.2-4.2)	1.95 (1.15-3.30)	.01	71	7.4 (5.4-9.5)	1.23 (0.87-1.74)		30	4.2 (2.5-6.3)	0.83 (0.51-1.34)	.44
CEA	21	1.7 (0.9-2.5)			57	6.2 (4.5-8.0)			35	4.5 (3.0-6.2)		
Myocardial Infarction												
Stenting	14	1.1 (0.5-1.7)	0.5 (0.26-0.94)	.01	–	–	–		–	–	–	
CEA	28	2.3 (1.5-3.1)			–	–	–		–	–		

The periprocedural period was defined, according to the study protocol, as the 30-day period after the procedure (for all patients who underwent the assigned procedure within 30 days after randomization) or the 36-day period after randomization (for all patients who did not undergo the assigned procedure within 30 days after randomization). The analysis of the periprocedural period plus 10-year follow-up was based on data for all the patients. The post-procedural-only period excluded patients who had a composite end point event during the periprocedural period or who withdrew during the periprocedural period; the number of periprocedural events plus the number of post-procedural events therefore does not add up to the total.

The primary end point was a composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or ipsilateral stroke within 10 years after randomization. One patient in the stenting group and one in the endarterectomy group had a stroke after a periprocedural myocardial infarction; these two strokes are not included in the stroke end point in the postprocedural-only period. Among the patients assigned to endarterectomy, one patient had a minor stroke during the periprocedural period and a major stroke during the postprocedural period and is therefore included in the stroke end point for both major stroke and minor stroke. Hazard ratios are for the 10-year period and were adjusted for age, symptomatic status, and sex. *P* values were calculated on the basis of the significance of the hazard ratio (per the study protocol). Patients may have had more than one event (eg, fatal stroke was counted as both a death and a stroke), patients may have had an ipsilateral stroke followed by a nonipsilateral stroke, and patients may have had a minor stroke followed by a major stroke.

Data from Brott et al Stenting vs. Endarterectomy for Treatment of Carotid Artery Stenosis. *N Engl J Med* 2010; 363:11-23; Brott et al Long Term results of Stenting vs. Endarterectomy for Carotid Artery Stenosis. *N Engl J Med.* 2016; 374:1021-31.

after CAS or CEA, with the degree of stenosis determined by the norms of the local laboratory. There was no significant difference between the two treatment groups in the proportion of patients who had restenosis or underwent revascularization. Restenosis occurred or revascularization was performed in 12.2% of the patients treated with stenting and in 9.7% of those treated with endarterectomy (hazard ratio, 1.24; 95% CI, 0.91-1.70)

Summary

The results of the CREST trial showed that both CEA and CAS are excellent treatment options. There was no difference in the outcomes in women versus men. The primary composite end point of periprocedural stroke, MI, or death was similar between CEA and CAS. The incidence of major disabling strokes or death was extremely low and was not different between the two treatment modalities. Periprocedural minor strokes were greater in the CAS group, but by 6 months, the deficits were not different. There was no survival disadvantage in patients with minor strokes. However, MI occurred more frequently in the CEA cohort, and this negatively impacted survival. At 1 year, stroke had a greater adverse effect on quality of life than did myocardial infarction.[139] Over a follow-up period that extended to 10 years, freedom from ipsilateral stroke and the risk of restenosis were similar for the CEA and CAS groups, supporting the clinical and device durability of CAS.

CAROTID STENTING IN ASYMPTOMATIC STANDARD CAROTID ENDARTERECTOMY RISK PATIENTS

ACT I,[9] a randomized prospective study, compared CAS performed with embolic protection (n = 1089) and CEA (n = 364) in patients 79 years of age or younger who had severe (≥ 70%) asymptomatic carotid stenosis and who would be considered standard risk for CEA. The trial was designed to enroll 1658 patients but was halted after 1453 patients underwent randomization because of slow enrollment. Subjects were randomized in a 3:1 ratio to the stenting and CEA groups, respectively. Patients were followed for up to 5 years. The primary composite end point of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke within 1 year was tested at a noninferiority margin of 3%.

The mean age was approximately 67 years, more than half were male, close to 90% were white, and approximately 40% had contralateral carotid disease. The mean angiographic stenosis was > 70%. Other than lesion length (19 ± 5.8 mm in the CAS group vs 18.0 ± 6.2 mm in the CEA group; $P < 0.05$) and lesions with thrombus (0.9% in the CAS group vs 2.8% in the CEA group; $P < 0.05$), none of the other baseline characteristics were different between the two groups

The study outcomes showed that CAS was noninferior to CEA with regard to the primary composite end point (3.8% vs 3.4%; $P = 0.01$ for noninferiority). The 30-day rate of death or major stroke was low in both groups (0.6%); the 30-day rate of minor stroke was numerically higher in the CAS group (2.4% vs 1.1%; $P = 0.20$). Hence, the overall rate of stroke or death within 30 days was 2.9% in the stenting group and 1.7% in the CEA group ($P = 0.33$). The rate of cranial nerve injury in the CEA group was 1.1%.

Between 30 days and 5 years after the procedure, the rate of freedom from ipsilateral stroke was 97.8% in the stenting group and 97.3% in the endarterectomy group, and the overall survival rates were 87.1% and 89.4%, respectively. The cumulative 5-year rate of stroke-free survival was 93.1% in the stenting group and 94.7% in the endarterectomy group. None of these differences were significant. Freedom from clinically driven target lesion revascularization at 1 year was 99.4% for CAS and 97.4% for CEA. These results support the durability of CAS when treating asymptomatic patients.

EVALUATION OF CAROTID STENTING AND CAROTID ENDARTERECTOMY IN VARIOUS SUBGROUPS

THE ELDERLY

Patients older than 80 years with carotid stenosis pose several challenges for revascularization. The association between advanced age and increased risk of adverse events after carotid artery stenting was observed in the CREST lead-in cohort,[140] the SPACE trial,[121] and the ICSS.[4] ACT I did not enroll patients older than 80 years of age. Octogenarian patients are more likely to be excluded because they have one or more features deemed high risk for carotid stenting (see Table 95–6). By excluding patients with adverse features, it has been shown that event rates comparable to those seen following CEA[141] can be achieved.

In the CREST study,[6] an interaction between age and treatment efficacy was detected with a crossover at approximately 70 years of age. This led the CREST investigators to conclude that "carotid-artery stenting tended to show greater efficacy at younger ages, and carotid endarterectomy at older ages." Treatment recommendations in the elderly patient need to be individualized and must take into account high-risk features that will make either stenting or CEA (or both) unsuitable. Elderly patients with severe asymptomatic carotid stenosis who have high-risk anatomic features or comorbidities that increase risk of CAS and CEA are often best managed with medical treatment and risk-factor optimization.

CONCOMITANT CAROTID AND CORONARY ARTERIAL DISEASE

The prevalence of > 50% carotid stenosis in patients undergoing coronary artery bypass grafting (CABG) is approximately 25%[142] and perioperative stroke risk following CABG may be as high as 11%.[143] Meta-analyses showed that stroke as a complication of CABG occurred in 1.7% of all cases.[144,145] The risk of stroke is 3% in patients with unilateral carotid stenosis 5% for patients with bilateral > 50% stenosis, and 7% to 11% for patients with carotid artery occlusion.[144] However, pathological and radiological examination revealed that only 40% of such strokes could be attributed to the ipsilateral stenosis. Therefore, even if it were 100% effective at preventing ipsilateral ischemia, carotid intervention can only reduce stroke rates by less than half.

Observational studies have shown that the perioperative stroke/death rate was 8.7% for combined CEA and CABG and 6.1% when a sequential approach of CEA followed by CABG[146] was used. There was an increased risk of MI with either strategy—3.6% for the synchronous procedure and 6.5% for the staged approach.[146]

When 64 patients with severe carotid and coronary stenoses treated with CAS followed by CABG were compared to 112 patients who underwent combined CEA and CABG, despite the CAS group being a higher risk group, there was a lower incidence of strokes (2% vs 9%; $P = 0.05$) and strokes and MI (6% vs 19%; $P = 0.02$).[147] In 356 patients with severe, asymptomatic carotid stenosis who underwent CAS prior to CABG, 30-day follow-up showed rates of stroke, TIA, MI, and death of 3.1%, 3.7%, 2.0%, and 3.7%, respectively.[148] In a meta-analysis of 11 trials[149] enrolling 760 patients (87% asymptomatic) who underwent staged CAS and CABG, the rates of ipsilateral stroke, MI, and death at day 30 were 3.3%, 1.8%, and 5.5%, respectively.

There are no guidelines or consenus as to the optimum approach to treating a patient with asymptomatic carotid artery stenosis who requires CABG. Patients with bilateral severe carotid artery disease or a contralateral occlusion may benefit from carotid revascularisation prior to CABG and CAS when feasible may be a safer alternative. Careful monitoring of hemodynamics is important and consideration

should be given for placing a TVP; an IABP during the CAS procedure may be required in patients with severe three-vessel CAD, left main disease, aortic stenosis, or severe LV dysfunction.

PRIOR NECK IRRADIATION

Carotid artery stenosis can present as a delayed complication of neck irradiation (radiation arteritis).[150] Patients with prior neck radiation frequently have long smooth lesions that are high (at or above the C2 vertebra) or low (at the level of the clavicle in the common carotid artery). Stenosis at multiple locations within the same artery may also occur. The typical interval between the radiation treatment and the detection of stenosis is 10 years or more.

Because radiation-induced vascular stenosis may be associated with fibrosis and scaring of the skin and subcutaneous tissue, surgical therapy is more complicated and may lead to postoperative necrosis, infections, wound breakdown, and cranial nerve injuries.[151]

For these reasons, CAS is safer and more effective in the post-radiated patient.[152,153] Reported periprocedural stroke and death rates have been low and have not exceeded those observed in general patient cohorts undergoing CAS. One limitation of stenting in this group is the possible increased risk of in-stent restenosis following the procedure. Restenosis rates from 5%[152] to 41%[153] have been reported at intervals from 12 to 24 months. Restenosis is often clinically asymptomatic and generally amenable to repeat percutaneous intervention.

The guidelines provide carotid stenting a Class IIa recommendation[24] in this setting. There may be incomplete endothelialization of the stent struts; therefore patients with prior neck radiation who undergo stenting should be given dual antiplatelet treatment for an extended period, preferably lifelong.

RESTENOSIS FOLLOWING PRIOR CAROTID ENDARTERECTOMY

If restenosis occurs in the early years after CEA, it is typically caused by intimal hyperplasia, whereas in later years, atherosclerosis is likely responsible.[154] Revision CEA is technically challenging and is associated with higher complication rates than primary surgery, with increased rates of stroke (4.8% vs 0.8%), TIA (4.0% vs 1.1%), and cranial nerve injury (17.0% vs 5.3%).[155]

CAS following prior CEA is associated with low complication[156] rates, and stent restenosis is not significantly higher than that seen with primary CAS.[157]

RESTENOSIS FOLLOWING CAROTID STENTING

Noncompliant balloons[158] are generally used for dilating in-stent restenosis; an additional stent may be required especially if the stenosis involves the distal edge of the index stent. Zhou and colleagues utilized cutting balloons in five of seven patients, and two required further stent implantation.[159] The use of an EPD remains mandatory when intervening on these lesions. Rates of target lesion revascularization in recently reported randomized prospective CAS trials have been in the low single digits.[9]

CURRENT RECOMMENDATIONS AND THE FUTURE OF CAROTID STENTING

CAS or CEA can be scientifically and ethically justified as a treatment option for symptomatic and asymptomatic patients if the operators and centers are experienced and have a verifiable periprocedural stroke risk that is less than 6% and 3%, respectively. Making decisions and providing treatment recommendations are very challenging in centers where interventional and surgical expertise and outcomes cannot be verified.[160,161] Carotid duplex diagnostic testing should only be performed in IAC accredited labs. All patients should be on at least one antiplatelet agent and a statin, and risk factors should be appropriately modified.

In symptomatic patients, there is consensus that most if not all patients with a ≥ 70% stenosis and a certain proportion of patients with a 50% to 70% stenosis on angiography should be offered a definitive revascularization procedure. Level I support for recommending CAS or CEA is provided by the results of the ICSS and CREST trials. The risk of procedural death and major stroke is low and similar with either procedure. Long-term follow-up has shown clinical durability. Although timing of the revascularization procudure in relation to the symptomatic event is still debated, data from the CREST study seem to indicate that risks with either procedure are equivalent even when the intervention is done within two weeks of the event.

For asymptomatic patients, the results of CREST as well as the ACT I trial reveal that both CEA and CAS are equivalent in terms of acute and 30-day outcomes and both procedures have clinical durability. It would seem reasonable to offer revascularization for asymptomatic patients with a ≥ 80% stenosis provided the periprocedural risk is less than 3%.

Despite the data from these large prospective randomized clinical trials, in 2016, the issue of which asymptomatic patient needs treatment and if invasive approaches are better than contemporary medical therapy is not settled because of the *speculation* that the stroke risk in all asymptomatic patients treated with modern medical therapy is much lower. The ongoing Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) will test this hypothesis by addressing the question of the relative benefits of revascularization over nonrevascularization in asymptomatic patients in the context of contemporary, intensive medical therapy. The European Carotid Surgery Trial 2 (ECST-2) is also comparing revascularization with nonrevascularization in asymptomatic patients and includes symptomatic patients who have been deemed at low risk for stroke. Assuming adequate numbers of asymptomatic patients with > 80% stenosis are enrolled in these trials, they will help define the optimum treatment for these patients.

Patient selection remains the single most important predictor of complications. Although embolic protection devices are routinely used, no protection device can replace critical risk analysis and sound operator judgment. In general, it is reasonable to recommend CAS over CEA in patients who are younger than 70 years of age. For patients between 70 and 80 years of age and certainly for those older than 80 years, the decision needs to be individualized and the recommendation for revascularization should be reached after critical analysis of the risks and benefits. Technological device-related improvements can be expected, and these may further reduce the periprocedural risk and improve the safety of carotid stenting.

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CHAPTER 96

DIAGNOSIS AND MANAGEMENT OF DISEASES OF THE PERIPHERAL ARTERIES

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Peripheral vascular diseases are a diverse collection of disorders that affect all organ systems. Peripheral artery disease (PAD) is the vascular disease most commonly encountered by the cardiologist; however, disease of the lymphatics and veins is equally common globally. For the cardiologist or internist with an interest in vascular disorders, a systematic and comprehensive approach is required. This chapter will cover commonly encountered areas of vascular disease, specifically the diagnosis and management of PAD. Accompanying chapters on lymphedema, venous disease, and aortic and cerebrovascular disease will address these topics in more detail.

PERIPHERAL ARTERY DISEASE

PAD caused by atherosclerosis is the most common cause of lower-extremity ischemic syndromes in Western societies.[1] PAD is a major cause of lifestyle changes, poor quality of life, loss of work, disability, and significant morbidity and mortality in the United States.[2,3] Symptoms of PAD are variable and, unfortunately, frequently lead to incorrect diagnoses.[4] Risk factors for PAD are the same as those for coronary artery disease (CAD), with tobacco and diabetes having an even greater effect (Table 96–1).[5,6] Tobacco use, current and past, is associated with a two- to fourfold increase in relative risk for PAD.[7,8] Diabetes mellitus has a similar increase in relative risk.[7] Other modifiable risk factors include hyperhomocysteinemia, hyperlipidemia, and hypertension.[9] Even when asymptomatic, PAD has been shown to be a strong predictor of cardiovascular (CV) disease, nonfatal CV events (eg, myocardial infarction and stroke), and lower-extremity ulcerations and amputations.[5] PAD has significant impact on mortality; individuals with PAD have a two- to sixfold higher relative risk of death over a 10-year period of time versus the general population.[10-12]

PREVALENCE

PAD affects a large and increasing number of individuals worldwide.[1] Exact numbers for prevalence and incidence are confounded by varying methods for assessment and criteria for diagnosis.[13] Expert and consensus statements estimate that 8 to 12 million people in the United States and 200 million people worldwide are affected by PAD.[14-16] It is estimated that 10 million people have symptomatic PAD and another 20 to 30 million have asymptomatic disease. Based on published US statistics, each year 413,000 patients with PAD are hospitalized, 88,000 lower-extremity angiograms are performed, and 30,000 patients undergo embolectomy or thrombectomy.[17] Ten percent of individuals over age 60 have PAD, and the prevalence continues to increases with age.[5,18] It is estimated that nearly two-thirds of those affected by PAD over the age of 65 are females.[19]

In the Framingham Offspring Study, the prevalence of PAD was determined in 1554 males and 1759 females from 1995 to 1998.[20] The mean age was 59 years. PAD, defined as an ankle-brachial blood pressure index (ABI) of < 0.90, was present in 3.9% of males and 3.3% of females. Lower-extremity bruits were present in 2.4% of males and 2.3% of females. However, the prevalence of claudication was only 1.9% in males and 0.8% in females, suggesting that only half of men and only a quarter of women had symptoms or recognized their symptoms.

The PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study assessed the prevalence of PAD in US patients older than age 70 and those age 50 to 69 with a smoking history or diabetes.[21] PAD was defined by an ABI of < 0.90; 29% of the population was found to have PAD. Nearly half of those with PAD had concurrent coronary or cerebral vascular disease.

Seven-thousand European individuals were evaluated for PAD in the Rotterdam study; 20% of patients older than 55 years of age and nearly 60% of men older than 85 years were found to have PAD.[22] One to twenty percent of patients in these studies diagnosed with PAD had self-reported claudication or symptoms by Rose questionnaire; this supports the conclusion that most individuals with PAD remain either asymptomatic or limit their activities due to numerous variables. Nearly 10% of asymptomatic individuals have advanced PAD with severe obstruction to blood flow in their lower extremities.[23]

NATURAL HISTORY

Death directly due to PAD is rare. Mortality and morbidity are more often due to concomitant coronary or cerebrovascular disease. The relative risk of death for all-cause mortality is two-to sixfold higher in PAD patients versus the general population.[10-12] The risk of death increases as the ABI decreases.[24,25] The 5-year mortality rate for an ABI < 0.85 is 10%; when the ABI is < 0.40, mortality approaches 50% per year.[26] Lower-extremity symptoms not associated with a decrease in the ABI do not demonstrate an increase in mortality.[27] In contrast, a decrease in ABI without symptoms still portends an increase in cardiovascular morbidity and mortality.[28] Patients with ABI > 1.40 and between 0.91 and 1.00 have a similar risk of having a MI, stroke, and/or MI/stroke.[29] Projects like the Atherosclerosis Risk in Communities study and others have demonstrated that an ABI > 1.40 is associated with an increase in morbidity such as foot ulcers, congestive heart failure, and stroke but not an increase in cardiovascular events.[30,31] An ABI between 0.90 and 0.99, which is classified as borderline, increases the risk of future walking impairment.[32]

TABLE 96–1. Risk Factors for Peripheral Artery Disease

High Risk	Moderate Risk	Low Risk
Two- to fourfold increase	One- to threefold increase	One- to twofold increase
Smoking	Hypertension	Hypercholesterolemia
Diabetes mellitus	Homocysteinemia	

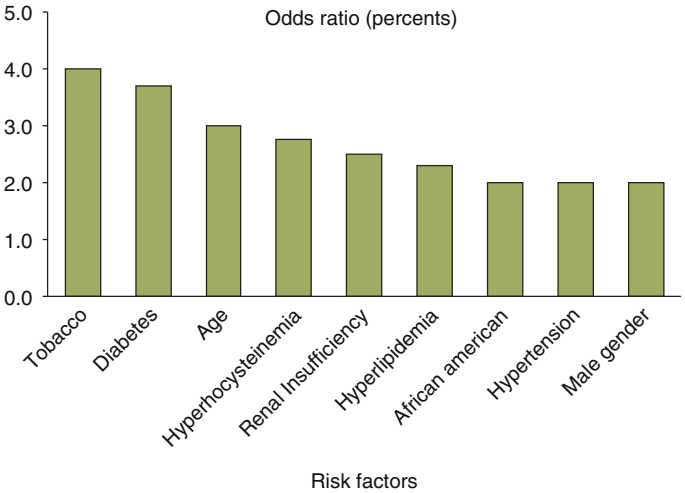
Although the cardiovascular mortality and morbidity of patients with PAD is sobering, the rate of progression of limb symptoms and need for limb revascularization or amputation are low.[33] Need for revascularization due to tissue loss (ulcer) or rest pain is 5% per year.[13] Amputation rates are even lower, at approximately 1% per year.[34] For those who present with acute critical limb ischemia, 30-day amputation rates are 10% to 30%, with a 1-year mortality rate of 15%.[35] Individuals with acute limb ischemia of > 24 hours is associated with higher 30-day (25.7%) and 1-year amputation (37.1%), with a 30-day mortality of 34%.[36]

RISK FACTORS

Numerous risk factors for PAD have been identified (Fig. 96–1).[14,37] The strongest correlation exists with advancing age; other comorbidities include tobacco abuse, diabetes mellitus, hypertension, hyperlipidemia, homocysteinemia, C-reactive protein, gender, and ethnicity.

Tobacco Abuse

Tobacco abuse is a strong risk factor for the development and progression of PAD.[38] Smoking is associated with increased PAD-related procedures, hospitalizations, and increased costs.[39] Results from the Edinburgh Artery Study demonstrate that tobacco users have a 3.7 higher relative risk of intermittent claudication compared with 3.0 among individuals who have discontinued smoking for less than 5 years.[23] Smoking increases the risk of lower-extremity amputation, peripheral graft occlusion, and mortality in a dose-dependent fashion. The rate of progression and amputation in those who continue to smoke is more than twofold higher than the rate in those who quit, with 15% of those who continue smoking undergoing amputation within 5 years.[40]



Adapted from the society for vascular surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. Journal of vascular surgery, volume 61, issue 3, supplement, 2015, 2s–41s.E1.

FIGURE 96–1. Risk factors associated with the development of peripheral artery disease (PAD). Adapted with permission from Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, et al: Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg.* 2015 Mar;61(3 Suppl):2S-41S.

Diabetes

Diabetes mellitus increases the risk of PAD development by two- to fourfold. A 1% increase in hemoglobin A1C levels is associated with a 26% increased risk of PAD.[41] Individuals who have insulin resistance demonstrate a higher prevalence of PAD.[42] There is an association between a low ankle-brachial index (ABI) and mortality that is similar in those with and without diabetes, whereas the association with high ABI has only been observed in patients with diabetes.[43] In addition, individuals with longstanding diabetes tend to have more severe PAD and are more likely to suffer from claudication symptoms (albeit many are asymptomatic because of peripheral neuropathy). Diabetics have an amputation rate of 25% over 10 years, which has changed little over time.[44,45]

Hypertension

Epidemiology studies demonstrate a strong association between increased systolic blood pressure and the development and progression of PAD.[46-48] Individuals with hypertension have a 2.5- to 4-fold increase of PAD compared to individuals with normal blood pressures.[49] Claudication is fourfold higher among those with hypertension and is proportional to the severity of hypertension.

Hyperlipidemia

The association between hyperlipidemia and PAD is inconsistent. Numerous studies show that increased total cholesterol is associated with an increased risk of PAD and claudication.[50,51] Each increase in total cholesterol of 10 mg/dL leads to a 5% to 10% increased risk in PAD.[49,50] Other studies demonstrate a protective effect against PAD among individuals with increased high-density lipoproteins (HDL).[52] When non-HDL and a total-to-HDL cholesterol ratio are used, individuals in the highest quartile have nearly four times the claudication risk of those in the lowest quartile.[53] For those with isolated hypertriglyceridemia there appears to be a nonsignificant relationship between increased triglycerides and PAD.

Homocysteinemia

Homocysteinemia plays an independent role in development of PAD. The mechanism is partially related to an inborn genetic mutation affecting methylenetetrahydrofolate reductase (MTHFR), resulting in accelerated intimal damage and early atherosclerosis.[45,54]

C-Reactive Protein

C-reactive protein (CRP), an inflammatory marker, increases among individuals with PAD.[55,56] CRP predicts PAD progression and severity.[57,58] In addition, CRP levels are higher in individuals with PAD than those with angiographically proven coronary artery disease.[59]

CLINICAL ASSESSMENT OF ARTERIAL DISEASE

History

The differential diagnosis of claudication is broad; an abbreviated list is given in Table 96–2. Information regarding risk for atherosclerosis, current medical problems, prior lower-extremity and back trauma, and all vascular and orthopedic procedures should be obtained on all patients. The description of claudication symptoms is unique to

TABLE 96–2. Differential Diagnosis of Claudication

Atherosclerosis obliterans
Arteritis (Takayasu, giant cell)
Embolic disease/acute arterial occlusion
Degenerative joint disease (hip, back, knee)
Spinal stenosis
Myopathy
Thromboangiitis obliterans
Popliteal entrapment
Venous claudication/varicosities
Baker cyst
Deconditioning
Aortic dissection
Aortic coarctation
Retroperitoneal fibrosis

each patient.[4,60] Symptom specifics, including onset, progression, and aggravating or alleviating factors, should be clarified. In some patients different types of discomfort caused by different etiologies occur and may complicate the clinical picture.[61,62]

Asymptomatic Most individuals with PAD have no lower-extremity symptoms[60] and the diagnosis will be missed if ABI testing is reserved exclusively for individuals with classic claudication symptoms. Identifying PAD in those without classic intermittent claudication symptoms remains challenging.[63] Appropriate criteria for screening individuals for suspected PAD includes a history of walking impairment, claudication, ischemic rest pain, and/or nonhealing wounds is recommended as a required component of a standard review of symptoms for adults 50 years and older who have atherosclerosis risk factors and for adults 70 years and older.[64] Screening patients for PAD should include those greater than 65 years old, individuals 50 years or older with history of diabetes mellitus or tobacco abuse, complaints of claudication, evidence of reduce pulses, or established atherosclerotic disease (renal, carotid, coronary, subclavian, etc.).[64]

Claudication Claudication, literally meaning *limping* (Latin), is a stereotypical, reproducible distress in single or multiple muscle groups of the lower extremity brought on by sustained exercise and relieved by rest. The distress is classically described as cramping but numbness, weakness, giving way, aching, and dull pain are all common concerns.[65] The distress changes in character and/or location as the flow-limiting lesion(s) progress. When workload is increased by rapid pace, a burden, or walking uphill or over rough terrain, the distance or time to onset will shorten. When the distance to onset or severity abruptly changes, thrombosis in situ or an embolic event should be considered. In general, symptoms occur distal to the level of stenosis or occlusion. Claudication occurs in muscle groups rather than joints. Relief with rest is independent of position and is usually complete within 5 minutes. When specific positions are required for relief, musculoskeletal or neurologic disorders should be suspected. Claudication often worsens after a period of inactivity, such as hospitalization, but returns to baseline with reconditioning. Although lifestyle limitation and changes in quality of life are an integral part of the history, quantification of disease severity by history alone is unreliable.[66] Standardized treadmill testing using ABIs at rest and after completion of an exercise protocol confirms the diagnosis, determines the severity, documents claudication distance for future follow-up, and independently predicts mortality.[65,67-69]

Acute Limb Ischemia Acute limb ischemia may be defined as an abrupt event caused by arterial occlusion. It is important to inquire about sudden appearance of a cold, painful forefoot/toe, especially in the presence of skin color changes. Associated signs and symptoms include pain, paralysis, paresthesia, pulselessness, pallor, and "polar" changes (cold).[70] The pain typically lessens in the dependent position and often is localized. Common findings of early acute limb ischemia include the loss of light touch sensation, proprioception, and vibratory perception. There may be temperature or color change in the extremity where occlusion has occurred. Acute limb ischemia may be caused by *in situ* arterial thrombosis, embolization (from a cardiac or proximal aneurysmal source, or secondary to plaque disruption during trauma, angiography, intra-aortic balloon pump counterpulsation, or surgery), or other causes. Rates of death and complications among individuals who present with acute limb ischemia range from 15% to 20% within 1 year from presentation, while amputation occurs in 10% to 15% of individuals during hospitalization.[70,71]

Critical Limb Ischemia Critical limb ischemia may be defined as tissue loss or rest pain in a limb, usually at the distal portion and rarely in the entire limb. Small, localized areas of ischemic pain or ulceration are often caused by minor trauma to an area with poor perfusion rather than progression of disease.[65] Many individuals are asymptomatic prior to developing critical limb ischemia.[72] It is important to inquire about new shoes, recent nail care, pets, and other potential sources of trauma. Rest pain is present when supine and is often relieved by dependency (such as hanging the limb off the bed or, paradoxically, by walking.) Pain may progress and become constant; this may interrupt sleep, suppress appetite, cause weight loss and delirium, or require large doses of analgesics for pain relief. Patients may sleep in a chair (with their legs dependent) to get better rest and often present with edema as a result.

Pseudoclaudication Pseudoclaudication is typically of neurogenic origin. The patient with neurogenic claudication describes exercise-induced distress with a dysesthetic quality that clears slowly or requires a specific posture for relief, usually with the hips flexed.[73] Clumsiness may develop as walking continues. Symptoms also occur with prolonged standing or when supine. Compression of the distal spinal cord by hypertrophic bone, disk protrusion, or tumor may be present. A history of back injury is common. Arterial and pseudoclaudication often coexist. In this situation, the dominant lesion can often be clarified by observing and timing symptoms that occur with standing versus those produced by exercise, as well as by measuring the arterial indices before and after exercise.[74]

Venous Claudication Venous claudication is described as a congestive, often *bursting*, distress of thighs and calves induced by standing, walking, or running. Relief with rest is slow and notably accelerated when the patient elevates the legs. Venous claudication typically occurs in the setting of iliocaval obstruction. Signs of venous hypertension of the legs and lower abdomen are often noted during examination.[75]

Arterial Examination

Inspection A red or purplish color of the forefoot during dependency (dependent rubor) is common with severe ischemia. Rubor caused by ischemia will change to pallor with elevation; in contrast, rubor caused by cellulitis usually persists with elevation.[76] Timing the onset of pallor and venous refilling time can be performed in the examination room (Table 96–3). Loss of normal hair growth is also a marker of ischemia.

TABLE 96–3. Elevation and Dependency

Grade	Pallor Onset
Elevation Pallor[a]	
Normal	None
Grade I	> 60 s
Grade II	< 60 s
Grade III	< 30 s
Grade IV	Pallor supine
Venous Refilling[b]	
Severity	Venous refill
Normal	< 15 s
Moderate	15-30 s
Severe	> 30 s

[a]Feet held passively at 60 degrees while supine.

[b]Legs dependent while sitting after elevation.

Livedo reticularis is a transient, bluish discoloration with a lacy pattern found on the extremities and sometimes the trunk that is variable in its extent and intensity. It is most apparent after exposure to cold or emotion and fades with warming or exercise. It is more common in women and fair-skinned individuals. Livedo reticularis is common, and when mild it is often overlooked. It is postulated that spasm of the cutaneous arterioles (with secondary dilation of the capillaries and venules) causes slow flow, increased oxygen uptake, and reduced oxygenation of hemoglobin, producing the color change. Livido racemosa is a secondary livedo reticularis that is patchy, focal, and asymmetric in distribution and typically fixed. It may be complicated by local infarction or ulceration (Fig. 96–2).

Palpation The aorta, radial, ulnar, subclavian, carotid, temporal, occipital, femoral, popliteal, posterior tibial, and dorsalis pedis arteries are accessible by palpation. Pulses are graded on a scale (Table 96–4).[77] If a pulse is not palpable, Doppler examination should be performed to establish whether flow is absent or below the level of detection by palpation. Surface temperature is reduced when perfusion is compromised. Temperature differences are best felt with the dorsum of the fingers; comparison to the contralateral limb or proximal ipsilateral limb should be made. The sizes of paired arteries are similar in magnitude. Ectasia or aneurysm is suspected when one side is larger or more forceful than the other. Tortuosity of the carotids, abdominal aorta, and subclavian arteries can mimic an aneurysm. Ultrasound or other imaging studies are needed to clarify the findings when the diagnosis of an aneurysm is entertained.

Auscultation Blood pressures should be taken in both arms and should be similar (but rarely identical, even when measured simultaneously.) Respiratory variation, positioning of the arm, and atrial fibrillation are just a few reasons for pressure variation. If a large difference is noted between arms (> 14 mm Hg), blood pressures should be rechecked. If still discrepant, simultaneous pressures are done to confirm the finding. The femoral, iliac, aortic, carotid, and subclavian arteries should be auscultated routinely. Simultaneous palpation of a radial artery during auscultation will improve detection of subtle bruits (especially abdominal bruits when bowel sounds are vigorous) and allow accurate timing of bruits. An epigastric bruit that varies with respiration is most often due to compression of the celiac artery by the median arcuate ligament.

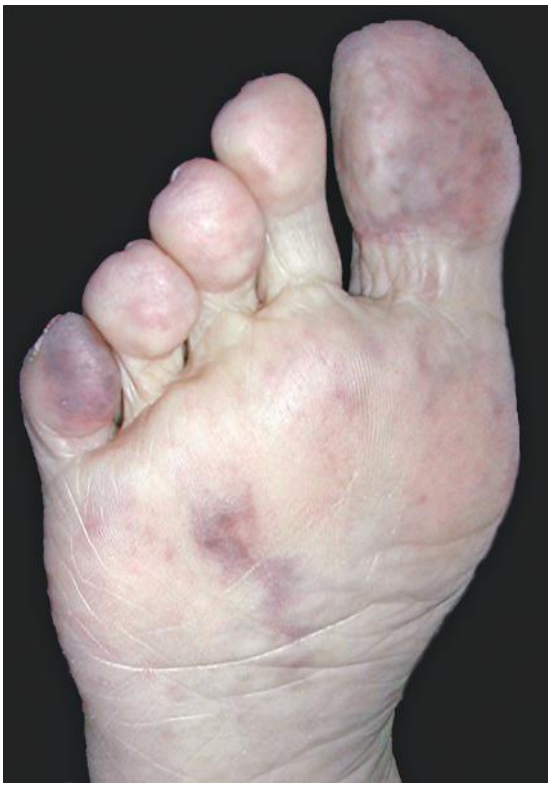


FIGURE 96–2. Livedo racemosa of the right foot caused by atheroembolism following cardiac catheterization.

LABORATORY ASSESSMENT OF ARTERIAL DISEASE

Objective testing of the arterial system is done for confirmation or clarification of the clinical findings, monitoring disease progression, or assessment of outcome after intervention.

Anatomic Studies

Conventional Angiography Conventional angiography is the standard by which all other imaging techniques are judged.[77] It provides reproducible information with high resolution not yet matched by other

TABLE 96–4. Pulse Grading Scale[a]

Mayo Grade	Physical Findings	ACC/AHA Grade
0	Absent	0
1	Severely reduced—palpable with great difficulty; unable to accurately count pulse	1
2	Moderately reduced—palpable with some difficulty; able to count pulse	1
3	Mildly reduced—easily palpable	1
4	Normal pulse—easily palpable	2
5	Enlarged/Bounding—widened, possibly aneurysmal	3

[a]Pulse grading scale. Presence of edema and other physical barriers at time of examination must be taken into account when grading.

Abbreviation: ACC/AHA, American College of Cardiology/American Heart Association.

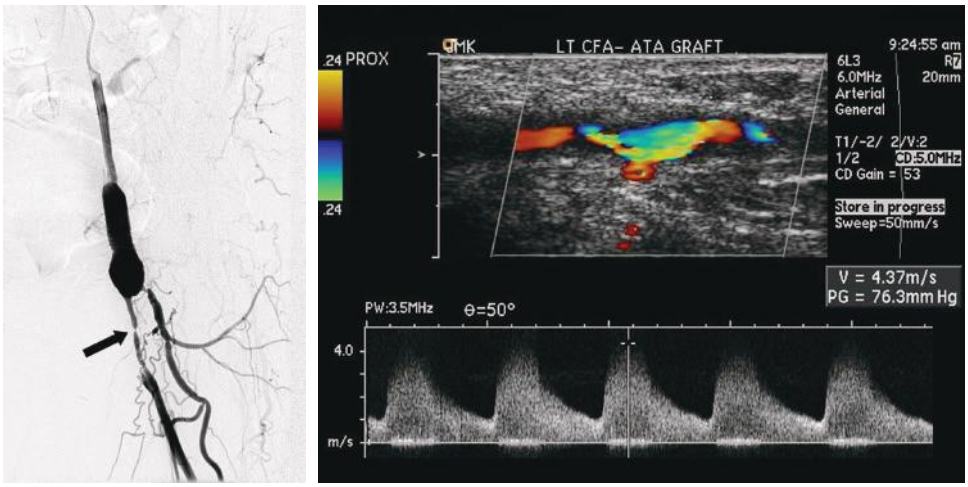


FIGURE 96–3. A. Conventional arteriogram showing a high-grade stenosis of the common femoral artery distal to a polytetrafluoroethylene graft (*arrow*). **B.** Duplex ultrasound of the same stenosis showing velocity elevation of > 400 cm/s.

modalities (Fig. 96–3A). Assessment of distal vessel fine structural detail and arteriovenous shunting are still best determined by angiography. Drawbacks include risk of distal embolization and arterial damage at the puncture site. Iodinated contrast is used and poses a small but real risk of anaphylactoid reaction and contrast nephropathy.

CT Angiography CT angiography (CTA) provides detailed anatomic information without need for arterial access.[78] Iodinated contrast is still required (Fig. 96–4). Three-dimensional (3D) reconstructions can include or exclude bony structures and other organs in the final images and also enable the image to be rotated on an axis. CTA is often used as an initial imaging modality when percutaneous intervention is unlikely.[79-81]

Magnetic Resonance Angiography Magnetic resonance angiography (MRA) provides information similar to CTA without the need for iodinated contrast. For those at risk of contrast nephropathy or anaphylactoid reaction, it is a safe and accurate alternative to CTA and conventional angiography.[79,82] However, most studies use gadolinium as a contrast agent which puts patients with a low creatinine clearance at risk of gadolinium-induced nephrogenic fibrosing dermopathy, also known as nephrogenic systemic fibrosis.[79,83] Noncontrast techniques can be used in some instances to avoid this potential complication. MRA, like CTA, provides a 3D image and can include or exclude structures of interest. Patients with implantable devices such as pacemakers, automated defibrillators, recently placed vascular stents, and intracranial clips cannot be safely placed into the magnetic field, limiting availability to a small extent.

Duplex Ultrasound Duplex ultrasound (2D gray-scale imaging plus Doppler) assesses not only arterial anatomy but also the hemodynamic effects of stenosis (see Fig. 96–3B). Contrast is not required and no ionizing radiation is used. Ultrasound is portable and captures images in real time, allowing both bedside and intraoperative monitoring of therapy (Fig. 96–5). Data acquisition may be limited by body habitus, overlying structures such as bowel gas, and other tissues that interfere with imaging. Surgical intervention using duplex as the sole imaging modality has proven effective in selected settings.[84]

Hemodynamic Studies

The hemodynamic significance of a stenosis may be assessed by multiple methods. Direct catheter measurement of a pressure gradient across a stenosis is still considered the gold standard. Duplex scanning is widely used; spectral broadening, poststenotic velocity increase, and dampening of the waveform are seen as the degree of stenosis increases. Continuous-wave Doppler (CWD) is available as a portable, handheld device and provides valuable information at minimal cost; the normal triphasic waveform becomes monophasic or absent wave as the severity of a stenosis increases to occlusion.[85] Other noninvasive techniques include the assessment of segmental pressures (see "Segmental Pressures" in the next section).

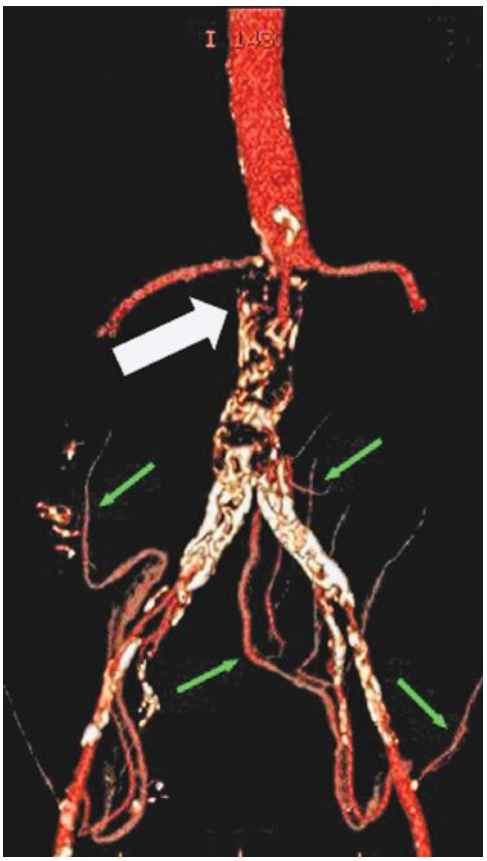
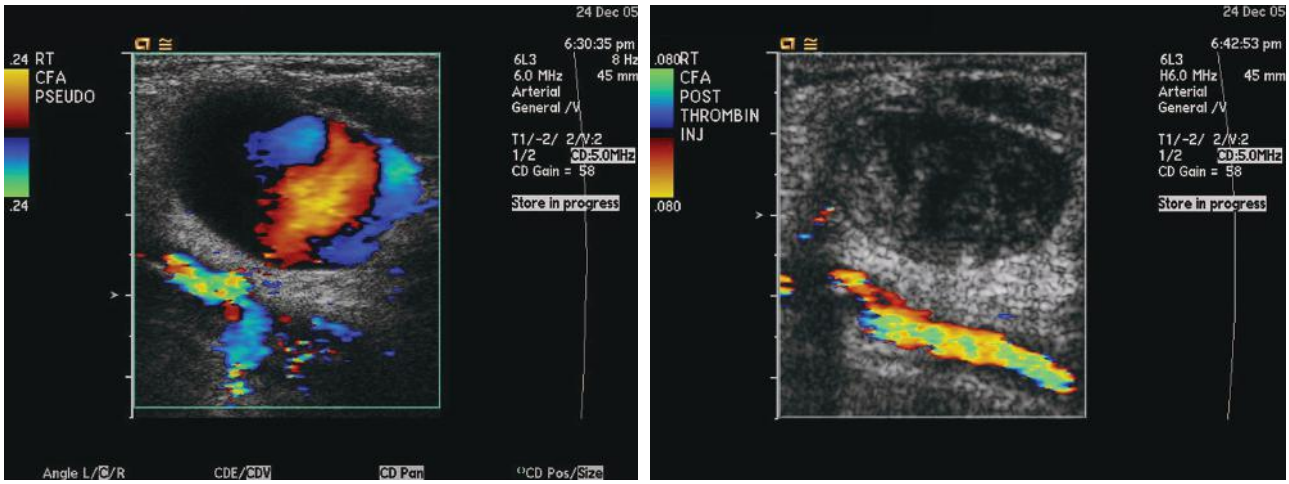


FIGURE 96–4. Computed tomography angiography of a distal aortic occlusion (*white arrow*), with numerous collaterals (*green arrows*) reconstituting the femoral vessels bilaterally.



A B

FIGURE 96–5. **A.** Duplex ultrasound of a femoral artery pseudoaneurysm showing flow within the aneurysm sac. **B.** Duplex following thrombin injection demonstrating no flow within the thrombosed pseudoaneurysm and preserved flow in the femoral artery.

Functional Studies

The information obtained by anatomic or hemodynamic testing at rest is often insufficient to explain symptoms or quantify the degree of impairment caused by the arterial lesion. Functional assessment, which usually involves some form of applied stress such as walking on a treadmill, may be necessary.

Segmental Pressures Segmental pressures and exercise testing provide a simple, reproducible, inexpensive, and accurate method of determining the presence, severity, and approximate location of stenotic lesions. Pneumatic cuffs are placed around the thigh, calf, ankle, upper or lower arm, or digits. A CWD probe is positioned over the artery at a site distal to the cuff, and the systolic pressure at which arterial flow ceases and resumes is recorded. Each segmental pressure is divided by a reference arterial pressure (usually the highest brachial artery pressure) to create an index. The most commonly reported segmental pressure is the ankle-brachial index (ABI). An ABI ≥ 1.0 is considered normal in most laboratories. Severe disease is present when the ABI is < 0.50 (Table 96–5).

Segmental pressure measurement is unreliable in patients with noncompressible or poorly compressible vessels, seen most commonly in diabetes.[86,87] The stiff vessels are caused by calcium deposition in the media of the arteries (Mönckeberg calcification). Many groups use the great toe index in these patients.[86] A toe-brachial pressure index > 0.70 is considered normal. The great toe is most often used, with the second toe as an alternative.[88] Even when the large vessels of the limb are noncompressible, the digital vessels in the toes and fingers often remain noncalcified and can be used to estimate pressure with an appropriate-sized cuff. Pulse volume recording, laser Doppler fluximetry (LDF), and transcutaneous oximetry can be useful in these patients (see following sections).

Lower-Extremity Arterial Exercise Testing Lower-extremity arterial exercise testing is performed by walking on a treadmill at a standardized protocol.[89] Protocols may be *fixed* (eg, 2 miles per hour at a 10% incline for a maximum of 5 minutes) or graded, (increasing speed and/or incline at set intervals, similar to those used in cardiac exercise studies.)[90] Select parts of the lower-extremity study (ie, ABIs or CWD at the common

TABLE 96–5. ABI Criteria[a]

	Rest	Postexercise	Symptoms	Time (min)
Normal	≥ 1.00[b]	≥ 0.90	None	5
Borderline	> 0.90	< 0.90	None	5
Mild	≥ 0.80	> 0.50	Present late	5
Moderate	< 0.80	≤ 0.50	Present, limiting	< 5
Severe	< 0.50[c]	< 0.15	Early, limiting	< 3

[a]ABI is the systolic blood pressure at the ankle measured in the supine position/systolic blood pressure of the higher arm. Postexercise values are after 5 minutes at a 10% grade at 2 miles per hour (the authors' laboratory protocol; other protocols may be used). Speed may be varied if patient is unable to maintain this speed.

[b]An ABI > 1.40 is considered noncompressible, and an alternative means of investigation should be considered.

[c]Some laboratories use < 0.40 as cutoff for severe.

Abbreviation: ABI, ankle-brachial index.

femoral level) are performed before and after exercise. With exercise, the systolic blood pressure increases as peripheral resistance decreases, resulting in a larger pressure gradient across the stenosis and lower ABI and abnormal Doppler signals distal to the stenosis. A decrease in ABI or a change in Doppler signal may be detected after exercise (Table 96–6). Even if the resting values are normal, a decreased ABI following exercise predicts an increase in mortality.[91-93] Exercise studies provide ancillary data such as the walking distance to onset of symptoms, absolute walking distance, and blood pressure response during exercise. They also correlate symptoms (which may be vague) with hemodynamic data, providing objective evidence of disease.[94] Toe tip exercise testing has good correlation to treadmill testing and is an excellent alternative in patients who are unable to walk safely on a treadmill, or when a treadmill is not available.[95]

Pulse Volume Recording Pulse volume recording assesses the magnitude of the arterial impulse entering a limb or segment of a limb. A pneumatic pressure cuff connected to a pressure transducer is placed around the limb and filled with air to a low pressure (typically 40 to 60 mm Hg). During systole, pulsatile inflow of the arterial system causes distension of the limb. This technique has the advantage of remaining accurate in the setting of poorly compressible vessels.[96,97]

TABLE 96–6. Secondary Causes of Raynaud Phenomenon

Collagen vascular disease
Scleroderma
Mixed connective tissue disease
Rheumatoid arthritis
Myositis
Sjögren syndrome
Necrotizing vasculitis
Hematologic disorders
Neurogenic
Thoracic outlet irritation
Carpal tunnel syndrome
Neuropathy
Myxedema
Acromegaly
Pulmonary hypertension
Medications
β-Blockers
Ergotamine
Methysergide
Vinblastine, bleomycin
Estrogens
Imipramine
Microcirculatory diseases
Buerger disease
Hypothenar hammer syndrome
Environmental
Cold injury
Vibration syndrome
Vinyl chloride disease

Transcutaneous Oxygen Transcutaneous oxygen pressure measurement ($TCPO_2$) assesses the microcirculation by quantifying the amount of oxygen that diffuses out of the skin.[98,99] It is dependent on a number of factors including the arterial partial pressure of oxygen, cutaneous blood flow, and the rate of oxygen consumption by the skin. $TCPO_2$ can be used to monitor the effect of therapy such as bypass graft or stenting, sympathectomy, or spinal cord stimulation.[100] It may also predict whether the cutaneous perfusion is adequate for healing at a given amputation site.[101] Values > 40 mm Hg are typically sufficient for healing, whereas those < 20 mm Hg are unlikely to heal.

Laser Doppler Fluximetry Laser Doppler fluximetry (LDF) is increasing in popularity for determination of cutaneous perfusion. Frequently, LDF is used to image skin flaps and burns to determine viability of the tissue.[102] Skin perfusion pressure may be assessed locally.[103]

TREATMENT OF ARTERIAL DISEASE

Once the diagnosis of PAD has been made, aggressive risk factor modification is the cornerstone of therapy. The slow rate of progression and high incidence of cardiovascular comorbidities create the optimal situation for modifying the underlying atherosclerotic process.

Claudication Treatment

The American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines on lower-extremity PAD nicely summarize the medical and interventional treatment options and level of evidence available[104] (Table 96–7). These guidelines were updated with new recommendations while outdated recommendations were removed in the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Focused Update of the Guideline for the Management of Patients with Peripheral Artery Disease.[64]

TABLE 96–7. Treatment of PAD ACC/AHA Indications[a]

Intervention	Class I	Class IIA	Class IIB
Smoking cessation	Yes		
Walking program	Supervised		Unsupervised
Lipid treatment	Statin to LDL < 100	Statin to LDL < 70	Fibric acid derivative High TG/low HDL
Antihypertensive treatment	SBP < 130; DBP < 80 β-Blockade	ACEI (symptomatic)	ACEI (asymptomatic)
Diabetes	Proper foot care	HbA1c < 7%	
Homocysteinemia			Folic acid
Antiplatelet therapy	Aspirin Clopidogrel		
Pharmacologics	Cilostazol		Pentoxifylline
Supplements			L-arginine p-L-carnitine Ginkgo biloba

[a]Summary of AHA/ACC level of evidence guidelines for therapies in claudication.

ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; SBP, systolic blood pressure; TG, triglyceride.

Behavioral Modification Therapy

Walking Programs Walking programs should be initiated in all patients with claudication, both with typical and atypical symptoms.[105,106] Supervised exercise programs appear superior to stent revascularization, even for those with aortoiliac peripheral artery disease.[107] However, exercise programs combined with endovascular revascularization have been shown to improve walking distances and health-related quality-of-life scores compared to supervised exercise alone.[108] Unfortunately, bicycling and other forms of exercise used for cardiovascular conditioning do not provide the same lower-extremity benefit as walking. The effectiveness of a supervised walking program is well-demonstrated, and supervised programs are more effective than non-supervised programs.[109-111] Community-based walking programs that implement structured training with monitoring and coaching commonly used in supervised exercise programs improve outcomes in PAD patients.[112-114] Exercise for 30 minutes on 4 to 5 days per week improves functional ability and exercise capacity; total and absolute walking distances increase from 50% to 300%.[115] Patients should walk until they near their maximal pain threshold, then rest for relief before walking until they reach their pain threshold again.[116] The mechanism of improvement is unclear, but increased collateral formation or recruitment, muscle training, improved oxygen uptake, and improved mechanics of walking may be involved.[117,118] Diligent foot care and protection must be emphasized, particularly in diabetics and those with severe reductions in ABI or $TCPO_2$ values. Footwear must be supportive and protective, and nail care should be performed regularly by professionals.[119]

Smoking Cessation Smoking cessation is important for the treatment of PAD. The increase in progression to amputation with tobacco use should be emphasized with the patient.[8] In a study of patients with intermittent claudication, the 10-year survival rate in tobacco users compared to former tobacco users was 46% and 82%, respectively. Recent study has demonstrated an independent association between active smoking and early graft failure.[120] Clinicians should advise smoking cessation programs and pharmacological treatment, such as varenicline or bupropion, if indicated.[121,122]

Pharmacologic Therapy

Antiplatelet agents including aspirin and clopidogrel have historically been considered first-line agent for patients with PAD.[123] However, a meta-analysis by Berger et al[124] showed no significant benefit of antiplatelet therapy, including aspirin or dipyridamole, on either all-cause or cardiovascular mortality but did show a reduction in nonfatal stroke. The Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index (AAA) trial further evaluated the role of aspirin in patients with PAD and showed no benefit on cardiovascular death, MI, stroke, or revascularization but was associated with increased bleeding.[125] The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed a benefit of clopidogrel over aspirin in all-cause cardiovascular mortality, with PAD patients having the most significant improvement.[126] In a subgroup analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study in patients with PAD, it was shown that a combination of clopidogrel and aspirin is more effective than aspirin alone in prevention of myocardial infarction, although with an increase in minor bleeding.[127,128] Based on the current data, it is appropriate to consider dual-antiplatelet therapy of clopidogrel 75 mg daily and aspirin 75 to 162 mg daily, or clopidogrel 75 mg daily alone, unless there are contraindications to antiplatelet therapy (such as a high risk of bleeding complications).

Lipid lowering has a beneficial role in patients with PAD, and targets are identical to those for patients with CAD. Statins are beneficial in lower rates of mortality and increase amputation-free survival in critical limb ischemia patients,[129] improve survival in critical limb ischemia patients 1 year after surgical revascularization,[130] and improve outcome in patients with peripheral artery disease.[131] Lipid lowering in PAD decreases progression of claudication symptoms.[132] It is appropriate to consider high-intensity statin therapy for individuals with PAD (for secondary cardiac prevention) unless they are unable to tolerate high-intensity statin therapy; if so, they may be treated with moderate-intensity statin therapy.[64,133] For individuals who are unable to tolerate any statin therapy, a nonstatin cholesterol-lowering drug may be considered.[133]

Hypertension control should be optimized to reduce adverse cardiovascular outcomes.[134] Angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers are effective in reducing cardiovascular mortality in a longitudinal study.[132] Angiotensin receptor blocker is as effective as ACEI at reducing cardiovascular death, MI, stroke, or hospitalization for heart failure in those with PAD.[135] A small study suggests that ramipril improves pain-free and maximal walking time.[136] The use of ACEI or angiotensin receptor blocker therapy in patients with vascular disease is appropriate, whereas the combination should not be used. β-Blockade was once contraindicated for patients with arteriosclerosis obliterans (ASO), but studies have refuted this idea.[137] Given the beneficial effects of β-blockade in patients with CAD, these agents should be used in patients with peripheral ASO.[138] In general, patients with established cardiovascular disease, including symptomatic PAD, should have optimization of their blood pressure.[139]

Cilostazol, a phosphodiesterase type 3 inhibitor, induces vasodilatation and inhibits platelet aggregation. Cilostazol is effective in increasing walking distance and quality of life when used in conjunction with a walking program.[140,141] The effect is lost when the drug is stopped.[142] Although effective, cilostazol should always be used as part of a comprehensive program including exercise and risk-factor reduction.[143] Cilostazol has side effects such diarrhea, headache, and dizziness, which may limit its tolerability.[144] The long-term adherence of cilostazol is poor, with more than 60% of individuals discontinuing therapy by 36 months.[145]

Vorapaxar, an oral protease-activated receptor [PAR]-1 antagonist, inhibits thrombin-induced platelet aggregation. The TRA2P-TIMI (Thrombin Receptor Antagonist for Secondary Prevention-TIMI Study Group) trial shows a benefit of vorapaxar on cardiovascular risk in stable patients with atherosclerotic vascular disease.[146] In a subgroup of the TRA2P-TIMI study in patients with PAD, vorapaxar reduces the occurrence of acute limb ischemia and peripheral revascularization.[147] However, in the recent Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, no benefit is seen in lower rates of ischemic end points, peripheral revascularization, and amputation among non–ST-segment elevation acute coronary syndrome with PAD who are treated with vorapaxar.[147]

Homocysteinemia may play an independent role in development of PAD. Treatment with folic acid and vitamins B_{12} and B_6 is appropriate when > 14 μmol/L.[148] While elevated homocysteine may contribute to development of PAD and B_6/B_{12}/folate can lower homocysteine, this combination has not been shown to reduce the risk of developing PAD.

Revascularization

The indication for revascularization is based on a number of factors including comorbidities, functional status, and severity of symptoms.[149] Surgical and endovascular treatment strategies are addressed in adjacent chapters. In general, proximal (iliac) stenosis and short segment occlusion are best treated endovascularly, with long lesions and occlusions best treated surgically. Outcomes for endovascular treatment of

the femoral to popliteal segment are improving, and this treatment should be considered by experienced operators for patients with good lesion characteristics.[150,151]

Critical Limb Ischemia

Revascularization is an option for patients with rest pain, tissue loss, or lifestyle-limiting symptoms.[150] Surgical revascularization is effective, durable, and has a good outcome with regard to limb salvage.[152] Percutaneous transluminal angioplasty (PTA), with or without stent placement, is useful and durable for lesions of the iliac and proximal superficial femoral arteries. Distal PTA has been less durable, but for patients at high risk for limb loss who are also poor surgical candidates (or technically unfeasible for surgical revascularization), it is reasonable to consider distal PTA for limb salvage.[150] Medical treatment for critical limb ischemia is challenging.[153] Intermittent pneumatic compression and angiogenesis with growth factors are emerging therapies.[154]

ACUTE ARTERIAL OCCLUSION

PRESENTATION

Acute arterial ischemia is a particularly ominous event, with a 20-day mortality rate of 25%.[155,156] It presents suddenly as a painful, cold pale, pulseless limb that progress to paresthesia and paralysis. Limb viability is at risk if flow is not restored quickly. Distal changes of livedo caused by microembolization may be present. Severe ischemia is suggested by pallor at rest, profound coolness, tender or hard muscles, and loss of motor and/or sensory functions. If caused by arterial dissection, variability in the pulse deficit and affected area over a short time (migratory signs and symptoms) will cause discrepancy between examiners, thus providing a valuable clue to the diagnosis.

ETIOLOGY

The etiology of acute arterial occlusions may be trauma, dissection, thrombosis in situ, or embolism from a proximal source. Aneurysms, clotting disorders, atherosclerosis, and recent arterial manipulation may precipitate acute occlusion by mechanical disruption of plaque. Cardiac thrombus is the most common source for large embolism. Both the left ventricle and atrium may harbor thrombus and should be interrogated with transesophageal echocardiography.[157] Paradoxical emboli from the right heart or limbs pass across cardiac septal defects or a patent foramen ovale and cause cerebrovascular events. Interrogation of the venous system should be done when paradoxical emboli are suspected.

TREATMENT

Immediate measures are needed to protect the limb and restore blood flow. Heparin should be started to prevent clot propagation and to stabilize the embolic source(s). Angiography (conventional or other) may be required to plan repair when there is preexisting occlusive or aneurysmal disease or when the etiology is unclear. Ideally, all occlusions should be considered for reestablishment of flow, but urgency is governed by the degree of ischemia. If the affected limb is not viable, amputation should be performed as quickly as possible to avoid further complications. Additional time may be taken to address ancillary problems in lesser degrees of ischemia. When critical ischemia is present, repair must occur within hours to salvage the limb, provided risks to the patient are acceptable.[158] When indicated, thrombolysis of acute thrombus can be effective, although the risks of bleeding and stroke must be considered.[159,160]

ARTERIAL DISEASE OF DIVERSE ETIOLOGIES

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (TAO), or Buerger disease, is an inflammatory vasculopathy affecting small and medium-sized arteries and veins caused by an inflammatory, highly cellular intraluminal thrombus.[161] TAO was thought to be exclusively associated with tobacco use, but cannabis, either on its own or because of contamination with tobacco, causes a similar entity, and its use should also be addressed.[162] Historically, TAO was seen in males in the second through fifth decades. Currently, the incidence in women has risen, reflecting the changing demographics of tobacco use. Clinically, TAO differs from atherosclerosis in that involvement of the upper extremity is common and usually present. The initial involvement is often in digital, pedal, and hand vessels; patients may present with ulceration of one or more digits. Rare manifestations include coronary, cerebral, and mesenteric artery lesions.[163] Episodes of recurrent superficial phlebitis are common. Biopsy of acute lesions, particularly superficial veins, is diagnostic, whereas angiographic features are characteristic but not diagnostic.

Improvement is possible only after all exposure to tobacco ceases, but the improvement remains variable.[164,165] Amputation of ulcerated digits and limbs is often required.[166,167] Progressive tissue loss is inevitable until tobacco exposure is stopped, with amputation rates approaching 50% in those who continue to use tobacco.[161,168]

GIANT CELL AND TAKAYASU ARTERITIS

Takayasu arteritis (TA) and giant cell (temporal) arteritis (GCA) are similar in pathologic process but affect different age groups. TA occurs in those younger than age 40 years, and GCA usually affects those older than age 50 years.[169,170] TA generally involves arteries below the neck and GCA generally involves arteries above the diaphragm, but involvement of the aorta and subclavian, axillary, renal, iliac, femoral, and superficial femoral arteries is described in both. Disease is usually bilateral and presents with rapidly progressive symptoms in the setting of a nonspecific systemic illness. Limb-threatening ischemia is rare but may occur when diagnosed late. Both GCA and TA have characteristic clinical and laboratory findings including an elevated sedimentation rate (> 90%, but not in all patients) and typical angiographic features of smooth, tapered narrowing in large and medium-sized arteries (Fig. 96–6).[170]

For GCA, confirmatory biopsy of the temporal artery within 3 days of steroid initiation is the gold standard.[171] A preceding history of polymyalgia rheumatica is present in > 50% of patients.[172] Visual changes in the setting of an elevated sedimentation rate, jaw claudication, or a pulse deficit should be treated as medical emergency with parenteral corticosteroids.[173] TA may also present as a medical emergency. The coronary arteries can be involved, resulting in unstable angina.[174] It may also affect the aortic root, causing acute aortic insufficiency with pulmonary edema.[175] This should be considered in a young person with absent pulse(s), dyspnea, and a diastolic murmur.

These diseases are unique among arteriopathies in that the acutely stenotic lesions improve rapidly with steroid therapy. Alternative immunosuppressive agents are often used, but corticosteroids remain the mainstay of treatment.[170] When required, revascularization is best performed when the inflammatory process is quiet or *burned out* and steroids have been discontinued or tapered to a maintenance dose.[176]

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia (FMD) most commonly affects women and has been described in almost all arteries.[177] The renal artery is most often involved; it occurs in approximately 75% of patients with FMD and

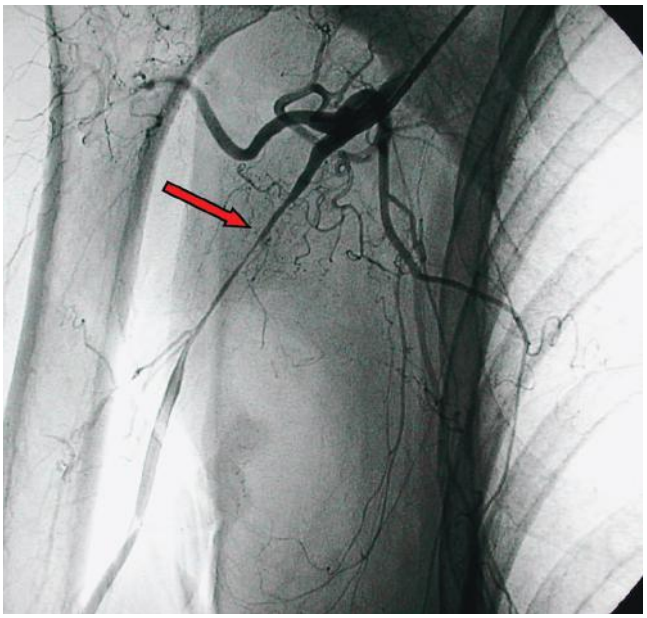


FIGURE 96–6. Extracranial giant cell arteritis affecting the brachial artery of an elderly woman. Note the smooth, tapered narrowing (*red arrow*) with normal-appearing vessel proximal and distal to the affected segment.

is bilateral in approximately > 35% of cases.[178] Although early reports described the renal arteries as being affected most often, more recent data from the US FMD registry suggest that FMD was found equally in the renal and carotid/vertebral arteries.[179] Treatment with angioplasty has generally good outcomes, with stent use reserved for complications such as angioplasty-associated dissection. Surgical repair is reserved for refractory cases or when distal renal disease is present.[179]

RAYNAUD PHENOMENON

Raynaud phenomenon is diagnosed by history, with the examination and laboratory findings playing a secondary role. The syndrome is classically defined as discoloration episodes of white ischemia, then blue stasis, and then red hyperemia during the recovery phase. In practice, most patients do not describe all three phases.[180] Fingers are involved more often than toes. The fingertips are affected more commonly than the palm or dorsum of the hand, as shown in Fig. 96–7. Prevalence

FIGURE 96–7. Hyperemic (red) phase in a patient with secondary Raynaud phenomenon. Note the pallor still present in the proximal digits.

was estimated at slightly < 10% of the population in the Framingham study.[181]

Allen and Brown[182] defined primary Raynaud phenomenon as episodes of bilateral color changes induced by cold or emotion without evidence of ischemia or other disease occurring for 2 years. This represents most cases and, in some sense, can be considered simply the exaggerated response of a normal reflex. The pathophysiology of exaggerated vasoconstriction is complex but appears to involve both local and systemic pathways.[180] Most patients with primary Raynaud phenomenon require no therapy and quickly learn to keep not only hands but the whole body warm. For those with severe symptoms, treatment options are similar to secondary Raynaud.

Secondary Raynaud phenomenon is caused by a specific etiology and is present in approximately 10% of patients at initial evaluation. For those without a secondary cause at presentation, one is identified at a rate of 2% per year over a 10-year interval.[183] Causes of secondary Raynaud phenomenon are diverse (see Table 96–6). Treatment of secondary Raynaud is directed at the underlying cause when feasible. Calcium channel blockers and α-blockers, either as monotherapy or in combination, can blunt the episodes in many patients but may have little impact on ischemic complications. ACEI, angiotensin II receptor inhibition, and endothelin receptor inhibition are promising in the setting of scleroderma.[184]

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CHAPTER 97

DIAGNOSIS AND MANAGEMENT OF DISEASES OF THE PERIPHERAL VENOUS SYSTEM

Daniella Kadian-Dodov and Jeffrey W. Olin

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INTRODUCTION

The lower extremity venous system includes the deep, superficial, and perforating veins, which work in concert to return blood to the heart (Fig. 97–1).[1] Unlike the arterial system, the venous system is low resistant and must overcome gravitational and hydrostatic pressure forces to achieve blood return to the heart. The venules and veins have very thin walls and low resting basal tone, which allows for enormous distensibility. As a result small changes in hydrostatic forces, central pressure, and/or external forces result in changes of the vein diameter. Venous blood flow is reliant upon muscular leg contraction, historically referred to as "the peripheral heart,"[2] as well as bicuspid venous valves that open and close to prevent backflow. Together, muscular leg contraction and venous valves help to overcome hydrostatic forces within the vein itself. Venous disease results from degeneration and dysfunction of the veins and/or valves, which may occur following an obstruction such as deep vein thrombosis or in the setting of increased central pressures as in congestive heart failure. Venous disease is associated with a wide array of clinical manifestations caused by complex hemodynamic and anatomic failures. A basic understanding of these complexities is essential in the evaluation, diagnosis, and appropriate treatment of venous disease.

ANATOMY

The veins of the lower extremities are divided into three main subgroups, which are interconnected and together ultimately drain into the external and common iliac veins to the inferior vena cava: (1) perforator veins, (2) superficial veins, and (3) deep veins. The *fascia muscularis* divides the deep and superficial vein compartments; the perforator veins cross the fascial plane to connect the deep and superficial venous systems.[3] A network of bicuspid venous valves exists in the deep and superficial veins to assist in venous return and prevent backflow. In the lower extremity, the deep veins accompany the corresponding arteries and their branches.[4] The popliteal vein is formed by the confluence of the calf veins, which include the gastrocnemius vein draining into the popliteal vein and the soleal veins emptying into the tibial and then popliteal veins. Subsequently, the popliteal vein empties into the femoral vein (previously called superficial femoral vein), common femoral and iliac veins. The common femoral and external iliac vein each have one venous valve approximately 63% of the time; in 37% of patients, there is no valve present in this location.[5,6]

The largest of the superficial veins, the great saphenous vein (GSV), is also the longest vein in the human body. It courses from the ankle medially up the calf and into the thigh to ultimately confluence with the common femoral vein at the saphenofemoral junction (see Fig. 97–1). Normal GSV caliber ranges from 3 to 4 mm in diameter, and 10 to 20 valves scattered along its course aide in venous outflow.[6] Almost all patients have a "terminal valve" located at the saphenofemoral junction. The second largest superficial vein is the small saphenous vein (SSV), which courses along the lateral calf and typically drains into the popliteal vein at the saphenopopliteal junction. The SSV contains 7 to 13 venous valves and is typically 3 mm in diameter. Notably, anatomic variants of the venous system are common, and alternative drainage routes can be seen in as many as 50% of patients.[6] Rich networks of subcutaneous and dermal vein plexuses exist as embryologic remnants of the venous system, which are spread across the lateral thigh and calf. In some conditions, abnormal development of the superficial veins may result in large varices across these networks, as seen in Klippel-Trénaunay or Parkes-Weber syndromes.[7]

VENOUS THROMBOSIS

Venous thrombosis may occur as a result of the risks as identified in Virchow's Triad: stasis, endothelial injury, and the hypercoagulable state, or may occur without any known risk factors (unprovoked venous thrombosis). The treatment approach and duration rely upon the patient's underlying risk factors, extent of thrombus, and/or affected venous segments. We will consider venous thrombosis in the superficial and deep venous systems separately.

SUPERFICIAL THROMBOPHLEBITIS

Superficial thrombophlebitis (STP) classically presents as a tender, red, and indurated cord that follows the line of the affected superficial vein. Most often, the GSV is involved. The disease is reported in up to 3% to 11% of the general population, although the annual incidence of disease is not known. Higher rates are seen in malignancy, women over age 60 years, obesity, thrombophilia, pregnancy or estrogen use, sclerotherapy, autoimmune disease, and those with varicose veins.[8,9] Overlap with deep vein thrombosis (DVT) or pulmonary embolism (PE) is reported in up to 25% of patients with STP.[10,11] Duplex ultrasonography is recommended to confirm the diagnosis of STP and exclude other causes of the swollen limb (Table 97–1), as well as screen for the presence of a concomitant DVT or extension of the clot into the deep venous system that would warrant treatment with anticoagulation.[9,12] First-line management of STP typically includes warm compresses and nonsteroidal anti-inflammatory agents for a period of 7 to 10 days. Most cases of STP are self-limited; however, anticoagulation should be considered in cases that do not respond to conservative management, or if the STP is in close proximity to the deep veins at the sapheno-popliteal (5 cm) or saphenofemoral junction (10 cm).[12,13] Both low-molecular-weight heparin and

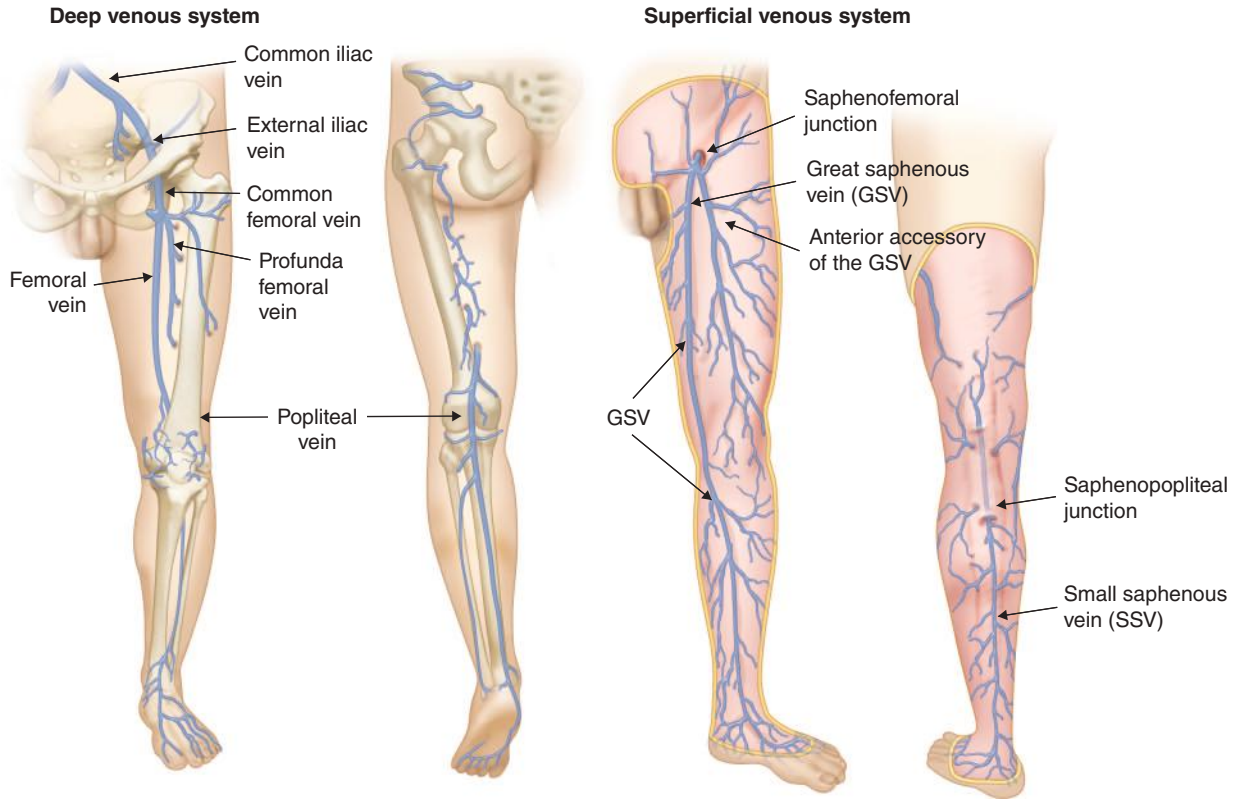


FIGURE 97–1. Peripheral Venous Anatomy.

fondaparinux at prophylactic or therapeutic doses are acceptable therapies for the prevention of DVT or PE in patients deemed to be high risk.[12,14] In cases of recurrent STP, testing for thrombophilias, search for systemic diseases (eg, thromboangiitis obliterans, Behçet syndrome), and investigation for underlying malignancy may be appropriate.[9]

DEEP VEIN THROMBOSIS

Presentation, Risk Factors, and Diagnosis

The classic clinical description of DVT includes unilateral pain, limb swelling, skin erythema, and warmth, with symptoms acute to subacute in onset. However, diagnostic testing is necessary to confirm the diagnosis, as the signs and symptoms of DVT are not reliable and cases may be clinically subtle.[15] The use of clinical prediction scores, like the Wells score (Table 97–2), can be helpful in the initial evaluation of a patient with possible DVT to guide health care providers in deciding who may warrant additional testing with D-dimer and duplex ultrasound.[16,17] If DVT is suspected, an evaluation to confirm and define the extent of DVT should be pursued.[17] Findings that support the diagnosis of DVT on duplex ultrasonography include a dilated noncompressible vein resulting from the presence of thrombus, direct visualization of thrombus, as well as altered venous flow dynamics

TABLE 97–1. Causes of the Swollen Limb

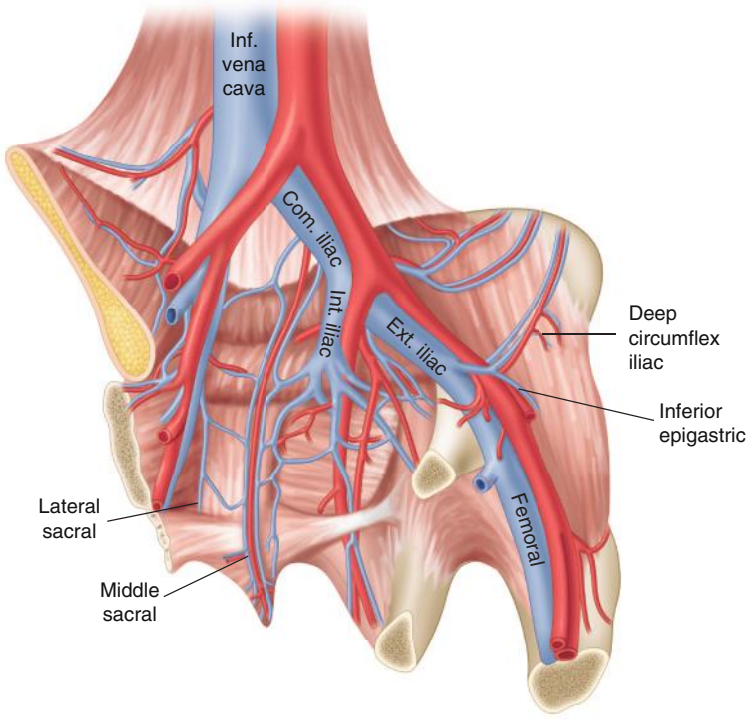
	Chronic Venous Insufficiency	Lymphedema	Lipedema	Cellulitis	Deep Venous Thrombosis
Distribution of edema	Below the knee. Around the ankle.	Distal; involves the foot ("buffalo hump") and toes ("sausage toes"). "Stemmer's sign"—inability to pinch skin between the base of the first and second toes.	Always bilateral. Spares the foot: "ankle cut-off sign"; concentrated edema over the malleolus: "fat pad sign."	Often unilateral and well demarcated. Skip areas of involved and uninvolved skin.	Often unilateral, limited to the affected limb and distal to the obstructed vein.
Skin findings	Telangiectasia, reticular veins, varicose veins, skin pigmentation and/or eczema, atrophie blanche, lipodermatosclerosis, ulcerations.	Skin pigmentation and/or fibrosis; verrucous changes.	Disproportionate fat distribution below the waist; tender to palpation.	Well-demarcated erythema, tender to palpation, warm.	Erythema, warmth, tenderness to palpation. Dilated superficial veins, suffusion of leg.

TABLE 97–2. Wells Score for Assessing Probability of Deep Vein Thrombosis[15,17]

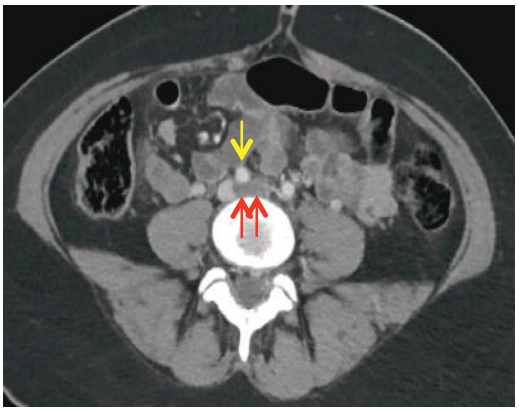
+1 Point Each:	
Active malignancy	
Paralysis, paresis, or recent plaster immobilization of lower limb	
Recently bedridden > 3 days and/or major surgery within 4 weeks	
Localized tenderness along distribution of lower extremity deep veins	
Entire lower limb swollen	
Calf swelling > 3 cm compared with the asymptomatic leg	
Strong family history of DVT (≥ 2 first-degree relatives with history of DVT)	
–2 Points if Alternative Diagnosis to DVT Is at Least as Likely	
Probability:	
High	≥ 3 points
Moderate	1-2 points
Low	≤ 0 points

with a lack of respiratory variation resulting from outflow obstruction or a lack of flow augmentation with calf muscle compression, indicating distal obstruction between the calf muscle and ultrasound transducer.[18] Catheter-based venography, magnetic resonance (MR), and computed tomographic (CT) venography may have a role in specific situations (eg, evaluation of the pelvic veins, assessing for extrinsic vein compression), although duplex ultrasonography is the standard method for detection of acute DVT in most cases.[18-20] Challenges with CT venography surround appropriate contrast timing of the target vein and subsequent difficulty in obtaining a diagnostic study; MR venography, on the other hand, shows promise in overcoming the contrast issue seen with CT, although its use is limited in patients with metallic implants.[20] Catheter-based venography is the gold-standard for the direct visualization of venous flow and collaterals, and allows for intraluminal pressure gradient measurements and the use of intravascular ultrasound to detect a significant stenosis within the venous segment.[20] The use of catheter-based venography is generally limited to the evaluation of cases with possible stenosis or venous compression, and patients in whom a therapeutic intervention to relieve the obstruction is considered.[18,20]

The morbidity and mortality associated with DVT are related to the proximal extent of the thrombus and risk for pulmonary embolism (PE).[21] Upper extremity DVT, at the level of the axillary veins or higher, carries risk for PE estimated as high as ~12%.[21,22] Up to 30% of patients with VTE suffer a mortal event within 30 days,[23] most often caused by PE, of which 25% to 30% present with hemodynamic compromise and higher risk of associated sudden death.[24] The number of people who experience VTE per year in the United States is not known. However, it is estimated that as many as 900,000 could be affected (1-2 per 100,000).[23,25] It is estimated that 60,000 to 100,000 people per year die from VTE in the United States. In general, unprovoked venous thromboembolism (VTE), including DVT and PE, tends to recur with a cumulative incidence of 10% at one year and 30% at 8 years after the first event.[26] Risk factors for DVT and PE are many, and may include both intrinsic and extrinsic factors such as sex, ethnicity, inherited or acquired thrombophilia, malignancy, pregnancy, exogenous estrogen hormones, chronic disease with prolonged bedrest, stroke, recent surgery, or injury. Anatomic variants leading to extrinsic vein compression, such as in May-Thurner (Fig. 97–2), are found in up to 20% to 24% of the general population[27,28] and may account for the left-sided predominance of DVT described in the lower extremity.[29] In the upper extremity, thoracic outlet obstruction (ie, pacemaker implantation, thoracic outlet syndrome, or "Paget-Schroetter" effort thrombosis) and the use of central venous catheters account for most cases.[30] Inherited thrombophilias such as factor V Leiden, prothrombin (G20210A) gene mutation, plasminogen-activator-inhibitor 1 (PAI-1) levels or gene abnormal PAI-1 gene polymorphism, antithrombin and protein C/S deficiency are present in approximately 30% of patients presenting with venous thromboembolism and may confer up to a fivefold increased risk of DVT or PE in their heterozygous state.[31-33] Despite these rates, routine testing for



A



B

FIGURE 97–2. May-Thurner anatomy and syndrome. **A.** Anatomic variant causing compression of the left common iliac vein by the overlying right common iliac artery, which results in an outflow obstruction that may predispose to DVT. **B.** May-Thurner syndrome diagnosed by CT venogram. Filling defect seen in the left common iliac vein (*red arrow*) consistent with DVT resulting from compression of the overlying right common iliac artery (*yellow arrow*).

thrombophilia is not recommended as the presence of an abnormal allele only rarely affects the management of a patient with DVT or PE. Of note, in 25% to 50% of all DVT and PE, no underlying cause or risk factor is identified (unprovoked VTE).[25]

Treatment

In the case of distal calf vein DVT, it is estimated that approximately 15% to 25% will progress to the popliteal vein and/or result in a pulmonary embolus (PE).[34,35] For this reason, it is recommended that patients be treated with anticoagulation (especially if symptomatic) or an ultrasound surveillance program (ie, 1-2 week follow-up, especially if there is a significant risk of bleeding on anticoagulation) to evaluate for thrombus propagation if anticoagulation is to be withheld.[21,36] Cases in which anticoagulation should be considered over surveillance include severe associated symptoms, extensive thrombus (> 5 cm in length or involving multiple veins), thrombosis in close proximity to the deep veins (5 cm from the sapheno-popliteal junction and 10 cm from the sapheno-femoral junction), lack of identifiable and reversible provoking factors, active cancer, recurrent VTE, and in-patient status.[21]

Treatment of DVT involving the popliteal veins, or subclavian-axillary veins in the upper extremity, and more proximal segments is dictated by the presence of reversible or modifiable provoking factors (eg, surgery or exogenous hormone use), the extent of thrombus (DVT versus PE), the patient's risk of bleeding with anticoagulation therapy, and patient preference. The guidelines for anticoagulation recommend that patients with an identifiable and reversible risk factor be treated with anticoagulation for at least 3 months prior to discontinuation.[21,37] In contrast, those without modifiable or identifiable risk factors should be considered for longer treatment duration if the risks of anticoagulation do not outweigh the perceived benefit.[21,37] Newer guidelines recognize the direct oral anticoagulants (DOACs) as first-line alternatives to warfarin therapy for the treatment of acute DVT and PE.[21,38] The DOACs include one direct thrombin inhibitor, dabigatran, as well as the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban (Table 97–3). There is variability in the recommended dosing regimens, use of heparin versus oral run-in to therapy, cost of drug, and recommended use in the setting of renal insufficiency. All have demonstrated noninferiority in comparison to warfarin for the acute treatment of venous thromboembolic disease.[39-43] Apixaban was superior compared to warfarin with regard to rates of major bleeding.[42] In patients that have completed the planned duration of anticoagulation and are deemed candidates for extended therapy, low-dose apixaban (2.5 mg twice daily) demonstrated a safety profile equal to placebo and was as effective as full-dose apixaban (5 mg twice daily) for the prevention of recurrent VTE.[44]

Advanced therapies including thrombolysis and inferior vena cava filter (IVC filter) placement may be considered in specific scenarios, although in general these treatments are recommended only on a case-by-case assessment. For patients with a contraindication to anticoagulation, IVC filter placement may be considered for the prevention of PE.[21,37,38] However, a recent randomized trial failed to demonstrate any benefit for the use of retrievable IVC filters in patients receiving concomitant treatment with anticoagulation or thrombolysis[45] and the most recent guidelines do not recommend routine use in this setting.[21,37,38] Catheter-directed thrombolysis (CDT) and mechanical thrombectomy are typically reserved for patients with occlusive iliofemoral DVT and symptoms ≤ 14 days duration. CDT is used in this setting to correct the outflow obstruction, rapidly relieve patient symptoms, and prevent the complication of the postthrombotic syndrome (PTS).[21] However, the data for use of CDT to prevent PTS are limited to small and/or non-randomized studies.[46-49] A large randomized trial entitled Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) has completed recruitment and is still actively following patients. The results of this trial will help to determine if the PTS can be prevented with more aggressive treatment.[50]

Phlegmasia Cerulea Dolens

Phlegmasia cerulea dolens (PCD) is the most severe manifestation of DVT and occurs when there is near-total venous outflow obstruction of the lower extremity, resulting in limb ischemia.[51] PCD is a life- and limb-threatening emergency with up to 50% of cases progressing to venous gangrene following complete occlusion of all deep and superficial veins, as well as microvascular venous collaterals.[51] Although literature is scarce, associated mortality rates of 25% to 40% are reported and up to 15% to 25% of survivors will require amputation.[51,52] The clinical triad of PCD includes acute limb pain, massive swelling, and cyanosis, which herald a reversible phase of venous occlusion before gangrene sets in (Fig. 97–3A). Urgent management is imperative at this phase and may include systemic or catheter-directed thrombolysis, mechanical or surgical thrombectomy with or without fasciotomy, or a combination of these modalities in addition to systemic anticoagulation.[37,52-54] The characteristic changes of gangrene begin distally and move proximal as ischemia progresses (Fig. 97–3B). There is a strong association with malignancy, as well as inherited thrombophilia.

VENOUS INSUFFICIENCY

Venous insufficiency occurs as a result of inadequate venous outflow resulting from incompetent venous valves or obstruction. It is estimated that up 25% of the adult population in the United States and Western Europe has varicose veins, and cross-sectional studies demonstrate that > 50% of the population has some clinical manifestations of venous disease.[55-57] The presentation is variable, and the CEAP Classification (Table 97–4) is often used to classify disease based on clinical, etiologic, anatomic, and pathophysiologic features.[58,59] Today, the clinical classification alone is most often used. For venous disease secondary to deep vein thrombosis, the Villalta scale[60] for the postthrombotic syndrome (PTS) is most often used to define and grade the severity of disease (Table 97–5).[61]

ETIOLOGY, RISK FACTORS, AND PRESENTATION

Venous insufficiency may be either primary or secondary in etiology. Primary disease is thought to be autosomal dominant with incomplete penetrance; patients may have up to a 90% chance of developing varicose veins if both parents are affected.[62] No candidate genes have been identified; however, familial studies in twins confirm a heritable influence on the development of disease.[63] Additional risk factors include female sex, obesity, prolonged standing, multiparity, and age.[64,65] Secondary causes of venous insufficiency include the PTS related to DVT or increased hydrostatic pressure as in congestive heart failure. The clinical signs and symptoms are widely varied and may range from cosmetic complaints such as spider veins and asymptomatic varicose veins to painful varicosities, edema, skin hyperpigmentation, lipodermatosclerosis, and ulceration.[1,64] A large proportion of patients may live indefinitely without symptoms related to their venous disease; however, the more severe manifestations like ulceration have a poor overall prognosis when present, with frequently delayed healing times and a high risk of recurrent ulceration.[66] Medical costs related to the management of venous disease in the United States are estimated to be upwards of $1 billion annually.[1,64] Additional indirect costs may be incurred as a result of missed workdays related to leg symptoms of chronic venous insufficiency often described as bursting, leg fullness

TABLE 97–3. Various Options for Oral Anticoagulation in the Treatment of VTE

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of Action	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Half-Life	40 h (mean)	12-17 h	5-9 h	8-15 h	8-10 h
Cost (30 d)	$	$$$	$$$	$$$	$$$
VTE Treatment					
Trial	[102,103]	*RE-COVER*[37]	*EINSTEIN*[38,39]	*AMPLIFY*[40]	*HOKUSAI-VTE*[41]
Heparin Run-in	Yes	Yes	No	No	Yes
Dosing Regimen	2-10 mg/d (INR 2-3)	150 mg BID	Acute VTE: initiate at 15 mg BID × 3 wks, then 20 mg daily for treatment duration	Acute VTE: initiate at 10 mg BID × 7 days, then 5 mg BID for treatment duration	60 mg daily or 30 mg daily[a]
eGFR < 30 mL/min	No adjustment	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Recurrent VTE (DOAC vs warfarin)		2.4% vs 2.1%, $P < .001$ (noninferiority)	2.1% vs 3.0%, $P < .001$[38]; 2.1% vs 1.8%, $P = .003$[39] (noninferiority)	2.3% vs 2.7%, RR 0.84, CI 0.6-1.18, $P < .001$ (noninferiority)	3.2% vs 3.5%, HR 0.89, CI 0.7-1.13, $P < .001$ (noninferiority)
Major Bleeding (DOAC vs warfarin)		1.6% vs 1.9%, HR 0.82, CI 0.45-1.48	0.8% vs 1.2%, $P = .21$[38]; 1.1% vs 2.2%, $P = .003$[39]	0.6% vs 1.8%, RR 0.31, CI 0.17-0.55, $P < .001$ (superiority)	1.4% vs 1.6%, HR 0.84, CI 0.59-1.21
Extended Treatment of VTE[b]					
Trial	*PREVENT*[104]	*RE-SONATE* and *RE-MEDY*[105]	*EINSTEIN-EXT*[106]	*AMPLIFY-EXT*[42]	NA
Dosing Regimen	2-10 mg/d (INR 1.5-2) vs placebo	Dabigatran 150 mg BID vs warfarin or placebo	Rivaroxaban 20 mg daily vs placebo	Apixaban (2.5 mg BID or 5 mg BID) vs placebo	
Recurrent VTE (OAC vs control)	2.6 vs 7.2 (per 100 person-yr), HR 0.36, CI 0.19-0.67, $P < .001$	0.4% vs 5.6% and 1.8% vs 1.3%, $P = .03$	1.3% vs 7.1%, $P < .001$ (superiority)	1.7% (2.5 mg) and 1.7% (5 mg) vs 8.8%, $P < .001$ (superiority)	
Major Bleeding (OAC vs control)	0.4 vs 0.9 (per 100 person-yr), HR 2.53, CI 0.49-13.03, $P = .25$	0.3% vs 0.0% and 0.9% vs 1.8%, $P = .06$	0.7% vs 0.0%, $P = .11$	0.2% (2.5 mg) and 0.1% (5 mg) vs 0.5% RR (2.5 mg vs control) 0.49, CI 0.09-2.64, RR (5 mg vs control) 0.25, CI 0.03-2.24	

[a] Patients with body weight below 60 kg or a creatinine clearance of 30-50 mL/min, as well as patients who were receiving P-glycoprotein inhibitors (ie, verapamil, quinidine) received 30 mg edoxaban instead of 60 mg daily.

[b] Patients with VTE completed at least 3 months of planned anticoagulation prior to study enrollment.

Adapted with permission from Makaryus JN, Halperin JL, Lau JF: Oral anticoagulants in the management of venous thromboembolism. *Nat Rev Cardiol*. 2013 Jul;10(7):397-409.

and heaviness, burning, cramping, pruritis, and restlessness.[67,68] Symptoms are exacerbated by prolonged standing and dependency, as well as during pregnancy or other volume overload states. Elevation typically relieves the symptoms.

DIAGNOSIS AND TREATMENT

The diagnosis of chronic venous insufficiency is often clinical as the characteristic skin changes and symptoms readily expose the disease. Skin hyperpigmentation is caused by hemosiderin deposition resulting from long-standing venous hypertension. Venous hypertension causes edema, which leads to transudation of interstitial fluid and hemosiderin in the skin and subcutaneous space usually above the medial malleolus leading to stasis dermatitis. If this remains untreated (lack of compression), lipodermatosclerosis occurs. In this advanced manifestation of venous insufficiency, the skin is indurated and fibrotic with more extensive pigmentation and erythema. Lipodermatosclerosis is a stasis-associated panniculitis that may mimic acute cellulitis. In its most severe form, the leg has the appearance of a "bowling pin" or "inverted champagne bottle." For most patients with venous

FIGURE 97–3. Phlegmasia cerulea dolens (**A**), a life- and limb-threatening emergency that heralds venous gangrene (**B**).

insufficiency, conservative management including compression therapy and good skin care are mainstay. We advise that our patients keep the feet clean, dry, and well moisturized to prevent any skin breakdown or seeding of a potential infectious nidus that may complicate the disease. Control of edema is also imperative, as the excess fluid in the legs is a setup for poor wound healing in the case of venous ulceration. Compression therapy has been used for over 2000 years as treatment of chronic venous insufficiency.[69] The goals of compression therapy include (1) reduction of limb size by alteration of the venous pressure gradient and improved effectiveness of the muscle pump, (2) maintaining the limb at the smallest possible size, and (3) prevention of the complications of venous insufficiency.[69] Initially, compression wraps are recommended to achieve a reduction in limb size as the wraps may be adjusted to the ever-decreasing limb girth day-to-day. Once edema control is achieved, a compression garment or stocking may be used to maintain edema control. Compression garments come in different grades of compression and lengths (knee-thigh, thigh-high, pantyhose). The most important area of compression is below the knee, where the standing venous pressure is greatest.[1] Most patients with varicose veins and venous insufficiency will require compression of 20 to 30 mm Hg, and some 30 to 40 mm Hg, for control. For those with an ulcer related to venous insufficiency, 30 to 40 mm Hg compression is usually needed. In patients with more severe disease related to lymphedema, compression therapy in the 40 to 50 mm Hg grade is recommended.[1,69].

Duplex Ultrasonography

For patients in whom therapies beyond conservative measures may be considered, such as recurrent venous ulceration or painful varicosities despite a trial of compression therapy, duplex ultrasonography is standard for evaluation. The goal of the exam is to define the anatomy and malfunctioning veins, as well as the extent of insufficiency. By consensus standards, evaluation should include the vein diameters, location, and competence of all saphenous junctions, perforating veins, and source veins of superficial varices.[70,71] The deep veins are also evaluated for competence, anatomy, and the presence of an obstructive lesion.[70] In addition to the maneuvers discussed in the evaluation for obstruction or DVT, the duplex exam for venous insufficiency includes provocative maneuvers to unmask abnormal reversal of flow in the vein. Normal valve mechanics include a period of proximal antegrade flow with calf muscle contraction followed by flow reversal, which leads to a

TABLE 97–4. CEAP Classification Scheme for Lower Extremity Venous Disease[a]

	Clinical Presentation	Etiology	Anatomy[b]	Pathophysiology
C_0	No venous disease	E_C congenital	A_S superficial veins	P_R reflux
C_1	Telangiectasia, or reticular veins			
C_2	Varicose veins	E_P primary	A_D deep veins	P_O obstruction
C_3	Edema without skin changes			
C_{4a}	Skin pigmentation or eczema	E_S secondary	A_P perforator veins	$P_{R,O}$ reflux and obstruction
C_{4b}	Lipodermatosclerosis or atrophie blanche			
C_5	Healed ulceration			
C_6	Active ulceration			

[a]Each category is scored independently of the others. For example, with this scheme, a patient with postphlebitic syndrome, an active venous ulcer, and hemodynamic evidence of reflux but no obstruction is scored as $C_6 E_S A_D P_R$. A patient with telangiectasias and no other symptoms or findings is $C_2 E_P A_S$.

[b]The complete anatomy classification also identifies the venous segment(s) involved.

Abbreviation: CEAP, clinical manifestation, etiologic factor, anatomic involvement, and pathophysiology feature.

TABLE 97–5. Villalta Post-Thrombotic Syndrome Scale[58]

Symptoms and Clinical Signs	None	Mild	Moderate	Severe
Symptoms				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Parasthesia	0 points	1 point	2 points	3 points
Pruritis	0 points	1 point	2 points	3 points
Clinical Signs				
Pretibial edema	0 points	1 point	2 points	3 points
Skin Induration	0 points	1 point	2 points	3 points
Hyperpigmentation/erythema	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous Ulcer	Absent	Present		

Points are summed into a total (range 0–33). PTS is defined as a score ≥ 5 or the presence of a venous ulcer. PTS is classified as *mild* if score is 5–9, *moderate* if score is 9–14, and *severe* if the score is ≥ 15 or a venous ulcer is present. To use the Villalta score as a continuous measure, it is recommended that those with severe PTS based solely on the presence of a venous ulcer (ie, total Villalta score < 15) should be assigned a score of 15.[59]

Reproduced with permission from Kahn SR, Partsch H, Vedantham S, et al: Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost*. 2009 May;7(5):879-883.

reversal of the transvalvular gradient and allows for vein valve closure. Clinically relevant reflux can be measured as prolonged flow reversal. The vein is interrogated with color-Doppler and spectral waveform analysis; incompetence is demonstrated as retrograde flow occurring above the baseline (Fig. 97–4A).[71] The Valsalva maneuver is performed by asking the patient to bear down, thereby increasing intrathoracic pressure and potentially reversing the transvalvular gradient. The Parana maneuver is more widely used outside of the United States, and works to initiate calf compression by having the patient stand and lean slightly forward and backward.[71] Compression of the proximal limb and release of the distal limb, either manually or with standardized pressure cuffs, also work to disturb and test the normal resting pressure gradient across the valves. All maneuvers may be performed with the patient supine and standing to reveal otherwise subtle reflux disease. The majority of normal valves will close within 0.5 seconds of a maneuver, although the defined normal duration is shorter in perforating veins (< 0.35 seconds) and longer in the deeper venous segments (> 1 second).[72] Although flow may also be detected by color-flow Doppler analysis, the duration of reflux may be underestimated as compared to measurement of flow via the spectral waveform.[73]

Other Noninvasive Testing

Physiologic testing with plethysmography relies on volume change in the limb as a result of venous outflow or reflux disease. The most common techniques are strain gauge plethysmography, air plethysmography, and impedance plethysmography (IPG). IPG is the best-studied technique, and useful for the evaluation of venous outflow obstruction (ie, DVT) as well as venous insufficiency.[74,75] To evaluate for venous insufficiency, the legs are raised to empty the veins followed by rapid lowering of the legs. If there is incompetence, blood rushes retrograde from the proximal veins into the calves, resulting in volume increase.[76] If in the superficial veins only, application of a light tourniquet around the legs will normalize the refilling time. Exercise plethysmography assesses ejection of blood by the calf pump as well as the subsequent refilling of the lower extremities. Unlike the duplex ultrasound assessment, these modalities do not precisely localize the level of disease and most vascular laboratories do not perform these physiologic tests.

Advanced Treatments

For patients with lifestyle-limiting symptoms or complications related to venous insufficiency, advanced therapies to ablate the offending veins may be considered.[77,78] There is variability in insurance requirements for these procedures, although most plans will consider advanced therapies for those patients that have failed a period of conservative therapy. The techniques to treat venous insufficiency depend upon the size and location of the veins, patient preference, and etiology of their disease. To date, endovenous procedures such as laser therapy or radiofrequency ablation are most often used for treatment of reflux in the GSV and SSV.[1,79-81] Both modalities use a thermal source to cause injury to the vein wall, which leads to vein occlusion. The procedures are performed under ultrasound guidance, and often in the outpatient setting, with only local anesthesia and instillation of perivenous tumescent anesthesia, which serves to encase the vein and protect adjacent structures from the heat source. Distal access is obtained (Fig 97–4B) and the catheter is tip is positioned ~2 cm from the sapheno-femoral junction. The vein is then ablated in a retrograde fashion with withdrawal of the active laser fiber. Postprocedure, all patients should return within 48 to 72 hours for an office clinical assessment and a duplex ultrasound exam to evaluate the result and exclude the complication of DVT.[77,78] Additional potential complications may include parasthesias, skin burns, thrombophlebitis, and transient pain or bruising.[82] Recently, mechanochemical endovenous ablation techniques have emerged in lieu of thermal therapies of the GSV and SSV, and this therapy does not require infiltration with perivenous tumescence.[83] The technique uses a rotational wire that induces vein spasm while infusing a chemical sclerosing agent to ablate the vein. The studies available to date report high short-term occlusion rates with lower reported pain scores in patients receiving mechanochemical endovenous therapies as

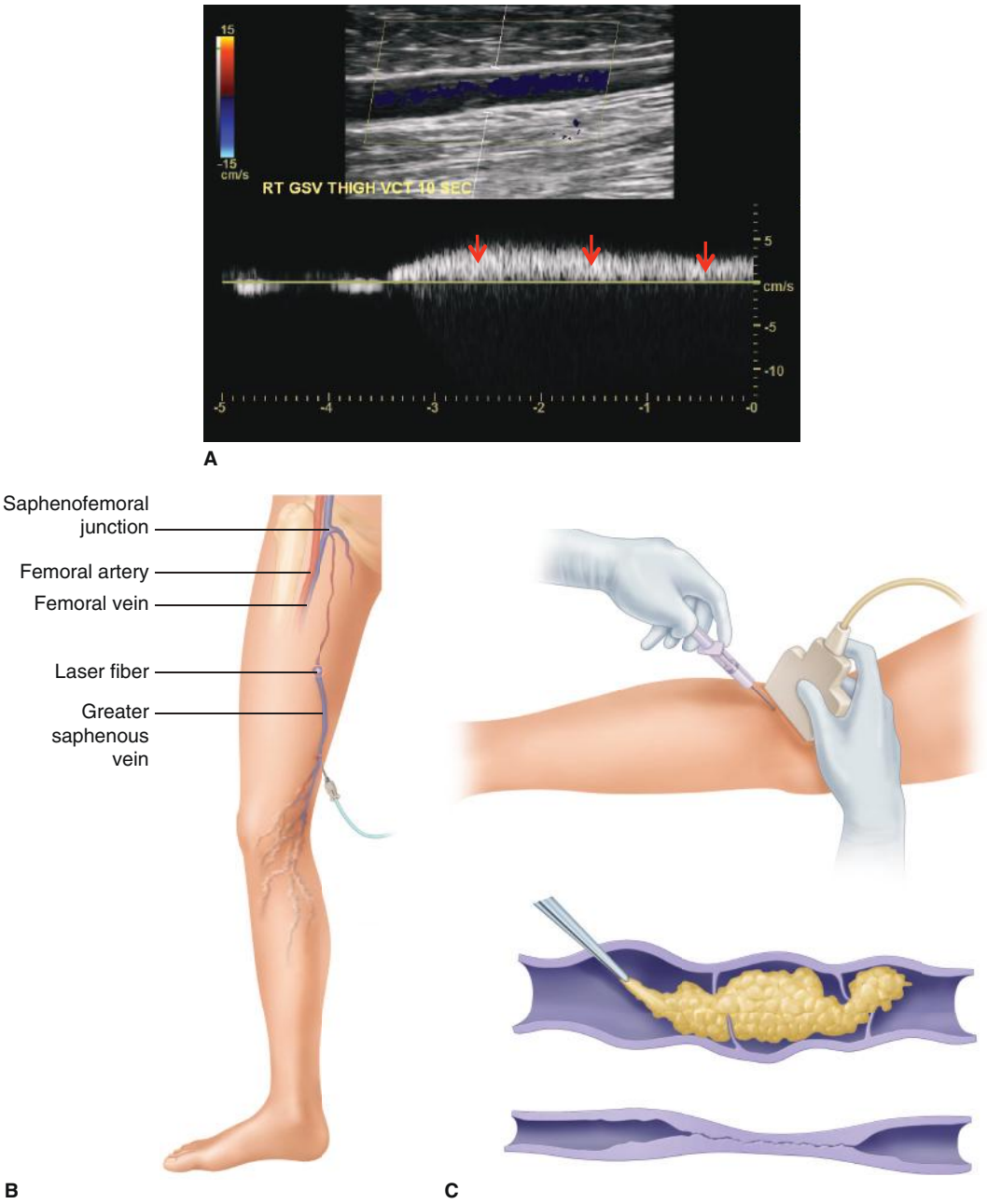


FIGURE 97–4. Invasive treatments for varicose veins and chronic venous insufficiency. **A.** Spectral waveform analysis demonstrating retrograde flow (*arrows*) across the terminal valve of the great saphenous vein at the saphenofemoral junction lasting 10 seconds consistent with venous insufficiency. **B.** Endovenous ablation involves treatment of the GSV with a laser fiber that is introduced via the distal GSV. The entire segment is treated from 2 cm distal to the saphenofemoral junction to the distal puncture site. **C.** Sclerotherapy of varicose veins under ultrasound guidance: sclerosing agent is directly injected into the varicose vein resulting in vein occlusion and obliteration.

compared to thermal ablation, although the long-term outcomes are not yet known.[84,85].

Chemical ablation with sclerosing agents is an alternative to thermal therapies, without the mechanical counterpart described above, most often for the treatment of varicose veins and larger spider veins. A variety of agents are available including hypertonic saline, glycerin, polidocanol, and sodium tetradecyl sulfate, which cause endothelial damage and subsequent thrombosis and fibrosis of the treated veins (Fig. 97–4C).[1,78] Complications may include hyperpigmentation or staining, caused by extravasation of the agent with hemosiderin deposition into the surrounding skin, as well as allergic reactions, matting, and rarely cutaneous ulceration. Most patients achieve a cosmetic improvement initially, although with a high risk of recurrence in their lifetime.[1]

Vein stripping and phlebectomy or microphlebectomy procedures are less often used today because of the prolific availability of less invasive procedures with lower pain rates and good success. However surgery may still be preferred in patients with very superficial veins (which carry a higher potential for skin thermal injury), extremely tortuous veins (which may not allow for passage of a catheter), previous failure of endovenous therapy, or the presence of thrombus.[86]

VENOUS ULCERS

Venous ulcers are the most common leg ulceration and the most severe manifestation of venous disease (Fig. 97–5A). Up to 10% of patients in the United States living with venous insufficiency have a healed or active venous ulcer (CEAP class 5 to 6 disease).[57,87] Despite the fact that most patients are treated in the outpatient setting, the per-patient cost of venous ulcer management is estimated to be $2500 per month.[88,89] This reflects the high intensity of care needed to manage these ulcerations, including wound care supplies, medications, patient education, facility costs, vascular testing, and provider reimbursements. For patients with a healed venous ulcer, up to 50% will experience a recurrence in their lifetime.

FIGURE 97–5. Chronic venous insufficiency and venous ulcerations. **A.** The left leg is markedly swollen in this 23-year-old man with chronic venous insufficiency. There is stasis pigmentation and lipodermatosclerosis present; several superficial venous ulcers are visualized above the medial malleolus. **B.** Typical venous ulcer located on the medial aspect of the leg. The ulcer bed is beefy red with healthy granulation tissue; these ulcers are typically wet and drain serous fluid. Edema control is the most effective way to heal these ulcerations.

The evaluation of a venous ulcer should include a thorough medical history and physical assessment, including area and depth measurements of the ulcer. A number of medical conditions are associated with leg ulcers, and these should be excluded.[89] Venous ulcers are generally wet, with good granulation tissue, and localize to the gaiter area of the leg with a predilection for the medial and malleoli. In contrast, arterial (ischemic) ulcers are extremely painful and often located distally (tip of toes, over pressure points). Unlike venous ulcers, they are dry and have a dark eschar because of lack of blood supply. Treatment involves revascularization and wound care. Neurotrophic ulcers (often referred to as diabetic ulcers) occur over pressure points on the foot (metatarsal area, toes, heel) and have the appearance of an open ulcer surrounded by callous. This type of ulcer occurs in patients with a peripheral neuropathy (most often from diabetes) because the patient cannot feel that they are putting abnormal pressure over a specific area. This ulcer is the most common ulcer to lead to osteomyelitis and amputation of the toe, foot, or leg. Treatment of this type of ulcer involves investigation (and treatment) for osteomyelitis, debriding the abnormal callous that is present, and fitting for a shoe that will unload this area of abnormal weight bearing. Once venous disease is confirmed, compression therapy with wound care is the foundation of venous ulcer treatment. However, four cardinal tenets (Table 97–6) promote wound healing, and in the setting of an active ulcer each should be considered and optimized. Notably, up to 26% of patients with a lower extremity ulcer have both peripheral artery (PAD) and venous disease, which may limit their tolerance of compression therapy because of impaired arterial perfusion.[90] PAD is diagnosed in the presence of an abnormal ankle-brachial index (ABI < 0.9), and PAD may be severe with an ABI < 0.5.[91] Above this threshold (ABI > 0.5) or with absolute ankle pressure > 60 mm Hg, inelastic compression may be tolerated up 40 mm Hg without impaired arterial perfusion.[89,90,92] Below this threshold, modified compression and/or revascularization may be necessary to achieve wound healing. We favor adjustable compression devices (ACE wraps, Profore four-layer wrap, Unna Boot, etc.) over compression garments (stockings) when treating an active ulcer in order to optimize edema control, as well as to allow for clean wound care supplies that are regularly turned over. Multilayer compression is superior to single-layer compression for the promotion of ulcer healing.[89,93] There is limited evidence regarding the use of intermittent pneumatic compression as an alternative to compression therapy, and in general this modality is not preferred. Once ulcer healing is achieved, continued edema control with compression garments and good skin care should be optimized to minimize the risk of recurrence.

TABLE 97–6. The Cardinal Tenets of Venous Ulcer Healing

1. Edema control: this is the most important. Without adequate control of edema, the ulcer will not heal.
2. Assure adequate arterial perfusion.
3. Good skin care.
4. Put a nonirritating dressing (ie, saline wet to dry, Profore four-layer wrap, Unna Boot) on the ulcer itself.

The main body of evidence surrounding the pharmacology of venous disease and venous ulcers includes pentoxifylline and the saposides (horse chestnut seed extracts). Horse chestnut seed (*Aesculus hippocastanum L.*) is thought to inhibit enzymes, such as hyaluronidase, which are activated by accumulated leukocytes in limbs affected by chronic venous disease, thereby reducing associated leg edema and pain, although long-term safety and efficacy have not been established.[94,95] In a Cochrane review examining the use of horse chestnut seed extract for the prevention of PTS, no improvement in symptoms of PTS was observed.[96] Pentoxifylline has been studied in the treatment of advanced venous disease and may promote venous ulcer healing via its anti-inflammatory properties and rheolytic activities.[97] Several trials suggest modestly improved healing rates with pentoxifylline, although the magnitude of effect is small and its role in the treatment of venous disease is unclear.[98-101] Diuretics are not useful to control limb swelling related to venous insufficiency in the absence of congestive heart failure.

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CHAPTER 98

PERIOPERATIVE EVALUATION FOR NONCARDIAC SURGERY

Daniel Alyesh and Kim Eagle

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Over time, the perioperative evaluation of cardiac disease in patients undergoing noncardiac surgery has been the object of much research and debate. The desire to optimally manage these patients is often confused with "cardiac clearance," but this term fails to capture the complexity of care. As with most clinical scenarios, the cornerstone of good perioperative management is a conscientious history and physical exam. Understanding a patient's functional status, cardiac symptoms and signs, and whether they are acutely worsening are of paramount importance in guiding management decisions. As in the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC)/European Society of Anesthesiology (ESA) guidelines,[1,2] we believe the best clinical approach to evaluating cardiac disease in patients prior to surgery is in the framework of whether the cardiac disease is active or stable while understanding the urgency and risk of the operation needed. A summary of our global approach to perioperative evaluation and management may be found in Fig. 98–1.[1]

TEMPORAL URGENCY AND RISK OF SURGERY

The time period in which surgery must take place is of critical importance in deciding how to evaluate patients preoperatively. This temporal urgency dictates the extent of clinical evaluation and potential changes in management prior to surgery. This is clearly reflected in the ACC/AHA clinical guideline writing group's classification scheme of emergent, urgent, time-sensitive, and elective for temporal necessity of surgery, which is summarized in Table 98–1.[1]

ACTIVE CARDIAC DISEASE

Active cardiac disease typically requires delay of nonemergent, nonurgent surgery. In elective surgery, management of acute cardiac conditions is similar to outside the context of imminent surgery. Active cardiac disease can exist in the form of active ischemia, arrhythmia, heart failure, and/or severe valve disease.

ACTIVE ISCHEMIA AND REVASCULARIZATION

In acute coronary syndromes, cardiac catheterization is generally recommended for defining coronary anatomy, risk stratification, and devising the optimal treatment and revascularization strategy if appropriate. The optimal revascularization strategy is based upon the weight of existing evidence and recent clinical practice guidelines.[1,2] Patients with ST-segment elevation myocardial infarction (STEMI) may benefit from immediate reperfusion, and non–ST-segment elevation myocardial infarction (NSTEMI) may benefit from an early invasive strategy within 72 hours in appropriately selected patients.

If percutaneous coronary intervention (PCI) is pursued, the timing of surgery must be considered. If noncardiac surgery must be performed within a manner of weeks, balloon angioplasty without stenting may be considered. If surgery is not essential but still time sensitive, bare metal stenting (BMS) can be used if lesion parameters permit. Although using BMS in this setting ideally portends one year of dual antiplatelet therapy, one can consider a shorter course of $P2Y_{12}$ platelet inhibition, and therefore may help reduce operative bleeding. If drug-eluting stents (DES) are implanted, surgery should also ideally be delayed for 1 year. However, surgery may be considered at 180 days as the risk of stent thrombosis may have stabilized in settings of noncardiac surgery, particularly in the era of second- and third-generation DES.[3-5]

MANAGEMENT OF ATRIAL FIBRILLATION

Atrial fibrillation (Afib) is the most commonly encountered perioperative cardiac arrhythmia. A known history of clinically stable Afib does not require modified management or special evaluation other than a consideration of how to manage perioperative anticoagulation. In determining a perioperative anticoagulation strategy, the risks of bleeding associated with a procedure must be weighed against that of bleeding. In cases where operative bleeding is minimal, such as cataract surgery, or implantation of cardiac rhythm devices, anticoagulation with vitamin K antagonists may continue uninterrupted. Observational data indicates that when pursued, bridging anticoagulation can be done safely.[6-8] However, when concerns over operative bleeding are significant, recent randomized data indicate brief interruptions in vitamin K–factor dependent anticoagulation may be superior to bridging anticoagulation in low-risk patients. Published in 2015, the Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation (BRIDGE) trial randomized 1884 patients to perioperative interruption of anticoagulation versus bridging anticoagulation with dalteparin. At 30-day follow-up, there was no difference in the rate of transient ischemia or stroke between the two groups, but there were higher rates of major and minor bleeding in the group that received bridging anticoagulation.[9] These randomized data inform the discussion very well, but limitations of the study included poor representation of patients with CHADSVASC scores of 5 and above as well as a lack of patients undergoing carotid endarterectomy, major cancer surgery, and other surgeries with high thromboembolic risk. All told, we believe the best strategy for patients and surgeries with atrial fibrillation and low thromboembolic risk is interruption of anticoagulation. In cases of high thromboembolic risk either resulting from patient comorbidities or prosthetic heart valves, an informed discussion should take place with patients with consideration of perioperative anticoagulation bridging. With regard to target-specific oral anticoagulants, stopping

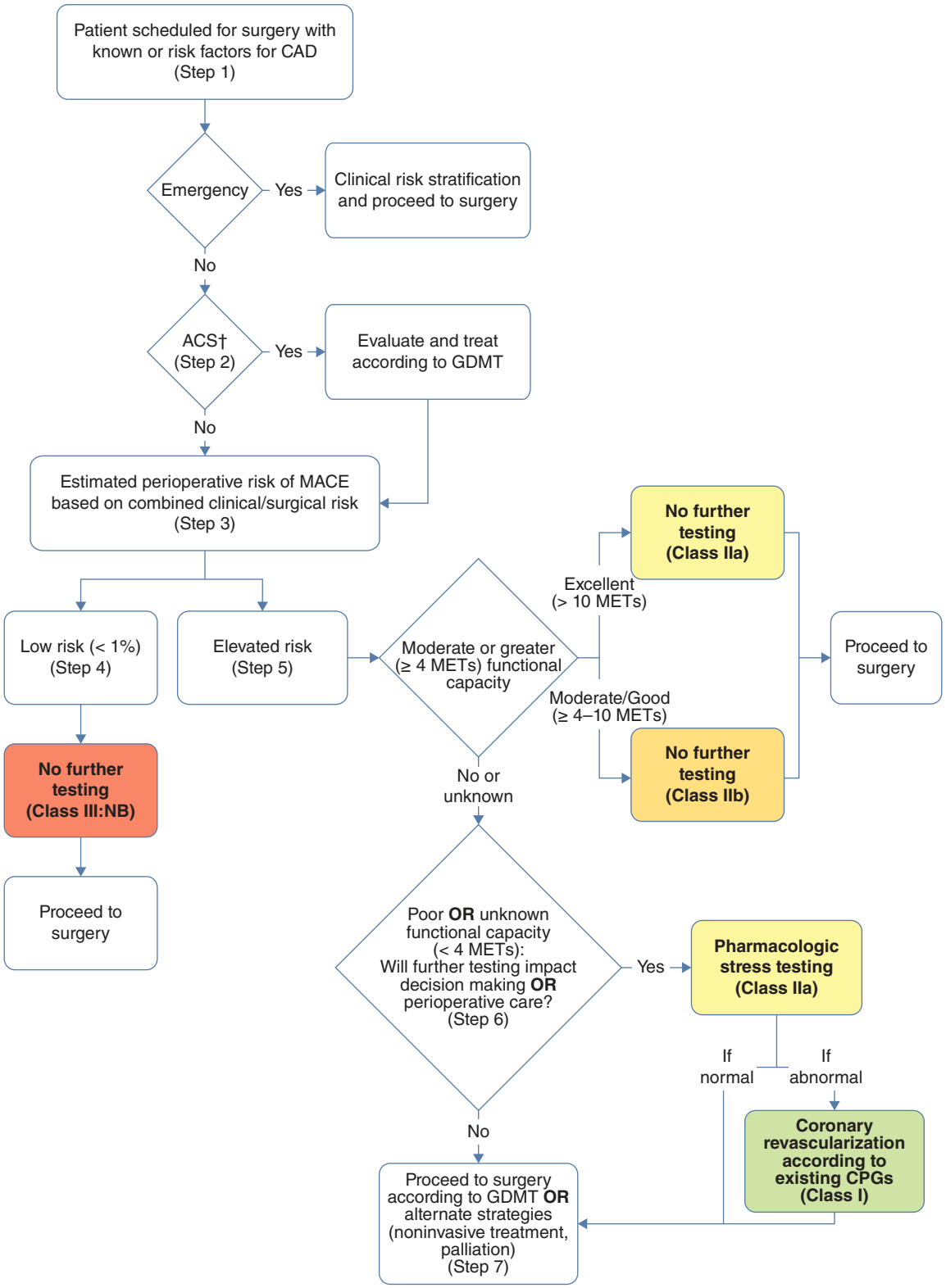

FIGURE 98–1. Summary algorithm for the cardiac evaluation and management of patients prior to noncardiac surgery from the 2014 ACC/AHA Clinical Practice Guidelines. Reproduced with permission from Fleisher LA, Fleischmann KE, Auerbach AD, et al: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014 Dec 9;130(24):e278-e333.

TABLE 98–1. Scheme for Classifying Surgical Urgency[1]

Classification	Definition
Emergent	No time or only time for very limited clinical evaluation, life or limb threatened, surgery needed in < 6 hours
Urgent	Time for a limited clinical evaluation, life or limb threatened, surgery needed in between 6 and 24 hours
Time sensitive	A delay of > 1 to 6 weeks will significantly affect outcome (eg, oncologic surgery)
Elective	Procedure may be delayed for up to one year

Data from Fleisher LA, Fleischmann KE, Auerbach AD, et al: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014 Dec 9;130(24):e278–e333.

these anticoagulants 48 hours prior to surgery and pursuing either an interruption or bridging approach based upon thromboembolic risk is reasonable. It is worth noting that dabigatran is the only anticoagulant currently with a reversal agent, although others agents are in development for the other anticoagulants.[10]

In the setting of atrial fibrillation with rapid uncontrolled rates (above a heart rate of 110 bpm), surgery may be delayed to determine a rhythm or rate control strategy. Before selecting an appropriate strategy, secondary causes of rapid rates such as sepsis, metabolic disturbance, and volume derangements should be thoroughly investigated. Once the management strategy is adequately achieved, surgery may again be considered. If rapid atrial fibrillation results in hemodynamic instability, then prompt rhythm control by electrical cardioversion is indicated. With other forms of supraventricular tachycardia (SVT), arrhythmia termination by vagotonic maneuvers, AV nodal or antiarrhythmic medications may be beneficial depending on the specific rhythm.

UNCONTROLLED ARRHYTHMIAS AND HIGH-DEGREE CONDUCTION DISEASE

In the setting of sustained ventricular tachycardia (VT), prompt arrhythmia termination by chemical or electric means is critical. Cases of polymorphic and monomorphic VT necessitate investigation of ischemia as a cause. As a general rule, monomorphic VTs are typically scar mediated while polymorphic VTs are more likely to have ischemic, metabolic, or iatrogenic etiologies. These rhythms have the potential to be life threatening and prompt stabilization must occur before undertaking elective noncardiac surgery.

High-degree conduction disease (symptomatic bradycardia, sick sinus syndrome, second-degree Mobitz type II heart block, and complete heart block) can significantly complicate the perioperative period. Temporary transvenous pacing or permanent pacemaker implantation may be necessary before proceeding with surgery.[11]

In patients with implanted cardiac rhythm devices, special attention should be paid to the use of monopolar electrocautery during surgery and its potential interaction with device programming and function. In cases where only bipolar cautery or a harmonic scalpel will be used, disruption of implanted rhythm devices is extremely unlikely. However, cases where monopolar electrocautery will be used above the umbilicus pose the highest risk of interaction with implanted rhythm devices. In pacemaker-dependent patients, reprogramming to the DOO or VOO setting can minimize oversensing and failure to pace. In patients with implanted cardioverter-defibrillators (ICDs), turning off tachytherapies is helpful to avoid unnecessary patient shocks. These changes can be accomplished by magnet placement or device reprogramming. If ICD tachytherapies are disabled, then connection to an external defibrillator until device reprogramming is highly advised. A dedicated discussion about rhythm device management should occur prior to surgery with a plan for immediate postoperative reprogramming to the original settings.[12]

HEART FAILURE

As the prevalence of heart failure increases, the need for perioperative management of heart failure becomes ever more common. It is important to discern whether heart failure is occurring with a reduced or preserved LVEF, or whether it is in the setting of hypertrophic obstructive cardiomyopathy (HOCM). Special care must be taken in HOCM to avoid arterial dilation and overdiuresis, as such conditions can exacerbate left ventricular intracavitary obstructive gradients and potentially lead to perioperative complications. Active heart failure (HF) is associated with a high risk of perioperative cardiac complications.[13-15] In prior iterations of the cardiac risk index, active heart failure had the strongest association with perioperative major adverse cardiac events (MACE) of the factors considered.[14] Natriuretic peptide measurement can help manage and predict perioperative events.[16-21] In the setting of active nonobstructive HF, it is optimal to delay surgery for diuresis until euvolemia is achieved. Prior investigation has found this approach to help mitigate the risk of MACE.[22]

VALVULAR HEART DISEASE

If significant valvular heart disease is suspected based on symptoms of dyspnea or a new or changing murmur on exam, echocardiography is critical for quantification of degree of stenosis or regurgitation and determination of surgical risk.

In patients with aortic stenosis (AS), anesthesia can cause hypotension, tachycardia, and decreased coronary perfusion leading to MACE.[14] Symptomatic severe AS patients should undergo valve replacement prior to surgery when possible, as retrospective data confirm higher risk of MACE, specifically in the form of HF in patients with severe AS who undergo surgery.[23] In poor surgical candidates, valvuloplasty has had good perioperative results and relatively low complication rates, although the results have limited durability and long-term mortality rates are high without definitive management with valve replacement.[24,25] Although not specifically studied, transcatheter aortic valve replacement (TAVR) may be considered for patients with severe symptomatic disease for whom open surgery is not an option. Results of the Placement of Aortic Transcatheter Valves (PARTNER) trials have shown favorable outcomes in appropriate candidates.[26,27] If surgery is attempted without treatment of severe AS, meticulous cardiac anesthesia and perioperative monitoring are critical in the operative and postoperative setting.

Patients with severe mitral stenosis (MS) are prone to tachycardia, hypotension, and reduced cardiac output in the perioperative setting. It is critical to recognize the presence of rheumatic or nonrheumatic mitral stenosis, and the characteristic physical exam finding in severe MS of an opening snap of the mitral valve and a long duration diastolic rumble. Symptomatic mitral stenosis patients who are good candidates for balloon valvulotomy or surgical commisurotomy should undergo treatment before elective surgery.[28]

As a general rule, left-sided regurgitant valve lesions are better tolerated than stenotic lesions.[29,30] The main pathology of mitral regurgitation stems from LV volume overload, and is best managed by maintaining preload and avoiding excessive afterload. Prior investigations have revealed that patients with moderate to severe and severe aortic regurgitation (AR) had higher in-hospital mortality than case-matched patients without AR (9.0% vs 1.7%, $P = .008$). Predictors of mortality were a reduced LVEF (< 55%) and renal dysfunction (Cr > 2.0).[29] In cases of asymptomatic moderate-severe or severe MR, noncardiac surgery may be considered with echocardiographic and selected invasive hemodynamic monitoring.[1] Postoperatively, patients should be monitored in the ICU. Prior investigation from a single tertiary care center of patients with moderate to severe or severe MR revealed worse outcomes in propensity matched cases (driven by 30-day mortality, MI, CHF, and stroke) in the group with MR.[30] Important predictors of poor outcome were ischemic source of MR, diabetes mellitus (DM), reduced LVEF < 35%, and a history of carotid endarterectomy.

STABLE CARDIAC DISEASE

Understanding how best to manage stable patients involves a more nuanced and predictive approach. In this circumstance, management has become more conservative over time, with fewer patients needing further cardiac testing or revascularization than in times past largely because of neither invasive or medical therapies in otherwise stable patients have shown substantial benefit. Prior randomized investigations in stable CAD patients have not proven that coronary revascularization is effective in patients without left main (LM) coronary disease for modifying the risk of perioperative events even for patients undergoing high-risk surgery.[31] Risk-stratification methodologies, approaches to perioperative testing, and medical management are all important components of the perioperative evaluation of stable cardiac patients.

PERIOPERATIVE RISK STRATIFICATION

Perioperative risk can generally be divided into two components: the inherent risk associated with an operation and the risk attributed to patient specific conditions. Three main risk-stratification algorithms exist: the revised cardiac risk index (RCRI), the American College of Surgeons National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest (NSQIP MICA), and the NSQIP Surgical Risk Calculator. We believe that the RCRI is most easily applied clinically, and the NSQIP tools are best for research. A comparison of the various tools is given in Table 98–2.

When assessing the inherent risk of an operation, typically low-stress surgeries with minimal fluid shifts are considered low risk (eg, cataracts, biopsies) and are associated with a < 1% risk of MACE.[31] Vascular surgeries are considered the highest risk, but up-front risk can be tempered if an endovascular approach is taken, although conversion to open surgery remains a possibility. The intrinsic risk of an operation is multifactorial and somewhat difficult to predict; the ACC/AHA guidelines divide operations into low- and elevated-risk procedures.[1] In the ESC/ESA guidelines, operative risk is divided into low (< 1%), intermediate (1%-5%), and high risk (> 5%).[2]

RCRI

The RCRI is a simple and validated tool that assesses the risk of a major cardiac perioperative event defined as MI, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block.[13] The RCRI uses six factors (surgical risk, history of ischemic heart disease, HF, cerebrovascular disease, insulin usage, and preoperative creatinine above 2), only one of which is directly attributable to the inherent risk of the operation (whether the surgery is suprainguinal vascular, intraperitoneal, and intravascular). A patient with no predictors or one predictor is considered low risk, and those with two or more predictors are considered high risk for MACE.

Biomarker testing with natriuretic peptide levels appears to independently predict the risk of cardiovascular events up to the first 30 days after vascular surgery and significantly improves the performance of the RCRI.[9-14, 16-21] Further study is needed to validate whether measuring biomarkers leads to management change that ultimately improves patient outcomes.

NSQIP and NSQIP MICA

The NSQIP MICA and NSQIP risk calculators are based on data from over 1 million operations collected from 525 participating centers.[32] The NSQIP MICA score was created in 2011 in a large derivation and validation study. The inherent risk of surgery was derived from odds ratios based on surgical site, with inguinal hernias used as the reference. The primary outcomes were cardiac arrest (defined as a chaotic rhythm requiring basic or advanced life support) or MI. The NSQIP MICA appears to outperform the RCRI, particularly in cases of vascular surgery.

The NSQIP uses procedure specific terminology, including whether surgery is emergent, to assess the perioperative risk of MACE, death, or eight other outcomes. It requires 21 patient-specific variables for effective calculation and is likely the closest estimate of surgery specific risk of any of the risk calculators. The drawbacks are that it has not been validated in an external population, and it relies upon the American Society of Anesthesiologists classification, which is subject to considerable inter observer variability.[33-35]

PERIOPERATIVE TESTING

Perioperative testing should be limited to circumstances that would change management independent of the surgery planned. Testing is not necessary for low-risk procedures, and in the current environment of overuse of perioperative testing, specialty societies have undertaken efforts to reduce unnecessary testing.[36,37] As has been noted previously, revascularization in stable coronary disease prior to surgery has not been associated with improved outcomes.[31] The cornerstone of determining the indication for further cardiac testing is assessment of a patient's symptoms, exercise status, and functional capacity. The risk of perioperative complications is indirectly proportional to functional status.[38] The conventional measurement standard for assessing functional status is metabolic equivalents (METs), where 1 MET is the basal oxygen consumption of a 40-year-old 70-kg man. If a patient has not had a recent exercise test, functional status can be estimated by performance during activities of daily living.[39] As an easy reference for functional status categories, METs and their examples may be found in Table 98–3.

Generally, formal functional testing is not indicated when a patient can easily and repetitively perform over 4 METs during activities of daily living, and an even stronger argument against testing can be made above 10 METs. Obtaining a 12-lead ECG should generally be reserved for patients with known arrhythmia, CAD, PVD, and structural heart disease. Preoperative left ventricular (LV) function assessment is appropriate in patients with dyspnea of unknown origin, and patients with known LV dysfunction and worsening or poorly controlled symptoms.

Functional Testing

Functional testing is potentially useful in patients with poor functional status when results will change management. Functional testing can

TABLE 98–2. Comparison of Perioperative Risk Calculators[1]

	RCRI	NSQIP MICA	NSQIP
Criteria	• Creatinine ≥ 2 • CHF • Insulin-dependent diabetes mellitus • Intrathoracic, intraabdominal, or suprainguinal vascular surgery • History of cerebrovascular accident or transient ischemic attack • Ischemic heart disease	• Increasing age • Partially or completely dependent functional status Surgery type: • Anorectal • Aortic • Bariatric • Brain • Breast • Cardiac • ENT • Foregut/hepatopancreatobiliary • Gallbladder/adrenal/appendix/spleen • Intestinal • Neck • Obstetric/gynecological • Orthopedic • Other abdomen • Peripheral vascular • Skin • Spine • Thoracic • Vein • Urologic	• Age • Acute renal failure • Functional status • Diabetes mellitus • Procedure (CPT code) • American Society of Anesthesiologists physical status class • Wound class • Ascites • Systemic sepsis • Ventilator dependent • Disseminated cancer • Steroid use • Hypertension • Previous cardiac event • Sex • Dyspnea • Smoker • COPD • Dialysis • Acute kidney injury • Body mass index • Emergency case
Use outside original cohort	Yes	No	No
Sites	Most often single center, but findings correlate with multicenter	Multicenter	Multicenter
Calculation	Single point per risk factor	Web-based (http://www.surgicalriskcalculator.com/miorcardiacarrest)	Web-based (www.riskcalculator.facs.org)

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TABLE 98–3. Functional Status Categories with Associated METs and Examples[68]

Classification	Quantification (METs)	Examples
Excellent	> 10	Boxing, judo, cross-country skiing at least 10 kph
Good	7-10	Bicycling at 10-30 kph, fencing, kayaking at 12.5 kph
Moderate	4-6	Golf while carrying clubs, doubles tennis, walking 7 kph, walking up a hill, climbing a flight of stairs, heavy housework
Poor	< 4	Driving, yoga, bowling, fishing from bank

Data from Jetté M, Sidney K, Blümchen G: Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990 Aug;13(8):555-565.

be used to diagnose CAD, assess angina, and decide how to treat LV dysfunction, dyspnea, or poor functional status. The evidence base for functional testing is fraught with limitations including a heavy focus on vascular surgical patients, outdated stress protocols, and a lack of contemporary CAD management techniques. Nonetheless, the data confirm that patients able to achieve 7 to 10 METs are at low risk of perioperative cardiac events, and those that are unable to achieve 4 to 5 METs are at elevated risk.[40-43]

The available evidence regarding the role for preoperative functional testing is primarily from single centers using dobutamine stress echocardiography (DSE) or radionuclide myocardial perfusion imaging (MPI).[44-61] The predominant findings are summarized below:

1. Moderate to large areas of ischemia are associated with higher perioperative risk of MI and/or death.
2. Functional testing has a high negative predictive value.
3. Evidence of prior MI without inducible ischemia has little predictive value for perioperative events.
4. Prior studies have demonstrated clinical value and safety of either type of stress test.

The data are quite equivocal as to which technique performs best. We believe these techniques should be viewed equally given variable institutional expertise and experience with either technique.

MEDICAL MANAGEMENT

After a thorough history, physical examination, and risk stratification, titration or addition of cardiac medications can be helpful in perioperative cardiac management. Most investigations and debate have centered on the role of beta-blockers prior to surgery; there is still equipoise about the role of this therapy in the perioperative setting. Our discussion of perioperative medical management will focus on the role of beta-blockade, statins, aspirin, dual antiplatelet therapy, and clonidine.

Beta-Blockers

The debate around the use of perioperative beta-blockade has nearly come full circle. Earlier, small randomized studies indicated possible benefit of beta-blockers surrounding vascular surgery that was subsequently confirmed in the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) studies.[47,62,63] However, later publications questioned beta-blocker utility, which was the impetus for the large randomized Perioperative Ischemic Evaluation (POISE) trial.[64] POISE revealed that perioperative beta-blockade improved perioperative cardiac events, but at the expense of more bradycardic and hypotensive episodes, strokes, and most importantly, deaths. After critical investigation, all but the initial DECREASE studies were withdrawn from the published literature as a result of concern for scientific misconduct.[65] Although some have criticized POISE for choices in beta-blocker dosing and frequency that may exceed those used in clinical practice, further investigations have also confirmed equivocal findings with perioperative beta-blockade.[66,67]

Based on the current literature, patients on longstanding stable beta-blocker doses should have the medication continued at the time of surgery because of the risk of discontinuing beta-blockade leading to subsequent withdrawal and related surges in heart rate and blood pressure.[66-69] Beta-blockers may help mitigate cardiac risk in moderate to high-risk patients, and specifically in patients with RCRI scores of ≥ 3.[70] Otherwise, beta-blockers should be used only for appropriate clinical circumstances irrespective of upcoming surgery as it is still unclear if they have any positive effects on perioperative outcomes for most patients. If beta-blockade use is pursued, initiation and titration should occur several days or weeks prior to surgery to avoid adverse events.

Statins

Statin therapy is effective for both primary and secondary prevention of cardiac events in patients with CAD, and statin indications are continuing to expand.[71,72] With regard to statin therapy's relationship to perioperative events, the randomized data are somewhat limited. A small trial of 100 patients randomized to either statin or placebo before vascular surgery found significantly lower MACE with statin use.[73] A Cochrane analysis revealed similar results but again with a small sample size and most events attributed to a single study.[74] Statins may be helpful if started before surgery and present a great opportunity to improve long-term outcomes after surgery, but should be reserved for patients with established atherosclerosis. Both the ACC/AHA and ESC/ESA guidelines recommend statin therapy be continued at the time of surgery and that they may be of benefit in patients with peripheral arterial disease undergoing vascular surgery.[1,2] The ESC/ESA stipulate that statins are best initiated at least two weeks prior to vascular surgery.[2] The ACC/AHA guidelines go a step further and indicate that it might be reasonable to initiate statin therapy in patients without known atherosclerosis who have an indication for statins undergoing elevated risk surgery.[1]

Aspirin and Dual Antiplatelet Therapy

There appears to be uncertain benefit of aspirin for preventing cardiac events in the perioperative period in nonstented patients. Observational data have suggested an increased risk of thrombotic events associated with discontinuation of aspirin.[75] Large randomized studies have not shown benefit of taking aspirin. The Pulmonary Embolism Prevention trial (PEP) randomized 13,356 patients to either 160 mg aspirin or placebo with no difference in outcome.[76] The POISE-2 trial was a 2×2 factorial trial studying the effects of aspirin and clonidine in perioperative events. It randomized 10,010 patients undergoing orthopedic, general, urologic, and gynecological surgery to 200 mg of aspirin or placebo, with no benefit of aspirin in this cohort with relatively low rates of CAD (23%) and with endarterectomy patients excluded. Further study is needed to understand aspirin's impact on high-risk patient groups. It is worth noting that POISE-2 also included relatively few patients with stents. In patients with coronary stents, aspirin is best continued during surgery and should be reinitiated as soon can be done safely if stopped.[77] Consensus should be reached between the surgeon, anesthesiologist, and cardiologist regarding the risk benefit profile (thrombosis vs bleeding) of continuing aspirin therapy in individual patients.

Several important factors must be considered regarding the timing of noncardiac surgery after coronary stent implantation. These factors are the risk of stent thrombosis, the consequences of delaying surgery, and the risk of procedural associated bleeding related to dual antiplatelet therapy (DAPT). DAPT is known to significantly reduce the risk of stent thrombosis, and these affects are most profoundly noted in the first 4 to 6 weeks after stent implantation.[78-82] Mechanistically, stent thrombosis at the time of surgery is believed to result from endothelial disruption and the proinflammatory and prothrombotic effects throughout the coronary.[83,84] Newer-generation DES are associated with a lower risk of stent thrombosis and often require a shorter duration of DAPT. Investigations of treating patients with newer-generation DES with 3 and 6 months of DAPT compared with longer durations after implantation did not reveal any significant difference in MACE, although these studies were underpowered.[85-89] Pooled analyses of these trials as well as data from the Patterns of Nonadherence to

Antiplatelet Regimens in Stented Patients (PARIS) registry involving physician-initiated DAPT interruptions are all reassuring for shorter DAPT durations.[90,91] For patients treated with any type of stent for any indication, elective surgery should be delayed and DAPT should not be interrupted within 30 days of stent implantation. In cases of patients treated for ACS, truly elective cases should ideally be delayed for 12 months to allow a full DAPT duration. Surgery can be considered after 30 days with BMS and 6 months after DES with interruption in DAPT. However, in cases of emergent, urgent, and time-sensitive surgery, interruption of DAPT can be considered 3 to 6 months after DES implantation with newer-generation DES.[5]

Clonidine

Initial investigations involving α-2 agonism at the time of surgery appeared to indicate that clonidine was beneficial. In 2004, randomized clinical data of 200 patients undergoing noncardiac surgery demonstrated better mortality rates up to 2 years in patients who took clonidine (15% vs 29%, $P = .035$).[92] Meta-analysis of 31 α-2 agonist trials also revealed promising effects, notably in vascular surgical patients.[93] However, the POISE-2 trial, which was orders of magnitude larger than prior investigations, failed to demonstrate these benefits and rather showed that clonidine increased the rate of nonfatal cardiac arrest and clinically important hypotension.[77] Therefore, clonidine is not recommended for mitigating cardiac risk at the time of noncardiac surgery.

CONCLUSIONS

With all the intricacies of perioperative evaluation, the best preoperative cardiac test remains a careful history and physical directed at finding and grading CAD, left ventricular dysfunction, valve disease, rhythm disorders, or previously unsuspected vascular disease. Any testing or treatment should be justified by the patient's disease alone, because there is little evidence that treatments for the sole purpose of improving perioperative outcomes have any substantial benefit.

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CHAPTER 99

ANESTHESIA AND THE PATIENT WITH CARDIOVASCULAR DISEASE

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INTRODUCTION

Anesthetizing patients with cardiovascular disease is one of the greatest challenges facing the anesthesiologist. The constellation of anesthetic drug effects, the physiologic stresses of surgery, and underlying cardiovascular diseases complicate and limit the choice of anesthetic techniques for any particular procedure. The anesthesiologist's approach to the patient with cardiovascular disease is to select agents and techniques that will optimize the patient's cardiopulmonary function. The perioperative management of a patient with cardiovascular disease requires close cooperation between the cardiologist/internist, surgeon, and anesthesiologist. Each specialist has a unique knowledge base that complements that of the others. The approach should emphasize a continuum of care from the preoperative evaluation through the postoperative period.

PREOPERATIVE EVALUATION

The assessment of cardiac risk and preoperative optimization of the patient's cardiovascular status are the traditional goals of the preoperative evaluation of patients with cardiovascular disease. In 1977, Goldman and associates[1] introduced the Cardiac Risk Index Score (CRIS) to guide more quantitatively the assignment of cardiac risk in patients undergoing noncardiac surgery. According to the CRIS, the risk for adverse cardiac events increases with the number of preexisting conditions such as heart failure, ischemic disease, cerebrovascular disease, diabetes, chronic kidney disease, as well as the type of planned procedure. This study had a major impact because clinicians concluded that preoperative improvements in some of these factors such as heart failure symptoms would decrease cardiac risk. Cardiac risk assessment continues to evolve, and is reviewed in detail in Chapter 98. The American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines published "Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery," which was last updated in 2014.[2] Preoperative evaluation should include a thorough history and physical examination, assessment of surgery specific risks, and advanced testing based on the severity of underlying cardiac disease as outlined in the AHA guidelines. The algorithmic approach to preoperative evaluation described in these guidelines is valuable in that more consistent clinical approaches have emerged (see Chapter 98, Fig. 98–1).

Specifically, the information derived from preoperative cardiac evaluation should address the following points:

1. Urgency assessment: If this is an emergency procedure, proceed to operating room and attempt risk modification (ie, surveillance/monitoring).
2. If surgery is not urgent, assess patient for signs of "active cardiac conditions." These include unstable "acute" coronary syndrome (ACS) or recent myocardial infarction, decompensated heart failure, severe valvular disease, and significant arrhythmia. If present, consider further evaluation and treatment as per AHA guidelines before surgery.
3. In chronic, less severe cardiac disease (no active cardiac conditions), surgery-related risk assessment suggests advancing to surgery in low-risk surgical procedures.
4. If surgery-related risk is intermediate or high, functional status can give invaluable information about the cardiac reserve in response to surgery-related stress (eg, large fluid shifts, sudden hemodynamic changes). Functional capacity is described using metabolic equivalents (METs); one MET is the oxygen consumption of a 70-kg, 40-year-old man at rest. With moderate (eg, climbing a flight of stairs) or excellent functional status, proceeding to surgery is suggested.
5. With poor functional status (not able to perform daily activities such as eating, dressing, bathing), assessment for risk factors associated with cardiac disease is suggested. These include mild angina, prior (not recent) myocardial infarction, compensated heart failure, diabetes, renal insufficiency, advanced age, abnormal ECG, rhythm other than sinus, history of stroke, and uncontrolled hypertension.
6. In patients with poor or unknown functional status (< 4 METs) and three or more cardiac risk factors, additional testing should be considered for intermediate-risk or vascular surgery if testing will change management.
7. Patients with poor or unknown functional status (< 4 METs), but less than three cardiac risk factors, may proceed with planned surgery. In that case, risk modification, for example using beta-blockade for heart rate control, is recommended unless contraindications apply.
8. Additional considerations may apply in patients with cardiac devices (pacemaker or implantable cardioverter-defibrillator) that may require interrogation/programming before going for surgery.
9. Patients on anticoagulant or antiplatelet therapy may need to have that adjusted prior to surgery
10. Patients may present contraindications for specific anesthetic techniques (see next paragraphs).

A cogent summary of the pertinent clinical, laboratory, radiologic, echocardiographic, radionuclide, and cardiac catheterization data comprises the ideal cardiac consultation for the anesthesiologist. With the benefit of this information, the two specialties can make intelligent decisions regarding the patient's preoperative therapy and the optimal timing of surgery.

ANTICOAGULANT AND ANTIPLATELET THERAPY

Cardiovascular disease management frequently includes anticoagulation as for stroke prophylaxis in patient with atrial fibrillation, and potent antiplatelet agents are required following percutaneous coronary interventions. Implications for surgery and anesthesia include timing of surgery and management of anticoagulation and antiplatelet therapy to minimize the risk of surgical bleeding without increasing the risk of stroke or increasing risk for stent thrombosis, respectively. Certain anesthetic techniques, such as neuraxial anesthesia, may be contraindicated in the presence of anticoagulant/antiplatelet regimens. Potentially life-threatening complications may occur if current guidelines and recommendations are not followed.

The increased risk of perioperative cardiac events following percutaneous coronary intervention is related to the perioperative hypercoagulability associated with surgical stress in the setting of non-endothelialized stent surfaces. The answers to when and if anticoagulant/antiplatelet medications can be safely discontinued for surgery is an ongoing process, as stent technology and drug therapies continue to evolve.[3,4] Ideally, elective noncardiac surgery should be delayed until the stent surface is fully endothelialized. The 2014 ACC/AHA guidelines do not recommend elective noncardiac surgery within 2 weeks of coronary balloon angioplasty or 4 weeks after bare metal stent implantation.[2] Elective surgery should be delayed for at least 1 year following DES. For nonelective surgery, the task force encourages a consensus decision among the clinicians involved whether delaying surgery outweighs the risk of stent thrombosis. If surgery cannot be deferred and dual antiplatelet therapy (DAPT) must be interrupted in patients with recently placed coronary stents, aspirin should be continued if possible, and DAPT should be restarted as soon as possible after the surgical procedure. Recommended time intervals between discontinuation of DAPT and surgery depend on patient risk factors, type of surgery, and even the surgeon's preference to accept an increased risk of surgical bleeding versus risking stent thrombosis with possibly catastrophic consequences. Many recommendations call for discontinuing clopidogrel 5 to 7 days, prasugrel 7 to 9 days, and ticagrelor 5 days before surgery. Bridging therapy in patients with long-term DAPT has been suggested in patients at high risk for cardiovascular events. However, unlike in patients on warfarin, unfractionated or low molecular weight heparin is not effective in patients who are depending on potent antiplatelet drugs. Alternatively, short-acting glycoprotein (GP) IIb/IIIa inhibitors and $P2Y_{12}$ inhibitors have been tried for bridging to surgery in patients on DAPT; however, experience is limited at this point. For certain procedures including neurosurgery, ophthalmology, or spine surgery, the risk of even continuing aspirin perioperatively may outweigh the risks of discontinuing the drug. In emergency procedures, patients on long-acting antiplatelet drugs have a significantly increased risk of hemorrhage, and platelet transfusions may be necessary to achieve hemostasis. Based on the ACC/AHA guidelines summarized earlier, the American Society of Anesthesiologists (ASA) issued a Practice Alert for the perioperative management of patients with coronary artery stents.[5]

Anticoagulation therapy is indicated in patients at risk for thromboembolism (atrial fibrillation, mechanical heart valves, heart failure). Vitamin K antagonists (warfarin) or any of the novel oral anticoagulants (NOACs) are discontinued prior to surgery based on the increased risk of bleeding complications. Drugs with longer half-lives such as warfarin may require bridging to surgery either with unfractionated (IV) heparin or low-molecular-weight heparins. Bridging anticoagulation is usually considered in patients at very high thromboembolic risk (mechanical heart valves, recent [< 12 weeks] embolic stroke, or venous thromboembolism). If surgery cannot be delayed, the risk of bleeding is increased and must be weighed against the urgency of the procedure. Many of the NOACs have shorter half-lives compared to warfarin. For example, current recommendations for dabigatran is to discontinue 1 to 2 days before the procedure if creatinine clearance is ≥ 50 mL/min, and 3 to 5 days if < 50 mL/min.

INTRAOPERATIVE ANESTHETIC MANAGEMENT

Cardiac risk assessment provides the clinician with an evidence-based approach to clinical decision making if a patient with known risk factors (according to the RCRI) for MACE should proceed for surgery or if prior optimization of risk factors should be attempted. However, if surgery in a patient with significant risk is unavoidable, the anesthesiologist must choose an anesthetic technique, continue implementing guideline-directed medical therapy, and choose appropriate monitoring to further reduce the risk of MACE.

CHOICE OF ANESTHETIC TECHNIQUE

The choice of anesthetic technique is inherently a difficult one because multiple factors must be considered. These include patient preferences, the requirements of the surgical procedure, and the patient's underlying medical condition(s). There is little scientific evidence that any particular anesthetic approach is superior to reasonable alternatives, or that anesthetic technique per se influences patient outcome.[6-12]

Most recently, Leslie and coworkers analyzed patients registered in the Perioperative Ischemic Evaluation 2 (POISE-2) trial regarding the effect of a neuraxial technique (spinal, lumbar epidural, or thoracic epidural) alone or in combination with general anesthetic on 30-day adverse cardiovascular outcomes (death, stroke, myocardial infarction).[13] Neuraxial block and postoperative epidural analgesia were not associated with adverse cardiovascular outcomes. Poeran and associates retrospectively analyzed 98,290 elective colectomies.[14] General anesthesia was used in the majority of cases (93.9%), while the remainder received a combined anesthetic that included a neuraxial technique. Although the addition of a neuraxial technique was associated with a decreased risk for thromboembolism and cerebrovascular events, myocardial infarction and other morbid outcomes, such as urinary tract infection, postoperative ileus, blood transfusion, and admission to the intensive care unit, were observed more frequently in the neuraxial group. Overall, the findings were inconsistent, not showing a clear advantage for either anesthetic technique. In a systematic review, Guay and colleagues[15] inferred that there is a moderate level of evidence that the addition of a neuraxial technique to a general anesthetic may reduce 30-day mortality and the risk of pneumonia, but does not impact rates of myocardial infarction.

Overall, there are no definite recommendations for choosing a particular anesthetic to decrease the risk of perioperative cardiac events. The most effective strategies remain preoperative optimization and vigilant perioperative monitoring to allow for early detection of hemodynamic compromise. In certain defined surgical procedures (eg, transurethral resection of prostate), a neuraxial technique may be advantageous in enabling early recognition of complications. This is not applicable in all circumstances, however, and clinical judgment must be exercised to make the best choices in individual circumstances. Regional anesthetics and monitored anesthesia care are not infrequently converted to general anesthetics intraoperatively as a result of unexpectedly long surgery, patient discomfort, or changes in the surgical plan. No practitioner can be certain that a particular technique will be adequate for the surgical procedure, given the unpredictability of the situation, and the anesthesiologist must have flexibility to alter the technique, as needed.

Therefore, it is essential that the cardiologist/internist does not recommend excluding specific anesthetic technique(s) during a preoperative consultation.

GENERAL ANESTHESIA

General anesthesia is defined as a reversible state consisting of amnesia, analgesia, immobility, and the prevention of undesirable reflexes. The general anesthetics include many drugs, almost all of which have cardiovascular side effects. Intravenous agents are nearly always used for the induction of anesthesia in adults. Anesthesia is maintained using inhalational agents, intravenous agents, or a combination of the two.

Neuromuscular blocking drugs (muscle relaxants) are used to facilitate tracheal intubation, to lower the requirements for anesthetic agents, and to prevent involuntary muscular activity in surgical cases where complete paralysis is mandatory. In children, the induction of anesthesia is highly individualized according to patient needs, the practitioner's preferences, and institutional standards. With the exception of brief operations, most general anesthetics include tracheal intubation and mechanical ventilation. As an alternative to tracheal intubation, supraglottic devices, such as the laryngeal mask airway, may be used to secure a patient's airway. Loss of consciousness is usually accompanied by a decrease in sympathetic tone. This, as well as the effects of positive pressure ventilation and the cardiac depressant properties of inhalational and most intravenous anesthetic agents, causes a moderate decrease in cardiac output.

General anesthesia masks many of the symptoms of cardiovascular decompensation, such as angina, dyspnea, dizziness, and palpitations. Other signs of cardiovascular disease, such as tachycardia, are nonspecific and may be misinterpreted as being cause by hypovolemia or light anesthesia. Depending on the type of surgery, large fluid shifts and decreased venous return may occur, sometimes unpredictably. It is for these reasons that appropriate monitoring and selection of anesthetic agents is vital to the intraoperative management of the patient with cardiovascular disease.

Intravenous Anesthetics

Intravenous anesthetic induction drugs are composed of lipophilic molecules that have an affinity for neuronal tissue or specific receptors. Their anesthetic actions (eg, hypnosis) are generally terminated by redistribution from the vessel-rich tissues (brain, heart, liver, and kidneys) to other tissues (muscle, fat, and skin). Elimination via hepatic metabolism and renal excretion is typically much slower and takes place over several hours. Most intravenous anesthetics exhibit some degree of cardiovascular depression in the form of reduced cardiac output or vasodilation. Reduced doses and slower injection of the drug (titrating to effect) will markedly decrease these cardiovascular effects. The use of synthetic opioids (fentanyl, sufentanil, or remifentanil), etomidate, or ketamine may be indicated in patients with severely compromised cardiac function, because they tend to maintain hemodynamic stability. Table 99–1 summarizes commonly used intravenous anesthetics.

Inhalational Anesthetics

Inhalational anesthetics include nitrous oxide and the potent volatile anesthetic agents. Nitrous oxide has analgesic properties, but it is not a potent anesthetic. Concentrations up to 75% may be given safely (so as to maintain an adequate FiO_2), but incomplete amnesia, postoperative nausea, and movement in response to painful stimuli are likely. Thus, nitrous oxide is nearly always administered with other anesthetic agents, such as opioids or potent volatile anesthetics, and neuromuscular blockers. Many anesthesiologists opt to avoid nitrous oxide altogether, because of the minimal analgesic benefits and increasingly recognized undesirable side effects.

The use of inhalational anesthesia with potent volatile anesthetics is the most common anesthetic technique because of its relatively low cost, ease of use, reliable amnesia, and overall safety record of these agents. The effect of these agents is rapidly changed when the inspiratory concentration is adjusted. The ability to easily titrate inhalational anesthetics is an advantage compared with intravenous drugs, because the duration of surgical procedures and the degree of surgical stimulation

TABLE 99–1. Intravenous Anesthetics

		Cardiovascular Effects				
Generic Name	Class	BP	HR	SVR	CO	Notes/Adverse Effects
Thiopental	Thiobarbiturate	↓	↑	–/↓	–/↓	Venodilation, cerebral vasoconstriction
Methohexital	Oxybarbiturate	↓	↑	–/↓	–/↓	Venodilation, cerebral vasoconstriction
Midazolam	Benzodiazepine	–/↓	–/↑	–/↓	–/↓	Anxiolysis, sedation, amnesia
Morphine	Opioid	↓	↓	↓	–/↓	Histamine release
Fentanyl	Opioid	–/↓	↓	–/↓	–/↓	Chest wall rigidity
Sufentanil	Opioid	–/↓	↓	–/↓	–/↓	Chest wall rigidity
Remifentanil	Opioid	–/↓	↓	–/↓	–/↓	Chest wall rigidity
Meperidine	Opioid	↓	↑			Histamine release, anti-shivering
Ketamine	Phencyclidine	↑	↑	↑	↑	Dissociative anesthesia, analgesia
Etomidate	Imidazole derivative	–/↓	–/↓	–/↓	–	Adrenocortical suppression
Propofol	Phenol derivative	↓	–	↓	↓	Rapid recovery
Dexmedetomidine, clonidine	α_2-Agonist	↓	↓	↓	↓	Sedation, sympatholysis, anxiolysis, analgesia, bolus administration may cause transient increase in BP, dexmedetomidine more selective α_2-agonist

Abbreviations: BP, arterial blood pressure; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance; –, no or minimal change; ↓, decrease; ↑, increase.

TABLE 99–2. Inhalational Anesthetics

Inhalational Agent	Cardiovascular Effects				Notes
	BP	HR	SVR	CO	
Nitrous oxide	–	–	–	–	Rapidly diffuses into closed air spaces
Isoflurane	↓	↑	↓	–	Coronary steal clinically not significant
Desflurane	↓	–/↑	↓	–	Rapid induction and emergence, sympathomimetic during rapid induction
Sevoflurane	↓	–	↓	–	Preferred inhalational induction agent for children, nonpungent, potential nephrotoxicity

Abbreviations: BP, arterial blood pressure; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance; –, no or minimal change; ↓, decrease; ↑, increase.

are often unpredictable. All volatile agents are myocardial depressants at higher doses and cause vasodilation resulting in some degree of hypotension. Table 99–2 summarizes commonly used inhalational anesthetics in current practice.

There is evidence that potent volatile anesthetics offer some degree of myocardial protection from ischemic insult. The mechanisms of anesthetic drug-induced protection from myocardial injury are complex, and related to adaptive and protective cellular processes that confer protection to recurrent ischemic events. Myocardial preconditioning to ischemic events (ie, temporary coronary occlusion) elicits these processes; however, some volatile anesthetic agents and certain anesthetic drugs, such as opioids, mimic ischemic preconditioning.[16-24] Substantial literature has been published on this topic. In clinical practice, however, no meaningful differences in major outcome parameters have been found. The time course of administration of potent volatile agents (pre- vs post-conditioning), other comorbidities (eg, diabetes mellitus), and drugs that may abolish protective effects (eg, ketamine, β-blockers, and certain sulfonylureas) must be considered.[25,26] Currently, there are no conclusive data regarding which patients may benefit from anesthetic preconditioning or postconditioning.

Neuromuscular Blockade

Two major classes of nondepolarizing neuromuscular blocking drugs are currently used: benzylisoquinolinium compounds (eg, cisatracurium) and aminosteroid derivates (eg, vecuronium and rocuronium). Cisatracurium undergoes a unique form of spontaneous degradation that is organ-independent (Hofmann elimination), and therefore is frequently used in patients with renal insufficiency or hepatic failure. Pancuronium is the classic aminosteroid nondepolarizing neuromuscular blocking drug. Its effects, however, are long lasting and it has been supplanted by shorter-acting compounds. Vecuronium is structurally very similar to pancuronium, but with an intermediate duration of action. Vecuronium does not have clinically significant cardiovascular adverse effects. Rocuronium has a more rapid onset of action, as a result of its lower potency and slightly increased heart rate. Although pancuronium elimination is almost entirely renal, the newer aminosteroid compounds are mainly degraded by the liver. These nondepolarizing neuromuscular blocking drugs require reversal at the end of a procedure to restore normal muscle function and respiration. The pharmacologic reversal is usually produced with a combination of neostigmine and glycopyrrolate, which may lead to bradycardia, tachycardia, or other arrhythmias in patients with cardiovascular disease, and has been associated with cardiac arrest even in patients with prior heart transplants. Recently, a new reversal agent, sugammadex, has been approved that produces none of these adverse cardiovascular effects.

Succinylcholine is a depolarizing short-acting neuromuscular blocker that is associated with rapid onset, and short duration of action. Its cardiovascular effects depend on whether nicotinic or muscarinic receptor effects predominate in a given patient. Thus, tachycardia and hypertension or bradycardia and hypotension may occur. Vagal effects tend to predominate with repeated doses or in children. In patients with various disorders (including neuromuscular diseases, recent burns, and massive trauma), hyperkalemic cardiac arrest may occur because of exaggerated release of intracellular potassium from myocytes. It is, therefore, not recommended for routine use, particularly in children.

REGIONAL ANESTHESIA AND NEURAXIAL ANESTHESIA

Cushing coined the term *regional anesthesia* for operations where local anesthetics were used to operate on localized areas of the body without loss of consciousness. Regional anesthesia typically involves the use of a local anesthetic to block sensation and pain from one or several large peripheral nerves and associated area(s) of distribution. Neuraxial anesthesia infers placement of a local anesthetic around the nerves of the central nervous system (spinal or epidural anesthesia). The advantages of either technique include simplicity, low cost, and minimal equipment requirements. Many of the adverse effects of general anesthesia are avoided, such as myocardial and respiratory depression. There are many surgical procedures, however, that are not amenable to a regional or neuraxial anesthetic technique. Serious side effects, such as hypotension, may be long-lasting and not reversed as easily compared to a general anesthetic. Additional contraindications include use of systemic anticoagulation, use of select antiplatelet therapy, patient refusal to be awake in the operating room, and local or systemic infections. The combination of a regional or neuraxial technique with a general anesthetic can be advantageous in providing adequate analgesia extending into the postoperative period with the added advantages of allowing for earlier mobilization and likely reducing thromboembolic risk.

Local Anesthetic Agents

Local anesthetics are classified based on their chemical structure as esters or amides. The esters are hydrolyzed by esterases in the plasma, and the amides are metabolized in the liver. The duration of action of local anesthetic agents is affected by the protein-binding characteristics of the molecule. Epinephrine and phenylephrine, which produce local vasoconstriction, may be added in small doses to local anesthetic solutions to prolong their duration of action. The systemic absorption of epinephrine occurs very slowly, and the β-adrenergic effects predominate. This results in slight tachycardia and diastolic hypotension, which is undesirable in patients with certain cardiovascular diseases. Toxic reactions to local anesthetics are generally characterized by central nervous system excitation (seizures), which may be followed by central nervous system depression and cardiovascular collapse. Table 99–3 provides an overview of commonly used local anesthetics in current practice.

Spinal Anesthesia

The injection of a relatively small dose of local anesthetic into the subarachnoid space produces profound motor and sensory blockade. The level of the anesthetic block is usually controlled by the choice of local anesthetic and the position of the patient. Spinal anesthesia also produces blockade of preganglionic sympathetic fibers, resulting in a sympathetic blockade that is generally two dermatomal segments

TABLE 99–3. Local Anesthetics

Generic	Class	Uses	Notes/Adverse Effects
Cocaine	Ester	T	Central nervous system toxicity, arrhythmias, myocardial ischemia
Procaine	Ester	S, I	Vasoconstriction
Chloroprocaine	Ester	E, S, C, I	
Tetracaine	Ester	S, I, T	
Lidocaine	Amide	E, S, C, I, T	Antiarrhythmic properties
Mepivacaine	Amide	E, S, C, I	
Prilocaine	Amide	E, C, I	Methemoglobinemia
Bupivacaine	Amide	E, S, C, I	High cardiotoxicity, cardiovascular collapse
Levobupivacaine	Amide	E, S, C, I	Less cardiotoxicity compared with bupivacaine
Ropivacaine	Amide	E, S, C, I	Less cardiotoxicity compared with bupivacaine

Abbreviations: C, caudal; E, epidural; I, infiltration; S, spinal; T, topical.

higher than the sensory dermatomal level. If the dermatomal level of sympathetic blockade reaches T1, then a complete sympathectomy is present until the block recedes. Higher levels of sympathetic blockade are associated with profound hypotension from arterial and venous vasodilatation, as well as bradycardia from the loss of cardiac accelerator fiber function. Blockade above a T2 level also produces respiratory insufficiency as a result of intercostal and phrenic nerve root blockade. Cardiovascular collapse and respiratory insufficiency (or apnea) are the signs of a "total spinal block," a life-threatening situation that must be treated with tracheal intubation and aggressive vasoactive support. Because of the risk of sudden severe vasodilation and hypotension, spinal anesthesia is contraindicated in patients with severe valvular stenosis or hypertrophic obstructive cardiomyopathy.

Epidural Anesthesia

The epidural space lies immediately external to the dura mater and is filled with loose areolar tissue and a venous plexus. An indwelling catheter is usually placed percutaneously for intermittent bolus injections or continuous infusions of local anesthetic or opioids. The epidural space may be entered by thoracic, lumbar, or caudal approaches. The hemodynamic effects of epidural anesthesia are similar to those of spinal anesthesia, except that the onset of sympathetic blockade is more gradual. Thus, with appropriate monitoring, cautious administration of epidural anesthetics can be performed safely, even in patients with valvular stenosis, or hypertrophic obstructive cardiomyopathy. In patients with cardiovascular disease, advanced monitoring techniques should be strongly considered. Beat-to-beat blood pressure monitoring via an intra-arterial catheter, and a secure route of central drug administration, for example via a central venous catheter, allows the practitioner to monitor and promptly treat changes in hemodynamic parameters.

In patients with known coronary artery disease, epidural anesthesia and analgesia, especially thoracic epidural catheters, have been shown to reduce intraoperative and early postoperative ischemic events, lower hormonal stress response, and reduce the incidence of atrial fibrillation.[27-30] Patient outcome data, however, were inconclusive when epidural anesthesia was compared with general anesthesia in patients at risk for perioperative cardiac events undergoing vascular surgery.[31,32]

When compared with spinal anesthesia, epidural anesthesia requires higher doses of local anesthetic. This increases the potential for complications and adverse effects from inadvertent intravascular injection or absorption that can cause severe arrhythmias, including ventricular fibrillation and cardiovascular collapse. Potent local anesthetics such as bupivacaine and, to a lesser degree, ropivacaine are more cardiotoxic compared with lidocaine. The slower rate of recovery of fast Na^+ channels in the conduction system and myocardium seen with bupivacaine is frequently identified as the reason for its increased cardiotoxicity. Cardiac resuscitation following inadvertent intravenous administration and cardiac arrest is difficult. Intravenous lipid emulsion has been successfully used to reverse local anesthetic toxicity,[33,34] and is now recommended to treat cardiovascular collapse from local anesthetic toxicity.[35] The hemodynamic consequences of inadvertent intravenous injections of epinephrine-containing solutions may be significant for patients who cannot tolerate tachycardia. Epidural infusions of opioids for postoperative analgesia may be complicated by pruritus, nausea, urinary retention, somnolence, and respiratory depression. Thus, appropriate monitoring and nursing care are required.

Nerve Blocks and Infiltration of Local Anesthetic

Nerve blocks and local anesthetic infiltration may be performed to facilitate surgery of localized areas of the body. For upper extremity surgery, the brachial plexus can be blocked by various approaches. The lower extremity may be anesthetized by blocking the femoral, obturator, and sciatic nerves. Local anesthetic infiltration ("field block") is performed in defined regions, such as the inguinal area. These blocks, when properly performed, have minimal cardiovascular effects. They do, however, require large volumes of local anesthetic solution, which result in toxic reactions if inadvertent intravascular injection occurs. Intercostal blocks are associated with high blood concentrations even without intravascular injection, because the neurovascular bundle enhances absorption of the local anesthetic, and multiple blocks are required for clinical efficacy. Recently, thoracic paravertebral blocks have been used more frequently for patients having unilateral surgery to avoid the hemodynamic effects of epidural blockade.

Regional Anesthesia and Anticoagulation Therapy

Appropriate patient selection is crucial to avoid potentially catastrophic complications (eg, paraplegia) when planning for an intraoperative central neuraxial anesthesia or postoperative neuraxial analgesia in patients with anticoagulation or potent antiplatelet therapy. A careful evaluation of drug history and bleeding diathesis provides essential information, because the risk of bleeding associated with many antiplatelet therapies will not be detected by standard preoperative coagulation tests.[36] The establishment of guidelines for the use of neuraxial anesthesia and analgesia in patients who have or will receive anticoagulants is an evolving process. Recommendations from the American Society of Regional Anesthesia and Pain Medicine for appropriate withdrawal of anticoagulant and antiplatelet therapy prior to neuraxial anesthesia can be found at the American Society of Regional Anesthesia and Pain Medicine website site (http://www.asra.com).[37] It is prudent to avoid neuraxial manipulation in patients who are receiving potent antiplatelet drugs that include glycoprotein IIb/IIIa antagonists, adenosine diphosphate inhibitors, and low molecular weight heparins at the time of the planned anesthesia. There are currently also very limited data on the safe use of new oral anticoagulants such as the direct thrombin inhibitors and factor Xa inhibitors in patients considered for neuraxial anesthesia. Safe time intervals between discontinuation of a specific drug and safe administration of a neuraxial anesthesia are an evolving process. Table 99–4 summarizes these guidelines and the current literature. Although guidelines can help in risk assessment, it is important to recognize that the decision to perform a neuraxial technique must be made on an individual basis.

TABLE 99–4. Anticoagulation and Antiplatelet Therapy: Recommendations for Neuraxial Anesthesia

Drug	Clinical Tests	Recommendations
UH	Activated partial thromboplastin time	1. UH IV: NA is contraindicated in fully anticoagulated patients. 2. Standard subcutaneous UH: no increased risk unless used for prolonged periods. 3. IV heparin infusion safe if started > 1 h after needle placement; catheter removal 1 h before subsequent dose and > 2-4 h following last heparin dose.
LMWH and heparinoids	Not useful	1. Increased risk for NA, especially when used in conjunction with antiplatelet therapy. 2. Safe time interval between last administration and neuraxial manipulation varies depending on type and dosing interval. Enoxaparin > 12-24 h, fondaparinux > 36-42 h. 3. Administration with catheter in place is contraindicated unless specifically cleared for the individual patient and anticoagulant used. 4. Catheter removal 10-12 h after last LMWH dose; next dose 6-24 h after catheter removal depending on anticoagulant.
Warfarin	PT	1. INR < 1.5 before administration of regional anesthesia (chronic oral anticoagulation). 2. Warfarin administration absolutely contraindicated while catheter in place. 3. Neuraxial catheters should be removed when the INR is < 1.5; wait at least 2 h after catheter removal before next dose administered.
Direct thrombin inhibitors: Dabigatran Argatroban Bivalirudin	Not useful	1. Significantly increased risk of spinal hematoma particularly with concomitant use of other drugs that affect hemostasis, as well as platelet inhibitors. 2. Safe time interval between last dose and safe neuraxial anesthesia not known. For dabigatran at least 4-5 days and longer wait times in renal insufficiency. 3. In patients taking argatroban or bivalirudin, neuraxial anesthesia is probably best avoided. 4. Routine coagulation assays, including ecarin clotting assays, unreliable for neuraxial anesthesia setting.
Direct factor Xa inhibitors: Rivaroxaban Apixaban Edoxaban	Not useful	1. Safe time interval between last dose and safe neuraxial anesthesia not known. 2. For rivaroxaban at least 22-26 h, and for apixaban 26-30 h, before neuraxial manipulation. Longer wait times in renal insufficiency. 3. Anti-factor Xa test of little value for neuraxial anesthesia setting.
Aspirin	Not useful	Very low risk unless used in conjunction with a second drug that affects the coagulation system or potent antiplatelet drugs.
Other NSAIDs	Not useful	No indication for increased risk unless used in conjunction with a second drug that affects the coagulation system.
Clopidogrel, prasugrel Ticlopidine Ticagrelor	Not useful	1. Recommend discontinuing clopidogrel for 7 d. 2. Prasugrel 7-10 d. 3. Ticlopidine 14 d. 2. Ticagrelor 5-7 d, prior to NA.
Tirofiban	Not useful	Recommend 8-h interval between drug administration and safe NA.
Abciximab	Not useful	Recommend 48-h interval between drug administration and safe NA.
Eptifibatide	Not useful	Recommend 8-h interval between drug administration and safe NA.

Abbreviations: DTI, direct thrombin inhibitor; INR, international normalized ratio; IV, intravenous; LMWH, low molecular weight heparins; NA, neuraxial anesthesia; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, prothrombin time; UH, unfractionated heparin.

Frequently, a combination of drugs is administered, and the response to certain drugs may vary between individuals, for example based on genetic variances, with unpredictable effects on the coagulation system. For patient safety, it is also crucial to monitor neurologic status carefully after administration of spinal or epidural anesthesia; rapid diagnosis and treatment of neuraxial hematoma probably improves outcome.[38]

PERIOPERATIVE MONITORING

Perioperative monitoring has significantly contributed to attainment of the level of safety provided by modern anesthesia, allowing for more complex surgeries in even the highest-risk patients. The American Society of Anesthesiologists established standards for basic intraoperative monitoring in 1986.[39] Intraoperative monitoring that is required based on these guidelines include the following: (1) heart rate, (2) electrocardiogram (ECG), (3) blood pressure, (4) pulse oximetry, (5) capnometry, and (6) body temperature. The indications for the use of more invasive monitors, such as intra-arterial and central venous monitoring, vary and depend on patient and surgery specific factors, as well as institution and practitioner preferences (Tables 99–5 and 99–6).[40] It must be recognized, though, that monitoring guidelines are almost entirely based on observational cohort analyses and expert opinion. Although adequate monitoring is essential for early detection of hemodynamic disturbances, a particular monitoring technique will

TABLE 99–5. Indications for Intra-Arterial Monitoring

- Major surgical procedures involving large fluid shifts and/or blood loss.
- Surgery requiring cardiopulmonary bypass.
- Major aortic surgery including surgery of the aorta requiring cross-clamping.
- Patients with recent myocardial infarctions, unstable angina, or severe coronary artery disease.
- Patients with decreased left ventricular function (congestive heart failure) or significant valvular heart disease.
- Patients in hypovolemic, cardiogenic, or septic shock, or with multiple organ failure.
- Procedures involving the use of deliberate hypotension or deliberate hypothermia.
- Massive trauma.
- Patients with right heart failure, chronic obstructive pulmonary disease, pulmonary hypertension, or pulmonary embolism.
- Patients with electrolyte or metabolic disturbances requiring frequent blood samples.
- Patients with pulmonary disease requiring frequent arterial blood gases.
- Inability to measure arterial pressure noninvasively (eg, morbid obesity).

not result in improved outcome unless timely and effective treatment is initiated and available. The indications for pulmonary arterial catheter (PAC) monitoring, for example, are especially controversial. Large randomized prospective studies of PAC use in various clinical settings have failed to demonstrate improved patient outcomes,[41-44] and some have even suggested potential harm.[45] As with all monitoring devices, the caregiver's competency in interpreting PAC-derived data and instituting appropriate treatment is essential to derive maximal benefit and avoid complications.[46-48] The American Society of Anesthesiologists published practice parameters to guide practitioners in the appropriate use of the PAC.[49] The decision to use perioperative PAC monitoring should be based on a combination of patient risk factors, surgical risk, and the experience of the practitioner. Many clinicians believe that patients with clinically significant pulmonary hypertension, significant valvular disease (eg, aortic stenosis), or severe cardiac dysfunction, undergoing surgery with expected large fluid shifts or hemodynamic instability will benefit from PAC monitoring.[50]

TABLE 99–6. Indications for Central Venous Line Placement

- Major operative procedures involving large fluid shifts and/or blood loss.
- Major trauma.
- Inadequate peripheral intravenous access.
- Frequent venous blood sampling.
- Rapid infusion of intravenous fluids (eg, major trauma, liver transplantation).
- Venous access for vasoactive or irritating drugs.
- Chronic drug administration (eg, antibiotics, chemotherapy).
- Total parenteral nutrition.
- Surgical procedures with a high risk of air embolism.
- Intravascular volume assessment when urine output is not reliable or unavailable.
- Patients with tricuspid stenosis.

Transesophageal echocardiography (TEE) has acquired a much larger role in perioperative management. The more widespread availability of these devices in the operating room and intensive care unit setting and the development of newer modalities, such as three-dimensional echocardiography and tissue Doppler, have enhanced the ability of anesthesiologists, cardiologists, and surgeons to make intraoperative diagnoses, evaluate hemodynamic aberrations, and assess the quality of cardiac surgical interventions. Standardized intraoperative examination guidelines for multiplane TEE[51] and training guidelines[52,53] have been published. The National Board of Echocardiography administers a certification process. The American College of Cardiology/American Heart Association/American Society of Echocardiography Task Force on Practice Guidelines has published practice guidelines that address perioperative TEE.[54] The American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists released the most recent update.[55] Based on these recommendations, the use of TEE is recommended for all cardiac or thoracic aortic surgery, and may be used for all patients undergoing transcatheter intracardiac procedures. In noncardiac surgery, TEE may be used if the planned procedure or the patient's known or suspected cardiovascular disease might result in severe hemodynamic, pulmonary, or neurologic compromise. During unexplained life-threatening circulatory instability, and in critical care patients, TEE should be used when diagnostic information that is expected to change management cannot be obtained by transthoracic echocardiography or other modalities in a timely manner. TEE may also be used for patients with oral, esophageal, or gastric disease, if the expected benefit outweighs the potential risk. These are guidelines only, and the practitioner should decide on intraoperative TEE monitoring based on his or her level of training and experience, as well as patient- and surgery-related factors.

Less invasive and noninvasive methods of cardiovascular monitoring are continually being developed. Cardiac output can be estimated using arterial pressure waveform analysis (pulse contour analysis), indicator dilution technique, electrical bioimpedance, and esophageal Doppler ultrasound. Parameters, such as intrathoracic blood volume and extravascular lung water, can also be estimated by some of these devices. Some of the less invasive cardiac output devices require calibrating against more invasive measurements. Additional limitations include poor correlation with more invasive methods in patients with rapidly changing hemodynamics and irregular rhythm.

Cardiac output as well as other monitoring modalities are used in an attempt to intervene and optimize target parameters early in the disease process. This early goal-directed therapy has been suggested to improve outcomes in some studies,[56] although clear evidence is still lacking.[57] The lack of outcomes evidence in support of invasive monitoring and the established problems (eg, central line–associated bloodstream infections) give further impetus for improvements and innovations in less invasive and noninvasive monitoring.

Various "brain function" monitors using proprietary electroencephalographic analysis have been developed for the purpose of monitoring depth of sedation and level of consciousness.[58] Incomplete amnesia leading to intraoperative awareness is rare with current anesthetic techniques, with a reported incidence of 0.1% to 0.2%.[59,60] The American Society of Anesthesiologists currently does not recommend routine brain function monitoring in patients undergoing general anesthesia.[61] Elevated risk of intraoperative awareness is associated with a prior history of intraoperative awareness, morbid obesity, substance abuse, chronic pain patients with opioid tolerance, and certain procedures (eg, trauma surgery). Brain function monitoring should thus be used on a case-by-case basis.

Near-infrared spectroscopy (NIRS) for measurement of cerebral oximetry is gaining increasing popularity for monitoring the oxygen supply-demand ratio of the brain. The cerebral tissue saturations (derived from the outer cortex of the frontal lobes) reflect mainly the

venous component, continuously, in real time. Thus it can be viewed as a correlate of the jugular bulb saturation, with a constant bias towards higher readings because of the approximately 25% to 30% admixture of arterial blood in cerebral tissue.[62] Variables affecting cerebral saturations include cardiac output, cerebral perfusion pressure, oxygen-carrying capacity, $PaCO_2$, anesthetic depth, and temperature. Technical problems, such as cardiopulmonary bypass cannula malpositioning in the superior vena cava or aorta, could lead to acute changes. Trend monitoring, compared with baseline values obtained during hemodynamically stable conditions, as well as absolute lower thresholds, have been recommended in clinical practice for decision making. Although there is increasing evidence that low cerebral saturations are associated with adverse outcomes, few studies show that interventions based on cerebral oximetry monitoring improve outcome. Murkin and colleagues monitored cerebral oximetry and targeted therapy to optimize cerebral tissue oxygenation in patients undergoing coronary artery bypass grafting.[63] They found that a composite measure of postoperative organ dysfunction was substantially improved in the treatment group where goal-directed therapy aimed to maintain the cerebral tissue oxygen saturation values within 25% of the pre-induction baseline. One of the strengths of cerebral oximetry monitoring is the detection of catastrophic events, particularly during periods of nonpulsatile flow, such as during cardiopulmonary bypass, with certain left ventricular assist devices, or extracorporeal membrane oxygenation.[64-66] Additional clinical settings where this technology is increasingly deployed include monitoring collateral cerebral blood flow during carotid endarterectomy,[67] ventricular tachycardia ablation in the electrophysiology lab,[68] and real-time assessment of advanced cardiac life support/resuscitation efforts.[69] Cerebral oximetry combined with invasive blood pressure monitoring has been used to determine cerebral autoregulation blood pressure limits in real time, allowing individualized blood pressure treatment.[70,71]

THE POSTOPERATIVE PERIOD AND CARDIAC COMPLICATIONS

Emergence from anesthesia is frequently accompanied by hypertension and tachycardia, which may result from incomplete analgesia, awakening with airway devices in the oropharynx or trachea, withdrawal from antihypertensive drugs, hypoxemia, hypercarbia, delirium, or bladder distension. Patients with multiple risk factors are particularly prone to postoperative complications, such as myocardial infarction, pulmonary edema, malignant ventricular arrhythmia, and cardiac death.[72] Inadequate pain control and shivering both cause tachycardia and high catecholamine levels, resulting in increased oxygen demand. Hypercoagulability from immobilization and surgery, discontinuation of antiplatelet therapy in patients with intracoronary stents, hypovolemia, anemia, and intravascular volume shifts all probably contribute to the high incidence of complications in the postoperative period.

The anesthesiologist plays a vital role in the postoperative period, providing adequate pain control through the development of multidisciplinary pain services that administer epidural analgesia, peripheral nerve blockade infusion catheters, patient-controlled analgesia, and multimodal therapies. Additionally, hemodynamic parameters must be optimized, especially in patients at increased risk for major adverse cardiac events. If tachycardia, hypertension, or hypotension persists, and an underlying modifiable cause is not identified, then intravenous drugs, such as nitroglycerin, labetalol, or esmolol, can be used to control hemodynamics in patients with cardiovascular disease. Shivering is another phenomenon that may occur as a result of hypothermia or emergence from volatile anesthetics. Although the mechanism is unknown, low doses of intravenous meperidine may decrease or eliminate shivering.

CONCLUSIONS

The optimal perioperative care of patients with cardiovascular disease is the joint responsibility of anesthesiologists, surgeons, and cardiologist/internists. Any anesthetic agent or technique has the potential for producing adverse effects, and the margin of safety is reduced in patients with cardiovascular disease. It is the anesthesiologist's role to acquire accurate and relevant information from the preoperative evaluation, to apply appropriate monitoring technology, to select an anesthetic technique that is suited to the planned procedure and the condition of the patient, and to manage hemodynamic alterations and analgesic requirements in the perioperative period. As cardiovascular disease continues to become more prevalent in the surgical population and preoperative testing and intraoperative monitoring become more sophisticated, the need for effective communication between the specialties of cardiology and anesthesiology will become even more important.

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CHAPTER 100

RHEUMATOLOGIC DISEASES AND THE CARDIOVASCULAR SYSTEM

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Rheumatologic conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and the vasculitides that affect multiple organ systems may also impact the cardiovascular system. These pathologic processes fall in the category of autoimmune diseases, which are initiated by a complex interplay between genetic factors and environmental stimuli. They are presumed to be driven by self-reactive T and B lymphocytes, which in tandem with a network of endogenous and exogenous signals, activate the immune system, producing tissue inflammation and damage (Table 100–1). The effects of autoimmunity on the cardiovascular system may be the result of local or systemic mechanisms. For example, locally aberrant immunity may selectively target the pericardium, myocardium, or conduction system in systemic sclerosis. On the other hand, in patients with SLE or systemic vasculitis, circulating immune complexes may deposit in blood vessels, where they evoke an inflammatory response, which in turn occludes the vessel lumen and causes ischemic manifestations distal to the site of critically limited blood flow. A hypercoagulable state from antiphospholipid antibody syndrome can lead to thrombotic occlusion, producing myocardial infarction, stroke, or ischemic damage of the visceral organs. Thus diverse pathways of a dysregulated immune system may converge to directly or indirectly damage the heart and vasculature.

This chapter aims to familiarize the cardiovascular specialist with the clinical features of rheumatologic diseases that affect the heart and blood vessels. These diseases derive from chronic inflammation and abnormal tissue repair. This chapter also covers the most common heritable diseases of connective tissue (eg, Marfan syndrome, Loeys-Dietz, Ehlers-Danlos, and pseudoxanthoma elasticum). Unlike autoimmune diseases, these rare disorders mostly result from mutations in specific genes encoding various components of connective tissue that maintain the structural integrity of the vasculature.

CARDIOVASCULAR MANIFESTATIONS OF SYSTEMIC RHEUMATIC DISEASES

RHEUMATOID ARTHRITIS

The prevalence of rheumatoid arthritis (RA) in the Western world is 1% to 2%, and is believed to be 1% worldwide[1]; RA thus ranks as the most common of the systemic autoimmune diseases. RA is a female-predominant disease characterized by a chronic symmetrical polyarthritis with a strong predilection for the small joints of the hands and feet that often leads to physical impairment and disability. The diagnosis is established on clinical grounds by recognizing the signs and symptoms of joint inflammation. It is supported by the results of laboratory studies and plain radiographs of the hands and feet. Approximately three-quarters of patients with RA test positive for serum rheumatoid factor or anticyclic citrullinated peptide antibodies.[2] X-rays of the hands and feet are often normal at the onset of RA, but later they may show the characteristic marginal joint erosions associated with this disease, as well as joint space narrowing from thinning of the articular cartilage. Much is known about the pathogenesis of synovial inflammation in RA. Briefly, the synovial tissue is characterized by a chronic inflammatory infiltrate comprised chiefly of T cells, B cells, macrophages, fibroblasts, and mast cells. There is increased production of a diverse array of proinflammatory mediators, such as tumor necrosis factor (TNF) α, interleukin (IL) 1, and IL-6, as well as many chemokines that work together to amplify the pathologic response, stimulate proliferation of synovial fibroblasts, upregulate expression of adhesion molecules on the surface of blood vessels, and promote angiogenesis.

Although RA is predominately an inflammatory joint disease, it produces systemic effects that can target other organs and tissues. Extraarticular manifestations include fatigue, low-grade fever, Sjögren syndrome, nodules, interstitial lung disease, and vasculitis. In RA, the most common cardiovascular manifestations are pericarditis, valvular disease, cardiomyopathy, coronary vasculitis, ischemic heart disease, and heart failure.

Pericarditis

In a necropsy series, evidence of pericarditis can be seen in as many as 54% of cases of RA.[3] Acute, symptomatic pericarditis, however, occurs in fewer than 10% of patients with severe RA.[4,5] RA patients with acute pericarditis are clinically indistinguishable from those with pericardial disease secondary to nonrheumatic conditions. Symptoms of positional chest pain may be reported or a pericardial friction rub may be apparent in up to 55% to 65% of patients.[6,7] Although in this setting electrocardiograms are often normal, 5% to 10% of patients may manifest abnormalities classically associated with acute pericarditis. Imaging may be useful in confirming the diagnosis of pericarditis. In one series, echocardiography revealed a pericardial effusion in 90% of patients with this clinical diagnosis.[6] Aspiration of the pericardial fluid, which is not usually required for diagnosis in the appropriate clinical setting, may reveal an elevated white blood cell count, protein, and lactate dehydrogenase; decreased glucose level; the presence of rheumatoid factor; and a low complement.[7] These features may help to differentiate RA pericarditis from other causes of pericarditis.

TABLE 100–1. Common Clinical and Cardiovascular Manifestations of Systemic Autoimmune Diseases

Disease	Sex Distribution	Clinical Manifestations	Cardiovascular Manifestations
Rheumatoid arthritis	F > M	Inflammatory polyarthritis, rheumatoid nodules, RF, anti-CCP	Pericarditis, coronary artery disease, cardiomyopathy, congestive heart failure
Systemic lupus erythematosus	F > M	Malar rash, arthritis, photosensitivity, serositis, nephritis, +ANA; may have concomitant APS	Pericarditis, Libman-Sacks endocarditis, coronary artery disease, hypertension
Inflammatory myopathies	F > M	Proximal muscle weakness, DM with Gottron papules, shawl sign, mechanics hands	Pericarditis, conduction system abnormalities, congestive heart failure, and myocarditis
Systemic sclerosis	F > M	Limited form is referred to as CREST. Diffuse form involves proximal skin and visceral organs	Pulmonary hypertension, pericarditis, cardiomyopathy, conduction system disease
Seronegative spondyloarthropathy	M > F	Spinal or sacroiliac involvement, enthesitis, absence of rheumatoid factor, and a high incidence of HLA-B27	Aortitis, conduction system disease

Abbreviations: ANA, antinuclear antibody; APS, antiphospholipid syndrome; CREST, calcinosis, Raynaud syndrome, esophageal dysmotility, sclerodactyly, telangiectasias; anti-CCP, anticyclic citrullinated peptide antibodies; DM, dermatomyositis; F, female; M, male; RF, rheumatoid factor.

In one cohort, the occurrence of pericarditis was associated with decreased survival at 10 years.[6] However, it is unlikely that the presence of pericarditis directly contributes to the increased risk of death as the presence of extraarticular disease in general is associated with increased mortality. Constrictive pericarditis, albeit rare, is associated with higher mortality rates than is uncomplicated pericarditis. It requires an urgent intervention, such as pericardial window or stripping procedure.[8] Constrictive pericarditis must be distinguished from restrictive cardiomyopathy, which may result from secondary amyloidosis rarely seen in patients with longstanding RA. Most patients with uncomplicated acute pericarditis will respond to treatment with nonsteroidal anti-inflammatory drugs or corticosteroids. Corticosteroid therapy is generally reserved for patients with moderate to severe pericarditis and usually consists of a short burst of high doses of prednisone (eg, 40-60 mg/d) with subsequent taper over a period of several weeks, depending on the clinical response.

Valvular Disease

Clinically significant valvular disease is relatively uncommon in RA. In autopsy reviews, only 3% to 5% of patients with RA had valvular involvement in the form of rheumatoid nodules.[9,10] Patients with subcutaneous rheumatoid nodules have a higher rate of mitral valve insufficiency than those without nodules,[11] but unlike patients with rheumatic heart disease, mitral valve disease associated with RA does not lead to valvular stenosis. Patients with severe or symptomatic valvular disease require surgical intervention.[12,13]

Cardiomyopathy

RA may cause a cardiomyopathy characterized by focal necrotizing or granulomatous myocarditis.[4] The granulomas may involve the conduction system, leading to varying degrees of atrioventricular block, which usually persists despite immunosuppressive therapy.[14] Rarely, cardiomyopathy may result from secondary amyloidosis, which manifests on echocardiography as a significant thickening of walls of the ventricles and of the interventricular septum.[15] Cardiac MRI (cMRI) may be used to differentiate the different causes of cardiomyopathy in patients with RA. Inflammation due to granulomatous myocarditis could be seen as multiple focal areas of increased myocardial signal intensity on T2-weighted images.[16] Images from cMRI showing delayed enhancement with gadolinium display a characteristic diffuse endocardial hyperenhancement pattern that may suggest cardiac amyloidosis.[17]

Coronary Vasculitis

Although as many as 20% of patients with RA show histologic evidence of coronary vasculitis by autopsy, the significance of this finding is poorly understood because it rarely manifests clinically.[9] The diagnosis of coronary vasculitis involving the epicardial vessels may be suggested by the angiographic findings of interspersed areas of smooth-walled stenosis and ectasia as well as focal aneurysms. However, these angiographic features are relatively nonspecific and may be due to atherosclerosis. Recognition of coronary vasculitis is important because it requires treatment with immunosuppressive therapy such as high-dose corticosteroids and possibly other agents.[18]

Accelerated Coronary Artery Atherosclerosis and Heart Failure

Overall mortality is increased in patients with RA compared with the general population.[19,20] It is striking that 40% of deaths in RA are attributable to cardiovascular disease.[21,22] In a recent study, the prevalence of cardiovascular disease in RA patients was comparable to that of patients with diabetes.[23] It is known that a significant proportion of patients with RA judged to be in clinical remission using standardized disease activity scores still show an elevated level of C-reactive protein (> 3 mg/L), a known risk factor for future cardiovascular mortality in patients with RA.[24] Increasing evidence supports a strong link between RA and accelerated atherosclerosis, highlighting it as an important risk factor for cardiovascular disease.

Atherosclerosis is an inflammatory process driven by many of the same mediators that are associated with rheumatoid inflammation.[25] Systemic inflammation in RA is hypothesized to accelerate atherosclerosis, as well as affect other tissues, such as liver, muscle, and fat, which influence other cardiovascular risk factors (Fig. 100–1). Additionally, RA appears to be an independent risk factor for multivessel coronary artery disease,[26] and as shown in the Nurses' Health Study, women with RA have a two-fold higher rate of myocardial infarctions compared with controls.[27] Other studies suggest that RA patients are less likely to be symptomatic from ischemic heart disease as non-RA controls and twice as likely to have sudden death and unrecognized myocardial infarction,[28] contributing to a higher incidence of death from coronary atherosclerosis.[29]

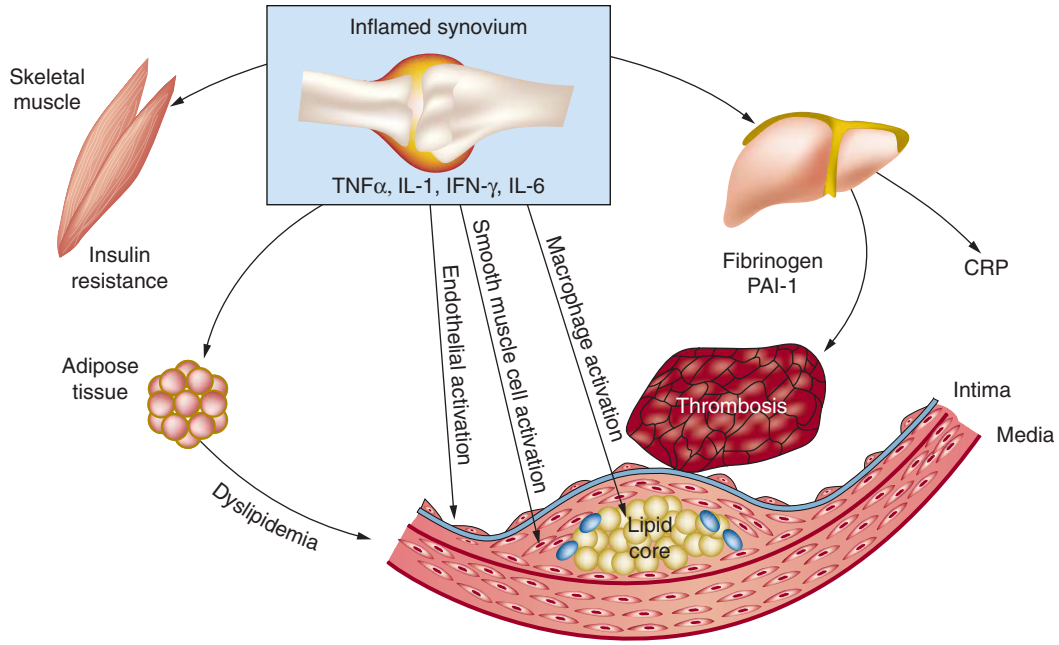


FIGURE 100–1. Systemic effects of inflammation in rheumatoid arthritis. The rheumatoid joint expresses high levels of various proinflammatory mediators, including tumor necrosis factor (TNF) α, interleukin (IL) 1, and IL-6, which amplify the inflammatory response. T-helper cells secrete interferon-γ (IFN-γ) and IL-17, which in turn activate the cellular constituents of the synovial tissue. These cytokines, which are also found in the vascular endothelium of the atherosclerotic blood vessel, serve to promote coronary artery disease and plaque rupture. Additionally, upregulation of these cytokines influences other cardiovascular risk factors by affecting skeletal muscle, adipose tissue, and the liver, leading to insulin resistance, dyslipidemia, and increased levels of C-reactive protein (CRP), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1), respectively. Reproduced with permission from Libby P: Role of inflammation in atherosclerosis associated with rheumatoid arthritis. *Am J Med*. 2008 Oct;121(10 Suppl 1):S21-S31.

Congestive heart failure also contributes to excess cardiovascular mortality in RA.[30] In recent echocardiographic studies, left ventricular systolic dysfunction was three times more common in RA patients compared with the general population.[31] Both right and left ventricular diastolic dysfunction (measured as a decrease in tricuspid E/A ratio by pulse wave Doppler) has been documented in this disease population despite the lack of clinically evident cardiovascular disease.[32] Other findings in RV diastolic dysfunction include lower peak E-wave velocity, and prolonged RV isovolumic relaxation time. Tricuspid E-wave deceleration time was significantly shorter only in those who had an LV restrictive filling pattern. The mechanisms by which RA patients develop heart failure are likely multifactorial depending on the underlying disease process (eg, myocarditis, amyloidosis, ischemia from accelerated atherosclerosis). It is important to note, however, that despite not having risk factors such as obesity or hypertension, patients with heart failure associated with RA still have an increased mortality.[33]

There is currently a lack of evidence-based guidelines for the management and prevention of cardiovascular disease in RA patients. In treating RA, the primary goal is tight control of joint inflammation, with conventional disease-modifying anti-rheumatic agents (eg, methotrexate) as well as biologic therapy (eg, TNFα inhibitors, tocilizumab, abatacept). A recent meta-analysis showed that methotrexate was associated with a 21% lower risk for CVD and an 18% lower risk for myocardial infarction.[34] TNFα inhibitors are generally avoided in RA patients with a history of heart failure because of increased morbidity and mortality in non-RA patients with congestive heart failure who were treated with such therapy.[35] In general, traditional cardiovascular risk factors should be aggressively managed in patients with RA until further studies have evaluated the relative benefits and risks of this approach.[35]

ADULT-ONSET STILL DISEASE

Adult-onset Still disease refers to a syndrome, usually affecting young adults, that presents with polyarthritis in the setting of fever, evanescent rash, and sore throat (similar to systemic juvenile inflammatory arthritis in children). Pericarditis is the most common cardiac manifestation of adult Still disease, occurring in up to 24% of patients.[36] There have been recent case reports, albeit rare, of pericarditis complicated by life-threatening cardiac tamponade.[37] Adult-onset Still disease is usually treated with corticosteroids and methotrexate, although TNFα inhibitors, such as etanercept and adalimumab, and the IL-1 antagonists, such as anakinra and rilonacept, as well as tocilizumab (anti-IL-6 receptor antibody), appear to be promising alternatives for severe or refractory cases.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a much less common systemic autoimmune disease that primarily affects young women, with peak incidence between the ages of 15 and 40 years. In the United States, its prevalence is estimated to be 1 in 2000 individuals and more commonly affects Hispanics and African Americans than Caucasians.[38] Although more than 95% of SLE patients test positive for serum antinuclear antibodies (ANA), not all patients with a positive ANA have SLE. Clinically, SLE patients are a heterogeneous group, with a wide range of disease severity and spectrum of organ system involvement. Cardiovascular involvement, in particular, occurs commonly in patients with SLE. It is noted in up to 70% of patients at autopsy[39-41] as well as antemortem on echocardiography.[41-44]

The pathogenesis of SLE is likely to be multifactorial with dependence on genetic risk factors. The mechanisms of disease are complex,

with contributions from both aberrantly regulated innate (eg, increased expression of genes stimulated by type 1 interferon) and adaptive immune responses (eg, autoantibodies). However, several lines of evidence support a prominent role for immune complex deposition in disease mechanisms, which may be relevant to the pathogenesis of vasculitis and possibly acceleration of atherosclerosis in SLE.

Pericarditis

The most common cardiovascular manifestation of SLE is pericarditis,[45] with up to 42% of patients in one echocardiographic study showing an effusion.[43] Pericardial effusions may be detected at any point in the disease and are usually asymptomatic and small. Acute pericarditis may occur in as many as 20% to 30% of patients with SLE.[46] Rarely, acute pericarditis may be associated with cardiac tamponade[47]; chronic pericarditis may occasionally lead to constriction.[48] Particular attention must be paid to differentiating lupus pericarditis from infectious causes in the setting of concomitant immunosuppressive therapy for SLE.[46] Treatment of lupus pericarditis depends on its severity. Although no therapy is required for asymptomatic, small effusions, symptomatic, acute pericarditis may warrant treatment with nonsteroidal anti-inflammatory drugs or corticosteroids. Moderate or severe acute lupus pericarditis is usually treated with a course of prednisone beginning at 40 to 60 mg daily followed by a subsequent taper in the dose over several weeks according to the clinical response.

Valvular Disease

Valvular disease associated with SLE can be quite common and take on many forms. Libman-Sacks endocarditis is characterized by noninfectious verrucous vegetations seen on cardiac valves (Fig. 100–2). Although any of the four valves may be affected, valvular abnormalities occur most commonly on the mitral valve followed in frequency by the aortic valve.[45] Valvular lesions are not uncommon, but usually are asymptomatic. According to one series, more than 50% of patients with SLE had valvular abnormalities by transesophageal echocardiography.[49] The most common abnormality in this study was valvular thickening, followed by vegetations, and then valvular insufficiency. The significance of valve thickening is unknown and may resolve over time or worsen. Complications of valvular vegetations included cerebral and/or coronary artery thromboemboli,[50,51] although the absolute risk is very low. Other abnormalities that have been reported in SLE include valvulitis,[52] valve fibrosis and mucoid degeneration, and aortic dissection.[53]

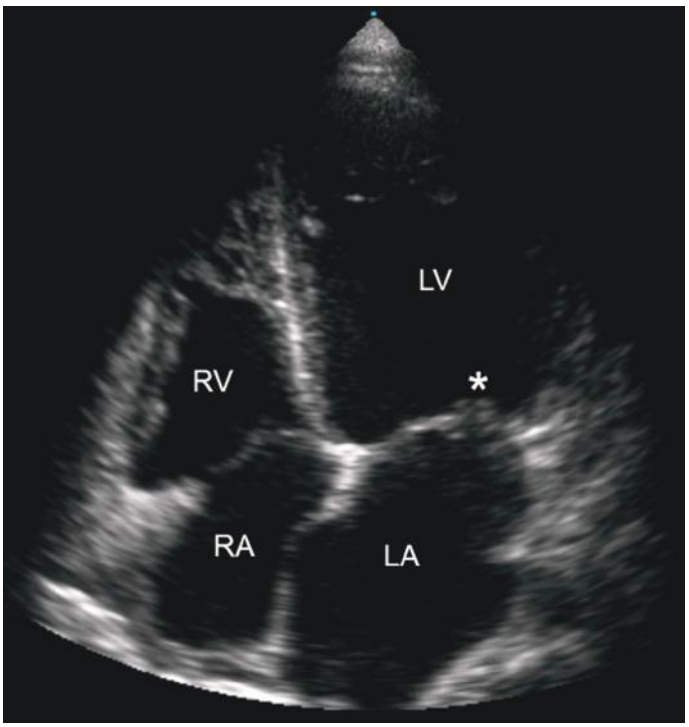


FIGURE 100–2. Echocardiographic image of Libman-Sacks endocarditis. Transthoracic echocardiogram (apical four-chamber view) of a patient with systemic lupus erythematosus and Libman-Sacks endocarditis. Note the thickening and vegetation (*asterisk*) of the mitral valve. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

There is a lack of consensus regarding the use of corticosteroids for treatment of valvular vegetations or other abnormalities. Valve replacement surgery is the usual course of action for the management of patients with clinically symptomatic or hemodynamically significant valve disease.[52,54] A less invasive transcatheter approach may be a future consideration in lupus patients deemed too high risk for surgery.[55] Although patients with lupus may have an increase lifetime risk of acquisition of infective endocarditis due to valvular abnormalities, the most recent American Heart Association guidelines do not recommend routine antibiotic prophylaxis for dental procedures in this patient population.[56]

Myocardial Disease

Myocardial dysfunction in SLE may result from valvular disease, coronary artery ischemia, or sustained hypertension and, in some cases, can lead to clinically significant heart failure. Lupus cardiomyopathy, which is defined as a cardiomyopathy in the absence of ischemic disease or hypertension, has been reported in many series but is not well understood from a pathophysiologic perspective.[57] Acute myocarditis should be suspected in any patient with SLE who presents with new-onset arrhythmia, fever, dyspnea, and chest pain. The diagnosis of lupus myocarditis is often based on clinical grounds after evaluation by coronary angiography and other cardiac imaging procedures. Cardiac enzymes are not usually elevated in lupus myocarditis. The role of endomyocardial biopsy is not well established; it is subject to sampling error, and the sensitivity and specificity of the biopsy findings in myocarditis are unknown.[56] Treatment of clinically significant myocarditis typically calls for high doses of prednisone therapy for a prolonged course of 3 to 6 months with or without other immunosuppressive agents.

Conduction System Disease and Neonatal Lupus

Lupus myocarditis may be complicated by tachyarrhythmias and conduction system disturbances. Additionally, injury to the conduction system, a rare occurrence, may result from small-vessel vasculitis, leading to various forms of atrioventricular block. Pericarditis may be associated with atrial fibrillation and flutter, although these are usually transient. Unexplained sinus tachycardia may also occur in SLE patients without obvious cardiac involvement and usually resolves with steroid therapy.[46]

A conduction system abnormality may occur in infants of mothers with SLE whose serum contains anti-Ro and anti-La antibodies. Some of these mothers may also have been previously diagnosed with primary Sjögren syndrome, whereas others may appear healthy. Fewer than 5% of women with anti-Ro and/or anti-La antibodies will give birth to infants with neonatal lupus syndrome or congenital heart block. Congenital heart block develops from the transmission of maternal anti-Ro and anti-La antibodies to the fetus, causing myocardial inflammation and fibrosis.[59] Additionally, the probability of congenital heart block

increases to almost 20% in subsequent offspring.[58] High-risk mothers with these serologic features should undergo fetal echocardiograms to look for evidence of myocardial dysfunction or screen for conduction system abnormalities by detecting a prolonged mechanical PR interval to identify a potentially reversible block.[60] Treatment with dexamethasone may be helpful in converting first- and second-degree heart block; however, third-degree heart block appears largely irreversible.[61]

Coronary Artery Disease

Coronary artery disease is prevalent in SLE and has emerged as a significant cause of morbidity and mortality for these patients.[62] Coronary artery disease may result from coronary arteritis or thrombosis, but is most often secondary to atherosclerosis. Making a diagnosis of coronary arteritis is challenging owing to the nonspecificity of the angiographic findings. It may require sequential angiographic studies showing changes in luminal blockages over time not expected with atherosclerosis. Coronary arteritis, if suspected, may be treated with high doses of corticosteroids, possibly in combination with another potent immunosuppressive agent such as cyclophosphamide. Coronary thrombosis may be associated with the presence of antiphospholipid antibodies (see next section) or embolism from a valvular vegetation, as seen in Libman-Sacks endocarditis.

Recent data suggest that subclinical atherosclerosis is highly prevalent amongst SLE patients.[62] Women with SLE between the ages of 35 and 44 years are 50 times more likely to have a myocardial infarction than are those without SLE.[63] Young women with SLE may have several risk factors for coronary atherosclerosis, such as hypertension, which may be secondary to renal disease and diabetes brought about or worsened by corticosteroid exposure. In epidemiologic studies, SLE has been shown to be an independent risk factor for cardiovascular disease, and this is supported with basic science data.[61] However, the mechanisms underlying this predisposition are unclear, and their relationship to the systemic inflammatory response in SLE remains an area of investigation. Recently, patients with SLE have been shown to produce proinflammatory forms of high-density lipoprotein that confer an increased risk for atherosclerosis.[64] It is important to recognize that because SLE is predominately a disease of young women and this group is at increased risk for coronary artery disease, prompt evaluation is warranted if they develop any symptoms of cardiac ischemia.

Drug-Induced Lupus

Drug-induced SLE (DIL) may be a rare complication of certain medications, including procainamide, quinidine, and hydralazine. Other medications associated with DIL include isoniazid, minocycline, clindamycin, and phenytoin. DIL, which affects males and females equally, is associated with the development of serum anti-histone antibodies, although only a few patients will actually develop the clinical syndrome. Common signs and symptoms of DIL include pericarditis, pleuritis, arthralgia, and fever. It is rare to develop renal or neurologic complications from DIL. The syndrome will usually resolve on its own after a short course of prednisone and discontinuation of the offending medication.[65]

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is a disorder characterized by the clinical triad of recurrent arterial or venous thromboses, pregnancy loss, and thrombocytopenia. Serologically, it is defined by the presence of anticardiolipin antibodies, anti-β_2 glycoprotein antibodies, or a positive lupus anticoagulant. APS may occur independently (primary APS) or in association with SLE or other autoimmune disease (secondary APS).

Because APS may produce thrombotic occlusion of many different types and sizes of blood vessels, it can produce a variety of cardiovascular manifestations. Valvular disease is the most common APS-related cardiovascular manifestation. It is seen in both primary and secondary APS and is essentially indistinguishable from Libman-Sacks endocarditis. Patients with asymptomatic valvular thickening should be treated with a low-dose daily aspirin (81 mg); however, those with evidence of vegetation or embolization should be treated with systemic anticoagulation (target INR 2-3).[66] Coronary artery disease and accelerated atherosclerosis have also been associated with APS, although it seems that all types of antiphospholipid antibodies do not equally contribute to atherosclerosis. In a study by Soltész and colleagues,[67] presence of lupus anticoagulant was more frequently associated with venous thrombosis, whereas anticardiolipin antibodies were more often associated with carotid, peripheral, and coronary artery disease. The link between myocardial infarction and APS is less certain. Although some studies have shown a positive correlation between serum antiphospholipid antibodies and myocardial infarction,[68,69] other large cohorts have not found this relationship.[70] Patients with a history of myocardial infarction should have aggressive treatment of all risk factors for atherosclerosis and be placed on statin therapy.[66] Intracardiac thrombi, cardiomyopathy, and pulmonary hypertension have also been associated with APS.[71] Overall, the immunosuppressive and antithrombotic management of APS has been somewhat controversial. Recent guidelines have agreed, however, that patients with definite APS and a first venous event receive oral anticoagulant therapy to a target INR of 2.0 to 3.0, grading this as a IA recommendation.[72] Other multidisciplinary task force recommendations agree, also assigning a grade of IA.[73]

DERMATOMYOSITIS AND POLYMYOSITIS

Dermatomyositis (DM) and polymyositis (PM) are two inflammatory muscle diseases in which there may be cardiovascular manifestations. Patients with DM usually present with skin involvement characterized by erythematous scaliness over the knuckles (Gottron papules), elbows, and knees, as well as periorbital swelling and a violaceous rash around the lids, known as a heliotropic rash. They may also display a photosensitive rash over the face, chest, and back in a shawl-like distribution. Both DM and PM are manifested by proximal muscle weakness and most affected individuals show increases in serum levels of muscle enzymes such as creatine kinase and aldolase. Although the pathophysiology of DM and PM is incompletely understood, these diseases are associated with a specific set of serum autoantibodies, including antiaminoacyl-tRNA synthetase (antihistidyl-tRNA synthetase and others), antisignal recognition particle, and anti-SNF2 superfamily nuclear helicase (anti-Mi-2). The histopathology of the muscle lesions is different in the two diseases. DM is characterized by a mixed T- and B-cell perivascular infiltrate with perifascicular atrophy. In contrast, muscle biopsies from patients with PM show a predominance of T cells and a diffuse or patchy inflammation of the muscle fascicles. DM may also be associated with a systemic angiopathy. In older patients, DM and PM may evolve as a paraneoplastic syndrome. Although these diseases primarily affect striated muscle, they may also cause cardiovascular complications.

Cardiovascular complications of DM/PM include pericarditis, conduction system abnormalities, heart failure, and myocarditis. Pericardial involvement has been noted most often in patients with overlap syndromes (ie, features of two or more connective tissue diseases). Conduction abnormalities, nonspecific ST-T changes, and left ventricular diastolic dysfunction have also been reported in DM/PM.[74] A serious cardiovascular complication is myocardial infarction secondary to coronary vasculitis.[75] Myocarditis may infrequently cause heart

failure, although newer imaging modalities, particularly cardiac MRI with gadolinium enhancement, may detect subclinical disease in as many as one-half of patients with DM/PM and be useful in monitoring response to therapy.[76]

It is important to rule out other forms of myopathy in patients who present with muscle weakness. Patients taking statins may develop a myopathy mimicking inflammatory muscle disease. Statin-related myopathy and inflammatory myopathy may be differentiated by certain aspects of the medical history (eg, statins usually associated with significant myalgia), the results of electromyography, and findings on muscle biopsy, if necessary. For statin-induced myopathy, withdrawal of the offending drug will lead to symptom resolution. The cornerstone of the treatment for DM/PM is high doses of corticosteroids, usually in doses of 1 mg/kg for several months with a slow taper. Adjunctive therapy often includes methotrexate or azathioprine. Intravenous immunoglobulin may be effective for treating refractory and severe cases.

SYSTEMIC SCLEROSIS

Systemic sclerosis (or scleroderma) is a rare disorder characterized by microvascular injury and excessive fibrotic changes that can affect multiple organ systems. Most commonly, systemic sclerosis causes hardening of the skin, but can also affect visceral organs, such as lungs, kidneys, and the heart. The diffuse or progressive type of systemic sclerosis results in widespread cutaneous involvement of the distal and proximal extremities as well as the trunk and is usually associated with early and serious visceral involvement. In contrast, limited cutaneous systemic sclerosis, also known as CREST syndrome, is characterized by calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias. Systemic sclerosis may be associated with late involvement of visceral organs, especially increased risk for pulmonary artery hypertension (PAH). Cardiovascular involvement of systemic sclerosis may occur with either the diffuse or limited forms, as well as overlap syndromes in which patients may have features of systemic sclerosis in combination with those of SLE, RA, or polymyositis.

Pericardial Disease

Pericardial disease in systemic sclerosis is usually benign. On the basis of autopsy results, the incidence of pericardial involvement is approximately 50%, but symptomatic pericarditis only manifests in approximately 16% of patients with diffuse scleroderma and in approximately 30% of patients with limited scleroderma.[77] Pericardial effusions rarely cause symptoms, although they can be detected in approximately 40% of patients by echocardiography. In most cases, the effusion is relatively small and of no clinical consequence. Routine pericardiocentesis in the absence of cardiac tamponade has no apparent effect on clinical outcomes.[77] Pericardial involvement can present either as acute pericarditis associated with dyspnea, chest pain, and pericardial friction rub, or as a chronic pericardial effusion leading to constrictive physiology. For the treatment of acute pericarditis, nonsteroidal anti-inflammatory therapy is recommended, provided renal function is unaffected. Pericardiocentesis or surgical intervention is considered only if pericarditis is complicated by tamponade or constriction or if acute infection is suspected. Corticosteroids are generally considered to be of limited benefit, but they may be lifesaving in the setting of associated myocarditis.

Myocardial Disease

Although interstitial lung disease (ILD) and PAH are the most common cardiopulmonary conditions that result in increased morbidity and mortality, other cardiac complications may occur. In one study, echocardiographic findings were analyzed over more than 5 years from 77 unselected patients with systemic sclerosis and compared with those from 45 normal subjects matched for age and sex.[78] At baseline, left ventricular (LV) systolic function was normal in both patients and controls, whereas LV diastolic function was found to be more prevalent in the patients compared with the controls (23 vs 1; $P < .001$). By the end of the follow-up period (~2-8 years), LV systolic dysfunction had developed in one patient, and diastolic dysfunction was documented in another six patients. Moreover, in the group with systemic sclerosis, diastolic dysfunction, left atrial dimension, and LV wall thickness significantly progressed over the course of the observation period. The change in LV diastolic function was independent of other factors including LV hypertrophy, systemic hypertension, age, and duration of disease, all of which could potentially affect LV relaxation. These results confirm that LV diastolic dysfunction is a frequent manifestation of systemic sclerosis.[78] Although diastolic dysfunction is common in this disease, it is rarely severe. When severe, diastolic dysfunction may worsen PAH.

Arrhythmias and Conduction System Disturbances

The most frequent cardiac rhythm disturbance is premature ventricular contractions, often appearing as monomorphic, single ectopic events, or rarely as bigeminy, trigeminy, or couplets.[79] Transient atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia have been reported in 20% to 30% of patients with systemic sclerosis. Nonsustained ventricular tachycardia has been described in 7% to 13%, whereas sudden cardiac death has been reported in 5% to 21% of unselected patients with systemic sclerosis. Conduction disturbances occur in 25% to 75% of patients. Although conduction abnormalities are mostly due to fibrosis in the sinoatrial node, direct involvement of the cardiac conduction tissue also occurs, leading to disturbances such as bundle and fascicular blocks.[76]

Pulmonary Arterial Hypertension

PAH is another serious cardiopulmonary complication of systemic sclerosis. It is included in the first group of the World Health Organization classification of pulmonary hypertension, characterized by precapillary PH with pulmonary capillary wedge pressure ≤ 15 mm Hg.[80] Primary pulmonary arteriopathy occurs most commonly in patients with the limited cutaneous form of systemic sclerosis. Although at autopsy 65% to 80% of patients with systemic sclerosis have histopathologic changes consistent with PAH, fewer than 10% develop clinically apparent disease.[81] PAH should always be considered in the setting of dyspnea or right-heart failure in patients with systemic sclerosis. Patients with PAH associated with systemic sclerosis appear to have a worse prognosis than patients with idiopathic PAH, showing an untreated 2-year survival rate as low as 40%.[82] Although there are an increasing number of clinical trials demonstrating the benefit of available PAH specific therapy (described later) and likely improvement in prognosis,[83] patients with scleroderma-related PAH still have a less favorable outcome than those with idiopathic PAH.[84]

The three main categories of medications used to treatment PAH include prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors. Randomized clinical trials in patients with PAH have often included PAH associated with systemic sclerosis and as such have led to approval by the US Food and Drug Administration of a number of agents for this patient population. The largest prospective, randomized trial to date that has focused on PAH in systemic sclerosis was a study of 111 patients with moderate to severe pulmonary hypertension.[86] It demonstrated that continuous intravenous epoprostenol therapy delivered over 12 weeks improved

exercise capacity and cardiopulmonary hemodynamics. Newer agents like selexipag, a non-prostanoid oral IP receptor agonist, and riociguat, a soluble guanine cyclase receptor agonist, are also now approved for PAH associated with systemic sclerosis.[87,89] Improvement has been shown using the standard 6-minute walk test, although some studies have shown benefit in pulmonary hemodynamics and quality of life.

Although lung or heart-lung transplantation has been performed in patients with ILD or severe PAH due to systemic sclerosis, this approach has been somewhat controversial. Several studies suggest that outcomes of patients with systemic sclerosis undergoing lung transplant were not significantly different from those of patients transplanted for other lung conditions during the same period.[88,90] Gastrointestinal dysmotility and associated gastroesophageal reflux are substantial concerns, as aspiration has been associated with chronic allograft rejection.[91] Unfortunately, patients with systemic sclerosis and PAH or ILD that might be severe enough for transplant commonly have multiple morbidities that render them less than ideal lung transplant candidates.

Finally, it is important that cardiopulmonary rehabilitation be considered in appropriately selected patients with systemic sclerosis and associated cardiopulmonary disease.[85] Caution is important with advanced pulmonary hypertension and syncope, as such patients should refrain from intensive rehabilitation.

SERONEGATIVE SPONDYLOARTHROPATHIES

The seronegative spondyloarthropathies (characterized by the absence of serum rheumatoid factor) are a group of multisystem inflammatory diseases sharing common features, including spinal or sacroiliac involvement, enthesitis (inflammation at the sites where tendons and ligaments insert onto bones), and a high incidence of HLA-B27. Among this group of related diseases are ankylosing spondylitis, reactive arthritis (previously referred to as Reiter syndrome), psoriatic arthritis, and inflammatory bowel disease–associated arthritis. In the United States, up to 10% of healthy Caucasians are positive for HLA-B27; the incidence is much lower in African Americans and Asians. HLA-B27 is most strongly associated with ankylosing spondylitis in Caucasians, occurring in 90% of patients with this disorder. Although most patients with ankylosing spondylitis will test positive for HLA-B27, it should be noted that the majority of patients with HLA-B27 do not have a spondyloarthropathy. A medical history and examination indicative of inflammatory spinal disease and enthesitis and typical radiographic findings form the basis for diagnosis after excluding other forms of inflammatory arthritis such as RA. In contrast to RA, the spondyloarthropathies occur more commonly in males than females and do not usually involve the small joints of the hands in a symmetrical pattern. Peripheral arthritis tends to involve larger, usually lower-extremity joints in an asymmetric distribution.

Among the group of spondyloarthropathies, ankylosing spondylitis and reactive arthritis are the most frequently associated with cardiovascular manifestations. The two most prevalent cardiovascular manifestations of the spondyloarthropathies are conduction system disease and aortitis, with or without aortic insufficiency. The conduction system disease presents mainly as atrioventricular block, which occurs more commonly in males that are HLA-B27 positive than in females; it often requires permanent pacemaker placement. Electrophysiologic studies reveal the block to be at the level of the AV node; it is usually not fascicular.[92] Aortic root involvement is also associated with HLA-B27 in patients with ankylosing spondylitis[93] and reactive arthritis.[94] Aortitis may lead to dilatation and stiffening of the aortic root with aortic valvular regurgitation. Aortic valvular regurgitation is usually a late complication of the spondyloarthropathies.[86] Other less common cardiac manifestations associated with spondyloarthropathies include clinically insignificant diastolic dysfunction, supraventricular tachycardias (especially atrial fibrillation),[92] myocarditis, and pericarditis.

Treatment of the spondyloarthropathies was previously limited to nonsteroidal anti-inflammatory drug therapy and physical therapy. More recent studies clearly demonstrate the clinical efficacy of TNFα inhibitors for treating symptoms of spondylitis. It is unknown whether the TNFα inhibitors will ameliorate cardiovascular manifestations of the spondyloarthropathies. Surgery has been successful for managing severe aortic regurgitation associated with ankylosing spondylitis.[95]

SYSTEMIC VASCULITIDES

The systemic vasculitides are multisystem diseases whose hallmark is inflammation of blood vessels (Table 100–2). Categorization of these diseases is based on the size of vessel involved (small, medium, and large) and the nature of organ system involvement. Vasculitis may be primary or secondary (eg, identifiable trigger such as a drug or infection). Primary vasculitides are presumably due to immune dysregulation in which genetic factors and environmental insults may play roles in their pathogenesis.

Giant-Cell (Temporal) Arteritis

Giant-cell arteritis (GCA), also known as temporal arteritis, is the most common vasculitis among patients older than 50 years.[96] It is more common in women than in men and seems to be more prevalent in persons of Northern European descent than African Americans. The clinical hallmarks of GCA are temporal artery tenderness, headache, jaw claudication, and visual loss. Many patients also manifest constitutional symptoms, such as fatigue and fever, and approximately one-third of cases are associated with polymyalgia rheumatica. Almost all patients with GCA have an elevated erythrocyte sedimentation rate (usually exceeding 50 mm/h) and serum C-reactive protein level. Temporal artery biopsy, the gold standard for diagnosis, shows evidence of transmural chronic granulomatous inflammation with destruction of elastic laminae. Negative biopsy results may indicate that the biopsy missed the area of vascular pathology (sampling error due to skip lesions), the biopsy was done on the wrong temporal artery (unilateral biopsy), the sample was too small (< 2 cm), or the patient does not have GCA. The disease may also target the extracranial large artery branches of the aortic arch. Peripheral artery involvement has become increasingly recognized as a complication of GCA and may be the presenting feature of this disease. Signs and symptoms of peripheral large artery involvement include intermittent upper-extremity claudication, decreased or absent peripheral pulses, and bruits over affected vessels.

GCA may also lead to thoracic and abdominal aortic aneurysm. In one study, 16 of 41 patients with GCA and aortic aneurysm had an acute aortic dissection, with 8 deaths.[97] Given these findings, it has been recommended that patients with GCA undergo yearly screening for aortic aneurysm using transthoracic echocardiography and abdominal ultrasonography.[98] Other cardiovascular complications rarely associated with GCA are pericarditis, myocarditis, and coronary arteritis.[99]

Although temporal artery biopsy remains the diagnostic gold standard for GCA, advances in imaging techniques have provided new diagnostic tools for assessing patients with this disease. A noninvasive approach for detecting vasculitis of the temporal arteries is duplex ultrasonography. Ultrasonography of involved temporal arteries demonstrates segmental, concentric hypoechogenic thickening of the arterial wall ("halo sign"). Sonography can also be important in diagnosis, assessment, and follow-up of peripheral artery disease.[100] Computed tomography (CT) angiography and magnetic resonance angiography (MRA) have the added capability of detecting mural inflammation,

TABLE 100–2. Common Clinical and Cardiovascular Manifestations of the Systemic Vasculitides

Disease	Vessel Size Involved	Clinical Manifestations	Cardiovascular Manifestations
Giant-cell vasculitis	Large	Temporal artery tenderness, headache, jaw claudication, visual loss, most patients > 50 y old, highest prevalence in northern Europeans	Aortitis, aortic dissection, limb claudication
Takayasu arteritis	Large	Fever, malaise, weight loss, arthralgia, headaches and myalgia; higher prevalence in women in their 30s and Asians	Upper-extremity claudication, "pulselessness," chest pain, hypertension from renal artery stenosis
Kawasaki disease	Large and medium	Fever, desquamative rash, conjunctivitis, lymphadenopathy; disease of children	Coronary arteritis and aneurysms
Wegener granulomatosis	Medium and small	Pansinusitis, nasal blood discharge, oral ulcers, and subglottic stenosis, hemoptysis with pulmonary infiltrates	Pericarditis, cardiomyopathy, and coronary arteritis
Churg-Strauss syndrome	Medium and small	Asthma, eosinophilia, and pulmonary infiltrates usually secondary to pulmonary vasculitis	Cardiomyopathy (restrictive or dilated), coronary arteritis
Polyarteritis nodosa	Medium	Nodules on the skin, neuropathy in the form of a mononeuritis multiplex, gastrointestinal vasculitis with abdominal pain, hypertension, sparing of the lungs	Congestive heart failure, angina, myocardial infarction, and pericarditis
Behçet disease	All sizes	Oral and genital ulcerations	Aortitis

aneurysms, and luminal narrowing[101] (Fig. 100–3). Although both CT angiography and MRI/MRA can provide excellent vascular detail, MRI/MRA does not expose the patient to ionizing radiation. Additionally, further information can be ascertained by MRI/MRA about the extent of arterial wall edema using gadolinium enhancement. Because arterial wall edema may correlate with the degree of vessel inflammation, MRI may be more useful than ultrasound for evaluating the extent of vessel inflammation and therefore may be superior for monitoring treatment response.[102] Finally, in recent studies, fluorine-18-deoxyglucose (FDG) positron emission tomography has been shown to be useful for detection of large-vessel vasculitis.[103] It is a whole-body scan that reportedly can detect arteritis at very early stages, and although it holds some promise, its use is still restricted by high costs and the relatively high radiation exposure.[101] Additionally, atherosclerosis can also increase uptake of FDG in the larger vessels, raising some problems with diagnostic specificity.

FIGURE 100–3. Magnetic resonance (MR) angiogram of giant-cell arteritis. MR angiogram, obtained in coronal projection of a patient with giant-cell arteritis, showing multiple stenoses of the left subclavian artery, a long segment of occlusion within the left axillary artery, and mild to moderate stenosis at the origin of the right common carotid artery (*arrow*).

Corticosteroids are the mainstay of therapy for GCA. High doses of prednisone (0.7-1 mg/kg/d) are employed initially and are then tapered slowly, depending on clinical improvement and the decrease in serum levels of acute phase reactants. Many patients with GCA do not achieve remission with high doses of prednisone and require long-term maintenance with prednisone in low doses. Other immunosuppressive agents, such as methotrexate, may be combined with prednisone, but the evidence supporting their clinical efficacy in this situation remains conflicting.[104] Controlled trials have failed to establish a role for TNFα inhibitors in the treatment of GCA.[105] However, in a case-control study, the addition of a low dose of aspirin reduced the rate of blindness and stroke in patients with GCA by three- to fourfold compared with those patients who did not receive aspirin.[106,107] In the absence of any contraindications, low-dose aspirin should be given to all patients with GCA.

Takayasu Arteritis

Takayasu arteritis (TA) is another large-vessel vasculitis that histologically is indistinguishable from GCA, but occurs preferentially in young women. It tends to affect the aorta and its major branches. It is a rare disease in the United States, with an estimated incidence in one study of 2.6 cases per million per year.[108] However, it is more common in women of Japanese, Indian, and African descent. Classically, clinical presentation begins with systemic manifestations such as fever, malaise, weight loss, arthralgias, and myalgias. Arterial stenoses are more common than aneurysms, and therefore the most common signs and symptoms are those of arterial occlusion, including "pulselessness," claudication, headaches, and chest pain. TA is often associated with hypertension, often secondary to renal artery stenosis, although this finding may be missed because subclavian stenosis may cause falsely low peripheral

blood pressure readings. Aneurysms may also develop secondary to large-vessel involvement, most commonly in the aortic root.

Diagnosis of TA is usually based on the results of vascular imaging studies that show a pattern of vascular involvement typical of this disease. Most patients with TA have elevated serum levels of acute-phase reactants, reflecting the systemic nature of the inflammatory response. Biopsies are not usually obtained for diagnosis because of the inaccessibility of the affected tissue. For the treatment of TA, patients usually receive initial dosing of prednisone at 1 mg/kg/d. Relapses are common when the steroids are tapered. If patients are refractory to corticosteroid therapy, then methotrexate or cyclophosphamide may be considered as an adjunctive immunosuppressive drug or steroid-sparing agent. The progression of disease may be monitored by repeat testing of acute-phase reactant levels and serial imaging studies, such as CT angiography or MRI/MRA (Fig. 100–4). However, normalization of acute-phase reactant levels does not necessarily exclude progression of vascular disease. Patients with TA frequently require vascular bypass surgery to correct clinically significant stenosis, especially in the setting of transient ischemic attacks and renal artery stenosis with hypertension. More recently, endovascular stents have been used in patients with chronic inactive TA lesions and appear to be associated with a good outcome.[109] Finally, aortic valve replacement may be necessary in patients with aortitis and severe aortic regurgitation.

Kawasaki Disease

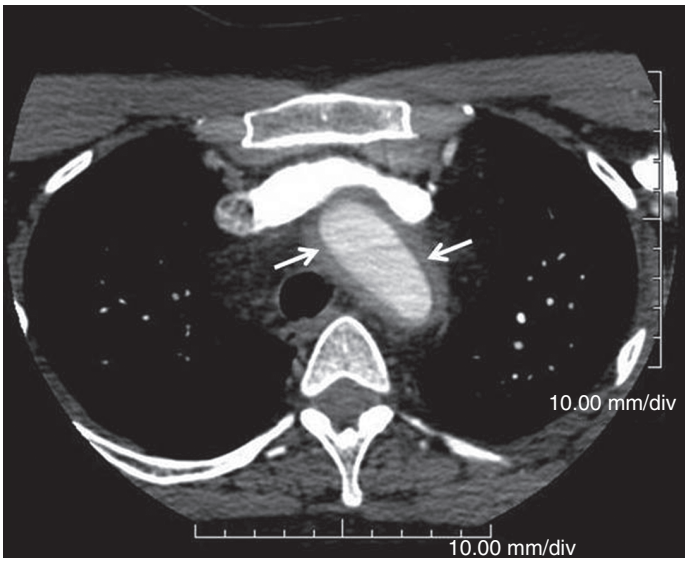
Kawasaki disease is an acute febrile illness affecting children from ages 6 months to 8 years. In the United States, its annual incidence is approximately 6 per 100,000 children younger than 5 years, occurring, in order of decreasing frequency, in children of Asian, African American, and Caucasian race. Although the etiology of this disease is unknown, epidemiologic studies have highlighted the geographic clustering of Kawasaki disease cases, and therefore it is speculated that this disease may be triggered by an infectious agent. The affected child presents with fever, desquamative rash, conjunctivitis, and lymphadenopathy.

During this acute phase of Kawasaki disease, the cardiovascular system may be affected in various ways. Pericarditis, myocarditis, mitral regurgitation, aortitis, aortic regurgitation, congestive heart failure, and arrhythmias have all been described in this illness.[110] Coronary vasculitis develops in as short a time as 2 weeks after symptom onset, but usually within 4 weeks after the onset of fever. If left untreated, this process may lead to the development of coronary aneurysms, the most serious complication of this disease.[111] Aneurysms measuring larger than 8 mm by echocardiography, termed *giant aneurysms*, are the most likely to thrombose and cause myocardial infarction. These giant aneurysms are also the least likely to regress with therapy.

Clinical studies of Kawasaki disease have shown that treatment with intravenous immunoglobulin (IVIg) and aspirin reduces the development and progression of coronary aneurysms.[112] IVIg is given at 2 g/kg as a single infusion, whereas aspirin is administered at 80 to 100 mg/kg/d.[113] The American Heart Association recommends long-term follow-up of children with multiple giant aneurysms or known obstructive lesions because of the risk for further cardiac complications. Management for these patients includes chronic low-dose aspirin therapy, stress testing in adolescence, and coronary artery bypass or percutaneous intervention if lesions are severe enough to be symptomatic.[114]

Wegener Granulomatosis

Wegener granulomatosis (WG) is a systemic necrotizing vasculitis of small vessels mainly targeting the respiratory tract and the kidneys.



A

B

FIGURE 100–4. Computed tomography (CT) angiogram of Takayasu arteritis. **A.** CT angiogram (axial image) of the aortic arch of a patient with Takayasu arteritis demonstrating marked thickening of the wall of the aortic arch (*arrows*). **B.** Three-dimensional volume-rendered image of the abdominal aorta of the same patient demonstrating several areas of narrowing (*arrows*) as a result of vasculitis.

Upper respiratory involvement may consist of pansinusitis, nasal blood discharge, oral ulcers, and subglottic stenosis. Symptoms of lung involvement are cough, dyspnea, and hemoptysis. The chest x-ray may show pulmonary nodules with or without cavitation, transient infiltrates, or evidence of alveolar hemorrhage. Glomerulonephritis is a harbinger of poor outcomes. Renal biopsy reveals the classic features of a pauci-immune, focal, segmental necrotizing glomerulonephritis. The laboratory hallmark of WG is the presence of serum antineutrophil cytoplasmic antibodies (ANCA). There are two predominant ANCA patterns: C-ANCA and P-ANCA, which are associated with serum

antibodies to proteinase-3 and myeloperoxidase, respectively. WG is predominately associated with anti–proteinase-3 antibodies, but a minority of patients with this disease have anti-myeloperoxidase antibodies. It is important to recognize that serum ANCA may be absent in some patients with WG, especially those with less severe forms of the disease.

In one study, cardiac involvement, including cardiomyopathy, pericarditis, and coronary arteritis, was described in 6% of 158 patients with WG.[115] Additionally, there have been case reports of aortic regurgitation and high-grade atrioventricular block. A recent study also suggested that patients with WG are at a significantly increased risk for complications of ischemic heart disease.[116]

Overall, the prognosis for severe WG has improved with the use of corticosteroid therapy combined with daily oral cyclophosphamide.[115] Studies also support the use of methotrexate combined with oral prednisone for treatment of patients with non–life-threatening WG.[117] Surgical valve replacement and pericardiectomy have been performed for hemodynamically or clinically significant valvular disease or constrictive pericarditis, respectively.[118,119]

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS) is a relatively rare type of systemic vasculitis characterized by asthma, peripheral eosinophilia, and radiographic evidence of pulmonary infiltrates usually secondary to pulmonary vasculitis. Histopathologic lesions usually reveal a small- and medium-sized vessel vasculitis with eosinophilic granulomas, distinguishing CSS from the medium-sized vessel vasculitis called polyarteritis nodosa. Other target organs of CSS include the kidneys, central nervous system, skin, and heart.

Heart disease is particularly prominent in CSS, with involvement of the cardiovascular system in up to 60% of cases; more importantly, it is the most common cause of death in these patients.[120] The pathophysiology for the development of cardiac disease has not been elucidated, and it is unclear whether manifestations such as cardiomyopathy are a result of small-vessel vasculitis, eosinophilic infiltration of the myocardium leading to fibrosis, or a combination of both processes. Pericardial effusion, myocardial infarction, and myocarditis have also been reported in patients with CSS. Treatment of CSS with corticosteroids is usually very effective in the early stages of disease, although critically ill patients usually require treatment with a second immunosuppressive agent, such as cyclophosphamide. Patients with severe cardiomyopathy have undergone heart transplant with mixed results.[121]

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is another relatively rare vasculitis that predominately affects the medium-sized arteries without granuloma formation. The evolution of the nosology of the systemic vasculitides has led to some recent confusion between the classification of PAN and microscopic polyangiitis (MPA). Patients with small-vessel involvement such as pulmonary capillaritis or glomerulonephritis are now deemed to have MPA and not classic PAN, and therefore many older studies of PAN have included patients with both classic PAN and MPA. The clinical presentation of PAN varies according to the affected organ system. Common manifestations include painful nodules on the skin, neuropathy in the form of a mononeuritis multiplex, gastrointestinal vasculitis with abdominal pain, and hypertension; characteristically, the lungs are spared.[122]

Cardiovascular complications of PAN have been reported in approximately 10% of patients in clinical studies and up to 78% in a histologic study.[120] The most common cardiovascular manifestations are heart failure, angina, myocardial infarction, and pericarditis. Various arrhythmias, mainly supraventricular tachycardias, have been associated with PAN, as well as hypertension from renal involvement. Treatment of PAN is similar to that of CSS and the other systemic necrotizing vasculitides. High-dose corticosteroids are the mainstay for initial treatment, with the addition of cytotoxic agents such as cyclophosphamide in severe cases. Overall, PAN is considered a more severe disease than CSS, with a higher incidence of mortality.[123]

Behçet Disease

Behçet disease is rare in the United States, but is prevalent in the countries bordering the Mediterranean and in Japan. Behçet disease consists of the clinical triad of oral and genital ulcerations as well as recurrent uveitis. Patients with Behçet disease may also develop vasculitis affecting blood vessels of different sizes, including the small-, medium-, and large-sized vessels.[124] Medium and large artery lesions are often aneurysmal. In addition, patients with Behçet disease are at risk of developing thrombosis of the deep veins of the lower extremities. Cases have been described of occlusive and aneurysmal lesions of the coronary arteries that have led to myocardial infarction.[125,126] Treatment of Behçet relies mainly on corticosteroids as well other immunomodulatory agents, such as methotrexate or azathioprine. Chronic anticoagulation is recommended for patients with recurrent thromboses.

CARDIOVASCULAR MANIFESTATIONS OF CONNECTIVE TISSUE DISEASES

The connective tissue diseases are a group of heritable conditions that can affect skin, joints, and vasculature. The following section reviews the most common connective tissue diseases that affect the cardiovascular system (Table 100–3).

MARFAN SYNDROME

Marfan syndrome is among the most prevalent of the heritable connective tissue diseases, with an estimated worldwide prevalence of 1 per 3000 to 5000 persons.[127] Although up to one-third of patients have no family history of Marfan syndrome, most cases are inherited as a result of a high penetrance of an autosomal-dominant mutation in the fibrillin (*FBN1*) gene. More than 1000 mutations in the *FBN1* gene have been identified to date. Marfan patients often have a tall stature, long extremities, high-arched palate, joint hypermobility, and ectopia lentis. Additionally, they can have musculoskeletal abnormalities including a pectus excavatum or carinatum chest deformity or scoliosis. Because some of these features are present in the general population, there has been increased attention given to improving the classification of this disease. The 2010 Ghent criteria place emphasis on aortic root dilatation, aortic dissection, and ectopia lentis as cardinal clinical features of Marfan syndrome and on testing for mutations in the FBN1 gene.[128]

The complications of Marfan syndrome with potential lethality involve the cardiovascular system. Such patients may develop dilatation of the proximal ascending aorta, dilatation of the proximal pulmonary artery, mitral valve prolapse, and cardiomyopathy. The fibrillin gene encodes proteins essential for the proper formation of microfibrils that uphold the integrity of the extracellular matrix. Patients with Marfan syndrome who have mutations in these genes produce a "weak collagen" in the arterial walls. In the aorta, these changes reduce vessel distensibility and increase wall stiffness. These effects, coupled with the hemodynamic stress in high-flow areas, over time lead to the development of aneurysms, which can be complicated by intimal dissection. Aortic root dilatation causes stretch of the aortic valve, which may lead to aortic valve regurgitation. Mitral valve prolapse is also commonly

TABLE 100–3. Cardiovascular Features of Connective Tissue Disease

Disease	Inheritance	Clinical Features	Cardiovascular Features	Gene
Marfan syndrome	AD	Tall stature, arachnodactyly, pectus excavatum, ectopia lentis	Aortic aneurysm/dissection, mitral valve prolapse	*FBN1*
Loeys-Dietz syndrome	AD	Hypertelorism, cleft palate/bifid uvula, arachnodactyly, easy bruising, pectus excavatum	Aortic aneurysm with tortuosity (corkscrew strictures), patent ductus arteriosus, bicuspid aortic valves	*TGF-βR*
Ehlers-Danlos syndrome	AD or AR	Joint hypermobility, hyperelastic skin, easy bruising (6 types of EDS; type 4 or vascular type is most associated with cardiovascular manifestations)	Aortic aneurysm, mitral valve prolapse	*COL3A1* (for type 4 vascular type)
Pseudoxanthoma elasticum	AD or AR	Hyperelastic skin, yellowish papular lesions on neck, axillae, groin, and flexural creases; angioid streaks	Intermittent claudication, coronary artery disease, angina	*ABCC6*
Osteogenesis imperfecta	AD	Blue sclerae, hearing loss, easy bruising increased risk of bleeding, and brittle bones (8 types of OI)	Aortic regurgitation, aortic root dilatation, aortic dissection, mitral regurgitation	*COL1A1 COL1A2*

Abbreviations: *ABCC*, ATP binding cassette subfamily C; *COL3A1*, collagen type 3 α-1; *COL1A1*, *COL1A2*, collagen type 1 α 1 and α 2; *FBN1*, fibrillin-1; *TGF-βR*, transforming growth factor β receptor.

associated with Marfan syndrome and occurs in up to one-quarter of patients. It may lead to mitral regurgitation, which if severe and uncorrected, can result in a dilated cardiomyopathy.[129] Cardiomyopathy in the absence of valvular disease has also been reported in patients with Marfan syndrome and is believed to be secondary to defective cardiac muscle function from fibrillin mutations.[130]

Life expectancy has significantly improved with proper identification and monitoring of patients with Marfan syndrome. The most common causes of death in these patients are rupture of an ascending aortic aneurysm with or without dissection or heart failure from aortic or mitral regurgitation. It is important that Marfan patients be counseled to avoid isometric or strenuous exercise, including contact sports (Table 100–4).

It is currently recommended that all Marfan patients receive the maximum-tolerated dose of a beta-blocker. The beneficial effects of beta-blockade are reduction in heart rate and in the rate of pressure increase in the aorta, which leads to less cumulative stress on the aorta.[131] Additionally, beta-blockers have demonstrated to both decrease the rate dilatation of the ascending aorta and to improve survival.[132] The addition of an angiotensin-converting enzyme should also be considered in this patient population. In a large prospective randomized trial of 233 patients with Marfan syndrome, the addition of losartan slowed aortic root enlargement.[133]

Patients with Marfan syndrome should undergo annual echocardiography. Recommendations vary with respect to the optimal time for prophylactic surgical intervention. The most recent guidelines recommend prophylactic surgery in patients with an aortic diameter of 5.0 cm or more, or in those with a diameter of 4.5 cm and one of the following: experiencing severe aortic valve regurgitation, undergoing aortic valve replacement, or having a family history of complications. Those with an annual growth rate of greater than 0.5 cm are also considered for prophylactic surgery.[134] After surgical intervention, yearly MRI or CT scan is recommended to monitor the graft.

Finally, female Marfan patients of child-bearing age should be counseled regarding the relatively high risk of transmission of their disease to their offspring. Further, if a woman already has aortic root dilatation greater than 40 mm, pregnancy should be avoided due to the high risk of complications when systemic blood pressure is increased during delivery. If the aortic root is less than 40 mm, then pregnancy need not be avoided. However, the woman must be carefully monitored during pregnancy with monthly or bimonthly transthoracic echocardiograms and have strict blood pressure goals to prevent stage II hypertension.[134]

TABLE 100–4. Task Force 4 Recommendations for Athletes With Marfan Syndrome

Marfan Syndrome Abnormality	Recommended Sports Participation Level	Class of Recommendation
No aortic root dilation, moderate to severe mitral regurgitation, or family history of dissection of sudden death[a]	Low and moderate static/low dynamic competitive sports No sports with potential for bodily collision	IA and IIA[b]
Aortic root dilatation > 40 mm, prior surgical aortic root construction, chronic aortic dissection, moderate to severe mitral regurgitation, family history of dissection or sudden death	Low-intensity competitive sports No sports with potential for bodily collision	IA[b]

[a]These patients should have echocardiographic measurement of aortic root dimension repeated every 6 months.
[b]IA: Evidence obtained from meta-analysis of randomized controlled trials. IIA: Evidence obtained from at least one well-designed controlled study without randomization.
Data from Maron BJ, Ackerman MJ, Nishimura RA, et al. Task Force 4: HCM and other cardiomyopathies, mitral valve prolapse, myocarditis, and Marfan syndrome. *J Am Coll Cardiol.* 2005;45(8):1340-1345.

LOEYS-DIETZ SYNDROME

Loeys-Dietz types I and II are among the more recently recognized of the heritable connective tissue diseases; their associated mutations reside in the genes encoding the transforming growth factor β receptors 1 and 2.[135] Although these patients were previously categorized as having either Marfan syndrome or Ehlers-Danlos syndrome of the vascular type, more sophisticated molecular analysis has led to disease reclassification. Similar to patients with Marfan syndrome, these patients may have aortic aneurysms and musculoskeletal abnormalities such as scoliosis or pectus excavatum. However, patients with type I Loeys-Dietz also display the clinical triad of hypertelorism, either bifid uvula or cleft palate, or both, and generalized vascular aneurysms.

The type II patients are characterized by cutaneous manifestations such as velvety translucent skin, easy bruising, and widened atrophic scars that are also seen in patients with Ehlers-Danlos vascular type. Loeys et al[135] studied 52 affected families and found that patients with Loeys-Dietz type I had shorter lives and underwent cardiovascular surgery earlier than type II patients. There was rapid formation of arterial aneurysms and a high incidence of pregnancy-related complications in both types. Distinguishing patients with Loeys-Dietz syndrome and transforming growth factor β receptor mutations from patients with Marfan syndrome and Ehlers-Danlos syndrome is important for guiding medical therapy, making decisions about the optimal timing of prophylactic surgery, and management of pregnancy. Aortic disease appears to be more aggressive in patients with Loeys-Dietz disease.[136] Current criteria for elective intervention for asymptomatic aneurysms in adults with Loeys-Dietz syndrome include an aortic diameter > 4.2 cm by TEE (internal diameter) or 4.4 to 4.6 cm or greater by CT and/or MRI (external diameter), and/or rapid expansion (> 0.5 cm/yr).[134,136]

EHLERS-DANLOS SYNDROME

Ehlers-Danlos syndrome comprises a group of disorders that are characterized by hyperextensibility of skin, easy bruising, and joint hypermobility. There are six clinical types of Ehlers-Danlos syndrome; the vascular type, or type IV, is associated with mutations of the *COL3A1* gene. Its prevalence is estimated to be 1 case per 100,000 to 250,000 persons and this subtype primarily affects the cardiovascular system.[137] Ehlers-Danlos of the vascular type, which can mimic Loeys-Dietz syndrome, leads to diffuse vascular aneurysms (including the thoracic and abdominal arteries) that have a tendency for spontaneous rupture. Although prophylactic surgery for thoracic aortic aneurysms for Loeys-Dietz and Marfan syndrome is well established, its role in Ehlers-Danlos is not clear. This is likely due to tissue fragility, a tendency to hemorrhage extensively, and poor wound healing that may complicate the surgical repair.[134] Approximately one in four people with vascular type Ehlers-Danlos syndrome develop morbidity by 20 years of age, and more than 80% develop life-threatening complications by age 40.[138] Pregnant women must receive care from a team of specialists familiar with high-risk situations because of the propensity for vascular complications and uterine rupture.

FAMILIAL THORACIC AORTIC ANEURYSMS AND DISSECTIONS

Familial thoracic aortic aneurysms and dissections are autosomal dominant diseases that account for approximately 20% of thoracic aortic aneurysms and dissections.[139] Although several gene mutations have been linked to this disease, the *ACTA2* gene mutation is the most common, accounting for approximately 14% to 20% of cases.[140] Mutation in *ACTA2* primarily affects the function of sarcomeres found in the vascular smooth muscle in the walls of the aorta. The sarcomeres lose the ability to prevent the aorta from stretching as blood courses through. As a result, patients develop aortic root dilatation, aneurysms, and eventual dissections. The second most common gene mutation is the *TGFBR2*, which interestingly is the same gene that is mutated in approximately two-thirds of patients with Loeys-Dietz syndrome. And much like Loeys-Dietz disease, aortic dissections occur in patients with *TGFBR2* mutation at diameters less than 5.0 cm, leading to the recommendation that aortic repair be considered at an internal diameter by echocardiography of 4.2 cm or greater.[134] Other gene mutations include *FBN1, TGFBR1, COL3A1*, and *MYH11*. If a mutant gene is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation should undergo aortic imaging. [134]

PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum is a rare disorder with an estimated prevalence of between 1 in 25,000 and 1 in 100,000 persons that can be transmitted either as an autosomal dominant or recessive trait.[141] It is characterized by progressive accumulation of mineral precipitants within elastic fibers of the skin, eyes, gastrointestinal tract, and blood vessels. Clinically, patients display yellow macules or papules on their skin that have a cobblestone appearance at areas where there is flexion, such as the axillae, groin, and popliteal spaces. They also develop angioid streaks on the retina that represent breaks in Bruch's membrane behind the eye. Mutations in the gene *ABCC6* (R1141X) have been implicated in the development of this disease, as well as in the increased risk for developing coronary artery disease in this setting.[142] The vascular manifestations of the disease are secondary to degeneration of the elastic lamina of blood vessels and subsequent development of calcifications. Clinical manifestations are angina, claudication, and gastrointestinal bleeding.

Echocardiography of affected patients may reveal calcification of the atrial and ventricular endocardium, valves, and calcified thrombi, which can result in mitral valve prolapse, mitral valve stenosis, or restrictive cardiomyopathy.[143] Surgery has been used to remove these calcium deposits, but otherwise, management involves proper identification of affected patients, strategies to reduce the propensity for bleeding, and intensive management of blood cholesterol levels.

OSTEOGENESIS IMPERFECTA

Another heritable connective tissue disease is osteogenesis imperfecta, also known as *brittle bone disease.* Individuals with this rare condition are susceptible to skeletal fractures from mild trauma. The disease occurs secondary to mutations in type 1 collagen, producing disease of varying clinical severity ranging from severe phenotypes that cause death *in utero* to mild phenotypes that may remain undetected until adulthood. Typical manifestations include blue sclerae, hearing loss, easy bruising, and increased risk of bleeding. Cardiovascular manifestations consist of aortic regurgitation, aortic root dilatations, aortic dissection, and mitral regurgitation.[144] Patients with severe valvular disease may require valve replacement surgery, although invasive procedures are problematic given the friability of tissues, easy bleeding, and poor wound healing.

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CHAPTER 101

THE DIAGNOSIS AND MANAGEMENT OF CARDIOVASCULAR DISEASE IN PATIENTS WITH CANCER

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INTRODUCTION AND EPIDEMIOLOGY

With the advent of more effective cancer treatments and the increasing likelihood of an earlier cancer diagnosis, patients with many forms of cancer can expect to either be cured of their disease or have their disease stabilized by maintenance therapy. Although the overall rate of cancer incidence has declined since the early 2000s,[1] cancers necessitating aggressive chemotherapy, including melanoma, non-Hodgkin lymphoma, leukemia, and those of the pancreas and esophagus have been on the rise. Accompanying this trend, the length of cancer survival has increased for all cancers combined. The 5-year survival rate for all cancers combined improved from 66.7% in 2003 to 68% in 2009.[1] This implies that cancer survivors now live longer, allowing the manifestation of potential cardiac side effects of chemotherapeutic agents as well as the age-related increase in the risk of cardiovascular disease.

For individuals free of cardiovascular disease at 50 years of age, more than half of men and nearly 40% of women will develop cardiovascular disease during their remaining lifetime. Other than the extended survival of cancer patients and the aging population, there has been an increase in the recognition of chemotherapy-induced cardiotoxicity, adding to the linkage between patients with cancer and their risk for cardiovascular diseases. In addition, some patients with cancer may be at a higher risk for cardiovascular complications as compared with the general population.[2] Multiple classes of potentially cardiotoxic anticancer agents are currently being developed. Indeed, the combination of increased use of chemotherapy, overall increased survival, and development of newer agents have led to the emergence of chemotherapy-induced cardiotoxicity as a growing public health issue.

Moreover, one of the most significant late toxicities in survivors of childhood cancers is late-onset cardiotoxicity, largely as a result of anthracycline and chest-directed radiation exposure. Survivors also have an increased prevalence of traditional cardiovascular risk factors as they age, which potentiates the risk for major adverse cardiac events. Prevention of cardiotoxicity is essential in this population. Minimizing anthracycline dose exposure in pediatric cancer patients is a primary method of cardioprotection. Dexrazoxane and enalapril have also been studied as primary (pre-exposure) and secondary (post-exposure) cardioprotectant agents, respectively. Additionally, the Children's Oncology Group has published exposure-driven, risk-based screening guidelines for long-term follow-up, which may be a cost-effective way to identify subclinical cardiac disease before progression to clinical presentation. Ongoing research is needed to determine the most effective diagnostic modality for screening (eg, echocardiography) and the most effective intervention strategies to improve long-term outcomes.[3]

Cardiologists dedicated to the care of patients with chemotherapy-induced cardiotoxicity and with concomitant cardiovascular problems in cancer patients are a part of an emerging subspeciality called "Cardio-Oncology" or "Onco-Cardiology." Many cancer centers and tertiary care hospitals in the United States are now establishing dedicated Cardio-Oncology clinics where cardiovascular specialists play a dedicated role in managing heart disease in cancer patients. The reason for this evolving need for specialized cardiac care in cancer patients is related to the acute and chronic cardiovascular complications of cancer therapy, emerging data that early detection of cardiotoxicity improves patient outcomes, and finally the observation that cardiovascular interventions have to be balanced with cancer therapeutics to provide the patient with the best possible oncological and cardiovascular outcomes.

Prior to initiation of any cancer therapy, cardiologists should make every effort to optimize the management of any underlying cardiovascular conditions, including coronary artery disease, hypertension, and arrhythmias. Furthermore, cardiologists should recognize and promptly manage the cardiovascular complications from cancer treatment. Cardiovascular toxicity of chemotherapy and antibody-based therapy encompasses diverse clinical manifestations, including and not limited to heart failure, cardiac ischemia, blood pressure changes, and arrhythmias (Table 101–1). Early recognition of this spectrum of cardiotoxicities, such as with new imaging techniques to detect subclinical left ventricular dysfunction prior to the development of overt heart failure, will allow for early cardiovascular intervention to improve outcomes.

TABLE 101–1. Cardiotoxicity of Chemotherapy and Antibody-Based Therapy

Heart Failure	Ischemia	Hypotension	Hypertension	Bradycardia	QT Prolongation or Torsade de Pointes	Thromboembolism	Pericarditis/ Pericardial Effusion
Anthracyclines	Bevacizumab (Avastin)	Alemtuzumab (Campath)	Bevacizumab (Avastin)	Paclitaxel (Taxol)	Asenic trioxide (Trisenox)	Bevacizumab (Avastin)	Doxorubicin (Adriamycin)
Mitoxantrone (Novantrone)	Capecitabine (Xeloda)	All-*trans*-retinoic acid (Atra; Tretinoin)	Sorafenib (Nexavar)	Thalidomide (Thalomid)	Dasatinib (Sprycel)	Cisplatin (Platinol-AQ)	Cyclophosphamide (Cytoxan)
Alkylating agents	Docetaxel (Taxotere)	Decitabine (Dacogen)	Sunitinib (Sutent)	Bortezomib (Velcade)	Lapatinib (Tykerb)	Erlotinib (Tarceva)	Busulphan (Myleran)
Cyclophosphamide (Cytoxan)	Erlotinib (Tarceva)	Denileukin (Ontak)	Imatinib (Gleevec)	Cisplatin (Platinol-AQ)	Nilotinib (Tasigna)	Lenalidomide (Revlimid)	Clofarabine (Clolar)
Ifosfamide (Ifex)	Fluorouracil (5-FU; Adrucil)	Etoposide (Vepisid)	Dasatinib (Sprycel)		Vorinostat (Zolinza)	Sunitinib (Sutent)	Dasatinib (Sprycel)
Antimicrotubule agent	Paclitaxel (Taxol)	Interferon-α	Mitoxantrone (Novantrone)		Pazopanib (Votrient)	Thalidomide (Thalomid)	Imatinib (Gleevec)
Docetaxel (Taxotere)	Sorafenib (Nexavar)	Interleukin-2				Vorinostat (Zolinza)	
Monoclonal antibody-based tyrosine kinase inhibitor	Sunitinib (Sutent)	Paclitaxel (Taxol)				Pomalidomide (Pomalyst)	
Bevacizumab (Avastin)	Lapatinib (Tykerb)	Rituximab (Rituxan)				Ponatinib (Iclusig)	
Trastuzumab (Herceptin)	Pazopanib (Votrient)						
Proteasome Inhibitor	Cytarabine (Depocyt)						
Bortezomib (Velcade)	Ifosfamide (Ifex)						
Carfilzomib (Krypolis)							
Small molecule tyrosine kinase inhibitors							
Dasatinib (Sprycel)							
Lapatinib (Tykerb)							
Imatinib (Gleevec)							
Sunitinib (Sutent)							
Antimetabolites							
Clofarabine (Clolar)							

DEFINITION OF CARDIOTOXICITY

The Common Terminology Criteria for Adverse Events, developed by the National Cancer Institute,[4] recognizes a broad array of cardiovascular events and subclinical laboratory and imaging-based functional changes that encompass under the broad definition of cardiotoxity.

Acute or subacute cardiotoxicity can include acute coronary syndrome, myocarditis, pericarditis, and/or supraventricular or ventricular arrhythmias. Such cardiotoxicity may manifest as electrocardiographic abnormalities (eg, QT prolongation) or fluctuations in blood pressure that may occur at the initiation of chemotherapy or up to 2 weeks following its termination.

Chronic cardiotoxicity includes the entire spectrum from asymptomatic systolic or diastolic left ventricular dysfunction to severe symptomatic heart failure, accelerated coronary artery disease, chronic pericardial syndromes, and valvulopathy.

FACTORS THAT CONTRIBUTE TO THE DEVELOPMENT OF CARDIOTOXICITY

Several risk factors contribute to the development of cardiotoxicity in patients being treated for cancer. These include nonchemotherapy-related risk factors such as age, preexisting hypertension, coronary artery disease

TABLE 101–2. Risk Factors for the Development of Anthracycline Cardiomyopathy[10]

Risk Factor	Hazard Ratio	Reference
Prior anthracycline use (cumulative dose)	NA	Von Hoff et al (1979)
Cardiac irradiation	NA	Steinherz et al (1991)
Other heart disease	1.53	Hershman et al (2008)
Hypertension	1.58	Hershman et al (2008)
Coronary artery disease	2.21	Hershman et al (2008)
Age > 65 years	2.25	Swain et al (2003)

Abbreviation: NA, not available.

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(CAD), and past radiation therapy as in the case of cardiotoxicity resulting from drugs such as anthracyclines (Table 101–2) and trastuzumab.[5-9]

The chemotherapy-related risk factors include the dose of the drug administered during each chemotherapy cycle, the cumulative dose, the schedule of delivery, the route of administration, concomitant use of other cardiotoxic drugs, and the sequence of administration of these drugs. Anthracyclines potentially can induce cardiac damage with the first administration, but more typically affect cardiac myocytes at higher cumulative doses with a much higher incidence of heart failure at doses exceeding 450 mg/m^2.[5] Cyclophosphamide causes cardiac dysfunction at high doses exceeding 180 mg/kg and when given concomitantly with other cardiotoxic drugs. Similarly, ifosfamide can induce low-grade arrhythmias at doses of 1.2 to 2 g/m^2/d for 5 days, but may result in heart failure when administered at a higher dose of 10 to 18 g/m^2/d for 5 days.

For some agents, the cardiac side effects depend on the schedule of administration. Interleukin (IL)-2, a T-cell growth factor, can cause body weight gain when given low dose as a continuous infusion at a rate of 9×10^6 IU/m^2/d and hypotension when given as a bolus at a dose of 600,000 IU/kg every 8 hours. Likewise, the administration schedule of anthracyclines and cyclophosphamide seems to play a role in the development of cardiac side effects. Administering anthracyclines by continuous infusion over 24 to 96 hours rather than by rapid intravenous (IV) infusion probably reduces the risk of cardiotoxicity of these drugs. Similarly, parenteral, though not oral, busulfan can result in tachyarrhythmias, hypertension, or hypotension, as well as left ventricular (LV) systolic dysfunction.

Changing the sequence in which drugs are administered can also influence the risk or severity of cardiotoxicity. For example, the combination of IL-2 and interferon given simultaneously produces pronounced hypotension, but interferon treatment alone for 2 weeks followed by IL-2 treatment has less effect on blood pressure.

PATHOPHYSIOLOGY OF CARDIOTOXICITIES

Among the various cardiac complications of cancer therapy, the most prominent one is LV systolic dysfunction as a direct result of myocardial damage. A large number of cancer therapeutics can cause direct myocardial damage (see Table 101–1). For example, trastuzumab (Herceptin), an antibody directed against the HER2-neu receptor in the treatment of selected patients with breast cancer, has been associated with an increased incidence of LV systolic dysfunction. Not all forms of cardiac dysfunction related to anticancer treatments are identical. LV dysfunction related to cancer therapy is currently defined by a decrease in cardiac function and is categorized into irreversible injury (type I) or reversible dysfunction (type II).[10,11]

Among the anthracyclines, doxorubicin, daunorubicin, epirubicin, and idarubicin are approved by the US Food and Drug Administration for the treatment of patients with a variety of hematologic malignancies and solid tumors. All anthracyclines are associated with both early and late toxicity. Anthracycline-induced cardiotoxicity has been classified as early or late onset using a cutoff of 1 year after anthracycline treatment. Cumulative incidences of cardiac events typically peaked at 1 year after anthracycline treatment. Early toxicity may be manifested as a myopericarditis with nonspecific electrocardiographic ST-segment and T-wave abnormalities; arrhythmias may be part of the clinical presentation. Late anthracycline cardiotoxicity is cumulative dose related, with heart failure incidences of 5%, 16%, and 26% estimated for cumulative doxorubicin doses of 400, 500, and 550 mg/m^2, respectively. Although the mechanism of such LV dysfunction was purported to be myocardial injury secondary to free radical formation, antioxidants have failed to prevent anthracycline-induced cardiotoxicity. Recent studies showed that anthracycline targets topoisomerase 2b in the cardiomyocytes to induce breaks in double-stranded DNA and changes in the transcription of antioxidative and mitochondrial electron transport chain genes, leading to increase in reactive oxygen species and mitochondrial dysfunction.[16] Dexrazoxane, the only FDA-approved drug for prevention of anthracycline cardiotoxicity, is a potent topoisomerase 2b inhibitor (Fig. 101–1).[12]

The mechanism of dexrazoxane cardioprotection was originally attributed to the iron chelation properties of its EDTA-like hydrolysis product, leading to decreased levels of hydroxyl free radicals. This notion was challenged by subsequent studies documenting lack of protection against doxorubicin-induced cardiomyopathy provided by deferasirox (another iron chelator) and several other free radical scavengers.[13] More recently, it was proposed that dexrazoxane-induced cardioprotection is related to its ability to antagonize the DNA damage caused by doxorubicin by means of interference with topoisomerase II (Top2). Mammalian cells express two types of Top2: Top2α and Top2β, both of which are targeted by doxorubicin. The efficacy of doxorubicin as a chemotherapeutic agent seems to result from the inhibition of Top2α, which is only expressed in proliferating and tumor cells. Contrariwise, Top2β is present in all cells, including postmitotic cells and the adult heart, in two possible states, free or DNA-bound. Dexrazoxane can bind to both free Top2β and DNA-bound Top2β. Binding of dexrazoxane to free Top2β stabilizes its conformation, preventing its interaction with chromosomal DNA. Likewise, binding of dexrazoxane to DNA-bound Top2β stabilizes the closed-clamp conformation of ATP-bound Top2β, which triggers proteasomal degradation of Top2β, finally resulting in Top2β downregulation.[14] Because the dexrazoxane binding sites are the same for the two Top2 isozymes, dexrazoxane has been expected to possibly reduce to some extent the antitumor activity of doxorubicin. However, dexrazoxane does not degrade Top 2α and in some studies may even synergize with doxorubicin in cancer cell killing.

Although the incidence of cardiomyopathy increases significantly in patients receiving cumulative doses of doxorubicin that exceed 450 mg/m^2, cardiomyopathy can still occur at lower cumulative doses.[5] The mortality rate in patients with advanced stages of heart failure secondary to anthracycline cardiotoxicity is as high as 30% to 60%. The prognosis can be greatly altered if cardiac dysfunction is recognized early, the offending agent is promptly discontinued, and optimal treatment is instituted with a regimen including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers

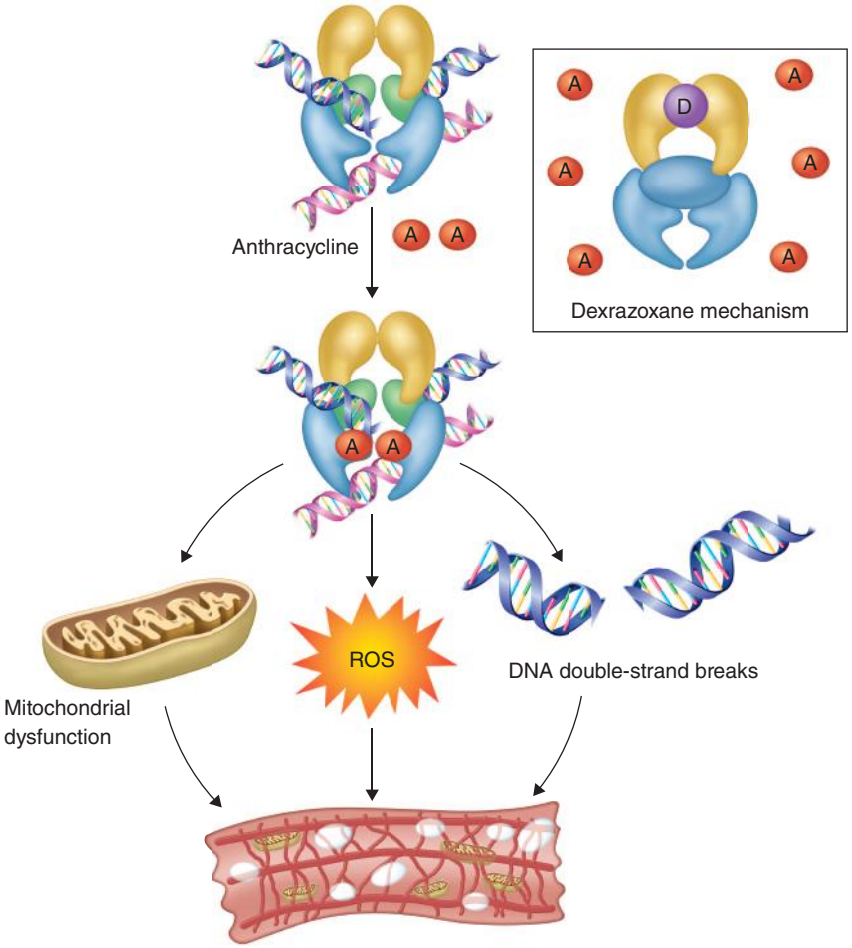


FIGURE 101–1. Mechanism of anthracycline-induced cardiotoxicity. Doxorubicin disrupts the normal catalytic cycle of topoisomerase (Top) 2β, causing DNA double-stranded breaks. It further changes the transcriptome, leading to defective mitochondrial biogenesis and increase in reactive oxygen species (ROS). As a result, cardiomyocytes showed myofibrillar disarray and vacuolization. In the inset, dexrazoxane was shown to bind to Top2β to prevent anthracycline binding. Reproduced with permission from Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. *J Am Coll Cardiol*. 2014 Sep 2;64(9):938-945.

(ARBs). Anthracyclines cause a unique pattern of histologic cardiac changes, including the vacuolization of myocardial cells, myofibrillar disarray and loss, and necrosis.[6] A direct relationship between biopsy grade of histopathologic change, the cumulative dose of the drug, and the clinical symptoms has been shown. Histopathologic and pathogenic information regarding the cardiotoxicity of other anticancer drugs is sparse.

On the other hand, trastuzumab-induced cardiac dysfunction seems to be different from anthracycline-induced cardiac dysfunction, leading to irreversible cardiac damage (type II). It has been shown that the HER2-HER4-neuregulin system in the heart may attenuate the response of cardiomyocytes to oxidative stress and is temporarily upregulated in response to cardiomyocyte stress. Inhibition of HER2 causes mitochondrial dysfunction in cardiomyocytes. Therefore, trastuzumab-induced cardiotoxicity may result from direct binding of trastuzumab to the HER2 receptor expressed on the myocardium and increased oxidative stress (eg, because of anthracycline use); causing HER2 upregulation increases the risk for trastuzumab-associated cardiotoxicity. Therefore, trastuzumab cardiotoxicity is not dose related but depends on whether the drug is given alone or in combination with other cardiotoxic agents.[7] The incidence of cardiotoxicity is also increased in older patients, those with preexisting cardiac disease, and those who previously received chemotherapy and radiation therapy. The incidence of toxicity associated with trastuzumab has been much lower, however, in more recent trials with closer monitoring and when the simultaneous administration of trastuzumab and anthracyclines is avoided.[8]

CLASSES OF CHEMOTHERAPEUTIC AGENTS AND COMMONLY ASSOCIATED CARDIOVASCULAR EFFECTS

These are outlined in Table 101–1, and a detailed discussion of heart failure, myocardial ischemia, changes in blood pressure, arrhythmias and QT prolongation, and thromboembolism follows below.

HEART FAILURE AND LEFT VENTRICULAR DYSFUNCTION

Heart failure related to cancer therapy is currently defined by a decrease in cardiac function and categorized into irreversible injury (type I) or reversible dysfunction (type II). Apart from the pathophysiological definition of cardiotoxicty, there is no consensus definition of cardiotoxicity in terms of cutoff for LV ejection fraction (LVEF) at present.[15,16] Trials studying cardiotoxicity in

anthracylines and trastuzumab have long relied on the definition of cardiac dysfunction as a ≥ 5% decline in LVEF to result in an LVEF < 55% with symptoms of heart failure, or a ≥ 10% decline to result in an LVEF < 55% without symptoms of heart failure.[5,7,11]

The Common Terminology Criteria for Adverse Events (CTCAE) by the National Cancer Institute defines LV dysfunction as a reduction in LVEF > 5% to < 55% with symptoms of heart failure or an asymptomatic reduction in LVEF > 10% to < 55%.[4] A most recent document released by the American Society of Echocardiography (ASE) defines chemotherapy-related cardiac dysfunction (CTRCD) as a decrease in the LVEF of greater than 10 percentage points, to a value < 53%, which is deemed the normal reference value for two-dimensional (2D) echocardiography as per this society.[15] Centers such as MD Anderson and the ESMO (European Society of Medical Oncolgy)[16] define CTRCD as a reduction in LVEF of 10% or more to < 50% with or without symptoms. As a consequence, at present, a consensus definition for cardiotoxicity is still lacking.

The basic pathophysiology of heart failure is essentially the same in both cancer and noncancer patients. The neurohormonal hypothesis that forms the basis of the diagnosis of heart failure and shapes the strategies for effective treatment is applicable in both groups of patients. Heart failure and cancer progression also share pathophysiologic characteristics. It is imperative to understand the cause of heart failure in these patients because this is one of the most important comorbidities that affects the lifespan of a cancer patient. Although the triggering event of the heart failure may be the chemotherapy, the contribution of preexisting and coexisting cardiovascular risk factors may be difficult to quantify separately.

Strategies for Diagnosing Heart Failure and Left Ventricular Dysfunction

The importance of the physical examination in confirming the presence of heart failure and LV systolic dysfunction in cancer patients cannot be overemphasized (see Chap. 69). Certain physical findings, such as a third heart sound or jugular venous distension, can be highly predictive of heart failure (see Chap. 11).

Table 101–3 summarizes the typical causes of LV systolic dysfunction and heart failure in cancer patients. All of the major contributors to heart failure need to be investigated and treated appropriately to optimally affect the course of illness (see Chap. 70).

Among basic laboratory studies, the ECG does not discern heart failure or LV dysfunction, although it can confirm suspected abnormalities or indicate potential underlying cardiac disease, such as ischemia, conduction abnormalities or chamber enlargement. Additional laboratory testing should include lipid panel to indicate risk for vascular disease and blood glucose monitoring to screen for diabetes, both clinical predictors for heart failure. Anemia, especially common in cancer patients, has been directly correlated with outcomes in heart failure patients and should be part of a basic laboratory screen (see Chap. 70). Other specific biomarkers that are crucial in the evaluation of patients with suspected heart failure, especially those with cancer, include cardiac troponin I as well as B-type natriuretic peptide (BNP). Troponins may have value in screening for LV systolic dysfunction that develops during the course of chemotherapy.[17] The role of BNP levels to detect early cardiotoxicity, LV dysfunction, or to detect volume overload has not been validated in this population. It may be falsely elevated without the presence of LV dysfunction or heart failure in cancer patients. A careful physical examination is still the most reliable means of characterizing volume status.

LVEF, most commonly determined by echocardiography, is currently the mainstay of detecting heart failure or asymptomatic LV dysfunction during chemotherapy. Monitoring protocols for patients undergoing anthracycline-based chemotherapy in the 1970s and 1980s were developed and validated based on radionuclide MUGA (multigated acquisition) scans. These, though highly reproducible, have been largely replaced by echocardiography today, and as such, the algorithms validated for MUGA may be applied to echocardiography imaging. Widespread availability, feasibility, lack of radiation exposure, and acquisition of additional cardiac imaging information (valvular, pericardial, and hemodynamic data) make echocardiography an attractive option for serial imaging. Echocardiographic strain imaging has recently emerged as a promising method for detection of early cardiotoxicity prior to LV dysfunction. Three-dimensional echo imaging has shown promising results with least inter- and intraobserver variability and reproducibility, which could be comparable to MUGA. However, there are certain circumstances in which one technique is favored over the other. In pediatric patients, echocardiography is preferred because of the lack of ionizing radiation. In obese patients, however, adequate echocardiographic windows will be difficult to attain. Furthermore, the usefulness of echocardiography is limited in other variations of thoracic anatomy, such as emphysema, tight intercostal spaces, and heavily calcified ribs. Three-dimensional echocardiography is dependent on patient ability to hold the breath and requires a longer offline analysis. MUGA is less feasible in patients with arrhythmias as a result of poor electrocardiography-based triggering, which is more often seen in patients with heart failure. Regrettably, the choice of technique used is often not determined by the question of which method is more accurate or more suitable for the individual patient but is rather governed by the availability of local resources and personal experience. Therefore, all the described noninvasive techniques should be used as complementary.

TABLE 101–3. Causes of Left Ventricular Systolic Dysfunction or Heart Failure in Cancer Patients

Preexisting Risk Factors or Underlying Disease
Coronary artery disease and ischemia
Hypertension
Alcohol-related cardiomyopathy
Diabetes
Nutritional deficiencies
Cardiac cachexia
Thyrotoxicosis or hypothyroidism
Related to Cancer Diagnosis
Amyloidosis
Myocarditis
Cardiotoxic chemotherapy
Radiation
Sepsis
Capillary leak phenomenon
Carcinoid syndrome
Other
Arterial venous fistula
Endocarditis
Pericardial disease, including constrictive pericarditis
Pulmonary emboli
Pulmonary hypertension
Hemochromatosis and iron overload (frequent transfusions)

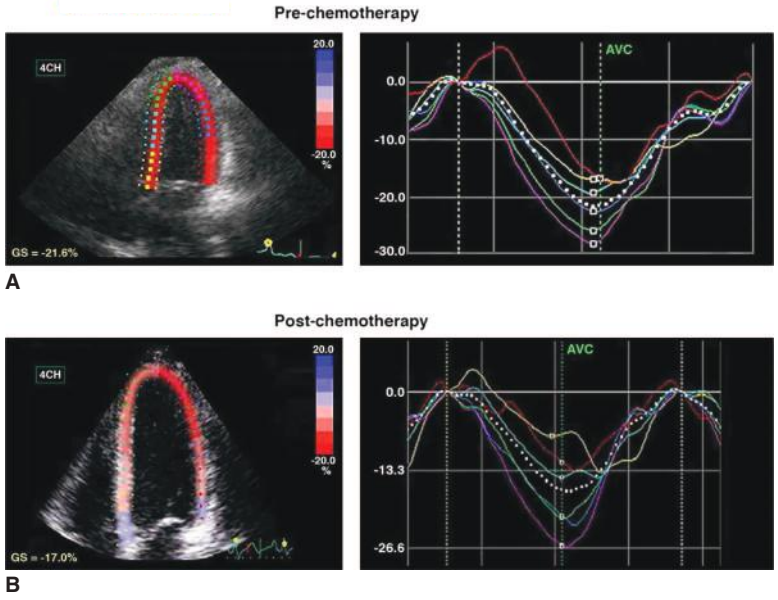


FIGURE 101–2. Two-dimensional (2D) speckle-tracking echocardiogram-based strain in a patient with invasive ductal carcinoma. A patient with invasive ductal carcinoma (estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2/neu positive), treated with the TCH regimen (docetaxel, carboplatin, and trastuzumab), had a baseline ejection fraction (EF) of 65%. The EF after 3 months of therapy was 58%. **A, B** utilize color to illustrate the global longitudinal strain (GLS) and regional strain values obtained at baseline (prechemotherapy) and 3 months after the initiation of trastuzumab-based regimen. The septal and anteroseptal segments exhibit abnormal regional strain after treatment. Reproduced with permission from Kongbundansuk S, Hundley WG2. Noninvasive Imaging of Cardiovascular Injury Related to the Treatment of Cancer. *JACC Cardiovasc Imaging*. 2014 Aug;7(8):824-838.

Of particular interest in detecting early cardiotoxicity is the application of strain imaging, which is a measure of regional deformation of the myocardium. It is mainly obtained by angle-independent 2D speckle-tracking echocardiography, which can evaluate all three domains of myocardial mechanics (longitudinal, circumferential, and radial) and derive data for deformation and rate of deformation for each myocardial segment (Fig. 101–2). Two-dimensional speckle-tracking echocardiography has been used in multiple independent studies, reporting changes in cardiac (mechanical) function before a decrease in LVEF and even before changes in diastolic function after chemotherapy.[15] Based on numerous studies of strain rate imaging during cancer chemotherapy, a greater than 10% change in global longitudinal strain (GLS) after completion of anthracycline-based chemotherapy relative to baseline is predictive of a future decrease in LVEF (Fig. 101–3). Conceivably, but subject to further studies, abnormal strain values before cancer therapy may signal higher baseline risk for chemotherapy-induced cardiotoxicity. Based on the above discussion, it seems appropriate to include strain imaging in monitoring algorithms for cardiotoxicity. Thereby, the ASE recommends strain rate imaging as an inherent part of a compreshensive echocardiogram for patients undergoing cancer chemotherapy. It also recommends 3D echocardiography as the preferred technique for monitoring of LV function and detecting CTRCD in patients with cancer, as LVEF determination by 2D echocardiography, with or without contrast, has

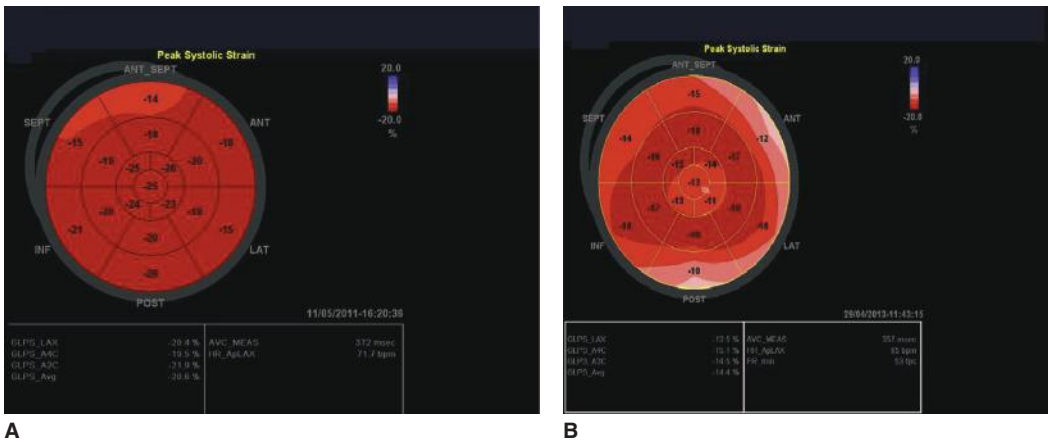


FIGURE 101–3. Bullseye plot showing GLS (global longitudinal strain) of a breast cancer patient. **A.** GLS and regional longitudinal strain at baseline. **B.** GLS and regional longitudinal strain 3 months during trastuzumab-based therapy after anthracyclines. GLS has decreased from −22.6% to −14.4% (30% decrease). The decrease in GLS is therefore considered of clinical significance (> 15% vs baseline). Reproduced with permission from Plana JC, Galderisi M, Barac A, et al: Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2014 Oct;15(10):1063-1093.

TABLE 101–4. Recommended Cardio-Oncology Echocardiogram Protocol

Standard transthoracic echocardiography
In accordance with ASE/EAE guidelines and IAC-Echo
2D strain imaging acquisition
Apical three-, four-, and two-chamber views
Acquire ≥ 3 cardiac cycles
Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
Frame rate between 40 and 90 frames/sec or ≥ 40% of HR
Aortic VTI (aortic ejection time)
2D strain imaging analysis
Quantify segmental and global strain (GLS)
Display the segmental strain curves from apical views in a quad format
Display the global strain in a bull's-eye plot
2D strain imaging pitfalls
Ectopy
Breathing translation
3D imaging acquisition
Apical four-chamber full volume to assess LV volumes and LVEF calculation
Single and multiple beats optimizing spatial and temporal resolution
Reporting
Timing of echocardiography with respect to the i.v. infusion (number of days before or after)
Vital signs (BP, HR)
3D LVEF/2D biplane Simpson's method
GLS (echocardiography machine, software, and version used)
In the absence of GLS, measurement of medial and lateral s' and MAPSE
RV: TAPSE, s', FAC

Abbreviations: BP, blood pressure; FAC, fractional area change; HR, heart rate; IAC-Echo, Intersocietal Accreditation Commission Echocardiography; MAPSE, mitral annular plane systolic excursion; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; VTI, velocity-time integral.

Reproduced with permission from Plana JC, Galderisi M, Barac A, et al: Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2014 Oct;15(10):1063–1093.

inherent inter- and intraobserver variability that may vary up to 10% (Table 101–4).

Other specific cardiac testing is frequently necessary to evaluate the extent of underlying heart disease that may be present in a patient with cancer. Exercise or pharmacologic stress testing can help investigate for coronary artery disease (see Chap. 13), and cardiac catheterization demonstrates angiographically the extent of coronary artery disease, LV systolic dysfunction, valvular abnormalities, and other hemodynamic disturbances. A myocardial biopsy may be appropriate when it is necessary to confirm a diagnosis of amyloidosis or myocarditis. Cardiac magnetic resonance imaging (CMR) may be extremely useful in the diagnosis of constrictive pericarditis, myopericarditis, or amyloidosis.

The Principles of Therapy for Heart Failure

The principles of therapy for heart failure and LV dysfunction in cancer patients are similar to those in patients without cancer. An often overlooked management component is the education of both the patient and family members regarding early recognition of the symptoms of fluid overload and decompensation. Management of patients who develop heart failure from cardiotoxicity during or after cancer therapy should be in keeping with the American Heart Association (AHA)/American College of Cardiology (ACC) heart failure guidelines (see Chap. 71). There is no reason to suspect that standard medical therapy would not be effective in most cancer patients as well.

ACE inhibitors and β-adrenergic blocking agents remain the cornerstone of therapy and have specifically been studied in cancer patients.[18-20] The timing from completion of anthracycline-based chemotherapy to initiation of heart failure therapy was identified as the crucial determinant of the response rate. Early initiation of these agents is key as the recovery of LV function is dependent on early intiation of heart failure treatment. The usefulness of ARBs, as alternatives to ACE inhibitors for the treatment of heart failure, can be extrapolated to the cancer population as well. The combination of nitrates and hydralazine is of special benefit in African American patients, as well as in patients with renal insufficiency not able to receive ACE inhibitors or ARBs. The precise role of aldosterone receptor antagonists (eg, spironolactone) in the treatment of chemotherapy-induced cardiomyopathy is currently unknown, but may be considered in those with New York Heart Association (NYHA) class > 1 symptoms and an LVEF of 35% or less.

Hemodynamic device support may become necessary if medical therapy fails. Acute hemodynamic support can be temporarily lifesaving, as in those with acute myopericarditis owing to drugs such as cyclophosphamide. Alternatively, chronic left ventricular assist device support may become a bridge to transplant or destination therapy in some resported cases as reported recently.[21] The most severe forms of heart failure are usually observed in patients receiving both chemotherapy and radiation therapy because of the profound injury and in those of young age.[3] Two key processes have been noted in children developing cardiotoxicity: reduction in contractility and/or increase in afterload. These have not been described in adults but may be of significance for the choice of therapy. At present, it is unknown whether the medical therapies outlined above are necessary for agents that cause type 2 cardiotoxicity. Initial studies on trastuzumab-associated cardiomyopathy reported improved cardiac function after withholding therapy alone.[10,22] This has remained the primary approach common to all published management algorithms for trastuzumab-associated cardiotoxicity. However, HER-2 inhibition is a vital element in the treatment of patients with breast cancer overexpressing this receptor, and thus "drug holiday" is of concern. It is currently undefined whether institution of cardioactive medication is necessary and would allow continuation of therapy without concerns for cardiac adverse effects. HER-2 upregulation, which is involved in trastuzumab-associated cardiotoxicity, merits investigation in targeted therapy of this pathway. Intriguingly, statins and nebivolol induce potent upregulation of this pathway. Whether such strategies would be counterproductive to the anticancer effects of therapy, however, remains an unanswered question.

In addition, risk factors for heart failure should also be aggressively treated in cancer patients. Moreover, the higher incidence of drug–drug interactions in cancer patients undergoing chemotherapy and heart failure therapy should be recognized. It is imperative that unnecessary medications are avoided in these patients and that the addition of a potentially beneficial heart failure medication is carefully weighed against the risk of possible interactions with anticancer agents. Several alternative approaches are being developed that may be particularly appropriate for use in cancer patients with heart failure. Stem cell

therapy for LV dysfunction, for instance, may become an important strategy in the future; methods of delivery and the enhancement of engraftment remain subject of intense investigation. There are a variety of other potentially useful agents for treating heart failure in cancer patients. IV immunoglobulin, which is used in patients who have immune deficiencies or even an excessive graft-versus-host response after bone marrow transplantation, may have important future implications. However, one randomized, controlled study did not show any clear benefit.[23]

Cardiac devices are an integral part of modern heart failure management. Placement of an implantable cardioverter-defibrillator is reasonable in patients with LVEF of < 30% to 35% of any origin with NYHA functional class II or III symptoms who are taking chronic optimal medical therapy and who have reasonable expectation of survival with good functional status of more than 1 year, as per the ACC/AHA heart failure guidelines. Similar considerations pertain to biventricular pacemakers in appropriate cancer patients.

Surgical therapy for heart failure has been intensely investigated, but as yet, there is no clearly established surgical technique for the management of heart failure (see Chap. 70). Coronary bypass grafting for the treatment of severe ischemic heart disease may be appropriate when dysfunctional yet viable myocardium can be revascularized, thereby restoring function. Other surgical techniques may be appropriate in selected situations resulting in heart failure, such as pericardial stripping for constrictive pericarditis or removal of intracardiac masses. Ethical concerns are also important when deciding on the appropriate therapy for a cancer patient with heart failure. One must consider to what extent the two entities interplay and to what extent they affect the patient's overall prognosis. It is important to openly address end-of-life issues with patients so that the treatment approach incorporates the wishes of the patient as well as the reality of the clinical condition. The diagnosis of cancer should not imply that the patient's heart failure cannot or should not be aggressively treated. Treatment decisions should be individualized.

In addition to standard treatment of heart failure, key management of LV dysfunction resulting from cancer chemotherapy includes correction of risk factors, early detection, and regular surveillance. Tables 101–5 and 101–6, adapted from the ESMO guidelines,[16] include key points for consideration while evaluating patients before and during administration of potentially cardiotoxic chemotherapy.

Future Developments

The ability to detect a cardiotoxic insult continues to be a major challenge. Recent use of established biomarkers, such as cardiac troponin I and myeloperoxidase (MPO), in patients receiving chemotherapy has shown promise as an effective tool for identifying toxicity at its earliest stages.[24] Use of global longitudinal strain imaging is emerging as a useful echocardiographic tool, but vendor-specific measurements and protocols need to be validated. Prevention of LV dysfunction from cardiotoxicity by use of of specific drugs such as candesartan (see "Prevention of Cardiotoxicity" later in the chapter) are emerging. Future research will include mapping genetic polymorphisms to identify cancer patients who are at increased risk for cardiomyopathy as a consequence of chemotherapy or to serve as a marker of an impaired ability to recover from a cardiotoxic insult.[25] This may be especially important when considering antiangiogenic therapy, in which the main goal is to decrease microvascular blood flow to a tumor.

MYOCARDIAL ISCHEMIA

Chest pain is a common symptom in cancer patients who are undergoing various forms of anticancer therapy. Chest pain often necessitates

TABLE 101–5. Evaluation of Patients Before Initiation of Chemotherapy

Prechemotherapy

- All patients undergoing chemo- and/or radiation therapy should have careful clinical evaluation and assessment of CV risk factors and comorbidities
- Patients with pre-existing cardiovascular disease, especially cardiomyopathy, cardiac arrhythmias, or coronary artery disease, or significant modifiable cardiovascular risk factors, especially hypertension, should be adequately managed before and during therapy, preferably by a Cardio-Oncology consultation
- TTE and 12-lead ECG should be obtained in all patients before potential cardiotoxic cancer treatment
- In patients at high risk for cardiotoxicity (especially pre-existing cardiomyopathy, heart failure, CAD, or hypertension, prior radiation or anthracycline therapy, age > 60-65), cardioprotective agents should be considered; ACE inhibitors are first-line therapy including for those with BP > 140/85 mm Hg, but recent data also support ARB, carvedilol, or nebivolol
- Dexarazoxane is recommended as a cardioprotectant by the American Society of Clinical Oncology only for patients with metastatic breast cancer who have already received more than 300 mg/m^2 of doxorubicin
- If low or borderline LVEF, may consider a non-anthracycline-containing regimen

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography.

Data from Curigliano G, Cardinale D, Suter T, et al: Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2012 Oct;23 Suppl 7:vii155-vii66.

TABLE 101–6. Evaluation of Patients During Chemotherapy

During chemotherapy

- If metastatic disease, left ventricular ejection fraction (LVEF) should be monitored at baseline and then infrequently in the absence of symptoms
- Serial monitoring of cardiac function at baseline, 3, 6, and 9 months during treatment, and then at 12 and 18 months after the initiation of treatment, revised as indicated
- LVEF reduction ≥ 15% from baseline with normal function (LFEV ≥ 50%) is not an indication to discontonue chemotherapy
- In case of LVEF decline to < 40% stop chemotherapy, discuss alternatives, and treat left ventricular (LV) dysfunction (standard guideline-based heart failure [HF] therapy)
- LVEF decline to < 50% during chemotherapy necessitates reassessment after 3 weeks; if confirmed, hold chemotherapy, consider therapy for LV dysfunction and further frequent clinical and echocardiographic checks
- Aggressive medical treatment of those patients, even asymptomatic, who show LV dysfunction on echocardiography after anthracycline therapy is mandatory, especially if the neoplasia could have a long-term survival; it consists of angiotensin-converting enzyme inhibitor and beta-blockers, and the earlier HF therapy is begun (within 2 months from the end of anthracycline therapy), the better the therapeutic response
- Patients who develop cardiac dysfunction during or following treatment with type II agents (trastuzumab) in the absence of anthracyclines can be observed if they remain asymptomatic and LVEF remains ≥ 40%

Modified from Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2012;23(suppl 7):vii155-vii166.

the interruption of chemotherapy, while serial cardiac enzyme assessments and ECGs are performed. If non–ST-segment elevation MI or Q-wave MI is confirmed, patients should be managed according to the current ACC/AHA guidelines (see Chaps. 11, 39, and 41). However, thrombocytopenia and brain metastases pose a particular problem for cancer patients with an ACS because anticoagulant/antiplatelet therapies may be contraindicated under these circumstances. Similarly continuing dual antiplatelet therapy after percutanetous coronary intervention in cancer patients with impending cancer surgery, active bleeding, or thrombocytopenia or in those undergoing bone marrow transplant poses a clinical challenge where risks for coronary thromboses have to be balanced against those for bleeding.

It is well established that radiation therapy to the mediastinum promotes an increased risk for infarction, and it appears more prevalent in patients with left-sided chest radiation. Additionally, several chemotherapy agents are known to precipitate or exacerbate an ischemic response. Cisplatin infusions can cause chest pain; palpitations; and occasionally, elevated cardiac enzyme levels indicative of an MI. Cisplatin can also cause cardiovascular complications such as hypertension, LV hypertrophy, myocardial ischemia, and MI as long as 10 to 20 years after the remission of metastatic testicular cancer.[6] 5-Fluorouracil (5-FU) can also cause an ischemic syndrome that may range from subclinical ischemia to acute MI. Subsequent rechallenge with 5-FU frequently reproduces the initial ischemic event. Nevertheless, the ischemia is usually reversed when 5-FU treatment is stopped and anti-ischemic therapy implemented. In some patients, pretreatment with nitrates and calcium channel–blocking agents has allowed therapy deemed crucial to be continued. Capecitabine, which is currently used in the treatment of breast and gastrointestinal cancers, is believed to be less toxic than 5-FU, although its use has been associated with cardiotoxic effects including ischemic phenomena[7] arrhythmias, ECG changes, and (rarely) cardiomyopathy. Vinca alkaloids, such as vinorelbine, also have been reported to cause angina associated with ECG changes and arrhythmias, as well as MI. Angina and MI are serious, but relatively rare, consequences of interferon-α therapy. Fatal MI and thrombosis have also been noted after the use of all-*trans*-retinoic acid (ATRA). Bevacizumab, a recombinant humanized monoclonal IgG_1 antibody that binds to and inhibits the activity of human vascular endothelial growth factor (VEGF), was recently shown to be associated with an increased risk of angina and MI, in addition to serious arterial thromboembolic events, including cerebrovascular accident and transient ischemic attacks. It is used for the treatment of metastatic colon carcinoma and is generally used in combination with other agents. A new class of chemotherapy agents, termed *vascular disrupting agents*, is currently undergoing clinical evaluation. These agents have been noted to cause asymptomatic creatinine kinase-myocardial bound release and may be associated with ACS.

BLOOD PRESSURE FLUCTUATIONS

The classic malignancy causing hypertension, often paroxysmal or episodic in nature, is pheochromocytoma, a rare catecholamine-secreting tumor most commonly benign, although malignant in 10% of cases. Pheochromocytomas may be isolated tumors, but can also be associated with multiple endocrine neoplasia (MEN) syndromes of the type 2 variety, particularly the MEN 2A and MEN 2B syndromes. Bilateral pheochromocytomas are also associated with von Hippel-Lindau disease and neurofibromatosis. Benign pheochromocytomas usually can be resected surgically, but patients with such tumors require special anesthetic considerations, including pretreatment with phenoxybenzamine followed by the administration of a β-adrenergic blocking agent. Other tumors may also cause hypertension, including hyperthyroidism associated with thyroid tumors.

Several cancer therapies may cause hypertension or hypotension (see Table 101–1). Newer targeted cancer therapies, which inhibit angiogenesis, frequently cause hypertension in cancer patients. Sorafenib is a potent inhibitor of the VEGFR-2, VEGFR-3, FLT-3, c-kit, and platelet-derived growth factor receptor in vitro and may affect the regulation of endothelial cell proliferation and survival. In clinical trials, sorafenib increases blood pressure in 17% to 43% of patients, whereas sunitinib is associated with slightly less hypertension, seen in 5% to 24% of patients. Similarly, hypertension has been observed in 4% to 35% of bevacizumab-treated patients. The mechanism by which these agents induce hypertension is not fully understood; however, it is thought to be related to VEGF inhibition, which decreases nitric oxide production in the wall of the arterioles and other resistance vessels. When treating hypertension in these patients, some antihypertensive agents may be preferred over others because each agent affects angiogenesis in different ways. ACE inhibitors may be selected as first-line therapy because of their ability to prevent proteinuria and plasminogen activator inhibitor-1 expression. In addition, in vivo, ACE inhibitors have demonstrated the potential to reduce microcirculatory changes, decrease the catabolism of bradykinin, and increase release of endothelial nitric oxide. Phosphodiesterase inhibitors and nitrates have also been suggested for the treatment of hypertension in these patients because of their ability to increase nitric oxide levels. Lastly, the β-blocker, nebivolol, which has the unique mechanism of action of blocking beta-adrenergic 1 receptors as well as causing vasodilation through the nitric oxide pathway, may also be beneficial in the treatment of hypertension caused by antiangiogenic cancer treatments.[17] Antirejection regimen such as cyclosporine A, especially when used in conjunction with corticosteroids, are associated with hypertension; the incidence may be greater than 50%. The complex mechanism of cyclopsporin-induced hypertension includes alterations in vascular reactivity that cause widespread vasoconstriction, vascular effects in the kidney leading to reduced glomerular filtration and impaired sodium excretion, stimulation of endothelin, and suppression of vasodilating prostaglandins. Effective therapy includes use of vasodilating agents, often calcium channel blockers.

Hypotension is the most common side effect of etoposide. The infusion of monoclonal antibodies commonly causes hypotension as a result of the massive release of cytokines (an acute transfusion reaction); these agents may also cause fever, dyspnea, hypoxia, and even death. Careful monitoring for hypotension is especially important for patients with preexisting cardiac disease. Cetuximab, a human/mouse chimeric monoclonal antibody that binds to the human epidermal growth factor receptor, may cause severe, potentially fatal infusion reactions characterized by hypotension, bronchospasm, and urticaria; this phenomenon occurs in approximately 3% of patients.[26,27] Rituximab, a chimeric murine/human monoclonal antibody directed against the CD20 antigen, may cause infusion-related side effects that occur within the first few hours of the start of infusion. Supportive measures that are usually effective include IV fluids, vasopressors, bronchodilators, diphenhydramine, and acetaminophen. Interferon-α usually causes acute symptoms during the first 2 to 8 hours after treatment; these include flulike symptoms, hypotension, tachycardia, and nausea, and vomiting.[28] The retinoic acid syndrome appears in approximately 26% of patients who receive ATRA, typically within the first 21 days of treatment. This syndrome includes fever, dyspnea, hypotension, and pericardial and pleural effusions.[29] High-dose treatment with IL-2 may result in adverse cardiovascular and hemodynamic effects similar to those of septic shock[28] and may lead to hypotension, vascular leak syndrome (hypotension, edema, hypoalbuminemia), and respiratory insufficiency requiring pressor agents and mechanical ventilation support.

Blood pressure variations that are unrelated to chemotherapy are much more common in cancer patients; the combination of

malnutrition and dehydration is one of the most common causes of hypotension. Other complications of malignancy, most notably sepsis, may be accompanied by profound and refractory hypotension.

ARRHYTHMIAS

Arrhythmia in cancer patients may be a consequence of cardiotoxic anticancer therapies, a response to an altered environment wherein the chemical, metabolic, or mechanical abnormalities promote abnormal impulse formation or propagation, or a manifestation of tumor spread. Cancer patients often require strategies for managing their arrhythmias that take into account the underlying condition responsible for the arrhythmia. Additionally, cancer-related arrhythmias encompass the spectrum from trivial to life threatening.

Types of Arrhythmia

Supraventricular Arrhythmias Supraventricular arrhythmias are a common occurrence in cancer patients. Atrial premature complexes are a well-recognized manifestation of early anthracycline cardiotoxicity and may be a harbinger of the more serious late LV dysfunction. More sustained supraventricular arrhythmias are seen commonly in patients with a chest malignancy, especially lung cancer, which is often associated with increased pulmonary artery pressure. Pulmonary hypertension often precedes atrial flutter or fibrillation. Mechanical effects of an expanding tumor mass, as well as atelectasis or infection in areas distal to occluded bronchi, further increase right-sided pressures and cause arrhythmias. Hypoxia confounds the problem. Supraventricular arrhythmias are especially frequent early in the postoperative period after lung resection. Supraventricular arrhythmias also occur in association with high-dose chemotherapy and stem cell transplantation. Various specific chemotherapeutic agents also have been associated with atrial fibrillation and include 5-FU, gemcitabine, docetaxel, and alemtuzumab. Radiation to the heart has a well-known association with arrhythmia; however, radiation to sites distant from the heart also has been associated with supraventricular arrhythmia. Other forms of sustained supraventricular tachycardia, including reentrant supraventricular tachycardia and multifocal atrial tachycardia, are also seen commonly in the cancer patient.

Intracardiac masses, including benign tumors and malignant processes such as primary cardiac lymphomas and cardiac metastases from lung, breast, or melanoma, often present with supraventricular arrhythmias. Atrial fibrillation is often associated with acute pulmonary embolism (PE) and pericarditis, conditions that may be encountered in cancer patients.

An important risk factor for sustained supraventricular arrhythmias is intrinsic cardiac disease. In particular, conditions resulting in increased atrial size or that are associated with inflammation contribute to elevated atrial pressure and result in atrial rhythm disturbances. Age, hypertension, lung disease, thyrotoxicosis, surgery, and other states that trigger increased catecholamine levels may all also contribute to elevated atrial pressure.

Ventricular Arrhythmias Cancer patients are more prone to ventricular arrhythmias than the noncancer population. These patients are exposed to stressful and potentially cardiotoxic anticancer treatments, the increased ingestion of multiple noncancer medicines that may be proarrhythmic, and coexisting hormonal and metabolic abnormalities. Hypokalemia, alkalotic states, hypomagnesemia, thyrotoxicosis, pheochromocytomas, and the release of mediators such as serotonin and kinins associated with the carcinoid syndrome are all associated with potentially life-threatening ventricular tachycardia.

Prolonged QT Interval and Torsade de Pointes Torsade de pointes, a form of ventricular tachycardia associated with prolongation of the QT interval, is related to an increasing list of medications, many of which are used in the management of malignancy and in their supportive care. Prolongation of the QT interval may also occur in association with the supplements that cancer patients sometimes ingest, among them cesium chloride, which is commonly used as an alternative therapy for various types of malignancies. Several anticancer agents may also lead to QT prolongation. Arsenic trioxide is associated with QT prolongation in more than 50% of treated patients.[30] Other cardiac side effects include sinus tachycardia, nonspecific ST-T changes, and torsade de pointes.[30] In one study, the most common acute side effect was fluid retention with pleural and pericardial effusions. Complete heart block and sudden cardiac death[31] have also been reported in patients receiving arsenic trioxide. Several newer cancer treatments such as dasatinib, lapatinib, nilotinib, and vorinostat have also been shown to prolong the QT interval. It is important to monitor the QT interval with serial ECGs, with particular attention to patients who are simultaneously receiving other drugs that have the potential to further prolong the QT interval.

Bradyarrhythmias and Atrioventricular Heart Block Thalidomide may cause sinus bradycardia that may be mitigated by adjusting the dosage and is often asymptomatic, but occasionally permanent pacing may be required. Paclitaxel is used extensively in the treatment of many solid tumors and has been reported to cause sinus bradycardia, heart block, premature ventricular contractions, and ventricular tachycardia.

The conduction system of the heart can be interrupted at all levels by primary and metastatic tumors or by infiltrative processes such as amyloidosis. Pheochromocytomas, thymomas, high-dose chemotherapy, and stem cell transplantation are all associated with block at the level of the atrioventricular (AV) node. Individual chemotherapy agents associated with transient AV block include paclitaxel and octreotide.

Treatment of Arrhythmias

In managing arrhythmias in cancer patients, one must first consider possible cancer-related causes for the rhythm disturbance. In many instances, correcting metabolic abnormalities or removing arrhythmogenic agents is the most successful approach. The arrhythmia may be sufficiently serious that the permanent elimination of the offending agent from the treatment regimen must be recommended. In some settings, the arrhythmia may be controlled by the use of standard medications or procedures, thereby permitting completion of highly effective anticancer treatment. The use of implantable devices should not be denied to appropriate patients who have malignancy and who have reasonable expectation of survival with good functional status of more than 1 year, as per the ACC/AHA heart failure guidelines.

THROMBOEMBOLISM

General Considerations

The incidence of thrombosis is higher in patients with cancer than in the general population and portends a worse prognosis. The prevention, recognition, and treatment of thromboembolism are clinical challenges for physicians treating patients with cancer. Venous thromboembolism (VTE) occurs in 5% to 7% of patients with malignancy, an incidence that is much greater than that for the general population (approximately 0.1%). Patients with cancer constitute nearly 20% of all cases of thrombosis. Approximately 10% of all noncancer patients with VTE will be diagnosed with malignancy within 2 years.

The incidence of arterial thromboembolism is less than that of VTE in cancer patients but occurs at a much higher incidence than in the general population. The source of arterial thromboembolism is most likely atherosclerosis, but the general inflammatory condition observed in patients with cancer and treatment with the new antiangiogenic agents are also important determinants. With the more widespread use of such

agents, the incidence of arterial thrombosis likely will increase. Thrombotic events, such as deep venous thrombosis (DVT), PE, and arterial thrombosis have also been observed in approximately 11% of patients treated with IL-2.[32] The risk of death for cancer patients diagnosed with a DVT or PE is substantially higher than that in cancer patients without such an event. The same is true for arterial thrombi. The in-hospital mortality rate may approach 20% to 30%, especially in those with pulmonary emboli. Nonbacterial endocarditis (marantic endocarditis) and disseminated intravascular coagulation are additional examples of life-threatening thrombotic conditions associated with cancer.

Another agent most recently linked to increased risk of life-threatening arterial thrombotic events is ponatinib, a third generation tyrosine-kinase inhibitor (TKI), which was developed for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL). Although ponatinib, similar to the other TKIs, acts as a platelet antagonist, paradoxically, in contrast to the bleeding side effects common to TKI chemotherapies, it can cause severe prothrombotic complications,[33] which resulted in the temporary suspension of the drug by the FDA in late 2013. The pathogenic mechanisms underlying the cardiovascular events observed in patients taking ponatinib remain poorly understood but can cause arterial thrombosis in up to 20% of patients. The FDA has since lifted the suspension of ponatinib after issuing a "black box warning" regarding the risks of arterial thrombosis to be weighed against the oncological benefits.

Pathophysiology of Thrombosis

The pathophysiology of thrombosis is discussed in Chaps. 32, 33, and 75, and varies somewhat depending on the underlying cause. This section focuses on venous and arterial thrombosis in the cancer patient. However, there is an incomplete understanding of the initial triggers for thrombosis, and no single explanation pertains to all conditions in which thrombosis occurs (Table 101–7).

TABLE 101–7. Risks for Thrombotic Events in Cancer Patients

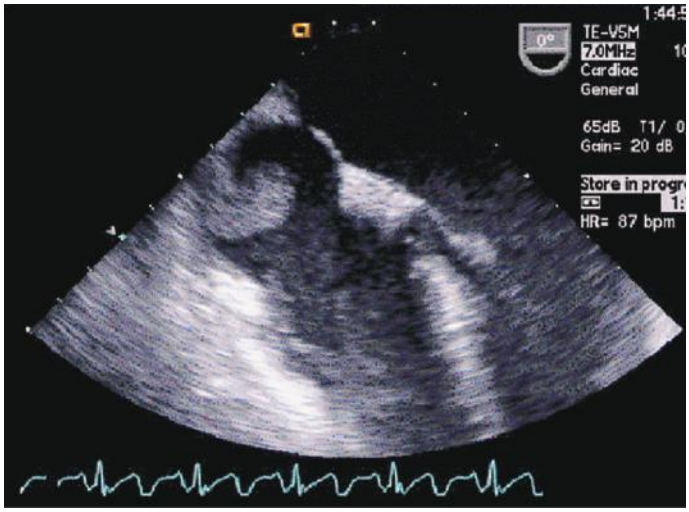
Immobilization
Genetic
Inherited coagulopathy
Polymorphism(s) at risk for thrombosis
Surgery
Trauma
Heart failure
Estrogen therapy
Prior thrombosis
Indwelling catheters
Chemotherapy or other agents
Tamoxifen
Thalidomide
Cisplatin (Platinol-AQ)
Erlotinib (Tarceva)
Lenalidomide (Revlimid)
Sunitinib (Sutent)
Vorinostat (Zolinza)
Bevacizumab
Ponatinib

VTE in cancer patients occurs as a result of the classic triad of stasis, endothelial disruption, and hypercoagulability. In each situation, one component may predominate and, if identified, can be effectively treated. If, for example, a patient has an abdominal tumor that is compressing the inferior vena cava, causing stasis, and this tumor can be removed or reduced by chemotherapy or radiation, then the likelihood of VTE may be markedly reduced. Indwelling IV catheters may cause thrombus formation (Fig. 101–4). Removal of an indwelling central catheter is also likely to be effective in reducing the risk of subsequent recurrence or progression of a thrombus after the stimulus for hypercoagulability has been removed.

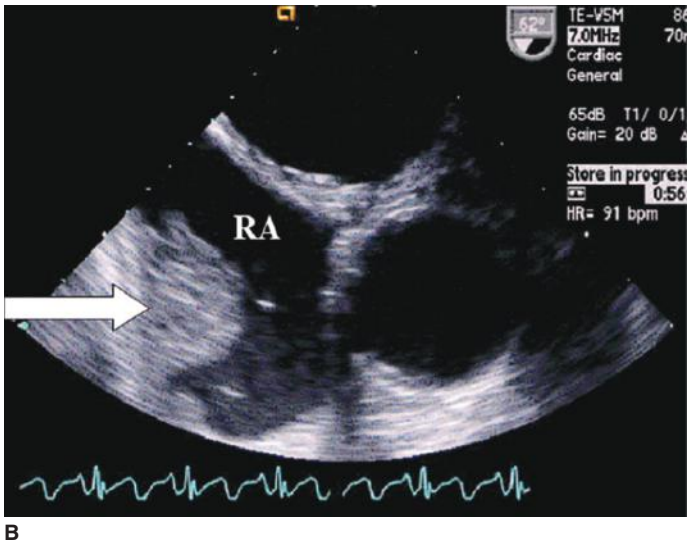
Arterial thrombosis in cancer patients is most commonly associated with platelet activation either in the presence or absence of atherosclerosis. The malignancy itself can lead to platelet activation. The exact mechanism also may include microvessel constriction and platelet activation.

Clinical Manifestations

The location of a thrombosis is of paramount importance with regard to how the thrombus will manifest itself. The extent and position of collateral vessels is also crucial in determining how the thrombus will



A



B

FIGURE 101–4. A, B. Two views from a transesophageal echocardiogram showing a large thrombus in the right atrium (RA) associated with an indwelling catheter.

affect the patient. A DVT in a lower extremity, for example, is likely to cause pain, swelling, and erythema of that extremity. A DVT of an arm may be revealed by unilateral arm swelling that develops fairly suddenly or a bluish discoloration caused by poor venous return. Arterial thrombi usually result in pain, pallor, and pulselessness in an extremity. An arterial thrombosis of an internal organ may be manifested by an episode of unstable angina, an ACS, a cerebral vascular accident, or intestinal ischemia that may be difficult to detect.

The most common presentation of VTE is unilateral leg edema. This can be associated with erythema, but typically it is difficult to discern VTE from cellulitis. Unilateral extremity swelling is, therefore, a hallmark of VTE. Bilateral lower extremity edema may be caused by a proximal venous thrombosis or even congestive heart failure, malnutrition, or other causes of edema. Pulmonary emboli are most commonly manifested by a sudden onset of shortness of breath, chest discomfort, and tachypnea. In addition, patients may report hemoptysis and tachycardia. Syncope, hypotension, and sudden cardiac death are manifestations of larger pulmonary emboli. Long-term effects of pulmonary embolus and DVT include pulmonary hypertension and the postphlebitic syndrome (see Chaps. 74 and 75).

The diagnostic approaches used to detect thrombosis, either venous or arterial, in cancer patients are similar to those used in patients without malignancy; these techniques are highlighted elsewhere. Computed tomographic (CT) angiography (see Chap. 17) is a reliable and sensitive tool for detecting pulmonary embolus, and peripheral extremity ultrasonography remains important in the evaluation of venous flow and thrombus (Fig. 101–5). The techniques used to detect arterial thrombus may vary and are determined mainly by the location of the arterial insufficiency. A combination of ultrasonography, sequential pressure measurements, angiography, CT, and magnetic resonance imaging forms the basis of diagnostic testing for patients with suspected arterial insufficiency.

Treatment of Thromboembolism

The optimal treatment of VTE is a challenge in cancer patients. Typically, these patients are at increased risk for bleeding and because they are often concurrently anemic, the consequences of bleeding are increased and disproportionate. Additional aggravating factors may be thrombocytopenia, hepatic failure, renal dysfunction, or development of a thrombus in a location that may predispose to bleeding complications. Antithrombotic therapy may consist of medications to prevent or limit the propagation of a thrombus or occasionally thrombolytic agents to promote thrombus dissolution. Furthermore, the risks associated with thrombus extension, distal embolization, or recurrence must be weighed against the risks of hemorrhage as part of the decision-making process.

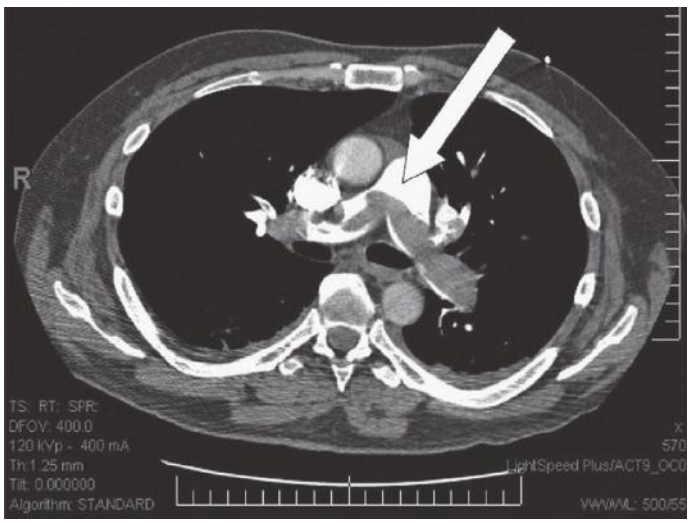


FIGURE 101–5. A contrast-enhanced computed tomography scan showing a massive pulmonary embolus (*arrow*).

Guidelines for antithrombotic therapy for VTE have been published by the Ninth American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy.[34] Standard treatment for VTE traditionally consists of low-molecular-weight heparin (LMWH), IV unfractionated heparin (UFH), or adjusted-dose subcutaneous heparin followed by long-term therapy with an oral anticoagulant. UFH has been superseded by LMWH as the initial treatment in most cancer patients with VTE in both inpatients and outpatients. Long-term treatment with warfarin may be complicated by several problems, including drug–drug interactions, malnutrition, nausea or vomiting during chemotherapy, and thrombocytopenia. Additionally, hepatic dysfunction in cancer patients may lead to unpredictable levels of anticoagulation and result in increased bleeding complications. LMWH is more effective than oral anticoagulant therapy with warfarin for the prevention of recurrent VTE in patients with cancer who have had acute, symptomatic proximal DVT, PE, or both.[35] Further advantages of LMWH are that the doses are more easily adjusted, the pharmacokinetic properties are more predictable, laboratory monitoring is minimized, and fewer drug interactions occur than is the case with oral anticoagulants. Also in favor of heparin therapy in cancer patients are reports that the heparins have antiproliferative, antiangiogenetic, and antimetastatic effects and that LMWH may increase the response to chemotherapy, thereby prolonging the survival of cancer patients.[36] For these several reasons, secondary prophylaxis with LMWH may be more effective and feasible than oral anticoagulant therapy in cancer patients with VTE, although the risk of bleeding is the same for both treatment approaches. More recently, low-dose aspirin was safely used to prevent thrombotic complications in patients with polycythemia vera and has been advocated as an alternative option in patients with cancer presenting with paraneoplastic thrombocytosis.

Newer oral antithrombotic agents or NOACs (novel oral anticoagulants) include thrombin inhibitors such as dabigatran and factor Xa inhibitors such as rivaroxiban, edoxaban, and apixaban. These seem to be as effective and safe as conventional treatment of VTE in patients with cancer as suggested in some small studies and meta-analyses.[37] Further clinical trials are warranted to validate effectiveness and safety of NOACs in patients with cancer-associated VTE. Moreover, mechanical treatments, such as compression stockings used to prevent postthrombotic syndrome, have value in the treatment of cancer patients with thromboembolism, as do selected surgical techniques to treat venous ulceration. Venacaval filters may be used instead of anticoagulation in patients with recurrent PEs who also have a high risk of serious bleeding.

Prevention of Thromboembolism

Prompted by the high incidence of VTE in patients undergoing ambulatory chemotherapy, the 2013 American Society of Clinical Oncology (ASCO) guidelines recommend a scoring method (commonly called the Khorana score) as a risk calculator for chemotherapy-associated VTE in the ambulatory setting.[38] They recommend that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. The prophylactic anticoagulation of high-risk patients is feasible, safe, and effective as suggested by several randomized clinical trials, including the Prophylaxis of Thromboembolism During Chemotherapy Trial (PROTECHT) and the SAVE-ONCO investigation, the largest thromboprophylaxis study ever conducted in cancer patients.

PREVENTION OF CARDIOTOXICITY

The key to prevention of cardiotoxicity is a standardized risk assessment (see Table 101–2). Such an approach allows for a universal standard of care for all patients, facilitates multidisciplinary communication, and aids in treatment decisions and follow-up planning. Recent meta-analyses support operational models that incorporate underlying patient-related risk factors, the cardiac toxicity potential of cancer therapies, and the anticipated therapeutic benefit of the anticancer regimen. These models can then be used to individualize the best oncological therapy for the patient balanced against the fewest cardiovascular risks.

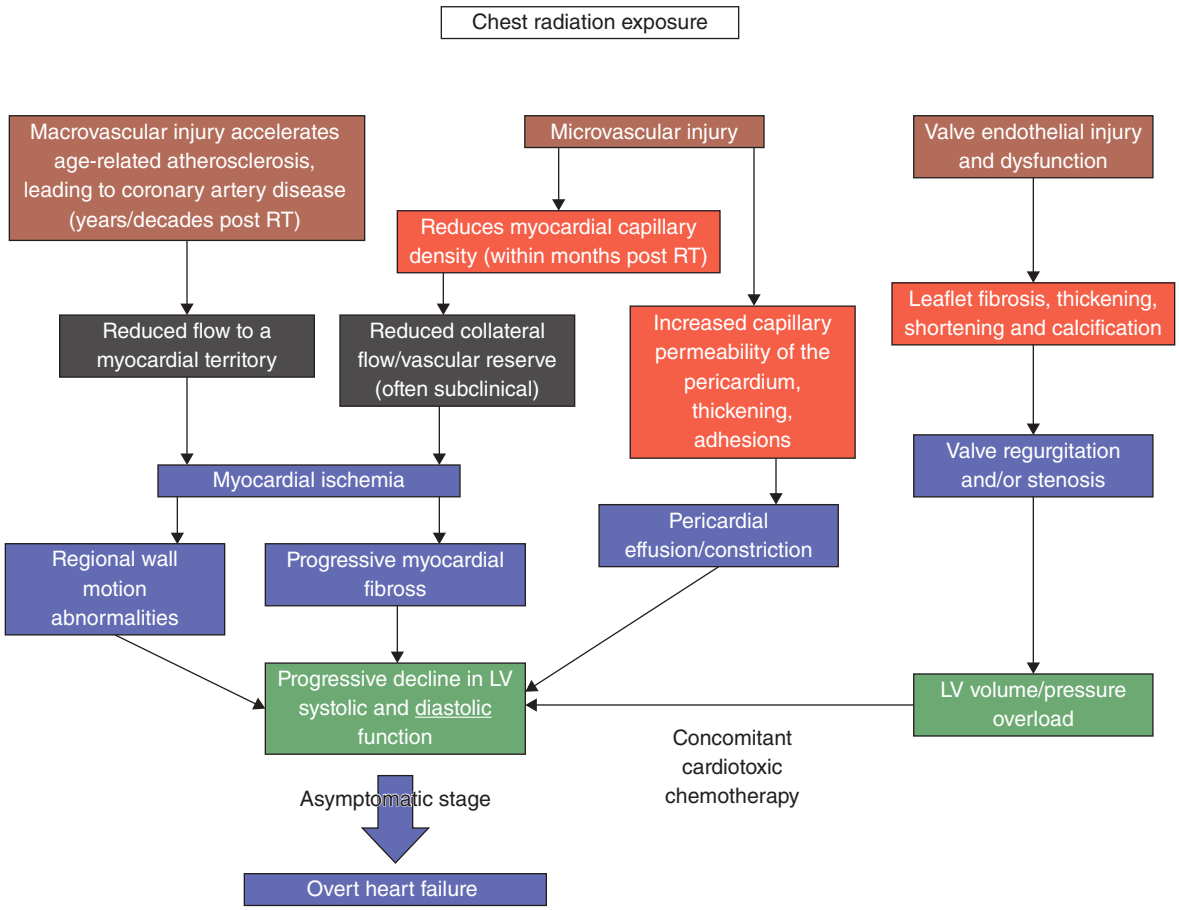
Two approaches for primary prevention of anthracycline-induced cardiotoxicity are to (1) reduce cardiotoxic potency by administering via continuous infusion, liposome encapsulation, or using a less cardiotoxic derivative (eg, epirubicin or idarubicin); and (2) use a cardioprotective agent (eg, dexrazoxane) in conjunction with treatment.[12] Other investigated agents include beta-blockers, ACE inhibitors, and ARBs. Earlier trials, such as the OVERCOME trial,[39] have studied the role of carvedilol and enalapril in prevention of LV dysfunction in patients with hematological malignancies undergoing stem cell transplantation with high-dose chemotherapy, while newer trials such as PRADA[40] have demonstrated the role of ARBs such as valsartan in primary prevention of LV dysfunction in patients receiving anthracyclines for breast cancer.

RADIATION-INDUCED CARDIOVASCULAR DISEASE

THE EFFECTS OF RADIATION THERAPY ON THE HEART

The basic mechanism of cardiotoxicity seems to involve damage to blood vessels, likely mediated by generation of reactive oxygen species, which causes DNA strands disruption and subsequent secondary inflammatory changes, finally resulting in extensive fibrosis. Common histologic changes observed in radiation-associated cardiotoxicity include diffuse interstitial fibrosis of the myocardium with significantly reduced ratio of capillaries to myocytes; arterial and capillary narrowing, leading to myocyte cell death, latent ischemia, and thrombosis; endothelial cell damage, triggering precocious atherosclerosis; replacement of the pericardial fat with dense connective tissue, leading to pericardial fibrosis, effusion, or even tamponade; as well as fibrosis and calcification of valvular leaflets/cusps, more commonly left-sided, which suggests a mechanistic role of blood pressure levels in the pathogenesis of the lesions (Fig. 101–6).

Multiple predisposing factors facilitating the development of radiation-induced cardiotoxicity have been recognized thus far, including total radiation dose and dose per fraction, the volume of heart irradiated, and the concurrent administration of additional cardiotoxic agents, such as anthracyclines and trastuzumab. Younger age at the time of irradiation



Pathophysiological manifestations of radiation-induced heart disease

FIGURE 101–6. Pathophysiological manifestations of radiation-induced heart disease for different radiosensitive structures within the heart. LV, left ventricle; RT, radiotherapy. Reproduced with permission from Lancellotti P, Nkomo VT, Badano LP, et al: Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging*. 2013 Aug;14(8):721-740.

and the presence of other risk factors for coronary heart disease, such as hypertension, diabetes, and smoking, are patient-specific dynamics that may heighten the risk of radiation-induced cardiotoxicity.[41]

Cardiac manifestations of irradiation may be seen even before completion of the anticipated exposure or may occur years or decades later. Patients treated for both Hodgkin and non-Hodgkin lymphoma and patients treated for left-sided breast cancer are the most likely to show these manifestations, because treatment for these tumors sometimes involves portals that overlie the heart and as a result of incremental risks imposed by concomitant use of cardiotoxic drugs such as anthracyclines.[42]

RADIATION EFFECTS ON THE PERICARDIUM

The pericardium is the most sensitive cardiac structure with regard to irradiation because it consists of tissue with rapid cell turnover. Initially, exposure can cause an acute radiation-associated pericarditis presenting with signs and symptoms that are clinically undistinguishable from those associated with acute pericarditis from other causes. Sometimes the symptoms may be masked by the underlying disease or the applied chemotherapy.

Acute pericarditis used to be the most frequent complication, but advances reduced its incidence from 25% to 2%.[43] Chronic pericarditis still develops with a clinical incidence of 3% at 20 years and 12% at 30 years in those who underwent chest radiation at a dose of 35 Gy or greater.[43] Fibrinous exudates, fibrous adhesions, and collagenous thickening (predominantly of the parietal pericardium) are characteristic features. The probability to develop radiation-induced pericarditis is influenced by the applied source, dose, its fractionation, duration, radiation exposed volume, form of mantle field therapy, and the age of the patients.

A normal ECG does not rule out acute radiation-associated pericarditis. The changes appear over a period of days and then dissipate. Imaging should start with echocardiography, followed by cardiac CT or MRI if necessary to rule out constriction. A chest radiograph is usually normal unless a large pericardial effusion is manifested as an increased cardiac silhouette.

Pericarditis without tamponade may be treated conservatively with the use of nonsteroidal anti-inflammatory agents. Pericardiocentesis might be indicated if there is an associated large pericardial effusion and if the patient is significantly hemodynamically compromised. It is important to exclude other etiologies in the setting of recurrent pericardial effusion such as infection, tumor invasion or recurrence, and hypothyroidism, which might be seen after mantle irradiation. Pericardial constriction may happen in up to 20% of patients, requiring pericardiectomy. The operative mortality is high (21%) and the postoperative 5-year survival rate is very low (1%), mostly the result of concomitant myocardial fibrosis.[44]

RADIATION EFFECTS ON THE MYOCARDIUM, HEART VALVES, AND CARDIAC VASCULATURE

The myocardium, heart valves, conduction system, and cardiac vasculature are all less frequently affected by radiation than is the pericardium. Rarely, congestive heart failure from myocardial fibrosis or ischemia stemming from small vessel injury, valve sclerosis with or without calcification, and conduction abnormalities that include prolongation of the PR interval and other degrees of AV nodal dysfunction, as well as intraventricular conduction delays, may all occur in cancer patients treated with radiation, especially in doses exceeding 35 Gy. The cardiac effects of radiation are worse in patients who were also treated with anthracyclines, such as survivors of Hodgkin lymphoma.[42]

Radiation-associated vascular injury is a well-described autopsy finding and is also frequent in young patients in the form of premature coronary occlusion. Radiation may also induce thickening of the arterial wall related to intimal thickening, thereby reducing the luminal area. Additionally, radiation may accelerate atherosclerosis and enhance cholesterol deposition and luminal ulceration. Usually the CAD is latent until at least 10 years after exposure (patients younger than 50 years tend to develop CAD in the first decade after treatment, while older patients have longer latency periods). Coronary ostia and proximal segments are typically involved. Several of these patients with radiation-associated CAD and valvular heart disease end up requiring cardiothoracic surgery and the prior radiation exposure protends an increased long-term mortality in these patients compared to matched control populations undergoing similar surgical procedures.[44] The increased cardiovascular risk underscores the importance of identifying individuals who might benefit from primary prevention and aggressive cardiovascular risk factor modification.

Screening echocardiography is advised at 5 years post-exposure in high-risk patients (who have had > 35 Gy of radiation and/or have multiple other CV risk factors) and at 10 years post-exposure for all others. Alternatively, stress echocardiography, myocardial perfusion imaging, coronary calcium scoring, and coronary CT angiography (CCTA) have been used as more sensitive functional screening methods and should be considered at 5 to 10 years after radiation treatment in high-risk patients (Fig. 101–7).

TUMORS AND MALIGNANCIES OF THE CARDIOVASCULAR SYSTEM

BENIGN AND MALIGNANT PRIMARY PERICARDIAL TUMORS

Both primary and metastatic tumors occur in the pericardium. Tumors are found to have spread to the pericardium in approximately 9% of cancer patients who come to autopsy. In the general population, approximately 7% of all patients who experience acute pericarditis either have a history of malignancy or are later found to have a malignancy related to their pericardial inflammation. Not surprisingly, 35% of invasive pericardial interventions are therefore performed on cancer patients. Among primary pericardial tumors, approximately 25% are malignant. Benign tumors present more frequently in infancy and childhood, and malignant tumors are more common after the age of 30 years; lipoma, a slow-growing benign tumor, is often seen later in life. Pericardial cysts, the most common pericardial tumor, are usually small and are most frequently seen along the right ventricular (RV) border. Pericardial cysts are often discovered as incidental findings at autopsy, but they may present with chest pain or arrhythmias or as a supplementary finding on chest radiography obtained for other purposes. Their presence can be confirmed by ultrasonography, CT scanning, or MRI. These lesions are not malignant, and patients have an excellent prognosis. Table 101–8 enumerates the incidence of tumors (benign and malignant) and cysts of the heart and pericardium, and Table 101–9 lists the general manifestations of neoplastic heart disease.

Pericardial teratomas are usually benign, usually occur in children, and are more common in girls. Compression of the right atrium (RA) is sometimes seen with these tumors, and large associated pericardial effusions are frequent. Surgery is the treatment of choice, and the prognosis is usually good when teratomas are benign.

The most common primary malignant tumor of the pericardium is *mesothelioma*; it usually presents in middle-aged adults, and men are afflicted more often than women. It is uncertain if this gender-related

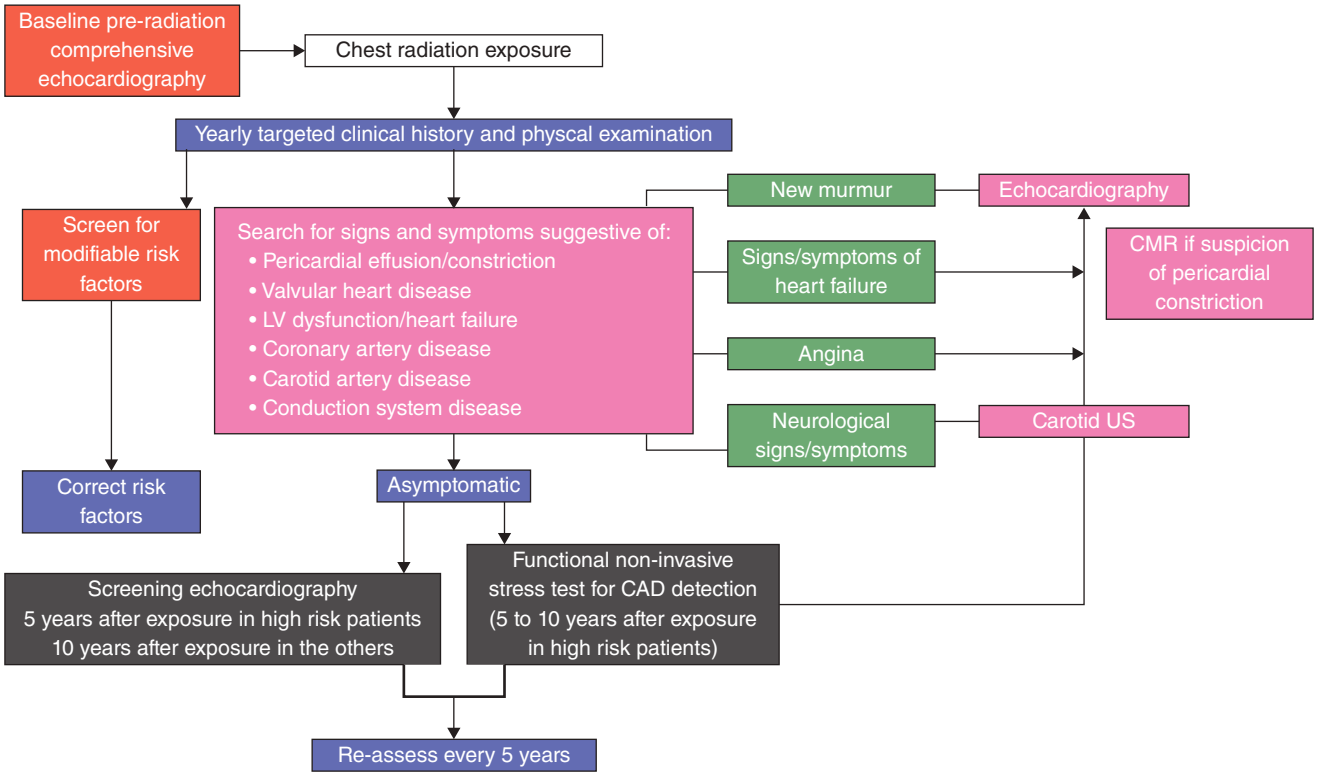


FIGURE 101–7. Algorithm for patient management after chest radiotherapy. CAD, coronary artery disease; CRM, cardiac magnetic resonance; LV, left ventricle; US, ultrasound. Reproduced with permission from Lancellotti P, Nkomo VT, Badano LP, et al: Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging*. 2013 Aug;14(8):721-740.

difference is linked to toxic exposure. Pericardial mesothelioma may present with pericardial effusion, pericarditis, constriction, and constitutional symptoms.

Angiosarcomas are the second most common primary pericardial malignancy; these tumors may originate in the RA or the pericardium, are usually seen in young adults, and are more common in young men. As with mesothelioma, the presentation may include pericarditis and pericardial effusion. Pericardial effusion is usually hemorrhagic; surgical treatment may be successful. When surgery is not possible, treatment options are limited; palliation with radiation and chemotherapy is suboptimal.

Pericardial lipomas are usually benign and surgically resectable; transformation to malignant liposarcoma is possible. These tumors may also be surgically resected, and repeated surgical resection is sometimes necessary. *Thymomas* may arise from the parietal pericardium without evidence of anterior mediastinal involvement and may be benign or malignant; they are not associated with myasthenia gravis.

Metastatic spread of tumors to the *pericardium* is common; it has been estimated that 10% of all malignancies spread to some portion of the heart, and 85% of these eventually involve the pericardium. Lung cancer, breast cancer, and hematologic malignancies together account for approximately two-thirds of the cases of metastatic disease to the pericardium. Melanoma is the tumor most likely to spread to the pericardium, with 70% of patients with metastatic melanoma having pericardial involvement at death. *Metastatic breast cancer* invades the pericardial space in approximately 21% of cases and lung cancer in approximately 19%.

The clinical presentation of metastatic disease to the pericardium is variable (Fig. 101–8). Sometimes pericardial involvement is an incidental finding at autopsy. It may also present as a catastrophic and life-threatening pericardial tamponade. More commonly, however, patients present with acute pericarditis, chronic effusion, and constrictive disease.

Echocardiography is the most helpful test for evaluating such patients (see Chap. 15), but CT scanning and MRI (see Chaps. 15 to 17) are helpful adjuncts. The diagnosis is often confirmed by cytologic analysis of pericardial fluid removed for diagnostic or therapeutic pericardiocentesis; however, cytologic findings are not always positive in patients with malignant effusions, and not all pericardial effusions in cancer patients are malignant. Effusions in these patients may be the result of heart failure, renal failure, inflammation, interruption of lymphatic or venous drainage, infection, hypoalbuminemia, toxicities of chemotherapeutic agents, and chest irradiation.

CARDIAC MYXOMAS

Intracardiac myxoma (Fig. 101–9) is the most frequent benign tumor of the heart. Although most (75%) are located in the left atrium (LA), myxomas are also found in the RA (18%), RV (4%), and LV (3%). Cardiac myxomas usually originate from the region of the fossa ovalis but may arise from a variety of locations within the atria. The DNA genotype of sporadic myxomas is normal in 80% of patients. Tumors are likely to be associated with other abnormal conditions and have a low recurrence rate. Approximately 5% of myxoma patients show a familial pattern of tumor development with autosomal dominant inheritance; 20% of those with sporadic myxoma have an abnormal DNA genotype chromosomal pattern. Carney complex, is characterized by cardiac and mucocutaneous myxomas, lentiginosis, and

TABLE 101–8. Tumors and Cysts of the Heart and Pericardium

Type	Number	Percentage
Benign		
Myxoma	130	24.4
Lipoma	45	8.4
Rhabdomyoma	36	6.8
Fibroma	17	3.2
Hemangioma	15	2.8
Teratoma	14	2.6
Mesothelioma of the atrioventricular node	12	2.3
Granular cell tumor	3	
Neurofibroma	3	
Lymphangioma	2	
Subtotal	319	59.8
Pericardial cyst	82	15.4
Bronchogenic cyst	7	1.3
Subtotal	89	16.7
Malignant		
Angiosarcoma	39	7.3
Rhabdomyosarcoma	26	4.9
Mesothelioma	19	3.6
Fibrosarcoma	14	2.6
Malignant lymphoma	7	1.3
Extraskeletal osteosarcoma	5	
Neurogenic sarcoma	4	
Malignant teratoma	4	
Thymoma	4	
Leiomyosarcoma	1	
Liposarcoma	1	
Synovial sarcoma	1	
Subtotal	125	23.5
Total	533	100.0

Reproduced with permission from McAllister H, Fenoglio JJ: Tumors of the cardiovascular system. Fascicle 15, second series. *Atlas of tumor pathology*. Washington, DC: Armed Forces Institute of Pathology, 1978.

TABLE 101–9. General Manifestations of Neoplastic Heart Disease

Pericardial Involvement
Pericarditis and pain
Pericardial effusion
Radiographic enlargement
Arrhythmia, predominantly atrial
Tamponade
Constriction
Myocardial Involvement
Arrhythmias, ventricular and atrial
ECG changes
Radiographic enlargement
Generalized
Localized
Conduction disturbances and heart block
Congestive HF
Coronary involvement
Angina, infarction
Intracavitary tumor
Cavity obliteration
Valve obstruction and valve damage
Embolic phenomena: systemic, neurologic, and coronary
Constitutional manifestations

Abbreviations: ECG, electrocardiography; HF, heart failure.

endocrine dysfunction including bilateral adrenal micronodular hyperplasia. The cardiac tumors are often multicentric, rarely metastasize and are amenable to surgical resection. There at least three different genetic loci with two identified genes for this complex. Most true myxomas arise only from the mural endocardium despite isolated reports that they arise from the cardiac valves, pulmonary vessels, and vena cava.

Pathology of Cardiac Myxomas

Attached to the endocardium by a broad base, myxomas are usually pedunculated, polypoid, and friable, although some may have a smooth surface and are rounded. A myxoma appears as a soft, gelatinous, mucoid, usually gray-white mass, often with areas of hemorrhage or thrombosis. Myxomas vary from 1 to 15 cm in diameter, with most measuring 5 to 6 cm.

On microscopic examination, the myxoma consists of an acid mucopolysaccharide myxoid matrix in which polygonal cells and occasional blood vessels are embedded. Channels, often containing red blood cells, communicate from the surface to deep within the tumor and are lined by endothelial-like cells resembling multipurpose mesenchymal cells, from which the tumor is purported to arise. Similar endothelial

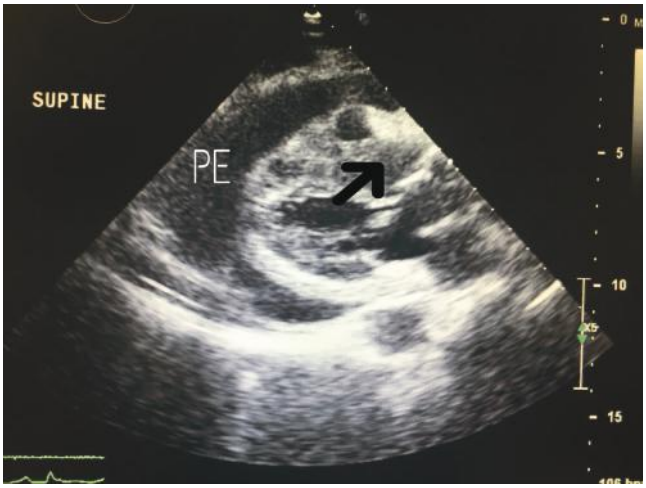


FIGURE 101–8. Parasternal long axis of a large circumferential pericardial effusion (PE) with involvement of the right ventricle with metastatic angiosarcoma (*arrow*) from the gluteal region. The right ventricular cavity and free wall have been infiltrated with the metastatic tumor. Used with permission from Gagan Sahni, MD. Mount Sinai Hospital, New York, NY.

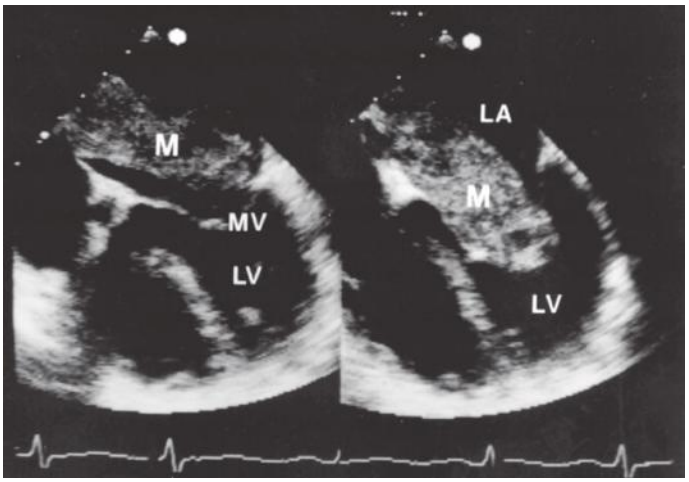


FIGURE 101–9. Transesophageal echocardiogram in the four-chamber view from a 50-year-old man who presented with exertional dyspnea and syncope. A large left atrial myxoma (M) attached to the interatrial septum is seen prolapsing across the mitral valve (MV) into the left ventricle (LV) in diastole (right panel). LA, left atrium. Used with permission from Susan Wilansky, MD, Medical Director, Noninvasive Imaging, St. Luke's Episcopal Hospital, Houston, Texas.

cells line the surface of the tumor; however, fibrin, erythrocytes, and organized thrombi also may be present on the surface. Cystic areas; focal or gross hemorrhage; calcification; glandular elements; rarely, bone formation; and even hematopoietic tissue constitute the multiple, less common, variations.

Although asymptomatic patients with myxoma have been reported, most present with one or more effects of a *triad* of constitutional, embolic, and obstructive manifestations. Cardiac myxomas provoke systemic manifestations in 90% of the patients, characterized by weight loss, fatigue, fever, anemia (often hemolytic), elevated erythrocyte sedimentation rate, and elevated serum immunoglobulin concentration formed in response to tumor embolization, degenerative changes within the tumor, or overproduction of IL-6 by the tumor.

Constitutional manifestations and embolic potential are relatively common in patients with myxoma in any intracavitary location. The cardiac manifestations, symptoms, and physical findings are the consequence of the intracavitary mass and the particular location of the tumor. Myxomas of the LA may obstruct either the mitral or pulmonary venous orifices and produce pulmonary venous hypertension, secondary pulmonary hypertension, and right-sided heart failure. The clinical symptoms include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, acute pulmonary edema, cough, and hemoptysis, along with palpitations, chest pain, fatigue, and peripheral edema. Episodes of syncope or dizziness are frequent, and sudden death may occur. A marked change in the severity of any symptom caused by a change in position of the patient, especially if recumbency relieves dyspnea, is suggestive of myxoma. On physical examination, the S_1 is loud and frequently split, with the second component corresponding to the tumor's expulsion from the mitral orifice in the case of left atrial myxoma (see Chap. 11). P_2 is accentuated, and an early diastolic sound, the "tumor plop," is usually heard 80 to 120 milliseconds after the A_2, resembling an opening snap. The tumor plop may be confused with either an opening snap or a third heart sound and follows A_2 at an intermediate interval between these events.

The value of transthoracic echocardiography in the noninvasive diagnosis of intracavitary tumors is well documented (see Chap. 15). M-mode recordings in patients with a prolapsing LA myxoma typically demonstrate a diminished ejection fraction slope of the anterior leaflet of the mitral valve, behind which a dense array of wavy tumor echoes is seen (see Chap. 15). The tumor plop coincides with the completion of this anterior movement of tumor echoes. A similar array of tumor echoes may be seen in the LA during ventricular systole. Transthoracic echocardiography and transesophageal echocardiography identify the size, shape, point of attachment, and motion characteristics of LA atrial myxomas. Transesophageal echocardiography permits superior imaging of the posterior cardiac structures and LA myxomas, especially their point of attachment. Visualization of all four chambers permits recognition of multiple tumors, as well as tumors in less common locations. Doppler assessment of the flow patterns of the mitral valve and pulmonary vein provides further information regarding the hemodynamic consequences of LA myxomas (see Fig. 101–9).

Surgical resection of a myxoma is the only acceptable therapy and, in view of the dangers of embolization and sudden death, should be performed promptly. For complete removal of LA myxoma, we use a biatrial approach, excising a full thickness of interatrial septum if the tumor is attached to the region of the fossa ovalis. RA myxomas are commonly attached to the fossa ovalis, and with right-sided tumors, a full thickness of atrial septum should also be resected. If a large portion of the septum is removed, a patch of knitted Dacron cloth should be used for repair to avoid distortion, arrhythmias, or possible atrial septal defect. Ventricular standstill with cardioplegia solution is induced before manipulating the heart to reduce the possibility of fragmentation of the gelatinous tumor. LA myxomas have been removed successfully during pregnancy, using cardiopulmonary bypass, with subsequent uncomplicated completion of a full-term pregnancy. Surgical removal of a RV myxoma in a neonate has been reported.[45]

PREOPERATIVE AND POSTOPERATIVE CARDIOVASCULAR CONSIDERATIONS IN PATIENTS UNDERGOING NONCARDIOVASCULAR SURGERY

Extensive literature has been published over the past 30 years on identifying and minimizing the risks for cardiac complications related to noncardiac surgery (see Chap. 98). Because the surgical treatment of patients with cancer can involve lengthy and complicated procedures, the attendant risks of surgery are often increased.

PREOPERATIVE EVALUATION

The overall preoperative risk assessment for cancer patients being considered for noncardiac surgery is largely similar to that applied to other groups of patients. The AHA/ACC guidelines (see Chap. 98) that have been developed and updated over the past decade are sufficiently extensive and detailed in this regard. Additional assessment of cancer patients undergoing surgery should also include a review of recent chemotherapy, bleeding risk in case of stents on antiplatelet therapy etc which are summarized in Table 101–10. Chemotherapy affects the immune system and may result in significant thrombocytopenia or neutropenia, which may predispose the patient to infection or bleeding. Also, chemotherapy may result in ECG prolongation of the QT interval and the associated increase in risks for ventricular arrhythmias. It is important to acquire information on such interactions preoperatively because of the bearing it can have intraoperatively and postoperatively. Radiation therapy may have an impact on surgical outcome as well.

A similar approach to the basic laboratory testing and stress testing for risk stratification is used in both patients with and without cancer. However, patients who are undergoing surgery for cancer may have

TABLE 101–10. Preoperative Evaluation of Cancer Patients Undergoing Noncancer Surgery

Risk assessment as per ACC/AHA guidelines and modifications
Identify if chemotherapy was recently administered
Clarify location and intensity of radiation therapy
Careful consideration of a patient with established CAD
Was a stent recently placed?
Was optimal treatment with cardioprotective medications given?
Device management
Recommended preoperative check of device
Establish whether patient is pacemaker dependent
Check device postoperatively
Cancer-specific concerns
Pheochromocytoma (preoperative α- and β-blockers)
Carcinoid (consideration of transesophageal echocardiography to guide volume replacement)
Assess whether there is a possible mass extension or thrombus present

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CAD, coronary artery disease.

greater debility and thus may not be able to exercise adequately. Consequently, pharmacologic stress testing (see Chap. 52) may be used more frequently in these patients. Although this provides information about myocardial perfusion and reversible ischemia, it does not provide insight into the overall physical capacity of these patients. This information may be relevant after surgery because a poor functional state will likely contribute to a protracted recovery. In several cases, preoperative testing may not influence the timing and choice of surgery, especially if the oncological benefits outweigh the risks. However, it may help the physician to assess the burden of perioperative cardiovascular risk.

Cancer surgery is a particular challenge in patients who have coexisting coronary artery disease. Preoperative coronary revascularization does not reduce the risk of the surgical procedure and may actually make patients more prone to complications. This is especially true with regard to percutaneous coronary interventions as stent thrombosis is a feared, albeit rare, complication of premature discontinuation of dual antiplatelet therapy. Conservative medical therapy, instead of percutaneous coronary intervention, may be a preferred management approach for select cancer patients with coronary artery disease and may eliminate the need for prolonged dual antiplatelet therapy. In patients with LV dysfunction, optimal management of their volume status perioperatively is equally necessary.

The perioperative management of implanted cardiac devices in patients undergoing surgery for cancer is another important consideration. This holds true especially for those who received prior radiation therapy with the pacemaker in close proximity of the radiation field, thereby making them susceptible to radiation induced device malfunction. The physical distance between the location of the surgery and the device is also important, with a greater likelihood of pacemaker malfunction from electromagnetic interference in case of patients undergoing procedures in the head and neck or chest. If electrocautery is to be used, pacemakers should be placed in a triggered or asynchronous mode; implantable cardioverter-defibrillators should have arrhythmia detection suspended before surgery. If defibrillation is to be used, the current flow between the paddles should be kept as far away from and perpendicular to the lead system as possible.

Patients with certain tumors with a predilection for mediator release present major preoperative challenges that may concern cardiologists. Specific strategies are required in patients with pheochromocytomas to prevent potentially life-threatening blood pressure elevations during the perioperative period, as noted above. Patients with carcinoid tumors may also demonstrate wide fluctuations in blood pressure during surgical resection, albeit through the release of different mediators. The volume status in these patients may also be difficult to discern, especially if concomitant tricuspid regurgitation is present. Transesophageal ultrasonography (see Chap. 15) during surgery may be particularly useful in assessing the intracardiac volume status in patients who are undergoing surgery to remove these challenging tumors.

POSTOPERATIVE CARE

The postoperative management of patients who undergo cancer surgery is similar to that of the noncancer population. For some surgeries, the incidence of postoperative atrial fibrillation, estimated to be as high as 33%, is disproportionately higher than in the noncancer population[46]; a number of these patients have persistent arrhythmias. Restoration of sinus rhythm as quickly as possible following the onset of atrial fibrillation may obviate the need for anticoagulation (see Chap. 81). It is also imperative to reinitiate preoperative cardioprotective medications as early as possible in the postoperative period to preserve stable cardiovascular status. The general principles of early ambulation and "pulmonary toilet" remain standard postoperative surgical principles that should be used aggressively in cancer patients as well.

CANCER SURVIVORSHIP

As per the Cancer Trends Progress Report 2009/2010 Update,[1] the length of cancer survival has increased for all cancers combined. The overall 5-year survival rate for all types of cancer increased from 49% in 1977 to 68% in 2008. Today there are 14 million Americans alive with a history of cancer.

This represents a growing aging population vulnerable to the late risks of potentially cardiotoxic chemotherapy and chest radiation. These patients should be aware of this risk and should subsequently undergo regular monitoring and treatment of cardiovascular risk factors such as hypertension, diabetes, and dyslipidemias. Risk factor modification and symptom awareness may play pivotal roles. Even those who are asymptomatic but are high risk for developing cardiovascular disease as a result of their past exposure to cardiotoxic chemotherapy such as anthracyclines, combined cardiotoxic chemotherapy regimens (such as doxorubicin with trastuzumab), high doses of chemotherpy (eg, doxorubicin > 350 mg/m^2) or radiation (> 35 Gy), and age greater than 65 years should have a cardiac assessment. This may include screening with imaging such as stress testing, echocardiography, or carotid artery imaging, although definitive guidelines to inform such testing do not exist.

FUTURE DEVELOPMENTS

Cancer genomics has focused on the discovery of mutations and chromosomal structural rearrangements that either increase susceptibility to cancer or support the cancer phenotype. Protein kinases are the most frequently mutated genes in the cancer genome, making them attractive therapeutic targets for drug design. However, the use of some

of the kinase inhibitors (KIs) has been associated with toxicities to the heart and vasculature, including acute coronary syndromes and heart failure. There are ongoing studies on the genetic basis of cancer, focusing on mutations in the kinase genome (kinome) that lead to tumorigenesis. This will allow an understanding of the real and potential power of modern cancer therapeutics and the underlying mechanisms that drive the cardiotoxicity of these KIs.[25]

CONCLUSIONS

Advances in cancer therapy and the outcome-limiting effect of their cardiovascular adverse effects have generated a growing need for the field of cardio-oncology. With this, the paradigm has shifted toward early recognition and treatment of cardiotoxicity and even precancer therapy, cardiovascular risk assessment, and prevention. The key practical steps in the cardio-oncology approach outlined in this chapter comprise the following:

1. A multidisciplinary approach with ongoing interaction between dedicated specialists comprising cardiologists, oncologists or hematologists, and radiation oncologists in a "cardio-oncology team" approach that evaluates potential cardiotoxic adverse effects of chemotherapeutic agents prior to the start of therapy.
2. Early and routine screening of cardiovascular diseases in cancer patients.
3. Risk stratification for the development of cardiotoxicity prior to the initiation of chemotherapy.
4. Institution-wide algorithms should be formulated based on current evidence-based medicine to guide use of cardiotoxic drugs like anthracyclines and trastuzumab.
5. Evolving imaging techniques such as longitudinal strain may establish themselves as a future modality for detection of early cardiotoxicity.
6. Awareness of cardiotoxic manifestations beyond LV dysfunction of various chemotherapeutic agents and radiation therapy.

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CHAPTER 102

HIV/AIDS AND THE CARDIOVASCULAR SYSTEM

William Lewis and Peter F. Currie

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INTRODUCTION

HIV/AIDS has become an important clinical entity in cardiovascular medicine. As a result of behavioral changes and improved therapy, HIV/AIDS patients are surviving longer and the prevalence of cardiovascular diseases now more closely mirrors that of the non-HIV/AIDS population. As such it is important to be aware of the cardiovascular effects of HIV/AIDS and side effects of therapy, such as highly active antiretroviral therapy (HAART), both of which are key factors in the development of cardiovascular disease in HIV/AIDS.

EPIDEMIOLOGY OF HIV/AIDS

The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 and is caused by the human immunodeficiency virus (HIV-1).[1] HIV-2 causes a similar illness to HIV-1 but is less aggressive and has so far been observed mostly in western Africa. HIV-1 is acquired through exposure to infected body fluids, particularly blood and semen. The commonest modes of spread are sexual (heterosexual or men who have sex with men [MSM]), parenteral (blood or blood product recipients, injection drug users, and occupational exposure to contaminated products), and vertical transmission (mother to fetus).

HIV/AIDS is now the second leading cause of death in the world, with a continuing global prevalence of 0.8%.[2] According to the World Health Organization, 35 million people are living with HIV/AIDS, with 2 million new infections and 1.2 million AIDS-related deaths reported in 2014.[2] The vast majority of deaths have occurred in sub-Saharan Africa, where over 13 million children have been orphaned and approximately two-thirds of the global HIV/AIDS burden exists.[3] More than 2.4 million people have been infected by HIV in North America and Europe although many are still unaware of their infectious status.[4] Prevention strategies may have helped reduce HIV prevalence rates in some countries where HIV infection may be on the decline,[5] and it is estimated that up to 15 million people worldwide are now accessing antiretroviral therapy.[2,5]

Many cultural and social factors impact demographic patterns of HIV/AIDS.[6,7] In the United States and northern Europe, HIV had predominantly involved MSM, although heterosexual transmission now is the dominant route of infection.[8-12] In Southern and Eastern Europe, Vietnam, Malaysia, Northeast India, and China the incidence has been greatest in injection drug users. However, in Africa, the Caribbean, and much of Southeast Asia, the dominant route of transmission has been heterosexual or vertical from mother to child, reflecting the high global proportion of relatively young women with HIV.[13]

NATURAL HISTORY AND BIOLOGY OF HIV/AIDS

HIV-1 is a single-stranded RNA retrovirus from the *Lentivirus* family that invades cells containing specific membrane receptors and incorporates a DNA copy of itself into the host's genome. Immune deficiency is the result of viral and immune-mediated destruction of $CD4^+$ lymphocytes caused by continuous high-level HIV-1 replication. The reduction in the number of $CD4^+$ cells circulating in peripheral blood is tightly correlated with the plasma viral load. Both viral load and $CD4^+$ count can be monitored from peripheral blood samples and are used as measures of disease progression

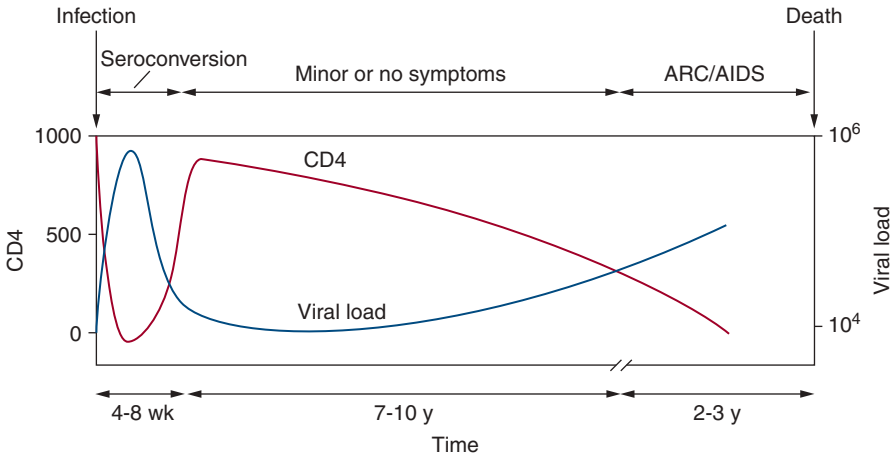

FIGURE 102–1. The natural history of HIV infection, ARC, and AIDS. Reproduced with permission from Boon NA, Davidson S: *Davidson's Principles & Practice of Medicine*, 20th ed. Edinburgh: Elsevier/Churchill Livingstone; 2006.

and therapeutic efficacy. Virus-specific CD8 cytotoxic T-cell lymphocytes develop rapidly after infection and can lyse infected CD4+ cells. They play a crucial role in controlling HIV-1 replication after infection and may therefore determine the rate of disease progression.

Any depletion in CD4+ cells renders the body susceptible to opportunistic infections and oncogenic virus-related tumors. The predominant opportunistic infections seen in HIV-1 disease are caused by intracellular parasites (eg, *Mycobacterium tuberculosis*) or pathogens that are more susceptible to cell-mediated rather than antibody-mediated immune responses. After the initial infection there is a dormant period before symptoms and disease supervenes (Fig. 102–1). In the absence of antiretroviral therapy (HAART), the average length of life after infection is approximately 10 years.[14] In contrast, HAART can essentially eliminate detectable HIV-1 viremia and transform the patients' prognosis to one of a chronic disease with associated organ-specific illnesses that require specialized treatment.

Primary infection is usually established 2 to 6 weeks after exposure.[15] Most (70% to 80%) patients experience a self-limiting illness, similar to infectious mononucleosis, characterized by fever, fatigue, pharyngitis, lymphadenopathy, and maculopapular rash. In many patients the illness is mild and only identified by retrospective enquiry at later presentation. Over 95% of patients seroconvert (ie, become serologically positive for HIV-1 infection) within 6 months. This usually coincides with a surge in plasma HIV-1 RNA levels to > 1 million copies/mL (peak between 4 and 8 weeks following exposure), and a fall in the CD4+ count to 300–400 cells/mm3. Symptomatic recovery is accompanied by a rise in the CD4+ count and a fall in viral load. Nevertheless, the CD4+ count rarely recovers to its original value (see Fig. 102–1).

CLASSIFICATION OF HIV/AIDS

A simple CDC classification has been used to describe the phases of disease (Table 102–1). With regard to cardiovascular diseases in HIV/AIDS, premature coronary artery disease, infective endocarditis, and problems associated with intravenous drug abuse may supervene at any time. Pericardial effusion and cardiomyopathy (CM) are more frequently described in late-stage (CDC Category C) disease, and may have been more prevalent before HAART. The classification is noted on the CDC website and updated occasionally in MMWR.

TABLE 102–1. CDC Classification of HIV Infection

Category A	Asymptomatic patients; progressive lymphadenopathy
Category B	Symptomatic patients without AIDS-defining illness
Category C	Symptomatic patients with AIDS-defining illness

ASYMPTOMATIC INFECTION (CDC CATEGORY A DISEASE)

Viral replication takes place in the lymphoid tissue throughout this stage; there is sustained viremia and the CD4+ count falls steadily (typically by between 50 and 150 cells/year). Although there may be persistent generalized lymphadenopathy, the patient remains well.

MILD SYMPTOMATIC DISEASE (CDC CATEGORY B DISEASE)

The median interval from infection to the development of symptoms is around 7 to 10 years. A variety of diseases known as AIDS-related complex conditions (eg, oral hairy leukoplakia, weight loss, night sweats, and chronic diarrhea) may supervene but are not AIDS-defining.

ACQUIRED IMMUNODEFICIENCY SYNDROME (CDC CATEGORY C DISEASE)

HIV/AIDS is defined by the development of one or more specific opportunistic infections, tumors, and other conditions. These include esophageal candidiasis, CMV retinitis, pulmonary or extra-pulmonary tuberculosis, Kaposi sarcoma (KS), and HIV-1 associated dementia. Most forms of HIV/AIDS CM and pericardial effusion occur at this stage.

HIV/AIDS AND THE CARDIOVASCULAR SYSTEM: HISTORICAL PERSPECTIVE

EARLY IN THE HIV/AIDS EPIDEMIC: THE ERA BEFORE HAART

Early in the epidemic, and before the significant clinical advances from HAART, it was suggested that more than 6% of HIV/AIDS patients had cardiovascular diseases with the heart as the principal target.[16] Pathological studies revealed nonbacterial thrombotic endocarditis (NBTE), CM and myocarditis, pericarditis and pericardial effusions, and metastatic neoplasms (predominantly KS and lymphoma).[16-20] Many of these pathological lesions were mild and HIV/AIDS heart disease probably caused symptoms in fewer than 10% and death in fewer than 2% of all patients with HIV/AIDS. Cardiovascular mortality and morbidity was primarily caused by the overwhelming problems of immune dysfunction and opportunistic infection that were so prevalent in the pre-HAART era. The common cardiovascular manifestations of HIV-1 infection are listed in Table 102–2. Today the interaction between environmental stresses, therapeutic toxicities, and the increased longevity afforded by the efficacy of HAART together changed the spectrum of cardiovascular disease in HIV/AIDS (Fig. 102–2).

CONTEMPORARY CARDIOVASCULAR DISEASE IN HIV/AIDS

Some of the cardiovascular illnesses seen early in the epidemic persist in contemporary patient cohorts, but some are more prominent in resource-limited settings. A recent meta-analysis of patients treated with HAART demonstrated left ventricular systolic dysfunction in 8.3% and diastolic dysfunction in 11% in minimally symptomatic

TABLE 102–2. Cardiac Manifestations of HIV/AIDS

Pericardial effusion	• Idiopathic • Infectious (viral, bacterial especially tuberculous, and fungal) • Neoplastic (Kaposi sarcoma and non-Hodgkin lymphoma)
Heart muscle disease	• Myocarditis (idiopathic/lymphocytic, specific infections, toxins) • Dilated cardiomyopathy and left ventricular dysfunction
Endocarditis	Marantic (nonbacterial thrombotic endocarditis) Infective
Tumors	• Kaposi sarcoma • Lymphoma
Right ventricular dysfunction and pulmonary hypertension	• Primary • Secondary (recurrent chest infections, thromboembolism)
Premature atherosclerosis and coronary artery disease	
Adverse drug effects	• Hyperlipidemia • Proarrhythmia
Vascular disease	
Autonomic dysfunction	

patients, and the risk of heart failure appears doubled for HIV patients compared to risk factor controls without infection.[21-23] Ischemic CM may be increasing in HIV/AIDS, as suggested by higher rates of coronary artery disease hospitalizations in patients with HIV/AIDS compared to non-HIV/AIDS.[24-26]

Tuberculous pericarditis remains an important cardiac manifestation of the disease, particularly in Africa.[23, 27-29] In the developed world with improved access to HAART, cardiovascular, pulmonary, and renal diseases predominate, bolstered by increased survival from HIV/AIDS and opportunistic infections. Atherosclerotic disease, which was rarely noted in the early days of the epidemic, is now more common and clinically relevant in the care of HIV/AIDS patients.[24, 30]

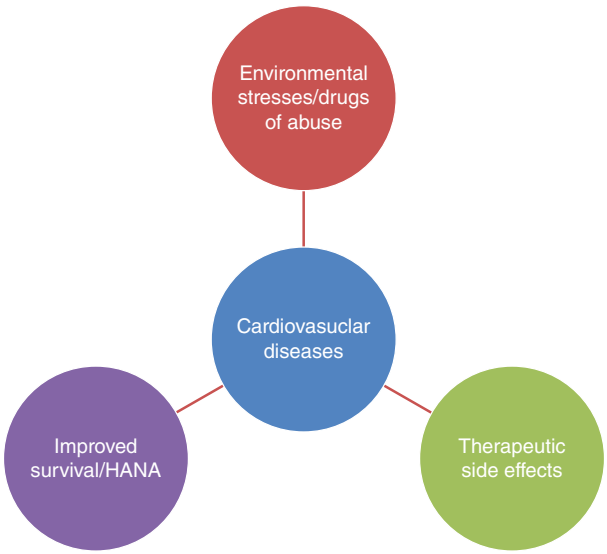

FIGURE 102–2. The nature of cardiovascular diseases in contemporary HIV/AIDS now includes increased longevity and related diseases of aging (like atherosclerotic disease), side effects of antiretroviral therapy, and environmental factors such as drugs of abuse. In the developing world, some of these factors may be more prominent while others are less so.

It should be recognized clearly that survival with HIV/AIDS improved because of HAART combinations that frequently utilize two NRTIs and one or two protease inhibitors (PI). Newer HAART preparations additionally utilize an integrase inhibitor and a CYP3A inhibitor in place of a PI in a single tablet. Other regimes may include non-nucleoside reverse transcriptase inhibitors (NNRTIs).[31] Such combinations prevent or attenuate HIV-1 replication through a "multiple hit" approach to infection analogous to anti-tuberculous therapy and to some antineoplastic therapies. HAART's success has resulted in a concomitant increase in the rolls of age-related illnesses in patients with HIV/AIDS that have no direct connection to the retroviral infection. This subset of chronic diseases, like cardiovascular diseases, with prevalent comorbidities, is termed HANA (HIV-associated non-AIDS illnesses).[32-34]

Some HANA conditions may be due (in part) to HAART-induced metabolic problems (particularly insulin resistance and hyperlipidemia), independent cardiovascular risk factors (like smoking and preexisting lipid abnormalities in HIV/AIDS), or side effects from HIV/AIDS therapeutics (see below).[35] HAART has, therefore, changed the pattern of disease in developed countries where premature coronary artery disease, metabolic syndrome, and other manifestations of atherosclerosis are emerging as key cardiovascular disorders in the HIV/AIDS patient.

CARDIOVASCULAR ASSESSMENT OF HIV/AIDS PATIENTS

It seems likely that as survival increases with improved therapy, more HIV/AIDS patients will be seen by cardiologists, and indeed the number of reports of cardiovascular problems in HIV/AIDS will grow.[27,36-38] Screening for cardiovascular disease in HIV/AIDS patients combines established principles with an evolving understanding of HIV/AIDS-specific pathophysiology and pharmacology. Known risk factors still contribute to cardiovascular disease in HIV/AIDS, and as such all HIV/AIDS patients should be subjected to cardiovascular risk stratification and periodic monitoring.[39]

Although it may have been possible to overlook the importance of blood pressure control and lipid management in this population,[40] traditional cardiovascular risk factors (dyslipidemia, insulin resistance, hypertension, smoking, sedentary lifestyle, weight, and family history) should routinely be assessed as part of the general care of HIV/AIDS patients. A fasting lipid panel is recommended when enrolling in HIV/AIDS care and one to three months after HAART initiation,[41-43] and hemoglobin $A1_c$ is a useful marker of metabolic derangement after starting HAART.[43]

Heart disease may be overlooked in HIV/AIDS patients because symptoms of breathlessness, fatigue, and poor exercise tolerance are frequently ascribed to other conditions associated with HIV infection.[36] As such, electrocardiography should be performed routinely to confirm sinus rhythm and allow assessment of the QT interval. The ECG may also alert the cardiologist to the possibility of coronary artery disease (Q-waves and ST/T-wave changes) or left ventricular hypertrophy. Echocardiographic assessment of HIV/AIDS patients is extremely useful and can be used easily to identify those cardiac conditions common in HIV/AIDS patients that may be associated with a poor outcome, including pericardial effusion,[23,29] left ventricular (LV) systolic dysfunction, heart muscle disease (cardiomyopathy), and intracardiac masses.[36,44] Echocardiography may also provide useful information on the appearance of the right ventricle (RV), provide an indirect assessment of pulmonary pressures, and reveal regional wall-motion abnormalities potentially suggestive of CAD.

A history of palpitation or near syncope may indicate the need for ambulatory ECG monitoring, as with Holter monitoring.[45] Functional stress testing may be useful for the investigation of anginal chest pain, while CT coronary angiography or cardiac magnetic resonance (CMR) may be used in specific clinical circumstances.[46]

It has been suggested that any HIV/AIDS patient with traditional risk factors for the development of, or who demonstrates any potential clinical manifestation of, cardiovascular disease should have a baseline echocardiogram performed. Thereafter, serial echocardiography should be performed every one to two years (Table 102–3).[47] Unfortunately, logistical limitations make it unlikely that these goals can be achieved in the developing world. Similarly, it may be justifiable to perform a baseline echocardiographic study at the time of diagnosis of HIV/AIDS with annual to biannual examination of select asymptomatic patients (see Table 102–3).[48] Clearly, more aggressive monitoring may be guided by the cardiologist on discovery of abnormalities or in those patients with significant, potentially cardiotropic viral infections or unexplained pulmonary symptoms.

HIV/AIDS AND THE PERICARDIUM

Pericardial effusion and pericarditis were the commonest cardiac abnormalities found in early HIV/AIDS autopsy studies and remain a significant problem in Africa, where the largest number of HIV/AIDS patients are found.[27, 29] Pericardial effusion is still found in up to 40% of patients, particularly in association with generalized fluid retention and advanced disease, and pulmonary hypertension.[19] Small effusions are common in patients with heart failure or malignant infiltration, but cardiac tamponade is rare. The finding of new cardiomegaly on chest radiography should prompt early echocardiographic assessment to evaluate for pericardial effusion.[49]

Clinically significant pericardial effusions are usually caused by viral or bacterial infection or malignant infiltration, particularly with Kaposi sarcoma (KS) or non-Hodgkin lymphoma (NHL). In Africa, pericardial effusion itself is suggestive of HIV-1 infection, and up to 72% of African patients with serosanguinous effusions have been found to be infected with HIV-1.[27-29] Pericarditis caused by *M. tuberculosis* or *M. avium-intracellulare* infection remains a pressing problem in Africa. Other unusual pathogens, including *Nocardia asteroides,* herpes simplex viru,s and Cytomegalovirus, should be considered and appropriate antituberculous or antiviral therapies may be helpful. Culture of pericardial biopsy or fluid from symptomatic effusions may also be also useful in identifying treatable opportunistic infections or malignancy.

Surgical intervention is not always beneficial in AIDS patients with large pericardial effusions and there are no data are available on the long-term outcome of such measures. Pericardiocentesis and pericardiectomy was used to treat a *Staphylococcus aureus* pericardial tamponade in an HIV/AIDS drug user, who remained well for more than 5 years.[50,51]

TABLE 102–3. Indications for Echocardiographic Assessment of HIV-Positive Patients

Possible baseline assessment at time of diagnosis of HIV infection

Baseline assessment and 1-2 yearly monitoring of patient with:

- Clinical manifestation of possible cardiac involvement
  - Unexplained dyspnea/hypoxia
  - Third heart sound/inappropriate tachycardia
  - Raised JVP
  - Peripheral edema/right heart failure
  - Radiographic evidence of cardiomegaly
- Viral coinfection
  - Cytomegalovirus
  - Epstein-Barr virus
  - Coxsackie virus
  - Adenovirus
- History of pre-existing cardiac disease
  - Left ventricular systolic dysfunction (all cause)
  - Valvular heart disease
  - Suspicion of infective endocarditis in IVDU
- High-risk HIV patients with :
  - Wasting
  - Encephalopathy
  - $CD4^+$ count < 100 cells/mm^3
  - Potentially cardiotoxic medication (see later in chapter)
  - Multiple hospitalizations

Possible 1-2 yearly monitoring of asymptomatic HIV positive patients

Frequent assessment of HIV positive patients with cardiovascular involvement (as guided by cardiologist)

HIV/AIDS AND THE MYOCARDIUM

MYOCARDITIS

Numerous pathological studies confirmed the presence of varying histological patterns of lymphocytic myocarditis in HIV/AIDS patients, although many do not fulfill the Dallas criteria formulated to secure the histopathological diagnosis.[19,52] Clinical correlation with myocarditis has been described in HIV/AIDS studies, and opportunistic infections were prominent comorbid conditions.[53] Interstitial mononuclear infiltrates have also been reported in other forms of CM (and non-CM), which further confounds diagnosis of authentic myocarditis.[54] The apparent difference in the prevalence of myocarditis in different studies may relate to clinical factors, sampling errors, and HAART. As such, estimates of the prevalence of myocarditis in HIV/AIDS varies from 53% in the pre-HAART era to much lower levels today in the developed world, with the conditions remaining prevalent and problematic in the developing world.[27,55] Of note, it is relatively uncommon for HIV/AIDS patients in the developed world to present initially with cardiac manifestations of HIV/AIDS, but it can be seen and merits consideration (Fig. 102–3).

Myocarditis may be precipitated by a variety of viral infections, and the inflammatory reaction can progress after the viral infection has apparently resolved. An immune reaction, either to viral antigen or to altered myocardial protein, may precipitate myocardial necrosis and inflammatory cell infiltration.[56] However, simple histopathological methods alone may be insufficient to exclude the diagnosis of myocarditis in HIV/AIDS patients. Infiltrating CD8 and CD45 lymphocytes have been found in association with increased major histocompatibility complex (MHC) class I antigen expression in histologically normal endomyocardial biopsies from HIV/AIDS with cardiac failure.[57]

It remains possible that a subgroup of HIV/AIDS patients may have immune-mediated heart disease despite pathologically nondiagnostic biopsies. An inflammatory process remains the likeliest substrate for the development of cardiac dysfunction, but this is not proven. There

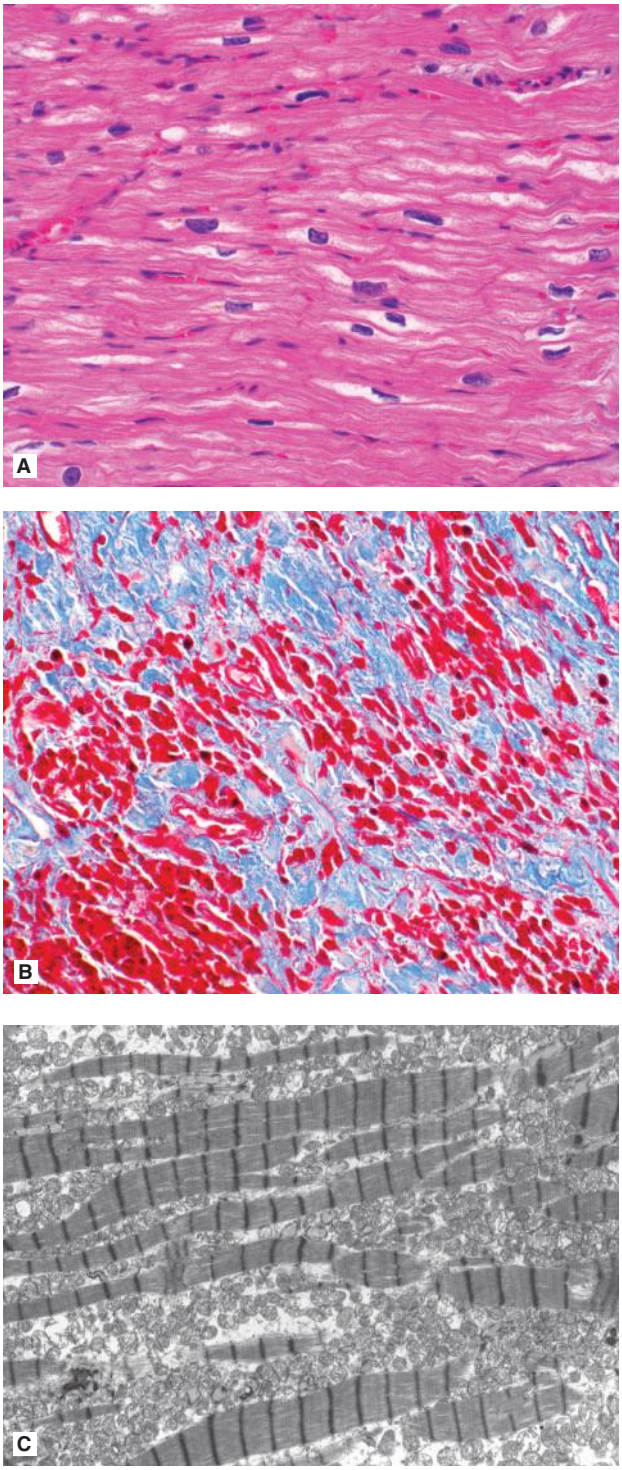

FIGURE 102–3. Heart failure in HIV/AIDS in absence of therapy. A 35-year-old male was admitted with acute onset of congestive heart failure and was found to be seropositive for HIV-1. Antiretroviral therapy started, but his cardiac performance required mechanical ventricular assistance. The LV core specimen from the placement of the assist device revealed abundant cardiac myocytes with hypertrophic and lytic changes, zones of scar suggesting possible older inflammatory injury, and scant foci of lymphoplasmacytic inflammation. Transmission electron microscopy revealed myocytes with decreased sarcomeres and structurally abnormal mitochondria. **A.** Hematoxylin and eosin; original magnification = 400×. **B.** Myocardial sample shows zonal replacement with fibrosis suggestive of previous inflammatory injury. Masson trichrome original magnification = 100×. **C.** Transmission electron microscopy of thin section of cardiac myocyte with disruption of sarcomeres and decreased abundance of sarcomeres and mitochondria. Original magnification = 5500×.

are several hypotheses regarding the etiology of myocarditis in HIV/AIDS including:

1. Primary HIV-1 myocarditis
2. Secondary HIV-1 myocarditis
3. Opportunistic infection

PRIMARY HIV-1 INFECTION OF THE MYOCARDIUM

Despite histopathological evidence supporting a myocardial inflammatory component in HIV/AIDS, HIV-1 has neither been universally accepted nor unambiguously proven as a causative agent of myocarditis. HIV-1 gains entry into cells through binding between its envelope glycoprotein group 120 and $CD4^+$ receptors, which are found on T4 (helper) lymphocytes and some other cell types. Although HIV-1 can infect monocytes/macrophages and myocardial interstitial cells, evidence proving that HIV-1 can infect human cardiac myocytes is less clear.

Some reports of cardiac infection by HIV-1 utilized *in situ* hybridization (ISH), which did not require extraction of target sequences, and thus preserved the histological architecture.[58] However, ISH is limited in defining the responsible cell that undergoes hybridization with HIV-1 probes. That signal could be masked by the dense silver reaction that occurs as part of that technique. Accordingly, precise localization and definite assignment of the hybridization signal to the cardiac myocyte was not possible. Cell culture and polymerase chain reaction (PCR) were equally limited, as such samples could easily be contaminated by the patient's own infected blood cells where a single virion contaminant (eg, from an infected interstitial cell) could be a contaminant and confuse interpretation. Similarly, examination of hearts from nonhuman primates (macaques) infected with Simian Immunodeficiency Virus (SIV) has been accomplished using such methods. Those studies confirmed that SIV infected the cardiac monocytes rather than actual myocytes.[59]

HIV-1 gene sequences were detected by PCR in microdissected endomyocardial biopsies from HIV-1 positive patients, some of whom had cardiac symptoms.[60] HIV-1 has also been shown to gain entry into the human fetal cardiac myocyte by ingestion through a specific Fc receptor and it remains possible that this or other, unidentified mechanisms may promote HIV-1 entry into the myocyte and facilitates a primary HIV-1 myocarditis.[61] It should be noted that such cardiomyocyte infection was only described before extensive use of HAART.

SECONDARY MYOCARDITIS IN HIV/AIDS

With respect to the pathogenesis of myocarditis, analogies may be made between HIV/AIDS immune responses and those responses that cause inflammatory damage in other infections. For example, in Chagas CM, uninfected cardiac myocytes are damaged by the host response to *Trypanosoma cruzi*. Interstitial lymphocytes and macrophages may form contact with myocytes, causing a focal loss of basement membrane through a local reaction. Proteolytic enzymes released through HIV-1 replication in the interstitium could also damage myocytes. Such "innocent bystander destruction" may be particularly relevant to diseases of the myocardium here.[62]

The HIV-1 envelope glycoprotein group 120 can induce tumor necrosis factor (TNF)-α expression from macrophages and has been shown to enhance interleukin (IL)-1β induced nitric oxide production in neonatal rat cardiac myocytes.[63] Cytokine IL-6, which has some effect on immune response and viral replication in murine myocarditis models, has been found in excess in a small number of HIV/AIDS patients with biopsy-proven myocarditis.[64] Therefore, just as cytokines may have a role in the development of congestive heart failure

in absence of HIV/AIDS, they also may be important in HIV/AIDS myocarditis and cardiomyopathy.

MYOCARDIAL OPPORTUNISTIC INFECTIONS IN HIV/AIDS

Autopsy has confirmed a variety of opportunistic infections of the myocardium in patients with AIDS. Infectious agents included *Toxoplasma gondii* in the hearts of adults and children, *Cryptococcus* species, CMV, *Candida* species, *Pneumocystis carinii*, *Microsporidium* species, *Histoplasma capsulatum,* atypical mycobacteria, and *Aspergillus* species involving the myocardium. Most of these have been part of a disseminated infection and are infrequently associated with localized myocarditis.[17] Acute Chagas' myocarditis in HIV/AIDS also has been reported and may be associated with a more frequent rate of myocarditis in up to 30% of cases in HIV/AIDS patients.[65]

CLINICAL FEATURES OF MYOCARDITIS IN HIV/AIDS

Myocarditis can be diagnosed clinically based on symptoms and physical findings, although this is often difficult in the HIV/AIDS patient. The symptoms are protean and include fatigue, dyspnea, and pleuritic chest pain, which may wrongly be ascribed to other conditions. The finding of an unexplained tachycardia, third heart sound, or a friction rub should alert the physician to the possibility of the myocarditis and guide investigation accordingly.

The ECG may be helpful, possibly demonstrating nonspecific conduction defects, repolarization abnormalities and ST–T wave changes. The chest x-ray may be normal or suggest cardiac enlargement with pulmonary congestion. Echocardiography is usually nondiagnostic but can show hyperdynamic LV function in HIV-1 positive children with myocarditis or occasionally LV dyskinesia in adult patients.[66] The utility of a myocardial biopsy remains unclear, but it may be helpful in some cases to try to fully establish a diagnosis of CM or myocarditis. However, sampling errors may reduce the diagnostic yield from this invasive procedure and finding a treatable cause of biopsy-proven myocarditis is rare.

TREATMENT OF MYOCARDITIS IN HIV/AIDS

Immunomodulatory therapy for HIV-1 patients remains largely unproven. Etanercept, a TNFα antagonist, and Pentoxifylline, a TNFα inhibitor, have been used in non-HIV/AIDS patients with some success.[67,68] Intravenous immunoglobulin therapy has been used successfully in children with symptomatic HIV/AIDS CM and may be protective against the development of LV dysfunction.[48] The mode of action is not clear but the treatment could be considered in pediatric patients with deteriorating cardiac function.

CM AND LV DYSFUNCTION IN HIV/AIDS

CM as a complication of HIV/AIDS was first described in 1986 and was identified frequently thereafter in the pre-HAART era.[18] The pathogenesis remains obscure, but there is overlap in clinical and pathological features of CM in HIV/AIDS and other forms of CM in uninfected individuals. An association between cardiac dysfunction and the lymphocytic myocarditis that was reported in HIV/AIDS postmortem series seems plausible, particularly in the pre-HAART era. Isolated LV dysfunction in HIV/AIDS patients may resolve spontaneously and may suggest self-limiting myocarditis.

In studies performed early in the epidemic, a cohort of 136 HIV/AIDS patients exhibited an incidence of systolic dysfunction of approximately 2% every 3 months.[69] Another showed 69 HIV/AIDS patients with an annual incidence of LV dysfunction of 18%.[64] CM in adults with HIV/AIDS was primarily seen in patients with low $CD4^+$ counts.

Diastolic dysfunction in asymptomatic HIV/AIDS patients was felt to be a marker of heart disease later in life.[70] In a small cohort of well-controlled HIV-1-infected patients with a low burden of cardiovascular risk factors, the estimated incidence was 8.2/100 person-years.[71]

It is not unreasonable to assess the impact of and role of any comorbid conditions or risk behavior before associating HIV/AIDS as the solitary etiological factor for CM in HIV/AIDS. The differential diagnosis, as for non-HIV/AIDS patients (see Chap. 70), includes LV dysfunction secondary to ischemic heart disease, diabetes or hypertension, reactions to or side effects of therapeutic drugs, toxins, or foreign injected material, and coronary spasm secondary to toxins.[72]

HIV/AIDS patients with evidence of LV systolic dysfunction should be assessed for micronutrient deficiency. Abnormally low levels of selenium and antioxidant vitamins in particular have been demonstrated and "oxidative stress" may be an important mechanism for cellular damage in HIV/AIDS.[73] Selenium deficiency is implicated in the pathogenesis of Keshan disease, a specific form of CM in China that may respond to dietary supplementation. In the same way decreased selenium content has been demonstrated in HIV/AIDS hearts and selenium replacement was associated with an improvement in LV dysfunction in a small group of HIV/AIDS patients.[74] *L*-Carnitine deficiency has also been described in HIV-1 patients possibly in association with cardiac symptoms, and supplementation may be advantageous.[75]

Overall, the prevalence of CM in HIV/AIDS appears to be around 4.4% for CM and 6.4% for isolated LV dysfunction, and these conditions may cause symptoms in up to 5.5% of HIV/AIDS patients.[76] CM is an ominous harbinger that is associated with poor survival in HIV/AIDS compared to similar HIV/AIDS patients with structurally normal hearts. This poor outlook remains after correcting for $CD4^+$ counts. A one-year consecutive enrollment study of patients admitted to the intensive care unit in an urban center revealed 6% of admissions with HIV/AIDS had echocardiographically documented CM with a short-term mortality of 25%.[77] The pathological features of CM in untreated HIV/AIDS are less commonly seen in the developed world presently (see Fig. 102–3).

In the HAART era, a cohort of 105 well-controlled HIV/AIDS patients (median $CD4^+$ count 350 cells/mm^3, 78% with HIV-1 RNA levels < 500 copies/mL) reported a prevalence of CM of 2.9%.[69,78-81] However, 1042 HIV/AIDS patients reported less cardiac involvement in HAART-treated compared to nucleoside reverse transcriptase inhibitor (NRTI) only treated patients (1.8 vs 8.1%, $P < 0.001$), suggesting that toxicity from NRTIs may be a consideration.[82] Others reported mild systolic dysfunction, but there is growing recognition of abnormalities of diastolic function.[83-86] Multiple studies demonstrated that HIV/AIDS patients with good virologic control exhibited abnormalities of diastolic function in 26% to 64% of cases.[71,83,85-87] Through meta-analysis of 11 studies in the HAART era, 2242 well-controlled, asymptomatic HIV/AIDS patients were studied. A prevalence of systolic dysfunction of 8.3% and diastolic dysfunction of 43.4% was found.[21] Risk factors for systolic dysfunction included high sensitivity C-reactive protein > 5 mg/L, tobacco use, and past myocardial infarction; whereas for diastolic dysfunction, risk factors were hypertension and older age.

The growing burden of coronary artery atherosclerosis in HIV/AIDS individuals may also significantly modify the risk for an ischemic CM in HIV/AIDS. It is well known that coronary disease can predispose patients to the development of CM and the mechanisms responsible for such diseases in this population are complex, though similar in many respects to those in non-HIV/AIDS patients.[88]

MECHANISMS OF CM IN HIV/AIDS

The pathogenesis of CM in HIV/AIDS is likely multifactorial. The proposed causes include direct infection of the myocardium by the HIV-1 virus with or without histopathologically documented inflammatory myocarditis, toxicity from the medications used to treat HIV-1 infection, opportunistic infections, as well as nutritional disorders, toxins, drugs of abuse, and other factors.[89, 90]

AUTOIMMUNITY AND CM IN HIV/AIDS

Autoimmune processes have been described in association with HIV/AIDS.[91] The significance of some autoantibodies such as antineutrophil cytoplasmic autoantibody or antiphospholipid antibodies in HIV/AIDS remains unclear. However, the presence of such antibodies with hypergammaglobulinemia, and elevated circulating immune complexes suggests an as yet undefined autoimmune process may occur in HIV/AIDS patients.[92]

Autoantibodies against α-myosin have been identified in HIV/AIDS patients both with CM and histologically proven active myocarditis. Antibodies to α-myosin, which are more highly cardiac specific, have also been found more frequently and in higher levels in HIV/AIDS patients with CM than in those with normal hearts.[93]

These findings support a possible autoimmune process in the pathogenesis of HIV/AIDS CM. In experimental models, susceptible mice developed CM with anti-myosin antibodies after exposure to Coxsackie B3 infection or immunization with α-myosin. Common cardiotropic viruses could facilitate development of cardiac autoimmunity in HIV/AIDS patients by modifying myocyte surface antigens. CMV infection is a common opportunistic infection in HIV/AIDS patients, but has been described only infrequently as a cause of myocarditis.[19] Although this might suggest that CMV is not strongly implicated, *in situ* hybridization studies have identified transcripts of CMV-specific DNA within the myocytes of HIV/AIDS patients with myocarditis and CM in the absence of typical histological features such as inclusion bodies.[57]

HAART THERAPY AND CM AS A SIDE EFFECT

Both HIV-1 infection *per se* and HAART, particularly where NRTIs are included, may have a negative impact on myocardial function.[94,95] NRTIs are key elements of HAART, and zidovudine has been implicated in the development of some cases of HIV/AIDS CM. In addition to inhibiting HIV-1 reverse transcriptase, the drug causes a dose-dependent reversible skeletal muscle myopathy by altering mitochondrial DNA replication.[96] Changes have been identified in the myocardium of rodents fed zidovudine but have been rarely seen in patients for many reasons.[97] Recent reports suggest that mitochondrial toxicity can also be caused by nucleoside analog therapy for hepatitis B, a common coinfection in patients with HIV-1, and makes treatment of both infections potentially more complex.[98, 99] The subcellular mechanism responsible for zidovudine CM in human HIV/AIDS remains unclear. Anecdotally, small numbers of HIV/AIDS patients developed LV dysfunction while taking the drug, which improved with its discontinuation.[81] Other evidence exists. Related antiviral thymidine analogs have exhibited profound toxicity to heart and liver. This was evident in a clinical trial with fialuridine (FIAU; (1-[2-deoxy-2-fluoro-β-D-arabinofuranosyl]-5-iodouracil) where FIAU treatment caused mitochondrial pol γ inhibition, mtDNA depletion in organs, and significant morbidity and mortality.[100] It established the antiviral class of drugs that includes NRTIs as group with *bona fide* mitochondrial toxicity. Moreover, NRTI-induced mtDNA depletion was amplified by a specific pol γ mutation that occurred with patients treated with antiretrovirals for hepatitis B virus infection.[101,102] Severe toxic mitochondrial skeletal myopathy resulted from treatment with NRTI clevudine (*L*-FMAU), a congener of FIAU.[98,99] Lodenosine, a purine NRTI (2′-fluoro-2′,3′-dideoxyadenosine) also caused severe mitochondrial toxicity.[103,104] The US FDA warned manufacturers of nucleotide analogs for treatment of hepatitis C because of cardiac toxicity events and death that appear to be mitochondrially driven, but some investigators suggested that the toxic target may be the mitochondrial RNA polymerase.[105]

DIAGNOSTIC FEATURES OF CM IN HIV/AIDS: ECHOCARDIOGRAPHIC FEATURES

It has been suggested that any HIV-1 positive patient who is at high risk of developing, or who demonstrates any potential clinical manifestation of, cardiovascular disease should have a baseline echocardiogram performed (see Table 102–3). Thereafter, serial echocardiography should be performed every one to two years.[47] Unfortunately, logistical limitations make it unlikely that these goals can be achieved in the developing world. Similarly, it may be justifiable to perform a baseline echocardiographic study at the time of diagnosis of HIV/AIDS, with annual to biannual examination of select asymptomatic patients.[48] Clearly more aggressive monitoring may be guided by the cardiologist on discovery of abnormalities or in those patients with significant, potentially cardiotropic viral infections or unexplained pulmonary symptoms.

Characteristic echocardiographic features of CM that occur in absence of HIV/AIDS are detailed elsewhere and remain relevant to HIV/AIDS (see Chapters 15 and 70). The hallmark in CM associated with HIV/AIDS is global LV systolic dysfunction. Abnormalities of mitral inflow, specifically reduced early mitral peak velocity (E) and other indices of diastolic dysfunction. have been noted early in the course of HIV/AIDS in patients with both reduced and preserved ejection fraction.[70] The importance of these Doppler findings requires further investigation. However, the utility of echocardiography should not be underestimated, particularly as ECG and chest x-ray may be unrewarding in these patients.

Cardiac magnetic resonance imaging (CMR) may also be useful in patients with reduced ejection fraction by echocardiography. The test may help exclude an ischemic etiology but may also reveal evidence of myocardial fibrosis and increased myocardial lipid levels in asymptomatic HIV patients on HAART.[46] Prospective CMR study may further help our understanding of cardiac disease in HIV/AIDS.

TREATMENT OF LV DYSFUNCTION IN HIV/AIDS

To date, randomized trials have not been reported to specifically examine effectiveness of current heart failure therapies in patients with HIV/AIDS. However, the prognostic significance of LV dysfunction, either in isolation or as part of a cardiomyopathic process, cannot be overlooked (Figs. 102–3 and 102–4).[76] Evidence-based treatment may prove applicable to HIV/AIDS patients to improve morbidity and mortality. Therefore, even in the presence of a seemingly poor prognosis, HIV/AIDS patients with LV dysfunction should be offered appropriate treatment.

Essentially the same armamentarium of heart failure drugs is available for use in HIV/AIDS patients with LV dysfunction as is for the non-HIV/AIDS population (see Chap. 70). Common agents such as

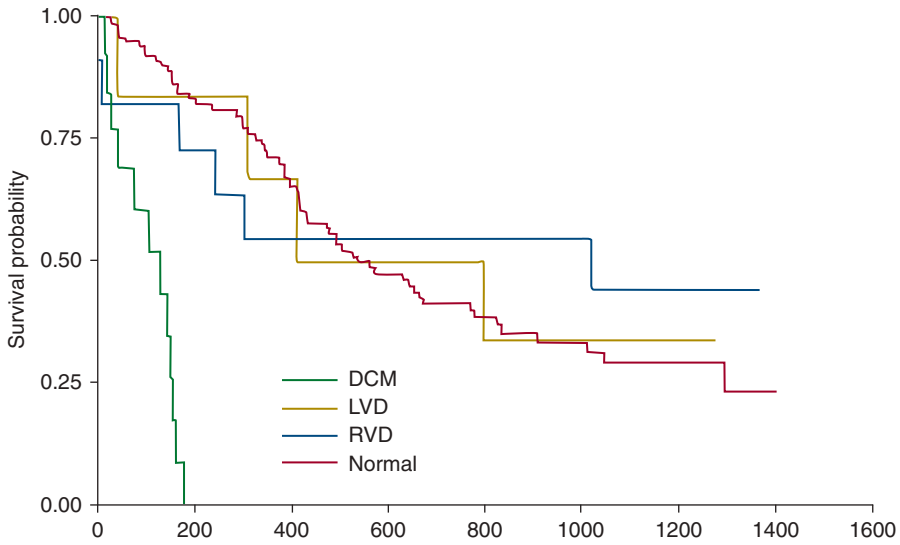

FIGURE 102–4. Kaplan-Meier survival curves for HIV-positive patients with structurally normal hearts and evidence of cardiac dysfunction. Reproduced with permission from Currie PF, Jacob AJ, Foreman AR, et al: Heart muscle disease related to HIV infection: prognostic implications. *BMJ*. 1994 Dec 17;309(6969):1605-7.

diuretics, aldosterone antagonists, and digoxin may bring about symptomatic improvement. Angiotensin-converting enzyme inhibitors may be poorly tolerated in patients who may already have a low systemic vascular resistance.[76] The use of cardiac resynchronization has not been described in the HIV/AIDS population. Case reports document successful use of LV assist devices and orthotopic heart transplant exist, although these remain uncommon treatments in the HIV/AIDS population.[106-108]

RV DYSFUNCTION AND PULMONARY HYPERTENSION IN HIV/AIDS

Isolated pulmonary hypertension is a rare and serious complication in HIV/AIDS. It occurs much more frequently than primary pulmonary hypertension in the non-HIV/AIDS population, with an incidence of 0.5%, which has remained static despite advances in treatment[109,110] and still has a grave prognosis with a survival rate of 50% at 1 year.

The association between pulmonary hypertension and HIV/AIDS is unclear but appears unrelated to $CD4^+$ count or history of pulmonary infections.[111] No detectable HIV-1 DNA, RNA, or p24 antigens have been found in the lung parenchyma or vasculature of HIV/AIDS patients with pulmonary hypertension, which indirectly supports the concept of inflammation-mediated damage to the pulmonary vasculature. The condition has been linked to HIV-1 gp120-induction of inflammatory cytokines (IL-1, IL-6, endothelin-1, and platelet-derived growth factor) and alpha-1-adrenoceptor activation[111,112]; and in vitro data suggest that both protease inhibitors and HIV gene products may be implicated in the development of pulmonary hypertension through downregulation of endothelial nitric oxide synthase and pulmonary vasomotor dysfunction.[113]

Although the mechanisms underlying pulmonary hypertension in HIV/AIDS may be different from those of primary pulmonary hypertension found in non–HIV-infected individuals, it is characterized by similar pathological lesions including intimal fibrosis, remodeling, and plexiform lesions and thus similar therapies may be useful.[110,114,115] Right heart catheterization may be worthwhile to determine whether patients demonstrate vasoreactivity with challenge with such agents as nitric oxide.[116] Continuous or intermittently delivered home oxygen therapy, calcium channel antagonists, and nitric oxide therapy may be as useful for the HIV/AIDS patient as for primary pulmonary hypertension patients (see Chap. 74).

The utilization of anticoagulation may be limited by thrombocytopenia in HIV/AIDS and heightened bleeding risk. Curiously, despite concerns about possible effects on pulmonary endothelial function, HAART itself may be beneficial in affecting outcomes from pulmonary hypertension.[55] Agents such as oral bosentan, intravenous epoprostenol, subcutaneous treprostinil, or sildenafil could improve feeling of well-being without necessarily altering prognosis.[116,117] However, sildenafil and bosentan should be used with care in HIV/AIDS patients who receive heart HAART because of potential drug interactions.

HIV/AIDS can also lead to pulmonary hypertension through other pathways including congestion from LV dysfunction (WHO Class II) or through a predisposition to chronic thromboembolic disease of the pulmonary arteries (WHO Class IV).[112,118,119] Irrespective of mechanism, treatment is similar to that applied to non-HIV/AIDS patients (see Chap. 74).

RV dysfunction may occur as part of HIV/AIDS pulmonary disease and should be treated accordingly. Isolated RV dysfunction without pulmonary hypertension is of unknown significance.[76] Therefore, bronchopulmonary infections should be treated aggressively and intravenous drug use, which may result in microvascular pulmonary emboli, should be discouraged.

ENDOCARDIAL DISEASE IN HIV/AIDS

Endocarditis is the principal cardiac endocardial lesion identified pathologically in HIV/AIDS, and both infectious and noninfectious forms have been described.[17] At present, the prevalence of noninfectious endocarditis is lower than originally reported, and HIV-1 itself has not emerged as a significant risk factor for infectious endocarditis. Nonetheless, these conditions remain a potential cause of significant morbidity.

NONBACTERIAL THROMBOTIC ENDOCARDITIS IN HIV/AIDS

Nonbacterial thrombotic endocardidis (NBTE) (marantic endocarditis) is a condition in which friable clumps of platelets and red blood cells adhere to the cardiac valves. Unlike bacterial endocarditis, these lesions are not infective and show no evidence of an inflammatory reaction. The pathogenesis of NBTE is not fully understood, but hypercoagulability, immune complex deposition, or specific vitamin deficiency may be important in conjunction with endothelial damage from intracardiac catheters or injected particulate matter.

Any heart valve may be affected, and multiple lesions are frequently found on different valves.[17] Systemic thromboembolism is a common sequela and contributes to the morbidity and mortality associated with the condition.[120, 121] NBTE was common in early postmortem series in HIV/AIDS but is now rarely reported. The reasons for this decline are not clear but are likely related to improvements in nutrition and HIV/AIDS therapy, including HAART.

INFECTIVE ENDOCARDITIS

The immunological abnormalities associated with HIV/AIDS render patients susceptible to bacterial infections, but despite this, there are few reports of infective endocarditis (IE) in HIV/AIDS. Injection drug use, rather than HIV-1 infection, appears to be the major risk factor for IE in the HIV/AIDS population.[122] IE has a similar presentation to non-HIV-1 patients but runs a more fulminant course in the late stages of HIV/AIDS.[123] However, asymptomatic HIV-1 infection appears to have little effect on the susceptibility to or the mortality from IE.

As with IE in patients without HIV/AIDS but who are intravenous drug users, the most common valve involved is the tricuspid valve, although left-sided involvement is possible.[123] The most frequently isolated organisms are *S. aureus* and *Streptococcus viridans*, but *A. fumigatus*, *Pseudallescheria boydii*, and other forms of fungal endocarditis can occur.

Clearly there is a need for adequate bacteriological investigations in cases of suspected IE in HIV/AIDS just as it would be for the non-HIV/AIDS population. However, an initial choice of antimicrobial treatment may have to be adjusted, particularly if fungal endocarditis is suspected. Valvular heart surgery has been performed cases of IE in HIV/AIDS patients who are intravenous drug users In these cases, lymphopenia that is associated with cardiopulmonary bypass was not associated with HIV/AIDS progression, although prognosis related to other factors such as continued drug use.[124,125] Given this, the indications for surgery for IE in HIV/AIDS patients remain the same as for the non-HIV/AIDS population (see Chap. 67).

OTHER VALVULAR HEART DISEASES IN HIV/AIDS

It appears now that diseases of cardiac valves, like mitral stenosis and aortic stenosis, are seen more frequently than seen previously in the HIV/AIDS population. This demographic change again is possibly related to the improved survival from HAART, and the valve lesions are pathologically indistinguishable from those of non-HIV/AIDS patients (Fig. 102–5). Valvular regurgitation can complicate CM through LV dilation and mitral annular distortion, and mitral regurgitation has also been described in HIV/AIDS patients with infective endocarditis.[126] This may contribute to secondary pulmonary hypertension and RV dilatation, although this more frequently occurs as part of CM, in isolation or in association with pulmonary hypertension.[76]

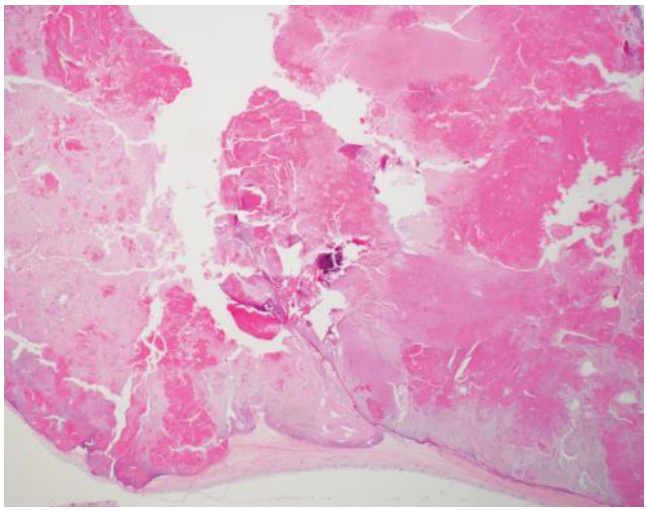

FIGURE 102–5. Aortic stenosis and repair of aortic valve from a 51-year-old male. The patient received a prosthetic valve for aortic stenosis. Histopathological changes seen in this specimen from this HIV/AIDS patient are similar to those seen in absence of HIV/AIDS. Hematoxylin and eosin. Original magnification = 40×.

CARDIAC TUMORS IN HIV/AIDS

KAPOSI SARCOMA AND THE HEART IN AIDS

KS may remain the commonest HIV/AIDS-related neoplasm that affects the heart. In contrast to the classical dermatological disease, there is often widespread and potentially fatal visceral KS involvement in HIV/AIDS. Therefore, although KS involving the heart is rare in the absence of HIV/AIDS, it is well recognized in HIV/AIDS patients. However, the prevalence of cardiac KS in HIV/AIDS appears to have decreased significantly since early reports, and appears to relate to effective HIV-1 suppression with HAART.

KS is an endothelial cell neoplasm and may infiltrate the subpericardial fat around coronary arteries in HIV/AIDS. The parietal pericardium or myocardium may also be involved.[17] Although fatal tamponade and heart failure associated with extensive KS have been reported, cardiac KS is not usually associated with symptoms.

KS may be treated with anthracyclines, although care is required as these drugs may themselves be cardiotoxic. Liposomal-encapsulated daunorubicin has an improved pharmacokinetic profile and may therefore be preferred in HIV/AIDS patients with KS, although there are few reports of these treatments being used specifically for cardiac involvement.[127] (See Chap. 101.)

CARDIAC LYMPHOMA IN HIV/AIDS

Primary cardiac lymphoma is rare in HIV-1 negative individuals, accounting for less than 10% of all primary malignant cardiac tumors. Disseminated lymphoma may involve the myocardium more frequently but usually only as part of widespread tumor involvement. However, both patterns of malignant cardiac involvement occur more commonly in HIV/AIDS, and although primary lymphoma involving the heart alone is uncommon in HIV/AIDS, surgical resection of a right atrial lymphoma was reported in an HIV-1 positive patient with limited short-term success.[128]

Non-Hodgkin's lymphoma can similarly involve the pericardium or myocardium in HIV/AIDS. Echocardiography is useful to detect any related intracavity masses or concomitant pericardial effusions. Radionuclide and MRI scans may be required to detect more diffuse cardiac involvement. In contrast to KS, lymphoma may more commonly lead to tamponade and heart failure, and conduction abnormalities and should be considered in HIV/AIDS patients whose cardiovascular symptoms progress rapidly.

ATHEROSCLEROTIC AND INFLAMMATORY ARTERIAL DISEASES IN HIV/AIDS

OVERVIEW

Vascular diseases, primarily arterial, have been described in HIV/AIDS, but today an emphasis on atherosclerotic disease is worthwhile. A number of clinical studies have documented an increased risk of adverse cardiovascular events in patients with HIV/AIDS who receive HAART. Although there is some variation among these different studies, the consensus is that HIV/AIDS patients have higher risk for atherosclerotic cardiovascular disease and myocardial infarction than uninfected controls.[30,129-135]

The Data Collection on Adverse Events of Anti-HIV-1 Drugs study (D:A:D) generated a risk equation for cardiovascular disease in HIV/AIDS while incorporating traditional risk factors (age, sex, family history of atherosclerotic disease, systolic blood pressure, smoking status, total cholesterol:HDL ratio) with duration of PI therapy, given their association with atherosclerotic cardiovascular disease.[129,130] D:A:D offered improved estimates for the risk of developing cardiovascular disease compared to the Framingham risk score, and identifies duration of HAART as a positive association factor.[129,130,136]

LIPODYSTROPHY AND THE METABOLIC SYNDROME IN HIV/AIDS

Lipodystrophy is an ill-defined syndrome comprising central fat accumulation and peripheral lipoatrophy in association with dyslipidemia and insulin resistance. A variety of antiretroviral agents may be implicated in the development of this syndrome in HIV/AIDS.[42] Patients with HIV/AIDS lipodystrophy exhibit both the metabolic and anthropometric abnormalities that are associated with increased risk of cardiovascular diseases, and lipodystrophy in HIV/AIDS patients closely resembles that of their non-HIV/AIDS counterparts.[137] It includes hypertriglyceridemia, hypercholesterolemia (particularly raised total and LDL cholesterol), insulin resistance, type II diabetes mellitus, lactic academia, and hepatic dysfunction.[137, 138]

The prevalence of these abnormalities may be dependent on the type and duration of HAART, but lipodystrophy can be seen in up to 35% of HIV/AIDS patients after 12 months of PI or NRTI therapies, particularly with older drugs.[139] Use of less lipotoxic HAART regimens and earlier initiation of therapy may be beneficial in reducing the risk of metabolic syndrome and cardiovascular disease in HIV/AIDS patients.

Fat wasting as a characteristic side effect in early-generation PI-related lipodystrophy extends from the face, buttocks, and extremities. It coexists with abnormal fat accumulation in the torso and neck.[41,111,140-143] These characteristic and disabling phenotypic changes lead to plasma lipid derangements with increased triglycerides, total cholesterol, and LDL-C and decreased HDL-C levels.

The pathogenesis of HIV/AIDS lipodystrophy is not known but may include lipid and adipocyte regulatory protein dysfunction through PI binding or NRTI-induced mitochondrial toxicity.[137,138,144] The syndrome does not appear to be a direct effect of HIV/AIDS itself, as lipodystrophy appears to occur exclusively in patients receiving antiretroviral therapy.[145] Similarly, although the dyslipidemia noted in these patients may merely be a consequence of insulin resistance and lipodystrophy, PI therapy in non-HIV/AIDS patients results in abnormal cholesterol, triglyceride, apolipoprotein B, and lipoprotein levels and rapidly induces insulin resistance.[146] Some PIs (ritonavir, indinavir, and amprenavir) can also lead secondarily to an upregulation of CD-36-dependent cholesteryl ester within vascular macrophages that promote atherosclerotic plaque formation.[111,142,147]

It should be noted that data suggest NRTI therapy also contributes to increased cardiovascular risk.[111,142,148-150] The HIV/AIDS Outpatient Study (HOPS) cohort helped define how HIV-specific factors contribute to the risk of atherosclerosis. Their investigation yielded the "attributable risk" for different factors on overall risk. A $CD4^+$ count of < 500 cells/mm^3 had an attributable risk of 25.6% that was comparable to tobacco use (26.7%) and less than the attributable risks of age (49.2%) and hypertension (34.4%). The attributable risk of a $CD4^+$ count of < 500 cells/mm^3 was higher than the attributable risk associated with an elevated LDL (21.5%), low HDL (21.5%), male gender (20.9%), and diabetes (2.4%).[151]

As mentioned previously, HIV/AIDS patients should be assessed for traditional risk factors for premature cardiovascular disease that are prevalent in HIV/AIDS patients irrespective of therapy. Thus family history and sedentary lifestyle that could be associated with the development of the metabolic syndrome in HIV/AIDS should be noted. Hypertension, diabetes, and tobacco use are more common in HIV/AIDS patients in comparison to non-HIV/AIDS patients, and because HIV-1 infection often leads to early decreases in HDL-C and elevations in triglycerides,[111,142,152-155] preexisting lipid abnormalities will be an additional risk for cardiovascular disease.

THERAPY FOR LIPODYSTROPHY AND RELATED CONDITIONS IN HIV/AIDS

Dietary therapy for dyslipidemia in HIV/AIDS remains contentious and has not been fully evaluated, although healthy diets rich in fruit, vegetables, and fish oils (possibly through supplementation) are encouraged. Drug therapy may also be necessary, particularly if antiretroviral treatment cannot be changed or interrupted. Bile acid sequestrants, although attractive from the point of view of drug interactions, may have adverse effects on serum triglyceride levels or impair absorption of antiretrovirals.

Most HMG-CoA reductase inhibitors (statins) are metabolized in the liver through the cytochrome P450 system. Simvastatin, lovastatin, and atorvastatin use the CYP 3A4 enzyme, and fluvastatin's metabolism is through the CYP 2C9 enzyme. Pravastatin is unique in that its breakdown takes place in absence of this enzyme system. Given that protease inhibitor and non-nucleoside transcriptase inhibitor metabolism is also CYP 3A4 dependent, co-prescription of some statins may be associated with increased risk of myopathy and rhabdomyolysis through competitive inhibition and significantly increased plasma statin levels.

For this reason, pravastatin and fluvastatin are attractive as agents of choice in patients receiving HAART. However, these statins are relatively weak and may not achieve target cholesterol levels. At present, it is recommended that hypercholesterolemia in HIV/AIDS patients treated with protease inhibitors are initially treated with pravastatin 20 mg/d with careful monitoring of virologic parameters and serum creatine kinase levels. Low-dose atorvastatin (10 mg/d) may be used with care and is generally well tolerated, but simvastatin and lovastatin are not recommended. Rosuvastatin is highly effective and is metabolized through the CYP 2C19 system. As such, it may be attractive for patients who do not respond to other statins (Table 102–4).[156]

TABLE 102–4. Drug Treatments for Lipid Abnormalities in HIV/AIDS

Lipid Abnormality	First Choice	Second Choice	Comments
Isolated high LDL, non-HDL cholesterol	Statin	Fibrate	Start with pravastatin* or atorvastatin* (available as generics). Use low statin dosages and titrate upward; patients taking Patients have increased risk of myopathy.
Isolated high TG	Fibrate	Statin, N-3 (omega-3) fatty acids	Start with gemfibrozil or fenofibrate. Combined statin and fibrate may increase myopathy risk.
High HDL and TG (TG level 200-500 mg/dL [2.3-5.6 mmol/L])	Statin	Fibrate	Start with pravastatin or atorvastatin* (available as generics). Use fluvastatin,* rosuvastatin,* pitavastatin,* gemfibrozil, or fenofibrate as alternatives. Combined statin and fibrate may increase myopathy risk.
High HDL and TG (TG level > 500 mg/dL [> 5.6 mmol/L])	Fibrate	N-3 (omega-3) fatty acids, niacin, statin	Start with gemfibrozil or fenofibrate. Niacin is associated with insulin resistance. May need to add statin if cholesterol is not controlled adequately.

*May have significant interactions with certain ARVs.

Modified with permission from *Drug Treatments for Lipid Abnormalities*. US Department of Health and Human Services, Health Resources and Services Administration, Guide for HIV/AIDS Clinical Care – 2014 edition. Rockville, MD: US Department of Health and Human Services, 2014.

HIV/AIDS patients may develop severe hypertriglyceridemia, and traditional secondary causes such as high alcohol consumption, hypothyroidism, renal disease, and diabetes mellitus should be excluded. A low-fat diet together with reductions in alcohol and refined carbohydrate intake should be advised. When this nondrug therapy fails to correct hypertriglyceridemia, gemfibrozil (600 mg twice daily) or fenofibrate (200 mg once daily) may be used in isolation, although combination of fibrates, gemfibrozil in particular, and statins are not recommended.[42] Other potential major cardiovascular drug interactions with specific HIV/AIDS therapies are noted in Table 102–5.

The treatment of glucose intolerance and diabetes also requires care, but if healthy diet and exercise are insufficient, drug treatment may again be necessary. Metformin reduces visceral adiposity and insulin resistance and remains the drug of choice in overweight individuals, but may infrequently cause lactic acidosis, particularly in the setting of renal dysfunction. Short-acting sulfonylureas may also be used in patients with normal renal function. Thiazolidinediones should be avoided in patients with liver disease, and although rosiglitazone, which is not metabolized through the P450 system, has been studied in HIV/AIDS patients, bringing about improvements in insulin sensitivity, at present it remains unlicensed for HIV/AIDS patients. In some cases insulin may be the safest drug therapy available.[41,157]

Tesamorelin is a growth–hormone-releasing agent that is associated with a 15% to 18% reduction in visceral fat in HIV/AIDS lipodystrophy, which may be useful for some patients.[158-160] Alternatives to HAART compound medication may also be helpful in the management of some aspects of lipodystrophy but should be carried out only after careful assessment of the potential risk to the patient's long-term management.

CLINICAL EVIDENCE FOR ATHEROSCLEROTIC DISEASE IN HIV/AIDS

Overall, controversy persists regarding the effect of HIV/AIDS on the development of atherosclerotic diseases. The D:A:D study of 23,437 patients demonstrated a risk of MI that was related to the duration of HAART treatment. This finding was refined to focus on PI therapy and the absence of such risk in patients treated with combinations that contained non-nucleosides (NNRTI).[130,133,161] HIV/AIDS disease markers such as $CD4^+$ count and viral load were not predictive of cardiovascular risk compared to correlates with traditional risk factors (age, gender, diabetes mellitus, smoking, hypertension, dyslipidemia).[130,155] However, it must be noted that the D:A:D study period examined the effects of the therapy that was available at the time, some of which was more toxic than current HAART.

The SMART study evaluated cut-offs for HAART termination and initiation as they reflected on HIV/AIDS-related deaths and cardiovascular diseases.[162] Participants received either continuous HAART or intermittent HAART treatment based on regularly assessed $CD4^+$ counts (initiation: $CD4^+ < 250$ cells/mm^3; discontinuation $CD4^+ > 350$ cells/mm^3). Interim analysis led to premature study termination because of a clear increase in adverse outcomes, including cardiovascular diseases in the intermittent treatment HAART cohort.[163]

A contemporary meta-analysis[164] points to an overall increased risk of 2.68 for acute myocardial infarction (AMI) in patients exposed to PI treatment. The reported incidence of AMI was 9.42% with an in-hospital death rate of 8% attributable to both cardiovascular events and cardiogenic shock. Coronary artery disease, however, was relatively infrequent (3%) in a large observational survey of South African HIV/AIDS patients, more than half of whom were taking HAART.[29] This indirectly contradicts previous evidence and is in keeping with an earlier meta-analysis that suggested that HIV-1 infection and PI exposure are not strong independent risk factors for subclinical atherosclerosis.[165]

Although controversy persists, it should be remembered that the benefits of consistent, early HAART are "highly favorable" over risks of HAART-associated cardiovascular complications.[131,142] A Veterans Affairs system study demonstrated that the overall death rate among HIV/AIDS patients dropped significantly after HAART initiation most likely through reduction in viral loads and improvement in $CD4^+$ counts.[131,166,167]

CORONARY ARTERY DISEASE (CAD) AND MYOCARDIAL ISCHEMIA IN HIV/AIDS

It remains likely that some HIV/AIDS patients are at risk of acute myocardial infarction (AMI) and coronary heart disease (CHD). Compared with national registries of non-HIV/AIDS patients, CHD in HIV/AIDS patients occurs mostly in men and at a younger age, suggesting that the age-adjusted incidence may be significantly higher.[164,168,169] The incidence of CHD appears to be up to three times that of a general male population and results in up to 40% higher rates of acute MI, hospitalization, and in-hospital deaths for acute coronary syndromes (ACS)

TABLE 102–5. Major Potential Cardiovascular Drug Interactions of Specific HIV Therapies

Drug Class	Examples	Possible Cardiovascular Drug Interactions	Potential Risk
Protease inhibitors (PIs)	Amprenavir Atazanavir Fosamprenavir Indinavir Lopinavir Nezfinavir Ritonavir Saquinavir Tipanavir Zalcitabine	• Antiarrhythmics (amiodarone/flecainide/propafenone/quinidine/lignocaine/mexilitine/disopyramide) • Anticoagulants (Coumadin) • Antimicrobials (erythromycin/elarithromycin) • Calcium channel antagonists (CCAs) • HMG CoA reductase inhibitors (statins) • Phosphodiesterase V inhibitors (PDVIs) (sildenafil) • Vasodilators (bosentan)	• ↑ Plasma concentration of antiarrhythmic drug Enhanced pro-arrhythmic effect • Enhanced/reduced anticoagulant effect • ↑ Risk of torsades de pointes • ↑ Plasma concentration of CCA. Enhanced antihypertensive effect • ↑ Risk of myopathy/rhabdomyolysis (avoid simvastatin/lovastatin) • Possible ↑ plasma concentration of PDVI (avoid use with ritonavir) • ↑ Plasma concentration of bosentan (use with care with Ritonavir)
Nucleoside reverse transcriptase inhibitors	Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zalcitabine Zidovudine	Few major cardiovascular drug interactions reported but clinical data limited	
Non-nucleoside reversible transcriptase inhibitors	Capravarine Delaviridine Efavirenz Nevirapine	• Antiarrhythmics • Anticoagulants (Coumadin) • CCA • Statins • PDVI	• ↑ Plasma concentration/proarrhythmic effect • May enhance/reduce anticoagulant effect • Delvavirine ↑ plasma concentration CCA toxicity • ↓/↑ Plasma concentration of statins • ↓ or ↑ plasma concentration of PDVI
Fusion inhibitors	Enfuviritide	No major cardiovascular drug interaction reported but clinical data limited	

Note: As major interactions are common with many HIV-specific therapies, clinicians are advised to consult the data sheet and prescribe cardiovascular medications in close liaison with an HIV specialist.

CCA, calcium channel antagonists; PDVI, phosphodiesterase V inhibitors.

compared with non-HIV/AIDS patients.[134,170-173] With the improvement in survival with HIV/AIDS, the therapy for cardiovascular diseases should be similar to that in the non-HIV/AIDS population.

The full mechanism underlying ACS in HIV patients remains unclear. AMI appears to be a common presentation of CHD, and a high ratio of AMI to stable angina exists in HIV/AIDS populations.[168] Because these acute coronary syndromes may involve low-volume, lipid-rich plaques, the metabolic syndrome of HIV/AIDS lipodystrophy may promote development of vulnerable lesions or influence acute plaque rupture. However, in a study of South African HIV/AIDS patients presenting with AMI, coronary intravascular ultrasound typically revealed fresh thrombus in the absence of underlying atherosclerotic disease and HAART did not appear to be a specific risk factor.[29] It remains difficult therefore to establish an absolute link between PI exposure and CHD, and further long-term studies are required.[164]

HIV-1 infection itself and HAART may contribute to a pro-thrombotic state, which increases proportionally with viral load and reduced $CD4^+$ count, or be further implicated in the atherosclerotic process through direct effects on cholesterol processing and intimal monocyte activation. Acute coronary syndromes are, however, not clearly related to HIV replication because HIV RNA may be undetectable in up to one-third of patients at the time of presentation.[168] Rapid changes in the immune state (immune reconstitution inflammatory syndrome [IRIS]) may emerge as a factor in future studies, but therapeutic improvements in immunological, metabolic, and cardiovascular risk profiles through time may counterbalance these factors and paradoxically result in an overall reduced cardiovascular risk.[174,175]

As a definitive diagnostic test, coronary angiography can be carried out safely in HIV/AIDS patients and frequently reveals patterns of coronary disease similar to that in young non-HIV/AIDS patients including proximal vessel involvement and single artery disease.[168] Treatment with percutaneous coronary intervention, fibrinolysis, and coronary artery bypass are all described with reasonable survival rates, although nonfatal reinfarction and restenosis after PCI is unexpectedly high.[176] Care is required over choice of antiplatelet agents for use in ACS to avoid potential interactions with HAART.[177] However, it seems

reasonable that the clinical situation should determine the use of invasive and noninvasive coronary investigations and treatments, rather than the HIV status of patients.[178]

MYOCARDIAL INFARCTION (MI) AND A SIDE EFFECT OF THERAPY IN HIV/AIDS

Abacavir (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate; ABC) is associated with MI in HIV/AIDS.[179-181] The relationship was emphasized in a World Health Organization report on adverse drug events that was published in 2005.[182] Clinical side effects of ABC include hypersensitivity in 5% to 8% of patients that is associated with HLA-B*5701, and suggests genetic screening to prevent the reaction in susceptible patients.[183-187] Other reports showed ABC was associated with increased risk of MI in HIV/AIDS.[188]

DISORDERS OF RHYTHM AND SUDDEN CARDIAC DEATH ASSOCIATED WITH HIV/AIDS

Sudden cardiac death (SCD) is common in HIV infection and accounts for up to 80% of cardiac-related deaths in this group. SCD occurs much more commonly than expected in the general population with similar risk factors.[189] As would be expected, SCD may be secondary to other cardiac pathology, including cardiomyopathy and pulmonary hypertension, while coronary heart disease, previous arrhythmia, hypertension, and hyperlipidemia are all prevalent comorbidities in patients with SCD.[189]

HIV/AIDS patients may be predisposed to QT prolongation, possibly as a consequence of some forms of treatment[44]; for example, pentamidine, which was used previously in the treatment and prophylaxis of *P. carinii* infection in select patients, is structurally similar to procainamide and may cause Torsades de pointes when used intravenously or intramuscularly. Ganciclovir, an acyclic nucleoside used in the treatment of severe CMV infection, may also be arrhythmogenic.

Concomitant electrolyte disturbance may be important in the development of cardiac arrhythmia, and careful evaluation of the QT interval and magnesium concentration should be used to minimize cardiac toxicity. ECG abnormalities and rhythm disturbances are common findings in HIV/AIDS patients with myocarditis or heart muscle disease, and ectopy and ventricular tachycardia have all been reported.

With increased life expectancy in HIV/AIDS, atrial fibrillation is emerging as a significant health problem. The dysrhythmia may be found in 2.6% of HIV patients and is associated with markers of HIV disease severity, namely $CD4^+$ cell count and high viral load,[190] as well as traditional risk factors. It has yet to be established if oral anticoagulation improves outcomes in this population, but anticoagulation should be considered as for the non-HIV/AIDS population. However, caution is required as there are potential important interactions between oral anticoagulants, particularly some novel oral anticoagulants and HAART drugs.[177] Careful monitoring is mandatory if warfarin is used. Caution is also required for the use of amiodarone and digoxin for rhythm or rate control in such circumstances because further potential drug interactions exist.[191,192]

Autonomic dysfunction is common in patients with HIV infection, and this may predispose to syncopal events and dysrhythmias because of excessive sympathetic tone.[193] Conduction abnormalities and arrhythmias have been demonstrated in HIV/AIDS children with ECG abnormalities, possibly related to small vessel vasculitis, neural tissue fibrosis, or myocarditis.[193] At the other extreme, as the age of HIV-infected people treated with HAART increases, coincidental cardiac rhythm disturbances will become more common. Sick sinus syndrome with symptomatic bradycardia requiring permanent pacing has been described in HIV/AIDS patients.[194]

VASCULITIS IN HIV/AIDS

Vascular changes, particularly vasculitis and endothelial cell structural changes, have been documented in HIV/AIDS. Examination of aortic endothelial cells from HIV-infected patients showed a disturbed intima, increased leukocyte adherence, and upregulation of vascular cell adhesion molecules.[195] This indicated profound and repeated activation of aortic endothelial cells in HIV/AIDS. It is possible that some HIV-1 structural proteins may play an integral role in the process.

The clinical importance of such findings is not clear and lesions affecting small- and medium-sized arteries are usually only evident by microscopy. However, fusiform aneurysms of the right coronary artery were found in a child who died suddenly.[196] These lesions were histologically distinct from other arteriopathies but other vascular abnormalities in children have been reported in the brain, thymus, spleen, and lymph nodes. Kawasaki disease, which may have a similar presentation, should be considered as a differential diagnosis that is excluded pathologically.

CARDIAC SURGERY IN HIV/AIDS

HIV/AIDS survival has improved. Consideration of cardiac surgery for treatment of cardiovascular diseases unrelated directly to HIV/AIDS, HANA, is now becoming increasingly common. Although studies are limited, excellent clinical outcomes are reported with 25 patients with HIV/AIDS with an in-hospital mortality of 4%.[197,198] There is neither increased perioperative risk from HIV/AIDS infection alone nor does surgery negatively impact the clinical course of HIV/AIDS or its therapy. Lesions seen in the hearts of patients with HIV/AIDS and HANA heart diseases, like aortic stenosis, are similar pathologically to those of patients without HIV/AIDS (see Fig. 102–5).[199] Some advocate consideration of HIV/AIDS patients as candidates for cardiac transplantation for appropriate cardiovascular indications and in absence of detractors although fears remain that immunosuppressant therapies in that scenario (peri- and post-transplant) may impact viral replication and interact with HAART agents.[200]

In the era of universal precautions and rapid treatment of accidental infection in the workplace, the burden of HIV/AIDS is becoming more a routine event. Fear of becoming infected with HIV-1 is understandable but universal precautions should limit potential risk to health care workers and as such should not preclude the HIV/AIDS patient from possible therapies should they be felt appropriate.

AGING AND HIV/AIDS

As alluded to throughout the chapter, over 30 million individuals worldwide carry a diagnosis of HIV/AIDS and more may be unaware of their infection.[2] HAART prevents or attenuates HIV-1 replication and improves survival, making HIV/AIDS a chronic illness, and with this, cardiovascular diseases are becoming increasingly prominent in this patient group.[201] Of note, long-term side effects from antiretroviral agents remain poorly understood and may be incompletely recognized despite the growing number of patients who have received decade-long HAART therapy.

The population with HIV/AIDS that is surviving into "senior citizenship" is growing because of those same therapeutic advances. This argues for the increased prevalence and recognition of important side effects. Both HIV/AIDS *per se* and its therapy contribute to the phenotype of immune senescence, including cardiovascular diseases, which are prevalent in aging in absence of HIV/AIDS.[202-211] The interplay

between HIV/AIDS and HAART is complex, but many features are shared between aging, cardiovascular diseases, and HAART toxicity in HIV/AIDS. As clinical studies unfold more information about this growing aspect of the population, therapy can be tailored to specific needs of HIV/AIDS patients with cardiovascular diseases.[212]

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CHAPTER 103

HEART DISEASE IN PREGNANCY

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INTRODUCTION

Preexisting and acquired cardiovascular disease (CVD) increases maternal and fetal morbidity and mortality during pregnancy.[1-4] Cardiovascular disease complicates more than 1% of pregnancies, accounts for 20% of nonobstetric maternal death,[2] and is the leading cause of indirect maternal mortality. Congenital heart disease (CHD) comprises more than 50% of CVD in pregnancy[5,6]; other common etiologies include rheumatic valve disease (more common in developing countries), connective tissue disease, and cardiomyopathies. Medical care begins in the preconception period with careful planning and anticipation of the possible complications that may occur during the antepartum, intrapartum, and postpartum periods. Risk-stratification models summarizing maternal and fetal outcomes have been developed to counsel women with CVD desiring pregnancy. Optimal patient care for the pregnant woman with CVD relies on understanding of the unique hemodynamic changes of pregnancy and the pathophysiology, signs and symptoms, and natural history specific to each heart condition that may impact pregnancy. A multidisciplinary team approach involving cardiologists, maternal fetal medicine specialists, and anesthesiologists in a center with experience is strongly advised for the care of pregnant women with heart disease.

PRECONCEPTION CONSIDERATIONS

Women with CVD should receive counseling regarding both maternal and fetal risks prior to conceiving a pregnancy. In addition, women with heart disease should be cared for in institutions with experience in treating CVD during pregnancy. There are extremely high-risk conditions in which pregnancy is not advised including pulmonary arterial hypertension, congenital cyanotic lesions, severe systemic ventricular dysfunction (ejection fraction < 30%, New York Heart Association [NYHA] class > II), severe mitral stenosis, severe symptomatic aortic stenosis, significantly dilated aorta in connective tissue disorders in women with Marfan syndrome and above 5 cm in women with bicuspid aortic valve (BAV).[1] Women with CVD considering pregnancy should undergo a complete workup including a detailed medical and surgical history and a physical exam including oxygen saturations, electrocardiogram (ECG), appropriate cardiac imaging, and consideration of cardiopulmonary stress testing for further risk stratification.[7]

Genetic counseling is appropriate for patients with family members affected by congenital and inherited heart diseases (eg, hypertrophic cardiomyopathy, Marfan syndrome, long-QT syndrome). In general, CHD is present in about 0.8% of the population, yet for an affected individual, the risk of bearing children with CHD is increased to 2% to 6% regardless of the congenital diagnosis.[8,9] Further recurrences of CHD in the same family are higher. A fetal echocardiogram is advised for parents with CHD between 18 and 22 weeks of gestation.[10]

Preconceptual counseling will allow for careful planning for any anticipated or potential events during pregnancy. All prepregnancy medications should be reviewed to ensure their safety in pregnancy. For example, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and endothelin receptor blockers are teratogenic and contraindicated during pregnancy, and should be discontinued. Women requiring anticoagulation must be advised of the challenges of managing anticoagulation during pregnancy and individualized strategies should be developed (discussed later in the chapter). Traditionally, the US Food and Drug Administration (FDA) classification system of five categories (A, B, C, D, X) to indicate the teratogenic potential of a drug was used to assign risk. The categories were determined by the reliability of documentation and the risk-to-benefit ratio. They did not take into account any risks from pharmaceutical agents or their metabolites in breast milk. However, in December 2014, the FDA published the Pregnancy and Lactation Labeling Rule, which requires removal of these categories from all human prescription drugs and biological products, and replacement with three subsections that provide details about the use of the drug in pregnancy and lactation in women and men of reproductive potential. These pregnancy subsections will include potential risks to the developing fetus, known dosing alterations in pregnancy, effects of timing and duration of exposure during pregnancy, adverse maternal reactions, effects of the drug on labor and delivery, and information on pregnancy exposure registry for the drug if it exists. These changes went into effect June 30, 2015.[11] Table 103–1 lists some of the common medications used in pregnancy and the FDA category for each.

HEMODYNAMIC CHANGES OF NORMAL PREGNANCY

The physiologic hemodynamic changes of pregnancy are marked and occur over a relatively condensed period of time (Fig. 103–1). Although the healthy cardiovascular system adapts remarkably well, women with underlying cardiac conditions may not tolerate such intense

TABLE 103–1. Common Medications Used in Cardiovascular Medicines: FDA Pregnancy Categories and Adverse Effects During Pregnancy

Drug Name	FDA Category[a]	Adverse Effects and Other Comments
Adenosine	C	Dyspnea, bradycardia
Amiodarone	D	Congenital goiter, thyroid disorders, growth retardation
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors	X	Oligohydramnios, IUGR, decreased fetal renal function, lung hypoplasia and skeletal malformations
Beta-blockers	C	Bradycardia, hypoglycemia, reduced birthweight
Calcium channel blockers (CCBs)	C	Prematurity, IUGR, fetal bradycardia with some CCB. Nifedipine commonly used for tocolysis and not associated with prematurity or IUGR
Digoxin	C	Low birthweight
Diuretics	C	Oligohydramnios, fetal electrolyte abnormalities
Dopamine	C	Limited data
Endothelin receptor antagonists	X	Associated with birth defects
Flecainide	C	Free transplacental passage. Used to treat fetal arrhythmias
Heparins/LMWH	B-Enoxaparin C-Heparin	Meticulous monitoring needed for anticoagulation in women with mechanical valves
Hydralazine	C	Lupus-like syndrome, thrombocytopenia
Lidocaine	B	CNS, cardiac and vascular tone effects
Methyldopa	B	
Iloprost	C	Limited data
Phosphdiesterase-5 inhibitors (PDE-5)	B	Limited data
Platelets aggregation inhibitors	N-Aspirin B-Clopidogrel	Aspirin is associated with IUGR, fetal bleeding, in first trimester. Neonatal acidosis High dose (325 mg) associated with premature closure of the ductus arteriosus Clopidogrel is probably safe; use with caution
Procainamide	C	Limited data
Propafenone	C	Limited data
Quinidine	C	Fetal thrombocytopenia
Statins	X	Limited data, congenital anomalies reported at a low risk—nevertheless should be avoided
Warfarin	X	Embryopathy in first trimester (nasal and limb hypoplasia, stippled epiphyses), CNS abnormalities, hemorrhage

[a]Categories: A, no demonstrated risk to the fetus based on well-controlled human studies; B, no demonstrated risk to the fetus based on animal studies; C, animal studies have demonstrated fetal adverse effects, no human studies, potential benefits may warrant use of the drug; D, demonstrated human fetal risk, potential benefits may warrant use of the drug; X, demonstrated high risk for human fetal abnormalities outweighing potential benefit; N, nonclassified.
Abbreviations: CNS, central nervous system; UGR, intrauterine growth restriction; LMWH, low-molecular-weight heparin.

hemodynamic changes. By 24 weeks of gestation, circulating plasma volume has increased by 40%, resulting in a 30% to 50% increase in cardiac output, which begins to rise as early as 5 weeks after the last menstrual cycle and steadily increases until 28 to 34 weeks.[1,12-18] A greater increase in plasma volume as compared to erythrocyte mass accounts for the physiologic anemia of pregnancy. In early pregnancy the rise in cardiac output is primarily achieved through a 40% increase in stroke volume, which peaks at 28 to 31 weeks of gestation.[13,14] In the third trimester, the increase in heart rate primarily mediates cardiac output augmentation, with an average heart rate rise of 10 to 15 beats per minute.[1,17,19] Cardiac output begins to decline late in third trimester, but does not return to prepregnancy values until 2 to 4 week postpartum.[14] Systemic vascular resistance falls early in pregnancy, primarily as a result of maturation of placental circulation and the effects of endogenous hormones, with a resulting 30% to 50% fall from prepregnancy values by the end of the second trimester, followed by an increase at the end of the third trimester.[12,14,19] In addition, local vasodilatory factors including prostacyclin and nitric oxide contribute to a fall in both systolic and diastolic blood pressure to 5 to 10 mm Hg below prepregnancy values, a change that begins as early as 6 to 8 weeks of gestation and nadirs in the second trimester before gradually increasing in the third trimester.[1,20] This increase in vascular compliance aids in accommodating the marked increase in plasma volume.[21,22]

THE HEMODYNAMICS OF LABOR AND THE POSTPARTUM PERIOD

Labor and delivery result in acute hemodynamic swings that place an additional stress on the maternal cardiovascular system. Cardiac output can increase by 15% to 25% in early labor, 50% during active labor, and up to 80% immediately postpartum as compared to pre-labor values, primarily mediated by an increase in stroke volume.[23,24] In the immediate postpartum period, preload acutely rises from autotransfusion from the uteroplacental circulation and increased venous return in the setting of relief of uterine compression on the inferior vena cava.[12]

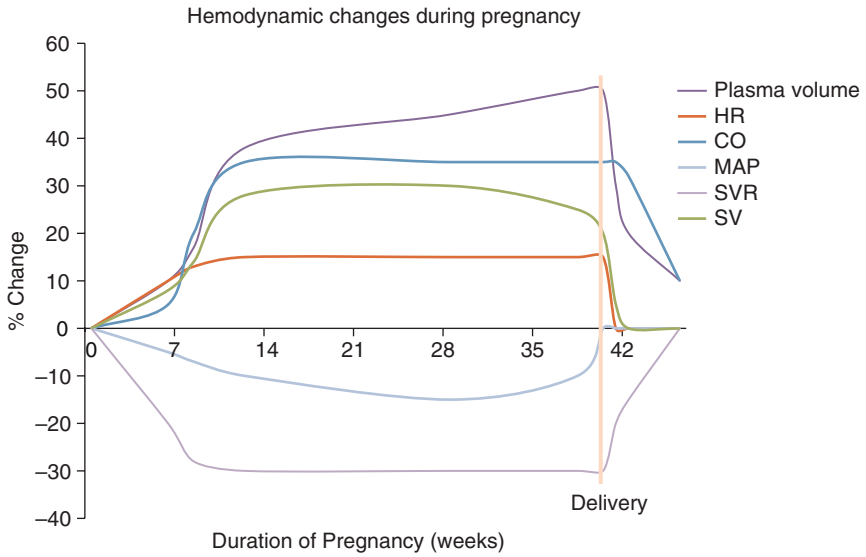

FIGURE 103–1. Hemodynamic changes of pregnancy, labor, and the postpartum period (PP). CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance; SV, stroke volume.

Within 48 hours of delivery, the heart rate falls 14%, followed by an additional 26% as compared to pregnancy values by 2 weeks postpartum.[18] Although much of the hemodynamic changes of pregnancy has resolved by 2 weeks postpartum, full return to prepregnancy physiology occurs over the following 6 months.[18,25]

STRUCTURAL ADAPTATIONS OF THE MATERNAL HEART

In response to the hemodynamic demands of pregnancy, the maternal heart undergoes physiologic hypertrophy with an appreciable increase in left ventricular mass that reverses 8 to 14 weeks postpartum.[14,16,26,27] In addition, right ventricular mass can increase up to 40% as measured by cardiac magnetic resonance imaging.[28] Echocardiographic studies have revealed that while left ventricular ejection fraction remains stable, in parallel with the increase in stroke volume, left ventricular cavity dimensions, and wall thickness, aortic size, and atrial dimensions all increase during pregnancy, with return to prepregnancy values in the postpartum period.[14,16,21,26,28-30] In addition, an increase in stroke work and decrease in left ventricular longitudinal strain has been observed in the later stages of pregnancy.[29] Increase in annular diameters resulting from chamber enlargement can result in physiologic mitral, tricuspid, and pulmonic regurgitation; the development of aortic insufficiency is rare given only a small (~5%) increase in left ventricular outflow tract diameter.[27,28,31] Despite the increase in valvular regurgitation, women rarely are symptomatic from these changes.[32] In addition, pericardial effusions without hemodynamic significance develop in 40% of women and resolve by 6 weeks postpartum.[33,34]

CLINICAL EVALUATION OF THE PREGNANT PATIENT

During pregnancy, it is often challenging to distinguish between common pregnancy symptoms and concerning cardiac manifestations. Women may sense dyspnea on exertion, decreased exercise capacity, hyperventilation, peripheral edema, and palpitations. When these symptoms are mild and arise prior to 20 weeks they are often attributable to the normal hemodynamic changes of pregnancy. Alerting symptoms during pregnancy include angina, significant resting dyspnea, paroxysmal nocturnal dyspnea, sustained palpitations, and syncope. Any symptoms that arise after 20 weeks and become progressively worse, or symptoms that significantly impair a woman from performing her daily activities, should prompt further evaluation. The cardiac exam reflects the increase in plasma volume and cardiac output in parallel to a decrease in systemic vascular resistance. Vital signs should demonstrate an expected increase in heart rate and slight decrease blood pressures with a widened pulse pressure. Women may develop a sense of dyspnea because of progesterone-mediated increase in minute ventilation. Resting oxygen saturation should remain normal. Examination of the cardiovascular system, particularly in later stages of gestation, may reveal elevated jugular venous pressures, mild lower extremity edema, and a bounding apical impulse that may be displaced leftward. A systolic flow murmur caused by flow across the semilunar valves is common, and a third heart sound may be physiologic.[20,35] A mammary souffle is a benign, high-pitched continuous murmur best heard over the breasts during the third trimester and lactation, representing superficial arterial flow. It is not affected by a Valsalva maneuver. Abnormal findings on cardiac exam include a holosystolic systolic murmur, any diastolic murmurs, fourth heart sound or an exaggerated second heart sound suggesting pulmonary hypertension.[36]

Electrocardiogram changes found in pregnancy include sinus tachycardia, left axis deviation, shortened PR interval, increased R/S ratio in leads V_1 and V_2, Q waves and inverted T waves in the inferior leads, and nonspecific transient ST-T changes.[1,37] Both atrial and ventricular premature beats are common in pregnant women.[38]

Echocardiography is very useful to assess ventricular function and valvular pathology during pregnancy.[27] Women should be referred for echocardiography if they present with unexplained symptoms, a history of CVD, unexpected ECG changes, a new holosystolic or diastolic murmur.[39]

Exercise stress testing is a useful objective tool for risk stratification of women with CVD prior to pregnancy. In a multicenter center trial of women with CHD, an abnormal chronotropic response correlated with adverse maternal cardiac outcomes.[40]

Cardiac MRI with gadolinium is generally avoided during pregnancy because of concern of fetal exposure to the contrast agent. That being said, these risks are predominantly theoretical with decreased concern for free radical exposure with newer gadolinium-based agents. Noncontrast MRI is thought to be safe during pregnancy. Concerns

of magnetic field effects or local heat produced by the coils have not been documented. Placing the patient in the left recumbent position is advisable after 20 weeks to avoid aortocaval compression by the gravid uterus.[28]

Cardiac catheterization during pregnancy is rarely employed because of its invasive nature and the radiation involved. It should particularly be avoided during the first trimester.[41] Cardiac catheterization in pregnancy is primarily used for emergent hemodynamic evaluation, balloon valvuloplasty, and coronary assessment and treatment.[42-44] At the time of catheterization of any pregnant woman, abdominal shielding should be performed and when possible left lateral uterine displacement achieved by using a wedge or other device.

Brain naturetic peptide (BNP) is emerging as a useful tool for screening women for CVD and follow-up of women with cardiomyopathies and preeclampsia. A BNP value within normal range in women with CHD has a strong negative predictive value for adverse outcomes.[45] Nevertheless, this value should be read with caution because it is falsely decreased in obese patients and may be lower in gestational diabetes.[46]

RISK STRATIFICATION OF CARDIOVASCULAR DISEASE DURING PREGNANCY

MATERNAL RISK

There are several risk score models available to assess both maternal and fetal risks in cardiac disease (Table 103–2). These include CARPREG (CARdiac disease in PREGnancy),[47,99] ZAHARA,[48] and the World Health Organization (WHO) classification.[49] A recent prospective validation study evaluating the three models suggested that the WHO classification is the most accurate prediction model.[45]

The CARPREG multicenter study is the most utilized tool for risk assessment and outcome prediction of cardiac disease in pregnancy. This risk model was developed from 599 pregnancies in which the majority of women had CHD. The maternal adverse outcomes rate was 13%, dominated predominantly by heart failure and arrhythmias. Rare outcomes included maternal embolic stroke and sudden cardiac death. The investigators identified four predictors of maternal morbidity including (1) prior cardiac event including transient ischemic attack or arrhythmia; (2) NYHA functional class > II or cyanosis (resting oxygen

TABLE 103-2. Predictors of Adverse Maternal Cardiovascular Events During Pregnancy

CARPREG[1]

Risk factors:

(1) Prior cardiovascular event

(2) New York Heart Association (NYHA) functional class (FC) > II or cyanosis (resting oxygen saturation < 90% at rest)

(3) Left-sided heart obstruction (peak left ventricular outflow tract [LVOT] gradient > 30 mm Hg, mitral valve area < 2 cm^2, aortic valve area < 1.5 cm^2)

(4) Systemic ventricular dysfunction, with an ejection fraction < 40%

Score	CV Risk
0	5%
1	27%
>1	75%

ZAHARA[2]

Risk factors:

(1) History of arrhythmia (1.5 points)

(2) > II NYHA FC (0.75 points);

(3) LVOT obstruction with a peak > 50 mm Hg or aortic valve area < 1 cm^2 (2.5 points)

(4) Mechanical valve prosthesis (4.25 points)

(5) Moderate/severe subpulmonic or systemic atrioventricular valve regurgitation (0.75 points)

(6) Use of cardiac medications prepregnancy (1.5 points)

(7) Repaired or unrepaired cyanotic heart disease (1 point)

Score	CV Risk
0 to 0.5	2.9%
0.51 to 1.50	7.5%
1.51 to 2.50	17.5%
2.51 to 3.50	43.1%
≥ 3.51	70.0%

WHO[3]

Class I: Low Risk

Mild pulmonic stenosis, small patent ductus arteriosus, mild mitral valve prolapse; successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, or anomalous pulmonary venous drainage); and isolated atrial or ventricular ectopic beats

Class II: Moderate Risk

Unoperated atrial or ventricular septal defect, repaired tetralogy of Fallot, and most arrhythmia.

Class II-III: Moderate to High Risk

Mild left ventricular impairment, hypertrophic cardiomyopathy, native or tissue heart valve disease not considered WHO I or IV, Marfan syndrome without aortic dilatation and aorta < 45 mm in aortic disease associated with bicuspid aortic valve.

Class III: High Risk

Mechanical valves, systemic right ventricle, Fontan circulation, unrepaired cyanotic heart disease, complex congenital heart disease, and aortic dilatation 40-45 mm in Marfan syndrome, 45-50 mm with bicuspid aortic valve.

Class IV: Extremely High Risk, Contraindicated

Pulmonary arterial hypertension of any cause, severe systemic ventricular dysfunction (left ventricular ejection fraction < 30%, NYHA III-IV), previous peripartum cardiomyopathy and any residual impairment of left ventricular function, severe mitral stenosis, severe symptomatic aortic stenosis, Marfan syndrome with dilated aorta > 45 mm and aortic dilatation > 50 mm in aortic disease associated with bicuspid aortic valve.

[1]Siu SC et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001;104 (5):515-521.

[2]Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J*. 2010;31(17)2124-2132.

[3]Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart*. 2006;92(10):1520-1525.

Abbreviation: CV, cardiovascular.

saturation < 90% at rest); (3) left-sided heart obstruction (peak left ventricular outflow tract (LVOT) gradient > 30 mm Hg, mitral valve area < 2 cm^2, aortic valve area < 1.5 cm^2); and (4) systemic ventricular dysfunction, with an ejection fraction < 40%. Women with one risk factor have a 25% chance of experiencing an adverse outcome, and this risk rises to above 70% with more than one risk factor. The CARPREG study has been validated in further studies, and in the CHD population, subpulmonary ventricular dysfunction, severe pulmonary regurgitation, and maternal smoking have been identified as additional risk factors.[50]

The ZAHARA investigators evaluated 1302 pregnancies from 60 countries, including 714 pregnancies in women with CHD. Predictors for adverse events included (1) history of arrhythmia (1.5 points); (2) NYHA functional class > II (0.75 points); (3) LVOT obstruction with a peak gradient > 50 mm Hg or aortic valve area < 1 cm^2 (2.5 points); (4) mechanical valve prosthesis (4.25 points); (5) moderate/severe systemic atrioventricular valve regurgitation (0.75 points); (6) moderate/severe subpulmonary atrioventricular valve regurgitation (0.75 points); (7) use of cardiac medications prepregnancy (1.5 points); and (8) repaired or unrepaired cyanotic heart disease (1 point). Women with a score of more than 3.5 have a risk of adverse cardiovascular events up to 70%.

The modified WHO classification is divided into four categories, listed in Table 103–2.[49] The recommended follow-up for women with WHO class II is every trimester; women with WHO class III and IV should be seen monthly or bimonthly.

The multinational Registry on Pregnancy and Cardiac Disease (ROPAC) summarized outcomes from 1321 pregnancies of women with CVD from 28 countries between 2007 and 2011.[52] WHO categories were strongly associated with maternal, obstetric, and fetal outcomes. Maternal death (1%), although rare, was significantly higher than that in the general population (0.007%), primarily from heart failure followed by thromboembolic complications and sepsis. Fetal and neonatal mortality were also higher in women with underlying CVD.

OBSTETRICAL RISK

Obstetric complications appear to be higher in women with CVD. Historically women with heart disease have been counseled to avoid the Valsalva maneuver during delivery; however, data from 113 pregnancies in 65 women with CHD suggested that women who were not allowed to Valsalva and had assisted second stage with either forceps or vacuum had increased rates of postpartum hemorrhage and vaginal lacerations.[4] Mode of delivery should generally be guided by obstetric indications. Most women with CVD will be able to undergo successful spontaneous vaginal delivery with careful monitoring. Consideration of assisted second stage should take into account known risks of instrumented delivery such as hemorrhage and significant perineal trauma balanced against theoretic benefits of avoidance of Valsalva. In women who are likely to have a low tolerance for Valsalva, a passive second stage where the head is allowed to labor down to a very low fetal station is recommended. At that point a trial of Valsalva may be attempted. For those women who become hemodynamically compromised with pushing in the second stage, forceps or vacuum instrumentation can be used to expedite delivery.

NEONATAL RISK

There is a strong association between maternal morbidity and neonatal adverse events. Rate of neonatal complications and mortality have been reported between 20% and 37%, and from 1% to 4%, respectively. Risk factors for neonatal events included cyanosis, poor functional class, smoking, multiple gestations, use of anticoagulants during pregnancy, and mechanical valve prosthesis. Events included small for gestational age and prematurity with its associated complications such as respiratory distress syndrome and cerebral hemorrhage.[51]

SPECIFIC FORMS OF HEART DISEASE IN PREGNANCY

HYPERTENSION AND RELATED DISORDERS

Up to 10% of pregnancies are complicated by hypertensive diseases, which may complicate maternal and fetal health during pregnancy and portend an increased risk of cardiovascular disease later in life.[53,54] Hypertensive disorders of pregnancy range from chronic hypertension (hypertension diagnosed prior to 20 weeks), gestational hypertension, preeclampsia, and eclampsia (Table 103–3). Hypertension is defined as a blood pressure exceeding 140/90 mm Hg on two readings measured 6 hours apart. Women with chronic hypertension are at increased risk for fetal growth restriction (particularly with concomitant proteinuria), placental abruption, preterm birth, and cesarean section.[55] In addition, superimposed preeclampsia occurs in 17% to 25% of women with chronic hypertension.[55] Treatment of high blood pressure in pregnancy is aimed at reducing periods of severe hypertension. Concerns regarding decreased fetoplacental perfusion and consequent risk for fetal growth restriction have led to blood pressure goals of 120/80 to 160/105 mm Hg in otherwise uncomplicated hypertensive pregnancies.[55-57] It is important to note that these recommendations are for women without underlying structural heart disease. Given that a 5 to 10 mm Hg drop in blood pressure is physiologic during pregnancy through the second trimester, antihypertensive therapies may actually require down-titration in early pregnancy for women with chronic prepregnancy hypertension. A recent prospective trial of tight control (target diastolic blood pressure 85 mm Hg) versus less-tight control (target diastolic 100 mm Hg) did not yield a difference in the composite primary outcome of pregnancy loss or need for high-level neonatal care or the secondary outcome of serious maternal complications despite a higher incidence of severe maternal hypertension (≥ 160/110 mm Hg) in the less-tight control group (40.6%) as compared to the tight-control group (27.5%, $P < .001$).[58] Further, antihypertensive therapy has not been demonstrated to reduce the risk of preeclampsia or placental abruption or to improve fetal outcomes/reduce growth restriction.[55]

Blood Pressure Targets and Therapies

Guideline committees differ with respect to blood pressure limits that warrant antihypertensive therapy. The American Congress of Obstetricians and Gynecologists recommends instituting antihypertensive therapy for gestational hypertension and preeclampsia in women without evidence of end-organ disease when blood pressures reach severe range (160/105 mm Hg),[59] and the European Society of Cardiology recommends treatment at blood pressures > 140/90 mm Hg.[1,57] These recommendations do not apply to women with comorbid medical conditions or evidence of end-organ damage. Acute elevations in systolic blood pressure to greater than 160 mm Hg, or diastolic blood pressure to greater than 110 mm Hg warrant prompt evaluation and treatment.

There are several choices for antihypertensive therapy in pregnant women. Some of the commonly used medications are included in Table 103–1. For acute management, intravenous labetalol, hydralazine, or oral nifedipine are most commonly used.[1] For oral antihypertensive therapy, labetalol and methyldopa are often used as first-line agents, with the recent addition of nifedipine.[60-62] Concerns regarding associations between beta-blocker use and fetal growth restriction stem from studies of atenolol use, and thus atenolol is discouraged in pregnancy (class D).[57,63] Data regarding the safety of calcium channel blockers primarily stem from long-acting nifedipine, which has not

TABLE 103–3. Hypertensive Diseases of Pregnancy

Condition	Definition	Other Features	Treatment
Chronic hypertension	Known preexisting hypertension or a blood pressure ≥ 140/90 mm Hg before the 20th week of gestation without proteinuria and/or persistence of hypertension > 12 weeks postpartum	• 1%-5% incidence • Increased risk of superimposed preeclampsia, fetal growth restriction, placental abruption, preterm birth, and cesarean section	• Preconception evaluation for secondary causes of hypertension, counseling regarding pregnancy-associated risks, and a 24-hour urine to evaluate for preexisting proteinuria • Recommendations for thresholds that merit antihypertensive therapy differ in the guidelines • First-line oral therapy: labetalol, nifedipine, methyldopa • Second-line oral therapy: beta-blockers (excluding atenolol), calcium channel blockers • Intravenous therapy with labetalol, hydralazine, sodium nitropursside, or nitroglycerine is indicated for acute development of hypertension (SBP ≥ 160 or DBP ≥ 110) • Contraindicated: ACE inhibitors, ARBs, atenolol • Low-dose aspirin (60-150 mg/d) is recommended after the 12th week of gestation for preeclampsia prevention
Gestational hypertension	Development of new hypertension (SBP ≥ 140 or DBP ≥ 90) after the 20th week of gestation without proteinuria	• 6%-7% incidence • Can capture women who may develop preeclampsia later in gestation and those with previously undiagnosed chronic hypertension	Hypertensive management as in patients with chronic hypertension
Preeclampsia	Development of new hypertension (SBP ≥ 140 or DBP ≥ 90) after the 20th week of gestation with proteinuria of ≥ 300 mg in a 24-hour urine sample	• 2%-5% incidence • Without proteinuria, preeclampsia is diagnosed by hypertension with at least 1 of the following: thrombocytopenia (< 100,000/mL), LFTs > 2 × ULN, sCr > 1.1 mg/dL or 2 × baseline sCr, pulmonary edema, cerebral or visual disturbances	• Low-dose aspirin is recommended after the 12th week of gestation for women at high risk for preeclampsia, including those with ≥ 1 of the following: history of preeclampsia, chronic hypertension, type 1 or 2 diabetes, renal disease autoimmune disease, or carrying multiple gestations • When complicated by pulmonary edema, intravenous nitroglycerin should be used • Delivery is recommended for patients with severe preeclampsia • Close monitoring is recommended for patients with mild disease at < 37 weeks of gestation • Delivery is recommended for all patients (even with mild disease) at ≥ 37 weeks of gestation • IV magnesium for eclampsia prophylaxis
Eclampsia	Features of preeclampsia plus seizures during pregnancy or the first 10 days postpartum	• < 0.1% incidence	• IV magnesium • Delivery
Preeclampsia superimposed on chronic hypertension	Chronic hypertension with new-onset proteinuria or an increase in proteinuria (if prepregnancy proteinuria was present) or worsening hypertension or the onset of HELLP syndrome	• Approximately 17%-25% of women with chronic hypertension develop superimposed preeclampsia	• Management as for patients with preeclampsia

Abbreviations: ACEi, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HELLP, hemolysis, elevated liver enzymes, low platelets; LFT, liver function tests; SBP, systolic blood pressure; sCr, serum creatinine; ULN, upper limit of normal.

been associated with adverse fetal or pregnancy outcomes.[64,65] Diuretics affect the normal volume expansion of pregnancy that is necessary to support uteroplacental blood flow, and should be used only when necessary to control pulmonary edema.[55,57,66] ACE inhibitors and angiotensin receptor blockers have been associated with fetal renal dysfunction, oligohydramnios, growth abnormalities, skull hypoplasia, neonatal anuria, and fetal and neonatal death, and are thus strictly contraindicated.[55,67-71]

Preeclampsia and Eclampsia

Preeclampsia is a multisystem disorder that affects 2% to 5% of pregnancies and is clinically characterized by the development of new-onset hypertension after the 20th week of gestation accompanied by proteinuria exceeding 300 mg.[72] When proteinuria is absent, preeclampsia is identified by hypertension accompanied by end organ damage as manifested by thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances.[73] Given that delivery is the mainstay of treatment for severe disease, it is associated with an increased risk of iatrogenic preterm delivery, accounting for 15% of preterm births.[74] The term "eclampsia" is applied when the disorder is accompanied by seizures during pregnancy or in the first ten postpartum days; it occurs in less than 0.1% of pregnancies.[75,76] Together, preeclampsia and eclampsia account for over one-third of severe obstetrical complications, 12% of maternal mortality, and double the risk of perinatal mortality.[73,74] Among women at high risk for preeclampsia, low-dose aspirin after the 12th week of gestation is recommended to decrease risk for preeclampsia, growth restriction, and preterm delivery.[73] High-risk women are those with a history of preeclampsia, chronic hypertension, diabetes, renal disease, autoimmune diseases, and those carrying multiple gestations.[73] Preeclampsia with severe clinical features is characterized by systolic blood pressures ≥ 160 mm Hg or diastolic blood pressures ≥ 110 mm Hg, a platelet count < 100,000/μL, impaired liver function (twice normal concentrations of liver enzymes, persistent right upper quadrant or epigastric pain, or both), progressive renal impairment (either a double of the serum creatinine or a value exceeding 1.1 mg/dL), pulmonary edema, or cerebral or visual disturbances; such features should prompt delivery.[53] HELLP syndrome, a variant of severe preeclampsia, is defined by hemolysis, elevated liver enzymes, and low platelet count. Although delivery is the mainstay of treatment for severe preeclampsia, select women who are remote from term may be expectantly managed with close monitoring until 34 weeks of gestation provided they remain clinically stable. Women with mild preeclampsia are typically delivered at 37 weeks gestation.[53] Women with a history of pregnancy-related hypertensive disorders—particularly preeclampsia—are at increased risk for future CVD.[77] The two may relate by overlapping risk profiles (including obesity, insulin resistance, hyperlipidemia, and renal disease) or through persistent endothelial dysfunction from hypertensive disorders of pregnancy increasing the risk for future CVD; the mechanism of this association is still unclear.[54,77-80]

CARDIAC ARRHYTHMIAS

Although cardiac arrhythmias remain uncommon in pregnancy, women both with and without a history of prior arrhythmia may be at increased risk during pregnancy.[38,81-83] Potential mechanisms underlying this predisposition include myocyte stretch in the setting of increased plasma volume and hormonal changes, with some evidence for proarrhythmic properties of progesterone.[38,84,85] Approximately 20% to 44% of women with preexisting tachyarrhythmias experience recurrence during pregnancy, with recurrent arrhythmia associated with an increased risk of adverse fetal and neonatal complications.[1,86] Nonetheless, although palpitations are a frequent complaint in pregnancy, most do not correlate with dangerous ectopy in women without structural heart disease.[81] Many women with structurally normal hearts experience premature atrial and ventricular ectopy during pregnancy,[81] yet sustained arrhythmias are rare.[87] Women with CHD are at higher risk for developing arrhythmias requiring treatment during pregnancy.[1,88] Those with pre-excitation are also more likely to experience arrhythmias during pregnancy, most commonly orthodromic atrioventricular reciprocating tachycardia.[38,89] When treatment is indicated, consideration should be made to avoid invasive procedures when possible, though many can now be performed with minimal or no radiation, and to use antiarrhythmic therapy sparingly given a lack of safety data with these agents, particularly in the first trimester. For hemodynamically unstable women, electrical cardioversion should be performed with close fetal monitoring, though the risk to the fetus has been low.[38,82,90,91] It is advisable to involve a cardiac electrophysiologist with expertise in caring for pregnant women when considering arrhythmia management.

Supraventricular Tachycardias

Paroxysmal supraventricular tachycardias (SVTs) are the most common sustained arrhythmias in pregnancy, with a frequency of 24/100,000 among pregnancy-related hospitalizations.[87] Although women with a history of SVT may experience recurrence, it is rare for a first episode of SVT to occur in pregnancy among women without structural heart disease, with an incidence of 3.9% among a cohort of women with symptomatic paroxysmal SVTs.[92] Among women who experience SVT in pregnancy, the most common arrhythmia is atrioventricular nodal reentrant tachycardia (AVNRT).[92] When possible, vagal maneuvers should first be attempted for arrhythmia termination (Fig 103–2).[1,38,82] If ineffective, adenosine successfully terminates the majority of AVNRT without adverse effect on the fetus given the drug's short half-life.[38,82,93] For those refractory to adenosine, intravenous metoprolol or propranolol should be trialed before intravenous verapamil, which has a higher association with maternal hypotension.[82] Intravenous procainamide is a reasonable alternative agent in the acute setting.[1,82] In all instances, use of amiodarone should be avoided unless absolutely necessary given a high incidence of adverse fetal effects, most notably a 17% incidence of fetal hypothyroidism.[82]

For suppressive therapy in those with frequent symptomatic episodes, oral beta-blockers (metoprolol or propranolol) and digoxin can be used as first-line therapy, with the addition of verapamil, sotalol, or flecainide or propafenone (in those without structural heart disease) if necessary.[38,82] As with all medications, antiarrhythmics should be avoided as much as possible in the first trimester and the lowest effective dose should be administered, with an understanding that up-titration may be necessary as the volume of distribution expands with pregnancy.[82] Older antiarrhythmic agents are preferred over newer agents (eg, dofetilide) given a lack of clinical experience in pregnancy with respect to safety.

Atrial tachycardias occur rarely in pregnancy, but are more likely to be resistant to medical therapy and more likely to recur after electrical cardioversion.[1] As with AVNRT, adenosine can be used acutely for diagnostic and therapeutic purposes and for those without response, beta-blockers, calcium channel blockers, or digoxin can be used for rate control.[38] For those who fail nodal agents, sotalol, flecainide, or propafenone can be utilized.[1,38]

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation (AF) and atrial flutter (AFL) occur rarely in women without a prior history of these arrhythmias or structural heart disease, although more than half of women with a history of AF/AFL will

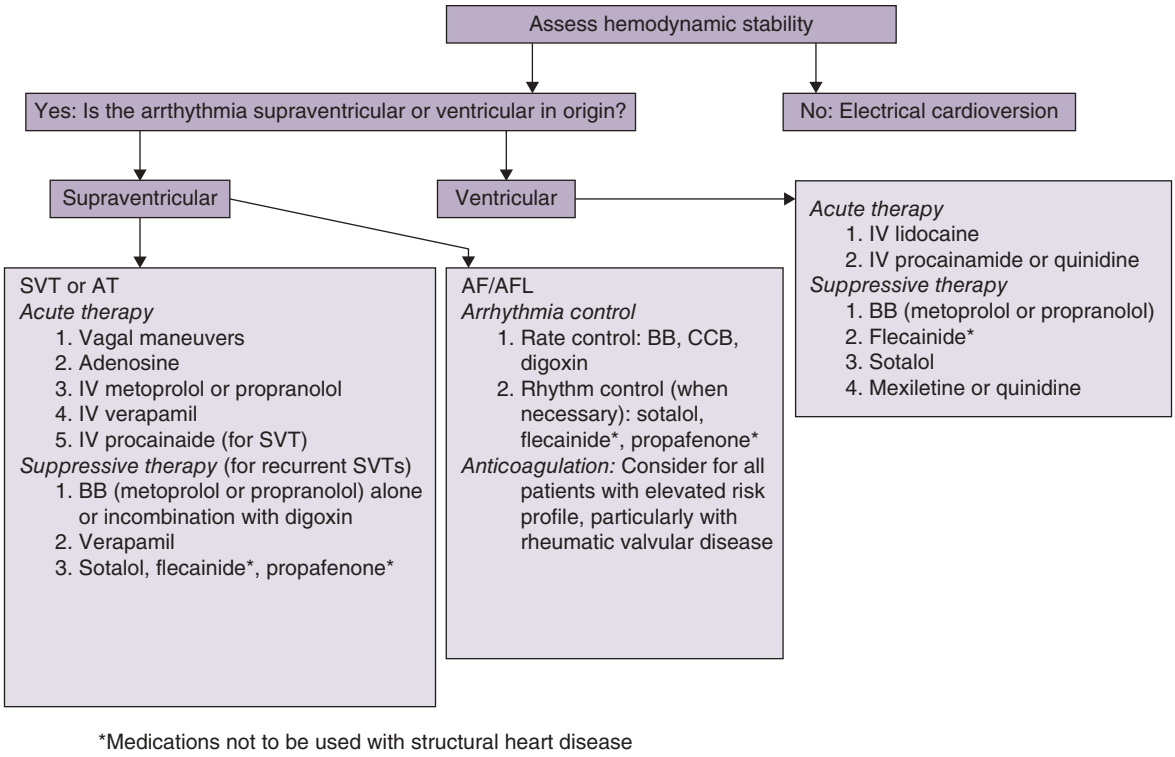

FIGURE 103–2. Management of cardiac arrhythmias in pregnancy AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; BB, beta-blocker; CCB, calcium channel blocker; IV, intravenous; SVT, supraventricular tachycardia.

experience recurrence with pregnancy.[38] In a registry of women with structural heart disease, the incidence of AF/AFL in pregnancy was 1.3%.[94] Risk factors for development of AF/AFL among women with structural heart disease include a prior history of AF/AFL, mitral and aortic valve diseases, and left ventricular cardiomyopathies, with the greatest risk for developing AF/AFL occurring in the second trimester.[94] Further, women with structural heart disease who experienced AF/AFL during pregnancy had a higher rate of maternal mortality and low birthweight as compared to those with structural heart disease who did not experience AF/AFL, though there were no differences between the two groups with respect to development of heart failure.[94]

As with other arrhythmias, women presenting with hemodynamic instability should undergo electrical cardioversion.[38] Although experience with chemical cardioversion is limited, intravenous ibutilide or flecainide can also be considered for restoration of sinus rhythm.[1] In those tolerating the rhythm adequately, beta-blockers, calcium channel blockers, and digoxin are options for both acute and chronic rate control.[1,38] In those with poor tolerance of AF/AFL in which a rhythm control strategy is necessary, sotalol is one potential option, or alternatively, flecainide, or propafenone can be trialed in women with structurally normal hearts.[1,38] Women with pre-excitation who develop AF/AFL should receive intravenous procainamide acutely and should avoid verapamil or digoxin because of the risk of rapid accessory pathway conduction.[38] Amiodarone, dronedarone, and dofetilide should be avoided because of lack of clinical experience and/or known adverse fetal effects.[38]

As with nonpregnant patients, thyroid function and the risk of thromboembolism should be assessed in pregnant women who have a history of or experience a first occurrence of AF or AFL in pregnancy. Pregnant women with valvular AF secondary to rheumatic mitral valve disease are at particularly high risk for thromboembolism, meriting careful consideration of anticoagulation in pregnancy[93]; strategies for anticoagulation are discussed later in this chapter. Although data are lacking to definitively guide this decision, some consider the hypercoagulable state of pregnancy in and of itself to warrant full anticoagulation in all pregnant women with AF or AFL.[93] Other authors suggest the use of low-dose aspirin in pregnant women with lone AF.[38] European guidelines, however, recommend employing the same means of risk stratification for thromboembolism in pregnancy as is used in the nonpregnant population.[1]

Ventricular Arrhythmias

Ventricular tachycardia and fibrillation are rare complications of pregnancy, occurring in 2/100,000 pregnancy-related hospitalizations.[87] Most arrhythmias occur in the setting of structural abnormalities, particularly among those with CHD in which the prevalence is 4.5 to 18.9 per 1000 pregnancies.[38,95] However, idopathic ventricular tachycardias occurring in structurally normal hearts can initially present in pregnancy, most frequently idiopathic right ventricular outflow tract tachycardias.[1,93] When ventricular arrhythmias occur in the absence of known structural heart disease, particularly in late pregnancy or the early postpartum period, a diagnosis of peripartum cardiomyopathy should be considered.[1,38] Given that ventricular arrhythmias are frequently poorly tolerated from a hemodynamic perspective, these arrhythmias should be particularly carefully evaluated and followed during pregnancy in women with a potential predisposition to them. As in all circumstances, women presenting with hemodynamic instability should undergo electric cardioversion.[1] If the ventricular arrhythmia is hemodynamically tolerated, intravenous lidocaine should be trialed as a first-line agent, with procainamide and quinidine as potential second-line options. As for other arrhythmias, amiodarone should be avoided whenever possible given adverse fetal effects. For long-term suppression, metoprolol or propranolol should be considered first, with sotalol as an option for those refractory to beta blockade.[38] Mexiletine

and quinidine can be considered for those who require further antiarrhythmic therapy. Given the length of most ventricular arrhythmia ablations, such procedures should be avoided in pregnancy given the risk of radiation to the fetus with long fluoroscopy times. Implantable cardioverter-defibrillators (ICDs) in and of themselves do not pose an increased risk in pregnancy.[1,38] In a retrospective analysis of 44 women with ICDs who became pregnant, 11 received ICD therapy during pregnancy without adverse fetal outcomes, and the device itself did not pose additional complications to pregnancy or vaginal delivery.[96]

Bradyarrhythmias

Sinus node dysfunction and atrioventricular block occur rarely in pregnancy in the absence of structural heart disease.[1,38,87,97] Asymptomatic women with complete heart block can be managed expectantly and generally do not require temporary pacing during labor and delivery even with Valsalva.[1,38,83,93,97] Given that a rise in heart rate is needed to augment cardiac output particularly during the third trimester of pregnancy, a subset of women with asymptomatic complete heart block prior to pregnancy may develop symptoms during pregnancy that then merit permanent pacing.[97] If required, permanent pacemakers can be placed safely with use of echocardiographic guidance, with minimal or no radiation exposure to the fetus.[1,83,97,98] Finally, it is currently unknown whether pacemaker settings should be increased during pregnancy to aid in augmenting cardiac output. This remains an area of investigation that merits further study, though prophylactic pacing of asymptomatic women does not provide any benefit.[1,97]

VALVULAR HEART DISEASE

Women with valvular heart disease may experience challenges either during pregnancy or in the postpartum period. Given the natural increase in heart rate and cardiac output during pregnancy, stenotic lesions, particularly those resulting in left heart obstruction, are often poorly tolerated and women with a mitral valve area < 2 cm^2 or aortic valve area < 1.5 cm^2 are at an increased risk for pregnancy-related cardiovascular complications.[1,99] Likely as a result of impaired forward flow with severe mitral and aortic stenosis, there is an increased risk with these lesions of intrauterine growth restriction, preterm delivery, and low birthweight.[100] By contrast, the reduction in systemic vascular resistance and thus afterload during pregnancy results in better tolerance of chronic regurgitant lesions. However, such women are at risk for postpartum heart failure in the context of increased volume load and sudden increase in the systemic venous resistance with delivery of the placenta and fluid shifts. Table 103–4 summarizes potential risks and proposed management strategies for valvular heart conditions during pregnancy. Please refer to the chapters on mitral (Chaps. 48-50) and aortic (Chap. 47) valvular diseases for further discussion regarding diagnosis and management in the nonpregnant population.

Mitral Stenosis

Given the risk to mother and fetus, women with moderate or severe mitral stenosis should be counseled to undergo valvular intervention prior to pregnancy when the diagnosis is known prior to conception.[1] When possible, percutaneous balloon valvuloplasty should be considered in appropriately selected patients to obviate the complications of either prosthetic or mechanical valve replacement. However, women with mitral stenosis are often unaware of their disease, with symptoms emerging first in pregnancy. In the developing world, rheumatic disease results in a significant burden of often previously undiagnosed mitral stenosis during pregnancy. Given the tachycardia and volume load of pregnancy, women asymptomatic prior to pregnancy may develop heart failure, particularly in the second and third trimesters.[1,100-102] Heart rate control is essential to help mitigate symptoms. Heart failure should be treated with β_1-selective blockers and diuretic therapy when needed for volume overload, with care to avoid overdiuresis.[1,103] The increased risk of thromboembolic events in the setting of concomitant atrial fibrillation mandates therapeutic anticoagulation in this particularly high-risk subset of women.[1,100,101,103] Percutaneous mitral valvuloplasty is an option for women refractory to optimal medical therapy in whom the valvular anatomy is suitable to such an approach; ideally it should be performed after 20 weeks of gestation with an experienced operator and measures to reduce fetal radiation exposure.[1,103] Given the exceptionally high risk of fetal demise with maternal cardiopulmonary bypass, maternal cardiac surgery should only be performed when other treatment strategies have been ineffective at stabilizing the mother.[1] Fetal risks are also high, with maternal mitral stenosis increasing the risk of fetal prematurity (20%-30%), intrauterine growth retardation (5%-20%), and stillbirth (1%-3%).[1,100-102] Although most women can be managed conservatively and delivered vaginally, planned cesarean section may be considered in women with severe disease with NYHA class III or IV symptoms with pulmonary hypertension that persists despite optimal medical and surgical therapy.[1]

Aortic Stenosis

Congenital bicuspid aortic valve (BAV) disease is the primary cause of aortic stenosis during pregnancy and as with mitral stenosis, may be asymptomatic and/or undetected until pregnancy.[102,103] When the diagnosis is known prior to conception, transthoracic echocardiography should be performed to assess gradients across the aortic valve and exercise testing is recommended in asymptomatic women.[1] Even in the context of severe disease, those with a high exercise capacity who remain asymptomatic and have a normal blood pressure response with exercise testing may tolerate pregnancy without complications, provided their left ventricular function remains normal.[1,104] Those with severe symptomatic aortic stenosis, rapid progression of stenosis, or concomitant impaired left ventricular function, however, should undergo valvular intervention prior to conception. Women with BAV may have associated dilatation of the ascending aorta and coarctation of the aorta with an increased risk of aortic dissection during pregnancy.[105,106] Cardiac MRI prior to pregnancy may delineate baseline aortic dimensions, and echocardiography is the modality of choice for follow-up of valve function and aortic dimensions during pregnancy.

As with mitral stenosis, women with aortic stenosis are at increased risk of heart failure (approximately 10%) and arrhythmias (up to 25%), with offspring at increased risk for preterm delivery, intrauterine growth retardation, and low birthweight.[1,107] Women who develop atrial fibrillation should be rate controlled with β-blockade, nondihydropyridine calcium channel antagonists, or digoxin when necessary. For women refractory to medical therapy, percutaneous balloon valvuloplasty remains an option in the absence of significant calcification or regurgitation, and should again be performed as late as possible in pregnancy and with measures to reduce fetal radiation exposure.[1] Most women including those with severe disease will be able to deliver vaginally. For women with severe symptomatic aortic stenosis, assisted second stage may be considered to shorten the duration of the second stage of labor. Cesarean delivery should be reserved for obstetric indications in all but the most critically ill women.

Pulmonic Stenosis

Congenital pulmonary stenosis (PS) is the most common cause of right ventricular outflow tract obstruction in pregnant women. In a small sample of women with pulmonic stenosis, all women tolerated

TABLE 103–4. Valvular Heart Disease in Pregnancy

Lesion	Common Etiologies in Pregnancy	Risk to Mother	Risk to Fetus	Possible Intervention
Mitral stenosis	Rheumatic	• Risk of heart failure, mortality risk up to 3%	• Prematurity (20%-30%) • IUGR (5%-20%) • Still birth (1%-3%) • Higher risk in women with NYHA class > II	• Prepregnancy: Consider intervention for moderate-severe MS • In pregnancy: Heart rate control with BB, diuretics, digoxin (for AF) • Percutaneous mitral commissurotomy in NYHA III/IV or PAP > 50 mm Hg on medical therapy
Aortic stenosis	Bicuspid	• Severe asymptomatic AS on exercise testing: Low risk[a] • Severe symptomatic AS or drop in BP on exercise testing: 10% risk of heart failure and risk of arrhythmias	• Risk of pre-term birth, IUGR, and low birth weight (in up to 25%) increase with AS severity	• Prepregnancy: Intervention for severe symptomatic AS or asymptomatic AS with LVEF < 50% or aortic dilation > 45 mm (for consideration of concomitant ascending aortic replacement) • In pregnancy: Consider percutaneous valvuloplasty with severely symptomatic patients despite medical therapy
Mitral regurgitation	Rheumatic, congenital	• Moderate-severe MR with good LV function: Low risk • Severe MR with LV dysfunction: high risk for heart failure or arrhythmia	• No increased fetal risk reported	• Prepregnancy: Surgery for patients with severe MR and symptoms or LVEF < 60% or LVESD ≥ 40 mm • In pregnancy: Diuretics for volume overload
Aortic regurgitation	Rheumatic, congenital, degenerative	• Moderate-severe AR with good LV function: Low risk • Severe AR with LV dysfunction: High risk for heart failure or arrhythmia	• No increased fetal risk reported	• Prepregnancy: Surgery for patients with severe AR and symptoms or LVEF < 50% or severe dilation (LVESD > 50 mm, LVEDD > 65 mm) • In pregnancy: Diuretics for volume overload
Tricuspid regurgitation	Functional, Ebstein anomaly, endocarditis	• Moderate-severe TR with good RV function: Risk of arrhythmia • Moderate-severe TR with impaired RV function: Risk of heart failure	• No increased fetal risk reported	• Prepregnancy: Surgery for patients with severe TR and symptoms or impaired LV or RV function or dilation • In pregnancy: Diuretics for volume overload

Abbreviations: AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; BB, beta-blockers; BP, blood pressure; HTN, hypertension; IUGR, intrauterine growth restriction; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; PAP, pulmonary arterial pressure; RV, right ventricular; TR, tricuspid regurgitation.

[a]Severe aortic stenosis is defined as an aortic valve area ≤ 1.0 cm^2, aortic velocity ≥ 4.0 m/s, or mean pressure gradient ≥ 40 mm Hg.

Modified with permission from Sliwa K, Johnson MR, Zilla P, et al: Management of valvular disease in pregnancy: a global perspective. *Eur Heart J.* 2015 May 7;36(18):1078-1089.

pregnancy without an increase in arrhythmia, need to initiate cardiovascular medications, maternal hospitalizations, or adverse fetal outcomes, and thus this lesion is likely well tolerated during pregnancy in women without symptoms prior to pregnancy.[100] In symptomatic women with favorable valve anatomy and without significant pulmonary regurgitation, balloon valvuloplasty may be performed with adequate fetal shielding. Interestingly, there is an increased incidence of preeclampsia and other hypertensive disorders in women with PS, and this association is not well understood.[108]

Regurgitant Lesions

Regurgitant lesions are better tolerated than stenotic lesions as a result of the decrease in systemic vascular resistance during pregnancy. As with mitral stenosis, rheumatic disease accounts for a large proportion of women with mitral regurgitation in pregnancy, with mitral valve prolapse representing another common etiology.[102,103] Common etiologies of aortic regurgitation include BAV, rheumatic disease, endocarditis, or aortic annular dilation.[103] With preserved left ventricular function, women with significant regurgitation usually tolerate pregnancy well, though they are at increased risk for the development of arrhythmias.[1,103] Those who develop atrial fibrillation during pregnancy are at particularly high risk for embolic events and anticoagulation should be considered. Women with severe regurgitation with left ventricular dysfunction or heart failure are at increased risk for adverse cardiovascular events during pregnancy, and thus women who require repair or replacement should be intervened upon prior to conception.[1] The decision to proceed with prophylactic valve replacement for regurgitation prior to pregnancy is challenging in women who do not meet do not meet standard guidelines in anticipation of pregnancy, as prosthetic valves increase the risk for pregnancy-related complications.[103] Postpartum, women with regurgitant lesions may be at increased risk for development of heart failure in the context of a normalization of the systemic vascular resistance in the face of a continued volume load as compared to the prepregnancy state, and thus women should be followed closely and treated with diuretic therapy if needed. Those who develop heart failure during pregnancy should be treated with diuretic therapy and afterload reduction with hydralazine and nitrate therapy.[103] As with other cardiac surgical procedures, surgical valve replacement should be avoided in pregnancy because of the high risk of fetal loss with cardiopulmonary bypass.[103]

Prosthetic Valves

Although surgical techniques increasing enable valve repair rather than replacement, in many instances valve characteristics or surgical expertise in a given center necessitates valve replacement in young patients. When valve replacements are required for treatment of valvular disease in a woman of childbearing age, there should be a discussion between the patient and cardiologist or cardiac surgeon regarding plans for future pregnancy, which may impact the choice of valve: bioprosthetic or mechanical. Women should be extensively counseled on the risks and benefits during pregnancy of each type of valve and understand that regardless of choice, prosthetic valves increase the potential for cardiovascular complications. In a prospective registry of women with cardiovascular disease in pregnancy, maternal mortality occurred in 1.4% and 1.5% of women with a mechanical and bioprosthetic valve, respectively, as compared to a 0.2% mortality rate in women with CVD without a prosthetic valve ($P < .05$), illustrating the high level of risk that pregnancy with a prosthetic valve carries even as compared to a high-risk population.[109] Further, only 79% of women with a bioprosthetic and 58% of women with a mechanical valve had pregnancies free of serious events, highlighting the risk that a prosthesis poses to the health of the mother and fetus in pregnancy and need to carefully follow these women in a multidisciplinary fashion.[109] The American Heart Association guidelines recommend use of low-dose aspirin for women in their second or third trimesters with any prosthetic valve.[110] Beyond the risks of potential valve failure or thrombosis (discussed below), however, patients with prosthetic heart valves are at increased risk for development of infective endocarditis, regardless of pregnancy status. Although current guidelines do not recommend antibiotic prophylaxis for delivery in women with prosthetic valves,[111] some authors report administering prophylactic antibiotics in women with prosthetic valves except in the instance of uncomplicated vaginal delivery.[112]

Bioprosthetic Valves

In light of persistent uncertainty regarding optimal management of anticoagulation in pregnancy—especially in women with mechanical valves—those desiring future pregnancy may elect to have a bioprosthesis.[1] Although bioprosthetic valves do not require anticoagulation and have a lower risk of thrombosis, women should be aware that they have a higher rate of structural valve deterioration irrespective of pregnancy than do mechanical valves.[1,112,113] Thus the decision to place a bioprosthesis in any young patient requires counseling on the near inevitability that they will require a repeat valve replacement in their lifetime, as well as careful periodic monitoring of their valve function. Potential modes of valve deterioration include calcification, degradation, and pannus overgrowth leading to leaflet immobility.[112] Whether pregnancy itself leads to accelerated valve deterioration remains unknown, with conflicting data in the existing literature and many postulating that deterioration during pregnancy may simply reflect the natural course of bioprosthetic valves as opposed to the increased demands of pregnancy.[1,112-116] In women with normal ventricular function with a well-functioning bioprosthetic valve, however, the risk of pregnancy is minimal, and thus a desire for pregnancy is a class IIb indication for placing a bioprosthetic valve in a young woman as per the European Society of Cardiology guidelines.[1]

Mechanical Valves

Although mechanical prostheses have a longer durability than bioprosthetic valves, which renders them the preference in young women who do not wish to become pregnant, they pose a significant challenge regarding management in pregnancy mainly because of their highly thrombogenic nature, which necessitates uninterrupted anticoagulation.[109] Mechanical valve thrombosis is a potentially devastating complication in any patient and has been reported to occur in 4.7% of pregnant women with mechanical valves in a prospective registry.[109] Hemorrhagic events occur significantly more commonly in women with mechanical valves (23.1%) as compared to those with bioprosthetic valves or those without prosthetic valves in pregnancy (5.1% and 4.9%, $P < .001$).[109] At present, there are inadequate studies to reassure women that any anticoagulation plan is completely safe during pregnancy, and this issue should be discussed extensively preconceptually in any woman of reproductive age. In particular, the hypercoagulability of pregnancy heightens the risk of valve thrombosis, the increased volume of distribution often leads to vacillations in therapeutic doses that necessitate frequent monitoring and dose adjustments to ensure consistent therapeutic anticoagulation, and pregnancy itself carries an increased risk of bleeding—particularly around the time of delivery. Mechanical prostheses in the mitral or tricuspid position, concomitant AF, and a history of thromboembolic events increase the risk of thrombosis during pregnancy.[112,117] Further, much discussion regarding the risk of valve thrombosis derives from study of older valves, with a potentially lower risk profile among those receiving newer-generation mechanical valves.[112]

Anticoagulation for Women with Mechanical Valves During Pregnancy

The optimal strategy for anticoagulation in pregnant women is controversial. Although warfarin is often the preferred agent in nonpregnant women with mechanical prostheses, the risk of embryopathy exceeds 8% with doses over 5 mg.[1,110] The use of warfarin beyond the first trimester is associated with an increased risk of adverse fetal outcomes including miscarriage, hemorrhage, and fetal loss, an effect that in some studies appears to be dose dependent.[1,109,112,117-120] However, in a recent study, rates of miscarriage or fetal loss did not differ between women who took high versus low (≤ 5 mg) doses of warfarin.[109] Low-molecular-weight heparin (LMWH) does not cross the placenta and guidelines recommend switching from warfarin to LMWH in women whose warfarin dose exceeds 5 mg. Unfortunately, available data suggest that women are at high risk for valve thrombosis during the transition from warfarin to heparin products.[1,109,110] However, LMWH is associated with an increased risk of valve thrombosis.[112] Although the factors responsible for this risk are incompletely understood, many authors postulate that inadequate monitoring rather than failure of the agent itself is responsible.[112] When LMWH is used during pregnancy, both peak and trough anti-Xa levels should be monitored weekly throughout to ensure consistent therapeutic anticoagulation, as the therapeutic dose required may significantly change with the increasing volume of distribution.[1,112,121-124] In one study of real-world use, however, anti-Xa levels were reported in only 57% of women treated with LMWH, suggesting inadequate monitoring of LMWH use in global clinical practice.[109] Further, among those who did have anti-Xa levels checked, the number of levels reported per pregnancy ranged from 3 to 42, again reinforcing concerns regarding the real-world use and monitoring of this anticoagulant.[109] Although inadequate data current exist to definitively recommend an anticoagulation strategy for pregnant women with mechanical prostheses, Table 103–5 summarizes a proposed algorithm adapted from several strategies in the literature. Although warfarin is the recommended strategy of anticoagulation in the second and third trimesters by guidelines, prospective studies of high-quality and consistently therapeutic anticoagulation during pregnancy are required to more definitively recommend an anticoagulation strategy during pregnancy.[1,110] At present there are no data to guide the use of non-vitamin K oral anticoagulants during pregnancy and thus their use cannot be recommended.

TABLE 103–5. Anticoagulation for Mechanical Valves During Pregnancy

Preconception

- Discuss with the patient an anticoagulation strategy for pregnancy including a thorough discussion of the risks/benefits of each strategy and arrive at a preformed plan individualized based on patient preference and risk profile.
- Counsel patient to monitor for pregnancy by tracking menstrual cycles and frequent pregnancy tests and contact her cardiologist as soon as pregnancy is known.

Pregnancy: Conception to 12 weeks

- If the warfarin dose is < 5 mg, it may be continued.
- If the warfarin dose is ≥ 5 mg or if the patient prefers to avoid warfarin altogether during pregnancy, switch to weight-based LMWH BID and adjust dose based on weekly peak/trough monitoring for goal peak anti-Xa levels of 0.6-1.2 IU/mL 4 hours post-dose. If trough levels are < 0.6 IU/mL with therapeutic peaks, dose TID.

Pregnancy: Weeks 13-35

- All patients can be switched to warfarin.
- For patients who prefer to avoid warfarin during pregnancy, LMWH can be continued with careful weekly monitoring as above.

Pregnancy: Week 36

- Switch patients on warfarin to LMWH or IV UFH. LMWH should be monitored weekly, with a goal peak anti-Xa level of 0.7-1.2 IU/mL 4 hours post dose. If trough levels are < 0.6 IU/mL with therapeutic peaks, dose TID.

Labor and Postpartum

- 36 hours prior to induction or caesarian delivery, all patients should be switched to IV UFH.
- 6 hours prior to delivery, IV UFH should be stopped.
- Restart IV UFH 4–6 hours after delivery (provided the risk of bleeding is not prohibitive from an obstetric perspective).
- Once safe to start long-term anticoagulation from a bleeding perspective, bridge with LMWH or IV UFH to warfarin with careful INR monitoring postpartum, especially in breastfeeding patients.

Abbreviations: BID, twice daily; INR, international normalized ratio; LMWH, low-molecular-weight heparin; TID, three times per day; UFH, unfractionated heparin.
Modified with permission from Pieper PG, Balci A, Van Dijk AP: Pregnancy in women with prosthetic heart valves. *Neth Heart J.* 2008 Dec;16(12):406-411.

Unsurprisingly, women with mechanical valves are at highest risk of maternal hemorrhage at the time of delivery and thus they require careful monitoring peripartum.[109] Well before delivery a multidisciplinary plan must be formulated in conjunction with cardiology, obstetrics, and anesthesia regarding the management of unexpected premature labor or emergency delivery and communicated to all physicians who may care for the patient in an emergent situation in order to minimize uncertainty. At 36 weeks of gestation, women on warfarin should be switched to either LMWH or unfractionated heparin in order to reduce the risk of fetal hemorrhage with vaginal delivery and delivery-associated maternal bleeding.[1,112,121] Women at increased risk for preterm labor and preterm birth should have their warfarin switched earlier based on clinical risk factors. For women who unexpectedly present in labor and require preterm emergent delivery, cesarean delivery is a reasonable option under general anesthesia with use of blood products and reversal agents. This is an extremely high-risk clinical scenario that requires significant surgical, anesthesia, and blood bank support. Cesarean delivery is advised predominantly for fetal protection as the fetus is also fully anticoagulated while the mother is taking warfarin. Prior to a scheduled induction or cesarean delivery, all women should be switched to unfractionated heparin and this should be stopped 6 hours prior to planned delivery.[112] Unfractionated heparin should be restarted 4 to 6 hours after delivery provided that the risk of bleeding from an obstetric perspective is not prohibitive.[112,121] Meticulous attention to hemostasis in operative deliveries and with significant vaginal lacerations is required. Use of pelvic and rectus-sheath drains may also be considered in women delivered by cesarean delivery.

There should remain a high suspicion for valve thrombosis in any woman with a mechanical valve during pregnancy or postpartum, especially with signs of new heart failure or an embolic event. A transthoracic echocardiogram should be used as the initial mode of investigation, though transesophageal echocardiography is often required for adequate visualization.[110] If unrevealing, fluoroscopy can and should be performed with minimal radiation for diagnosis.[1,110,112,125] For women with evidence of thrombosis but adequate valve function and clinical stability, optimization of anticoagulation can be trialed.[1,112,125] Critical valve thrombosis, however, has been associated with a high rate of maternal mortality and should be treated with either fibrinolytics or surgically, though the former strategy is associated with a high risk of bleeding and cardiac surgery during pregnancy is associated with a high risk of fetal loss, with little experience with either strategy to guide recommendations during pregnancy.[1,112,127,128]

INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) during pregnancy is extremely rare, yet has high maternal and fetal mortality, both up to 33%.[129,130] Risk factors for the development of IE include underlying valve disease (eg, rheumatic), CHD, intravenous drug use, and recent dental work. The most common pathogen is *Streptococcus viridans* and the most commonly involved valve is the mitral valve followed by the aortic and tricuspid valves. Maternal morbidity is attributed to embolic events and valvulopathy-related heart failure.[131] Because IE in pregnancy is a life-threatening condition, intravenous antibiotics, close surveillance, and anticipation of valve surgery are mandated. Open-heart valve surgery during pregnancy is associated with high fetal mortality and prematurity as well as a high maternal complication rate. Clinical indications for surgery remain the same as in the general population (see Chap. 67). Antibiotic prophylaxis is reasonable during vaginal delivery at the time of membrane rupture in women with prosthetic cardiac valves, presence of prosthetic material used for valve repair, or unrepaired or cyanotic heart disease.[7]

CARDIOPULMONARY BYPASS IN PREGNANCY

Cardiopulmonary bypass (CPB) results in utero-placental hypoperfusion. The fetus experiences acidosis, hypoxemia, increased systemic vascular resistance, and decreased cardiac output. CPB may be associated with poor neonatal outcome (16%-33% mortality).[132,133] Other neonatal complications include premature deliveries, intrauterine growth restriction (IUGR), respiratory distress syndrome, and developmental delay. Maternal outcomes are more reassuring and contrary to older data, they are considered to be similar to cardiac surgery in nonpregnant women.[133] CPB is reserved for extreme conditions such as acute decompensating valvular endocarditis. The best perfusion strategies to improve fetal outcomes during CPB include using high perfusion flow rates and pressures, employing the shortest bypass time, and maintaining normothermia.[134]

CARDIOMYOPATHY IN PREGNANCY

Women with more than mild systolic dysfunction (LVEF < 40%) and/or NYHA functional class III/IV are advised against pregnancy given the high rate of maternal and fetal complications.[10,135] It should be

underscored that decreases in ventricular function and remodeling during pregnancy may not recover postpartum, which portends a worse long-term prognosis. ACE inhibitors are contraindicated during pregnancy and spironolactone has an antiandrogenic effect and is not recommended.

Newly diagnosed cardiomyopathy during pregnancy is challenging, because both dilated cardiomyopathy (DCM) and peripartum cardiomyopathy (PPCM) may represent a disease within the spectrum of similar pathophysiology.[126] In both cases, it is important to exclude reversible causes of cardiomyopathy (eg, myocarditis, hypertension, underlying valve disease, toxin-induced, ischemia). A family history is useful to aid in the diagnosis of DCM.[135] The basic tenets of heart failure treatment during pregnancy include sodium and fluid restriction, afterload reduction (eg, nitrates, hydralazine), rhythm control (eg, beta-blockers, digoxin), diuretics, and anticoagulation if necessary for other indications. See Chapter 73 for a detailed discussion of the treatment of cardiogenic shock.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare form of pregnancy-related cardiomyopathy that often progresses rapidly and is associated with considerable morbidity and mortality. PPCM is defined as newly diagnosed systolic cardiomyopathy (LVEF < 45% or fractional shortening < 30%) without a reversible cause, presenting between the last month of gestation and 5 months postpartum (most commonly in the first month postpartum) in a woman without known CVD.[136] That is, PPCM is a diagnosis of exclusion. Although enlarged left ventricular dimensions > 2.7 cm/m^2 are part of the modified echocardiographic criteria for PPCM, the left ventricular dimensions may also be normal in size.[137]

Several pathophysiological pathways have been implicated in the disease process including an angiogentic imbalance between placental vascular endothelial growth factor (VEGF) and its inhibitors (eg, soluble Flt1), oxidative stress and pro-apoptotic effects mediated by prolactin subfragments (16-kDa isoform), and an exaggerated inflammatory response and possible autoimmune component (eg, anti-troponin I and cardiac sarcomeric myosin antibodies).[138] The levels of soluble Flt1(sFlt1) have been shown to be elevated both in preeclampsia and in PPCM, suggesting a potential shared vascular disorder. Higher levels of sFlt1 have also been associated with worse NYHA functional class and adverse clinical outcomes, whereas higher levels of relaxin-2, a potent vasodilator, are predictive of early ventricular recovery. Inflammatory markers such as TNF-alpha, IL-6, and CRP are elevated in PPCM and an elevated Fas/Apo-1, a plasma marker of apoptosis, has been associated with mortality.[139]

There is geographical and racial variability in the incidence of PPCM, suggesting that there is interplay in genetic and environmental mechanisms in the pathogenesis of this disease. In the United States, the risk for PPCM is 1 in 2289 to 4000, whereas in South Africa it is 1 in 1000 and in Haiti reportedly as high as 1 in 300.[140-142] The African American population has a significantly higher risk of PPCM and often presents with more severe systolic dysfunction.[143,144] Genetically, 26 distinct truncations in eight genes have been identified in women with PPCM, predominantly of the sarcomeric titin gene (TTN) with similar mutation rates and characteristics as in DCM.[145] Presence of the TTN truncation is associated with reduced LV function.[146]

Predisposing risk factors to PPCM include advanced maternal age, multiparity, multiple gestation, diabetes, family history, race/ethnicity (eg, African American), smoking, cocaine use, long-term (> 4 weeks) use of beta-adrenergic tocolytic therapy (eg, terbutaline), hypertension, and preeclampsia.[136,147] Maternal mortality has been reported between 6% and 10%, and as high as 15% in African Americans.[10,126,148] Endomyocardial biopsy usually does not add useful information that warrants the risk of the procedure and shows tissue edema, myocardial hypertrophy, and varying degrees of fibrosis.[149]

Management strategies include afterload reduction with hydralazine or nitrates, rhythm control with beta-blockers and digoxin, as well as diuretics and consideration of anticoagulation for LV thrombi. Severe heart failure should be managed in the ICU setting with close monitoring and use of inotropes as needed. Vaginal delivery with epidural anesthesia is preferred for a hemodynamically stable patient, whereas in the unstable patient with advanced heart failure, an expedited delivery with cesarean section may be required.[10]

The use of bromocriptine as an anti-prolactin agent has been a subject of investigation. The rationale behind bromocriptine stemmed from the observation that in PPCM there is increased cleavage of prolactin to a 16-kDa prolactin subfragment isoform that has properties that promote apoptosis and inflammation while suppressing angiogenesis.[150] Early promising results in a small proof-of-concept pilot study still warrant larger randomized controlled trials.[10,151] Other agents that may improve outcomes and require further investigation include pentoxifylline, a TNF-alpha inhibitor, and certain immunoglobulins.[152,153]

Outcomes in PPCM are predominantly related to the degree of ventricular dysfunction encountered at the diagnosis. Partial or full recovery of LV function is expected in the majority of cases.[154] Predictors of recovery include normal ventricular size, LVEF > 30% at the time of diagnosis, lack of troponin leak, low BNP level, non-African American race, absence of LV thrombus, diagnosis after delivery, and breast feeding.[126,154] Although the systolic function may return to normal levels, these women may have abnormal contractile reserve, predisposing them to worsening heart failure in subsequent pregnancies. Because the recurrence rate is about 20% when complete recovery is achieved and 50% when there is persistent LV dysfunction, women wishing to have a subsequent pregnancy should be carefully counseled. Women without recovery of the LV function should be counseled against future pregnancy. Intracardiac defibrillators, cardiac resynchronization therapy, and advanced heart failure therapy should be delayed as long as possible during the first 6 months following diagnosis given the high rate of recovery of ventricular function.

Hypertrophic Cardiomyopathy

Women with HCM commonly tolerate pregnancy well. Maternal mortality is low (~1%) and morbidity is predominantly related to left ventricular outflow tract (LVOT) obstruction and arrhythmia.[155,156] In fact, the increased plasma volume during pregnancy may lessen the LVOT obstruction. Preconception evaluation includes NYHA assessment, degree of LVOT obstruction, and surveillance for arrhythmias.

CONNECTIVE TISSUE DISORDERS

Pregnancy is associated with a dilatation of aorta in women with connective tissue disorders secondary to estrogen effects, increased protease activity in the extracellular matrix, and defective collagen synthesis.[157] The greatest concern remains an aortic dissection, the risk of which significantly increases throughout gestation and is associated with high maternal mortality. The high-risk syndromes for aortic dissections include Marfan,[158] Loeys-Dietz, Ehler-Danlos type IV (vascular type), and SMAD3 aortopathy. In fact, Ehler-Danlos type IV is a contraindication to pregnancy because vascular rupture has been reported in 50% of patients.[159] Other syndromes in which there is an increased risk of dissection include BAV and Turner syndrome. In women with Marfan syndrome, the aortic

root size may not return to the prepregnancy dimensions and there appears to be an increased risk of future aortic events or need for aortic root replacement after pregnancy.[160] For women who are interested in conception, genetic counseling should be given, as these syndromes are commonly inherited in an autosomal dominant manner. Chest magnetic resonance angiography is advised to have a better delineation of the aortic dimensions at baseline. During pregnancy, frequent echocardiograms are advised and in some cases on a monthly basis if there is concern of aortic root enlargement.[1] In Marfan syndrome, normal aortic dimensions at baseline portend a low risk of dissection. Women with Marfan syndrome considering pregnancy are counseled to undergo elective aortic root replacement and are counseled against pregnancy when the aortic root diameter exceeds 4.0 cm.[161] Those with aortic root size between 4.0 and 4.5 cm are at increased risk of an event especially in the setting of a family history of dissection or rapid growth. Women with BAV commonly have dilated ascending aorta, yet have a significantly lower risk of dissection compared to those with Marfan syndrome. For women with BAV considering pregnancy, surgical repair of the aorta should be recommended when the ascending aorta exceeds 5.0 cm, and pregnancy is not recommended beyond these dimensions.[1] Women with Turner syndrome are advised to undergo repair when the aortic diameter > 2.7 cm/m^2. In Loeys-Dietz syndrome, aortic replacement is recommended with aortic dimensions above 4.0 cm or a rapidly expanding aneurysm > 0.5 cm per year.[162] Medical management of aortic disease in pregnancy includes blood pressure control and beta-blockers, as ACE inhibitors and angiotensin receptor blockers are contraindicated during pregnancy. Epidural anesthesia with vaginal delivery is the preferred mode of delivery with an expedited second stage. Because of the arterial frailty, cesarean delivery is often recommended for women with Ehlers-Danlos type IV syndrome, due to the risk of arterial, bowel, and uterine rupture.[163] Careful counseling and meticulous coordinated care are necessary in the delivery plan for all high-risk women with connective tissue disorders.

CORONARY ARTERY DISEASE

As a result of increasing maternal age and a higher prevalence of CVD risk factors, the incidence of ischemic heart disease complications during pregnancy is rising. In a review of 146 pregnancies associated with ischemic heart disease, 95% of women presented with chest pain, the majority of which occurred in the third trimester or postpartum period. Major causes of ischemia were found to be coronary artery dissection (35%) or thrombus/emboli (35%). Maternal mortality was 8% and the premature delivery rate was 56%.[164]

Although acute myocardial infarction during pregnancy is rare, coronary artery dissection must be ruled out and can occur up to six weeks postpartum. Risk factors for coronary artery dissection include systemic hypertension, diabetes, tobacco use, advanced maternal age, thrombophilia, and postpartum infections.[165]

Pregnancy associated myocardial infarction is distinctly different from myocardial infarction not occurring during pregnancy, with more frequent involvement of the left main and left anterior descending arteries, and a high incidence of shock and mortality presumably because of frequent involvement of the anterior wall in these women.[166]

Cardiovascular invasive strategies in women during pregnancy should be limited to those with severe clinical decompensation and/or unresponsive to medical interventions. Extracorporeal membrane oxygenation (ECMO) has been successfully employed for respiratory failure in pregnancy.[167] In rare cases where cardiac bypass surgery is required in pregnancy, maternal survival is good; however, fetal loss remains high.[168] When cardiopulmonary bypass is needed, the use of high-flow, high-pressure, pulsatile, normothermic bypass with continuous fetal and uterine monitoring is recommended.[169]

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) constitutes an extreme high-risk condition (class IV WHO) with high maternal mortality ranging between 30% and 56%, and therefore pregnancy is contraindicated and preconception counseling should be provided.[170,171] PAH refers to WHO group I pulmonary hypertension including idiopathic, heritable, congenital, and drug- or toxin-induced PAH. Even though new advanced therapies for PAH have become available, outcomes remain poor. Fetal mortality is also significant (10%-28%). The vulnerable period for the development of a pulmonary hypertensive crisis and death occurs during the later stage of pregnancy, labor, and into the postpartum period. During pregnancy, women with PAH do not exhibit a physiological decrease in pulmonary vascular resistance (PVR) (similar to the fall in systemic vascular resistance) resulting in further right ventricular (RV) dysfunction; this is then challenged by an increase in circulating plasma volume and stroke volume. During delivery, the increase in cardiac output together with blood loss and fluid shifts alters hemodynamics, and postpartum the acute return of systemic vascular resistance (SVR) to baseline promotes an acute deterioration. Risk factors associated with maternal mortality include late hospitalization, severity of pulmonary hypertension, and general anesthesia. In terms of pregnancy planning, there is no known cutoff value of the pulmonary pressures to portend an increased risk of complications. Therefore, women with PAH should be counseled on appropriate forms of contraception and to avoid pregnancy. However, despite this, some women with PAH elect to proceed with pregnancy, and advanced pulmonary hypertension therapies may decrease the risk of complications[172]; although the experience is limited and certain agents such as the endothelin receptor antagonists (eg, bosentan, category X) are teratogenic. Calcium channel blockers may be continued for those who demonstrated vasoreactivy on cardiac catheterization. Intravenous prostanoids (epoprostenol, treprostinil, category B) provide the best effect among agents and should be given to women with functional class (FC) IV symptoms and RV dysfunction. Attention should be given to their possible interference in platelet aggregation and possible bleeding. PDE-5 inhibitors (eg, sildenafil, tadalafil, category B) cause both PVR and SVR decrease and may be used in women with normal RV function and FC WHO I and II symptoms. A combination of prostanoids and PDE-5 inhibitors may be beneficial.[173] Anticoagulation throughout pregnancy in women with PAH is advised in women who already have been on therapy prior to pregnancy with either only a short interruption during delivery or a transition to unfractionated heparin. Oxygen supplementation is often necessary. Close follow-up is advocated during the pregnancy with repeated echocardiograms to assess RV function and pulmonary peak systolic pressures. A coordinated team effort is advised and delivery should be monitored in the ICU setting. Caution should be given to placement of a Swan-Ganz catheter because of the risk of vascular rupture and is not routinely recommended, yet a central line may aid in volume management. Intravenous prostanoids may be initiated in untreated women who show RV dysfunction or hemodynamic concerns. Vaginal delivery is preferred to cesarean section because of smaller volume shifts, although the latter may allow better monitoring and more efficient hemostasis if bleeding occurs. Epidural anesthesia causes less peripheral vasodilatation than general and spinal anesthesia and may provide the safest anesthesia.

CONGENITAL HEART DISEASE IN PREGNANCY

Remarkable advancements in surgical and medical treatment of children with CHD have led to increasing numbers of women with CHD becoming pregnant. The hemodynamic changes of pregnancy may unmask previously unrecognized CHD or exacerbate residual hemodynamic lesions. Meticulous knowledge of the congenital heart condition and potential complications is key for the management of CHD patients. Guidelines advise the referral of CHD patients to experienced centers where the full range of maternal fetal medicine and congenital heart expertise are available.[7]

Shunt Lesions

Atrial septal defects (ASDs) are the most common congenital lesions encountered in women in the childbearing age. Unrepaired ASDs usually exhibit left-to-right shunting with subsequent right atrial and ventricular enlargement, potential RV dysfunction, arrhythmias, and in rare cases paradoxical emboli or pulmonary hypertension. Thromboembolic complications have been reported in up to 5% of these women and meticulous intravenous line care with filter placement is recommended during delivery and postpartum as well as deep vein thrombosis prophylaxis.[88] Unrepaired ASDs have been implicated with increased risk of preeclampsia, small for gestational age neonates, and increased neonatal mortality.[174] Women with repaired ASDs should tolerate pregnancy well, unless they have preexisting RV dysfunction.

Hemodynamically significant ventricular septal defects (VSDs) cause left-sided heart volume overload, with potential ventricular dysfunction, arrhythmia, and rarely pulmonary hypertension. Large unrepaired VSDs in childhood may advance to Eisenmenger physiology and pregnancy is contraindicated in these women. Women with small, pressure-restrictive VSDs and normal left ventricular size are at low risk for complications during pregnancy; however, there is a reported increased risk of preeclampsia in women with unrepaired VSDs.[175]

A large patent ductus arteriosus (PDA) causes pulmonary artery enlargement, left-sided volume overload, and may lead to pulmonary hypertension.[7] Ductal flow decreases during pregnancy as a result of the decrease in systemic vascular resistance. However, small PDAs should not have hemodynamic significance during pregnancy.

Ebstein Anomaly

Outcomes in pregnancy in women with Ebstein anomaly are directly related to the degree of tricuspid valve displacement, degree of tricuspid regurgitation, RV dysfunction, cyanosis, and arrhythmia. In general, women with Ebstein anomaly tolerate pregnancy fairly well with overall risk of heart failure or arrhythmia in less than 5%.[88] Because many of these women have an atrial communication, embolic stroke and cyanosis may occur. Women are also at risk for atrial arrhythmias during pregnancy, as Wolff-Parkinson-White syndrome, is present as many as 20% of women with Ebstein anomaly. Atrial arrhythmias in women with Ebstein anomaly may further deteriorate the RV function or result in life-threatening atrial fibrillation during pregnancy.[176,177] Neonatal outcomes include increased prematurity, fetal loss, and CHD.[178] Pre-conception counseling should focus on tricuspid valve function with repair or replacement consideration and arrhythmia evaluation and intervention when appropriate.

Transposition of the Great Arteries

Women with D-loop transposition of the great arteries who underwent an atrial switch (ie, Senning or Mustard operations) or those with physiologically corrected transposition of the great arteries (congenitally corrected TGA [cc-TGA]) have a morphological right ventricle functioning as the systemic ventricle. The long-standing volume and pressure overload affecting the systemic ventricle often leads to ventricular dysfunction. Systemic ventricular failure in pregnancy has been reported in 5% to 10% of these women.[88] Additional cardiovascular complications include tricuspid valve regurgitation, atrial arrhythmias, and cyanosis if there is an atrial level shunt present. Baseline systemic ventricular function and the burden of arrhythmia should be preemptively evaluated, because both may worsen during pregnancy. In women with D-loop TGA who had previously undergone the Mustard procedure, it was shown that the increased systemic ventricular dimensions, decreased systolic function, and increased degree of tricuspid regurgitation may persist after pregnancy and not return to baseline values.[179] Presently, children born with D-loop TGA will undergo an arterial switch procedure in the neonatal period. Data are scarce in this emerging population; however, a recent publication summarizing 17 pregnancies from 9 women reported two cardiac complications related to preexisting conditions (nonsustained ventricular arrhythmia in an impaired ventricle and a thrombosis of a mechanical valve).[180]

Coarctation of the Aorta

The most common complication encountered in women in pregnancy with coarctation of the aorta is systemic hypertension, yet aortic wall complications, although rare, are of concern.[181] The increased flow across the narrowed isthmus coupled with hypertension may cause left ventricular failure and decreased fetal perfusion. Careful evaluation of the aortic dimensions prior to and during pregnancy and blood pressure control throughout gestation are imperative. Women with repaired coarctation may have residual stenosis (peak gradient > 20 mm Hg) or aneurysms at the repair site that should be adequately imaged and treated prior to pregnancy.[7] Aortic diameters < 1.2 cm have been correlated with higher maternal cardiovascular events.[182] During pregnancy, women with coarctation of the aorta have increased incidence of hypertensive complications, cesarean section delivery, longer hospital stay, and higher hospital charges.[183]

Tetralogy of Fallot

Repaired tetralogy of Fallot (TOF) is a common lesion encountered in women of childbearing age. The hemodynamic lesions of concern in repaired TOF during pregnancy are pulmonary regurgitation, RV dilation and dysfunction. The volume overload of pregnancy exacerbates the degree of valve regurgitation and may cause further deterioration of RV function. The most common cardiac maternal events include heart failure and atrial arrhythmias.[88,184,185] It is important to consider pulmonary valve replacement prior to pregnancy in women with severe pulmonary regurgitation. There is evidence that women with repaired TOF who have undergone pregnancy have higher right ventricular end-diastolic volumes than nulligravid women.[186] Women with unrepaired TOF or those women palliated with only a systemic-to-pulmonary arterial shunt are counseled to avoid pregnancy because of the cyanosis and the risk of paradoxical emboli. Women with TOF should be offered genetic counseling to assess for 22q11 deletion, which is associated with conotruncal abnormalities.[7]

Cyanotic Conditions

Women with cyanotic heart conditions should be counseled to obtain a permanent form of sterilization, as pregnancy is contraindicated because of the high prevalence of maternal and fetal mortality. Cyanosis secondary to right-to-left intracardiac shunting is increased during pregnancy as a result of the decrease in systemic vascular resistance. Cyanosis is associated with increased risk of thrombosis causing paradoxical emboli and hyperviscosity from erythrocytosis. There is a

very low delivery rate of less than 12% and high maternal complications when the maternal oxygen saturation is < 85%.[187] Common maternal complications with cyanosis include heart failure, endocarditis, and thrombosis. Cyanosis associated with Eisenmenger syndrome carries an extremely high maternal mortality rate (at least 50%). Women with Eisenmnenger syndrome are advised against pregnancy.

Single Ventricle with Fontan Palliation

Pregnancies in women with a single ventricle palliated with a Fontan circulation are associated with high maternal and neonatal risk.[188] There are high rates of miscarriages, with maternal complications such as supraventricular arrhythmias (most common), heart failure, and valve regurgitation.[189,190] Baseline functional capacity, arrhythmia burden, single ventricular function, and degree of cyanosis are the basic determinants of pregnancy risk. Women with cyanosis, ventricular dysfunction, moderate or more atrioventricular valve regurgitation, or the presence of protein-losing enteropathy should be advised against pregnancy.[1] Pregnancies in women with Fontan physiology have higher rates of miscarriage, heart failure, arrhythmia, and bleeding.[188-190] Neonatal outcomes include prematurity and small for gestational age neonates.[191] Anticoagulation throughout pregnancy should be considered in the Fontan patient due the higher risk of thrombosis during pregnancy coupled with the inherent hypercoaguable state of the Fontan circulation.[192]

SUMMARY

Cardiovascular disease complicates more than 1% of pregnancies and is the leading cause of indirect maternal mortality. Medical care begins in the preconception period with careful planning and anticipation of the possible complications that may arise during the antepartum, intrapartum, and postpartum periods. Pregnant women with CVD should be cared for by a multidisciplinary team that understands the unique hemodynamic changes that occur and how these changes affect women and their offspring both during pregnancy and beyond.

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CHAPTER 104

TRAUMATIC HEART DISEASE

T. Bruce Ferguson, Jr.

CARDIAC INJURY / 2364
Penetrating Cardiac Injuries / 2364
Blunt Cardiac Injury / 2364
Delayed Sequelae of Cardiac Injury / 2367

GREAT VESSEL INJURY / 2367
Penetrating Injury of the Great Vessels / 2367
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Trauma is the leading cause of death and disability among young people in the United States.[1-3] Thoracic injures account for 20% to 25% of deaths from trauma, and contribute to 25% to 50% of the remaining deaths. Thus thoracic injures are a contributing factor in up to 75% of all trauma-related deaths.[4] Cardiac and great vessel injuries are common contributors to the morbidity and mortality of severely injured patients.[5] Causes of injury to the heart and thoracic aorta can be broadly divided into penetrating or blunt mechanisms.

CARDIAC INJURY

PENETRATING CARDIAC INJURIES

Penetrating injury to the heart must be suspected with any missile or knife wound to the thorax or upper abdomen. The mechanism of injury may be categorized as low, medium, or high velocity. Knife wounds are low velocity, shotgun injuries are medium velocity, and high-velocity injuries include bullet wounds caused by rifles and wounds resulting from military and civilian weapons. The amount of tissue damage is directly related to the amount of energy exchange between the penetrating object and the body part.[4]

Traumatic cardiac penetration injuries are highly lethal at 70% to 80%. The anteriorly positioned right ventricle is most frequently injured followed by the left ventricle, right atrium, and left atrium (Table 104–1).[6] Other potentially injured structures include the interatrial or interventricular septum, coronary arteries, valves, subvalvular apparatus, and conduction system.[7] Low-velocity injuries, such as stab wounds, produce damage commensurate to the structure penetrated and size of the defect. High-velocity missiles produce injury beyond the region of myocardial penetration secondary to concussive effects and are more frequently lethal.[8-11]

The primary manifestations of cardiac penetration are hemorrhage and tamponade. Valve or coronary injury may, of course, produce acute valvular incompetence or myocardial infarction. Stab victims often present with tamponade when clot and surrounding pericardial fat partially seal the pericardial defect. Injuries to the left ventricle more commonly result in overt hemorrhage. Patients presenting with tamponade may have a survival advantage, with mortality rates as low as 8% in experienced trauma centers.[8] Early diagnosis is critical to survival, and this is only possible with a high index of suspicion, bearing in mind that patients with potentially fatal wounds can be stable at presentation. Echocardiography can confirm the diagnosis of cardiac injury, but the lack of an effusion does not disprove injury.[12] The diagnostic gold standard, short of exploration, is a subxiphoid window.

Management of penetrating wounds to the heart depends on the stability of the patient. If the patient presents with a recent loss of vital signs or in a moribund state, a left anterior thoracotomy performed in the emergency department is potentially lifesaving. Emergent thoracotomy may salvage as many as 20% of unstable or pulseless patients who have isolated penetrating trauma to the heart, but results are less favorable with missile wounds.[13,14] Most cardiac wounds can be repaired through a left thoracotomy. Additionally, the thoracic aorta can be compressed or clamped to improve cerebral and cardiac perfusion while volume is restored. More stable patients are transported to the operating room, where a median sternotomy is the preferred approach. A sternotomy allows adequate exposure of all cardiac structures and permits rapid institution of cardiopulmonary bypass when required. Most injuries are repaired with simple pledgeted sutures using finger control to stop bleeding once identified. Coronary artery injuries are common, and the surgeon must use his or her judgment regarding coronary artery bypass versus ligation. An effort should be made to bypass large epicardial vessels, whereas smaller terminal branches or side branches can be ligated. The principal objective is to relieve tamponade and stop life-threatening hemorrhage. Further procedures, once again, require individualized surgical judgment based on the severity of the lesion and the physiologic significance on echocardiogram.

BLUNT CARDIAC INJURY

The reported incidence of blunt cardiac trauma varies widely in the literature, but blunt injury is involved in up to 20% of all motor vehicle collision deaths.[15] The Centers for Disease Control and Prevention estimates 30,000 cases per year in the United States of blunt cardiac injuries.[16] Blunt cardiac injury results from either a rapid deceleration mechanism or a direct blow to the precordium; in all cases, blunt cardiac injury requires significant force, such as occurs in motor vehicle crashes, pedestrians struck by motor vehicles, falls from heights, and sports-related injuries. Severe sudden abdominal compression can acutely increase pressure and blood flow to the heart, resulting in right-sided rupture. The absence of a clear definition and rapid laboratory testing makes the diagnosis of blunt cardiac injury difficult.

Resulting injuries include cardiac contusion, valve disruption, atrial or ventricular septal defects, or frank cardiac rupture. These injuries vary by anatomic location (Table 104–2). Once again, because of its anterior position, the right ventricle is the chamber most frequently involved. Cardiac rupture is a common mechanism of death in blunt trauma, with survival after medical care being uncommon.[15,17] In patients reaching medical care with vital signs, however, a reasonable survival rate can be expected if cardiac injury is promptly recognized and operated on.[18] Those surviving cardiac rupture more frequently have injuries to the right heart.[19] Myocardial contusion encompasses a spectrum of injuries. In its mildest form, cardiac contusion results in mild epicardial ecchymosis without functional significance. More severe contusion can cause muscular injury, dysfunction, and infarction. The true incidence of myocardial contusion following blunt trauma is difficult to discern. It is important to note that severe myocardial injury can occur with little evidence of external chest trauma.

A high index of suspicion along with careful evaluation of mechanism should accompany all trauma patients from these accident scenarios, as a majority of patients with blunt cardiac trauma are asymptomatic. Diagnostic testing including chest x-ray, electrocardiogram (ECG), Holter monitoring, cardiac markers, transthoracic and transesophageal echocardiography, and cardiac computed tomography (CT) and magnetic resonance imaging (MRI) may be needed to make

TABLE 104–1. Spectrum of Penetrating Cardiac Injury by Anatomic Location[50]

Right ventricle	43%
Left ventricle	34%
Right atrium	16%
Left atrium	7%

TABLE 104–2. Spectrum of Blunt Cardiac Injury by Anatomy Location

Right atrium	8%-65%
Right ventricle	17%-32%
Left ventricle	8%-15%
Left atrium	0%-31%
Coronary artery	0%-5%
Left anterior descending artery most common	0%-5%
Valve injury	
Aortic valve most common	0%-3%
Blunt pericardial rupture	

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the diagnosis.[4] All patients who have a significant mechanism of injury should have a screening ECG. Findings suggestive of cardiac contusion include nonspecific ST- and T-wave changes. Arrhythmias such as atrial fibrillation, atrial flutter, and premature ventricular complexes are also common and are usually self-limiting. Ventricular tachycardia and fibrillation are uncommon in patients surviving to the hospital. With a normal ECG in an otherwise uninjured patient, the risk of complications is low. Serial cardiac enzyme measurements are nonspecific for the diagnosis of myocardial contusion in the blunt injury patient.[20] In the patient who remains unstable or responds poorly to standard resuscitative efforts, echocardiography is indicated to look for regional wall-motion abnormalities or structural defects.

The American Association for the Surgery of Trauma (AAST) Injury Scale for Cardiac Injuries is one way of quantifying the extent of injury (Table 104–3).

The management of myocardial contusion is often expectant, particularly in the patient who remains hemodynamically stable after treatment of concurrent injuries. Arrhythmias are treated with standard agents for rate control and suppression of ectopy as well as optimization of electrolytes. In patients with hemodynamic instability, definitive echocardiography should be obtained. In cases of severe ventricular dysfunction and low cardiac output, inotropic support is appropriate with perhaps less concern for extension of injury than with a primary ischemic event. If inotropic support does not produce satisfactory improvement, intra-aortic balloon counterpulsation should be considered.

Pericardial injury results from direct high-energy impact of acute increase in intra-abdominal pressure. The presence of absence of a sternal fracture is not diagnostic. The pericardium may rupture along the diagphragmatic or pleural surface parallel to the phrenic nerve, resulting in evisceration of the heart and/or torsion of the great vessels. Pneumopericardium, abnormal gas pattern, or displacement of the cardiac silhouette may be present. Emergency surgical intervention via sternotomy is mandatory.

TABLE 104–3. American Association for the Surgery of Trauma Injury Scale: Cardiac Injuries

Grade I
1. Blunt cardiac injury with minor ECG abnormality (nonspecific ST- or T-wave changes, premature atrial or ventricular contractions, or persistent sinus tachycardia).
2. Blunt or penetrating pericardial wound without cardiac injury, tamponade, or cardiac herniation.

Grade II
1. Blunt cardiac injury with heart block or ischemic changes without cardiac failure.
2. Penetrating tangential cardiac wound, up to but not extending through endocardium, without tamponade.

Grade III
1. Blunt cardiac injury with sustained or multifocal ventricular contractions.
2. Blunt or penetrating cardiac injury with septal rupture, pulmonary or tricuspid incompetence, papillary muscle dysfunction, or distal coronary artery occlusion without cardiac failure.
3. Blunt pericardial laceration with cardiac herniation.
4. Blunt cardiac injury with cardiac failure.
5. Penetrating tangential myocardial wound, up to but not through endocardium, with tamponade.

Grade IV
1. Blunt or penetrating cardiac injury with septal rupture, pulmonary or tricuspid incompetence, papillary muscle dysfunction, or distal coronary artery occlusion producing cardiac failure.
2. Blunt or penetrating cardiac injury with aortic or mitral incompetence.
3. Blunt or penetrating cardiac injury of the right ventricle, right or left atrium.

Grade V
1. Blunt or penetrating cardiac injury with proximal coronary artery occlusion.
2. Blunt or penetrating left ventricular perforation.
3. Stellate injuries, less than 50% tissue loss of the right ventricle, right or left atrium.

Grate VI
1. Blunt avulsion of the heart.
2. Penetrating wound producing more than 50% tissue loss of a chamber.

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Direct coronary artery injury may cause arterial thrombosis, resulting in myocardial infarction, post-myocardial infarction ventricular septal defect, cardiac failure, or malignant arrhythmias.

Valve injury following blunt trauma is uncommon. The aortic valve is most frequently involved and can result from commissural avulsion, leaflet tears, or aortic dissection, all resulting in acute aortic insufficiency.[21,22] Isolated injury of the mitral valve is less common and most frequently involves rupture of the papillary muscle or chordal apparatus. Tricuspid valve injury is more commonly reported than mitral injury perhaps because the latter is frequently fatal. Figure 104–1 shows the two-dimensional transthoracic echocardiogram in a female patient who was kicked in the anterior chest wall by her horse.[23] Tricuspid valve injury may become evident at a time remote from the injury as right heart failure develops.[24-26]

Recently a case of traumatic left ventricular intramural dissection has been reported (Fig. 104–2).[27]

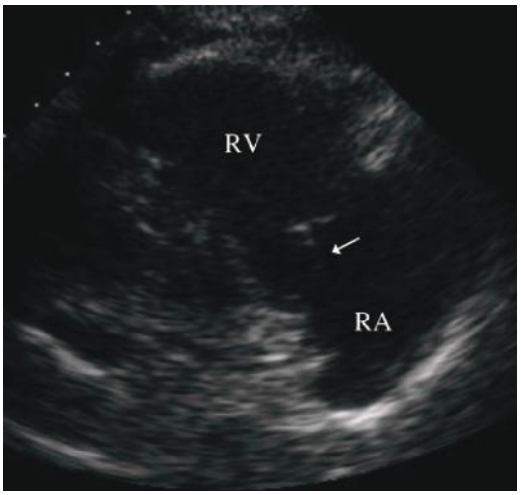
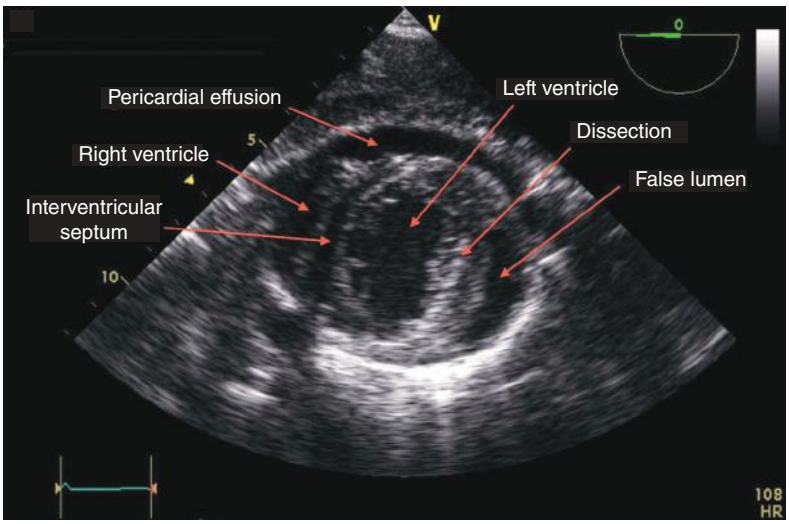
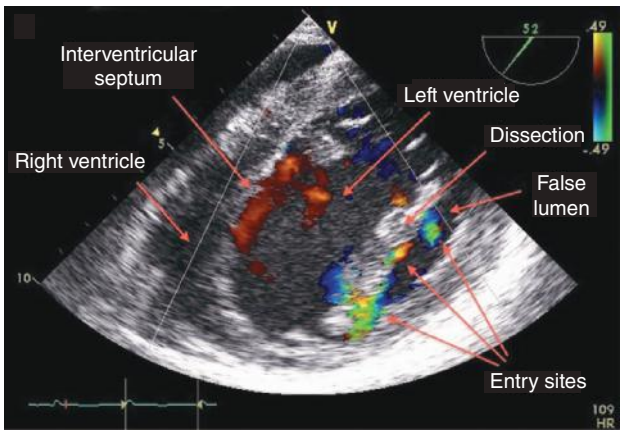


FIGURE 104–1. A 53-year-old woman was kicked by her horse, with the hoof striking her in the center of the chest. She developed severe chest pain. Cardiac auscultation was normal. Rib radiographs did not show any rib fractures, and chest x-ray showed clear lung fields and a normal cardiac silhouette. Electrocardiogram (12-lead) demonstrated sinus tachycardia with a minor right ventricular conduction delay and no ischemic changes. Troponin I was elevated. Two-dimensional echocardiogram demonstrated a partially flail septal leaflet of the tricuspid valve (*white arrow*). RA, right atrium; RV, right ventricle. Reproduced with permission from Morsli H, Weissman G, Cooper HA: Images in Cardiovascular Medicine. Blunt Cardiac Injury- A case report. *Circulation*. 2008 May 13;117(19):e333-e335.



A



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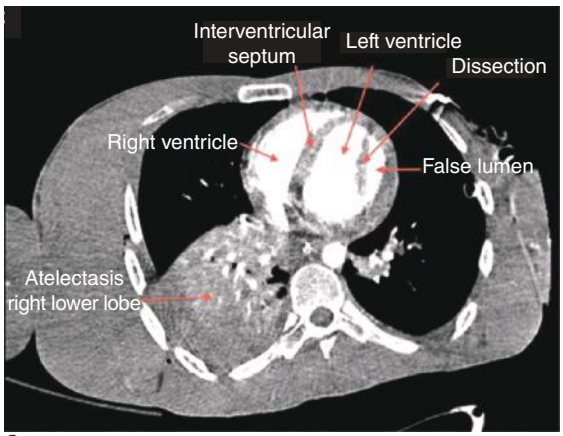

C

FIGURE 104–2. Traumatic left ventricular intramural dissection. A 30-year-old male sustained severe blunt chest injury from a hydraulic pipe thruster. He required high-dose vasopressors and inotropes. Transesophageal echocardiography (TEE) revealed a small pericardial effusion (panel **A**, top) and an extended intramural dissection (panels **A-C**) of the left ventricle involving the anterolateral papillary muscle and the apical and mid-segments of the anterior and lateral ventricular walls. An epicardial patch was placed over a severely thinned part of the anterolateral wall to prevent apical rupture. Reproduced with permission from Groves DS, Schmidt C: Traumatic left ventricular intramural dissection. *Eur Heart J*. 2010 Oct;31(20):2481.

DELAYED SEQUELAE OF CARDIAC INJURY

Patients sustaining significant blunt or penetrating cardiac injuries require long-term follow-up. Injuries may not be appreciated at the time of trauma. Possible late sequelae include evolving atrial or ventricular septal defects, progressive valvular incompetence, aortocardiac or aortopulmonary fistulas, coronary artery fistulas, ventricular aneurysms, and post-traumatic pericarditis.[28-31]

GREAT VESSEL INJURY

PENETRATING INJURY OF THE GREAT VESSELS

The great vessels of the chest include the aorta, its major branches at the arch (innominate, carotid, subclavian) and the major pulmonary arteries. The primary venous conduits include the superior and inferior vena cavae, their main tributaries (eg, azygous vein), and the pulmonary veins. The prevalence of great vessel injuries ranges from 0.3% to 10%. More than 90% of thoracic great vessel injuries are caused by penetrating trauma.[4,15]

The pathophysiology of penetrating wounds to the great vessels is similar to penetrating wounds of the heart, with the extent of injury being determined by the specific structures injured and the velocity of the weapon. Cardiac tamponade may develop if the wound is below the pericardial reflection. Delayed sequelae of great vessel injury include pseudoaneurysm formation with delayed rupture and arteriovenous malformation with development of congestive heart failure.

Penetrating injuries of the great vessels have a historically high mortality rate. The trauma surgeon must resuscitate, diagnose, and treat the patient within minutes following admission to the trauma emergency unit. Through an emergent left thoracotomy, operative repair of thoracic aortic injuries is virtually always possible by direct aortic repair with short cross-clamp times. Only rarely is an interposition graft required, and adjunctive measures of cardiopulmonary bypass, bypass shunts, or active aortic shunts (eg, a centrifugal pump) are usually not described for penetrating injuries but are almost exclusively used for blunt injury. Paraplegia following successful repair of penetrating aortic injuries is rare, even with prolonged aortic clamping following emergency thoracotomy.[4]

AORTIC RUPTURE

Aortic transection is second only to closed head injury as a cause of death in blunt trauma patients, resulting in an estimated 8000 deaths in the United States annually.[32-35] It is believed that approximately 20% of patients sustaining descending aortic transections survive to reach medical care.[33] The injury mechanism involves any type of severe deceleration, most commonly a motor vehicle accident. Tears are most often encountered at the aortic isthmus just beyond the subclavian artery where the aorta is tethered by the ligamentum arteriosum.[34,35] Patients acutely surviving aortic injury have partial or complete transections contained by adventitia and surrounding structures forming a false aneurysm. Avulsion of the innominate, carotid, or subclavian arteries occurs less frequently.[36,37]

Aortic transaction must be suspected based on the mechanism of injury. Patients may have multiple other injuries or have remarkably few other manifestations of severe trauma. The classic findings of a widened mediastinum, apical capping, or depression of the left mainstem bronchus may not be evident on plain films of the chest in a patient with an aortic injury. Aortography has previously been the definitive means of diagnosis, but advancements in multidetector CT have made CT angiography a more commonly used tool to identify aortic injury in major trauma centers. Transesophageal echocardiography can be performed at the bedside or in the operating room in the patient too unstable for the CT scanner. In skilled hands, this has a sensitivity similar to that of helical CT scanning.[38,39]

Once a diagnosis of aortic transection from blunt aortic trauma is made, several emergent/urgent treatment options are available.[4] Immediate repair through a left thoracotomy should be considered depending on the patient's stability and other injuries. Delayed repair is appropriate in the multiply injured patient requiring ongoing resuscitation, and this management strategy has grown in popularity. Nonoperative management is not risk free, however, with as many as 4% of patients thought to be candidates for delayed repair experiencing rupture within a week of injury in some series.[40,41] A more recent additional option is endovascular stent graft insertion in selected patients, which has yielded promising results (Fig. 104–3) when compared with traditional repair.[42-48] The Society for Vascular Surgery database documented endovascular treatment for acute aortic transections. Ninety-seven percent were the result of a motor vehicle accident. Sixty symptomatic patients were treated with an aortic endograft, with an all-cause mortality rate of 9.1% at 30 days, and a mean operative time of 125 minutes.[49] An endovascular approach may be preferred in patients

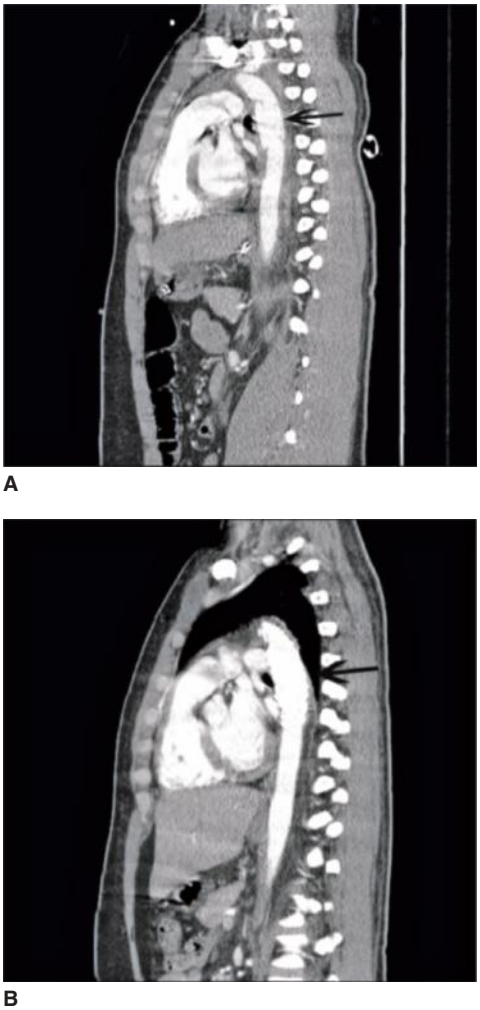

FIGURE 104–3. A. CT angiogram of a patient who sustained an aortic transection following a motor vehicle accident. **B.** CT angiogram of the same patient following insertion of a thoracic stent graft with successful exclusion of the false aneurysm.

who are higher risk for open repair such as the elderly or those with significant lung or head injuries, making thoracotomy and heparinization less appealing.

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CHAPTER 105

THE KIDNEY IN HEART DISEASE

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BACKGROUND

Cardiac and renal physiology are intimately intertwined. Impaired cardiac function can lead to kidney injury and vice versa. Furthermore, many cardiovascular therapeutic interventions may cause renal injury. Impaired renal function is common among patients with heart disease and is one of the strongest predictors of worse outcome for these patients. Reports suggest that renal disease is underdiagnosed among patients with heart disease, which increases the risk of avoidable adverse outcomes.[1-4]

RENAL PHYSIOLOGY AND IMPORTANT CONCEPTS

The main functions of the kidneys are to maintain water balance and body fluid homeostasis and to eliminate metabolic waste products. This is achieved by filtration of plasma in the glomerulus, as well as by secretion and reabsorption of water and solutes along the renal tubules. An average human filters 150 to 200 L of plasma across the glomeruli and produces 0.5 to 2.5 L of urine per day. Urine output greater than 2.5 L/d is termed polyuria; urine output less than 400 mL/d is termed oliguria; and urine output less than 100 mL/d is termed anuria.

Renal Clearance

The concept of renal clearance is based on Fick's principle, predicated on the law of conservation of mass. A substance that is neither synthesized nor metabolized within the kidney must enter and leave the kidney in equal amounts. A substance can enter the kidney only via the renal artery but can leave the kidney either via the renal vein or via the urine. Renal clearance refers to the excretory function of the kidney and therefore considers only the rate at which a substance is excreted into the urine, not the rate at which it is returned to the circulation through the venous system. In terms of mass balance, the excretion rate of substance *y* (U_y^*V), where U_y is the concentration of *y* in the urine and *V* is urine volume/time, is proportional to the plasma concentration of *y* (P_y). In a steady state, the rate at which *y* is moved from the plasma to the urine is the renal clearance (C_y):

$$C_y = U_y^* V/P_y$$

Hence, renal clearance represents a volume of plasma from which the substance of interest has been removed and excreted into the urine per unit time. For substances that are eliminated from the body predominantly through the kidney, plasma concentrations in blood samples from peripheral venous blood will closely approximate arterial concentrations. Depending on the properties of the substance measured, renal clearance can be used to estimate glomerular filtration rate (GFR) and renal plasma flow (RPF). Substances such as inulin, which are only filtered by the glomerulus, are the gold standard for measurement of clearance, but because they need to be administered intravenously are not practical for routine clinical use. Creatinine, while also excreted and reabsorbed to some extent in the tubules, provides sufficient accuracy for routine estimation of renal function, especially with 24-hour urine collection.

Glomerular Filtration Rate and Creatinine Clearance

Glomerular ultrafiltration is the first step of urine formation. The glomerular filtration barrier restricts the filtration of molecules on the basis of size and molecular charge (ie, the reflection coefficient [σ] for these molecules across the glomerular membrane is ~ 1). As a consequence, the plasma ultra-filtrate is devoid of cells and has a very low concentration of plasma proteins in healthy individuals. Glomerular filtration is determined by Starling forces (hydrostatic and oncotic pressures) across the glomerular membrane and the ultrafiltration coefficient (*Kf*):

$$K_f [(P_{GC} - P_{BS}) - \sigma(\pi_{GC} - \pi_{BS})]$$

Where $P_{GC} - P_{BS}$ and $\pi_{GC} - \pi_{BS}$ are the differences in hydrostatic (*P*) and osmotic (π) pressures between the glomerulus (*GC*) and Bowman's capsule (*BS*).

GFR is the sum of the glomerular filtration rate across all nephrons and is an important index of renal function.[1] A normal GFR ranges between 90 and 120 mL/min/1.73 m^2. GFR is commonly estimated in clinical practice from the renal clearance of creatinine. Creatinine, a degradation product of creatine phosphate metabolism that predominantly originates from skeletal muscles, is freely filtered across the glomeruli and is only minimally secreted and reabsorbed by the renal tubules. Hence the clearance of creatinine is a reasonable estimate of the GFR. A reduction in GFR initially results in a drop in creatinine excretion. However, as plasma creatinine levels increase due to unchanged creatinine production, a new steady state is reached as production and excretion equilibrate at a higher plasma creatinine concentration. Hence plasma

creatinine levels correlate with GFR, but this relationship is nonlinear. Moreover, the relationship between GFR and creatinine is different across gender, age, and race. Therefore the common clinical practice of defining impaired renal function by serum creatinine cutoffs may lead to significant errors. Laboratories should report results as estimated GFR.

Several formulas exist that estimate GFR from plasma creatinine levels, with the Cockcroft-Gault (GC), the Modification of Diet in Renal Disease (MDRD),[2] and the CKD-EPI[3] equations. The Cockcroft-Gault equation was derived by measuring creatinine clearance in men, with an assumed correction factor of 0.85 in women[4]:

$$\text{CG clearance} = [(140 - \text{age}) \times \text{weight (kg)} \times 0.85 \text{ if female}]/(72 \times SCr),$$

adjusted for BSA by 1.73 m^2/BSA, where *SCr* = serum creatinine in mg/dL.

The CG equation tends to overestimate GFR as creatinine is not only filtered by the glomerulus but to some extent excreted by the tubules.[5] In recent years the MDRD equation,[6,7] created by a stepwise regression analysis of measured GFR (mGFR) in 1628 chronic kidney disease subjects of the MDRD study, has gained widespread use for estimating GFR from serum creatinine. Originally, a six-variable equation, the MDRD was further modified to a four-variable equation and then reexpressed for use with standardized creatinine assays[8]:

$$\text{GFR} = 175 * \text{standardized serum creatinine}^{1.154} * \text{age}^{0.203}$$

To account for differences across gender and race, the estimated GFR should be multiplied by 1.212 if the patient is black and/or by 0.742 for women.

The reexpressed MDRD equation, having been derived in patients with CKD, tends to underestimate kidney function at higher GFR. To address this limitation, a third equation [CKD-EPI(3)], which has now been adopted by most commercial labs and was endorsed by KDIGO (Kidney Disease Improving Global Outcomes; kdigo.org) in 2013, was developed using data from 12,150 subjects in diverse populations (8254 for development and 3896 for validation). The CKD-EPI equation, expressed as a single equation, is:

$$\text{GFR} = 141 * \min(SCr/\kappa,1)^{\alpha} * \max(SCr/\kappa, 1)^{-1.209} * 0.993^{\text{Age}} * 1.018 \text{ [if female]} * 1.159 \text{ [if black]}$$

where *SCr* is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of *SCr*/κ or 1, and max indicates the maximum of *SCr*/κ or 1.

Online calculators are available to calculate these formulas (http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/adults-conventional-unit-ckd-epi/Pages/default.aspx and http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/adults-conventional-unit/Pages/adults-conventional-unit.aspx).

Tubular Excretion and Reabsorption

Selective reabsorption of water and solutes and excretion of solutes occur along the tubular portion of the nephron. Transport of solutes across the tubular membrane is an energy-demanding process and may be impacted in various metabolic derangements.

Renal Blood Flow

Together the kidneys constitute less than 0.5% of total body weight but receive approximately 25% of the cardiac output during resting conditions (1.25 L/min). Renal blood flow (RBF) is an important determinant of glomerular filtration rate, solute and water reabsorption by the proximal tubule, concentration and dilution of urine, and excretion of substances in the urine. Another important function is to deliver oxygen, nutrients, and endocrine substances to the cells of the nephron and to return carbon dioxide and reabsorbed solutes to the circulation.

Like other organs, the kidneys regulate their blood flow by adjusting vascular resistance in response to arterial pressure. Two autoregulatory mechanisms that regulate the tone of the afferent arteriole contribute to RBF and GFR (of which RBF is a major determinant), remaining particularly constant over a wide range of systemic arterial pressures.[9] The first is the *myogenic mechanism*, which is related to the intrinsic property of vascular smooth muscle cells to contract when it is stretched. The second mechanism is mediated by the juxtaglomerular apparatus at the macula densa and is termed *tubuloglomerular feedback*. When GFR increases and causes the NaCl concentration of the tubular fluid at the macula densa to increase, the afferent arteriole constricts. Nitric oxide produced by the macula densa attenuates, whereas angiotensin II enhances, tubuloglomerular feedback. In addition to these autoregulatory mechanisms, sympathetic nerves and angiotensin II play major roles in regulating RBF and GFR. Prostaglandins, nitric oxide, endothelin, bradykinin, ATP, and adenosine also affect RBF and GFR.

Regulation of Effective Circulatory Volume

Total body water accounts for 60% of total body weight and is divided into intracellular (40%) and extracellular (20%) fluid. The extracellular fluid volume is largely influenced by Na^+ content and is further divided into the interstitial fluid and blood plasma. The regulation of ECF volume involves a complex system of sensors and effector signals that act primarily on the kidneys to alter NaCl excretion.[10,11] The effective circulatory volume (ECV) refers to the portion of the blood plasma that effectively perfuses the tissues that contain the volume sensors that participate in ECF volume regulation. The kidneys adjust NaCl excretion in response to changes in the ECV. In a healthy person, any change in ECF volume results in a parallel change in plasma volume, ECV, blood pressure, and cardiac output. However, this relationship is disrupted in some pathological conditions, including heart failure.

Potassium and Acid–Base Balance

Excretion of K^+ by the kidneys is determined predominantly by the distal tubule and collecting duct and is regulated by plasma [K^+], aldosterone, and vasopressin. Renal K^+ handling is linked to acid–base balance. Alkalosis increases whereas acidosis reduces K^+ excretion.

AGING AND RENAL FUNCTION

Renal function gradually decreases with increasing age.[12] The mean estimated GFR among individuals over 70 years has been shown to be slightly below the threshold for chronic kidney disease (CKD; < 60 mL/min/1.73 m^2).[13] It is difficult to separate the effects of "normal" aging from the effects of a cumulative disease burden (eg, diabetes, hypertension, heart disease) because many of the morphological features of CKD are observed in the senescent kidney.[14,15] Nevertheless, the senescent kidney is more susceptible to injurious stimuli (Table 105–1), and an age-related decline in renal function needs to be taken into consideration when administering drugs that are cleared through the kidney.[16,17]

BIOMARKERS TO ASSESS RENAL FUNCTION

With the emergence of genomics, proteomics, and metabolomics in recent years, an increasing number of biomarkers of tissue injury and/or organ dysfunction have been detected. A myriad of potential biomarkers of renal disease have been studied and a few candidates are being tested in preclinical and clinical models. Table 105–2 lists some of these biomarkers. Unfortunately, the diagnostic and prognostic performances of these biomarkers have been heterogeneous across studies. For now, the traditional biomarkers (eg, serum creatinine and urine albumin) remain the most practical for diagnosis and risk stratification of patients with renal disease. Among the novel biomarkers, cystatin C and neutrophil

TABLE 105–1. Age-Dependent Changes in Renal Structure and Function

Changes	Renal Effects	Clinical Consequences
Glomerulosclerosis, reduced cortical renal mass	Loss of functioning nephrons	Decreased GFR and renal reserve
Renal atherosclerosis	Decreased renal plasma flow	Decreased GFR and renal oxygenation
Tubular atrophy, interstitial fibrosis, medullary hypotonicity	Impaired sodium and water resorption	Decreased ability to concentrate urine
Relative aldosterone resistance, low serum aldosterone	Decreased potassium secretion	Susceptibility to develop hyperkalemia
Imbalance in pro- and antiapoptotic factors	Increased apoptosis	Impaired renal recovery in AKI
Decreased growth factor synthesis, impaired progenitor cell function	Impaired cell regeneration	Impaired renal recovery in AKI

Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate.

Data from Musso CG, Oreopoulos DG. Aging and physiological changes of the kidneys including changes in glomerular filtration rate. *Nephron Physiology*. 2011;119 Suppl 1:p1-5; and Schmitt R, Cantley LG. The impact of aging on kidney repair. *American Journal of Physiology - Renal physiology*. 2008;294:F1265-72.

gelatinase-associated lipocalin (NGAL) have emerged as the most promising and may be useful in clinical decision making.[18,19]

DEFINITION AND CLASSIFICATION OF ACUTE AND CHRONIC KIDNEY INJURY

Impaired renal function has traditionally been classified into two distinct syndromes, acute and chronic renal failure. However, these syndromes are closely connected and are not two inherently distinct entities. Acute kidney injury is a risk factor for development of chronic renal disease, chronic renal disease is a risk factor for acute kidney injury, and both acute and chronic renal disease are risk factors for cardiovascular disease.[20]

Definition of Acute Kidney Injury

Acute kidney injury (AKI) can be classified according to its etiology. The causes of AKI can be categorized as prerenal (upstream of the glomerulus), intrarenal (intrinsic renal disease), and postrenal (urinary tract obstruction) causes. Functional definitions, which classify patients into stages of AKI based on changes in serum creatinine concentration and urinary output, complement the anatomical approach to diagnosis (Table 105–3).[21] These functional classifications have been shown to be strongly associated with outcomes, including progression of renal disease, ischemic coronary events, and mortality.[22,23] The most important of these classifications is the RIFLE (risk, injury, and heart failure, loss, and end-stage renal disease) criteria, a consensus-based classification formalized by the Acute Dialysis Quality Initiative.[24]

Definition of Chronic Renal Disease

Chronic kidney disease (CKD) is defined as the presence of persistent (> 3 months) functional or structural kidney abnormalities. A urine albumin-to-creatinine (ACR) ratio > 30 μg/mg from the first voided urine specimen and acquired under resting conditions is considered abnormal and an indicator of renal damage. An abnormal ACR is classified as either microalbuminuria (30–300 μg/mg) or macroalbuminuria (> 300 μg/mg). CKD is typically classified according to the GFR, supplanted by markers of kidney damage (eg, urinary albumin-to-creatinine ratio) (Table 105–4). CKD stages correlate with increased prevalence of hypertension and diabetes and an increased risk of end-stage renal failure, ischemic coronary events, and death.[25,26]

ACUTE KIDNEY INJURY IN CARDIAC PATIENTS

Patients who are hospitalized due to heart disease are at increased risk of AKI regardless of baseline kidney function.[27,28] AKI is associated with adverse events, including an increased mortality risk.[29]

ACUTE KIDNEY INJURY AS A COMPLICATION OF MYOCARDIAL INFARCTION, CARDIOGENIC SHOCK, AND ACUTE DECOMPENSATED HEART FAILURE

AKI may occur when renal hemodynamics become deranged secondary to acutely impaired cardiac function. Whereas renal arterial hypotension due to decreased cardiac output has traditionally been believed to be the principal cause of AKI, recent data imply that venous congestion is more important.[30-33] Increased central venous pressure and intra-abdominal pressure is transmitted to the renal veins, interstitium, and tubules. This causes a reduction in renal perfusion pressure and GFR. A reduced GFR and a lower effective circulating volume activate the RAAS, with resultant sodium retention, worsened congestion, and parenchymal ischemia. Inflammatory cytokines, which are consistently observed in decompensated acute heart failure, may also contribute to tubular damage.[30]

AKI is common in patients with acutely and advanced decompensated heart failure, including patients with ST elevation myocardial infarction (STEMI) who develop signs and symptoms of heart failure.[29] It occurs in 50% of patients who develop cardiogenic shock.[34,35] Preexisting CKD and/or heart failure, diabetes, hypertension, obesity, anemia, and old age all increase the risk of developing AKI.

Management of such patients is challenging and several currently ongoing trials are trying to identify more effective treatment alternatives. Reversible causes of cardiac decompensation need to be swiftly addressed. The therapeutic window for optimizing renal status is narrow because drugs that reduce congestion, including loop diuretics, typically cause arterial hypotension and worsened renal perfusion, with subsequent stimulation of the RAAS (Fig. 105–1).[36] Judicious administration of loop diuretics to relieve congestion is the cornerstone of acute heart failure complicated by AKI. Ultrafiltration achieves more effective fluid removal and decongestion than medical therapy but does not influence prognosis.[37-39] Inotropes (eg, dobutamine, milrinone, and levosimendan) can be used to augment cardiac function, but may induce ventricular arrhythmias and have not been shown to improve prognosis of AKI.[40,41] In the worst cases where renal function continuous to deteriorate, continuous renal replacement therapy (CRRT) may be necessary.

ACUTE KIDNEY INJURY IN CORONARY AND PERIPHERAL PROCEDURES

Major technological advancements over the last decades allow for sophisticated percutaneous coronary (or peripheral) artery interventions. These interventions improve the quality of life for patients with coronary artery disease and improve the prognosis for patients with acute coronary syndromes. However, they require imaging, often repeatedly, of the vasculature. This is achieved by intravascular injection of iodinated contrast material, which is potentially nephrotoxic. Despite a decreasing incidence over the last decade, contrast-induced

TABLE 105–2. Current and Potential Biomarkers of Acute and Chronic Kidney Disease

Biomarker	Description	Acute Kidney Injury (AKI)	Chronic Kidney Disease (CKD)
Creatinine[18]	Degradation product of creatine. Released predominantly by skeletal muscles and cleared by glomerular filtration. Can be used to estimate GFR.	Established biomarker. Influenced by several factors (eg, preexisting CKD, muscle mass, ingested protein). Delayed detection of AKI.	Established biomarker. Influenced by several factors (eg, muscle mass, ingested protein).
Albumin[224]	Important plasma protein that is normally not excreted in urine.	–	Established biomarker of kidney damage. Inexpensive. Does not predict total proteinuria.
Cystatin C[18,225-227]	Expressed in all nucleated cells. Filtered by the glomerulus and subsequently reabsorbed (and not secreted) in the tubules.	Earlier detection of AKI compared to creatinine. Inconsistent results in different studies.	Not affected by muscle mass and dietary protein intake. No conclusive evidence of superiority to creatinine.
NGAL[227-232]	Expressed in neutrophils as well as renal tubular cells of the proximal tubule.	Earlier detection of AKI compared to creatinine. Influenced by extrarenal factors (eg, nonrenal systemic inflammation, hematopoietic comorbidities). Not all studies have shown good predictive power for AKI.	Appears to have incremental prognostic value beyond GFR. Influenced by extrarenal factors (eg, nonrenal systemic inflammation, hematopoietic comorbidities).
Interleukins[233]	Interleukins 1, 6, 8, and 18 are inflammatory proteins, originating from monocytes, dendritic cells, macrophages, and epithelial cells, which are filtered freely across the glomeruli and subsequently reabsorbed in the tubules (no secretion).	May be predictive of need for dialysis and appear to be markers of worse prognosis. Do not appear to be kidney-specific.	Do not appear to be sufficiently kidney-specific.
KIM-I[234]	Transmembrane glycoprotein that is upregulated in proximal tubule cells after ischemic/toxic injury.	Earlier detection of AKI compared to creatinine. Requires validation. May be affected by nonrenal factors.	May predict worse outcomes. Insufficiently studied; requires validation.
L-FABP[235]	Present in hepatocytes and cells in the renal proximal tubule. Believed to be markers of renal tubular injury.	May detect AKI earlier than creatinine. May provide incremental prognostic value in AKI when combined with NGAL. Insufficiently studied; requires validation.	Insufficiently studied.
NAG[236]	Present in several tissues, including the renal tubules.	Has been shown to have similar ability to predict AKI as cystatin C and NGAL. May be predictive of need for dialysis and appear to be markers of worse prognosis. Insufficiently studied; requires validation.	Insufficiently studied.
CRP[237]	Acute-phase protein and nonspecific inflammatory marker.	Not useful.	Chronically elevated CRP associated with CKD. Not selective for CKD.
Other Potential Future Biomarkers of Kidney Injury			
Tubular enzymes		αGST, πGST, GGT, AP	
Low molecular proteins		HGF, α1MG, β2MG	
Cell cycle components		IGFBP7, TIMP-2	
Chemokines		MCP-1	
Urinary fibrosis markers		CTGF, TGF-β1, collagen IV	
Glomerular cell injury markers		Podocalyxin, nephrin	
Others		miRNA panels, TAS, AOPP	

Abbreviations: AP, alkaline phosphatase; AOPP, advanced oxidation protein products; CRP, C-reactive protein; CTGF, connective tissue growth factor; GFR, glomerular filtration rate; GGT, gammaglutamyl transpeptidase; GST, glutathione S transferase; HGF, hepatocyte growth factor; IGFBP7, insulin-like growth factor-binding protein 7; KIM-I, kidney injury molecule I; L-FABP, liver fatty acid binding protein; MCP-1, monocyte chemoattractant protein-1; MG, microglobulin; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocain; IL, interleukin; TAS, total antioxidant status; TGF, transforming growth factor; TIMP-2, tissue inhibitor of metalloproteinases-2.

acute kidney injury (CI-AKI) occurs in as many as 10% of all interventional procedures and as many as 20% of procedures in patients with acute myocardial infarction.[42,43] Patients who develop AKI during coronary and/or peripheral intervention have increased risk of serious complications, including death.

Rarely, periprocedural AKI may also be caused by embolization of cholesterol to the renal arteries due to catheter manipulation of atheromatous plaques in the aorta. AKI caused by atheroembolization has a poor prognosis, with a high risk of the patient requiring chronic dialysis.[44-46] Because of the poor prognosis related to atheroembolic

TABLE 105–3. Classification of Acute Kidney Injury

RIFLE: Risk, Injury, and Heart Failure, Loss, and End-Stage Kidney Disease[24]

Stage	Assessments	
	Serum Creatinine Concentration/GFR	*Urine Output*
Risk	1.5-2.0 × baseline; or > 25% reduction in GFR	< 0.5 mL/kg/h for < 6 h
Injury	2.0-3.0 × baseline; or > 50% reduction in GFR	< 0.5 mL/kg/h for > 12 h
Failure	≥ 3.0 × baseline; or ≥ 4.0 mg/dL with an acute rise ≥ 0.5 mg/dL; or > 75% reduction in GFR	< 0.3 mL/kg/h for ≥ 24 h (oliguria); or anuria for ≥ 12 h

KDIGO

Stage	Assessments	
	Serum Creatinine Concentration	*Urine Output*
1	1.5-1.9 × baseline or ≥ 0.3 mg/dL	< 0.5 mL/kg/h for 6-12 h
2	2.0-2.9 × baseline	< 0.5 mL/kg/h for ≥ 24 h
3	≥ 3.0 × baseline, ≥ 4.0 mg/dL, or initiation of RRT	< 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

AKIN

1	1.5-1.9 × baseline or ≥ 0.3 mg/dL within 48 h	< 0.5 mL/kg/h for < 6 h
2	2.0-2.9 × baseline	< 0.5 mL/kg/h for > 12 h
3	≥ 3.0 × baseline or baseline ≥ 4.0 mg/dL with increase ≥ 0.5 mg/dL	< 0.3 mL/kg/h for ≥ 24 h (oliguria); or anuria for ≥ 12 h; or need for RRT

Abbreviations: AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy.

TABLE 105–4. Classification of Chronic Renal Disease: Chronic Kidney Disease According to Glomerular Filtration Rate (GFR=mL/min/1.73 m^2)

Stage	Assessments	
1	Kidney damage with normal GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3A	Mild to moderate decrease in GFR	45-59
3B	Moderate to severe decrease in GFR	30-44
4	Severe decrease in GFR	15-29
5	End-stage renal disease	< 15

AKI, it is important to differentiate between this and CI-AKI. Delayed (subacute) but sudden onset of renal insufficiency is common with atheroembolic AKI. Eosinophilia and eosinophiluria are common and concomitant skin findings (livedo reticularis, purpura, ulceration, or gangrene) should raise the level of suspicion. Renal biopsy may be necessary for establishing the diagnosis.[46]

Contrast-Induced Acute Kidney Injury: Pathophysiology

Currently used iodinated contrast agents are highly water soluble iso-osmolar (~ 290 mOsm/kg) or low-osmolar (700-850 mOsm/kg) solutions. Higher osmolality increases the risk of vascular symptoms of warmth and pain as well as of AKI.[47] Injection of iodinated contrast causes transient vasodilation followed by vasoconstriction. In the renal vessels, this vasoconstriction can persist for hours, which may result in hypoperfusion of the renal parenchyma, including the renal medulla.[48]

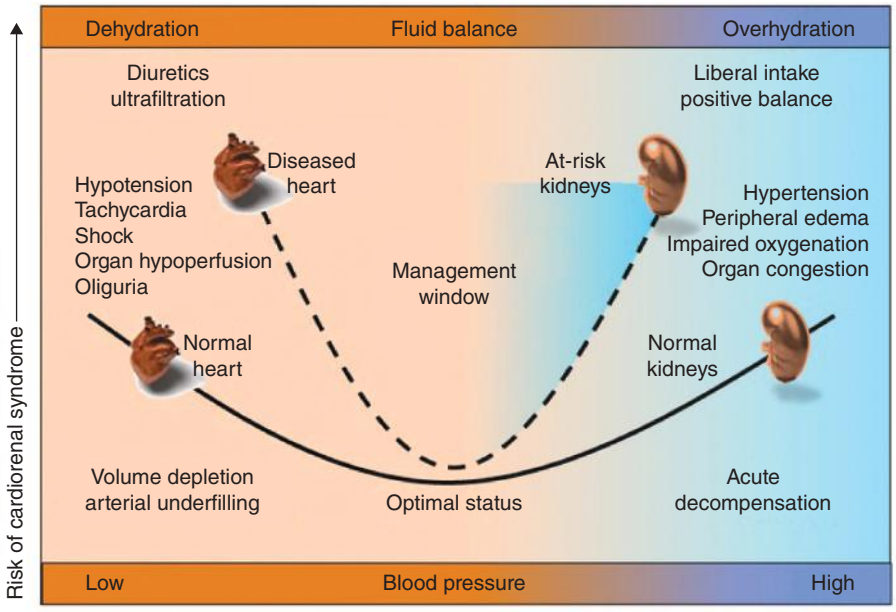

FIGURE 105–1. Treatment challenges in acute kidney injury complicating acute cardiac dysfunction. There is a narrow therapeutic window for optimal blood pressure and fluid balance in patients with acute kidney injury in the setting of acute cardiac dysfunction. Reproduced with permission from Ronco C, Cicoira M, McCullough PA et al. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol*. 2012 Sep 18;60(12):1031-42.

Contrast media, excreted in the glomerulus, are readily absorbed by the renal tubuli. The media therefore accumulate in the interstitial space and may cause direct cellular toxicity. Contrast material can reach very high concentrations in the renal medulla, where the osmolality of the interstitium is high. Contrast-mediated tubular cell death leads to sloughing of cellular constituents into the tubular space, which further impedes urine flow and contrast clearance. Hence the iodinated contrast agents cause renal injury as a consequence of both hypoperfusion and direct cytotoxicity.

Glomerular function is intact in CI-AKI but GFR decreases after 24 to 48 hours secondary to tubuloglomerular feedback triggered by the injury to the proximal tubule.[49] Hence serum creatinine levels initially remain normal in CI-AKI, and an increase in serum creatinine may only be detected after 48 to 72 hours from exposure to iodinated contrast. Because the glomerulus remains uninjured with an intact filtration barrier to blood cells, there is typically no hematuria in CI-AKI.

Contrast-Induced Acute Kidney Injury: Prevention and Treatment

The most important measures to reduce the risk of CI-AKI are to use as little contrast material as possible and to identify patients at increased risk of AKI. Whereas low-osmolar agents can be used for most patients, only iso-osmolar agents should be administered to high-risk patients. Clearance of contrast can be facilitated by intravascular volume expansion by isotonic crystalloid solutions, which increase GFR and tubular flow. More aggressive volume expansion, driven either by the left ventricular end-diastolic pressure or by urine output, reduces the risk of CI-AKI.[50,51] Volume expansion may be even more effective at reducing AKI if combined with forced diuresis.[39]

No established pharmacological treatment alternatives exist for complete prevention or treatment of CI-AKI. A number of promising substances (eg, *N*-acetylcysteine, ascorbic acid, and fenoldopam) have failed to demonstrate superiority to placebo when tested in randomized trials.[52,53] However, statins appear to reduce the risk of CI-AKI, whereas renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]) may increase the risk.[54-56] Statins may mediate their protective effect through several mechanisms (including inhibition of contrast reabsorption, attenuation of inflammation, oxidative stress, and endothelial dysfunction, and protection of podocytes in the glomerulus), whereas ACEIs/ARBs are thought to interfere with protective autoregulatory mechanisms, including tubuloglomerular feedback.

Patients with end-stage renal disease should receive immediate hemodialysis after receiving contrast media if they develop pulmonary congestion or hyperkalemia, but the value of routine immediate hemodialysis for such patients is uncertain.[57]

Risk Stratification of Patients Undergoing Coronary and/or Peripheral Procedures

Diabetes mellitus and preexisting CKD are important risk factors for CI-AKI. The risk increases gradually with increasing CKD severity.[58] STEMI and cardiogenic shock are also important risk factors, due at least in part to renal hypoperfusion. The need for acute intervention in STEMI precludes adequate volume expansion prior to the procedure, as does the concomitant acute left ventricular dysfunction. Other independent predictors of CI-AKI are increasing age, anemia, and congestive heart failure.[58,59] Several risk scores have been developed to predict the risk of CI-AKI, but none has been widely adopted in clinical practice. Many of these risk scores incorporate variables that are not known until during or after the procedure. They are therefore less helpful for preprocedural counseling.[58,59] As a general rule, the presence of diabetes and/or preexisting CKD warrants the preventive measures discussed above and special consideration of alternatives and conservative management without the invasive procedure.

ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

AKI is common (~ 20%) after transcatheter aortic valve replacement (TAVR) and is associated with increased mortality.[60-62] Similar to patients who undergo coronary angiography, patients who have TAVR receive periprocedural contrast. Furthermore, transient or sustained hemodynamic derangements are common during and/or after the TAVR procedure. Hence, all the mechanisms leading to AKI that were discussed in the previous sections may play a role in TAVR-related AKI.

The most important risk factors for AKI post-TAVR include preexisting CKD, hemodynamic instability and/or the need for circulatory support, blood transfusions, transapical access, amount of contrast used, diabetes, and age.[61,63]

In order to prevent AKI among patients undergoing TAVR, it is important to optimize hydration before the procedure, use as little contrast as possible, withhold nephrotoxic drugs, restrict the use of unnecessary blood transfusions, and allow sufficient time between any preprocedural contrast-requiring imaging and the TAVR procedure.[64]

ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING CARDIAC SURGERY

AKI is a common complication after cardiac surgery and is linked to reduced survival.[65-67] Impaired renal function (RIFLE risk or AKIN stage 1; see Table 105–3) is observed in 17% to 49% of patients who have cardiac surgery, and AKI (defined as RIFLE injury or AKIN stage 2) occurs in almost 10%.[65,66,68-70] Approximately 2% will require dialysis due to new-onset renal failure.[71] Among patients who require extracorporeal membraneous oxygenation (ECMO), the incidence of AKI may be as high as 80%.[72]

The pathogenesis of AKI in the setting of cardiac surgery is incompletely understood. It is likely multifactorial, with the following factors playing a role:

- Nephrotoxins, both endogenous (eg, heme and iron pigments released secondary to blood trauma and hemolysis caused by blood pumps) and exogenous (eg, nonsteroidal anti-inflammatory drugs [impair autoregulation of renal blood flow] and intravenous contrast).[73-75]
- Tissue hypoxia and ischemia-reperfusion injury. Intraoperative alterations in systemic or local renal hemodynamics and/or release of atherosclerotic emboli (eg, during aortic cross-clamping) may lead to tissue ischemia.[76,77] The renal medulla, which has a high metabolic demand and a low baseline PaO_2, is particularly susceptible to ischemia.[78]
- The systemic inflammatory response syndrome (SIRS) is triggered by major surgery and artificial conduits, with activation of neutrophils, platelets, cytokines, coagulation factors, and fibrinolysis.[79]

Risk factors for AKI in the setting of cardiac surgery are similar to those described earlier for AKI in other settings, and include CKD, reduced LVEF, use of intravenous contrast agents, diabetes, and older age.[80-82] Chronic obstructive pulmonary disease, female gender, and emergent surgery have also been reported as risk factors for AKI in this setting.[80,81]

No pharmacological treatment strategies that effectively prevent or treat AKI in the setting of cardiac surgery have been identified.

Therefore, the clinician must try to prevent AKI by optimizing each patient's pre-, intra-, and postoperative risk profile. Preoperative measures include optimization of glucose control for patients with diabetes, withholding of ACEIs and/or ARBs, and withholding surgery for up to 48 hours after contrast administration. Intra- and postoperative measures include minimizing cardiopulmonary bypass and cross-clamp times, favoring vasopressin over α-adrenoceptor agonists for blood pressure control, avoiding overly strict intra- and postoperative glucose control, basing decisions regarding blood transfusions on physiologic data (including lactate and central venous O_2 saturation) with restrictive transfusion thresholds (7.0-8.0 mg/dL), and hemodynamic goal-directed therapy (focus on cardiac output and central venous O_2 saturation, etc., rather than traditional hemodynamic indices such as arterial blood pressure) with judicious use of diuretics.[83-95]

DRUG PHARMACOKINETICS IN ACUTE KIDNEY INJURY

AKI influences the pharmacokinetics of water-soluble drugs that are eliminated by the kidneys. The plasma concentration of these drugs may increase in the setting of AKI. It is important to reduce or temporarily stop some drugs in patients with AKI. As an example, metformin-induced lactic acidosis is a rare but potentially life-threatening complication of AKI.[96] Metformin is therefore typically withheld for at least 48 hours following iodinated contrast administration, particularly in patients with an elevated serum creatinine.

CARDIOVASCULAR DISEASE IN THE PATIENT WITH CHRONIC KIDNEY DISEASE

EPIDEMIOLOGY AND CHRONIC KIDNEY DISEASE–SPECIFIC DISEASE MECHANISMS

CKD dramatically increases the risk of developing CVD (3-30 times depending on CKD stage and study).[97-99] Nearly half of all deaths in CKD patients are from cardiovascular events, and CKD patients are more likely to die from CVD than progress to ESRD during their lifetime.[100,101]

Risk factors for the development of CVD in patients with CKD can be divided into traditional and nontraditional factors. Traditional factors include hyperlipidemia, hypertension, diabetes, and smoking and are important risk factors for cardiovascular disease also among patients without CKD. These risk factors are also risk factors for CKD, and their prevalence has been reported to be twice as high among CKD patients compared to non-CKD patients.[102] Nontraditional risk factors refer to the effects of chronic renal dysfunction on cardiac health. These factors are consequences of CKD and include volume overload, increased sympathetic tone, activation of the renin-angiotensin-aldosterone system (RAAS), oxidative stress, uremic toxins, abnormal mineral metabolism (calcium, phosphorous, vitamin D), anemia, and malnutrition. The importance of the nontraditional risk factors is highlighted by the poor performance of the Framingham Risk Criteria in CKD patients.[103] Three important mechanisms contribute to CVD progression in CKD: autonomic dysfunction, vascular pathology, and cardiac pathology.

Autonomic Dysfunction

Autonomic function is impaired in CKD patients, with a relative dominance of sympathetic over parasympathetic activity.[104-107] The autonomic nervous system constitutes the efferent arm of the baro- and chemoreceptor reflex arcs. These reflexes are impaired in CKD. The detailed mechanisms through which CKD leads to autonomic dysfunction are unknown, but autonomic dysfunction in CKD is improved after transplantation, nephrectomy, or renal denervation. Hence local pathological processes within the diseased kidney likely play a role.[108,109]

Signs of autonomic dysfunction in CKD patients include reduced heart rate variability (a marker of vagal autonomic sensitivity and a poor prognostic sign) and greater low-frequency oscillations of systolic blood pressure variability (a marker of sympathetic tone).[110-112]

Increased sympathetic tone promotes smooth muscle cell and fibroblast proliferation in blood vessels and activates the RAAS pathway.[113,114] Hence autonomic dysfunction contributes to cardiovascular pathological remodeling. Through these mechanisms, autonomic dysfunction also causes worsening of renal function.[104]

Vascular Pathology

CKD exacerbates atherosclerotic processes.[115] CKD patients have more severe arterial hypertrophy and calcification and have stiffer arteries compared to non-CKD patients.[116]

The mechanisms leading to arterial pathology and endothelial dysfunction in CKD are incompletely understood, but increased oxidative stress, low-grade inflammation, uremic toxins, increased wall stress (associated with arterial hypertension), and impaired calcium/phosphorous homeostasis likely contribute.[117-119] Sympathetic hyperactivity promotes smooth muscle proliferation via norepinephrine, and indirectly via salt and fluid retention and arterial hypertension.

Cardiac Pathology

Left ventricular hypertrophy is present in 40% of CKD patients (mostly of the eccentric type), and the prevalence increases with declining GFR; for ESRD patients on hemodialysis, it is over 75%.[120] Left ventricular hypertrophy is likely promoted by chronic hypertension (increased afterload), anemia (reduced oxygen delivery), sympathetic and RAAS hyperactivity (increased cardiac fibrosis), and volume overload. Cardiomyocyte hypertrophy is not accompanied by a similar degree of neovascularization. Hence the cardiomyocyte-to-capillary ratio increases, leading to relative ischemia of the myocardium. This is believed to explain why some CKD patients present with angina even in the absence of significant coronary artery disease.[121]

Almost 50% of CKD patients have either mitral or aortic calcification, and CKD is a strong predictor for valvular dysfunction (stenosis and/or regurgitation).[122] Valvular disorders increase left ventricular afterload (aortic stenosis) and/or preload (aortic regurgitation, mitral regurgitation).

Heart failure is common in CKD, with a prevalence > 50% among ESRD patients. Heart failure with preserved ejection fraction accounts for approximately half of these cases and carries a worse prognosis than heart failure with reduced ejection fraction.[123] The etiologies of heart failure in CKD patients include pathological left ventricular remodeling secondary to sympathetic and RAAS overstimulation, left ventricular hypertrophy, valvular heart disease, and ischemic heart disease. Chronic anemia and uremic toxins may also contribute.

MANAGEMENT OF CARDIOVASCULAR RISK FACTORS IN THE PATIENT WITH CHRONIC KIDNEY DISEASE

The majority of the pivotal large-scale multicenter trials on which most cardiovascular guidelines are based excluded patients with CKD. Therefore, the management of cardiovascular disease in the CKD patient requires judicious extrapolation of treatment effects in non-CKD patients, supplanted by knowledge derived from observational studies and with consideration of CKD pathophysiology.

Hypertension

Hypertension is prevalent among CKD patients. CKD-associated (nontraditional) risk factors include sodium retention and hypervolemia, increased RAAS activity, autonomic imbalance, and endothelial

damage. Furthermore, traditional risk factors for hypertension are prevalent among patients with CKD and hypertension is itself an important risk factor for CKD.

Current guidelines[124] recommend a blood pressure goal of 140/90 mm Hg for CKD patients, which is the same as for non-CKD patients. Restriction of sodium intake reduces systolic blood pressure, extracellular fluid volume, and proteinuria compared to patients on a regular diet.[125] The NIH funded SPRINT study randomized 9361 patients with hypertension, of whom 28% had preexisting CKD, to a systolic blood pressure goal of < 140 mm Hg versus < 120 mm Hg. The trial was stopped prematurely due to a significant 25% reduction in the composite primary end point of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes and a 27% reduction in total mortality.[126] Guidelines are expected to be updated to more aggressive goals.

ACEIs and ARBs are considered first-line medical therapy, especially in cases of concomitant proteinuria or diabetes. These drugs lower blood pressure and slow the decline in renal function in CKD patients.[127-130] ACEI/ARB treatment may result in hyperkalemia. Serum creatinine levels therefore need to be monitored in these patients. An increase in serum creatinine > 25% should prompt further evaluation. Inadequate volume status, too low blood pressure, drugs that may reduce GFR (nonsteroidal anti-inflammatory drugs), or excessive potassium intake should be corrected. If these reversible causes are absent, the ACEI/ARB should be stopped, which should result in the return of kidney function to baseline.[131,132] The combination of an ACEI and ARB can further lower blood pressure but carries a considerable risk of hyperkalemia.[133] Dual therapy is therefore not recommended.

Calcium channel blockers and/or beta-blockers are considered second-line agents.[134,135] Diuretics should be considered as second-line agents to be used in cases of volume overload, with loop diuretics being the preferred drugs in later stages of CKD.

Hyperlipidemia

Lipid abnormalities are common in nearly all stages of CKD. The most common abnormality is hypertriglyceridemia, as nearly 50% of CKD patients have fasting triglyceride levels above 200 mg/dL,[136] the result of impaired removal of triglycerides from blood, secondary to changes in the composition of triglycerides (enrichment in apolipoprotein C3), as well as reductions in hepatic lipoprotein lipase activity. CKD patients also frequently have decreased apo-A1 and HDL levels. The typical association with greater LDL and greater risk of cardiovascular events is not as robust in this population. In dialysis patients, in particular, those with both the highest and lowest levels of LDL are at greatest risk for cardiovascular disease, likely related to confounding by malnutrition in those with significantly impaired renal function.[137,138] Patients with nephrotic syndrome typically have markedly increased LDL-C levels related to increased hepatic protein production.

In a post-hoc analysis of the JUPITER (Justification for the Use of Statins in Prevention—An Intervention Trial Evaluating Rosuvastatin)[139] primary prevention trial of rosuvastatin 20 mg compared with placebo, among those with moderate CKD (eGFR < 60 mL/min/1.73 m^2 at study entry, n = 3267), rosuvastatin was associated with a 44% reduction in all-cause mortality (hazard ratio [HR], 0.56; 95% CI, 0.37–0.85; $P = .005$) and a 45% reduction in risk of myocardial infarction, stroke, hospital stay for unstable angina, arterial revascularization, or confirmed cardiovascular death (HR, 0.55; 95% CI, 0.38–0.82; $P = .002$). LDL-C and hsCRP reductions as well as adverse events with rosuvastatin were similar among those with and without CKD.

In contrast, the German Diabetes and Dialysis Study[140] enrolled 1255 subjects with type 2 diabetes mellitus receiving maintenance hemodialysis who were randomized to receive 20 mg of atorvastatin per day versus placebo. The primary end point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke. After a median follow-up of 4 years there was no significant reduction in the primary composite end point. Cardiac events were reduced with an HR of 0.82, while cerebrovascular events were increased twofold. The more recent SHARP (Study of Heart and Renal Protection)[141] trial randomized 9270 patients with chronic kidney disease (3023 on dialysis and 6247 not) without prior MI or revascularization to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo. The primary end point—a composite of first major atherosclerotic event, nonfatal myocardial infarction or coronary death, nonhemorrhagic stroke, or any arterial revascularization procedure—was reduced by 17% without an increase in nonvascular mortality. Notably, results were consistent in the dialysis group. Given that there was no ezetimibe-only group in SHARP, it is not clear whether the results were driven by ezetimibe, simvastatin, or both.

Treatment guidelines generally reflect those found in non-CKD patients, with a particular emphasis on statin therapy for patients with moderate renal dysfunction. Indeed, as CKD is a coronary heart disease equivalent in ACC/AHA hyperlipidemia guidelines,[142] most CKD patients are candidates for statin therapy. KDIGO guidelines recommend statin or statin/ezetimibe in patients greater than age 49, and statin therapy if there are other known risk factors in patients age 18 to 49.[143] The KDIGO guidelines recommend against the use of LDL-C levels as a target of therapy in patients with CKD, focusing instead on treatment of high-risk patients irrespective of LDL-C levels. For patients with hypertriglyceridemia alone, the most recent KDIGO guidelines only recommend lifestyle modification therapy. Fibrates have only weak evidence of reducing pancreatitis risk or cardiovascular risk in CKD patients with elevated triglycerides, and are thus not recommended.[143]

Anemia of Chronic Kidney Disease

Anemia is common in CKD and is almost uniformly present at late stages of CKD.[144] It is associated with increased risk for heart failure, stroke, and death.[145-147] CKD-associated anemia is normocytic and normochromic. It is caused by decreased production of erythropoietin by the kidney as well as by reduced red blood cell survival in the uremic environment. It contributes to the symptoms observed in patients with CKD (fatigue, reduced exercise tolerance, dyspnea) and may exacerbate angina symptoms in patients with concomitant ischemic heart disease. Anemia has also been shown to be a causative factor in left ventricular hypertrophy.

Therapeutic options include erythropoiesis-stimulating agents and red blood transfusion, with iron supplementation as appropriate. Alternative causes of anemia should be identified and corrected if possible. These include iron deficiency anemia and anemia of chronic disease, which are relatively common among patients with CKD. The optimal time to start treating CKD-associated anemia is unknown but a target hemoglobin concentration between 10 and 12 g/dL is associated with improvements in physical activity, less fatigue, and less left ventricular hypertrophy. However, both blood transfusions and erythropoiesis-stimulating agents carry the risk of serious adverse events, including thrombosis and stroke. Therefore, current FDA and KDIGO guidelines emphasize a personalized approach to care.[148] No strict recommendations are given in regards to hemoglobin targets, but because three major randomized trials (CHOIR, CREATE, and NHCT) showed an increased mortality risk at Hb levels above 13 g/dL,[149-151] KDIGO guidelines recommend an upper limit of 11.5 g/dL (although the guidelines acknowledge that some patients may benefit from higher levels).

ACUTE CORONARY SYNDROME IN THE PATIENT WITH CHRONIC KIDNEY DISEASE

CKD is an important risk factor for coronary artery disease, including acute coronary syndrome (ACS).[152] The difficulty in diagnosing ACS in CKD patients tends to delay treatment, and prognosis after ACS is worse for CKD patients than for non-CKD patients.[153] As is the case in other areas of cardiology, the majority of the pivotal multicenter randomized trials on which guidelines for ACS treatment are based have excluded CKD patients.[154]

Diagnosis

CKD patients with ACS are less likely to present with chest pain (at least partly due to autonomic dysfunction). CKD patients are also more likely to have preexisting ST-segment depressions and/or Q waves on resting ECG (caused by cardiac hypertrophy and/or previous ischemic injury), which considerably decrease the specificity of the ECG for diagnosing ongoing ACS. Furthermore, plasma biomarkers of cardiac damage, including creatine kinase (CK) and troponins, are often elevated at baseline due to reduced clearance, low-grade inflammation and silent myocardial injury due to small vessel disease. This reduces the specificity of these tests.[155,156] The ACS diagnosis is therefore more likely to be missed in CKD patients than non-CKD patients.[155] It is recommended to focus on temporal trends in troponin levels and ST-segment depressions and on angina-equivalent symptoms such as worsening dyspnea.[157]

Management

In the absence of dedicated trials for patients with CKD, ACS treatment guidelines are similar to those for patients without CKD. However, current guidelines recommend a judicious use of antithrombotic agents in patients with CKD (who have an increased bleeding risk) with consideration of CKD as well as other risk factors before initiating particularly potent antithrombotic therapy (eg, triple therapy).[158] Importantly, drugs that are cleared from the body predominantly through the kidneys need to be dose-adjusted (Table 105–5).

There are a paucity of high-quality data regarding the relative benefits of medical therapy (a conservative strategy) and revascularization by either PCI or CABG for patients with CKD and ACS. Retrospective analyses imply that revascularization is favorable compared to a conservative approach.[159-161] CABG is associated with particularly high risks of stroke and mortality for patients with CKD, but appears to offer a better long-term prognosis compared to PCI for patients with multi-vessel disease.[162-164] Hence guideline recommendations relating to reperfusion strategies are similar for patients with and without CKD, including the importance of individualized decisions based on risk scores (eg, surgical risk, ability to tolerate dual antiplatelet therapy) as well as patient preference[165] and use of a heart team approach.

CARDIOVASCULAR DRUG PHARMACOKINETICS IN THE PATIENT WITH CHRONIC KIDNEY DISEASE

Many cardiovascular drugs are eliminated from the body by the kidneys. Dose adjustments of some of these drugs are necessary in CKD. Unfortunately, failure to dose-adjust is a common cause of drug toxicity in CKD patients.

Renal clearance of drugs depends on GFR as well as tubular function (reabsorption and/or secretion) and the relative contributions of these mechanisms vary according to drug. Through alterations in body fluid composition and acid–base balance, CKD also affects drug absorption, distribution volume, protein binding, and affinity for drug target molecules.[166] Drug clearance in dialysis patients depend on water solubility, distribution volume, protein binding, and diffusion across the dialysis membrane. It can therefore be difficult to accurately predict plasma concentrations and therapeutic effect in patients with CKD. Target doses of cardiovascular drugs defined in current guidelines may be difficult to achieve. A general principle is to "start low and go slow" and consider the highest tolerable dose as the optimal dose.

Table 105–5 lists common cardiovascular drugs that need particular attention for patients with CKD. It is recommended to consult specific drug manufacturers' dose adjustment recommendations when administering drugs to patients with CKD.

TABLE 105–5. Cardiovascular Drugs That Need Special Attention in Renal Patients

Medications	Precaution
Warfarin	Requires close monitoring of INR and other OTC medications.
$P2Y_{12}$ antagonist and aspirin	Combination in dialysis patient increases risk of bleeding.[238]
Low-molecular-weight heparins	Dose adjustment and monitoring of anti-factor Xa.[239]
ACEI and ARB	Risk of acute worsening of renal function when used with aggressive diuretic regimen.[240]
	Risk for hyperkalemia increases when used with potassium-sparing diuretics.[241]
	All ACEIs except fosinopril need dose adjustment for renal impairment.[242]
	ARBs do not need dose adjustment in CKD.[207]
Spironolactone and eplerenone	Use along with ACEI/ARB and β-blockers increases risk for hyperkalemia.[241]
α-Adrenergic blockers	Methyldopa, doxazosin, prazosin, and reserpine active metabolite can accumulate in CKD.[243]
β-Blockers	Acebutolol, nadolol, and sotalol need dose reduction in CKD.[243]
Calcium channel blockers	No need for dose reduction in CKD.[243]
	Verapamil, diltiazem, amlodipine, and nicardipine may significantly increase cyclosporine and tacrolimus levels in transplant recipients.
Nitroprusside	Risk of thiocyanate toxicity in CKD, limit exposure.
Hydralazine	Need dose reduction for eGFR less than 50 mL/min.
Lipid-lowering drugs	Statins when used in combination with cyclosporine may increase risk of rhabdomyolysis.
Antiarrhythmics	Bretylium, digoxin, flecainide, and procainamide need dose adjustments in CKD.[243]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; OTC, over the counter.

HEART DISEASE IN PATIENTS ON DIALYSIS

More than 80% of dialysis patients have concomitant cardiovascular disease, and cardiovascular disease is the leading cause of death for dialysis patients (including heart failure, myocardial infarction, and sudden cardiac death).[167-170] Three major mechanisms contribute to worsening cardiovascular disease in patients with end-stage renal disease: volume overload, pressure overload, and nonhemodynamic factors such as atherosclerosis, vascular calcification, oxidative stress, inflammation, and stimulation of profibrotic factors.[169,171] Managing a patient's cardiovascular risk profile is therefore important in dialysis patients.

The New York Heart Association (NYHA) functional classification for heart failure assessment is less useful in dialysis patients because dyspnea can be related to other factors than heart failure. More importantly, the severity of heart failure–related symptoms changes considerably in relation to the timing of fluid removal. Alternative classification systems have been proposed that take into account the renal component (Fig. 105–2).[170]

IMPORTANT CARDIAC COMPLICATIONS IN THE PATIENT WITH CHRONIC KIDNEY DISEASE

Pericarditis

Patients with CKD can develop pericarditis secondary to uremia or as a complication of dialysis.[172] Rarely, these patients develop chronic constrictive pericarditis. The incidence of uremic pericarditis has declined considerably in the dialysis era but it still occurs in 5% to 20% of uremic patients. Its exact cause is unknown but appears related to the accumulation of uremic toxins.[172] Uremic pericarditis is less responsive to anti-inflammatory therapy and should be treated by intensive hemodialysis (daily for at least 1 week). Dialysis-related pericarditis typically occurs after several months of dialysis therapy. Whether the etiology is different is debated, but dialysis-related pericarditis is less responsive to intensified dialysis.[173] Pericardiostomy and pericardiectomy may be necessary, with the latter the primary treatment for constrictive pericarditis.[172] Pericardial effusions are common (volume overload is likely a contributing factor) but tamponade is rare.

Importantly, the differential workup must consider that patients with CKD can also develop viral, fungal, or bacterial pericarditis (particularly if on dialysis), drug-induced pericarditis, and pericarditis due to other underlying disease states.

Infective Endocarditis

Patients undergoing hemodialysis have an age-adjusted incidence of infective endocarditis (IE) almost 20 times higher than the general population.[174] Patients who are dialyzed through tunneled catheters are at particularly high risk.[175] The most common pathogen is *Staphylococcus aureus* (~ 50%) followed by coagulase-negative staphylococci, enterococci, and *Streptococcus viridans*.[175] The mitral valve is the most commonly involved valve, but ~ 20% of patients have involvement of more than one valve. Dialysis patients with IE have considerably higher mortality (30%-50%) than nondialysis patients with IE.[175] Mitral valve involvement and septic embolization are poor prognostic factors.[176]

IE should be suspected in all hemodialysis patients with fever and/or bacteremia. Classical symptoms and signs include a new regurgitant murmur, focal neurological deficits, or heart failure symptoms. Transesophageal echocardiography (sensitivity > 90%) is considerably superior to transthoracic echocardiography (sensitivity ~ 50%) at establishing the diagnosis.[177-179]

As a general rule, current pathogen-specific treatment guidelines for IE apply to both dialysis and nondialysis patients with a required minimum of 4 to 6 weeks of parenteral therapy.[180-182] Antimicrobial therapy is typically delivered after the dialysis session due to the difficulty in maintaining long-term peripheral venous access in dialysis patients. Coordination between nephrologists and infectious disease staff to select optimal antibiotic agent and dosing schedule is recommended. Indications for surgery for dialysis patients with IE are similar to those for nondialysis patients, but operative mortality is considerably higher for dialysis patients.[175,180-182] Whether dialysis patients who undergo valve replacement should receive mechanical (increased risk of valve thrombosis, requires anticoagulation) or bioprosthetic (accelerated degeneration and calcification in the dialysis patient) valves has not

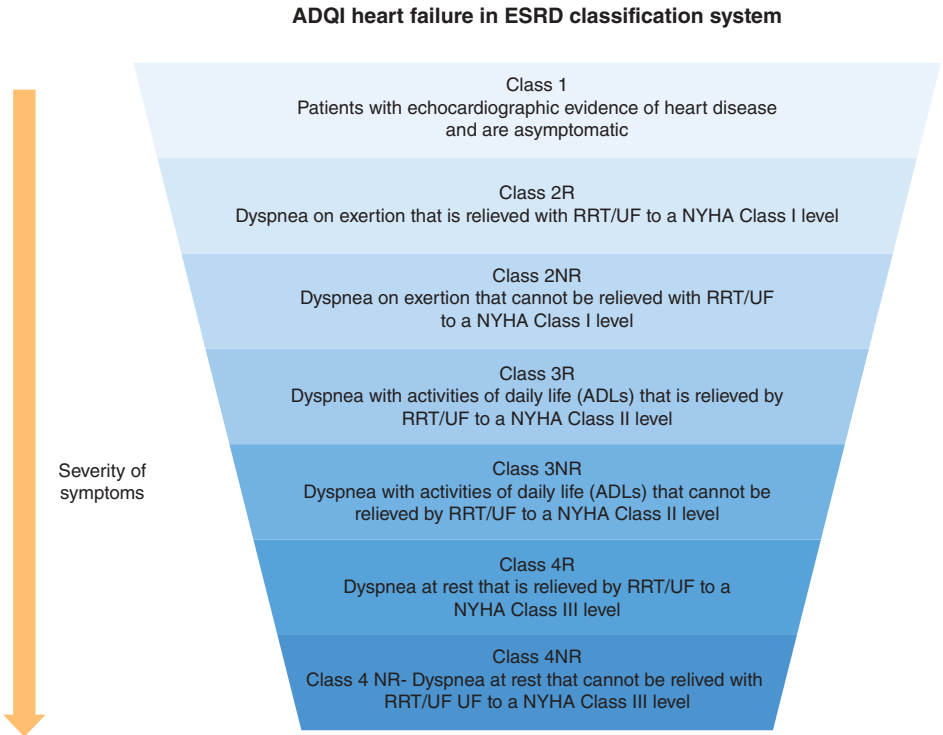

FIGURE 105–2. Classification system for heart failure in dialysis patients. Heart failure classification in dialysis patients need to consider that the severity of heart failure symptoms will vary with volume status. Reproduced with permission from Chawla LS, Herzog CA, Costanzo MR, et al. Proposal for a functional classification system of heart failure in patients with end-stage renal disease: proceedings of the acute dialysis quality initiative (ADQI) XI workgroup. *J Am Coll Cardiol*. 2014 Apr 8;63(13):1246-1252.

been sufficiently studied.[183] A case-to-case decision based on individual risk factors, suitability for long-term anticoagulant therapy, and life expectancy is recommended.

Cardiac Arrhythmias

Sudden cardiac death (SCD) is estimated to account for almost 25% of all deaths among dialysis patients.[101] Causes include ventricular tachycardia, Torsades de pointes, and ventricular fibrillation as well as pronounced bradycardia. Ischemic heart disease, heart failure, vascular calcification, electrolyte and acid–base disturbances, and dialysis-induced electrolyte shifts are believed to contribute to the risk of ventricular arrhythmias in dialysis patients.[184,185]

Predictors for SCD include atrioventricular or intraventricular conduction delays, left ventricular hypertrophy, QRS or QT-interval prolongation, decreased heart rate variability, documented episodes of nonsustained ventricular tachycardia, exercise-induced arrhythmia, multi-vessel coronary artery disease, and hypo- or hyperkalemia.[186]

Primary and secondary prevention with beta-blockers and ACEIs/ARBs is recommended for dialysis patients. Implantable cardioverter-defibrillators (ICDs) trials have systematically excluded patients on dialysis, and the majority of dialysis patients who experienced SCD did not fulfill current criteria for ICD implantation.[187] For those dialysis patients with ICDs implanted for VF/SCD, however, observational data suggest that the benefit in terms of risk reduction is similar to patients without CKD, with a 42% risk reduction,[188] suggesting that this potentially lifesaving therapy is underutilized. However, long-term prognosis is still poor for dialysis patients irrespective of ICD implantation.[189,190]

Cardiovascular Risk Stratification Prior to Renal Transplantation

Cardiovascular disease remains the most common cause of death for patients with CKD even if they receive a kidney transplant.[191] Cardiovascular events are common within the first 3 months following transplantation but are thereafter less common compared to patients who remain on dialysis.[192] Risk factors for posttransplant ischemic cardiac events include presence of coronary artery disease, heart failure, diabetes, male gender, age, an abnormal resting ECG, and smoking. Observational data suggest that asymptomatic patients with obstructive CAD benefit from revascularization before transplantation, but randomized trials are lacking.

Screening for CAD is considered warranted before transplantation, but the optimal risk stratification algorithm remains to be established. Whether noninvasive tests (pharmacologic stress echocardiography or nuclear imaging) should be preferred for initial screening, and coronary angiography reserved for patients who have objective evidence of ischemia or who are symptomatic, is debatable. Apart from screening for CAD, the pretransplant cardiac evaluation should seek to identify cardiovascular risk factors amenable to modification (eg, diabetes, hypertension, heart failure) and to identify patients who are unlikely to benefit from transplantation due to poor prognosis related to an extra-renal condition.[193]

WORSENING RENAL FUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE

Worsening renal function in chronic heart failure is associated with adverse outcomes and prolonged hospitalization. The prevalence of CKD among patients with chronic heart failure is at least 25%, and even relatively small reductions in GFR (> 9 mL/min) increase the risk of dying.

CARDIORENAL SYNDROME TYPE 2

The term "cardiorenal syndrome" (CRS) has been coined to describe the entity in which concomitant cardiac and renal dysfunction is present in the same patient. CRS is subdivided according to the temporal pattern of cardiac and renal disease (Table 105–6). Herein we focus on the most common CRS type 2 (CRS-2), in which chronic heart failure leads to CKD.

The pathophysiology behind the development of renal dysfunction in CRS-2 is incompletely understood. There does not appear to be a strong correlation between LVEF and estimated GFR among patients with CHF.[194] Proposed mechanisms underlying the development of kidney dysfunction in CHF are outlined in Fig. 105–3.

Regardless of its exact mechanisms, declining renal function in the CHF patient has important therapeutic implications. Patients with CHF typically take a considerable number of medications. Many of these are cleared by the kidneys and need to be dose-adjusted when renal function declines.[195,196] Although most heart failure therapies are beneficial for patients with CKD, careful monitoring of renal function is necessary and changes in drug regimen may be appropriate. .

An important principle in the treatment of CRS-2 is to optimize cardiac function in order to slow or reverse the pathophysiology outlined in Fig. 105–3. Cardiac resynchronization therapy, when indicated, appears to improve both ejection fraction and GFR in patients with CRS-2.[197] Beta-blockers also appear to be beneficial.[198] Antagonism of the RAAS is an important component in both heart failure and CKD therapy. Both ACEIs/ARBs and aldosterone antagonists attenuate excessive RAAS activation and thereby prevent renal vasoconstriction and fibrosis. However, although ACEI/ARBs are beneficial in CRS-2, there is a risk of hyperkalemia as well as of inducing arterial hypotension resulting in worsening renal function. The risk of these complications is higher for patients with CKD than in patients without renal disease.[199,200] Hence caution, frequent monitoring of electrolyte status, and involvement of a nephrologist is recommended.[199]

Management of volume status is particularly challenging in patients with CRS-2. Restricting sodium intake is important. Diuretic therapy is recommended but is complicated by the development of diuretic resistance, which carries a poor prognosis.[201]

DIURETIC RESISTANCE

The definition of diuretic resistance (DR) is not straightforward and no consensus exists. One approach is to define diuretic efficacy as the change in weight, net fluid balance, or urine output per a defined diuretic dose (eg, 40 mg of intravenous furosemide-equivalent dose). Patients with DR typically have lower GFR than patients without DR, and DR is a predictor of worse outcomes independent of GFR.[202]

TABLE 105–6. Cardiorenal Syndromes

CRS type 1	Acute worsening of cardiac function leading to kidney injury and/or dysfunction
CRS type 2	Chronic abnormalities in cardiac function leads to kidney injury and/or dysfunction
CRS type 3	Acute worsening of kidney function leads to cardiac injury and/or dysfunction
CRS type 4	Chronic kidney disease leads to heart injury and/or dysfunction
CRS type 5	Systemic extrarenal and extracardiac condition leading to simultaneous injury and/or dysfunction of both the heart and kidney

Abbreviation: CRS, cardiorenal syndrome.

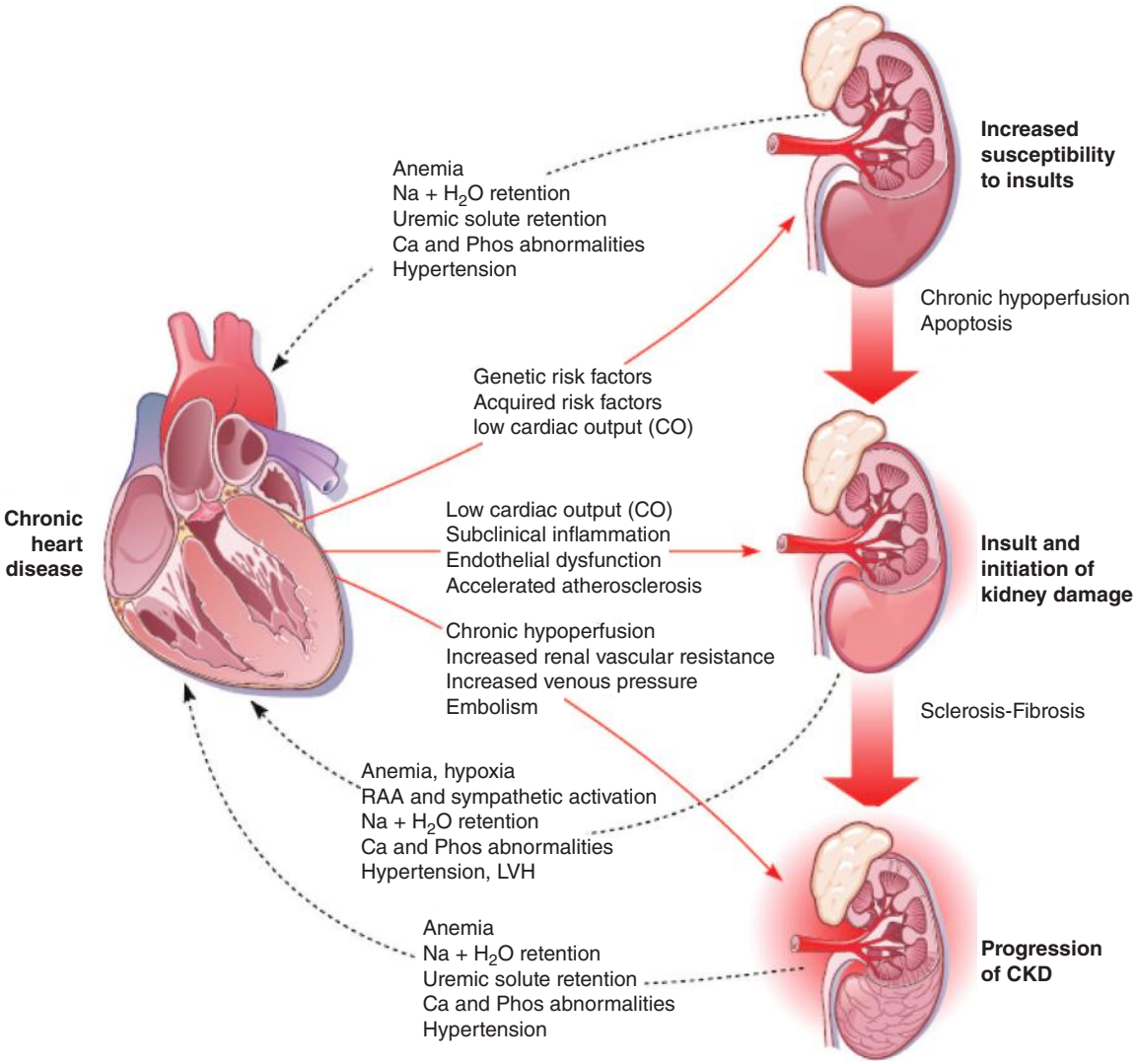

FIGURE 105–3. Proposed mechanisms of renal injury and damage in patients with congestive heart failure. Reduced cardiac function in chronic heart failure leads to a low-output state with renal hypoperfusion and congestion of the venous system (which is effectively transmitted retrograde from the great veins to the renal veins). This results in relative hypoxia of the renal parenchyma. Reduced effective circulatory (low-output heart failure) volume also leads to renin-angiotensin-aldosterone (RAA) system activation and release of vasoconstrictors (angiotensin, adrenaline, noradrenaline), which increases renal vascular resistance and further reduces renal perfusion. Chronic heart failure is associated with subclinical inflammation and impaired endothelial function with interfere with the kidneys' autoregulatory mechanisms. Low-output heart failure also increases the risk of embolization of thrombotic material from the heart or central arteries. Microembolization may further aggravate renal hypoxia. Lastly, most risk factors for cardiovascular disease and heart failure are also risk factors for kidney disease. Accelerated atherosclerosis of the renal vessels and progression of kidney disease due to genetic or acquired risk factors likely also play a role. CKD, chronic kidney disease; LVH, left ventricular hypertrophy. Reproduced with permission from Ronco C, Haapio M, House AA, et al: Cardiorenal syndrome. *J Am Coll Cardiol*. 2008 Nov 4;52(19):1527–1539.

Although intimately intertwined, DR and GFR probably represent different aspects of renal function. Whereas GFR is reflective of the clearance of metabolites (renal ultrafiltration), DR may be a better index of volume and electrolyte homeostasis (tubular function). Even at a severely depressed GFR of 20 mL/min, almost 30 L of fluid (~ 4000 mEq of sodium) is filtered through the glomeruli each day. Volume overload and organ congestion are the main drivers of readmissions and adverse outcomes in CHF.[203] This provides a pathophysiological rationale for the strong independent association between DR and poor outcome.

Pharmacokinetic and Pharmacodynamic Considerations

Loop diuretics inhibit the sodium-potassium-chloride cotransporter in the luminal surface of tubular cells in the thick ascending loop of Henle and are typically first-line diuretics used in CHF.[204] Several characteristics of the loop diuretics, which are not related to tubular damage and/or dysfunction, may explain diuretic resistance. Orally administered loop diuretic absorption may be reduced in congestive heart failure due to gut edema and poor intestinal perfusion. In the plasma, > 90% of the loop diuretics will be bound to plasma protein and are therefore not filtered across the glomerulus. In order to reach the tubular lumen they must be secreted by anion transporters in the proximal tubules. Organic anions (eg, urate) compete with the loop diuretics and their transport is inhibited by acidosis. Significant proteinuria increases protein-binding of loop diuretics in the tubular lumen and prevents their pharmacological action.[201,205-208] All these mechanisms lead to a shift to the right in the dose–response curve for loop diuretics. Lastly, sufficient Na must be present in the tubule for loop diuretics to work. If proximal tubular sodium reabsorption is sufficiently increased (for example, due to poor renal perfusion and

increased neurohormonal activity), too little NaCl may be delivered to the distal nephron for loop diuretics to work efficiently. Hence a multitude of factors can cause diuretic resistance.[204]

Managing Diuretic Resistance

After verifying compliance with therapy, the next step in the management of patients with apparent diuretic resistance is to establish whether intravascular volume overload is present. When intravascular volume overload is not present, volume reduction by diuretics will not unload the heart but may instead worsen neurohormonal activation. Clinical signs and symptoms (eg, orthopnea, jugular venous distension, rales, hepatomegaly, and edema) are helpful but lack sufficient sensitivity. Body weight (unless an accurate estimate of "dry weight") and natriuretic peptides (which track better with wall stress than volume overload per se) are also helpful but imperfect means of assessing volume status. Hence establishing whether a lack of response to diuretics is due to diuretic resistance or relative intravascular depletion remains to some extent an art of medicine.

In the absence of high-quality data from randomized clinical trials, treatment approaches in diuretic resistance are based on knowledge of heart failure pathophysiology and pharmacology (Fig. 105–4). First, the treatment should aim to optimize renal perfusion. This includes optimizing cardiac function, which may include use of inotropes and mechanical assist devices.[209] Second, addition of non-loop diuretics should be tried. Thiazide-type diuretics are the most commonly used diuretics in patients who develop resistance to loop diuretics. Thiazide

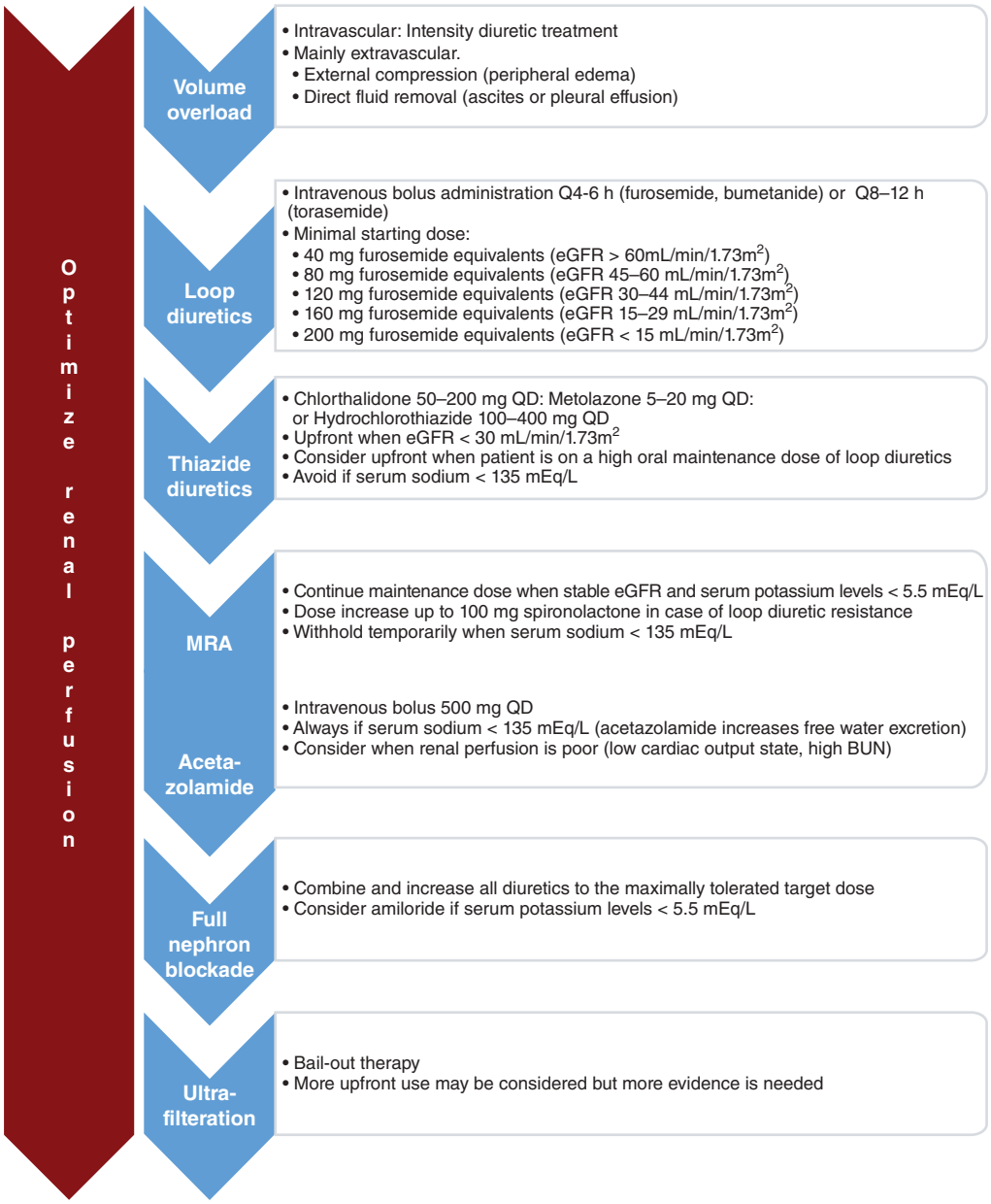

FIGURE 105–4. Proposed approach to treatment in heart failure patients with diuretic resistance. BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LVAD, left ventricular assist device; MAP, mean arterial blood pressure; MRA, mineralocorticoid receptor antagonists; QD, once daily. Reproduced with permission from Verbrugge FH, Mullens W, Tang WH: Management of Cardio-Renal Syndrome and Diuretic Resistance. *Curr Treat Options Cardiovasc Med*. 2016 Feb;18(2):11.

diuretics are a good choice because they act on the distal tubule NaCl symporter, which largely mediates the intrinsic renal adaptations to loop diuretics called the "braking phenomenon." In other words, with prolonged loop diuretic use, the kidney adapts by upregulating thiazide-sensitive NaCl reabsorption. Mineralocorticoid receptor antagonists and acetazolamide may also be considered, the latter being particularly useful in the setting of diuretic-induced alkalosis. Ultrafiltration may also be effective in diuretic resistance, but unfortunately the only large-scale RCT was terminated early.[204,210,211]

Decreased diuretic absorption due to gut edema is particularly common in the patient with right-sided congestion (increased CVP, a surrogate of which can be detected at the bedside by examining for jugular venous distention). Torsemide has been shown to have better oral bioavailability than furosemide and may be useful in the patient with diuretic resistance due to poor absorption.

ELECTROLYTE ABNORMALITIES IN PATIENTS WITH HEART DISEASE

An important function of the kidney is to maintain electrolyte homeostasis. Electrolyte homeostasis may be disturbed in patients with chronic heart failure and may be acutely impaired during acute decompensated heart failure. An important contributing factor is often the fact that many cardiovascular drugs affect renal handling of electrolytes. The pathophysiological consequences of heart failure per se are hyponatremia (activation of vasopressin) and hypokalemia (increased secretion of K^+ driven by the RAAS). However, because of the use of RAAS inhibitors in clinical practice and concomitant CKD, hyperkalemia is a greater clinical problem in these patients than hypokalemia. Worsening renal function in the patient with heart failure may lead to dangerous electrolyte abnormalities.

HYPONATREMIA

Hyponatremia is defined as serum $[Na^+] < 135$ mEq/L and is the most common electrolyte disorder among hospitalized patients. It is common in chronic as well as in acute decompensated heart failure and is associated with increased mortality.[212,213] Hyponatremia can lead to neurological dysfunction, decreased mental function, cerebral edema, gait disturbances resulting in falls, and osteoporosis/fractures.

Under normal conditions, osmotic homeostasis is largely mediated by arginine vasopressin (AVP) and is controlled predominantly by osmo-receptors in the hypothalamus. Volume status and blood pressure (arterial pressure sensors) affect AVP release to a lesser degree. AVP increases free water reabsorption in the distal tubules by increasing the number of aquaporins (water channels). Water is then moved passively down its chemical gradient, driven by the hyperosmotic renal medullary interstitium. AVP levels are elevated and aquaporin expression is increased in heart failure.[214-216]

The first step in the approach to a patient with suspected hyponatremia is to confirm plasma hypotonicity. Plasma tonicity may be normal or even increased in hyponatremia if unmeasured osmoles are present (eg, glucose in uncontrolled diabetes).[217] Once hyponatremia has been established, it is important to differentiate between dilutional hyponatremia (primary increase in water reabsorption) and depletional hyponatremia (net loss of sodium), as these will necessitate different treatment approaches.[218]

Dilutional hyponatremia occurs when effective circulatory volume is reduced and is mediated by baroreceptor activation as well as angiotensin II and sympathetic overdrive (the latter also increases nonosmotic AVP release).[218] Dilutional hyponatremia should be corrected by limiting water intake and by promoting free water excretion, eg, by administering an AVP antagonist such as tolvaptan or by loop diuretics. Loop diuretics increase fluid delivery to the distal nephron and reduce interstitial hypertonicity, thereby decreasing water reabsorption. Hypertonic or isotonic saline may be co-administered with loop diuretics to increase efficacy. Acute treatment of dilutional hyponatremia should focus on free water excretion, whereas prevention of a positive free water balance is the focus in the chronic setting. Vasodilators and/or inotropes may in theory improve effective circulatory volume and reduce the nonosmotic release of AVP. Tolvaptan, a selective vasopressin V2 receptor antagonist, is approved for up to 30-day treatment of hyponatremia ($Na < 125$ mEq/L) in the setting of hyper- or euvolemia. The risk of hypernatremia, too rapid correction of the hyponatremia, and hepatic toxicity have limited the use of this drug. Of note, the EVEREST[219] trial failed to demonstrate a benefit of the drug for heart failure outcomes.

Depletional hyponatremia may occur secondary to loss of sodium into third spaces (diarrhea, ascites), excessive diuresis (diuretic use or osmotic diuresis [eg, diabetes]), and/or potassium or magnesium deficiency. Depletional hyponatremia should be corrected with isotonic saline, which provides the necessary sodium. Diluted urine can then be produced to reestablish eutonicity.[218] Any potassium and magnesium deficiencies should also be corrected. Chronic hyponatremia should be corrected slowly (< 5 mEq/L/d) due to the risk of central pontine myelinolysis with too rapid correction of plasma osmolality.[220]

HYPERKALEMIA

Hyperkalemia is defined as serum potassium > 5.0 mEq/L (severe hyperkalemia is defined as > 6.5 mEq/L) and is associated with increased mortality risk. Elevation of plasma potassium concentration reduces the electrochemical gradient for potassium across the cell membrane, leading to partial depolarization of the cardiac cells. This may lead to conduction delay (reflected on the ECG by widening of the QRS complex), which increases the risk of ventricular arrhythmias including ventricular fibrillation. Severe hyperkalemia can alter the resting membrane potential sufficiently to reduce automaticity of cardiac pacemaker cells, leading to severe bradycardia or even asystole.[221]

Potassium homeostasis is controlled by potassium secretion at the distal renal tubule (distal convulated tubule and proximal collecting duct). In CKD the kidneys can compensate for reductions in GFR and loss of functioning nephrons (tubulointerstitial injury) by increasing K^+ secretion. However, they become vulnerable to acute increases in K^+ load, which increases the risk of hyperkalemic episodes.[222] Importantly, hyperkalemia is an important potential side effect of many drugs used for treatment of cardiovascular disease. The clinically most important are the RAAS inhibitors, which directly inhibit K^+ secretion. Patients with CKD who receive RAAS inhibitors are at particularly high risk of developing hyperkalemia.[223]

Interventions used to reduce serum potassium or the effects of hyperkalemia are outlined in Table 105–7. Urgent management is typically indicated at $[K^+] > 6.0$ mEq/L, but additional factors should be considered (eg, electrocardiographic changes [peaked T waves and prolonged P-R interval or QRS complex, ventricular arrhythmias, or pronounced bradycardia]). Acute management should focus on swiftly lowering $[K^+]$ and stabilize membrane potential, whereas a cornerstone of chronic management is to identify and correct the causes of hyperkalemia (eg, dietary intake, diuretic regimen, hemodynamics).

TABLE 105–7. Treatment Interventions in Hyperkalemia

Treatment	Administration Route	Onset of Action; Duration of Effect	Mechanism	Comment
Calcium (6.8 mmol)	Intravenous (acute)	1-3 min; 30-60 min	Stabilizes membrane potential	May normalize ECG. Dose can be repeated. Caution if receiving digoxin.
Hypertonic saline	Intravenous (acute)	5-10 min; ~ 2 h	Stabilizes membrane potential	Effective only in patients with concomitant hyponatremia.
Sodium bicarbonate (50-100 mmol)	Intravenous; oral (chronic)	5-10 min; ~ 2 h	Redistribution of potassium due to ionic shift (potassium enters and H^+ "exits" the cells)	Efficacy has been questioned for acute treatment of patients with dialysis.
β_2-Receptor antagonists	Intravenous or nebulized (acute)	30 min; 2-4 h	Redistribution of potassium in to cells	Effect is independent of insulin. Caution if hemodynamically unstable.
Insulin (10 units)	Intravenous (acute)	30 min; 4-6 h	Redistribution of potassium in to cells	Administer 50 g of glucose intravenously to prevent hypoglycemia.
Furosemide (40 mg or higher)	Intravenous (acute) Oral (chronic)	Variable	Excretion secondary to increased solute load to distal tubules	Loop diuretic recommended for acute therapy. Loop or thiazide for chronic therapy.
Fludrocortisone (0.1 -1.0 mg/d)	Oral (chronic)	N/A	Aldosterone agonist, increased excretion	Recommended in patients with aldosterone deficiency. May require large doses. May lead to edema and/or hypertension.
Patiromer	Oral (chronic)	N/A	Binds potassium ions in the gut, thereby promoting their excretion in feces	Can bind other oral medications and prevent their absorption. Recommend taking other oral medications at least 6 hours before or after patiromer.
Cation exchange resins 25-50 g	Oral or rectal (acute or chronic)	1-2 h; 4-6 h	Promotes excretion by binding potassium, which is excreted with the drug	New agents in development.
Dialysis	Hemodialysis (acute or chronic)	Minutes; until end of dialysis	Removal	Effects of dialysis on serum sodium, bicarbonate, calcium, and/or magnesium can affect results.

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CHAPTER 106

EXERCISE IN HEALTH AND CARDIOVASCULAR DISEASE

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Exercise and/or physical activity is beneficial for healthy individuals and for those at high risk for cardiovascular disease (CVD), as well as those with manifest CVD. This chapter addresses the hemodynamics and health benefits of physical activity and exercise conditioning programs, both in healthy individuals and those with or at risk for CVD.

ACUTE HEMODYNAMICS

During physical activity, energy expenditure increases, and the compensatory cardiovascular response represents an integration of neural, biochemical, and physiologic factors. The cardiovascular *control center* is believed to reside in the ventrolateral medulla of the brain and to respond to both central and peripheral inputs. Central impulses arise from somatomotor centers of the brain. Peripheral impulses are generated by mechanoreceptors, found in muscles, joints, and the vascular system; chemoreceptors, found in the muscles and the vascular system; and baroreceptors, found in the vascular system. These impulses are transmitted by autonomic afferent fibers. The central control center regulates cardiac output (CO) and its distribution to organs and tissues according to metabolic demand.

The *feed-forward* command system located in the motor cortex provides a coordinated and rapid cardiovascular response to optimize tissue perfusion and maintain central blood pressure. This central command provides the greatest control over heart rate (HR) during exercise[1] and is also involved in the preexercise anticipatory response. Stimulation of the central control center by the higher command centers leads to alteration of autonomic tone. This may explain the influence of "emotions" on the cardiovascular response.

The cardiovascular control center also receives input from peripheral receptors. Stretch and tension of muscular and articular mechanoreceptors trigger afferent impulses that are important in the regulation of the circulatory response to dynamic exercise. Muscle chemoreceptors stimulated by products of metabolism influence the control center as well. This reflex neural input (termed the *exercise pressor reflex*) provides rapid feedback modifying the autonomic outflow in response to physical activity and exercise.[2]

Vascular baroreceptors are located in the aortic arch and carotid sinuses. They respond to changes in arterial blood pressure and regulate HR by eliciting reciprocal changes in both sympathetic and parasympathetic activity.[3] The arterial baroreceptors protect the cardiovascular system from relatively short-term changes in blood pressure, as seen during physical exercise. Cardiopulmonary mechanoreceptors in the atria, ventricles, and pulmonary vessels aid in regulation of the circulatory response. An increase in blood pressure elicits reflex slowing of the heart, and the converse applies with hypotension. During physical activity, this feedback mechanism is altered so that blood pressure can rise. The aortic and carotid bodies contain chemoreceptors sensitive to arterial oxygen, carbon dioxide, and hydrogen ion concentrations. Whereas decreased arterial oxygen levels trigger an increase in arterial pressure, changes in carbon dioxide and hydrogen ion concentration have a relatively small effect.

CIRCULATORY ADJUSTMENTS WITH EXERCISE

The circulatory response to exercise involves a complex series of adjustments resulting in an increase in CO proportional to metabolic demands. These changes ensure that the metabolic needs of exercising muscles are met, that hyperthermia does not occur, and that blood flow to essential organs is protected. Adequate blood flow is delivered to exercising muscles through increased CO and redistribution of blood flow away from the viscera. CO is defined as the product of stroke volume (SV) and HR. The average CO at rest is approximately 5 L/min for both trained and untrained men. In women, the value is approximately 25% lower.

Resting CO increases immediately before the onset of physical exercise as a result of *anticipatory changes* in the autonomic nervous system resulting in tachycardia and increased venous return. After the onset

of exercise, CO increases rapidly until steady-rate exercise is reached. CO then increases gradually until a plateau is achieved. The magnitude of the hemodynamic response during physical activity depends on the intensity and the muscle mass involved. In sedentary individuals, CO during maximal exercise increases approximately four times, to an average of 20 to 22 L/min. In elite-class athletes, the CO can increase eight-fold, to values of 35 to 40 L/min.

HEART RATE RESPONSE TO EXERCISE

From rest to strenuous exercise, HR rapidly increases to levels of 160 to 180 bpm or higher. The initial rapid increase is likely the result of central command influences or a rapid reflex from muscle mechanoreceptors. The instant acceleration in HR is largely caused by vagal withdrawal. Later increases result from reflex activation of the pulmonary stretch receptors, which trigger increased sympathetic tone and more parasympathetic withdrawal. Increased circulating catecholamines play a role as well. During exercise, changes in HR account for a greater percentage of the increase in CO than does SV. SV plateaus when the CO has increased to only half of its maximum. Further increases in CO occur by increases in the HR, although HR response in older subjects can be *blunted*.

STROKE VOLUME CHANGES WITH EXERCISE

Two physiologic mechanisms influence SV. Increased venous return elicits enhanced diastolic filling and more forceful systolic contraction. Neurohormonal influences also enhance contractility through direct effects.

ENHANCED DIASTOLIC FILLING

Diastolic ventricular filling (preload) is enhanced by slower HR or increased venous return. Increased end-diastolic volume stretches myocardial fibers, enhancing overlap of sarcomere myofilaments and improving ventricular compliance. This in turn results in enhanced contractility and greater SV. It is believed that this mechanism is responsible for increased SV during the transition from rest to exercise or from the upright to the supine position. Resting CO and SV are highest in the supine position. Supine SV is nearly maximal at rest and increases only slightly during exercise. In normal supine individuals, increased CO with exercise results predominantly from an increase in HR, with little contribution from SV. Venous return to the heart is lower in the upright position, resulting in a lower resting SV and CO. During upright exercise, however, SV can approach maximum SV observed in the recumbent position, usually without an increase in ventricular diastolic dimensions.

IMPROVED SYSTOLIC EMPTYING

Increases in SV during upright exercise most likely occur through the combined effect of enhanced diastolic filling and more complete emptying during systole. Exercise-induced increases in circulating catecholamines enhance myocardial contractility. In the early phase of upright exercise, CO increases because of a simultaneous increase in SV and HR. In the later phases of exercise, increases in HR are primarily responsible for further increases in CO.

DISTRIBUTION OF CARDIAC OUTPUT DURING EXERCISE

Blood flow to tissues is generally proportional to metabolic activity. At rest, approximately 20% of CO is distributed to the skeletal muscle. However, during physical activity, the majority (≤ 85%) of the increased CO is diverted to the working muscles. This represents an increase from 4 to 7 to 50 to 75 mL/min of blood per 100 g of muscle. Even within active muscle, the increased blood flow is highly regulated, with the greatest amount of blood being delivered to the oxidative portions of the muscle at the expense of the tissue with high glycolytic capacity. Local metabolic conditions, as well as neural and hormonal regulation of vasomotor tone, control the shunting of blood to active muscles. The local response is primarily caused by the buildup of vasodilatory metabolites in exercising muscle.

During exertion, parasympathetic activity is withdrawn, and sympathetic discharge is maximal, which results in increased release of norepinephrine from sympathetic postganglionic nerve endings. Plasma epinephrine levels are also increased. As a result, most vascular beds constrict, except those in exercising muscles, which are influenced by vasodilating metabolites. Blood flow to the skin increases during light and moderate exercise, favoring body cooling. Further increases in workload cause a progressive decrease in skin flow as the increasing cutaneous sympathetic vascular tone overcomes the thermoregulatory vasodilatory response. The kidneys and splanchnic tissues extract only 10% to 25% of the oxygen available in their blood supply. Consequently, considerable reductions in blood flow to these tissues can be tolerated through increased oxygen extraction. At rest, the heart extracts approximately 75% of the oxygen in the coronary blood flow. Because of limited margin of reserve and increased myocardial demands, coronary blood flow increases four-fold during exercise. Cerebral blood flow also increases during exercise by approximately 25% to 30%.[4] During maximal exercise, however, cerebral flow may decrease because of hyperventilation and respiratory alkalosis.

On cessation of exercise, there is a decrease in HR and CO secondary to withdrawal of sympathetic tone and reactivation of vagal activity. In contrast, systemic vascular resistance remains lower for some time because of persistent vasodilatation in the muscles. As a result, arterial pressure decreases, often below preexercise levels, for periods up to 12 hours into recovery.[5] Blood pressure is then stabilized at normal levels by baroreceptor reflexes.

EXERCISE TYPE AND CARDIOVASCULAR RESPONSE

Different types of exercise impose different loads on the cardiovascular system. Isotonic (dynamic) exercise is defined as muscular contraction of large muscle groups resulting in movement, which induces a volume load to the heart. Isometric (static) exercise is defined as a constant muscular contraction of a smaller muscle group without movement. It provokes more pressure than volume load to the heart. Significant increases in both CO and oxygen consumption (VO_2) and a decrease in systemic vascular resistance characterize the load posed by isotonic exercise. In contrast, isometric exercise increases systemic vascular resistance while producing only minimal changes in CO and VO_2.[6] A third type of exercise is resistance exercise. This is a combination of isometric and isotonic exercise evoked by using muscular contraction with movement, as in free-weight lifting. Most activities, such as sports or those that are job related, combine all three types of exercise (Table 106–1).

ISOTONIC (DYNAMIC) EXERCISE

The response to isotonic exercise is mediated through central and peripheral adaptations that increase oxygen delivery to exercising muscles. In normal sedentary individuals, VO_2 typically increases 10-fold from rest to maximal exertion,[7] but in world-class athletes, the increase is significantly greater. Maximal VO_2 is therefore considered an indicator of the level or degree of conditioning.[8]

TABLE 106–1. Types of Exercises

	Isotonic	Isometric	Resistance
Alternative terminology	Dynamic	Static	Resistive
Example	Running	Static hand grip	Weight lifting
Oxygen uptake	Greatest	Least	Intermediate
CO	Greatest	Least	Intermediate
Peripheral resistance	Greatest decrease	Least decrease	Intermediate

Abbreviation: CO, cardiac output.

During isotonic exercise, such as running, peripheral vascular resistance decreases, and marked vasodilatation of vessels in exercising muscles occurs in conjunction with vasoconstriction of the splanchnic and renal vessels. In active muscles, local autoregulation in response to hypoxia, decreasing pH, and increased local temperature results in vasodilatation.

During prolonged dynamic exercise, skeletal muscle metabolism is primarily aerobic and requires a significant increase in oxygen supply to meet the increased demand for adenosine triphosphate (ATP). The increased oxygen requirements are met by an augmentation of the local blood flow and improved oxygen extraction.

ISOMETRIC (STATIC) EXERCISE

The cardiovascular response to isometric exercise is different. Less oxygen is required to sustain the contraction of smaller muscle groups. With isometric exercise, the necessary VO_2 is maintained with a smaller increase in CO. Increases in regional blood flow are limited by mechanical compression of blood vessels during sustained muscular contraction, and regional blood flow can actually decrease. To maintain regional perfusion, a pressor response is evoked, which is mediated, at least in part, by reflexes originating in the contracting muscles. The increase in blood pressure is proportional both to the relative muscle tension and the mass of the muscle groups involved.

SV usually declines as a result of increased left ventricular afterload and the absence of augmented venous return. In its *pure state*, static exercise represents a pressure, or systolic, load. To maintain the higher CO, the HR must increase, often out of proportion to the metabolic needs of the active muscle groups.

RESISTANCE (RESISTIVE) EXERCISE

Resistance exercises are activities that use repetitive movements against a resistance, generating a low to moderate increase in muscle tension. The response to resistance exercise is determined by the extent of both the isotonic and isometric components. Physiologic responses are described relative to the percentage of maximal voluntary contraction (MVC). Static contractions (< 15%-25% MVC) do not fully occlude intramuscular blood flow, and oxygen can still be delivered to active muscles. If one can perform more than 30% MVC with no occlusion of blood flow, there is increased VO_2, thus the aerobic or isotonic component of resistance exercise.[9]

Weight lifting is considered the prototype resistance exercise and is thought to have a high isometric component. Blood pressure and HR responses during weight lifting are proportional to the relative intensity of muscle contraction, the mass of the muscle groups involved, and the duration of the contraction. Weight training exercises have been shown to cause a significant increase in blood pressure. This is thought to be the result of restricted muscle perfusion and a centrally mediated pressor response caused by enhanced muscle tension. The HR response during maximal upper body resistance exercise is lower than that seen during maximal isotonic exercise.[10] This contributes to a lower HR-blood pressure product during maximal resistance exercise compared with maximal dynamic exercise.

Previous concerns regarding the safety of resistance training have been rebutted by several reports that reveal that moderate resistance training programs are safe even in subjects with cardiac disease.[11,12] At this time, it is believed that resistance training (done on a regular schedule) is useful for promoting muscle strength, flexibility, and functionality but probably contributes less significantly than does isotonic exercise to overall cardiovascular health and longevity. Resistance exercise should be done with care and in moderation in subjects with aortic or aortic valve disease.

EXERCISE CONDITIONING TRAINING

Physical conditioning affects the cardiovascular and musculoskeletal systems in a variety of ways that improve work performance and exercise capacity.[13] Maximal VO_2 can increase two- to three-fold through conditioning induced by repetitive periods of dynamic exercise. Increased CO and peripheral adaptations that improve oxygen extraction contribute equally. Conditioning alters cardiac structure and function, enhancing exercise-induced increases in SV.

At rest, CO is similar for both trained and untrained individuals. Endurance training induces an increase in resting parasympathetic tone and reduces resting sympathetic activity. Heart rates below 30 bpm have been recorded for some healthy athletes. CO is maintained in such individuals by increased SV. Training-induced increase in blood volume and intrinsic myocardial factors have been cited as the source of this enhanced resting and exercise SV (Table 106–2). During exercise, trained individuals achieve a larger maximal CO than do sedentary persons. In untrained persons, there is only a small increase in SV during the transition from rest to exercise, and the major augmentation in CO is induced by tachycardia. The improved cardiac performance after conditioning is secondary to both the Frank-Starling mechanism and augmented myocardial contraction and relaxation.

In previously sedentary individuals, 8 weeks of aerobic training increased SV. This change is associated with increased left ventricular end-diastolic dimension with preservation or even reduction of the end-systolic size.[14] The enhanced end-diastolic dimensions are, however, much lower than those of well-trained athletes.[15] It is not known whether this discrepancy results from prolonged training, genetic factors, or a combination of both. After cessation of training, changes largely regress

TABLE 106–2. Clinical Effects of Exercise Training

Increase in oxygen consumption
Increase in cardiac SV
Increase in maximal exercise CO
Increase in resting parasympathetic tone
Decrease in resting sympathetic tone
Decrease in resting HR

Abbreviations: CO, cardiac output; HR, heart rate; SV, stroke volume.

within only 3 weeks, which is of great concern in adherence to exercise programs. Unfortunately, cardiovascular conditioning is more easily lost than gained, which accounts for the effort dyspnea often experienced by subjects with resumption of activity after a long absence.

Several factors contribute to the cardiac adaptations of exercise training. Parasympathetically mediated bradycardia prolongs diastolic filling time, and expanded plasma volume also increases preload.[16] These changes enhance contractility through Frank-Starling mechanisms. Some studies have shown that endurance training results in increased compliance of the left ventricle, which is probably secondary to enhanced early diastolic filling and increased peak myocardial lengthening during exercise (see Table 106–2). These physiologic changes are accompanied by biochemical and ultrastructural alterations of the myocardial fibers, which have been demonstrated in the hearts of physically conditioned animals. There is an increase in lactic dehydrogenase and pyruvate kinase activity, which enhances the respiratory capacity of the cardiac myocytes. Myocytes enlarge and manifest more mitochondria and myofibrils. Observed ultrastructural changes in the sarcolemma and sarcoplasmic reticulum probably influence intracellular calcium

The cross-sectional area of the epicardial coronary arteries increases in response to exercise. Alterations in the coronary microcirculation have also been identified. Animal studies reveal increased capillary density and capillary-to-fiber ratio with training. Decreased diffusion distance between the capillaries and myocytes has also been observed. Some data suggest that training can promote coronary collateral formation in ischemic vascular beds.[17] These adaptations may enable the heart to better tolerate transient ischemia and to function at a lower percentage of its total oxidative capacity during exercise.[18] Thus, training-induced myocardial adaptations appear to protect against myocardial ischemia.

Skeletal muscle also adapts to long-term training with changes that enhance oxygen extraction. Capillary density and capillary-to-fiber ratio increase. The number of mitochondria increases, as do mitochondrial concentrations of oxidative enzymes. Other cellular adaptations include increases in myoglobin levels, increased concentrations of enzymes involved in lipid metabolism, and enhanced adenosine triphosphatase (ATPase) activity.[19]

SEX DIFFERENCES

Available data suggest qualitatively similar responses to dynamic and static exercise in both women and men. Some quantitative differences have been demonstrated in adolescent females who manifest a 5% to 10% greater CO than adolescent males at any level of submaximal oxygen uptake. This is likely related to a 10% lower hemoglobin concentration in females. To be able deliver the same amount of oxygen, there is a proportionate increase in CO. The gross maximal aerobic capacity in women is approximately 50% lower than it is in men,[20] but when adjusted to lean body mass, the difference is only 10% to 15%, a more accurate reflection of sex-related differences. The absolute number of skeletal muscle fibers and the fiber-type distribution are similar in women and men; however, for reasons that are unclear, muscle fibers in men are hypertrophied relative to those in women, resulting in greater cross-sectional muscle mass. Although strength adjusted to cross-sectional muscle area is similar in men and women, men's increased muscle mass usually yields greater isometric strength.[21,22]

Exercise-induced increases in SV also differ between the sexes. Men manifest a progressive increase in ejection fraction with little or no increase in end-diastolic volume; in contrast, women tend to increase end-diastolic volume without a significant increase in ejection fraction.[23] This results in a plateau of the ejection fraction during exercise in women compared with a progressive increase in men. Regardless of these differences in men and women, a recently reported meta-analysis of cardiorespiratory fitness in both healthy mean and women revealed no sex differences in all-cause mortality and cardiovascular events in healthy men and women. Those subjects with maximal exercise capacity of 7.9 metabolic equivalents (METs) or more had substantially lower rates of all-cause mortality and cardiovascular events compared with those with a capacity of less than 7.9 METs.[24]

AGE-RELATED DIFFERENCES

Special considerations must be addressed when prescribing exercise for elderly individuals. In these subjects, maximal end-diastolic volume increases, but maximal HR, left ventricular ejection fraction, and CO are all lower than in young individuals. Coronary disease is common in elderly individuals and can affect the cardiac response to exercise. In addition, the increased potential for exercise-related myocardial ischemia and arrhythmias can increase the risk of adverse events. A critical factor in an elderly (> 65 years of age) person's ability to function independently is mobility. The overall focus for exercise training should be to enhance health-related fitness, reduce the risk of various chronic diseases, and improve overall quality of life. Considerable evidence demonstrates that physical activity, both endurance and resistance-type exercise, can significantly improve these indices and facilitate functional independence and overall well-being.[25-31]

Studies in community-dwelling older adults have revealed benefits in those who are physically active. One observational study involved 3075 adults (52% women, 42% black), age 70 to 79 years, who performed a long-distance corridor walking test. Those who could complete the test with no difficulty walking had less overall mortality and less CVD as well as less limitation of mobility and disability. Another smaller study evaluated free-living activity expenditure including walking, climbing stairs, caregiving, and working for pay. Total energy expenditure was assessed using doubly labeled water and indirect calorimetry in 302 community dwellings of older adults (70-82 years of age) followed over a mean of 6 to 15 years. Results revealed that objectively measured free-living activity is strongly associated with lower mortality in healthy older adults. Therefore, credible data exist to support the benefits of a physically active lifestyle in the aging population.

Elderly persons should ideally undergo a medical evaluation before initiating an exercise program. This assessment should not only include a *focused* history and physical examination but should also identify psychosocial limitations to participation that are prevalent in this age group.[25,31,32] For older, apparently healthy persons desiring to participate in a low- to moderate-intensity activity such as walking, an exercise test is usually not required. However, for more vigorous activities and for all cardiac patients, an exercise test is appropriate.[33] A review of the individual's medication regimen for possible interactions with activity programs should also be performed.

As with young persons, the combination of endurance and resistance exercise is best for achieving the health and fitness goals in elderly individuals.[34,35] However, some specific comments regarding the intensity, frequency, duration, progression, and mode of exercise for elderly persons are required. The exercise capacity of elderly individuals, both before and after exercise training, is usually lower.[25,36,37] Furthermore, because some in this age group may have been sedentary for years, specific muscle groups are often markedly deconditioned. In addition, musculoskeletal limitations, particularly arthritis, can be severely limiting. Thus, it is important to prescribe an exercise program with low-level energy expenditure, particularly during the first few weeks, with gradual increases thereafter. In these instances, however, participants

can be encouraged to increase the frequency of exercise (with shorter duration), even to perhaps several times per day. Higher intensity training must be recommended with caution in this age group because of the potential for musculoskeletal injury.

Those whose exercise duration is limited (< 15 minutes per session) because of physical or psychosocial limitations should attempt to exercise more frequently or intermittently. Certain subjects can benefit more because of this intermittent activity. One study supporting this was done in overweight women assigned to the same caloric restriction but randomized in an exercise program to either 40 minutes of continuous exercise or to four 10-minute "bouts" or periods. At the end of the activity program, those in the intermittent (bouts) group lost 8.9 kg of weight versus 6.4 kg in the continuous group. In the intermittent group, there was also improved adherence and a higher VO_2 compared with the continuous exercise group.[37] Conversely, for those who are not limited, increasing the duration of activity to as much as 45 to 60 minutes per session is valuable for increasing caloric expenditure and improvement of risk factors, including obesity, lipid abnormalities, hypertension, and elevated blood glucose level. Published science advisories and scientific statements from the American Heart Association have summarized current knowledge of the health outcomes of those who are overweight and the impact on cardiovascular risk of patients with type 2 diabetes mellitus.[38]

Many elderly persons have symptomatic concomitant medical and physical limitations (orthopedic, neurologic, and vascular) that can be exacerbated by weight-bearing exercise, especially higher impact activities such as jogging. Walking can be difficult for some older and/or functionally limited persons. Thus, even seemingly innocent activities should be carefully considered for potential adverse effects for some in this age group, especially when the activity requires individuals to bear their entire weight. Select older patients may better tolerate cycle and water exercises, and these should be offered as options.

IMPLEMENTATION OF EXERCISE TRAINING

The type of activity, frequency, duration, intensity, and progression determine the effect of an exercise training program. Epidemiologic studies suggest that moderate-intensity activities, such as brisk walking, performed on a regular basis confer cardioprotection to both men and women.[39-42] More vigorous activity can confer greater cardioprotection, but the majority of the benefit is accrued with moderate levels of exertion.[39,42] Moreover, fitness appears to be a powerful, independent predictor of cardiovascular risk. High-intensity exercise programs are often associated with poor adherence rates and more musculoskeletal injuries. Thus, a highly structured program of vigorous exercise, especially in elderly individuals, is not generally recommended.

Current guidelines recommend that persons of all ages perform exercise of moderate intensity for 30 to 60 minutes, four to six times weekly or at least 30 minutes of moderate-intensity physical activity on a daily basis.[43-46] At present, only 10% to 20% of the population meets this recommendation.[46,47] Because only a small percentage of the population is employed in physically demanding occupations, most need to perform this activity in their leisure time. Examples of recommended activities include brisk walking, cycling, swimming, and active yard work. The duration of any period of activity should be at least 10 minutes, and the accumulated daily duration should be at least 30 minutes. Those who choose shorter exercise periods can benefit (as discussed previously) from the effects of intermittent exercise on improved adherence and greater increases in VO_2. In addition, during the recovery period (or periods) in an intermittent (discontinuous) exercise program, additional calories are expended in the postexercise state while the body returns to the resting metabolic state. These calories are not usually counted with those expended with the activity and amount to 20 to 30 kcal per exercise session, which could be doubled if one exercised twice daily.[48]

Those who are sedentary should be encouraged to initially perform a duration of activity that is "comfortable" and to gradually increase to 30 to 60 minutes of daily activity. People who meet these daily standards and who wish to increase their activity further should be encouraged to do so. Resistance exercises should be added to the activity program to increase muscle strength. Resistance training using 8 to 10 different exercise sets with 10 to 15 repetitions each (arms, shoulders, chest, trunk, back, hips, and legs) performed at a moderate to high intensity (eg, 10-15 lb [4.5-6.8 kg] of free weight) for a minimum of 2 days per week is recommended.

Physicians and other health professionals should encourage the general public and their patients to follow these guidelines. Incorporating preventive services into medical practice is challenging because of time and financial constraints. To address these issues, the Centers for Disease Control and Prevention developed the Physician-Based Assessment and Counseling for Exercise (PACE) project.[49] This system includes a simple discussion of physical activity counseling and illustrates how a clinician can efficiently incorporate physical activity counseling into a busy clinical practice through the use of paramedical personnel.

As the problem with overweight and obesity continues to increase worldwide, new physical activity guidelines have been developed to hopefully combat this problem more effectively. A consensus conference was held in Bangkok with experts in exercise, energy expenditure, and body weight reduction in attendance. It was concluded that 60 to 90 min/d of moderate-intensity exercise is needed for prevention of weight regain (lesser amounts of vigorous activity). To prevent transition of overweight to obesity, 45 to 60 min/d of moderate-intensity exercise is needed. The 2005 US government recommendation is for 60 minutes of exercise on most days to prevent weight gain and 60 to 90 minutes on most days for previously overweight people who have lost weight.

TRAINING IN INDIVIDUALS WITH CARDIOVASCULAR DISEASE (SECONDARY PREVENTION)

HISTORICAL PERSPECTIVE

Exercise training has assumed a prominent role in contemporary prevention and management of CVD.[33,43,45,46,50-53] In the 1950s, traditional management of patients with acute myocardial infarction (MI) did not include physical exertion of any kind. Hospitalization and strict bedrest were recommended for at least 6 weeks after acute MI. In 1951, Levine and Lown described reductions in post-MI morbidity and mortality associated with limited early mobilization. This "chair treatment" involved progressive periods of sitting in an armchair starting 1 day after MI. By the end of that same decade, early inpatient mobilization was included in programs of physical activity. By the 1970s, a series of small randomized controlled trials of exercise training (typically starting 3-6 months after MI) suggested significant benefits after MI. Although these studies were individually underpowered to demonstrate survival advantage, meta-analysis suggested a 24% reduction in CVD mortality with exercise-based cardiac rehabilitation.[41]

Early rehabilitation programs focused almost exclusively on exercise training. As the discipline matured, patient education; risk factor management; psychological screening and intervention; and dietary, vocational, and smoking cessation counseling were integrated to forge the comprehensive cardiac rehabilitation risk reduction programs of today. In the past three decades, the benefits of comprehensive cardiac

TABLE 106–3. Centers for Medicare and Medicaid Services Recognized Indications for Cardiac Rehabilitation

Before 2006	Added in 2006
After MI[a]	After PTCA or intracoronary stent implantation[a]
After CABG[a]	After valve surgery[a]
Chronic stable angina	After cardiac transplantation[a]
Intermittent claudication	

[a]Within 1 year before initiating cardiac rehabilitation.

Abbreviations: CABG, coronary artery bypass surgery; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

TABLE 106–4. Effects of Exercise-Based Cardiac Rehabilitation on Study End Points

Outcome	Mean Difference (%)[a]	95% Confidence Limit	*P* Value
Total mortality	−20	−7% to −32%	.005
Cardiac mortality	−26	−10% to −29%	.002
Nonfatal MI	−21	−43% to 9%	.150
CABG	−13	−35% to 16%	.400
PTCA	−19	−51% to 34%	.400

[a]Mean difference is the percentage of difference between exercise-trained and usual-care control group.

Abbreviations: CABG, coronary artery bypass graft; MI, myocardial infarction; PTCA, percutaneous coronary angioplasty.

Data from Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2004;116(10):682-692; Reproduced from Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2005;111(3):369-376.

rehabilitation programs have become widely recognized.[43,50,54,55] Furthermore, the population deemed appropriate for this intervention continues to expand, incorporating higher-risk individuals, including those with left ventricular systolic dysfunction or valvular heart disease and recipients of surgical or percutaneous revascularization (Table 106–3).

More recently, secondary prevention of cardiovascular events through optimizing proven pharmacologic therapies has been woven into the fabric of contemporary cardiac rehabilitation programs.[50,54]

EXERCISE AND SECONDARY PREVENTION

Acute and chronic therapy of coronary artery disease (CAD) has evolved significantly since early meta-analyses[41] suggested survival benefit from exercise-based cardiac rehabilitation. Major advances in the therapy of patients with CAD over the past quarter century call into question the validity of those potentially dated conclusions. However, more contemporary meta-analyses of randomized controlled trials of exercise-based cardiac rehabilitation have largely confirmed the findings of the 1980s.[56] One study added more than 4000 additional patients enrolled in studies of comprehensive and exercise-only rehabilitation programs for CAD published through March 2003.[56] A more recent update included 48 trials enrolling nearly 9000 individuals. Although the older studies enrolled primarily low-risk, middle-aged, white men, this review included a larger number of women (20%), elderly people (≥ 65 years), and recipients of coronary revascularization. In this analysis, cardiac rehabilitation was associated with a 20% reduction in all-cause mortality (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.68-0.93) and a 26% reduction in CVD mortality (OR, 0.74; 95% CI, 0.61-0.96) compared with usual care (Table 106–4). Based on data from a limited number of trials, significant improvements in total cholesterol, triglycerides, systolic blood pressure, and self-reported smoking rates were also noted. As also shown in Table 106–4, there was a favorable trend in the rates of MI and revascularization that failed to meet statistical significance. Cardiac rehabilitation did not yield significant reductions in high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol or diastolic blood pressure. Contrary to their previous review, subgroup analysis did not reveal a discrepancy in mortality rates between exercise-only programs and comprehensive cardiac rehabilitation programs. Similarly, there was no distinction between studies published before and after 1995.

Analysis of the US Medicare database showed a 21% to 34% lower mortality in older patients who had cardiac rehabilitation as part of their treatment for CAD versus patients who did not undergo rehabilitation, extending the benefit to older patients.[57]

EXERCISE AND FUNCTIONAL CAPACITY

Exertional intolerance is one of the principal clinical features of symptomatic CVD even in the absence of heart failure (HF). Exercise-based cardiac rehabilitation is consistently associated with improvements in functional capacity that significantly impact quality of life.[55] Exercise training reduces HR and blood pressure at submaximal workloads, improves the metabolic efficiency of both skeletal and cardiac muscle, enhances the mechanical performance of the myocardium, favorably influences autonomic tone, and prolongs the time to angina and ischemic electrocardiographic (ECG) changes during treadmill exercise.[43] These physiologic adaptations translate into improved ability to perform activities of daily living with fewer symptoms and fewer limitations. Furthermore, enhanced exercise capacity is associated with significantly lower CVD mortality and fewer nonfatal CVD events.

The landmark Agency for Health Care Policy and Research practice guidelines of 1995 summarized the results of 114 scientific reports on the effect of exercise-based cardiac rehabilitation on measures of exercise tolerance. These included 46 randomized controlled trials, of which 35 compared exercise-based rehabilitation with a no-exercise control group. Of these 35 trials, 30 demonstrated statistically significant improvement in exercise capacity in those assigned to exercise intervention.[55] Supervised exercise programs lasting 3 to 6 months have been associated with an 11% to 36% improvement in peak VO_2. The most deconditioned derive the greatest benefit.[50]

EXERCISE AND RISK FACTOR MODIFICATION

CAD is a chronic, progressive condition associated with numerous metabolic, toxic, and hemodynamic precipitants, most of which respond favorably to exercise training. Consensus guidelines emphasize the role of exercise in managing hypertension, diabetes, hyperlipidemia, the metabolic syndrome, and obesity.

BLOOD PRESSURE

Meta-analyses of randomized controlled trials of exercise in both hypertensive and normotensive individuals suggest a 3- to 4-mm Hg decline in systolic blood pressure and a 2- to 3-mm Hg decline in

diastolic blood pressure with both aerobic and resistive exercise training.[57,58] From a public health perspective, even such modest effects on blood pressure significantly impact CVD mortality.[59]

BLOOD GLUCOSE (DIABETES)

When combined with dietary intervention, exercise lowers the incident rate of new diabetes in high-risk individuals by 42%.[60] Furthermore, it is superior to metformin in the prevention of type 2 diabetes, and at least a portion of its beneficial effects appears to be independent of weight loss.[60]

LIPIDS

The effect of exercise on blood lipids varies among available studies. Despite these mixed results, it appears that exercise can lower plasma triglycerides, very low-density lipoprotein (VLDL) cholesterol, and, in some individuals, LDL cholesterol. It also raises HDL cholesterol. A meta-analysis of 51 studies of "moderate to hard" intensity aerobic exercise on blood lipids involved approximately 4700 participants.[61] Nearly all studies involved exercise three to five times per week, lasting at least 12 weeks. The estimated weekly exercise expenditure during structured programs ranged from 500 to more than 5000 kcal/wk, with a mean of 1408.8 ± 824.7 kcal/wk. On average, LDL cholesterol decreased 5.0% ($P < .05$), and triglycerides decreased 3.7% ($P < .05$). HDL cholesterol increased by 4.6% ($P < .05$).

The Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study prospectively evaluated serial blood lipids in a diverse population of 675 healthy, sedentary, normolipidemic individuals undergoing 20 weeks of supervised cycle ergometer exercise.[62] They demonstrated a 3.6% increase in HDL cholesterol (1.1 mg/dL in men and 1.4 mg/dL in women). The improvement in HDL cholesterol levels was primarily caused by an increase in the HDL_2 subfraction with an associated increase in apolipoprotein (apo) A-1 ($P < .001$). They noted only a transient reduction in plasma total and VLDL triglycerides, reflecting the acute effects of the last training session. There were no significant changes in total, LDL, and VLDL cholesterol or apo B.

As is the case for managing hypertension, diabetes, and weight, combining diet and exercise appears to be more effective in lowering LDL cholesterol. One significant study randomized 377 men and postmenopausal women with low HDL cholesterol and moderately elevated LDL cholesterol to aerobic exercise, the National Cholesterol Education Program Step 2 diet, combined diet and exercise, or no intervention.[63] Serial lipids revealed significant reductions in LDL cholesterol in both men and women only in the group assigned to combined diet and exercise. Along with other studies, this study suggests that exercise mitigates the reduction in HDL cholesterol typically seen with low-fat diets.

WEIGHT

Weight loss is also associated with improvements in blood pressure, lipid profile, and glycemic control in those with type 2 diabetes. As little as a 10-lb (4.5-kg) weight loss reduces blood pressure. Weight loss by dietary means improves plasma triglyceride levels by 2% to 44%, total cholesterol by 0% to 18%, and LDL cholesterol by 3% to 22%. Although exercise is an important component of weight-management strategies, exercise alone is a rather inefficient method of achieving weight loss. A meta-analysis of 28 studies of exercise compared with diet or control groups calculated an average weight loss of 3 kg in men and 1.4 kg in women assigned to exercise intervention compared with control subjects.[64] On average, diet alone yields a 3-kg greater weight loss than exercise alone. The combination of diet and exercise is most effective and, on average, yields 8.5 kg of weight loss.[65]

Contrary to its role in initial weight loss, exercise plays a significant role in weight loss maintenance. Six randomized controlled trials examining the effects of exercise on weight loss maintenance concluded that higher levels of exercise were significantly more successful in maintaining weight loss over an average follow-up interval of 2.7 years. Those performing higher levels of physical activity maintained 54% of their initial weight loss, twice that of those assigned to lower levels of physical activity. Thus, exercise is an important component of strategies for weight management and offers synergistic benefits to weight loss itself in risk factor control. This is particularly important in the management of metabolic syndrome, a constellation of metabolic risk factors associated with increased risk for diabetes and CVD. The components of the metabolic syndrome all respond favorably to aerobic exercise, making exercise a mainstay in its management.

Resistance training has also gained favor in the treatment of obesity. Substantial evidence supports that resistance training increases total fat-free mass, muscular strength, and resting metabolic rate, as well as mobilizing visceral adipose tissue in the abdominal region.[66]

More recently, high-calorie expenditure exercise has been shown to promote greater weight loss and more favorable metabolic rate profiles than usual and customary practice in overweight patients in cardiac rehabilitation. Significant weight loss was maintained for 1 year after a 5-month program.[67]

OTHER EFFECTS OF EXERCISE IN SECONDARY PREVENTION

PROGRESSION OF CORONARY ARTERY DISEASE

A number of studies have investigated the effect of exercise on progression of atherosclerotic disease. The majority of these studies incorporated exercise into a multifaceted intervention, including diet. A significant study reported long-term follow-up of one of these carefully controlled trials of diet and exercise in 113 men with stable CAD.[68] The men were randomized to an intensive diet and exercise intervention or limited diet and exercise advice. The exercise group was encouraged to perform 30 minutes of daily cycle ergometer exercise at home and attend at least two supervised 60-minute group exercise sessions weekly. The intervention group improved their physical work capacity by 28%, but the control group remained unchanged. There was no distinction between the two groups in temporal changes in total cholesterol, triglycerides, or body mass index. After 6 years, 66 patients underwent follow-up angiography. Analyzing serial quantitative coronary angiograms on a per-patient basis, these investigators found significantly less progression (59% vs 74%) and significantly more regression (19% vs 0%) in the intervention group compared with the control group.

Finally, the numbers of bone marrow–derived endothelial progenitor cells increase in the peripheral blood of mice and patients with stable CAD subjected to exercise training. Because these cells are thought to exert beneficial effects on vascular repair, angiogenesis, and CAD, much remains to be learned about the fundamental mechanisms underlying the protective and therapeutic benefits of exercise in normal humans and those with CVD.[69]

SYSTEMIC INFLAMMATION

Systemic inflammation is emerging as a significant predictor of cardiovascular risk.[68] Elevated serum levels of interleukin-6; tumor necrosis factor-α; high-sensitivity C-reactive protein (HS-CRP); and a number of other cytokines, acute-phase reactants, and soluble cytokine receptors have been associated with increased risk of CVD events and diabetes.[70-73] Modest elevation of CRP, in particular, has been associated

with CVD risk in observational studies.[72] Furthermore, some data support that lowering HS-CRP with hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitor therapy reduces risk beyond the benefits accrued from LDL cholesterol lowering alone. Obesity and visceral adiposity are associated with increased levels of CRP, and diet-induced weight loss reduces CRP levels.[70] Physical inactivity also correlates with elevated CRP levels in observational studies. Randomized controlled trials examining the effect of exercise on CRP levels are limited.[74] Three small, prospective trials of the impact of exercise training on inflammatory markers have enrolled only 104 participants. Two of the three included a control group and showed significantly greater reductions in CRP with exercise training. One small, noncontrolled prospective trial demonstrated a trend toward lower CRP after 6 months of supervised exercise.

ENDOTHELIAL FUNCTION

Exercise training enhances endothelium-dependent coronary and peripheral arterial vasodilatation in individuals with CAD, peripheral arterial disease, HF, diabetes, and hypertension.[71-73,75,76] The effect of exercise on vascular function in individuals free of atherosclerotic risk factors has been mixed.[77] Exercise's influence on vascular function appears to be mediated through increased arterial wall shear stress, which promotes enhanced expression and activation of endothelial nitric oxide synthase by means of Akt-dependent phosphorylation.[72] In addition to influencing vascular tone, nitric oxide also conveys significant antiatherogenic and antithrombotic effects.[78] Exercise also has beneficial effects of thrombotic tendencies and autonomic function in secondary prevention.

The type of exercise has been studied in 209 patients after recent acute infarction. The four groups compared included aerobic training, resistance training, resistance plus aerobic, and no training over a 4-week period. Improved endothelial function was associated with all training modalities, but this effect was no longer seen after 1 month of detraining.[79] Additional effects of exercise in secondary prevention are on coagulation, autonomic function, anti-ischemic and antiarrhythmic effects and a decrease in age-related disability.

EXERCISE IN PATIENTS WITH HEART FAILURE

There is a daily increase in the millions of people diagnosed with HF, creating a significant impact on the health care system. Exercise endurance is limited in these subjects despite advanced drug therapy.[80,81] Cardiopulmonary exercise testing is often done to risk stratify HF patients and is readily available in transplant centers. However, the treadmill exercise time with the Naughton protocol, a far simpler test available in a much larger number of hospitals and clinics, provides an inexpensive prognostic screening tool. Based on substantial data, exercise training can improve both cardiac and noncardiac indices.[80] Recommendations based on randomized, controlled trials encourage exercise training for individuals with HF to impact both functional and symptomatic improvement.[82,83] Home-based exercise has been used in 173 subjects with systolic HF. The investigators recorded no differences between the experimental and control groups in the combined clinical end point at 12 months and in functional status, quality of life, or psychological states at 6 months. However, the exercise group had a reduced hospitalization rate (12.8% vs 26.6%; $P = .018$). Exercise training can improve physiologic indices, including exercise tolerance, ventricular function, skeletal muscle function, peripheral blood flow, endothelial function, diastolic function, and quality of life.[83,84] Experience has revealed that exercise in HF is safe and well tolerated if it is appropriately prescribed and augments the benefits of cardiac resynchronization therapy.[85,86]

The largest and most important trial, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), randomized 2331 stable patients (mean age, 59 years; 28% women) with HF and reduced left ventricular ejection fraction (LVEF) to aerobic exercise training (36 supervised sessions followed by home-based training) plus standard pharmacologic treatment versus standard pharmacologic treatment plus usual recommendations regarding physical activity. After a mean follow-up of 2.5 years, there were no statistically significant differences in the primary end point of all-cause mortality and hospitalization (65% exercise training group vs 68% usual care) and secondary end points of mortality (16% vs 17%), CVD morality, or CVD hospitalization (55% vs 58%) or CVD mortality or HF hospitalization (30% vs 34%). In a prespecified supplemental analysis, adjusting for known major prognostic risk factors in HF (HF cause, exercise duration, LVEF, history of atrial fibrillation or flutter, and the Beck Depression Inventory), the primary end point of all-cause mortality or hospitalization was reduced by 11% in the training group (hazard ratio [HR], 0.89; 95% CI, 0.81-0.99; $P = .03$).[86] CVD mortality or CVD hospitalization was reduced 9% (HR, 0.91; 95% CI, 0.82-1.01; $P = .09$), and CVD mortality or HF hospitalization was reduced 15% (HR, 0.85; 95% CI, 0.74-0.99; $P = .03$). Because exercise was safe in this patient population in which rates of CVD events, implantable cardioverter-defibrillator firing, and fractures of the hip and pelvis were similar, exercise training of HF patients appears most appropriate.

In the same trial, the health status of the participants was assessed by the Kansas City Cardiomyopathy Questionnaire. There were improvements in the overall summary scale for the exercise group but also in key subscales, including physical limitations, symptoms, quality of life, and social limitations. Their improvements were considered modest but significant ($P < .001$) and add to the overall benefit of the exercise training.[84]

COMPONENTS OF CONTEMPORARY CARDIAC REHABILITATION

Historically, cardiac rehabilitation has been arbitrarily divided into successive phases, typically starting during hospitalization for an acute event (Table 106–5). As clinical care and medical economics have evolved, these traditional phases have lost much of their relevance. Contemporary cardiac rehabilitation emphasizes a continuum of care. The American Association of Cardiovascular and Pulmonary Rehabilitation recommends a more descriptive paradigm incorporating three levels of intervention—inpatient, early outpatient, and lifetime cardiac rehabilitation.[87-89]

INPATIENT REHABILITATION

The contemporary management of acute coronary syndromes focuses on timely reperfusion, risk stratification, and introduction of proven pharmacotherapy in appropriately selected individuals. The timeline of this intervention has become quite truncated with many patients discharged within 3 days of an acute ST-elevation MI. Accordingly, inpatient cardiac rehabilitation has assumed an introductory role. It is focused on early mobilization, starting as soon as patients are hemodynamically stable and free of symptoms of ischemia, arrhythmia, or HF. As the patient progresses to an ECG telemetry environment, progressive ambulation is appropriate, initially with assistance and hemodynamic assessment before, during, and after exercise.

Patients are often unable to assimilate the large amount of information that needs to be introduced. Therefore, the current emphasis is on providing written information for the patient and family, ensuring stable clinical status with activities of daily living, and referring the

TABLE 106–5. Phases of Traditional Cardiac Rehabilitation

Phase	Location or Timing	Description	Duration
I	Inpatient Starting as soon as clinically stable	Gradual progressive activity and introductory education (ie, disease process, cardiovascular symptoms, risk factor management, and lifestyle changes)	Days
II	Outpatient shortly after discharge	Multidisciplinary intervention, including progressive exercise, exercise prescription, psychological screening or intervention, smoking cessation, dietary counseling, verification of optimal pharmacologic and device therapy for secondary prevention and functional status, and in-depth education (ie, disease process, risk factor management medications, and weight loss)	2-12 wk
III	Outpatient immediately after phase II is complete	Supervised exercise and reinforcement of the principles promulgated during phase II; implementation of progressive exercise prescription; transitional to independent exercise venue; can serve as a long-term exercise facility for those lacking alternatives	6-12 mo after phase II
IV	Outpatient	Maintenance Focus on adherence to exercise prescription, healthy eating, weight management, tobacco abstinence, medications, and cardiovascular symptom surveillance	Indefinite

Adapted with permission from Squires RW, Gau GT, Miller TD, et al. Cardiovascular rehabilitation: status, 1990. *Mayo Clin Proc.* 1990 May;65(5):731-755.

patient to an appropriate comprehensive cardiac rehabilitation program. In addition, ensuring that patients are discharged from the hospital on appropriate medical therapy is an important part of the initial intervention. A number of practice tools are available to help address the gap between recommended therapy and that which is delivered in practice. Patients are usually more adherent to drug therapy when it is initiated in the inpatient environment.

EARLY OUTPATIENT REHABILITATION

When formal cardiac rehabilitation programs first evolved in the 1960s and 1970s, the primary concern was the safety of *early* exercise. As such, ECG telemetry *monitoring* was incorporated as a means of surveillance for significant arrhythmias. Currently, this monitoring goes beyond telemetry and includes surveillance of symptoms; hemodynamics; glycemic response to exercise (in diabetics); weight; tobacco use; emotional status; and adherence to medications, diet, and home exercise. It also includes review of each individual's pharmacologic and device therapy to ensure adherence with consensus guidelines. This monitored phase is an intensive, multidisciplinary intervention focused on educating the individual about the disease, its manifestations, and all aspects of its treatment. The goal is to provide each participant with the tools needed to slow disease progression, maintain optimal functional status, and become an informed and active participant in managing his or her condition.

MAINTENANCE

The distinction between traditional phase III (medically supervised) and IV (nonmedically supervised) cardiac rehabilitation has been unclear for some time. Most participants progress to independent exercise without a transitional "phase III." Nonetheless, some patients are concerned by the prospect of continuing exercise in unfamiliar surroundings and elect to continue exercising at a cardiac rehabilitation facility where they feel safe and are familiar with the personnel, protocol, facilities, and clientele. Clinical features occasionally mandate closer supervision than an unmonitored independent exercise program because of adherence, cognitive limitations, serious comorbidities, hemodynamics, or arrhythmias that require medical supervision during exercise. Unfortunately, continuing cardiac rehabilitation services under such circumstances is generally not reimbursed by third-party payers. Regardless of the venue and the degree of medical surveillance, the goal of this maintenance phase is exercise independence and adherence to exercise prescription, healthy diet, weight management, tobacco abstinence, and medications. For further information, please refer to Chapter 45, Rehabilitation of the Patient with Coronary Heart Disease.

CONCLUSION

For subjects with CVD, exercise and/or proper physical activity is a significant component of overall long-term management. Such activity must be individually "prescribed" considering age, body habits, type and degree of CVD, medications, history of physical activity, and general attitude regarding a long-term commitment to an "active lifestyle." With these considerations being met, a physical activity/exercise program can be a significant benefit to patients with stable CVD.

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SECTION 16

Populations and Social Determinants of Cardiovascular Disease

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CHAPTER 107

SOCIAL DETERMINANTS OF CARDIOVASCULAR DISEASE

Holly G. Atkinson

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INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death around the globe, now accounting for about one in three deaths.[1] More than 80% of these CVD deaths take place in low- and middle-income countries.[2] Although mortality from CVD in the United States has been declining since the 1970s, heart disease is still the leading cause of death in America as well, accounting for approximately 31.3% of deaths in 2011.[3] The US decline in CVD mortality has been attributed to advances in prevention, diagnosis, and treatment. However, if current trends prevail, the prevalence of CVD in the United States is expected to *rise* 10% between 2010 and 2030.[4] This projected rise in CVD prevalence is attributed to a number of factors: an aging populace, an increase in major risk factors (hypertension, lack of physical activity, obesity, and diabetes), and growing socioeconomic inequality that accentuate the deleterious social determinants of health. Further, the clinical advances made in the diagnosis, treatment, and prevention of CVD have not been equally available to all individuals throughout our society.[5] The United States is one of the richest nations in the world and spends more per capita on health care than any other nation, and yet America has one of the shortest life expectancies at birth of any industrialized nation, ranking 27th out of 34 Organization for Economic Cooperation and Development countries.[6]

This chapter, unlike preceding chapters that have primarily focused on clinical issues and proximal determinants of CVD, explores the social determinants of CVD that operate at the population level. As the World Health Organization (WHO) Commission on Social Determinants of Health noted in its report, "heart disease is caused not by a lack of coronary care units but by the lives people lead, which are shaped by the environments in which they live."[7] The broader social context in which individuals lead their lives has a major impact on health status and ultimately on longevity. CVD is at heart a "lifestyle" disease, driven by our contemporary way of life, marked as it is by the overconsumption of highly processed foods, little physical activity, obesity, use of tobacco products, and elevated levels of chronic stress. But CVD is also a disease propelled by deeply entrenched social inequalities. Decades of research have yielded a large body of literature that clearly exposes the numerous societal factors that have a profound impact on the development of CVD and significantly contribute to the disparities in health and longevity among various populations and subpopulations. This chapter explores the role that social determinants of health play in driving CVD.

THE SOCIAL DETERMINANTS OF HEALTH

DEFINITIONS

WHO defines *social determinants of health* as "the circumstances in which people grow, live, work, and age, and the systems put in place to deal with illness. The conditions in which people live and die are, in turn, shaped by political, social, and economic forces."[7] This broad definition recognizes that the social determinants of health are multifactorial, deeply interrelated, complex, and driven by a multitude of forces, including social, cultural, economic, and political forces.

Although every individual is affected by the society in which he or she lives, some are more burdened than others by social and economic disadvantages, which in turn can result in *health disparities*. Health disparities are defined as "differences that occur by gender, race or ethnicity, education or income, disability, geographic location, or sexual orientation."[8] With respect to differences in health outcomes, the term refers to those outcomes that persist despite controlling for access to care and patient clinical factors. These outcome disparities signal the effects of institutional barriers, provider barriers (such as cultural insensitivity, language barriers, unconscious bias, or frank racism), and patient issues (such as cultural beliefs, health literacy, adherence, and trust of the medical profession).[9] The term *health disparities* not only typically connotes that the observed differences are unnecessary and avoidable, but that they are unjust as well. Some prefer to use the term *health inequalities* rather than health disparities to highlight the injustice of the observed differences in health status and health outcomes that characterize our society, while others use the two terms interchangeably.[10]

Given the complexity of our social environments and the myriad factors and forces that combine and interact to give rise to them, it is challenging to identify concisely and measure accurately the full range of the social determinants of health. Nevertheless, decades of research have given us important insights into key determinants of health and how they interact to create health disparities.

THE SOCIOECONOMIC GRADIENT OF HEART DISEASE

Public health experts have long recognized that social factors play a role in determining health status. Rudolf Virchow, the 19th century German physician and public health activist, queried: "Do we not always find the diseases of the populace traceable to defects in society?"

> Do we not always find the diseases of the populace traceable to defects in society?
>
> —Rudolf Virchow, 19th-century German physician and public health activist

Virchow went on to identify lack of education, unemployment, poverty, and political disenfranchisement as drivers of disease.[11] The 19th century saw the rise of sanitary campaigns, which focused on the connections between people's living conditions and their sickness. During the latter half of the 20th century, the scientific evidence linking the social determinants of health with disease prevalence and health outcomes rapidly accumulated up to the present day, when the study of social disadvantage and its effects on health is an extensive and penetrating focus of inquiry and policy action.

Heart disease is considered a disease of affluence. It has emerged in both developed and developing countries as industrialization and urbanization have homogenized patterns of consumption and lifestyle practices. Evidence shows that the rise and fall in the prevalence of CVD varies according to a country's stage of economic development.[12] And while the poorest regions of the world still see relatively low rates of CVD, regions within developing countries that are marked by increasing wealth and adoption of the "Western" lifestyle have seen a rapid rise in heart disease. The epidemiologic transition we are witnessing in developing countries has been compressed into a few decades, whereas the epidemic of heart disease observed in Western developed nations took place over the course of a century.[13] The swift pace of economic globalization and the rapid diffusion of the Western lifestyle are thought to be powerful drivers of the present-day, expanding global epidemic of heart disease.[14]

Evidence also reveals a gradient of heart disease not only *across* countries according to the stage of development, but also *within* societies. Inequalities in the distribution of heart disease change according to the stage of epidemiologic transition reached by a country.[15] Early in the transition, individuals in the higher socioeconomic positions are usually the first to adopt a lifestyle (eg, physical inactivity, smoking, poor diet) that leads to the development of CVD risk factors (eg, hyperlipidemia, hypertension, obesity, metabolic syndrome, diabetes) and the development of the disease itself. However, in the later stages of the transition, these individuals are the first to experience a reduction in behavioral risk factors and a decline in the prevalence of the disease. In the most advanced economies, as the epidemic has matured, the socioeconomic gradients of heart disease and risk factors have reversed over time, and heart disease has become more prevalent among people in lower socioeconomic positions. As countries develop—both developed and developing nations—the social pattern converges to a more homogeneous one, as the disadvantaged socioeconomic position progressively becomes a systematic risk factor for heart disease.[15] The landmark Whitehall study, led by Sir Michael Marmot, conducted on over 17,500 male British civil servants in the 1970s, revealed the pervasive effects of social gradient on health. It showed that occupational grade has a powerful effect on health and longevity. In the Whitehall study, those at the lowest occupational grades had the worst health (heavier weight, more tobacco use, less exercise, and higher blood pressure and blood glucose) and highest CVD mortality (three to six times the mortality of men in the highest grade). Health and longevity improved at each successive level of occupational grade, up to the very highest level (Fig. 107–1).[16]

As the later stages of socioeconomic development in a nation are reached, the relationship between low socioeconomic status (SES) and the behavioral risk factors for heart disease also becomes more homogeneous; the relationship becomes more consolidated and consistent across individual-level and area-level indicators.[17] For example, tobacco use is more prevalent almost everywhere in the lower socioeconomic groups than in the higher socioeconomic groups.[18] It is important to note, however, that while behavioral risk factors for heart disease become more common among less privileged groups than privileged groups in both affluent and less affluent societies as they develop, evidence indicates that conventional risk factors account for only a small proportion of the observed social gradient in heart disease.[19] Additional findings from the Whitehall study, which investigated mortality from coronary heart disease over a 25-year period, showed that traditional coronary heart disease risk factors accounted for less than one-third of the social gradient in mortality.[19] These findings stimulated further investigations of additional factors that could explain the other two-thirds of the observed social gradient of heart disease.

THE GROWTH AND EVOLUTION IN HEALTH DISPARITIES RESEARCH

Over the past several decades, investigators from a wide range of disciplines, in their exploration of the social determinants of health, have looked critically at several distinct areas of interest, asking more complex questions as the field has evolved.[20] First, poverty was explored as a categorical determinant of health; it was approached from a threshold framework. Researchers found that the greatest drop in mortality occurred as income increased at the lowest levels of income. However, even as income increased to ever higher levels, mortality continued to decline. Researchers then examined the graded associations between socioeconomic resources and health status across the entire SES hierarchy, exploring the linkage between SES position—indicated by education, occupational status, and/or income—and social disadvantage related to race/ethnicity and sex. The next focus of inquiry moved to exploring the mechanisms by which various social determinants resulted in poor health outcomes. SES is now recognized as only one key factor among many. It is the intersection and interaction of these

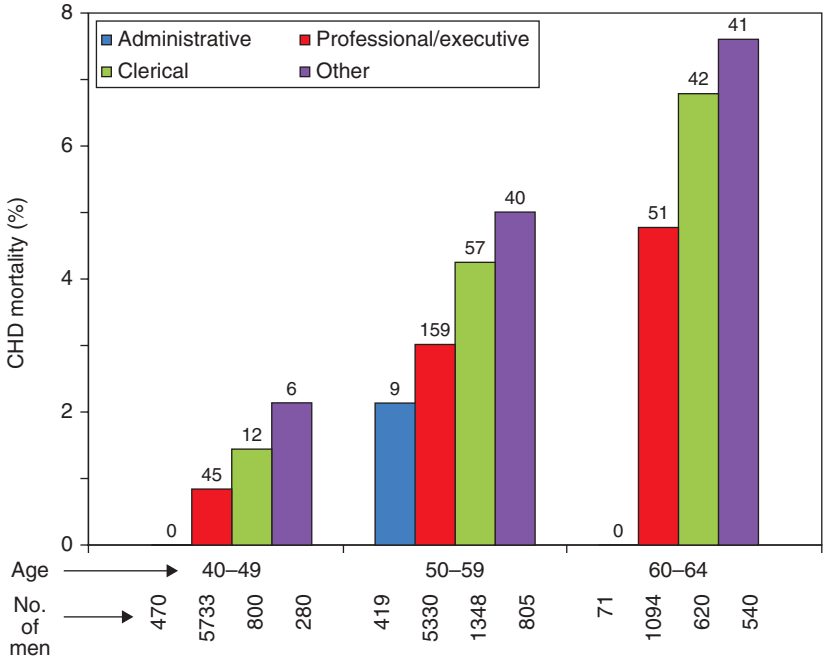

FIGURE 107–1. Coronary heart disease (CHD) mortality (and number of deaths) in 7.5 years by civil service grade and age. The figures on top of the histograms are the numbers of CHD deaths. Reproduced with permission from Marmot MG, Rose G, Shipley M, et al: Employment grade and coronary heart disease in British civil servants. *J Epidemiol Community Health*. 1978 Dec;32(4):244-249.[16]

myriad factors that constitutes social disadvantage, whereby the whole is greater than the sum of the parts in creating a stressful *social context* in which an individual is born, lives, and falls ill. We have now moved into an era in which researchers are teasing out the complexity of the multilevel effects of the range of social determinants of health, from individual characteristics to numerous aspects of the environment. Given the complexity of social context, there are methodologic challenges in establishing causality between the various factors and health status. Nevertheless, over the past 25 years, we have witnessed an explosion in research focused specifically on health disparities, and we now have a better understanding of the biology of disadvantage.

As part of this research endeavor, the Institute of Medicine (IOM), at the request of the US Congress, undertook a review of more than 100 studies in order to assess the extent of racial and ethnic disparities in health care, explore contributing factors, and recommend policies to eliminate the inequities. Published in 2002, the IOM report stated the following: "Racial and ethnic minorities tend to receive a lower quality of healthcare than non-minorities, even when access-related factors, such as patients' insurance status and income, are controlled. The sources of these disparities are complex, are rooted in historic and contemporary inequities, and involve many participants at several levels" and "studies of racial and ethnic differences in cardiovascular care provide some of the most convincing evidence of healthcare disparities."[9]

The IOM report received widespread media coverage and deepened national concern. In 2005, the WHO, acting on the global stage, set up an independent Commission on the Social Determinants of Health, with the mission to link knowledge to action and assist countries around the world in addressing health inequities. Although much has been done in the intervening years and progress has been made in some areas, the issue of racial and ethnic disparities remains a difficult and complex problem to address. According to the US Agency for Healthcare Research and Quality's 2014 National Healthcare Quality and Disparities Report, regarding the situation in the United States, "disparities in quality and outcomes by income and race and ethnicity are large and persistent, and were not, through 2012, improving substantially."[21] Over the past decade, few health disparities have been eliminated in the United States, despite the issue having been on the national agenda.[21,22]

THE MAJOR SOCIAL DETERMINANTS OF CARDIOVASCULAR DISEASE

Among the major social determinants of health are SES, race/ethnicity, sex, the environment (including social relationships, neighborhood physical and social environments, and work environment), and access to care (Table 107–1). There is a substantial body of literature on each of these social determinants of health and also on theories of how they interact to maintain health or contribute to illness. It is beyond the scope of this chapter to explore each in detail; salient points regarding each will be briefly explored in relation to the current status of cardiovascular health in the United States.

TABLE 107–1. Major Social Determinants of Health

- Socioeconomic status
  - Education
  - Employment and occupation
  - Income and wealth
  - Actual access to resources
  - Social ranking and privilege
- Race/ethnicity
- Sex
- Environment
  - Social relationships
  - Neighborhood physical environment
    - Exposures (eg, toxins, pesticides, biologic agents)
    - Availability and quality of food
    - Availability and quality of housing
    - Built environment (eg, walkability and natural spaces)
    - Services
  - Neighborhood social environment
    - Safety/level of violence
    - Cultural norms
    - Local institutions
  - Work environment
    - Job stress
    - Physical and chemical hazards
    - Organizational structure
    - Job insecurity
- Access to care[a]
  - Approachability
  - Acceptability
  - Availability and accommodation
  - Affordability
  - Appropriateness

[a]Access to care as defined in Levesque JF, Harris MF, Russell G. Patient-centered access to health care: conceptualising access at the interface of health systems and populations. *Int J Equity Health*. 2013;12:18.

Socioeconomic Status

One of the most studied and important social determinants of health is SES, which is defined as a "multidimensional concept comprising measures of resources such as income, wealth, and educational credentials, and the access to goods, services, and knowledge that these resources afford those who have them."[23] It is challenging to investigate SES, as it comprises a number of domains. Nevertheless, it has been most commonly measured using educational attainment, income, threshold poverty status, and/or occupational grade level. Decades of research have taught us that the effects of SES are substantial and occur at all levels of the socioeconomic gradient. Thousands of studies now document an association between higher educational attainment or higher income and better health and longevity. An international study of the United States and 11 other Western nations showed that in all countries total CVD mortality is higher among individuals with lower educational level or lower occupational class, although the magnitude of the association varied across countries.[24]

The effects begin early in life and extend across the lifespan. Children of parents of low SES—children who thus start out in life with few material or psychosocial resources—experience greater morbidity and mortality. A systematic review of the 40 studies revealed robust data that establish an association between parental SES, poor childhood circumstances, and increased CVD risk, although findings sometimes varied among specific outcomes, socioeconomic measures, and sex.[25,26] In part, the effect of low

SES in childhood is mediated through its effect on adult health behaviors and the subsequent development of conventional risk factors for CVD.[27,28] Health behaviors that are associated with CVD risk are more common among individuals in lower socioeconomic groups than those in higher socioeconomic groups (see later section, Health Behaviors).

SES is also related to, among other issues, the type of the neighborhoods in which people live and their work environments, as well as to insurance status and the ability to access health care. Over the course of the lifespan, there is a dynamic relationship between SES and health, whereby those in the higher socioeconomic groups have greater access to numerous resources, including economic, social, cultural, physical, and medical resources, that interact to promote health and well-being.

*Race/Ethnicity**

Racial and ethnic minority populations are disproportionately burdened with more illness, premature death, and disability, and often suffer higher mortality rates compared to whites.[10,29] It is CVD that accounts for the largest proportion of inequality in life expectancy between blacks and whites: in the United States, blacks are two to three times more likely to die of heart disease than whites.[3] Blacks and other ethnic minorities tend to have more CVD risk factors and a greater prevalence of disease, and they experience greater premature CVD death than whites.[30,31] Racial and ethnic minorities are less likely to have health insurance,[32] face greater barriers in accessing health care, and often receive lower quality care.[9,33] Even when minority patients have the same type of health insurance as whites, evidence reveals they tend to receive lower quality of care.[9,33] A number of studies have documented the race-based invasive procedural gap. Data from the CRUSADE† Quality Improvement and National Registry of Myocardial Infarction registries reveal racial and ethnic (as well as sex-based) differences in comorbidities, evidence-based therapies and procedures, and prolonged time to reperfusion.[31,34,35] For example, African American and Hispanic patients have been shown to have longer delays to reperfusion, with door-to-balloon times ≤ 90 minutes observed in 83% of white patients compared with 75% and 76% of black and Hispanic patients, respectively.[31] However, the gap may be narrowing; one study found that, although small differences in door-to-balloon times persist among different races/ethnicities, the proportion achieving door-to-balloon times ≤ 90 minutes has increased substantially for all patients over time.[35] Black patients have been found to be transferred more slowly to revascularization hospitals after acute myocardial infarction than white patients. One-year mortality rates for black patients with acute myocardial infarction were shown to be 12% to 35% higher than those for white patients, even after adjusting for SES, age, sex, comorbidity, and severity of illness.[36] Studies also show that blacks are less likely to receive longitudinal guideline-compliant care; they are less likely to have consistently controlled blood pressure or to achieve low-density lipoprotein treatment goals than non-Hispanic whites.[31,37-40]

SES, which varies considerably by race and ethnicity in the United States, contributes to these health disparities. Black and Hispanics are disproportionately represented among the lower socioeconomic groups and face numerous obstacles in gaining access to high-quality education, employment, adequate income, and housing. However, although SES across racial/ethnic groups explains some portion of observed health disparities, it does not account for all of it. Racial disparities in health persist at every level of SES. SES is only part of the multifaceted context that constitutes social disadvantage. The social construct of race and racism—prejudice, stereotyping, and discrimination—comprises multiple dimensions of social inequality and ongoing injustices that intersect and interact in complex ways, giving rise to powerful impacts on health and well-being.

Sex

CVD disease is the leading cause of death in women in the United States, and it kills more women than the next three leading causes of death combined.[3] Significant disparities exist in cardiovascular risk factors, treatment, and outcomes based on sex.[3] Scientific evidence shows that women receive less significant treatment for CVD risk factors,[41,42] are often not treated according to recommended guidelines for a number of CVD diagnoses,[43] have lower long-term adherence with statins[44] and antihypertensive medications,[45] are given significantly lower priority for emergent ambulance service than men,[46] undergo fewer invasive procedures (eg, percutaneous coronary intervention and bypass surgery),[47,48] are more likely to experience a delay in door-to-balloon times,[49,50] suffer greater in-hospital mortality before age 55 after myocardial infarction,[51,52] experience greater long-term mortality after myocardial infarction,[53,54] and are significantly less likely to be referred to cardiac rehabilitation.[55] Further, women continue to be underrepresented in clinical trials, and publications often lack sex-stratified analyses, which limits the ability to identify sex differences and provide evidence-based care that ensures safety and efficacy by sex.[47] (US legislation that requires sex-specific analysis is expected to improve these sex inequities in biomedical research.) Although biology may underlie some of these observed differences, sex bias is thought to play a substantial role in creating these health disparities.

It is important to note that sex intersects with other social determinants of health, most importantly, race and ethnicity. Almost 50% of African American women in the United States have some form of CVD.[3] Comparisons of the risk factor burden according to sex and ethnicity show that black women have the greatest burden of risk factors.[56] For example, they have a 46.1% prevalence of hypertension compared with 30.1% in non-Hispanic white women and 29.9% in Hispanic women,‡ and they are more likely to have metabolic syndrome than white women.[3] Black women are less likely to receive evidence-based therapies and have higher CVD mortality than white women (248.6/100,000 vs 188.1/100,000).[3]

Hispanics, the largest minority in the United States, have a higher prevalence of several cardiovascular risk factors than non-Hispanic whites. Notably, Hispanic women have twice the prevalence of diabetes as white woman (about 12% vs 6%) and often face the challenge of low SES and poor access to health care, and yet Hispanics have lower mortality rates than non-Hispanic whites. This has been called the "Hispanic paradox" and has been confirmed by recent cardiovascular data.[57] Further studies are needed to identify the mechanisms mediating this protective cardiovascular effect in Hispanics.

Clinicians need to recognize that there is compelling evidence regarding the ongoing sex disparities that powerfully impact cardiovascular outcomes in women, especially among specific subpopulations who are also burdened with racial and ethnic inequalities.

Environment

Social Relationships In a provocative article published in 1988 on the link between social relationships and mortality, the authors proposed

* Race and ethnicity are used as terms here to connote social constructs with little biological or genetic basis.

† Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines.

‡ Including men in the comparison, the statistics are as follows: In 2009 to 2012, the age-adjusted prevalence of hypertension was 44.9% and 46.1% among non-Hispanic black men and women, respectively; 32.9% and 30.1% among non-Hispanic white men and women, respectively; and 29.6% and 29.9% among Hispanic men and women, respectively.

a *causal* association and declared, "Social relationships, or the relative lack thereof, constitute a major risk factor for health—rivaling the effect of well-established health risk factors such as cigarette smoking, blood pressure, blood lipids, obesity and physical activity."[58,59] The body of evidence accumulated since then consistently shows that a dearth of social relationships is linked to the development and progression of heart disease.[60-63] Small social networks, poor functional support, loneliness, and/or a sense of poor emotional support all have been shown to increase the risk for cardiac events.[64,65] A gradient relationship has been observed between the degree of reduced social support and the likelihood of adverse cardiac events.[66]

A meta-analysis of 148 studies involving 308,849 participants from North America (51%), Europe (37%), Asia (11%), and Australia (1%) determined the extent to which social relationships influenced the risk for mortality. Investigators found that individuals with adequate social relationships experienced a 50% greater likelihood of survival compared to those with poor or insufficient relationships during an average follow-up time of 7.5 years.[59] The effect remained after controlling for age, sex, initial health status, follow-up period, and cause of death. Given the magnitude of the effect, the investigators make a compelling case for adding social relationship factors to the list of major conventional risk factors for morbidity and mortality, along with smoking, physical inactivity, poor nutrition, and obesity.

Although "social relationships" is a concept that is difficult to define concisely and various methods have been used to measure it, three major components are consistently evaluated: "(a) the degree of integration in social networks,[67] (b) the social interactions that are intended to be supportive (ie, received social support), and (c) the beliefs and perceptions of support availability held by the individual (ie, perceived social support)."[59] All three have been shown to be associated with morbidity and mortality, although they may exert their effects on health through different mechanisms, including cognitive, affective, and behavioral pathways. For example, one study[68] investigated interactions between social support and sleep in the prediction of inflammation in prehypertensive and hypertensive individuals at high risk for CVD. It found that social support moderated the association between sleep and circulating levels of both interleukin-6 and C-reactive protein, such that poor sleep appeared to confer a risk of increased inflammation only in those participants who also reported low social support. The same relationship was observed for tumor necrosis factor-α in women. Studies have also shown that the salutary—or deleterious—effects of social relationships start early in life. For example, one study found that greater emotional and instrumental support in childhood was associated with less biologic dysregulation in midlife, even after accounting for socioeconomic disadvantage in childhood and other potential confounders.[69]

Neighborhood Environment Over the past two decades, neighborhoods and residential areas have become an intense focus of research, because they have the capacity to affect individuals through various factors, including social influences, multiple aspects of the built environment, and potential exposures to myriad hazards.[70] Where one lives is strongly determined by socioeconomic position and race/ethnicity, and thus neighborhood is deeply interrelated with the other determinants of health and is an important contributor to health disparities. However, attributes of the neighborhoods themselves can promote and maintain health or promote illness and disease, independent of the socioeconomic position of individuals. The effects of these community-level factors often operate over the course of a lifetime, starting in childhood and lasting into old age. Today, the study of neighborhood health effects is multifaceted and complex, with investigative methodologies and techniques having become more sophisticated and nuanced as the field has developed.

In one of the seminal studies investigating neighborhoods and CVD, researchers examined the relation between characteristics of four neighborhoods in four different states and the incidence of coronary heart disease. After controlling for income, education, and occupation, data revealed that living in a disadvantage neighborhood was associated with a 70% to 90% higher risk of coronary heart disease in whites and a 30% to 40% higher risk in blacks compared with high-income persons in the most advantaged neighborhoods.[71] Other subsequent studies have found a similar association between neighborhood SES and cardiovascular health,[71,72] conventional risk factors for CVD including hypertension[73] and diabetes,[74] mortality after myocardial infarction,[75] and all-cause mortality.[76-79]

Other studies have explored how health behaviors may be influenced by place of residence. Poorer neighborhoods tend to have fewer health-promoting community resources, including healthy food options, parks and recreational facilities, built walkable areas, and accessible transportation. Compared to moderate- or high-income communities, the poorest neighborhoods have fewer supermarkets and fruit and vegetable markets but more liquor stores.[80] Adverse social environments are thought to influence health behaviors deleteriously.[81] Increasing evidence reveals the association between neighborhood built environment and health behaviors, such as physical activity levels[82,83] and eating patterns,[84-87] and obesity rates in the community.[88-90] Higher levels of crime add to the adverse social environment and may affect people's level of outdoor physical activity.[91,92]

Environmental exposure is an important but underappreciated risk factor for the development of CVD[93] and is a particularly salient issue for those living in low-quality neighborhoods. Individuals in highly urbanized, densely populated, and poor residential areas are exposed to a number of environmental health threats, including toxic chemicals, biologic agents, noise and congestion, and air pollution, which is now identified as the world's largest single environmental health risk.[94] The burgeoning field of environmental justice[§] research focuses on a number of critical issues, including proximity to potentially harmful locations and fair remediation procedures of hazardous sites. It also explores whether some populations face higher exposures to contaminants than others and whether exposure levels have larger impacts on some groups more than on others.[95] Given the widespread prevalence of environment exposures, policy interventions that target the reduction of such threats can have a substantial impact on cardiovascular health.

Work Environment A large body of literature substantiates that people with better jobs enjoy better health. Research over the last several decades has focused on the relationship between CVD health and a number of workplace factors, including the role of status in a hierarchical setting, the role of psychosocial stress on the job, the effects of physical and chemical hazards exposures in the workplace, the role of work organizational structure, and role of job insecurity and job loss in a changing global economic environment.[96] Also under intense investigation is whether the observed correlations are *causal*, and if so, via what mechanisms.

The most widely studied factor has been psychosocial work stress, which has been associated with CVD in a number of studies.[97-99] There are two main epidemiologic models of psychosocial job stress in the literature: job strain (high demands and low control) and effort-reward imbalance (high effort, low reward, and overcommitment). Both models have been shown to significantly predict myocardial infarction and CVD mortality.[100-103] The INTERHEART study, the largest case-control

[§] The US Environmental Protection Agency (EPA) uses "environmental justice" to refer to "fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies" (source: http://www.epa.gov/environmentaljustice/plan-ej/index.html).

study of its kind, compared 15,000 patients with myocardial infarction and 15,000 healthy controls[104] and found that job strain doubled the risk of coronary heart disease, with a stronger effect in men than women.[105] However, subsequent studies have found a smaller risk,[106] with similar effects between sexes.[107,108] A more recent meta-analysis of 13 published and unpublished cohort studies found that job strain is associated with a small, but consistent, increased risk (1.2-1.3 times) of an incident event of cardiovascular heart disease.[98] This association is apparent across strata of sex, age, SES status, and region, and after adjustments for SES status, as well as lifestyle and conventional risk factors. Another meta-analysis of seven cohort studies comprising 102,128 men and women showed that the risk of coronary artery disease was highest among subjects who reported both job strain and an unhealthy lifestyle; those with job strain and a healthy lifestyle had half the rate of disease.[109] These data suggest that people with job strain—notably hard to eliminate—may be able to substantially reduce their risk of coronary artery disease by adopting a healthy lifestyle.

Long working hours have also been implicated in the risk of CVD.[99] In two meta-analyses of published cohort studies, the relative risk of coronary heart disease was about 1.4 in employees working long hours compared to those working standard hours.[110,111] A systematic review and meta-analysis of published and unpublished data for almost 604,000 individuals found that working more than 55 hours per week was associated with an increase in risk of incident coronary heart disease (relative risk, 1.13) and incident stroke (relative risk, 1.33).[112] The researchers found a dose-response association for stroke.

Job insecurity and job loss have also been associated with increased risk of CVD. A meta-analysis of 13 cohort studies revealed a modest association between perceived job insecurity and incident coronary heart disease, partly attributable to poorer socioeconomic circumstances and less favorable risk factor profiles among people with job insecurity.[113] In a prospective cohort study of 13,451 US adults, researchers found that unemployment status, multiple job losses, and short periods without work are all significant risk factors for acute cardiovascular events. Risks for AMI were particularly elevated within the first year of unemployment (hazard ratio, 1.27; 95% CI, 1.01-1.60) but not thereafter. Results were robust after adjustments for multiple clinical, socioeconomic, and behavioral risk factors.[114]

Access to Care

Unequal access to health care is a key social determinant of health and one of the important drivers of health disparities. As of 2014, after the Patient Protection and Affordable Care Act's major coverage provisions went into effect, 32 million Americans still lacked health insurance,[115] with most of them disproportionately drawn from racial and ethnic minorities and living at the lowest income levels. Hispanics and blacks have significantly higher uninsured rates (20.9% and 12.7%, respectively) compared with whites (9.1%).[116] Data reveal that uninsured US adults are less likely to receive medical care, including screening for CVD risk factors.[117-120] US adults without health insurance coverage are, perhaps as a result, also less likely to have ideal cardiovascular health, as measured by seven factors (blood pressure, body mass index, cholesterol, fasting blood glucose, smoking status, physical activity, and dietary intake).[121] Numerous studies have found an association between lack of insurance and all-cause mortality.[122,123] Specifically, lack of insurance is associated with an increased risk of stroke and CVD death.[124]

However, insurance is only part of the equation. Even among those who are insured, there are disparities in the quality of health care according to income. Those at the lowest SES levels experience gaps in access to care and quality services. Clinicians are less likely to refer low-income patients for diagnostic testing and treatment for heart disease.[120,125-127] Compared with individuals with private insurance, Medicaid beneficiaries reported more barriers (unable to get through on telephone, unable to obtain appointment soon enough, long wait in the physician's office, limited clinic hours, lack of transportation) to timely primary care and had higher associated emergency room utilization.[128] Barriers to specialty care exist as well. A study of community health centers revealed that referrals to off-site specialty services are frequently needed, yet medical directors reported major problems obtaining access to specialized medical and mental health services for uninsured patients and Medicaid recipients.[129] Given the structural barriers in the health care system, expanding Medicaid eligibility or other forms of insurance coverage alone is insufficient to improve health care access for disadvantaged groups.[130]

Other barriers include lack of proximity to heart centers, transportation issues, lack of flexibility in work schedules, low Medicaid payment rates, health literacy issues, language and cultural barriers, patient beliefs, and perceived racial bias. A review of the literature on the effects of interpersonal and institutional racism and discrimination occurring within health care settings revealed that up to 52% of African Americans, 13% of Latinos, and 6% of whites reported receiving biased treatment based on their race or ethnicity.[131] Health care providers' racial and ethnic attitudes are a factor in creating health disparities. According to the IOM's *Unequal Treatment* report, "research to date demonstrated that health care providers' diagnostic and treatment decisions, as well as their feelings about patients, are influenced by patients' race or ethnicity and stereotypes associated with them . . . [al]though myriad sources contribute to these disparities, some evidence suggests that bias, prejudice and stereotyping on the part of healthcare providers may contribute to differences in care."[9] Studies reveal that clinicians, similar to the general population, display substantial bias and prejudice in their implicit (unconscious) attitudes.[132-134]

The sources of disparities embedded in the health care system are complex and involve participants and factors that operate at many levels of the system. A comprehensive, multilevel strategy is needed to eliminate health care disparities.

HOW DOES SOCIAL DISADVANTAGE MEDIATE THE DEVELOPMENT OF CARDIOVASCULAR DISEASE?

We have presented evidence in this chapter that clearly establishes the strong correlation between social disadvantage and ill health. The central question, then, is how does social disadvantage mediate the development of disease? In other words, what is the biology of disadvantage?[20] Based on accumulating evidence, myriad investigators have proposed a number of different mediating pathways by which numerous social factors interact to produce poor health outcomes. Figure 107–2 shows a simplified model of how personal characteristics (race, ethnicity, sex, and SES) may interact with a variety of social stressors and environmental factors to influence health behavior, psychological reactions, and biological substrates, which, in concert with other factors such as access to health care, ultimately determine health outcomes.

PSYCHOSOCIAL FACTORS

Researchers have come to appreciate the role that psychosocial risk factors play in mediating CVD. The emerging field of behavior cardiology has divided psychosocial factors into two broad categories, emotional factors and chronic stressors: "Emotional factors include affective disorders such as major depression and anxiety disorders as well as hostility and anger. Chronic stressors include factors such as low social support, low SES, work stress, marital stress, and caregiver strain."[65] A vast body of literature now links emotional states—depression, anxiety, and hostility/anger—with increased cardiovascular risk, a

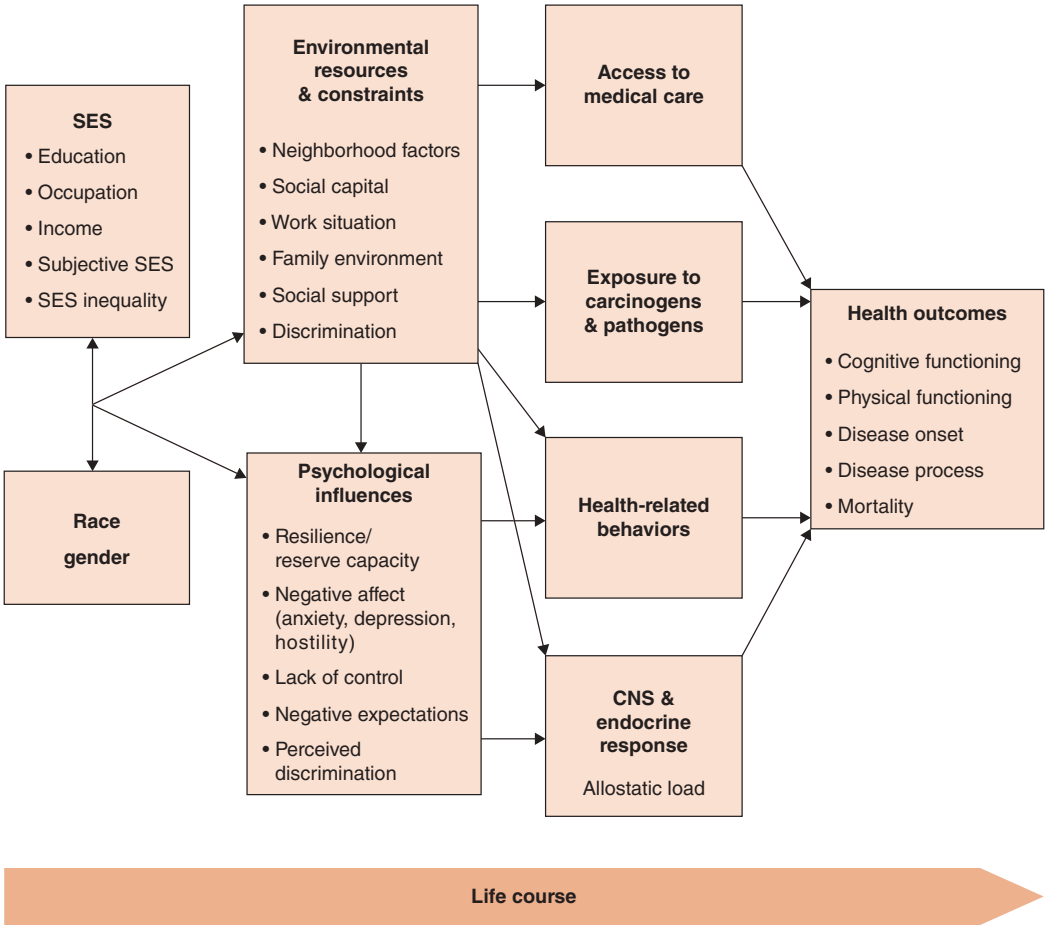

FIGURE 107–2. Pathways linking socioeconomic status (SES) to health. CNS, central nervous system. Reproduced with permission from Adler NE, Stewart J: Health disparities across the lifespan: Meaning, methods, and mechanisms. *Ann N Y Acad Sci*. 2010 Feb;1186:5-23.[20]

worse cardiometabolic profile, adverse outcomes, and mortality.[135,136] A meta-analysis of the association between perceived stress and incident CHD found that high perceived stress is associated with a moderately increased risk of incident CHD.[137]

MULTIPLE RISK EXPOSURE

One proposed pathway that may explain the link between social determinants and health is the concept of multiple risk exposure.[138] Socially disadvantaged individuals are particularly exposed to multiple, clustered psychosocial and physical stressors, either sequentially or simultaneously, while concurrently having fewer resources to cope. The stressors that accompany deprivation, many of them discussed earlier, include adverse circumstances in childhood; low educational attainment; poverty, financial worry, and low social status; racial discrimination; poor housing; work strain and job insecurity; crowded and unsafe neighborhoods; exposure to toxins, pollutants, noise, and congestion; early pregnancy; family conflict and divorce; incarceration; and lack of quality health care, among others. The frequency and intensity of exposure to these stressors and related emotional responses are thought to constitute the primary pathway of how social disadvantage is biologically linked to CVD. Evidence reveals a strong dose-response relationship for most psychosocial risk factors, with data suggesting that adverse clinical effects may begin to occur with even minimal levels of distress.[66] A meta-analysis of 10 large, community-based cohort studies, each of which assessed psychological distress by using the 12-item General Health Questionnaire, found that even minor elevations in General Health Questionnaire-12 scores were associated with a 25% increase in cardiac mortality.[139]

ALLOSTATIC LOAD AND CHRONIC STRESS

Allostatic load (AL) is a useful heuristic model that helps conceptualize how chronic stress drives pathophysiologic mechanisms. Cumulative chronic stress is thought to lead to long-term dysregulation of allostasis, through activation of the sympathetic nervous system and hypothalamic-pituitary axis, which promotes maladaptive wear-and-tear on the brain and body that, in turn, compromises resiliency.[140] Evidence is accumulating that shows individuals of low SES have higher AL scores (indicating greater dysregulation and increased vulnerability to disease) than individuals in high SES groups. One investigation studied AL scores based on 10 biomarkers and examined cardiovascular/diabetes-related mortality disparities between blacks and whites. Researchers found that black men and women had higher AL scores than whites, and they concluded that AL burden partially explains higher mortality among blacks, independent of SES and health behaviors.[141] This may be one of the mechanisms through which racism and discrimination exert their destructive effects. Discrimination is a source of acute and chronic stress for many oppressed group members.[142-145]

Another study looked at whether greater life-course SES adversity experience was associated with higher scores on a multisystem AL index of physiologic function in adulthood.[146] Based on 24 biomarkers from 7 different physiologic systems, researchers found that greater SES adversity experience at each phase of, and cumulatively across, the

life course was associated with higher AL scores, even when adjusted for a wide array of health status, behavioral, and psychosocial factors.

SES adversity experience may accumulate throughout life and have a negative impact on multiple organ systems in adulthood, especially the cardiovascular system.[146-148] Numerous studies in the literature now document the deleterious effects of chronic stress on the cardiovascular system, including activation of the inflammatory response, endothelial dysfunction, thrombosis, vascular hyperactivity, and metabolic disturbances.[149-153]

HEALTH BEHAVIORS

Deleterious health behaviors (eg, smoking, inactivity, poor diet, medication nonadherence) increase the risk of CVD. Correspondingly, alterations in these behaviors reduce the risk of developing the disease and its associated morbidity and mortality.[3] A body of literature also firmly establishes that socioeconomic gradients exist for major health behaviors over the course of the lifespan. That is, smoking, inactivity, poor diet, and medication nonadherence tend to be more prevalent among people in lower SES groups,[154-159] and these individuals, in turn, tend to have more cardiovascular risk factors, including hypertension, lipid abnormalities, obesity, insulin resistance, and diabetes mellitus.

For example, tobacco use—the health behavior that accounts for the greatest number of premature deaths, 480,000 in the United States alone in 2014[160]—was equally prevalent among all socioeconomic groups in the United States 50 years ago but now is more common among people with less education and lower incomes.[161] According to the most recent American Heart Association statistics, between 2003 and 2012, obesity decreased among those of higher SES but increased among those of lower SES.[3]

Children in lower socioeconomic groups have a steeper weight gain trajectory from birth, with a strong socioeconomic gradient in the prevalence of child and adult obesity.[162] It appears the die is cast early in life, as childhood SES has been shown to account for both the uptake of unhealthy behaviors and subsequent health risk in the adult years. For example, a long-term British cohort study of 2132 individuals that determined mortality risk between the ages of 26 and 66 found that childhood and adult SES accounted for a significant portion of health inequalities observed in mortality risk. The investigators concluded that the combination of material and psychosocial conditions in childhood was almost as powerful as smoking in accounting for the inequality in adult mortality seen in the cohort. These effects of early life circumstances were seen to continue far into adulthood and to influence mortality risk by their impact on smoking and other health behaviors.[163]

Health behaviors vary according to race and ethnicity as well as SES. Compared with non-Hispanic whites, nonwhite groups—blacks, Hispanics, and Native Americans—tend to have more unfavorable health behaviors, including smoking, physical inactivity, unhealthy eating habits, obesity, medication nonadherence, and lower health care use.[153,164-170] For example, non-Hispanic blacks (41.4%) and Hispanics (42.9%) are less likely to meet current aerobic physical activity guidelines than non-Hispanic whites (53.4%).[3] High rates of obesity are found among all racial/ethnic groups, but in particular among American Indians and Alaska Native populations, of whom 39.4% are obese compared with 24.3% of non-Hispanic whites.[171] Numerous studies have documented that nonwhites are significantly less likely to adhere to CVD medications, including statins, antihypertensives, and heart failure regimens.[44,172-176] A number of factors, including patient self-efficacy and depression, patient-provider communication, trust in physicians, and health care system–related factors, have been shown to be associated with medication nonadherence.[177-179] Furthermore, studies have shown that medication nonadherence mediates the association between ethnicity and CVD outcomes.[180]

Differences in health behaviors are seen among racial and ethnic minorities. This presents the opportunity to focus interventions to promote behavioral change among high-risk populations. However, although differences in health behaviors account for some of the observed socioeconomic gradient in CVD, they do not account for all of it.

TAKING ACTION ON THE SOCIAL DETERMINANTS OF HEALTH

If the major determinants of health are socially driven, then policy initiatives—both health policy and wider social and economic policy—are critical to improving health outcomes and reducing health disparities. In response to the continuing challenge posed by the reality of entrenched health disparities, broad, intensive, well-coordinated efforts are now under way to address this most urgent and complex issue. There is still a profound mismatch between the evidence that documents the human toll and economic burden posed by CVD and the efforts aimed at addressing it.[181] More must be done to galvanize the effort.

Comprehensively speaking, initiatives to address the CVD epidemic must entail addressing individual-level actions, health care systems, and population-wide efforts. Proximate risk factors for CVD (genomic, biologic, and behavioral) must be addressed at the individual level, and diagnosis and treatment of CVD must always receive high priority. Within this context, individual-level approaches should target high-risk individuals, especially those who are socially disadvantaged. But individual-level approaches are not enough. Public policy initiatives are needed that focus on improving access to health insurance. Further, barriers to access to care, which are multiple, need to be addressed systemically across the health care system. Evidence suggests that performance measure-based quality improvement, provider cultural competency training, team-based care, and patient education are effectively strategies in mitigating disparate CVD care and may improve outcomes.[31] The American College of Cardiology's Coalition to Reduce Racial and Ethnic Disparities in Cardiovascular Disease Outcomes (CREDO) is predicated on these strategies. CREDO seeks to provide cardiologists and other clinicians who treat patients with CVD with evidence-based tools and information to reduce health disparities. Although access to medical care and quality of treatment are critical, it has been estimated that only 10% of premature mortality is due to shortfalls and failures of health care.

Public policy needs to address the social, environmental, and economic conditions that contribute to the development of illness. Two broad types of policies will make a difference in promoting health and reducing disparities: (1) policies that reduce inequalities between the socioeconomic classes, and (2) policies that buffer the adverse consequences of living at the lowest socioeconomic levels.[182] Policies that reduce inequalities include those that address educational attainment, job training, income and occupational status, and wealth distribution. Policies that buffer the adverse consequences of low SES include those that address affordable housing, the built environment, workplace issues, occupational safety, exposure to toxins, and interventions that promote healthier behaviors. The American Heart Association (AHA) has endorsed changing the social context so that individuals will make healthy decisions by default. In the AHA's view, this shift potentially has the greatest impact on population-wide health promotion and risk reduction.[5] Societal-level approaches also include public policies aimed at the agriculture, food, and tobacco industries, as well as at changes in urban planning and efforts to contain environmental pollution. Future research is needed to discover which of the social factors can be modified, as well as how findings can best be formulated into policies that have the greatest impact on promoting health, preventing CVD and reducing disparities in the most disadvantaged populations.

Importantly, many public and private actors are engaged in addressing the social determinants of health; the US federal government, state governments, many foundations, nonprofit and community-based organizations, and a number of professional medical societies have initiated programs to reduce health disparities. Although it is beyond the scope of this chapter to enumerate the various initiatives under way, of note are the activities of the US federal government. The US Department of Health and Human Services' (DHHS) Office of Minority Health, established in 1986, is charged with improving the health of racial and ethnic minority populations through the development of health policies and programs to eliminate health disparities. The Affordable Care Act of 2010[183] extended the reach of this federal initiative by establishing Offices of Minority Health within six federal agencies.** The Affordable Care Act also elevated the National Institute on Minority Health and Health Disparities (NIMHD) to an institute level at the National Institutes of Health. The mission of NIMHD is to lead scientific research to improve minority health and eliminate health disparities. To accomplish this, NIMHD (1) plans, coordinates, reviews and evaluates minority health and health disparities research and activities of the National Institutes of Health; (2) conducts and supports research in minority health and health disparities; (3) promotes and supports the training of a diverse research workforce; (4) translates and disseminates research information; and (5) fosters innovative collaborations and partnerships.[184]

In 2011, the DHHS published its "Action Plan to Reduce Racial and Ethnic Health Disparities."[185] The goals of the plan are to (1) transform health care; (2) strengthen the nation's health and human services infrastructure and workforce; (3) advance the health, safety, and well-being of the American people; (4) advance scientific knowledge and innovation; and (5) increase the efficiency, transparency, and accountability of DHHS programs. Figure 107–3 shows the overarching

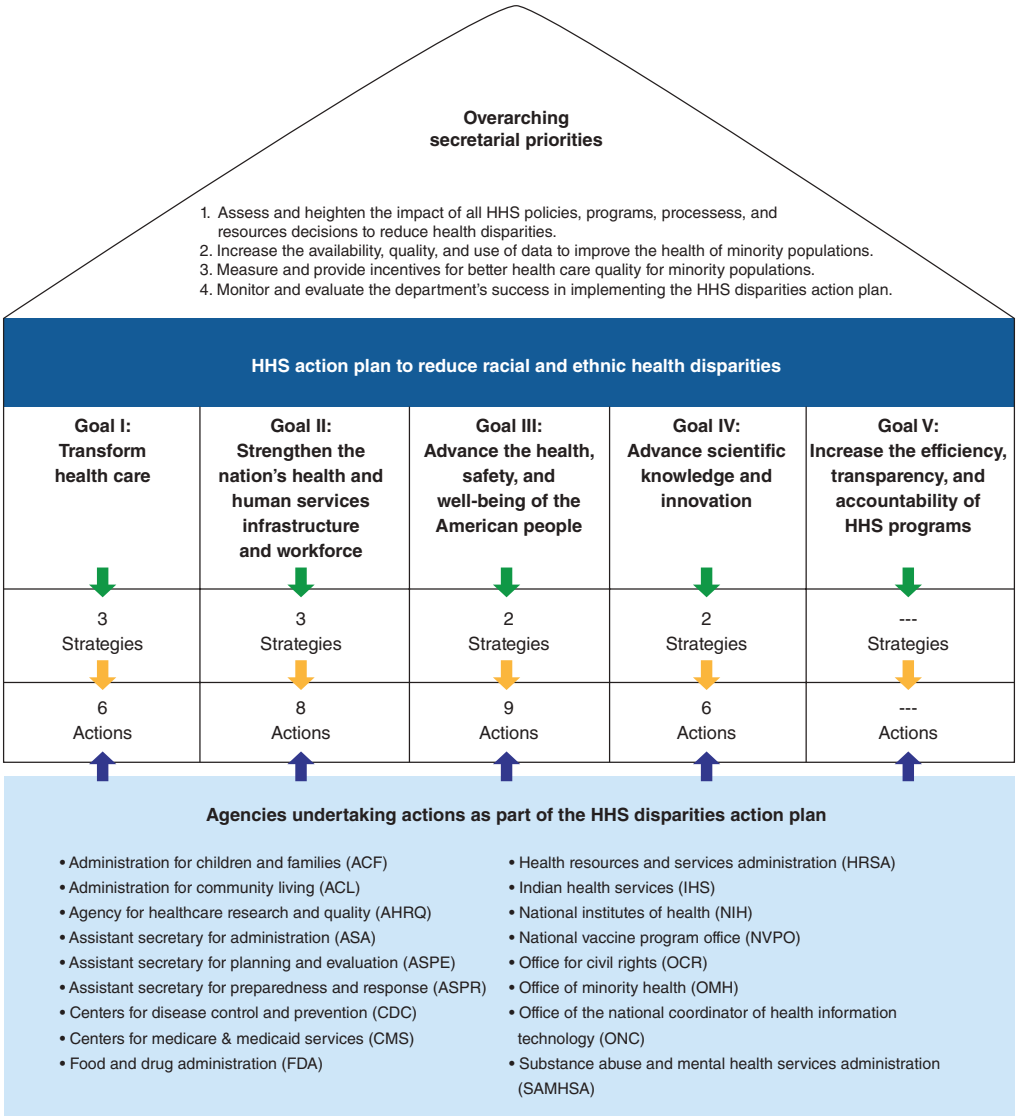

FIGURE 107–3. Department of Health and Human Services (HHS) Disparities Action Plan to reduce racial and ethnic health disparities. Reproduced with permission from US Department of Health and Human Services, Office of the Secretary, Office of the Assistant Secretary for Planning and Evaluation and Office of Minority Health.[185]

**The six agencies are the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Health Resources and Services Administration, the Centers for Medicare and Medicaid Services, and the Substance Abuse and Mental Health Services Administration.

priorities and goals of the DHHS Disparities Action Plan. Table 107–2 enumerates the plan's strategies. The DHHS Disparities Action Plan was developed in concert with the National Partnership for Action's (NPA) *2011 National Stakeholder Strategy for Achieving Health Equity* (available at http://minorityhealth.hhs.gov/npa). The NPA Stakeholder Strategy, which proposes a comprehensive, community-driven approach to reduce health disparities, resulted from a public-private collaboration that solicited broad community input with the assistance of state and local government and federal agencies. It reflects the commitment of thousands of people across the country representing myriad sectors. The DHHS Disparities Action Plan builds on the goals and objectives previously articulated in Healthy People 2020 (available at http://www.healthypeople.gov/) to reduce health disparities, and it leverages a number of important provisions of the Affordable Care Act and other cutting-edge DHHS initiatives.[186]

TABLE 107–2. Goals and Strategies of the Department of Health and Human Services (HHS) Action Plan to Reduce Racial and Ethnic Health Disparities

Goal I: Transform Health Care

1. Reduce disparities in health insurance coverage and access to care.
2. Reduce disparities in access to primary care services and care coordination.
3. Reduce disparities in the quality of health care.

Goal II: Strengthen the Nation's Health and Human Services Infrastructure and Workforce

1. Increase the ability of all health professions and the healthcare system to identify and address racial and ethnic health disparities.
2. Promote the use of community health workers and promotoras.
3. Increase the diversity of the healthcare and public health workforces.

Goal III: Advance the Health, Safety, and Well-Being of the American People

1. Reduce disparities in population health by increasing the availability and effectiveness of community-based programs and policies.
2. Conduct and evaluate pilot tests of health disparity impact assessments of selected proposed national policies and programs.

Goal IV: Advance Scientific Knowledge and Innovation

1. Increase the availability and quality of data collected and reported on racial and ethnic minority populations.
2. Conduct and support research to inform disparities reduction initiatives.

Goal V: Increase Efficiency, Transparency, and Accountability of HHS Programs

1. Streamline grant administration for health disparities funding.
2. Monitor and evaluate implementation of the HHS Disparities Action plan.
3. Goal-level disparities monitoring and surveillance: annually track progress on measures selected from multipurpose national data systems such as population-based surveys to track progress.
4. Strategy-level evaluation: develop an evaluation plan for relevant actions within the HHS Disparities Action Plan.
5. Action-level monitoring: monitor agency and office progress in completing actions within the HHS Disparities Action Plan.

Reproduced with permission from US Department of Health and Human Services, Office of the Secretary, Office of the Assistant Secretary for Planning and Evaluation and Office of Minority Health. *HHS Action Plan to Reduce Racial and Ethnic Health Disparities*. Washington, DC: Office of the Assistant Secretary for Planning and Evaluation; 2011.

CONCLUSION

CVD is the leading cause of death worldwide, including in the United States. Epidemiologic trends document enduring patterns of inequalities. Complex interrelated social factors drive these inequalities and the resulting health disparities. But health disparities are neither inevitable nor immutable.[187,188] In our efforts to reduce the profound human toll and vast economic burden posed by CVD, we urgently need to broaden our notion of what constitutes "intervention." Focusing on health as a problem of the individual, as clinical medicine does, is insufficient. Heath care providers and organizations need to further extend their responsibility for reducing disparities, and specifically target high-risk populations with culturally sensitive interventions. We must continue to examine what has been called the "causes of the causes,"[189] and develop evidence-based public policy—including health, social, development, and economic policy—that prioritizes the social determinants of health. In the end, this will not only have major ramifications on the health status of vast populations around the world and reduce morbidity and premature mortality, especially from CVD, but it will also drive development and prosperity across the globe and address one of the major social justice issues of our time.

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CHAPTER 108

WOMEN AND ISCHEMIC HEART DISEASE: AN EVOLVING SAGA

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INTRODUCTION

Throughout the 20th century, coronary heart disease (CHD) was viewed as predominantly a problem of middle-aged men, and little information was available regarding its impact on women. Recent decades have witnessed an emerging interest in CHD in women, with consequent performance of research studies and the acquisition of data specific to women. There now exists a burgeoning evidence base on sex differences in the presentation, diagnostic evaluation, management, and clinical outcomes for women as compared with men with suspected and known ischemic heart disease (IHD).[1-8] This evidence base has evolved rapidly over the past several decades but remains incomplete with regard to understanding the biologic basis for sex differences, distinct pathophysiologic alterations, and variability in treatment effectiveness, which contribute to the largely elevated risk for morbid and fatal outcomes related to cardiovascular disease (CVD) among women as compared to men.

Historic evidence is replete with documentation of under-referral, -testing, and -treatment of women.[9,10] For women, outcomes are further impacted by delays in seeking care.[11] The ensuing impact of reduced financial means and other socioeconomic factors contribute to higher risk status for women. Although recent improvements have been reported, the lack of public awareness has resulted in an insufficient knowledge regarding CVD in women.[12] The gamut of cultural, social, and financial differences among women profoundly impact prompt diagnosis, clinical management, and outcomes of at-risk women. These factors result in women presenting older, with a greater risk factor burden and more comorbidity, and often with more frequent and untreated symptom burden. Much of the earlier sex bias data[13] are highly relevant to the practices of care for women today. This early evidence prompted more recent explorations regarding biologic and clinical differences between women and men, revealing insight into varying pathophysiologic mechanisms between the sexes. Explorations as to varying pathophysiology, particularly in atherosclerosis development and the clinical sequelae of IHD, remain a focus of ongoing research activities.

This chapter will highlight recent research findings on IHD diagnosis, management, and clinical outcomes for women with stable and acute IHD. Women have greater CVD mortality and report more disability and decreased quality of life. They present later and with more comorbid conditions yet receive less medical therapies and fewer interventions than men, contributing to sex-specific gaps in outcomes. These differences probably reflect both lingering diagnostic and treatment disparities and underlying biological differences. The underuse of guideline-based preventive and therapeutic strategies for women is a substantial contributor to their less favorable coronary outcomes, but the spectrum of sex differences likely reflects a combination of biology and bias.

The term IHD will be used in this chapter to identify myocardial ischemia as the culprit for symptom burden among women. The term IHD is advantageous for women because of their lower prevalence of anatomic obstructive coronary artery disease (CAD), despite greater myocardial ischemia and associated mortality when compared to men.[14-16] Although obstructive atherosclerotic disease of the epicardial coronary arteries remains the major cause of acute myocardial infarction (MI) for women, symptomatic females with myocardial ischemia remain at risk even with no or minimal epicardial CAD.[17] Sex differences in nonobstructive CAD are an area of active investigation. Plaque characteristics also differ for women, with recent data suggesting a greater role of microvascular disease and nonobstructive CAD in the pathophysiology of coronary events in women.[18] Other contributors to myocardial ischemia include coronary vasospasm, microvascular disease, endothelial dysfunction, and intramural coronary atherosclerosis, (ie, atherosclerotic plaque in the luminal wall with external remodeling).[4,19-21] The paradox of acute coronary events in women is that despite older age and a greater risk factor and anginal symptom burden with consequent morbidity and mortality, women have less severe obstructive CAD at angiography.[18] A paradigm shift must occur from the consideration of anatomic obstructive CAD to IHD. Earlier risk detection must resolve the less intensive patterns of care that is more often common among women relative to men, which likely contributes to the sex-based mortality gap.[22]

DEFINING SEX DIFFERENCES

Sex differences are biologic differences, such as genetic and hormonal, increasingly acknowledged to exist even at the cellular level.[6,23-25] Sex differences are all encompassing in IHD including anatomic (eg, smaller

coronary blood vessels), physiologic (eg, higher resting coronary blood flow), age/hormonal, comorbid, and other varied risk factors uniquely impacting women. For definitional purposes, the term *gender* relates to self-identification, behavior, and its interaction with societal expectations and roles that impact all facets of IHD detection, risk, and treatment, which also uniquely influence women when compared to men.

CARDIOVASCULAR DISEASE EPIDEMIOLOGY AND DISPARITIES IN CARE FOR WOMEN

IHD is the leading cause of morbidity, mortality, and disability in US women.[26] Only 18% of patients with MI had antecedent angina, with this feature being more common in women than in men.[27] Chronic stable angina affects 7.8 million patients in the United States, with over half of the patients being women.[28] Women have a higher age-adjusted prevalence of angina, the main symptom of IHD. Approximately 15.5 million Americans live with CAD, a disease that affects over 5% of adult women and nearly 8% of adult men. In addition to substantial morbidity and mortality, there is a heavy economic burden associated with IHD.[29] At all ages, even among elderly individuals, women have a lesser prevalence of CAD. However, once clinical manifestations of IHD develop, women have a less favorable outcome than their male peers in the setting of stable IHD, acute coronary syndromes (ACS), and coronary revascularization.

Importantly, over the last decade, mortality rates from CVD have declined nearly 30% (Fig. 108–1).[30,31] During this time, mortality has also declined for women, in large part due to increased awareness from public health campaigns, focused clinical research on sex-related differences, and the application of guideline-directed strategies of care.[32] CVD is the leading cause of death for nearly one in every four women.[33] However, declines for women, across all ages, are far less than those reported for men (Fig. 108–2).[8] From the National Inpatient Sample, declines in fatal MI were observed for women yet mortality remained higher for women age < 55 years as compared to similarly aged men.[34] Moreover, a recent population survey noted an increasing MI prevalence among midlife women, whereas declines were observed among men.[35] Hospitalization rates for MI in women ≤ 55 years increased and their excess risk of 30-day mortality persisted, in contrast to the overall MI hospitalization and 30-day mortality rates which significantly declined in women in general and in men.[36A] More than one-quarter of a million women are hospitalized each year for an ACS.[30] For women hospitalized with acute MI, reports document longer length of stays, elevated in-hospital mortality, higher readmission rates, and persistently higher death rates through 5 to 10 years of follow-up when compared to men.[36B-41] From an analysis of international, randomized trials in ACS, 30-day mortality was higher among women with ST-segment elevation MI (STEMI) but lower for women presenting with unstable angina or non–ST-segment elevation MI (NSTEMI).[42] Moreover, MI hospitalization rates remain lower,[43] whereas rates of undocumented MI[44] are higher, for women as compared to men. Sex differences for in-hospital outcomes related to ACS have been attributed to variability in comorbidities, clinical presentation, and the severity and extent of CAD, yet these observed patterns persist over decades of treatment advances.[42]

The burden of de novo and persistent chest pain among women impacts heavily on the clinical evaluation of IHD. There are varying symptom characteristics unique to women, including less typical, exertional chest pain than is reported for men.[45] This confounds and complicates the index evaluation, which may contribute to the reported high rates of persistent symptoms among women—a rate two-fold higher than that of men.[46-49] Men and women do share common qualities of their symptom profile including more angina that is stress related; with men, angina is often related to physical exertion, whereas women more often have emotional provocation.[45] Today, the typical symptom profile among women includes more frequent symptoms often occurring at rest, more persistent angina, reduced physical work capacity, and reduced quality of life.

Sex-related differences in morbid and fatal outcomes have persisted over the past several decades, despite advances in treatment and guideline-directed management of IHD.[43] The evidence consistently reports that progressive declines in CVD risk are documented for women,

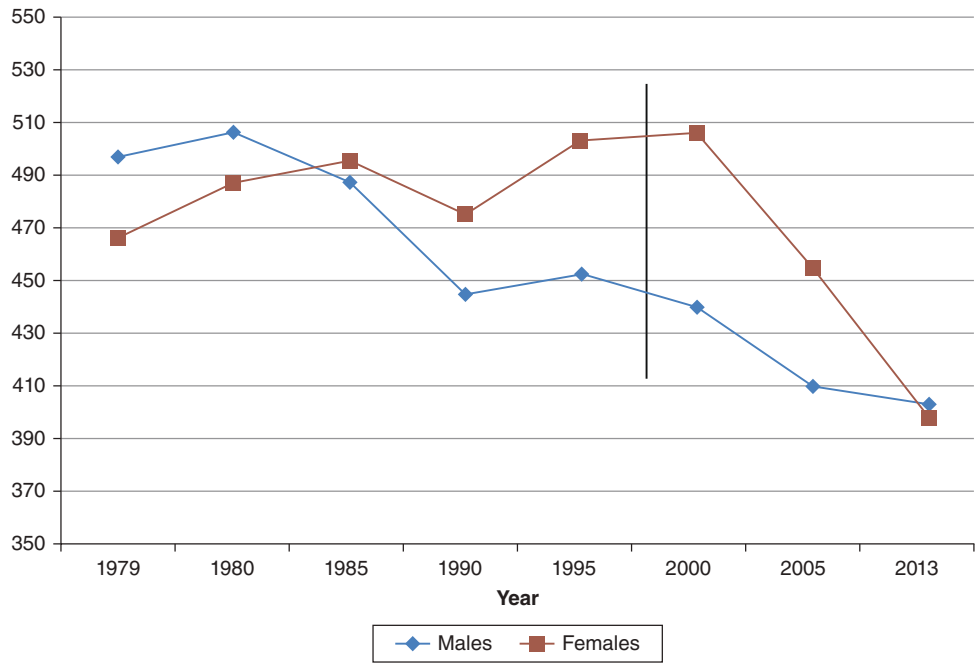

FIGURE 108–1. Cardiovascular disease mortality trends for males and females, United States: 1979–2013. Reproduced with permission from the National Center for Health Statistics (NCHS).

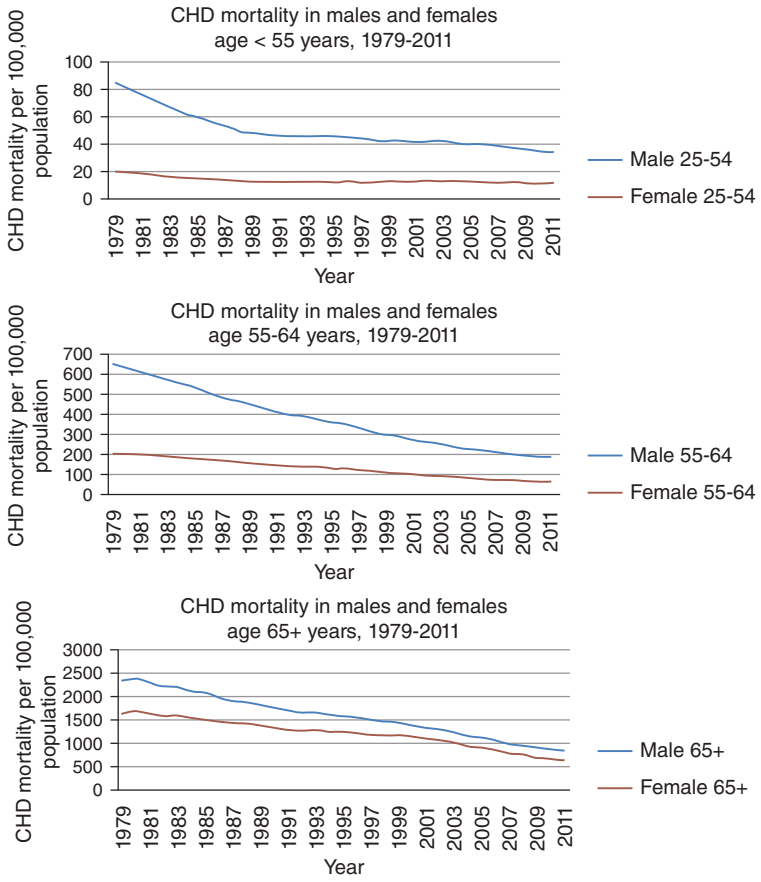

FIGURE 108–2. Trends in age-specific coronary heart disease (CHD) mortality from 1979 to 2011 across age subsets of < 55, 55 to 64, and ≥ 65 years. Reproduced with permission from Wilmot KA, O'Flaherty M, Capewell S, et al: Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. *Circulation*. 2015 Sep 15;132(11):997-1002.[8]

yet females remain at high risk and, in many instances, with elevated event rates when compared to men. A synthesis of this data remains challenging as older data may be less relevant to contemporary CVD practice. Of note, more recent evidence supports that black women consistently have a high prevalence of risk factors and are at particularly high risk of CVD events when compared to white women.[15,34,50,51] These disparities in detection and treatment of CVD impact large sectors of our female population who are now characterized as a targeted priority population for appropriate care consistent with guideline-directed strategies.[51] Expanding on disparities of care, there is an extensive literature on reduced use of risk-factor modifying and anti-ischemic treatments, less noninvasive and invasive procedural use, less coronary revascularization, and reduced referral to cardiac rehabilitation and other lifestyle recommendations.[10,12,13,47,52-54] This less intensive pattern of care for women has an unknown but sizeable impact on not only their quality of care but also worsening clinical outcomes. In this chapter, we will highlight contemporary data on sex-related differences in IHD and synthesize variable patterns in the published literature related to women as compared to men with stable or acute IHD.

PATHOLOGIC AND PATHOPHYSIOLOGIC BASIS FOR SEX DIFFERENCES IN ISCHEMIC HEART DISEASE

Pathologic data have revealed varied atherosclerotic plaque characteristics as precursors for a fatal cardiac event including plaque rupture, erosion, and calcified nodules, findings that were also confirmed with invasive methods.[55-57] This evidence supports common mechanisms for acute events uniquely different for women and men. For men, plaque rupture is common and is defined within the culprit lesion as a thin fibrous cap with a large thrombogenic lipid-rich necrotic core, expansive remodeling, and extensive plaque burden.[56-63] Although plaque rupture explains 76% of fatal coronary events among men, only half of events in women were due to plaque rupture.[64] By comparison, plaque erosion is more common in women and is defined as being more fibrous ($P < .001$), with a smaller plaque burden ($P = .003$) and reduced positive remodeling ($P = .003$).[58,65-70] These data support sex-specific differences in atherosclerotic plaque, which may underlie the varying presentation and clinical outcome differences that are commonly observed in ACS registries and treatment trials. Moreover, the varying plaque features may also require future development of sex-specific targeted treatment strategies that have yet to be elucidated in current stable or acute IHD trials.

Given that MI in the absence of obstructive CAD is more common among younger ages and among women,[42,71] the rarity of plaque rupture in premenopausal women has been proposed to suggest a protective effect of estrogen.[72] From 7% to 32% of women with documented ACS have no angiographically obstructive CAD, such that their MI may be a result of plaque rupture and ulceration, plaque erosion, vasospasm, and embolism.[42,73] Despite the high prevalence of nonobstructive CAD, plaque disruption is evident in almost 40% of women with ACS.[29] In a recent report addressing mechanisms of MI among women without obstructive CAD, there was evidence of plaque erosion with distal embolization of atherosclerotic debris and/or vasospasm as potentially etiologic. Plaque rupture and ulceration were common in women with MI in the absence of obstructive CAD.[73]

Contemporary in vivo invasive imaging of atherosclerotic plaque has similarly compiled evidence on sex-specific patterns that are concordant with previously described pathologic findings.[61,74] Culprit plaques identified using intravascular ultrasound (IVUS) include those with features of echolucency (ie, with a lipid-rich necrotic core), large plaque burden, and positive remodeling.[59,61,75,76] The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) registry included 697 patients (n = 168 women) who underwent three-vessel IVUS and were followed for approximately 3 years for documentation of major CAD events.[77] From PROSPECT, culprit lesions more often had a higher plaque burden (≥ 70% of the cross-sectional area), smaller minimal luminal area, and thin cap fibroatheroma (all $P < .001$).[77] In a secondary analysis from PROSPECT, women less often had documented plaque rupture ($P = .002$).[55] These data are consistent with prior pathologic data supporting varying atherosclerotic plaque features in women as compared with men, although the evidence base is limited and less defined as to the role of arterial size, physiologic impairment, and other factors that may further contribute to sex-specific outcome differences.

CORONARY PREVENTION: TRADITIONAL AND NONTRADITIONAL CORONARY RISK FACTORS

The American Heart Association's (AHA) CVD prevention guidelines for women, updated in 2011,[53] highlighted that substantially different approaches were needed to assure adequate preventive interventions for women. This relates both to nontraditional atherosclerotic CVD risk factors that are unique to or predominant in women and to the fact that

traditional atherosclerotic CVD risk factors impart differential risk for women and men. The importance of prevention is highlighted by the information that two of three US women have at least one major coronary risk factor, with that percentage increasing with age.[9] Additionally, for women age 35 to 54 years, in contrast to the total population of women, CHD mortality has increased, reversing the favorable trend of the past four decades. In this population, increasing Framingham risk scores over the past two decades are likely the result of the epidemic of obesity and sedentary lifestyle.[35,78] These characteristics support the importance of providing preventive CVD screening for women.

Although women represent 46% of the US population with CHD, they constituted only 25% of participants in CHD prevention trials, with sex-specific data cited in only 31% of primary trial publications.[79] It must be appreciated that women are not a homogeneous group. Almost half of African American women have some form of CVD, with a 44% prevalence of hypertension (which is earlier in onset), an increase in metabolic syndrome, higher CVD rates, and higher mortality than their white counterparts, and in all studies, they receive less guideline-directed therapies. Black women have the greatest risk factor burden at hospitalization for an acute MI.[34] By contrast, Hispanic women have double the occurrence of diabetes compared with non-Hispanic white women (12.6% vs 6.5%) yet have the paradox of lower mortality and increased life expectancy compared with non-Hispanic white women.[80-82]

RISK FACTORS UNIQUE TO OR PREDOMINANT IN WOMEN

Pregnancy Complications

Pregnancy complications, including preeclampsia, gestational diabetes, pregnancy-induced hypertension, preterm delivery, and small for gestational age at birth, are early indicators of increased CVD risk. Preterm delivery (< 34 weeks of gestation) appears as an independent risk factor for subsequent long-term CVD morbidity and hospitalizations.[83A] This mandates a detailed pregnancy history as an integral component of risk assessment for all women. It has been suggested that pregnancy is the first "stress test" a woman undergoes, in that the CVD and metabolic stresses of pregnancy have the potential for early prediction of future CVD risk. It is likely that shared risk factors for preeclampsia and CVD are unmasked by the pregnancy, rather than risk being specifically caused by the preeclampsia. Preeclampsia and gestational hypertension increase by three- to six-fold the risk for subsequent hypertension and double the risk for subsequent CVD events including stroke. Prehypertension during a normotensive pregnancy appears as an independent risk factor for predicting postpartum metabolic syndrome.[83B] An increased later risk of cardiomyopathy has also been reported in women with hypertensive disorders of pregnancy.[84A] Further, gestational diabetes increases by seven-fold the risk of subsequent development of type 2 diabetes.[53,84B-87]

Oral Contraceptive Therapy

Although there is no apparent increase in CVD risk for healthy women with no risk factors receiving oral contraceptive therapy, smoking increases their risk by seven-fold, and there may be an increase in blood pressure for hypertensive women.[88-91] There is also a nearly two-fold increase in stroke risk, which increases with older age at oral contraceptive therapy use. There are differences among the oral contraceptives, with earlier forms, particularly levonorgestrel, increasing MI risk, and more recent oral contraceptives associated with a lesser increase in blood pressure or even a decrease, but all carry an elevated risk of venous thromboembolism. The recommendations are for precise risk factor ascertainment and control in women using oral contraceptive preparations.[88-91]

Hormonal Fertility Therapy

A new area of risk is hormonal fertility therapy, best delineated in a Canadian population cohort from 1993 to 2010.[92] These women had a decreased risk of all-cause mortality, stroke, thromboembolism, and heart failure with successful fertility therapy that was evident across age and income subsets. However, unsuccessful fertility therapy in the same cohort was associated with an increase in adverse CVD events.[93]

Menopausal Hormone Therapy

Menopausal hormone therapy is an area where clinical trial data have dramatically altered clinical recommendations and practice. Based on data from the Women's Health Initiative (in healthy women) and the Heart and Estrogen/Progestin Replacement Study (in women with CHD), menopausal hormone therapy is not recommended for the primary or secondary prevention of CVD. The US Preventive Services Task Force recommendations state that menopausal hormone therapy should not be recommended for the primary prevention of chronic conditions.[94-98]

Systemic Autoimmune Disorders

Systemic autoimmune disorders are highly prevalent among women and have adverse consequences, increasing the risk of CHD and stroke. CHD is a leading cause of both morbidity and mortality in women with systemic lupus erythematosus. There is a two- to three-fold increase in MI and CVD mortality among women with rheumatoid arthritis, and increased CVD risk has also been reported among women with psoriasis.[53,99,100] The recommendation is that precise screening for CVD risk factors and risk intervention is warranted for women with systemic autoimmune disorders.

TRADITIONAL CARDIOVASCULAR DISEASE RISK FACTORS

Misperception among physicians of lower CVD risk status for women correlates with suboptimal application of CVD risk interventions for women.

Hypertension

Hypertension is the leading cause of CVD worldwide, with a doubled population-adjusted risk for CVD mortality in women compared with men (29.0% vs 14.9%). Hypertension is more strongly associated with MI in women than men.[101] Although women are less likely than men to have hypertension before 45 years of age, hypertension predominates among women compared with men after age 65 years. Of concern is that 80% of US women age 75 and older have hypertension. Importantly, only 29% of elderly women in the United States have adequate control of their blood pressure compared with 41% of men.[81,101-104] Important is the impressive correlation of body mass index and elevated systolic blood pressure in women, indicating another potential intervention to control hypertension.

Controversy remains as to blood pressure targets, with recommendations varying from 150/90 to 140/90 mm Hg. In the Systolic Blood Pressure Intervention Trial (SPRINT), a systolic blood pressure of < 120 mm Hg compared with < 140 mm Hg resulted in a 25% lower risk of fatal and nonfatal major CVD events and deaths from any cause.[105] However, women were underrepresented in this trial and the age range of 50 to 80 years excluded young as well as elderly women with hypertension; in addition, by the trial design, diabetic patients were excluded.[106]

Cigarette Smoking

Smoking is the most important preventable cause of MI in women.[107] Although cigarette smoking rates have decreased globally, the decline is less for women than men; in fact, the number of female smokers is increasing, particularly in developing countries. Nearly one in five

women in the United States smoke cigarettes, with smoking among younger women more common than in younger men. The CVD risk for female smokers is 25% higher than for male smokers, with cigarette smoking tripling the MI risk for women. Moreover, smoking in association with oral contraceptive use increases the risk of acute MI, stroke, and venous thromboembolism.[108] Smoking cessation is the most cost-effective risk-modifying program.[81,109]

Diabetes Mellitus

Diabetes confers greater risk for CVD death in women compared with men, and the rate of diabetes in Hispanic women is more than double that of non-Hispanic white women. Women with diabetes have a three-fold excess risk of CAD mortality as compared with nondiabetic women and a higher adjusted hazard for CAD death when compared to men. A meta-analysis of 850,000 individuals showed that the relative risk of CVD was 44% greater in diabetic women than diabetic men.[110] Diabetic women have a more adverse CVD risk factor status than their male peers including impaired endothelium-dependent vasodilation, a hypercoagulable state, dyslipidemia, and the metabolic syndrome.[111]

The 2015 AHA Scientific Statement on Sex Differences in the CVD Consequences of Diabetes Mellitus noted that the prevalence of diabetes is increasing rapidly in the United States, with 9.3% of the population being diabetic.[111] Overall, the prevalence of type 2 diabetes is similar for women and men, with about 12.6 million women over age 20 years estimated to have type 2 diabetes. At hospitalization for acute MI, women are more likely than men to have diabetes mellitus (25.5% vs 16.2%). CVD is the leading cause of morbidity and mortality among type 2 diabetics, accounting for more than 75% of the hospitalizations and 50% of all deaths.[112] Although nondiabetic women have fewer CVD events than comparably aged nondiabetic men, this sex-specific advantage is lost once type 2 diabetes develops.[113,114] Diabetes confers a greater CVD risk for women than men (19.1% vs 10.1%). Diabetic women have a 40-fold increase in the risk of incident CHD and a 25-fold increase in the risk of stroke.

The reasons for the sex differences are not well delineated but likely are contributed to by inherent physiologic differences including the impact of sex hormones, differences in CVD risk factors, and differences between the sexes in the treatment of diabetes and CVD.[115] It remains uncertain whether differences are related to increased adiposity, increased abdominal adiposity, and/or possibly insulin resistance among diabetic women. In all studies, diabetic women receive less treatment and reduced control of their CVD risk factors than diabetic men.[116-120] Women with diabetes are less likely to be appropriately treated than are men, which is contributory to worsening outcomes.[121] Diabetic women are the sole group without a documented mortality reduction, based on recent population surveys. These surveys showed a decreased mortality among men with and without diabetes and women without diabetes (13%, 36%, and 27.1%, respectively). Conversely, mortality has increased in diabetic women (23%).

Hypercholesterolemia

Hypercholesterolemia imparts the highest population-adjusted risk for women (47%), with all studies showing similar statin benefit for women and men. In the US population, fewer than half of adults eligible for cholesterol medications actually took them,[122] with women less likely to be prescribed statin therapy[123,124] and with variable compliance.[125] The 2013 American College of Cardiology (ACC)/AHA guidelines for cholesterol management promulgated significant change in the management of dyslipidemia.[126] First, the new pooled cohort risk equations were to be used, and these include sex-specific calculations.[127] Lifestyle guidelines are offered for diet and physical activity for low-density lipoprotein (LDL) lowering. Fixed-dose statin therapy for women is based on their risk categorization by the new pooled cohort risk equations, without use of target LDL cholesterol levels. Lifestyle modifications, particularly diet and exercise, are important for primary and secondary prevention of atherosclerotic CVD, with the use of pharmacologic therapy for secondary prevention being equally effective among women and men for the reduction of recurrent CAD events and mortality. Nonstatin therapies are generally not recommended. Moderate-dose statins are recommended after age 75 years, as a result of altered statin metabolism in the elderly.[128-132] The outcome of these new guidelines will likely increase statin use for women, decrease inappropriate statin use, decrease the use of nonstatin therapies, and decrease the use of LDL cholesterol laboratory testing. Recommendations for ezetimibe and PCSK9 inhibitors were not included in these guidelines, because the clinical trial results were not available by 2013. Ezetimibe added to statin therapy decreases LDL cholesterol by approximately 15% and has been associated with a decrease in CVD events,[133] and although there are no clinical trial outcome results to date, the recently approved PCSK9 inhibitors have resulted in dramatic lowering of LDL cholesterol.[134,135] Women appeared to have a greater likelihood than men of developing diabetes on statins.[136]

Obesity/Overweight

Two out of three US women are either obese or overweight; obesity is closely associated with hypertension, dyslipidemia, physical inactivity, and insulin resistance. In the Framingham Heart Study, obesity increased CAD risk by 64% in women compared with 46% in men.[137] Obesity is a major risk factor for MI in women, increasing their risk nearly three-fold.[138] Overall, the prevalence of obesity is double in women compared with men in low- to middle-income nations, although it is equivalent among women and men in higher income countries.[101,139] Detailed guidelines released by the ACC/AHA in 2013 are available for the management of obesity.[139]

Physical Inactivity

Nearly one-third of adults in the United States are physically inactive (32.2% of women vs 29.9% of men). In the INTERHEART study (Effect of Potentially Modifiable Risk Factors Associated With Myocardial Infarction in 52 Countries), the protective effects of exercise were more prominent for women than for men. Physical inactivity is the most prevalent risk factor for women, with one-quarter of US[101] women reporting no regular physical activity and three-quarters reporting less than the recommended amount of activity. Moreover, the development of diabetes and risk of CVD events are decreased for women who exercise regularly. For secondary prevention, exercise-based rehabilitation is a Class IA recommendation in all coronary guidelines, yet women are 55% less likely to participate than men.[101,130,140,141] The recommended levels in the physical activity guidelines for adult Americans are at least 150 minutes per week of moderate-intensity aerobic activity such as walking, 75 minutes per week of vigorous-intensity aerobic activity such as jogging, or a combination of both, with muscle strength training activity recommended on 2 or more days of the week.[28] Higher levels of physical activity are associated with lower rates of CVD.[142,143]

Psychosocial Issues: Depression and Stress

Psychosocial issues, particularly depression, preferentially disadvantage women. In the INTERHEART study, psychosocial factors increased CVD mortality more for women than men (45.2% vs 22.8%).[101] These factors include stress at work or home, financial stress, and major life events.[101] There is growing evidence that psychological factors and emotional stress influence the onset and

clinical course of IHD, particularly for women. From the Variation in Recovery: Role of Gender on Outcomes of Young Acute MI Patients (VIRGO) registry, young women had significantly higher stress scores compared with young men.[144] Depression among women appears to be a powerful predictor of early-onset MI, and in the VIRGO registry, young women were more likely than young men to have a history of depression.[145]

Depression is associated with a 1.6-fold increase in CVD mortality independent of the severity of the depression. In addition, increased mortality has been reported among depressed young women (< 65 years of age) with established CAD. Depression is also a risk factor for adverse outcomes with ACS.[101,146-150] Likely contributors are the high-risk behaviors and nonadherence to therapies associated with depression. Depression after MI occurs with increased frequency in women, with the greatest risk in younger women.[151] Depression may be a component of the increased CAD event risk of younger women following both MI and coronary artery bypass graft (CABG) procedures.[152,153]

Aspirin Therapy

The preventive use of aspirin for CVD varies by sex. Aspirin is routinely recommended for primary prevention in men but not in women, based on the Women's Health Study.[154] In this study, 38,876 healthy low-risk women older than age 45 years were randomized to either 100 mg of aspirin every other day or placebo. Aspirin prevented stroke but not MI or CVD death among those younger than age 65 years, with a sizeable potential for gastrointestinal bleeding. In women over age 65 years, aspirin prevented stroke, MI, and CVD death; however, an increased risk of gastrointestinal bleeding was comparable to the preventive benefits, thus mandating treatment individualization. By contrast, in the Physicians' Health Study, in which men were randomized to the same aspirin regimen, a reduction in MI (but not stroke) was observed.[155] Comparable sex-specific recommendations for aspirin use are routine in all clinical practice guidelines for secondary prevention.[156,157]

CLASS III INTERVENTIONS: NOT USEFUL/EFFECTIVE AND MAY BE HARMFUL FOR CARDIOVASCULAR DISEASE PREVENTION IN WOMEN

Menopausal Hormone Therapy

The Heart and Estrogen/Progestin Replacement Study[98] and the Women's Health Initiative hormone trials[96] documented that menopausal hormone therapy did not prevent incident or recurrent CVD in women but increased their risk of stroke. These trials displaced menopausal hormone therapy as the ubiquitous solution to women's cardiovascular problems, refocusing attention on established cardiovascular preventive therapy. In summary, hormone therapy and selective estrogen receptor modulators should not be used for the primary or secondary prevention of CVD. This is emphasized in recommendations from the US Preventive Services Task Force.[94]

Antioxidant Supplements and Folic Acid

The Women's Antioxidant CVD and the Women's Antioxidant and Folic Acid CVD studies demonstrated that vitamins E, C, and β-carotene and folic acid and B vitamin supplements, respectively, did not prevent incident or recurrent CVD in women. Antioxidant supplements (eg, vitamins E, C, and β-carotene) should not be used for the primary or secondary prevention of CVD.[158,159] In addition, folic acid, with or without vitamin B_6 and B_{12} supplementation, should not be used for the primary or secondary prevention of CVD.[160]

SYMPTOMATIC EVALUATION OF STABLE ISCHEMIC HEART DISEASE IN WOMEN

In the de novo evaluation of suspected cardiac symptoms, the clinical diagnosis of angina can be challenging for women. Population evidence supports that stable chest pain is a more prominent presenting symptom for women compared with men (who more commonly present with acute MI or sudden cardiac arrest).[161] Higher rates of suspected cardiac symptoms (eg, angina) are reported in women.[45,162] From a meta-analysis of 13,331 women and 11,511 men, the prevalence of angina was 20% higher among women as compared to men ($P < .0001$).[162] The evidence further supports a more variable symptom profile for women compared with men.[45] Women with angina more frequently report provocation following emotional stress that may occur at rest; this varies from the typical exertional pattern of angina as triggered during physical work that is typical of male patients.[45] Moreover, the consistent pattern among women presenting with de novo chest pain includes worsening angina frequency and stability along with reduced quality of life,[163] even for younger women (< 55 years old).[164] A major challenge with reported symptoms among women is that women receive less intensive antiischemic therapies, which leads to worsening CAD outcomes.[10,13,52,53]

During the chest pain evaluation, a careful history is required to assess the likelihood of CAD and to aid decision making regarding additional testing for myocardial ischemia or anatomic CAD. Preconceived bias can impact a physician's perception of CAD risk for women.[7,165] Adequate assessment of CAD risk requires synthesis of multiple risk factors, clinical history, and a detailed assessment of activities of daily living and factors related to symptom frequency and stability.[45] McSweeney et al[166] have identified five prominent prodromal symptoms in women, including discomfort in jaw or teeth, unusual fatigue, arm discomfort, shortness of breath, and general chest discomfort. The relative hazard for CAD events (at 2 years of follow-up) was elevated four-fold for women reporting more than one of these symptoms.[166]

The integration of clinical symptomatology and risk factors into an assessment of clinical risk for women is challenging. Many of the risk scores were developed several decades ago, were derived from largely male cohorts with limited representation of women, and included patients with a higher prevalence of significant and severe CAD than is observed in contemporary practice.[167,168] Current patient populations are decidedly lower risk and have less prevalent obstructive CAD, resulting in marked overestimation in risk, particularly for women.[169,170] When relying solely on the typicality of chest pain symptoms, CAD likelihood estimates will result in the majority of women being at lower risk.[45] In one recent example, low- and intermediate-risk women were, on average, 10 years older than their male counterparts and had a higher mortality risk.[171] In the 2014 AHA consensus statement on the diagnostic evaluation of IHD in women, a simplified approach to categorize risk was presented (Fig. 108–3).[45] For women with stable symptoms, risk is broadly categorized as low, intermediate, and high for women in their 50s, 60s, and 70s (or older), respectively.[45] Risk may be accentuated by one category (eg, low to intermediate risk) for those with multiple CAD risk factors, functional disability, or extensive comorbidity. Additionally, high-risk equivalent women are those with longstanding or poorly controlled diabetes or those with peripheral arterial disease. Although this approach remains imperfect, it provides a simplistic means to define risk in women and captures the prominent impact of age as driving clinical outcomes and CAD prevalence. Women allocated to low-risk status do not require prompt diagnostic testing, whereas optimal candidates for noninvasive functional or anatomic testing include women with intermediate or high CAD risk (Fig. 108–4).[45]

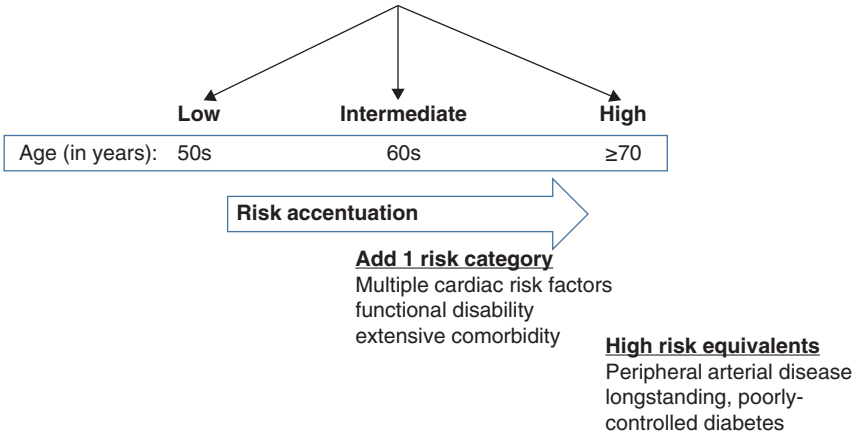

FIGURE 108–3. Defining clinical ischemic heart disease (IHD) risk in symptomatic women, from the American Heart Association expert consensus statement on the role of noninvasive testing in the clinical evaluation of women with suspected IHD. Reproduced with permission from Mieres JH, Gulati M, Bairey Merz N, et al: Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. *Circulation*. 2014 Jul 22;130(4):350-379.[45]

DIAGNOSIS OF MYOCARDIAL ISCHEMIA AMONG WOMEN WITH SUSPECTED ISCHEMIC HEART DISEASE

There has long been a misperception that women have a low risk of CAD and that documented ischemic or other stress test abnormalities are associated with false-positive findings.[13,47] The result of these misperceptions is that women with abnormalities on stress testing disproportionately receive minimal to no post-test change in management. In one recent trial, less than 10% of women with abnormal stress test findings received any intensification or new anti-ischemic therapies or referral to invasive coronary angiography.[47] An evolution in thought regarding the importance of ischemia as elevating risk in women has occurred over the past decade. A landmark population registry reported that coronary mortality was significantly elevated for women with ischemic findings on noninvasive testing, particularly for those < 75 years old, in whom the relative hazard for CAD death was higher as compared to similarly aged men.[17] Although issues remain on potential technical artifact relevant to ischemic abnormalities among women (eg, breast artifact in stress myocardial perfusion single-photon emission computed tomography [SPECT]), contemporary approaches to documented ischemia now include the extensive evidence on the prognostic accuracy of ischemic findings among women. Moreover, there is an expanded focus on detection of obstructive CAD but also, more recently, an expanded understanding of risk associated with nonobstructive CAD, including high-risk atherosclerotic plaque features, as also driving risk for women with suspected IHD.[4,172]

Noninvasive diagnostic testing can refine the management of symptomatic women largely as a result of their more nonspecific clinical presentation. There are currently two diagnostic approaches for the evaluation of suspected IHD: (1) noninvasive or invasive anatomic testing using coronary computed tomographic angiography (CCTA) or invasive coronary angiography and (2) stress testing using exercise electrocardiography (ECG), echocardiography, myocardial perfusion SPECT or positron emission tomography (PET), or cardiac magnetic resonance (CMR) imaging.

The mainstay of functional or stress testing has been the exercise ECG, with strong evidence on its diagnostic and prognostic accuracy for women.[45,173,174] The exercise ECG is indicated for intermediate-risk women who are capable of performing activities of daily living (or ~5 metabolic equivalents [METs] of exercise [or higher]).[1] Candidates for the exercise ECG, based on the 2012 guidelines for stable IHD, are those without disabling comorbidity including younger patients, patients without marked obesity or orthopedic limitations, and patients with no existing peripheral arterial disease or chronic obstructive pulmonary disease.[1] Additionally, women who report limitations in performing routine activities of daily living may also be categorized as those with limited physical work capacity and may not be candidates for exercise testing. Given the predominance of these factors among female patient cohorts, the candidate pool for women capable of maximal levels of exercise is limited. The commonly applied Bruce protocol may be too rigorous for many women and precipitate premature fatigue; reviews and consensus statements suggest exercise protocols with smaller incremental grades of

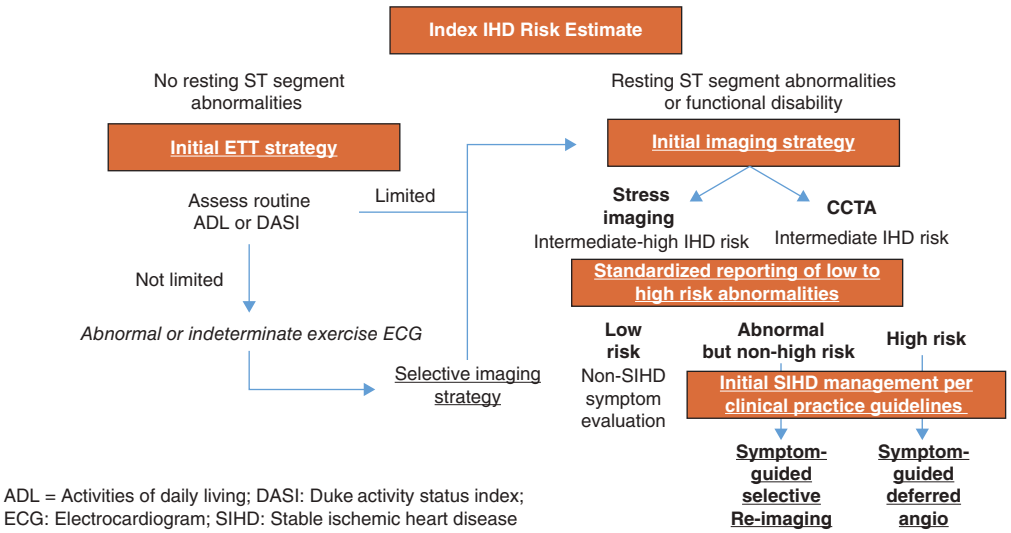

FIGURE 108–4. The American Heart Association consensus statement: role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease (IHD) clinical evaluation algorithm. CCTA, cardiac computed tomography angiography; ETT, exercise tolerance test. Reproduced with permission from Mieres JH, Gulati M, Bairey Merz N, et al: Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association, *Circulation*. 2014 Jul 22;130(4):350-379.[45]

work and lower starting MET levels as preferred for females (eg, modified asymptomatic cardiac ischemia pilot protocol).[45,175]

However, for women presenting with de novo chest pain who are capable of exercising maximally, the exercise ECG has a high negative predictive value for excluding obstructive CAD.[45] The high negative predictive value is based on women achieving maximal levels of exercise and heart rate until the point of volitional fatigue without ECG changes. In a younger, lower risk cohort, the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial revealed similar 2-year outcomes (ie, CAD death or hospitalization for heart failure or an ACS) for women randomized to an exercise ECG as compared to exercise myocardial perfusion SPECT (P = .59).[47] Based on this trial, the recent AHA consensus statement introduced the concept of an exercise ECG first strategy (see Fig. 108–4), whereby selective imaging is performed in women whose index exercise ECG identifies indeterminate or positive findings. Women incapable of performing 5 or more METs of exercise are at high risk of all-cause mortality and other major CAD events.[45] Among those incapable of performing adequate levels of exercise, stress imaging should be performed with pharmacologic stress.

The diagnostic accuracy of the exercise ECG is decidedly lower in women than men.[176,177] From 29 studies (n = 3392 women), the diagnostic sensitivity and specificity are 62% and 68%, respectively.[176] For women and men, early provocation of ST-segment changes at low workloads denotes high-risk status.[175] Care should be taken when no ECG abnormalities are detected in a woman failing to achieve maximal levels of exercise. However, significant ventricular arrhythmias (eg, seven or more premature ventricular contractions per minute or ventricular tachycardia/fibrillation), a drop in systolic blood pressure or blunted heart rate response with increasing physical work, a 1-minute recovery heart rate that has dropped from peak exercise by < 12 bpm, and the occurrence or worsening horizontal or downsloping ST-segment changes of ≥ 1 mm (at 60-80 milliseconds beyond the J point) all signify high-risk findings on the exercise tolerance test for women.[175,178A] Additionally, ≥ 1 mm of ST-segment elevation (at 60-80 milliseconds after the J point) in a non–Q-wave lead is also a high-risk marker associated with transmural ischemia.[175] Sex-specific clinical and exercise risk scores are described to identify patients at the highest risk for all- cause mortality.[178B] Documentation of significant ST-segment elevation in lead aVR is associated with a high risk of severe CAD including proximal left anterior descending or left main involvement.[175] The interpretation of ST-segment changes is dependent on the quality of the ECG tracing. Use of computer-averaged ECGs is not advised unless the quality of the raw tracings is reviewed for motion artifact and baseline wander.[175] Sex-specific clinical and exercise risk scores are described to identify patients at the highest risk for all- cause mortality.[178B]

Older reports highlight the prognostic accuracy of the Duke treadmill score (Exercise Time – [5 × Max ST] – [4 × Angina Index]) in women, and care should be taken when applying absolute risk or CAD estimates in contemporary lower risk cohorts who are also more functionally disabled.[45,179] However, the categorization of low (score ≥ +5) to high risk (score ≤ –11) women based on the Duke treadmill score remains a valuable means to identify candidates for follow-up stress or anatomic imaging. Those with intermediate/high risk (score ≤ +4) are generally considered candidates for further risk assessment with noninvasive imaging and, in select high-risk cases, invasive coronary angiography. The addition of a noncontrast computed tomographic coronary artery calcium (CAC) score may provide additional information as to the presence of atherosclerosis to guide clinical management and further testing and estimate future risk of CAD events.[180-182] From a large symptomatic cohort, significant obstructive CAD was rarely observed in symptomatic women and men with a low-risk CAC score ≤ 10.[182] In a recent trial, patients with a CAC score of 0 did not have any CAD events over 1 year of follow-up.[183]

There are decades of available evidence in women indicating that stress imaging, including stress echocardiography, myocardial perfusion SPECT or PET, and CMR imaging, has an improved diagnostic and prognostic accuracy when compared to the exercise ECG.[45,184,185] Candidates for stress imaging include intermediate- or high-risk women who meet the following clinical criteria: (1) functionally disabled (defined earlier); (2) an abnormal resting ECG precluding accurate assessment of exercise-induced changes (eg, left ventricular hypertrophy with repolarization changes or significant resting ST-T–wave changes); or (3) high CAD likelihood.[1,45] Additional details on the appropriate candidates for stress imaging are detailed in the ACC's multimodality appropriate use criteria.[186]

Stress echocardiography is particularly useful for ruling out wall motion abnormalities with a high diagnostic accuracy (sensitivity, 79%; specificity, 83%) in women; this aim may be helpful for younger and lower risk women.[2,176] Image quality, particularly for obese women or those with lung disease, may be improved with the use of intravenous contrast.[45] Stress echocardiography has many Class I indications for testing, based on multicenter trials and large registries, that support its utility in women and men with stable IHD.[1] For women capable of exercising, no inducible wall motion abnormality in the setting of maximal exercise identifies those at low risk of future CAD events.[187] Following the principles of demand ischemia, an inducible wall motion abnormality is more likely to be elicited in the setting of more severe stenosis, and thus, a failure to document a new wall motion abnormality may occur in a woman with single-vessel CAD.[188] Each test has its limitations, which will be discussed herein, but importantly, nonechocardiographic risk parameters during stress testing may improve detection of at-risk women and men. Echocardiography can also be helpful in assessing noncoronary etiologies for symptoms such as diastolic dysfunction, abnormal filling pressures, or abnormal myocardial mechanics using tissue Doppler or speckle tracking.[2]

There is a similarly robust evidence base as to the utility of stress myocardial perfusion SPECT in women that is reflected in the numerous Class I indications in the 2012 stable IHD clinical practice guideline.[1] Based on the systematic review from the Agency for Healthcare Research and Quality, the diagnostic sensitivity and specificity were 81% and 78%, respectively, for women; these statistics include older reports using the radioisotope thallium-201, which is associated with reduced accuracy due to breast tissue artifact in women.[176] Breast tissue artifact reduces diagnostic accuracy of SPECT for women who are obese and/or for those with large breasts. Significant improvements in diagnostic accuracy have been reported using validated attenuation correction algorithms or the addition of two-position supine/prone imaging.[189-191] Decades of evidence support the effectiveness of risk stratification using the extent and severity of rest and stress myocardial perfusion SPECT abnormalities, with moderate to severe ischemia defined as ≥ 10% of the myocardium.[192] There is an increasing CAD event risk that is proportional to the extent and severity of rest and stress SPECT abnormalities (ie, a gradient relationship with percent abnormal myocardium). A low risk of CAD events is consistently reported for those with normal SPECT findings, and an intermediate to high risk of CAD events is reported for those with mild and moderate/severe findings.[188,192] Risk stratification evidence is similarly effective for women and men.[45,188,193,194] This evidence is expansive on the prognostic utility of SPECT imaging in women undergoing exercise or pharmacologic stress, in the obese, in diabetics, and in women of diverse race and ethnicity.[50,195] One challenge with the use of stress myocardial perfusion SPECT is that the overall radiation burden is higher than for CCTA or PET imaging; rest and stress technetium-99m SPECT has an effective dose of 10 to 15 mSv.[196,197] Optimization of dose-reduction techniques is a primary goal for nuclear cardiology. For women, stress imaging

should be performed first, and if findings are normal, elimination of the follow-up resting scan can reduce radiation exposure considerably (ie, stress only imaging).[197] Importantly, for the purposes of justification of exposure, only women with appropriate indications for testing should undergo SPECT, CCTA, or invasive coronary angiography.[1,186] There should be limited use of SPECT imaging for younger women (ie, < 50 years old), but if clinical indications warrant, they should undergo target procedures with low-dose exposure (eg, PET) or, if possible, a test without radiation exposure.

More recently, stress myocardial perfusion PET has gained increasing attention with its improved image quality translating into high diagnostic accuracy for women, particularly for the obese,[198] its reduced breast tissue artifact, and its ability to segment subepicardial and epicardial perfusion and quantify rest and stress absolute myocardial blood flow and coronary flow reserve (CFR).[2, 199] Conventional cardiac PET using the perfusion tracers rubidium-82 or ^{13}N-ammonia has a markedly reduced radiation exposure with effective doses of only 2 to 3 mSv.[196]

Stress myocardial perfusion PET has a very high diagnostic accuracy when compared to SPECT (88% vs 67%; $P = .009$).[198,200] Risk stratification evidence based on the rest and stress percent abnormal or ischemic myocardium appears to similarly risk stratify women and men, similar to SPECT imaging.[200-202] One clear advantage of PET is the added contribution of CFR measures documenting the ratio of stress-to-rest absolute myocardial blood flow. An interesting finding is that approximately 20% to 40% of patients with normal or low-risk PET also have reduced CFR,[203-205] which signifies underlying atherosclerosis and higher CAD event risk. The evidence supports that a CFR ≤ 2 is associated with an elevated CAD event risk.[206, 207] Additionally, an understanding of flow and ischemic abnormalities in relation to high-risk atherosclerotic plaque features may importantly improve detection of at-risk women and guide future treatment strategies.[21,208-210] A reduced CFR combined with ischemia severity accelerates CAD event rates.[202,207] Reductions in CFR are proportional to stenosis severity, but in the patient with angiographically normal coronary arteries, they reflect dysfunction in the microvasculature.[211] Evidence of impaired CFR can be particularly helpful in understanding abnormalities of flow for women with nonobstructive CAD in whom underlying high-risk atherosclerotic plaque (that is not obstructive) may be eliciting reduced myocardial blood flow and provoking anginal symptoms.[201] When considering women with prior stress-induced ischemia or reduced CFR, the addition of CCTA may help to document normal, mild (even diffuse), or obstructive epicardial CAD. This is an area of active investigation focusing on the utility of PET with CFR, with the addition of CCTA findings of no obstructive CAD, to define coronary microvascular dysfunction (CMD). The defining of epicardial, atherosclerotic plaque, particularly if high risk or more diffuse, but no obstructive CAD, may improve IHD risk detection and foster targeted treatment strategies for this large cohort with nonobstructive but functionally limiting atherosclerosis (ie, reduced CFR).[4]

Stress CMR imaging is our final functional testing modality that has evidence as to its utility in evaluating women with suspected IHD.[2] A meta-analysis of the combined diagnostic accuracy of stress CMR perfusion and wall motion imaging reveals comparable sensitivity and specificity to SPECT and echocardiography in women.[176] The development of rapid high-resolution techniques has fostered the use of CMR perfusion imaging.[2] Relevant to IHD evaluation of women, a subset analysis of the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) trial compared women who were randomized to a multiparametric CMR evaluation including angiography, function, perfusion, and scar imaging, versus myocardial perfusion SPECT.[212] For CMR, the sensitivity in women was 89%, and the specificity was 84%, whereas for SPECT, the sensitivity was 51%, but the specificity was the same (84%). In this subset analysis, CMR outperformed SPECT with a higher diagnostic accuracy ($P < .0001$). Recently, it has been shown that CMR perfusion also effectively risk stratifies women with demonstrable ischemia, identifying females with worsening prognosis ($P < .001$).[213] Additionally, CMR techniques can measure myocardial flow reserve on vasodilator stress CMR, which may improve detection of CMD in symptomatic women; although the evidence base is minimal when compared to PET imaging. A final important consideration is the evidence as to the value of late gadolinium enhancement CMR imaging to improve detection of scarred or infarcted myocardium, which has been shown to identify women with previously undocumented MI.[214,215]

DIAGNOSIS OF ATHEROSCLEROTIC PLAQUE AND OBSTRUCTIVE CORONARY ARTERY DISEASE AMONG WOMEN WITH SUSPECTED ISCHEMIC HEART DISEASE

Separate indications are warranted for invasive versus noninvasive angiographic procedures. Current indications for invasive coronary angiography within the diagnostic evaluation includes use as a front-line procedure for women who may be categorized as high risk or for those whose symptom burden is considered unstable.[1] In addition, invasive angiography is also indicated in the setting of demonstrable ischemia by stress imaging. Indications for CCTA are similar to those of stress imaging (limited functional capacity or abnormal 12-lead ECG) for those with an intermediate pretest risk.[1,186] There are selected indications for CCTA as an index procedure that may be advantageous for the female patient with de novo chest pain.[1,186] CCTA may be preferable for women with persistent symptoms or for those with indeterminate or prior inconclusive stress test findings.

For invasive angiography and CCTA, there is a proportional increase in the risk of major CAD events with the number of vessels with obstructive CAD.[172,216,217] Women have a higher risk of major CAD events in the setting of more severe and extensive multivessel CAD, perhaps related to their advanced age or comorbidity. The role of coronary revascularization in women with obstructive CAD is detailed in a later section of this chapter. For the remainder of women undergoing invasive angiography, data have recently revealed that the presence of (normal and mild obstructive) nonobstructive CAD is associated with worsening prognosis, including in women undergoing invasive coronary angiography or CCTA.[4,18,172,193]

Our current approach within the noninvasive stable IHD evaluation, particularly for women, has expanded beyond detection of obstructive CAD to understanding the prognostic significance associated with nonobstructive CAD, especially among those with evidence of high-risk atherosclerotic plaque. The anatomic approach now includes a focus for women on the importance of prognostically significant mild but nonobstructive CAD as well as obstructive CAD. Across all female patient subsets with acute and stable IHD, there is a higher frequency of nonobstructive CAD as compared with male patients.[4,15,218] Included in this analysis are women with mild but obstructive CAD with < 50% stenosis. Approximately half of women referred for angiography do not have obstructive CAD, including women with previously documented ischemia.[4,18,172,193,201,219] For example, a report from the ACC's CathPCI Registry (n = 375,886 [~50% women] from > 600 hospitals) reported higher rates of nonobstructive CAD for women (58%, 55%, 46%, 47%, and 51% for black, Hispanic, Native American, Asian, and white women with stable IHD, respectively) than men.[15]

In cohorts of symptomatic women with IHD and documented nonobstructive CAD, reports document as much as 80% of females with

epicardial atherosclerosis.[21] In the setting of no obstructive CAD, prognosis significantly worsens in the setting of diffuse segmental atherosclerosis (ie, more than four segments involved in the epicardial vessels).[220] The adjusted hazard for major CAD events is increased approximately 90% for women and men with diffuse nonobstructive CAD.[218]

Documented myocardial ischemia or evidence of vascular dysfunction in the setting of angiographically normal coronary arteries (ie, CMD) has been the focus of much research, in large part, because of its frequent occurrence in women. There are no diagnostic techniques that are capable of interrogating the coronary microcirculation.[208,221] Invasive and PET CFR measures flow alterations within the epicardial coronary arteries (including diffuse atherosclerosis), the impact of vessel remodeling, and impairments in flow within the microvasculature. Previous discussions focused on worsening prognosis associated with impaired CFR on PET with nonobstructive CAD.[201,210,219] There are also evolving invasive techniques for measuring microvascular resistance, such as the index of microvascular resistance or hyperemic microvascular resistance.[222,223] Limited female-specific data are available.

With the introduction of noninvasive CCTA, the presence of atherosclerotic plaque, mild CAD stenosis, or obstructive CAD can be easily determined with minimal radiation exposure (average, 5-7 mSv or less).[224,225] Similar to invasive angiography, women have more nonobstructive CAD on CCTA,[15,170,226,227] and their mortality risk is accentuated in the setting of multivessel CAD.[172] More careful attention to mild CAD burden and, in particular, a focus on the presence of atherosclerotic plaque have led to evolutionary approaches to understanding risk for women with suspected IHD. From a large multicenter registry of 23,854 patients with suspected IHD, the presence of nonobstructive CAD on CCTA was associated with worsening mortality.[172] Similarly, death risk increased nearly three-fold for every vessel with nonobstructive plaque.[216,228-230] In women with suspected IHD, nonobstructive CAD was associated with an approximate two-fold increased risk of major CAD events.[231,232]

Several recent randomized trials compared CCTA versus the exercise ECG for 1-year CAD outcomes and costs of care in suspected IHD patients.[183,233] In both trials, 1-year CAD outcomes were improved, angina was more often reduced, and costs of care were lower for CCTA versus the exercise ECG, although no subset analysis was performed in women. Given the reduced diagnostic accuracy of the exercise ECG, these data suggest that CCTA may be a favorable option. In the Computed Tomography Versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) trial, a CAC score was initially performed, and CCTA was limited to patients with detectable plaque.[183] This approach of applying CAC scoring either as the index approach or along with the exercise ECG may be one alternative to improve detection of women with underlying atherosclerosis. Importantly, in the CRESCENT trial, there were no events documented in the 40% of patients without detectable CAC.

Secondary analysis by sex was recently reported in the National Heart, Lung, and Blood Institute–sponsored Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial.[234,235] From PROMISE (n = 8966), women had less documented CAD (8%) on CCTA as compared to positive stress test findings (12%, $P < .001$), whereas men had roughly a similar rate of positive findings on CCTA and stress testing (14%-16%, $P = .046$). Women with obstructive CAD on CCTA had a nearly 10-fold higher ($P < .001$) hazard of death, MI, or unstable angina hospitalization, whereas females with a positive stress test had only a 5-fold ($P = .002$) hazard for the clinical outcome, resulting in a significantly higher risk noted with CCTA versus stress testing ($P = .043$). These data suggest that CCTA may aid in the evaluation of symptomatic women as a result of its ability to detect risk and provide details on nonobstructive atherosclerotic plaque. One may envision a symptomatic evaluation approach that applies CCTA: (1) as a secondary test following stress testing or (2) as an index procedure with stress testing limited to individuals with at least mild CAD. Although subset analysis among women has not been published, the Scottish Computed Tomography of the Heart Trial (SCOT-HEART) randomized 4146 patients to a strategy of CCTA versus standard of care. Interestingly, the randomization occurred following the index evaluation, which largely included the use of the exercise ECG (ie, in 85% of enrollees). The main findings from the SCOT-HEART trial revealed a trend toward improved 25-month CHD death or MI among patients randomized to CCTA versus the standard of care ($P = .053$). These data confirm prior findings that CCTA has supportive evidence as an index or follow-up diagnostic procedure.

ACUTE CORONARY SYNDROME

A review of 59 studies challenged whether a classical chest pain presentation for an ACS was truly typical for either sex.[236] In this review, 37% of women, as compared with 27% of men, had no chest pain or discomfort, with absent chest pain increasing with advancing age. Data from the National Registry of Myocardial Infarction (NRMI) showed that the odds ratio of older age was greater than the odds ratio of female sex for absent chest pain with MI (1.28 vs 1.06). Further, women presenting with ACS were far more likely than men to have associated symptoms (2.6 vs 1.8). In the Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature ACS registry, although chest pain was the most prevalent symptom in both sexes, women were more likely to have additional symptoms and less chest pain as compared to men.[237] More prominent in women were back, neck, and jaw pain; dyspnea; paroxysmal nocturnal dyspnea; nausea; indigestion; and weakness or fatigue, challenging the clinician to identify both the woman with a non–chest pain presentation and one in whom the chest pain may be overwhelmed by a multiplicity of other symptoms.[238] This is often associated with misdiagnosis, delayed revascularization, and higher ACS mortality rates.[239] Women characteristically have longer presentation delays and greater time-to-treatment delays, which exacerbate in-hospital mortality.[240] Contributors also include the lack of awareness of risk, inaccurate symptom attribution, and other barriers to self-care.[241,242] Despite their more prevalent nonobstructive CAD, women have higher mortality, and the absence of chest pain at presentation appears more predictive of mortality in younger women than for other age groups.[243]

Women have different clinical profiles, presentations, and outcomes with ACS. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial included 3662 women and 8480 men.[244] At ACS presentation, women were more likely to have unstable angina than documented MI; even with documented MI, fewer women than men had an STEMI.[245] Women with ACS tended to be older and were more likely to have diabetes, hypertension, and heart failure, typically with intact ventricular systolic function, and to have an excess of both hospital complications and bleeding complications. Women had greater delays than men in seeking emergency care. GUSTO showed a reduced use of coronary angiography among women versus men (53% vs 59%). At angiography, more women than men were described to have "clinically insignificant" obstructive CAD, with clinically insignificant indicating no lesions amenable to percutaneous coronary intervention (PCI). However, the episode was not clinically insignificant for the woman hospitalized for ACS. In an ACS and stable IHD registry from British Columbia, women with obstructive CAD had higher rates of adverse events and readmission rates.[246] For the women with ACS, a greater rate of in-hospital mortality was observed. In addition, women with NSTEMI had more complications than men, including bleeding, heart failure, shock, renal failure, reinfarction, stroke, and readmission.

Coronary artery spasm is a rare mechanism for ACS,[247,248] as is spontaneous coronary artery dissection (SCAD).[249] SCAD is the primary cause of peripartum myocardial infarction and accounts for 10-30% of myocardial infarction in women under age 50. These women have an increased occurrence of fibromuscular dysplasia in the carotid, iliac and renal vessels; and genetic components remain uncertain. Women with SCAD have few traditional coronary risk factors, and describe precipitants including emotional, hormonal or other stressors, and exercise. Despite the overall low early mortality rate with SCAD, complications are high in PCI-treated patients, because PCI may propagate the dissection.[250] There was a high recurrence rate (17%), as based on the Mayo Clinic SCAD registry, occurring solely in women. A high prevalence of tortuosity of the coronary vessels appears to predict recurrence. The 10-year mortality was also high at 7.7% and with a high incidence (47%) of major CAD events.[250] Recommended therapy includes a single antiplatelet agent, avoidance of statins unless hypercholesterolemia is present, use of beta blockade, and avoidance of systemic hormones, including oral contraceptives.

Age is a major covariate interacting with sex and impacting outcomes. In the NRMI, there was significant interaction between sex and age.[153] Among 384,878 NRMI patients age 30 to 89 years, women had a greater mortality than their male peers to age 70, with women younger than age 50 having a doubled hospital mortality with MI compared with men. Women with CAD, and in particular women younger than 50 years old, have a doubled mortality after MI,[153] although the greater improvement in hospital mortality for younger women than younger men over time appears to be narrowing the sex gap.[251] The absolute reduction was three times greater in women than men younger than 55 years old, suggesting a decrease in treatment-related sex bias.

A uniform finding among studies is that women with ACS are less likely to be treated with guideline-directed medical therapies, less likely to undergo cardiac catheterization and coronary revascularization,[252-254] and less likely to receive timely reperfusion.[36,255-257] The reduced frequency of PCI and CABG is largely related to the reduced rate of obstructive CAD. The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) data challenge whether the adverse outcomes of women with ACS reflected their baseline risk, their suboptimal admission and discharge therapies, or both. In the National Cardiovascular Data Registry, women of all ethnic backgrounds were less likely to undergo PCI and CABG revascularization than their male counterparts,[15] with characteristic documentation of disparities in referral rates of black women to coronary angiography and reperfusion compared with both white women and black men.

Added data regarding sex disparities in ACS are available from the CRUSADE National Quality Improvement Initiative, which addressed patients with NSTEMI.[252,258,259] CRUSADE derived data from 391 US hospitals between 2000 and 2002, representing 35,875 patients, 41% of whom were women. Women were less likely to acutely receive heparin, an angiotensin-converting enzyme (ACE) inhibitor, or glycoprotein IIb/IIIa inhibitor therapy and were less likely to receive coronary interventions. Women had an increased risk of in-hospital death, reinfarction, heart failure, stroke, and transfusion (ie, highlighting the bleeding problem in women); at discharge, despite their high-risk status, women were less likely to be prescribed guideline-based aspirin, ACE inhibitors, and statin drugs. Women had an excess dosing of antiplatelet and antithrombin agents, which correlated with an increase in bleeding, mortality, and longer length of stay. Twenty-five percent of the increased bleeding risk among women, as compared with men, seen with glycoprotein IIb/IIIa inhibitors was secondary to excess dosing. Dosing of many of these agents relates to glomerular filtration rate, which should be the parameter used rather than simply inspection of the creatinine level.

Data from the Get with the Guidelines CAD registry encompassing 78,254 patients with acute MI in 420 hospitals between 2001 and 2006 highlighted sex differences.[254] Women were older, more likely to have comorbidities, and less likely to have STEMI than men. Although there were no sex differences in hospital mortality, women with STEMI had higher adjusted mortality rates than men (10.2% vs 5.5%), with increased STEMI mortality evident very early, within the initial 24 hours. This was associated with lesser likelihood of early aspirin and early β-blocker use, a decrease in reperfusion therapy, and a decrease in timely reperfusion. Underuse of evidence-based treatment for women and delayed reperfusion represent opportunities to decrease the sex disparities in the care and outcomes of women with STEMI.[254] Also in this registry, in a subset of 49,358 patients age 65 years and older, women were less likely than men to receive optimal care at discharge. The authors concluded that approximately 69% of the sex disparity may potentially be reduced by providing optimal quality of care to women; however, the higher mortality in African American patients of both sexes could not be accounted for by differences in the quality of care as measured in this study.[260] Moreover, from the VIRGO registry of women and men 18 to 55 years of age with acute MI,[261,262] women were less likely to return to work after MI than were men.[263]

Women with MI are more likely than men to have recurrent MI and be subsequently disabled by heart failure.[264] The Canadian ACS registry assessed the factors influencing the underutilization of evidence-based therapies in women.[265] Canadian women in this ACS cohort had higher death rates than men but had lower rates of use of ACE inhibitors, β-blockers, and statins. There was apparent lower assessment of patient risk, as evidenced by the decision for not scheduling cardiac catheterization. Despite adjustment for these biasing confounders, female sex remained associated with underutilization of therapy with lipid-modifying agents and ACE inhibitors.

Cardiac rehabilitation is an essential component of comprehensive care after ACS with unquestionable morbidity and mortality benefits, with a Class IA recommendation in all coronary guidelines.[266] Women are 55% less likely to participate in cardiac rehabilitation than men, with one contributor being the lack of referral by the treating physician.[267,268] Women particularly absent from cardiac rehabilitation include the uninsured, unmarried, socioeconomically disadvantaged, smokers, depressed, obese, sedentary, elderly, and nonwhite and also those with less education, social support, and competing family obligations. Depressive symptoms are linked to suboptimal cardiac rehabilitation attendance despite evidence that cardiac rehabilitation exercise training improves depression in women.[269,270] Home-based cardiac rehabilitation may prove effective for women with significant barriers to attending structured outpatient programs.

Further data derive from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN)–Thrombolysis in Myocardial Infarction (TIMI) 36 trial evaluating ranolazine in the management of ACS.[271] A total of 6650 patients with NSTEMI were randomized to ranolazine versus placebo, which had no effect on the primary end point: CVD death, MI, or recurrent ischemia. In the subset analysis, for CVD death or MI, the hazard ratio was 0.99 (P = .87), whereas the reduction in recurrent ischemia was significant, with a hazard ratio of 0.87 (P = .03). A post hoc analysis examining the results by sex showed striking differences.[272] The MERLIN-TIMI 36 population was composed of 2291 women and 4269 men. Women were older and more likely to have diabetes, hypertension, heart failure, prior angina, ECG ST depression, and increased brain natriuretic peptide levels. However, they had lower rates of obstructive CAD and of elevated troponin levels. Women in the MERLIN-TIMI 36 trial were more likely than men to report angina, despite less obstructive CAD. They had more ischemic episodes on

continuous ECG recording during the hospitalization, with ECG ischemia predictive of an unfavorable outcome.[272] The primary end point was significant in women, with a *P* value of .03. Although there was no sex difference in CVD death and MI, ranolazine significantly reduced recurrent ischemia in women ($P = .002$).

Reperfusion data from the NSTEMI and STEMI guidelines[273-276] provide no sex-specific recommendations for the utility of agents. In STEMI strategies, reperfusion with thrombolytic therapy carries a higher risk of mortality and bleeding complications compared with PCI. Although thrombolysis is rarely used today, the complications of thrombolysis are greater in women than in men, especially hemorrhagic stroke. In the GUSTO trial, one-third of an increase in bleeding complications and a doubled mortality rate related to thrombolysis were documented for women.[273-276] Primary PCI has a lower 30-day mortality rate than thrombolysis and a reduced risk of intracranial bleeding, but a persistent high risk of vascular complications. Decreased major CAD events and target vessel revascularization are characteristic with stenting compared with balloon angioplasty. PCI is the preferred reperfusion strategy, but there are no sex-specific guideline recommendations. Women with STEMI undergoing CABG have an increased in-hospital mortality compared with men, but no specific guideline recommendations are offered on utility. PCI revascularization for NSTEMI reduces mortality and recurrent MI in high-risk women who should undergo an early invasive strategy.

Numerous studies document that women with NSTEMI with high-risk features benefit from an early invasive strategy. Although early invasive management of ACS is an effective treatment strategy for women, major bleeding independently predicts 30-day mortality. Women have an increased risk of procedural bleeding complications, such that an early invasive management strategy showed benefit only in the higher risk ACS women. The ACC/AHA guidelines recommend an initial conservative strategy for low-risk women with an ACS, in that an early invasive strategy for such women affords no benefit.[277,278]

Regarding medical management, aspirin reduces the risk of recurrent ischemic events, and antithrombotic agents reduce the risk of thrombotic complications. However, women have an increased bleeding risk with antiplatelet and antithrombotic agents, mandating careful attention to weight and renal calculation of doses.[278] Women with NSTEMI are recommended to receive the same pharmacologic therapy as men—aspirin, $P2Y_{12}$ receptor inhibitors, anticoagulants, statins, β-blockers, and ACE inhibitors, both in the ACS setting and for secondary prevention. Women with both STEMI and NSTEMI are recommended to receive aggressive behavioral interventions including smoking cessation; referral to a comprehensive cardiac rehabilitation program that includes education on lifestyle and stress management; and appropriate weight maintenance, dietary interventions, and physical activity.[273,278]

Hormone therapy with estrogen plus progestin should not be given de novo to menopausal women after ACS for secondary prevention of coronary events. Women taking estrogen plus progestin or estrogen at the time of ACS should discontinue these agents.[273,278]

Although the 2014 ACC/AHA NSTEMI guidelines recommend that women with NSTEMI be treated with the same pharmacologic agents as men in both the acute care and secondary prevention setting,[276] with consideration of weight and renal dosing of antiplatelet and anticoagulant agents because of the higher bleeding risks in women,[259,279,280] most data show that women with nonobstructive CAD and ACS are less likely to be prescribed secondary prevention medications (including antiplatelet agents and statins)[281] despite their increased rates of readmission, reinfarction, and death in the first year after MI. The 2013 ACC/AHA STEMI guidelines identify female sex as a risk factor for bleeding complications after STEMI but provide no sex-specific recommendations for use of antiplatelet or anticoagulant therapies.[274] In premenopausal women who are still menstruating, antiplatelet therapy may significantly increase menstrual bleeding.

Statin therapy is an effective secondary prevention intervention for both women and men, but women had no benefit for stroke or all-cause mortality.[282] Important for younger women who may become pregnant is that both statins and ACE inhibitors/angiotensin II receptor blockers are contraindicated during pregnancy.

Complication rates following MI are higher in women than men, despite similar success rates with treatment. Women sustain more bleeding complications, often secondary to pharmacologic therapies or invasive procedures. Mechanical complications such as acute severe mitral regurgitation, septal rupture, free wall rupture, and heart failure are more likely to occur in women, whereas ventricular arrhythmias do not differ by sex. Data from the Global Registry of Acute Coronary Events registry indicated that women had a 43% increased risk of bleeding during hospitalization.[283] Women undergoing PCI also incurred more in-hospital major bleeding, including access-related complications,[259] in part due to inappropriate dosing of antithrombotic therapies.

CORONARY REVASCULARIZATION

CORONARY ARTERY BYPASS GRAFT SURGERY

Women constitute 20% to 30% of the CABG surgical population, about 180,000 procedures annually. Mortality is greater for women than for men, especially among younger women. Contributing factors may be an increase in nonelective surgery or late referral, reduced use of an arterial conduit, and an excess of procedural complications. From the Society of Thoracic Surgeons (STS) registry,[284] 28% of the 344,913 patients were women. Women were older and more likely to have diabetes, hypertension, peripheral vascular disease, and nonelective procedures. Operative mortality was 4.5% for women versus 2.6% for men. Women had increased operative mortality for every risk factor examined univariately. Data from the National CVD Network registry (n = 51,187 patients, with 30% women) also reported that women were at greater CABG risk.[152] For women younger than age 50, there was a 3-fold increase in hospital mortality, whereas women age 50 to 59 years had a 2.4-fold increase, with this sex difference decreasing with advancing age.[152] Women of all ages had a better left ventricular ejection fraction and a smaller number of diseased vessels at surgery. In the Northern New England CVD registry of 26,725 CABG patients, hospital mortality rate was 4.1% for women and 2.1% for men.[285] The majority of excess mortality in women was related to diabetes or to an urgent/emergent presentation. Studies have shown trending improvement in 30-day CABG mortality rates for women from 1991 to 1994, with a steeper decrease in mortality in women than in men (5.6% to 1.9% vs 1.4% to 1.9%). This was likely due to the increased use of arterial CABGs for women.[286] Compared with men, women younger than 50 years old had a greater burden of comorbidities and were more likely to have emergency surgery and decreased use of arterial grafts, the latter possibly explaining the excess mortality among younger women. In a case-control study of CABG, women had higher perioperative risk in all comorbidity categories compared with matched male controls.[284] As with all other coronary presentations, women undergoing CABG have an excess of bleeding complications, and to date, it has not been elucidated whether sex differences in blood vessels or blood factors underlie the increased bleeding risk.

In another report from the STS registry, data suggested that off-pump CABG surgery reduces the sex disparity and may advantage women. Women who had on-pump CABG were older and had more comorbidity; they had an increased adjusted mortality, an increased duration of ventilation, and a longer length of stay. However, women

who had off-pump CABG surgery had comparable mortality to men; in addition, the women with off-pump CABG had a reduced risk of reexploration.[287,288] Improved outcomes have also been realized with improved glucose control among diabetic patients typically treated with continuous insulin infusion postoperatively. In addition, better anemia control can improve outcomes because anemia is an independent risk factor for adverse outcome, as is the need for transfusion.[264,289]

CABG for acute MI is rare, but in a review of 23 CABG studies that reported data stratified by sex,[290] women were older and sicker at the time of CABG. Adjustment for baseline differences reduced but did not eliminate the increased in-hospital mortality for women. In this review, women were less likely to receive an internal mammary artery graft and had more postoperative complications including renal failure, neurologic complications, and postoperative MI.[290]

PERCUTANEOUS CORONARY INTERVENTIONS

Among patients undergoing PCI, women tend to be older and to have more comorbidities. However, the improvement in outcomes with the use of stenting has preferentially advantaged women,[291] with newer generation stents further improving outcomes.[292] In the National Heart, Lung, and Blood Institute Dynamic Registry of PCI, women were more likely to have high-risk characteristics than men, including older age, diabetes, hypertension, hypercholesterolemia, heart failure, and unstable angina.[293] Sex differences in procedural outcome have diminished markedly over time, such that there are now similar PCI procedural and clinical success rates in women and men. The improved outcomes in women over time seem related to the better appreciation of pathophysiologic variables specific to women.[291] Women have a thick small chamber left ventricle, such that changes in pressure and volume are more likely to precipitate a myocardial ischemic event. In addition, the increased use of stenting and adjunctive pharmacologic agents selectively advantages women. Nonetheless, women continue to have an increased bleeding risk, transfusion requirement, and vascular complications as well as post-PCI renal failure.[294] The latter likely reflects lack of appreciation of preprocedural chronic kidney disease and consequent therapeutic measures for renal protection. Women younger than age 50 years have less severe angiographic CAD but have an increased risk of target vessel and target lesion failure.[295]

Following PCI, women have more residual angina than do men. Moreover, 1-year mortality remains greater in women than men (6.5% vs 4.3%), with the combined occurrence of death, MI, and need for CABG being greater for women (18.3% vs 14.4%). A recent study examining sex-stratified outcomes following PCI linked 426,996 patients (42% women) in the ACC's CathPCI registry to Medicare inpatient claims. Women experienced worse in-hospital outcomes compared with men.[38] Among female veterans undergoing coronary angiography, women had lower rates of epicardial obstructive CAD compared with men and improved 1-year mortality; this cohort differed from previous studies in that the rate of traditional risk factors was lower among female than male veterans.[296]

An important exception to adverse outcomes for women is PCI, where the application of stenting and adjunctive therapeutic agents appears to selectively benefit women; current PCI procedures result in comparable clinical and angiographic improvement for both sexes.[291,297,298] Recent pooled data show that newer generation drug-eluting stents (DES) have better safety and efficacy profiles in women compared with older DES and bare metal stents.[292] Although women have almost twice the rate of bleeding after PCI as men,[299] the Study of Access Site for Enhancement of PCI for Women randomized trial showed reductions in bleeding or vascular complications with radial access.[300]

GLOBAL PERSPECTIVES

CVD accounts for 48% of all noncommunicable disease deaths, with 80% occurring in low- and middle-income countries. The global prevalence of CVD is anticipated to increase 15% to 20% from 2010 to 2020. This is related to unfavorable changes in lifestyle in developing nations including urbanization, Western diets, processed foods, and increasing rates of obesity, hypertension, dyslipidemia, and diabetes. In 2008, there were more than 9 million CVD deaths among women worldwide, representing 33% of all female deaths. From 1990 to 2020, a 120% increase is anticipated in CVD mortality among women in developing countries, contrasted with a 29% mortality increase for women within industrialized countries. In the INTERHEART study, modifiable risk factors accounted for 94% of the population-adjusted CVD mortality in women.[101,301-303]

In 2012, the United Nations held a Summit on Noncommunicable Diseases, the first health summit in several decades. It highlighted sex disparities in risk and access to diagnosis and treatment and established compelling linkages with the empowerment of women and education of girls. The vulnerability of women was highlighted in this summit by the finding that 60% of the world's poor are women and two-thirds of illiterate adults are women.[304] Women are often a focal point of a majority of households throughout the world, with the matriarch of the family central to understanding and adapting habits of a heart-healthy lifestyle.[301] Because women often serve as role models in the lives of others, their examples of good CVD health (eg, exercising, not smoking, omitting alcohol, managing high blood pressure and diabetes, managing stress, and eating right) can not only improve their personal health but also positively influence others to do the same, improving CVD outcomes for women and globally.[305] Key global issues are to educate women about CVD risk factors, specifically the modifiable behavioral risk factors. Prominent among these are smoking cessation, a diet decreased in sodium and saturated fats and increased in fresh fruits and vegetables, and an increase in physical exercise.[101,301,306] This requires that women be equipped, enabled, empowered and engaged.

UNMET NEEDS

In 2015, the First National Policy and Science Summit on Women's CVD Health[307] highlighted three unanswered research questions likely to improve CVD outcomes for women:

1. What biological variables are most influential in the development and clinical outcomes of CHD, and what can be done to reduce mortality rates among women?
2. What are the best strategies to assess, modify, and prevent a woman's risk of CHD?
3. What factors influence and explain disparities in CVD epidemiology and outcomes between men and women?

A woman's CVD health is not solely a medical issue. Eradication or lessening of the burden requires a multifaceted approach and involvement from the community, government, social advocates, and others in order to support social change meeting the diverse needs of women. Both in the developing world and in developed nations, a focus on preventive care should not only target high-risk populations but also create population programs to globally reduce the burden of CVD. Recent regulations in the United States require the reporting and tracking of targeted priority populations including women. From the Centers for Medicaid and Medicare Services, there is a focus to report and track services by sex and race/ethnicity but also a focus on population health. This population health focus extends beyond the traditional health

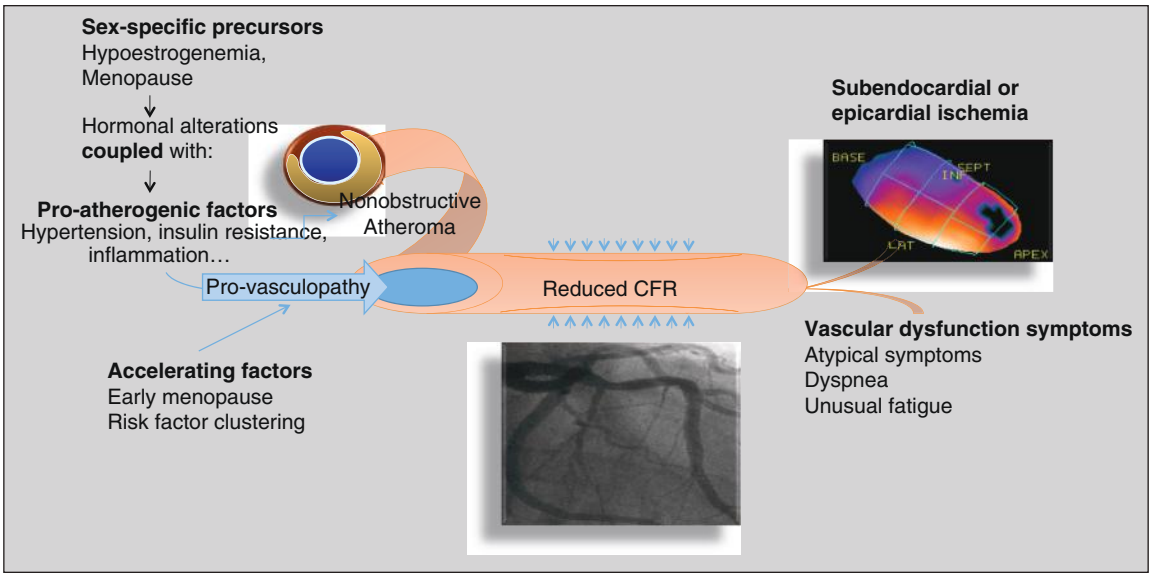

FIGURE 108–5. Hypothetical model of female-specific angina. Reproduced with permission from Shaw LJ, Bugiardini R, Merz CN: Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol.* 2009 Oct 20;54(17):1561-1575.[193]

care facilities to engage with community leaders and organizations to provide optimal environments for healthy living and access to quality health care services. This includes an environment where women can safely engage in daily exercise and have access to heart-healthy food, which requires the help of community leaders and prioritization of public regulatory officials. Increasingly important is the use of social media to create a cultural change to understand individual and societal responsibilities.[34,51]

SUMMARY

This chapter highlights the evidence on sex differences in the pathophysiology and the clinical presentations of IHD among women and identifies significant disparities in primary prevention and stable and acute management strategies resulting in the often reported high adverse outcomes for females. The greater risk factor and comorbidity burden as well as advanced age of women undergoing CVD care compound the challenges of care for women and accelerate CHD risk.[193,194] Women often present with variable symptom characteristics and with a reduced frequency of obstructive CAD that may be etiologic for sex-specific atherosclerotic plaque.[4,20] A working model of female-specific angina is detailed in Figure 108–5. The role of vascular dysfunction and flow abnormalities as they relate to CMD as driving worsening clinical outcomes has yet to be fully elucidated.[4] Currently, guideline-directed strategies for nonobstructive CAD are not defined. However, considerable research has focused on strategies to improve the high-risk status of women referred for coronary revascularization with some success. In general, there are considerable unmet needs of women at risk for CVD, and without concentrated population health and health care strategies tailored for women, it remains unlikely that marked reductions in the observed high clinical adverse outcomes for women will occur. Goals for reducing CVD risk tailored to women remain underexplored, including the role of biology. Clinical and population needs of women and the socioeconomic disparities between women and men remain sizeable hurdles to effecting changes in the large population of young and older women at risk for CVD.

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CHAPTER 109

RACE, ETHNICITY, AND CARDIOVASCULAR DISEASE

George A. Mensah and Patrice Desvigne-Nickens

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INTRODUCTION

Race and ethnicity are social, political, historical, and cultural constructs.[1,2] As such, they are flawed as biological concepts and inappropriate or, at best, imprecise when used as proxy for genetic or other biological phenomena.[1-5] Consistent with this premise, racial and ethnic differences observed in the incidence, prevalence, morbidity, and mortality of cardiovascular diseases (CVD) should not be construed as necessarily resulting from genetic or other biological differences. Additionally, race and ethnicity are often confounded by socioeconomic status (SES). Thus, observed racial and ethnic differences that are not appropriately adjusted for SES and related factors could lead to erroneous conclusions with potentially adverse clinical and public health implications. Despite these challenges, data on race and ethnicity, when properly collected, analyzed, and interpreted, can be invaluable in clinical and public health practice.[6-8] In particular, the appropriate collection and use of data on race and ethnicity are crucial in the quest to eliminate racial and ethnic disparities in cardiovascular health and advance health equity.[9,10]

In this chapter, we first address the historical origins and definitions of race and ethnicity and how the terms have been used within the context of clinical and public health practice in the United States. The established racial and ethnic differences in the magnitude, distribution, outcomes, and trends of leading cardiovascular causes of morbidity and mortality are then presented with emphasis on their trends over the last 25 years. The role that research has played in advancing knowledge on race, ethnicity, and CVD is summarized. We identify the critical gaps in knowledge about race, ethnicity, and CVD that present strategic opportunities for future cardiovascular research to advance health equity.

BACKGROUND AND HISTORICAL PERSPECTIVE

Historical and anthropologic data suggest that the ideology of race was well established in the United States by the 18th century.[3] At that time, the three major labels that were used to define, group, and rank people were "European whites," "Native Americans" or "Indians," and "Negroes" from Africa.[3] These were purely social, legal, and political constructs that had no basis in biological evidence. As Richard Cooper eloquently stated, although race is devoid of any aspects of the "dominant empiricism of modern biology," clinical medicine and public health practice in the United States have embraced racial/ethnic categories as "fundamental structural elements."[11] This use of race/ethnic categories in clinical medicine and public health has remained contentious and controversial, especially when race is viewed or interpreted as a biological construct.[12]

Historically, the biological concept of race has been associated with hierarchical ranking, biological determinism, eugenics, and justification for genocide, colonialism, slavery and other social inequities.[13] It should not be a surprise that the use of racial classifications in medicine is met with skepticism and fear. A major problem with using race as an identifier is the lack of clear definition.[14] Racial admixture and not knowing family ancestry further erode the utility of race classification. Race as a surrogate for biological characteristics and geographic origin is therefore imprecise. Culture, language, religion, and ethnicity have strong sociocultural components and are often poor indicators of ancestry.[13] Finding better ways to measure ancestry and diversity is more likely to yield greater conceptual precision and could enable identification of useful genetic determinants of complex diseases.[13,15] Importantly, race and ethnicity have been shown to introduce provider bias about an individual's ability or willingness to accept care and may adversely impact disease management.[16,17] Despite these limitations, race and ethnicity are associated with differences in disease prevalence, expression, and outcome, as discussed in other sections of this chapter.

In October 1977, the US Government's Office of Management and Budget (OMB) announced government-wide standards for the collection of federal data on race and ethnicity. This has since been revised to account for the changing demographics of the United States.[18] These standards are required for federal data collection and routinely used in medical and clinical research.[19,20] The revised standards contain five minimum categories for race and two categories for ethnicity, as shown in Table 109–1.[19]

RESEARCH ADVANCES IN RACE, ETHNICITY, AND CARDIOVASCULAR DISEASE

Population-based cohort studies[21] have advanced the understanding of CVDs in racial and ethnic minority populations. As shown in Table 109–2, these cohort studies include the Jackson Heart Study, an African American cohort; Strong Heat Study, a Native American and Alaskan cohort; Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a cohort of Central Americans, Cubans, Dominicans, Mexicans, Puerto Ricans, and South Americans; Coronary Artery Disease Risk in Young Adults (CARDIA), a biracial cohort of young adults; Atherosclerosis Risk in Communities (ARIC), a biracial cohort; and Multi-Ethnic Study of Atherosclerosis (MESA), a multiethnic cohort. These cohort studies have advanced and refined our understanding

TABLE 109–1. Categories of Race and Ethnicity as Defined in the 1997 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity

Race	Definition
American Indian or Alaska Native	A person having origins in any of the original peoples of North and South America (including Central America) and who maintains tribal affiliation or community attachment
Asian	A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam
Black or African American	A person having origins in any of the black racial groups of Africa; terms such as *Haitian* and *Negro* can be used in addition to black or African American
Native Hawaiian or other Pacific Islander	A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands
White	A person having origins in any of the original peoples of Europe, the Middle East, or North Africa
Ethnicity	**Definition**
Hispanic or Latino	A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race; the term *Spanish origin* can be used in addition to Hispanic or Latino
Not Hispanic or Latino	A person not of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race; the term *not of Spanish origin* can be used in addition to not Hispanic or Latino

Reproduced with permission from Racial and Ethnic Categories and Definitions for NIH Diversity Programs and for Other Reporting Purposes; NOT-OD-089; April 8 2015. Available at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-089.html.

of disease progression and outcomes in population subgroups and remain a continuing resource for further research in racial and ethnic minority populations and research training in cardiovascular health in racial and ethnic minorities. Examples of intervention studies are shown in Table 109–3. The results from many of these intervention studies have played a crucial role in the improvements in outcomes for hypertension, coronary artery disease, heart failure, and other CVDs. These improvements have not impacted all populations equally. In the next section of this chapter, we review the progress made and persisting challenges in racial and ethnic disparities in CVD.

THE STATE OF RACIAL AND ETHNIC DIFFERENCES IN CARDIOVASCULAR RISK FACTORS AND DISEASE

Racial and ethnic differences in cardiovascular risk factors and CVD have been well described in the United States for decades. For example, using national survey data on risk factor prevalence and indexes of morbidity, mortality, and overall quality of life in adults 18 years of age or older, Mensah et al[22] assessed the magnitude of disparities in CVD in the United States in 2005. That assessment concluded that disparities in CVD were pervasive. In particular, racial and ethnic disparities were common in all risk factors examined. For example, hypertension prevalence was highest among blacks (48.7%) regardless of sex or educational status. Hypercholesterolemia was highest among white and Mexican-American men (49.2%) and white women (56.9%) regardless of educational status. In men, the highest prevalence of obesity was found in Mexican Americans (29.2%) who had completed a high school education.[22] Black women (47.7%) with or without a high school education had a high prevalence of obesity among Medicare enrollees; congestive heart failure hospitalization was higher in blacks, Hispanics, and American Indians/Alaska Natives than among whites; and stroke hospitalization was highest in blacks. Age-adjusted mortality from CVD at all ages tended to be highest in blacks. Overall life expectancy was higher in whites (77.2 years) than in blacks (71.8 years) by approximately 5 years. Although disparities by race and ethnicity were prominent, so were differences by sex, educational attainment, SES,

TABLE 109–2. Examples of Epidemiologic Cohorts of Racial and Ethnic Minorities

Study	Description (No.)	Age (y)	Measures	Findings
Jackson Heart Study	African Americans (5392)	20-80	PE, ECG, ECHO	Multiple risks, HTN control
Strong Heart Study	13 Native American tribes, Arizona, Oklahoma, North and South Dakota (4549) Family cohort (3776) 94 families	35-74	PE, ECG	Reduction in physical activity, changes in diet, and increased rates of smoking leading to DM, obesity, HTN, and increasing rates of heart disease
Hispanic Community Health Study-(HCHS) Study of Latinos (SOL)	Central Americans, Cubans, Dominicans, Mexicans, Puerto Ricans, and South Americans (16,400)	18-74	PE, ECHO	Prevalent risk factors: DM, HTN low awareness and poor control
Atherosclerotic Risk in Communities (ARIC)	Biracial cohort	45-64	PE, biomarkers	Physical activity; healthy lifestyles; obesity control reduce future risk
Coronary Artery Disease in Young Adults (CARDIA)	Young adults	20-45	PE, ECG, ECHO	Prevalence of hypertrophic cardiomyopathy
Multi-Ethnic Study of Atherosclerosis (MESA)	Ethnically diverse (6814)	45-84	Coronary calcium; ventricular mass and function by CMRI	Ethnic differences in coronary calcification not explained by risk factors

Abbreviations: CMRI, cardiac magnetic resonance imaging; DM, diabetes mellitus; ECG, electrocardiogram; ECHO, echocardiogram; HTN, hypertension; PE: physical exam.

TABLE 109–3. Selected Examples of Intervention Studies

Study	Sample Size	Intervention	End Point/Outcome	Comment
ALLHAT	33,357 38% AAs 18% Hispanics	3 interventions: Chlorthalidone Lisinopril Amlodipine	Composite of fatal and nonfatal myocardial infarction	Diuretic is superior first-step therapy
SPRINT	9361 29.5% AAs 10.8% Hispanics 2.1% other	Strategy Intensive therapy < 120 mm Hg systolic Standard therapy < 140 mm Hg systolic	Composite MI or other acute coronary syndrome, stroke, heart failure, cardiovascular death	Intensive strategy reduced primary outcome in all prespecified subgroups
Hip Hop to Health Jr.	409 99% AAs 1% Other	14-week intervention addressing healthy eating and exercise	BMI	Intervention group had smaller increases in BMI compared to controls
Barbershop Intervention	17 shops: 1297 100% AAs	HTN education, BP check, model story, interaction with PCP by barber intervention	Change in BP	Intervention group demonstrated superior HTN control over comparison group
Patient-centered intervention for hypertension control	284 100% AAs	Physician communication skills training and patient coaching (crossover)	Change in BP, process measures	Intervention improved patient-centered communication; BP similar across groups

Abbreviations: AAs, African Americans; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; BMI, body mass index; BP, blood pressure; HTN, hypertension; MI, myocardial infarction; PCP, primary care physician; SPRINT, Systolic Blood Pressure Intervention Trial.

and geographic location. Nevertheless, racial and ethnic disparities in CVD and risk factors were pervasive even in 2005.[22]

PROGRESS IN REDUCING DISPARITIES

In the decade since that assessment, some progress has been made in the quest to improve health care quality and reduce or eliminate health disparities.[23] Although most health disparities have remained unchanged and some have widened, there is evidence to demonstrate that, in some areas, disparities in the burden of CVD and quality of health care have improved. For example, in federally funded research on equity and quality of care in US hospitals, Trivedi et al[24] assessed performance rates for 17 objective quality measures covering three conditions (six measures for acute myocardial infarction, four for heart failure, and seven for pneumonia). The performance rates were adjusted for patient- and hospital-level covariates and compared among non-Hispanic white, non-Hispanic black, and Hispanic patients who received care between 2005 and 2010 in acute care hospitals throughout the United States. The adjusted performance rates for the 17 quality measures improved by 3.4 to 57.6 percentage points between 2005 and 2010 for white, black, and Hispanic adults ($P < .001$ for all comparisons).[24] Figure 109–1 shows changes in within-hospital and between-hospital differences from 2005 to 2010. The three measures (in black-white comparisons, panel A) and six measures (in Hispanic-white comparisons, panel B) shown are those with adjusted rate differences that exceeded 5 percentage points in 2005. As the figure demonstrates, significant improvement in performance on quality measures for white, black, and Hispanic adults hospitalized for acute myocardial infarction, heart failure, or pneumonia was accompanied by significant reduction in racial and ethnic disparities in performance rates both within and among US hospitals.[24] As another sign of progress, Cohen et al[25] reported that among 443 hospitals participating in the Get With the Guidelines–Coronary Artery Disease national quality monitoring and improvement program between January 2002 and June 2007, racial/ethnic differences in individual and composite care were reduced or eliminated. Individual core performance measures included appropriate use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, use of β-blockers at discharge, appropriate use of lipid-lowering drugs, use of smoking cessation counseling, use of aspirin within 24 hours of admission, and use of aspirin at discharge. The composite performance measure of defect-free care was defined as the proportion of patients who received all interventions for which they were eligible.

PERSISTING DISPARITIES IN HEALTH BEHAVIORS AND CARDIOVASCULAR RISK FACTORS

Although examples of successful reduction or elimination of racial and ethnic disparities in CVD exist as demonstrated in the preceding studies,[23-25] there are many more instances showing persistence or widening of disparities. For example, Chang et al[26] used underlying cause of death data and population estimates from the National Vital Statistics System to calculate age-adjusted death rates for CVD and nine other leading causes of death during 1999 to 2010 in order to explore temporal trends in disparities in death rates by sex and race/ethnicity in the United States during this time period. Substantial declines in age-adjusted mortality rate for CVD were noted in all race/ethnic groups, as shown in Table 109–4.[26] Among the 10 leading causes of death, age-adjusted death rates by sex and race/ethnicity declined from 1999 to 2010 for six causes and increased for four causes; however, sex and racial/ethnic disparities between groups persisted for each year and cause of death.[26] For heart disease in 2010, the race/ethnic group with the largest disparity relative to the most favorable group, Asian/Pacific Islander (men 127.3; women 81.4), was the non-Hispanic blacks

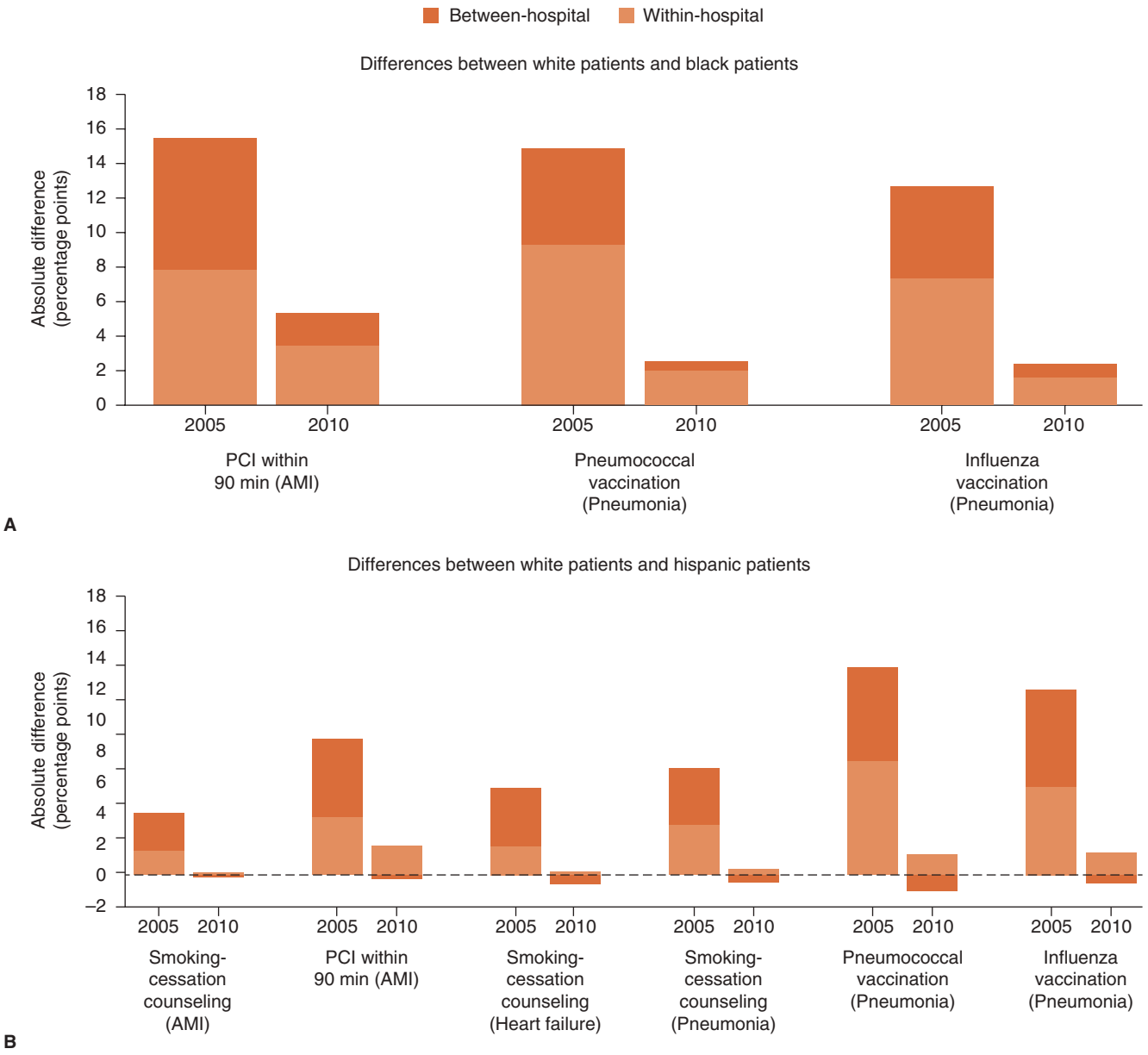

FIGURE 109–1. Absolute differences in performance rates on quality measures in 2005 and 2010. Data on four measures (percutaneous coronary intervention [PCI] within 90 minutes after arrival at the hospital, pneumococcal vaccination, influenza vaccination, and smoking-cessation counseling) for patients who were hospitalized for acute myocardial infarction (AMI), heart failure, or pneumonia are shown. **A.** Changes from 2005 to 2010 are shown for the three measures with adjusted rate differences between white patients and black patients that exceeded 5 percentage points in 2005. **B.** Changes from 2005 to 2010 are shown for the six measures with adjusted differences between white patients and Hispanic patients that exceeded this same threshold in 2005. Reproduced from Trivedi AN, Nsa W, Hausmann LR, et al: Quality and equity of care in U.S. hospitals. *N Engl J Med*. 2014 Dec 11;371(24):2298-308.[24]

(men 286.3; women 189.1). Death rates reported were age-adjusted per 100 000 persons based on the 2000 US Census standard population.[26] The primary drivers of these persisting disparities included those attributed to cardiovascular health behaviors and risk factors.

In their estimates of age-adjusted mortality from individuals from 3099 counties in the United States, Vaughan et al[27] observed county-level race-sex disparities in heart disease mortality trends. For example, from 1973 to 2010, they observed continual strong declines in 73.2%, 44.6%, 15.5%, and 17.3% of white men, white women, black men, and black women, respectively (Fig. 109–2).[27] Additionally, during the period of 1998 to 2010, delayed strong declines occurred in 15.4%, 42.0%, 75.5%, and 76.6% of counties for white men, white women, black men, and black women, respectively (see Fig. 109–2).[27] The authors concluded that over the nearly four-decade period of the analysis, patterns of decline in age-adjusted mortality for heart disease differed by race and geography, possibly reflecting disparities in national and local drivers of these declines.[27] Better understanding of racial and geographic disparities in the diffusion of heart disease prevention and treatment may allow us to make progress toward achieving racial and geographic equity in heart disease survival.

Not surprisingly, hypertension remains a major contributor to the persisting large disparity in age-adjusted mortality rates from heart disease. The age-adjusted hypertension-related mortality rate in non-Hispanic blacks is significantly higher than the rate seen in

TABLE 109–4. Annual Age-Adjusted Death Rate and Absolute and Relative Change in Age-Adjusted Death Rate From 1999 to 2010 for Heart Disease by Race/Ethnicity and Sex in the United States, 1999-2010[24]

Race/Ethnicity	Sex	Age-Adjusted Death Rate per 100,000 Population												Absolute Change From 1999 to 2010	Relative Change (%) from 1999 to 2010 (SE)	*P* Value for Absolute Change From 1999 to 2010	*P* Value for Relative Change From 1999 to 2010
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	No. (SE)			
Non-Hispanic white	Male	330.0	319.9	307.0	302.9	291.6	273.6	267.9	254.6	244.0	240.0	230.4	226.9	−103.0 (0.8)	−31.2 (0.2)	< .001	< .001
	Female	213.9	206.8	201.3	196.4	190.0	178.6	174.8	165.2	157.3	154.6	145.4	142.5	−71.4 (0.5)	−33.4 (0.2)	< .001	< .001
Non-Hispanic black	Male	410.3	396.6	390.9	383.0	377.1	356.4	344.2	334.4	318.5	307.6	294.9	286.3	−124.0 (2.8)	−30.2 (0.6)	< .001	< .001
	Female	286.7	281.0	275.2	270.7	262.1	245.6	238.3	221.9	213.8	206.2	194.7	189.1	−97.6 (1.8)	−34.0 (0.5)	< .001	< .001
Hispanic or Latino	Male	249.2	238.2	234.9	231.2	218.9	208.4	210.5	193.7	183.1	171.2	169.4	165.1	−84.0 (2.8)	−33.7 (0.8)	< .001	< .001
	Female	172.3	163.7	162.1	156.5	153.1	138.8	139.9	130.1	123.2	117.6	109.6	107.8	−64.5 (1.8)	−37.4 (0.8)	< .001	< .001
Asian/Pacific Islander	Male	198.4	185.8	172.6	176.2	164.8	154.1	149.5	145.1	134.4	133.6	130.2	127.3	−71.1 (3.5)	−35.8 (1.3)	< .001	< .001
	Female	124.5	115.6	114.3	111.7	108.3	100.6	97.6	93.8	89.1	88.7	83.7	81.4	−43.1 (2.4)	−34.6 (1.4)	< .001	< .001
American Indian/ Alaska Native	Male	269.3	247.7	243.8	253.7	261.2	242.1	228.0	224.3	217.7	204.9	208.4	202.8	−66.5 (10.4)	−24.7 (3.3)	< .001	< .001
	Female	176.7	158.8	149.8	153.1	159.5	155.3	153.1	149.1	135.3	130.0	129.0	128.2	−48.5 (6.8)	−27.4 (3.2)	< .001	< .001

Abbreviation: SE, standard error.

non-Hispanic whites and Hispanics.[28,29] The disparity is more dramatic when examined by sex (Fig. 109–3).[28] For example, in 2013, the death rates per 100,000 population were 51.6 for non-Hispanic black men but 18.9 for non-Hispanic white men, and 20.0 for Hispanic males.[28] The corresponding rates for women were 36.5 for non-Hispanic black women, 15.8 for non-Hispanic white women, and 15.3 for Hispanic women.[28]

Prominent racial and ethnic differences are also seen in the prevalence of other CVD risk factors. For example, although overweight and obesity are common in US adults, with a 2011 to 2012 prevalence approaching 70% in adult men, there is a greater prevalence in non-Hispanic whites (73%) and Hispanics (80%) than in non-Hispanic blacks (69%).[28] On the other hand, in women, the prevalence of obesity and overweight is much higher in non-Hispanic blacks (82%) than in Hispanics (76%) or non-Hispanic whites.[28] Among children and adolescents age 2 to 19 years, the prevalence of overweight and obesity in the 2011 to 2012 National Health and Nutrition Examination Survey (NHANES) was 31.8%.[28] In general, among all children age 2 to 19 years, the prevalence of overweight and obesity tends to be higher in non-Hispanic black, non-Hispanic white, and Hispanic children than in non-Hispanic Asian children.[28] Additionally, within the Hispanic population, important differences in the prevalence of overweight have been demonstrated. For example, Mexican NHANES participants have a higher mean age-adjusted prevalence of being overweight compared with Puerto Ricans and Cubans.[30]

The 2011 to 2012 NHANES data have also shown that dyslipidemia, assessed by a total cholesterol of 240 mg/dL or greater, was more prevalent in Hispanic adults (14.2% overall) and non-Hispanic white adults (13.5% overall) than in non-Hispanic black adults (9.8% overall).[28] Age-adjusted prevalence estimates from the 2014 National Health Interview Survey (NHIS) in adults demonstrated a greater prevalence of physical inactivity among Hispanics (40.1%) and non-Hispanic blacks (38.3%) than in non-Hispanic whites (26.3%). Finally, the prevalence of current smoking or tobacco use varies significantly by race and ethnicity. Data from the 2014 NHIS in adults age 18 years and older showed a greater prevalence of current smoking in non-Hispanic black men (21.4%), non-Hispanic white men (19.9%), and Alaska Native men (18.6%) than in Asian men (13.8%) and Hispanic men (13.8%).[28] Similarly, non-Hispanic black women (13.4%), non-Hispanic white women (18.3%), and American Indian or Alaska Native women (21.6%) had a greater prevalence of current smoking than Asian women (5.5%) and Hispanic women (7.4%).[28]

Racial and ethnic differences have also been demonstrated for estimated heart age, the predicted age of a person's vascular system based on their cardiovascular risk factor profile.[31] Using data from Behavioral Risk Factor Surveillance System applied to the sex-specific Framingham risk score models, Yang et al[31] compared heart age to chronological age and demonstrated that, on average, predicted heart ages for adult men and women were 7.8 and 5.4 years older than their chronological ages, respectively. Importantly, the prevalence of excess heart age of 5 years or greater (measured as the difference between heart age and chronological age) was greater in non-Hispanic black men (58.7 years) and women (58.9 years) than in other racial/ethnic groups, including non-Hispanic white men (55.3 years) and women (52.5 years).[31]

PERSISTING DISPARITIES IN CARDIOVASCULAR DISEASES AND CONDITIONS

The American Heart Association's *Heart Disease and Stroke Statistics* provides a comprehensive annual update that includes data on race/ethnicity and health behaviors, risk factors, and specific cardiovascular conditions and diseases as well as their clinical and public health outcomes.[28] For example, the 2016 report shows that age-adjusted prevalence estimates for coronary heart disease (CHD) from the 2014 NHIS data are higher in

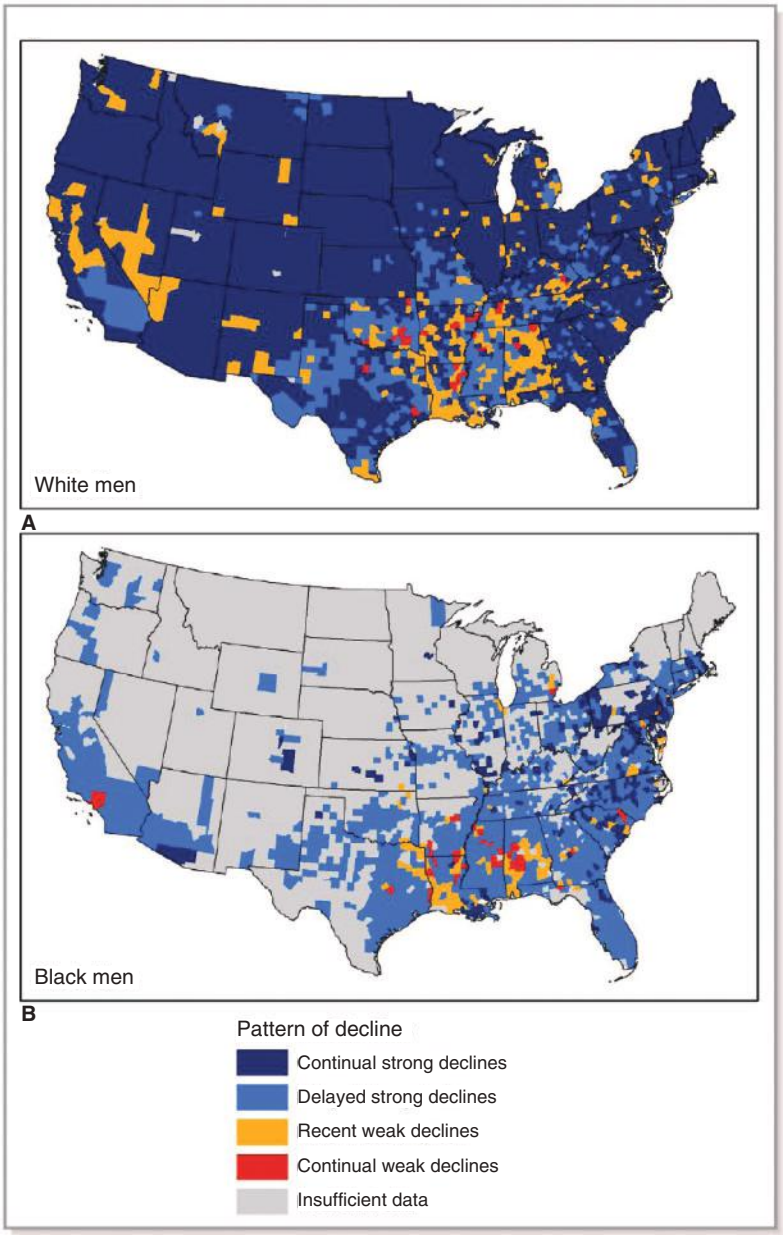

FIGURE 109–2. Patterns of declining county-level heart disease mortality for men (**A**) and women (**B**) in the continental United States from 1973 to 2010. Continual strong or weak declines were statistically faster or slower, respectively, than the total decline for the entire study period; delayed strong or recent weak declines were statistically faster or slower, respectively, than the total decline in the last time period (1998-2010). Reproduced with permission from Vaughan AS, Quick H, Pathak EB, Kramer MR, Casper M. Disparities in Temporal and Geographic Patterns of Declining Heart Disease Mortality by Race and Sex in the United States, 1973-2010. *J Am Heart Assoc*. 2015 Dec 15;4(12). pii: e002567.[27]

native Hawaiians/Pacific Islanders (6.9%), non-Hispanic whites (5.6%), and non-Hispanic blacks (5.6%) than in Asians (3.3%) and Hispanics (4.9%).[28] The reported age-adjusted prevalence for American Indians and Alaska Natives of 6.0% is known to be statistically unreliable. The age-adjusted CHD mortality rates per 100,000 population in men were higher in non-Hispanic blacks (155.1) and non-Hispanic whites (141.8) than in Hispanics (104.7); the corresponding rates in women were also higher in non-Hispanic blacks (94.7) and non-Hispanic whites (75) than in Hispanics (61.3).[28]

There are racial/ethnic disparities in the risk for developing congestive heart failure (CHF).[28,32] In the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort study of 6814 participants of four ethnicities—white (38.5%), African American (27.8%), Hispanic (21.9%), and Chinese American (11.8%)—African Americans had the highest incidence rate of CHF, followed by Hispanic, white, and Chinese American participants (incidence rates: 4.6, 3.5, 2.4, and 1.0 per 1000 person-years, respectively).[32] In addition, African Americans had the highest proportion of incident CHF not preceded by clinical myocardial infarction (75%) compared with other ethnic groups.[32] Importantly, however, differences in the prevalence of hypertension, diabetes mellitus, and socioeconomic factors explained the higher risk of incident CHF among African Americans.[32] Data from the Atherosclerosis Risk in Communities (ARIC) cohort showed that incident heart failure per 1000 person-years was higher in African American men (9.1) and women (8.1) than in white men (6.0) and women (3.4); however, these racial differences in heart failure incidence were largely explained by risk factor differences.[33] In the ARIC cohort, heart failure case fatality rates 5 years after an incident heart failure hospitalization were significantly higher in African American men (51.8%) and women (46.1%) than in white men (41.2%) and women (35.8%).[33]

Additional information on racial and/or ethnic differences in prevalence and mortality of total CVD; prevalence, mortality, and distribution of new and recurrent strokes; mortality of myocardial infarction; and the distribution of physician-diagnosed and undiagnosed diabetes and related mortality are presented for adult men and women in Tables 109–5 and 109–6, respectively. Similarly, the race/ethnic distribution of congenital cardiovascular defects and the distribution of major cardiovascular risk factors in children and youth are presented in Table 109–7. Figure 109–4 shows additional data on racial and ethnic variations in the prevalence of congenital cardiovascular malformations.[34]

In contrast to the excess CVD mortality observed in non-Hispanic blacks in the general US population, Kovesdy et al[35] reported that, in a large cohort of more than 3 million contemporary US veterans with an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2, black veterans had lower all-cause mortality, lower incidence of CHD, and a similar incidence of ischemic stroke (Fig. 109–5). These data were derived from multivariable-adjusted Cox models in a nationwide cohort of 547,441 black and more than 2.5 million white veterans receiving care from the US Veterans Health Administration (VHA).[35] The findings also do not apply to women because the cohort consisted predominantly of men. Compared with the observations in the general US population, the findings could not be explained based on differences in demographic factors, comorbidity, or socioeconomic characteristics; however, the open access to health care and the provision of comprehensive health care based on a veteran status within the US VHA may have contributed.[35] Kuller and Neaton[36] and the VHA study authors and others[35,37] caution that the findings may also be attributable to selection for military service and the subsequent use of VHA services among blacks and whites, and thus, the findings may not be generalizable to the overall US population.

MULTILEVEL FACTORS IN RACIAL AND ETHNIC DISPARITIES

Many factors operating at multiple levels account for the racial and ethnic differences in the distribution of health behaviors, risk factors, disease burden, and associated morbidity and mortality. These factors operate

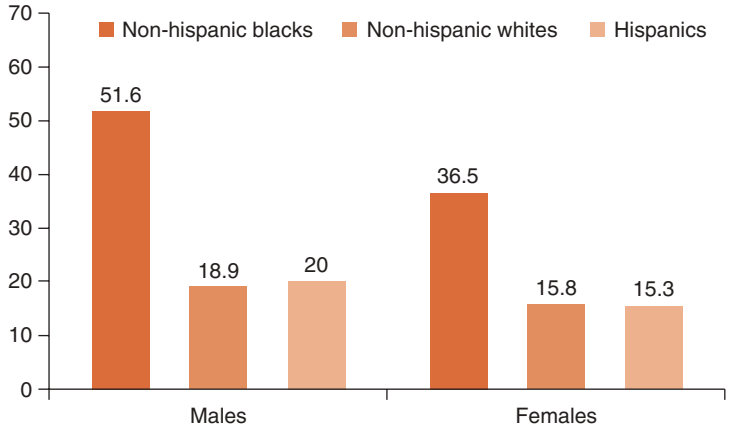

FIGURE 109–3. Disparities in hypertension-related mortality rates by race, ethnicity, and sex in the United States in 2013. Data from Centers for Disease Control and Prevention (CDC).

at the levels of individual patients, health care providers, health systems, health policies, and the communities within which patients live.

PATIENT-LEVEL FACTORS AND SOCIAL DETERMINANTS OF HEALTH

Some of the most often cited patient-level factors are behavioral and lifestyle choices, cultural beliefs and practices, patient preferences, mistrust, and nonadherence to health provider recommendations for healthful behaviors and practices. However, these factors do not exist in isolation and are often influenced by the social determinants of health or, as defined by the World Health Organization, "the circumstances in which people are born, grow, live, work, and age, and the systems put in place to deal with illness."[38] Important within this category are conditions of residential or neighborhood environment and policies at the local, state, and national levels that also impact health and the provision of health-promoting services and resources.

A scientific statement from the American Heart Association addressed *socioeconomic position*—a broader term that encompasses wealth and income, education, employment/occupational status, and other factors. The statement also addressed the "psychological, behavioral, and biological mechanisms through which social determinants precipitate and perpetuate CVD."[39] All of these factors also contribute to the racial and ethnic disparities discussed in this chapter.

HEALTH SYSTEM FACTORS AND DISPARITIES IN CARDIOVASCULAR DISEASE

In addition to these social determinants, there are important health system factors such as access to health care in general and availability of high-quality health care that play important roles in disparities. Within the health system are also myriad financial, organizational, cultural, and linguistic barriers.[39] The amount of contact patients have with the health care system, access to specialty care and referral, and availability of hospitals and health care facilities with advanced technologies in diagnostic and therapeutic interventions represent health systems factors that may affect disparate CVD outcomes.[40,41] For example, in an assessment of hospital emergency department crowding as measured by ambulance diversion, Shen and Hsia[41] demonstrated that hospitals serving a high volume of black patients spent more hours in diversion status compared with other hospitals and that patients who experienced the highest level of diversion had a low probability of admission to hospitals with capabilities for cardiac catheterization, cardiac intensive care, and coronary artery bypass surgery.[41] Most importantly, patients who faced diversion had a 9.6% higher mortality at 1 year.[41] Independent of the health system factors are individual provider-level factors that also contribute to racial and ethnic differences in cardiovascular health.

PROVIDER-LEVEL FACTORS AND RACIAL AND ETHNIC DISPARITIES

Individual provider-level factors are also important in racial and ethnic disparities in CVD. In a landmark report on confronting unequal treatment and related racial and ethnic disparities in health, the Institute of Medicine found that "bias, stereotyping, prejudice, and clinical uncertainty on the part of healthcare providers may contribute to racial and ethnic disparities in healthcare" and may be important factors in the persisting racial and ethnic disparities in health and health care in the United States.[42] Although the Institute of Medicine found no direct evidence that racism, bias, or prejudice among health care professionals affects the quality of care for racial and ethnic minority patients, it concluded that the evidence was strong, albeit circumstantial, and urged further research in this arena.[42]

In fact, several studies have demonstrated that health care providers' diagnostic, treatment, and referral decisions are influenced by the race/ethnicity of patients and that these influences are complex and may be modified by both patient and provider sex.[42] For example, Schulman et al[16] developed a computerized survey instrument in which actors portrayed patients (Fig. 109–6) with particular characteristics in scripted interviews about their symptoms in order to assess physicians' recommendations for cardiac catheterization in the evaluation of chest pain. Their findings suggested that the race and sex of a patient independently influenced how physicians managed chest pain. Although the study found no difference in the referral rate for black men and white men, analysis of race-sex interactions revealed that black women were approximately 60% less likely to be referred for cardiac catheterization than white men.[16] In another study assessing implicit bias, Green et al[43] also demonstrated that health care providers' unconscious biases may contribute to racial/ethnic disparities in use of clinical interventions such as thrombolytic therapy for acute myocardial infarction.

A recent American Heart Association scientific statement shows that although clinicians demonstrate little explicit or intentional bias, there is evidence to suggest that they exhibit substantial bias in their implicit (unconscious) attitudes and the statement presents three ways in which bias may operate in this setting.[44] The study by Schulman et al[16] is cited as an example of how providers' implicit bias, manifesting as stereotypical assumptions, may influence clinicians' decisions regarding referral for diagnostic or therapeutic interventions leading to substandard quality of care. Two other ways in which implicit bias may operate include (1) the generation of lower quality clinical interactions and communication between (more biased) clinicians and racial and ethnic minority patients and (2) stereotype threat wherein "individuals, often unconsciously, fear being judged negatively according to racial stereotypes."[44] The scientific statement calls attention to the need for developing effective interventions to address these phenomena and help improve patient-provider communication as well as patient satisfaction and trust in an effort to improve the delivery of quality health care to racial and ethnic minority populations.

TABLE 109–5. At-a-Glance Data on Cardiovascular Diseases and Risk Factors in Adult Men by Race, Ethnicity, and Sex

Diseases and Risk Factors	Both Sexes	Total Males	NH White Males	NH Black Males	Hispanic Males	NH Asian Males	NH American Indian/Alaska Native Males
Smoking	43.9 M (16.9%)	24.3 M (18.8%)	19.9%	21.4%	13.8%	13.8%	18.6%
Prevalence, 2014*							
PA†							
Prevalence, 2014, %*	21.4%	25.4%	23.6%‡	20.0%‡	15.3%‡	17.0%‡	24.0%‡
Overweight and obesity							
Prevalence, 2012							
Blood cholesterol							
Prevalence, 2012							
HBP							
Prevalence, 2012§	80.0 M (32.6%)	38.3 M (33.5%)	32.9%	44.9%	29.6%	. . .	26.4%*‡
Mortality, 2013	71 942	33 563	22 392	7344	2546	1875‡	420‡
DM							
Prevalence, 2012							
Physician-diagnosed DM§	21.1 M (8.5%)	10.5 M (9.0%)	7.6%	13.8%	12.5%	. . .	. . .
Undiagnosed DM§	8.1 M (3.3%)	5.1 M (4.4%)	4.0%	4.8%	6.8%	. . .	. . .
Prediabetes§	80.8 M (35.3%)	46.4 M (42.4%)	43.0%	36.3%	43.0%	. . .	. . .
Incidence, diagnosed DM§	1.7 M	. . .	. . .	. . .	. . .	. . .	. . .
Mortality, 2013	75 578	39 841	27 807	6298	3934	2271‡	922‡
Total CVD							
Prevalence, 2012§	85.6 M (35.0%)	41.8 M (36.4%)	36.1%	46.0%	32.4%	. . .	. . .
Mortality, 2013¶	800 937	402 851	317 499	48 098	23 892	18 819‡	3895‡
Stroke							
Prevalence, 2012§	6.6 M (2.6%)	3.0 M (2.6%)	2.2%	4.2%	2.8%	. . .	3.0%*‡
New and recurrent strokes	795.0 K	370.0 K	325.0 K	45.0 K	. . .	. . .	. . .
Mortality, 2013	128 978	53 691	40 350	7266	3841	4147‡	569‡
CHD							
Prevalence, CHD, 2012§	15.5 M (6.2%)	8.9 M (7.6%)	7.8%	7.2%	6.7%	. . .	6.0%*‡
Prevalence, MI, 2012§	7.6 M (2.8%)	4.9 M (4.0%)	4.1%	3.4%	3.5%	. . .	. . .
Prevalence, AP, 2012§	8.2 M (3.3%)	4.0 M (3.4%)	3.4%	3.3%	3.2%	. . .	. . .
New and recurrent MI and Fatal CHD#**	965.0 K	560.0 K	480.0 K	80.0 K	. . .	. . .	. . .
New and recurrent MI#**	750.0 K	440.0 K	. . .	. . .	. . .	. . .	. . .
Incidence, AP (stable angina)††	565.0 K	370.0 K	. . .	. . .	. . .	. . .	. . .
Mortality, 2013, CHD	370 213	208 515	168 228	20 758	12 518	8477‡	1949‡
Mortality, 2013, MI	116 793	66 051	53 434	6456	4099	2616‡	589‡
HF							
Prevalence, 2012§	5.7 M (2.2%)	2.7 M (2.3%)	2.2%	2.8%	2.1%	. . .	. . .
Incidence, 2012#‡‡	915.0 K	440.0 K	385.0 K	55.0 K	. . .	. . .	. . .
Mortality, 2013	65 120	28 513	23 847	2933	1144	954‡	230‡

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes heart attack, AP chest pain, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (. . .), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and PA, physical activity. *Age ≥ 18 years (National Health Interview Survey, 2014). †Met 2008 full federal PA guidelines for adults. ‡Both sexes (National Health Interview Survey, 2014). §Age ≥ 20 years. All ages. ¶Total CVD mortality includes deaths of congenital heart disease. #Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races. **Age ≥ 35 years. ††Age ≥ 45 years. ‡‡Age ≥ 55 years.

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Table 109–6. At-a-Glance Data on Cardiovascular Diseases and Risk Factors in Adult Women by Race, Ethnicity, and Sex

Diseases and Risk Factors	Both Sexes	Total Females	NH White Females	NH Black Females	Hispanic Females	NH Asian Females	NH American Indian/Alaska Native Females
Smoking							
Prevalence, 2014*	43.9 M (16.9%)	19.5 M (15.1%)	18.3%	13.4%	7.4%	5.5%	21.6%
PA†							
Prevalence, 2014, %*	21.4%	17.6%	23.6%‡	20.0%‡	15.3%‡	17.0%‡	24.0%‡
Overweight and obesity							
Prevalence, 2012							
Blood cholesterol							
Prevalence, 2012							
HBP							
Prevalence, 2012§	80.0 M (32.6%)	41.7 M (31.7%)	30.1%	46.1%	29.9%	…	26.4%*‡
Mortality, 2013	71 942	38 379	27 446	7230	2362	1875‡	420‡
DM							
Prevalence, 2012							
Physician-diagnosed DM§	21.1 M (8.5%)	10.6 M (8.0%)	6.1%	14.6%	11.8%	…	…
Undiagnosed DM§	8.1 M (3.3%)	3.0 M (2.4%)	1.7%	2.3%	5.0%	…	…
Prediabetes§	80.8 M (35.3%)	34.4 M (28.4%)	28.9%	27.8%	26.0%	…	…
Incidence, diagnosed DM§	1.7 M	…	…	…	…	…	…
Mortality, 2013	75 578	35 737	23 490	6941	3698	2271‡	922‡
Total CVD							
Prevalence, 2012§	85.6 M (35.0%)	43.8 M (33.7%)	31.9%	48.3%	32.5%	…	…
Mortality, 2013¶	800 937	398 086	317 321	48 138	20 976	18 819‡	3895‡
Stroke							
Prevalence, 2012§	6.6 M (2.6%)	3.6 M (2.7%)	2.5%	4.7%	2.0%	…	3.0%*‡
New and recurrent strokes	795.0 K	425.0 K	365.0 K	60.0 K	…	…	…
Mortality, 2013	128 978	75 287	59 409	8845	4286	4147‡	569‡
CHD							
Prevalence, CHD, 2012§	15.5 M (6.2%)	6.6 M (5.0%)	4.6%	7.0%	5.9%	…	6.0%*‡
Prevalence, MI, 2012§	7.6 M (2.8%)	2.7 M (1.8%)	1.8%	2.2%	1.7%	…	…
Prevalence, AP, 2012§	8.2 M (3.3%)	4.2 M (3.2%)	2.9%	5.0%	3.8%	…	…
New and recurrent MI and fatal CHD#**	965.0 K	405.0 K	340.0 K	65.0 K	…	…	…
New and recurrent MI#**	750.0 K	310.0 K	…	…	…	…	…
Incidence, AP (stable angina)††	565.0 K	195.0 K	…	…	…	…	…
Mortality, 2013, CHD	370 213	161 698	129 273	18 441	9270	8477‡	1949‡
Mortality, 2013, MI	116 793	50 742	40 461	6004	2858	2616‡	589‡
HF							
Prevalence, 2012§	5.7 M (2.2%)	3.0 M (2.2%)	2.2%	3.2%	2.1%	…	…
Incidence, 2012#‡‡	915.0 K	475.0 K	405.0 K	70.0 K	…	…	…
Mortality, 2013	65 120	36 607	30 940	3585	1400	954‡	230‡

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes heart attack, AP chest pain, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (. . .), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); NH, non-Hispanic; and PA, physical activity. *Age ≥ 18 years (National Health Interview Survey, 2014). †Met 2008 full federal PA guidelines for adults. ‡Both sexes (National Health Interview Survey, 2014). §Age ≥ 20 years. All ages. ¶Total CVD mortality includes deaths of congenital heart disease. #Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races. **Age ≥ 35 years. ††Age ≥ 45 years. ‡‡Age ≥ 55 years.

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TABLE 109–7. At-a-Glance Data on Cardiovascular Diseases and Risk Factors in Children and Youth by Race, Ethnicity, and Sex

				NH Whites		NH Blacks		Hispanic	
Diseases and Risk Factors	Both Sexes	Total Males	Total Females	Males	Females	Males	Females	Males	Females
Smoking %									
Prevalence, ages 12-17 y, 2013*									
Current cigarette smoking, 2013	5.6%	5.7%	5.5%	7.2%		3.2%		3.7%	
Current cigar smoking, 2013	2.3%	3.2%	1.4%						
Current smokeless tobacco use, 2013	2.0%	3.4%	0.4%						
PA†									
Prevalence, grades 9–12, 2013									
Met currently recommended levels of PA‡	27.1%	36.6%	17.7%	37.5%	18.7%	37.2%	16.0%	33.9%	17.4%
Overweight and obesity									
Prevalence, 2012§									
Children and adolescents, aged 2–19 y, overweight or obese	23.7 M (31.8%)	12.2 M (32.0%)	11.5 M (31.6%)	27.8%	29.2%	34.4%	36.1%	40.7%	37.0%
Children and adolescents, aged 2–19 y, obese	12.6 M (16.9%)	6.3 M (16.7%)	6.3 M (17.2%)	12.6%	15.6%	19.9%	20.5%	24.1%	20.6%
Blood cholesterol, mg/dL, 2012									
Mean total cholesterol									
Ages 6–11 y	160.2	160.5	159.8	158.6	158.2	163.7	159.8	160.5	161.2
Ages 12–19 y	158.3	155.2	161.6	155.2	163.2	153.9	158.6	157.0	160.4
Mean HDL-C									
Ages 6–11 y	53.9	55.4	52.4	55.1	52.5	58.5	54.5	53.5	51.4
Ages 12–19 y	51.4	49.4	53.4	48.9	52.4	52.6	55.1	48.1	53.6
Mean LDL-C									
Ages 12–19 y	89.3	88.3	90.3	89.5	91.1	86.7	90.9	87.4	88.9
Congenital cardiovascular defects									
Mortality, 2013	3051	1634	1417	973	869	268	234	299	253

"Overweight" indicates a body mass index in the 95th percentile of the Centers for Disease Control and Prevention 2000 growth chart. CVD indicates cardiovascular disease; ellipses (. . .), data not available; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; NH, non-Hispanic; and PA, physical activity. *National Survey on Drug Use and Health; respondents were asked, "During the past 30 days, have you smoked part or all of a cigarette?" †Kann L, Kinchen S, Shanklin S, Flint KH, Hawkins J, Harris WA, Lowry R, Olsen EO, McManus T, Chyen D, Whittle L, Taylor E, Demissie Z, Brener ND, Thornton J, Moore J, Zaza S. Youth risk behavior surveillance: United States, 2013 [published correction appears in *MMWR Morb Wkly Rep*. 2014;63:576]. *MMWR Surveill Summ*. 2014;63(suppl 4):1–168. ‡Physically active at least 60 min/d on all 7 days. §Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA*. 2014;311:806–814. doi: 10.1001/ jama.2014.732. All ages.

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RESEARCH PRIORITIES REGARDING RACE/ETHNICITY AND CARDIOVASCULAR DISEASE

In an effort to help advance conceptual thinking and progress in health disparities research within the health care system, Kilbourne et al[45] proposed a framework that organizes the research agenda in three sequential phases: detection, understanding, and reduction or elimination of health disparities. Although work in none of these phases is complete, substantial research investments have been made in the detection, documentation, and follow-up (phase 1) of racial and ethnic disparities in cardiovascular health, especially regarding non-Hispanic black and white persons in the United States.[22,23,28] Further research is needed in American Indians, Alaska Natives, and other race/ethnic groups in whom inadequate data preclude reliable detection of racial and ethnic disparities. In addition, more rigorous definitions of what constitute vulnerable populations within the concept of racial and ethnic disparities are necessary. Methodologic challenges regarding confounders and residual confounding in analyses of racial and ethnic disparities need further work.

Second, further research to clarify the underlying mechanisms of racial and ethnic disparities and improve our understanding (phase 2) of these disparities is necessary. In particular, a deeper understanding of the roles played by stereotyping, provider uncertainty, and implicit bias is needed. Similarly, further research to elucidate other provider- and patient-level factors and how they interact in the clinical and public health settings is needed. Additionally, the role of health systems and health care policies and how they impact racial and ethnic disparities need further work. Novel strategies are needed to help disentangle the complexities and interrelationships in the roles played by individual patient behaviors and lifestyles, ancestry, social and environmental determinants, provider and health systems factors, and policies in the health and nonhealth sectors in the real world.

Of all phases of the research framework, it is phase 3 where further research is most sorely needed. With rare exceptions, we lack examples with compelling evidence of sustained elimination of racial and ethnic

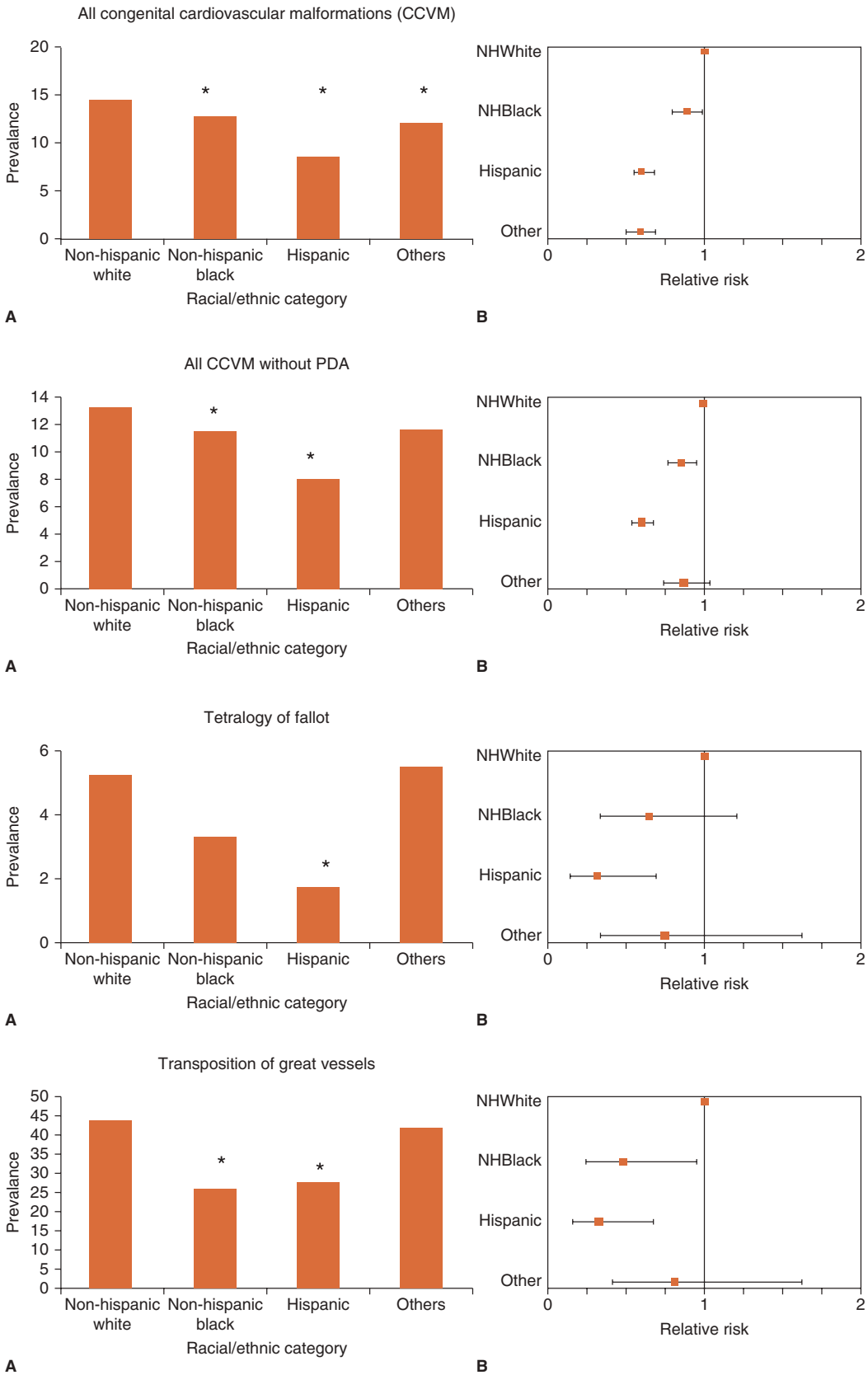

FIGURE 109–4. Racial and ethnic variation in the prevalence of congenital cardiovascular malformations (CCVM) from 1992 to 2001. All CCVM: (**A**) Prevalence is per 1000 live births. *$P < .05$ in comparison to non-Hispanic white. (**B**) Rate ratios of 95% confidence interval. All CCVM without patent ductus arteriosus (PDA): (**A**) Prevalence is per 1000 live births. *$P < .05$ in comparison to non-Hispanic white. (**B**) Rate ratios of 95% confidence interval. Tetralogy of Fallot: (**A**) Prevalence is per 10,000 live births. *$P < .05$ in comparison to non-Hispanic white. (**B**) Rate ratios of 95% confidence interval. Transposition of great vessels: (**A**) Prevalence is per 10,000 live births. *$P < .05$ in comparison to non-Hispanic white. (**B**) Rate ratios of 95% confidence interval. Ventricular septal defects: (**A**) Prevalence is per 10,000 live births. *$P < .05$ in comparison to non-Hispanic white. (**B**) Rate ratios of 95% confidence interval. NH, non-Hispanic. Reproduced with permission from Mangones T, Manhas A, Visintainer P, Hunter-Grant C, Brumberg HL. Prevalence of congenital cardiovascular malformations varies by race and ethnicity. *Int J Cardiol*. 2010 Sep 3;143(3):317-322.[34] (*Continued*)

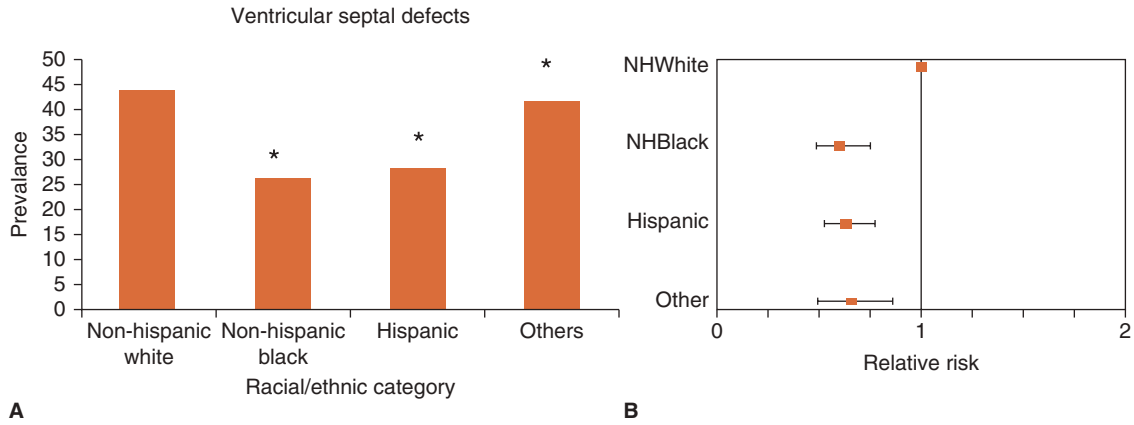

FIGURE 109–4. (*Continued*)

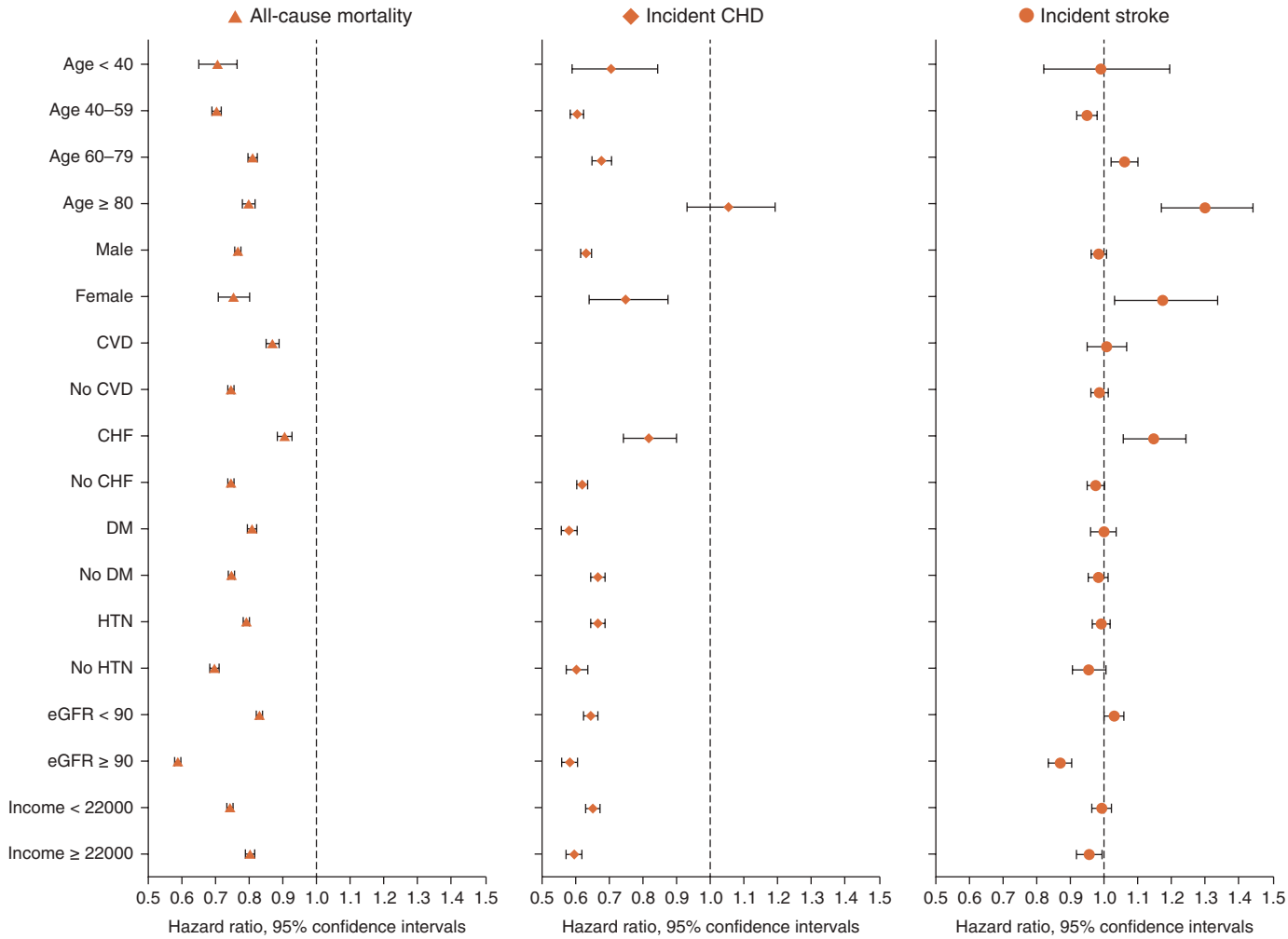

FIGURE 109–5. Association of black race with various outcomes in predefined subgroups of the overall cohort of 3,072,966 veterans. White patients served as referent. Models were adjusted for age, sex, baseline estimated glomerular filtration rate (eGFR), comorbidities, baseline body mass index, systolic and diastolic blood pressures, mean income, marital status, service connectedness, area-level housing stress, low education, low employment, persistent poverty, frequency of Veterans Affairs (VA) health care encounters, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins, receipt of influenza vaccination(s), and each patient's VA health care center. CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension. Reproduced with permission from Kovesdy CP, Norris KC, Boulware LE et al. Association of Race With Mortality and Cardiovascular Events in a Large Cohort of US Veterans. *Circulation*. 2015 Oct 20;132(16):1538-1548.[35]

FIGURE 109–6. The effect of race and sex on physicians' recommendations for cardiac catheterization. Patients as portrayed by actors in the video component of the survey: (**A**) a 55-year-old black woman, (**B**) a 55-year-old black man, (**C**) a 70-year-old black woman, (**D**) a 70-year-old black man, (**E**) a 55-year-old white woman, (**F**) a 55-year-old white man, (**G**) a 70-year-old white woman, and (**H**) a 70-year-old white man. Reproduced from Schulman KA, Berlin JA, Harless W et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. *N Engl J Med*. 1999 Feb 25;340(8):618-626.[16]

disparities in health. For example, in an effort to assess the effectiveness of quality improvement strategies in reducing disparities in health and health care, McPheeters et al[46] identified papers published between 1983 and 2011 that reported metrics enabling the impact on a health disparity to be measured. The review focused on disparities in several clinical conditions including heart failure, hypertension, coronary artery disease, and diabetes. Although most studies focused on racial or ethnic disparities, with some targeted interventions demonstrating greater effect in racial minorities, the report concluded that it was unclear whether the interventions were effective at reducing disparities.[46]

Heart failure is an important contributor to health disparities, with blacks suffering a disproportionate burden of disease. Overall, few potentially eligible patients with reduced ejection fraction heart failure are treated with combination hydralazine plus isosorbide dinitrate (H-ISDN), and among African Americans, less than one-quarter of eligible patients receive guideline-recommended H-ISDN therapy. Yet strong evidence for the H-ISDN recommendation included the landmark African American Heart Failure Trial (A-HeFT), a randomized, placebo-controlled trial that demonstrated 43% and 39% reductions in mortality and heart failure hospitalizations, respectively, in patients receiving guideline therapy plus H-ISDN compared to patients receiving guideline therapy alone. The study population was restricted to self-identified African Americans, which led to a race-based label for the combination pill, BiDil, used in A-HeFT.[47] African Americans in whom heart failure occurs at an earlier age, with structural and functional changes that predate symptoms by a decade, are disproportionately affected by heart failure. Slow adoption of potentially life-saving H-ISDN therapy is problematic not only for high-risk African Americans, but also for eligible patients who may benefit from H-ISDN and is an example of a race construct that undermines more appropriate biologic and physiologic correlates. Chap. 70 addresses treatment of heart failure.

In an assessment of interventions targeted toward reducing disparities in hypertension control, 39 interventions and several state and national policy initiatives that targeted the reduction of racial and ethnic disparities in blood pressure control were identified. Of the six studies that examined disparities, three reduced and two increased disparities, whereas one had no effect on disparities.[48] Thus, although several effective interventions exist to improve blood pressure in racial and ethnic minorities, the evidence that they reduce disparities is limited, and many race/ethnic groups remain understudied.[48] The review concluded with a call for "rigorous evaluation of pragmatic, sustainable, multilevel interventions; institutional support for training implementation researchers, and creating broad partnerships among payers, patients, providers, researchers, policymakers, and community-based organizations" in order to strengthen the evidence and translate it into practice and policy.[48] Fully embracing implementation research as an important part of the health disparities research agenda will go a long way in identifying effective strategies for reducing and eliminating racial and ethnic disparities in cardiovascular health.[49,50]

SUMMARY AND CONCLUSIONS

Race and ethnicity are sociocultural and political constructs that are flawed when used as proxy for genetic or other biological phenomena. As such, racial and ethnic differences observed in the distribution or outcomes of CVDs should not be construed as necessarily reflecting genetic or other biological differences. When properly collected, analyzed, and interpreted, epidemiologic data grouped by race and ethnicity can be invaluable in the quest to eliminate related disparities in cardiovascular health and advance health equity. In the United States, the federal government standards for data collection contain five minimum categories for race and two categories for ethnicity. Using these race/ethnic categories, we have summarized the state of racial and ethnic disparities in CVDs in the United States and shared examples of successful reduction or elimination of disparities and instances showing persistence or widening of disparities. Cardiovascular epidemiologic cohorts of ethnic minority populations represent an important past and future resource for elucidating outcomes in specific minority groups and health disparities. A framework to advance conceptual thinking and progress in health disparities research within the health care system was discussed. The need for novel strategies to help disentangle the complexities of racial and ethnic disparities and cardiovascular health outcomes was emphasized. Additionally, advancing implementation research is essential in the quest to reduce and eliminate racial and ethnic disparities in cardiovascular health and will require researchers skilled in implementation science.

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CHAPTER 110

ENVIRONMENT AND HEART DISEASE

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People in today's ever more densely populated, tightly interconnected, highly urbanized and warming world are surrounded by a complex array of environmental threats to health that include air pollution, water pollution, toxic chemicals, changing dietary patterns, emerging infectious diseases, the urban built environment, noise, and global climate change. Numerous etiologic associations have been established between environmental exposures and disease, including cardiovascular disease.[1]

Pollution is the single most important environmental cause of disease and death.[2,3] The World Health Organization estimates that household air pollution causes 4.3 million deaths annually in persons of all ages[4,5]; many of these deaths are due to heart disease and stroke.[6] Ambient air pollution causes 3.7 million deaths,[7] and many are due to heart disease and stroke. Polluted drinking water, poor sanitation, and inadequate hygiene cause 842,000 deaths.[8] Polluted dust and soil at active and abandoned mines, smelters, industrial facilities, and hazardous waste sites kill tens of thousands more.[9]

Toxic chemicals in the environment are significant causes of disease, specifically cardiovascular disease.[2] Substances known to be cardiotoxic and reviewed in this chapter include air pollution[2,3]; metals,[9] including lead, mercury, arsenic, cobalt, and thallium; halogenated hydrocarbons, including chlorinated, brominated, and fluorinated compounds; organophosphate insecticides; nitrates; and carbon disulfide. Diseases of the heart and cardiovascular system that are linked to toxic chemical exposures in the environment include arrhythmias, hypertension, peripheral vascular injury, cardiomyopathy, acute myocardial infarction (MI), stroke, and sudden death. Toxic chemicals that disrupt endocrine signaling can increase risk for cardiovascular disease by causing elevated lipid levels and increasing risk for obesity, the metabolic syndrome, and diabetes.[10,11]

Likelihood is high that beyond the known cardiotoxic chemicals there are other chemicals in the modern environment whose toxicity to the heart and cardiovascular system has not yet been recognized.[12] These undiscovered cardiotoxins will be found hidden in plain sight among the more than 80,000 new synthetic chemicals that have been invented in the past half century, that are used widely today in myriad consumer products, and that because of failure of stewardship by the chemical industry and by governments have never been tested for safety or toxicity.[12] People are widely exposed to these materials, and annual national surveys conducted by the Centers for Disease Control and Prevention find measurable levels of more than 100 untested synthetic chemicals in the bodies of virtually all Americans.[13]

Two additional environmental exposures that increase risk of cardiovascular disease are noise and global climate change. These are discussed in this chapter.

Given the widespread exposure of the American population to multiple environmental chemicals of unexamined toxicity, every physician is advised to obtain a brief history of occupational and environmental exposure from every new patient and to ask more detailed follow-up questions or seek consultation with a specialist in occupational and environmental medicine if the initial screen raises suspicion of toxic exposure. Straightforward screening algorithms have been developed in occupational and environmental medicine.[14] The most intense exposures typically occur in occupational settings, and most discoveries of new associations between toxic chemicals and disease have been made by physicians examining working populations.

Cardiovascular and other diseases caused by harmful exposures in the environment can be prevented. Alert physicians who have recognized "sentinel events"—previously undiscovered linkages between disease in their patients and toxic hazards in the environment—have time and again played critically important roles in disease prevention.[15] Examples include Irving Selikoff's recognition of the associations between asbestos, lung cancer, and malignant mesothelioma, a discovery that led to bans on most uses of asbestos[16]; Herbert Needleman's discovery of widespread, low-level lead toxicity in American children, which led to the removal of lead from paint and gasoline[17]; and discovery by the investigators in the Framingham Heart Study of the major environmental risk factors for cardiovascular disease, discoveries that have contributed to a greater than 50% reduction over the past five decades in mortality from cardiovascular disease in the United States and in countries around the world.[18] Alert physicians who discover previously unrecognized associations between environmental hazards and cardiovascular disease have the opportunity to make similarly important contributions to the prevention of disease.

AIR POLLUTION

Air pollution is a complex mix of gases—ozone, oxides of nitrogen, and carbon monoxide—and particulate matter.[2,3] A rapidly expanding body of research, especially large epidemiologic studies that combine state-of-the-art assessments of pollution exposure and chemistry with sophisticated markers of cardiovascular disease have substantially advanced knowledge of the effects of air pollution on health and disease.[19-21] These studies consistently find that airborne particulate matter, especially fine particles with mean diameter of less than 2.5 μm, is

closely linked to diseases of the heart and cardiovascular system.[22-24] Especially informative have been epidemiologic studies that combine state-of-the-art measures of air pollution with sophisticated assessments of the pathophysiologic changes that are recognized precursors of cardiovascular disease such as elevations in blood pressure, alterations in cardiac rhythm, the development and progression of atherosclerosis, and the development of insulin resistance.[1,25,26]

PARTICULATE AIR POLLUTION

Particulate air pollution is a complex mix of airborne particles that vary in size and chemical composition depending on their origin. Many contain toxic metals and other potentially harmful materials, and their toxicity is magnified by their high surface-to-volume ratio, which increases their biological reactivity.[2,3]

Combustion of fossil fuels is the most important source of atmospheric particulates in the modern urban environment. Emissions from both stationary sources—factories and coal-fired power plants—as well as from mobile sources—cars, trucks, and buses—contribute to overall exposure, and the mix of stationary and mobile sources varies from city to city.[2,3,5] By contrast, in much of the developing world, the major source of airborne particulates is household air pollution created by the burning of biomass—wood and dried cow dung—in poorly ventilated cook stoves.[4,19,20]

Particle size is a major determinant of the health impacts of airborne particulates. Larger particles with mass median airborne diameters of 10 μm and above (PM10) are usually filtered out of inhaled air in the upper airways and do not penetrate deeply into the lungs except when concentrations are so high that the normal physiologic defenses are overwhelmed, as happened in New York City after the attacks on the World Trade Center[27] and as occurs in highly polluted indoor environments in the developing world.[20] By contrast, fine particles (< 2.5 μm in diameter) are capable of penetrating deep into the tracheobronchial tree. Ultrafine particles (< 0.1 μm) may actually translocate from inhaled air across the alveolar membranes to enter the systemic circulation. Most current US air regulations focus on fine particles.[28]

The association between particulate air pollution and cardiovascular health has been studied extensively, and knowledge in this field has grown rapidly in the past decade. Particulate pollution is associated with hypertension,[26] increased serum lipid levels, and accelerated progression of atherosclerosis.[29-31] Clinically, elevated levels of airborne particulate are associated with increased numbers of emergency department visits and increased hospital admissions for acute MI.[32-35] Particulate air pollution is associated also with increased incidence of cardiac arrhythmias,[35,36] increased cardiovascular disease mortality,[22,23] and increased incidence of stroke.[24] In a recent national US study, it was estimated that each 10-μg/m^3 decrease in concentration of fine particulate matter is associated with an increased life expectancy of 0.61 years.[37]

The mechanisms through which airborne particulates increase the risk of cardiovascular morbidity and mortality are the subject of active investigation. Toxicologic studies suggest that exposures to fine particles induce atherosclerosis and accelerate development of atherosclerotic plaques by increasing oxidative stress, insulin resistance, endothelial dysfunction, and propensity to coagulation.[38-40] Forastiere and Agabiti[38] have developed a schematic to explain this sequence (Fig. 110–1).

CARBON MONOXIDE

Carbon monoxide (CO) is a colorless, odorless, highly toxic gas produced by the incomplete combustion of hydrocarbons. Automotive exhaust is the major environmental source in modern cities. Other sources include improperly adjusted gas heaters, old appliances, wall

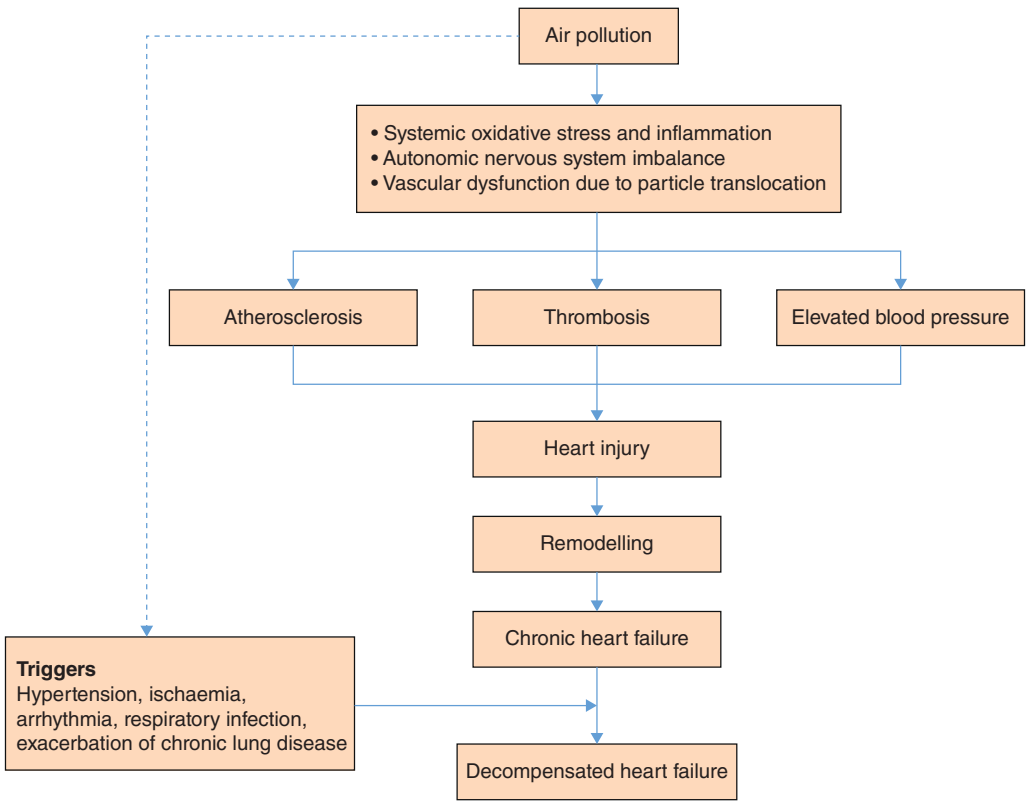

FIGURE 110–1. Possible mechanisms linking air pollution and heart failure. Reproduced with permission from Forastiere F, Agabiti N: Assessing the link between air pollution and heart failure. *Lancet*. 2013 Sep 21; 382(9897):1008-1010.[38]

ovens, stoves, tobacco smoking, and charcoal grilles. CO exerts its toxicity by binding strongly to hemoglobin to block transport of oxygen to tissues. The heart and brain are especially vulnerable. At high doses, CO is acutely toxic, and inhalation exposure can be rapidly fatal.

Initial recognition of the relationship between chronic CO exposure and heart disease came from studies of cigarette smokers who had stopped smoking. Although the incidence of nonmalignant lung disease and lung cancer took years to return to baseline following cessation of smoking, the incidence of acute cardiac events decreased sharply within 24 hours of smoking cessation, a time course consistent with acute reduction in exposure to CO.[41] The relationship between CO exposure and heart disease is further substantiated by studies showing that daily variation in ambient CO levels is associated with concomitant variation in hospital admissions for ischemic heart disease and heart failure.[42,43]

METALS

The metals lead, cadmium mercury, arsenic, cobalt, and thallium have all been documented to cause disease and dysfunction of the heart and cardiovascular system.[9,44]

LEAD

Lead is a heavy metal and a chemical element that composes 0.002% of the Earth's crust. It has a low melting point, is easily molded and shaped, and can be combined with other metals to form alloys. Because of these properties, lead has been used by humans for millennia and is used today in products as diverse as pipes, storage batteries, pigments, glazes, vinyl products, weights, shot and ammunition, cable covers, and radiation shielding. From the 1930s to the 1970s, lead was used extensively as a gasoline additive to improve engine performance.[45] Lead is widespread in the modern environment. Global consumption of lead continues to increase mainly because of rising demand for batteries.[46]

Patients may be exposed to lead by either inhalation or ingestion. Inhalation is the most common route of adult exposure, and the most serious exposures occur among workers exposed occupationally.[47] Workers at greatest risk include smelter and foundry workers, hazardous waste workers, construction workers exposed to lead-painted steel, shipyard workers, electrical workers, and home renovators sanding or removing old lead paint.[47] For children, ingestion of lead paint chips or, more commonly, ingestion of the lead dust eroded from lead paint is the most common route of exposure.[48] Persons of all ages may be exposed by ingestion of lead in drinking water.[48] Ayurvedic and other nonprescription medications are further sources of exposure.[49]

Lead is best known as a neurotoxin. At high levels, lead can cause acute encephalopathy with coma, convulsions, and death.[48] At lower levels, it can cause injury to the central and peripheral nervous systems with loss of intelligence, shortening of attention span, disruption of behavior, and slowing of nerve conduction velocity. Children are especially vulnerable to these effects.[50] There appears to be no threshold below which lead causes no injury to the human brain.[50,51]

Cardiovascular toxicity, specifically increased incidence of hypertension and stroke, was reported more than a century ago among workers with poorly controlled, high-dose occupational exposures to lead.[52] Recent large-scale epidemiologic studies have confirmed a relationship between lead and hypertension in the general US population even at very low blood lead levels.[53-55] A recent systematic review found that the relationship between lead and hypertension is consistent across numerous high-quality studies and concluded that the association is causal.[56] The hypertensive effects of lead have been confirmed experimentally.[56]

Positive associations have also been identified between lead and coronary heart disease, stroke, alterations in cardiac rhythm, and peripheral arterial disease.[57-59] The number of studies examining each of these outcomes is, however, relatively small, and the associations less well established than that between lead and hypertension.[56] Associations between lead and cardiovascular effects have been observed at blood lead levels as low as 5 μg/dL.[56]

CADMIUM

Cadmium is a metallic element used in batteries, electronic equipment, metal coatings, and pigments.[60] Virtually all high-dose exposure occurs in the workplace, and inhalation is the principal route of exposure.[47] Workers at greatest risk of exposure include miners, smelter workers, electroplaters, battery manufacturers, and electronics workers. Nonoccupational exposure can occur through consumption of contaminated drinking water.[60] Tobacco contains cadmium, and smokers consistently have higher body burdens of cadmium than nonsmokers. After it has been absorbed, cadmium is stored in the kidneys and liver and may remain in those organs for decades.[61] Cadmium has been characterized as a human carcinogen by the International Agency for Research on Cancer.[62] High-level exposure to cadmium is associated with impaired renal function and lung cancer.[63-65]

A positive association between cadmium levels and increased blood pressure has been found in the general US population.[66] Increased cadmium burden is associated with an elevated risk of coronary heart disease, stroke, and peripheral arterial disease.[67] Cadmium exposure is associated with elevated circulating levels of inflammatory markers such as C-reactive protein and fibrinogen.[68] Cadmium has been found to be an independent risk factor for atherosclerosis. Elevated cadmium levels are associated with increased carotid arterial intima-media thickness.[69,70]

MERCURY

Mercury is a toxic metal that since antiquity has been used in pharmaceuticals and cosmetics and, more recently, in pesticides, dental fillings, and scientific and medical instruments.[71] Two-thirds of all mercury in the environment is of anthropogenic origin. Combustion of coal in the generation of electricity (all coal contains some mercury) is the single major source of mercury emission to the environment.[71] Waste incineration, including incineration of medical waste, is another important source. Artisanal gold mining, which uses mercury to remove gold from ore, is a major source of mercury exposure, especially in low-income and middle-income countries.[72] Mercury exists in several distinct chemical forms with quite different toxicities. Metallic mercury and methylmercury are the two forms most highly toxic to the cardiovascular system.[73]

Exposure to metallic mercury occurs most commonly in industry.[47] Workers at highest risk of exposure today are artisanal gold miners, chloralkali workers, instrument makers, and workers in the electronics industry. In these workplaces, mercury vaporizes at ambient temperature, and inhalation is the principal route of occupational exposure. Ingestion exposure is not important because metallic mercury is poorly absorbed from the gut.

Acute exposure to metallic mercury is associated with pneumonitis and, at very high levels, encephalopathy. Chronic exposure is linked to peripheral neuropathy with tremor, personality changes (erethism), and renal toxicity with proteinuria.[47]

The cardiovascular effects of chronic occupational exposure to metallic mercury include dose-related increases in hypertension, increased carotid arterial intima-media thickness, coronary heart disease, MI, cerebrovascular accident, and cardiac death.[9,74]

Methyl mercury is formed when airborne particles of metallic mercury emitted by industrial sources deposit in lakes, rivers, and oceans. The deposited mercury is transformed to methylmercury by marine microorganisms. Methylmercury is lipophilic and highly persistent in

the environment. It bioaccumulates to reach particularly high levels in predatory fish at the top of the aquatic food chain such as bluefin tuna, shark, king mackerel, and swordfish. Consumption of contaminated fish is the major route of human exposure to methylmercury.[74]

Methylmercury is a potent neurotoxin.[73] The fetal brain is especially sensitive, and methylmercury crosses freely during pregnancy between the maternal and fetal circulations. Methylmercury has been associated with major outbreaks of developmental neurotoxicity, notably Minamata disease,[75] as well as with widespread subclinical neurotoxicity.[76]

Methylmercury is also a cardiovascular toxin. Methylmercury exposure is associated with disturbances in cardiac rhythm, specifically decreased heart rate variability,[77] hypertension,[78,79] increased carotid arterial intima-media thickness,[80] accelerated progression of carotid atherosclerosis,[81] increased risk of MI,[80] and increased risk of coronary and cardiovascular death.[80] Epidemiologic studies of populations exposed to methylmercury through consumption of fish and marine mammals have had to disentangle the adverse effects of methylmercury from the potentially beneficial effects of omega-3 fatty acids.[81] Experimental studies corroborate the cardiovascular toxicity of methylmercury and suggest that methylmercury may contribute to progression of cardiovascular disease by causing oxidative stress,[82] enhancing procoagulant activity of erythrocytes,[83] or activating inflammatory mediators.[84]

ARSENIC

Arsenic is a toxic metalloid element that occurs naturally in the earth's crust.[85] Drinking water is the principal source of human exposure worldwide, and major problems of arsenic in drinking water are found in southeast Asia, Taiwan, Chile, Argentina, northern New England, and the American Southwest. High concentrations of arsenic are also released into the environment by polluting industries, and inhalation can be an important exposure route for people living near such industries as well as for workers exposed occupationally.[85]

The International Agency for Research on Cancer classifies arsenic as a proven human carcinogen.[86] Inorganic arsenic compounds have been shown in epidemiologic studies to cause cancer of the lung, urinary bladder, and skin. In addition, positive associations have been observed between inorganic arsenic compounds and cancer of the kidney, liver, and prostate.

Arsenic exposure is strongly associated with increased risk of cardiovascular disease.[1,87,88] Positive dose-response relationships have been documented between chronic arsenic exposure and carotid atherosclerosis,[89] hypertension,[90] and ischemic heart disease.[91] Arsenic exposure has also been linked to increased risk of diabetes.[91,92]

Chronic arsenic exposure is strongly associated with peripheral vascular disease. The severity appears related to cumulative dose and is greatest when exposure begins in utero or early childhood. The most severe cases can progress to endarteritis obliterans with frank gangrene of the extremities (black foot disease).[93]

Experimental studies have found that arsenic appears to increase the production of reactive oxygen species and triggers inflammatory responses in endothelial cells. These changes appear to increase risk for atherosclerosis and cardiovascular disease.[94]

COBALT

Cobalt is a relatively rare element with properties similar to those of iron and nickel.[47,95] It is an essential trace element necessary for the formation of vitamin B_{12}.

Excessive exposure to cobalt has been linked to cardiac disease. In 1966, a syndrome labeled "beer drinker's cardiomyopathy" was recognized among heavy beer drinkers in Quebec City, Canada, and was characterized by pericardial effusion, elevated hemoglobin concentrations, and congestive heart failure. The appearance of the syndrome coincided temporally with addition of cobalt to beer.[96] A similar cardiomyopathy has been reported in other groups chronically exposed to cobalt, among them beer-drinking populations and workers producing "hard metal," an alloy that contains cobalt.[47,97]

Experimental studies in a rat models suggest that cobalt may cause myocardial dysfunction and disease by suppressing respiratory chain enzymes in myocardial cells, thus leading to mitochondrial dysfunction.[98]

THALLIUM

Thallium is a highly toxic metallic element.[99] It has been used as a rodenticide, although this use has not been permitted in the United States since 1972. It can be absorbed orally and transdermally. It has neither an odor nor a taste and has been used in poisonings and assassinations. Symptoms of acute intoxication include gastrointestinal symptoms, polyneuropathy, and dermatologic changes. Alopecia typically develops 3 to 4 weeks after exposure.[100]

Cardiovascular manifestations of acute thallium poisoning are hypotension and bradycardia, apparently secondary to direct toxic effects of thallium on the sinus node and myocardium. Diagnosis is made by toxicologic screen. Because thallium exerts its toxicity by displacing potassium, treatment consists of potassium chloride and Prussian blue (potassium ferric hexacyanoferrate) plus supportive measures.[100]

HALOGENATED HYDROCARBONS

The halogenated hydrocarbons are a large and diverse family of synthetic chemicals that have as their common feature a chemical bond between a carbon atom and one or more halogen atoms (chlorine, bromine, or fluorine). The carbon-halogen bond is extremely strong. Consequently, many halogenated hydrocarbons are extremely persistent in the human body and in the environment.

Halogenated hydrocarbons have been used in a wide range of products from electrical insulation (polychlorinated biphenyls [PCBs]) to flame retardants (polybrominated diphenyl ethers [PBDEs]) and water repellents (perfluorinated compounds). Some, such as dioxins and furans, are produced as inadvertent by-products in chemical manufacture or released to the environment through combustion of materials containing chlorine. Because of their lipophilic nature, halogenated hydrocarbons readily cross the placenta and blood-brain barrier. They concentrate and may persist for years in adipose tissues. Depending on their chemical composition and structure, halogenated hydrocarbons have multiple and varied toxicities, among them neurotoxicity, carcinogenicity, and ability to disrupt endocrine function. A number of halogenated hydrocarbons are toxic to the heart and cardiovascular system.

Manufacture and use of many of the older, chlorine-based halogenated hydrocarbons has declined sharply in countries around the world in recent years under the terms of the Stockholm Convention, a global treaty designed to protect human health and the environment against these persistent pollutants by restricting and ultimately eliminating their production, use, trade, release, and storage.[101] By contrast, manufacture and use of the brominated hydrocarbons and of many of the fluorocarbons is strong and increasing.

HALOGENATED ALKANES

Some volatile halogenated alkanes (eg, halothane, methoxyflurane, enflurane) were used many years ago as anesthetics. These compounds are cardiotoxic and depress heart rate, conduction, and contractility.

They can also provoke arrhythmias.[102] Experimental evidence suggests that these compounds exert their toxicity by interacting with cardiac potassium channels as well as with calcium and sodium channels.[103] This toxicity appears to be potentiated by catecholamines. These compounds have, for the most part, been replaced by less toxic anesthetic agents.

HALOGENATED SOLVENTS

High-level, brief exposures to halogenated solvents (eg, trichloroethylene 1,1,1-trichloroethane) have been recognized for many decades to be associated with central nervous system intoxication and acute death, caused apparently by sudden cardiac arrhythmias.[47] High-dose exposures to these compounds may occur in occupational settings and also among persons who "sniff" solvents as a means of intoxication. The suspected mechanism of toxicity, as in the case of halogenated anesthetics, appears to involve disruption of potassium, calcium, and sodium channels.[103]

Methylene Chloride

The halogenated solvent dichloromethane (methylene chloride) is uniquely toxic to the heart and cardiovascular system because its metabolism produces significant amounts of CO.[104] Epidemiologic studies of chemical workers occupationally exposed to dichloromethane have observed excess mortality from heart disease.[105-107]

Dioxins

Dioxins are a family of chlorinated hydrocarbon compounds with a common cyclic chemical structure.[108] Dioxins are highly persistent in humans and the environment. They are lipophilic and bioaccumulative. Exposures to dioxin, and specifically to the highly toxic dioxin congener 2,3,7,8-tetracloro-*p*-dibenzodioxin (TCDD), have occurred among workers in the chemical industry, particularly workers producing herbicides,[109] and in military personnel in the Vietnam War who applied dioxin-contaminated herbicide (Agent Orange). In the general population, exposure results most commonly from consumption of foods, especially meats, in which TCDD has accumulated. TCDD exposure has also occurred in community populations exposed to TCDD from industrial releases.[110]

TCDD has been linked to elevations in population prevalence of cardiovascular risk factors, specifically increased rates of insulin resistance and type 2 diabetes in studies of American and Korean Vietnam War veterans exposed militarily to TCDD-contaminated herbicide,[111,112] in persons in the general US population examined through the National Health and Nutrition Examination Survey (NHANES) study,[113] and in the general population of Japan.[114] TCDD was associated with increased mortality from diabetes among community residents in Seveso, Italy, exposed after an industrial explosion.[115] TCDD and other persistent organic pollutants are associated with hypertension in the general population[116] and with increased risk of obesity and the metabolic syndrome.[117]

A systematic review of 12 epidemiologic studies (10 of them in occupationally exposed populations) found a consistently positive, dose-related, statistically significant association between high-level TCDD exposure and mortality from ischemic heart disease as well as a more modest association with mortality from all forms of cardiovascular disease.[118]

Toxicologic studies of TCDD corroborate these epidemiologic findings. Chronic exposure of rats to TCDD produced a dose-related increased incidence of degenerative cardiovascular lesions, including cardiomyopathy and degenerative arteritis.[119] Mice exposed subchronically to TCDD had increased blood pressure, elevated triglycerides, elevated low-density lipoprotein, elevated total cholesterol, increased cardiac weight, and increased risk of cardiovascular disease.[120] They also showed elevated levels of markers of oxidative stress. Atherogenic apolipoprotein E (apoE) –/– mice exposed subchronically to TCDD developed earlier and more severe atherogenic plaques.[121] Mixtures of TCDD and other halogenated pollutants have been shown to induce insulin resistance and to downregulate two insulin-induced genes centrally involved in lipid homeostasis.[122] TCDD and structurally similar PCBs appear to exert their cardiovascular toxicity through a variety of pathophysiologic mechanisms, including oxidative stress, inflammation, and direct cardiotoxicity, possibly mediated through disruption of mitochondrial function.[123]

Polychlorinated Biphenyls

PCBs, another family of chlorinated hydrocarbons, were previously used in a wide variety of industrial applications, most notably as insulating liquids in electrical generators and capacitors.[124] Because of their environmental persistence and toxicity, manufacture and use of PCBs was banned in the United States in 1977, but PCBs released to the environment many decades ago are still abundant in the environment, especially in riverine and marine sediments. PCBs bioaccumulate in the aquatic food chain and reach the highest levels in predatory marine species such as bluefin tuna, shark, king mackerel, and swordfish. Consumption of contaminated fish is the major current route of exposure.

The most highly cardiotoxic PCBs are congeners that most closely resemble TCDD, (eg, PCB-126). Dioxin-like PCBs have been linked to cardiovascular risk factors, specifically to components of the metabolic syndrome, high blood pressure, elevated triglycerides, and glucose intolerance[116,125-127] and to increased risk for obesity and diabetes.[117,128]

Epidemiologic studies of industrial workers exposed occupationally to PCBs find excess mortality from cardiovascular disease that increases with the duration of employment.[129] Studies of Native American populations heavily exposed to PCBs through a traditional diet high in fish find associations of serum PCB levels with elevated serum lipids and cardiovascular disease risk.[130]

Toxicologic data on PCBs are consistent with these epidemiologic findings. Chronic exposure of rats to PCB-126 produced a dose-related increased incidence of degenerative cardiovascular lesions, including cardiomyopathy and degenerative arteritis.[131] PCB-126 also increased heart weight, serum cholesterol, and blood pressure.[131]

Polybrominated Diphenyl Ethers

PBDEs are a class of bromine-based synthetics used as flame retardants in polymers and textiles.[132] They are incorporated into numerous consumer products, including computers, television sets, mobile phones, electronics and electrical items, polyurethane foam mattresses, carpets, upholstered furniture, and draperies. PBDEs typically constitute between 5% and 30% of these products' net weight. Their use has increased substantially in the past decade, and PBDEs have become major environmental pollutants. PBDEs are lipophilic, accumulate in adipose tissue, and are biologically persistent.

PBDEs are not firmly bound to the materials into which they are incorporated and consequently are released from consumer products to contaminate the home environment. Exposures to PBDEs in house dust are estimated to account for more than 80% of current US intake.[133] In the developing world, PBDE exposure is linked to contact with electronic waste (e-waste).[134]

Human body burdens of PBDEs have increased markedly in recent years. Reflecting differences in regulatory strategy between the United States and the European Union, PBDE levels in US residents are 10 to 20 times higher than in Europeans. PBDE levels in US

residents are doubling every 4 to 6 years.[135] PBDEs are endocrine disruptors, and they disrupt thyroid function.[128] They are developmental neurotoxicants.[136]

PBDE levels are significantly associated with the metabolic syndrome and diabetes at levels of exposure currently seen in the general US population.[137] A recent report suggests an association between PBDE exposure and children's cardiovascular responses to stress.[138] No data are currently available on possible associations between PBDEs and other risk factors for cardiovascular disease.

Perfluorinated Compounds

Perfluoroalkyl acids (PFAAs)—perfluorooctanyl sulfonate (PFOS), perfluorooctanoic acid (PFOA), and their congeners—have been used extensively in the production of fluoropolymers. Members of this class of synthetic chemicals have powerful surfactant and water-repelling properties and have been used in textiles, carpets, upholstery, food packaging, lubricants, electronics, and frying pans.[139]

PFAAs have become widely distributed in the global environment, and like many other halogenated hydrocarbons, they are environmentally persistent. Measurable levels of PFOS and PFOA are found in the serum of a high proportion of US residents through national biomonitoring surveys conducted by the Centers for Disease Control and Prevention.[13] Environmental concentrations have begun to decline since 2000 when 3M, the major manufacturer, instituted a phase-out in production of materials containing PFOS.[140]

Acute, high-level exposures to perfluorinated solvents have been associated with cardiac arrhythmias in laboratory technicians using these compounds to prepare frozen sections for microscopic examination.[141] Cardiac arrhythmias have also been documented in refrigeration technicians chronically exposed to fluorocarbon compounds.[142]

Data on possible chronic cardiovascular toxicity of PFAAs are limited and inconsistent. A cross-sectional study undertaken in Denmark found that increased levels of perfluorinated compounds in overweight 8- to 10-year-old children were associated with higher insulin and triglyceride concentrations.[143] A cohort mortality study of US workers occupationally exposed to PFAAs found borderline significant increases in mortality from diabetes and cerebrovascular disease (standardized mortality ratio, 1.8).[144] However, by contrast, a prospective, population-based cohort mortality study in rural Sweden found no statistically significant associations between levels of seven of the eight perfluoroalkyl substances at baseline and subsequent risk for developing coronary heart disease.[145]

ORGANOPHOSPHATE INSECTICIDES

The organophosphates are a large family of synthetic compounds designed to induce acute neurotoxicity through inhibition of the enzyme acetylcholinesterase. The first organophosphates were produced in the 1930s for use in chemical warfare. Now classified as weapons of mass destruction, production of these highly toxic organophosphate "nerve gases" is strictly limited by international treaty. Nonetheless, in recent years, they have been used in warfare (in Kurdistan) and in terrorist attacks (in Tokyo). The possibility of future use is, unfortunately, real.

Less acutely, toxic organophosphates are widely used today as insecticides in agriculture as well as in the home environment. Acetylcholinesterase inhibition is the mechanism of their insecticidal action. Populations at greatest risk of exposure include farm workers, pesticide applicators, farm workers' children inadvertently exposed to pesticides carried home on workers' clothing, and persons living near farms who may be exposed to airborne "drift."[146] Exposure of the general population occurs through consumption of pesticide-treated fruits and vegetables and also results from pesticide application in houses and apartments.[147] Children are particularly at risk of exposure because of their diets and oral-exploratory behavior coupled with their unique biological vulnerability.[148,149] Prenatal exposures are especially dangerous and can result in persistent neurodevelopmental impairment with loss of cognition (lowered IQ) and altered behavior.

Acute organophosphate poisoning can result from ingestion, inhalation, or dermal or ocular absorption.[47] Signs and symptoms of acute organophosphate poisoning include miosis (pathognomonic but not always present), excessive salivation, vomiting, diarrhea, muscle fasciculation, respiratory depression, bronchospasm, and acute pulmonary edema. Deaths are most commonly caused by respiratory failure. Management consists of supportive care, oxygen, and atropine in escalating doses. In the case of occupational exposure, it is important to decontaminate the skin because of risk of transdermal absorption.

Key cardiac manifestations of acute organophosphate poisoning are bradycardia, ST-segment elevation, and atrioventricular conduction disturbances. Sinus tachycardia is seen in some cases.[150] Longer lasting cardiac changes include QT prolongation and polymorphic tachycardia (torsade de pointes). Complex ventricular arrhythmias are a frequently overlooked and potentially lethal aspect of acute organophosphate poisoning that can cause sudden cardiac death. Cardiac monitoring of acutely intoxicated patients for relatively long periods of time and early aggressive treatment of arrhythmias are critically important to patient survival.[150]

The cardiovascular consequences of chronic exposure to organophosphates are largely unexplored. In rodents chronically exposed to organophosphates at dose levels that produced no overt toxicity, cardiac enlargement was observed and was attributed to hypertrophy of cardiac myocytes.[151]

ORGANOPHOSPHATE CHEMICAL WEAPONS

The most important decision to be made in the immediate aftermath of a suspected chemical weapons attack is whether the causal agent is an organophosphate. This decision is crucial because of all the currently known chemical weapons, only organophosphate intoxication has a readily available, rapidly acting, specific antidote—atropine.[152] On-scene medical triage and treatment are additional key components of management that are proven to save many lives in response to terrorist events. Decontamination of the skin of patients and provision of personal protective equipment for health care workers are essential.[153]

The clinical manifestations of poisoning by the organophosphate "nerve gases" are similar to those of acute organophosphate insecticide poisoning but with more rapid onset and greater severity. Cardiac manifestations include premature ventricular contractions, QT prolongation, and rarely cardiomyopathy.[150,154]

NITRATES AND OTHER NITROGEN COMPOUNDS

Occupational exposures to nitroglycerin and other aliphatic nitrates are strongly linked to excess risks of acute angina, MI, and cardiovascular death.[47] These associations have been studied especially closely among workers in the explosives industry, where the risk of death from cardiac disease among workers exposed to nitroglycerin and trinitrotoluene was elevated two- to three-fold after 20 years of employment. Exposures to these compounds may also occur among workers in the pharmaceutical manufacturing industry.[155]

CARBON DISULFIDE

Carbon disulfide (CS_2) is an industrial solvent, a colorless, highly volatile liquid used in the manufacture of rayon, cellophane, carbon tetrachloride, dyes, and rubber.[156] CS_2 has been used in the production of rocket fuels and in grain fumigation. Exposure occurs primarily in occupational settings, and inhalation is the typical route of exposure.[47]

Long-term occupational exposure to CS_2 is associated with an increased risk of cardiovascular disease.[157,158] CS_2 increases oxidative stress,[159] interferes with lipid metabolism,[160] increases risk of hypertension,[161] and causes functional changes in vessel walls, indicative of atherosclerosis.[162,163] The atherogenic effects of CS_2 have been replicated in an experimental study.[164]

NOISE

A growing body of evidence indicates that chronic exposure to noise, especially in modern urban environments, can adversely affect health and increase risk for ischemic heart disease. A recent meta-analysis of 10 studies examining the cardiovascular effects of road and aircraft noise exposure conducted since the mid-1990s found that relative risk for ischemic heart disease increased by 6% with each 10-dB increase in average noise exposure. The exposure-response relationship was linear and appeared to begin at an average noise level of 50 dB.[165] Concomitant exposure to air pollution does not appear to account for the association between noise exposure and heart disease.[166]

Noise appears to exert its adverse effects on the cardiovascular system primarily by increasing risk for hypertension, which in turn increases risk for MI and stroke. Chronic night time noise appears to be especially hazardous and is associated with disruptions of sleep and increases in stress hormone levels and oxidative stress, which in turn may result in endothelial dysfunction and arterial hypertension.[167] Epidemiologic findings on the association between noise and cardiovascular disease are corroborated by experimental studies.[168]

CLIMATE CHANGE

The principal driver of global climate change is a steady increase in atmospheric levels of carbon dioxide, methane, and other so-called "greenhouse gases" that trap heat above the surface of the earth. Expert scientific reviews have determined that increasing combustion of fossil fuels is the major underlying cause of the increase in greenhouse gases.[169]

Global climate change has multiple consequences relevant to human health. These include including increasing global surface temperatures; changing patterns of precipitation; increased frequency, intensity, duration, and spatial extent of extreme weather events; and rising sea levels with coastal flooding.[169,170]

The health effects of climate change include disease or injury directly associated with extreme weather and climate events, such as dehydration from extreme heat exposure and drowning secondary to flooding following heavy precipitation. Additionally there are indirect effects such as injuries, illnesses, and deaths resulting from changes to ecosystems and diminished air quality.[171,172]

The cardiovascular consequences of global climate change will largely be the result of increased surface temperatures. It is projected that by 2050, major US cities such as New York and Chicago may experience as many as three times their current average number of days hotter than 32°C (90°F). High temperatures are strongly associated with elevated levels of air pollution.[171] The combination of extreme heat and increased levels of air pollution will lead to increased incidence and mortality from heart disease and stroke.[22-25] The posttraumatic stress disorder and depression, which are associated with climate-related natural disasters such as extreme storms, coastal flooding, and forced migration, will further exacerbate the impacts of heat and pollution and may be expected to further increase risk of cardiovascular disease, especially in highly vulnerable populations.[172]

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CHAPTER 111

BEHAVIORAL CARDIOLOGY: EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND CLINICAL MANAGEMENT

Alan Rozanski

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SUMMARY / 2470

Behavioral cardiology is a dynamic new field that studies the role of psychological, social, and behavioral factors that contribute to health and cardiac disease. The field includes various components, as summarized in Table 111–1. These include the epidemiologic study of psychosocial factors that serve as risk factors for cardiovascular disease (CVD) and the pathophysiologic basis for this risk. In addition, the field has become increasingly focused on examining positive psychosocial factors that promote health and longevity and the physiologic basis for such buffering. In the clinical realm, the field seeks to examine psychological approaches for modifying adverse health behaviors that promote disease, such as poor diet and physical inactivity, and for developing approaches that help manage psychosocial risk factors, such as chronic stress, which can contribute to adverse health behaviors and promote disease. Due to the large breadth of this growing field, each of these areas will be reviewed in a general rather than in-depth manner, with references limited to examples of representative studies.

NEGATIVE BEHAVIORAL AND PSYCHOSOCIAL RISK FACTORS

By the late 1990s, considerable evidence had accumulated to identify the role that acute stress can exert in precipitating myocardial ischemia as well as to establish the role of chronic psychosocial factors that are associated with an increased risk for CVD, including depression, hostility, work stress, and social isolation.[1] The epidemiologic evidence supporting the clinical importance of behavioral and psychosocial risk factors has since grown and now includes a number of meta-analyses concerning individual psychosocial risk factors. A comprehensive list of behavioral and psychosocial factors that have now been studied for their relationship to clinical heart disease is listed in Table 111–2.

HEALTH BEHAVIORS

Various negative health behaviors are strongly associated with an increased risk for CVD, including poor nutrition and or weight control, physical inactivity, and smoking. Each of these behaviors is covered in other chapters of this book (see Chaps. 27, 30, 31, and 106).

SLEEP

Poor sleep is a newer arena that has been increasingly studied for its adverse health effects. The study of sleep has included both the examination of sleep duration and the quality of sleep. The definition of short and long sleep is arbitrary, but in most studies, short sleep has been defined as ≤ 5 to 6 hours a night and long sleep as > 8 to 9 hours a night. Repeatedly, studies have found that both short and long sleep, fragmented sleep, and insomnia have been linked to an increased risk for CVD. A meta-analysis of 15 studies found short sleep to be associated with a greater risk of either developing or dying from CVD (relative risk [RR], 1.48; 95% confidence interval [CI], 1.22-1.80), and a similar risk was associated with long sleep.[2] Similarly, a meta-analysis of 13 prospective studies involving 122,501 subjects found that insomnia was associated with a risk ratio of 1.45 (95% CI, 1.29-1.63) for the development of CVD or cardiac events.[3]

These epidemiologic studies have been complemented by a wide variety of studies that have documented consistent pathophysiologic abnormalities in combination with poor sleep, both on an observational basis and in experimental studies that have acutely reduced sleep by various lengths of time among healthy volunteers. These abnormalities include alterations in neuroendocrine and autonomic function, elevation in levels of inflammatory proteins, and an increase in appetite and weight gain, which may be mediated in part through the reduction in the secretion of leptin, an appetite-suppressing hormone, and an increase in ghrelin, an appetite-stimulating hormone, as people get less sleep.[4-6] Meta-analytic studies have also demonstrated an association between short sleep duration and two important mediators of CVD: hypertension[7] and type 2 diabetes.[8]

The future study of sleep duration, however, may benefit from more investigation that relates outcomes according to the reasons for short sleep. For instance, it is yet to be distinguished how short-sleepers who restrict sleep in the pursuit of highly purposeful activity differ in health effects from those who are short-sleepers due to worry or other psychological factors.

TABLE 111–1. The Clinical Scope of Behavioral Cardiology

- Identification of the psychosocial factors that promote coronary heart disease
  - Epidemiologic evidence
  - Pathophysiologic basis
- Identification of psychosocial factors that promote health
  - Epidemiologic evidence
  - Physiologic basis
- Management of adverse health behaviors
- Management of psychosocial risk factors
  - Through fostering better health behaviors (eg, exercise)
  - Through use of psychological interventions

DEPRESSION

Depression, which ranges from mild symptoms to major depressive disorder, is particularly common in cardiac populations. Major depression, which is characterized by depressed mood and/or lack of interest in nearly all activities for ≥ 2 weeks, in conjunction with at least four to five out of nine other psychological symptoms (eg, change in appetite, insomnia, fatigue, guilt), is found in approximately 15% of cardiac patients, and milder depressive symptoms also occur in another 15% of cardiac patients.[9] Epidemiologic studies have consistently demonstrated the potency of depression as a risk factor for cardiac events among community cohorts without preexisting CVD; it is also a risk factor for recurrent events among patients with preexisting CVD. In a large meta-analysis of 54 studies, the adjusted risk ratio for cardiac events was increased nearly two-fold among depressed versus nondepressed subjects in both community cohorts and patients with prior CVD.[10] Epidemiologic studies have also demonstrated a gradient relationship between the magnitude of depressive symptoms and the occurrence of adverse cardiac events. Notably, even mild levels of depression or of overall psychological distress have been found to be associated with an increased risk of adverse events compared to patients without symptoms, as demonstrated, for instance, in a recent large follow-up of 68,222 individuals who were assessed for psychological distress using the 12-item General Health Questionnaire (Fig. 111–1).[11]

TABLE 111–2. Behavioral Risk Factors Associated With Cardiovascular Disease

A. Physical health behaviors
  - Physical inactivity
  - Poor diet and obesity
  - Smoking
  - Poor or inadequate sleep

B. Negative emotions and mental mindsets
  - Depressive symptoms
  - Anxiety
  - Pessimism
  - Anger and hostility

C. Chronic stress
  - Situational stressors
    - Work stress
    - Marital stress
    - Social stressors
    - Caregiver strain
    - Childhood and adult abuse
    - Medical illness
  - Perceived stress

D. Social factors
  - Poor social support
  - Loneliness
  - Low socioeconomic status

E. Lack of life purpose

ANXIETY SYNDROMES

Anxiety is another negative emotion that is common in medical practice. Anxiety symptoms may range from mild symptoms to severe psychiatric conditions, including phobias, panic disorder, generalized anxiety disorder, and post-traumatic stress disorder (PTSD). The presence of anxiety symptoms was found to be associated with an increased incidence of CVD in a meta-analysis of 20 studies (hazard ratio, 1.48; 95% CI, 1.15-1.38), but the analysis was notable for considerable variability in results among individual studies, with only 50% of the studies manifesting a significant adjusted association between anxiety and CVD.[12] Another meta-analysis of 12 studies involving 5750 post–myocardial infarction (MI) patients found a 36% increased risk in overall mortality for those with anxiety symptoms.[13]

Anxiety syndromes requiring psychiatric help are consistently associated with substantial cardiac risk. For instance, in a 10-year follow-up of 438 acute post-MI patients, Roest et al[14] noted an approximately two-fold adjusted risk for adverse outcomes among patients with generalized anxiety disorder, and comparable risk was reported in the Heart and Soul Study.[15] A meta-analysis of 12 studies reported an adjusted hazard ratio of 1.49 (95% CI, 1.24-1.74) for CVD among individuals with panic disorders,[16] and a meta-analysis of six community cohort studies found a hazard ratio of 1.55 (95% CI, 1.34-1.79) for CVD among those with PTSD.[17] The risk associated with PTSD is further highlighted by a study of 562 twins who were followed for a mean of 13 years.[18] The presence of PTSD was associated with a 2.2-fold increase in CVD and greater abnormalities on myocardial perfusion imaging for twins who had PTSD compared to their counterpart twins without a history of PTSD.

HOSTILITY AND ANGER

Hostility is a negative cognitive state that has been widely studied with respect to its potential link to CVD. Hostility is a broad construct that encompasses the traits of anger, cynicism, and mistrust. Interest in this construct was an outgrowth of original work regarding "type A behavior pattern," a triad of hostility, impatience/time urgency, and a highly competitive drive that is no longer studied as a result of inconsistent findings regarding this proposed behavioral construct. A variety of studies have linked hostility/anger to various pathophysiologic determinants of CVD and to progression of atherosclerosis,[9] but epidemiologic study in this arena has been inconsistent. A meta-analysis

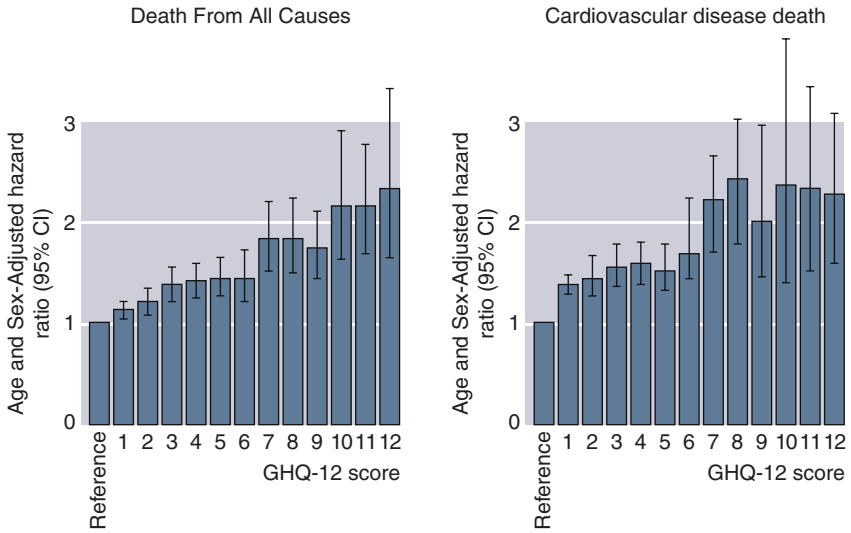

FIGURE 111–1. Association between psychological distress as assessed by General Health Questionnaire (GHQ)-12 scores and the hazard ratios for all-cause mortality (*left*) and cardiovascular death (*right*) among 68,222 individuals. Even mild elevations in GHQ-12 scores were associated with an elevated risk for all-cause mortality and cardiac death. Reproduced with permission from Russ TC, Stamatakis E, Hamer M, et al. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ*. 2012 Jul 31;345:e4933.[11]

of 25 studies found a modestly increased risk for cardiac events in association with anger/hostility among healthy population (RR, 1.19; 95% CI, 1.05-1.03), and a similar increase in a meta-analysis of 19 studies involving patients with known CVD was noted (RR, 1.24; 95% CI, 1.08-1.42).[19] Both a tendency toward some degree of self-denial or lack of self-awareness among patients with hostility and anger and potential limitations in the questionnaires that have been used to assess this psychosocial construct represent challenges in studying this domain.[20]

PESSIMISM

The role of optimism versus pessimism has attracted increasing attention as a risk factor for cardiac events. Pessimism is commonly characterized as a general personality disposition toward expecting negative outcomes in the future; optimists tend toward expecting positive outcomes. Prior study has also assessed optimism versus pessimism according to one's "explanatory style." Pessimists have an explanatory style of invoking self-blame for negative events, as well as a tendency to view negative events as persistent and affecting many aspects of their lives. Optimists, in contrast, tend to avoid self-blame, and view negative events as transitioning and limited in scope. Both dispositional and explanatory pessimism have been linked to negative health outcomes. An increasing number of studies have established a consistent relationship between pessimism and reduced longevity and increased risk of cardiovascular events and stroke.[21] As with most psychosocial risk factors, a dose-response relationship has been noted between the level of pessimism/optimism and the occurrence of cardiac events.

CHRONIC STRESS

Chronic stress can be studied objectively through exposure of experimental animals to stress under controlled circumstances. A particularly useful model in this regard has been the study of chronic stress in cynomolgus monkeys (*Macaca fascicularis*), since these animals both exhibit social behaviors that can be well quantified and develop atherosclerosis in a manner that is similar to humans. When male monkeys are placed into social groups, they fight among each other until they establish a pecking order from the most dominant to submissive monkeys.[22] Fighting then subsides. However, by periodically rearranging the distribution of monkeys within groups, a condition of chronic fighting is established. Among male monkeys who were subjected to the experimental condition of changing groups, dominant male monkeys (who tend to do the most fighting) developed considerably greater atherosclerosis compared to dominant monkeys in stable social groups or to submissive monkeys (Fig. 111–2).

Among individuals, chronic stress has most commonly been studied in relationship to work stress. One of the earliest models of work stress that continues to be studied is that of "job strain." The model posits that job strain is present when individuals demonstrate a high sense of job demand with little job latitude. Studies have consistently shown an increased risk for CVD among those individuals reporting job strain, but the relationship has been relatively modest. For instance, a recent meta-analysis found only a 1.23-fold increase in the incident risk of CVD in association with measurement of job strain.[23] Various other factors may be important to consider when assessing work stress, including the chronicity of the stress. In the INTERHEART study (Effect of Potentially Modifiable Risk Factors Associated With Myocardial Infarction in 52 Countries), the odds ratio for developing MI was 1.38 (95% CI, 1.19-1.61) for those experiencing intermittent work stress, but 2.14 (95% CI, 1.73-2.64) for those experiencing chronic work stress.[24]

Another common stressor is marital stress. Research in this regard has focused on both marital status and strain within marriages. A large

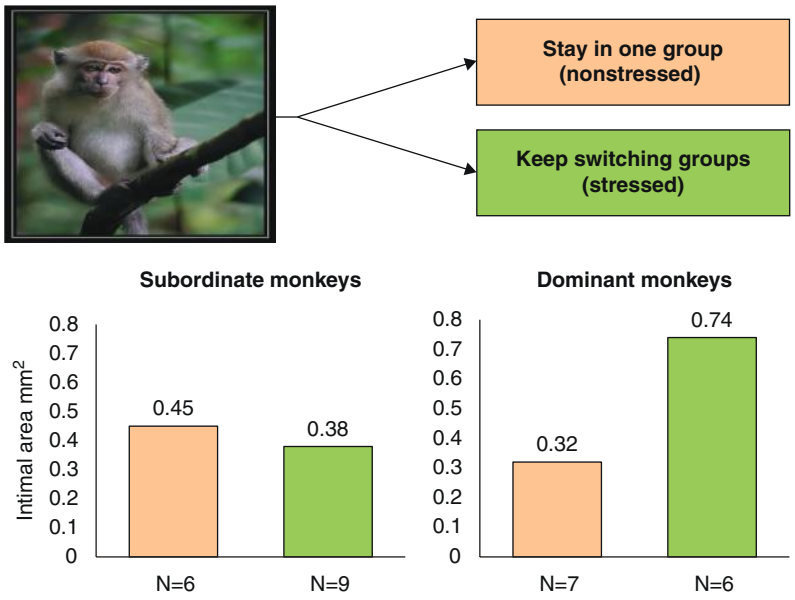

FIGURE 111–2. Comparison of the amount of atherosclerosis at necropsy (vertical axis) among male cynomolgus monkeys that were experimentally divided into "stable" groups (no regrouping) versus "unstable" groups (period regrouping, to ensure continual fighting among monkeys). All monkeys were fed the same atherogenic diet. Dominant males in the unstable group had substantially more atherosclerosis.

meta-analysis of 104 studies that examined data concerning the mortality risk associated with marital dissolution found that the risk of death among those who divorced or separated, compared to married individuals, was age dependent, with risk being highest among younger men who experienced divorce or separation (Fig. 111–3).[25] Study into the cardiovascular health effects of psychological stress within marriages, however, has been quite limited. A few epidemiologic studies, primarily in women, have found that measures of marital stress were associated with an increased frequency of cardiac events, but more consistent study is needed to better evaluate this common stressor.

A third stressor is the enduring effects of childhood abuse or trauma. A meta-analysis of 24 studies has linked childhood abuse to an increased risk of CVD and other adverse medical outcomes in adulthood.[26] In a particularly large study, the Nurses' Health Study 2,[27] which involved a 16-year follow-up of 66,798 women, a history of childhood abuse was common, having occurred in approximately one-fifth of the women, and within this subgroup, it was associated with an approximately 1.5-fold increase in the onset of cardiovascular events by middle age. Adult risk factors such as smoking, diabetes, and body mass index, as well as psychosocial factors, such as depression, accounted for the majority of this risk. Childhood abuse can also induce persistent neuroendocrine and immune dysfunction in adulthood.[28,29]

Acute and chronic illness can also produce stress. For instance, Edmondson et al[30] recently reported a 12% prevalence of PTSD among acute coronary syndrome (ACS) patients in a meta-analysis of 24 studies; in three of these studies, subsequent outcome data indicated a doubling of subsequent mortality risk among ACS patients who had PTSD.

Future study regarding situational stressors may further evaluate how individual differences in perceived stress may affect clinical outcomes. Individuals vary widely in their perceived sense of stress in response to a given life situation, depending on personality, resilient resources, and other factors. One of the interesting aspects regarding stress, in this regard, is an apparent U-shaped relationship between the degree of life adversity and an individual's sense of satisfaction (Fig. 111–4).[31] A likely reason for this U-shaped relationship may be a basic human need to seek growth and meaning, as described by Ryff.[32] That is, people are driven to seek goal-oriented activities and challenges, which provide a source of purpose, life satisfaction, and self-esteem. In the absence of challenge, humans may develop boredom and dissatisfaction, which may lead to negative downstream health effects.

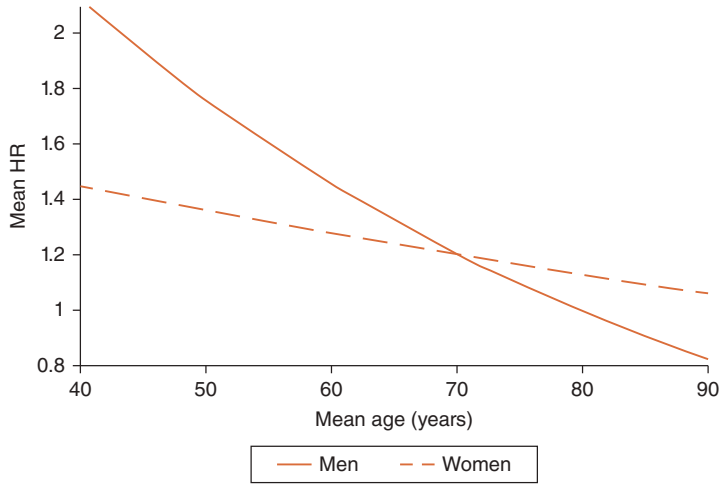

FIGURE 111–3. Mean hazard ratio (HR) for all-cause mortality by mean age in men and women experiencing divorce or separation, based on a meta-analysis of 104 studies. The HR was highest among young men, with the difference among men and women decreasing with increasing age. Reproduced with permission from Shor E, Roelfs DJ, Bugyi P, Schwartz JE. Meta-analysis of marital dissolution and mortality: reevaluating the intersection of gender and age. *Soc Sci Med.* 2012 Jul;75(1):46-59.[25]

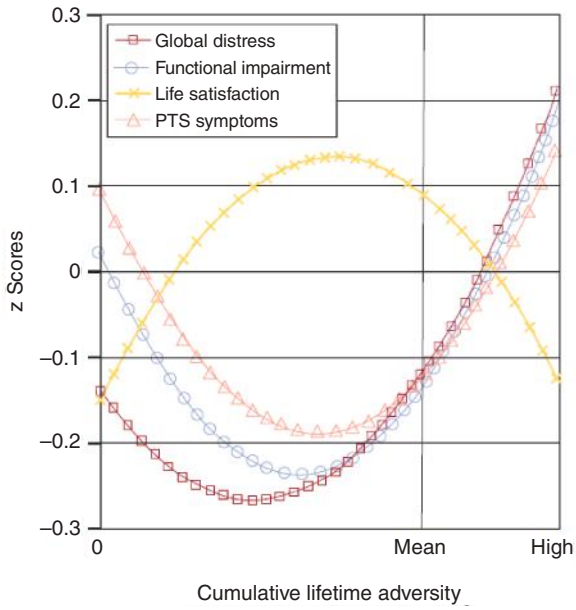

FIGURE 111–4. U-shaped relationship between the magnitude of cumulative adversity and four measures of well-being: global distress, functional impairment, life satisfaction, and posttraumatic stress (PTS) symptoms as assessed among 2398 individuals reporting lifetime exposure to negative events. The presence of some versus no exposure to stress predicted lower global distress, functional impairment, and PTS symptoms and higher life satisfaction scores. Adapted with permission from Seery MD, Holman EA, Silver RC. Whatever does not kill us: cumulative lifetime adversity, vulnerability, and resilience. *J Pers Soc Psychol.* 2010;99:1025-41.[31]

In addition, the meaning that is invested within a given life situation may be a potential modifier of perceived stress and clinical outcomes. For instance, caregiving is a stress that has not been uniformly found to be associated with an increased frequency of clinical events. Potentially, the amount of meaning associated with the caregiving experience could be an important modifying factor,[33] but this postulate requires prospective study.

A further aspect regarding perceived stress is the self-beliefs or concerns that patients may have regarding the potential toxicity of stress. This issue was recently studied by Keller et al.[34] They assessed mortality rates in a representative US sample of 28,753 individuals, who rated both their level of perceived stress and their perception as to whether their stress was impacting their health. Among those who reported a high level of stress, increased mortality occurred only among those who also self-appraised their stress as harmful to their health. Pending more prospective study, this finding suggests that modifying patients' self-beliefs regarding the toxicity of stress might be a potentially useful behavioral intervention.

SOCIAL ISOLATION AND POOR SOCIAL SUPPORT

As with chronic stress, the pathophysiologic effects of social isolation can be studied experimentally in social animal species. As summarized by Capiocci et al,[35] placing social animals into isolation has been shown to produce adverse physiologic effects. A direct effect of social isolation upon atherosclerosis has been assessed quantitatively in female cynomolgus monkeys. Compared with dominant female monkeys, female monkeys who are submissive are more prone to atherosclerosis when fed a high-cholesterol diet, but placing monkeys in a single cage results in

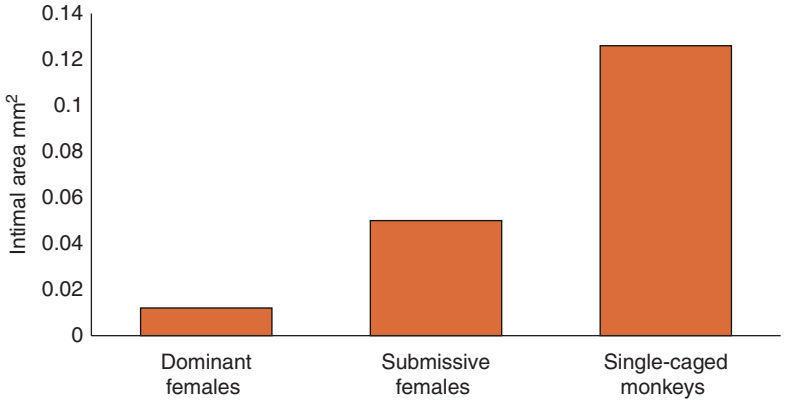

FIGURE 111–5. Comparison of the amount of atherosclerosis at necropsy among female cynomolgus monkeys in social groups and in monkeys that were housed in single cages, all fed the same atherogenic diet. Among the social groups, female monkeys that were submissive had more atherosclerosis, but the single caged monkeys had substantially greater atherosclerosis than the monkeys who were in groups. Data from Shively CA, Clarkson TB, Kaplan JR. Social deprivation and coronary artery atherosclerosis in female cynomolgus monkeys. *Atherosclerosis*. 1989 May;77(1):69-76.[36]

substantially greater amounts of atherosclerosis compared to monkeys housed in social groups (Fig. 111–5).[36]

The role of social factors upon human health has been repeatedly demonstrated. The classic Alameda County study was the first to link mortality risk to the size of one's social network in a large epidemiologic study.[37] This study demonstrated a strong inverse gradient relationship between the size of one's social network and subsequent risk of mortality (Fig. 111–6). The study of social health has subsequently expanded to include many aspects of social life, including the size, structure, and frequency of contact within social networks, and various aspects of functional support, including informational and emotional support. Both structural and functional support are important mediators of health outcomes. A recent meta-analysis of 148 studies indicated a large effect size regarding the health buffering provided by strong social support.[38] An index of social integration was associated with an approximately two-fold increase in survival in this meta-analysis.

LOW SOCIOECONOMIC STATUS

Socioeconomic status (SES) is generally characterized as a composite of factors, such as education, occupational status, economic resources, and social status. Longitudinal studies have consistently demonstrated a strong inverse gradient between various measures of SES and adverse cardiac events,[39] including recent novel data based on tax and Social Security records, which demonstrate a marked gradient between income and life expectancy in the United States.[40] Among children, low SES status also augurs for a greater risk of adult CVD risk factors and adverse cardiac outcomes.[41] Low SES has the capacity to serve as a composite chronic stressor because of the various factors that make stressful experiences more likely in low SES environments, including a greater likelihood of more financial strain, less job security and latitude, poorer housing conditions, more impoverished neighborhoods, and/or a diminished sense of public safety. Several mechanisms appear to account for the increased risk associated with low SES. First, low SES is associated with a higher frequency of poor health habits, such as poor nutrition and overeating, smoking, and physical inactivity.[42] Second, the stress associated with low SES (eg, economic hardship, job insecurity) increases the prevalence of depression and other mental status parameters that may in turn increase CVD.[43] In addition, pathophysiologic mechanisms that can promote CVD are also more prevalent in low SES populations, such as more autonomic and metabolic dysfunction.[44,45]

SYNERGY AMONG PSYCHOSOCIAL RISK FACTORS

Although epidemiologic study tends to assess individual psychosocial risk factors in isolation, these factors have a high tendency to cluster in real life. Various lines of evidence indicate that clustering of psychosocial risk factors increases the risk of clinical events. For instance, poor social support can augment the health impact of life stress. In an early study in this regard, Ruberman et al[46] found that high levels of life stress or social isolation each doubled the risk of all-cause mortality compared to patients with low levels of each risk factor among 2230 post-MI patients followed for 3 years. However, when both risk factors were present, mortality risk was substantially increased compared to the presence of one risk factor alone (Fig. 111–7).

Similarly, psychological stressors are also potentiated when occurring among individuals with low SES.[47,48] Depression and anxiety are highly comorbid, and when both are present, the likelihood for future clinical event rates is elevated compared to the presence of either emotion alone.[49] The prognosis associated with psychosocial stress may also be potentiated by the presence of poor health habits, such as physical inactivity (Fig. 111–8).[50]

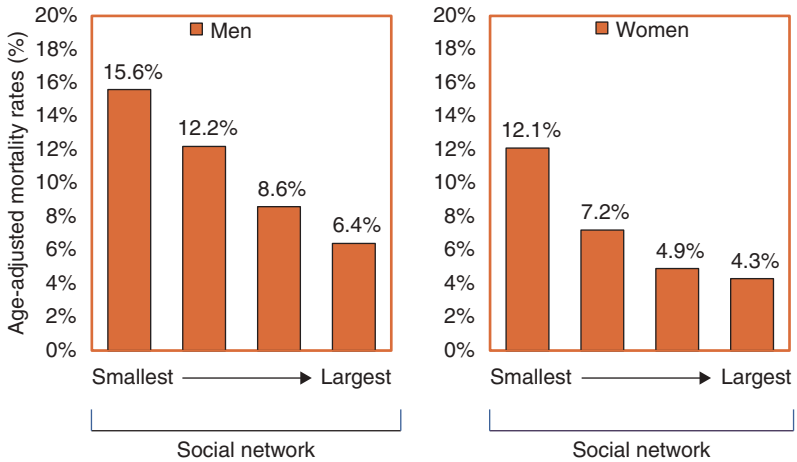

FIGURE 111–6. Age-adjusted mortality rates among men and women during a 9-year follow-up of Alameda County residents divided according to the size of their social network.

PATHOPHYSIOLOGY OF NEGATIVE PSYCHOSOCIAL STRESSORS

The pathophysiologic mechanisms by which psychosocial risk factors promote atherosclerosis and increase the risk for cardiac events has been extensively studied, both in human studies and in experimental animal studies. Psychosocial risk factors exert their deleterious effects by two basic pathways: a wide variety of direct pathophysiologic effects and negative impact on health behaviors (Fig. 111–9).[9,21] When psychosocial stress is chronic, such as in depression, it can result in persistent activation of the hypothalamic-pituitary-adrenal axis and dysregulation of the sympathetic nervous system, leading to a rise in serum cortisol levels and elevated norepinephrine levels. The result is widespread systemic effects, which vary in presentation according to the type and magnitude of stress. In depression, these effects include autonomic dysfunction; a variety of endocrine-related abnormalities, including central obesity, insulin resistance, and a three-fold

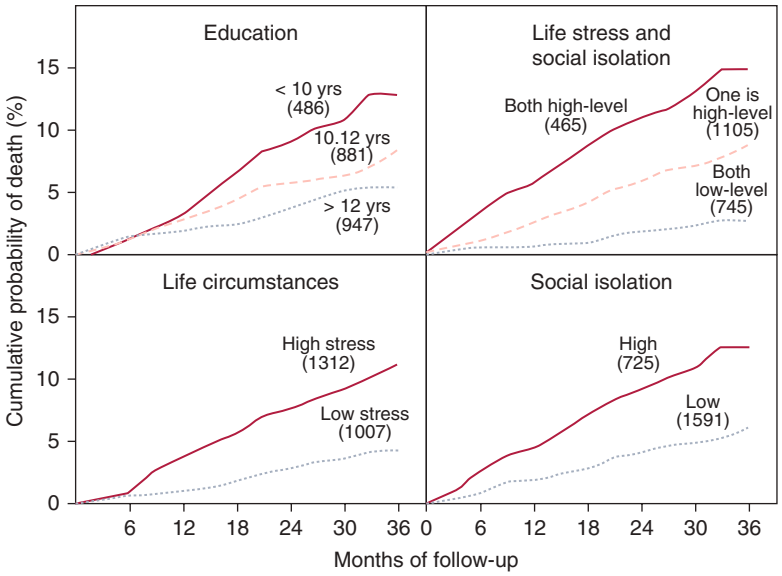

FIGURE 111–7. Cumulative mortality curves among post–myocardial infarction patients followed for 36 month, according to baseline levels of education, life stress, and social isolation. When both life stress and social isolation were considered together, there was a substantially larger gradient of risk compared to consideration of either factor alone. Reproduced with permission from Ruberman W, Weinblatt E, Goldberg JD. et al: Psychosocial influences on mortality after myocardial infarction. *N Engl J Med*. 1984 Aug 30;311(9):552-559.[46]

increase in the risk for diabetes; increased risk for ovarian dysfunction and osteoporosis; endothelial dysfunction; a variety of platelet abnormalities; and unfavorable alterations in brain plasticity, including enlargement of the amygdala (the brain's fear center) and reduction in the size of the hippocampus and prefrontal cortex.[1,9] Other pathophysiologic effects of chronic stressors may include increased risk of arrhythmias, hypertension, and enhanced cardiovascular reactivity (ie, the tendency to manifest increased heart rate and blood pressure responses to physiologic stimuli with prolonged time to recovery to baseline measurements). Cardiovascular reactivity has been linked to a higher frequency of subsequent hypertension and carotid intima-medial thickness according to a meta-analysis of 36 studies.[51]

There are two principal behavioral mechanisms by which psychosocial risk factors also exert their pathogenic effects. First, extensive study has repeatedly demonstrated that unhealthy behaviors, such as overeating, poor nutritional choices, physical inactivity, and smoking, are more common among patients with psychosocial risk factors, such as depression, anxiety, pessimism, loneliness, and chronic stress. Second, these same psychosocial factors tend to impede the ability of patients to comply with behavioral changes recommended by their physicians. For instance, a meta-analysis of 122 studies found that various aspects of social support each had a significant negative effect upon patient adherence to medical regimens.[52] Similarly, another meta-analysis found a three-fold increase in poor patient adherence among depressed versus nondepressed patients.[53]

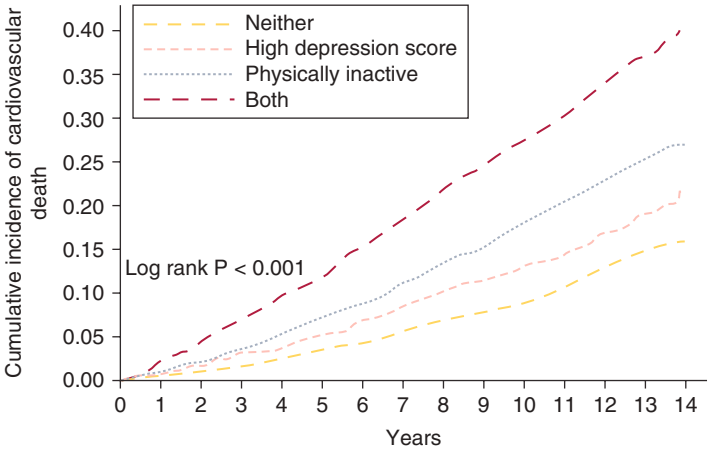

FIGURE 111–8. Cumulative incidence of cardiovascular death in the Cardiovascular Health Study. Both depression and physical inactivity each individually increased the risk of cardiovascular mortality, but when both were present, there was greater mortality than the presence of either risk factor alone. Reproduced with permission from Win S, Parakh K, Eze-Nliam CM, et al. Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: the Cardiovascular Health Study. *Heart*. 2011 Mar;97(6):500-505.[50]

POSITIVE PSYCHOSOCIAL FACTORS

In recent years, there has been an increasing focus on the health benefits associated with positive psychological factors. It is now well recognized that each of the major psychosocial domains can be characterized according to a spectrum, ranging from positive factors that promote health to negative factors that promote disease (Fig. 111–10).[21] Increasing evidence has delineated several mechanisms by which positive psychosocial functioning promotes health. This includes physiologic buffering, which may be, in part, a result of reduced activation of the neuroendocrine and immune systems (as opposed to the hyperarousal seen with negative stressors), as evidenced, for example, by optimism.[54-56] Second, positive psychosocial factors are associated with an increased likelihood of positive health behaviors.[57] Third, positive psychosocial factors may help enhance coping resources, including cognitive functions, social resources, and problem-solving capacities.[9,58]

Epidemiologic data support the importance of positive psychosocial factors. For instance, Chida and Steptoe[59] performed a meta-analysis of studies that assessed the impact of positive psychological well-being upon mortality in both community cohorts and diseased populations. Psychological well-being had a favorable effect on survival in both groups. This initial meta-analysis included a broad definition of well-being, including such factors as positive mood, optimism, and life satisfaction. Recent study has begun to further focus on the relationship between specific positive psychological constructs and cardiovascular outcomes.

An important construct in this regard is that of life purpose, which has been proposed as a basic psychological need by many theorists. In a recent meta-analysis of 10 prospective studies involving over 136,000 subjects assessed for both all-cause mortality and cardiovascular events, the risk ratio for cardiac events was 0.65 prior to risk adjustment and 0.83 after risk adjustment.[60] Similar findings were noted for all-cause mortality. The results were highly consistent among the studies constituting this meta-analysis. A higher sense of purpose has also been linked to a reduced risk of stroke,[61] future physical disability,[62] and dementia.[63] Purpose in life may be health promoting through a number of mechanisms. Preliminary data suggest that life purpose may provide positive physiological buffering,[60] although the data are scant in this regard. Purpose in life may also serve to promote healthier behaviors and less use of medical services. In addition, purpose in life may be associated with greater resilience, as suggested by a meta-analysis of 70 studies that found that purpose in life was associated with a greater sense of competence, stronger social integration, and more positive affect.[64]

Another measure of positive health is the presence of vitality, defined as the subjective sense of feeling energetic, which is both pleasurable

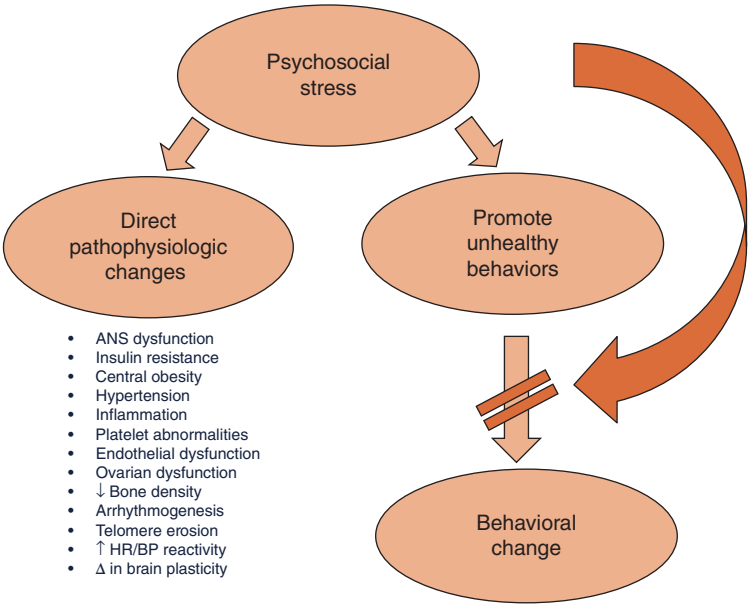

FIGURE 111–9. Psychosocial risk factors promote coronary disease risk through two basic mechanisms: direct pathophysiologic effects, which may vary according to the type and intensity of psychosocial stress, and behavioral effects, including a greater propensity toward unhealthy behaviors when psychosocial stress is present and a decreased likelihood of adhering to behavioral recommendations. ANS, autonomic nervous system; BP, blood pressure; HR, heart rate.

and activating (ie, creating a greater tendency to do things).[65] As previously proposed,[9] the presence of vitality is a function of both physical and psychological well-being (Fig. 111–11). The presence of vitality can help support coping mechanisms for dealing with life stress and the regulation of emotions, which are important resilience mechanisms. Conversely, successful coping and emotional regulation are mechanisms that help preserve energy and promote vitality.

Kubzansky and Thurston[66] assessed the significance of a baseline measurement of vitality in a 15-year follow-up of 6265 individuals who were initially free of CVD. A dose-response curve was evident between baseline vitality and subsequent development of CVD. Those having the highest vitality at baseline had the least development of CVD. Similarly, emotional vitality has been associated with a decreased risk of stroke[67] and hypertension.[68] On the other end of the spectrum is the presence of "vital exhaustion," a condition of excessive fatigue, feelings of demoralization, and increased irritability, which has been postulated to be often a result of prolonged distress.[69] Epidemiologic study has linked vital exhaustion or measurements of exhaustion to an increased risk of cardiac events and/or all-cause mortality. Vital exhaustion was recently compared to other CVD risk factors in a follow-up of 8882 individuals who were initially free from CVD in the Copenhagen City Heart Study.[70] Vital exhaustion was found to be a strong independent risk factor for the development of CVD in both sexes, with manifestation of a strong risk-adjusted gradient relationship. Vital exhaustion has been found to be associated with metabolic and coagulation abnormalities, inflammation, and low cortisol levels.

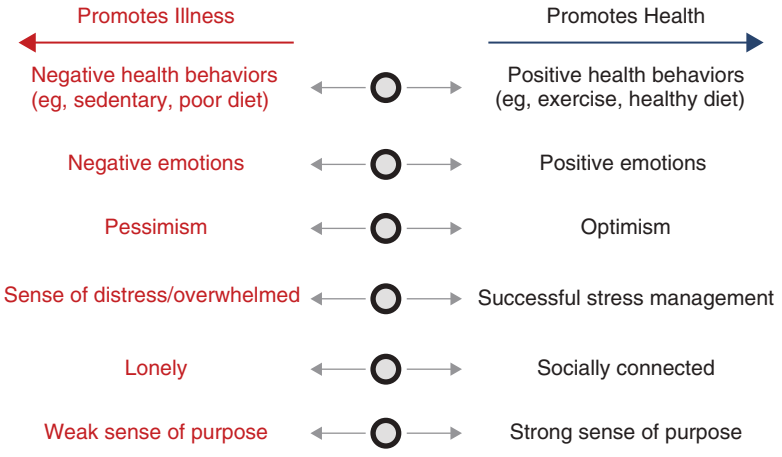

FIGURE 111–10. Each domain of behavioral and psychosocial functioning ranges along a continuum, from positive functioning that promotes health and longevity to negative functioning that is pathophysiologic and increases the risk for clinical events. Reproduced with permission from Rozanski A. Behavioral cardiology: current advances and future directions. *J Am Coll Cardiol*. 2014 Jul 8; 64:100-110.

PATIENT MANAGEMENT

Behavioral cardiology targets both the management of behavioral risk factors for CVD, such as physical inactivity, poor diet, weight management, and sleep hygiene, and the management of the psychosocial risk factors that contribute to the pathogenesis of CVD, promote adverse health behaviors, and impede adherence to behavioral recommendations.

A foundational principle in clinical management is the strong reciprocal relationship that exists between the management of health behaviors and psychosocial risk factors. The management of health behaviors can promote psychological well-being through multiple mechanisms. For instance, a strong evidence base relates exercise to psychological well-being through at least four pathways, as summarized in Fig. 111–12.

First, exercise can favorably impact psychological mood, as evidenced through cross-sectional studies of community cohorts that have observed less depressive symptoms among those who exercise, as well as by longitudinal studies that have demonstrated a lower frequency of subsequent depression among subjects who were physically active at baseline.[71] In addition, a meta-analysis of 25 randomized studies that compared exercise with either standard therapy for depression, placebo, or no treatment found a large treatment effect for reducing depression among those randomized to exercise.[72] The strongest evidence comes from three randomized trials conducted by Blumenthal and colleagues. In each trial, exercise training was as effective as antidepressant medication in the reduction of depressive symptoms.[73-75] Second, exercise has been shown to improve executive function and cognitive vitality and appears to provide a protective effect against the development of dementia.[76,77] Third, newer data indicate that exercise serves to reduce the pathophysiologic effects associated with psychosocial risk factors. For instance, studies indicate that physical fitness is associated with reduced heart rate, blood pressure, and cortisol responses to psychosocial stress.[78] Physical fitness can also buffer the relationship between depression and inflammation,[79] reduce the likelihood of impaired glucose metabolism in response to chronic stress,[80] and reduce the effect of chronic stress on telomere length.[81] Fourth, exercise can aid in the management of other health behaviors, including diet and sleep. Conversely, psychosocial interventions can be used to improve health behaviors, as will be discussed next.

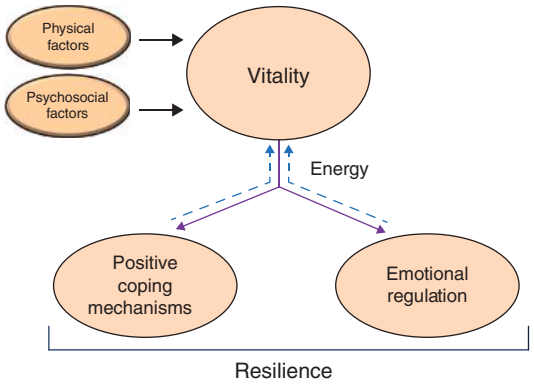

FIGURE 111–11. Vitality, the subjective sense of feeling alive and energetic, is a composite variable of well-being that is promoted by both physical health and psychological well-being. Vitality is a resource for positive coping and for the regulation of negative emotions. In turn, resilience mechanisms such as successful coping and emotional regulation help preserve vitality. Adapted with permission from Rozanski A, Blumenthal JA, Davidson KW, et al: The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol*. 2005 Mar 1; 45(5):637-651.[9]

MANAGEMENT OF HEALTH BEHAVIORS

The management of patients' health behaviors is intrinsically challenging. Poor adherence to medication usage is common, and poor adherence to diet, exercise, and other behavioral suggestions is even more common. Physician management of patients' health behaviors can be addressed according to a three-component model of behavioral change: (1) promoting patients' motivation for initiating behavioral change; (2) assisting patients in their execution of behavioral health goals; and (3) helping patients to sustain the long-term practice of new health behaviors. Each of these phases of behavioral change has its particular challenges. Instilling motivation is essential, as patients are unlikely to either initiate or maintain new health practices for long without motivation. However, motivation itself is often not sufficient. In fact, extensive study has shown that motivation only accounts for approximately 30% of the variance in human behavior. More often, patients fail to maintain new health behaviors either because of poor execution of health goals or because of relapse into old behavioral patterns. Representative techniques that can be used to assist patients in the management of their health behaviors are listed in Table 111–3.

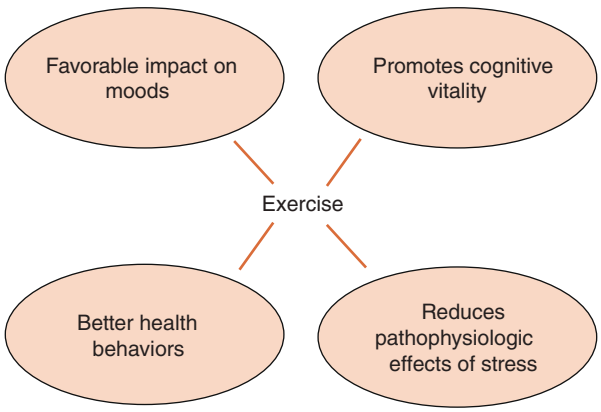

FIGURE 111–12. Four mechanisms by which exercise promotes healthy behaviors and/or positive psychological well-being.

TABLE 111–3. Approaches Toward the Management of Patient Health Behaviors

1. Motivation
   - Educate patient regarding health risk
   - Provide inspiration
   - Use of incentives
   - Instrumental support
   - Promote autonomy
   - Self-efficacy
   - Peer motivation
   - Motivational interviewing
2. Execution
   - Set specific measurable goals
   - Establish specific action steps
   - Self-monitoring
   - Implementation intentions
   - Time management
3. Long-term maintenance
   - Feedback
   - Social support
   - Contingency plans
   - Obligation intentions
   - Stress management
   - Energy management
   - Address psychosocial dysfunction

ENHANCING MOTIVATION

The receptive patient is often responsive to well-delineated information as to his or her risk for disease and the modifications in lifestyle that are thus needed. In addition, the enthusiasm with which physicians impart health information and behavioral advice can have an impact on the motivation of receptive patients. Often, however, additional motivational techniques are needed to encourage the unreceptive patient. These techniques can take the form of external or internal motivation. Examples of external forms of motivation include the use of incentives and warnings and providing instrumental support (eg, case manager, follow-up calls). Although these techniques can be useful in individual patients, fostering patient autonomy by increasing patients' intrinsic motivation is particularly desirable, because long-term maintenance of behavioral change is more likely with intrinsic versus extrinsic motivation. A practical technique for fostering intrinsic motivation involves having patients pause after imparting health advice and then asking patients why they might want to take on a suggested health goal. Having patients contemplate their own "why" for initiating a health goal and then verbalizing it improves patients' ownership over their own health goals. Similarly, patients should be encouraged to identify the methods (ie, the "how") by which they would prefer to pursue their new health goals.

Another important motivational approach is establishing health goals according to the principle of "self-efficacy." As first established by Bandura,[82] this principle establishes that the more someone believes that

a certain goal can be accomplished, the more that person is willing to try. This principle guides physicians to modulate patients' health goals toward "small wins" that patients believe they can achieve. For example, guidelines recommend that individuals should aim for 30 minutes of moderate aerobic exercise four to five times per week as well as strength training at least two times per week. However, most sedentary patients will not initially be able to comply with such a goal. In such cases, physicians should reduce the goal of exercise to whatever level patients believe they can first achieve, with the aim of getting patients accustomed to a habit of doing something physically on most days. Then, the exercise goal can be gradually increased. Motivation can also be increased by exposing patients to the inspiration and support that can be provided by peers.[83,84]

PROMOTING EXECUTION

Even if motivated, lack of goal execution may result from many factors, such as competing priorities, lack of sustained willpower, or lack of know-how in executing behavioral goals. In the face of competing priorities, health goals may also be vulnerable to disregard as a result of the phenomenon of "intertemporal discounting,"[85] which is the tendency to overvalue goals that are present-oriented (eg, immediate work obligations) while simultaneously discounting the value of goals that are more future-oriented (Fig. 111–13). The more time pressure a person feels as a result of daily obligations, the less likely he or she is to regard the importance of health goals.

For this reason, it is helpful to capitalize on the inspiration provided by a clinical event or office visit by helping patients to anchor health goals with a committed action plan. The health goal should be specific and measurable. The action plan should be detailed rather than vague and involve an action step that will be carried forward as a daily commitment, just as a work goal would. For instance, the desire to start exercising is a vague goal. The intention to join a health goal is more specific but not specifically measurable. By contrast, the commitment to exercise at the gym three times per week provides a specific and measurable goal that can be anchored in one's daily planning and followed by one's health care team.

Another important means for inducing goal execution is to promote the use of self-monitoring techniques. Self-monitoring serves as an anchor for self-awareness and personal feedback. For instance, overweight individuals who weigh themselves daily are more successful in maintaining weight loss compared to individuals who do not.[86] Similarly, the use of pedometers promotes physical activity. For example, a review of medical studies found that the use of pedometers was associated with a 27% increase in physical activity compared to physical activity before initiating pedometer use.[87] Pedometer use was also associated with reduction in weight and systolic blood pressure.

A specific technique that can be used to foster habit intention is the use of implementation intentions. When an individual commits to a new health goal, the new "practice" must be repeated on a daily basis for a period of time before it becomes a habit. Habit formation is desirable because it represents automatic behavior. To strengthen habit formation, Gollwitzer[88] developed the technique of implementation intentions (Fig. 111–14).[88] An implementation intention involves the use of an external stimulus to cue a specific behavior. The cue can be a stimulus in time, place, or situation, and the formulation takes the following form: "When it is X, I will do Y," where X is the cue and Y is the behavior. A large meta-analysis has revealed that implementation intentions are associated with a moderate to large effect in stimulating successful goal achievement.[89]

MAINTENANCE

Developing strategies to promote long-term maintenance is essential in promoting successful behavioral change as a result of the high frequency of relapse after the adoption of new health behaviors, such as diet plans and exercise activity. Life events, increasing stress, problems with work-life balance, fatigue, and waning motivation are some of the common factors that may impede long-term goal maintenance. Two central principles in fostering long-term maintenance include developing provisions for ongoing feedback from patients' health care teams and encouraging and providing social support. Social support can be combined with the use of implementation intensions to create "obligation intentions," whereby individuals feel beholden to honoring their commitments to friends or significant others (see Fig. 111–14).

In addition, it is helpful to have patients develop a contingency plan for maintaining their health goals when stress, competing priorities, or other factors that loosen goal commitment intervene. During such times, the effort should be made to continue with some level of goal commitment rather than completely stop, because complete cessation of activity increases the risk that the health goal will not be reinstituted. For instance, if an individual has assumed a new goal of working out at a gym for 30 minutes each day, the contingency plan may be to reduce the goal to three workouts per week or a shorter walking regimen that can be accomplished without going to the gym.

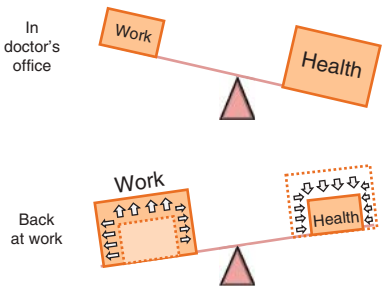

FIGURE 111–13. Schematic representation of how patients' prioritization of health goals can be negatively affected by the phenomenon of "intertemporal discounting"—the universal tendency to overvalue goals that are presently oriented and undervalue those goals that are future oriented. While in the doctor's office, patients may become motivated to prioritize their health needs ahead of their work goals. However, when back in the real-world setting of their work life, patients will often tend to overvalue their work goals because of their immediate nature, while simultaneously undervaluing their health goals, which are not as pressing in nature.

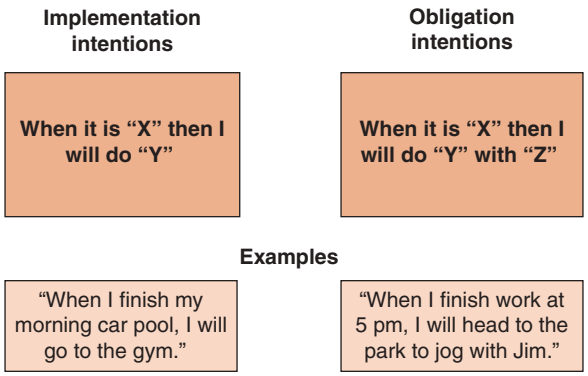

FIGURE 111–14. Goal setting according to the use of implementation and obligation intentions. An implementation intention is the agreement to have one's behavior cued by an external stimulus ("X"), such as specific time, place, or designated situation. "Y" is the intended action. Obligation intentions add social support or social pressure to implementation intentions by designating a person or group ("Z") with whom a designated activity will be performed. Reproduced with permission from Rozanski A. Behavioral cardiology: current advances and future directions. *J Am Coll Cardiol*. 2014 Jul 8; 64:100-110.[21]

Long-term management of behaviors also includes recognizing and addressing negative stress and emotional problems, such as anxiety and depression, which are often common in medical patients. The role of the cardiologist in this regard is addressed next.

MANAGEMENT OF PSYCHOSOCIAL RISK FACTORS

There are multiple reasons to promote the management of psychosocial risk factors. As previously mentioned, psychosocial risk factors are directly pathogenic, promote adverse health behaviors, and impede adherence to treatment regimens. They also tend to cluster over time when untreated and appear quite commonly in cardiac populations. Psychosocial risk factors such as anxiety and depression are also frequently associated with somatization, and thus may be the underlying cause for chest pain, dyspnea, fatigue, and palpitations.[9] European guidelines contain specific recommendations for screening and treating psychosocial risk factors in clinical practice,[90] but to date, only a screening guideline (for depression) has been recommended in the United States.[91] However, physicians can contribute to the management of psychosocial risk factors in a number of ways. Psychosocial interventions within cardiac practice can be organized according to a tiered approach consisting of three basic tiers,[9] as illustrated in Fig. 111–15.

Physicians can readily screen for the presence of psychosocial risk factors and then decide if any specific factor is something that they can either handle themselves or refer for treatment by ancillary staff or specialists. One approach to screening for psychosocial dysfunction is to use a series of open-ended questions. Open-end questioning often provides rich information and can be readily incorporated into a standard review of systems. Examples of open-ended questions that can be used are listed in Table 111–4. Alternatively, structured questionnaires may be convenient to use if kept brief in nature. To that end, a multidisciplinary council has recommended a stepped screening approach for depression, as shown in Fig. 111–16.[91] The approach is based on the use of the two-item Patient Health Questionnaire, which asks patients to rate how often over the last 2 weeks they have been bothered by: (1) little interest in or pleasure in doing things and (2) feeling down, depressed, or hopeless, with each rated according to a 4-point scale (0 = not at all, 3 = every day). Those who respond positively to either question are recommended to complete the full nine-item version of the Patient Health Questionnaire, which includes additional questions regarding fatigue, sleep, appetite, and suicide risk. Anxiety can also be screened for by using a two-item subscale of the seven-item Generalized Anxiety Disorder scale.

Depending on severity, various psychosocial risk factors may be addressed directly by physicians without referral to staff or behavioral specialists. For instance, patients with mild insomnia may be given tips on how to improve sleep hygiene. For patients who are socially isolated or lonely, the physician can emphasize the need to spend more time with friends and family and/or recommend community-based social programs. Chronic stress is a ubiquitous problem that may also benefit from recommendations that can be made by a physician, including a recommendation to use practical stress reduction techniques (eg, breathing or progressive relaxation exercises) and/or instructional videos or apps for reducing stress.

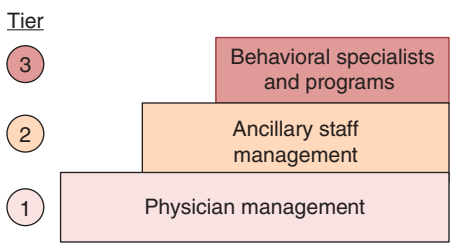

FIGURE 111–15. Clinical management can be facilitated by a tiered approach to behavioral and psychosocial interventions, centered around basic screening and counseling functions that can be performed by the physician (tier 1), with referral of patients to ancillary office staff (tier 2), and/or by behavioral specialists or organized hospital or community programs (tier 3) when appropriate.

TABLE 111–4. Open-Ended Questions to Screen for Psychosocial Risk Factors

1. How has your mood been recently?
2. Do you feel anxious or unduly worried?
3. How is your sleep?
4. How would you describe your energy level?
5. Do you have people you can turn to for support?
6. Are you under undue pressure at work or at home?

The physician should also be cognizant of the practical ways in which promoting positive health behaviors may aid in the management of chronic stress. A useful paradigm in this regard is borne out by classic work by Thayer et al.[92-93] They asked experimental subjects to periodically assess their levels of tension and levels of energy and characterize their moods and behaviors during various times of the day. This work revealed that when individuals were both tense and tired ("tense-tiredness"), low mood levels often ensued, accompanied by a higher frequency of "quick fix" behaviors (eg, smoking, watching television, eating sugary snacks) (Fig. 111–17). By contrast, if patients were tense but energetic ("tense energy"), mood levels were substantially better and quick fix behaviors were less common. These data suggest that individuals with higher levels of energy are more resilient to the effects of stress. Physicians can encourage patients in this regard to adopt exercise routines, maintain a healthy diet, and obtain adequate rest and relaxation as a means for managing chronic stress.

The second tier of psychosocial management calls for the referral of patients with greater psychosocial dysfunction to ancillary support staff, such as a physician's own office staff, or hospital or community programs. For instance, a trained office staff member may be available to aid a patient with moderate stress symptoms by instructing them more fully in muscle relaxation, guided imagery, or diaphragmatic breathing or by teaching behavioral strategies (eg, problem solving, improved goal setting, or instruction in self-monitoring strategies). Alternatively, patients can be referred to structured programs, such as mindfulness-based stress reduction programs or a typically wide array of stress management interventions that may be offered by integrative medicine programs.

The third tier of psychosocial management involves the referral of patients with moderate to severe psychological dysfunction to appropriate mental health care specialists. For instance, patients who are recognized to be significantly depressed or highly anxious or who have high scores on the Patient Health Questionnaire or Generalized Anxiety Disorder scales should be referred to professionals who treat these psychiatric conditions. In addition, patients may be referred to specialists for other forms of overt psychological problems. For instance, those with high anger can be successfully treated by referral to anger management programs, and recent approaches have also been developed for treating pessimism.[94] Those with severe sleep problems

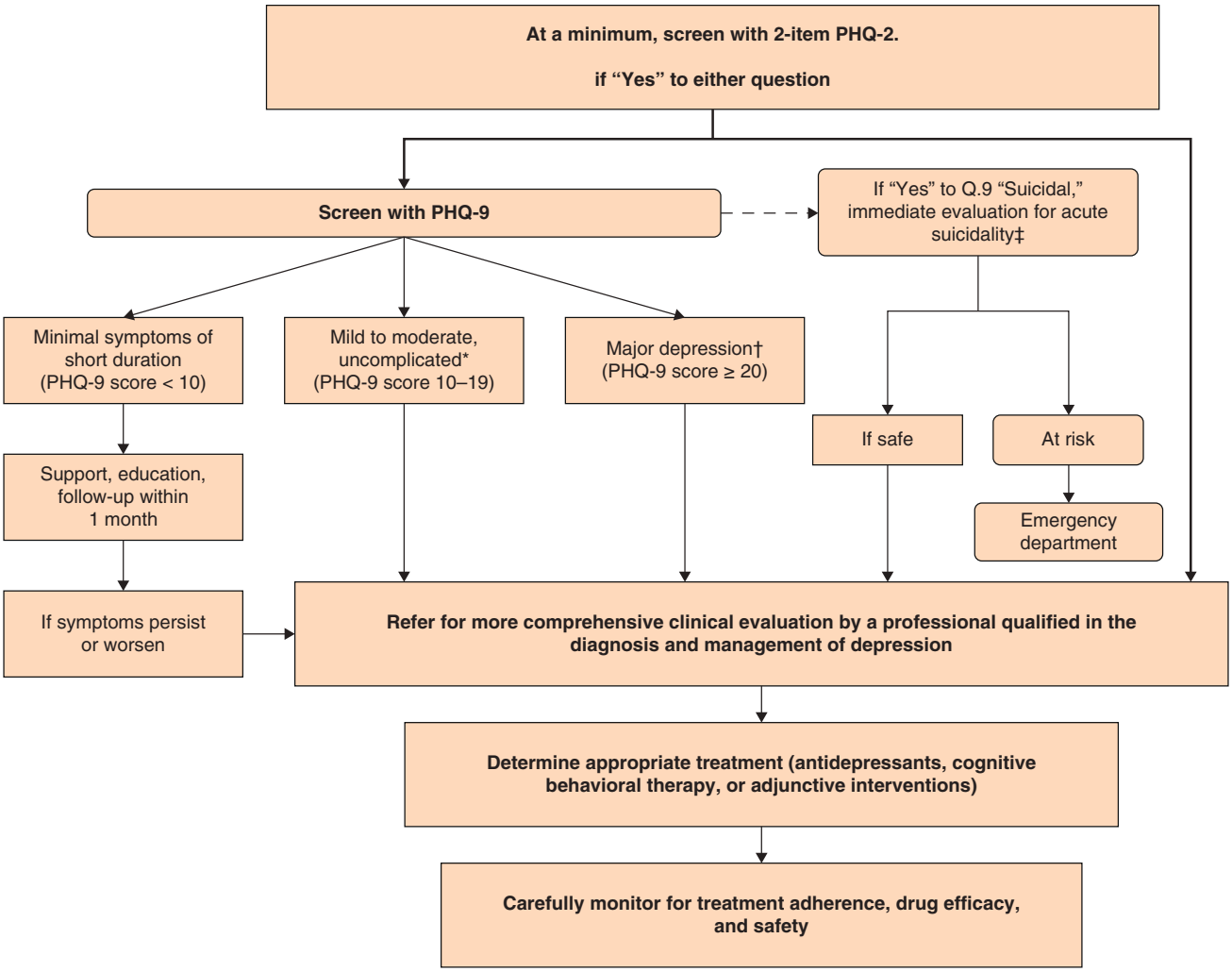

FIGURE 111–16. Screening algorithm for depression in patients with coronary heart disease as suggested by an advisory from a combined council of the American Heart Association. *Meets diagnostic criteria for major depression, has a Patient Health Questionnaire (PHQ)-9 score of 10 to 19, has had no more than one or two prior episodes of depression, and screens negative for bipolar disorder, suicidality, significant substance abuse, or other major psychiatric problems. †Meets the diagnostic criteria for major depression and (1) has a PHQ-9 score ≥ 20; (2) has had three or more prior depressive episodes; or (3) screens positive for bipolar disorder, suicidality, significant substance abuse, or other major psychiatric problem. ‡If "Yes" to Question 9 "suicidal," immediately evaluate for acute suicidality. If safe, refer for more comprehensive clinical evaluation; if at risk for suicide, escort the patient to the emergency department. Reproduced with permission from Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation*. 2008 Oct 21;118(17):1768-1775.

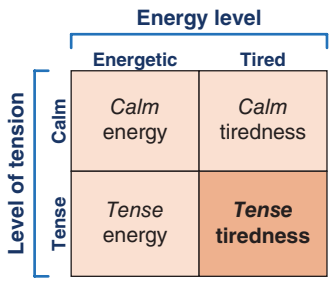

FIGURE 111–17. A paradigm for linking moods and behaviors to tension and energy levels based on the work of Thayer.[92] Their research found that when people experienced calmness with either high or low energy ("calm energy" or "calm tiredness"), positive moods prevailed. Under conditions of high tension, relatively positive moods still prevailed when individuals felt energetic ("tense energy"), but the state of tense-tiredness was associated with a substantial increase in negative moods and "quick fix" coping behaviors. Reproduced with permission from Herzog HE: *The Cardiac Care Unit Survival Guide*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

may be referred to either mental health experts or to organized sleep programs, depending on expertise and problem.

As hospitals organize into larger health care systems, the opportunity to align services to provide psychosocial interventions may increase. Preliminary data suggest that provision of tiered behavioral interventions can result in more efficient and effective interventions. For instance, Davidson et al[95] recently tested the feasibility of a tiered care approach for managing depressive symptoms in a controlled randomized trial involving patients with ACS. This trial compared active stepped care versus conventional care among 150 patients with elevated depressive symptoms following recovery from an ACS. The active care approach, which involved problem-focused cognitive behavioral therapy, delivered by phone or the Internet, and stepped every 6 to 8 weeks, resulted in a greater reduction in depressive symptoms than in the usual care group. This improvement occurred without incurring greater overall health care costs in the stepped care group. Accordingly, more trials are indicated to test this type of approach.

SUMMARY

A wide variety of psychosocial risk factors have now been consistently linked to cardiac disease. Those most studied have been depression, anxiety, work stress, anger/hostility, poor social support, and low socioeconomic status. In recent years, additional factors such as insomnia, pessimism, and lack of life purpose have been linked to incidence of CVD and/or cardiac events as well. Psychosocial risk factors exert their effects through both direct pathophysiologic mechanisms and through their negative impact on health behaviors. An important advance over the past decade is the increasing recognition that positive psychosocial functioning is protective of health, as a result of both physiologic buffering and a positive impact on health behaviors.

The management of health behaviors and psychosocial risk factors is interrelated, and improvement in one arena can enhance the other. An increasing number of techniques and tools have been developed to promote patient motivation and assist in the execution and long-term maintenance of new health behaviors, as well as to manage psychosocial risk factors in the context of medical practice. However, to date, there has been relatively modest translation of these interventions into conventional practice, and practical barriers, such as developing more affordable interventions, must still be addressed. However, as a result of the increasing frequency of adverse health behaviors within society during recent decades and the high concentration of psychological risk factors within medical populations, interest and advances in integrating the management of psychosocial risk factors into the practice of medicine are likely to accelerate.

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CHAPTER 112

ECONOMICS AND COST-EFFECTIVENESS IN CARDIOLOGY

Daniel B. Mark

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CONCLUDING PERSPECTIVE / 2490

In March 2010, the US Congress passed and President Obama signed a historic new health care legislation, the Patient Protection and Affordable Care Act (PPACA). The full impact of this complex bill on medical practice and US health care expenditures will likely not be clear for many years. The passage of this legislation was preceded by a vigorous public debate on the US health care system and options for its reform. Complex arguments about the best way to organize, deliver, and pay for health care became the stuff of the daily news reports and editorials. Major participants in the health care industry and other interest groups jostled to advance their perspectives before the US Congress and the court of public opinion. One major reason for all this attention and the justification given for both supporting and resisting passage of this legislation was a widespread concern about the current and future costs of health care and tremendous uncertainty about the best way to control these costs. According to the Centers for Medicare and Medicaid Services (CMS), the United States spent 17.5% of its gross domestic product (GDP) on health care in 2014, amounting to approximately $3 trillion.[1] Approximately 52% of this expenditure went for hospital care or physician/clinical services. Drug therapy accounted for another 10%. While the rate of growth in health care spending has varied in recent years, the trajectory for the national health care bill will continue to be upward for the foreseeable future. However, despite leading the world in health care spending, the United States has a system with which no one seems happy.[2]

Four major reasons can be offered to explain why health care spending is expected to keep increasing: (1) technological innovations that improve medical care[3]—the care of the cardiovascular patient in 2017 is vastly different (and largely better) than it was in 1980, but innovation in diagnosis and therapy generally increases costs relative to the prior patterns of care, as is reviewed in the second part of this chapter; (2) the aging of the population—an issue for all developed countries and one that has just begun to manifest itself (the vanguard baby boomers born in 1945 reached retirement age in 2010); (3) inflation, which refers to an increase in the cost of the same good or service (contrasted with an improved medical care service described in the first reason, above); and (4) raised expectations of the public regarding what medicine can and should offer them when they become ill, in part as a result of the global information revolution created by the Internet and search engines such as Google. Patients are no longer dependent on their doctor to tell them what is possible in a particular medical situation, and there appears to be no limit to the human desire to subdue morbidity and mortality technologically.

"Disruptive innovation" has been suggested as a guide to solving the ever rising health care cost dilemma. First proposed by Clayton Christensen in 1995, the concept was used to explain why certain complicated, expensive, but very mainstream products and services were driven to extinction by simpler, more affordable ones. Such innovations have clearly transformed modern life. It is unclear, however, that such innovations can be intentionally produced for the primary purpose of lowering health care costs as some have hoped.[4] One key part of the disruptive innovation pattern was that leading companies and institutions are rarely the source of disruption; often, they are very late to recognize an impending disruption. With regard to health care, the continuing upward trajectory of costs is partly due to the "personal service" aspect of medicine, a feature that, together with certain regulatory barriers, resists attempts to make delivery of care more efficient.[5]

The cost of health care is not a unique concern for the United States. Other developed nations around the globe have all experienced unwelcome upward pressure on their medical care spending. Switzerland, France, Germany, Belgium, Austria, and Canada each spend approximately 10% to 11% of GDP on health care. Many of the remaining countries of the European Union spend between 8% and 10% of GDP on health care. The difference in spending between these countries and the United States appears primarily to be a result of a higher rate of increase in spending in the United States since 1980. Developing nations, although spending proportionately much less on health care at present, are projected to be facing an explosion of cardiovascular and other chronic diseases over the next half-century as they develop greater affluence and their populations adopt ever more atherogenic lifestyles.[6] Clearly, health care costs will continue to be a major focus of attention at the policy level and a major pressure point in clinical practice for years to come.

This chapter has two overarching goals. The first is to explain briefly what the discipline of health or medical economics is (and is not) and what useful roles it might be able to play in debates about dealing with the ever-rising costs of the medical care system. To do this, we will need to examine the sorts of questions that health economics studies and the tools it uses. The second goal of the chapter is to review some of the recent and/or important health economics literature covering specific therapies and strategies used in the care of cardiovascular patients.

WHAT IS ECONOMICS?

Economics is the discipline that uses formal models and statistical analysis to study how society manages and allocates its collective resources.[7,8] Medical economics, by extension, is the study of the

production and allocation of health care resources.[9] The standard model of (neoclassical) economics holds as axiomatic the proposition that society's collective resources are finite and that there are many more possible uses for these resources than there are resources to be used. Consequently, choices need to be made about the best ways to use these limited (or scarce) resources to fulfill the needs and desires of society.[10] The role of economics is thus conceptualized as serving to facilitate making these choices in an informed, rational manner. In the health care arena, for example, health economics offers tools to study the efficiency with which different health care goods and services can produce the product of interest, improved health. In the properly functioning free market envisioned in neoclassical economic models, buyers and sellers collectively determine the amount of a product that should be produced, with variations in price serving as the primary signal that connects these groups. Unfortunately, however, health care does not meet any of the standard criteria for a properly functioning free market, and thus prices cannot be relied upon to ensure that the "optimal" amount of health care services is being produced.

In a simplistic sense, economic analysis focuses on aspects of the efficiency of the health care system, whereas policy analysis is concerned with the directions it should take.[11] The two domains are connected by an ideological debate about the proper balance point between market-driven efficiencies and government management of health care. Those who believe that free markets, as conceived by neoclassical economic theory, are the best, most efficient way to allocate health care resources tend to favor a much more limited role for government in health policy. Deficiencies in the current health care system, according to this perspective, reflect too much, rather than too little, government intervention.[12] Economic analysis of the sort presented in this chapter serve (at best) a relatively minor role for advocates of the free market approach to health care. Conversely, those who feel that health care markets do not function as theory predicts (or who hold that the theory has major flaws) are much more supportive of government intervention at the policy level. In the context of "market failure" in health care, economists argue that the analysis methods (reviewed in this chapter) provide a guide, a "map" to inform rational policy-level decisions about how and where to allocate resources (spend money) and to what ends.[13] The United Kingdom's National Health Service and National Institute for Health and Care Excellence provide a well-developed example of how economic analysis methods can be used to inform and guide national health policy. In the United States, large payers, large provider groups, professional societies, the pharmaceutical and device industries, and the government interact in very complex ways to affect the levels of production and the patterns of distribution of health care. Thus, the role of economic analyses is less well defined in the United States, and its influence on policy is much more variable.

One other assumption that helps explain the worldview of health economic practitioners is that decision makers are "rational utility maximizers." Utility is a concept borrowed from philosophy that refers to the amount of pleasure or satisfaction that is provided by something.[14] In health economics, utilities provide a quantitative realization of the relative satisfaction felt by patients in various health states. In addition, health economics assumes that if one has two or more choices for treatment, one will always pick the one with the greater utility value. Because, in order to be satisfied, one must be alive, utilities and survival get combined to form the well-known but poorly understood metric of quality-adjusted life-years (QALYs). To give a concrete example, if treatments A and B both cost $1000, but treatment A yields on average 0.1 QALYs while treatment B yields 0.3 QALYs, health economists would always expect that B would be chosen over A. In order for this to be the case, however, decision makers would need to be indifferent to who gains from these choices and who loses, and such is rarely, if ever, the case. The "real world" is rarely as orderly, rational, and value neutral as it is portrayed in the economics literature.[15] So health economics can perhaps be best thought of as providing simplified models of the health care economy, with the expectation that these models can provide some insights useful for decision making but are never the complete answer to any decision problem.

RELATIONSHIP BETWEEN HEALTH ECONOMICS AND COMPARATIVE EFFECTIVENESS

Comparative effectiveness refers to research that seeks to answer important clinical questions related to real diagnostic and therapeutic options faced by significant numbers of patients.[16] In short, it has the ambitious goal of developing the evidence needed to practice medicine. This is to be contrasted, perhaps, with evidence that is developed to seek regulatory approval for marketing of new products from the US Food and Drug Administration (FDA), where the comparator therapy in a pivotal trial might be "placebo." It can also be contrasted with evidence developed in very focused, optimized clinical trials that seek to demonstrate a proof of concept.

Some have proposed that comparative effectiveness research will serve as a counterweight to health care policy decision making that seeks primarily to maximize efficiency/minimize costs.[17] The 2010 PPACA established the Patient-Centered Outcomes Research Institute (PCORI) as a nonprofit organization independent of the federal government. The institute is advisory in that none of its findings about comparative effectiveness bind the Secretary of Health and Human Services to cover or not cover specific types of medical care. Further, this new institute is specifically prohibited from using cost-effectiveness as a threshold to establish what types of care are recommended or reimbursed. The role of cost and economic considerations in comparative effectiveness research varies according to the source consulted. In the case of PCORI, high sensitivities about the possibility of the federal government rationing care as a way to save money resulted in a de-emphasis of the role of economics. However, there is not really any inherent tension between comparative effectiveness and high-quality health economics work, because both are built on the foundations of clinical comparative effectiveness questions. Thus, it may be useful to consider health economics research a comprehensive form of comparative effectiveness research that adds an extra dimension, that of efficiency.

THE TOOLS AND CONCEPTS OF THE HEALTH ECONOMIST

THE THREE BIG HEALTH ECONOMICS QUESTIONS

Although it is natural to expect that the most important questions for a health economics analysis would deal with some aspect of cost, understanding the clinical effectiveness is actually almost always much more important.[18] The first question of importance regarding a particular health care service or technology is: What long-term effects (both positive and negative) does it have on health outcomes, and what is the level of evidence supporting the current state of understanding about clinical effectiveness? Without a clear answer to this question, no economic analysis can be of much use. Sometimes the most important service an economic analysis can perform is to focus a bright light on the fact that the answer to this seemingly simple question is not at all clear. It is not uncommon to encounter a model-based economic analysis in the published literature where the authors have reached some conclusion about whether or not a given medical intervention is cost effective, yet the clinical literature is not at all settled even on what health effects that intervention produces.

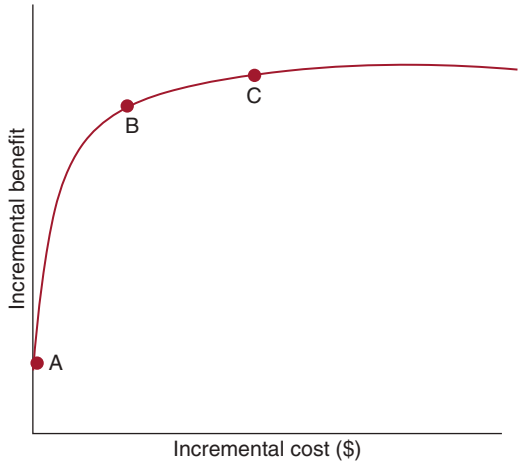

FIGURE 112–1. This graph shows the relationship between investment of incremental health care resources and the resulting incremental health care benefit. *A* represents a point where large health benefits are generated at low cost. *C* represents a point where vanishingly small health benefits are realized despite large investments, also known as "flat of the curve" medicine. *B* represents a cut point, or benchmark, beyond which therapies are no longer considered economically attractive.

The second critical health economics question is: Is it good value for the money? By good value, we basically mean that a given health care service or product can be used to produce a relatively large amount of "health" for relatively little money (Fig. 112–1). Another way to phrase this question is: How efficiently does this new therapy or strategy we are studying produce extra units of health (sometimes expressed as QALYs)? Answering this question requires that we combine our best understanding of the long-term clinical effectiveness with our best understanding of the long-term resource use/cost effects of the intervention in question. To do this, one of three possible economic efficiency analysis methods is often used (Fig. 112–2). These methods differ primarily in the way in which the health benefits are expressed in the analyses. *Cost-benefit analysis* requires all incremental health benefits to be converted to their monetary equivalent. As might be imagined, the methods for doing this are controversial because they require answers to some of society's most difficult value questions.[11,19] *Cost-effectiveness analysis* avoids this hornet's nest of difficulty by valuing all units of survival the same regardless of who benefits. *Cost-utility analysis* modifies this by using utility values (patient or societal preference weights) to adjust the survival data. Thus, survival in a severely disabled state or in severe pain would be valued significantly less (lower utilities and thus lower calculated QALYs) than survival in good or excellent health. Although the notion of utility might seem like a good solution to the difficult problem of valuing on a common scale all the types of health outcomes produced by the health care system, that solution hides considerable difficulties.[20] For example, who is best equipped to decide the utility weight of a year with a severe stroke or a year with severe heart failure? Should it be the member of the general public whose primary encounters with the medical system have been in the form of annual physicals? How much information about the health states being ranked do such individuals need in order to make informed judgments? Should it be health care professionals who are most familiar with the outcomes of these patients? Should it be the patients themselves? Two specific difficulties present themselves in the last option. First, some patients may be medically unable to participate in any assessment process. Second, no matter how severe or unpleasant the health state may seem to an outsider, humans have a remarkable ability to adapt and to accommodate to their disabilities and limitations (sometimes referred to as hedonic adaptation), and so their own valuation of their health state may be considerably higher than that given by a member of the general public.[21]

Cost-effectiveness analysis provides an estimate of the relationship between money spent and health benefits produced, but unlike cost-benefit analysis, the cost-effectiveness and cost-utility ratios have no natural interpretation. Thus, benchmarks are needed to help interpret

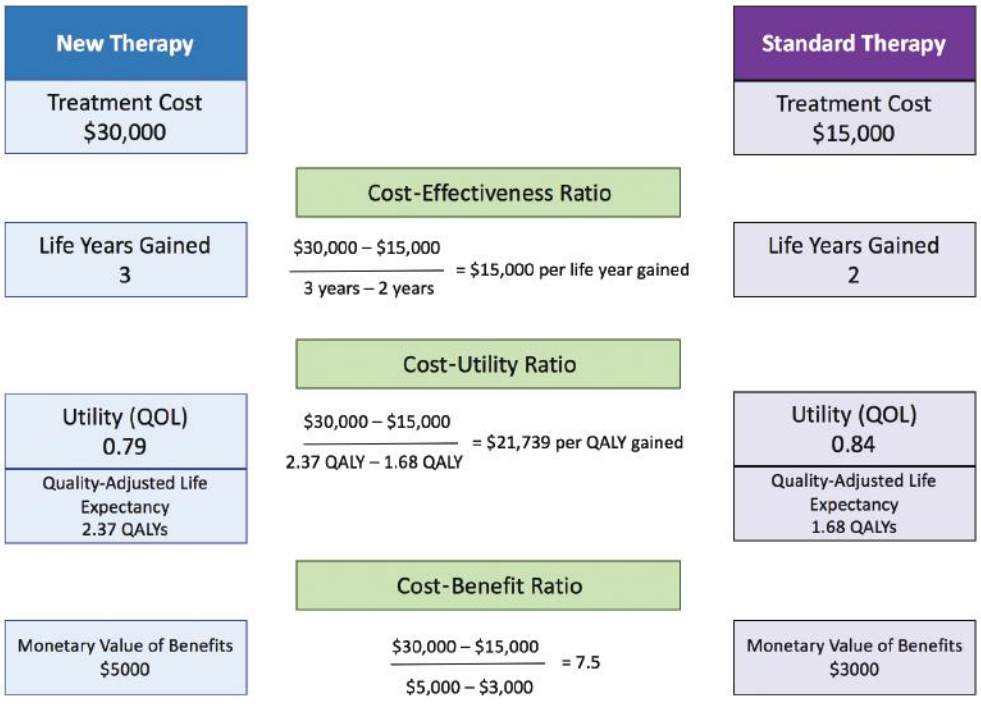

FIGURE 112–2. Major types of economic analysis in medicine relating costs and health outcomes. QALY, quality-adjusted life-year; QOL, quality of life.

the results of these analyses. Typically in the United States, a cost-effectiveness ratio of $50,000 or less per life-year (or QALY) saved has been considered "economically attractive," whereas values of $100,000 or more per life-year (or QALY) saved have been considered "economically unattractive." The $50,000 figure was apparently initially chosen because it was the cost to keep an end-stage renal failure patient alive on hemodialysis for a year relative to no dialysis. Dialysis is a form of medical care that Congress had guaranteed to fund for all affected renal failure patients and thus represents an explicit policy statement by the US federal government (representing "society") of how much it is willing to pay to save a life-year. One criticism of this benchmark is that it has never been updated. A recent evaluation of 13 studies published between 1968 and 1998 on the cost of renal replacement therapy found that the cost of center dialysis was between $55,000 and $80,000 per life-year saved.[22] A more recent analysis of this issue using a computer simulation model and data from 1996 to 2003 found that renal dialysis had a cost per QALY of $129,000.[23] Recent proposals to increase the benchmark to $150,000 per QALY have been variably adopted in published research.[24] Other countries use different, more conservative benchmarks. For example, the National Institute for Health and Care Excellence in the United Kingdom uses a benchmark of less than or equal to £20,000 per QALY to define economic attractiveness, although this is applied with some flexibility.[25,26]

The third major question of health economics is: Can we afford it? This question really represents the intersection of policy and health economics. Public policy is concerned with the large decisions about how much of society's resources to devote to producing more health care. In the United States, this is defined both by the amount of funding provided to Medicare (primary public funder of health care) by Congress and the health care investment and reimbursement policies in the private sector. Economics can then address the question of what the aggregate cost to society or to individual payers will be from funding different diagnostic and management strategies. In Canada and much of Europe, where health care spending levels are mostly controlled by central governments, the effect of new therapies and tests on the health care budget is always an issue, and reimbursement policies are carefully crafted to control dissemination. In the United States, Medicare is prohibited from explicitly considering cost in coverage decisions and the lack of a single central payer means that funding decisions get made in a more fragmentary and disjointed way. However, even with central decision making, funding decisions are not necessarily made to optimize health production. One major obstacle is that it is much easier in such a system to say no to some new innovation than to stop or reduce funds for some existing therapy because it is not evidence based or because it is now a less efficient method of producing more population health.

DATA FOR HEALTH ECONOMICS

As with any form of empirical research, the value of economic analysis is highly dependent on the quality and relevance of both the clinical and economic data available for the work. Ideally, data at the patient level can be obtained on both clinical outcomes and resource consumptions/costs from the same cohort. However, even this condition does not ensure the best quality. For example, there are many pivotal guideline-changing clinical trials that provide excellent clinical outcomes data but have almost no useful resource use or cost information. Estimating costs from the few possibly relevant variables in such a data set may be the best that can be done, but the limitations of this should not be overlooked. Alternatively, a small clinical trial may provide detailed economic data, but its clinical efficacy data are not reliable as a result of the sample size.

When we refer to "economic data," generally we mean resource use information and associated costs. Specifically, economists wish to assess the *incremental resources* needed to produce a good or service, by which they mean only the extra resources required. If we are comparing a new treatment with standard care, for example, and both of them will involve 5 days in the hospital at the same level of intensity of care from doctors and nurses, then there is no incremental hospital stay involved in the new treatment. Incremental costs then are the monetary value of the incremental resources consumed. The primary emphasis on resource consumption rather than money is deliberate. Money is a tool that facilitates the functioning of markets, so that barter is not required. The meaning of money is always traced back to the resources consumed. Economists refer to *opportunity cost* to designate what was given up or lost to society when a decision was made to produce something else: the value of (relevant) choices not made.[8] If we decide to produce 10,000 more coronary bypass surgeries in the United States, for example, we will lose the resources consumed in that process to alternative uses. In the world of limited or scarce resources and rational utility-maximizing individuals referred to earlier, this notion of trade-off underlies the economists' fundamental concept of cost.

Neoclassical economics further maintains that in a well-functioning free market, the equilibrium price of the good or service in question represents its opportunity cost. Because, as noted earlier, the medical marketplace violates a number of key conditions required to qualify as a well-functioning free market, the economic meaning of medical prices is problematic. Costs that reflect the production process of the medical care are a reasonable surrogate for economic value. However, the (uncorrected) charges that are contained on US medical bills are completely unreliable for economic analysis purposes,[27] and the reimbursements paid to hospitals and physicians are typically less suitable for this use outside of very specific questions relevant to payers or providers. Methods for estimating medical costs are reviewed elsewhere.[28,29]

Induced costs/savings are the costs and cost savings that occur consequent to some treatment or strategy used in patient care. For example, use of thrombolytic therapy for ST-segment elevation acute myocardial infarction (MI) would entail the initial cost of the drug (for tenecteplase, > $2000). If the patient in question had an intracranial hemorrhage, the extra costs of caring for that complication would be induced costs, and clearly, those costs would most likely extend for the rest of that patient's lifetime. If, instead, treating the patient during the first hour of her large anterior MI prevented her from developing debilitating heart failure later, then all the money that would not have to be spent over the ensuing years of her life caring for that complication would need to be counted as an induced cost savings. In an analysis that extends many years into the future, future costs and savings need to be discounted (typically at 3% per year) to calculate the present value of the lifetime cost stream. The reason is straightforward. We are not indifferent to the prospect of receiving $100 today or receiving the same amount in 10 years. We recognize that in 10 years that money will be worth less to us than it is today, because we could have had it in the bank earning interest for 10 years if we had received it today. Thus, discounting is a way of reducing the nominal value of future spending and savings to their present value equivalents.

A further complexity about the concept of cost is that a perspective (sometimes termed a viewpoint) must always be defined in order to measure and understand costs.[9] For example, if a patient undergoes a successful percutaneous coronary intervention (PCI) with a drug-eluting stent and is discharged from the hospital without complications but is readmitted 3 months later with a stent thrombosis, that readmission is a cost from the payer's perspective and from the societal perspective but not from the hospital's perspective or the physician's

perspective unless they are operating in a capitated system. If a patient comes to clinic with chest pain and gets a clinical workup and a stress test, the cost of all that from the patient's perspective (assuming they are insured) may simply be his co-pay. The clinic and society, however, each have different perspectives on that same episode of care. In most economic analyses, the primary analyses should be done using the societal perspective, which is the perspective in which the winner/loser problem described in the above examples is minimized.

The problem of measuring and comparing costs across international borders is a difficult one that offers no easy solution but is increasingly important in the current era of international cardiology mega-trials.[30,31] To the extent that practice patterns are converging around common standards that cross international boarders, it may make sense to pool resource use data across countries and assign common costs. However, local variations in price data make it problematic to decide what prices to use in such an exercise. Further, there is still good evidence that local practice patterns differ substantially in different regions of the world. For example, length of stay after acute MI and the rate of referral for invasive angiography vary considerably across countries.[32]

MODELS IN HEALTH ECONOMICS

Several different types of models are now commonly used in health economics. Descriptive and predictive statistical cost models are mathematical models that treat cost as a probabilistic quantity. Although that might sound quite technical and arcane, these models are quite analogous to descriptive and predictive regression models of clinical outcome variables. Such models might be developed to understand the major clinical correlates of cost in a particular cohort or to be able to predict the cost of future patients with particular clinical features treated in a specific way. To develop these sorts of models, one needs patient-level data—ideally for both clinical and cost descriptors of interest. More complex models based on regression methods are also now commonly used in health economics. For example, multilevel (sometimes called hierarchical) models can be used to explore patient-level, provider-level, institutional-level, and even country-level influences on cost and outcomes. High-quality patient-level data and regression modeling techniques can be used to estimate both lifetime costs and lifetime clinical outcomes in a cost-effectiveness analysis.

These patient-level models can be contrasted with deterministic models used in health economics, including decision models. These latter models have been most often used to estimate lifetime costs and outcomes for cost-effectiveness analysis. Typically, they do not use patient-level data but instead employ group-level summary data obtained from various (unrelated) published sources. Their strength lies in providing a framework for combining such disparate data estimates into a summary model focused on a specific question. Because these data do not incorporate any measure of the variability in the estimates, the resulting models are often interpreted as showing what will happen (deterministic) rather than what might happen (probabilistic or stochastic). The simplest decision models employ basic probability calculations to estimate the (uncertain) outcomes from each strategy or therapy being studied. More complex methods of handling the uncertainty in such models includes the use of Markov models (also called state transition models), where the probability of moving from one health outcome state to another in each time cycle of the model (eg, 1 month or 1 year) is represented as an explicitly specified transition probability. The limitations to incorporating more of the nuances of clinical practice in such models are that the models become quite complex to manipulate and to explain, and also that the data sources available to populate the model may not be sufficient to support the complexity the analyst desires to examine.

One major reason that so much modeling is done in health economics is that clinical studies, even the best ones, rarely provide all the data that are needed for a comprehensive health economics analysis. The time frame relevant for a health economics analysis is the full time span during which some residual effect of the testing or treatment strategy being studied might be expected. For most clinical problems involving patients with a chronic disease such as the ones discussed in the second part of this chapter, the lifetime of the patient cohort is the appropriate time frame of interest. If the full stream of costs and outcomes over this time frame could be observed and measured, no modeling-based extrapolation would be required. Because for adult chronic diseases this is almost never possible, some amount of model-based extrapolation is required. The question of how best to do that has no simple answer, and different authorities in the field favor different approaches. Since the models are quite difficult to validate empirically, the matter of which approach is to be preferred has not been resolved.

Given this state of affairs, the consumers of these models can best arm themselves for forays into this literature by keeping in mind a few basic questions.[33] First, are the assumptions clear? All models require assumptions, and in some cases, the assumptions are quite important in deciding how much credence to give the results. Second, are the important cost and outcome inputs clearly specified? Third, are the major moving parts of the analysis sufficiently transparent for readers to understand the final results? The model should not be presented simply as a black box where data go in one end and an "answer" emerges from the other. Health economics is not discovery science. A cost-effectiveness model, therefore, is not a method of uncovering new medical insights, but rather should provide a clearer understanding between money spent and health outcomes produced for that money. Whenever possible, intermediate outputs from the model should be validated against empirical data. Finally, are the key uncertainties in the analysis fully explored via stochastic and sensitivity analysis methods?

PATTERNS OF RELATIONS BETWEEN COSTS AND OUTCOMES

The primary concern of economics is choosing among alternatives. Thus, economic efficiency metrics, such as a cost-effectiveness ratio, must be expressed in terms that are common to all the alternatives of the choices to be made. When analysts want to be able to compare medical investment choices with choices in other sectors of the economy such as education, transportation, and defense, it is often necessary to use cost-benefit analysis because there is no other common method of expressing the outcome being produced by the investment being considered. However, when all choices reside in the health care arena, cost-effectiveness and cost-utility analyses are much more commonly used, with the most common effectiveness metric being the added life-year or the QALY. In such circumstances, from a cost-effectiveness analysis perspective, all medical outcomes must be translated into a composite metric reflecting their effect on length and quality of life. When dealing with an intermediate outcome such as a change in a biomarker or a change in the degree of stenosis of a coronary artery, this requirement may seem overly burdensome. However, using therapies that have both risk and cost to alter biomarkers or coronary artery appearances without some reasonable expectation that the patient will benefit over the long term either in terms of length or quality of life is hard to justify on a number of different grounds. And if there is a belief that these outcomes are benefited but the amount is uncertain because of a lack of appropriate clinical data, then that uncertainty is an important part of the story about the therapy or management strategy being studied.

The pattern by which quantity and quality of life are altered by therapies can vary in several different ways. For example, all the

incremental outcomes differences may accrue early (eg, by 30 days), they may accrue steadily in a linear fashion over time, or they may even amplify over time. The pattern of cost differences over time also can vary in different circumstances and does not have to mirror the pattern of incremental outcome benefits. Cost differences may be large or small and may accrue early, steadily over time, or as a step function. Surgical therapies such as coronary artery bypass graft surgery (CABG) and heart transplant have very high upfront costs, and the initial clinical benefits may even be negative as a result of operative mortality. Outcome benefits may take years to be fully expressed in such cases so that the incremental outcomes calculated from short-term follow-up (eg, 1 year) are quite likely to underestimate such benefits. Secondary prevention, on the other hand, often involves a steady cost stream year after year and, in some cases, a small clinical benefit that tends to amplify over time. The key point that these examples serve to highlight is that a high-quality economic analysis must assess outcomes and costs over the long term, defined operationally as the period for which the effects of the therapy in question, both direct and induced, might reasonably be expected to persist.

SOME CAVEATS ABOUT HEALTH ECONOMICS

A few points that have been made earlier in this chapter are worth emphasizing because they are so central to understanding the perspective of health economics. First, the focus is typically on systems, countries, or society and not on individual doctors or patients. Health economics, then, does not usually focus on decision making at the level of the individual patient, nor is it intended that individual physicians should be using these methods to make individual "funding decisions" about what care to provide to patients.

Second, health economics is neutral on the issue of who benefits and who is deprived of health care services. If it were possible to generate more QALYs by treating an 80-year-old patient with advanced heart failure than a 30-year-old with hypertension or a premature infant with respiratory distress, and only one could be chosen, health economics would favor going the way of more efficiency. Clinicians usually do not face such overt choices, although triage situations do come close, as when coronary care unit beds or donor hearts must be allocated and there are more candidates than resources to satisfy all who could benefit. Health economics in this context is a tool that may clarify some important issues about the choices being considered. However, societal values and preferences may and often should override the maximal efficiency answer.

Finally, because clinicians are now accustomed to using fairly rigorous standards to decide whether new therapies and clinical strategies "work" and practice medicine using guidelines that rank recommendations according to the strength of the evidence, they may not appreciate that policy decisions are often made on the basis of "evidence" that would not pass rudimentary quality screens in medical/outcomes research. Thus, clinicians who are informed, discerning consumers of health economics research will be critical to help drive comparative effectiveness research toward higher quality rather than political expediency.

SELECTED HEALTH ECONOMICS APPLICATIONS

HEART FAILURE

(See also Chaps. 68 to 73.) According to statistics compiled by the American Heart Association, approximately 5.7 million people in the United States have heart failure (the prevalence), and every year, 915,000 new cases are diagnosed (the incidence).[34] In the Medicare population (age ≥ 65 years), heart failure is the most common reason for hospitalization listed on medical claims data. In the total US population, the estimated number of annual heart failure hospitalizations is approximately 1 million a year. Further, patients who are hospitalized for this diagnosis have a substantially elevated risk of being rehospitalized (~25% within 30 days [approximately one-third for heart failure, the remainder for other medical problems] and ≥ 50% within the following 6 months [about 50% related to heart failure]).[35,36] The overall annual US medical spending attributed to heart failure in 2012 was approximately $30.7 billion, with 68% attributable to direct medical costs.[34] It must be kept in mind that given the difficulties in identifying heart failure on a population level, these estimates are extremely crude. However, the data are sufficient to conclude that heart failure is common and accounts for a large amount of health care spending. It follows to reason that if we could allocate resources to prevent the disease or, failing that, prevent it from progressing to decompensation, we might improve the health of these patients efficiently and without a massive increase in health care spending. Heart failure prevention means better control of the disorders most likely to progress to heart failure, primarily coronary artery disease (CAD) and hypertension (each confer a two- to three-fold increased risk of heart failure). However, because of the time spans involved (typically decades), the true population health benefits and efficiencies of primary prevention strategies are difficult to study empirically.[37] In the remainder of this section, we will examine three general types of care used to manage the established heart failure state: maintenance medical care to relieve symptoms, improve functional status, and improve prognosis; strategies to reverse the heart failure state and to prevent sudden cardiac death; and comprehensive management strategies to improve functioning and reduce acute decompensations.

Medical Therapy of Heart Failure With Reduced Ejection Fraction

Medical therapy of heart failure focuses on symptom relief and improvement of prognosis. As reviewed elsewhere in this text, the main agents shown to enhance survival are angiotensin-converting enzyme (ACE) inhibitors, β-blockers, angiotensin receptor blockers (ARBs), and sacubitril/valsartan, as well as isosorbide-hydralazine and aldosterone antagonists in selected populations. Unfortunately, much of the literature examining the economics of these therapies is now either dated or most pertinent to a non-US health care system. In addition, few of the pivotal trials that changed our clinical practice included careful prospective measurement of resource use and costs, so most of the literature is based on decision modeling frameworks.

In one such analysis, Glick and colleagues[38] examined the cost effectiveness of enalapril using data from the Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial, which randomized 2569 symptomatic heart failure patients with left ventricular ejection fraction ≤ 0.35 to receive either enalapril or placebo. Over a projected 7-year life expectancy, these authors estimated that enalapril would add 0.3 discounted life-years (0.21 discounted QALYs) and would have a net lifetime incremental cost of $25, with a cost-effectiveness ratio of $80 per life-year added ($115 per QALY added) (Table 112–1). Given that generic enalapril (along with lisinopril and benazepril) can now be obtained in the United States and that the Glick analysis probably underestimated the long-term effects of therapy on reducing hospitalizations, it is very possible that enalapril as used in the SOLVD Treatment trial was cost saving over the long run.

Three β-blockers have been shown to improve survival in heart failure patients when added to ACE inhibitors: sustained release metoprolol, bisoprolol, and carvedilol. The clinical data show that these drugs also reduce all-cause hospitalization, although the magnitude

TABLE 112–1. US Cost-Effectiveness Analyses for Heart Failure Treatments

Data From Trial Data/ Cohort (References)	Population	Treatment	Benefit	Incremental Cost (Year)	Incremental Cost-Effectiveness
Medical therapy of heart failure with reduced ejection fraction					
SOLVD (38)	Symptomatic heart failure patients with left ventricular ejection fraction ≤ 0.35	Enalapril vs placebo	Enalapril adds 0.3 discounted life-years and 0.21 discounted QALYs over a projected 7-year life expectancy	Enalapril adds net lifetime incremental cost of $25 (unknown)	$80/LY $115/QALY
US Carvedilol Heart Failure Program (39)	Patients with chronic heart failure	Carvedilol vs conventional therapy alone	Carvedilol adds 0.31 to 0.95 life-years	$7600 (1997 USD)	$30,000/LY
MERIT-HF (40)	Patients with chronic heart failure in NYHA functional class II-IV and with ejection fraction of 0.40 or less	ER metoprolol succinate vs standard therapy alone	Metoprolol would prevent 7 deaths per 100 patients over 2 years	Cost savings of $395 to $1112/patient (2001 USD)	N/A
PARADIGM-HF (48)	Patients with class II-IV heart failure and an ejection fraction of ≤ 40%	200 mg twice daily sacubitril/valsartan vs lisinopril	Sacubitril/valsartan adds 2.2 life-years and 0.57 QALYs	Sacubitril/valsartan adds $29,138 lifetime incremental costs (unknown)	$50,915/QALY
A-HeFT (50)	African American patients who had symptomatic NYHA functional class III-IV heart failure for 3 months or more	Isosorbide-hydralazine combination vs placebo	Reduced heart failure hospitalizations over 13-month follow-up from 0.47 per patient to 0.33	Cost saving (2004 USD)	N/A
RALES (51)	Patients with NYHA functional class III-IV heart failure symptoms and EF < 35%	Spironolactone vs placebo	Spironolactone added 0.13 QALYs over 35 months	Cost saving (1999 USD)	N/A
EPHESUS (52)	Patients with acute myocardial infarction, pulmonary rales, and EF 40% or less	Eplerenone	Eplerenone added approximately 0.10 to 0.13 life-years over a lifetime	$1400 lifetime costs (2001 USD)	Under $20,000/LY
Left ventricular assist device (LVAD) therapy					
REMATCH and HeartMate Destination Therapy Trial (59)	Patients with predominantly NYHA functional class IV symptoms and a left ventricular ejection fraction of 25% or less	Continuous-flow LVAD vs optimal medical management	Continuous-flow LVAD patients gained 1.5 more QALY and 1.78 more life-years	Over 5 years, continuous-flow LVAD patients had $297,551 higher costs compared with medically managed patients (2009 USD)	$198,184/QALY $167,208/LY
Cardiac resynchronization therapy (CRT)					
MADIT-CRT (64)	NYHA functional class I or II heart failure patients with an ejection fraction of 30% or less and a QRS duration of 130 ms or more	CRT-ICD vs ICD alone	Adding CRT to ICD therapy reduced heart failure events by 41%	Health care costs over 4 years were an average $5550 higher in the CRT-ICD patients (2008 USD)	$58,330/QALY
Prevention of sudden cardiac death with ICD therapy					
MADIT-II (68)	Patients with reduced ejection fraction after myocardial infarction	ICD vs medical therapy alone	Over 3.5 years, the average survival gain from the ICD was 0.167 years	Additional costs were $39,200 over 3.5 years (2001 USD)	$235,000/LY
SCD-HeFT (70)	Patients with NYHA functional class II or III heart failure and left ventricular ejection fraction of 35% or less	ICD vs optimal medical therapy alone	Estimated lifetime incremental survival gain of 1.63 years for ICD	Estimated lifetime incremental costs for ICD strategy were $62,420 (2003 USD)	$38,389/LY $41,530/QALY
Transcatheter aortic valve replacement (TAVR)					
PARTNER B (73)	Elderly NYHA class III or IV patients with inoperable aortic stenosis	TAVR vs medical therapy	Estimated lifetime incremental gain of 1.6 life-years and 1.3 QALYs for TAVR	Estimated lifetime incremental costs for TAVR of $79,837 (2010 USD)	$50,212/LY $61,889/QALY
PARTNER A (75)	Patients with severe aortic stenosis and NYHA class II function or worse	TAVR vs surgical aortic valve replacement	Similar benefits out to 3 years	Similar costs (2010 USD)	N/A

Abbreviations: ER, extended-release; ICD, implantable cardioverter-defibrillator; LY, life-year; N/A, not applicable; NYHA, New York Heart Association; QALY, quality-adjusted life-year; USD, US dollars.

of this effect varies among the trials. Carvedilol is now available in a generic form. The US Carvedilol Heart Failure Program, consisting of four trials, was used as the basis for a Markov decision model analysis, combining the trial data with varying assumptions about what would happen to benefits as the trial data were projected to a lifetime time horizon.[39] Life expectancy without carvedilol was estimated at 6.7 years, and carvedilol therapy was projected to add 0.31 to 0.95 life-years at an incremental lifetime cost (1999 costs) of $7600. Given the difference between proprietary drug costs used in that analysis and current generic costs, carvedilol would now be expected to have a cost-effectiveness ratio much more favorable than the $30,000 per life-year calculated in this older model. Bisoprolol is also available in generic form, but the trials supporting this drug were done in Europe, and no high-quality economic data are available for the United States. The MERIT-HF (Metoprolol Randomized Intervention Trial in Congestive Heart Failure) study group conducted an economic analysis of extended-release metoprolol succinate compared with standard therapy alone using a discrete event simulation, which assumes risks based on individual patient characteristics and then assigns health and economic consequences of associated events, management, and outcomes.[40] Costs were reported in 2001 US dollars, and the proprietary price of extended-release metoprolol was $912 over 2 years. The model predicted that metoprolol would prevent 7 deaths and 15 hospitalizations from heart failure per 100 patients over 2 years and result in a cost savings of $395 to $1112 per patient.

ARBs improve survival and reduce cardiovascular hospitalizations in heart failure patients unable to tolerate ACE inhibitors,[41,42] but their benefit as a first-line treatment in place of or as an adjunct to ACE inhibitors is less clear.[43-45] There are no prospective economic analyses from a US perspective of the major clinical trials comparing ARBs with placebo or with ACE inhibitors. An economic analysis from a European perspective of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program found the use of candesartan to be economically efficient compared with placebo in heart failure patients with an ejection fraction ≤ 0.40, with candesartan achieving economic dominance (better clinical outcomes and lower costs) in some scenarios.[46] Several ARBs are now available generically.

The FDA approved the angiotensin-neprilysin inhibitor combination drug sacubitril/valsartan in 2015 for use in heart failure patients with reduced left ventricular ejection fraction. The pivotal trial supporting this approval, the PARADIGM-HF (Prospective Comparison of Angiotensin-Neprilysin Inhibitor With ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, assessed 200 mg twice daily of sacubitril/valsartan versus 10 mg twice daily of enalapril in 8442 patients with class II to IV heart failure and an ejection fraction of ≤ 40%.[47] The trial was stopped after a median follow-up of 27 months because of significant benefit with this combination therapy. The primary composite outcome of death from cardiovascular causes or hospitalization for heart failure occurred in 21.8% of the sacubitril/valsartan group versus 26.5% in the enalapril group (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73-0.87; $P < .001$). The price of sacubitril/valsartan is approximately $12.00 to $13.00 per day (National Average Drug Acquisition Cost reference file, February 3, 2016). A Markov model–based analysis used published data from the PARADIGM-HF trial and other published data to assess the cost-effectiveness of sacubitril/valsartan compared with lisinopril.[48] This model predicted 6.78 years of survival and 5.56 QALYs together with total costs of $123,578 for the lisinopril arm. The corresponding projections for sacubitril/valsartan were 8.98 years of survival, 6.13 QALYs, and total costs of $152,716. The incremental cost-effectiveness ratio was $50,915 per QALY gained. A 5-year US budget model on the impact of this drug projected about 1.7 million patients taking sacubitril/valsartan for more than 1 year and annual costs per year of $3 billion.[48] Early evidence on prescriptions for the drug in the United States suggest this is a substantial overestimate.[49]

The isosorbide-hydralazine combination studied in the African American Heart Failure Trial (A-HeFT) reduced heart failure hospitalizations during the study's mean 13-month follow-up (from 0.47 per patient to 0.33) and reduced total medical costs during the study follow-up by approximately $4300, exclusive of drug costs.[50] Even with the assumed drug cost per day of $6, the isosorbide-hydralazine combination was economically dominant. Because the specific proprietary combination drug studied is no longer available, the cost of these two drugs would now be significantly less, reinforcing the likelihood that this treatment is very economically attractive for the population studied in A-HeFT.

Two aldosterone antagonists have been studied in selected populations with heart failure: spironolactone in the Randomized Aldactone Evaluation Study (RALES) and eplerenone in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). A decision model–based analysis looking at the first 35 months of the RALES trial found that spironolactone added 0.13 QALYs and had a net lower cost than the placebo arm.[51] In a lifetime analysis of the EPHESUS trial results, eplerenone added approximately 0.10 to 0.13 life-years and had a net cost of approximately $1400 as a result of the drug cost (in this analysis, ~$3.60 per day).[52] The cost-effectiveness ratio, using several different data sets upon which to base the long-term extrapolations, was consistently under $20,000 per life-year added.

One interesting analysis addressed the economic impact of underuse of effective therapies by modeling the effect of increasing the use of ACE inhibitors, β-blockers, spironolactone, and digoxin each by 10% in a Canadian cohort of 86,000 patients with heart failure.[53] After accounting for the extra cost of the drug therapy ($4.3 million in Canadian prices), this strategy was estimated to save $2.3 million net in the first year as a result of reduced avoidable hospitalizations.

Heart Transplant and Left Ventricular Assist Device Therapy

(See also Chaps. 72 and 73.) For patients with advanced refractory heart failure, cardiac replacement therapy may offer the best option to restore quality of life and improve longevity. The economic impact of orthotopic heart transplant is strongly influenced by the fact that the supply of donor hearts for transplant has remained limited to approximately 2000 per year, with no signs this number is likely to increase. A review using data from the Nationwide Inpatient Sample between 2005 and 2009 found that the cost (calculated from charges using overall hospital cost-to-charge ratios) of the index procedure hospitalization for transplant increased 40% from $120,000 to $168,576.[54] Total annual costs to the US health care system for procedure admissions were over $375 million in 2009, representing the costs of 2227 heart transplants.[54] In one academic center, transplant patients averaged 2.1 hospitalizations and 11.9 outpatient encounters during the first posttransplant year.[55] Cumulative costs for the first year after transplant at another center averaged about $330,000 (2010 US dollars), with the index admission representing > 50% of that amount.[56] Contemporary annual posttransplant costs after the first year can total more than $70,000 per patient in part as a result of the need for expensive immunosuppressive drugs and the need for complex hospitalizations to treat rejection episodes and infections. Despite its high procedural and follow-up costs, the substantial increase in life expectancy (one of the largest of any cardiovascular therapy) and improvement in quality of life for transplant patients make it likely to be economically attractive compared with medical therapy alone in this population.

Because left ventricular assist devices (LVADs) are not limited in number the way donor hearts currently are, the potential exists for this form of cardiac replacement therapy to have a much larger clinical and

economic impact. The technology and ancillary care have evolved significantly since the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial. In 2009, the unadjusted mean per-patient cost of the index hospitalization for LVAD transplant was $208,522.[54] Cumulative first-year costs in a small cohort at a different center averaged about $370,000.[56] With 2298 LVAD implants nationwide, the total cost to the US health care system was estimated at $479 million.[54] Although LVAD therapy is quite expensive initially, the therapy has the potential to be cost effective if, like heart transplant, it provides a significant enhancement of survival and/or quality of life. In 2038 patients receiving LVADs, hospital survival improved from 2008 (53%) to 2011 (87%).[57] Hospital costs increased during this period, reaching $235,000 between 2008 and 2011. Of those discharged alive with a device, during an average follow-up of 11 months, patients required an average of 2.2 readmissions.[58] Mean time to first readmission was 35 days, and 44% were readmitted within 30 days. Most common causes of readmission were gastrointestinal bleeding, driveline infection, and stroke. A model-based analysis examined the cost-effectiveness of continuous-flow LVADs for destination therapy versus optimal medical management in advance heart failure patients.[59] Continuous-flow LVAD patients had higher 5-year costs compared with medically managed patients ($360,407 vs $62,856), higher quality-adjusted life-years (1.87 vs 0.37), and more life-years (2.42 vs 0.64). The incremental cost-effectiveness ratio for the continuous-flow LVAD was $198,184 per QALY and $167,208 per life-year. A second model-based analysis came to a similar result: compared with inotrope-dependent medical therapy (life expectancy, 9.4 months), destination LVAD (life expectancy, 4.4 years) had a cost-effectiveness ratio of $202,000 per QALY.[60]

Cardiac Resynchronization Therapy

Another quite different approach to the treatment of patients with advanced heart failure derives from observations that some patients have severe left ventricular dysfunction accompanied by a dyssynchronous pattern of depolarization and contraction usually as a result of left bundle branch block. In such patients, the use of biventricular pacing for cardiac resynchronization has been shown to improve heart failure symptoms (by approximately one New York Heart Association [NYHA] class) and to improve survival. An economic analysis of the Cardiac Resynchronization in Heart Failure (CARE-HF) trial done using United Kingdom (UK) cost weights found a cost-effectiveness ratio for cardiac resynchronization therapy (CRT) plus medical therapy of €19,319 per QALY and €43,596 per life-year compared with medical therapy alone, indicating the important contribution of quality-of-life improvements to the estimated cost-effectiveness in this trial.[61]

In Europe, many CRT devices are implanted without implantable cardioverter-defibrillator (ICD) function (CRT-P), whereas in the United States, most of the CRT devices include an ICD function (CRT-D), a factor that influences the cost of the device. The incremental contribution of the ICD function versus the CRT function in these patients to the survival benefits seen remains unsettled. An economic model based on the US Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial data found that with extrapolation to 7 years, CRT-P had a cost-effectiveness ratio of $19,600 per QALY relative to medical therapy alone, and CRT-D had a cost-effectiveness ratio of $43,000 per QALY relative to medical therapy alone.[62] What was left unaddressed by the COMPANION trial is the incremental benefits and cost-effectiveness of CRT-D relative to CRT-P.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT)-CRT trial examined CRT-D versus ICD alone in 1820 NYHA class I or II heart failure patients (both ischemic and nonischemic) with an ejection fraction ≤ 0.30 and a QRS duration of 130 milliseconds or more and found that the addition of CRT to ICD therapy reduced heart failure events by 41% (22.8% for ICD-only group vs 13.9% for ICD plus CRT; $P < .001$).[63] No effect was seen on all-cause mortality. A prospective cost study was conducted alongside the main MADIT-CRT trial in a total of 1271 patients.[64] Health care costs at 4 years after randomization were higher in the CRT-ICD patients largely as a result of device and implantation costs. CRT-ICD had an incremental cost-effectiveness ratio of $58,330 per QALY compared to ICD alone. A Markov decision model of this same treatment choice using the published trial results estimated that CRT-D increased life expectancy (9.8 years vs 8.8 years for ICD alone), QALYs (8.6 years vs 7.6 years), and costs ($286,500 vs $228,600).[65] The base case cost-effectiveness ratio was $61,700 per QALY.

Prevention of Sudden Cardiac Death With Implantable Cardioverter-Defibrillator Therapy

(See also Chap. 91.) The MADIT-II trial and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) established that ICD therapy improves survival over medical therapy alone in patients with reduced left ventricular ejection fraction.[66,67] A prospective economic analysis of the MADIT-II trial found ICD therapy in patients with reduced left ventricular ejection fraction after MI to have an estimated incremental cost-effectiveness ratio of $235,000 per life-year saved based on an average survival gain of 0.167 years after 3.5 years of follow-up.[68] However, this analysis made the overly conservative assumption for the base case analysis that no further survival benefits would accrue from ICD therapy beyond the empirical follow-up period of the trial. Empirical 10-year follow-up from MADIT-II subsequently showed that survival benefits from ICD therapy continued to amplify over time, indicating that the initial published economic analysis from this study was too conservative. A separate economic model based on MADIT-II eligibility criteria found that the estimated cost-effectiveness ratio in this patient population varied depending on follow-up time horizon, from $367,200 at 3 years to $67,800 at 15 years.[69]

A prospective economic analysis of the SCD-HeFT trial using a lifetime time horizon found a more favorable cost-effectiveness ratio for ICD therapy compared with medical therapy alone in stable, moderately symptomatic heart failure patients with a left ventricular ejection fraction ≤ 0.35. In this economic analysis, the base case lifetime cost-effectiveness ratio was $38,389 per life-year saved and $41,530 per quality-adjusted life-year saved.[70] Similar to the aforementioned economic analyses, the SCD-HeFT investigators estimated the cost-effectiveness ratio would improve with extended follow-up, with $127,503 per life-year saved at 5 years and $58,510 per life-year saved at 12 years. However, in subgroup analyses, ICD therapy in patients with NYHA class III heart failure was found to increase costs without an incremental benefit and thus was dominated by medical therapy alone.

A Markov model using data from several clinical trials of ICD therapy was constructed to estimate the cost-effectiveness of ICD therapy under different assumptions.[71] This analysis found that prophylactic ICD therapy added between 1.01 and 2.99 quality-adjusted life-years at a cost of $68,300 to $101,500 in patients with left ventricular systolic dysfunction. The incremental cost-effectiveness of ICD therapy in this analysis ranged from $34,000 to $70,200 per QALY, with ICD therapy remaining below the upper cost-effectiveness benchmark of $100,000 per QALY if the incremental survival benefit of ICD therapy lasted ≥ 7 years.[71]

Transcatheter Aortic Valve Replacement

The Placement of Aortic Transcatheter Valves (PARTNER) trials (see Chap. 47) examined the use of transcatheter aortic valve replacement (TAVR) in patients with and without operable aortic stenosis (AS).

The PARTNER B cohort consisted of very symptomatic (93% NYHA class III or IV) elderly patients with inoperable AS. TAVR increased life expectancy from 1.2 to 3.1 years, and quality of life was substantially improved, with between 25% and 40% of patients benefitting dramatically from the procedure by gaining years of high-quality survival.[72] The cost of the TAVR procedure was estimated at $43,000 and included the cost of the device, which was about $35,400.[73] Hospitalization for the procedure averaged $79,000. After accounting for resource use in the year following the procedure, total costs at 1 year for the TAVR patients averaged $52,000 more than the conservatively treated patients. The incremental cost-effectiveness ratio was $50,200 per life-year added and $61,889 per QALY. The PARTNER A cohort consisted of patients who were eligible for surgical aortic valve replacement.[74] Mortality in the TAVR and surgical aortic valve replacement groups was similar out to 3 years (~50%), but the TAVR group had 2.1 per 100 more major strokes and more early major vascular complications, and the surgical aortic valve replacement group experienced higher rates of early major bleeding. Index costs were $72,000 for the TAVR group and $74,40 for the surgical aortic valve replacement group.[75] Periprocedural complications accounted for approximately $12,475 per patient in the TAVR group and 2.4 days of hospitalization.[76] One-year cumulative costs for each group were around $100,000. These two treatment strategies were essentially comparable in terms of outcomes and costs.[77]

ATRIAL FIBRILLATION

(See also Chap. 83.) Atrial fibrillation (AF) affects between 2.7 and 6.1 million Americans, and approximately 1.6 million new cases are diagnosed each year.[34] AF is associated with a shorter life expectancy, and it adversely impacts patient quality of life, increases the risk of cardiovascular events, complicates heart failure, and significantly increases the likelihood and severity of stroke, all of which are associated with substantial medical costs.

Because of its co-occurrence with common cardiovascular diseases such as CAD and heart failure, determining the unique economic burden of AF is difficult. In 2010, AF was the primary discharge diagnosis for approximately 479,000 hospitalizations in the United States. Kim et al[78] performed a retrospective, observational cohort study using administrative claims data and estimated the total annual incremental cost to be $8705 per AF patient which extrapolated to between $6.0 and $26.0 billion for the US health care system.

Analysis of a large claims database with charges converted to costs found the cost for a hospital admission with AF as a primary or secondary diagnosis was $15,000 to $16,800.[79] The costs associated with complications of AF have recently been reported from two registries. In Ontario, Canada, average costs, in Canadian dollars, were $19,937 for an ischemic stroke event, $22,347 for intracranial hemorrhage, and $12,313 for a minor stroke/transient ischemic attack (TIA).[80] In a US claims database, hospital reimbursements by insurance were $20,933 for an ischemic stroke, $59,034 for a hemorrhagic stroke, and $8616 for a TIA.[81] The cost of a major bleeding episode requiring hospitalization in a fourth claims registry was $16,830.[82]

Oral Anticoagulation

Warfarin therapy has been found to reduce the risk of stroke in AF patients by 62% (compared with a 22% risk reduction with aspirin) and is recommended in current practice guidelines. Unfortunately, the efficacy of warfarin therapy in preventing strokes is tempered in practice by its variable anticoagulation effects and associated risk of bleeding. For an optimal risk-benefit ratio with warfarin therapy, frequent monitoring must be performed to ensure that the international normalized ratio (INR) is maintained within the target therapeutic range. Such monitoring is particularly important in patients at high risk for bleeds (eg, elderly individuals). However, in clinical practice, regular monitoring poses logistical difficulties and increases the cost of care, thereby increasing the likelihood of poorly controlled anticoagulation. Despite these difficulties, warfarin is highly effective, and its generic price for maintenance therapy is less than $1 per day in the United States and pennies a day in European countries, which makes it very efficient from an economic perspective.

Novel oral anticoagulants (NOACs) that target either thrombin or factor Xa have emerged as an alternative to vitamin K antagonists (Table 112–2). Compared to warfarin, the NOACs provide a better pharmacologic profile including a more rapid onset of action with a more predictable response, which eliminates the need for regular monitoring. Dabigatran is a novel direct thrombin inhibitor that, at a 150-mg dose twice a day, has been shown to be superior to warfarin at reducing stroke or systemic embolism in AF patients (relative risk, 0.66; 95% CI, 0.53-0.82; $P < .001$), with both treatments showing similar rates of mortality and major hemorrhage after 2 years of follow-up.[83] Several model-based analyses have examined the cost-effectiveness of dabigatran at the 150-mg twice-daily dose compared with warfarin and found incremental cost-effectiveness ratios ranging from $25,000 per QALY to $86,000 per QALY under conservative base case assumptions.[84,85] The price of dabigatran and the rate of intracranial hemorrhage were the main cost drivers in these analyses.

Three direct factor Xa inhibitors have been approved by the FDA for the prevention of stroke in nonvalvular AF: rivaroxaban, apixaban, and edoxaban. The use of rivaroxaban 20 mg/d versus dose-adjusted warfarin in nonvalvular AF was tested in 14,264 patients in the ROCKET-AF randomized trial.[86] The investigators found that rivaroxaban reduced the primary end point of stroke or systemic embolism by 21% (HR, 0.79; 95% CI, 0.66-0.96). No economic analysis of ROCKET-AF by the original trial team has been done. Using published data from the ROCKET-AF trial and a variety of other sources, Lee et al[87] constructed a Markov model to assess the cost-effectiveness of rivaroxaban compared with warfarin from a US payer perspective. Rivaroxaban (assigned a monthly cost of $205) produced an average of 10.03 QALYs at a lifetime treatment cost of $94,456 (2011 US dollars), whereas warfarin produced an average of 9.81 QALYs at a lifetime treatment cost of $88,544. The incremental cost-effectiveness ratio for rivaroxaban was $27,498 per QALY for the base case analysis, with results most sensitive to risk of intracranial hemorrhage and stroke, drug cost, and time horizon. Current US pricing for rivaroxaban is approximately $10.75 per day (National Average Drug Acquisition Cost reference file, February 3, 2016) compared with the $6 per day this model assumed.

The cost-effectiveness of apixaban compared to warfarin has been assessed using patient-level data from the ARISTOTLE trial.[88] This prospective economic analysis was conducted from the US perspective using within-trial resource use paired with external cost weights from AF patients in a large registry of US hospitals. The analysis found similar costs in patients treated with apixaban and warfarin (excluding the cost of apixaban), but significantly longer life expectancy with apixaban (7.94 vs 7.54 QALYs), which resulted in an incremental cost-effectiveness ratio of $53,925 per QALY.[88] Edoxaban was compared with warfarin in 21,105 patients with moderate- to high-risk AF in the ENGAGE AF-TIMI 48 trial who were followed for a median of 2.8 years.[89] Edoxaban was noninferior to warfarin for the prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding and cardiovascular death. Magnuson et al[90] performed a cost-effectiveness analysis using patient-level data from this trial together with a Markov model. Cost for edoxaban was $9.24 per day (2015 costs). Edoxaban had lifetime incremental costs of $16,384

TABLE 112–2. US Cost-Effectiveness Analyses for Novel Oral Anticoagulation in Atrial Fibrillation

Data From Trial/Cohort (First Author)	Population	Treatment	Benefit	Incremental Cost (Year)	Incremental Cost-Effectiveness
RE-LY (Freeman)	Patients 65 years or older with nonvalvular atrial fibrillation and risk factors for stroke	110 mg twice daily or 150 mg twice daily dabigatran vs warfarin	Low-dose dabigatran produced 0.42 more QALYs than warfarin, and high-dose dabigatran produced 0.56 more QALYs	Total costs were $21,383 higher for low-dose dabigatran and $25,205 higher for high-dose dabigatran (2008 USD)	Low-dose dabigatran: $51,229/QALY High-dose dabigatran: $45,372/QALY
RE-LY (Kamel)	Patients 70 years or older with nonvalvular atrial fibrillation and prior stroke or transient ischemic attack	150 mg twice daily dabigatran vs warfarin	Dabigatran produced 0.36 more QALYs	Incremental cost for dabigatran was $9000 (2010 USD)	$25,000/QALY
RE-LY (Shah)	Patients 70 years old with atrial fibrillation	110 mg twice daily or 150 mg twice daily dabigatran vs warfarin	Low-dose dabigatran produced 0.14 more QALYs than warfarin, and high-dose dabigatran produced 0.25 more QALYs	Total costs were $53,500 higher for low-dose dabigatran and $37,500 higher for high-dose dabigatran (2010 USD)	Low-dose dabigatran: $150,000/QALY High-dose dabigatran: $86,000/QALY
ROCKET-AF (Lee)	Patients 65 years old with atrial fibrillation and high risk for stroke	Rivaroxaban vs warfarin	Rivaroxaban produced 0.22 more QALYs	Incremental costs for rivaroxaban were $5912 (2011 USD)	$27,498/QALY
ARISTOTLE (Cowper)	Patients with atrial fibrillation and at least 1 risk factor for stroke	Apixaban vs warfarin	Apixaban produced 0.40 more QALYs	Incremental cost for apixaban was $6000 (2014 USD)	$53,925/QALY
ENGAGE AF-TIMI 48 (Magnuson)	Patients with moderate- to high-risk atrial fibrillation	Edoxaban versus warfarin	Edoxaban produced 0.444 more QALYs	Incremental costs for edoxaban were $16,384 (2013 USD)	$36,862/QALY

Abbreviations: QALY, quality-adjusted life-year; USD, US dollars.

and incremental QALYs of 0.444 (QALY: 7.16 years with edoxaban vs 6.72 years with warfarin), resulting in an incremental cost-effectiveness ratio of $36,862 per QALY.[90]

Rate Control Versus Rhythm Control

The two primary approaches to managing AF are establishing and maintaining sinus rhythm (rhythm control) and controlling ventricular rate (rate control). Despite their conceptual appeal, rhythm control strategies have failed to demonstrate incremental reductions in death, stroke, worsening heart failure, or hospitalizations when compared with rate control.[91-94] In the Pharmacologic Intervention in Atrial Fibrillation (PIAF) pilot study, rhythm control therapy did not produce superior quality of life or symptom improvements over rate control, and it came with a higher rate of hospital admissions and adverse drug effects.[91] The Comparison of Rate Control and Rhythm Control in Patients With Recurrent Persistent Atrial Fibrillation (RACE) trial, which randomly assigned 522 patients with persistent AF to either rate or rhythm control, found no significant differences in a composite primary end point of cardiovascular death, heart failure, thromboembolic complications, bleeding, pacemaker implantation, and severe adverse drug effects.[92] The rhythm control arm experienced higher rates of thromboembolic events and adverse drug effects. In the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial, 4060 AF patients with a high risk of stroke or death were randomly assigned to rate or rhythm control and followed for up to 6 years. There was no significant difference in survival (the primary end point), and similar to earlier studies, the rhythm control strategy produced more hospitalizations and more adverse drug effects.[93] In a heart failure population with AF, in which the theoretical benefits of rhythm control over rate control should be easier to demonstrate, the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial investigators found no significant differences between the two strategies in all-cause mortality, stroke, or worsening heart failure.[94] Consistent with earlier studies, the rhythm control arm experienced more frequent hospitalizations compared with the rate control arm (64% vs 59%; $P = .06$), with significantly more hospitalizations for AF (14% vs 9%; $P = .001$). Additionally, the rhythm control arm required more electrical cardioversion (59% vs 9%; $P < .001$).

Although there have been no prospective economic analyses in rate versus rhythm control trials, a retrospective economic evaluation of the AFFIRM trial found that rate control had a cost savings of $5077 per person over rhythm control and was more effective, thus dominating rhythm control from an economic perspective.[95]

Atrial Fibrillation Ablation

Catheter ablation is a procedure that uses thermal energy or cryoenergy to selectively ablate electrical triggers and susceptible atrial substrate in an effort to eliminate AF.[96] As ablation techniques have

evolved, pulmonary vein isolation (PVI) has emerged as the core ablation approach used in these procedures. Currently, PVI is primarily reserved for symptomatic AF patients who have not responded to at least one antiarrhythmic drug.

Several randomized trials have compared catheter ablation with antiarrhythmic drug therapy (AAD) and have focused largely on a reduction in AF recurrence as the primary end point.[97-102] The current evidence base shows that ablation with or without AAD consistently outperforms AAD alone at preventing recurrence of AF.[97-102] Two studies found significantly fewer hospitalizations in the ablation group compared with AAD alone,[99,101] whereas one study found no statistically significant difference in the median per-patient number of hospitalizations between the groups.[100] Three studies found significantly better improvements in quality-of-life measures for ablation compared with AAD.[97,101,102] One meta-analysis found radiofrequency ablation to have higher rates of efficacy with lower rates of complications than AAD therapy,[103] and another found higher rates of efficacy for PVI when compared with medical therapy, with the risk of complications associated with PVI comparable to that of other interventional procedures.[104]

Although several studies have reported on the incremental economic effects of AF relative to no AF, there have been as yet no large-scale empirical cost studies of the contemporary AF ablation procedure.[105,106] An economic evaluation of the Radiofrequency Ablation for Atrial Fibrillation Trial (RAAFT) pilot study found the ablation strategy in that trial to be cost neutral at 2 years.[107] One literature-based decision model has explored some preliminary aspects of the cost-effectiveness of ablation therapy for AF and found it to be cost effective in patients with AF at moderate risk for stroke.[108] A Markov disease simulation model found ablation either in combination with AAD or alone to be cost effective for a hypothetical cohort of symptomatic, drug-refractory paroxysmal AF patients compared with AAD alone, with a cost-effectiveness ratio for ablation of $51,431 per QALY.[109]

The National Heart, Lung, and Blood Institute–supported Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA; NCT00911508) trial randomized 2203 patients to receive either percutaneous left atrial catheter ablation as a first-line therapy or current state-of-the-art medical therapy using either rate control or rhythm control drugs. The primary end point is all-cause mortality, and the secondary end point is a composite end point of total mortality, disabling stroke, serious bleeding, and cardiac arrest. Prospective economic and quality-of-life assessments are part of the research program. Because the comparator strategy in CABANA is outpatient medical therapy, the ablation strategy will be significantly more expensive in the short- to intermediate-term follow-up period because it requires both an invasive procedure and periprocedure inpatient therapy. The magnitude of this difference, based on current Medicare reimbursement rates, may exceed $10,000. If the expected reduction of AF is demonstrated, literature suggests that return to sinus rhythm will be accompanied by fewer physician and ED visits and a reduced rate of follow-up hospitalizations.[110-112] This may allow the ablation strategy to recoup at least a portion of the upfront procedural costs.[113-115]

CORONARY ARTERY DISEASE: PREVENTION OF CORONARY ARTERY DISEASE

CAD is still the number one cause of death in the United States. It is a major force of morbidity, disability, and human suffering and is a major driver in the growing cost of medical care. It is estimated that more than 15.5 million Americans ≥ 20 years of age have CAD and that one in every seven deaths is the result of CAD.[34] The combined direct and indirect burden of CAD was estimated to total more than $207.3 billion in expenditures in 2011 to 2012.[34] The conceptual appeal of prevention as an approach to the problem of CAD is clear. Although use of these terms in the literature is not always consistent, for this discussion, we shall take *primary prevention* to refer to therapies applied for the purpose of preventing overt disease manifestations, such as death, MI, angina, or heart failure in individuals without overt signs of atherosclerotic cardiovascular disease. The major therapeutic targets for primary prevention include smoking, lipid disorders, diabetes, hypertension, and physical inactivity. *Secondary prevention* refers to the application of therapeutics to prevent progression of disease in patients who already have manifest atherosclerotic cardiovascular disease. In addition to the therapies directed at the list of targets for primary prevention given above, secondary prevention adds pharmacologic agents according to the clinical presentation, which can include antiplatelet therapies, ACE inhibitors and ARBs, and β-blockers.

It is worth acknowledging that the seemingly sharp borders now present between primary and secondary prevention may become increasingly blurred as the growing use of coronary computed tomography angiography identifies more and more subjects with clear atherosclerotic arterial lesions that have not yet progressed to clinical disease. Whether and under what circumstances the more aggressive therapeutic strategies of secondary prevention should be applied to such subjects will need to be determined in large-scale clinical trials.

The economic analysis of CAD prevention illustrates well how cost-effectiveness analysis reflects the efficacy of production of health benefits. In both primary and secondary prevention, the general goal is the same: prevent death and morbidity. The risks (ie, the number of available events that need to be prevented) are of course much higher in secondary prevention patients. The incremental costs of prevention, however, tend to be relatively insensitive to the primary and secondary prevention distinction. In fact, a treatment as secondary prevention may have a lower net cost than the same treatment as primary prevention because of prevention of more expensive complications (eg, MIs) and expensive palliative procedures (eg, coronary revascularization). So secondary prevention costs the same or less and, for any relative reduction in major events, prevents a larger absolute number of complications. Primary prevention is often inefficient economically because many individuals with risk factors will never develop disease complications regardless of how they are treated. For this reason, many studies of primary prevention have attempted to identify higher-risk subsets of the at-risk population in which therapy may be more economically and clinically efficient. The use of a multicomponent inexpensive polypill in older adults is an alternate approach to efficient primary prevention targeting intervention at a population level based on simple demographic features.[116,117]

Cholesterol Abnormalities

Although abnormalities of high-density lipoprotein (HDL) levels and other lipid subfractions appear to play a role in the risk some individuals have to develop and worsen atherosclerotic disease, our primary therapeutic evidence to date involves the use of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins). For secondary prevention, a 2006 meta-analysis of four trials including 27,548 patients comparing intensive versus standard statin therapy in patients with stable CAD or acute coronary syndromes concluded that intensive lipid lowering with high-dose statin therapy significantly reduced nonfatal cardiovascular events.[118] A model-based analysis of hypothetical 60-year-olds found that high-dose statin therapy in patients with acute coronary syndromes added 0.35 QALYs, with the cost-utility ratio remaining below $44,000 per QALY and with a net daily price difference between high dose and conventional dose of $3.50.[119] In patients with stable CAD, high-dose statin therapy added

0.10 QALYs, but for the cost-effectiveness ratio to remain below $50,000 per QALY, the net daily cost difference would need to remain below $1.70.

Recently, monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) (alirocumab, evolocumab) have been shown to lower low-density lipoprotein (LDL) cholesterol to levels beyond that achievable with statin therapy (by ~50%). Early clinical trial evidence suggests these drugs, which are administered by subcutaneous injection every 2 weeks, may also significantly reduce cardiovascular events (HR, ~0.50).[120,121] Use of these agents in one pilot study achieved LDL cholesterol levels < 70 mg/dL in 75% of high-risk subjects versus 9% of patients on maximally tolerated statins alone.[122] Pivotal clinical 5-year outcome trials are expected to report results in 2017. Following FDA approval of the first two agents in this class in 2015, pricing was set at around $14,000 to $15,000 per year (~$40/day). Preliminary economic analyses using the Coronary Heart Disease (CHD) Policy Model estimated cost-effectiveness ratios above $500,000 per QALY for secondary prevention and for treatment of familial hypercholesterolemia.[123] Five-year budget impact projections estimate 2.6 million persons receiving these therapies for 1 year or more at an annual cost of up to $74 billion. The drug cost estimated to achieve a cost-effectiveness threshold was $2412 per year, substantially below current prices. Updated economic analyses are expected once the long-term outcome trial data are published.

There are a number of important primary prevention trials of statin therapy, but none included prospective assessment of economics. A CHD Policy Model analysis of primary prevention strategies for lipid lowering assessed the cost-effectiveness and public health impact of Adult Treatment Panel III guidelines for targeting statin therapy in persons age 35 to 85 years.[124,125] This analysis found that starting statin therapy in 9.7 million adults and intensifying statin therapy in an additional 1.4 million adults would reduce the number of MIs by 20,000 per year and the number of CAD deaths by 10,000 per year. Assuming a cost of $2.11 per low-intensity tablet and $2.81 per high-intensity tablet, over 30 years, the cost-effectiveness ratio for full adherence to Adult Treatment Panel III primary prevention guidelines would be $42,000 per QALY. In addition to drug costs, CAD risk level and age affected the economic attractiveness of statin therapy. Hypothetically, providing low-cost statin therapy to men over age 44 regardless of lipid levels might be an effective and economically attractive prevention strategy, although it seems unlikely to be viable on other grounds.[126]

Oral Antiplatelet Agents

Aspirin Long-term aspirin therapy is one of the primary pillars of secondary prevention. A recent patient-level meta-analysis estimated the benefit of aspirin as 10 fewer coronary events and 5 fewer strokes per 1000 patients treated.[127] Aspirin is now very inexpensive, with the generic drug costing approximately 1.5 cents per day. A cost-effectiveness analysis using the CHD Policy Model developed by Weinstein and Goldman estimated a cost per QALY with aspirin of approximately $11,000.[128] No large-scale empirical trials have studied the economics of aspirin for prevention, but it is quite likely that given the extremely low cost, the reduction in cardiac events would make it actually cost saving and therefore economically dominant.

The situation with primary prevention is more complex as a result of the ambiguity of the clinical data supporting this form of therapy.[129] A recent patient-level meta-analysis calculated that primary prevention with aspirin produced a 5 per 10,000 reduction in nonfatal MI but no effect on death and a 3 per 10,000 increase in major bleeding.[94] A randomized trial of 100 mg of aspirin versus placebo in 29,980 subjects without known cardiovascular disease who were age 50 to 75 years at study onset and who were judged to be at increased risk as a result of a low ankle-brachial index failed to detect a difference in vascular events or in mortality over a mean of 8.2 years.[130] However, a meta-analysis of primary prevention in men versus women showed that aspirin reduced MI in men by approximately one-third and reduced stroke in women by 17%.[131] This meta-analysis was used as the basis for a model-based cost-effectiveness analysis that calculated that primary prevention aspirin had a cost per QALY of more than 100,000 for low-risk 55-year-old men but was economically attractive for higher risk 55-year-old men and all men age 65 or older.[132] An economically attractive cost-effectiveness ratio was obtained only in the women who were 75 years of age and in the highest risk women 65 years of age. A separate model-based analysis calculated that aspirin therapy was less costly and more effective than no therapy in 45-year-old men with a cardiovascular risk of 7.5% or higher over 10 years.[133] That same level of cardiovascular risk in 65-year-old women produced a cost per QALY of $13,300 with primary prevention aspirin therapy.[134] Although these economic analyses are interesting and potentially useful, the ambiguities of the underlying data should be kept firmly in mind, because a therapy that is not clearly clinically effective cannot be cost effective.[135] For both primary and secondary prevention, proper dosing and frequency remain unsettled.[136] PCORI has just funded a 20,000-patient secondary prevention trial comparing 81 mg versus 325 mg of aspirin that will hopefully clarify some aspects of this issue (theaspirinstudy.org).

Clopidogrel The use of clopidogrel in addition to aspirin is considered here as part of the treatment of acute coronary syndrome (ACS). The additional question to be considered in this section is the value of extending therapy beyond the first year and possibly indefinitely. One model-based analysis that examined this issue found that, although therapy was very economically attractive for the first year, as it was extended beyond 2 years, economic attractiveness dropped substantially, particularly in lower risk patients.[137] A second model-based analysis that examined the cost-effectiveness of lifetime clopidogrel therapy added to aspirin for secondary prevention yielded a cost per QALY of greater than $130,000.[128] These results are dependent on two important variables: first, the use of a proprietary cost for clopidogrel, which is now generic and much less expensive, and second, the assumption that the treatment benefits of clopidogrel attenuate over time. Regarding this second point, the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial randomized 15,603 patients with clinical CAD or multiple risk factors to clopidogrel or placebo plus low-dose aspirin and followed them for a median of 28 months.[138] Overall, the clopidogrel arm was not superior in the prevention of cardiovascular death, MI, or stroke, the primary composite end point. However, in the subgroup with clinically evident atherosclerosis, clopidogrel reduced the composite end point by 1 per 100 patients treated. A cost-effectiveness analysis of the secondary prevention subgroup of the CHARISMA trial projected a $2607 higher cost for the clopidogrel arm (using proprietary drug costs) and a 0.072 increase in life expectancy as a result of events prevented during the active treatment phase of the trial.[139] The resulting incremental cost-effectiveness ratio was $36,343 /year life-year saved. Although no updated analyses of this treatment comparison have been done for the United States since the advent of generic clopidogrel, a substantially lower drug cost would make the results described above more economically attractive. The results are primarily dependent on the assumptions of the analysis about the life expectancy losses attributable to a nonfatal MI (3.3-7 years) and to a nonfatal stroke (4-13 years dependent on severity). In this analysis, the assumption was made that clopidogrel would be stopped at the end of the CHARISMA treatment period, so these data do not address the value of longer-term prevention

therapy with this drug. The Dual Antiplatelet Therapy (DAPT) study found that at least part of the incremental clinical benefit of 30 months of clopidogrel and aspirin over 12 months came in the form of prevention of cardiovascular events unrelated to the patient's coronary stent.[140] However, a meta-analysis including the DAPT study failed to find a benefit for extended-duration dual therapy.[141]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors have been tested in several different secondary prevention patient subsets, including early after acute MI, with or without a long-term chronic phase of therapy, and in patients with chronic stable CAD. The Survival and Ventricular Enlargement (SAVE) trial was pivotal in establishing the benefit of captopril started within 3 to 16 days of an acute MI in patients with an ejection fraction of 40% or less.[142] After a mean of 42 months of therapy, captopril produced an increase in survival of 5 per 100 patients, as well as significant reductions in severe heart failure, follow-up hospitalizations for heart failure, and recurrent MIs. A model-based cost-effectiveness analysis of SAVE found that captopril therapy was very economically attractive (cost-effectiveness ratio of $10,400 per QALY or less) as long as the benefits of therapy persisted at least for 4 years.[143] Similar clinical results were observed in the Trandolapril Cardiac Evaluation (TRACE) trial, which randomized 1749 patients 3 to 7 days after acute MI who had an ejection fraction ≤ 35% to trandolapril or placebo.[144] During a follow-up period of between 2 and 4 years, trandolapril produced 7 extra survivors per 100 patients treated relative to placebo. The beneficial effects of trandolapril were still evident at the 10- to 12-year follow-up of the study cohort, even though all patients were recommended for ACE inhibitor therapy at the end of the study's active treatment period.[145] TRACE and SAVE together show a strong and persuasive mortality benefit for ACE inhibitor use in the post-MI population with left ventricular dysfunction. Given the number of serious and expensive complications prevented by the ACE inhibitors in these trials, had a detailed cost analysis been done assuming the use of a generic ACE inhibitor and all other things being equal, the ACE arms would almost certainly have been cost saving, thus making this form of therapy economically dominant.

In the Valsartan in Acute Myocardial Infarction (VALIANT) trial, acute MI patients with left ventricular dysfunction and/or heart failure had equivalent outcomes from the ARB valsartan or the ACE inhibitor captopril.[45] An economic analysis of the trial showed that the availability of generic captopril made this option the better choice from an efficiency perspective.[146]

Use of ACE inhibitors as secondary prevention in patients with stable CAD without left ventricular dysfunction or clinical heart failure has been tested in three large trials: Heart Outcomes Prevention Evaluation (HOPE), European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), and Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE). A combined analysis of these three trials involving 29,805 patients found that ACE inhibitors significantly reduced both all-cause mortality and nonfatal MI each by 1.1 patient per 100 patients treated.[147] A post hoc economic analysis of ramipril use in the HOPE trial showed that estimated cumulative 4.5-year costs did not differ between the ramipril and placebo arms.[148] In the EUROPA trial, the incremental cost-effectiveness for perindopril based on assigning costs to events prevented was £9700 per QALY.[149] The issue that remains unsettled regarding this form of secondary prevention is whether the ACE inhibitors are affecting outcome through their antihypertensive effects or through some other antiatherosclerotic mechanism.[150]

Exercise

Physical inactivity is an established risk factor for cardiovascular disease,[151] and the American Heart Association recommends that healthy adults age 18 to 65 years engage in 30 minutes of moderate-intensity exercise 5 days per week or 20 minutes of vigorous exercise 3 days per week to improve physical health.[152] Although these exercise recommendations appear modest, 23.7% of adults report being physically inactive, and more than 50% do not engage in minimum physical activity recommendations.[153] A population-based analysis by Wang et al[154] using a nationally representative sample estimated the burden of cardiovascular disease as a result of physical inactivity at $23.7 billion in direct medical expenditures in the United States during the year 2001. Although clinicians tend to favor pharmacology over lifestyle interventions for secondary prevention, the available evidence suggests they offer comparable benefits.[155]

A recent analysis used a Markov model to estimate the cost-effectiveness of seven different public health programs aimed at improving participation in physical activity in healthy adults age 25 to 64 years when compared with no intervention.[156] Data from clinical trials, population-based surveys, and published literature were used to estimate resulting reductions in disease burden. Cost-utility ratios ranged from $14,286 per QALY for an intensive 8-week paid media campaign to promote walking among sedentary adults to $68,557 per QALY for a community-wide campaign involving media messaging to promote physical activity, community walking events, and work and school programs.

A 2005 meta-analysis of 63 trials involving 21,295 patients with CAD found that exercise-based rehabilitation was associated with significant reductions in all-cause mortality (at 24 months but not at 12 months) and recurrent MI.[157] Although prospective economic analyses of exercise intervention in US patients with CAD are limited, a 2009 systematic literature review found various exercise interventions to be cost effective compared with usual care in trials from several countries.[158]

Smoking Cessation

Eliminating tobacco use is an essential component of interventions to reduce the burden of cardiovascular disease. According to the US Centers for Disease Control and Prevention, smokers are at greater risk than nonsmokers of debilitating and costly chronic conditions, cardiovascular and respiratory diseases, and cancer, resulting in an average loss of 14 years of life per smoker as well as substantial productivity losses.[159] The costs of tobacco use in the United States were estimated at $193 billion annually between the years 2000 and 2004.[160] Understanding the complex issues surrounding tobacco, however, also involves recognition of its economic benefits. The tobacco industry is a source of substantial employment in some regions and huge tax revenues for most high-income countries.[161]

A 2003 comprehensive review of tobacco smoking and its direct medical costs in cardiovascular diseases found clinically based smoking cessation therapies in several studies between 1977 and 1997 to have cost-effectiveness ratios between $1216 and $15,777 per life-year saved.[162] Most of these studies reported on transdermal nicotine patches or nicotine gum therapy plus physician counseling compared with no treatment. A 2008 review of various tobacco control strategies from public policy interventions to quit lines to pharmacotherapy found the vast majority to be cost saving or highly cost effective.[163] One study conducted a model-based economic analysis of cognitive behavioral therapy added to nicotine replacement therapy for up to 40 weeks versus a 12-week smoking cessation program (using 2010 US dollars) and found the extended smoking cessation approach to be cost effective at $6324/QALY.[164]

Blood Pressure Control

Hypertension is an established risk factor for MI, congestive heart failure, and stroke, all of which incur substantial economic and personal costs. The American Heart Association estimated the annual direct and indirect costs of high blood pressure to be $48.6 billion in 2011.[34]

A 2009 meta-analysis of 147 randomized trials examining the use of blood pressure–lowering pharmacotherapy for the prevention of cardiovascular disease concluded that ACE inhibitors, ARBs, β-blockers, calcium channel blockers, and thiazides were all similarly effective at reducing cardiovascular events and stroke for a given reduction in blood pressure in both primary and secondary prevention cohorts.[165] β-Blockers were found to be significantly more effective in preventing recurrent cardiovascular events in post-MI patients, and calcium channel blockers were more effective at preventing stroke but less effective at reducing the incidence of heart failure.[165]

The literature on the economics of hypertension therapy is not as mature as might be expected as a result of wide variations in methods, data sources, and analytical approaches.[166] In general, the costs related to therapy can be broken down into the direct costs of drug therapy, the costs associated with treatment of side effects of therapy, the cost savings as a result of reduced cardiovascular events, and the costs related to increased or decreased productivity, particularly related to employment. An economic analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared lisinopril and amlodipine with chlorthalidone as first-line treatment in patients with hypertension and one additional cardiovascular risk factor.[167] In this analysis, lisinopril had higher incremental cost and lower incremental life-years gained compared with chlorthalidone and thus was dominated from an economic perspective. Amlodipine had higher incremental cost but provided an incremental gain of 0.016 life-years, with a cost-effectiveness ratio of $160,000 per life-year saved compared with chlorthalidone at 6 years of follow-up. Lifetime projections were a gain of 0.099 life-years and a cost-effectiveness ratio of $48,400 per life-year saved. The drug cost of amlodipine in this analysis was calculated at $2.47 per 10-mg tablet using 2004 wholesale prices for a proprietary formulation, whereas chlorthalidone was valued at $0.19 per 25-mg tablet. The patent for amlodipine expired in 2007, and generic versions are now available at a retail cost of $0.17 per 10-mg tablet versus $0.43 per 25-mg tablet of chlorthalidone, suggesting that amlodipine could economically dominate chlorthalidone given today's drug prices.[168] These price fluctuations underscore the temporal limitations of cost-effectiveness analyses.

A cost-effectiveness analysis of the implementation of the 2014 guidelines for hypertension therapy relative to the status quo (reflected in National Health and Nutrition Examination Survey data from 2007 to 2010) found that full implementation of the guideline recommendations would reduce cardiovascular deaths and nonfatal events in the United States while also being cost saving.[169] Treatment of stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg) was cost saving even if drug therapy costs were doubled over the base case. Treatment of stage 1 hypertension (systolic blood pressure 140-154 mm Hg) had a cost-effectiveness ratio < $50,000 per QALY for all men and for women age 45 to 74 years.

CORONARY ARTERY DISEASE: ACUTE CORONARY SYNDROMES

(See also Chaps. 39 and 40.) ACS is commonly divided into ST-segment elevation MI or non–ST-segment elevation ACS because of the different initial therapeutic approaches required. The most important initial decision in the ST-segment elevation acute MI patient with important economic implications is the assessment for and selection of acute reperfusion therapy, either primary PCI or fibrinolytic therapy. For the non–ST-segment elevation ACS population, the major management decision with important economic ramifications relates to the risk stratification strategy to be used, either early invasive or early conservative. All patients also receive secondary prevention, which is discussed elsewhere in this chapter.

Acute Reperfusion Therapy

As noted at the beginning of this chapter, economic analysis is centrally concerned with trade-offs: What are the (long-term) consequences of doing X rather than Y? This means that the relevant economic questions about acute reperfusion therapy depend on what alternatives are available. At some centers, for example, primary PCI may not be available, and the options may be treat with fibrinolytic therapy or transfer for primary PCI. At primary PCI centers, the fibrinolytic option may not be relevant unless all the catheterization laboratories are full, with almost all reperfusion-eligible patients going for emergent catheterization. But even in such referral centers, current guidelines recommend different choices depending on how quickly patients can reach the catheterization laboratory. When both primary PCI and fibrinolytic therapy are available, the weight of evidence favors primary PCI as a result of improved survival (~2 extra survivors per 100 patients treated) and lower stroke risk.[170,171]

A recent cross-sectional study from Europe of acute ST-segment elevation MI care in 2010 to 2011 found a substantial number of patients still not receiving any reperfusion therapy and large variations in the amount and type of therapies used in different countries.[172] The largest modern trial, The Danish Acute Myocardial Infarction 2 (DANAMI-2) study, recently reported that, at a median follow-up of 7.8 years, the primary end point of death or MI had occurred in 35% of the primary PCI group and 41% of the fibrinolysis group (HR, 0.78).[173] Importantly, the relative benefits of primary PCI appeared to be the same in older and younger patients.[174] In addition, DANAMI-2 reported that at 1 month, several major dimensions of quality of life were better in the primary PCI arm.[175] Whether these benefits persisted for the longer term is unknown.

The only relatively modern empirical cost comparison of these two strategies comes from the 123-patient Canadian Stenting Versus Thrombolysis in Acute Myocardial Infarction Trial (STAT).[176] The cost of alteplase in Canada when this study was conducted in 1999 was $1809, whereas the cost of the primary PCI procedure itself was estimated at $2009. In this unblinded trial, the primary PCI arm had a 2-day shorter hospital stay and fewer unscheduled invasive coronary angiograms than the alteplase arm during the index hospitalization and fewer follow-up readmissions. By 6 months, the primary PCI arm had approximately $2500 lower medical costs than the fibrinolytic arm. Taking the clinical data showing superior survival effects in the short term that persist long term and the suggestion of lower costs, the evidence available suggests that in situations when primary PCI has clinical superiority over fibrinolysis, it is economically dominant (lower costs as well). One important caveat about these comparisons is that changes in the price of fibrinolytics or stents over time can affect the incremental differences. For example, in the early stent era, the STENT PAMI (Primary Angioplasty in Myocardial Infarction) trial estimated that the PCI arm had higher hospital costs as a result of the higher costs of the stents, although these costs were partially recouped by the lower need for follow-up invasive procedures.[177] Over the intervening years, the costs of stents, particularly bare metal stents, have come down sharply, whereas the costs of t-PA and tenecteplase have remained stable (primarily because of the lack of generic competition).

Several European model-based analyses have examined the cost-effectiveness of primary PCI versus fibrinolysis and found either economic dominance[178] or a cost-effectiveness ratio of less than £20,000.[179]

Early Invasive Versus Early Conservative Management Strategies

In the patient with non–ST-segment elevation ACS, two major management options have been used and tested in clinical trials. The *early invasive strategy* involves routine referral to invasive angiography for

all patients without contraindications, typically within the first 18 to 48 hours after presentation. The *early conservative strategy* reserves invasive study for a subgroup of patients known to be at particularly high risk because of specific features, such as ongoing ischemic symptoms that cannot be controlled medically, and treats all others with initial medical therapy. In evaluating the comparisons of these two strategies, it is important to recognize that there have been many variations of the early conservative strategy tested, some of which used early angiography in only approximately 10% of patients, whereas others referred more than 50% of such patients. In addition, the options for adjunctive medical therapy have been evolving over time, first with the use of intravenous glycoprotein IIb/IIIa inhibitors and more recently with adenosine diphosphate (ADP) receptor antagonist antiplatelet agents.

A meta-analysis from the Cochrane Library involving five trials and 7818 patients found a trend toward harm with the early invasive strategy for in-hospital mortality (relative risk, 1.6), with no evidence for a longer-term mortality benefit.[180] Both MI rates and refractory angina were reduced in the early invasive strategy, and early and intermediate rehospitalization rates were also reduced. The invasive strategy was associated with a two-fold increased risk of a periprocedural MI. The complexity of attempting to get an "answer" about the best strategy using meta-analysis can be illustrated by comparing trials with different versions of the early conservative strategy. In the Fast Revascularization During Instability in Coronary Artery Disease (FRISC) II trial, 10% of the conservative arm received catheterization during the index hospitalization.[181] In this trial, the early invasive strategy was associated with a 1.7 per 100 absolute reduction in mortality and a 2 per 100 absolute reduction in MIs. In the Randomized Intervention Treatment of Angina (RITA) 3 trial, only 16% of the early conservative group was referred for angiography during the index admission.[182] No difference in death or MI was observed early in the trial, but at 5 years, the early invasive arm had a 22% lower mortality rate.[183] By contrast, in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS-TIMI 18) trial, 51% of patients in the early conservative arm were referred for cardiac catheterization during the index hospitalization.[184] No difference in mortality between the two arms was evident out to 6 months, but there was a 2 per 100 patients treated absolute reduction in the rate of MI. Economic analysis of this trial showed that the index hospitalization was approximately $1600 more expensive for the early invasive arm, but follow-up costs out to 6 months were approximately $1000 lower in this group.[185] Thus, the net 6-month incremental costs of the early invasive strategy were $670. Costs per life-year added for the invasive arm relative to the conservative arm were approximately $13,000. This result rests on the pivotal assumption that the MIs prevented during the early phase of the trial would translate into added survival with much longer follow-up of the study cohort.

In the Timing of Intervention in Acute Coronary Syndromes (TIMACS) study, Medicare diagnosis-related group reimbursements were used to compare the costs of an early versus delayed (> 36 hours) invasive strategy in ACS patients.[186] The early invasive group averaged $1170 lower costs overall and $3720 lower costs in high-risk patients (Global Registry of Acute Coronary Events score ≥ 141). The primary source of the difference in costs was a shorter length of stay for the early invasive patients.[187]

Anticoagulant Therapy

Intravenous unfractionated heparin has been a standard part of medical therapy for ACS since before the initial American College of Cardiology/American Heart Association Guidelines were published in 1994, but it is quite inexpensive, and the economics have not been studied empirically relative to medical therapy without anticoagulation. Instead, heparin has formed the "usual care" group in comparisons with newer anticoagulation therapies. Clinical outcomes for the low-molecular-weight heparin enoxaparin have been compared with unfractionated heparin in several meta-analyses.[188,189] These analyses show a 9% to 16% relative reduction in death or MI for enoxaparin. However, these benefits were not evident in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, in which 92% of patients underwent diagnostic catheterization and the majority received clopidogrel and/or a glycoprotein IIb/IIIa inhibitor.[190] These benefits were also not seen in the A-to-Z Trial in patients who received tirofiban and were intended for an early invasive strategy.[191] However, there was a large benefit evident in the patients treated with tirofiban and an intended early conservative strategy.

The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS)-5 trial, which compared enoxaparin with fondaparinux in 20,078 patients with non–ST-segment elevation ACS, found a reduction in death, MI, or refractory ischemia with fondaparinux that was primarily a result of an unexpected mortality reduction.[192] A model-based analysis of the OASIS-5 trial from a US perspective found that over the first 6 months, the fondaparinux regimen was associated with a cost savings of approximately $550.[193] A long-term extrapolation indicated that the fondaparinux strategy would be economically dominant in most scenarios considered.

Antiplatelet Regimens

Three oral ADP receptor antagonist antiplatelet agents are of relevance to management of ACS patients during the first year after hospitalization: clopidogrel, prasugrel, and ticagrelor (Table 112–3). The issue of longer term antiplatelet therapy is addressed in the portion of this chapter devoted to prevention.

The clinical benefits of clopidogrel therapy in this clinical context were firmly established by the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial, which randomized 12,562 patients with non–ST-segment elevation ACS to a load (300 mg of clopidogrel or placebo) followed by daily maintenance therapy (75 mg of clopidogrel or placebo).[194] Over the mean study follow-up of 9 months, clopidogrel significantly reduced the primary composite end point (death, MI, or stroke) from 11.4% to 9.3% and nonfatal MI from 6.7% to 5.2%. Cardiovascular death alone was also reduced from 5.5% to 5.1%, but the reduction was not statistically significant. An economic analysis from the CURE trial reported that the clopidogrel arm generated $325 per patient in hospital cost savings and had $766 of extra costs for the clopidogrel, resulting in a net cost of $442 per clopidogrel patient.[195] Using Framingham Study data to project life expectancy for the trial patients (0.069 life-years per clopidogrel patient), these investigators calculated a cost per life-year saved of $6318. A second model-based analysis using the published results of CURE and assuming a year of clopidogrel therapy calculated a similar incremental cost-effectiveness ratio.[137]

Prasugrel has a more rapid onset of effect and more platelet-inhibiting potency than clopidogrel. This enhanced potency translated into a significant reduction in the composite of cardiovascular death, MI, or stroke in the pivotal phase III trial used for FDA approval, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis In Myocardial Infarction (TRITON-TIMI)-38.[196] Over a median follow-up of 15 months, 9.9% of patients in the prasugrel arm and 12.1% in the clopidogrel arm had a primary event. The cost-effectiveness analysis used prospective data from eight countries participating in the trial.[197] Hospitalization costs were estimated using US diagnosis-related group weights. The cost of the drug regimens was assigned using net wholesale prices: $4.62 per day for clopidogrel and $5.45 per day for prasugrel. Life

TABLE 112–3. US Cost-Effectiveness Analyses for Antiplatelet Regimens in Acute Coronary Syndromes

Data From Trial Data/ Cohort (First Author)	Population	Treatment	Benefit	Incremental Cost (Year)	Incremental Cost-Effectiveness
CURE (Weintraub)	Patients hospitalized with onset of ACS symptoms and no ST-segment elevation	Clopidogrel vs placebo	Clopidogrel added 0.069 life-years	Incremental costs for clopidogrel were $442 (2001 USD)	$6318/LY
TRITON-TIMI-38 (Mahoney)	Patients with moderate- to high-risk ACS undergoing planned PCI	Prasugrel vs clopidogrel	Incremental life expectancy with prasugrel was 0.102 life-years gained	Cost saving (2005 USD)	N/A
PLATO (Cowper)	Patients with ACS	Ticagrelor vs clopidogrel	Ticagrelor added 0.137 QALYs	Incremental costs for ticagrelor were $4058 (2013 USD)	$29,665/QALY

Abbreviations: ACS, acute coronary syndrome; LY, life-year; N/A, not applicable; QALY, quality-adjusted life-year; USD, US dollars.

expectancy for the study cohort was estimated using long-term survival data from the Saskatchewan Health Database. Over the median study follow-up, the prasugrel arm saved $221 per patient, primarily as a result of reduced need for follow-up PCI. Incremental life expectancy with prasugrel was calculated as 0.102 life-years per patient, primarily as a result of the early reduction in nonfatal MIs. Given better life expectancy and lower cost, prasugrel was economically dominant over clopidogrel in this analysis. Substituting generic clopidogrel at a cost of $1 per day yielded a cost-effectiveness ratio for prasugrel of approximately $10,000 per life-year saved. As with the PURSUIT economic analysis discussed earlier, this result is dependent on the assumption that prevention of end point MIs as occurred in this trial is of continuing long-term prognostic benefit. The population of TRITON-TIMI-38 comprised ACS patients referred for PCI. The TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial evaluated the use of prasugrel (10 mg daily) versus clopidogrel (75 mg daily) for up to 30 months in 7243 patients < 75 years of age with unstable angina or non–ST-segment elevation MI who did not undergo revascularization but were receiving aspirin.[198] Among this group of patients, prasugrel did not significantly reduce the frequency of a composite of death from cardiovascular causes, MI, or stroke, and similar risks of bleeding were observed.

Ticagrelor, an oral, reversible ADP receptor antagonist, has recently been shown to be superior to clopidogrel in the Platelet Inhibition and Patient Outcomes (PLATO) trial involving 18,624 ACS patients with or without ST-segment elevation.[199] At 12 months, the composite of vascular death, MI, or stroke occurred in 9.8% of the ticagrelor patients and 11.7% of the clopidogrel patients. All-cause death was reduced from 5.9% to 4.5% ($P < .001$) by ticagrelor. No difference in major bleeding was observed. An economic analysis of this study assessed the cost-effectiveness of ticagrelor versus clopidogrel from the perspective of the US health care system.[200] Within-trial resource use was estimated using the portion of the US cohort on low-dose aspirin therapy to match the FDA-approved indication. Quality-adjusted life expectancy was assessed using the total PLATO population combined with long-term survival data from the PURSUIT cohort. Ticagrelor therapy in this population had a cost-effectiveness ratio of $29,665 per QALY relative to clopidogrel.

A decision model–based analysis using the perspective of the Ontario Ministry of Health found ticagrelor had a cost-effectiveness ratio of $12,205 (Canadian dollars) per QALY relative to clopidogrel, whereas prasugrel had a cost-effectiveness ratio of $57,630 per QALY.[201] A second analysis found that genotyping might improve the cost-effectiveness of prasugrel and ticagrelor, although the strategies require clinical trial validation.[202]

CORONARY ARTERY DISEASE: CHRONIC STABLE CORONARY ARTERY DISEASE

Atherosclerosis is a chronic progressive disorder that commonly involves the epicardial coronary arteries. In the absence of effective therapy, it tends to progress to symptomatic limitation of function from angina pectoris, acute MI, progressive left ventricular dysfunction, and death. The course of individual patients, however, can be quite variable. Two main therapeutic strategies have evolved to address the symptomatic and prognostic consequences of this disease, preventive medical therapy (see the prevention section of this chapter) and coronary revascularization.

Coronary Revascularization Overview

(See also Chaps. 42 and 44.) The number of revascularization procedures in the United States peaked in 2010 and has been declining since then.[203] In 2010, 397,000 CABG procedures and 954,000 PCI procedures were performed.[34] Unfortunately, the evidence pertaining to the clinical questions of most importance (which patients derive significant clinical benefit from CABG and which from PCI) is largely out of date and therefore of unclear relevance to contemporary practice. The trials of CABG versus medicine that demonstrated a survival benefit for CABG in high-risk anatomic CAD subsets were all done before the elements of current optimal medical therapy were in use. In addition, the operations that were done during that era did not routinely employ internal mammary arteries for the left anterior descending graft and did not employ aggressive secondary prevention after surgery.[204] In a 1994 meta-analysis of the CABG versus medicine trials, Yusuf et al[205] estimated that CABG extended the life expectancy of left main disease patients by 19 months and that of three-vessel disease patients by 5 months over a projected 10-year follow-up. Although there are

no modern empirical cost studies relevant to this comparison, model-based analyses demonstrate that with such a large survival benefit, even an incremental cost of $30,000 or more per patient treated with CABG rather than medicine yields an economically attractive cost-effectiveness ratio under most reasonable assumptions.[206] It should also be noted that model-based analyses suggest that CABG is also cost effective in highly symptomatic patients in whom durable and effective symptomatic control cannot be achieved with medicine alone.[206]

The advent of PCI, initially as percutaneous transluminal coronary angioplasty followed by bare metal stents and then first- and second-generation drug-eluting stents (DES), has altered both the clinical playing field and the way economic questions about this area are framed. As with the CABG and medicine comparisons, evaluation of the PCI clinical trials is made challenging by the evolving technology, changes in the population considered suitable for the procedure, and changes in the adjunctive medical therapy used during and after the procedure. Two sorts of clinical trials have been performed with PCI, asking very different but complementary questions. The first set of trials, comparisons with medicine and with CABG, attempt to define the role of PCI in the larger management picture of CAD. The second set of trials compares various improvements in PCI technology and adjunctive medical management in order to determine how to make the procedure as effective as possible. None of these latter trials by themselves, however, establish which patients should receive a PCI rather than an alternative therapy.

Percutaneous Coronary Intervention Versus Medicine

In a meta-analysis using data from more than 25,000 patients with stable CAD, no form of PCI (including use of DES) reduced the risk of death or MI relative to medical therapy.[207] However, a larger meta-analysis found a mortality benefit for second-generation DES versus medicine.[208] As with medical therapy and CABG, the clinical and economic effects of PCI have evolved substantially over the last two decades.[209] The most recent large-scale trial of PCI versus medicine is Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), which randomized 2287 stable CAD patients at 50 North American sites between 1999 and 2004 to medical therapy or medical therapy plus PCI with bare metal stents.[210] As with the meta-analysis just discussed, the primary end point of death or nonfatal MI was not different in the two arms after a median follow-up of 4.6 years. One important feature of the COURAGE trial was a careful prospective analysis of angina relief and quality of life.[211] Six months after randomization, the PCI group had a small but statistically significant advantage in angina relief and quality of life, but this treatment effect attenuated over time and was gone by 3 years. Using Medicare reimbursement rates to assign cost weights, the COURAGE investigators estimated an incremental cost of PCI of $11,410 initially, falling slightly to $9451 when projected over the study cohort's lifetime (~12 years).[212] Using only the empirical trial follow-up, the COURAGE investigators estimated a 0.03 life-year survival advantage for PCI and a 0.05 QALY advantage. In the lifetime extrapolation, the QALY advantage for PCI was 0.06 (95% CI, –0.21 to 0.43). In the lifetime extrapolation, the cost per QALY produced with PCI was $168,000, and only 10% of 5000 bootstrap replications fell below $50,000 per QALY. The message from COURAGE clearly is that routine PCI in this population is a very inefficient (and societally unattractive) way to produce extra health benefits. This result, as with most cost-effectiveness analyses, is primarily driven by the very small (and statistically insignificant) treatment effect of PCI on hard clinical outcomes. What remains unclear is whether a different result might have been obtained if COURAGE had required all patients to have a significant inducible ischemia on functional testing. This question is the subject of the ongoing approximately 5000-patient International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (ISCHEMIA; NCT01471522).

The most recent comparison of medicine versus revascularization is the Bypass Angioplasty Revascularization Investigation (BARI) 2D trial, which randomized 2368 patients with type 2 diabetes and stable CAD.[213] Overall, total mortality (the primary end point) did not differ in the two arms. One interesting feature of the BARI 2D was a prospective definition of a PCI and a CABG subset before randomization. In the CABG subset, major cardiovascular events were reduced by CABG relative to medicine alone. Economic analysis results differed substantially in these two strata.[214] In the PCI stratum, at the end of 4 years, PCI costs were higher by $5600 and clinical outcomes were better in the medical arm. Extrapolating to a lifetime perspective, total costs for the medical arm were approximately $200 higher than PCI, but life expectancy was longer and the cost-effectiveness ratio for medicine versus PCI was $600 per added life-year. In the CABG stratum, 4-year costs were $20,300 higher for the CABG patients. In the lifetime projections, CABG increased survival by 0.52 life-years per patient at an incremental cost that remained at approximately $20,000. The cost-effectiveness ratio for CABG versus medicine was $47,000 per added life-year.

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Graft

Trials performed to evaluate, among patients requiring revascularization, which procedure should be performed have gone through several stages, largely reflecting evolution in the technology of PCI. One interesting observation from a comparison of the BARI randomized and registry cohorts is that compared with the registry patients, patients randomized into this trial tended to be higher risk than the typical percutaneous transluminal coronary angioplasty patients and lower risk than the typical CABG patients.[215] Thus, when interpreting the clinical trials comparing these two revascularization strategies, it is worth keeping in mind that the patients are not likely representative of unguided clinical practice. A 2014 meta-analysis of CABG with one or more arterial grafts versus PCI with stents included six trials involving 6055 patients and found that CABG reduced total mortality at 4 years as well as MI and repeat revascularization.[216]

Economic analyses of the trials from the bare metal stent era of PCI versus CABG comparisons (the Arterial Revascularization Therapy Study [ARTS] and the Stent or Surgery [SOS] trial) typically showed the expected initial advantage of PCI that narrows over the first year as a result of repeat procedures. Longer-term economic follow-up was not reported for these trials.

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with DES versus CABG in three-vessel or left main disease patients.[217] After 5 years of follow-up, there were statistically significant differences favoring CABG in all-cause mortality (9.2% vs 14.6% for PCI) and the composite of death/stroke/MI (14% vs 22% for PCI) as well as MI alone (4% vs 9.2% for PCI).[218] Cohen et al[219] used a model-based analysis to assess the costs and cost-effectiveness of CABG relative to PCI using within-trial data from SYNTAX. PCI had higher initial procedural costs ($3415 per patient), whereas CABG had higher total hospitalization costs ($10,036 per patient). PCI had higher 5-year costs (excluding the index revascularization procedure) as a result of more frequent hospitalizations, revascularizations, and medication costs. CABG had higher projected lifetime costs ($92,509 vs $87,428 for PCI; difference of $5081), higher QALYs (10.46 vs 10.12 for PCI; difference of 0.34), and a base case cost-effectiveness ratio of $16,537 per QALY and $12,329 per life-year.

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes mellitus and multivessel CAD to PCI with DES or CABG. The primary end point of death, MI,

or stroke was significantly lower in the CABG-treated group (18.7%) versus PCI (26.6%) at 5 years of follow-up.[220] A prospective economic evaluation was conducted alongside the trial, with costs assessed from the perspective of the US health care system. The CABG group had $8622 per-patient higher index hospitalization costs and $3641 higher per-patient 5-year cumulative costs.[221] Life expectancy was higher in the CABG group (4.665 vs 4.613 years) and remained higher when quality adjusted (3.719 QALYs vs 3.688 QALYs). With within-trial survival extended to a lifetime horizon, the incremental cost-effectiveness ratio for CABG versus PCI was $6791 per life-year and $8132 per QALY gained.

CONCLUDING PERSPECTIVE

Although the full impact is presently far from clear, the passage of the PPACA has initiated a reshaping of the medical economy that will play out for decades to come and is equaled in potential impact only by the creation of Medicare and Medicaid in 1965. What the PPACA has done most clearly is expand some level of health insurance coverage to millions of uninsured Americans. Its effects on the cost of US medical care are much less clear, and some analysts have predicted that the bill will actually increase costs by 2019 over projections made before the bill was passed. Many in the policy world may look to the bill's new support for comparative effectiveness research as a tool for controlling the growth of medical spending. The perspective advanced in this chapter is that an understanding of the concepts, tools, and approaches of medical economics can help make cardiovascular clinicians more effective advocates in the debates sure to come about what forms of care are worth supporting with societal health care dollars. However, neither medical economics nor comparative effectiveness provides the whole story. Questions of value and justice and how we see ourselves as a society will always be critical elements in deciding how much and what types of health care get supported in the United States. The only thing that is certain is that the American health care system is very much a work in progress.

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